New Cation-Mediated Enantioselective Transformations

and

Catalytic Enantioselective Photocyclization

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

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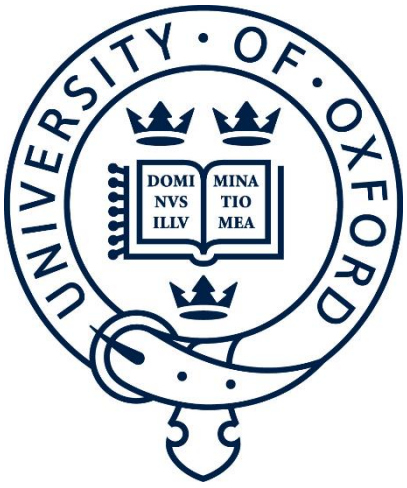

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Declaration

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

Benjamin Jones

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List of Abbreviations

Δ	error
δ	chemical shift
µL	micro litre(s)
µmol	micro mole
Ac	acetyl
app.	apparent
Ar	*denotes a generic aromatic group*
ATR	attenuated total reflectance
aq.	aqueous solution
BINAP	2,2'-bis(diphenylphosphaneyl)-1,1'-binaphthalene
BINOL	1,1'-bi-2-naphthol
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
bpy	2,2’-bipyridine
br.	broad
°C	degree(s) Celsius
cm	centimetre(s)
COSY	correlation spectroscopy
CPME	cyclopentyl methyl ether
D	doublet
DavePhos	2-dicyclohexylphosphino-2’-(*N*,*N*-dimethylamino)biphenyl
dba	dibenzylideneacetone
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyazodicarboxylate
dFppy	2-(2,4-difluorophenyl)pyridine
DFT	density functional theory
DIAD	diisopropylazodicarboxylate
DIPK	diisopropyl ketone
DIPEA	diisopropylethylamine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide

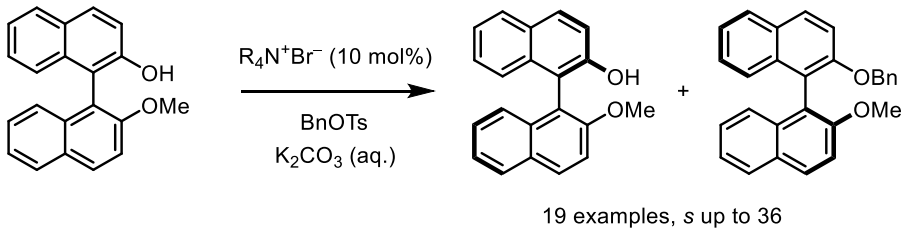
DMSO	dimethylsulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio
dtbbpy	4,4’-di-*tert*-butyl 2,2’-bipyridine
EDG	electron-donating group
ee	enantiomeric excess
equiv.	equivalent(s)
er	enantiomeric ratio
ESI	electrospray ionisation
Et	ethyl
EWG	electron withdrawing group
Fppy	2-(4-fluorophenyl)pyridine
FTIR	fourier-transform infrared
g	gram(s)
h	hour(s)
hv	light
HFIP	1,1,1,3,3,3-hexafluoroisopropanol
HMBC	heteronuclear multiple bond correlation
HMDS	bis(trimethylsilyl)amide
HMTA	hexamethylene tetramine
HOMO	highest occupied molecular orbital
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
HSQC	heteronuclear single quantum correlation
Hz	hertz
^{i}Pr	isopropyl
IUPAC	international union of pure and applied chemistry
J	coupling constant
K	Kelvin
kcal	kilocalorie (s)
L	litre
LED	light-emitting diode
LUMO	lowest unoccupied molecular orbital

m	multiplet
M	mol/L
*m*CPBA	3-chloroperbenzoic acid
Me	methyl
MeBINOL	2'-methoxy-[1,1'-binaphthalen]-2-ol
mg	milligram(s)
MHz	megahertz
min	minute(s)
mL	millilitre(s)
mmol	millimole
NBS	*N*-bromosuccinimide
^{n}Bu	normal-butyl
NHC	N-heterocyclic carbene
NMR	nuclear magnetic resonance (spectroscopy)
NOBIN	2-amino-2'-hydroxy-1,1'-binaphthyl
P	product
Ph	phenyl
Piv	pivaloyl
ppm	parts per million
ppy	2-phenylpyridine
PTC	phase transfer catalysis
q	quartet
rt	room temperature
S_0	lowest energy singlet state
S_1	lowest energy singlet excited state
s	singlet
s	selectivity (factor)
sat.	saturated
SM	starting material
SPINOL	1,1′-spirobiindane-7,7′-diol
t	triplet
T_1	lowest energy triplet excited state
TBA	tetrabutylammonium

TBAB	tetrabutylammonium bromide
TEEDA	tetraethylethylenediamine
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMEDA	tetramethylethylenediamine
Ts	*para*-toluenesulfonyl
UV	ultraviolet

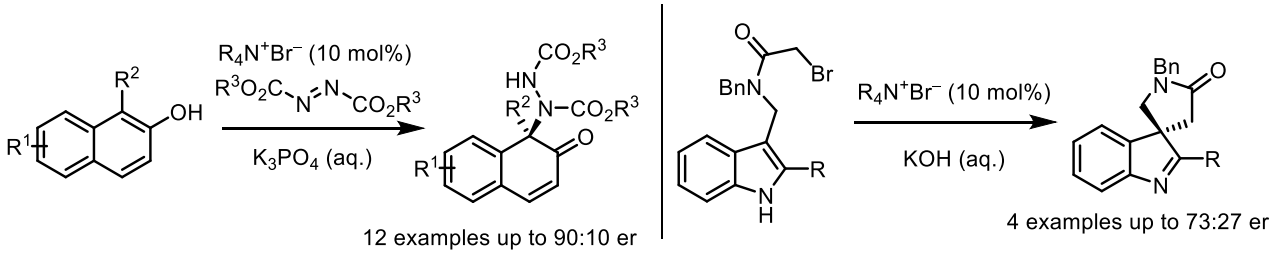
Abstract

This thesis describes the development of novel catalytic enantioselective reactions. Chapter 1 describes the development of transformations mediated by chiral ammonium salts. The historical context of enantioselective phase transfer catalysis is provided and the key fundamental advances are detailed. The development of a cation-mediated kinetic resolution of atropisomeric biaryls is described as well as the synthesis and resolution of a range of substituted BINOLs.



Scheme 1: Cation-mediated kinetic resolution of BINOLs.

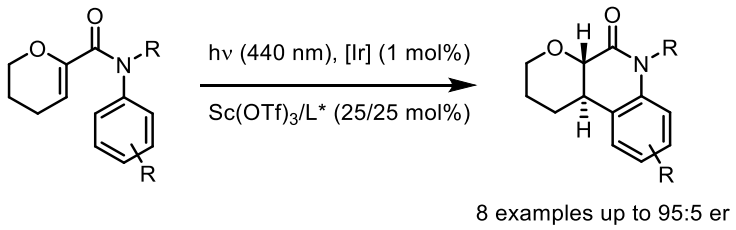
The extension of the chiral cation mediated approach to the dearomatization of 2-naphthols by electrophilic amination and of indoles by *C*3 alkylation is also described. In both cases, good reactivity and moderate enantioselectivity were achieved.



Scheme 2: Left: Enantioselective dearomative amination of 2-naphthols. Right: Alkylative dearomatization of indoles.

Chapter 2 focuses on the development of a Lewis acid mediated approach to the catalytic enantioselective [6π] photocyclization of acrylanilides. The work is contextualized by a discussion of the previous approaches to enantioselective photochemical reactions covering direct irradiation, triplet energy transfer and photoredox strategies. The elucidation of competing triplet energy

transfer and photoredox pathways to the same product is described alongside an account of the design and development of a photocatalyst that engages predominantly in the photoredox pathway. The reaction was tested on a range of substrates to determine the scope and limitations of the method.



Scheme 3: Enantioselective photocyclization of acrylanilides.

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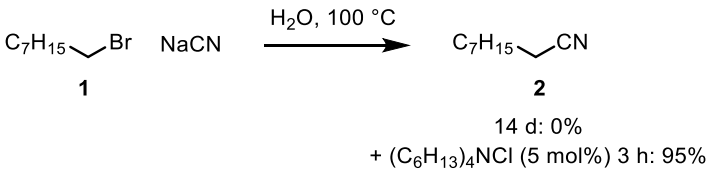
1. New Cation Mediated Enantioselective Transformations

1.1. Introduction

1.1.1 Phase-Transfer Catalysis

Phase-transfer catalysis (PTC) is a synthetic method that exploits lipophilic counterions to solubilise and promote the reaction of otherwise unreactive ionised nucleophiles.[1] PTC was first described by Starks in 1971 when studying the reaction of potassium cyanide with 1-bromooctane (**1**) in various solvents (Scheme 4).[2] Starks found that the reaction proceeded efficiently in DMSO but not at all in water. When water was used as the solvent, 1-bromooctane separated into a distinct phase and potassium cyanide partitioned exclusively into the aqueous phase. The reactants were not mutually soluble in either phase, so no reaction could occur. By introducing a quaternary ammonium salt as a catalyst, ion-metathesis gave organic soluble tetraalkylammonium cyanide which could migrate into the organic phase and react. Starks' findings initiated the development of phase-transfer catalysis for a range of reactions. The method has repeatedly been noted for its scalability and ease of use.[3]



Scheme 4: Influence of an ammonium salt on the biphasic alkylation of cyanide.

1.1.2. Mechanisms of PTC

In Starks' cyanide alkylation, the quaternary ammonium salt is believed to undergo counterion metathesis with sodium cyanide in the aqueous phase to give the ammonium-cyanide salt, which migrates into the organic phase where it can react with the alkyl halide.[4] While this mechanism is applicable to a number of quaternary ammonium salt catalysed reactions, the mechanism of phase

transfer catalysis has proven to be much more complicated and highly specific to the reaction in question.[5]

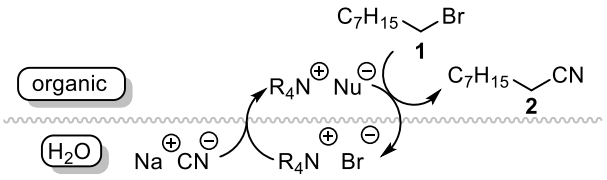


Figure 1: The extractive mechanism of phase-transfer catalysis.

Starks' mechanism, known as the 'extractive' mechanism, is typical of nucleophiles which are fully ionised and therefore partitioned into the aqueous phase (Figure 1).[5] This applies to metal salts (e.g. NaCN, NaN_3) and also low pKa nucleophiles (e.g. carboxylic acids) that are fully deprotonated by an aqueous base.

For pro-nucleophiles with higher pKa values (16-23) an 'interfacial' mechanism as proposed by Makosza is commonly implicated (Figure 2).[6] In the interfacial mechanism, the quaternary ammonium salt never enters the organic phase. Instead, an equilibrium concentration of the deprotonated pro-nucleophile is formed at the interface of the two phases and is extracted into the organic phase following counterion metathesis with the catalyst. Interfacial reactions show a strong rate dependence on stirring speed since faster stirring increases the interfacial area.

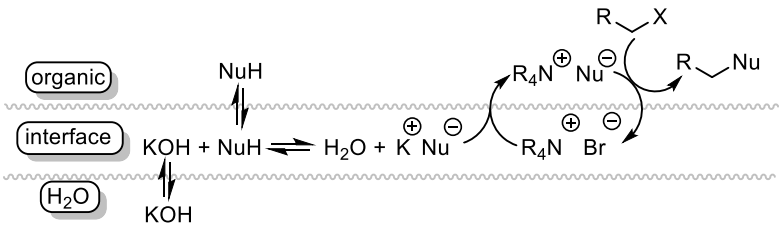


Figure 2: The interfacial mechanism of phase transfer catalysis.

For very weakly acidic substrates (pKa > 23) a variant of the extractive mechanism can operate (Figure 3). The catalyst extracts a hydroxide ion into the organic phase where its basicity is enhanced

by desolvation.[7, 8] The hydroxide extraction mechanism has been used to explain how reactions such as the isomerisation of allylbenzene (**3**) (pKa = 34) can occur using hydroxide bases.

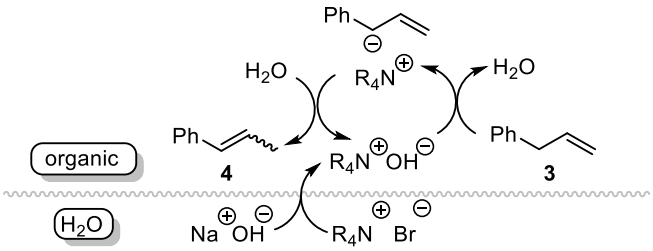
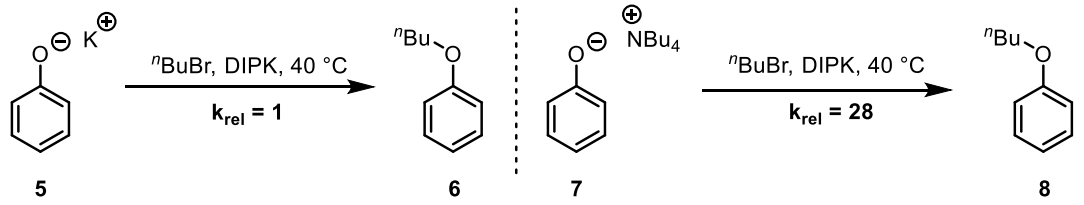


Figure 3: The hydroxide extractive mechanism of phase transfer catalysis.

Phase transfer catalysis is also known to increase the rate of the intrinsic rate of reaction of the electrophile (Scheme 5).[5] Tetraalkylammonium salts are large, charge-diffuse cations that interact weakly with their counteranions. For example, the tetrabutylammonium cation is much larger than the potassium cation (4.37 vs. 1.33 Å) and has a lower interaction energy with anions.[9] A consequence of this is that the nucleophile is more reactive and the reaction with the electrophile is faster. This effect was quantified by Denmark and co-workers studying the counterion influence of the rate of alkylation of phenoxide with *n*-butyl bromide. The reaction of tetrabutylammonium phenoxide (**7**) was found to be 28 times faster than that of potassium phenoxide (**5**).

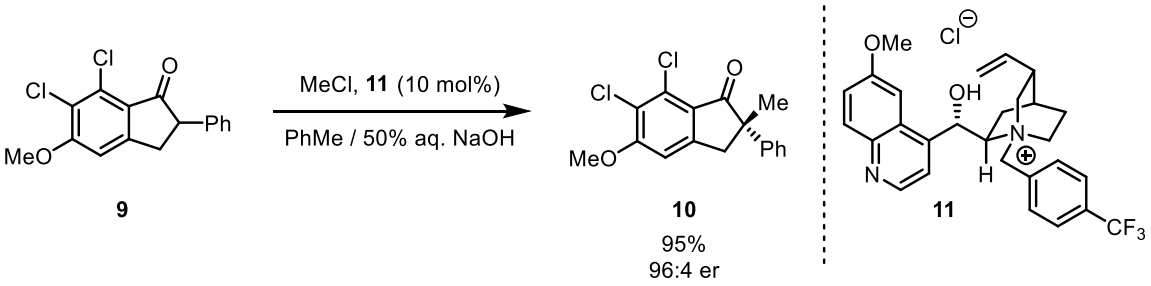


Scheme 5: Counterion dependence of the rate of alkylation of phenolates.

1.1.3. Seminal Examples of Enantioselective PTC

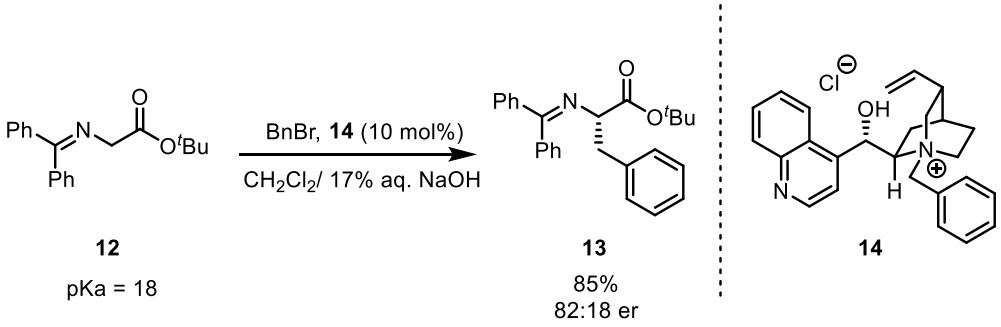
Several studies throughout the 1970s investigated enantioselective reactions using chiral ammonium salts as phase-transfer catalysts.[10-15] Enantioselectivity was poor in every case, but the principle of inducing asymmetry through ion-pairing was unambiguously demonstrated. Dolling and co-workers reported a breakthrough in 1984 in which an indanone derivative (**9**) was alkylated in

95% yield and 96:4 er using a cinchonine-based phase-transfer catalyst (**11**) (Scheme 6).[16] This was the first highly enantioselective cation-mediated enantioselective transformation, the first highly enantioselective catalytic alkylation and at the time a rare example of efficient asymmetric catalysis.



Scheme 6: Enantioselective PTC alkylation of an indanone (**9**).

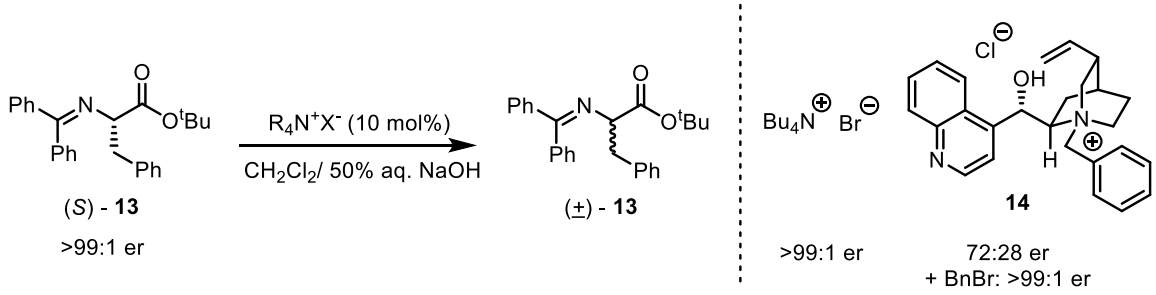
Another key development came 5 years later when O'Donnell reported the enantioselective alkylation of benzophenone imine protected glycine esters (**12**) (Scheme 7).[17] This extended the scope of enantioselective PTC to acyclic enolates and enabled the synthesis of valuable unnatural amino-acids in up to 85% yield and 82:18 er. Protecting the primary amine functionality as the benzophenone imine served to prevent unwanted *N*-alkylation and also lower the pKa of the α-proton by formation of a stabilised aza-allyl anion.[18] Crucially, the monoalkylated product had a pKa roughly 4 units higher than that of the starting material, preventing double alkylation and minimising product racemisation. The alkylation of O'Donnell's imine remains one of the most important applications of enantioselective PTC and has since been adopted as a benchmarking reaction when testing novel phase-transfer catalysts.[19, 20]



Scheme 7: Enantioselective PTC synthesis of α-amino acids.

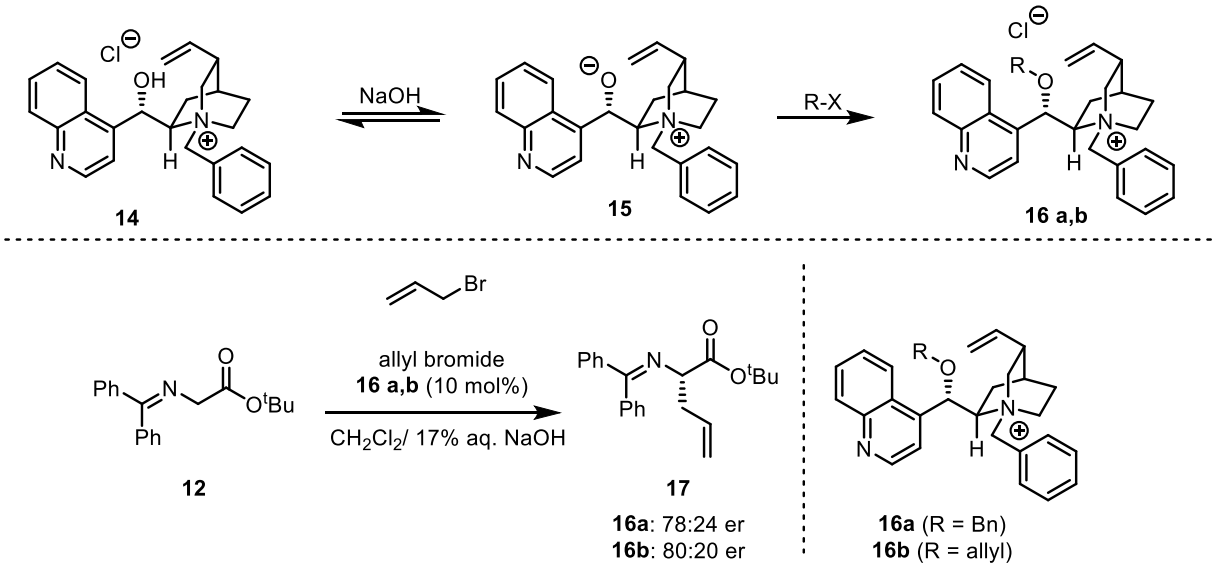
1.1.4. Developments in Chiral Phase-Transfer Catalyst Design

A subsequent study by O'Donnell investigated product racemisation in the presence of different ammonium salt catalysts (Scheme 8).[21] In this work, the enantiopure monoalkylated product (**13**) was stirred in biphasic CH_2Cl_2-aqueous sodium hydroxide and the er of the product was monitored over time. No racemisation was observed in the absence of catalyst or when using TBAB. When the experiment was repeated using *N*-benzylcinchonidinium chloride (**14**), the er dropped to 72:28 over 10 hours.



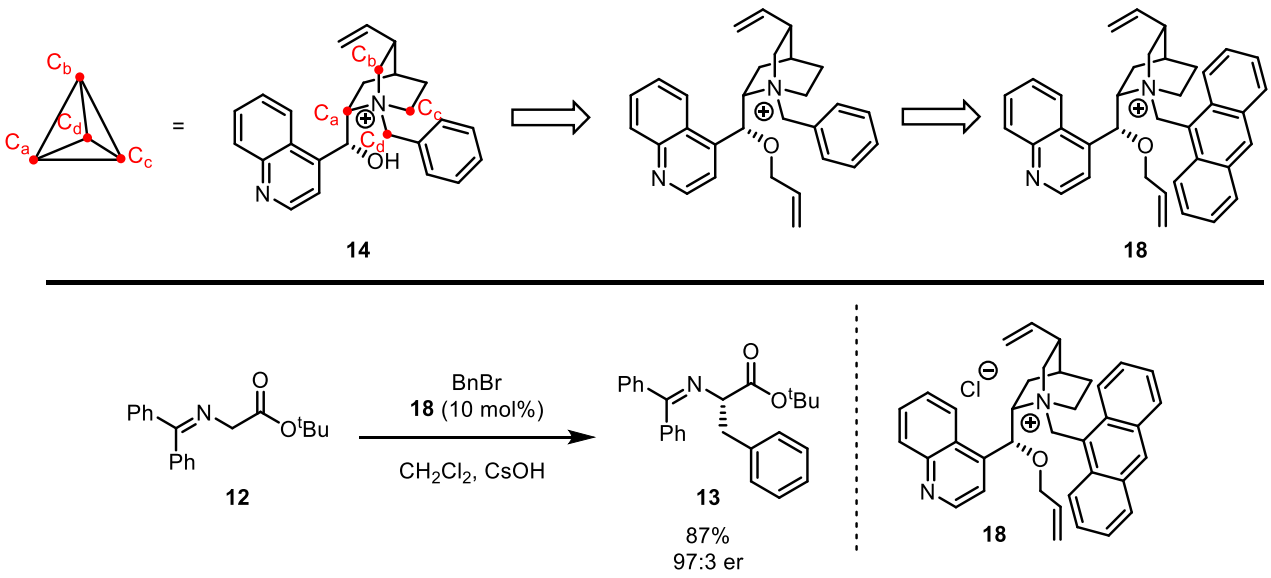
Scheme 8: Effect of ammonium salts on the optical stability of protected glycine imines under basic conditions.

These observations were explained by the deprotonation of the catalyst to form a zwitterion (**15**) that acts as an organic soluble base capable of racemising the product (Scheme 9). In the case of TBAB, which has no β-hydroxy substituent, zwitterion formation is impossible, so no racemisation occurred. The fact that no racemisation occurred with *N*-benzylcinchonidinium chloride (**14**) in the presence of benzyl bromide was attributed to *in situ O*-alkylation of the catalyst which prevented zwitterion formation. It was found that, under the reaction conditions, the catalyst was rapidly alkylated on the oxygen atom to give what was suspected to be the true catalyst. This was evidenced by the identical performance of both the *OH* and *O*-benzyl catalysts in PTC alkylation. Examination of different *O*-substituents ultimately led to the discovery of *N*-benzyl-*O*-allylcinchoninium chloride (**16b**) as a slightly improved catalyst.



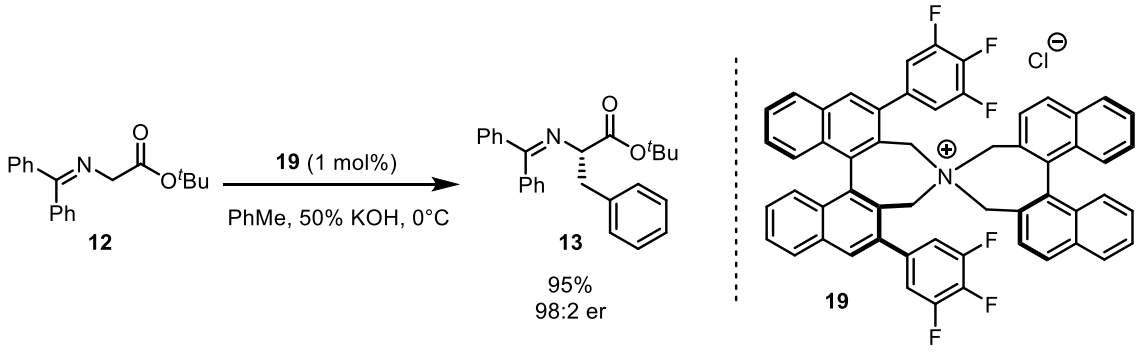
Scheme 9: Top: Zwitterion formation and in situ *O*-alkylation of *N*-benzylquinidinium salt. Bottom: Improved catalyst for the enantioselective alkylation of protected glycine (**12**).

To explain the structural requirements required to achieve high enantioselectivity, Corey introduced a model that considers a tetrahedron centred around the quaternary nitrogen centre (Scheme 10).[22] Corey proposed that in an ideal catalyst, 3 faces of the tetrahedron should be sterically encumbered to prevent close contact of the anion and the only accessible face should provide a suitable chiral environment for asymmetric induction. In cinchonidine-derived phase-transfer catalysts, binding was proposed to occur predominantly on the C_a-C_b-C_d face. Binding on the C_a-C_b-C_c face is impossible due to the quinuclidine backbone and binding on the remaining faces occurs to a lesser degree and is detrimental to the enantioselectivity. Reasoning that the *O*-allylation sufficiently blocked the C_a-C_c-C_d face, contemporaneously with Lygo,[23] Corey introduced a bulky anthracenylmethyl group that was shown by X-ray crystallographic analysis to block the C_b-C_c-C_d face. In line with the hypothesis, the newly synthesized catalyst showed improved enantioselectivity in O'Donnell's alkylation reaction to give the product in 97:3 er. Although Corey's model would be extremely challenging to validate experimentally, considering faces surrounding a central tetrahedron has informed the design of subsequent phase-transfer catalysts.[24, 25]



Scheme 10: Top: Design logic for improved phase transfer catalyst. Bottom: Improved phase transfer catalyst (**18**) for the enantioselective alkylation of protected glycine (**12**).

In 1999 Maruoka and co-workers reported BINOL-derived spiroammonium salts (**19**) as highly enantioselective catalysts for the O'Donnell alkylation (Scheme 11).[26] The key to the success of these catalysts was to exploit C_2 symmetry as a design element, which served to minimise the number of different chiral environments for anion binding. Aromatic groups at the binaphthalene *C*3/3' position were found to be essential for achieving high enantioselectivity. Due to the absence of β-hydrogens, the catalysts were not prone to Hofmann elimination and could therefore be used at a catalyst loading of only 1 mol%. In later work it was found that simplified catalysts, where the unsubstituted binaphthalene system was replaced by simple alkyl groups, were equally effective.[27]



Scheme 11: Maruoka's spiroammonium salt for the enantioselective alkylation of protected glycine (**12**).

1.2. Cation-Mediated Kinetic Resolution of BINOLs

1.2.1. Introduction: Catalytic Enantioselective Synthesis of Atropisomers

Axial Chirality and Atropisomerism

Although point chirality is the most common cause of chirality in organic molecules, chirality is a geometrical property that can be present even in the absence of sp^3 centres.[28] For example, enantiomers of certain allenes (**21**) and spiro compounds (**22**) can be distinguished by the orientation of groups around a hypothetical axis; hence this form of stereogenicity is termed axial chirality (Figure 4).

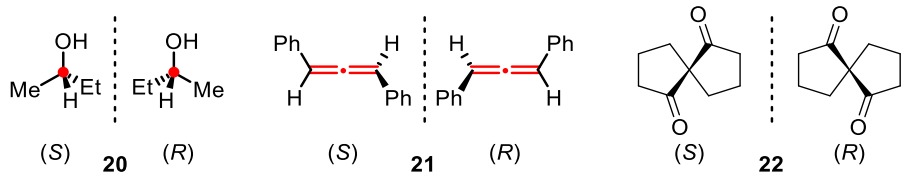


Figure 4: Representative point chiral (left) and axially chiral (centre, right) molecules.

Axial chirality can often be observed as a consequence of conformation; atropisomers are conformational isomers in which the rotational barrier is sufficiently high as to allow separation of stereoisomers (Figure 5).[29] As defined by Oki, atropisomers undergo thermal racemisation with a half-life of >1000 s at a defined temperature. The rotational barrier required to meet Oki's definition therefore varies with temperature. For example, atropisomerism at 300 K requires an energy barrier to bond inversion of >23.3 kcal mol^{-1}.

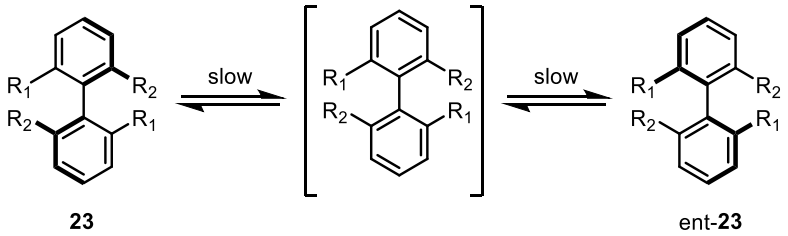


Figure 5: Generalised depiction of atropisomer interconversion.

Atropisomerism is most commonly observed between two σ-bonded π-systems where bulky substituents in close proximity to the axis lead to high rotational barriers. Examples of atropisomeric molecules include biaryls (**24**),[30] anilides (**25**),[31] carboxamides (**26**) [32] and diarylamines (**27**) (Figure 6).[33] Atropisomerism has been exploited as a design element in a large number of enantioselective catalysts, and has been encountered in drug discovery as in the case of KRas inhibitor AMG 510 (**28**), and in natural products such as marinopyrrole A (**29**).[34, 35]

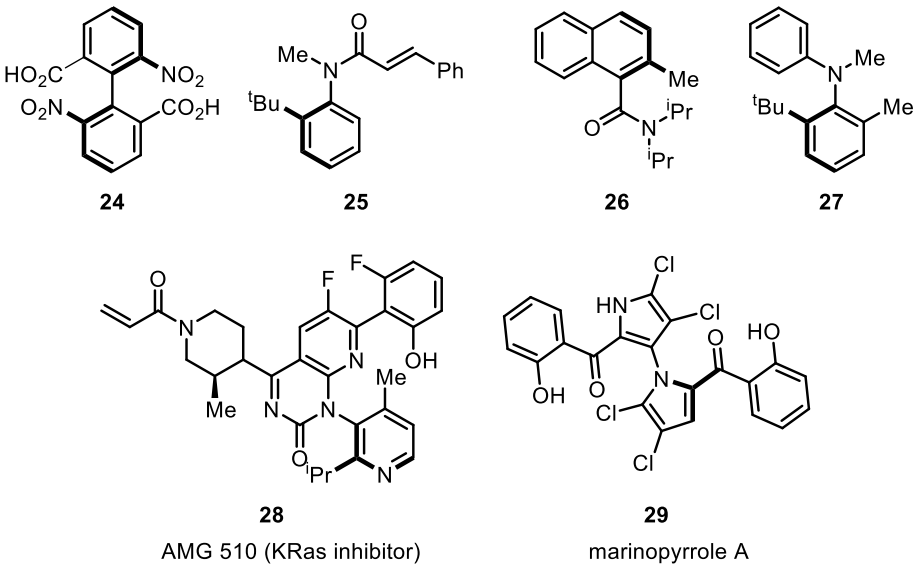


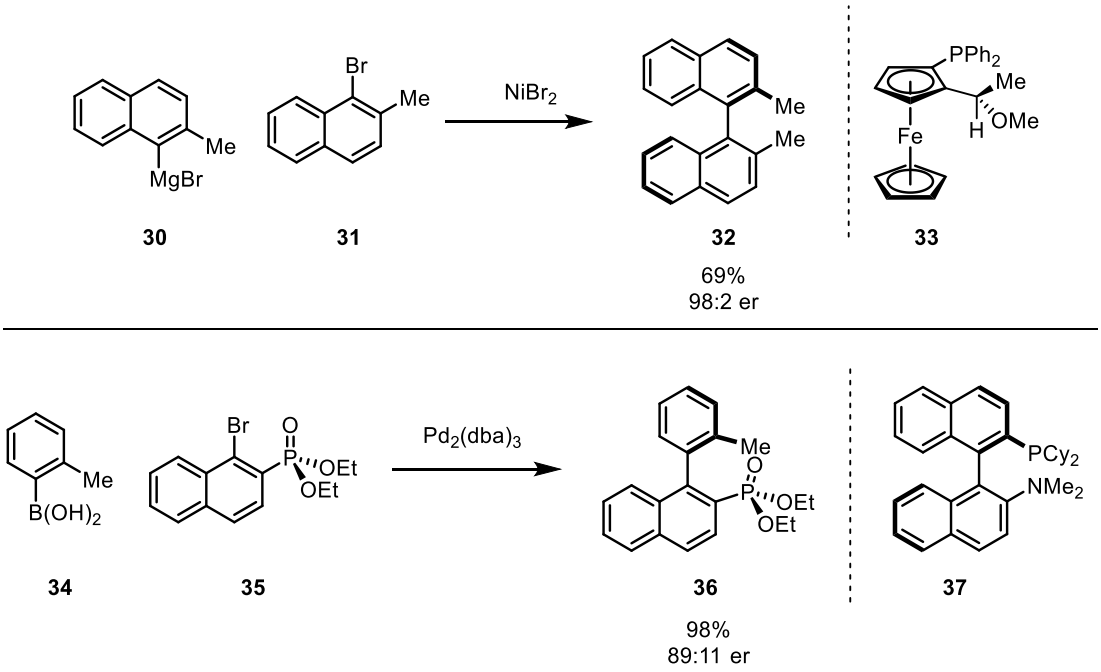
Figure 6: Examples of atropisomeric molecules.

Many different methods for the preparation of atropisomers have been reported over several decades.[36, 37] Accordingly, this introduction will not comprehensively cover the field but instead highlight different strategies for the catalytic enantioselective synthesis of atropisomers using selected illustrative examples.

Biaryl Bond Forming Reactions

Owing to the prevalence of cross-coupling reactions, biaryl bond forming reactions are arguably the most intuitive disconnection when considering biaryl atropisomers. The challenge of atropselective biaryl bond formation was first addressed successfully by Ito in 1988 using a nickel catalysed Kumada coupling (Scheme 12, top).[38] By employing a planar chiral *P,O* ligand (**33**), cross coupling of naphthyl

Grignard reagent **30** with naphthyl bromide **31** was achieved in an impressive 69% yield and 98:2 er.

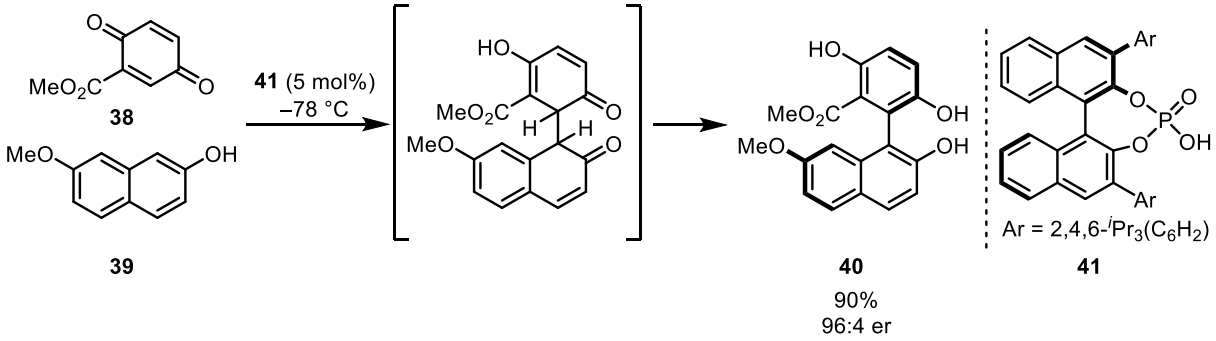


Scheme 12: Top: Enantioselective nickel catalysed Kumada coupling. Bottom: Enantioselective palladium catalysed Suzuki coupling.

An asymmetric Suzuki coupling was not forthcoming until over a decade later (Scheme 12, bottom).[39] The difficulty of achieving high enantioselectivity was compounded by the well-known sensitivity of the reaction to bulky *ortho* substituents.[40] Having previously reported that electron rich biaryl monophosphines promote the challenging reductive elimination step,[41] Buchwald and co-workers showed that atropisomeric *P,N* ligand **37** enabled the atropselective cross coupling of phosphite ester bearing naphthyl bromide **35** with a range of *ortho*-substituted phenylboronic acids (**34**). Subsequently, several groups have reported similarly competent metal/ligand systems for atropselective Suzuki coupling that have expanded the generality of the method.[37]

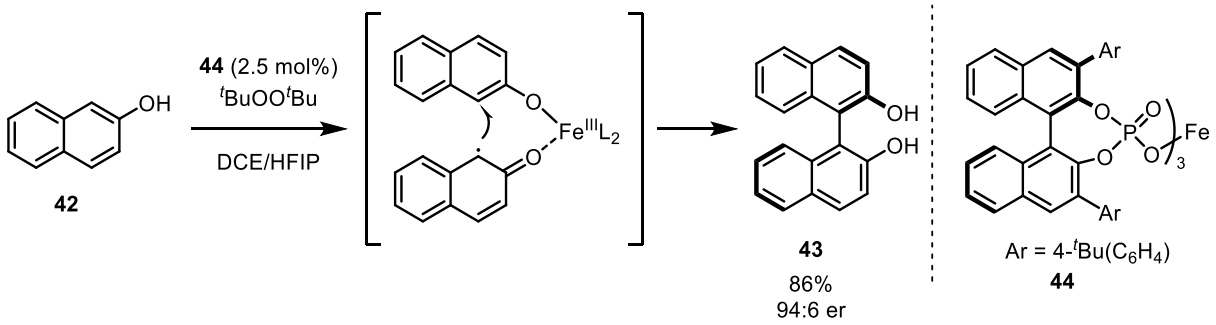
More recently, organocatalysis has emerged as a complementary method for atropselective biaryl bond formation. The Tan group has developed several chiral phosphoric acid mediated reactions in which electron rich aromatics are coupled with electrophilic arylating reagents to give

enantioenriched atropisomers.[42] A comparatively early example is the BINOL-phosphoric acid catalysed coupling of 2-naphthols (**39**) with quinones (**38**) (Scheme 13).[43] The reaction proceeds *via* chiral phosphoric acid (**41**) promoted addition of 2-naphthols to quinones to give a point chiral intermediate. Aromatization then occurs by tautomerization with point to axial chirality transfer to yield the product (**40**).



Scheme 13: Chiral phosphoric acid catalysed atropselective biaryl bond formation.

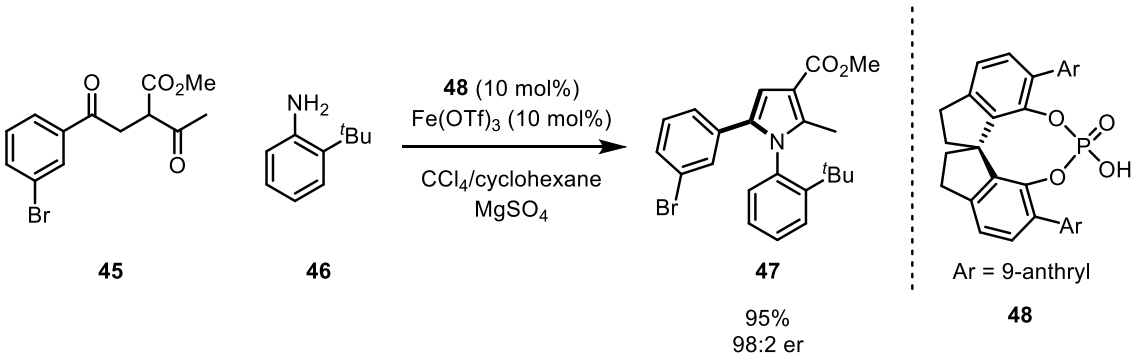
Another method for atropselective biaryl bond formation is oxidative phenol coupling. In these reactions, phenols are oxidized to transient phenoxy radicals by a high-oxidation state metal and undergo dimerization to give biaryls. One particularly successful example was reported recently by Pappo and Toste (Scheme 14).[44] In this case, a chiral iron (III) phosphate catalyst is used in combination with di-*tert*-butyl peroxide as a stoichiometric reoxidant for the dimerization of 2-naphthols (**42**) to BINOLs (**43**).



Scheme 14: Iron(III) catalysed enantioselective oxidative dimerization of 2-naphthols.

Atropselective Ring Formation

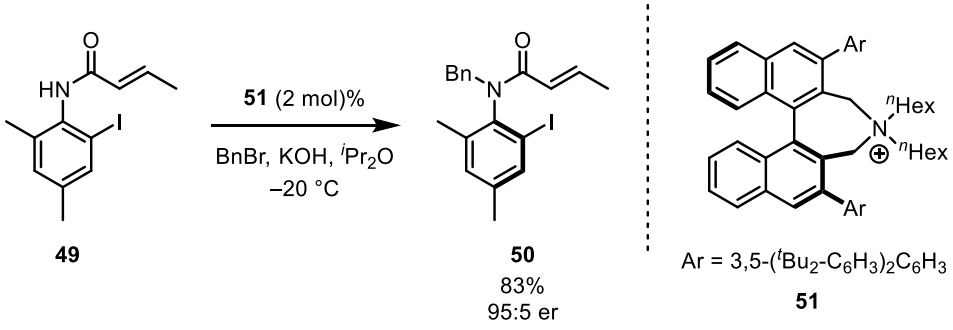
Tan and co-workers used an aromatic ring formation strategy for the synthesis of atropisomeric *N*-arylpyrroles (**47**) (Scheme 15).[45] A chiral phosphoric acid catalyst (**48**) in combination with catalytic iron (III) triflate was shown to promote the enantioselective condensation of aniline **46** with 1,4-diketone **45** to give atropisomeric *N*-arylpyrrole (**47**) in 95% yield and 98:2 er.



Scheme 15: Enantioselective synthesis of atropisomeric pyrroles.

Increasing Steric Hinderance Around a Low Barrier Axis

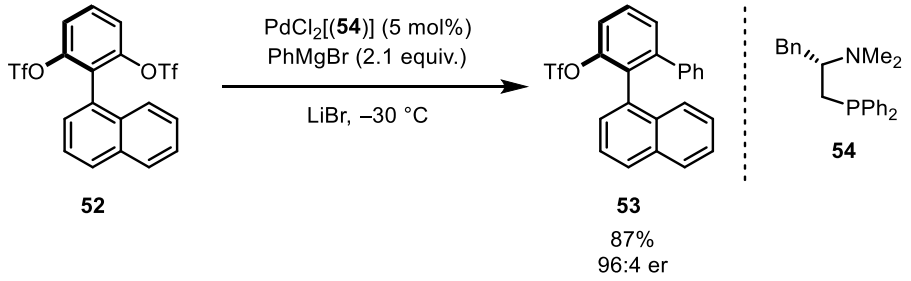
Another commonly employed strategy is introducing a substituent around a low barrier axis to give a conformationally stable product. Maruoka and co-workers adopted this approach for the synthesis of atropisomeric anilides (**50**) (Scheme 16).[46] In this reaction, the starting *N-H* anilide (**49**) has a low rotational barrier and racemises rapidly under the reaction conditions. Enantioselective *N*-alkylation with a chiral phase transfer catalyst (**51**) gave a higher barrier product (**50**) that was stable to racemisation at room temperature.



Scheme 16: Atropselective N-alkylation.

Desymmetrization

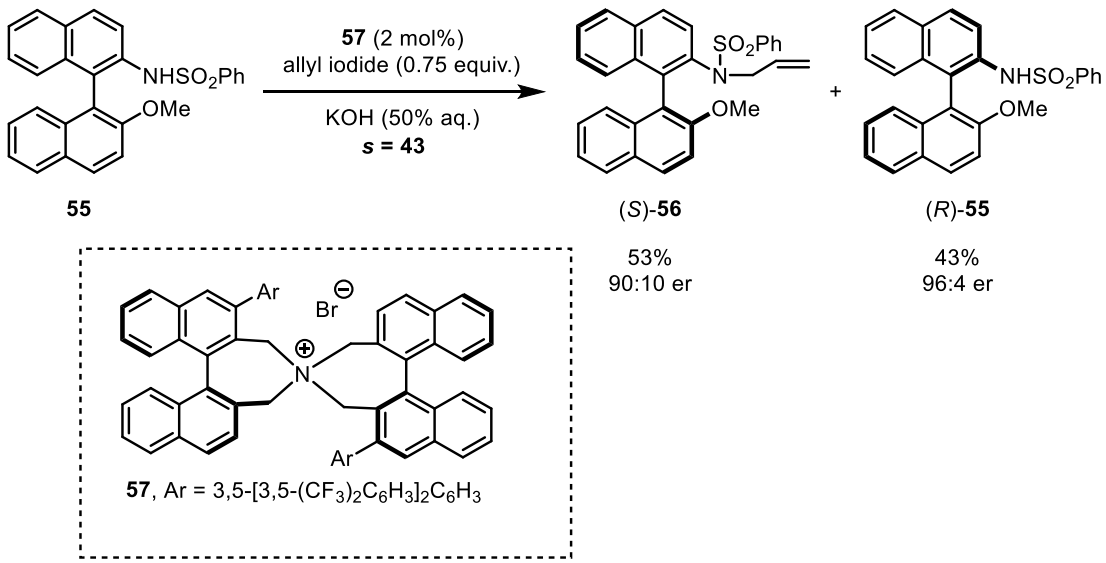
Desymmetrization of symmetrically substituted systems is another common strategy for the synthesis of atropisomers. This approach was pioneered by Hayashi and co-workers when they reported the enantioselective desymmetrization of high rotational barrier, symmetric biaryl bis-triflates (**52**) (Scheme 17).[47] Using a $PdCl_2$ chiral ligand (**54**) complex as the catalyst facilitated an enantioselective Kumada coupling with aryl Grignard reagents, in which the oxidative addition to the enantiotopic Ar-OTf bond was the enantiodetermining step. The enantioselectivity of the desymmetrization was found to be reinforced by a secondary kinetic resolution arising from the cross coupling of the remaining unreacted triflate.



Scheme 17: Palladium catalysed desymmetrizing atropselective Kumada coupling.

Kinetic Resolution

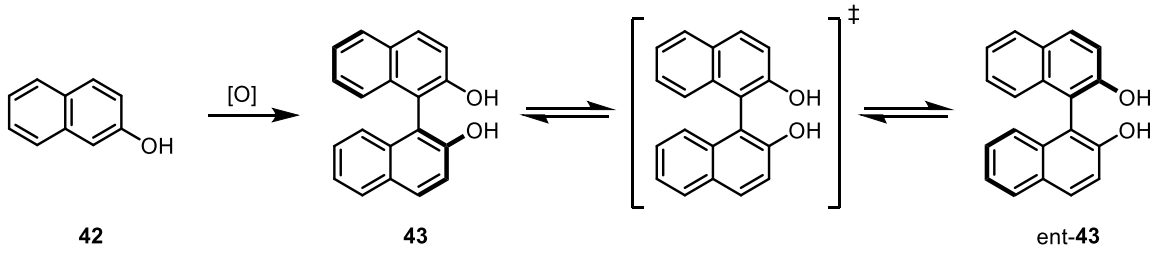
Kinetic resolution is a strategy that has been applied to the separation of high-barrier, non-symmetrical atropisomers. It has a unique advantage over other methods in that it can allow the re-isolation of starting material in extremely high enantioenrichment. One relevant example was reported by Maruoka in 2013, in which a chiral ammonium salt was employed as a phase transfer catalyst for the resolution of high-barrier biaryls by *N*-alkylation (Scheme 18).[48] In this reaction, one enantiomer of BINAM derivative **55** was found to react with a rate constant 43 times that of the other ($s = K_S/K_R = 43$), thereby enabling the re-isolation of the starting material in 43% yield and 96:4 er alongside the *N*-allylated product (**56**) in 53% yield and 90:10 er.



Scheme 18: Phase transfer catalysed kinetic resolution of axially chiral anilines.

BINOLs in Asymmetric Catalysis

BINOL (**43**) is a well-known atropisomeric biaryl from which many highly efficient chiral ligands and catalysts have been derived. Its history can be traced as far back as 1873 when it was synthesized by Dianin by treatment of 2-naphthol with iron (III) chloride although its atropisomeric properties were not studied until significantly later (Scheme 19).[49] Oxidative dimerization of 2-naphthol (**42**) remains the preferred method for the synthesis of BINOL (**43**). A variety of metal-based oxidants have been employed in both a stoichiometric and catalytic fashion. A copper catalyst employing air as the terminal oxidant has proven to be particularly efficient.[50]



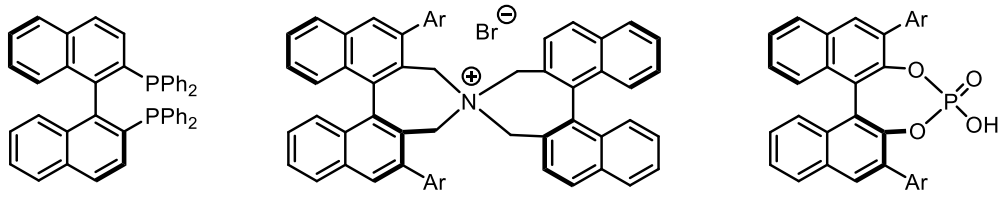
Scheme 19: Synthesis and atropisomerism of BINOL.

Owing to its well-defined C_2 symmetric chiral structure and high rotational barrier, BINOL (**43**) was popularised as a chiral building block for catalysis in 1980 when Noyori reported BINAP (**58**) as a

bidentate phosphine ligand for ruthenium-catalysed enantioselective hydrogenation.[51] The success of BINAP has subsequently inspired others to incorporate axial chirality as a design element in numerous other chiral phosphine ligands.[52]

BINOL-derived scaffolds have also been broadly applied in the field of organocatalysis. In 1999, Maruoka reported a novel class of quaternary ammonium salts (**19**) and demonstrated their efficacy in the asymmetric α-alkylation of glycine derivatives.[26] 'Maruoka catalysts' have since found application in a broad range of cation-mediated transformations.[53]

Chiral anions prepared from BINOL have also been shown to be extremely useful in catalysis. A seminal report from Terada in 2004 introduced BINOL derived phosphoric acids (**59**) as Brønsted acid catalysts for asymmetric Mannich reactions.[54] The field has rapidly expanded to develop BINOL phosphates as a remarkably general class of organocatalysts, finding applications as Brønsted acids, chiral counterions, ligands for metals and anionic phase transfer catalysts.[55] Other BINOL based organocatalysts have been developed and successfully applied, including chiral phosphines for nucleophilic catalysis,[56] chiral DMAP equivalents[57] and chiral tertiary amines (Figure 7).[58]



58 **19** **59**

Figure 7: BINOL derived chiral catalysts. Left: BINAP. Centre: 'Maruoka' phase transfer catalyst. Right: BINOL phosphoric acid.

BINOL derived catalysts are typically modified at *C*2 by transformation of the *OH* groups, at *C*3 using ortholithiation chemistry, or at *C*6 by electrophilic aromatic substitution (Figure 8). Modification of other positions on the BINOL scaffold are more difficult to achieve and can require resolution steps to obtain enantiopure material.[59] There are also relatively few strategies for the synthesis of non-C_2

symmetric BINOLs, where only one of the naphthalene rings is modified. Accordingly, strategies that could enable the synthesis of more diversely substituted BINOLs would be of value in the field of catalyst design.

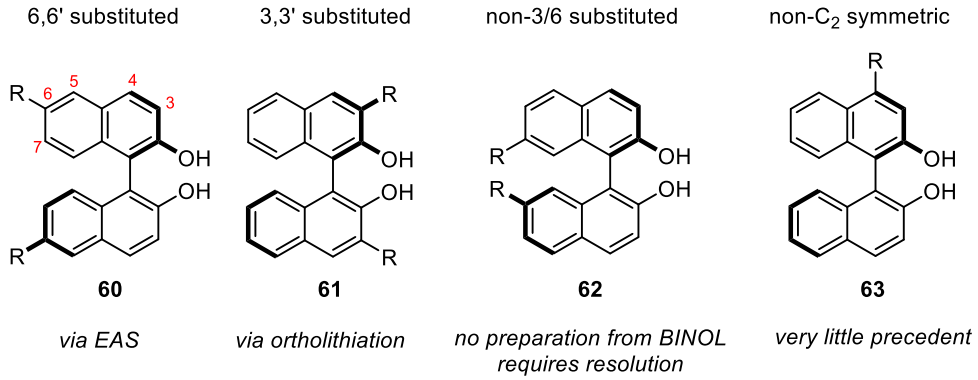
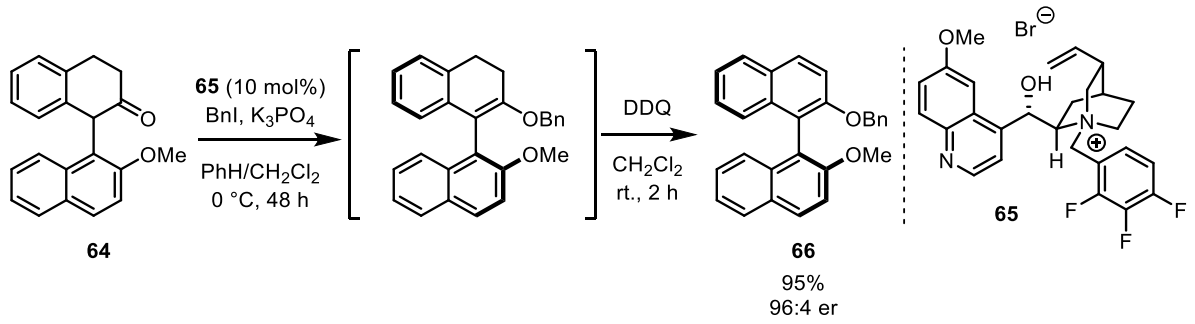


Figure 8: Modification points of BINOL.

1.2.2. Project Background

Previous work in the Smith Group by Dr. John Jolliffe sought to address the limited availability of substituted BINOLs (Scheme 20).[60] In this method, point chiral and racemic β-tetralones (**64**) undergo atropselective *O*-alkylation directed by a chiral ammonium salt catalyst (**65**). The resulting axially chiral enol ethers are then oxidised to the corresponding BINOL derivatives (**66**) with full retention of stereochemistry. This method allows access to non-C_2 symmetric BINOLs substituted at positions 3-7 in high yield and enantioenrichment.



Scheme 20: Enantioselective synthesis of BINOLs by phase-transfer catalysed O-alkylation.

Although this method is highly effective for the enantioselective synthesis of BINOLs, there were certain limitations we thought it would be beneficial to address. Firstly, the β-tetralone starting materials are unstable and prone to oxidation on storage, this led to severe practical difficulty in

their preparation and handling. Secondly, the synthetic route to the starting materials was not well suited to the preparation of valuable C_2 symmetric BINOLs. Thirdly, perhaps the major limitation of the method is the enantioselectivity; although the enantioselectivity is very good, BINOLs for asymmetric catalysis applications require extremely high (>99:1 er) enantioenrichment which is difficult to achieve using asymmetric catalysis. With these limitations in mind, we sought to develop an alternative strategy which would allow access to a broader range of substituted BINOLs in greater enantioenrichment.

1.2.3. Kinetic Resolution

With these limitations in mind, we proposed kinetic resolution of BINOLs as an alternative strategy (Figure 9). Kinetic resolution is a means of separating a mixture of enantiomers by exploiting a difference in their reaction rates when employing a chiral reagent or catalyst.[61] In a kinetic resolution, one enantiomer is preferentially reacted, thereby giving enantioenriched product and starting material. Since the enantioenrichment of both the product and starting material vary with conversion, enantioselectivity cannot be evaluated using either value alone, and instead the selectivity factor (*s*) is used. The selectivity factor is the ratio of the reaction rate constant of one enantiomer to that of the other and can be obtained from the er values of the starting material and product (assuming simple first order kinetics). In the proposed kinetic resolution, racemic BINOL monoethers (**67**) are alkylated under enantioselective phase transfer catalysis to give enantioenriched alkylated product (**68**) and recovered starting material (**67**).

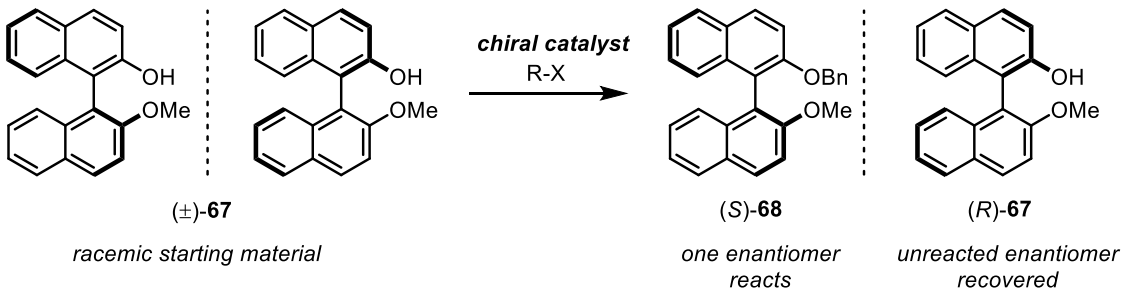


Figure 9: Proposed kinetic resolution of BINOLs.

Graphs representing a hypothetical kinetic resolution show how the ee value for starting material and product vary with conversion (Figure 10). Product ee is initially high, but as conversion increases more of the less reactive enantiomer is consumed leading to a decrease in product ee. At high conversion the product ee approaches 0% as both enantiomers are consumed. For the starting material the opposite is true; ee increases from 0% as the reactive enantiomer is converted to product and as the reaction approaches 100% conversion of starting material, the starting material ee nears 100%.

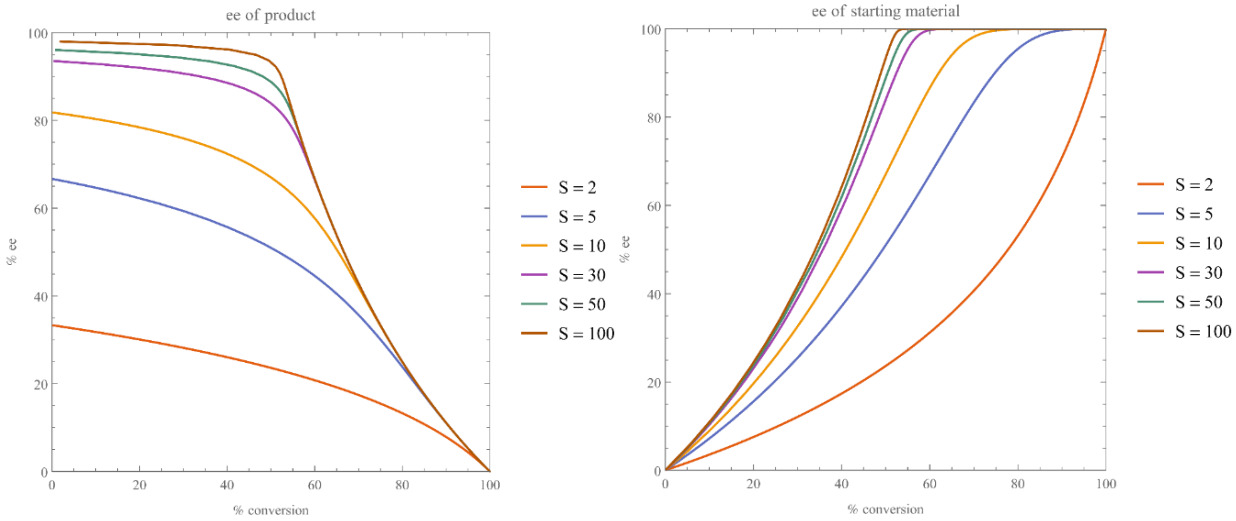


Figure 10: Left: ee of product vs. conversion. Right: ee of starting material vs. conversion.

Changing the *s* factor alters the steepness of the curve. In a relatively inefficient kinetic resolution (*s* = 5) product enantioenrichment is initially low and decreases gradually towards 0% with conversion. The starting material ee increases gradually and only approaches high enantioenrichment at high conversion. For a near perfect kinetic resolution (*s* = 100) the product

enantioenrichment is initially high and is maintained until 50% conversion, at which point it drops sharply with increasing values of conversion. The starting material ee increases sharply approaching 50% conversion and very high enantioenrichment is attained with just over 50% conversion.

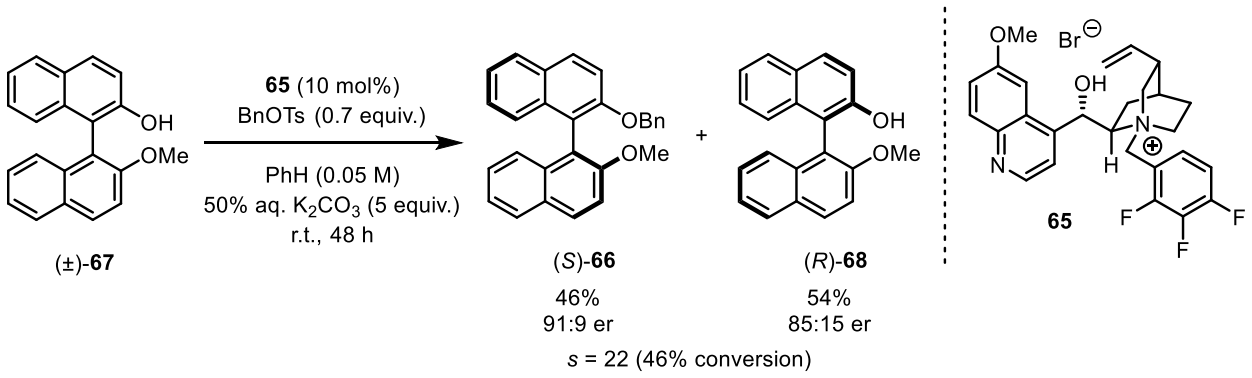
A major advantage of a kinetic resolution is that a highly enantioenriched starting material can, in theory, always be recovered by allowing the reaction to run to higher conversion. In such a case, the yield of recovered starting material is sacrificed to obtain greater enantioenrichment in starting material. Since product ee decreases with conversion extremely high values of *s* are required to obtain useful yields of product in high ee. Resultingly, kinetic resolution is more commonly used to recover starting materials rather than to isolate products.

We were attracted to kinetic resolution as a strategy towards our goal of preparing a broad range of BINOLs with enantioenrichment high enough for catalysis applications. The possibility of running reactions to higher conversion could potentially enable us to access BINOLs in very high ee even for more challenging substrates.

1.2.4. Reaction Optimization

Dr. John Jolliffe had previously shown that, under conditions similar to those of the original tetralone synthesis of BINOLs, kinetic resolution of MeBINOL (**67**) could be achieved with *s* = 24, enabling the re-isolation of (*R*)-MeBINOL (**67**) in 85:15 er at 46% conversion (Scheme 21). At this stage we sought to further increase *s* and conversion with the aim to ultimately resolve the starting material to near enantiomeric purity.

This project was carried out in collaboration with Dr. Tudor Balan, compounds and experimental data collected by Tudor Balan will be denoted **TBXX** to distinguish our relative contributions to this work.

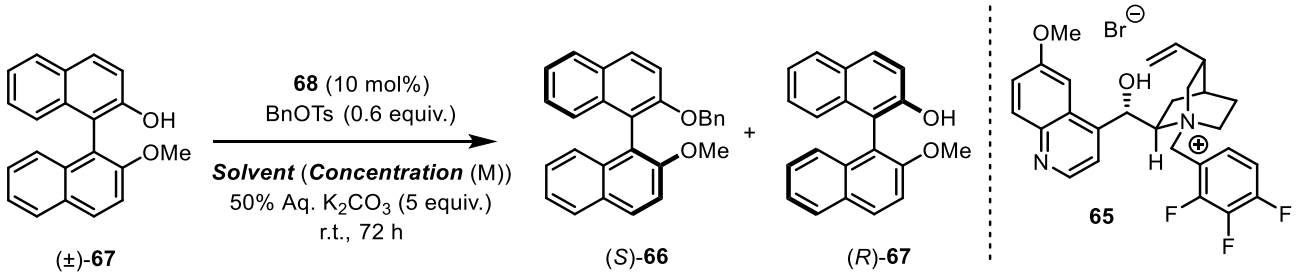


Scheme 21: Kinetic resolution of MeBINOL (**67**) developed by Dr. John Jolliffe.

Solvent Screening

Firstly, a range of solvents were evaluated (Table 1). Reaction aliquots were analysed by chiral stationary phase HPLC to give er values for the starting material and product. Assuming simple first order kinetics, conversion and *s* were calculated from the measured er values.[61] All subsequent optimization reactions were analysed in this manner. Aromatic hydrocarbons were found to be preferable for the reaction (entries 1-5); benzene, toluene, *m*-xylene, *p*-xylene and trifluorotoluene all gave similar *s* factors. Benzene was chosen as the optimal solvent due to having the highest conversion since the differences in *s* were likely within experimental error.

Halogenated solvents (entries 6,7) and ethers (entries 8-10) were found to be inferior. Increasing the concentration from 0.1 to 0.2 M (entry 11) significantly decreased conversion and *s*. Dilution to 0.05 M (entry 12) gave no discernible benefit; however, further dilution to 0.025 M (entry 13) increased *s* to 25. Although this improvement came at the expense of conversion (44% vs. 55% for 0.1M at 72 h), it was ultimately deemed beneficial.

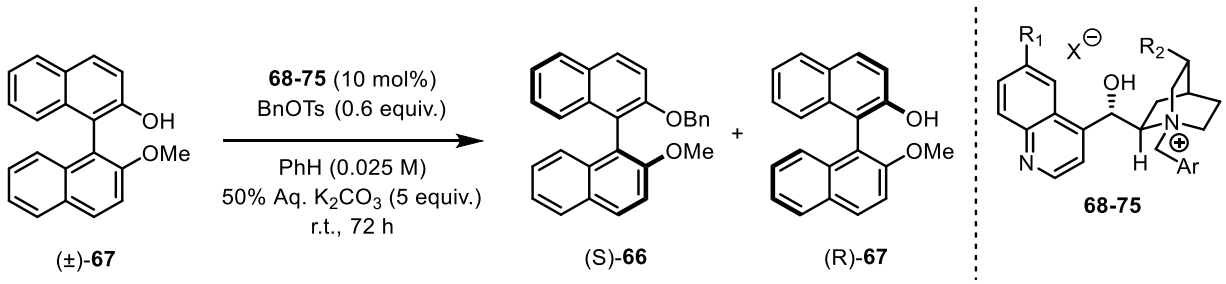


Entry	Solvent	conc. (M)	er (SM)	er (P)	Conversion (%)	*s*
1	PhH	0.1	94:6	88:12	55	21
2	PhMe	0.1	81:19	91:9	53	19
3	*m*-xylene	0.1	82:18	91.9	44	19
4	*p*-xylene	0.1	84:16	89:11	47	22
5	$PhCF_3$	0.1	60:40	86:14	22	8
6	CH_2Cl_2	0.1	67:33	86:14	31	9
7	$CHCl_3$	0.1	79:21	85:15	45	10
8	Et_2O	0.1	84:16	85:15	49	12
9	$^{i}Pr_2O$	0.1	64:36	81:19	31	5
10	^{t}BuOMe	0.1	81:19	85:15	47	11
11	PhH	0.2	80:20	87:13	41	12
12	PhH	0.05	81:19	91:9	43	19
13	PhH	0.025	84:16	92:8	44	25

Table 1: Effect of solvent on kinetic resolution of MeBINOL (**67**).

Catalyst Optimization

Having improved the solvent system for the reaction, we next examined alterations to the catalyst structure (Table 2). The 2,3,4-trifluorobenzyl group was found to be critical for good enantioselectivity; other electron deficient benzyl groups (**69**-**73**, entries 2-6) gave much lower values of *s*. Using cinchonine rather than quinine as the starting alkaloid improved *s* by 5 (**74**, entry 7). Further improvement was made by hydrogenating the alkene on the cinchonine backbone to give the optimal catalyst (**75)** with *s* = 32 and 46% conversion.

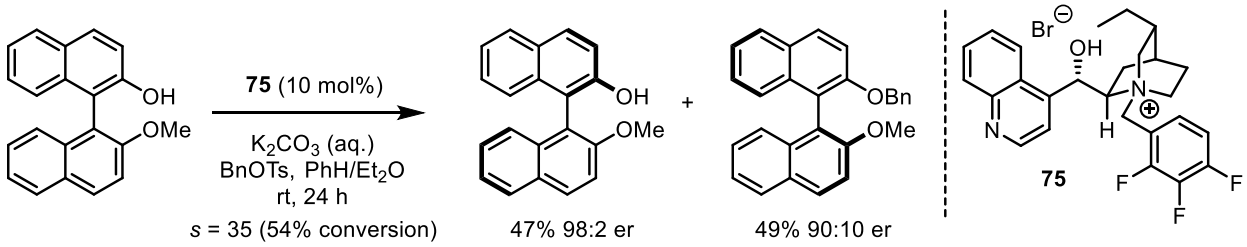


Entry	$R_4N^+X^-$	Ar =	R_1 =	R_2 =	er (SM)[a]	er (P)[a]	Conversion (%)[a]	*S*[b]
1	**68**	2,3,4-$F_3(C_6H_2)$	OMe	C_2H_3	84:16	92:8	44	25
2	**69**	3-F-(C_6H_4)	H	C_2H_3	69:31	74:26	40	5
3	**70**	C_6F_5	H	C_2H_3	67:33	81:19	36	6
4	**71**	4-(CF_3)-(C_6H_4)	H	C_2H_3	60:40	63:37	43	2
5	**72**	3,5-$(CF_3)_2$-(C_6H_3)	H	C_2H_3	62:38	72:28	35	3
6	**73**	4-(NO_2)-(C_6H_4)	H	C_2H_3	57:43	59:41	44	2
7	**74**	2,3,4-$F_3(C_6H_2)$	H	C_2H_3	93:7	83:7	43	30
8	**75**	2,3,4-$F_3(C_6H_2)$	H	C_2H_5	94:6	87:13	46	32

Table 2: Effect of ammonium salt of the MeBINOL kinetic resolution.

Increasing Reaction Conversion

To achieve a high degree of enantioenrichment in the recovered starting material we required conditions that could reliably drive the reaction to conversions greater than 50%. Experiments by Tudor Balan identified that performing the reaction in 9:1 PhMe-Et_2O and increasing the amount of benzyl tosylate to 1.5 equivalents delivered the required increase in the rate of reaction and increased the *s* factor to 35. Under the optimized reaction conditions, after 24 hours the product was isolated in 49% yield and 90:10 er and the starting material was recovered in 47% yield and 98:2 er.



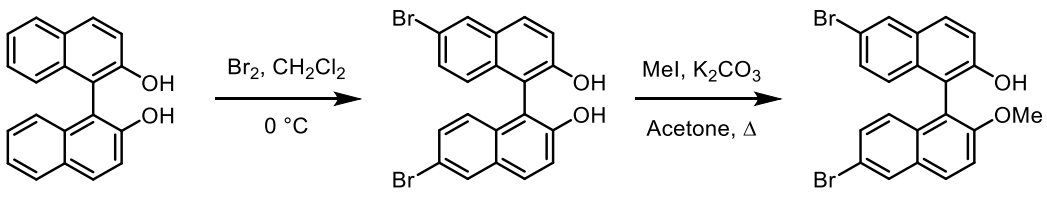
Scheme 22: Optimized conditions for the kinetic resolution of MeBINOL.

1.2.5. Synthesis of Racemic BINOLs

Having identified suitable conditions for the kinetic resolution of MeBINOL, we sought to examine the scope of the reaction. For this we required a library of substituted BINOLs. To enable our goal of preparing a range of C_2 and non- C_2 symmetric BINOLs, we would require an adaptable synthetic strategy for the preparation of diversely substituted analogues. At the outset we decided to exclude cross-coupling methods (e.g. Suzuki coupling) since cross couplings to form highly hindered biaryl systems such as BINOL are known to be exceedingly challenging.[40]

An ideal approach would be amenable to the synthesis of both C_2 and non- C_2 symmetric BINOLs and allow for structural diversification at a late stage to minimise the synthetic effort required for each substrate.

One substrate was prepared by treating BINOL (**43**) with bromine followed by methylation with methyl iodide to give the 6,6-dibrominated MeBINOL (**77**) (Scheme 23). We were attracted to the idea of transforming both *C-Br* bonds to other functionalities to obtain a range of 6,6 substituted BINOLs in just 1 step. Furthermore, if we could obtain BINOLs brominated at other positions, this approach could be generalised to obtain C_2-symmetric BINOLs substituted at every position. However, it was not obvious how we could extend this strategy to the more challenging non-C_2 symmetric BINOLs. Attempts at monobromination of BINOL would likely give a mixture of mono and di-brominated BINOLs. Assuming these were separable, monomethylation of the mono-bromo-BINOL would likely occur unselectively on either phenol to give a mixture of regioisomers.

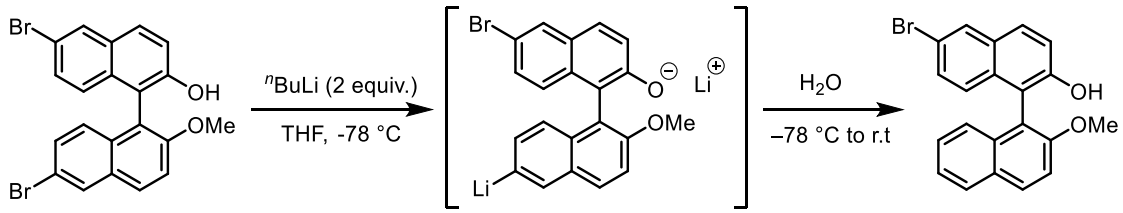


43 **76** 100% **77** 59%

Scheme 23: Dibromination and monomethylation of BINOL (**43**).

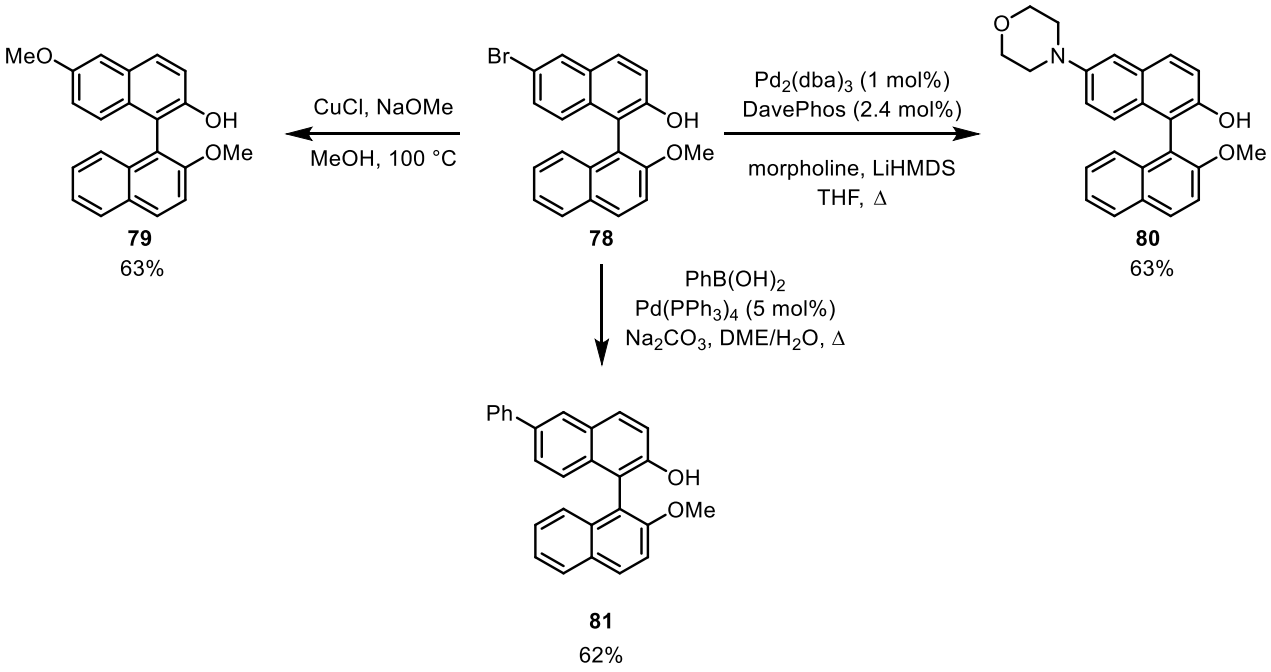
To solve this problem, we reasoned that it may be possible to differentiate the two bromine atoms by exploiting an electronic difference between the two naphthalene rings. Upon treatment with one equivalent of strong base, the unprotected phenol would be deprotonated and the top (as drawn) naphthalene ring should be rendered significantly more electron rich than the bottom. Reasoning that lithium-halogen exchange would be slower for the more electron rich aryl bromide, we expected that exchange of the bromine atom on the naphthoxide ring would be slower and the other bromine atom should selectively form the aryl lithium.

To test this hypothesis, monomethylated, dibrominated MeBINOL **77** was dissolved in THF and cooled to −78 °C. Two equivalents of ^{n}BuLi were added over the course of 1 hour and after stirring for a further hour at room temperature, the generated aryl lithium was quenched with water. Gratifyingly, the desired product (**78**) was obtained in 82% yield (Scheme 24). Importantly, the regioisomeric monobromide was not observed, indicating good selectivity in the lithium halogen exchange.



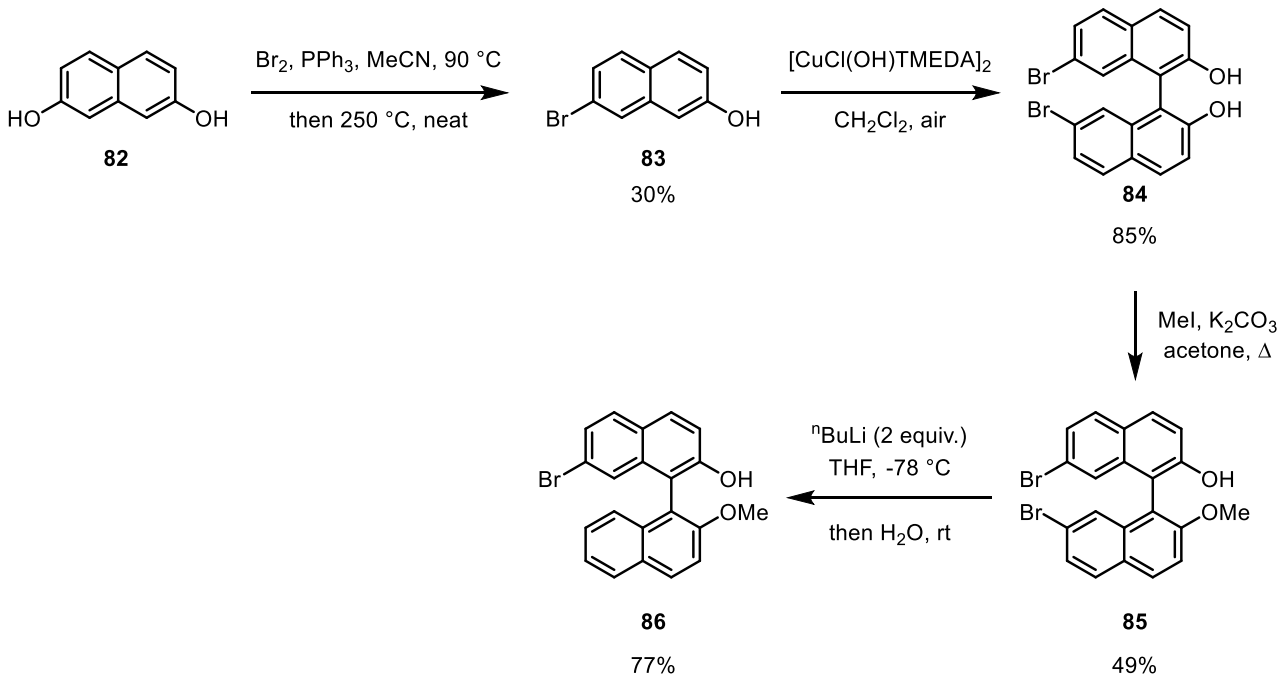
Scheme 24: Synthesis of non-C_2 symmetric BINOL by selective debromination.

With the non-C_2 symmetric brominated BINOL in hand we set about exploiting the *C-Br* bond for structural diversification (Scheme 25). Starting from the monobromo-BINOL **78**, a methoxy group was introduced by Ullmann etherification (**79**), a phenyl ring was introduced by a Suzuki coupling (**81**), and a morpholine ring was introduced by Buchwald-Hartwig amination (**80**).



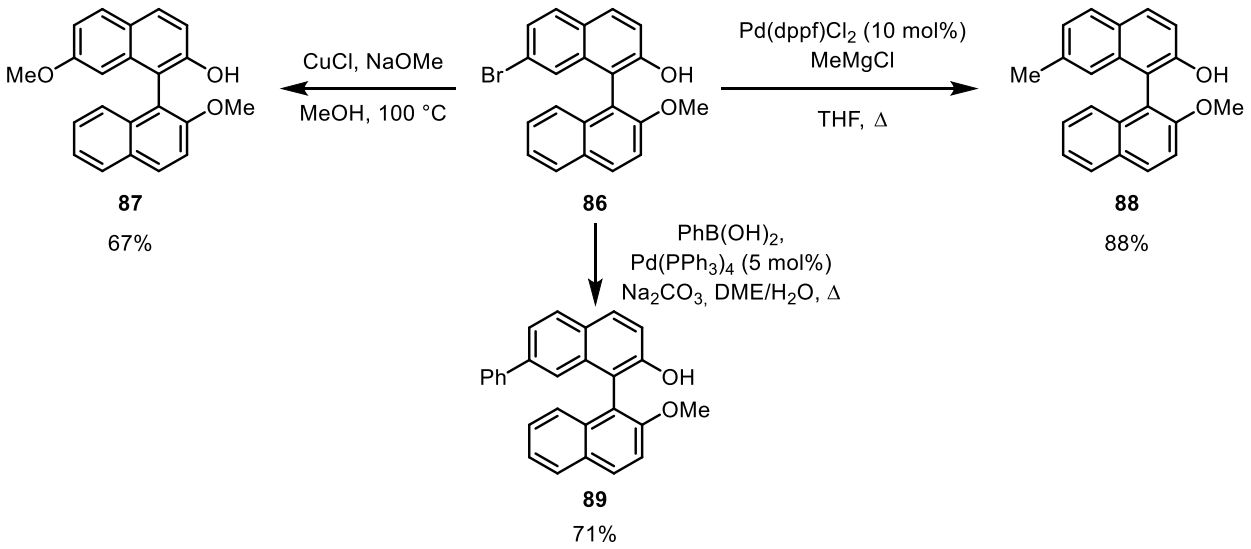
Scheme 25: Synthesis of C6-substituted BINOLs **79-81**.

Since the remaining positions on the naphthalene ring cannot be accessed by direct bromination, an alternative synthesis was required. In the case of the 7 position, 7-bromo-2-naphthol (**83**) was synthesised by heating bromotriphenylphosphonium bromide with 2,7-dihydroxynaphthalene (**82**) at 250 °C. Oxidative coupling using $[CuClOH(TMEDA)]_2$ as the catalyst and air as the stoichiometric oxidant afforded 7,7-dibromo-BINOL (**84**). Monomethylation and monodehalogenation afforded the C_2 and non C_2 symmetric bromo-BINOLs (**85** and **86** respectively) (Scheme 26).



Scheme 26: Synthesis of 7-Bromo-MeBINOL (**86**).

