Palladium catalysis for natural product synthesis

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Palladium Catalysis

for Natural Product Synthesis

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Signed…….. Date……..

Abstract

This thesis details investigations towards the total synthesis of the naturally occurring alkaloid hodgkinsine, utilising palladium catalysis to achieve desymmetrisation of a *meso*-chimonanthine derivative.

Initially, a Suzuki cross-coupling approach was envisaged. *Meso*-chimonanthine is functionalised as its C-7 bisiodide derivative by directed *ortho*-lithiation. Suitable electrophiles are screened for the successful preparation of additional bisbromide and bistriflate derivatives to broaden the scope of the cross-coupling. The synthesis of a suitable indole-3-boronic ester coupling partner is also achieved.

Investigations into the post-Suzuki coupling elaboration of the indole moiety were conducted with model substrates to assess the viability of a proposed alkylation-cyclisation procedure. C-3 alkylation of various *N*-protected C-3 phenylindole derivatives was unsuccessful when employing aziridines, sulfamidites and sulfamidates as electrophilic two carbon fragments. Therefore a second generation boronic ester with latent enolate functionality for increased nucleophilicity was prepared in six high yielding steps from oxindole, *via* trapping 3-bromo-*N*-BOC-oxindole as the TIPS enol ether and subsequent C-3 palladium catalysed borylation.

The Suzuki coupling of the new boronic ester with *meso*-chimonanthine derivatives was shown to be unsuccessful in a broad range of anhydrous and aqueous solvent systems. Palladium catalysts, ligands, bases and measures to reduce steric interactions were all screened in an attempt to achieve coupling.

Subsequently the palladium catalysed arylation of *N*-protected oxindole enolates is developed; aryl bromides, chlorides and triflates are all suitable coupling partners, whilst a broad range of *ortho*, *meta* and *para* functionalised arenes are well tolerated providing C-3 aryl oxindoles in high yield. Extension of this methodology to a C-7 bisbromo *meso*-chimonanthine substrate was successful, furnishing the desymmetrised product under racemic conditions in 45% yield with the dicoupled product also observed in 20% yield.

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Acknowledgements

First and foremost I would like to thank Dr Mike Willis for providing me with this opportunity and for his help, patience and continual optimism over the course of this synthetic journey. I would also like to take this opportunity to thank members of the group past and present who have made the experience of being in the group so enjoyable over the last three years and, in particular, Jimmy, Luke, Fletch and Ai for their help and guidance in the lab.

Big thanks also go out to Luke Powell for getting the ball rolling on the early stages of the synthesis, and good luck to Rob taking over the reins for the next phase of the project.

Many technical and support staff, both at the University of Bath and the University of Oxford, have been involved in making my research possible and to whom I am grateful for all their hard work.

Finally I would like to thank my parents for their unwavering support over the course of my university studies, and for giving me such a strong platform to build my career upon to date.

Abbreviations and Acronyms

δ	Chemical shift
η	Hapticity
μ-wave	Microwave
ν	Frequency
Å	Angstrom
Ac	Acyl
app.	Apparent
aq.	Aqueous
Ar	Generic aryl group
9-BBN	9-Borabicyclo-[3.3.1]nonane
BE	Boronic ester
BINAP	2,2′-Bis(diphenyl-phosphino)-1,1′-binaphthyl
BINAs	2,2′-Bis(diphenyl-arsino)-1,1′-binaphthyl
Bn	Benzyl
BOC	*tert*-Butoxycarbonyl
BPPFA	(*N*,*N*-Dimethyl-1-[2,1′-bis(diphenyl-phosphino)-ferrocenyl]ethylamine)
BPPFOAc	(2,1′-Bis(diphenyl-phosphino)ferrocenyl) ethyl acetate
br	Broad
Bs	Benzenesulfonyl
Bu	*n*-Butyl
BUS	*tert*-Butylsulfonyl
°C	Degrees Celsius
cat.	Catalytic
CBz	Benzyloxycarbonyl
Chiraphos	2,3-Bis(diphenyl-phosphino)butane
CI	Chemical ionisation
cm	Centimeter(s)
COSY	Correlation spectroscopy
Cy	Cyclohexyl
d	Doublet
DACH	Diaminocyclohexane
Davephos	2-Dicyclohexyl-phosphino-2′-(*N*,*N*-dimethylamino)biphenyl
dba	*trans*,*trans*-Dibenzylideneacetone
DBU	1,8-Diazabicyclo-[5.4.0]undec-7-ene
DCM	Dichloromethane
dec.	Decomposed
dist.	Distilled
DM	Dimethyl
DMA	*N*,*N*′-Dimethylacetamide
DMAP	4-(Dimethylamino)-pyridine
DME	Dimethoxyethane
DMF	*N*,*N*′-Dimethylformamide
DMSO	Dimethylsulfoxide
DPEphos	Bis-(2-diphenyl-phosphinophenyl)ether

dppb	Bis(diphenylphosphino) butane	LRMS	Low resolution mass spectrometry
dppf	1,1′-Bis(diphenyl-phosphino)ferrocene	m	Multiplet
		M	Molar
ee	Enantiomeric excess	M^+	Molecular ion
EI	Electron impact	MAP	2-Diphenylphosphino-2′-dimethylamino-1,1′-binaphthyl
eq.	Equivalent(s)		
ESI	Electrospray ionization		
Et	Ethyl	*m*-CPBA	*meta*-Chloroperoxy-benzoic acid
GC	Gas chromatography		
g	Gram(s)	Me	Methyl
h	Hour(s)	MeO	Methoxy
HIV	Human immuno-deficiency virus	MeO-MOP	2-Diphenylphosphino-2′-methoxy-1,1′-binaphthyl
HMQC	Heteronuclear multiple-quantum coherence		
		mg	Milligram(s)
HPLC	High performance liquid chromatography	MHz	Megahertz
		min	Minute(s)
HRMS	High resolution mass spectrometry	^{t}Bu-Miniphos	Bis(*tert*-butylmethyl-phosphino)methane
^{i}Pr	*Iso*propyl	mL	Milliliter(s)
IR	Infra-red	mmol	Millimole(s)
J	Coupling constant	MS	Molecular sieves
Josiphos	2-(Diphenyl-phosphino)ferrocenyl ethyldicyclohexyl-phosphine	*m/z*	Mass to charge ratio
		naph	Naphthyl
		NaHMDS	Sodium bis(trimethylsilyl)amide
KHMDS	Potassium bis(trimethylsilyl) amide	NBS	*N*-Bromosuccinimide
		NCS	*N*-Chlorosuccinimide
L	Ligand	NFSI	*N*-Fluorodibenzene-sulfonimide
LDA	Lithium di*iso*propylamide		
		NHC	*N*-Heterocyclic carbene
		NMDA	*N*-Methyl *D*-aspartate

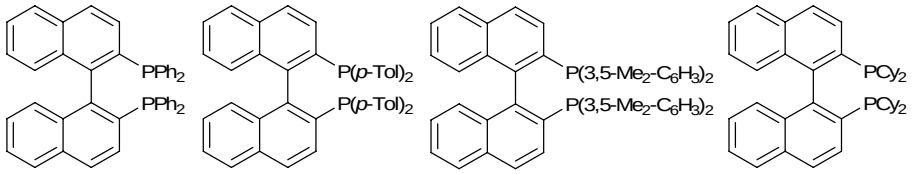
NMP	*N*-Methyl pyrroldine	PS	Proton sponge
NMR	Nuclear magnetic resonance	Py	Pyridine
		q	Quartet
NR	No reaction	quin	Quintet
Nuc.	Nucleophile	QUINAP	1-(2-Diphenyl-phosphino-1-naphthyl)-*iso*quinoline
PEPPSI-^{i}Pr	[1,3-Bis(2,6-Di*iso*propylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium (II) dichloride	R	Generic group or substituent
		rac	Racemic
PEPPSI-s^{i}Pr	[1,3-Bis(2,6-di*iso*propylphenyl)-imidazolidene](3-chloropyridyl)-palladium(II) dichloride	Red-Al	Sodium bis(2-methoxy-ethoxy)aluminum dihydride
		r.t.	Room temperature
		s	Singlet
PG	Protecting group	*sec*	Secondary
Ph	Phenyl	sept	Septet
Pin	Pinacol, 2,3-Dimethyl-2,3-butanediol	SM	Starting material
		S-Phos	2-Dicyclohexyl-phosphino-2′, 6′-dimethoxybiphenyl
Piv	Trimethylacetyl (pivolyl)		
PMB	*para*-Methoxybenzyl	*t*	Time
PMP	Pentmethylpyrrolidine	t	Triplet
PPFA	*N*,*N*-Dimethyl-1-[2-(diphenylphosphino)-ferrocenyl]ethyl amine	*T*	Temperature
		TBDMS	*tert*-Butyldimethylsilyl
		^{t}Bu	*tert*-Butyl
PPFOMe	*N*,*N*-Dimethyl-1-[2-(diphenylphosphino)fer-rocenyl]ethyl methyl ether	tetra-Me X-Phos	(3,4,5,6-Tetramethyl)-2-dicyclohexylphosphino-2′,4′,6′-tri*iso*propyl-biphenyl
ppm	Parts per million	TfO	Trifluoromethane-sulfonate (triflate)
Pr	*n*-Propyl		
Prod	Product	TFA	Trifluoroacetic acid

THF	Tetrahydrofuran
TIPS	Tri*iso*propylsilyl
TLC	Thin layer chromatography
TMEDA	*N*,*N*,*N*′,*N*′-Tetramethylethylene-diamine
TMS	Trimethylsilyl
Tol	Tolyl
Ts	Tosyl
UV	Ultraviolet
X	Generic halide or triflate
X-Phos	2-Dicyclohexyl-phosphino-2′,4′,6′-tri*iso*propylbiphenyl

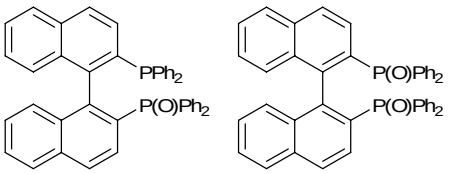
Ligands

Binaphthyls

BINAP family:

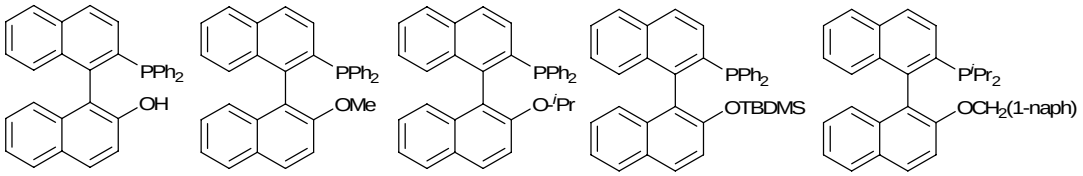


BINAP **L1** Tol-BINAP **L2** DM-BINAP **L3** Cy-BINAP **L4**



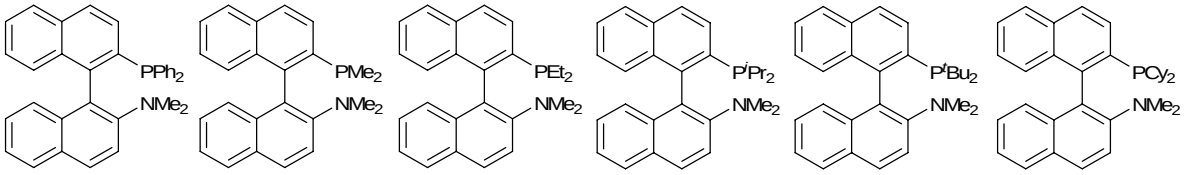
BINAP(O) **L5** BINAP(O)$_2$ **L6**

MOP family:



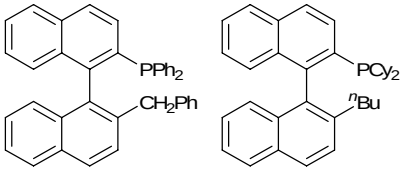
OH-MOP **L7** MeO-MOP **L8** O^{i}Pr-MOP **L9** OTBDMS-MOP **L10** OCH$_2$(1-naph)-MOP **L11**

MAP family:



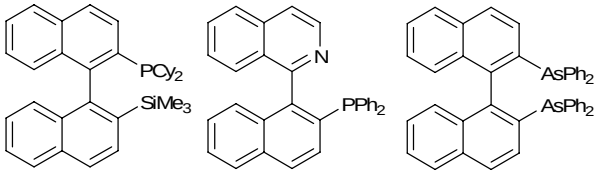
MAP **L12** Me-MAP **L13** Et-MAP **L14** ^{i}Pr-MAP **L15** ^{t}Bu-MAP **L16** Cy-MAP **L17**

Hiyashi-type binaphthyls:



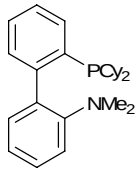
L18 **L19**

Others:

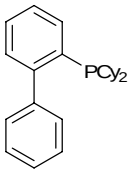


L20 QUINAP **L21** BINAs **L22**

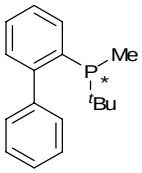
Biphenyls



DavePhos **L23**



L24



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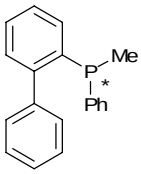

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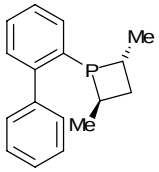

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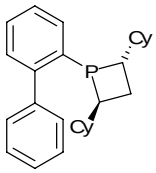
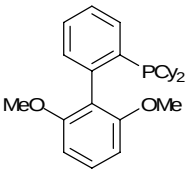
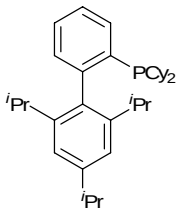


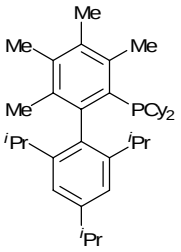
L28



S-Phos **L29**

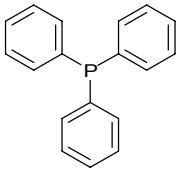


X-Phos **L30**

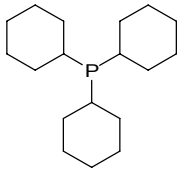


tetra-methyl X-Phos **L31**

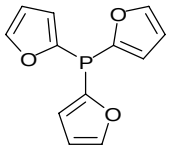
Monophosphines



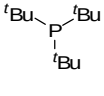
PPh_3 **L32**



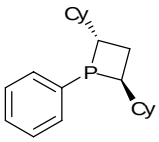
PCy_3 **L33**



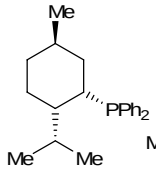
P(2-furyl)$_3$ **L34**



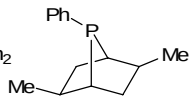
P^{t}Bu$_3$ **L35**



L36

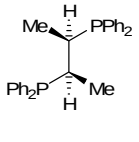


L37

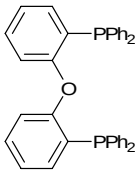


L38

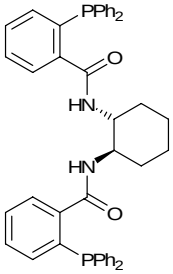
Bisphosphines and bisamines



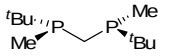
(*R*,*R*)-Chiraphos **L39**



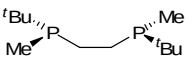
DPEphos **L40**



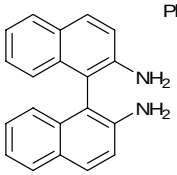
Trost Ligand **L41**



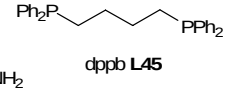
(*R*,*R*)-^{t}Bu-MiniPhos **L42**



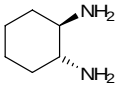
L43



BINAM **L44**

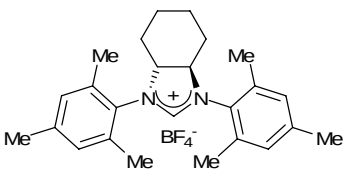


dppb **L45**

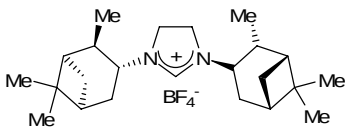


(1*R*-2*R*)-DACH **L46**

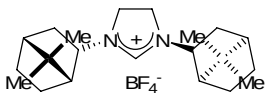
Carbenes (NHC's)



L47

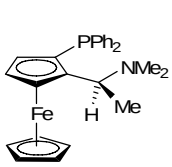


L48

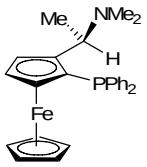


L49

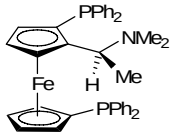
Ferrocenes



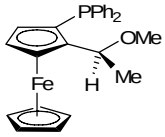
(*S*)-(*R*)-PPFA **L50**



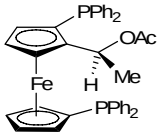
(*R*)-(*S*)-PPFA **L51**



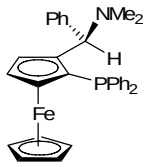
(*S*)-(*R*)-BPPFA **L52**



(*S*)-(*R*)-PPFOMe **L53**



(*S*)-(*R*)-BPPFOAc **L54**



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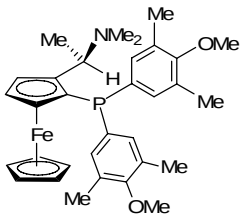
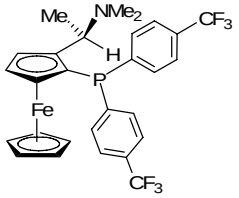


L56



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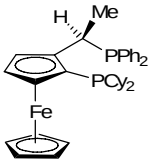

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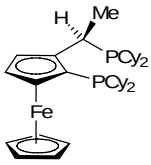

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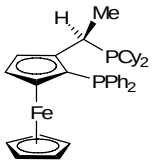
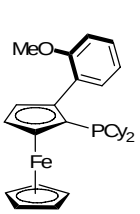


(*R*)-(*S*)-Josiphos **L60**



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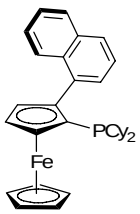

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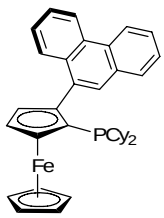

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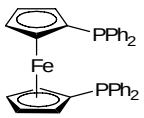
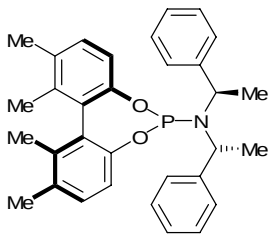


dppf **L64**

Phosphoramidites



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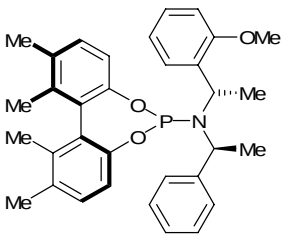

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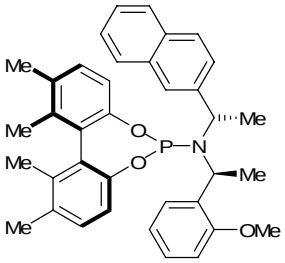

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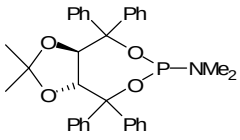


L68

Introduction

The synthesis of biologically active molecules presents a continual challenge to the organic chemist, whether synthesising novel targets or developing new methodology to provide more efficient routes to current active pharmaceutical ingredients. The degree of structural complexity of target molecules is extremely diverse. Successful syntheses range from the comparatively simple structure of morphine[1] to the incredibly complex aminoglycoside vancomycin,[2-4] anticancer agent discodermolide[5] and the poison ciguatoxin,[6] all of which exhibit multiple stereodefined carbon-carbon and carbon-heteroatom bonds and represent milestones in natural product synthesis (Figure 1).

