Catalytic Enantioselective Synthesis of Heterobiaryl Atropisomers

Richard Surgenor

University College

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

Doctor of Philosophy

of the

University of Oxford



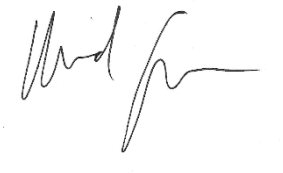
Chemistry Research Laboratory

12 Mansfield Road, Oxford,

OX1 3TA

Declaration

This dissertation describes work carried out in the Chemistry Research Laboratory at the University of Oxford between September 2017 and June 2021. This dissertation is a product of my own work and included no results obtained through collaboration, except where specifically indicated in the text.



Richard Surgenor

Acknowledgments

Firstly, I would like to thank Martin for all of his supervision and enthusiasm throughout my time in Oxford, and for nourishing a supportive environment in his research group where we are free to be creative, explore our own ideas and grow as researchers.

Many thanks also go to my internship supervisor in Boston, Philip Collier, and in Milton Park, Mike O'Donnell. These unforgettable experiences provided me with a great deal of confidence in my ability as a chemist that I was able to take back for the final stretch of my PhD in Oxford. Thank you both so much for these fantastic opportunities and for all of your support.

For this project, countless thanks must go to Xiangqian for all of your extremely hard work for helping to get this project across the line, I wish you and your family all the best of luck for your future! Thanks also go to Will for being patient with my demands and putting up with my ignorance about EPR!

My time in the CRL has been made special by the many individuals I have been lucky enough to cross paths with. In the lab, thank you to Alison for teaching me all things HPLC and for bringing a glass bin to Nando's that one time for some reason. Minh, thank you for all the cat memes. Ben R, thank you for popularising tracksuit bottoms as the only choice for lab comfort. Antti, thank you for showing me first-hand the dangers of what can happen to a man when chemistry pushes them to the brink of madness. Yao, thank you for being such a kind and supportive member of the lab, and for being so willing to give advice or lend a hand. Pascal, it was a privilege to serve my sentence in F4 with you. Thank you for all the skittles, tennis matches, and for your haunting mash-ups of whale sounds, Japanese recorder bands and the Chicago metropolitan police radio. Tudor, thank you for your dank sense of humour. Owen, my fume hood foe, thank you for your friendship over these last few years, and for being so patient with me giving you garbage crystals. Ben J, I will never forgive you for making me cycle up Streatly hill. Zac, a true orangeman, hopefully we can bike round the north coast some time. Mihai, I hope your dreams of never running a reaction again come true. Ben D, thank you for correcting my terrible French homeworks. Pearse, the MDS group is greatly indebted to your talents and servitude, I hope your patronage does not go unnoticed. Maddie, you have been a great addition to F4 and best of luck for the rest of your time.

Thanks to my friends outside of chemistry. My friends at Univ, particularly Dee, Jess R, James and Sam, and to my volleyball friends, Dave R, Dave G, Spencer, Jess A and Jamie, I count myself lucky to have been able to spend so much time with you all. Finally, to my parents. Thank you for all of your unconditional support over these last few years. I hope I can make it up to you all one day.

Abbreviations

Å	Ångström(s)
Ac	acetyl
ACI	ammonia chemical ionization
AIBN	azobisisobutyronitrile
aq	aqueous
Ar	aryl (generic)
BINOL	1,1′-bi-2-naphthol
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BOX	bis(oxazoline)
bp	boiling point
Bu	butyl
°C	degrees Celsius
CDC	cross-dehydrogenative coupling
CDI	carbonyldiimidazole
Conc.	concentrated
CPA	chiral phosphoric acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
1,2-DFB	1,2-difluorobenzene
DFT	density functional theory
DIBAL	diisobutylaluminium hydride
DIPEA	diisopropylethylamine (Hünig's base)
DKR	dynamic kinetic resolution
DMF	N,N-dimethylformamide
DMAP	4-dimethylaminopyridine
DMP	Dess-Martin periodinane
DMPO	5,5-Dimethyl-1-pyrroline *N*-oxide
DMSO	dimethylsulfoxide
DPP	diphenyl phosphate

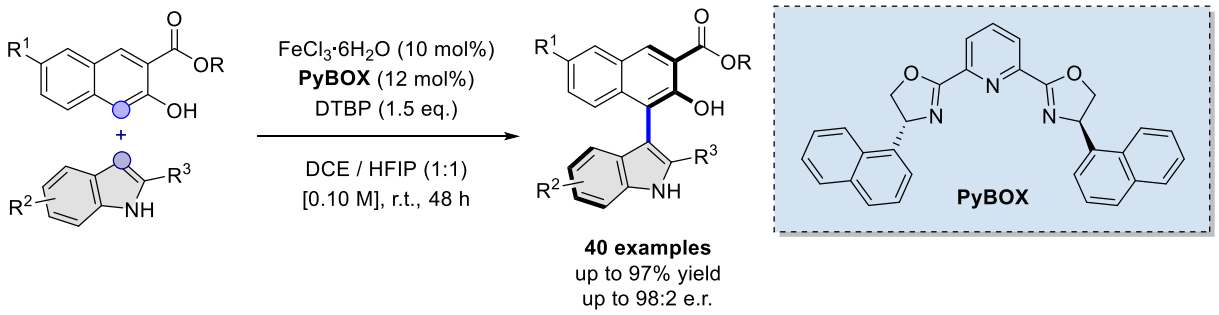
d.r.	diastereoisomeric ratio
DTBP	di-*tert*-butyl peroxide
E	electrophile (generic)
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EI	electron-impact ionization
Equiv.	equivalent(s)
e.r.	enantiomeric ratio
e.e.	enantiomeric excess
ESI	electrospray ionization
ESR	electron spin resonance
Et	ethyl
FDA	Food and drug administration
FI	field ionization
FTIR	fourier-transform infra-red spectroscopy
g	gram(s)
h	hour(s)
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
HOMO	highest occupied molecular orbital
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
Hz	Hertz
i	iso
IBX	2-iodoxybenzoic acid
IPA	isopropyl alcohol
IUPAC	International Union of Pure and Applied Chemistry
J	coupling constant (NMR)
k	rate constant
k_{rac}	rate constant of racemization
L	litre(s)
λ	wavelength
LDA	lithium diisopropylamide
LRMS	low-resolution mass spectrometry
μ	micro-

m	milli-
M	moles per litre
m	multiplet (NMR)
m-	meta
MALDI	matrix assisted laser desorption ionisation
MCI	methane chemical ionization
m-CPBA	meta-chloroperbenzoic acid
Me	methyl
min	minute(s)
mol	moles
M.P.	melting point
NBS	N-bromosuccinimide
NHC	*N*-heterocyclic carbene
NHS	N-hydroxysuccinimidyl
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
o-	ortho
p-	para
Ph	phenyl
PIDA	(diacetoxyiodo)benzene
PIFA	bis(trifluoroacetoxy)iodobenzene
PPA	polyphosphoric acid
ppm	parts per million
Pr	propyl
PPTS	pyridinium para-toluenesulfonate
PTC	phase-transfer catalyst
PTSA	para-toluenesulfonic acid
PyBOX	pyridine-bis(oxazoline)
Quant.	quantitative
Quat	quaternary
R	substituent (generic)
RBF	round-bottomed flask
rt	room temperature

s	*sec*-
SALEN	bis(salicylidene)ethylenediamine
SET	single electron transfer
SOMO	singly-occupied molecular orbital
t	*tert*-
T	temperature
T3P®	1-propanephosphonic anhydride solution
TDO	thiourea dioxide
Tf	trifluoromethylsulfonate
TFA	trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMEDA	tetramethylethylenediamine
τ_R	retention time (for HPLC)
wt%	weight percent
X	group (generic)

Abstract

Heterobiaryl atropisomers comprise a privileged class of compounds whose applications span the fields of medicinal chemistry, asymmetric catalysis and materials science. In particular, axially chiral indoles have recently emerged as an important member of the atropisomeric heterobiaryl family. This thesis comprises two research projects. Initially, we describe our efforts towards an atropselective Fischer indolisation from acyclic phenylhydrazones; this highlights the challenges associated with forging a heterobiaryl axis with a sufficiently high rotational barrier. Secondly, we disclose a cheap and abundant iron catalyst ($FeCl_3 \cdot 6H_2O$) that facilitates oxidative cross-coupling between 2-naphthols and C-2 substituted indoles in the presence of a chiral C_2-symmetric PyBOX ligand. This reaction creates the desired aryl-aryl linkage from two C–H bonds, yielding atropisomeric heterobiaryls with excellent levels of enantioselectivity, in enantiomeric ratios of up to 98:2. The reaction also exhibits remarkable chemoselectivity, yielding exclusively the cross-coupled products without competing homocoupling of the naphthol or indole fragments. Mechanistic investigations enabled us to propose that the reaction proceeds through highly selective oxidation of the heterocycle by the Fe(III)-PyBOX complex, generating an indolyl radical. This species is then trapped by a chiral Fe(III)-bound naphtholate *via* a radical–anion type cross-coupling process. In due course, we envision that this simple, cheap and sustainable catalytic manifold will facilitate access to a range of heterobiaryl compounds and enable their applications across a variety of fields.



Scheme I: Atropselective synthesis of indoles *via* iron catalysed oxidative cross-coupling

Table of Contents

Introduction

Chapter 1: Introduction to Atropisomerism

1.1 Atropisomerism 1
1.2 Atropisomers in Enantioselective Catalysis 1
1.3 Atropisomers in Medicinal Chemistry 3
1.4 Barriers to Rotation 4
1.5 Heterobiaryl Atropisomers 6
1.6 Strategies for Constructing Heterobiaryl Atropisomers 7
1.7 Catalytic Enantioselective Synthesis of Atropisomeric Indole-based Heterobiaryls 9
1.7.1 Strategy A: Direct Coupling 9
1.7.2 Strategy B: Atropselective Heteroaryl Ring Construction 14
1.7.3 Strategy C: Central-to-Axial Chirality Transfer 19
1.7.4 Strategy D: Modification of an Existing Heterobiaryl 21
1.8 Project Aims: Enantioselective Synthesis of Atropisomeric Indoles 24

Research Project A - Chapter 2: Atropselective Fischer Indolisation

Chapter 2: Atropselective Fischer Indolisation

2.1 Introduction 25
2.2 Mechanism of the Fischer Indole Synthesis 25
2.3 Relevance and Challenges 26
2.4 Catalytic Asymmetric Fischer Indolisation 26
2.5 Project Design: Atropselective Fischer Synthesis of C-3 Aryl Indoles 29
2.6 Synthesis of Phenylhydrazones 30
2.6.1 Strategy A: Benzylic Metalation and Acylation 30
2.6.2 Strategy B: Epoxide Ring Opening and Oxidation 32
2.7 Fischer Indole Synthesis of C-3 Aryl Indoles 33
2.8 Determination of the Rotational Barrier of 130 38
2.9 Project Design: Atropselective Fischer Synthesis of C-2 Aryl Indoles 39
2.10 Synthesis of Aryl Ketones 40
2.11 Fischer Indole Synthesis of C-2 Aryl Indoles 42
2.12 Conclusion 44

Research Project B - Chapters 3-7: Enantioselective Synthesis of Atropisomeric Indoles *via* Iron Catalysed Oxidative Cross-Coupling

Chapter 3: Oxidative Cross-Couplings

3.1 Synthesis of Biaryls *via* Cross-Coupling Reactions 45
3.2 Mechanistic Principles of Oxidative Cross-Couplings 46
3.3.1 Hypervalent Iodine (III) Reagents 47
3.3.2 Electrochemical Oxidations 48
3.3.3 Transition Metal Mediated Oxidative Cross-Couplings 49
3.4 Mechanism of Transition Metal Catalysed Oxidative Cross-Couplings 50
3.5 Catalytic Enantioselective Synthesis of Biaryls *via* Oxidative Homo-Couplings 52
3.6 Catalytic Enantioselective Synthesis of Biaryls *via* Oxidative Hetero-Couplings 53
3.7 Oxidative Cross-Coupling of Indoles 56
3.4 Project Design: Synthesis of Atropisomeric Indoles *via* Oxidative Cross-Coupling 59

Chapter 3: Proof of Concept & Mechanistic Hypothesis

4.1 Proof of Concept 61
4.2 Optimisation of Racemic Reaction Conditions 62
4.3 Mechanistic Hypothesis 65
4.4 Metal and Ligand Effects on the Oxidative-Cross Coupling 67
4.5 Synthesis of Achiral Ligands 68
4.6 Evaluation of Metal Salt and Ligand Combinations 71

Chapter 5: Optimisation of Enantioselective Reaction Conditions

5.1 Synthesis of Chiral Oxazolines and other Miscellaneous Ligands 75
5.2 Preliminary Evaluation of Iron(III) Salts with Oxazoline Ligands 80
5.3 Evaluation of Chiral Oxazoline Ligands 82
5.4 Evaluation of Miscellaneous Chiral Ligands 84
5.5 Evaluation of Conditions for *In Situ* Formation of Chiral Iron Complex 87
5.6 Screening of Reaction Concentration 88
5.7 Screening of Different Ester Substituents 89
5.8 Screening of Co-Solvents 91
5.9 Screening of Terminal Oxidant 92
5.10 Screening of Reaction Temperature 93
5.11 Synthesis of PyBOX Ligands: Part 1 94

5.12 Evaluation of PyBOX Ligands: Part 1 96
5.13 Synthesis of PyBOX Ligands: Part 2 98
5.14 Evaluation of PyBOX Ligands: Part 2 102
5.15 Optimisation of Equivalents of Chiral Ligand and Reactants 105
5.16 Screening of *N*-Substituents 106
5.17 Screening of Ester Substituents 108
5.18 Screening of Additives 111
5.19 Final Optimisations 112

Chapter 6: Substrate Scope of Oxidative Cross-Coupling

6.1 Retrosynthetic Strategy 115
6.2 Indole Synthesis: Madelung Cyclisation 115
6.3 Indole Synthesis: Castro Annulation 117
6.4 Indole Synthesis: Fischer Indolisation 120
6.5 Synthesis of Naphthoates 120
6.6 Substrate Scope of Enantioselective Oxidative Cross-Coupling 121

Chapter 7: Mechanistic Investigations

6.7 Derivitization of Heterobiaryls 126
7.1 Measurement of Oxidation Potentials 128
7.2 Radical trapping Experiments 129
7.3 Electron Spin Resonance 130
7.4 HRMS Analysis of Reaction Mixture 133
7.5 Control Experiments 135
7.6 Mechanistic Proposal 137

Conclusions and Future Work

8.1 Conclusions 139
8.2 Future Work 141

Experimental Details

9.1 General Information 142
9.2 Naming and Numering 143
9.3 General Procedures 144
9.4 Characterisation of Compounds 155
9.5.1 Atropselective Fischer Indolisation 155

9.5.2 Achiral Ligands 170
9.5.3 Chiral Ligands 181
9.5.4 Naphthol Substrates 219
9.5.5 Indole Substrates 233
9.5.6 Heterobiaryl Products 258
9.5.7 Derivitization 294
10. Appendices 301
10.1 Determination of Rotational Barriers 301
10.2 ESR Experiments 305
10.3 X-Ray Crystallography 312

References

11. References 315

Chapter 1: Introduction to Atropisomerism

1.1 Atropisomerism

Atropisomerism (from the Greek "*a*" meaning "no"; and "*tropos*" meaning "turning") is the term coined by Kuhn[1] to describe the phenomenon whereby steric (or indeed, electronic) constraints impede molecular rotation around a single bonded axis.[2] Ōki further refined this definition,[3] stipulating that any molecule can be considered to be atropisomeric at temperatures where the half-life to the interconversion of its conformers is >1000 seconds (16.7 min). At 298 K, this corresponds to a Gibb's free energy barrier of $\Delta G^{\ddagger} = 22.2$ kcal mol^{-1}. By these definitions, a wide array of molecules may exhibit atropisomerism if the temperature is sufficiently low. For example, even *n*-butane, a relatively unencumbered molecule, becomes atropisomeric on cooling to 53 K.[4]

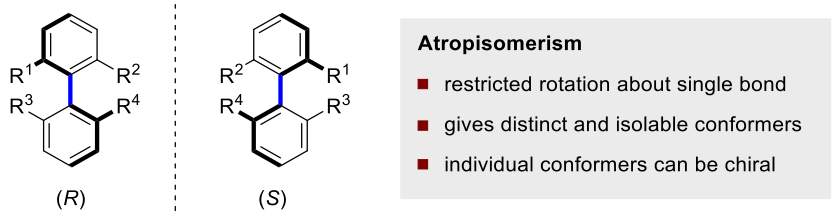


Figure 1.0: Atropisomerism and axial chirality

Around one century ago, Christie and Kenner recorded the first example of atropisomerism within a non-coplanar biaryl system (**Figure 1.0**).[5] In these seminal findings, not only was restricted rotation observed around the sp^2-sp^2 biaryl axis of 2,2'-dinitro-6,6'-diphenic acid, but crucially, the authors also demonstrated that the distinct and non-interconvertible conformeric forms were chiral.

1.2 Atropisomers in Enantioselective Catalysis

Despite this early discovery, almost 60 years elapsed before the true importance of axially chiral biaryls became apparent. In 1980, Noyori first developed BINAP, a powerful atropisomeric chiral bis(phosphine) ligand for enantioselective Rh(I)-catalysed hydrogenations.[6] In these reactions,

the unique steric influence and polarizability of the atropisomeric binaphthalene skeleton was deemed to be instrumental for the asymmetric induction and chiral recognition processes.[7]

Following this breakthrough, the importance of the atropisomeric biaryl architecture has become increasingly well recognised as a remarkably general and privileged structural class for enantioselective catalysis. A diverse catalogue of complimentary atropisomeric chiral ligands and organocatalysts based on the BINOL core have since been developed for a broad range of applications. A selection of these structures is presented (**Figure 1.1**), along with their associated applications, which range from chiral ligand backbones (BINAP and the phosphoramidites),[8] Brønsted acids (TRIP),[9] Lewis acids (chiral titanium complexes),[10] hydrogen bonding catalysis (Gouverneur catalyst)[11] and phase transfer catalysis (Maruoka catalyst).[12] As such, new atropisomeric scaffolds and architectures are continuously sought after.[13]

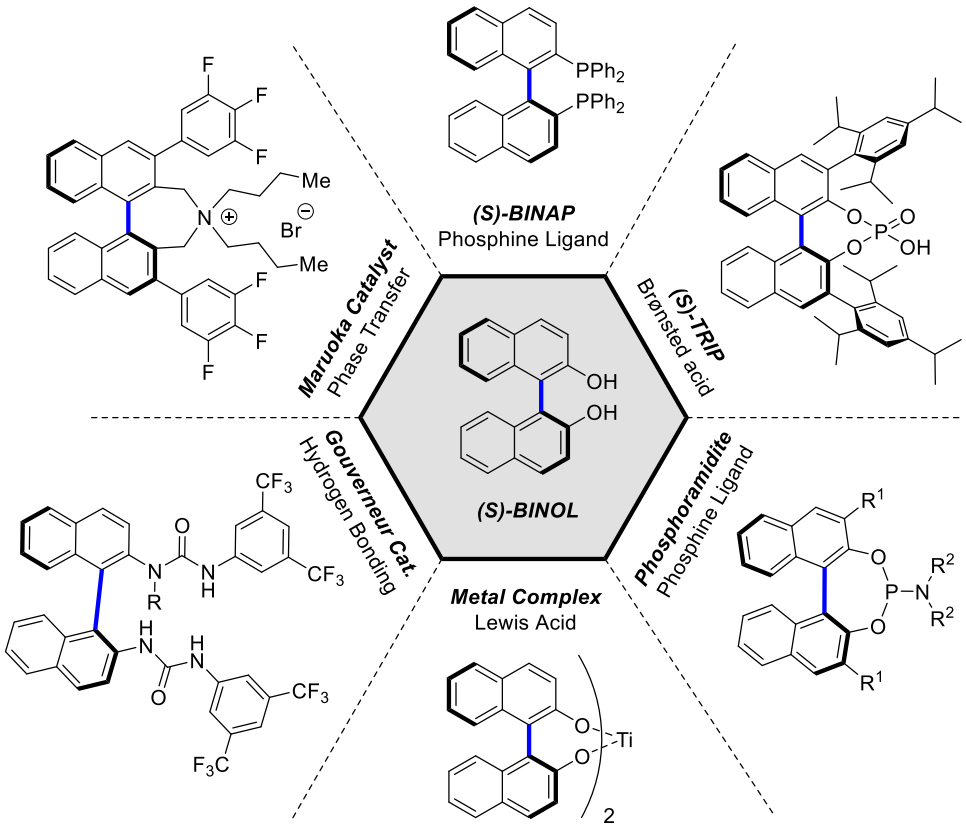


Figure 1.1: Selected examples of atropisomeric ligands and organocatalysts

1.3 Atropisomers in Medicinal Chemistry

Whilst the pivotal role of atropisomerism in catalysis is undisputed, this molecular property is now also becoming increasingly important in medicinal chemistry. For many years, this phenomenon has been described as a "lurking menace", with the potential to drastically increase the overheads in pharmaceutical research and development.[14] In addition, there are currently no guidelines on how to address the problem of time dependant racemisation within drug substances. Nevertheless, due to the recent advances in the development of new synthetic methodologies, and the overall improvement in the understanding of atropisomerism within the pharmaceutical industry, drug candidates featuring restricted rotational axes are now more frequently populating the later stages of drug discovery campaigns.[15] It is well established that the enantiomers of chiral drugs can behave extremely differently *in vivo*, so the development of drugs in a single enantiomeric form is strictly preferred by the FDA and other regulatory agencies.[16] By analogy, this is also true for atropisomeric drug candidates. In one selected example (**Figure 1.2**), researchers at Gilead sciences have developed a conformationally rigid phosphoinositide 3-kinase inhibitor **3**, where hindered rotation is observed about the quinoline-benzimidazole N–C linkage. In this system, the more active (*P*)-eutomer demonstrated a 500-fold increase in potency (IC_{50} = 2 nm) as well as improved selectivity and metabolic stability over the (*M*)-enantiomer.[17] This fittingly illustrates that if the issue of atropisomerism is encountered in a discovery campaign, it should not necessarily spell a death sentence for the project.

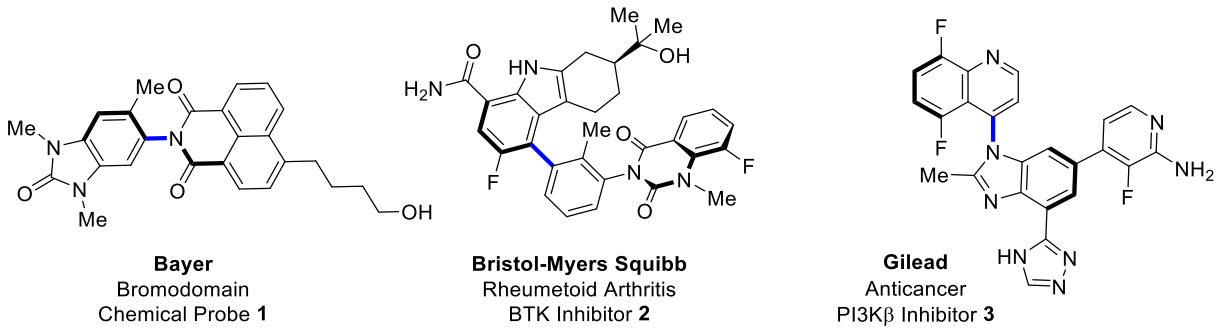


Figure 1.2: Selected examples of atropisomeric drug molecules

1.4 Barriers to Rotation

Atropisomers have the capacity to undergo spontaneous racemisation *via* bond rotation, rather than through chemical transformations into achiral intermediates that ablate the stereochemistry.[15] The half-lives to racemisation ($t_{1/2}$) and barriers to rotation may be calculated from simple kinetic experiments using enantioenriched starting materials.

The rate of racemisation (k_{rac}) describes the macroscopic and statistical process where an optically active compound (e.r. ≠ 50:50) is irreversibly transformed into a racemic mixture.[18] This is calculated from the thermal erosion of the enantiomeric excess (e.e.) at a given temperature (T) over time (t). Plotting ln $\left(\frac{100}{e.e.}\right)$ vs. time will therefore give a straight line, with k_{rac} as the gradient:[19]

$$ln\left(\frac{100}{e.e.}\right) = k_{rac}t\ + ln\left(\frac{100}{e.e._{t=0}}\right)$$

The half-life to racemisation ($t_{1/2}$) corresponds to the time taken for the enantiomeric excess to fall from 100% to 50%. Once k_{rac} is known, $t_{1/2}$ may be determined:

$$t_{\frac{1}{2}}(rac) = \frac{\ln(2)}{k_{rac}}$$

By contrast, the rate of enantiomerisation (k_{ent}) is a microscopic property representative of an individual chiral molecule, describing reversible R to S interconversion. It follows that:

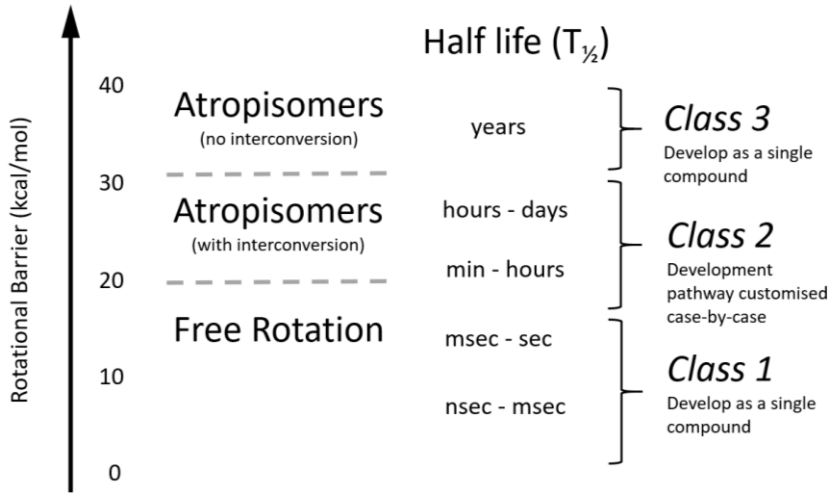
$$k_{rac} = 2k_{ent}$$

k_{rac} is also required to calculate the barrier to rotation ($\Delta G^{\ddagger}_{T}$) at the given temperature (T). Halving k_{rac} gives k_{ent}, which substitutes into the Eyring equation:

$$\Delta G^{\ddagger}_{T} = \ln\left(\frac{k_B T}{h\ \times\ k_{ent}}\right) RT$$

In the interest of developing new atropisomeric catalyst architectures or drug candidates, careful consideration of the half-life to racemisation ($t_{1/2}$) and the barrier to rotation ($\Delta G^{\ddagger}_{T}$) is of

paramount importance if downstream complications are to be avoided.[20] LaPlante has examined several industrial screening decks for atropisomeric molecules and classified them based upon their rotational barriers (**Scheme 1.3**).[21] When there is little hindrance to rotation about the chiral axis (class 1; $\Delta G_T^{\ddagger}$ < 20 kcal mol^{-1}) the enantiomers rapidly interconvert [$t_{1/2}$ (37 °C) < 60 s] and can be considered achiral for development purposes. Contrastingly, if rotation is restricted (class 3; $\Delta G_T^{\ddagger}$ > 30 kcal mol^{-1}) thermal racemisation is extremely slow [$t_{1/2}$ (37 °C) > years]. These compounds should therefore be developed in an optically pure form in order to avoid off-target effects elicited by the undesired enantiomer, and as such, asymmetric synthesis or chiral resolution is necessary. If the molecule has an intermediate rotational barrier (class 2; $\Delta G_T^{\ddagger}$ = 20 to 30 kcal mol^{-1}) *in vivo* racemisation is a high risk [$t_{1/2}$ (37 °C) = minutes to days] so strategies must be adopted to either impede rotation in the molecule, "locking it out" as one conformer, or indeed, by unencumbering or symmetrising the molecule in order to eliminate the problematic element of stereochemistry.



Scheme 1.3: LaPlante's classification of atropisomers based on torsional rotation barriers

Whilst these guidelines were primarily created as a reference for drug discovery, the same basic principles also apply to design of new atropisomeric organocatalysts or ligands. In the timescale of a chemical reaction (minutes to days), a class 2 atropisomeric catalyst manifold is at risk of

racemising under certain reaction conditions (particularly under high temperatures), so efforts should be made to design atropisomers that exhibit high barriers to rotation (class 3).

1.5 Heterobiaryl Atropisomers

Atropisomeric biaryls, where restricted bond rotation is observed between two six-membered carbocyclic arenes, are by far the most well studied class of atropisomeric molecules.[22] Due to the rampant success achieved in this field and the diverse utility of axially chiral products, much research attention has now been redirected towards discovery of new atropisomeric frameworks.[23] The heterobiaryl atropisomers constitute one such family of compounds, where one of the rings at the terminus of the stereogenic axis contains a heteroatom (**Figure 1.4**).

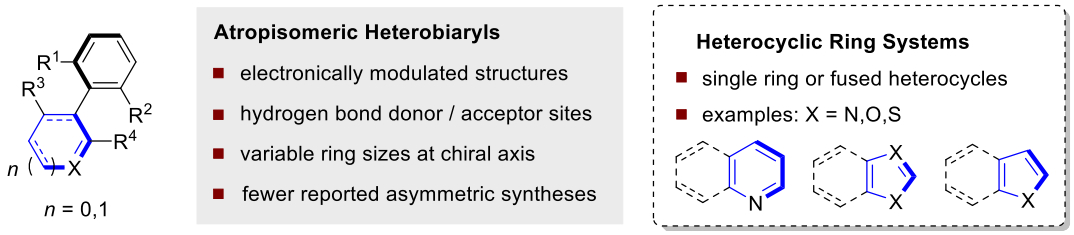
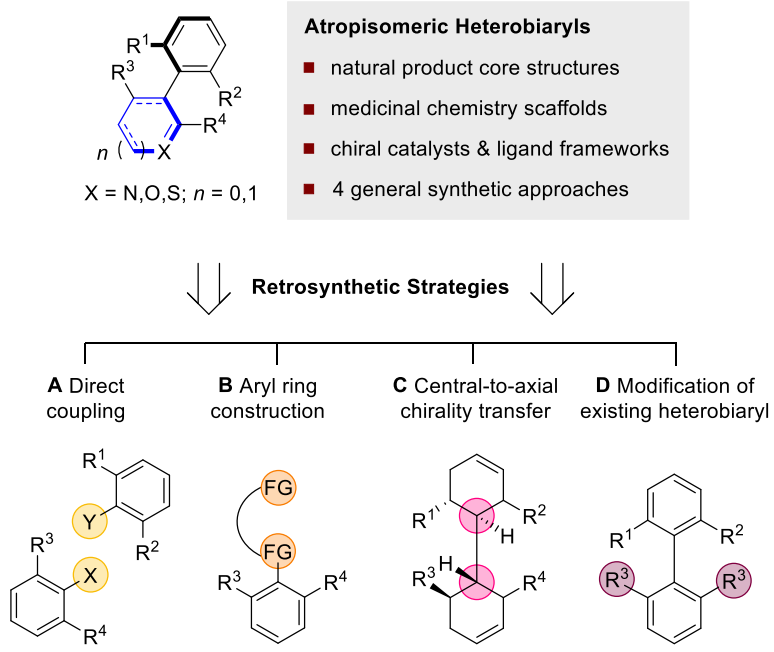


Figure 1.4: Atropisomeric Heterobiaryls

By inserting a nitrogen, oxygen or sulfur atom into the biaryl core, the chemical properties can be significantly modulated. The heteroatoms primarily serve to modify the electron density around the biaryl axis, whilst also creating new hydrogen bond donor and acceptor sites. Additionally, the 3D structure and bond angles may also be fine-tuned by altering the ring size of the heterocyclic fragment.[24] Therefore, through judicious choice of the heterocycle, a series of complimentary electrostatic and π-stacking interactions may be generated around a well-defined atropisomeric scaffold. These changes have the potential to drastically influence the binding affinity of an atropisomeric drug candidate, or indeed the outcome of a stereochemical reaction involving an axially chiral catalyst.[25] Therefore, expanding the catalogue of synthetic methods for accessing heterobiaryl atropisomers is an important goal, which could reveal new realms of potential applications.

1.6 Strategies for Constructing Heterobiaryl Atropisomers

Whilst the biaryls and heterobiaryls are distinct classes of atropisomers with their own associated synthetic challenges, the majority of catalytic enantioselective methods targeting these architectures have implemented a common set of synthetic strategies. The four fundamental approaches outlined below are well established within the chemical literature, and many specific examples of each strategies have already been expansively reviewed (**Scheme 1.5**).[26] These are:



Scheme 1.5: Strategies for biaryl / heterobiaryl atropisomer synthesis

Strategy A: The atropselective coupling of two hindered fragments with direct formation of a stereogenic axis;[27]

The first strategy represents the most obvious retrosynthetic disconnection and signifies the most convergent and direct way of constructing a chiral axis enantioselectively. However, in order to generate atropisomers that possess high rotational barriers (>30 kcal mol^{-1}), the chiral axis within the product must generally be tetra-*ortho*-substituted. The main synthetic challenge

associated with this approach is therefore the of melding of such sterically demanding coupling partners in the cross-coupling step.

Strategy B: *De novo* construction of an aryl ring from an acyclic tether in the enantiodetermining step;[28]

The construction of heterocyclic cores *via* the annulation or condensation of functionalised acyclic pre-cursors are extremely well-established protocols within the chemical literature. Whilst several elegant and atroposelective variants of these classical reactions have been developed in recent years, the synthetic routes to the products are more linear by design.

Strategy C: Stereospecific "central-to-axial" chirality transfer between two non-aromatic ring systems;[29]

This approach generally requires two synthetic steps: The enantioselective synthesis of a benzylic stereogenic centre within a cyclic system, followed by the subsequent destruction of the internal chiral centre (*via* oxidation, aromatisation or dehydration) to generate a chiral axis. The degree of stereospecificity for the chirality exchange step is usually quantified as the conversion percentage (defined as cp (%) = $ee_{reactant}/ee_{product}$).

Strategy D: Modification of an existing meso biaryl *via* desymmetrization or atropselective functionalisation of a rapidly interconverting set of conformers;[30]

The final strategy has two facets, with both approaches involving the modification of a preformed achiral heterobiaryl:

1) If the barrier to rotation around the heterobiaryl axis is low, the two conformers are in rapid equilibration. A chiral catalyst may then serve to discriminate between the two rapidly interconverting forms, enabling the selective addition of a "blocking group" that increases the barrier to rotation in the product. This dynamic kinetic resolution approach essentially "locks out" one of the conformers in a single atropenantiomeric form.

2) In the second method, if the barrier to rotation in a *meso* heterobiaryl starting material is high, a desymmetrization reaction may be possible by chiral catalyst-controlled substitution of one of the enantiotopic groups.

1.7 Catalytic Enantioselective Synthesis of Atropisomeric Indole-based Heterobiaryls

Until very recently, the synthesis of axially chiral indoles remained a completely unexplored avenue of asymmetric catalysis. However, over the last five years this field has flourished into a dynamic and rapidly evolving and area of research. So much so, that this area has now become the subject of a recent review,[31] and a diverse variety of atropisomeric indole architectures have now been prepared. The atropisomeric indole structures prepared may be classified into one of four groups: The C-2 or C-3 arylindoles, *N*-arylindoles, bisindoles and other indole-containing scaffolds that do not fall into one of the previous categories (**Figure 1.6**).

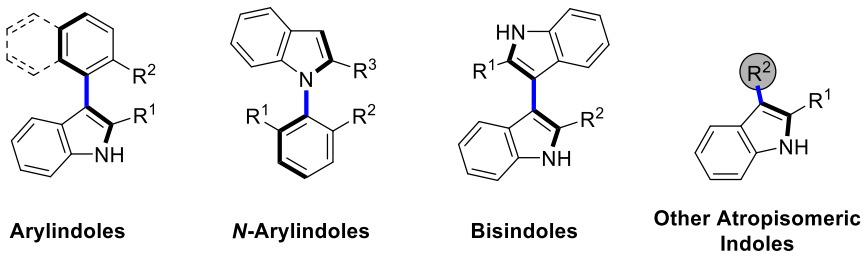


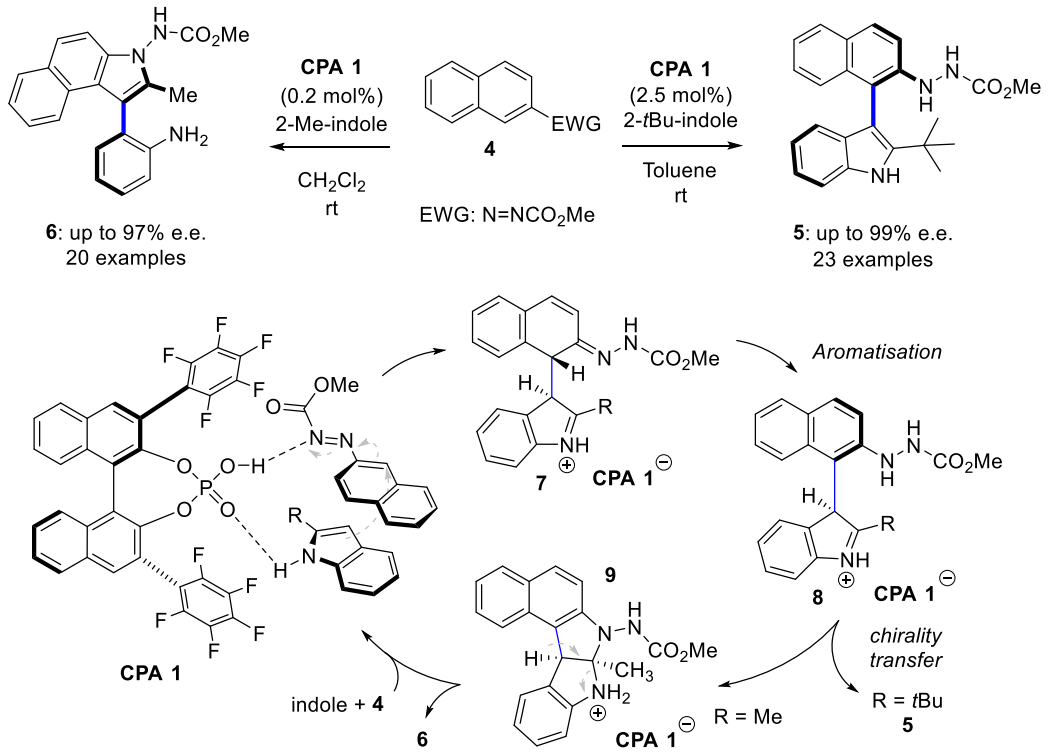
Figure 1.6: Atropisomeric indoles prepared through catalytic enantioselective methods

Additionally, the methods used to access these structures may be further categorised into one of the four retrosynthetic strategies previously outlined (Section **1.6**). For the purposes of this section, a review of the catalytic enantioselective approaches towards indole-containing atropisomers is presented, being organised by the synthetic strategy employed, rather than the structure class that is represented.

1.7.1 Strategy A: Direct Coupling

Asymmetric organocatalysis has emerged as the most powerful tool for enabling access to enantioenriched indoles *via* direct coupling processes. In a landmark report, Tan has shown that

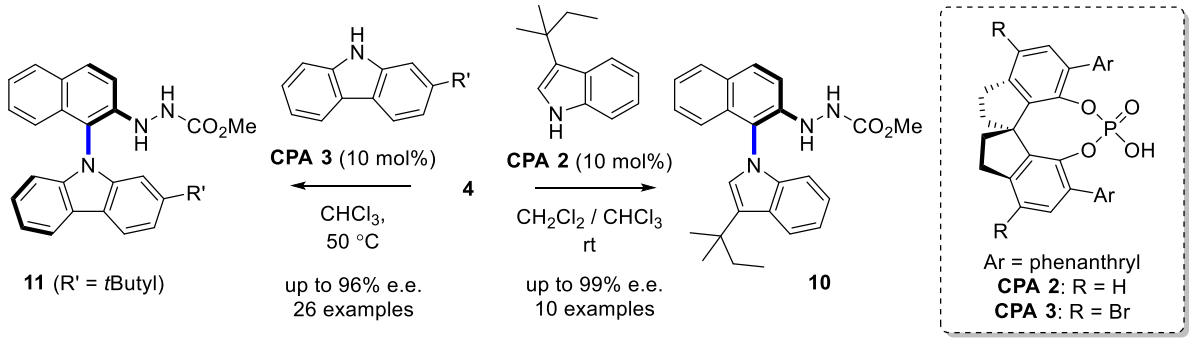
chiral Brønsted acids can effectively activate arenes bearing azo-groups towards enantioselective nucleophilic aromatic substitution reactions with indoles (**Scheme 1.7**).[32] In the proposed mechanism, bifunctional **CPA 1** hydrogen bonds to the azo-arene **4**, rendering it more electrophilic. The chiral catalyst then directs the stereoselective nucleophilic attack of the indole towards the α-carbon of **4**, forming a new C–C bond in intermediate **7** with two contiguous point chiral centres. When the 2-substituent of the indole is a bulky *tert*-butyl group, the point chiral intermediate **7** collapses to form the high-barrier axially chiral indole **5** in near perfect levels of enantioselectivity. Over the course of this investigation, it was serendipitously found that if the C-2 substituent of the indole is replaced with a smaller methyl group, a different atropisomeric heterobiaryl product **6** predominates.



Scheme 1.7: Tan's Azo-group enabled direct organocatalytic arylation of indoles

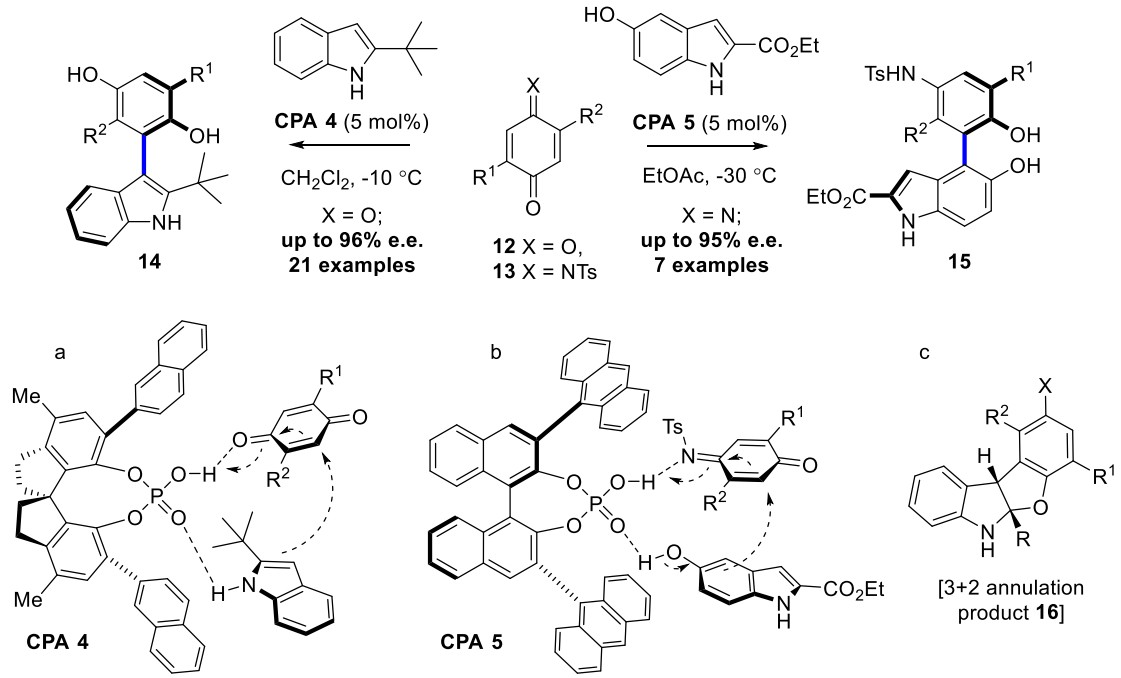
This process was believed to occur *via* intramolecular addition of the pendant nitrogen into the iminium ion intermediate **8;** a cyclisation which is forbidden in the *tert*-butyl case due to steric congestion. The fused polycyclic species **9** that forms then undergoes β–H elimination followed by C2-N bond cleavage. This unexpected process was also optimised for enantioselectivity,

providing a route to a complimentary and unprecedented class of aniline-indole atropisomers from one common reactive intermediate. Very recently, Tan has also developed analogous atropselective C–H amination reactions of azo-substrate **4**, invoking a similar mode of activation (**Scheme 1.8**).[33] In this scenario, bulky C-3 substituted indoles and carbazoles were shown to react as *N*-nucleophiles with **4** to give *N*-arylated products **10** and **11** respectively. In these reactions, C-2 symmetric phenanthryl substituted SPINOL-derived phosphoric acids were found to proficient in both transformations.



Scheme 1.8: Tan's Azo-group enabled direct organocatalytic *N*-arylation

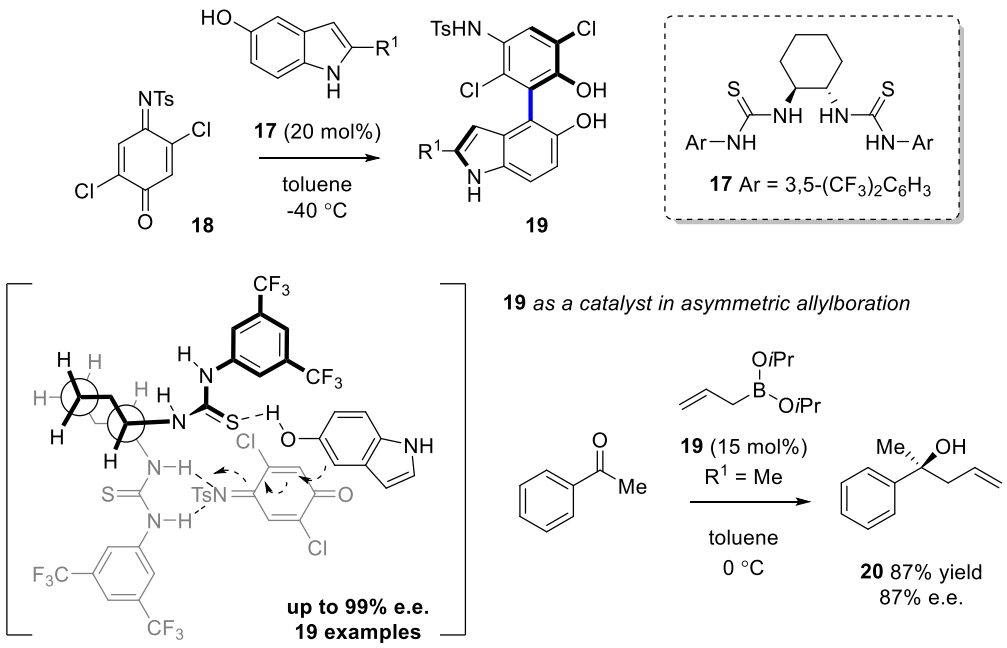
In an extension to the organocatalysed C–C and C–N couplings with indoles, the scope has also been elaborated to include a serious of other electrophiles (**Scheme 1.9**). Tan now illustrated that **CPA 4** mediates enantioselective conjugate additions of C-2 substituted indoles with quinones **12** in a highly chemo- and stereoselective manner to yield atropisomeric phenyl-indole products **14**.[34]



Scheme 1.9: Chiral phosphoric acid mediated coupling of indoles with quinones

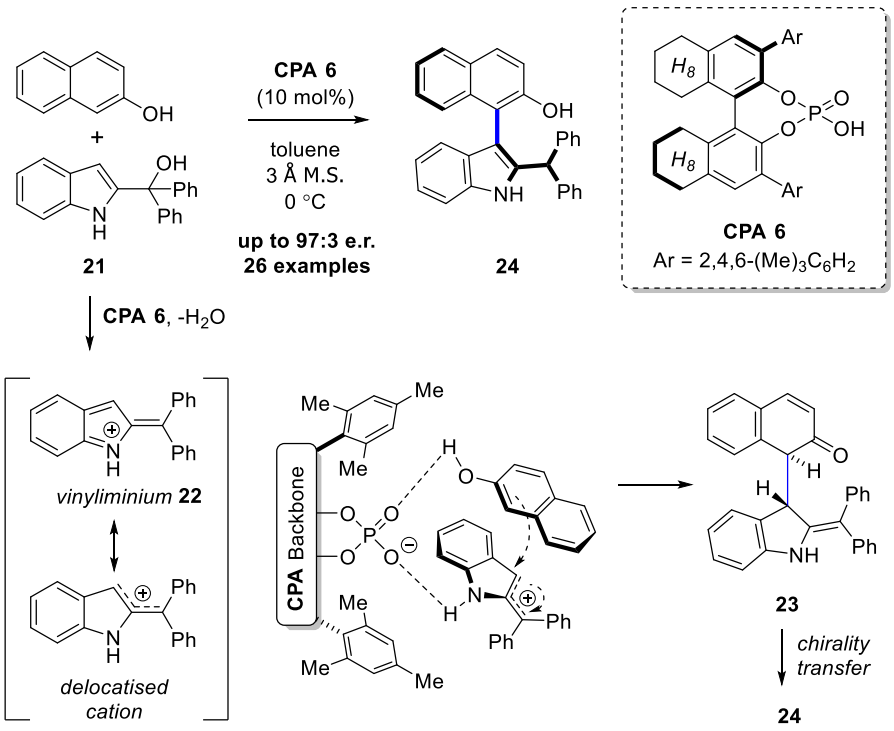
In addition, 5-hydroxyindoles were also shown to participate in these C–C bond forming processes with iminoquinone derivatives **13** under a similar set of conditions. This is the first example of the generation of atropisomeric aryl indoles where the chiral axis located at the C–4 position of the indole. It is noteworthy that in both of these reactions, careful modulation of the steric and electronic properties within the substrates were necessary to generate the desired atropisomeric products and overcome the regio- and chemoselectivity issues that would lead to the formation of **16** through a competing [3+2] annulation process.[35]

In a back-to-back report, Xu similarly constructed indole atropisomers where the chiral axis is situated on the carbocyclic, rather than on the heterocyclic ring.[36] Interestingly, under these conditions, chiral phosphoric acids were found to be catalytically inactive. In this case, employing the C_2-symmetric bis-thiourea hydrogen-bond donor organocatalyst **17** was optimal. The product heterobiaryl diols **19** were shown to exhibit promising utility as organocatalysts in an enantioselective allylboration of acetophenone. Catalyst **19** facilitated the formation of **20** in 87% yield and 87% e.e., which was markedly superior to the performance of the other BINOL or biphenol catalysts tested.



Scheme 1.10: Hydrogen-bond donor mediated synthesis of indole atropisomers

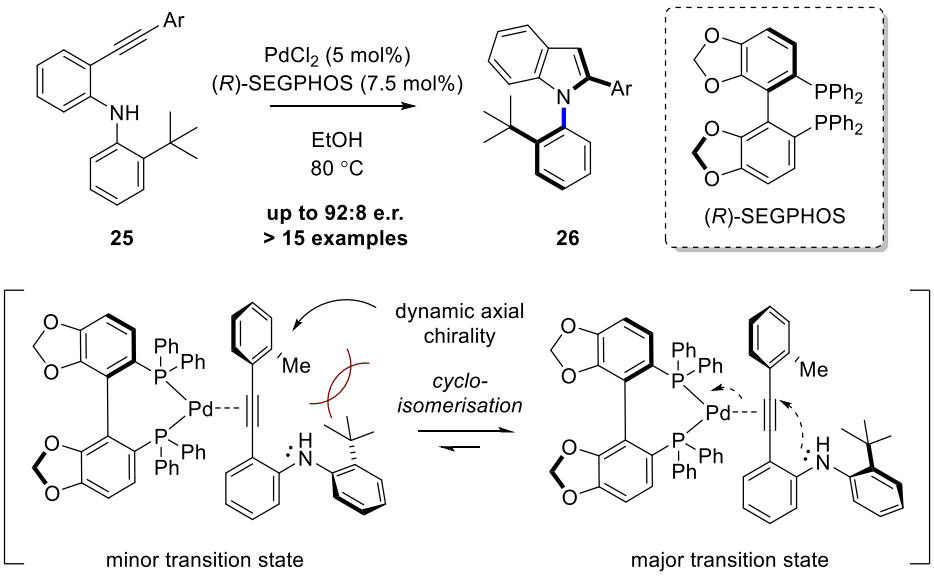
In an alternate approach involving direct fragment coupling, Shi has disclosed the synthesis of naphthyl-indole skeletons by capitalising on the Umpolung reactivity of an indole species (**Scheme 1.11**).[37] In this approach, treatment of 2-indolylmethanols with a Brønsted acid generates a highly delocalised vinyliminium cation **22** with concomitant loss of water. This electrophilic indolyl cation then forms a contact ion-pair with the chiral phosphate. In the presence of the bulky nucleophilic 2-naphthol, enantioselective C–C coupling then occurs, furnishing a point chiral intermediate **23** which then undergoes stereospecific point-to-axial chirality transfer to the configurationally stable naphthyl-indole product **24**. The choice of the benzhydryl substituent on **21** was found to be crucial not only to stabilise the cationic intermediate, but also to enable the C–C coupling to occur regioselectively at the C-3 position of the indole.[38]



Scheme 1.11: Shi's synthesis of naphthyl-indole skeletons *via* vinyliminium ions

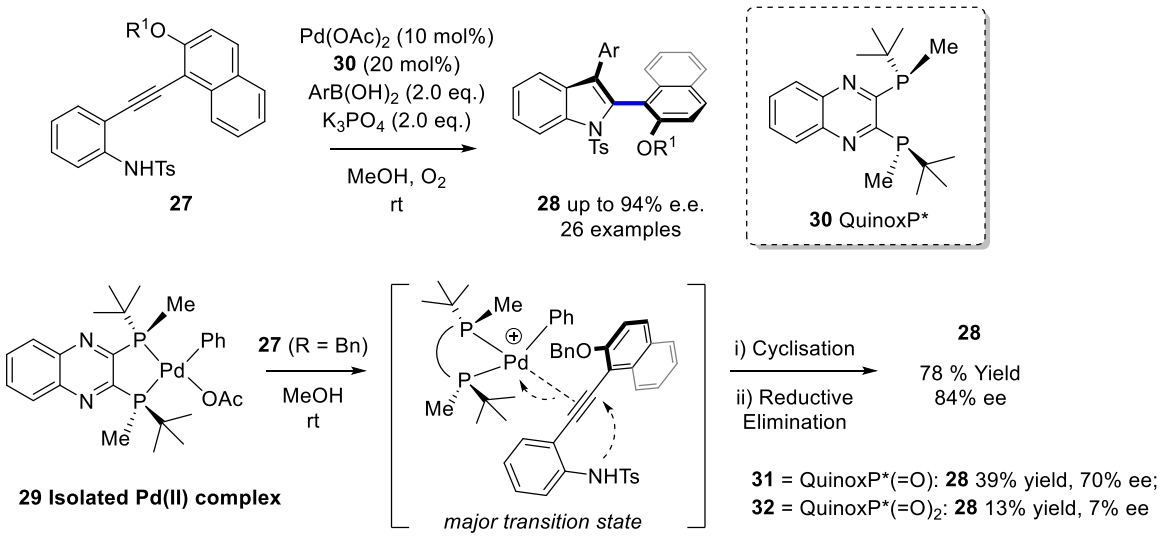
1.7.2 Strategy B: Atropselective Heteroaryl Ring Construction

In Kitagawa's seminal work describing the first catalytic enantioselective synthesis of a non-amide N–C atropisomer, a Pd(II) catalysed 5-endo-hydroaminocyclisation of a bulky *o*-alkynylanilide **25** was accomplished (**Scheme 1.12**). From a survey of ligands, SEGPHOS was found to be the most selective, with substrates bearing an *ortho* substituent on the aryl group granting a further boost in enantioselectivity. This observation was attributed to the "dynamic axial chirality" generated about the C_{alkyne}-C_{aryl} bond; on complexation of the Pd(II) species with the alkyne moiety, the chiral information on the ligand is poorly transferred to the distal stereogenic N–C bond that is being formed. When a bulky *ortho* substituent is present however, this stereochemical information is more effectively transmitted due to the fixed conformation of the aryl substituent.



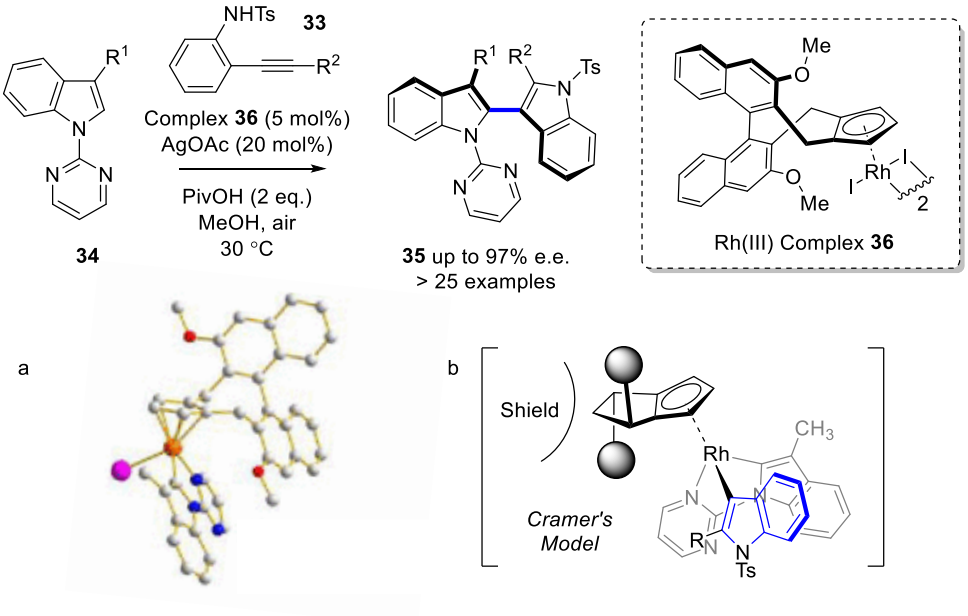
Scheme 1.12: Kitagawa's enantioselective 5-endo-hydroaminocyclisation

In a related approach, Zhu has reported a Pd(II) catalysed asymmetric Cacchi reaction of **27** with aryl boronic acids under an O_2 atmosphere, which leads the formation of 2,3-disubstituted indoles **28** with a stereogenic C-2 aryl axis (**Scheme 1.13**).[39] Of the chiral ligands screened, QuinoxP* **30** was identified as the optimal structure. The cyclizative cross-coupling was found to be tolerant of a wide variety of electron-withdrawing and electron-donating substituents on the aryl rings, without compromising yield or enantioselectivity. Mechanistic investigations using ^{31}P NMR and X-ray crystallography were also carried out, indicating that transmetalation of the aryl boronic acid to form **29** occurs prior to the aminopalladation event. Furthermore, under the reaction conditions, the ligand was found to slowly oxidise to the corresponding QuinoxP*(=O) **31** and QuinoxP*(=O)$_2$ **32** species, which were both inefficient for the desired transformation, which led to slightly diminished enantioselectivities in the overall process.



Scheme 1.13: Pd(II) catalysed enantioselective Cacchi cyclisation

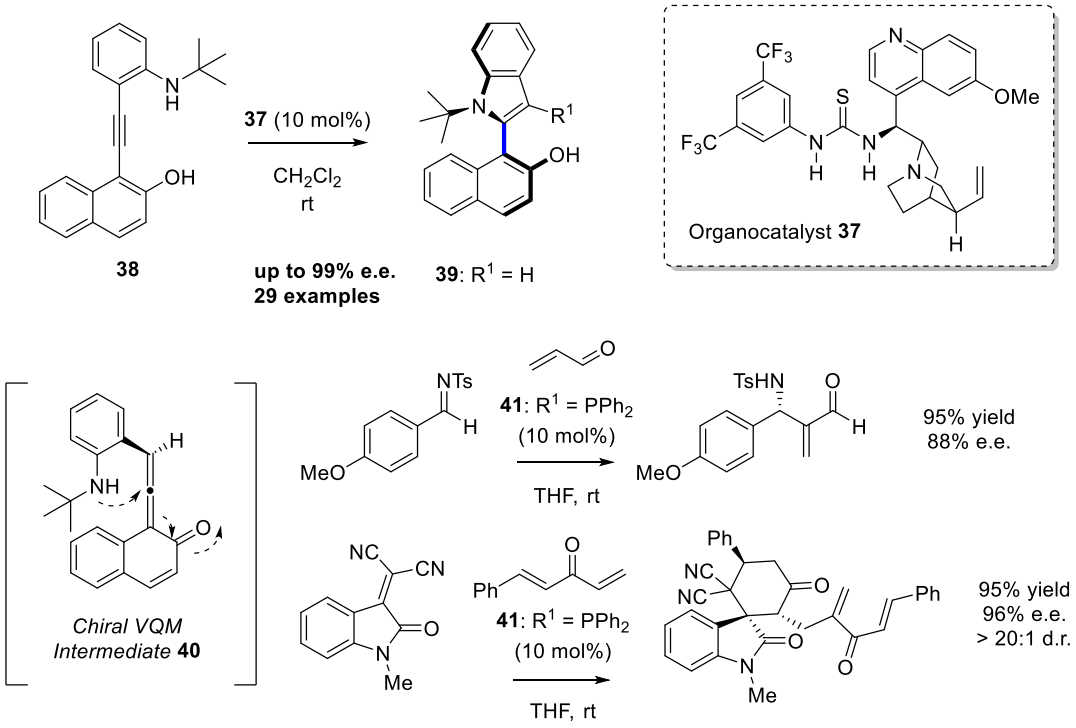
In an analogous report, Li has harnessed *N*-tosyl-*o*-alkynylanilides **33** as synthetic pre-cursors for axially chiral indoles **35** (**Scheme 1.14**).[40] In this instance, given the high Lewis acidity and reactivity of Rh(III) catalysts within C–H activation reactions, a chiral Rh(III) complex **36** was successfully implemented as a "merger" for a C–H activation/nucleophilic cyclisation cascade between **33** and **34**. The pyrimidyl substituted indole **34** was chosen as a the reactive arene to direct the C–H activation of the rhodium complex.



Scheme 1.14: Rh(III) catalysed asymmetric synthesis of 2,3'-biindolys

Deuterium labelling experiments and crystallisation of the product of a stoichiometric reaction between **34** and complex **36** evidenced the initial formation of an enantiomerically pure C-2 rhodacycle-indolyl intermediate. The reaction was therefore deemed to proceed *via* initial C–H activation of **34**, followed by co-ordination of anilide **33**, nucleophilic cyclisation and finally, reductive elimination. The stereoselectivity of the reaction was rationalised according to Cramer's model[41]. This approach provided access to unprecedented 2,3'-biindolyls **35** in an enantioenriched form. However, it should be noted that due to the chiral axis being located between a [5,5] heterobiaryl system, the rotational barriers of the products were relatively low, generally as class 2 atropisomers (25–32 kcal mol^{-1}).

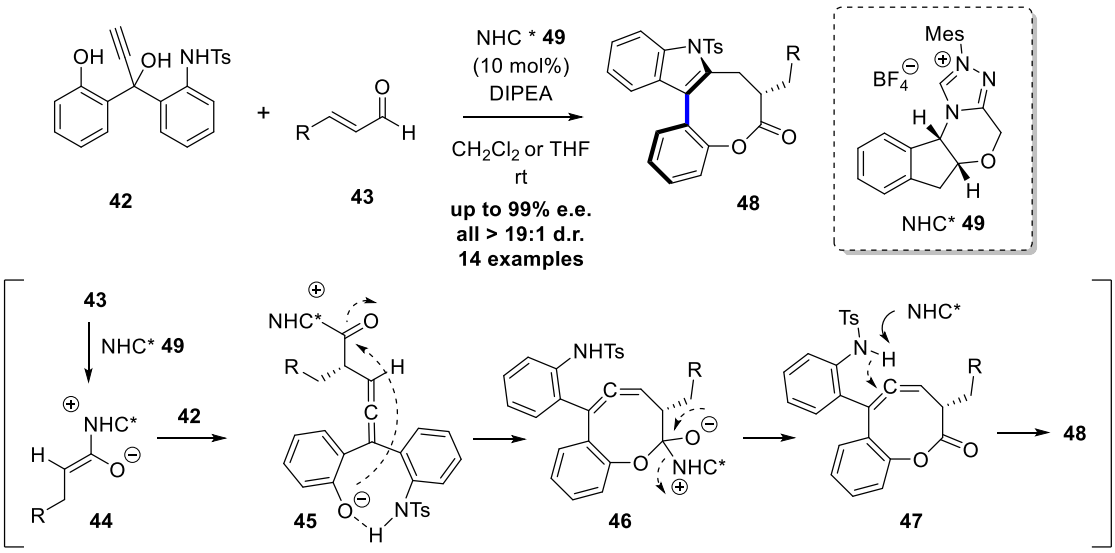
In an organocatalytic example involving the *de novo* construction of an indole, Yan has employed a chiral Brønsted base **37** to facilitate the enantioselective annulation of *ortho*-alkynylanilines **38** (**Scheme 1.15**). [42] This approach provides a robust route to C-2 aryl indole atropisomer skeletons **39** that was thought to proceed *via* vinylidene *ortho*-quinone methide (VQM) intermediates **40**.



Scheme 1.15: Organocatalytic asymmetric annulation of *o*-alkynylanilides

In this impressive account, not only was the optimised reaction scalable on up to 50 g **38** with exquisite enantioselectivity, but the organocatalyst **37** was also readily recovered and reused in subsequent reaction cycles without detriment to the product yield or enantioselectivity. Furthermore, the unsubstituted C-3 positions of the enantiomerically pure indole products **39** were derivatized into a range of highly valuable atropisomeric scaffolds in a perfectly stereospecific manner, with the C-3 diphenylphosphine product **41** showing promising catalytic utility in asymmetric aza-Baylis Hillman and a [4+2] cycloaddition reactions.

Using chiral *N*-heterocyclic carbene organocatalyst **49**, Zhao has reported a stereoselective synthesis of bridged heterobiaryls **48** with defined axial and point chirality.[43] DFT calculations were performed to help elucidate the reaction mechanism. It was found that the formation of allene **45** through the direct addition of the azolium enolate **44** to propargylic alcohol **42** had the lowest activation barrier (by 5.9 kcal mol^{-1}). Lactonisation of **45** *via* attack of the phenolate onto the acyl azolium moiety then establishes the 8-membered ring **46**. Finally, the NHC acts as a base to facilitate ring closure of aniline **47** to furnish product **48**.

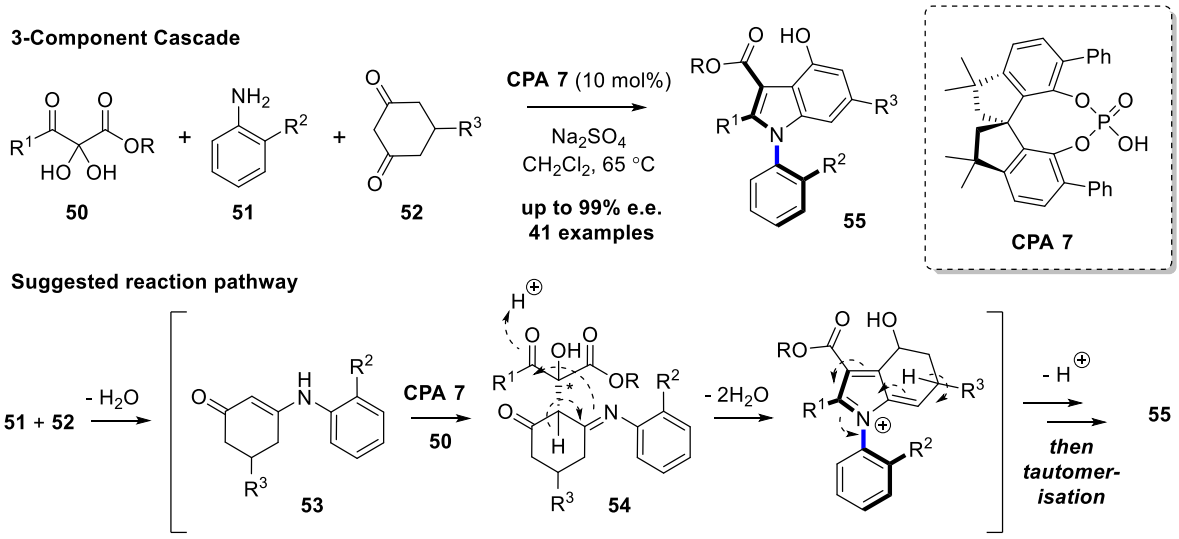


Scheme 1.16: NHC catalysed enantioselective synthesis of bridged indole heterobiaryls

As the 8-membered ring was found to be rigid, the conformation of the chiral axis was highly correlated to that of the lactone. The barriers to interconversion between *S*-cis and *S*-trans

intermediate conformers were calculated to be low (< 15 kcal mol^{-1}) so the high diastereoselectivity was thermodynamically controlled by the relative energies difference (4.2 kcal mol^{-1}) between the *M* and *P* forms.

Lin has devised an elegant three-component cascade for the atroposelective construction of *N*-aryl indole motifs **54** (**Scheme 1.17**).[38] In this sequence, the authors propose that aniline **51** initially condenses with 1,3-diketone **52** to form **53**. The key intermediate **53** then undergoes chiral Brønsted acid catalysed aldol condensation with the dehydrated 2,3-diketoester of **50** to furnish **54**. This is followed by dehydrative cyclisation and aromatisation to generate the *N*-aryl indole scaffold **55**. It is suggested that this "second generation" chiral phosphoric acid serves to control the stereoselectivity of the aldol reaction in the enantiodetermining step, forming a point chiral centre. This is then transformed to an axis of chirality on aromatisation to the heterobiaryl at the end of the sequence.



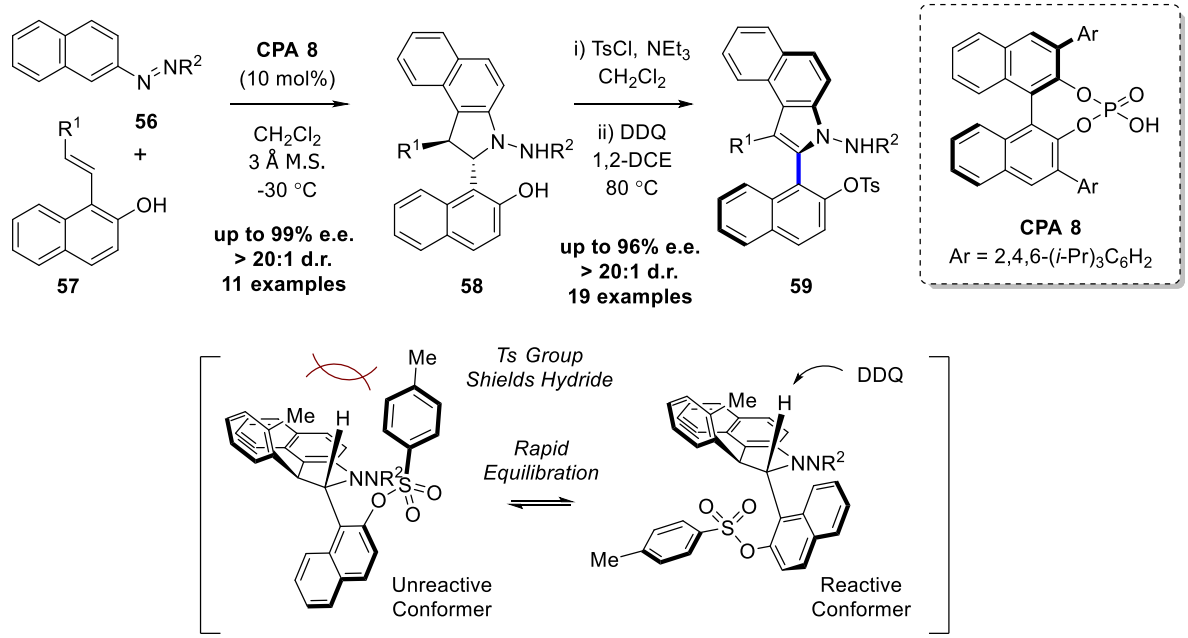
Scheme 1.17: Lin's synthesis of *N*-aryl indoles *via* three-component cascade

1.7.3 Strategy C: Central-to-Axial Chirality Transfer

Although this method constitutes one of the key strategies for the synthesis of atropisomeric molecules, only two examples of this approach have yet been implemented for the preparation of

indole based heterobiaryls. This is most likely due to the monumental challenge of successfully executing two consecutive sterocontrolled steps.

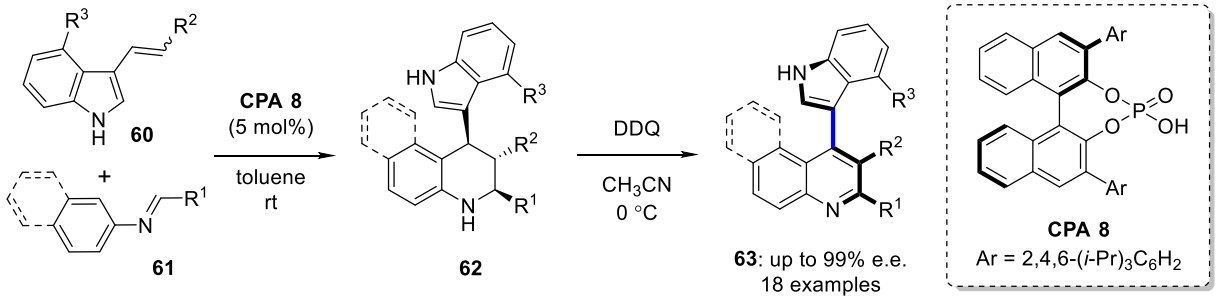
Nevertheless, Zhou was the first to realise a successful chirality transfer protocol, harnessing a chiral phosphoric acid to facilitate asymmetric [3+2] cycloaddition of 1-styrylnaphthols **57** with azonaphthalenes **56** (**Scheme 1.18**).[44] In the 2,3-diarylbenzoindole intermediates **58**, it was demonstrated that the addition of a bulky substituent in close proximity to the pro-chiral axis was necessary in order to prevent racemisation of the atropisomeric final product and prevent loss of enantiopurity in the chirality conversion step.



Scheme 1.18: Synthesis of 2,3-diarylbenzoindoles *via* central-to-axial chirality transfer

To this end, tosylation of **58** followed by mild DDQ oxidation was most suitable for smooth central-to-axial chirality transfer to the desired naphthyl-indole **59**. It is notable that in benzoindoles bearing *ortho*-substituted aryl groups, the oxidation step yields vicinal benzoindole atropisomers with two stereogenic axes in perfect diastereoselectivity (> 20:1 dr). DFT experiments were also carried out to provide additional mechanistic insights to support the high levels of chirality conversion observed.

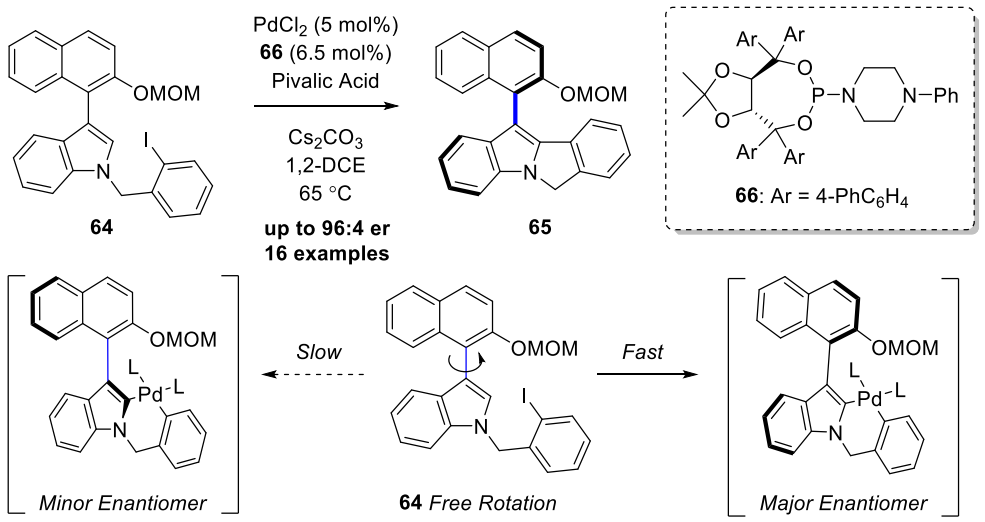
In a very similar strategy, Corti, Bertuzzi and coworkers have executed an enantioselective Povarov cycloaddition of 3-alkenylindoles **60** with N-arylimines **61** to furnish highly substituted and enantioenriched 1,2,3,4-tetrahydroquinolines **62** (**Scheme 1.19**).[45] The subsequent oxidation of **62** with DDQ gave novel axially chiral quinolinylindoles **63** in generally high yields and enantioselectivities. The high stereospecificity of the chirality transfer step was proposed to arise from kinetic quenching of the more stable enamine intermediate of **62** through hydride transfer to oxygen (HTO), which occurs faster than conformational rearrangement about the pro-chiral axis.



Scheme 1.19: Synthesis of quinolinylindoles *via* Povarov reaction and chirality transfer

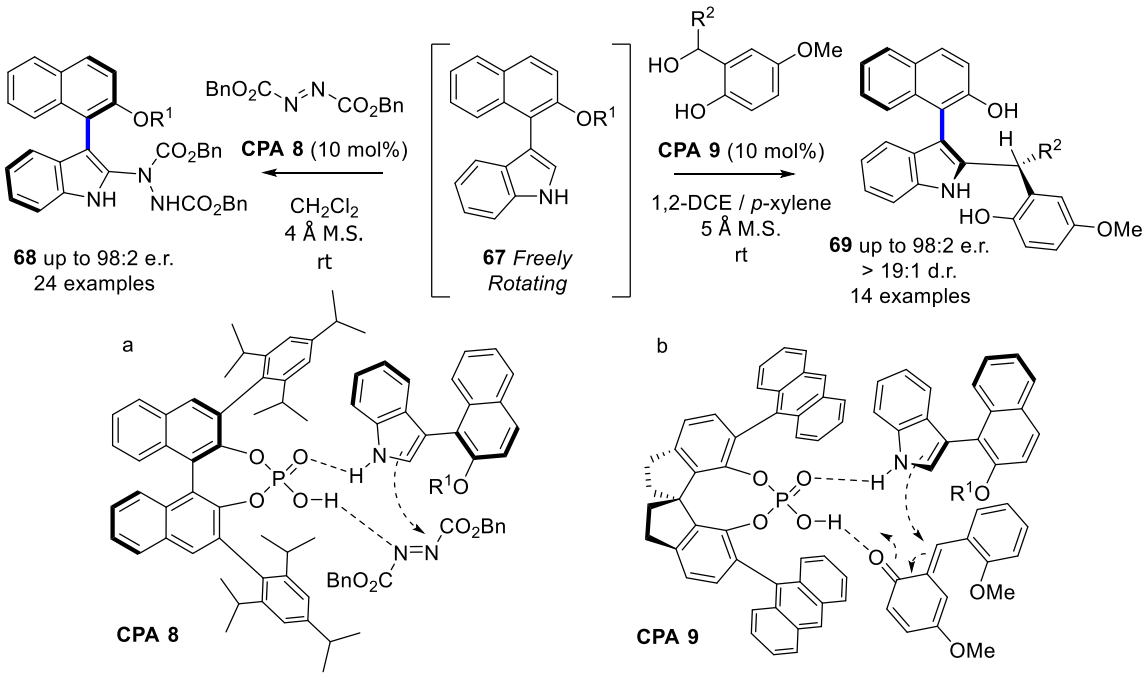
1.7.4 Strategy D: Modification of an Existing Heterobiaryl

Gu first implemented this strategy in an intramolecular fashion within a naphthyl-indole system (**Scheme 1.20**).[46] In the starting material **64**, the small C-2 H-substituent of the indole leads to free rotation about the heterobiaryl axis. However, in the presence of a Pd(II)-TADDOL complex, oxidative addition into the pendant aryliodide brings the metal centre into close proximity to the C-2 position of the indole. Directed C–H activation then occurs to generate a 6-membered palladacycle intermediate, which reductively eliminates in an atropselective manner to generate a product **65** that can no longer freely rotate about the heterobiaryl axis.



Scheme 1.20: Pd(II)-catalysed intramolecular DKR of indole heterobiaryls

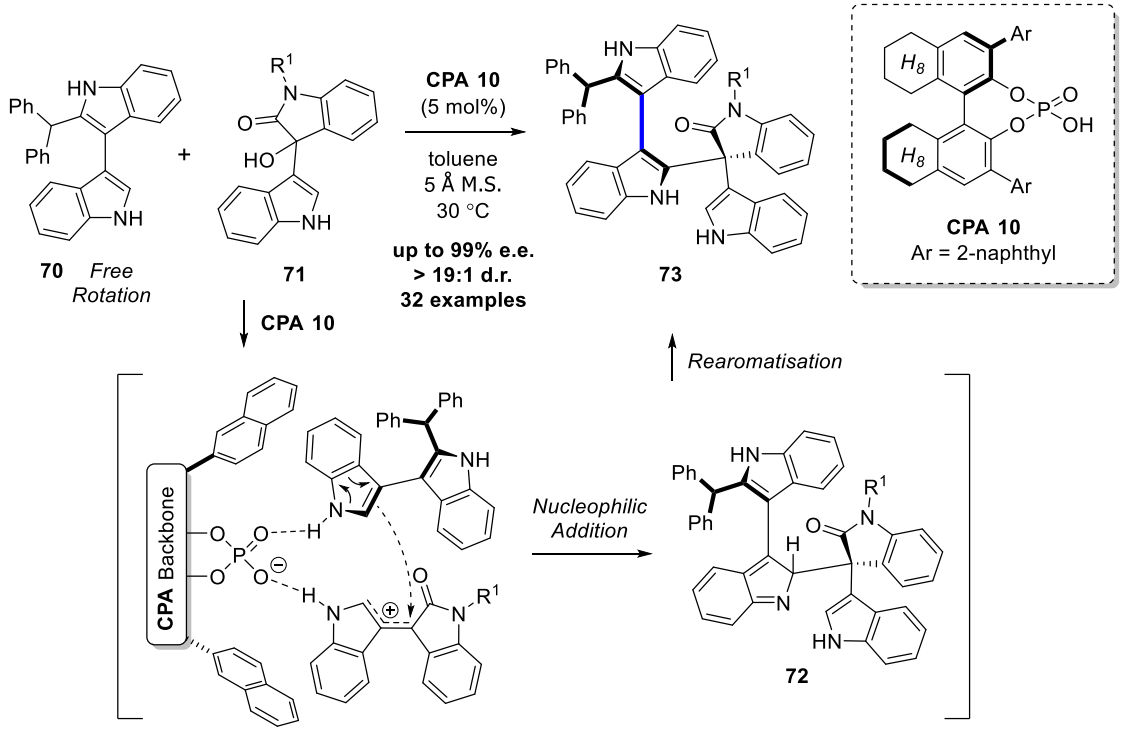
Shi has further extended this approach to include intermolecular dynamic kinetic resolutions. In one report, a freely rotating naphthyl-indole system was shown to undergo Brønsted acid catalysed atropselective C-2 functionalisation of the indole with a variety of reactive electrophiles (**Scheme 1.21**).[47]



Scheme 1.21: Dynamic kinetic resolution of heterobiaryls with bulky electrophiles

This method proved compatible with azodicarboxylates as well as *o*-hydroxy-benzyl alcohols, with the latter functionalisation providing exquisite simultaneous stereocontrol over the axial and point chirality.

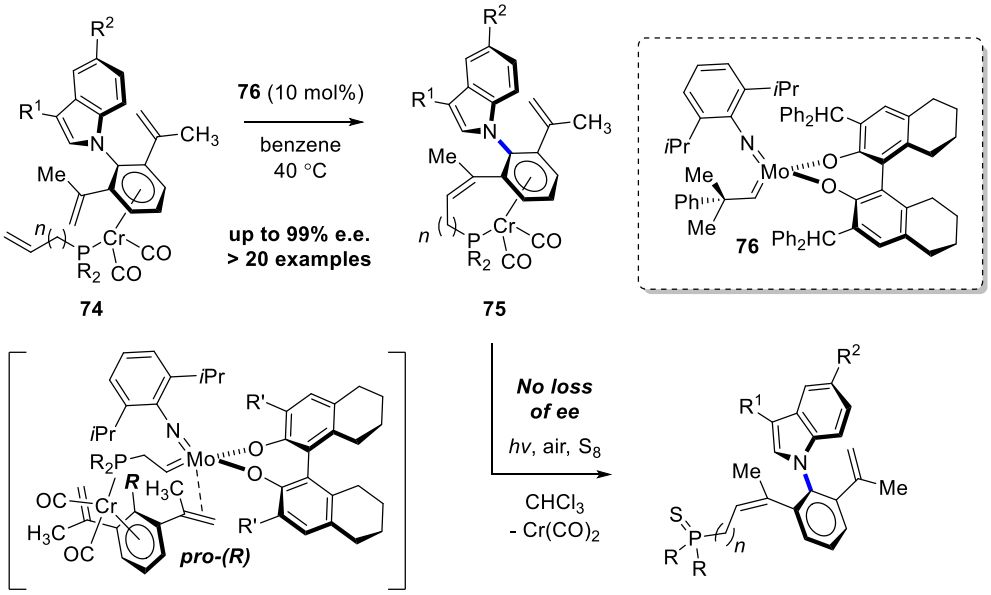
In a separate example, the dynamic kinetic resolution of indole heterobiaryls *via* C-2 functionalisation of the indole was extended to 3,3'-bisindoles substrates **70**.[48] This substrate class is particularly challenging due to the pro-chiral axis being fixed between a [5,5] ring system. The small ring size creates an increased distance between the *ortho*-substituents around the axis, which is likely to lead to poor conformational stability (**Scheme 1.22**).



Scheme 1.22: Dynamic kinetic resolution of 3,3'-bisindoles using bulky 3-indolylmethanols

Building on their previous work, Shi addressed this challenge by designing bulky 3-indolylmethanols **71** to serve as the reactive cationic electrophiles as well as blocking groups, raising the barriers to rotation within the products. This strategy proved fruitful, with C-2 functionalised 3,3'-bisindole products **73** (which exhibit exceptionally high rotational barriers of 48.8 kcal mol^{-1}) being synthesised in enantioselectivities of up to 99% ee.

Finally, Kamikawa, Takahashi and Ogasawara have devised a Mo-alkylidene **76** catalysed desymmetrization of pro-chiral *N*-indole substituted (π-arene) chromium complexes **74** *via* ring closing metathesis.[45] This method furnishes products **75** that exhibit both axial and planar chirality, in near perfect levels of enantioselectivity. The authors also demonstrate oxidative dechromation of the products in sunlight, showing retention of the axis of chirality and without erosion of the enantiomeric purity.



Scheme 1.23: Synthesis of axially and planar chiral *N*-aryl indole π-arene chromium complexes

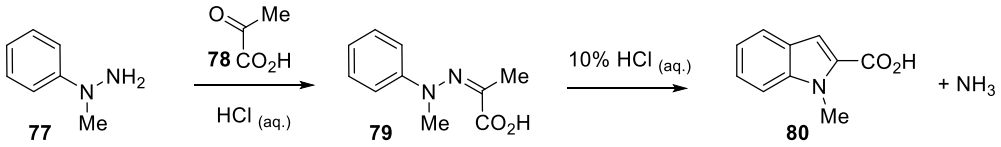
1.8 Project Aims: Enantioselective Synthesis of Atropisomeric Indoles

Our group has a longstanding interest in the synthesis of atropisomeric molecules. This has included biaryl,[49] non-biaryl[50] and heterobiaryl[51] architectures. In this PhD work, we focus on the heterobiaryl class of atropisomers, and in particular, the atropisomeric indoles. Our broader aims for this project were to devise a new catalytic and enantioselective method for the construction of atropisomeric indoles, which are clearly emerging as an important member of the family of axially chiral molecules.

Chapter 2: Atropselective Fischer Indolisation

2.1 Introduction

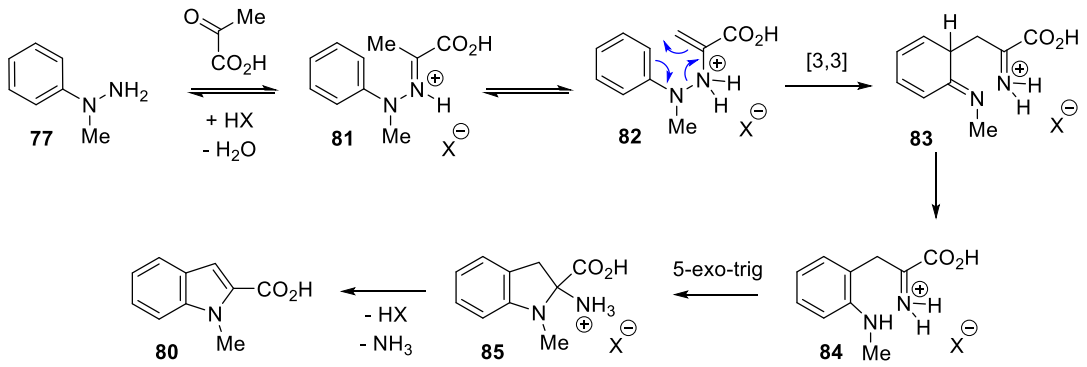
In 1883, Fischer studied the synthesis and chemical properties of various phenylhydrazone derivatives under different conditions. In the course of these experiments, hydrazone **79** (derived from the condensation of **77** with **78**) unexpectedly formed a new product when heated in hydrochloric acid.[52] Fischer and Hess later elucidated the structure of this compound as indole **80**, which was believed to have been formed from **79** *via* the formal loss of ammonia (**Scheme 2.1**).[53]



Scheme 2.1: Fischer's original indole synthesis from phenylhydrazones

2.2 Mechanism of the Fischer Indole Synthesis

Forty years later, Robinson deconvoluted the mechanism of this transformation (**Scheme 2.2**).[54] It was suggested that under the acidic reaction conditions, protonation of the imine nitrogen of hydrazone **79** occurs, forming **81**.



Scheme 2.2: Robinson's widely accepted mechanism for Fischer's indole synthesis

This intermediate exists in equilibrium with its corresponding ene-hydrazine tautomer, **82**. The protonated ene-hydrazine **82** was then suggested to undergo a [3,3]-sigmatropic rearrangement to generate **83**. Rearomatisation of **83** by a proton shift produces aniline **84**, which subsequently attacks the iminium carbon *via* a 5-exo-trig process. Loss of ammonia (*via* elimination) from **85** finally generates the aromatic indole product **80**.

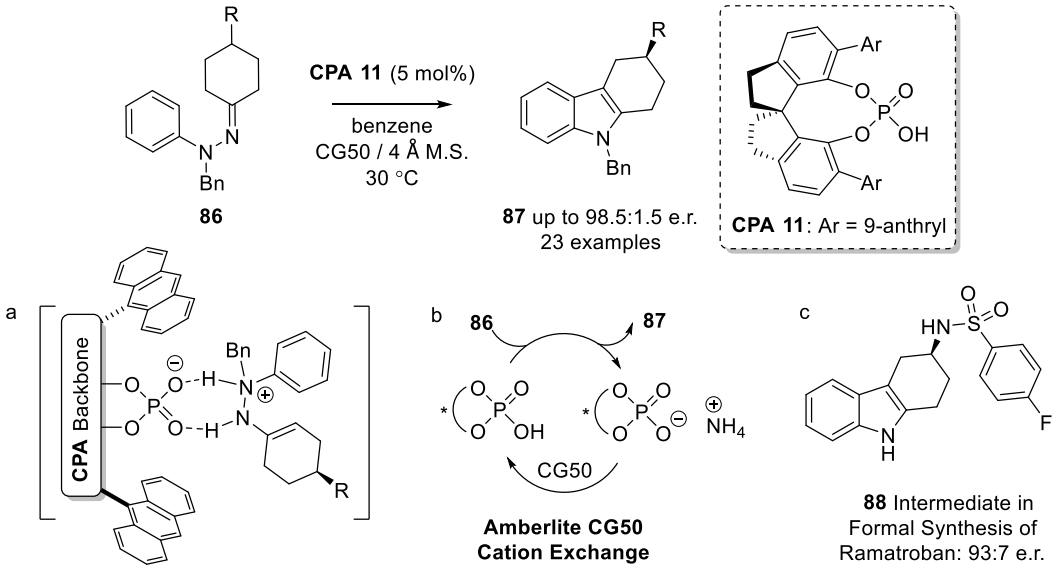
2.3 Relevance and Challenges

Despite Fischer's reaction being the first reported *de novo* synthesis of an indole, this approach has remained a practical and viable synthetic strategy for the construction of these heterocyclic cores.[55] The popularity and longevity of this method likely stems from the low cost of the reagents and starting materials, the operational simplicity and the scalability of the reaction. Although many advances have been made in broadening the scope of this reaction, catalytic methods are still in relatively short supply. This is likely due to the production of stoichiometric ammonia as a by-product, which can poison Brønsted or Lewis acid catalysts by ammonium ion formation or complexation, thereby inhibiting catalyst turnover. Furthermore, due to the lack of any intrinsic chirality on the indole nucleus, there is no obvious site for asymmetric induction to develop an enantioselective variant.

2.4 Catalytic Asymmetric Fischer Indolisation

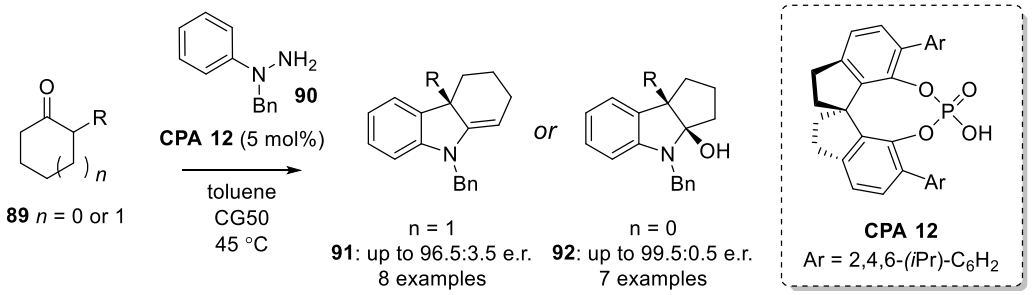
List was the first to successfully address the challenge of a catalytic enantioselective Fischer indole synthesis (**Scheme 2.3**). In their seminal report, the desymmetrization of phenyl hydrazones derived from 4-substituted cyclohexanones **86** was accomplished using a SPINOL phosphoric acid **CPA 11**.[56] In this reaction, **CPA 11** initially serves to hydrogen-bond with the imine, facilitating hydrazone-ene-hydrazine tautaumerisation. Subsequent proton transfer to the more basic *N*-benzylanilinic nitrogen atom then leads to the formation of a chiral hydrogen-bond-assisted ion pair (**Scheme 2.3a**). Through dual activation of this substrate, acceleration of the

irreversible [3,3]-sigmatropic rearrangement is made possible in one of the diastereomeric contact ion pairs, giving rise to enantioenriched tetrahydrozarbazoles **87**.



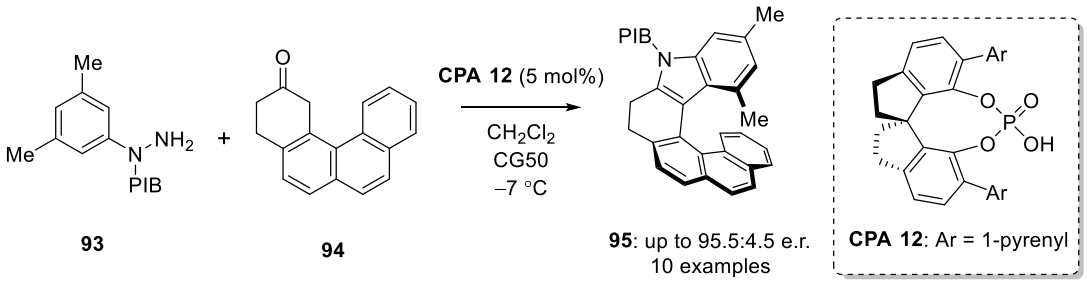
Scheme 2.3: The catalytic asymmetric Fischer indolisation

To overcome catalyst poisoning by ammonia, it was necessary to dope the reactions with Amberlite CG50: a weakly acidic cation exchange resin. This additive regenerates the phosphoric acid catalyst from the corresponding chiral ammonium phosphate salts allowing for quantitative yields to be attained even at low organocatalyst loadings, and without detriment to the enantioselectivity (**Scheme 2.3b**). Indeed, it was found that without the resin, catalytic quantities (5 mol%) of the chiral acids afforded very low yields (approx. 9% yield) of **87**. Additionally, the utility of this method was also illustrated in the formal synthesis of a thromboxane receptor antagonist, ramatroban. The enantioselective indolisation step was accomplished on 2.0 mmol scale, affording **88** in 93:7 er and 73% yield (**Scheme 2.3c**).Having recognised the potential far reaching applications of the asymmetric Fischer indolisation, List and co-workers then turned their attention towards other scaffolds (**Scheme 2.4**).[57] They hypothesised that upon condensation of phenylhydrazine **90** with α-substituted cyclic ketone **89**, a Brønsted acid catalysed rearrangement would take place from the more substituted ene-hydrazine to form a 3,3-disubstituted fused indoline.



Scheme 2.4: Catalytic asymmetric Fischer synthesis of 3,3-disubstituted indolines

This reaction was found to be broad in scope, with 2-substituted cyclohexanones providing access to a range of substituted indolines of type **91** in excellent yields and enantioselectivities. It is notable that all of these reactions were perfectly regioselective, with the rearrangement taking place consistently from the most substituted α-position of the starting ketone. Encouraged by these results, the cyclisations were also tested with 2-susbtituted cyclopentenones. Interestingly, the 2-hydroxyindolines **92** were isolated on this occasion, rather than the indoline-enamines. In a further extension to these methods, the catalytic asymmetric synthesis of azahelicenes **95** *via* Fischer indolisation has now also been achieved (**Scheme 2.5**). In this case, the *in situ* condensation of phenylhydrazine **93** with the polyaromatic ketone **94** generates a prochiral ene-hydrazine. In an analogous transition state to their previous reports (**Scheme 2.3a**), the chiral counterion was similarly thought to direct the stereochemical outcome in the [3,3]-sigmatropic rearrangement of the protonated intermediate.



Scheme 2.5: The Fischer indolisation approach towards azahelicenes

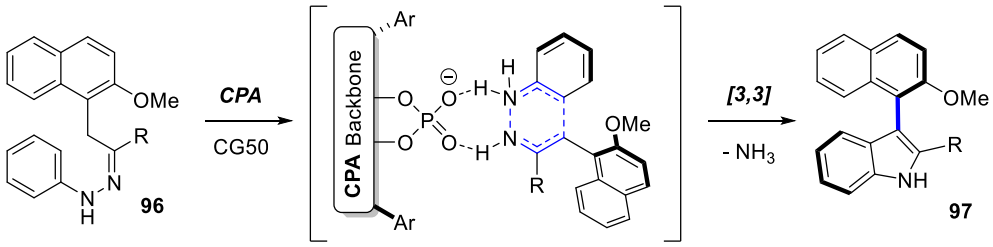
In this report, List also stressed the importance of considering the length and scale of the organocatalyst in order to achieve good control over the asymmetric induction step. This was

successfully realised by using 1-pyrenyl substituents at the 3,3'-positions of SPINOL derived **CPA 12**. The extended π-surfaces were envisaged to provide long range control over the screw sense of the forming helicene in the enantiodetermining step by engaging the polyaromatic substrates in π-π stacking interactions. The barriers to racemisation of the products were also determined through thermal racemisation experiments to be > 41 kcal mol^{-1}.

2.5 Project Design: Atropselective Fischer Synthesis of C-3 Aryl Indoles

Whilst List has already demonstrated that the catalytic enantioselective Fischer indolisation is an elegant method for furnishing both point and helically chiral indole derivates, axially chiral indoles remain unaccounted for *via* this approach. We initially envisaged that C-3 aryl indoles **97** (**Scheme 2.6**) might also be accessible *via* a catalytic atropenantioselective Fischer indolisation from the corresponding hydrazones of type **96**.

We were attracted to this strategy as it allows for all of the sterically demanding components to be incorporated into the acyclic hydrazone pre-cursor in a straightforward fashion prior to the indolisation event, rather than relying on a intermolecular coupling of the fragments at a late stage to complete the synthesis. We also reasoned that a bulky substituent (such as *t*-butyl, *i*-propyl or cyclohexyl) would be necessary at the C-2 position of the indole ring in order to increase the barrier to rotation and prevent racemisation of the products.

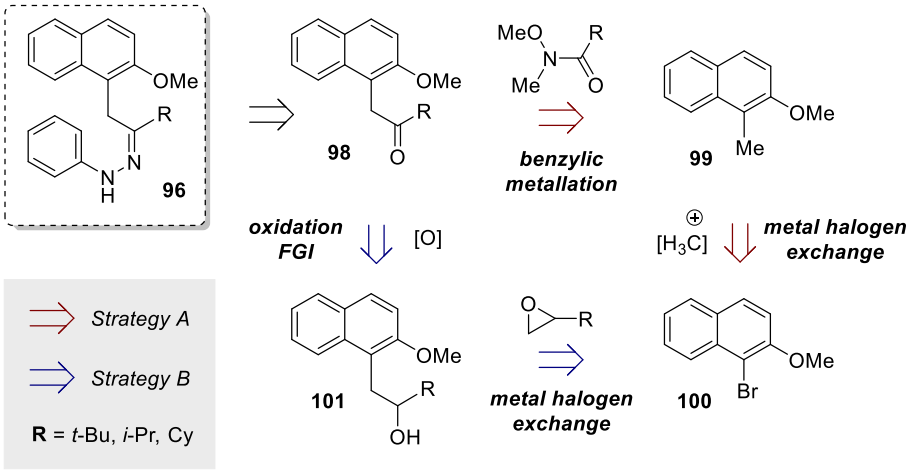


Scheme 2.6: Catalytic atropselective Fischer synthesis of C-3 aryl indoles **97**

For similar reasons, we also decided to begin with a methoxy substituent at the C-2 position of the naphthol as this would further slow the rate of racemisation, as well as providing a versatile synthetic handle for downstream modification of the products.

2.6 Synthesis of Phenylhydrazones

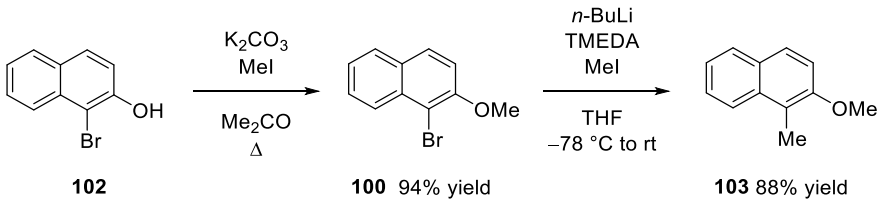
To this end, our Fischer indolisation demanded the synthesis of hydrazones **96** (**Scheme 2.7**). Inspired by the work of List, we envisaged that these could be obtained *via* a facile condensation of phenylhydrazine with the corresponding ketone **98**. To access **98**, two different retrosynthetic strategies were proposed. The first (A) was based upon directed benzylic metalation and acylation of **99**; the second (B) upon the oxidation of the homobenzylic alcohol **101** generated through ring opening of a terminal epoxide. Both approaches commence from the same 1-bromo-2-methoxynapthalene starting material **100**.



Scheme 2.7: Retrosynthetic strategies towards ketone **98**: Strategy A: maroon; Strategy B: navy

2.6.1 Strategy A: Benzylic Metalation and Acylation

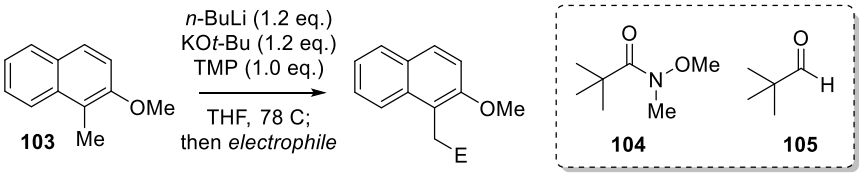
Setting out from commercially available 1-bromo-2-naphthol **102**, anisole **100** was prepared simply on 25 g scale *via* base mediated *O*-alkylation of the phenol in 94% yield. Next, (**Scheme 2.8**) lithium halogen exchange of **100** was performed at low temperature using *n*-BuLi and TMEDA. The organolithium generated *in situ* was then trapped with MeI to furnish **103** in 88% yield.



Scheme 2.8: Synthesis of **103**

In our inspiration for strategy A (**Scheme 2.7**), O'Shea has demonstrated the use of a *n*-BuLi/KO*t*-Bu/TMP triad for the *in situ* generation of mixed Li/K amides for benzylic metalation and subsequent anion trapping of *o*-methylanisoles.[58] These literature conditions were then tested in our system in conjunction with **103** and a variety of different electrophiles (**Table 2.9**). Using Weinreb amide **104**, no acylation was observed, and only unreacted starting materials were recovered. The failure of this reaction was attributed to the extreme steric bulk around the carbonyl group in **104**. In an attempt to remedy this, a more reactive and less congested electrophile **105** was tested, which only provided a low yield (11% yield; **Table 2.9**, Entry 2) of the corresponding secondary alcohol.

Table 2.9: Attempted benzylic metalation



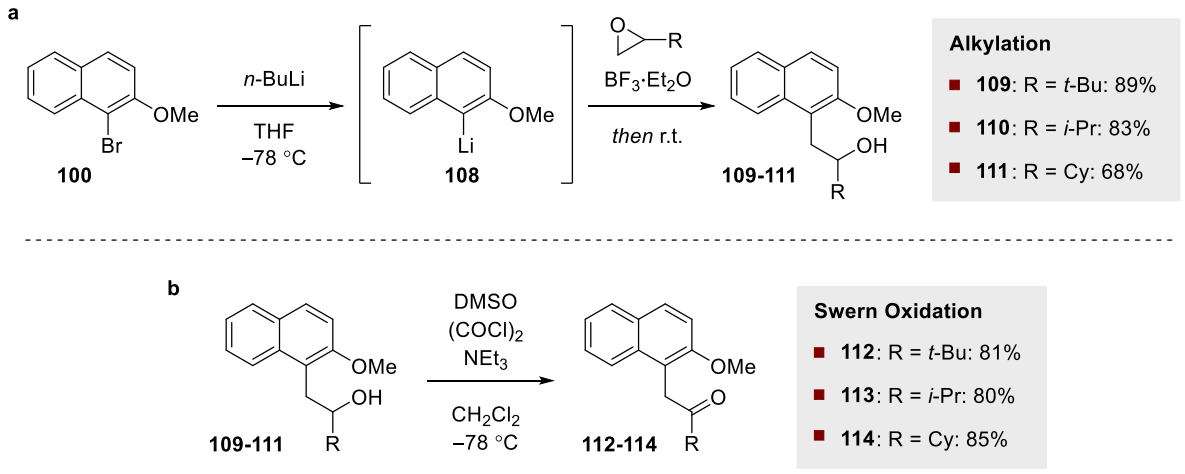
Entry	Electrophile	Product	E	Yield
1	**104**	**106**	C(O)t-Bu	0%
2	**105**	**107**	CH(OH)t-Bu	11%
3	D_2O	D-**103**	D	38%

To probe the extent to which the benzyl metalation was occurring, the reaction was quenched with D_2O, affording D-**103** with 38% deuterium incorporation at the benzylic position (**Table 2.9**, Entry 3). This unsatisfactory result was attributed to the presence of adventitious water in the reaction, which was difficult to eliminate. Furthermore, the close proximity of the carbonyl to the

tert-butyl group points towards a slow 1,2-addition process, so it is possible that not all of the metalated species had reacted before quenching after 24 h. Due to these complications, we elected to move on to the next approach.

2.6.2 Strategy B: Epoxide Ring Opening and Oxidation

For synthetic strategy B (**Scheme 2.7**), we implemented a $BF_3{\cdot}Et_2O$ mediated ring opening of epoxides using aryl lithiums. Treatment of bromide **100** with *n*-BuLi presumably generated the organolithium **108** *via* metal-halogen exchange (**Scheme 2.10**). Gratifyingly, addition of the epoxides and the Lewis acid to **108** in rapid succession gave the corresponding secondary alcohol **109** in 89% yield by regioselective ring opening at the unsubstituted terminus. In this approach, placement of the bulky group one carbon further away from the electrophilic site was instrumental to its success.

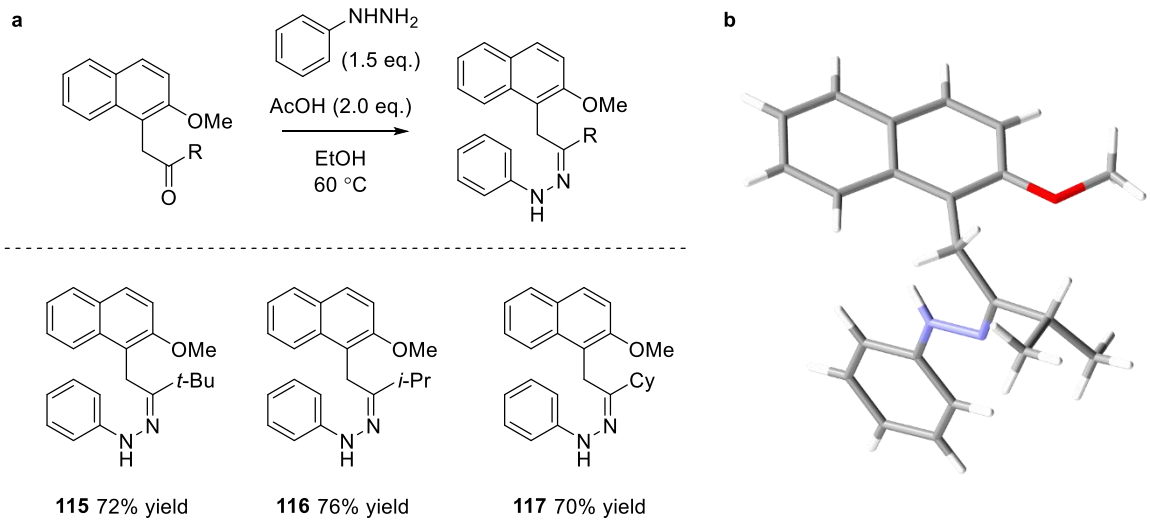


Scheme 2.10: Synthesis of ketones *via* a) epoxide ring opening and b) Swern oxidation

As this method proved fruitful for the synthesis of **109**, we also tested a variety of bulky alcohol substrates under the same conditions. The *i*-propyl and cyclohexyl substrates were also compatible, providing the desired secondary alcohols **110** and **111** in similarly good yields. Having established conditions for installing the acyclic chain *via* C–C bond formation, the oxidation of the alcohols to the corresponding ketones was then investigated. This was realised

in our first attempts without difficulties through a low temperature Swern oxidation. Good yields of 80-85% for **112-114** were achieved.

For the final step in this sequence, acid mediated condensation of phenyl hydrazine with ketones **112-114** was accomplished using Loh's method,[59] furnishing phenyl hydrazones **115-117** in good yields. The products readily hydrolysed on attempting chromatographic purification over silica gel, but fortuitously, the products could be obtained in a pure form by recrystallisation from hot EtOH. ^{1}H NMR and single crystal X-ray structure analysis of **116** revealed that the hydrazones prepared were formed exclusively as the E-isomer.



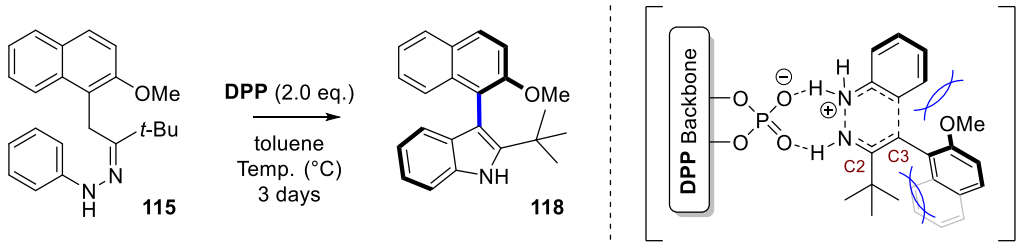
Scheme 2.11: a) Synthesis of phenylhydrazones; b) X-Ray crystal structure of **116**

2.7 Fischer Indole Synthesis of C-3 Aryl Indoles

With phenylhydrazones **115-117** in hand, we set out to evaluate conditions for the Fischer indolisation. At first, the *t*-butyl substituted heterobiaryl products **118** were targeted as these were predicted to have the highest rotational barriers within the series (**Table 2.12**). To simplify the process and eliminate any complications that could arise from catalyst poisoning due to the production of ammonia, we began with superstoichiometric quantities (2.0 equiv.) of diphenyl phosphate (DPP) as a model Brønsted acid.

Under these conditions, hydrazone **115** failed to react at 40 °C, even after 3 days (**Table 2.12**, Entry 1). We therefore examined more forcing conditions by heating the reaction to reflux (110 °C) over the same time period (**Table 2.12**, Entry 2) but still could not detect the formation of the desired product. We attributed the failure of these reactions to the severe steric clashes occurring within the transition state of the proposed [3,3]-sigmatropic rearrangement. If enolization occurs, σ-bond formation at C-3 is clearly a formidable challenge.

Table 2.12: Fischer indolisation of *t*-butyl substituted hydrazone **115**



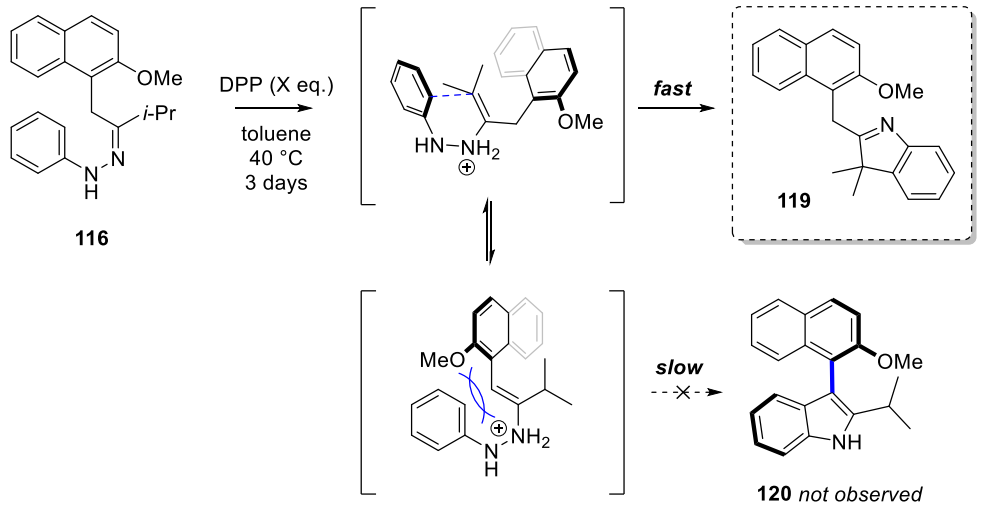
Entry	Temp. (°C)	Yield
1	40	0%
2	110	0%

We therefore proceeded to examine the smaller *i*-propyl substituted hydrazone **116**, which we hoped would be slightly more accommodating to the steric constraints of the cyclisation. Compound **116** was subjected to the same indolisation conditions. In this case, we were somewhat unsurprised to observe the formation of the undesired indolenine product **119** in a modest 23% yield (**Table 2.13**, Entry 1). In this scenario, there is an additional enolisable α-proton present within the hydrazone substrate. As described by List,[57] the Brønsted acid accelerates enolization to form the more substituted ene-hydrazine intermediate. Of the two possible intermediates in this case, the tetrasubstituted thermodynamic form is clearly favoured.[60]

Furthermore, the rate of the intramolecular [3,3]-sigmatropic rearrangement occurring *via* the more substituted double bond is also likely to be much faster due to the lower degree of steric

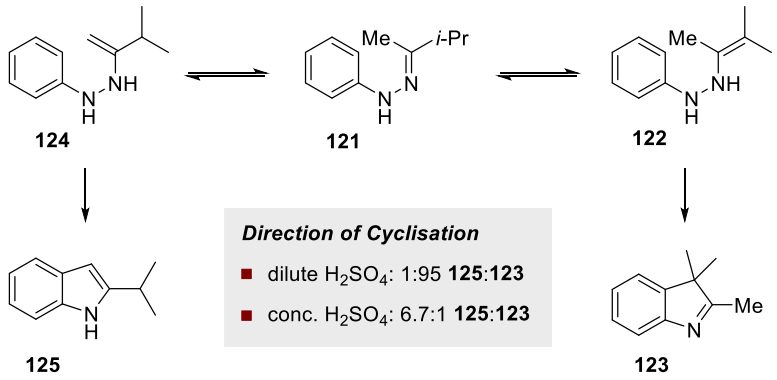
crowding within the transition state than would be expected for the formation of the atropisomeric indole. This combination of factors accounts for the exclusive formation of the unwanted product, albeit in a low yield of 13%. The catalytic variation of this reaction was also attempted using 20 mol% DPP and CG50 as an additive, which also gave the undesired product in trace quantities.

Table 2.13: Formation of Indolenine **119**



Entry	Equiv. DPP	Additive	Product	Yield
1	2.0	None	**119**	13%
2	0.2	CG50	**119**	<5%

In an early study, Funderburk showed that the direction of the ring closure in the Fischer indole synthesis for the isopropyl substituted phenylhydrazone case is strongly dependant on both the strength and the amount of acid catalyst,[61] and tentatively suggests that the protonation of both N-atoms may be required to obtain the indole that arises from the less substituted ene-hydrazine intermediate.



Scheme 2.14: Funderburk's study on the direction of Fischer indolisation of **121**

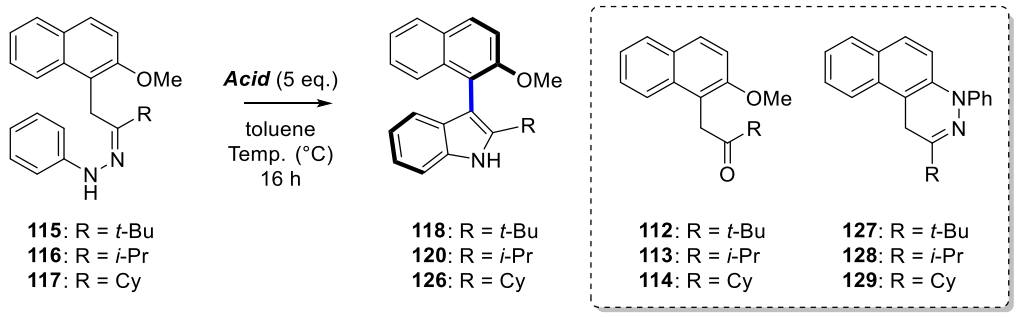
In their study, a range of strong inorganic acids were studied with isopropyl-methyl phenylhydrazone **121** in toluene, and it was found that dilute H_2SO_4 favoured the formation of **123** in a product ratio of 95:1. However, when a large excess of concentrated (78%) H_2SO_4 was used, the selectivity was switched to favour the 2-isopropylindole **125** in a 6.7:1 ratio.

Although it was difficult to conceive how such harsh reaction conditions could be rendered into a catalytic and enantioselective reaction, we maintained that this approach could still provide utility in generating the racemic heterobiaryls in reasonable quantities for the study of their rotational barriers. We therefore proceeded to examine a range of strong inorganic acids under Funderburk's conditions within our system.

The Fischer reactions mediated by HCl and H_2SO_4 gave intractable mixtures of decomposition products when mixed with hydrazone **116** (**Table 2.15**, Entries 1 & 2). $ZnCl_2$ in refluxing toluene gave the unwanted indolenine isomer **119** in 74% yield (**Table 2.15**, Entry 3). Contrastingly, we were pleased to find that T3P® switched the selectivity, affording the desired heterobiaryl **120** as the sole indolisation product (**Table 2.15**, Entry 4). Although this was produced in a low yield of 16%, this was the first occasion that this class of molecules has been prepared *via* a Fischer indolisation approach. In this reaction, the corresponding ketone **113** was also recovered in 25% yield following *in situ* hydrolysis of hydrazone **116**. Interestingly, the extremely high acidity of the reaction medium led to the formation of 1,4-dihydrocinnoline derivative **128** as an unexpected major product. This product was presumably formed *via* deprotection of the methyl

ether, followed by keto-enol tautaumerisation of the naphthol to the β-tetralone and subsequent intramolecular condensation of the pendant anilinic nitrogen atom.

Table 2.15: Synthesis of C-3 aryl indoles *via* Fischer Indole Synthesis



115: R = *t*-Bu
116: R = *i*-Pr
117: R = Cy

118: R = *t*-Bu
120: R = *i*-Pr
126: R = Cy

112: R = *t*-Bu
113: R = *i*-Pr
114: R = Cy

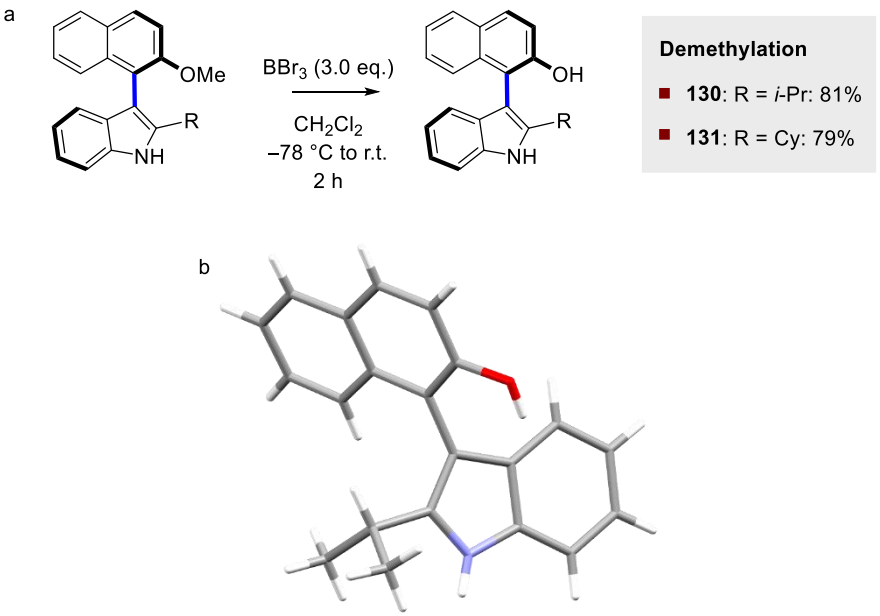
127: R = *t*-Bu
128: R = *i*-Pr
129: R = Cy

Entry	Hydrazone	Acid	T (°C)	Reaction Product [Yield]
1	**116**	HCl	60	N/A
2	**116**	H_2SO_4	60	N/A
3	**116**	$ZnCl_2$	110	**119** [74%]
4	**116**	T3P®	110	**120** [16%]; **113** [25%]; **128** [38%]
5	**116**	H_3PO_4	40	**120** [33%]; **113** [50%]; **128** [6%]
6	**117**	H_3PO_4	40	**126** [26%]; **114** [48%]; **129** [5%]
7	**115**	H_3PO_4	40	**118** [0%]; **112** [65%]; **127** [12%]

Orthophosphoric (H_3PO_4) acid was found to be the optimal reagent for furnishing product **120**, with a synthetically workable yield of 33% (**Table 2.15**, Entry 5). Notably, these conditions almost completely suppressed the formation of the corresponding cinnoline **128** by-product; however, significant hydrolysis and formation of **113** was also observed. Although the extent of the hydrolysis was far from ideal, we found that the ketone could be easily recycled through chromatographic purification, so these conditions were applied to the synthesis of other indole derivatives. The 2-cyclohexyl substituted indole was also successfully furnished in 26% yield (**Table 2.15**, Entry 6). Disappointingly, the severe steric constraints of *t*-butyl substituted hydrazone **115** again inhibited the formation of the desired product **118** (**Table 2.15**, Entry 7).

After constructing the crucial heterobiaryl C–C bonds in **120** and **126**, the methyl ethers were cleaved with BBr_3 to afford the corresponding 2-naphthols in good yields (**Scheme 2.16**). X-ray

quality crystals of racemic **130** were obtained by slow evaporation from CH_2Cl_2, with the resulting structure clearly demonstrating the twisted, non-coplanar conformation of the heterobiaryl core.



Scheme 2.16: a) Synthesis of phenylhydrazones; b) X-ray crystal structure of **130**

2.8 Determination of the Rotational Barrier of 130

With the racemic heterobiaryls in hand, we strived to glean insights into the conformational stability of this novel class of compounds. The enantiomers of **130** were physically separated by semi-preparative HPLC using a chiral stationary phase which provided an analytical sample of enantioenriched **130** in 96% e.e. The barrier to rotation of **130** was then probed through thermal racemisation experiments. After dissolving enantioenriched **130** in *o*-xylene, the sample was incubated at a constant temperature of 80 °C within a pre-heated oil bath. Through periodic removal of small aliquots from the heated solution, we monitored the enantiomeric erosion over time. After 60 minutes, the enantiomeric excess had fallen from 96% e.e. to 40% e.e., as shown in **Figure 2.17**. A first order plot of ln(100/e.e.) against time gives a straight line, the gradient of which was used to determine the barrier to rotation [$\Delta G^{\ddagger}$(ent.)]. We calculated that **130** has a rotational barrier of 27.1 kcal mol^{-1}, which corresponds to a $t_{1/2}$ (rac) of 46.5 days at room

temperature (See appendix **10.1** for full details). Compound **130** can therefore be categorised as a class 2 atropisomer.

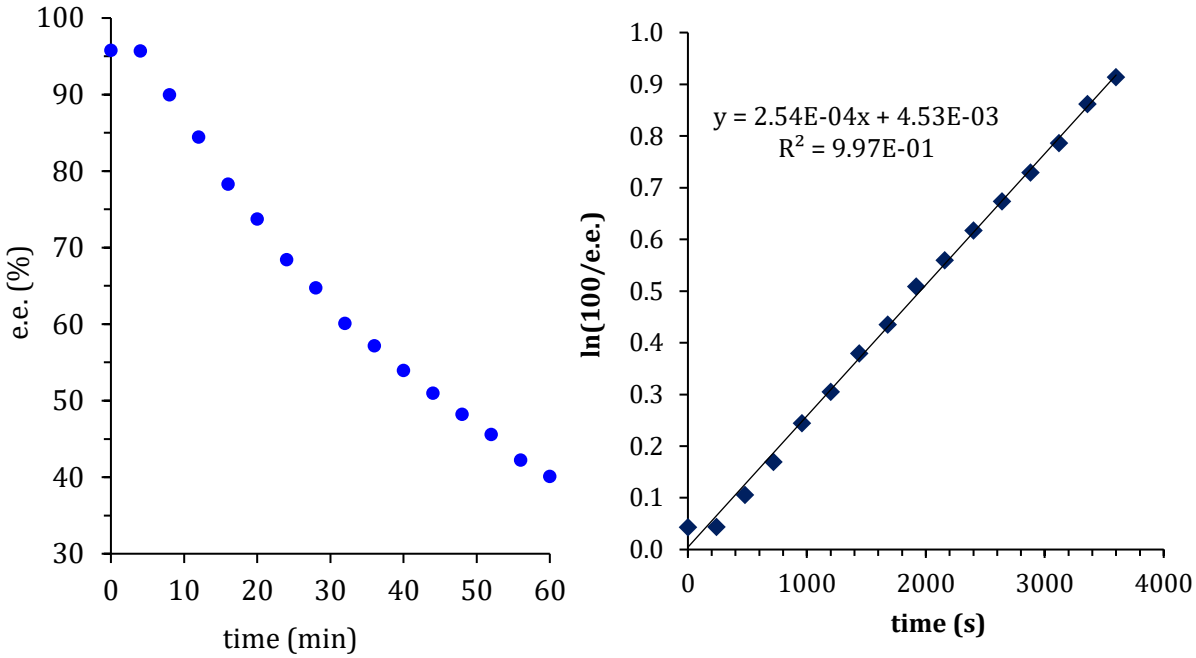
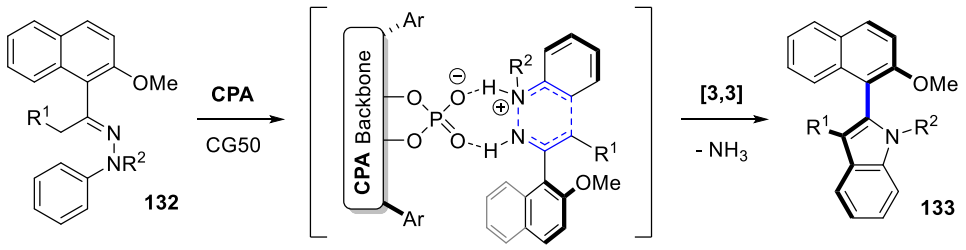


Figure 2.17: Determination of the rotational barrier of **130**

2.9 Project Design: Atropselective Fischer Synthesis of C-2 Aryl Indoles

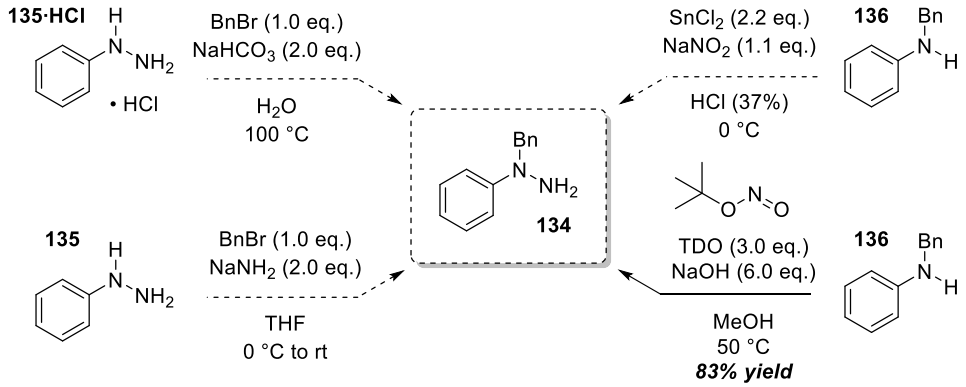
Due to the reactivity and regioselectivity issues encountered in the synthesis of the C-3 aryl indole atropisomers and the low barrier to rotation of the products, we decided to divert our attention to the construction of C-2 aryl indole analogues. In these examples, the hydrazones have the distinct advantage of having only one set of enolisable α-C–H bonds, which we hoped would eliminate some of the complications that were encountered in our previous efforts. However, we also recognised that for this class of heterobiaryls, much lower barriers to rotation might be expected due to the close proximity of the sterically small indole N–H bond to the chiral axis.