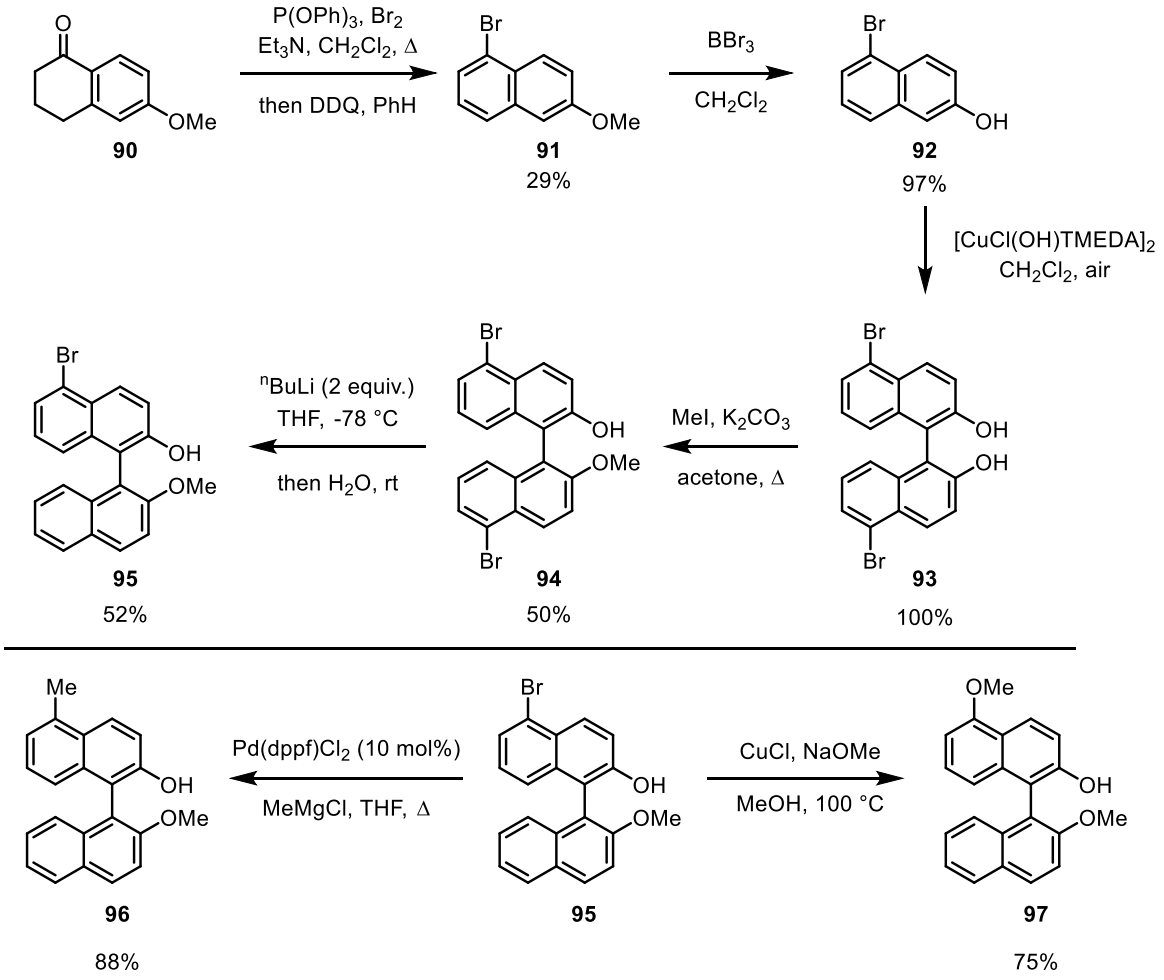
Diversification at the 7 position was achieved as before using a Suzuki coupling to introduce a phenyl group (**89**), an Ullmann coupling to introduce a methoxy group (**87**) and additionally a methyl group could be introduced (**88**) using a Kumada coupling (Scheme 27).



Scheme 27: Synthesis of 7-substituted MeBINOLs **87**-**89**.

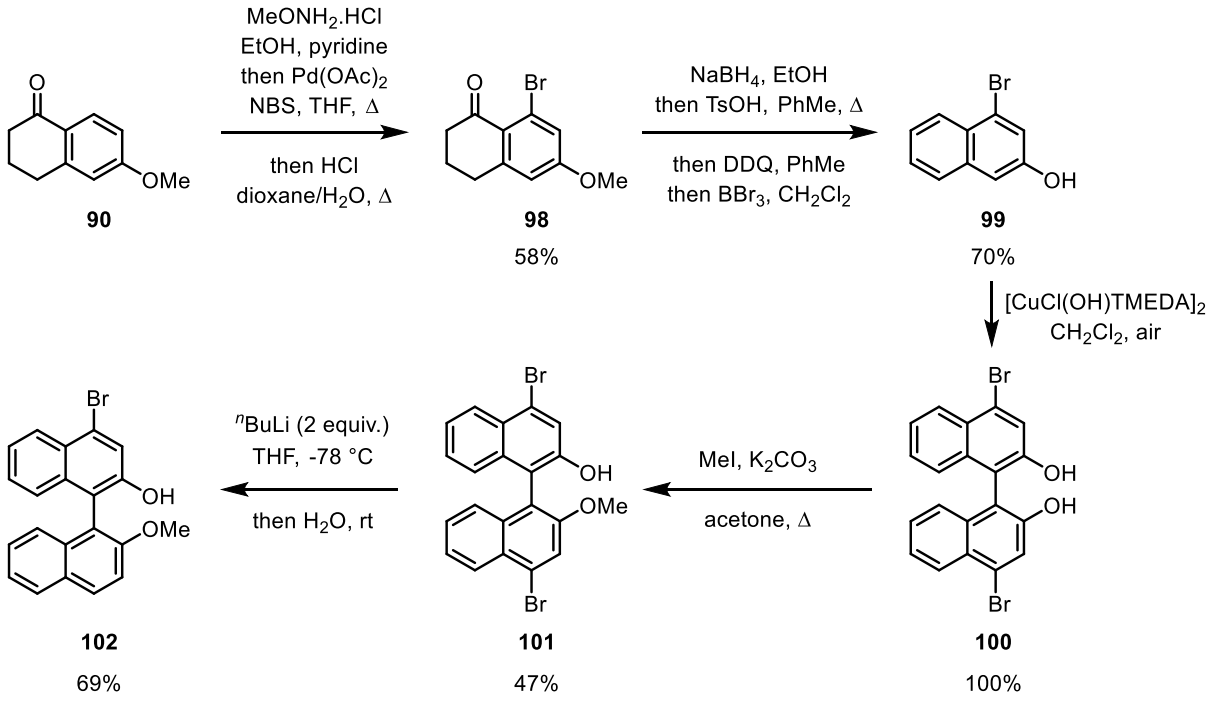
5-Bromo-2-naphthol (**92**) was prepared by conversion of 6-methoxy-1-tetralone (**90**) to vinyl bromide **91** with $P(OPh)_3$ and Br_2 followed by oxidation with DDQ and demethylation with BBr_3.

Dimerisation, monomethylation and monodebromination as before gave 5-bromo-MeBINOL (**95**) and 5,5'-dibromo-MeBINOL (**94**). Methyl (**96**) and methoxy (**97**) groups were introduced at the 5 position by Kumada and Ullmann couplings, respectively (Scheme 28).



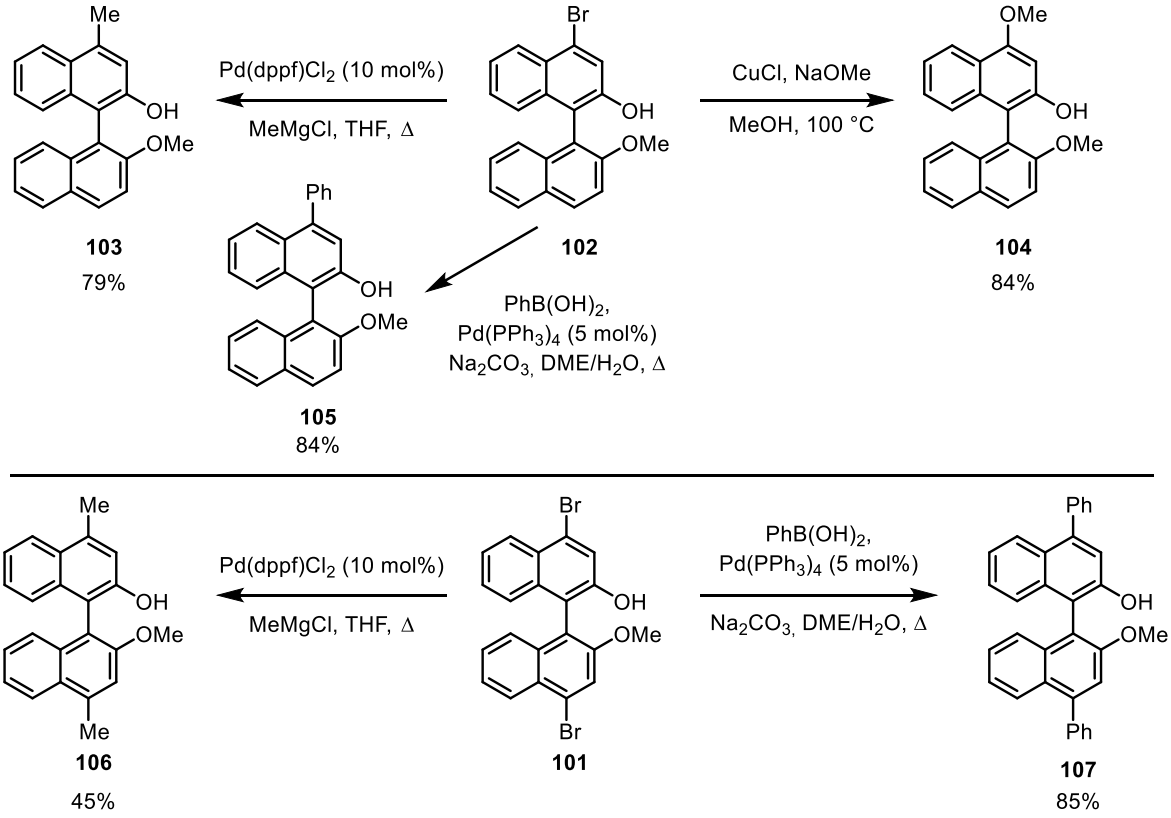
Scheme 28: Synthesis of 5-substituted MeBINOLs **95**-**97**.

Substituting at the 4 position was relatively challenging. To prepare 4-bromo-2-naphthol (**99**), 6-methoxy-1-tetralone (**90**) was converted to the oxime ether and brominated using the method of Sanford and co-workers.[62] Removal of the oxime ether in aqueous hydrochloric acid gave brominated tetralone **98**. Reduction of the ketone followed by acid catalysed elimination, oxidation with DDQ and finally demethylation with BBr_3 gave 4-bromo-2-naphthol (**99**). Dimerisation, monomethylation and monodebromination gave 4-bromo-MeBINOL (**102**) and 4,4'-dibromo-MeBINOL (**101**) (Scheme 29).



Scheme 29: Synthesis of 4-bromo-MeBINOL (**102**).

From here methyl (**103**), phenyl (**105**) and methoxy (**104**) groups could be incorporated at the 4 position and 4,4' substitution was achieved with methyl (**106**) and phenyl (**107**) groups (Scheme 30).

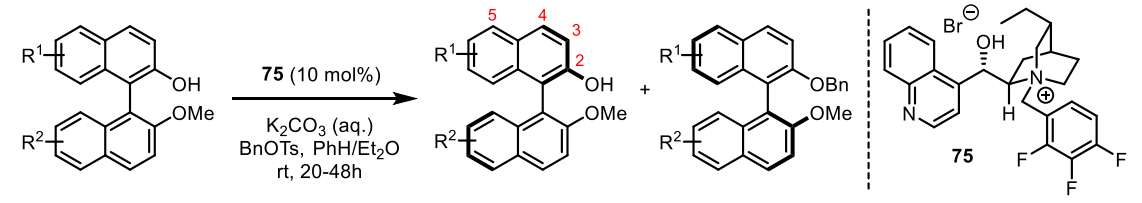


Scheme 30: Synthesis of 4 and 4,4'-substituted MeBINOLs **101**-**107**.

1.2.6. Reaction Scope

Kinetic resolution of our racemic MeBINOL library was performed on a 0.15 mmol scale (Scheme 31). Reaction times were varied from 20-48 hours to achieve sufficiently high conversion. Resolution of MeBINOL (**67**) proceeded as observed on optimization scale with an *s* factor of 35, enabling re-isolation of the starting material in 47% yield at 98:2 er at 54% conversion. Substitution of the 7-position with bromine (**86**, *s* = 28, >99:1 er at 58% conversion), methoxy (**87**, *s* = 34, 99:1 er at 56% conversion), methyl (**88**, *s* = 29, >99:1 er at 58% conversion) and phenyl (**89**, *s* = 30, 97:3 er at 54% conversion) could all be achieved while retaining high selectivity. 6-Methoxy (**79**, *s* = 37, >99:1 er at 56% conversion), 6-morpholino (**80**, *s* = 26, 99:1 er at 57% conversion), 6-phenyl (**81**, *s* = 28, 99:1 er at 57% conversion) and 6-bromo (**78**, *s* = 33, 99:1 er at 57% conversion) substituted MeBINOLs are all viable reaction substrates. The 5-position could also be substituted without compromising enantioselectivity: 5-methyl (**96**, *s* = 45, >99:1 er at 56% conversion) and 5-bromo (**95**, *s* = 31, 98:2 er at 55% conversion) MeBINOLs were both efficiently resolved. In the case of 5-methoxy-MeBINOL (**97**), where the *s* factor was somewhat lower (*s* = 16), good enantioenrichment in starting material could still be obtained simply by extending the reaction time to increase conversion (>99:1 er at 65% conversion at 30 hours), thus exemplifying the value of kinetic resolution when highly enantioenriched material is required. Introduction of functionality at the 4-position was found to have no detrimental effect on the reaction: methyl (**103**, *s* = 26, >99:1 er at 62% conversion), phenyl (**105**, *s* = 30 , 95:5 er at 53% conversion), methoxy (**104**, *s* = 26, 99:1 er at 58% conversion) and bromine (**102**, *s* = 26, 99:1 er at 58% conversion) substituents were all well tolerated. Finally, 4,4'-substituted MeBINOLs bearing phenyl (**106**, *s* = 16, 99:1 er at 62% conversion), methyl (**106**, *s* = 34, 99:1 er at 56% conversion) and bromine (**101**, *s* = 21, 93:7 er at 53% conversion) were all successful reaction substrates. 4,4'-Diphenyl-MeBINOL (**107**) gave slightly lower selectivity; but, as for 5-

methoxy-MeBINOL (**79**), high enantioenrichment in the recovered starting material could still be achieved by extending the reaction time.



s = 35, 54% conv.
67 98:2 er; 47% yield
66 (90:10 er; 49% yield)

s = 28, 58% conv.
86 99.5:0.5 er; 40% yield
108 (85:15 er; 53% yield)

s = 36, 55% conv.
87 99:1 er; 48% yield
109 (89:11 er; 52% yield)

s = 29, 58% conv.
88 99.5:0.5 er; 39% yield
110 (86:14 er; 56% yield)

s = 30, 54% conv.
89 97:3 er; 42% yield
111 (90:10 er; 50% yield)

s = 35, 57% conv.
79 99.5:0.5 er; 47% yield
112 (88:12 er; 57% yield)

s = 26, 57% conv.
80 99:1 er; 34% yield
113 (87:13 er; 47% yield)

s = 28, 57% conv.
81 99:1 er; 39% yield
114 (84:16 er; 56% yield)

s = 33, 57% conv.
78 99:1 er; 39% yield
115 (87:13 er; 49% yield)

s = 31, 59% conv.
96 99.5:0.5 er; 40% yield
116 (85:15 er; 57% yield)

s = 16, 65% conv.
97 99.5:0.5 er; 33% yield
117 (77:23 er; 59% yield)

s = 31, 55% conv.
95 98:2 er; 39% yield
118 (89:11 er; 48% yield)

s = 26, 62% conv.
103 >99.5:0.5 er; 33% yield
119 (81:19 er; 61% yield)

s = 30, 53% conv.
105 95:5 er; 46% yield
120 (91:9 er; 51% yield)

s = 26, 58% conv.
104 99:1 er; 34% yield
121 (85:15 er; 54% yield)

s = 26, 58% conv.
102 99:1 er; 40% yield
122 (86:14 er; 54% yield)

s = 16, 62% conv.
107 99:1 er; 33% yield
123 (80:20 er; 62% yield)

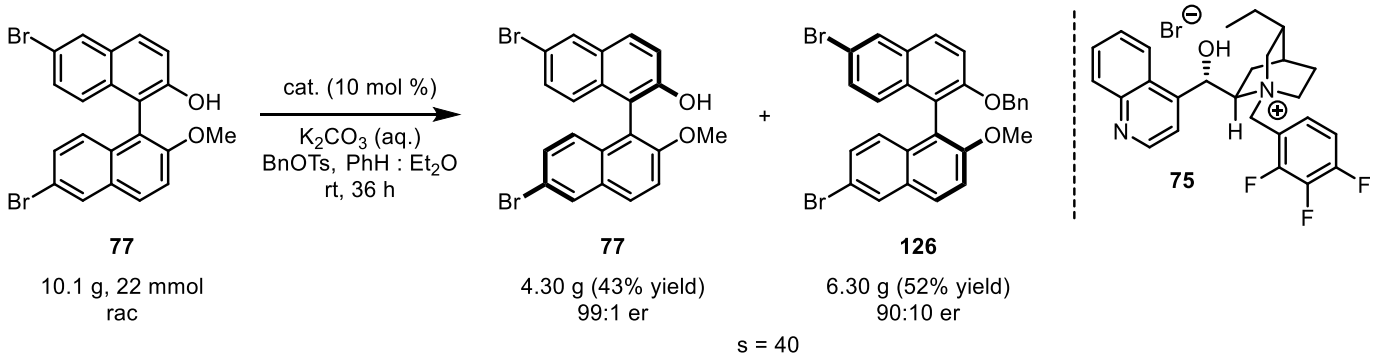
s = 33, 56% conv.
106 99:1 er; 39% yield
124 (88:12 er; 54% yield)

s = 21, 53% conv.
101 93:7 er; 45% yield
125 (88:12 er; 50% yield)

Scheme 31: Kinetic resolution of substituted MeBINOLs. Conversion and *s* were calculated from the er of the product and unreacted starting material. Yields and er refer to the isolated yield of the unreacted starting material. Yields and er in parentheses refer to the product.

1.2.7. Multi-Gram Scale Kinetic Resolution

Having demonstrated the broad applicability of our reaction on a range of different substrates, we next examined how our protocol may be applied to kinetic resolution on a multi-gram scale (Scheme 32). 6,6'-Dibromo-MeBINOL (**77**, 10.1 g, 22 mmol) was reacted using our optimized reaction conditions with no change in loading of catalyst, base, concentration, or electrophile. Practically, the only difference when scaling up from 0.15 mmol to 22 mmol was in the reaction vessel. Concerned by the well-known rate dependence of phase-transfer catalysed transformations on the rate of stirring, we opted to perform the scaled-up reaction in a 3-neck round-bottom flask equipped with an overhead stirrer to ensure sufficient agitation. After 36 hours the reaction proceeded to 54% conversion with an *s* factor of 40. As a result, 6.3 g of product (**126**, 42% yield, 90:10 er) was obtained and 4.3 g (**77**, 43% yield) of starting material was recovered with 99:1 er. This result clearly shows the utility of our reaction for the synthesis of large quantities of highly enantioenriched BINOLs.



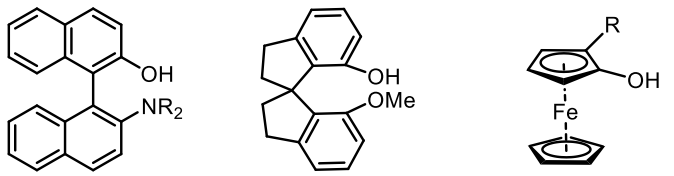
Scheme 32: Multi-gram scale kinetic resolution of 6,6'-dibromo MeBINOL (**77**).

1.2.8. Conclusion and Future Work

We have shown that enantioselective phase transfer catalysis is a simple, efficient, practical and scalable method for the kinetic resolution of BINOL monoethers. The reaction is general over a broad range of substituted BINOLs and enables re-isolation of the starting materials with enantioenrichment suitable for catalysis applications. We have also developed a synthetic approach

to C_2 and non-C_2 symmetric BINOLs, which in combination with the kinetic resolution protocol enables access to diversely substituted, previously unobtainable BINOLs in excellent enantioenrichment.

Future work could potentially expand the scope of the protocol to other systems (Figure 11). For example, resolution of the valuable chiral building blocks NOBIN (**127**) and SPINOL (**128**) could be possible under similar reaction conditions. Kinetic resolution of planar chiral ferrocene complexes (**129**) is another possibility.



127 NOBIN derivative

128 SPINOL monoether

129 planar chiral alcohol

Figure 11: Potential substrates for future kinetic resolution.

1.3. Cation-Mediated Enantioselective Dearomatization Reactions

The kinetic resolution of BINOLs can be described as an enantioselective *O*-functionalisation of a phenol. Considering naphtholate as an ambident nucleophile that can react on oxygen or carbon, we questioned if we could carry out an enantioselective *C*-functionalisation under similar reaction conditions (Figure 12). The proposed reaction would require formation of a quaternary stereocenter to prevent tautomerisation of the product and therefore serve to dearomatize the naphthalene ring. Catalytic enantioselective dearomatization is a vibrant research field that employs a range of catalytic systems.[63, 64] However, relatively few methods have employed chiral ammonium salts as catalysts.[65, 66] With this in mind we reasoned that enantioselective phase-transfer catalysis might offer a unique reactivity profile that could lead to valuable new dearomatization processes.

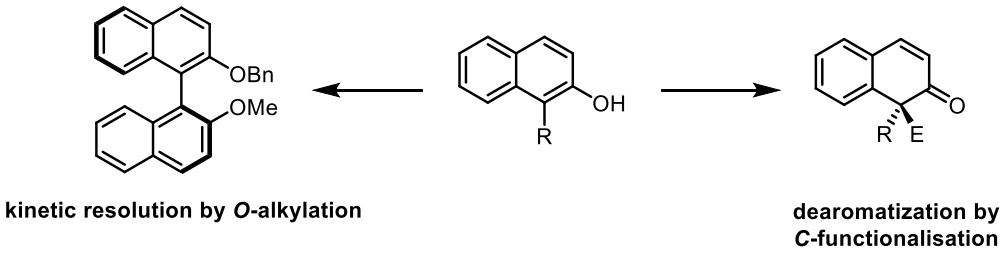


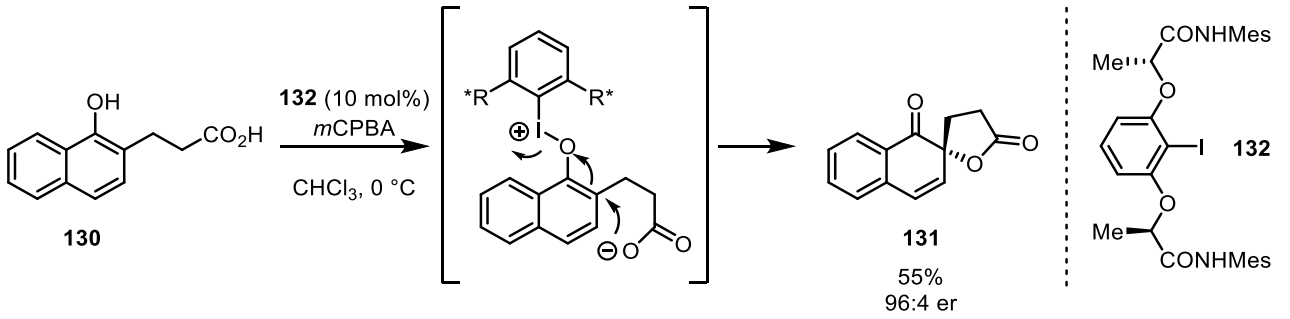
Figure 12: Proposed dearomatization by naphthol C-alkylation.

1.3.1. Introduction: Catalytic Enantioselective Dearomatization

Dearomatization of aromatic feedstock compounds is a long-established strategy for the synthesis of aliphatic ring systems.[67-69] Recent decades have seen growing interest in the development of catalytic enantioselective methods for dearomatization.[63, 70] This approach generates a quaternary stereocenter by necessity and typically leaves the dearomatized ring system with functionality intact for further elaboration. Accordingly, catalytic enantioselective dearomatization reactions have great potential for the synthesis of complex chiral ring systems.

Hypervalent Iodine Mediated Dearomatization

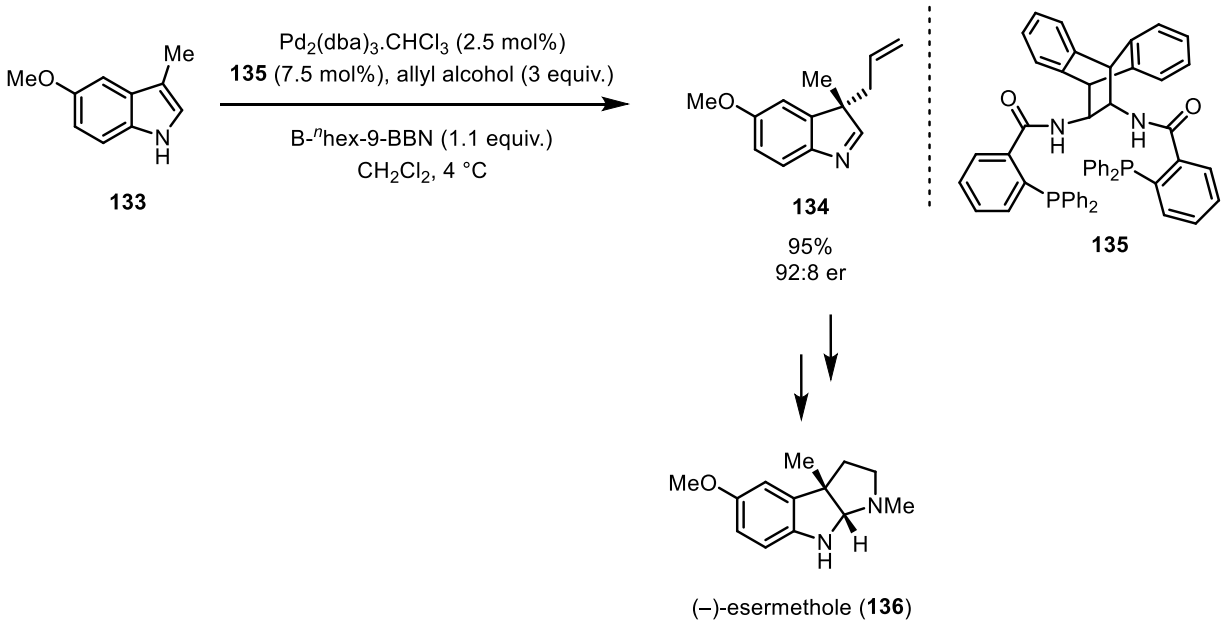
Oxidative cyclization of phenols employing chiral hypervalent iodine catalysts is a valuable method for enantioselective dearomatization.[71] Ishihara and co-workers have employed a C_2-symmetric iodoarene (**132**) as a pre-catalyst for the spirocyclization of naphthols with tethered carboxylic acids (**130**) (Scheme 33).[72] Oxidation of the iodoarene by *m*CPBA generates an iodine (III) species that activates the naphthol towards nucleophilic attack by the tethered carboxylic acid. The catalyst is covalently bound to the naphthol in the enantiodetermining step and so is able to enantioselectivity in the cyclization to give a spirolactone (**131**).



Scheme 33: Hypervalent iodine catalysed dearomative spirocyclization.

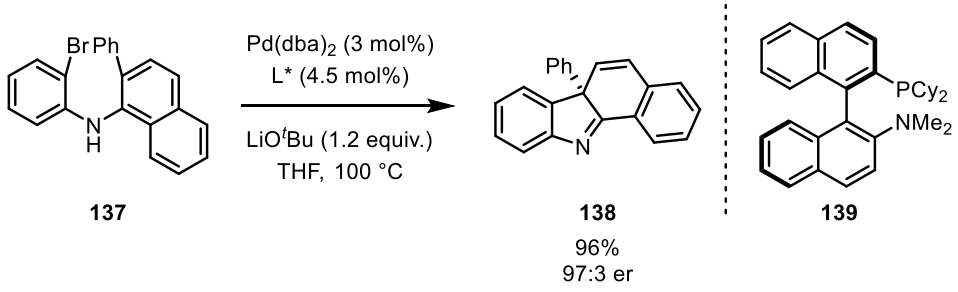
Transition Metal Catalysed Dearomatization

Transition metal catalysis has been applied successfully in many enantioselective dearomatization reactions. The most broadly applied approach is the asymmetric allylic alkylation strategy pioneered by Trost and further developed by You.[73, 74] In Trost's seminal report, $Pd_2(dba)_3.CHCl_3$ was used in combination with a chiral bisphosphine ligand (**135**) to promote the dearomative allylation of indoles with a high level of enantioselectivity (Scheme 34). *N*-Hexyl 9-BBN was used as a Lewis acid to facilitate oxidative addition to palladium to form the key electrophilic palladium(II) allyl complex, which carries out the dearomatization of indoles (**133**). The reaction provides concise access to the core of several natural products and was applied to the enantioselective synthesis of (−)-esermethole (**136**).



Scheme 34: Enantioselective dearomatization by palladium catalysed asymmetric allylic alkylation and the synthesis of (−)-esermethole (**136**).

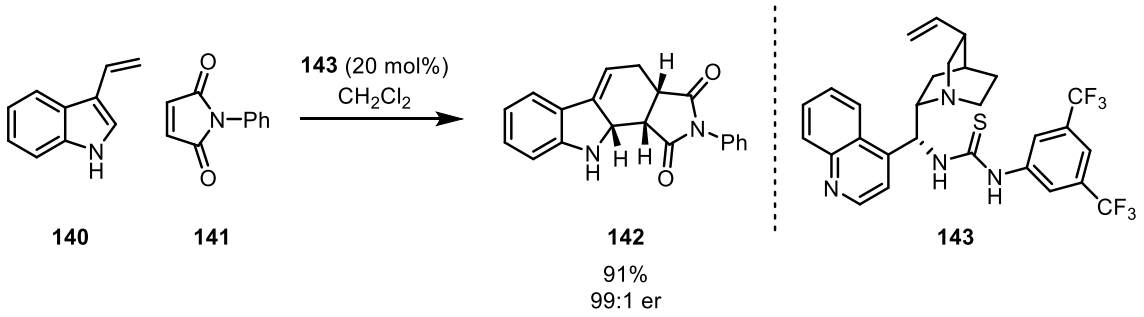
Buchwald and co-workers have developed a related arylation-based approach also employing palladium catalysis (Scheme 35).[75] In this reaction, a palladium (0) complex bearing an axially chiral biaryl monophosphine ligand (**139**) undergoes oxidative addition to an aryl bromide (**137**) to give a palladium (II) intermediate which cyclizes onto a tethered naphthylamine. The use of LiO^{t}Bu as a strong base was necessary to deprotonate the naphthylamine and increase the nucleophilicity of the aromatic ring. The method was useful in producing a range of benzocarbazole derivatives (**138**) in high yield and enantioselectivity.



Scheme 35: Enantioselective dearomatization by palladium catalysed arylation.

Dearomative Cycloadditions

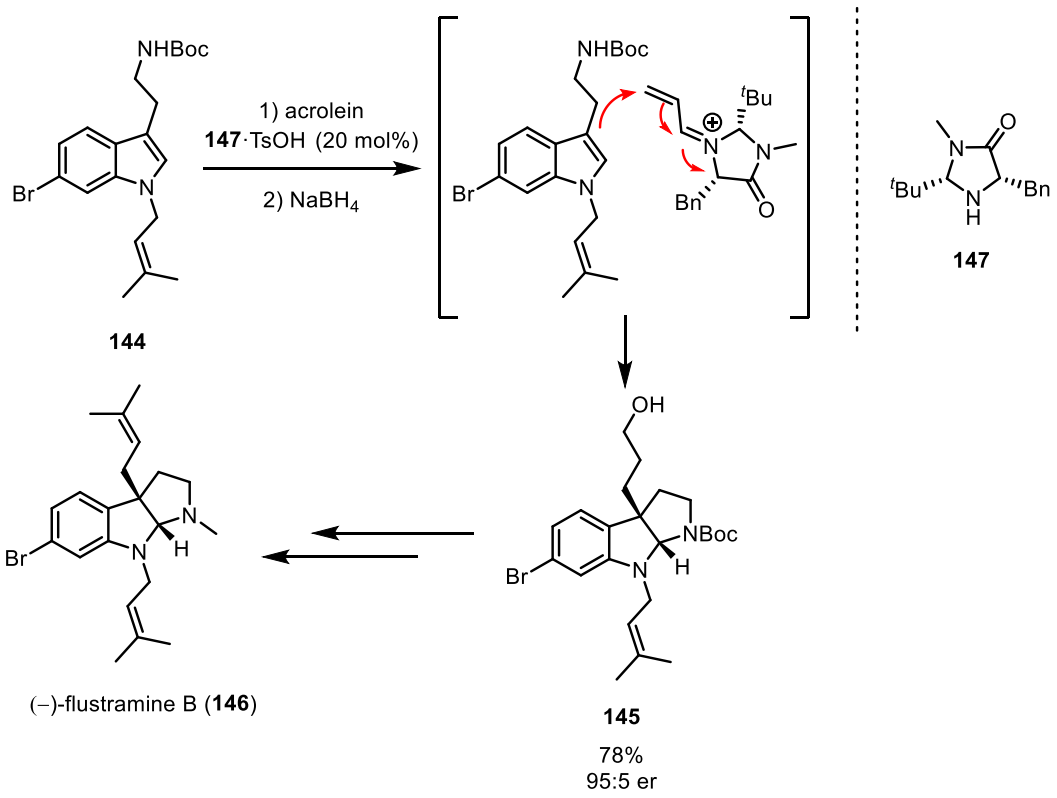
Cycloaddition chemistry has proven to be another useful tool for enantioselective dearomatization that can sometimes obviate the requirement to form a quaternary centre. Bernardi, Ricci and co-workers applied a bifunctional cinchona alkaloid-derived thiourea catalyst to promote the dearomatization of a 3-vinyl indole derivative (**140**) with maleimides (**141**) (Scheme 36).[76] The organocatalyst was proposed to accelerate the reaction by synergistic Brønsted base activation of the indole HOMO and lowering of the maleimide LUMO through hydrogen bonding. Excellent yield and enantioselectivity was observed with a very strong preference for formation of the *endo* cycloadduct (**142**).



Scheme 36: Organocatalysed enantioselective dearomative Diels-Alder reaction.

Organocatalytic Dearomatization

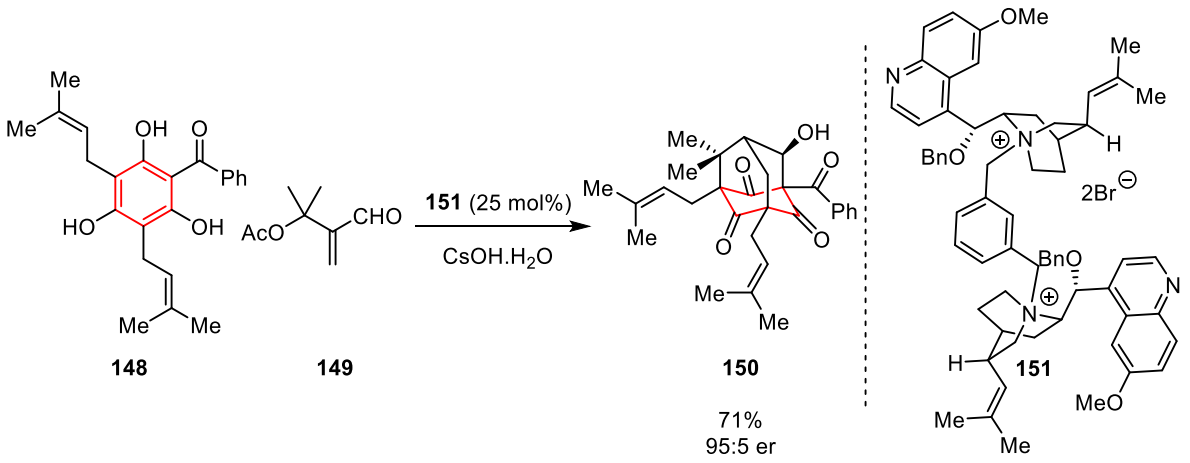
MacMillan and co-workers adopted a dearomatization approach exploiting iminium catalysis as a key step in the synthesis of (−)-Flustramine B (**146**) (Scheme 37).[77] In this reaction, a secondary amine catalyst (**147**) was condensed with acrolein, assisted by toluene sulfonic as a co-catalyst, to give an α,β-unsaturated iminium ion. Nucleophilic attack by indole **144** gave the indoline-iminium cation, which was trapped by the tethered Boc-protected amine to construct the fused pyrrolidine ring (**146)**.



Scheme 37: Dearomatization by iminium catalysis in the synthesis of (−)-flustramine B (**146**).

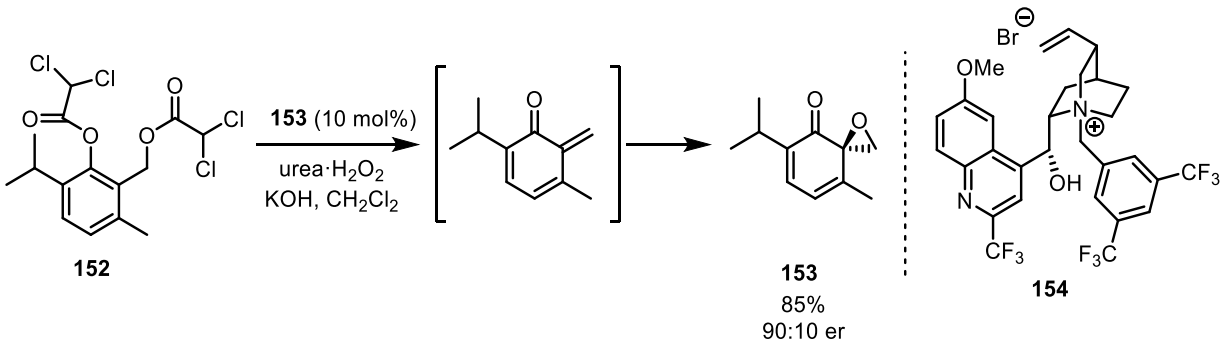
Ammonium Salt Catalysed Dearomatization Reactions

Examples of enantioselective dearomatization reactions catalysed by chiral ammonium salts are limited. During the course of their studies towards the synthesis of (−)-hyperibone K, Porco and co-workers developed a cascade Michael addition−elimination−aldol cascade dearomatization of a trihydroxybenzene derivative (**148**) to give the adamantane core (**150**) of the natural product in 71% yield and 95:5 er (Scheme 38).[65] A dimeric cinchona alkaloid derived phase-transfer catalyst (**151**) was identified as optimal in which modification of the vinyl group and *O*-benzylation of the alcohol was necessary to achieve high enantioselectivity.



Scheme 38: Ammonium salt catalysed dearoamatization of a triphenol (**148**).

Another example of enantioselective dearomatization catalysed by a chiral ammonium salt was reported by Johnson and co-workers for the dearomatization of *ortho*-hydroxymethyl phenols (Scheme 39).[66] In this process, the starting materials were activated as the dichloromethyl esters (**152**) and the phase-transfer catalyst (**154**) served the dual role of first hydrolysing the phenol ester to initiate an eliminative formation of a transient *ortho*-quinone methide and then catalysing the nucleophilic epoxidation by activation of the hydroperoxide anion.



Scheme 39: Ammonium salt catalysed enantioselective dearomatization of phenols *via* ortho-quinone-methides.

1.3.2. Project Outline

Following the successful development of our BINOL kinetic resolution, we were interested to further explore cation-directed enantioselective reactions of naphthols. Specifically, if we could divert the site of nucleophilic attack from oxygen to carbon, we could potentially carry out an enantioselective dearomatization to give transformable partially aromatic products (**160**). An outline of our reaction plan is depicted below (Figure 13). In the presence of base and a quaternary ammonium salt catalyst, the ammonium naphtholate ion pair would be formed; this species could then react with a suitable electrophile to give the dearomatized product. The primary challenge in such a reaction would be controlling *O vs.* C selectivity. Identifying a suitable electrophile would be crucial to this end.

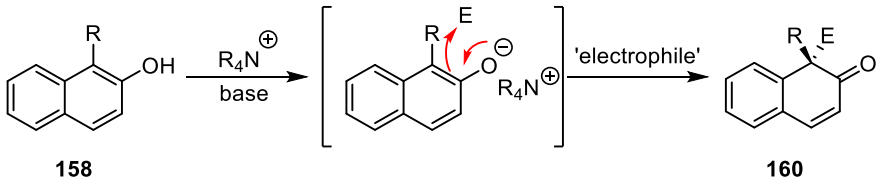


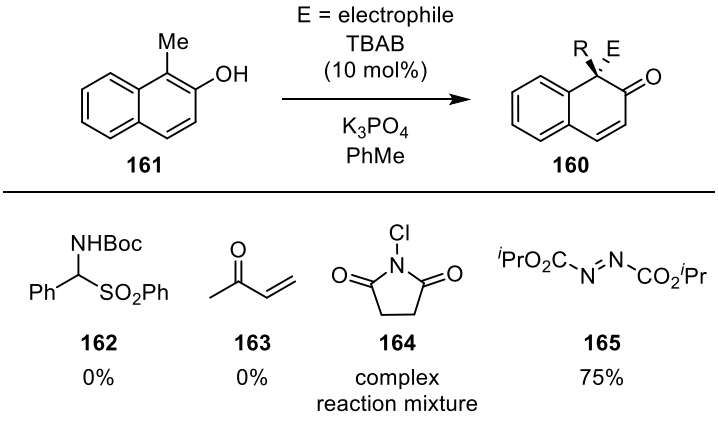
Figure 13: Proposed dearomatization of 2-naphthols.

This work was carried out in collaboration with Harriet Moore as part of her final year undergraduate research project. All compounds synthesized and optimization data obtained by Harriet Moore will be denoted **HMXX** to distinguish our respective contributions to this work.

1.3.3. Dearomative Amination

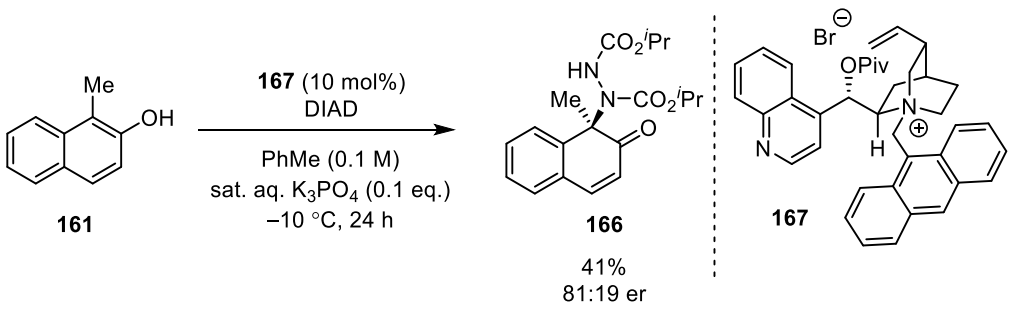
We began by screening a range of electrophiles in toluene using TBAB as the catalyst and solid K_3PO_4 as the base (Scheme 40). *N*-Boc imine precursor **162** and methyl vinyl ketone (**163**) both failed to afford any dearomatized product and only starting material could be observed by ^{1}H NMR analysis of the crude reaction mixture. *N*-Chlorosuccinimide (**164**) gave a complex reaction mixture that

could not easily be separated into its components. The most promising electrophile was DIAD (**165**), which reacted efficiently to give the dearomatized product in 75% yield.



Scheme 40: Identification of azodicarboxylate esters for dearomatization by Harriet Moore.

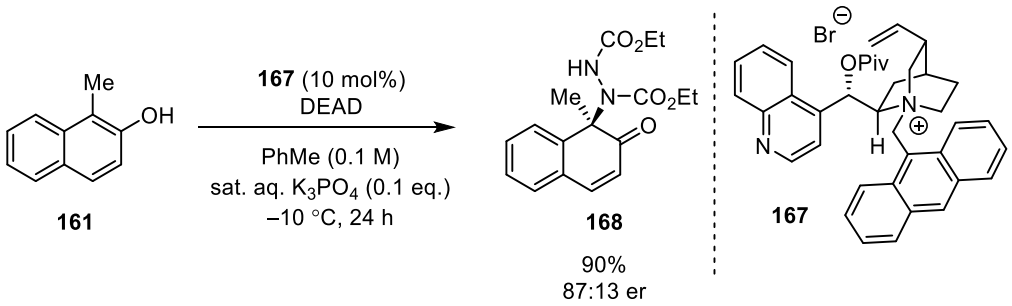
Harriet Moore identified a promising set of reaction conditions for the dearomative amination employing DIAD as the electrophile (Scheme 41). Under Harriet's conditions, the desired product (**166**) could be isolated in 41% yield and 81:19 er. A cinchonine-derived phase transfer catalyst (**167**) delivered the best enantioselectivity. *O*-Functionalization was found to be critical for enantioselectivity, with a pivaloyl group being optimal. *N*-Quaternization with a bulky anthracenylmethyl group gave the best enantioselectivity. Only 0.1 equivalents of base were required for the reaction; increasing the base loading gave no major change in enantioselectivity. The reaction proceeded rapidly at room temperature; running the reaction at −10 °C and extending the reaction time to 24 hours gave a modest increase in enantioselectivity. At this stage Harriet had concluded her undergraduate research project and I began further optimization of the reaction.



Scheme 41: Enantioselective dearomatization reaction developed by Harriet Moore.

Reaction Optimization

We first examined the effect of the electrophile on the reaction. Reasoning that steric hinderance from the isopropyl groups might explain the poor yield, we employed diethylazodicarboxylate (DEAD) as the electrophile. Pleasingly, DEAD increased the yield from 41% to 90% and the enantioselectivity from 83:17 to 87:13 (Scheme 42).

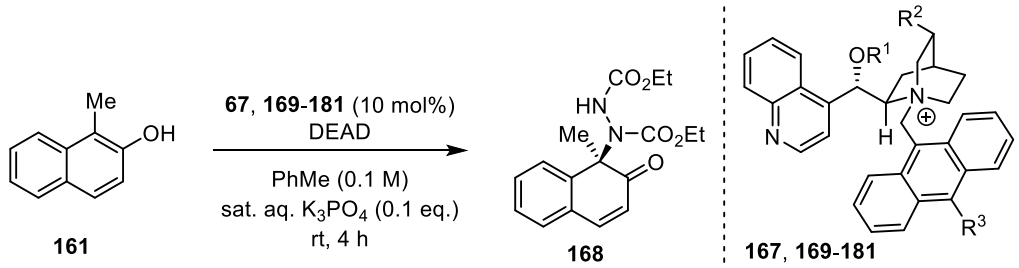


Scheme 42: DEAD as an improved electrophile.

We next examined the effect of the oxygen-capping group on the cinchonine-derived ammonium salt catalyst (Table 3). For practicality, optimization experiments were performed at room temperature. Enantioselectivity was found to be highly dependent on the *O*-substituent of the catalyst. Acetyl (Table 3, entry 1) and CO_2(allyl) (Table 3, entry 2) gave dramatically worse enantioselectivity. Alkyl groups (allyl, methyl and benzyl. Table 3, entries 3-5) gave lower enantioselectivity. The pyrimidine *O*-capping group previously employed by Deng gave comparable enantioselectivity to the pivaloyl group (Table 3, entry 7). [25] It appears that bulky esters are ideal, with pivaloyl (Table 3, entry 7) being optimal: Isopropyl, benzoyl and adamantyl esters all gave slightly diminished enantioselectivity in comparison.

The vinyl group on the catalyst backbone is known to influence the enantioselectivity of other transformations.[24] In the case of our dearomative amination, there appears to be only a minor influence of vinyl group modification on enantioselectivity. Vinyl (Table 3, entry 1) remains the

optimal group whereas ethyl (Table 3, entry 10) and ethynyl (Table 3, entry 11) groups gave a small decrease in enantioselectivity.



Entry	$R_4N^+X^-$	R^1 =	R^2 =	R^3 =	er
1	169	Ac	C_2H_3	H	59:41
2	170	Allyl	C_2H_3	H	73:27
3	171	Me	C_2H_3	H	71:29
4	172	Bn	C_2H_3	H	72:28
5	173	pyr*	C_2H_3	H	80:20
6	167	Piv	C_2H_3	H	83:17
7	174	$CO_2{}^i$Pr	C_2H_3	H	81:19
8	175	COPh	C_2H_3	H	77:23
9	176	CO(Adamantyl)	C_2H_3	H	77:23
10	177	Piv	C_2H_5	H	81:19
11	178	Piv	C_2H	H	80:20
12	179	Piv	C_2H_3	Cl	79:21
13	180	Piv	C_2H_3	CN	79:21
14	181	Piv	C_2H_3	Ph	82:18

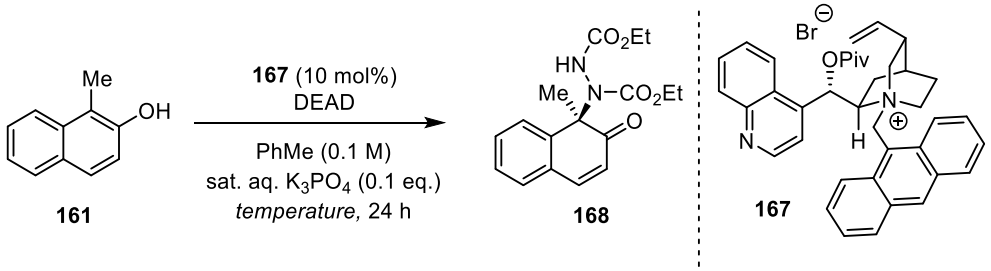
Table 3: Influence of catalyst structure on dearomative amination. *pyr = 3-bromo-2,5-diphenylpyrimidine.

We next examined substituting the 10-position of the catalyst anthracenyl group in the hope that a change in the electronic properties would enhance the enantioselectivity. Unfortunately, as was the case with vinyl group modification, substitution at the anthracene 10-position appeared to have little effect. Chloro (Table 3, entry 12), cyano (Table 3, entry 13) and phenyl (Table 3, entry 14) groups all gave slightly worse er than the unsubstituted anthracene (Table 3, entry 1).

The Effect of Temperature on Enantioselectivity

Having previously observed an increase in enantioselectivity with DIAD upon lowering the reaction temperature, we comprehensively studied the effect of temperature on the reaction with DEAD, a more reactive electrophile (Table 4).[78] Decreasing the reaction temperature from 20 to −10 °C gave

a significant increase in er from 83:17 to 87:13. Further cooling the reaction to −30 °C gave a slight increase in er to 90:10. Cooling the reaction further gave a modest increase in er. However, this came at the expense of rate with unreacted starting material remaining after 24 hours in all cases. We therefore settled on −30 °C as the optimal reaction temperature.



Temperature (°C)	er
20	83:17
−10	87:13
−30	90:10
−40	90:10
−50	92:8
−60	92:8

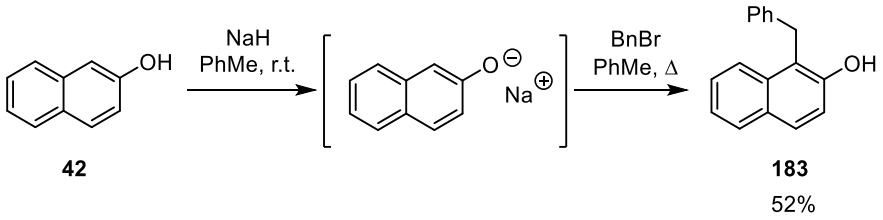
Table 4: Effect of temperature on enantioselectivity in the dearomative amination.

Synthesis of a Substrate Library

It was clear at this stage that any further increase in enantioselectivity would be difficult to achieve. We decided not to pursue any further optimization of the reaction but, to instead examine the substrate scope. For this we would require a library of *C*1-alkylated 2-naphthols.

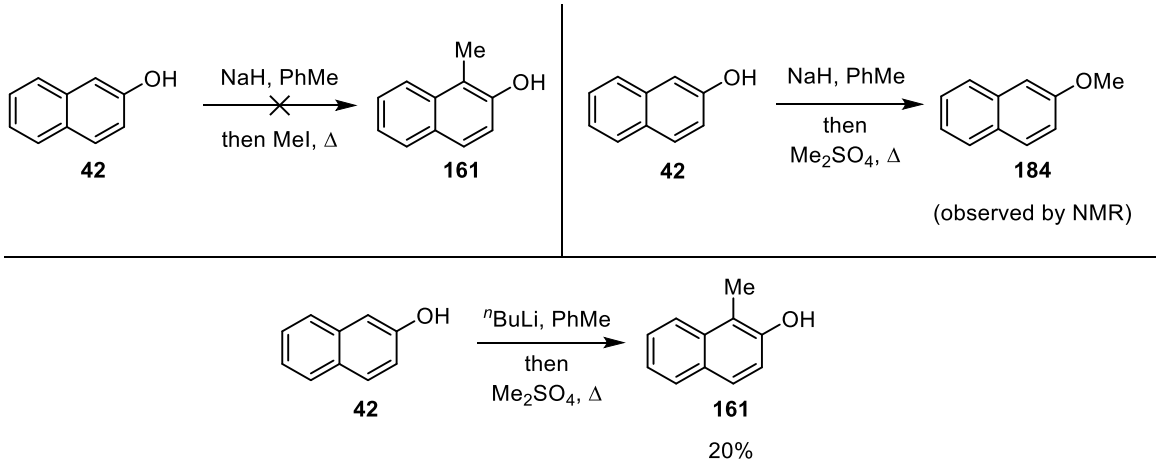
It is known that, under certain reaction conditions, direct *C*1-alkylation of 2-naphthols with alkyl halides is possible. We were drawn to a report from Luan where the sodium salt of 2-naphthol is reacted with iodoethane in toluene to give the *C*1-alkylated product.[79] In our hands it was more practical to general the sodium naphtholate *in situ* from 2-naphthol (**42**), employing sodium hydride as the base. Benzyl bromide was then added and the reaction was subsequently heated under reflux for 2 hours, giving 1-benzyl-2-naphthol (**183**) as the major reaction product (Scheme 43). In contrast to the typical chemoselectivity observed with phenolates, the *O*-alkylated product was not formed.

This occurred because the sodium counterion is poorly solvated in toluene and closely associated with the naphtholate oxygen. Alkylation on oxygen was resultingly blocked and alkylation occurred exclusively at the *C*1 position.



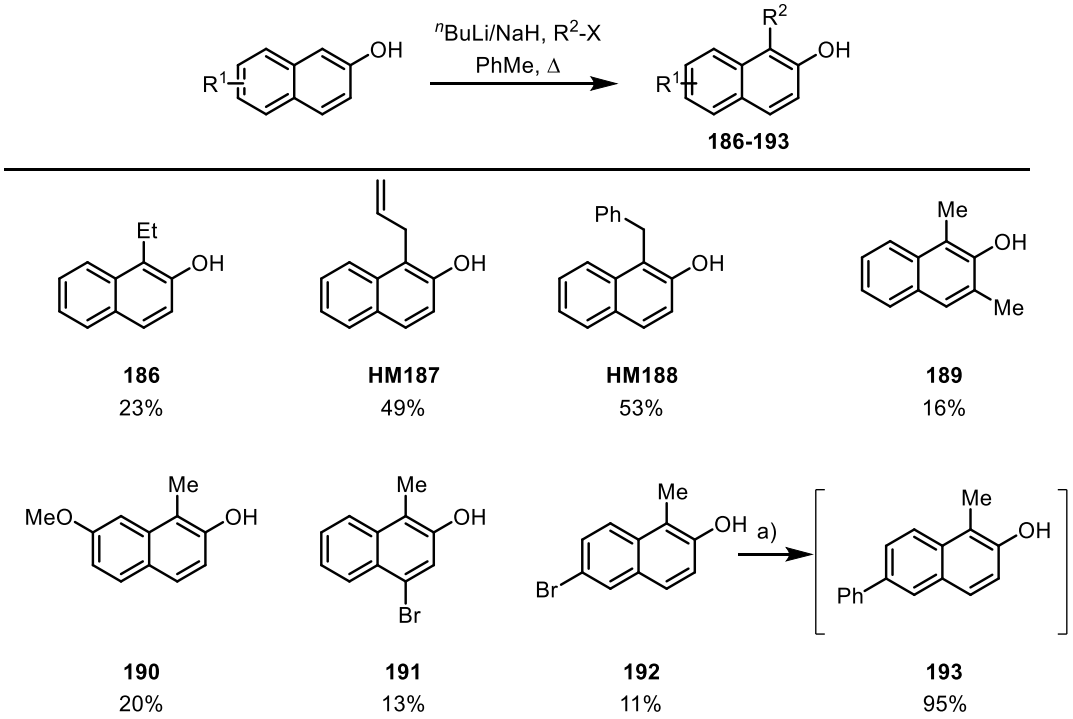
Scheme 43: Direct *C*-benzylation of 2-naphthol (**42**).

When iodomethane was used in place of benzyl bromide, no reaction was observed under the reaction conditions even under prolonged heating (Scheme 44). This was either due to its lower electrophilicity or loss due to its volatility. When dimethyl sulfate was used the reaction occurred exclusively on oxygen to give 2-methoxynaphthalene (**145**). Reasoning that a more Lewis acidic counterion would favour reaction on carbon, we changed the base to ^{n}BuLi. As expected, 20% of the desired *C*-alkylated product (**161**) was obtained alongside a mixture of product arising from *O*-and *C*-alkylation. Due to its expediency, this method was employed for the synthesis of starting materials despite its low yield.



Scheme 44: Direct *C*-methylation of 2-naphthol.

Using our direct naphthol alkylation conditions we prepared a small library of 2-naphthol derivates in a single step (Scheme 45). The yields when using activated alkyl halides (BnBr, allyl-Br) were significantly higher than those of alkyl sulfates (Me_2SO_4, Et_2SO_4) which were poor but still allowed for the preparation of synthetically useful amounts of material. The 6-phenyl substituted 2-naphthol (**193**) was prepared from brominated naphthol **192** by Suzuki coupling.

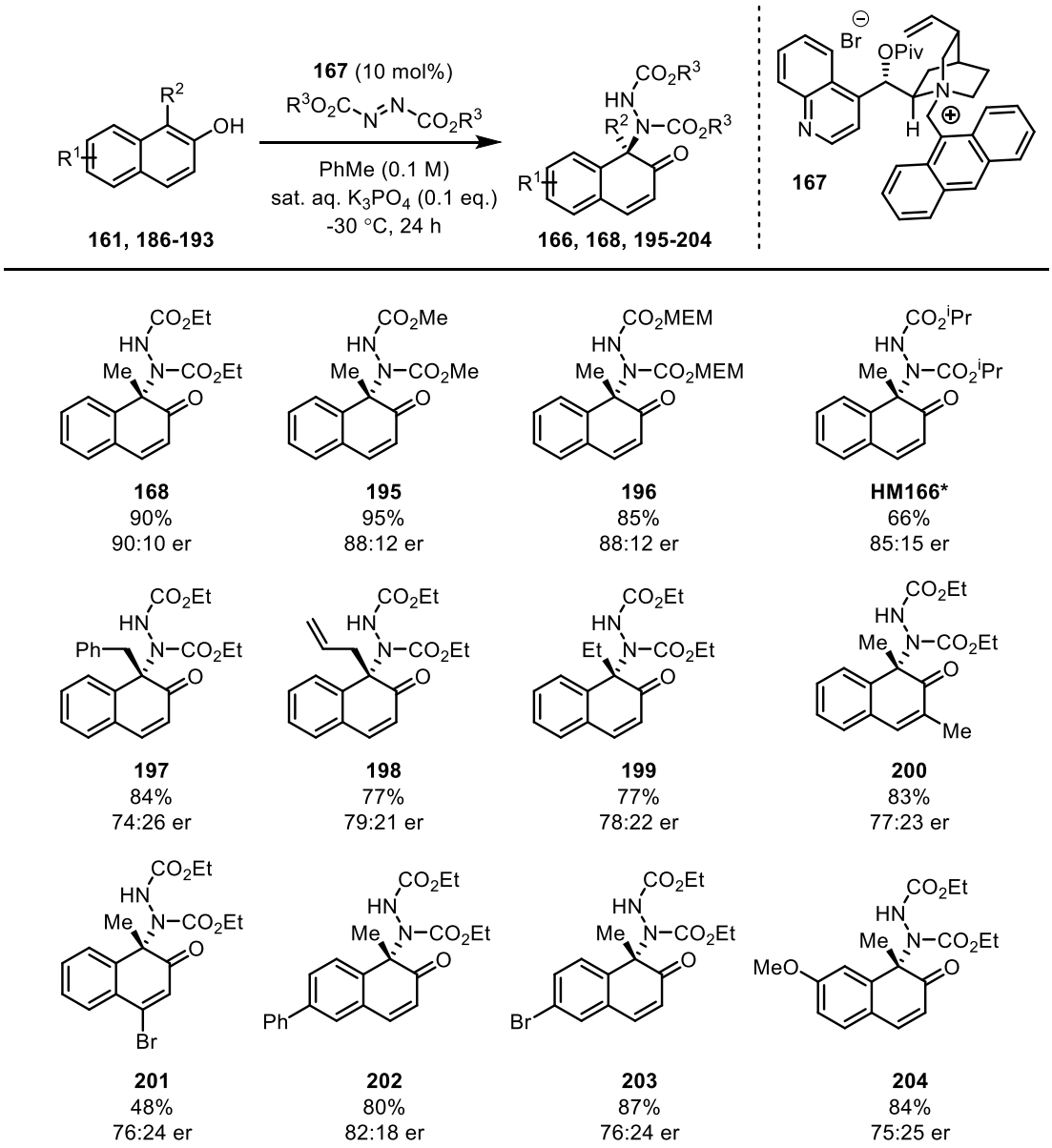


Scheme 45: Synthesis of 1-alkyl-2-naphthol derivatives (**186-193**) by direct alkylation. a) $PhB(OH)_2$, $Pd(PPh_3)_4$ (5 mol%), Na_2CO_3 DME/H_2O, Δ.

Reaction Scope

With a library of substrates in hand, we proceeded to investigate the scope of the reaction (Scheme 46). We first evaluated different azodicarboxylate esters and found the ethyl (**168**), methyl (**195**) and methoxyethyl (**196**) variants to all be competent reaction partners. Diisopropyl azodicarboxylate gave reduced yield and selectivity (**HM166**). Varying the *C*1 substituent significantly decreased the selectivity: benzyl (**197**), allyl (**198**) and ethyl (**199**) groups all gave much lower er. Substituting other positions around the naphthalene was also detrimental to the reaction:

3-Methyl (**200**), 4-bromo (**201**), 6-phenyl (**202**), 6-bromo (**203**) and 7-methoxy (**204**) substituted substrates all gave significantly worse enantioselectivity than the unsubstituted 1-methyl-2-naphthol.



Scheme 46: Scope of the enantioselective dearomative amination. *The reaction was performed at −10 °C.

Reaction Mechanism

Based on the observation that only 0.1 equivalents of base are required, we propose that a cation directed, phase transfer-initiated mechanism is most likely (Figure 14).[80] 1-Methyl-2-naphthol (**161**) is deprotonated at the toluene/K_3PO_4 interface to give the potassium naphtholate which undergoes

counterion metathesis with the ammonium salt (**167**). Nucleophilic addition to DEAD then generates a basic anion that is protonated by another naphthol molecule to regenerate the ammonium naphtholate and deliver the product (**166**). The proposed catalytic cycle operates exclusively in the organic phase.

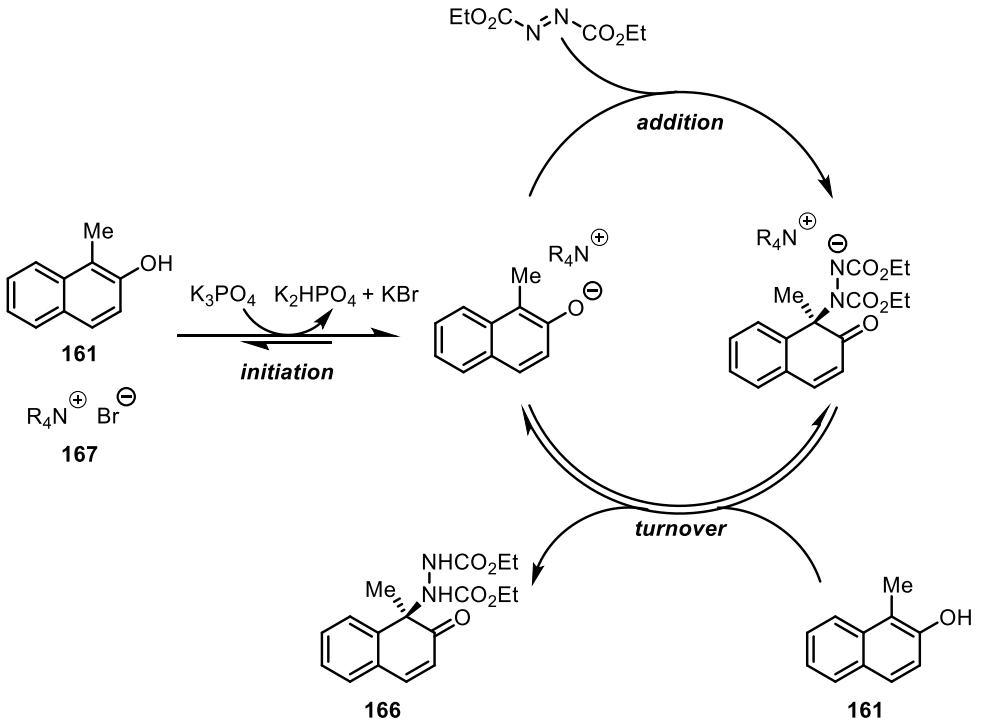
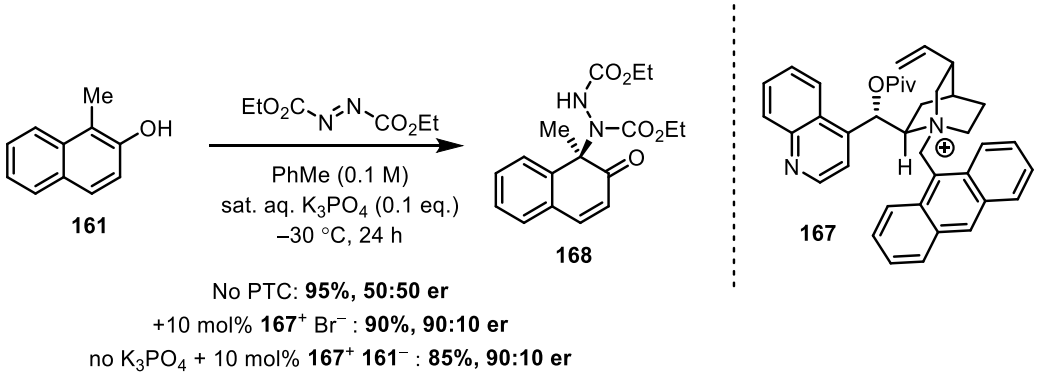


Figure 14: Proposed mechanism of the enantioselective dearomative amination.

During the course of optimization, we noticed that the reaction proceeded efficiently in the absence of a phase transfer catalyst. To evaluate the extent of background reactivity we performed the reaction under the optimized conditions, but without a phase transfer catalyst (Scheme 47). Interestingly, after 24 h, a 95% yield of the racemic product was observed with full conversion of starting material. With such a high rate for the uncatalyzed reaction, it is surprising that enantioselectivity as high as 90:10 er could be achieved. To better understand the role of background reactivity we performed the reaction with 10 mol% of the catalyst-substrate ion-pair prepared using an ion-exchange resin. We observed enantioselectivity identical to the reaction using 10 mol% K_3PO_4, suggesting that the selectivity observed in the standard reaction reflects the innate

selectivity of the catalyst and that the rate of the potassium-catalysed background reaction is negligible. It is possible that the ammonium salt has an inhibitory effect on the potassium-catalysed dearomatization process.



Scheme 47: Investigation of background reactivity.

1.3.4. Dearomatization with Alkyl Halide Electrophiles

Despite the fact that we had not observed the generality or enantioselectivity we had hoped for with the dearomative amination, we considered the above results as proof of concept and decided to look at extending the strategy to other electrophiles. Alkyl halides are by far the most reliable class of electrophile employed in enantioselective phase transfer catalysis and are far less common in other forms of organocatalysis (e.g. enamine, tertiary amine bases, NHCs).[3, 81-84] As such, we reasoned that cation-mediated dearomatization with alkyl halides would be a valuable addition to the field and leverage a key advantage of enantioselective phase-transfer catalysis.

The obvious challenge when using alkyl halides for enantioselective dearomatization of 2-naphthols is their tendency to react selectively and irreversibly on oxygen.[85] We hypothesized that a tethering strategy could be used to override this natural *O*-selectivity. In the proposed reaction, an alkyl halide would be tethered at the 1-position by a 4-atom chain. We reasoned that cyclization through carbon to give a 5-membered ring might be favoured over *O*-alkylation to give a 7-membered ring.

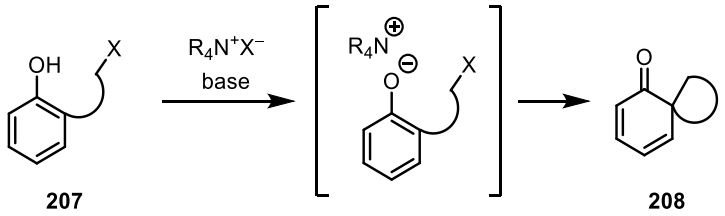
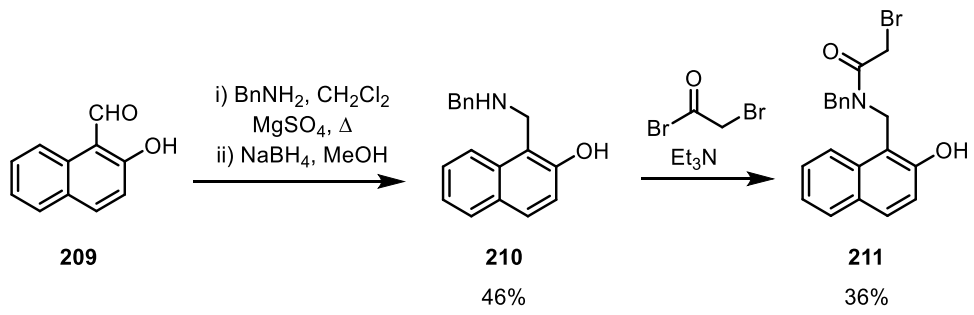


Figure 15: Proposed dearomatization by alkylation.

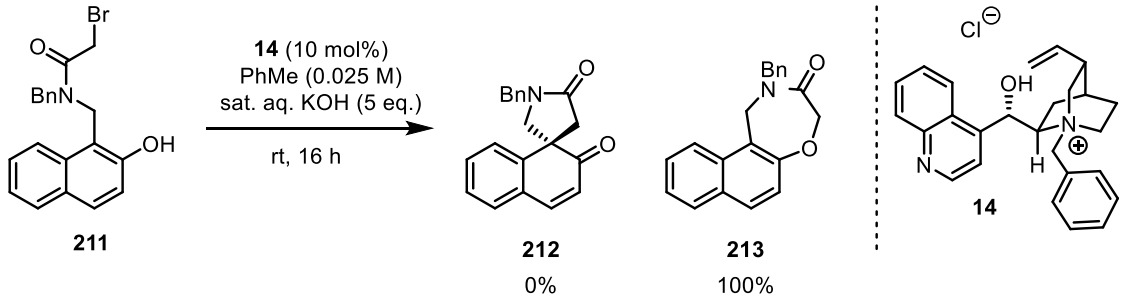
2-Naphthol Dearomatization with Alkyl Halides

A suitable substrate to test our hypothesis was proposed and synthesized in 2 steps (Scheme 48). Starting from 1-formyl-2-naphthol (**209**), reductive amination with benzylamine followed by acylation with bromoacetyl bromide afforded test substrate **211** bearing a 4-atom tether. Additionally, the presence of an activated alkyl halide (α-halocarbonyl) was expected to increase reactivity.



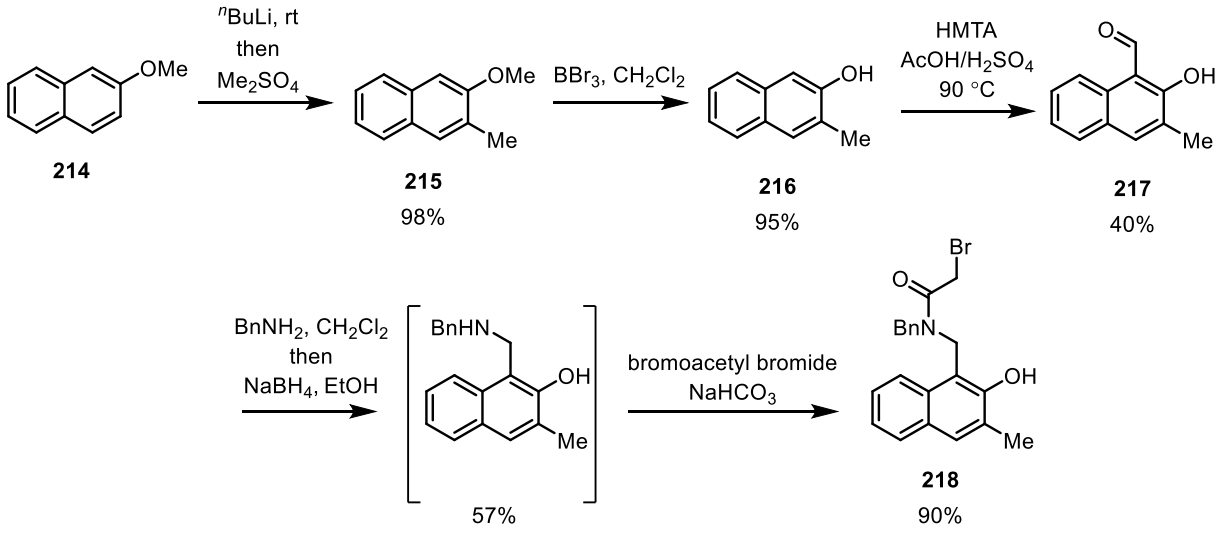
Scheme 48: Synthesis of dearomative alkylation substrate.

Under typical phase-transfer reaction conditions using *N*-benzylcinchoninium chloride (**14**) as the catalyst, exclusive *O*-alkylation was observed to give cyclic ether **213** (Scheme 49). Evidently, the preference of 2-naphthols to *O*-alkylate under our reaction conditions was too strong to be overridden using a tethering strategy.



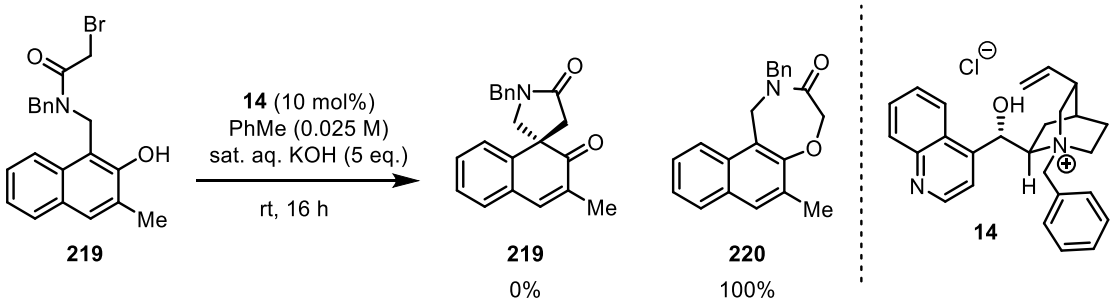
Scheme 49: Attempted dearomative alkylation of naphthol **211**.

There are several examples in the literature of naphthol dearomatization in which groups at *C*3 are incorporated to block reaction on oxygen and favour reaction at *C*1.[86-88] We decided to incorporate a *C*3 blocking group in our substrate in the hope that it might bias the reaction towards dearomative *C*1 alkylation (Scheme 50). Starting from 2-methoxynaphthalene (**214**), *ortho*-lithiation at *C*3 followed by quenching with dimethyl sulfate gave the alkylated product (**215**). The methyl ether group was then cleaved with BBr_3 to give 3-methyl-2-naphthol (**216**). Formylation with hexamethylenetetramine delivered aromatic aldehyde (**217**) which was transformed to the required α-bromoamide (**218**) using the reductive amination/acylation sequence employed previously.



Scheme 50: Synthesis of *C*3-alkylated dearomative alkylation substrate.

The *C*3-substituted substrate (**219**) was reacted under the same conditions as the previous substrate and, disappointingly, also alkylated exclusively on oxygen (Scheme 51).



Scheme 51: Attempted dearomative alkylation with C3 blocking group.

Alkylative Dearomatization of Indoles

It was clear at this stage that naphthols have a very strong preference to react with alkyl halides on oxygen under phase-transfer catalysis conditions. Accepting that this bias would be extremely difficult to overcome, we decided to evaluate other substrates. We were attracted to indoles for a number of reasons: Firstly, the resonance stabilization energy of indole (**221**) (196 kJ mol^{-1}) is less than that of naphthalene (**222**) (252 kJ mol^{-1}). Considering that most of the resonance stabilisation energy of indole is attributable to the fused benzene ring (the resonance energy of benzene (**223**) is 152 kJ mol^{-1}), dearomatization of indole is significantly less energetically challenging.[89] Secondly, the pKa of the indole *N-H* proton is 21 in DMSO, which, although slightly higher than ideal, should be reactive using hydroxide bases.[90] Thirdly, and crucially, intramolecular alkylation on nitrogen should be geometrically precluded since the tether is not long enough. Finally, if we used the same tethering system devised for the naphthol dearomatization, the resulting indoline product (**225**) would share the same core structure as many alkaloid natural products such as tabersonine (**226**) and strychnine (**227**).[91]

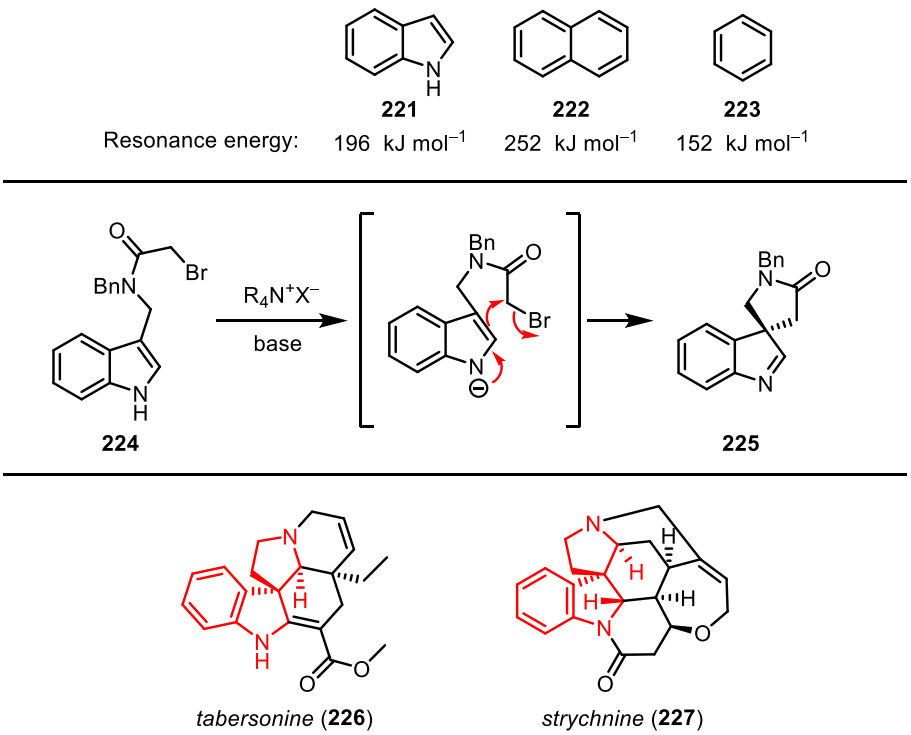
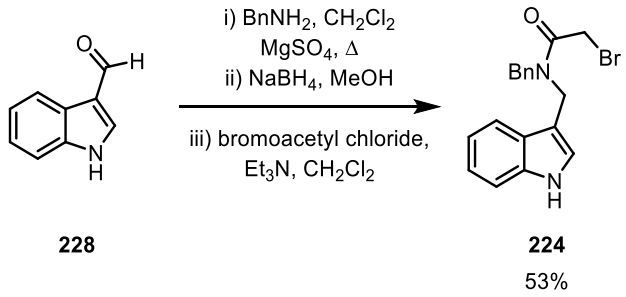


Figure 16: Top: Resonance stabilisation energy of indole (**221**), naphthalene (**222**) and benzene (**223**) compared. Middle: Proposed dearomative alkylation of indoles. Bottom: Potentially accessible natural products tabersonine (**226**) and strychnine (**227**).

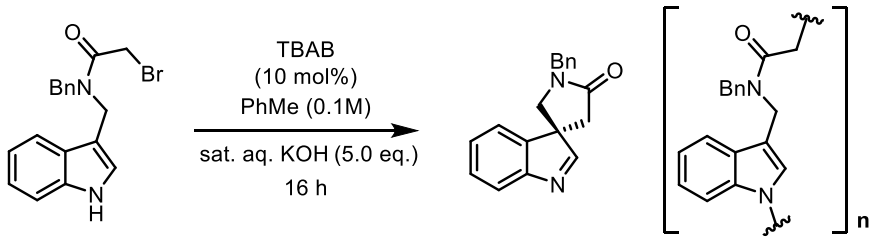
The required substrate was prepared using the same tactics used in the naphthol dearomatization: Starting from 3-formylindole (**228**), reductive amination followed by acylation afforded the desired α-bromoamide (**224**) (Scheme 52).



Scheme 52: Synthesis of indole dearomatization substrate **224**.

When the reaction substrate (**224**) was treated with 50% KOH solution in toluene in the presence of catalytic TBAB, the proposed spirocyclic indoline (**225**) was produced in trace amounts (<5%) (Figure 17). At the end of the reaction, a precipitate was observed that was insoluble in common organic

solvents, the crude ^{1}H NMR spectrum of which was dominated by broad peaks at 4.5-5.0 ppm and 7.0-7.5 ppm. We hypothesised that these observations were consistent with polymer formation occurring by intermolecular *N*-alkylation, which would explain the poor yield. To address this, we first looked at the effect of concentration, expecting that dilution would favour intramolecular cyclization and disfavour intermolecular polymerisation. Upon diluting the reaction from 0.1 to 0.025 M, a modest increase in yield from <5 to 8% was observed. A much larger increase in yield to 33% was observed when the solvent was switched from toluene to CH_2Cl_2. It is known that, in phase-transfer-catalysed alkylation of ambident nucleophiles, the use of more polar solvents (e.g. CH_2Cl_2 vs. toluene) biases the reaction towards the less electronegative site (carbon in this case).[92] This is because the electronegative site carries most of the negative charge and so is more solvated by the polar solvent and thus less able to react with the electrophile. We attribute the greater yield in CH_2Cl_2 vs. toluene to this effect. Unfortunately, more polar solvents are typically detrimental to enantioselectivity in ion-pairing catalysis, so we decided to halt solvent screening and explore alternative strategies to increase the yield.



Solvent (conc. (M))	Base	Yield (%)*	Conversion (%)
PhMe (0.1)	50% KOH	<5	100
PhMe (0.025)	50% KOH	8	100
CH_2Cl_2 (0.025)	50% KOH	33	100

Figure 17: Solvent and concentration effects on the reaction yield. *Determined by quantitative ^{1}H NMR analysis using CH_2Br_2 as an internal standard.

We decided to investigate a blocking strategy like we had attempted for the naphthol dearomatization. We hoped that by installing a group at the indole *C*2 position a steric clash between the *C*2 substituent and the incoming nucleophile would minimise polymerisation (Figure 18). We postulated that, in the desired dearomative *C*-alkylation the intramolecular approach of the electrophile would be less affected by the size of the *C*2 substituent.

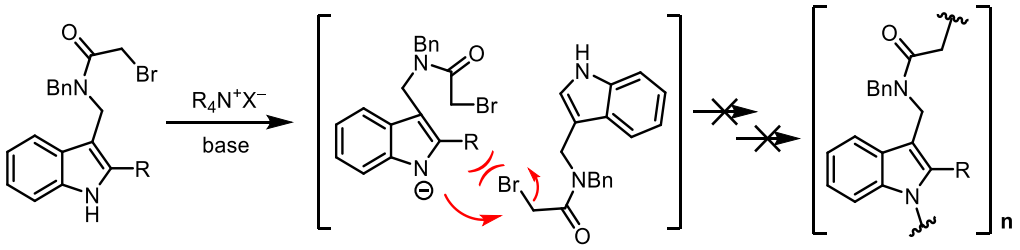
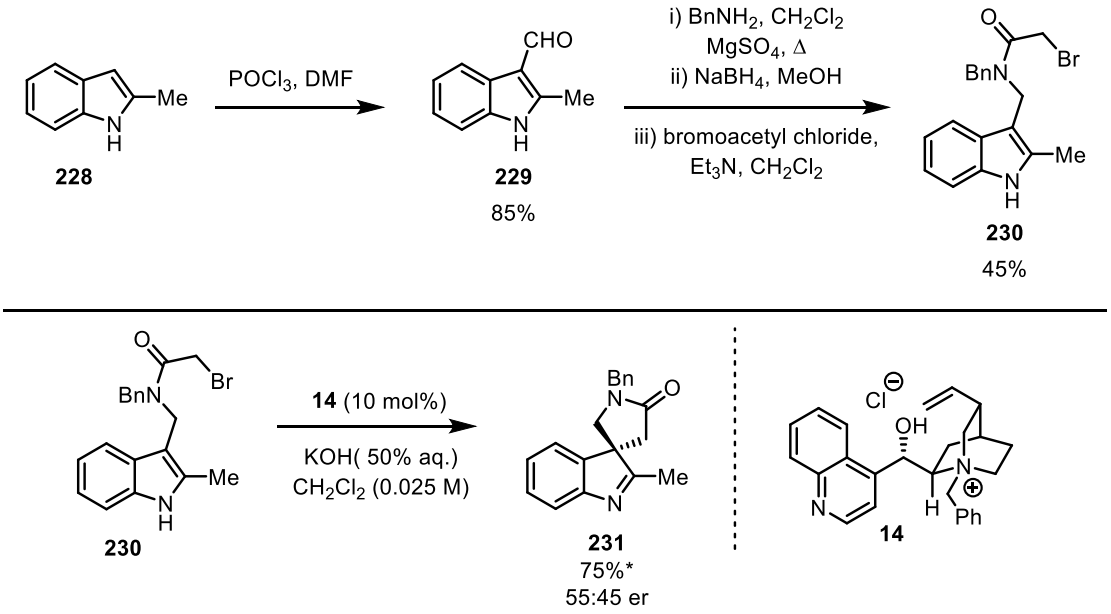


Figure 18: Proposed C3 blocking strategy to minimise polymerisation.