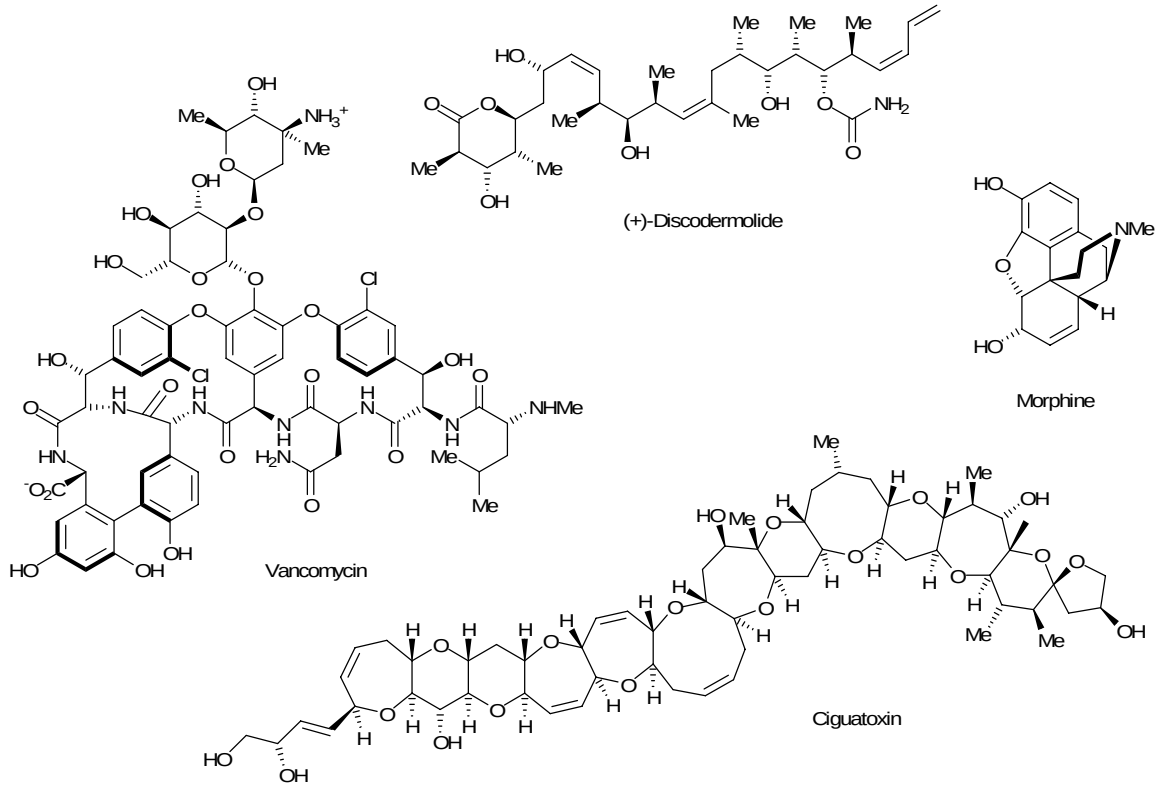


Figure 1

Such stereoselective syntheses have been made more feasible by advances in, and greater understanding of, transition metal chemistry. Catalytic and asymmetric applications of rhodium,[7] manganese,[8] ruthenium,[9-11] titanium,[12] iridium,[13, 14] osmium[15, 16] and copper catalysts[17] amongst others, have been utilised to effect a variety of transformations with high chemo- and/or stereoselectivity and yield.

Highly successful and versatile catalytic systems have been developed around palladium metal centres. Typically, reactions proceed under mild conditions and display impressive functional group tolerance for the generation of new carbon-oxygen, carbon-nitrogen, carbon-sulphur and, most importantly, carbon-carbon bonds.[18] The enantioselective construction of carbon-carbon bonds has advanced markedly in the last decade, great advances in the preparation of chiral ligands has led to the application of chiral palladium catalysts to achieve highly stereoselective transformations and yield products with high stereoselectivity. It is beyond the scope of this thesis to review all areas of palladium catalysis, thus only major and relevant asymmetric examples will be discussed. Broader discussions have been detailed on other major reviews.[19, 20]

1. Palladium Catalysis

Palladium catalysis is achieved with either a palladium(II) salt or a palladium(0) complex as the metal source. To achieve enantioselective synthesis with a palladium(II) salt, efficient reduction of the metal centre to palladium(0) is an essential requirement to allow coordination of the chiral ligand, generating the active fourteen electron complex. This can be achieved by a number of methods including β-hydride elimination or reduction in the presence of a phosphine.[21-26] The resulting phosphine oxide by-product is generally accepted to be a non-active component in the subsequent reactions, although active palladium-phosphine oxide catalysts are known.[27] Subsequently, control of the metal-ligand ratio can be an important factor in achieving the desired catalytic activity.

One of the most commonly studied transformations is the Heck coupling. Seminal publications by Mizoroki and Heck described the union of an aryl or vinyl halide or triflate with an alkene to prepare substituted (*E*)-alkenes.[28,29] Further major developments in palladium chemistry were achieved by organometallic cross-coupling of aryl or vinyl halides and triflates. Prominent couplings with organometallic reagents include the Stille reaction, employing an organo-tin reagent (of the kind R-SnR′$_3$);[30, 31] the Negishi coupling involving organo-zinc reagents (R-ZnX);[32] the Suzuki-Miyaura coupling, employing organo-boron species (R-

$B(OR')_2$);[33, 34] the Kumada coupling with organo-magnesium reagents (R-MgX);[35] and Sonogashira couplings employing alkynyl cuprates (Figure 1.1).[36, 37]

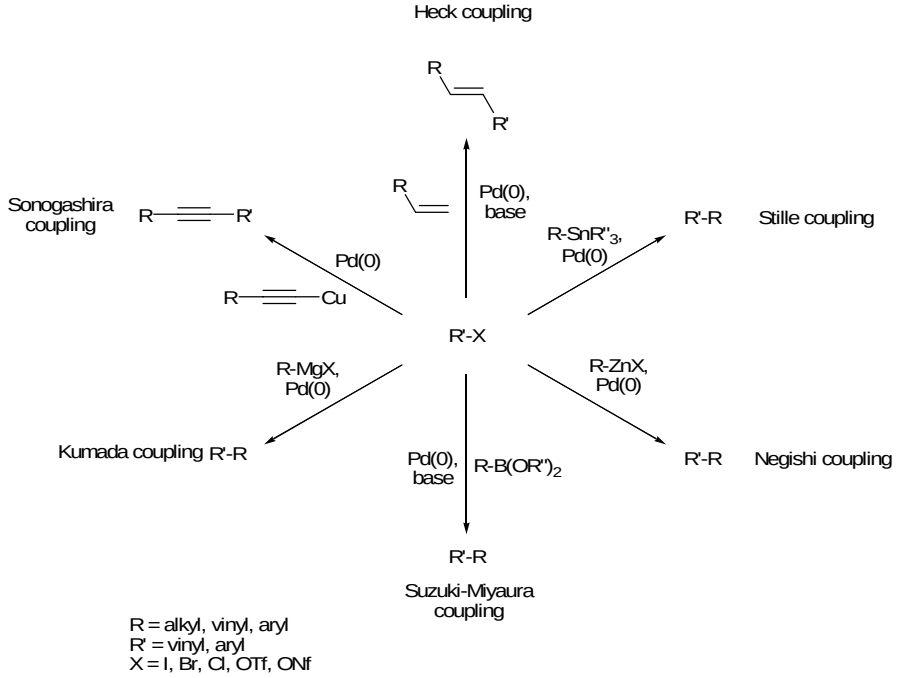


Figure 1.1

The catalytic cycles of all such cross couplings involve three key steps, with an extra isomerisation step a fundamental feature of the Heck reaction. However, the exact mechanisms have not been elucidated in all cross-coupling protocols. The first step involves oxidative addition of ligated palladium(0) **1** to an aryl or vinyl halide or triflate to generate a carbon-palladium(II) σ-bond as in **2** *via* either direct addition or an initial interaction with the π-system followed by addition. In the presence of an organometallic reagent, transmetallation of an aryl or vinyl moiety to the palladium(II) centre to give species **3** occurs, effectively substituting the halide or triflate. This is often proposed to be the rate determining step and is the area where mechanistic aspects may not always be defined, particularly in the Suzuki-Miyaura coupling where the active boron species is somewhat unclear, although generally accepted to be a boronate ($R\text{-}B^{-}(OR')_3$) generated by addition of base.[38] In the Heck reaction, where there is no organometallic reagent for transmetallation, the second step involves the coordination and *syn* 1,2-insertion of an alkene across the palladium-carbon bond to give intermediate **4** followed by a rotation of the carbon-carbon bond to **5**. This rotation facilitates the final step; a *syn* β-hydride elimination

to generate the alkene, and base promoted loss of H-X from the hydridopalladium centre regenerates the palladium(0) catalyst (Figure 1.3). In couplings where transmetallation occurs, the desired carbon-carbon bond and regenerated palladium(0) species are formed directly by the reductive elimination step. As there is no acid by-product, a base is not required (Figure 1.2).

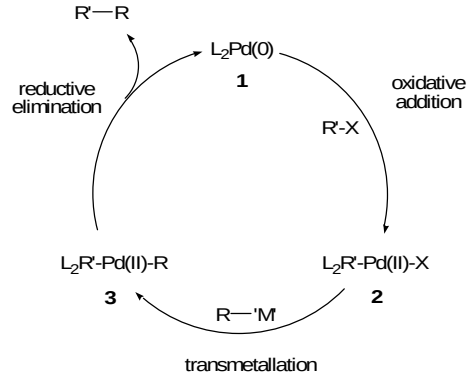


Figure 1.2 General cross-coupling catalytic cycle

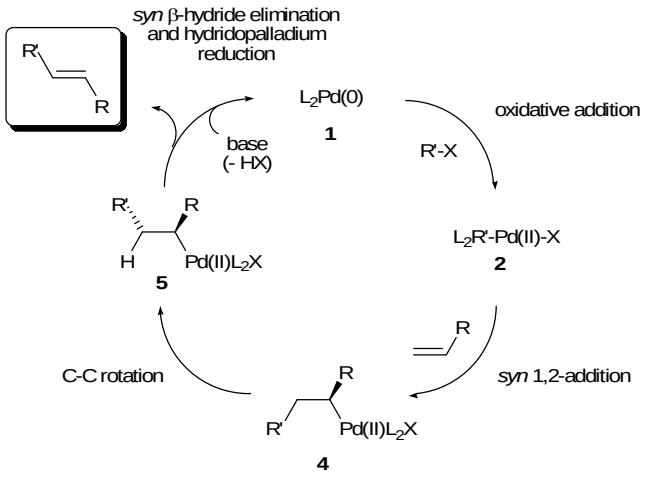
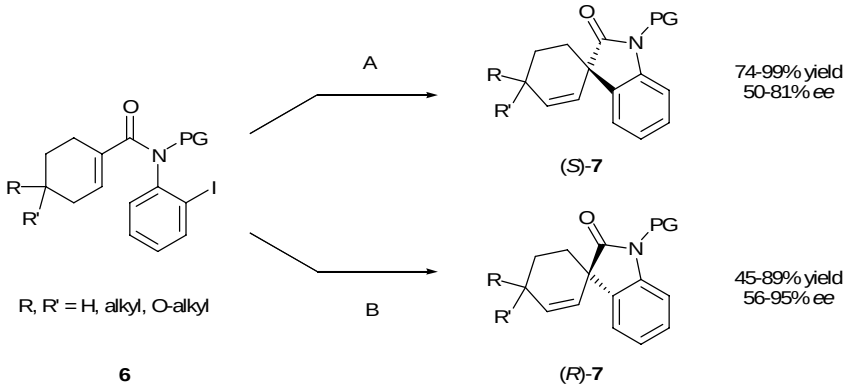


Figure 1.3 Heck reaction catalytic cycle

1.1. Asymmetric Palladium Catalysis

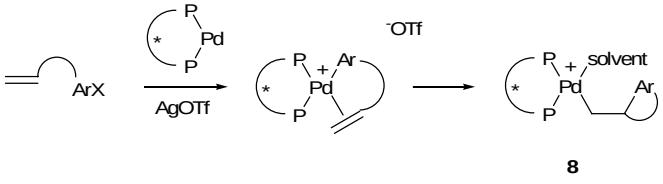
1.1.1. Asymmetric Heck Reactions

Efficient preparation of quaternary carbon centres remains a considerable challenge to organic chemists. One of the first, and most impressive, examples of an asymmetric Heck reaction was the preparation of stereodefined quaternary carbon centres by Overman *et al*. The reaction, extending their previous investigations in the field, achieved the intramolecular cyclisation of iodo-anilides of the type **6** providing both enantiomers of C-3 disubstituted spiro-oxindoles **(*S*)-7** and **(*R*)-7** in high yield (Scheme 1.1). Although enantioselectivities were modest, the ability to control the enantiomer of the product from a single enantiomer of ligand by choice of a silver salt or amine additive was an intriguing feature of the reaction.[39]



Scheme 1.1: *Reagents and Conditions*: (**A**) iodo-anilide **6** (1 eq.), Pd_2dba_3 (5 mol%), (*R*)-BINAP **(*R*)-L1** (10 mol%), Ag_3PO_4 (1-2 eq.), DMA, 80 °C; (**B**) iodo-anilide **6** (1 eq.), Pd_2dba_3 (5 mol%), (*R*)-BINAP **(*R*)-L1** (10 mol%), PMP (5 eq.), DMA, 80 °C.

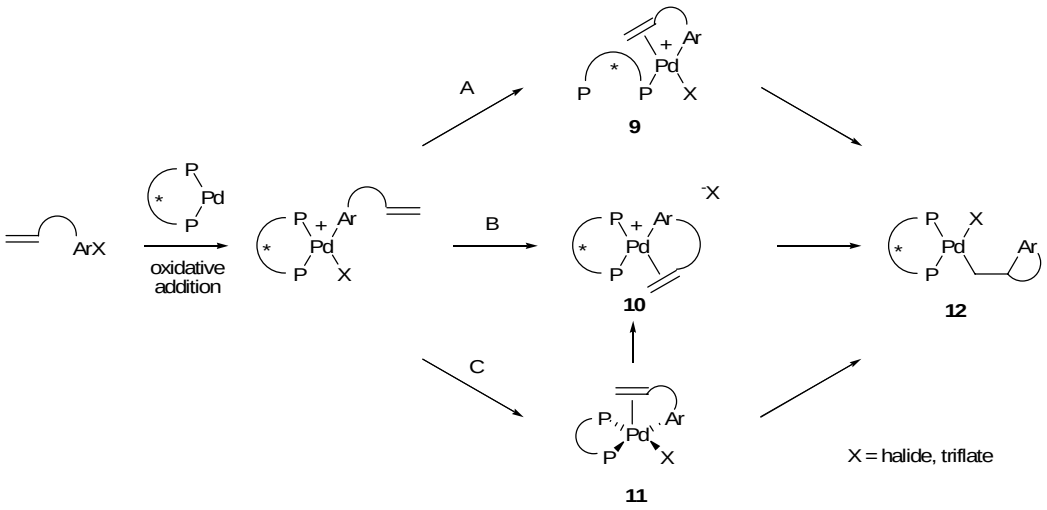
As a much simplified concept, the Heck reaction of halides was thought to proceed *via* a cationic palladium intermediate in the presence of a silver or thallium salt as a halide scavenger. The mechanism was believed to proceed *via* a cationic 16 electron palladium(II) intermediate where the reaction solvent stabilises the post-insertion palladium complex **8** (Scheme 1.2).



Scheme 1.2

The success of the Overman coupling with iodo-anilides **6** in the presence of a tertiary amine contradicted the previous hypotheses that silver or thallium salts were essential for achieving successful asymmetric Heck couplings. This insight suggested that a neutral palladium(II) species could also be the active catalyst whereby the halide remains coordinated to the metal centre.[40, 41]

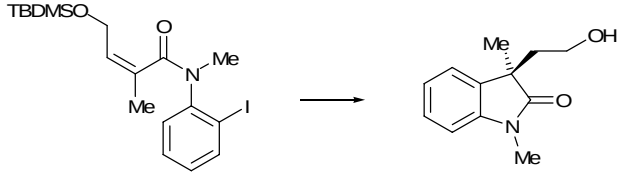
The neutral catalytic mechanism has three possible pathways following oxidative addition to allow coordination of the internal alkene to the four coordinate palladium centre. Dissociation of a phosphine (path A, Scheme 1.3) or the halide (path B) could provide a vacant coordination site for alkene coordination through intermediates **9** and **10**, or direct alkene association to give pentavalent palladium intermediate **11** could result (path C). 1,2-Insertion from either intermediate would allow for formation of complex **12**.[40, 41]



Scheme 1.3

Experimental observations from cyclisations of iodo-anilide **13** (Table 1.1) employing monodentate and hemi-labile binaphthyl ligands instead of (*R*)-BINAP **(*R*)-L1** resulted in reduced enantioselectivity (entries 1-4), leading to the conclusion that bidentate phosphine coordination was crucial to determining enantioselection and dissociation to the monophosphine intermediate **9** (path A, Scheme 1.3) could be rejected. A combination of paths B and C was proposed whereby alkene association is followed by halide dissociation before the insertion step.[41]

Table 1.1: Effect of ligand coordination on Heck cyclisation selectivity

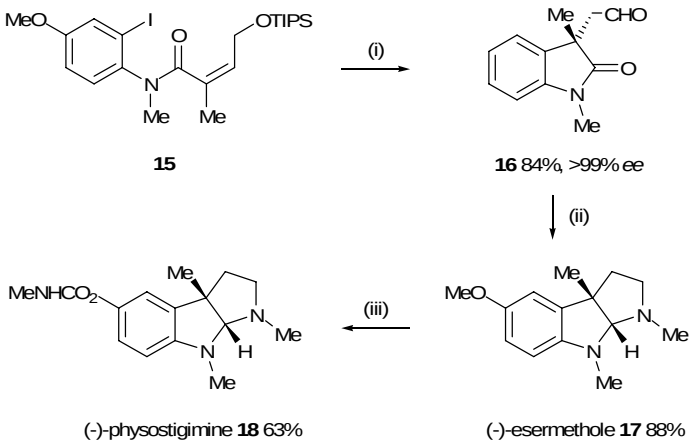


13 **14**

Entry	Ligand	*ee* **14** (%)
1	***(R)*-L1**	91
2	***(R)*-L10**	27
3	***(R)*-L9**	23
4	***(R)*-L18**	19

(i) iodo-anilide **13** (1 eq.), $Pd_2dba_3.CHCl_3$ (5 mol%), ligand (10 mol%), PMP (4 eq.), additive (1 eq.), DMA, 100 °C; (ii) 3 M HCl, THF.