Scheme 2.18: Catalytic atropenantioselective Fischer synthesis of C-2 aryl indoles **133**

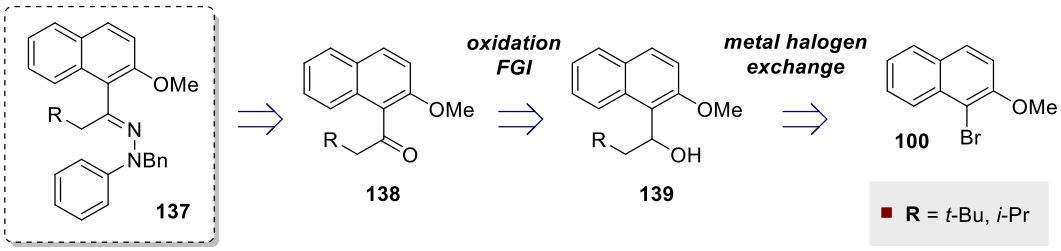
2.10 Synthesis of Aryl Ketones

We reasoned that if these targets were to be pursued, *N*-substitution would be necessary. To this end, we set out to prepare *N*-benzylphenylhydrazine **134** (**Scheme 2.19**). In our hands, List's base mediated *N*-benzylation of the anilinic nitrogen failed to generate the desired product from the hydrochloride salt of phenylhydrazine **135**. Along a similar vein, we then attempted the $NaNH_2$ mediated benzylation of the free base of phenylhydrazine **135**. As it was unclear why these previously reported methods were unsuccessful, we then turned towards a *N*-amination approach. To accomplish this goal, we opted for the *in situ* formation of diazonium salt generated through a Sandmeyer type process, followed by reduction to the corresponding hydrazine. Although $NaNO_2$ and $SnCl_2$ in concentrated HCl failed to provide target **134**, we were pleased to find that the combination of *t*-butylnitrite with thiourea dioxide (TDO) in basic methanol was optimal for the preparation of **134** in 83% yield.[62]



Scheme 2.19: Synthesis of phenylhydrazine **134**

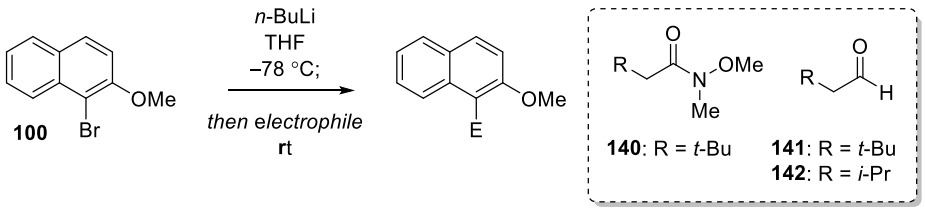
As our previously implemented *C*-alkylation strategy was highly successful for the synthesis of the C-3 aryl indoles, we invoked a similar approach for the synthesis of the C-2 aryl analogues. As before, we speculated that a bulky R-group would still be required at the C-3 position of the indole, so the synthesis of *t*-butyl and *i*-propyl containing tethers were targeted.



Scheme 2.20: Retrosynthetic strategy towards phenylhydrazone **137**

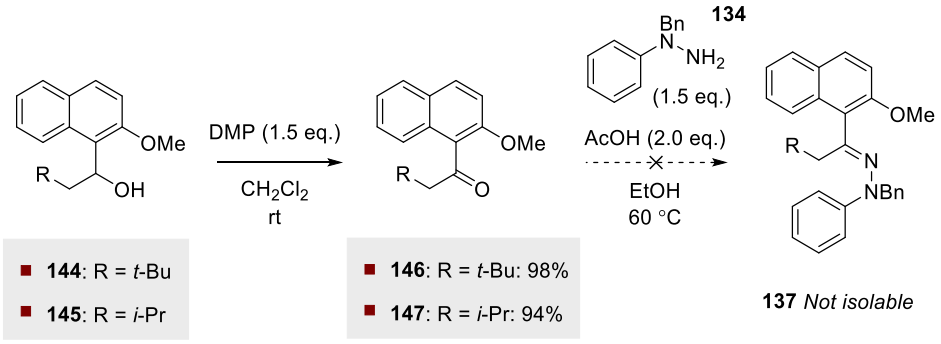
Setting out from **100**, we began investigating conditions for the alkylation. Unfortunately, the addition of Weinreb amide **140** to the organolithium failed to provide direct access to the corresponding ketone, and returned only the protodebromination product (**Table 2.21**, Entry 1). However, we were pleased to find that *t*-butylacetaldehyde **141** bearing the neopentyl group was a competent electrophile in this transformation, affording the secondary benzylic alcohol **144** in 73% yield without the need to add an external Lewis acid (**Table 2.21**, Entry 2). Similarly, the addition of isovaleraldehyde **142** to lithiated **100** gave **145** in a very good yield of 84% (**Table 2.21**, Entry 3).

Table 2.21: *C*-alkylation of compound **100**



Entry	Electrophile	E	Product	Yield
1	**140**	$C(O)CH_2(t\text{-Bu})$	**143**	0%
2	**141**	$CH(OH)CH_2(t\text{-Bu})$	**144**	73%
3	**142**	$CH(OH)CH_2(i\text{-Pr})$	**145**	84%

Following the alkylation reactions, **144** and **145** were treated with a slight excess of Dess-Martin periodinane (DMP) in CH_2Cl_2 to yield the corresponding ketones **146** and **146** in near quantitative yields for both substrates (**Scheme 2.22**).



Scheme 2.22: Synthesis of phenylhydrazone **137**

Loh's procedure (which had previously proven successful in the preparation of **115**-**117**) was then applied for the synthesis of the key phenylhydrazones **137**. Although the formation the hydrazones were detected by LRMS analysis of the crude reaction mixtures, we were unable to find a suitable method for the purification of the products. After examining a range of solvents, we found that the hydrazones were reluctant to recrystallise from the crude reaction mixture.

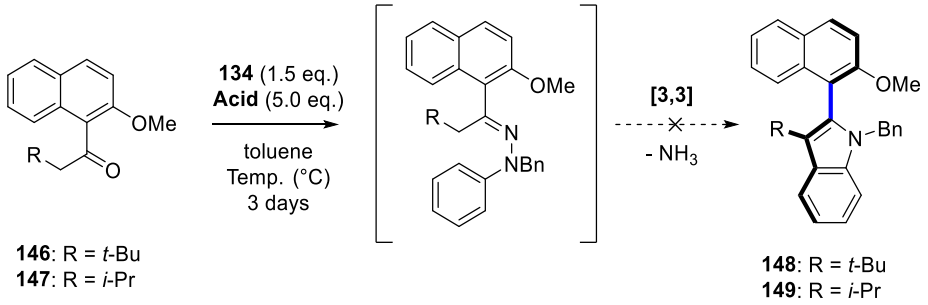
2.11 Fischer Indole Synthesis of C-2 Aryl Indoles

Though we were unable to isolate **137** in a pure form, we reasoned that the acidic reagent used to mediate the indolisation could also serve the dual purpose of catalysing the *in situ* condensation of phenylhydrazine **134** with the ketones. Consequently, a range of Brønsted and Lewis acids were evaluated for this purpose (**Table 2.23**).

Although fewer undesirable by-products were isolated, disappointingly, we found that DPP, $Mg(ClO_4)_2$ and $ZnCl_2$ (**Table 2.23**, Entries 1-3) all failed to provide the *t*-butyl substituted indole **148**, even after exposing the substrates to a large excess of the selected acid at elevated temperatures for extended reaction times. The composition of the reactions were monitored by

LRMS. The LRMS spectrum of the reaction mediated by DPP qualitatively revealed that a significant amount of the ketone remained after the 3-day period.

Table 2.23: Synthesis of C-2 aryl indoles *via* Fischer Indole Synthesis

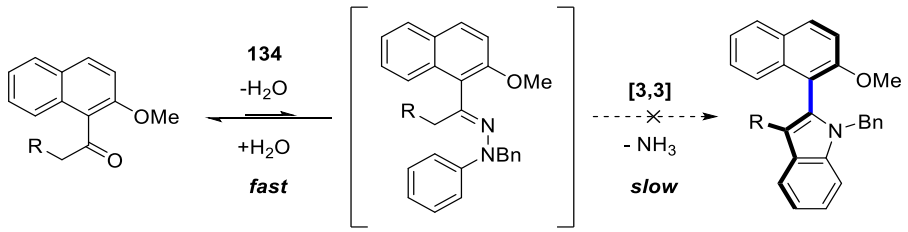


146: R = *t*-Bu
147: R = *i*-Pr

148: R = *t*-Bu
149: R = *i*-Pr

Entry	Hydrazone	Acid	Additive	Temp. (°C)	Product (Yield)
1	**146**	DPP	-	60	**148** (0%)
2	**146**	$Mg(ClO_4)_2$	-	80	**148** (0%)
3	**146**	$ZnCl_2$	-	110	**148** (0%)
4	**146**	DPP	3 Å MS	60	**148** (0%)
5	**146**	H_3PO_4	-	40	**148** (0%)
6	**147**	H_3PO_4	-	40	**149** (0%)

In an attempt to overcome the reversible hydrolysis, we repeated this reaction with the addition of 3 Å molecular sieves to drive the equilibrium towards the formation of the indole, but to no avail (**Table 2.23**, Entry 4). Finally, we turned to our best conditions for the synthesis of the C-3 aryl indoles (**Table 2.15**, Entry 5 & 6). An excess of orthophosphoric acid was tested with ketones **146** and **147** but similarly, we were only able to detect the formation of the hydrazone intermediates and recover the ketone starting materials. We concluded that as these substrates required such sterically encumbered substituents, the Fischer indolisation process is likely to be slow. Additionally, in this case, the hydrazone may be more activated towards hydrolysis in the acidic reaction medium than the hydrazones required for the C-3 arylindoles, which are flanked by two electron donating alkyl substituents. As a result, as the rate of indolisation is slower than the rate of hydrolysis, the hydrazone intermediates hydrolyses back to the ketone starting material before the sigmatropic rearrangement can occur (**Scheme 2.24**).



Scheme 2.24: Plausible explanation for the failure of this Fischer indole synthesis

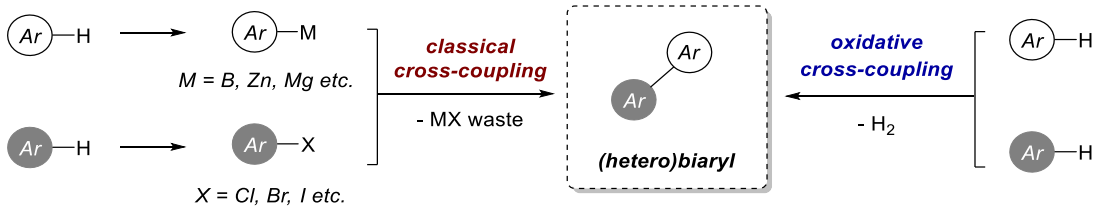
2.12 Conclusion

We maintain that the synthesis of these C-3 and C-2 aryl indoles *via* a Fischer indolisation approach represents an elegant solution for the *de novo* atropselective construction of indole based hetrobiaryls. However, in practise, we found the construction of a chiral axis that provides sufficient steric encumbrance to confer high conformational stability to the products to be a fundamental challenge.

Chapter 3: Oxidative Cross-Couplings

3.1 Synthesis of Biaryls *via* Cross-Coupling Reactions

Cross-coupling reactions are widely recognised as one of the most powerful and convergent synthetic tools for constructing biaryl or heterobiaryl cores. To access these compounds, classical cross-couplings are usually the methods of choice, which require an aryl halide, organometallic reagent (e.g. M=[B], Suzuki[63]; M=[Zn], Negishi[64]; M=[Mg], Kumada[65] etc.) and a transition metal catalyst to facilitate formation of the aryl-aryl linkage. Although these reactions generally provide the cross-coupled products with high yields and in predictable levels of chemo- and regioselectivity, these benefits are often precluded by the requirement to pre-functionalise the arene pre-cursors prior to the C–C bond forming step. Not only does this add at least two additional steps to the synthesis, but it also generates a significant amount of waste from the stoichiometric (and often toxic) metal salt by-products, reaction solvents, unrecovered metal catalysts and chromatographic materials (**Scheme 3.1**).



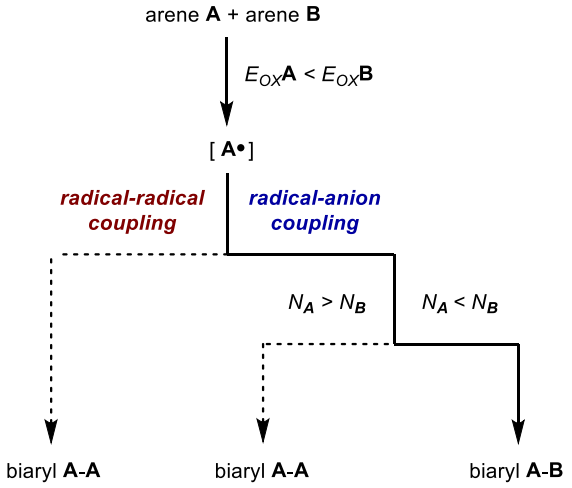
Scheme 3.1: Cross-coupling approaches towards atropisomeric compounds

In principle, if the unfunctionalised arene pre-cursors were to participate directly in the cross-coupling process, this would eliminate the need to pre-functionalise each component and eradicate all waste associated with those steps. Furthermore, hydrogen is formally produced as the only stoichiometric (but environmentally benign) by-product. In the pursuit of more sustainable and straightforward approaches towards industrially important atropisomeric biaryls and heterobiaryls, the issue of the waste produced from the most widely adopted cross-coupling approaches should not be ignored. As a consequence, the development of new oxidative

cross-couplings methods [otherwise known as cross dehydrogenative couplings (CDC)] should therefore be regarded as important and pressing goals.

3.2 Mechanistic Principles of Oxidative Cross-Couplings

For selective oxidative cross-coupling to be achieved, it is crucial for each coupling partner to have separate and well differentiated roles within the reaction mechanism. To address the challenge of oxidative biaryl couplings (where neither component contains an activating group), selective oxidation of a single arene has emerged as the predominant strategy. Pappo has introduced a model for predicting the cross-coupling selectivity in transition metal catalysed reactions, but the general principles hold true regardless of the oxidising agent used (**Scheme 3.2**).[66] Pappo stressed that the selectivity is based not only on redox potentials of the substrates *but also* their global nucleophilicities, *N*.



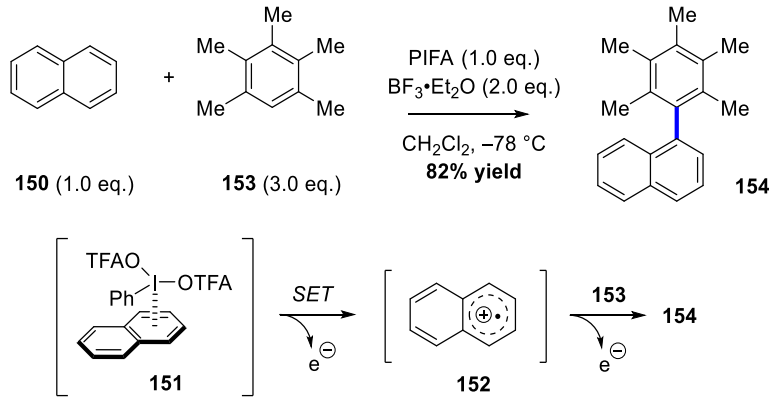
Scheme 3.2: Pappo's parameters illustrating requirements for oxidative cross-couplings

If two arenes **A** and **B** have significantly different oxidation potentials [E_{OX}**A** < E_{OX}**B**], judicious choice of an external oxidant should result in the selective oxidation of the more electron rich component (**A**), generating an electrophilic radical species **A•**. At this stage, radical-radical dimerisation can occur to give homocoupled biaryl **A**-**A**. If **A** is also a stronger nucleophile than **B**, trapping of the **A•** species *via* a radical–anion mechanism (discussed in more detail in section **3.4**)

will also give the same homocoupling product. However, if $N_A < N_B$ heterocoupling should predominate. In addition to the primary challenge of controlling the reaction's chemoselectivity, in the absence of specific activating or directing groups it is also important for each arene fragment to be biased towards C–C bond formation at a single reactive site. If these conditions are not carefully controlled, the combination of these two factors could lead to catastrophic reaction outcomes with intractable mixtures of homocoupled and heterocoupled regioisomeric products.

3.3.1 Hypervalent Iodine (III) Reagents

To address the challenges associated with biaryl synthesis by oxidative cross-coupling, several different synthetic approaches have been implemented. Kita and co-workers have made significant contributions to the oxidative cross-coupling of electron rich arenes using hypervalent iodine (III) reagents (**Scheme 3.3**).



Scheme 3.3: Kita's synthesis of biaryls using hypervalent iodine (III) reagents

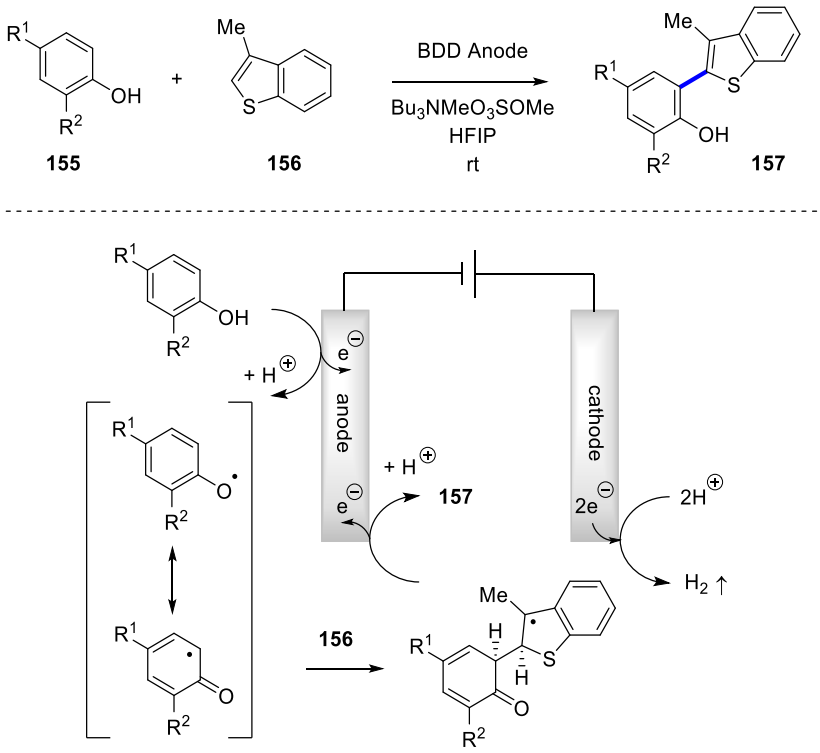
In their seminal report,[67] this group proposed that coordination of PIFA to electron rich arene **150** leads to the formation of π complex **151**. As $BF_3{\cdot}Et_2O$ is essential in this reaction, it was suggested to play a role in activating the π complex towards single electron transfer (SET) by coordinating to one of the trifluoroacetate groups. A SET event then generates the reactive radical cation species **152** which then undergoes nucleophilic attack by **153** to afford the cross-coupled product **154**. As naphthalene **150** [E_{OX} = 1.64 V] and **153** [E_{OX} = 1.58 V] have very similar oxidation potentials, steric factors presumably attenuate coordination of PIFA to the π cloud of

153, contributing to the highly selective oxidation of only component **150**. Notwithstanding the high degree of cross-coupling selectivity observed, the extremely low atom economy of this process must be highlighted. Indeed, stoichiometric quantities of iodine-containing waste are produced for a transformation that formally results in the net loss of hydrogen.

3.3.2 Electrochemical Oxidations

The replacement of stoichiometric oxidants with electricity undoubtedly offers a more sustainable, cost effective, atom-efficient and environmentally friendly approach towards biaryl frameworks.[68] Electrochemical synthesis is predicated upon electron transfers taking place at the interface between the solid electrode and the substrate dissolved in charge conductive media. Waldvogel has realised the synthesis of numerous biaryl cores *via* anodic dehydrogenative C–C coupling. To illustrate, a scalable regio- and chemoselective arylation of benzo[*b*]thiophenes **156** was achieved using a boron-doped diamond (BDD) anodes (**Scheme 3.4**).[69]

The authors propose that single electron oxidation of the dissolved phenol occurs at the anode to generate an electrophilic phenoxyl radical, with loss of a proton. Key to the success of the coupling was the use of 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) as a reaction medium, which is known to dramatically increase the lifetime of phenoxyl radicals through hydrogen bonding.[70] This reactive intermediate is then intercepted by the nucleophilic benzo[*b*]thiophene fragment. Following regioselective C–C bond formation, a successive anodic oxidation then occurs (coupled with the loss of another proton) to generate the heterobiaryl product. Hydrogen is produced at the cathode by reduction of the H^+ generated. Despite the clear environmental advantages, the practical constraints of electrochemical synthesis have seriously delayed its take off in mainstream synthesis.[71] The costs and maintenance of a complete electrochemical device can be prohibitively expensive. Additionally, addressing challenges in engineering and instrument design is notoriously tedious and dissuasive for the conventional synthetic chemist.[72] While notable efforts have been made by Baran to make this technology more accessible, the uptake of this technology by the synthetic chemistry community remains slow.[73]

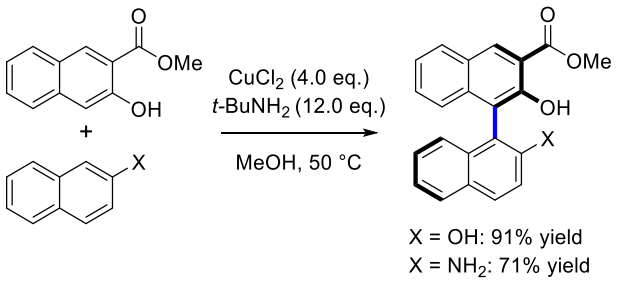


Scheme 3.4: Waldvogel's electrosynthesis of biaryls

3.3.3 Transition Metal Mediated Oxidative Cross-Couplings

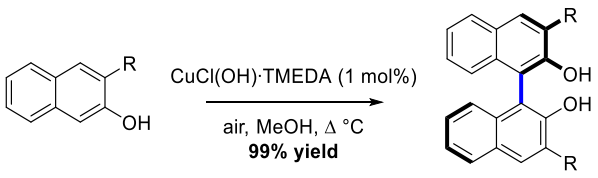
Amongst the panoply of methods for mediating the oxidative coupling of arenes, arguably the most widely adopted protocols have involved the use of oxidising first row transition metals (e.g. V, Cr, Mn, Fe, Co, Cu).[74] These elements have numerous stable oxidation states and as such, participate proficiently in redox processes. The advantages of these methods originate from the low costs of the earth abundant transition metal salts, the operational simplicity of the reactions and the prospect of developing atroposelective cross-coupling variants through the appropriate choice of a chiral ligand. Many of these reports have drawn inspiration from important oxidative phenolic couplings mediated by metal containing enzymes in biocatalytic processes.[75] Over the past 50 years, the lion's share of efforts have been directed towards the oxidative synthesis of 1,1'-bi(2-naphthol (BINOL) and 2-amino-2'-hydroxy-1,1'-binaphthyl (NOBIN) frameworks (**Scheme 3.5**).[76] In pioneering efforts, Hovorka[77] and Kočovský[78] similarly disclosed the hetero to homocoupling ratios of a series of Cu(II) amine mediated couplings involving different naphthyl units. Through this mix-and-match approach, the high observed cross-coupling selectivities were

correlated with the different substitution patterns and redox potentials (ΔE ≥ 0.25 V) between the reacting fragments.



Scheme 3.5: Synthesis of biaryls using superstoichiometric copper amine complex

Nevertheless, the requirement for a super-stoichiometric excess of a metal salt in this seminal transformation is clearly undesirable. The first efficient catalytic variant was described by Nakajima,[79] albeit, for the oxidative *homo*-coupling of 2-naphthol derivatives (**Scheme 3.6**). It was found that in this case, only 1 mol% CuCl(OH)·TMEDA was necessary, and catalyst turnover could be achieved simply by leaving the reaction open to air for its duration. The extremely low catalyst loadings and the environmentally benign conditions make this process extremely attractive from green chemistry perspective. Several mechanistic possibilities have been laid out to describe these processes and are discussed in more detail in the next section **3.4**.

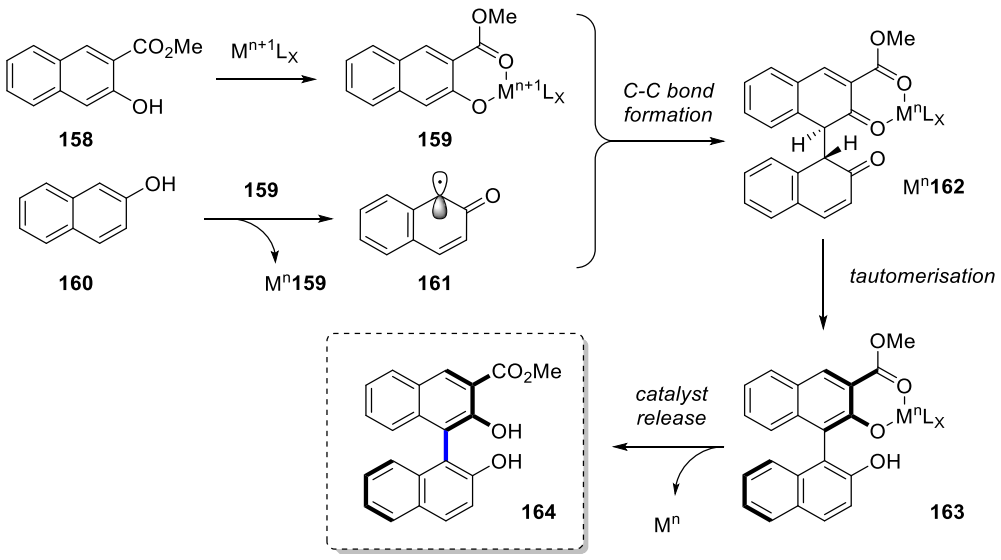


Scheme 3.6: Synthesis of C_2-symmetric BINOL using catalytic copper-TMEDA complex

3.4 Mechanism of Transition Metal Catalysed Oxidative Cross-Couplings

It is now widely accepted that in the catalytic variation of the heterocoupling devised by Hovorka and Kočovský, the more acidic naphthol **158** (substituted with an EWG) initially binds to the metal centre, forming a metal phenolate complex **159** after loss of a proton.[80] Moreover, the carbonyl group at the 3-position is also envisaged to also engage in metal binding to form a rigid

bidentate manifold. The more electron rich coupling partner **160** then undergoes single electron oxidation by the complex **159** to generate electrophilic phenoxyl radical **161**.



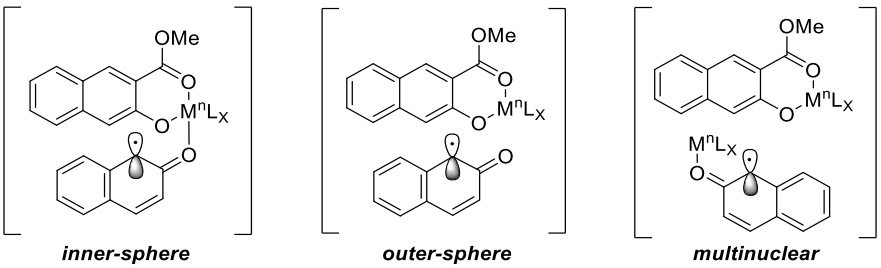
Scheme 3.7: Oxidative cross-couplings of 2-naphthols *via* radical–anion mechanism

The metal bound phenolate anion **159** is normally the most nucleophilic species within the reaction and will therefore attack the electrophilic radical **161**. In the case of highly chemoselective oxidative cross-couplings, the radical–anion mode is thought to be the dominant reaction mechanism (**Scheme 3.7**).[66] The C–C bond forming event may differ depending on the co-ordination environment of the phenoxyl radical. The possibilities are (**Scheme 3.8**):

(1) [Inner-sphere coupling] where the radical undergoes ligand exchange with the metal complex baring the phenolate, leading to intramolecular C–C bond formation;

(2) [Outer-sphere coupling] where the solvated radical does not bind to the metal centre and is intercepted in an intermolecular fashion, or;

(3) [Multinuclear coupling] where two metal complexes are involved in the C–C coupling step.



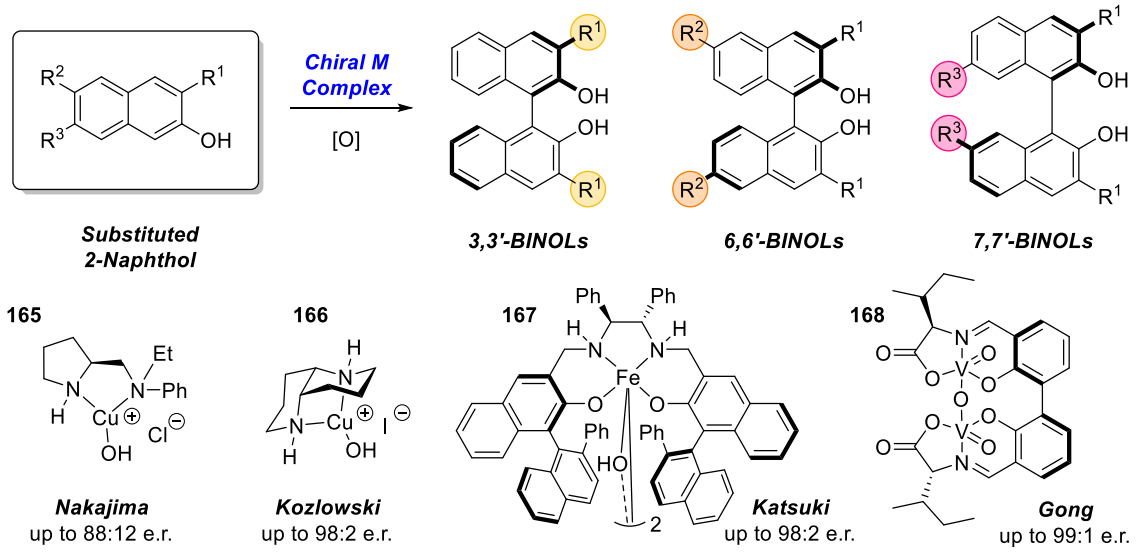
Scheme 3.8: Possible mechanisms for C–C bond formation within radical–anion coupling

Once the C–C bond has been forged, the cross-coupled intermediate **162** undergoes keto-enol tautaumerisation, followed by release of the reduced form of the chiral metal complex from **163**. Reoxidation of the reduced metal with the terminal oxidant then regenerates the active (M^{n+1}) species, which may then continue to catalyse further reactions.

Whilst the mechanistic scenarios outlined are helpful for summarising the possible modes of reactivity for the cross-coupling, in reality, the reaction solvent, metal catalyst, coordination geometry, ligand properties and ligandability of the radical all have the potential to influence the mechanism of the reaction. As such, the exact nature of the oxidative coupling cannot be easily predicted without thorough mechanistic investigation on a case specific basis.

3.5 Catalytic Enantioselective Synthesis of Biaryls *via* Oxidative Homo-Couplings

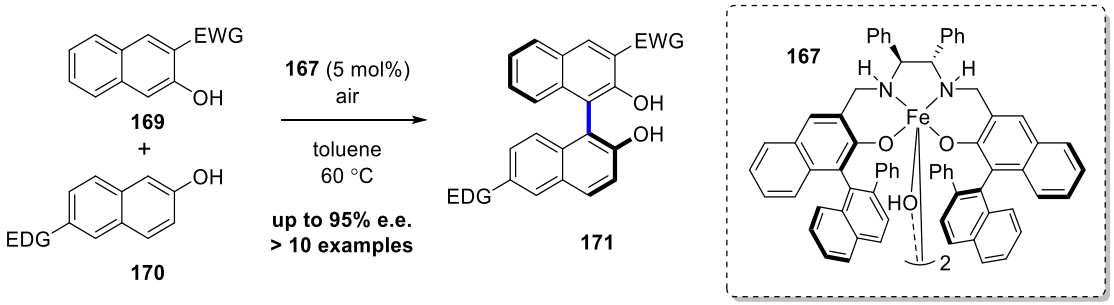
Inspired by the work of Nakajima, a great deal of effort has since been placed on the discovery of new chiral ligands for the enantioselective synthesis of C_2-symmetric BINOLs (**Scheme 3.9**). In early reports, Nakajima[81] and Kozlowski[82] disclosed the first catalytic enantioselective syntheses of 3,3'-disubstituted BINOLS using chiral copper diamine complexes **165** and **166**. Similarly, Katsuki[83] has illustrated the synthesis of 6,6'-disubstituted BINOLs using a chiral Fe(III) salan complex **167** and molecular oxygen as the terminal oxidant. Additionally, Gong[84] has also shown that diastereomeric dinuclear V(IV) oxo-complex **168** is an efficient catalyst for facilitating the homocoupling of naphthols bearing a 7-substituent.



Scheme 3.9*:* Enantioselective oxidative homocoupling of 2-naphthols

3.6 Catalytic Enantioselective Synthesis of Biaryls *via* Oxidative Hetero-Couplings

Given the intrinsic chemo- and regioselectivity challenges, there have been comparatively few attempts to control the enantioselectivity in oxidative cross-coupling reactions. In Katsuki's early work[85], highly significant strides towards a catalytic enantioselective cross-coupling protocol were achieved. The Katsuki Fe(III) salan complex **167** initially developed for homocoupling reactions was repurposed for cross-couplings between electron-rich naphthol **170** and electron-poor 2-naphthols **169** (**Scheme 3.10**).

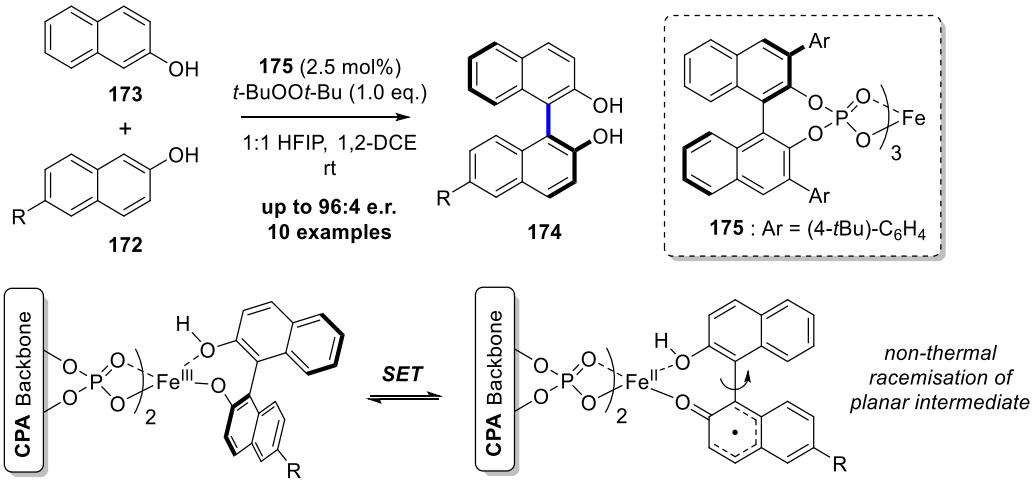


Scheme 3.10: Katsuki's Fe(III) salan catalysed oxidative cross-coupling of 2-naphthols

On the basis of numerous kinetic experiments, the cross-coupling selectivity was rationalised. The Fe(III) di-μ-hydroxo complex **167** was shown to participate in facile ligand exchange with

the two different 2-naphthol species. Of these intermediates, it was suggested that the more electron rich phenolate complex underwent more rapid oxidation with triplet oxygen to form an oxidising Fe(IV) centre that can undergo reversible inner-sphere SET with the bound phenolate, forming a phenoxyl radical. The more acidic phenolate of **169** (bound to another iron centre) then attacks the electrophilic phenoxyl radical. This leads to the formation of the stereogenic axis *via* multinuclear radical–anion coupling to give the cross coupled product. Various substitution effects were also explored, achieving yields of up to 70% of the desired heterocoupled product, generally with exquisite enantioselectivity.

Pappo and Toste have described a new catalytic manifold for oxidative cross-couplings based on chiral Fe(III) phosphate complexes, with 4-substituted-3,3'-biarylphosphates providing the highest levels of enantioselectivities (**Scheme 3.11**).[85] The triphosphate complex **175** serves as the pre-catalyst in this transformation, forming the active bisphosphate after dissociation of a single anionic ligand. Two vacant cis-coordination sites were required to accommodate the different naphtholic units in order for the proposed inner-sphere radical–anion coupling to occur.

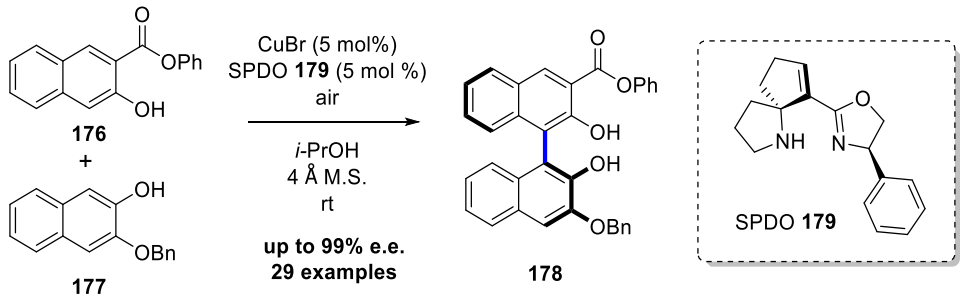


Scheme 3.11: Pappo's Fe(III) phosphate catalysed oxidative cross-coupling of 2-naphthols

Pappo also reported that the BINOL products were configurationally unstable under the metal catalysed reaction conditions. Chelation of BINOL to Fe(III) or Cu(II) was found to lead to a competing SET process involving a planarized binapthoxyl radical intermediate, facilitating

undesired racemisation and lowering the overall enantioselectivity. It should be noted that in this report, as the oxidation potentials and theoretical *N* values were similar between the reacting fragments, the reported cross coupling selectivities were low, with a maximum yield of 48% being isolated amongst the heterocoupling products.

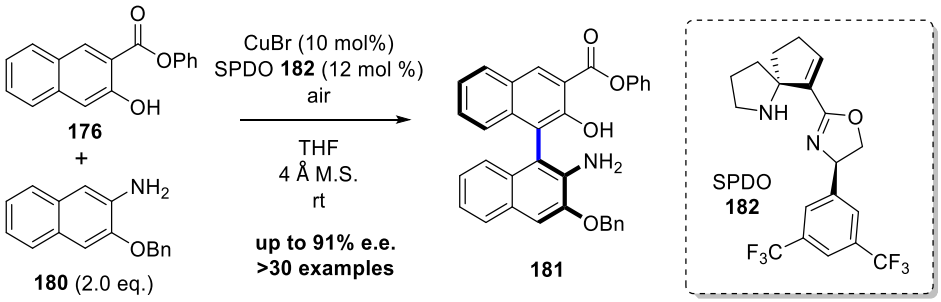
More recently, Tu and Chen have reported a highly heteroselective coupling between 3-subsituted-2-naphthols with contrasting electronics (**Scheme 3.12**).[86] For this reaction, a novel bidentate spirocyclic pyrrolidine ligand **179** (SPDO) was designed for a Cu(I) catalyst. This procedure is noteworthy not only because of the high chemo and enantioselectivities, but because of the extremely mild and environmentally benign reaction conditions, employing an alcohol as the reaction solvent and air as the terminal oxidant. This process was also amenable on > 1 gram scale, making this reaction highly attractive from a practical perspective. The products were also derivatized into a chiral aldehyde organocatalyst that demonstrated utility a direct α-alkylation of amino esters. However, in this heterocoupling protocol, addition of naphthoate fragment **176** in two charges was necessary to suppress the undesired homocoupling.



Scheme 3.12: Tu's Cu(I) SPDO catalysed oxidative cross-coupling of 2-naphthols

Similarly, the same group has also recently disclosed the first direct enantioselective synthesis of NOBINs by oxidative cross-coupling using the same Cu(I)/SPDO catalytic manifold (**Scheme 3.13**).[87] Several control experiments and DFT studies were carried out to shed light on the reaction mechanism. The first step of the cycle was oxidation of the Cu^{I} SPDO complex in air. The Cu^{II} species was then proposed to oxidise the electron rich naphthylamine **180** *via* and outer-sphere process (the radical of which was caught by DMPO in radical trapping experiments and

the adduct detected by HRMS-ESI). Association of the more acidic naphthoate with the copper centre generates the corresponding phenolate complex. The DFT calculations suggest strong π···π interactions between the naphthyl unit of **176** and the ligand's aryl substituent, which were thought to be crucial in controlling the reaction's enantioselectivity. Approach of the amino-naphthoxy radical to the copper centre from the *Re* face is favoured and is followed by C–C bond formation.



Scheme 3.13: Tu's Cu(I) SPDO catalysed oxidative synthesis of NOBINs

3.7 Oxidative Cross-Coupling of Indoles

Outside the realm of biaryl synthesis, indoles have also been shown to engage in oxidative-cross coupling reactions. The direct oxidative cross-coupling of phenols and indoles is thought to be a decisive step in the biosynthesis of several natural products that showcase the benzofuro[3,2-*b*]indoline core. Selected examples include diazonamide A,[88] bipleiophylline[89] and azonazine,[90] whose structures are illustrated (**Figure 3.14**).

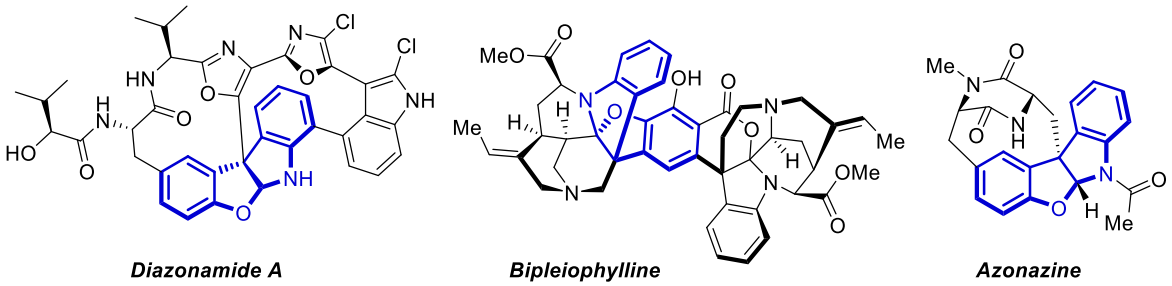
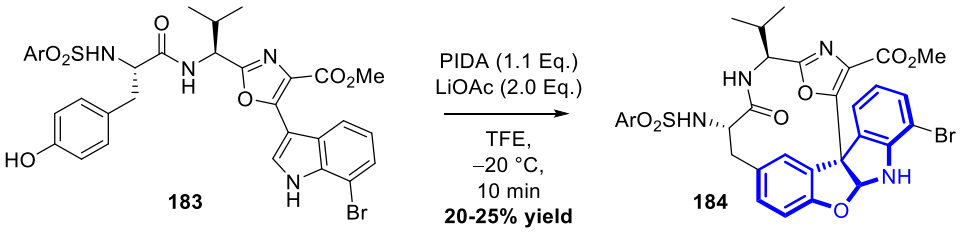


Figure 3.14: Natural products containing the benzofuro[3,2-b]indoline core

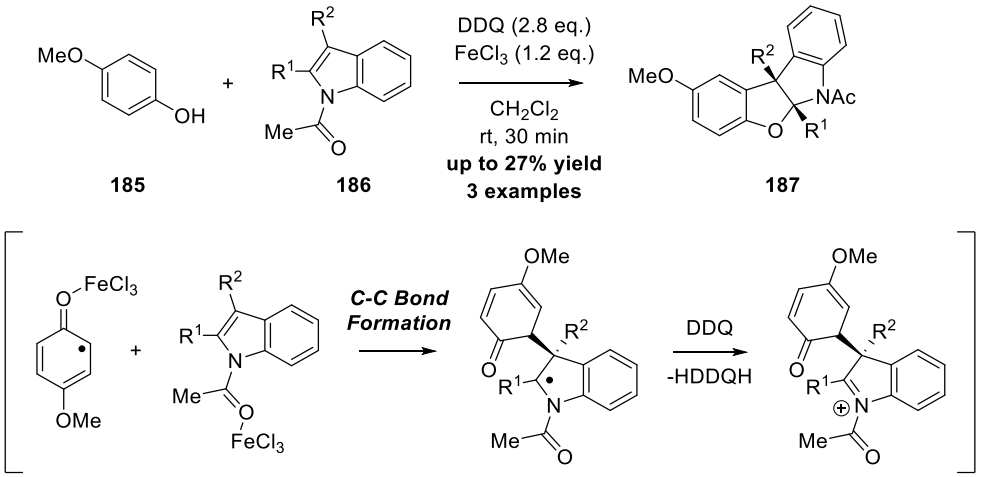
Danishefsky reasonably suggested that the biosynthetic [3+2] annulation commences with oxidation of the phenol to generate an electrophilic species, followed by C–C bond formation from the most nucleophilic C-3 position of the indole and subsequent trapping of the indolenine.[91] This idea has provided the inspiration for many elegant biomimetic total syntheses using hypervalent iodine (III) reagents as the oxidant.[92] This is exemplified below in an late step of Harran's total synthesis of (-)-Diazonamide A (**Scheme 3.15**).[93]



Scheme 3.15: Indole-Phenol cross-coupling in Harran's total synthesis of (-)-Diazonamide A

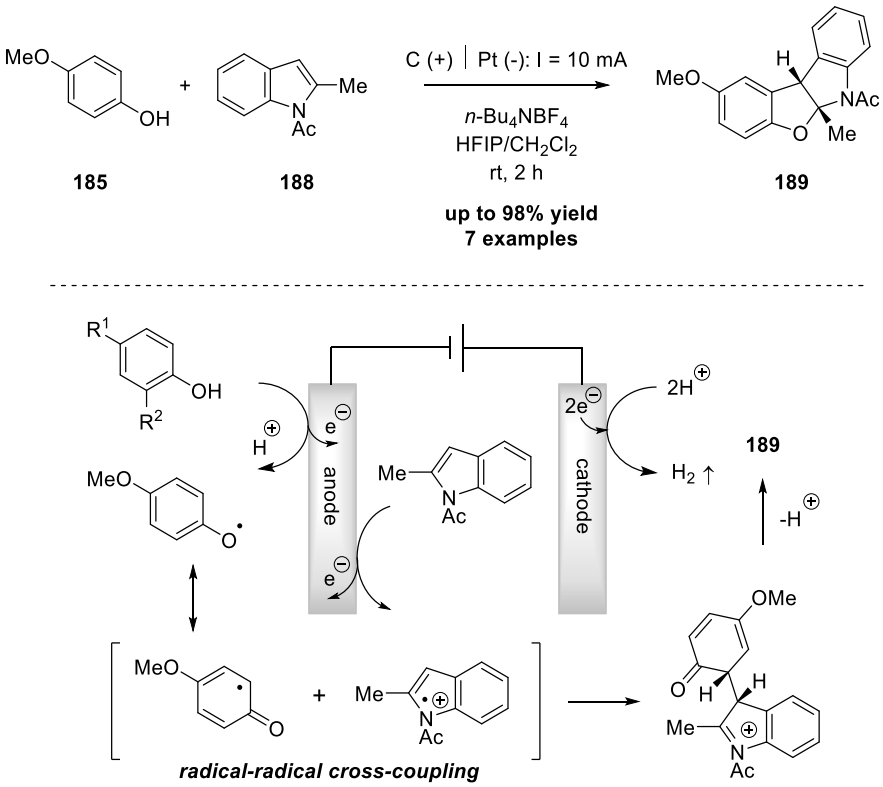
Although an advanced synthetic intermediate was prepared using this method, the reaction was low yielding and required strict consideration of the reaction time. Additionally, numerous unwanted overoxidation by-products were also isolated. To address these challenges, several synthetic methodologies towards these tetracyclic systems have since been presented. Vincent has reported a dual activation strategy for the oxidative cross-coupling of 2,3-disubstituted *N*-acetyl indoles with phenols (**Scheme 3.16**).[94] Both DDQ and stoichiometric $FeCl_3$ were required to promote the reaction, proving their synergistic effect. The authors suggest that the oxygen of the indole acetyl group complexes to $FeCl_3$, disrupting the aromaticity of the indole nucleus through delocalisation of the *N*-lone pair into the carbonyl, making the indole more reactive towards the iron-bound phenoxyl radical.

After C–C bond formation at the C-3 position of the indole, DDQ oxidation of the C-2 centred *tert*iary radical generates a highly electrophilic *N*-acyl iminium ion which is then rapidly intercepted by the phenolic oxygen, forming product **187**. Despite the poor published yields and harshly oxidising reaction conditions, this method compared relatively favourably to the more linear syntheses of these cores recorded previously.[95]



Scheme 3.16: Vincent's Synthesis of Benzofuroindolines with DDQ and $FeCl_3$

In a more efficient account, Lei has disclosed a scalable, regio- and chemoselective electrochemical dehydrogenative [3+2] annulation of 2-substituted indoles and phenols in an undivided cell (**Scheme 3.17**).[96]

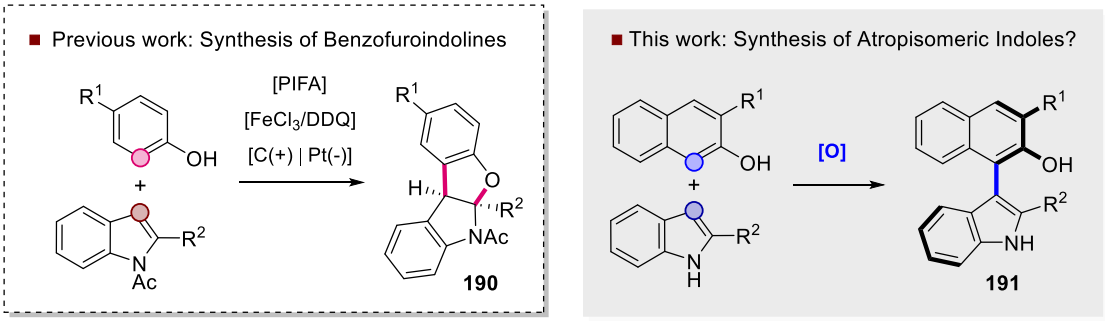


Scheme 3.17: Lei's electrochemical synthesis of benzofuroindolines

Through physical measurements of the oxidation potentials of the substrates and radical trapping studies with $P(OEt)_3$, this reaction was deemed to proceed *via* the indole radical cation intermediate generated by anodic oxidation. It has been well documented that radical cations of aromatic compounds in HFIP are highly persistent.[97] Another single electron oxidation of *p*-methoxyphenol at the anode generates phenoxyl radical which then undergoes direct radical–radical cross-coupling to form *N*-acyl iminium ion. Following intramolecular cyclisation and deprotonation, product **189** is generated along with hydrogen gas. The remarkable chemoselectivity of this reaction is noteworthy, as oxidative heterocouplings that yield exclusively the cross-coupled products are rare.

3.4 Project Design: Synthesis of Atropisomeric Indoles *via* Oxidative Cross-Coupling

In the quest for developing a new method for constructing atropisomeric indoles, we realised that our targets of interest showed a striking resemblance to the benzofuroindoline cores that have been exhaustively prepared through different oxidative cross-coupling protocols. As previously outlined, compounds of type **190** is generally furnished *via* C–C bond formation between the C-2 position of the indole and the C-2 position of the phenol, followed by intramolecular [3+2] annulation (**Scheme 3.18**).



Scheme 3.18: Synthesis of atropisomeric indoles via oxidative cross-coupling

We reasoned that if the steric bulk of the phenol and (in particular) the indole fragments were increased, the rate of rearomatisation of the oxidised intermediate could exceed the rate of annulation in the overall process to generate the corresponding heterobiaryl atropisomer **191**.

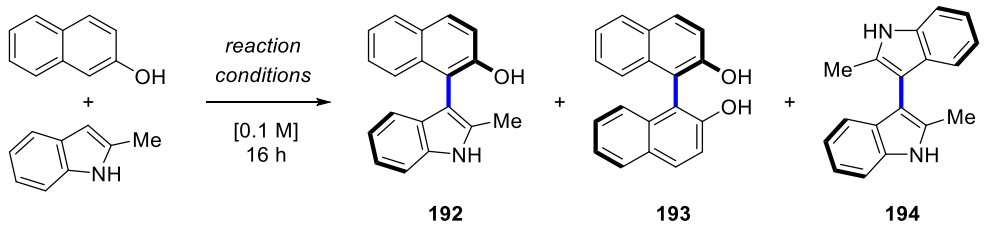
Given the attention that the benzofuroindolines have received, we were astonished to learn that this hypothesis had not been tested.

Chapter 4: Proof of Concept & Mechanistic Hypothesis

4.1 Proof of Concept

We began by probing a range of oxidation conditions for the reaction between a 1:1.1 mixture of 2-naphthol and 2-methylindole (**Table 4.1**). We hoped to find a method for preparing heterobiaryl **192** whilst avoiding the production of the homocoupling products: BINOL **193** and 3,3'-bisindole **194**. In a preliminary screen of methods, we found that hypervalent iodine reagents [as used by Danishiefsky[91] (Entry 1), Kita[98] (Entry 2) and Harran[93] (Entry 3)] were poorly selective for the desired heterocoupling process. In these reactions, **192** was obtained in low yields, and with low isolated purity due to the formation of a mixture of other over-oxidation by-products.

Table 4.1: Study of various oxidative cross-coupling protocols for synthesis of **192**



192 **193** **194**

Entry	Reaction Conditions	192[a]	193[a]	194[a]
1	PIFA (1.1 equiv.), MeCN, rt	14%	<5%	0%
2	PIDA (1.1 equiv.), $BF_3{\cdot}Et_2O$ (1.1 equiv.), CH_2Cl_2, rt	<5%	<5%	0%
3	PIDA (1.1 equiv.), LiOAc (2.0 equiv.), TFE, 0 °C	<5%	<5%	0%
4	VOF_3 (1.1 equiv.), TFA (1.1 equiv.), CH_2Cl_2, 0 °C to rt	10%	0%	0%
5	Cu(OH)Cl [TMEDA] (10 mol%), MeOH, air, 60 °C	0%	61%	0%
6	$FeCl_3$ (10 mol%), DTBP (1.2 equiv.), HFIP / DCE, rt	96%	0%	0%

Reaction Conditions: [a] Isolated yield.

Next, we tried Kupchan's conditions for arene-arene oxidative cross-coupling using VOF_3 and TFA (**Table 4.1,** Entry 4).[99] Promisingly, this afforded **192** as the sole product, but in a low yield of 10%. In contrast, the aerobic Cu(OH)Cl[TMEDA] catalytic system developed by Nakajima[79] gave

highly chemoselective formation of BINOL as the undesired homocoupling product, albeit in a good yield of 61% (**Table 4.1,** Entry 5). Finally, we tested Pappo's catalytic $FeCl_3$/DTBP system in 1:1 HFIP/DCE.[100] We were delighted to find that under these conditions, the desired heterobiaryl product **192** was obtained in 96% yield, as a single C-3 aryl regioisomer, and with no detectable homocoupling of either **193** or **194** (**Table 4.1,** Entry 6). Although we were spurred by this result, given the lessons gleaned from our previous work, we expected **192** to have a low barrier to rotation. To measure the barrier, the enantiomers of **192** were separated by semi-preparative HPLC and thermal erosion of the enantioenriched product was monitored over 60 minutes at 80 °C in hexan-1-ol (**Figure 4.2**). Over this time, the enantiomeric excess of the sample dropped rapidly from 92% to 0%. We thus determined that **192** had a rotational barrier of 26.0 kcal mol^{-1}, which corresponds to a half-life to racemisation of 7.4 days at 298 K. This makes **192** a class 2 atropisomer, and as such, is largely unsuitable for downstream practical applications.

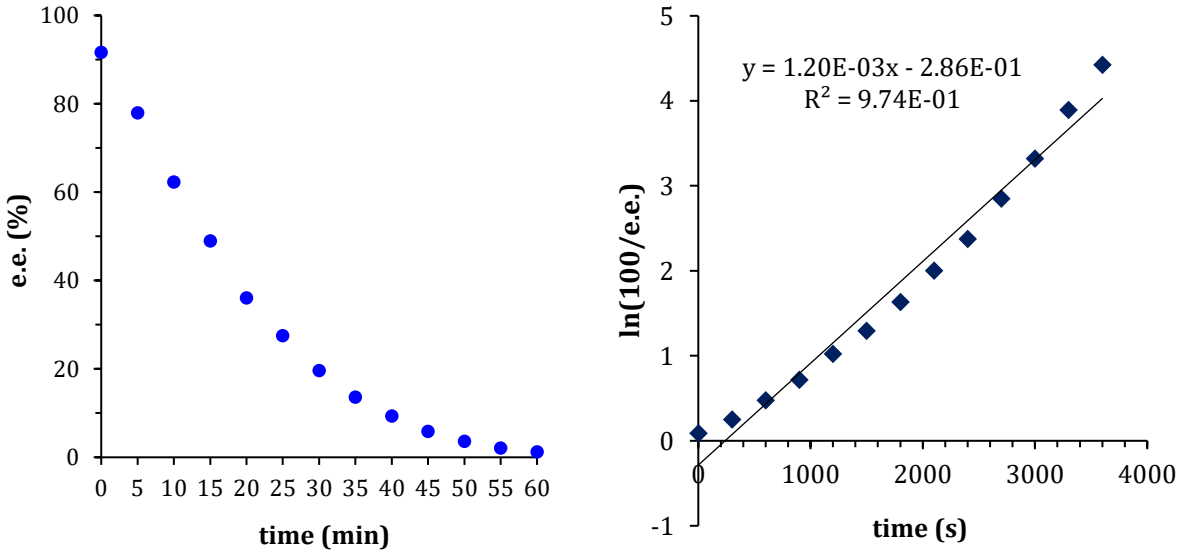
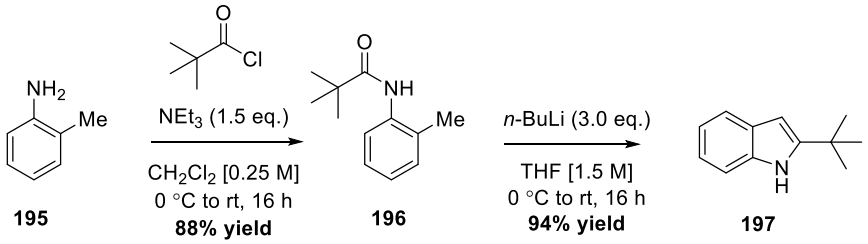


Figure 4.2: Thermal erosion of **192** at 80 °C over time (left); First order kinetic plot (right)

4.2 Optimisation of Racemic Reaction Conditions

We reasoned that a larger substituent would be required at the C-2 position of the indole in order to prevent racemisation of the products *via* bond rotation. To this end, 2-*tert*-butylindole **197** was

prepared in 2 steps from *o*-toluidine **195** using a known procedure.[101] Amidation of **195** with pivaloyl chloride gave anilide **196** in 88% yield, which was followed by Madelung cyclisation with *n*-BuLi to yield indole **197** in near quantitative yield.

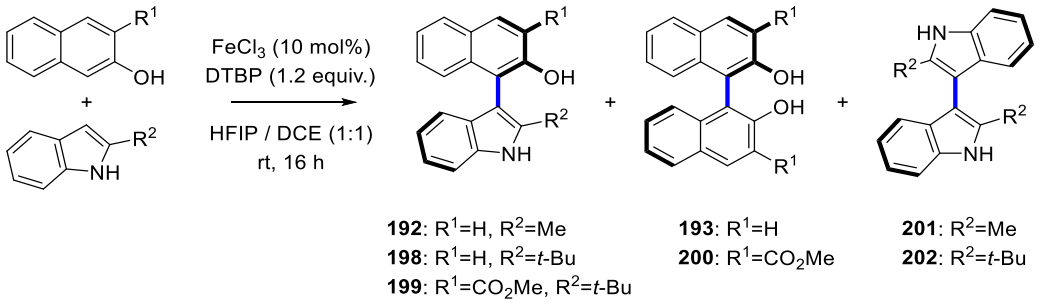


Scheme 4.3: Synthesis of 2-*tert*-butylindole **197** via Madelung cyclisation

With indole **197** in hand, we tested its compatibility in the oxidative cross-coupling under Pappo's conditions (**Table 4.4**). We were thrilled to find that this heterocoupling reaction was tolerant of the extreme steric bulk of the substrate, to yield heterobiaryl **198** in 39%. However, in this case we also found that dimerization of 2-naphthol became competitive as the steric bulk on the indole was increased, giving BINOL in 49% yield (**Table 4.4**, Entry 2). To combat this chemoselectivity issue, we added a large excess of the indole (5 equiv.) to the reaction mixture (**Table 4.4**, Entry 3). In this case, the chemoselectivity ratio was improved from 5:6 to 8:5 of **198**:**193** in favour of the heterobiaryl product. However, the use of such a large excess of **197** was highly inefficient. We therefore reasoned that as the homocoupling of 2-naphthol was an issue, the slow addition of this component into a concentrated pool of the indole should favour the heterocoupling process. This was indeed the case and resulted in almost complete suppression of the BINOL product, giving **198** in 85% yield (**Table 4.4**, Entry 4). Although this approach proved successful in furnishing **198** in good levels of chemoselectivity, the practical issues with syringe pump addition make this process fairly unattractive. We then decided to invoke the strategy put forward by Hovorka[77] and Kočovský,[78] where installation of an electron withdrawing group onto one of the reacting partners serves to modulate its redox potential, enabling highly selective oxidation of the other component. In a "one-pot" procedure, 3-carbomethoxy-2-naphthol **203** was cross-

coupled with 1.1 equiv. of **197** to give **199** in 89% yield, with perfect levels of regio- and chemoselectivity (**Table 4.4**, Entry 5).

Table 4.4: Study of Substituent Effects on Oxidative-Cross Coupling



192: R^1=H, R^2=Me
198: R^1=H, R^2=*t*-Bu
199: R^1=CO_2Me, R^2=*t*-Bu

193: R^1=H
200: R^1=CO_2Me

201: R^2=Me
202: R^2=*t*-Bu

Entry	R_1	R_2	Heterobiaryl[a]	BINOL[a]	3,3'-Bisindole[a]	Molar Ratio[e]
1	H	Me	**192** (96%)	**193** (0%)	**201** (0%)	>50:1:N.D.
2	H	*t*-Bu	**198** (39%)	**193** (48%)	**201** (0%)	5:6: N.D.
3[b]	H	*t*-Bu	**198** (61%)	**193** (38%)	**201** (0%)	8:5: N.D.
4[c]	H	*t*-Bu	**198** (85%)	**193** (6%)	**201** (0%)	14:1: N.D.
5[d]	CO_2Me	*t*-Bu	**199** (89%)	**200** (0%)	**202** (0%)	>50:1:N.D.

Reaction Conditions: N.D. = not detected. [a] Product shown in numerals, isolated yield shown in parenthesis. [b] 2-*tert*-butylindole in excess (5.0 equiv.); [c] 2-naphthol (1.0 equiv.) in DCE added slowly *via* syringe pump to a solution of 2-*tert*-butylindole (1.1 equiv.), $FeCl_3$ (0.1 equiv.) and DTBP (1.2 equiv.) in HFIP; [d] One-pot procedure. [e] Molar ratio of [Heterobiaryl:BINOL:3,3'-bisindole] products shown in square brackets.

We then measured the rotational barrier of the 2-*tert*-butyl substituted heterobiaryl products. For simplicity reasons, the C-3 unsubstituted product **198** was studied. The enantiomers of **198** were separated by semi-preparative HPLC using a chiral stationary phase. The enantioenriched sample was incubated at 140 °C in hexan-1-ol over a period of 14 days (**Figure 4.5**). During this period, the enantiomeric excess fell slowly from 99.5% to 87.5%. This corresponds to a rotational barrier of 38.3 kcal mol^{-1}, which essentially precludes racemisation at room temperature, with a $t_{1/2}$(rac) of 21.9 million years at 298 K. We were extremely excited about these results; not only is this reaction tolerant of the extreme steric demands of the substrates, but it also provides highly conformationally stable atropisomeric heterobiaryl products in near perfect levels of regio- and

chemoselectivity in one-pot, and without the need for large excesses of either coupling partner. It should be noted that oxidative cross-coupling reactions that achieve these levels of selectivity are extremely rare.[74] Furthermore, we also envisaged that the ester substituent of the naphthol in **199** could serve as a useful handle for the derivitization of the products and provide access to a range of useful heterobiaryl architectures.

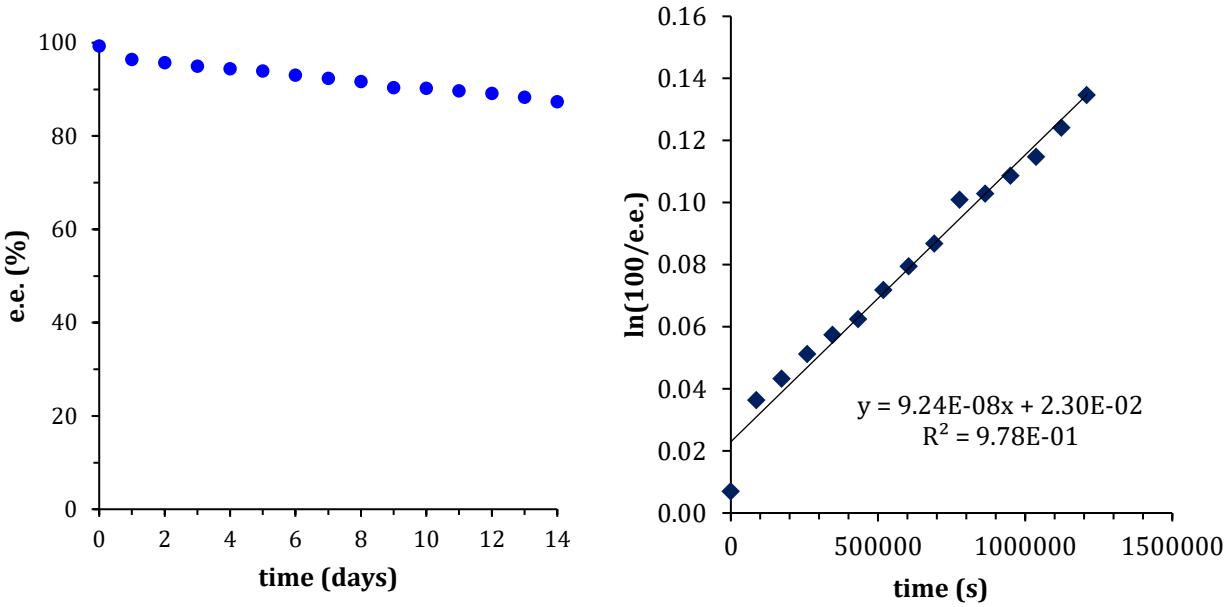


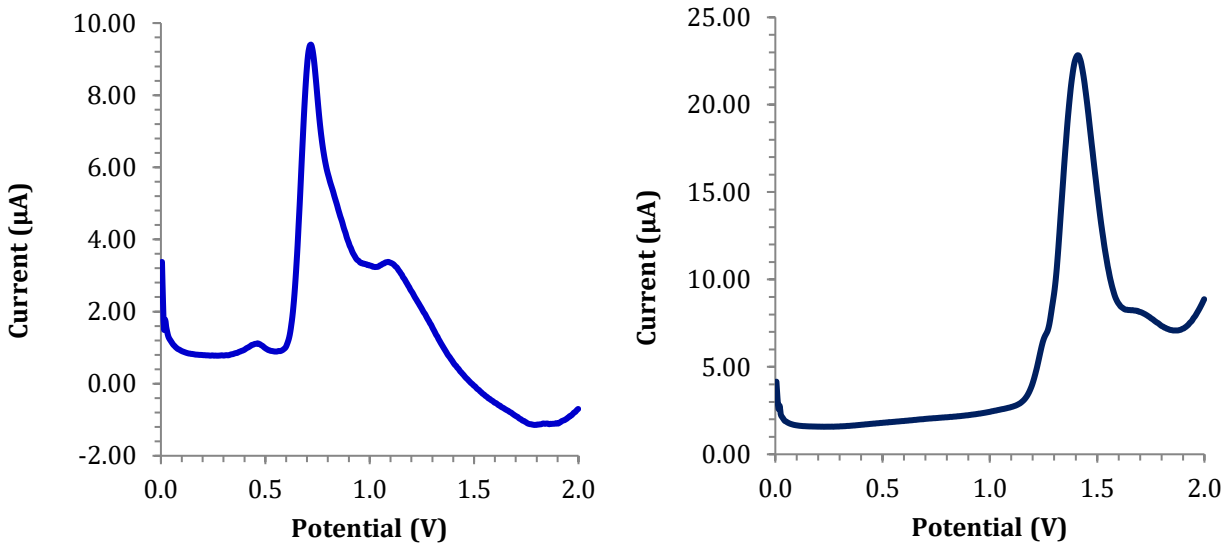
Figure 4.5: Thermal erosion of **198** at 140 °C over time (left); First order kinetic plot (right)

4.3 Mechanistic Hypothesis

As previously outlined (section **3.4**), oxidative cross-coupling should be favoured if there is a significantly large difference in oxidation potential (ΔE_{ox}) and global nucleophilicity (ΔN) between the two reacting partners. At this stage, we deemed it necessary to measure the E_{ox} and *N* values of the indole and naphthoate components to gain preliminary insights into the reaction mechanism.

We measured the oxidation potentials of the indole **197** (0.71 V vs. Ag/AgCl) and 3-carbomethoxy-2-naphthol **203** (1.42 V vs. Ag/AgCl) in HFIP by Square-Wave voltammetry. The global nucleophilicities, *N*, were calculated computationally (by Mihai Popescu) using B3LYP at 6-311+G(d,p) level of theory. The energy of the highest occupied molecular orbital (HOMO) was

referenced against the HOMO energy of tetracyanoethylene (TCE). This provided us with *N* values for the indole **197** (*N* = 3.27 eV) and the naphthol **203** (*N* = 2.93 eV). The value for the naked naphtholate anion (*N* = 4.28 eV) was also determined.

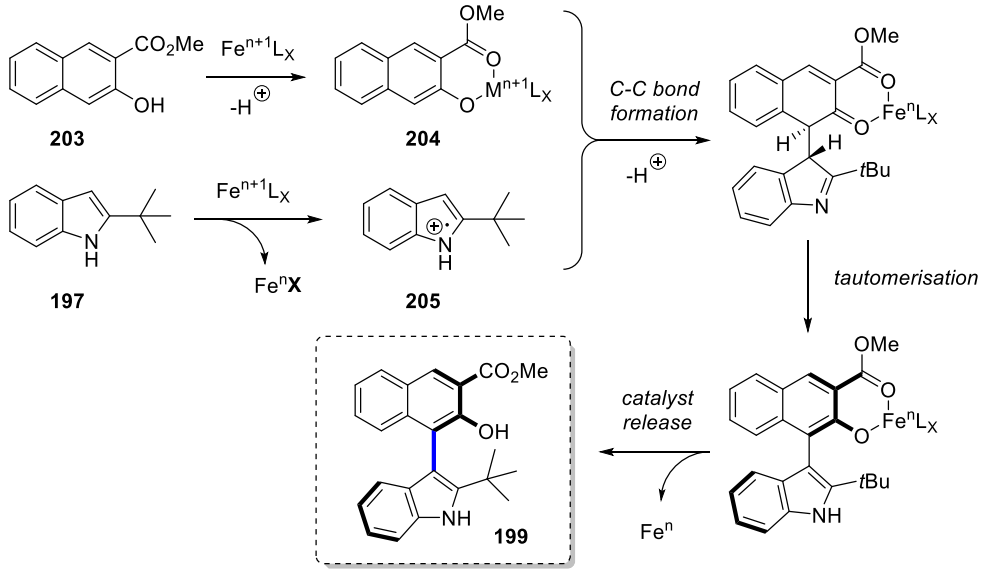


Scheme 4.6: Oxidation potentials of indole **197** (left) and naphthol **203** (right)

Based on these measurements, and the excellent levels of chemoselectivity observed in the synthesis of atropisomeric indole **197**, the following mechanistic hypothesis was proposed (**Scheme 4.7**). In HFIP, the indole is clearly significantly easier to oxidise than the naphthol partner. Therefore, in the presence of the oxidising iron species, we tentatively suggested that selective single electron oxidation of indole component occurs to generate an indole radical cation **205**. As the naphthol is the most acidic component, we proposed that this coupling partner forms an iron phenolate complex **204** following loss of a proton.[102] Furthermore, the 3-ester substituent can also potentially enable the naphthol to act as a bidentate ligand, increasing the strength of metal binding. Our global nucleophilicity measurements show that the naked naphtholate anion is more nucleophilic than the indole (although the accuracy of these calculations for the anionic species is questionable).

Given selective oxidation of the indole, and selective binding of the naphthol, we invoked an outer-sphere radical–anion type coupling mechanism to explain the high levels of cross-coupling

selectivity. Following C–C bond formation, rearomatisation of the phenol and the naphthol leads to the metal bound heterobiaryl, which finally undergoes ligand exchange to release the iron catalyst and give the desired product.



Scheme 4.7: Mechanistic hypothesis: Radical–anion coupling

4.4 Metal and Ligand Effects on the Oxidative-Cross Coupling

Having swiftly identified a system for efficiently preparing racemic **199** *via* an oxidative cross-coupling, we turned our sights towards the discovery of a chiral ligand that could render this process enantioselective. Although Katsuki[85] and Pappo[103] have demonstrated the enantioselective synthesis of C_1-symmetric BINOLs *via* Fe(III)-catalysed protocols, examples of this chemistry are extremely rare. At this stage, we had limited mechanistic understanding of the reaction, so it was unclear how the chemoselectivity of the reaction could be influenced by the addition of different ligand architectures. We hypothesised that a host of factors such as the metal catalyst, denticity of the ligand, nature of the donor atoms and coordination geometry all had the potential to alter the reaction mechanism and thus, the observed chemoselectivity. Despite our previous success in implementing Pappo's $FeCl_3$/DTBP system, we elected not to limit our initial study of ligands architectures with only Fe(III) salts. As $VOCl_3$, $MnCl_2{\cdot}4H_2O$ and CuCl have all

previously been implemented in oxidative coupling reactions, a broader screen of conditions was thought to give us the best chance for success for the enantioselective campaign (**Figure 4.8**).

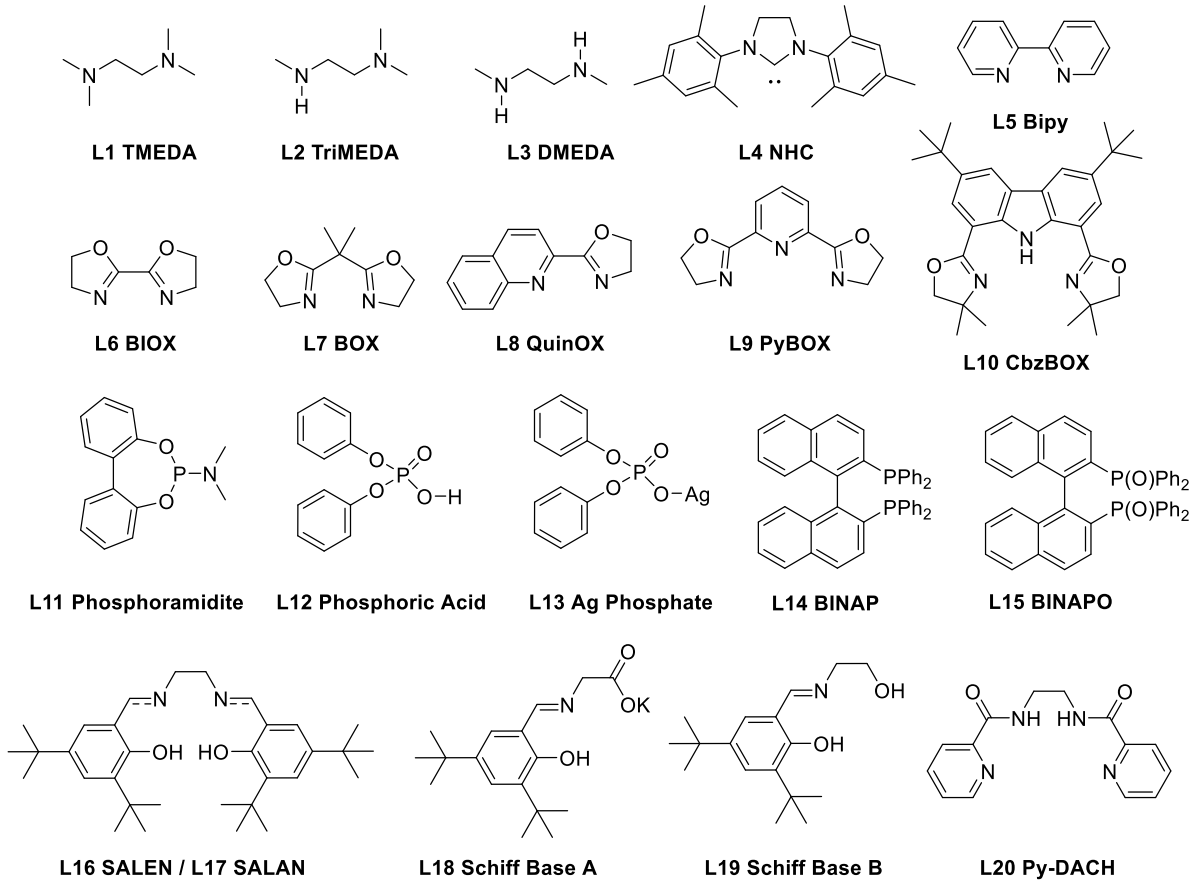
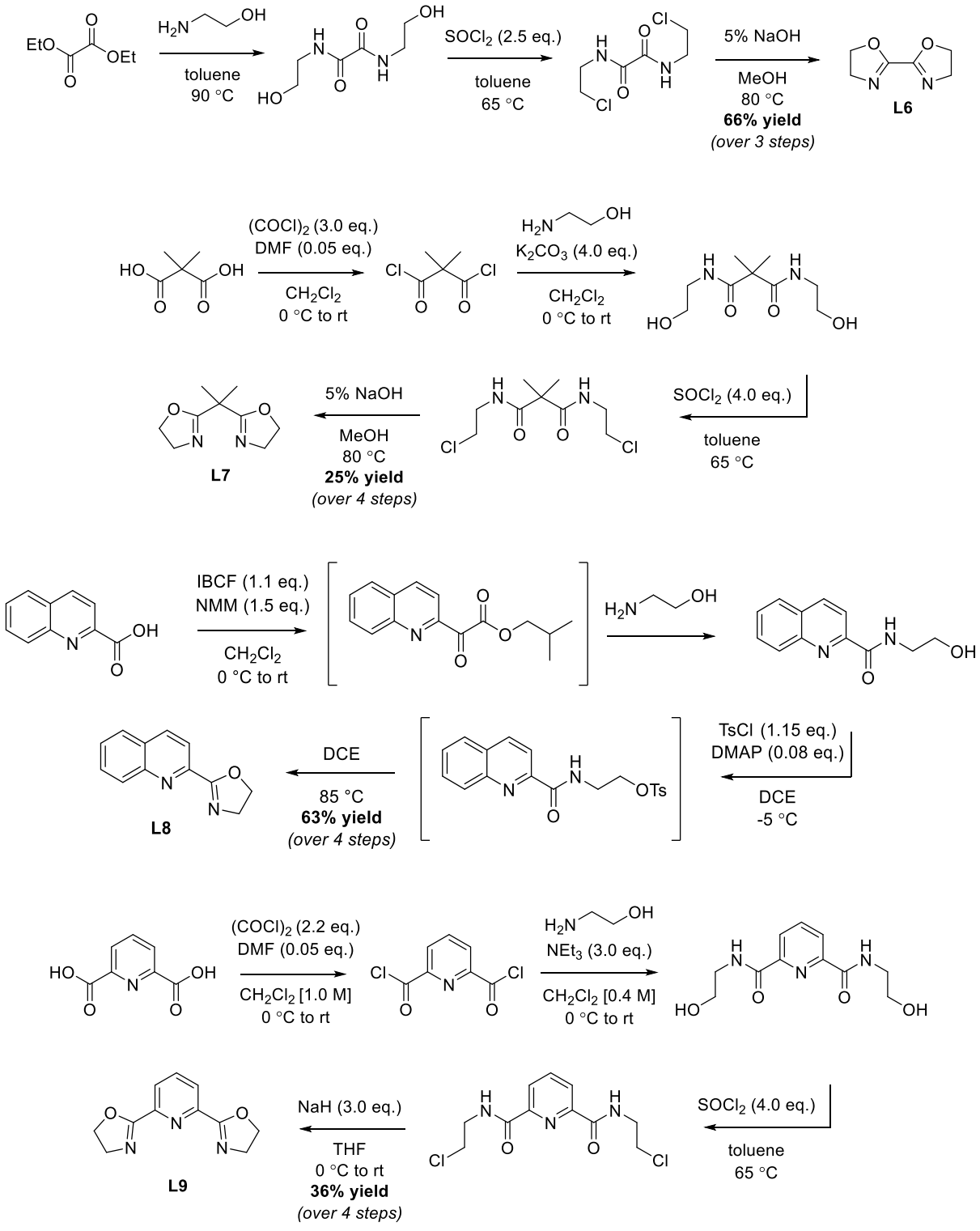


Figure 4.8: Achiral ligand manifolds studied in combination with metal salts

4.5 Synthesis of Achiral Ligands

Consequently, a range of 20 different ligand manifolds were selected to be used in conjunction with these metal salts in the oxidative heterocoupling reaction. For simplicity, achiral ligand manifolds were also chosen as we hoped to initially select for highly active and heteroselective metal-ligand combinations. As this was a new area of research for our group, the *de novo* synthesis of this library was required. Ligands **L1-5** and **L11-15** were either commercially available or had been prepared by previous members of the group.

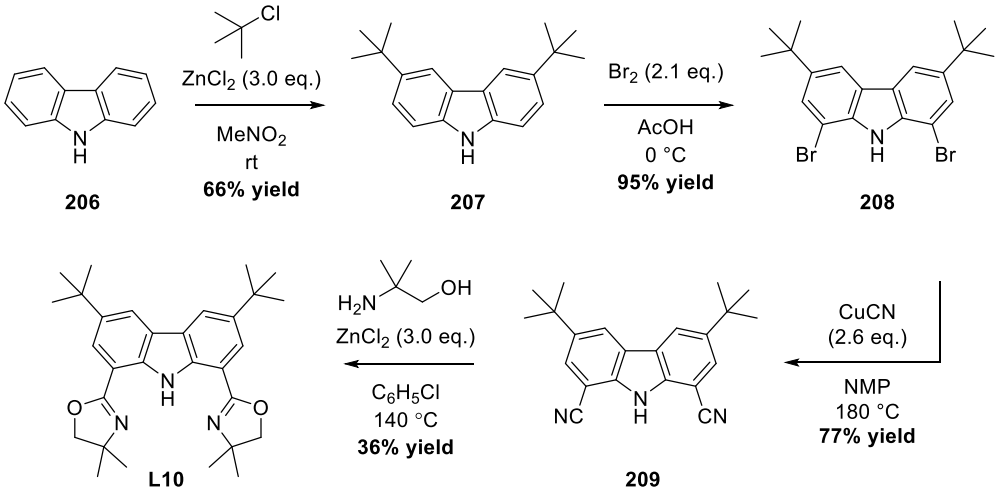


Scheme 4.9: Synthesis of the oxazoline family of ligands

Starting with the synthesis of the oxazoline family, BIOX **L6**, BOX **L7**, QuinOX **L8** and PyBOX **L9** were prepared *via* similar multistep sequences. These collectively began with the construction of a key bisamide intermediate *via* amide coupling of the selected carbonyl compound with

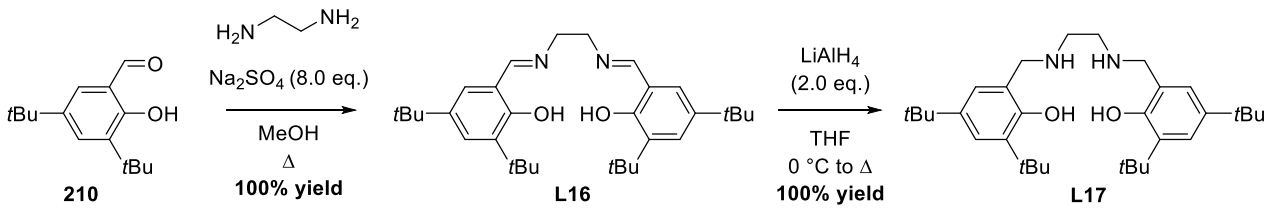
ethanolamine, which was followed by chlorination (or tosylation in the case of **L8**) of the pendant alcohols. Finally, intramolecular *O*-alkylation of the amides *via* a 5-*exo*-*tet* cyclisation afforded the oxazoline ligand products in reasonable yields (**Scheme 4.9**).

Next, the synthesis of CbzBOX **L10** was targeted. In the first step, carbazole **206** underwent double Friedel-Crafts alkylation with *tert*-butyl chloride and $ZnCl_2$ at the C-3 and C-6 positions of the carbazole backbone to give **207** in 66% yield. Subsequent electrophilic dibromination of **207** in acetic acid at the C-1 and C-8 positions afforded product **208** in 95% yield. This substrate then underwent Rosenmund-von Braun cyanation in *N*-methylpyrrolidone at high temperatures to give a 77% yield of the key intermediate **209**. The final product was furnished by the reaction of **209** with the substituted amino alcohol in the presence of $ZnCl_2$ in a yield of 36%.



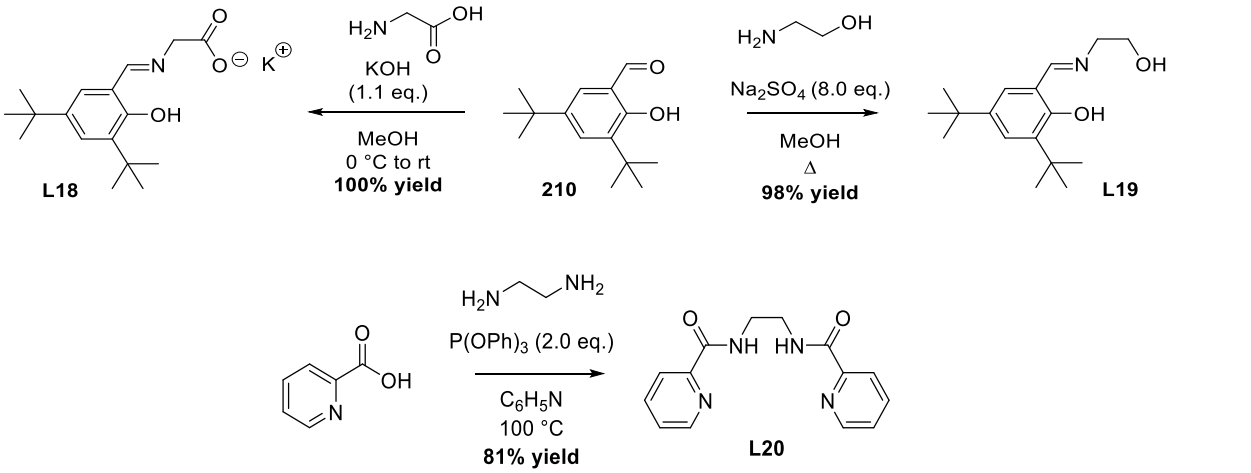
Scheme 4.10: Synthesis of CbzBOX **L10**

Having obtained the final family member of the oxazolines, we moved onto the SALEN and SALAN ligands. Condensation of ethylenediamine with **210** in the presence of Na_2SO_4 as the drying agent gave the tetradentate SALEN ligand **L16** in quantitative yield. A portion of this product was then reduced with $LiAlH_4$ to give the corresponding SALAN derivative **L17**, also in excellent yield.



Scheme 4.11: Synthesis of the SALEN **L16** and SALAN **L17**

Next, a duo of Schiff base ligands was prepared. **L18** was furnished from the condensation of ethanolamine with **210** in 98% yield. Similarly, the tridentate ligand **L19** was synthesised *via* the condensation of glycine with **210** under basic conditions to yield the potassium salt as the final product. Last but not least, Py-DACH **L20** was synthesised from 2-picolinic acid and ethylenediamine in 81% yield, utilising triphenyl phosphite to mediate the amide couplings (**Scheme 4.12**).



Scheme 4.12: Synthesis of the Schiff Base A **L18**, Schiff base B **L19** and Py-DACH **L20**

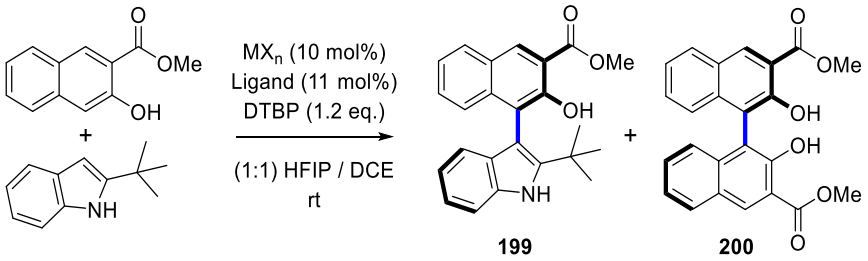
4.6 Evaluation of Metal Salt and Ligand Combinations

With this library of ligands at our disposal, we set out to test the activity and selectivity of **L1-20** in conjunction with each of the four different metal salts within the described heterocoupling reaction. The ligands were pre-stirred with the metal salt in DCE for 30 minutes at room temperature, prior to the addition of the substrates and oxidant in HFIP. We evaluated the performance of each combination in this 1:1 solvent mixture as we suspected that HFIP played a

crucial role in increasing the lifetime of the radical species generated through SET. The results are summarised in **Table 4.13**, and also in **Figures 4.14** to **4.17** for clarity. For the oxovanadium (V) complexes, the indole heterobiaryl products **199** were produced in a highly chemoselective fashion, however, the yields failed to breach a maximum of 25% of the desired product. Due to the high hydrolytic susceptibility of the $VOCl_3$ pre-cursor, we questioned whether hydrolysis was occurring during the reaction to generate vanadic acid, which could then go on to protonate the substrates and impede further oxidation. Contrastingly, the $MnCl_2 \cdot 4H_2O$ catalysed reactions gave exclusively the BINOL derived product **200**, but in extremely poor yields of 17% or lower. Since only 10 mol% of catalyst was used, we tentatively suggested that the catalyst was only able to perform a single turnover and was largely incapable of being re-oxidised to the active form under these conditions. For the $FeCl_3$ catalysed reactions, we were aware that a strong background reaction from unligated Fe(III) salts was possible. Being wary of the prospect of false positives, we found that the $FeCl_3$ complexes provided consistently good yields of exclusively the cross-coupled products across the board of ligands tested. In particular, the oxazoline family (**L6**-**L9**) outperformed the other ligand classes, giving **199** in yields of 45-90%. Additionally, whilst the Fe(III)-SALEN complex was completely inactive, the corresponding SALAN catalyst gave the heterobiaryl product in a promising 67% yield. Finally, the CuCl complexes were examined. With all ligands, the Cu(I)-complexes were extremely selective for the formation of the undesired BINOL homocoupling by-product, with good yields of up to 71% being obtained, with the copper amine (**L1**-**L3**) and oxazoline (**L6**-**L9**) complexes being particularly proficient at this transformation.

From this study, we found that the innate chemoselectivity of this process is governed primarily by the nature of the metal salt and is largely independent of the choice of ligand. The contrasting selectivities of the metal salts also highlight that different mechanisms are in operation between the catalytic species. Clearly, the Fe(III)-complexes formed *in situ* were the most promising candidates for the development of an enantioselective variant of this reaction.

Table 4.13: Study of metal salt and ligand combinations in oxidative cross-coupling



Entry	Ligand	$VOCl_3$		$MnCl_2{\cdot}4H_2O$		$FeCl_3$		CuCl	
		199 [a]	**200** [a]	**199** [a]	**200** [a]	**199** [a]	**200** [a]	**199** [a]	**200** [a]
1	L1	8%	-	-	6%	26%	-	-	61%
2	L2	3%	-	-	5%	32%	-	-	45%
3	L3	10%	-	N.R.	N.R.	28%	-	-	35%
4	L4	Trace	-	-	trace	50%	-	-	40%
5	L5	5%	-	-	4%	73%	-	-	45%
6	L6	22%	-	-	trace	81%	-	-	46%
7	L7	13%	-	-	17%	45%	-	-	71%
8	L8	5%	-	-	5%	90%	-	-	66%
9	L9	10%	-	-	14%	71%	-	N.R.	N.R.
10	L10	12%	-	-	3%	N.R.	N.R.	-	12%
11	L11	5%	-	-	8%	12%	-	-	24%
12	L12	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.
13	L13	25%	-	-	11%	28%	-	-	24%
14	L14	Trace	-	-	5%	12%	-	-	36%
15	L15	8%	-	N.R.	N.R.	45%	-	-	21%
16	L16	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.
17	L17	N.R.	N.R.	-	7%	67%	-	-	4%
18	L18	9%	-	N.R.	N.R.	38%	-	N.R.	N.R.
19	L19	N.R.	N.R.	N.R.	N.R.	20%	-	N.R.	N.R.
20	L20	trace	-	N.R.	N.R.	21%	-	N.R.	N.R.

Reaction Conditions: Metal Salt (0.1 equiv.), DCE, 30 min; then HFIP, naphthol **203** (1.0 equiv. mmol), indole **197** (1.1 equiv.), DTBP (1.2 equiv.), room temperature, 16 h. [a]Calculated by crude quantitative ^1H NMR analysis using anisole as an internal standard. N.R. = no reaction.

Figure 4.14: Yield of **199** using $VOCl_3$ with Ligands **L1-20**

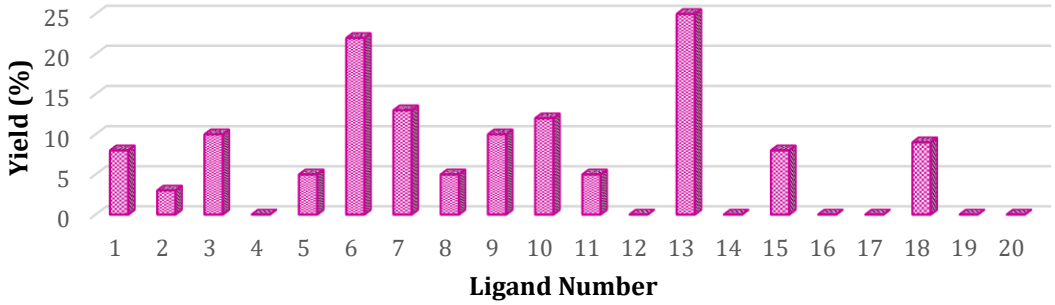


Figure 4.15: Yield of **200** using $MnCl_2$ with Ligands **L1-20**

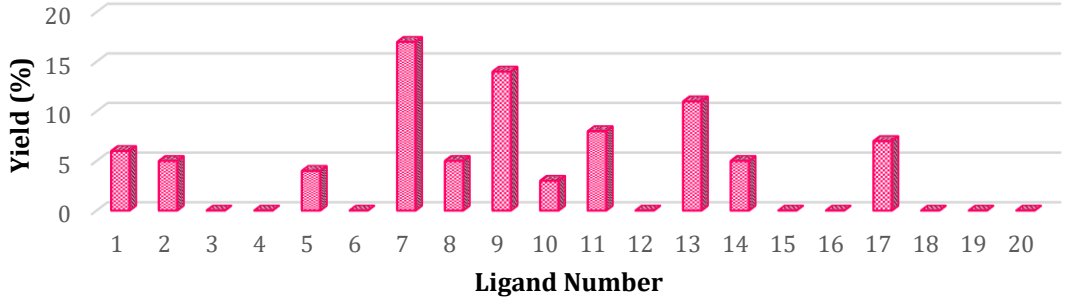


Figure 4.16: Yield of **199** using $FeCl_3$ with Ligands **L1-20**

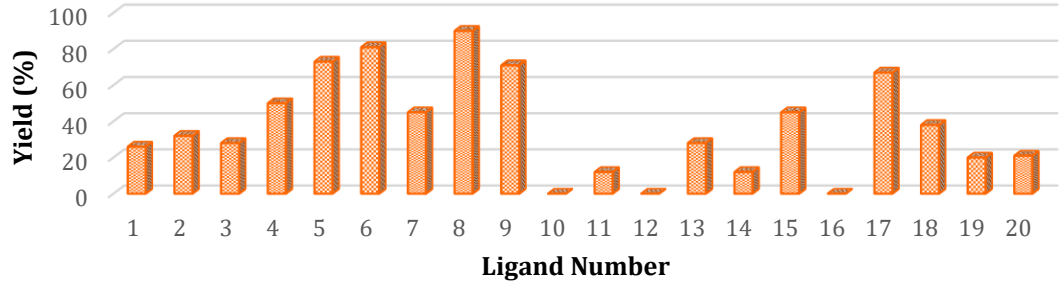
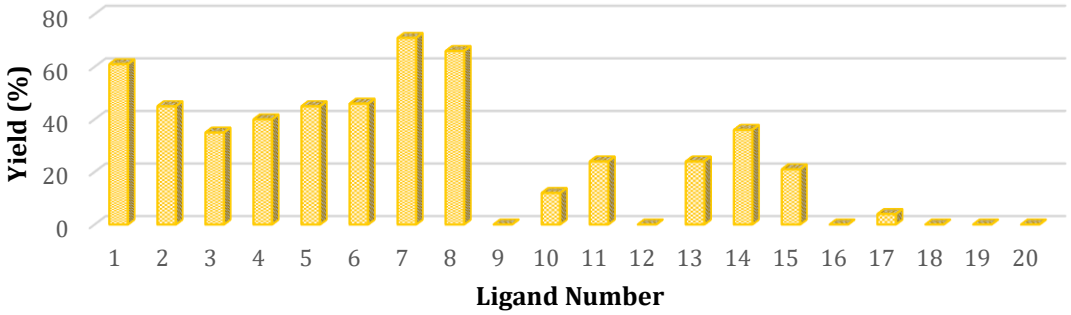


Figure 4.17: Yield of **200** using CuCl with Ligands **L1-20**



Chapter 5: Optimisation of Enantioselective Reaction Conditions

5.1 Synthesis of Chiral Oxazolines and other Miscellaneous Ligands

The oxazolines have emerged as a prominent family of chiral ligands for enantioselective reactions catalysed by transition metals, and their use in conjunction with iron salts is gaining increasing attention.[104] In chapter 4, we achieved promising yields of **199** in excellent levels of chemoselectivity when oxazoline ligands **L6**-**9** were used in combination with $FeCl_3$ (Section **4.6**). Therefore, we decided to focus on this family of molecules in our search for enantioselectivity. To bolster our 'in-house' ligand library, the synthesis of a range of these oxazolines was required. The number represents the parent ligand manifold, and the following letter signifies the oxazoline unit present, and is presented as **Figure 5.1**.

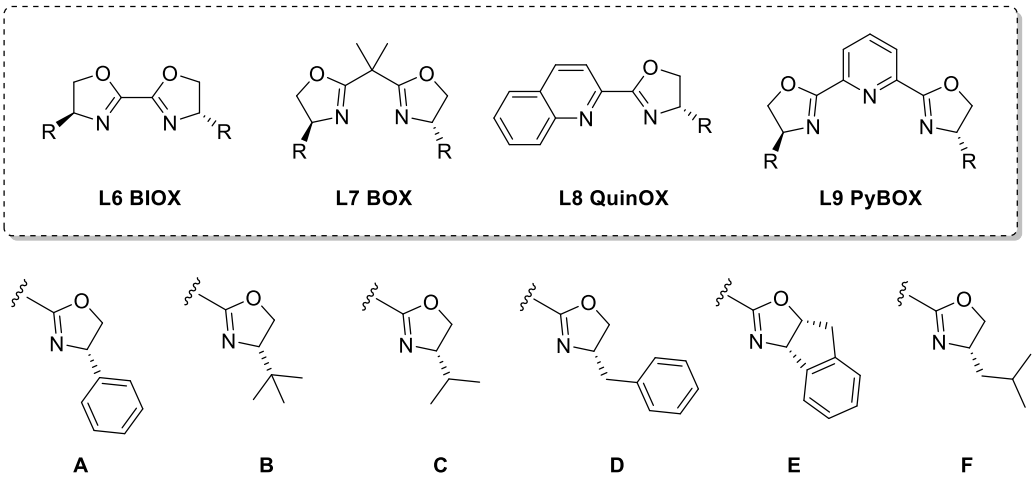
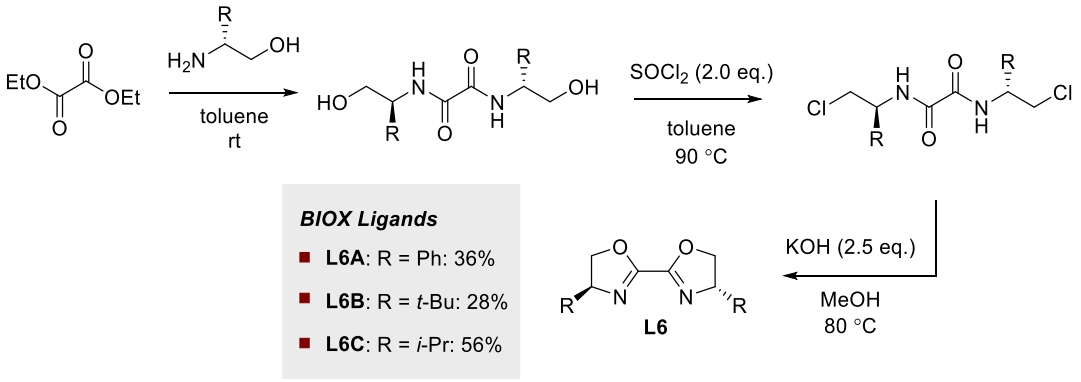


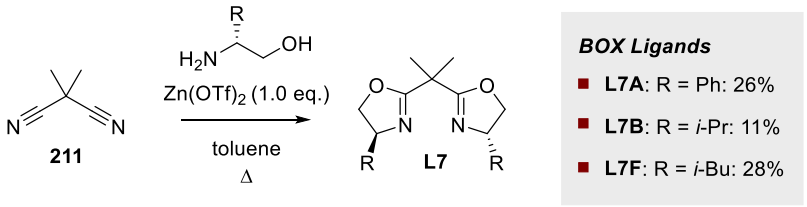
Figure 5.1: Oxazoline ligands targeted

We began by preparing the BIOX class of ligands in a similar fashion to that previously outlined in Section **4.5** (**Scheme 4.9**). Diethyl oxalate was mixed with the chosen chiral-pool amino alcohols and stirring in toluene at ambient temperature gave the corresponding bisamide products. Telescoping this material through to the next step, chlorination of the pendant alcohols was achieved using $SOCl_2$. Finally, base mediate cyclisation furnished the C_2-symmetric BIOX ligands **L6** in yields of 28% to 56% over these 3-steps (**Scheme 5.2**).[105]



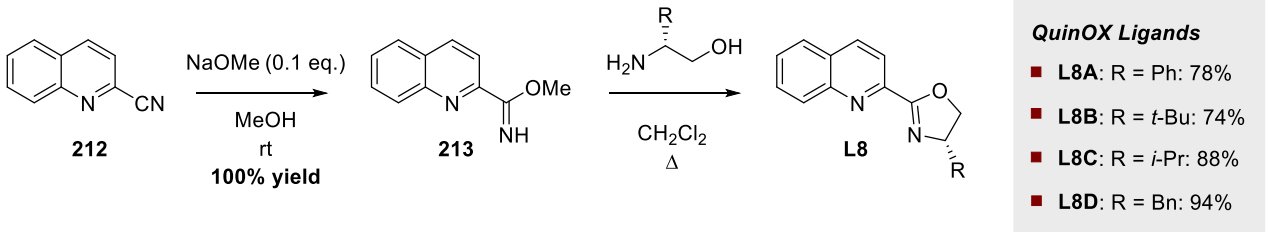
Scheme 5.2: Synthesis of the C_2-symmetric BIOX **L6** series

For the C_2-symmetric BOX ligands, a more direct strategy was brought into play. In a one-step procedure, dimethylmalononitrile **211** was mixed with two equivalents of the chosen amino alcohol and $Zn(OTf)_2$ in refluxing toluene for 2-3 days.[106] Reasonably poor yields of the bis(oxazolines) were isolated; still, this method was effective in generating sufficient quantities of the products for screening purposes (**Scheme 5.3**).



Scheme 5.3: Synthesis of the C_2-symmetric BOX **L7** series

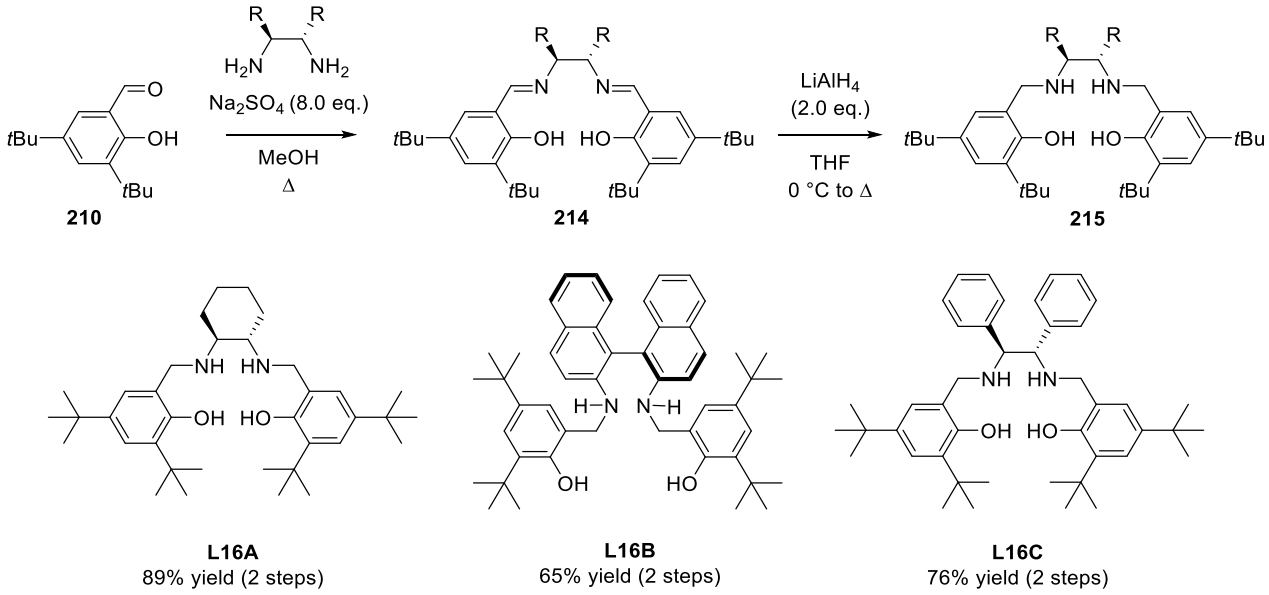
Similarly, an abbreviated synthesis was selected for the preparation of QuinOX ligands **L8** (**Scheme 5.4**). Quinoline-2-carbonitrile **212** was converted into carbimidate **213** through base catalysed 1,2-addition of methanol to the cyano group in quantitative yield.[107] Subsequent condensation of the amino alcohols with **213** gave QuinOX ligands **L8** in excellent isolated yields.



Scheme 5.4: Synthesis of QuinOX **L8** series

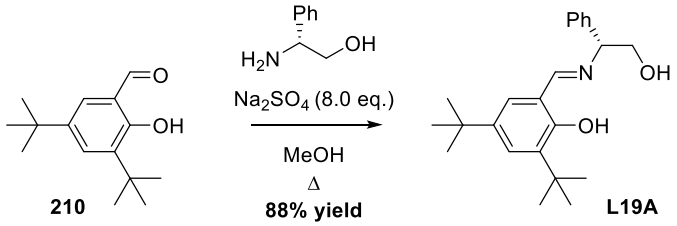
A variety of C_2-symmetric PyBOX ligands had already been prepared by a previous member of the group, so their synthesis was not necessary.

To maximise our chances of success in developing an enantioselective variant of the heterobiaryl cross-coupling, a range of other chiral ligands were identified for testing. From section **4.6**, SALAN ligands emerged as a promising scaffold for promoting the heterocoupling process.[108] Three different SALAN ligands were prepared from 3,5-di-*tert*-butylsalicylaldehyde **210** *via* condensation with a chiral diamine backbone, followed by reduction of the imines with $LiAlH_4$. SALAN ligands **L16A-C** were prepared in 65-89% yield over these two steps (**Scheme 5.5**).



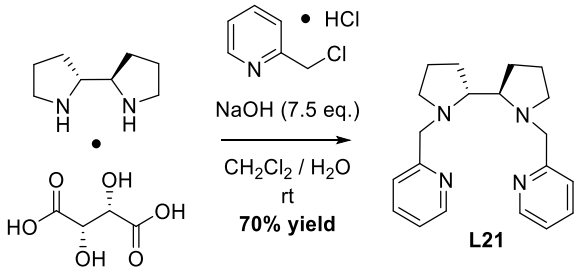
Scheme 5.5: Synthesis of chiral SALAN ligands

Additionally, we constructed a chiral variant of the tridentate Schiff base **L19** *via* a condensation of (*R*)-phenylglycinol with aldehyde **210** (**Scheme 5.6**).



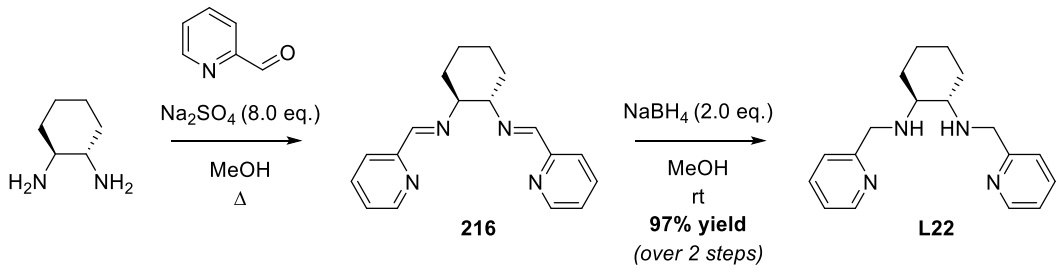
Scheme 5.6: Synthesis of **L19A**

Next, we targeted the White-Chen ligand **L21** that was initially developed for the task of iron catalysed aliphatic C–H oxidations in the presence of hydrogen peroxide and acetic acid.[109] The tartrate salt of the chiral bipyrrolidine was mixed with two equivalents of the hydrochloride salt of 2-picolyl chloride in a 1:1 mixture of CH_2Cl_2 / H_2O. On the addition of excess NaOH, free basing of the amine was accomplished, which was followed by double *N*-alkylation to give **L21** in 70% yield (**Scheme 5.7**).



Scheme 5.7: Synthesis of White-Chen ligand **L21**

The N_2Py_2 ligand platform has been thoroughly investigated as a Rieske dioxygenase mimetic, and has shown proficiency in the iron catalysed enantioselective oxidation of alkenes.[110]

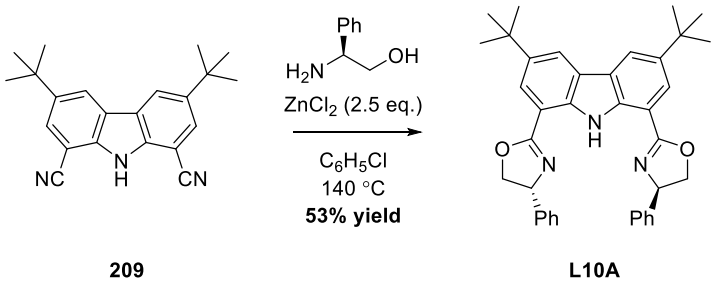


Scheme 5.8: Synthesis of BPMEN ligand **L22**

BPMEN ligand **L22** was prepared simply in two steps, involving condensation of (1*S*,2*S*)-(+)-1,2-diaminocyclohexane with two equivalents of 2-pyridinecarboxaldehyde. Reduction of the chiral diimine **216** furnished **L22** in near quantitative yield (97%) over the two steps (**Scheme 5.8**).

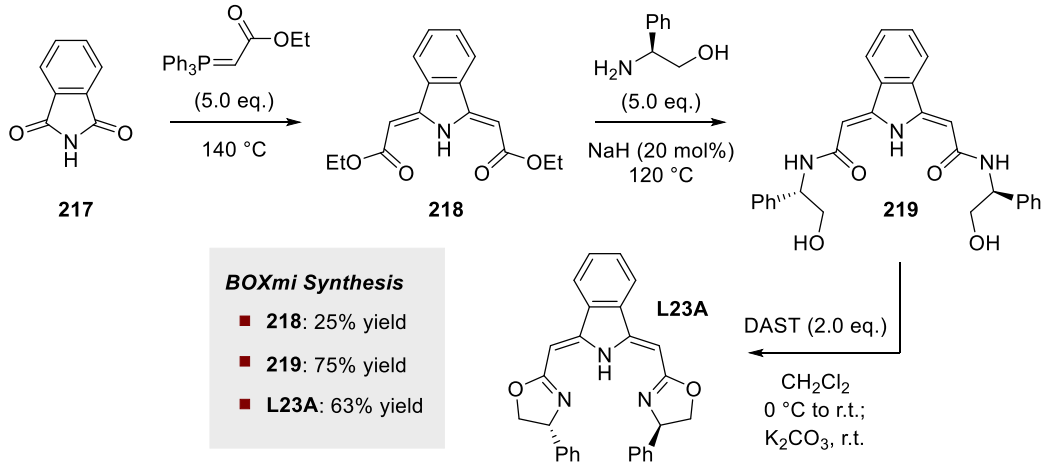
Although the combination of ligand **L10** with $FeCl_3$ in Section **4.6** failed to provide any of the cross-coupling product, similar CbzBOX ligands have been shown to exhibit non-heme iron(III)

porphyrin-like properties that are capable of asymmetric alkene epoxidation.[110] We therefore synthesised chiral ligand **L10A** *via* the method highlighted in Section **4.5** (**Scheme 5.9**).



Scheme 5.9: Synthesis of the CbzBOX ligand **L10A**

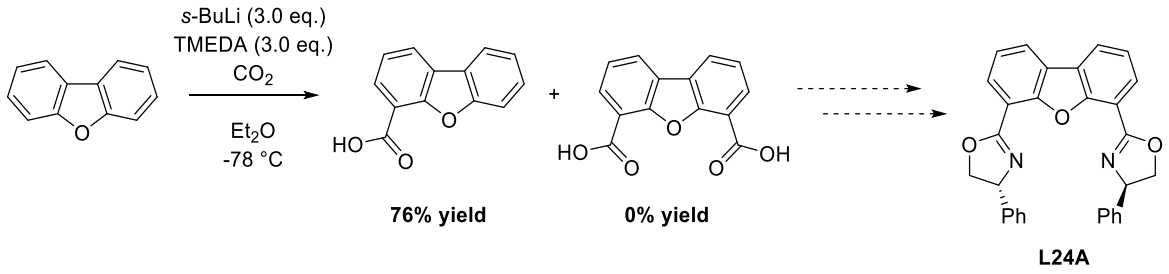
Subsequently, we targeted another monoanionic *N*,*N*,*N*-tridentate pincer ligand, BOXmi **L23A**. In the first step, an excess of phosphorus ylide was mixed with pthalimide **217**, giving predominantly the *mono*-Wittig product plus the desired dienenoate **218** in a low yield of 25%.



Scheme 5.10: Synthesis of BOXmi ligand

Amide bond formation of **219** with (*R*)-(–)-phenylglycinol in the presence of 20 mol% NaH then gave **218** in 75% yield. Finally, cyclisation of bisamide **219** with DAST at 0 °C gave the desired bisoxazoline product **L23A** in 63% yield (**Scheme 5.10**).

Finally, we attempted the preparation of DbFOX **L24A**.[111] The double *ortho*-lithiation of dibenzofuran with *s*-BuLi and TMEDA was difficult to reproduce in our hands and gave only the undesired monosubstutited acid in 76% (**Scheme 5.11**).



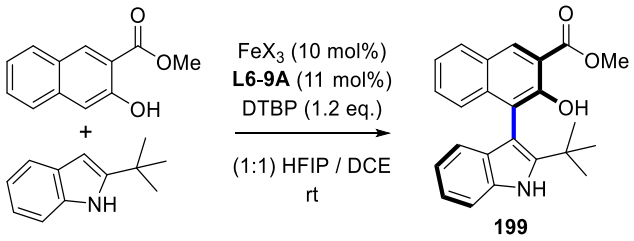
Scheme 5.11: Attempted synthesis of DbFOX **L24A**

5.2 Preliminary Evaluation of Iron(III) Salts with Oxazoline Ligands

Before conducting an in-depth evaluation of our chiral ligand library, we initially opted to examine the effect of the iron salt. In the first instance, a quantity of 10 mol% of the iron source was mixed with 11 mol% of several different oxazoline ligands in DCE for 30 min, prior to the addition of the substrates and oxidant as a stock solution in HFIP. We hypothesised that the enantioselectivity of the reaction could be influenced by dispersive π···π interactions between aryl substituents on the ligand and the aromatic substrates, so we began by testing the phenyl substituted BIOX **L6**, BOX **L7**, QuinOX **L8** and PyBOX **L9** ligands with the various iron(III) salts.

The combination of anhydrous $FeCl_3$ with the bidentate oxazoline ligands **L6A**, **L7A** and **L8A** all gave nearly racemic heterobiaryl product **199**, in yields of 63-68% (**Table 5.12**, Entry 1). However, a glimmer of enantioenrichment in **199** (60:40 e.r.) was observed when $FeCl_3$ was pre-stirred with diphenyl PyBOX ligand **L9A** (**Table 5.12**, Entry 1). More promisingly, on pre-stirring **L9A** with $FeCl_3 \cdot 6H_2O$, **199** was prepared in 80% yield and with an improved enantioselectivity (70:30 e.r.; **Table 5.12**, Entry 2) The combination of **L6A** and **L7A** with the hexahydrate salt also gave slightly higher enantioselectivities than with the anhydrous variant. $FeBr_3$ with **L9A** gave **199** in a significantly lower yield of 13% yield of **199** and slightly diminished 67:33 e.r. (**Table 5.12**, Entry 5) A range of other iron salts were also tested with these ligands, including FeF_3, $FeF_3 \cdot 3H_2O$, $Fe(ClO_4)_3 \cdot H_2O$, $Fe(OTf)_3$, $Fe(acac)_3$ and $Fe(NO_3)_3$, but all failed to catalyse the heterocoupling reaction (**Table 5.12**, Entries 3-4, 7-10).

Table 5.12: Study of ligands **L6-9A** with different iron(III) salts



199

Entry	Fe(III) Salt	L6A BIOX		L7A BOX		L8A QuinOX		L9A PyBOX	
		Yield[a]	e.r.[b]	Yield[a]	e.r.[b]	Yield[a]	e.r.[b]	Yield[a]	e.r.[b]
1	$FeCl_3$	68%	49:51	64%	53:47	63%	50:50	56%	60:40
2	$FeCl_3 \cdot 6H_2O$	72%	48:52	79%	56:44	56%	50:50	80%	70:30
3	FeF_3	N.R.	-	N.R.	-	N.R.	-	N.R.	-
4	$FeF_3 \cdot 3H_2O$	N.R.	-	N.R.	-	N.R.	-	N.R.	-
5	$FeBr_3$	26%	50:50	34%	54:46	24%	50:50	13%	67:33
6	$FeCl_3 + AgPF_6$	N.R.	-	N.R.	-	N.R.	-	N.R.	-
7	$Fe(ClO_4)_3 \cdot H_2O$	N.R.	-	N.R.	-	N.R.	-	N.R.	-
8	$Fe(OTf)_3$	N.R.	-	N.R.	-	N.R.	-	N.R.	-
9	$Fe(acac)_3$	N.R.	-	N.R.	-	N.R.	-	N.R.	-
10	$Fe(NO_3)_3$	N.R.	-	N.R.	-	N.R.	-	N.R.	-

Reaction Conditions: [a] Determined by quantitative ^1H NMR using 1,3,5-trimethoxybenzene as internal standard; [b] e.r. = enantiomeric ratio, determined by HPLC (chiral stationary phase). N.R. = no reaction.

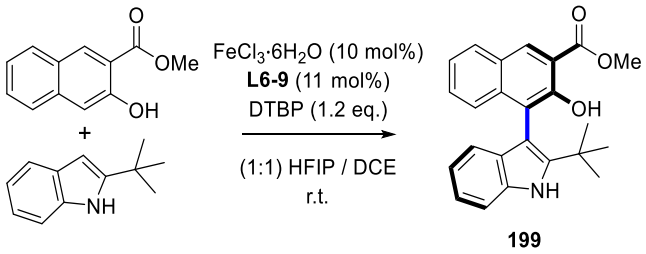
Additionally, we also tested the activity of anhydrous $FeCl_3$ in the presence of three equivalents of $AgPF_6$ with the oxazolines (**Table 5.12**, Entry 6). The silver salt facilitates anion metathesis of the chloride to the non-coordinating tris(hexafluorophosphate) iron species, with the loss of insoluble AgCl; this strategy has been shown to increase the reactivity of chiral Lewis acids.[112] However, in this case, anion exchange led to the complete loss of activity of the iron catalyst. These results suggest that ligation of the chloride ions to the iron centre is essential for reactivity within the oxidative cross-coupling. The superior performance of the hexahydrate salt of iron(III) chloride was a pleasing discovery, as it is not only cheaper and easier to handle than the other forms tested, but it eliminates the need to maintain rigorously dry conditions.

5.3 Evaluation of Chiral Oxazoline Ligands

Having identified $FeCl_3 \cdot 6H_2O$ as a superior source of iron for this transformation, we proceeded to test our library of chiral ligands for asymmetric induction in the oxidative cross-coupling. The substituted BIOX ligands **L6** gave good yields of the atropisomeric indole product **199** after 16 hours, but failed to provide any enantioselectivity, regardless of the substituent on the oxazoline core (**Table 5.13**, Entries 1-4). Similarly, the BOX **L7** (**Table 5.13**, Entries 5-10) and QuinOX ligands **L8** (**Table 5.13**, Entries 11-14) failed to promote the reaction in an enantioselective fashion. Ligands **L6**, **L7** and **L8** are bidentate *N*-donors, that occupy two *cis* coordination sites on the metal. Contrastingly, the PyBOX ligands **L9** are tridentate *N*-donors. The additional point of attachment for these ligands may provide a more rigid and well-defined chiral coordination environment around the metal, which may account for the improved levels of enantioselectivity observed.

As we had initially anticipated, the phenyl substituents on the PyBOX scaffold **L9A** were crucial for both the yield and enantioselectivity of the reaction (**Table 5.13**, Entry 15). By contrast, the indane PyBOX gave poorer results (**Table 5.13**, Entry 19), illustrating that either A) substitution at the β-oxazoline carbon is detrimental, and/or B) rotational freedom of about the aryl α-carbon axis is important.

Table 5.13: Evaluation of oxazoline ligands in oxidative cross-coupling



199

Entry	Ligand	Oxazoline	Yield[a]	e.r.[b]
1	**L6 BIOX**	A	72%	48:52
2		B	65%	50:50
3		C	78%	50:50
4		D	75%	50:50
5	**L7 BOX**	A	68%	48:52
6		B	80%	49:51
7		C	69%	50:50
8		D	42%	50:50
9		E	71%	50:50
10		F	36%	49:51
11	**L8 QuinOX**	A	56%	50:50
12		B	53%	53:47
13		C	74%	54:46
14		D	68%	51:49
15	**L9 PyBOX**	A	77%	70:30
16		B	30%	53:47
17		C	24%	57:43
18		D	60%	51:49
19		E	23%	54:46
20		F	75%	56:44

Reaction Conditions: [a] Determined by quantitative ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard; [b] e.r. = enantiomeric ratio, determined by HPLC (chiral stationary phase).

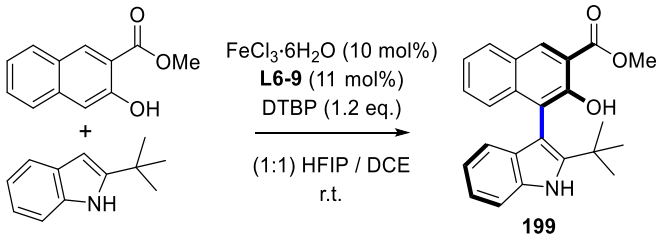
5.4 Evaluation of Miscellaneous Chiral Ligands

After our systematic evaluation of bis(oxazoline) ligands, we began assessing the library of miscellaneous chiral ligand manifolds prepared in Section **5.1**, in addition to a selection of other chiral ligand scaffolds that we had access to in our inventory. The structures tested are shown in **Figure 5.15**.

Pappo and Toste have demonstrated the use of iron phosphate complexes in the oxidative homo- and heterocoupling of BINOLs,[103] and that the triphosphate species is a pre-catalyst that dissociates into the active diphosphate form. In our case however, we found that **L25** was not a suitable manifold, giving **199** in 33% yield and 53:47 e.r. (**Table 5.14**, Entry 1). We then tried hydrogen bond donors **L26** and **L27**. These ligands are not conventionally used in combination with transition metals; nevertheless, we questioned if the Lewis basic nitrogen atom would allow these structures to associate with the iron. Whilst good yields of 68% and 79% were obtained for the squaramide and thiourea ligands respectively, the enantioselectivities were negligible (**Table 5.14**, Entries 2-3). Next, we tested the reaction with 22 mol% TADDOL **L28**, which resulted in the production of a 50:50 e.r. sample of **199** in 76% yield (**Table 5.14**, Entry 4). Similarly, Feng ligand **L29** provided racemic **199** in 34% yield (**Table 5.14**, Entry 5). The addition of $(DHQD)_2PHAL$ **L30** led to complete suppression of the reaction (**Table 5.14**, Entry 6), and DACH-py **L31** gave only a trace amount of racemic product (**Table 5.14**, Entry 7). Of the SALAN ligands prepared, only **L16B** led to the production of **199**, albeit in a moderate yield of 55% and a meek 55:45 e.r. (**Table 5.14**, Entry 9). Whilst the Corey ligand **L32** promoted the oxidative cross-coupling in an excellent yield of 98%, the product was obtained as a racemate (**Table 5.14**, Entry 11). Similarly, the addition of 11 mol% of the other diamine ligands **L35**, **L26** and **L38** all provided **199** in reasonably good yields, but with no discernible enantioselectivity (**Table 5.14**, Entries 14, 18 & 22). Chiral iron diphosphine oxide complexes have also been reported to catalyse the oxidative coupling of 2-naphthols by Ishihara,[110] but we found **L33** to be inappropriate in this application, giving **199** in 48% yield and 55:45 e.r. (**Table 5.14**, Entry 12). The addition of the iron containing

ligand Josiphos **L34** led to a complete loss of reactivity, possibly due to phosphine oxidation (**Table 5.14**, Entry 13). The chelating ligands **L19A**, **L21** and **L22** similarly led to disappointing yields of **199** (16-24%) and gave poor levels of enantioselectivity (**Table 5.14**, Entries 15, 16 & 17). Notably, the addition of **L37** to a suspension of $FeCl_3 \cdot 6H_2O$ in DCE instantly formed a black solution, which was not observed in the other examples (**Table 5.14**, Entry 19). One possible explanation for this observation is single electron oxidation of the electron rich *tert*iary amine of the PyBIM ligand itself, which may account for the complete loss of activity. Finally, as we had previously observed in our study in section **4.6**, the addition of monoanionic *N*-pincer ligands **L10A** and **L23A** to the iron salt resulted in the loss of all catalytic activity (**Table 5.14**, Entries 21 and 22).

Table 5.14: Evaluation of miscellaneous chiral ligands



199

Entry	Ligand	Mol%	Yield[a]	e.r.[b]
1	**L25**	30	33%	53:47
2	**L26**	11	68%	51:49
3	**L27**	11	79%	52:48
4	**L28**	22	76%	50:50
5	**L29**	11	34%	50:50
6	**L30**	11	N.R.	-
7	**L31**	11	6%	50:50
8	**L16A**	11	9%	53:47
9	**L16B**	11	55%	55:45
10	**L16C**	11	<5%	-
11	**L32**	11	98%	51:49
12	**L33**	22	48%	55:45
13	**L34**	11	N.R.	-
14	**L35**	11	74%	50:50
15	**L19A**	11	23%	53:47
16	**L21**	11	16%	52:48
17	**L22**	11	24%	54:46
18	**L26**	11	56%	50:50
19	**L37**	11	N.R.	-
20	**L10A**	11	N.R.	-
21	**L23A**	11	N.R.	-
22	**L38**	11	61%	50:50

Reaction Conditions: [a] Determined by quantitative ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard; [b] e.r. = enantiomeric ratio, determined by HPLC (chiral stationary phase). N.R. = no reaction.