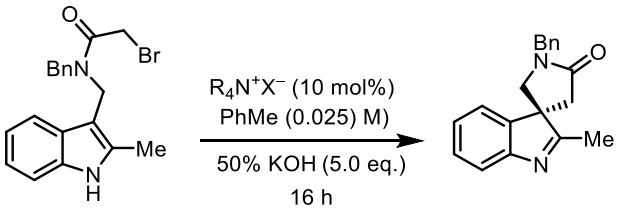
We first examined a methyl group as the blocking substituent (Scheme 53). Starting from 2-methyl indole (**228**), Vilsmeier formylation gave the aldehyde (**229**). Reductive amination with benzylamine followed by acylation with bromoacetyl bromide delivered the *C*2-blocked dearomatization substrate (**230**). Pleasingly, when we treated **230** with 50% aqueous KOH solution in the presence of 10 mol% *N*-benzylcinchoninium chloride in CH_2Cl_2 the desired product (**231**) was produced in 75% yield and modest enantioselectivity (55:45 er).



Scheme 53: Top: Synthesis of indole dearomatization substrate with C2 blocking group. Bottom: Dearomative alkylation of C2-blocked indole. *Determined by quantitative ^{1}H NMR analysis using CH_2Br_2 as an internal standard.

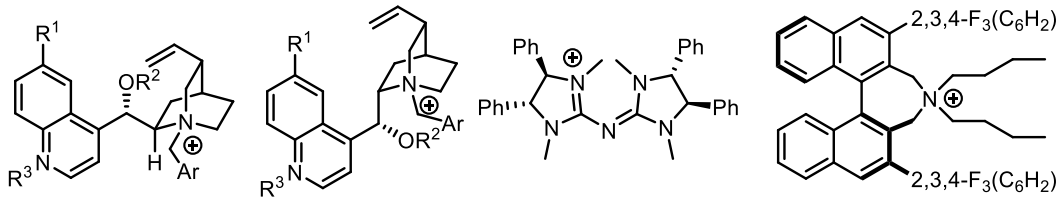
At this point we were satisfied that the product could be obtained in good yield. We therefore proceeded to screen a range of phase-transfer catalysts in the pursuit of higher enantioselectivity. For the purpose of catalyst screening, toluene was chosen as the reaction solvent since it typically gives better enantioselectivity than CH_2Cl_2 in enantioselective phase-transfer catalysis.[81]

In toluene, *N*-benzylcinchoninium chloride gave 57:43 er (Table 5, entry 1). Changing Ar to a range of substituted phenyl groups (Table 5, entries 2-5) or a 9-anthracenyl group (Table 5, entry 6) gave no improvement in enantioselectivity. The best catalyst identified was the pseudoenantiomer, *N*-benzylcinchonidinium chloride (Table 5, entry 7), which gave the opposite enantiomer in 64:36 er. Disappointingly, cinchonidinium catalysts with fluoroalkyl substituted benzyl groups (Table 5, entries 8, 9) gave worse enantioselectivity, as did a 9-anthracenyl substituted catalyst (Table 5, entry 10) and its *O*-allylated variant (Table 5, entry 11).



230 **231**

Entry	$R_4N^+X^-$	Scaffold	R^1	R^2	R^3	Ar	er
1	14	CN	H	H	-	Ph	57:43
2	71	CN	H	H	-	4-$(CF_3)(C_6H_4)$	56:44
3	70	CN	H	H	-	C_6F_5	46:54
4	74	CN	H	H	-	2,3,4-$F_3(C_6H_2)$	58:42
5	233	CN	H	H	-	3,5-^{t}Bu$_2(C_6H_3)$	53:47
6	234	CN	H	H	-	9-anthracenyl	53:47
7	235	CD	H	H	-	Ph	36:64
8	236	CD	H	H	-	4-$(CF_3)C_6H_4$	38:62
9	237	CD	H	H	-	3,5-$((CF_3)_2CF)_2(C_6H_3)$	48:52
10	238	CD	H	H	-	9-anthracenyl	42:58
11	18	CD	H	allyl	-	9-anthracenyl	40:60
12	239	QN	OMe	H	-	4-Me(C_6H_4)	45:55
13	240	CD	H	H	CH_2-3,5-$(CF_3)_2(C_6H_3)$	3,5-$(CF_3)_2(C_6H_3)$	64:36
14	241	QN	OMe	H	CH_2-4-$(NO_2)(C_6H_4)$	4-$(NO_2)(C_6H_4)$	43:47
15	242	QD	OMe		CH_2-2-Br-4-OMe$)(C_6H_3)$	2-Br-4-OMe$)(C_6H_3)$	50:50
16	243	-	-	-	-	-	50:50
17	244	-	-	-	-	-	60:40



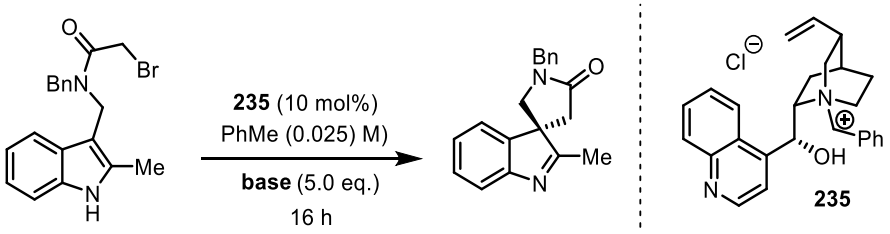
CN/QD **CD/QN** **243** **244**

Table 5: Effect of catalyst structure on the dearomative alkylation.

A quininium catalyst was also screened but gave lower enantioselectivity (Table 5, entry 12). We also examined three doubly quaternized catalysts: the cinchonidine catalyst (Table 5, entry 13) gave 64:36 er, making it the joint-best catalyst identified; the doubly quaternized quininium (Table 5, entry 14) and quinidinium (Table 5, entry 15) catalysts both gave poor enantioselectivity. Finally, we examined two non-natural catalysts scaffolds: the bisguanidinium salt developed by Tan (Table 5,

entry 16) which gave racemic product; and Maruoka's spiro-ammonium catalyst (Table 5, entry 17), which gave 60:40 er.[26, 93]

Next, we examined the effect of the base. It was immediately clear that hydroxide bases were necessary for good reactivity. With the exceptions of aqueous potassium phosphate (Table 6, entry 2), solid and aqueous lithium carbonate (Table 6, entries 5,6) and aqueous caesium carbonate (Table 6, entry 12), all of the carbonate bases gave no detectable product.

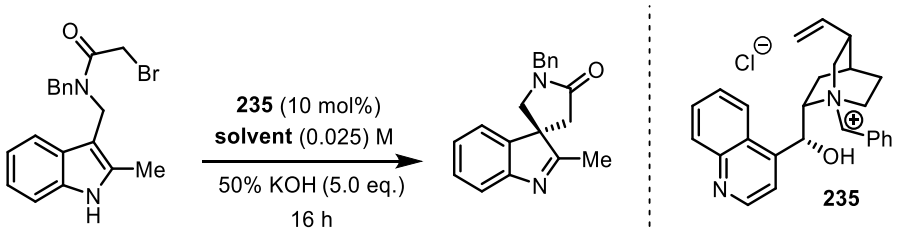


Entry	Base	er	Entry	Base	er
1	$K_3PO_{4\,(s)}$	-	**11**	$Cs_2CO_{3\,(s)}$	-
2	$K_3PO_{4\,(sat.aq.)}$	56:44	**12**	$Cs_2CO_{3\,(sat.\,aq.)}$	65:35
3	$Na_3PO_{4\,(s)}$	-	**13**	$LiOH_{(s)}$	50:50
4	$Na_3PO_{4\,(sat.\,aq.)}$	-	**14**	$LiOH_{(sat.\,aq.)}$	50:50
5	$Li_2CO_{3\,(s)}$	50:50	**15**	$NaOH_{(s)}$	61:39
6	$Li_2CO_{3\,(sat.\,aq.)}$	50:50	**16**	$NaOH_{(sat.\,aq.)}$	62:38
7	$Na_2CO_{3\,(s)}$	-	**17**	$KOH_{(s)}$	-
8	$Na_2CO_{3\,(sat.\,aq.)}$	-	**18**	$KOH_{(sat.\,aq.)}$	62:38
9	$K_2CO_{3\,(s)}$	-	**19**	$CsOH_{(s)}$	53:47
10	$K_2CO_{3\,(sat.\,aq.)}$	-	**20**	$CsOH_{(sat.\,aq.)}$	61:39

Table 6: Effect of base on the dearomative alkylation.

We then investigated the effect of solvent on enantioselectivity. Aromatic hydrocarbons (Table 7, entries 1-3) all gave comparable enantioselectivities. Acetonitrile (Table 7, entry 4) gave racemic product. Chlorinated solvents gave variable outcomes: CH_2Cl_2 (Table 7, entry 5) led to a decrease in enantioselectivity, $CHCl_3$ (Table 7, entry 6) gave a complex reaction mixture from which no product could be isolated while CCl_4 (Table 7, entry 7) gave the product in 66:34 er. Ethereal solvents (Table 7, entries 8-11) gave good enantioselectivities with the exception of THF (Table 7, entry 11);

although, in the cases of diethyl ether (Table 7, entry 9) and diisopropyl ether (Table 7, entry 10) conversion was very low. Ethyl acetate gave diminished enantioselectivity (Table 7, entry 12). Toluene–$CHCl_3$ mixtures (Table 7, entries 13,14) gave messy reaction mixtures, only in the case of a 9:1 mixture (Table 7, entry 13) could a trace amount of product be isolated, though enantioselectivity was retained compared to chloroform. CH_2Cl_2-toluene mixtures gave similar enantioselectivities to neat toluene (Table 7, entries 15, 16).



Entry	Solvent	Yield (%)	er
1	PhMe	64	61:39
2	PhH	-	61:39
3	*p*-xylene	-	62:38
4	MeCN	-	50:50
5	CH_2Cl_2	87	56:44
6	$CHCl_3$	-	-
7	CCl_4	-	66:34
8	CPME	72	63:37

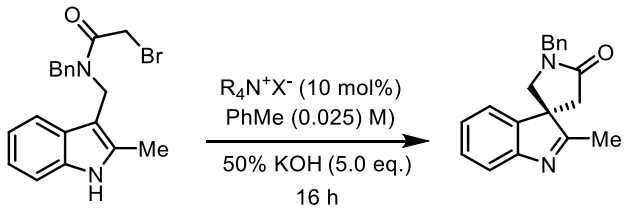
Entry	Solvent	Yield (%)	er
9	Et_2O	-	39:61
10	$^{i}Pr_2O$	-	62:38
11	THF	-	50:50
12	EtOAc	-	45:55
13	9:1 PhMe- $CHCl_3$	-	38:62
14	7:3 PhMe- $CHCl_3$	-	-
15	9:1 PhMe- CH_2Cl_2	-	62:38
16	7:3 PhMe- CH_2Cl_2	88	62:38

Table 7: Effect of solvent on the dearomative alkylation yield and enantioselectivity.

Yields were determined for the most promising solvent systems. CH_2Cl_2 (Table 7, entry 5) gave a better yield than toluene (Table 7, entry 1) as did 7:3 toluene- CH_2Cl_2 (Table 7, entry 16). CPME (Table 7, entry 8) gave a slight increase in yield. 7:3 Toluene- CH_2Cl_2 was selected as the best solvent system as it gave the best yield and er.

At this stage we were concerned about the insensitivity of the observed enantioselectivity to any changes in the reaction conditions. In a final effort to improve the enantioselectivity we screened a

further 8 catalysts (Table 8). Unfortunately, none of the cinchona alkaloid derived catalysts gave an increase in er and neither did cyclopropenium salt **251**.



Entry	$R_4N^+X^-$	Scaffold	R^1	R^2	Ar	er
1	72	CN	H	H	3,5-$(CF_3)_2(C_6H_3)$	50:50
2	170	CN	H	allyl	9-anthracenyl	44:56
3	246	CD	H	allyl	Ph	61:39
4	247	CD	H	H	2-naphthyl	59:41
5	248	QN	OMe	H	Ph	56:44
6	249	QN	OMe	H	Ar	55:45
7	250	-	-	-	-	55:45
8	251	-	-	-	-	52:48

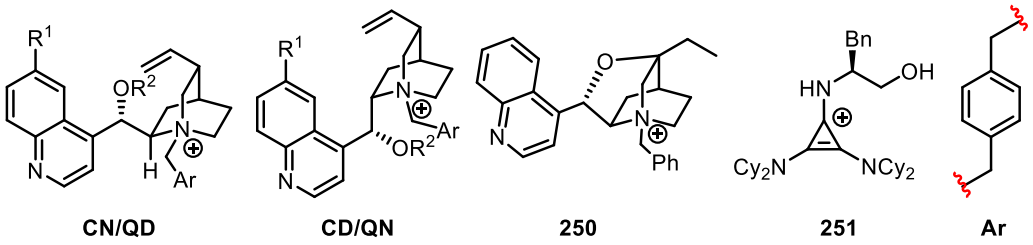
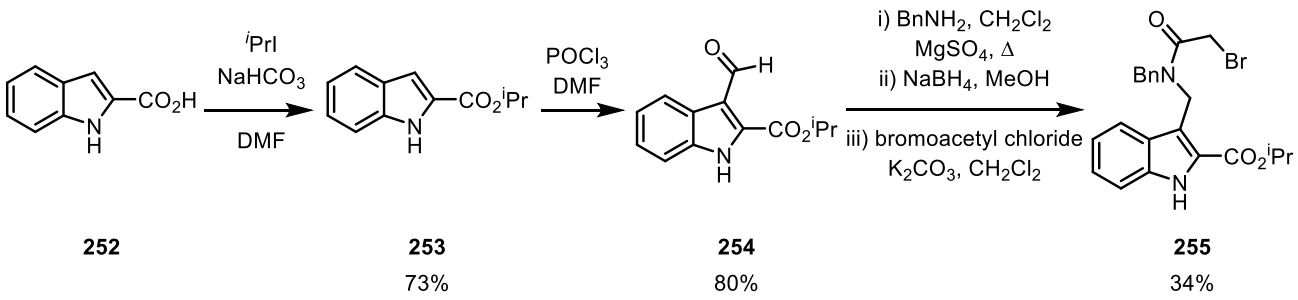


Table 8: Effect of phase-transfer catalysts on enantioselectivity.

It had become apparent that high enantioselectivity would not be achievable using our catalyst library. We therefore decided to modify the reaction substrate with a view to improving catalyst–substrate binding. The obvious site for modification was the indole *C*2 position. The methyl group, which was initially chosen arbitrarily, was replaced with an electron-withdrawing 2-carboxylate ester.

Starting from indole-2-carboxylic acid, alkylation with 2-iodopropane gave the isopropyl ester which was then formylated under Vilsmeier conditions to give the aldehyde (**254**). Reductive amination

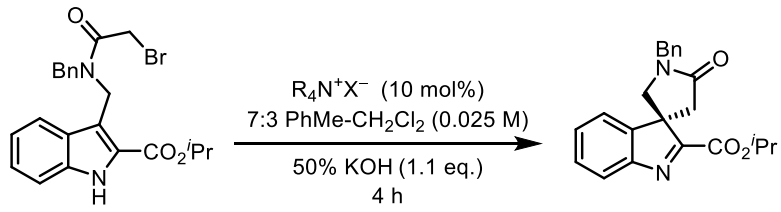
followed by acylation with bromoacetyl chloride gave the cyclization substrate with a *C*2 isopropyl ester (**255**).



252 **253** 73% **254** 80% **255** 34%

Scheme 54: Synthesis of a reaction substrate bearing a C2 isopropyl ester.

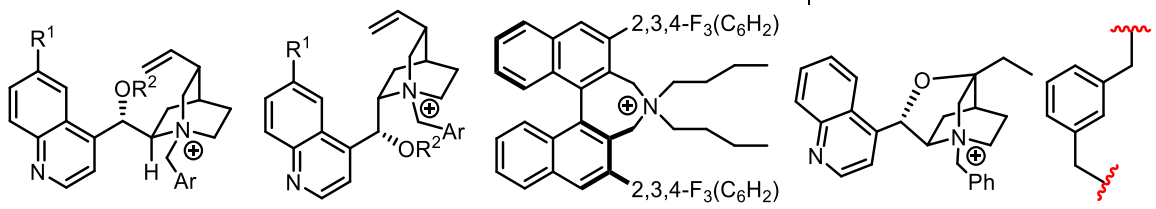
With the isopropyl ester substrate in hand, we then screened a range of chiral phase transfer catalysts in the hope of finding a more selective catalyst (Table 9). Unfortunately, of the 34 catalysts screened, none gave an improvement in selectivity over the initially identified cinchonidine derived phase transfer catalyst, which gave the product in a modestly improved er of 66:34.



255 **256**

Entry	$R_4N^+X^-$	Scaffold	R^1	R^2	Ar	Er
1	14	CN	H	H	Ph	32:68
2	248	QN	OMe	H	Ph	60:40
3	258	QD	OMe	H	Ph	41:59
4	74	CN	H	H	2,3,4-$F_3(C_6H_2)$	37:63
5	234	CN	H	H	9-anthracenyl	40:60
6	170	CN	H	allyl	9-anthracenyl	39:61
7	233	CN	H	H	3,5-^{t}Bu$_2(C_6H_3)$	33:67
8	238	CD	H	H	9-anthracenyl	63:37
9	18	CD	H	allyl	9-anthracenyl	67:33
10	244	M	-	-	-	41:59
11	246	CD	H	Allyl	Ph	64:36
12	247	CD	H	H	2-naphthyl	68:32
13	236	CD	H	H	4-$(CF_3)(C_6H_4)$	69:31
14	257	CD	H	H	1-naphthyl	69:31
15	258	CD	H	H	3-F(C_6H_4)	68:32
16	259	CD	H	H	4-$(NO_2)(C_6H_4)$	69:31
17	260	CD	H	H	3,5-$(CF_3)_2(C_6H_3)$	64:36

Entry	$R_4N^+X^-$	Scaffold	R^1	R^2	Ar	er
18	237	CD	H	H	3,5-$((CF_3)_2CF)_2(C_6H_3)$	66:34
19	261	CD	H	H	3,5-$((CF_2)_2$-$CF_3)_2$-(C_6H_3)	66:34
20	262	CD*	H	H	Ph	69:31
21	263	CD*	H	H	2,3,4-$F_3(C_6H_2)$	65:35
22	71	CN	H	H	4-$(CF_3)(C_6H_4)$	34:66
23	256	*iso*-CN	-	-	-	52:48
24	72	CN	H	H	3,5-$(CF_3)_2(C_6H_3)$	36:64
25	264	CN	H	H	4-F(C_6H_3)	34:66
26	70	CN	H	H	C_6F_5	51:49
27	265	CN	H	H	3,5-(3,5-$(CF_3)_2C_6H_3)_2(C_6H_3)$	42:58
28	266	CN	H	H	3,5-(3,5-^{t}Bu$_2C_6H_3)_2(C_6H_3)$	37:63
29	267	CN	H	H	4-^{t}Bu(C_6H_4)	33:67
30	268	CN	H	H	1-naphthyl	35:65
31	269	CN	H	H	3,4,5-$F_3(C_6H_2)$	44:56
32	270	CN	H	allyl	3,4,5-$F_3(C_6H_2)$	44:56
33	271	CN	H	allyl	3,5-$(CF_3)_2(C_6H_3)$	46:54
34	272	CN	H	H	Ar	49:51

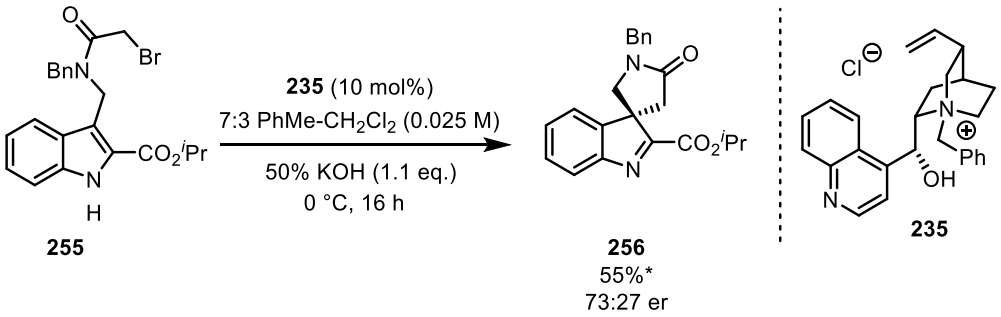


CN/QD **CD/QN** **Maruoka** ***iso*-CN** **Ar**

Table 9: Effect of catalysts on indole dearomatization substrate bearing a C2 isopropyl ester group.

During the course of catalyst screening, we noticed that the reaction with the isopropyl ester substrate was faster than for the methyl substrate. This suggested to us that the enantioselectivity may be improved by running the reaction at a lower temperature (Scheme 55). As expected, a

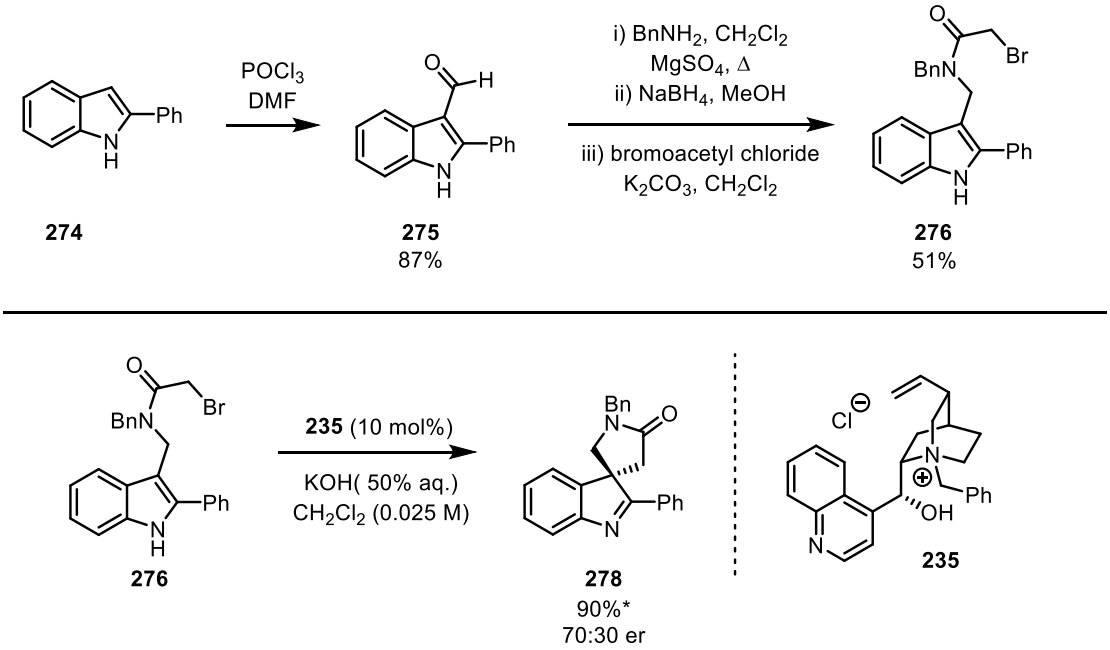
modest improvement in the enantioselectivity was observed by running the reaction at 0 °C and extending the reaction time to 16 hours.



Scheme 55: Optimized conditions for the dearomtization of the isopropyl ester substrate (**255**).

*Determined by quantitative ^{1}H NMR analysis using CH_2Br_2 as an internal standard.

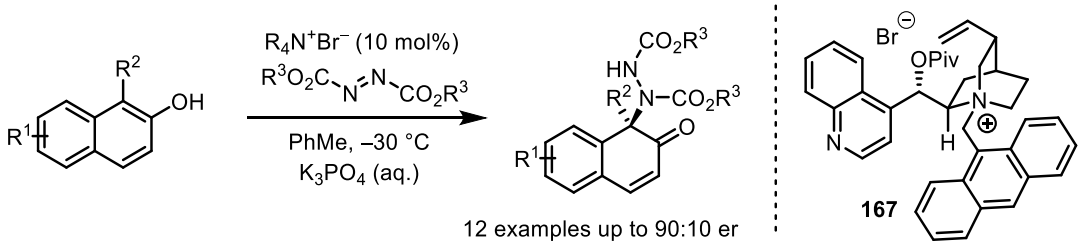
We next examined the effect of an aromatic group at the indole *C*2 position (Scheme 56). The required starting material was prepared by Vilsmeier formylation of 2-phenylindole followed by reductive amination and acylation with bromoacetyl bromide. Disappointingly, when subjected to the optimized reaction conditions the enantioselectivity was similarly low compared to the *C*2-methyl and *C*2-ester substrates.



Scheme 56: Top: Synthesis of C2-aryl dearomatization substrate. Bottom: Alkylative dearomatization under the best conditions. *Determined by quantitative ^{1}H NMR analysis using CH_2Br_2 as an internal standard.

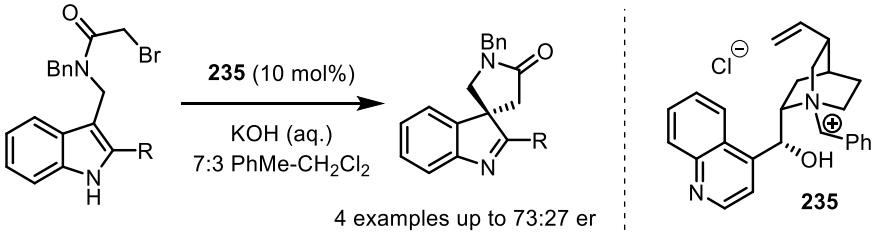
1.3.5. Conclusion and Future Work

We have demonstrated the viability of electrophilic catalytic enantioselective dearomatization of naphthols and indoles under phase transfer catalysis. The reactions are high yielding, but high enantioselectivity could not be achieved. The intermolecular dearomatization of 2-naphthols with azodicarboxylate esters occurs with excellent yield and promising enantioselectivity (Scheme 57). However, the reaction showed poor generality over a range of substituted naphthols and a fast rate of uncatalyzed reaction in the absence of a chiral ammonium salt raised concerns regarding background reactivity.



Scheme 57: Dearomative amination summary.

In contrast to azodicarboxylate esters, alkyl halides react only in the presence of the phase transfer catalyst. However, they have a strong preference to react on the heteroatom to give aromatic products. This can be overcome by appropriate substrate design using an indole *C*3 tethering strategy (Scheme 58). These reactions are highly selective for the dearomatized *C*-alkylated products and give good yields. However, despite screening a broad range of chiral ammonium salts, poor enantioselectivity was observed in every case. At this stage it is unclear whether the failure to achieve high enantioselectivity is due to poor catalyst selection or due to an inherent difficulty in the reaction architecture.



Scheme 58: Dearomative alkylation summary.

It is clear that the nature of the electrophile will be key in the design of subsequent phase-transfer-catalysed dearomatization reactions. The rate of uncatalysed background reactivity should be minimal and the electrophile should have a preference for *C* over *N*/*O*-alkylation, although this can be addressed to some degree using a tethering approach. It is not clear which electrophiles might meet these requirements.

2. Catalytic Enantioselective Photocyclization

2.1. Introduction

2.1.1. Synthetic Organic Photochemistry

The use of light energy to drive chemical reactions is a well-established strategy to access reactivity unachievable in the ground state.[94, 95] Typically, an organic molecule will absorb a photon and be promoted to an excited singlet state (S_1) (Figure 19). From the S_1 state the molecule can either react directly, relax to the ground state (by internal conversion or fluorescence) or undergo intersystem crossing (ISC) to the lowest energy excited triplet state (T_1). The T_1 state is longer lived and possesses reactivity distinct to that of the S_1 state.

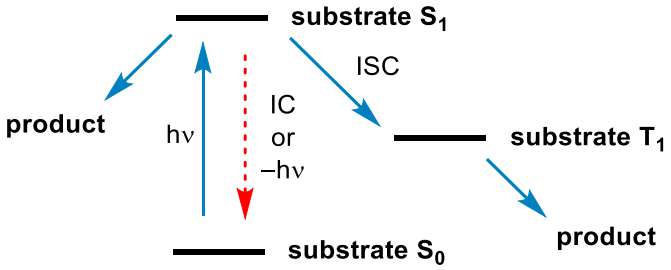


Figure 19: Jablonski diagram for a hypothetical photochemical reaction.

Representative photochemical reactions include [2+2] photocycloadditions, radical translocation-recombination processes and cyclization reactions - the subject of this chapter.[96]

2.1.2. Photosensitization

The organic molecules employed as substrates in synthetic organic photochemistry typically have high energy S_1 states that necessitate the use of hazardous UV light to achieve reactivity. In contrast, the T_1 state is lower in energy and may in principle be accessed using lower energy light. However, the S_0 to T_1 transition is spin-forbidden and therefore not a viable route to access excited states.[95]

A photosensitizer is a compound that undergoes efficient S_1/T_1 intersystem crossing and is capable of transferring energy to another molecule by dipole-dipole coupling (Förster resonance energy transfer (FRET)), or, more commonly, an exchange (Dexter) mechanism.[97] In the Dexter energy transfer process, a high energy electron is exchanged for a low energy electron, thereby promoting the acceptor molecule from its S_0 state to the T_1 excited state (Figure 20).[98]

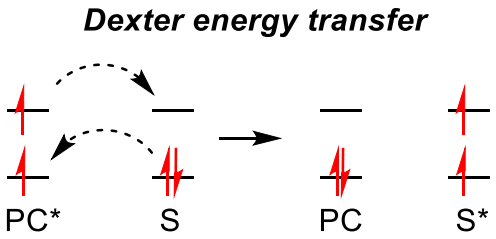
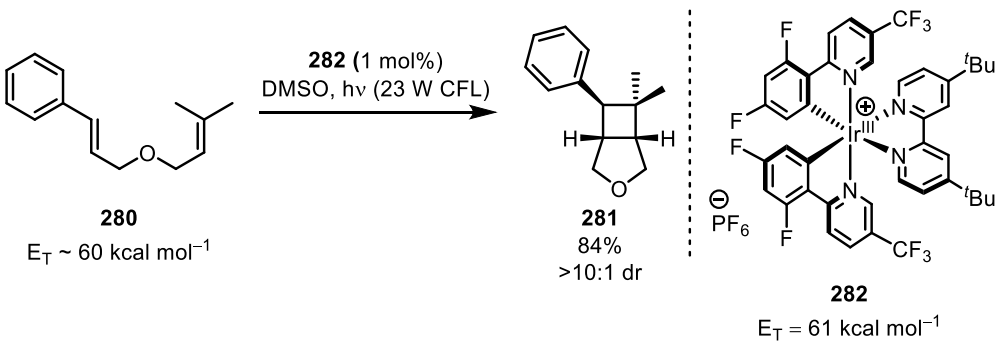


Figure 20: Dexter mechanism for energy transfer.

In 2012, Yoon and co-workers demonstrated that iridium complex **282** could serve as an efficient sensitizer for intramolecular [2+2] photocycloadditions (Scheme 59).[99] Crucially, the triplet energy (E_T) of the iridium complex had to exceed that of the substrate (**280**), or energy transfer was slow and the reaction did not proceed. This constraint limited the scope of the reaction to styrenes. Electron rich and deficient styrenes were both employed successfully, suggesting an energy transfer mechanism instead of electron transfer since the presence of electron withdrawing or donating groups will alter the redox properties of the starting material and compromise photoredox mechanisms, whereas electron poor or deficient styrenes both have suitable triplet energies for energy transfer.



Scheme 59: Sensitized [2+2] photocycloaddition.

2.1.3. Enantioselective Photochemical Reactions

Catalytic enantioselective ground state reactions work by catalyst lowering of the activation energy required to overcome the highest energy transition state (Figure 21). Catalytic enantioselective photochemical reactions are much more challenging owing to the fact that high-energy excited states generally react rapidly *via* lower-barrier transition states without catalysis.[100] Successful approaches have relied on catalysis of the excitation event itself. By using this approach, the excited state is formed preferentially in the presence of the chiral catalyst and racemic, uncatalyzed background reactivity is minimised.

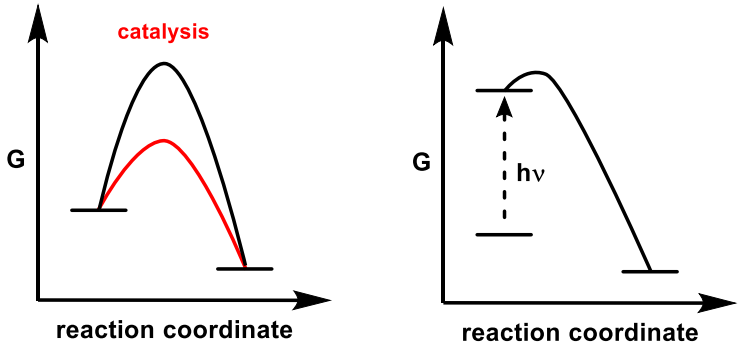
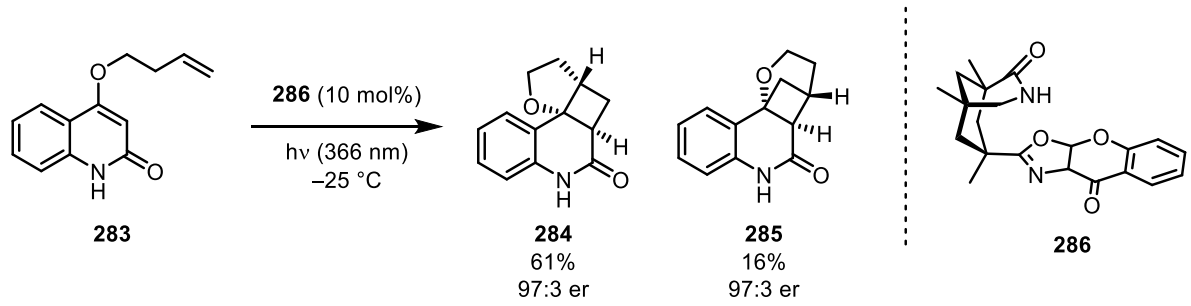


Figure 21: Generalised reaction coordinate for ground state (left) vs. photochemical (right) reactions.

Reactions with Chiral Photosensitizers

The first highly enantioselective example of catalysis using a chiral triplet sensitizer was reported by Bach in 2009 (Scheme 60).[101] In this reaction a xanthone sensitizer with an amide hydrogen bonding motif (**286**) was able to catalyse an intramolecular [2+2] photocycloaddition of quinolone substrate **283** to deliver cyclobutanes (**284**, **286**) in 97:3 er. The catalyst was able to achieve this by binding to the substrate, then, upon absorbing a photon, transferring energy to the substrate. Crucially, the catalyst remains hydrogen bonded to the substrate until the cyclobutane is formed. This highlights the necessity that substrate catalyst dissociation is considerably slower than reaction from the excited state to ensure the reaction happens within the chiral environment of the catalyst.

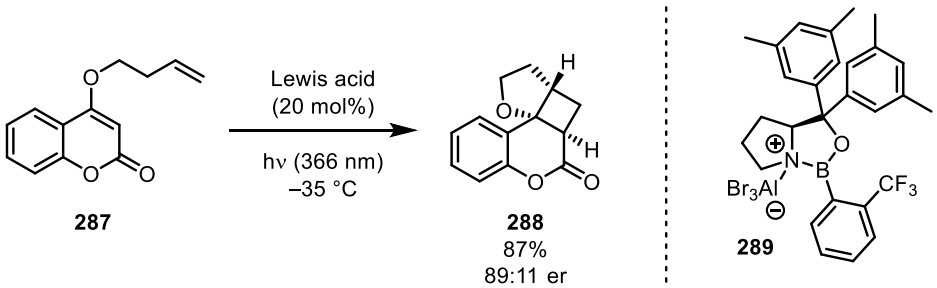


Scheme 60: Catalytic enantioselective [2+2] photocycloaddition using a chiral hydrogen bonding photosensitizer.

Reactions Under Direct Irradiation Using Chiral Lewis Acid Catalysts

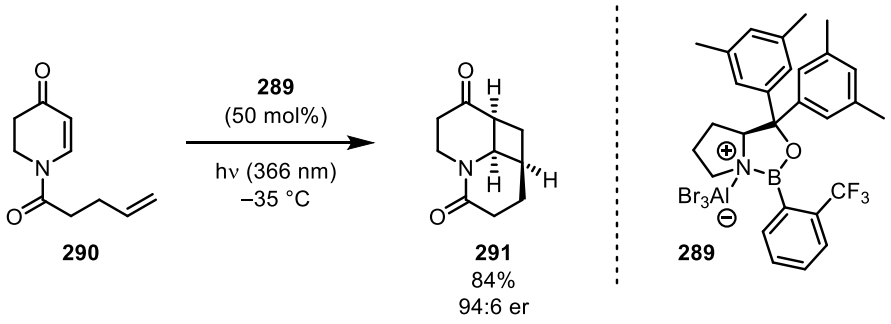
While some success has been achieved using chiral photosensitizers, the approach is challenging due to the requirement of the catalyst to perform well both in promoting the reactant to the excited state and controlling the enantioselectivity of the subsequent transformation. Under a direct irradiation regime, it has been possible to induce enantioselectivity in photochemical reactions using chiral Lews acids.[100] This has the advantage that enantioselective Lewis acid catalysis is a well-developed area that provides a wide selection of chiral catalysts to draw from.

In 2010, Bach and co-workers demonstrated that an $AlBr_3$ activated oxazaborolidine catalyst (**289**) catalysed the intramolecular [2+2] photocycloadditions of coumarin **287** in 84% yield and 91:9 er (Scheme 61).[102] The catalyst is believed to promote the reaction by inducing a bathochromic shift in the substrate to facilitate UV light absorption and stabilising the resulting singlet excited state from which the [2+2] photocycloaddition occurs.[103, 104]



Scheme 61: Lewis acid catalysed enantioselective [2+2] photocycloaddition of a coumarin (**287**).

In subsequent work from Bach, it was shown that the same Lewis acid catalyst (**289**) promoted the enantioselective [2+2] photocycloaddition of dihydropyridone **290** in 84% yield and 94:6 er (Scheme 62) to give cyclobutane **291**.[105] In this case, catalysis was attributed to a large bathochromic shift in the substrate UV spectrum from the π-π* transition upon coordination to the Lewis acid. A bathochromic shift of 50-60 nm was observed and the resulting band absorbed strongly ($\varepsilon > 10\,000\ M^{-1}\ cm^{-1}$) with a maximum at 343 nm. Upon irradiation with a light source centred at 366 nm, the light is absorbed exclusively by the substrate-Lewis acid complex and the reaction only occurs only with the involvement of the chiral catalyst.

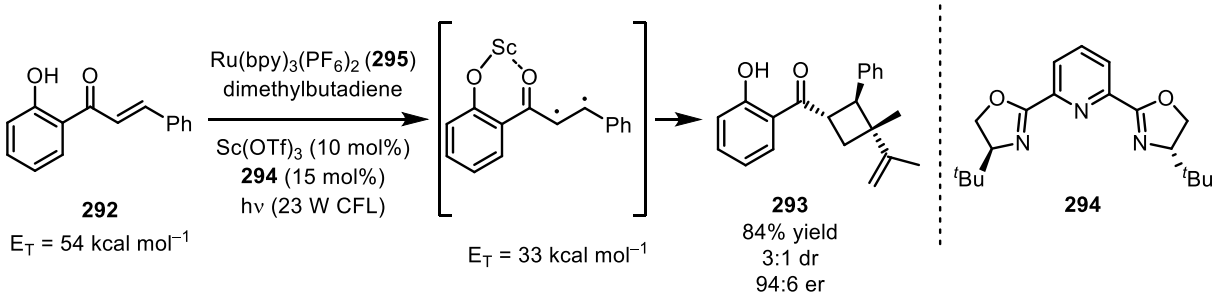


Scheme 62: Enantioselective [2+2] photocycloaddition of a dihydropyridone (**290**) with a chiral Lewis acid catalyst.

Reactions Using Achiral Sensitizers with Chiral Co-Catalysts

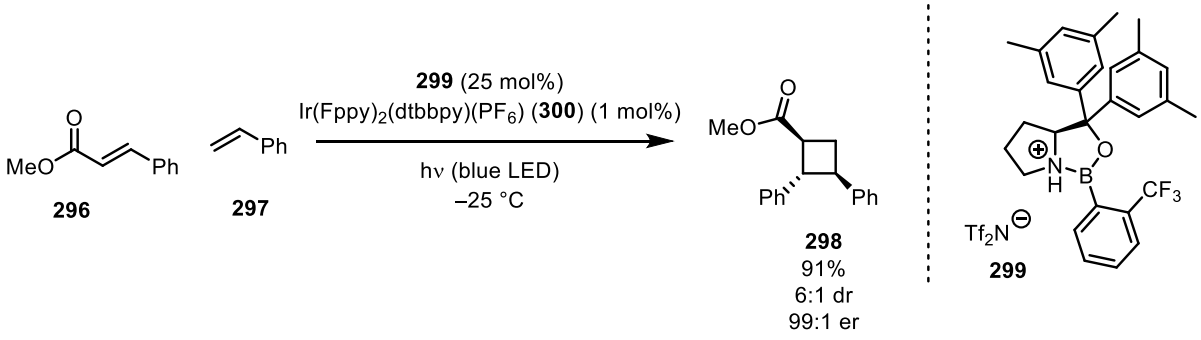
In 2016, Yoon and co-workers introduced the concept of Lewis acid catalysed triplet energy transfer applied to the [2+2] photocycloadditions of hydroxychalcone (**292**) with dimethylbutadiene (Scheme 63).[106] The triplet energy of hydroxychalcone (**292**) was dramatically lowered from 54 to 32 kcal mol^{-1} in the presence of a scandium (III)-pybox (**294**) complex. This observation was exploited by using a ruthenium sensitizer (**295**) with a triplet energy of 46 kcal mol^{-1} which was capable of transferring energy to the Lewis acid bound substrate but not the unbound substrate. As a result, the reaction could be carried out with low loading of both Lewis acid and sensitizer, and, upon

irradiation with visible light, afforded the intermolecular [2+2] cycloadduct with diene **293** in 84% yield, 3:1 dr and 94:6 er.



Scheme 63: Enantioselective [2+2] photocycloadditions by Lewis acid catalysed triplet energy transfer.

In subsequent work, Yoon and co-workers applied the same reaction design to the crossed [2+2] photocycloaddition of cinnamate esters (**296**) with styrenes (**297**) (Scheme 64).[107] In contrast to hydroxychalcone, the cinnamate ester did not display a strong reduction in triplet energy upon coordination to a range of Lewis acids. However, a rate enhancement in the energy transfer process was observed nonetheless. It was suggested that the Lewis acid served to lower the absolute energy of the substrate frontier molecular orbitals to improve orbital overlap with those of the sensitizer. The thermodynamics of the energy transfer process are largely unchanged, but the reaction is kinetically more favourable upon addition of the Lewis acid. By using an oxazaborolidine catalyst (**299**) as a monodentate Lewis acid, the authors were able to catalyse the [2+2] photocycloaddition of cinnamate ester (**296**) with styrene (**297**) in 91% yield, 6:1 dr and 99:1 er.

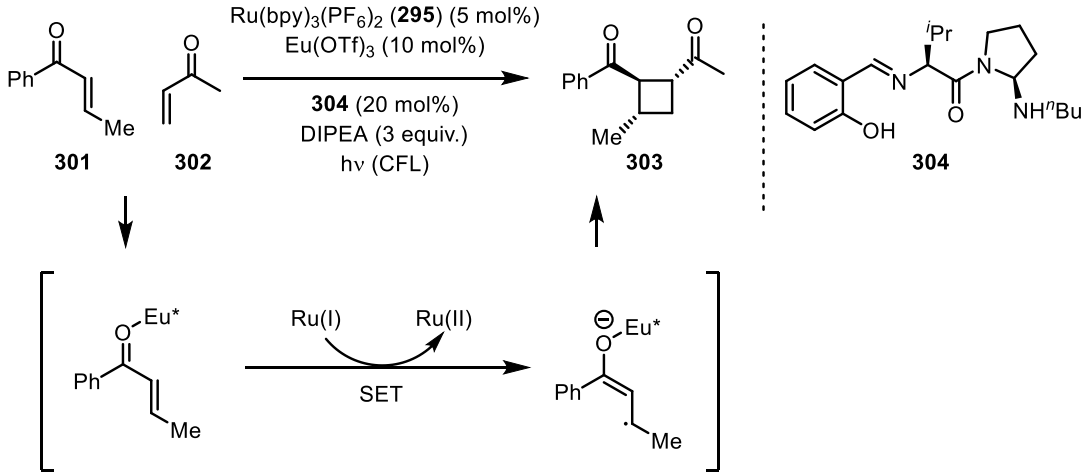


Scheme 64: Extension of Lewis acid catalysed triplet energy transfer to cinnamate [2+2] photocycloaddition.

2.1.4. Enantioselective Photoredox Catalysis with Chiral Lewis Acids

Ruthenium and iridium polypyridyl complexes, as well as serving as photosensitizers, are simultaneously more potent reductants and oxidants in their triplet excited states.[108] Upon promotion to T_1 *via* S_1, the excited state complexes can quench by donating an electron (oxidative quenching) or by accepting an electron (reductive quenching). The question of which path is followed is dictated by the redox properties of the excited-state photocatalyst relative that of the reactants.

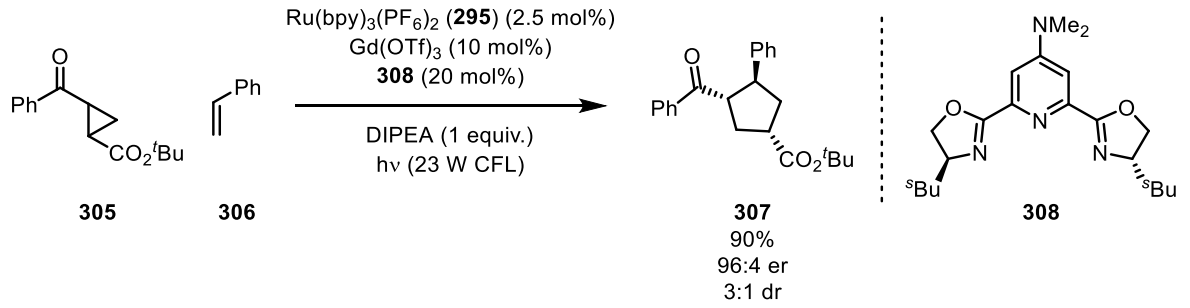
Chiral Lewis acids have been applied successfully in enantioselective photoredeox catalysis.[109] Yoon and co-workers have reported that a europium-imine complex catalyses the crossed [2+2] photocycloaddition of enones (**301**, **302**) under photoredox catalysis (Scheme 65).[110-112] In this case, the europium Lewis acid lowers the reduction potential of the enone (**301**) to facilitate single electron reduction by the reduced state ruthenium photocatalyst.[113] The resulting radical-anion then undergoes cycloaddition with methyl vinyl ketone (**302**) to give cyclobutanes in high enantioenrichment.



Scheme 65: Photoredox-Lewis acid catalysed enantioselective [2+2] photocycloaddition.

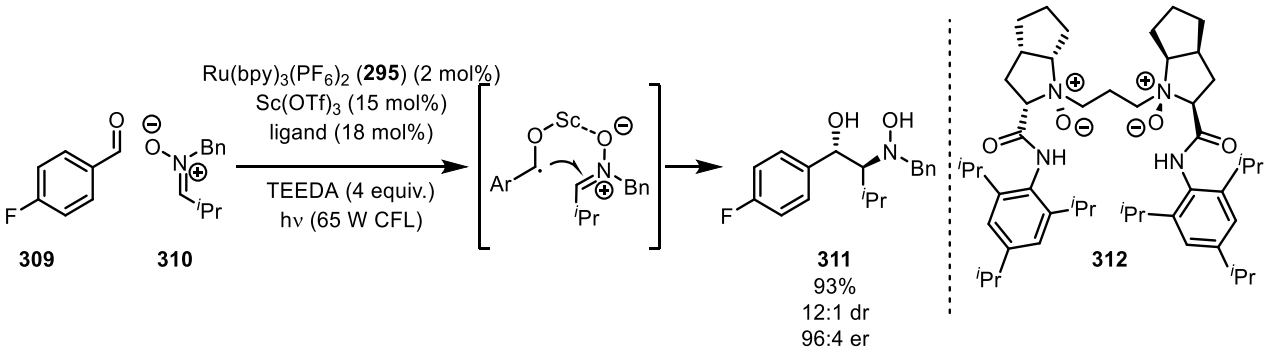
In subsequent work by Yoon and co-workers, a related approach was applied to the [3+2] cycloadditions of arylcyclopropyl ketones (**305**) with alkenes (**306**) (Scheme 66).[114] In this reaction,

a gadolinium-pybox (**308**) complex was used in conjunction with $Ru(bpy)_3(PF_6)_2$ as a photocatalyst to generate radical anions which underwent cycloaddition with alkenes to give trisubstituted cyclopentanes.



Scheme 66: Photoredox-Lewis acid catalysed enantioselective [3+2] photocycloaddition.

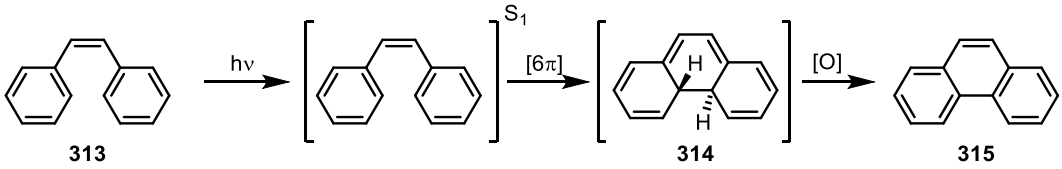
More recently, Zheng and co-workers employed a Lewis acid-catalysed approach to the reductive coupling of aryl aldehydes (**309**) with nitrones (**310**) (Scheme 67).[115] Here, a chiral scandium triflate/*N*,*N*-dioxide (**312**) complex was used to lower the reduction potential of aldehydes to facilitate reduction by a reduced state ruthenium photocatalyst. The resulting radical anion underwent coupling with a nitrone to give to give α-amino alcohols (**311**). The authors proposed a transition state in which both the radical anion and nitrone are coordinated to the Lewis acid in a Zimmerman-Traxler like transition state, leading to high diastereo- and enantioselectivity.



Scheme 67: Lewis acid-catalysed enantioselective reductive aldehyde-nitrone coupling.

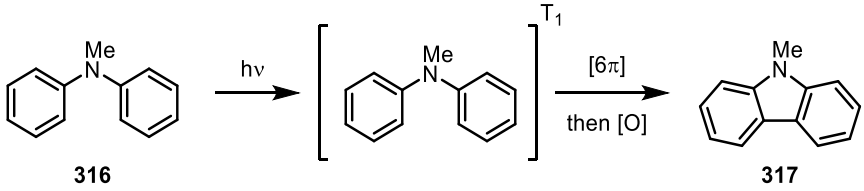
2.1.5. [6π] Photocyclization

Photochemical mediation of (formal) electrocyclic reactions has a long history that can be traced back to the cyclization of stilbenes (**313**) under oxidative conditions to give phenanthrenes (**315**) (Scheme 68).[116] The reaction proceeds *via* a stereospecific singlet excited state electrocyclic ring closure to give the trans-fused dihydrophenanthrene intermediate (**314**), which is oxidised *in situ* by an external oxidant to give phenanthrene (**315**). When the reaction is carried out under a sensitization regime, no cyclized product is observed and a mixture of *cis* and *trans* stilbenes is recovered.[117] This indicates that the reaction occurs exclusively in the S_1 excited state.



Scheme 68: [6π] Photocyclization of stilbene (**313**).

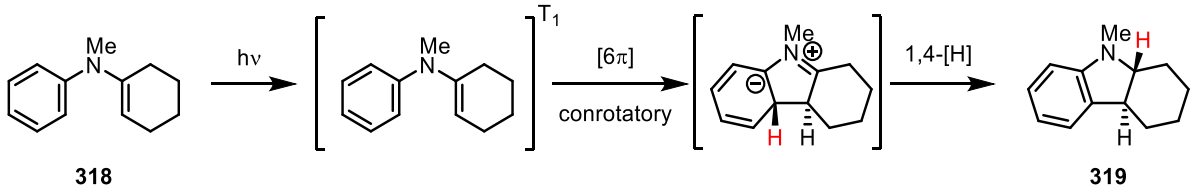
A related reaction is also known for diphenylamines (**316**) to give carbazoles (**317**) (Scheme 69).[118] In contrast to the stilbene photocyclization, these reactions occur *via* the triplet excited state as determined by flash photolytic studies.



Scheme 69: [6π] photocyclization of diphenylamines.

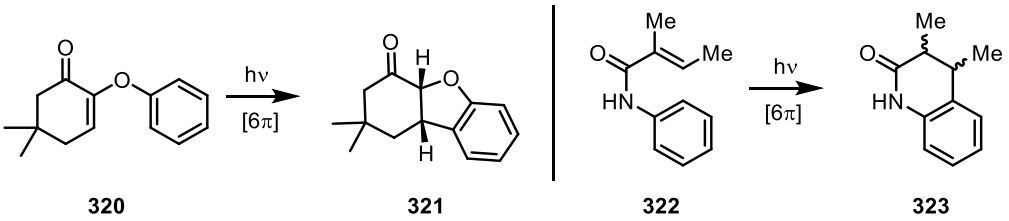
Under non-oxidative conditions, phenyl vinyl amines (**318**) cyclize to give indoline derivatives (**319**) (Scheme 70). This reaction also operates *via* the triplet excited state and is amenable to photosensitization using xanthone as a photocatalyst. Mechanistically, a conrotatory [6π] photocyclization analogous to the diphenylamine photocyclization was proposed, leading to an

azomethine ylid. Deuterium labelling experiments were used to deduce a [1,4]-hydride shift leading to the re-aromatized indoline product.[119, 120]



Scheme 70: [6π] photocyclization of *N*-vinylanilines.

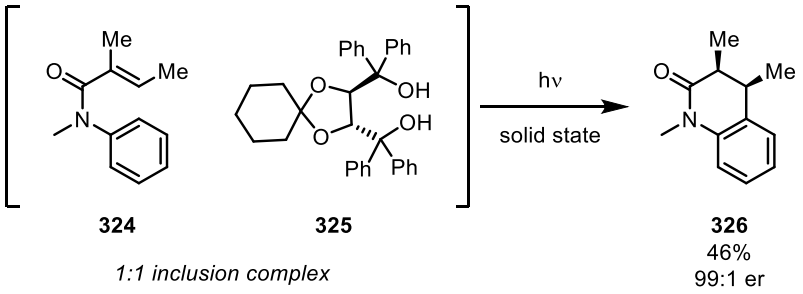
The photocyclization approach has also been applied to *O*-linked systems (**321**) to give dihydrobenzofurans (**321**) and to acrylanilides (**322**) to give dihydroquinolones (**323**) (Scheme 71).[121-124] In the case of the dihydrobenzofuran system, the cyclic enone chromophore was necessary to ensure good light absorption.



Scheme 71: Left: [6π] photocyclization of α-aryloxyenone (**320**). Right: [6π] photocyclization of acrylanilide (**322**).

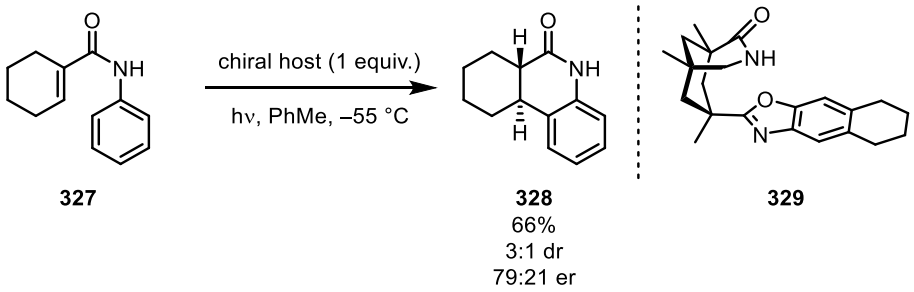
Enantioselective Approaches

The earliest enantioselective [6π] photocyclization was reported by Toda and co-workers in 1992 in the solid state (Scheme 72).[125] The authors were able to co-crystallise an acrylanilide (**324**) with a chiral diol (**325**). Photolysis of the resulting inclusion complex in the solid state afforded the cyclized product (**326**) in 99:1 er and 46% yield. Co-crystallisation in an inclusion complex imposed conformational control on the starting material and therefore biased the torquoselectivity of the excited state conrotatory electrocyclization to give a single enantiomer.



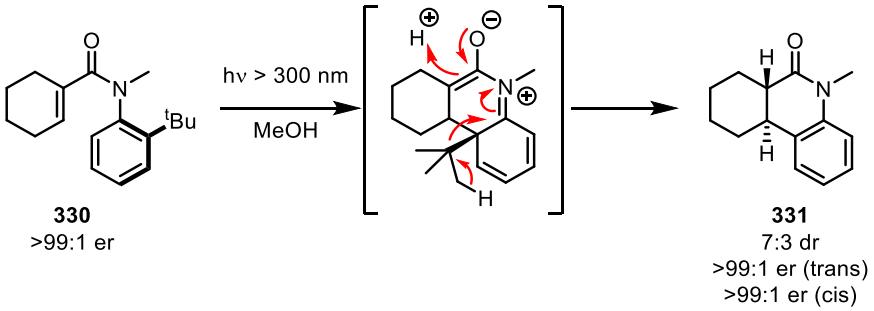
Scheme 72: Solid-state enantioselective [6π] photocyclization in an inclusion complex.

A decade later, Bach and co-workers attempted a similar reaction in solution (Scheme 73).[126] A chiral host compound (**329**) featuring an amide hydrogen bonding unit was able to associate with an acrylanilide (**327**) and control the enantioselectivity of photocyclization. The enantioselectivity observed was modest (79:21 er) and the reaction required a stoichiometric amount of chiral inducer.



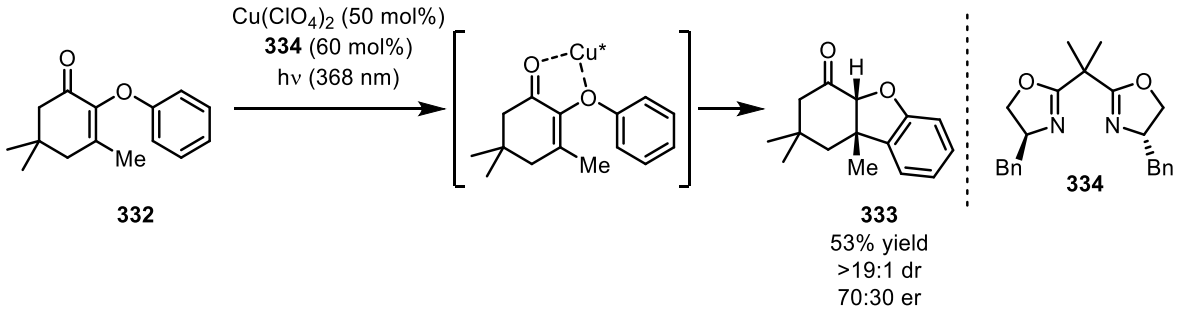
Scheme 73: Enantioselective [6π] photocyclization using a stoichiometric chiral host.

Sivaguru and co-workers reported an alternative approach exploiting axial to point chirality transfer using atropisomeric acrylanilides (**330**) (Scheme 74).[127] The reaction occurred with complete transfer of chirality from the starting material to the product and loss of the *tert*-butyl group as isobutylene following photocyclization onto the *ipso*-carbon. The synthetic worth of the reaction was severely limited by the requirement to separate the enantiomers of the starting material by preparative chiral HPLC. Moreover, the authors failed to report yields for the reactions, which can be assumed to be poor based on the reported conversion (<50%).



Scheme 74: Axial to point chirality transfer in the photocyclization of atropisomeric acryanilides.

More recently the Bach group has revisited enantioselective photocyclization using a Lewis acid catalysed approach (Scheme 75).[128] In analogy to their work on enantioselective [2+2] photocycloadditions of cyclic enones, a chiral copper Lewis acid complex was used to induce a bathochromic shift in the UV absorbtion of α-aryloxyenone **332**. Selective irradiation of the substrate-Lewis acid complex was achievable using monochromatic light to deliver the product (**333**) as a single diastereomer in 70:30 er and 53% yield. The moderate enantioselectivity observed was attributed to background reactivity arising from excitation to the nπ* singlet excited state.

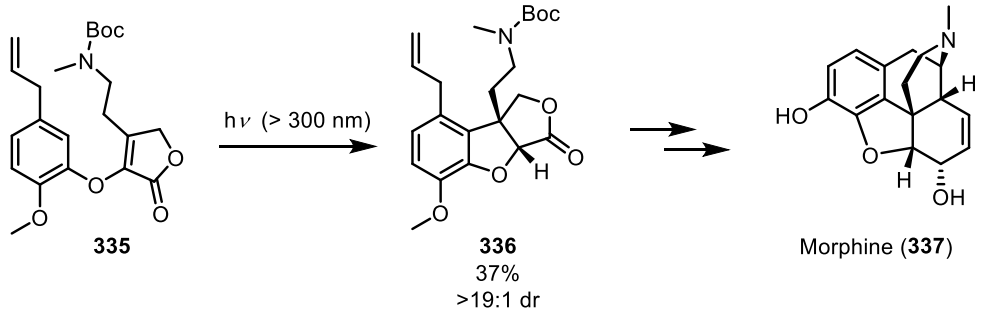


Scheme 75: Lewis acid-catalysed enantioselective [6π] photocyclization.

Previous Work in the Smith Group

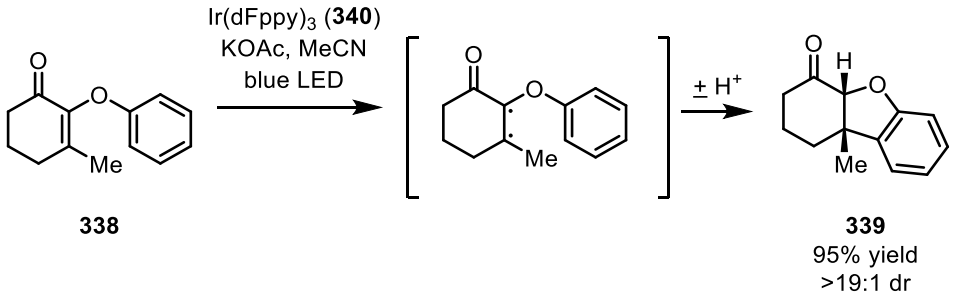
The Smith group became interested in photocyclization reactions in the context of natural product synthesis. Previous work in the group by Dr. Shuyu Chu used a UV mediated [6π] photocyclization as a step in the total synthesis of morphine (**337**) (Scheme 76).[129] The reaction enabled rapid access to the benzofuran core (**336**) of morphine and was a key feature of the synthetic route. However,

the reaction was low yielding and required the use of a hazardous UV light source which was a practical concern.



Scheme 76: UV mediated [6π] photocyclization in the total synthesis of morphine.

Subsequent work by Dr. Neils Muenster and Dr. Nicholas Parker aimed to address these issues by using visible light photocatalysis (Scheme 77).[130] It was found that $Ir(dFppy)_3$ (**340**) could act as a photosensitizer for the related photocyclization of α-aryloxyenones (**338**) at catalyst loadings as low as 0.05 mol% to promote the reaction of a wide range of substrates. An energy transfer mechanism was proposed based on the observation that the yield correlated with increasing triplet energy of the photocatalyst and not with its redox properties. Furthermore, the triplet energy of the starting material was predicted by DFT to be 58.2 kcal mol^{-1}, suggesting favourable energy transfer from the excited state photocatalyst (E_T = 60.1 kcal mol^{-1}).



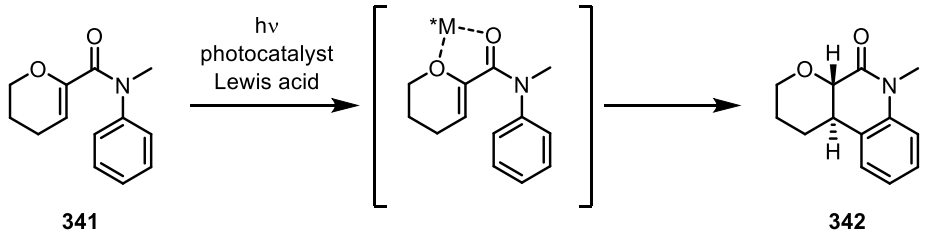
Scheme 77: Visible light mediated [6π] photocyclization using a photosensitizer.

2.2. Proposed Enantioselective Photocyclization and Substrate Synthesis

This work was carried out in collaboration with Pearse Solon and Mihai Popescu. All compounds synthesized and data obtained by Pearse Solon and Mihai Popescu will be denoted **PSXX**/**MPXX** to distinguish our respective contributions to this work.

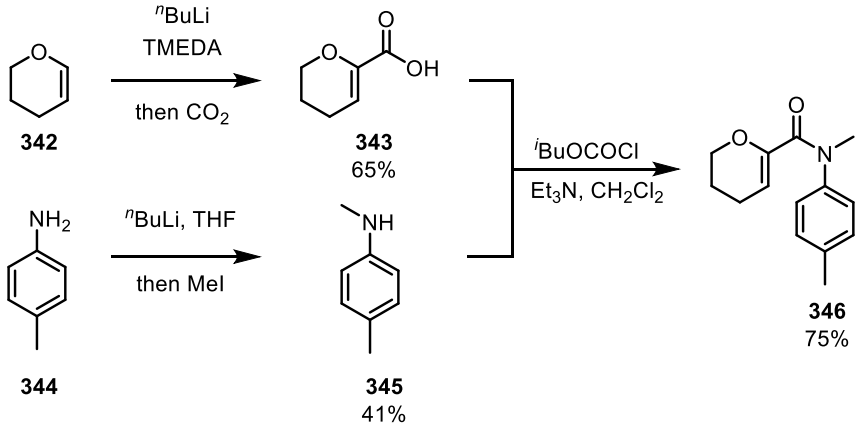
The reported examples of enantioselective [6π] photocyclizations clearly demonstrate that the reactions are amenable to enantioinduction using external chiral controllers, but an effective means of catalysing the reactions had not yet been identified. In approaching this problem, we decided to adopt the Lewis acid-catalysed triplet energy transfer strategy pioneered by Yoon.[106] We reasoned that this would minimise the uncatalyzed background reaction observed by Bach under direct irradiation and enable us to use blue LEDs rather than hazardous UV light.[128] The possibility to tailor the sensitizer to match the triplet energy of the substrate-Lewis acid complex was also appealing.

Since Bach and co-workers had observed limited success with the 2-aryloxyenone cyclization, we opted to instead focus our efforts on the acrylanilide cyclizations developed by Chapman.[121, 128] We reasoned that modification of Chapmans original substrates would be necessary to render the reaction amenable to enantioselective catalysis. With this in mind, we proposed the dihydropyran containing anilide **341** as a suitable starting material for three reasons (Scheme 78). Firstly, the presence of an α-alkoxy substituent would lower the triplet energy to within range of common photosensitizers. Secondly, the dihydropyran ring should control the alkene geometry to minimise the number of possible diastereomeric transition states. Thirdly and finally, the formation of a β-stereocenter should avoid the problem of epimerization that could be expected on forming a stereocenter at the α position. The proposed substrate was also expected to engage in 2-point binding with a Lewis acid.



Scheme 78: Proposed enantioselective Lewis acid catalysed [6π] photocyclization.

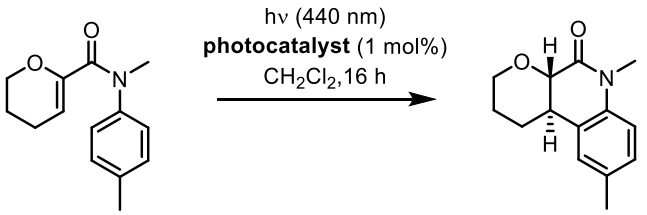
The required starting material was prepared by lithiation of dihydropyran (**342**) at *C*2 followed by trapping with CO_2 to give the dihydropyran carboxylic acid (**343**). *N*-Methylation of *p*-toluidine (**344**) followed by amide coupling with the dihydropyran acid afforded the anilide (**346**) in good yield.



Scheme 79: Synthesis of the reaction substrate **346**.

2.3. Influence of $Sc(OTf)_3$ on the Racemic Photocyclization

We then began examining the racemic cyclization reaction. Irradiation of **346** with 440 nm LEDs in CH_2Cl_2 using $Ir(dFppy)_3$ as a high triplet energy sensitizer gave the racemic product in 96% yield and >19:1 dr. The reaction was significantly slower using $Ir(ppy)_3$ as a lower energy sensitizer. When $Sc(OTf)_3$ was used in combination with $Ir(ppy)_3$, the reaction was evidently faster, with the product being formed in 37% yield; however, significant by-product formation was observed by analysis of the crude ^1H NMR spectrum.



346 347

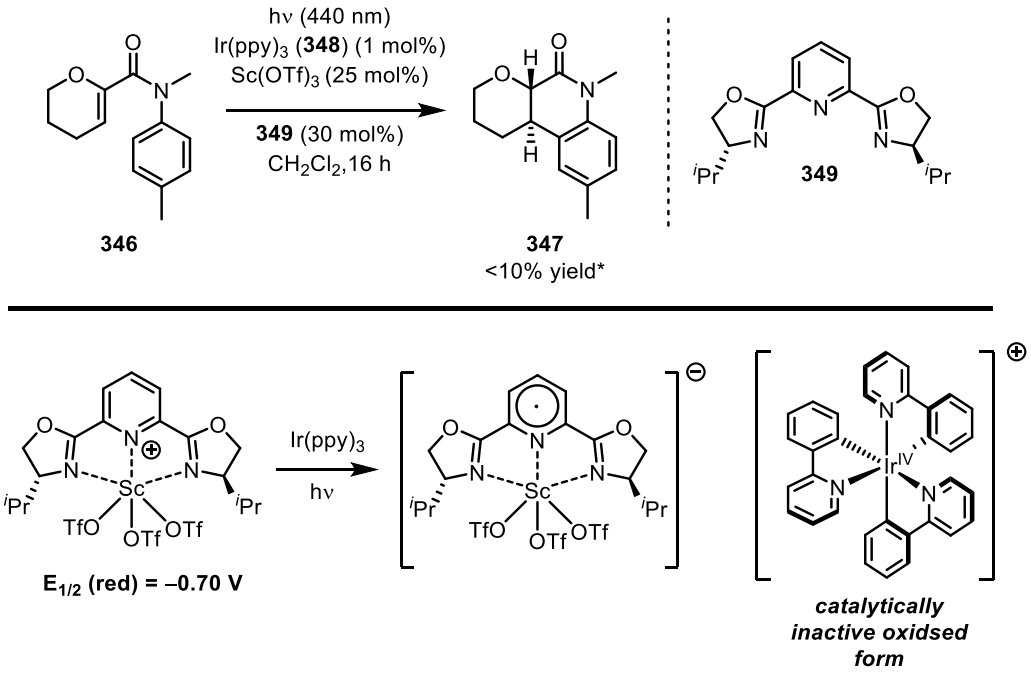
Photocatalyst	Photocatalyst E_T (kcal mol^{-1})	Lewis acid	Yield (%)*	dr
$Ir(dFppy)_3$ (**340**)	60.0	none	95	>19:1
$Ir(ppy)_3$ (**348**)	55.4	none	14	3:1
$Ir(ppy)_3$ (**348**)	55.4	$Sc(OTf)_3$ (25 mol%)	37	>19:1

Table 10: Influence of different photocatalyst and Lewis acid on the racemic photocyclization. *Determined by quantitative ^1H NMR analysis using CH_2Br_2 as an internal standard.

2.4. Reaction Optimization

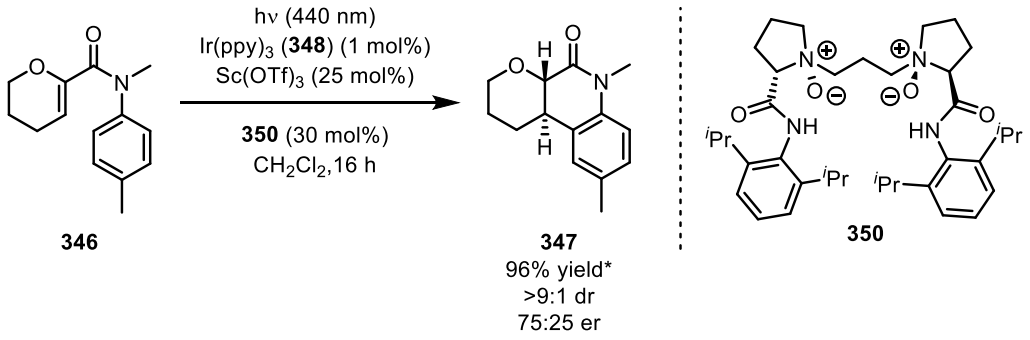
2.4.1. Identification of a Suitable Chiral Ligand

Having demonstrated the catalytic effect of a Lewis acid, we next began investigating chiral ligands for use with scandium. Surprisingly, the reaction was much slower when pybox ligand **349** was used and photocatalyst fluorescence was not observed, suggesting photocatalyst deactivation. To confirm our suspicions, we turned to square wave voltammetry to examine the redox properties of the pybox ligand. Pybox ligand **349** showed an irreversible reduction wave at −2.02 V which was lowered to −0.70 V in the presence of $Sc(OTf)_3$; easily reducible by excited state of $Ir(ppy)_3$ (**348**) ($E_{1/2}^{red}$ = −1.81 V). Based on this information, we propose that the scandium pybox complex is irreversibly reduced, which serves to deactivate the photocatalyst and stall the reaction.



Scheme 80: Inhibitory effect of pybox ligand and proposed photocatalyst deactivation. *Determined by quantitative ^{1}H NMR analysis using CH_2Br_2 as an internal standard.

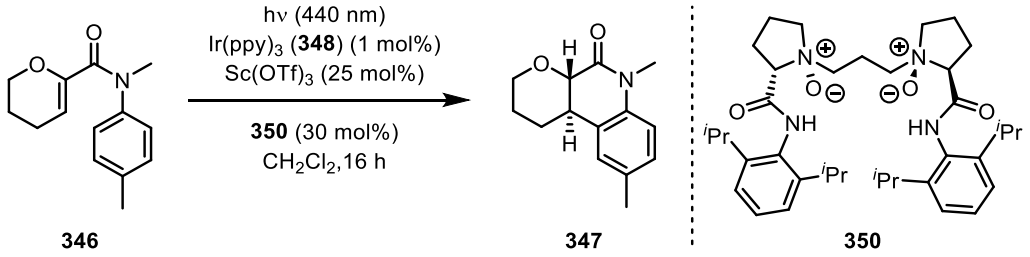
We then sought a chiral ligand that would be resistant to decomposition by strongly-reducing excited state photocatalysts. Feng ligands are proline-derived *N*-oxides that coordinate to a variety of metals through the *N*-oxide oxygens and amide carbonyl groups.[131, 132] Feng ligands have been broadly applied in a range of Lewis acid catalysed reactions and often give very high enantioselectivity. Pleasingly, when Feng ligand **350** was used in our photocyclization the product was delivered in 96% yield, >9:1 dr and a promising 75:25 er. Evidently, the Feng ligand is less susceptible to reduction by the excited state photocatalyst and attenuates the Lewis acidity of $Sc(OTf)_3$ to minimise by-product formation.



Scheme 81: Enantioselective photocyclization with Feng ligand. *Determined by quantitative ^{1}H NMR analysis using CH_2Br_2 as an internal standard.

2.4.2. Elucidation of a Radical-Anion Pathway

Having identified a promising chiral ligand for the reaction, we next set out to identify a photocatalyst capable of selectively exciting the substrate-Lewis acid complex in preference to the unbound substrate. Surprisingly, heteroleptic catalysts **351**, **300** and **352**, which span a range of triplet energies slightly below and above that of $Ir(ppy)_3$, were all found to give the product in very low er. This observation prompted us to question our assumption that the reaction was operating by energy transfer and not photoredox catalysis.



Photocatalyst	Photocatalyst E_T (kcal mol^{-1})	Yield (%)*	dr	er
$Ir(ppy)_3$ (**348**)	55.2	14	>9:1	75:25
$Ir(ppy)_2(dtbbpy)(PF_6)$ (**351**)	49.2	<5	-	55:45
$Ir(Fppy)_2(dtbbpy)(PF_6)$ (**300**)	53.0	12	>9:1	56:44
$Ir(dFppy)_2(dtbbpy)(PF_6)$ (**352**)	55.4	80	>9:1	51:49

Table 11: Influence of photocatalysts on the enantioselective photocyclization. *Determined by quantitative ^{1}H NMR analysis using CH_2Br_2 as an internal standard.

To clarify this issue, we turned to DFT and square wave voltammetry to determine the triplet energy and redox properties of the substrate (**346**). All calculations and voltammetry studies were performed by Mihai Popescu. The uncoordinated substrate has a calculated triplet energy of 56.7 kcal mol^{-1} which is only marginally lowered to 54.9 kcal mol^{-1} in the presence of $ScCl_3$ (as a simplified model of the scandium triflate/ligand complex). In contrast, the unbound substrate has a reduction potential of −2.54 V in MeCN but this is dramatically lowered to −1.21 V in the presence of $Sc(OTf)_3$. This suggests that both quenching mechanisms are viable; however, the effect of Lewis acid catalysis on the radical-anion pathway should be much more pronounced than on the triplet pathway and therefore the best selectivity should be observable under a single electron transfer regime.

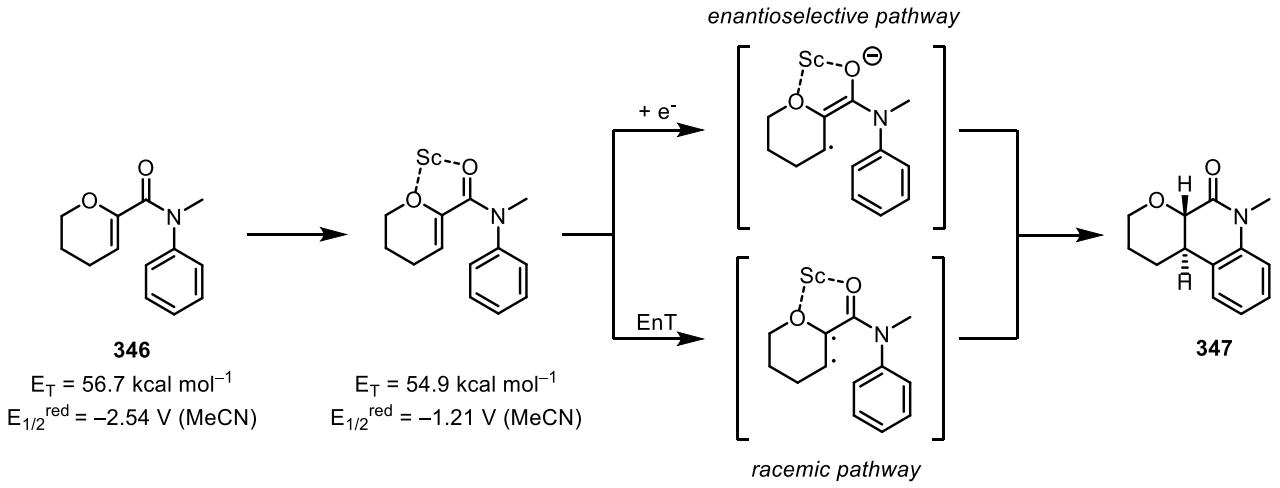
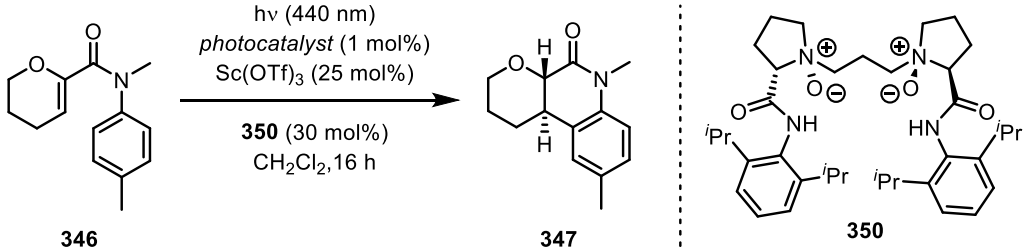


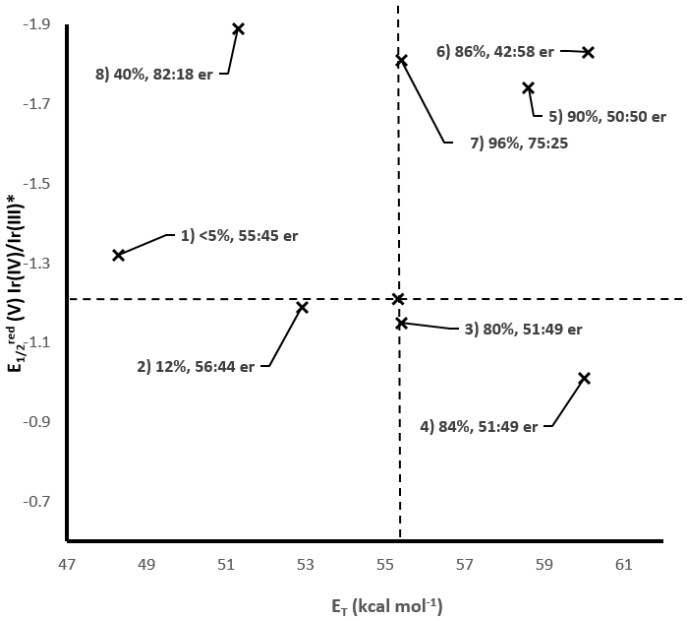
Figure 22: Proposed competitive photoredox/energy transfer mechanisms for [6π] photoyclization.

Our proposal suggested that the photocatalyst properties should have a major effect on selectivity and reactivity. Table 12 shows the excited state reduction potentials of photocatalysts against their triplet energies. The graph can be divided into four quadrants by plotting lines representing the triplet energy and reduction potential of the substrate-scandium complex. Photocatalysts in, or near to the bottom-left quadrant (entries 1 and 2) have triplet energy and reduction potential both less than that of the substrate-scandium complex and are unable to promote the reaction by either mechanism and give low yield and enantioselectivity. Photocatalysts in the bottom-right quadrant (entries 3 and 4) have high triplet energies but are poor photoreductants, so the energy transfer

pathway dominates and the product is formed in high yield but poor enantioselectivity. When strongly reducing photocatalysts with high triplet energies are used (top-right quadrant, entries 5 and 6), the energy transfer pathway appears to dominate, giving the product in high yield and low selectivity. This is probably because the photocatalysts are capable of sensitizing the unbound substrate which is present in much higher concentration than the bound substrate.



346 347 350



Entry	Photocatalyst	E_T (kcal mol^{-1})	$E_{1/2}^{red}$ (V) Ir(IV)/Ir(III)*	Yield (%)*	dr	er
1	$Ir(ppy)_2(dtbbpy)(PF_6)$ (**351**)	48.2	−1.32	<5	-	55:45
2	$Ir(Fppy)_2(dtbbpy)(PF_6)$ (**300**)	52.9	−1.19	12	>9:1	56:44
3	$Ir(dFppy)_2(dtbbpy)(PF_6)$ (**352**)	55.4	−1.15	80	>9:1	51:49
4	$Ir(dFCF_3ppy)_2(dtbbpy)(PF_6)$ (**282**)	60.0	−1.01	84	>9:1	51:49
5	$Ir(Fppy)_3$ (**354**)	58.6	−1.74	90	>9:1	50:50
6	$Ir(dFppy)_3$ (**340**)	60.0	−1.83	86	>9:1	42:58
7	$Ir(ppy)_3$ (**348**)	55.4	−1.81	14	>9:1	75:25
8	Ir((3'MeO)ppy)$_3$ (**355**)	51.3	−1.89	40	>9:1	82:18

Table 12: Influence of photocatalyst properties on the enantioselective photoyclization. *Determined by quantitative ^{1}H NMR analysis using CH_2Br_2 as an internal standard.

$Ir(ppy)_3$ (entry 7) has a strongly reducing excited state ($E_{1/2}^{red}$ = −1.81 V) and a triplet energy of 55.4 kcal mol^{-1} so can engage readily in electron transfer, but is on the limit of being able to engage in energy transfer. This suggested that we could observe improved selectivity in the reaction using a strongly reducing photocatalyst with a triplet energy lower than 55 kcal mol^{-1} (top left quadrant). A catalyst with suitable properties was reported by MacMillan and co-workers based on $Ir(ppy)_3$ but functionalised with methoxy groups at C3′ of the phenypyridine ligands (entry 8).[133] Pleasingly, when used in our reaction, the photocatalyst delivered the product in improved enantioselectivity but decreased yield. Taking this as good evidence for our proposed mechanism we set about designing photocatalysts with the desired properties to further improve the yield and selectivity of the reaction.