Synthetic application of the intramolecular Heck cyclisation of iodo-anilides allowed for the preparation of both enantiomers of esermethole **17** and physostigimine **18**, examples of monopyrrolidinoindoline alkaloids. Iodo-anilide **15** was cyclised in the presence of (*S*)-BINAP **(*S*)-L1** and pentamethylpiperidine, then hydrolysed to provide oxindole **16** in 84% yield and 95% *ee*. Recrystallisation achieved enantiopurity (Scheme 1.4).[42]



15

16 84%, >99% *ee*

(-)-esermethole **17** 88%

(-)-physostigimine **18** 63%

Scheme 1.4: *Reagents and Conditions*: (i) iodo-anilide **15** (1 eq.), $Pd_2dba_3.CHCl_3$ (5 mol%), (*S*)-BINAP **(*S*)-L1** (23 mol%), PMP (4 eq.), DMA, 100 °C then 3 *N* HCl, THF; (ii) $MeNH_3Cl$, NEt_3, $MgSO_4$ then $LiAlH_4$, reflux; (iii) BBr_3, Na then MeNCO.

Reductive amination-cyclisation of the aldehyde with methylamine hydrochloride and lithium aluminium hydride provided enantiopure (-)-esermethole **17** in 88% yield. Demethylation of the aryl enol ether of (-)-esermethole **17** and trapping of the resultant phenol moiety with methyl isocyanate gave (-)-physostigimine **18** in 63% yield (Scheme 1.4). The opposite enantiomers could be prepared from (*R*)-BINAP **(*R*)-L1**.[42]

1.1.2. Application to the Total Synthesis of Polypyrrolidinoindoline Alkaloids

Having achieved the successful synthesis of both enantiomers of the monopyrrolidinoindolines esermethole **17** and physostigimine **18**, Overman demonstrated the preparation of higher order pyrrolidinoindolines with asymmetric Heck reactions an integral feature of the syntheses.[43]

Polypyrrolidinoindoline alkaloids have been isolated from many natural sources, including bacteria, fungi, shrubs and trees, and exhibit varying degrees of biological activity.[44-46] Higher order pyrrolidinoindolines are characterised by the linkage of cyclotryptamine units through quaternary carbon centres. In the case of the dimer *meso*-chimonanthine ***meso*-19** and both of its enantiomeric diasteriomers ***rac*-19**, a stereodefined C-3a/C-3a′ linkage between the two benzylic carbons defines the structural motif. Higher order pyrrolidinoindolines such as hodgkinsine **20** and quadrigemine C **21** exhibit a stereodefined C-7/C-3a linkage between the one cyclotryptamine unit and another, in addition to a *meso*-chimonanthine core (Figure 1.4).

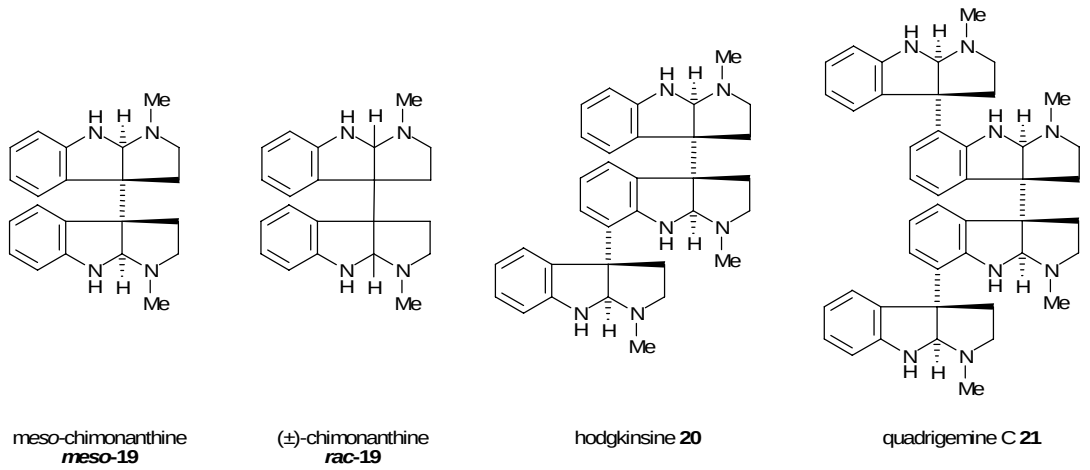
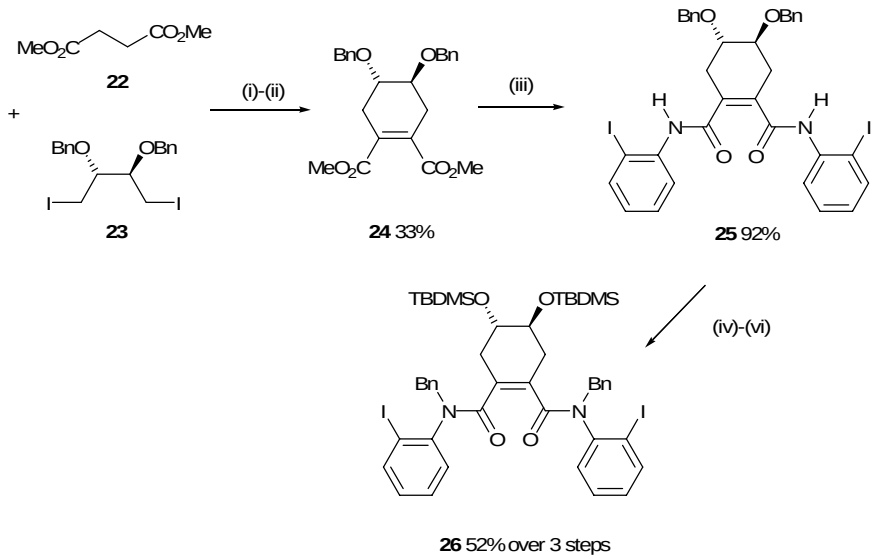


Figure 1.4

To achieve the preparation of higher order pyrrolidinoindolines an efficient preparation of the challenging chimonanthine core was required. Contiguous stereodefined quaternary carbon centres are a considerable challenge in organic synthesis not least because of the large steric effects involved, and this represented the major synthetic problem to be solved. Amongst syntheses by other groups,[47] Overman has achieved the stereo-controlled preparation of *meso*-chimonanthine

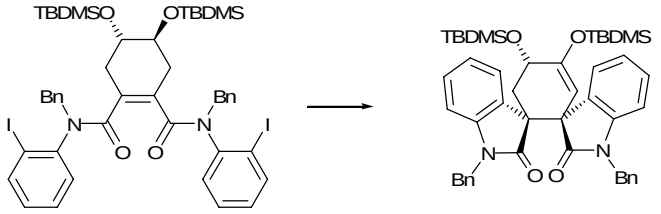
***meso*-19** by three separate methods,[48-50] the most impressive of which employs a double intramolecular asymmetric Heck cascade.[43, 51]

The synthesis began by the preparation of the C_2-symmetric Heck cyclisation precursor **26** from dimethyl succinate **22** and the diiodo-tartrate derivate **23** (Scheme 1.5). Treatment of **23** with lithium di*iso*propylamide followed by addition of succinate **22** and an iodination-elimination protocol provided enantiopure substituted cyclohexene **24**. Trimethylaluminium promoted aminolysis of **24** with 2-iodoaniline and subsequent benzylation of the secondary amides gave **25**. Benzyl ether deprotection and reprotection of the free alcohols as the *tert*-butyldimethylsilyl ethers gave Heck precursor **26** in 16% over 6 steps. It was hoped that the desired *meso* stereochemistry of the Heck product could be dictated by the *trans* stereochemistry of the silyl ethers.[51]



Scheme 1.5: *Reagents and Conditions*: (i) diiodide **23** (1 eq.), succinate **22** (1.5 eq.), LDA, THF, -78 °C; (ii) LDA, I_2, THF, -78 °C; (iii) 2-iodoaniline, $AlMe_3$, toluene; (iv) NaH, BnBr, DMF; (v) BCl_3, -78 °C; (vi) TBDMSCl, imidazole, DCM.

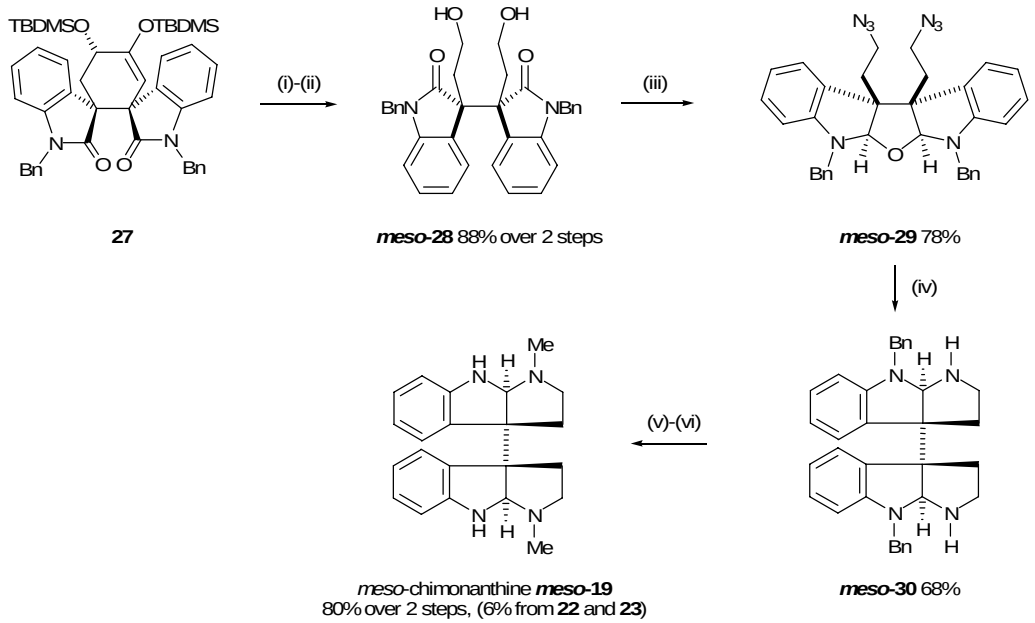
The key Heck transformation, using bis(triphenylphosphine) palladium dichloride and triethylamine in dimethylacetamide at 100 °C, proceeded in excellent yield (71%) providing bisoxindole **27** as the single product (Scheme 1.6). Considering the complexity of the substrate and steric crowding of the resultant tetra-substituted alkene in bisoxindole **27**, this is an extremely impressive transformation. The preparation of **27** as the single product suggests that the original hypothesis of stereochemical control imparted by the *trans* silyl ethers was a successful design feature of the synthesis.



26 **27** 71%

Scheme 1.6: *Reagents and Conditions*: diiodide **26** (1 eq.), $(PPh_3)_2PdCl_2$ (10 mol%), NEt_3, DMA, 100 °C.

Silyl ether deprotection with hydrogen fluoride and reduction with sodium borohydride gave the cyclohexane diol which was cleaved with lead tetraacetate to form a dialdehyde that was immediately reduced, again with sodium borohydride, to furnish bisalcohol ***meso*-28** in 88% yield from **27**. Red-Al reduction of the oxindole provided an unstable diol which was immediately converted to the bisazide ***meso*-29** in 78% yield. Azide reduction to the amine allowed for cyclisation to bisbenzyl derivative ***meso*-30** from which reductive methylation and debenzylation provided *meso*-chimonanthine ***meso*-19** in 6% overall yield from succinate **22** and diiodo-tartrate derivative **23** over 13 steps (Scheme 1.7).[49, 51]



27 ***meso*-28** 88% over 2 steps ***meso*-29** 78%

meso-chimonanthine ***meso*-19** 80% over 2 steps, (6% from **22** and **23**) ***meso*-30** 68%

Scheme 1.7: *Reagents and Conditions*: (i) bisoxindole **27** (1 eq.), HF, MeCN then $NaBH_4$, MeOH; (ii) $Pb(OAc)_4$, toluene then $NaBH_4$, MeOH; (iii) Red-Al, THF, reflux then HN_3, PPh_3, EDC, THF; (iv) PPh_3, H_2O, THF then $AlMe_3$, toluene, reflux; (v) CH_2O, $NaCNBH_3$, MeCN, H_2O; (vi) Na, NH_3, THF, -78 °C.

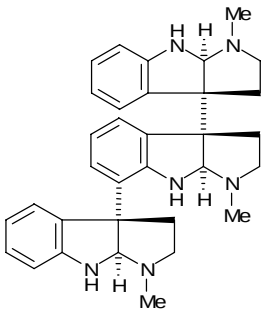
The two alternative routes to *meso*-chimonanthine ***meso*-19** developed by Overman utilise a dialkylation protocol of a dihydro*iso*indigo derivative mediated by

samarium diiodide or sodium bis(trimethylsilyl)amide. Both syntheses intercept the Heck cyclisation protocol, bisalcohol ***meso*-28** being the common intermediate.

With the preparation of *meso*-chimonanthine ***meso*-19** in hand, Overman proceeded to demonstrate the preparation of higher order pyrrolidinoindolines.[52, 53] The syntheses again utilise a Heck reaction as a key carbon-carbon bond forming step. However, a resolution step in the preparation of hodgkinsine **20** is not ideal and allows for the development of a more efficient construction of the C-7/C-3a linkage. This limitation could be potentially be overcome by development of an enantioselective palladium catalysis protocol.

1.1.3. Overmans Synthesis of Hodgkinsine[54, 55]

Hodgkinsine **20** (Figure 1.5) is one of the most abundant members of the polypyrrolidinoindoline family. First isolated from the shrub *Hodgkinsonia frutescens* in Queensland, Australia, hodgkinsine **20** was subsequently isolated (with other alkaloids) as a major component from plants of the *Psychotria* genus in the Amazon basin, in particular *Psychotria colorata*.[56] These plants have been used for many years by natives of the area as a treatment for pain, a feature which led to investigation of hodgkinsine as a potential analgesic.



hodgkinsine **20**

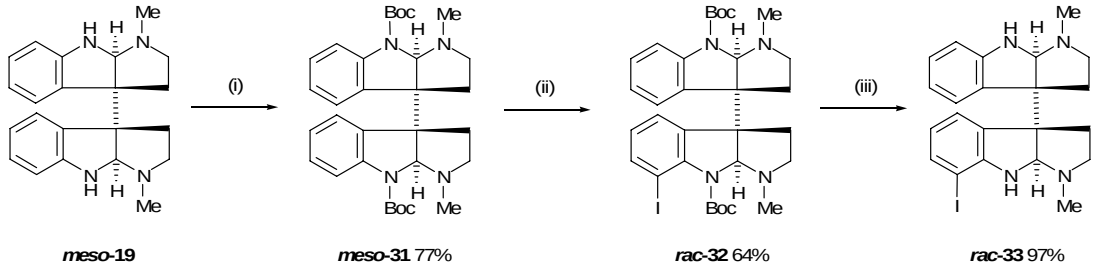
Figure 1.5

Subsequent pharmacological analyses revealed hodgkinsine **20** exhibits dose-dependent, analgesic activity against capsaicin induced pain, suggesting the involvement of NMDA receptors in its mode of action. It also acts as a micromolar agonist of μ-opioid receptors, which are widely distributed throughout the central

and peripheral nervous system. This dual mode of action has led to the consideration of hodgkinsine **20** as a new analgesic and as a replacement for morphine and other opiates as a treatment for chronic pain.[57, 58] To enable further study of this possibility a concise, high yielding yet relatively cheap synthesis of hodgkinsine **20** would be desirable.

From *meso*-chimonanthine ***meso*-19** the synthetic problem for the preparation of hodgkinsine **20** reduces to the stereoselective attachment of the third pyrrolidinoindoline motif, between the enantiotopic C-7 position of the *meso*-chimonanthine core to the C-3a position of the third motif with *R* absolute configuration. Overman proposed that this stereocentre could also be prepared by an intramolecular asymmetric Heck coupling, provided a suitable precursor could be prepared.

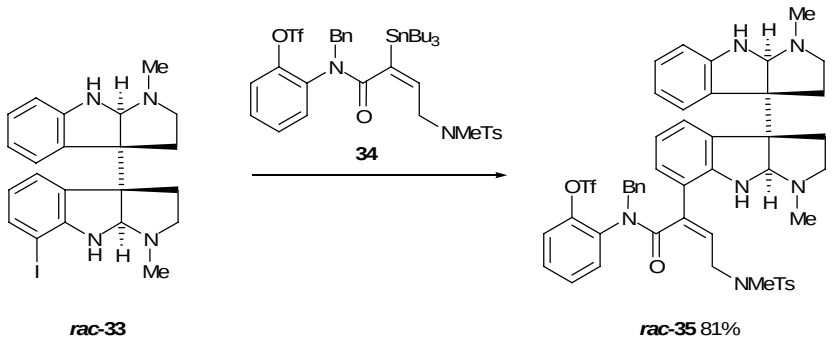
Their synthesis began from *meso*-chimonanthine ***meso*-19** by protection of the free amines with an excess of sodium bis(trimethylsilyl)amide and di-*tert*-butyl dicarbonate to give biscarbamate ***meso*-31**. This allows for a directed *ortho*-lithiation protocol with two equivalents of *sec*-butyllithium and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine followed by quenching of the resulting anion with 1,2-diiodoethane to give a racemic mixture of the monoiodide ***rac*-32**. Deprotection with trimethylsilyl triflate to diamine ***rac*-33** proceeded in excellent yield (Scheme 1.8).[54]



Scheme 1.8: *Reagents and Conditions*: (i) ***meso*-19** (1 eq.), Boc_2O (2.2 eq.), NaHMDS (4.5 eq.), THF; (ii) *sec*-BuLi (2 eq.), TMEDA (2 eq.), diiodoethane, THF, -78 to 0 °C; (iii) TMSOTf, DCM.

Diamine ***rac*-33** was subsequently employed in a room temperature stoichiometric Stille coupling with stannane **34**, which itself is synthesised in four steps from commercially available 3*H*-benzooxazol-2-one, in a procedure previously developed

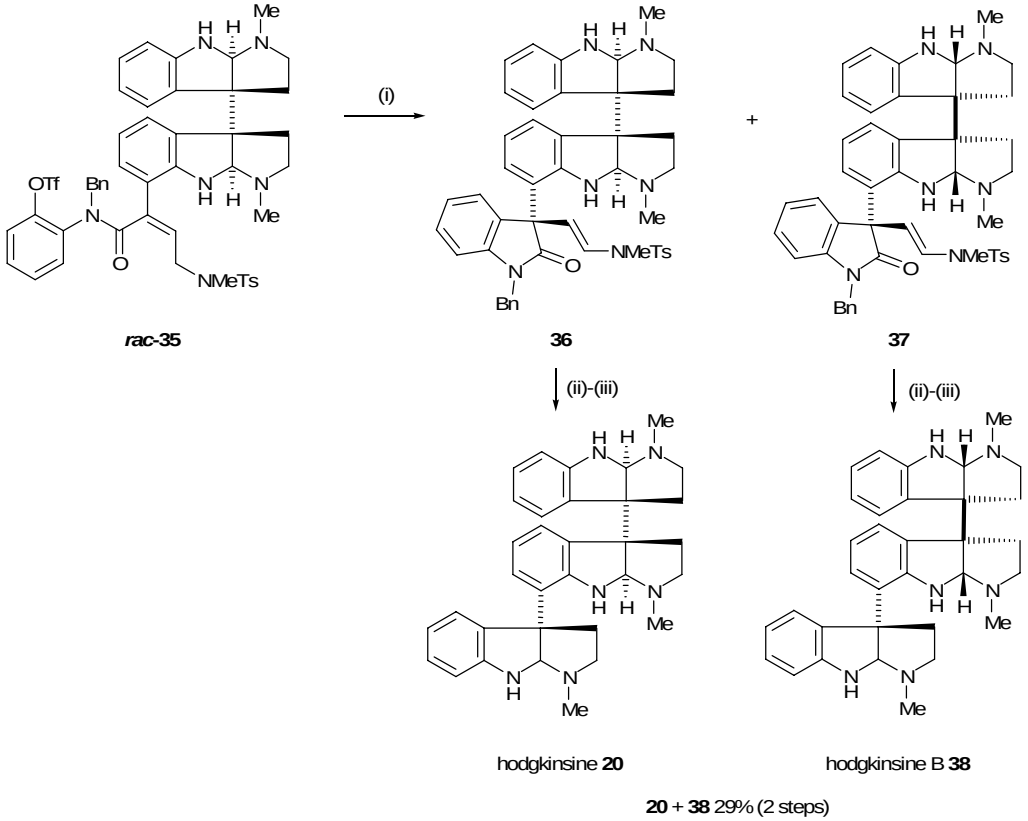
by Overman *et al*. This provided intramolecular Heck cyclisation precursor ***rac*-35** in 39% yield from *meso*-chimonanthine ***meso*-19 (**Scheme 1.9).[54]



***rac*-33** ***rac*-35** 81%

Scheme 1.9: *Reagents and Conditions*: iodide ***rac*-33** (1 eq.), $Pd_2(dba)_3.CHCl_3$ (1 eq. Pd), P(2-furyl)$_3$ **L34** (4 eq.), CuI, DMA.