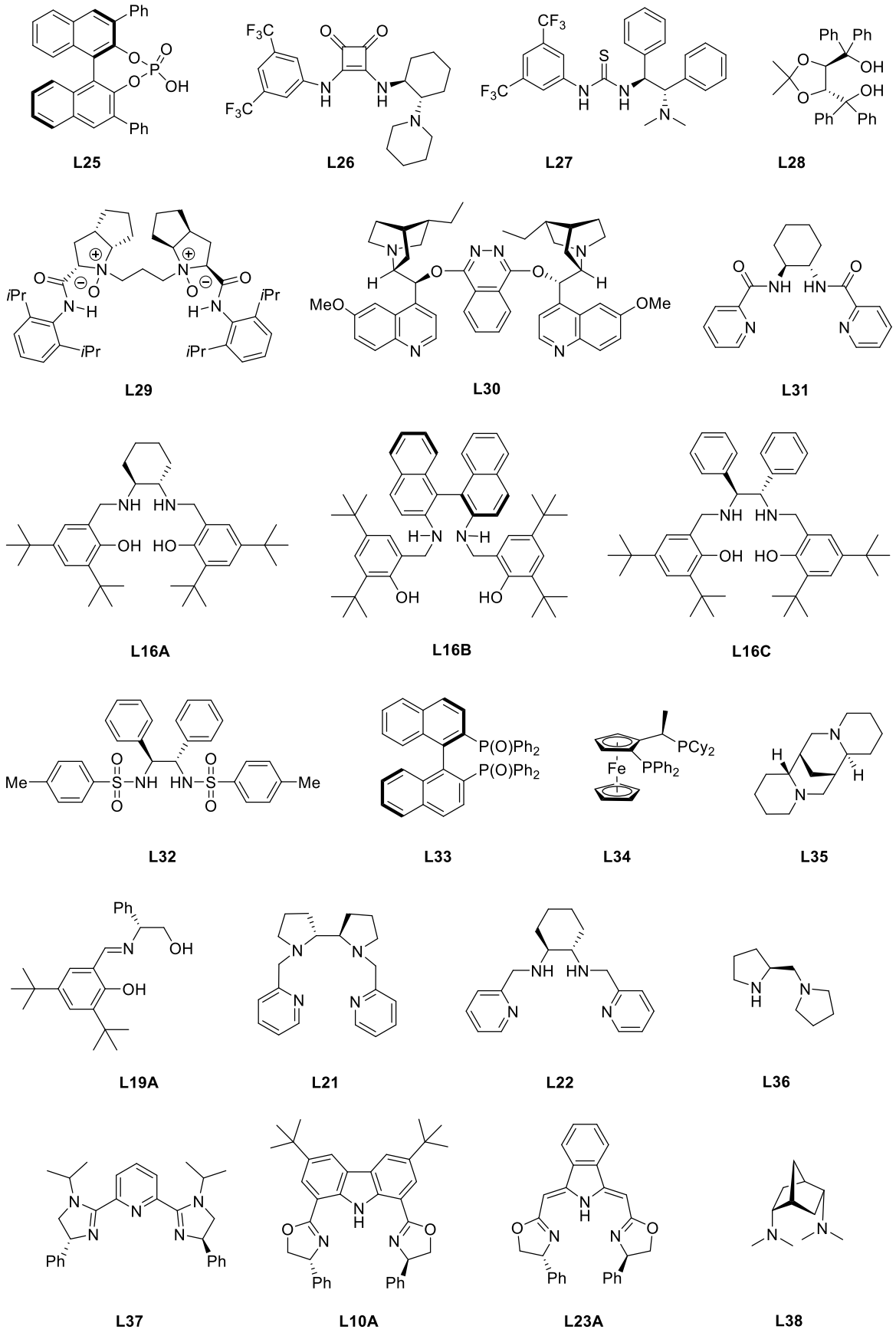
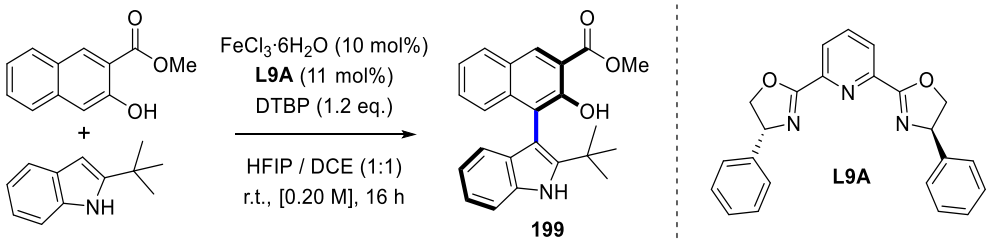


Figure 5.15: Miscellaneous chiral ligands studied in **Table 5.14**

5.5 Evaluation of Conditions for *In Situ* Formation of Chiral Iron Complex

The diphenyl PyBOX-$FeCl_3 \cdot 6H_2O$ system (which provided **199** in 80% yield and 70:30 e.r., and with perfect chemoselectivity) was by far the most promising combination achieved in our initial study of iron sources and chiral ligands. Moving forwards, we decided to re-evaluate the conditions for the *in-situ* formation of the chiral iron complex in more detail. We were conscious of a possible background reaction with unligated Fe(III) salts, so efforts were made to supress this process.

Table 5.16: Evaluation of conditions for in-situ formation chiral iron(III) complex



Entry	Pre-form Solvent	Pre-form Temp.	Pre-form Time (h)	Additive	Yield[a]	e.r.[b]
1	DCE	rt	0.5	None	80%	70:30
2	DCE	65 °C	0.5	None	90%	60:40
3	DCE	rt	0.5	4 Å M.S.	8%	58:42
4	DCE	rt	0.5	3 Å M.S.	44%	56:44
5	DCE then Celite®	rt	0.5	None	82%	65:35
6	1:1 HFIP/DCE	rt	0.5	None	<5%	N.D.
7	1:1 DCE then HFIP	rt	2.5	None	77%	71:29

Reaction Conditions: [a] Determined by quantitative ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard; [b] e.r. = enantiomeric ratio, determined by HPLC (chiral stationary phase). N.D. = Not Determined

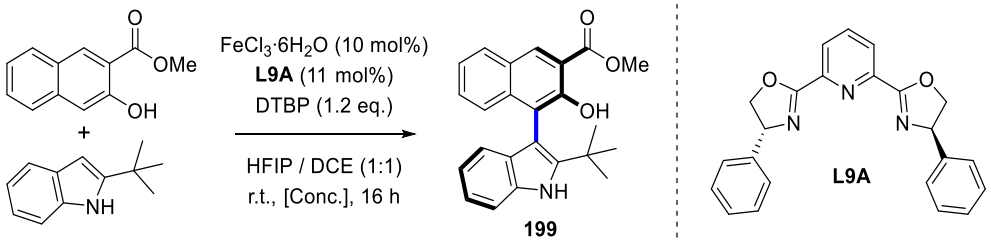
Under our standard conditions (**Table 5.16**, Entry 1), the PyBOX ligand **L9A** was mixed with the iron salt for 30 minutes at room temperature, prior to the addition of the substrates. In an attempt to force complete complexation of the iron salts by the ligand, we tried stirring these components at 65 °C in DCE during the complexation phase (**Table 5.16**, Entry 2). This gave **199** in a higher yield of 90%, but a lower e.r. of 60:40. At higher temperatures, the adventitious water from the

iron(III) chloride hexahydrate salt was thought to be responsible for the partial hydrolysis of the iron PyBOX complex to form a highly active PyDIC species, giving rise to lower enantioselectivities.[113] With this revelation, we wondered if this process was also occurring at room temperature. To combat this, both 3 Å and 4 Å M.S. were added to the reaction during the complexation phase in an effort to prevent the destruction of the PyBOX complex (**Table 5.16**, Entries 3 & 4). As can be seen, the drying interfered with the formation of the complex. Subsequently, we tried to remove any insoluble iron salts by filtering the solution through Celite® after mixing with ligand **L9A**. Unfortunately, this failed to provide any improvements in enantioselectivity (82% yield, 65:35 e.r.; **Table 5.16**, Entry 5) Next, we tried forming the iron complex in a 1:1 mixture of HFIP and DCE, rather than DCE alone. This gave only a trace amount of **199**, and the e.r. was not determined (82% yield, 65:35 e.r., **Table 5.16**, Entry 5). Finally, since the premature addition of HFIP was detrimental to the reaction, we decided to increase the length of the initial complexation time in DCE to 2 hours. Then, HFIP was added, followed by a further 30 minutes of stirring before introducing the substrates. This method gave the optimal results, improving the e.r. slightly to 71:29 (**Table 5.16**, Entry 6).

5.6 Screening of Reaction Concentration

Our initial studies on this reaction were conducted at a moderately high concentration of 0.20 M. At 0.50 M, quantitative conversions were obtained but at a heavy cost to the reaction's enantioselectivity, providing **199** in only 58:42 e.r. (**Table 5.17**, Entry 1). Gratifyingly, dilution of the reaction to 0.10 M led to a further increase in reaction's enantioselectivity, albeit at a slight expense to the yield (60% yield, 75:25 e.r.; **Table 5.17**, Entry 3). Further dilution of the reaction to 0.05 M failed to provide any further benefits (**Table 5.17**, Entry 4).

Table 5.17: Screening of different reaction concentrations

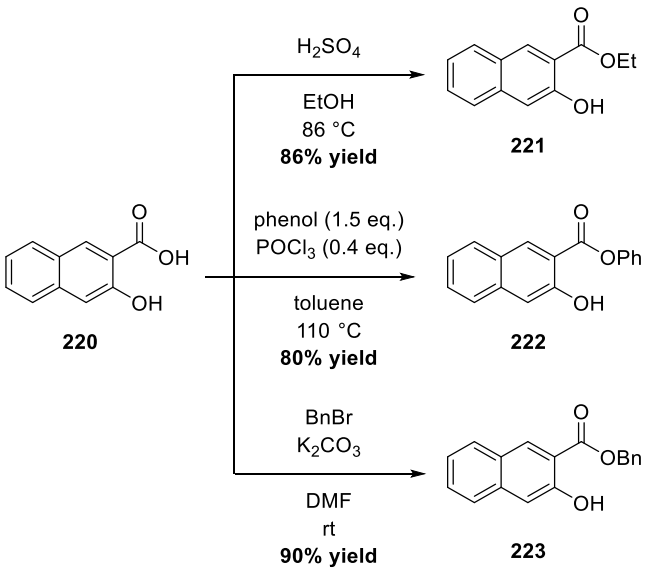


Entry	Conc. (M)	Yield[a]	e.r.[b]
1	0.50	100%	58:42
2	0.20	77%	71:29
3	0.10	60%	75:25
4	0.05	22%	65:35

Reaction Conditions: [a] Determined by quantitative ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard; [b] e.r. = enantiomeric ratio, determined by HPLC (chiral stationary phase).

5.7 Screening of Different Ester Substituents

The incorporation of an electron-withdrawing C-3 ester group on the naphthol was previously found to dramatically improve the chemoselectivity of the reaction (Section **4.2**, **Table 4.4**). At this stage, we recognised that the nature of this substituent (in particular, the parent alcohol from which it is derived) might also influence the enantioselectivity of the reaction.

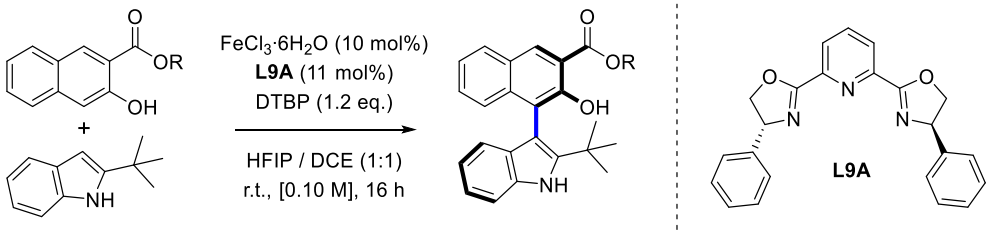


Scheme 5.18: Preparation of various substituted 2-hydroxy-3-naphthoates

A range of substituted naphthoates were therefore prepared from **220** for testing in the cross-coupling reaction (**Scheme 5.18**). Fischer esterification of **220** in ethanol gave the ethyl substituted naphthoate **221** in 86% yield. The aryl ester was prepared in 80% yield by mixing phenol in the presence of **222** and $POCl_3$ in boiling toluene for several days. Finally, the benzyl substituted product **223** was constructed in 90% yield *via* the base mediated alkylation of **220** with benzyl bromide

We tested the effect of these coupling partners at the new optimal concentration of 0.10 M. In each case, variation of this R-group led to no change in the reaction's chemoselectivity. Changing from methyl (**Table 5.19**, Entry 1) to ethyl (**Table 5.19**, Entry 2) made little difference to the outcome. However, we were delighted to find that a phenyl substituent at this position provided a boost to both the yield and enantioselectivity in the oxidative cross-coupling (67% yield, 80:20 e.r.; **Table 5.19**, Entry 3). The benzyl substituted substrate was found to be even more selective (**Table 5.19**, Entry 4), however, due to the low yield of the product, we decided to proceed with the phenyl substituted naphthoate **222** as the optimal substrate.

Table 5.19: Screening of different ester substituents on oxidative cross-coupling



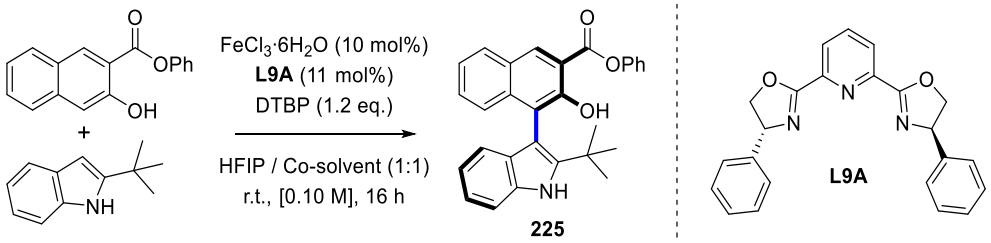
Entry	R	Product	Yield[a]	e.r.[b]
1	Me	**199**	60%	75:25
2	Et	**224**	54%	76:24
3	Ph	**225**	67%	80:20
4	Bn	**226**	23%	82:18

Reaction Conditions: [a] Determined by quantitative ^1H NMR using 1,3,5-trimethoxybenzene as internal standard; [b] e.r. = enantiomeric ratio, determined by HPLC (chiral stationary phase).

5.8 Screening of Co-Solvents

Having already made steady improvements in the reaction's enantioselectivity, we moved on to examine the effect of the co-solvent. As HFIP was thought to be essential for stabilising the radical intermediates, we decided to vary only the co-solvent in this study.

Table 5.20: Screening of co-solvents



Entry	Co-Solvent	Yield[a]	e.r.[b]
1	DCE	62%	84:16
2	CH_2Cl_2	45%	80:20
3	$CHCl_3$	89%	74:26
4	1,2-TCE	25%	72:28
5	C_6H_5Cl	63%	80:20
6	C_6H_5F	14%	74:26
7	$C_6H_5CF_3$	14%	76:24
8	1,2-DFB	36%	76:24
9	$C_6H_5OCH_3$	39%	70:30
10	MTBE	<5%	58:42
11	MeOH	22%	53:47
12	EtOH	37%	57:43
13	IPA	27%	57:43
14	TFE	47%	63:37
15	MeCN	<5%	69:31
16	EtOAc	<5%	67:33

Reaction Conditions [a] Determined by quantitative ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard; [b] e.r. = enantiomeric ratio, determined by HPLC (chiral stationary phase).

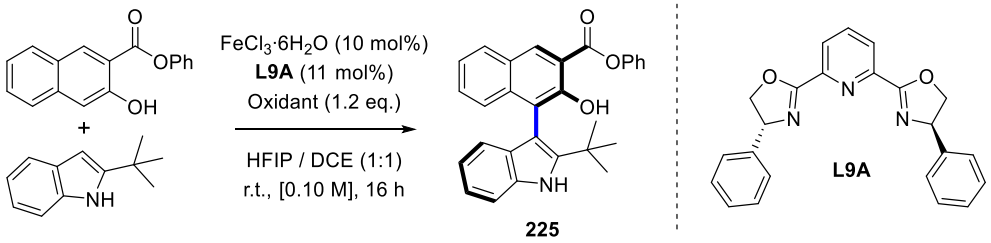
Of the chlorinated solvents tested (**Table 5.20**, Entries 2-5), all gave lower enantioselectivities than DCE. Fluorinated aromatic solvents (**Table 5.20**, Entries 6-8) similarly led to severely diminished catalyst performance. Ethereal solvents (**Table 5.20**, Entries 9-10) were also

unsuitable. A range of alcohols were also tested (**Table 5.20**, Entries 11-14). Although the iron salt showed an improved solubility in each of these solvents during the complexation phase of the procedure, all of these protic solvents showed markedly lower yields and enantioselectivities. Furthermore, the polar solvents MeCN and EtOAc (**Table 5.20**, Entries 15-16) gave only trace quantities of the heterobiaryl product. It is noteworthy that the optimal solvent conditions for this application are identical to those selected by Pappo and Toste for their iron(III) catalysed oxidative cross-coupling.[103] The properties of this mixed solvent combination is clearly important for both reactivity and selectivity in these iron(III) catalysed processes.

5.9 Screening of Terminal Oxidant

Next, we evaluated terminal oxidants. The organic peroxide BzOOBz (**Table 5.21**, Entry 2) performed significantly worse than DTBP (**Table 5.21**, Entry 1), providing **225** in 25% yield and 70:30 e.r. The reaction with DTBP led to exceptionally smooth formation of the heterocoupling product, whilst BzOOBz resulted in the production of numerous overoxidation by-products. Whilst dicumyl peroxide provided **225** in the same enantioselectivity as DTBP (**Table 5.21**, Entry 3), the yield was once again inferior due to product decomposition. The addition of peroxides *t*-BuOOH (**Table 5.21**, Entry 4) and the urea hydrogen peroxide complex (**Table 5.21**, Entry 5) also failed to improve activity or enantioselectivity. Iodosobenzene and DDQ (**Table 5.21**, Entries 6-7) resulted in almost complete decomposition of the products and starting materials; only traces of **225** were obtained. The inorganic salt potassium persulfate, $K_2S_2O_8$ is a powerful two-electron oxidant and was reasonably suitable for this cross-coupling, affording 48% **225** in 81:19 e.r. (**Table 5.21**, Entry 8). Finally, numerous works have illustrated that molecular oxygen is sufficient to promote the turnover of the transition metal catalyst in oxidative cross-coupling reactions.[81] To this end, the reaction was also tested with an oxygen balloon present, but this gave **225** in poorer yield and enantiselectivity (33% yield, 75:25 e.r.; **Table 5.21**, Entry 9).

Table 5.21: Screening of Terminal Oxidants



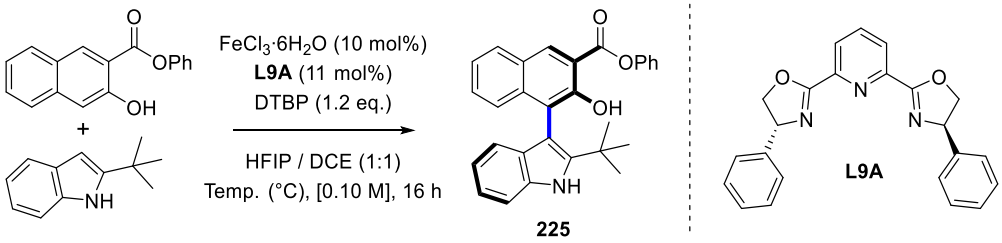
Entry	Oxidant	Yield[a]	e.r.[b]
1	DTBP	62%	84:16
2	BzOOBz	25%	70:30
3	Dicumyl Peroxide	38%	84:16
4	*t*-BuOOH	63%	66:34
5	Urea ·H_2O_2	15%	60:40
6	C_6H_5IO	<5%	58:42
7	DDQ	<5%	64:36
8	$K_2S_2O_8$	48%	81:19
9	O_2 Balloon	33%	75:25

Reaction Conditions [a] Determined by quantitative ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard; [b] e.r. = enantiomeric ratio, determined by HPLC (chiral stationary phase).

5.10 Screening of Reaction Temperature

The temperature dependence of enantioselective reactions is well documented.[9] We hoped to gain an increase in enantioselectivity by lowering the reaction temperature. Deviating from our standard conditions (**Table 5.22**, Entry 3), we found that cooling the reaction to 0 °C resulted in almost complete loss of reactivity (<5% yield, 81:19 e.r.; **Table 5.22**, Entry 1). Intermediate temperatures were therefore evaluated. Even at 10 °C, the yield and enantioselectivity of the reaction suffered (19% yield, 81:19 e.r.; **Table 5.22**, Entry 2). We then decided to increase the temperature slightly, in the hopes of finding optimal reactivity and enantioselectivity. Although we obtained a higher product yield of 85% at 35 °C, a slightly lower enantioselectivity of 82:18 e.r. was achieved (**Table 5.22**, Entry 4). Further increasing the temperature to 45 °C led to complete consumption of the starting materials, but at this temperature some product decomposition was observed (**Table 5.22**, Entry 5).

Table 5.22: Screening of Reaction Temperature

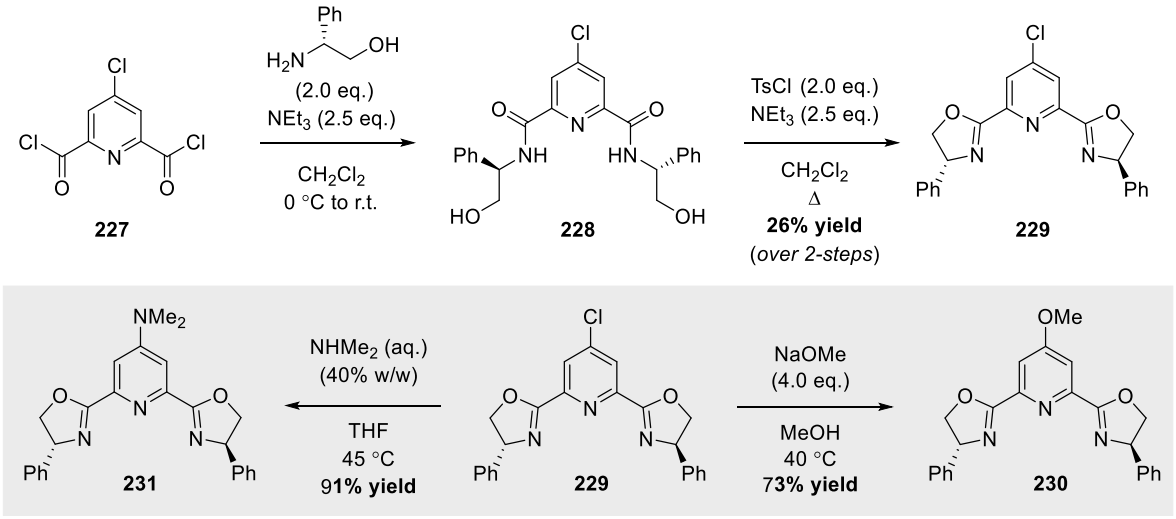


Entry	Temp. (°C)	Yield[a]	e.r.[b]
1	0	<5%	81:19
2	10	19%	81:19
3	rt	62%	84:16
4	35	85%	82:18
5	45	80%	80:20

Reaction Conditions [a] Determined by quantitative ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard; [b] e.r. = enantiomeric ratio, determined by HPLC (chiral stationary phase).

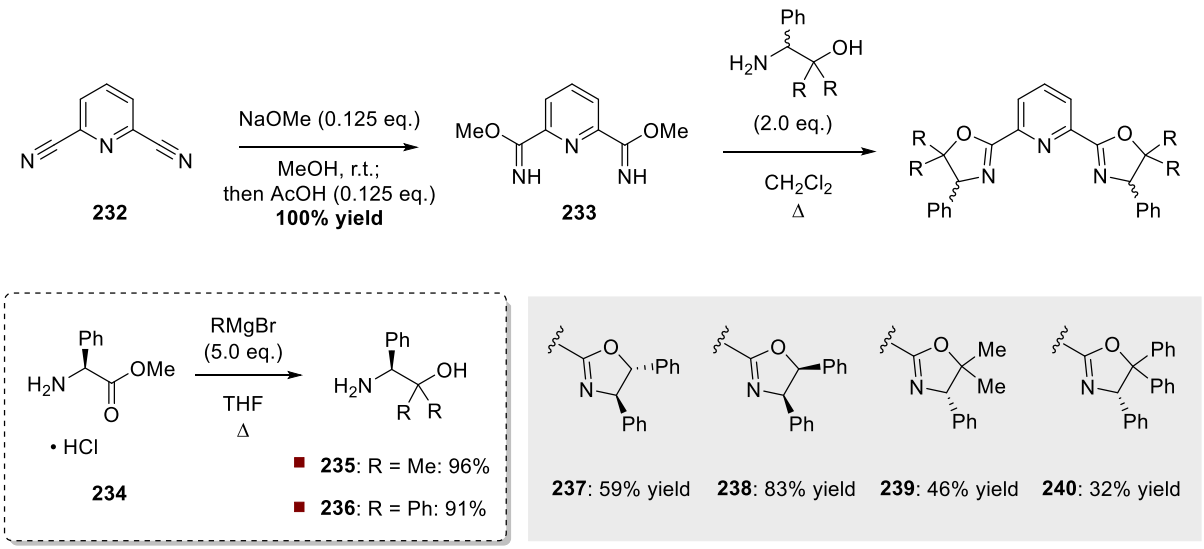
5.11 Synthesis of PyBOX Ligands: Part 1

Having extensively studied the reaction conditions, we turned our sights towards a second wave of chiral ligand design. We were initially interested in two different substituent effects on the diaryl PyBOX ligand backbone. These were: A) The 4-substituents on the pyridyl moiety, and B) the substituents on the β-carbon of the oxazolines. Nishiyama has shown that the 4-substituents of the pyridine skeleton can be tuned to modulate the electron density of the *N*-donor atom and, in turn, the metal centre to which the PyBOX is bound.[114] We hypothesised that this remote structural modification could increase the performance of the iron-PyBOX complex in our redox transformation. We therefore targeted PyBOX **229**, which was prepared from **227** in two-steps *via* double amide bond formation with (*R*)-phenylglycinol, followed by tosylation and cyclisation of **228** to yield the desired bis(oxazoline) core **229** in 26% over the two-steps. With **229** in our grasp, we performed two divergent nucleophilic aromatic substitutions (S_NAr). The reaction of **229** with excess NaOMe gave *p*-methoxy substituted ligand **230** in 73% yield. Similarly, the reaction of **229** with aqueous dimethylamine gave **231** in a yield of 91%.



Scheme 5.23: Preparation of 4-substituted PyBOX ligands

Next, we turned towards the synthesis of PyBOX ligands bearing substituents at the β-carbon (**Scheme 5.24**). We reasoned that these modifications would have substantial influence on the steric environment around the iron centre that could improve the enantioselectivity of the oxidative cross-coupling. In search for a more direct route towards these ligands than that described in Section **4.5**, we began with the base catalysed 1,2-addition of methanol to pyridine-2,6-dicarbonitrile **232**, yielding **233** in quantitative yield. The substituted PyBOX ligands were then prepared by mixing two equivalents of the desired amino alcohols with **233** in refluxing CH_2Cl_2 for 2 days. The anti-1,2-diphenyl PyBOX **237** and syn-1,2-diphenyl PyBOX **238** diastereomers were prepared by this approach in 59% and 83% yields respectively from commercially available amino alcohols. The β-disubstituted aryl glycinols **239** and **240** had to be prepared from the reaction of (*R*)-(−)-phenylglycine methyl ester hydrochloride with the corresponding Grignard reagents. **235** and **236** were then combined with **233** to give ligands **239** in 46% and **240** in 32% yields.



Scheme 5.24: Preparation of β-Substituted PyBOX Ligands

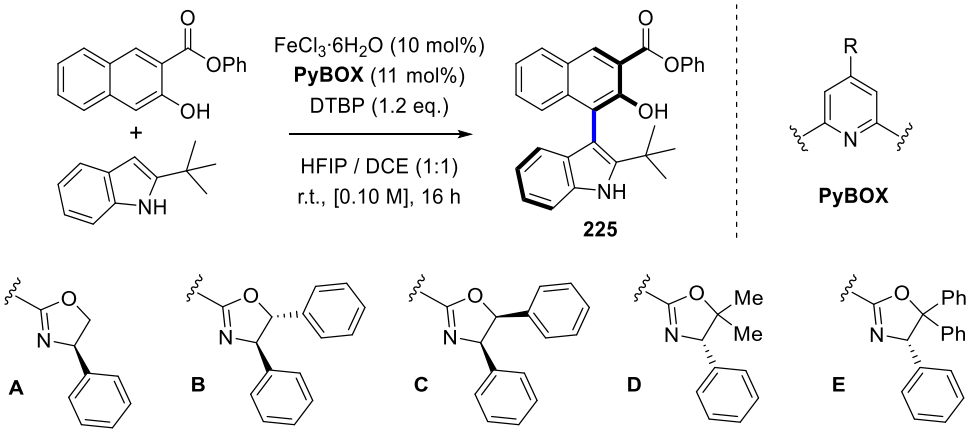
5.12 Evaluation of PyBOX Ligands: Part 1

Following the successful synthesis of the substituted PyBOX ligands, we tested their suitability in the oxidative cross-coupling. For the 4-substituted pyridines, a clear trend between the electron density of the ligands and the catalytic performance was observed. The electron withdrawing 4-chloro substituent in **229** provided **225** in a lower yield and enantioselectivity (42% yield, 79:21 e.r.; **Table 5.25**, Entry 2) versus the unsubstituted derviative **L9A** (62% yield, 84:16 e.r.; **Table 5.25**, Entry 1). The electron rich *p*-methoxy substituent in PyBOX **230** led to a marked increase in the yield of the cross-coupling reaction to 75%, without compromising the enantioselectivity (**Table 5.25**, Entry 3). A further increase in electron density in **231** resulted in an even higher yield of 85%, but at the expense of the enantioenrichment of the product (**Table 5.25**, Entry 4). This trend in reactivity may be explained the stabilisation of highly electron deficient iron species formed during the oxidative cross-coupling by the EDGs on the pyridine.

We then examined the β-substituted bis(oxazoline) derivatives. Both the syn- and anti-1,2-diphenyl PyBOX ligands **237** and **238** had a highly detrimental impact upon the yield and enantioselectivity of the reaction (**Table 5.25**, Entries 5 & 6). The deleterious effect of

β-substitution was even more pronounced for the β-disubstituted examples. The geminal dimethyl ligand **239** gave a severe reduction in the yield and almost complete loss of enantioselectivity (16% yield, 45:55 e.r.,; **Table 5.25**, Entry 7). Moreover, the *gem*-diphenyl ligand **240** completely shut down the reactivity of the chelated iron species, with no product detected (**Table 5.25**, Entry 8). These results highlight the extreme sensitivity of this reaction to steric bulk, as only β-unsubstituted PyBOX ligands were productive.

Table 5.25: Evaluation of PyBOX Ligands: Part 1



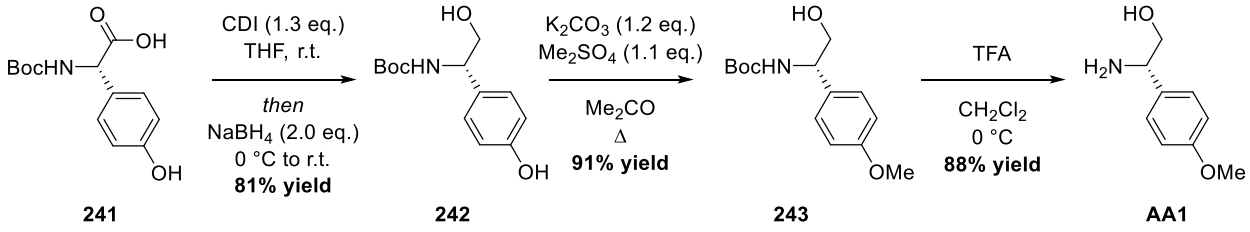
Entry	PyBOX	PyBOX R	Oxazoline	Yield[a]	e.r.[b]
1	**L9A**	H	A	62%	84:16
2	**229**	Cl	A	42%	79:21
3	**230**	OMe	A	75%	84:16
4	**231**	NMe_2	A	85%	75:25
5	**237**	H	B	33%	63:37
6	**238**	H	C	29%	53:47
7	**239**	H	D	16%	45:55
8	**240**	H	E	N.R.	-

Reaction Conditions [a] Determined by quantitative ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard; [b] e.r. = enantiomeric ratio, determined by HPLC (chiral stationary phase). [c] N.R. = no reaction.

5.13 Synthesis of PyBOX Ligands: Part 2

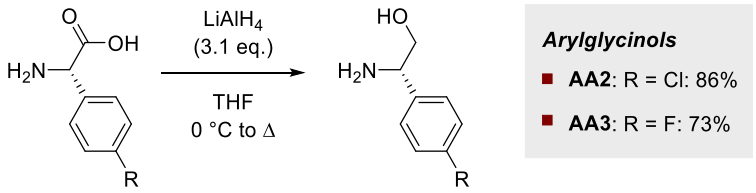
Undeterred by these results, we continued to strive towards a more enantioselective oxidative cross-coupling. The only option remaining for ligand modification was to vary the aryl substituents on the flanking oxazoline units of the ligands. We envisaged that fine-tuning the steric and electronic properties of these groups could enable more selective formation of one atropenantiomeric form of **225**, through the generation of favourable π···π substrate-complex interactions, or through the creation of a better-defined chiral pocket.

This was a daunting synthetic undertaking, as only a handful of enantiomerically pure arylglycines were commercially available. Initially, we purchased **241** and transformed it into amino alcohol **AA1** in three concise steps (**Scheme 5.26**). The Boc-protected carboxylic acid **241** was activated with CDI and then reduced to the corresponding primary alcohol with $NaBH_4$, giving **242** in 81% yield. Selective methylation of the phenol in **242** was accomplished using K_2CO_3 and Me_2SO_4 in hot acetone. Finally, the Boc protecting group was cleaved by stirring **243** in the presence of TFA to reveal the final electron rich amino alcohol **AA1** in 88% yield.



Scheme 5.26: Synthesis of amino alcohol **AA1**

A duo of enantiomerically pure 4-halo-substituted aryl glycinols were then acquired. Direct reduction of these compounds with $LiAlH_4$ using the procedure of Topczewski[115] afforded the highly sought-after amino alcohols in good yields of 86% for the 4-chloro **AA2** and 73% for the 4-fluoro substituted arylglycinol **AA3** (**Scheme 5.27**).

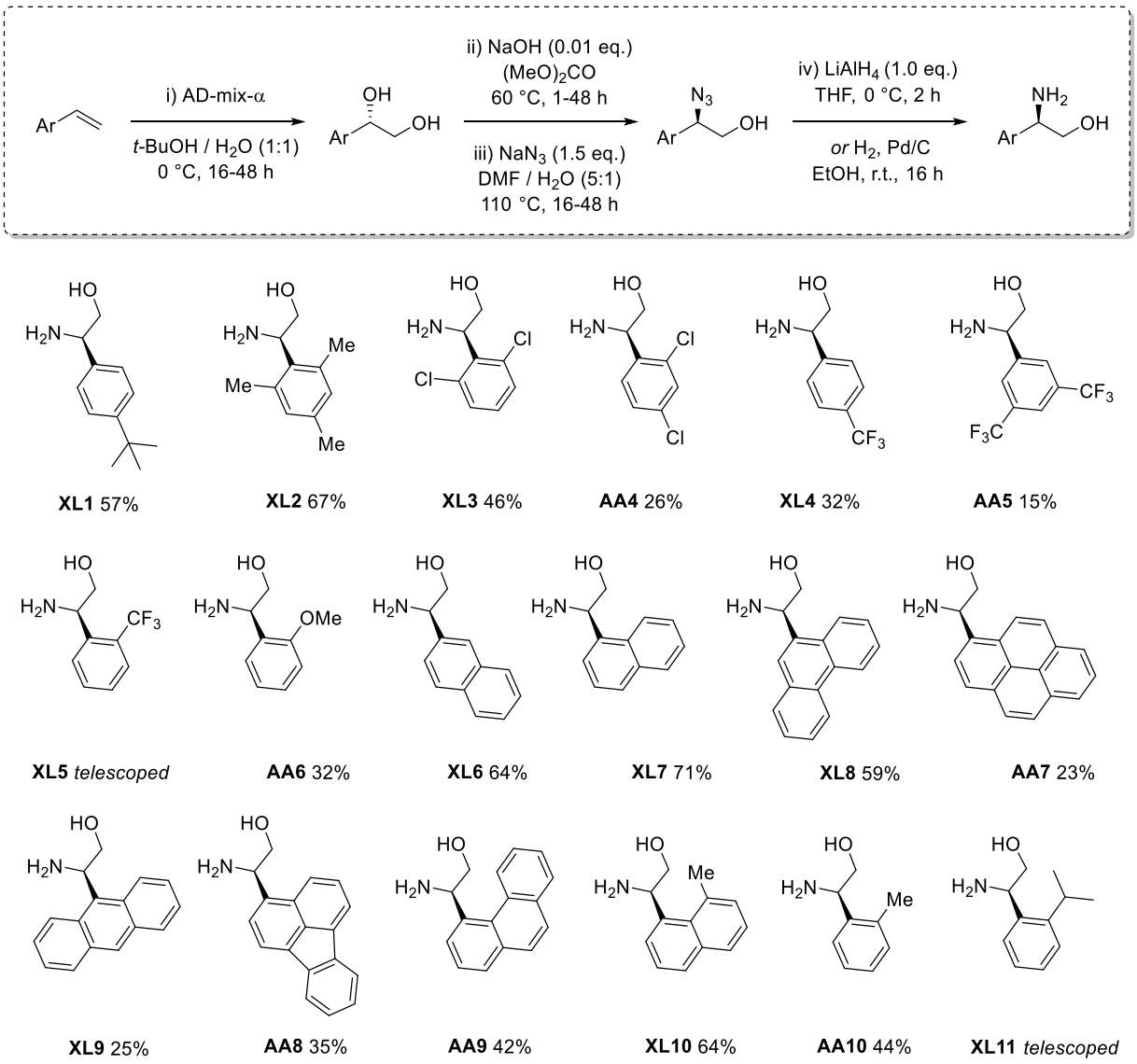


Scheme 5.27: Synthesis of Amino Alcohols **AA2** and **AA3**

We conceded that this humble collection of three amino alcohols would be insufficient to fully optimise the enantioselectivity of the reaction. Therefore, our only option was to establish our own catalogue of aryl PyBOX ligands *via* the *de novo* enantioselective synthesis of a range of aryl glycinols.

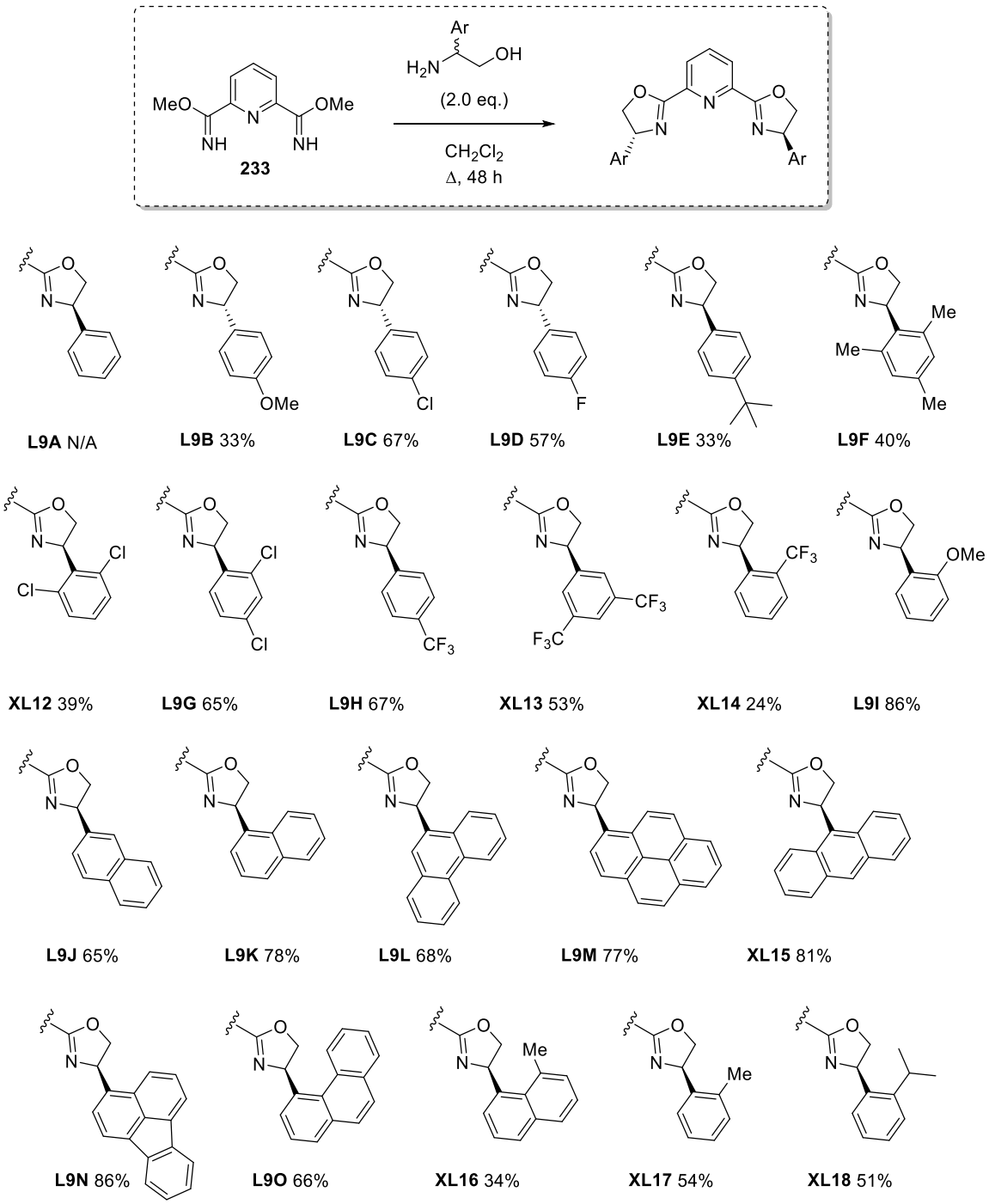
To accomplish this formidable task, Dr. Xiangqian Liu joined the project at this stage to expedite the synthesis of this ligand library. Compounds made by Dr. X. Liu are clearly denoted by the prefix **XL**. It should also be noted that the synthesis and evaluation of the PyBOX ligands was performed in parallel, using the stream of results to guide ligand selection.

A general and concise route for preparing substituted aryl glycinols has been established by Sharpless,[116] and implemented by a number of other groups for a similar goal. This route consists of 1) asymmetric dihydroxylation of the chosen styrene; 2) formation of a benzylic carbonate ester; 3) regioselective ring-opening azidation of the carbonate; and finally 4) reduction of the azide to furnish enantiomerically pure aryl glycinols.



Scheme 5.28: Sharpless route towards enantiomerically pure amino alcohols. [Compounds made by Xiangqian Liu are denoted with the prefix "XL"]

The use of AD-mix-α gave the (*S*)-diols in exquisite levels of enantioselectivity (>95% e.e.). After formation of the carbonate, the S_N2 attack of azide at the benzylic positions led to an inversion of stereochemistry, yielding the (*R*)-azido alcohols. After reduction, high enantiomeric purities of the amino alcohols were ensured by recrystallisation of the products from boiling toluene.



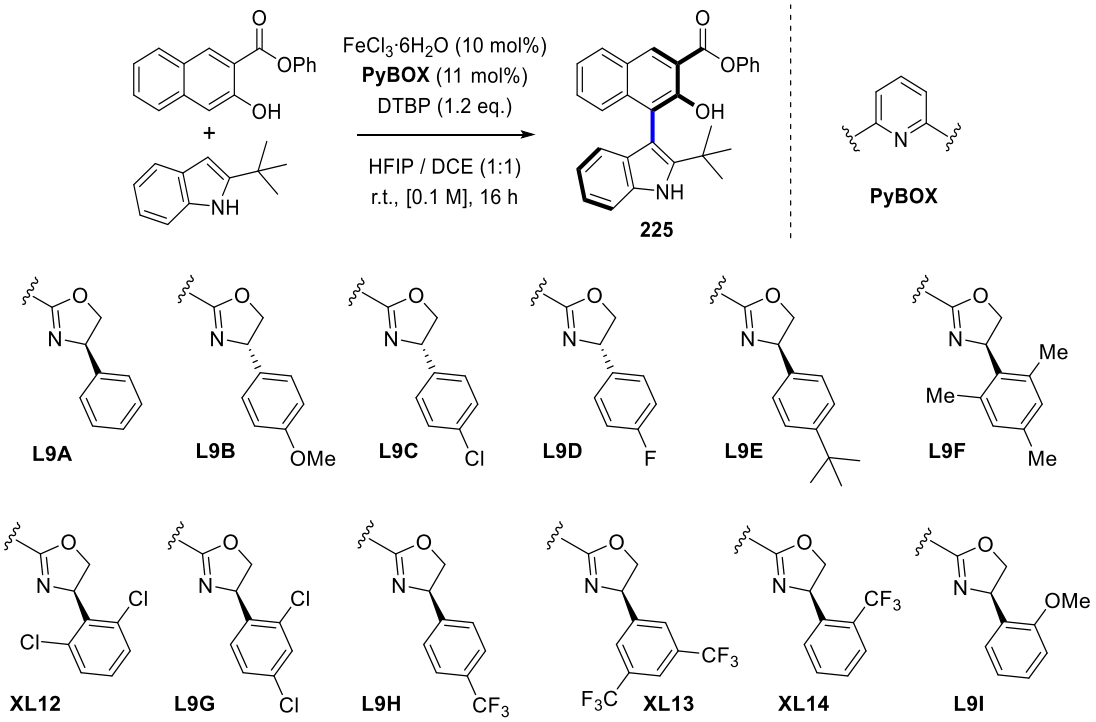
Scheme 5.29: Synthesis of C_2-symmetric diaryl PyBOX ligands [Compounds made by Xiangqian Liu are denoted with the prefix "XL"]

The C_2-symmetric diaryl PyBOX ligands were then prepared from **233** and the enantiomerically pure aryl glycinols. The products were recrystallised from EtOH or EtOAc after chromatographic purification to maximise the enantiomeric purity of the ligands for testing.

5.14 Evaluation of PyBOX Ligands: Part 2

At the commencement of this study, the addition of different substituents at the *para*-positions of the ligand's aryl groups were tested first. The electron withdrawing 4-fluoro substituent on **L9D** was found to decrease the yield of the reaction, giving **225** in only 26% but an unchanged e.r. of 84:16 (**Table 5.30**, Entry 4). The 4-methoxy **L9B** (**Table 5.30**, Entry 2) and 4-chloro **L9C** (**Table 5.30**, Entry 3) groups gave **225** in essentially identical yields in comparison to ligand **L9A**; but gratifyingly, **L9C** also afforded the product in a greater level of enantioselectivity (56% yield, 87:13 e.r.). This improved result motivated us to proceed with this approach. It should also be noted that the ligands derived from the commercially available aryl glycines displayed the opposite stereochemistry to those prepared *via* the Sharpless route. As such, these gave the opposite enantiomer of the products. The 4-*tert*-butyl PyBOX **L9E** gave **225** in a lower yield and a diminished enantioselectivity (33% yield, 82:18 e.r.; **Table 5.30**, Entry 5). The dimesityl PyBOX **L9F** performed even worse, giving only a trace quantity of **225** in a poor 78:22 enantiomeric ratio (**Table 5.30**, Entry 6). These results again alluded to the sensitivity of this reaction towards extreme steric crowding around the iron centre. Since the *para* substituents are rather remote from the points of attachment of the PyBOX ligands to the metal, we questioned whether proximal *ortho* substituents could lead to enhanced enantioselectivities. The di-*ortho*-chloro ligand **XL12** was therefore prepared, but this gave **225** in only a moderate yield of 57%, and a poor 60:40 e.r. (**Table 5.30**, Entry 7). The *ortho*-*para*-dichloro analogue **L9G** also failed to improve the enantioselectivity, and significantly retarded the reaction (22% yield, 74:26 e.r.; **Table 5.30**, Entry 8). The *ortho*-methoxy ligand **L9I** on the other hand, led to a slight boost in enantioselectivity to 87:13 e.r. (**Table 5.30**, Entry 12). Trifluoromethyl groups are privileged moieties that feature frequently in the architectures of chiral ligands and organocatalysts.[9] However, in this reaction, we found that the strongly electron withdrawing properties of this substituent inhibited the performance of the iron complex. This effect was particularly pronounced with ligand **XL13**, which led to a trace yield of **225** in a very low e.r. (<5% yield, 65:35 e.r.; **Table 5.30**, Entry 10).

Table 5.30: Screening of C_2-Symmetric PyBOX Ligands – Part 1 of 2



Entry	PyBOX	Yield[a]	e.r.[b]
1	**L9A**	62%	84:16
2	**L9B**	58%	18:82
3	**L9C**	56%	13:87
4	**L9D**	26%	16:84
5	**L9E**	33%	82:18
6	**L9F**	<5%	78:22

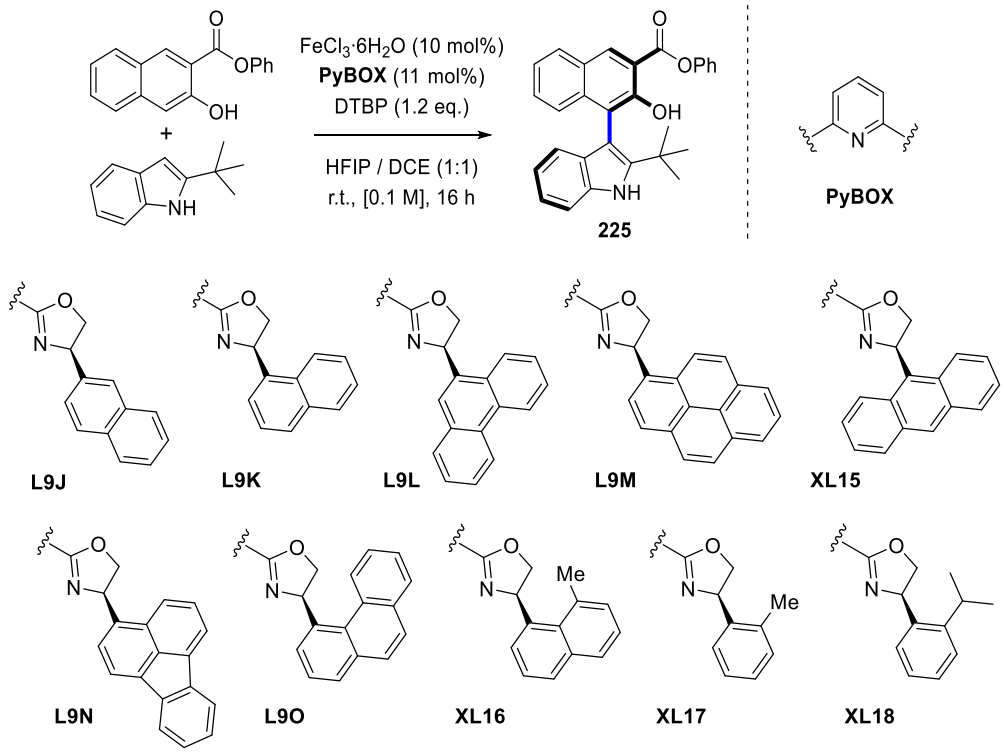
Entry	PyBOX	Yield[a]	e.r.[b]
7	**XL12**	57%	60:40
8	**L9G**	22%	74:26
9	**L9H**	24%	86:14
10	**XL13**	<5%	65:35
11	**XL14**	39%	84:16
12	**L9I**	40%	87:13

Reaction Conditions*:* [a] Determined by quantitative ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard; [b] e.r. = enantiomeric ratio, determined by HPLC (chiral stationary phase).

We then moved on to examine the influence of some polyaromatic substituents. We were pleased to find that the 2-naphthyl substituted ligand **L9J** gave rise to a more enantioselective oxidative heterocoupling, providing a sample of **225** in 63% yield and very good e.r. of 88:12 (**Table 5.31**, Entry 13). We then tested the 1-naphthyl isomer **L9K** and were delighted to discover that an even higher enantioselectivity was obtained (71% yield, 89:11 e.r.; **Table 5.31**, Entry 14). These results further consolidated our suspicions about the importance of π···π interactions between

the ligand and the substrate. In response to these findings, we pursued the synthesis of a number of other polyaromatic substituted ligands based on the 1-naphthyl core, with a view to further improve the enantioselectivity.

Table 5.31: Screening of C_2-Symmetric PyBOX Ligands – Part 2 of 2



Entry	PyBOX	Yield[a]	e.r.[b]
13	**L9J**	63%	88:12
14	**L9K**	71%	89:11
15	**L9L**	61%	85:15
16	**L9M**	68%	87:13
17	**XL15**	58%	75:25

Entry	PyBOX	Yield[a]	e.r.[b]
18	**L9N**	49%	87:13
19	**L9O**	61%	85:15
20	**XL16**	67%	84:16
21	**XL17**	70%	88:12
22	**XL18**	60%	84:16

Reaction Conditions: [a] Determined by quantitative ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard; [b] e.r. = enantiomeric ratio, determined by HPLC (chiral stationary phase).

The 9-phenanthryl **L9L** and 1-pyrenyl **L9M** ligands were tested and found to be slightly less proficient (**Table 5.31**, Entries 15 & 16). The 9-anthracenyl PyBOX **XL14** was pointedly worse, providing **225** in only 58% yield and 75:25 e.r. (**Table 5.31**, Entry 17). This finding is consistent

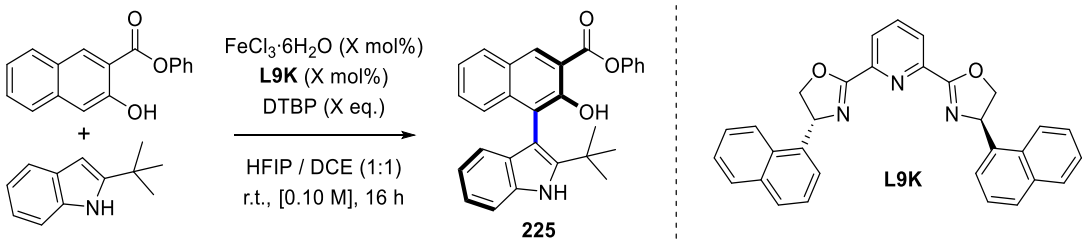
with our previous di-*ortho*-substituted ligands studied; and the observation that only one *ortho* substituent can be tolerated. The bespoke 3-fluoranthyl **L9N** (**Table 5.31**, Entry 18) and 4-phenanthryl **L9O** (**Table 5.31**, Entry 19) PyBOX ligands were then synthesised, but both showed weaker performance than the parent 1-naphthyl complex. For the larger polyaromatic PyBOX ligands (three rings and up), we also observed much poorer solubilities of the ligand in DCE during the complexation phase; this may have contributed to the poorer results. Penultimately, we tested the 8-methyl-1-naphthyl ligand **XL16** in hopes of pinpointing optimal steric parameters around the metal, but our efforts were in vain, resulting in **225** in only 84:16 e.r (**Table 5.31**, Entry 20). Finally, we concluded this study with a couple of *ortho*-alkyl substituted aryl PyBOX ligands, **XL17** and **XL18**. These performed reasonably well, giving 88:12 and 84:16 e.r. of **225** respectively, but failed to improve upon our optimal result (**Table 5.31**, Entries 21 & 22).

5.15 Optimisation of Equivalents of Chiral Ligand and Reactants

Although we were happy to find a significantly improved ligand in the C_2-symmetric 1-naphthyl substituted PyBOX **L9K**, we were yet to break through the crucial 90:10 e.r. checkpoint. Taking **L9K** through to the next stage, we embarked upon another phase of optimisation in an effort to further stretch the enantioselectivity. In this round, we focussed upon fine-tuning the concentration of each of the reaction components. To curtail the background reaction, we increased the ratio of Fe(III) to ligand from 1.0:1.1 to 1.0:1.2 (**Table 5.32**, Entry 2) which provided an excellent enantioselectivity of **225** in 90:10 e.r. A 1.0:2.0 ratio of Fe(III):**L9K** led to a complete loss of reactivity, which was thought to be caused by the formation of a catalytically inactive $Fe(PyBOX)_2$ complex (**Table 5.32**, Entry 3). We were curious if the catalyst loading could be lowered without compromising catalyst performance. Using 5 mol% $FeCl_3 \cdot 6H_2O$ with 6 mol% **L9K**, the yield of the reaction was largely maintained at 61%, but the e.r. slumped to 89:11 (**Table 5.32**, Entry 4). Running the reaction at this lower catalyst loading of 5 mol% was problematic on a 0.1 mmol scale as it required weighing out small quantities of material. We were pleased to find

that we were also able to increase the conversion to 75% by increasing the number of equivalents of both the indole and DTBP to 1.5 equiv. each, without detriment to the enantioselectivity (**Table 5.32**, Entry 7).

Table 5.32: Optimisation of equivalents of chiral ligand and reactants

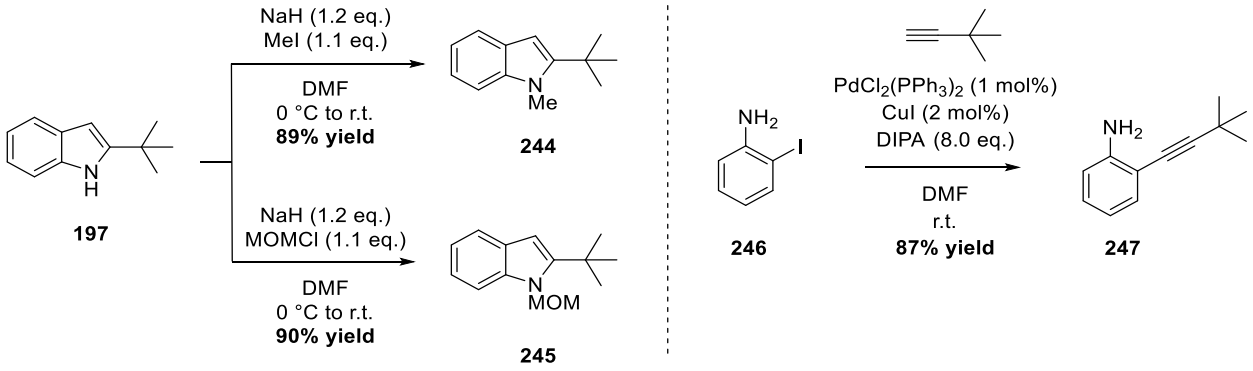


Entry	$FeCl_3·6H_2O$	Ligand	Eq. Indole	Eq. DTBP	Yield[a]	e.r.[b]
1	10 mol%	11 mol%	1.1	1.2	71%	89:11
2	10 mol%	12 mol%	1.1	1.2	68%	90:10
3	10 mol%	20 mol%	1.1	1.2	N.R.	-
4	5 mol%	6 mol%	1.1	1.2	61%	89:11
5	10 mol%	12 mol%	1.2	1.2	66%	90:10
6	10 mol%	12 mol%	1.5	1.2	71%	90:10
7	10 mol%	12 mol%	1.5	1.5	75%	90:10

Reaction Conditions*:* [a] Determined by quantitative ^1H NMR using 1,3,5-trimethoxybenzene as internal standard; [b] e.r. = enantiomeric ratio, determined by HPLC (chiral stationary phase). [c] N.R. = no reaction.

5.16 Screening of *N*-Substituents

Since our oxidative cross-coupling is highly direct and appealing from an atom economy and functional group tolerance perspective, we were reluctant to introduce protecting groups as they would add additional steps to the substrate synthesis. However, the variables left to modify were becoming scarce, so we evaluated the steric and electronic effects of various *N*-substituents on the cross-coupling in the hopes of achieving greater levels of enantioinduction (**Scheme 5.33**).



Scheme 5.33: Synthesis of *N*-protected indole derivatives – Part 1 of 2

Starting with the free N–H indole **197**, the *N*-methyl derivative **244** was synthesised in 89% yield by NaH mediated deprotonation, followed by alkylation with MeI. Using the same method, replacement of the alkylating agent with MOMCl gave **245** in 90% yield. Next, we prepared **247** *via* a Sonogashira coupling of **246** with *tert*-butylacetylene in a good yield of 87%. With synthetic intermediate **247**, we then capped the aniline with a range of electron withdrawing groups (**Scheme 5.34**). Formation of the amide **246**, carbamate **247** and sulfonamide **248** all proceeded in good yields. All of these intermediates were then cyclised with 5 mol% $PdCl_2$ in acetonitrile to give the corresponding *N*-protected indoles in excellent yields.

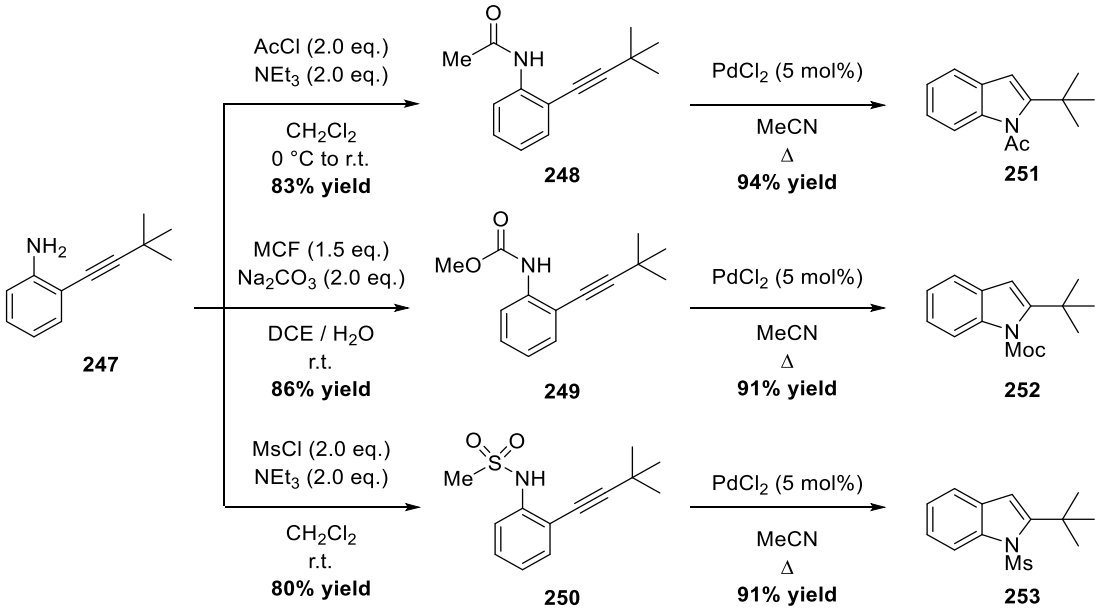
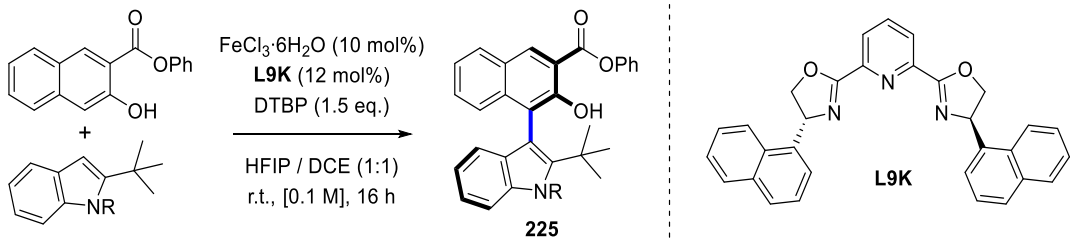


Table 5.34: Synthesis of *N*-protected indole derivatives – Part 2 of 2

We then tested the *N*-alkyl substituted indoles **244** and **245** in the oxidative cross-coupling. In these reactions, we observed the production of a new species by TLC, but we were unable to isolate the desired products (**Table 5.35**, Entries 2 & 3). The inductively donating alkyl groups increase the electron density on the heteroaromatic ring, which potentially makes the products more susceptible to over-oxidation. Next, we tested the indoles bearing an electron withdrawing group on the *N*-atom. In these cases, we failed to detect any cross-coupling product, and only unreacted indole starting material was recovered (**Table 5.35**, Entries 4- 6). These results allude to the importance of the free indole N–H for both reactivity of the starting materials, but also stability of the products.

Table 5.35: Evaluation of Indole *N*-Substituents



Entry	R Group	Indole	Yield[a]	e.r.[b]
1	H	**197**	75%	90:10
2	Me	**244**	P.D.[c]	-
3	MOM	**245**	P.D.[c]	-
4	Ac	**251**	N.R.[d]	-
5	CO_2Me	**252**	N.R.[d]	-
6	Ms	**253**	N.R.[d]	-

Reaction Conditions: [a] Determined by quantitative ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard; [b] e.r. = enantiomeric ratio, determined by HPLC (chiral stationary phase). [c] P.D. = product decomposition. [d] N.R. = no reaction.

5.17 Screening of Ester Substituents

After failing to find any improvements on modifying the indole, we circled back to another wave of ester modification. Evidently, the aryl substituent is highly important for the enantioselectivity

of the reaction. However, we postulated that further steric and electronic amendments on this group could improve the results. Furthermore, as substituted phenols are extremely cheap starting materials, the actual structure of this group was unimportant, and would not lead to a higher step count for the synthesis of the heterobiaryl targets.

To this end, a variety of substituted naphthoates were synthesised in generally good yields using a $POCl_3$ mediated esterification of **220** with the selected phenols. The results are presented in Scheme **5.36**. These substituted naphthoates were then tested in the oxidative cross-coupling with indole **197** (**Table 5.36**).

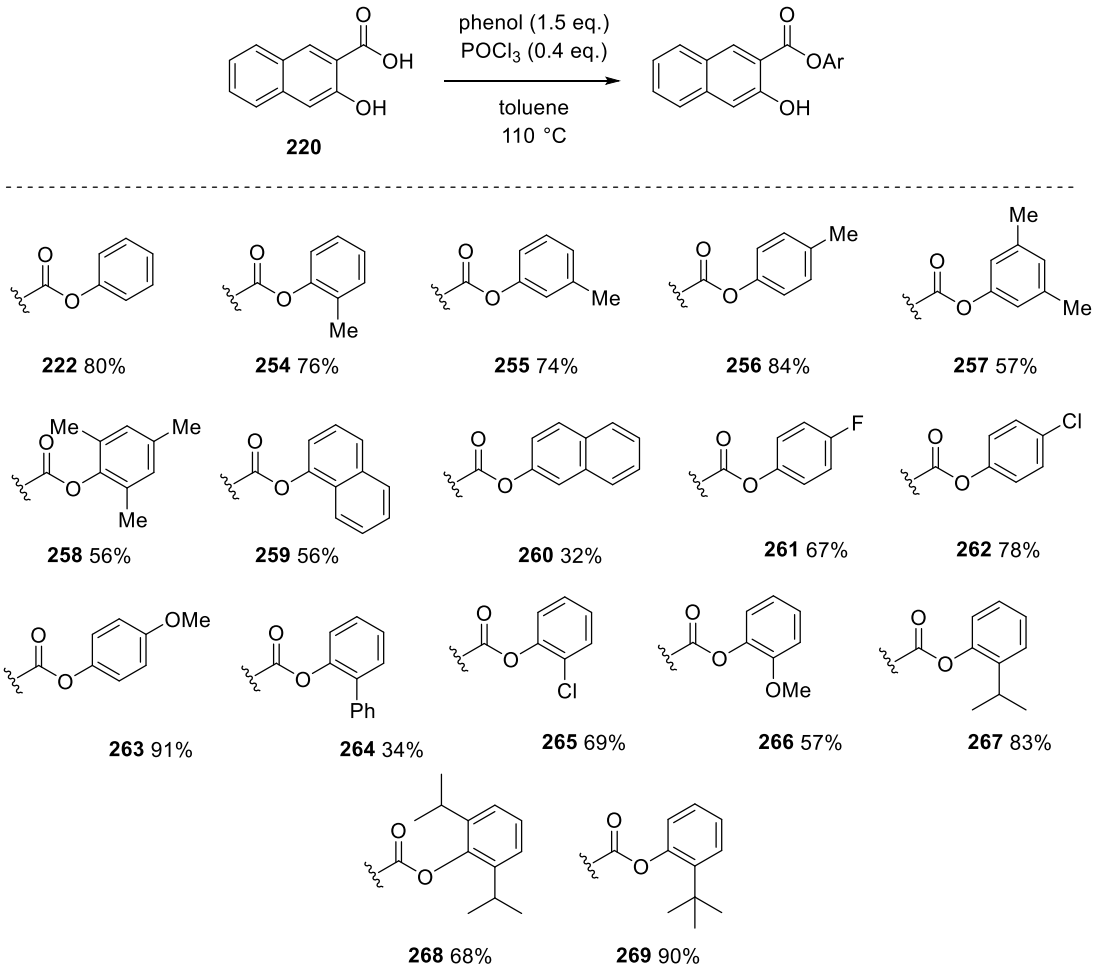
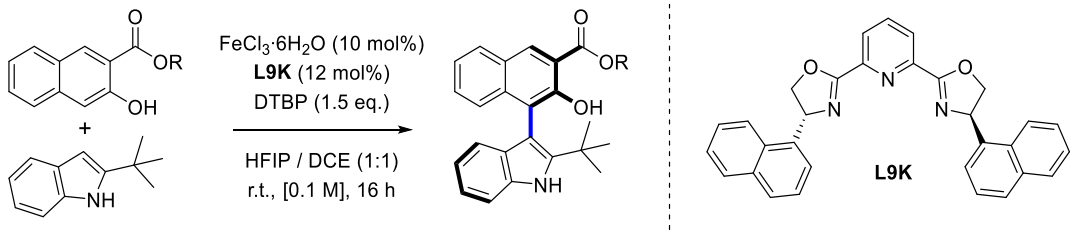


Table 5.36: Synthesis of aryl naphthoates with different ester substituents

Broadly speaking, the substitution pattern on the ester played only a small role in influencing the stereoselectivity of the reaction. This is probably because the C-3 ester substituent is remote with respect to the C-1 position of the naphthol, where the new C–C bond is formed.

Table 5.37: Variation of Aryl Ester Substituent



Entry	Naphthol	R Group	Yield[a]	e.r.[b]
1	**222**	Ph	75%	90:10
2	**261**	4-(F)-C_6H_4	58%	90:10
3	**262**	4-(Cl)-C_6H_4	78%	90:10
4	**256**	4-(Me)-C_6H_4	62%	89:11
5	**263**	4-(MeO)-C_6H_4	79%	90:10
6	**258**	2,4,6-$(Me)_3$-C_6H_2	48%	90.5:9.5
7	**257**	3,5-$(Me)_2$-C_6H_3	75%	90:10
8	**255**	3-(Me)-C_6H_4	61%	90.5:9.5
9	**254**	2-(Me)-C_6H_4	82%	91.5:9.5
10	**259**	1-naphthyl	52%	90:10
11	**260**	2-naphthyl	40%	90:10
12	**265**	2-(Cl)-C_6H_4	50%	90:10
13	**266**	2-(MeO)-C_6H_4	59%	90:10
14	**267**	2-(*i*Pr)-C_6H_4	63%	92:8
15	**269**	2-(*t*Bu)-C_6H_4	30%	89:11
16	**264**	2-(Ph)-C_6H_4	46%	87:13
17	**268**	2,6-$(i\text{Pr})_2$-C_6H_3	33%	90:10

Reaction Conditions: [a] Determined by quantitative ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard; [b] e.r. = enantiomeric ratio, determined by HPLC (chiral stationary phase).

Varying the electronics, and substitution at the *meta* and *para* positions of the aryl ester appeared to make no significant difference (**Table 5.37**, Entries 2-4, 7 & 8). Similarly, no tangible change

was made with the 1-naphthyl and 2-naphthyl esters (**Table 5.37**, Entries 10 & 11). Interestingly, we did find that the combination of ligand **L9K** with the *ortho*-methyl phenyl ester **254** gave the product in a good yield of 82% and an improved enantioselectivity of 91.5:9.5 e.r. (**Table 5.37**, Entry 9). We then explored a variety of other substituents at the *ortho*-positions. The *ortho*-chloro (**Table 5.37**, Entry 12) and *ortho*-methoxy (**Table 5.37**, Entry 13) naphthoates were tried, but both were only as selective as the unsubstituted case. Delightfully, increasing the steric bulk of the *ortho*-alkyl substituent from methyl to *i*-propyl provided a further increase in enantioselectivity to 92:8 e.r. (**Table 5.37**, Entry 14). Extending the steric bulk further to a *t*-butyl or phenyl group gave diminishing returns of the product (**Table 5.37**, Entries 15 & 16).

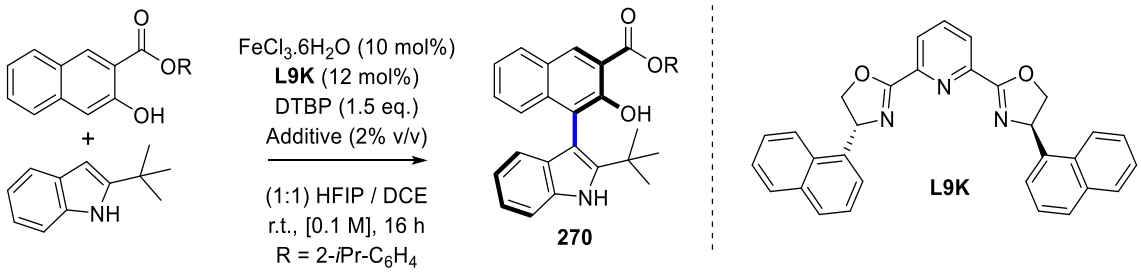
5.18 Screening of Additives

Still haunted by the spectre of a possible background reaction, additional efforts were made to increase the solubility of the iron salt during the complexation phase in the hope of eliminating the residual racemic reaction catalysed by unligated metal salts. We previously noted that the PyBOX ligands are capable of binding to the iron in a 1:2 metal-to-ligand ratio (Section **5.15**) as evidenced by the complete loss of activity when 20 mol% of the PyBOX is present. By initially dissolving the iron salt, we hoped that this would encourage the formation of the 1:1 iron-PyBOX complex, rather than sequestering the iron by two *N*,*N*,*N*-tridentate ligands. As $FeCl_3 \cdot 6H_2O$ is insoluble in DCE, we envisaged slow coordination of the PyBOX ligands to the Fe^{3+} at the solid-solvent interface. Once a single PyBOX ligand coordinates to the surface iron of the bulk metal salt, the 1:1 iron-PyBOX complex enters solution. At this stage, a consecutive solvated PyBOX ligand may then bind to the 1:1 iron-PyBOX complex, giving the coordinatively saturated and catalytically redundant $M:L_2$ complex. Since the majority of the metal salt is buried within the bulk insoluble solid at the start of the complexation phase, and coordination to the solvated complex should be reasonably facile, we suggested that uncoordinated iron salts are highly likely to remain even after the addition of a slight excess of PyBOX. To this end, we doped the reactions

with a minuscule volume (20 μL) of solvents in which the hexahydrate salt was extremely soluble, prior to the addition of the ligand.

The results of this study are presented in **Table 5.38**. Deplorably, we found that the addition of 2% (v/v) Et_2O, EtOH or THF led to reduced enantioselectivities in all cases. Whilst all additives were successful in solubilising the inorganic salts, and gave higher yields, it is clear that their presence was detrimental to the reaction's enantioselectivity.

Table 5.38: Screening of Additives



Entry	Additive	Amount	Yield[a]	e.r.[b]
1	none	-	63%	92:8
2	Et_2O	2% (v/v)	82%	90:10
3	THF	2% (v/v)	86%	89:11
4	EtOH	2% (v/v)	84%	89:11

Reaction Conditions: [a] Determined by quantitative ^1H NMR using 1,3,5-trimethoxybenzene as internal standard; [b] e.r. = enantiomeric ratio, determined by HPLC (chiral stationary phase).

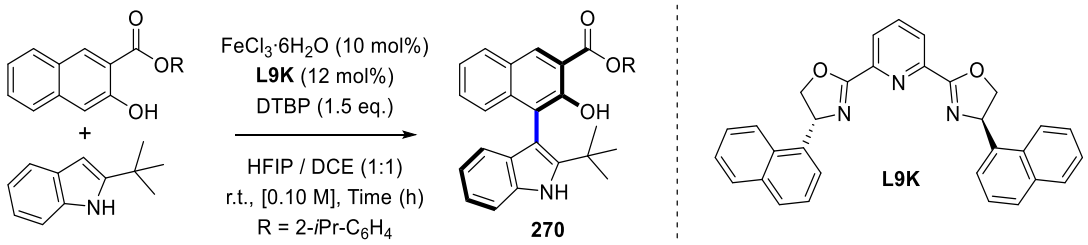
5.19 Final Optimisations

Although the addition of small quantities of solubilising agents were detrimental to the enantioselectivity of the oxidative cross-coupling, we were adamant in our reasoning about the background reaction caused by the poor solubility of the iron salts. Since a chemical solution to this problem could not be found, we wondered if mechanically reducing the particle size of the iron salts prior to the addition of the ligand would provide a more favourable outcome.

As shown in **Figure 5.40a**, $FeCl_3 \cdot 6H_2O$ is completely insoluble in DCE. In this effort, we subjected the suspended inorganic material to high frequency sonication in a water bath for 30 minutes to

reduce the particle size of the iron salt. After this time, we found the solid particles had been broken down into a fine yellow suspension (**Figure 5.40b**). Next, we added the ligand at room temperature, which instantly produced an orange solution (**Figure 5.40c**). After the addition of HFIP, followed by the ligands and oxidant, the reaction was stirred overnight. Using this protocol, the product was produced in a significantly higher e.r. of 94:6 (**Table 5.39**, Entry 2). This result not only represents the best conditions identified to date, but also provided strong evidence that a racemic background reaction mediated by unligated metals salts competes with the enantioselective process. During our optimisation campaign, the reactions conversions typically proceeded to around 70% with a reaction time of 16 h. We decided to increase the reaction time to 48 h under the new set of conditions. Gratifyingly, this provided us with a 91% isolated yield of **270**, without a change in e.r., under our optimal set of conditions (**Table 5.39**, Entry 3).

Table 5.39: Final Optimisations



Entry	Fe Salt Sonicated?	Time	Yield[a]	e.r.[b]
1	No	16 h	63%	92:8
2	Yes	16 h	60%	94:6
3	Yes	48 h	91%[c]	94:6

Reaction Conditions: [a] Determined by quantitative ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard; [b] e.r. = enantiomeric ratio, determined by HPLC (chiral stationary phase). [c] Isolated yield.

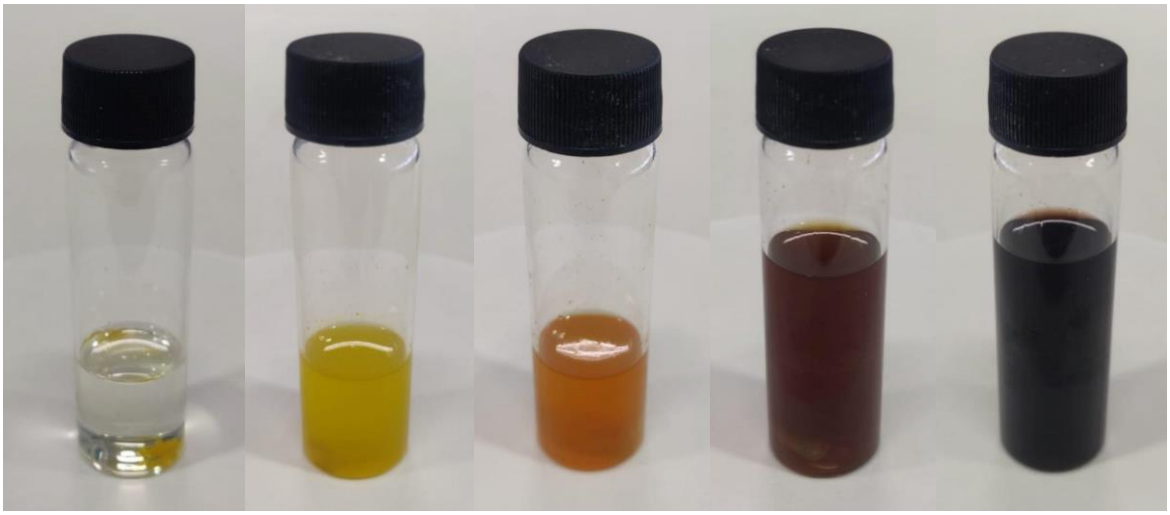
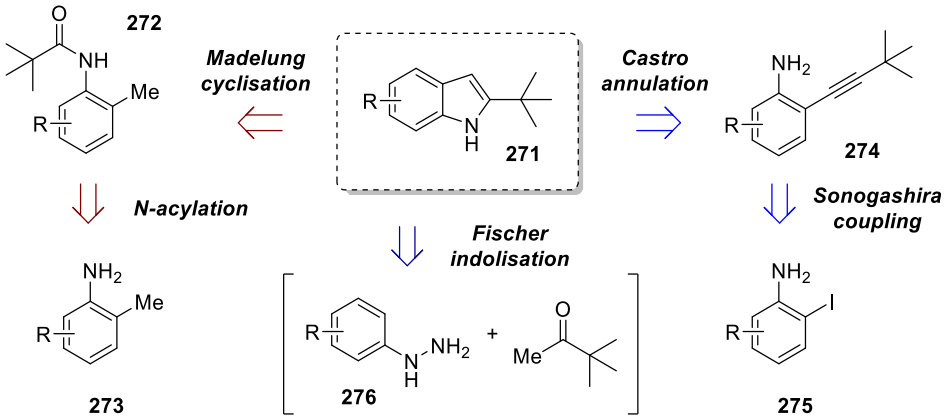


Figure 5.40: Graphical guide showing effect of sonication: a) solid lumps of $FeCl_3 \cdot 6H_2O$ resting in DCE; b) Fine yellow suspension of $FeCl_3 \cdot 6H_2O$ in DCE after 30 min sonication; c) orange homogeneous solution formed 2 h after addition of PyBOX **L9K** to the suspension; d) brown solution formed 30 min after addition of HFIP; e) dark solution formed after addition of substrates and DTBP

Chapter 6: Substrate Scope

6.1 Retrosynthetic Strategy

With the optimised conditions in hand, we set out to investigate the functional group tolerance of the enantioselective oxidative cross-coupling. Fortunately, as the reaction does not require any specific activating groups, we envisaged the substrate synthesis to be relatively straightforward. The key building block was C-2 substituted indole **271**, which we proposed could be prepared *via* three orthogonal retrosynthetic strategies (**Scheme 6.1**). We reasoned that the combination of these complimentary approaches would enable access to a wide variety of indole derivatives for testing. These approaches were: A) Madelung cyclisation of an *o*-methyl anilide **272**,[117] B) Castro annulation of an *o*-alkynyl aniline **274**,[118] and C) Fischer indolisation of a substituted phenylhydrazine **276**.[119]

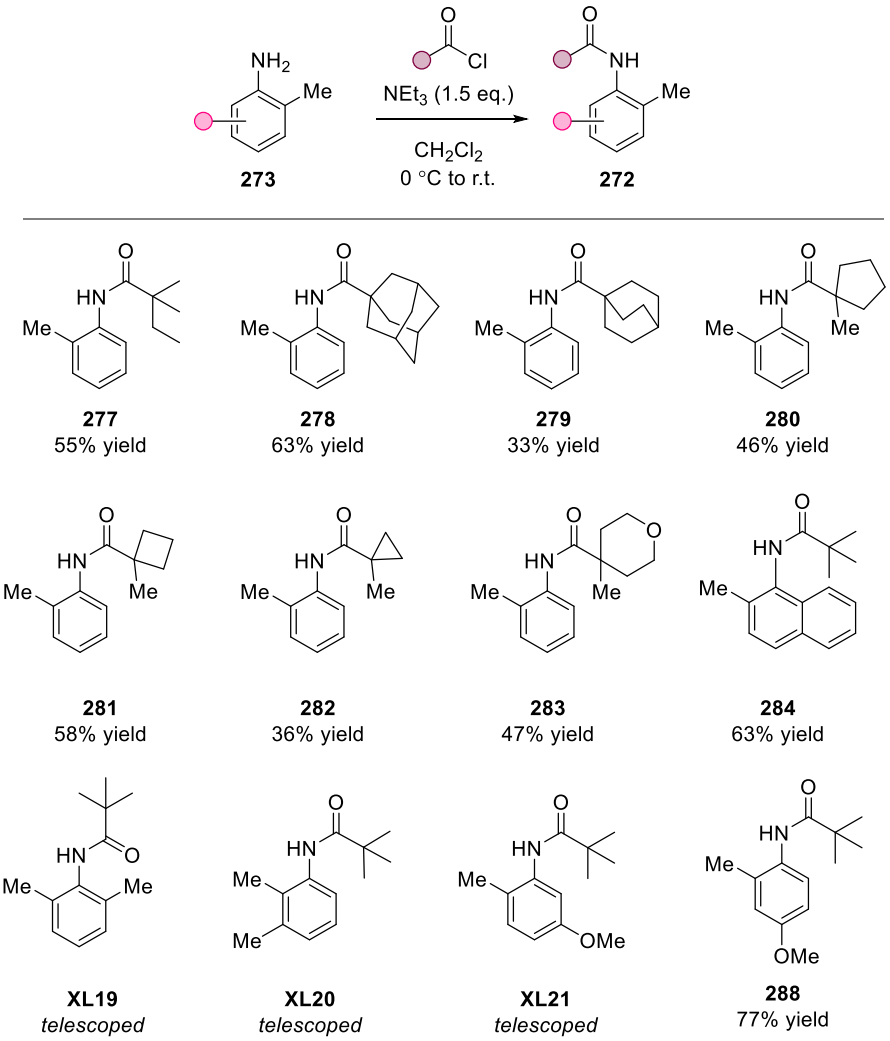


Scheme 6.1: Retrosynthesis of C-2 substituted Indoles

6.2 Indole Synthesis: Madelung Cyclisation

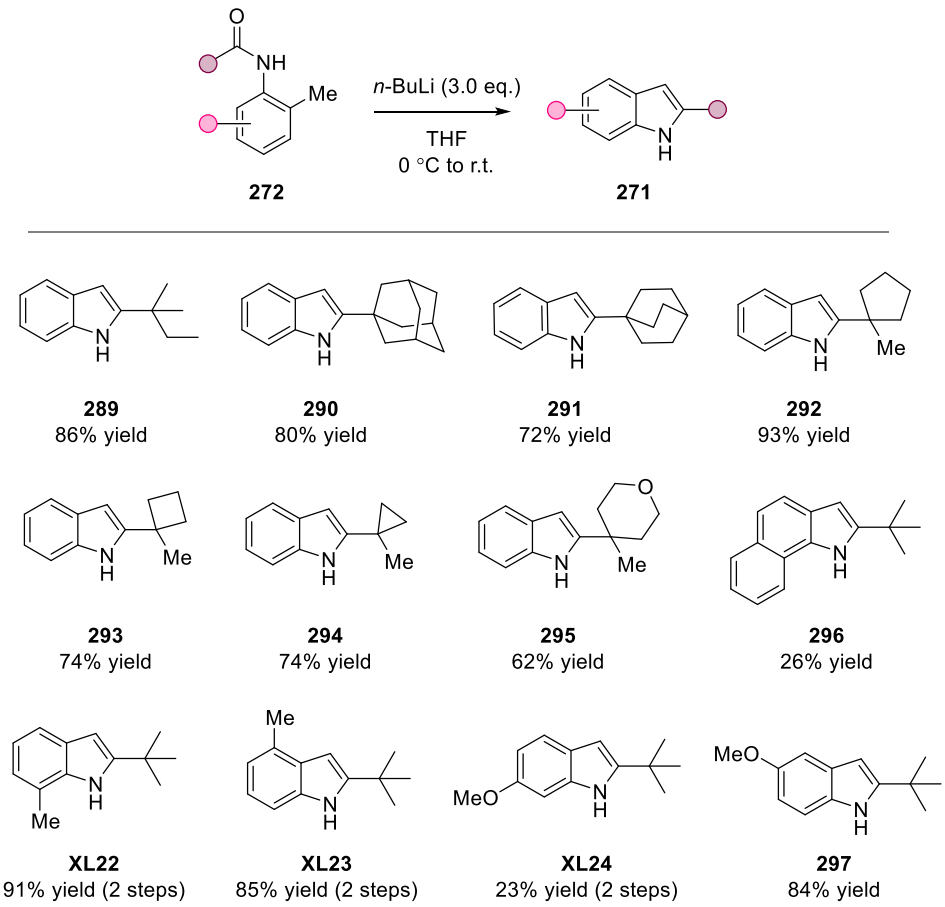
Starting with the Madelung cyclisation route, we prepared the indole pre-cursors of type **272** *via* the *N*-acylation of a range *o*-toluidines **273**. This method was successfully implemented in the synthesis of indole **197**, which was used throughout the optimisation. During the synthesis of this material, we noted that the indole precursor **196** was highly crystalline. With this knowledge, we carried out the amide coupling reactions on a relatively large scale (up to 5 g) and the crude

products were purified by recrystallisation from hot EtOAc. This allowed us to prioritise expediency and enabled facile access to a broad range of anilides in this step. We were interested in the effect of the indole C-2 substituent on the coupling reaction, so a variety of acid chlorides bearing different *tert*iary alkyl groups were combined with *o*-toluidine in the presence of NEt_3. This reliably produced the amides **277**-**283** in moderate yields of 33-63%. We then targeted several substrates bearing substituents on the arene ring. This allowed for the synthesis of anilides **284** and **288** in good yields of 63 and 77%. The crude material of substrates **XL19**-**XL21** was carried forwards to the next step without purification.



Scheme 6.2: Synthesis of *o*-methyl anilides [Compounds made by Xiangqian Liu are denoted with the prefix "XL"]

Having prepared a variety of amides, we continued to the Madelung cyclisation step (**Scheme 6.3**). In the presence of excess strong base (*n*-BuLi), double deprotonation of the anilide N–H and the benzylic C–H occurs. The benzylic organolithium species then attacks the carbonyl of the amide, which is ultimately followed by the loss of water to produce the indole products. Using this method, the various C-2 substituted indoles **289**-**295** were prepared in very good yields of 62-93%. Similarly, the indoles with the different aryl backbones were also furnished without complications, in yields of 23-91%.

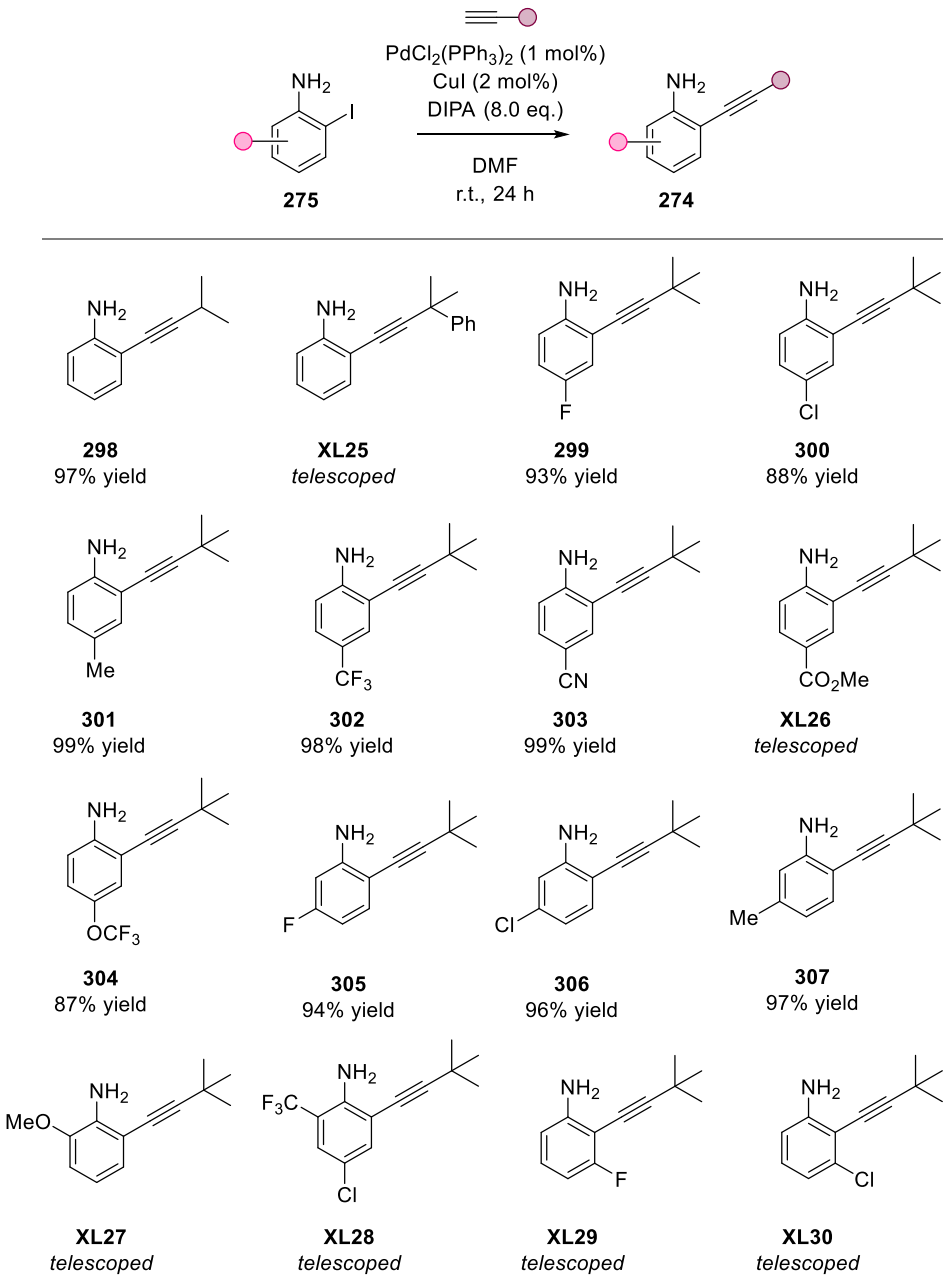


Scheme 6.3: Synthesis of indoles *via* Madelung cyclisation [Compounds made by Xiangqian Liu are denoted with the prefix "XL"]

6.3 Indole Synthesis: Castro Annulation

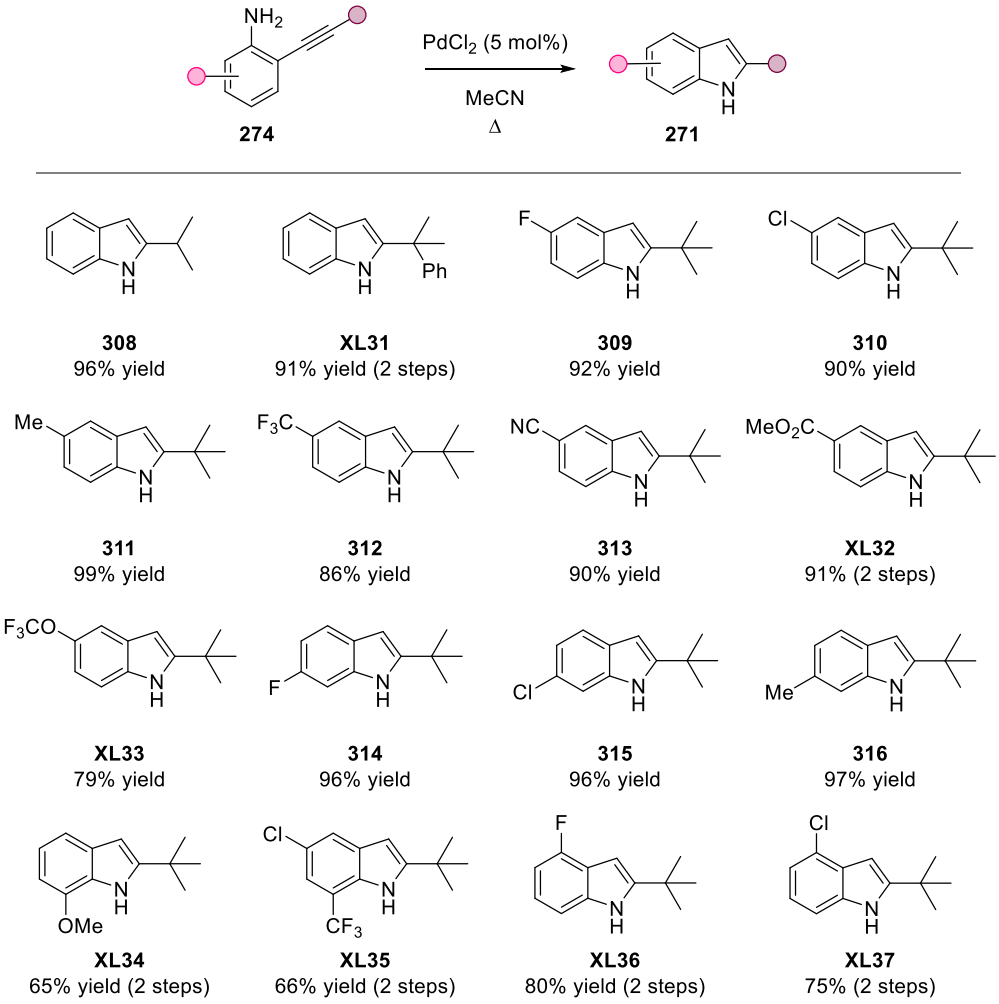
Next, explored more in-depth substitution on the indole backbone through the Castro annulation (**Scheme 6.4**). A wide range of *o*-iodoanilines with various substitution patterns are

commercially available. We opted for a two-step rather than a one-pot Castro synthesis based on previously reported syntheses of similar indoles.[32] For the first step, using the method of Tan, *o*-iodoanilines **275** were subjected to a Sonogashira coupling with *tert*-butylacetylene (**Scheme 6.4**). Generally, this reaction was exceptionally high yielding, usually affording the alkyne products in yields above 90%.



Scheme 6.4: Sonogashira Coupling [Compounds made by Xiangqian Liu are denoted with the prefix "XL"]

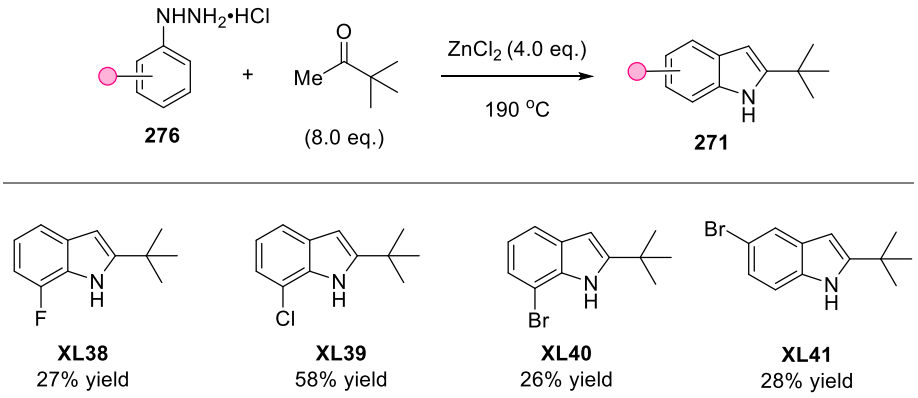
Substrates **XL26** and **XL27**-**XL30** were also prepared *via* this method, but these were carried into the next step without purification. Having furnished a range of alkynes of type **274**, the Castro indole synthesis was then carried out (**Scheme 6.5**). In these reactions, the catalytic $PdCl_2$ serves as a π-acid that complexes with the alkyne, activating the substrate towards a 5-*endo*-dig cyclisation with the anilinic *N*-atom. This method was highly fruitful and allowed us to synthesise a variety of C-2 substituted indoles bearing a range of functionality at the 4, 5, 6 and 7-positions around the indole nucleus in excellent yields.



Scheme 6.5: Synthesis of indoles *via* Castro annulation [Compounds made by Xiangqian Liu are denoted with the prefix "XL"]

6.4 Indole Synthesis: Fischer Indolisation

For the final approach, we performed small number of Fischer indolisation reactions to construct the indoles that were incompatible with the Madelung and Castro pathways (**Scheme 6.6**). To this end, the hydrochloride salt of phenylhydrazine was mixed with pinacolone in the presence of excess $ZnCl_2$ at high temperatures. These reactions were fairly low yielding (26-58%), but still afforded synthetically useful quantities of indoles **XL38**-**XL41** for evaluation in the substrate scope.

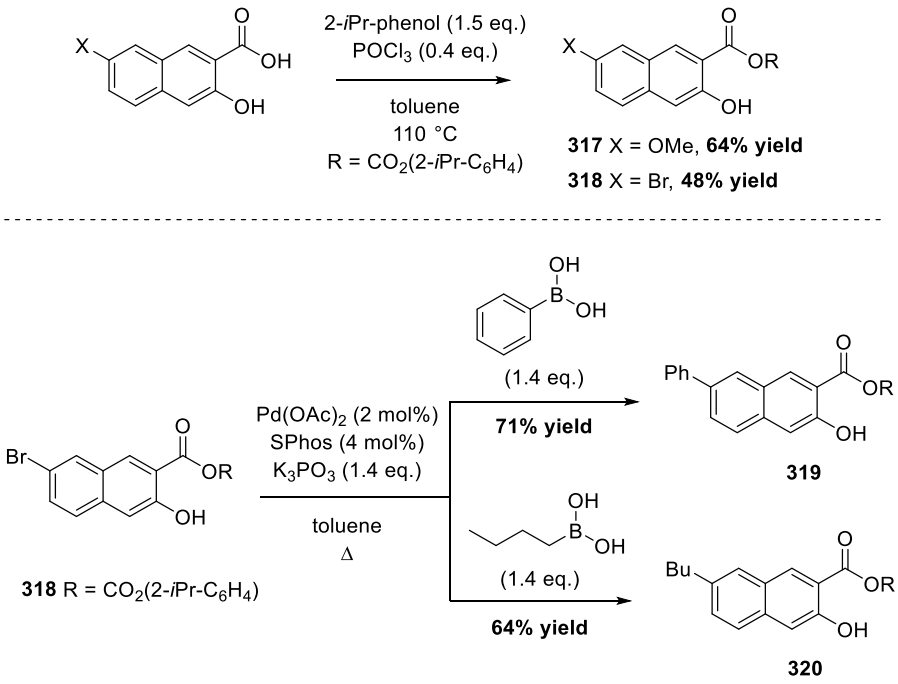


Scheme 6.6: Synthesis of indoles *via* Fischer-Indolisation [Compounds made by Xiangqian Liu are denoted with the prefix "XL"]

6.5 Synthesis of Naphthoates

Following the successful preparation of the substituted indoles, we moved on to the synthesis of various naphthoates (**Scheme 6.7**). The 6-position of BINOL derivatives is known to be important for fine-tuning their steric and electronic properties, so we opted to focus only on changing the substituent at this site in the naphthol coupling partners.[9] The 6-methoxy and 6-bromo naphthoic acids are commercially available, so these were first esterified into **317** and **318** using the procedure previously outlined in 64% and 48% yields respectively.

With the 6-bromo naphthoate derivative, several Suzuki-Miyaura couplings were performed using the procedure described by Tan.[120] This gave access to the corresponding 6-phenyl **319** and 6-butyl **320** naphthoates in good yields of 71% and 64%.



Scheme 6.7: Synthesis of 6-substituted naphthoates

6.6 Substrate Scope of Enantioselective Oxidative Cross-Coupling

With a wide array of both coupling partners in hand, we began subjecting these substrates to our optimised enantioselective oxidative cross-coupling conditions. In the following scope tables, the numbers in square brackets represent the molar ratio of the [heterobiaryl product : 3,3'-BINOL **322**]. The mass balance of the recovered naphthol is also accounted for in curved brackets in all reactions (**Tables 6.8** & **6.9**).

The size of the indole C-2 substituent is important in determining the rotational barrier of the biaryl products and hence we explored substrates with sterically hindered groups in this position. An indole bearing a *tert*-amyl group couples effectively to afford **322** in 83% yield and in high enantioselectivity (95:5 er) with no trace of other products. Similarly, 2-admanatyl and [2.2.2.] bicyclooctane groups are also tolerated to afford **323** (71% yield; 91:9 e.r.) and **324** (80% yield; 86:14 e.r.) with good levels of selectivity. Other cycloalkyl groups including 2-methylcyclopentyl and 2-methylcyclobutyl are also effective in this reaction, affording biaryls **325** (75% yield,

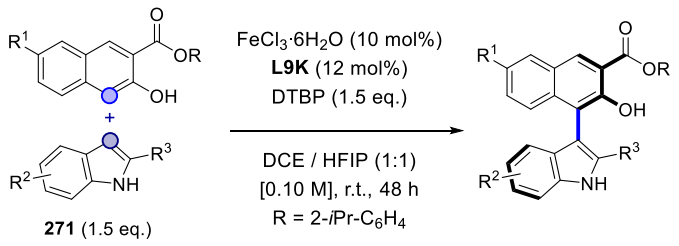
94:6 e.r.) and **326** (90% yield, 96:4 e.r.) respectively. Changing to a smaller group at this position such as 2-methylcycpropyl or *iso*-propyl does not impact the efficiency of the coupling itself (affording **327** and **328** in 74% and 93% yield as the sole products) but does lead to a significant reduction in enantioselectivity (to 82:18 and 60:40 e.r.). The pyran substituted heterobiaryl **329** was prepared in 70% yield and a lower e.r. of 67:33 e.r. Enantioselectivity is restored with an indole bearing an α,α-dimethylbenzyl group (to afford **XL42** in 80% yield and 97:3 e.r.). A phenyl ester on the naphthol is also a viable and more selective substrate, generating **XL43** in 85% yield and 98:2 e.r. We subsequently explored substitution around the indole ring. At the C-4 position of the indole, the methyl group leads to a lower yield and complete ablation of the enantioselectivity in **330** (51% yield and 51:49 e.r.). However, indoles bearing halogens such as fluorine or chlorine at this position both undergo oxidation without incident to afford biaryls **331** (80% yield, 90:10 e.r.) and **332** (82% yield, 94:6 e.r.) respectively. We next examined C-5 substitution on the indole reactant.

Electron donating groups such as methoxy are highly effective, affording biaryl **333** in 97% yield and 93:7 e.r. 5-alkyl groups are also well tolerated, affording biaryl **334** in 78% yield and 93:7 e.r. We observed that electron withdrawing groups such as fluorine in this position led to lower conversions as in **335** (60% yield, 92:8 e.r.), and considered that this may provide some insight into the mechanism of this transformation. Consequently, we decided to study a series of different electron withdrawing groups in this position to evaluate the impact on the reaction. A 5-chloro indole was incompatible under these conditions, yielding **336** in lower levels of enantioselectivity (71:29 e.r.). A 5-bromo substituent led to biaryl **337** in only 40% yield, but with a relatively high enantioselectivity (90:10 e.r.). More powerful electron withdrawing groups on the indole coupling partner led to the generation of biaryls bearing as an ester **338** (40% yield, 64:46 e.r.), a trifluoromethyl group **339** (28% yield, 72:28 e.r.) or a cyano group **340** (13% yield, 85:15 e.r.) in lower yields and enantioselectivities; we also saw a reduction in chemoselectivity as seen through the competitive formation of small quantities of the C_2-symmetric 3,3'-BINOL product. It is clear that the electronic nature of the substituents on the indole has an impact on conversion

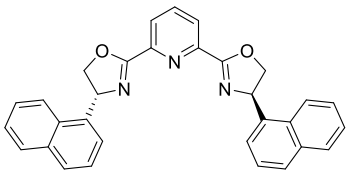
and selectivity (see Chapter **7** for further discussion). We also tried 5-trifluoromethoxy indole, which gave **XL44** in much lower yield and enantioselectivity (40% yield, 57:43 e.r.). 5-PMP indole performed reasonably well, producing **XL45** in good yield and moderate enantioselectivity (80% yield, 80:20 e.r.). C-6 substitution is tolerated albeit with slightly lower levels of enantioselectivity: 6-methyl **341** (79% yield, 88:12 e.r.), 6-fluoro **342** (63% yield, 84:16 e.r.) and 5-chloro **343** (56% yield, 89:11 e.r.) are all effectively produced. A 6-methoxy group on the indole gave **XL46** in an excellent yield (90% yield) but somewhat surprisingly, as a racemate, which may again elude to the sensitivity of this reaction to the electronic nature of the indole. An indole bearing a C-7 methyl group is also a competent partner in this reaction, leading to the corresponding biaryl **344** in 85% yield and 86:14 e.r., and the C-5,7-dimethyl indole was similarly selective (85% yield, 84:16 e.r.). However, the placement of a fluoro **XL47** (36% yield, 83:17 e.r.), chloro **XL48** (30% yield, 63:37 e.r.) or methoxy **XL49** (70% yield, 69:31 e.r.) groups at this position led to diminished yields and enantioselectivities of the corresponding heterobiaryls. The highly electron deficient heterobiaryl **346** was isolated in trace yield after 48 h, and so the enantioselectivity was not determined. The tricyclic indole decomposed under the oxidative reactions conditions, and we could not recover the desired heterobiaryl product **347**.

We next examined the introduction of different groups on the naphthol coupling partner was possible. A 7-bromo substituent coupled effectively to afford biaryl **348** in 66% yield and 93:7 e.r.; a more conjugating group in 7-phenyl was also successful to afford **351** with lower conversion (52% yield) and 90:10 e.r. We are able to accommodate groups on both coupling partners: a 7-methyl indole coupled with a 7-bromo naphthol to exclusively afford the *hetero*-coupled biaryl **349** (67% yield; 87:13 e.r.). This principle can be extended to the formation of different biaryls such as **350** (76% yield, 91:9 e.r.). Different substituents on the naphthol component can also be combined with different C-2 substituents on the indole component to afford an array of different products; these are exemplified by the formation of biaryl compounds bearing bromo **351** (54% yield, 95:5 e.r.), methoxy **354** (82% yield, 92:8 e.r.), aryl **353** (45% yield, 95:5 e.r.) and alkyl **355** (66% yield, 93:7 e.r.) groups.

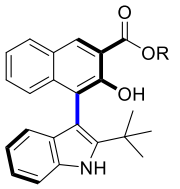
Table 6.8: Substrate scope of enantioselective oxidative cross-coupling – Part 1 of 2



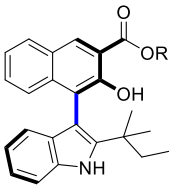
271 (1.5 eq.)



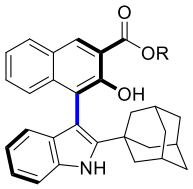
L9K



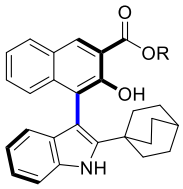
270 91% yield; (93%)
[>50:1]; 94:6 e.r.



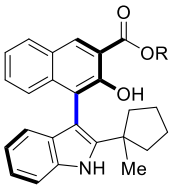
322 83% yield; (92%)
[>50:1]; 95:5 e.r.



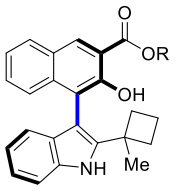
323 71% yield; (88%)
[>50:1]; 91:9 e.r.



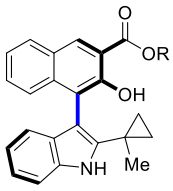
324 80% yield; (86%)
[>50:1]; 86:14 e.r.



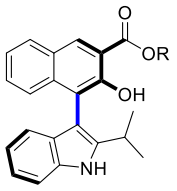
325 75% yield; (95%)
[>50:1]; 94:6 e.r.



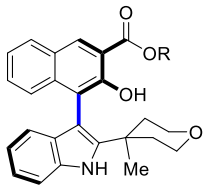
326 90% yield; (94%)
[>50:1]; 96:4 e.r.



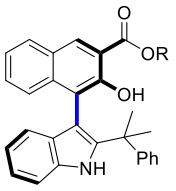
327 74% yield; (96%)
[>50:1]; 82:18 e.r.



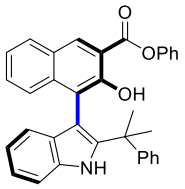
328 93% yield; (98%)
[>50:1]; 60:40 e.r.



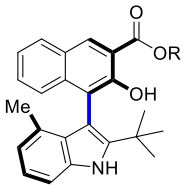
329 70% yield; (90%)
[>50:1]; 67:33 e.r.



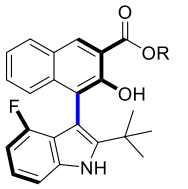
XL42 80% yield; (91%)
[>50:1]; 96:4 e.r.



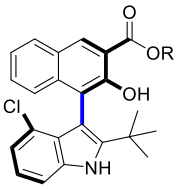
XL43 85% yield; (90%)
[>50:1]; 98:2 e.r.



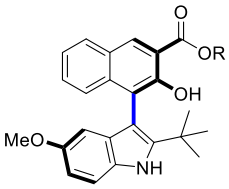
330 51% yield; (89%)
[>50:1]; 51:49 e.r.



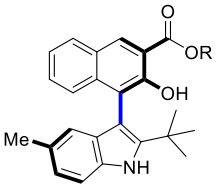
331 80% yield; (94%)
[>50:1]; 90:10 e.r.



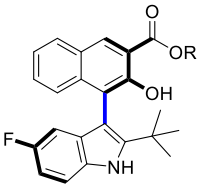
332 82% yield; (90%)
[>50:1]; 94:6 e.r.



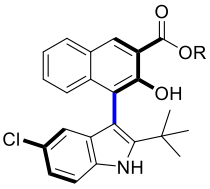
333 97% yield; (99%)
[>50:1]; 93:7 e.r.



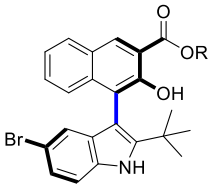
334 78% yield; (89%)
[>50:1]; 93:7 e.r.



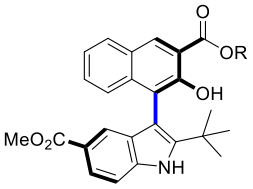
335 60% yield; (90%)
[44:1]; 92:8 e.r.



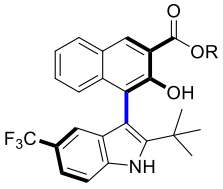
336 63% yield; (86%)
[38:1]; 71:29 e.r.



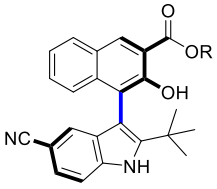
337 40% yield; (87%)
[21:1]; 90:10 e.r.



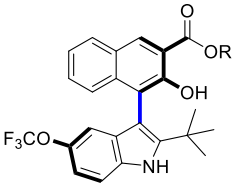
338 40% yield; (92%)
[18:1]; 85:15 e.r.



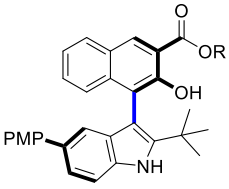
339 28% yield; (97%)
[17:1]; 72:28 e.r.



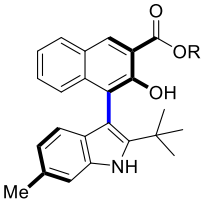
340 13% yield; (97%)
[16:1]; 85:15 e.r.



XL44 40% yield; (97%)
[22:1]; 57:43 e.r.



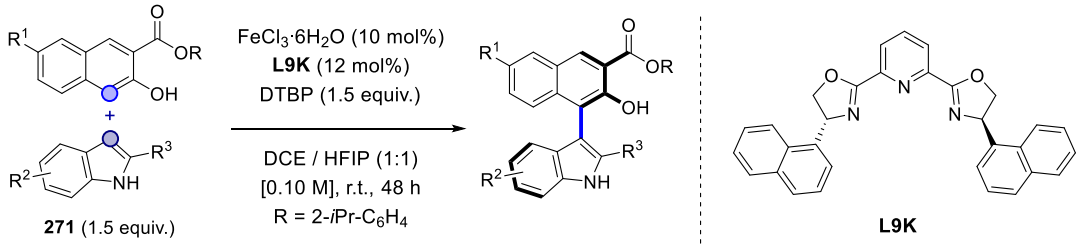
XL45 80% yield; (95%)
[>50:1]; 80:20 e.r.

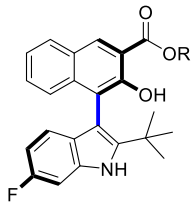


341 79% yield; (98%)
[>50:1]; 88:12 e.r.

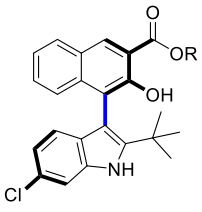
Reaction Conditions: All performed on 0.1 mmol scale: $FeCl_3 \cdot 6H_2O$ (10 mol%), ligand **L9K** (12 mol%) naphthol (1.0 eq.), indole (1.5 eq.), DTBP (1.5 eq.), DCE / HFIP, 1:1 (v/v); [naphthol] = 0.10 M, r.t., 48 h

Table 6.9: Substrate scope of enantioselective oxidative cross-coupling – Part 2 of 2

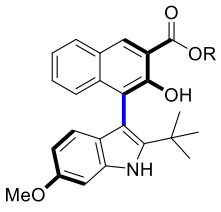




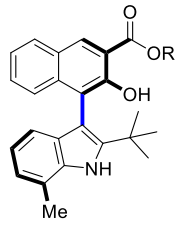
342 63% yield; (100%)
[45:1]; 84:16 e.r.



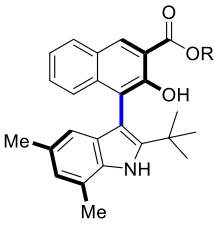
343 56% yield; (86%)
[36:1]; 89:11 e.r.



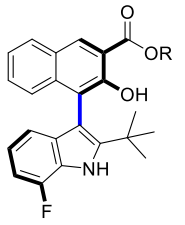
XL46 90% yield; (94%)
[>50:1]; 50:50 e.r.



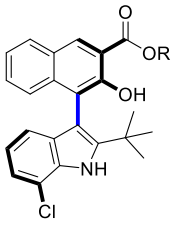
344 66% yield; (89%)
[>50:1]; 86:14 e.r.



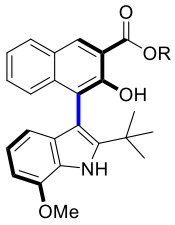
345 85% yield; (90%)
[>50:1]; 84:16 e.r.



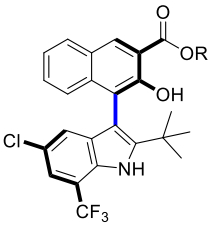
XL47 36% yield; (90%)
[21:1]; 83:17 e.r.



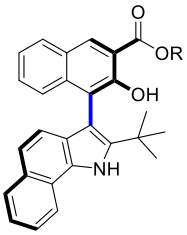
XL48 30% yield; (90%)
[30:1]; 63:37 e.r.



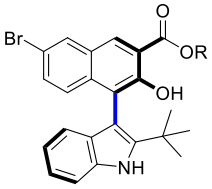
XL49 70% yield; (90%)
[>50:1]; 69:31 e.r.



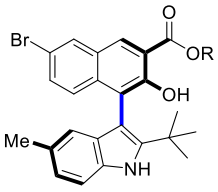
346 <5% yield;
(94% BRSM)



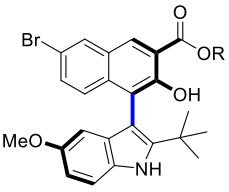
347 *product not isolated*



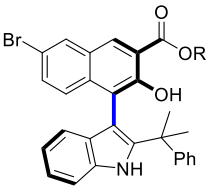
348 66% yield; (92%)
[>50:1]; 93:7 e.r.



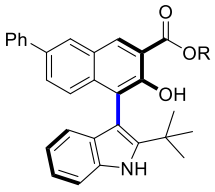
349 67% yield; (89%)
[>50:1]; 87:13 e.r.



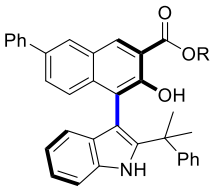
350 76% yield; (92%)
[>50:1]; 91:9 e.r.



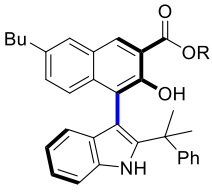
351 54% yield; (87%)
[>50:1]; 95:5 e.r.



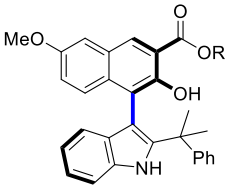
352 52% yield; (86%)
[>50:1]; 90:10 e.r.



353 45% yield; (85%)
[>50:1]; 95:5 e.r.



354 66% yield; (80%)
[>50:1]; 93:7 e.r.

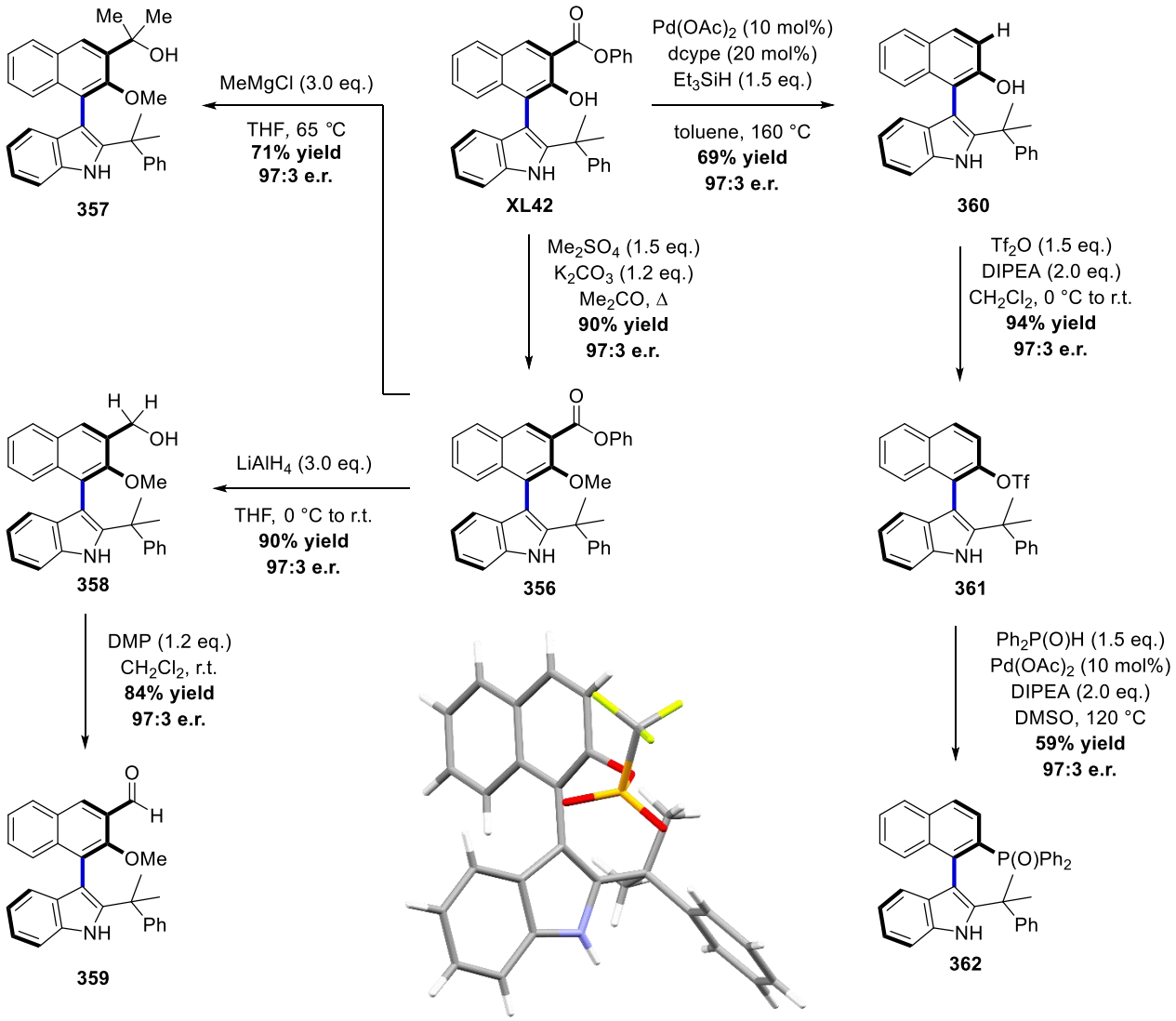


355 82% yield; (90%)
[>50:1]; 92:8 e.r.

Reaction Conditions: All performed on 0.1 mmol scale: $FeCl_3 \cdot 6H_2O$ (10 mol%), ligand **L9K** (12 mol%) naphthol (1.0 eq.), indole (1.5 eq.), DTBP (1.5 eq.), DCE / HFIP, 1:1 (v/v); [naphthol] = 0.10 M, r.t., 48 h

6.7 Derivitization of Heterobiaryls

These atropisomeric heterobiaryls contains a number of different functional groups, and to demonstrate their orthogonality, chemoselective derivatizations were implemented (**Scheme 6.10**). To do this, we performed a tenfold scale-up of our best performing substrate **XL42** (from 0.1 mmol to 1.0 mmol scale). This effectively provided several hundred milligrams of **XL42** in and without significant detriment to the enantioselectivity (85% yield, 97:3 e.r.).



Scheme 6.10: Derivitization of heterobiaryls and X-Ray structure of **361**

The C-3 ester on the naphthol **XL42** (97:3 e.r.), which is implicated in the observed selectivity in the cross-coupling process, can be transformed into *tert*iary alcohol **357**, a group valuable in

catalysis, *via O*-alkylation to **356**, followed the addition of an excess of Grignard reagent. Reduction of this functional group is also possible, without destruction of the enantioselectivity, yielding **358** (90% yield, 97:3 e.r.). The benzylic alcohol product may also be transformed into the corresponding aldehyde **359** with DMP (84% yield, 97:3 e.r.). Pleasingly, under these oxidising conditions the enantioenrichment of the product is preserved. The C-3 ester group can also be conveniently removed by a palladium(II) catalysed reductive decarboxylation in the presence of stoichiometric triethylsilane to afford **360** (69% yield, 97:3 e.r.). Although this requires high temperatures, the magnitude of the aryl-aryl barrier enables this to be performed without compromising enantiointegrity. The phenol in **360** can be simply transformed into triflate **361**. We were also able to obtain single crystals of the highly enantioenriched aryl triflate by slow evaporation of CH_2Cl_2 from hexane. X-ray crystallography then allowed us to confirm the absolute configuration of this compound as R_a [when (*R*,*R*)-PyBOX is used]. This intermediate can also function as a divergent intermediate for a range of cross-coupling reactions, as exemplified by the formation of phosphine oxide **362**, through palladium catalysed coupling with diphenylphosphine oxide (59% yield, 97:3 e.r.).

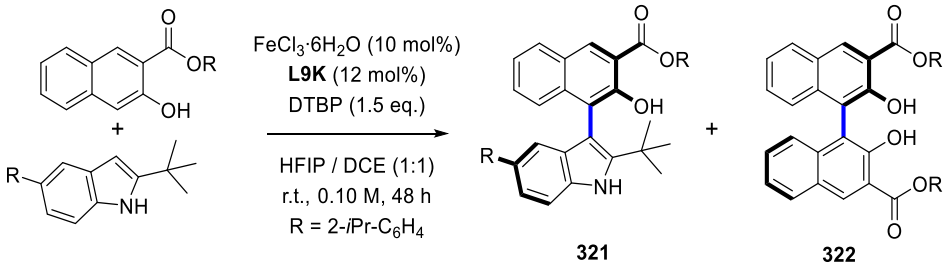
These reactions highlight the broad synthetic utility of these axially chiral cores. Although the ester group is essential for the chemoselectivity of this reaction, we have demonstrated that this need not limit the synthetic utility of the products. This group can serve as a useful handle for further functionalisation or can be removed entirely. Furthermore, due to the extremely high rotational barriers of the heterobiaryl products, the enantiomeric integrity of the products is preserved even under harsh reaction conditions.

Chapter 7: Mechanistic Investigations

7.1 Measurement of Oxidation Potentials

In chapter 4, we made preliminary investigations into the reaction mechanism by measuring the oxidation potentials and global nucleophilicities of both the indole and naphthol components, invoking a radical–anion mechanism to explain the high levels of cross-coupling selectivity. In this section, we delve deeper into this reaction and provide further evidence to support this hypothesis. From the substrate scope, we recognised that the electronic nature of the indole was highly influential in determining both the yield, chemo- and enantioselectivity of the reaction (Section **6.5**). We observed divergent reactivity based on the 5-substituents on the indole nucleus, so we decided to measure the oxidation potentials of the indoles across this series.

Table 7.1: Selected oxidation potentials of various substrates



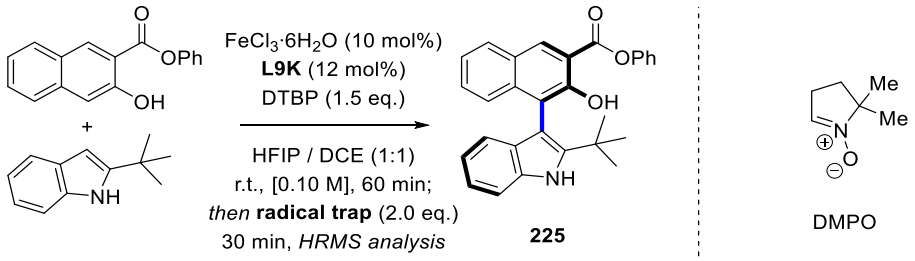
Entry	Indole 5-Subtituent (R)	E_{ox}	Yield[a]	[321:322] m.r.[b]	e.r.[c]
1	MeO	0.81	97%	>50:1	93:7
2	Me	0.78	78%	>50:1	93:7
3	H	0.71	91%	>50:1	94:6
4	F	0.92	60%	44:1	92:8
5	Br	0.97	40%	21:1	90:10
6	CO_2Me	1.00	40%	18:1	85:15
7	CF_3	1.03	28%	17:1	72:28
8	CN	1.22	13%	15:1	85:15

Reaction Conditions: [a] isolated yield; [b] m.r. = molar ratio of **321**:**322**; Determined by quantitative ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard; [c] e.r. = enantiomeric ratio, determined by HPLC (chiral stationary phase).