2.4.3. Photocatalyst Optimization

Iridium phenylpyridine complexes have been well-studied for their use in OLED applications where their triplet energies dictate the emission wavelength. Accordingly, the structural effects that dictate their redox properties and triplet energies are well-understood.[134-136] Based on OLED literature we were able to propose a design logic for photocatalysts with the desired properties (Figure 23). The triplet energy depends on the HOMO-LUMO gap where the LUMO has its greatest coefficient on the pyridine ligand and the HOMO has its greatest coefficient on the iridium centre, but is largely influenced by the substitution on the benzene ring. Accordingly, the triplet energy of the complex can be lowered by stabilising the LUMO through the incorporation of electron-withdrawing groups on the pyridine or by destabilizing the HOMO by incorporating electron-donating groups on the benzene ring, thereby increasing its relative electronic energy. The redox properties depend largely on the presence of electron donating or withdrawing substituents which give stronger or weaker photoreductants respectively.

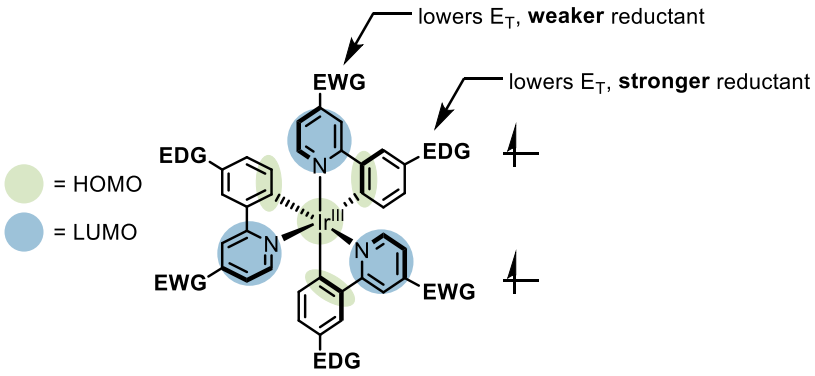
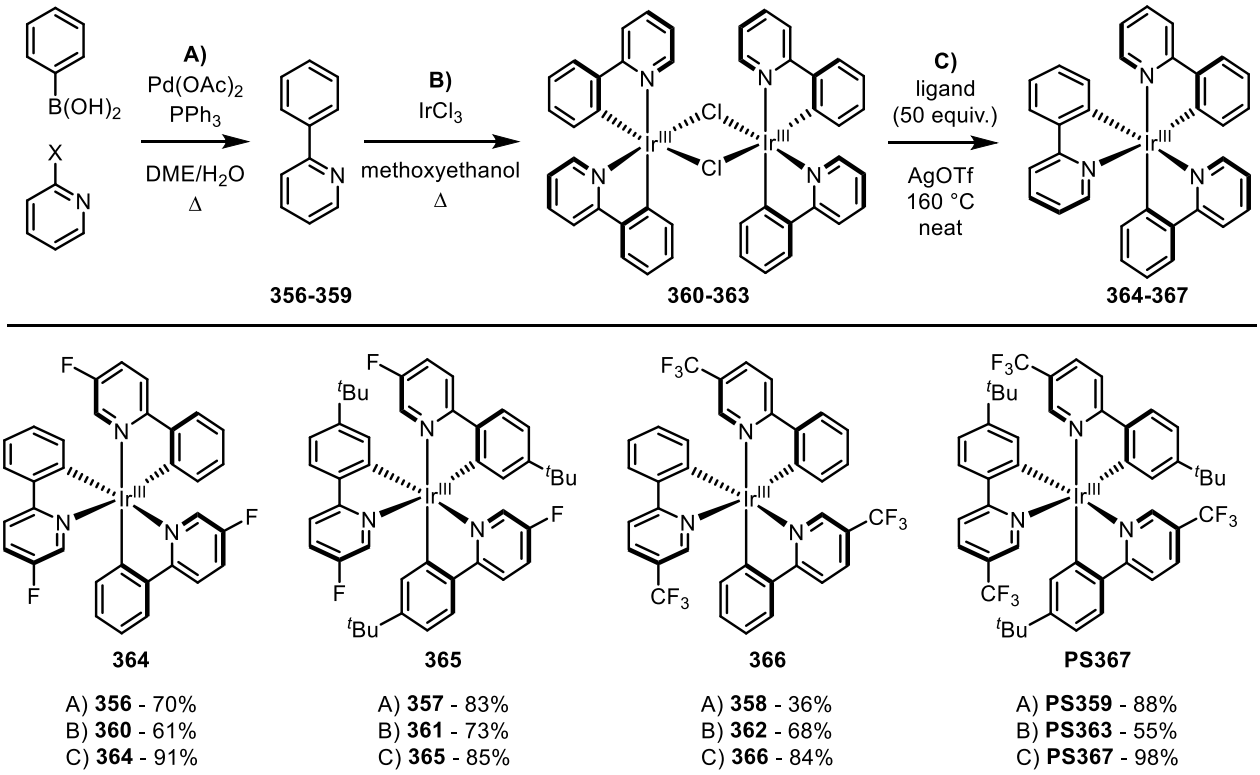


Figure 23: Design logic for improved photocatalysts.

Synthesis of New Photocatalysts

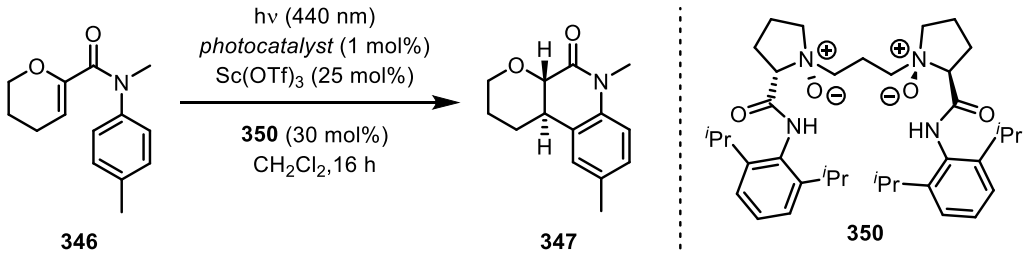
Based on this approach, we proposed iridium complexes **364**-**367** as catalysts for the reaction. The required phenylpyridine ligands (**356**-**359**) were prepared by Suzuki-Miyuara coupling of 2-halopyridines with phenylboronic acids (Scheme 82). It was possible to cyclometallate two phenylpyridine ligands to $IrCl_3$ by refluxing in methoxyethanol-water to give the chloride-bridged dimers (**360**-**363**). However, cyclometallating the third ligand proved substantially more challenging. It was ultimately preferable to prepare the tris-cyclometallated homoleptic complexes from the chloride-bridged dimers by heating to 160 °C under solvent free conditions using a 50-fold excess of the ligand and silver triflate as an additive. This synthesis enabled the preparation of iridium complexes **364**-**367** in moderate to good yields over the three steps.



Scheme 82: Synthesis of new iridium photocatalysts **364**-**367**.

Effect of Photocatalysts on Selectivity

The newly synthesized iridium complexes were fully characterized by Mihai Popescu using square wave voltammetry and fluorescence spectroscopy to determine their redox potentials and triplet energies. As intended, all of the catalysts had a triplet energy lower than $Ir(ppy)_3$ (**348**) and maintained strong excited state reduction potentials. $Ir((5\text{-}F)ppy)_3$ (**364**) gave 98% yield and an improved er of 84:16. $Ir((5\text{-}F)(4'\text{-}^tBu)ppy)_3$ (**365**), which has a slightly lower triplet energy and is slightly more reducing gave improved enantioselectivity but decreased yield. $Ir((5\text{-}CF_3)ppy)_3$ (**366**) is lower still in triplet energy and less reducing, but gives similar yield and selectivity. $Ir((5\text{-}CF_3)(4'\text{-}^tBu)ppy)_3$ (**PS367**) has near identical triplet energy but is a stronger photoreductant and gives the best yield and enantioselectivity. We believe that **PS367** is the optimal photocatalyst as it best able to sustain a catalytic cycle of oxidative quenching and back electron transfer, with the least degree of competitive energy transfer.

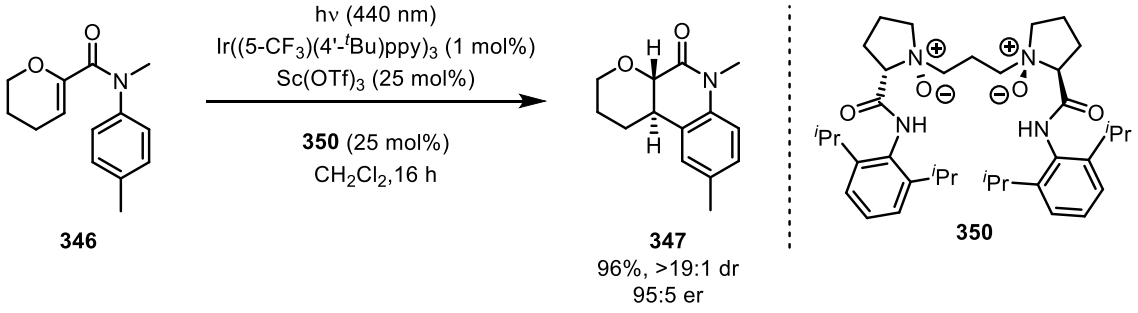


Photocatalyst	E_T (kcal mol^{-1})	$E_{1/2}^{red}$ (V) Ir(IV)/Ir(III)*	$E_{1/2}^{red}$ (V) Ir(IV)/Ir(III)	Yield (%)*	dr	er
Ir((5-F)ppy)$_3$ (**364**)	52.7	−1.73	0.84	98	>19:1	84:16
Ir((5-F)(4′-^{t}Bu)ppy)$_3$ (**365**)	51.9	−1.81	0.75	65	>19:1	89:11
Ir((5-CF$_3$)ppy)$_3$(**366**)	50.9	−1.46	0.97	45	>19:1	89:11
Ir((5-CF$_3$)(4′-^{t}Bu)ppy)$_3$ (**PS367**)	50.3	−1.55	0.87	95	>19:1	94:6

Table 13: Influence of designed photocatalysts on the enantioselective photocyclization. *Determined by quantitative ^{1}H NMR analysis using CH_2Br_2 as an internal standard.

2.4.4. Optimization of Reaction Conditions

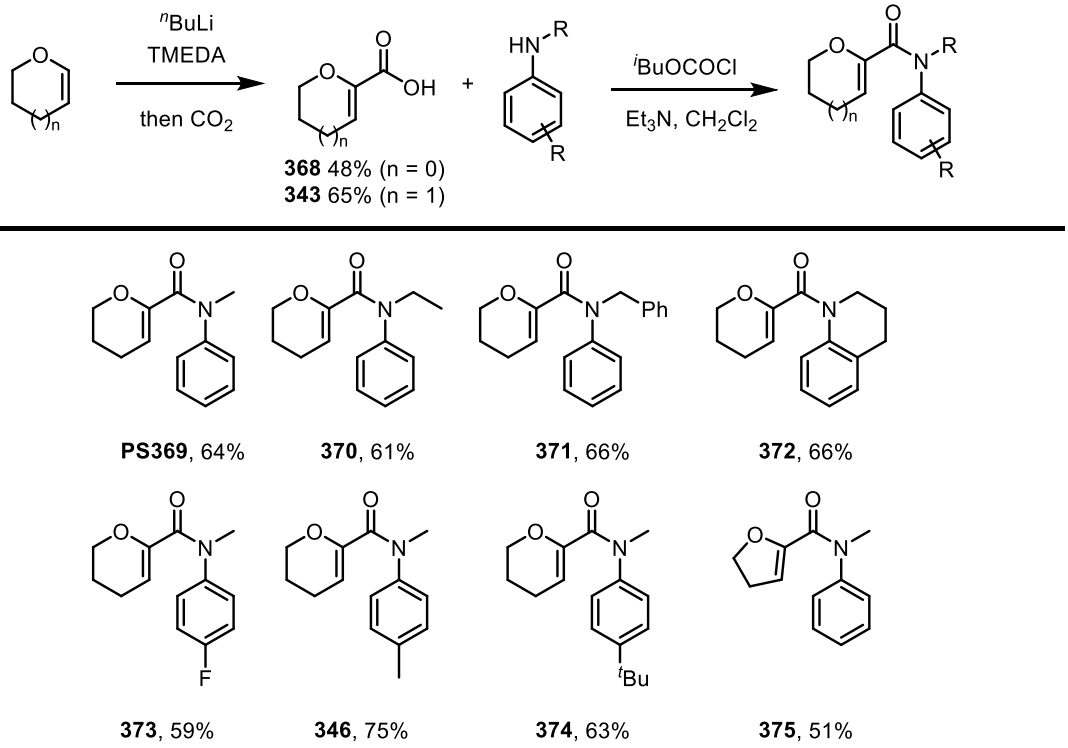
During optimization, we noticed that scandium (III) triflate was not fully soluble in dichloromethane at the concentration required. Reasoning that this may be detrimental to the reaction, we opted to pre-form the Lewis acid complex in a 60 °C sonication bath. Under this new reaction protocol, the loading of the chiral ligand could be reduced to 25 mol% to give the optimised reaction conditions. Employing the new protocol, the product was delivered in 96% yield, >19:1 dr and 95:5 er.



Scheme 83: Optimized conditions for the enantioselective photocyclization.

2.5. Synthesis of a Substrate Library

Having identified optimized reaction conditions for the reaction we set about exploring the reaction scope. A library of substrates was prepared following the same route used for the optimization substrate. Dihydropyran and dihydrofuran were lithiated at *C*2 using ^{n}BuLi/TMEDA and reacted with CO_2 to give the carboxylic acids (**343**, **368**). *N*-Alkyl anilines were coupled with the dihyropyran/dihydrofuran acids *via* their mixed isobutyl anhydrides to give anilides **346**, **369-375**.

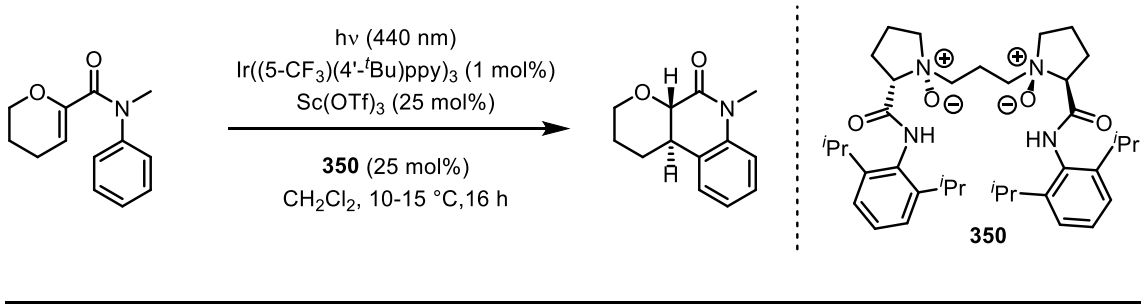


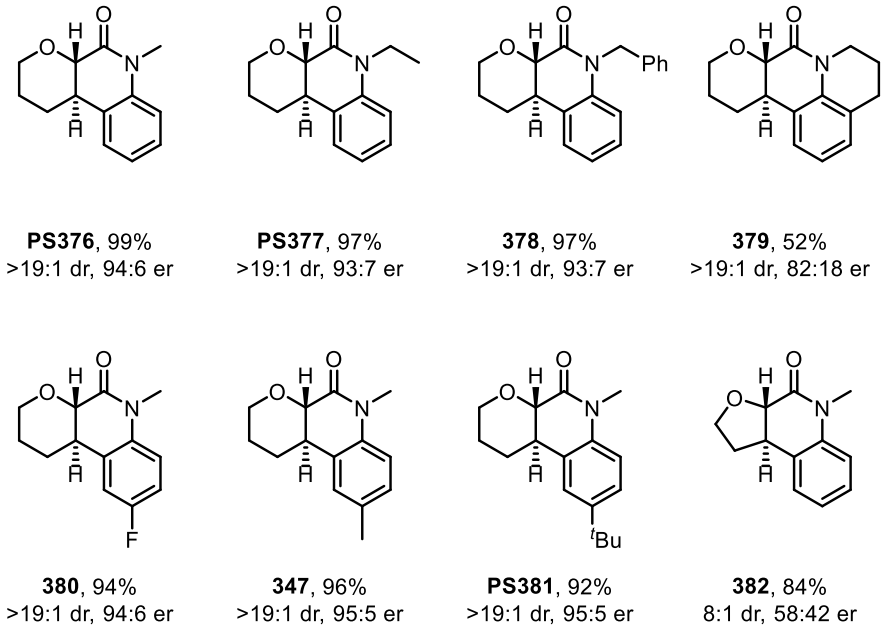
Scheme 84: Synthesis of a library of photocyclization substrates.

2.6. Reaction Scope

With a library of substituted anilides in hand, we next began exploring the scope of the reaction. *N*-Methyl (**PS376**), *N*-ethyl (**PS377**) and *N*-benzyl (**378**) substituents were all well tolerated and gave the product in high yield, dr and er. The tetrahydroquinoline derived substrate (**379**) reacted to give the product in lower yield, dr and er. Substitution of the para position of the benzene ring with fluoro (**380**), methyl (**347**) and *tert*-butyl (**381**) groups did not compromise the reaction and in each case the product was isolated in high yield, dr and er. Changing the dihydropyran moiety in the

starting material to a dihydrofuran was found to negatively influence the reaction. The product (**382**) was isolated in 84% yield, 8:1 dr and 58:42 er, indicating that the dihydropyran is a necessary element in the substrate design.





Scheme 85: Scope of the enantioselective photocyclization.

2.7. Proposed Reaction Mechanism

We propose that the reaction proceeds by a redox-neutral photoinduced electron transfer mechanism *via* a radical anion intermediate. Coordination of the scandium-ligand complex to the substrate results in a significant lowering of the redox potential from −2.54 to −1.21 V which enables single electron reduction by the excited state Ir(III)* photocatalyst. The resulting radical anion then undergoes cyclization onto the aromatic ring to give a transient intermediate, which is oxidized by

the oxidized photocatalyst to give a zwitterion. A [1,5]-hydride shift as previously proposed for the energy transfer cyclization then delivers the product.

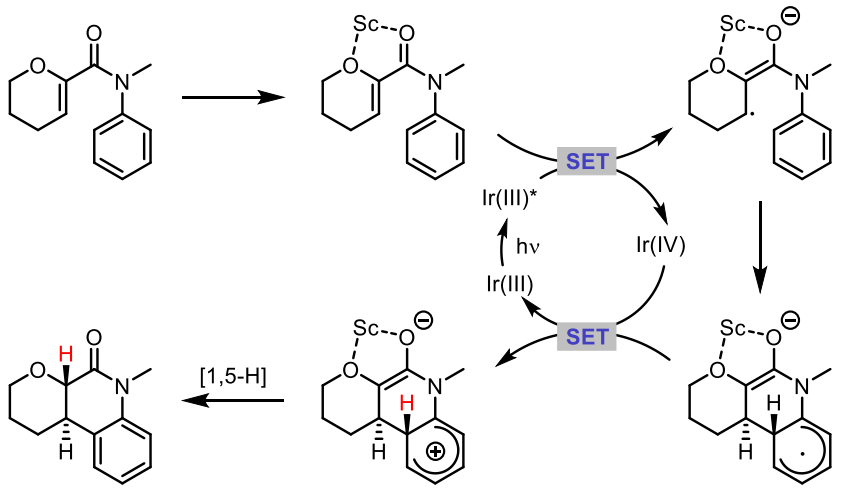
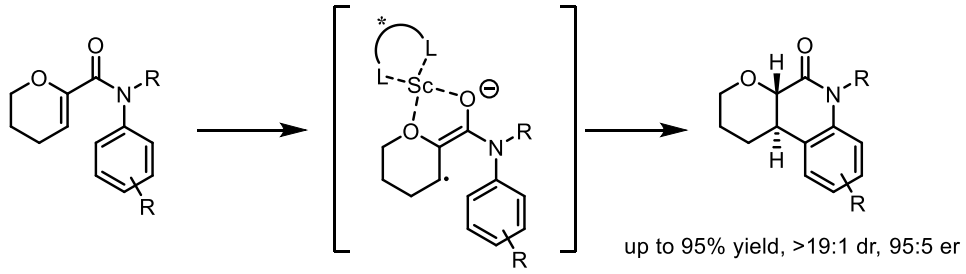


Figure 24: Proposed photoredox mechanism for the enantioselective photocyclization.

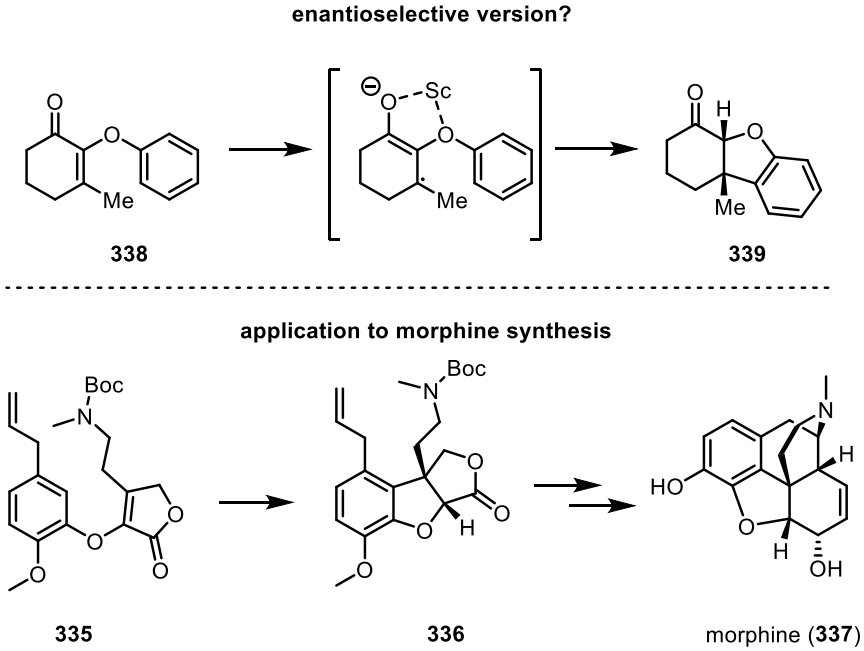
2.8. Conclusion and Future Work

In conclusion, we have developed the first highly enantioselective [6π] photocyclization under Lewis acid/iridium co-catalysis. The reaction operates *via* a photoredox radical-anion pathway instead of the expected triplet diradical mechanism. The radical-anion mechanism is inherently more dependent on the presence of the Lewis acid than the triplet state reaction and therefore avoids the problem of background reactivity which has thwarted previous attempts towards enantioselective photocyclization. Central to the success of the reaction was the use of a bespoke photocatalyst that engages preferentially in the photoredox process and not the unwanted racemic energy transfer process. The reaction was demonstrated on a range of acrylanilides and successfully delivered the cyclized quinolone products in good yield and stereoselectivity.



Scheme 86: Summary of the enantioselective photocyclization.

Future work will focus on applying the same approach to other photocyclization reactions. For example, the *α*-aryloxyenone photocyclization previously developed under energy transfer catalysis could be rendered enantioselective using the radical anion approach. Furthermore, the photocyclization employed in the morphine total synthesis may also be amenable to redox neutral photocatalysis, thus enabling an enantioselective synthesis.



Scheme 87: Proposed enantioselective α-aryloxyenone photocyclization and potential application to the total synthesis of morphine.

3. Experimental

3.1. General Information

Naming and Numbering

Systematic compound names in accordance with regulations set forth by the International Union for Pure and Applied Chemistry (IUPAC) have been generated from the appropriate structures using the PerkinElmer Informatics software ChemDraw® (version 15.0.0.106, or 17.1.0.105).

Reaction Conditions

Reactions requiring moisture-sensitive reagents performed in flame-dried glassware, under an atmosphere of argon (balloon pressure). Room temperature refers to 20–25 °C. Temperatures of 0 °C were obtained using an ice/water bath. Temperatures of −78 °C were obtained using a dry ice/acetone bath. Temperatures of 0 °C to −40 °C were obtained using a polar bear plus. 10-15 °C refers to reactions carried out in a water-jacketed beaker filled with water. Reflux and heating conditions were obtained using a Drysyn® heating block or an oil bath equipped with a thermometer where the reported temperature refers to the temperature of the Drysyn® block or oil bath.

Solvents and Reagents

Anhydrous dichloromethane and tetrahydrofuran were obtained after purification according to Grubbs et al.[137] All other solvents were used without further purification. Degassed solvents were prepared by sparging with argon for 10 minutes. Reagents were used directly as supplied by major chemical suppliers.

Chromatography

Thin layer chromatography was carried out on Merck Kieselgel 60, F_{254} 0.25 mm precoated aluminium plates and visualisation was achieved by UV light (λ_{max} = 254 nm) and/or by staining with

potassium permanganate solution. Column chromatography was performed using VWR silica gel 60 (40-63 m particle size) of Aldrich silca gel 60 (40-63 nm particle size) using pressure by means of a nitrogen line.

NMR Spectroscopy

NMR spectra were recorded on a Bruker Avance spectrometers at room temperature (unless otherwise stated) in the deuterated solvent stated and are referenced to the residual non-deuterated solvent peak. Chemical shifts are quoted in ppm with signal splittings recorded as singlet (s), doublet (d), triplet (t), quartet (q), hept. (heptet), and multiplet (m). The abbreviation br. denotes broad. Coupling constants, *J*, are measured to the nearest 0.1 Hz and are presented as observed. All ^{19}F NMR spectra are proton decoupled.

Infrared

Infrared spectra were recorded on a Bruker Tensor 27 FTIR spectrometer equipped with a diamond ATR module. Absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}).

Mass Spectrometry

Accurate masses (HRMS) were recorded on Bruker MicroTOF and Micromass GCT spectrometers under conditions of electrospray ionisation (ESI).

Polarimetry

Optical Rotations were determined using Perkin-Elmer 241 polarimeter with a path length of 1 dm (using the sodium D line, 589 nm). Concentrations are reported in g/100 mL. Temperatures are reported in °C.

Chiral HPLC

Chiral HPLC was performed on a Dionex Ultimate 3000 system comprising of a Dionex LPG-3400A pump, WPS-3000SL autosampler, TCC-3000SD column compartment, DAD-3000 diode array detector fitted with the appropriate Daicel Chiralpak column (dimensions: 0.46 cm ø × 25 cm) and corresponding guard column (0.4 cm ø × 1 cm). Wavelengths (λ) are reported in nm, retention times (τ_R) are reported in minutes and solvent flow rates are reported in mL min^{-1}.

Melting Points

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

Synthesis of catalysts

The phase transfer catalysts, chiral ligands and photocatalysts that were not commercially available were prepared following reported literature methods.[134, 138-141]

Determination of *s*-Factors

Conversion and selectivity factors (*s*) for the BINOL kinetic resolution were determined from the enantiomeric ratio of the product and starting material using the equations developed by Kagan.[61]

Voltammetry studies

Voltammetry measurements were made using an EmStat3 with a glassy carbon electrode as the working electrode, a platinum wire as counter electrode and a leak free Ag/AgCl (sat. KCl) reference electrode. Voltammograms were referenced to the Fc/Fc+ couple as an internal reference. Square wave voltammograms were acquired with a 5 mV step potential, 50 mV modulation amplitude and 5 Hz frequency. The supporting electrolyte, (tetra-n-butylammonium hexafluorophosphate, Bu_4NPF_6, TBAP) was prepared as a 0.1 M solution in either MeCN or CH_2Cl_2. Samples were measured at 0.01 M concentration.

Fluorescence spectroscopy

Emission spectra were recorded on a perkin elmer FL55 spectrometer. Emission spectra were recorded as 10 µM solutions in degassed MeCN by irradiating at 390 nm and recording between 400 and 600 nm.

3.2. General Experimental Procedures

General procedure A: Kinetic resolution of BINOLs

The appropriate methyl BINOL (0.150 mmol, 1.00 equiv.), benzyl tosylate* (59.1 mg, 0.225 mmol, 1.50 equiv.) and *N*-(2,3,4-trifluorobenzyl)hydrocinchoninium bromide (7.8 mg, 0.015 mmol, 0.10 equiv.) were added to a 7 mL vial equipped with a magnetic stirrer bar under air. Benzene (5.40 mL) and diethyl ether (0.60 mL) were added followed by K_2CO_3 (sat. aq., 208 µL). The reaction was stirred at 1000-1400 rpm at room temperature (20-25°C) for the required reaction time**. Piperidine*** (0.30 mL) was added and stirring was continued for a further 30 minutes. Hydrochloric acid (3 M aq., 0.50 mL) was added dropwise and the phases were separated and the aqueous phase was extracted with EtOAc (2 × 5.00 mL). The combined organic layers were concentrated *in vacuo* and purified by flash column chromatography using the appropriate eluent to give the corresponding enantioenriched benzylated product and recovered starting material.

*Benzyl tosylate was prepared following a literature procedure and stored at −20 °C in the dark.[142]

**The reaction time was varied between different substrates to achieve the desired conversion. Typical reaction times were between 24 and 48 hours.

***Piperidine was added to consume excess benzyl tosylate. This is done to stop the reaction at the desired conversion and to prevent side product formation during purification.

General Procedure B: Dearomative amination of 2-naphthols

The appropriate 2-naphthol (0.200 mmol, 1.00 equiv.), *N*-(anthracen-9-ylmethyl)-*O*-pivaloylcinchoninium bromide (**167**) (0.0200 mmol, 0.100 equiv.) and K_3PO_4 (4.2 mg, 0.0200 mmol, 0.100 equiv.) were added to a 7 mL vial equipped with a magnetic stirrer bar under air. Toluene (2 mL) was added and the reaction was stirred at 1000 rpm at room temperature for 30 minutes. The vial was transferred to a polar bear plus chiller-stirrer equipped with a 7 mL vial adaptor. The reaction was stirred at 1000 rpm with the plate temperature set to −30 °C for 30 minutes. The vial was briefly removed from the chiller-stirrer, opened under air and *the appropriate azodicarboxylate diester* (0.240 mmol, 1.20 equiv.) was added. The vial lid was replaced and the vial was returned to the chiller-stirrer plate. Stirring was continued at 1000 rpm, plate temperature −30 °C, for the required reaction time as determined by TLC analysis. The vial was removed from the chiller-stirrer and the reaction mixture was purified by flash column chromatography using the appropriate eluent to give the corresponding dearomatized product.

General Procedure C: Preparation of photocyclization substrates by amide coupling

The appropriate carboxylic acid (1.00 equiv.) was dissolved in CH_2Cl_2 (0.5 M) and cooled to 0 °C and Et_3N (1.10 equiv.) followed by isobutyl chloroformate (1.00 equiv.) were added. After 30 minutes at 0 °C, *the appropriate N-alkyl aniline* (1.10 equiv.) was added and the reaction was warmed to room temperature and stirring was continued for 16 hours. Water was added and the phases were separated, the aqueous phase was extracted twice with CH_2Cl_2 and the combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated to give crude product, which was purified by flash column chromatography to afford the corresponding acrylanilides.

General Procedure D: Enantioselective Photocyclization

$Sc(OTf)_3$ (51.7 mg, 0.105 mmol, 1.05 equiv.) and ligand (78.2 mg, 0.126 mmol, 1.26 equiv.) were added to a 25 mL vial equipped with a stirrer bar. The vial was capped then evacuated and backfilled with argon three times. CH_2Cl_2 (21 mL) which had been sparged with argon for 15 minutes was added by syringe and the vial was heated to 60 °C with stirring for 30 minutes then cooled to room temperature to give a stock solution of the Lewis acid complex.

$Ir(5\text{-}CF_3)(4'\text{-}^tBu)ppy)_3$ (1.0 mg, 0.001 mmol, 0.0100 equiv.) and *the appropriate starting material* (0.100 mmol) were added to a 10 mL vial equipped with a stirrer bar. The vial was capped then evacuated and backfilled with argon three times. The Lewis acid complex solution was drawn into a 24 mL syringe and the syringe was equipped with a syringe filter. 5 mL of the Lewis acid complex solution was dispensed into each reaction vial and the reaction vials were placed in a 10-15 °C water bath and irradiated with a kessil lamp centred at 440 nm for 16 h. The reaction was transferred to a separating funnel using an additional 5 mL CH_2Cl_2 and washed with 1 M aqueous sodium hydroxide solution (10 mL). The aqueous phase was extracted twice with CH_2Cl_2 (10 mL) and the combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product. The diastereomeric ratio was determined by quantitative ^1H NMR analysis of the crude reaction mixture. The crude product was purified by column chromatography (EtOAc-pentane) to give the pure cyclization product.

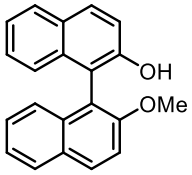
General Procedure E: Racemic Photocyclization

$Ir(dFppy)_3$ (0.8 mg, 0.001 mmol, 1 mol%) and *the appropriate starting material* (0.100 mmol) were added to a 10 mL microwave vial. The vial was capped then evacuated and backfilled with argon three times. THF (2 mL) which had been sparged with argon for 20 minutes was added by syringe

and the reaction was placed in a water jacketed beaker filled with water and irradiated with a kessil lamp centred at 440 nm for 16 h. LiHMDS (1 M in THF, 100 µL, 0.100 mmol, 1.00 equiv.) was added and the reaction was stirred at room temperature for 30 minutes. Acetic acid (100 µL) was added and the reaction was stirred for a further 10 minutes. The reaction mixture was passed through a pipette column filled with silica (~1 g) and concentrated. ^{1}H NMR analysis of the crude reaction mixture facilitated identification of the minor diastereomer peaks for determination of the dr for the enantioselective reactions. A small sample of the crude product was purified by small scale preparative TLC to give the racemic reference material for the chiral HPLC analysis.

3.3. Experimental Procedures for Individual Compounds

2'-Methoxy-[1,1'-binaphthalen]-2-ol (67)



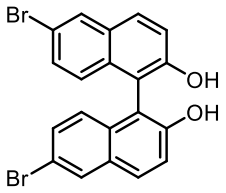
[1,1'-Binaphthalene]-2,2'-diol (5.00 g, 17.4 mmol, 1.00 equiv.) and K_2CO_3 (3.14 g, 22.7 mmol, 1.30 equiv.) were suspended in acetone (140 mL) and iodomethane (2.73 g, 1.20 mL, 19.2 mmol, 1.10 equiv) was added. The resulting suspension was heated under reflux for 16 hours after which time the reaction was cooled to room temperature. The solvent was removed by evaporation and the residue was partitioned between water and CH_2Cl_2. The phases were separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product. Purification *via* flash column chromatography (1:1 CH_2Cl_2 – petroleum ether 40-60 to 3:1 CH_2Cl_2 – petroleum ether 40-60) afforded 2'-methoxy-[1,1'-binaphthalen]-2-ol (**67**) (2.27 g, 43%) as a white solid.

m.p. = 151-153 °C (CH_2Cl_2/petroleum ether 40-60)

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.06 (d, *J* = 9.1 Hz, 1H), 7.95 (d, *J* = 9.2 Hz, 1H), 7.93 (d, *J* = 9.3 Hz, 1H), 7.91 (d, *J* = 10.6 Hz, 1H), 7.49 (d, *J* = 9.1 Hz, 1H), 7.42 (d, *J* = 1.9 Hz, 2H), 7.36 (t, *J* = 7.4 Hz, 1H), 7.32 (t, *J* = 7.7 Hz, 1H), 7.27 (t, *J* = 8.3 Hz, 1H), 7.24 (d, *J* = 9.0 Hz, 1H), 7.12 (d, *J* = 8.4 Hz, 1H), 5.00 (s, 1H), 3.81 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δC = 156.1, 151.3, 134.1, 133.9, 131.1, 129.9, 129.5, 129.2, 128.2, 127.4, 126.5, 125.0, 124.9, 124.3, 123.3, 117.6, 115.4, 115.1, 113.9, 56.7

6,6'-Dibromo-[1,1'-binaphthalene]-2,2'-diol (76)



(±)-BINOL (14.3 g, 50.0 mmol, 1.00 equiv.) was dissolved in acetonitrile (250 mL) and the resulting solution cooled to 0 °C. Bromine (7.70 mL, 24.0 g, 150 mmol, 3.00 equiv.) was added dropwise over 10 minutes. The reaction was stirred for 3 hours at 0 °C after which time saturated Na_2SO_3 solution was added. The solution was extracted three times with CH_2Cl_2 and the combined organic layers were dried over sodium sulfate, filtered and concentrated to give 6,6'-dibromo-[1,1'-binaphthalene]-2,2'-diol (**76**) (22.2 g, 100%) as an off-white solid.

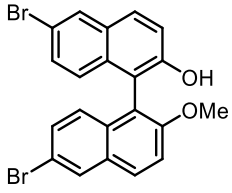
m.p. = 115-117 °C (CH_2Cl_2).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.05 (d, J = 2.0 Hz, 2H), 7.90 (d, J = 9.0 Hz, 2H), 7.40 (d, J = 9.0 Hz, 2H), 7.37 (dd, J = 2.0, 9.0 Hz, 2H), 6.96 (d, J = 9.0 Hz, 2H), 5.04 (s, 2H).

^{13}C NMR (127 MHz, $CDCl_3$) δ = 153.1, 132.0, 131.0, 130.9, 130.7, 130.6, 126.0, 119.1, 118.2, 110.8.

Data in agreement with literature reported.[143]

6,6'-Dibromo-2'-methoxy-[1,1'-binaphthalen]-2-ol (77)



6,6'-Dibromo-[1,1'-binaphthalene]-2,2'-diol (**76**) (22.20 g, 50.0 mmol, 1.00 equiv.) and K_2CO_3 (8.97 g, 55.0 mmol, 1.10 equiv.) were suspended in acetone (400 mL) and iodomethane (7.80 g, 3.43 mL,

65.0 mmol, 1.30 equiv) was added. The resulting suspension was heated under reflux for 16 hours after which time the reaction was cooled to room temperature. The solvent was removed by evaporation and the residue was partitioned between water and CH_2Cl_2. The phases were separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product. Purification *via* flash column chromatography (1:1 CH_2Cl_2 – petroleum ether) afforded 6,6'-dibromo-2'-methoxy-[1,1'-binaphthalen]-2-ol (**77**) (13.5 g, 59%) as a white solid.

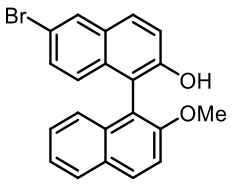
m.p. = 115-117 °C (CH_2Cl_2/petroleum ether 40-60).

IR (film) ν_{max}/cm^{-1}: 3480, 3059, 2935, 2837, 1614, 1440, 1325, 1246, 1171, 1133, 1087, 1068, 1046, 904, 611.

^{1}H NMR (400 MHz, CDCl3) δ 8.05 (s, 1H), 8.01 (s, 1H), 7.96 (d, J = 9.1 Hz, 1H), 7.81 (d, J = 8.9 Hz, 1H), 7.49 (d, J = 9.1 Hz, 1H), 7.39-7.24 (m, 2H), 7.00 (d, J = 9.0 Hz, 1H), 6.86 (d, J = 8.9 Hz, 1H), 4.90 (s, 1H), 3.81 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.2, 151.7, 132.5, 132.3, 130.9, 130.5, 130.4, 130.3, 130.2, 129.9, 129.2, 126.6, 126.6, 118.8, 118.2, 117.3, 115.0, 114.8, 114.7, 56.7.

6-Bromo-2'-methoxy-[1,1'-binaphthalen]-2-ol (78)



6,6'-Dibromo-2'-methoxy-[1,1'-binaphthalen]-2-ol (**77**) (1.95 g, 4.26 mmol, 1.00 equiv.) was dissolved in THF (43 mL) and cooled to −78 °C. ^{n}BuLi (1.6 M in hexane, 5.33 mL, 8.52 mmol, 2.00 equiv.) was added by syringe pump over 1 hour after which time the reaction was stirred for a

further 1 hour at −78 °C. The reaction was quenched by dropwise addition of water. After warming to room temperature, saturated ammonium chloride solution was added. EtOAc was added and the phases were separated. The aqueous phase was extracted twice with EtOAc and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product. Purification *via* flash column chromatography (4:1 petroleum ether 40-60 – EtOAc) afforded 6-bromo-2'-methoxy-[1,1'-binaphthalen]-2-ol (**78**) (1.27 g, 82%)

m.p. = 132-133 °C (EtOAc/petroleum ether 40-60).

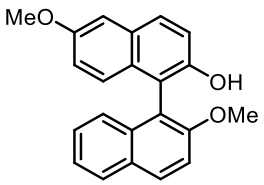
IR (film) ν_{max}/cm^{-1}: 3514, 3059, 1588, 1432, 1350, 1331 1262, 1167, 1085, 936, 879, 747, 673.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.97 (d, *J* = 9.1 Hz, 1H), 8.02 (d, *J* = 2.1 Hz, 1H), 7.91 (d, *J* = 8.1 Hz, 1H), 7.81 (d, *J* = 8.9 Hz, 1H), 7.48 (d, *J* = 9.1 Hz, 1H), 7.41 (obs. m, 1H), 7.37 (d, *J* = 8.8 Hz, 1H), 7.33–7.26 (m, 2H), 7.14 (d, *J* = 8.5 Hz, 1H), 6.93 (d, *J* = 9.0 Hz, 1H), 4.96 (s, 1H, OH), 3.81 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.0, 151.6, 133.9, 132.3, 131.4, 130.3, 130.1, 129.6, 129.4, 128.9, 128.3, 127.5, 126.7, 124.6, 124.3, 118.6, 117.0, 115.3, 114.5, 113.7, 56.0

HRMS (ESI^-) $C_{21}H_{15}O_2{}^{79}Br$ $[M-H]^-$ requires 377.01827; found 377.01807, Δ −0.5 ppm.

2',6-Dimethoxy-[1,1'-binaphthalen]-2-ol (79)



6-Bromo-2'-methoxy-[1,1'-binaphthalen]-2-ol (**78**) (190 mg, 0.500 mmol, 1.00 equiv.) was dissolved in DMF (5.0 mL) then CuCl (149 mg, 1.50 mmol 3.00 equiv.) and NaOMe (4.4 M in MeOH, 1.37 mL, 6.00 mmol, 12.0 equiv.) were added sequentially. The reaction was heated at 100 °C for 1 hour then

cooled to room temperature. Ice water was added followed by hydrochloric acid (3 M). The resulting suspension was extracted 3 times with EtOAc and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product. Purification *via* flash column chromatography (3:1 CH_2Cl_2 – petroleum ether 40-60 to 9:1 CH_2Cl_2 – petroleum ether 40-60) afforded 2',6-dimethoxy-[1,1'-binaphthalen]-2-ol (**79**) as an off-white solid (104 mg, 63%).

m.p. = 160-162 °C (CH_2Cl_2/petroleum ether 40-60).

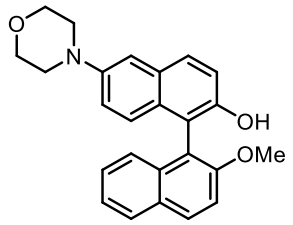
IR (film) ν_{max}/cm^{-1}: 3430, 3007, 2936, 2839, 1620, 1508, 1464, 1433, 1331, 1249, 1209, 1148, 1083, 1056, 852, 752.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.04 (d, J = 9.1 Hz, 1H), 7.90 (d, J = 8.2 Hz, 1H), 7.81 (d, J = 8.9 Hz, 1H), 7.47 (d, J = 9.1 Hz, 1H), 7.38 (ddd, J = 1.2, 6.9, 8.1 Hz, 1H), 7.35 (d, J = 8.9 Hz, 1H), 7.29 (ddd, J = 1.3, 6.9, 8.4 Hz, 1H), 7.22-7.18 (m, 2H), 6.98 (d, J = 9.2 Hz, 1H), 6.92 (dd, J = 2.6, 9.2 Hz, 1H), 4.82 (s, 1H), 3.90 (s, 3H), 3.81 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 156.0, 155.9, 149.8, 134.1, 131.1, 130.1, 129.5, 129.1, 128.5, 128.3, 127.4, 126.5, 125.0, 124.3, 119.0, 118.0, 115.6, 115.4, 113.9, 106.6, 56.8, 55.4.

HRMS (ESI^+) $C_{22}H_{19}O_3^+$ $[M+H]^+$: requires: 331.13287, found: 331.13303, Δ +0.5 ppm.

2'-Methoxy-6-morpholino-[1,1'-binaphthalen]-2-ol (80)



6-Bromo-2'-methoxy-[1,1'-binaphthalen]-2-ol (**78**) (379 mg, 1.00 mmol, 1.00 equiv.), $Pd_2(dba)_3$ (9.2 mg, 0.0100 mmol, 1 mol%) and DavePhos (4.7 mg, 0.0120 mmol, 1.2 mol%) were added to a Schlenk flask. The flask was evacuated and backfilled with argon three times. Morpholine (105 mg, 105 µL, 1.20 mmol, 1.20 equiv.) was added followed by LiHMDS solution (1 M in THF, 2.2 mL, 2.2 mmol, 2.2 equiv.) and the reaction was stirred at room temperature for 16 hours. 1 M HCl solution was added and the reaction was stirred for 30 minutes. 1 M $NaHCO_3$ solution was added and the aqueous solution was extracted three times with CH_2Cl_2. The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product which was purified by column chromatography (3:2 petroleum ether 40-60 – EtOAc) to give 2'-methoxy-6-morpholino-[1,1'-binaphthalen]-2-ol (**80**) (244 mg, 63%) as an off-white solid.

m.p. = 231-232 °C (EtOAc/petroleum ether 40-60).

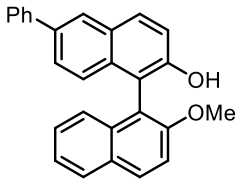
IR (film) ν_{max}/cm^{-1}: 3283, 1608, 1506, 1449, 1356, 1309, 1265, 1228, 1182, 1146, 1113, 1062, 1022, 934, 856, 817, 779, 759, 731, 666, 616.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.94 (d, *J* = 9.0 Hz, 1H), 7.79 (d, *J* = 8.1 Hz, 1H), 7.66 (d, *J* = 8.8 Hz, 1H), 7.37 (d, *J* = 9.1 Hz, 1H), 7.26 (ddd, *J* = 8.1, 6.7, 1.3 Hz, 1H), 7.20 (d, *J* = 8.9 Hz, 1H), 7.18–7.14 (m, 1H), 7.09 (m, 2H), 6.93–6.83 (m, 2H), 4.69 (br. s, 1H), 3.81–3.74 (m, 4H), 3.69 (s, 3H), 3.15–3.05 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 155.9, 149.8, 147.2, 134.0, 130.9, 130.0, 129.4, 128.9, 128.6, 128.1, 127.3, 125.9, 125.0, 124.2, 119.6, 117.9, 115.6, 115.1, 113.9, 111.0, 67.0, 56.7, 50.1.

HRMS (ESI^+) $C_{25}H_{23}O_3N$ $[M+H]^+$ requires 386.17507; found 386.17477, Δ -0.8 ppm.

2'-Methoxy-6-phenyl-[1,1'-binaphthalen]-2-ol (81)



6-Bromo-2'-methoxy-[1,1'-binaphthalen]-2-ol (**21**) (365 mg, 1.00 mmol, 1.00 equiv.), phenyl boronic acid (144 mg, 1.20 mmol, 1.20 equiv.) and $Pd(PPh_3)_4$ (57.8 mg, 0.0500 mmol, 0.0500 equiv.) were charged to a flask fitted with a water-cooled condenser. The flask was evacuated and backfilled with argon three times. Argon sparged 1,2-dimethoxyethane (10 mL) was added followed by argon sparged aqueous Na_2CO_3 solution (2 M, 1.25 mL, 2.50 equiv.). The flask was fitted with an argon balloon and heated at 90 °C for 16 hours. After cooling to room temperature, 1 M HCl solution was added and the solution was extracted three times with CH_2Cl_2, the combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product which was purified by column chromatography (9:1 petroleum ether 40-60 – EtOAc) to give 2'-methoxy-6-phenyl-[1,1'-binaphthalen]-2-ol (**20**) (233 mg, 62%) as a white solid.

m.p. = 208-209 °C (EtOAc/petroleum ether 40-60).

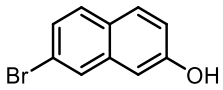
IR (film) ν_{max}/cm^{-1}: 3513, 1507, 1493, 1145, 817, 755, 705.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.01–7.93 (m, 2H), 7.87 (d, *J* = 8.9 Hz, 1H), 7.82 (d, *J* = 8.1 Hz, 1H), 7.58 (m, 2H), 7.44–7.11 (m, 9H), 7.05–7.01 (m, 1H), 4.86 (br. S, 1H), 3.73 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.0, 151.4, 141.2, 136.0, 134.0, 133.0, 131.2, 130.1, 129.5, 129.4, 128.8, 128.2, 127.4, 127.2, 127.0, 126.1, 126.1, 125.4, 124.9, 124.2, 117.9, 115.2, 115.0, 113.8, 56.7.

HRMS (ESI^+) $C_{27}H_{20}O_2$ $[M+H]^+$ requires 377.15361; found 377.15365, Δ +0.1 ppm.

7-Bromonaphthalen-2-ol (83)



Following a modified literature procedure.[144] Bromine (6.14 mL, 19.1 g, 120 mmol, 1.20 equiv.) was added dropwise over 30 minutes to a suspension of PPh_3 (31.4 g, 120 mmol, 1.20 equiv.) in acetonitrile (50 mL) at 0 °C. The reaction was warmed to room temperature, 2,7-dihydroxynaphthalene (16.0 g, 100 mmol, 1.00 equiv.) was added and the reaction was heated at 90 °C for 1 hour. Acetonitrile was removed *in vacuo,* the flask was fitted with a gas trap filled with saturated Na_2SO_3 solution and the reaction was heated at 250 °C for 1 hour. The resulting mixture was dissolved in CH_2Cl_2 and filtered through a plug of silica and concentrated. Purification *via* flash column chromatography (50% CH_2Cl_2 – petroleum ether to 100% CH_2Cl_2) afforded 7-bromonaphthalen-2-ol (**83**) (7.48 g, 30%) as a brown solid.

m.p. = 119-120 °C (CH_2Cl_2/petroleum ether 40-60).

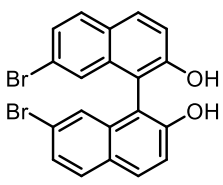
IR (film) ν_{max}/cm^{-1}: 3366, 2923, 1652, 1577, 1558, 1506, 1473, 1457, 1253, 1209, 921, 626.

^{1}H NMR (500 MHz, $CDCl_3$) δ =7.87 (d, *J* = 1.68 Hz, 1H), 7.74 (d, *J* = 8.82 Hz, 1H), 7.65 (d, *J* = 8.66 Hz, 1H), 7.42 (dd, *J* = 8.71, 1.92 Hz), 7.13 (dd, *J* = 8.81, 2.49 Hz, 1H), 7.08 (d, *J* = 2.35 Hz), 5.05 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 154.1, 135.8, 129.9, 129.4, 128.3, 127.3, 127.0, 120.8, 118.2, 108.7.

HRMS (ESI^-) $C_{10}H_7{}^{79}BrO$ $[M-H]^-$ requires 220.9608; found 220.9607, Δ -0.5 ppm.

7,7'-Dibromo-[1,1'-binaphthalene]-2,2'-diol (84)



7-Bromonaphthalen-2-ol (**83**) (7.48 g, 33.5 mmol, 1.00 equiv.) was dissolved in CH_2Cl_2 (220 mL) and $[Cu(TMEDA)OHCl)]_2$ (155 mg, 0.0350 mmol, 1 mol%) was added. The reaction was stirred for 16 hours at room temperature open to air. The reaction mixture was filtered through a short silica plug eluting with CH_2Cl_2. Evaporation of the solvent gave 7,7'-dibromo-[1,1'-binaphthalene]-2,2'-diol (**84**) (6.28 g, 85%) as an off-white solid.

m.p. = 115-117 °C (CH_2Cl_2).

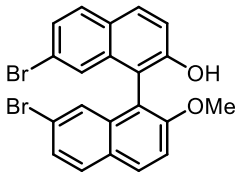
IR (film) ν_{max}/cm^{-1}: 3466, 1611, 1500, 1418, 1378, 1349, 1317, 1213, 1195, 1171, 1128, 836, 739.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.94 (d, *J* = 8.9 Hz, 2H), 7.76 (d, *J* = 8.6 Hz, 2H), 7.47 (d, *J* = 8.7 Hz, 2H), 7.37 (d, *J* = 8.9 Hz, 2H), 7.23 (s, 2H), 5.04 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 153.6, 134.6, 131.7, 130.2, 127.9, 127.8, 125.9, 122.4, 118.3, 109.5.

HRMS (ESI^-) $C_{20}H_{12}Br_2O_2$ $[M-H]^-$ requires 440.91310, found: 440.91330, Δ +0.5 ppm.

7,7'-Dibromo-2'-methoxy-[1,1'-binaphthalen]-2-ol (85)



7,7'-Dibromo-[1,1'-binaphthalene]-2,2'-diol (**84**) (6.38 g, 14.4 mmol, 1.00 equiv.) was dissolved in acetone (115 mL) and K_2CO_3 (2.58 g, 18.7 mmol, 1.30 equiv.) followed by iodomethane (984 µL, 2.24 g, 15.8 mmol, 1.10 equiv.) were added. The reaction was heated under reflux for 16 hours. Upon cooling to room temperature, the solvent was removed *in vacuo*. The residue was partitioned between water and CH_2Cl_2 and the phases were separated. The aqueous layer was extracted twice with CH_2Cl_2 and the organic layers were combined, dried over anhydrous sodium sulfate, filtered

and concentrated to give the crude product. Purification *via* flash column chromatography (1:1 CH_2Cl_2 – petroleum ether 40-60) gave 7,7'-dibromo-2'-methoxy-[1,1'-binaphthalen]-2-ol (**85**) (3.21 g, 49%) as an off-white solid.

m.p. = 179-181 °C (CH_2Cl_2/petroleum ether 40-60).

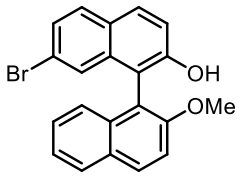
IR (film) ν_{max}/cm^{-1}: 3503, 1612, 1497, 1255, 1088, 830, 754.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.02 (d, J = 9.1 Hz, 1H), 7.87 (d, J = 8.9 Hz, 1H), 7.76 (d, J = 8.7 Hz, 1H), 7.73 (d, J = 8.7 Hz, 1H), 7.47 (d, J = 9.1 Hz, 1H), 7.46 (dd, J = 8.7, 1.9 Hz, 1H), 7.40 (dd, J = 8.6, 1.9 Hz, 1H), 7.35 (d, J = 8.9 Hz, 1H), 7.28 (d, J = 1.9 Hz, 1H), 7.15 (d, J = 1.9 Hz, 1H), 4.88 (s, 1H), 3.81 (s, 3H).

^{13}C NMR (127 MHz, $CDCl_3$) δ = 156.9, 152.1, 135.3, 135.1, 131.6, 130.2, 130.1, 130.1, 128.0, 127.9, 127.8, 127.0, 126.7, 126.5, 122.5, 121.4, 118.1, 114.0, 113.8, 113.7, 56.7.

HRMS (ESI^-) $C_{21}H_{14}{}^{79}Br_2O_2$ $[M-H]^-$: requires 454.92878, found: 454.92905 Δ +0.6 ppm.

7-Bromo-2'-methoxy-[1,1'-binaphthalen]-2-ol (86)



7,7'-Dibromo-2'-methoxy-[1,1'-binaphthalen]-2-ol (**85**) (2.52 g, 5.50 mmol, 1.00 equiv.) was dissolved in THF (55 mL) and cooled to −78 °C. ^{n}BuLi (1.6 M in hexane, 6.87 mL, 11.0 mmol, 2.00 equiv.) was added by syringe pump over 1 hour after which time the reaction was stirred for a further 1 hour at −78 °C. The reaction was quenched by dropwise addition of water. After warming to room temperature, saturated ammonium chloride solution was added. EtOAc was added and the phases were separated. The aqueous phase was extracted twice with EtOAc and the combined

organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product which was purified by column chromatography (20% EtOAc-petroleum ether 40-60) to give 7-bromo-2'-methoxy-[1,1'-binaphthalen]-2-ol (**86**) (1.54 g, 77%)

m.p. = 171-172 °C (EtOAc/petroleum ether 40-60).

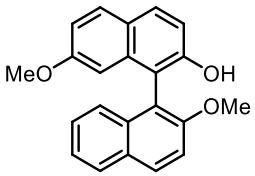
IR (film) ν_{max}/cm^{-1}: 3496, 1612, 1501, 1429, 1352, 1250, 1168, 828, 809, 754.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.08 (d, *J* = 9.1 Hz, 1H), 7.91 (d, *J* = 8.1 Hz, 1H), 7.86 (d, *J* = 9.0 Hz, 1H), 7.72 (d, *J* = 8.6 Hz, 1H), 7.49 (d, *J* = 9.1 Hz, 1H), 7.42–7.37 (m, 2H, 1), 7.35 (d, *J* = 8.9 Hz, 1H), 7.32 (ddd, *J* = 8.2, 6.8, 1.4 Hz, 1H), 7.19 (d, *J* = 1.8 Hz, 1H), 7.15 (dd, *J* = 8.4, 1.1 Hz, 1H), 4.93 (s, 1H), 3.82 (s, 4H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 156.2, 152.2, 135.2, 133.9, 131.6, 129.9, 129.9, 129.6, 128.4, 127.7, 127.0, 126.8, 124.6, 124.4, 121.2, 118.0, 114.6, 114.3, 113.8, 56.7.

HRMS (ESI^-) $C_{21}H_{15}O_2{}^{79}Br$ $[M-H]^-$ requires 377.01827; found 377.01807, Δ −0.5 ppm.

2',7-Dimethoxy-[1,1'-binaphthalen]-2-ol (87)



7-Bromo-2'-methoxy-[1,1'-binaphthalen]-2-ol (**86**) (170 mg, 0.448 mmol, 1.00 equiv.) was dissolved in DMF (4.5 mL) then CuCl (133 mg, 1.34 mmol 3.00 equiv.) and NaOMe (4.4 M in MeOH, 1.22 mL, 5.38 mmol, 12.0 equiv.) were added sequentially. The reaction was heated at 100 °C for 16 h then cooled to room temperature. Ice water was added followed by hydrochloric acid (3 M). The resulting suspension was extracted 3 times with EtOAc and the combined organic layers were washed with

brine, dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product. Purification *via* flash column chromatography (3:1 CH_2Cl_2 – petroleum ether 40-60 to 9:1 CH_2Cl_2 – petroleum ether 40-60) afforded 2',7-dimethoxy-[1,1'-binaphthalen]-2-ol (**87**) as an off-white solid (99.7 mg, 67%).

m.p. = 137-139 °C (CH_2Cl_2/ petroleum ether 40-60).

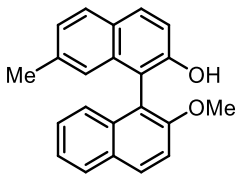
IR (film) ν_{max}/cm^{-1}: 3495, 3427, 3058, 3007, 2936, 1621, 1511, 1464, 1368, 1264, 1221, 1166, 1148, 833, 815, 752.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.05 (d, *J* = 9.1 Hz, 1H), 7.90 (d, *J* = 8.1 Hz, 1H), 7.83 (d, *J* = 8.8 Hz, 1H), 7.77 (d, *J* = 8.9 Hz, 1H), 7.48 (d, *J* = 9.1 Hz, 1H), 7.38 (ddd, *J* = 1.2, 6.8, 8.1 Hz, 1H), 7.30 (ddd, *J* = 1.3, 6.8, 8.4 Hz, 1H), 7.25-7.20 (m, 2H), 6.99 (dd, *J* = 2.5, 8.9 Hz, 1H), 6.37 (d, *J* = 2.5 Hz, 1H), 4.92 (s, 1H), 3.82 (s, 3H), 3.51 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 158.3, 156.0, 151.9, 135.2, 133.9, 131.2, 129.8, 129.6, 129.6, 128.2, 127.4, 125.0, 124.7, 124.3, 115.5, 115.2, 115.1, 114.3, 113.9, 104.3, 56.8, 55.1.

HRMS (ESI$^+$) $C_{22}H_{19}O_3^+$ $[M+H]^+$: requires: 331.13287, found: 331.13297, Δ +0.3 ppm.

2'-Methoxy-7-methyl-[1,1'-binaphthalen]-2-ol (88)



7-Bromo-2'-methoxy-[1,1'-binaphthalen]-2-ol (**86**) (443 mg, 1.20 mmol, 1.00 equiv.) and $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (98 mg, 0.12 mmol, 10 mol%) were dissolved in THF (15 mL) and MeMgCl solution (3 M in Et_2O, 2.00 mL, 6.00 mmol, 5.00 equiv.) was added. The resulting solution was heated under reflux for 16 hours. On cooling to room temperature, saturated ammonium chloride solution was

added and phases were separated. The aqueous phase was extracted twice with EtOAc and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product which was purified by column chromatography (9:1 petroleum ether 40-60 – EtOAc) to give 2'-methoxy-7-methyl-[1,1'-binaphthalen]-2-ol (**88**) (334 mg, 88%) as an off-white solid.

m.p. = 87-88 °C (EtOAc/petroleum ether 40-60).

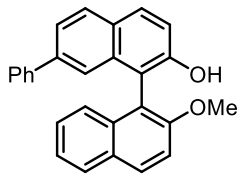
IR (film) ν_{max}/cm^{-1}: 3481, 1704, 1621, 1508, 1459, 1378, 1332, 1265, 1220, 1172, 1129, 1053, 1020, 977, 859, 775, 676.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.06 (1H, d, *J* = 9.0 Hz), 7.92 (1H, d, *J* = 8.1 Hz), 7.87 (1H, d, *J* = 8.9 Hz), 7.78 (1H, d, *J* = 8.3 Hz), 7.50 (1H, d, *J* = 9.1 Hz), 7.40 (1H, ddd, *J* = 8.1, 6.6, 1.3 Hz), 7.35–7.28 (2H, m), 7.24–7.15 (2H, m), 6.84 (1H, s), 4.90 (1H, s), 3.82 (3H, s), 2.27 (3H, s).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.0, 151.3, 136.2, 134.1, 134.0, 131.0, 129.5, 129.5, 128.1, 128.0, 127.4, 127.3, 125.6, 125.0, 124.2, 123.8, 116.5, 115.6, 114.5, 113.9, 56.7, 29.8.

HRMS (ESI^-) $C_{22}H_{18}O_2$ $[M-H]^-$ requires 313.12340; found 313.12326, Δ -0.5 ppm.

2'-Methoxy-7-phenyl-[1,1'-binaphthalen]-2-ol (89)



7-Bromo-2'-methoxy-[1,1'-binaphthalen]-2-ol (**86**) (548 mg, 1.50 mmol, 1.00 equiv.), phenyl boronic acid (220 mg, 1.80 mmol, 1.20 equiv.) and $Pd(PPh_3)_4$ (86.7 mg, 0.0750 mmol, 5 mol%) were charged to a flask fitted with a water-cooled condenser. The flask was evacuated and backfilled with argon three times. 1,2-Dimethoxyethane (Argon sparged, 15 mL) was added followed by aqueous Na_2CO_3 solution (Argon sparged, 2 M, 1.87 mL, 2.50 equiv.). The flask was fitted with an argon balloon and

heated at 90 °C for 16 hours. After cooling to room temperature, 1 M HCl solution was added and the solution was extracted three times with CH_2Cl_2, the combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product which was purified by column chromatography (9:1 petroleum ether 40-60 – EtOAc) to give 2'-methoxy-7-phenyl-[1,1'-binaphthalen]-2-ol (**89**) (410 mg, 71%) as a white solid.

m.p. = 86-87 °C (EtOAc/petroleum ether 40-60).

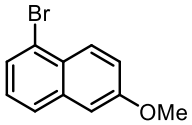
IR (film) ν_{max}/cm^{-1}: 3489, 3055, 2935, 2837, 2361, 1619, 1591, 1507, 1456, 1377, 1264, 1247, 1166, 1131, 1055, 839, 811, 752, 697.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H =7.93 (d, *J* = 9.0 Hz, 1H), 7.86–7.82 (m, 2H), 7.79 (dt, *J* = 8.3, 1.0 Hz, 2H), 7.48 (dd, *J* = 8.5, 1.8 Hz, 2H), 7.37 (d, *J* = 9.1 Hz, 2H), 7.31–7.24 (m, 4H), 7.23–7.10 (m, 6H), 3.70 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 156.0, 151.7, 141.6, 139.2, 134.1, 134.0, 131.2, 129.6, 129.5, 128.7, 128.6, 128.4, 128.3, 127.5, 127.4, 127.1, 124.9, 124.3, 123.2, 123.0, 117.6, 115.4, 115.2, 113.8, 56.7.

HRMS (ESI^+) $C_{27}H_{20}O_2$ $[M+H]^+$ requires 377.15361; found 377.15363, Δ +0.1 ppm.

1-Bromo-6-methoxynaphthalene (91)



Following a modified literature procedure.[145] Triphenylphosphite (28.9 mL, 34.1 g, 110 mmol, 1.1 equiv.) was dissolved in CH_2Cl_2 (300 mL) and the resulting solution was cooled to −78 °C. Bromine (6.15 mL, 20.3 g, 120 mmol, 1.20 equiv.) was added followed by dropwise addition of Et_3N (18.1 mL, 13.2 g, 130 mmol, 1.30 equiv.) over 30 minutes. 6-Methoxy-3,4-dihydronaphthalen-1(2H)-one (17.6

g, 100 mmol, 1.00 equiv.) was added and the reaction was warmed to room temperature and stirred for 16 hours after which time the reaction was heated to 45 °C for 2 hours. Upon cooling to room temperature saturated Na_2SO_3 solution was added and the resulting solution was extracted three times with CH_2Cl_2. The combined organic layers were washed with water, dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product. Purification *via* flash column chromatography (39:1 petroleum ether 40-60 – CH_2Cl_2 to 19:1 petroleum ether 40-60 – CH_2Cl_2) afforded the vinyl bromide which was found to be unstable and was therefore used immediately in the next reaction.

The product of the previous step (18.5 g, crude) was dissolved in benzene (155 mL) and DDQ (19.3 g, 85.1 mmol) was added and the reaction was stirred at room temperature for 2 hours after which time saturated Na_2SO_3 solution was added and the resulting suspension was extracted 3 times with EtOAc. The combined organic layers were washed 3 times with saturated $NaHCO_3$ solution, brine, dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product. Purification *via* flash column chromatography (39:1 petroleum ether 40-60 – CH_2Cl_2 to 19:1 petroleum ether 40-60 – CH_2Cl_2) afforded 1-bromo-6-methoxynaphthalene (**91**) (6.93 g, 29% over 2 steps) as a light-yellow oil.

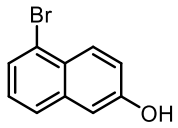
IR (film) ν_{max}/cm^{-1} 1623, 1501, 1469, 1424, 1359, 1263, 1236, 1197, 1169, 1125, 1032, 957, 916, 840, 818, 803, 775, 745, 658.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.16 (d, *J* = 9.28 Hz, 1H), 7.72 (d, *J* = 8.35 Hz, 1H), 7.64 (d, *J* = 7.19 Hz, 1H), 7.32-7.24 (m, 2H), 7.15 (d, *J* = 2.50 Hz, 1H), 3.96 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ =158.2, 135.9, 128.8, 127.6, 127.5, 126.8, 126.7, 122.7, 120.0, 106.1, 55.4.

Data in agreement with literature reported.[145]

5-Bromonaphthalen-2-ol (92)



1-Bromo-6-methoxynaphthalene (**91**) (6.93 g, 29.2 mmol, 1.00 equiv.) was dissolved in CH_2Cl_2 (146 mL) and the resulting solution was cooled to 0 °C. BBr_3 (3.37 mL, 8.75 g, 35.4 mmol, 1.20 equiv.) was added dropwise over 5 minutes. The reaction was allowed to warm to room temperature and was stirred for 16 hours. The reaction was quenched with water and extracted 3 times with CH_2Cl_2. The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product. Purification *via* flash column chromatography (1:1 CH_2Cl_2 – petroleum ether) gave 5-bromonaphthalen-2-ol (**92**) (6.35 g, 97%) as an off-white solid.

m.p. = 104-105 °C (CH_2Cl_2/petroleum ether 40-60).

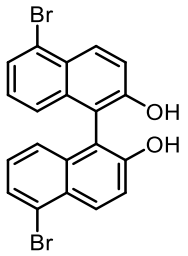
IR (film) ν_{max}/cm^{-1}: 3244, 1625, 1563, 1504, 1427, 1382, 1252, 1230, 965, 773.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.18 (d, *J* = 9.1 Hz, 1H), 7.69-7.62 (m, 2H), 7.28 (app. t, partially obscured, *J* = 8.8 Hz), 7.22 (dd, *J* = 9.1, 2.6 Hz, 1H), 7.18 (d, *J* = 2.5, 1H), 5.09 (br. s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 154.0, 135.8, 129.4, 127.7, 127.5, 127.0, 126.4, 122.8, 119.0, 109.9.

HRMS (ESI^-) $C_{10}H_7{}^{79}BrO$ $[M-H]^-$ requires 220.96081, found: 220.96070, Δ -0.5 ppm.

5,5'-Dibromo-[1,1'-binaphthalene]-2,2'-diol (93)



5-Bromonaphthalen-2-ol (**92**) (6.35 g, 28.5 mmol, 1.00 equiv.) was dissolved in CH_2Cl_2 (190 mL) and $[Cu(TMEDA)OHCl)]_2$ (130 mg, 0.280 mmol, 1 mol%) was added. The reaction was stirred for 16 hours at room temperature open to air. The reaction mixture was filtered through a short silica plug eluting with CH_2Cl_2. Evaporation of the solvent gave 5,5'-dibromo-[1,1'-binaphthalene]-2,2'-diol (**93**) (6.28 g, 100%) as an off-white solid.

m.p. = 79-80 °C (CH_2Cl_2).

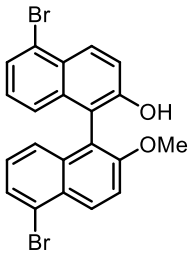
IR (film) ν_{max}/cm^{-1}: 3367, 2923, 2360, 1698, 1615, 1572, 1541, 1497, 1395, 1331, 1252, 1197, 1132, 981, 913, 820, 799, 656.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.46 (d, *J* = 9.48 Hz, 2H), 7.70 (dd, *J* = 7.15, 0.89, 2H), 7.51 (d, *J* = 9.30 Hz, 2H), 7.17 (dd, *J* = 8.41, 7.33 Hz, 2H), 7.09 (d, *J* = 8.59 Hz, 2H), 5.09 (s, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 153.4, 134.7, 131.0, 128.4, 128.0, 128.0, 124.0, 123.5, 119.0, 111.0.

HRMS (ESI^+) $C_{20}H_{11}{}^{79}Br_2O_2$ $[M+H]^+$ requires 440.91203, found: 440.91260, Δ +1.3 ppm.

5,5'-Dibromo-2'-methoxy-[1,1'-binaphthalen]-2-ol (94)



5,5'-Dibromo-[1,1'-binaphthalene]-2,2'-diol (**93**) (5.80 g, 13.1 mmol, 1.00 equiv.) was dissolved in acetone (115 mL) and K_2CO_3 (2.35 g, 17.0 mmol, 1.30 equiv.) followed by iodomethane (900 µL, 2.04 g, 14.4 mmol, 1.10 equiv.) were added. The reaction was heated under reflux for 16 hours. Upon cooling to room temperature, the solvent was removed *in vacuo*. The residue was partitioned between water and CH_2Cl_2 and the phases were separated. The aqueous layer was extracted twice with CH_2Cl_2 and the organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product. Purification *via* flash column chromatography (1:1 CH_2Cl_2 – petroleum ether 40-60) gave 5,5'-dibromo-2'-methoxy-[1,1'-binaphthalen]-2-ol (**94**) (3.02 g, 50%) as an off-white solid.

m.p. = 133-135 °C (CH_2Cl_2/petroleum ether 40-60).

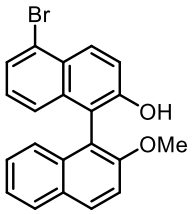
IR (film) ν_{max}/cm^{-1}: 3525, 2923, 2360, 1772, 1716, 1684, 1611, 1560, 1371, 1050, 752, 690, 668, 655.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 8.53 (d, *J* = 9.5 Hz, 1H), 8.37 (d, *J* = 9.3 Hz, 1H), 7.69 (dd, *J* = 6.49, 1.9 Hz, 1H), 7.63 (dd, *J* = 7.38, 1.0 Hz, 1H), 7.60 (d, *J* = 9.4 Hz, 1H), 7.47 (d, *J* = 9.2 Hz, 1H), 7.16-7.10 (m, *2*H), 7.07 (dd, *J* = 8.40, 7.4 Hz, 1H), 6.98 (d, *J* = 8.5 Hz, 1H), 4.91 (s, 1H), 3.86 (s, 3H).

^{13}C NMR (127 MHz, $CDCl_3$) δ_C: 156.6, 151.9, 135.2, 135.0, 130.9, 129.4, 128.3, 127.9, 127.8, 127.6, 127.5, 126.9, 124.7, 124.7, 123.2, 123.2, 118.8, 115.1, 115.1, 114.6, 56.6.

HRMS (ESI^+) $C_{21}H_{13}O_2{}^{79}Br_2$ $[M-H]^-$ requires 454.92878; found 454.92850, Δ −0.6 ppm.

5-Bromo-2'-methoxy-[1,1'-binaphthalen]-2-ol (95)



5,5'-Dibromo-2'-methoxy-[1,1'-binaphthalen]-2-ol (**94**) (2.37 g, 5.17 mmol, 1.00 equiv.) was dissolved in THF (52 mL) and cooled to −78 °C. ^{n}BuLi (2.5 M in hexane, 4.14 mL, 10.3 mmol, 2.00 equiv.) was added by syringe pump over 1 hour after which time the reaction was stirred for a further 1 hour at −78 °C. The reaction was quenched by dropwise addition of water. After warming to room temperature, saturated ammonium chloride solution was added. EtOAc was added and the phases were separated. The aqueous phase was extracted twice with EtOAc and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product. Purification *via* flash column chromatography (4:1 petroleum ether 40-60 – EtOAc) afforded 5-bromo-2'-methoxy-[1,1'-binaphthalen]-2-ol (**95**) (1.03 g, 52%)

m.p. = 152-153 °C (EtOAc/petroleum ether 40-60).

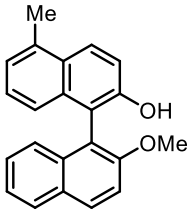
IR (film) ν_{max}/cm^{-1}: 3486, 3409, 2980, 1613, 1507, 1461, 1346, 1268, 1252, 1214, 1173, 1147, 1131, 1086, 807, 751.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.35 (d, *J* = 9.3 Hz, 1H), 8.07 (d, *J* = 9.1 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.61 (dd, *J* = 5.9, 2.5 Hz, 1H), 7.48 (d, *J* = 9.0 Hz, 1H), 7.45 (d, *J* = 9.0 Hz, 1H), 7.38 (ddd, *J* = 8.1, 6.8, 1.3 Hz, 1H), 7.30 (ddd, *J* = 8.3, 6.8, 1.4 Hz, 1H), 7.13 (d, *J* = 7.5 Hz, 1H), 7.07–7.00 (m, 2H), 4.98 (s, 1H), 3.81 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.1, 152.1, 135.2, 134.0, 131.5, 129.5, 129.2, 128.4, 127.7, 127.7, 127.5, 126.9, 125.0, 124.8, 124.4, 123.3, 118.9, 115.6, 114.8, 113.8, 56.7.

HRMS (ESI$^+$) $C_{21}H_{13}O_2{}^{79}Br$ $[M+H]^+$ requires 377.01827; found 377.01822, Δ −0.1 ppm.

2'-Methoxy-5-methyl-[1,1'-binaphthalen]-2-ol (96)



5-Bromo-2'-methoxy-[1,1'-binaphthalen]-2-ol (**95**) (379 mg, 1.00 mmol, 1.00 equiv.) and $Pd(dppf)Cl_2.CH_2Cl_2$ (98 mg, 0.100 mmol, 10 mol%) were dissolved in THF (10 mL) and MeMgCl solution (3 M in Et_2O, 1.70 mL, 5.00 mmol, 5.00 equiv.) was added. The resulting solution was heated under reflux for 16 hours. On cooling to room temperature, saturated ammonium chloride solution was added and phases were separated. The aqueous phase was extracted twice with EtOAc and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product which was purified by column chromatography (9:1 petroleum ether 40-60 – EtOAc) to give 2'-methoxy-7-methyl-[1,1'-binaphthalen]-2-ol (**96**) (334 mg, 88%) as an off-white solid.

m.p. = 135-136 °C (EtOAc/petroleum ether 40-60).

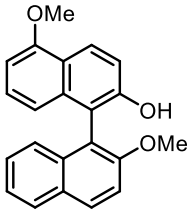
IR (film) ν_{max}/cm^{-1}: 3507, 1592, 1272, 1210, 1186, 1067, 808, 800, 752.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.00 (d, *J* = 9.1 Hz, 1H), 7.94 (d, *J* = 9.0 Hz, 1H), 7.80 (d, *J* = 8.3 Hz, 1H), 7.37 (d, *J* = 9.1 Hz, 1H), 7.30 (d, *J* = 9.2 Hz, 1H), 7.27–7.24 (m, 1H), 7.20–7.14 (m, 1H), 7.09–6.98 (m, 3H), 6.83 (d, *J* = 8.2 Hz, 1H), 4.81 (s, 1H), 3.70 (s, 3H), 2.65 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.0, 151.0, 134.5, 134.1, 133.9, 131.0, 129.4, 128.2, 128.1, 127.3, 126.3, 126.0, 125.0, 124.3, 124.2, 123.4, 117.0, 115.6, 115.6, 113.8, 56.7, 19.8.

HRMS (ESI$^+$) $C_{22}H_{20}O_2$ $[M+H]^+$ requires 315.13796; found 315.13797, Δ 0.0 ppm.

2',5-Dimethoxy-[1,1'-binaphthalen]-2-ol (97)



5-Bromo-2'-methoxy-[1,1'-binaphthalen]-2-ol (**95**) (190 mg, 0.500 mmol, 1.00 equiv.) was dissolved in DMF (5 mL) then CuCl (149 mg, 1.50 mmol 3.00 equiv.) and NaOMe (4.4 M in MeOH, 1.37 mL, 6.00 mmol, 12.0 equiv.) were added sequentially. The reaction was heated at 100 °C for 1 hour then cooled to room temperature. Ice water was added followed by hydrochloric acid (3 M). The resulting suspension was extracted 3 times with EtOAc and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product. Purification *via* flash column chromatography (1:1 CH_2Cl_2 – petroleum ether 40-60 to 4:1 CH_2Cl_2 – petroleum ether 40-60) afforded 2',5-dimethoxy-[1,1'-binaphthalen]-2-ol (**97**) as an off-white solid (123 mg, 75%).

m.p. = 80-81 °C (CH_2Cl_2/ petroleum ether 40-60).

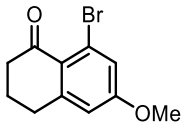
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.38 (d, *J* = 9.1 Hz, 1H), 8.04 (d, *J* = 9.1 Hz, 1H), 7.97-7.86 (m, 1H), 7.47 (d, *J* = 9.1 Hz, 1H), 7.42-7.32 (m, 2H), 7.29 (ddd, *J* = 8.2, 6.7, 1.4 Hz, 1H), 7.20 (dd, *J* = 8.5, 1.2 Hz, 1H), 7.14 (dd, *J* = 8.5, 7.6 Hz, 1H), 6.68 (d, *J* = 7.6 Hz, 1H), 6.64 (d, *J* = 8.5 Hz, 1H), 4.93 (s, 1H), 4.02 (s, 3H), 3.81 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.0, 155.9, 151.8, 135.0, 134.1, 131.0, 129.4, 128.1, 127.3, 126.7, 125.0, 124.2, 124.0, 121.0, 117.4, 116.4, 115.6, 114.9, 113.8, 101.7, 56.7, 55.5.

IR (film) ν_{max}/cm^{-1}: 3493, 3434, 3063, 3003, 2958, 2936, 2838, 1620, 1591, 1464, 1431, 1415, 1333, 1301, 1268, 1252, 1223, 1165, 1149, 1122, 1076, 1052, 1020.

HRMS (ESI^+) $C_{22}H_{18}O_3$ $[M+H]^+$ requires 331.13287; found 31.13293, Δ +0.2 ppm

8-Bromo-6-methoxy-3,4-dihydronaphthalen-1(2H)-one (98)



Following a modified literature procedure,[62] 6-methoxy-3,4-dihydronaphthalen-1(2H)-one (25.0 g, 142 mmol, 1.00 equiv.) and methoxyamine hydrochloride (23.4 g, 284 mmol, 2.00 equiv.) were dissolved in ethanol (284 mL) and pyridine (28.4 mL) was added. The resulting solution was stirred at room temperature for 16 hours. The solution was concentrated *in vacuo* and 2 M HCl solution was added followed by CH_2Cl_2. The organic phase was separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic layers were washed with 1 M $NaHCO_3$ solution, brine, dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product which was used without further purification.

The crude oxime ether was dissolved in acetic acid (568 mL). $Pd(OAc)_2$ (1.59 g, 7.01 mmol, 5 mol% equiv.) and *N*-bromosuccinimide (30.3 g, 170 mmol, 1.20 equiv.) were added and the reaction was heated at 80°C for 1 hour. On cooling to room temperature, the reaction mixture was filtered through celite and concentrated. The residue was dissolved in Et_2O and the resulting solution was washed with water, washed three times with NaOH solution (1 M), washed with brine and concentrated to give the crude product which was used without further purification.

The crude brominated oxime ether was dissolved in 2:3 dioxane-6M HCl (710 mL) and the solution was heated under reflux for 1 hour. On cooling to room temperature, the solution was extracted three times with Et_2O and the combined organic layers were washed with NaOH solution (1 M), brine and concentrated to give the crude product. Recrystallization from hexane-EtOAc afforded 8-bromo-6-methoxy-3,4-dihydronaphthalen-1(2H)-one (**98**) (21.0 g, 58%) as an off-white solid.

m.p. = 115-117 °C (hexane-EtOAc)

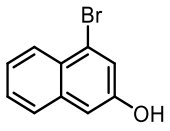
IR (film) ν_{max}/cm^{-1}: 1946, 1675, 1586, 1555, 1245, 1121, 1038, 884, 874, 841, 791.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.06 (d, *J* = 2.6 Hz, 1H), 6.68 (dd, *J* = 2.6, 1.1 Hz, 1H), 3.82 (s, 3H), 2.93 (app. t, *J* = 6.1 Hz, 2H), 2.62 (dd, *J* = 7.2, 6.0 Hz, 2H) 2.05 (tt, *J* = 7.3, 6.2 Hz, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 195.4, 161.8, 148.8, 124.2, 123.6, 119.9, 113.0, 55.7, 39.9, 31.5, 22.5.

HRMS (ESI^+) $C_{11}H_{11}O_2Br$ $[M+H]^+$ requires 255.00152; found 255.00160, Δ +0.3 ppm.

1-Bromo-3-methoxynaphthalene (99)



8-Bromo-6-methoxy-3,4-dihydronaphthalen-1(2H)-one (**98**) (21.0 g, 82.3 mmol, 1.00 equiv.) was dissolved in ethanol (164 mL) and the solution was cooled to 0 °C. $NaBH_4$ (6.22 g, 165 mmol, 2.00 equiv.) was added portionwise and the reaction was allowed to warm to room temperature over 16 hours. Saturated ammonium chloride solution was added and the mixture was extracted three times with CH_2Cl_2. The combined organic layers were washed with water, dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product which was used without further purification.

The crude alcohol was dissolved in PhMe (411 mL), $TsOH.H_2O$ (1.57 g, 8.23 mmol, 0.100 equiv.) was added and the reaction was heated under reflux for 30 minutes. On cooling to room temperature, powdered KOH (462 mg, 8.23 mmol, 0.100 equiv.) and stirring was continued for 10 minutes. DDQ (24.2 g, 107 mmol, 1.30 equiv.) was added and the reaction was heated at 40 °C for 2 hours and cooled to room temperature. The solvent was removed *in vacuo* and the residue was suspended in 1:4 CH_2Cl_2 – petroleum ether 40-60 and filtered through a short silica plug eluting with the same solvent mixture. The solvent was removed *in vacuo* to give the crude product which was used without further purification.

The crude alkene was dissolved in CH_2Cl_2 (411 mL) and cooled to 0 °C. BBr_3 (9.50 mL, 24.7 g, 99.0 mmol, 1.20 equiv.) was added dropwise over 5 minutes and the reaction was allowed to warm to room temperature and stirred for 16 hours. The reaction was cooled to 0 °C and quenched by dropwise addition of water. The resulting biphasic solution was extracted three times with CH_2Cl_2 and the combined organic layers were washed with water, dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product which was recrystallised from hexane-EtOAc to give give 1-bromo-3-methoxynaphthalene (**99**) (12.9 g, 70%) as a yellow solid.

m.p. = 91-92 °C (*n*-hexane/EtOAc)

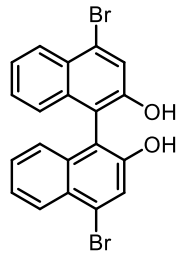
IR (film) ν_{max}/cm^{-1}: 3173, 2944, 2914, 1599, 1566, 1243, 1117, 1078, 1041, 1015, 855, 807.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.14 (d, J = 7.4 Hz, 1H), 7.66 (d, J = 7.6 Hz, 1H), 7.55–7.35 (m, 3H, H_7), 7.14 (d, J = 2.4 Hz, 1H), 5.38 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 153.1, 135.3, 127.7, 127.4, 127.1, 127.0, 125.1, 123.8, 122.0, 109.9.

HRMS (ESI^+) $C_{10}H_5O^{79}Br$ $[M+H]^+$ requires 220.96075; found 220.96065, Δ −0.5 ppm.