The intramolecular asymmetric Heck cyclisation was employed as a means for the resolution of ***rac*-33**. As a result hodgkinsine B **38**, a C-3a stereoisomer of hodgkinsine **20**, was also prepared (Scheme 1.10).[54]



***rac*-35** **36** **37**

hodgkinsine **20** hodgkinsine B **38**

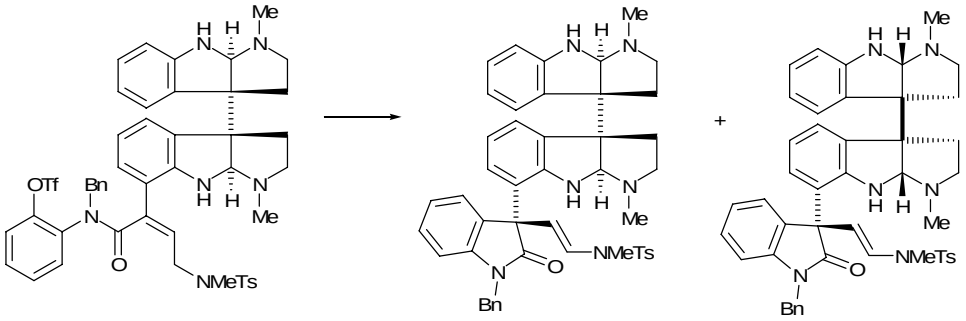
20 + **38** 29% (2 steps)

Scheme 1.10: *Reagents and Conditions*: (i) triflate ***rac*-35** (1 eq.), $Pd(OAc)_2$ (10 mol%), ligand (20 mol%), base, MeCN, 80 °C; (ii) $Pd(OH)_2$, H_2 (80 psi), EtOH, 80 °C; (iii) Na, $NH_{3(l)}$, -78 °C, NH_4Cl quench.

Initial investigations into the possibility of substrate controlled diastereoselection with achiral diphosphine ligands with a palladium catalyst produced poor results, a

maximum diastereoselection of 2:1 was achieved in favour of the desired product hodgkinsine precursor **36** over its stereoisomer **37** when employing palladium acetate and bis(diphenylphosphino)butane **L45** (Table 1.2, entry 1).

Table 1.2: Intramolecular Heck cyclisation of hodgkinsine precursor



***rac*-35** **36** **37**

Entry	Ligand	Base	Yield **36** (%)	*ee* **36** (%)	Yield **37** (%)	*ee* **37** (%)
1	**L45**	PS	50	-	24	-
2	**(*R*)-L1**	PS	40	68	38	69
3	**(*R*)-L2**	PS	37	78	37	82
4[a]	**(*R*)-L2**	PS	31	71	28	82
5[b]	**(*R*)-L2**	PS	24	55	24	48
6	**(*R*)-L2**	PMP	48	79	45	83

Reagents and Conditions: ***rac*-35** (1 eq.), $Pd(OAc)_2$ (10 mol%), ligand (20 mol%), base (4 eq.), MeCN, 80 °C. [a] DMA as solvent. [b] Toluene as solvent.

The use of chiral binaphthyl ligands in conjunction with palladium acetate produced more favourable results, with (*R*)-Tol-BINAP **(*R*)-L2** providing the most selective catalyst system (entries 2-4). Stereoselectivity was slightly enhanced in polar solvents and substitution of proton sponge for pentamethylpiperidine provided the optimum catalyst system, providing a near quantitative conversion to a 1:1 mixture of diastereomers which gave hodgkinsine precursor **36** with 79% *ee* (entries 4-6).

Thus, having successfully achieved the cyclisation, the enamine double bond was reduced and a reductive deprotection-cyclisation procedure with sodium in liquid ammonia gave hodgkinsine **20** in 29% yield from the Heck cyclisation product **36**, 5% from *meso*-chimonanthine ***meso*-19** in seven steps (Scheme 1.10).[54]

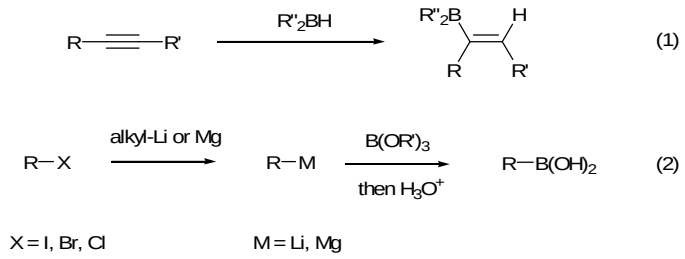
The total synthesis can be traced back to chiral pool starting materials, tartrate derivative **23** providing the stereochemical environment to control the stereochemistry of the first Heck cyclisation. Overall, although hodgkinsine **20** was prepared in just 0.003% yield over 20 steps, the synthesis demonstrates the powerful

application of asymmetric Heck couplings particularly in the preparation of stereodefined tetra-substituted alkenes.

The use of the second Heck cyclisation as a means of resolution represents an ingenious solution for the preparation of enantiomerically pure hodgkinsine **20** from the racemic materials generated from monoiodination of biscarbamate ***meso*-31**. However, the need for a resolution inherently limits the chemical yield of the Heck cyclisation to 50%. If the preparation of racemic intermediates could be avoided, instead achieving the construction of the stereodefined C-7/C-3a linkage by an asymmetric cross coupling, the yield could be greatly improved and would represent a more efficient synthesis.

1.2. Suzuki-Miyaura Couplings

Since the initial discovery of the coupling of organoboron reagents with vinyl halides in 1979, the scope of the Suzuki coupling has broadened considerably. Vinyl and aryl boronic species represent attractive substrates due to their simple preparation *via* hydroboration of an alkyne or quenching of an organometallic species with a trialkylborate and subsequent hydrolysis to the boronic acid (equations 1-2, Scheme 1.11). Suzuki-Miyaura couplings use consistently mild conditions with low catalyst loadings and exhibit excellent functional group tolerance. The stability of the boronic species allows for the application of aqueous and heterogeneous reaction conditions, generating non-toxic by-products.[33, 59, 60]



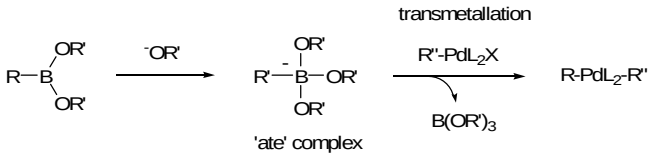
Scheme 1.11

1.2.1. Transmetallation Considerations

As described previously the reaction mechanism follows the general catalytic cycle for organometallic species (Figure 1.2). However, whereas other couplings proceed with direct transmetallation of the nucleophilic species to the palladium centre, Suzuki couplings of halides and triflates are observed to proceed primarily in the presence of an aqueous inorganic base.

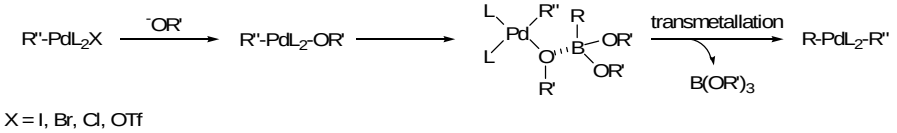
The carbon-boron bond is highly covalent, so transmetallation of a neutral vinyl boronic species is an unfeasible process with a high energy barrier. The addition of a base allows for three possible transmetallation mechanisms based on activation of the boron to an 'ate' complex, which polarises the carbon-boron bond and favours transmetallation. The first process to consider is the nucleophilic attack of base on the empty perpendicular p orbital of the sp_2 boron centre (Scheme 1.12).[61-64] Typical coupling conditions employ an aqueous hydroxide base, with carbonates,

phosphates, alkoxides and fluorides also effective promoters through the same mechanism.



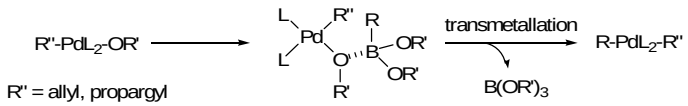
Scheme 1.12

The second process to consider is the substitution of halide in the palladium(II) coordination sphere by the base (Scheme 1.13). In the case of a hydroxide base, the subsequent oxo-palladium(II) complex would then direct the boronic species toward the palladium centre by coordination of the oxygen to the empty boron p orbital. This mechanism was originally favoured by Suzuki *et al*.[65] However, computational studies have suggested that the substitution of halide is a very high energy process and the authors suggest such a mechanism is unlikely. Furthermore, electrospray mass spectrometry analysis of biaryl couplings did not observe any oxo-palladium(II) intermediates.[64]



Scheme 1.13

The final process to consider stems from the observation that Suzuki couplings of allylic acetates and propargyl carbonates proceed under neutral conditions. The oxo-palladium(II) species resulting from oxidative addition is formed directly, not *via* halide substitution, and can then direct the boronic species for transmetallation (Scheme 1.14).[64] Theoretical calculations support the experimental observations for this mechanism.[65]

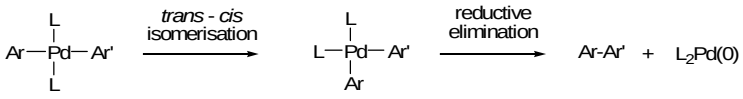


Scheme 1.14

In conclusion, for common Suzuki couplings of organic halides and triflates a nucleophilic base is required to activate the boronic acid or ester to the "ate" complex. This activation polarises the boron-carbon bond, generating a suitably

nucleophilic organic moiety for transmetallation. Less common couplings of acetates and carbonates achieve boron activation by intermolecular coordination and don't require an additive.

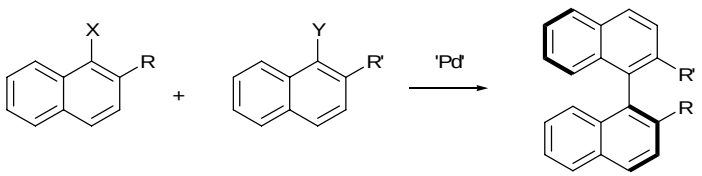
Electrospray mass spectrometry measurements also suggested that the transmetallation process is not the rate determining step, as is conventionally accepted. Rather, in the Suzuki coupling of biaryls, a pre reductive elimination *trans*-*cis* isomerisation *via* ligand exchange is proposed to be rate-limiting (Scheme 1.15).[66]



Scheme 1.15

1.2.2. Asymmetric Suzuki-Miyaura couplings

The following review of asymmetric Suzuki couplings discusses the work of individual research groups in chronological order. Since the publication of the first asymmetric Suzuki couplings by Cammidge *et al.*,[67] successful couplings have focused on the preparation of axially chiral binaphthyls and biaryls. Efficient synthesis of these atropisomeric compounds is a desirable procedure due to their extensive use in a variety of other cross-coupling reactions, and the most attractive and efficient method would be the catalytic union of naphthyl derivatives (Scheme 1.16). Binaphthyls require at least three *ortho*-substituents to achieve configurational stability, therefore a considerable challenge to a viable dimerisation would be the need to overcome the steric hindrance of *ortho*-substitution.

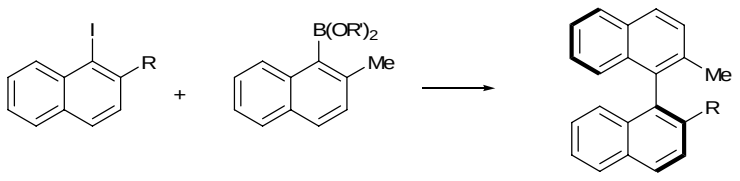


Scheme 1.16

Cammidge *et al.* achieved the union of binaphthyls under a range of catalytic conditions. Employing naphthyliodide derivatives **39**-**40** and either boronic acid **41** or boronic esters **42**-**43**, a variety of chiral ligands with palladium(II) chloride

yielded the desired binaphthyls. Combinations of solvents giving hetero- and homogeneous systems (dimethoxyethane, dimethoxyethane/water, toluene/ethanol/water) gave successful coupling along with a variety of bases, most consistently barium hydroxide and cesium fluoride (Table 1.3).[68]

Table 1.3: Asymmetric preparation of binaphthyls (Cammidge *et al.*)



39 R = H
40 R = Me

41 R' = H
42 $(OR')_2$ = pinacol,
43 $(OR')_2$ = -OCH_2CH_2O-

44 R = H
45 R = Me

Entry	Iodide/ Boronate	Ligand	Solvent	Base	Prod.	*t* (h)	Yield (%)	*ee* (%)
1	**39/41**	**L50**	DME/H_2O	$Ba(OH)_2$	**(*S*)-44**	17	44	63
2	**39/41**	**L50**	DME/H_2O	$Ba(OH)_2$	**(*S*)-44**	5	44	61
3	**39/41**	**L50**	DME	CsF	**(*S*)-44**	17	44	55
4	**39/41**	**L50**	Tol/EtOH/H_2O	$Ba(OH)_2$	**(*S*)-44**	17	45	52
5	**39/41**	**L53**	DME/H_2O	$Ba(OH)_2$	**(*S*)-44**	2	82	2
6	**39/41**	**L52**	DME/H_2O	$Ba(OH)_2$	**(*S*)-44**	17	73	4
7	**39/41**	**L25**	DME/H_2O	$Ba(OH)_2$	**(*S*)-44**	17	83	10
8	**39/41**	**L26**	DME/H_2O	$Ba(OH)_2$	**(*S*)-44**	17	73	24
9	**40/43**	**L50**	DME	CsF	**(*S*)-45**	6 days	60	85
10	**40/42**	**(*R*)-L1**	DME	CsF	**(*S*)-45**	4 days	17	10

Reagents and Conditions: iodide (1 eq.), boronate (1.1 eq.), $PdCl_2$ (3 mol%), ligand (6 mol%), base, solvent, reflux.

The most successful enantioselectivities were achieved with ferrocenyl ligand (*S*)-(*R*)-PPFA **L50**, providing the desired binaphthyls in consistent yields and 52-63% *ee* (entries 1-4). Variation of solvents, base and reaction duration had no substantial effect on selectivity. Almost identical yield and enantioselectivity was obtained when the reaction time was reduced from seventeen to five hours, suggesting catalyst or substrate decomposition occurs over extended periods of time (entries 1-2). Ligands **L52, L53, L25 and L26** provided a more active catalyst system by giving higher yields but did not achieve higher enantioselection (entries 5-8). The best conversion and selectivity was achieved under anhydrous conditions employing more sterically hindered iodide **40** and boronic ester **43**. With the optimal ferrocenyl ligand (*S*)-(*R*)-PPFA **L50**, binaphthyl **(*S*)-45** was furnished in a comparatively high yield (60%) and selectivity (85% *ee*), over a much extended reaction time of 6 days (entry 9).[68]

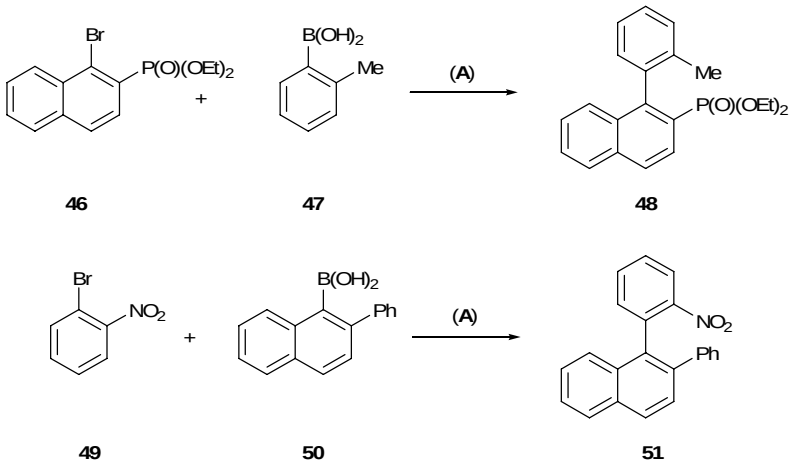
Chiral bisphosphines **L42**-**L43** and chiral diamines **L44** and **L46** performed very poorly giving low yields and very low enantioselectivities. Overall observations suggest that hemilabile P/N ligands provide optimum yields and selectivities in the asymmetric Suzuki cross-coupling.[68]

Cammidge *et al.* also reported a switch in enantioselectivity when employing boronic esters **42** and **43** under otherwise identical reaction conditions, leading to the proposal that the reaction operates under kinetic conditions and that the enantio-determining step is transmetallation. Thermodynamic control would lead to the same enantiomers being formed.

Almost simultaneously, Buchwald *et al.* reported the results of their studies into the preparation of functionalised axially chiral biaryls.[69] Initial protocols investigated the efficiency of the reaction by swapping the role of coupling partners in the presence of binaphthyl phosphine ligands. The reactions between bromo diethylphosphite **46** and 2-methylphenylboronic acid **47**, along with 2-nitrobromobenzene **49** and 2-phenylnaphthyl boronic acid **50** were studied (Table 1.4).