The most electron rich indoles (where R = MeO, Me or H) gave the corresponding heterobiaryls with the highest yields, and the greatest cross-coupling selectivities, with no homocoupling products being observed (**Table 7.1**, Entries 1-3). The oxidation potentials of the indoles began to rise as electron withdrawing groups are placed at the 5-position. The increase in oxidation potentials across this series is strongly correlated to the rate of conversion to the corresponding heterobiaryl. Furthermore, installation of electron withdrawing groups onto the indole is also marked by a decrease in chemoselectivity of the reaction (**Table 7.1**, Entries 4-8). As the indole becomes harder to oxidise, formation of the C_2-symmetric BINOL product **332** becomes competitive. In cases where the yield of **331** was low, we were also able to recover the unreacted indole and naphthols. These results are consistent with indole oxidation being rate limiting.

7.2 Radical trapping Experiments

To capture any putative radical intermediates generated over the course of the oxidative coupling reaction, the radical trapping agents DMPO & $P(OEt)_3$ (2 equiv.) were separately added 60 min after the addition of the substrates and DTBP to the preformed catalyst. The reaction mixtures were then stirred at room temperature for an additional 30 min and an aliquot was analysed by HRMS-ESI.



Scheme 7.2: Radical trapping experiments

For both of the spin traps added, we were able to identify an adduct by HRMS-ESI that was consistent with the capture of an indole radical (**Figure 7.3**). Furthermore, we were also unable to observe the corresponding radicals adducts that would arise from oxidation of the naphthol.

These results again point towards highly selective single electron oxidation of the indole, and a radical–anion type coupling mechanism.

With DMPO, the proposed intermediate **363** was caught and detected. **HRMS** (ESI^+) m/z Calcd. for $C_{18}H_{25}N_2O$ $(M)^+$ 285.1961, found 285.1964; With $P(OEt)_3$, the proposed intermediate **364** was caught and detected. **HRMS** (ESI^-) m/z Calcd. for $C_{16}H_{25}NO_3P$ $(M+H)^+$ 310.1567, found 310.1567.

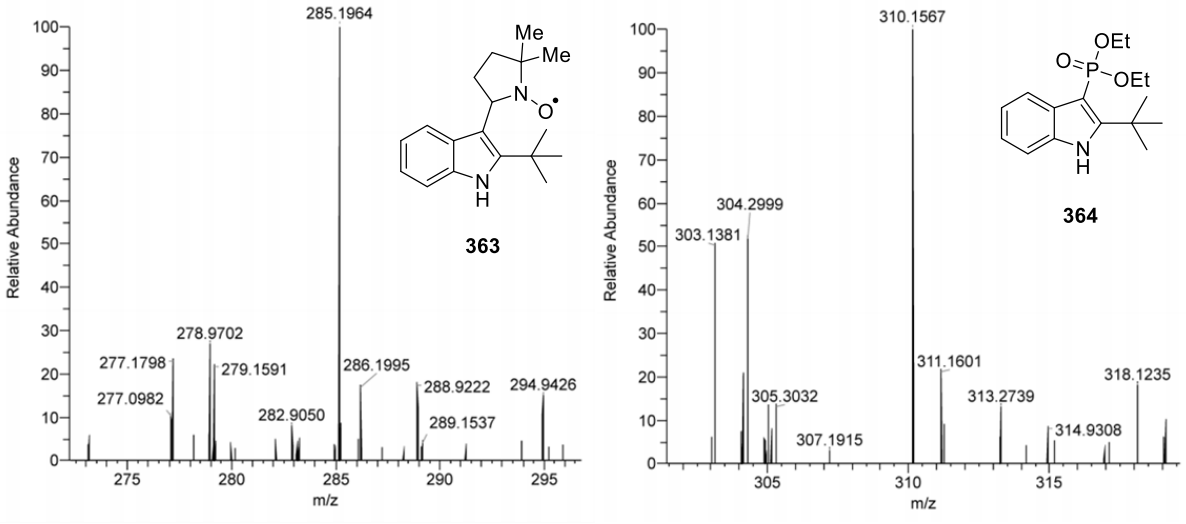


Figure 7.3: HRMS ESI spectra for observed indole radical adducts

7.3 Electron Spin Resonance

To further shed light on the reaction mechanism, we employed ESR to determine whether our oxidation state measurements and radical trapping experiments were reflected by the presence of radical species in solution. This was done in collaboration with Dr. William Myers at the University of Oxford CAESR institution. We conducted a series of control experiments with the individual coupling partners in the presence and absence of the pre-formed iron(III)-PyBOX complex and terminal oxidant.

By mixing indole **197** in a 1:1 mixture of HFIP/DCE, without any iron species or DTBP present, we were able to observe a radical species with a small spin concentration of 21 μM that we identified as the *N*-centred indole radical cation (g = 2.0051) by virtue of its characteristic ^{14}N hyperfine splitting pattern (**Figure 7.4a**). We made no precautions to exclude oxygen from

the solvents in these measurements, which illustrates that to indole oxidation is facile and can even occur air (to a small degree), and in the absence of any iron species. In the presence of the pre-formed Fe(III)-PyBOX complex, a different radical species with a higher spin concentration of 268 μM was generated, which is also consistent with an indole radical (g = 2.0036) (**Figure 7.4b**). This ESR trace lacks the ^{14}N hyperfine structure observed previously, most likely due to reduced nitrogen character in the wavefunction and rapid relaxation as a consequence of being proximal to the metal centre.[121] For these reasons, we proposed that the indole radical was bound to the iron centre *via* nitrogen.

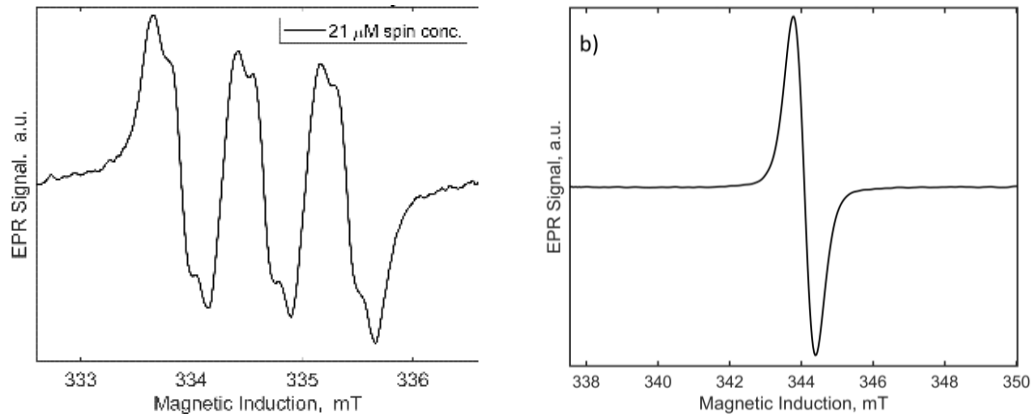
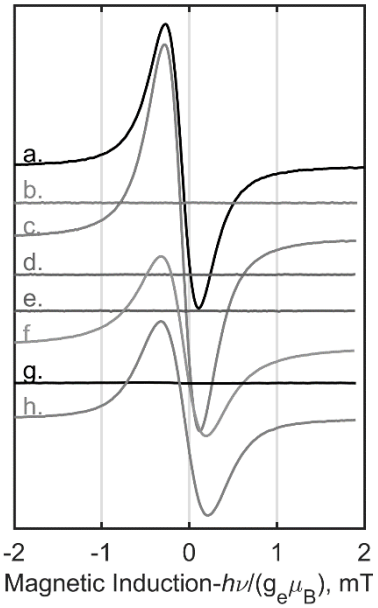


Figure 7.4: ESR Spectra for a) indole in HFIP/DCE; b) indole + Fe Complex in HFIP/DCE

When DTBP was mixed with the Fe(III)-PyBOX complex, no other signals were observed (**Figure 7.5b**). When the indole was present with the oxidant and Fe(III) complex, the iron-bound indole radical species is again observed (**Figure 7.5c**), in a higher spin concentration. By contrast, when the naphthol is present with the Fe(III) complex, and with (**Figure 7.5d**) or without DTBP, no radical signal was observed (**Figure 7.5e**). This demonstrated that oxidation of the naphthol component by the Fe(III)-PyBOX complex is more challenging than indole oxidation. We then tested equimolar quantities of the Fe(III)-PyBOX complex with both the indole and naphthol, which again showed the signal consistent with oxidation of the heteroaromatic component (**Figure 7.5f**). In the final control experiment, with all components of the reaction present, the Fe-bound indole radical species can again be observed (**Figure 7.5h**).



a) 0.1 M indole with 0.01 M Chiral Fe(III);

b) 0.1 M DTBP and with 0.01 M Chiral Fe(III);

c) 0.1 M indole and oxidant with 0.01 M Chiral Fe(III);

d) 0.1 M naphthol with 0.01 M Chiral Fe(III);

e) 0.1 M naphthol and oxidant with 0.01 M Chiral Fe(III);

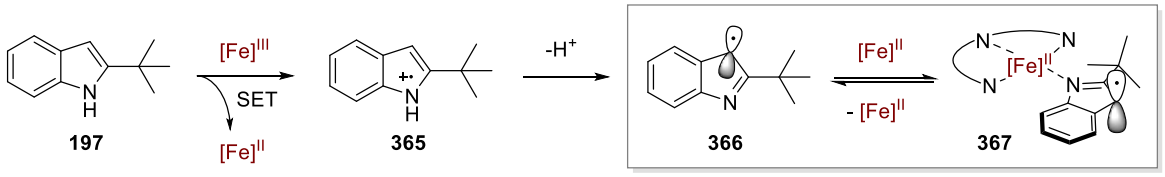
f) 0.01 M indole with 0.01 M Chiral Fe(III);

g) 0.01 M naphthol with 0.01 M Chiral Fe(III);

h) 0.01 M Chiral Fe(III) with 0.1 M DTBP, indole and naphthol.

Figure 7.5: Control Experiments: The modulation amplitude was 0.05 mT at 100 kHz. Non-saturating conditions were found with a microwave power of 1 mW, while the microwave frequency was 9.3888 GHz.

From these ESR experiments, we have shown that the Fe(III) complex in the absence of DTBP is sufficient oxidise the indole and generate an indole radical species. Whilst the exact mechanism of this process remains unclear, and the identity of the indole radical formed in the presence of Fe(III) is unknown, we tentatively suggest outer-sphere single electron oxidation of the indole by Fe(III) to generate an indole radical cation **365**, plus the reduced ferrous form of the PyBOX complex. We then envisaged the loss of a proton from **365** to give the solvated indoleninyl radical species **366**, which may be stabilised by hydrogen bonding of the *N*-atom to HFIP, or reversible complexation with the Fe(II) centre to give **367**. This may confer extra stability to this species and potentially render it persistent;[122] this is consistent with our observation that the homocoupled 3,3'-bisindole is not a product of the reaction. (**Scheme 7.6**).



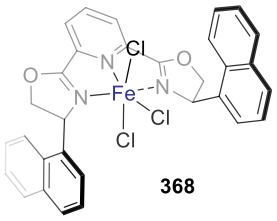
Scheme 7.6: Indole oxidation by Fe(III)-PyBOX complex

7.4 HRMS Analysis of Reaction Mixture

To glean additional information about the structure of the iron(III) complex and identify putative intermediates in the catalytic cycle, we analysed the composition of the reaction mixture by MALDI-TOF following pre-formation of the iron complex and addition of the substrates. The first species that we were able to identify the 1:1 Fe(III)-PyBOX complex formed on mixing $FeCl_3 \cdot 6H_2O$ with the ligand in DCE. We proposed that this is consistent with **368**, where an octahedral iron complex has three meridional *N*-atoms bound to the metal centre, and the other three coordination sites are occupied by chloride ligands.[104] The species found by HRMS is the cationic iron complex formed after loss of a chlorine atom (**Figure 7.7**).

MALDI-TOF on Bruker AutoFlex (DCTB Matrix)

$[M\text{-}Cl]^+$ $C_{31}H_{23}Cl_2FeN_3O_2$: Exact Mass: 595.0517



368

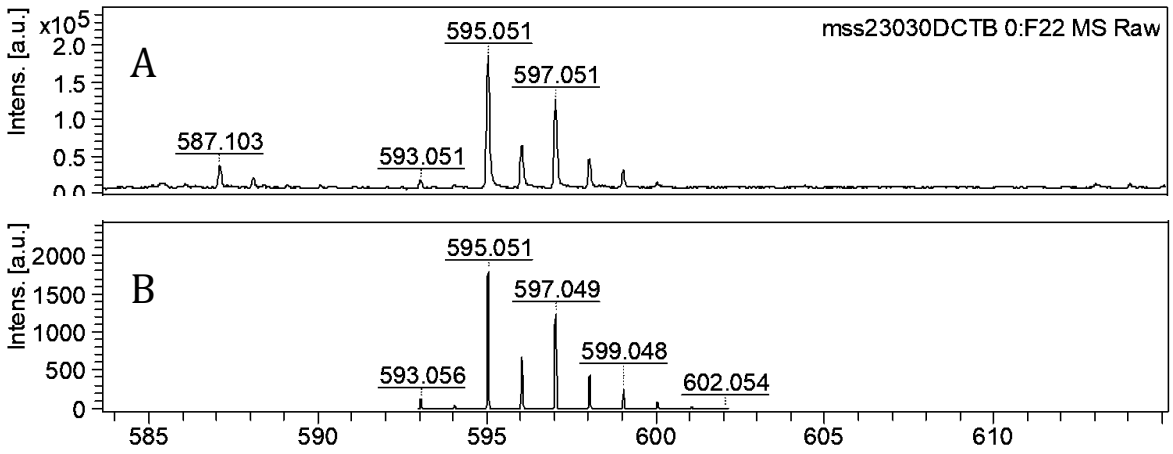
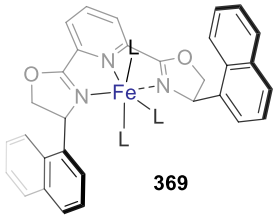


Figure 7.7: MALDI-TOF Spectra of complex **368**; A = Measured spectra; B = Predicted specta

MALDI-TOF on Bruker AutoFlex (Dithranol Matrix)

$[M+H]^+$ $C_{40}H_{27}FeN_3O_5F_{18}$: Exact Mass: 1027.1007

L = 1,1,1,3,3,3-hexafluoro-2-propoxide



369

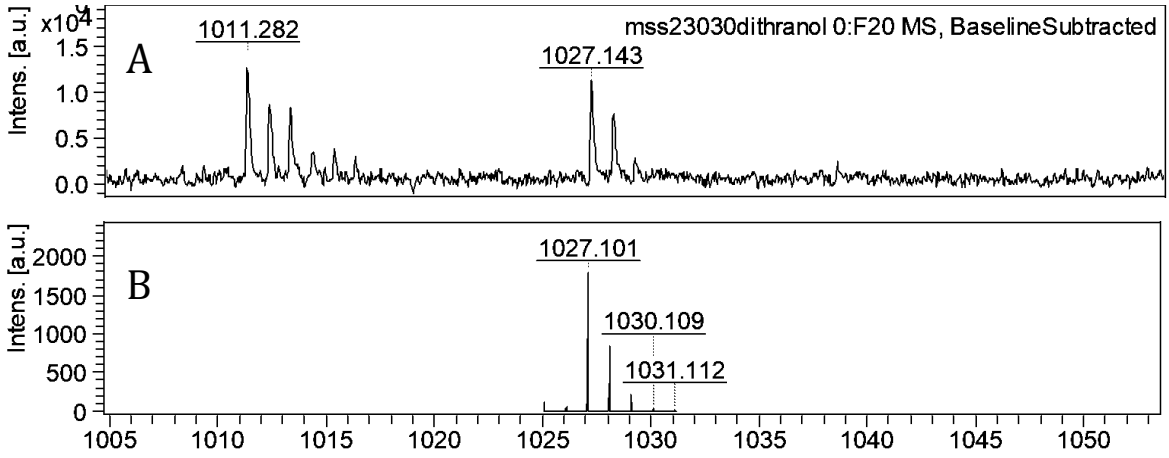


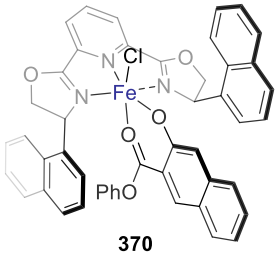
Figure 7.8: MALDI-TOF Spectra of complex **369**; A = Measured spectra; B = Predicted specta

We then identified a similar iron containing species. This corresponds to the same 1:1 Fe(III)-PyBOX core, but in this instance, all chlorides have been exchanged with 1,1,1,3,3,3-hexafluoroisopropoxide ligands on the iron centre. The identification of this species highlights that ligand exchange between the iron(III) chloride and the other species in solution is facile (**Figure 7.8**).

The final species we detected is consistent with the ligand exchange product between the octahedral Fe(III)-PyBOX complex **368** and the naphthoate. We suggest this structure (**370**) is likely to act as a bidentate ligand to the metal, forming an X-type naphthoxide ligand bond to the metal centre, in addition to L-type binding from the carbonyl (**Figure 7.9**).[87]

MALDI-TOF on Bruker AutoFlex (DCTB Matrix)

$[M\text{-}Cl]^+$ $C_{48}H_{34}Fe^{II}N_3O_5$: Exact Mass: 788.1848



370

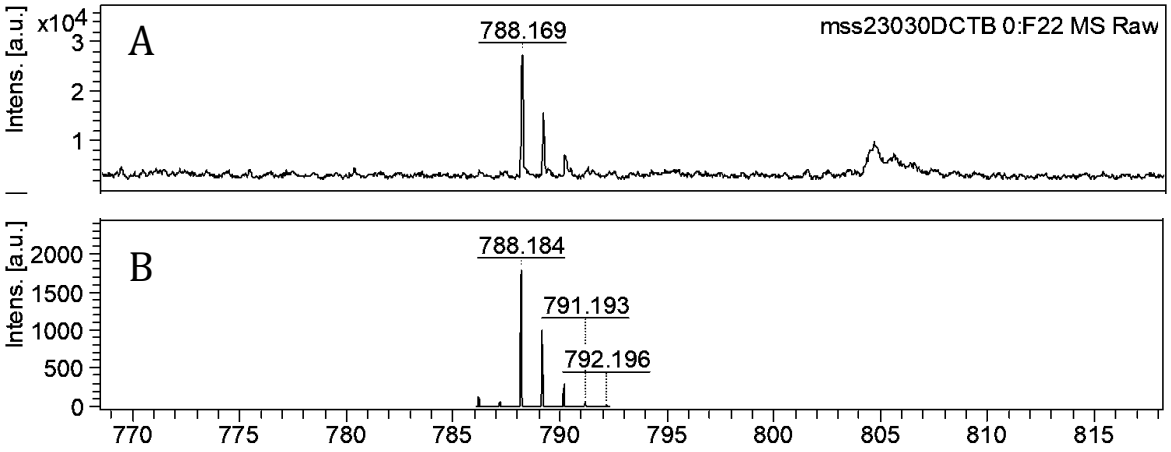


Figure 7.9: MALDI-TOF Spectra of complex **370**; A = Measured spectra; B = Predicted specta

7.5 Control Experiments

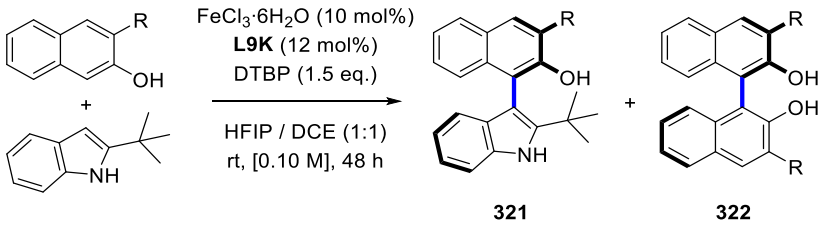
We then carried out a series of control experiments to ascertain the roles of the iron and the co-oxidant in our cross-selective reaction. The majority of mechanisms proposed for iron catalysed oxidative cross-couplings are based upon an Fe(III)/Fe(IV) cycle, which broadly parallel the accepted mechanisms for the operation of heme-containing enzymes.[123]

In the absence of the Fe(III) salt, no reaction occurs (**Table 7.9**, Entry 2). With 10 mol% of Fe(III) catalyst and ligand, but in the absence of any stoichiometric oxidant, we observed a 6% of the cross-coupled product (90:10 e.r.) (**Table 7.9**, Entry 3). We questioned whether in this case, an iron(II)/(III) cycle was possible, as this result suggests a single catalyst turnover by an Fe(III) species. To probe this further, we then performed a reaction with a stoichiometric amount (1.0 equiv.) of Fe(III)-PyBOX complex, again in the absence of any other oxidant. This led to isolation of the cross-coupled product in 47% yield and an e.r. of 89:11 e.r. (**Table 7.9**, Entry 4).

In this reaction, a maximum 50% yield of the heterobiaryl should be expected as two equivalents of the iron complex are required to generate one equivalent of product *via* two single electron oxidations. This demonstrates that the Fe(III)/PyBOX combination is an effective and enantioselective cross-coupling system, which is consistent with the viability of an Fe(II)/Fe(III) mediated coupling process. We also probed whether the stoichiometric Fe(III)/PyBOX combination was able to oxidize 2-isopropylphenyl 3-hydroxy-2-naphthoate; after 48h we observed 18% of the C_2-symmetric BINOL (**Table 7.9**, Entry 5). This lower conversion is consistent with our measured oxidation potentials but is distinct from Katsuki's Fe(III)-salan system, which was shown be inert in the absence of oxygen.[83]

Additionally, we further investigated the role of the 3-ester substituent on the naphthol. If this group is removed, not only is there a loss of chemoselectivity, but racemic heterobiaryl product is also generated (**Table 7.9**, Entry 6). Since the binding of the naphthoate to the iron(III)-complex was observed by MALDI-TOF analysis, we suggest that the carbonyl group of the ester may be essential in anchoring the substrate to the metal in a bidentate fashion, which is likely to increase the rigidity of the adduct and lead to better enantioinduction.[82] With one-point binding, it is conceivable that there is increased conformational freedom about the metal-ligand bond, so both faces of the bound naphtholate may be exposed to intercept the indole radical. Without the indole, homocoupling of the naphthol occurs to generate the C_2-symmetric BINOL product, in a reasonable 68% yield and 67:33 e.r. (**Table 7.9**, Entry 7). Without HFIP, no reaction occurs (**Table 7.10**, Entry 8), which may highlight the important role of this solvent in stabilising the radical intermediates formed over the course of the reaction.

Table 7.10: Deviations from optimal reaction conditions



321 322

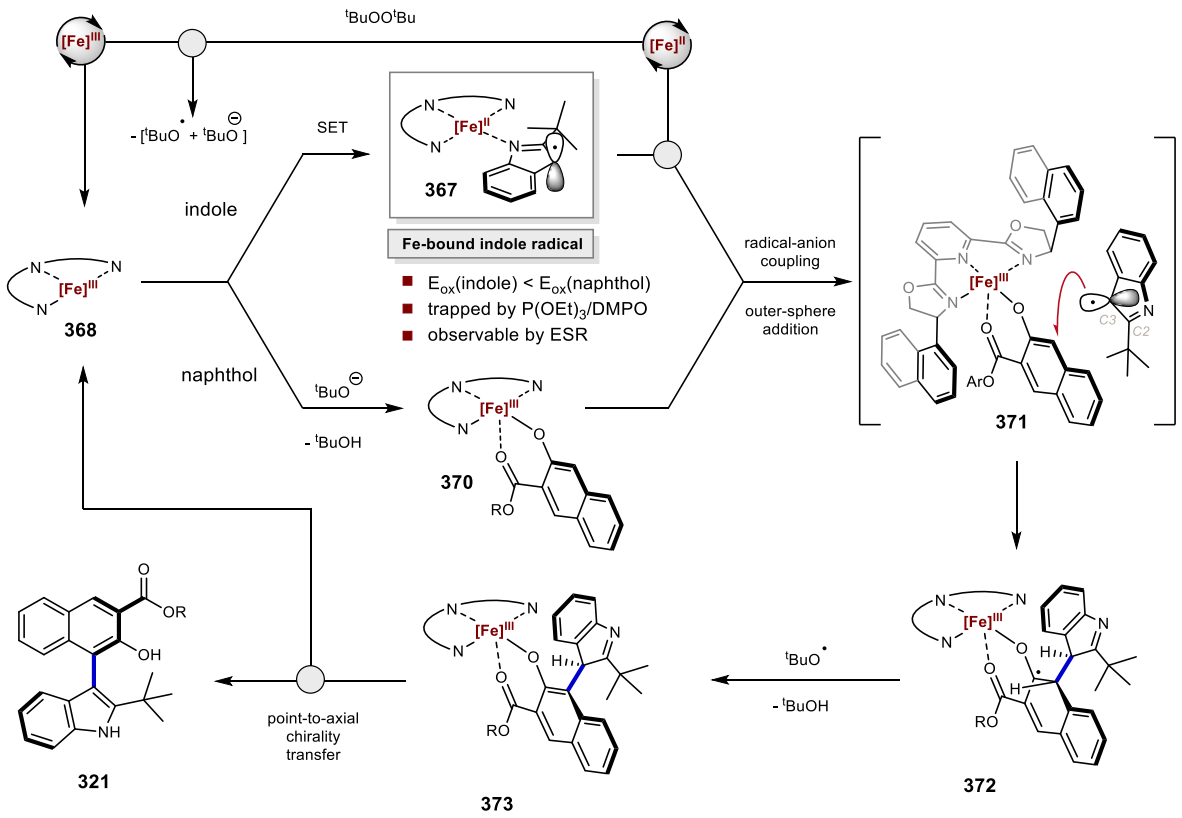
Entry	Deviation from Conditions	R Group	Yield 321[a]	e.r. 321[b]	Yield 322[a]	e.r. 322[b]
1	No Change	CO_2(2-*i*Pr)-C_6H_4	91%	94:6	0%	-
2	Without $FeCl_3 \cdot 6H_2O$	CO_2(2-*i*Pr)-C_6H_4	N.R.[c]	-	N.R.[c]	-
3	Without DTBP	CO_2(2-*i*Pr)-C_6H_4	6%	90:10	0%	-
4	1 eq. Fe(III)-Complex [Without DTBP]	CO_2(2-*i*Pr)-C_6H_4	47%	89:11	0%	-
5	1 eq. Fe(III)-Complex [No DTBP/ No indole]	CO_2(2-*i*Pr)-C_6H_4	-	-	18%	-
6	No Change	H	38%	50:50	45%	50:50
7	Without Indole	CO_2(2-*i*Pr)-C_6H_4	0%	-	68%	67:33
8	Without HFIP	CO_2(2-*i*Pr)-C_6H_4	N.R.	-	N.R.	-

Reaction Conditions: [a] Isolated yield; [b] e.r. = enantiomeric ratio, determined by HPLC (chiral stationary phase).[c] N.R. = no reaction.

7.6 Mechanistic Proposal

From our mechanistic investigations in this chapter, we outline the following process to account for the excellent levels of chemoselectivity and enantioselectivity observed in this reaction (**Scheme 7.11**). From the mechanistic experiments described above, it is apparent that the indole and naphthol coupling partners play well differentiated roles within the cross-coupling process. We propose that initially, selective single electron oxidation of the indole by the octahedral Fe(III)-PyBOX complex **368** occurs, forming the Fe(II)-bound indole radical species **367** (which is supported by oxidation potential measurements, radical trapping experiments and ESR observations). We have also observed the formation of the Fe(III)-PyBOX-naphthoate complex **370** by MALDI-TOF. In our system, binding both an indole and a bidentate naphthol on the same

metal centre makes the requirement for close approach of the radical/anion partners extremely challenging from a geometric perspective. As such, we tentatively propose that the addition of the indole radical could occur via an outer-sphere mechanism in which the key facially selective addition to **370** is directed by the C_2-symmetric ligand, or indeed a multinuclear mechanism where the iron-bound indole radical and iron-bound naphthoxide species are both involved in the enantiodetermining step. A transition state for the outer-sphere radical–anion coupling and C–C bond formation is shown in **371**. This generates a cyclohexadienyl radical **372** which could undergo rearomatization by hydrogen atom abstraction or oxidation to afford **373**, followed by ligand exchange to enable release of the enantioenriched heterobiaryl system. Reoxidation of the Fe(II) complex to Fe(III) may then be performed by the terminal oxidant (DTBP). Even though we have demonstrated the ability of an Fe(III) species to perform the observed enantioselective oxidative coupling does not preclude the possibility of an Fe(III)/Fe(IV) cycle being operative in this catalytic reaction, and as such, this mechanism needs further study.[123]



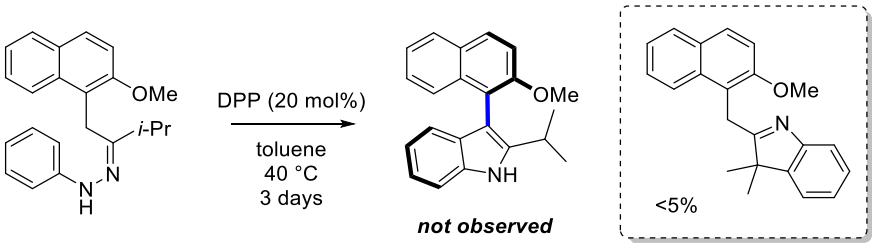
Scheme 7.11: Proposed Reaction Mechanism

Chapter 8: Conclusions & Future Work

8.1 Conclusions

This thesis describes the development of novel methods for the catalytic enantioselective synthesis of indole-containing heterobiaryl atropisomers. In chapter 1, the theme of atropisomerism is discussed, along with contemporary methods for the synthesis of these molecules. A particular emphasis is also placed upon recent developments in the catalytic enantioselective synthesis of atropisomeric indoles.

In chapter 2, we describe preliminary efforts towards the synthesis of C-2 and C-3 aryl indole atropisomers *via* a Fischer indolisation strategy from acyclic phenylhydrazones. However, due to the severe steric demands of the substrates and the regioselectivity issues encountered in the [3,3]-sigmatropic rearrangement, limited success was achieved, and this approach was eventually abandoned.



Scheme 8.1: Regioselectivity issues in atropselective Fischer indole synthesis

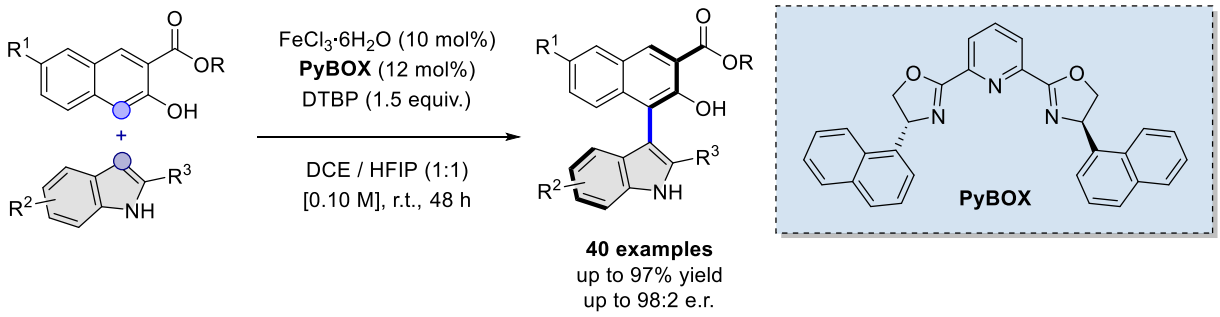
In chapter 3, we introduced oxidative cross-couplings as an alternate strategy for the synthesis of biaryls in a highly direct and atom economic fashion, and the challenges associated with achieving regio- and chemoselectivity in the cross-coupling event in the absence of specific functional groups.

In chapter 4, we have laid out our initial efforts towards the synthesis of indole-naphthol atropisomers *via* an oxidative cross-coupling approach. We identified Pappo's catalytic $FeCl_3$/DTBP/HFIP system as a powerful and highly *hetero*-selective method for forging the unison

of the indole and naphthol fragments. By increasing the size of the indole C-2 substituent and modulating of the oxidation potential of the naphthol by installing the C-3 ester group, we were able to prepare a novel class of high barrier (38.3 kcal mol^{-1}) heterobiaryl atropisomers in excellent yields, and exquisite levels of cross-coupling selectivity. Preliminary investigations into the compatibility of different ligands were also conducted.

In chapter 5, the optimisation of an enantioselective oxidative cross-coupling is detailed. After an intensive screen of chiral manifolds, C_2-symmetric 1-naphthyl PyBOX ligand in combination with $FeCl_3 \cdot 6H_2O$ and the 2-isopropylphenyl ester naphthol substrate was viable for a highly enantioselective transformation. Modulation of the reaction time, an increase in the quantity of indole and sonication of the iron salt prior to ligand addition all continued the aggregation of marginal gains to ultimately afford the desired heterocoupled biaryl product in 91% yield and 94:6 e.r.

In chapter 6, we disclose the substrate scope of the enantioselective oxidative cross-coupling. The reaction is broadly tolerant of various groups at the C-2 position of the indole, as well as mildly electron donating or withdrawing substituents around the indole backbone, or 6-position of the naphthol (40 examples, up to 97% yield and 98:2 e.r.). When stronger electron withdrawing groups are placed on the C-5 position of the indole, conversion and chemoselectivity was diminished, giving preliminary insights into the reaction mechanism. The synthetic utility of the enantioenriched products was also explored through a number of stereospecific derivatizations.

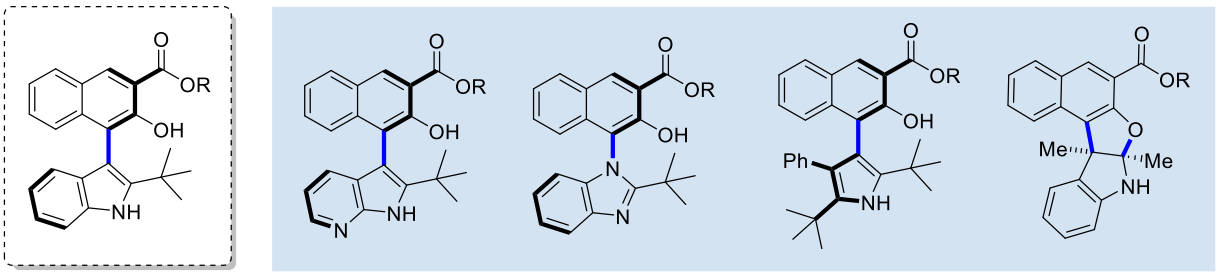


Scheme 8.2: Enantioselective Synthesis of Atropisomeric Indoles *via* Fe(III)-Catalysed Oxidative Cross-Coupling

In chapter 7, we delved deeper into our mechanistic investigations. By virtue of oxidation potential measurements, radical trapping experiments and EPR observations, we proposed single electron oxidation of the indole by the Fe(III)-PyBOX catalyst to generate an indolyl radical. We suggest that this reactive intermediate is trapped by an iron-bound naphtholate in a face selective fashion *via* a radical–anion type mechanism, which furnishes the heterobiaryl products.

8.2 Future Work

This thesis had a focus on the catalytic enantioselective synthesis of atropisomeric indoles *via* an iron catalysed oxidative cross-coupling. However, as we have found multiple pieces of evidence that support single electron oxidation of the indole component, we are curious to explore the compatibility of other heterocyclic coupling partners with low oxidation potentials in this reaction. The method developed in this thesis could provide a general platform for the synthesis of a range of other novel heterobiaryl atropisomers. Furthermore, the benzofuroindolines may also be viable targets for enantioselective synthesis.



Scheme 8.3: Potential heterobiaryl atropisomer targets that may be accessible

Additionally, whilst we have provided preliminary mechanistic insights into this oxidative cross-coupling, more information would prove highly valuable for the development of new oxidative cross-coupling protocols. Work in this area should focus on clarifying the mechanism of heterocycle oxidation, the development of more powerful and selective metal oxidants through ligand design and the discovery of new enantioselective manifolds.

9. Experimental Details

9.1 General Information

Unless otherwise stated, all reagents were purchased from major commercial suppliers (Sigma-Aldrich, Merck, Fluorochem, Apollo Scientific, Fischer Scientific, Tokyo Chemical Industry, Acros Organics) and used without further purification. Unless otherwise stated, solvents were used without prior drying/degassing. Reactions requiring anhydrous conditions are clearly stated and were conducted after flame-drying of the appropriate reaction vessel (round-bottom or Schlenk flasks) under an inert atmosphere of N_2. Dry solvents were obtained fresh from an MBRAUN SPS-800 solvent purification system having been passed through anhydrous alumina columns. The 1,2-dichloroethane (DCE, anhydrous, 99.8%) and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP, 99%) used in the oxidative coupling reactions were respectively purchased from Sigma Aldrich and Fluorochem. The $FeCl_3 \cdot 6H_2O$ (for analysis, ≥99%) was purchased from ACROS Organics. The Luperox® DI, *tert*-butyl peroxide ($^tBuO^tBu$) was purchased from Sigma Aldrich. The $FeCl_3 \cdot 6H_2O$ was pulverised into a fine suspension in DCE by an Ultrawave U1250D Ultrasonic water bath (50-60 Hz). Reactions were monitored by thin layer chromatography (TLC) on silica gel pre-coated aluminium sheets (Merck Kieselgel 60 F_{254}). Visualisation was achieved with ultraviolet irradiation (254 nm), and/or with permanganate or vanillin stains. Flash column chromatography (FCC) was carried out using Merck Geduran® Silicagel (particle size 40-63 μm). Melting points were determined using a Reichert melting point apparatus and are uncorrected. All NMR spectra were recorded using Bruker AVIIIHD 400, AVIIIHD 500 or VII 500. ^1H and ^{13}C NMR spectral data are reported as chemical shifts (δ) in parts per million (ppm) relative to the residual non-deuterated solvent signal using the Bruker internal referencing procedure (edlock). ^{19}F NMR spectra are referenced relative to $CFCl_3$. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, pent = pentet, sept = septet, br = broad, m = multiplet), coupling constants (Hz) and integration. NMR spectra were processed with MestReNova 11.0. High resolution mass spectra (HRMS, m/z) were recorded on a Thermo

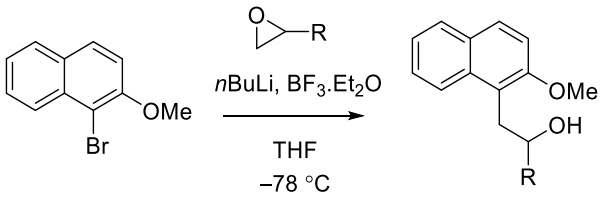
Exactive mass spectrometer equipped with Waters Acquity liquid chromatography system using either the heated electrospray (HESI-II) probe for positive electrospray ionization (ESI+) or the atmospheric pressure chemical ionization (APCI) probe. Infrared spectra were recorded as the neat compound or in solution using a Bruker tensor 27 FT-IR spectrometer. Absorptions are reported in wavenumber (cm^{-1}). Optical rotations were recorded on a Perkin-Elmer 241 polarimeter at 589 nm, 25 °C. Data are reported as: $[\alpha]_D^T$, concentration (c in g/100 mL), and solvent. The absolute configuration was determined by X-ray analysis of compound **361**. The configuration of the other products was assigned by analogy. HRMS was carried out using Bruker MicroTOF and Micromass GCT spectrometers under ESI or FI conditions respectively. Analytical chiral HPLC was carried out using a Dionex Ultimate 3000 HPLC system comprising a Dionex LPG-3400A pump, WPS-3000SL autosampler and TCC-3000SD column compartment, and a Daicel Chiralpak column (0.46 cm x 25 cm), equipped with an appropriate guard column (0.4 cm x 1 cm).

9.2 Naming and Numering

Compounds have been named according to IUPAC recommendations or according to commonly utilised names where appropriate. The atomic numbering system for compounds does not correspond to IUPAC names, but numbered arbitrarily to allow for simple assignment of spectra.

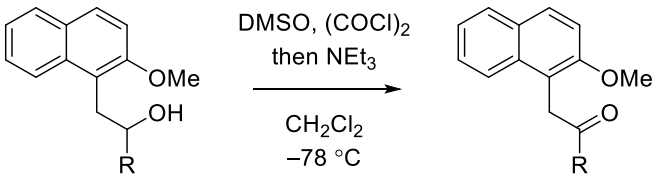
9.3 General Procedures

General Procedure A: Ring Opening of Terminal Epoxides



The procedure is based on a modified literature method.[124] In a flame-dried, argon filled round-bottomed flask 1-bromo-2-methoxynapthalene (1.15 equiv.) was dissolved in dry THF (0.1 M). The solution was cooled to –78 °C and *n*-BuLi (2.5 M in hexanes, 1.20 equiv.) was added dropwise. After stirring for 30 min, a solution of the chosen terminal epoxide (1.00 equiv., 1.0 M in THF) was added, followed immediately by $BF_3.Et_2O$ (1.15 equiv.). The resulting solution was stirred for 2 h at –78 °C before being slowly warmed to room temperature. After complete consumption of the terminal epoxide (16-24 h) the reaction was quenched by the addition of NEt_3 (3.0 equiv.) and sat. $NH_4Cl_{(aq)}$ at room temperature. The layers were separated, and the product was then extracted three times with Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was then purified by flash column chromatography [silica gel, refer to compound for specific conditions] to afford secondary alcohol.

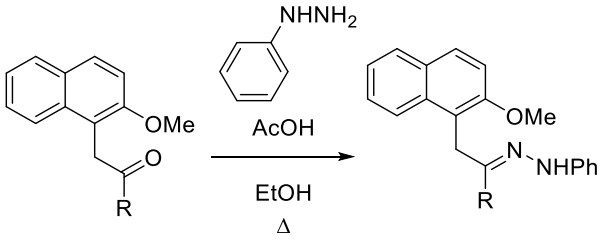
General Procedure B: Swern oxidation of 2° alcohols



The procedure is based on a modified literature method.[125] In a flame-dried, argon filled round-bottomed flask, $(COCl)_2$ (1.20 equiv.) was dissolved in dry CH_2Cl_2 (0.1 M) and cooled to –78 °C. At this temperature, DMSO (2.00 equiv.) was added dropwise. After 5 min of stirring, a solution of the secondary alcohol (1.0 M in CH_2Cl_2, 1.00 equiv.) was added, followed

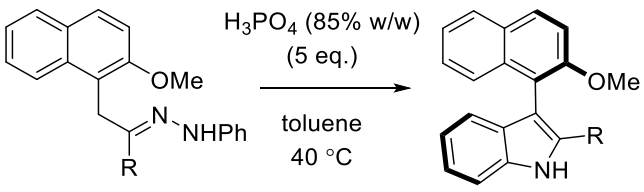
by an additional 30 min of stirring at the same temperature. NEt_3 (4.00 equiv.) was then introduced and the mixture was allowed to warm to room temperature over 1 h before quenching with 1.0 M $HCl_{(aq)}$. The layers were separated, and the product was extracted three times with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was then purified by flash column chromatography [silica gel, refer to compound for specific conditions] to afford ketone.

General Procedure C: Phenylhydrazone Formation from Ketones



The procedure is based on a modified literature method.[59] An oven dried round-bottomed flask equipped with a condenser was charged with the selected ketone (1.00 equiv.), phenylhydrazine (1.50 equiv.) and glacial AcOH (2.00 equiv.). The contents were dissolved in EtOH (1.6 M in ketone) and the resulting solution was heated to 60 °C. After complete consumption of the ketone (2-6 h) the mixture was cooled slowly to –20 °C. The precipitate that formed was collected by filtration, washed with ice-cold EtOH and dried *in vacuo* to yield phenylhydrazone, which was used in the next step without further purification.

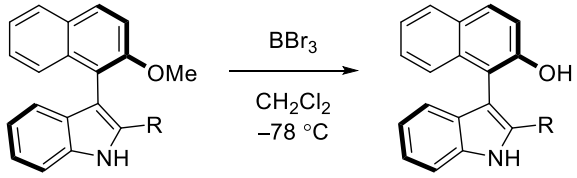
General Procedure D: Fischer-Indolisation of Phenylhydrazones



In an oven-dried vial, 85% (w/v) $_{(aq)}$ H_3PO_4 (5.00 equiv.) was added to a solution of the chosen hydrazone (1.00 equiv.) in dry toluene (0.5 M). The vial was flushed with argon before being heated to 40 °C until complete consumption of the hydrazone (6 h) was observed by LRMS

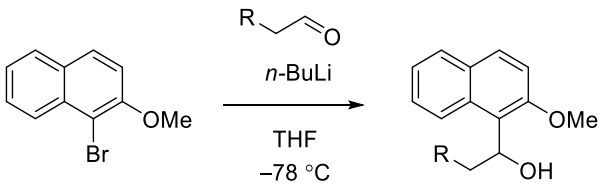
analysis. After this time, the mixture was cooled to room temperature, diluted with CH_2Cl_2 and neutralised with sat. $NaHCO_{3\ (aq)}$. The product was extracted three times with CH_2Cl_2 and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was then purified by flash column chromatography [silica gel, refer to compound for specific conditions] to afford the indole.

General Procedure E: Demethylation of Indoles



The procedure is based on a modified literature method.[126] In a flame-dried, argon filled round-bottomed flask, the selected indole (1.00 equiv.) was dissolved in anhydrous CH_2Cl_2 (0.5 M). The solution was cooled to –78 °C at which temperature BBr_3 (1.0 M in CH_2Cl_2, 3.00 equiv.) was added dropwise. The resultant mixture was then allowed to warm to room temperature and stirred for 2 h. The reaction was quenched by the addition of ice-cold water and the layers were separated. The aqueous phase was extracted three times with CH_2Cl_2 and the organic extracts were pooled, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography [silica gel, refer to compound for specific conditions] to afford the demethylated indole.

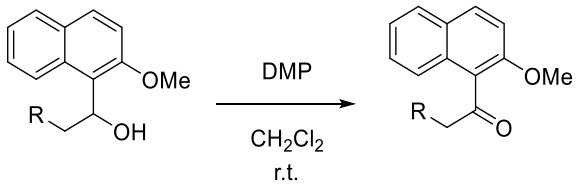
General Procedure F: 1,2-Addition to Aldehydes



In a flame-dried, argon filled round-bottomed flask 1-bromo-2-methoxynapthalene (1.00 equiv.) was dissolved in anhydrous THF (0.1 M) and cooled to –78 °C. At this temperature, *n*-BuLi (2.5 M in hexanes, 1.30 equiv.) was added and the resulting solution was stirred for 1 h. After this time,

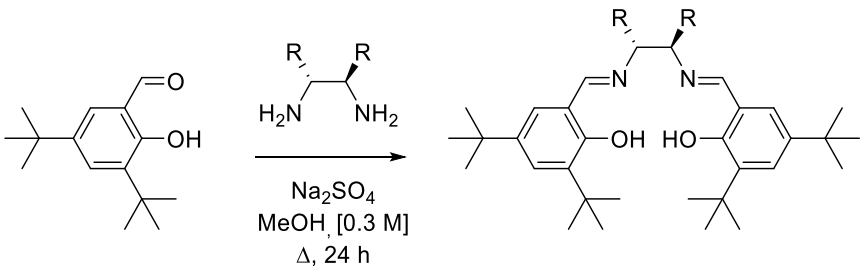
the aldehyde (1.50 equiv.) was added dropwise and the solution was allowed to warm slowly to room temperature and stirring was continued for 16 h. The reaction was quenched by the addition of sat. $NH_4Cl_{(aq.)}$, and the layers were separated. The product was extracted three times with Et_2O and the combined extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography [silica gel, refer to compound for specific conditions] to afford the alcohol.

General Procedure G: Dess-Martin Oxidation of Alcohols



To a solution of the selected alcohol (1.00 equiv.) in CH_2Cl_2 (0.10 M) was added DMP (1.50 equiv.). The mixture was stirred for 16 h at room temperature, after which time the contents were filtered through a pad of Celite®. The filtrate was concentrated *in vacuo*, and the crude product was purified by flash column chromatography [silica gel, refer to compound for specific conditions] to afford the corresponding ketone.

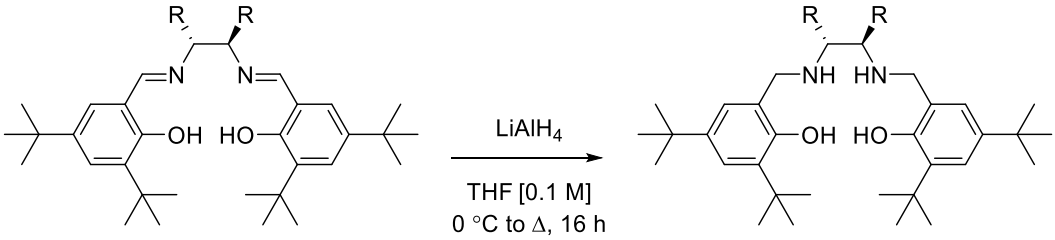
General Procedure H: Synthesis of SALEN Ligands



The procedure is based on a modified literature method.[127] An RBF was charged with 3,5-di-*tert*-butylsalicylaldehyde (2.00 equiv.), Na_2SO_4 (8.00 equiv.) and MeOH (0.3 M with respect to the vicinal diamine). The chosen vicinal diamine (1.00 equiv.) was added to the suspension and the reaction mixture was heated to reflux for 24 h. The contents were then cooled to room

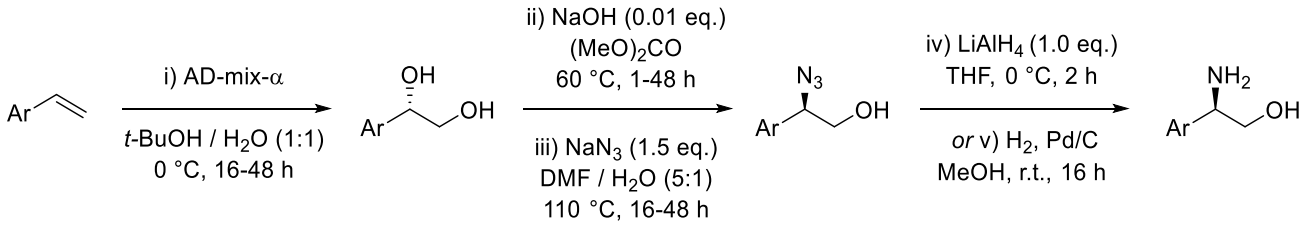
temperature and the solvent removed by rotary evaporation. The crude product was dissolved in CH_2Cl_2 and the drying agent was removed by gravity filtration. The filtrate was concentrated *in vacuo* to afford the pure SALEN ligand.

General Procedure I: Synthesis of SALAN Ligands



In a flame dried, argon filled RBF, the chosen the SALEN ligand (1.00 equiv.) was dissolved in THF (0.1 M). The solution was cooled to 0 °C at which temperature $LiAlH_4$ (*ground pellet*, 2.00 equiv.) was *slowly* added. The reaction was then heated to reflux for a period of 16 h. After this time, the mixture was cooled to 0 °C and diluted with Et_2O. Water (1 mL per g $LiAlH_4$), 15% NaOH $_{(aq.)}$ (w/v) (1 mL per g $LiAlH_4$) and an additional portion of water (1 mL per g $LiAlH_4$) were then *carefully* added to the flask in sequence. The contents were warmed to room temperature and stirred for 15 min. The mixture was then dried over $MgSO_4$ and stirred for an additional 15 min. The solids were removed by gravity filtration and the filter cake was washed liberally with Et_2O. The filtrate was concentrated by rotary evaporation to afford the SALAN ligand.

General procedure J: Enantioselective Synthesis of (*R*)-Aryl Glycinols



Step i) A 250-mL round-bottomed flask equipped with a magnetic stirrer was charged with AD-mix-α (14 g), *t*-BuOH (50 mL) and H_2O (50 mL). The mixture was cooled to 0 °C and the styrene (10.00 mmol, 1.00 equiv.) was added. The resulting heterogeneous slurry was stirred

vigorously at 0 °C for 6-24 h. On completion of the reaction (as indicated by TLC analysis), Na_2SO_3 (14 g) was added and the mixture was allowed to warm to room temperature and stirred for an additional 30 min. EtOAc (30 mL) was then added to the reaction mixture, and the layers were separated. The aqueous phase was further extracted three times with EtOAc. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography [silica gel, EtOAc in petroleum ether b.p. 40–60 °C] to afford the (*S*)-1,2-diol.

Step ii) A 50 mL flask equipped with a reflux condenser and a magnetic stir bar was charged with the (*S*)-1,2-diol (~10.00 mmol, 1.00 equiv.), NaOH (40 mg, 0.10 mmol, 0.01 equiv.) and dimethyl carbonate (10 mL). The reaction mixture was heated at 60 °C for 1-48 h. On completion of the reaction (as indicated by TLC analysis), the mixture was concentrated to dryness *in vacuo*. The resulting residue was then diluted with THF (20 mL) filtered through a pad of Celite® and concentrated to afford the (*S*)-carbonate which was used in the next step without further purification.

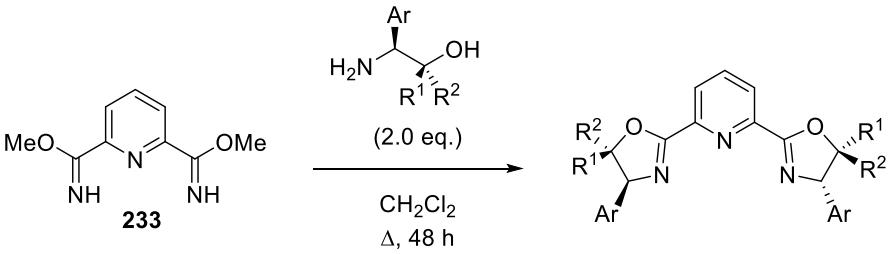
Step iii) The crude (*S*)-carbonate (~10.00 mmol, 1.00 equiv.) was transferred to a 50 mL flask equipped with a reflux condenser. To the flask, H_2O (2 mL), DMF (10 mL) and NaN_3 (975 mg, 15.00 mmol, 1.50 equiv.) were added. Under N_2, the mixture was heated in an oil bath at 110 °C for 16-48 h. On completion of the reaction (as determined by crude ^1H NMR analysis of a small aliquot) the solvents were removed under reduced pressure by rotary evaporation. The residue was then suspended in Et_2O (20 mL), and the contents filtered through a pad of Celite®. The filtrate was concentrated to afford the (*R*)-azidoalcohol which was used in the next step without further purification.

Step iv) To a solution of the (*R*)-azidoalcohol (~10.00 mmol, 1.00 equiv.) in THF (30 mL) at 0 °C was added powdered $LiAlH_4$ (569 mg, 15.00 mmol, 1.50 equiv.). The reaction was then allowed to slowly warm to room temperature and stirring continued for 2 h. After this time, the mixture was diluted with Et_2O (20 mL) and cooled once again to 0 °C. At this temperature, the reaction

was quenched by the slow addition of 1.6 M $KF_{(aq.)}$ (2 mL). The resulting suspension was then filtered through a pad of Celite®, dried over Na_2SO_4 and concentrated *in vacuo* to give the crude (*R*)-arylglycinol. The product was purified by recrystallisation from hot toluene, unless otherwise specified; *or*:

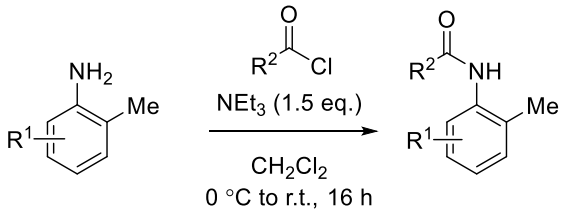
Step v) To a solution of the (*R*)-azidoalcohol (~10.00 mmol, 1.00 equiv.) in MeOH (25 mL) was added 10% Pd on charcoal (150 mg). The flask was evacuated and backfilled with a hydrogen balloon three times. The reaction was then vigorously stirred under a hydrogen balloon at room temperature for 16 h. The solution was filtered through a pad of Celite® and the filtrate was concentrated *in vacuo* to give the crude (*R*)-arylglycinol. The product was purified by recrystallisation from hot toluene, unless otherwise specified.

General Procedure K: Synthesis of C_2-Symmetric PyBOX Ligands



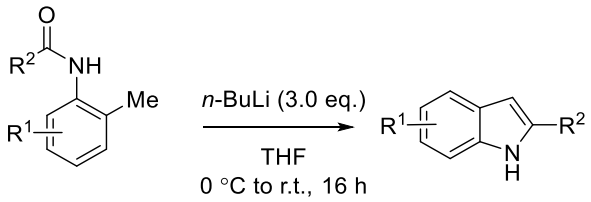
The procedure is based on a modified literature method.[128] A screw-top 2-dram vial was charged with dimethyl pyridine-2,6-bis(carbimidate) (**233**) (100 mg, 0.52 mmol, 1.00 equiv.), the chiral amino alcohol (1.04 mmol, 2.00 equiv.) and CH_2Cl_2 (2 mL). The vial was then sealed and heated to reflux. After 48 h, the reaction was cooled to room temperature and the solvent removed *in vacuo*. The crude product was generally purified by flash column chromatography [silica gel, EtOAc in petroleum ether b.p. 40–60 °C + 1% NEt_3] followed by recrystallisation from hot EtOH or EtOAc (see specific compounds for exact conditions).

General Procedure L: Synthesis of Anilides



The procedure is based on a modified literature method.[101] The *o*-toluidine (1.00 equiv.) was dissolved in CH_2Cl_2 (0.25 M with respect to the *o*-toluidine) and the resulting solution was cooled to 0 °C. At this temperature, NEt_3 (1.50 equiv.) and the acid chloride (1.20 equiv.) were sequentially added. The mixture was then slowly warmed to room temperature and stirred for 16 h. On completion of the reaction (as indicated by TLC analysis) the mixture was treated with 5% (v/v) $HCl_{(aq.)}$ and the layers were separated. The product was extracted three times with CH_2Cl_2 and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified either by recrystallisation from EtOAc or flash column chromatography [silica gel, refer to compound for specific conditions] to afford the pure anilide.

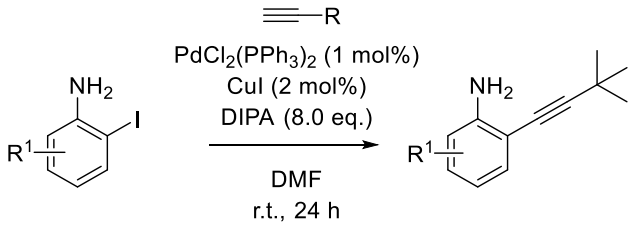
General Procedure M: Madelung Cyclisation



The procedure is based on a modified literature method.[101] The amide (1.00 equiv.) was added to a flame dried, argon filled RBF. Anhydrous THF (1.5 M with respect to the amide) was then added and the resulting solution was cooled to 0 °C. At this temperature, *n*-BuLi (2.5 M in hexanes, 3.00 equiv.) was slowly introduced. The mixture was then warmed to room temperature and stirred for 16 h. On completion of the reaction (as indicated by TLC analysis) the reaction was cooled to 5 °C, diluted with Et_2O and quenched by the addition of sat. $NH_4Cl_{(aq.)}$. After warming

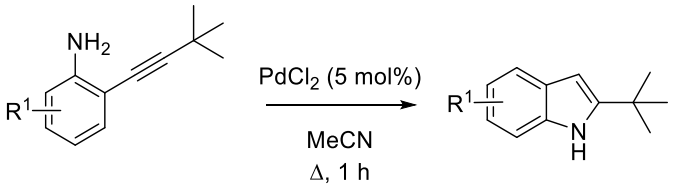
again to room temperature, the layers were partitioned, and the aqueous phase was extracted three times with Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography [silica gel, refer to exact compound for specific conditions] to afford pure indole.

General Procedure N: Sonogashira Coupling



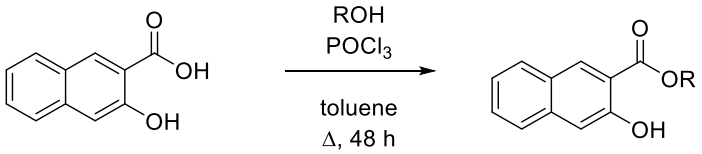
The procedure is based on a modified literature method.[129] The 2-iodoaniline (1.00 equiv.), $PdCl_2(PPh_3)_2$ (0.01 equiv.) and CuI (0.02 equiv.) were added to a flame dried, argon filled 2-necked RBF. The contents were evacuated and back filled with argon three times. Under an argon atmosphere, N_2-sparged DMF (1.0 M with respect to the 2-iodoaniline), DIPA (8.00 equiv.) and the chosen terminal alkyne (1.20 equiv.) were sequentially added. The reaction was stirred under argon for 24 h and after confirming completion of the reaction (as indicated by TLC and LRMS analysis) the contents were poured onto sat. $NH_4Cl_{(aq.)}$. The layers were separated and the product was further extracted three times with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography [silica gel, refer to exact compound for specific conditions] to afford pure alkynylaniline.

General Procedure O: Castro Annulation



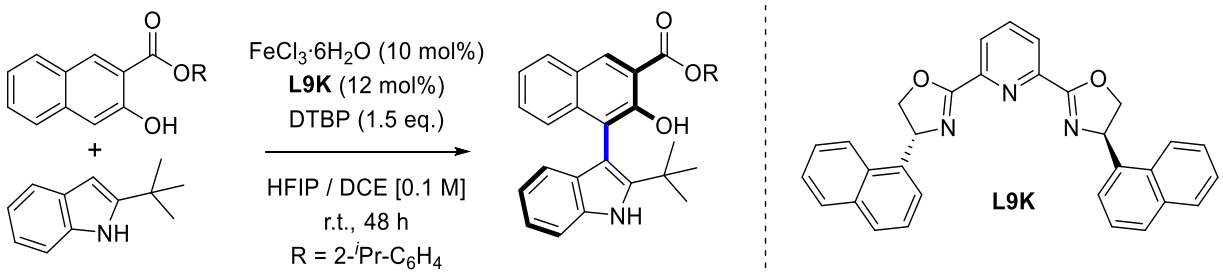
The procedure is based on a modified literature method.[130] An RBF was charged with the chosen alkyne (1.00 equiv.) and $PdCl_2$ (0.05 equiv.). MeCN was added (0.2 M with respect to the alkyne) and the mixture was heated to reflux for 1 h. On completion of the reaction (as indicated by TLC analysis), the reaction was cooled to room temperature and the solvent was removed *in vacuo*. The residue was then dissolved in a mixture of EtOAc and water. The layers were separated and the aqueous phase was further extracted three times with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography [silica gel, refer to exact compound for specific conditions] to afford pure indole.

General Procedure P: Naphthoic Acid Esterification



To a suspension of 3-hydroxy-2-naphthoic acid (1.00 equiv.) and the chosen phenol (1.50 equiv.) in toluene (40 mL), $POCl_3$ (0.40 equiv.) was slowly added. The mixture was then heated to reflux for 48 h and after the allotted time, the reaction was cooled to room temperature, diluted with Et_2O and quenched by the slow addition of sat. $Na_2CO_{3\,(aq.)}$. The layers were separated, and the product was extracted three times with Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography [silica gel, refer to exact compound for specific conditions] to afford the pure naphthoate.

General Procedure Q: Enantioselective Oxidative Cross-Coupling



i) In-Situ Formation of Chiral Fe-Complex

A ½ dram PTFE screw-top vial was charged with $FeCl_3 \cdot 6H_2O$ (2.7 mg, 0.010 mmol, 0.10 equiv.) and DCE (500 µL). The mixture was then sonicated in a water bath for 30 min at room temperature to pulverise the solid into a fine yellow suspension. [*NOTE: It is crucial reduce the particle size of the $FeCl_3 \cdot 6H_2O$ by sonication prior to the addition of the ligand, otherwise lower enantioselectivities will be observed*.] Following sonication, a magnetic stir bar and **L9K** (5.6 mg, 0.012 mmol, 0.12 equiv.) were added. The mixture was then stirred for 2 h at room temperature to form an orange coloured homogeneous solution. HFIP (500 µL) was then introduced and stirring was continued for an additional 30 min, giving a brown solution.

ii) Reaction, Work-Up, Analysis and Purification

At room temperature, the chosen naphthol (0.100 mmol, 1.00 equiv.) and indole (0.150 mmol, 1.50 equiv.) were simultaneously added to the solution of the pre-formed complex, forming a dark coloured solution. DTBP (27.4 µL, 0.150 mmol, 1.50 equiv.) was then introduced using a micropipette. The reaction mixture was sealed and stirred under an atmosphere of air at room temperature for 48 h. After this time, the solvent was removed *in vacuo* and the crude product was taken up in CH_2Cl_2 and filtered through a short plug of silica [eluting liberally with CH_2Cl_2]. The filtrate was concentrated to dryness and the chemoselectivities and BRSMs were obtained by quantitative ^1H NMR analysis of the crude product using 1,3,5-trimethoxybenzene as an internal standard. The crude products were purified by flash column chromatography [silica gel, see specific compounds for exact conditions]. The enantiomeric ratios were obtained by HPLC (chiral stationary phase) of the purified products.

Synthesis of Racemates

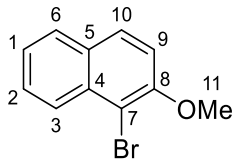
A screw-top vial or RBF was charged with $FeCl_3$ (anhydrous, 0.10 equiv.), the chosen naphthol (1.00 equiv.) and indole (1.50 equiv.). The solids were dissolved in [1:1] CH_2Cl_2/HFIP [0.1 M with respect to naphthol] and DTBP (1.50 equiv.) was added. The reaction was then stirred for 16 h at

room temperature. After this time, the reaction was concentrated *in vacuo* and the residue was purified by flash column chromatography [silica gel, see specific compounds for exact conditions].

9.4 Characterisation of Compounds

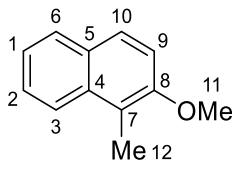
9.5.1 Atropselective Fischer Indolisation

1-Bromo-2-methoxynapthalene (100)



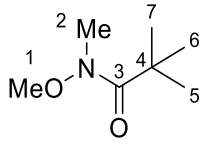
The title compound was prepared according to a modified literature procedure**.** The data is consistent with those previously reported.[131] To a solution of 1-bromo-2-napthol (**102**) (25.00 g, 112.07 mmol, 1.00 equiv.) in dry DMF (560 mL) was added NaH (60 % mineral oil dispersion, 5.38 g, 134.48 mmol, 1.20 equiv.) at 0 °C under a stream of argon. After stirring for 30 min, MeI (7.67 mL, 123.28 mmol, 1.10 equiv.) was added and the mixture was then warmed to room temperature and stirred for 4 h. The reaction was quenched by the slow addition of 1.0 M $HCl_{(aq)}$ (300 mL). The product was extracted four times with Et_2O and the combined organic extracts were washed with brine (three times), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, 10% EtOAc in petroleum ether b.p. 40–60 °C) to afford the product as a white solid (94%, 24.98 g). **M.P.** = 83-85 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.20 (dd, *J* = 8.6, 0.8 Hz, 1H, H3), 7.81 – 7.77 (m, 1H, H10), 7.75 (ddt, *J* = 8.2, 1.2, 0.6 Hz, 1H, H6), 7.54 (ddd, *J* = 8.5, 6.8, 1.3 Hz, 1H, H2), 7.37 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H, H1), 7.24 (d, *J* = 4.3 Hz, 1H, H9), 4.03 (s, 3H, $H11_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.0 (C8), 133.3 (C4), 130.0 (C5), 129.1 (C10), 128.2 (C6), 127.9 (C2), 126.3 (C3), 124.5 (C1), 113.9 (C9), 108.9 (C7), 57.3 (C11); **IR** (thin layer film) ν = 2972, 1622, 1595, 1501, 1455, 1352, 1270, 1246, 1155, 1063, 891, 804, 745 cm^{-1}; **HRMS** ($APCI^+$) *m/z* Calcd. for $C_{11}H_{10}O^{79}Br$ $(M+H)^+$ 236.9910, found 236.9908.

2-methoxy-1-methylnaphthalene (103)



The title compound was prepared according to a modified literature procedure**.** The data is consistent with those previously reported.[132] In a flame dried, argon filled 250 mL RBF, 1-bromo-2-methoxynapthalene (**100**) (6.50 g, 27.40 mmol, 1.00 equiv.) was dissolved in dry THF (120 mL) and the solution was cooled to -78 °C. At this temperature TMEDA (3.82 g, 4.93 mL, 32.90 mmol, 1.50 equiv.) was added, followed by the slow addition of *n*-BuLi (2.5 M in hexanes, 13.1 mL, 32.90 mmol, 1.50 equiv.). The reaction was stirred at –78 °C for 90 min, after which time MeI (7.00 g, 3.07 mL, 49.30 mmol, 1.80 equiv.) was introduced. The mixture was then allowed to warm very slowly to room temperature with stirring for 24 h. The reaction was quenched by the *slow* addition of H_2O at this temperature. The layers were separated, and the aqueous phase was extracted three times with Et_2O. The combined extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica gel, 5% EtOAc in petroleum ether b.p. 40–60 °C) to afford the product as a colourless oil (88%, 4.13 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.01 – 7.94 (m, 1H, H3), 7.81 (t, *J* = 8.3 Hz, 1H, H6), 7.75 (d, *J* = 8.9 Hz, 1H, H10), 7.56 – 7.49 (m, 1H, H1), 7.42 – 7.33 (m, 1H, H2), 7.33 – 7.26 (m, 1H, H9), 3.98 (s, 3H, $H11_3$), 2.59 (s, 3H, $H12_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.4 (C8), 133.7 (C4), 129.0 (C5), 128.3 (C6), 127.1 (C10), 126.1 (C2), 123.4 (C3), 123.2 (C1), 119.4 (C9), 113.7 (C7), 56.8 (C11), 10.6 (C12); **LRMS** (ESI$^+$) *m/z* Calcd. for $C_{12}H_{13}O$ $(M+H)^+$ 173.1, found 173.1.

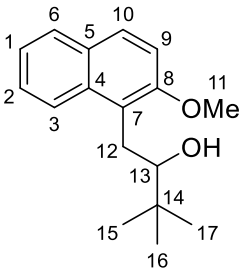
***N*-methoxy-*N*-methylpivalamide (104)**



The title compound was prepared according to a modified literature procedure**.** The data is consistent with those previously reported.[133] To a stirred suspension of *N*-methoxymethylamine hydrochloride salt (1.19 g, 12.18 mmol, 1.00 equiv.) in CH_2Cl_2 (60 mL) at 0 °C was added NEt_3 (2.46 g, 3.40 mL, 24.36 mmol, 2.00 equiv.). Pivaloyl chloride (1.46 g, 1.50 mL, 12.18 mmol, 1.00 equiv.) was then added and the mixture was warmed to room temperature and stirred for 1 h. The reaction was quenched by the

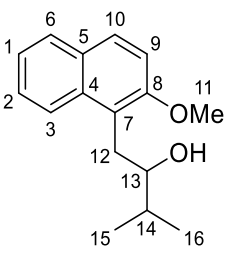
addition of $NaHCO_3$ and the layers were separated, and the aqueous phase was extracted three times with CH_2Cl_2. The combined extracts were washed with 1.0 M HCl, brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was isolated as a colourless oil and used in the next step without any further purification (95%, 1.68 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.69 (s, 3H, $H1_3$), 3.20 (s, 3H, $H2_3$), 1.27 (s, 9H, $H5_3$, $H6_3$ & $H7_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 179.2 (C3), 60.6 (C1), 39.4 (C2), 33.6 (C4), 27.1 (C5, C6 & C7); **LRMS** (ESI^+) *m/z* Calcd. for $C_7H_{16}NO_2$ $(M+H)^+$ 146.1, found 146.1.

1-(2-methoxynaphthalen-1-yl)-3,3-dimethylbutan-2-ol (109)



Prepared according to General Procedure A with 1-bromo-2-methoxynapthalene (**100**) (1.50 g, 6.38 mmol) and 2-(*tert*-butyl)oxirane (0.54 g, 5.42 mmol). Reaction time: 23 h. Product was purified by flash column chromatography (silica gel, 5% EtOAc in petroleum ether b.p. 40–60 °C : EtOAc) to afford the product as a yellow oil (89%, 1.24 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.6 Hz, 1H, H3), 7.83 – 7.75 (m, 2H, H6 & H10), 7.54 – 7.46 (m, 1H, H2), 7.36 (ddd, *J* = 8.0, 6.8, 1.1 Hz, H1), 7.30 (d, *J* = 9.0 Hz, 1H, H9), 3.97 (s, 3H, $H11_3$), 3.56 (ddd, *J* = 10.6, 3.8, 2.0 Hz, 1H, H13), 3.32 (dd, *J* = 14.0, 2.0 Hz, 1H, $H12_A$), 3.28 – 3.17 (m, 1H, $H12_B$), 2.27 (d, *J* = 3.7 Hz, 1H, OH), 1.12 (s, 9H, $H15_3$, $H16_3$ & $H17_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.9 (C8), 133.5 (C4), 129.6 (C5), 128.8 (C10), 128.4 (C6), 126.6 (C2), 123.5 (C3), 123.3 C1), 121.3 (C7), 113.0 (C9), 80.5 (C13), 56.6 (C11), 35.7 (C14), 27.6 (C12), 25.9 (C15, C16 & C17); **IR** (thin layer film) ν = 3452, 2953, 2905, 2868, 1624, 1595, 1513, 1465, 1383, 1382, 1249, 1145, 1091, 1010, 805, 745 cm^{-1}; **HRMS** (ESI^+) *m/z* Calcd. for $C_{17}H_{22}O_2{}^{23}Na$ $(M+Na)^+$ 281.1512, found 281.1511.

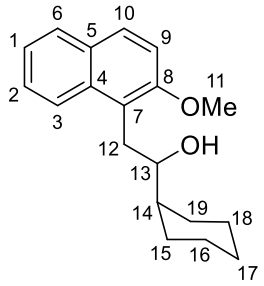
1-(2-methoxynaphthalen-1-yl)-3-methylbutan-2-ol (110)



Prepared according to General Procedure A with 1-bromo-2-methoxynapthalene (**100**) (1.39 g, 5.87 mmol) and 2-isopropyloxirane (0.43 g, 5.00 mmol). Reaction time: 16 h. Product was purified by flash column chromatography (silica gel, 10% EtOAc in petroleum ether b.p.

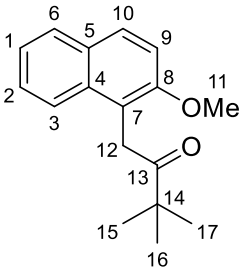
40–60 °C) to afford the product as a yellow oil (83%, 1.01 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.7 Hz, 1H, H3), 7.85 – 7.66 (m, 2H, H6 & H10), 7.55 – 7.44 (m, 1H, H2), 7.42 – 7.32 (m, 1H, H1), 7.30 (d, *J* = 9.0 Hz, 1H, H9), 3.97 (s, 3H, $H11_3$), 3.71 (dt, *J* = 8.7, 4.4 Hz, 1H, H13), 3.37 – 3.14 (m, 2H, $H12_2$), 2.09 (d, *J* = 3.9 Hz, 1H, OH), 1.95 – 1.83 (m, 1H, H14), 1.11 (dd, *J* = 6.8, 3.6 Hz, 6H, $H15_3$ & $H16_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.0 (C8), 133.5 (C4), 129.6 (C5), 128.7 (C10), 128.4 (C6), 126.6 (C2), 123.5 (C1), 123.3 (C3), 120.8 (C7), 113.1 (C9), 77.5 (C13), 56.6 (C11), 34.4 (C14), 29.9 (C12), 18.9 (C15), 17.8 (C16); **IR** (thin layer film) ν = 3299, 2951, 2923, 2867, 1487, 1452, 1067, 1039, 1001, 775, 739 cm^{-1}; **HRMS** (ESI$^+$) *m/z* Calcd. for $C_{16}H_{20}O_2{}^{23}Na$ $(M+Na)^+$ 267.1356, found 267.1355.

1-cyclohexyl-2-(2-methoxynaphthalen-1-yl)ethan-1-ol (111)



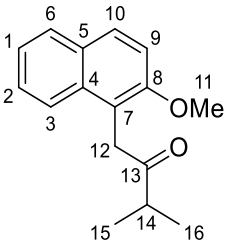
Prepared according to General Procedure A with 1-bromo-2-methoxynapthalene (**100**) (5.00 g, 21.00 mmol) and 2-cyclohexyloxirane (2.26 g, 17.91 mmol). Reaction time: 22 h. Product was purified by flash column chromatography (silica gel, 10% EtOAc in petroleum ether b.p. 40–60 °C) to afford the product as a yellow oil (68%, 3.46 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.00 – 7.93 (m, 1H, H3), 7.83 – 7.74 (m, 2H, H6 & H10), 7.48 (ddd, *J* = 8.4, 6.7, 1.4 Hz, 1H, H2), 7.35 (ddd, *J* = 8.0, 6.8, 1.1 Hz, 1H, H1), 7.29 (d, *J* = 9.0 Hz, 1H, H9), 3.96 (s, 3H, $H11_3$), 3.70 (ddt, *J* = 9.2, 5.2, 3.5 Hz, 1H, H13), 3.41 – 3.12 (m, 2H, $H12_2$), 2.10 – 1.99 (m, 2H, $H16_A$ & OH), 1.96 – 1.79 (m, 4H, $H15_2$ & $H19_2$), 1.77 – 1.69 (m, 1H, $H18_A$), 1.64 – 1.52 (m, 1H, H14), 1.40 – 1.11 (m, 4H, $C16H_B$, $C17H_2$ & $C18H_B$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.0 (C8), 133.6 (C4), 129.6 (C5), 128.7 (C10), 128.4 (C6), 126.6 (C2), 123.5 (123.5), 123.4 (C3), 120.9 (C7), 113.1 (C9), 77.0 (C13), 56.6 (C11), 44.5 (C14), 30.0 (C12), 29.4 (C15), 28.3 (C18), 26.9 (C16), 26.6 (C19), 26.5 (C17); **IR** (thin layer film) ν = 3452, 2980, 2922, 2850, 1595, 1513, 1463, 1450, 1382, 1249, 1146, 1090, 1024, 805, 745 cm^{-1}; **HRMS** (ESI$^+$) *m/z* Calcd. for $C_{19}H_{24}O_2{}^{23}Na$ $(M+Na)^+$ 307.1669, found 307.1669.

1-(2-methoxynaphthalen-1-yl)-3,3-dimethylbutan-2-one (112)



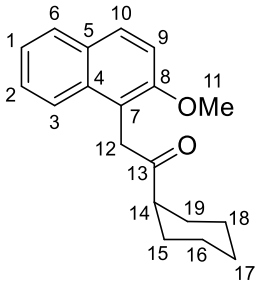
Prepared according to General Procedure B with 1-(2-methoxynaphthalen-1-yl)-3,3-dimethylbutan-2-ol (**109**) (2.23 g, 8.63 mmol). Product was purified by flash column chromatography (silica gel, 5% EtOAc in petroleum ether b.p. 40–60 °C) to afford the product as a pale yellow solid (81%, 1.79 g). **M.P.** = 74-76 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.85 – 7.78 (m, 2H, H6 & H10), 7.68 (d, *J* = 8.6 Hz, 1H, H2), 7.47 (ddd, *J* = 8.4, 6.8, 1.3 Hz, 1H, H1), 7.39 – 7.32 (m, 1H, H3), 7.30 (d, *J* = 9.5 Hz, 1H, H9), 4.34 (s, 2H, $H12_2$), 3.92 (s, 3H, $H11_3$), 1.37 (s, 9H, $H15_3$, $H16_3$ & $H17_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 213.1 (C13), 154.8 (C8), 133.8 (C4), 129.2 (C5), 128.8 (C6), 128.7 (C10), 126.6 (C1), 123.3 (C3), 123.0 (C2), 117.3 (C7), 113.1 (C9), 56.5 (C11), 44.9 (C14), 33.8 (C12), 27.1 (C15, C16 & C17); **IR** (thin layer film) ν = 2963, 1703, 1596, 1515, 1475, 1328, 1267, 1255, 1094, 1070, 1007, 812, 743 cm^{-1}; **HRMS** (ESI^+) *m/z* Calcd. for $C_{17}H_{20}O_2{}^{23}Na$ $(M+Na)^+$ 279.1356, found 279.1355.

1-(2-methoxynaphthalen-1-yl)-3-methylbutan-2-one (113)



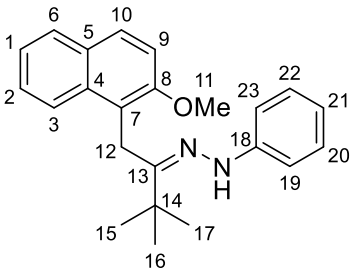
Prepared according to General Procedure B with 1-(2-methoxynaphthalen-1-yl)-3-methylbutan-2-ol (**110**) (15.15 g, 62.00 mmol). Product was purified by flash column chromatography (silica gel, 5% EtOAc in petroleum ether b.p. 40–60 °C) to afford the product as a yellow oil (80%, 12.01 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.89 – 7.77 (m, 3H, H3, H6 & H10), 7.56 – 7.46 (m, 1H, H2), 7.42 – 7.35 (m, 1H, H1), 7.33 (d, *J* = 9.1 Hz, 1H, H9), 4.27 (s, 2H, $H12_2$), 3.97 (s, 3H, $H11_3$), 2.81 (hept, *J* = 6.9 Hz, 1H, H14), 1.15 (d, *J* = 6.9 Hz, 6H, $H15_3$ & $H16_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 213.1 (C13), 154.7 (C8), 133.6 (C4), 129.2 (C5), 129.0 (C10), 128.6 (C6), 126.9 (C1), 123.5 (C3), 123.1 (C2), 116.5 (C7), 113.0 (C9), 56.4 (C11), 39.5 (C14), 38.3 (C12), 18.7 (C15 & C16); **IR** (thin layer film) ν = 1419, 1249, 1214, 1142, 1059, 1012, 901, 809, 764, 738, 621 cm^{-1}; **HRMS** (ESI^+) *m/z* Calcd. for $C_{16}H_{18}O_2{}^{23}Na$ $(M+Na)^+$ 265.1199, found 265.1198.

1-cyclohexyl-2-(2-methoxynaphthalen-1-yl)ethan-1-one (114)



Prepared according to General Procedure B with 1-cyclohexyl-2-(2-methoxynaphthalen-1-yl)ethan-1-ol (**111**) (2.60 g, 9.14 mmol). Product was purified by flash column chromatography (silica gel, 5% EtOAc in petroleum ether b.p. 40–60 °C) to afford the product as a yellow oil (85%, 2.04 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83 – 7.73 (m, 3H, H3, H6 & H10), 7.46 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H, H2), 7.33 (ddd, *J* = 8.1, 6.8, 1.1 Hz, 1H, H1), 7.30 (d, *J* = 9.1 Hz, 1H, H9), 4.21 (s, 2H, H12), 3.94 (s, 3H, H11), 2.64 – 2.39 (m, 1H, H14), 1.91 – 1.83 (m, 2H, $H15_A$ & $H19_A$), 1.82 – 1.72 (m, 2H, $H16_A$ & $H18_A$), 1.68 – 1.59 (m, 1H, $H17_A$), 1.48 – 1.35 (m, 2H, $H15_B$ & $H19_B$), 1.31 – 1.15 (m, 3H, $H16_B$, $H17_B$ & $H18_B$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 212.0 (C13), 154.7 (C8), 133.6 (C4), 129.1 (C5), 128.9 (C10), 128.5 (C6), 126.8 (C1), 123.4 (C3), 123.1 (C2), 116.6 (C7), 113.1 (C9), 56.5 (C11), 49.7 (C14), 38.2 (C15 & C19), 28.8 (C17), 25.9 (C16), 25.7 (C18); **IR** (thin layer film) ν = 2929, 2852, 1709, 1626, 1514, 1464, 1449, 1264, 1251, 1145, 1090, 1025, 809, 745 cm^{-1}; **HRMS** (ESI^+) *m/z* Calcd. for $C_{19}H_{22}O_2{}^{23}Na$ $(M+Na)^+$ 305.1512, found 305.1512.

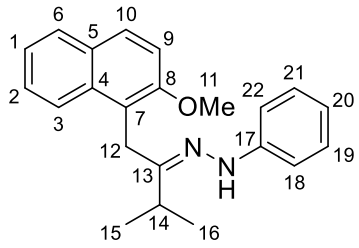
(Z)-1-(1-(2-methoxynaphthalen-1-yl)-3,3-dimethylbutan-2-ylidene)-2-phenylhydrazine (115)



Prepared according to General Procedure C with 1-(2-methoxynaphthalen-1-yl)-3,3-dimethylbutan-2-one (**112**) (2.00 g, 7.80 mmol). Reaction time = 6 h. The product was obtained by filtration from the crude reaction mixture as a white crystalline solid (72%, 1.95 g). **M.P.** = 88-90 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.6 Hz, 1H, H3), 7.81 – 7.71 (m, 2H, H6 & H10), 7.51 – 7.44 (m, 1H, H2), 7.39 (bs, 1H, NH), 7.35 – 7.28 (m, 1H, H1), 7.18 (d, *J* = 8.9 Hz, 1H, H9), 7.05 – 6.96 (m, 2H, H20 & H22), 6.61 (td, *J* = 7.3, 1.3 Hz, 1H, H21), 6.58 – 6.51 (m, 2H, H19 & H23), 3.99 (s, 2H, $H12_2$), 3.80 (s, 3H, $H11_3$), 1.18 (s, 9H, $H15_3$, $H16_3$ & $H17_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.0 (C13), 152.6 (C8), 146.6 (C18), 132.8 (C4), 129.6 (C5), 129.2 (C10), 129.1 (C6), 129.0 (C20 & C22), 127.3 (C2), 123.8 (C1), 123.0

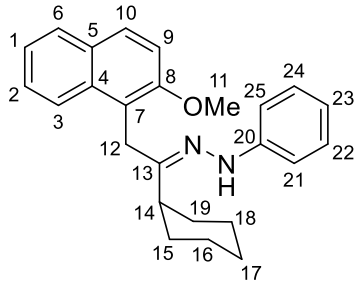
(C3), 119.0 (C21), 118.4 (C7), 113.3 (C9), 112.5 (C19 & C23), 56.3 (C11), 40.1 (C14), 29.4 (C15, C16 & C17), 24.2 (C12); **IR** (thin layer film) ν = 3355, 2980, 2969, 1598, 1502, 1473, 1462, 1276, 1247, 1125, 1091, 1080, 1063, 810, 744, 692 cm^{-1}; **HRMS** (ESI^+) *m/z* Calcd. for $C_{23}H_{27}ON_2$ $(M+H)^+$ 347.2118, found 347.2117.

(Z)-1-(1-(2-methoxynaphthalen-1-yl)-3-methylbutan-2-ylidene)-2-phenylhydrazine (116)



Prepared according to General Procedure C with 1-(2-methoxynaphthalen-1-yl)-3-methylbutan-2-one (**113**) (6.00 g, 24.76 mmol). Reaction time = 2 h. The product was obtained by filtration from the crude reaction mixture as a white crystalline solid (76%, 6.23 g). **M.P.** = 110-112 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.6 Hz, 1H, H3), 7.74 – 7.68 (m, 2H, H6 & H10), 7.67 (bs, 1H, NH), 7.46 – 7.36 (m, 1H, H1), 7.27 (t, *J* = 7.5 Hz, 1H, H2), 7.18 (d, *J* = 9.1 Hz, 1H, H9), 7.16 – 7.09 (m, 2H, H19 & H21), 6.98 – 6.89 (m, 2H, H18 & H22), 6.70 (t, *J* = 7.3 Hz, 1H, H20), 3.93 (s, 2H, $H12_2$), 3.88 (s, 3H, $H11_3$), 2.32 (hept, *J* = 6.8 Hz, 1H, H14), 0.99 (d, *J* = 6.8 Hz, 6H, $H15_3$ & $H16_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.7 (C13), 152.7 (C8), 146.7 (C17), 133.5 (C4), 129.5 (C5), 129.2 (C10), 129.0 (C6), 128.9 (C19 & C21), 127.2 (C2), 123.8 (C1), 123.1 (C3), 119.3 (C20), 118.1 (C7), 113.0 (C9), 112.9 (C18 & C22), 56.6 (C11), 34.2 (C14), 25.3 (C12), 21.2 (C15 & C16); **IR** (thin layer film) ν = 3352, 2963, 2950, 1597, 1504, 1461, 1273, 1259, 1135, 1273, 1259, 1090, 1047, 1026, 939, 875, 804, 692 cm^{-1}; **HRMS** (ESI^+) *m/z* Calcd. for $C_{22}H_{25}ON_2$ $(M+H)^+$ 333.1961, found 333.1962.

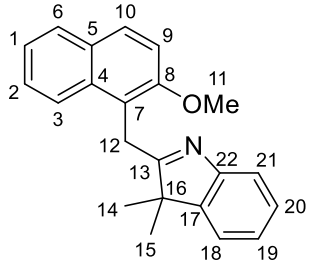
(Z)-1-(1-cyclohexyl-2-(2-methoxynaphthalen-1-yl)ethylidene)-2-phenylhydrazine (117)



Prepared according to General Procedure C with 1-cyclohexyl-2-(2-methoxynaphthalen-1-yl)ethan-1-one (**114**) (2.20 g, 7.80 mmol). Reaction time = 5 h. The product was obtained by filtration from the crude reaction mixture as a white crystalline solid (70%, 2.02 g). **M.P.** = 145-148 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.99 – 7.93 (m, 1H, H3), 7.88

(bs, 1H, NH), 7.82 – 7.82 (m, 2H, H6 & & H10), 7.56 (ddd, *J* = 8.5, 6.8, 1.4 Hz, 1H, H2), 7.42 (ddd, *J* = 8.0, 6.7, 1.1 Hz, 1H, H1), 7.32 (d, *J* = 9.0 Hz, 1H, H9), 7.29 – 7.21 (m, 2H, H22 & H24), 7.08 – 6.98 (m, 2H, H21 & H25), 6.82 (tt, *J* = 7.3, 1.2 Hz, 1H, H23), 4.06 (s, 2H, $H12_2$), 4.02 (s, 3H, $H11_3$), 2.14 (tt, *J* = 11.5, 3.3 Hz, 1H, H14), 1.91 – 1.79 (m, 2H, $H15_A$ & $H19_A$), 1.75 (dt, *J* = 13.1, 3.5 Hz, 2H, $H15_B$ & $H19_B$), 1.63 (dddd, *J* = 11.5, 4.5, 3.3, 1.5 Hz, 1H, $H17_A$), 1.54 – 1.41 (m, 2H, $H16_A$ & $H18_A$), 1.30 – 1.06 (m, 3H, $H16_B$, $H17_B$ & $H18_B$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.6 (C13), 152.3 (C8), 146.8 (C20), 133.4 (C4), 129.5 (C5), 129.2 (C22 & C24), 129.0 (C10), 128.9 (C6), 127.1 (C2), 123.8 (C1), 123.1 (C3), 119.2 (C23), 118.2 (C7), 113.0 (C9), 112.9 (C21 & C25), 56.6 (C11), 44.6 (C14), 31.7 (C15 & C19), 26.7 (C16 & C18), 26.4 (C17), 25.4 (C12); **IR** (thin layer film) ν = 3354, 2980, 2924, 1598, 1503, 1261, 1249, 1147, 1122, 1084, 1066, 1025, 878, 803, 742, 691 cm^{-1}; **HRMS** (ESI^+) *m/z* Calcd. for $C_{25}H_{29}ON_2$ $(M+H)^+$ 373.2274, found 373.2276.

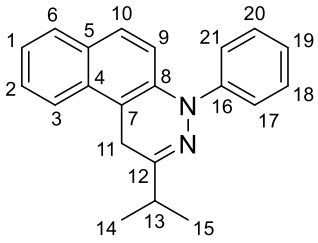
2-((2-methoxynaphthalen-1-yl)methyl)-3,3-dimethyl-3H-indole (119)



Isolated as an undesired regioisomer in the Fischer-indolisation of (2-methoxynaphthalen-1-yl)-3-methylbutan-2-ylidene)-2-phenylhydrazine (**116**): In a flame-dried vial filled with argon, $ZnCl_2$ (0.5 M in THF, 400 µL, 0.20 mmol, 2.00 equiv.) was added to a solution of hydrazone (**116**) (33 mg, 0.10 mmol, 1.00 equiv.) in dry THF (500 µL). The vial was flushed with argon before being heated to 65 °C for 2 h. After this time, the mixture cooled to room temperature and quenched with H_2O. The product was extracted three times with Et_2O and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was then purified by flash column chromatography (silica gel, 20% CH_2Cl_2 in petroleum ether b.p. 40–60 °C) to afford the product as a yellow oil (74%, 23 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.17 (dq, *J* = 8.7, 0.9 Hz, 1H, H3), 7.88 – 7.82 (m, 2H, H6 & H10), 7.61 (dt, *J* = 7.7, 0.9 Hz, 1H, H18), 7.50 (ddd, *J* = 8.5, 6.8, 1.4 Hz, 1H, H2), 7.40 – 7.35 (m, 2H, H1 & H9), 7.32 (td, *J* = 7.5, 1.5 Hz, 1H, H19), 7.28 (ddd, *J* = 7.4, 1.5, 0.7 Hz, 1H, H20), 7.22 (td, *J* = 7.3, 1.1 Hz, 1H, H21), 4.54 (s, 2H, $H12_2$), 4.02 (s, 3H, $H11_3$), 1.33 (s, 6H, $H14_3$ & $H15_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 189.3 (C13), 154.6 (C8),

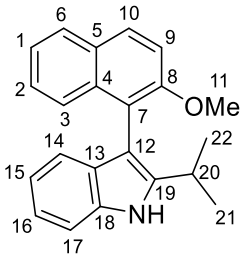
153.6 (C17), 146.5 (C22), 134.1 (C4), 129.3 (C5), 129.0 (C10), 128.4 (C6), 127.4 (C19), 126.7 (C2), 125.1 (C21), 124.0 (C3), 123.5 (C1), 121.0 (C20), 120.3 (C18), 117.8 (C7), 113.3 (C9), 56.6 (C11), 54.3 (C16), 27.3 (C12), 23.5 (C14 & C15); **IR** (thin layer film) ν = 2962, 1625, 1595, 1572, 1512, 1455, 1265, 1251, 1199, 1086, 1024, 908, 805, 773, 731, 700 cm^{-1}; **HRMS** (ESI^+) *m/z* Calcd. for $C_{22}H_{22}ON$ $(M+H)^+$ 316.1696, found 316.1699.

2-isopropyl-4-phenyl-1,4-dihydrobenzo[f]cinnoline (128)



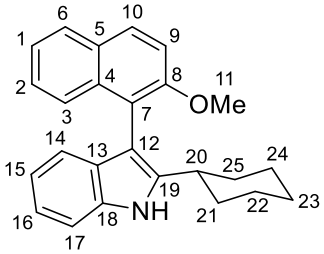
Isolated as a major by-product of the Fischer-indolisation of (2-methoxynaphthalen-1-yl)-3-methylbutan-2-ylidene)-2-phenylhydrazine (**116**): In an oven-dried vial, crystalline H_3PO_4 (49 mg, 0.50 mmol, 5.00 equiv.) was added to a solution of hydrazone (**116**) (33 mg, 0.10 mmol, 1.00 equiv.) in dry toluene (500 µL). The vial was flushed with argon before being heated to 80 °C until complete consumption of the hydrazone (2 h) was observed by TLC analysis. After this time, the mixture cooled to room temperature, diluted with CH_2Cl_2 and neutralised with sat. $NaHCO_{3\ (aq)}$. The product was extracted three times with CH_2Cl_2 and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was then purified by flash column chromatography (silica gel, 20% CH_2Cl_2 in petroleum ether b.p. 40–60 °C) to afford the product as a yellow oil (45%, 14 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.82 – 7.76 (m, 1H, H3), 7.64 (dd, *J* = 8.2, 1.2 Hz, 1H, H6), 7.47 – 7.41 (m, 4H, H2, H10, H18 & H20), 7.32 (dd, *J* = 8.5, 7.3 Hz, 2H, H9 & H19), 7.25 (ddd, *J* = 8.0, 6.7, 1.1 Hz, 1H, H1), 7.12 – 7.04 (m, 2H, H21 & H17), 3.57 (s, 2H, $H11_2$), 2.66 (hept, *J* = 6.9 Hz, 1H, H13), 1.16 (d, *J* = 6.9 Hz, 6H, $H14_3$ & $H15_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.0 (C12), 144.6 (C16), 137.8 (C8), 131.4 (C5), 130.3 (C4), 129.2 (C10), 128.6 (C6), 126.9 (C19), 126.8 (C9), 124.7 (C1), 123.7 (C18 & C20), 123.6 (C2), 121.6 (C3), 114.8 (C17 & C21), 110.5 (C7), 35.3 (C13), 24.1 (C11), 20.0 (C14 & C15); **IR** (thin layer film) ν = 3057, 2962, 2925, 2854, 1597, 1522, 1499, 1453, 1389, 1303, 1210, 1175, 798, 767, 741, 701, 670 cm^{-1}; **HRMS** (ESI^+) *m/z* Calcd. for $C_{21}H_{21}N_2$ $(M+H)^+$ 301.1699, found 301.1701.

2-isopropyl-3-(2-methoxynaphthalen-1-yl)-1H-indole (120)



Prepared according to General Procedure D with (2-methoxynaphthalen-1-yl)-3-methylbutan-2-ylidene)-2-phenylhydrazine (**116**) (2.00 g, 6.02 mmol). Product was purified by flash column chromatography (silica gel, 20% CH_2Cl_2 in petroleum ether b.p. 40–60 °C) to afford the product as a yellow oil (33%, 0.63 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.12 (bs, 1H, NH), 7.91 (dd, *J* = 9.0, 0.7 Hz, 1H, H10), 7.86 – 7.81 (m, 1H, H3), 7.54 – 7.50 (m, 1H, H6), 7.44 – 7.38 (m, 2H, H2 & H9), 7.33 (ddd, *J* = 8.1, 6.7, 1.4 Hz, 1H, H1), 7.29 – 7.24 (m, 1H, H17), 7.15 (ddd, *J* = 8.1, 6.7, 1.5 Hz, 1H, H16), 7.06 – 6.92 (m, 2H, H14 & H15), 3.80 (s, 3H, $H11_3$), 2.94 (hept, *J* = 7.0 Hz, 1H, H20), 1.24 (dd, *J* = 41.2, 7.8 Hz, 6H, $H21_3$ & $H22_3$);**^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.6 (C8), 143.0 (C19), 135.5 (C18), 135.0 (C4), 129.6 (C5), 129.3 (C13), 129.0 (C3), 127.9 (C10), 126.2 (C17), 126.1 (C6), 123.5 (C1), 121.2 (C16), 119.6 (2C, C14 & C15), 118.1 (C7), 114.2 (C2), 110.6 (C9), 106.1 (C12), 56.7 (C11), 26.6 (C20), 22.6 (C21), 22.3 (C22); **IR** (thin layer film) ν = 3414, 2960, 1620, 1593, 1460, 1332, 1295, 1267, 1249, 1098, 1063, 1019, 808, 746, 669 cm^{-1}; **HRMS** (ESI^+) *m/z* Calcd. for $C_{22}H_{22}ON$ $(M+H)^+$ 316.1696, found 316.1697.

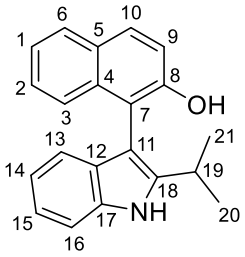
2-cyclohexyl-3-(2-methoxynaphthalen-1-yl)-1H-indole (126)



Prepared according to General Procedure D with (1-(1-cyclohexyl-2-(2-methoxynaphthalen-1-yl)ethylidene)-2-phenylhydrazine (**117**) (500 mg, 1.34 mmol). Product was purified by flash column chromatography (silica gel, 20% CH_2Cl_2 in petroleum ether b.p. 40–60 °C) to afford the product as a pale yellow solid (26%, 124 mg). **M.P.** = 65-67 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.19 (bs, 1H, NH), 7.98 (dd, *J* = 9.1, 0.8 Hz, 1H, H10), 7.92 (dd, *J* = 8.1, 1.5 Hz, 1H, H3), 7.65 – 7.57 (m, 1H, H6), 7.47 (d, *J* = 9.0 Hz, 1H, H1), 7.44 – 7.38 (m, 2H, H2 & H9), 7.34 (ddd, *J* = 8.2, 6.7, 1.5 Hz, 1H, H17), 7.21 (ddd, *J* = 8.2, 6.7, 1.6 Hz, 1H, H16), 7.12 – 7.01 (m, 2H, H14 & H15), 3.85 (s, 3H, $H11_3$), 2.64 (tt, *J* = 12.2, 3.4 Hz, 1H, H20), 2.15 – 2.04 (m, 1H, $H23_A$), 1.91 – 1.79 (m, 2H, $H21_A$ & $H25_A$), 1.79 – 1.67 (m, 2H, $H21_B$ & $H25_B$), 1.59 – 1.41 (m, 2H, $H22_B$ & $H24_A$),

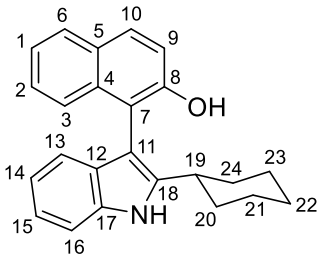
1.38 – 1.13 (m, 3H, $H22_B$, $H23_B$ & $H24_B$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.5 (C8), 142.5 (C19), 135.4 (C18), 135.0 (C4), 129.5 (C5), 129.3 (C13), 128.9 (C3), 127.9 (C10), 126.3 (2C, C6 & C17), 126.1 (C1), 123.5 (C2), 121.1 (C16), 119.6 (C14), 119.5 (C15), 118.3 (C7), 110.6 (C9), 106.0 (C12), 56.7 (C11), 36.6 (C20), 33.2 (C21), 32.8 (C25), 26.6 (C22), 26.5 (C24), 26.2 (C23); **IR** (thin layer film) ν = 3417, 2928, 2851, 1593, 1507, 1459, 1449, 1330, 1292, 1266, 1251, 1240, 1216, 1065, 1019, 809, 745 cm^{-1}; **HRMS** (ESI^+) *m/z* Calcd. for $C_{25}H_{26}ON$ $(M+H)^+$ 356.2009, found 356.2010.

1-(2-isopropyl-1H-indol-3-yl)naphthalen-2-ol (130)



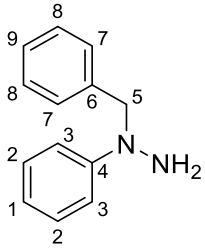
Prepared according to General Procedure E with 2-isopropyl-3-(2-methoxynaphthalen-1-yl)-1H-indole (**120**) (500 mg, 1.59 mmol). Product was purified by flash column chromatography (silica gel, 20% CH_2Cl_2 in petroleum ether b.p. 40–60 °C) to afford the product as a white solid (81%, 387 mg). **M.P.** = 141-143 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.33 (bs, 1H, NH), 7.88 – 7.82 (m, 2H, H10 & H3), 7.47 (dt, *J* = 8.1, 0.9 Hz, 1H, H16), 7.41 – 7.37 (m, 1H, H1), 7.35 – 7.27 (m, 3H, H2, H6 & H9), 7.23 (ddd, *J* = 8.2, 7.0, 1.3 Hz, 1H, H15), 7.12 (ddt, *J* = 7.9, 1.4, 0.8 Hz, 1H, H13), 7.05 (ddd, *J* = 7.9, 6.9, 1.0 Hz, 1H, H14), 5.39 (s, 1H, OH), 2.94 (hept, 1H, H19), 1.24 (dd, *J* = 17.2, 7.0 Hz, 6H, $H20_3$ & $H21_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.3 (C8), 144.9 (C18), 135.9 (C17), 134.7 (C4), 129.6 (C3), 129.2 (C5), 128.8 (C12), 128.2 (C10), 126.4 (C2), 125.2 (C1), 123.2 (C6), 122.2 (C15), 120.4 (C14), 119.5 (C13), 117.0 (C9), 113.1 (C7), 110.9 (C16), 102.6 (C11), 26.5 (C19), 22.7 (C21), 22.5 (C20); **IR** (thin layer film) ν = 3476, 3414, 2964, 1620, 1596, 1460, 1433, 1386, 1338, 1300, 1264, 1225, 1198, 1169, 1139, 817, 748, 712 cm^{-1}; **HRMS** (ESI^+) *m/z* Calcd. for $C_{21}H_{20}ON$ $(M+H)^+$ 302.1539, found 302.1540. **HPLC** (Daicel Chiralpak IA, hexane / IPA = 70:30, flow rate 1.0 mL min^{-1}, T = 25 °C, 330 nm): tR = 7.67 min, tR = 13.31 min.

1-(2-cyclohexyl-1H-indol-3-yl)naphthalen-2-ol (131)



Prepared according to General Procedure E with 2-cyclohexyl-3-(2-methoxynaphthalen-1-yl)-1H-indole (**126**) (355 mg, 1.00 mmol). Product was purified by flash column chromatography (silica gel, 20% CH_2Cl_2 in petroleum ether b.p. 40–60 °C) to afford the product as a white solid (79%, 270 mg). **M.P.** = 90-92 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.35 (bs, 1H, NH), 7.94 – 7.88 (m, 2H, H3 & H10), 7.47 – 7.38 (m, 3H, H1, H9 & H16), 7.38 – 7.30 (m, 2H, H2 & H6), 7.29 – 7.23 (m, 1H, H15), 7.15 (dd, *J* = 7.8, 1.2 Hz, 1H, H13), 7.09 (ddd, *J* = 7.8, 6.8, 1.0 Hz, 1H, H14), 5.49 (s, 1H, OH), 2.61 (tt, *J* = 12.2, 3.5 Hz, 1H, H19), 1.96 – 1.84 (m, 2H, $H20_A$ & $H24_A$), 1.82 – 1.64 (m, 3H, $H21_A$, $H22_A$ & $H23_A$), 1.56 – 1.38 (m, 2H, $H20_B$ & $H24_B$), 1.32 – 1.09 (m, 3H, $H21_B$, $H22_B$ & $H23_B$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.2 (C8), 144.3 (C18), 135.9 (C17), 134.7 (C4), 129.6 (C3), 129.2 (C5), 128.8 (C12), 128.2 (C10), 126.4 (C2), 125.2 (C1), 123.2 (C6), 122.1 (C15), 120.3 (C14), 119.5 (C13), 117.0 (C9), 113.2 (C7), 110.8 (C16), 102.6 (C11), 36.3 (C19), 33.1 (C20), 33.0 (C24), 26.3 (2C, C21 & C23), 25.9 (C22); **IR** (thin layer film) ν = 3468, 3416, 2927, 2852, 1620, 1597, 1458, 1433, 1345, 1332, 1265, 1216, 1198, 1143, 818, 748 cm^{-1}; **HRMS** (ESI^+) *m/z* Calcd. for $C_{24}H_{24}ON$ $(M+H)^+$ 342.1852, found 342.1853. **HPLC** (Daicel Chiralpak IA, hexane / IPA = 80:20, flow rate 1.0 mL min^{-1}, T = 25 °C, 330 nm): tR = 6.21 min, tR = 15.24 min.

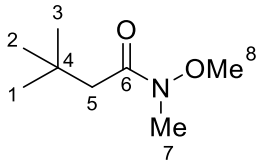
N-methoxy-N,3,3-trimethylbutanamide (134)



Aniline (1.85 g, 10.10 mmol, 1.00 equiv.) and *t*-butylnitrite (1.25 g, 1.44 mL, 12.12 mmol, 1.00 equiv.) were added to a 25 mL round-bottomed flask and the mixture was stirred at room temperature for 10 min. The contents were then dissolved in MeOH (20 mL) and transferred to a 250 mL round-bottomed flask. To this solution was added 1M NaOH (60 mL, 60.60 mmol, 6.00 equiv.) at room temperature, followed by thiourea dioxide (TDO) (3.27 g, 30.30 mmol, 3.00 equiv.). The resulting mixture was then heated at 50 °C for 4 h, and then cooled again to room temperature. The reaction was diluted with CH_2Cl_2 (60 mL) and the layers were separated. The aqueous phase was further extracted

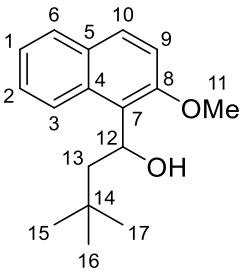
three times with CH_2Cl_2 and the combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography [silica gel, 20% Et_2O in petroleum ether bp 40–60 °C] to afford the product as an orange oil (83%, 1.66 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 – 7.27 (m, 7H, $H2_2$, $H7_2$, $H8_2$ & H9), 7.17 – 7.09 (m, 2H, $H3_2$), 6.86 (tt, *J* = 7.2, 1.1 Hz, 1H, H1), 4.63 (s, 2H, $H5_2$), 3.60 (bs, 2H, NH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.7 (C4), 137.5 (C6), 129.1 (C2), 128.7 (C8), 128.0 (C7), 127.4 (C9), 118.7 (C1), 113.8 (C3), 60.4 (C5); **IR** (thin layer film) ν = 1595, 1494, 1452, 1354, 1213, 1028, 989, 879, 749, 729, 693 cm^{-1}; **HRMS** (ESI^+) *m/z* Calcd. for $C_{13}H_{15}N_2$ $(M+H)^+$ 199.1230, found 199.1230.

N-methoxy-N,3,3-trimethylbutanamide (140)



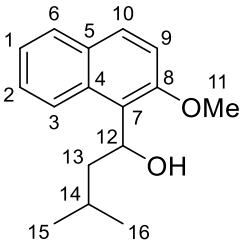
To a stirred suspension of *N*-methoxymethylamine hydrochloride salt (975 mg, 10.00 mmol, 1.00 equiv.) in CH_2Cl_2 (50 mL) at 0 °C was added NEt_3 (2.02 g, 2.79 mL, 20.00 mmol, 2.00 equiv.). 3,3-dimethylbutanoyl chloride (1.35 g, 1.40 mL, 10.00 mmol, 1.00 equiv.) was then added and the mixture was warmed to room temperature and stirred for 1 h. The reaction was quenched by the addition of $NaHCO_3$ and the layers were separated and the aqueous phase was extracted three times with CH_2Cl_2. The combined extracts were washed with 1.0 M HCl, brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was isolated as a colourless oil used in the next step without any further purification (97%, 1.54 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.65 (s, 3H, $H8_3$), 3.16 (s, 3H, $H7_3$), 2.30 (s, 2H, $H5_2$), 1.04 (s, 9H, $H1_3$, $H2_3$ & $H3_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.5 (C6), 61.0 (C8), 43.8 (H5), 31.4 (C4), 30.1 (C1, C2 & C3); **IR** (thin layer film) ν = 2980, 2888, 1381, 1252, 1153, 1084, 948, 750 cm^{-1}; **HRMS** (ESI^+) *m/z* Calcd. for $C_8H_{28}O_2N$ $(M+H)^+$ 160.1332, found 160.1332.

1-(2-methoxynaphthalen-1-yl)-3,3-dimethylbutan-1-ol (144)



Prepared according to General Procedure F with 1-bromo-2-methoxynapthalene (**100**) (4.50 g, 18.97 mmol) and 3,3-dimethylbutanal (2.86 g, 3.60 mL, 28.46 mmol). Product was purified by flash column chromatography [silica gel, 5-10% EtOAc in petroleum ether bp 40–60 °C] to afford the product as a yellow oil (73%, 3.56 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.25 – 8.12 (m, 1H, H3), 7.88 – 7.77 (m, 2H, H6 & H10), 7.53 (ddd, *J* = 8.5, 6.8, 1.4 Hz, 1H, H1), 7.40 (ddd, *J* = 8.0, 6.7, 1.1 Hz, 1H, H2), 7.31 (d, *J* = 9.0 Hz, 1H, H9), 5.86 – 5.75 (m, 1H, H12), 4.03 (s, 3H, $H11_3$), 2.17 (dd, *J* = 14.6, 9.3 Hz, 1H, $H13_A$), 1.71 (dd, *J* = 14.7, 3.0 Hz, 1H, $H13_B$), 1.14 (s, 9H, $H15_3$, $H16_3$ & $H17_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.4 (C8), 129.6 (C4), 129.1 (C5), 128.8 (C10), 126.7 (C6), 126.5 (C2), 123.7 (C1), 123.2 (C3), 117.5 (C9), 112.3 (C7), 67.7 (C12), 56.5 (C11), 51.2 (C13), 31.1 (C15, C16 & C17), 30.3 (C14); **IR** (thin layer film) ν = 2951, 1624, 1596, 1511, 1464, 1363, 1334, 1246, 1086, 1024, 806, 746 cm^{-1}; **HRMS** (ESI^+) *m/z* Calcd. for $C_{17}H_{23}O_2$ $(M+H)^+$ 259.1693, found 259.1694.

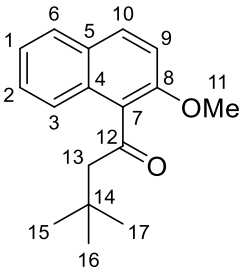
1-(2-methoxynaphthalen-1-yl)-3-methylbutan-1-ol (145)



Prepared according to General Procedure F with 1-bromo-2-methoxynapthalene (**100**) (2.23 g, 10.00 mmol) and isovaleraldehyde (**142**) (1.29 g, 1.65 mL, 15.00 mmol). The product was purified by flash column chromatography [silica gel, 10% EtOAc in petroleum ether b.p. 40–60 °C] to afford the product as a yellow oil (84%, 2.05 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.7 Hz, 1H, H3), 7.90 – 7.73 (m, 2H, H6 & H10), 7.51 (ddd, *J* = 8.6, 6.8, 1.4 Hz, 1H, H1), 7.38 (ddd, *J* = 8.0, 6.8, 1.1 Hz, 1H, H2), 7.36 – 7.24 (m, 1H, H9), 5.67 (d, *J* = 8.1 Hz, 1H, H12), 4.03 (s, 3H, $H11_3$), 2.09 (ddd, *J* = 13.8, 9.7, 5.0 Hz, 1H, $H13_A$), 2.02 – 1.90 (m, 1H, $H13_B$), 1.61 (ddd, *J* = 13.8, 8.6, 4.5 Hz, 1H, H14), 1.05 (dd, *J* = 14.7, 6.6 Hz, 6H, $H15_3$ & $H16_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.6 (C8), 131.6 (C4), 129.5 (C5), 129.2 (C10), 128.8 (C6), 126.7 (C2), 125.5 (C1), 123.7 (C3), 123.0 (C9), 113.5 (C7), 68.3 (C12), 56.5 (C11), 46.9 (C13), 25.2 (C14), 23.8 (C15), 22.1 (C16); **IR** (thin layer

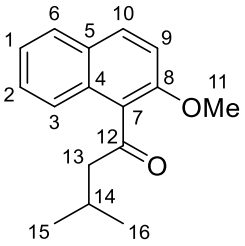
film) ν = 2954, 1623, 1596, 1511, 1465, 1246, 1081, 1025, 806, 747 cm^{-1}; **HRMS** (ESI^+) *m/z* Calcd. for $C_{16}H_{21}O_2$ $(M+H)^+$ 245.1536, found 245.1536.

1-(2-methoxynaphthalen-1-yl)-3,3-dimethylbutan-1-one (146)



Prepared according to General Procedure G with 1-(2-methoxynaphthalen-1-yl)-3-methylbutan-1-ol (**144**) (3.30 g, 12.77 mmol). The product was purified by flash column chromatography [silica gel, 5-10% EtOAc in petroleum ether bp 40–60 °C] to afford the product as a colourless oil (98%, 3.20 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 9.1 Hz, 1H, H3), 7.85 – 7.79 (m, 1H, H10), 7.77 (dt, *J* = 8.6, 0.9 Hz, 1H, H6), 7.50 (ddd, *J* = 8.5, 6.8, 1.4 Hz, 1H, H2), 7.38 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H, H1), 7.28 (d, *J* = 9.1 Hz, 1H, H9), 3.98 (s, 3H, $H11_3$), 2.92 (s, 2H, $H13_2$), 1.16 (s, 9H, $H15_3$, $H16_3$ & $H17_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 207.3 (C12), 153.7 (C8), 131.2 (C4), 130.5 (C5), 129.1 (C10), 128.3 (2C, C2 & C6), 126.3 (C3), 124.1 (C1), 123.8 (C9), 113.1 (C7), 57.4 (C11), 56.6 (C13), 31.6 (C14), 30.0 (C15, C16 & C17); **IR** (thin layer film) ν = 2963, 1680, 1594, 1476, 1250, 1066, 809, 753 cm^{-1}; **HRMS** (ESI^+) *m/z* Calcd. for $C_{17}H_{21}O_2$ $(M+H)^+$ 257.1536, found 257.1536.

1-(2-methoxynaphthalen-1-yl)-3-methylbutan-1-one (147)

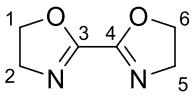


Prepared according to General Procedure G with 1-(2-methoxynaphthalen-1-yl)-3-methylbutan-1-ol (**145**) (1.00 g, 4.09 mmol). The product was purified by flash column chromatography [silica gel, 5-10% EtOAc in petroleum ether bp 40–60 °C] to afford the product as a colourless oil (94%, 931 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.92 – 7.87 (m, 1H, H3), 7.85 – 7.79 (m, 1H, H10), 7.74 (dq, *J* = 8.6, 0.9 Hz, 1H, H6), 7.49 (ddd, *J* = 8.5, 6.8, 1.4 Hz, 1H, H2), 7.38 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H, H1), 7.29 (d, *J* = 9.1 Hz, 1H, H9), 3.97 (s, 3H, $H11_3$), 2.86 (d, *J* = 6.8 Hz, 2H, $H13_2$), 2.40 (dt, *J* = 13.4, 6.7 Hz, 1H, H14), 1.06 (d, *J* = 6.7 Hz, 6H, $H15_3$ & $H16_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 207.5 (C12), 153.8 (C8), 131.3 (C4), 130.7 (C5), 129.0 (C10), 128.3 (C6), 127.6 (C2), 125.6 (C3), 124.1 (C1), 123.7 (C9), 113.0 (C7), 56.5 (C11), 54.2 (C13), 24.6 (C14), 23.0 (C15 & C16); **IR** (thin layer film)

ν = 2956, 1694, 1623, 1594, 1510, 1465, 1433, 1339, 1271, 1251, 1183, 1149, 1063, 1023, 808, 747 cm^{-1}; **HRMS** (ESI^+) *m/z* Calcd. for $C_{16}H_{19}O_2$ $(M+H)^+$ 243.1380, found 243.1380.

9.5.2 Achiral Ligands

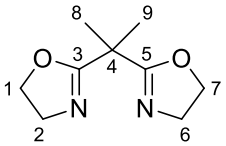
4,4',5,5'-tetrahydro-2,2'-bioxazole (L6)



The procedure is based on a modified 3-step literature sequence. Data is in agreement with those previously reported.[105] Diethyl oxalate (1.00 g, 0.93 mL, 6.84 mmol, 1.00 equiv.) was added to a solution of 1-aminoethanol (836 mg, 826 µL, 13.68 mmol, 2.00 equiv.) in toluene (27 mL). The mixture was heated to 90 °C and stirred at this temperature for 24 h. The reaction was then cooled to room temperature and the solvent removed *in vacuo*. The solid was dried *in vacuo* to afford the crude bis-oxalamide which was used in the subsequent step without further purification. In a flame-dried, argon filled RBF equipped with reflux condenser, the crude bis-oxalamide (assumed no product loss from previous step*:* 1.21 g, 6.84 mmol, 1.00 equiv.) was suspended in toluene (13.7 mL) and $SOCl_2$ (2.03 g, 1.24 mL, 17.10 mmol, 2.50 equiv.) was added. The contents were then heated to 90 °C for 3 h. After this time, the volatiles were removed *in vacuo* (the excess $SOCl_2$ was removed by further azeotropic distillation with toluene). The residue was redissolved in CH_2Cl_2 (15 mL), basified with sat. $NaHCO_{3\ (aq.)}$ (20 mL) and the layers were separated. The product was further extracted three times with CH_2Cl_2 and the combined extracts were dried over Na_2SO_4, filtered and concentrated by rotary evaporation to give the crude dichlorooxalamide, which was used in the next step without further purification. An RBF equipped with reflux condenser was charged with the crude dichlorooxalamide (assumed no product loss from previous step: 1.46 g, 6.84 mmol, 1.00 equiv.), KOH (pellets, 959 mg, 17.10 mmol, 2.50 equiv.) and MeOH (10 mL) and the mixture heated to reflux for 16 h. After the allotted time, the contents were cooled to room temperature and the solvent was removed *in vacuo*. The residue was then dissolved in a mixture of water (15 mL) and CH_2Cl_2 (15 mL) and the layers were separated. The aqueous phase was extracted three times with CH_2Cl_2 and the organic extracts were pooled, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography [silica gel, 50% EtOAc in

petroleum ether b.p. 40–60 °C + 1% NEt_3] to afford the product as a pale yellow solid (66% over 3 steps, 631 mg). **M.P.** = 201-206 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.44 (t, *J* = 9.8 Hz, 4H, $H1_2$ & $H6_2$), 4.06 (t, *J* = 9.8 Hz, 4H, $H2_2$ & $H5_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.9 (C3 & C4), 68.54 (C1 & C6), 55.29 (C2 & C5); **HRMS** (ESI^+) m/z Calcd. for $C_6H_9O_2N_2$ $(M+H)^+$ 141.0659, found 141.0658.

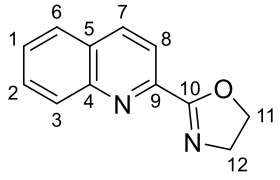
2,2'-(propane-2,2-diyl)bis(4,5-dihydrooxazole) (L7)



The procedure is based on a modified 4-step literature sequence. Data is in agreement with those previously reported.[134] In an oven dried, argon filled RBF, dimethylmalonic acid (1.50 g, 11.35 mmol, 1.00 equiv.) and DMF (42 mg, 44 μL, 0.568 mmol, 0.05 equiv.) were dissolved in CH_2Cl_2 (22 mL) and the resulting solution cooled to 0 °C. Oxalyl chloride (4.32 g, 2.88 mL, 34.05 mmol, 3.00 equiv.) was then slowly added and the mixture was warmed to room temperature and stirred for 16 h. The volatiles were then removed *in vacuo* to afford crude dimethylmalonyl chloride, which was used immediately in the next step. To a suspension of K_2CO_3 (1.57 g, 45.40 mmol, 4.00 equiv.) and ethanolamine (1.46 g, 1.44 mL, 23.84 mmol, 2.10 equiv.) in CH_2Cl_2 (28 mL) at 0 °C was added a solution of dimethylmalonyl chloride (assumed no product loss from previous step*:* ~1.92 g, 11.35 mmol, 1.00 equiv.) in CH_2Cl_2 (10 mL). The reaction was then allowed to warm to room temperature. After stirring for 24 h, MeOH (100 mL) was added and the mixture was stirred for a further 30 min. The slurry was then filtered through a pad of Celite® and concentrated *in vacuo* to afford the crude diamide which was used in the subsequent step without further purification. The crude diamide (assumed no product loss from previous step ~2.48 g, 11.35 mmol, 1.00 equiv.) was suspended in toluene (65 mL). At room temperature, $SOCl_2$ (5.40 g, 3.31 mL, 45.40 mmol, 4.00 equiv.) was added and the mixture was heated to 65 °C for 5 h. The reaction was then cooled to room temperature and the solvent removed *in vacuo* (the excess $SOCl_2$ was removed by further azeotropic distillation with toluene). The residue was then redissolved in CH_2Cl_2 (25 mL), basified with sat. $NaHCO_{3\ (aq.)}$ (50 mL) and the layers were separated. The product was further extracted

three times with CH_2Cl_2 and the combined extracts were dried over Na_2SO_4, filtered and concentrated by rotary evaporation to give the crude dichloroamide. In an RBF, the crude dichloroamide (assumed no product loss from previous step, ~2.90 g, 11.35 mmol, 1.00 equiv.) was treated with 5% (w/v) methanolic KOH (36 mL) and the resulting mixture was heated to 80 °C for 2 h. The reaction was then cooled to room temperature and concentrated *in vacuo*. Water was then added (20 mL) and the product was extracted four times with 3:1 $CHCl_3$/MeOH. The organic extracts were pooled, dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the product as an off-white solid. No further purification was required (25% over 4 steps, 524 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.32 – 4.21 (m, 4H, $H1_2$ & $H7_2$), 3.90 – 3.80 (m, 4H, $H2_2$ & $H6_2$), 1.50 (s, 6H, $H8_3$ & $H9_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.9 (C3 & C5), 68.0 (C1 & C7), 54.4 (C2 & C6), 38.6 (C4), 24.3 (C8 & C9); **FTIR** (neat) ν = 3420, 2984, 1655, 1354, 1253, 1197, 1143, 1113, 982, 955, 914 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_9H_{15}O_2N_2$ $(M+H)^+$ 183.1129, found 183.1128.

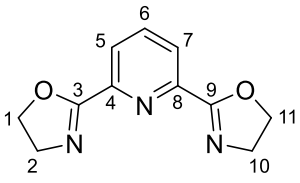
2-(quinolin-2-yl)-4,5-dihydrooxazole



The procedure is based on a modified 2-step literature sequence. Data is in agreement with those previously reported.[135] In an oven dried, argon filled RBF, quinaldic acid (1.75 g, 10.00 mmol, 1.00 equiv.) was dissolved in CH_2Cl_2 (100 mL) and cooled to 0 °C. At this temperature, *N*-methyl morpholine (1.51 g, 1.44 mL, 15.00 mmol, 1.50 equiv.) and isobutylchloroformate (1.57 g, 1.51 mL, 11.50 mmol, 1.15 equiv.) were then introduced. The reaction was stirred at 0 °C for 30 min, prior to the addition of freshly distilled ethanolamine (702 mg, 695 µL, 11.50 mmol, 1.15 equiv.). The mixture was then allowed to warm to room temperature and stirring was continued for 2 h. After this time, the reaction was quenched with sat. $NaHCO_{3(aq.)}$ (50 mL) and the layers were separated. The aqueous phase was further extracted three times with CH_2Cl_2. The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude amide. In a flame dried three necked round-bottomed flask equipped with reflux condenser, TsCl (2.23 g, 11.50 mmol, 1.15 equiv.) and DMAP (95 mg, 0.78 mmol, 0.08 equiv.) were dissolved in DCE (30 mL) under an

argon atmosphere, and the contents cooled to –5 °C. In a separate flame dried, argon filled pear shaped flask, the crude amide (assumed no product loss from previous step*)* was dissolved in DCE (40 mL) and transferred to the cooled reaction mixture *via* syringe. The mixture was then slowly warmed to room temperature and stirring was continued for 3 h. After this time, the reaction was then heated to reflux for an additional 3 h. The contents were then cooled again to room temperature, and the reaction was quenched with sat. $NaHCO_{3(aq.)}$ (50 mL). The layers were separated, and the aqueous phase was further extracted three times with CH_2Cl_2. The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography [silica gel, 2% MeOH in CH_2Cl_2] to afford the product as a white solid (63%, 1.25 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.28 (ddm, *J* = 8.4, 0.7 Hz, 1H, H7), 8.26 (dd, *J* = 7.9, 0.9 Hz, 1H, H6), 8.18 (d, *J* = 8.6 Hz, 1H, H3), 7.87 (dd, *J* = 8.2, 1.6 Hz, 1H, H8), 7.77 (ddd, *J* = 8.4, 6.9, 1.6 Hz, 1H, H2), 7.62 (ddd, *J* = 8.2, 7.0, 1.3 Hz, 1H, H1), 4.63 (ddd, *J* = 9.9, 9.6, 0.8 Hz, 2H, $H11_2$), 4.21 (ddd, *J* = 9.7, 9.4, 0.5 Hz, 2H, $H12_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.4 (C10), 147.8 (C9), 147.0 (C4), 137.0 (C7), 130.6 (C5), 130.3 (C2), 129.0 (C3), 128.2 (C6), 127.8 (C1), 120.9 (C8), 68.7 (C11), 55.4 (C12); **LRMS** (ESI^+) m/z Calcd. for $C_{12}H_{11}ON_2$ $(M+H)^+$ 199.1, found 199.1.

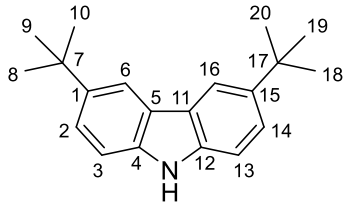
2,6-bis(4,5-dihydrooxazol-2-yl)pyridine (L9)



The procedure is based on a modified 4-step literature sequence. Data is in agreement with those previously reported.[136] In an oven dried, argon filled RBF, 2,6-pyridinedicarboxylic acid (3.16 g, 18.92 mmol, 1.00 equiv.) and DMF (69 mg, 73 µL, 0.946 mmol, 0.05 equiv.) were dissolved in CH_2Cl_2 (20 mL) and the resulting solution cooled to 0 °C. Oxalyl chloride (5.28 g, 3.52 mL, 41.62 mmol, 2.20 equiv.) was then *slowly* added and the mixture was warmed to room temperature and stirred for 16 h. The volatiles were then removed *in vacuo* to afford crude 2,6-pyridinedicarbonyl chloride, which was used immediately in the next step. To a solution of NEt_3 (5.74 g, 7.91 mL, 56.72, 3.00 equiv.) and ethanolamine (2.43 g, 2.40 mL, 39.73 mmol, 2.10 equiv.) in CH_2Cl_2 (47 mL) at 0 °C was added

a solution of 2,6-pyridinedicarbonyl chloride (assumed no product loss from previous step*:* ~3.86 g, 18.92 mmol, 1.00 equiv.) in CH_2Cl_2 (10 mL). The reaction was then allowed to warm to room temperature. After continual stirring for 24 h, the reaction was again cooled to 0 °C and $SOCl_2$ (20 mL) was added. The contents were then heated to 65 °C for 2 h, cooled to room temperature and the volatiles removed by rotary evaporation (the excess $SOCl_2$ was removed by further azeotropic distillation with toluene). The residue was taken up in CH_2Cl_2 (20 mL) and the organic phase was washed with water (20 mL), brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude dichloroamide. In a flame dried, argon filled RBF, the dichloroamide (assumed no product loss from previous step*:* ~ 5.48 g, 18.92 mmol, 1.00 equiv.) was dissolved in THF (10 mL). The mixture was cooled to 0 °C and NaH (60% in mineral oil, 2.27 g, 56.76 mmol, 3.00 equiv.) was added. The mixture was warmed to room temperature and stirred for 16 h. The reaction was diluted with Et_2O (30 mL) and was quenched by the addition of water (50 mL). The layers were separated, and the product was further extracted three times with Et_2O. The organic extracts were pooled, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the product as an off-white solid. No further purification was required (36% over 4 steps, 1.47 g). **M.P.** = 226-228 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 7.8 Hz, 2H, H5 & H7), 7.85 (t, *J* = 7.9 Hz, 1H, H6), 4.55 – 4.47 (m, 2H, t, *J* = 9.6 Hz, 4H, $H1_2$ & $H11_2$), 4.10 (t, *J* = 9.6 Hz, 4H, $H2_2$ & $H10_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.5 (C3 & C9), 146.9 (C4 & C8), 137.4 (C6), 125.6 (C5 & C7), 68.4 (C1 & C11), 55.2 (C2 & C10); **FTIR** (neat) ν = 3049, 2975, 2932, 2900, 2875, 1659, 1643, 1570, 1454, 1357, 1324, 1275, 1238, 1151, 1126, 1096, 1066, 992, 975, 955, 938, 911, 895, 842, 660, 649 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{11}H_{12}O_2N_3$ $(M+H)^+$ 218.0925, found 218.0924.