4,4'-Dibromo-[1,1'-binaphthalene]-2,2'-diol (100)



4-Bromonaphthalen-2-ol (**99**) (12.9 g, 58.0 mmol, 1.00 equiv.) was dissolved in CH_2Cl_2 (400 mL) and $[Cu(TMEDA)OHCl)]_2$ (269 mg, 0.580 mmol, 1 mol%) was added. The reaction was stirred for 16 hours at room temperature open to air. The reaction mixture was filtered through a short silica plug eluting with CH_2Cl_2. Evaporation of the solvent gave 4,4'-dibromo-[1,1'-binaphthalene]-2,2'-diol (**100**) (12.9 g, 100%) as an off-white solid.

m.p. = 212-213°C (CH_2Cl_2).

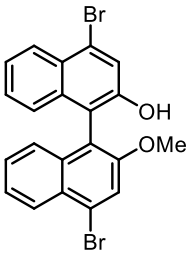
IR (film) ν_{max}/cm^{-1}: 3509, 3464, 1573, 1371, 1217, 1189, 1175, 1148, 1131, 933, 871, 758.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.29 (d, *J* = 8.8 Hz, 2H), 7.74 (s, 2H), 7.49 (ddd, *J* = 8.3, 6.8, 1.2 Hz, 2H), 7.36 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 2H), 7.14 (d, *J* = 8.4 Hz, 2H), 5.04 (s, 2H, OH).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 152.4, 134.0, 128.6, 128.3, 128.0, 126.1, 125.7, 124.6, 122.1, 110.6.

HRMS (ESI^-) $C_{20}H_{12}O_2{}^{79}Br_2$ $[M-H]^-$ requires 442.91108; found 442.91085, Δ -0.2 ppm.

4,4'-Dibromo-2'-methoxy-[1,1'-binaphthalen]-2-ol (101)



4,4'-Dibromo-[1,1'-binaphthalene]-2,2'-diol (**100**) (12.9 g, 29.0 mmol, 1.00 equiv.) was dissolved in acetone (230 mL) and K_2CO_3 (5.20 g, 37.7 mmol, 1.30 equiv.) followed by iodomethane (1.99 mL, 4.53 g, 31.9 mmol, 1.10 equiv.) were added. The reaction was heated under reflux for 16 hours. Upon cooling to room temperature, the solvent was removed *in vacuo*. The residue was partitioned between water and CH_2Cl_2 and the phases were separated. The aqueous layer was extracted twice with CH_2Cl_2 and the organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product. Purification *via* flash column chromatography (1:1 CH_2Cl_2 – petroleum ether) gave 4,4'-dibromo-2'-methoxy-[1,1'-binaphthalen]-2-ol (**101**) (6.42 g, 47%) as an off-white solid.

m.p. = 83-84 °C (CH_2Cl_2/petroleum ether 40-60)

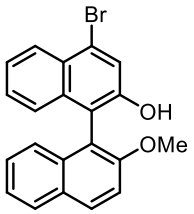
IR (film) ν_{max}/cm^{-1} 3511, 3394, 3360, 3352, 3333, 1499, 1316, 1241, 1211, 1169, 1131, 1060, 946, 842, 744.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.32–8.24 (m, 2H), 7.82 (s, 1H), 7.71 (s, 1H), 7.49 (ddd, *J* = 8.4, 6.8, 1.2 Hz, 1H), 7.43 (ddd, *J* = 8.3, 6.9, 1.2 Hz, 1H), 7.33 (ddd, *J* = 8.1, 6.7, 1.2 Hz, 1H), 7.27 (ddd, *J* = 8.2, 5.6, 1.2 Hz, 1H), 7.19 (br. d, *J* = 8.5 Hz, 1H), 7.04 (br. d, *J* = 8.7 Hz, 1H), 4.89–4.84 (m, 1H), 3.81 (s, 3H).

^{13}C NMR ($CDCl_3$, 121 MHz) δ = 155.6, 151.1, 134.6, 134.4, 128.4, 128.2, 127.9, 127.7, 127.5, 127.5, 125.9, 125.8, 125.3, 125.2, 124.8, 124.2, 121.8, 118.2, 114.9, 114.7, 57.0.

HRMS (ESI^-) $C_{21}H_{14}O_2{}^{79}Br_2$ $[M-H]^-$ requires 456.92673; found 456.92651, Δ +0.1 ppm.

4-Bromo-2'-methoxy-[1,1'-binaphthalen]-2-ol (102)



4,4'-Dibromo-2'-methoxy-[1,1'-binaphthalen]-2-ol (**101**) (3.66 g, 8.00 mmol, 1.00 equiv.) was dissolved in THF (80 mL) and cooled to −78 °C. ^{n}BuLi (2.5 M in hexane, 6.40 mL, 16.0 mmol, 2.00 equiv.) was added by syringe pump over 1 hour after which time the reaction was stirred for a further 1 hour at −78 °C. The reaction was quenched by dropwise addition of water. After warming to room temperature, saturated ammonium chloride solution was added. EtOAc was added and the phases were separated. The aqueous phase was extracted twice with EtOAc and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product which was purified by column chromatography (4:1 petroleum ether 40-60 – EtOAc) to give 7-bromo-2'-methoxy-[1,1'-binaphthalen]-2-ol (**102**) (2.09 g, 69%).

m.p. = 171-172 °C (EtOAc/petroleum ether 40-60).

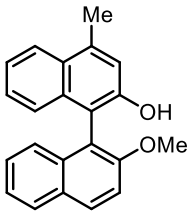
IR (film) ν_{max}/cm^{-1}: 3457, 3435, 3424, 3416, 1588, 1261, 1247, 1209, 1173, 1149, 806, 745.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.16 (d, *J* = 8.7 Hz, 1H), 7.97 (d, *J* = 9.1 Hz, 1H), 7.81 (d, *J* = 8.5 Hz, 1H), 7.63 (s, 1H), 7.38 (d, *J* = 9.1 Hz, 1H), 7.31 (m, 2H), 7.23–7.15 (m, 2H), 7.06 (d, *J* = 8.5 Hz, 1H), 6.97 (d, *J* = 7.7 Hz, 1H), 4.84 (s, 1H), 3.72 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.9, 151.0, 134.5, 133.8, 131.4, 129.4, 128.2, 127.7, 127.5, 127.4, 127.2, 125.3, 124.7, 124.6, 124.3, 123.7, 121.7, 115.3, 114.4, 113.6, 56.6.

HRMS (ESI^{+}) $C_{21}H_{13}O_2Br$ $[M+H]^{+}$ requires 377.01827; found 377.01785, Δ -1.1 ppm.

2'-Methoxy-4-methyl-[1,1'-binaphthalen]-2-ol (103)



4-Bromo-2'-methoxy-[1,1'-binaphthalen]-2-ol (**102**) (379 mg, 1.00 mmol, 1.00 equiv.) and Pd(dppf)Cl_2.CH_2Cl_2 (82.6 mg, 0.100 mmol, 10 mol%) were dissolved in THF (10 mL) and MeMgCl solution (3 M in Et_2O, 1.7 mL, 5.00 mmol, 5.00 equiv.) was added. The resulting solution was heated under reflux for 16 hours. On cooling to room temperature, saturated ammonium chloride solution was added and phases were separated. The aqueous phase was extracted twice with EtOAc and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product which was purified by column chromatography (9:1 petroleum ether 40-60 – EtOAc) to give 2'-methoxy-4-methyl-[1,1'-binaphthalen]-2-ol (**103**) (249 mg, 79%) as an off-white solid.

m.p. = 137-138 °C (EtOAc/petroleum ether 40-60).

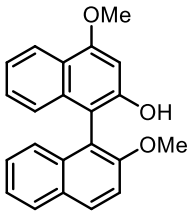
IR (film) ν_{max}/cm^{-1}: 3504, 3434, 3388, 1592, 1508, 1262, 1247, 1223, 1183, 1093, 1065, 804, 754, 744, 666, 643.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.96–7.87 (m, 2H), 7.79 (d, *J* = 7.3 Hz, 1H), 7.37 (d, *J* = 9.1 Hz, 1H), 7.26 (m, 2H), 7.19–7.08 (m, 4H), 6.98 (d, *J* = 8.6 Hz, 1H), 4.78 (br. s, 1H), 3.70 (s, 3H), 2.69 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.1, 150.7, 136.5, 134.2, 134.0, 131.0, 129.4, 128.5, 128.1, 127.3, 126.2, 125.4, 125.1, 124.4, 124.1, 123.1, 118.3, 115.6, 113.8, 113.0, 56.7, 19.6.

HRMS (ESI^+) $C_{22}H_{18}O_2$ $[M+H]^+$ requires 315.13796; found 315.13791, Δ −0.2 ppm.

2',4-Dimethoxy-[1,1'-binaphthalen]-2-ol (104)



4-Bromo-2'-methoxy-[1,1'-binaphthalen]-2-ol (**102**) (379 mg, 1.00 mmol, 1.00 equiv.) was dissolved in DMF (10 mL) then CuCl (279 mg, 3.00 mmol, 3.00 equiv.) and NaOMe (4.4 M in MeOH, 2.70 mL, 12.0 mmol, 12.0 equiv.) were added sequentially. The reaction was heated at 100 °C for 1 hour then cooled to room temperature. Ice water was added followed by hydrochloric acid (3 M). The resulting suspension was extracted 3 times with EtOAc and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product. Purification *via* flash column chromatography (1:1 CH_2Cl_2 – petroleum ether 40-60 to 4:1 CH_2Cl_2 – petroleum ether 40-60) afforded 2',4-dimethoxy-[1,1'-binaphthalen]-2-ol (**104**) as an off-white solid (276 mg, 84%).

m.p. = 171-172 °C (CH_2Cl_2/petroleum ether 40-60).

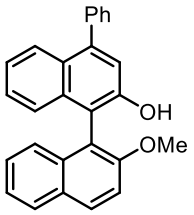
IR (film) ν_{max}/cm^{-1}: 3490, 3430, 2961, 2938, 1619, 1591, 1388, 1263, 1247, 1230, 1174, 1115, 763.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.17 (d, *J* = 8.4 Hz, 1H), 7.93 (d, *J* = 9.1 Hz, 1H), 7.80 (d, *J* = 8.1 Hz, 1H), 7.37 (d, *J* = 9.1 Hz, 1H), 7.27 (ddd, *J* = 8.0, 6.4, 1.6 Hz, 1H), 7.23–7.10 (m, 4H), 6.90 (d, *J* = 8.3 Hz, 1H), 6.66 (s, 1H), 4.85 (s, 1H), 3.98 (s, 3H), 3.71 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.9, 156.3, 151.5, 134.5, 134.3, 130.9, 129.5, 128.1, 127.2, 127.1, 125.1, 124.5, 124.1, 122.6, 122.2, 121.6, 115.4, 113.9, 106.9, 96.5, 56.7, 55.7.

HRMS (ESI^+) $C_{22}H_{18}O_3$ $[M+H]^+$ requires 331.13287; found 31.13272, Δ −0.5 ppm.

2'-Methoxy-4-phenyl-[1,1'-binaphthalen]-2-ol (105)



4-Bromo-2'-methoxy-[1,1'-binaphthalen]-2-ol (**102**) (379 mg, 1.00 mmol, 1.00 equiv.), phenyl boronic acid (144 mg, 1.20 mmol, 1.20 equiv.) and $Pd(PPh_3)_4$ (57.8 mg, 0.0500 mmol, 0.0500 equiv.) were charged to a flask fitted with a water-cooled condenser. The flask was evacuated and backfilled with argon three times. 1,2-Dimethoxyethane (Ar sparged, 10 mL) was added followed by aqueous Na_2CO_3 solution (Ar sparged, 2 M, 1.25 mL, 2.50 equiv.). The condenser was fitted with an argon balloon and heated at 90 °C for 16 hours. After cooling to room temperature, 1 M HCl solution was added and the solution was extracted three times with CH_2Cl_2, the combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product which was purified by column chromatography (9:1 petroleum ether 40-60 – EtOAc) to give 2'-methoxy-4-phenyl-[1,1'-binaphthalen]-2-ol (**105**) (314 mg, 84%) as a white solid.

m.p. = 103-104 °C (EtOAc/petroleum ether 40-60).

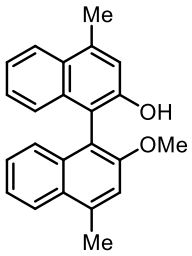
IR (film) ν_{max}/cm^{-1}: 3657, 2980, 2888, 1382, 1261, 1169, 1142, 1088, 1060, 945, 809, 762, 749, 702.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.96 (d, J = 9.0 Hz, 1H), 7.85–7.75 (m, 2H), 7.53 (dt, J = 6.1, 1.4 Hz, 2H), 7.47–7.34 (m, 4H), 7.29 (ddd, J = 8.1, 6.3, 1.7 Hz, 1H), 7.25–7.09 (m, 5H), 7.03 (dd, J = 8.1, 1.7 Hz, 1H), 4.87 (s, 1H), 3.74 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.1, 150.6, 142.1, 140.5, 134.2, 134.1, 131.1, 130.2, 129.5, 128.3, 128.2, 127.6, 127.4, 127.4, 126.4, 126.3, 125.2, 125.0, 124.2, 123.3, 118.5, 115.3, 114.6, 113.8, 56.7.

HRMS (ESI^+) $C_{27}H_{20}O_2$ $[M+H]^+$ requires 377.15361; found 377.15358, Δ −0.1 ppm.

2'-Methoxy-4,4'-dimethyl-[1,1'-binaphthalen]-2-ol (106)



4,4'-Dibromo-2'-methoxy-[1,1'-binaphthalen]-2-ol (**101**) (687 mg, 1.50 mmol, 1.00 equiv.) and $Pd(dppf)Cl_2.CH_2Cl_2$ (122 mg, 0.15 mmol, 10 mol%) were dissolved in THF (15 mL) and MeMgCl solution (3 M in Et_2O, 5.00 mL, 15.0 mmol, 10.0 equiv.) was added. The resulting solution was heated under reflux for 16 hours. On cooling to room temperature, saturated ammonium chloride solution was added and phases were separated. The aqueous phase was extracted twice with EtOAc and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product which was purified by column chromatography (9:1 petroleum ether 40-60 – EtOAc) to give 2'-methoxy-4,4'-dimethyl-[1,1'-binaphthalen]-2-ol (**106**) (224 mg, 45%) as an off-white solid.

m.p. = 178-180 °C (EtOAc – petroleum ether 40-60).

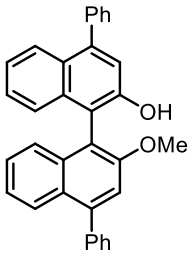
IR (film) ν_{max}/cm^{-1}: 3519, 2980, 1591, 1342, 1264, 1220, 1179, 1171, 1136, 1111, 1058, 999, 869, 758.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.13–7.92 (m, 2H), 7.48–7.21 (m, 7H), 7.15–7.09 (m, 1H), 4.92 (s, 1H), 3.83 (s, 3H), 2.89 (s, 3H), 2.82 (s, 3H).

^{13}C NMR ($CDCl_3$, 121 MHz) δ = 155.6, 150.8, 137.9, 136.4, 134.3, 134.1, 128.7, 128.5, 127.0, 126.1, 125.6, 125.5, 124.4, 124.3, 124.0, 123.0, 118.2, 115.0, 113.4, 113.2, 56.7, 20.1, 19.6.

HRMS (ESI^+) $C_{23}H_{20}O_2$ $[M+H]^+$ requires 329.15361; found 329.15279, Δ −1.4 ppm.

2'-Methoxy-4,4'-diphenyl-[1,1'-binaphthalen]-2-ol (107)



4,4'-Dibromo-2'-methoxy-[1,1'-binaphthalen]-2-ol (**101**) (458 mg, 1.00 mmol, 1.00 equiv.), phenyl boronic acid (293 mg, 2.40 mmol, 2.40 equiv.) and $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol, 5 mol%) were charged to a flask fitted with a water-cooled condenser. The flask was evacuated and backfilled with argon three times. 1,2-Dimethoxyethane (Argon sparged, 10 mL) was added followed by aqueous Na_2CO_3 solution (Argon sparged, 2 M, 2.50 mL, 5.00 equiv.). The flask was fitted with an argon balloon and heated at 90 °C for 16 hours. After cooling to room temperature, 1 M HCl solution was added and the solution was extracted three times with CH_2Cl_2, the combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product which was purified by column chromatography (9:1 petroleum ether 40-60 – EtOAc) to give 2'-methoxy-4,4'-diphenyl-[1,1'-binaphthalen]-2-ol (**107**) (384 mg, 85%) as a white solid.

m.p. = 118-120 °C (EtOAc – petroleum ether 40-60).

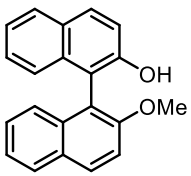
IR (film) ν_{max}/cm^{-1}: 3526, 3407, 3056, 2970, 2935, 1587, 1344, 1224, 1175, 1144, 763, 702, 658.

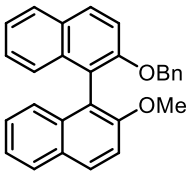
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.87–7.82 (m, 2H), 7.58–7.35 (m, 11H), 7.29–7.11 (m, 7H), 4.95 (s, 1H), 3.77 (s, 3H).

^{13}C NMR ($CDCl_3$, 121 MHz) δ =155.4, 150.7, 143.6, 142.2, 140.5, 140.5, 134.6, 134.3, 130.2, 130.1, 128.5, 128.3, 127.8, 127.8, 127.6, 127.4, 127.3, 126.5, 126.4, 126.4, 125.4, 125.3, 124.3, 123.3, 118.5, 114.9, 114.7, 114.6, 56.7.

HRMS (ESI^+) $C_{33}H_{24}O_2$ $[M+H]^+$ requires 453.18491; found 453.18411, Δ −1.8 ppm.

Kinetic resolution of 2'-methoxy-[1,1'-binaphthalen]-2-ol (67)





Following **general procedure A,** 2'-methoxy-[1,1'-binaphthalen]-2-ol (**1**) (45.0 mg, 0.15 mmol) was reacted for 24 h. Purification *via* flash column chromatography (30% CH_2Cl_2 – petroleum ether 40-60 to 80% CH_2Cl_2 – petroleum ether 40-60) afforded 2-(benzyloxy)-2'-methoxy-1,1'-binaphthalene (**66**) as an off-white solid (28.6 mg, 49%, 90:10 er) and recovered starting material (**67**) (21.2 mg, 47%, 98:2 er).

(*S*)-2-(Benzyloxy)-2'-methoxy-1,1'-binaphthalene (66):

m.p. = 130-132 °C (CH_2Cl_2/petroleum ether 40-60).

IR (film) ν_{max}/cm^{-1}: 3058, 3037, 2933, 1591, 1506, 1262, 1249, 1220, 1090, 1061, 806, 746, 734.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.01 (d, *J* = 9.0 Hz, 1H), 7.92 (d, *J* = 9.4 Hz, 1H), 7.90–7.85 (m, 2H), 7.47 (d, *J* = 9.0 Hz, 1H), 7.44 (d, *J* = 9.0 Hz, 1H), 7.34 (m, 1.3 Hz, 2H), 7.25–7.20 (m, 3H), 7.20–7.12 (m, 4H), 7.02–6.95 (m, 2H), 5.35–4.85 (m, 2H), 3.77 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 155.1, 154.2, 137.7, 134.3, 134.2, 129.6, 129.6, 129.5, 129.4, 129.1, 128.3, 128.1, 128.0, 127.4, 126.9, 126.5, 126.4, 125.6, 125.5, 123.9, 123.6, 121.0, 119.6, 116.3, 114.0, 71.4, 56.8.

HRMS (ESI^+) $C_{28}H_{22}O_2$ $[M+Na]^+$ requires 413.15120; found 413.15147, Δ 0.6 ppm.

Chiral HPLC: (Chiralpak IC, 1% ^{i}PrOH, 99% hexane, 1.0 mL min^{-1}, λ = 289 nm) τ_R (major) = 8.0 min, τ_R (minor) = 11.8 min.

$[\alpha]_D^{25}$ = -58.7 (*c* = 1.00, $CHCl_3$).

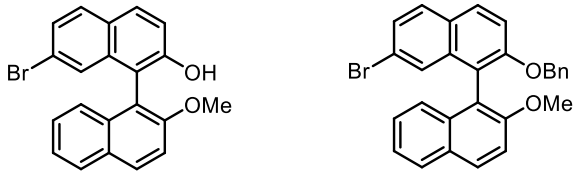
(*R*)-2'-Methoxy-[1,1'-binaphthalen]-2-ol (67):

m.p. = 108-109 °C (CH_2Cl_2/petroleum ether b.p. 40-60 °C).

Chiral HPLC: (Chiralpak ADH, 7.5% ^{i}PrOH, 92.5% hexane, 1.0 mL min^{-1}, λ = 290 nm) τ_R (major) = 25.7 min, τ_R (minor) = 16.6 min.

$[\alpha]_D^{25}$ = +42.0(*c* = 0.50, acetone).

Kinetic resolution of 7-bromo-2'-methoxy-[1,1'-binaphthalen]-2-ol (86)



Following **general procedure A,** 7-bromo-2'-methoxy-[1,1'-binaphthalen]-2-ol (**86**) (56.9 mg, 0.150 mmol) was reacted for 36 h. Purification *via* flash column chromatography (3:7 CH_2Cl_2 – petroleum ether 40-60 to 4:1 CH_2Cl_2 – petroleum ether 40-60) afforded 2-(benzyloxy)-7-bromo-2'-methoxy-1,1'-binaphthalene (**108**) as an off-white solid (37.3 mg, 53%, 85:15 er) and recovered starting material (**86**) (22.5 mg, 40%, 99.5:0.5 er).

(*S*)- [2-(Benzyloxy)-7-bromo-2'-methoxy-1,1'-binaphthalene] (108):

m.p. = 64-65 °C (CH_2Cl_2/petroleum ether 40-60).

IR (film) ν_{max}/cm^{-1}: 3061, 3032, 2837, 1613, 1497, 1267, 1255.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.92 (d, *J* = 9.1 Hz, 1H), 7.81 (d, *J* = 8.2 Hz, 1H), 7.77 (d, *J* = 9.3 Hz, 1H), 7.62 (d, *J* = 8.7 Hz, 1H), 7.37 (d, *J* = 9.0 Hz, 1H), 7.33–7.23 (m, 4H), 7.19–7.12 (m, 1H), 7.10–6.99 (m, 4H), 6.91–6.85 (m, 2H), 5.03–4.91 (m, 3H), 3.68 (s, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 154.9, 154.7, 137.3, 135.4, 133.9, 129.8, 129.7, 129.2, 129.2, 128.2, 128.0, 127.8, 127.4, 127.4, 127.2, 126.7, 126.5, 125.1, 123.6, 121.0, 120.1, 118.4, 116.2, 113.7, 71.0, 56.6.

HRMS (ESI^+) $C_{28}H_{21}O_2{}^{79}Br$ $[M+Na]^+$ requires 491.06171; found 491.06180, Δ +0.2 ppm.

Chiral HPLC: (Chiralpak ADH, 10% ^{i}PrOH, 90% hexane, 1.0 mL min^{-1}, λ = 295 nm) τ_R (major) = 7.5 min, τ_R (minor) = 8.7 min.

$[\alpha]_D^{25}$ = −23.2 (*c* = 1.00, $CHCl_3$).

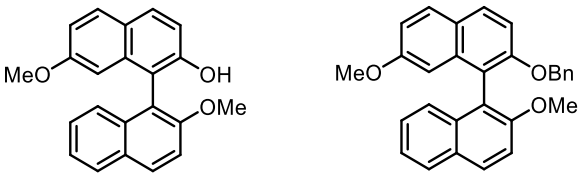
(*R*)- 7-Bromo-2'-methoxy-[1,1'-binaphthalen]-2-ol (86):

m.p. = 178-179 °C (CH_2Cl_2/petroleum ether 40-60).

Chiral HPLC: (Chiralpak ADH, 10% ^{i}PrOH, 90% hexane, 1.0 mL min^{-1}, λ = 295 nm) τ_R (minor) = 11.6 min, τ_R (major) = 13.7 min.

$[\alpha]_D^{25}$ = −53.8 (*c* = 1.00, $CHCl_3$).

Kinetic resolution of 2',7-dimethoxy-[1,1'-binaphthalen]-2-ol (87)



Following **general procedure A**, 2',7-dimethoxy-[1,1'-binaphthalen]-2-ol (**87**) (49.6 mg, 0.150 mmol) was reacted for 27 h. Purification *via* flash column chromatography (3:1 petroleum ether 40-

60/CH_2Cl_2 to 1:3 petroleum ether 40-60/CH_2Cl_2) afforded 2-(benzyloxy)-2',7-dimethoxy-1,1'-binaphthalene (**109**) as an off-white solid (32.5 mg, 52%, 88.5:11.5 er) and recovered starting material (**87**) (21.2 mg, 43%, 99.0:1.0 er).

(*S*)-2-(Benzyloxy)-2',7-dimethoxy-1,1'-binaphthalene (109)

m.p. = 51-53 °C (CH_2Cl_2/petroleum ether 40-60).

IR (film) ν_{max}/cm^{-1}: 3060, 2934, 1624, 1593, 1461, 1354, 1318, 1224, 1178, 1092, 1045, 812, 749, 696.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 8.00 (d, *J* = 9.1 Hz, 1H), 7.90 (d, *J* = 8.1 Hz, 1H), 7.84 (d, *J* = 8.9 Hz, 1H), 7.77 (d, *J* = 8.9 Hz, 1H), 7.47 (d, *J* = 9.1 Hz, 1H), 7.34 (ddd, *J* = 8.1, 6.6, 1.4 Hz, 1H), 7.28 (d, *J* = 8.9 Hz, 1H), 7.26-7.19 (m, 2H), 7.19-7.12 (m, 3H), 7.02 (dd, *J* = 8.9, 2.45 Hz, 1H), 7.00-6.93 (m, 2H), 6.49 (d, *J* = 2.4 Hz, 1H), 5.10-5.00 (m, 2H), 3.78 (s, 3H), 3.51 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 158.2, 155.1, 154.8, 137.8, 135.6, 13.1, 129.6, 129.5, 129.4, 129.1, 128.2, 128.0, 127.4, 126.8, 126.4, 125.6, 125.1, 123.6, 119.8, 119.7, 116.3, 114.0, 113.6, 104.2, 71.2, 56.8, 55.1.

HRMS (ESI^+) $C_{29}H_{25}O_3^+$ $[M+H]^+$ requires 421.17982; found: 421.17953, Δ 0.7 ppm.

Chiral HPLC: (Chiralpak ODH, 5% ^{i}PrOH, 95% hexane, 1.00 mL min^{-1}, λ = 290 nm) τ_R (major) = 8.8 min, τ_R (minor) = 9.9 min.

$[\alpha]_D^{25}$ = −5.2 (*c* = 1.00, $CHCl_3$).

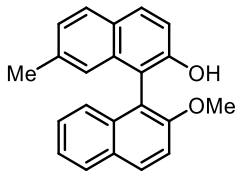
(*R*)-2',7-Dimethoxy-[1,1'-binaphthalen]-2-ol (87)

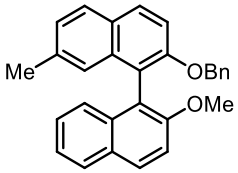
m.p. = 103-105 °C (CH_2Cl_2/petroleum ether 40-60).

Chiral HPLC: (Chiralpak ADH, 15% ^{i}PrOH, 85% hexane, 1.00 mL min^{-1}, λ = 290 nm) τ_R (major) = 17.9 min, τ_R (minor) = 13.5 min.

$[\alpha]_D^{25}$ = −105.3 (*c* = 1.00, $CHCl_3$).

Kinetic resolution of 2'-methoxy-7-methyl-[1,1'-binaphthalen]-2-ol] (88)





Following **general procedure A,** 2'-methoxy-7-methyl-[1,1'-binaphthalen]-2-ol (**88**) (47.2 mg, 0.150 mmol) was reacted for 24 h. Purification *via* flash column chromatography (3:7 CH_2Cl_2 – petroleum ether 40-60 to 4:1 CH_2Cl_2 – petroleum ether 40-60) afforded 2-(benzyloxy)-2'-methoxy-7-methyl-1,1'-binaphthalene (**110**) as an off-white solid (34.0 mg, 56%, 86:14 er) and recovered starting material (**88**) (18.6 mg, 39%, 99.5:0.5 er).

(*S*)- 2-(Benzyloxy)-2'-methoxy-7-methyl-1,1'-binaphthalene (110):

m.p. = 69-70 °C (CH_2Cl_2/petroleum ether 40-60).

IR (film) ν_{max}/cm^{-1}: 3054, 2836, 1624, 1593, 1506, 1470, 1452, 1263, 826, 810.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.02 (d, *J* = 9.0 Hz, 1H), 7.91 (d, *J* = 8.2 Hz, 1H), 7.88 (d, *J* = 9.0 Hz, 1H), 7.77 (d, *J* = 8.3 Hz, 1H), 7.48 (d, *J* = 9.0 Hz, 1H), 7.41–7.31 (m, 2H), 7.25–7.13 (m, 6H), 6.99–6.95 (m, 3H), 3.77 (s, 2H), 2.27 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.0, 154.1, 137.7, 136.0, 134.3, 134.2, 129.3, 129.2, 129.0, 128.1, 127.9, 127.8, 127.8, 127.3, 126.7, 126.2, 125.5, 124.3, 124.2, 123.5, 120.2, 119.7, 115.2, 114.0, 71.2, 56.7, 22.0.

HRMS (ESI$^+$) $C_{29}H_{24}O_2$ $[M+H]^+$ requires 405.18491; found 405.18488, Δ −0.1 ppm.

Chiral HPLC: (Chiralpak OJH, 3% EtOH, 97% hexane, 1.0 mL min^{-1}, λ = 300 nm) τ_R (minor) = 9.4 min, τ_R (major) = 15.1 min.

$[\alpha]_D^{25}$ = −23.8 (*c* = 1.00, $CHCl_3$).

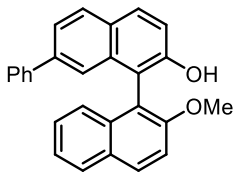
(*R*)- 2'-Methoxy-7-methyl-[1,1'-binaphthalen]-2-ol (88):

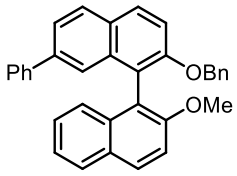
m.p. = 124-125 °C (CH_2Cl_2/petroleum ether 40-60).

Chiral HPLC: (Chiralpak ADH, 10% ^{i}PrOH, 90% hexane, 1.0 mL min^{-1}, λ = 290 nm) τ_R (minor) = 12.8 min, τ_R (major) = 15.6 min.

$[\alpha]_D^{25}$ = −59.0 (*c* = 1.00, $CHCl_3$).

Kinetic resolution of 2'-methoxy-7-phenyl-[1,1'-binaphthalen]-2-ol (89)





Following **general procedure A,** 2'-methoxy-7-phenyl-[1,1'-binaphthalen]-2-ol (**89**) (56.4 mg, 0.150 mmol) was reacted for 24 h. Purification *via* flash column chromatography (3:7 CH_2Cl_2 – petroleum ether 40-60 to 4:1 CH_2Cl_2 – petroleum ether 40-60) afforded 2-(benzyloxy)-2'-methoxy-7-phenyl-1,1'-binaphthalene (**111**) as an off-white solid (35.1 mg, 50%, 90:10 er) and recovered starting material (**89**) (23.6 mg, 42%, 97:3 er).

***(S)*-2-(Benzyloxy)-2'-methoxy-7-phenyl-1,1'-binaphthalene (111):**

m.p. = 68-89 °C (CH_2Cl_2/petroleum ether 40-60).

IR (film) ν_{max}/cm^{-1}: 3058, 3032, 2935, 2837, 1621, 1594, 1509, 1493, 1454, 1265, 1250, 1221, 1093, 1063, 908, 809, 747, 733, 697.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.90 (d, *J* = 9.1 Hz, 1H), 7.83 (d, *J* = 8.7 Hz, 2H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.50 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.36 (d, *J* = 9.0 Hz, 1H), 7.33 (d, *J* = 9.0 Hz, 1H), 7.30–7.26 (m, 3H), 7.21 (m, 3H), 7.17–7.10 (m, 4H), 7.08–7.04 (m, 3H), 6.92–6.84 (m, 2H), 5.02–4.91 (m, 2H), 3.67 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.0, 154.5, 141.5, 139.0, 137.6, 134.4, 134.2, 129.6, 129.2, 129.0, 128.7, 128.6, 128.5, 128.2, 127.9, 127.5, 127.3, 127.1, 126.8, 126.4, 125.4, 123.7, 123.5, 123.5, 121.2, 119.3, 116.3, 113.8, 71.3, 56.7.

HRMS (ESI^+) $C_{34}H_{26}O_2$ $[M+Na]^+$ requires 489.18250; found 489.18233, Δ -0.3 ppm.

Chiral HPLC: (Chiralpak IC, 2% ^{i}PrOH, 98% hexane, 1.0 mL min^{-1}, λ = 289 nm) τ_R (major) = 20.5 min, τ_R (minor) = 23.5 min.

$[\alpha]_D^{25}$ = +28.3 (*c* = 1.00, $CHCl_3$).

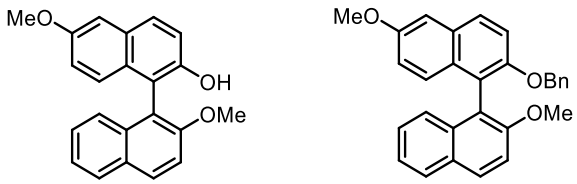
(*R*)-2'-Methoxy-7-phenyl-[1,1'-binaphthalen]-2-ol (89):

m.p. = 190-191 °C (CH_2Cl_2/petroleum ether 40-60).

Chiral HPLC: (Chiralpak ADH, 10% ^{i}PrOH, 90% hexane, 1.0 mL min^{-1}, λ = 272 nm) τ_R (major) = 11.6 min, τ_R (minor) = 14.1 min.

$[\alpha]_D^{25}$ = −118.1 (*c* = 1.00, $CHCl_3$).

Kinetic resolution of 2',6-dimethoxy-[1,1'-binaphthalen]-2-ol (79)



Following **general procedure A,** 2',6-dimethoxy-[1,1'-binaphthalen]-2-ol (**79**) (49.6 mg, 0.150 mmol) was reacted for 27 h. Purification *via* flash column chromatography (1:1 petroleum ether 40-60 – CH_2Cl_2 to 1:3 petroleum ether 40-60 – CH_2Cl_2) afforded 2-(benzyloxy)-2',6-dimethoxy-1,1'-binaphthalene (**112**) as an off-white solid (35.8 mg, 57%, 87.5:12.5 er) and recovered starting material (**79**) (20.8 mg, 42%, 99.5:0.5 er).

(*S*)-2-(Benzyloxy)-2',6-dimethoxy-1,1'-binaphthalene (112)

m.p. = 108-100 °C (CH_2Cl_2/petroleum ether 40-60).

IR (film) ν_{max}/cm^{-1}: 3061, 2935, 2836, 1594, 1462, 1376, 1351, 1267, 1239, 1168, 1130, 1061, 849, 808, 696.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 8.00 (d, *J* = 9.1 Hz, 1H), 7.89 (d, *J* = 8.1 Hz, 1H), 7.82 (d, *J* = 8.9 Hz, 1H), 7.46 (d, *J* = 9.0 Hz, 1H), 7.40 (d, *J* = 9.0 Hz, 1H), 7.37-7.31 (m, 1H), 7.26-7.21 (m, 1H), 7.21-7.13 (m, 4H), 7.11 (d, *J* = 9.1 Hz, 1H), 7.01-6.92 (m, 2H), 6.94 (dd, *J* = 9.2, 2.6 Hz, 1H), 5.06-4.96 (m, 2H), 3.91 (s, 3H), 3.77 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 156.4, 155.1, 152.8, 137.9, 134.2, 130.6, 129.6, 129.5, 129.3, 128.2, 128.0, 127.9, 127.4, 127.2, 127.0, 126.5, 125.5, 123.6, 121.5, 119.6, 119.2, 117.3, 114.0, 106.1, 71.8, 56.8, 55.4.

HRMS (ESI^+) $C_{29}H_{25}O_3$ $[M+H]^+$ requires 421.17982; found 421.17975, Δ −0.2 ppm.

Chiral HPLC: (Chiralpak IC, 1% ^{i}PrOH, 99% hexane, 1.00 mL min^{-1}, λ = 290 nm) τ_R (major) = 15.3 min, τ_R (minor) = 30.6 min

$[\alpha]_D^{25}$ = −34.9 (*c* = 1.00, $CHCl_3$).

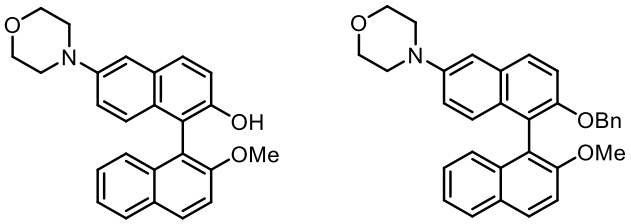
(*R*)-2',6-Dimethoxy-[1,1'-binaphthalen]-2-ol (79)

m.p. = 160-162 °C (CH_2Cl_2/petroleum ether 40-60).

Chiral HPLC: (Chiralpak ADH, 15% ^{i}PrOH, 85% hexane, 1.00 mL min^{-1}, λ = 290 nm) τ_R (major) = 27.0 min, τ_R (minor) = 13.9 min

$[\alpha]_D^{25}$ = −38.6 (*c* = 1.00, $CHCl_3$).

Kinetic resolution of 2'-methoxy-6-morpholino-[1,1'-binaphthalen]-2-ol (80)



Following **general procedure A,** 2'-methoxy-6-morpholino-[1,1'-binaphthalen]-2-ol (**80**) (57.8 mg, 0.150 mmol) was reacted for 24 h. Purification *via* flash column chromatography (4:1 petroleum ether 40-60 – EtOAc to 7:3 petroleum ether 40-60 – EtOAc) afforded 4-(2-(benzyloxy)-2'-methoxy-[1,1'-binaphthalen]-6-yl)morpholine (**113**) as an off-white solid (33.3 mg, 47%, 87:13 er) and recovered starting material (**80**) (19.6 mg, 34%, 99:1 er).

(*S*)- 4-(2-(Benzyloxy)-2'-methoxy-[1,1'-binaphthalen]-6-yl)morpholine (113):

m.p. = 144-145 °C (EtOAc/petroleum ether 40-60).

IR (film) ν_{max}/cm^{-1}: 3059, 3031, 2954, 2928, 2853, 2837, 1592, 1506, 1266, 1250, 1227, 1120, 1092.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.99 (d, *J* = 9.0 Hz, 1H), 7.89 (d, *J* = 8.2 Hz, 1H), 7.78 (d, *J* = 9.0 Hz, 1H), 7.45 (d, *J* = 9.0 Hz, 1H), 7.37 (d, *J* = 9.0 Hz, 1H), 7.33 (app. t, *J* = 8.0 Hz, 1H), 7.22 (m, 1H), 7.16 (m, 5H), 7.10 (d, *J* = 9.4 Hz, 1H), 7.02 (dd, *J* = 9.3, 2.5 Hz, 1H), 6.99–6.91 (m, 2H), 5.06–4.92 (m, 2H), 3.92–3.85 (m, 4H), 3.76 (s, 3H), 3.24–3.16 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.1, 152.8, 147.8, 137.9, 134.3, 130.6, 129.5, 129.4, 129.3, 128.2, 128.1, 128.0, 127.4, 127.0, 126.7, 126.4, 125.6, 123.6, 121.3, 119.8, 119.7, 117.3, 114.0, 110.6, 71.8, 67.1, 56.8, 50.1.

HRMS (ESI^+) $C_{31}H_{29}O_3N$ $[M+H]^+$ requires 476.22202; found 476.22162, Δ −0.8 ppm.

Chiral HPLC: (Chiralpak IC, 3% ^{i}PrOH, 97% hexane, 1.0 mL min^{-1}, λ = 289 nm) τ_R (major) = 23.3 min, τ_R (minor) = 30.4 min.

$[\alpha]_D^{25}$ = −4.2 (*c* = 1.00, $CHCl_3$).

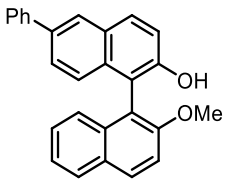
(*R*)- 2'-Methoxy-6-morpholino-[1,1'-binaphthalen]-2-ol (80):

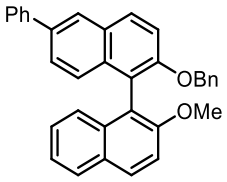
m.p. = 124-125 °C (EtOAc/petroleum ether 40-60).

Chiral HPLC: (Chiralpak ADH, 15% ^{i}PrOH, 85% hexane, 1.0 mL min^{-1}, λ = 272 nm) τ_R (minor) = 20.4 min, τ_R (major) = 30.4 min.

$[\alpha]_D^{25}$ = −31.2 (*c* = 1.00, $CHCl_3$).

Kinetic resolution of [2'-methoxy-6-phenyl-[1,1'-binaphthalen]-2-ol] (81)





Following **general procedure A,** 2'-methoxy-6-phenyl-[1,1'-binaphthalen]-2-ol (**81**) (56.4 mg, 0.150 mmol) was reacted for 24 h. Purification *via* flash column chromatography (3:7 CH_2Cl_2 – petroleum ether 40-60 to 4:1 CH_2Cl_2 – petroleum ether 40-60) afforded 2-(benzyloxy)-2'-methoxy-6-phenyl-1,1'-binaphthalene (**114**) as an off-white solid (39.1 mg, 56%, 86:14 er) and recovered starting material (**81**) (22.0 mg, 39%, 99:1 er).

(*S*)- 2-(Benzyloxy)-2'-methoxy-6-phenyl-1,1'-binaphthalene (114):

m.p. = 78-79°C (CH_2Cl_2/petroleum ether 40-60).

IR (film) ν_{max}/cm^{-1}: 3060, 2933, 2837, 1743, 1592, 1507, 1454, 1349, 1222, 1093, 1027, 806, 757, 750, 696.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.10 (d, *J* = 1.9 Hz, 1H), 8.05 (d, *J* = 9.1 Hz, 1H), 8.01 (d, *J* = 9.0 Hz, 1H), 7.94 (d, *J* = 8.1 Hz, 1H), 7.76–7.66 (m, 2H), 7.59 – 7.45 (m, 5H), 7.38 (ddd, *J* = 8.2, 6.5, 1.5 Hz, 2H), 7.32–7.25 (m, 2H), 7.25–7.16 (m, 4H), 7.08–6.99 (m, 2H), 5.18–5.03 (m, 2H), 3.82 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 155.0, 154.2, 141.2, 137.6, 136.5, 134.7, 134.1, 133.4, 129.7, 129.6, 129.5, 129.2, 128.8, 128.2, 128.0, 127.4, 127.3, 127.1, 126.8, 126.4, 126.1, 126.0, 125.9, 125.4, 123.5, 120.7, 119.3, 116.6, 113.9, 71.3, 56.7.

Chiral HPLC: (Chiralpak IC, 1% ^{i}PrOH, 99% hexane, 1.0 mL min^{-1}, λ = 259 nm) τ_R (major) = 10.2 min, τ_R (minor) = 19.7 min.

$[\alpha]_D^{25}$ = −77.0 (*c* = 1.00, $CHCl_3$).

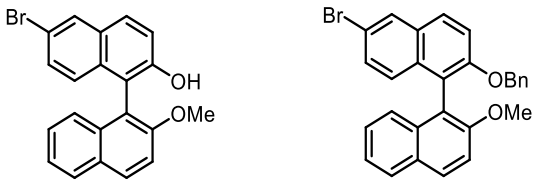
(*R*)- 2'-Methoxy-6-phenyl-[1,1'-binaphthalen]-2-ol (81):

m.p. = 58-59 °C (CH_2Cl_2/petroleum ether 40-60).

Chiral HPLC: (Chiralpak ADH, 10% ^{i}PrOH, 90% hexane, 1.0 mL min^{-1}, λ = 259 nm) τ_R (minor) = 13.2 min, τ_R (major) = 21.2 min.

$[\alpha]_D^{25}$ = −5.7 (*c* = 1.00, $CHCl_3$).

Kinetic resolution of 6-bromo-2'-methoxy-[1,1'-binaphthalen]-2-ol (78)



Following **general procedure A,** 6-bromo-2'-methoxy-[1,1'-binaphthalen]-2-ol (**78**) (56.9 mg, 0.150 mmol) was reacted for 24 h. Purification *via* flash column chromatography (3:7 CH_2Cl_2 – petroleum ether 40-60 to 4:1 CH_2Cl_2 – petroleum ether 40-60) afforded 2-(benzyloxy)-6-bromo-2'-methoxy-1,1'-binaphthalene (**115**) as an off-white solid (34.3 mg, 49%, 87:13 er) and recovered starting material (**78**) (22.0 mg, 39%, 99:1 er).

(*S*)- 2-(Benzyloxy)-6-bromo-2'-methoxy-1,1'-binaphthalene (115):

m.p. = 115-115 °C (CH_2Cl_2/petroleum ether 40-60).

IR (film) ν_{max}/cm^{-1}: 3061, 3033, 2837, 1584, 1494, 1268, 1065, 734.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.93–7.88 (m, 2H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.71 (d, *J* = 9.0 Hz, 1H), 7.34 (app. t, *J* = 9.4 Hz, 2H), 7.26–7.22 (m, 1H), 7.21–7.11 (m, 3H), 7.11–7.05 (m, 3H), 7.01 (d, *J* = 8.6 Hz, 1H), 6.96 (d, *J* = 9.0 Hz, 1H), 6.91–6.86 (m, 2H), 5.15–4.79 (m, 2H), 3.66 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.1, 154.4, 137.5, 134.1, 132.8, 130.6, 129.9, 129.8, 129.7, 129.3, 128.4, 128.3, 128.1, 127.5, 127.5, 126.8, 126.6, 125.3, 123.7, 121.2, 118.8, 117.7, 117.2, 113.8, 71.3, 56.7.

HRMS (ESI^+) $C_{28}H_{21}O_2{}^{79}Br$ $[M+Na]^+$ requires 491.06171; found 491.06180, Δ +0.2 ppm.

Chiral HPLC: (Chiralpak IC, 1% ^{i}PrOH, 99% hexane, 1.0 mL min^{-1}, λ = 295nm) τ_R (major) = 6.2 min, τ_R (minor) = 9.7 min.

$[\alpha]_D^{25}$ = −25.8 (*c* = 1.00, $CHCl_3$).

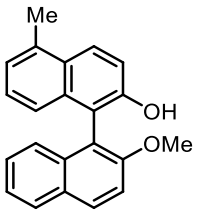
(*R*)- 6-Bromo-2'-methoxy-[1,1'-binaphthalen]-2-ol (78):

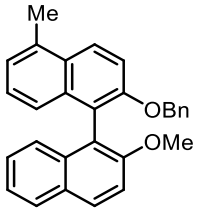
m.p. = 71-72 °C (CH_2Cl_2/petroleum ether 40-60).

Chiral HPLC: (Chiralpak ADH, 1% ^{i}PrOH, 99% hexane, 1.0 mL min^{-1}, λ = 281 nm) τ_R (major) = 19.1 min, τ_R (minor) = 14.3 min.

$[\alpha]_D^{25}$ = −49.6 (*c* = 1.00, $CHCl_3$).

Kinetic resolution of 2'-methoxy-5-methyl-[1,1'-binaphthalen]-2-ol (96)





Following **general procedure A,** 2'-methoxy-5-methyl-[1,1'-binaphthalen]-2-ol (**116**) (47.2 mg, 0.150 mmol) was reacted for 24 h. Purification *via* flash column chromatography (3:7 CH_2Cl_2 – petroleum ether 40-60 to 4:1 CH_2Cl_2 – petroleum ether 40-60) afforded 2-(benzyloxy)-2'-methoxy-5-methyl-

1,1'-binaphthalene (**116**) as an off-white solid (33.8 mg, 56%, 89:11 er) and recovered starting material (**96**) (18.9 mg, 40%, 99.5:0.5 er).

(*S*)-2-(Benzyloxy)-2'-methoxy-5-methyl-1,1'-binaphthalene (116):

m.p. = 84-85 °C (CH_2Cl_2/petroleum ether 40-60).

IR (film) ν_{max}/cm^{-1}: 3020, 3937, 1801, 1742, 1521, 1494, 1347, 1265, 1237, 1217, 1175, 1053, 749, 691, 666.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.10 (d, *J* = 9.2 Hz, 1H), 8.01 (d, *J* = 9.0 Hz, 1H), 7.90 (d, *J* = 8.3 Hz, 1H), 7.51–7.42 (m, 2H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.24–7.04 (m, 8H), 7.03–6.97 (m, 2H), 5.15–5.02 (m, 2H), 3.77 (s, 3H), 2.75 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.1, 153.9, 137.8, 134.4, 134.4, 134.3, 129.5, 129.3, 128.7, 128.3, 128.0, 127.4, 126.9, 126.4, 126.3, 125.6, 124.8, 124.1, 123.6, 121.4, 119.9, 115.8, 114.0, 71.2, 56.8, 19.8.

HRMS (ESI^+) $C_{29}H_{24}O_2$ $[M+H]^+$ requires 405.18491; found 405.18494, Δ +0.1 ppm.

Chiral HPLC: (Chiralpak IC, 1% ^{i}PrOH, 99% hexane, 1.0 mL min^{-1}, λ = 295 nm) τ_R (major) = 6.9 min, τ_R (minor) = 13.6 min.

$[\alpha]_D^{25}$ = −41.4 (*c* = 1.00, $CHCl_3$).

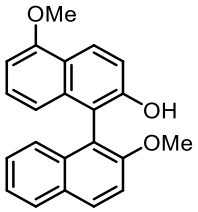
(*R*)-2'-Methoxy-5-methyl-[1,1'-binaphthalen]-2-ol (96):

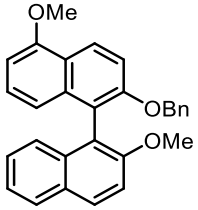
m.p. = 74-75 °C (CH_2Cl_2/petroleum ether 40-60).

Chiral HPLC: (Chiralpak ADH, 10% ^{i}PrOH, 90% hexane, 1.0 mL min^{-1}, λ = 295 nm,) τ_R (major) = 20.0 min, τ_R (minor) = 12.8 min.

$[\alpha]_D^{25}$ = −13.3 (*c* = 1.00, $CHCl_3$).

Kinetic resolution of 2',5-dimethoxy-[1,1'-binaphthalen]-2-ol (97)





Following **general procedure A,** 2',5-dimethoxy-[1,1'-binaphthalen]-2-ol (**97**) (49.6 mg, 0.150 mmol) was reacted for 30 h. Purification *via* flash column chromatography (3:7 CH_2Cl_2 – petroleum ether 40-60 to 4:1 CH_2Cl_2 – petroleum ether 40-60) afforded 2-(benzyloxy)-2',5-dimethoxy-1,1'-binaphthalene (**117**) as an off-white solid (37.6 mg, 59%, 77:23 er) and recovered starting material (**97**) (16.4 mg, 33%, 99.5:0.5 er).

(*S*)- 2-(Benzyloxy)-2',5-dimethoxy-1,1'-binaphthalene (117):

m.p. = 151-152 °C (CH_2Cl_2/petroleum ether 40-60).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.38 (d, *J* = 8.4 Hz, 1H), 7.99 (d, *J* = 9.0 Hz, 1H), 7.89 (d, *J* = 8.2 Hz, 1H), 7.46 (d, *J* = 9.0 Hz, 1H), 7.41 (d, *J* = 9.3 Hz, 1H), 7.33 (ddd, *J* = 8.1, 6.6, 1.3 Hz, 1H), 7.23 (m, 1.4 Hz, 1H), 7.16 (m, 5H), 7.00 (m, 2H), 6.77 (d, *J* = 8.6 Hz, 1H), 6.68 (d, *J* = 6.8 Hz, 1H), 5.15–4.95 (m, 2H), 4.02 (s, 3H), 3.76 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.8, 155.1, 154.7, 137.7, 135.5, 134.2, 129.4, 129.3, 128.2, 128.0, 127.4, 126.9, 126.6, 126.4, 125.6, 123.6, 121.6, 120.5, 120.0, 118.0, 115.1, 114.1, 102.0, 71.1, 56.8, 55.6.

HRMS (ESI^+) $C_{29}H_{24}O_3$ $[M+H]^+$ requires 421.17982; found 421.17923, Δ −1.4 ppm.

Chiral HPLC: (Chiralpak ADH, 10% ^{i}PrOH, 90% hexane, 1.0 mL min^{-1}, λ = 293 nm) τ_R (minor) = 17.2 min, τ_R (major) = 27.9 min.

$[\alpha]_D^{25}$ = −37.3 (*c* = 1.00, $CHCl_3$).

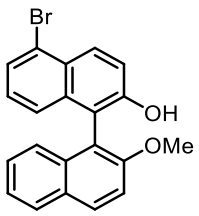
(*R*)- 2',5-Dimethoxy-[1,1'-binaphthalen]-2-ol (97):

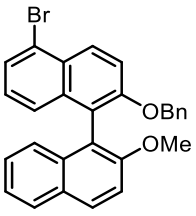
m.p. = 165-167 °C (CH_2Cl_2/petroleum ether 40-60).

Chiral HPLC: (Chiralpak ADH, 10% ^{i}PrOH, 90% hexane, 1.0 mL min^{-1}, λ = 293 nm) τ_R (major) = 17.3 min, τ_R (minor) = 28.0 min.

$[\alpha]_D^{25}$ = −35.7 (*c* = 1.00, $CHCl_3$).

Kinetic resolution of 5-bromo-2'-methoxy-[1,1'-binaphthalen]-2-ol (95)





Following **general procedure A**, 5-bromo-2'-methoxy-[1,1'-binaphthalen]-2-ol (**95**) (56.9 mg, 0.150 mmol) was reacted for 24 h. Purification *via* flash column chromatography (3:7 CH_2Cl_2 – petroleum ether 40-60 to 4:1 CH_2Cl_2 – petroleum ether 40-60) afforded 2-(benzyloxy)-5-bromo-2'-methoxy-1,1'-binaphthalene (**118**) as an off-white solid (33.6 mg, 48%, 89:11 er) and recovered starting material (**95**) (22.4 mg, 39%, 98:2 er).

(*S*)-2-(Benzyloxy)-5-bromo-2'-methoxy-1,1'-binaphthalene (118):

IR (film) ν_{max}/cm^{-1}: 3077, 3063, 3019, 2941, 1802, 1747, 1521, 1495, 1347, 1267, 1233, 1176, 1053, 749.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.35 (d, *J* = 9.3 Hz, 1H), 8.02 (d, *J* = 9.0 Hz, 1H), 7.90 (d, *J* = 8.2 Hz, 1H), 7.62 (d, *J* = 7.3 Hz, 1H), 7.52 (d, *J* = 9.4 Hz, 1H), 7.47 (d, *J* = 9.0 Hz, 1H), 7.35 (dd, *J* = 8.1, 6.8 Hz, 1H), 7.25–7.21 (m, 1H), 7.20–7.15 (m, 4H), 7.12–7.04 (m, 2H), 7.04–6.93 (m, 2H), 5.35–4.88 (m, 2H), 3.77 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 155.0, 154.6, 137.3, 135.4, 134.0, 129.7, 129.2, 128.6, 128.2, 128.0, 127.8, 127.4, 126.7, 126.7, 126.5, 125.5, 125.2, 123.6, 122.9, 121.0, 118.9, 116.9, 113.7, 70.9, 56.6.

HRMS (ESI$^+$) $C_{28}H_{21}O_2{}^{79}Br$ $[M+Na]^+$ requires 491.06171; found 491.06180, Δ +0.2 ppm.

Chiral HPLC: (Chiralpak ADH, 10% ^{i}PrOH, 90% hexane, 1.0 mL min^{-1}, λ = 295 nm) τ_R (major) = 22.2 min, τ_R (minor) = 12.3 min.

$[\alpha]_D^{25}$ = −56.3 (*c* = 1.00, $CHCl_3$).

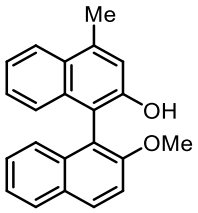
(*R*)-5-Bromo-2'-methoxy-[1,1'-binaphthalen]-2-ol (95):

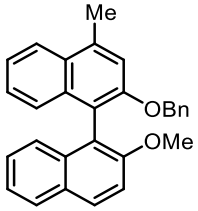
m.p. = 109-110 °C (CH_2Cl_2/petroleum ether 40-60).

Chiral HPLC: (Chiralpak ADH, 10% ^{i}PrOH, 90% hexane, 1.0 mL min^{-1}, λ = 295 nm) τ_R (major) = 22.5 min, τ_R (minor) = 12.5 min.

$[\alpha]_D^{25}$ = +6.5 (*c* = 1.00, $CHCl_3$).

Kinetic resolution of 2'-methoxy-4-methyl-[1,1'-binaphthalen]-2-ol (103)





Following **general procedure A,** 2'-methoxy-4-methyl-[1,1'-binaphthalen]-2-ol (**103**) (49.2 mg, 0.150 mmol) was reacted for 36 h. Purification *via* flash column chromatography (3:7 CH_2Cl_2 – petroleum ether 40-60 to 4:1 CH_2Cl_2 – petroleum ether 40-60) afforded 2-(benzyloxy)-2'-methoxy-4-methyl-1,1'-binaphthalene (**119**) as an off-white solid (37.4 mg, 61%, 81:19 er) and recovered starting material (**103**) (16.4 mg, 33%, >99.5:0.5 er).

(*S*)- 2-(Benzyloxy)-2'-methoxy-4-methyl-1,1'-binaphthalene (119):

m.p. = 54-55 °C (CH_2Cl_2/petroleum ether 40-60).

IR (film) ν_{max}/cm^{-1}: 3062, 3033, 2936, 2836, 1593, 1508, 1342, 1266, 1252, 1101, 754.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.06–7.97 (m, 2H), 7.90 (d, *J* = 8.2 Hz, 1H), 7.47 (d, *J* = 9.1 Hz, 1H), 7.43–7.30 (m, 3H), 7.29–7.11 (m, 7H), 7.03–6.94 (m, 2H), 5.10–5.01 (m, 3H), 3.77 (s, 3H), 2.80 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.2, 153.7, 137.8, 136.0, 134.4, 134.4, 129.4, 129.3, 128.9, 128.2, 128.0, 127.4, 126.9, 126.4, 126.2, 125.6, 124.3, 123.7, 123.5, 119.7, 119.0, 117.5, 117.5, 114.0, 71.5, 56.8, 20.1.

HRMS (ESI^+) $C_{29}H_{24}O_2$ $[M+H]^+$ requires 405.18491; found 405.18494, Δ +0.1 ppm.

Chiral HPLC: (Chiralpak IC, 2% ^{i}PrOH, 98% hexane, 1.0 mL min^{-1}, λ = 291 nm) τ_R (major) = 15.6 min, τ_R (minor) = 24.7.

$[\alpha]_D^{25}$ = −33.4 (*c* = 1.00, $CHCl_3$).

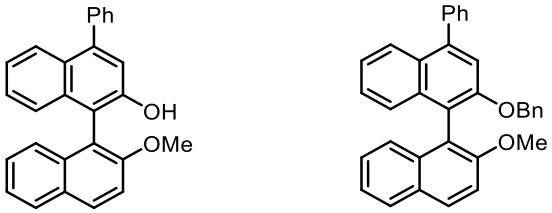
(*R*)- 2'-Methoxy-4-methyl-[1,1'-binaphthalen]-2-ol (103):

m.p. = 170-171 °C (CH_2Cl_2/petroleum ether 40-60).

Chiral HPLC: (Chiralpak ADH, 10% ^{i}PrOH, 90% hexane, 1.0 mL min^{-1}, λ = 291 nm) τ_R (major) = 15.6 min, τ_R (minor) = 20.7 min.

$[\alpha]_D^{25}$ = +37.8 (*c* = 1.00, $CHCl_3$).

Kinetic resolution of 2'-methoxy-4-phenyl-[1,1'-binaphthalen]-2-ol (105)



Following **general procedure A**, 2'-methoxy-4-phenyl-[1,1'-binaphthalen]-2-ol (**105**) (56.4 mg, 0.150 mmol) was reacted for 24 h. Purification *via* flash column chromatography (3:7 CH_2Cl_2 – petroleum ether 40-60 to 4:1 CH_2Cl_2 – petroleum ether 40-60) afforded 2-(benzyloxy)-2'-methoxy-4-phenyl-1,1'-binaphthalene (**120**) as an off-white solid (35.4 mg, 51%, 91:9 er) and recovered starting material (**105**) (26.0 mg, 46%, 95:5 er).

(*S*)-2-(Benzyloxy)-2'-methoxy-4-phenyl-1,1'-binaphthalene (120):

m.p. = 120-121 °C (CH_2Cl_2/petroleum ether 40-60).

IR (film) ν_{max}/cm^{-1}: 3066, 1585, 1342, 1188, 1024, 911, 766, 731, 705.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.92 (d, *J* = 9.1 Hz, 1H), 7.86–7.77 (m, 2H), 7.49 (m, 2H), 7.46–7.41 (m, 2H), 7.40–7.34 (m, 2H), 7.31 (s, 1H), 7.24 (m, 1H), 7.20–7.11 (m, 5H), 7.04 (m, 3H), 6.86 (m, 2H), 5.02–4.91 (m, 2H), 3.69 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.2, 153.5, 141.7, 140.9, 137.6, 134.7, 134.3, 130.3, 129.6, 129.3, 128.4, 128.2, 128.0, 127.9, 127.5, 127.4, 127.0, 126.5, 126.3, 126.3, 125.9, 125.6, 124.0, 123.6, 120.5, 119.5, 117.6, 114.0, 71.5, 56.8.

HRMS (ESI^+) $C_{34}H_{27}O_2$ $[M+H]^+$ requires 467.20056; found 467.20050, Δ −0.1 ppm.

Chiral HPLC: (Chiralpak ADH, 2% ^{i}PrOH, 98% hexane, 1.0 mL min^{-1}, λ = 297 nm) τ_R (minor) = 14.8 min, τ_R (major) = 24.5 min.

$[\alpha]_D^{25}$ = −54.9 (*c* = 1.00, $CHCl_3$).

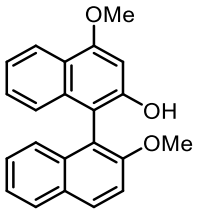
(*R*)- 2'-Methoxy-4-phenyl-[1,1'-binaphthalen]-2-ol (105):

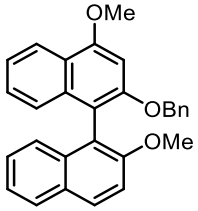
m.p. = 88-89 °C (CH_2Cl_2/petroleum ether 40-60).

Chiral HPLC: (Chiralpak ADH, 10% ^{i}PrOH, 90% hexane, 1.0 mL min^{-1}, λ = 295 nm) τ_R (minor) = 18.8 min, τ_R (major) = 26.2 min.

$[\alpha]_D^{25}$ = −1.5 (*c* = 1.00, $CHCl_3$).

Kinetic resolution of 2',4-dimethoxy-[1,1'-binaphthalen]-2-ol (104)





Following **general procedure A**, 2',4-dimethoxy-[1,1'-binaphthalen]-2-ol (**104**) (49.6 mg, 0.150 mmol) was reacted for 30 h. Purification *via* flash column chromatography (3:7 CH_2Cl_2 – petroleum ether 40-60 to 4:1 CH_2Cl_2 – petroleum ether 40-60) afforded 2-(benzyloxy)-2',4-dimethoxy-1,1'-binaphthalene (**121**) as an off-white solid (34.0 mg, 54%, 85:15 er) and recovered starting material (**104**) (17.0 mg, 34%, 99:1 er).

(*S*)- 2-(Benzyloxy)-2',4-dimethoxy-1,1'-binaphthalene (121):

m.p. = 125-126 °C (CH_2Cl_2/petroleum ether 40-60).

IR (film) ν_{max}/cm^{-1}: 2996, 2980, 2971, 2936, 1620, 1588, 1508, 1460, 1344, 1265, 1253, 1241, 1195, 1144, 1116, 1097, 1066, 1022, 906, 809, 764, 733, 697.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.16 (d, *J* = 8.4 Hz, 1H), 7.89 (d, *J* = 9.0 Hz, 1H), 7.81–7.76 (m, 1H), 7.35 (d, *J* = 9.1 Hz, 1H), 7.22 (m, 2H), 7.17–7.10 (m, 3H), 7.09–7.01 (m, 4H), 6.91–6.86 (m, 2H), 6.70 (s, 1H), 4.90 (m, 2H), 3.92 (s, 3H), 3.66 (d, *J* = 1.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.4, 155.3, 154.4, 137.7, 134.5, 134.5, 129.3, 129.2, 128.2, 127.9, 127.4, 127.0, 127.0, 126.3, 125.6, 125.2, 123.4, 123.2, 122.0, 122.0, 119.6, 114.0, 113.3, 96.8, 72.0, 56.7, 55.6.

Chiral HPLC: (Chiralpak IC, 3% ^{i}PrOH, 97% hexane, 1.0 mL min^{-1}, λ = 292 nm) τ_R (major) = 6.1 min, τ_R (minor) = 8.2 min.

$[\alpha]_D^{25}$ = −46.0 (*c* = 1.00, $CHCl_3$).

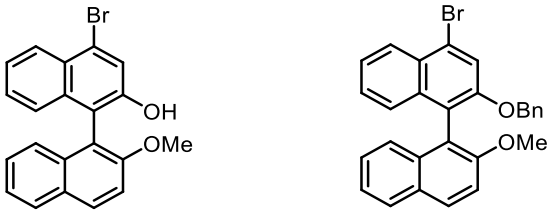
(*R*)- 2',4-Dimethoxy-[1,1'-binaphthalen]-2-ol (104):

m.p. = 161-162 °C (CH_2Cl_2/petroleum ether 40-60).

Chiral HPLC: (Chiralpak ADH, 15% ^{i}PrOH, 85% hexane, 1.0 mL min^{-1}, λ = 231 nm) τ_R (minor) = 8.7 min, τ_R (major) = 12.7 min.

$[\alpha]_D^{25}$ = −2.0 (*c* = 1.00, $CHCl_3$).

Kinetic resolution of 4-bromo-2'-methoxy-[1,1'-binaphthalen]-2-ol (102)



Following **general procedure A,** 4-bromo-2'-methoxy-[1,1'-binaphthalen]-2-ol (**102**) (56.9 mg, 0.150 mmol) was reacted for 24 h. Purification *via* flash column chromatography (3:7 CH_2Cl_2 – petroleum ether 40-60 to 4:1 CH_2Cl_2 – petroleum ether 40-60) afforded 2-(benzyloxy)-4-bromo-2'-methoxy-1,1'-binaphthalene (**122**) as an off-white solid (38.0 mg, 54%, 86:14 er) and recovered starting material (**102**) (23.0 mg, 40%, 99:1 er).

(*S*)- 2-(Benzyloxy)-4-bromo-2'-methoxy-1,1'-binaphthalene (122):

m.p. = 54-55 °C (CH_2Cl_2/petroleum ether 40-60).

IR (film) ν_{max}/cm^{-1}: 3062, 3033, 2930, 2837, 1583, 1501, 1453, 1315, 1270, 1261, 1251.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.15 (d, *J* = 7.2 Hz, 1H), 7.91 (d, *J* = 9.0 Hz, 1H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.68 (s, 1H), 7.37–7.31 (m, 2H), 7.26–7.21 (m, 1H), 7.20–7.09 (m, 3H), 7.08–7.00 (m, 4H), 6.89–6.83 (m, 2H), 5.04–4.87 (m, 2H), 3.66 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 154.9, 153.7, 137.0, 134.8, 133.9, 129.8, 129.1, 128.2, 128.1, 128.0, 127.5, 127.1, 127.1, 126.8, 126.5, 125.9, 125.2, 123.6, 123.2, 121.2, 120.6, 120.6, 118.5, 113.6, 71.6, 56.6.

HRMS (ESI^+) $C_{28}H_{21}O_2{}^{79}Br$ $[M+Na]^+$ requires 491.06171; found 491.06171, Δ 0.0 ppm.

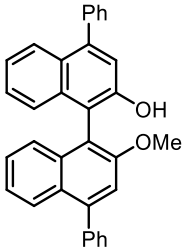
Chiral HPLC: (Chiralpak IC, 1% ^{i}PrOH, 99% hexane, 1.0 mL min^{-1}, λ = 232 nm) τ_R (major) = 15.0 min, τ_R (minor) = 18.0 min.

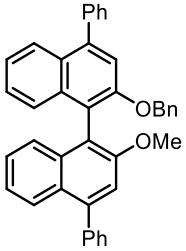
$[\alpha]_D^{25}$ = −39.6 (*c* = 1.00, $CHCl_3$).

(*R*)- 4-Bromo-2'-methoxy-[1,1'-binaphthalen]-2-ol (102):

Chiral HPLC: (Chiralpak ADH, 10% ^{i}PrOH, 90% hexane, 1.0 mL min^{-1}, λ = 293 nm) τ_R (major) = 13.2 min, τ_R (minor) = 23.0 min.

Kinetic resolution of [2'-methoxy-4,4'-diphenyl-[1,1'-binaphthalen]-2-ol] (107)





Following **general procedure A,** 2'-methoxy-4,4'-diphenyl-[1,1'-binaphthalen]-2-ol (**107**) (67.9 mg, 0.150 mmol) for 30 h. Purification *via* flash column chromatography (3:7 CH_2Cl_2 – petroleum ether 40-60 to 4:1 CH_2Cl_2 – petroleum ether 40-60) afforded 2-(benzyloxy)-2'-methoxy-4,4'-diphenyl-1,1'-binaphthalene (**123**) as an off-white solid (50.3 mg, 62%, 80:20 er) and recovered starting material (**107**) (22.2 mg, 33%, 99:1 er).

(*S*)- 2-(Benzyloxy)-2'-methoxy-4,4'-diphenyl-1,1'-binaphthalene (123):

m.p. = 117-119 °C (CH_2Cl_2/petroleum ether 40-60).

IR (film) ν_{max}/cm^{-1}: 3060, 3029, 2935, 1586, 1342, 1224, 764, 703.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.94 (m, 2H), 7.71–7.65 (m, 2H), 7.63–7.47 (m, 8H), 7.44 (m, 2H), 7.39 (m, 1H), 7.35–7.22 (m, 5H), 7.17 (m, 2H), 7.00 (m, 3H), 5.42–4.89 (m, 2H), 3.81 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 154.4, 153.5, 141.9, 141.6, 141.1, 140.8, 137.6, 134.6, 134.6, 130.2, 128.4, 128.3, 128.1, 127.9, 127.5, 127.5, 127.4, 127.4, 126.9, 126.3, 126.3, 126.2, 126.2, 125.9, 125.9, 123.9, 123.6, 120.5, 118.9, 117.6, 115.0, 71.5, 56.7.

HRMS (ESI^+) $C_{40}H_{30}O_2$ $[M+H]^+$ requires 543.23186; found 543.23132, Δ −0.1 ppm.

Chiral HPLC: (Chiralpak ODH, 2% ^{i}PrOH, 98% hexane, 1.0 mL min^{-1}, λ = 295 nm) τ_R (minor) = 9.0 min, τ_R (major) = 10.7 min.

$[\alpha]_D^{25}$ = −31.1(*c* = 1.00, $CHCl_3$).

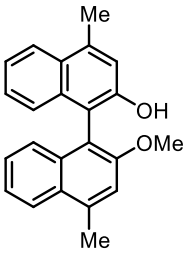
(*R*)- [2'-methoxy-4,4'-diphenyl-[1,1'-binaphthalen]-2-ol] (107):

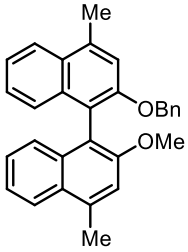
m.p. = 125-127 °C (CH_2Cl_2/petroleum ether 40-60).

Chiral HPLC: (Chiralpak ADH, 20% ^{i}PrOH, 80% hexane, 1.0 mL min^{-1}, λ = 300 nm) τ_R (major) = 20.8 min, τ_R (minor) = 36.0 min..

$[\alpha]_D^{25}$ = +16.9 (*c* = 1.00, $CHCl_3$).

Kinetic resolution of 2'-methoxy-4,4'-dimethyl-[1,1'-binaphthalen]-2-ol (106)





Following **general procedure A**, 2'-methoxy-4,4'-dimethyl-[1,1'-binaphthalen]-2-ol (**106**) (49.3 mg, 0.150 mmol) was reacted for 30 h. Purification *via* flash column chromatography (3:7 CH_2Cl_2 – petroleum ether 40-60 to 4:1 CH_2Cl_2 – petroleum ether 40-60) afforded 2-(benzyloxy)-2'-methoxy-4,4'-dimethyl-1,1'-binaphthalene (**124**) as an off-white solid (33.8 mg, 54%, 88:12 er) and recovered starting material (**106**) (19.4 mg, 39%, 99:1 er).

(*S*)- 2-(Benzyloxy)-2'-methoxy-4,4'-dimethyl-1,1'-binaphthalene (124):

m.p. = 155-157 °C (CH_2Cl_2/petroleum ether 40-60).

IR (film) ν_{max}/cm^{-1}: 3063, 2937, 2911, 1593, 1342, 757.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.06 (d, *J* = 8.5, 1H), 8.03 (d, *J* = 8.5, 1H), 7.42–7.36 (m, 2H), 7.35 (s, 1H), 7.33 (s, 1H), 7.28–7.21 (m, 4H), 7.22–7.15 (m, 3H), 7.06–6.98 (m, 2H), 5.09 (d, *J* = 12.5 Hz, 1H), 5.05 (d, *J* = 12.6 Hz, 1H), 3.78 (s, 3H), 2.88 (s, 3H), 2.81 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 154.5, 153.7, 137.8, 135.9, 135.8, 134.5, 128.8, 128.4, 128.1, 127.2, 126.8, 126.2, 126.2, 126.0, 126.0, 124.2, 124.1, 123.6, 123.3, 119.2, 117.7, 117.5, 115.1, 71.3, 56.7, 20.0, 20.0.

HRMS (ESI^+) $C_{30}H_{26}O$ $[M+Na]^+$ requires 441.18250; found 441.18280, Δ +0.7 ppm.

Chiral HPLC: (Chiralpak ADH, 3% ^{i}PrOH, 97% hexane, 1.0 mL min^{-1}, λ = 250 nm) τ_R (major) = 19.7 min, τ_R (minor) = 12.0 min.

$[\alpha]_D^{25}$ = −36.0 (*c* = 1.00, $CHCl_3$).

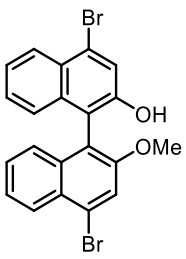
(*R*)- 2'-Methoxy-4,4'-dimethyl-[1,1'-binaphthalen]-2-ol (106):

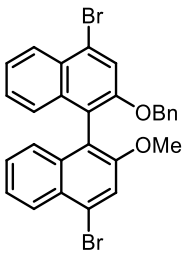
m.p. = 201-202 °C (CH_2Cl_2/petroleum ether 40-60).

Chiral HPLC: (Chiralpak ADH, 10% ^{i}PrOH, 90% hexane, 1.0 mL min^{-1}, λ = 293 nm) τ_R (major) = 20.9 min, τ_R (minor) = 23.3 min.

$[\alpha]_D^{25}$ = −31.7 (*c* = 1.00, $CHCl_3$).

Kinetic resolution of 4,4'-dibromo-2'-methoxy-[1,1'-binaphthalen]-2-ol (101)





Following **general procedure A**, 4,4'-dibromo-2'-methoxy-[1,1'-binaphthalen]-2-ol (**101**) (68.7 mg, 0.150 mmol) was reacted for 36 h. Purification *via* flash column chromatography (3:7 CH_2Cl_2 –

petroleum ether 40-60 to 4:1 CH_2Cl_2 – petroleum ether 40-60) afforded 2-(benzyloxy)-4,4'-dibromo-2'-methoxy-1,1'-binaphthalene (**125**) as an off-white solid (30.7 mg, 45%, 88:12 er) and recovered starting material (**101**) (41.4 mg, 50%, 93:7 er).

(*S*)-2-(Benzyloxy)-4,4'-dibromo-2'-methoxy-1,1'-binaphthalene (125):

m.p. = 148-150 °C (CH_2Cl_2/petroleum ether 40-60).

IR (film) ν_{max}/cm^{-1}: 3064, 2934, 1582, 1497, 1314, 1259, 1243, 1025, 907, 756, 733.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.35–8.19 (m, 3H), 7.79–7.76 (m, 2H), 7.52–7.39 (m, 2H), 7.32–7.22 (m, 2H), 7.21–7.11 (m, 5H), 7.05–6.92 (m, 2H), 5.12–4.92 (m, 2H), 3.75 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 154.7, 153.8, 136.9, 134.7, 128.4, 128.2, 127.9, 127.8, 127.4, 127.3, 126.9, 125.8, 125.8, 125.4, 125.1, 123.9, 123.7, 120.4, 120.2, 118.9, 118.2, 71.6, 56.9.

HRMS (ESI^+) $C_{28}H_{20}O_2{}^{79}Br$ $[M+Na]^+$ requires 568.97223; found 568.97217, Δ −0.1 ppm.

Chiral HPLC: (Chiralpak ADH, 1% ^{i}PrOH, 99% hexane, 1.0 mL min^{-1}, λ = 295 nm) τ_R (major) = 16.2 min, τ_R (minor) = 11.1 min.

$[\alpha]_D^{25}$ = −47.2 (*c* = 0.50, $CHCl_3$).

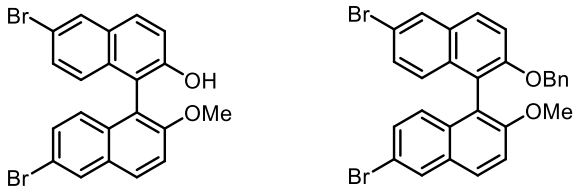
(*R*)-4,4'-Dibromo-2'-methoxy-[1,1'-binaphthalen]-2-ol (101):

m.p. = 178-180 °C (CH_2Cl_2/petroleum ether 40-60).

Chiral HPLC: (Chiralpak ADH, 10% ^{i}PrOH, 90% hexane, 1.0 mL min^{-1}, λ = 293 nm) τ_R (major) = 15.3 min, τ_R (minor) = 31.2 min.

$[\alpha]_D^{25}$ = +23.4 (*c* = 0.50, $CHCl_3$).

10 g Scale Kinetic Resolution



6,6'-Dibromo-2'-methoxy-[1,1'-binaphthalen]-2-ol (**77**) (10.1 g, 22.0 mmol, 1.00 equiv.), benzyl tosylate (8.66 g, 33.0 mmol, 1.50 equiv.) and *N*-(2,3,4-trifluorobenzyl)hydrocinchoninium bromide (1.15 g, 2.20 mmol, 1.00 equiv.) were added to a 2 L 3 necked round bottom flask fitted with an overhead stirrer (pictured below). 9:1 PhH-Et_2O (880 mL) was added followed by K_2CO_3 (saturated aq., 30.4 mL) and stirring was commenced (1100 RPM). After 36 hours piperidine (44.0 mL) was added and stirring was continued for a further 30 minutes. NH_4Cl (saturated aq., 300 mL) was added and the mixture was transferred to a separating funnel. The phases were separated and the aqueous phase was extracted with EtOAc (2 × 300 mL). The combined organic layers were washed with water (200 mL), dried over anhydrous sodium sulfate, concentrated *in vacuo* and purified by flash column chromatography (3:7 CH_2Cl_2 – petroleum ether 40-60 to 3:2 CH_2Cl_2 – petroleum ether 40-60) to give 2-(benzyloxy)-6,6'-dibromo-2'-methoxy-1,1'-binaphthalene (**126**) (6.32 g, 52%, 90:10 er) and recovered starting material (**77**) (4.32 g, 43%, 99:1 er).

2-(Benzyloxy)-6,6'-dibromo-2'-methoxy-1,1'-binaphthalene (126):

m.p. = 54-55 °C (CH_2Cl_2/petroleum ether 40-60).

IR (film) ν_{max}/cm^{-1}: 2917, 1584, 1494, 1327, 1268, 1069, 906, 730.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 8.06 (d, *J* = 1.8 Hz, 1H), 8.03 (d, *J* = 1.7 Hz, 1H), 7.93 (d, *J* = 9.1 Hz, 1H), 7.84 (d, *J* = 9.0 Hz, 1H), 7.48 (d, *J* = 9.1 Hz, 1H), 7.46 (d, *J* = 9.1 Hz, 1H), 7.33-7.27 (m, 2H), 7.22-7.17 (m, 3H), 7.03-6.96 (m), 5.09 (s, 2H), 3.78 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 155.2, 154.3, 137.2, 132.51, 132.48, 130.5, 130.2, 129.92, 129.87, 129.8, 128.8, 128.6, 128.3, 127.5, 127.0, 126.7, 120.3, 119.0, 117.7, 117.3, 116.9, 114.7, 71.1, 56.6.

HRMS ($APCI^-$) $C_{28}H_{21}{}^{79}Br_2O_2^-$ $[M-H]^-$ requires 546.9914; found: 546.9907, Δ -1.10 ppm.

Chiral HPLC: (Chiralpak ADH, 7.5% ^{i}PrOH, 92.5% hexane, 1.00 mL min^{-1}, λ = 290 nm) τ_R (major) = 13.3 min, τ_R (minor) = 10.8 min.

$[\alpha]_D^{25}$ = −9.8 (*c* = 1.00, $CHCl_3$)

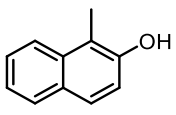
6,6'-Dibromo-2'-methoxy-[1,1'-binaphthalen]-2-ol (77):

m.p. = 71-73 °C (CH_2Cl_2/petroleum ether 40-60).

Chiral HPLC: (Chiralpak ADH, 7.5% ^{i}PrOH, 92.5% hexane, 1.0 mL min^{-1}, λ = 290 nm) τ_R (major) = 25.4 min, τ_R (minor) = 20.2 min.

$[\alpha]_D^{25}$ = −106.0 (*c* = 1.00, $CHCl_3$)

1-Methylnaphthalen-2-ol (161)



Naphthalene-2-ol (288 mg, 2.00 mmol, 1.00 equiv.) was dissolved in toluene (10 mL) and ^{n}BuLi (1.6 M in hexane, 1.25 mL, 2.00 mmol, 1.00 equiv.) was added dropwise. The reaction was heated to reflux and dimethyl sulfate (189 µL 252 mg, 2.00 mmol, 1.00 equiv.) was added. Heating was

continued for 2 hours after which time the reaction was cooled to room temperature. Water was added and the phases were separated. The aqueous phase was extracted twice with EtOAc and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product which was purified by column chromatography (20% EtOAc in pentane) to give 1-methylnaphthalen-2-ol (**161**) (63.2 mg, 20%).

m.p. = 84-86 °C (EtOAc-pentane).

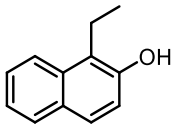
IR (film) ν_{max}/cm^{-1}: 3309 (broad), 1583, 1457, 1334, 1221, 1169, 1140, 1017, 859, 767, 727, 644, 606.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.93 (d, *J* = 8.5 Hz, 1H), 7.79 (d, *J* = 8.1 Hz, 1H), 7.64 (dd, *J* = 8.8, 0.6 Hz, 1H), 7.51 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H), 7.36 (ddd, *J* = 8.0, 6.8, 1.2 Hz, 1H), 7.07 (d, *J* = 8.8 Hz, 1H), 4.94 (br. s, 1H), 2.55 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 150.6, 134.0, 129.3, 128.6, 127.5, 126.4, 123.3, 117.7, 115.4, 10.6.

Data in agreement with literature reported.[146]

1-Ethylnaphthalen-2-ol (186)



Naphthalene-2-ol (288 mg, 2.00 mmol, 1.00 equiv.) was dissolved in toluene (10 mL) and ^{n}BuLi (1.6 M in hexane, 1.25 mL, 2.00 mmol, 1.00 equiv.) was added dropwise. The reaction was heated to reflux and diethyl sulfate (261 µL 308 mg, 2.00 mmol, 1.00 equiv.) was added. Heating was continued for 2 hours after which time the reaction was cooled to room temperature. Water was added and the phases were separated. The aqueous phase was extracted twice with EtOAc and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and

concentrated to give the crude product which was purified by column chromatography (20% EtOAc in pentane) to give 1-ethylnaphthalen-2-ol (**186**) (123 mg, 36%).

m.p. = 82-83 °C (EtOAc/pentane).

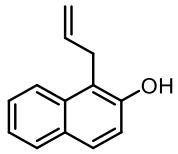
IR (film) ν_{max}/cm^{-1}: 2963, 1619, 1594, 1447, 1388, 1193, 1139, 812, 746.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.95 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.79 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.63 (d, *J* = 8.7 Hz, 1H), 7.50 (ddd, *J* = 8.4, 6.7, 1.4 Hz, 1H), 7.34 (ddd, *J* = 8.0, 6.8, 1.2 Hz, 1H), 7.07 (d, *J* = 8.8 Hz, 1H), 4.89 (s, 1H, OH), 3.08 (q, *J* = 7.6 Hz, 1H), 1.30 (t, *J* = 7.6 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ = ^{13}C NMR (126 MHz, Chloroform-*d*) δ 150.0, 132.9, 129.5, 128.7, 127.6, 126.4, 123.1, 122.9, 121.6, 117.7, 18.2, 14.2.

HRMS (ESI^-) $C_{12}H_{12}O$ $[M-H]^-$ requires 171.0815; found 171.0811, Δ 2.7ppm.