In support of the results of Cammidge *et al.* the investigations by Buchwald *et al.* also achieved optimal yield and selectivity with hemilabile P/N ligands, (*S*)-Cy-MAP **(*S*)-L17** giving quantitative conversion with 87% *ee* for the preparation of biaryl **48** (Table 1.4, entry 3). The need for a second coordinating group to achieve high selectivities was evident by the reduced enantioselectivities observed when employing monodentate phosphines **(*S*)-L19** and **(*S*)-L20** though conversions were good or excellent (entries 1-2). Application of (*S*)-^{i}Pr-MAP **(*S*)-L15** or (*S*)-MAP **(*S*)-L12** resulted in reduced enantioselectivities for both couplings although conversions remained high (entries 4-5). Bidentate ligand **(*S*)-L1** performed poorly, with low yields and selectivity (entry 6).[69]

Table 1.4: Asymmetric preparation of biaryls (Buchwald *et al.*)

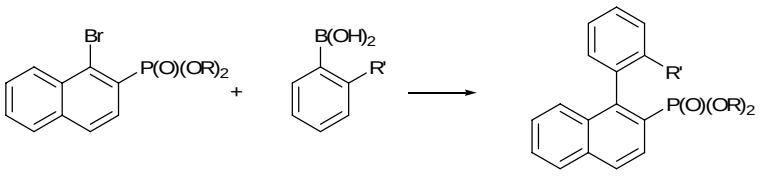


Entry	Ligand	Conv. **48** (%)[a]	*ee* **48** (%)	Conv. **50** (%)[a]	*ee* **50** (%)
1	**(*S*)-L19**	100	54	100	32
2	**(*S*)-L20**	100	23	60	62
3	**(*S*)-L17**	100	87	81	73
4	**(*S*)-L15**	61	86	92	65
5	**(*S*)-L12**	76	75	67	38
6	**(*S*)-L1**	40	n.d.	46	22

Reagents and Conditions: (**A**) bromide (1 eq.), boronic acid (1.5 eq.), $Pd_2(dba)_3$ (1 mol%), ligand (2.4 mol%), K_3PO_4 (2 eq.), toluene, 70 °C. [a] GC conversion.

With optimal ligand (*S*)-Cy-MAP **(*S*)-L17** the scope of the reaction was explored, coupling dimethyl and diethylphosphites with a variety of *ortho*-substituted boronic acids (Table 1.5).

Table 1.5: Scope of Suzuki coupling for the preparation of axially chiral biaryls (Buchwald *et al.*)



R = Me, Et

R' = Me, Et, ^{i}Pr

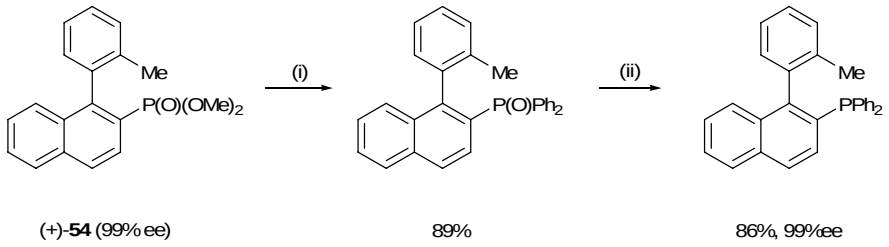
48 R = Et, R' = Me
52 R = Et, R' = Et
53 R = Et, R' = ^{i}Pr
54 R = Me, R' = Me

Entry	R	R′	Pd (mol%)	*T* (°C)	*t* (h)	Product	Yield (%)	*ee* (%)
1	Et	Me	4	70	88	**48**	98	87
2	Et	Me	1	70	17	**48**	93	87[a]
3	Et	Et	1	70	24	**52**	94	92
4	Et	^{i}Pr	2	80	24	**53**	89	85[a]
5	Me	Me	2	70	24	**54**	91	84
6	Me	Me	0.2	60	24	**54**	95	86

Reagents and Conditions: bromide (1 eq.), boronic acid (1.5 eq.), $Pd_2(dba)_3$ (1 mol%), (*S*)-Cy-MAP **(*S*)-L17** (2.4 mol%), K_3PO_4 (2 eq.), toluene, 70 °C. [a] 3 eq. NaI added.

The couplings proceeded with excellent yields and enantioselectivities. Near quantitative yield was achieved for the coupling of bromo dimethylphosphite with 2-ethyl phenylboronic acid in 87% *ee* (Table 1.5, entry 1). Catalyst loading could be reduced by 75% to 1 mol%, in conjunction with an 80% decrease in reaction time to 17 hours, with no loss of enantioselectivity (87% *ee*) and a negligible decrease in chemical yield (entry 2). The catalyst tolerated an increase in steric bulk of the phosphite, diethyl phosphite **46** achieving the greatest enantioselectivity of all couplings studied (entries 3-4). Very low palladium loadings were also efficient indicating a highly stable catalyst in which protodeboronation is not a competing mechanism, in contrast to observations by Cammidge *et al*.

The biaryl products also exhibited high thermal stablility to racemisation. Recrystallisation of the Suzuki product to enantiopurity, alkylation with a Grignard reagent and then reduction of the subsequent phosphite yielded chiral monophosphines as single enantiomers (Scheme 1.17).[69]

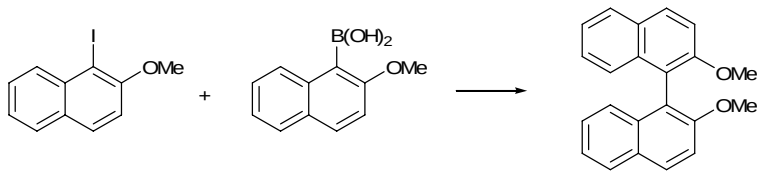


Scheme 1.17: *Reagents and Conditions*: (i) biaryl **54**, PhMgBr, DME, 45 °C; (ii) PMHS, $Ti(O^iPr)_4$, THF, 70 °C.

In conclusion, Buchwald *et al.* have developed a highly efficient method for the preparation of functionalised axially chiral biaryls with impressive yields and enantioselectivity. Catalyst stability and turnover was also excellent. Although not discussed here, the preparation of binaphthyls did not achieve such high enantioselectivities (57-73%), though good to excellent yields were again observed (80-97%).

In 2002 Colobert *et al.* published their investigations into the asymmetric Suzuki coupling of 2-methoxynaphthyl iodide **55** and 2-methoxynaphthyl boronic acid **56** (Table 1.6). The couplings presented a considerable challenge as the Suzuki coupling of two di-*ortho*-substituted fragments exhibits very high sensitivity to sterics.

Table 1.6: Asymmetric preparation of alkoxybinaphthyls (Colobert *et al.*)



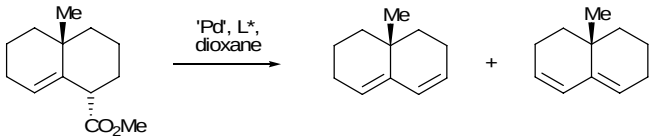
55 **56** **57**

Entry	Pd source	Solvent	Ligand	L/Pd	*t* (h)	Yield **57** (%)	*ee* **57** (%)	rot.
1	$Pd(OAc)_2$	DME	**(*R*)-L1**	0.85	6	84	22	(-)
2	$Pd(OAc)_2$	DME	**(*R*)-L1**	1.28	6	86	29	(+)
3	$Pd(OAc)_2$	DME	**(*R*)-L1**	1.85	4	94	28	(+)
4	$(\eta_3\text{-allylPdCl})_2$	DME	**(*R*)-L1**	0.97	3	85	22	(-)
5	$(\eta_3\text{-allylPdCl})_2$	DME	**(*R*)-L1**	2.00	3.5	79	26	(+)
6	$(\eta_3\text{-allylPdCl})_2$	DME	**(*R*)-L2**	0.96	12	67	22	(-)
7	$(\eta_3\text{-allylPdCl})_2$	DME	**(*R*)-L2**	1.93	7	50	24	(+)
8	$(\eta_3\text{-allylPdCl})_2$	dioxane	**(*R*)-L1**	0.92	7	76	30	(-)

Reagents and Conditions: iodide **55** (1 eq.), boronic acid **56** (2 eq.), $Pd(OAc)_2$ or $(\eta_3\text{-allylPdCl})_2$ (10 mol% Pd), (*R*)-BINAP **(*R*)-L1** or (*R*)-Tol-BINAP **(*R*)-L2**, CsF (6 eq.), solvent, 70 °C.

These results represented the first synthesis of heteroaromatic binaphthyls *via* an asymmetric Suzuki coupling. Although overall chemical yields were good to excellent (50-94%), the dimethoxybinaphthyls were prepared with low enantioselectivity (22-30%), despite changing solvent, palladium source, catalyst loading and the ligand/palladium ratio. The major observation from these investigations was the extremely sensitive dependence of the binaphthyl product **57** on the ligand/palladium ratio. When a ratio of less than one was employed the (-)-**57** enantiomer was prepared (Table 1.6, entries 1, 4, 6 and 8). When the ratio greater than one the (+)-**57** enantiomer was the major product (entries 2, 3, 5 and 7).

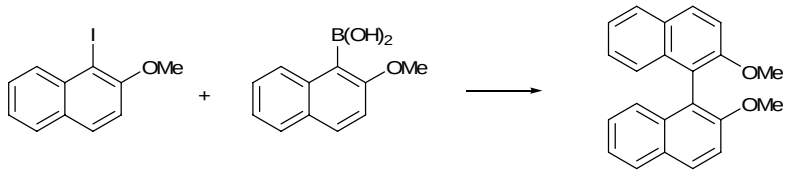
Similar chirality reversal has been observed by Genet and Shimizu in separate catalytic palladium reactions.[70] Shimizu, employing a $Pd(OAc)_2$/(*S*)-BINAP **(*S*)-L1** catalyst system for asymmetric allylic carbonate elimination (Scheme 1.18), proposed (*S*)-BINAP(O) **(*S*)-L5** and (*S*)-$BINAP(O)_2$ **(*S*)-L6** could be formed in the reaction,[71] the phosphine having reduced the palladium(II) species to palladium(0) in a process analogous to observed reductions with of $Pd(OAc)_2$ with triphenylphosphine. Phosphine oxides have been increasingly acknowledged as active ligands in catalytic processes,[27] and subsequently Shimizu demonstrated that Pd(0)/(*S*)-BINAP **(*S*)-L1** and Pd(0)/(*S*)-BINAP(O) **(*S*)-L5** catalysts have opposite enantiomeric selectivity.



Scheme 1.18

Colobert *et al.* subsequently compared the selectivities of $Pd_2(dba)_3$/(*R*)-BINAP **(*R*)-L1** and $Pd_2(dba)_3$/(*R*)-BINAP(O) **(*R*)-L5** catalyst systems (Table 1.7). In both instances the (+)-**57** enantiomer was prepared, thus eliminating phosphine oxidation as a cause of selectivity reversal. Similar effects of ligand to metal ratio have been attributed to the formation of polynuclear active complexes, which are favoured at high ligand loading. The asymmetric environment of such a catalyst may be highly complex and difficult to predict and represents a viable explanation, though unproven, of chirality reversal.

Table 1.7: Phosphine oxide in the asymmetric preparation of alkoxybinaphthyls (Colobert *et al.*)

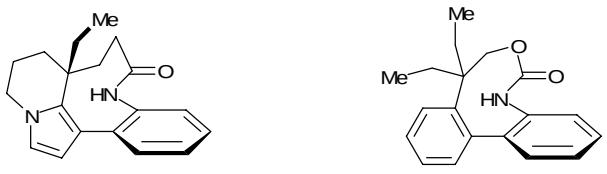


55 **56** **57**

Entry	Pd source	Solvent	Ligand	*t* (h)	Yield **57** (%)	*ee* **57** (%)	rot.
1	$Pd_2(dba)_3$	dioxane	**(*R*)-L1**	7.5	46	15	(+)
2	$Pd_2(dba)_3$	dioxane	**(*R*)-L5**	12	22	24	(+)

Reagents and Conditions: iodide **55** (1 eq.), boronic acid **56** (2 eq.), $Pd(OAc)_2$ or $(\eta_3\text{-allylPdCl})_2$ (10 mol% Pd), ligand (11 mol%), CsF (6 eq.), solvent, 70 °C.

Baudoin *et al.* were the first to apply an asymmetric Suzuki coupling to the preparation of a biologically active target, di-*ortho*-substituted carbamate **59** an analogue of (-)-rhazinilam **58** (Figure 1.6).[72, 73]

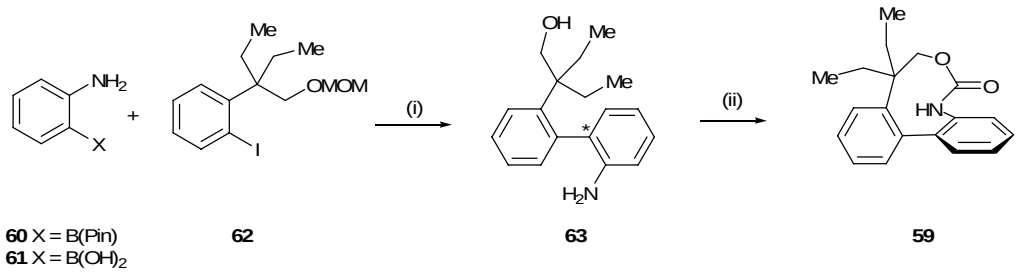


58 (-)-rhazinilam **59**

Figure 1.6

Disubstituted biphenyl compounds such as **59** are more difficult to prepare by this method due to their low energy barrier to rotation, therefore racemisation is a more facile process and the scope of reaction conditions is limited particularly with respect to temperature.

Their synthesis relied on a degree of stability of the proposed Suzuki product **59** (Scheme 1.19). Investigations into the configurational stability of **59**, prepared racemically with enantiomers separated by chiral HPLC, under thermal conditions gave surprising results. No racemisation was observed after 1 hour at 80 °C and only 5% loss in *ee* after one hour at 100 °C. This unexpected stability was attributed to the bulky quaternary carbon centre hindering rotation, therefore an asymmetric Suzuki coupling could be envisaged.



60 X = B(Pin)
61 X = $B(OH)_2$

62 **63** **59**

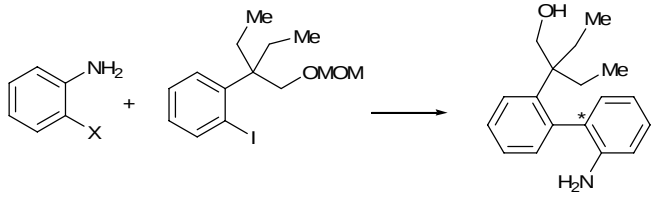
Scheme 1.19: *Reagents and Conditions*: (i) iodide **62** (1 eq.), boronate (1.5 eq.), $Pd_2(dba)_3.CHCl_3$ (2.5 mol%), ligand (6 mol%), $Ba(OH)_2.8H_2O$ (2 eq.), dioxane/H_2O 9:1, 80 °C, 1 h then *c*HCl/MeOH, reflux; (ii) $(Cl_3CO)_2CO$, py, DCM, -78 °C.

Following their success in previous asymmetric Suzuki couplings, a series of binaphthyl and ferrocenyl ligands were prepared and investigated as active ligands in the coupling of *ortho*-substituted iodide **62** and boronic species **60**-**61** (Table 1.8). Ligands included commercial (*R*)-BINAP **(*R*)-L1**, ferrocenyl ligand (*R*)-(*S*)-PPFA **L51** and a range of hemilabile MAP derivatives, shown to be successful by Colobert, Cammidge and Buchwald respectively. In addition, Baudoin proposed that electron-rich ligands of the kind (aryl)$P(alkyl)_2$ were the most efficient ligands therefore monodentate phosphetanes **L27**, **L28** and **L36** were also investigated.[72]

Bidentate phosphines proved unsuccessful in the preparation of biphenyl **63** from pinacol ester **60**, binaphthyl (*R*)-BINAP **(*R*)-L1** providing the desired product **63** in racemic form and just 12% yield (Table 1.8, entry 1). A variety of MAP ligands achieved selective coupling though yields and enantioselectivities were moderate.

When employing acid **61** as the substrate (*S*)-Cy-MAP **(*S*)-L17** achieved comparable enantioselectivity to those achieved with esters, with a slight increase in chemical yield to 56% (entries 2-7). (*S*)-Cy-MAP **(*S*)-L17** achieved comparable enantioselectivity of 40% with (*S*)-^{i}Pr-MAP **(*S*)-L15**, with a slight increase in chemical yield to 56%. These results observe a direct correlation with increasing cone angle of the phosphine (Me < Et < ^{i}Pr < Cy) with cyclohexyl (cone angle = 170°) providing the optimum catalyst system.[74] As observed by Buchwald, (*S*)-^{t}Bu-MAP **(*S*)-L16** gave a marked decrease in catalyst efficiency (entry 4), presumably due to the cone angle being too great and destabilising the catalyst. However, it should also be noted that the increase in selectivity correlates directly with increased phosphine basicity.

Table 1.8: Ligand screen for the asymmetric preparation of biphenyl **63** (Baudoin *et al.*)



60 X = B(Pin) **62** **63**
61 X = B(OH)$_2$

Entry	Ligand	Boronate	Yield **63** (%)	*ee* **63** (%)
1	**(*R*)-L1**	pin	12	0
2	**(*S*)-L17**	pin	56	(-) 40
3	**(*S*)-L15**	pin	49	(-) 41
4	**(*S*)-L16**	pin	8	(-) 3
5	**(*S*)-L14**	pin	35	(-) 36
6	**(*S*)-L13**	pin	35	(-) 30
7	**(*S*)-L17**	acid	31	(-) 32
8	**(*R*)-L8**	pin	51	(+) 6
9	**L51**	pin	38	(-) 5
10	**L61.HBF$_4$**	pin	39	(-) 10
11	**L27**	pin	21	(+) 6
12	**L28**	pin	37	(+) 17
13	**L36**	pin	19	0

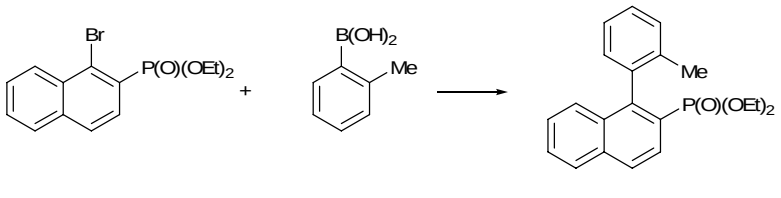
Reagents and Conditions: (i) iodide **62** (1 eq.), boronate (1.5 eq.), $Pd_2(dba)_3.CHCl_3$ (2.5 mol%), ligand (6 mol%), $Ba(OH)_2.8H_2O$ (2 eq.), dioxane/H_2O 9:1, 80 °C, 1 h, then *c*HCl/MeOH, reflux.

With optimum hemilabile ligand (*S*)-Cy-MAP **(*S*)-L17**, boronic acid **61** could be coupled with iodide **62** though yield and enantioselectivity were unfavourable in comparison to boronic ester **60** (entry 7). The hemilabile binaphthyl ligand (*R*)-MeO-MOP **(*R*)-L8**, provided **63** in good yield (51%) but in near racemic form (entry 8). Ferrocenyl and alkyl-phosphetane derivatives performed poorly (entries 9-13). Enantioselectivity was poor (0-17%) and yields only moderate (19-39%).[72]

Although having attained only a moderate *ee* of 40% for biaryl **63**, the coupling represents an impressive achievement in asymmetric Suzuki couplings due to the steric hindrance of the substrates and propensity for racemisation of the product under prolonged reaction times. Baudoin *et al.* attribute this success to the choice of reaction conditions (barium hydroxide/dioxane/water) which allow reaction completion in one hour, thus minimising the potential for racemisation.

Baudoin *et al.* extended their investigations to apply the new ligands studied in the synthesis of biphenyl **63** to the preparation of biaryls from bromide **46** and 2-methylphenylboronic acid **47**, as demonstrated previously by Buchwald *et al*. (*S*)-^{t}Bu-MAP **(*S*)-L16** and (*S*)-Et-MAP **(*S*)-L14** gave good enantioselectivity though slightly less than (*S*)-Cy-MAP **(*S*)-L17** and chemical yields were greatly reduced (Table 1.9, entries 1-3). Ferrocenyl derivatives **L51** and **L61.HBF$_4$** gave good conversions but much lower enantioselectivities (entries 4-5). Finally, cyclohexyl phosphetane **L28** gave a better *ee* (40%) than observed in the preparation of biphenyls but the chemical yield was very low (entry 6).