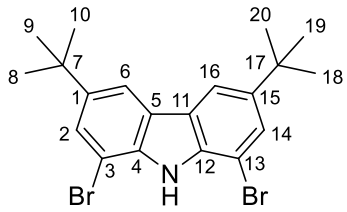
3,6-di-*tert*-butyl-9H-carbazole (207)



The procedure is based on a modified literature method. Data is in agreement with those previously reported.[137] In a flame-dried argon filled RBF, 9-*H*-carbazole (**206**) (3.34 g, 20.00 mmol, 1.00 equiv.) and $ZnCl_2$ (8.10 g, 60.00 mmol, 3.00 equiv.) were

suspended in $MeNO_2$ (100 mL). *Tert*-butyl chloride (5.55 g, 6.53 mL, 60.00 mmol, 3.00 equiv.) was then added *via* syringe and stirring was continued for 16 h at ambient temperature. After this time, water (100 mL) and CH_2Cl_2 (30 mL) were added to the mixture and the phases were separated. The aqueous layer was extracted three times with CH_2Cl_2 and the combined organic extracts were washed successively with water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by recrystallisation from [10% Et_2O in petroleum ether b.p. 40–60 °C] to afford the product as an off-white solid (66%, 3.68 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.10 (dt, *J* = 2.0, 0.7 Hz, 2H, H6 & H16), 7.82 (bs, 1H, NH), 7.48 (dd, *J* = 8.5, 1.9 Hz, 2H, H2 & H14), 7.33 (dd, *J* = 8.5, 0.7 Hz, 2H, H3 & H13), 1.47 (s, 18H, $H8_3$, $H9_3$, $H10_3$, $H18_3$, $H19_3$ & $H20_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.4 (C1 & C15), 138.17 (C4 & C12), 123.7 (C2 & C14), 123.5 (C5 & C11), 116.3 (C6 & C16), 110.1 (C3 & C13), 34.8 (C7 & C17), 32.2 (C8, C9, C10, C18, C19 & C20); **LRMS** (ESI^-) m/z Calcd. for $C_{20}H_{24}N$ $(M-H)^-$ 278.2, found 278.2.

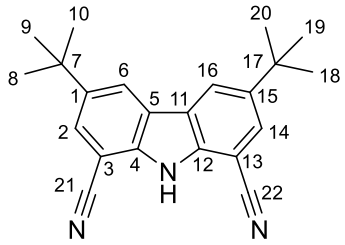
1,8-Dibromo-3,6-di-*tert*-butyl-9H-carbazole (208)



The procedure is based on a modified literature method. Data is in agreement with those previously reported.[137] 3,6-Di-*tert*-butyl-9H-carbazole (**207**) (3.48 g, 12.45 mmol, 1.00 equiv.) was added to AcOH (32 mL) and the mixture was cooled to 0 °C in an ice bath. To the stirred reaction mixture, bromine (4.28 g, 1.34 mL, 16.15 mmol, 2.10 equiv.) was then *slowly* added. The ice bath was removed, and the contents were stirred for 3 h at room temperature before concentrating *in vacuo*. The resulting residue was then dissolved in EtOAc (30 mL) and washed successively washed with 10% (w/v) $Na_2SO_{3\,(aq.)}$ (50 mL) and 1 M NaOH (50 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the product as an off-white solid. No further purification was required (95%, 5.20 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.13 (bs, 1H, NH), 7.98 (dd, *J* = 1.7, 0.6 Hz, 2H, H6 & H16), 7.64 (d, *J* = 1.6 Hz, 2H, H2 & H14), 1.44 (s, 18H, $H8_3$, $H9_3$, $H10_3$, $H18_3$, $H19_3$ & $H20_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.9 (C1 & C15), 136.5 (C4 & C12), 126.8 (C2 & C14), 125.0 (C5 & C11), 116.1 (C6 & C16), 104.2 (C3 & C13), 35.1 (C7 &

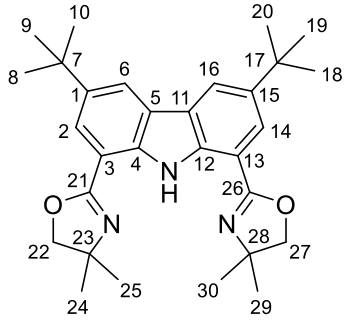
C17), 32.1 (C8, C9, C10, C18, C19 & C20); **LRMS** (ESI$^-$) m/z Calcd. for $C_{20}H_{22}Br_2N$ $(M-H)^-$ 434.0, found 434.0.

3,6-di-*tert*-butyl-9H-carbazole-1,8-dicarbonitrile (209)



The procedure is based on a modified literature method. Data is in agreement with those previously reported.[138] In a flame dried argon filled RBF, 1,8-dibromo-3,6-di-*tert*-butyl-9H-carbazole (**209**) (5.00 g, 11.49 mmol, 1.00 equiv.) was dissolved in *N*-methyl-2-pyrrolidinone (75 mL) and CuCN (2.69 g, 30.10 mmol, 2.60 equiv.) was added. The reaction was then heated to 180 °C for 24 h. After the allotted time, the contents were cooled to room temperature and poured onto sat. $NH_4OH_{(aq.)}$ (170 mL). EtOAc (85 mL) was added and the biphasic mixture was stirred for 30 min. The suspension was filtered through a pad of Celite®, which was then washed liberally with EtOAc. The layers were separated and the aqueous layer was further extracted with EtOAc three times. The combined organic extracts were washed with brine five times, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was recrystallised from hot EtOAc to afford the product as a beige solid (77%, 2.91 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.53 (bs, 1H, NH), 8.31 (dd, *J* = 1.8, 0.6 Hz, 2H, H6 & H16), 7.83 (d, *J* = 1.8 Hz, 2H, H2 & H14), 1.46 (s, 18H, $H8_3$, $H9_3$, $H10_3$, $H18_3$, $H19_3$ & $H20_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.2 (C1 & C15), 139.2 (C4 & C12), 128.6 (C2 & C14), 124.0 (C5 & C11), 122.3 (C6 & C16), 117.1 (C21 & C22), 94.5 (C3 & C13), 35.1 (C7 & C17), 31.9 (C8, C9, C10, C18, C19 & C20); **LRMS** (ESI$^-$) m/z Calcd. for $C_{22}H_{22}N_3$ $(M-H)^-$ 328.2, found 328.2.

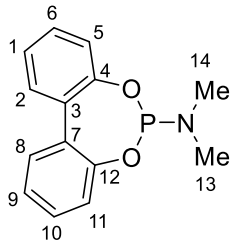
2,2'-(3,6-di-*tert*-butyl-9H-carbazole-1,8-diyl)bis(4,4-dimethyl-4,5-dihydrooxazole) (L10)



The procedure is based on a modified literature method. Data is in agreement with those previously reported.[138] A flame dried, argon filled RBF was charged with 3,6-di-*tert*-butyl-9H-carbazole-1,8-dicarbonitrile (**209**) (150 mg, 0.46 mmol, 1.00 equiv.), $ZnCl_2$ (155 mg, 1.14 mmol, 2.50 equiv.) and 2-methyl-2-aminopropanol (81 mg,

0.91 mmol, 2.00 equiv.). Chlorobenzene (4.5 mL) was added and the mixture was heated at 140 °C for 3 days. After the allotted time, the reaction was cooled to room temperature and ethylene diamine (0.5 mL) in water (5 mL) was added. The resulting biphasic mixture was stirred for 60 min and the layers were then separated. The product was extracted three times with CH_2Cl_2 and the combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography [silica gel, 80% CH_2Cl_2 in petroleum ether b.p. 40–60 °C] to afford the product as a white solid (36%, 78 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.87 (s, 1H, NH), 8.19 (d, *J* = 1.8 Hz, 2H, H23 & H28), 7.89 (d, *J* = 1.8 Hz, 2H, H2 & H14), 4.16 (s, 4H, $H22_2$ & $H24_2$), 1.47 (s, 12H, $H24_3$, $H25_3$, $H29_3$ & $H30_3$), 1.45 (s, 18H, $H8_3$, $H9_3$, $H10_3$, $H18_3$, $H19_3$ & $H20_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.3 (C21 & C26), 141.3 (C1 & C15), 137.6 (C4 & C12), 123.2 (C5 & C11), 122.7 (C2 & C14), 119.6 (C6 & C16), 109.7 (C3 & C13), 78.3 (C22 & C27), 67.6 (C23 & C28), 34.7 (C24, C25, C29 & C30), 32.3 (C7 & C17), 28.8 (C8, C9, C10, C18, C19 & C20); **LRMS** (ESI$^+$) m/z Calcd. for $C_{30}H_{40}O_2N_3$ $(M+H)^+$ 474.3, found 474.3.

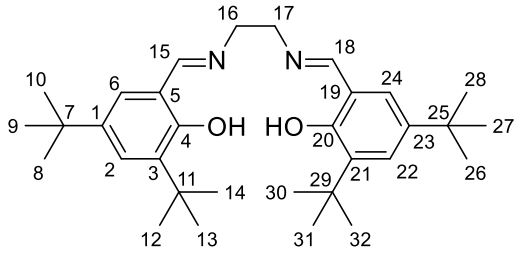
N,N-dimethyldibenzo[d,f][1,3,2]dioxaphosphepin-6-amine (L11)



The procedure is based on a modified literature method. Data is in agreement with those previously reported.[139] To an RBF equipped with reflux condenser, 2,2'-dihydroxybiphenyl (500 mg, 2.68 mmol, 1.00 equiv.), NH_4Cl (1.4 mg, 26.8 µL, 0.01 equiv.) and benzene (9 mL) were added. Tris(dimethylamino)phosphine (656 mg, 730 µL, 4.02 mmol, 1.50 equiv.) was then introduced and the mixture was heated to reflux for 16 h. The contents were cooled to room temperature and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography [silica gel, 5% EtOAc in petroleum ether b.p. 40–60 °C] to afford the product as a colourless oil (93%, 644 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 7.6, 1.7 Hz, 2H, H2 & H8), 7.34 (td, *J* = 7.7, 1.7 Hz, 2H, H6 & H10), 7.24 (tt, *J* = 7.4, 1.2 Hz, 2H, H1 & H9), 7.17 (dt, *J* = 8.0, 1.1 Hz, 2H, H5 & H11), 2.65 (d, *J* = 9.0 Hz, 6H, $H13_3$ & $H14_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.7 (d, *J* = 4.8 Hz, C4 & C12), 131.3 (d, *J* = 3.2 Hz, C3 & C7), 129.8 (C2 & C8), 129.3 (C5 & C11), 124.6 (C6 & C10), 122.1 (C1 & C9), 36.0 (d, *J* = 20.8 Hz, C13 & C14); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 149.3 (s, P); **FTIR** (neat)

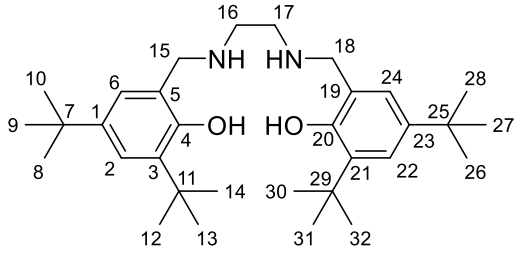
ν = 2924, 1498, 1475, 1436, 1246, 1209, 1194, 1097, 979, 883, 869, 847, 745, 692 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{14}H_{15}O_2NP$ $(M+H)^+$ 260.0836, found 260.0835.

6,6'-((1E,1'E)-(ethane-1,2-diylbis(azaneylylidene))bis(methaneylylidene))bis(2,4-di-*tert*-butylphenol) (L16)



The title compound was prepared according to General Procedure H using ethylene diamine (257 mg, 285 μL, 4.27 mmol). The crude product was isolated as a yellow solid and no further purification was required (100%, 2.10 g). **M.P.** = 166-170 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 13.66 (s, 2H, OH), 8.40 (s, 2H, H15 & H18), 7.38 (d, *J* = 2.5 Hz, 2H, H2 & H22), 7.08 (d, *J* = 2.4 Hz, 2H, H6 & H24), 3.93 (s, 4H, H16 & H17), 1.45 (s, 18H, $H12_3$, $H13_3$, $H14_3$, $H30_3$, $H31_3$ & $H32_3$), 1.30 (s, 18H, $H8_3$, $H9_3$, $H10_3$, $H26_3$, $H27_3$ & $H28_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.7 (C4 & C20), 158.2 (C1 & C23), 140.2 (C3 & C21), 136.7 (C2 & C22), 127.2 (C6 & C24), 126.2 (C5 & C19), 118.0 (C16 & C17), 59.8 (C7 & C25), 34.3 (C11 & C29), 31.6 (C8, C9, C10, C26, C27 & C28), 29.6 (C12, C13, C14, C30, C31 & C32); **FTIR** (neat) ν = 2956, 2908, 2869, 1631, 1470, 1440, 1392, 1361, 1273, 1252, 1236, 1202, 1174, 827, 773 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{32}H_{49}O_2N_2$ $(M+H)^+$ 493.3787, found 493.3789.

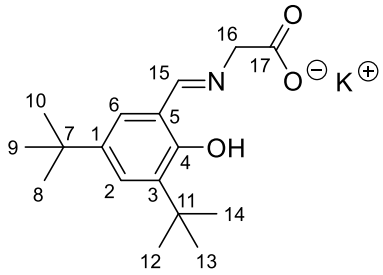
6,6'-((ethane-1,2-diylbis(azanediyl))bis(methylene))bis(2,4-di-*tert*-butylphenol)



The title compound was prepared according to General Procedure I using **L16** (1.00 g, 2.03 mmol). The crude product was isolated as a white solid and no further purification was required (100%, 1.01 g). **M.P.** = 180-182 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 2.4 Hz, 2H, 22 & H22), 6.87 (d, *J* = 2.4 Hz, 2H, H6 & H24), 3.97 (s, 4H, $H15_2$ & $H18_2$), 2.88 (s, 4H, $H16_2$ & $H17_2$), 1.41 (s, 18H, $H12_3$, $H13_3$, $H14_3$ $H30_3$, $H31_3$ & $H32_3$), 1.28 (s, 18H, $H8_3$, $H9_3$ $H10_3$, $H26_3$ $H27_3$ & $H28_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.4 (C4 & C20), 141.0 (C1 & C23), 136.3 (C3 & C21), 123.6 (C6 & C24), 123.4 (C2 & C22), 121.8 (C5 & C19), 53.4 (C15 & C18), 47.9 (C16 & C17), 35.1 (C7 & C25), 34.3 (C11 & C29),

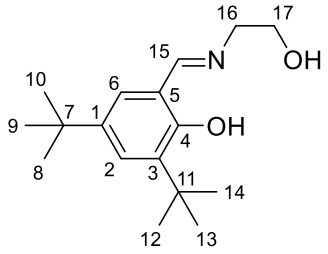
31.8 (C8, C9, C10, C26, C27 & C28), 29.8 (C12, C13, C14, C30, C31 & C32); **FTIR** (neat) ν = 2953, 2905, 2866, 1479, 1445, 1391, 1361, 1302, 1236, 1203, 1165, 1125, 878, 822, 762, 724 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{32}H_{53}O_2N_2$ $(M+H)^+$ 497.4097, found 497.4101.

Potassium (E)-2-((3,5-di-*tert*-butyl-2-hydroxybenzylidene)amino)acetate (L18)



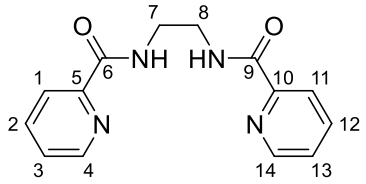
The procedure is based on a modified literature method. Data is in agreement with those previously reported.[134] An RBF was charged with KOH $_{(s)}$ (263 mg, 4.69 mmol, 1.10 equiv.), glycine (0.35 g, 4.69 mmol, 1.10 equiv.) and MeOH (25 mL) and the solids were dissolved by sonication. The resulting solution was then sparged with N_2 for 30 minutes and cooled to 0 °C. A solution of 3,5-di-*tert*-butylsalicylaldehyde (1.00 g, 4.27 mmol, 1.00 equiv.) in MeOH (10 mL, N_2 sparged) was then added to the cooled reaction mixture. The contents were then warmed to room temperature and stirred for 3 h before removal of the solvent *in vacuo*. A 50:50 mixture of hexane/Et_2O (20 mL) was then added to the residue and the mixture was thoroughly agitated. The insoluble material was removed by gravity filtration, and the filtrate was concentrated *in vacuo* to afford the product as a yellow solid. No further purification was required (100%, 1.41 g). **M.P.** = 194-200 °C*;* **^{1}H NMR** (400 MHz, CD_3OD) δ 8.37 (t, *J* = 1.1 Hz, 1H, H16), 7.37 (d, *J* = 2.5 Hz, 1H, H2), 7.19 (d, *J* = 2.5 Hz, 1H, H6), 4.23 (d, *J* = 1.2 Hz, 2H, $H16_2$), 1.43 (s, 9H, $H8_3$, $H9_3$& $H10_3$), 1.31 (s, 9H, $H12_3$, $H13_3$ & $H14_3$); **^{13}C NMR** (101 MHz, CD_3OD) δ 175.9 (C17), 167.7 (C15), 158.6 (C4), 139.3 (C1), 136.2 (C3), 126.3 (C2), 126.0 (C6), 118.2 (C5), 62.6 (C16), 34.5 (C7), 33.6 (C11), 30.5 (C8, C9 & C10), 28.6 (C12, C13 & C14); **FTIR** (neat) ν = 3378, 2955, 1635, 1527, 1482, 1398, 1362, 1299, 1260, 1204, 1157, 912, 868 cm^{1}; **HRMS** (ESI^+) m/z Calcd. for $C_{17}H_{28}O_2N$ [M = *protonated carboxylic acid*] $(M+H)^+$ 292.1906, found 292.1907.

(E)-2,4-di-*tert*-butyl-6-(((2-hydroxyethyl)imino)methyl)phenol (L19)



The procedure is based on a modified literature method. Data is in agreement with those previously reported.[127] An RBF was charged with 3,5-di-*tert*-butylsalicylaldehyde (1.00 g, 4.27 mmol, 1.00 equiv.), Na_2SO_4 (4.85 g, 34.16 mmol, 8.00 equiv.) and MeOH (30 mL). Ethanolamine (261 mg, 258 µL, 4.27 mmol, 1.00 equiv.) was added to the suspension and the reaction mixture was heated to reflux for 24 h. The contents were then cooled to room temperature and the solvent removed by rotary evaporation. The crude product was dissolved in CH_2Cl_2 (25 mL) and the drying agent was removed by gravity filtration. The filtrate was concentrated *in vacuo* to afford the product as a yellow solid. No further purification was required (98%, 1.16 g). **M.P.** = 52-54 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.42 (t, *J* = 1.2 Hz, 1H, H15), 7.42 (d, *J* = 2.5 Hz, 1H, H2), 7.13 (d, *J* = 2.4 Hz, 1H, H6), 3.90 (dd, *J* = 5.9, 4.5 Hz, 2H, $H16_2$), 3.72 (ddd, *J* = 6.1, 4.4, 1.2 Hz, 2H, $H17_2$), 1.47 (s, 9H, $H12_3$, $H13_3$ & $H14_3$), 1.33 (s, 9H, $H8_3$, $H9_3$ & $H10_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.1 (C15), 158.2 (C4), 140.3 (C1), 136.8 (C3), 127.2 (C2), 126.2 (C6), 117.9 (C5), 62.3 (C17), 61.8 (C16), 35.1 (C7), 34.2 (C11), 31.6 (C9, C10 & C11), 29.6 (C12, C13 & C14); **FTIR** (neat) ν = 3331, 2955, 2908, 2908, 2870, 1633, 1470, 1440, 1391, 1361, 1274, 1251, 1202, 1173, 1065, 901, 879, 827, 803, 773, 730, 645 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{17}H_{28}O_2N$ $(M+H)^+$ 278.2116, found 278.2115.

N,N'-(ethane-1,2-diyl)dipicolinamide (L20)

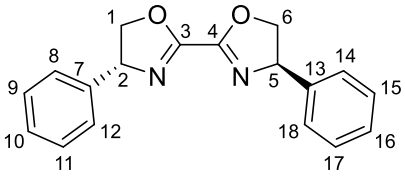


The title compound was prepared according to a modified literature procedure and the data is in agreement with those previously reported. [140] In a flame dried RBF, 2-picolinic acid (504 mg, 4.10 mmol, 2.00 equiv.) and ethylenediamine (123 mg, 137 µL, 2.05 mmol, 1.00 equiv.) were dissolved in pyridine (5 mL). At room temperature, triphenyl phosphite (1.08 mL, 1.27 g, 4.10 mmol, 2.00 equiv.) was added and the resulting mixture was heated at 100 °C for 16 h. The contents were then cooled to room temperature and poured onto ice-cold H_2O. The mixture was extracted three times with CH_2Cl_2 and the combined organic phases were dried over $MgSO_4$,

filtered and concentrated *in vacuo*. The crude material was purified by flash column chromatography [silica gel, 100% EtOAc] to afford the product as a white powder (81%, 449 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.55 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 2H, H4 & H14), 8.40 (bs, 2H, NH), 8.19 (dt, *J* = 7.8, 1.1 Hz, 2H, H1 & H11), 7.83 (td, *J* = 7.7, 1.7 Hz, 2H, H2 & H12), 7.41 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 2H, H3 & H13), 3.85 – 3.64 (m, 4H, $H7_2$ & $H8_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.2 (C6 & C9), 149.9 (C5 & C10), 148.3 (C4 & C14), 137.4 (C2 & C12), 126.3 (C3 & C13), 122.4 (C1 & C11), 39.7 (C7 & C8); **HRMS** (ESI^+) m/z Calcd. for $C_{14}H_{15}O_2N_4$ $(M+H)^+$ 271.1190, found 271.1189.

9.5.3 Chiral Ligands

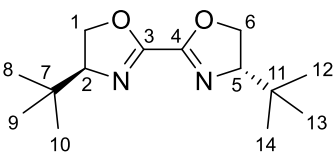
(4*R*,4'*R*)-4,4'-diphenyl-4,4',5,5'-tetrahydro-2,2'-bioxazole (L6A)



The procedure is based on a modified 3-step literature sequence.[105] Data is in agreement with those previously reported. Diethyl oxalate (250 mg, 232 µL, 1.71 mmol, 1.00 equiv.) was added to a solution of (*R*)-phenylglycinol (470 mg, 3.42 mmol, 2.00 equiv.) in toluene (6.5 mL) and the mixture was stirred at room temperature for 24 h. The resulting solid formed was then collected by vacuum filtration and washed with cold toluene (5 °C, 5 mL). The solid was dried *in vacuo* to afford the crude bis-oxalamide which was used in the subsequent step without further purification. In a flame-dried, argon filled RBF equipped with reflux condenser, the crude bis-oxalamide (assumed no product loss from previous step*:* 561 mg, 1.71 mmol, 1.0 equiv.) was suspended in toluene (3.5 mL) and $SOCl_2$ (407 mg, 251 µL, 3,42 mmol, 2.00 equiv.) was added. The contents were then heated to 90 °C for 3 h. After this time, the volatiles were removed *in vacuo* (the excess $SOCl_2$ was removed by further azeotropic distillation with toluene). The residue was redissolved in CH_2Cl_2 (10 mL), basified with sat. $NaHCO_{3\ (aq.)}$ (15 mL) and the layers were separated. The product was further extracted three times with CH_2Cl_2 and the combined extracts were dried over Na_2SO_4, filtered and concentrated by rotary evaporation to give the crude dichlorooxalamide which was used in the next step without further purification. An RBF equipped with reflux condenser was charged with the crude dichlorooxalamide (assumed

no product loss from previous step: 624 mg, 1.71 mmol, 1.00 equiv.), KOH (pellets, 239 mg, 4.20 mmol, 2.50 equiv.) and MeOH (10 mL) and the mixture heated to reflux for 16 h. After the allotted time, the contents were cooled to room temperature and the solvent was removed *in vacuo*. The residue was then dissolved in a mixture of water (10 mL) and CH_2Cl_2 (10 mL) and the layers were separated. The aqueous phase was extracted three times with CH_2Cl_2 and the organic extracts were pooled, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography [silica gel, 30% EtOAc in petroleum ether b.p. 40–60 °C + 1% NEt_3] to afford the product as a yellow solid (36% over 3 steps, 180 mg). **M.P.** = 182-184 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34 – 7.17 (m, 10H, H8, H9, H10, H11, H12, H14, H15, H16, H17 & H18), 5.38 (dd, *J* = 10.4, 8.9 Hz, 2H), 4.79 (dd, *J* = 10.4, 8.7 Hz, 2H), 4.29 (t, *J* = 8.8 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.7 (C3 & C4), 140.5 (C7 & C13), 128.9 (C9, C11, C15 & C17), 128.0 (C10 & C16), 126.7 (C8, C12, C14 & C18), 75.4 (C2 & C5), 70.4 (C1 & C6); **FTIR** (neat) ν = 3278, 2905, 1669, 1615, 1455, 1130, 1082, 1040, 943, 756, 698, 640 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{18}H_{17}O_2N_2$ $(M+H)^+$ 293.1285, found 293.1283.

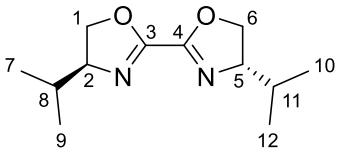
(4*S*,4'*S*)-4,4'-di-*tert*-butyl-4,4',5,5'-tetrahydro-2,2'-bioxazole (L6B)



The procedure is based on a modified 3-step literature sequence.[105] Data is in agreement with those previously reported. Diethyl oxalate (250 mg, 232 µL, 1.71 mmol, 1.00 equiv.) was added to a solution of L-*tert*-leucinol (400 mg, 445 µL, 3.42 mmol, 2.00 equiv.) in toluene (6.5 mL). The mixture was heated to 90 °C and stirred at this temperature for 24 h. The reaction was then cooled to room temperature and the solvent removed *in vacuo*. The solid was dried *in vacuo* to afford the crude bis-oxalamide which was used in the subsequent step without further purification. In a flame-dried, argon filled RBF equipped with reflux condenser, the crude bis-oxalamide (assumed no product loss from previous step*:* 493 mg, 1.71 mmol, 1.00 equiv.) was suspended in toluene (3.5 mL) and $SOCl_2$ (407 mg, 251 µL, 3,42 mmol, 2.00 equiv.) was added. The contents were then heated to 90 °C for 3 h. After this time, the volatiles were removed *in vacuo* (the excess $SOCl_2$ was

removed by further azeotropic distillation with toluene). The residue was redissolved in CH_2Cl_2 (10 mL), basified with sat. $NaHCO_{3\ (aq.)}$ (15 mL) and the layers were separated. The product was further extracted three times with CH_2Cl_2 and the combined extracts were dried over Na_2SO_4, filtered and concentrated by rotary evaporation to give the crude dichlorooxalamide which was used in the next step without further purification. An RBF equipped with reflux condenser was charged with the crude dichlorooxalamide (assumed no product loss from previous step: 556 mg, 1.71 mmol, 1.00 equiv.), KOH (pellets, 239 mg, 4.20 mmol, 2.50 equiv.) and MeOH (10 mL) and the mixture heated to reflux for 16 h. After the allotted time, the contents were cooled to room temperature and the solvent was removed *in vacuo*. The residue was then dissolved in a mixture of water (10 mL) and CH_2Cl_2 (10 mL) and the layers were separated. The aqueous phase was extracted three times with CH_2Cl_2 and the organic extracts were pooled, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography [silica gel, 30% EtOAc in petroleum ether b.p. 40–60 °C + 1% NEt_3] to afford the product as a yellow solid (28% over 3 steps, 123 mg). **M.P.** = 188-192 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.34 (dd, *J* = 10.4, 8.8 Hz, 2H, $H1_A$ & $H6_A$), 4.20 (t, *J* = 8.9 Hz, 2H, $H1_B$ & $H6_B$), 4.05 (dd, *J* = 10.4, 8.9 Hz, 2H, H2 & H5), 0.92 (s, 18H, $H8_3$, $H9_3$, $H10_3$, $H12_3$, $H13_3$ & $H14_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.6 (C3 & C4), 76.8 (C2 & C5), 69.6 (C1 & C6), 33.8 (C7 & C11), 26.0 (C8, C9, C10, C12, C13, C14); **FTIR** (neat) ν = 2952, 2906, 2870, 1624, 1359, 1121, 1066, 1022, 947, 738 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{14}H_{25}O_2N_2$ $(M+H)^+$ 253.1911, found 253.1911.

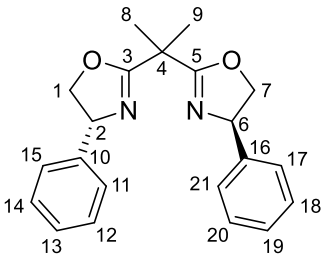
(4*S*,4'*S*)-4,4'-diisopropyl-4,4',5,5'-tetrahydro-2,2'-bioxazole (L6C)



The procedure is based on a modified 3-step literature sequence.[105] Data is in agreement with those previously reported. Diethyl oxalate (250 mg, 232 µL, 1.71 mmol, 1.00 equiv.) was added to a solution of L-valinol (353 mg, 3.42 mmol, 2.00 equiv.) in toluene (6.5 mL) and the mixture was stirred at room temperature for 24 h. The resulting solid formed was then collected by vacuum filtration and washed with cold toluene (5 °C, 5 mL). The solid was dried *in vacuo* to afford the

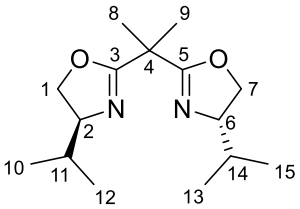
crude bis-oxalamide which was used in the subsequent step without further purification. In a flame-dried, argon filled RBF equipped with reflux condenser, the crude bis-oxalamide (assumed no product loss from previous step*:* 445 mg, 1.71 mmol, 1.00 equiv.) was suspended in toluene (3.5 mL) and $SOCl_2$ (407 mg, 251 µL, 3,42 mmol, 2.00 equiv.) was added. The contents were then heated to 90 °C for 3 h. After this time, the volatiles were removed *in vacuo* (the excess $SOCl_2$ was removed by further azeotropic distillation with toluene). The residue was redissolved in CH_2Cl_2 (10 mL), basified with sat. $NaHCO_{3\ (aq.)}$ (15 mL) and the layers were separated. The product was further extracted three times with CH_2Cl_2 and the combined extracts were dried over Na_2SO_4, filtered and concentrated by rotary evaporation to give the crude dichlorooxalamide which was used in the next step without further purification. An RBF equipped with reflux condenser was charged with the crude dichlorooxalamide (assumed no product loss from previous step: 508 mg, 1.71 mmol, 1.00 equiv.), KOH (pellets, 239 mg, 4.20 mmol, 2.50 equiv.) and MeOH (10 mL) and the mixture heated to reflux for 16 h. After the allotted time, the contents were cooled to room temperature and the solvent was removed *in vacuo*. The residue was then dissolved in a mixture of water (10 mL) and CH_2Cl_2 (10 mL) and the layers were separated. The aqueous phase was extracted three times with CH_2Cl_2 and the organic extracts were pooled, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography [silica gel, 30% EtOAc in petroleum ether b.p. 40–60 °C + 1% NEt_3] to afford the product as a yellow oil (56% over 3 steps, 215 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.42 (td, *J* = 7.6, 1.6 Hz, 2H, $H1_A$ & $H6_A$), 4.20 – 3.95 (m, 4H, $H1_B$ H2, H5 & $H6_B$), 1.91 – 1.78 (m, 2H, H8 & H11), 0.96 (dd, *J* = 41.2, 6.7 Hz, 12H, $H7_3$, $H9_3$, $H10_3$ & $H10_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.7 (C3 & C4), 73.3 (C2 & C5), 71.2 (C2 & C6), 32.6 (C8 & C11), 19.1 (C7 & C10), 18.4 (C9 & C12); **FTIR** (neat) ν = 2959, 2876, 1617, 1469, 1131, 1117, 946 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{12}H_{21}O_2N_2$ $(M+H)^+$ 225.1598, found 225.1598.

(4*R*,4'*R*)-2,2'-(propane-2,2-diyl)bis(4-phenyl-4,5-dihydrooxazole) (L7A)



The procedure is based on a modified literature method.[106] Data is in agreement with those previously reported. A flame dried 2-necked RBF fitted with a reflux condenser was charged with 2,2-dimethylmalononitrile (150 mg, 1.59 mmol, 1.00 equiv.) and $Zn(OTf)_2$ (578 mg, 1.59 mmol, 1.00 equiv.). The system was evacuated, back filled with argon and toluene (5.5 mL) was added. The contents were stirred at room temperature for 5 min and (*R*)-(–)phenylglycinol (438 mg, 3.19 mmol, 2.00 equiv.) was added. The reaction was then heated to reflux for 48 h. After the allotted time, the mixture was cooled to room temperature and diluted with EtOAc (5 mL). Stirring was continued for 15 min and sat. $NaHCO_{3\ (aq.)}$ (10 mL) was then added. The layers were separated and the aqueous phase was extracted three times with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography [silica gel, 20-30% EtOAc in petroleum ether b.p. 40–60 °C + 1% NEt_3] to afford the product as a yellow oil (26%, 137 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 – 7.32 (m, 4H, H12, H14, H18 & H20) 7.32 – 7.26 (m, 6H, H11, H13, H15, H17, H19 & C21), 5.26 (dd, *J* = 10.1, 7.6 Hz, 2H, H2 & H6), 4.70 (dd, *J* = 10.1, 8.3 Hz, 2H, $H1_A$ & $H7_A$), 4.19 (dd, *J* = 8.4, 7.6 Hz, 2H, $H1_B$ & $H7_B$), 1.71 (s, 6H, $H8_3$ & $H9_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.4 (C3 & C5), 142.4 (C10 & C16), 128.7 (C12, C14, C18 & C20), 127.6 (C13 & C19), 126.7 (C11, C15, C17 & C21), 75.5 (C1 & C7), 69.5 (C2 & C6), 39.0 (C4), 24.5 (C8 & C9); **FTIR** (neat) ν = 2984, 1655, 1494, 1472, 1455, 1241, 1145, 1115, 980, 914, 760, 700 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{21}H_{23}O_2N_2$ $(M+H)^+$ 335.1754, found 335.1754.

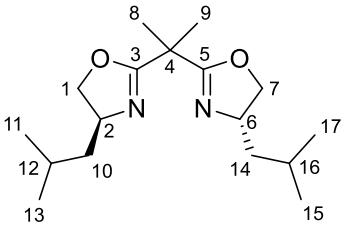
(4*S*,4'*S*)-2,2'-(propane-2,2-diyl)bis(4-isopropyl-4,5-dihydrooxazole) (L7B)



The procedure is based on a modified literature method.[106] Data is in agreement with those previously reported. A flame dried 2-necked RBF fitted with a reflux condenser was charged with 2,2-dimethylmalononitrile (150 mg, 1.59 mmol, 1.00 equiv.) and $Zn(OTf)_2$ (578 mg, 1.59 mmol,

1.00 equiv.). The system was evacuated, back filled with argon and toluene (5.5 mL) was added. The contents were stirred at room temperature for 5 min and L-valinol (329 mg, 3.19 mmol, 2.00 equiv.) was added. The reaction was then heated to reflux for 48 h. After the allotted time, the mixture was cooled to room temperature and diluted with EtOAc (5 mL). Stirring was continued for 15 min and sat. $NaHCO_{3\ (aq.)}$ (10 mL) was then added. The layers were separated, and the aqueous phase was extracted three times with EtOAc. The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography [silica gel, 20-30% EtOAc in petroleum ether b.p. 40–60 °C + 1% NEt_3] to afford the product as a colourless oil (11%, 58 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.19 (td, *J* = 7.8, 1.1 Hz, 2H, $H1_A$ & $H7_A$), 4.06 – 3.89 (m, 4H, $H1_B$, H2, H6 & $H7_B$), 1.91 – 1.69 (m, 2H, H11 & H14), 1.51 (s, 6H, $H8_3$ & $H9_3$), 0.88 (dd, *J* = 25.3, 6.8 Hz, 12H, $H10_3$, $H12_3$, $H13_3$ & $H15_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.9 (C3 & C5), 71.7 (C2 & C6), 70.1 (C1 & C7), 38.7 (C4), 32.4 (C11 & C14), 24.6 (C8 & C9), 18.7 (C10 & C13), 17.5 (C12 & C15); **FTIR** (neat) ν = 2959, 2874, 1658, 1468, 1387, 1248, 1148, 1116, 979, 925 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{15}H_{27}O_2N_2$ $(M+H)^+$ 267.2065, found 267.2065.

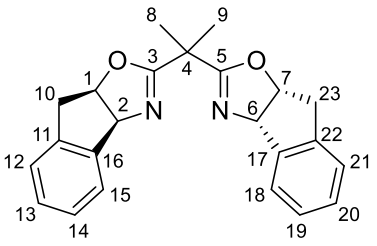
(4*S*,4'*S*)-2,2'-(propane-2,2-diyl)bis(4-isobutyl-4,5-dihydrooxazole) (L7F)



The procedure is based on a modified literature method.[106] Data is in agreement with those previously reported. A flame dried 2-necked RBF fitted with a reflux condenser was charged with 2,2-dimethylmalononitrile (150 mg, 1.59 mmol, 1.00 equiv.) and $Zn(OTf)_2$ (578 mg, 1.59 mmol, 1.00 equiv.). The system was evacuated, back filled with argon and toluene (5.5 mL) was added. The contents were stirred at room temperature for 5 min and L-leucinol (374 mg, 3.19 mmol, 2.00 equiv.) was added. The reaction was then heated to reflux for 48 h. After the allotted time, the mixture was cooled to room temperature and diluted with EtOAc (5 mL). Stirring was continued for 15 min and sat. $NaHCO_{3\ (aq.)}$ (10 mL) was then added. The layers were separated, and the aqueous phase was extracted three times with EtOAc. The

combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography [silica gel, 20-30% EtOAc in petroleum ether b.p. 40–60 °C + 1% NEt_3] to afford the product as a colourless oil (26%, 121 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.17 (dd, *J* = 9.6, 7.6 Hz, 2H, $H1_A$ & $H7_A$), 4.09 (ddd, *J* = 9.6, 6.8, 4.9 Hz, 2H, H2 & H6), 3.99 (dd, *J* = 7.6, 6.8 Hz, 2H, $H1_B$ & $H7_B$), 1.73 – 1.59 (m, 2H, H12 & H16), 1.51 (s, 6H, $H8_3$ & $H9_3$), 1.48 – 1.36 (m, 2H, $H10_A$ & $H14_A$), 1.14 (ddt, *J* = 13.5, 8.4, 7.2 Hz, 2H, $H10_B$ & $H14_B$), 0.91 (t, *J* = 7.4 Hz, 6H, $H11_3$ & $H17_3$), 0.78 (d, *J* = 6.8 Hz, 6H, $H13_3$ & $H15_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.8 (C3 & C5), 70.2 (C2 & C6), 69.4 (C1 & C7), 38.70 (C4), 38.66 (C12 & C16), 26.2 (C10 & C14), 24.6 (C8 & C9), 13.8 (C13 & C15), 11.9 (C11 & C17); **FTIR** (neat) ν = 2959, 2874, 1658, 1468, 1387, 1248, 1148, 1116, 979, 925 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{17}H_{31}O_2N_2$ $(M+H)^+$ 295.2377, found 295.2380.

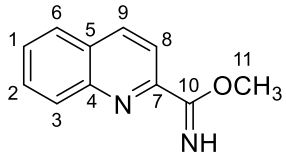
(3a*S*,3a'*S*,8a*R*,8a'*R*)-2,2'-(propane-2,2-diyl)bis(3a,8a-dihydro-8H-indeno[1,2-d]oxazole) (L7E)



The procedure is based on a modified literature method.[106] Data is in agreement with those previously reported. A flame dried 2-necked RBF fitted with a reflux condenser was charged with 2,2-dimethylmalononitrile (150 mg, 1.59 mmol, 1.00 equiv.) and $Zn(OTf)_2$ (578 mg, 1.59 mmol, 1.00 equiv.). The system was evacuated, back filled with argon and toluene (5.5 mL) was added. The contents were stirred at room temperature for 5 min and (1*S*,2*R*)-1-amino-2-indanol (468 mg, 3.19 mmol, 2.00 equiv.) was added. The reaction was then heated to reflux for 48 h. After the allotted time, the mixture was cooled to room temperature and diluted with EtOAc (5 mL). Stirring was continued for 15 min and sat. $NaHCO_{3\ (aq.)}$ (10 mL) was then added. The layers were separated, and the aqueous phase was extracted three times with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography [silica gel, 20-30% EtOAc in petroleum ether b.p. 40–60 °C + 1% NEt_3] to afford the product as a colourless oil (19%, 107 mg). **^{1}H NMR**

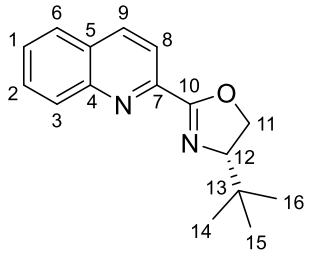
(400 MHz, $CDCl_3$) δ 7.52 – 7.19 (m, 8H, H12, H13, H14, H15, H18, H19, H20 & H21), 5.51 (d, *J* = 7.8 Hz, 2H, H2 & H6), 5.24 (ddd, *J* = 7.8, 7.0, 1.8 Hz, H1 & H7), 3.29 (dd, *J* = 18.0, 7.3 Hz, 2H, $H10_A$ & $H23_A$), 2.94 (dd, *J* = 18.0, 1.4 Hz, 2H, $H10_B$ & $H23_B$), 1.41 (s, 6H, $H8_3$ & $H9_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.2 (C3 & C5), 141.8 (C11 & C22), 139.8 (C16 & C17), 128.5 (C14 & C19), 127.4 (C13 & C20), 125.7 (C12 & C21), 125.3 (C15 & C18), 83.3 (C1 & C7), 76.5 (C2 & C6), 39.6 (C10 & C23), 38.5 (C4), 23.9 (C8 & C9); **FTIR** (neat) ν = 2979, 2931, 1647, 1480, 1426, 1246, 1223, 1142, 1100, 1043, 1003, 850 750 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{23}H_{23}O_2N_2$ $(M+H)^+$ 359.1755, found 359.1754.

methyl quinoline-2-carbimidate (213)



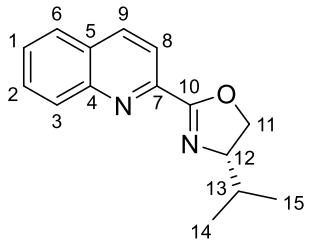
The procedure is based on a modified literature method. Data is in agreement with those previously reported.[113] To an RBF containing quinoline-2-carbonitrile (1.00 g, 6.49 mmol, 1.00 equiv.) MeOH (22 mL) and NaOMe (35 mg, 0.649 mmol, 0.10 equiv.) were added. The mixture was then stirred at room temperature for 40 h and after this time, neutralised by the addition of AcOH (39 mg, 37 µL, 0.649 mmol, 0.10 equiv.). After stirring for 5 min, the solvent was removed by rotary evaporation. The residue was then taken up in CH_2Cl_2 (20 mL), washed with water (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford pure product as a white solid (100%, 1.20 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.42 (s, 1H, NH), 8.27 (dd, *J* = 8.5, 0.8 Hz, 1H, H9), 8.17 (dq, *J* = 8.6, 0.9 Hz, 1H, H3), 7.96 (d, *J* = 8.5 Hz, 1H, H8), 7.87 (dd, *J* = 8.2, 1.4 Hz, 1H, H6), 7.77 (ddd, *J* = 8.4, 6.8, 1.5 Hz, 1H, H2), 7.60 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H, H1), 4.08 (s, 3H, $H11_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.1 (C10), 156.1 (C7), 147.6 (C4), 137.6 (C9), 130.21 (C2), 130.18 (C3), 128.9 (C5), 127.8 (C6), 127.7 (C1), 118.3 (C8), 54.2 (C11); **HRMS** (ESI^+) m/z Calcd. for $C_{11}H_{11}ON_2$ $(M+H)^+$ 187.0866, found 187.0867.

(*S*)-4-(*tert*-butyl)-2-(quinolin-2-yl)-4,5-dihydrooxazole (L8B)



The procedure is based on a modified literature method.[107] Data is in agreement with those previously reported. To a 7 mL screw-top vial was added methyl quinoline-2-carbimidate (**213**) (200 mg, 1.07 mmol, 1.00 equiv.), L-*tert*-leucinol (125 mg, 1.07 mmol, 1.00 equiv.) and CH_2Cl_2 (5 mL). The vial was sealed, and the contents were heated at 40 °C for 48 h. After this time, the reaction mixture was cooled to room temperature and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography [silica gel, 20% EtOAc in petroleum ether b.p. 40–60 °C] to afford the product as a white solid (74%, 201 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.29 – 8.20 (m, 3H, H3, H6 & H9), 7.90 – 7.80 (m, 1H, H8), 7.74 (ddd, *J* = 8.5, 6.9, 1.5 Hz, 1H, H2), 7.59 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H, H1), 4.53 (dd, *J* = 10.3, 8.7 Hz, 1H, H12), 4.40 (t, *J* = 8.5 Hz, 1H, $H11_A$), 4.18 (dd, *J* = 10.3, 8.3 Hz, 1H, $H11_B$), 1.00 (s, 9H, $H14_3$, $H15_3$ & $H16_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.9 (C10), 147.7 (C7), 147.2 (C4), 136.7 (C9), 130.5 (C5), 130.1 (C2), 128.9 (C3), 128.0 (C6), 127.6 (C1), 121.1 (C8), 76.7 (C12), 69.7 (C11), 34.2 (C13), 26.1 (C14, C15 & C16); **LRMS** (ESI^+) m/z Calcd. for $C_{16}H_{19}ON_2$ $(M+H)^+$ 255.1, found 255.1.

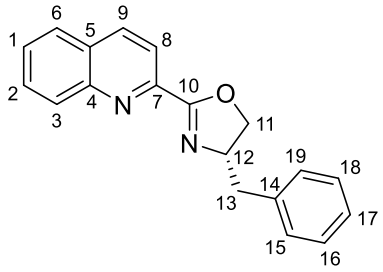
(*S*)-4-isopropyl-2-(quinolin-2-yl)-4,5-dihydrooxazole (L8C)



The procedure is based on a modified literature method.[107] Data is in agreement with those previously reported. To a 7 mL screw-top vial was added methyl quinoline-2-carbimidate (**213**) (200 mg, 1.07 mmol, 1.00 equiv.), L-valinol (110 mg, 1.07 mmol, 1.00 equiv.) and CH_2Cl_2 (5 mL). The vial was sealed, and the contents were heated at 40 °C for 48 h. After this time, the reaction mixture was cooled to room temperature and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography [silica gel, 20-30% EtOAc in petroleum ether b.p. 40–60 °C] to afford the product as a white solid (88%, 226 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.27 (ddt, *J* = 8.6, 1.2, 0.6 Hz, 1H, H9), 8.22 (d, *J* = 1.0 Hz, 2H, H3 & H6), 7.84 (ddd, *J* = 8.2, 1.5, 0.7 Hz, 1H, H8), 7.74 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H, H2), 7.59 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H, H1), 4.59 (dd, *J* = 9.7, 8.2 Hz, 1H, H12), 4.30 (t, *J* = 8.3 Hz, 1H, $H11_A$), 4.22 (ddd, *J* = 9.7, 8.3,

6.3 Hz, 1H, $H11_B$), 1.94 (dq, *J* = 13.3, 6.7 Hz, 1H, H13), 1.08 (d, *J* = 6.8 Hz, 3H, $H14_3$), 0.97 (d, *J* = 6.8 Hz, 3H, $H15_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.0 (C10), 147.7 (C7), 147.1 (C4), 136.8 (C9), 130.5 (C5), 130.1 (C2), 128.9 (C3), 128.0 (C6), 127.6 (C1), 121.0 (C8), 73.1 (C11), 71.1 (12), 33.0 (C13), 19.2 (C14), 18.3 (C15); **LRMS** (ESI^+) m/z Calcd. for $C_{15}H_{17}ON_2$ $(M+H)^+$ 241.1, found 241.1.

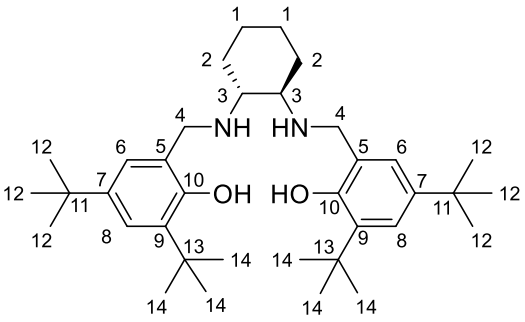
(*S*)-4-benzyl-2-(quinolin-2-yl)-4,5-dihydrooxazole (L8D)



The procedure is based on a modified literature method.[107] Data is in agreement with those previously reported. To a 7 mL screw-top vial was added methyl quinoline-2-carbimidate (**213**) (200 mg, 1.07 mmol, 1.00 equiv.), L-phenylalaninol (162 mg, 1.07 mmol, 1.00 equiv.) and CH_2Cl_2 (5 mL). The vial was sealed, and the contents were heated at 40 °C for 48 h. After this time, the reaction mixture was cooled to room temperature and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography [silica gel, 20-40% EtOAc in petroleum ether b.p. 40–60 °C] to afford the product as a white solid (94%, 290 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.33 – 8.16 (m, 3H, H3, H6 & H9), 7.94 – 7.81 (m, 1H, H8), 7.76 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H, H2), 7.60 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H, H1), 7.41 – 7.17 (m, 5H, H15, H16, H17, H18 & H19), 4.72 (tdd, *J* = 9.1, 7.6, 5.2 Hz, 1H, H12), 4.53 (dd, *J* = 9.5, 8.6 Hz, 1H, $H11_A$), 4.32 (dd, *J* = 8.6, 7.6 Hz, 1H, $H11_B$), 3.33 (dd, *J* = 13.7, 5.2 Hz, 1H, $H13_A$), 2.81 (dd, *J* = 13.8, 9.0 Hz, 1H, $H13_B$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.5 (C10), 147.7 (C7), 146.9 (C4), 137.9 (C14), 136.9 (C9), 130.5 (C5), 130.2 (C2), 129.4 (C3), 128.9 (C16 & C18), 128.8 (C6), 128.1 (C15 & C19), 127.7 (C1), 126.8 (C17), 120.9 (C8), 72.9 (C11), 68.4 (C12), 41.8 (C13); **LRMS** (ESI^+) m/z Calcd. for $C_{19}H_{17}ON_2$ $(M+H)^+$ 289.1, found 289.1.

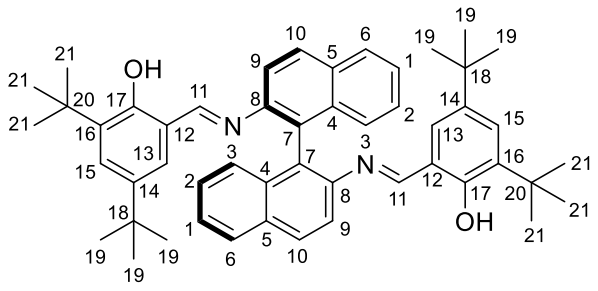
6,6'-((((1*R*,2*R*)-cyclohexane-1,2-diyl)bis(azanediyl))bis(methylene))bis(2,4-di-*tert*-butylphenol) (L16A)

The title compound was prepared according to General Procedure I using 6,6'-((1E,1'E)-(((1R,2R)-cyclohexane-1,2-diyl)bis(azaneylylidene))bis(methaneylylidene))bis(2,4-di-*tert*-



butylphenol) (260 mg, 0.475 mmol). The crude product was purified by flash column chromatography [silica gel, 50-100% CH_2Cl_2 in petroleum ether b.p. 40–60 °C] to afford the product as a white solid **(***Yield* = 89%, 234 mg). **M.P.** = 125-127 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.22 (d, *J* = 2.4 Hz, 2H, $H8_2$), 6.87 (d, *J* = 2.4 Hz, 2H, $H6_2$), 4.05 (d, *J* = 13.3 Hz, 2H, $H4_{A2}$), 3.91 (d, *J* = 13.3 Hz, 2H, $H4_{B2}$), 2.53 – 2.42 (m, 2H, $H3_2$), 2.18 (d, *J* = 11.5 Hz, 2H, $H2_{A2}$), 1.81 – 1.64 (m, 2H, $H2_{B2}$), 1.38 (s, 18H, $H14_{18}$), 1.31 – 1.20 (m, 4H, $H1_4$), 1.29 (s, 18H, $H12_{18}$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.5 ($C10_2$), 140.8 ($C7_2$), 136.1 ($C9_2$), 123.3 ($C8_2$), 123.2 ($C10_2$), 122.5 ($C7_2$), 60.1 ($C4_2$), 51.0 ($C3_2$), 35.0 ($C11_2$), 34.3 ($C13_2$), 31.8 ($C14_6$), 30.9 ($C2_2$), 29.8 ($C12_6$), 24.3 ($C1_2$); **FTIR** (neat) ν = 2953, 2863, 1480, 1446, 1391, 1361, 1236, 1203, 1165, 876 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{36}H_{59}O_2N_2$ $(M+H)^+$ 551.4571, found 551.4564.

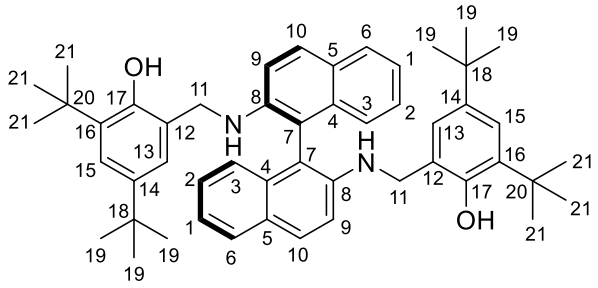
2,2'-[(1*R*)-[1,1'-Binaphthalene]-2,2'-diylbis(nitrilomethylidyne)]bis[4,6-bis(1,1'-di-*tert*-butyl)phenol]



The title compound was prepared according to General Procedure H using (*R*)-(+)-1,1′-binaphthyl-2,2′-diamine (100 mg, 0.352 mmol). The crude product was purified by flash column chromatography [basic activated alumina, 5% Et_2O in petroleum ether b.p. 40–60 °C] to afford the product as a yellow foam (89%, 225 mg). **M.P.** = 118-123 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.73 (s, 2H, OH), 8.66 (s, 2H, $H11_2$), 8.08 – 8.00 (m, 2H, $H10_2$), 7.95 (dt, *J* = 8.2, 0.9 Hz, 2H, $H3_2$), 7.58 (d, *J* = 8.8 Hz, 2H, $H9_2$),

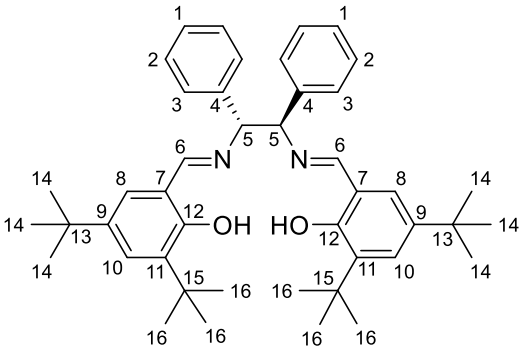
7.44 (ddd, *J* = 8.1, 6.5, 1.5 Hz, 2H, $H2_2$), 7.37 – 7.22 (m, 4H, $H1_2$ & $H6_2$), 7.25 (d, *J* = 2.4 Hz, 2H, $H13_2$), 7.05 (d, *J* = 2.4 Hz, 2H, $H15_2$), 1.23 (s, 18H, $H21_{18}$), 1.22 (s, 18H, $H19_{18}$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.9 ($C11_2$), 158.3 ($C17_2$), 144.2 ($C8_2$), 139.9 ($C14_2$), 136.7 ($C16_2$), 133.5 ($C4_2$), 132.7 ($C5_2$), 129.8 ($C10_2$), 129.4 ($C7_2$), 128.3 ($C13_2$), 127.6 ($C3_2$), 126.9 ($C1_2$), 126.7 ($C6_2$), 126.6 ($C15_2$), 125.6 ($C2_2$), 118.3 ($C12_2$), 117.4 ($C9_2$), 35.0 (C20), 34.2 (C18), 31.5 ($C21_6$), 29.3 ($C19_6$); **FTIR** (neat) ν = 2956, 2870, 1612, 1582, 1467, 1439, 1392, 1361, 1250, 1200, 1173, 818, 772, 746 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{50}H_{57}O_2N_2$ $(M+H)^+$ 717.4415, found 717.4406.

2,2'-[(1*R*)-[1,1'-binaphthalene]-2,2'-diylbis(iminomethylene)]bis[4,6-bis(1,1-di-*tert*-butyl)phenol] (L16B)



The title compound was prepared according to General Procedure I using 2,2'-[(1R)-[1,1'-binaphthalene]-2,2'-diylbis(nitrilomethylidyne)]bis[4,6-bis(1,1'-di-*tert*-butyl)phenol] (134 mg, 0.187 mmol). The crude product was purified by flash column chromatography [silica gel, 5% EtOAc in petroleum ether b.p. 40–60 °C] to afford the product as a yellow solid (73%, 98 mg). **M.P.** = 117-126 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.32 (s, 2H, OH), 7.96 (d, *J* = 8.9 Hz, 2H, $H11_2$), 7.88 – 7.81 (m, 2H, $H10_2$), 7.52 (d, *J* = 9.0 Hz, 2H, $H3_2$), 7.33 (ddd, *J* = 8.1, 6.7, 1.3 Hz, 2H, $H9_2$), 7.30 – 7.25 (m, 2H, $H2_2$), 7.23 (d, *J* = 2.4 Hz, 2H, $H6_2$), 7.05 (dd, *J* = 8.3, 1.3 Hz, 2H, $H1_2$), 6.94 (d, *J* = 2.4 Hz, 2H, $H13_2$), 4.57 – 4.35 (m, 4H, $H11_4$), 3.83 (t, *J* = 6.2 Hz, 2H, NH), 1.34 (s, 18H, $H21_{18}$), 1.26 (s, 18H, $H19_{18}$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.6 ($C17_2$), 143.7 ($C8_2$), 141.6 ($C8_2$), 136.5 ($C14_2$), 133.4 ($C16_2$), 130.6 ($C4_2$), 129.7 ($C5_2$), 128.5 ($C10_2$), 127.5 ($C7_2$), 124.2 ($C13_2$), 124.0 ($C3_2$), 123.7 ($C1_2$), 122.1 ($C6_2$), 116.6 ($C15_2$), 116.4 ($C2_2$), 50.3 ($C11_2$), 35.1 (C20), 34.4 (C18), 31.8 ($C21_6$), 29.8 ($C19_6$); **FTIR** (neat) ν = 3223, 2955, 2867, 1620, 1595, 1512, 1480, 1423, 1361, 1231, 812, 746 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{50}H_{61}O_2N_2$ $(M+H)^+$ 721.4728, found 721.4720.

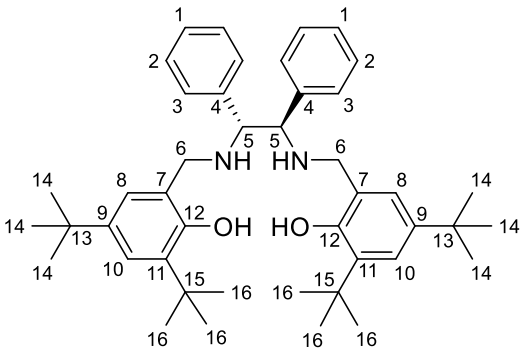
6,6'-((1E,1'E)-(((1*R*,2*R*)-1,2-diphenylethane-1,2-diyl)bis(azaneylylidene))bis(methaneylylidene))bis(2,4-di-*tert*-butylphenol)



The title compound was prepared according to General Procedure H using (1R,2R)-(+)-1,2-diphenylethylenediamine (500 mg, 2.36 mmol). The crude product was isolated as a yellow solid and no further purification was required (100%, 1.57 g). **M.P.** = 188-191 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 13.63 (s, 2H, OH), 8.44 (s, 2H, $H6_2$), 7.35 (d, *J* = 2.4 Hz, 2H, $H10_2$), 7.27 – 7.17 (m, 10H, $H1_2$. $H2_4$ & $H3_4$), 7.02 (d, *J* = 2.4 Hz, 2H, $H8_2$), 4.77 (s, 2H, $H5_2$), 1.46 (s, 18H, $H16_{18}$), 1.26 (s, 19H, $H14_{18}$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.4 ($C6_2$), 158.1 ($C12_2$), 140.2 ($C9_2$), 140.0 ($C11_2$), 136.5 ($C4_2$), 128.4 ($C3_4$), 128.2 ($C2_4$), 127.5 ($C1_2$), 127.3 ($C10_2$), 126.5 ($C8_2$), 118.0 ($C7_2$), 80.3 ($C5_2$), 35.1 ($C15_2$), 34.2 ($C13_2$), 31.6 ($C16_6$), 29.6 ($C14_6$); **FTIR** (neat) ν = 2956, 2869, 1625, 1598, 1469, 1454, 1440, 1361, 1273, 1250, 1173, 774, 697 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{44}H_{57}O_2N_2$ $(M+H)^+$ 645.4415, found 645.4416.

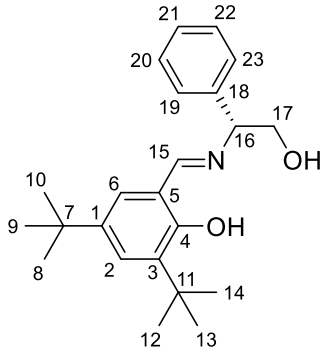
6,6'-((((1R,2R)-1,2-diphenylethane-1,2-diyl)bis(azanediyl))bis(methylene))bis(2,4-di-*tert*-butylphenol) (L16C)

The title compound was prepared according to General Procedure I using 6,6'-((1E,1'E)-(((1*R*,2*R*)-1,2-diphenylethane-1,2-diyl)bis(azaneylylidene))bis(methaneylylidene))bis(2,4-di-*tert*-butylphenol) (500 mg, 0.775 mmol). The crude product was purified by flash column chromatography [silica gel, 10-20% CH_2Cl_2 in petroleum ether b.p. 40–60 °C] to afford the product as a white solid (76%, 384 mg). **M.P.** = 159-162 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.42 (s, 2H, OH), 7.33 – 7.23 (m, 8H, $H1_2$, $H3_4$ & $H10_2$), 7.05 – 6.97 (m, 4H, $H2_4$), 6.68 (d, *J* = 2.4 Hz, 2H, $H8_2$), 4.15 – 4.05 (m, 2H, $H5_2$), 3.84 (d, *J* = 13.2 Hz, 2H, $H6_{A2}$), 3.67



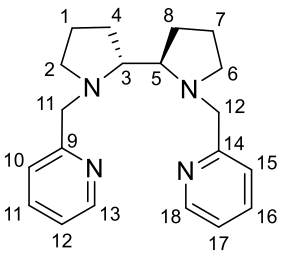
(d, *J* = 13.4 Hz, 2H, $H6_{B2}$), 1.49 (s, 18H, $H16_{18}$), 1.28 (s, 18H, $H14_{18}$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.4 ($C12_2$), 140.8 ($C9_2$), 137.7 ($C11_2$), 136.2 ($C4_2$), 128.6 ($C3_4$), 128.4 ($C2_4$), 128.1 ($C1_2$), 123.6 ($C8_2$), 123.3 ($C10_2$), 121.9 ($C7_2$), 66.7 ($C5_2$), 51.4 ($C6_2$), 35.1 ($C15_2$), 34.3 ($C13_2$), 31.8 ($C16_6$), 29.8 ($C14_6$); **FTIR** (neat) ν = 2954, 2905, 2867, 1480, 1456, 1436, 1391, 1361, 1234, 1203, 876, 760 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{44}H_{61}O_2N_2$ $(M+H)^+$ 649.4728, found 649.4733.

(*R*,E)-2,4-di-*tert*-butyl-6-(((2-hydroxy-1-phenylethyl)imino)methyl)phenol (L19A)



The procedure is based on a modified literature method.[141] Data is in agreement with those previously reported. An RBF was charged with 3,5-di-*tert*-butylsalicylaldehyde (234 mg, 1.00 mmol, 1.00 equiv.), Na_2SO_4 (1.14 g, 8.00 mmol, 8.00 equiv.) and MeOH (30 mL). (*R*)-(–)-phenylglycinol (137 mg, 1.00 mmol, 1.00 equiv.) was added to the suspension and the reaction mixture was heated to reflux for 24 h. The contents were then cooled to room temperature and the solvent removed by rotary evaporation. The crude product was dissolved in CH_2Cl_2 (25 mL) and the drying agent was removed by gravity filtration. The filtrate was concentrated *in vacuo* to afford the product as a yellow solid. No further purification was required (88%, 311 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 13.50 (s, 1H, OH), 8.50 (s, 1H, H15), 7.45 – 7.24 (m, 6H, H6, H19, H20, H21, H22 & H23), 7.12 (s, 1H, H2), 4.45 (dd, J = 7.6, 5.4 Hz, 1H, H16), 4.03 – 3.84 (m, 2H, $H17_2$), 1.46 (d, J = 1.7 Hz, 9H, $H8_3$, $H9_3$ & $H10_3$), 1.30 (d, J = 1.8 Hz, 9H, $H12_3$, $H13_3$ & $H14_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.8 (C15), 158.1 (C4), 140.6 (C18), 136.9 (C1), 128.9 (C3), 128.0 (C2), 127.6 (C6), 127.3 (C19 & C23), 126.6 (C20 & C22), 125.9 (C21), 118.0 (C5), 76.4 (C16), 67.9 (C17), 35.2 (C7), 34.3 (C11), 31.6 (C8, C9 & C10), 29.6 (C12, C13 & C14); **LRMS** (ESI^+) m/z Calcd. for $C_{23}H_{32}O_2N$ $(M+H)^+$ 354.2, found 354.2.

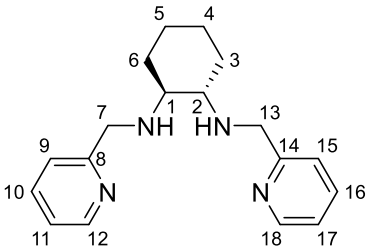
(2*R*,2'*R*)-1,1'-bis(pyridin-2-ylmethyl)-2,2'-bipyrrolidine (L21)



The procedure is based on a modified literature method.[110] Data is in agreement with those previously reported. To a stirred suspension of (*R*,*R*)-2,2′-bipyrrolidine L-tartrate trihydrate (1.00 g, 2.90 mmol, 1.00 equiv.) in CH_2Cl_2 (6 mL) and water (6 mL) was added solid NaOH

(870 mg, 21.75 mmol, 7.50 equiv.) and 2-picolyl chloride hydrochloride salt (951 mg, 5.80 mmol, 2.00 equiv.). The biphasic mixture was then vigorously stirred for 16 h at room temperature. After this time, the layers were separated and the aqueous phase was extracted three times with CH_2Cl_2. The combined extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was isolated as a brown oil and was used without further purification (70%, 655 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.43 (d, *J* = 6.6 Hz, 2H, H13 & H18), 7.53 (t, *J* = 7.6 Hz, 2H, H11 & H16), 7.33 (d, J = 7.8 Hz, 2H, H10 & H15), 7.04 (t, *J* = 5.3 Hz, 2H, H12 & H17), 4.13 (d, *J* = 14.3 Hz, 2H, $H11_A$ & $H12_A$), 3.44 (d, J = 14.3 Hz, 2H, $H11_B$ & $H12_B$), 2.95 – 2.89 (m, 2H, $H2_A$ & $H6_A$), 2.77 – 2.68 (m, 2H, $H2_B$ & $H6_B$), 2.15 – 2.11 (m, 2H, H3 & H5), 1.80 – 1.68 (m, 4H, $H1_2$ & $H7_2$), 1.68 – 1.59 (m, 4H, $H4_2$ & $H8_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.4 (C9 & C14), 148.8 (C13 & C18), 136.2 (C11 & C16), 122.6 (C10 & C15), 121.6 (C12 & C17), 65.4 (C3 & C5), 61.2 (C11 & C12), 55.3 (C2 & C6), 25.9 (C4 & C8), 23.6 (C1 & C7); **LRMS** (ESI$^+$) m/z Calcd. for $C_{20}H_{27}N_4$ $(M+H)^+$ 323.2, found 323.2.

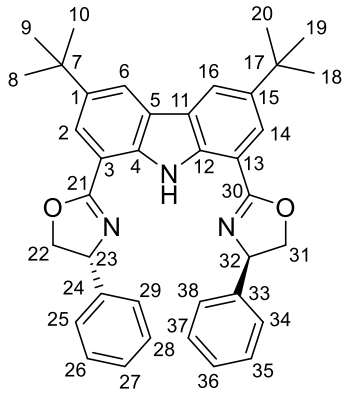
(1*S*,2*S*)-*N*1,*N*2-bis(pyridin-2-ylmethyl)cyclohexane-1,2-diamine (L22)



The procedure is based on a modified literature method.[142] Data is in agreement with those previously reported. An RBF was charged with 2-pyridine carboxaldehyde (428 mg, 380 µL, 4.00 mmol, 2.00 equiv.), Na_2SO_4 (2.28 g, 16.00 mmol, 16.00 equiv.) and MeOH (30 mL). (1*S,2S*)-(–)-1,2-diaminocyclohexane (228 mg, 2.00 mmol, 1.00 equiv.), was then added to the suspension and the reaction mixture was heated to reflux for 24 h. The contents were then cooled to room temperature and the solvent removed by rotary evaporation. The crude product was dissolved in CH_2Cl_2 (25 mL) and the drying agent was removed by gravity filtration. The filtrate was concentrated *in vacuo* to afford the product as a yellow solid. No further purification was required. In the next step, the solid was suspended in MeOH (10 mL) and cooled to 0 °C. At this temperature, $NaBH_4$ (151 mg, 4.00 mmol, 2.00 equiv.) was added in small portions. The mixture was then allowed to warm to room temperature and stirring was continued for an additional 2 h. The reaction was then quenched by the addition of

2 N NaOH, and the product extracted three times with CH_2Cl_2. The combined extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo* to yield the pure product as a yellow oil (97%, 575 mg over 2 steps). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.44 (dd, *J* = 7.7, 3.3 Hz, 2H, H12 & H18), 7.54 (dt, J = 7.6, 1.8 Hz, 2H, H10 & H16), 7.33 (d, J = 7.8 Hz, 2H, H9 & H15), 7.05 (m, 2H, H11 & H17), 3.96 (d, J = 14.2 Hz, 2H, $H7_A$ & $H13_A$), 3.78 (d, J = 14.2 Hz, 2H, $H7_B$ & $H13_B$), 2.42 (bs, 2H, NH), 2.26 (dd, J = 5.2, 3.7 Hz, 2H, H1 & H2), 2.07 (dd, J = 10.6, 2.5 Hz, 2H, $H3_A$ & $H6_A$), 1.64 (m, 2H, $H3_B$ & $H6_B$), 1.10 (m, 4H, $H4_2$ & $H5_2$);**^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.7 (C8 & C14), 149.0 (C12 & C18), 136.3 (C10 & C16), 122.2 (C11 & C17), 121.7 (C9 & C15), 61.3 (C1 & C2), 52.5 (C7 & C13), 31.6 (C3 & C6), 25.0 (C4 & C5); **LRMS** (ESI^+) m/z Calcd. for $C_{20}H_{29}N_4$ $(M+H)^+$ 325.2, found 325.2.

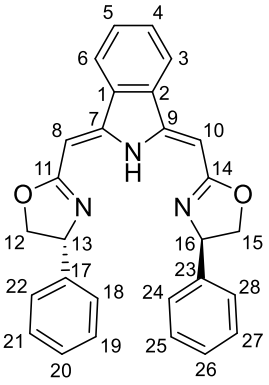
(4*R*,4'*R*)-2,2'-(3,6-di-*tert*-butyl-9H-carbazole-1,8-diyl)bis(4-phenyl-4,5-dihydrooxazole) (L10A)



The procedure is based on a modified literature method. Data is in agreement with those previously reported.[138] A flame dried, argon filled RBF was charged with 3,6-di-*tert*-butyl-9H-carbazole-1,8-dicarbonitrile (**209**) (150 mg, 0.46 mmol, 1.00 equiv.), $ZnCl_2$ (155 mg, 1.14 mmol, 2.50 equiv.) and (*R*)-(−)-2-phenylglycinol (125 mg, 0.91 mmol, 2.00 equiv.). Chlorobenzene (4.5 mL) was added and the mixture was heated at 140 °C for 3 days. After the allotted time, the reaction was cooled to room temperature and ethylene diamine (0.5 mL) in water (5 mL) was added. The resulting biphasic mixture was stirred for 60 min and the layers were then separated. The product was extracted three times with CH_2Cl_2 and the combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography [silica gel, 50-80% CH_2Cl_2 in petroleum ether b.p. 40–60 °C] to afford the product as a yellow solid (53%, 137 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 2.0 Hz, 2H, H6 & H16), 7.71 (d, *J* = 2.0 Hz, 2H, H2 & H14), 6.72 – 6.58 (m, 2H, H27 & H36), 6.50 (t, *J* = 7.6 Hz, 4H, H26, H28, H35 & H37), 5.86 – 5.70 (m, 4H, H25, H29, H34 & H38), 4.39 – 4.20 (m, 4H, $H22_A$, H23, $H31_A$ & H32), 3.85 (dd, *J* = 7.6, 5.8 Hz, 2H, $H22_B$ & $H31_B$), 1.57 (s, 18H, $H8_3$, $H9_3$, $H10_3$, $H18_3$, $H19_3$

& $H20_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.9 (C21 & C30), 147.7 (C1 & C15), 140.9 (C4 & C12), 137.1 (C24 & C33), 126.8 (C26, C28, C35 & C37), 126.7 (C5 & C11), 126.02 (C27 & C36), 125.96 (C25, C29, C34 & C38), 123.0 (C2 & C14), 120.0 (C6 & C16), 108.0 (C3 & C13), 74.2 (C22 & C31), 68.9 (C23 & C32), 34.6 (C7 & C17), 32.4 (C8, C9, C10, C18, C19 & C20); **[α]**$_D^{25}$ = –443 ° (*c* 1.0, $CHCl_3$).

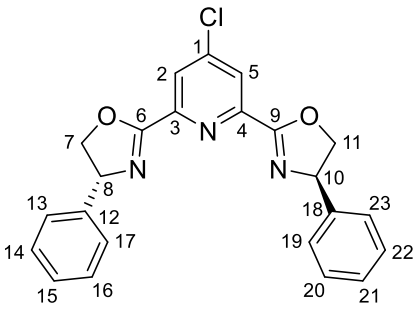
(1Z,3Z)-1,3-bis(((*R*)-4-phenyl-4,5-dihydrooxazol-2-yl)methylene)isoindoline (L23A)



The procedure is based on a modified literature method.[143] Data is in agreement with those previously reported. Pthalimide (**217**) (14.71 g, 10.00 mmol, 1.00 equiv.) and (carboethoxymethylene)triphenylphosphorane (17.42 g, 50.00 mmol, 5.00 equiv.) were added to a flame dried Schlenk tube under an argon atmosphere. The solid mixture was then stirred at 140 °C in an oil bath for 24 h, and the crude product was purified directly by flash column chromatography [silica gel, 20% EtOAc in petroleum ether b.p. 40–60 °C] to afford the diene product. The diene (**218**) (287 mg, 1.00 mmol, 1.00 equiv.) and (*R*)-phenylglycinol (686 mg, 5.00 mmol, 5.00 equiv.) were mixed and melted in a Schlenk tube under argon. NaH (60% dispersion in mineral oil, 8 mg, 0.20 mmol, 0.20 equiv.) The solid mixture was then heated at 120 °C in an oil bath, under slightly reduced pressure for 7 h. The contents were then cooled to room temperature and the crude product was purified by flash column chromatography [silica gel, 2% MeOH in $CHCl_3$] to afford the bisamide product (**219**). In a flame dried, argon filled round bottomed flask, the bisamide (**219**) (234 mg, 0.50 mmol, 1.00 equiv.) was dissolved in anhydrous CH_2Cl_2 (5 mL) and the solution was cooled to 0 °C. At this temperature, DAST (201 mg, 165 µL, 1.25 mmol, 2.50 equiv.) was added and the solution was stirred at 0 °C for 1 h. After this time, the reaction was quenched with solid K_2CO_3 (207 mg, 1.50 mmol, 3.00 equiv.), and the reaction was stirred for 16 h. Water was then added and the layers were separated. The product was extracted with CH_2Cl_2 three times, and the combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude

residue was purified by flash column chromatography [silica gel, 25% EtOAc in pentane] to afford the product as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 3.0, 5.4 Hz, 2H, H3 & H6), 7.52 (dd, *J* = 3.0, 5.4 Hz, 2H, H4 & H5), 7.37 (t, *J* = 7.2 Hz, 4H, H18, H22, H24 & H28), 7.30 (t, *J* = 7.2 Hz, 2H, H20 & H26), 7.16 (d, J = 7.2 Hz, 4H, H19, H21, H25 & H27), 5.86 (s, 2H, H8 & H10), 5.72 (dd, *J* = 3.0, 8.4 Hz, 2H, H13 & H16), 4.48 (t, J = 8.4 Hz, 2H, $H12_A$ & $H15_A$), 4.08 (dd, J = 3.0, 8.4 Hz, 2H, $H12_B$ & $H15_B$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.4 (C11 & C14), 158.6 (C7 & C9), 144.4 (C17 & C23), 137.7 (C1 & C2), 130.1 (C4 & C5), 128.9 (C19, C21, C25 & C27), 127.7 (C18, C22, C24 & C28), 126.6 (C20 & C26), 120.6 (C3 & C6), 82.3 (C8 & C10), 74.8 (C12 & C15), 67.5 (C13 & C16); **LRMS** (ESI^+) m/z Calcd. for $C_{28}H_{24}N_3O_2$ $(M+H)^+$ 434.2, found 434.2.

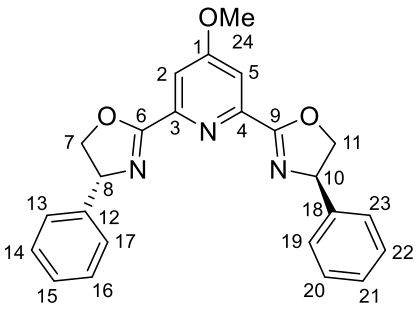
(4*R*,4'*R*)-2,2'-(4-chloropyridine-2,6-diyl)bis(4-phenyl-4,5-dihydrooxazole) (229)



The procedure is based on a modified 2-step literature method.[144] In a pear-shaped flask, 4-chloropyridine-2,6-dicarbonyl dichloride (**227**) (1.27 g, 5.37 mmol, 1.00 equiv.) was dissolved in CH_2Cl_2 (5 mL) and transferred to a separate mixture of (*R*)-phenylglycinol (1.47 g, 10.74 mmol, 2.00 equiv.) and NEt_3 (1.36 g, 1.87 mL, 13.42 mmol, 2.50 equiv.) in CH_2Cl_2 (20 mL) at 0 °C. The contents were allowed to warm to room temperature and stirred for 16 h. Sat. $NaHCO_{3\ (aq.)}$ (25 mL) was then added and the layers were separated. The aqueous phase was further extracted three times with CH_2Cl_2, the organic phases pooled and dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude bis amide as a yellow oil which was used without further purification in the subsequent step. An RBF equipped with reflux condenser was charged with the crude bisamide (assumed no product loss from previous step*:* 2.36 g, 5.37 mmol, 1.00 equiv.) and TsCl (2.05 g, 10.74 mmol, 2.00 equiv.). The solids were dissolved in CH_2Cl_2 (25 mL) and NEt_3 (2.17 g, 3 mL, 21.48 mmol, 4.00 equiv.) was added. The reaction mixture was then refluxed for 24 h before cooling to room temperature. Sat. $NaHCO_{3\ (aq.)}$ (25 mL) was then added and the layers were separated. The aqueous phase was further extracted three times with CH_2Cl_2, dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude product which was purified by flash

column chromatography [silica gel, 30-50% EtOAc in petroleum ether b.p. 40–60 °C + 1% NEt_3] and recrystallisation from hot EtOH to afford the product as a white crystalline solid (26% over 2 steps, 575 mg). **M.P.** = 125-130 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.36 (s, 2H, H2 & H5), 7.41 – 7.35 (m, 4H, H14, H16, H20 & H22), 7.34 – 7.28 (m, 6H, H13, H15, H17, H19, H21 & H23), 5.47 (dd, *J* = 10.3, 8.6 Hz, 2H, H8 & H10), 4.94 (dd, *J* = 10.4, 8.7 Hz, 2H, $H7_A$ & $H11_A$), 4.44 (t, *J* = 8.7 Hz, 2H, $H7_B$ & $H11_B$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.7 (C6 & C9), 148.0 (C3 & C4), 145.6 (C1), 141.4 (C12 & C18), 128.9 (C14, C16, C20 & C22), 128.0 (C15 & C21), 126.9 (C13, C17, C19 & C23), 126.5 (C2 & C5), 75.8 (C7 & C11), 70.4 (C8 & C10); **FTIR** (neat) ν = 3030, 2901, 1639, 1563, 1454, 1382, 1268, 1129, 979, 952, 924, 789, 754, 700 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{23}H_{19}O_2N_3{}^{35}Cl$ $(M+H)^+$ 404.1153, found 404.1160; **[α]**$_D^{25}$ = +117.9 ° (*c* 1.0, $CHCl_3$).

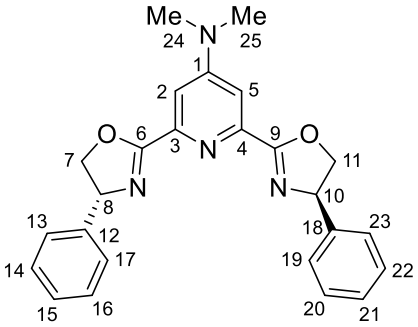
(4*R*,4'*R*)-2,2'-(4-methoxypyridine-2,6-diyl)bis(4-phenyl-4,5-dihydrooxazole) (230)



The procedure is based on a modified 2-step literature method.[144] An RBF was charged with (4R,4'R)-2,2'-(4-chloropyridine-2,6-diyl)bis(4-phenyl-4,5-dihydrooxazole) (**229**) (100 mg, 0.248 mmol, 1.00 equiv.), NaOMe (54 mg, 0.992 mmol, 4.00 equiv.) and MeOH (2 mL). The mixture was then stirred at 40 °C for 24 h. After the allotted time, the reaction was cooled to room temperature and diluted with water (10 mL). The product was extracted with a 3:1 mixture of $CHCl_3$/MeOH four times and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography [silica gel, 40-70% EtOAc in petroleum ether b.p. 40–60 °C + 1% NEt_3] *and* recrystallisation from hot EtOH to afford the product as a white crystalline solid (73%, 72 mg). **M.P.** = 104-107 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.86 (s, 2H, H2 & H5), 7.41 – 7.26 (m, 10H, H13, H14, H15, H16, H17, H19, H20, H21, H22 & H23), 5.44 (dd, *J* = 10.4, 8.6 Hz, 2H, H8 & H10), 4.91 (dd, *J* = 10.4, 8.7 Hz, 2H, $H7_A$ & $H11_A$), 4.41 (t, *J* = 8.6 Hz, 2H, $H7_B$ & $H11_B$), 3.93 (s, 3H, $H24_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.8 (C6 & C9), 163.7 (C1), 148.4 (C3 & C4), 141.8 (C12 & C18), 129.0 (C13, C16, C20 & C22), 127.9 (C15 & C21), 127.0 (C13, C17, C19 & C23), 112.5 (C2 & C5), 75.7 (C7 & C11), 70.4 (C8 & C10), 56.1 (C24); **FTIR** (neat)

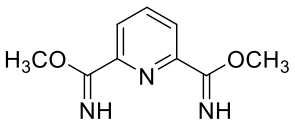
ν = 2979, 1639, 1590, 1566, 1494, 1457, 1396, 1270, 1221, 1091, 1039, 982, 956, 924, 862, 757, 700 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{24}H_{22}O_3N_3$ $(M+H)^+$ 400.1665, found 400.1666; **[α]**$_D^{25}$ = +100.2 ° (*c* 1.0, $CHCl_3$).

***N*,*N*-dimethyl-2,6-bis((*R*)-4-phenyl-4,5-dihydrooxazol-2-yl)pyridin-4-amine (231)**



The procedure is based on a modified literature method.[144] An RBF was charged with (4*R*,4'*R*)-2,2'-(4-chloropyridine-2,6-diyl)bis(4-phenyl-4,5-dihydrooxazole) (**229**) (100 mg, 0.248 mmol, 1.00 equiv.), dimethylamine solution $_{(aq.)}$ (40% w/w, 8 mL) and THF (2.5 mL). The mixture was then stirred at 45 °C for 24 h. After the allotted time, the reaction was cooled to room temperature and diluted with water (10 mL). The product was extracted with a 3:1 mixture of $CHCl_3$/MeOH four times and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by recrystallisation from hot EtOH to afford the product as a white solid (91%, 74 mg). **M.P.** = 124-127 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.56 (s, 2H, H2 & H5), 7.40 – 7.26 (m, 10H, H13, H14, H15, H16, H17, H19, H20, H21, H22 & H23), 5.41 (dd, *J* = 10.3, 8.5 Hz, 2H, H8 & H10), 4.89 (dd, *J* = 10.4, 8.6 Hz, 2H, $H7_A$ & $H11_A$), 4.38 (t, *J* = 8.6 Hz, 2H, $H7_B$ & $H11_B$), 3.09 (s, 6H, $H24_3$ & $H25_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.7 (C6 & C9), 155.2 (C1), 147.0 (C3 & C4), 142.2 (C12 & C18), 128.9 (C14, C16, C20 & C22), 127.9 (C15 & C21), 127.1 (C13, C17, C19 & C23), 108.7 (C2 & C5), 75.5 (C7 & C11), 70.4 (C8 & C10), 39.7 (C24 & C25); **FTIR** (neat) ν = 2899, 1638, 1598, 1540, 1509, 1454, 1405, 1107, 1003, 755, 700 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{25}H_{25}O_2N_4$ $(M+H)^+$ 413.1971, found 413.1972; **[α]**$_D^{25}$ = +47.4 ° (*c* 0.5, $CHCl_3$).

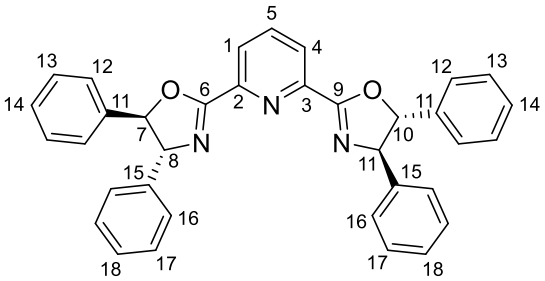
Dimethyl pyridine-2,6-bis(carbimidate) (233)



Prepared according to a modified literature method and the Data is in agreement with those previously reported.[5] To an RBF containing 2,6-pyridinedicarbonitrile (1.00 g, 7.74 mmol, 1.00 equiv.) MeOH (20 mL) and NaOMe (52 mg, 0.968 mmol, 0.125 equiv.) were added. The mixture was then stirred at room temperature for

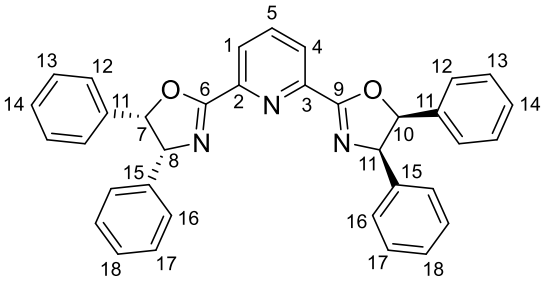
40 h and after this time, neutralised by the addition of AcOH (58 mg, 55 μL, 0.968 mmol, 0.125 equiv.). After stirring for 5 min, the solvent was removed by rotary evaporation. The residue was then taken up in CH_2Cl_2 (20 mL), washed with water (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford pure product as a white solid (100%, 1.50 g). **M.P.** = 91-96 °C **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.22 (bs, 2H), 7.92 – 7.89 (m, 3H), 4.02 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.1, 147.1, 139.0, 122.7, 54.2; **FTIR** (neat) ν = 3289, 3268, 3008, 2956, 1654, 1640, 1571, 1457, 1434, 1338, 1268, 1210, 1194, 1158, 1080, 998, 946, 914, 874, 824, 751 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_9H_{11}O_2N_3Na$ $(M+H)^+$ 216.0743, found 216.0745.

2,6-bis((4*R*,5*R*)-4,5-diphenyl-4,5-dihydrooxazol-2-yl)pyridine (237)



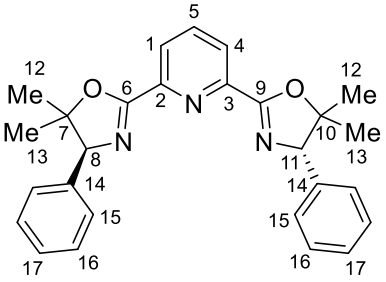
The title compound was prepared according to General Procedure K using dimethyl pyridine-2,6-bis(carbimidate) (100 mg, 0.518 mmol) and (1*R*,2*R*)-(+)-2-amino-1,2-diphenylethanol (221 mg, 1.04 mmol). The crude product was purified by flash column chromatography [silica gel, 30-40% EtOAc in petroleum ether b.p. 40–60 °C + 1% NEt_3] then recrystallisation from hot EtOH to afford the product as a white crystalline solid (59%, 160 mg). **M.P.** = 235-236 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.39 (d, *J* = 7.9 Hz, 2H, H1 & H4), 7.98 (t, *J* = 7.9 Hz, 1H, H5), 7.42 – 7.28 (m, 20H, $H12_4$, $H13_4$, $H14_2$, $H16_4$, $H17_4$ & $H18_2$), 5.54 (d, *J* = 8.3 Hz, 2H, H7 & H10), 5.33 (d, *J* = 8.4 Hz, 2H, H8 & H11); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.1 (C6 & C9), 147.3 (C2 & C3), 141.4 ($C15_2$), 139.9 ($C11_2$), 137.6 (C5), 129.0 (2C, $C14_4$ & $C17_4$) , 128.7 ($C16_4$), 128.0 ($C18_2$), 127.1 ($C14_2$), 126.7 ($C12_4$), 126.4 (C5), 90.2 (C7 & C10), 79.2 (C8 & C11); **FTIR** (neat) ν = 3036, 1639, 1573, 1497, 1455, 1350, 1258, 1108, 1073, 972, 764, 698 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{35}H_{28}O_2N_3$ $(M+H)^+$ 522.2176, found 522.2174; **[α]**$^{D}_{25}$ = +39.0 ° (*c* 1.0, $CHCl_3$).

2,6-bis((4*R*,5*S*)-4,5-diphenyl-4,5-dihydrooxazol-2-yl)pyridine (238)



The title compound was prepared according to General Procedure K using dimethyl pyridine-2,6-bis(carbimidate) (**233**) (100 mg, 0.518 mmol) and (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol (221 mg, 1.04 mmol). The crude product was purified by flash column chromatography [silica gel, 3% MeOH in CH_2Cl_2] then recrystallisation from hot EtOAc to afford the product as a white crystalline solid (83%, 223 mg). **M.P.** = 235-236 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.43 (d, *J* = 7.8 Hz, 2H, H1 & H4), 8.03 (t, *J* = 7.9 Hz, 1H, H5), 7.10 – 7.01 (m, 12H, $H13_4$, $H14_2$, $H17_4$ & $H18_2$), 7.09 – 7.01 (m, *J* = 7.4, 5.1, 2.3 Hz, 8H, $H12_4$ & $H16_4$), 6.12 (d, *J* = 10.3 Hz, 2H, H7 & H10), 5.83 (d, *J* = 10.3 Hz, 2H, H8 & H11); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.1 (C6 & C9), 147.2 (C2 & C3), 137.8 ($C15_2$), 137.3 ($C11_2$), 136.1 (C5), 128.1 ($C13_4$), 127.84 ($C17_4$), 127.76 ($C16_4$), 127.6 ($C18_2$), 127.2 ($C14_2$), 126.7 ($C12_4$), 126.6 (C5), 86.5 (C7 & C10), 74.6 (C8 & C11); **FTIR** (neat) ν = 3451, 1661, 1566, 1452, 1326, 1173, 1076, 973, 772, 693 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{35}H_{28}O_2N_3$ $(M+H)^+$ 522.2176, found 522.2172; **[α]**$^{D}_{25}$ = –326.5 ° (*c* 1.0, $CHCl_3$).

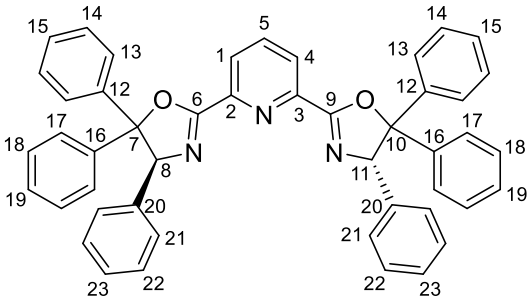
2,6-bis((*S*)-5,5-dimethyl-4-phenyl-4,5-dihydrooxazol-2-yl)pyridine (239)



The title compound was prepared according to General Procedure K using dimethyl pyridine-2,6-bis(carbimidate) (**233**) (100 mg, 0.518 mmol) and (*S*)-1-amino-2-methyl-1-phenylpropan-2-ol (**235**) (172 mg, 1.04 mmol). The crude product was purified by flash column chromatography [silica gel, 30% EtOAc in petroleum ether b.p. 40–60 °C + 1% NEt_3] then recrystallisation from hot EtOH to afford the product as a white crystalline solid (46%, 101 mg). **M.P.** = 166-170 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 7.8 Hz, 2H, H1 & H4), 7.94 (t, *J* = 7.8 Hz, 1H, H5), 7.46 – 7.21 (m, 10H, $H15_4$, $H16_4$ & $H17_4$), 5.14 (s, 2H, H8 & H11), 1.73 (s, 6H, $H12_6$), 1.02 (s, 6H, $H13_6$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.9 (C6 & C9), 147.7 (C2 & C3), 138.5 ($C14_2$), 137.3 (C5), 128.4 ($C15_4$), 127.7 ($C17_2$), 127.4 ($C16_4$), 126.2 (C1 & C4), 88.9 (C7 & C10), 78.7 (C8 & C11), 29.4 ($C13_2$), 24.1 ($C12_2$); **FTIR** (neat) ν = 2982, 1634, 1576,

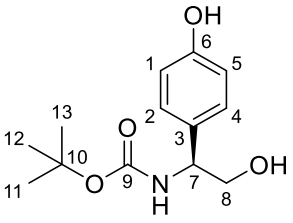
1459, 1375, 1101, 1074, 831, 756, 697 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{27}H_{28}O_2N_3$ $(M+H)^+$ 426.2156, found 426.2152; **[α]**$^{D}_{25}$ = +12.5 ° (*c* 1.0, $CHCl_3$).

2,6-bis((*S*)-4,5,5-triphenyl-4,5-dihydrooxazol-2-yl)pyridine (240)



The title compound was prepared according to General Procedure K using dimethyl pyridine-2,6-bis(carbimidate) (**233**) (100 mg, 0.518 mmol) and (*S*)-2-amino-1,1,2-triphenylethan-1-ol (**236**) (172 mg, 1.04 mmol). The crude product was purified by flash column chromatography [silica gel, 25% EtOAc in petroleum ether b.p. 40–60 °C + 1% NEt_3] to afford the product as a viscous yellow oil (32%, 112 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 7.9 Hz, 2H, H1 & H4), 7.99 (t, *J* = 7.9 Hz, 1H, H5), 7.84 (dd, *J* = 7.6, 1.7 Hz, 4H, $H21_4$), 7.44 (dd, *J* = 8.4, 6.9 Hz, 4H, $H22_4$), 7.39 – 7.31 (m, 2H, $H23_2$), 7.16 – 6.95 (m, 20H, $H13_4$, $H14_4$, $H15_2$, $H17_4$, $H18_4$, $H19_2$), 6.23 (s, 2H, H8 & H11); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.6 (C6 & C9), 147.4 (C2 & C3), 144.7 ($C12_2$), 140.3 ($C16_2$), 138.2 ($C20_2$), 137.6 (C5), 128.71 ($C21_4$), 128.67 ($C17_4$), 128.2 ($C15_2$), 127.9 ($C14_4$), 127.5 ($C19_2$), 127.4 ($C18_4$), 127.0 ($C22_4$), 126.9 ($C23_2$), 126.7 ($C13_4$), 126.4 (C1 & C4), 95.2 (C7 & C10), 80.4 (C8 & C11); **FTIR** (neat) ν = 3059, 1649, 1571, 1489, 1454, 1363, 1130, 969, 758, 696 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{47}H_{36}O_2N_3$ $(M+H)^+$ 674.2798, found 674.2802; **[α]**$^{D}_{25}$ = –149.2 ° (*c* 1.0, $CHCl_3$).

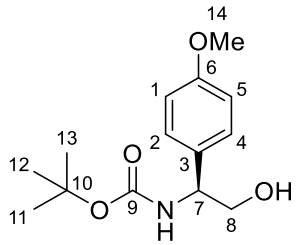
***tert*-butyl (*S*)-(2-hydroxy-1-(4-hydroxyphenyl)ethyl)carbamate (242)**



CDI (4.85 g, 30.00 mmol, 1.30 equiv.) was added to a solution of (*S*)-2-((*tert*-butoxycarbonyl)amino)-2-(4-hydroxyphenyl)acetic acid (**241**) (6.15 g, 23.00 mmol, 1.00 equiv.) in THF (96 mL) at room temperature. The mixture was stirred for 15 min before cooling the contents to 0 °C. At this temperature, a solution of $NaBH_4$ (1.74 g, 46.00 mmol, 2.00 equiv.) in H_2O (40 mL) was added. The reaction was then allowed to warm to room temperature and stirring was continued for a further 2 h. The reaction was quenched by the *slow* addition of 1M HCl (100 mL) at 0 °C. The

layers were separated and the aqueous phase was extracted three times with EtOAc, and the combined organic extracts were washed successively with sat. $NaHCO_{3\,(aq.)}$ and brine. The organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography [silica gel, 50-100% EtOAc in petroleum ether b.p. 40–60 °C] to afford the product as a white solid (81%, 4.72 g). **M.P.** = 155-158 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.22 (s, 1H, OH), 7.13 – 6.99 (m, 2H, H2 & H4), 6.77 – 6.55 (m, 2H, H1 & H5), 4.69 (t, J = 5.7 Hz, 1H, OH), 4.51 – 4.30 (m, 1H, H7), 3.45 – 3.40 (m, 2H, $H8_2$), 1.36 (s, 9H, $H11_3$, $H12_3$ & $H13_3$); **^{13}C NMR** (101 MHz, DMSO-d_6) δ 156.1 (C6), 155.2 (C9), 132.1 (C3), 127.9 (C2 & C4), 114.8 (C1 & C5), 77.6 (C10), 65.0 (C8), 56.3 (C7), 28.3 (C11, C12 & C13); **FTIR** (neat) ν = 3353, 1681, 1519, 1363, 1251, 1163, 1055, 834, 773, 752 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{13}H_{19}O_4N^{23}Na$ $(M+Na)^+$ 276.1206, found 276.1206; **[α]**$^{D}_{25}$ = +41.6 ° (*c* 1.0, MeOH).

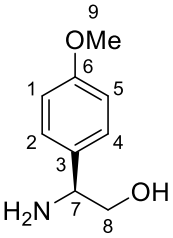
***tert*-butyl (*S*)-(2-hydroxy-1-(4-methoxyphenyl)ethyl)carbamate (243)**



K_2CO_3 (327 mg, 2.36 mmol, 1.20 equiv.) and Me_2SO_4 (257 mg, 193 µL, 2.04 mmol, 1.05 equiv.) were added to a solution of *tert*-butyl (*S*)-(2-hydroxy-1-(4-hydroxyphenyl)ethyl)carbamate (**242**) (500 mg, 1.97 mmol, 1.00 equiv.) in acetone (10 mL) at room temperature. The mixture was then heated at reflux for 16 h. After this time, the contents were cooled to room temperature and concentrated to dryness *in vacuo*. Sat. $NH_4Cl_{\,(aq.)}$ was added and the product was extracted three times with EtOAc, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography [silica gel, 40% EtOAc in petroleum ether b.p. 40–60 °C] to afford the product as a white solid (91%, 482 g). **M.P.** = 120-122 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.24 – 7.16 (m, 2H, H2 & H4), 6.92 – 6.81 (m, 2H, H1 & H5), 4.72 (t, J = 5.7 Hz, 1H, H7), 4.45 (q, J = 7.2 Hz, 1H, OH), 3.71 (s, 3H, $H14_3$), 3.50 – 3.39 (m, 2H, $H8_2$), 1.35 (s, 9H, $H11_3$, $H12_3$ & $H13_3$); **^{13}C NMR** (101 MHz, DMSO-d_6) δ 158.1 (C6), 155.2 (C10), 133.8 (C3), 127.9 (C2 & C4), 113.4 (C1 & C5), 77.6 (C10), 64.9 (C8), 56.2 (C7), 55.0 (C14), 28.3 (C11, C12 & C13);

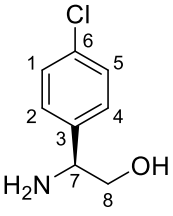
FTIR (neat) ν = 3379, 2938, 1683, 1514, 1366, 1248, 1170, 1033, 835 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{14}H_{21}O_4N^{23}Na$ $(M+Na)^+$ 290.1362, found 290.1362; **[α]**$^{D}_{25}$ = +40.8 ° (*c* 1.0, MeOH);

(*S*)-2-amino-2-(4-methoxyphenyl)ethan-1-ol (AA1)



Prepared according to a modified literature method and the data is in agreement with those previously reported.[145] TFA (3.84 g, 2.58 mL, 33.67 mmol, 50.00 equiv.) was added to a solution of *tert*-butyl (*S*)-(2-hydroxy-1-(4-methoxyphenyl)ethyl)carbamate (**243**) (180 mg, 0.67 mmol, 1.00 equiv.) in CH_2Cl_2 (10 mL) at 0 °C. The mixture was then warmed to room temperature and stirring was continued for 16 h. After this time, the reaction was concentrated to dryness *in vacuo*. The residue was then redissolved in CH_2Cl_2 (10 mL) and washed with 1M NaOH $_{(aq.)}$ (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The product was isolated as a yellow solid and was used without further purification (88%, 98 mg). **M.P.** = 82-84 °C; **^{1}H NMR** (400 MHz, MeOH-d_4) δ 7.27 (dt, *J* = 8.6, 1.5 Hz, 2H, H2 & H4), 6.89 (dt, *J* = 8.7, 1.5 Hz, 2H, H1 & H5), 3.96 – 3.84 (m, 1H, H7), 3.77 (t, *J* = 1.5 Hz, 3H, $H9_3$), 3.64 (ddt, *J* = 10.8, 4.7, 1.5 Hz, 1H, $H8_A$), 3.51 (ddt, *J* = 10.7, 8.2, 1.4 Hz, 1H, $H8_B$); **^{13}C NMR** (101 MHz, MeOH-d_4) δ 160.5 (C6), 135.3 (C3), 129.0 (C2 & C4), 114.9 (C1 & C5), 68.9 (C8), 58.1 (C7), 55.7 (C9); **FTIR** (neat) ν = 3335, 2940, 1686, 1517, 1458, 1366, 1240, 1166, 1030, 828 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_9H_{14}O_2N$ $(M+H)^+$ 168.1025, found 168.1022; **[α]**$^{D}_{25}$ = +27.0 ° (*c* 0.5, MeOH).

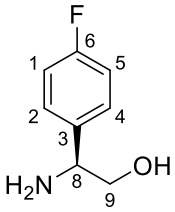
(*S*)-2-amino-2-(4-chlorophenyl)ethan-1-ol (AA2)



$LiAlH_4$ powder (353 mg, 9.31 mmol, 3.10 equiv.) was carefully added to a solution of (*S*)-2-amino-2-(4-chlorophenyl)acetic acid (557 mg, 3.00 mmol, 1.00 equiv.) in THF (15 mL) at 0 °C. The mixture was heated at reflux for 3 h and then cooled again to 0 °C. With caution, H_2O (350 µL) and 15% (w/v) NaOH $_{(aq.)}$ (350 µL) were sequentially added. An additional potion of H_2O (1 mL) was then introduced and the mixture was warmed to room temperature and stirred for 15 min. $MgSO_4$ was then added and stirring continued for an additional 15 min. The solids were removed by filtration through a pad of Celite® and the filter cake was washed with EtOAc. The filtrate was concentrated *in vacuo* and

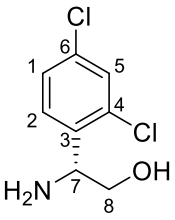
the residue was purified by recrystallisation from toluene to afford the product as a pale yellow solid (86%, 443 mg). **M.P.** = 67-69 °C; **^{1}H NMR** (400 MHz, MeOH-d_4) δ 7.42 – 7.23 (m, 4H, H1, H2, H4 & H5), 4.83 (bs, 2H, NH_2), 3.93 (dd, *J* = 7.6, 4.9 Hz, 1H, H7), 3.65 (dd, *J* = 10.8, 4.9 Hz, 1H, $H8_A$), 3.53 (dd, *J* = 10.8, 7.6 Hz, 1H, $H8_B$); **^{13}C NMR** (101 MHz, MeOH-d_4) δ 142.5 (C3), 134.0 (C6), 129.6 (C1 & C5), 129.5 (C2 & C4), 68.6 (C8), 58.1 (C7); **FTIR** (neat) ν = 3314, 2867, 1588, 1488, 1409, 1359, 1089, 1047, 1013, 827 cm^{-1}; **HRMS** (ESI$^+$) m/z Calcd. for $C_8H_{10}ONClNa$ $(M+Na)^+$ 194.0343, found 194.0343; **[α]**$^{D}_{25}$ = +22.0 ° (*c* 1.0, MeOH).

(*S*)-2-amino-2-(4-fluorophenyl)ethan-1-ol (AA3)



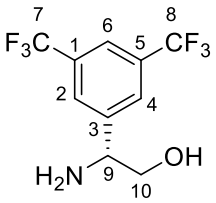
$LiAlH_4$ powder (353 mg, 9.31 mmol, 3.10 equiv.) was carefully added to a solution of (*S*)-2-amino-2-(4-fluorophenyl)acetic acid (466 mg, 3.00 mmol, 1.00 equiv.) in THF (15 mL) at 0 °C. The mixture was heated at reflux for 3 h and then cooled again to 0 °C. With caution, H_2O (350 µL) and 15% (w/v) NaOH $_{(aq.)}$ (350 µL) were sequentially added. An additional potion of H_2O (1 mL) was then introduced and the mixture was warmed to room temperature and stirred for 15 min. $MgSO_4$ was then added and stirring continued for an additional 15 min. The solids were removed by filtration through a pad of Celite® and the filter cake was washed with EtOAc. The filtrate was concentrated *in vacuo* and the residue was purified by recrystallisation from toluene to afford the product as a pale yellow solid (73%, 342 mg). **M.P.** = 84-86 °C; **^{1}H NMR** (400 MHz, MeOH-d_4) δ 7.44 – 7.32 (m, 2H, H2 & H4), 7.15 – 6.99 (m, 2H, H1 & H5), 4.85 (s, 2H, NH_2), 3.94 (dd, *J* = 7.7, 4.9 Hz, 1H, H8), 3.65 (dd, *J* = 10.8, 4.9 Hz, 1H, $H9_A$), 3.53 (dd, *J* = 10.8, 7.8 Hz, 1H, $H9_B$); **^{13}C NMR** (101 MHz, MeOH-d_4) δ 163.5 (d, *J* = 243.7 Hz, C6), 139.6 (d, *J* = 3.1 Hz, C3), 129.8 (d, *J* = 8.0 Hz, C2 & C4), 116.0 (d, *J* = 21.5 Hz, H1 & H5), 68.81 (C9), 58.05 (C8); **^{19}F NMR** (377 MHz, MeOH-d_4) -117.9; **FTIR** (neat) ν = 3276, 2844, 1603, 1510, 1224, 1161, 1078, 1046, 886, 835, 759 cm^{-1}; **HRMS** (ESI$^+$) m/z Calcd. for $C_8H_{11}ONF$ $(M+H)^+$ 156.0820, found 156.0820; **[α]**$^{D}_{25}$ = +29.1 ° (*c* 1.0, MeOH).

(*R*)-2-amino-2-(2,4-dichlorophenyl)ethan-1-ol (AA4)



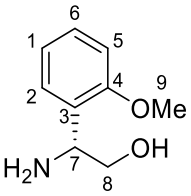
Prepared according to General Procedure J from 2,4-dichlorostyrene (1.72 g, 1.39 mL, 10.00 mmol). The final product was purified by recrystallisation from hot toluene and isolated as a white crystalline solid (26% over 4 steps, 534 mg). **M.P.** = 101-104 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.4 Hz, 1H, H1), 7.42 – 7.32 (m, 1H, H2), 7.32 – 7.25 (m, 1H, H5), 4.50 (dd, *J* = 7.6, 3.9 Hz, 1H, H7), 3.82 (dd, *J* = 10.8, 3.9 Hz, 1H, $H8_A$), 3.54 (dd, *J* = 10.8, 7.6 Hz, 1H, $H8_B$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.0 (C3), 133.7 (C6), 133.6 (C4), 129.5 (C5), 128.5 (C1), 127.4 (C2), 65.4 (C8), 52.5 (C7); **FTIR** (neat) ν = 3356, 3288, 2844, 1588, 1560, 1471, 1357, 1100, 1045, 868, 823, 753 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_8H_{10}ONCl_2$ $(M+H)^+$ 206.0134, found 206.0137; **[α]**$^{D}_{25}$ = –51.7 ° (*c* 1.0, MeOH).

(*R*)-2-amino-2-(3,5-bis(trifluoromethyl)phenyl)ethan-1-ol (AA5)



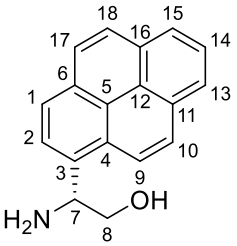
Prepared according to General Procedure J from 3,5-bis(trifluoromethyl)styrene (2.40 g, 1.81 mL, 10.00 mmol). The final product was purified by recrystallisation from hot toluene and isolated as a white crystalline solid (15% over 4 steps, 410 mg). **M.P.** = 95-97 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 1.6 Hz, 2H, H2 & H4), 7.82 (s, 1H, H6), 4.26 (dd, *J* = 7.5, 4.2 Hz, 1H, H9), 3.81 (dd, *J* = 10.7, 4.2 Hz, 1H, $H10_A$), 3.61 (dd, *J* = 10.7, 7.5 Hz, 1H, $H10_B$), 2.11 (bs, 2H, NH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.3 (C3), 131.8 (q, *J* = 33.3 Hz, C1 & C5), 127.0 (q, *J* = 4.1 Hz, C2 & C4), 123.3 (d, *J* = 272.5 Hz, C7 & C8), 121.5 (q, *J* = 3.8 Hz, C6), 67.7 (C10), 56.7 (C9); **^{19}F NMR** (377 MHz, $CDCl_3$) δ -62.8; **FTIR** (neat) ν = 3204, 2867, 1531, 1382, 1202, 1197, 904, 842 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{10}H_9F_6ONNa$ $(M+Na)^+$ 296.0481, found 296.0483; **[α]**$^{D}_{25}$ = –8.6 ° (*c* 1.0, MeOH). Data is in agreement with those previously reported.[146]

(*R*)-2-amino-2-(2-methoxyphenyl)ethan-1-ol (AA6)



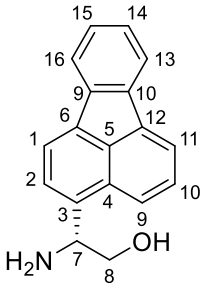
Prepared according to General Procedure J from 2-methoxystyrene (1.34 g, 1.34 mL, 10.00 mmol). The final product was purified by recrystallisation from hot toluene and isolated as a colourless oil (32% over 4 steps, 531 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35 – 7.21 (m, 2H, H2 & H6), 6.97 (td, *J* = 7.5, 1.1 Hz, 1H, H1), 6.89 (dd, *J* = 8.2, 1.1 Hz, 1H, H5), 4.30 (dd, *J* = 8.3, 4.3 Hz, 1H, H7), 3.84 (s, 3H, $H9_3$), 3.77 (dd, *J* = 10.6, 4.3 Hz, 1H, $H8_A$), 3.63 (dd, *J* = 10.6, 8.3 Hz, 1H, $H8_B$), 2.54 (bs, 2H, NH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.6 (C4), 132.8 (C3), 128.5 (C6), 126.5 (C2), 120.8 (C1), 110.7 (C5), 65.5 (C8), 55.3 (C9), 52.9 (C7); **FTIR** (neat) ν = 3355, 3290, 2837, 1600, 1492, 1463, 1439, 1290, 1240, 1049, 1028, 755 cm^{-1}; **HRMS** (ESI$^+$) m/z Calcd. for $C_9H_{14}O_2N$ $(M+H)^+$ 168.1019, found 168.1020; **[α]**$^D_{25}$ = –32.0 ° (*c* 1.0, MeOH).

(*R*)-2-amino-2-(pyren-1-yl)ethan-1-ol (AA7)



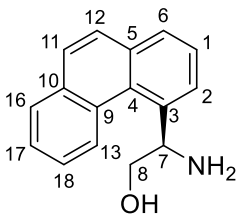
Prepared according to General Procedure J from 1-vinylpyrene (2.28 g, 10.00 mmol). [*N.B.* Step i) required the addition of methanesulfonamide (951 mg, 10.00 mmol, 1.00 equiv.) in order for the dihydroxylation to proceed.] The final product contained <5% of the corresponding amino alcohol as an impurity after recrystallisation from hot toluene, but no further purification was performed. Isolated as a white solid (23% over 4 steps, 601 mg). **M.P.** = 143-146 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 9.4 Hz, 1H, H13), 8.19 (dd, *J* = 7.9, 2.7 Hz, 3H, H15, H17 & H18), 8.14 (dd, *J* = 8.7, 4.5 Hz, 2H, H10 & H14), 8.09 – 7.98 (m, 3H, H1, H2 & H9), 5.22 (dd, *J* = 8.2, 4.2 Hz, 1H, H7), 4.02 (dd, *J* = 10.8, 4.2 Hz, 1H, $H8_A$), 3.80 (dd, *J* = 10.8, 8.3 Hz, 1H, $H8_B$), 1.97 (bs, 2H, NH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 136.2 (C3), 131.6 (C11), 130.8 (C4), 130.7 (C16), 128.3 (C12), 128.1 (C13), 127.6 (C15), 127.5 (C17), 126.2 (C18), 125.5 (C10), 125.2 (3C, C5, C9 & C14), 125.1 (C6), 123.2 (C2), 122.2 (C1), 68.1 (C8), 53.2 (C7); **FTIR** (neat) ν = 3347, 3279, 1419, 1309, 1207, 1034, 843, 718, 718, 681 cm^{-1}; **HRMS** (ESI$^+$) m/z Calcd. for $C_{18}H_{15}ONNa$ $(M+Na)^+$ 283.1046, found 284.1047; **[α]**$^D_{25}$ = –30.4 ° (*c* 0.2, MeOH).

(*R*)-2-amino-2-(fluoranthen-3-yl)ethan-1-ol (AA8)



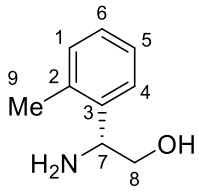
Prepared according to General Procedure J from 3-vinylfluoranthene (1.40 g, 6.13 mmol). [*N.B.* Step i) required the addition of methanesulfonamide (583 mg, 6.13 mmol, 1.00 equiv.) in order for the dihydroxylation to proceed.] The final product was purified by trituration with ice-cold CH_2Cl_2 and was isolated as a yellow solid (35% over 4 steps, 563 mg). **M.P.** = 129-134 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.4 Hz, 1H, H13), 7.99 – 7.80 (m, 4H, H9, H14, H15 & H16), 7.73 – 7.58 (m, 2H, H1 & H11), 7.45 – 7.28 (m, 2H, H2 & H10), 4.93 (dd, *J* = 8.0, 4.1 Hz, 1H, H7), 3.97 (dd, *J* = 10.8, 4.1 Hz, 1H, $H8_A$), 3.78 – 3.61 (m, 1H, $H8_B$), 2.04 (bs, 2H, NH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 139.6 (2C, C9 & C10), 139.2 (C3), 137.8 (C12), 136.7 (C6), 132.9 (C4), 128.4 (C5), 128.3 (C14), 127.8 (C15), 127.7 (C9), 124.8 (C1), 122.9 (C2), 121.6 (2C, C13 & C16), 120.2 (C10), 120.1 (C11), 68.2 (C8), 53.2 (C7); **FTIR** (neat) ν = 3352, 3055, 1589, 1441, 1303, 1211, 1047, 845, 777, 756, 742 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{18}H_{16}ON$ $(M+H)^+$ 262.1226, found 262.1227; **[α]**$^{D}_{25}$ = –55.7 ° (*c* 0.5, MeOH).

(*R*)-2-amino-2-(phenanthren-4-yl)ethan-1-ol (AA9)



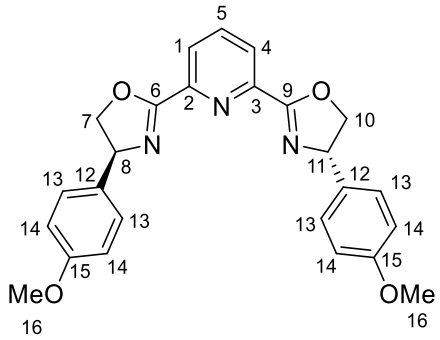
Prepared according to General Procedure J from 4-vinylphenanthrene (786 mg, 3.85 mmol). (26% over 4-steps, 575 mg). **M.P.** = 136-140 °C; **^{1}H NMR** (400 MHz, MeOH-d_4) δ 8.68 (dd, *J* = 7.4, 2.0 Hz, 1H, H13), 7.96 – 7.90 (m, 1H, H12), 7.84 (ddd, *J* = 13.5, 7.6, 1.4 Hz, 2H, H2 & H16), 7.70 (s, 2H, H6 & H11), 7.69 – 7.52 (m, 3H, H1, H17 & H18), 5.30 (d, *J* = 5.8 Hz, 1H, H7), 4.06 – 3.91 (m, 1H, $H8_A$), 3.87 (dd, *J* = 11.1, 8.4 Hz, 1H, $H8_B$); **^{13}C NMR** (101 MHz, MeOH-d_4) δ 133.7 (C3), 133.5 (C10), 129.7 (C5), 129.6 (C9), 128.2 (C4), 127.8 (2C, C6 & C16), 127.2 (C11), 126.6 (C12), 126.0 (2C, C17 & C18), 125.9 (C6), 125.8 (C1), 125.3 (C2), 67.7 (C8), 54.4 (C7); **FTIR** (neat) ν = 3290, 3049, 1594, 1455, 1381, 1163, 1045, 950, 867, 831, 831, 803, 745, 726 cm^1; **HRMS** (ESI^+) m/z Calcd. for $C_{16}H_{16}ON$ $(M+H)^+$ 238.1226, found 238.1228; **[α]**$^{D}_{25}$ = –35.1 ° (*c* 0.5, MeOH).

(*R*)-2-amino-2-(o-tolyl)ethan-1-ol (AA10)



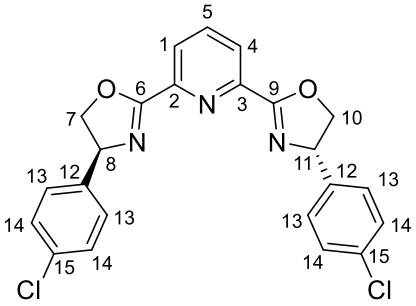
Prepared according to General Procedure J from 2-methylstyrene (1.18 g, 1.29 mL, 10.00 mmol). The final product was purified by recrystallisation from hot toluene and isolated as a white crystalline solid (44% over 4 steps, 659 mg). **M.P.** = 69-72 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 – 7.31 (m, 1H, H4), 7.25 – 7.07 (m, 3H, H1, H5 & H6), 4.30 (dd, *J* = 8.5, 4.0 Hz, 1H, H1), 3.69 (dd, *J* = 10.9, 4.0 Hz, 1H, $H8_A$), 3.51 (dd, *J* = 10.9, 8.5 Hz, 1H, $H8_B$), 2.59 (bs, 2H, NH_2), 2.36 (s, 3H, $H9_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.5 (C3), 135.4 (C2), 130.7 (C1), 127.3 (C6), 126.5 (C5), 125.3 (C4), 66.9 (C8), 53.1 (C7), 19.4 (C9); **FTIR** (neat) ν = 3351, 3287, 2993, 2858, 1578, 1489, 1461, 1361, 1050, 885, 756, 726 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_9H_{13}ONNa$ $(M+Na)^+$ 174.0889, found 174.0887; **[α]**$^{D}_{25}$ = –37.3 ° (*c* 1.0, MeOH).

2,6-bis((*S*)-4-(4-methoxyphenyl)-4,5-dihydrooxazol-2-yl)pyridine (L9B)



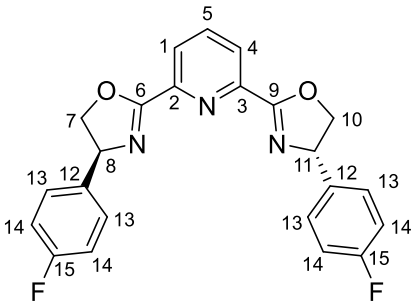
Prepared according to General Procedure K using dimethyl pyridine-2,6-bis(carbimidate) (**233**) (100 mg, 0.518 mmol) and (S)-2-amino-2-(4-methoxyphenyl)ethan-1-ol (**AA1**) (174 mg, 1.04 mmol). The crude product was purified by flash column chromatography [silica gel, 50-80% EtOAc in petroleum ether b.p. 40–60 °C + 1% NEt_3] then recrystallisation from hot EtOAc to afford the product as a white crystalline solid (33%, 74 mg). **M.P.** = 198-201 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.33 (d, *J* = 7.8 Hz, 2H, H1 & H4), 7.90 (t, *J* = 7.8 Hz, 1H, H5), 7.25 (dd, *J* = 8.8, 2.2 Hz, 4H, $H13_4$), 7.04 – 6.78 (m, 4H, $H14_4$), 5.41 (dd, *J* = 10.3, 8.5 Hz, 2H, H8 & H11), 4.89 (dd, *J* = 10.3, 8.6 Hz, 2H, $H7_A$ & $H10_A$), 4.40 (t, *J* = 8.6 Hz, 2H, $H7_B$ & $H10_B$), 3.80 (s, 6H, $H16_6$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.4 ($C15_2$), 159.4 (C6 & C9), 147.0 (C2 & C3), 137.5 (C5), 134.0 ($C12_2$), 128.2 ($C13_3$), 126.4 (C1 & C4), 114.4 ($C14_4$), 75.7 (C7 & C10), 70.0 (C8 & C11), 55.5 ($C16_2$); **FTIR** (neat) ν = 2966, 2897, 1641, 1614, 1512, 1461, 1377, 1305, 1250, 1179, 1106, 1030, 953, 825, 7445, 652 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{25}H_{24}O_4N_3$ $(M+H)^+$ 430.1761, found 430.1752; **[α]**$^{D}_{25}$ = –165.3 ° (*c* 1.0, $CHCl_3$).

2,6-bis((*S*)-4-(4-chlorophenyl)-4,5-dihydrooxazol-2-yl)pyridine (L9C)



Prepared according to General Procedure K using dimethyl pyridine-2,6-bis(carbimidate) (**233**) (100 mg, 0.518 mmol) and (*S*)-2-amino-2-(4-chlorophenyl)ethan-1-ol (**AA2**) (161 mg, 1.04 mmol). The crude product was purified by flash column chromatography [silica gel, 50-90% EtOAc in petroleum ether b.p. 40–60 °C + 1% NEt_3] then recrystallisation from hot EtOAc to afford the product as a white crystalline solid (67%, 153 mg). **M.P.** = 225-230 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 7.9 Hz, 2H, H1 & H4), 7.95 (t, *J* = 7.8 Hz, 1H, H5), 7.37 – 7.33 (m, 4H, $H13_4$), 7.30 – 7.24 (m, 4H, $H14_4$), 5.46 (dd, *J* = 10.3, 8.5 Hz, 2H, H8 & H11), 4.93 (dd, *J* = 10.4, 8.7 Hz, 2H, $H7_A$ & $H10_A$), 4.38 (t, *J* = 8.6 Hz, 2H, $H7_B$ & $H10_B$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.8 (C6 & C9), 146.7 (C2 & C3), 140.3 ($C12_2$), 137.7 (C5), 133.7 ($C15_2$), 129.1 ($C13_4$), 128.3 ($C14_4$), 126.5 (C1 & C4), 75.5 (C8 & C11), 69.8 (C7 & C10); **FTIR** (neat) ν = 2938, 1642, 1572, 1482, 1460, 1379, 1258, 1105, 1065, 1012, 949, 827, 754 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{23}H_{18}O_2N_3{}^{35}Cl_2$ $(M+H)^+$ 438.0770, found 438.0768; **[α]**$^{D}_{25}$ = –212.5 ° (*c* 1.0, $CHCl_3$).

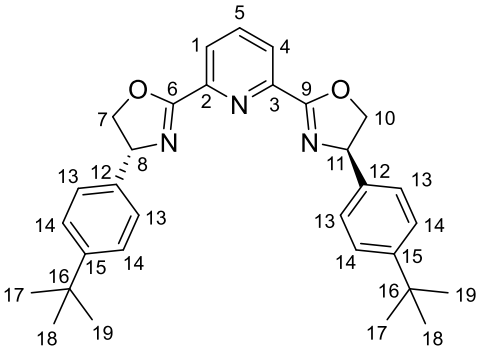
2,6-bis((*S*)-4-(4-fluorophenyl)-4,5-dihydrooxazol-2-yl)pyridine (L9D)



Prepared according to General Procedure K using dimethyl pyridine-2,6-bis(carbimidate) (**233**) (100 mg, 0.518 mmol) and (S)-2-amino-2-(4-fluorophenyl)ethan-1-ol (**AA3**) (178 mg, 1.04 mmol). The crude product was purified by flash column chromatography [silica gel, 50-70% EtOAc in petroleum ether b.p. 40–60 °C + 1% NEt_3] then recrystallisation from hot EtOAc to afford the product as a white crystalline solid (57%, 120 mg). **M.P.** = 179-182 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.33 (d, *J* = 7.9 Hz, 2H, H1 & H4), 7.92 (t, *J* = 7.9 Hz, 1H, H5), 7.28 (ddd, *J* = 10.2, 5.3, 2.6 Hz, 4H, $H13_4$), 7.10 – 6.94 (m, 4H, $H14_4$), 5.44 (dd, *J* = 10.3, 8.5 Hz, 2H, H8 & H11), 4.91 (dd, *J* = 10.4, 8.7 Hz, 2H, $H7_A$ & $H10_A$), 4.37 (t, *J* = 8.6 Hz, 2H, $H7_B$ & $H10_B$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.6 (C6 & C9), 162.4 (d, *J* = 224.5 Hz, $C15_2$), 146.8 (C2 & C3), 137.64 (C5), 137.60 (d, *J* = 3.5 Hz, $C12_2$),

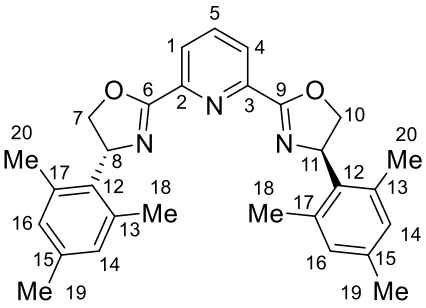
128.5 (d, *J* = 32.8 Hz, $C13_4$), 126.5 (C1 & C4), 115.8 (d, *J* = 21.5 Hz, $C14_4$), 75.6 (C8 & C11), 69.8 (C7 & C10); **^{19}F NMR** (377 MHz, $CDCl_3$) δ -114.6; **FTIR** (neat) ν = 2945, 1636, 1600, 1569, 1508, 1377, 1224, 1224, 1159, 1107, 975, 834 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{23}H_{18}O_2N_3F_2$ $(M+H)^+$ 406.1362, found 406.1358; **[α]**$^D_{25}$ = –175.3 ° (*c* 1.0, $CHCl_3$);

2,6-bis((*R*)-4-(4-(*tert*-butyl)phenyl)-4,5-dihydrooxazol-2-yl)pyridine (L9E)



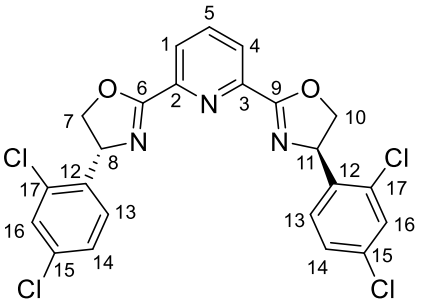
Prepared according to General Procedure K using dimethyl pyridine-2,6-bis(carbimidate) (**233**) (100 mg, 0.518 mmol) and (R)-2-amino-2-(4-(*tert*-butyl)phenyl)ethan-1-ol (**XL1**) (174 mg, 1.04 mmol). The crude product was purified by flash column chromatography [silica gel, 50-80% EtOAc in petroleum ether b.p. 40–60 °C + 1% NEt_3] then recrystallisation from hot EtOAc to afford the product as a white crystalline solid (33%, 74 mg). **M.P.** = 192-196 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.33 (d, *J* = 7.8 Hz, 2H, H1 & H4), 7.90 (t, *J* = 7.9 Hz, 1H, H5), 7.43 – 7.36 (m, 4H, $H13_4$), 7.30 – 7.23 (m, 4H, $H14_4$), 5.43 (dd, *J* = 10.3, 8.6 Hz, 2H, H8 & H11), 4.91 (dd, *J* = 10.3, 8.6 Hz, 2H, $H7_A$ & $H10_B$), 4.46 (t, *J* = 8.6 Hz, 2H, $H7_B$ & $H10_B$), 1.31 (s, 18H, $H17_6$, $H18_6$ & $H19_6$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.4 (C6 & C9), 150.9 (C2 & C3), 146.9 ($C15_2$), 138.7 ($C12_2$), 137.5 (C5), 126.8 ($C14_4$), 126.4 (C1 & C4), 125.9 ($C13_4$), 75.6 (C7 & C10), 70.2 (C8 & C11), 34.7 ($C16_2$), 31.5 ($C17_2$, $C18_2$ & $C19_2$); **FTIR** (neat) ν = 2962, 1639, 1572, 1511, 1474, 1462, 1411, 1380, 1363, 1267, 1107, 1076, 923, 831, 755, 697 cm^1; **HRMS** (ESI^+) m/z Calcd. for $C_{31}H_{36}O_2N_3$ $(M+H)^+$ 482.2802, found 482.2803; **[α]**$^D_{25}$ = +188.7 ° (*c* 0.45, $CHCl_3$).