1-Allylnaphthalen-2-ol (HM187)



This compound was prepared and characterised by Harriet Moore

To a suspension of 60% w/w NaH (80.0 mg, 2.00 mmol, 1.00 eq.) in toluene (10 mL) was added naphthalen-2-ol (288 mg, 2.00 mmol, 1.00 eq.). Allyl bromide (288 mg, 2.00 mmol, 1.00 eq.) was added and the reaction was heated under reflux for 4 hours. The mixture was then cooled to room temperature and quenched with sat. aq. ammonium chloride solution (10 mL). The mixture was extracted with EtOAc (3 × 10 mL) and the combined organic layers were then dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was then purified by column chromatography

eluting with 40% CH_2Cl_2 – petrol 40-60 to give 1-allyl-naphthalene-2-ol (**187**) (134 mg, 38%) as a colourless oil.

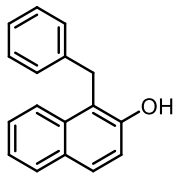
IR (film) ν_{max}/cm^{-1}: 3420, 3074, 2980, 2361, 2341, 1628, 1515, 1438, 1355, 1262, 968, 809

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.93 (1H, dd, *J* = 8.6, 1.0 Hz), 7.84–7.77 (1H, m), 7.69 (1H, d, *J* = 8.8 Hz), 7.50 (1H, ddd, *J* = 8.4, 6.8, 1.4 Hz), 7.36 (1H, ddd, *J* = 8.1, 6.8, 1.2 Hz), 7.11 (1H, d, *J* = 8.8 Hz), 6.10 (1H, ddt, *J* = 17.1, 10.1, 5.8 Hz), 5.18–5.02 (2H, m), 3.85 (2H, dt, *J* = 5.8, 1.8, 1.8 Hz)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 151.2, 135.8, 133.3, 129.5, 128.6, 128.4, 126.5, 123.2, 123.0, 118.0, 116.9, 116.0, 29.3.

HRMS (ESI$^+$) $C_{13}H_{12}O$ $[M+H]^+$ requires 184.0883; found 184.0885, Δ 1.2 ppm.

1-Benzylnaphthalen-2-ol (HM188)



This compound was prepared and characterised by Harriet Moore

To a suspension of 60 % w/w NaH (80.0 mg, 2.00 mmol, 1.00 eq.) in toluene (10 mL) was added naphthalen-2-ol (288 mg, 2.00 mmol, 1.00 eq.). Benzyl bromide (342 mg, 2.00 mmol, 1.00 eq.) was added and the reaction was heated under reflux for 2 hours. The mixture was then cooled to room temperature and quenched with sat. aq. ammonium chloride solution (10 mL). The mixture was extracted with EtOAc (3 × 10 mL) and the combined organic layers were then dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was then purified by column chromatography

eluting with 30% CH_2Cl_2 – petrol 40-60 to give 1-benzyl-naphthalene-2-ol (**188**) (260 mg, 55%) as a light pink solid.

m.p. = 99 – 101 °C (petrol 40 – 60)

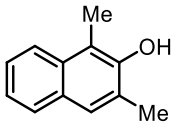
IR (film) ν_{max}/cm^{-1}: 3428, 3029, 2923, 1631, 1507, 1452, 1306, 1230, 1169, 1029, 804, 748

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.95 (1H, d, *J* = 8.5 Hz), 7.83 (1H, d, *J* = 8.1 Hz), 7.73 (1H, d, *J* = 8.8 Hz), 7.47 (1H, ddd, *J* = 8.4, 6.7, 1.4 Hz), 7.37 (1H, t, *J* = 7.4 Hz), 7.31–7.15 (5H, m), 7.11 (1H, d, *J* = 8.8 Hz), 4.96 (1H, s), 4.49 (2H, s)

^{13}C NMR (101 MHz, $CDCl_3$) δ = 151.2, 140.0, 133.7, 129.5, 128.7, 128.6, 128.3, 126.8, 126.2, 123.4, 123.3, 118.2, 117.9, 30.7.

HRMS (ESI^-) $C_{17}H_{14}O$ $[M-H]^-$ requires 233.0972; found 233.0968, Δ 1.5 ppm.

1,3-Dimethylnaphthalen-2-ol (189)



3-Methyl-naphthalene-2-ol (316 mg, 2.00 mmol, 1.00 equiv.) was dissolved in toluene (10 mL) and ^{n}BuLi (1.6 M in hexane, 1.25 mL, 2.00 mmol, 10.0 equiv.) was added dropwise. The reaction was heated to reflux and dimethyl sulfate (189 µL, 256 mg, 2.00 mmol, 1.00 equiv.) was added. Heating was continued for 2 hours after which time the reaction was cooled to room temperature. Water was added and the phases were separated. The aqueous phase was extracted twice with EtOAc and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product which was purified by column chromatography (7.5% EtOAc in pentane) to give 1,3-dimethylnaphthalen-2-ol (**189**) (53.9 mg, 16%).

m.p. = 84-86 °C (EtOAc-pentane).

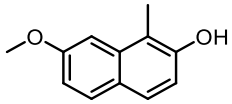
IR (film) ν_{max}/cm^{-1}: 3344, 3333, 3318, 3250, 3056, 3028, 2922, 2850, 1670, 1629, 1598, 1492, 1445, 1357, 1334, 1261, 1232, 1208, 1191, 1155, 1071, 905, 888, 823, 803, 770, 752, 731, 695.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.87 (d, *J* = 8.6 Hz, 1H), 7.71 (d, *J* = 8.1 Hz, 1H), 7.50 (s, 1H), 7.44 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H), 7.32 (ddd, *J* = 8.0, 6.8, 1.2 Hz, 1H), 4.94 (br. s, 1H), 2.54 (s, 3H), 2.44 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 150.1, 132.6, 129.1, 127.7, 127.1, 125.5, 125.4, 123.1, 122.9, 114.4, 17.0, 10.7.

Data in agreement with literature reported.[147]

7-Methoxy-1-methylnaphthalen-2-ol (190)



7-Methoxynaphthalene-2-ol (348 mg, 2.00 mmol, 1.00 equiv.) was dissolved in toluene (10 mL) and ^{n}BuLi (1.6 M in hexane, 1.25 mL, 2.00 mmol, 1.00 equiv.) was added dropwise. The reaction was heated to reflux and dimethyl sulfate (190 µL 252 mg, 2.00 mmol, 1.00 equiv.) was added. Heating was continued for 2 hours after which time the reaction was cooled to room temperature. Water was added and the phases were separated. The aqueous phase was extracted twice with EtOAc and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product which was purified by column chromatography (20% EtOAc in pentane) to give 7-methoxy-1-methylnaphthalen-2-ol (**190**) (75.2 mg, 20%).

m.p. = 116-117 °C (EtOAc/pentane).

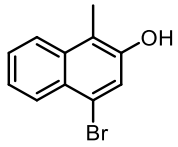
IR (film) ν_{max}/cm^{-1}: 3377, 1629, 1509, 1460, 1210, 1177, 1015, 827, 791.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.70 (d, *J* = 8.8 Hz, 1H), 7.57 (d, *J* = 8.7 Hz, 1H), 7.19 (d, *J* = 2.4 Hz, 1H), 7.05 (dd, *J* = 8.9, 2.5 Hz, 1H), 6.94 (d, *J* = 8.7 Hz, 1H), 4.94 (br. s, 1H), 3.98 (s, 3H), 2.52 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 158.2, 151.0, 135.2, 130.0, 127.1, 124.6, 115.3, 115.1, 114.3, 102.2, 55.3, 10.7.

HRMS (ESI^+) $C_{12}H_{12}O_2$ $[M+H]^+$ requires 189.0916; found 189.0912, Δ 1.0 ppm.

4-Bromo-1-methylnaphthalen-2-ol (191)



4-Bromo-naphthalene-2-ol (669 mg, 3.00 mmol, 1.00 equiv.) was dissolved in toluene (15 mL) and ^{n}BuLi (1.6 M in hexane, 1.88 mL, 3.00 mmol, 10.0 equiv.) was added dropwise. The reaction was heated to reflux and dimethyl sulfate (285 µL, 378 g, 3.00 mmol, 1.00 equiv.) was added. Heating was continued for 2 hours after which time the reaction was cooled to room temperature. Water was added and the phases were separated. The aqueous phase was extracted twice with EtOAc and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product which was purified by column chromatography (7.5% EtOAc in pentane) to give 4-bromo-1-methylnaphthalen-2-ol (**191**) (90.5 mg, 13%).

m.p. = 84-86 °C (EtOAc-pentane).

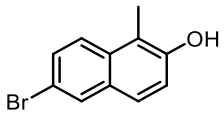
IR (film) ν_{max}/cm^{-1}: 3402, 3394, 3380, 1620, 1595, 1571, 1510, 1454, 1418, 1374, 1335, 1290, 1261, 1235, 1207, 1174, 1158, 1143, 1080, 1062, 1024, 904, 851, 751, 613.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.17 (d, *J* = 8.4 Hz, 1H), 7.90 (d, *J* = 0.5 Hz, 1H), 7.53 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H), 7.45 (ddd, *J* = 8.2, 6.8, 1.2 Hz, 1H), 7.42 (s, 1H), 4.97 (s, 1H), 2.50 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 150.3, 134.7, 127.8, 127.7, 127.2, 124.6, 123.7, 121.8, 120.9, 115.8, 10.8.

HRMS (ESI^+) $C_{11}H_9BrO$ $[M+H]^+$ requires 274.9764; found 274.9760, Δ 1.6 ppm.

6-Bromo-1-methylnaphthalen-2-ol (192)



6-Bromo-naphthalene-2-ol (4.46 g, 20.0 mmol, 1.00 equiv.) was dissolved in toluene (100 mL) and ^{n}BuLi (1.6 M in hexane, 12.5 mL, 20.0 mmol, 10.0 equiv.) was added dropwise. The reaction was heated to reflux and dimethyl sulfate (1.88 mL, 2.52 g, 20.0 mmol, 1.00 equiv.) was added. Heating was continued for 2 hours after which time the reaction was cooled to room temperature. Water was added and the phases were separated. The aqueous phase was extracted twice with EtOAc and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product which was purified by column chromatography (7.5% EtOAc in pentane) to give 6-bromo-1-methylnaphthalen-2-ol (**192**) (542 mg, 11%) as an off-white solid.

m.p. = 116-118 °C (EtOAc/pentane).

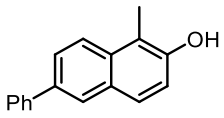
IR (film) ν_{max}/cm^{-1}: 3377, 1629, 1509, 1460, 1210, 1177, 1015, 827, 791.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.91 (d, *J* = 2.1 Hz, 1H), 7.77 (d, *J* = 9.0 Hz, 1H), 7.54 (dd, *J* = 9.0, 1.9 Hz, 1H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.07 (d, *J* = 8.8 Hz, 1H), 4.96 (s, 1H), 2.51 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 150.9, 132.5, 130.5, 130.4, 129.6, 126.6, 125.2, 118.8, 117.1, 115.8, 10.6.

HRMS (ESI$^-$) $C_{11}H_9BrO$ $[M+H]^-$ requires 234.9764; found 234.9764, Δ 0.1 ppm.

1-Methyl-6-phenylnaphthalen-2-ol (193)



1-Methyl-6-bromonaphthalen-2-ol (119 mg, 0.500 mmol, 100 equiv.), phenylboronic acid (73.3 mg, 0.600 mmol, 1.20 equiv.) and $Pd(PPh_3)_4$ (28.9 mg, 0.0500 mmol, 0.0500 equiv.) were added to a 2-neck round bottom flask fitted with a reflux condenser. The flask was evacuated and backfilled with argon three times and DME (5 mL) followed by 2 M aqueous sodium carbonate solution (623 µL, 1.25 mmol, 2.50 equiv.) was added. The reaction was heated under reflux for 16 hours then cooled to room temperature. The reaction mixture was transferred to a separating funnel and partitioned between water and EtOAc. The phases were separated and the aqueous phase was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product which was purified by column chromatography eluting with 20% CH_2Cl_2-petroleum ether 40-60 to give 1-methyl-6-phenylnaphthalen-2-ol (**193**) (111 mg, 95%) as a white solid.

m.p. = 118-110 °C (CH_2Cl_2/petroleum ether 40-60).

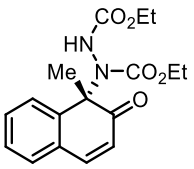
IR (film) ν_{max}/cm^{-1}: 3344, 3318, 2922,, 1629, 1492, 1445, 1334, 1191, 1071, 888, 803, 752, 731, 695.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.01–7.97 (m, 2H), 7.78 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.74–7.71 (m, 2H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.51–7.45 (m, 2H), 7.40–7.33 (m, 1H), 7.10 (d, *J* = 8.7 Hz, 1H), 4.91 (s, 1H), 2.57 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 150.6, 141.1, 135.8, 133.0, 129.5, 128.8, 127.7, 127.2, 127.1, 126.3, 125.9, 123.8, 118.0, 115.2, 10.5.

HRMS (ESI$^+$) $C_{17}H_{14}O$ $[M-H]^-$ requires 233.0973; found 233.0968, Δ 1.9 ppm.

Diethyl (*S*)-1-(1-methyl-2-oxo-1,2-dihydronaphthalen-1-yl)hydrazine-1,2-dicarboxylate (168)



Following **general procedure B** using 1-methylnaphthalen-2-ol (**161**) (31.6 mg, 0.200 mmol) and diethylazodicarboxylate (37.6 μL, 41.8 mg, 0.240 mmol, 1.20 equiv.) for 24 hours. Purification *via* flash column chromatography (20% EtOAc – pentane) afforded diethyl (*S*)-1-(1-methyl-2-oxo-1,2-dihydronaphthalen-1-yl)hydrazine-1,2-dicarboxylate (**168**) as an off-white solid (59.8 mg, 90%, 90:10 er). This compound is rotameric by NMR, VT-NMR was used to coalesce rotamer peaks.

m.p. = 78-79 °C (EtOAc – pentane).

IR (film) ν_{max}/cm^{-1}: 3256, 3241, 2983, 2360, 2339, 2180, 2160, 2032, 2025, 2020, 2008, 1992, 1976, 1712, 1670, 1240, 1046, 764.

^{1}H NMR (500 MHz, PhMe-d_8, 90 °C) δ = 8.50 (s, 1H), 7.19 (t, J = 7.5 Hz, 1H), 6.95 (m, 3H), 6.82 (s, 1H), 6.01 (d, J = 9.9 Hz, 1H), 4.10 (m, 2H), 3.72 (m, 2H), 1.41 (s, 3H), 1.10 (t, J = 7.1 Hz, 3H), 0.74 (t, J = 6.9 Hz, 3H).

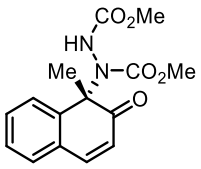
^{13}C NMR (500 MHz, PhMe-d_8, 90 °C) δ = 200.9, 156.8, 155.3, 147.8, 144.4, 130.3, 128.8, 128.7, 128.0, 126.5, 123.5, 69.9, 61.9, 61.3, 26.7, 14.0, 13.4.

HRMS (ESI$^+$) $C_{17}H_{21}N_2O_5$ $[M+H]^+$ requires 333.1450; found 333.1455, Δ 0.0 ppm.

Chiral HPLC: (Chiralpak ADH, 20% ^{i}PrOH, 80% hexane, 1.0 mL min^{-1}, λ = 260 nm) τ_R (major) = 17.3 min, τ_R (minor) = 14.9 min.

$[\alpha]_D^{25}$ = −67.2 (*c* = 1.00, acetone).

Dimethyl (*S*)-1-(1-methyl-2-oxo-1,2-dihydronaphthalen-1-yl)hydrazine-1,2-dicarboxylate (195)



Following **general procedure B** using 1-methylnaphthalen-2-ol (**161**) (31.6 mg, 0.200 mmol, 1.00 equiv.) and dimethylazodicarboxylate (35.4 µL, 35.0 mg, 0.240 mmol, 1.20 equiv.) for 24 hours. Purification *via* flash column chromatography (20% EtOAc – pentane) afforded dimethyl (*S*)-1-(1-methyl-2-oxo-1,2-dihydronaphthalen-1-yl)hydrazine-1,2-dicarboxylate (**195**) as an off-white solid (58.0 mg, 95%, 88:12 er).This compound is rotameric by NMR, VT-NMR was used to coalesce rotamer peaks.

m.p. = 136-137 °C (EtOAc – pentane).

IR (film) ν_{max}/cm^{-1}: 3264, 3254, 2954, 2177, 2161, 2028, 1978, 1724, 1712, 1673, 1524, 1438, 1353, 1261, 1244, 1048, 765, 758.

^{1}H NMR (500 MHz, PhMe-d_8, 90 °C) δ = 8.42 (s, 1H), 7.17–7.12 (m, 1H), 6.99–6.87 (m, 3H), 6.83 (s, 1H), 5.98 (d, *J* = 9.8 Hz, 1H), 3.49 (s, 3H), 3.15 (s, 3H), 1.35 (s, 3H).

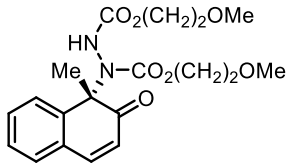
^{13}C NMR (126 MHz, PhMe-d_8, 90 °C) δ = 201.7, 157.9, 156.7, 148.2, 145.4, 131.1, 129.7, 127.4, 124.2, 70.8, 53.2, 52.7, 27.5.

HRMS (ESI$^+$) $C_{15}H_{16}N_2O_5$ $[M+Na]^+$ requires 327.0957; found 327.0952, Δ 0.0 ppm.

Chiral HPLC: (Chiralpak ADH, 20% ^{i}PrOH, 80% hexane, 1.0 mL min^{-1}, λ = 260 nm) τ_R (major) = 17.5 min, τ_R (minor) = 12.6 min.

$[\alpha]_D^{25}$ = −71.3 (*c* = 1.00, acetone).

Bis (2-methoxyethyl) (*S*)-1-(1-methyl-2-oxo-1,2-dihydronaphthalen-1-yl)hydrazine-1,2-dicarboxylate (196)



Following **general procedure B** using 1-methylnaphthalen-2-ol (**161**) (31.6 mg, 0.200 mmol, 1.00 equiv.) and di-2-methoxyethylazodicarboxylate (56.2 mg, 0.240 mmol, 1.20 equiv.) for 24 hours. Purification *via* flash column chromatography (20% EtOAc – pentane) afforded bis(2-methoxyethyl) (*S*)-1-(1-methyl-2-oxo-1,2-dihydronaphthalen-1-yl)hydrazine-1,2-dicarboxylate (**196**) as a colourless oil (66.8 mg, 85%, 88:12 er). This compound is rotameric by NMR, the reported peaks refer to the major rotamer.

IR (film) ν_{max}/cm^{-1}: 3280, 3268, 3259, 3244, 3234, 2982, 2954, 2932, 2893, 1717, 1669, 1238, 1052.

^{1}H NMR (400 MHz, DMSO-d6) δ = 10.00 (s, 1H), 8.37 (d, *J* = 8.0, 1H), 7.71–7.65 (m, 1H), 7.52–7.47 (d, *J* = 6.9 Hz, 1H), 7.45–7.38 (m, 1H), 7.36–7.30 (m, 1H), 6.17 (d, *J* = 9.9 Hz, 1H), 4.29–4.22 (m, 2H), 4.01–3.92 (m, 2H), 3.57 (t, *J* = 4.6 Hz, 2H), 3.49–3.39 (m, 2H), 3.33 (s, 2H), 3.30 (s, 3H), 1.38–1.25 (m, 3H).

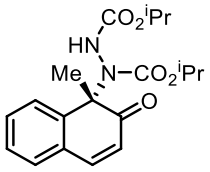
^{13}C NMR (101 MHz, DMSO-d6) δ = 200.0, 157.6, 155.1, 147.2, 145.6, 130.8, 129.9, 127.6, 126.2, 123.9, 123.4, 70.5, 70.3, 70.0, 65.9, 64.7, 58.8, 58.6, 27.0.

HRMS (ESI^{+}) $C_{19}H_{24}N_2O_7$ $[M+H]^+$ requires 415.1481; found 415.1476, Δ 2.1 ppm.

Chiral HPLC: (Chiralpak ADH, 20% ^{i}PrOH, 80% hexane, 1.0 mL min^{-1}, λ = 260 nm) τ_R (major) = 22.0 min, τ_R (minor) = 18.8 min.

$[\alpha]_D^{25}$ = −58.3 (*c* = 1.00, acetone).

Diisopropyl 1-(1-methyl-2-oxo-1,2-dihydronaphthalen-1-yl)hydrazine-1,2-dicarboxylate (HM166)



This compound was prepared and characterised by Harriet Moore

Prepared according to **general procedure B** using 1-methylnaphthalen-2-ol (31.6 mg, 0.200 mmol, 1.00 eq.) (**161**) at −10 °C. The compound was purified by column chromatography eluting with 15% EtOAc in *n*-pentane to obtain the pure compound as a yellow oil (29.3 mg, 41%, 81:19 er). This compound is rotameric by NMR, VT-NMR was used to coalesce rotamer peaks.

IR (film) ν_{max}/cm^{-1}: 3300, 2982, 2937, 1720, 1673, 1617, 1375, 1244, 1180, 1108, 830, 765.

^{1}H NMR (500 MHz, DMSO-d_6, 90 °C) δ_H = 8.95 (1H, br. s), 8.31 (1H, br. s), 7.64 (1H, d, *J* = 9.8 Hz), 7.45 (2H, dd, *J* = 15.9, 7.5 Hz), 7.32 (1H, t, *J* = 7.4, 7.4 Hz), 6.15 (1H, d, *J* = 9.9 Hz, ArH), 4.95 (1H, s), 4.62 – 4.15 (1H, m), 1.35 (3H, s), 1.30 (8H, dd, *J* = 13.2, 6.3 Hz), 1.01 – 0.83 (3H, m), 0.78 (3H, s)

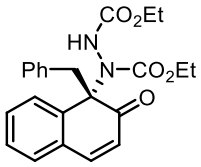
^{13}C NMR (126 MHz, DMSO-d_6, 90 °C) δ_C = 199.5, 154.6, 145.4, 130.5, 129.7, 129.0, 127.4, 126.2, 123.8, 70.0, 69.8, 69.0, 40.9, 40.9, 40.8, 40.7, 40.6, 40.5, 40.4, 40.4, 40.3, 40.1, 39.9, 27.1, 22.3, 22.3, 21.8, 21.6

HRMS (ESI$^+$) $C_{17}H_{14}O$ $[M+Na]^+$ requires 383.1577; found = 383.1576 Δ 0.2 ppm.

Chiral HPLC: (Chiralpak ADH, 20% ^{i}PrOH, 80% *n*-hexane, 1.0 mL min^{-1}, λ = 308 nm) τ_R (major) = 8.1 min, τ_R (minor) = 12.8 min

$[\alpha]_D^{25}$ = −48.3 (c = 0.5, acetone)

Diethyl (*S*)-1-(1-benzyl-2-oxo-1,2-dihydronaphthalen-1-yl)hydrazine-1,2-dicarboxylate (197)



Following **general procedure B** using 1-benzylnaphthalen-2-ol] (**188**) (46.8 mg, 0.200 mmol) and diethylazodicarboxylate (37.6 µL, 41.8 mg, 0.240 mmol, 1.20 equiv.) for 16 hours. Purification *via* flash column chromatography (20% EtOAc – pentane) afforded diethyl (*S*)-1-(1-benzyl-2-oxo-1,2-dihydronaphthalen-1-yl)hydrazine-1,2-dicarboxylate (**197**) as an off-white solid (66.3 mg, 84%, 74:26 er). This compound is rotameric by NMR, VT-NMR was used to coalesce rotamer peaks.

m.p. = 99-100 °C (EtOAc – pentane).

IR (film) ν_{max}/cm^{-1}: 3290, 2981, 1719, 1664, 1239.

^{1}H NMR (500 MHz, PhMe-d8, 90 °C) δ = 8.69 (s, 1H), 7.25 (t, *J* = 7.7 Hz, 1H), 7.14 – 6.57 (m, 8H), 5.79 (d, *J* = 10.0 Hz, 1H), 4.26 – 4.09 (m, 2H), 3.71 (q, *J* = 7.0 Hz, 2H), 3.51 (d, *J* = 12.0 Hz, 1H), 3.19 (d, *J* = 12.0 Hz, 1H), 1.14 (t, *J* = 7.1 Hz, 3H), 0.72 (t, *J* = 7.1 Hz, 3H).

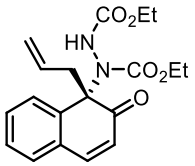
^{13}C NMR (126 MHz, PhMe-d8, 90 °C) δ = 201.4, 157.0, 155.2, 145.6, 144.1, 133.0, 131.1, 130.6, 129.8, 128.1, 127.0, 126.7, 126.5, 125.5, 72.0, 62.0, 61.4, 48.1, 14.0, 13.4.

HRMS (ESI$^+$) $C_{23}H_{24}N_2O_5$ $[M+H]^+$ requires 409.1758; found 409.1758, Δ 0.0 ppm.

Chiral HPLC: (Chiralpak ADH, 30% ^{i}PrOH, 70% hexane, 1.0 mL min^{-1}, λ = 260 nm) τ_R (major) = 7.3 min, τ_R (minor) = 15.8 min.

$[\alpha]_D^{25}$ = +3.3 (*c* = 1.00, $CHCl_3$).

Diethyl (*S*)-1-(1-allyl-2-oxo-1,2-dihydronaphthalen-1-yl)hydrazine-1,2-dicarboxylate (198)



Following **general procedure B** using 1-allylnaphthalen-2-ol (**198**) (36.8 mg, 0.200 mmol) and diethylazodicarboxylate (37.6 µL, 41.8 mg, 0.240 mmol, 1.20 equiv.) for 24 hours. Purification *via* flash column chromatography (20% EtOAc – pentane) afforded diethyl (*S*)-1-(1-allyl-2-oxo-1,2-dihydronaphthalen-1-yl)hydrazine-1,2-dicarboxylate (**198**) as an off-white solid (44.9 mg, 62%, 79:21 er). This compound is rotameric by NMR, VT-NMR was used to coalesce rotamer peaks.

m.p. = 115-116 °C (EtOAc – pentane).

IR (film) ν_{max}/cm^{-1}: 3286, 2982, 2360, 2341, 1719, 1665, 1232.

^{1}H NMR (500 MHz, PhMe-d8, 90 °C) δ = 8.67 (d, *J* = 7.8 Hz, 1H), 7.17 (app. t, *J* = 7.6, 1H), 6.95–6.90 (app. t, *J* = 7.6, 1H), 6.81 (m, 2H), 6.06 (d, *J* = 9.9 Hz, 1H), 5.43–5.23 (m, 1H), 4.79–4.50 (m, 2H), 4.11–3.93 (m, 2H), 3.72-3.58 (m, 2H), 2.80 (dd, *J* = 12.9, 7.9 Hz, 1H), 2.68 (dd, *J* = 12.9, 6.6 Hz, 1H), 1.02 (t, *J* = 7.1 Hz, 3H), 0.76-0.56 (m, 3H).

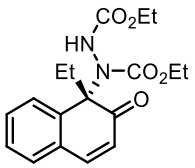
^{13}C NMR (126 MHz, PhMe-d8, 90 °C) δ = 200.8, 156.8, 155.3, 145.6, 144.7, 130.6, 130.1, 129.9, 126.7, 124.9, 118.6, 71.9, 61.9, 61.3, 45.4, 29.3, 14.0, 13.4.

HRMS (ESI^{+}) $C_{19}H_{22}N_2O_5$ $[M+H]^+$ requires 259.1601; found 359.1601, Δ 0.1 ppm.

Chiral HPLC: (Chiralpak ADH, 30% ^{i}PrOH, 70% hexane, 1.0 mL min^{-1}, λ = 260 nm) τ_R (major) = 8.5 min, τ_R (minor) = 9.7 min.

$[\alpha]_D^{25}$ = −78.0 (*c* = 1.00, $CHCl_3$).

Diethyl (*S*)-1-(1-ethyl-2-oxo-1,2-dihydronaphthalen-1-yl)hydrazine-1,2-dicarboxylate (199)



Following **general procedure B** using 1-ethylnaphthalen-2-ol (**186**) (34.4mg, 0.200 mmol) and diethylazodicarboxylate (37.6 μL, 41.8 mg, 0.240 mmol, 1.20 equiv.) for 16 hours. Purification *via* flash column chromatography (20% EtOAc – pentane) afforded diethyl (*S*)-1-(1-ethyl-2-oxo-1,2-dihydronaphthalen-1-yl)hydrazine-1,2-dicarboxylate (**199**) as an off-white solid (51.1 mg, 77%, 78:22 er). This compound is rotameric by NMR, VT-NMR was used to coalesce rotamer peaks.

m.p. = 132-133 °C (EtOAc – pentane).

IR (film) ν_{max}/cm^{-1}: 3287, 2981, 1718, 1666, 1401, 1376, 1325, 1271, 1236, 1057.

^{1}H NMR (500 MHz, PhMe-d8, 90 °C) δ = 8.66 (d, *J* = 7.9 Hz, 1H), 7.20 (app. t, *J* = 7.6, 1H), 6.96 (app. t, 1H), 6.89-6.84 (m, 2H), 6.11 (d, *J* = 9.9 Hz, 1H), 4.17 – 4.00 (m, 2H), 3.68 (d, *J* = 10.2 Hz, 2H), 2.11–2.05 (m, 1H), 1.97–1.86 (m, 1H), 1.07 (t, *J* = 7.1 Hz, 3H), 0.75-0.65 (m, 3H), 0.55 (t, *J* = 7.5 Hz, 4H).

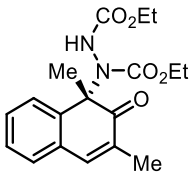
^{13}C NMR (126 MHz, PhMe-d8, 90 °C) δ = 201.5, 156.8, 155.4, 145.9, 144.7, 130.3, 129.9, 126.5, 125.1, 72.4, 61.9, 61.3, 34.1, 14.0, 13.4, 7.2.

HRMS (ESI^{+}) $C_{18}H_{22}N_2O_5$ $[M+H]^+$ requires 347.1601; found 347.1603, Δ 0.4 ppm.

Chiral HPLC: (Chiralpak ADH, 30% ^{i}PrOH, 70% hexane, 1.0 mL min^{-1}, λ = 260 nm) τ_R (major) = 10.4 min, τ_R (minor) = 8.9 min.

$[\alpha]_D^{25}$ = −89.7 (*c* = 1.00, $CHCl_3$).

Diethyl (*S*)-1-(1,3-dimethyl-2-oxo-1,2-dihydronaphthalen-1-yl)hydrazine-1,2-dicarboxylate (200)



Following **general procedure B** using 1,3-dimethylnaphthalen-2-ol (**189**) (57.2 mg, 0.200 mmol) and diethylazodicarboxylate (37.6 µL, 41.8 mg, 0.240 mmol, 1.20 equiv.) for 16 hours. Purification *via* flash column chromatography (20% EtOAc – pentane) afforded diethyl (*S*)-1-(1,3-dimethyl-2-oxo-1,2-dihydronaphthalen-1-yl)hydrazine-1,2-dicarboxylate (**200**) as an off-white solid (57.2 mg, 83%, 77:23 er). This compound is rotameric by NMR, VT-NMR was used to coalesce rotamer peaks.

m.p. = 119-120 °C (EtOAc – pentane).

IR (film) ν_{max}/cm^{-1}: 3294, 2982, 1719, 1661, 1376, 1339, 1242, 1227, 1053, 761.

^{1}H NMR (500 MHz, PhMe-d8, 90 °C) δ = 9.09 (d, *J* = 7.1 Hz, 1H), 7.57 (app. t, *J* = 7.6, 1.4 Hz, 1H), 7.52–7.48 (m, 1H), 7.29 (d, *J* = 7.6 Hz, 1H), 7.19 (s, 1H), 4.51–4.31 (m, 2H), 4.15-4.00 (m, 2H), 2.34 (s, 3H), 1.79 (s, 3H), 1.42 (t, *J* = 7.1 Hz, 3H), 1.25-1.10 (m, 3H).

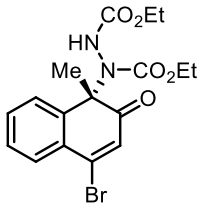
^{13}C NMR (500 MHz, PhMe-d8, 90 °C) δ = 201.6, 156.8, 155.4, 146.9, 141.2, 131.0, 129.3, 128.8, 128.7, 128.0, 127.8, 126.5, 69.8, 61.8, 61.3, 27.0, 14.8, 14.0, 13.5.

HRMS (ESI^{+}) $C_{18}H_{22}N_2O_5$ $[M+H]^+$ requires 347.1601; found 347.1605, Δ 0.9 ppm.

Chiral HPLC: (Chiralpak ADH 30% ^{i}PrOH, 70% hexane, 1.0 mL min^{-1}, λ = 260 nm) τ_R (major) = 10.5 min, τ_R (minor) = 13.8 min.

$[\alpha]_D^{25}$ = −10.5 (*c* = 1.00, $CHCl_3$).

Diethyl (*S*)-1-(4-bromo-1-methyl-2-oxo-1,2-dihydronaphthalen-1-yl)hydrazine-1,2-dicarboxylate (201)



Following **general procedure B** using 4-bromo-1-methylnaphthalen-2-ol (**191**) (47.4 mg, 0.200 mmol) and diethylazodicarboxylate (37.6 μL, 41.8 mg, 0.240 mmol, 1.20 equiv.) for 16 hours. Purification *via* flash column chromatography (20% EtOAc – pentane) afforded diethyl (*S*)-1-(4-bromo-1-methyl-2-oxo-1,2-dihydronaphthalen-1-yl)hydrazine-1,2-dicarboxylate (**201**) as an off-white solid (39.2 mg, 48%, 76:24 er). This compound is rotameric by NMR, peaks refer to the major rotamer peaks

m.p. = 80-81°C (EtOAc – pentane).

IR (film) ν_{max}/cm^{-1}: 3303, 3293, 3287, 2982, 1718, 1671, 1599, 1558, 1376, 1338, 1321, 1277, 1240, 1051, 760.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.21 (s, 1H), 7.56 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.52 – 7.46 (m, 1H), 7.43 (d, *J* = 9.9 Hz, 1H), 6.26 (d, *J* = 9.9 Hz, 1H), 4.40 – 4.18 (m, 2H), 4.17 – 3.81 (m, 2H), 1.47 (s, 3H), 1.36 (t, *J* = 7.1 Hz, 2H), 1.26 – 1.11 (m, 3H).

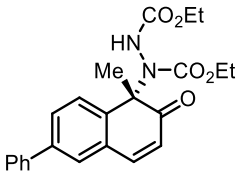
^{13}C NMR (101 MHz, $CDCl_3$) δ = 201.6, 155.6, 144.3, 133.7, 131.8, 130.0, 128.0, 124.6, 120.9, 69.5, 63.0, 62.2, 26.9, 14.5, 14.1.

HRMS (ESI$^+$) $C_{17}H_{19}BrN_2O_5$ $[M+H]^+$ requires 411.0550; found 411.0544, Δ 1.4 ppm.

Chiral HPLC: (Chiralpak ADH, 30% ^{i}PrOH, 70% hexane, 1.0 mL min^{-1}, λ = 260 nm) τ_R (major) = 6.4 min, τ_R (minor) = 8.4 min.

$[\alpha]_D^{25}$ = −57.3 (*c* = 1.00, $CHCl_3$).

Diethyl (*S*)-1-(1-methyl-2-oxo-6-phenyl-1,2-dihydronaphthalen-1-yl)hydrazine-1,2-dicarboxylate (202)



Following **general procedure B** using 1-methyl-6-phenylnaphthalen-2-ol (**193**) (46.8 mg, 0.200 mmol) and diethylazodicarboxylate (37.6 µL, 41.8 mg, 0.240 mmol, 1.20 equiv.) for 24 hours. Purification *via* flash column chromatography (20% EtOAc – pentane) afforded diethyl (*S*)-1-(1-methyl-2-oxo-6-phenyl-1,2-dihydronaphthalen-1-yl)hydrazine-1,2-dicarboxylate (**202**) as an off-white solid (65.2 mg, 80%, 82:18 er). This compound is rotameric by NMR, VT-NMR was used to coalesce rotamer peaks.

m.p. = 61-62 °C (EtOAc – pentane).

IR (film) ν_{max}/cm^{-1}: 3302, 3288, 3277, 2982, 1718, 1671, 1485, 1402, 1376, 1339, 1296, 1277, 1234, 1072, 1051, 761.

^{1}H NMR (500 MHz, PhMe-d8, 90 °C) δ = 8.59 (br. s, 1H), 7.46 (dd, *J* = 8.1, 2.0 Hz, 1H), 7.42–7.36 (m, 2H), 7.26–7.20 (m, 3H), 7.07 (s, 1H), 6.80 (br. s, 1H), 6.08 (d, *J* = 9.9 Hz, 1H), 4.19-4.07 (m, 2H), 3.80-3.70 (m, 2H), 1.47 (s, 3H), 1.11 (t, *J* = 7.0 Hz, 3H), 0.78 (t, *J* = 7.1 Hz, 3H).

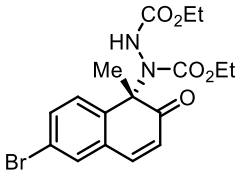
^{13}C NMR (500 MHz, PhMe-d8, 90 °C) δ = 200.8, 156.9, 155.4, 146.5, 144.6, 140.3, 140.0, 129.1, 128.9, 128.7, 128.5, 127.8, 127.1, 126.8, 123.8, 69.7, 62.0, 61.3, 61.2, 26.7, 14.0, 13.5.

HRMS (ESI$^+$) $C_{23}H_{24}N_2O_5$ $[M+H]^+$ requires 409.1758; found 409.1764, Δ 1.5 ppm.

Chiral HPLC: (Chiralpak ADH, 30% ^{i}PrOH,70% hexane, 1.0 mL min^{-1}, λ = 260 nm) τ_R (major) = 21.5 min, τ_R (minor) = 13.4 min.

$[\alpha]_D^{25}$ = −10.5(*c* = 1.00, $CHCl_3$).

Diethyl (*S*)-1-(6-bromo-1-methyl-2-oxo-1,2-dihydronaphthalen-1-yl)hydrazine-1,2-dicarboxylate (203)



Following **general procedure B** using 6-bromo-1-methylnaphthalen-2-ol (**192**) (47.4 mg, 0.200 mmol) and diethylazodicarboxylate (37.6 µL, 41.8 mg, 0.240 mmol, 1.20 equiv.) for 24 hours. Purification *via* flash column chromatography (20% EtOAc – pentane) afforded diethyl (*S*)-1-(6-bromo-1-methyl-2-oxo-1,2-dihydronaphthalen-1-yl)hydrazine-1,2-dicarboxylate (**203**) as an off-white solid (72.9 mg, 87%, 76:24 er). This compound is rotameric by NMR, major rotamer peaks are reported.

m.p. = 84-85°C (EtOAc – pentane).

IR (film) ν_{max}/cm^{-1}: 3292, 2982, 1718, 1675, 1376, 1340, 1278, 1240, 1048.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.21 (s, 1H), 7.56 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.52 – 7.46 (m, 1H), 7.43 (d, *J* = 9.9 Hz, 1H), 6.26 (d, *J* = 9.9 Hz, 1H), 4.40 – 4.18 (m, 2H), 4.17 – 3.81 (m, 2H), 1.47 (s, 3H), 1.36 (t, *J* = 7.1 Hz, 2H), 1.26 – 1.11 (m, 3H).

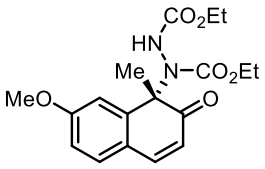
^{13}C NMR (101 MHz, $CDCl_3$) δ = 201.6, 155.6, 144.3, 133.7, 131.8, 130.0, 128.0, 124.6, 120.9, 69.5, 63.0, 62.2, 26.9, 14.5, 14.1.

HRMS (ESI$^+$) $C_{17}H_{19}BrN_2O_5$ $[M+H]^+$ requires 411.0550; found 411.0554, Δ 1.0 ppm.

Chiral HPLC: (Chiralpak ADH 20% ^{i}PrOH, 80% hexane, 1.0 mL min^{-1}, λ = 260 nm) τ_R (major) = 17.4 min, τ_R (minor) = 14.5 min.

$[\alpha]_D^{25}$ = −12.2 (*c* = 1.00, $CHCl_3$).

Diethyl (*S*)-1-(7-methoxy-1-methyl-2-oxo-1,2-dihydronaphthalen-1-yl)hydrazine-1,2-dicarboxylate (204)



Following **general procedure B** using 7-methoxy-1-methylnaphthalen-2-ol (**190**) (37.6mg, 0.200 mmol) and diethylazodicarboxylate (37.6 μL, 41.8 mg, 0.240 mmol, 1.20 equiv.) for 24 hours. Purification *via* flash column chromatography (20% EtOAc – pentane) afforded diethyl (*S*)-1-(7-methoxy-1-methyl-2-oxo-1,2-dihydronaphthalen-1-yl)hydrazine-1,2-dicarboxylate (**204**) as an off-white solid (60.8 mg, 84%, 75:25 er). This compound is rotameric by NMR, VT-NMR was used to coalesce rotamer peaks.

m.p. = 80-82 °C (EtOAc – pentane).

IR (film) ν_{max}/cm^{-1}: 3290, 2982, 1720, 1667, 1602, 1238.

^{1}H NMR (500 MHz, PhMe-d8, 90 °C) δ = 8.25 (br. s, 1H), 6.92 (d, *J* = 9.8 Hz, 1H), 6.84 (d, *J* = 8.3 Hz, 1H), 6.76 (s, 1H), 6.63 (dd, *J* = 8.4, 2.6 Hz, 1H), 5.91 (d, *J* = 9.9 Hz, 1H), 4.13–3.96 (m, 2H), 3.76–3.67 (m, 2H), 3.60 (s, 3H), 1.39 (s, 3H), 1.13–1.02 (m, 3H), 0.77–0.68 (m, 3H).

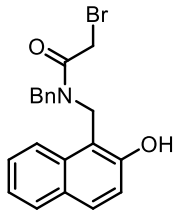
^{13}C NMR (126 MHz, PhMe-d8, 90 °C) δ = 200.6, 162.5, 157.1, 155.2, 150.4, 144.3, 130.3, 126.5, 121.8, 120.8, 111.3, 70.2, 61.9, 61.3, 54.8, 27.1, 13.9, 13.4.

HRMS (ESI$^+$) $C_{18}H_{22}N_2O_6$ $[M+H]^+$ requires 363.1550; found 363.1551, Δ 0.3 ppm.

Chiral HPLC: (Chiralpak ADH, 20% ^{i}PrOH, 80% hexane, 1.0 mL min^{-1}, λ = 260 nm) τ_R (major) = 17.4 min, τ_R (minor) = 14.5 min.

$[\alpha]_D^{25}$ = −96.2 (*c* = 1.00, $CHCl_3$).

_N_-Benzyl-2-bromo-_N_-((2-hydroxynaphthalen-1-yl)methyl)acetamide (211)



2-Hydroxy-1-naphthaldehyde (1.72 g, 10.0 mmol, 1.00 equiv.) and benzylamine (1.30 mL, 1.28 g, 12.0 mmol. 1.20 equiv.) and $MgSO_4$ (5 g) in CH_2Cl_2 (50 mL) were heated under reflux for 16 hours. After cooling to room temperature, the solvent was removed (rotavap) and the crude imine was dissolved in EtOH (20 mL) and cooled to 0 °C. $NaBH_4$ (453 mg, 12.0 mmol, 1.20 equiv.) was added and the reaction was stirred for 30 minutes. Water was added and the resulting solution was extracted three times with EtOAc, the combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated to give the crude amine (1.21 g, 46%) which was used without further purification (**210**).

The crude amine (132 mg, 0.500 mmol, 1.00 equiv.) was dissolved in CH_2Cl_2 and Et_3N (76.5 µL, 55.5 mg, 0.550 mmol, 1.10 equiv.) was added followed by bromoacetyl chloride (83.0 µL, 157 mg, 0.500 mmol, 1.00 equiv.) and the reaction was stirred at room temperature for 16 hours. The reaction mixture was transferred to a separating funnel and diluted with additional CH_2Cl_2 and washed three times with water, dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product which was purified by column chromatography eluting with 20% EtOAc-pentane to give *N*-

benzyl-2-bromo-*N*-((2-hydroxynaphthalen-1-yl)methyl)acetamide (**211**) (70.0 mg, 38%) as a colourless oil.

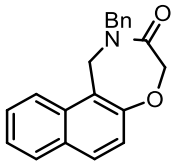
IR (film) ν_{max}/cm^{-1}: 3195 (broad), 1624, 1468, 1451, 1438, 1274, 819, 731.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.52 (s, 1H), 7.72–7.67 (m, 2H), 7.53–7.47 (m, 1H), 7.39 (ddd, *J* = 7.8, 6.3, 1.6 Hz, 2H), 7.36–7.25 (m, 2H), 7.25–7.12 (m, 4H), 4.95 (s, 2H), 4.60 (s, 2H), 3.84 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.4, 155.5, 134.7, 133.9, 130.9, 129.4, 129.0, 128.8, 128.3, 126.9, 126.1, 122.8, 121.2, 119.9, 112.3, 51.5, 40.2, 25.4.

HRMS (ESI^+) $C_{20}H_{18}O_2NBr$ $[M+Na]^+$ requires 406.0413; found 406.1413, Δ 0.1 ppm.

2-Benzyl-1,2-dihydronaphtho[1,2-f][1,4]oxazepin-3(4H)-one (213)



N 1-((benzylamino)methyl)naphthalen-2-ol (**211**) (38.4 mg, 0.100 mmol, 1.00 equiv.), and *N*-benzylcinchoninium chloride (**14)** (4.20 mg, 0.0100 mmol, 0.100 equiv.) were dissolved in toluene (4 mL) and saturated aqueous potassium hydroxide solution (42.6 µL) was added. The reaction was stirred at 1000 rpm overnight then quenched by addition of 1 M aqueous HCl solution. The phases were separated and the aqueous phase was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product which was purified by column chromatography (30% EtOAc in pentane) to give 2-benzyl-1,2-dihydronaphtho[1,2-f][1,4]oxazepin-3(4H)-one (**213**) (30.3 mg, 100%) as a colourless oil.

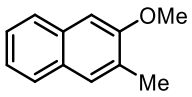
IR (film) ν_{max}/cm^{-1}: 3060, 3029, 2917, 1636, 1626, 1225, 1092, 1027, 822, 747, 729, 697.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.76 (dd, *J* = 8.7, 0.8 Hz, 2H), 7.33 (ddd, *J* = 8.0, 6.6, 1.4 Hz, 1H), 7.29 – 7.20 (m, 8H), 4.82 (s, 2H), 4.81 (s, 2H), 4.78 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.5, 156.4, 136.7, 131.0, 131.0, 130.6, 129.1, 128.8, 128.5, 127.9, 127.0, 124.9, 124.4, 122.0, 120.2, 73.1, 51.8, 42.0.

HRMS (ESI^+) $C_{20}H_{17}O_2N$ $[M+H]^+$ requires 304.1332; found 304.1333, Δ 0.2 ppm.

2-Methoxy-3-methylnaphthalene (215)



2-Methoxynaphthalene (3.16 g, 20.0 mmol, 1.00 equiv.) in THF (40 mL) was cooled to −78 °C and ^{n}BuLi (2.5 M in hexane, 8.8 mL, 22.0 mmol, 1.10 equiv.) was added and the solution was warmed to room temperature and stirred for 3 hours. The reaction was cooled to −78 °C and Me_2SO_4 (2.08 mL, 2.77 g, 22.0 mmol, 1.10 equiv.) was added and the reaction was warmed to room temperature and stirred for 16 hours. Water was added and resulting solution was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product, which was recrystallized from ethanol to give 2-methoxy-3-methylnaphthalene (**215**) (2.24 g, 67%) as a white solid.

m.p. = 62-64 °C (EtOH).

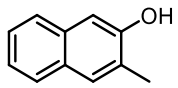
IR (film) ν_{max}/cm^{-1}: 3006, 2944, 2922, 1504, 1474, 1253, 1239, 1156, 1107, 862, 747.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.66–7.58 (m, 2H), 7.49 (s, 1H), 7.30 (ddd, *J* = 8.2, 6.9, 1.3 Hz, 1H), 7.22 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 6.99 (s, 1H), 3.86 (s, 3H), 2.30 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.9, 133.4, 128.8, 128.7, 128.5, 126.8, 126.3, 125.4, 123.5, 104.4, 55.3, 16.9.

Data in agreement with literature reported.[148]

3-Methylnaphthalen-2-ol (216)



2-Methoxy-3-methylnaphthalene (**215**) (1.72 g, 10.0 mmol, 1.00 equiv.) in CH_2Cl_2 (20 mL) was cooled to 0 °C and BBr_3 (1.13 mL, 3.00 g, 12.0 mmol, 1.20 equiv.) was added. The reaction was warmed to room temperature and stirred for 16 hours. Water was added and the phases were separated. The aqueous phase was extracted twice with CH_2Cl_2 and the combined organic layers were washed with water, dried over anhydrous sodium sulfate, filtered and concentrated to give 3-methylnaphthalen-2-ol (**216**) (1.50 g, 95%) as a white solid.

m.p. = 132-133 °C (CH_2Cl_2).

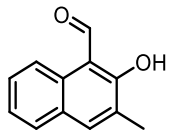
IR (film) ν_{max}/cm^{-1}: 3528, 1629, 1515, 1395, 1381, 1344, 1243, 1192, 1153, 1143, 1094, 889, 867, 842, 745, 669.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.70 (d, *J* = 1.3 Hz, 1H), 7.64 (d, *J* = 1.1 Hz, 1H), 7.61 (s, 1H), 7.38 (ddd, *J* = 8.2, 6.9, 1.4 Hz, 1H), 7.32 (ddd, *J* = 8.1, 6.8, 1.3 Hz, 1H), 7.09 (s, 2H), 5.02 (s, 2H), 2.44 (s, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 152.7, 133.4, 129.4, 129.2, 127.0, 126.4, 125.9, 125.6, 123.6, 109.1, 16.5.

Data in agreement with literature reported.[149]

2-Hydroxy-3-methyl-1-naphthaldehyde (217)



3-methylnaphthalen-2-ol (**216**) (316 mg, 2.00 mmol, 1.00 equiv.) and hexamethylenetetramine (336 mg, 2.40 mmol, 1.20 equiv.) were dissolved in acetic acid (0.6 mL) and heated at 60 °C for 1 hour. The reaction was heated to 90 °C and concentrated H_2SO_4 (0.3 mL) was added. The temperature was raised to 100 °C and heating was continued for 16 hours after which time the reaction was cooled to room temperature. Saturated Na_2CO_3 solution was added and stirring was continued for 10 minutes. The aqueous phase was extracted twice with EtOAc and the combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product which was purified by column chromatography (20% CH_2Cl_2-pentane) to give 2-hydroxy-3-methyl-1-naphthaldehyde (**217**) (148 mg, 40%) as an off-white solid.

m.p. = 65-66 °C (CH_2Cl_2/pentane).

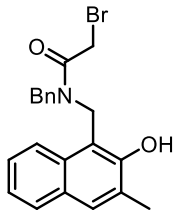
IR (film) ν_{max}/cm^{-1}: 2917, 2901, 2890, 1635, 1619, 1441, 1307, 1260, 1220, 746.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 13.47 (a, 1H), 10.71 (s, 1H), 8.22 (d, *J* = 8.4 Hz, 1H), 7.74 (s, 1H), 7.65 (d, *J* = 8.1 Hz, 1H), 7.47 (ddd, *J* = 8.5, 7.0, 1.4 Hz, 1H), 7.33 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H), 2.32 (d, *J* = 1.1 Hz, 43).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 193.3, 164.6, 138.3, 131.8, 128.7, 128.1, 127.6, 124.4, 118.2, 110.7, 15.8.

Data in agreement with literature reported.[150]

_N_-Benzyl-2-bromo-_N_-((2-hydroxy-3-methylnaphthalen-1-yl)methyl)acetamide (218)



2-Hydroxy-3-methyl-1-naphthaldehyde (**217**) (140 mg, 0.750 mmol, 1.00 equiv.) and benzylamine (98.5 µL, 98.5 mg, 0.900 mmol. 1.20 equiv.) and $MgSO_4$ (375 mg) in CH_2Cl_2 (3.75 mL) were heated under reflux for 16 hours. After cooling to room temperature, the solvent was removed (rotavap) and the crude imine was dissolved in EtOH (1.5 mL) and cooled to 0 °C. $NaBH_4$ (34.6 mg, 0.900 mmol, 1.20 equiv.) was added and the reaction was stirred for 30 minutes. Water was added and the resulting solution was extracted three times with EtOAc, the combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated to give the crude amine (118 mg, 57%) which was used without further purification.

The crude amine (**218**) (83.1 mg, 0.300 mmol, 1.00 equiv.) was dissolved in CH_2Cl_2 and was added followed by bromoacetyl chloride (83.0 µL, 157 mg, 0.500 mmol, 1.00 equiv.) and the reaction was stirred at room temperature for 16 hours. The reaction mixture was transferred to a separating funnel and diluted with additional CH_2Cl_2 and washed three times with water, dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product which was purified by column chromatography eluting with 20% EtOAc-pentane to give _N_-benzyl-2-bromo-_N_-((2-hydroxynaphthalen-1-yl)methyl)acetamide (**218**) (70.0 mg, 38%) as a white solid.

m.p. = 102-104 °C (EtOAc/pentane).

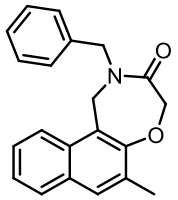
IR (film) ν_{max}/cm^{-1}: 3086, 3065, 3030, 1630, 1617, 1462, 1448, 1408, 1244, 732, 696.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.75 (br. s, 1H), 7.70 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.62 (s, 1H), 7.55–7.45 (m, 2H), 7.45–7.37 (m, 1H), 7.33–7.23 (m, 5H), 5.02 (s, 2H), 4.67 (s, 2H), 3.92 (s, 2H), 2.44 (d, *J* = 1.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.5, 155.0, 134.8, 132.9, 130.4, 129.5, 128.9, 128.7, 128.4, 128.3, 126.2, 126.0, 122.8, 121.2, 111.8, 51.5, 40.5, 25.6, 17.6.

HRMS (ESI$^+$) $C_{21}H_{20}O_2N_1{}^{79}Br$ $[M+Na]^+$ requires 420.0570; found 420.0569, Δ 0.1 ppm.

2-Benzyl-6-methyl-1,2-dihydronaphtho[1,2-f][1,4]oxazepin-3(4H)-one (221)



N-Benzyl-2-bromo-*N*-((2-hydroxy-3-methylnaphthalen-1-yl)methyl)acetamide (**218**) (19.9 mg, 0.0500 mmol, 1.00 equiv.), and *N*-benzylcinchoninium chloride (2.10 mg, 0.00500 mmol, 0.100 equiv.) were dissolved in toluene (2 mL) and saturated aqueous potassium hydroxide solution (21.3 µL) was added. The reaction was stirred at 1000 rpm overnight then quenched by addition of 1 M aqueous HCl solution. The phases were separated and the aqueous phase was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product which was purified by column chromatography (30% EtOAc in pentane) to give 2-benzyl-6-methyl-1,2-dihydronaphtho[1,2-f][1,4]oxazepin-3(4H)-one (**221**) (15.8 mg, 100%) as a white solid.

m.p. = 68-60 °C (EtOAc/pentane).

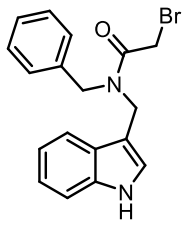
IR (film) ν_{max}/cm^{-1}: 3062, 3029, 2918, 1638, 1454, 1112, 750, 736.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.64 (d, *J* = 8.3 Hz, 1H), 7.57 (s, 1H), 7.34 (ddd, *J* = 8.2, 6.4, 1.6 Hz, 1H), 7.31-7.29 (m, 4H), 7.18–7.14 (m, 1H), 7.13–7.10 (m, 1H), 4.79 (s, 2H), 4.76 (s, 2H), 4.71 (s, 2H), 2.37 (d, *J* = 1.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.4, 155.5, 136.7, 131.1, 130.0, 129.6, 129.3, 128.9, 128.4, 127.9, 127.8, 125.9, 125.2, 124.8, 121.9, 72.2, 51.7, 41.8, 16.3.

HRMS (ESI^+) $C_{21}H_{19}NO_2$ $[M+H]^+$ requires 318.1489; found 318.1490, Δ 0.5 ppm.

N-((1*H*-indol-3-yl)methyl)-*N*-benzyl-2-bromoacetamide (224)



Indole-3-carbaldehyde (1.45 g, 10.0 mmol, 1.00 equiv.) and benzylamine (1.20 mL, 1.18 g, 11.0 mmol, 1.1 equiv.) in CH_2Cl_2 (20 mL) were heated under reflux for 16 hours. The reaction was cooled to room temperature and the solvent was removed under vacuum. The crude imine was dissolved in ethanol (20 mL) and cooled to 0 °C. $NaBH_4$ (378 mg, 10.0 mmol, 1.00 equiv.) was added and the reaction was continued at 0 °C for 1 hour. Water was added and the resulting solution was extracted three times with ethyl acetate, the combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give the crude amine. The crude amine was dissolved in CH_2Cl_2 (20 mL) and the resulting solution was cooled to 0 °C. Saturated $NaHCO_3$ solution (18 mL) was added followed by bromoacetyl bromide (735 µL, 1.22 g, 10.0 mmol, 1.00 equiv.). The reaction was continued at 0 °C for 1 hour then water was added. The phases were separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic layers were washed with

water, dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product which was purified by flash column chromatography eluting with 30% ethyl acetate-pentane to give *N*-((1*H*-Indol-3-yl)methyl)-*N*-benzyl-2-bromoacetamide (**224**) (1.89 g, 53%) as a colourless oil. This compound is rotameric by NMR, major rotamer peaks are reported for ^{1}H NMR and all peaks for ^{13}C NMR.

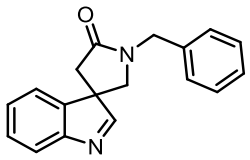
IR (film) ν_{max}/cm^{-1}: 3292, 1634, 1452, 1431, 733, 696, 612.

1H NMR (400 MHz, C_6D_6): (major rotamer peaks) δ = 8.95 (br. s., 1H), 7.88–7.81 (m, 1H), 7.22–7.01 (m, 5H), 6.89–6.74 (m, 2H), 6.70 (d, J = 2.4 Hz, 1H), 4.77 (s, 2H), 4.07 (s, 2H), 3.43 (s, 2H).

13C NMR (101 MHz, C_6D_6) (all peaks) δ = 167.3, 166.9, 165.5, 138.4, 137.8, 137.2, 136.9, 129.1, 128.9, 128.8, 128.4, 128.4, 128.2, 128.0, 127.7, 127.7, 127.6, 126.7, 126.7, 124.8, 122.8, 122.7, 122.7, 120.3, 120.2, 119.8, 118.8, 112.0, 111.7, 111.3, 111.0, 53.4, 50.0, 48.5, 44.0, 43.9, 40.3, 29.0, 27.2, 27.1.

HRMS (ESI$^+$) $C_{18}H_{17}{}^{79}BrN_2O$ $[M+Na]^+$ requires 379.0422; found 379.0416, Δ 0.4 ppm.

1'-Benzylspiro[indole-3,3'-pyrrolidin]-5'-one (225)



N-((1H-Indol-3-yl)methyl)-*N*-benzyl-2-bromoacetamide (179 mg, 0.500 mmol, 1.00 equiv.) was dissolved in toluene (5 mL) and LiHMDS (1M in toluene, 500 µL, 0.500 mmol, 1.00 equiv.) was added. The reaction was stirred at room temperature for 16 hours then quenched with water and diluted with EtOAc. The phases were separated and the aqueous phase was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered

and concentrated to give 1'-Benzylspiro[indole-3,3'-pyrrolidin]-5'-one (**225**) (133 mg, 96%) as a colourless oil.

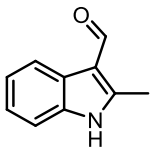
IR (film) ν_{max}/cm^{-1}: 3314, 3290, 3274, 3254, 1692, 1670, 1639, 1453, 740, 699, 664.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.07 (s, 1H), 7.61 (dt, *J* = 7.7, 0.9 Hz, 1H), 7.43–7.17 (m, 7H), 4.63 (d, *J* = 14.5 Hz, 1H), 4.55 (d, *J* = 14.5 Hz, 1H), 3.49 (d, *J* = 7.2 Hz, 1H), 3.38 (d, *J* = 10.2 Hz, 1H), 2.88 (d, *J* = 17.1 Hz, 1H), 2.70 (d, *J* = 17.1 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 173.9, 172.1, 154.5, 140.5, 135.7, 129.0, 128.9, 128.4, 128.1, 127.2, 121.6, 121.1, 55.7, 50.4, 47.1, 36.7.

HRMS (ESI^+) $C_{18}H_{16}N_2O$ $[M+H]^+$ requires 277.1335; found 277.1336, Δ 0.4 ppm.

2-Methyl-1*H*-indole-3-carbaldehyde (229)



DMF (5 mL) was cooled to 0 °C and $POCl_3$ (560 µL, 918 mg, 6.00 mmol, 1.20 equiv.) was added, stirring was continued to 20 minutes. 2-Methylindole (655 mg, 5.00 mmol, 1.00 equiv.) was added and the reaction was heated at 35 °C for 40 minutes then cooled to room temperature. 2M aqueous NaOH solution was added and stirring was continued for 10 minutes. Additional water (ca. 10 mL) was added and the precipitated solid was collected by vacuum filtration, washed three times with water and dried under vacuum to give 2-methyl-1*H*-indole-3-carbaldehyde (**229**) (679 mg, 85%) as an off-white solid.

m.p. = 185-186 °C (H_2O).

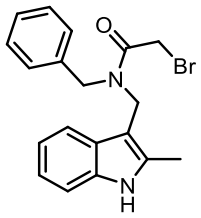
IR (film) ν_{max}/cm^{-1}: 3450 (br.), 1640, 1550, 1475, 1423, 1251.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 10.23 (s, 1H), 8.63 (s, 1H), 8.27 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.37–7.35 (m, 1H), 7.31–7.24 (m, 3H), 2.77 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 184.6, 146.5, 134.9, 126.1, 123.5, 122.8, 120.9, 114.8, 110.6, 12.3).

HRMS (ESI^+) $C_{10}H_9ON$ $[M+H]^+$ requires 160.0757; found 160.0757, Δ 0.1 ppm.

N-Benzyl-2-bromo-*N*-((2-methyl-1*H*-indol-3-yl)methyl)acetamide (230)



2-Methyl-1*H*-indole-3-carbaldehyde (636 mg, 4.00 mmol, 1.00 equiv.) was dissolved in CH_2Cl_2 (8 mL). Benzylamine (436 µL, 428 mg, 4.00 mmol, 1.00 equiv.) and anhydrous magnesium sulfate (2 g) were added. The reaction was stirred under reflux for 16 hours and after cooling to room temperature the solvent was removed *in vacuo*. Methanol (8 mL) was added and the solution was cooled to 0 °C. $NaBH_4$ (227 mg, 6.00 mmol, 1.50 equiv.) was added and stirring was continued for 1 hour. The reaction mixture was quenched with water and extracted 3 times with CH_2Cl_2. The combined organic layers were washed with water, dried over anhydrous sodium sulfate, filtered and concentrated. CH_2Cl_2 (8 mL) and saturated aqueous K_2CO_3 solution (5.5 mL) was added. Bromoacetyl chloride (364 µL, 691 mg, 4.40 mmol, 1.10 equiv.) was added and the reaction was stirred at 1000 rpm for 1 hour. The reaction mixture was diluted with CH_2Cl_2, washed 3 times with water, dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product which was purified by flash chromatography (30% EtOAc-pentane) to afford *N*-benzyl-2-bromo-*N*-((2-methyl-1*H*-indol-3-yl)methyl)acetamide (**230**) (670 mg, 45%) as a white solid. This compound is rotameric by NMR, rotamer peaks are reported separately.

m.p. = 97-98 °C (EtOAc/pentane).

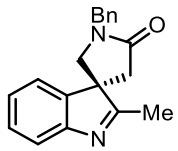
IR (film) ν_{max}/cm^{-1}: 3363, 3338, 3244, 1685, 1458, 1436, 1245, 749, 732.

^{1}H NMR (400 MHz, $CDCl_3$) Major rotamer: δ = 8.13 (s, 1H), 7.50 (d, *J* = 7.7 Hz, 1H), 7.38 (m, 2H), 7.32 (m, 2H), 7.20–7.06 (m, 4H), 4.86 (s, 2H), 4.46 (s, 2H), 3.93 (s, 2H), 2.23 (s, 3H). Minor rotamer: δ = 8.24 (s, 1H), 7.42–7.27 (m, 4H), 7.22–7.03 (m, 5H), 4.67 (s, 2H), 4.58 (s, 2H), 4.21 (s, 2H), 2.14 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) Major rotamer: δ = 167.2, 136.3, 135.2, 134.6, 129.0, 127.8, 127.7, 126.1, 121.6, 119.9, 118.5, 110.3, 106.4, 49.4, 38.6, 27.0, 11.5. Minor rotamer: δ = 167.2, 137.0, 135.3, 133.7, 128.9, 128.5, 128.4, 127.3, 121.7, 120.1, 117.9, 110.7, 105.0, 47.0, 43.1, 27.0.

HRMS (ESI$^+$) $C_{19}H_{19}BrN_2O$ $[M+Na]^+$ requires 393.0573; found 393.0574, Δ 0.3 ppm.

1'-Benzyl-2-methylspiro[indole-3,3'-pyrrolidin]-5'-one (231)



This compound was unstable to purification on silica. An analytically pure sample was obtained for the racemic reaction using LiHMDS in THF for characterisation. The yield for the enantioselective reaction was obtained by quantitative ^{1}H NMR analysis of the crude reaction mixture using dibromomethane (3.46 µL, 0.05 mmol) as an internal standard.

Racemic reaction:

N-benzyl-2-bromo-*N*-((2-methyl-1*H*-indol-3-yl)methyl)acetamide (**230)** (37.1 mg, 0.100 mmol, 1.00 equiv.) was dissolved in THF (4 mL) and NaH (4.0 mg, 0.110 mmol, 1.10 equiv.) was added. The reaction was stirred at room temperature for 16 hours then quenched with water and diluted with

EtOAc. The phases were separated and the aqueous phase was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give 1'-benzyl-2-methylspiro[indole-3,3'-pyrrolidin]-5'-one (**231**) (26.8 mg, 92%) as a colourless oil.

IR (film) ν_{max}/cm^{-1}: 2980, 2967, 2957, 2930, 2918, 1678, 1422, 1254, 784, 754, 743, 700, 669.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.49 (dt, *J* = 7.7, 0.9 Hz, 1H), 7.39–7.27 (m, 6H), 7.19 (td, *J* = 7.4, 1.1 Hz, 1H), 4.70 (d, *J* = 14.3 Hz, 1H), 4.45 (d, *J* = 14.4 Hz, 1H), 3.45 (d, *J* = 10.3 Hz, 1H), 3.32 (d, *J* = 10.4 Hz, 1H), 2.78 (dd, *J* = 17.4, 0.7 Hz, 1H), 2.67 (d, *J* = 17.4 Hz, 1H), 2.16 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 182.8, 172.0, 154.1, 141.6, 135.5, 129.0, 128.8, 128.7, 128.2, 126.1, 121.2, 120.3, 55.3, 52.0, 47.1, 38.6, 15.7.

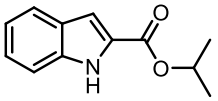
HRMS (ESI^+) $C_{19}H_{18}N_2O$ $[M+H]^+$ requires 291.1492; found 291.1491, Δ 0.3 ppm.

Enantioselective reaction:

N-Benzyl-2-bromo-*N*-((2-methyl-1*H*-indol-3-yl)methyl)acetamide (**230**) (37.1 mg, 0.100 mmol, 1.00 equiv.) and *N*-benzylcinchonidinium chloride (4.2 mg, 0.0100 mmol, 0.100 equiv.) were dissolved in CH_2Cl_2 (4 mL). Saturated potassium hydroxide solution (56.1 µL) was added and the reaction was stirred (1000 rpm) at room temperature for 16 hours. Water was added and the phases were separated. The aqueous phase was extracted twice with EtOAc and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated to give the crude product. The crude product was dissolved in $CDCl_3$ (1.0 mL) and dibromomethane (3.46 µL, 0.05 mmol) was added. The product yield was determined by quantitative ^{1}H NMR analysis to be 88% with no starting material remaining.

Chiral HPLC: (Chiralpak ADH, 25% ^{i}PrOH, 75% hexane, 1.0 mL min^{-1}, λ = 290 nm) τ_R (major) = 8.9 min, τ_R (minor) = 7.9 min.

Isopropyl 1*H*-indole-2-carboxylate (253)



1*H*-indole-2-carboxylic acid (483 mg, 3.00 mmol, 1.00 equiv.) was dissolved in DMF (3 mL) and $NaHCO_3$ (1.26 g, 15.0 mmol, 5 equiv.) was added followed by 2-iodopropane (360 µL, 612 mg, 3.60 mmol, 1.200 equiv.) and the reaction was heated to 45 °C and stirred for 16 hours. Water was added and the resulting precipitate was collected by vacuum filtration to give isopropyl 1*H*-indole-2-carboxylate (**253**) (210 mg, 35%) as a white solid

m.p. = 102-103 °C (H_2O).

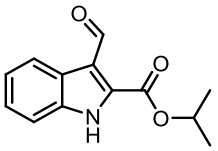
IR (film) ν_{max}/cm^{-1}: 3309, 2981, 1689, 1526, 1308, 1255, 1205, 1106, 772, 745.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.94 (s, 1H), 7.71 (d, *J* = 8.1 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.34 (dd, *J* = 9.0, 6.3 Hz, 1H), 7.25 (s), 7.18 (app. t, *J* = 7.3 Hz, 1H), 5.32 (hept, *J* = 6.3 Hz, 1H), 1.42 (d, *J* = 6.3 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 161.5, 136.7, 127.9, 127.5, 125.3, 122.6, 120.7, 111.8, 108.5, 68.6, 22.0.

HRMS (ESI$^+$) $C_{12}H_{13}NO_2$ $[M+H]^+$ requires 204.1019; found 214.1021, Δ 1.1 ppm.

Isopropyl 3-formyl-1*H*-indole-2-carboxylate (254)



$POCl_3$ (111 µL, 184 mg, 1.20 mmol, 1.20 equiv.) was added to DMF (1 mL) at 0 °C and stirred for 20 minutes. Isopropyl 1*H*-indole-2-carboxylate (**253**) (203 mg, 1.00 mmol, 1.00 equiv.) was added and the reaction was heated to 60 °C for 3 hours. 1M sodium hydroxide solution was added and the resultingly suspension was stirred for 30 minutes. The precipitate was collected by vacuum filtration and washed with water to give isopropyl 3-formyl-1*H*-indole-2-carboxylate (**254**) (185 mg, 80%) as a white solid.

m.p. = 195-196 °C (H_2O).

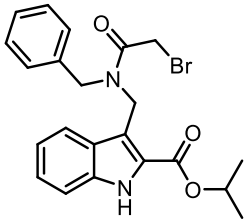
IR (film) ν_{max}/cm^{-1}: 3317, 3145, 3012, 1721, 1692, 1454, 1435, 1252, 1201, 974, 739.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 10.79 (s, 1H), 9.37 (s, 1H), 8.51 (d, *J* = 8.1 Hz, 1H), 7.51–7.48 (m, 1H), 7.45 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.38 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 4.56 (hept., *J* = 7.1 Hz), 1.51 (t, *J* = 7.1 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 188.3, 160.6, 135.0, 131.8, 126.7, 125.5, 124.0, 123.9, 119.6, 111.8, 62.4, 14.3.

HRMS (ESI^+) $C_{13}H_{13}NO_3$ $[M+Na]^+$ requires 254.0789; found 254.0788, Δ 0.4 ppm.

Isopropyl 3-((*N*-benzyl-2-bromoacetamido)methyl)-1*H*-indole-2-carboxylate (255)



Isopropyl 3-formyl-1*H*-indole-2-carboxylate (**254**) (139 mg, 0.600 mmol, 1.00 equiv.) was dissolved in CH_2Cl_2 (1.2 mL). Benzylamine (65.0 µL, 64.2 mg, 0.600 mmol, 1.00 equiv.) and anhydrous magnesium sulfate (300 mg) were added. The reaction was stirred under reflux for 16 hours and after cooling to room temperature the solvent was removed *in vacuo*. Methanol (1.2 mL) was added and the solution was cooled to 0 °C. $NaBH_4$ (34 mg, 0.900 mmol, 1.50 equiv.) was added and stirring was continued for 1 hour. The reaction mixture was quenched with water and extracted 3 times with CH_2Cl_2. The combined organic layers were washed with water, dried over anhydrous sodium sulfate, filtered and concentrated. CH_2Cl_2 (1.2 mL) and saturated aqueous K_2CO_3 solution (1 mL) was added. Bromoacetyl chloride (54.5 µL, 204 mg, 0.66 mmol, 1.10 equiv.) was added and the reaction was stirred at 1000 rpm for 1 hour. The reaction mixture was diluted with CH_2Cl_2, washed 3 times with water, dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product which was purified by flash chromatography (30% EtOAc-pentane) to afford isopropyl 3-((*N*-benzyl-2-bromoacetamido)methyl)-1*H*-indole-2-carboxylate (**255**) (183mg, 70%) as a white solid.

m.p. = 85-86 °C (EtOAc-pentane).

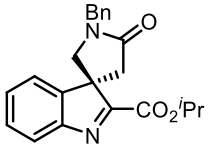
IR (film) ν_{max}/cm^{-1}: 3322, 3273, 2981, 1699, 1638, 1450, 1248, 1094,745, 732.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.84 (s, 1H), 7.80 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.45–7.03 (m, 6H), 7.02–6.95 (m, 2H), 5.04 (sept., *J* = 6.4 Hz, 1H), 4.45 (s, 2H), 3.75 (s, 2H), 1.03 (d, *J* = 6.3 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.4, 161.6, 136.7, 135.8, 129.0, 128.4, 127.6, 127.5, 126.1, 125.6, 122.3, 121.1, 117.4, 111.6, 69.2, 49.6, 39.5, 26.9, 21.6.

HRMS (ESI^+) $C_{22}H_{23}{}^{79}BrN_2O_3$ $[M+Na]^+$ requires 465.0784; found 465.0784, Δ 0.1 ppm.

Isopropyl (*S*)-1'-benzyl-5'-oxospiro[indole-3,3'-pyrrolidine]-2-carboxylate (256)



This compound was unstable to purification on silica. An analytically pure sample was obtained for the racemic reaction using NaH in THF for characterisation. The yield for the enantioselective reaction was obtained by quantitative ^1H NMR analysis of the crude reaction mixture using dibromomethane (3.46 µL, 0.05 mmol) as an internal standard.

Racemic reaction:

Isopropyl 3-((*N*-benzyl-2-bromoacetamido)methyl)-1*H*-indole-2-carboxylate (**255)** (44.3 mg, 0.100 mmol, 1.00 equiv.) was dissolved in THF (4 mL) and NaH (4.0 mg, 0.110 mmol, 1.10 equiv.) was added. The reaction was stirred at room temperature for 16 hours then quenched with water and diluted with EtOAc. The phases were separated and the aqueous phase was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give (**256**) (28.9 mg, 80%) as an off-white solid.

m.p. = 68-70 °C (EtOAc).

IR (film) ν_{max}/cm^{-1}: 2981, 2968, 1700, 1689, 1665, 1650, 1255, 1127, 1095, 1029, 744, 699.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.80 (dd, *J* = 7.7, 0.8 Hz, 1H), 7.40 (td, *J* = 7.5, 1.5 Hz, 1H), 7.38–7.27 (m, 8H), 5.29 (hept, *J* = 6.3 Hz, 1H), 4.72 (d, *J* = 14.6 Hz, 1H), 4.52 (d, *J* = 14.5 Hz, 1H), 3.93 (d, *J* = 9.7 Hz, 1H), 3.35 (d, *J* = 16.9 Hz, 1H), 3.22 (d, *J* = 9.7 Hz, 1H), 2.57 (d, *J* = 16.9 Hz, 1H), 1.37 (t, *J* = 6.6 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.1, 171.0, 160.7, 152.0, 145.3, 135.7, 129.5, 129.1, 128.8, 128.4, 127.9, 123.9, 120.9, 70.5, 55.2, 51.9, 47.2, 38.5, 29.7, 21.7 (d, *J* = 1.6 Hz).

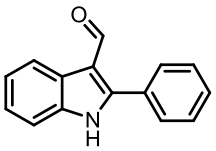
HRMS (ESI$^+$) $C_{22}H_{22}N_2O_3$ $[M+H]^+$ requires 363.1703; found 363.1702, Δ 0.3 ppm.

Enantioselective reaction:

Isopropyl 3-((*N*-benzyl-2-bromoacetamido)methyl)-1*H*-indole-2-carboxylate (**255**) (44.3 mg, 0.100 mmol, 1.00 equiv.) and *N*-benzylcinchonidinium chloride (4.2 mg, 0.0100 mmol, 0.100 equiv.) were dissolved in toluene (2.8 mL) and CH_2Cl_2 (1.2 mL). The reaction was cooled to 0 °C, saturated potassium hydroxide solution (56.1 µL) was added and the reaction was stirred (1000 rpm) at room temperature for 16 hours. Water was added and the phases were separated. The aqueous phase was extracted twice with EtOAc and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated to give the crude product. The crude product was dissolved in $CDCl_3$ (1.0 mL) and dibromomethane (3.46 µL, 0.05 mmol) was added. The product yield was determined by quantitative ^{1}H NMR analysis to be 55%.

Chiral HPLC: (Chiralpak ADH, 20% ^{i}PrOH, 80% hexane, 1.0 mL min^{-1}, λ = 290 nm) τ_R (major) = 14.3 min, τ_R (minor) = 12.3 min.

2-Phenyl-1*H*-indole-3-carbaldehyde (275)



DMF (5 mL) was cooled to 0 °C and $POCl_3$ (556 µL, 918 mg, 6.00 mmol, 1.20 equiv.) was added, stirring was continued to 20 minutes. 2-Phenylindole (965 mg, 5.00 mmol, 1.00 equiv.) was added and the reaction was heated at 60 °C for 3 hours then cooled to room temperature. 2M aqueous NaOH solution was added and stirring was continued for 30 minutes. Additional water (ca. 10 mL) was added and the precipitated solid was collected by vacuum filtration, washed three times with water and dried under vacuum to give 2-phenyl-1*H*-indole-3-carbaldehyde (**275**) (963 mg, 87%) as an off-white solid.

m.p. >250 °C (H_2O).

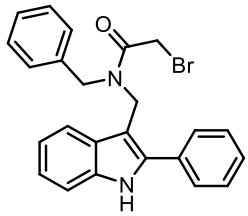
IR (film) ν_{max}/cm^{-1}: 3338, 1685, 1630, 1454, 1438, 1373, 1245, 742, 696.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 12.40 (s, 1H), 9.97 (s, 1H), 8.22 (d, *J* = 7.0 Hz, 1H), 7.81–7.74 (m, 2H), 7.64–7.56 (m, 3H), 7.51 (d, *J* = 7.3 Hz, 1H), 7.30 (td, *J* = 7.6, 1.5 Hz, 1H), 7.25 (td, *J* = 7.4, 1.3 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 186.0, 149.6, 136.4, 130.4, 130.3, 130.3, 129.4, 126.2, 124.2, 122.9, 121.5, 114.0, 112.5.

HRMS (ESI^+) $C_{15}H_{11}NO$ $[M+H]^+$ requires 222.0913; found 222.0915, Δ 0.5 ppm.

N-Benzyl-2-bromo-*N*-((2-phenyl-1*H*-indol-3-yl)methyl)acetamide (276)



2-Phenyl-1*H*-indole-3-carbaldehyde (**275**) (884 mg, 4.00 mmol, 1.00 equiv.) was dissolved in CH_2Cl_2 (1.2 mL). Benzylamine (436 µL, 428 mg, 4.00 mmol, 1.00 equiv.) and anhydrous magnesium sulfate (2 g) were added. The reaction was stirred under reflux for 16 hours and after cooling to room temperature the solvent was removed *in vacuo*. Methanol (8 mL) was added and the solution was cooled to 0 °C. $NaBH_4$ (227 mg, 6.00 mmol, 1.50 equiv.) was added and stirring was continued for 1 hour. The reaction mixture was quenched with water and extracted 3 times with CH_2Cl_2. The combined organic layers were washed with water, dried over anhydrous sodium sulfate, filtered and concentrated. CH_2Cl_2 (8 mL) and saturated aqueous K_2CO_3 solution (5.5 mL) was added. Bromoacetyl chloride (364 µL, 691 mg, 4.40 mmol, 1.10 equiv.) was added and the reaction was stirred at 1000 rpm for 1 hour. The reaction mixture was diluted with CH_2Cl_2, washed 3 times with water, dried over

anhydrous sodium sulfate, filtered and concentrated to give the crude product which was purified by flash chromatography (30% EtOAc-pentane) to afford isopropyl *N*-benzyl-2-bromo-*N*-((2-phenyl-1*H*-indol-3-yl)methyl)acetamide (**276**) (930 mg, 51%) as a white solid.

m.p. = 60-62 °C (CH_2Cl_2/petroleum ether 40-60).

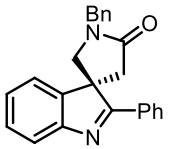
IR (film) ν_{max}/cm^{-1}: 3282, 3275, 3268, 3259, 1631, 1450, 739, 696.

^{1}H NMR (400 MHz, C_6D_6) δ = 8.02 (d, *J* = 7.4 Hz, 1H), 7.94 (s, 1H), 7.25 (d, *J* = 3.7 Hz, 2H), 7.10–7.01 (m, 5H), 6.99–6.84 (m, 5H), 6.53 (d, *J* = 7.1 Hz, 2H), 5.05 (s, 2H), 3.98 (s, 2H), 3.42 (s, 2H).

^{13}C NMR (101 MHz, C_6D_6) δ = 166.4, 137.5, 136.3, 136.2, 132.2, 128.5, 128.5, 128.4, 126.9, 126.0, 122.8, 120.5, 120.3, 119.1, 111.4, 111.0, 107.6, 48.9, 38.6, 26.7.

HRMS (ESI$^+$) $C_{24}H_{21}{}^{79}BrN_2O$ $[M+Na]^+$ requires 455.0729; found 455.0728, Δ 0.3 ppm.

1'-Benzyl-2-phenylspiro[indole-3,3'-pyrrolidin]-5'-one (278)



This compound was unstable to purification on silica. An analytically pure sample was obtained for the racemic reaction using NaH in THF for characterisation. The yield for the enantioselective reaction was obtained by quantitative ^{1}H NMR analysis of the crude reaction mixture using dibromomethane (3.46 µL, 0.05 mmol) as an internal standard.

Racemic reaction:

N-Benzyl-2-bromo-*N*-((2-phenyl-1*H*-indol-3-yl)methyl)acetamide (**276)** (43.3 mg, 0.100 mmol, 1.00 equiv.) was dissolved in THF (4 mL) and NaH (4.0 mg, 0.110 mmol, 1.10 equiv.) was added. The

reaction was stirred at room temperature for 16 hours then quenched with water and diluted with EtOAc. The phases were separated and the aqueous phase was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give (**278**) (31.6 mg, 90%) as an off-white solid.

m.p. = 120-122 °C (EtOAc).

IR (film) ν_{max}/cm^{-1}: 2918, 1678, 1443, 757, 700.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.81–7.69 (m, 2H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.44–7.36 (m, 1H), 7.35–7.26 (m, 7H), 7.25–7.15 (m, 3H), 4.71 (d, *J* = 14.3 Hz, 1H), 4.49 (d, *J* = 14.3 Hz, 1H), 3.76 (d, *J* = 10.6 Hz, 1H), 3.43 (d, *J* = 10.7 Hz, 1H), 3.30–2.91 (d, *J* = 22.9 Hz, 1H), 2.91–2.68 (d, *J* = 22.9 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 178.9, 172.1, 153.2, 146.3, 135.5, 131.4, 130.9, 129.1, 129.0, 128.7, 128.6, 128.2, 127.8, 127.0, 121.1, 120.3, 54.0, 53.1, 47.3, 40.7.

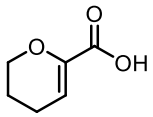
HRMS (ESI^+) $C_{24}H_{20}N_2O$ $[M+H]^+$ requires 353.1648; found 353.1649, Δ 0.3 ppm.

Enantioselective reaction:

N-Benzyl-2-bromo-*N*-((2-phenyl-1*H*-indol-3-yl)methyl)acetamide (**278**) (43.3 mg, 0.100 mmol, 1.00 equiv.) and *N*-benzylcinchonidinium chloride (4.2 mg, 0.0100 mmol, 0.100 equiv.) were dissolved in toluene (2.8 mL) and CH_2Cl_2 (1.2 mL). Saturated potassium hydroxide solution (56.1 µL) was added and the reaction was stirred (1000 rpm) at room temperature for 16 hours. Water was added and the phases were separated. The aqueous phase was extracted twice with EtOAc and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated to give the crude product. The crude product was dissolved in $CDCl_3$ (1.0 mL) and dibromomethane (3.46 µL, 0.05 mmol) was added. The product yield was determined by quantitative ^{1}H NMR analysis to be 90%.

Chiral HPLC: (Chiralpak ODH, 20% ^{i}PrOH, 80% hexane, 1.0 mL min^{-1}, λ = 290 nm) τ_R (major) = 14.4 min, τ_R (minor) = 12.0 min.