Table 1.9: Ligand screen for the asymmetric preparation of biaryl **48** (Baudoin *et al.*)



46 **47** **48**

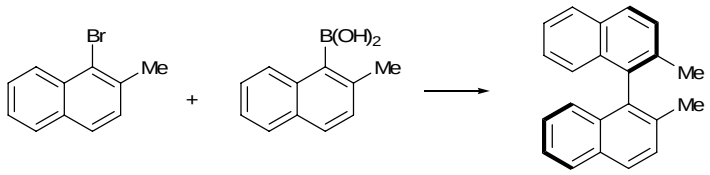
Entry[a]	Ligand	*t* (h)	Yield **48** (%)	*ee* **48** (%)
1	**(*S*)-L17**	17	93	87
2	**(*S*)-L16**	17	37	81
3	**(*S*)-L14**	56	5	77
4	**(*S*)-L51**	12	60	44
5	**L61.HBF$_4$**	44	52	3
6	**L28**	61	10	40

Reagents and Conditions: bromide **46** (1 eq.), boronic acid **47** (1.5 eq.), $Pd_2(dba)_3$ (2.5 mol%), ligand (6 mol%), K_3PO_4 (3 eq.), NaI (3 eq.), toluene, 70 °C.

Cy-MAP **(*S*)-L17** and to a lesser degree its derivatives appear to be the most versatile of all ligands studied so far, achieving good to excellent yields and enantioselectivity. Ferrocenyl, binaphthyl, MeO-MOP **L8** and phosphetane ligands exhibit substrate dependency, as has been observed in racemic Suzuki couplings, and do not represent useful ligands for the substrates studied.

Johannsen and Jensen reported the asymmetric preparation of tetra-*ortho*-substituted binaphthyls employing a range of novel ferrocenyl ligands under a variety of conditions (Table 1.10). From their studies on the preparation of racemic biphenyls with these ligands, they made a number of observations with regard to catalyst activity. Room temperature couplings proceeded with an optimal ligand/palladiun ratio of 1.2 with a TOF of 180000 h^{-1}, compared with a TOF of 67 h^{-1} when the ligand/palladium ratio was 2. This suggested a highly active monoligated palladium species was the active catalyst. However, when the coupling was conducted at an elevated temperature of 60 °C the optimum ligand/palladium ratio increased to 2.5 due to catalyst decomposition and to prevent deposition of palladium black.[75]

Table 1.10: Asymmetric preparation of binaphthyls (Johannsen and Jensen)



64 **41** **(*R*)-45**

Entry	Ligand	Base	Solvent	Yield **(*R*)-45** (%)	*ee* **(*R*)-45** (%)
1	**L61**	K_3PO_4	toluene	62	43
2	**L61**	CsF	DME	28	46
3	**L61**	$Ba(OH)_2$	DME	30	46
4	**L62**	K_3PO_4	toluene	65	54
5	**L63**	K_3PO_4	toluene	<1	-
6	**L63**	K_3PO_4	THF	32	45

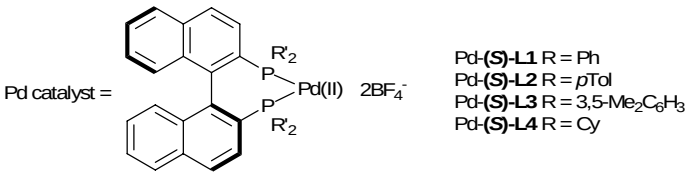
Reagents and Conditions: bromide **64** (1 eq.), boronate **41** (1.5 eq.), $Pd_2(dba)_3$ (2 mol%), ligand (5 mol%), base (2-3 eq.), H_2O (8 eq.), solvent, 60-75 °C.

In contrast to the palladium(0) mediated couplings published to this point, Mikami *et al.* demonstrated a cationic palladium(II) catalysed asymmetric Suzuki coupling, achieving the coupling of *ortho*-substituted naphthyl bromides **65**-**68** with naphthyl boronic acid **69** to yield the tri-*ortho*-substituted binaphthyls **70**-**73** with some impressive results (Table 1.11).[76]

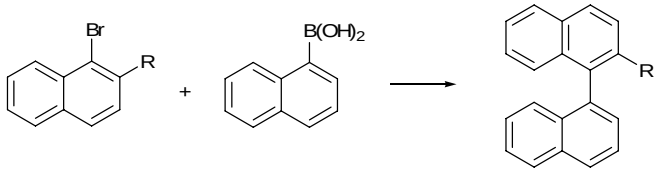
Mikami *et al.* had noted that the coupling of bromide **65** with naphthyl boronic acid **69** in the presence of the palladium(II) source $[(MeCN)_4Pd](BF_4)_2$ and (*S*)-BINAP **(*S*)-L1** proceeded to completion in one hour, whereas employing palladium(0) source $Pd_2(dba)_3.CHCl_3$ with (*S*)-BINAP **(*S*)-L1** the reaction was more sluggish, reaching completion over thirteen hours. Improved conditions by pre-preparation of

the palladium(II)/ligand catalyst and addition of an extra equivalent of the bidentate phosphine gave binaphthyl **70** in 91% yield and 56% *ee* in just 30 minutes (Table 1.11, entry 1).

Table 1.11: Asymmetric preparation of binaphthyls by palladium(II) catalysis (Mikami *et al.*)



Pd-(*S*)-L1 R = Ph
Pd-(*S*)-L2 R = *p*Tol
Pd-(*S*)-L3 R = 3,5-$Me_2C_6H_3$
Pd-(*S*)-L4 R = Cy



65 R = OMe
66 R = O^{i}Pr
67 R = OBn
68 R = NMe_2

69

70 R = OMe
71 R = O^{i}Pr
72 R = OBn
73 R = NMe_2

Entry	Bromide	Pd Catalyst	*t* (h)	Product	Yield (%)	*ee* (%)
1	**65**	Pd-(***S***)-**L1**	0.5	**70**	91	56
2	**65**	Pd-(***S***)-**L2**	1	**70**	97	40
3	**65**	Pd-(***S***)-**L3**	4	**70**	0	-
4	**65**	Pd-(***S***)-**L4**	1	**70**	92	70
5[a]	**65**	Pd-(***S***)-**L4**	6	**70**	17	84
6	**66**	Pd-(***S***)-**L1**	0.5	**71**	99	50
7	**67**	Pd-(***S***)-**L4**	4	**72**	99	54
8	**68**	Pd-(***S***)-**L1**	0.5	**73**	61	58

Reagents and Conditions: bromide (1 eq.), boronic acid (1.5 eq.), Pd cat. (2 mol%), $Ba(OH)_2$ (2 eq.), DME, 80 °C. [a] at room temperature.

Bulkier derivatives of (*S*)-BINAP **(*S*)-L1** gave reduced enantioselectivity as expected, (*S*)-Tol-BINAP **(*S*)-L2** reduced the *ee* to 56% while (*S*)-3,5-DM-BINAP **(*S*)-L3** generated an inactive palladium(II) catalyst (entries 2 and 3). In contrast to this expected trend (*S*)-Cy-BINAP **(*S*)-L4** gave excellent yield and an increase in enantioselectivity to 70%, and coupling at room temperature gave a further increase to 84% though the yield was greatly reduced, even over a longer reaction time (entries 4 and 5). The authors attribute this increased selectivity to the highly sterically demanding nature of the palladium complex, though increased basicity of the phosphine could again be a contributing factor. Variation of the *ortho*-substituent was well tolerated though enantioselectivities were not improved (entries 6-8).[76]

The work of Mikami *et al.* represented the first successful asymmetric Suzuki coupling with a palladium(II) catalyst. Their conditions gave improved yield and

enantioselectivity with a range of bisphosphine ligands, in comparison with the work of Castanet *et al.* discussed previously. However, again, enantioselectivities were not as impressive as those achieved by Buchwald with hemilabile Cy-MAP **L17** (Table 1.5), though increased *ortho*-substitution may be an important factor.

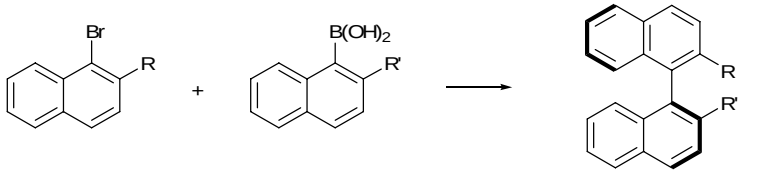
Espinet *et al.* observed that the asymmetric Suzuki coupling of naphthyl boronic acids proceeds with greater efficiency after simple purification through a silica plug to remove residual hydrochloric acid that can remain after initial purification of the boronic acid.[77] This can act as the proton source to promote protodeboronation, especially in sterically hindered systems.

They proceeded to demonstrate the importance of this purification in the asymmetric Suzuki coupling of naphthyl boronic acids **41**, **56** and **74** with naphthyl bromides **64-65** and **67**, to yield alkoxybinaphthyls analogous to those prepared by Castanet *et al.* (Table 1.12). A variety of palladium sources, loadings, ferrocenyl ligands and ligand/palladium ratios were investigated with cesium fluoride as base in anhydrous dimethoxyethane or tetrahydrofuran. It was found that other solvent systems previously applicable to asymmetric Suzuki couplings (toluene/ethanol/water, dioxane/water) were not suitable for this coupling. Cesium fluoride was also the only efficient base; barium hydroxide, potassium phosphate, potassium fluoride, sodium hydroxide and sodium carbonate gave poor conversions in both anhydrous and aqueous conditions.[77]

The most successful couplings were achieved with a relatively high catalyst loading of 10 mol%, in contrast to previous examples where 2-3 mol% provided an active catalyst system. A reduction in loading to 5 mol% palladium with ferrocenyl ligand **L51** had no effect on the yield of **45** (Table 1.12, entries 1-2) though a marked decrease was observed in the preparation of bisalkoxybinaphthyls **45**, **75-78** even with extended reaction times, though different palladium sources were employed (entries 4-7). A loading of 3 mol% with catalyst **L51** achieved the greatest enantioselectivity (90%) of the study for the preparation of bismethylbinaphthyl **45** but with a moderate yield (55%) and increased ligand/palladium ratio of 4 (entry 3).

A general trend of increased enantioselectivity with lower catalyst loading was observed but with a concomitant decrease in chemical yield.

Table 1.12: Asymmetric preparation of binaphthyls (Espinet *et al.*)



64 R = Me
67 R = OBn
65 R = OMe

41 R = Me
74 R = OBn
56 R = OMe

45 R = R' = Me
75 R = R' = OBn
76 R = R' = OMe
77 R = Me, R' = OMe
78 R = OBn, R' = OMe

Entry	Bromide	Boronic Acid	Pd source (mol%)	Ligand	*t* (h)	Product	yield (%)	*ee* (%)
1	**64**	**41**	$Pd(dba)_2.CHCl_3$ (10)	**L51**	72	**45**	85	85
2	**64**	**41**	$Pd(dba)_2.CHCl_3$ (5)	**L51**	72	**45**	85	85
3[a]	**64**	**41**	$Pd(MeCN)(BF_4)_2$ (3)	**L51**	96	**45**	55	90
4[b]	**67**	**74**	$Pd(OAc)_2$ (10)	**L51**	72	**75**	95	60
5	**67**	**74**	$Pd(dba)_2.CHCl_3$ (5)	**L51**	96	**75**	50	88
6[b]	**65**	**56**	$Pd(OAc)_2$ (10)	**L51**	72	**76**	95	50
7	**65**	**56**	$Pd(dba)_2.CHCl_3$ (5)	**L51**	96	**76**	50	57
8	**64**	**41**	$Pd(dba)_2.CHCl_3$ (10)	**L55**	72	**45**	62	73
9	**64**	**41**	$Pd(dba)_2.CHCl_3$ (10)	**L56**	72	**45**	50	68
10	**64**	**41**	$Pd(dba)_2.CHCl_3$ (10)	**L57**	72	**45**	66	68
11	**65**	**41**	$Pd(dba)_2.CHCl_3$ (5)	**L51**	96	**77**	77	65
12	**67**	**56**	$Pd(dba)_2.CHCl_3$ (5)	**L51**	48	**78**	93	62

Reagents and Conditions: bromide (1 eq.), boronic acid (1.8 eq.), Pd source, ligand (20 mol%), CsF (3.1 eq.), DME, 65 °C. [a] ligand (12 mol%), [b] reaction temperature 50 °C.

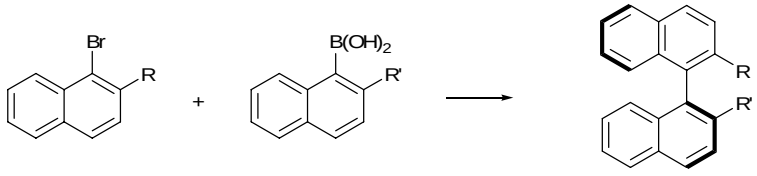
Increasing the steric hindrance of the ferrocenyl ligand resulted in reduced yield and enantioselectivity under otherwise identical conditions (entries 8-10). Preparation of mixed alkoxy and alkoxy/alkyl binaphthyls proceeded with excellent yield but moderate enantioselectivity (entries 11-12). The authors note that in all couplings protodeboronated material is still observed, despite the purification of the boronic acid prior to use.[77]

Despite not achieving uniformly high selectivity, the overall degree of protodeboronation is minimised, generating high chemical yields and allowing for less equivalents of boronic acid to be used compared to other methods. However, extended reaction times (three to four days) at moderate temperatures are required to achieve useful yields.

The most recent examples, again from Espinet *et al.*, demonstrated the first microwave promoted asymmetric Suzuki couplings. Racemic Suzuki couplings have recently been achieved under microwave conditions, and the potential to control more precisely the energy imparted to the reaction conditions suggests control of the sensitive asymmetric environment could be achieved more successfully. The potential for shortened reaction times could also limit the extent of protodeboronation of the starting materials, resulting in a marked increase in yield.[78]

In correlation with their previous study, the coupling of silica purified of naphthyl bromides with naphthyl boronic acids were investigated with chiral ferrocene (*R*)-(*S*)-PPFA **L51** (Table 1.13).

Table 1.13: Asymmetric preparation of binaphthyls under μ-wave conditions (Espinet *et al.*)



64 R = Me
67 R = OBn
65 R = OMe
79 R = H

41 R = Me
74 R = OBn
56 R = OMe

45 R = R' = Me
75 R = R' = OBn
76 R = R' = OMe
44 R = H, R' = Me

Entry	Bromide	Acid	Pd source.	Prod.	*T* (°C)	Yield (%)[a]	*ee* (%)[a]
1	**64**	**41**	dba	**45**	100	29 (85)	70 (85)
2	**64**	**41**	dba	**45**	120	36 (85)	59 (85)
3	**64**	**41**	oac	**45**	150	65 (85)	53 (85)
4	**67**	**74**	oac	**75**	120	95 (95)	43 (60)
5	**65**	**56**	dba	**76**	120	95 (95)	51 (50)
6	**79**	**41**	dba	**44**	120	95 (95)	51 (64)

Reagents and Conditions: bromide (1 eq.), boronic acid (1.8 eq.), Pd source (10 mol% Pd), (*R*)-(*S*)-PPFA **L51** (20 mol%), CsF (3 eq.), THF with $Pd_2(dba)_3$, DME with $Pd(OAc)_2$, μ-wave, 100 °C, 1 h. [a] numbers in parenthesis represent corresponding oil bath results

Overall, microwave conditions resulted in reduced enantioselectivity. Sterically demanding binaphthyl product **45** proved particularly sensitive to reaction conditions with increased yields but decreased enantioselectivity at elevated temperatures (Table 1.13, entries 1-3). Alkoxybinaphthyls **75** and **76**, and tri-*ortho*-substituted binaphthyl **44** were prepared with comparable yield and enantioselectivity. The major improvement under microwave conditions is the large reduction in reaction time from several days to just one hour. This reduces greatly the potential for protodeboronation though this may be offset by the high temperatures required

which offers an explanation for the low yields obtained for the preparation of binaphthyl **45**.[78]

1.2.3. Summary

Asymmetric Suzuki couplings represent a difficult transformation in organic synthesis due to the sensitivity of the reaction to steric hindrance. This effect is enhanced in the preparation of chiral biaryls, whereby the need for at least three *ortho*-substituents to prevent racemisation of the product under the reaction conditions makes the coupling itself more challenging. This steric hindrance allows for more facile protodeboronation, a major obstacle in Suzuki couplings in general. The studies discussed in this report represent all published works in the field to date. The most successful and versatile catalysts were developed with hemilabile MAP type ligands by Buchwald *et al*. In particular Cy-MAP **L17** achieved excellent yield (98%) and enantioselectivity (87%) in the preparation of biaryl **48**, and proved to be the most efficient in the preparation of biphenyl **63**. Ferrocenyl and diphosphine based ligands also exhibit selectivity for the preparation of biaryls though their applications display a degree of substrate specificity.

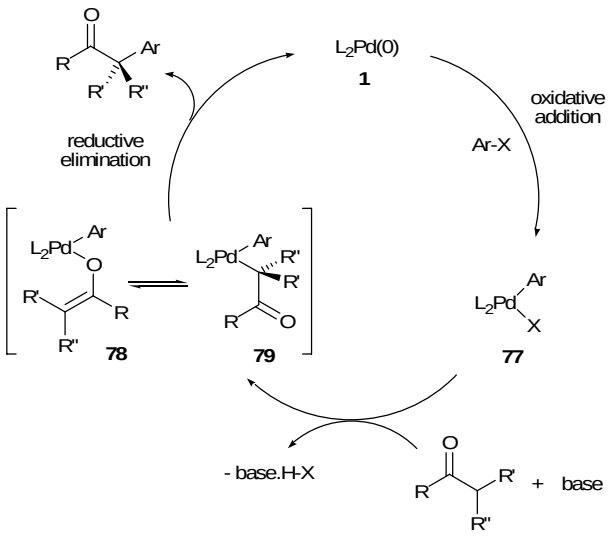
Under mixed aqueous/organic solvent systems barium hydroxide is frequently employed as the base to activate the boronic moiety. In the only example of asymmetric coupling under anhydrous conditions, cesium fluoride was the only efficient base.

1.3. Asymmetric Enolate Arylation

The synthesis of α-aryl carbonyl compounds has received a great deal of attention over recent years. Advances in catalysis have improved previous syntheses that employed stoichiometric reagents, most notably nickel complexes, to achieve the coupling of an enolate nucleophile with an aromatic halide.