2,6-bis((*R*)-4-mesityl-4,5-dihydrooxazol-2-yl)pyridine (L9F)



Prepared according to General Procedure K using dimethyl pyridine-2,6-bis(carbimidate) (**233**) (100 mg, 0.518 mmol) and (*R*)-2-amino-2-mesitylethan-1-ol (**XL2**) (186 mg, 1.04 mmol). The crude product was purified by flash column chromatography [silica gel, 30-50% EtOAc in petroleum ether b.p. 20-40 °C + 1% NEt_3] then recrystallisation from hot EtOH to afford the product as a white crystalline solid (40%, 95 mg). **M.P.** = 158-161 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 7.8 Hz, 2H, H1 & H4), 7.89 (t, *J* = 7.8 Hz, 1H, H5), 6.86 (s, 4H, $H14_2$ & $H16_2$), 5.87 (dd, *J* = 11.5, 10.5 Hz, 2H, H8 & H11), 4.89 (dd, *J* = 11.5, 8.6 Hz, 2H, $H7_A$ & $H10_A$), 4.41 (dd, *J* = 10.5, 8.6 Hz, 2H, $H7_B$ & $H10_B$), 2.33 (s, 12H, $H18_6$ & $H20_6$), 2.26 (s, 6H, $H19_6$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.1 (C6 & C9), 147.0 (C2 & C3), 137.6 ($C12_2$), 137.4 (C5), 137.1 ($C15_2$), 133.1 ($C13_2$ & $C17_2$), 130.5 ($C14_2$ & $C16_2$) 126.1 (C1 & C4), 73.0 (C7 & C10), 66.7 (C8 & C11), 20.9 ($C19_2$), 20.6 ($C18_2$ & $C20_2$); **FTIR** (neat) ν = 2971, 2917, 1642, 1571, 1484, 1463, 1377, 1267, 1104, 1076, 972, 919, 851, 754 cm^{-1}; **HRMS** (ESI$^+$) m/z Calcd. for $C_{29}H_{32}O_2N_3$ $(M+H)^+$ 454.2489, found 454.2488; **[α]**$^D_{25}$ = +243.0 ° (*c* 0.8, $CHCl_3$).

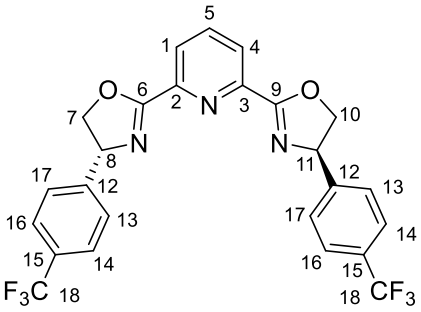
2,6-bis((*R*)-4-(2,4-dichlorophenyl)-4,5-dihydrooxazol-2-yl)pyridine (L9G)



Prepared according to General Procedure K using dimethyl pyridine-2,6-bis(carbimidate) (**233**) (100 mg, 0.518 mmol) and (*R*)-2-amino-2-(2,4-dichlorophenyl)ethan-1-ol (**AA4**) (205 mg, 1.04 mmol). The crude product was purified by flash column chromatography [silica gel, 40–60% EtOAc in petroleum ether b.p. 40–60 °C + 1% NEt_3] then recrystallisation from hot EtOH to afford the product as a white crystalline solid (65%, 168 mg). **M.P.** = 184-187 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 7.8 Hz, 2H, H1 & H4), 7.92 (dd, *J* = 8.7, 7.1 Hz, 1H, H5), 7.40 – 7.28 (m, 4H, $H14_2$ & $H16_2$), 7.20 – 7.14 (m, 2H, $H13_2$), 5.68 (dd, *J* = 10.5, 8.6 Hz, 2H, H8 & H11), 4.99 (dd, *J* = 10.5, 8.7 Hz, 2H, $H7_A$ & $H10_A$), 4.16 (t, *J* = 8.7 Hz, 2H, $H7_B$ & $H10_B$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.5 (C6

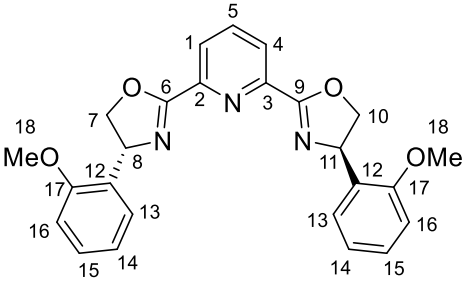
& C9), 146.8 (C2 & C3), 138.8 ($C12_2$), 137.8 (C5), 134.1 ($C17_2$), 133.0 ($C15_2$), 129.3 ($C16_2$), 128.9 ($C14_2$), 127.6 ($C13_2$), 126.6 (C1 & C4), 74.9 (C8 & C11), 67.1 (C7 & C10); **FTIR** (neat) ν = 2980, 1643, 1588, 1560, 1471, 1384, 1251, 1137, 1109, 1078, 970, 922, 866, 823, 754 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. $C_{23}H_{16}O_2N_3Cl_4$ $(M+H)^+$ 507.9962, found 507.9960; **[α]**$^{D}_{25}$ = –74.0 ° (*c* 0.3, $CHCl_3$).

2,6-bis((*R*)-4-(4-(trifluoromethyl)phenyl)-4,5-dihydrooxazol-2-yl)pyridine (L9H)



Prepared according to General Procedure K using dimethyl pyridine-2,6-bis(carbimidate) (**233**) (100 mg, 0.518 mmol) and (*R*)-2-amino-2-(4-(trifluoromethyl)phenyl)ethan-1-ol (**XL4**) (224 mg, 1.04 mmol). The crude product was purified by flash column chromatography [silica gel, 30-60% EtOAc in petroleum ether b.p. 40–60 °C + 1% NEt_3] then recrystallisation from hot EtOAc to afford the product as a white crystalline solid (67%, 176 mg). **M.P.** = 112-116 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.34 (d, *J* = 7.8 Hz, 2H, H1 & H4), 7.95 (t, *J* = 7.8 Hz, 1H, H5), 7.62 (d, *J* = 8.0 Hz, 4H, $H13_{2\ \&}$ $H17_2$), 7.45 (d, *J* = 8.0 Hz, 4H, $H14_2$ & $H16_2$), 5.53 (dd, *J* = 10.4, 8.6 Hz, 2H, H8 & H11), 4.96 (dd, *J* = 10.4, 8.7 Hz, 2H, $H7_A$ & $H10_A$), 4.39 (t, *J* = 8.7 Hz, 2H, $H7_B$ & $H10_B$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.1 (C6 & C9), 146.7 (C2 & C3), 145.7 ($C12_2$), 137.8 (C5), 130.2 (q, *J* = 32.5 Hz, $C14_2$ & $C16_2$), 127.3 ($C15_2$), 126.6 (C1 & C4), 125.9 (q, *J* = 3.7 Hz, $C13_2$ & $C17_2$), 124.2 (q, *J* = 272.3 Hz, $C18_2$), 75.3 (C7 & C10), 70.0 (C8 & C11); **^{19}F NMR** (377 MHz, $CDCl_3$) δ -62.6. **FTIR** (neat) ν = 2919, 1641, 1574, 1460, 1325, 1263, 1164, 1121, 1068, 1018, 840, 755 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{25}H_{18}O_2N_3F_6$ $(M+H)^+$ 506.1298, found 506.1298; **[α]**$^{D}_{25}$ = +100.6° (*c* 0.3, $CHCl_3$).

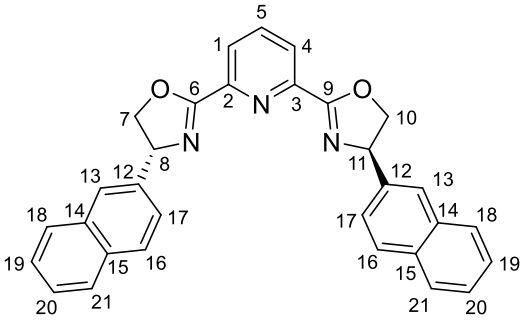
2,6-bis((*R*)-4-(2-methoxyphenyl)-4,5-dihydrooxazol-2-yl)pyridine (L9I)



Prepared according to General Procedure K using dimethyl pyridine-2,6-bis(carbimidate) (**233**) (75 mg, 0.39 mmol) and (*R*)-2-amino-2-(2-methoxyphenyl)ethan-1-ol (**AA6**) (130 mg, 0.78 mmol). The crude product was purified by flash column chromatography [silica gel, 50-80% EtOAc in

petroleum ether b.p. 40–60 °C + 1% NEt_3] then recrystallisation from hot EtOH to afford the product as a white crystalline solid (86%, 143 mg). **M.P.** = 200-205 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 7.8 Hz, 2H, H1 & H4), 7.94 (t, *J* = 7.9 Hz, 1H, H5), 7.41 – 7.35 (m, 2H, $H15_2$), 7.26 (td, *J* = 7.8, 1.8 Hz, 2H, $H13_2$), 6.95 (td, *J* = 7.5, 1.1 Hz, 2H, $H14_2$), 6.89 (dd, *J* = 8.2, 1.1 Hz, 2H, $H16_2$), 5.70 (dd, *J* = 10.5, 8.9 Hz, 2H, H8 & H11), 4.97 (dd, *J* = 10.5, 8.5 Hz, 2H, $H7_A$ & $H10_A$), 4.24 (t, *J* = 8.7 Hz, 2H, $H7_B$ & $H10_B$), 3.85 (s, 6H, $H18_6$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.7 (C6 & C9), 156.4 ($C17_2$), 147.1 (C2 & C3), 137.5 (C5), 130.8 ($C12_2$), 128.6 ($C13_2$), 127.1 ($C15_2$), 126.2 (C1 & C4), 120.9 ($C14_2$), 110.2 ($C16_2$), 75.5 (C7 & C10), 65.2 (C8 & C11), 55.5 ($C18_2$); **FTIR** (neat) ν = 2964, 1645, 1587, 1573, 1491, 1462, 1438, 1380, 1241, 1173, 1173, 1108, 1077, 1047, 1028, 968, 754 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{25}H_{24}O_4N_3$ $(M+H)^+$ 430.1761, found 430.1762; **[α]**$^{D}_{25}$ = –50.3 ° (*c* 0.5, $CHCl_3$).

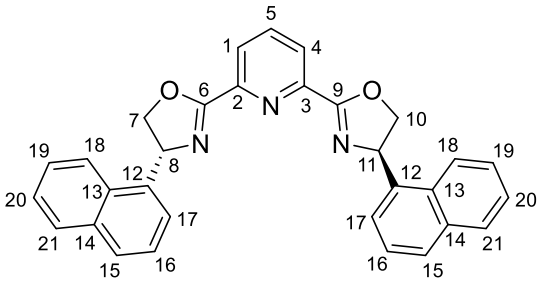
2,6-bis((*R*)-4-(naphthalen-2-yl)-4,5-dihydrooxazol-2-yl)pyridine (L9J)



Prepared according to General Procedure K using dimethyl pyridine-2,6-bis(carbimidate) (**233**) (100 mg, 0.518 mmol) and (*R*)-2-amino-2-(naphthalen-2-yl)ethan-1-ol (**XL6**) (204 mg, 1.04 mmol). The crude product was purified by flash column chromatography [silica gel, 50-80% EtOAc in petroleum ether b.p. 40–60 °C + 1% NEt_3] then recrystallisation from hot EtOH to afford the product as a white crystalline solid (65%, 158 mg). **M.P.** = 204-208 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 7.9 Hz, 2H, H1 & H4), 7.96 (t, *J* = 7.8 Hz, 1H, H5), 7.89 – 7.80 (m, 8H, $H13_2$, $H16_2$, $H18_2$ & $H21_2$), 7.52 – 7.45 (m, 4H, $H19_2$ & $H20_2$), 7.43 (dd, *J* = 8.5, 1.8 Hz, 2H, $H17_2$), 5.65 (dd, *J* = 10.3, 8.5 Hz, 2H, H8 & H11), 5.01 (dd, *J* = 10.4, 8.7 Hz, 2H, $H7_A$ & $H10_A$), 4.52 (t, *J* = 8.6 Hz, 2H, $H7_B$ & $H10_B$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.8 (C6 & C9), 147.0 (C2 & C3), 139.1 ($C12_2$), 137.7 (C5), 133.5 ($C14_2$), 133.1 ($C15_2$), 129.0 ($C17_2$), 128.1 ($C21_2$), 127.8 ($C18_2$), 126.6 ($C16_2$), 126.4 (C1 & C4), 126.2 ($C13_2$), 125.9 ($C19_2$), 124.8 ($C20_2$), 75.6 (C7 & C10), 70.7 (C8 & C11); **FTIR** (neat) ν = 3053, 1642, 1568, 1474, 1461, 1375, 1263, 1102,

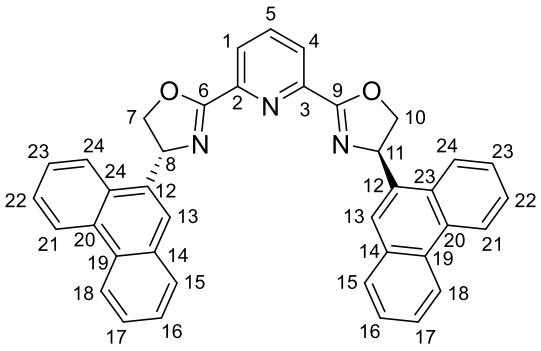
1070, 1037, 974, 925, 831, 754, 740 cm^{1}; **HRMS** (ESI^{+}) m/z Calcd. for $C_{31}H_{24}O_2N_3$ $(M+H)^+$ 470.1863, found 470.1863; **[α]**$^{D}_{25}$ = +245.0 ° (*c* 1.0, $CHCl_3$).

2,6-bis((R)-4-(naphthalen-1-yl)-4,5-dihydrooxazol-2-yl)pyridine (L9K)



Prepared according to General Procedure K using dimethyl pyridine-2,6-bis(carbimidate) (**233**) (426 mg, 2.20 mmol) and (R)-2-amino-2-(naphthalen-1-yl)ethan-1-ol (**XL7**) (826 mg, 4.40 mmol). The crude product was twice recrystallised from hot EtOH to afford the product as a white crystalline solid (78%, 804 mg). **M.P.** = 228-230 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.48 (d, *J* = 7.9 Hz, 2H, H1 & H4), 8.01 (t, *J* = 7.9 Hz, 1H, H5), 7.89 (ddd, *J* = 17.0, 7.9, 1.3 Hz, 4H, $H18_2$ & $H21_2$), 7.81 (d, *J* = 8.2 Hz, 2H, $H15_2$), 7.63 – 7.50 (m, 6H, $H16_2$, $H19_2$ & $H20_2$), 7.48 (dd, *J* = 8.2, 7.2 Hz, 2H, $H17_2$), 6.31 – 6.11 (m, 2H, H8 & H11), 5.19 (dd, *J* = 10.5, 8.5 Hz, 2H, $H7_A$ & $H10_A$), 4.37 (t, *J* = 8.6 Hz, 2H, $H7_B$ & $H10_B$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.9 (C6 & C9), 147.0 (C2 & C3), 138.1 (C5), 137.7 ($C12_2$), 134.0 ($C14_2$), 130.7 ($C13_2$), 129.2 ($C21_2$), 128.2 ($C15_2$), 126.6 (C1, C4 & $C16_2$), 125.9 ($C18_2$ & $C19_2$), 123.7 ($C20_2$), 122.9 ($C17_2$), 75.4 (C7 & C10), 67.1 (C8 & C11); **FTIR** (neat) ν = 3056, 2928, 1646, 1574, 1510, 1397, 1258, 1108, 1077, 978, 918, 800 778, 753 cm^{1}; **HRMS** (ESI^{+}) m/z Calcd. for $C_{31}H_{24}O_2N_3$ $(M+H)^+$ 470.1863, found 470.1864; **[α]**$^{D}_{25}$ = –232.8 ° (*c* 1.0, $CHCl_3$).

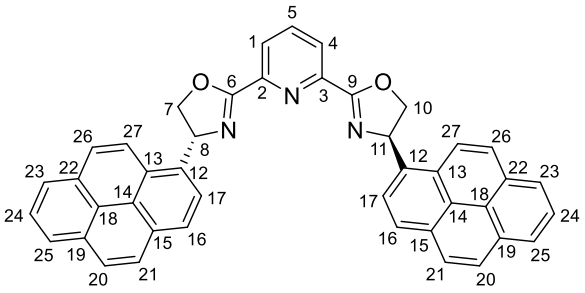
2,6-bis((*R*)-4-(phenanthren-9-yl)-4,5-dihydrooxazol-2-yl)pyridine (L9L)



Prepared according to General Procedure K using dimethyl pyridine-2,6-bis(carbimidate) (**233**) (50 mg, 0.259 mmol) and (*R*)-2-amino-2-(phenanthren-9-yl)ethan-1-ol (**XL8**) (123 mg, 0.518 mmol). The crude product was purified by hot filtration from EtOH to afford the product as a white solid (68%, 100 mg). **M.P.** = 288-290 °C; **^{1}H NMR** (600 MHz, DMSO-d_6) δ 8.95 (dd, *J* = 7.8, 2.0 Hz, 2H, $H21_2$), 8.85 (d, *J* = 7.9 Hz, 2H, $H18_2$),

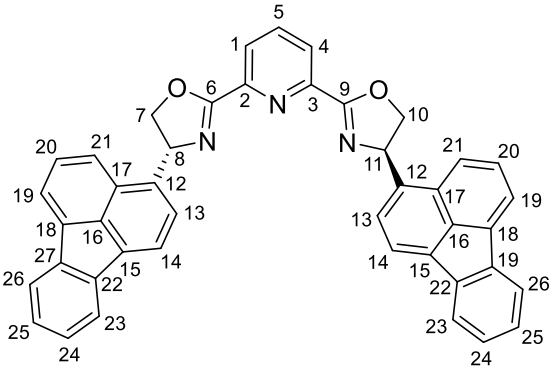
8.50 (d, *J* = 7.9 Hz, 2H, H1 & H4), 8.27 (t, *J* = 7.8 Hz, 1H, H5), 8.13 (dd, *J* = 7.7, 1.8 Hz, 2H, $H24_2$), 8.01 (dd, *J* = 7.9, 1.4 Hz, 2H, $H15_2$), 7.86 (s, 2H, $H13_2$), 7.81 – 7.73 (m, 4H, $H17_2$ & $H22_2$), 7.70 (ddd, *J* = 8.4, 7.0, 1.4 Hz, 2H, $H16_2$), 7.64 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 2H, $H23_2$), 6.28 (t, *J* = 9.5 Hz, 2H, H8 & H11), 5.33 (dd, *J* = 10.5, 8.4 Hz, 2H, $H7_A$ & $H10_A$), 4.28 (t, *J* = 8.5 Hz, 2H, $H7_B$ & $H10_B$); **^{13}C NMR** (151 MHz, DMSO-*d*$_6$) δ 163.5 (C6 & C9), 146.8 (C2 & C3), 139.0 (C5), 137.4 ($C12_2$), 131.5 ($C14_2$), 130.8 ($C20_2$), 129.9 ($C23_2$), 129.1 ($C15_2$), 127.7 ($C16_2$), 127.5 ($C17_2$), 127.3 (2C, $C22_2$ & $C23_2$), 127.0 (C1 & C4), 124.6 ($C13_2$), 124.1 ($C18_2$), 123.8 ($C21_2$), 123.2 ($C24_2$), 74.7 (C7 & C10), 66.8 (C8 & C11); **FTIR** (neat) ν = 3026, 2986, 1635, 1570, 1462, 1382, 1106, 770, 744, 722 cm^{-1}; **HRMS** (ESI$^+$) m/z Calcd. for $C_{39}H_{28}N_3O_2$ $(M+H)^+$ 570.2176, found 570.2173; **[α]$^D_{25}$** = –0.6° (*c* 0.05, $CHCl_3$).

2,6-bis((*R*)-4-(pyren-1-yl)-4,5-dihydrooxazol-2-yl)pyridine (L9M)



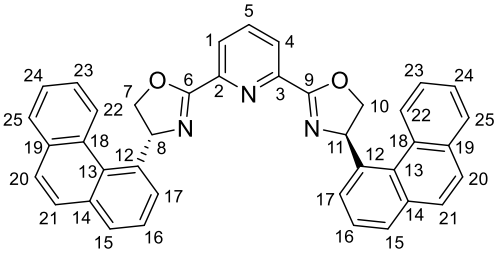
Prepared according to General Procedure K using dimethyl pyridine-2,6-bis(carbimidate) (**233**) (50 mg, 0.259 mmol) and (*R*)-2-amino-2-(pyren-1-yl)ethan-1-ol (**AA7**) (135 mg, 0.518 mmol). The crude product was purified by hot filtration from EtOH to afford the product as a white solid (77%, 124 mg). **M.P.** = 284-289 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.57 (d, *J* = 7.8 Hz, 2H, $H25_2$), 8.25 – 8.11 (m, 11H, H1, H4, H5, $H23_2$, $H25_2$, $H20_2$, $H21_2$), 8.11 – 8.01 (m, 8H, $H17_2$, $H24_2$, $H26_2$ & $H27_2$), 6.56 (t, *J* = 9.7 Hz, 2H, H8 & H11), 5.33 (dd, *J* = 10.6, 8.5 Hz, 2H, $H7_A$ & $H10_A$), 4.51 (t, *J* = 8.7 Hz, 2H, $H7_B$ & $H10_B$); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 163.9 (C6 & C9), 147.0 (C2 & C3), 138.3 (C5), 137.7 ($C12_2$), 135.6 ($C19_2$), 131.4 ($C15_2$), 130.8 ($C25_2$), 130.7 ($C24_2$), 128.2 ($C20_2$), 127.8 ($C21_2$), 127.5 ($C23_2$), 127.3 ($C17_2$), 126.6 ($C22_2$), 126.1 (C1 & C4), 125.5 ($C16_2$), 125.3 ($C18_2$), 125.2 ($C14_2$), 125.0 ($C12_2$), 123.9 ($C27_2$), 75.7 (C7 & C10), 67.3 (C8 & C11); **FTIR** (neat) ν = 3043, 1646, 1573, 1459, 1381, 1264, 1244, 1107, 979, 846, 826, 754 cm^{-1}; **HRMS** (ESI$^+$) m/z Calcd. for $C_{43}H_{28}O_2N_3$ $(M+H)^+$ 618.2176, found 618.2176; **[α]$^D_{25}$** = –136.2 ° (*c* 0.15, $CHCl_3$).

2,6-bis((*R*)-4-(fluoranthen-3-yl)-4,5-dihydrooxazol-2-yl)pyridine (L9N)



Prepared according to General Procedure K using dimethyl pyridine-2,6-bis(carbimidate) (**233**) (30 mg, 0.153 mmol) and (*R*)-2-amino-2-(fluoranthen-3-yl)ethan-1-ol (**AA8**) (80 mg, 0.306 mmol). The crude product was purified by recrystallisation from hot EtOH to afford the product as a yellow solid (86%, 81 mg). **M.P.** = 272-276 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.51 (d, *J* = 7.9 Hz, 2H, H1 & H4), 8.04 (t, *J* = 7.8 Hz, 1H, H5), 7.96 (d, *J* = 6.9 Hz, 2H, $H21_2$), 7.89 (dd, *J* = 7.9, 5.8 Hz, 8H, $H23_2$, $H24_2$, $H25_2$ & $H26_2$), 7.68 (d, *J* = 7.2 Hz, 4H, $H19_2$ & $H20_2$), 7.46 – 7.32 (m, 4H, $H13_2$ & $H14_2$), 6.26 (t, *J* = 9.7 Hz, 2H, H8 & H11), 5.26 – 5.14 (m, 2H, $H7_A$ & $H10_A$), 4.53 (t, *J* = 8.7 Hz, 2H, $H7_B$ & $H10_B$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.0 (C6 & C9), 147.0 (C2 & C3), 139.6 ($C22_2$), 139.3 ($C27_2$), 138.6 (4C, $C17_2$ & $C18_2$), 137.8 ($C16_2$), 137.1 (C5), 133.0 ($C12_2$), 128.5 ($C24_2$), 128.1 ($C15_2$), 127.9 ($C25_2$), 127.8 ($C14_2$), 126.7 (C1 & C4), 125.8 ($C21_2$), 122.8 ($C20_2$), 121.7 (4C, $C13_2$ & $C23_2$), 120.3 ($C26_2$), 120.2 ($C19_2$), 75.7 (C8 & C11), 67.2 (C7 & C10); **FTIR** (neat) ν = 3056, 2904, 1638, 1570, 1491, 1473, 1452, 1441, 1380, 1335, 1262, 1240, 1154, 1106, 1073, 934, 847, 779, 756 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{42}H_{28}O_2N_3$ $(M+H)^+$ 618.2176, found 618.2174; **[α]**$^{D}_{25}$ = +90.9° (*c* 0.15, $CHCl_3$).

2,6-bis((*R*)-4-(phenanthren-4-yl)-4,5-dihydrooxazol-2-yl)pyridine (L9M)

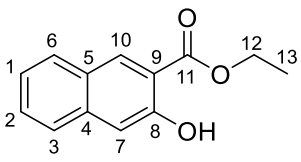


Prepared according to General Procedure K using dimethyl pyridine-2,6-bis(carbimidate) (**233**) (50 mg, 0.259 mmol) and (*R*)-2-amino-2-(phenanthren-4-yl)ethan-1-ol (**AA9**) (122.9 mg, 0.518 mmol). The crude product was purified by flash column chromatography [silica gel, 40–60% EtOAc in petroleum ether b.p. 40–60 °C + 1% NEt_3] then recrystallisation from hot EtOH to afford the product as a white crystalline solid (66%, 97 mg). **M.P.** = 228-230 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.71 (d, *J* = 8.2 Hz, 2H, $H22_2$), 8.46 (d, *J* = 7.9 Hz, 2H, $H25_2$), 8.00 – 7.92 (m, 3H, H5 & $H21_2$), 7.83

(t, *J* = 7.2 Hz, 4H, H1, H4 & $H17_2$), 7.78 – 7.56 (m, 10H, $H15_2$, $H16_2$, $H20_2$, $H23_2$ & $H24_2$), 6.81 – 6.54 (m, 2H, H8 & H11), 5.21 (t, *J* = 9.6 Hz, 2H, $H7_A$ & $H10_A$), 4.72 (t, *J* = 8.2 Hz, 2H, $H7_B$ & $H10_B$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.3 (C6 & C9), 147.1 (C2 & C3), 139.4 ($C12_2$), 137.7 (C5), 133.8 ($C19_2$), 133.5 ($C14_2$), 129.9 ($C18_2$), 129.4 ($C13_2$), 128.9 ($C25_2$), 128.7 ($C21_2$), 127.8 ($C24_2$), 127.6 ($C20_2$), 127.3 ($C23_2$), 127.2 ($C16_2$), 126.7 (C1 & C4), 126.6 (2C, $C15_2$ & $C16_2$), 126.1 ($C22_2$), 76.6 (C7 & C10), 69.3 (C8 & C11); **FTIR** (neat) ν = 2981, 2892, 1638, 1571, 1457, 1383, 1257, 1113, 1077, 970, 831, 743, 726 cm^{1}; **HRMS** (ESI^{+}) m/z Calcd. for $C_{39}H_{28}N_3O_2$ $(M+H)^+$ 570.2176, found 570.2175; **[α]**$^{D}_{25}$ = –141.9 ° (*c* 0.5, $CHCl_3$).

9.5.4 Naphthol Substrates

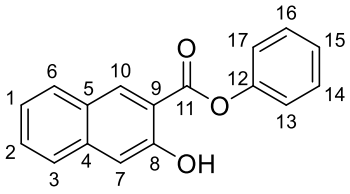
Ethyl 3-hydroxy-2-naphthoate (221)



The procedure is based on a modified literature method.[147] 3-Hydroxy-2-naphthoic acid (**220**) (2.00 g, 10.63 mmol, 1.00 equiv.) was suspended in EtOH (20 mL) and conc. H_2SO_4 (1 mL) was added. The reaction mixture was then heated to reflux for 48 h. After this time, the mixture was cooled to room temperature and the solvent was removed *in vacuo*. The residue was then dissolved in EtOAc (20 mL) and basified with sat. $NaHCO_{3(aq.)}$ (50 mL). The layers were separated, and the aqueous phase was extracted three times with EtOAc. The organic extracts were pooled, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography [silica gel, 50% CH_2Cl_2 in petroleum ether b.p. 40–60 °C] to afford the product as a yellow solid (86%, 1.98 g). **M.P.** = 69-72 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.53 (s, 1H, OH), 8.49 (s, 1H, H10), 7.81 (dd, *J* = 8.3, 1.1 Hz, 1H, H3), 7.72 – 7.63 (m, 1H, H6), 7.49 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H, H1), 7.36 – 7.28 (m, 2H, H2 & H7), 4.49 (q, *J* = 7.1 Hz, 2H, $H12_2$), 1.48 (t, *J* = 7.1 Hz, 3H, $H13_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.0 (C11), 156.5 (C8), 138.0 (C4), 132.5 (C10), 129.3 (C3), 129.2 (C1), 127.2 (C5), 126.4 (C6), 124.0 (C2), 114.6 (C9), 111.8 (C7), 61.9 (C12), 14.4 (C13); **FTIR** (neat) ν = 3225, 1677, 1634, 1514, 1462, 1420, 1371, 1281, 1210, 1170,

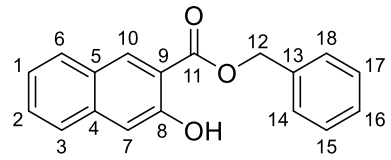
1145, 1072, 1014, 915, 870, 788, 745, 693, 624 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{13}H_{13}O_3$ $(M+H)^+$ 217.0860, found 217.0859.

Phenyl 3-hydroxy-2-naphthoate (222)



To a suspension of 3-hydroxy-2-naphthoic acid (**220**) (6.00 g, 31.88 mmol, 1.00 equiv.) and phenol (4.5 g, 47.83 mmol, 1.50 equiv.) in toluene (40 mL), $POCl_3$ (1.95 g, 1.91 mL, 12.75 mmol, 0.40 equiv.) was slowly added. The mixture was then heated to reflux for 48 h and after the allotted time, the reaction was cooled to room temperature, diluted with Et_2O (60 mL) and quenched by the slow addition of sat. $Na_2CO_{3\,(aq.)}$ (100 mL). The layers were separated, and the product was further extracted three times with Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography [silica gel, 2-5% EtOAc in petroleum ether b.p. 40–60 °C] to afford the product as a yellow solid (80%, 6.72 g). **M.P.** = 116-120 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.18 (s, 1H, OH), 8.78 (s, 1H, H10), 7.90 (dd, *J* = 8.4, 1.1 Hz, 1H, H3), 7.75 (dd, *J* = 8.4, 1.0 Hz, 1H, H6), 7.57 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H, H1), 7.55 – 7.49 (m, 2H, H14 & H16), 7.43 – 7.35 (m, 3H, H13, H15 & H17), 7.33 – 7.28 (m, 2H, H2 & H7); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.8 (C11), 156.6 (C8), 150.3 (C12), 138.5 (C4), 133.3 (C10), 129.9 (C14 & C16), 129.7 (C3), 129.5 (C1), 127.3 (C5), 126.7 (C15), 126.6 (C6), 124.3 (C2), 121.8 (C13 & C17), 113.8 (C9), 112.2 (C7); **FTIR** (neat) ν = 3227, 1690, 1513, 1486, 1462, 1415, 1323, 1284, 1205, 1185, 1144, 1046, 907, 874, 781, 747, 690 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{17}H_{13}O_3$ $(M+H)^+$ 265.0860, found 265.0859.

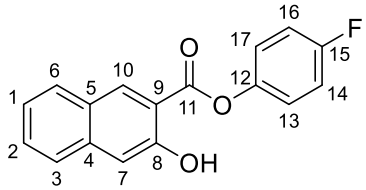
Benzyl 3-hydroxy-2-naphthoate (223)



The procedure is based on a modified literature method.[82] 3-Hydroxy-2-naphthoic acid (**220**) (2.00 g, 10.63 mmol, 1.00 equiv.) and K_2CO_3 (735 mg, 5.32 mmol, 0.50 equiv.) were dissolved in DMF (5 mL) and the mixture was stirred for 1 h at room temperature. At this temperature, benzyl bromide (2.18 g, 1.52 mL, 12.76 mmol, 1.20 equiv.) was added and the

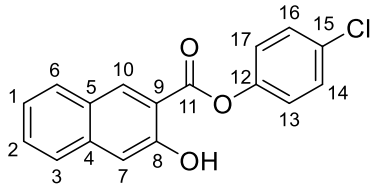
reaction was stirred for a further 24 h. The contents were then diluted with water (50 mL) and the product was extracted three times with EtOAc. The combined organic extracts were washed five times with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography [silica gel, 40% CH_2Cl_2 in petroleum ether b.p. 40–60 °C] to afford the product as a yellow solid (90%, 2.66 g). **M.P.** = 76-81 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.44 (s, 1H, OH), 8.53 (s, 1H, H10), 7.79 (dd, *J* = 8.3, 1.1 Hz, 1H, H3), 7.68 (dd, *J* = 8.4, 1.0 Hz, 1H, H6), 7.54 – 7.37 (m, 6H, H1, H14, H15, H16, H17 & H18), 7.36 – 7.28 (m, 2H, H2 & H7), 5.47 (s, 2H, $H12_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.8 (C11), 156.5 (C8), 138.1 (C4), 135.3 (C13), 132.6 (C10), 129.4 (C3), 129.3 (C1), 128.9 (C14 & C18), 128.8 (C16), 128.6 (C15 & C17), 127.2 (C5), 126.5 (C6), 124.1 (C2), 114.3 (C9), 111.9 (C7), 67.5 (C12); **FTIR** (neat) ν = 3225, 1677, 1634, 1514, 1462, 1420, 1371, 1281, 1210, 1170, 1145, 1072, 1014, 915, 870, 788, 745, 693, 624 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{18}H_{15}O_3$ $(M+H)^+$ 279.1016, found 279.1016;

4-fluorophenyl 3-hydroxy-2-naphthoate (261)



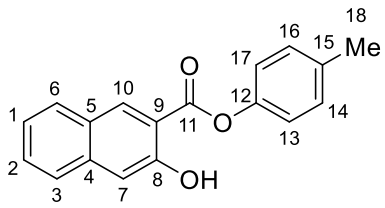
The title compound was prepared according to General Procedure P using 3-hydroxy-2-naphthoic acid (**220**) (1.00 g, 5.31 mmol) and 4-fluorophenol (715 mg, 6.37 mmol). The crude product was purified by flash column chromatography [silica gel, 5-10% EtOAc in petroleum ether b.p. 40–60 °C] to afford the product as a yellow solid (67%, 1.01 g). **M.P.** = 108-110 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.09 (s, 1H, OH), 8.75 (s, 1H, H10), 7.89 (dd, *J* = 8.4, 1.1 Hz, 1H, H3), 7.75 (dd, *J* = 8.5, 1.1 Hz, 1H, H6), 7.57 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H, H1), 7.43 – 7.36 (m, 2H, H2 & H7), 7.31 – 7.24 (m, 2H, H13 & H17), 7.24 – 7.15 (m, 2H, H14 & H16); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.7 (C11), 160.8 (d, *J* = 245.5 Hz, C15), 156.6 (C8), 146.1 (d, *J* = 3.1 Hz, C12), 138.5 (C4) , 133.3 (C10), 129.8 (C3), 129.5 (C1), 127.3 (C5), 126.5 (C6), 124.4 (C2), 123.3 (d, *J* = 8.6 Hz, C13 & C17), 116.5 (d, *J* = 23.5 Hz, C14 & C16), 113.5 (C9), 112.2 (C7); **^{19}F NMR** (377 MHz, $CDCl_3$) δ -115.8; **FTIR** (neat) ν = 3279, 3058, 1693, 1637, 1501, 1461, 1409, 1320, 1282, 1204, 1177, 1144, 1130, 1044, 874, 780, 747 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{17}H_{12}O_3F$ $(M+H)^+$ 283.0765, found 283.0766.

4-chlorophenyl 3-hydroxy-2-naphthoate (262)



The title compound was prepared according to General Procedure P using 3-hydroxy-2-naphthoic acid (**220**) (1.00 g, 5.31 mmol) and 4-chlorophenol (820 mg, 5.83 mmol). The crude product was purified by flash column chromatography [silica gel, 5-10% EtOAc in petroleum ether b.p. 40–60 °C] to afford the product as a yellow solid (78%, 1.23 g). **M.P.** = 98-100 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.01 (s, 1H, OH), 8.76 – 8.69 (m, 1H, H10), 7.93 – 7.82 (m, 1H, H3), 7.73 (dd, *J* = 8.5, 1.0 Hz, 1H, H6), 7.55 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H, H7), 7.49 – 7.43 (m, 2H, H1 & H2), 7.41 – 7.33 (m, 2H, H14 & H16), 7.29 – 7.17 (m, 2H, H13 & H17); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.1 (C11), 157.9 (C8), 156.6 (C12), 143.7 (C4), 138.4 (C10), 133.2 (C15), 129.7 (C14 & C16), 129.5 (C6), 127.3 (C2), 126.5 (C13 & C17), 124.3 (C5), 122.5 (C3), 114.9 (C1), 113.9 (C9), 112.1 (C7); **FTIR** (neat) ν = 3309, 2981, 1692, 1637, 1512, 1488, 1462, 1404, 1320, 1285, 1207, 1145, 1044, 1014, 826, 741 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{17}H_{12}O_3Cl$ $(M+H)^+$ 299.0469, found 299.0469.

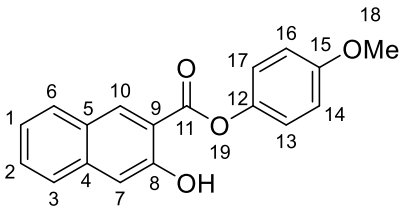
***p*-tolyl 3-hydroxy-2-naphthoate (256)**



The title compound was prepared according to General Procedure P using 3-hydroxy-2-naphthoic acid (**220**) (1.00 g, 5.31 mmol) and *p*-cresol (630 mg, 610 µL, 5.83 mmol). The crude product was purified by flash column chromatography [silica gel, 5% EtOAc in petroleum ether b.p. 40–60 °C] to afford the product as a yellow solid (84%, 1.24 g). **M.P.** = 86-88 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.20 (s, 1H, OH), 8.77 (s, 1H, H10), 7.94 – 7.86 (m, 1H, H3), 7.80 – 7.72 (m, 1H, H6), 7.57 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H, H1), 7.44 – 7.34 (m, 2H, H2 & H7), 7.30 (dd, *J* = 7.0, 4.9 Hz, 2H, H14 & H16), 7.22 – 7.10 (m, 2H, H13 & C17), 2.43 (s, 3H, $H18_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.0 (C11), 156.7 (C8), 148.1 (C12), 138.4 (C4), 136.4 (C15), 133.3 (C10), 130.4 (C14 & C16), 129.7 (C3), 129.5 (C1), 127.3 (C15), 126.5 (C5), 124.3 (C6), 121.5 (C13 & C17), 113.9 (C2), 112.1

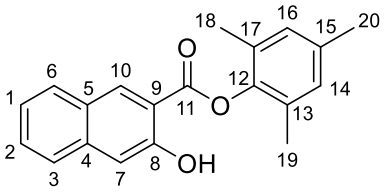
(C7), 21.1 (C18); **FTIR** (neat) ν = 3261, 1690, 1636, 1506, 1326, 1283, 1190, 1165, 1046, 815, 781, 747 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{18}H_{15}O_3$ $(M+H)^+$ 279.1016, found 279.1016.

4-methoxyphenyl 3-hydroxy-2-naphthoate (263)



The title compound was prepared according to General Procedure P using 3-hydroxy-2-naphthoic acid (1.00 g, 5.31 mmol) (**220**) and 4-methoxyphenol (790 mg, 5.83 mmol). The crude product was purified by flash column chromatography [silica gel, 2-5% EtOAc in petroleum ether b.p. 40–60 °C] to afford the product as a yellow solid (91%, 1.42 g). **M.P.** = 89-94 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.17 (s, 1H, OH), 8.74 (d, *J* = 0.7 Hz, 1H, H10), 7.87 (ddq, *J* = 8.3, 1.3, 0.6 Hz, 1H, H3), 7.72 (dd, *J* = 8.4, 1.0 Hz, 1H, H6), 7.54 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H, H7), 7.40 – 7.31 (m, 2H, H1 & H2), 7.24 – 7.10 (m, 2H, H13 & H17), 7.03 – 6.93 (m, 2H, H14 & H16), 3.85 (s, 3H, $H18_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.5 (C11), 156.6 (C15), 148.8 (C12), 138.6 (C4), 133.3 (C10), 132.2 (C6), 129.9 (C2), 129.5 (C5), 127.3 (C3), 126.6 (C1), 124.5 (C13 & C17), 123.2 (C14 & C16), 113.5 (C9), 112.3 (C7); **FTIR** (neat) ν = 3264, 2836, 1689, 1637, 1504, 1461, 1411, 1321, 1282, 1249, 1205, 1177, 1144, 1046, 873, 823, 781, 741, 668 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{18}H_{15}O_4$ $(M+H)^+$ 295.0965, found 295.0965.

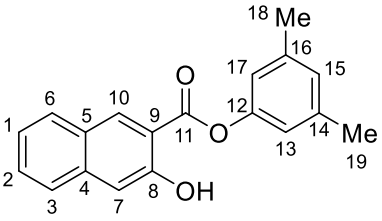
mesityl 3-hydroxy-2-naphthoate (258)



The title compound was prepared according to General Procedure P using 3-hydroxy-2-naphthoic acid (**220**) (1.00 g, 5.31 mmol) and mesitol (794 mg, 5.83 mmol). The crude product was purified by flash column chromatography [silica gel, 5% EtOAc in petroleum ether b.p. 40–60 °C] to afford the product as a yellow solid (56%, 910 mg). **M.P.** = 102-104 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.26 (s, 1H, OH), 8.83 (s, 1H, H10), 7.90 (dd, *J* = 8.3, 1.1 Hz, 1H, H3), 7.74 (dd, *J* = 8.4, 1.1 Hz, 1H, H6), 7.56 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H, H1), 7.48 – 7.33 (m, 2H, H2 & H7), 7.07 – 6.88 (m, 2H, H14 & H16), 2.33 (s, 3H, $H20_3$), 2.21 (s, 6H, $H18_3$ & $H19_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.4 (C11), 156.7 (C8), 145.5 (C12), 138.5 (C4), 136.2 (C15), 133.1 (C10), 130.0 (C3),

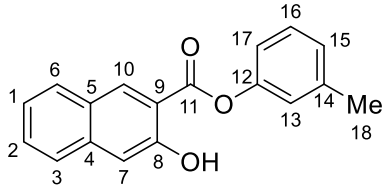
129.7 (C1), 129.6 (C14 & C16), 129.5 (C13 & C17), 127.3 (C5), 126.6 (C6), 124.3 (C2), 113.5 (C9), 112.2 (C7), 21.0 (C20), 16.4 (C18 & C19); **FTIR** (neat) ν = 3262, 2921, 1688, 1512, 1461, 1412, 1321, 1283, 1207, 1186, 1135, 1047, 850, 783, 742 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{20}H_{19}O_3$ $(M+H)^+$ 307.1329, found 307.1330.

3,5-dimethylphenyl 3-hydroxy-2-naphthoate (257)



The title compound was prepared according to General Procedure P using 3-hydroxy-2-naphthoic acid (**220**) (1.00 g, 5.31 mmol) and 3,5-dimethylphenol (712 mg, 5.83 mmol). The crude product was purified by flash column chromatography [silica gel, 5% Et_2O in petroleum ether b.p. 40–60 °C] to afford the product as a yellow solid (57%, 860 mg). **M.P.** = 90-92 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.18 (s, 1H, OH), 8.72 (s, 1H, H10), 7.86 (dd, *J* = 8.4, 1.1 Hz, 1H, H3), 7.72 (dd, *J* = 8.5, 1.0 Hz, 1H, H6), 7.54 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H, H1), 7.41 – 7.33 (m, 2H, H2 & H7), 6.97 (tt, *J* = 1.7, 0.8 Hz, 1H, H15), 6.95 – 6.86 (m, 2H, H13 & H17), 2.38 (s, 6H, $H18_3$ & $H19_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.0 (C11), 156.7 (C8), 150.2 (C12), 139.8 (C4), 138.4 (C14 & C16), 133.2 (C10), 129.6 (C3), 129.5 (C1), 128.4 (C15), 127.3 (C5), 126.5 (C6), 124.3 (C2), 119.3 (C13 & C17), 113.9 (C9), 112.1 (C7), 21.4 (C18 & C19); **FTIR** (neat) ν = 3265, 2919, 1690, 1619, 1606, 1511, 1323, 1276, 1205, 1146, 1059, 835, 741 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{19}H_{17}O_3$ $(M+H)^+$ 293.1172, found 293.1172.

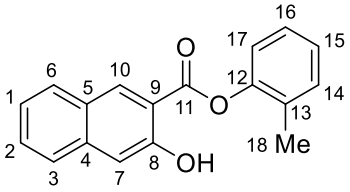
***m*-tolyl 3-hydroxy-2-naphthoate (255)**



The title compound was prepared according to General Procedure P using 3-hydroxy-2-naphthoic acid (**220**) (1.00 g, 5.31 mmol) and *m*-cresol (631 mg, 5.83 mmol). The crude product was purified by flash column chromatography [silica gel, 5% EtOAc in petroleum ether b.p. 40–60 °C] to afford the product as a yellow solid (74%, 1.10 g). **M.P.** = 78-82 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.18 (s, 1H, OH), 8.74 (s, 1H, H10), 7.87 (dd, *J* = 8.2, 1.0 Hz, 1H, H3), 7.73 (dd, *J* = 8.4, 1.1 Hz, 1H, H6), 7.55 (ddd, *J* = 8.2, 6.8, 1.2 Hz, 1H, H1), 7.44 – 7.31 (m, 3H, H2, H7 & H13),

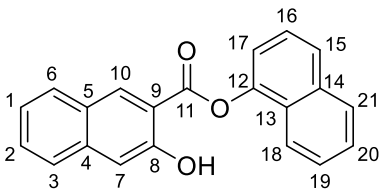
7.16 (ddt, *J* = 7.6, 1.7, 0.9 Hz, 1H, H17), 7.12 – 7.01 (m, 2H, H15 & H16), 2.43 (s, 3H, $H18_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.9 (C11), 156.6 (C8), 150.2 (C12), 140.2 (C4), 138.4 (C14), 133.3 (C10), 129.7 (C3), 129.6 (C1), 129.5 (C16), 127.5 (C15), 127.3 (C5), 126.5 (C6), 124.3 (C2), 122.3 (C13), 118.7 (C17), 113.9 (C9), 112.1 (C7), 21.5 (C18); **FTIR** (neat) ν = 3275, 3055, 1689, 1511, 1461, 1410, 1320, 1283, 1202, 1146, 1049, 917, 781, 746, 685 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{18}H_{15}O_3$ $(M+H)^+$ 279.1016, found 279.1017.

_o_-tolyl 3-hydroxy-2-naphthoate (254)



The title compound was prepared according to General Procedure P using 3-hydroxy-2-naphthoic acid (**220**) (1.00 g, 5.31 mmol) and *o*-cresol (630 mg, 5.83 mmol). The crude product was purified by flash column chromatography [silica gel, 5% EtOAc in petroleum ether b.p. 40–60 °C] to afford the product as a yellow solid (76%, 1.12 g). **M.P.** = 104-106 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.22 (s, 1H, OH), 8.82 (s, 1H, H10), 7.91 (dd, *J* = 8.4, 1.1 Hz, 1H, H3), 7.76 (dd, *J* = 8.5, 1.0 Hz, 1H, H6), 7.58 (ddd, *J* = 8.2, 6.8, 1.2 Hz, 1H, H1), 7.44 – 7.31 (m, 4H, H2, H7, H14 & H16), 7.29 (td, *J* = 7.5, 1.5 Hz, 1H, H15), 7.22 (dd, *J* = 7.7, 1.5 Hz, 1H, H17), 2.32 (s, 3H, $H18_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.6 (C11), 156.7 (C8), 148.9 (C12), 138.5 (C4), 133.2 (C10), 131.6 (C14), 130.5 (C13), 129.7 (C3), 129.5 (C1), 127.33 (C16), 127.30 (C5), 126.8 (C15), 126.6 (C6), 124.4 (C2), 122.0 (C17), 113.7 (C9), 112.2 (C7), 16.4 (C18); **FTIR** (neat) ν = 3277, 3058, 1691, 1512, 1461, 1322, 1283, 1222, 1205, 1169, 1145, 1110, 1049, 748 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{18}H_{15}O_3$ $(M+H)^+$ 279.1016, found 279.1016.

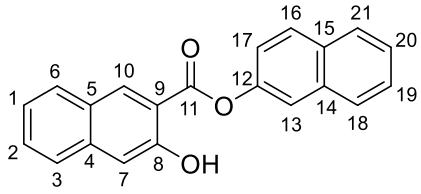
naphthalen-1-yl 3-hydroxy-2-naphthoate (259)



The title compound was prepared according to General Procedure P using 3-hydroxy-2-naphthoic acid (**220**) (1.00 g, 5.31 mmol) and 1-naphthol (841 mg, 5.83 mmol). The crude product was purified by flash column chromatography [silica gel, 5% EtOAc in petroleum ether b.p. 40–60 °C] to afford the product as a yellow solid (56%, 917 mg). **M.P.** = 78-82 °C; **^{1}H NMR**

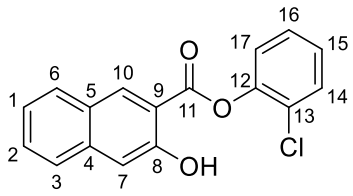
(400 MHz, $CDCl_3$) δ 10.14 (s, 1H, OH), 8.97 (s, 1H, H10), 8.00 – 7.91 (m, 3H, H3, H18 & H21), 7.87 (dd, *J* = 8.2, 1.1 Hz, 1H, H6), 7.77 (dd, *J* = 8.5, 1.1 Hz, 1H, H7), 7.63 – 7.50 (m, 4H, H1, H15, H19 & H20), 7.47 – 7.36 (m, 3H, H2, H16 & H17); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.9 (C11), 156.7 (C8), 146.2 (C12), 138.6 (C4), 134.9 (C14), 133.3 (C2), 129.9 (C6), 129.6 (2C, C5 & C21), 128.4 (C10), 127.4 (C13), 127.0 (C20), 126.9 (3C, C3, C16 & C19), 126.6 (C15), 125.6 (C1), 124.4 (C18), 121.1 (C9), 118.5 (C17), 113.6 (C7); **FTIR** (neat) ν = 3280, 3057, 1688, 1509, 1461, 1318, 1281, 1200, 1143, 1081, 1050, 873, 781, 766, 739, 667 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{21}H_{15}O_3$ $(M+H)^+$ 315.1016, found 315.1017.

naphthalen-2-yl 3-hydroxy-2-naphthoate (260)



The title compound was prepared according to General Procedure P using 3-hydroxy-2-naphthoic acid (**220**) (1.00 g, 5.31 mmol) and 2-naphthol (841 mg, 5.83 mmol). The crude product was purified by flash column chromatography [silica gel, 5% EtOAc in petroleum ether b.p. 40–60 °C] to afford the product as a yellow solid (32%, 521 mg). **M.P.** = 128-134 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.16 (s, 1H, OH), 8.82 (s, 1H, H10), 7.96 (d, *J* = 8.9 Hz, 1H, H3), 7.93 – 7.86 (m, 4H, H6, H7, H18 & H21), 7.74 (dd, *J* = 8.0, 1.6 Hz, 2H, H1 & H16), 7.63 – 7.50 (m, 2H, H2 & H20), 7.48 – 7.33 (m, 3H, H13, H17 & H19); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.0 (C11), 156.7 (C8), 147.9 (C12), 138.5 (C4), 133.9 (C14), 133.4 (C10), 131.9 (C16), 129.9 (C2), 129.8 (C6), 129.6 (C15), 128.1 (C21), 127.9 (C5), 127.3 (C19), 127.0 (C18), 126.6 (C3), 126.3 (C1), 124.4 (C20), 121.0 (C17), 119.0 (C9), 113.8 (C7), 112.2 (C13); **FTIR** (neat) ν = 3259, 3057, 1690, 1633, 1600, 1572, 1511, 1460, 1319, 1283, 1203, 1146, 1044, 958, 890, 745 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{21}H_{15}O_3$ $(M+H)^+$ 315.1016, found 315.1017.

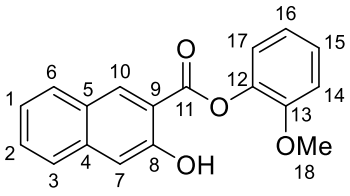
2-chlorophenyl 3-hydroxy-2-naphthoate (265)



The title compound was prepared according to General Procedure P using 3-hydroxy-2-naphthoic acid (**220**) (1.00 g, 5.31 mmol) and 2-chlorophenol (752 mg, 606 μL, 5.83 mmol). The crude product

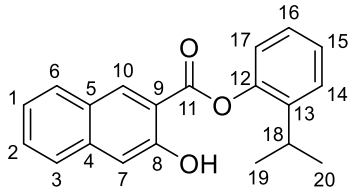
was purified by flash column chromatography [silica gel, 5% EtOAc in petroleum ether b.p. 40–60 °C] to afford the product as a yellow solid (69%, 1.09 g). **M.P.** = 116-118 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.00 (s, 1H, OH), 8.85 (s, 1H, H10), 7.97 – 7.87 (m, 1H, H3), 7.81 – 7.72 (m, 1H, H6), 7.64 – 7.56 (m, 2H, H1 & H7), 7.48 – 7.28 (m, 5H, H2, H14, H15, H16 & H17); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.8 (H11), 156.5 (H8), 146.5 (C12), 138.5 (C4), 133.6 (C10), 130.7 (C14), 129.8 (C6), 129.6 (C2), 128.1 (C5), 127.8 (C13), 127.3 (C16), 127.1 (C15), 126.5 (C3), 124.4 (C1), 123.9 (C17), 113.2 (C9), 112.2 (C7); **FTIR** (neat) ν = 3285, 3055, 1697, 1635, 1512, 1477, 1462, 1407, 1320, 1284, 1214, 1145, 1062, 1042, 777, 747 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{17}H_{12}O_3Cl$ $(M+H)^+$ 299.0480, found 299.0471.

2-methoxyphenyl 3-hydroxy-2-naphthoate (266)



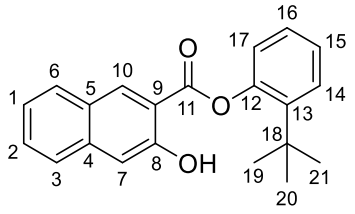
The title compound was prepared according to General Procedure P using 3-hydroxy-2-naphthoic acid (**220**) (1.00 g, 5.31 mmol) and guaiacol (726 mg, 643 μL, 5.83 mmol). The crude product was purified by flash column chromatography [silica gel, 5-10% EtOAc in petroleum ether b.p. 40–60 °C] to afford the product as a yellow solid (57%, 891 mg). **M.P.** = 78-80 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.15 (s, 1H, OH), 8.99 – 8.67 (m, 1H, H10), 7.90 – 7.84 (m, 1H, H3), 7.73 (dd, *J* = 8.4, 1.0 Hz, 1H, H6), 7.54 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H, H7), 7.40 – 7.35 (m, 2H, H1 & H2), 7.35 – 7.29 (m, 1H, H17), 7.23 (dd, *J* = 7.8, 1.6 Hz, 1H, H16), 7.09 – 7.02 (m, 2H, H14 & H15), 3.85 (s, 3H, $H18_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.3 (C11), 156.6 (C8), 151.3 (C13), 139.3 (C12), 138.4 (C4), 133.5 (C10), 129.6 (2C, C2 & C6), 127.7 (C5), 127.3 (C15), 126.5 (C3), 124.2 (C1), 123.0 (C16), 121.1 (C17), 113.8 (C11), 112.7 (C14), 112.0 (C7), 56.1 (C18); **FTIR** (neat) ν = 3266, 1694, 1636, 1500, 1461, 1411, 1322, 1284, 1258, 1205, 1170, 1144, 1110, 1026, 779, 746 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{18}H_{15}O_4$ $(M+H)^+$ 295.0965, found 295.0966.

2-isopropylphenyl 3-hydroxy-2-naphthoate (267)



The title compound was prepared according to General Procedure P using 3-hydroxy-2-naphthoic acid (**220**) (1.00 g, 5.31 mmol) and 2-isopropylphenol (795 mg, 787 µL, 5.83 mmol). The crude product was purified by flash column chromatography [silica gel, 5% EtOAc in petroleum ether b.p. 40–60 °C] to afford the product as a yellow solid (83%, 1.35 g). **M.P.** = 62-67 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.21 (s, 1H, OH), 8.77 (s, 1H, H10), 7.89 (d, *J* = 8.3 Hz, 1H, H3), 7.74 (d, *J* = 8.4 Hz, 1H, H6), 7.56 (ddd, *J* = 8.2, 6.8, 1.2 Hz, 1H, H7), 7.45 – 7.35 (m, 3H, H1, H2 & H14), 7.35 – 7.27 (m, 2H, H15 & H17), 7.17 (dt, *J* = 7.4, 1.6 Hz, 1H, H16), 3.14 (hept, *J* = 6.9 Hz, 1H, H18), 1.27 (dd, *J* = 6.9, 1.4 Hz, 6H, $H19_3$ & $H20_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.0 (C11), 156.7 (C8), 147.7 (C12), 140.6 (C4), 138.5 (C13), 133.2 (C10), 130.0 (C6), 129.6 (C2), 127.3 (C5), 127.2 (2C, C14 & C16), 127.0 (C3), 126.6 (C15), 124.4 (C1), 122.4 (C17), 113.8 (C9), 112.2 (C7), 27.8 (C18), 23.2 (C19 & C20); **FTIR** (neat) ν = 3272, 2964, 1691, 1637, 1512, 1461, 1410, 1320, 1281, 1202, 1172, 1131, 1082, 1047, 873, 781, 747 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{20}H_{19}O_3$ $(M+H)^+$ 307.1329, found 307.1329.

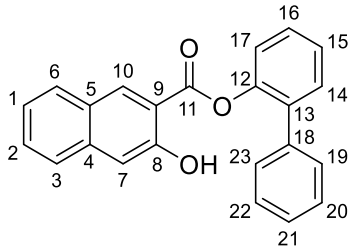
2-(*tert*-butyl)phenyl 3-hydroxy-2-naphthoate (269)



The title compound was prepared according to General Procedure P using 3-hydroxy-2-naphthoic acid (**220**) (1.00 g, 5.31 mmol) and 2-*tert*-butylphenol (876 mg, 895 µL, 5.83 mmol). The crude product was purified by flash column chromatography [silica gel, 2% Et_2O in petroleum ether b.p. 40–60 °C] to afford the product as a yellow solid (55%, 935 mg). **M.P.** = 102-104 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.20 (s, 1H, OH), 8.65 (s, 1H, H10), 7.79 (d, *J* = 8.3 Hz, 1H, H3), 7.63 (d, *J* = 8.4 Hz, 1H, H6), 7.50 – 7.37 (m, 2H, H1 & H7), 7.31 – 7.12 (m, 4H, H2, H14, H16 & H17), 7.03 (dd, *J* = 7.6, 1.8 Hz, 1H, H15), 1.32 (s, 9H, $H19_3$, $H20_3$ & $H21_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.2 (C11), 156.8 (C8), 148.7 (C12), 141.6 (C13), 138.4 (C4), 133.2 (C10), 129.8 (C6), 129.6 (C2), 127.8 (C5), 127.3 (C14), 127.2 (C3), 126.6 (C16), 126.5 (C15), 124.3 (C1), 124.1 (C18), 114.1 (C9), 112.3 (C7), 34.8

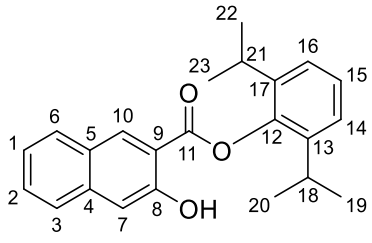
(C18), 30.5 (C19, C20 & C21); **FTIR** (neat) ν = 3272, 2966, 1694, 1513, 1411, 1280, 1203, 1180, 1144, 1086, 1042, 873, 781, 748 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{21}H_{21}O_3$ $(M+H)^+$ 321.1485, found 321.1486.

[1,1'-biphenyl]-2-yl 3-hydroxy-2-naphthoate (264)



The title compound was prepared according to General Procedure P using 3-hydroxy-2-naphthoic acid (**220**) (1.00 g, 5.31 mmol) and 2-hydroxybiphenyl (996 mg, 5.83 mmol). The crude product was purified by flash column chromatography [silica gel, 5% EtOAc in petroleum ether b.p. 40–60 °C] to afford the product as a yellow solid (34%, 610 mg). **M.P.** = 138-142 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.89 (s, 1H, OH), 8.45 (s, 1H, H10), 7.71 (d, *J* = 8.3 Hz, 1H, H3), 7.60 (d, *J* = 8.3 Hz, 1H, H6), 7.53 – 7.29 (m, 6H, H1, H2, H7, H14, H19 & H23), 7.29 – 7.10 (m, 6H, H15, H16, H17, H20, H21 & H22); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.6 (C11), 156.5 (C8), 147.3 (C12), 138.3 (C4), 137.2 (C18), 135.2 (C13), 133.3 (C10), 131.3 (C14), 129.7 (C2), 129.5 (C6), 129.0 (2C, C20 & C22), 128.8 (C16), 128.5 (2C, C19 & C23), 127.8 (C5), 127.2 (C21), 127.1 (C3), 126.5 (C15), 124.2 (C1), 122.9 (C17), 113.7 (C9), 112.0 (C7); **FTIR** (neat) ν = 3279, 3058, 1692, 1637, 1511, 1461, 1410, 1319, 1282, 1203, 1179, 1049, 779 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{23}H_{17}O_3$ $(M+H)^+$ 341.1172, found 341.1174.

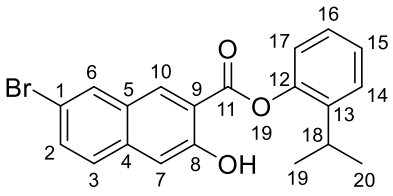
2,6-diisopropylphenyl 3-hydroxy-2-naphthoate (268)



The title compound was prepared according to General Procedure P using 3-hydroxy-2-naphthoic acid (**220**) (1.00 g, 5.31 mmol) and 2,6-diisopropylphenol (1.04 g, 5.83 mmol). The crude product was purified by flash column chromatography [silica gel, 2% Et_2O in petroleum ether b.p. 40–60 °C] to afford the product as a yellow solid (64%, 1.18 g). **M.P.** = 80-82 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.28 (s, 1H, OH), 8.81 (s, 1H, H10), 7.92 (dd, *J* = 8.4, 1.1 Hz, 1H, H3), 7.75 (dd, *J* = 8.4, 1.0 Hz, 1H, H6), 7.56 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H, H7), 7.43 – 7.36 (m, 2H, H1 & H2), 7.32 (dd, *J* = 8.8, 6.4 Hz, 1H, H15), 7.29 – 7.22 (m, 2H, H14 & H16), 3.01

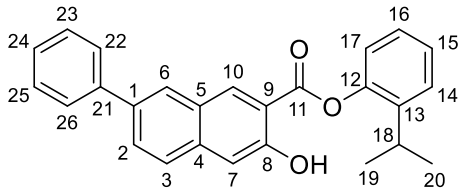
(hept, *J* = 6.9 Hz, 2H, H18 & H21), 1.24 (dd, *J* = 8.6, 6.9 Hz, 12H, $H19_3$, $H20_3$, $H22_3$ & $H23_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.9 (C11), 156.7 (C8), 145.0 (C12), 140.5 (C4), 138.4 (2C, C13 & C17), 132.9 (C10), 129.6 (C6), 129.4 (C2), 127.2 (2C, C15 & C5), 126.4 (C1), 124.3 (2C, C14 & C16), 113.4 (C11), 112.1 (C7), 27.7 (C18 & C21), 23.9 (C19 & C22), 22.8 (C20 & C23); **FTIR** (neat) ν = 3271, 2964, 1688, 1512, 1461, 1318, 1282, 1202, 1161, 1143, 1095, 1052, 873, 789, 745 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{23}H_{25}O_3$ $(M+H)^+$ 349.1798, found 349.1800.

2-isopropylphenyl 3-hydroxy-2-naphthoate (318)



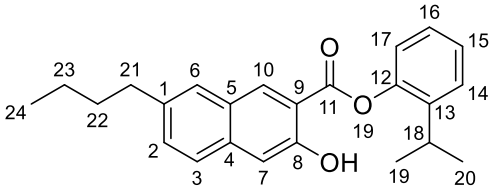
To a suspension of 7-bromo-3-hydroxy-2-naphthoic acid (4.00 g, 14.98 mmol, 1.00 equiv.) and 2-isopropylphenol (2.22 mL, 2.24 g, 16.47 mmol, 1.10 equiv.) in toluene (20 mL), $POCl_3$ (559 µL, 918 mg, 5.99 mmol, 0.40 equiv.) was *slowly* added. The mixture was then heated to reflux for 48 h and after the allotted time, the reaction was cooled to room temperature, diluted with Et_2O (20 mL) and quenched by the slow addition of sat. $Na_2CO_{3\,(aq.)}$ (40 mL). The layers were separated, and the product was further extracted three times with Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography [silica gel, 2-5% EtOAc in petroleum ether b.p. 40–60 °C] to afford the product as a yellow solid (48%, 2.79 g). **M.P.** = 126-131 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.24 (s, 1H, OH), 8.71 – 8.65 (m, 1H, H10), 8.05 (s, 1H, H6), 7.70 – 7.55 (m, 2H, H2 & H3), 7.46 – 7.40 (m, 1H, H14), 7.37 (s, 1H, H7), 7.36 – 7.28 (m, 2H, H15 & H17), 7.20 – 7.11 (m, 1H, H16), 3.12 (hept, *J* = 6.9 Hz, 1H, H18), 1.27 (d, *J* = 6.9 Hz, 6H, $H19_3$ & $H20_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.7 (C11), 157.1 (C8), 147.6 (C12), 140.5 (C13), 136.8 (C4), 133.0 (C10), 132.0 (C2), 131.3 (C6), 128.2 (C14), 127.3 (C16), 127.1 (C15), 122.3 (C17), 117.8 (C1), 114.6 (C11), 112.5 (C7), 27.8 (C18), 23.2 (C19 & C20); **FTIR** (neat) ν = 3259, 2963, 1692, 1633, 1568, 1505, 1339, 1400, 1346, 1298, 1275, 1198, 1172, 1142, 1082, 1050, 925, 866, 780, 753, 735, 667 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{20}H_{16}O_3Br$ $(M+H)^+$ 383.0286, found 383.0286.

2-isopropylphenyl 3-hydroxy-2-naphthoate (319)



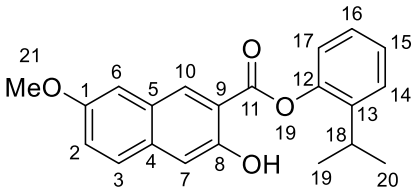
Prepared according to a modified literature method.[120] A flame dried, argon filled 2-necked 10 mL RBF equipped with a reflux condenser and magnetic stirring bar was charged with 2-isopropylphenyl 7-bromo-3-hydroxy-2-naphthoate (**318**) (250 mg, 0.649 mmol, 1.00 equiv.), $Pd(OAc)_2$ (2.9 mg, 0.013 mmol, 0.02 equiv.), SPhos (10.66 mg, 0.026 mmol, 0.04 equiv.), K_3PO_4 (193 mg, 0.909 mmol, 1.40 equiv.) and phenylboronic acid (101 mg, 0.909 mmol, 1.40 equiv.). The flask was evacuated and back filled with argon three times, prior to the addition of sparged toluene (2 mL). After heating at reflux for 3 days, the reaction was cooled to room temperature, diluted with EtOAc (10 mL) and $NH_4Cl_{(aq.)}$ (sat.) (10 mL) was added. The layers were separated and the aqueous phase was further extracted three times with EtOAc. The combined organic extracts were pooled, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography [silica gel, 5% Et_2O in petroleum ether b.p. 40–60 °C] to afford the product as a yellow oil (71%, 167 mg). **M.P.** = 88-100 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.25 (s, 1H, OH), 8.84 (s, 1H, H10), 8.10 (s, 1H, H7), 7.89 – 7.79 (m, 2H, H3 & H6), 7.76 – 7.68 (m, 2H, H2 & H14), 7.55 – 7.47 (m, 2H, H15 & H17), 7.47 – 7.37 (m, 3H, H23, H24 & H25), 7.37 – 7.27 (m, 2H, H22 & H26), 7.22 – 7.13 (m, 1H, H16), 3.16 (hept, *J* = 6.9 Hz, 1H, H18), 1.29 (d, *J* = 6.9 Hz, 6H, $H19_3$ & $H20_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.0 (C11), 156.9 (C8), 147.7 (C12), 140.6 (2C, C13 & C21), 137.6 (C4), 137.2 (C1), 133.4 (C10), 129.6 (C2), 129.1 (2C, C23 & C25), 127.6 (2C, C3 & C5) , 127.3 (3C, C22, C24 & C26), 127.2 (2C, C6 & C14), 127.1 (2C, C15 & C17), 122.4 (C16), 114.2 (C9), 112.1 (C7), 27.8 (C18), 23.2 (2C, C19 & C20); **FTIR** (neat) ν = 3261, 2926, 1693, 1636, 1516, 1490, 1405, 1356, 1312, 1279, 1250, 1201, 1173, 1152, 1052, 869, 780, 753, 697 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{26}H_{23}O_3$ $(M+H)^+$ 383.1642, found 383.1642.

2-isopropylphenyl 3-hydroxy-2-naphthoate (320)



A flame dried, argon filled 2-necked 10 mL RBF equipped with a reflux condenser and magnetic stirring bar was charged with 2-isopropylphenyl 7-bromo-3-hydroxy-2-naphthoate (**318**) (250 mg, 0.649 mmol, 1.00 equiv.), $Pd(OAc)_2$ (2.9 mg, 0.013 mmol, 0.02 equiv.), SPhos (10.66 mg, 0.026 mmol, 0.04 equiv.), K_3PO_4 (193 mg, 0.909 mmol, 1.40 equiv.) and butylboronic acid (93 mg, 0.909 mmol, 1.40 equiv.). The flask was evacuated and back filled with argon three times, prior to the addition of sparged toluene (2 mL). After heating at reflux for 3 days, the reaction was cooled to room temperature, diluted with EtOAc (10 mL) and $NH_4Cl_{(aq.)}$ (sat.) (10 mL) was added. The layers were separated and the aqueous phase was further extracted three times with EtOAc. The combined organic extracts were pooled, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography [silica gel, 5% Et_2O in petroleum ether b.p. 40–60 °C] to afford the product as a yellow oil (71%, 167 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.14 (s, 1H, OH), 8.71 (s, 1H, H10), 7.69 – 7.63 (m, 2H, H3 & H6), 7.49 – 7.38 (m, 2H, H2 & H14), 7.36 (s, 1H, H7), 7.35 – 7.28 (m, 2H, H15 & H17), 7.19 – 7.11 (m, 1H, H16), 3.14 (hept, *J* = 6.9 Hz, 1H, H18), 2.76 (t, *J* = 7.7 Hz, 2H, $H21_2$), 1.75 – 1.63 (m, 2H, $H22_2$), 1.41 (dq, *J* = 14.6, 7.3 Hz, 2H, $H23_2$), 1.27 (d, *J* = 6.9 Hz, 6H, $H19_3$ & $H20_3$), 0.97 (t, *J* = 7.4 Hz, 3H, $H24_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.1 (C11), 156.2 (C8), 147.7 (C12), 140.6 (C13), 138.9 (C1), 137.0 (C4), 132.5 (C10), 131.6 (C2), 127.6 (C5), 127.5 (C6), 127.2 (C14), 127.1 (C16), 127.0 (C15), 126.4 (C3), 122.4 (C17), 113.6 (C9), 112.0 (C7), 35.7 (C21), 33.5 (C22), 27.8 (C18), 23.2 (C19 & C20), 22.5 (C23), 14.1 (C24); **FTIR** (neat) ν = 3273, 2960, 2928, 1690, 1640, 1571, 1515, 1489, 1465, 1403, 1354, 1311, 1278, 1209, 1173, 1147, 1083, 1049, 915, 866, 781, 753, 673 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{24}H_{27}O_3$ $(M+H)^+$ 363.1955, found 363.1957.

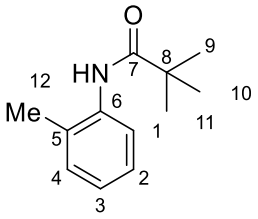
2-isopropylphenyl 3-hydroxy-7-methoxy-2-naphthoate (317)



The title compound was prepared according to General Procedure P using 3-hydroxy-7-methoxy-2-naphthoic acid (1.00 g, 4.58 mmol, 1.00 equiv.) and 2-isopropylphenol (678 µL, 686 mg, 1.10 equiv.). The crude product was purified by flash column chromatography [silica gel, 10% Et_2O in pentane] to afford the product as a yellow solid (64%, 986 mg). **M.P.** = 102-104 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.10 (s, 1H, OH), 8.68 (s, 1H, H10), 7.67 (d, *J* = 9.0 Hz, 1H, H3), 7.50 – 7.42 (m, 1H, H2), 7.38 (s, 1H, H6), 7.37 – 7.32 (m, 2H, H14 & H15), 7.30 – 7.25 (m, 1H, H7), 7.22 – 7.13 (m, 2H, H16 & H17), 3.95 (s, 3H, $H21_3$), 3.17 (hept, *J* = 6.9 Hz, 1H, H18), 1.30 (d, *J* = 6.9 Hz, 6H, $H19_3$ & $H20_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.1 (C11), 156.5 (C1), 155.4 (C8), 147.7 (C12), 140.6 (C13), 134.2 (C4), 131.2 (C10), 128.1 (C5), 128.0 (C3), 127.2 (C14), 127.1 (C16), 127.0 (C15), 123.4 (C17), 122.4 (C2), 113.8 (C9), 112.4 (C6), 106.4 (C7), 55.5 (C21), 27.7 (C18), 23.2 (C19 & C20); **FTIR** (neat) ν = 3275, 2963, 1692, 1613, 1574, 1517, 1489, 1401, 1354, 1303, 1281, 1228, 1196, 1172, 1150, 1127, 1083, 1050, 1030, 904, 866, 831, 780, 754, 709, 670, 612 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{21}H_{21}O_4$ $(M+H)^+$ 337.1434, found 337.1434.

9.5.5 Indole Substrates

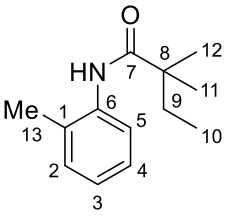
N-(*o*-tolyl)pivalamide (196)



The title compound was prepared according to General Procedure L using *o*-toluidine (**195**) (5.00 g, 4.95 mL, 46.66 mmol) and pivaloyl chloride (6.75 g, 6.89 mL, 56.00 mmol). This crude product was purified by recrystallisation from hot EtOAc and the product was collected by vacuum filtration as a white crystalline solid (88%, 7.88 g). **M.P.** = 96-100 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.88 – 7.80 (m, 1H, H1), 7.25 (bs, 1H, NH), 7.23 – 7.15 (m, 2H, H2 & H3), 7.06 (td, *J* = 7.5, 1.3 Hz, 1H, H4), 2.25 (s, 3H, $H12_3$), 1.34 (s, 9H, $H9_3$, $H10_3$ & $H11_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.5 (C7), 136.0 (C6), 130.5 (C2), 128.9 (C5), 126.9 (C3), 125.0 (C4), 123.0 (C1), 39.8 (C8), 27.8 (C9,

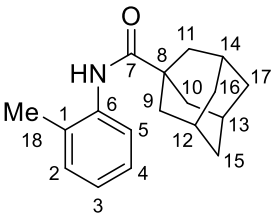
C10 & C11), 17.7 (C12); **FTIR** (neat) ν = 3474, 3378, 2927, 2852, 1612, 1492, 1455, 1306, 1157, 1157, 746 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{12}H_{18}ON$ $(M+H)^+$ 192.1383, found 192.1383.

2,2-dimethyl-N-(o-tolyl)butanamide (277)



The title compound was prepared according to General Procedure L using *o*-toluidine (**195**) (857 mg, 850 µL, 8.00 mmol) and 2,2-dimethylbutanoyl chloride (1.34 g, 10.00 mmol). The crude product was purified by recrystallisation from hot EtOAc. The product was collected by vacuum filtration as a white crystalline solid [product contains ~5% impurity by ^1H NMR, no further purification performed] (55%, 896 mg). **M.P.** = 102-104 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 – 7.79 (m, 1H, H2), 7.24 – 7.15 (m, 3H, NH, H3 & H5), 7.06 (td, *J* = 7.4, 1.3 Hz, 1H, H4), 2.25 (s, 3H, $H13_3$), 1.67 (q, *J* = 7.5 Hz, 2H, $H9_2$), 1.29 (s, 6H, 11_3 & $H12_3$), 0.95 (t, *J* = 7.5 Hz, 3H, $H10_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.9 (C7), 136.0 (C1), 130.5 (C5), 128.8 (C6), 126.9 (C3), 125.0 (C4), 123.0 (C2), 43.6 (C8), 34.3 (C9), 25.3 (C11 & C12), 17.8 (C13), 9.4 (C10); **FTIR** (neat) ν = 3304, 2965, 1646, 1511, 1379, 1257, 1167, 1113, 954, 748, 647 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{13}H_{20}ON$ $(M+H)^+$ 206.1539, found 206.1541.

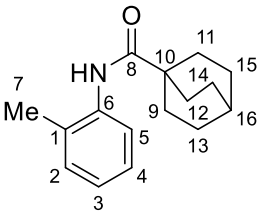
(3r,5r,7r)-N-(o-tolyl)adamantane-1-carboxamide (278)



The title compound was prepared according to General Procedure L using *o*-toluidine (991 mg, 983 µL, 9.25 mmol) and (3r,5r,7r)-adamantane-1-carbonyl chloride (2.19 g, 11.10 mmol). The crude product was purified by recrystallisation from hot EtOAc. The product was collected by vacuum filtration as a white crystalline solid [product contains ~6% impurity by ^1H NMR, no further purification performed] (63%, 1.88 g). **M.P.** = 171-175 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 8.1, 1.2 Hz, 1H, H2), 7.25 – 7.13 (m, 3H, NH, H3 & H5), 7.05 (td, *J* = 7.5, 1.3 Hz, 1H, H4), 2.25 (s, 3H, $H18_3$), 2.11 (m, 3H, H12, H13 & H14), 1.99 (d, *J* = 2.9 Hz, 6H, $H9_2$, $H10_2$ & $H11_2$), 1.76 (qt, *J* = 9.4, 5.4 Hz, 6H, $H15_2$, $H16_2$ & $H17_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.0 (C8), 136.0 (C1), 130.4 (C5), 128.7 (C6), 126.9 (C3), 124.9 (C4), 122.9 (C2), 41.8 (C8), 39.6 (C9, C10 &

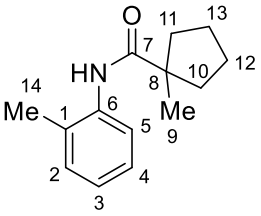
C11), 36.6 (C15, C16 & C17), 28.3 (C12, C13 & C14), 17.8 (C18); **FTIR** (neat) ν = 3280, 2901, 2851, 1639, 1509, 1452, 1372, 1268, 1110, 1080, 922, 741 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{18}H_{24}ON$ $(M+H)^+$ 270.1852, found 270.1854.

N-(o-tolyl)bicyclo[2.2.2]octane-1-carboxamide (279)



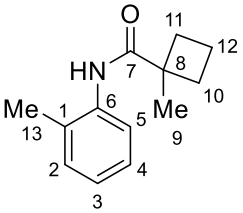
A flame dried 2-necked round-bottomed flask was charged with $NiCl_2 \cdot 6H_2O$ (40 mg, 0.17 mmol, 0.10 equiv.) and 2,6-di-*tert*-butylpyridine (93 mg, 0.35 mmol, 0.20 equiv.). The flask was purged with a N_2 balloon for 5 min and DMF (1.7 mL) was added. The mixture was stirred for 10 min at room temperature before the addition of THF (7.4 mL), *i*-PrOH (0.9 mL) and 1,3-dioxoisoindolin-2-yl 4-(o-tolylcarbamoyl)bicyclo[2.2.2]octane-1-carboxylate (750 mg, 1.73 mmol, 1.0 equiv.). Zn dust (57 mg, 0.87 mmol, 0.50 equiv.) was then added, followed immediately by $PhSiH_3$ (320 µL, 2.59 mmol, 1.5 equiv.). The mixture was heated at 40 °C for 90 min. After this time, the reaction was cooled to room temperature and quenched with H_2O (distilled) and sat. $NH_4Cl_{(aq.)}$ (1:1 v/v). The mixture was extracted three times with EtOAc and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography [silica gel, 5-10% EtOAc in pentane] to afford the product as a white solid (33%, 140 mg). **M.P.** = 140-148 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 8.1, 1.2 Hz, 1H, H5), 7.22 – 7.15 (m, 2H, H2 & H3), 7.13 (bs, 1H, NH), 7.04 (td, *J* = 7.5, 1.3 Hz, 1H, H4), 2.24 (s, 3H, $H7_3$), 1.89 – 1.79 (m, 6H, $H9_2$, $H11_2$ & $H12_2$), 1.67 (ddt, *J* = 14.8, 7.3, 3.1 Hz, 7H, $H13_2$, $H14_2$ $H15_2$ & H16); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.3 (C8), 136.1 (C6), 130.4 (C2), 128.6 (C1), 126.9 (C3), 124.9 (C4), 122.9 (C5), 39.6 (C10), 28.8 (C9, C11 & C12), 25.7 (C13, C14 & C15), 23.8 (C16), 17.8 (C7); **FTIR** (neat) ν = 3312, 3263, 2938, 2917, 2863, 1640, 1513, 1513, 1457, 1268, 1134, 1114, 1078, 1037, 919, 853, 745, 698 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{16}H_{22}ON$ $(M+H)^+$ 244.1696, found 244.1695.

1-methyl-N-(o-tolyl)cyclopentane-1-carboxamide (280)



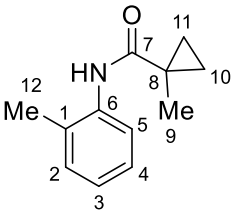
The title compound was prepared according to General Procedure L using *o*-toluidine (**195**) (857 mg, 850 µL, 8.00 mmol) and 1-methylcyclopentane-1-carbonyl chloride (1.47 g, 10.00 mmol). The crude product was purified by recrystallisation from hot EtOAc. The product was collected by vacuum filtration as a white crystalline solid (46%, 800 mg). **M.P.** = 108-110 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 8.1, 1.2 Hz, 1H, H5), 7.24 – 7.15 (m, 3H, NH, H2 & H3), 7.06 (td, *J* = 7.5, 1.3 Hz, 1H, H4), 2.26 (s, 3H, $H14_3$), 2.23 – 2.13 (m, 2H, $H10_A$ & $H11_A$), 1.82 – 1.73 (m, 4H, $H12_2$ & $H13_2$), 1.61 (dddd, *J* = 11.7, 8.8, 4.8, 3.2 Hz, 2H, $H10_B$ & $H11_B$), 1.39 (s, 3H, $H9_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.8 (C7), 136.2 (C6), 130.5 (C2), 128.7 (C1), 127.0 (C3), 124.9 (C4), 122.9 (C5), 51.1 (C8), 38.1 (C10 & C11), 25.9 (C9), 25.1 (C12 & C13), 17.8 (C14); **FTIR** (neat) ν = 3316, 2961, 2871, 1651, 1584, 1517, 1460, 1380, 1305, 1263, 1122, 1042, 950, 752, 653 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{14}H_{20}ON$ $(M+H)^+$ 218.1539, found 218.1539.

1-methyl-N-(o-tolyl)cyclobutane-1-carboxamide (281)



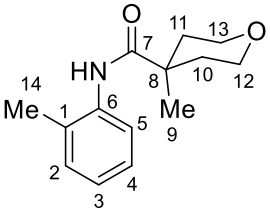
The title compound was prepared according to General Procedure L using *o*-toluidine (**195**) (2.14 g, 2.13 mL, 20.00 mmol) and 1-methylcyclobutane-1-carbonyl chloride (2.92 g, 22.00 mmol). The crude product was purified by recrystallisation from hot EtOAc. The product was collected by vacuum filtration as a white crystalline solid [product contains ~20% impurity by ^{1}H NMR, no further purification performed] (58%, 2.37 g). **M.P.** = 82-84 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.89 – 7.78 (m, 1H), 7.24 – 7.12 (m, 2H), 7.06 (tt, *J* = 7.5, 1.8 Hz, 1H), 7.02 – 6.89 (m, 1H), 2.61 – 2.48 (m, 1H), 2.47 – 2.33 (m, 2H), 2.23 (s, 3H), 2.10 – 1.96 (m, 1H), 1.96 – 1.81 (m, 2H), 1.55 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.5, 135.8, 130.4, 128.7, 126.8, 124.9, 122.8, 40.7, 31.4, 25.5, 18.1, 17.6; **FTIR** (neat) ν = 3268, 2941, 2865, 1649, 1586, 1519, 1457, 1378, 1288, 1259, 1194, 1148, 1044, 947, 747, 685 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{13}H_{20}ON$ $(M+H)^+$ 206.1539, found 206.1541.

1-methyl-N-(o-tolyl)cyclopropane-1-carboxamide (282)



The title compound was prepared according to General Procedure L using *o*-toluidine (**195**) (2.14 g, 2.13 mL, 20.00 mmol) and 1-methylcyclopropane-1-carbonyl chloride (2.61 g, 22.00 mmol). The crude product was purified by flash column chromatography [silica gel, 10-15% Et_2O in pentane] to afford the product as a white solid (36%, 1.36 g). **M.P.** = 72-75 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 8.0, 1.3 Hz, 1H, H5), 7.42 (bs, 1H, NH), 7.21 – 7.13 (m, 2H, H2 & H3), 7.05 (td, *J* = 7.4, 1.3 Hz, 1H, H4), 2.25 (s, 3H, $H12_3$), 1.47 (s, 3H, $H9_3$), 1.30 (q, *J* = 3.8 Hz, 2H, $C10_A$ & $C11_A$), 0.76 – 0.50 (m, 2H, $C10_B$ & $C11_B$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.1 (C7), 136.1 (C6), 130.3 (C2), 128.7 (C1), 126.7 (C3), 124.8 (C4), 122.8 (C5), 19.9 (C8), 19.8 (C9), 17.6 (C12), 16.5 (C10 & C11); **FTIR** (neat) ν = 3265, 2965, 1645, 1603, 1416, 1494, 1444, 1332, 1242, 1203, 1182, 1117, 1040, 948, 927, 872, 742, 669 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{12}H16ON$ $(M+H)^+$ 190.1226, found 190.1226.

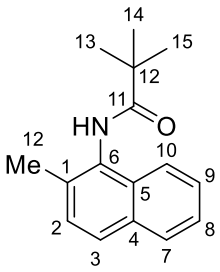
4-methyl-N-(o-tolyl)tetrahydro-2H-pyran-4-carboxamide (283)



The title compound was prepared according to General Procedure L using *o*-toluidine (**195**) (857 mg, 850 µL, 8.00 mmol) and 4-methyltetrahydro-2H-pyran-4-carbonyl chloride (1.63 g, 10.00 mmol). The crude product was purified by recrystallisation from hot EtOAc. The product was collected by vacuum filtration as a white crystalline solid (47%, 1.10 g). **M.P.** = 145-147 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 7.5, 1.9 Hz, 1H, H5), 7.33 (bs, 1H, NH), 7.18 (t, *J* = 7.0 Hz, 2H, H2 & H3), 7.08 (td, *J* = 7.2, 6.7, 1.2 Hz, 1H, H4), 3.75 (ddd, *J* = 11.9, 5.8, 3.9 Hz, 2H, $H12_A$ & $H13_A$), 3.66 (ddd, *J* = 11.7, 8.5, 3.1 Hz, 2H, $H12_B$ & $H13_B$), 2.20 (s, 3H, $H14_3$), 2.12 – 2.00 (m, 2H, $H10_A$ & $H11_A$), 1.58 (ddd, *J* = 13.2, 8.5, 3.8 Hz, 2H, $H10_B$ & $H11_B$), 1.32 (s, 3H, $H9_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.9 (C7), 135.6 (C6), 130.5 (C2), 130.4 (C1), 126.7 (C3), 125.7 (C4), 124.2 (C5), 64.8 (C12 & C13), 41.2 (C8), 35.6 (C10 & C11), 26.1 (C9), 17.9 (C14); **FTIR** (neat)

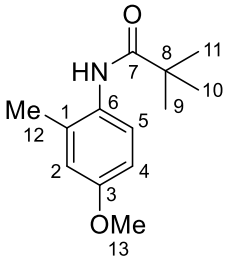
ν = 3305, 2958, 2927, 2843, 1642, 1512, 1460, 1252, 1203, 1103, 1035, 1015, 925, 750 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{14}H_{20}O_2N$ $(M+H)^+$ 234.1489, found 234.1490.

N-(2-methylnaphthalen-1-yl)pivalamide (284)



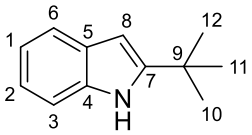
The title compound was prepared according to General Procedure L using 2-methyl-1-naphthylamine (1.00 g, 6.36 mmol). The crude product was purified by recrystallisation from hot EtOAc. The product was collected by vacuum filtration as a white crystalline solid (63%, 963 mg). **M.P.** = 143-144 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 7.9, 1.4 Hz, 1H, H2), 7.79 – 7.74 (m, 1H, H3), 7.71 (d, *J* = 8.4 Hz, 1H, H10), 7.45 (dddd, *J* = 22.6, 8.0, 6.8, 1.3 Hz, 2H, H8 & H9), 7.34 (d, *J* = 8.4 Hz, 1H, H7), 7.30 – 7.23 (bs, 1H, NH), 2.35 (s, 3H, $H12_3$), 1.44 (s, 9H, $H13_3$, $H14_3$ & $H15_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.2 (C11), 133.4 (C6), 132.9 (C4), 130.9 (C5), 130.0 (C1), 128.9 (C7), 128.3 (C2), 127.5 (C10), 126.7 (C9), 125.3 (C8), 122.0 (C3), 39.6 (C12), 28.1 (C13, C14 & C15), 18.6 (C12); **FTIR** (neat) ν = 3269, 3052, 2963, 1649, 1503, 1367, 1242, 1202, 1174, 1027, 942, 806, 740 640 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{16}H_{20}ON$ $(M+H)^+$ 242.1539, found 242.1540.

N-(4-methoxy-2-methylphenyl)pivalamide (288)



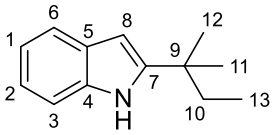
The title compound was prepared according to General Procedure L using 4-methoxy-2-methylaniline (1.50 g, 10.93 mmol) and pivaloyl chloride (1.61 mL, 1.58 g, 13.11 mmol). The crude product was purified by recrystallisation from hot hexane/EtOAc. The product was collected by vacuum filtration as a white crystalline solid (77%, 1.87 g). **M.P.** = 80-82 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.60 – 7.44 (m, 1H, H4), 7.09 (bs, 1H, NH), 6.78 – 6.67 (m, 2H, H2 & H5), 3.77 (s, 3H, $H13_3$), 2.21 (s, 3H, $H12_3$), 1.32 (s, 9H, $H9_3$, $H10_3$ & $H11_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.8 (C7), 157.2 (C3), 132.3 (C1), 128.9 (C6), 125.6 (C4), 116.1 (C2), 111.6 (C5), 55.5 (C13), 39.6 (C8), 27.9 (C9, C10 & C11), 18.1 (C8); **FTIR** (neat) ν = 3268, 2955, 1645, 1615, 1587, 1499, 1463, 1293, 1229, 1158, 1117, 1055, 919, 882, 798 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{13}H_{20}O_2N$ $(M+H)^+$ 222.1489, found 222.1489.

2-(*tert*-butyl)-1H-indole (197)



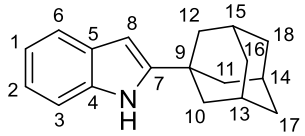
The title compound was prepared according to General Procedure M using N-(*o*-tolyl)pivalamide (**196**) (7.65 g, 40.00 mmol). The crude product was purified by flash column chromatography [silica gel, 5% EtOAc in petroleum ether b.p. 40–60 °C] to afford the product as a white solid (94%, 6.51 g). **M.P.** = 60-63 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.94 (bs, 1H, NH), 7.60 (ddt, *J* = 7.6, 1.5, 0.8 Hz, 1H, H6), 7.40 – 7.32 (m, 1H, H3), 7.21 – 7.16 (m, 1H, H2), 7.13 (td, *J* = 7.4, 1.2 Hz, 1H, H1), 6.31 (dd, *J* = 2.3, 0.9 Hz, 1H, H8), 1.44 (s, 9H, $H10_3$, $H11_3$ & $H12_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.9 (C7), 135.9 (C4), 128.7 (C5), 121.2 (C2), 120.1 (C6), 119.7 (C1), 110.5 (C3), 97.1 (C8), 32.0 (C9), 30.4 (C10, 11 & C12); **FTIR** (neat) ν = 3419, 2963, 1542, 1460, 1406, 1366, 1349, 1291, 784, 751, 737, 693 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{12}H_{16}N$ $(M+H)^+$ 174.1277, found 174.1278.

2-(*tert*-pentyl)-1H-indole (289)



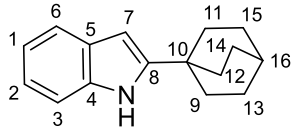
The title compound was prepared according to General Procedure M using 2,2-dimethyl-N-(o-tolyl)butanamide (**277**) (750 mg, 3.65 mmol). The crude product was purified by flash column chromatography [silica gel, 5% EtOAc in pentane] to afford the product as a yellow oil (86%, 584 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 (bs, 1H, NH), 7.56 (dt, *J* = 7.5, 1.0 Hz, 1H, H6), 7.33 (d, *J* = 7.8 Hz, 1H, H3), 7.17 – 7.11 (m, 1H, H1), 7.09 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H, H2), 6.32 – 6.22 (m, 1H, H8), 1.69 (q, *J* = 7.5 Hz, 2H, $H10_2$), 1.37 (s, 6H, $H11_3$ & $H12_3$), 0.80 (t, *J* = 7.5 Hz, 3H, $H13_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.4 (C7), 135.9 (C4), 128.7 (C5), 121.1 (C2), 120.0 (C6), 119.7 (C1), 110.4 (C3), 98.5 (C8), 36.1 (C10), 35.5 (C9), 27.7 (C11 & C12), 9.3 (C13); **FTIR** (neat) ν = 3421, 2965, 1543, 1459, 1406, 1300, 1228, 1012, 923, 783, 749, 736, 694 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{13}H_{18}N$ $(M+H)^+$ 188.1434, found 188.1435.

2-((3r,5r,7r)-adamantan-1-yl)-1H-indole (290)



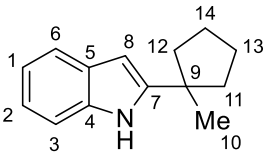
The title compound was prepared according to General Procedure M using (3r,5r,7r)-N-(o-tolyl)adamantane-1-carboxamide (**278**) (1.60 g, 5.94 mmol). The crude product was purified by flash column chromatography [silica gel, 5% EtOAc in petroleum ether b.p. 40–60 °C] to afford the product as a white solid (80%, 1.19 g). **M.P.** = 136-140 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.00 (bs, 1H, NH), 7.58 (dd, *J* = 7.5, 1.3 Hz, 1H, H6), 7.34 (d, *J* = 7.8 Hz, 1H, H3), 7.17 – 7.12 (m, 1H, H2), 7.09 (td, *J* = 7.4, 1.2 Hz, 1H, H1), 6.26 (s, 1H, H8), 2.14 (p, *J* = 3.1 Hz, 3H, H13, H14 & H15), 2.02 (d, *J* = 2.8 Hz, 6H, $H10_2$, $H11_2$ & $H12_2$), 1.90 – 1.75 (m, 6H, $H16_2$, $H17_2$ & $H18_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.3 (C7), 135.5 (C4), 128.5 (C5), 121.0 (C2), 120.0 (C6), 119.6 (C2), 110.4 (C3), 96.4 (C8), 42.6 (C10, C11 & C12), 36.8 (C16, C17 & C18), 33.8 (C9), 28.5 (C13, C14 & C15); **FTIR** (neat) ν = 3417, 2900, 2848, 1542, 1458, 1405, 1346, 1313, 1287, 1101, 979, 780, 748, 684 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{18}H_{22}N$ $(M+H)^+$ 252.1747, found 252.1747.

2-(bicyclo[2.2.2]octan-1-yl)-1H-indole (291)



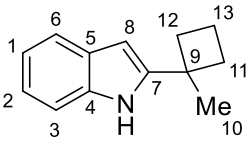
The title compound was prepared according to General Procedure M using N-(o-tolyl)bicyclo[2.2.2]octane-1-carboxamide (**279**) (100 mg, 0.40 mmol). The crude product was purified by flash column chromatography [silica gel, 5% EtOAc in petroleum ether b.p. 40–60 °C] to afford the product as a white solid (72%, 65 mg). **M.P.** = 94-96 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.90 (bs, 1H, NH), 7.52 (ddt, *J* = 7.6, 1.6, 0.8 Hz, 1H), 7.30 (dq, *J* = 8.0, 1.0 Hz, 1H), 7.14 – 7.07 (m, 1H), 7.05 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 6.19 (dd, *J* = 2.2, 0.9 Hz, 1H), 1.90 – 1.81 (m, 6H), 1.76 – 1.65 (m, 7H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.4 (C8), 135.8 (C4), 128.6 (C5), 121.1 (C2), 120.0 (C6), 119.6 (C1), 110.5 (C3), 97.1 (C7), 31.6 (C9, C11 & C12), 31.4 (C10), 26.2 (C12, C13 & C14), 24.2 (C16); **FTIR** (neat) ν = 3416, 2940, 2860, 1459, 1406, 1344, 1292, 781, 750, 739, 683 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{16}H_{20}N$ $(M+H)^+$ 226.1590, found 226.1591.

2-(1-methylcyclopentyl)-1H-indole (292)



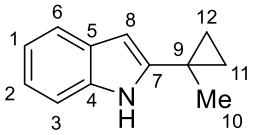
The title compound was prepared according to General Procedure M using 1-methyl-N-(o-tolyl)cyclopentyl-1-carboxamide (**280**) (800 mg, 3.68 mmol). The crude product was purified by flash column chromatography [silica gel, 5% EtOAc in pentane] to afford the product as a white solid (93%, 681 mg). **M.P.** = 36-38 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 (bs, 1H, NH), 7.57 (ddt, *J* = 7.6, 1.5, 0.8 Hz, 1H, H6), 7.34 (dt, *J* = 8.0, 0.9 Hz, 1H, H3), 7.18 – 7.13 (m, 1H, H2), 7.10 (td, *J* = 7.4, 1.2 Hz, 1H, H1), 6.36 – 6.22 (m, 1H, H8), 2.11 – 1.99 (m, 2H, $H11_A$ & $H12_A$), 1.88 – 1.73 (m, 6H, $H11_B$, $H12_B$, $H13_2$ & $H14_2$), 1.43 (s, 3H, $H10_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.3 (C7), 136.0 (C4), 128.6 (C5), 121.1 (C2), 120.0 (C6), 119.7 (C1), 110.4 (C3), 97.7 (C8), 43.3 (C9), 40.1 (C11 & C12), 27.9 (C10), 24.5 (C13 & C14); **FTIR** (neat) ν = 3416, 2957, 2869, 1544, 1458, 1405, 1319, 1288, 1321, 1148, 782, 749, 736, 696, 610 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{14}H_{18}N$ $(M+H)^+$ 200.1434, found 200.1434.

2-(1-methylcyclobutyl)-1H-indole (293)



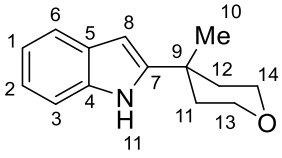
The title compound was prepared according to General Procedure M using 1-methyl-N-(o-tolyl)cyclobutane-1-carboxamide (**281**) (1.02 g, 5.00 mmol). The crude product was purified by flash column chromatography [silica gel, 5% EtOAc in pentane] to afford the product as a white solid (74%, 685 mg). **M.P.** = 38-40 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.92 (bs, 1H, NH), 7.58 (dt, *J* = 7.6, 0.9 Hz, 1H, H6), 7.38 – 7.31 (m, 1H, H3), 7.18 – 7.08 (m, 2H, H1 & H2), 2.50 – 2.41 (m, 2H, $H11_A$ & $H12_A$), 2.17 – 2.05 (m, 3H, $H11_B$, $H12_B$ & $H13_A$), 2.00 (dddt, *J* = 9.2, 7.9, 6.1, 4.0 Hz, 1H, $H13_B$), 1.60 (s, 3H, $H10_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.1 (C7), 136.1 (C4), 128.7 (C5), 121.2 (C2), 120.1 (C6), 119.8 (C1), 110.5 (C3), 97.5 (C8), 38.4 (C9), 34.5 (C11 & C12), 27.5 (C10), 15.8 (C13); **FTIR** (neat) ν = 3410, 2958, 1546, 1458, 1406, 1297, 1235, 1013, 780, 749, 692 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{13}H_{16}N$ $(M+H)^+$ 186.1277, found 186.1278.

2-(1-methylcyclopropyl)-1H-indole (294)



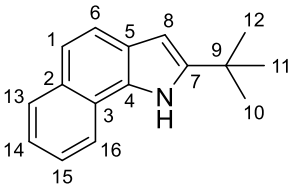
The title compound was prepared according to General Procedure M using 1-methyl-N-(o-tolyl)cyclopropane-1-carboxamide (**282**) (400 mg, 2.11 mmol). The crude product was purified by flash column chromatography [silica gel, 5% EtOAc in pentane] to afford the product as a white solid (90%, 324 mg). **M.P.** = 47-49 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.85 (bs, 1H, NH), 7.53 (ddt, *J* = 7.6, 1.6, 0.8 Hz, 1H, H6), 7.30 (dq, *J* = 8.0, 1.0 Hz, 1H, H3), 7.16 – 7.11 (m, 1H, H2), 7.08 (td, *J* = 7.4, 1.3 Hz, 1H, H1), 6.23 (dd, *J* = 2.2, 0.9 Hz, 1H, H8), 1.52 (s, 3H, $H10_3$), 1.02 – 0.95 (m, 2H, $H11_A$ & $H12_A$), 0.86 – 0.79 (m, 2H, $H11_B$ & $H12_B$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.9 (C7), 135.8 (C4), 128.9 (C5), 121.2 (C2), 119.9 (C6), 119.8 (C1), 110.4 (C3), 98.1 (C8), 23.8 (C10), 15.7 (C11 & C12), 14.5 (C9); **FTIR** (neat) ν = 3424, 2965, 1583, 1550, 1563, 1408, 1385, 1339, 1312, 1235, 1014, 945, 923, 788, 748, 735, 680 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{14}H_{14}N$ $(M+H)^+$ 172.1121, found 172.1124.

2-(4-methyltetrahydro-2H-pyran-4-yl)-1H-indole (295)



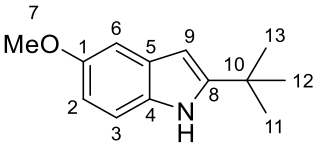
The title compound was prepared according to General Procedure M using 4-methyl-N-(o-tolyl)tetrahydro-2H-pyran-4-carboxamide (**283**) (800 mg, 3.43 mmol). The crude product was purified by flash column chromatography [silica gel, 15% EtOAc in pentane] to afford the product as a white solid (62%, 458 mg). **M.P.** = 112-115 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96 (bs, 1H, NH), 7.57 (dt, *J* = 7.6, 1.0 Hz, 1H, H6), 7.34 (d, *J* = 7.9 Hz, 1H, H3), 7.15 (ddd, *J* = 8.1, 7.1, 1.3 Hz, 1H, H2), 7.10 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H, H1), 6.35 – 6.27 (m, 1H, H8), 3.81 (ddd, *J* = 11.7, 6.3, 3.7 Hz, 2H, $H13_A$ & $H14_A$), 3.71 (ddd, *J* = 11.6, 8.1, 3.2 Hz, 2H, $H13_B$ & $H14_B$), 2.11 (dddd, *J* = 13.7, 6.0, 3.2, 1.2 Hz, 2H, $H11_A$ & $H12_A$), 1.86 – 1.73 (m, 2H, $H11_B$ & $H12_B$), 1.40 (s, 3H, $H10_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.8 (C7), 134.0 (C4), 128.6 (C5), 121.5 (C2), 120.2 (C6), 119.9 (C1), 110.6 (C3), 98.9 (C8), 64.5 (C13 & C14), 37.6 (C11 & C12), 33.5 (C9), 29.1 (C10); **FTIR** (neat) ν = 3417, 3302, 2955, 2864, 1540, 1459, 1410, 1346, 1301, 1179, 1098, 1033, 1013, 858, 786, 750, 736, 699 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{14}H_{18}NO$ $(M+H)^+$ 216.1383, found 216.1384.

2-(*tert*-butyl)-1H-benzo[g]indole (296)



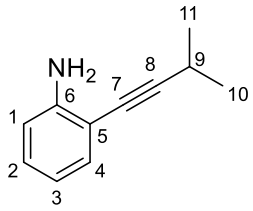
The title compound was prepared according to General Procedure M using N-(2-methylnaphthalen-1-yl)pivalamide (**284**) (3.66 g, 15.16 mmol). The reaction time for this example was 72 h. The crude product was purified by flash column chromatography [silica gel, 5% Et_2O in pentane] to afford the product as a white solid (26%, 890 mg). **M.P.** = 78-80 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.62 (bs, 1H, NH), 8.01 (dq, *J* = 8.2, 0.8 Hz, 1H, H13), 7.95 – 7.89 (m, 1H, H16), 7.67 (dd, *J* = 8.6, 0.7 Hz, 1H, H6), 7.56 – 7.47 (m, 2H, H1 & H14), 7.40 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H, H15), 6.43 (d, *J* = 2.3 Hz, 1H, H8), 1.48 (s, 9H, $H10_3$, $H11_3$ & $H13_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.1 (C7), 130.1 (C4), 129.9 (C2), 129.1 (C16), 125.3 (C14), 124.4 (C5), 123.4 (C15), 121.6 (C3), 120.6 (C6), 120.5 (C1), 119.2 (C13), 98.9 (C8), 32.1 (C9), 30.8 (C10, C11 & C12); **FTIR** (neat) ν = 3454, 2963, 1524, 1457, 1391, 1365, 1295, 1223, 1157, 1028, 939, 856, 809, 740, 684 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{16}H_{18}N$ $(M+H)^+$ 224.1434, found 224.1434.

2-(*tert*-butyl)-5-methoxy-1H-indole (297)



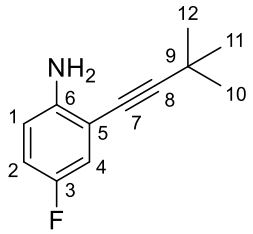
The title compound was prepared according to General Procedure M using N-(4-methoxy-2-methylphenyl)pivalamide (**288**) (1.77 g, 8.71 mmol). The crude product was purified by flash column chromatography [silica gel, 10% EtOAc in pentane] to afford the product as a white solid (84%, 1.49 g). **M.P.** = 89-94 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.87 (bs, 1H, NH), 7.21 (d, *J* = 8.7 Hz, 1H, H3), 7.05 (d, *J* = 2.5 Hz, 1H, H6), 6.80 (dd, *J* = 8.7, 2.5 Hz, 1H, H2), 6.25 – 6.15 (m, 1H, H9), 3.86 (s, 3H, $H7_3$), 1.40 (s, 9H, $H11_3$, $H12_3$ & $H13_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.3 (C1), 149.8 (C8), 131.0 (C4), 129.1 (C5), 111.2 (C3), 111.1 (C2), 102.4 (C6), 97.0 (C9), 56.1 (C7), 32.0 (C10), 30.4 (C11, C12 & C13); **FTIR** (neat) ν = 3422, 2963, 1624, 1589, 1486, 1409, 1309, 1223, 1205, 1152, 1115, 1030, 944, 835, 804, 776, 752, 695 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{13}H_{18}NO$ $(M+H)^+$ 204.1383, found 204.1385.

2-(3-methylbut-1-yn-1-yl)aniline (298)



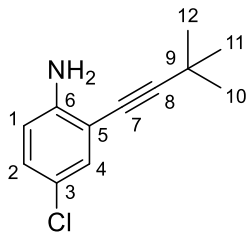
The title compound was prepared according to General Procedure N using 2-iodoaniline (5.00 g, 22.83 mmol) and 2-methyl-1-butyne (1.87 g, 2.80 mL, 27.39 mmol). The crude product was purified by flash column chromatography [silica gel, 5% EtOAc in petroleum ether b.p. 40–60 °C] to afford the product as a yellow oil (97%, 3.53 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31 – 7.25 (m, 1H, H4), 7.11 (ddd, *J* = 8.1, 7.4, 1.6 Hz, 1H, H2), 6.74 – 6.64 (m, 2H, H1 & H3), 4.12 (bs, 2H, NH_2), 2.88 (hept, *J* = 6.9 Hz, 1H, H9), 1.33 (d, *J* = 6.9 Hz, 6H, $H10_3$ & $H11_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.6 (C6), 132.1 (C4), 128.9 (C2), 117.9 (C3), 114.2 (C1), 108.9 (C5), 101.4 (C8), 76.2 (C7), 23.4 (C10 & C11), 21.5 (C19); **FTIR** (neat) ν = 3474, 3379, 1613, 1493, 1456, 1320, 1157, 747 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{11}H_{14}N$ $(M+H)^+$ 160.1121, found 160.1120.

2-(3,3-dimethylbut-1-yn-1-yl)-4-fluoroaniline (299)



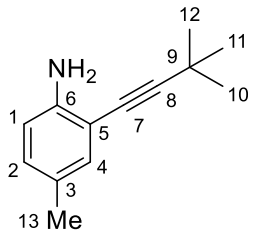
The title compound was prepared according to General Procedure N using 4-fluoro-2-iodoaniline (1.19 g, 595 µL, 5.00 mmol) and 3,3-dimethyl-1-butyne (493 mg, 739 µL, 6.00 mmol). The crude product was purified by flash column chromatography [silica gel, 10% EtOAc in pentane] to afford the product as an orange oil (93%, 889 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.99 – 6.90 (m, 1H, H4), 6.80 (ddd, *J* = 8.8, 8.3, 3.0 Hz, 1H, H2), 6.62 (dd, *J* = 8.8, 4.8 Hz, 1H, H1), 3.85 (bs, 2H, NH_2), 1.34 (s, 9H, $H10_3$, $H11_3$ & $H12_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.5 (d, *J* = 235.4 Hz, C3), 143.9 (d, *J* = 2.7 Hz, C6), 117.9 (d, *J* = 23.1 Hz, C4), 116.0 (d, *J* = 23.0 Hz, C2), 115.1 (d, *J* = 8.5 Hz, C1), 109.9 (d, *J* = 9.5 Hz, C5), 105.1 (C8), 74.9 (C7), 31.3 (C10, C11 & C12), 28.4 (C9); **^{19}F NMR** (377 MHz, $CDCl_3$) δ -127.37 (td, *J* = 8.7, 4.8 Hz); **FTIR** (neat) ν = 3474, 2968, 1602, 1582, 1495, 1454, 1364, 1309, 1276, 1248, 1145, 869, 807, 783, 695 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{12}H_{15}NF$ $(M+H)^+$ 192.1183, found 192.1184.

2-(3,3-dimethylbut-1-yn-1-yl)-4-chloroaniline (300)



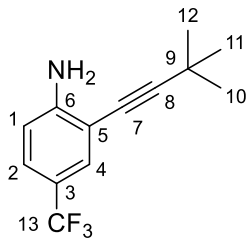
The title compound was prepared according to General Procedure N using 4-chloro-2-iodoaniline (1.27 g, 5.00 mmol) and 3,3-dimethyl-1-butyne (493 mg, 739 µL, 6.00 mmol). The crude product was purified by flash column chromatography [silica gel, 5-10% EtOAc in pentane] to afford the product as a yellow solid (88%, 916 mg). **M.P.** = 46-48 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 2.5 Hz, 1H, H4), 7.02 (d, *J* = 2.5 Hz, 1H, H2), 7.00 (d, *J* = 2.5 Hz, 1H, H1), 4.00 (s, 2H, NH_2), 1.34 (s, 9H, $H10_3$, $H11_3$ & $H12_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.1 (C6), 131.4 (C4), 128.8 (C2), 122.3 (C3), 115.3 (C1), 110.4 (C5), 105.4 (C8), 74.6 (C7), 31.3 (C10, C11 & C12), 28.4 (C9); **FTIR** (neat) ν = 3478, 3386, 2968, 1612, 1488, 1409, 1362, 1303, 1249, 1201, 1148, 1089, 941, 879, 850, 810, 683, 648 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{12}H_{15}NCl$ $(M+H)^+$ 208.0888, found 208.0889.

2-(3,3-dimethylbut-1-yn-1-yl)-4-methylaniline (301)



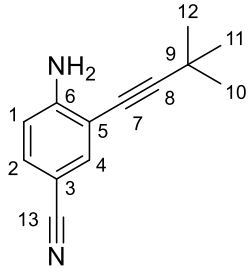
The title compound was prepared according to General Procedure N using 4-methyl-2-iodoaniline (1.17 g, 5.00 mmol) and 3,3-dimethyl-1-butyne (493 mg, 739 µL, 6.00 mmol). The crude product was purified by flash column chromatography [silica gel, 10% EtOAc in pentane] to afford the product as a yellow solid (99%, 929 mg). **M.P.** = 58-60 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.11 – 7.05 (m, 1H, H4), 6.89 (dd, *J* = 8.2, 2.1 Hz, 1H, H2), 6.61 (d, *J* = 8.2 Hz, 1H, H1), 3.96 (bs, 2H, NH_2), 2.21 (s, 3H, $H13_3$), 1.36 (s, 9H, $H10_3$, $H11_3$ & $H12_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.1 (C6), 132.2 (C4), 129.7 (C2), 127.2 (C3), 114.4 (C1), 109.0 (C5), 103.9 (C8), 75.7 (C7), 31.4 (C10, C11 & C12), 28.4 (C9), 20.4 (C13); **FTIR** (neat) ν = 3472, 3376, 2967, 1618, 1598, 1502, 1475, 1457, 1362, 1304, 1254, 1156, 881, 811 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{13}H_{18}N$ $(M+H)^+$ 188.1434, found 188.1435.

2-(3,3-dimethylbut-1-yn-1-yl)-4-(trifluoromethyl)aniline (302)



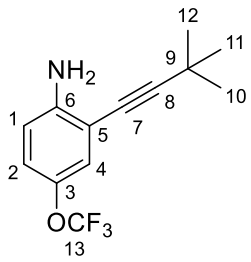
The title compound was prepared according to General Procedure N using 2-iodo-4-(trifluoromethyl)aniline (1.44 g, 5.00 mmol) and 3,3-dimethyl-1-butyne (493 mg, 739 µL, 6.00 mmol). The crude product was purified by flash column chromatography [silica gel, 10-15% EtOAc in pentane] to afford the product as an amber solid (98%, 1.18 g). **M.P.** = 46-48 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.56 – 7.42 (m, 1H, H4), 7.29 (ddd, *J* = 8.5, 2.2, 0.8 Hz, 1H, H2), 6.72 – 6.67 (m, 1H, H1), 4.43 (s, 2H, NH_2), 1.35 (s, 9H, $H10_3$, $H11_3$ & $H12_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.1 (C6), 129.4 (q, *J* = 3.9 Hz, C4), 125.9 (q, *J* = 3.9 Hz, C2), 124.6 (q, *J* = 271.6 Hz, C13), 119.8 (q, *J* = 32.6 Hz, C3), 113.5 (C1), 108.6 (C5), 105.5 (C8), 74.4 (C7), 31.3 (C10, C11 & C12), 28.5 (C9); **^{19}F NMR** (377 MHz, $CDCl_3$) δ -61.42 (d, *J* = 2.8 Hz); **FTIR** (neat) ν = 3492, 3395, 2970, 1623, 1511, 1431, 1333, 1268, 1146, 1113, 1072, 903, 821, 632 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{13}H_{15}NF_3$ $(M+H)^+$ 242.1151, found 242.1151.

4-amino-3-(3,3-dimethylbut-1-yn-1-yl)benzonitrile (303)



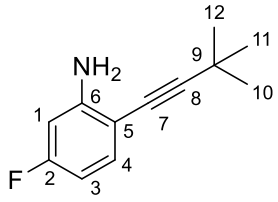
The title compound was prepared according to General Procedure N using 4-amino-3-iodobenzonitrile (1.22 g, 5.00 mmol) and 3,3-dimethyl-1-butyne (493 mg, 739 µL, 6.00 mmol). The crude product was purified by flash column chromatography [silica gel, 20% EtOAc in pentane] to afford the product as an orange solid (99%, 981 mg). **M.P.** = 64-67 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 1.9, 0.4 Hz, 1H, H4), 7.29 (dd, *J* = 8.5, 2.0 Hz, 1H, H2), 6.65 (dd, *J* = 8.4, 0.5 Hz, 1H, H1), 4.67 (bs, 2H, NH_2), 1.33 (s, 9H, $H10_3$, $H11_3$ & $H12_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.0 (C6), 136.1 (C4), 132.6 (C2), 119.7 (C13), 113.7 (C1), 109.1 (C5), 106.1 (C3), 99.9 (C8), 73.5 (C7), 31.1 (C10, C11 & C12), 28.4 (C9); **FTIR** (neat) ν = 3479, 3364, 2969, 2218, 1616, 1500, 1418, 1362, 1269, 898, 821, 605 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{13}H_{15}N_2$ $(M+H)^+$ 199.1230, found 199.1231.

2-(3,3-dimethylbut-1-yn-1-yl)-4-(trifluoromethyl)aniline (304)



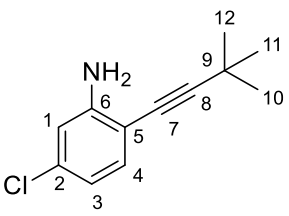
The title compound was prepared according to General Procedure N using 2-iodo-4-(trifluoromethoxy)aniline (1.51 g, 5.00 mmol) and 3,3-dimethyl-1-butyne (493 mg, 739 μL, 6.00 mmol). The crude product was purified by flash column chromatography [silica gel, 10-15% EtOAc in pentane] to afford the product as an amber solid (87%, 1.12 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.11 (dq, *J* = 2.9, 1.0 Hz, 1H, H4), 6.94 (ddq, *J* = 8.8, 2.8, 1.0 Hz, 1H, H1), 6.64 (d, *J* = 8.8 Hz, 1H, H2), 4.02 (s, 2H, NH_2), 1.35 (s, 9H, $H10_3$, $H11_3$ & $H12_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.3 (C6), 140.5 (C3), 124.8 (C4), 122.3 (C1), 120.9 (d, *J* = 255.7 Hz, C13), 114.7 (C2), 109.7 (C5), 105.5 (C8), 74.6 (C7), 31.3 (C10, C11 & C12), 28.5 (C9); **^{19}F NMR** (377 MHz, $CDCl_3$) δ -58.5; **FTIR** (neat) ν = 3490, 3379, 2971, 1619, 1499, 1255, 1226, 1211, 1153, 887, 857, 818 690 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{13}H_{15}ONF_3$ $(M+H)^+$ 258.1100, found 258.1099.

2-(3,3-dimethylbut-1-yn-1-yl)-5-fluoroaniline (305)



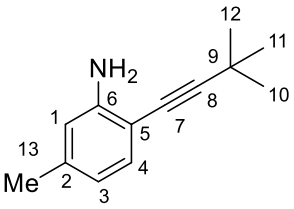
The title compound was prepared according to General Procedure N using 5-fluoro-2-iodoaniline (1.10 g, 4.64 mmol) and 3,3-dimethyl-1-butyne (458 mg, 687 μL, 5.57 mmol). The crude product was purified by flash column chromatography [silica gel, 5% Et_2O in pentane] to afford the product as a white solid (94%, 832 g). **M.P.** = 45-46°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.23 – 7.12 (m, 1H, H4), 6.48 – 6.24 (m, 2H, H1 & H3), 4.24 (bs, 2H, NH_2), 1.34 (s, 9H, $H10_3$, $H11_3$ & $H12_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.3 (d, *J* = 245.6 Hz, C2), 149.2 (d, *J* = 11.3 Hz, C6), 133.4 (d, *J* = 10.3 Hz, C4), 105.0 (d, *J* = 22.5 Hz, C3), 105.0 (d, *J* = 3.0 Hz, C5), 103.9 (d, *J* = 1.0 Hz, C8), 101.0 (d, *J* = 25.4 Hz, C1), 74.7 (C7), 31.4 (C10, C11 & C12), 28.4 (C9); **^{19}F NMR** (377 MHz, $CDCl_3$) δ -111.48 (ddd, *J* = 10.6, 8.8, 6.4 Hz); **FTIR** (neat) ν = 3484, 3387, 2968, 1617, 1501, 1441, 1363, 1280, 1258, 1166, 1117, 1065, 976, 839, 793, 618 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{12}H_{15}NF$ $(M+H)^+$ 192.1183, found 192.1184.

2-(3,3-dimethylbut-1-yn-1-yl)-5-chloroaniline (306)



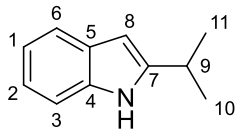
The title compound was prepared according to General Procedure N using 5-chloro-2-iodoaniline (1.10 g, 4.34 mmol) and 3,3-dimethyl-1-butyne (428 mg, 641 µL, 5.21 mmol). The crude product was purified by flash column chromatography [silica gel, 5% Et_2O in pentane] to afford the product as a yellow solid (81%, 731 g). **M.P.** = 46-47°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.14 (d, *J* = 8.2 Hz, 1H, H4), 6.67 (d, *J* = 2.0 Hz, 1H, C1), 6.62 (dd, *J* = 8.2, 2.0 Hz, 1H, C3), 4.20 (bs, 2H, NH_2), 1.34 (s, 9H, $H10_3$, $H11_3$ & $H12_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.5 (C6), 134.4 (C2), 132.9 (C4), 118.1 (C3), 113.9 (C1), 107.5 (C5), 105.1 (C8), 74.7 (C7), 31.3 (C10, C11 & C12), 28.4 (C9); **FTIR** (neat) ν = 3483, 3386, 2968, 1610, 1561, 1490, 1474, 1422, 1362, 1304, 1251, 1203, 1094, 1057, 928, 888, 846, 797, 690 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{12}H_{15}NCl$ $(M+H)^+$ 208.0888, found 208.0888.

2-(3,3-dimethylbut-1-yn-1-yl)-5-methylaniline (307)



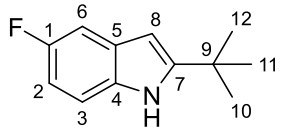
The title compound was prepared according to General Procedure N using 5-methyl-2-iodoaniline (920 mg, 3.95 mmol) and 3,3-dimethyl-1-butyne (389 mg, 585 µL, 4.74 mmol). The crude product was purified by flash column chromatography [silica gel, 5-10% EtOAc in pentane] to afford the product as a yellow oil (97%, 719 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.13 (d, *J* = 7.7 Hz, 1H, H4), 6.52 – 6.40 (m, 2H, H1 & H3), 4.07 (bs, 2H, NH_2), 2.25 (s, 3H, $H13_3$), 1.40 – 1.29 (m, 9H, $H10_3$, $H11_3$ & $H12_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.4 (C6), 139.0 (C2), 131.8 (C4), 119.1 (C3), 114.9 (C1), 106.2 (C5), 103.5 (C8), 75.6 (C7), 31.5 (C10, C11 & C12), 28.4 (C9), 21.6 (C13); **FTIR** (neat) ν = 3474, 3379, 2967, 1615, 1566, 1505, 1455, 1362, 1314, 1295, 1257, 1203, 952, 859, 799 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{13}H_{18}N$ $(M+H)^+$ 188.1434, found 188.1436.

2-isopropyl-1H-indole (308)



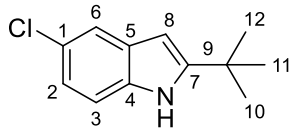
The title compound was prepared according to General Procedure O using 2-(3-methylbut-1-yn-1-yl)aniline (**298**) (3.18 g, 20.00 mmol). The crude product was purified by flash column chromatography [silica gel, 5% EtOAc in petroleum ether b.p. 40–60 °C] to afford the product as a yellow solid (96%, 3.06 g). **M.P.** = 62-63 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.85 (s, 1H, NH), 7.64 – 7.57 (m, 1H, H6), 7.37 – 7.28 (m, 1H, H3), 7.19 (td, *J* = 8.0, 7.5, 1.5 Hz, 1H, H2), 7.14 (td, *J* = 7.4, 1.3 Hz, 1H, H1), 6.43 – 6.14 (m, 1H, H8), 3.07 (hept, *J* = 6.9 Hz, 1H, H9), 1.40 (d, *J* = 6.9 Hz, 6H, $H10_3$ & $H11_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.1 (C7), 135.8 (C4), 128.7 (C5), 121.1 (C2), 120.0 (C6), 119.7 (C1), 110.5 (C3), 97.5 (C8), 27.7 (C9), 22.5 (C10 & C11); **FTIR** (neat) ν = 3388, 3050, 2966, 2926, 2871, 1547, 1461, 1411, 1382, 1360, 1342, 1303, 1175, 1032, 780, 748, 688, 630 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{11}H_{14}N$ $(M+H)^+$ 160.1121, found 160.1121.

2-(*tert*-butyl)-5-fluoro-1H-indole (309)



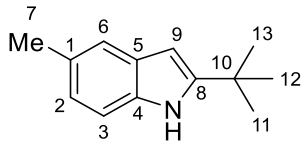
The title compound was prepared according to General Procedure O using 2-(3,3-dimethylbut-1-yn-1-yl)-4-fluoroaniline (**299**) (860 mg, 4.50 mmol). The crude product was purified by flash column chromatography [silica gel, 5-10% EtOAc in pentane] to afford the product as a white solid (92%, 792 mg). **M.P.** = 42-44 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.93 (bs, 1H, NH), 7.25 – 7.14 (m, 2H, H3 & H6), 6.86 (ddd, *J* = 9.4, 8.7, 2.5 Hz, 1H, H2), 6.23 (dd, *J* = 2.3, 0.9 Hz, 1H, H8), 1.39 (s, 9H, $H10_3$, $H11_3$ & $H12_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.1 (d, *J* = 233.1 Hz, C1), 150.9 (C7), 132.4 (C4), 129.0 (d, *J* = 10.3 Hz, C5), 111.0 (d, *J* = 10.0 Hz, C3), 109.3 (d, *J* = 26.2 Hz, C2), 105.0 (d, *J* = 23.2 Hz, C6), 97.4 (C8), 32.1 (C9), 30.4 (C10, C11 & C12); **^{19}F NMR** (377 MHz, $CDCl_3$) δ -125.27 (dd, *J* = 9.8, 4.5 Hz); **FTIR** (neat) ν = 3469, 3434, 2964, 1626, 1581, 1487, 1451, 1412, 1367, 1308, 1250, 1223, 1139, 1104, 954, 851, 804, 780, 758, 695 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{12}H_{15}NF$ $(M+H)^+$ 192.1183, found 192.1185.