3,4-Dihydro-2H-pyran-6-carboxylic acid (343)



^{n}BuLi (2.5 M in hexane, 20 mL, 50.0 mmol, 1.00 equiv.) was cooled to 0 °C and dihydropyran (1.00 equiv.) was added. TMEDA (7.48 mL, 5.80 g, 50.0 mmol, 1.00 equiv.) was added and the reaction was warmed to room temperature and stirred for 2 hours. THF (50 mL) was added and the reaction was cooled to −78 °C. Powdered dry ice (~10 g) was added and the reaction was allowed to warm to room temperature and stirred for 3 hours. Et_2O was added and the resulting solution was extracted three times with water. The combined aqueous layers were acidified with 37% hydrochloric acid and extracted three times with EtOAc. The combined EtOAc extracts were washed with water, and concentrated to give 3,4-dihydro-2*H*-pyran-6-carboxylic acid (**343**) (4.14 g, 65%) as a waxy solid.

m.p. = 40-43 °C (EtOAc).

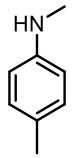
IR (film) ν_{max}/cm^{-1}: broad signal 3467-3039, 2937, 2882, 1703, 1644, 1263, 1218, 1188, 1120, 1080, 1068, 1046, 919, 760, 702.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.36 (br. s, 1H), 6.22 (t, *J* = 4.2 Hz, 1H), 4.19–4.02 (m, 2H), 2.31–2.15 (m, 2H), 1.93–1.79 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.6, 143.5, 113.9, 66.9, 21.4, 20.8.

HRMS (ESI$^+$) $C_6H_8O_3$ $[M+Na]^+$ requires 151.0366; found 151.0366, Δ 0.4 ppm.

N,4-Dimethylaniline (345)



4-Methylaniline (1.07 g, 10.0 mmol, 1.00 equiv.) was dissolved in THF (20 mL) and cooled to −78 °C. ^{n}BuLi (2.5 M in hexane, 4.00 mL, 10.0 mmol, 1.00 equiv.) was added and the reaction was stirred at −78 °C for 30 minutes. Iodomethane (623 µL, 1.42 g, 10.0 mmol, 1.00 equiv.) was added and the reaction was warmed to room temperature and stirred for 3 hours. Water was added and the reaction mixture was transferred to a separating funnel and extracted three times with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated to give the crude product which was purified by flash column chromatography eluting with 3% Et_2O-pentane to give *N*,4-dimethylaniline (**345**) (486 mg, 41%) as a colourless oil.

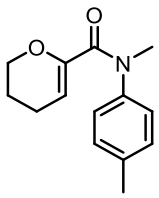
IR (film) ν_{max}/cm^{-1}: 3409, 2980, 2918, 1616, 1519, 1315, 1259, 806.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.25 (d, *J* = 0.7 Hz, 2H), 6.79 (d, *J* = 8.4 Hz, 1H), 3.06 (s, 3H), 2.49 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 147.3, 129.8, 126.6, 112.8, 31.2, 20.5.

HRMS (ESI$^+$) $C_8H_{11}N$ $[M+H]^+$ requires 122.0964; found 122.0965, Δ 0.4 ppm.

N-Methyl-*N*-(p-tolyl)-3,4-dihydro-2*H*-pyran-6-carboxamide (346)



Prepared following **general procedure C** using *N,*4-dimethylaniline (**345**) (532 mg, 4.40 mmol, 1.10 equiv.) and 3,4-dihydro-2*H*-pyran-6-carboxylic acid (**343**) (512 mg, 4.00 mmol, 1.00 equiv.). Column chromatography eluting with 20% EtOAc-pentane afforded *N*-methyl-*N*-(p-tolyl)-3,4-dihydro-2H-pyran-6-carboxamide (**346**) (693 mg, 75%) as a white solid.

m.p. = 46-48 °C (EtOAc-pentane).

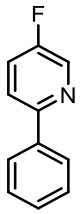
IR (film) ν_{max}/cm^{-1}: 2977, 2931, 1633, 1511, 1366, 1053, 917, 826, 748.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.16–7.10 (m, 2H), 7.08–7.01 (m, 2H), 5.34 (t, *J* = 4.0 Hz, 1H), 3.57–3.50 (m, 3H), 3.29 (s, 3H), 2.34 (s, 3H), 2.02–1.93 (m, 3H), 1.68–1.59 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.1, 148.5, 142.4, 136.2, 129.4, 125.4, 106.6, 65.7, 38.0, 21.6, 21.0, 20.0.

HRMS (ESI^+) $C_{14}H_{17}NO_2$ $[M+H]^+$ requires 232.1332; found 232.1332, Δ 0.2 ppm.

5-Fluoro-2-phenylpyridine (356)



2-Bromo-5-fluoropyridine (440 mg, 2.50 mmol, 1.00 equiv.), phenylboronic acid (266 mg, 3.00 mmol, 1.20 equiv.), $Pd(OAc)_2$ (14.0 mg, 0.0625 mmol, 0.0250 equiv.), PPh_3 (65.5 mg, 0.0250 mmol, 0.100 equiv.) and K_2CO_3 (931 mg, 6.75 mmol, 2.70 equiv.) were dissolved in dimethoxyethane (2.5 ml) and water (3.3 mL). The resulting mixture was sparged with argon for 15 minutes then heated under reflux for 16 hours. Upon cooling to room temperature, the reaction mixture was transferred to a separating funnel, diluted with water and extracted three times with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and

concentrated to give the crude product which was purified by column chromatography eluting with 5% CH_2Cl_2-pentane to give 5-fluoro-2-phenylpyridine (**356**) (303 mg, 70%) as a white solid.

m.p. = 38-40 °C (CH_2Cl_2/pentane).

IR (film) ν_{max}/cm^{-1}: 2980, 1465, 1445, 1376, 1221, 1185, 1123, 1010, 833, 773, 727, 686.

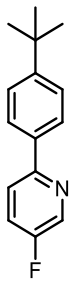
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.55 (d, *J* = 2.9 Hz, 1H), 7.98–7.88 (m, 2H), 7.72 (ddd, *J* = 8.8, 4.3, 0.6 Hz, 1H), 7.55–7.39 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 159.0 (d, *J* = 256.1 Hz), 153.9 (d, *J* = 3.7 Hz), 138.6, 137.9 (d, *J* = 23.6 Hz), 129.0, 128.9, 126.9, 123.6 (d, *J* = 18.4 Hz), 121.4 (d, *J* = 4.3 Hz).

^{19}F NMR (377 MHz, $CDCl_3$) δ = −129.9.

HRMS (ESI^+) $C_{11}H_8FN$ $[M+H]^+$ requires 174.0714; found 174.0714, Δ 0.2 ppm.

2-(4-(Tert-butyl)phenyl)-5-fluoropyridine (357)



2-Bromo-5-fluoropyridine (880 mg, 5.00 mmol, 1.00 equiv.), 4-tert-butylphenylboronic acid (1.07 g, 6.00 mmol, 1.20 equiv.), $Pd(OAc)_2$ (28.0 mg, 0.125 mmol, 0.0250 equiv.), PPh_3 (131 mg, 0.0500 mmol, 0.100 equiv.) and K_2CO_3 (1.86 g, 13.5 mmol, 2.70 equiv.) were dissolved in dimethoxyethane (5 ml) and water (6.6 mL). The resulting mixture was sparged with argon for 15 minutes then heated under reflux for 16 hours. Upon cooling to room temperature, the reaction mixture was transferred to a separating funnel, diluted with water and extracted three times with EtOAc. The combined

organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product which was purified by column chromatography eluting with 3% EtOAc-pentane to give 2-(4-(tert-butyl)phenyl)-5-fluoropyridine (**357**) (949 mg, 83%) as a white solid.

m.p. = 64-66 °C (EtOAc-pentane).

IR (film) ν_{max}/cm^{-1}: 2963, 1470, 1260, 1224, 823, 729.

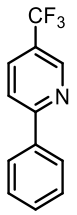
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.53 (d, *J* = 2.9 Hz, 1H), 7.90–7.84 (m, 2H), 7.70 (ddd, *J* = 8.8, 4.3, 0.6 Hz, 1H), 7.52–7.48 (m, 2H), 7.45 (ddd, *J* = 8.7, 8.1, 2.9 Hz, 1H), 1.36 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 158.8 (d, *J* = 255.6 Hz), 153.9, 153.9, 137.8 (d, *J* = 23.6 Hz), 135.7, 126.6, 125.9, 123.6 (d, *J* = 18.4 Hz), 121.2 (d, *J* = 4.1 Hz), 34.8, 31.4.

^{19}F NMR (377 MHz, $CDCl_3$) δ = 130.3 (dd, *J* = 8.1, 4.4 Hz).

HRMS (ESI^+) $C_{16}H_{16}F_3N$ $[M+H]^+$ requires 230.1340; found 230.1340, Δ 0.3 ppm.

2-Phenyl-5-(trifluoromethyl)pyridine (358)



2-Bromo-5-trifluoromethylpyridine (2.26 g, 10.0 mmol, 1.00 equiv.), phenylboronic acid (1.46 g, 12.0 mmol, 1.20 equiv.), $Pd(OAc)_2$ (56.0 mg, 0.250 mmol, 0.0250 equiv.), PPh_3 (262 mg, 0.100 mmol, 0.100 equiv.) and K_2CO_3 (3.73 g, 13.5 mmol, 2.70 equiv.) were dissolved in dimethoxyethane (10 ml) and water (13.5 mL). The resulting mixture was sparged with argon for 15 minutes then heated

under reflux for 16 hours. Upon cooling to room temperature, the reaction mixture was transferred to a separating funnel, diluted with water and extracted three times with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product which was purified by column chromatography eluting with 5% EtOAc-pentane then recrystallization from hexane to give 2-phenyl-5-(trifluoromethyl)pyridine (**358**) (949 mg, 36%) as a white needles.

m.p. = 60-62 °C (hexane).

IR (film) ν_{max}/cm^{-1}: 2980, 1598, 1388, 1330, 1293, 1241, 1085, 974, 955, 940, 739, 692, 652, 641.

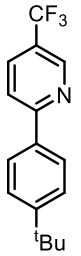
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.99–8.89 (m, 1H), 8.07–8.01 (m, 2H), 7.98 (dd, *J* = 8.3, 0.7 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.55–7.45 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 160.7, 146.6 (q, *J* = 4.1 Hz), 138.0, 133.9 (q, *J* = 3.5 Hz), 130.1, 129.0, 127.3, 124.8 (q, *J* = 33.1 Hz), 123.8 (q, *J* = 272.2 Hz), 120.0.

^{19}F NMR (377 MHz, $CDCl_3$) δ = −62.2.

HRMS (ESI^+) $C_{12}H_8F_3N$ $[M+H]^+$ requires 224.0682; found 224.0682, Δ 0.1 ppm.

2-(4-(Tert-butyl)phenyl)-5-(trifluoromethyl)pyridine (PS358)



2-Chloro-5-trifluoromethylpyridine (908 mg, 5.0 mmol, 1.00 equiv.), (4-(tert-butyl)phenyl)boronic acid (1.07 g, 6.0 mmol, 1.20 equiv.), Pd(OAc)2 (28.0 mg, 0.125 mmol, 0.0250 equiv.), PPh_3 (131 mg, 0.050 mmol, 0.100 equiv.) and K_2CO_3 (1.87 g, 6.75 mmol, 2.70 equiv.) were dissolved in

dimethoxyethane (5 ml) and water (6.75 mL). The resulting mixture was sparged with argon for 15 minutes then heated under reflux for 16 hours. Upon cooling to room temperature, the reaction mixture was transferred to a separating funnel, diluted with water and extracted three times with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product which was purified by column chromatography eluting with 5% EtOAc-pentane to give 2-(4-(tert-butyl)phenyl)-5-(trifluoromethyl)pyridine (**PS358**) (1.23 g, 88%) as a white crystalline solid.

m.p. = 64-66°C (EtOAc-pentane).

IR (film) ν_{max}/cm^{-1}: 2917, 2849, 1601, 1326, 1163, 1122, 1084, 1012, 831.

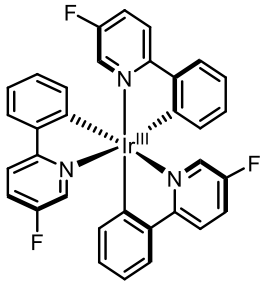
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.97 – 8.91 (m, 1H), 8.00 – 7.92 (m, 3H), 7.83 (dt, J = 8.4, 0.8 Hz, 1H), 7.58 – 7.50 (m, 2H), 1.46 – 1.29 (m, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 160.7, 153.5, 146.5 (q, J = 4.1 Hz), 135.2, 133.8 (q, J = 3.5 Hz), 127.0, 126.0, 124.5 (q, J = 32.9 Hz), 123.9 (q, J = 272.1 Hz), 119.6, 34.8, 31.2.

^{19}F NMR (377 MHz, $CDCl_3$) δ = -62.2.

HRMS (ESI^+) $C_{16}H_{16}F_3N$ $[M+H]^+$ requires 280.1308; found 280.1309, Δ 0.6 ppm.

Ir(5-Fppy)$_3$ (364)



$IrCl_3$ (450 mg, 1.50 mmol, 1.00 equiv.) and 5-fluoro-2-phenylpyridine (**356**) (585 mg, 3.39 mmol, 2.26 equiv.) in methoxyethanol-water (20/10 mL) were heated under reflux for 16 hours then cooled to

room temperature. The resulting precipitate was collected by vacuum filtration and washed with water to give the chloride dimer (**360**) (670 mg, 61%) as a yellow solid.

The chloride dimer (**360**) (22.8 mg, 0.0200 mmol, 1.00 equiv.), AgOTf (15.4 mg, 0.0600 mmol, 3.00 equiv.) and 5-fluoro-2-phenylpyridine (173 mg, 1.00 mmol, 50.0 equiv.) were added to a 10 mL reaction vial. The vial was sealed and evacuated and backfilled with argon three times. The reaction was heated to 160 °C for 16 h then cooled to room temperature. The reaction mixture was diluted with CH_2Cl_2 and purified directly by flash column chromatography eluting with 70% CH_2Cl_2-pentane to give Ir(5-Fppy)$_3$ (**364**) (25.7 mg, 91%) as a yellow solid.

m.p. > 250 °C (CH_2Cl_2/pentane).

IR (film) ν_{max}/cm^{-1}: 3041, 1477, 1442, 1431, 1260, 1230, 831, 774, 736, 722.

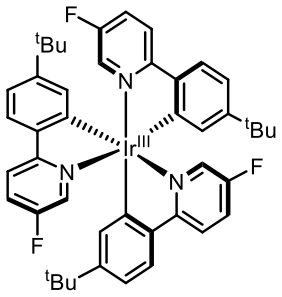
^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.89 (dd, *J* = 8.9, 4.7 Hz, 3H), 7.59 (dd, *J* = 7.7, 1.4 Hz, 3H), 7.45 – 7.37 (m, 6H), 6.93 (ddd, *J* = 7.7, 7.5, 1.4 Hz, 3H), 6.85 (ddd, *J* = 7.3, 7.3, 1.4 Hz, 3H), 6.77 (dd, *J* = 7.6, 1.3 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 163.3 (d, *J* = 3.3 Hz), 158.6 (d, *J* = 251.2 Hz), 158.6, 142.5, 137.0, 135.1 (d, *J* = 28.8 Hz), 129.9, 124.1 (obs. d), 124.0, 120.4, 119.8 (d, *J* = 5.7 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) δ = −128.5.

HRMS (ESI$^+$) $C_{33}H_{21}F_3IrN_3$ $[M+H]^+$ requires 710.1391; found 710.1384, Δ 0.7 ppm.

Ir((5-F)(4'-^{t}Bu)ppy)$_3$ (365)



$IrCl_3$ (450 mg, 1.50 mmol, 1.00 equiv.) and 2-(4-(tert-butyl)phenyl)-5-fluoropyridine (**357**) (585 mg, 3.39 mmol, 2.26 equiv.) in methoxyethanol-water (20/10 mL) were heated under reflux for 16 hours then cooled to room temperature. The resulting precipitate was collected by vacuum filtration and washed with water to give the chloride dimer (**361**) (125 mg, 73%) as a yellow solid.

The chloride dimer (**361**) (68.4 mg, 0.0500 mmol, 1.00 equiv.), AgOTf (38.6 mg, 0.0600 mmol, 3.00 equiv.) and 2-(4-(tert-butyl)phenyl)-5-fluoropyridine (572 mg, 1.00 mmol, 50.0 equiv.) were added to a 10 mL reaction vial. The vial was sealed and evacuated and backfilled with argon three times. The reaction was heated to 160 °C for 16 h then cooled to room temperature. The reaction mixture was diluted with CH_2Cl_2 and purified directly by flash column chromatography eluting with 70% CH_2Cl_2-pentane to give Ir((5-F)(4'-^{t}Bu)ppy)$_3$ (**365**) (74.5 mg, 85%) as a yellow solid.

IR (film) ν_{max}/cm^{-1}: 2961, 1584, 1473, 1259, 1234, 843, 806, 629.

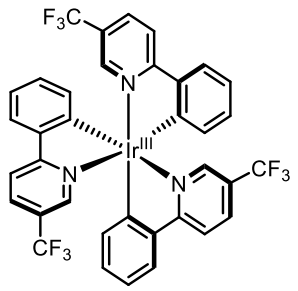
^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.80 (dd, *J* = 9.2, 5.0 Hz, 3H), 7.48 (d, *J* = 8.2 Hz, 3H), 7.44 (app. t, *J* = 2.5 Hz, 3H), 7.35 (ddd, *J* = 9.0, 7.6, 2.8 Hz, 3H), 6.95 (dd, *J* = 8.2, 2.1 Hz, 3H), 6.82 (d, *J* = 2.1 Hz, 3H), 1.08 (s, 27H).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 163.6 (d, *J* = 3.4 Hz), 158.5 (d, *J* = 250.2 Hz), 158.5, 152.2, 140.0, 135.0 (d, *J* = 28.6 Hz), 134.3, 123.8 (d, *J* = 19.1 Hz), 123.2, 119.2 (d, *J* = 5.6 Hz), 117.4, 34.5, 31.4.

^{19}F NMR (471 MHz, $CDCl_3$) δ = −129.6.

HRMS (ESI$^+$) $C_{45}H_{44}N_3F_3Ir$ $[M+H]^+$ requires 877.3192; found 877.3190, Δ 0.1 ppm.

Ir((5-CF$_3$)ppy)$_3$ (366)



$IrCl_3$ (75 mg, 0.250 mmol, 1.00 equiv.) and 2-phenyl-5-(trifluoromethyl)pyridine (**358**) (125 mg, 0.562 mmol, 2.26 equiv.) in methoxyethanol-water (3/2 mL) were heated under reflux for 16 hours then cooled to room temperature. The resulting precipitate was collected by vacuum filtration and washed with water to give the chloride dimer (**362**) (125 mg, 68%) as a yellow solid.

The chloride dimer dimer (**362**) (67.2 mg, 0.0500 mmol, 1.00 equiv.), AgOTf (38.6 mg, 0.0600 mmol, 3.00 equiv.) and 2-phenyl-5-(trifluoromethyl)pyridine (557 mg, 1.00 mmol, 50.0 equiv.) were added to a 10 mL reaction vial. The vial was sealed and evacuated and backfilled with argon three times. The reaction was heated to 160 °C for 16 h then cooled to room temperature. The reaction mixture was diluted with CH_2Cl_2 and purified directly by flash column chromatography eluting with 70% CH_2Cl_2-pentane to give Ir((5-CF_3)ppy)$_3$ (**366**) (74.5 mg, 84%) as an orange solid.

IR (film) ν_{max}/cm^{-1}: 2359, 1612, 1582, 1328, 1309, 1265, 1232, 1175, 1135, 1084, 1054, 1034.

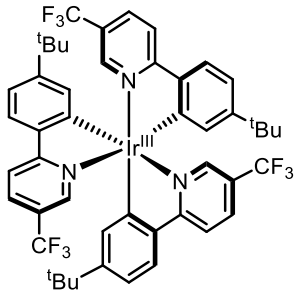
^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.01 (d, *J* = 8.6 Hz, 3H), 7.84 (dd, *J* = 8.6, 2.1 Hz, 3H), 7.73 (dd, *J* = 7.8, 1.5 Hz, 3H), 7.67 (s, 3H), 6.99 (ddd, *J* = 7.8, 7.5, 1.4 Hz, 3H), 6.92 (ddd, *J* = 7.4, 7.2, 1.4 Hz, 3H), 6.82 (dd, *J* = 7.6, 1.3 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 170.2, 144.0 (q, *J* = 4.7 Hz), 142.0, 137.3, 133.9 (d, *J* = 3.2 Hz), 131.6, 125.8, 125.1 (d, *J* = 33.8 Hz), 122.9 (d, *J* = 272.0 Hz), 121.0, 119.0.

^{19}F NMR (471 MHz, $CDCl_3$) δ = −62.7.

HRMS (ESI^+) $C_{36}H_{21}F_9IrN_3$ $[M+H]^+$ requires 860.1295; found 860.1288, Δ 0.3 ppm.

Ir((5-CF_3)(4'-^{t}Bu)ppy)$_3$ (PS367)



$IrCl_3$ (45 mg, 0.150 mmol, 1.00 equiv.) and 2-(4-(tert-butyl)phenyl)-5-(trifluoromethyl)pyridine (**PS359**) (95 mg, 0.340 mmol, 2.26 equiv.) in methoxyethanol-water (2/1 mL) were heated under reflux for 16 hours then cooled to room temperature. The resulting precipitate was collected by vacuum filtration and washed with water to give the chloride dimer (**PS363)** (129 mg, 55%) as a yellow solid.

The chloride dimer (78.0 mg, 0.050 mmol, 1.00 equiv.), AgOTf (39.0 mg, 0.150 mmol, 3.00 equiv.) and 2-(4-(tert-butyl)phenyl)-5-(trifluoromethyl)pyridine (**PS359**) (390 mg, 2.50 mmol, 50.0 equiv.) were added to a 10 mL reaction vial. The vial was sealed and evacuated and backfilled with argon three times. The reaction was heated to 160 °C for 16 h then cooled to room temperature. The reaction mixture was diluted with CH_2Cl_2 and purified directly by flash column chromatography eluting with 50% CH_2Cl_2-pentane followed by 5% EtOAc-pentane to give Ir((5-CF_3)(4'-^{t}Bu)ppy)$_3$ (**PS367**) (50.4 mg, 98%) as an orange solid.

IR (film) ν_{max}/cm^{-1}: 2963, 1693, 1611, 1586, 1328, 1310, 1128, 1087, 812, 773, 762, 736.

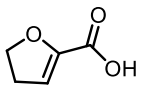
^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.91 (d, *J* = 8.6 Hz, 3H), 7.75 (dd, *J* = 8.6, 2.1 Hz, 3H), 7.72 (s, 3H), 7.63 (d, *J* = 8.3 Hz, 3H), 7.02 (dd, *J* = 8.3, 2.1 Hz, 3H), 6.90 (d, *J* = 2.1 Hz, 3H), 1.11 (s, 27H).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 170.4, 161.3, 154.2, 143.9 (d, *J* = 4.7 Hz), 139.5, 134.6, 133.5 (q, *J* = 3.3 Hz), 125.1, 124.7 (q, *J* = 33.9 Hz), 123.1 (q, *J* = 271.9 Hz), 118.6, 118.2, 34.7, 31.3.

^{19}F NMR (471 MHz, $CDCl_3$) δ = −62.8.

HRMS (ESI^+) $C_{48}H_{44}N_3F_9Ir$ $[M+H]^+$ requires 1027.3097; found 1027.3099, Δ 0.3 ppm.

4,5-Dihydrofuran-2-carboxylic acid (368)



^{n}BuLi (2.5 M in hexane, 20 mL, 50.0 mmol, 1.00 equiv.) was cooled to 0 °C and dihydrofuran (3.78 mL, 3.50 g, 50 mmol, 1.00 equiv.) was added. TMEDA (7.48 mL, 5.80 g, 50.0 mmol, 1.00 equiv.) was added and the reaction was warmed to room temperature and stirred for 2 hours. THF (100 mL) was added and the reaction was cooled to −78 °C. Powdered dry ice (~10 g) was added and the reaction was allowed to warm to room temperature and stirred for 3 hours. Et_2O was added and the resulting solution was extracted three times with water. The combined aqueous layers were acidified with 37% hydrochloric acid and extracted three times with EtOAc. The combined EtOAc extracts were washed with water, and concentrated to give 4,5-dihydrofuran-2-carboxylic acid (**368**) (2.74 g, 48%) as a waxy solid.

m.p. = 88-90 °C (EtOAc).

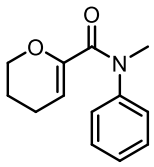
IR (film) ν_{max}/cm^{-1}: 3121-2566 (broad), 1689, 1632, 1622, 1443, 1310, 1262, 1221, 1179, 1132, 1086, 1072, 999, 932, 901, 739.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 11.48 (br. s, 1H), 6.13 (t, *J* = 3.1 Hz, 1H), 4.51 (t, *J* = 9.8 Hz, 3H), 2.84 (td, *J* = 9.9, 3.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 165.2, 148.0, 114.3, 71.0, 30.8.

HRMS (ESI$^+$) $C_5H_6O_3$ $[M+Na]^+$ requires 137.0209; found 137.0210, Δ 0.4 ppm.

N-methyl-*N*-phenyl-3,4-dihydro-2*H*-pyran-6-carboxamide (PS369)



This compound was prepared and characterised by Pearse Solon.

Prepared following **general procedure C** using *N*-methylaniline (238 mg, 2.20 mmol, 1.10 equiv.) and 3,4-dihydro-2H-pyran-6-carboxylic acid (**343**) (256, mg, 2.00 mmol, 1.00 equiv.). Column chromatography eluting with 20% EtOAc-pentane afforded *N*-methyl-*N*-phenyl-3,4-dihydro-2*H*-pyran-6-carboxamide (**PS369**) (279 mg, 64%) as a white solid.

m.p. = 56-58°C (EtOAc-pentane).

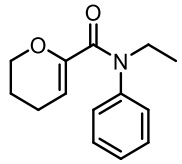
IR (film) ν_{max}/cm^{-1}: 2978, 2938, 1643, 1596, 1498, 1379, 1370, 1055, 920, 775, 740, 703.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.41–7.32 (m, 2H), 7.32–7.22 (m, 1H), 7.25–7.15 (m, 2H), 5.42 (t, J = 4.0 Hz, 1H), 3.55–3.48 (m, 2H), 3.35 (s, 3H), 2.02 (td, J = 6.4, 4.0 Hz, 2H), 1.72–1.61 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.1, 148.6, 145.2, 129.0, 126.6, 125.7, 107.1, 65.8, 38.1, 21.7, 20.2.

HRMS (ESI$^+$) $C_{13}H_{15}NO_2$ $[M+Na]^+$ requires 240.0995; found 240.0997, Δ 1.0 ppm.

_N_-Ethyl-_N_-phenyl-3,4-dihydro-2_H_-pyran-6-carboxamide (370)



Prepared following **general procedure C** using *N*-ethylaniline (244 mg, 2.20 mmol, 1.10 equiv.) and 3,4-dihydro-2H-pyran-6-carboxylic acid (**343**) (256 mg, 2.00 mmol, 1.00 equiv.). Column chromatography eluting with 30% EtOAc-pentane afforded *N*-ethyl-*N*-phenyl-3,4-dihydro-2H-pyran-6-carboxamide (**370**) (284 mg, 61%) as a white solid.

m.p. = 84-86 °C (EtOAc-pentane).

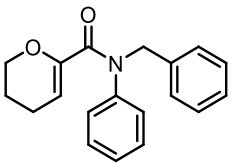
IR (film) ν_{max}/cm^{-1}: 2977, 2958, 2931, 2874, 1629, 1493, 1402, 1305, 1282, 768, 747, 700.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.37–7.30 (m, 2H), 7.25–7.20 (m, 1H), 7.17–7.10 (m, 2H), 5.36 (t, *J* = 4.0 Hz, 1H), 3.80 (q, *J* = 7.1 Hz, 2H), 3.51–3.37 (m, 2H), 1.99–1.94(m, 2H), 1.65–1.58 (m, 2H), 1.13 (t, *J* = 7.1 Hz, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 165.6, 148.8, 143.4, 128.9, 126.8, 126.7, 106.9, 65.7, 45.1, 21.7, 20.2, 13.0.

HRMS (ESI^+) $C_{14}H_{17}NO_2$ $[M+H]^+$ requires 232.1332; found 232.1333, Δ 0.4ppm.

_N_-Benzyl-_N_-phenyl-3,4-dihydro-2_H_-pyran-6-carboxamide (371)



Prepared following **general procedure C** using *N*-benzylaniline (201 mg, 1.10 mmol, 1.10 equiv.) and 3,4-dihydro-2*H*-pyran-6-carboxylic acid (**343**) (128 mg, 1.00 mmol, 1.00 equiv.). Column chromatography eluting with 30% Et_2O-pentane afforded *N*-benzyl-*N*-phenyl-3,4-dihydro-2*H*-pyran-6-carboxamide (**371**) (195 mg, 66%) as a white solid.

m.p. = 60-62°C (Et_2O-pentane).

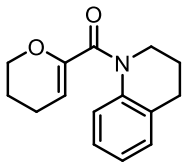
IR (film) ν_{max}/cm^{-1}: 2976, 2962, 1636, 1392, 751, 699.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.32–7.23 (m, 7H), 7.23–7.16 (m, 1H), 7.08–7.02 (m, 2H), 5.45 (t, *J* = 4.0 Hz, 1H), 4.98 (s, 2H), 3.56–3.39 (m, 2H), 2.06–1.94 (m, 2H), 1.72–1.58 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.0, 148.6, 143.6, 137.5, 128.7, 128.6, 128.5, 127.4, 126.7, 126.6, 107.4, 65.8, 53.6, 21.7, 20.2.

HRMS (ESI^+) $C_{19}H_{19}NO_2$ $[M+H]^+$ requires 294.1489; found 294.1490, Δ 0.5 ppm.

(3,4-Dihydro-2*H*-pyran-6-yl)(3,4-dihydroquinolin-1(2*H*)-yl)methanone (372)



Prepared following **general procedure C** using 1,2,3,4-tetrahydroquinoline (199 mg, 1.50 mmol, 1.00 equiv.) and 3,4-dihydro-2*H*-pyran-6-carboxylic acid (**343**) (192 mg, 1.50 mmol, 1.00 equiv.). Column chromatography eluting with 20% EtOAc-pentane afforded (3,4-dihydro-2*H*-pyran-6-yl)(3,4-dihydroquinolin-1(2*H*)-yl)methanone (**372**) (195 mg, 66%) as a white solid.

m.p. = 62-64 °C (EtOAc-pentane).

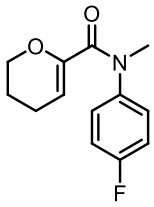
IR (film) ν_{max}/cm^{-1}: 2975, 2961, 2931, 2875, 1629, 1579, 1492, 1376, 1361, 1338, 1327, 1281, 1046, 913, 762, 743.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.29 – 7.20 (m, 1H), 7.14 – 7.07 (m, 2H), 7.07 – 7.00 (m, 1H), 5.44 (t, *J* = 4.0 Hz, 1H), 3.83 – 3.74 (m, 5H), 2.75 (t, *J* = 6.6 Hz, 2H), 2.10 (td, *J* = 6.4, 4.0 Hz, 2H), 1.97 (p, *J* = 6.6 Hz, 2H), 1.84 – 1.74 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 165.6, 149.3, 139.4, 131.0, 128.4, 125.8, 124.6, 123.2, 106.9, 66.2, 44.3, 26.9, 24.0, 21.8, 20.4.

HRMS (ESI$^+$) $C_{15}H_{17}NO_2$ $[M+H]^+$ requires 244.1332; found 244.1333, Δ 0.3 ppm.

N-(4-Fluorophenyl)-*N*-methyl-3,4-dihydro-2*H*-pyran-6-carboxamide (373)



Prepared following **general procedure C** using 4-fluoro-*N*-methylaniline (208 mg, 1.65 mmol, 1.10 equiv.) and 3,4-dihydro-2*H*-pyran-6-carboxylic acid (**343**) (192 mg, 1.50 mmol, 1.00 equiv.). Column chromatography eluting with 20% EtOAc-pentane afforded *N*-(4-fluorophenyl)-*N*-methyl-3,4-dihydro-2*H*-pyran-6-carboxamide (**373**) (208 mg, 59%) as a white solid.

m.p. = 62-64 °C (EtOAc-pentane).

IR (film) ν_{max}/cm^{-1}: 2932, 1641, 1465, 1432, 1371, 1286, 1164, 1058, 841, 767, 721, 631.

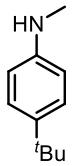
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.16–7.10 (m, 2H), 7.07–6.96 (m, 2H), 5.41 (t, *J* = 4.0 Hz, 1H), 3.57–3.48 (m, 3H), 3.28 (s, 3H), 2.08–1.97 (m, 2H), 1.67–1.60 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 165.9, 161.0 (d, J = 246.1 Hz), 148.3, 140.9, 127.4 (d, J = 8.6 Hz), 115.6 (d, J = 22.7 Hz), 107.1, 65.7, 38.1, 21.5, 20.0.

^{19}F NMR (377 MHz, $CDCl_3$) δ = −115.4.

HRMS (ESI^+) $C_{13}H_{14}N_1O_2F$ $[M+Na]^+$ requires 258.0901; found 258.0903, Δ 0.9 ppm.

4-(*tert*-butyl)-*N*-methylaniline (383)



Prepared from 4-(tert-butyl)-aniline (636 µL, 596 mg, 4.00 mmol) was dissolved in THF (20 mL) and cooled to −78 °C. ^{n}BuLi (2.5 M in hexane, 1.60 mL, 4.00 mmol, 1.00 equiv.) was added and the reaction was stirred at −78 °C for 30 minutes. Iodomethane (249 µL, 568 mg, 4.00 mmol, 1.00 equiv.) was added and the reaction was warmed to room temperature and stirred for 3 hours. Water was added and the reaction mixture was transferred to a separating funnel and extracted three times with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated to give the crude product which was purified by flash column chromatography eluting with 10% Et_2O-pentane afforded 4-(tert-butyl)-*N*-methylaniline (**383**) (290 mg, 44%) as a yellow oil.

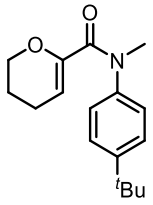
IR (film) ν_{max}/cm^{-1}: 3412, 2959, 2900, 2868, 1617, 1521, 1481, 1461, 1392, 1320, 1263, 1156, 1059, 820.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.30–7.24 (m, 2H), 6.67–6.60 (m, 2H), 2.87 (s, 3H), 1.33 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 146.8, 140.3, 126.0, 112.4, 33.9, 31.6, 31.1.

HRMS (ESI^+) $C_{11}H_{17}N$ $[M+H]^+$ requires 164.1434; found 164.1435, Δ 0.7ppm.

_N_-(4-(_Tert_-butyl)phenyl)-_N_-methyl-3,4-dihydro-2_H_-pyran-6-carboxamide (374)



Prepared from 4-(*tert*-butyl)-*N*-methylaniline (269 mg, 1.65 mmol, 1.10 equiv.) and 3,4-dihydro-2*H*-pyran-6-carboxylic acid (**343**) (192 mg, 1.50 mmol, 1.00 equiv.) following **general procedure C**. Purification by flash chromatography (20-30% EtOAc-pentane) afforded *N*-(4-(*tert*-butyl)phenyl)-*N*-methyl-3,4-dihydro-2*H*-pyran-6-carboxamide (**374**) (259 mg, 63%) as a colourless oil.

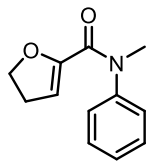
IR (film) ν_{max}/cm^{-1}: 2961, 1644, 1511, 1383, 1371, 1343, 1284, 1059, 920.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.37–7.30 (m, 2H), 7.14–7.04 (m, 2H), 5.37 (t, *J* = 4.0 Hz, 1H), 3.52–3.43 (m, 2H), 3.31 (s, 3H), 2.02–1.93 (m, 2H), 1.73–1.58 (m, 2H), 1.31 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.2, 149.6, 148.7, 142.3, 125.7, 125.2, 106.8, 65.7, 38.0, 34.6, 31.5, 21.7, 20.2.

HRMS (ESI$^+$) $C_{17}H_{24}NO_2$ $[M+H]^+$ requires 274.1802; found 274.1802, Δ 0.2 ppm.

_N_-methyl-_N_-phenyl-4,5-dihydrofuran-2-carboxamide (375)



Prepared following **general procedure C** using *N*-methylaniline (235 mg, 2.20 mmol, 1.10 equiv.) and 4,5-dihydrofuran-2-carboxylic acid (**368**) (228, mg, 2.00 mmol, 1.00 equiv.). Column

chromatography eluting with 30% EtOAc-pentane afforded *N*-methyl-*N*-phenyl-4,5-dihydrofuran-2-carboxamide (**375**) (208 mg, 51%) as an off-white solid.

m.p. = 48-50°C (EtOAc-pentane).

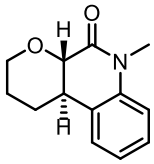
IR (film) ν_{max}/cm^{-1}: 2980, 2971, 1786, 1647, 1593, 1495, 1381, 932, 697.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.40–7.33 (m, 2H), 7.31–7.25 (m, 1H), 7.22–7.15 (m, 2H), 5.08–4.95 (m, 1H), 4.14 (t, *J* = 9.6 Hz, 2H), 3.36 (s, 3H), 2.54 (td, *J* = 9.7, 2.9 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 162.0, 150.9, 144.3, 129.2, 127.3, 126.4, 107.3, 70.1, 38.1, 30.4.

HRMS (ESI$^+$) $C_{12}H_{13}NO_2$ $[M+H]^+$ requires 204.1019; found 204.1021, Δ 0.8 ppm.

(4a*S*,10b*R*)-6-Methyl-2,3,6,10b-tetrahydro-1*H*-pyrano[2,3-c]quinolin-5(4a*H*)-one (PS376)



This compound was prepared and characterised by Pearse Solon.

Prepared from *N*-methyl-*N*-phenyl-3,4-dihydro-2*H*-pyran-6-carboxamide (21.7 mg, 0.100 mmol) following **general procedure D**. Purification by flash chromatography (60% EtOAc-pentane) afforded 4a*S*,10b*R*)-6-methyl-2,3,6,10b-tetrahydro-1*H*-pyrano[2,3-c]quinolin-5(4a*H*)-one (**PS376**) (21.6 mg, 95%, >19:1 dr, 94:6 er) as an off-white solid.

m.p. = 78-80 °C

IR (film) ν_{max}/cm^{-1}: 2935, 2920, 2849, 1688, 1602, 1459, 1380, 1253, 1110.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.33 – 7.28 (m, 1H), 7.22 (d, *J* = 7.7 Hz, 1H), 7.10 (ddd, *J* = 7.5, 7.5, 1.2 Hz, 1H), 7.00 (d, *J* = 1.2 Hz, 1H), 4.32 – 4.22 (m, 1H), 3.71 (d, *J* = 13.1 Hz, 1H), 3.50 (ddd, *J* = 11.9, 11.8, 2.7 Hz, 1H), 3.40 (s, 3H), 2.97 – 2.75 (m, 1H), 2.61 – 2.47 (m, 1H), 1.95 – 1.73 (m, 2H), 1.70 – 1.54 (m, 1H).

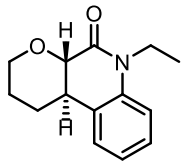
^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.3, 139.3, 128.0, 127.2, 124.6, 123.4, 114.8, 76.0, 68.3, 36.5, 30.1, 26.2, 24.8.

HRMS (ESI^+): $C_{13}H_{15}NO_2$ $[M+H]^+$ requires 218.1176; found 218.1177, Δ 0.8 ppm.

Chiral HPLC: (Chiralpak ODH, 30% ^{i}PrOH, 70% hexane, 1.0 mL min^{-1}, λ = 260 nm) τ_R (major) = 11.1 min, τ_R (minor) = 16.5 min.

$[\alpha]_D^{25}$ = +159.1 (*c* = 0.50, $CHCl_3$).

(4a*S*,10b*R*)-6-Ethyl-2,3,6,10b-tetrahydro-1*H*-pyrano[2,3-c]quinolin-5(4a*H*)-one (PS377)



This compound was prepared and characterised by Pearse Solon.

Prepared from *N*-ethyl-*N*-phenyl-3,4-dihydro-2*H*-pyran-6-carboxamide (23.1 mg, 0.100 mmol) following **general procedure D**. Purification by flash chromatography (50% EtOAc-pentane) afforded (4a*S*,10b*R*)-6-ethyl-2,3,6,10b-tetrahydro-1*H*-pyrano[2,3-c]quinolin-5(4a*H*)-one (**PS377**) (22.2 mg, 97%, >19:1 dr, 93:7 er) as an off-white solid.

m.p. = 80-82 °C

IR (film) ν_{max}/cm^{-1}: 2970, 2935, 2850, 1687, 1458, 1389, 1242, 1113.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.32–7.27 (m, 1H), 7.22 (dt, *J* = 7.7, 1.5 Hz, 1H), 7.09 (ddd, *J* = 7.6, 7.5, 1.1 Hz, 1H), 7.04 (dd, *J* = 8.2, 1.1 Hz, 1H), 4.27 (ddt, *J* = 11.5, 4.5, 1.7 Hz, 1H), 4.16–4.03 (m, 1H), 4.02–3.85 (m, 1H), 3.71 (d, *J* = 13.2 Hz, 1H), 3.50 (td, *J* = 11.8, 2.7 Hz, 1H), 2.92–2.79 (m, 1H), 2.58–2.41 (m, 1H), 1.95–1.70 (m, 2H), 1.68–1.48 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 3H).

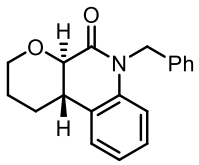
^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.9, 138.3, 128.1, 127.7, 125.0, 123.4, 114.9, 76.06, 68.4, 38.0, 36.7, 26.4, 24.9, 12.9.

HRMS (ESI^+): $C_{14}H_{17}NO_2$ $[M+Na]^+$ requires 254.1152; found 254.1153, Δ 0.6 ppm.

Chiral HPLC: (Chiralpak ODH, 30% ^{i}PrOH, 70% hexane, 1.0 mL min^{-1}, λ = 260 nm) τ_R (major) = 8.6 min, τ_R (minor) = 12.4 min.

$[\alpha]_D^{25}$ = +154.7(*c* = 0.50, $CHCl_3$).

(4a*R*,10b*S*)-6-Benzyl-2,3,6,10b-tetrahydro-1*H*-pyrano[2,3-c]quinolin-5(4a*H*)-one (378)



Prepared from *N*-benzyl-*N*-phenyl-3,4-dihydro-2*H*-pyran-6-carboxamide (**371**) (29.3 mg, 0.100 mmol) following **general procedure D**. Purification by flash chromatography (70% EtOAc-pentane) afforded (4a*R*,10b*S*)-6-benzyl-2,3,6,10b-tetrahydro-1*H*-pyrano[2,3-c]quinolin-5(4a*H*)-one (**378**) (28.3 mg, 97%, >19:1 dr, 93:7 er) as an off-white solid.

m.p. = 154-156 °C (EtOAc-pentane).

IR (film) ν_{max}/cm^{-1}: 2937, 2850, 1691, 1495, 1457, 1389, 1210, 1115, 754.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.23–7.12 (m, 6H), 7.11–7.05 (m, 1H), 6.98 (td, *J* = 7.5, 1.2 Hz, 1H), 6.84 (dd, *J* = 8.1, 1.2 Hz, 1H), 5.34 (d, *J* = 16.1 Hz, 1H), 4.93 (d, *J* = 16.1 Hz, 1H), 4.29–4.19 (m, 1H), 3.83 (d, *J* = 13.2 Hz, 1H), 3.48 (ddd, *J* = 11.9, 11.8, 2.6 Hz, 1H), 2.94–2.82 (m, 1H), 2.54–2.42 (m, 1H), 1.90–1.69 (m, 2H), 1.65–1.50 (m, 1H).

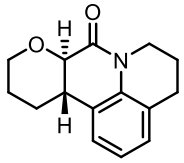
^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.7, 138.5, 136.9, 128.8, 128.1, 127.5, 127.3, 126.8, 124.8, 123.7, 115.8, 76.1, 68.4, 46.6, 36.7, 26.5, 24.9.

HRMS (ESI^+) $C_{19}H_{19}NO_2$ $[M+H]^+$ requires 294.1489; found 294.1488, 0.1 ppm.

Chiral HPLC: (Chiralpak ODH, 30% ^{i}PrOH, 70% hexane, 1.0 mL min^{-1}, λ = 260 nm) τ_R (major) = 10.7 min, τ_R (minor) = 12.7 min.

$[\alpha]_D^{25}$ = +81.1 (*c* = 0.50, $CHCl_3$).

(8a*R*,12a*S*)-5,6,10,11,12,12a-Hexahydro-4*H*-pyrano[2,3-c]pyrido[3,2,1-ij]quinolin-8(8a*H*)-one (379)



Prepared from (3,4-dihydro-2*H*-pyran-6-yl)(3,4-dihydroquinolin-1(2*H*)-yl)methanone (24.3 mg, 0.100 mmol) following **general procedure D**. Purification by flash chromatography (20→75% EtOAc-pentane) afforded (8a*R*,12a*S*)-5,6,10,11,12,12a-hexahydro-4*H*-pyrano[2,3-c]pyrido[3,2,1-ij]quinolin-8(8a*H*)-one (**379**) (12.7 mg, 52%, >19:1 dr, 82:18 er) as an off-white solid and recovered starting material (9.9 mg, 41%)

m.p. = 134-136 °C (EtOAc-pentane).

IR (film) ν_{max}/cm^{-1}: 2935, 2853, 2849, 1684, 1390, 1246, 1111.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.08–6.95 (m, 3H), 4.37–4.21 (m, 2H), 3.74 (d, *J* = 13.3 Hz, 1H), 3.55–3.45 (m, 2H), 2.89–2.68 (m, 3H), 2.51 (ddt, *J* = 12.7, 5.6, 3.1 Hz, 1H), 2.03–1.73 (m, 4H), 1.67–1.53 (obs. m, 1H).

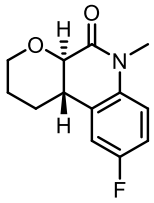
^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.7, 134.9, 128.5, 126.7, 125.5, 123.0, 122.6, 76.2, 68.4, 41.3, 36.7, 27.4, 26.4, 25.1, 21.5.

HRMS (ESI$^+$) $C_{15}H_{17}NO_2$ $[M+Na]^+$ requires 266.1152; found 266.1153, 0.4 ppm.

Chiral HPLC: (Chiralpak ODH, 30% ^{i}PrOH, 70% hexane, 1.0 mL min^{-1}, λ = 260 nm) τ_R (major) = 13.2 min, τ_R (minor) = 15.7 min.

$[\alpha]_D^{25}$ = +87.2 (*c* = 0.50, $CHCl_3$).

(4a*R*,10b*S*)-9-Fluoro-6-methyl-2,3,6,10b-tetrahydro-1*H*-pyrano[2,3-c]quinolin-5(4a*H*)-one (380)



Prepared from *N*-(4-fluorophenyl)-*N*-methyl-3,4-dihydro-2*H*-pyran-6-carboxamide (**373**) (23.5 mg, 0.100 mmol) following **general procedure D**. Purification by flash chromatography (60% EtOAc-pentane) afforded (4a*R*,10b*S*)-9-fluoro-6-methyl-2,3,6,10b-tetrahydro-1*H*-pyrano[2,3-c]quinolin-5(4a*H*)-one (**380**) (22.1 mg, 94%, >19:1 dr, 94:6 er) as a colourless oil.

IR (film) ν_{max}/cm^{-1}: 2938, 2852, 1689, 1499, 1436, 1110.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.02–6.90 (m, 3H), 4.32–4.24 (m, 1H), 3.69 (d, *J* = 13.1 Hz, 1H), 3.50 (ddd, *J* = 11.8, 11.7, 2.9 Hz, 1H), 3.38 (d, *J* = 0.6 Hz, 3H), 2.86 (dddd, *J* = 13.0, 11.5, 4.2, 1.3 Hz, 1H), 2.53–2.40 (m, 1H), 1.91–1.74 (m, 2H), 1.63–1.50 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.0, 159.3 (d, *J* = 243.1 Hz), 135.6, 129.5 (d, *J* = 7.3 Hz), 116.2 (d, *J* = 8.2 Hz), 114.3 (d, *J* = 22.5 Hz), 112.2 (d, *J* = 23.9 Hz), 75.8, 68.4, 36.5, 30.5, 26.3, 24.8.

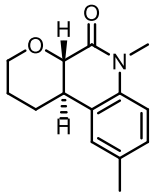
^{19}F NMR (101 MHz, $CDCl_3$) δ = −119.3.

HRMS (ESI^+) $C_{13}H_{14}FNO_2$ $[M+Na]^+$ requires 258.0901; found 258.0901, Δ 0.3 ppm.

Chiral HPLC: (Chiralpak ODH, 30% ^{i}PrOH, 70% hexane, 1.0 mL min^{-1}, λ = 260 nm) τ_R (major) = 12.8 min, τ_R (minor) = 17.8 min.

$[\alpha]_D^{25}$ = +95.4 (*c* = 0.50, $CHCl_3$).

(4aS,10bR)-6,9-Dimethyl-2,3,6,10b-tetrahydro-1H-pyrano[2,3-c]quinolin-5(4aH)-one (347)



Prepared from *N*-methyl-*N*-(p-tolyl)-3,4-dihydro-2H-pyran-6-carboxamide (**346**) (23.2 mg, 0.100 mmol) following **general procedure D**. Purification by flash chromatography (70% EtOAc-pentane) afforded (4aS,10bR)-6,9-Dimethyl-2,3,6,10b-tetrahydro-1H-pyrano[2,3-c]quinolin-5(4aH)-one (**347**) (22.2 mg, 96%, >19:1 dr, 95:5 er) as a white solid.

m.p. = 112-114 °C (EtOAc-pentane).

IR (film) ν_{max}/cm^{-1}: 2980, 2970, 1682, 1503, 1385, 1375, 1258, 1158, 1138, 1104, 1088, 1063, 959, 819.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.10 (d, *J* = 8.3 Hz, 1H), 7.01 (s, 1H), 6.88 (d, *J* = 8.2 Hz, 1H), 4.31–4.22 (m, 1H), 3.68 (d, *J* = 13.1 Hz, 1H), 3.49 (td, *J* = 11.7, 2.7 Hz, 1H), 3.37 (s, 3H), 2.85 (td, *J* = 12.3, 4.2 Hz, 1H), 2.55–2.47 (m, 1H), 2.34 (s, 3H), 1.93–1.71 (m, 2H), 1.60 (tdd, *J* = 12.8, 11.5, 4.3 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.3, 137.0, 133.1, 128.4, 127.1, 125.4, 114.9, 76.3, 68.4, 36.6, 30.2, 26.4, 25.0, 21.0.

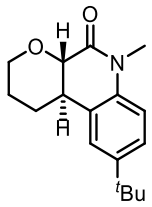
HRMS (ESI^+) $C_{14}H_{17}NO_2$ $[M+H]^+$ requires 232.1332; found 232.1335, Δ 1.5 ppm.

Chiral HPLC: (Chiralpak ODH, 40% ^{i}PrOH, 60% hexane, 1.0 mL min^{-1}, λ = 260 nm) τ_R (major) = 8.0 min, τ_R (minor) = 11.2 min.

$[\alpha]_D^{25}$ = +155.6 (*c* = 0.50 $CHCl_3$).

(4a*S*,10b*R*)-9-(tert-butyl)-6-methyl-2,3,6,10b-tetrahydro-1*H*-pyrano[2,3-c]quinolin-5(4a*H*)-one

(PS381)



This compound was prepared and characterised by Pearse Solon.

Prepared from *N*-(4-(tert-butyl)phenyl)-*N*-methyl-3,4-dihydro-2*H*-pyran-6-carboxamide (**374**) (27.3 mg, 0.100 mmol) following **general procedure D**. Purification by flash chromatography (50% EtOAc-pentane) afforded (4a*S*,10b*R*)-9-(tert-butyl)-6-methyl-2,3,6,10b-tetrahydro-1*H*-pyrano[2,3-c]quinolin-5(4a*H*)-one (**PS381**) (25.1 mg, 92%, >19:1 dr, 95:5 er) as a colourless oil.

IR (film) ν_{max}/cm^{-1}: 2956, 2905, 2858, 1691, 1507, 1377, 1109, 1086.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.34–7.28 (m, 1H), 7.24–7.19 (m, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 4.34–4.20 (m, 1H), 3.72 (d, *J* = 13.1 Hz, 1H), 3.51 (ddd, *J* = 11.8, 11.8, 2.7 Hz, 1H), 3.38 (s, 3H), 2.93–2.79 (m, 1H), 2.61–2.51 (m, 1H), 1.96–1.75 (m, 2H), 1.71–1.52 (m, 1H), 1.32 (s, 9H).

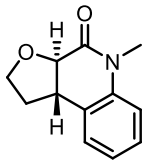
^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.3, 146.3, 136.8, 126.6, 124.6, 121.5, 114.5, 76.2, 68.3, 36.7, 34.5, 31.4, 30.0, 29.7, 26.2, 24.9.

HRMS (ESI$^+$): $C_{17}H_{24}NO_2$ $[M+H]^+$ requires 274.1802; found 274.1801, Δ 0.0 ppm.

Chiral HPLC: (Chiralpak ODH, 30% ^{i}PrOH, 70% hexane, 1.0 mL min^{-1}, λ = 260 nm) τ_R (major) = 9.8 min, τ_R (minor) = 13.3 min.

$[\alpha]_D^{25}$ = +134.7 (*c* = 0.50, $CHCl_3$).

(3a*R*,9b*S*)-5-Methyl-1,2,5,9b-tetrahydrofuro[2,3-c]quinolin-4(3a*H*)-one (382)



Prepared from *N*-methyl-*N*-phenyl-4,5-dihydrofuran-2-carboxamide (**375**) (20.3 mg, 0.100 mmol) following **general procedure D**. Purification by flash chromatography (60% EtOAc-pentane) afforded (3a*R*,9b*S*)-5-methyl-1,2,5,9b-tetrahydrofuro[2,3-c]quinolin-4(3a*H*)-one (**382**) (17.0 mg, 84%, 8:1 dr, 58:42 er) as an off-white solid.

m.p. = 122-124 °C (EtOAc-pentane).

IR (film) ν_{max}/cm^{-1}: 2888, 1693, 1459, 1121, 1094, 1019.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.34 – 7.29 (m, 1H), 7.17 (ddd, *J* = 7.4, 1.5, 1.5 Hz, 1H), 7.09 (ddd, *J* = 7.5, 7.4, 1.1 Hz, 1H), 7.03 (d, *J* = 1.1 Hz, 1H), 4.33 – 4.26 (m, 2H), 3.90 (dd, *J* = 13.7, 0.7 Hz, 1H), 3.39 (d, *J* = 0.6 Hz, 3H), 3.30 – 3.17 (m, 1H), 2.53 – 2.43 (m, 1H), 2.20 – 2.07 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.2, 141.0, 128.0, 127.3, 125.1, 123.3, 115.3, 79.1, 70.0, 42.2, 29.7, 27.5.

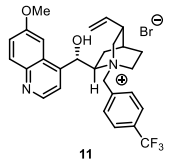
HRMS (ESI^+) $C_{12}H_{21}NO_2$ $[M+Na]^+$ requires 226.0838; found 226.0840, Δ 0.9 ppm.

Chiral HPLC: (Chiralpak IC, 40% ^{i}PrOH, 60% hexane, 1.0 mL min^{-1}, λ = 260 nm) τ_R (major) = 51.5 min, τ_R (minor) = 55.8 min.

$[\alpha]_D^{25}$ = +32.8 (*c* = 0.50, $CHCl_3$).

4. Appendices

4.1. Index of Phase-Transfer Catalysts



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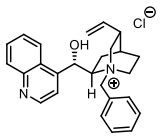

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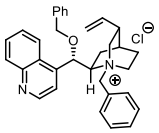

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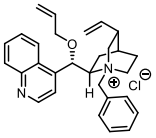

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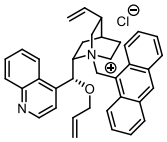

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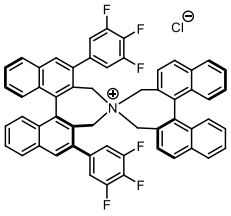

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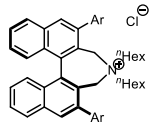
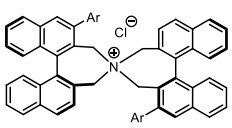


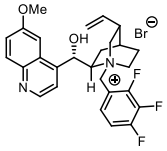
Ar = 3,5-(^{t}Bu$_2$-C$_6$H$_3$)$_2$C$_6$H$_3$

51



Ar = 3,5-[3,5-(CF$_3$)$_2$C$_6$H$_3$]$_2$C$_6$H$_3$

57



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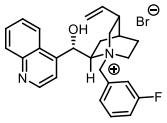

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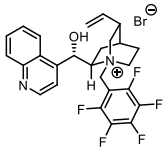

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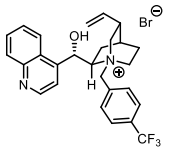

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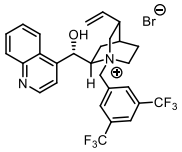

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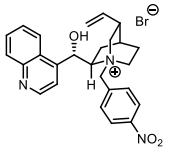

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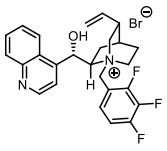

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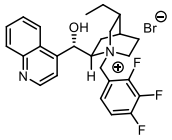

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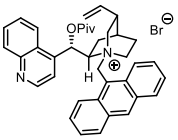

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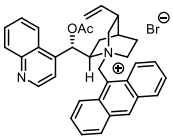

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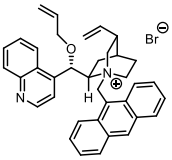

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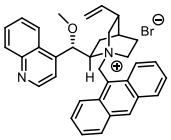

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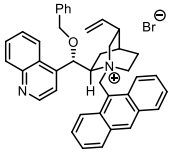

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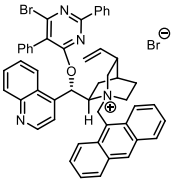

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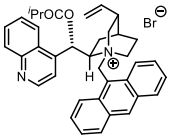

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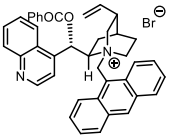

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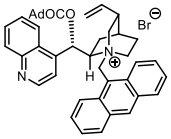

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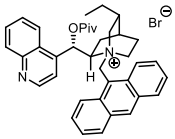

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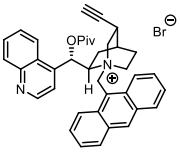

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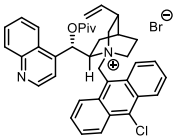

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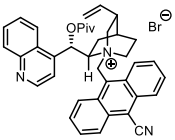

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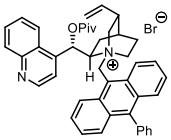

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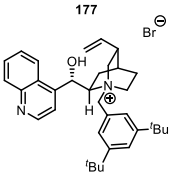

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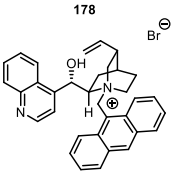

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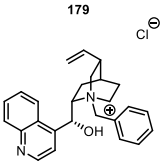

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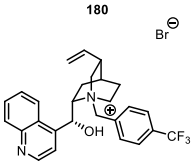

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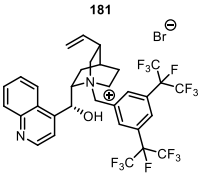

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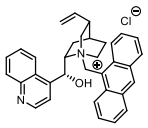

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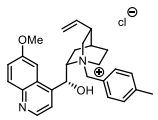

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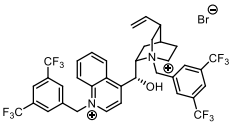

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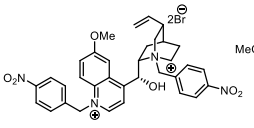

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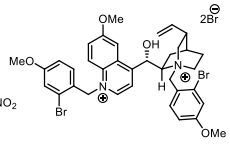

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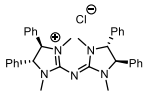

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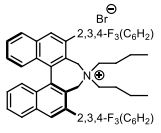

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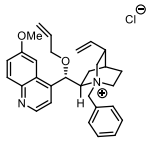

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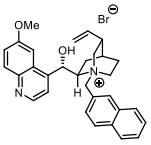

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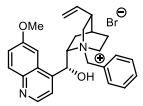

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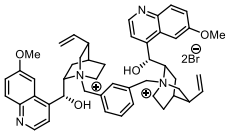

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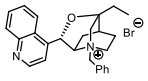

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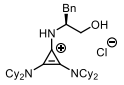

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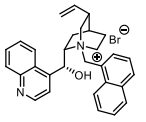

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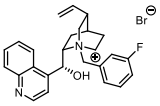

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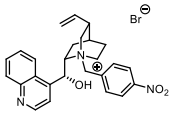

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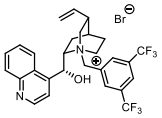

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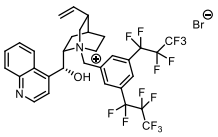

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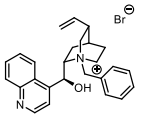

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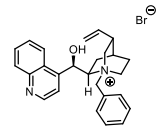

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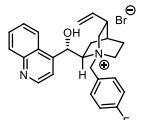

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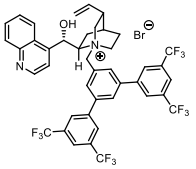

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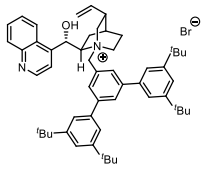

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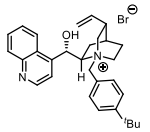

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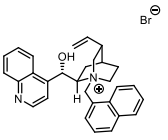

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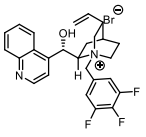

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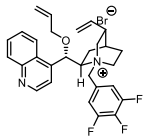

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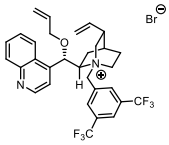

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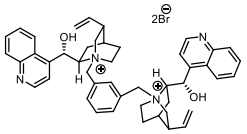

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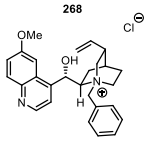

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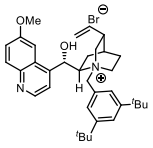

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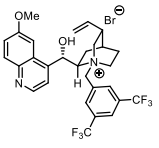

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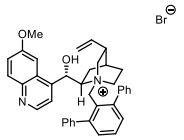

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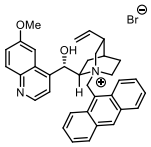

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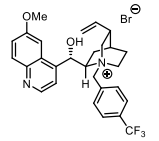

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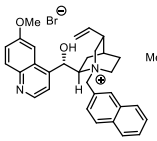

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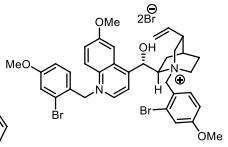

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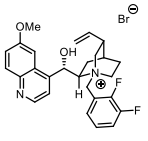

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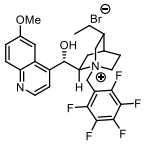

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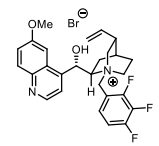

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4.2. Extended Optimization Table for the BINOL Kinetic Resolution

Entry	$R_4N^+X^-$	Base	Solvent	R-X (eq)	Time	*s*	Conv	Starting material er	Product er
1	**14**	KOH (25% aq, 5.0 eq)	$PhCH_3$ (0.1 M)	BnBr (0.6)	18h	1.1	55%	52.5:47.5	52:48
2	**238**	KOH (25% aq, 5.0 eq)	$PhCH_3$ (0.1 M)	BnBr (0.6)	18h	1.1	50%	51.5:48.5	51.5:48.5
3	**385**	KOH (25% aq, 5.0 eq)	$PhCH_3$ (0.1 M)	BnBr (0.6)	18h	1.2	42%	52.5:47.5	52.5:47.5
4	**248**	KOH (25% aq, 5.0 eq)	$PhCH_3$ (0.1 M)	BnBr (0.6)	18h	1.1	50%	51:49	51:49
5	**385**	NaOH (25% aq, 5.0 eq)	$PhCH_3$ (0.1 M)	BnBr (0.6)	18h	1.2	36%	52:48	53.5:46.5
6	**385**	RbOH (25% aq, 5.0 eq)	$PhCH_3$ (0.1 M)	BnBr (0.6)	18h	1.3	35%	55.5:44.5	51.5:48.5
7	**385**	CsOH (25% aq, 5.0 eq)	$PhCH_3$ (0.1 M)	BnBr (0.6)	18h	1.2	42%	52.5:47.5	52.5:46.5
8	**385**	K_2CO_3 (50% aq, 5.0 eq)	$PhCH_3$ (0.1 M)	BnBr (0.6)	18h	2.7	12%	53:47	72:28
9	**385**	Cs_2CO_3 (50% aq, 5.0 eq)	$PhCH_3$ (0.1 M)	BnBr (0.6)	18h	2.5	13%	53:47	71:29
10	**385**	K_3PO_4 (50% aq, 5.0 eq)	$PhCH_3$ (0.1 M)	BnBr (0.6)	18h	3.1	13%	53:47	73.5:26.5
11	**386**	K_3PO_4 (50% aq, 5.0 eq)	$PhCH_3$ (0.1 M)	BnBr (0.6)	48h	9.3	24%	62:38	89:11
12	**387**	K_3PO_4 (50% aq, 5.0 eq)	$PhCH_3$ (0.1 M)	BnBr (0.6)	48h	2.3	16%	53.5:46.5	68.5:31.5
13	**388**	K_3PO_4 (50% aq, 5.0 eq)	$PhCH_3$ (0.1 M)	BnBr (0.6)	48h	1.9	18%	53:47	64:36
14	**390**	K_3PO_4 (50% aq, 5.0 eq)	$PhCH_3$ (0.1 M)	BnBr (0.6)	48h	4.8	3%	51:49	79.5:20.5
15	**391**	K_3PO_4 (50% aq, 5.0 eq)	$PhCH_3$ (0.1 M)	BnBr (0.6)	48h	2.8	10%	52.5:47.5	73.5:26.5
16	**389**	K_3PO_4 (50% aq, 5.0 eq)	$PhCH_3$ (0.1 M)	BnBr (0.6)	48h	3.0	2%	51:49	74.5:25.5
17	**11**	K_3PO_4 (50% aq, 5.0 eq)	$PhCH_3$ (0.1 M)	BnBr (0.6)	48h	2.9	4%	51:49	76:24
18	**390**	K_3PO_4 (50% aq, 5.0 eq)	$PhCH_3$ (0.1 M)	BnBr (0.6)	48h	5.3	29%	62.5:37.5	80:20
19	**391**	K_3PO_4 (50% aq, 5.0 eq)	$PhCH_3$ (0.1 M)	BnBr (0.6)	48h	7.3	13%	55.5:45.5	88:12
20	**4**	K_3PO_4 (50% aq, 5.0 eq)	$PhCH_3$ (0.1 M)	BnBr (0.6)	48h	13	27%	65:35	90:10
21	**68**	K_3PO_4 (50% aq, 5.0 eq)	$PhCH_3$ (0.1 M)	BnBr (0.6)	48h	7.6	5%	52:48	91:9
22	**393**	K_3PO_4 (50% aq, 5.0 eq)	$PhCH_3$ (0.1 M)	BnBr (0.6)	48h	5.6	13%	55:45	83:17
23	**394**	K_3PO_4 (50% aq, 5.0 eq)	$PhCH_3$ (0.1 M)	BnBr (0.6)	48h	7.4	14%	56:44	87:13
24	**395**	K_3PO_4 (50% aq, 5.0 eq)	$PhCH_3$ (0.1 M)	BnBr (0.6)	48h	N/A	N/A	50:50	51:49
25	**396**	K_3PO_4 (50% aq, 5.0 eq)	$PhCH_3$ (0.1 M)	BnBr (0.6)	48h	8.9	6%	52.5:47.5	90.5:9.5
26	**392**	K_3PO_4 (50% aq, 5.0 eq)	$PhCH_3$ (0.1 M)	Allyl-Br (0.6)	48h	7.2	13%	55:45	85:15
27	**392**	K_3PO_4 (50% aq, 5.0 eq)	$PhCH_3$ (0.1 M)	Allyl-I (0.6)	48h	7.1	35%	68:32	83:17
28	**392**	K_3PO_4 (50% aq, 5.0 eq)	$PhCH_3$ (0.1 M)	MeI (0.6)	48h	3.5	19%	56:44	76:24
29	**392**	K_3PO_4 (50% aq, 5.0 eq)	$PhCH_3$ (0.1 M)	BnI (0.6)	48h	12	35%	71:29	89:11
30	**392**	K_3PO_4 (s, 2.0 eq)	$PhCH_3$ (0.1 M)	BnI (0.6)	48h	6.4	45%	74.5:25.5	80:20
31	**392**	K_3PO_4 (s, 5.0 eq)	$PhCH_3$ (0.1 M)	BnI (0.6)	48h	4.4	44%	70:30	75:25
32	**392**	K_3PO_4 (s, 10.0 eq)	$PhCH_3$ (0.1 M)	BnI (0.6)	48h	5.5	55%	81:29	75:25
33	**392**	Na_3PO_4 (s, 5.0 eq)	$PhCH_3$ (0.1 M)	BnI (0.6)	48h	8.5	12%	55:45	88.5:11.5
34	**392**	Na_3PO_4 (15% aq.)	$PhCH_3$ (0.1 M)	BnI (0.6)	48h	6.1	42%	71.5:28.5	80:20

35	**392**	Na_2CO_3 (s, 5.0 eq)	$PhCH_3$ (0.1 M)	BnI (0.6)	48h	N/A	N/A	50:50	75:25
36	**392**	Na_2CO_3 (25% aq, 5.0 eq)	$PhCH_3$ (0.1 M)	BnI (0.6)	48h	9.7	9%	54:46	90:10
37	**392**	K_2CO_3 (s, 5.0 eq)	$PhCH_3$ (0.1 M)	BnI (0.6)	48h	8.8	11%	55:45	89:11
38	**392**	K_2CO_3 (50% aq, 5.0 eq)	$PhCH_3$ (0.1 M)	BnI (0.6)	48h	12	12%	55.5:45.5	91.5:8.5
39	**392**	Cs_2CO_3 (s, 2.0 eq)	$PhCH_3$ (0.1 M)	BnI (0.6)	48h	1.7	39%	56.5:43.5	60:40
40	**392**	Cs_2CO_3 (50% aq, 5.0 eq)	$PhCH_3$ (0.1 M)	BnI (0.6)	48h	8.2	26%	62.5:37.5	86.5:13.5
41	**392**	NaOH (25% aq, 5.0 eq)	$PhCH_3$ (0.1 M)	BnI (0.6)	48h	2.7	57%	70:30	65:35
42	**392**	KOH (25% aq, 5.0 eq)	$PhCH_3$ (0.1 M)	BnI (0.6)	48h	3.0	63%	76:24	65.5:34.5
43	**392**	CsOH (25% aq, 5.0 eq)	$PhCH_3$ (0.1 M)	BnI (0.6)	48h	3.8	60%	78.5:21.5	69:31
44	**392**	RbOH (25% aq, 5.0 eq)	$PhCH_3$ (0.1 M)	BnI (0.6)	48h	6.1	56%	83.5:16.5	76:24
46	**392**	K_3PO_4 (50% aq, 5.0 eq)	Et_2O (0.1 M)	BnI (0.6)	48h	7.7	34%	68:32	84.5:15.5
47	**392**	K_3PO_4 (50% aq, 5.0 eq)	^tBuOMe (0.1 M)	BnI (0.6)	48h	4.7	42%	69.5:30.5	76.5:23.5
48	**392**	K_3PO_4 (50% aq, 5.0 eq)	Mesityl oxide (0.1 M)	BnI (0.6)	48h	2.4	73%	76.5:23.5	60:40
49	**392**	K_3PO_4 (50% aq, 5.0 eq)	CH_2Cl_2 (0.1 M)	BnI (0.6)	48h	8.2	68%	97:3	72:28
50	**392**	K_3PO_4 (50% aq, 5.0 eq)	$CHCl_3$ (0.1 M)	BnI (0.6)	48h	10	57%	91:9	79.5:20.5
51	**392**	K_3PO_4 (50% aq, 5.0 eq)	PhH (0.1 M)	BnI (0.6)	48h	14	53%	90:10	85:15
52	**392**	K_3PO_4 (50% aq, 5.0 eq)	$PhCF_3$ (0.1 M)	BnI (0.6)	48h	2.4	43%	62:38	66:34
53	**392**	K_3PO_4 (50% aq, 5.0 eq)	m-Xylene (0.1 M)	BnI (0.6)	48h	15	10%	55:45	93:17
54	**392**	K_3PO_4 (50% aq, 5.0 eq)	p-Xylene (0.1 M)	BnI (0.6)	48h	13	7%	53:47	92.5:7.5
55	**392**	K_3PO_4 (50% aq, 5.0 eq)	1,2-DCE (0.1 M)	BnI (0.6)	48h	7.6	72%	98:2	69:31
56	**392**	K_3PO_4 (50% aq, 5.0 eq)	CCl_4 (0.1 M)	BnI (0.6)	48h	8.6	29%	65:35	86.5:13.5
57	**392**	K_3PO_4 (50% aq, 5.0 eq)	2-MeTHF (0.1 M)	BnI (0.6)	48h	9.7	34%	69:31	87:13
58	**392**	K_3PO_4 (50% aq, 5.0 eq)	$^iPr_2O$ (0.1 M)	BnI (0.6)	48h	2.1	8%	51.5:48.5	67.5:32.5
59	**392**	K_3PO_4 (50% aq, 5.0 eq)	THF (0.1 M)	BnI (0.6)	48h	2.5	67%	74.5:25.5	62:38
60	**392**	K_3PO_4 (50% aq, 5.0 eq)	1,4-Dioxane (0.1 M)	BnI (0.6)	48h	6.6	60%	88:12	75:25
61	**392**	K_3PO_4 (s, 5.0 eq)	9:1 PhH/ $CHCl_3$ (0.1 M)	BnOTs (0.6)	72h	2.5	56%	68:32	64:36
62	**392**	K_2CO_3 (50% aq, 5.0 eq)	PhH (0.1 M)	BnOTs (0.6)	72h	8.5	48%	80:20	81:19
63	**392**	Cs_2CO_3 (50% aq, 5.0 eq)	PhH (0.1 M)	BnOTs (0.6)	72h	6.0	41%	80:20	71:29
64	**395**	K_2CO_3 (50% aq, 5.0 eq)	PhH (0.1 M)	BnOTs (0.6)	72h	15	55%	92:8	85:15
65	**391**	K_2CO_3 (50% aq, 5.0 eq)	PhH (0.1 M)	BnOTs (0.6)	72h	13.9	57%	94:6	83:17
66	**386**	K_2CO_3 (50% aq, 5.0 eq)	PhH (0.1 M)	BnOTs (0.6)	72h	5.8	43%	72:28	79:21
67	**393**	K_2CO_3 (50% aq, 5.0 eq)	PhH (0.1 M)	BnOTs (0.6)	72h	3.4	50%	70.5:29.5	70:30
68	**393**	K_2CO_3 (50% aq, 5.0 eq)	PhH (0.1 M)	BnOTs (0.6)	72h	6.5	57%	85:15	76:24
69	**397**	K_2CO_3 (50% aq, 5.0 eq)	PhH (0.1 M)	BnOTs (0.6)	72h	21	54%	94.5:5.5	88:12
70	**71**	K_2CO_3 (50% aq, 5.0 eq)	PhH (0.1 M)	BnOTs (0.6)	48h	1.8	50%	60:40	60:40
71	**398**	K_2CO_3 (50% aq, 5.0 eq)	PhH (0.1 M)	BnOTs (0.6)	48h	3.9	44%	68.5:31.5	73.5:26.5
72	**74**	K_2CO_3 (50% aq, 5.0 eq)	PhH (0.1 M)	BnOTs (0.6)	48h	2.7	37%	61:39	68.5:31.5
73	**264**	K_2CO_3 (50% aq, 5.0 eq)	PhH (0.1 M)	BnOTs (0.6)	48h	2.4	47%	63.5:36.5	65.5:34.5

74	**75**	K_2CO_3 (50% aq, 5.0 eq)	PhH (0.1 M)	BnOTs (0.6)	48h	21	48%	87:13	91.5:9.5
75	**14**	K_2CO_3 (50% aq, 5.0 eq)	PhH (0.1 M)	BnOTs (0.6)	48h	2.9	51%	68:32	67:33
76	**268**	K_2CO_3 (50% aq, 5.0 eq)	PhH (0.1 M)	BnOTs (0.6)	48h	4.3	37%	65.5:34.5	76:24
77	**269**	K_2CO_3 (50% aq, 5.0 eq)	PhH (0.1 M)	BnOTs (0.6)	48h	17	44%	82:18	90:10
78	**396**	K_2CO_3 (50% aq, 5.0 eq)	PhH (0.1 M)	BnOTs (0.6)	72h	21	55%	94:6	88:12
79	**396**	K_2CO_3 (50% aq, 5.0 eq)	PhH (0.1 M)	BnOTs (0.6)	72h	19	43%	81:19	90.5:9.5
80	**396**	K_2CO_3 (50% aq, 5.0 eq)	CH_2Cl_2 (0.1 M)	BnOTs (0.6)	72h	9	31%	66.5:33.5	86:14
81	**396**	K_2CO_3 (50% aq, 5.0 eq)	$CHCl_3$ (0.1 M)	BnOTs (0.6)	72h	10	45%	79:21	85:15
82	**396**	K_2CO_3 (50% aq, 5.0 eq)	m-Xylene(0.1 M)	BnOTs (0.6)	72h	19	44%	82:18	90.5:9.5
83	**396**	K_2CO_3 (50% aq, 5.0 eq)	p-Xylene (0.1 M)	BnOTs (0.6)	72h	22	47%	84:16	89:11
84	**396**	K_2CO_3 (50% aq, 5.0 eq)	$PhCF_3$ (0.1 M)	BnOTs (0.6)	72h	7.5	22%	60:40	86:14
85	**396**	K_2CO_3 (50% aq, 5.0 eq)	Et_2O (0.1 M)	BnOTs (0.6)	72h	12	49%	84:16	85:15
86	**396**	K_2CO_3 (50% aq, 5.0 eq)	$^{i}Pr_2O$ (0.1 M)	BnOTs (0.6)	72h	5.0	31%	64:36	80.5:19.5
87	**396**	K_2CO_3 (50% aq, 5.0 eq)	^{t}BuOMe (0.1 M)	BnOTs (0.6)	72h	11	47%	81:19	85:15
88	**396**	K_2CO_3 (50% aq, 5.0 eq)	PhH (0.2 M)	BnOTs (0.6)	72h	12	41%	79.5:20.5	87:13
89	**396**	K_2CO_3 (50% aq, 5.0 eq)	PhH (0.05 M)	BnOTs (0.6)	72h	19	43%	81:19	90.5:9.5
90	**396**	K_2CO_3 (50% aq, 5.0 eq)	PhH (0.025 M)	BnOTs (0.6)	72h	25	44%	83.5:16.5	92:8
91	**269**	K_2CO_3 (50% aq, 5.0 eq)	PhH (0.025 M)	BnOTs (0.6)	72h	26	43%	83:17	93:7
92	**75**	K_2CO_3 (50% aq, 5.0 eq)	PhH (0.025 M)	BnOTs (0.6)	72h	32	46%	87:13	93.5:6.5
93	**75**	NaOH (25% aq, 2.0 eq)	PhH (0.025 M)	BnOTs(0.6)	24h	9.2	51%	83.5:16.5	82.5:17.5
94	**75**	KOH (25% aq, 2.0 eq)	PhH (0.025 M)	BnOTs (0.6)	24h	7.8	50%	81:19	81:19
95	**75**	CsOH (25% aq, 2.0 eq)	PhH (0.025 M)	BnOTs (0.6)	24h	19	49%	88:12	89:11
96	**75**	$KHCO_3$ (25% aq, 5.0 eq)	PhH (0.025 M)	BnOTs (0.6)	24h	33	4%	51.5:48.5	94:6
97	**75**	KF (25% aq, 5.0 eq)	PhH (0.025 M)	BnOTs (0.6)	24h	20	8%	54:46	95:5
98	**75**	CsF (25% aq, 5.0 eq)	PhH (0.025 M)	BnOTs (0.6)	24h	40	2%	51:49	97.5:2.5
99	**75**	K_2CO_3 (50% aq, 5.0 eq)	PhH (0.025 M)	BnOTs (1.0)	24h	32	53%	96.5:3.5	90.5:9.5
100	**75**	K_2CO_3 (50% aq, 5.0 eq)	PhH (0.025 M)	BnOTs (1.0)	24h	32	44%	84.5:15.5	94:6
101	**75**	Na_3PO_4 (s, 5.0 eq)	PhH (0.025 M)	BnOTs (0.6)	24h	30	28%	67.5:32.5	95.5:4.5
102	**75**	K_3PO_4 (50% aq, 5.0 eq)	PhH (0.025 M)	BnOTs (0.6)	24h	34	48%	90.5:9.5	93:7
103	**75**	Rb_2CO_3 (50% aq, 5.0 eq)	PhH (0.025 M)	BnOTs (0.6)	24h	29	40%	79.5:20.5	94:6
104	**75**	NaOH (25% aq, 2.0 eq)	PhH (0.025 M)	BnOTs (0.6)	48h	10	54%	87.5:12.5	82:18
105	**75**	KOH (25% aq, 2.0 eq)	PhH (0.025 M)	BnOTs (0.6)	48h	8.2	8%	85.5:14.5	80:20
106	**75**	CsOH (25% aq, 2.0 eq)	PhH (0.025 M)	BnOTs (0.6)	48h	20	55%	95:5	87:13
107	**75**	$KHCO_3$ (25% aq, 5.0 eq)	PhH (0.025 M)	BnOTs (0.6)	48h	27	4%	53:47	96.5:3.5
108	**75**	KF (25% aq, 5.0 eq)	PhH (0.025 M)	BnOTs (0.6)	48h	53	10%	55:45	98:2
109	**75**	CsF (25% aq, 5.0 eq)	PhH (0.025 M)	BnOTs (0.6)	48h	25	4%	52:48	96:4
110	**75**	K_2CO_3 (50% aq, 5.0 eq)	PhH (0.025 M)	BnOTs (1.0)	48h	25	58%	99:1	85.5:14.5
111	**75**	K_2CO_3 (50% aq, 5.0 eq)	PhH (0.025 M)	BnOTs (1.0)	48h	32	51%	93:7	92:8

112	**75**	Na_3PO_4 (s, 5.0 eq)	PhH (0.025 M)	BnOTs (0.6)	48h	29	35%	74:26	94.5:5.5
113	**75**	K_3PO_4 (50% aq, 5.0 eq)	PhH (0.025 M)	BnOTs (0.6)	48h	31	54%	96.5:3.5	90.5:9.5
114	**75**	Rb_2CO_3 (50% aq, 5.0 eq)	PhH (0.025 M)	BnOTs (0.6)	48h	31	47%	88:12	93:7
115	**75**	K_2CO_3 (sat. aq, 5.0 eq)	PhH (0.025 M)	BnOTs (0.6)	48h	35	50%	93:7	93:7
116	**75**	K_2CO_3 (sat. aq, 5.0 eq)	PhH (0.025 M)	BnOTs (0.7)	48h	35	55%	98.5:1.5	89.5:10.5
117	**75**	K_2CO_3 (sat. aq, 5.0 eq)	PhH (0.025 M)	BnOTs (0.8)	48h	34	57%	99.5:0.5	87.5:12.5
118	**75**	K_2CO_3 (sat. aq, 5.0 eq)	PhH (0.025 M)	BnOTs (0.9)	48h	25	60%	99.5:0.5	83.5:16.5
119	**75**	K_2CO_3 (sat. aq, 5.0 eq)	PhH (0.025 M)	BnOTs (1.0)	48h	26	60%	>99.5:0.5	83:17
120	**75**	K_2CO_3 (sat. aq, 5.0 eq)	PhH (0.025 M)	BnOTs (1.5)	48h	13	69%	>99.5:0.5	72:28
121	**75**	K_2CO_3 (sat. aq, 5.0 eq)	9:1 PhH /CH_2Cl_2 (0.025 M)	BnOTs (0.6)	48h	31	45%	85.5:14.5	93.5:6.5
122	**75**	K_2CO_3 (sat. aq, 5.0 eq)	9:1 PhH /$CHCl_3$ (0.025 M)	BnOTs (0.6)	48h	31	46%	87:13	93:7
123	**75**	K_2CO_3 (sat. aq, 5.0 eq)	9:1 PhH /Et_2O (0.025 M)	BnOTs (0.6)	48h	34	48%	90:10	93.5:6.5
124	**75**	K_2CO_3 (s, 5.0 eq)	9:1 PhH /Et_2O (0.025 M)	BnOTs (0.6)	48h	34	46%	87.5:12.5	94:6
125	**75**	K_3PO_4 (sat. aq, 5.0 eq)	9:1 PhH /Et_2O (0.025 M)	BnOTs (0.6)	48h	32	46%	87.5:12.5	93.5:6.5
126	**75**	K_2CO_3 (sat. aq, 5.0 eq)	9:1 PhH /Et_2O (0.025 M)	BnOTs (1.0)	24h	36	49%	91.5:8.5	93.5:6.5
127	**75**	K_2CO_3 (sat. aq, 5.0 eq)	9:1 PhH /Et_2O (0.025 M)	BnOTs (1.5)	24h	35	54%	98:2	90:10