Initial couplings required the pre-formation of a zinc or tin enolate[79] but simultaneous work by Buchwald *et al.* and Hartwig *et al.* has developed the palladium catalysed inter- and intramolecular α-arylation of a variety of carbonyl compounds. Ketones,[80-82] amides,[83-86] imides,[87] malonates,[81] esters[84, 88-91] and aldehydes,[92, 93] as well as nitriles,[94-96] have all proven to be suitable nucleophilic partners under basic conditions. Pre-formed silyl enol ethers also exhibit application to the cross coupling.[87, 97, 98]

A proposed catalytic cycle is outlined in scheme 1.20. Oxidative addition of an aryl halide or triflate to palladium(0) complex **1** followed by substitution of the halide in the coordination sphere of palladium(II) complex **77** by an enolate could result in the formation of palladium enolate species **78** or **79**. Whether the palladium centre is oxygen or carbon bound is uncertain. Finally, reductive elimination yields the desired α-arylated product and regenerates the palladium(0) catalyst **1**.[94]

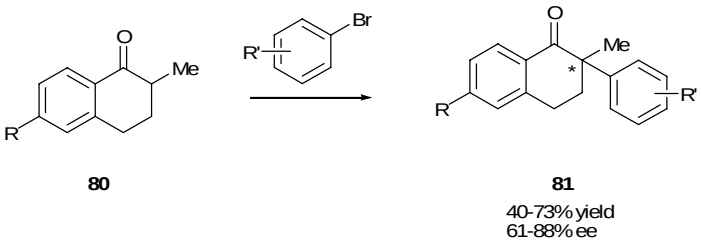


Scheme 1.20

Although not strictly a cross-coupling process, the enolate arylation protocol is of great interest due the wide range of carbonyl substrates and the potential to prepare tertiary and stereodefined quaternary benzylic carbon centres.

1.3.1. Asymmetric Arylation of Ketones

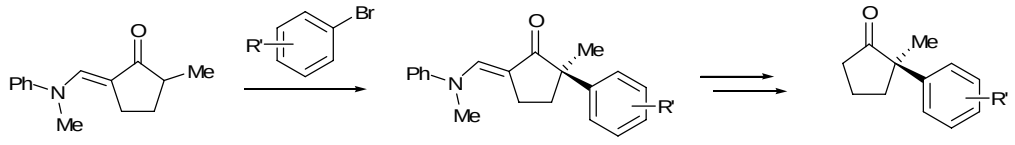
Extension of the arylation protocol with chiral ligands has achieved the preparation of stereodefined α-aryl carbonyls through both inter- and intramolecular approaches. The first asymmetric couplings were achieved by Buchwald *et al.* with the arylation of 2-methyl-α-tetralone **80** to give 2,2-disubstituted tetralones of the type **81** containing a stereodefined quaternary carbon centre (Scheme 1.21).[99] Initial studies were focused on producing tertiary carbon centres; however these couplings were unsuccessful presumably due to the basicity of the reaction media facilitating a number of side reactions, including racemisation.



Scheme 1.21: *Reagents and Conditions*: tetralone **80** (1 eq.), bromoarene (2 eq.), $Pd_2(dba)_3$ or $Pd(OAc)_2$ (10-20 mol% Pd), (*S*)-BINAP **(*S*)-L1** (1.2 L/Pd), NaO^tBu (2 eq.), toluene, 100 °C.

These couplings proved difficult to achieve with good yield and enantioselectivity. High temperatures and catalyst loading plus two equivalents of both the base and aryl bromide were necessary to drive the reaction to completion, and a number of side reactions were observed including biaryl formation and aldol condensation products.

The same group has subsequently reported much improved conditions for the α-arylation of ketones. The formation of stereodefined quaternary carbon centres was studied on tri α-substituted cyclopentanone **82**; the anilinomethylene moiety could be cleaved after arylation to give stereodefined 2,2-disubstituted cyclopentanones (Scheme 1.22).[100]

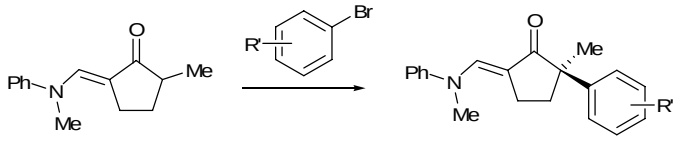


82

Scheme 1.22: *Reagents and Conditions*: cyclopentanone **82** (1 eq.), bromoarene (2 eq.), $Pd_2(dba)_3$ (1 mol%), ligand (2.5 mol%), NaO^tBu (2 eq.), toluene, r.t.

A screen of commercially available chiral ligands including (*S*)-BINAP **(*S*)-L1**, (*S*)-MOP **(*S*)-L8**, (*R*)-QUINAP **(*R*)-L21** and (*R*)-(*S*)-PPFA **L51** produced mixed results. Only (*S*)-BINAP **(*S*)-L1** gave products with good enantioselectivity though high temperatures and catalyst loading were still required (Table 1.14, entries 1-3). Hemilabile MAP type ligands were also evaluated, and a significant rate enhancement was observed with this class of ligand that allowed the reaction to be performed at room temperature over eighteen hours with a greatly reduced catalyst loadings. Electron-rich (*S*)-Cy-MAP **(*S*)-L17** gave the best yields and enantioselectivities though (*S*)-^{i}Pr-MAP **(*S*)-L15** also performed well (entries 4-6). It was clear highly electron-rich phosphines performed best in the reaction and a series of MOP derivatives were evaluated due to their similar hemilabile properties to the MAP family of ligands. Evaluation of alkoxy and phosphine substituents led to novel MOP derivative **(*S*)-L11** providing optimal enantioselectivities (entries 6-10).[100]

Table 1.14: Ligand screen for the asymmetric arylation of cyclopentanone **82**



82

Entry	R′	Ligand	Yield (%)	*ee* (%)
1	4-^{t}Bu	**(*S*)-L1**	65	88
2	4-^{t}Bu	**(*S*)-L1**	70	89
3	3-MeO	**(*S*)-L1**	87	85
4[a]	4-^{t}Bu	**(*S*)-L17**	93	68
5[b]	4-^{t}Bu	**(*S*)-L17**	99	67
6	4-^{t}Bu	**(*S*)-L15**	80	70
7	4-Me	**(*S*)-L11**	84	93
8	3-MeO	**(*S*)-L11**	80	89
9	4-MeO	**(*S*)-L11**	80	94
10	4-^{t}Bu	**(*S*)-L11**	84	93

Reagents and Conditions: cyclopentanone **82** (1 eq.), aryl bromide (2 eq.), $Pd_2(dba)_3$ (1 mol%), ligand (2.5 mol%), NaO^tBu (2 eq.), toluene, r.t. [a] Pd_2dba_3 (2.5 mol%), **(*S*)-L17** (6.25 mol%). [b] $Pd(OAc)_2$ (2 mol%), **(*S*)-L17** (2.5 mol%) as catalyst.

MOP derivative **(*S*)-L11** also tolerated greater steric hindrance, increasing alkyl chain length of the α-substituent resulted in no significant loss of enantioselectivity (Figure 1.7).

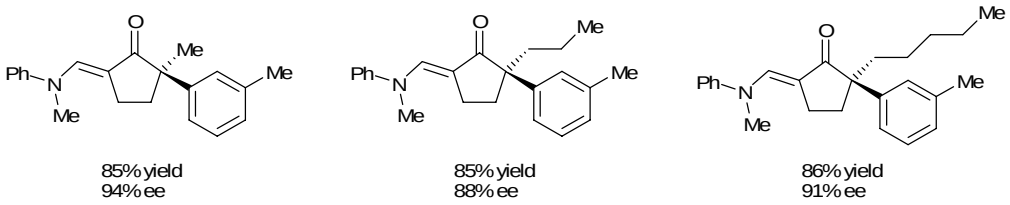
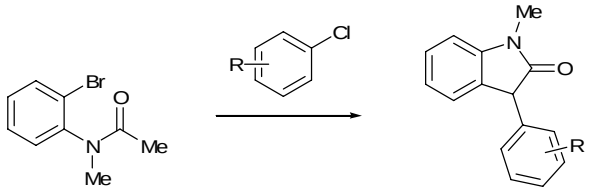


Figure 1.7

To date this remains the only asymmetric intermolecular α-arylation of α-carbonyl compound by palladium catalysis providing products with high enantioselectivity.

1.3.2. Asymmetric Arylation of Amides

Successful asymmetric intramolecular arylations have been achieved by Hartwig *et al.* with a broad range of aryl amides to yield substituted oxindoles. Their initial investigations into racemic cyclisations had prepared C-3 mono and disubstituted oxindoles in good to excellent yields employing bulky monophosphine ligands. A one-pot double arylation *via* sequential intra- then intermolecular coupling was also developed (Scheme 1.23).[101]

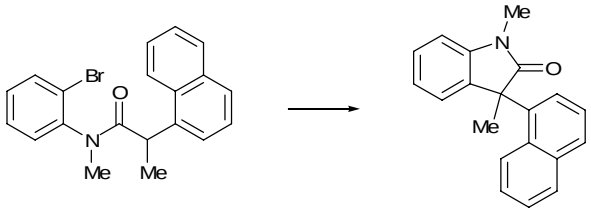


Scheme 1.23: *Reagents and Conditions*: bromide **83** (1 eq.), chloroarene (2 eq.), $Pd(OAc)_2$ (10 mol%), PCy_3 **L33** (10 mol%), NaO^{t}Bu (3 eq.), dioxane, 70 °C, 12 h.

Investigations into asymmetric transformations were conducted on bromide **84** to prepare the C-3 disubstituted oxindole **85** (Table 1.15), and began with a screen of commercially available mono and bisphosphine ligands. Although a number of such ligands provided the desired oxindole **85** in good yield, high enantioselectivities were not achieved. The highest enantioselectivity was observed with electron-rich

bisphosphine ferrocenes **L58** and **L59**, whilst (*R*)-BINAP **(*R*)-L1** gave a lower *ee* than that achieved in ketone arylations (Table 1.15, entries 1-3). Neomenthyl monophosphine **L37** proved to be an active catalyst at slightly lower temperatures but again selectivity was only moderate (entry 4). Monophosphine **L38** gave the best yield but gave poor enantioselectivity (entry 5).

Table 1.15: Ligand screen for intramolecular asymmetric arylation



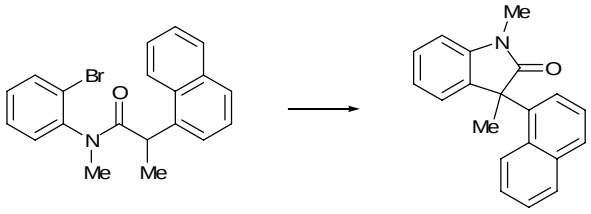
84 **85**

Entry	Ligand	*T* (°C)	*t* (h)	Yield **85** (%)	*ee* **85** (%)
1	**(*R*)-L1**	100	3	49	46
2	**L58**	100	24	70	61
3	**L59**	100	24	56	61
4	**L37**	70	9	75	53
5	**L38**	50	24	82	20

Reagents and Conditions: bromide **84** (1 eq.), $Pd(OAc)_2$ (5 mol%), ligand (5 mol%), NaO^tBu (1.5 eq.), dioxane, Δ.

N-heterocyclic carbenes had exhibited activity in the racemic cyclisation investigations therefore chiral derivatives were prepared to assess their selectivity in comparison to the inefficient phosphine derivatives (Table 1.16).

Table 1.16: NHC ligands in intramolecular amide arylations



84 **85**

% $Pd(dba)_2$/L	T (°C)	*t* (h)	Yield **85** (%)	*ee* **85** (%)
10%/**L48**	25	24	88	67
10%/**L49**	10	40	75	76

Reagents and Conditions: bromide **84** (1 eq.), $Pd(dba)_2$, ligand (L/Pd 1:1), NaO^tBu (1.5 eq.), DME, Δ.

Trans-diaminocyclohexane derived NHC **L47** gave selectivities that were only comparable to those obtained with phosphine ligands. To improve the catalyst it was proposed that a more sterically demanding ligand could be beneficial therefore chiral

NHC's **L48** and **L49** were prepared from (-)-*iso*pinocampheylamine and (+)-bornylamine respectively. Under optimised conditions NHC **L48** achieved the cyclisation of bromide **84** at room temperature in DME to give oxindole **85** in 88% yield and 67% *ee*. NHC **L49** proved to be a more highly active catalyst and allowed the reaction to be conducted below room temperature and achieve higher enantioselectivities though extended reaction times were required.[94, 101]

1.4. Summary

The intermolecular asymmetric arylation of ketones by Buchwald *et al.* and the intramolecular cyclisation of amides developed by Hartwig *et al.* represent the only palladium catalysed syntheses of optically active α-aryl carbonyls, in contrast to the range of established methods for the racemic arylation of a broad range of carbonyl derivatives. The intramolecular protocol struggled to achieve high enantioselectivities, the highest enantioselectivity reported being 76% with NHC **L49**. The intermolecular arylation of ketones was more successful, high to excellent enantioselectivities were reported for a range of substrates to prepare 2,2-disubstituted cyclopentanones, though incorporation and removal of a blocking group was required to control arylation regioselectivity.

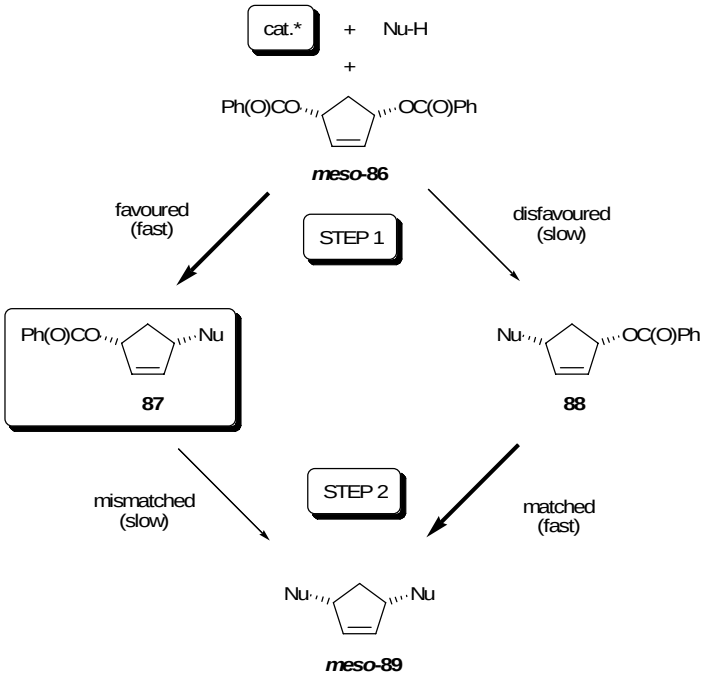
2. Enantioselective Desymmetrisation

Enantioselective desymmetrisation[102] is an attractive technique in asymmetric organic synthesis with the potential for rapid construction of structural complexity from comparatively simple substrates. When a functionalised *meso* or achiral molecule is treated with a chiral reagent, the success of the desymmetrisation is dependent on the chiral reagents ability to discriminate between enantiotopic functional groups, to furnish products with a degree of enantioselectivity.

A range of stoichiometric and catalytic desymmetrisation techniques have been developed[103-110] but as part of our interest in the field of asymmetric palladium catalysis and carbon-carbon bond formation, only achievements in this area will be considered as part of this review.

2.1. The Concept of Enantioselective Desymmetrisation in Synthesis

The concept of enantioselective desymmetrisation is better explained by the hypothetical example in scheme 2.1 where bisbenzoate ***meso*-86** undergoes an asymmetric allylic substitution to prepare an optically active product **87**.[111]

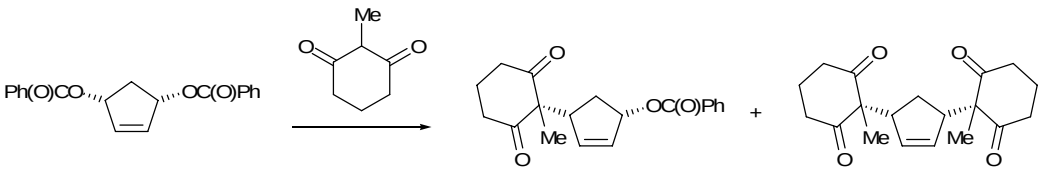


Scheme 2.1

Under standard conditions it is feasible for either enantiotopic group of bisbenzoate ***meso*-86** to be ionised and generate an intermediate π-allyl complex. The use of a chiral catalyst achieves differentiation between the groups and allows for the formation of diastereomeric complexes of different energies. The energetically favoured pathway results in preferential formation of enantiomer **87**. The reaction of the favoured pathway is not exclusive and the unfavoured enantiomer **88** may still be formed. However, the remaining functional group of enantiomer **88** remains matched with the chiral catalyst and a second substitution now becomes a favoured pathway, resulting in the formation of unwanted *meso* product ***meso*-89** and achieving an *in-situ* kinetic resolution (enantio-enrichment of the major enantiomer **87)**.

This *in-situ* kinetic resolution is demonstrated in the allylic substitution of benzoate ***meso*-86** with 2-methyl cyclohexanedione (Table 2.1). When one equivalent of base is employed, the enantioselectivity of 91% directly constitutes the selectivity of the reaction with near quantitative conversion (entry 1). When 1.2 equivalents are employed the enantioselectivity of the product is raised to 98% by allowing a small amount of conversion to the unwanted dialkylated product ***meso*-91**. The drawback of this enhanced enantiopurity is a concomitant reduction in yield to 84% of the desired enantiomer **90** (entry 2).[112]

Table 2.1: Effect of base equivalents on the selectivity of benzoate substitution



***meso*-86** **90** ***meso*-91**

Entry	Base (eq.)	Yield **90** (%)	*ee* **90** (%)
1	DBU (1.0)	95	91
2	DBU (1.2)	84	98

Reagents and Conditions: benzoate ***meso*-86** (1 eq.), dione (1.2 eq.), $Pd_2(dba)_3.CHCl_3$ (2.5 mol%), ligand **L41** (15 mol%), DBU, THF, 0 °C.

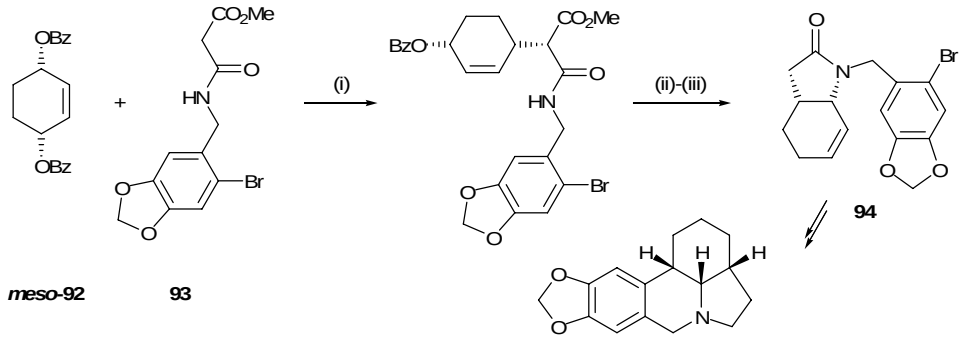
2.2. Palladium Catalysed Enantioselective Desymmetrisation

2.2.1. Asymmetric Allylic Alkylation

Asymmetric allylic alkylations have received considerable interest, particularly since pioneering advances by Trost *et al.* in the area of rational ligand design and the preparation of their novel diamine derived ligands.[112] The ability to generate chirality from the electrophile, nucleophile or both coupling partners leads to incredible versatility and the area has been extensively reviewed.[112]

An excellent recent application of asymmetric allylic alkylation was demonstrated by Ojima and Chapsal in the total synthesis of (+)-γ-lycorane **95** from bisbenzoate ***meso*-92** (Table 2.2). Previous syntheses had prepared the natural product in 54% *ee* with BINAP(O) **L6**, but fine-tuning and application of a series of monodentate phosphoramidites **L65-L67** achieved extremely high differentiation of the enantiotopic benzoate groups in the key alkylation step to achieve the synthesis in extremely high enantiopurity.[113]

Table 2.2: Phosphoramidite optimisation in the asymmetric synthesis of (+)-γ-lycorane **95**



Entry	Ligand	Yield **94** (%)	*ee* **94** (%)
1	**L65**	93	86.2
2	**L66**	76	99.7
3	**L67**	83	99.4

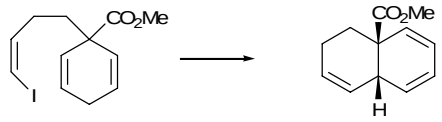
Reagents and Conditions: (i) bisbensoate ***meso*-92** (1 eq.), ester **93** (1.2 eq.), $[PdCl(allyl)]_2$ (2 mol%), ligand (8 mol%), LDA (1.2 eq.), -60 °C, 8 h; (ii) $[PdCl(allyl)]_2$ (2 mol%), dppb **L64** (10 mol%), LDA (1.1 eq.), MeCN/THF, -50 °C to r.t., 2.5 h; (iii) NaCl, DMSO/H_2O, 175 °C, 2.5 h.