2-(*tert*-butyl)-5-chloro-1H-indole (310)



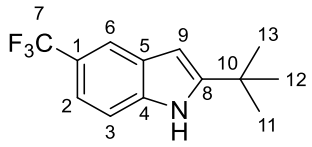
The title compound was prepared according to General Procedure O using 2-(3,3-dimethylbut-1-yn-1-yl)-4-chloroaniline (**300**) (930 mg, 4.50 mmol). The crude product was purified by flash column chromatography [silica gel, 10% EtOAc in pentane] to afford the product as a white solid (90%, 837 mg). **M.P.** = 60-62 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.97 (bs, 1H, NH), 7.51 (d, *J* = 2.0 Hz, 1H, H6), 7.22 (d, *J* = 8.5 Hz, 1H, H3), 7.08 (dd, *J* = 8.5, 2.1 Hz, 1H, H2), 6.22 (dd, *J* = 2.2, 0.9 Hz, 1H, H8), 1.40 (s, 9H, $H10_3$, $H11_3$ & $H12_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.5 (C7), 134.2 (C4), 129.8 (C5), 125.3 (C1), 121.4 (C2), 119.5 (C6), 111.4 (C3), 97.0 (C8), 32.0 (C9), 30.4 (C10, C11 & C12); **FTIR** (neat) ν = 3439, 2964, 1572, 1450, 1392, 1367, 1304, 1275, 1249, 1061, 914, 867, 791, 692 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{12}H_{15}NCl$ $(M+H)^+$ 208.0888, found 208.0891.

2-(*tert*-butyl)-5-methyl-1H-indole (311)



The title compound was prepared according to General Procedure O using 2-(3,3-dimethylbut-1-yn-1-yl)-4-methylaniline (**301**) (810 mg, 4.32 mmol). The crude product was purified by flash column chromatography [silica gel, 5-10% Et_2O in pentane] to afford the product as a yellow solid (84%, 677 mg). **M.P.** = 87-90 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.85 (bs, 1H, NH), 7.35 (s, 1H, H6), 7.22 (d, *J* = 8.2 Hz, 1H, H3), 7.01 – 6.93 (m, 1H, H2), 6.26 – 6.15 (m, 1H, H9), 2.45 (s, 3H, $H7_3$), 1.40 (s, 9H, $H11_3$, $H12_3$ & $H13_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.0 (C8), 134.2 (C4), 128.93 (C5), 129.87 (C1), 122.7 (C2), 119.8 (C6), 110.1 (C3), 96.6 (C9), 32.0 (C10), 30.4 (C11, C12 & C13), 21.6 (C7); **FTIR** (neat) ν = 3421, 2963, 1586, 1547, 1485, 1460, 1410, 1365, 1309, 1296, 1249, 868, 792, 744, 693 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{13}H_{18}N$ $(M+H)^+$ 188.1434, found 188.1436.

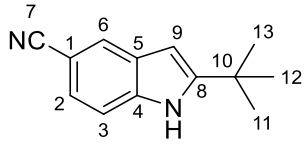
2-(*tert*-butyl)-5-(trifluoromethyl)-1H-indole (312)



The title compound was prepared according to General Procedure O using 2-(3,3-dimethylbut-1-yn-1-yl)-4-(trifluoromethyl)aniline (**302**)

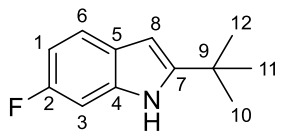
(1.08 g, 4.50 mmol). The crude product was purified by flash column chromatography [silica gel, 10% Et_2O in pentane] to afford the product as a white solid (86%, 925 mg). **M.P.** = 36-39 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.13 (bs, 1H, NH), 7.83 (dq, *J* = 1.7, 0.9 Hz, 1H, H6), 7.40 – 7.32 (m, 2H, H2 & H3), 6.34 (dd, *J* = 2.2, 0.7 Hz, 1H, H9), 1.41 (s, 9H, $H11_3$, $H12_3$ & $H13_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.8 (C8), 137.3 (C4), 128.1 (C5), 125.6 (q, *J* = 272.7 Hz, C7), 122.1 (q, *J* = 31.3 Hz, C1), 118.0 (q, *J* = 3.6 Hz, C6), 117.8 (q, *J* = 4.3 Hz, C2), 110.6 (C3), 98.0 (C9), 32.1 (C10), 30.3 (C11, C12 & C13); **^{19}F NMR** (377 MHz, $CDCl_3$) δ -60.1; **FTIR** (neat) ν = 3484, 2968, 1626, 1549, 1458, 1416, 1329, 1317, 1273, 1157, 1109, 1053, 926, 889, 807, 789, 753, 694, 660 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{13}H_{15}NF_3$ $(M+H)^+$ 242.1151, found 242.1153.

2-(*tert*-butyl)-1H-indole-5-carbonitrile (313)



The title compound was prepared according to General Procedure O using 4-amino-3-(3,3-dimethylbut-1-yn-1-yl)benzonitrile (**303**) (900 mg, 4.54 mmol). The crude product was purified by flash column chromatography [silica gel, 10-15% EtOAc in pentane] to afford the product as a white solid (90%, 812 mg). **M.P.** = 125-129 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.64 (bs, 1H, NH), 7.87 (dt, *J* = 1.4, 0.7 Hz, 1H, H6), 7.40 (dt, *J* = 8.4, 0.8 Hz, 1H, H3), 7.35 (dd, *J* = 8.4, 1.5 Hz, 1H, H2), 6.32 (dd, *J* = 2.2, 0.8 Hz, 1H, H9), 1.42 (s, 9H, $H11_3$, $H12_3$, $H13_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.6 (C8), 137.9 (C4), 128.5 (C5), 125.4 (C6), 124.2 (C2), 121.4 (C7), 111.4 (C3), 102.3 (C1), 97.7 (C9), 32.1 (C10), 30.2 (C11, C12 & C13); **FTIR** (neat) ν = 3328, 2979, 2888, 2219, 1615, 1544, 1476, 1419, 1367, 1318, 1295, 1261, 1128, 1073, 944, 883, 804, 787, 704 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{13}H_{15}N_2$ $(M+H)^+$ 199.1230, found 199.1231.

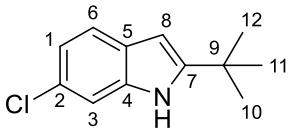
2-(*tert*-butyl)-6-fluoro-1H-indole (314)



The title compound was prepared according to General Procedure O using 2-(3,3-dimethylbut-1-yn-1-yl)-5-fluoroaniline (**305**) (712 mg, 3.72 mmol). The crude product was purified by flash column chromatography [silica gel, 5% EtOAc in pentane] to afford the product as a white solid (96%,

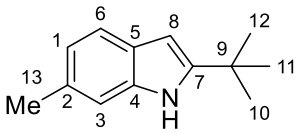
682 mg). **M.P.** = 76-80 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.95 (bs, 1H, NH), 7.47 (dd, *J* = 8.6, 5.4 Hz, 1H, H6), 7.03 (dd, *J* = 9.8, 2.3 Hz, 1H, H1), 6.88 (ddd, *J* = 9.8, 8.6, 2.4 Hz, 1H, H3), 6.26 (dd, *J* = 2.3, 1.0 Hz, 1H, H8), 1.41 (s, 9H, $H10_3$, $H11_3$ & $H12_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.5 (d, *J* = 236.3 Hz, C2), 149.4 (d, *J* = 3.8 Hz, C7), 135.8 (d, *J* = 12.1 Hz, C4), 125.1 (C5), 120.6 (d, *J* = 10.2 Hz, C6), 108.2 (d, *J* = 24.0 Hz, C3), 97.01 (d, *J* = 26.2 Hz, C1), 96.95 (C8), 32.0 (C9), 30.3 (C10, C11 & C12); **^{19}F NMR** (377 MHz, $CDCl_3$) δ -122.32 (d, *J* = 5.5 Hz); **FTIR** (neat) ν = 3427, 2971, 1620, 1590, 1549, 1496, 1456, 1370, 1347, 1255, 1227, 1137, 945, 847, 808, 739, 693, 612 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{12}H_{15}NF$ $(M+H)^+$ 192.1183, found 192.1185.

2-(*tert*-butyl)-6-chloro-1H-indole (315)



The title compound was prepared according to General Procedure O using 2-(3,3-dimethylbut-1-yn-1-yl)-5-chloroaniline (**306**) (670 mg, 3.23 mmol). The crude product was purified by flash column chromatography [silica gel, 5% EtOAc in pentane] to afford the product as a white solid (96%, 642 mg). **M.P.** = 79-83 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.94 (bs, 1H, NH), 7.45 (d, *J* = 8.3 Hz, 1H, H6), 7.31 (d, *J* = 1.8 Hz, 1H, H3), 7.06 (dd, *J* = 8.4, 1.9 Hz, 1H, H1), 6.30 – 6.21 (m, 1H, H8), 1.40 (s, 9H, $H10_3$, $H11_3$ & $H12_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.7 (C7), 136.3 (C4), 127.2 (C8), 126.9 (C5), 120.9 (C6), 120.3 (C1), 110.5 (C3), 97.2 (C8), 32.0 (C9), 30.3 (C10, C11 & C12); **FTIR** (neat) ν = 3445, 2964, 1613, 1578, 1540, 1384, 1368, 1342, 1292, 1244, 1228, 1057, 914, 855, 813, 742, 691 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{12}H_{15}NCl$ $(M+H)^+$ 208.0888, found 208.0889.

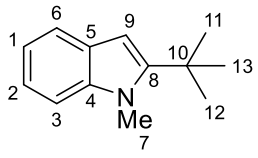
2-(*tert*-butyl)-6-methyl-1H-indole (316)



The title compound was prepared according to General Procedure O using 2-(3,3-dimethylbut-1-yn-1-yl)-5-methylaniline (**307**) (640 mg, 3.42 mmol). The crude product was purified by flash column chromatography [silica gel, 10% EtOAc in pentane] to afford the product as a white solid (97%, 621 mg). **M.P.** = 61-63 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.82 (bs, 1H, NH), 7.45 (d, *J* = 7.9 Hz, 1H, H6), 7.14 (d, *J* = 1.5 Hz, 1H, H3), 6.94 (ddd, *J* = 7.9, 1.5, 0.6 Hz, 1H, H1), 6.23 (d, *J* = 2.2 Hz, 1H, H8), 2.48 (s, 3H, $H13_3$), 1.41 (s, 9H, $H10_3$,

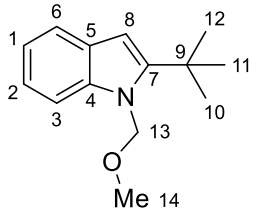
H11$_1$ & H12$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.2 (C7), 136.4 (C4), 130.9 (C2), 126.4 (C5), 121.4 (C1), 119.7 (C6), 110.5 (C3), 96.8 (C8), 31.9 (C9), 30.4 (C10, C11 & C12), 21.8 (C13); **FTIR** (neat) ν = 3421, 2964, 1625, 1543, 1460, 1365, 1302, 1254, 1200, 1129, 936, 806, 745, 691, 635 cm^{-1}; **HRMS** (ESI$^+$) m/z Calcd. for $C_{13}H_{18}N$ $(M+H)^+$ 188.1434, found 188.1434.

2-(*tert*-butyl)-1-methyl-1H-indole (244)



NaH (60% in mineral oil, 220 mg, 5.48 mmol, 1.20 equiv.) was added to a stirred solution of 2-(*tert*-butyl)-1H-indole (**197**) (790 mg, 4.57 mmol, 1.00 equiv.) in anhydrous DMF (12 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min and then MeI (714 mg, 313 µL, 5.03 mmol, 1.10 equiv.) was added. The reaction was slowly warmed to room temperature and stirring was continued for 16 h. After this time, the reaction was diluted with EtOAc and quenched with sat. $NH_4Cl_{(aq.)}$ at 0 °C. The layers were separated, and the aqueous phase was further extracted three times with EtOAc. The combined organic extracts were washed with water, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography [silica gel, 5% EtOAc in petroleum ether b.p. 40–60 °C] to afford the product as a yellow oil (89%, 761 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.61 (t, *J* = 7.2 Hz, 1H, H6), 7.33 (dd, *J* = 8.9, 4.4 Hz, 1H, H3), 7.28 – 7.20 (m, 1H, H2), 7.18 – 7.08 (m, 1H, H1), 6.38 (s, 1H, H9), 3.94 (s, 3H, H7$_3$), 1.55 (s, 9H, H11$_3$, H12$_3$ & H13$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.2 (C8), 138.8 (C4), 127.3 (C5), 121.0 (C2), 120.1 (C6), 119.4 (C1), 108.7 (C3), 98.1 (C9), 32.4 (C7), 31.8 (C10), 30.4 (C11, C12 & C13); **FTIR** (neat) ν = 3049, 2961, 1530, 1469, 1353, 1331, 1313, 1245, 1229, 1209, 1130, 1013, 780, 749, 730, 678 cm^{-1}; **HRMS** (ESI$^+$) m/z Calcd. for $C_{13}H_{18}N$ $(M+H)^+$ 188.1434, found 188.1437.

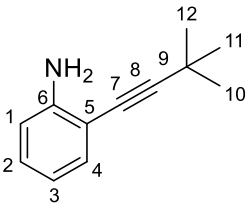
2-(*tert*-butyl)-1-(methoxymethyl)-1H-indole



NaH (60% in mineral oil, 220 mg, 5.48 mmol, 1.20 equiv.) was added to a stirred solution of 2-(*tert*-butyl)-1H-indole (790 mg, 4.57 mmol, 1.00 equiv.) in anhydrous DMF (12 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min and then MOMCl (405 mg, 382 µL, 5.03 mmol, 1.10 equiv.)

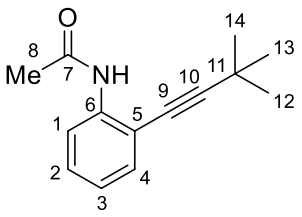
was added. The reaction was slowly warmed to room temperature and stirring was continued for 16 h. After this time, the reaction was diluted with EtOAc and quenched with sat. $NH_4Cl_{(aq.)}$ at 0 °C. The layers were separated, and the aqueous phase was further extracted three times with EtOAc. The combined organic extracts were washed with water, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography [silica gel, 5% EtOAc in petroleum ether b.p. 40–60 °C] to afford the product as a colourless oil (90%, 890 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.56 – 7.50 (m, 1H, H6), 7.41 (dt, *J* = 8.2, 0.8 Hz, 1H, H1), 7.19 (ddt, *J* = 8.2, 7.0, 1.1 Hz, 1H, H2), 7.11 (ddd, *J* = 7.9, 7.1, 1.0 Hz, 1H, H3), 6.37 (d, *J* = 0.8 Hz, 1H, H8), 5.61 (s, 2H, $H13_2$), 3.38 (s, 3H, $H14_3$), 1.49 (s, 9H, $H10_3$, $H11_3$ & $H12_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.3 (C7), 139.1 (C4), 127.8 (C5), 121.6 (C2), 120.3 (C6), 120.2 (C1), 109.6 (C3), 100.6 (C8), 75.3 (C13), 55.7 (C14), 32.7 (C9), 31.0 (C10, C11 & C12); **FTIR** (neat) ν = 2959, 1536, 1461, 1397, 1352, 1307, 1249, 1197, 1166, 1125, 1096, 1079, 1050, 1014, 959, 911, 842, 787, 749, 734, 681, 610 cm^{-1}; **HRMS** (ESI$^+$) m/z Calcd. for $C_{14}H_{20}ON$ $(M+H)^+$ 218.1539, found 218.1542.

N-(2-(3,3-dimethylbut-1-yn-1-yl)phenyl)acetamide (247)



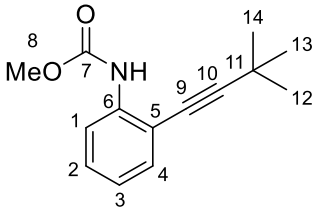
The title compound was prepared according to General Procedure N using 2-iodoaniline (**246**) (2.00 g, 9.13 mmol) and 3,3-dimethyl-1-butyne (900 mg, 1.35 mL, 10.96 mmol). The crude product was purified by flash column chromatography [silica gel, 10% EtOAc in petroleum ether b.p. 40–60 °C] to afford the product as a yellow oil (87%, 1.31 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.86 – 7.77 (m, 1H, H4), 7.64 (ddd, *J* = 8.2, 7.4, 1.6 Hz, 1H, H2), 7.27 – 7.21 (m, 2H, H1 & H3), 4.70 (bs, 2H, NH_2), 1.93 (s, 9H, $H10_3$, $H11_3$ & $H12_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.5 (C6), 132.0 (C4), 128.9 (C2), 117.9 (C3), 114.2 (C1), 108.9 (C5), 104.3 (C8), 75.5 (C7), 31.4 (C10, C11 & C12), 28.4 (C9); **FTIR** (neat) ν = 3477, 3380, 2967, 1613, 1492, 1474, 1456, 1362, 1307, 1291, 1255, 1204, 1157, 920 747 cm^{-1}; **HRMS** (ESI$^+$) m/z Calcd. for $C_{12}H_{16}N$ $(M+H)^+$ 174.1277, found 174.1278.

N-(2-(3,3-dimethylbut-1-yn-1-yl)phenyl)acetamide (248)



To a solution of 2-(3,3-dimethylbut-1-yn-1-yl)aniline (**247**) (400 mg, 2.31 mmol, 1.00 equiv.) in anhydrous CH_2Cl_2 (8 mL) at 0 °C was added NEt_3 (645 µL, 467 mg, 4.62 mmol, 2.00 equiv.) and AcCl (330 µL, 362 mg, 4.62 mmol, 2.00 equiv.). The reaction mixture was stirred at room temperature and stirred for 16 h. The mixture was then treated with sat. $NH_4Cl_{(aq.)}$ (10 mL) and the layers were separated. The aqueous phase was extracted three times with CH_2Cl_2 and the combined extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography [silica gel, 10% EtOAc in petroleum ether b.p. 40–60 °C] to afford the product as a white solid (83%, 412 mg). **M.P.** = 76-80 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.3 Hz, 1H, H1), 7.89 (bs, 1H, NH), 7.26 (dd, *J* = 7.7, 1.6 Hz, 1H, H4), 7.23 – 7.14 (m, 1H, H2), 6.91 (td, *J* = 7.6, 1.2 Hz, 1H, H3), 2.12 (s, 3H, $H8_3$), 1.30 (s, 9H, $H12_3$, $H13_3$ & $H14_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.0 (C7), 138.9 (C6), 131.2 (C4), 129.0 (C2), 123.2 (C3), 118.9 (C1), 112.4 (C5), 106.3 (C10), 74.6 (C9), 31.2 (C12, C13 & C14), 28.5 (C11), 24.9 (C8); **FTIR** (neat) ν = 3392, 2967, 1699, 1579, 1518, 1446, 1365, 1304, 1244, 1204, 1159, 1105, 1040, 1003, 915, 754, 631 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{14}H_{18}NO$ $(M+H)^+$ 216.1383, found 216.1384.

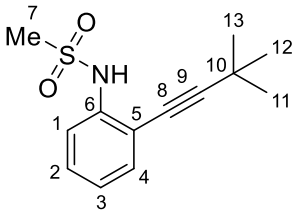
methyl (2-(3,3-dimethylbut-1-yn-1-yl)phenyl)carbamate (249)



A solution of 2-(3,3-dimethylbut-1-yn-1-yl)aniline (**247**) (400 mg, 2.31 mmol, 1.00 equiv.) in 1,2-DCE (6 mL) was added to a solution of Na_2CO_3 (490 mg, 4.62 mmol, 2.00 equiv.) in H_2O (6 mL). Methyl chloroformate (327 mg, 268 µL, 3.46 mmol, 1.50 equiv.) was added and the reaction mixture was stirred at room temperature for 24 h. The mixture was then treated with sat. $NH_4Cl_{(aq.)}$ (10 mL) and the layers were separated. The aqueous phase was extracted three times with CH_2Cl_2 and the combined extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography [silica gel, 10% EtOAc in petroleum ether b.p. 40–60 °C] to afford the product as a white solid (86%, 458 mg). **M.P.** = 60-63 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.3 Hz, 1H, H1), 7.42 (bs, 1H,

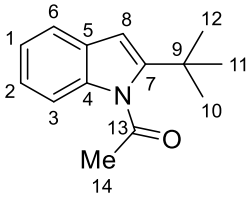
NH), 7.32 (ddd, *J* = 7.7, 1.6, 0.5 Hz, 1H, H4), 7.30 – 7.23 (m, 1H, H2), 6.95 (td, *J* = 7.5, 1.2 Hz, 1H, H3), 3.80 (s, 3H, $H8_3$), 1.37 (s, 9H, $H12_3$, $H13_3$ & $H14_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.8 (C7), 138.9 (C6), 131.4 (C4), 129.0 (C2), 122.4 (C3), 117.4 (C1), 112.1 (C5), 106.2 (C10), 74.4 (C9), 52.5 (C8), 31.2 (C12, C13 & C14), 28.5 (C11); **FTIR** (neat) ν = 3399, 2970, 1736, 1580, 1521, 1454, 1363, 1308, 1292, 1244, 1217, 1064, 1041, 918, 845, 756 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{14}H_{18}NO_2$ $(M+H)^+$ 232.1332, found 232.1334.

N-(2-(3,3-dimethylbut-1-yn-1-yl)phenyl)methanesulfonamide (250)



To a solution of 2-(3,3-dimethylbut-1-yn-1-yl)aniline (**247**) (400 mg, 2.31 mmol, 1.00 equiv.) in anhydrous CH_2Cl_2 (8 mL) at 0 °C was added NEt_3 (645 µL, 467 mg, 4.62 mmol, 2.00 equiv.) and MsCl (358 µL, 529 mg, 4.62 mmol, 2.00 equiv.). The reaction mixture was stirred at room temperature and stirred for 16 h. The mixture was then treated with sat. $NH_4Cl_{(aq.)}$ (10 mL) and the layers were separated. The aqueous phase was extracted three times with CH_2Cl_2 and the combined extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography [silica gel, 10% EtOAc in petroleum ether b.p. 40–60 °C] to afford the product as a white solid (80%, 463 mg). **M.P.** = 94-98 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 8.2, 1.1 Hz, 1H, H1), 7.40 (dd, *J* = 7.7, 1.6 Hz, 1H, H4), 7.34 – 7.27 (m, 1H, H2), 7.10 (td, *J* = 7.6, 1.2 Hz, 1H, H3), 6.92 (bs, 1H, NH), 2.98 (s, 3H, $H7_3$), 1.36 (s, 9H, $H11_3$, $H12_3$ & $H13_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.7 (C6), 132.1 (C4), 129.3 (C2), 124.9 (C3), 119.8 (C1), 115.3 (C5), 106.8 (C9), 74.2 (C8), 39.6 (C7), 31.1 (C11, C12 & C13), 28.5 (C10); **FTIR** (neat) ν = 3255, 2956, 1489, 1421, 1404, 1334, 1273, 1156, 1099, 1036, 976, 962, 898, 830, 751, 729, 659, 628 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{13}H_{17}NO_2SNa$ $(M+Na)^+$ 274.0872, found 274.0872.

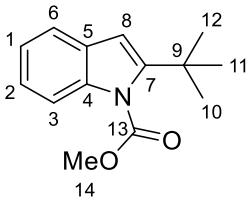
1-(2-(*tert*-butyl)-1H-indol-1-yl)ethan-1-one (251)



The title compound was prepared according to General Procedure O using N-(2-(3,3-dimethylbut-1-yn-1-yl)phenyl)acetamide (**248**) (380 mg, 1.76 mmol). The crude product was purified by flash column

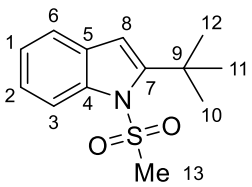
chromatography [silica gel, 5-10% EtOAc in pentane] to afford the product as a colourless oil (94%, 358 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.54 – 7.44 (m, 2H, H1 & H3), 7.26 – 7.15 (m, 2H, H2 & H6), 6.53 (d, *J* = 0.8 Hz, 1H, H8), 2.82 (s, 3H, $H14_3$), 1.48 (s, 9H, $H10_3$, $H11_3$ & $H12_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.7 (C13), 151.9 (C7), 136.7 (C4), 129.4 (C5), 123.2 (C2), 122.4 (C6), 120.8 (C1), 113.4 (C3), 106.7 (C8), 34.2 (C9), 30.7 (C10, C11 & C12), 28.2 (C14); **FTIR** (neat) ν = 2963, 1716, 1549, 1457, 1362, 1286, 1218, 1194, 1105, 1028, 984, 809, 738, 672, 610 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{14}H_{18}ON$ $(M+H)^+$ 216.1383, found 216.1386.

methyl 2-(*tert*-butyl)-1H-indole-1-carboxylate (252)



The title compound was prepared according to General Procedure O using methyl (2-(3,3-dimethylbut-1-yn-1-yl)phenyl)carbamate (**249**) (403 mg, 1.74 mmol). The crude product was purified by flash column chromatography [silica gel, 5-10% EtOAc in pentane] to afford the product as a colourless oil (91%, 365 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 (dq, *J* = 8.3, 0.8 Hz, 1H, H3), 7.47 (ddd, *J* = 7.4, 1.6, 0.7 Hz, 1H, H1), 7.27 – 7.22 (m, 1H, H2), 7.19 (td, *J* = 7.3, 1.2 Hz, 1H, H6), 6.53 (d, *J* = 0.8 Hz, 1H, H9), 4.07 (s, 3H, $H14_3$), 1.51 (s, 9H, $H10_3$, $H11_3$ & $H12_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.0 (C13), 150.6 (C7), 137.5 (C4), 128.9 (C5), 123.7 (C2), 122.8 (C6), 120.2 (C1), 115.3 (C3), 107.4 (C8), 53.7 (C14), 34.2 (C9), 30.6 (C10, C11 & C12); **FTIR** (neat) ν = 2955, 1746, 1555, 1455, 1439, 1362, 1320, 1287, 1260, 1224, 1192, 1142, 1069, 969, 813, 741, 675 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{14}H_{18}O_2N$ $(M+H)^+$ 232.1332, found 232.1333.

2-(*tert*-butyl)-1-(methylsulfonyl)-1H-indole (253)

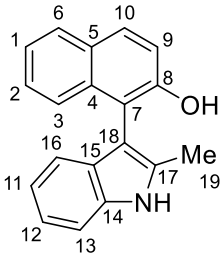


The title compound was prepared according to General Procedure O using N-(2-(3,3-dimethylbut-1-yn-1-yl)phenyl)methanesulfonamide (**250**) (251 mg, 1.00 mmol). The crude product was purified by flash column chromatography [silica gel, 10% EtOAc in pentane] to afford the product as a colourless oil (91%, 229 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.14 – 7.92 (m, 1H, H3), 7.50 – 7.35 (m, 1H, H1), 7.31 – 7.13 (m, 2H, H2 & H6), 6.54 (d, *J* = 0.9 Hz, 1H, H8), 2.86 (s, 3H, $H13_3$), 1.49 (s, 9H, $H10_3$, $H11_3$ & $H13_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.1 (C7), 138.7 (C4), 129.6 (C5), 124.7 (C2), 124.0 (C6), 120.7 (C1), 115.6 (C3), 110.3 (C8), 39.7 (C13), 34.9 (C9), 31.0 (C10, C11 & C12); **FTIR** (neat) ν = 2958, 1452, 1370, 1358, 1325, 1247, 1189, 1175, 1126, 1090, 1025, 958, 821, 766, 747, 645 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{13}H_{18}O_2NS$ $(M+H)^+$ 252.1053, found 252.1054.

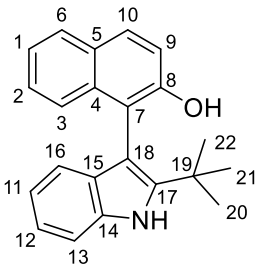
9.5.6 Heterobiaryl Products

1-(2-methyl-1H-indol-3-yl)naphthalen-2-ol (192)



The title compound was prepared according to General Procedure Q using 2-naphthol (4.33 g, 30.00 mmol) and 2-methylindole (4.32 g, 33.00 mmol). The crude product was purified by flash column chromatography [silica gel, 50% CH_2Cl_2 in petroleum ether b.p. 40–60 °C] to afford the product as a white solid (96%, 7.87 g). **M.P.** = 152-155 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.30 (s, 1H, NH), 7.91 – 7.80 (m, 2H, H3 & H10), 7.46 – 7.39 (m, 2H, H1 & H13), 7.37 – 7.29 (m, 3H, H2, H6 & H9), 7.23 (ddd, *J* = 8.2, 7.0, 1.3 Hz, 1H, H12), 7.20 – 7.13 (m, 1H, H16), 7.07 (ddd, *J* = 7.9, 6.9, 1.0 Hz, 1H, H11), 5.42 (s, 1H, OH), 2.28 (s, 3H, $H19_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.2 (C8), 136.1 (C17), 135.1 (C14), 134.3 (C4), 129.6 (C3), 129.2 (C5), 128.7 (C15), 128.3 (C10), 126.4 (C2), 125.3 (C13), 123.2 (C6), 122.2 (C12), 120.4 (C11), 119.5 (C16), 117.2 (C9), 113.0 (C7), 110.7 (C1), 104.8 (C18), 12.6 (C19); **FTIR** (neat) ν = 3406, 3058, 2972, 1619, 1596, 1460, 1430, 1383, 1345, 1329, 1266, 1233, 1199, 1163, 1142, 817, 747 cm^{-1}; **HRMS** (ESI^+) *m/z* Calcd. for $C_{19}H_{16}ON$ $(M+H)^+$ 274.1226, found 274.1228.

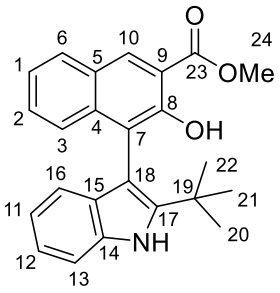
1-(2-(*tert*-butyl)-1H-indol-3-yl)naphthalen-2-ol (198)



The title compound was prepared according to General Procedure Q using 2-naphthol (200 mg, 1.39 mmol) and 2-(*tert*-butyl)-1H-indole (**197**) (265 mg, 1.53 mmol). The crude product was purified by flash column chromatography [silica gel, 50-75% CH_2Cl_2 in petroleum ether b.p. 40–60 °C] to afford the heterocoupled product as a white foam (39%, 174 mg). [*BINOL was isolated as the homocoupled by-product* (49%, 93 mg)]. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.48 (bs, 1H,

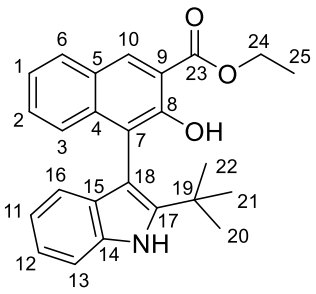
NH), 7.99 – 7.92 (m, 2H, H3 & H10), 7.48 – 7.34 (m, 5H, H1, H2, H6, H9 & H13), 7.31 (ddd, *J* = 8.2, 6.2, 2.0 Hz, 1H, H12), 7.14 – 7.06 (m, 2H, H11 & H16), 5.47 (s, 1H, OH), 1.33 (s, 9H, $H20_3$, $H21_3$ & $H22_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.1 (C8), 146.5 (C17), 135.11 (C14), 135.08 (C4), 130.0 (C5), 129.6 (C3), 129.1 (C15), 128.1 (C10), 126.3 (C2), 125.6 (C13), 123.1 (C6), 122.3 (C12), 120.2 (C11), 119.2 (C16), 116.9 (C9), 115.0 (C7), 110.5 (C1), 102.0 (C18), 33.4 (C19), 30.1 (C20, C21 & C22); **FTIR** (neat) ν = 3434, 2964, 1619, 1597, 1463, 1428, 1384, 1324, 1265, 1227, 1200, 1170, 1138, 817, 747, 712 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{22}H_{22}ON$ $(M+H)^+$ 316.1696, found 316.1695.

Methyl 4-(2-(*tert*-butyl)-1H-indol-3-yl)-3-hydroxy-2-naphthoate (199)



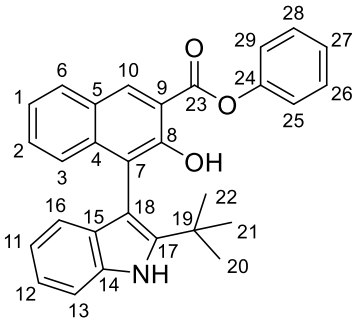
The title compound was prepared according to General Procedure Q using methyl 3-hydroxy-2-naphthoate (202 mg, 1.00 mmol) and 2-(*tert*-butyl)-1H-indole (**197**) (191 mg, 1.10 mmol). The crude product was purified by flash column chromatography [silica gel, 50% CH_2Cl_2 in petroleum ether b.p. 40–60 °C] to afford the heterocoupled product as a pale yellow solid (89%, 332 mg). **M.P.** = 236-239 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.69 (s, 1H, OH), 8.64 (s, 1H, H10), 8.25 (s, 1H, NH), 7.89 (dd, *J* = 7.9, 1.6 Hz, 1H, H3), 7.46 – 7.40 (m, 2H, H1 & H6), 7.39 – 7.30 (m, 2H, H2 & H13), 7.17 (ddd, *J* = 8.2, 7.0, 1.3 Hz, 1H, H12), 6.97 (ddd, *J* = 7.9, 6.9, 1.0 Hz, 1H, H11), 6.89 (dd, *J* = 8.0, 1.1 Hz, 1H, H16), 4.07 (s, 3H, $H24_3$), 1.29 (s, 9H, $H20_3$, $H21_3$ & $H22_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.8 (C23), 154.8 (C8), 144.2 (C17), 138.7 (C14), 134.8 (C4), 132.1 (C10), 130.1 (C5), 129.5 (C3), 129.0 (C2), 127.0 (C15), 126.1 (C6), 123.8 (C13), 121.6 (C12), 119.7 (C11), 118.9 (C16), 118.8 (C9), 114.0 (C7), 110.5 (C1), 104.8 (C18), 52.8 (C24), 33.4 (C19), 30.1 (C20, C21 & C22); **FTIR** (neat) ν = 3428, 3215, 3056, 2956, 1678, 1625, 1501, 1478, 1443, 1322, 1288, 1265, 1250, 1217, 1152, 1099, 1064, 956, 939, 802, 791, 749, 715 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{24}H_{24}O_3N$ $(M+H)^+$ 374.1751, found 374.1749.

Ethyl 4-(2-(*tert*-butyl)-1H-indol-3-yl)-3-hydroxy-2-naphthoate (224)



The title compound was prepared according to General Procedure Q using ethyl 3-hydroxy-2-naphthoate (**221**) (156 mg, 0.719 mmol) and 2-(*tert*-butyl)-1H-indole (**197**) (137 mg, 0.791 mmol). The crude product was purified by flash column chromatography [silica gel, 60% CH_2Cl_2 in petroleum ether b.p. 40–60 °C] to afford the heterocoupled product as a pale yellow solid (82%, 228 mg). **M.P.** = 190-193 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.75 (s, 1H, OH), 8.62 (s, 1H, H10), 8.21 (s, 1H, NH), 7.97 – 7.81 (m, 1H, H3), 7.44 – 7.36 (m, 2H, H1 & H6), 7.36 – 7.27 (m, 2H, H2 & H13), 7.14 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H, H12), 6.93 (ddd, *J* = 7.9, 6.9, 0.9 Hz, 1H, H11), 6.87 – 6.82 (m, 1H, H16), 4.52 (q, *J* = 7.1 Hz, 2H, $H24_2$), 1.52 (t, *J* = 7.1 Hz, 3H, $H25_3$), 1.27 (s, 12H, $H20_3$, $H21_3$ & $H22_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.5 (C23), 154.9 (C8), 144.2 (C17), 138.7 (C14), 134.8 (C4), 132.0 (C10), 130.2 (C5), 129.5 (C3), 128.9 (C2), 127.0 (C15), 126.1 (C6), 123.7 (C13), 121.7 (C12), 119.7 (C11), 119.0 (C16), 118.7 (C9), 114.2 (C7), 110.5 (C1), 104.9 (C18), 62.0 (C24), 33.4 (C19), 30.2 (C20, C21 & C22), 14.5 (C25); **FTIR** (neat) ν = 3428, 3215, 3056, 2956, 1678, 1501, 1478, 1443, 1364, 1337, 1364, 1321, 1288, 1265, 1250, 1217, 1168, 1152, 1099, 1064, 956, 939, 791, 749, 715 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{25}H_{26}O_3N$ $(M+H)^+$ 388.1895, found 388.1907.

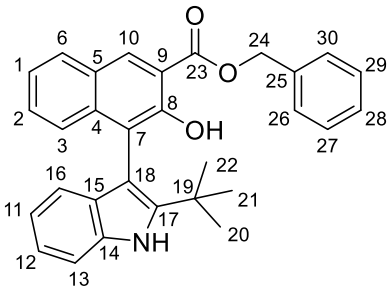
Phenyl 4-(2-(*tert*-butyl)-1H-indol-3-yl)-3-hydroxy-2-naphthoate (225)



The title compound was prepared according to General Procedure Q using phenyl 3-hydroxy-2-naphthoate (**222**) (264 mg, 1.00 mmol) and 2-(*tert*-butyl)-1H-indole (**197**) (191 mg, 1.10 mmol). The crude product was purified by flash column chromatography [silica gel, 60% CH_2Cl_2 in petroleum ether b.p. 40–60 °C] to afford the heterocoupled product as a yellow foam (84%, 366 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.35 (s, 1H, OH), 8.86 (s, 1H, H10), 8.22 (s, 1H, NH), 7.93 (dd, *J* = 7.8, 1.6 Hz, 1H, H3), 7.55 – 7.46 (m, 2H, H1 & H6), 7.46 – 7.28 (m, 7H, H2, H13, H25, H26, H27, H28 & H29),

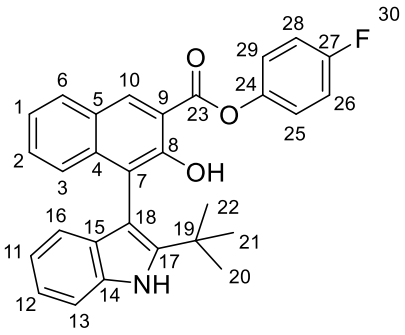
7.15 (ddd, *J* = 8.2, 7.0, 1.3 Hz, 1H, H12), 6.94 (ddd, *J* = 7.9, 7.0, 1.0 Hz, 1H, H11), 6.90 – 6.82 (m, 1H, H16), 1.28 (s, 9H, $H20_3$, $H21_3$ & $H22_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.3 (C23), 155.0 (C8), 150.4 (C24), 144.2 (C17), 139.1 (C14), 134.8 (C4), 132.8 (C10), 130.1 (C5), 129.9 (C25 & C29), 129.7 (C27), 129.5 (C3), 127.1 (C2), 126.6 (C15), 126.2 (C6), 124.1 (C13), 121.9 (C26 & C28), 121.7 (C12), 119.7 (C11), 119.2 (C16), 118.9 (C9), 113.4 (C7), 110.5 (C1), 104.7 (C18), 33.4 (C19), 30.2 (C20, C21 & C22); **FTIR** (neat) ν = 3436, 2965, 1788, 1499, 1458, 1432, 1317, 1288, 1201, 1164, 1097, 1040, 939, 787, 771, 738, 714, 689 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{29}H_{26}O_3N$ $(M+H)^+$ 436.1905, found 436.1907.

Benzyl 4-(2-(*tert*-butyl)-1H-indol-3-yl)-3-hydroxy-2-naphthoate (226)



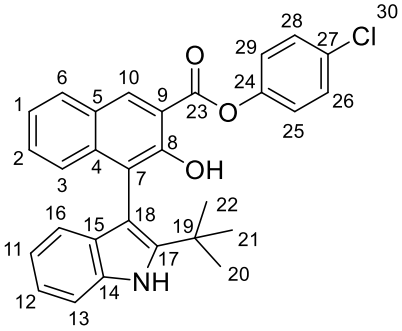
The title compound was prepared according to General Procedure Q using benzyl 3-hydroxy-2-naphthoate (**222**) (200 mg, 0.719 mmol) and 2-(*tert*-butyl)-1H-indole (**197**) (137 mg, 0.791 mmol). The crude product was purified by flash column chromatography [silica gel, 60% CH_2Cl_2 in petroleum ether b.p. 40–60 °C] to afford the heterocoupled product as a yellow solid (84%, 270 mg). **M.P.** = 94-100 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.65 (s, 1H, OH), 8.65 (s, 1H, H10), 8.22 (s, 1H, NH), 7.93 – 7.79 (m, 1H, H3), 7.60 – 7.53 (m, 2H, H1 & H6), 7.51 – 7.44 (m, 2H, H26 & H30), 7.44 – 7.38 (m, 2H, H27 & H29), 7.38 – 7.28 (m, 2H, H2 & H13), 7.15 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H, H28), 6.94 (ddd, *J* = 7.9, 7.0, 1.0 Hz, 1H, H12), 6.86 (ddt, *J* = 7.9, 1.3, 0.7 Hz, 1H, H11), 5.50 (s, 2H, $H24_2$), 1.27 (s, 9H, $H20_3$, $H21_3$ & $H22_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.2 (C23), 154.9 (C8), 144.2 (C17), 138.8 (C14), 135.4 (C25), 134.8 (C4), 132.2 (C10), 130.1 (C5), 129.5 (C3), 129.1 (C28), 128.9 (C2), 128.8 (C27 & C29), 128.7 (C26 & C30), 127.0 (C15), 126.1 (C6), 123.8 (C13), 121.7 (C12), 119.7 (C11), 118.9 (C16), 118.8 (C9), 114.0 (C7), 110.5 (C1), 104.9 (C18), 67.5 (C24), 33.4 (C19), 30.2 (C20, C21 & C22); **FTIR** (neat) ν = 3436, 3196, 2963, 1675, 1625, 1500, 1457, 1433, 1336, 1306, 1286, 1265, 1205, 1168, 1152, 1099, 1058, 939, 790, 748, 699 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{30}H_{28}O_3N$ $(M+H)^+$ 450.2060, found 450.2064.

4-chlorophenyl 4-(2-(*tert*-butyl)-1H-indol-3-yl)-3-hydroxy-2-naphthoate (374)



The title compound was prepared according to General Procedure Q using 4-fluorophenyl 3-hydroxy-2-naphthoate (**261**) (141 mg, 0.500 mmol) and 2-(*tert*-butyl)-1H-indole (**197**) (95 mg, 0.550 mmol). The crude product was purified by flash column chromatography [silica gel, 50% CH_2Cl_2 in pentane] to afford the heterocoupled product as a yellow foam (77%, 175 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.18 (s, 1H), 8.76 (s, 1H), 8.15 (bs, 1H), 7.89 – 7.79 (m, 1H), 7.41 – 7.23 (m, 4H), 7.23 – 7.14 (m, 2H), 7.14 – 7.02 (m, 3H), 6.86 (ddd, *J* = 7.9, 7.0, 1.0 Hz, 1H), 6.78 (ddt, *J* = 8.0, 1.3, 0.7 Hz, 1H), 1.19 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.2, 160.8 (d, *J* = 245.5 Hz), 154.9, 146.2 (d, *J* = 2.9 Hz), 144.3, 139.2, 134.9, 132.8, 130.1, 129.6 (d, *J* = 9.4 Hz), 127.1, 126.2, 124.1, 123.4 (d, *J* = 8.7 Hz), 121.8, 119.8, 119.3, 118.9, 116.7, 116.5, 113.2, 110.5, 104.6, 33.4, 30.2; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -115.9; **FTIR** (neat) ν = 3435, 3266, 3056, 3056, 2970, 1692, 1625, 1503, 1459, 1432, 1333, 1317, 1288, 1200, 1181, 1142, 1097, 1038, 939, 845, 787, 746 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{29}H_{25}O_3NF$ $(M+H)^+$ 454.1813, found 454.1811.

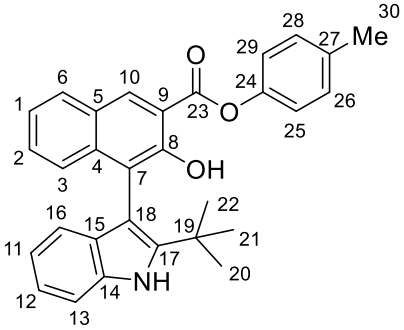
4-chlorophenyl 4-(2-(*tert*-butyl)-1H-indol-3-yl)-3-hydroxy-2-naphthoate (375)



The title compound was prepared according to General Procedure Q using 4-chlorophenyl 3-hydroxy-2-naphthoate (**262**) (147 mg, 0.500 mmol) and 2-(*tert*-butyl)-1H-indole (**197**) (95 mg, 0.550 mmol). The crude product was purified by flash column chromatography [silica gel, 50-60% CH_2Cl_2 in pentane] to afford the heterocoupled product as a yellow foam (52%, 121 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.13 (s, 1H), 8.75 (d, *J* = 0.7 Hz, 1H), 8.15 (s, 1H), 7.87 – 7.80 (m, 1H), 7.42 – 7.23 (m, 6H), 7.21 – 7.14 (m, 2H), 7.06 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 6.86 (ddd, *J* = 7.9, 7.0, 1.0 Hz, 1H), 6.78 (ddt, *J* = 7.7, 1.2, 0.7 Hz, 1H), 1.19 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.0, 154.9, 148.9, 144.3, 139.2, 134.9, 132.9, 132.1, 130.1, 129.9 (2C), 129.7, 129.6, 127.1, 126.2, 124.2, 123.3, 121.8, 119.8, 119.7, 118.9, 110.5, 104.6, 33.4, 30.2; **FTIR** (neat) ν = 3436, 3268, 3058, 1693, 1487,

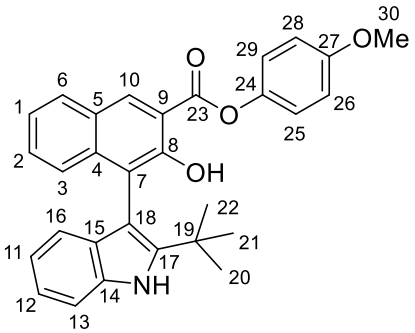
1459, 1316, 1288, 1199, 1165, 1142, 1037, 939, 746 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{29}H_{25}O_3NCl$ $(M+H)^+$ 470.1517, found 470.1514.

p-tolyl 4-(2-(*tert*-butyl)-1H-indol-3-yl)-3-hydroxy-2-naphthoate (376)



The title compound was prepared according to General Procedure Q using 4-methylphenyl 3-hydroxy-2-naphthoate (**256**) (139 mg, 0.500 mmol) and 2-(*tert*-butyl)-1H-indole (**197**) (95 mg, 0.550 mmol). The crude product was purified by flash column chromatography [silica gel, 50-60% CH_2Cl_2 in pentane] to afford the heterocoupled product as a yellow foam (84%, 189 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.32 (s, 1H), 8.78 (s, 1H), 8.14 (bs, 1H), 7.90 – 7.81 (m, 1H), 7.39 – 7.24 (m, 4H), 7.23 – 7.17 (m, 2H), 7.15 – 7.01 (m, 3H), 6.86 (ddd, *J* = 7.9, 7.0, 1.0 Hz, 1H), 6.79 (ddt, *J* = 7.9, 1.4, 0.7 Hz, 1H), 2.33 (s, 3H), 1.20 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.5, 155.0, 148.2, 144.2, 139.1, 136.4, 134.8, 132.8, 130.4, 130.1, 129.7, 129.4, 127.1, 126.2, 124.0, 121.7, 121.5, 119.8, 119.1, 118.9, 113.5, 110.5, 104.7, 33.4, 30.2, 21.1; **FTIR** (neat) ν = c3434, 3265, 3056, 2964, 1687, 1506, 1432, 1334, 1318, 1288, 1197, 1166, 1149, 939, 787, 744 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{30}H_{28}O_3N$ $(M+H)^+$ 450.2064, found 450.2057.

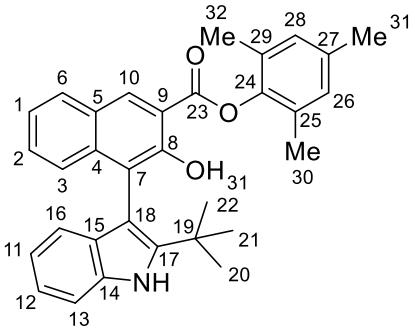
4-methoxyphenyl 4-(2-(*tert*-butyl)-1H-indol-3-yl)-3-hydroxy-2-naphthoate (377)



The title compound was prepared according to General Procedure Q using 4-methoxyphenyl 3-hydroxy-2-naphthoate (**263**) (149 mg, 0.500 mmol) and 2-(*tert*-butyl)-1H-indole (**197**) (95 mg, 0.550 mmol). The crude product was purified by flash column chromatography [silica gel, 60-65% CH_2Cl_2 in pentane] to afford the heterocoupled product as a yellow foam (70%, 164 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.41 (s, 1H), 8.90 – 8.83 (m, 1H), 8.25 (s, 1H), 7.99 – 7.87 (m, 1H), 7.47 – 7.32 (m, 4H), 7.28 – 7.20 (m, 3H), 7.16 (ddd, *J* = 8.2, 7.0, 1.3 Hz, 1H), 7.03 – 6.98 (m, 1H), 6.97 – 6.92 (m, 1H), 6.89 (ddt, *J* = 8.0, 1.4, 0.7 Hz, 1H), 3.86 (s, 3H), 1.29 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.6, 157.9, 155.0, 144.2, 143.8, 139.1, 134.9, 132.8, 130.1, 129.6, 129.4, 127.1, 126.2, 124.0,

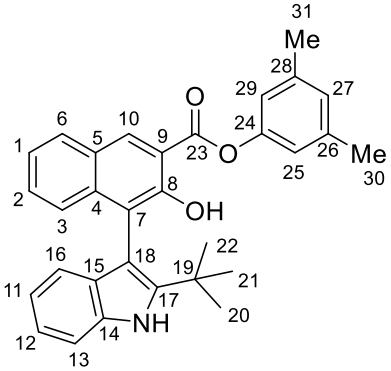
122.6, 121.7, 119.8, 119.2, 118.9, 114.9, 113.5, 110.5, 104.7, 55.8, 33.4, 30.2; **FTIR** (neat) ν = 3434, 3251, 3966, 2909, 1689, 1625, 1505, 1459, 1433, 1333, 1250, 1190, 1149, 1098, 1041, 745 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{30}H_{28}O_4N$ $(M+H)^+$ 466.2013, found 466.2010.

mesityl 4-(2-(*tert*-butyl)-1H-indol-3-yl)-3-hydroxy-2-naphthoate (378)



The title compound was prepared according to General Procedure Q using mesityl 3-hydroxy-2-naphthoate (**258**) (153 mg, 0.500 mmol) and 2-(*tert*-butyl)-1H-indole (**197**) (95 mg, 0.550 mmol). The crude product was purified by flash column chromatography [silica gel, 40-50% CH_2Cl_2 in pentane] to afford the heterocoupled product as a yellow foam (73%, 175 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.48 (s, 1H), 8.95 (s, 1H), 8.25 (bs, 1H), 8.01 – 7.90 (m, 1H), 7.49 – 7.33 (m, 4H), 7.17 (ddd, *J* = 8.1, 6.7, 1.5 Hz, 1H), 7.04 – 6.87 (m, 4H), 2.35 (s, 3H), 2.28 (s, 6H), 1.31 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.8, 155.1, 145.6, 144.2, 139.2, 136.1, 134.8, 132.6, 130.1, 130.0, 129.6, 129.4, 127.1, 126.2, 124.0, 121.7, 119.7, 119.2, 118.9, 113.1, 110.5, 104.7, 33.4, 30.2, 21.0, 16.6; **FTIR** (neat) ν = 3434, 3253, 2965, 1686, 1458, 1333, 1318, 1203, 1188, 1150, 1039, 854, 788, 743, 710 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{32}H_{32}O_3N$ $(M+H)^+$ 478.2377, found 478.2372.

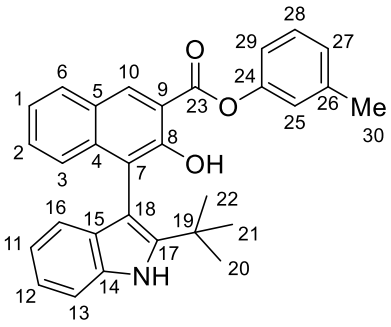
3,5-dimethylphenyl 4-(2-(*tert*-butyl)-1H-indol-3-yl)-3-hydroxy-2-naphthoate (379)



The title compound was prepared according to General Procedure Q using 3,5-dimethylphenyl 3-hydroxy-2-naphthoate (**257**) (146 mg, 0.500 mmol) and 2-(*tert*-butyl)-1H-indole (**197**) (95 mg, 0.550 mmol). The crude product was purified by flash column chromatography [silica gel, 50-60% CH_2Cl_2 in pentane] to afford the heterocoupled product as a yellow foam (49%, 114 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.42 (s, 1H), 8.91 – 8.79 (m, 1H), 8.24 (s, 1H), 8.00 – 7.90 (m, 1H), 7.49 – 7.32 (m, 4H), 7.16 (ddd, *J* = 8.1, 6.9, 1.3 Hz, 1H), 7.05 – 6.82 (m, 5H), 2.40 (s, 6H), 1.29 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.5, 155.0, 150.3, 144.2, 139.8, 139.1, 134.9, 132.8, 130.1, 129.7, 129.4, 128.4, 127.1, 126.2, 124.0, 121.7, 119.8, 119.4, 119.1,

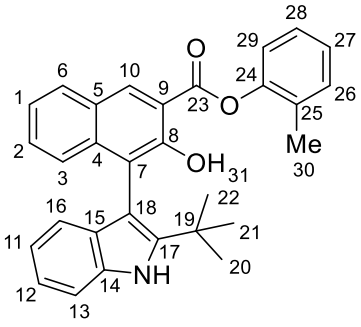
118.9, 113.5, 110.5, 104.7, 33.4, 30.2, 21.4; **FTIR** (neat) ν = 3430, 3264, 2962, 1686, 1620, 1432, 1333, 1318, 1201, 1150, 1053, 938, 848, 787, 741, 718, 681 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{31}H_{30}O_3N$ $(M+H)^+$ 464.2220, found 464.2217.

m-tolyl 4-(2-(*tert*-butyl)-1H-indol-3-yl)-3-hydroxy-2-naphthoate (380)



The title compound was prepared according to General Procedure Q using 3-methylphenyl 3-hydroxy-2-naphthoate (**255**) (139 mg, 0.500 mmol) and 2-(*tert*-butyl)-1H-indole (**197**) (95 mg, 0.550 mmol). The crude product was purified by flash column chromatography [silica gel, 50-60% CH_2Cl_2 in pentane] to afford the heterocoupled product as a yellow foam (80%, 180 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.40 (s, 1H), 8.86 (s, 1H), 8.24 (bs, 1H), 8.00 – 7.88 (m, 1H), 7.47 – 7.31 (m, 5H), 7.19 – 7.06 (m, 4H), 6.96 (ddd, *J* = 7.9, 6.9, 1.0 Hz, 1H), 6.89 (ddt, *J* = 8.0, 1.4, 0.7 Hz, 1H), 2.44 (s, 3H), 1.29 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.4, 155.0, 150.4, 144.2, 140.2, 139.1, 134.9, 132.8, 130.1, 129.7, 129.6, 129.4, 127.4, 127.1, 126.2, 124.0, 122.4, 121.7, 119.8, 119.2, 118.9, 118.8, 113.5, 110.5, 104.7, 33.4, 30.2, 21.5; **FTIR** (neat) ν = 3433, 3250, 3055, 2963, 1687, 1625, 1488, 1458, 1432, 1334, 1201, 1151, 1043, 938, 787, 742, 713, 687 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{30}H_{28}O_3N$ $(M+H)^+$ 450.2064, found 450.2057.

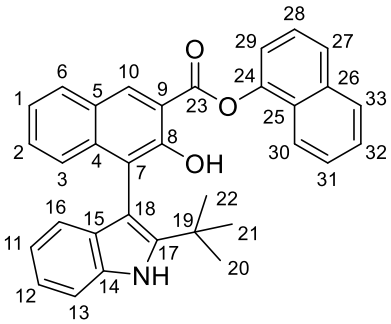
o-tolyl 4-(2-(*tert*-butyl)-1H-indol-3-yl)-3-hydroxy-2-naphthoate (381)



The title compound was prepared according to General Procedure Q using 2-methylphenyl 3-hydroxy-2-naphthoate (**254**) (139 mg, 0.500 mmol) and 2-(*tert*-butyl)-1H-indole (**197**) (95 mg, 0.550 mmol). The crude product was purified by flash column chromatography [silica gel, 50-60% CH_2Cl_2 in pentane] to afford the heterocoupled product as a yellow foam (41%, 92 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.30 (d, *J* = 1.0 Hz, 1H), 8.81 (s, 1H), 8.14 (bs, 1H), 7.85 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.39 – 7.19 (m, 6H), 7.19 – 7.11 (m, 2H), 7.06 (ddd, *J* = 8.2, 6.9, 1.3 Hz, 1H), 6.88 – 6.84 (m, 1H), 6.84 – 6.78 (m, 1H), 2.26 (s,

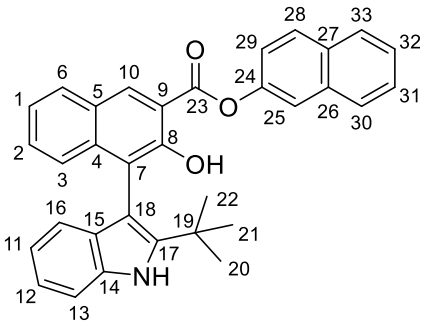
3H), 1.20 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.0, 155.0, 149.1, 144.3, 139.2, 134.9, 132.7, 131.6, 130.5, 130.1, 129.7, 129.5, 127.3, 127.1, 126.8, 126.2, 124.1, 122.1, 121.8, 119.8, 119.3, 118.9, 113.3, 110.5, 104.7, 33.4, 30.2, 16.5; **FTIR** (neat) ν = 3430, 3264, 2962, 1686, 1620, 1432, 1333, 1318, 1201, 1150, 1053, 938, 848, 787, 741, 718, 681 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{30}H_{28}O_3N$ $(M+H)^+$ 450.2064, found 450.2061.

naphthalen-1-yl 4-(2-(*tert*-butyl)-1H-indol-3-yl)-3-hydroxy-2-naphthoate (382)



The title compound was prepared according to General Procedure Q using naphthalen-1-yl 3-hydroxy-2-naphthoate (**259**) (157 mg, 0.500 mmol) and 2-(*tert*-butyl)-1H-indole (**197**) (95 mg, 0.550 mmol). The crude product was purified by flash column chromatography [silica gel, 50-60% CH_2Cl_2 in pentane] to afford the heterocoupled product as a yellow foam (78%, 189 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.36 (s, 1H), 9.10 (s, 1H), 8.26 (bs, 1H), 8.13 – 8.04 (m, 1H), 8.05 – 7.93 (m, 2H), 7.87 (dt, *J* = 8.3, 1.0 Hz, 1H), 7.65 – 7.55 (m, 3H), 7.53 – 7.36 (m, 5H), 7.18 (ddd, *J* = 8.1, 6.8, 1.5 Hz, 1H), 7.03 – 6.90 (m, 2H), 1.32 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.4, 155.1, 146.3, 144.3, 139.3, 134.9 (2C), 132.9, 130.1, 129.7, 129.6, 128.3, 127.2, 127.0 (2C), 126.9 (2C), 126.2, 125.6, 124.2, 121.8, 121.3, 119.8, 119.4, 118.9, 118.5, 113.2, 110.5, 104.7, 33.5, 30.2; **FTIR** (neat) ν = 3442, 3266, 3056, 2970, 1691, 1500, 1342, 1334, 1309, 1225, 1200, 954, 746, 703 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{33}H_{28}O_3N$ $(M+H)^+$ 486.2064, found 486.2062.

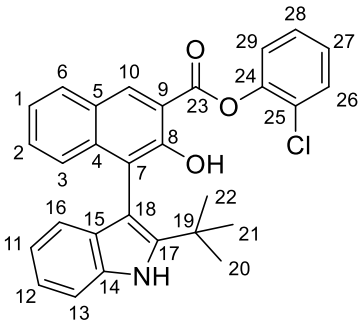
naphthalen-2-yl 4-(2-(*tert*-butyl)-1H-indol-3-yl)-3-hydroxy-2-naphthoate (383)



The title compound was prepared according to General Procedure Q using naphthalen-2-yl 3-hydroxy-2-naphthoate (**260**) (157 mg, 0.500 mmol) and 2-(*tert*-butyl)-1H-indole (**197**) (95 mg, 0.550 mmol). The crude product was purified by flash column chromatography [silica gel, 50-60% CH_2Cl_2 in pentane] to afford the heterocoupled product as a yellow foam (50%, 120 mg). **^{1}H NMR** (400

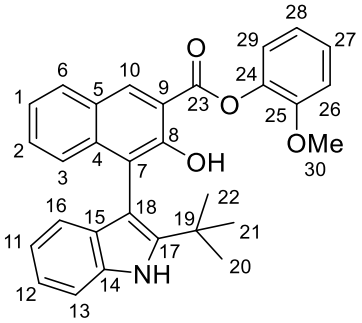
MHz, $CDCl_3$) δ 10.37 (s, 1H), 8.93 (s, 1H), 8.24 (bs, 1H), 7.97 (ddd, *J* = 6.1, 5.1, 3.2 Hz, 2H), 7.94 – 7.85 (m, 2H), 7.79 (d, *J* = 2.3 Hz, 1H), 7.61 – 7.49 (m, 2H), 7.49 – 7.33 (m, 5H), 7.16 (ddd, *J* = 8.2, 7.0, 1.3 Hz, 1H), 6.96 (ddd, *J* = 7.9, 7.0, 1.0 Hz, 1H), 6.92 – 6.85 (m, 1H), 1.29 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.5, 155.0, 148.0, 144.3, 139.2, 134.9, 133.9, 132.9, 131.9, 130.1, 129.9, 129.7, 129.5, 128.0, 127.9, 127.2, 127.0, 126.2 (2C), 124.1, 121.8, 121.1, 119.8, 119.3, 119.1, 118.9, 113.5, 110.5, 104.7, 33.4, 30.2; **FTIR** (neat) ν = 3441, 3257, 3056, 1690, 1625, 1500, 1458, 1432, 1316, 1288, 1200, 1155, 1039, 787, 744 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{33}H_{28}O_3N$ $(M+H)^+$ 486.2064, found 486.2063.

2-chlorophenyl 4-(2-(*tert*-butyl)-1H-indol-3-yl)-3-hydroxy-2-naphthoate (384)



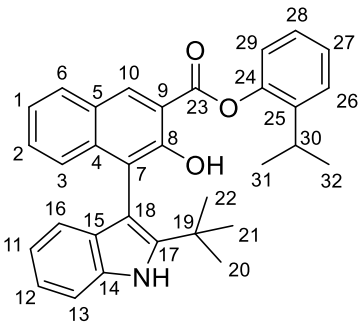
The title compound was prepared according to General Procedure Q using 2-chlorophenyl 3-hydroxy-2-naphthoate (**265**) (149 mg, 0.500 mmol) and 2-(*tert*-butyl)-1H-indole (**197**) (95 mg, 0.550 mmol). The crude product was purified by flash column chromatography [silica gel, 40–60% CH_2Cl_2 in pentane] to afford the heterocoupled product as a yellow foam (80%, 188 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.14 (s, 1H), 8.95 (s, 1H), 8.25 (s, 1H), 8.00 – 7.92 (m, 1H), 7.57 (dt, *J* = 8.0, 1.1 Hz, 1H), 7.48 – 7.35 (m, 6H), 7.35 – 7.26 (m, 1H), 7.23 – 7.13 (m, 1H), 6.98 (ddd, *J* = 7.8, 6.8, 0.9 Hz, 1H), 6.94 – 6.90 (m, 1H), 1.30 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.1, 154.7, 146.6, 144.2, 139.2, 134.7, 133.1, 130.6, 130.0, 129.7, 129.5, 129.1, 128.0, 127.7, 127.1 (2C), 126.1, 124.0, 123.9, 121.7, 119.7, 119.2, 118.8, 112.8, 110.4, 33.3, 30.1; **FTIR** (neat) ν = 3434, 3283, 3057, 1696, 1626, 1500, 1432, 1316, 1199, 1141, 1061, 1029, 785, 744 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{29}H_{25}O_3NCl$ $(M+H)^+$ 470.1517, found 470.1517.

2-methoxyphenyl 4-(2-(*tert*-butyl)-1H-indol-3-yl)-3-hydroxy-2-naphthoate (385)



The title compound was prepared according to General Procedure Q using 2-methoxyphenyl 3-hydroxy-2-naphthoate (**266**) (147 mg, 0.500 mmol) and 2-(*tert*-butyl)-1H-indole (**197**) (95 mg, 0.550 mmol). The crude product was purified by flash column chromatography [silica gel, 50-60% CH_2Cl_2 in pentane] to afford the heterocoupled product as a yellow foam (65%, 151 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.35 (s, 1H), 8.91 (s, 1H), 8.23 (bs, 1H), 7.97 – 7.91 (m, 1H), 7.47 – 7.29 (m, 5H), 7.29 – 7.23 (m, 1H), 7.16 (ddd, *J* = 8.2, 6.9, 1.3 Hz, 1H), 7.12 – 7.02 (m, 2H), 6.96 (ddd, *J* = 7.8, 6.9, 1.0 Hz, 1H), 6.93 – 6.88 (m, 1H), 3.89 (s, 3H), 1.29 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.8, 155.0, 151.4, 144.2, 139.4, 139.1, 134.9, 133.1, 130.1, 129.7, 129.3, 127.7, 127.1, 126.1, 124.0, 123.1, 121.7, 121.1, 119.7, 119.0 (2C), 113.4, 112.8, 110.5, 104.8, 56.2, 33.4, 30.2; **FTIR** (neat) ν = 3431, 3248, 3055, 2955, 1691, 1626, 1501, 1458, 1433, 1317, 1287, 1258, 1201, 1170, 1150, 938, 786, 744, 715 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{30}H_{28}O_4N$ $(M+H)^+$ 466.2013, found 466.2012.

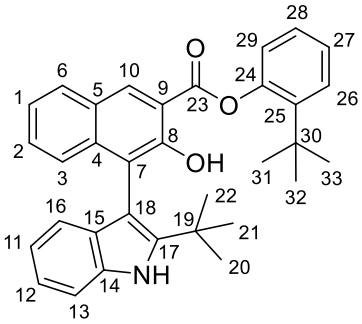
2-isopropylphenyl 4-(2-(*tert*-butyl)-1H-indol-3-yl)-3-hydroxy-2-naphthoate (321)



The title compound was prepared according to General Procedure Q using 2-isopropylphenyl 3-hydroxy-2-naphthoate (**267**) (30.6 mg, 0.10 mmol) and 2-(*tert*-butyl)-1H-indole (**197**) (26.0 mg, 0.15 mmol). The crude product was purified by flash column chromatography [silica gel, 50% CH_2Cl_2 in pentane] to afford the product as a yellow foam (91%, 43.4 mg, 93% BRSM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.42 (s, 1H), 8.89 (s, 1H), 8.24 (s, 1H), 7.99 – 7.92 (m, 1H), 7.48 – 7.42 (m, 3H), 7.42 – 7.39 (m, 1H), 7.39 – 7.35 (m, 1H), 7.35 – 7.28 (m, 2H), 7.24 – 7.19 (m, 1H), 7.16 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H), 6.97 (ddd, *J* = 7.8, 6.9, 1.0 Hz, 1H), 6.91 (ddt, *J* = 7.9, 1.4, 0.7 Hz, 1H), 3.23 (hept, *J* = 6.9 Hz, 1H), 1.33 (dd, *J* = 6.9, 2.3 Hz, 6H), 1.30 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.4, 155.1, 147.8, 144.3, 140.6, 139.2, 134.9, 132.7, 130.1, 129.7, 129.5, 127.2, 127.1 (2C), 127.0, 126.2, 124.1, 122.4,

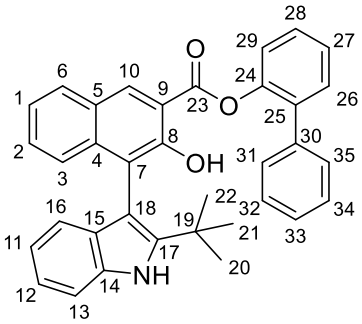
121.8, 119.8, 119.3, 118.9, 113.4, 110.5, 104.7, 33.4, 30.2, 27.7, 23.3, 23.2; **FTIR** (neat) ν = cm^{-1}; **HRMS** (ESI+) m/z Calcd. for $C_{32}H_{32}O_3N$ $(M+H)^+$ 478.2377, found 478.2375; **$[\alpha]^{D}_{25}$** = +5.1° (*c* 1.0, $CHCl_3$); **HPLC** Daicel ChiralPak IC (5% *i*-PrOH in hexane, 1.0 mL min^{-1}, T = 25 °C, 307 nm); τ_R (minor) = 7.5 min, τ_R (major) = 10.9 min; **e.r.** = 94:6.

2-(*tert*-butyl)phenyl 4-(2-(*tert*-butyl)-1H-indol-3-yl)-3-hydroxy-2-naphthoate (386)



The title compound was prepared according to General Procedure Q using 2-(*tert*-butyl)phenyl 3-hydroxy-2-naphthoate (**269**) (160 mg, 0.500 mmol) and 2-(*tert*-butyl)-1H-indole (**197**) (95 mg, 0.550 mmol). The crude product was purified by flash column chromatography [silica gel, 40–60% CH_2Cl_2 in pentane] to afford the heterocoupled product as a yellow foam (48%, 119mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.49 (s, 1H), 8.88 (s, 1H), 8.25 (s, 1H), 8.03 – 7.92 (m, 1H), 7.53 (dd, *J* = 7.7, 1.9 Hz, 1H), 7.50 – 7.25 (m, 6H), 7.22 – 7.13 (m, 2H), 7.01 – 6.85 (m, 2H), 1.48 (s, 9H), 1.30 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.6, 155.2, 148.9, 144.3, 141.7, 139.2, 134.9, 132.8, 130.1, 129.7, 129.5, 127.8, 127.3, 127.2, 126.6, 126.2, 124.2, 124.1, 121.8, 119.8, 119.4, 118.9, 113.8, 110.5, 104.7, 34.8, 33.4, 30.6, 30.2; **FTIR** (neat) ν = 3433, 3249, 3057, 2959, 1687, 1625, 1431, 1333, 1199, 1182, 1086, 1038, 938, 800, 746 cm^{-1}; **HRMS** (ESI+) m/z Calcd. for $C_{33}H_{34}O_3N$ $(M+H)^+$ 492.2533, found 492.2533.

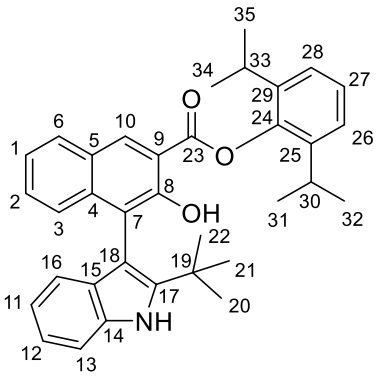
[1,1'-biphenyl]-2-yl 4-(2-(*tert*-butyl)-1H-indol-3-yl)-3-hydroxy-2-naphthoate (387)



The title compound was prepared according to General Procedure Q using [1,1'-biphenyl]-2-yl 3-hydroxy-2-naphthoate (**264**) (170 mg, 0.500 mmol) and 2-(*tert*-butyl)-1H-indole (**197**) (95 mg, 0.550 mmol). The crude product was purified by flash column chromatography [silica gel, 40-50% CH_2Cl_2 in pentane] to afford the heterocoupled product as a yellow foam (76%, 194 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.04 (s, 1H), 8.54 (s, 1H), 8.11 (bs, 1H), 7.83 – 7.73 (m, 1H), 7.45 (ddt, *J* = 7.1, 2.8, 1.5 Hz, 2H), 7.42 – 7.18 (m, 10H), 7.05 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 6.85 (ddd, *J* = 7.9, 7.0, 1.0 Hz, 1H), 6.75

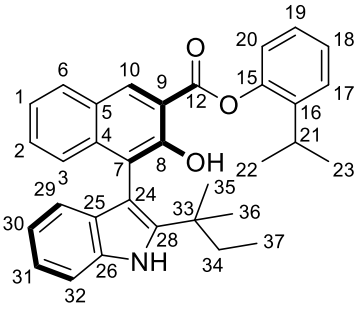
(dq, *J* = 8.0, 0.8 Hz, 1H), 1.15 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.0, 154.8, 147.6, 144.2, 139.0, 137.3, 135.2, 134.8, 132.8, 131.3, 130.1, 129.6, 129.3, 129.1, 128.8, 128.5, 127.8, 127.0, 127.0, 126.1, 123.9, 123.0, 121.7, 119.7, 119.0, 118.9, 113.4, 110.5, 104.7, 33.4, 30.2; **FTIR** (neat) ν = 3433, 3259, 3057, 1687, 1625, 1458, 1309, 1200, 1183, 1149, 1009, 773, 742, 700 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{34}H_{30}O_3N$ $(M+H)^+$ 512.2220, found 512.2219.

2-cyclohexylphenyl 4-(2-(*tert*-butyl)-1H-indol-3-yl)-3-hydroxy-2-naphthoate (388)



The title compound was prepared according to General Procedure Q 2,6-diisopropylphenyl 3-hydroxy-2-naphthoate (**268**) (174 mg, 0.500 mmol) and 2-(*tert*-butyl)-1H-indole (**197**) (95 mg, 0.550 mmol). The crude product was purified by flash column chromatography [silica gel, 40–60% CH_2Cl_2 in pentane] to afford the heterocoupled product as a yellow foam (33%, 86 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.45 (s, 1H), 8.91 (d, *J* = 0.6 Hz, 1H), 8.24 (s, 1H), 8.10 – 7.95 (m, 1H), 7.48 – 7.34 (m, 4H), 7.34 – 7.26 (m, 3H), 7.16 (ddd, *J* = 8.2, 6.7, 1.5 Hz, 1H), 6.97 (ddd, *J* = 7.7, 6.7, 1.0 Hz, 1H), 6.93 (ddt, *J* = 8.0, 1.5, 0.7 Hz, 1H), 3.09 (hept, *J* = 6.9 Hz, 2H), 1.30 (s, 9H), 1.29 – 1.24 (m, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.4, 155.2, 145.4, 144.3, 140.8, 140.6, 139.2, 134.9, 132.5, 130.1, 129.7, 129.5, 127.3, 127.2, 126.2, 124.4, 124.4, 124.1, 121.8, 119.8, 119.3, 118.9, 113.1, 110.5, 104.7, 33.4, 30.2, 27.9, 27.8, 24.2, 24.1, 22.9; **FTIR** (neat) ν = 3433, 3256, 3058, 2963, 1686, 1500, 1459, 1432, 1333, 1307, 1200, 1163, 1143, 938, 787, 772, 742 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{35}H_{38}O_3N$ $(M+H)^+$ 520.2846, found 520.2845.

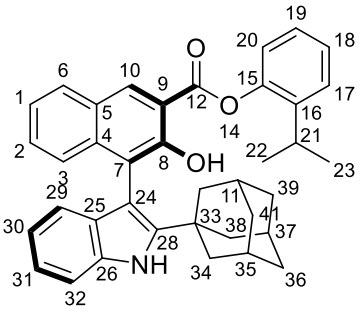
2-isopropylphenyl 3-hydroxy-4-(2-(*tert*-pentyl)-1H-indol-3-yl)-2-naphthoate (322)



The title compound was prepared according to General Procedure Q using 2-isopropylphenyl 3-hydroxy-2-naphthoate (**267**) (30.6 mg, 0.10 mmol) and 2-(*tert*-pentyl)-1H-indole (**289**) (28.1 mg, 0.15 mmol). The crude product was purified by flash column chromatography [silica gel, 50% CH_2Cl_2 in pentane] to

afford the product as a yellow foam (83%, 40.6 mg, 92% BRSM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.40 (s, 1H), 8.89 (s, 1H), 8.21 (s, 1H), 8.02 – 7.90 (m, 1H), 7.50 – 7.43 (m, 3H), 7.43 – 7.36 (m, 2H), 7.36 – 7.29 (m, 2H), 7.25 – 7.22 (m, 1H), 7.17 (ddd, *J* = 8.1, 6.8, 1.3 Hz, 1H), 6.97 (ddd, *J* = 7.9, 6.9, 1.0 Hz, 1H), 6.92 (dd, *J* = 7.8, 1.1 Hz, 1H), 3.24 (hept, *J* = 6.9 Hz, 1H), 1.77 – 1.56 (m, 2H), 1.33 (dd, *J* = 6.9, 3.1 Hz, 6H), 1.23 (d, *J* = 18.7 Hz, 6H), 0.83 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.4, 155.1, 147.8, 143.2, 140.6, 139.2, 134.9, 132.6, 130.1, 129.7, 129.4, 127.2, 127.1 (2C), 127.0, 126.2, 124.0, 122.4, 121.7, 119.7, 119.3, 118.9, 113.4, 110.5, 105.7, 37.1, 36.4, 27.7, 27.7, 26.9, 23.3, 23.2, 9.6; **FTIR** (neat) ν = 3436, 3249, 2965, 1688, 1625, 1489, 1456, 1432, 1333, 1316, 1290, 1201, 1173, 1151, 1098, 1082, 1041, 939, 774, 747, 712 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{33}H_{34}O_3N$ $(M+H)^+$ 492.2533, found 492.2525; **$[\alpha]^{D}_{25}$** = +3.0° (*c* 1.0, $CHCl_3$); **HPLC** ChiralPak IC (5% *i*-PrOH in hexane, 1.0 mL min^{-1}, T = 25 °C, 276 nm); τ_R (minor) = 6.6 min, τ_R (major) = 8.7 min; **e.r.** = 95:5.

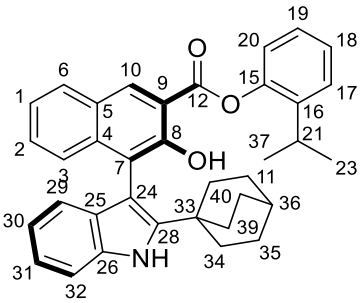
2-isopropylphenyl 4-(2-((3r,5r,7r)-adamantan-1-yl)-1H-indol-3-yl)-3-hydroxy-2-naphthoate (323)



The title compound was prepared according to General Procedure Q using 2-isopropylphenyl 3-hydroxy-2-naphthoate (**267**) (30.6 mg, 0.10 mmol) and 2-((3r,5r,7r)-adamantan-1-yl)-1H-indole (**290**) (37.7 mg, 0.15 mmol). The crude product was purified by flash column chromatography [silica gel, 50% CH_2Cl_2 in pentane] to afford the product as a yellow foam (71%, 39.5 mg, 88% BRSM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.42 (s, 1H), 8.91 (s, 1H), 8.32 (s, 1H), 8.01 – 7.94 (m, 1H), 7.47 (ddt, *J* = 5.7, 4.4, 2.0 Hz, 2H), 7.44 – 7.37 (m, 3H), 7.37 – 7.31 (m, 2H), 7.29 – 7.24 (m, 1H), 7.17 (ddd, *J* = 8.1, 6.9, 1.3 Hz, 1H), 6.97 (ddd, *J* = 7.9, 6.9, 0.9 Hz, 1H), 6.93 – 6.86 (m, 1H), 3.26 (hept, *J* = 6.9 Hz, 1H), 2.00 (d, *J* = 2.7 Hz, 6H), 1.95 (s, 3H), 1.75 – 1.58 (m, 6H), 1.35 (dd, *J* = 6.9, 2.2 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.4, 155.0, 147.8, 144.4, 140.6, 139.2, 134.7, 132.6, 130.1, 129.6, 129.4, 127.2, 127.1 (2C), 127.0, 126.3, 124.0, 122.4, 121.6, 119.6, 119.5, 118.8, 113.3, 110.5, 104.4, 41.7, 36.7, 35.7,

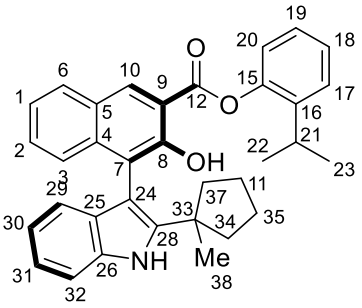
28.5, 27.7, 23.3, 23.2; **FTIR** (neat) ν = 3435, 3261, 2964, 2849, 1688, 1626, 1488, 1458, 1433, 1316, 1285, 1201, 1174, 1153, 1082, 937, 743, 704, 668 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{38}H_{38}O_3N$ $(M+H)^+$ 556.2846, found 556.2847; **$[\alpha]^D_{25}$** = –13.2° (*c* 1.0, $CHCl_3$); **HPLC** ChiralPak IC (5% *i*-PrOH in hexane, 1.0 mL min^{-1}, T = 25 °C, 266 nm); τ_R (minor) = 7.4 min, τ_R (major) = 10.6 min; **e.r.** = 91:9.

2-isopropylphenyl 4-(2-(bicyclo[2.2.2]octan-1-yl)-1H-indol-3-yl)-3-hydroxy-2-naphthoate (324)



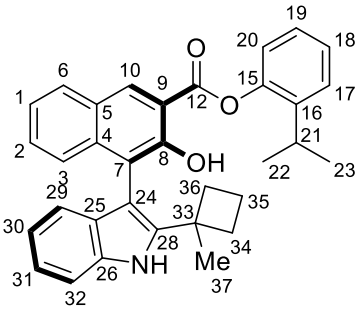
The title compound was prepared according to General Procedure Q using 2-isopropylphenyl 3-hydroxy-2-naphthoate (**267**) (30.6 mg, 0.10 mmol) and 2-(bicyclo[2.2.2]octan-1-yl)-1H-indole (**291**) (33.8 mg, 0.15 mmol). The crude product was purified by flash column chromatography [silica gel, 50% CH_2Cl_2 in pentane] to afford the product as a yellow foam (80%, 42.4 mg, 86% BRSM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.36 (s, 1H), 8.88 (s, 1H), 8.20 (s, 1H), 7.95 (ddt, *J* = 6.2, 3.4, 1.7 Hz, 1H), 7.47 – 7.34 (m, 5H), 7.34 – 7.28 (m, 2H), 7.25 – 7.20 (m, 1H), 7.13 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 6.93 (ddd, *J* = 7.9, 7.0, 1.0 Hz, 1H), 6.84 (d, *J* = 7.9 Hz, 1H), 3.24 (hept, *J* = 6.9 Hz, 1H), 1.88 – 1.70 (m, 6H), 1.66 – 1.42 (m, 6H), 1.32 (dd, *J* = 6.9, 3.8 Hz, 6H), 0.98 – 0.77 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.4, 155.0, 147.9, 143.9, 140.6, 139.2, 134.9, 132.6, 130.1, 129.7, 129.4, 127.2, 127.1 (2C), 127.0, 126.3, 124.0, 122.4, 121.7, 119.6, 119.4, 118.8, 113.4, 110.5, 104.8, 33.1, 30.7, 27.7, 26.2, 23.7, 23.3, 23.2; **FTIR** (neat) ν = 3431, 3235, 2959, 2862, 1685, 1559, 1473, 1435, 1332, 1317, 1287, 1201, 1174, 1155, 1082, 936, 749, 680, 668, 658 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{36}H_{36}O_3N$ $(M+H)^+$ 530.2690, found 530.2688; **$[\alpha]^D_{25}$** = +6.4° (*c* 1.0, $CHCl_3$); **HPLC** ChiralPak IC (5% *i*-PrOH in hexane, 1.0 mL min^{-1}, T = 25 °C, 289 nm; τ_R (minor) = 7.9 min, τ_R (major) = 11.2 min; **e.r.** = 86:14.

2-isopropylphenyl 3-hydroxy-4-(2-(1-methylcyclopentyl)-1H-indol-3-yl)-2-naphthoate (325)



The title compound was prepared according to General Procedure Q using 2-isopropylphenyl 3-hydroxy-2-naphthoate (**267**) (30.6 mg, 0.10 mmol) and 2-(1-methylcyclopentyl)-1H-indole (**292**) (29.9 mg, 0.15 mmol). The crude product was purified by flash column chromatography [silica gel, 50% CH_2Cl_2 in pentane] to afford the product as a yellow foam (75%, 37.8 mg, 95% BRSM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.44 (s, 1H), 8.91 (s, 1H), 8.20 (s, 1H), 8.02 – 7.92 (m, 1H), 7.53 – 7.45 (m, 2H), 7.45 – 7.38 (m, 3H), 7.38 – 7.30 (m, 2H), 7.28 – 7.23 (m, 1H), 7.19 (ddd, *J* = 8.1, 6.5, 1.7 Hz, 1H), 7.04 – 6.91 (m, 2H), 3.26 (hept, *J* = 6.9 Hz, 1H), 2.06 – 1.97 (m, 1H), 1.92 – 1.80 (m, 1H), 1.70 – 1.56 (m, 6H), 1.35 (dd, *J* = 7.0, 2.2 Hz, 6H), 1.33 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.4, 155.1, 147.8, 144.7, 140.6, 139.1, 135.1, 132.6, 129.9, 129.7, 129.4, 127.2, 127.1 (2C), 127.0, 126.2, 124.1, 122.4, 121.6, 119.7, 119.0, 118.9, 113.4, 110.5, 104.7, 44.5, 38.9, 38.5, 27.7, 26.7, 23.5, 23.4, 23.3, 23.2; **FTIR** (neat) ν = 3429, 3263, 2962, 2870, 1687, 1625, 1499, 1488, 1459, 1433, 1318, 1286, 1201, 1174, 1151, 1082, 1043, 937, 774, 747 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{34}H_{34}O_3N$ $(M+H)^+$ 504.2533, found 504.2532; **$[\alpha]^{D}_{25}$** = –28.7° (*c* 1.0, $CHCl_3$); **HPLC** ChiralPak IC (5% *i*-PrOH in hexane, 1.0 mL min^{-1}, T = 25 °C, 248 nm); τ_R (minor) = 7.7 min, τ_R (major) = 11.5 min; **e.r.** = 94:6.

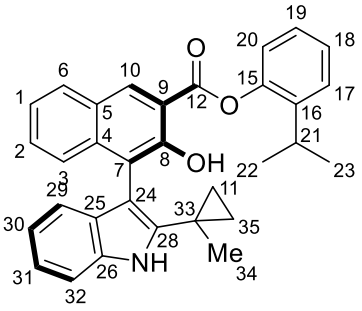
2-isopropylphenyl 3-hydroxy-4-(2-(1-methylcyclobutyl)-1H-indol-3-yl)-2-naphthoate (326)



The title compound was prepared according to General Procedure Q using 2-isopropylphenyl 3-hydroxy-2-naphthoate (**267**) (30.6 mg, 0.10 mmol) and 2-(1-methylcyclobutyl)-1H-indole (**293**) (27.8 mg, 0.15 mmol). The crude product was purified by flash column chromatography [silica gel, 50% CH_2Cl_2 in pentane] to afford the product as a yellow foam (90%, 44.1 mg, 94% BRSM). **^{1}H NMR** (400 MHz, $CDCl_3$)

δ 10.46 (s, 1H), 8.90 (s, 1H), 8.08 (s, 1H), 8.03 – 7.93 (m, 1H), 7.61 – 7.52 (m, 1H), 7.48 – 7.37 (m, 4H), 7.37 – 7.31 (m, 2H), 7.26 – 7.22 (m, 1H), 7.19 (ddd, *J* = 8.2, 5.5, 2.7 Hz, 1H), 7.06 – 6.98 (m, 2H), 3.25 (hept, *J* = 6.9 Hz, 1H), 2.54 – 2.41 (m, 1H), 2.35 – 2.25 (m, 1H), 2.06 – 1.92 (m, 1H), 1.82 – 1.70 (m, 3H), 1.59 (s, 3H), 1.34 (dd, *J* = 6.9, 3.2 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.4, 155.1, 147.8, 144.9, 140.6, 139.0., 135.3, 132.6, 129.8, 129.7, 129.4, 127.2, 127.1 (2C), 127.0, 126.2, 124.1, 122.4, 121.6, 119.8, 119.0, 118.2, 113.3, 110.6, 104.1, 39.3, 33.6, 33.1, 27.7, 26.9, 23.3, 23.2, 16.6; **FTIR** (neat) ν = 3416, 3249, 2963, 1687, 1625, 1488, 1460, 1435, 1312, 1289, 1200, 1173, 1152, 1082, 1042, 937, 774, 746 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{33}H_{32}O_3N$ $(M+H)^+$ 490.2377, found 490.2378; **$[\alpha]^{D}_{25}$** = –14.7° (*c* 1.0, $CHCl_3$); **HPLC** ChiralPak IC (5% *i*-PrOH in hexane, 1.0 mL min^{-1}, T = 25 °C, 258 nm); τ_R (minor) = 8.2 min, τ_R (major) = 12.1 min; **e.r.** = 96:4.

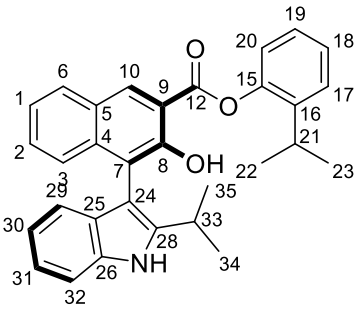
2-isopropylphenyl 3-hydroxy-4-(2-(1-methylcyclopropyl)-1H-indol-3-yl)-2-naphthoate (327)



The title compound was prepared according to General Procedure Q using 2-isopropylphenyl 3-hydroxy-2-naphthoate (**267**) (30.6 mg, 0.10 mmol) and 2-(1-methylcyclopropyl)-1H-indole (**294**) (25.7 mg, 0.15 mmol). The crude product was purified by flash column chromatography [silica gel, 50-60% CH_2Cl_2 in pentane] to afford the product as a yellow oil (74%, 35.2 mg, 96% BRSM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.45 (s, 1H), 8.91 (d, *J* = 0.7 Hz, 1H), 8.25 (s, 1H), 8.02 – 7.90 (m, 1H), 7.50 – 7.37 (m, 5H), 7.36 – 7.29 (m, 2H), 7.25 – 7.21 (m, 1H), 7.18 (ddd, *J* = 8.2, 6.6, 1.6 Hz, 1H), 7.07 – 6.97 (m, 2H), 3.25 (hept, *J* = 6.9 Hz, 1H), 1.37 (s, 3H), 1.33 (dd, *J* = 6.9, 3.1 Hz, 6H), 0.93 – 0.84 (m, 1H), 0.77 – 0.69 (m, 1H), 0.50 – 0.41 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.5, 155.0, 147.8, 141.0, 140.6, 138.8, 135.2, 132.7, 129.8, 129.5, 129.4, 127.2, 127.1, 127.0, 124.1, 122.4, 121.9, 119.9, 119.2, 117.9, 113.4, 110.7, 106.4, 27.7, 24.7, 23.3, 23.2, 14.6, 13.5; **FTIR** (neat) ν = 3431, 3258, 2937, 2862, 1686, 1625, 1389, 1458, 1434, 1317, 1287, 1201, 1174, 1155, 1082, 936, 750, 706, 668 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{32}H_{30}O_3N$ $(M+H)^+$ 476.2220, found 476.2221; **$[\alpha]^{D}_{25}$** = –10.0° (*c* 1.0, $CHCl_3$); **HPLC**

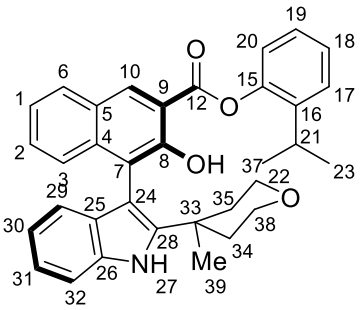
ChiralPak IC (5% *i*-PrOH in hexane), 1.0 mL min^{-1}, 255 nm; τ_R (minor) = 9.1 min, τ_R (major) = 15.1 min; **e.r.** = 82:18.

2-isopropylphenyl 3-hydroxy-4-(2-isopropyl-1H-indol-3-yl)-2-naphthoate (328)



The title compound was prepared according to General Procedure Q using 2-isopropylphenyl 3-hydroxy-2-naphthoate (**267**) (30.6 mg, 0.10 mmol) and 2-(1-methylcyclopentyl)-1H-indole (**308**) (29.9 mg, 0.15 mmol). The crude product was purified by flash column chromatography [silica gel, 50% CH_2Cl_2 in pentane] to afford the product as a yellow foam (93%, 37.8 mg, 98% BRSM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.46 (s, 1H), 8.91 (s, 1H), 8.21 (s, 1H), 8.03 – 7.93 (m, 1H), 7.58 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.49 – 7.38 (m, 4H), 7.38 – 7.30 (m, 2H), 7.25 – 7.16 (m, 2H), 7.10 (d, *J* = 7.7 Hz, 1H), 7.04 (ddd, *J* = 7.9, 6.8, 0.9 Hz, 1H), 3.25 (hept, *J* = 6.9 Hz, 1H), 3.06 (hept, *J* = 7.0 Hz, 1H), 1.38 – 1.32 (m, 9H), 1.24 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.4, 155.0, 147.8, 143.4, 140.6, 138.8, 135.6, 132.6, 129.8, 129.4, 129.2, 127.24, 127.17, 127.1, 127.0, 126.0, 124.1, 122.4, 121.4, 119.9, 119.4, 117.4, 113.5, 110.8, 104.9, 27.7, 26.7, 23.3, 23.2, 22.8, 22.3; **FTIR** (neat) ν = 3431, 3258, 2937, 2962, 1686, 1625, 1489, 1458, 1434, 1317, 1287, 1201, 1174, 1155, 1082, 936, 750, 706, 668 cm^{-1}; **HRMS** (ESI$^+$) m/z Calcd. for $C_{31}H_{30}O_3N$ $(M+H)^+$ 464.2220, found 464.2219; **[α]$^D_{25}$** = –1.9 ° (*c* 1.0, $CHCl_3$); **HPLC** ChiralPak IC (5% *i*-PrOH in hexane), 1.0 mL min^{-1}, 248 nm; τ_R (minor) = 9.3 min, τ_R (major) = 12.9 min; **e.r.** = 60:40.

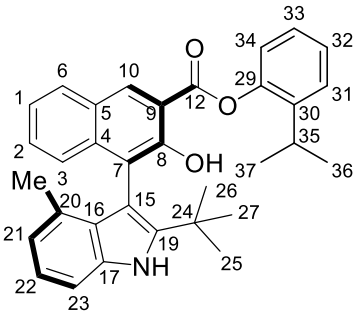
2-isopropylphenyl 3-hydroxy-4-(2-(4-methyltetrahydro-2H-pyran-4-yl)-1H-indol-3-yl)-2-naphthoate (329)



The title compound was prepared according to General Procedure Q using 2-isopropylphenyl 3-hydroxy-2-naphthoate (**267**) (30.6 mg, 0.10 mmol) and 2-(4-methyltetrahydro-2H-pyran-4-yl)-1H-indole (**295**) (32.0 mg, 0.15 mmol). The crude product was purified by flash column chromatography [silica gel, 20-30% EtOAc in pentane] to afford the product as a yellow oil (70%, 36.3 mg, 90% BRSM). **^{1}H NMR** (400

MHz, $CDCl_3$) δ 10.52 (s, 1H), 8.92 (s, 1H), 8.36 (s, 1H), 8.09 – 7.95 (m, 1H), 7.52 – 7.39 (m, 6H), 7.39 – 7.30 (m, 2H), 7.25 – 7.17 (m, 1H), 7.00 (ddd, *J* = 7.9, 6.9, 1.0 Hz, 1H), 6.96 – 6.91 (m, 1H), 3.78 – 3.66 (m, 2H), 3.58 (qdt, *J* = 11.6, 7.3, 3.6 Hz, 2H), 3.25 (hept, *J* = 6.9 Hz, 1H), 2.18 – 1.99 (m, 2H), 1.72 – 1.55 (m, 2H), 1.47 (s, 3H), 1.35 (dd, *J* = 6.9, 4.1 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.3, 154.9, 147.8, 142.2, 140.6, 138.7, 135.0, 132.9, 130.0, 129.8, 129.6, 127.2, 127.1, 127.0, 126.1, 124.2, 122.4, 122.0, 119.9, 119.1, 118.7, 113.4, 110.6, 105.7, 64.4, 37.5, 36.9, 35.0, 29.8, 27.7, 26.6, 23.3; **FTIR** (neat) ν = 3430, 1689, 1625, 1434, 1317, 1201, 1175, 1101, 1035, 795, 774, 748 cm^{-1}; **HRMS** (ESI$^+$) m/z Calcd. for $C_{34}H_{34}O_4N$ $(M+H)^+$ 520.2482, found 520.2483; **$[\alpha]^{D}_{25}$** = +13.8° (*c* 1.0, $CHCl_3$); **HPLC** ChiralPak IC (15% *i*-PrOH in hexane), 1.0 mL min^{-1}, 258 nm; τ_R (minor) = 9.1 min, τ_R (major) = 15.1 min; **e.r.** = 67:33.

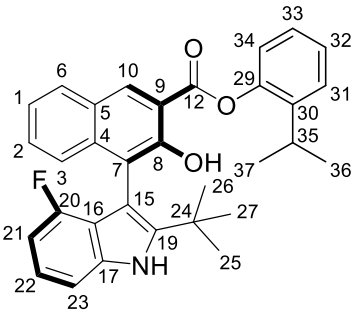
2-isopropylphenyl 4-(2-(*tert*-butyl)-4-methyl-1H-indol-3-yl)-3-hydroxy-2-naphthoate (330)



The title compound was prepared according to General Procedure Q using 2-isopropylphenyl 3-hydroxy-2-naphthoate (**267**) (30.6 mg, 0.10 mmol) and 2-(*tert*-butyl)-4-methyl-1H-indole (**XL23**) (28.1mg, 0.15 mmol). The crude product was purified by flash column chromatography [silica gel, 50% CH_2Cl_2 in pentane] to afford the product as a yellow oil (51%, 25.1 mg, 89% BRSM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.41 (s, 1H), 8.87 (s, 1H), 8.23 (s, 1H), 7.98 – 7.87 (m, 1H), 7.48 (ddt, *J* = 8.6, 1.5, 0.8 Hz, 1H), 7.46 – 7.40 (m, 2H), 7.40 – 7.35 (m, 1H), 7.35 – 7.30 (m, 2H), 7.30 – 7.27 (m, 1H), 7.26 – 7.20 (m, 1H), 7.04 (dd, *J* = 8.2, 7.1 Hz, 1H), 6.70 (dt, *J* = 7.1, 1.0 Hz, 1H), 3.22 (hept, *J* = 6.9 Hz, 1H), 1.70 (s, 3H), 1.31 (dd, *J* = 6.9, 3.1 Hz, 6H), 1.24 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.4, 155.3, 147.8, 143.2, 140.6, 140.0, 135.0, 132.7, 130.7, 129.6, 127.9, 127.2, 127.1, 127.0, 126.8, 126.6, 124.1, 122.5, 121.6, 121.3, 113.0, 108.6, 104.6, 33.5, 30.3, 27.8, 23.2, 18.7; **FTIR** (neat) ν = 3446, 3287, 2965, 1685, 1499, 1457, 1435, 1312, 1276, 1201, 1173, 1082, 939, 796, 771 cm^{-1}; **HRMS** (ESI$^+$) m/z Calcd. for $C_{33}H_{34}O_3N$ $(M+H)^+$ 492.2533, found 492.2535; **$[\alpha]^{D}_{25}$** = +0.4° (*c* 1.0, $CHCl_3$); **HPLC** ChiralPak ODH

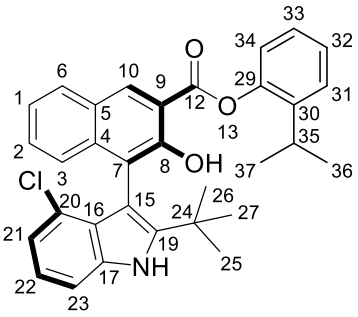
(5% *i*-PrOH in hexane), 1.0 mL min^{-1}, 238 nm; τ_R (minor) = 8.5 min, τ_R (major) = 10.7 min; **e.r.** = 51:49.

2-Isopropylphenyl 4-(2-(*tert*-butyl)-4-fluoro-1*H*-indol-3-yl)-3-hydroxy-2-naphthoate (331)



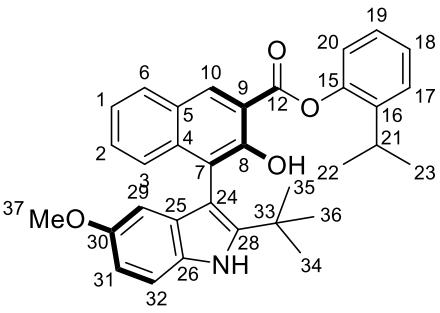
The title compound was prepared according to General Procedure Q using 2-isopropylphenyl 3-hydroxy-2-naphthoate (**267**) (30.6 mg, 0.10 mmol) and 2-(*tert*-butyl)-4-fluoro-1*H*-indole (**XL36**) (29.0 mg, 0.15 mmol). The crude product was purified by flash column chromatography [silica gel, 5% EtOAc in petroleum ether b.p. 40–60 °C] to afford the product as a yellow foam (87%, 43mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.52 (s, 1H), 8.89 (s, 1H), 8.35 (s, 1H), 7.96 (d, *J* = 7.3 Hz, 1H), 7.51 (d, *J* = 8.6 Hz, 1H), 7.48 – 7.41 (m, 2H), 7.42 – 7.34 (m, 2H), 7.35 – 7.29 (m, 2H), 7.26 – 7.22 (m, 1H), 7.20 (d, *J* = 8.2 Hz, 1H), 7.06 (td, *J* = 7.9, 4.9 Hz, 1H), 6.62 (ddd, *J* = 11.0, 7.8, 0.7 Hz, 1H), 3.25 (hept, *J* = 6.9 Hz, 1H), 1.33 (d, *J* = 6.8 Hz, 6H), 1.29 (s, 9H); **^{19}F NMR** (377 MHz, $CDCl_3$) δ -125.94 – -126.02 (m); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.3, 156.6 (d, *J* = 247.6 Hz), 154.8, 147.7, 144.1, 140.5, 139.2, 137.5, 137.4, 132.6, 129.6, 129.3, 127.0, 126.9, 126.9, 126.8, 125.8, 123.8, 122.3, 121.8 (d, *J* = 7.9 Hz), 118.4 (d, *J* = 17.7 Hz), 113.0, 106.6 (d, *J* = 3.6 Hz), 104.9 (d, *J* = 19.2 Hz), 102.1 (d, *J* = 1.9 Hz), 30.0, 27.5, 23.1, 23.09; **FTIR** (neat) ν = 3654, 3436, 2980, 2888, 2360, 1687, 1626, 1503, 1434, 1311, 1201, 1172, 1082, 939, 795, 771, 751cm^{-1}; **HRMS** (ESI$^+$) m/z Calcd. for $C_{32}H_{31}FNO_3$ $(M+H)^+$ 496.2282, found 496.2279; **$[\alpha]^{D}_{25}$** = +166.2° (*c* 1.0, $CHCl_3$); **HPLC** Daicel ChiralPak IC (5% *i*-PrOH in hexane, 1.0 mL min^{-1}, T = 25 °C, 254 nm); τ_R (major) = 6.4 min, τ_R (minor) = 10.9 min; **e.r.** = 90:10.

2-Isopropylphenyl 4-(2-(*tert*-butyl)-4-chloro-1*H*-indol-3-yl)-3-hydroxy-2-naphthoate (332)



The title compound was prepared according to General Procedure Q using 2-isopropylphenyl 3-hydroxy-2-naphthoate (**267**) (30.6 mg, 0.10 mmol) and 2-(*tert*-butyl)-4-chloro-1*H*-indole (**XL37**) (31.0 mg, 0.15 mmol). The crude product was purified by flash column chromatography [silica gel, 5% EtOAc in petroleum ether b.p. 40–60 °C] to afford the product as a yellow foam (82%, 42 mg). **M.P.** = 60-63 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.40 (s, 1H), 8.79 (s, 1H), 8.27 (s, 1H), 7.84 (d, *J* = 8.2 Hz, 1H), 7.36 – 7.32 (m, 3H), 7.30 – 7.22 (m, 4H), 7.17 – 7.13 (m, 1H), 6.96 (t, *J* = 7.8 Hz, 1H), 6.84 (dd, *J* = 7.6, 0.9 Hz, 1H), 3.14 (hept, *J* = 6.9 Hz, 1H), 1.22 (d, *J* = 6.8 Hz, 6H), 1.18 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.3, 155.3, 147.7, 144.9, 140.5, 140.0, 136.0, 132.7, 129.4, 129.2, 127.0, 126.9, 126.8, 126.6, 126.13, 125.9, 125.6, 123.8, 122.3, 121.9, 120.8, 119.5, 112.8, 109.3, 104.1, 33.4, 30.0, 27.5, 23.08, 23.07; **FTIR** (neat) ν = 3660, 2980, 2888, 1690, 1462, 1382, 1251, 1152, 1073, 954, 815 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for C32H31ClNO3 (M+H)+ 512.1987, found 512.1981; **$[\alpha]^{D}_{25}$** = –55.1° (*c* 1.0, $CHCl_3$); **HPLC** Daicel ChiralPak IC (5% *i*-PrOH in hexane, 1.0 mL min^{-1}, T = 25 °C, 254 nm); τ_R (major) = 7.5 min, τ_R (minor) = 11.2 min; **e.r.** = 94:6.

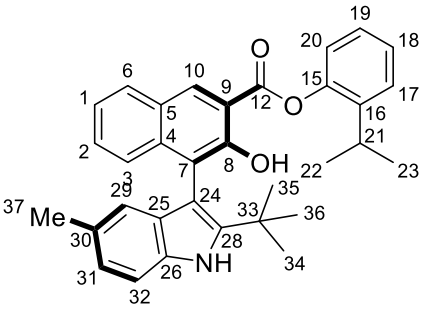
2-isopropylphenyl 4-(2-(*tert*-butyl)-5-methoxy-1H-indol-3-yl)-3-hydroxy-2-naphthoate (333)



The title compound was prepared according to General Procedure Q using 2-isopropylphenyl 3-hydroxy-2-naphthoate (**267**) (30.6 mg, 0.10 mmol) and 2-(*tert*-butyl)-5-methoxy-1H-indole (**297**) (30.5 mg, 0.15 mmol). The crude product was purified by flash column chromatography [silica gel, 50-80% CH_2Cl_2 in pentane] to afford the product as a yellow foam (97%, 49.2 mg, 99% BRSM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.43 (s, 1H), 8.90 (s, 1H), 8.14 (s, 1H),

8.03 – 7.92 (m, 1H), 7.49 – 7.42 (m, 2H), 7.42 – 7.35 (m, 2H), 7.35 – 7.28 (m, 3H), 7.25 – 7.21 (m, 1H), 6.83 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.36 (d, *J* = 2.4 Hz, 1H), 3.64 (s, 3H), 3.24 (hept, *J* = 6.9 Hz, 1H), 1.33 (dd, *J* = 6.9, 1.5 Hz, 6H), 1.28 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.4, 155.1, 154.4, 147.8, 145.2, 140.6, 139.2, 132.7, 130.6, 133.0, 129.6, 129.5, 127.2 (2C), 127.1, 127.0, 126.2, 124.1, 122.4, 119.3, 113.4, 111.5, 111.2, 104.6, 101.3, 56.1, 33.5, 30.2, 27.7, 23.3, 23.2; **FTIR** (neat) ν = 3442, 3260, 1689, 1624, 1486, 1447, 1331, 1311, 1282, 1202, 1171, 1140, 1082, 1042, 938, 836, 797, 752 cm^{-1}; **HRMS** (ESI$^+$) m/z Calcd. for $C_{33}H_{34}O_4N$ $(M+H)^+$ 508.2482, found 508.2481; **$[\alpha]^{D}_{25}$** = +12.8 ° (*c* 1.0, $CHCl_3$); **HPLC** ChiralPak IC (10% *i*-PrOH in hexane, 1.0 mL min^{-1}, T = 25 °C, 279 nm; τ_R (minor) = 7.2 min, τ_R (major) = 9.5 min; e.r. = 93:7.

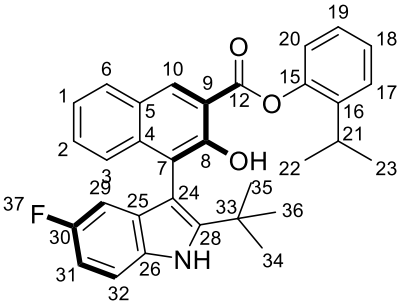
2-isopropylphenyl 4-(2-(*tert*-butyl)-5-methyl-1H-indol-3-yl)-3-hydroxy-2-naphthoate (334)



The title compound was prepared according to General Procedure Q using 2-isopropylphenyl 3-hydroxy-2-naphthoate (**267**) (30.6 mg, 0.10 mmol) and 2-(*tert*-butyl)-5-methyl-1H-indole (**311**) (28.0 mg, 0.15 mmol). The crude product was purified by flash column chromatography [silica gel, 40-50% CH_2Cl_2 in pentane] to afford the product as a yellow foam (78%, 38.3 mg, 89% BRSM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.41 (s, 1H), 8.90 (s, 1H), 8.15 (s, 1H), 8.02 – 7.90 (m, 1H), 7.50 – 7.44 (m, 2H), 7.44 – 7.36 (m, 2H), 7.36 – 7.29 (m, 3H), 7.26 – 7.21 (m, 1H), 6.99 (ddd, *J* = 8.2, 1.7, 0.6 Hz, 1H), 6.73 – 6.65 (m, 1H), 3.25 (hept, *J* = 6.9 Hz, 1H), 2.29 (s, 3H), 1.34 (dd, *J* = 6.9, 1.3 Hz, 6H), 1.29 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.4, 155.1, 147.8, 144.3, 140.6, 139.2, 133.1, 132.6, 130.3, 129.4, 129.0, 127.2 (2C), 127.1 (2C), 127.0, 126.3, 124.1, 123.3, 122.4, 119.5, 118.5, 113.4, 110.2, 104.2, 33.4, 30.2, 27.7, 23.3, 23.2, 21.6; **FTIR** (neat) ν = 3440, 3253, 1689, 1625, 1487, 1434, 1308, 1284, 1201, 1172, 1082, 1040, 937, 797, 751 cm^{-1}; **HRMS** (ESI$^+$) m/z Calcd. for $C_{33}H_{34}O_3N$ $(M+H)^+$ 492.2533, found 492.2531; **$[\alpha]^{D}_{25}$** = +41.3 ° (*c* 1.0, $CHCl_3$); **HPLC** ChiralPak ODH

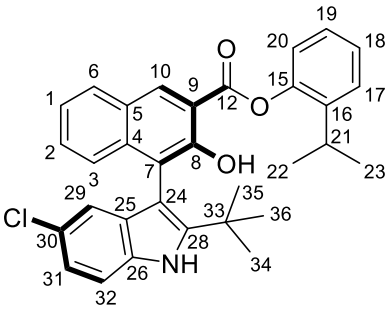
(5% *i*-PrOH in hexane, 1.0 mL min^{-1}, T = 25 °C, 265 nm); τ_R (minor) = 7.7 min, τ_R (major) = 12.3 min; **e.r.** = 93:7.

2-isopropylphenyl 4-(2-(*tert*-butyl)-5-fluoro-1H-indol-3-yl)-3-hydroxy-2-naphthoate (335)



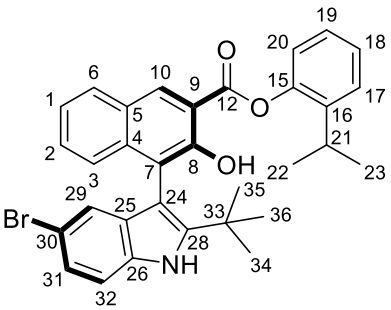
The title compound was prepared according to General Procedure Q using 2-isopropylphenyl 3-hydroxy-2-naphthoate (**267**) (30.6 mg, 0.10 mmol) and 2-(*tert*-butyl)-5-fluoro-1H-indole (**309**) (28.7 mg, 0.15 mmol). The crude product was purified by flash column chromatography [silica gel, 50% CH_2Cl_2 in pentane] to afford the product as a yellow foam (60%, 29.6 mg, 90% BRSM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.48 (s, 1H), 8.90 (s, 1H), 8.23 (s, 1H), 7.97 (dt, *J* = 7.6, 1.4 Hz, 1H), 7.47 – 7.35 (m, 4H), 7.35 – 7.29 (m, 3H), 7.25 – 7.21 (m, 1H), 6.90 (ddd, *J* = 9.3, 8.7, 2.6 Hz, 1H), 6.56 (dd, *J* = 9.5, 2.5 Hz, 1H), 3.24 (hept, *J* = 6.9 Hz, 1H), 1.33 (dd, *J* = 6.9, 1.5 Hz, 6H), 1.29 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.3, 158.2 (d, *J* = 233.8 Hz), 154.9, 147.7, 146.2, 140.5, 138.9, 132.8, 131.2, 130.5 (d, *J* = 9.5 Hz), 129.7, 129.5, 127.1 (2C), 127.0, 126.9, 125.8, 124.1, 122.3, 118.5, 113.3, 111.0 (d, *J* = 9.6 Hz), 109.8 (d, *J* = 26.6 Hz), 104.9 (d, *J* = 4.2 Hz), 103.7 (d, *J* = 23.7 Hz), 33.4, 30.0, 27.6, 23.2, 23.1; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -124.76; **FTIR** (neat) ν = 3458, 3229, 1688, 1626, 1486, 1447, 1435, 1332, 1311, 1275, 1201, 1170, 1085, 1040, 938, 798, 751, 702 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{32}H_{31}O_3NF$ $(M+H)^+$ 496.2282, found 496.2281; **$[\alpha]^{D}_{25}$** = +2.7 ° (*c* 1.0, $CHCl_3$); **HPLC** ChiralPak ODH (5% *i*-PrOH in hexane, 1.0 mL min^{-1}, T = 25 °C, 226 nm); τ_R (minor) = 9.2 min, τ_R (major) = 13.1 min; **e.r.** = 92:8.

2-isopropylphenyl 4-(2-(*tert*-butyl)-5-chloro-1H-indol-3-yl)-3-hydroxy-2-naphthoate (336)



The title compound was prepared according to General Procedure Q using 2-isopropylphenyl 3-hydroxy-2-naphthoate (**267**) (30.6 mg, 0.10 mmol) and 2-(*tert*-butyl)-5-chloro-1H-indole (**310**) (31.2 mg, 0.15 mmol). The crude product was purified by flash column chromatography [silica gel, 50% CH_2Cl_2 in pentane] to afford the product as a yellow oil (63%, 32.2 mg, 86% BRSM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.48 (s, 1H), 8.90 (s, 1H), 8.26 (s, 1H), 8.01 – 7.92 (m, 1H), 7.49 – 7.35 (m, 4H), 7.35 – 7.28 (m, 3H), 7.25 – 7.19 (m, 1H), 7.11 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.86 (d, *J* = 2.0 Hz, 1H), 3.24 (hept, *J* = 6.9 Hz, 1H), 1.33 (d, *J* = 6.8 Hz, 6H), 1.29 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.4, 155.1, 147.8, 146.0, 140.6, 139.0, 133.2, 133.0, 131.3, 129.8, 129.7, 127.2, 127.1, 125.9, 125.5, 124.2, 122.4, 122.0, 118.3, 113.4, 111.6, 104.7, 33.5, 30.1, 27.7, 23.3, 23.2; **FTIR** (neat) ν = 3443, 3249, 2963, 1688, 1626, 1479, 1432, 1364, 1309, 1269, 1201, 1172, 1144, 1082, 1039, 936, 792, 751 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{32}H_{31}O_3NCl$ $(M+H)^+$ 512.1987, found 512.1987; **$[\alpha]^{D}_{25}$** = +5.7 ° (*c* 1.0, $CHCl_3$); **HPLC** ChiralPak ODH (5% *i*-PrOH in hexane), 1.0 mL min^{-1}, 292 nm; τ_R (minor) = 9.1 min, τ_R (major) = 16.6 min; **e.r.** = 71:29.

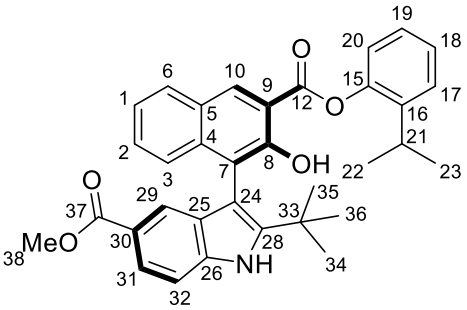
2-isopropylphenyl 4-(5-bromo-2-(*tert*-butyl)-1H-indol-3-yl)-3-hydroxy-2-naphthoate (337)



The title compound was prepared according to General Procedure Q using 2-isopropylphenyl 3-hydroxy-2-naphthoate (**267**) (30.6 mg, 0.10 mmol) and 5-bromo-2-(*tert*-butyl)-1H-indole (**XL41**) (37.8 mg, 0.15 mmol). The crude product was purified by flash column chromatography [silica gel, 50% CH_2Cl_2 in pentane] to afford the product as a yellow foam (40%, 22.3 mg, 87% BRSM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.51 (s, 1H), 8.92 (s, 1H), 8.30 (s, 1H), 8.03 – 7.93 (m, 1H), 7.44 (s, 1H), 7.44

– 7.37 (m, 3H), 7.37 – 7.31 (m, 2H), 7.29 (dd, *J* = 8.5, 0.6 Hz, 1H), 7.27 – 7.22 (m, 2H), 7.07 – 7.02 (m, 1H), 3.26 (hept, *J* = 6.9 Hz, 1H), 1.35 (d, *J* = 6.9 Hz, 6H), 1.30 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.4, 155.1, 147.8, 145.8, 140.6, 139.0, 133.5, 133.0, 131.9, 129.8, 129.7, 127.2, 127.1 (2C), 127.0, 125.8, 124.5, 124.2, 122.4, 121.3, 118.3, 113.4, 113.1, 112.1, 104.5, 33.5, 30.1, 27.7, 23.3, 23.2; **FTIR** (neat) ν = 3443, 3260, 1688, 1626, 1500, 1478, 1461, 1431, 1310, 1270, 1202, 1173, 1144, 1103, 1082, 1049, 1038, 936, 866, 791, 774, 751, 694 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{32}H_{31}O_3NBr$ $(M+H)^+$ 556.1482, found 556.1482; **$[\alpha]^{D}_{25}$** = +30.4 ° (*c* 1.0, $CHCl_3$); **HPLC** ChiralPak IC (5% *i*-PrOH in hexane, 1.0 mL min^{-1}, T = 25 °C, 255 nm); τ_R (minor) = 5.5 min, τ_R (major) = 6.5 min; **e.r.** = 90:10.

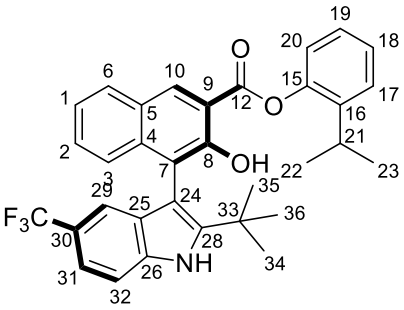
Methyl 2-(*tert*-butyl)-3-(2-hydroxy-3-((2-isopropylphenoxy)carbonyl)naphthalen-1-yl)-1*H*-indole-5-carboxylate (338)



The title compound was prepared according to General Procedure Q using 2-isopropylphenyl 3-hydroxy-2-naphthoate (**267**) (30.6 mg, 0.10 mmol) and methyl 2-(*tert*-butyl)-1H-indole-5-carboxylate (**XL32**) (35.0 mg, 0.15 mmol). The crude product was purified by flash column chromatography [silica gel, 5% EtOAc in petroleum ether b.p. 40–60 °C] to afford the product as a yellow solid (41%, 22 mg). **M.P.** = 258-261 °C**; ^{1}H NMR** (600 MHz, $CDCl_3$) δ 10.45 (s, 1H), 8.90 (s, 1H), 8.40 (s, 1H), 7.96 (d, *J* = 8.6 Hz, 1H), 7.88 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.66 (d, *J* = 1.5 Hz, 1H), 7.44 (dd, *J* = 7.3, 2.2 Hz, 1H), 7.41 (d, *J* = 8.5 Hz, 1H), 7.40 – 7.34 (m, 3H), 7.33 – 7.29 (m, 2H), 7.22 (dd, *J* = 7.6, 1.7 Hz, 1H), 3.79 (s, 3H), 3.24 (hept, *J* = 7.0 Hz, 1H), 1.33 (d, *J* = 6.9 Hz, 6H), 1.29 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 169.2, 168.2, 155.0, 147.6, 145.6, 140.5, 138.9, 137.5, 132.9, 129.6, 129.5, 127.0, 127.0, 126.9, 125.7, 124.0, 123.2, 122.2, 121.8, 121.7, 118.0, 113.3, 110.1, 106.0, 51.6, 33.3, 29.9, 27.5, 23.2, 23.0; **FTIR** (neat) ν = 3659, 3336, 2980, 1688, 1616, 1383, 1312, 1289, 1202, 1171, 1145, 943, 790, 769, 751 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{34}H_{34}NO_5$ $(M+H)+$ 536.2443, found 536.2431; **$[\alpha]^{D}_{25}$** = –18.4 ° (*c* 1.0, $CHCl_3$); **HPLC** Daicel

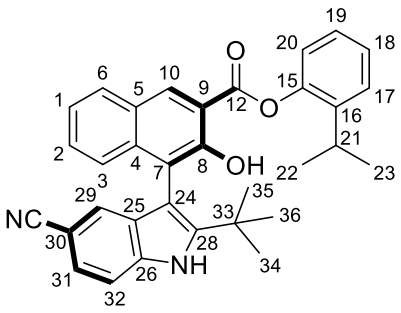
ChiralPak ODH (10% *i*-PrOH in hexane, 1.0 mL min^{-1}, T = 25 °C, 254 nm); τ_R (major) = 9.9 min, τ_R (minor) = 12.8 min; **e.r.** = 85:15.

2-isopropylphenyl 4-(2-(*tert*-butyl)-5-(trifluoromethyl)-1H-indol-3-yl)-3-hydroxy-2-naphthoate (339)



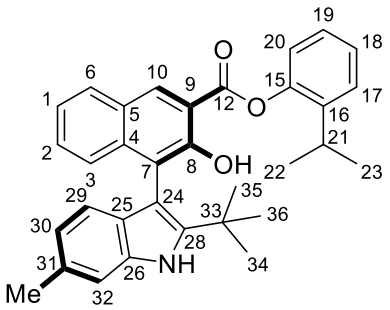
The title compound was prepared according to General Procedure Q using 2-isopropylphenyl 3-hydroxy-2-naphthoate (**267**) (30.6 mg, 0.10 mmol) and 2-(*tert*-butyl)-5-(trifluoromethyl)-1H-indole (**312**) (36.2 mg, 0.15 mmol). The crude product was purified by flash column chromatography [silica gel, 30-45% CH_2Cl_2 in pentane] to afford the product as a yellow foam (28%, 15.2 mg, 99% BRSM). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.54 (s, 1H), 8.95 (s, 1H), 8.46 (s, 1H), 8.04 – 7.95 (m, 1H), 7.52 – 7.45 (m, 2H), 7.45 – 7.36 (m, 4H), 7.36 – 7.31 (m, 2H), 7.27 – 7.24 (m, 1H), 7.23 (d, *J* = 1.6 Hz, 1H), 3.27 (hept, *J* = 6.9 Hz, 1H), 1.36 (d, *J* = 6.9 Hz, 6H), 1.32 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.9, 155.1, 147.8, 146.3, 140.6, 139.0, 136.3, 133.2, 129.9, 129.8, 129.5, 127.2 (3C), 127.1, 125.7, 125.5 (q, *J* = 272.2 Hz), 124.3, 122.4, 122.2 (q, *J* = 31.5 Hz), 118.6 (q, *J* = 3.8 Hz), 118.0, 116.6 (q, *J* = 4.3 Hz), 113.4, 110.8, 105.7, 33.6, 30.1, 27.7, 23.3, 23.2; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -124.76; **FTIR** (neat) ν = 3431, 3268, 1688, 1626, 1501, 1437, 1328, 1270, 1203, 1162, 1112, 1040, 937, 794, 751, 655 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{33}H_{31}O_3NF_3$ $(M+H)^+$ 546.2251, found 546.2248; **$[\alpha]^{D}_{25}$** = +22.6 ° (*c* 1.0, $CHCl_3$); **HPLC** ChiralPak IA (5% *i*-PrOH in hexane), 1.0 mL min^{-1}, 254 nm; τ_R (minor) = 6.3 min, τ_R (major) = 7.8 min; **e.r.** = 72:28.

2-isopropylphenyl 4-(2-(*tert*-butyl)-5-cyano-1H-indol-3-yl)-3-hydroxy-2-naphthoate (340)



The title compound was prepared according to General Procedure Q using 2-isopropylphenyl 3-hydroxy-2-naphthoate (**267**) (30.6 mg, 0.10 mmol) and 2-(*tert*-butyl)-1H-indole-5-carbonitrile (**313**) (29.7 mg, 0.15 mmol). The crude product was purified by flash column chromatography [silica gel, 60–80% CH_2Cl_2 in pentane] to afford the product as a yellow foam (13%, 6.5 mg, 97% BRSM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.54 (s, 1H), 8.92 (s, 1H), 8.62 (s, 1H), 8.02 – 7.93 (m, 1H), 7.49 – 7.36 (m, 5H), 7.36 – 7.28 (m, 3H), 7.26 – 7.20 (m, 2H), 3.23 (hept, *J* = 6.9 Hz, 1H), 1.33 (dd, *J* = 6.9, 1.2 Hz, 6H), 1.30 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.4, 155.1, 147.7, 147.0, 140.6, 138.8, 136.8, 133.3, 130.0, 129.9 (2C), 127.2 (3C), 127.1, 125.5, 124.8, 124.6, 124.3, 122.4, 121.0, 117.3, 113.4, 111.5, 105.7, 102.7, 33.6, 30.0, 27.7, 23.3, 23.2;**FTIR** (neat) ν = 3344, 3238, 3109, 2248, 1690, 1625, 1501, 1481, 1435, 1317, 1281, 1202, 1174, 1163, 1083, 1041, 938, 795, 751 cm^{-1}; **HRMS** (ESI$^+$) m/z Calcd. for $C_{33}H_{31}O_3N_2$ $(M+H)^+$ 503.2329, found 503.2329; **$[\alpha]^{D}_{25}$** = –21.2 ° (*c* 0.5, $CHCl_3$); **HPLC** ChiralPak ODH (5% *i*-PrOH in hexane), 1.0 mL min^{-1}, 239 nm; τ_R (minor) = 8.5 min, τ_R (major) = 10.7 min; **e.r.** = 85:15.

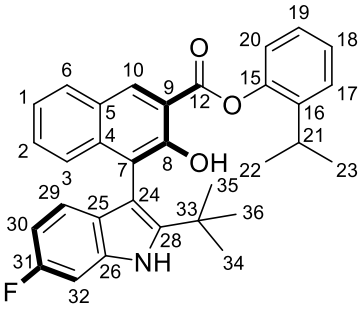
2-isopropylphenyl 4-(2-(*tert*-butyl)-6-methyl-1H-indol-3-yl)-3-hydroxy-2-naphthoate (341)



The title compound was prepared according to General Procedure Q using 2-isopropylphenyl 3-hydroxy-2-naphthoate (**267**) (30.6 mg, 0.10 mmol) and 2-(*tert*-butyl)-6-methyl-1H-indole (**316**) (28.1 mg, 0.15 mmol). The crude product was purified by flash column chromatography [silica gel, 40-50% CH_2Cl_2 in pentane] to afford the product as a yellow foam (79%, 38.8 mg, 98% BRSM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.28 (s, 1H), 8.78 (s, 1H), 8.01 (s, 1H), 7.89 – 7.79 (m, 1H), 7.40 – 7.32 (m,

2H), 7.32 – 7.25 (m, 2H), 7.25 – 7.19 (m, 2H), 7.14 – 7.10 (m, 2H), 6.70 (d, *J* = 1.1 Hz, 2H), 3.13 (hept, *J* = 6.9 Hz, 1H), 2.36 (s, 3H), 1.22 (dd, *J* = 6.9, 2.5 Hz, 6H), 1.18 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.4, 155.0, 147.8, 143.6, 140.6, 139.2, 135.3, 132.5, 131.5, 129.6, 129.4, 127.9, 127.2, 127.1 (2C), 127.0, 126.2, 124.0, 122.4, 121.4, 119.5, 118.5, 113.4, 110.6, 104.4, 33.4, 30.2, 27.7, 23.3, 23.2, 21.9; **FTIR** (neat) ν = 3446, 3257, 2965, 2929, 1686, 1558, 1458, 1417, 1334, 1316, 1290, 1201, 1174, 1156, 1082, 1042, 939, 792, 751, 668 cm^{-1};**HRMS** (ESI$^+$) m/z Calcd. for $C_{33}H_{34}O_3N$ $(M+H)^+$ 492.2533, found 492.2531; **$[\alpha]^{D}_{25}$** = +2.3° (*c* 1.0, $CHCl_3$); **HPLC** ChiralPak IA (8% *i*-PrOH in hexane), 1.0 mL min^{-1}, T = 25 °C, 247 nm); τ_R (minor) = 7.5 min, τ_R (major) = 14.0 min; **e.r.** = 89:11.