4.3. Extended Optimization Table for the Enantioselective Indole Dearomatization

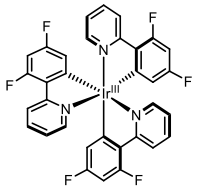
Entry	R =	$R_4N^+X^-$	Solvent (M)	Base (eq.)	Time (h)	Yield (%)	er
1	H	**14**	PhMe (0.1)	50% KOH (5.0)	16	<5	-
2	H	**14**	PhMe (0.025)	50% KOH (5.0)	16	8	-
3	H	**14**	PhMe (0.025)	20% KOH (5.0)	16	6%	-
4	H	**14**	CH_2Cl_2 (0.025)	50% KOH (5.0)	16	33	-
5	H	**14**	CH_2Cl_2 (0.025)	20% KOH (5.0)	16	37	-
6	Me	**14**	CH_2Cl_2 (0.025)	50% KOH (5.0)	16	75	55:45
7	Me	**14**	PhMe (0.025)	50% KOH (5.0)	16	-	58:42
8	Me	**235**	PhMe (0.025)	50% KOH (5.0)	16	-	36:64
9	Me	**71**	PhMe (0.025)	50% KOH (5.0)	16	-	56:44
10	Me	**70**	PhMe (0.025)	50% KOH (5.0)	16	-	46:54
11	Me	**74**	PhMe (0.025)	50% KOH (5.0)	16	-	58:42
12	Me	**234**	PhMe (0.025)	50% KOH (5.0)	16	-	53:47
13	Me	**266**	PhMe (0.025)	50% KOH (5.0)	16	-	53:47
15	Me	**244**	PhMe (0.025)	50% KOH (5.0)	16	-	60:40
16	Me	**238**	PhMe (0.025)	50% KOH (5.0)	16	-	42:58
17	Me	**18**	PhMe (0.025)	50% KOH (5.0)	16	-	40:60
18	Me	**236**	PhMe (0.025)	50% KOH (5.0)	16	-	38:62
19	Me	**237**	PhMe (0.025)	50% KOH (5.0)	16	-	48:52
20	Me	**240**	PhMe (0.025)	50% KOH (5.0)	16	-	65:35
22	Me	399	PhMe (0.025)	50% KOH (5.0)	16	-	45:55
23	Me	**241**	PhMe (0.025)	50% KOH (5.0)	16	-	43:57
24	Me	**242**	PhMe (0.025)	50% KOH (5.0)	16	-	50:50
25	Me	**235**	PhMe (0.025)	K_3PO_4 (5.0)	16	-	-
26	Me	**235**	PhMe (0.025)	sat. aq. K_3PO_4 (5.0)	16	-	56:44
27	Me	**235**	PhMe (0.025)	Na_3PO_4 (5.0)	16	-	-
28	Me	**235**	PhMe (0.025)	sat. aq. Na_3PO_4 (5.0)	16	-	-
29	Me	**235**	PhMe (0.025)	Na_2CO_3 (5.0)	16	-	-
30	Me	**235**	PhMe (0.025)	sat. aq. Na_2CO_3 (5.0)	16	-	-
31	Me	**235**	PhMe (0.025)	K_2CO_3 (5.0)	16	-	-
32	Me	**235**	PhMe (0.025)	sat. aq. K_2CO_3 (5.0)	16	-	-
33	Me	**235**	PhMe (0.025)	Cs_2CO_3 (5.0)	16	-	-
34	Me	**235**	PhMe (0.025)	sat. aq. Cs_2CO_3 (5.0)	16	-	35:65
35	Me	**235**	PhMe (0.025)	NaOH (5.0)	16	-	39:61
36	Me	**235**	PhMe (0.025)	sat. aq. NaOH (5.0)	16	-	38:62
37	Me	**235**	PhMe (0.025)	KOH (5.0)	16	-	-

38	Me	**235**	PhMe (0.025)	sat. aq. KOH (5.0)	16	-	38:62
39	Me	**235**	PhMe (0.025)	CsOH (5.0)	16	-	47:53
40	Me	**235**	PhMe (0.025)	sat. aq. CsOH (5.0)	16	-	39:61
41	Me	**235**	PhMe (0.025)	Li_2CO_3 (5.0)	16	-	50:50
42	Me	**235**	PhMe (0.025)	sat. aq. Li2CO3 (5.0)	16	-	50:50
43	Me	**235**	PhMe (0.025)	LiOH (5.0)	16	-	50:50
44	Me	**235**	PhMe (0.025)	sat. aq. LiOH (5.0)	16	-	50:50
45	Me	**235**	PhMe (0.025)	50% KOH (5.0)	16	64	39:61
46	Me	**235**	PhH (0.025)	50% KOH (5.0)	16	-	39:61
47	Me	**235**	p-xylene (0.025)	50% KOH (5.0)	16	-	38:62
48	Me	**235**	MeCN (49:51)	50% KOH (5.0)	16	-	50:50
49	Me	**235**	CH_2Cl_2 (0.025)	50% KOH (5.0)	16	87	44:56
50	Me	**235**	CHCl3	50% KOH (5.0)	16	-	-
51	Me	**235**	CCl4	50% KOH (5.0)	16	-	34:66
52	Me	**235**	CPME	50% KOH (5.0)	16	72	37:63
53	Me	**235**	Et2O	50% KOH (5.0)	16	-	39:61
54	Me	**235**	iPr2O	50% KOH (5.0)	16	-	38:62
55	Me	**235**	THF	50% KOH (5.0)	16	-	50:50
56	Me	**235**	EtOAc	50% KOH (5.0)	16	-	45:55
57	Me	**235**	9:1 PhMe-$CHCl_3$	50% KOH (5.0)	16	-	38:62
58	Me	**235**	7:3 PhMe-$CHCl_2$	50% KOH (5.0)	16	-	-
59	Me	**235**	9:1 PhMe-CH_2Cl_2	50% KOH (5.0)	16	-	38:62
60	Me	**235**	7:3 PhMe-CH_2Cl_2	50% KOH (5.0)	16	88	38:62
61	Me	**251**	7:3 PhMe-CH_2Cl_2	50% KOH (5.0)	16	-	48:52
62	Me	**250**	7:3 PhMe-CH_2Cl_2	50% KOH (5.0)	16	-	45:55
63	Me	**72**	7:3 PhMe-CH_2Cl_2	50% KOH (5.0)	16	-	50:50
64	Me	**170**	7:3 PhMe-CH_2Cl_2	50% KOH (5.0)	16	-	56:44
65	Me	**403**	7:3 PhMe-CH_2Cl_2	50% KOH (5.0)	16	-	39:61
66	Me	**247**	7:3 PhMe-CH_2Cl_2	50% KOH (5.0)	16	-	41:69
67	Me	**401**	7:3 PhMe-CH_2Cl_2	50% KOH (5.0)	16	-	45:55
68	Me	**248**	7:3 PhMe-CH_2Cl_2	50% KOH (5.0)	16	-	44:56
69	Me	**402**	7:3 PhMe-CH_2Cl_2	50% KOH (5.0)	16	-	45:55
73	$CO_2{}^iPr$	**235**	7:3 PhMe-CH_2Cl_2	50% KOH (5.0)	2	40	31:69
74	$CO_2{}^iPr$	**235**	7:3 PhMe-CH_2Cl_2	20% KOH (5.0)	16	60	31:69
75	$CO_2{}^iPr$	**235**	7:3 PhMe-CH_2Cl_2	KOH (5.0)	2	30	33:67
76	$CO_2{}^iPr$	**235**	7:3 PhMe-CH_2Cl_2	50% KOH (1.5 eq.)	2	75	31:69
77	$CO_2{}^iPr$	**235**	7:3 PhMe-CH_2Cl_2	50% KOH (1.1 eq.)	4	90	31:69
79	$CO_2{}^iPr$	**235**	7:3 PhMe-CH_2Cl_2	50% KOH (1.1 eq.)	4	-	31:69

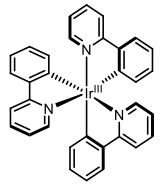
80	$CO_2{}^iPr$	**248**	7:3 PhMe-CH_2Cl_2	50% KOH (1.1 eq.)	4	-	60:40
81	$CO_2{}^iPr$	**385**	7:3 PhMe-CH_2Cl_2	50% KOH (1.1 eq.)	4	-	41:59
82	$CO_2{}^iPr$	**74**	7:3 PhMe-CH_2Cl_2	50% KOH (1.1 eq.)	4	-	37:63
83	$CO_2{}^iPr$	**234**	7:3 PhMe-CH_2Cl_2	50% KOH (1.1 eq.)	4	-	40:60
84	$CO_2{}^iPr$	**170**	7:3 PhMe-CH_2Cl_2	50% KOH (1.1 eq.)	4	-	39:61
85	$CO_2{}^iPr$	**266**	7:3 PhMe-CH_2Cl_2	50% KOH (1.1 eq.)	4	-	33:67
86	$CO_2{}^iPr$	**238**	7:3 PhMe-CH_2Cl_2	50% KOH (1.1 eq.)	4	-	63:37
87	$CO_2{}^iPr$	**18**	7:3 PhMe-CH_2Cl_2	50% KOH (1.1 eq.)	4	-	67:33
88	$CO_2{}^iPr$	**240**	7:3 PhMe-CH_2Cl_2	50% KOH (1.1 eq.)	4	-	64:36
89	$CO_2{}^iPr$	**244**	7:3 PhMe-CH_2Cl_2	50% KOH (1.1 eq.)	4	-	41:59
90	$CO_2{}^iPr$	**403**	7:3 PhMe-CH_2Cl_2	50% KOH (1.1 eq.)	4	-	64:36
91	$CO_2{}^iPr$	**247**	7:3 PhMe-CH_2Cl_2	50% KOH (1.1 eq.)	4	-	68:32
92	$CO_2{}^iPr$	**236**	7:3 PhMe-CH_2Cl_2	50% KOH (1.1 eq.)	4	-	69:31
93	$CO_2{}^iPr$	**404**	7:3 PhMe-CH_2Cl_2	50% KOH (1.1 eq.)	4	-	
94	$CO_2{}^iPr$	**257**	7:3 PhMe-CH_2Cl_2	50% KOH (1.1 eq.)	4	-	69:31
95	$CO_2{}^iPr$	**258**	7:3 PhMe-CH_2Cl_2	50% KOH (1.1 eq.)	4	-	68:32
96	$CO_2{}^iPr$	**259**	7:3 PhMe-CH_2Cl_2	50% KOH (1.1 eq.)	4	-	69:31
97	$CO_2{}^iPr$	**260**	7:3 PhMe-CH_2Cl_2	50% KOH (1.1 eq.)	4	-	64:36
98	$CO_2{}^iPr$	**237**	7:3 PhMe-CH_2Cl_2	50% KOH (1.1 eq.)	4	-	66:34
99	$CO_2{}^iPr$	**261**	7:3 PhMe-CH_2Cl_2	50% KOH (1.1 eq.)	4	-	66:34
100	$CO_2{}^iPr$	**262**	7:3 PhMe-CH_2Cl_2	50% KOH (1.1 eq.)	4	-	69:31
101	$CO_2{}^iPr$	**401**	7:3 PhMe-CH_2Cl_2	50% KOH (1.1 eq.)	4	-	65:35
102	$CO_2{}^iPr$	**71**	7:3 PhMe-CH_2Cl_2	50% KOH (1.1 eq.)	4	-	34:66
103	$CO_2{}^iPr$	**250**	7:3 PhMe-CH_2Cl_2	50% KOH (1.1 eq.)	4	-	52:48
104	$CO_2{}^iPr$	**72**	7:3 PhMe-CH_2Cl_2	50% KOH (1.1 eq.)	4	-	36:64
105	$CO_2{}^iPr$	**264**	7:3 PhMe-CH_2Cl_2	50% KOH (1.1 eq.)	4	-	34:66
106	$CO_2{}^iPr$	**70**	7:3 PhMe-CH_2Cl_2	50% KOH (1.1 eq.)	4	-	51:49
107	$CO_2{}^iPr$	**265**	7:3 PhMe-CH_2Cl_2	50% KOH (1.1 eq.)	4	-	42:58
108	$CO_2{}^iPr$	**266**	7:3 PhMe-CH_2Cl_2	50% KOH (1.1 eq.)	4	-	37:63
109	$CO_2{}^iPr$	**267**	7:3 PhMe-CH_2Cl_2	50% KOH (1.1 eq.)	4	-	33:67
110	$CO_2{}^iPr$	**268**	7:3 PhMe-CH_2Cl_2	50% KOH (1.1 eq.)	4	-	35:65
111	$CO_2{}^iPr$	**269**	7:3 PhMe-CH_2Cl_2	50% KOH (1.1 eq.)	4	-	38:62
112	$CO_2{}^iPr$	**270**	7:3 PhMe-CH_2Cl_2	50% KOH (1.1 eq.)	4	-	44:56
113	$CO_2{}^iPr$	**271**	7:3 PhMe-CH_2Cl_2	50% KOH (1.1 eq.)	4	-	46:54
114	$CO_2{}^iPr$	**272**	7:3 PhMe-CH_2Cl_2	50% KOH (1.1 eq.)	4	-	49:51
116	Ph	**14**	7:3 PhMe-CH_2Cl_2	50% KOH (5.0 eq.)	16	-	63:36
117	Ph	**235**	7:3 PhMe-CH_2Cl_2	50% KOH (5.0 eq.)	16	-	30:70
118	Ph	**248**	7:3 PhMe-CH_2Cl_2	50% KOH (5.0 eq.)	16	-	43:57

119	Ph	**385**	7:3 PhMe-CH_2Cl_2	50% KOH (5.0 eq.)	16	-	62:38

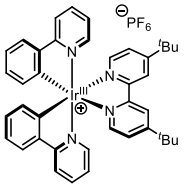
4.4. Index of Photocatalysts



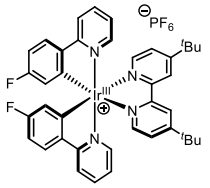
Ir(dFppy)$_3$ (**340**)



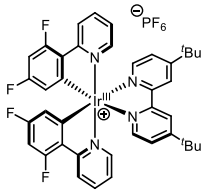
Ir(ppy)$_3$ (**348**)



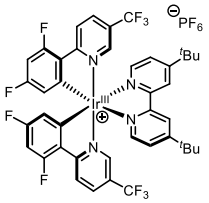
Ir(ppy)$_2$(dtbbpy)(PF$_6$) (**351**)



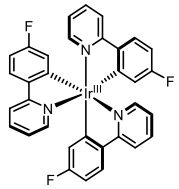
Ir(Fppy)$_2$(dtbbpy)(PF$_6$) (**300**)



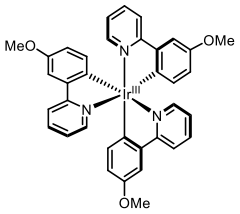
Ir(dFppy)$_2$(dtbbpy)(PF$_6$) (**352**)



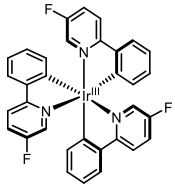
Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)(PF$_6$) (**282**)



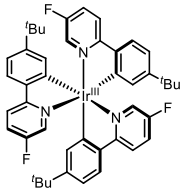
Ir(Fppy)$_3$ (**354**)



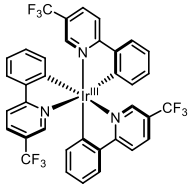
Ir((3'-OMe)ppy)$_3$ (**355**)



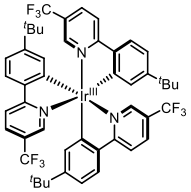
Ir((5-F)ppy)$_3$ (**364**)



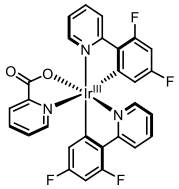
Ir((5-F)(4'-^{t}Bu)ppy)$_3$ (**365**)



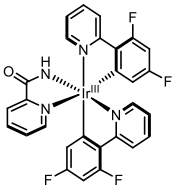
Ir((5-CF$_3$)ppy)$_3$ (**366**)



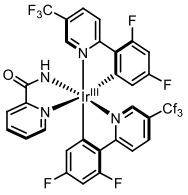
Ir((5-CF$_3$)(4'-^{t}Bu)ppy)$_3$ (**367**)



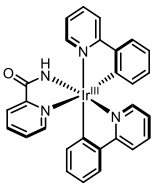
Ir(dFppy)$_2$(pic) (**410**)



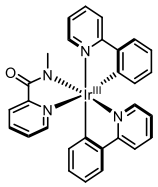
Ir(dFppy)$_2$(pca) (**411**)



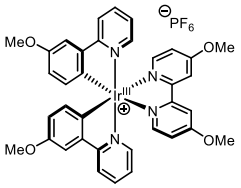
Ir(dF(CF$_3$)ppy)$_2$(pca) (**412**)



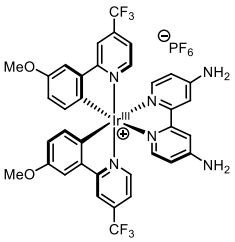
Ir(ppy)$_2$(pca) (**413**)



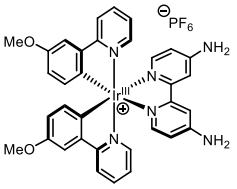
Ir(ppy)$_2$((*N*-Me)pca) (**414**)



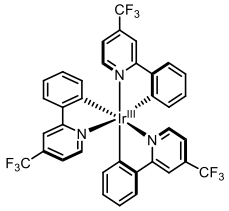
Ir((3'-OMe)ppy)$_2$(4,4'-(OMe)$_2$bpy)(PF$_6$) (**415**)



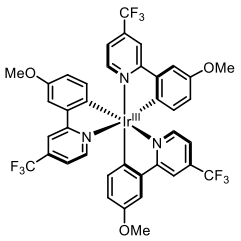
Ir((3'-OMe)(4-CF$_3$)ppy)$_2$((4,4'-NH$_2$)bpy)(PF$_6$) (**416**)



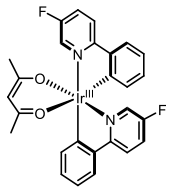
Ir((3'OMe)ppy)$_2$((4,4'-NH$_2$)bpy)(PF$_6$) (**417**)



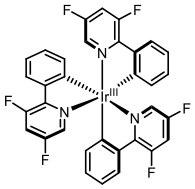
Ir((4-CF3)ppy)$_3$ (**418**)



Ir((3'-OMe)(4-CF$_3$)ppy)$_3$ (**419**)



Ir((5-F)ppy)$_2$(acac) (**420**)



Ir((3,5-dF)ppy)$_3$ (**421**)

4.5. Characterisation of novel photocatalysts

All data was obtained and analysed my Mihai Popescu

To be able to compare the properties of different photocatalysts, all excited state redox properties were calculated from ground state redox potentials in acetonitrile and λ (10%) values which were either recorded or available in the literature.[133, 134, 151, 152]

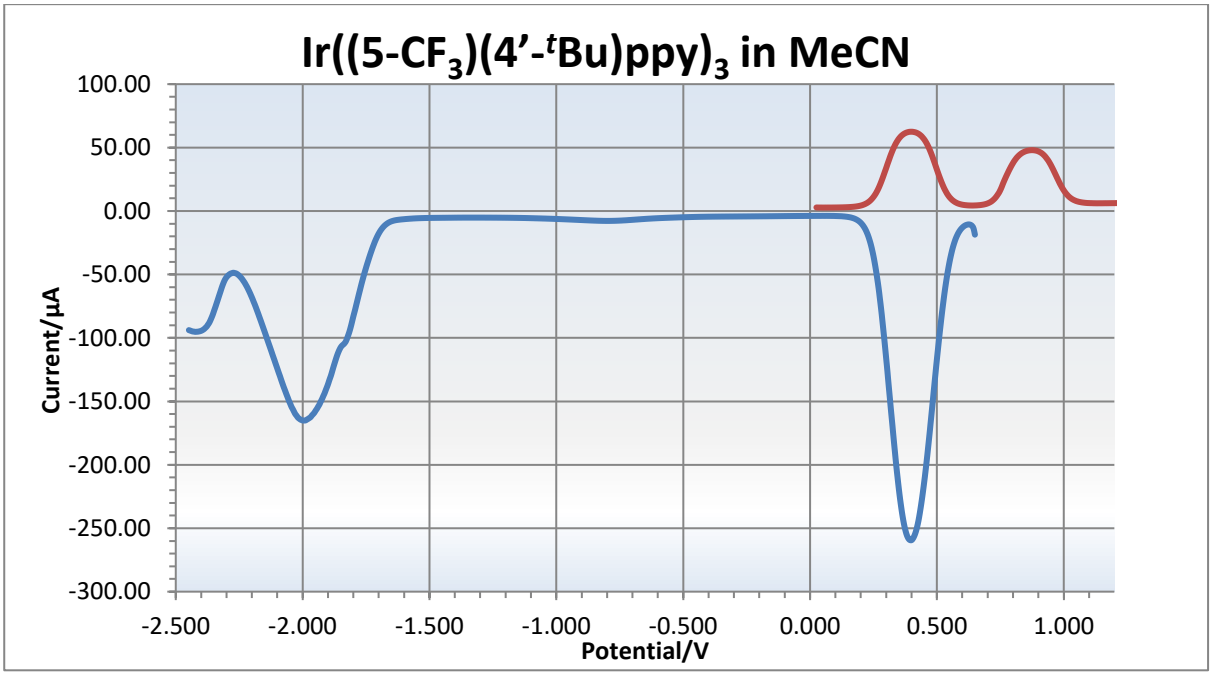
The excited state redox properties were calculated using the Rahm-Weller equations:[153]

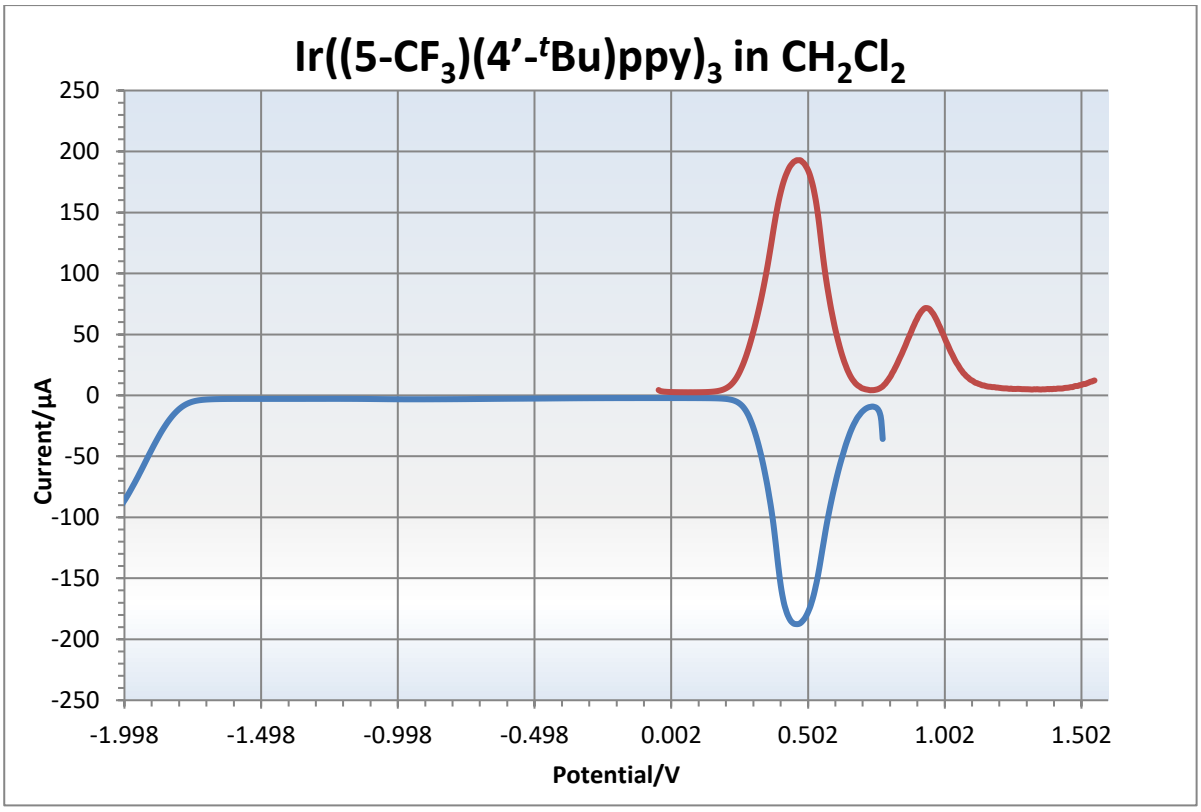
$$E_{1/2}^{red}\ Ir(IV)/*(III) = E_{1/2}^{red}\ Ir(IV)/(III) - E^{0\text{-}0}$$

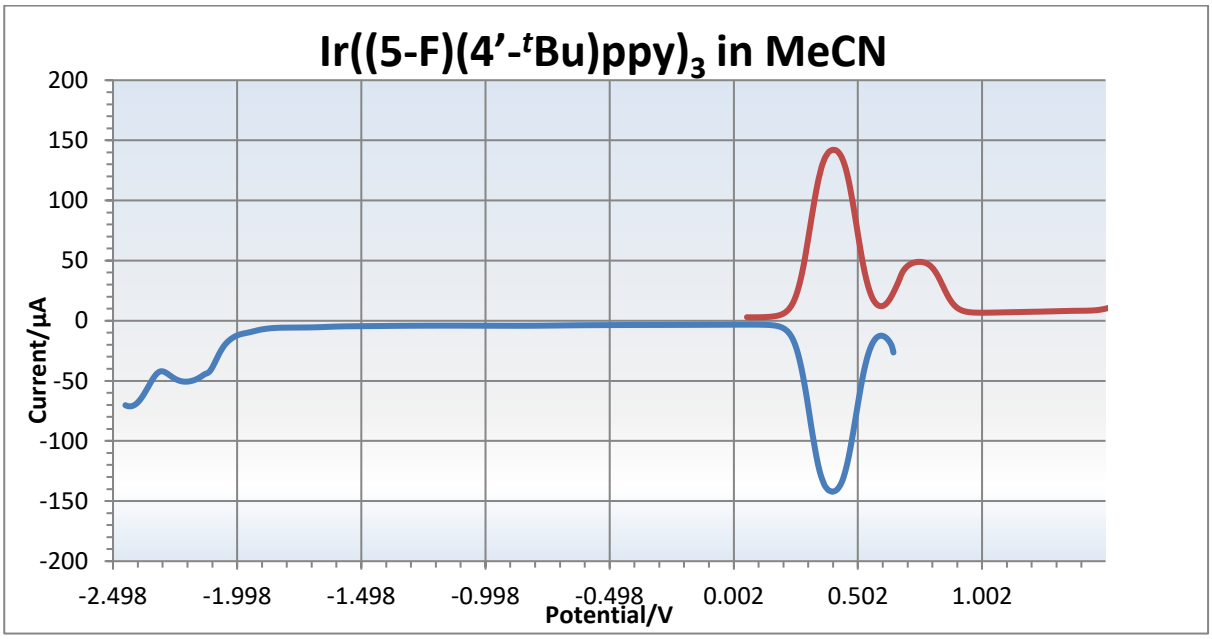
$$E_{1/2}^{red}\ Ir*(III)/(II) = E_{1/2}^{red}\ Ir(III)/(II) + E^{0\text{-}0}$$

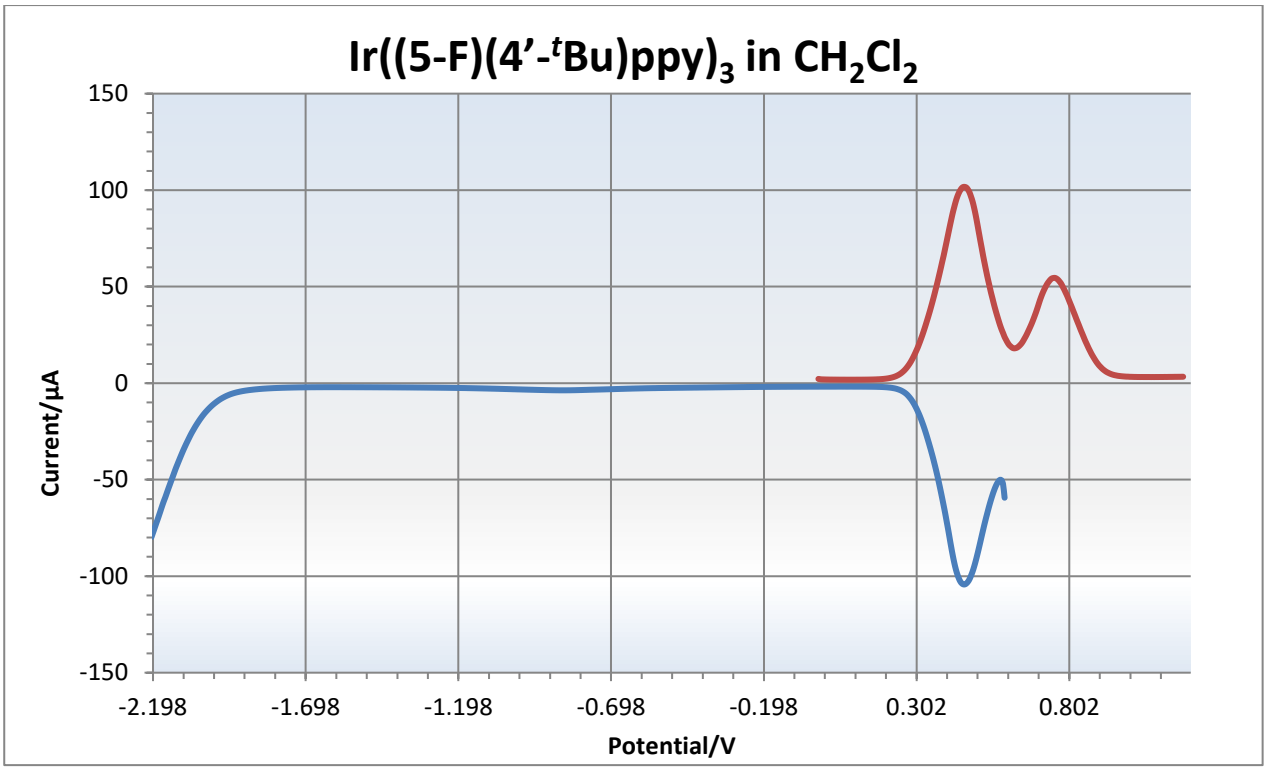
Where $E^{0\text{-}0}$ is the energy gap between the zero-level vibrational levels of the ground and excited state; estimated as the high-energy onset of phosphorescence where the emission intensity is 10% of the observed maximum.

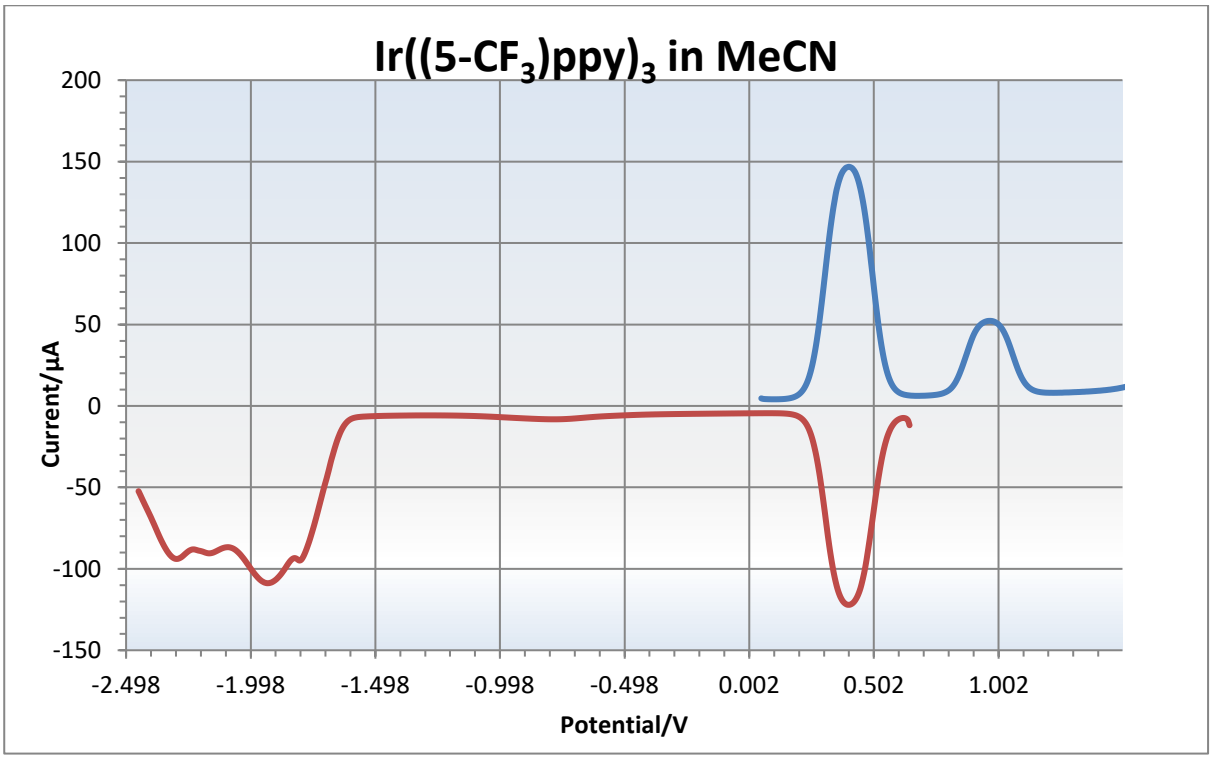
Determination of photocatalyst ground state redox properties

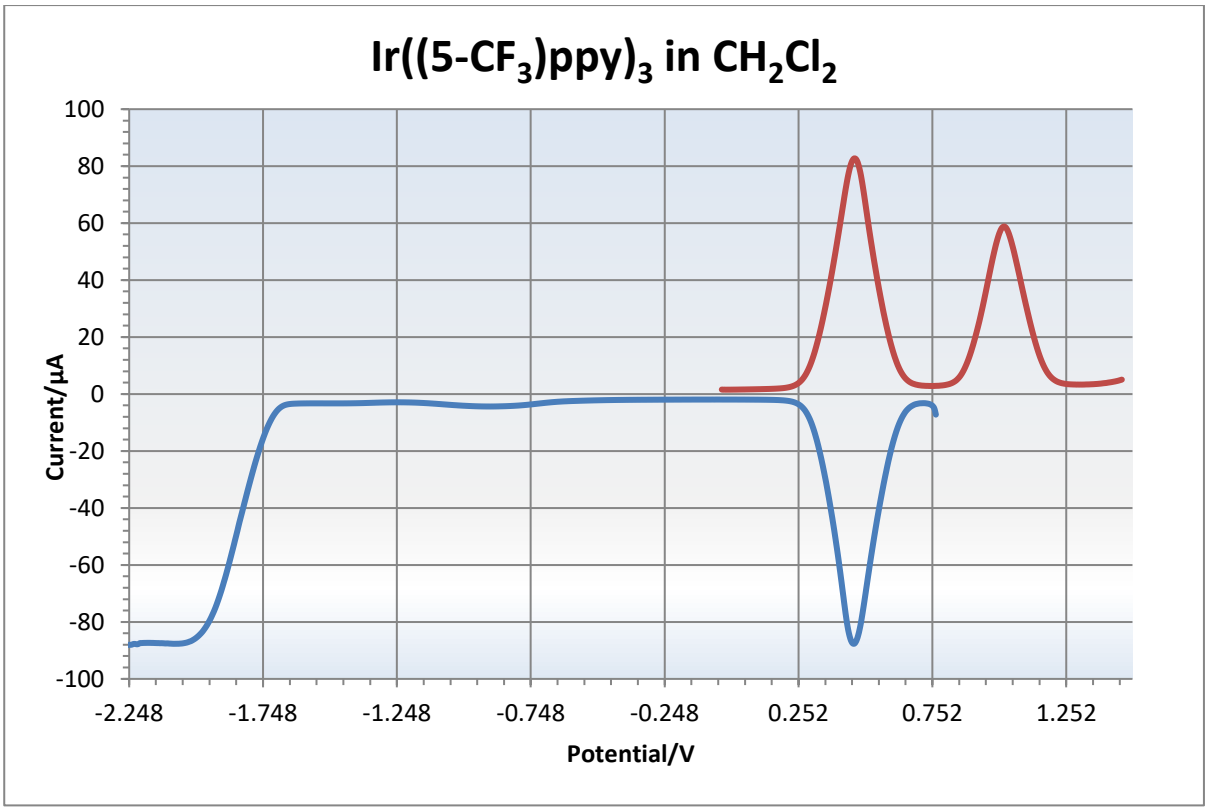


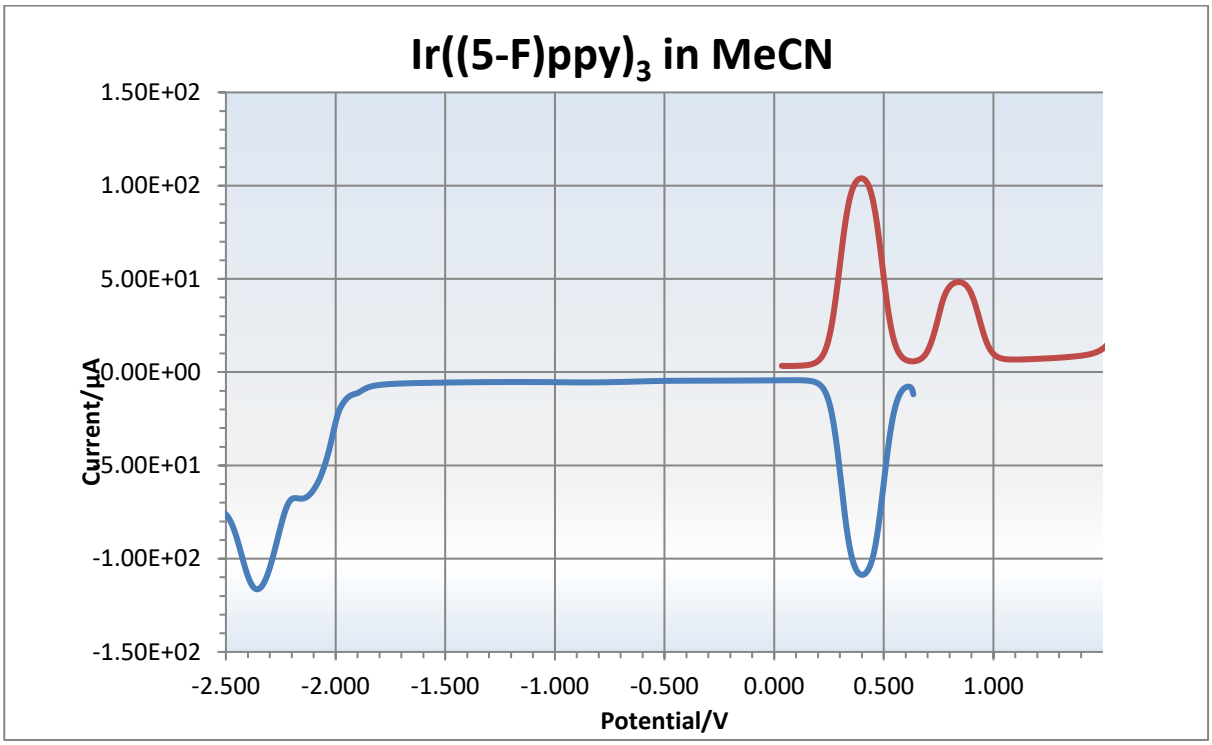

Ir((5-CF3)(4'-tBu)ppy)3 in CH2Cl2
250
200
150
100
50
0
-50
-100
-150
-200
-250
Current/µA
-1.998
-1.498
-0.998
-0.498
0.002
0.502
1.002
1.502
Potential/V

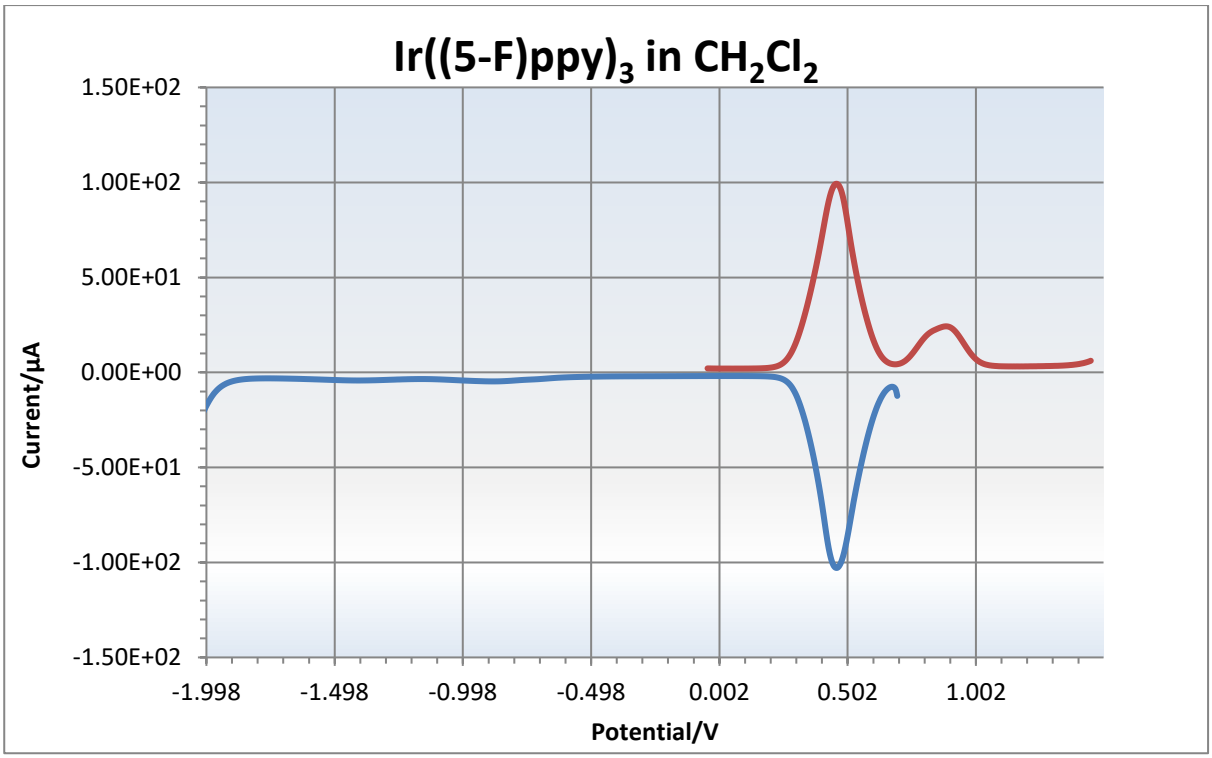

Ir((5-F)(4'-tBu)ppy)3 in MeCN
200
150
100
50
0
-50
-100
-150
-200
Current/µA
-2.498
-1.998
-1.498
-0.998
-0.498
0.002
0.502
1.002
Potential/V


Ir((5-F)(4'-tBu)ppy)3 in CH2Cl2
150
100
50
0
-50
-100
-150
Current/µA
-2.198
-1.698
-1.198
-0.698
-0.198
0.302
0.802
Potential/V

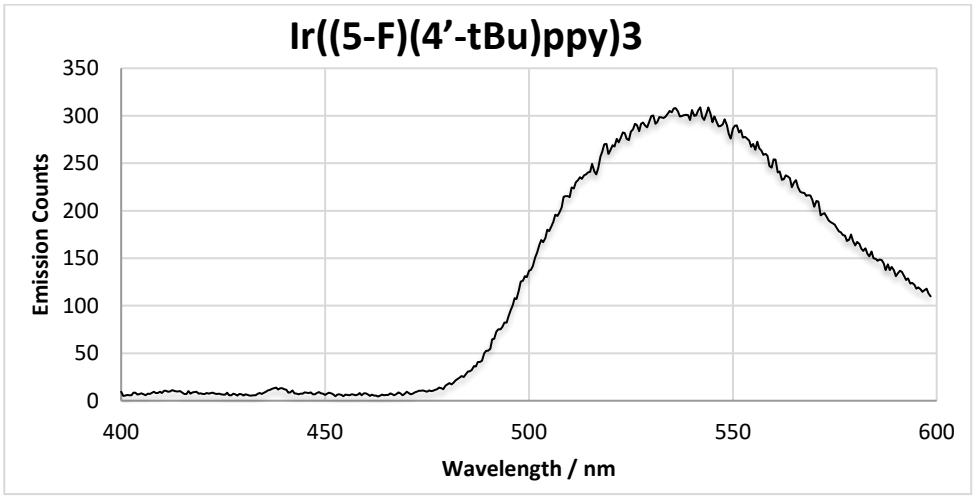

Ir((5-CF3)ppy)3 in MeCN
200
150
100
50
0
-50
-100
-150
Current/µA
-2.498
-1.998
-1.498
-0.998
-0.498
0.002
0.502
1.002
Potential/V

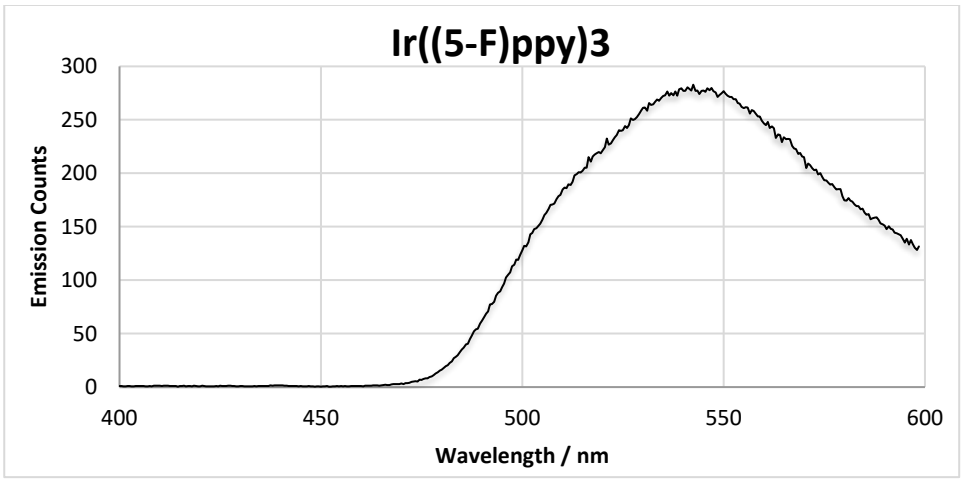

Ir((5-CF3)ppy)3 in CH2Cl2
100
80
60
40
20
0
-20
-40
-60
-80
-100
Current/µA
-2.248
-1.748
-1.248
-0.748
-0.248
0.252
0.752
1.252
Potential/V

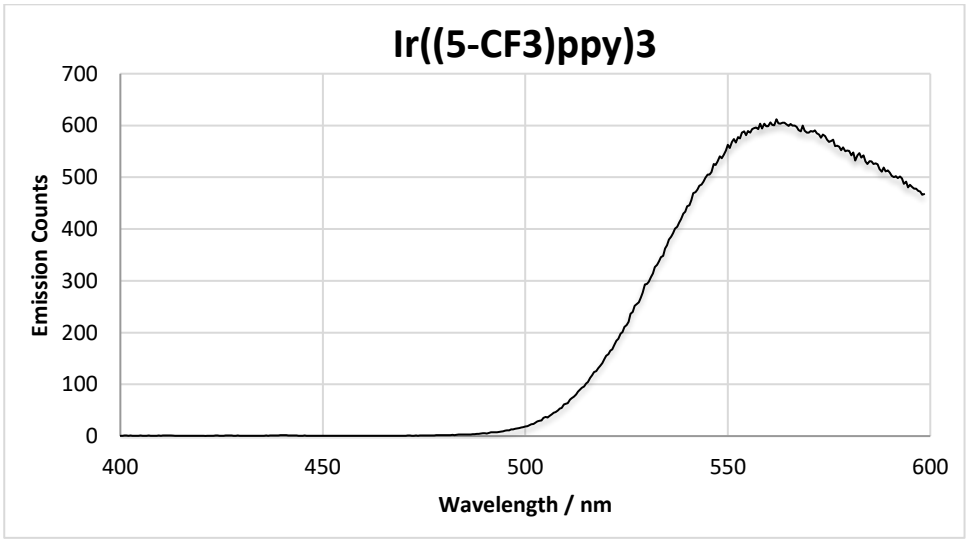

Ir((5-F)ppy)3 in MeCN
1.50E+02
1.00E+02
5.00E+01
0.00E+00
-5.00E+01
-1.00E+02
-1.50E+02
Current/µA
-2.500
-2.000
-1.500
-1.000
-0.500
0.000
0.500
1.000
Potential/V

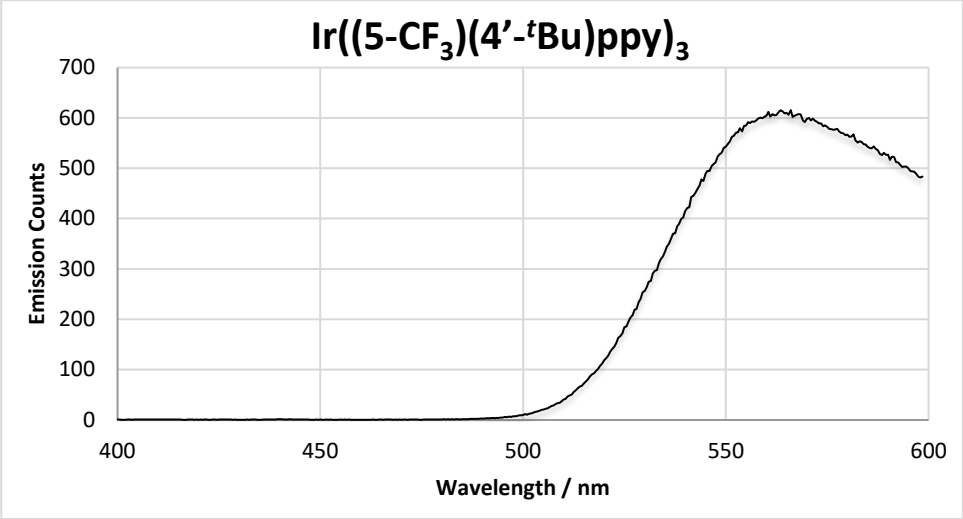

Ir((5-F)ppy)3 in CH2Cl2
1.50E+02
1.00E+02
5.00E+01
0.00E+00
-5.00E+01
-1.00E+02
-1.50E+02
Current/µA
-1.998
-1.498
-0.998
-0.498
0.002
0.502
1.002
Potential/V

Emission Spectra of Photocatalysts







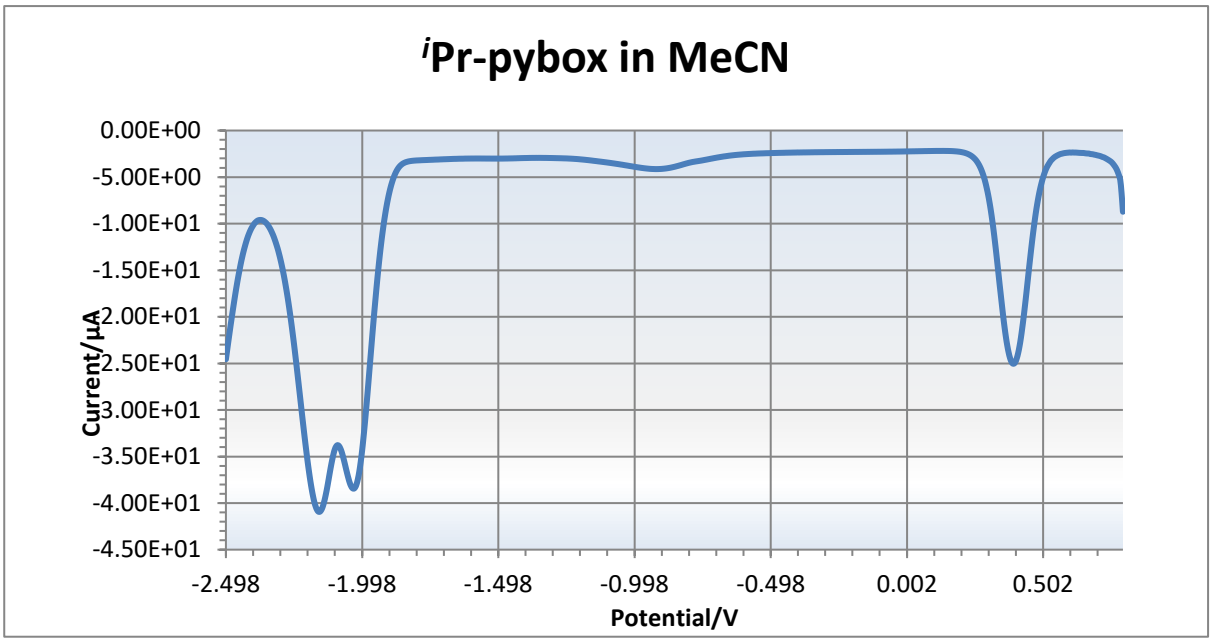


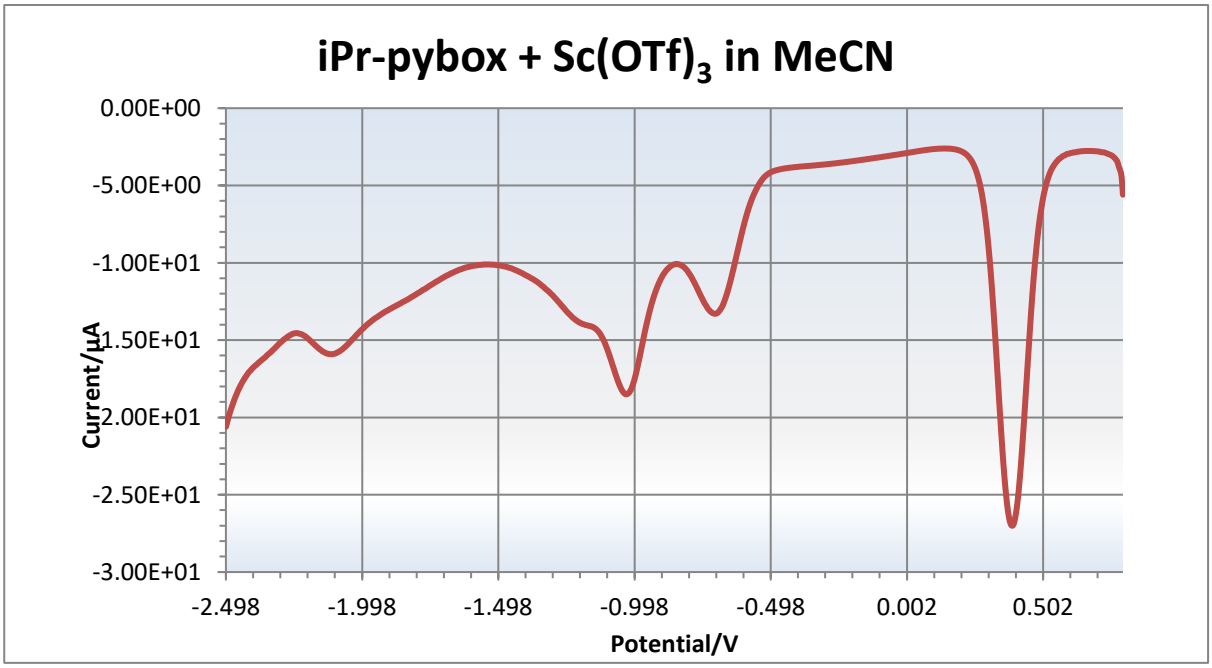
Summary of Photocatalyst Properties

Photocatalyst	$E_{1/2}^{red}$ vs. SCE in CH_2Cl_2 (V)		$E_{1/2}^{red}$ vs. SCE in MeCN (V)				Emission in MeCN (nm)		E_T (kcal/mol)	
	$Ir^{IV/III}$	$Ir^{IV/*III}$	$Ir^{IV/III}$	$Ir^{IV/*III}$	$Ir^{III/II}$	$Ir^{*III/II}$	λ (10%)	λ (max)	λ (10%)	λ (max)
$Ir(ppy)_3$[133]	+0.69	-1.88	+0.77	-1.81	-2.23	+0.35	481	516	59.4	55.4
$Ir((4'\text{-}^tBu)ppy)_3$[133]	+0.60	-1.97	+0.66	-1.90	-2.33	+0.23	485	525	59.0	54.5
$Ir(Fppy)_3$[134]	N/A	N/A	+0.96	-1.74	-2.18	+0.52	459[a]	488	62.3	58.6
$Ir(dFppy)_3$[134]	N/A	N/A	+0.94	-1.83	-1.87	+0.90	448[a]	476	63.8	60.0
$Ir(dF(CF_3)ppy)_2(dtbbpy)(PF_6)$[134]	N/A	N/A	+1.73	-1.01	-1.40	+1.34	452[a]	476	63.3	60.0
$Ir(dFppy)_2(dtbbpy)(PF_6)$[134]	N/A	N/A	+1.59	-1.15	-1.47	+1.27	452[a]	516	63.3	55.4
$Ir(Fppy)_2(dtbbpy)(PF_6)$[134]	N/A	N/A	+1.45	-1.19	-1.50	+1.14	469[a]	540	61.0	52.9
$Ir(ppy)_2(dtbbpy)(PF_6)$[152]	N/A	N/A	+1.33	-1.32	-1.34	-0.84	500[151][a]	571[151]	56.4	48.3
$Ir((3'\text{-}OMe)ppy)_3$[133]	+0.70	-1.95	+0.76	-1.89	-2.34	+0.26	517	557	55.3	51.3
$Ir((5\text{-}F)ppy)_3$	+0.88	-1.69	+0.84	-1.73	-2.17	+0.40	483	543	59.2	52.7
$Ir((5\text{-}F)(4'\text{-}^tBu)ppy)_3$	+0.75	-1.81	+0.75	-1.81	-2.22	+0.34	485	551	59.0	51.9
$Ir((5\text{-}CF_3)ppy)_3$	+1.02	-1.41	+0.97	+1.46	-1.80	+0.63	510	562	56.0	50.9
$Ir((5\text{-}CF_3)(4'\text{-}^tBu)ppy)_3$	+0.93	-1.49	+0.87	+1.55	-1.83	+0.59	513	568	55.7	50.3

4.6. Voltammetry Studies

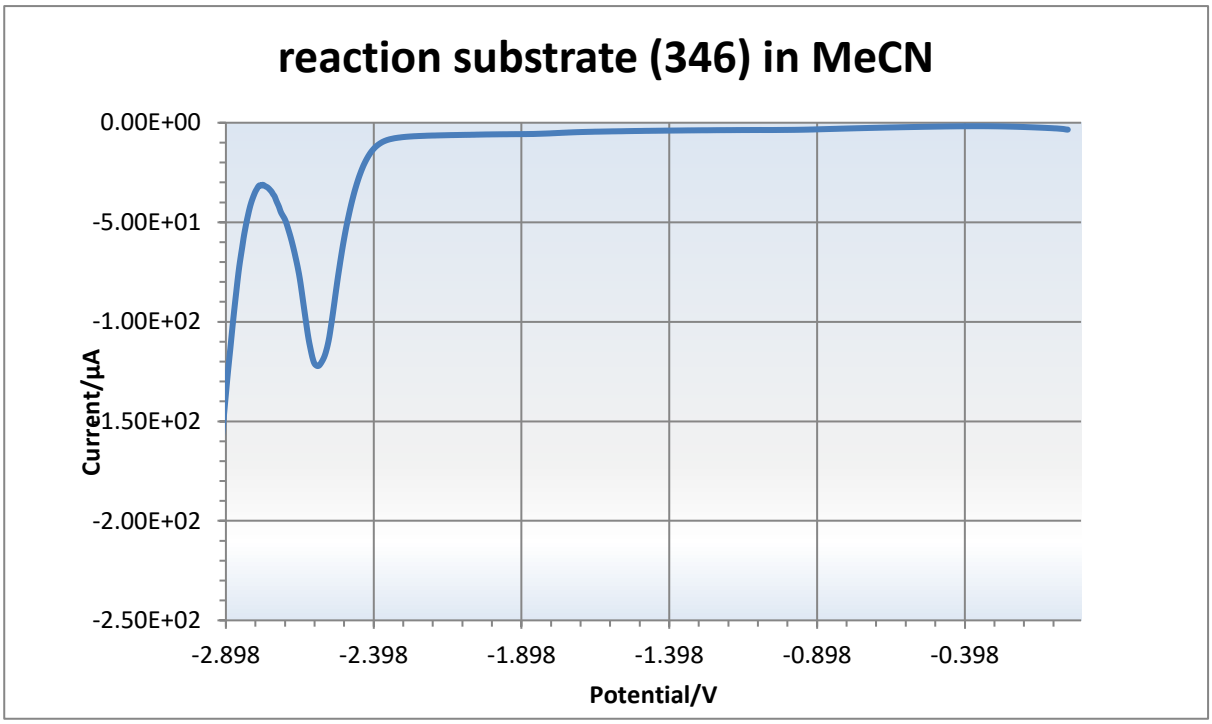
Determination of ^{i}Pr-pybox redox potentials and the effect of $Sc(OTf)_3$

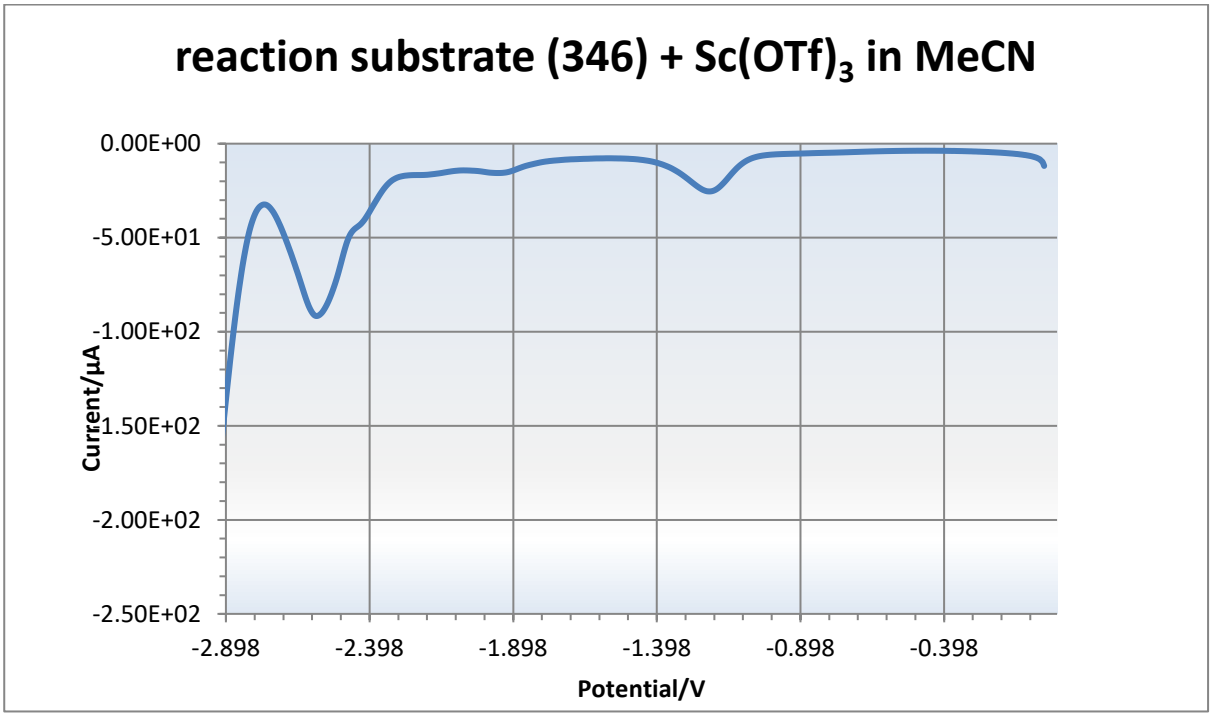




Determination of Substrate Redox Potentials and the Effect of $Sc(OTf)_3$

All data was obtained and analysed my Mihai Popescu





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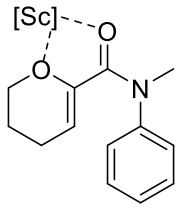
4.7. Calculation of Substrate Triplet Energy and the Effect of Scandium Salts

All calculations were performed by Mihai Popescu



[Sc] =	E_T (kcal mol^{-1})
none	56.7
$ScCl_3$	54.9
$[Sc(H_2O)_4]^{3+}$	55.3
Sc^{3+}	45.9

Computational details

Methods:

The range-separated dispersion-corrected uM06-2X[154] density functional and the 6.31+G(d,p)[155-159] basis set were used with the CPCM[160, 161] solvation model (solvent = dichloromethane) to account for solvent effects. When scandium atoms were included in the structures, genECP was used with the def2TZVP[162, 163] basis set for scandium atoms and 6.31+G(d,p) for the remaining ones. Gaussian 16[164] was employed for all density functional theory (DFT) calculations, using an "ultrafine" pruned (99,590) grid for numerical integration of the exchange-correlation functional and its derivatives. We performed vibrational frequency calculations to verify that stationary points were either minima or first-order saddle points on the potential energy surface, and to calculate thermal corrections to Gibbs free energies (G). The computed thermochemistry data were corrected following Grimme's quasiharmonic (QHA)[165] model for entropy with a frequency cut-off value of 100.0 cm^{-1} using the GoodVibes program at 298.15 K (25˚C). Molecular graphics were generated using PyMol.

GoodVibes information and input line:

```
   GoodVibes v3.0.1 2021/06/14 13:36:47
   REF: Luchini, G.; Alegre-Requena J. V.; Guan, Y.; Funes-Ardoiz, I.; Paton, R. S. (2019).
        GoodVibes: GoodVibes 3.0.1 http://doi.org/10.5281/zenodo.595246
   Requested: --xyz

   Temperature = 298.15 Kelvin   Pressure = 1 atm
   All energetic values below shown in Hartree unless otherwise specified.
x  Caution! Different levels of theory found:
        -M062X/GenECP: SM-S0-Sc-H2O.log, SM-S0-Sc.log, SM-S0-ScCl3.log, SM-T1-Sc-H2O.log, SM-T1-Sc.log, SM-T1-
ScCl3.log
        -M062X/6-31+G(d,p): SM-S0.log, SM-T1.log
   Using vibrational scale factor 1.0: differing levels of theory detected.

   Caution! Implicit solvation (SMD/CPCM) detected. Enthalpic and entropic terms cannot be safely separated. Use
them at your own risk!

   Entropic quasi-harmonic treatment: frequency cut-off value of 100.0 wavenumbers will be applied.
   QS = Grimme: Using a mixture of RRHO and Free-rotor vibrational entropies.
   REF: Grimme, S. Chem. Eur. J. 2012, 18, 9955-9964
```

	Structure	E	ZPE	H	T.S	T.qh-S	G(T)	qh-G(T)
o	SM-S0-Sc-H2O	-1775.379213	0.364579	-1774.986801	0.084388	0.079977	-1775.071188	-1775.066778
o	SM-S0-Sc	-1469.616444	0.264131	-1469.336040	0.059714	0.057645	-1469.395754	-1469.393685
o	SM-S0-ScCl3	-2850.883684	0.266534	-2850.594684	0.075843	0.071366	-2850.670527	-2850.666051
o	SM-S0	-709.344848	0.260277	-709.069228	0.057977	0.055608	-709.127205	-709.124836
o	SM-T1-Sc-H2O	-1775.286829	0.360860	-1774.897622	0.085755	0.081665	-1774.983377	-1774.979287
o	SM-T1-Sc	-1469.539101	0.261098	-1469.261460	0.060807	0.059095	-1469.322266	-1469.320554
o	SM-T1-ScCl3	-2850.791094	0.263409	-2850.504755	0.077329	0.073178	-2850.582084	-2850.577932
o	SM-T1	-709.250326	0.257128	-708.977541	0.059116	0.057007	-709.036657	-709.034547

The generation of xyz files was automated with GoodVibes using the --xyz option:

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44
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C  -2.771132  -0.822591   0.004019
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H   4.699684   1.288828   0.384074
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32
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35
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31
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31
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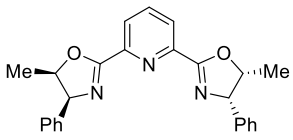
4.8. Index of Chiral Ligands



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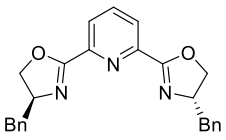

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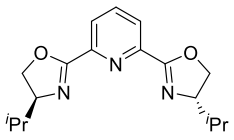

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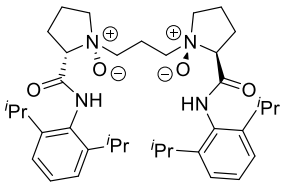

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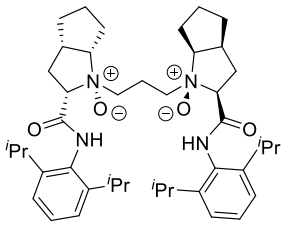

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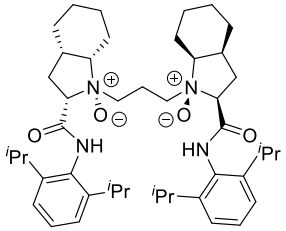

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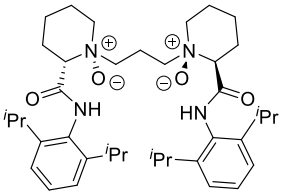

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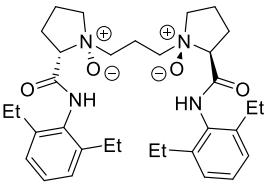

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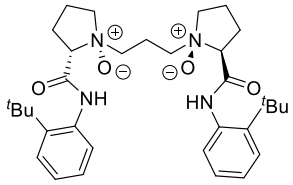

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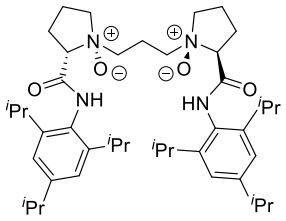

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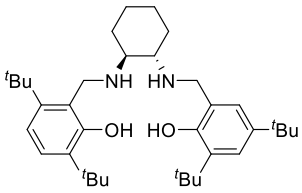

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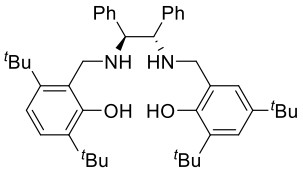

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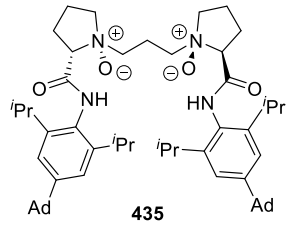

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4.9. Extended Optimization Table for the Enantioselective Photocyclization

Entry	Photocatalyst	Lewis acid (mol %)	Ligand (mol%)	Solvent/conc. (M)	Temp. (°C)	Conversion (%)	Yield (%)	er	dr
1	$Ir(ppy)_3$ (**348**)	$Sc(OTf)_3$ (25)	**425** (30)	CH_2Cl_2 (0.02)	10-15	11	10	-	1.1
2	$Ir(ppy)_3$ (**348**)	$Sc(OTf)_3$ (25)	**426** (30)	CH_2Cl_2 (0.02)	10-15	9	10	50:50	-
3	$Ir(ppy)_3$ (**348**)	$Sc(OTf)_3$ (25)	**349** (30)	CH_2Cl_2 (0.02)	10-15	<10	5	70:30	-
4	$Ir(ppy)_3$ (**348**)	$Sc(OTf)_3$ (25)	**350** (30)	CH_2Cl_2 (0.02)	10-15	100	96	75:25	>19.1
5	$Ir(ppy)_3$ (**348**)	$Sc(OTf)_3$ (25)	**350** (30)	DCE (0.02)	10-15	59	40	67:33	>19.1
6	$Ir(ppy)_3$ (**348**)	$Sc(OTf)_3$ (25)	**350** (30)	PhMe (0.02)	10-15	37	17	64:35	>19.1
7	$Ir(ppy)_3$ (**348**)	$Sc(OTf)_3$ (25)	**350** (30)	CPME (0.02)	10-15	55	64	-	3:1
8	$Ir(ppy)_3$ (**348**)	$Sc(OTf)_3$ (25)	**350** (30)	EtOAc (0.02)	10-15	79	<10	-	-
9	$Ir(ppy)_3$ (**348**)	$Sc(OTf)_3$ (25)	**427** (30)	CH_2Cl_2 (0.02)	10-15	n.d.	n.d.	51:49	n.d.
10	$Ir(ppy)_3$ (**348**)	$Sc(OTf)_3$ (25)	**428** (30)	CH_2Cl_2 (0.02)	10-15	n.d.	n.d.	51:49	n.d.
11	$Ir(ppy)_3$ (**348**)	$Sc(OTf)_3$ (25)	**429** (30)	CH_2Cl_2 (0.02)	10-15	n.d.	n.d.	70:30	n.d.
12	$Ir(ppy)_2(dtbbpy)PF_6$ (**351**)	$Sc(OTf)_3$ (25)	**430** (30)	CH_2Cl_2 (0.02)	10-15	<5	<5	55:45	-
13	$Ir(Fppy)_2(dtbbpy)PF_6$ (**300**)	$Sc(OTf)_3$ (25)	**429** (30)	CH_2Cl_2 (0.02)	10-15	17	12	56:44	>19.1
14	$Ir(dFppy)_2(dtbbpy)PF_6$ (**352**)	$Sc(OTf)_3$ (25)	**429** (30)	CH_2Cl_2 (0.02)	10-15	100	80	51:49	3.1
15	$Ir(ppy)_3$ (**348**)	$Cu(OTf)_2$ (25)	**350** (30)	CH_2Cl_2 (0.02)	10-15	65	<5	63:37	-
16	$Ir(ppy)_3$ (**348**)	$Mg(OTf)_2$ (25)	**350** (30)	CH_2Cl_2 (0.02)	10-15	84	40	50:50	-
17	$Ir(ppy)_3$ (**348**)	$La(OTf)_3$ (25)	**350** (30)	CH_2Cl_2 (0.02)	10-15	84	50	50:50	4:01
18	$Ir(ppy)_3$ (**348**)	$Sc(OTf)_3$ (10)	**350** (12)	CH_2Cl_2 (0.02)	10-15	100	80	50:50	7.1
19	$Ir(ppy)_3$ (**348**)	$Sc(OTf)_3$ (25)	**350** (30)	CH_2Cl_2 (0.02)	10-15	79	73	75:25	10.1
20	$Ir(ppy)_3$ (**348**)	$Sc(OTf)_3$ (50)	**350** (60)	CH_2Cl_2 (0.02)	10-15	-	-	64:36	-
21	$Ir(ppy)_3$ (**348**)	$Sc(OTf)_3$ (25)	**350** (30)	CH_2Cl_2 (0.02)	-30	82	48	42:58	3.1
22	$Ir(ppy)_3$ (**348**)	$Sc(OTf)_3$ (25)	**350** (30)	CH_2Cl_2 (0.01)	10-15	79	71	75:25	10.1
23	$Ir(ppy)_3$ (**348**)	$Sc(OTf)_3$ (25)	**350** (30)	CH_2Cl_2 (0.05)	10-15	90	62	54:46	5.1
24	$Ir(ppy)_3$ (**348**)	none	none	CH_2Cl_2 (0.02)	10-15	83	7	-	>19:1
25	none	$Sc(OTf)_3$ (25)	none	CH_2Cl_2 (0.02)	10-15	100	<5	-	-
26	Ir(dFppy)3 (**340**)	$Sc(OTf)_3$ (25)	**350** (30)	CH_2Cl_2 (0.02)	10-15	100	86	42:58	7.1
27	$Ir(dFppy)_2(pic)$ (**410**)	$Sc(OTf)_3$ (25)	**350** (30)	CH_2Cl_2 (0.02)	10-15	82	64	52:48	5.1
28	$Ir(dFppy)_2(PCA)$ (**411**)	$Sc(OTf)_3$ (25)	**350** (30)	CH_2Cl_2 (0.02)	10-15	43	25	77:23	1.1
29	$Ir(dFCF3ppy)_2(PCA)$ (**412**)	$Sc(OTf)_3$ (25)	**350** (30)	CH_2Cl_2 (0.02)	10-15	100	75	71:29	14.1
30	Ir(dFppy)3 (**340**)	$Sc(OTf)_3$ (25)	**350** (30)	CH_2Cl_2 (0.02)	-30	79	45	37:63	2.1
31	$Ir(ppy)_3$ (**348**)	$Sc(OTf)_3$ (25)	**430** (30)	CH_2Cl_2 (0.02)	10-15	79	70	54:46	5.1
32	$Ir(ppy)_3$ (**348**)	$Sc(OTf)_3$ (25)	**431** (30)	CH_2Cl_2 (0.02)	10-15	89	70	50:50	4.1
33	$Ir((3'\text{-}OMe)ppy))_3$ (**355**)	$Sc(OTf)_3$ (25)	**350** (30)	CH_2Cl_2 (0.02)	10-15	60	40	82:18	>19.1
34	$Ir(dF(CF3)ppy)_2(bpy)(PF_6)$ (**282**)	$Sc(OTf)_3$ (25)	**350** (30)	CH_2Cl_2 (0.02)	10-15	84	50	52:48	5.1

35	Ir(Fppy)$_3$ (**354**)	Sc(OTf)$_3$ (25)	**350** (30)	CH_2Cl_2 (0.02)	10-15	86	90	50:50	7.1
36	Ir(ppy)$_2$(pca) (**413**)	Sc(OTf)$_3$ (25)	**350** (30)	CH_2Cl_2 (0.02)	10-15	37	17%	63:37	26
37	Ir(ppy)$_2$((N-Me)pca) (**414**)	Sc(OTf)$_3$ (25)	**350** (30)	CH_2Cl_2 (0.02)	10-15	7%	<5%	78:22	-
38	Ir((3'-OMe)ppy)$_2$(4,4'-(OMe)$_2$bpy)(PF6) (**415**)	Sc(OTf)$_3$ (25)	**350** (30)	CH_2Cl_2 (0.02)	10-15	<5	<5	71:29	-
39	Ir((3'-OMe)(4-CF_3)ppy)$_2$((4,4'-NH_2)bpy)(PF_6) (**416**)	Sc(OTf)$_3$ (25)	**350** (30)	CH_2Cl_2 (0.02)	10-15	30	<5	82:18	-
40	Ir((3'-OMe)ppy)$_2$((4,4'-NH_2)bpy)(PF_6) (**417**)	Sc(OTf)$_3$ (25)	**350** (30)	CH_2Cl_2 (0.02)	10-15	56	40	79:21	7.1
41	Ir((4-CF_3)ppy)3 (**418**)	Sc(OTf)$_3$ (25)	**350** (30)	CH_2Cl_2 (0.02)	10-15	<5	<5	86:14	-
42	Ir((3'OMe)(4-CF_3)ppy)$_3$ (**419**)	Sc(OTf)$_3$ (25)	**350** (30)	CH_2Cl_2 (0.02)	10-15	<5	<5	71:29	-
43	Ir((3'-OMe)ppy))$_3$ (**355**)	Sc(OTf)$_3$ (25)	**350** (30)	MeCN (0.02)	10-15	30	<5	70:30	-
44	Ir((3'-OMe)ppy))$_3$ (**355**)	Sc(OTf)$_3$ (25)	**432** (30)	CH_2Cl_2 (0.02)	10-15	47	32	84:16	5:1
45	Ir((3'-OMe)ppy))$_3$ (**355**)	Sc(OTf)$_3$ (25)	salen-1	CH_2Cl_2 (0.02)	10-15	40	33	53:47	4.1
46	Ir((3'-OMe)ppy))$_3$ (**355**)	Sc(OTf)$_3$ (25)	salen-2	CH_2Cl_2 (0.02)	10-15	33	36	52:48	4.1
47	Ir((3'-OMe)ppy))$_3$ (**355**)	Gd(OTf)$_3$ (25)	**432** (30)	CH_2Cl_2 (0.02)	10-15	<5	<5	-	-
48	Ir((3'-OMe)ppy))$_3$ (**355**)	Y(OTf)$_3$ (25)	**432** (30)	CH_2Cl_2 (0.02)	10-15	<5	<5	-	-
49	Ir((3'-OMe)ppy))$_3$ (**355**)	Yb(OTf)$_3$ (25)	**432** (30)	CH_2Cl_2 (0.02)	10-15	<5	<5	-	-
50	Ir((3'-OMe)ppy))$_3$ (**355**)	Eu(OTf)$_3$	**432** (30)	CH_2Cl_2 (0.02)	10-15	<5	<5	-	-
51	Ir((3'-OMe)ppy))$_3$ (**355**)	Zn(OTf)$_3$	**432** (30)	CH_2Cl_2 (0.02)	10-15	<5	<5	-	-
52	Ir((5-F)ppy)$_3$ (**364**)	Sc(OTf)$_3$ (25)	**432** (30)	CH_2Cl_2 (0.02)	10-15	100	98	84:16	>19.1
53	Ir((5-F)ppy)$_3$ (**364**)	Sc(OTf)$_3$ (25)	**432** (30)	CH_2Cl_2 (0.02)	0	100	91	86:14	>19.1
54	Ir((5-F)ppy)$_3$ (**364**)	Sc(OTf)$_3$ (25)	**432** (30)	CH_2Cl_2 (0.02)	−30	100	92	88:12	>19.1
55	Ir((5-F)ppy)$_3$ (**364**)	Sc(OTf)$_3$ (25)	**432** (30)	CH_2Cl_2 (0.02)	−50	<5	<5	-	-
56	Ir((5-F)ppy)$_3$ (**364**)	Sc(OTf)$_3$ (25)	**432** (30)	CH_2Cl_2 (0.02)	−30	100	82	88:12	>19.1
57	Ir((5-F)ppy)$_3$ (**364**)	Sc(OTf)$_3$ (25)	**350** (30)	CH_2Cl_2 (0.02)	−30	15	12	72:28	-
58	Ir((5-F)ppy)$_3$ (**364**)	Sc(OTf)$_3$ (25)	**435** (30)	CH_2Cl_2 (0.02)	−30	29	<5	80:20	-
59	Ir((5-F)ppy)$_2$(acac) (**420**)	Sc(OTf)$_3$ (25)	**432** (30)	CH_2Cl_2 (0.02)	−30	15	<5	88:12	-
60	Ir((5-F)ppy)$_3$ (**364**)	Sc(OTf)$_3$ (25)	**432** (30)	CH_2Cl_2 (0.02)	−20	88	80	88:12	>19.1
61	Ir((5-F)ppy)$_3$ (**364**)	Sc(OTf)$_3$ (25)	**350** (30)	CH_2Cl_2 (0.02)	−20	72	56	88:12	>19.1
62	Ir[(5-F)ppy]2(acac)	Sc(OTf)$_3$ (25)	**432** (30)	CH_2Cl_2 (0.02)	−20	<5	<5	87:13	-
63	Ir((5-F)(4'-^{t}Bu)ppy)$_3$ (**365**)	Sc(OTf)$_3$ (25)	**432** (30)	CH_2Cl_2 (0.02)	−30	<5	<5	80:20	-
64	Ir((5-F)(4'-^{t}Bu)ppy)$_3$ (**365**)	Sc(OTf)$_3$ (25)	**432** (30)	CH_2Cl_2 (0.02)	10-15	100	65	89:11	>19.1
65	Ir((5-F)ppy)$_3$ (**364**)	Sc(OTf)$_3$ (25)	**432** (27.5)	CH_2Cl_2 (0.02)	−30	100	90	89:11	>19.1
66	Ir((5-F)ppy)$_3$ (**364**)	Sc(OTf)$_3$ (20)	**432** (22)	CH_2Cl_2 (0.02)	−30	85	70	89:11	>19.1
67	Ir((5-F)ppy)$_3$ (**364**)	Sc(OTf)$_3$ (15)	**432** (16.5)	CH_2Cl_2 (0.02)	−30	74	57	89:11	>19.1
68	Ir((5-F)ppy)$_3$ (**364**)	Sc(OTf)$_3$ (10)	**432** (12)	CH_2Cl_2 (0.02)	−30	69	46	86:14	>19.1
69	Ir((5-F)ppy)$_3$ (**364**)	Sc(OTf)$_3$ (25)	**350** (30)	CH_2Cl_2 (0.02)	10-15	90	70	86:14	>19.1
70	Ir((5-F)ppy)$_3$ (**364**)	Sc(OTf)$_3$ (25)	**432** (30)	CH_2Cl_2 (0.02)	10-15	90	90	84:16	>19.1

71	Ir((5-F)ppy)$_3$ (**364**)	Sc(OTf)$_3$ (10)	**432** (12)	CH_2Cl_2 (0.05)	10-15	88	77	84:16	>19.1
72	Ir((5-F)(4'-^{t}Bu)ppy)$_3$ (**365**)	Sc(OTf)$_3$ (15)	**350** (16)	CH_2Cl_2 (0.02)	10-15	85	65	88:12	>19.1
73	Ir((5-F)(4'-^{t}Bu)ppy)$_3$ (**365**)	Sc(OTf)$_3$ (15)	**350** (18)	CH_2Cl_2 (0.02)	−10	77	61	90:10	>19:1
74	Ir((5-F)(4'-^{t}Bu)ppy)$_3$ (**365**)	Sc(OTf)$_3$ (25)	**350** (27)	CH_2Cl_2 (0.02)	−10	88	74	89:11	>19:1
75	Ir((5-F)(4'-^{t}Bu)ppy)$_3$ (**365**)	Sc(OTf)$_3$ (25)	**432** (27)	CH_2Cl_2 (0.02)	−10	87	84	89:11	>19:1
76	Ir[(3,5-dF)ppy]$_3$ (**421**)	Sc(OTf)$_3$ (25)	**432** (27)	CH_2Cl_2 (0.02)	10-15	72	58	83:17	>19:1
77	Ir((5-CF_3)ppy)$_3$ (**366**)	Sc(OTf)$_3$ (25)	**432** (27)	CH_2Cl_2 (0.02)	10-15	55	45	89:11	>19:1
78	Ir((5-CF_3)(4'-^{t}Bu)ppy)$_3$ (**PS367**)	Sc(OTf)$_3$ (25)	**350** (27)	CH_2Cl_2 (0.02)	10-15	100	95	94:6	>19:1
79	Ir((5-CF_3)(4'-^{t}Bu)ppy)$_3$ (**PS367**)	Sc(OTf)$_3$ (25)	**350** (25)	CH_2Cl_2 (0.02)	10-15	100	95	95:5	>19:1

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