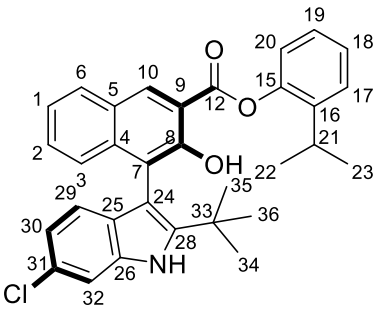
2-isopropylphenyl 4-(2-(*tert*-butyl)-6-fluoro-1H-indol-3-yl)-3-hydroxy-2-naphthoate (342)



The title compound was prepared according to General Procedure Q using 2-isopropylphenyl 3-hydroxy-2-naphthoate (**267**) (30.6 mg, 0.10 mmol) and 2-(*tert*-butyl)-6-fluoro-1H-indole (**314**) (28.7 mg, 0.15 mmol). The crude product was purified by flash column chromatography [silica gel, 50% CH_2Cl_2 in pentane] to afford the product as a yellow foam (63%, 31.2 mg, 100% BRSM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.51 (s, 1H), 8.93 (s, 1H), 8.26 (s, 1H), 7.99 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.50 – 7.43 (m, 3H), 7.43 – 7.37 (m, 1H), 7.37 – 7.30 (m, 2H), 7.26 – 7.23 (m, 1H), 7.12 (dd, *J* = 9.6, 2.2 Hz, 1H), 6.85 (dd, *J* = 8.6, 5.4 Hz, 1H), 6.76 (ddd, *J* = 9.7, 8.6, 2.2 Hz, 1H), 3.26 (hept, *J* = 6.9 Hz, 1H), 1.36 (dd, *J* = 6.9, 2.4 Hz, 6H), 1.31 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.4, 160.0 (d, *J* = 236.4 Hz), 155.0, 147.8, 144.6 (2C), 140.6, 139.1, 134.7 (d, *J* = 12.7 Hz), 132.8, 129.7, 129.6, 127.2, 127.1, 127.0, 126.5, 125.9, 124.1, 122.4, 119.6 (d, *J* = 9.8 Hz), 118.8, 113.4, 108.2 (d, *J* = 24.5 Hz), 104.7, 97.1 (d, *J* = 26.3 Hz), 33.4, 30.1, 27.7, 23.3, 23.2; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -121.96; **FTIR** (neat) ν = 3442, 3249, 1688, 1626, 1461, 1418, 1334, 1316, 1286, 1251, 1201, 1174, 1143, 1113, 1082, 1042, 939, 834, 792, 751 cm^{-1}; **HRMS** (ESI$^+$) m/z Calcd. for $C_{32}H_{31}O_3NF$ $(M+H)^+$ 496.2282, found

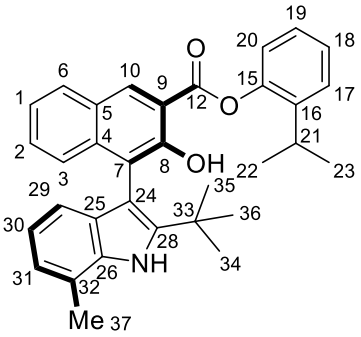
496.2281; **[α]$^{D}_{25}$** = +5.7° (*c* 1.0, $CHCl_3$); **HPLC** ChiralPak IC (5% *i*-PrOH in hexane, 1.0 mL min^{-1}, T = 25 °C, 254 nm); τ_R (minor) = 6.9 min, τ_R (major) = 8.0 min; e.r. = 84:16.

2-isopropylphenyl 4-(2-(*tert*-butyl)-6-chloro-1H-indol-3-yl)-3-hydroxy-2-naphthoate (343)



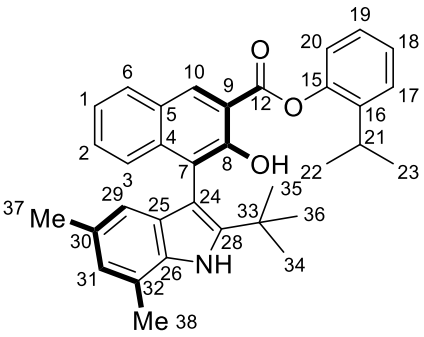
The title compound was prepared according to General Procedure Q using 2-isopropylphenyl 3-hydroxy-2-naphthoate (**267**) (30.6 mg, 0.10 mmol) and 2-(*tert*-butyl)-6-chloro-1H-indole (**315**) (31.2 mg, 0.15 mmol). The crude product was purified by flash column chromatography [silica gel, 50% CH_2Cl_2 in pentane] to afford the product as a yellow foam (56%, 28.7 mg, 86% BRSM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.48 (s, 1H), 8.91 (s, 1H), 8.25 (s, 1H), 7.97 (dt, *J* = 7.1, 1.5 Hz, 1H), 7.49 – 7.44 (m, 1H), 7.44 – 7.36 (m, 4H), 7.36 – 7.30 (m, 2H), 7.25 – 7.20 (m, 1H), 6.94 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 3.24 (hept, *J* = 6.9 Hz, 1H), 1.34 (dd, *J* = 6.9, 2.3 Hz, 6H), 1.30 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.2, 153.9, 146.6, 143.9, 139.4, 137.8, 134.0, 131.7, 128.6, 128.5, 127.5, 126.3, 126.0 (3C), 129.9, 125.9, 124.7, 123.0, 121.2, 119.3, 118.6, 117.4, 109.4, 103.7, 32.3, 28.9, 26.6, 22.1, 22.0; **FTIR** (neat) ν = 3226, 3057, 2965, 2903, 1687, 1419, 1316, 1261, 1202, 1173, 1145, 1083, 938, 791, 751, 668 cm^{-1}; **HRMS** (ESI^{+}) m/z Calcd. for $C_{32}H_{31}O_3NCl$ $(M+H)^+$ 512.1987, found 512.1987; **[α]$^{D}_{25}$** = +9.0° (*c* 1.0, $CHCl_3$); **HPLC** ChiralPak IC (5% *i*-PrOH in hexane, 1.0 mL min^{-1}, T = 25 °C, 250 nm); τ_R (minor) = 6.4 min, τ_R (major) = 7.3 min; **e.r.** = 89:11.

2-isopropylphenyl 4-(2-(*tert*-butyl)-7-methyl-1H-indol-3-yl)-3-hydroxy-2-naphthoate (344)



The title compound was prepared according to General Procedure Q using 2-isopropylphenyl 3-hydroxy-2-naphthoate (**267**) (30.6 mg, 0.10 mmol) and 2-(*tert*-butyl)-7-methyl-1H-indole (**XL22**) (28.1mg, 0.15 mmol). The crude product was purified by flash column chromatography [silica gel, 50% CH_2Cl_2 in pentane] to afford the product as a yellow oil (85%, 41.7 mg, 90% BRSM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.45 (s, 1H), 8.92 (s, 1H), 8.11 (s, 1H), 8.02 – 7.95 (m, 1H), 7.53 – 7.45 (m, 2H), 7.45 – 7.38 (m, 2H), 7.38 – 7.31 (m, 2H), 7.25 (d, *J* = 9.1 Hz, 1H), 7.00 (dt, *J* = 7.0, 1.1 Hz, 1H), 6.93 (t, *J* = 7.5 Hz, 1H), 6.80 (d, *J* = 7.8 Hz, 1H), 3.27 (hept, *J* = 6.9 Hz, 1H), 2.61 (s, 3H), 1.39 – 1.36 (m, 6H), 1.35 (d, *J* = 1.6 Hz, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.4, 155.0, 147.8, 143.9, 140.6, 139.1, 134.3, 132.6, 129.6 (2C), 129.4, 127.1 (3C), 127.0, 126.2, 124.1, 122.5, 122.4, 120.0, 119.6, 119.5, 116.7, 113.4, 105.3, 33.4, 30.3, 27.7, 23.3, 23.2, 16.8; **FTIR** (neat) ν = 3446, 3266, 2964, 2870, 1686, 1625, 1625, 1499, 1436, 1412, 1316, 1200, 1172, 1145, 1082, 939, 781, 747 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{33}H_{34}O_3N$ $(M+H)^+$ 492.2533, found 492.2534; **$[\alpha]^D_{25}$** = +3.1 ° (*c* 1.0, $CHCl_3$); **HPLC** ChiralPak IC (5% *i*-PrOH in hexane), 1.0 mL min^{-1}, 225 nm; τ_R (minor) = 6.0 min, τ_R (major) = 7.0 min; **e.r.** = 86:14.

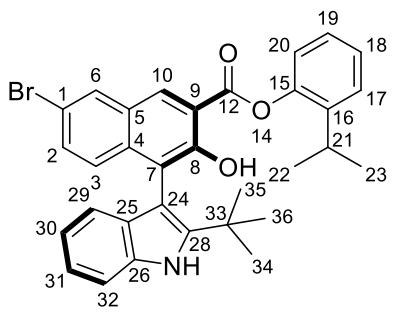
2-isopropylphenyl 4-(2-(*tert*-butyl)-5,7-dimethyl-1H-indol-3-yl)-3-hydroxy-2-naphthoate (345)



The title compound was prepared according to General Procedure Q using 2-isopropylphenyl 3-hydroxy-2-naphthoate (**267**) (30.6 mg, 0.10 mmol) and 2-(*tert*-butyl)-5,7-dimethyl-1H-indole (30.2 mg, 0.15 mmol). The crude product was purified by flash column chromatography [silica gel, 30-45% CH_2Cl_2 in pentane] to afford the product as a yellow foam (85%, 43.0 mg, 90% BRSM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.42 (s, 1H), 8.99 – 8.86

(m, 1H), 8.06 – 7.91 (m, 2H), 7.54 – 7.45 (m, 2H), 7.45 – 7.37 (m, 2H), 7.37 – 7.30 (m, 2H), 7.27 – 7.22 (m, 1H), 6.90 – 6.77 (m, 1H), 6.63 – 6.53 (m, 1H), 3.27 (hept, *J* = 6.9 Hz, 1H), 2.57 (s, 3H), 2.28 (s, 3H), 1.38 – 1.33 (d, *J* = 7.2 Hz, 6H), 1.32 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.4, 155.0, 147.8, 144.0, 140.6, 139.2, 132.6, 132.5, 129.9, 129.6, 129.4, 129.3, 127.1 (3C), 127.0, 126.4, 124.2, 124.0, 122.4, 119.8, 119.3, 116.2, 113.4, 104.8, 33.4, 30.3, 27.7, 23.3, 23.2, 21.5, 16.7; **FTIR** (neat) ν = 3468, 3257, 2964, 1686, 1559, 1474, 1457, 1436, 1309, 1201, 1171, 1083, 938, 841, 798, 751, 668 cm^{-1}; **HRMS** (ESI$^+$) m/z Calcd. for $C_{34}H_{36}O_3N$ $(M+H)^+$ 506.2690, found 506.2687; **$[\alpha]^{D}_{25}$** = +22.4 ° (*c* 1.0, $CHCl_3$); **HPLC** ChiralPak ODH (2 % *i*-PrOH in hexane, 1.0 mL min^{-1}, T = 25 °C, 260 nm); τ_R (minor) = 8.1 min, τ_R (major) = 9.4 min; **e.r.** = 84:16.

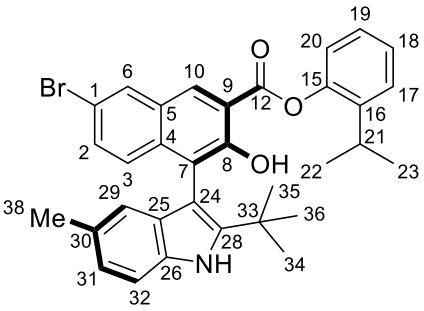
2-isopropylphenyl 7-bromo-4-(2-(*tert*-butyl)-1H-indol-3-yl)-3-hydroxy-2-naphthoate (348)



The title compound was prepared according to General Procedure Q using 2-isopropylphenyl 2-isopropylphenyl 7-bromo-3-hydroxy-2-naphthoate (**318**) (38.5 mg, 0.10 mmol) and 2-(*tert*-butyl)-1H-indole (**197**) (26.0 mg, 0.15 mmol). The crude product was purified by flash column chromatography [silica gel, 50% CH_2Cl_2 in pentane] to afford the product as a yellow foam (66%, 36.7 mg, 92% BRSM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.48 (s, 1H), 8.79 (s, 1H), 8.26 (s, 1H), 8.13 (d, *J* = 2.0 Hz, 1H), 7.48 – 7.40 (m, 3H), 7.38 – 7.29 (m, 3H), 7.28 – 7.21 (m, 1H), 7.18 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 6.98 (ddd, *J* = 7.9, 7.0, 0.9 Hz, 1H), 6.89 (dd, *J* = 7.9, 1.0 Hz, 1H), 3.22 (hept, *J* = 6.9 Hz, 1H), 1.33 (dd, *J* = 6.9, 2.7 Hz, 6H), 1.30 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.1, 155.5, 147.7, 144.5, 140.5, 137.5, 134.8, 132.6, 131.5, 131.3, 129.9, 128.1, 127.2 (3C), 127.1, 122.3, 121.9, 119.9 (2C), 118.7, 117.9, 114.3, 110.6, 104.1, 33.4, 30.2, 27.7, 23.3, 23.2; **FTIR** (neat) ν = 3432, 3248, 2963, 1692, 1620, 1574, 1488, 1459, 1330, 1281, 1213, 1188, 1172, 1147, 1082, 937, 744 cm^{-1}; **HRMS** (ESI$^+$) m/z Calcd. for $C_{32}H_{31}O_3NBr$ $(M+H)^+$ 556.1481, found 556.1481; **$[\alpha]^{D}_{25}$** = –26.7 °

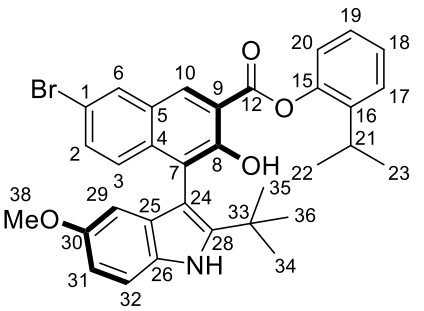
(*c* 1.0, $CHCl_3$); **HPLC** ChiralPak IC (5% *i*-PrOH in hexane, 1.0 mL min^{-1}, T = 25 °C, 206 nm); τ_R (minor) = 6.8 min, τ_R (major) = 9.9 min; **e.r.** = 93:7.

2-isopropylphenyl 7-bromo-4-(2-(*tert*-butyl)-5-methyl-1H-indol-3-yl)-3-hydroxy-2-naphthoate (349)



The title compound was prepared according to General Procedure Q using 2-isopropylphenyl 7-bromo-3-hydroxy-2-naphthoate (**318**) (38.5 mg, 0.10 mmol) and 2-(*tert*-butyl)-5-methyl-1H-indole (**311**) (28.1 mg, 0.15 mmol). The crude product was purified by flash column chromatography [silica gel, 40-50% CH_2Cl_2 in pentane] to afford the product as a yellow foam (67%, 38.2 mg, 89% BRSM). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.45 (s, 1H), 8.79 (s, 1H), 8.16 (s, 1H), 8.13 (d, *J* = 2.0 Hz, 1H), 7.49 – 7.41 (m, 2H), 7.37 – 7.28 (m, 4H), 7.24 – 7.21 (m, 1H), 7.00 (dd, *J* = 8.3, 1.7 Hz, 1H), 6.65 (s, 1H), 3.22 (hept, *J* = 6.9 Hz, 1H), 2.29 (s, 3H), 1.33 (dd, *J* = 6.9, 1.9 Hz, 6H), 1.27 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.1, 155.4, 147.7, 144.5, 140.5, 137.6, 133.1, 132.6, 131.4, 131.3, 130.2, 129.2, 128.2, 128.1, 127.2 (2C), 127.1, 123.4, 122.3, 120.1, 118.3, 117.8, 114.3, 110.3, 103.5, 33.4, 30.2, 27.7, 23.3, 23.2, 21.6; **FTIR** (neat) ν = 3434, 3266, 2964, 1689, 1641, 1624, 1487, 1434, 1330, 1308, 1201, 1172, 1082, 1041, 937, 797, 779, 752 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{33}H_{33}O_3NBr$ $(M+H)^+$ 570.1638, found 570.1640; **$[\alpha]^D_{25}$** = +13.3 ° (*c* 1.0, $CHCl_3$); **HPLC** ChiralPak ODH (5% *i*-PrOH in hexane, 1.0 mL min^{-1}, T = 25 °C, 300 nm); τ_R (minor) = 7.8 min, τ_R (major) = 14.9 min; **e.r.** = 88:12.

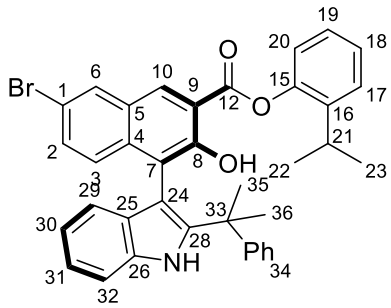
2-isopropylphenyl 7-bromo-4-(2-(*tert*-butyl)-5-methoxy-1H-indol-3-yl)-3-hydroxy-2-naphthoate (350)



The title compound was prepared according to General Procedure Q using 2-isopropylphenyl 7-bromo-3-hydroxy-2-naphthoate (**318**) (38.5 mg, 0.10 mmol) and 2-(*tert*-butyl)-5-methoxy-1H-indole (**297**) (30.5 mg, 0.15 mmol). The crude

product was purified by flash column chromatography [silica gel, 50-75% CH_2Cl_2 in pentane] to afford the product as a yellow foam (76%, 44.6 mg, 92% BRSM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.47 (s, 1H), 8.79 (t, *J* = 0.6 Hz, 1H), 8.16 (s, 1H), 8.13 (s, 1H), 7.49 – 7.42 (m, 2H), 7.39 – 7.28 (m, 4H), 7.25 – 7.20 (m, 1H), 6.84 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.33 (d, *J* = 2.4 Hz, 1H), 3.65 (s, 3H), 3.22 (hept, *J* = 6.9 Hz, 1H), 1.33 (dd, *J* = 6.9, 1.5 Hz, 6H), 1.27 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.1, 155.5, 154.5, 147.7, 145.4, 140.5, 137.5, 132.6, 131.5, 131.3, 130.5, 129.9, 128.1, 127.2 (3C), 127.1, 122.3, 119.9, 117.9, 114.3, 111.6, 111.3, 103.9, 101.1, 56.1, 33.5, 30.2 27.7, 23.3, 23.2; **FTIR** (neat) ν = 3432, 3244, 2963, 2925, 1690, 1621, 1574, 1486, 1447, 1395, 1377, 1330, 1281, 1204, 1187, 1170, 1143, 1082, 1044, 936, 826, 753, 735, 701 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{33}H_{33}O_4NBr$ $(M+H)^+$ 586.1587, found 586.1589; **$[\alpha]^{D}_{25}$** = +12.7 ° (*c* 1.0, $CHCl_3$); **HPLC** ChiralPak ODH (5% *i*-PrOH in hexane, 1.0 mL min^{-1}, T = 25 °C, 267 nm; τ_R (minor) = 7.2 min, τ_R (major) = 10.0 min; **e.r.** = 91:9.

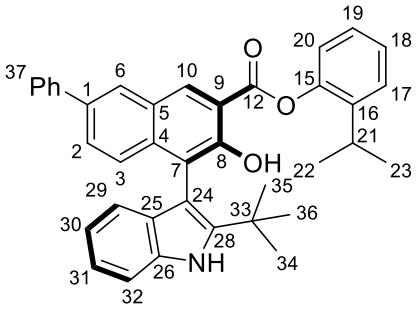
2-isopropylphenyl 7-bromo-3-hydroxy-4-(2-(2-phenylpropan-2-yl)-1H-indol-3-yl)-2-naphthoate (351)



The title compound was prepared according to General Procedure Q using 2-isopropylphenyl 2-isopropylphenyl 7-bromo-3-hydroxy-2-naphthoate (**318**) (38.5 mg, 0.10 mmol) and 2-(2-phenylpropan-2-yl)-1H-indole (**XL31**) (35.3 mg, 0.15 mmol). The crude product was purified by flash column chromatography [silica gel, 50% CH_2Cl_2 in pentane] to afford the product as a yellow foam (54%, 33.3 mg, 87% BRSM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.50 (s, 1H), 8.76 (s, 1H), 8.12 (d, *J* = 1.9 Hz, 1H), 7.80 (s, 1H), 7.53 – 7.42 (m, 2H), 7.42 – 7.36 (m, 2H), 7.36 – 7.32 (m, 2H), 7.32 – 7.28 (m, 1H), 7.28 – 7.22 (m, 3H), 7.22 – 7.19 (m, 1H), 7.19 – 7.13 (m, 2H), 6.98 (ddd, *J* = 7.9, 6.9, 1.0 Hz, 1H), 6.93 (dd, *J* = 7.8, 1.3 Hz, 1H), 3.22 (hept, *J* = 6.9 Hz, 1H), 1.60 (d, *J* = 14.7 Hz, 6H), 1.34 (dd, *J* = 6.9, 3.9 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.1, 155.5, 148.3, 147.7, 143.7, 140.5, 137.4, 135.3, 132.7, 131.5, 131.4, 129.7, 128.4, 128.4 (2C), 127.9, 127.2 (2C), 127.1, 126.7 (2C), 126.5, 122.3,

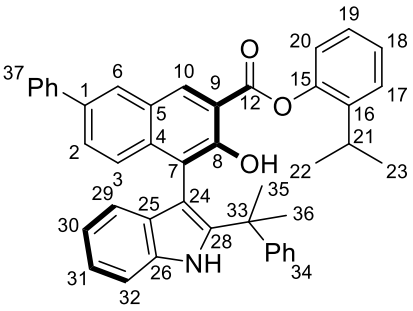
122.2, 119.9, 119.5, 119.0, 117.8, 114.2, 110.7, 105.5, 41.6, 29.3, 29.2, 27.8, 23.3, 23.2; **FTIR** (neat) ν = 3413, 3269, 2964, 2925, 1691, 1602, 1488, 1459, 1331, 1280, 1206, 1190, 1151, 1067, 932, 821, 752, 700 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{37}H_{33}O_3NBr$ $(M+H)^+$ 618.1638, found 618.1638; **$[\alpha]^{D}_{25}$** = –5.9 ° (*c* 1.0, $CHCl_3$); **HPLC** ChiralPak IC (3% *i*-PrOH in hexane, 1.0 mL min^{-1}, T = 25 °C, 294 nm); τ_R (minor) = 9.1 min, τ_R (major) = 19.0 min; **e.r.** = 95:5.

2-isopropylphenyl 4-(2-(*tert*-butyl)-1H-indol-3-yl)-3-hydroxy-7-phenyl-2-naphthoate (352)



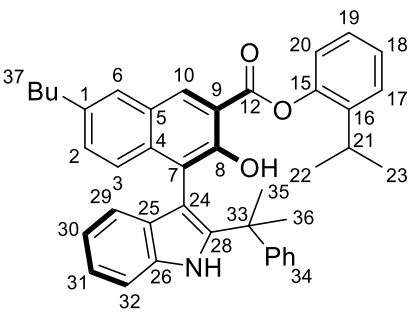
The title compound was prepared according to General Procedure Q using 2-isopropylphenyl 3-hydroxy-7-phenyl-2-naphthoate (**319**) (38.2 mg, 0.10 mmol) and 2-(*tert*-butyl)-1H-indole (**XL31**) (26.0 mg, 0.15 mmol). The crude product was purified by flash column chromatography [silica gel, 50% CH_2Cl_2 in pentane] to afford the product as a yellow foam (52%, 28.8 mg, 86% BRSM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.36 (s, 1H), 8.84 (s, 1H), 8.14 (s, 1H), 8.05 (d, *J* = 1.9 Hz, 1H), 7.65 – 7.52 (m, 3H), 7.42 (d, *J* = 8.9 Hz, 1H), 7.40 – 7.29 (m, 4H), 7.29 – 7.23 (m, 1H), 7.23 – 7.18 (m, 2H), 7.14 – 7.11 (m, 1H), 7.07 (ddd, *J* = 8.2, 6.4, 1.8 Hz, 1H), 6.91 – 6.82 (m, 2H), 3.14 (hept, *J* = 6.9 Hz, 1H), 1.22 (dd, *J* = 2.2, 1.1 Hz, 6H), 1.22 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.6, 155.2, 147.8, 144.3, 140.6, 140.6, 138.3, 136.8, 134.9, 132.9, 130.1, 129.2, 129.0, 127.5, 127.4, 127.3, 127.2 (2C), 127.1, 127.0, 126.8, 122.4, 121.8, 119.8, 119.3, 118.9, 113.8, 110.6, 104.6, 33.5, 30.3, 27.7, 23.3, 23.2; **FTIR** (neat) ν = 3441, 3269, 2965, 1690, 1627, 1489, 1458, 1440, 1400, 1377, 1341, 1302, 1256, 1213, 1172, 1082, 1043, 1043, 944, 910, 834, 784, 742, 699 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{38}H_{36}O_3N$ $(M+H)^+$ 554.2690, found 554.2687; **$[\alpha]^{D}_{25}$** = –45.9 ° (*c* 1.0, $CHCl_3$); **HPLC** ChiralPak IA (5% *i*-PrOH in hexane, 1.0 mL min^{-1}, T = 25 °C, 286 nm); τ_R (minor) = 8.5 min, τ_R (major) = 13.4 min; **e.r.** = 90:10.

2-isopropylphenyl 3-hydroxy-7-methoxy-4-(2-(2-phenylpropan-2-yl)-1H-indol-3-yl)-2-naphthoate (353)



The title compound was prepared according to General Procedure Q using 2-isopropylphenyl 3-hydroxy-7-phenyl-2-naphthoate (**319**) (38.2 mg, 0.10 mmol) and 2-(2-phenylpropan-2-yl)-1H-indole (**XL31**) (35.3 mg, 0.15 mmol). The crude product was purified by flash column chromatography [silica gel, 40-45% CH_2Cl_2 in pentane] to afford the product as a yellow foam (45%, 27.7 mg, 85% BRSM). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.54 (s, 1H), 8.97 (s, 1H), 8.20 (d, *J* = 1.8 Hz, 1H), 7.83 – 7.71 (m, 4H), 7.67 (d, *J* = 8.8 Hz, 1H), 7.54 (t, *J* = 7.8 Hz, 2H), 7.51 – 7.46 (m, 3H), 7.45 – 7.35 (m, 3H), 7.35 – 7.25 (m, 4H), 7.25 – 7.22 (m, 1H), 7.22 – 7.17 (m, 1H), 7.08 – 6.98 (m, 2H), 3.29 (hept, *J* = 6.9 Hz, 1H), 1.67 (d, *J* = 18.5 Hz, 6H), 1.38 (dd, *J* = 6.9, 4.3 Hz, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.3, 155.3, 148.6, 147.8, 143.6, 140.6, 138.2, 136.7, 135.4, 132.9, 129.8, 129.3, 129.1, 128.4, 127.5, 127.4, 127.4, 127.3, 127.2, 127.1, 127.0, 126.8, 126.6, 126.5, 122.4, 122.1, 119.8, 119.1, 118.9, 113.7, 110.6, 106.1, 41.7, 29.4, 29.2, 27.8, 23.3, 23.2; **FTIR** (neat) ν = 3433, 3241, 2968, 2925, 1690, 1489, 1444, 1342, 1332, 1257, 1214, 1172, 1082, 1042, 945, 910, 831, 755, 713, 699 cm^{-1}; **HRMS** (ESI$^+$) m/z Calcd. for $C_{43}H_{38}O_3N$ $(M+H)^+$ 616.2846, found 616.2842; **$[\alpha]^{D}_{25}$** = –5.9 ° (*c* 1.0, $CHCl_3$); **HPLC** ChiralPak IC (3% *i*-PrOH in hexane, 1.0 mL min^{-1}, T = 25 °C, 275 nm); τ_R (minor) = 9.1 min, τ_R (major) = 19.0 min; **e.r.** = 95:5.

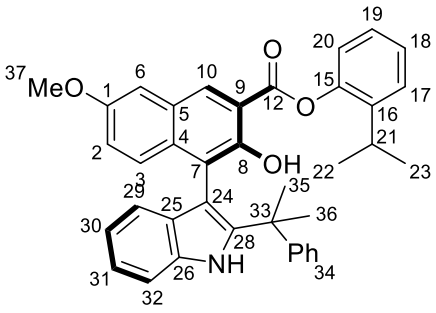
2-isopropylphenyl 7-butyl-3-hydroxy-4-(2-(2-phenylpropan-2-yl)-1H-indol-3-yl)-2-naphthoate (354)



The title compound was prepared according to General Procedure Q using 2-isopropylphenyl 7-butyl-3-hydroxy-2-naphthoate (**320**) (36.2 mg, 0.10 mmol) and 2-(2-phenylpropan-2-yl)-1H-indole (**XL31**) (35.3 mg, 0.15 mmol). The crude product was purified by flash column

chromatography [silica gel, 40% CH_2Cl_2 in pentane] to afford the product as a yellow foam (66%, 39.3 mg, 80% BRSM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.36 (s, 1H), 8.76 (s, 1H), 7.68 (s, 1H), 7.45 – 7.37 (m, 4H), 7.31 – 7.27 (m, 2H), 7.27 – 7.21 (m, 4H), 7.20 – 7.14 (m, 2H), 7.14 – 7.07 (m, 1H), 6.94 – 6.91 (m, 2H), 3.20 (hept, *J* = 6.9 Hz, 1H), 2.73 (t, *J* = 2.0 Hz, 2H), 1.68 (tt, *J* = 9.1, 7.6 Hz, 2H), 1.58 (s, 3H), 1.54 (s, 3H), 1.41 (q, *J* = 2.0 Hz, 2H), 1.29 (dd, *J* = 6.9, 3.5 Hz, 6H), 0.95 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.5, 154.7, 148.7, 147.9, 143.4, 140.6, 138.5, 137.7, 135.6, 132.0, 131.4, 129.9, 128.4, 127.8, 127.3, 127.2, 127.0 (2C), 126.8, 126.5, 125.9, 122.5, 122.0, 119.7, 119.2, 118.7, 113.2, 110.5, 106.4, 41.7, 35.5, 33.4, 29.3, 29.2, 27.7, 23.3, 23.2, 22.6, 14.2; **FTIR** (neat) ν = 3456, 3269, 2965, 2929, 1689, 1488, 1447, 1400, 1338, 1309, 1210, 1172, 1149, 1082, 1041, 916, 829, 751, 701 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{41}H_{42}O_3N$ $(M+H)^+$ 596.3159, found 596.3155; **$[\alpha]^D_{25}$** = –17.7 ° (*c* 1.0, $CHCl_3$); **HPLC** ChiralPak IA (2% *i*-PrOH in hexane, 1.0 mL min^{-1}, T = 25 °C, 245 nm; τ_R (minor) = 10.3 min, τ_R (major) = 17.1 min; **e.r.** = 93:7.

2-isopropylphenyl 3-hydroxy-7-methoxy-4-(2-(2-phenylpropan-2-yl)-1H-indol-3-yl)-2-naphthoate (355)

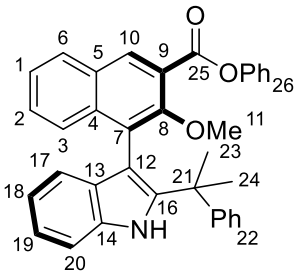


The title compound was prepared according to General Procedure Q using 2-isopropylphenyl 3-hydroxy-7-methoxy-2-naphthoate (**317**) (33.6 mg, 0.10 mmol) and 2-(2-phenylpropan-2-yl)-1H-indole (**XL31**) (35.3 mg, 0.15 mmol). The crude product was purified by flash column chromatography [silica gel, 50-70% CH_2Cl_2 in pentane] to afford the product as a yellow foam (70%, 39.9 mg, 90% BRSM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.29 (s, 1H), 8.73 (s, 1H), 7.70 (s, 1H), 7.48 – 7.36 (m, 4H), 7.34 – 7.28 (m, 2H), 7.28 – 7.20 (m, 4H), 7.20 – 7.13 (m, 2H), 7.13 – 7.08 (m, 2H), 6.97 – 6.90 (m, 2H), 3.92 (s, 3H), 3.21 (hept, *J* = 6.9 Hz, 1H), 1.57 (d, *J* = 17.9 Hz, 6H), 1.30 (dd, *J* = 6.9, 3.4 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.4, 156.3, 154.0, 148.6, 147.8, 143.5, 140.6, 135.3, 134.9, 130.7, 129.9, 128.4, 127.9, 127.6, 127.2, 127.1, 127.0, 126.8, 126.5, 122.9, 122.4, 122.0, 119.8, 119.3, 119.1, 113.5, 110.6, 106.7, 106.3, 55.5, 41.6, 29.3, 29.2, 27.7, 23.3, 23.2;

FTIR (neat) ν = 3417, 3256, 2963, 2923, 2853, 1690, 1503, 1459, 1390, 1336, 1287, 1227, 1195, 1172, 1138, 1094, 1031, 920, 829, 756, 701, 668 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{38}H_{36}O_4N$ $(M+H)^+$ 570.2639, found 570.2637; **$[\alpha]^D_{25}$** = –8.4 ° (*c* 1.0, $CHCl_3$); **HPLC** ChiralPak ODH (5% *i*-PrOH in hexane, 1.0 mL min^{-1}, T = 25 °C, 278 nm; τ_R (minor) = 10.9 min, τ_R (major) = 13.3 min; **e.r.** = 92:8.

9.5.7 Derivitization

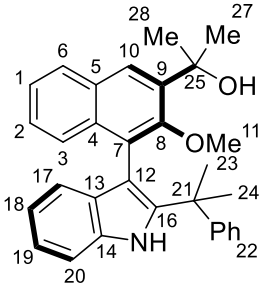
phenyl 3-methoxy-4-(2-(2-phenylpropan-2-yl)-1H-indol-3-yl)-2-naphthoate (356)



A round-bottomed flask equipped with magnetic stirring bar and reflux condenser was charged with phenyl 3-hydroxy-4-(2-(2-phenylpropan-2-yl)-1H-indol-3-yl)-2-naphthoate (**XL42**) (300 mg, 0.60 mmol, 1.00 equiv.). After dissolving the substrate in acetone (6 mL), K_2CO_3 (100 mg, 0.72 mmol, 1.20 equiv.) and Me_2SO_4 (114 mg, 85 µL, 0.90 mmol, 1.50 equiv.) were added. The reaction mixture was then heated at reflux for 24 h. After this time, the solvent was removed *in vacuo* and sat. $NH_4OH_{(aq.)}$ (10 mL) was added. The mixture was stirred at room temperature for 1 h, the product was then extracted three times with CH_2Cl_2. The combined extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography [silica gel, 10% EtOAc in pentane] to afford the product as white foam (90%, 276 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 7.90 – 7.82 (m, 1H), 7.63 (bs, 1H), 7.45 (ddd, *J* = 8.1, 1.6, 0.8 Hz, 1H), 7.39 – 7.31 (m, 4H), 7.29 (dt, *J* = 8.1, 1.1 Hz, 2H), 7.26 – 7.21 (m, 2H), 7.21 – 7.10 (m, 4H), 7.10 – 7.00 (m, 2H), 6.90 – 6.83 (m, 2H), 3.48 (s, 3H), 1.54 (s, 3H), 1.34 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.1, 155.6, 151.2, 148.7, 143.9, 137.4, 135.1, 132.9, 130.7, 129.6, 129.6, 129.2, 128.6, 128.5, 127.6, 126.7, 126.5, 126.0, 125.6, 124.5, 122.0, 121.9, 119.9, 119.3, 110.4, 106.2, 61.9, 41.8, 29.4, 28.7; **FTIR** (neat) ν = 3412, 2980, 1741, 1621, 1590, 1493, 1444, 1382, 1282, 1225, 1191, 1073, 955, 768 cm^{-1}; **HRMS** (ESI^-) m/z Calcd. for $C_{35}H_{29}NO_3Na$ $(M+Na)^+$ 534.2040, found 534.2037; **$[\alpha]^D_{25}$** = –25.2 ° (*c* 1.0, $CHCl_3$); **HPLC** Daicel ChiralPak IA (5% *i*-PrOH

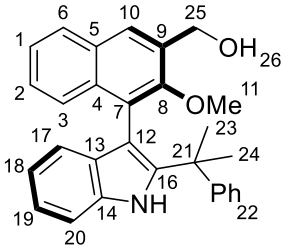
in hexane, 1.0 mL min^{-1}, T = 25 °C, 235 nm); τ_R (major) = 11.6 min, τ_R (minor) = 13.4 min; **e.r.** = 97:3.

2-(3-methoxy-4-(2-(2-phenylpropan-2-yl)-1H-indol-3-yl)naphthalen-2-yl)propan-2-ol (357)



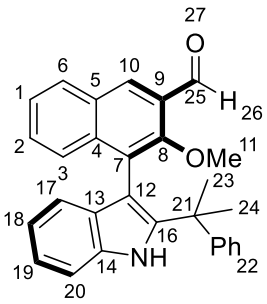
A flame dried 2-necked round-bottomed flask equipped with magnetic stirring bar and reflux condenser was charged with phenyl 3-methoxy-4-(2-(2-phenylpropan-2-yl)-1H-indol-3-yl)-2-naphthoate (**356**) (51 mg, 0.10 mmol, 1.00 equiv.). At room temperature anhydrous THF (1 mL) was added, followed by MeMgCl (3.0 M in THF, 100 µL, 0.30 mmol, 3.00 equiv.). The resulting solution was heated at 65 °C for 16 h, and then cooled to ambient temperature. The reaction was diluted with Et_2O (10 mL) and quenched with sat. $NH_4Cl_{(aq.)}$ (10 mL). The layers were separated, and the aqueous phase was further extracted three times with Et_2O. The combined extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography [silica gel, 10-20% Et_2O in pentane] to afford the product as white foam (71%, 32 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.75 – 7.71 (m, 1H), 7.69 (s, 1H), 7.35 (dt, *J* = 8.4, 1.0 Hz, 1H), 7.29 (ddd, *J* = 8.1, 6.8, 1.3 Hz, 1H), 7.24 – 7.19 (m, 2H), 7.19 – 7.12 (m, 4H), 7.10 – 7.02 (m, 2H), 6.96 – 6.91 (m, 1H), 6.89 (ddd, *J* = 7.9, 6.7, 1.0 Hz, 1H), 4.29 (bs, 1H), 3.34 (s, 3H), 1.69 (s, 3H), 1.64 (s, 3H), 1.54 (s, 3H), 1.24 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.6, 148.6, 143.8, 139.8, 135.1, 134.6, 130.8, 130.1, 128.5, 128.2, 126.5 (2C) 126.1, 125.9, 124.9 (2C), 124.1, 122.0 (2C), 119.7, 110.4, 107.2, 73.0, 61.2, 41.6, 31.5, 30.1, 29.3, 28.1; **FTIR** (neat) ν = 3445, 2970, 2927, 1494, 1447, 1364, 1227, 1161, 1047, 994, 950, 890, 751, 701 cm^{-1}; **HRMS** (ESI^-) m/z Calcd. for $C_{31}H_{31}NO_2Na$ $(M+Na)^+$ 472.2247, found 472.2247; **[α]**$^{D}_{25}$ = –84.9 ° (*c* 1.0, $CHCl_3$). **HPLC** Daicel ChiralPak IA (2% *i*-PrOH in hexane, 1.0 mL min^{-1}, T = 25 °C, 229 nm); τ_R (major) = 29.1 min, τ_R (minor) = 33.2 min; **e.r.** = 97:3.

(3-methoxy-4-(2-(2-phenylpropan-2-yl)-1H-indol-3-yl)naphthalen-2-yl)methanol (358)



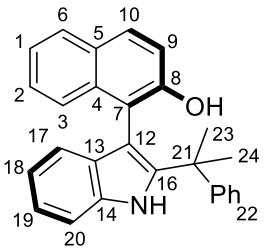
A flame dried round-bottomed flask equipped with magnetic stirring bar was charged with phenyl 3-methoxy-4-(2-(2-phenylpropan-2-yl)-1H-indol-3-yl)-2-naphthoate (**356**) (102 mg, 0.20 mmol, 1.00 equiv.). Under an argon atmosphere, the substrate was dissolved in anhydrous THF (2 mL) and the resulting solution was cooled to 0 °C. At this temperature, powdered $LiAlH_4$ (23 mg, 0.60 mmol, 3.00 equiv.) was added. The reaction was then allowed to warm to ambient temperature and stirring was continued for 2 h. After this time, the mixture was diluted with Et_2O (5 mL) and cooled again to 0 °C. The reaction was quenched by the careful sequential addition of water (50 µL), 15% (w/v) $NaOH_{(aq.)}$ and another portion of water (150 µL). The mixture was then warmed to room temperature and stirred for an additional 15 min. $MgSO_4$ was added, and stirring continued for an additional 15 min. The slurry was then filtered through a plug of Celite®, washing liberally with Et_2O. The filtrate was concentrated *in vacuo* and the crude product was purified by flash column chromatography [silica gel, 15-20% EtOAc in pentane] to afford the product as colourless oil (Yield = 90%, 76 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78 – 7.72 (m, 2H), 7.67 (bs, 1H), 7.40 (dd, *J* = 8.5, 1.2 Hz, 1H), 7.33 – 7.23 (m, 3H), 7.23 – 7.14 (m, 4H), 7.12 – 7.01 (m, 2H), 6.90 – 6.84 (m, 2H), 4.94 (dd, *J* = 13.1, 0.8 Hz, 1H), 4.68 (dd, *J* = 13.0, 0.7 Hz, 1H), 3.36 (s, 3H), 1.50 (s, 3H), 1.30 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.9, 148.7, 143.7, 135.1, 133.6, 130.8, 130.6, 128.5, 127.9, 127.6, 126.6 (2C), 126.5, 126.3, 126.2, 124.9, 124.5, 121.9, 119.9, 119.6, 110.4, 106.8, 63.0, 60.9, 41.7, 29.4, 28.5; **FTIR** (neat) ν = 3403, 3056, 2922, 2852, 1457, 1319, 1296, 1233, 1102, 1083, 1030, 889, 751, 701, 680 cm^{-1}; **HRMS** (ESI^-) m/z Calcd. for $C_{29}H_{26}NO_2$ $(M-H)^-$ 420.1969, found 420.1967; **[α]**$^{D}_{25}$ = –69.5 ° (*c* 1.0, $CHCl_3$); **HPLC** Daicel ChiralPak ODH (3% *i*-PrOH in hexane, 1.0 mL min^{-1}, T = 25 °C, 240 nm); τ_R (major) = 9.9 min, τ_R (minor) = 12.8 min; **e.r.** = 97:3.

3-methoxy-4-(2-(2-phenylpropan-2-yl)-1H-indol-3-yl)-2-naphthaldehyde (359)



To a solution of (3-methoxy-4-(2-(2-phenylpropan-2-yl)-1H-indol-3-yl)naphthalen-2-yl)methanol (**358**) (57 mg, 0.136 mmol, 1.00 equiv.) in CH_2Cl_2 (1.4 mL) was added DMP (70 mg, 0.163 mmol, 1.20 equiv.) at room temperature. The reaction was then stirred for 24 h and after this time, the slurry was filtered through a plug of Celite®. The filter cake was washed liberally with CH_2Cl_2 and the filtrate was collected and concentrated *in vacuo*. The crude product was purified by flash column chromatography [silica gel, 10% EtOAc in pentane] to afford the product as white foam (Yield = 84%, 48 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.57 (s, 1H), 8.47 (s, 1H), 8.04 – 7.97 (m, 1H), 7.76 (bs, 1H), 7.52 (ddd, *J* = 7.9, 1.8, 0.8 Hz, 1H), 7.50 – 7.40 (m, 2H), 7.39 – 7.34 (m, 2H), 7.33 – 7.21 (m, 3H), 7.16 (dddd, *J* = 9.6, 5.8, 2.9, 1.4 Hz, 2H), 7.01 – 6.90 (m, 2H), 3.55 (s, 3H), 1.62 (s, 3H), 1.43 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 191.3, 157.7, 148.4, 144.0, 138.5, 135.1, 130.9, 130.6, 130.2, 129.8, 129.1, 128.5, 128.5, 126.6 (3C), 126.2, 125.7, 122.1, 120.0, 119.3, 110.5, 105.8, 62.5, 41.7, 29.3, 28.8; **FTIR** (neat) ν = 3390, 2970, 2924, 2852, 1683, 1618, 1590, 1496, 1459, 1350, 1221, 1102, 1068, 1105, 752, 701, 669 cm^{-1}; **HRMS** (ESI^-) m/z Calcd. for $C_{29}H_{25}NO_2Na$ $(M+H)^+$ 442.1778, found 442.1778; **[α]**$^D_{25}$ = –41.4 ° (*c* 1.0, $CHCl_3$); **HPLC** Daicel ChiralPak IA (3% *i*-PrOH in hexane, 1.0 mL min^{-1}, T = 25 °C, 254 nm); τ_R (major) = 13.3 min, τ_R (minor) = 15.5 min; **e.r.** = 97:3.

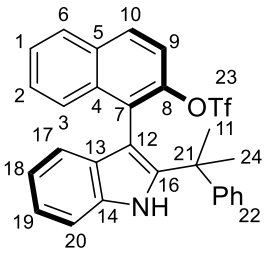
1-(2-(2-Phenylpropan-2-yl)-1*H*-indol-3-yl)naphthalen-2-ol (360)



Inside a nitrogen filled glovebox, a flame-dried Schlenk tube equipped with a magnetic stirrer bar was charged with phenyl 3-hydroxy-4-(2-(2-phenylpropan-2-yl)-1H-indol-3-yl)-2-naphthoate (**XL42**) (50 mg, 0.10 mmol, 1.00 equiv.), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 0.10 equiv.) and 1,2-bis(dicyclohexylphosphino)ethane (8.5 mg, 0.02 mmol, 0.20 equiv.). The vessel was then removed from the glovebox and placed under a positive pressure of argon. Et_3SiH (17.5 mg, 24 μL, 0.15 mmol, 1.50 equiv.) and anhydrous toluene (1 mL) were added and the resulting solution was

degassed by three freeze-pump-thaw cycles with liquid N_2. The mixture was then placed in a preheated oil bath at 160 °C and stirred for the 16 hours at this temperature. After this time, the mixture was cooled to room temperature, diluted with CH_2Cl_2 (10 mL), filtered through a pad of Celite® and concentrated *in vacuo*. The crude product was purified by flash column chromatography [silica gel, 5% EtOAc in petroleum ether b.p. 40–60 °C] to afford the product as white foam (Yield = 69%, 26 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.90 – 7.80 (m, 3H), 7.42 – 7.22 (m, 10H), 7.19 (ddd, *J* = 8.1, 4.7, 3.5 Hz, 1H), 7.05 – 6.96 (m, 2H), 5.28 (bs, 1H), 1.53 (d, *J* = 17.6 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.2, 147.8, 145.5, 135.3, 134.9, 129.6 (2C), 128.9, 128.6, 128.0, 126.7, 126.3 (2C), 125.3, 123.0, 122.5, 120.2, 119.4, 116.8, 114.5, 110.5, 103.2, 41.4, 29.0, 28.8; **FTIR** (neat) ν = 3430, 3057, 1619, 1463, 1426, 1202, 1174, 1029, 816, 748, 701 cm^{-1}; **HRMS** (ESI$^-$) m/z Calcd. for $C_{27}H_{22}NO$ $(M-H)^-$ 376.1707, found 376.1705; **[α]**$^D_{25}$ = –66.5 ° (*c* 1.0, $CHCl_3$); **HPLC** Daicel ChiralPak OD-H (5% *i*-PrOH in hexane, 1.0 mL min^{-1}, T = 25 °C, 254 nm); τ_R (major) = 9.9 min, τ_R (minor) = 12.8 min; **e.r.** = 97:3.

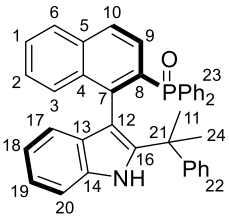
1-(2-(2-phenylpropan-2-yl)-1H-indol-3-yl)naphthalen-2-yl trifluoromethanesulfonate (361)



In a flame dried argon filled round-bottomed flask, 1-(2-(2-phenylpropan-2-yl)-1*H*-indol-3-yl)naphthalen-2-ol (**360**) (70 mg, 0.186 mmol, 1.00 equiv.) was dissolved in anhydrous CH_2Cl_2 (1 mL) and DIPEA (48 mg, 65 µL, 0.372 mmol, 2.0 equiv.) was added. The mixture was then cooled to 0 °C and Tf_2O (78.7 mg, 47 µL, 0.279 mmol, 1.50 equiv.) was introduced. The reaction was then allowed to warm to ambient temperature and stirring was continued for 48 h. After complete consumption of the starting material (*as indicated by TLC analysis*), the reaction was quenched by the addition of 1M $HCl_{(aq.)}$ at room temperature and the layers were separated. The aqueous phase was further extracted three times with CH_2Cl_2 and the combined organic layers were washed with sat. $NaHCO_{3\,(aq.)}$, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography [silica gel, 5% EtOAc in petroleum

ether b.p. 40–60 °C] to afford the product as white solid (Yield = 94%, 89 mg). **M.P.** = 150-153 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 – 7.82 (m, 2H), 7.70 (bs, 1H), 7.58 (dt, *J* = 8.5, 1.0 Hz, 1H), 7.46 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H), 7.39 (d, *J* = 8.9 Hz, 1H), 7.34 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H), 7.26 – 7.20 (m, 2H), 7.20 – 7.12 (m, 3H), 7.11 – 7.03 (m, 2H), 6.87 (ddd, *J* = 7.9, 6.8, 1.0 Hz, 1H), 6.82 (dd, *J* = 8.0, 1.2 Hz, 1H), 1.49 (s, 3H), 1.35 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.1, 146.4, 143.7, 135.0, 134.9, 132.5, 130.1, 130.0, 128.5, 128.2, 127.8, 127.6, 127.5, 127.0, 126.7, 126.6, 122.3, 119.9 (2C), 119.4, 118.4 (q, *J* = 321.4 Hz), 110.3, 104.3, 41.6, 29.5, 29.0; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -74.6; **FTIR** (neat) ν = 3449, 2972, 2918, 1460, 1420, 1213, 1141, 1085, 961, 942, 836, 811, 766, 747, 701, 682, 625 cm^{-1}; **HRMS** (ESI^-) m/z Calcd. for $C_{28}H_{23}NO_3SF_3$ $(M+H)^+$ 510.1345, found 510.1345; **[α]**$^{D}_{25}$ = –68.5 ° (*c* 1.0, $CHCl_3$); **HPLC** Daicel ChiralPak IA (2% *i*-PrOH in hexane, 1.0 mL min^{-1}, T = 25 °C, 250 nm); τ_R (major) = 9.5 min, τ_R (minor) = 11.7 min; **e.r.** = 97:3.

Diphenyl(1-(2-(2-phenylpropan-2-yl)-1*H*-indol-3-yl)naphthalen-2-yl)phosphineoxide (362)



Under argon atmosphere, DMSO (degassed by sonication, 1 mL) was added to a mixture of 1-(2-(2-phenylpropan-2-yl)-1H-indol-3-yl)naphthalen-2-yl trifluoromethanesulfonate (**361**) (41 mg, 0.08 mmol, 97:3 er, 1.00 equiv.), $Ph_2P(O)H$ (65 mg, 0.32 mmol, 4.00 equiv.), $Pd(OAc)_2$ (3.6 mg, 0.016 mmol, 0.20 equiv.) and dppp (9.9 mg, 0.024 mmol, 0.30 equiv.). Then, *i*-Pr_2NEt (70 µL, 52 mg, 0.40 mmol, 5.00 equiv.) was added to the reaction mixture, which was heated at 120 °C for 4 days. After this time, the mixture was cooled down to room temperature, diluted by dichloromethane and quenched with hydrochloric acid (1.0 M). The resultant mixture was extracted three times with CH_2Cl_2, and the organic layer was washed successively by sat. $NaHCO_{3(aq.)}$ and brine. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography [silica gel, 5% EtOAc in CH_2Cl_2] to afford the product as white solid (56%, 94% BRSM, 25 mg); **M.P.** 68-71 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.1 Hz, 1H), 7.87 (dd, *J* = 8.7, 1.7 Hz, 1H), 7.85 – 7.76 (m, 2H), 7.68 (d, *J* = 8.6

Hz, 1H), 7.60 – 7.49 (m, 6H), 7.51 – 7.41 (m, 2H), 7.40 – 7.27 (m, 5H), 7.23 – 7.13 (m, 1H), 7.11 – 7.02 (m, 1H), 7.01 – 6.85 (m, 4H), 6.53 (ddd, *J* = 7.9, 6.9, 1.0 Hz, 1H), 6.31 (dd, *J* = 7.9, 1.0 Hz, 1H), 1.89 (s, 3H), 1.37 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.4, 144.0, 141.7 (d, *J* = 7.7 Hz), 135.4, 134.9 (d, *J* = 11.5 Hz), 134.5 (d, *J* = 2.2 Hz), 134.3, 134.2, 132.0 (d, *J* = 9.0 Hz), 132.0 (d, *J* = 52.9 Hz), 131.3 (d, *J* = 2.8 Hz), 131.0 (d, *J* = 9.7 Hz), 130.9 (d, *J* = 52.0 Hz), 130.2 (d, *J* = 2.8 Hz), 129.7, 129.0 (d, *J* = 13.6 Hz), 128.3 (d, *J* = 11.6 Hz), 128.3, 128.1, 127.9 (d, *J* = 6.2 Hz), 127.2 (d, *J* = 12.2 Hz), 127.0 (d, *J* = 12.8 Hz), 126.8, 126.6, 126.2, 121.0, 119.5, 118.8, 109.3, 109.1 (d, *J* = 5.5 Hz), 42.1, 29.2, 28.8; **^{31}P NMR** (162 MHz, $CDCl_3$) δ 27.3; **FTIR** (neat) ν = 3450, 3242, 3055, 2971, 2341, 1617, 1561, 1494, 1458, 1436, 1217, 1183, 1113, 908, 865, 817, 745, 721, 698 cm^{-1}; **HRMS** (ESI^+) m/z Calcd. for $C_{39}H_{33}NOP$ $(M+H)^+$ 562.2294, found 562.2294; **$[\alpha]^{D}_{25}$** = –27.8° (*c* 0.1, $CHCl_3$); **HPLC** Daicel ChiralPak IC (10% *i*-PrOH in hexane, 1.0 mL min^{-1}, T = 25 °C, 220 nm); τ_R (minor) = 10.1 min, τ_R (major) = 12.4 min; **e.r.** = 97:3.

10. Appendix

10.1 Determination of Rotational Barriers

The rotational barriers for the cross-coupled products were obtained by monitoring the thermal racemisation of the enantioenriched samples over time [*at a constant temperature*]. The enantioenriched samples were obtained by semi-preparative HPLC.

General Method for Thermal Racemisation Experiments

In a 2 mL screw-top vial, the enantiomerically enriched sample (*approx.* 2 mg) was dissolved in hexan-1-ol (500 μL). The vial was then immersed into a pre-heated oil bath and subjected to constant heating at the temperature specified. At designated intervals, 5 μL aliquots were taken [*with a Hamilton microliter syringe*] and diluted with cold (~5 °C) hexane (250 μL) in an HPLC vial. The sample was then analysed by HPLC (chiral stationary phase).

The *Eyring equation* was then used to determine the rotational barrier ($\Delta G^{\ddagger}$) from the enantiomerisation constant (k_{ent} =½ k_{rac}). The racemisation constant (k_{rac}) was determined from the gradient of a plot of $ln\left(\frac{1}{ee\,\%}\right)$ *vs.* time.

$$(1)\ \textit{Eyring Equation}:\ \Delta G^{\ddagger} = RT\ ln\left(\frac{k_B T}{h k_{ent}}\right)$$

$$(2)\ k_{ent} = \frac{k_B T}{h} e^{-\frac{\Delta G^{\ddagger}}{RT}} \qquad (3)\ k_{rac} = 2k_{ent} \qquad (4)\ t_{½}rac = \frac{ln(2)}{k_{rac}}$$

$$\textit{First Order Integrated Rate Law}:\ ln\left(\frac{100}{\%\ ee}\right) = tk_{rac} + ln\left(\frac{100}{\%\ ee_{t=0}}\right)$$

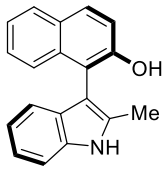
R = 8.314 $JK^{-1}mol^{-1}$; h = Planck's Constant = 6.626 10^{-34} Js;

k_B =Boltzmann's Constant = 1.381 10^{-23} JK^{-1}

The rotational barriers ($\Delta G^{\ddagger}$) recorded in the following pages of supplementary material are reported at the temperature used for the thermal racemisation experiments. The reported $t_{½}rac$

has been converted to the half-life at 298 K, calculated with the assumption that the rotational barrier ($\Delta G^{\ddagger}$) is independent of temperature.

Compound 192



Racemisation at T = 80 °C = 353 K

From slope, $k_{rac} = 1.20 \times 10^{-3}$ s^{-1}

(1) $\Delta G^{\ddagger} = RT\, ln\left(\frac{k_B T}{h k_{ent}}\right)$

$\Delta G^{\ddagger} = 108727$ J mol^{-1} = **26.1 kcal mol^{-1}**

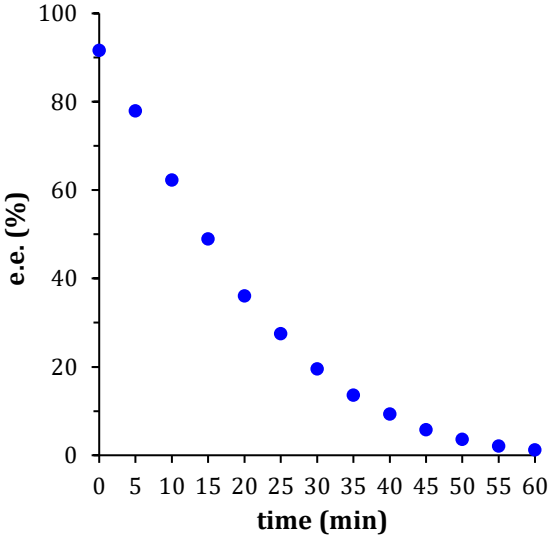
(2) $k_{ent}(298\ K) = \frac{k_B T}{h} e^{-\frac{\Delta G^{\ddagger}}{RT}}$

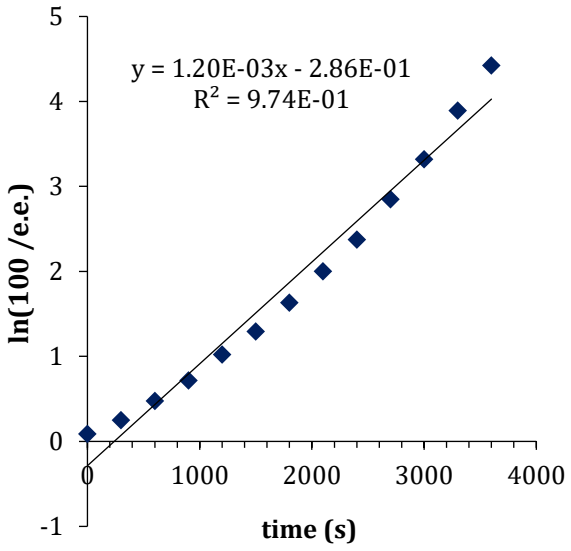
$k_{ent}(298\ K) = 5.43 \times 10^{-7}$ s^{-1}

(3) $k_{rac}(298\ K) = 2k_{ent}$ = **1.085×10^{-6} s^{-1}**

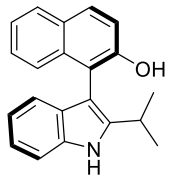
t/(min)	*E1 (%)*	*E2 (%)*	*e.e. (%)*	*ln(100/e.e.)*
0	95.82	4.18	91.64	0.09
5	88.97	11.03	77.94	0.25
10	81.12	18.88	62.24	0.47
15	74.47	25.53	48.94	0.71
20	68.01	31.99	36.02	1.02
25	63.76	36.24	27.52	1.29
30	59.78	40.22	19.56	1.63
35	56.78	43.22	13.56	2.00
40	54.66	45.34	9.32	2.37
45	52.90	47.10	5.80	2.85
50	51.81	48.19	3.62	3.32
55	51.02	48.98	2.04	3.89
60	50.60	49.40	1.20	4.42

(4) $t_{½}rac$ (298 K) = $\frac{ln(2)}{k_{rac}}$ = **7.4 days**





Compound 130



t/(min)	*E1 (%)*	*E2 (%)*	*e.e. (%)*	*ln(1/e.e.)*
0	97.89	2.11	95.78	0.04
4	97.84	2.16	95.68	0.04
8	94.98	5.02	89.96	0.10
12	92.21	7.79	84.42	0.16
16	89.14	10.86	78.28	0.24
20	86.85	13.15	73.70	0.31
24	84.21	15.79	68.42	0.38
28	82.36	17.64	64.72	0.44
32	80.05	19.95	60.10	0.51
36	78.57	21.43	57.14	0.56
40	76.96	23.04	53.92	0.62
44	75.49	24.51	50.98	0.67
48	74.11	25.89	48.22	0.73
52	72.78	27.22	45.56	0.79
56	71.11	28.89	42.22	0.86
60	70.04	29.96	40.08	0.91

Racemisation at T = 80 °C = 353 K

From slope, $k_{rac} = 2.54 \times 10^{-4}$ s^{-1}

(1) $\Delta G^{\ddagger} = RT\, ln\left(\frac{k_B T}{h k_{ent}}\right)$;

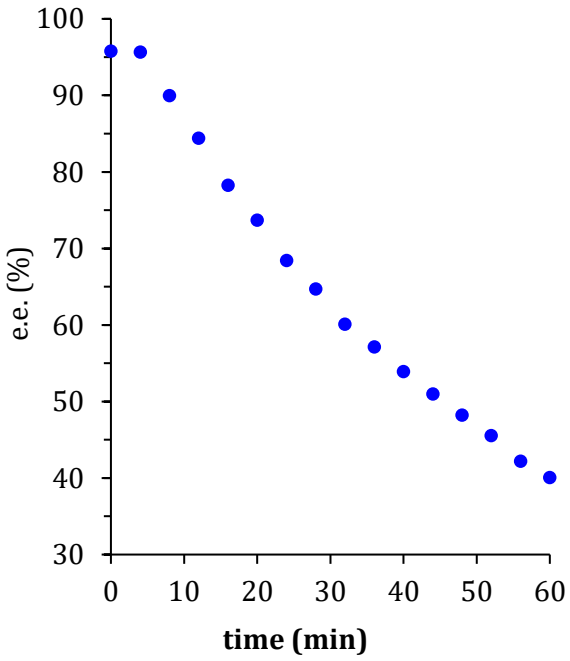
$\Delta G^{\ddagger} = 113282$ J mol^{-1} = **27.1 kcal mol^{-1}**

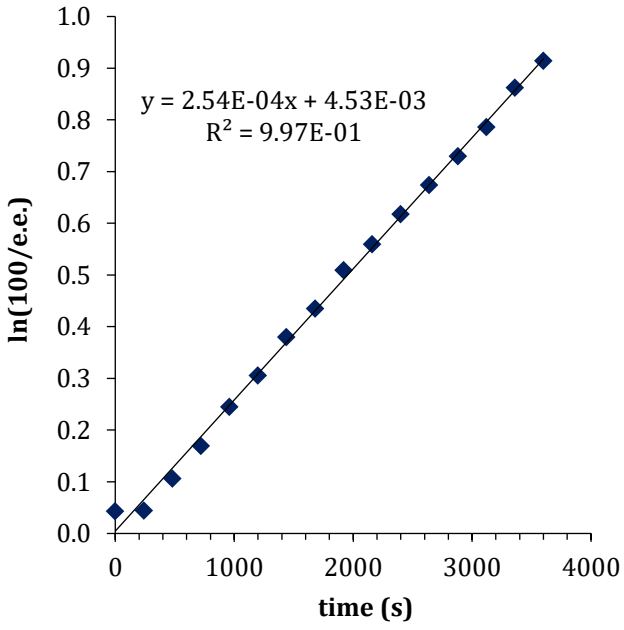
(2) $k_{ent}(298\ K) = \frac{k_B T}{h} e^{-\frac{\Delta G^{\ddagger}}{RT}}$

$k_{ent}(298\ K) = 8.627 \times 10^{-8}$ s^{-1}

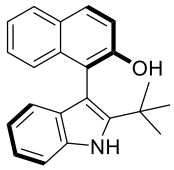
(3) $k_{rac}(298\ K) = 2k_{ent}$ = **1.725×10^{-7} s^{-1}**

(4) $t_{½}rac$ (298 K) = $\frac{ln(2)}{k_{rac}}$ = **46.5 days**





Compound 198



Racemisation at T = 140 °C = 413 K

From slope, $k_{rac} = 9.24 \times 10^{-8}$ s^{-1}

(1) $\Delta G^{\ddagger} = RT\, ln\left(\frac{k_B T}{h k_{ent}}\right)$;

$\Delta G^{\ddagger} = 160266$ J mol^{-1} = **38.3 kcal mol^{-1}**

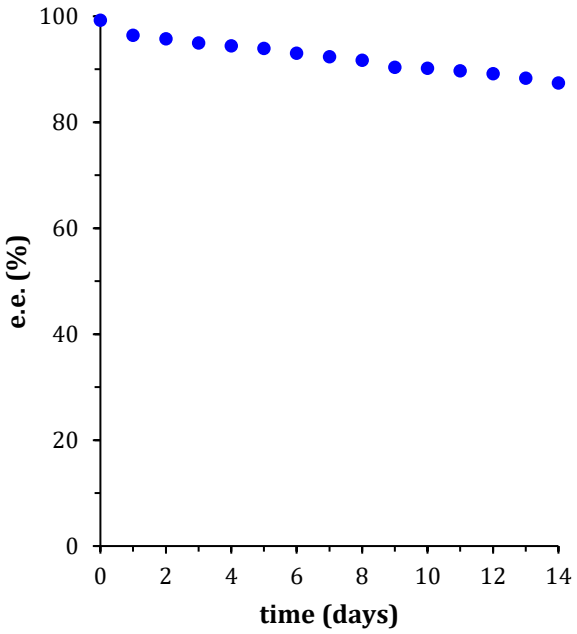
(2) $k_{ent}(298\ K) = \frac{k_B T}{h} e^{-\frac{\Delta G^{\ddagger}}{RT}}$

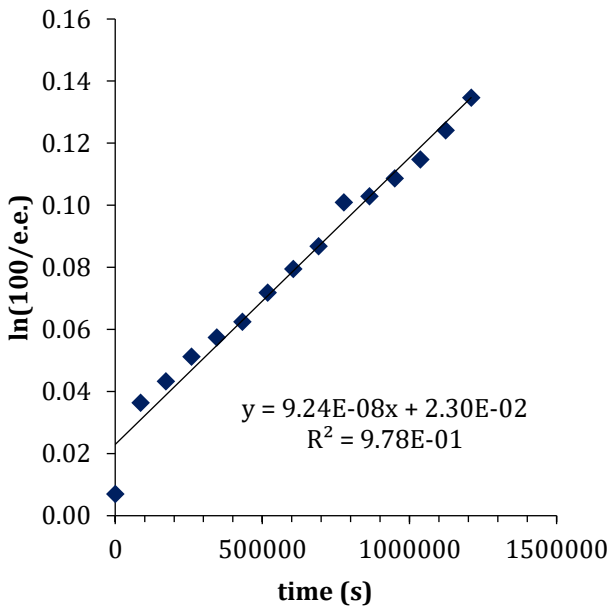
$k_{ent}(298\ K) = 5.012 \times 10^{-16}$ s^{-1}

(3) $k_{rac}(298\ K) = 2k_{ent}$ = $\mathbf{1.002 \times 10^{-15}}$ **s^{-1}**

(4) $t_{½}rac$ (298 K) = $\frac{ln(2)}{k_{rac}}$ = **21.9 million years**

t/(days)	*E1 (%)*	*E2 (%)*	*e.e. (%)*	*ln(1/e.e.)*
0	99.65	0.35	99.30	0.01
1	98.21	1.79	96.42	0.04
2	97.88	2.12	95.76	0.04
3	97.50	2.50	95.00	0.05
4	97.21	2.79	94.42	0.06
5	96.97	3.03	93.94	0.06
6	96.53	3.47	93.06	0.07
7	96.18	3.82	92.36	0.08
8	95.84	4.16	91.68	0.09
9	95.20	4.80	90.40	0.10
10	95.11	4.89	90.22	0.10
11	94.85	5.15	89.70	0.11
12	94.58	5.42	89.16	0.11
13	94.16	5.84	88.32	0.12
14	93.70	6.30	87.40	0.13





10.2 ESR Experiments

All ESR measurements were done in collaboration with Dr. William Myers at the Centre for Advanced Electron Spin Resonance (CAESR) in the Inorganic chemistry laboratory at the University of Oxford.

Preparation of $FeCl_3$-**L9K** Complex

A 100 mL RBF was charged with $FeCl_3 \cdot 6H_2O$ (270 mg, 1.00 mmol, 1.00 equiv.) and DCE (25 mL). The mixture was then sonicated in a water bath for 30 min at room temperature. Following sonication, a magnetic stir bar and **L9K** (469 mg, 1.00 mmol, 1.00 equiv.) were added and the mixture was stirred for 2 h at room temperature. The solution was then dried over Na_2SO_4, and the solids were removed by filtration. The filtrate was concentrated *in vacuo* to give the crude $FeCl_3$-**L9K** complex.

EPR Measurements

Measurements of the $FeCl_3$-**L9K** complex point to fractional radical character in solution that correlates inversely with the conditions of Fe(III) EPR signal intensity. The initial conditions at 21 uM spin concentration of an indolyl radical [simulation: g = 2.0051, $A_{iso}(^{14}N)$ = 20.9 MHz, 2x $A_{iso}(^{1}H)$ = 5.25, 4.92 MHz, with linewidths of pseudoVoigt components of 0.092 and 0.291 mT of Gaussian and Lorentzian, respectively], of 100 mM total molecular concentration, under *in situ* reactions in a 1.2 mm I.D. quartz capillary lead to loss of radicals over the first eight minutes and slow growth of a new radical species of 68 uM at 72 hours (**Figure S1, panel A**). The final radical has EPR simulation values of g = 2.00265, with linewidths of pseudoVoigt components of 0.205 and 0.536 mT of Gaussian and Lorentzian, respectively.

The radical at reaction conclusion can only be reproduced under mixtures that contain indole and the $FeCl_3$-**L9K** complex (**Figure S1, panel B**, traces a, c, f, and h). Under conditions of high local spin concentration and/or exchange with iron, and correspondingly fast relaxation, the characteristic ^{14}N hyperfine signature may not be observed. However, the g-value shift between the two species is consistent with a different open-shell wavefunction character. Further

evidence that the radical is metal associated is seen in **Figures S2** and **S3** (panels a, b, and d), where the radical is observed at 8 K and is not saturated under conditions used in the orthorhombic coordination Fe(III) EPR signal, with characteristic Fe(III) features seen at field values of 74 and 163 mT.[148] Electron transfer may be inferred between the catalyst radical species and the radical in the apparent loss of Fe(III) signal and converse, intense radical feature. This may be a reductive process leading to ferrous iron; however, parallel-mode EPR that can measure some high-spin Fe(II) species did not yield a signal (**Figure S3**, panels c and e). Ferrous species may still be present, regardless of the absence of a parallel-mode signal, as low-spin would not be detectable by EPR and the zero-field splitting of a high-spin Fe(II) species could be unfavourable for parallel mode detection. Broad signals apparent in the centre of the spectra, ca. 340 mT at 8 K (**Figure S2**), may represent altogether different multi-metal ion character.[121] Notably, the broad central feature is not prominent in the reaction mixture of trace f, such as it is dominant in the terminal oxidant (^{t}BuOO^tBu), naphthol, and catalyst in (**Figure S2**, trace e).

Calculations with DFT of the cation and neutral radical using a functional of B3LYP and basis set of EPR-II give isotropic ^{14}N hyperfine values of -0.38 and 5.96 MHz, respectively.[149] The measured hyperfine of nitrogen, $A_{iso}(^{14}N)$ = 20.9 MHz by simulation, is much more than either of these values. Additionally, the calculated g-value is keeping in the range expected for a typical indole such as g = 2.0028 found in tryptophan[150] whereas a value of 2.0051 is far closer to a 1-oxyl derivative of the aminyl radical. In DFT calculations a scaling factor derived from a standard 2,2,5,5-tetramethyl-3pyrroline-1-oxyl provides a value about 60% of typical experimental values for nitroxide spin labels ($\boldsymbol{A}(^{14}N)\approx$[87 15 17]/MHz).[151] Calculated values of $A_{iso}(^{14}N)$ = 10.6 MHz for a 1-oxyl derivative of the aminyl radical are scaled with the factor to the closest agreement with the experimental hyperfine value, of several candidate species shown (**Table S1**). Values of ^{1}H hyperfine in the *t*-Butyl derivative are not reliable in the present calculations due to the motional nature and averaging on the measurement timescale. Hence, absent certain species identification, it is clear that coordination of the aminyl radical through the nitrogen increases the

isotropic hyperfine value and the isotropic g-value in a manner consistent with experimental data, in contrast to a freely-diffusing indole radical.

In the freeze-trapped reaction condition at 8 K (**Figure S3**, panel d.) it appears that the same radical is present in the rigid limit as one determines a 2* $A_{max}(^{14}N)$ splitting from the upward low-field peak to the downward high field peak giving $A_{max}(^{14}N)$ = 55 MHz. The spectrum is fit by a Simplex optimisation algorithm to one component (**Figure S3**, panel f), and best-fit principle g-values are [2.0023 2.0057 2.0069] with $\boldsymbol{A}(^{14}N)$ = [55.4 2.3 4.2] / MHz and the linewidths were 0.6739 and 0.46 mT for pseudoVoigt components of 0.09 and 0.29 mT of Gaussian and Lorentzian. The isotropic value of g = 2.0050 is in good agreement room temperature isotropic g-value, given the increased linewidth at 8 K. Likewise the principle hyperfine values of $\boldsymbol{A}(^{14}N)$ give an $A_{iso}(^{14}N)$ = 20.6, which is exactly the value determined from the room temperature isotropic spectrum.

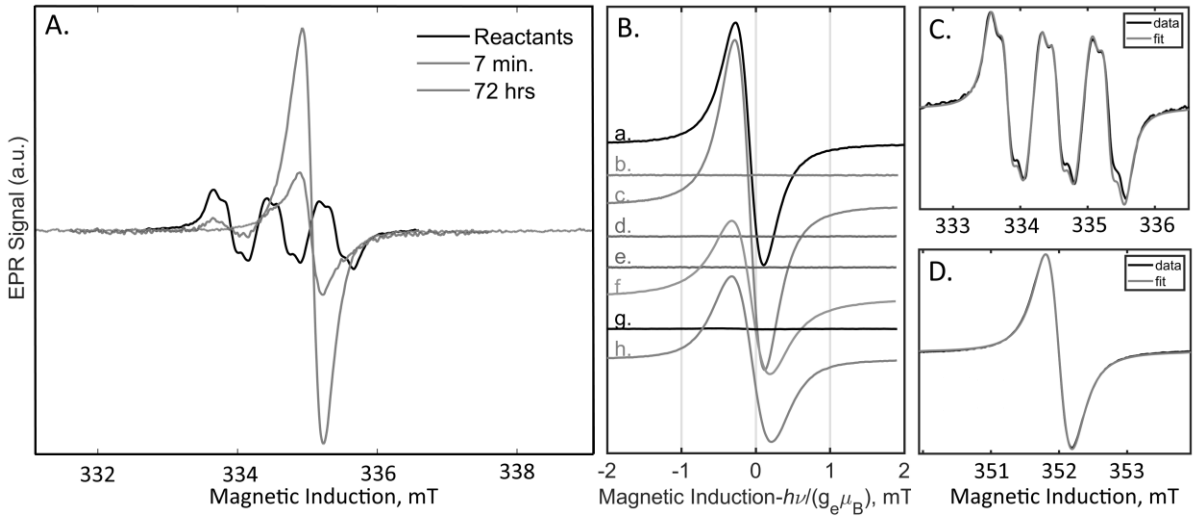


Figure S1. X-band CW-EPR at 295 K of a chiral $FeCl_3$-**L9K** complex. Select reaction progress points shown on the right (Panel A). In Panel B, traces are a) 0.1 M **197** with 0.01 M $FeCl_3$-**L9K** complex; b) 0.1 M ^{t}BuOO^{t}Bu and with 0.01 M $FeCl_3$-**L9K** complex; c) 0.1 M **197**and ^{t}BuOO^{t}Bu with 0.01 M $FeCl_3$-**L9K** complex; d) 0.1 M **222** with 0.01 M $FeCl_3$-**L9K** complex; e) 0.1 M **222** and ^{t}BuOO^{t}Bu with 0.01 M $FeCl_3$-**L9K** complex; f) 0.01 M **197**with 0.01 M $FeCl_3$-**L9K** complex; g) 0.01 M **222** with 0.01 M $FeCl_3$-**L9K** complex; h) Reaction of 0.01 M $FeCl_3$-**L9K** complex with 0.1 M

^{t}BuOO^{t}Bu, **222** and **2b**. The modulation amplitude was 0.05 mT at 100 kHz. Non-saturating conditions were found with a microwave power of 1 mW, while the microwave frequency was 9.3888 GHz. Simulations shown in panels C and D are discussed in the supplemental text.

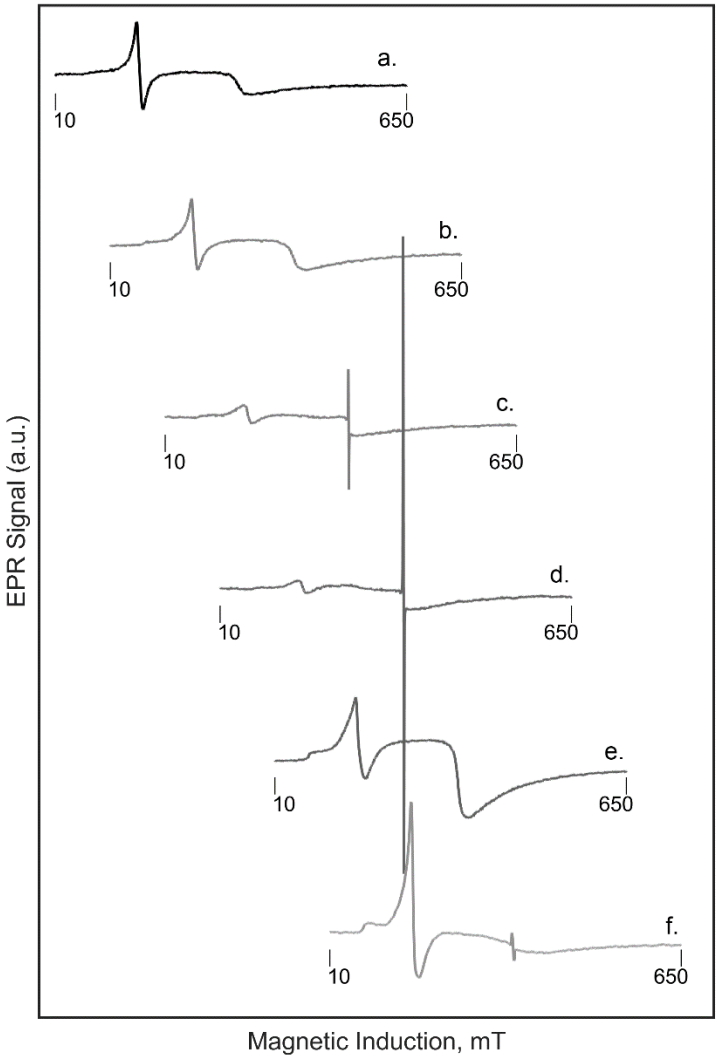


Figure S2. X-band CW-EPR at 8 K of $FeCl_3$-**L9K** complex of 0.01 M alone (a.); with 0.1 M ^{t}BuOO^{t}Bu (b.); with 0.1 M **197**(c.); with 0.1 M ^{t}BuOO^{t}Bu and **197**(d.); with 0.1 M ^{t}BuOO^{t}Bu and **222** (e.); with 0.1 M ^{t}BuOO^{t}Bu, **1c**, and **197**(f.). Select central, g≈2, regions are shown in Figure S3. The modulation amplitude was 0.5 mT at 100 kHz. Non-saturating conditions were found with a microwave power of 10 mW, while the microwave frequency was at 9.6437 GHz.

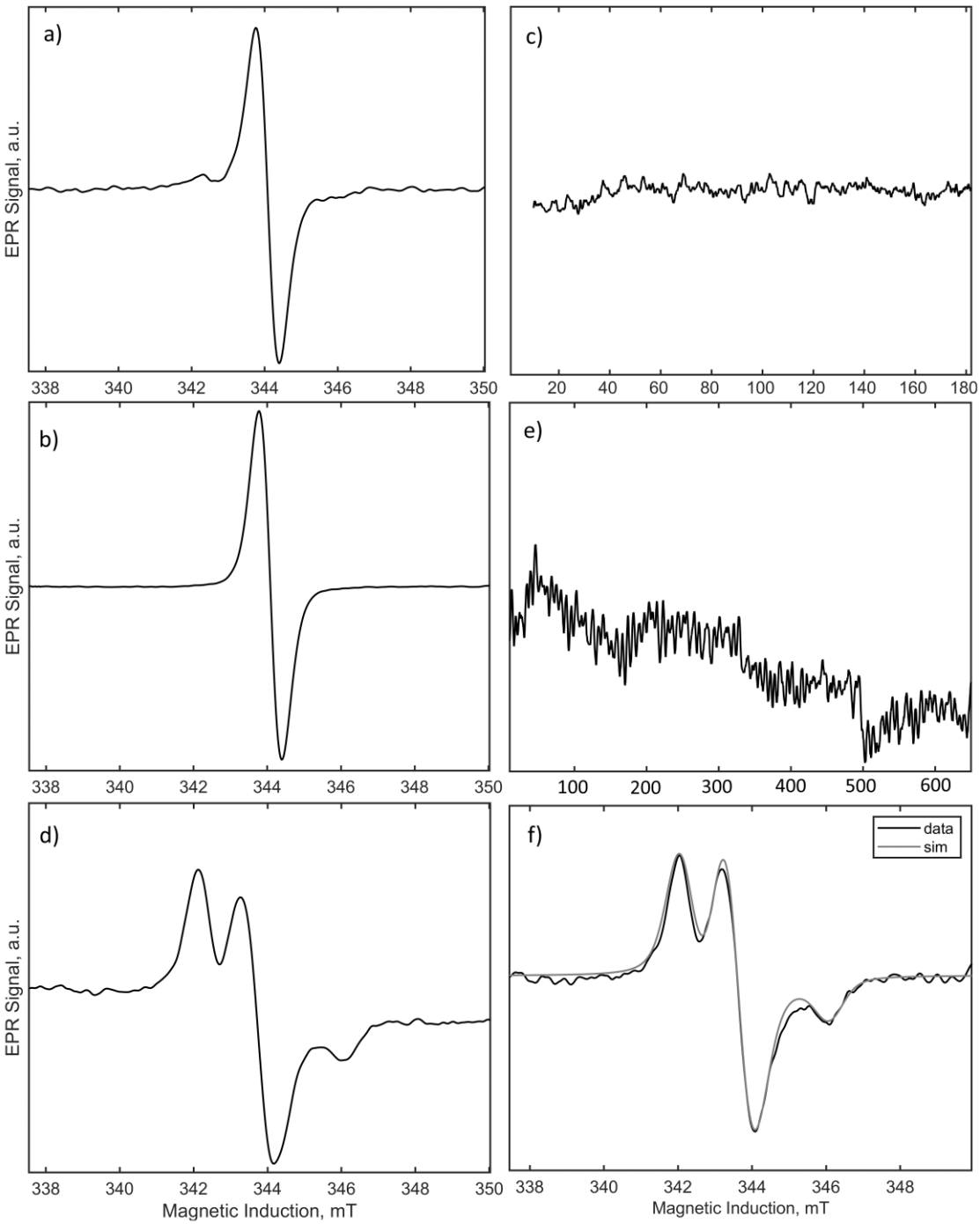
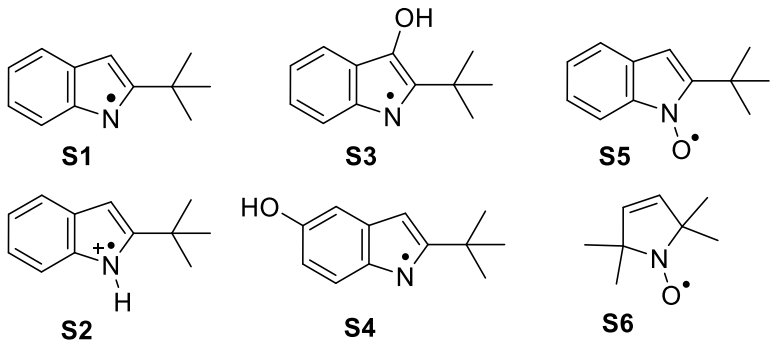


Figure S3. X-band CW-EPR at 8 K of $FeCl_3$-**L9K** complex of 0.01 M with 0.1 M **197**(a.); $FeCl_3$-**L9K** complex with 0.1 M ^{t}BuOO^{t}Bu and **197**(b. and parallel-mode, c.); $FeCl_3$-**L9K** complex with 0.1 M ^{t}BuOO^{t}Bu, **1c**, and **197**(d. and parallel-mode, e.). Perpendicular mode measurements used a microwave frequency of 9.6441 GHz, microwave power of 159 uW, and a field modulation amplitude of 0.3 mT. Parallel mode acquisitions were at used a microwave frequency of 9.3883

GHz, microwave power of 10 mW, and a field modulation amplitude of 0.5 mT. For the simulation of panel d), shown in panel f), the principle g-values are [2.0023 2.0057 2.0069]; A(14N) = [55.4 2.3 4.2] / MHz and the linewidths were 0.6739 and 0.46 mT for pseudoVoigt components of 0.09 and 0.29 mT of Gaussian and Lorentzian, respectively. Acquisition of data for panel f) used a microwave frequency of 9.6438 GHz, microwave power of 0.63 mW and a 100 kHz field modulation amplitude of 0.3 mT. Simulations shown in panel f are discussed in the supplemental text.

Table S1. DFT calculations of EPR parameters with B3LYP functional and EPR-II basis

	species	$A_{iso}(^{14}N)$	$A_{iso}(^{1}H\text{-}1)$	$A_{iso}(^{1}H\text{-}2)$	$A_{iso}(^{1}H\text{-}3)$	g_{iso}
S1	tBu-Indole•	5.96				2.0026
S2	HtBu-Indole•+	-0.38				2.0026
S3	2-tBu-3-OH-indole	7.03	-11.7	-11.5	-9.3	2.0032
S4	2-tBu-8-OH-indole	9.42	-41.1	-17.0	-8.13	2.0029
S5	tBu-indolNO•	10.6	-17.8	-4.52		2.0057
S6	2,2,5,5-tetramethyl-3-pyrroline-1-oxyl	26	-2.14	1.68		2.0057
	experiment	20.9	5.25	4.92		2.0051

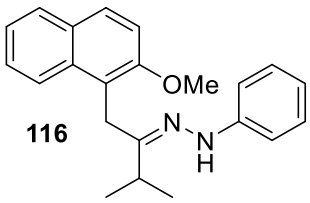


Scheme 1. Molecules used in DFT calculations, corresponding to Table S1.

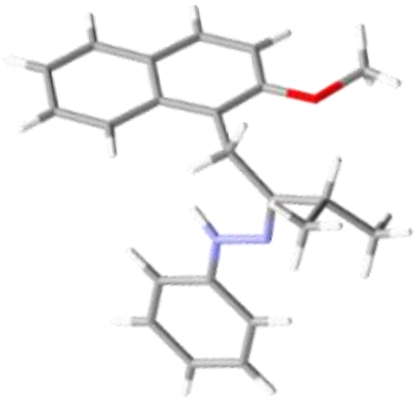
ESR Methods

Continuous wave electron paramagnetic resonance (CW-EPR) was performed in the Centre for Advanced ESR (CAESR) in the Department of Chemistry in the University of Oxford. Room temperature CW-EPR was collected on a Bruker BioSpin EMXmicro Premium spectrometer with an ER4122-SHQE-W resonator coupled to an Oxford Instruments ESR900 cryostat with an Oxford Instruments ITC-503s temperature controller. Liquid helium was used as a cryogen. Room temperature samples were in quartz capillaries of 1.2 mm ID x 20 mm filling height, giving a Q-factor of about 3500. Low temperature samples were held in 3.8 mm O.D. by 10 cm height clear-fused quartz tubes and involved use of the *dual-mode resonator* (Bruker BioSpin, ER 4119DM). EPR data was plotted using the MatLAB software environment (Mathworks, Natick, NJ), while simulations involved use of the EasySpin routines in Matlab[152] DFT calculations for EPR parameter values were performed with the ab-initio package ORCA.[153]

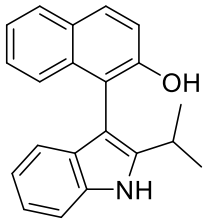
10.3 X-Ray Crystallography



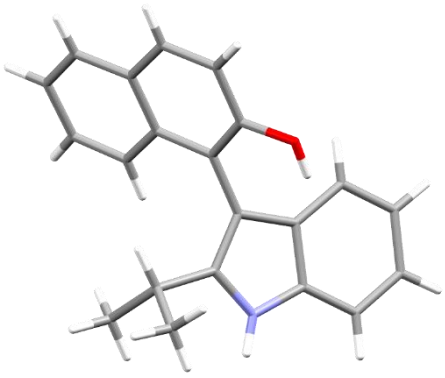
116



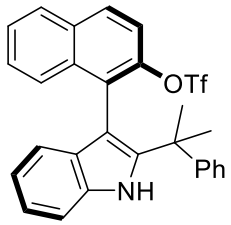
Empirical formula	$C_{22}H_{24}N_2O$	
Formula weight	332.45	
Temperature	100K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	P 21/c	
Unit cell dimentions	a = 16.0218 Å	α = 90°
	b = 12.2234 Å	β = 105.3358°
	c = 19.2816 Å	γ = 90°
Volume	3641.67 $Å^3$	
Z	8	
Density (calculated)	1.213 Mg/m^3	
Absorption coefficient	0.581 mm^{-1}	
F(000)	1424	
Crystal size	0.45 x 0.18 x 0.15 mm^3	
Theta range for data collection	4.329 to 76.150°	
Reflections collected	34633	
Independent reflections	7554	
Absorption correction	**S**emi-empirical from equivalents	
Refinement method	Full-matrix least-squares on F^2	
Goodness-of-fit on F^2	0.9970	
Final R indices [I>2σ(I)]	R^1 = 0.0379, wR^2 = 0.0997	
R indices (all data)	R^1 = 0.0421, wR^2 = 0.1040	



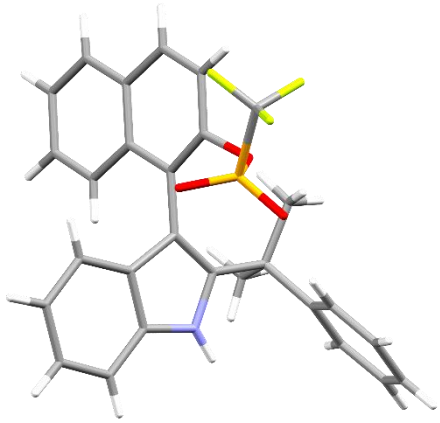
130



Empirical formula	$C_{21}H_{19}NO$	
Formula weight	301.39	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 9.8972(2) Å	α= 90°.
	b = 12.7408(3) Å	β= 90°.
	c = 25.9862(6) Å	γ = 90°.
Volume	3276.81(13) Å3	
Z	8	
Density (calculated)	1.222 Mg/m3	
Absorption coefficient	0.580 mm^{-1}	
F(000)	1280.000	
Crystal size	0.25 x 0.20 x 0.20 mm^3	
Theta range for data collection	3.864 to 76.132°.	
Index ranges	-12<=h<=9, -15<=k<=15, -32<=l<=30	
Reflections collected	21159	
Independent reflections	6790 [R(int) = 0.037]	
Completeness to theta = 74.610°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.89 and 0.86	
Refinement method	Full-matrix least-squares on F2	
Data / restraints / parameters	6789 / 262 / 576	
Goodness-of-fit on F^2	1.0055	
Final R indices [I>2sigma(I)]	R1 = 0.0452, wR2 = 0.1118	
R indices (all data)	R1 = 0.0500, wR2 = 0.1171	



361



Identification Code	016OS21
Empirical Formula	$C_{28}H_{22}F_3N_1O_3S$
Formula Weight	509.55
Temperature	150 K
Wavelength	λ = 1.54184 Å (Cu K_α)
Crystal System	Monoclinic
Space Group	P 21
Unit Cell Dimensions	a = 10.50570(10) Å α = 90 ° b = 22.73520(10) Å β = 113.8617(8) ° c = 11.10230(10) Å γ = 90 °
Volume	2425.11(4) ($Å^3$)
Z	4
Density (Calculated)	1.396 Mg m^{-3}
Absorption Coefficient	1.663 mm^{-1}
Crystal Size	0.12 × 0.16 × 0.32 mm^3
Theta range for data collection	3.889 to 76.092°
Index Ranges	-12<=h<=13, -28<=k<=28 , -13<=l<=13
Reflections Collected	42981
Independent Reflections	[10032 R(int)] = 0.031]
Completeness to theta = 76.092 °	99.7%
Absorption Correction	multi-scan
Refinement method	Full-matrix least-squares on F^2
Goodness-of-fit on F^2	0.886
Final R indices [I>2sigma(I)]	R1 = 0.0287, wR2 = 0.0809
R indices (all data)	R1 = 0.0292, wR2 = 0.0821
Flack x parameter	0.004(8)
Hooft y parameter	0.0000(13)

Crystals of X-ray quality were grown by slow evaporation of CH_2Cl_2 from a solution of **361** (2 mg, 97:3 e.r.) in hexane. The flack x parameter was refined to 0.004(8). Bayesian analysis of the Bijvoet pairs gave the Hooft y parameter as 0.0000(13) giving a >99.99% P2 and P3 probability that the structure is the correct hand. HPLC analysis of the single crystal used for X-ray diffraction studies found the material was >99:1 e.r. confirming that the X-ray diffraction study was carried out on an enantiopure crystal of the major enantiomer.

11. References

1. Kuhn, R. Molekulare Asymmetrie in Stereochemie. *Freuberg, H., Ed.; Franz, Deutike Leipzig-Wien* 803 (1933).
2. Mikami, K., Aikawa, K., Yusa, Y., Jodry, J. J. & Yamanaka, M. Tropos or atropos? That is the question! *Synlett* **2002**, 1561–1578 (2002).
3. Ōki, M. Recent Advances in Atropisomerism. *Top. Stereochem.* 1–81 (1983).
4. Eliel, E. L. & Wilen, S. H. Stereochemistry of Organic Compounds. *Wiley, New York* (1994).
5. Christie, G. H. & Kenner, J. - The molecular configurations of polynuclear aromatic compounds. Part I. The resolution of γ-6:6′-dinitro- and 4:6:4′:6′- tetranitro-diphenic acids into optically active components. *J. Chem. Soc. Trans.* **121**, 614–620 (1922).
6. Miyashita, A. *et al.* Synthesis of 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), an Atropisomeric Chiral Bis(triaryl) phosphine, and Its Use in the Rhodium(I)-Catalyzed Asymmetric Hydrogenation of α-(Acylamino)acrylic Acids. *J. Am. Chem. Soc.* **102**, 7932–7934 (1980).
7. Noyori, R. & Takaya, H. BINAP: An Efficient Chiral Element for Asymmetric Catalysis. *Acc. Chem. Res.* **23**, 345–350 (1990).
8. Teichert, J. F. & Feringa, B. L. Phosphoramidites: Privileged ligands in asymmetric catalysis. *Angew. Chem. Int. Ed.* **49**, 2486–2528 (2010).
9. Parmar, D., Sugiono, E., Raja, S. & Rueping, M. Complete field guide to asymmetric BINOL-phosphate derived Brønsted acid and metal catalysis: History and classification by mode of activation; Brønsted acidity, hydrogen bonding, ion pairing, and metal phosphates. *Chem. Rev.* **114**, 9047–9153 (2014).
10. Hashimoto, T., Omote, M. & Maruoka, K. 6,6′-Substituent effect of BINOL in bis-titanium chiral Lewis acid catalyzed 1,3-dipolar cycloaddition of nitrones. *Org. Biomol. Chem.* **6**, 2263–2265 (2008).
11. Pupo, G. *et al.* Asymmetric nucleophilic fluorination under hydrogen bonding phase-transfer catalysis. *Science* **360**, 638–642 (2018).
12. Hashimoto, T., Sakata, K., Tamakuni, F., Dutton, M. J. & Maruoka, K. Phase-transfer-catalysed asymmetric synthesis of tetrasubstituted allenes. *Nat. Chem.* **5**, 240–244 (2013).
13. Yoon, T. P. & Jacobsen, E. N. Privileged chiral catalysts. *Science* **299**, 1691–1693 (2003).
14. Laplante, S. R. *et al.* Assessing atropisomer axial chirality in drug discovery and development. *J. Med. Chem.* **54**, 7005–7022 (2011).
15. Clayden, J., Moran, W. J., Edwards, P. J. & LaPlante, S. R. The Challenge of Atropisomerism in Drug Discovery. *Angew. Chem. Int. Ed.* **48**, 6398–6401 (2009).
16. Tomaszewski, J. & Rumore, M. M. Stereoisomeric drugs: FDA's policy statement and the impact on drug development. *Drug Dev. Ind. Pharm.* **20**, 119–139 (1994).
17. Chandrasekhar, J. *et al.* Atropisomerism by Design: Discovery of a Selective and Stable Phosphoinositide 3-Kinase (PI3K) β Inhibitor. *J. Med. Chem.* **61**, 6858–6868 (2018).
18. Reist, M., Testa, B., Carrupt, P.-A., Jung, M. & Schurig, V. Racemization, enantiomerization, diastereomerization, and epimerization: Their meaning and pharmacological

significance. *Chirality* **7**, 396–400 (1995).

19. Rickhaus, M., Jundt, L. & Mayor, M. Determining inversion barriers in atropisomers - A tutorial for organic chemists. *Chimia (Aarau).* **70**, 192–202 (2016).

20. Toenjes, S. T. & Gustafson, J. L. Atropisomerism in medicinal chemistry: Challenges and opportunities. *Future Med. Chem.* **10**, 409–422 (2018).

21. LaPlante, S. R., Edwards, P. J., Fader, L. D., Jakalian, A. & Hucke, O. Revealing Atropisomer Axial Chirality in Drug Discovery. *ChemMedChem* **6**, 505–513 (2011).

22. Baudoin, O. The Asymmetric Suzuki Coupling Route to Axially Chiral Biaryls. *European J. Org. Chem.* **2005**, 4223–4229 (2005).

23. Kumarasamy, E., Raghunathan, R., Sibi, M. P. & Sivaguru, J. Nonbiaryl and Heterobiaryl Atropisomers: Molecular Templates with Promise for Atropselective Chemical Transformations. *Chem. Rev.* **115**, 11239–11300 (2015).

24. Bonne, D. & Rodriguez, J. Enantioselective syntheses of atropisomers featuring a five-membered ring. *Chem. Commun.* **53**, 12385–12393 (2017).

25. Glunz, P. W. Recent encounters with atropisomerism in drug discovery. *Bioorganic and Med. Chem. Lett.* **28**, 53–60 (2018).

26. Bringmann, G. *et al.* Atroposelective Synthesis of Axially Chiral Biaryl Compounds. *Angew. Chemie Int. Ed.* **44**, 5384–5427 (2005).

27. Cherney, A. H., Kadunce, N. T. & Reisman, S. E. *Enantioselective and Enantiospecific Transition-Metal-Catalyzed Cross-Coupling Reactions of Organometallic Reagents to Construct C-C Bonds*. *Chem. Rev.* **115**, 9587–9652 (2015).

28. Tanaka, K. Transition-Metal-Catalyzed Enantioselective [2+2+2] Cycloadditions for the Synthesis of Axially Chiral Biaryls. *Chem. Asian J.* **4**, 508–518 (2009).

29. Guo, F., Konkol, L. C. & Thomson, R. J. Enantioselective synthesis of biphenols from 1,4-diketones by traceless central-to-axial chirality exchange. *J. Am. Chem. Soc.* **133**, 18–20 (2011).

30. Ma, G. & Sibi, M. P. Catalytic Kinetic Resolution of Biaryl Compounds. *Chem. Eur. J.* **21**, 11644–11657 (2015).

31. Li, T.-Z., Liu, S.-J., Tan, W. & Shi, F. Catalytic Asymmetric Construction of Axially Chiral Indole-Based Frameworks: An Emerging Area. *Chem. Eur. J.* **26**, 15779–15792 (2020).

32. Qi, L. W., Mao, J. H., Zhang, J. & Tan, B. Organocatalytic asymmetric arylation of indoles enabled by azo groups. *Nat. Chem.* **10**, 58–64 (2018).

33. Xia, W. *et al.* Chiral Phosphoric Acid Catalyzed Atroposelective C−H Amination of Arenes. *Angew. Chem. Int. Ed.* **59**, 6775–6779 (2020).

34. Lu, D. L. *et al.* Atroposelective Construction of Arylindoles by Chiral Phosphoric Acid-Catalyzed Cross-Coupling of Indoles and Quinones. *Org. Lett.* **21**, 6000–6004 (2019).

35. Liu, Q.-J. *et al.* Highly Enantioselective [3+2] Annulation of Indoles with Quinones to Access Structurally Diverse Benzofuroindolines. *Angew. Chem. Int. Ed.* **57**, 3810–3814 (2018).

36. Liu, J. Y. *et al.* An Atropo-enantioselective Synthesis of Benzo-Linked Axially Chiral Indoles via Hydrogen-Bond Catalysis. *Org. Lett.* **21**, 5219–5224 (2019).

37. Zhang, H.-H. *et al.* Design and Enantioselective Construction of Axially Chiral Naphthyl-

Indole Skeletons. *Angew. Chem. Int. Ed.* **56**, 116–121 (2017).

38. Wang, L., Zhong, J. & Lin, X. Atroposelective Phosphoric Acid Catalyzed Three-Component Cascade Reaction: Enantioselective Synthesis of Axially Chiral N-Arylindoles. *Angew. Chem. Int. Ed.* **58**, 15824–15828 (2019).

39. He, Y., Wu, H., Wang, Q. & Zhu, J. Palladium-Catalyzed Enantioselective Cacchi Reaction: Asymmetric Synthesis of Axially Chiral 2,3-Disubstituted Indoles. *Angew. Chem. Int. Ed.* **132**, 2121–2125 (2020).

40. Tian, M., Bai, D., Zheng, G., Chang, J. & Li, X. Rh(III)-Catalyzed Asymmetric Synthesis of Axially Chiral Biindolyls by Merging C-H Activation and Nucleophilic Cyclization. *J. Am. Chem. Soc.* **141**, 9527–9532 (2019).

41. Ye, B. & Cramer, N. A tunable class of chiral Cp ligands for enantioselective rhodium(III)-catalyzed C-H allylations of benzamides. *J. Am. Chem. Soc.* **135**, 636–639 (2013).

42. Peng, L. *et al.* Organocatalytic Asymmetric Annulation of *ortho* -Alkynylanilines: Synthesis of Axially Chiral Naphthyl-C2-indoles. *Angew. Chem. Int. Ed.* **58**, 17199–17204 (2019).

43. Lu, S. *et al.* Diastereo- And Atroposelective Synthesis of Bridged Biaryls Bearing an Eight-Membered Lactone through an Organocatalytic Cascade. *J. Am. Chem. Soc.* **141**, 17062–17067 (2019).

44. Hu, Y. L. *et al.* Conversion of two stereocenters to one or two chiral axes: Atroposelective synthesis of 2,3-diarylbenzoindoles. *Chem. Sci.* **10**, 6777–6784 (2019).

45. Bisag, G. D. *et al.* Central-to-Axial Chirality Conversion Approach Designed on Organocatalytic Enantioselective Povarov Cycloadditions: First Access to Configurationally Stable Indole–Quinoline Atropisomers. *Chem. Eur. J.* **25**, 15694–15701 (2019).

46. He, C., Hou, M., Zhu, Z. & Gu, Z. Enantioselective Synthesis of Indole-Based Biaryl Atropisomers via Palladium-Catalyzed Dynamic Kinetic Intramolecular C-H Cyclization. *ACS Catal.* **7**, 5316–5320 (2017).

47. Jiang, F. *et al.* A Strategy for Synthesizing Axially Chiral Naphthyl-Indoles: Catalytic Asymmetric Addition Reactions of Racemic Substrates. *Angew. Chem. Int. Ed.* **58**, 15104–15110 (2019).

48. Ma, C. *et al.* Design and Catalytic Asymmetric Construction of Axially Chiral 3,3′-Bisindole Skeletons. *Angew. Chem. Int. Ed.* **58**, 3014–3020 (2019).

49. Jolliffe, J. D., Armstrong, R. J. & Smith, M. D. Catalytic enantioselective synthesis of atropisomeric biaryls by a cation-directed O-alkylation. *Nat. Chem.* **9**, 558–562 (2017).

50. Fugard, A. J. *et al.* Hydrogen-Bond-Enabled Dynamic Kinetic Resolution of Axially Chiral Amides Mediated by a Chiral Counterion. *Angew. Chem. Int. Ed.* **58**, 2795–2798 (2019).

51. Armstrong, R. J. & Smith, M. D. Catalytic Enantioselective Synthesis of Atropisomeric Biaryls: A Cation-Directed Nucleophilic Aromatic Substitution Reaction. *Angew. Chem.* **126**, 13036–13040 (2014).

52. Fischer, E. & Jourdan, F. Ueber die Hydrazine der Brenztraubensäure. *Berichte der Dtsch. Chem. Gesellschaft* **16**, 2241–2245 (1883).

53. Fischer, E. & Hess, O. Synthese von Indolderivaten. in *Untersuchungen über Triphenylmethanfarbstoffe Hydrazine und Indole* 454–462 (1924).

54. Robinson, G. M. & Robinson, R. C. The mechanism of E. Fischer's synthesis of indoles.

Application of the method to the preparation of a pyrindole derivative. *J. Chem. Soc. Trans.* **125**, 827–840 (1924).

55. Hughes, D. L. Organic Preparations and Procedures International Progress in the Fischer indole reaction. A review. *Org. Prep. Proced. Int.* **25**, 609–632 (1993).

56. Müller, S., Webber, M. J. & List, B. The catalytic asymmetric Fischer indolization. *J. Am. Chem. Soc.* **133**, 18534–18537 (2011).

57. Martínez, A., Webber, M. J., Müller, S. & List, B. Versatile Access to Chiral Indolines by Catalytic Asymmetric Fischer Indolization. *Angew. Chem. Int. Ed.* **52**, 9486–9490 (2013).

58. Fleming, P. & Oshea, D. F. Controlled anion migrations with a mixed metal Li/K-TMP amide: General application to benzylic metalations. *J. Am. Chem. Soc.* **133**, 1698–1701 (2011).

59. Zhu, M.-K., Chen, Y.-C. & Loh, T.-P. Radical-Mediated Diamination of Alkenes with Phenylhydrazine and Azodicarboxylates: Highly Diastereoselective Synthesis of *trans* -Diamines from Cycloalkenes. *Chem. Eur. J.* **19**, 5250–5254 (2013).

60. Zhu, M.-K. K., Chen, Y.-C. C. & Loh, T.-P. P. No Title. *Chem. Eur. J.* **19**, 5250–5254 (2013).

61. Illy, H. & Funderburk, L. Fischer Indole Synthesis. Direction of Cyclization of Isopropylmethyl Ketone Phenylhydrazone. *J. Org. Chem.* **33**, 4283–4285 (1968).

62. Chaudhary, P., Gupta, S., Muniyappan, N., Sabiah, S. & Kandasamy, J. An efficient synthesis of: N -nitrosamines under solvent, metal and acid free conditions using tert -butyl nitrite. *Green Chem.* **18**, 2323–2330 (2016).

63. Miyaura, N. & Suzuki, A. Palladium-Catalyzed Cross-Coupling Reactions of Organoboron Compounds. *Chem. Rev.* **95**, 2457–2483 (1995).

64. Negishi, E. I. A genealogy of Pd-catalyzed cross-coupling. *J. Organomet. Chem.* **653**, 34–40 (2002).

65. Feldman, K. S., Eastman, K. J. & Lessene, G. Diazonamide synthesis studies: Use of negishi coupling to fashion diazonamide-related biaryls with defined axial chirality. *Org. Lett.* **4**, 3525–3528 (2002).

66. Libman, A. *et al.* Synthetic and Predictive Approach to Unsymmetrical Biphenols by Iron-Catalyzed Chelated Radical-Anion Oxidative Coupling. *J. Am. Chem. Soc.* **137**, 11453–11460 (2015).

67. Dohi, T., Ito, M., Morimoto, K., Iwata, M. & Kita, Y. Oxidative Cross-Coupling of Arenes Induced by Single-Electron Transfer Leading to Biaryls by Use of Organoiodine(III) Oxidants. *Angew. Chem.* **120**, 1321–1324 (2008).

68. Röckl, J. L., Pollok, D., Franke, R. & Waldvogel, S. R. A Decade of Electrochemical Dehydrogenative C,C-Coupling of Aryls. *Acc. Chem. Res.* **53**, 45–61 (2020).

69. Lips, S., Schollmeyer, D., Franke, R. & Waldvogel, S. R. Regioselective Metal- and Reagent-Free Arylation of Benzothiophenes by Dehydrogenative Electrosynthesis. *Angew. Chem. Int. Ed.* **57**, 13325–13329 (2018).

70. Elsler, B. *et al.* Source of Selectivity in Oxidative Cross-Coupling of Aryls by Solvent Effect of 1,1,1,3,3,3-Hexafluoropropan-2-ol. *Chem. Eur. J.* **21**, 12321–12325 (2015).

71. Yuan, Y. & Lei, A. Is electrosynthesis always green and advantageous compared to traditional methods? *Nat. Commun.* **11**, 1–3 (2020).

72. Yan, M., Kawamata, Y. & Baran, P. S. Synthetic Organic Electrochemistry: Calling All Engineers. *Angew. Chem. Int. Ed.* **57**, 4149–4155 (2018).

73. Horn, E. J., Rosen, B. R. & Baran, P. S. Synthetic organic electrochemistry: An enabling and innately sustainable method. *ACS Cent. Sci.* **2**, 302–308 (2016).

74. Lee, Y. E., Cao, T., Torruellas, C. & Kozlowski, M. C. Selective oxidative homo-and cross-coupling of phenols with aerobic catalysts. *J. Am. Chem. Soc.* **136**, 6782–6785 (2014).

75. Que, L. & Tolman, W. B. Biologically inspired oxidation catalysis. *Nature* **455**, 333–340 (2008).

76. Wang, H. Recent advances in asymmetric oxidative coupling of 2-naphthol and its derivatives. *Chirality* **22**, 827–837 (2010).

77. Hovorka, M., Günterová, J. & Závada, J. Highly selective oxidative cross-coupling of substituted 2-naphthols: A convenient approach to unsymmetrical 1,1′-binaphthalene-2,2′-diols. *Tetrahedron Lett.* **31**, 413–416 (1990).

78. Smrčina, M. *et al.* Selective Cross-Coupling of 2-Naphthol and 2-Naphthylamine Derivatives. A Facile Synthesis of 2,2′,3-Trisubstituted and 2,2′,3,3′-Tetrasubstituted 1,1′-Binaphthyls. *J. Org. Chem.* **59**, 2156–2163 (1994).

79. Noji, M., Nakajima, M. & Koga, K. A new catalytic system for aerobic oxidative coupling of 2-naphthol derivatives by the use of CuCl-amine complex: A practical synthesis of binaphthol derivatives. *Tetrahedron Lett.* **35**, 7983–7984 (1994).

80. McDonald, P. D. & Hamilton, G. A. Mechanisms of Phenolic Oxidative Coupling Reactions. in *Organic Chemistry* **5**, 97–134 (Elsevier, 1973).

81. Nakajima, M. *et al.* Enantioselective synthesis of binaphthol derivatives by oxidative coupling of naphthol derivatives catalyzed by chiral diamine-copper complexes. *J. Org. Chem.* **64**, 2264–2271 (1999).

82. Li, X., Hewgley, J. B., Mulrooney, C. A., Yang, J. & Kozlowski, M. C. Enantioselective oxidative biaryl coupling reactions catalyzed by 1,5-diazadecalin metal complexes: Efficient formation of chiral functionalized BINOL derivatives. *J. Org. Chem.* **68**, 5500–5511 (2003).

83. Egami, H. & Katsuki, T. Iron-catalyzed asymmetric aerobic oxidation: Oxidative coupling of 2-naphthols. *J. Am. Chem. Soc.* **131**, 6082–6083 (2009).

84. Luo, Z. *et al.* Novel Achiral Biphenol-Derived Diastereomeric Oxovanadium(IV) Complexes for Highly Enantioselective Oxidative Coupling of 2-Naphthols. *Angew. Chem. Int. Ed.* **41**, 4532–4535 (2002).

85. Egami, H., Matsumoto, K., Oguma, T., Kunisu, T. & Katsuki, T. Enantioenriched synthesis of C 1-symmetric BINOLs: Iron-catalyzed cross-coupling of 2-naphthols and some mechanistic insight. *J. Am. Chem. Soc.* **132**, 13633–13635 (2010).

86. Tian, J. *et al.* Copper-Complex-Catalyzed Asymmetric Aerobic Oxidative Cross-Coupling of 2-Naphthols: Enantioselective Synthesis of 3,3′-Substituted C_1 -Symmetric BINOLs. *Angew. Chem. Int. Ed.* **58**, 11023–11027 (2019).

87. Zhao, X. *et al.* Enantioselective Synthesis of 3,3′-Disubstituted 2-Amino-2′-hydroxy-1,1′-binaphthyls by Copper-Catalyzed Aerobic Oxidative Cross-Coupling. *Angew. Chem. Int. Ed.* **60**, 7061–7065 (2021).

88. Li, J., Burgett, A. W. G., Esser, L., Amezcua, C. & Harran, P. G. Total Synthesis of Nominal Diazonamides-Part 2: On the True Structure and Origin of Natural Isolates. *Angew. Chem.*

Int. Ed. **40**, 4770–4773 (2001).

89. Kam, T. S., Tan, S. J., Ng, S. W. & Komiyama, K. Bipleiophylline, an unprecedented cytotoxic bisindole alkaloid constituted from the bridging of two indole moieties by an aromatic spacer unit. *Org. Lett.* **10**, 3749–3752 (2008).

90. Wu, Q. X. *et al.* Azonazine, a novel dipeptide from a Hawaiian marine sediment-derived fungus, Aspergillus insulicola. *Org. Lett.* **12**, 4458–4461 (2010).

91. Chan, C., Li, C., Zhang, F. & Danishefsky, S. J. Studies toward the total synthesis of phalarine: a survey of some biomimetic possibilities. *Tetrahedron Lett.* **47**, 4839–4841 (2006).

92. Zhao, J. C., Yu, S. M., Liu, Y. & Yao, Z. J. Biomimetic synthesis of ent -(-)-azonazine and stereochemical reassignment of natural product. *Org. Lett.* **15**, 4300–4303 (2013).

93. Burgett, A. W. G., Li, Q., Wei, Q. & Harran, P. G. A Concise and Flexible Total Synthesis of (−)-Diazonamide A. *Angew. Chem. Int. Ed.* **42**, 4961–4966 (2003).

94. Tomakinian, T., Guillot, R., Kouklovsky, C. & Vincent, G. Direct Oxidative Coupling of *N* -Acetyl Indoles and Phenols for the Synthesis of Benzofuroindolines Related to Phalarine. *Angew. Chem. Int. Ed.* **126**, 12075–12079 (2014).

95. Trzupek, J. D., Lee, D., Crowley, B. M., Marathias, V. M. & Danishefsky, S. J. Total synthesis of enantiopure phalarine via a stereospecific pictet-spengler reaction: Traceless transfer of chirality from L -tryptophan. *J. Am. Chem. Soc.* **132**, 8506–8512 (2010).

96. Liu, K., Tang, S., Huang, P. & Lei, A. External oxidant-free electrooxidative [3 + 2] annulation between phenol and indole derivatives. *Nat. Commun.* **8**, 1–8 (2017).

97. Colomer, I., Chamberlain, A. E. R., Haughey, M. B. & Donohoe, T. J. Hexafluoroisopropanol as a highly versatile solvent. *Nat. Rev. Chem.* **1**, 1–12 (2017).

98. Tohma, H., Morioka, H., Takizawa, S., Arisawa, M. & Kita, Y. Efficient oxidative biaryl coupling reaction of phenol ether derivatives using hypervalent iodine(III) reagents. *Tetrahedron* **57**, 345–352 (2001).

99. Kupchan, S. M. & Kameswaran, V. On the Mechanism of Formation of Spirodienone Products of Nonphenol Oxidative Coupling. *J. Am. Chem. Soc.* **97**, 5622–5623 (1975).

100. Gaster, E. *et al.* Significant Enhancement in the Efficiency and Selectivity of Iron-Catalyzed Oxidative Cross-Coupling of Phenols by Fluoroalcohols. *Angew. Chem. Int. Ed.* **54**, 4198–4202 (2015).

101. Houck, H. A. *et al.* Design of a thermally controlled sequence of triazolinedione-based click and transclick reactions. *Chem. Sci.* **8**, 3098–3108 (2017).

102. Shalit, H., Dyadyuk, A. & Pappo, D. Selective Oxidative Phenol Coupling by Iron Catalysis. *J. Org. Chem.* **84**, 1677–1686 (2019).

103. Narute, S., Parnes, R., Toste, F. D. & Pappo, D. Enantioselective Oxidative Homocoupling and Cross-Coupling of 2-Naphthols Catalyzed by Chiral Iron Phosphate Complexes. *J. Am. Chem. Soc.* **138**, 16553–16560 (2016).

104. Ollevier, T. Iron bis(oxazoline) complexes in asymmetric catalysis. *Catal. Sci. Technol.* **6**, 41–48 (2016).

105. Campbell, C. D., Concellón, C. & Smith, A. D. Catalytic enantioselective Steglich rearrangements using chiral N-heterocyclic carbenes. *Tetrahedron Asymmetry* **22**, 797–811 (2011).

106. Cornejo, A. *et al.* An efficient and general one-pot method for the synthesis of chiral bis(oxazoline) and pyridine bis(oxazoline) ligands. *Synlett* **2005**, 2321–2324 (2005).

107. Wang, H. *et al.* Palladium-Catalyzed Amide-Directed Enantioselective Hydrocarbofunctionalization of Unactivated Alkenes Using a Chiral Monodentate Oxazoline Ligand. *J. Am. Chem. Soc.* **140**, 3542–3546 (2018).

108. Bryliakov, K. P. & Talsi, E. P. Evidence for the formation of an iodosylbenzene(salen)iron active intermediate in a (salen)iron(III)-catalyzed asymmetric sulfide oxidation. *Angew. Chem. Int. Ed.* **43**, 5228–5230 (2004).

109. Chen, M. S. & White, M. C. Combined effects on selectivity in Fe-catalyzed methylene oxidation. *Science.* **327**, 533–571 (2010).

110. Yazerski, V. A. *et al.* Making Fe(BPBP)-catalyzed C-H and CC oxidations more affordable. *Org. Biomol. Chem.* **12**, 2062–2070 (2014).

111. Itoh, K. & Sibi, M. P. Dibenzofuran-4,6-bis(oxazoline) (DBFOX). A novel trans -chelating bis(oxazoline) ligand for asymmetric reactions. *Org. Biomol. Chem.* **16**, 5551–5565 (2018).

112. Evans, D. A., Miller, S. J., Lectka, T. & Von Matt, P. Chiral bis(oxazoline)copper(II) complexes as lewis acid catalysts for the enantioselective Diels-Alder reaction. *J. Am. Chem. Soc.* **121**, 7559–7573 (1999).

113. Tse, M. K. *et al.* Ruthenium-Catalyzed Asymmetric Epoxidation of Olefins Using H2O2, Part I: Synthesis of New ChiralN,N,N-Tridentate Pybox and Pyboxazine Ligands and Their Ruthenium Complexes. *Chem. Eur. J.* **12**, 1855–1874 (2006).

114. Nishiyama, H., Yamaguchi, S., Hondo, M. & Itoh, K. Electronic Substituent Effect of Nitrogen Ligands in Catalytic Asymmetric Hydrosilylation of Ketones: Chiral 4-Substituted Bis(oxazolinyl)pyridines. *J. Org. Chem.* **57**, 4306–4309 (1992).

115. Liu, E. C. & Topczewski, J. J. Enantioselective Copper Catalyzed Alkyne-Azide Cycloaddition by Dynamic Kinetic Resolution. *J. Am. Chem. Soc.* **141**, 5135–5138 (2019).

116. Chang, H. T. & Sharpless, K. B. A practical route to enantiopure 1,2-aminoalcohols. *Tetrahedron Lett.* **37**, 3219–3222 (1996).

117. Djakovitch, L., Dufaud, V. & Zaidi, R. Heterogeneous palladium catalysts applied to the synthesis of 2- and 2,3-functionalised indoles. *Adv. Synth. Catal.* **348**, 715–724 (2006).

118. Larock, R. C., Yum, E. K., Doty, M. J. & Sham, K. K. C. Synthesis of Aromatic Heterocycles via Palladium-Catalyzed Annulation of Internal Alkynes. *J. Org. Chem.* **60**, 3270–3271 (1995).

119. Inman, M. & Moody, C. J. Indole synthesis-something old, something new. *Chemical Science.* **4**, 29–41 (2013).

120. Zhu, S. *et al.* Organocatalytic atroposelective construction of axially chiral arylquinones. *Nat. Commun.* **10**, 1–10 (2019).

121. Muñoz, S. B., Daifuku, S. L., Brennessel, W. W. & Neidig, M. L. Isolation, Characterization, and Reactivity of Fe_8Me_{12}-: Kochi's S = 1/2 Species in Iron-Catalyzed Cross-Couplings with MeMgBr and Ferric Salts. *J. Am. Chem. Soc.* **138**, 7492–7495 (2016).

122. Leifert, D. & Studer, A. The Persistent Radical Effect in Organic Synthesis. *Angew. Chem. Int. Ed.* **59**, 74–108 (2020).

123. McDonald, A. R. & Que, L. High-valent nonheme iron-oxo complexes: Synthesis, structure, and spectroscopy. *Coord. Chem. Rev.* **257**, 414–428 (2013).

124. Mangas-Sánchez, J., Busto, E., Gotor-Fernández, V. & Gotor, V. Straightforward Synthesis of Enantiopure 2,3-Dihydrobenzofurans by a Sequential Stereoselective Biotransformation and Chemical Intramolecular Cyclization. *Org. Lett.* **12**, 3498–3501 (2010).

125. Ema, T., Ura, N., Yoshii, M., Korenaga, T. & Sakai, T. Empirical method for predicting enantioselectivity in catalytic reactions: demonstration with lipase and oxazaborolidine. *Tetrahedron* **65**, 9583–9591 (2009).

126. Lukeman, M., Simon, H., Wan, P. & Wang, Y.-H. Photocyclization and Photoaddition Reactions of Arylphenols via Intermediate Quinone Methides. *J. Org. Chem.* **80**, 11281–11293 (2015).

127. Thevenon, A. *et al.* Indium Catalysts for Low-Pressure CO2/Epoxide Ring-Opening Copolymerization: Evidence for a Mononuclear Mechanism? *J. Am. Chem. Soc.* **140**, 6893–6903 (2018).

128. Eno, M. S., Lu, A. & Morken, J. P. Nickel-Catalyzed Asymmetric Kumada Cross-Coupling of Symmetric Cyclic Sulfates. *J. Am. Chem. Soc.* **138**, 7824–7827 (2016).

129. Peng, C. *et al. p* -Toluenesulfonic Acid Promoted Annulation of 2-Alkynylanilines with Activated Ketones: Efficient Synthesis of 4-Alkyl-2,3-Disubstituted Quinolines. *Eur. J. Org. Chem.* **2010**, 818–822 (2010).

130. Iritani, K., Matsubara, S. & Utimoto, K. Palladium catalyzed reaction of 2-alkynylanilines with allyl chlorides. Formation of 3-allylindoles. *Tetrahedron Lett.* **29**, 1799–1802 (1988).

131. Kalgutkar, A. S., Kozak, K. R., Crews, B. C., Hochgesang, G. P. & Marnett, L. J. Covalent modification of cyclooxygenase-2 (COX-2) by 2-acetoxyphenyl alkyl sulfides, a new class of selective COX-2 inactivators. *J. Med. Chem.* **41**, 4800–4818 (1998).

132. Liu, X. *et al.* Lewis Acid Assisted Nickel-Catalyzed Cross-Coupling of Aryl Methyl Ethers by C–O Bond-Cleaving Alkylation: Prevention of Undesired β-Hydride Elimination. *Angew. Chem. Int. Ed.* **55**, 6093–6098 (2016).

133. Kerr, W. J., Morrison, A. J., Pazicky, M. & Weber, T. Modified shapiro reactions with bismesitylmagnesium as an efficient base reagent. *Org. Lett.* **14**, 2250–2253 (2012).

134. Liu, S. *et al.* Highly efficient and convenient asymmetric hydrosilylation of ketones catalyzed with zinc Schiff base complexes. *Tetrahedron* **68**, 1371–1375 (2012).

135. Michel, B. W., Camelio, A. M., Cornell, C. N. & Sigman, M. S. A general and efficient catalyst system for a wacker-type oxidation using TBHP as the terminal oxidant: Application to classically challenging substrates. *J. Am. Chem. Soc.* **131**, 6076–6077 (2009).

136. Ito, F., Nakamura, T., Yorita, S., Danjo, H. & Yamaguchi, K. Ionic probe attachment ionization mass spectrometry. *Tetrahedron Lett.* **50**, 6252–6255 (2009).

137. Hinz, A. Pseudo-One-Coordinate Tetrylenium Salts Bearing a Bulky Carbazolyl Substituent. *Chem. Eur. J.* **25**, 3267–3271 (2019).

138. Zou, J., Berg, D. J., Stuart, D., McDonald, R. & Twamley, B. Carbazole-bis(oxazolines) as monoanionic, tridentate chelates in lanthanide chemistry: Synthesis and structural studies of thermally robust and kinetically stable dialkyl and dichloride complexes. *Organometallics* **30**, 4958–4967 (2011).

139. Bartels, B., García-Yebra, C., Rominger, F. & Helmchen, G. Iridium-Catalysed Allylic Substitution: Stereochemical Aspects and Isolation of IrIII Complexes Related to the Catalytic Cycle. *Eur. J. Inorg. Chem.* **2002**, 2569–2586 (2002).

140. Muthu, S., Yip, J. H. K. & Vittal, J. J. Coordination polymers of d10 metals and N,N′ -bis(3-pyridinecarboxamide)-1,2-ethane. *J. Chem. Soc. Dalt. Trans.* 3577–3584 (2001).

141. Huang, W. S. *et al.* Catalytic asymmetric bromochlorination of aromatic allylic alcohols promoted by multifunctional Schiff base ligands. *Org. Biomol. Chem.* **14**, 7927–7932 (2016).

142. Tretbar, M. & Stark, C. B. W. Large-Scale Synthesis of Symmetric Tetramine Ligands by Using a Modular Double Reductive Amination Approach. *Eur. J. Org. Chem.* **2017**, 6942–6946 (2017).

143. Deng, Q. H., Wadepohl, H. & Gade, L. H. The synthesis of a new class of chiral pincer ligands and their applications in enantioselective catalytic fluorinations and the Nozaki-Hiyama-Kishi reaction. *Chem. Eur. J.* **17**, 14922–14928 (2011).

144. Knipe, P. C. & Smith, M. D. Enantioselective one-pot synthesis of dihydroquinolones via BINOL-derived Lewis acid catalysis. *Org. Biomol. Chem.* **12**, 5094–5097 (2014).

145. O'Brien, P., Osborne, S. A. & Parker, D. D. Asymmetric aminohydroxylation of substituted styrenes: Applications in the synthesis of enantiomerically enriched arylglycinols and a diamine. *J. Chem. Soc. - Perkin Trans. 1* **0**, 2519–2526 (1998).

146. Bigler, R. *et al.* Asymmetric Hydrogenation of Unfunctionalized Tetrasubstituted Acyclic Olefins. *Angew. Chem. Int. Ed.* **59**, 2844–2849 (2020).

147. Ahmed, S. A., Tanaka, M., Ando, H., Iwamoto, H. & Kimura, K. Synthesis and Photochromism of Novel Chromene Derivatives Bearing a Monoazacrown Ether Moiety. *European J. Org. Chem.* **2003**, 2437–2442 (2003).

148. Castner, T., Newell, G. S., Holton, W. C. & Slighter, C. P. Note on the paramagnetic resonance of iron in glass. *J. Chem. Phys.* **32**, 668–673 (1960).

149. Barone, V., Structure, Magnetic Properties and Reactivities of Open-Shell Species From Density Functional and Self-Consistent Hybrid Methods. in 287–334 (1995).

150. Stoll, S. *et al.* Hydrogen bonding of tryptophan radicals revealed by EPR at 700 GHz. *J. Am. Chem. Soc.* **133**, 18098–18101 (2011).

151. Setaka, M. & Lagercrantz, C. Orientation of Some Nitroxide Spin Labels in the Lamellar Mesophases of Aerosol-OT-Water and Decanol-Decanoate-Water Systems. **16**, (UTC, 2021).

152. Stoll, S. & Schweiger, A. EasySpin, a comprehensive software package for spectral simulation and analysis in EPR. *J. Magn. Reson.* **178**, 42–55 (2006).

153. Neese, F. Software update: the ORCA program system, version 4.0. *Wiley Interdiscip. Rev. Comput. Mol. Sci.* **8**, 1327 (2018).