Fine-tuning of the nitrogen substituents of phosphoramidites **L65-L67** achieved excellent enantioselectivity in the alkylation of bisbenzoate ***meso*-92** with ester **93**.

Non-symmetrical amine moieties proved crucial in achieving high enantioselectivity, particularly when one substituent is a 2-methoxyphenyl, though yields were slightly reduced (Table 2.2, entries 1-3). It is likely that the oxygen of the methoxy moiety has an interaction with the palladium metal centre, thus fixing the orientation of the phenyl group and creating a more rigid asymmetric environment.[113]

2.2.2. Asymmetric Heck Desymmetrisation

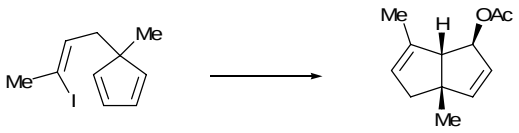
Pioneering work by Shibasaki *et al.* in 1989 demonstrated an intramolecular asymmetric Heck cyclisation of prochiral vinyl iodide **96** to prepare bicyclic triene **97** with moderate yield and enantioselectivity (Scheme 2.2).[114]



96 **97** 74%, 46% ee

Scheme 2.2: *Reagents and Conditions*: iodide **96** (1 eq.), $Pd(OAc)_2$ (5 mol%), (*R*)-BINAP **(*R*)-L1** (5.5 mol%), Ag_2CO_3 (2 eq.), NMP, 60 °C, 37 h.

This protocol was applied to the synthesis of a key intermediate in the synthesis of capnellenols, a family of sesquiterpene alcohols, in a process termed a one-pot cascade carbon-carbon bond formation with acetate anion capture.[115]

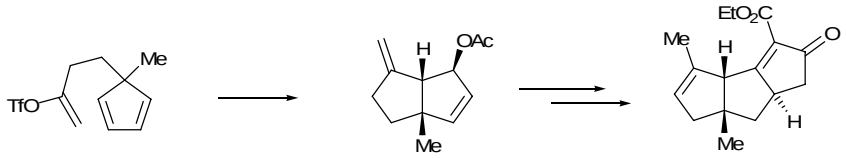


98 **99** 61%, 20% ee

Scheme 2.3: *Reagents and Conditions*: iodide **98** (1 eq.), $[PdCl(allyl)]_2$ (10 mol%), (*R*,*R*)-Chiraphos **L39** (10 mol%), Bu_4NOAc (2.9 eq.), toluene, 60 °C, 144 h.

The cyclisation of vinyl iodide **98** was attempted in the presence of a silver salt, thought to be crucial in achieving high enantioselectivity by promoting a cationic sixteen electron palladium(II) complex. However, decomposition of the starting material predominated, presumably due to the presence of the cyclopentadiene moiety. Cyclisation with no silver salt gave biscyclopentene **99** in only 20% *ee* (Scheme 2.3).

Preparation and cyclisation of vinyl triflate **100**, in the absence of a silver salt, with trapping of the subsequent π–allyl species with an acetate anion in a regio- and stereocontrolled manner gave the desired dipentacycle **101** in 89% yield with 80% *ee*. The reaction conditions were significantly improved with reduced catalyst loadings, temperature and reaction time. Bispentacycle **101** was easily elaborated to the key tricyclic intermediate **102** (Scheme 2.4).[115]

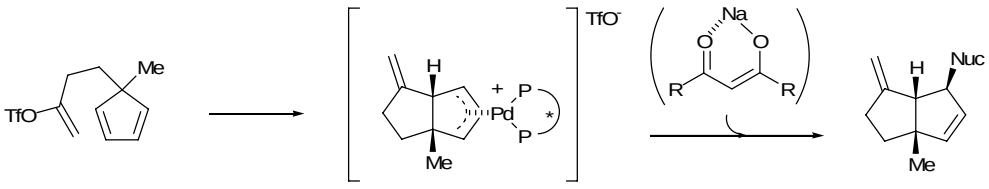


100 **101** 89%, 80% ee **102**

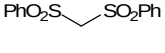
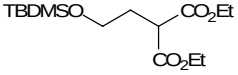
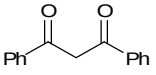
Scheme 2.4: *Reagents and Conditions*: triflate **100** (1 eq.), $Pd(OAc)_2$ (1.7 mol%), (*S*)-BINAP **(*S*)-L1** (10 mol%), Bu_4NOAc (1.7 eq.), DMSO, 20 °C, 2.5 h.

The scope of the reaction was extended to examine a variety of carbanions as the nucleophile source. It was found that the π–allyl species **103** generated from cyclisation of triflate **100** (Table 2.3) could be successfully trapped to give the expected bicyclic product. The addition of sodium bromide to the reaction was found to give optimal enantioselectivity by complexation with the nucleophile, thus preventing exchange of the nucleophile with the triflate counter-ion of the palladium(II) species and encouraging a 16 electron palladium (II) intermediate. [116]

Table 2.3: Variation of pro-nucleophile for π–allyl trapping

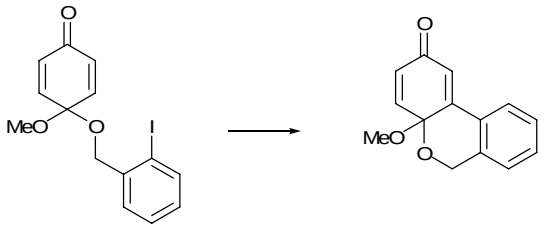


100 **103**

Pro-nucleophile	Yield (%)	*ee* (%)
	92	83
	83	94
	77	87
	90	80

Reagents and Conditions: triflate **100** (1 eq.), pro-nucleophile (2 eq.), NaH (2 eq.), $[PdCl(allyl)]_2$ (10 mol%), (*S*)-BINAP **(*S*)-L1** (6.3 mol%), NaBr (2 eq.), DMSO, 20 °C, 2.5 h.

Feringa *et al.* have reported the highly selective intramolecular Heck cyclisation of iodide **104** to give tricyclic enone **105**. Employing phosphoramidite **L68**, the degree of selectivity was found to be sensitive to the nature of the base used (Scheme 2.5).[117]

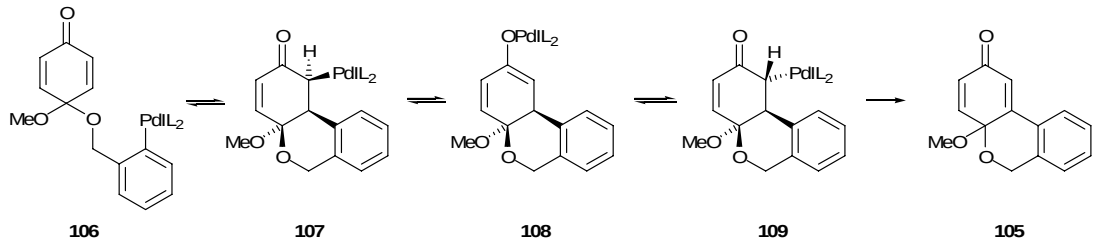


104 **105** 100% conv., 96% ee

Scheme 2.5: *Reagents and Conditions*: iodide **104** (1 eq.), $Pd(OAc)_2$ (6 mol%), phosphoramidite **L68** (12 mol%), Cy_2NMe (4 eq.), $CHCl_3$, reflux, 2 days.

Weak inorganic bases such as potassium carbonate or cesium carbonate gave good conversion and selectivity whilst triethylamine gave excellent enantioselectivity but poor conversion. A screen of tertiary amines concluded that dicyclohexylmethylamine gave optimal enantioselectivity with complete conversion (Scheme 2.5).

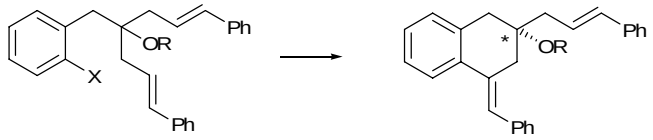
Initial analysis of the 1,2-insertion from oxidative addition product **106** to give intermediate **107** suggests there is no *syn* β-hydride to achieve the elimination step (cf. Figure 1.3), The catalytic cycle can be rationalised by an η_1-η_3-η_1 isomerisation through an oxo π-allylpalladium intermediate **108** to reach the required *syn* relationship **109**, effecting a net *trans* elimination to product **105** (Scheme 2.6).[117]



106 **107** **108** **109** **105**

Scheme 2.6

The most recent publications by Oestreich *et al.* concern investigations into the intramolecular Heck cyclisation of bisvinylic precursor of the type **110** to prepare benzannulated carbocycles **111**, with a new quaternary stereocentre being formed remote from the new carbon-carbon bond (Scheme 2.7).[118]



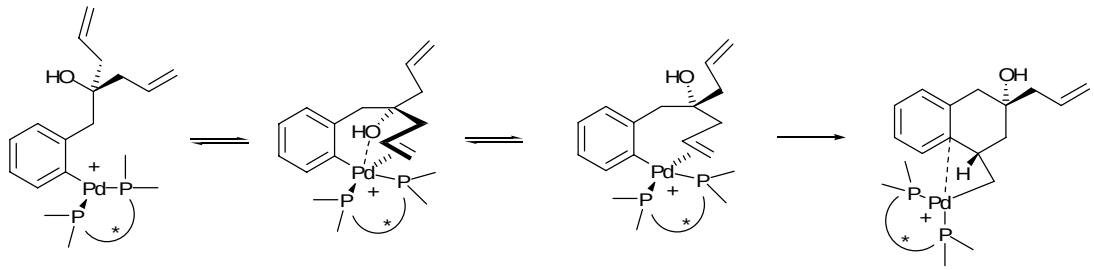
110 X = Br, OTf **111**

Scheme 2.7: *Reagents and Conditions*: halide or triflate **110** (1 eq.), $Pd(OAc)_2$ (5 mol%), (*R*)-BINAP **(*R*)-L1** (7.5 mol%), base, toluene, Δ.

The levels of enantioselectivity proved to be heavily dependent on a number of factors, particularly the Lewis basicity of the oxygen moiety and the nature of the palladium counterion where triflates performed more successfully than bromides, presumably by enforcing the cationic pathway of the reaction mechanism. The increase in enantioselectivity when silver salt additives were used with the bromide substrate confirmed this favoured pathway.[119]

The importance of the Lewis basicity of the oxygen moiety was observed when the free hydroxy moiety was derivitised to the methyl ether, which gave comparable selectivity, or the triethylsilyl ether which gave essentially racemic product (2% *ee*). Studies of the addition of an external Lewis acid showed a direct correlation of enantioselectivity when the free alcohol was treated with lithium tetrafluoroborate under the cyclisation conditions, whereby three equivalents of the acid was sufficient to reduce the enantioselectivity from 84% to ~20%.

These observations reinforce the authors' proposal, with corroborating computational analysis, that the oxygen moiety acts as a mediator in the insertion of the alkene to the aryl-palladium bond, coordinating to the palladium centre to allow rapid ligand exchange and selection of the alkene with the most facile 1,2-insertion (Scheme 2.8). When the oxygen has low Lewis basicity or is not present in the substrate, no coordination occurs and the diastereotopic alkenes are of essentially the same energy and no selection is observed.[119]



Scheme 2.8 (*trans* phenyl moieties of alkenes omitted for clarity)

Although directing effects of heteroatoms have been confirmed in other Heck reactions, this study represents the first time such an effect has been observed in an asymmetric Heck coupling, let alone with such a marked effect. It also highlights the effect of such donor atoms in any cross-coupling reaction, and the effects they have should not be underestimated.

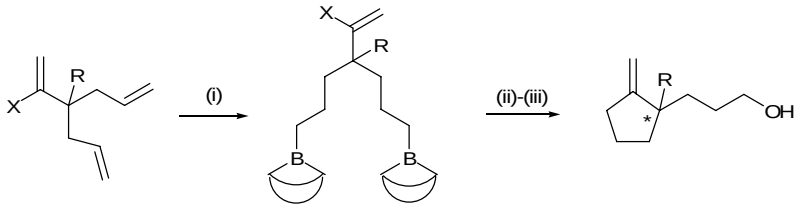
2.2.3. Asymmetric Suzuki Desymmetrisation

Further to their work with asymmetric Heck desymmetrisations, Shibasaki *et al.* have investigated the application of an intramolecular Suzuki-Miyaura coupling to achieve desymmetrisation of prochiral molecules and generate stereodefined tertiary and quaternary carbon centres.

Bromide **112** and triflates **113-114**, were easily prepared by hydroboration of the corresponding terminal alkenes with 9-BBN. After screening a range of palladium sources and bases it was determined that $Pd_2(dba)_3.CHCl_3$ and potassium carbonate were the most effective. With this catalyst system in hand a study of chiral ligands was undertaken to achieve asymmetric induction. Oxidative work-up would furnish the cyclopentane derivatives **115** or **116** (Table 2.4).[120]

Cyclisations to prepare tertiary carbon centres gave generally disappointing results for both substrates. Bromide **112** gave particularly disappointing results, achieving a maximum *ee* of 10% with low to moderate yields (Table 2.4, entries 1-3). Though cyclisation was unsuccessful with (*R*)-BINAP **(*R*)-L1**, triflate **113** gave improved chemical yields with hemilabile MOP derivatives **(*R*)-L7** and **(*R*)-L8** but again very low enantioselectivity was observed (entries 4-6). Bidentate ferrocenes ligands **L50** and **L54** gave the best selectivity observed in the study, (*S*)-(*R*)-BPPFOAc **L54** providing cyclopentane **115** in 28% *ee* in THF (entries 7-8). Investigation of solvent effects with optimal ferrocene ligand **L54** did not improve selectivity, the reaction performing best in THF (entries 9-10).[120]

Table 2.4: Ligand screen for asymmetric intramolecular Suzuki desymmetrisation



112 R = H, X = Br
113 R = H, X = OTf
114 R = $CH_2OTBDMS$, X = OTf

115 R = H
116 R = $CH_2OTBDMS$, X = OTf

Entry	Substrate	Ligand	Solvent	Product	Yield (%)	*ee* (%)
1	**112**	**L54**	THF	**115**	41	10 (*S*)
2	**112**	**(*R*)-L1**	THF	**115**	trace	-
3	**112**	**(*R*)-L22**	THF	**115**	37	0
4	**113**	**(*R*)-L1**	THF	**115**	0	-
5	**113**	**(*R*)-L8**	THF	**115**	67	14 (*S*)
6	**113**	**(*R*)-L7**	THF	**115**	59	6 (*S*)
7	**113**	**L50**	THF	**115**	48	20 (*S*)
8	**113**	**L54**	THF	**115**	58	28 (*R*)
9	**113**	**L54**	DCM	**115**	33	8 (*R*)
10	**113**	**L54**	DMF	**115**	17	12 (*R*)
11	**114**	**(*R*)-L1**	THF	**116**	trace	-
12	**114**	**L54**	THF	**116**	65	2 (*S*)
13	**114**	**L50**	THF	**116**	42	31 (*R*)
14	**114**	**(*R*)-L9**	THF	**116**	90	9 (*R*)

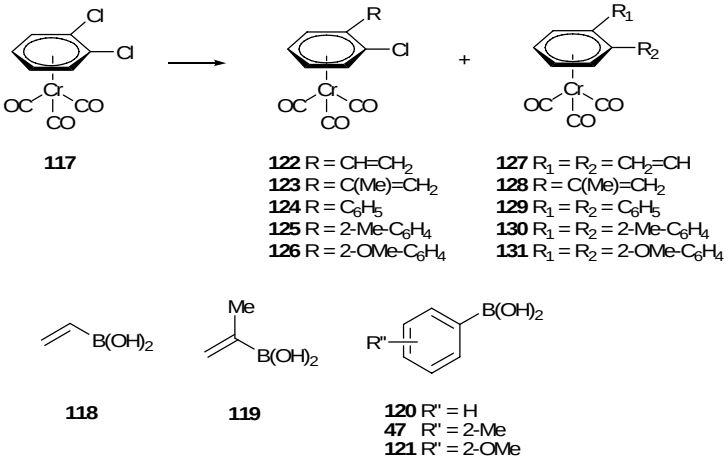
Reagents and Conditions: (i) 9-BBN, THF, 40 °C, 1 h; (ii) alkene (1 eq.), $Pd_2dba_3.CHCl_3$ (10 mol%), ligand (20 mol%), K_2CO_3 (5 eq.), THF, 40 °C; (iii) 3 *N* HCl, 35% H_2O_2.

Despite the disappointing results preparing tertiary centres, the cyclisation of triflate **114** to alcohol **116** was extended to generate quaternary carbon centres. Again (*R*)-BINAP **(*R*)-L1** was unsuccessful in the cyclisation (Table 2.4, entry 11). (*S*)-(*R*)-BPPFOAc **L54** achieved good yields but enantioselectivity was negligible, while hemilabile ferrocene (*S*)-(*R*)-PPFA **L50** gave reduced yield but achieved the best enantioselectivity of 31% (entries 12-13). (*R*)-^{i}Pr-MOP **(*R*)-L9** gave excellent conversion to the cyclic product but, as in the earlier studies, exhibited low selectivity (entry 14).[120]

Although the enantioselectivities achieved were not as high as would be desired, this was the first example of an asymmetric intramolecular Suzuki-Miyaura desymmetrisation with the generation of stereodefined tertiary and quaternary carbon centres. The viability of such a reaction has been observed and the scope remains for significant progress in the area.

Hayashi *et al.* have investigated the intermolecular desymmetrisation of a tricarbonyl chromium complex, breaking the symmetry plane to generate chirality by Suzuki coupling. Employing tricarbonyl(*o*-dichlorobenzene)chromium **117** as the substrate, enantioselection of the enantiotopic halides was investigated by cross coupling with vinyl boronic acids **118**-**119** and aryl boronic acids **47**, **120**-**121** with a range of ligands (Table 2.5). Although Suzuki coupling of aryl chlorides is traditionally difficult, the electron-withdrawing nature of the coordinated chromium metal centre makes oxidative addition to the carbon-chlorine bond a more facile process. A large excess of the boronic species was employed, presumably due to competing protodeboronation processes, however this led to the competing preparation of dicoupled products though an *in-situ* kinetic resolution may occur and improve enantioselectivity.[121]

Table 2.5: Ligand screen for the asymmetric Suzuki desymmetrisation of bischloride **117**



Entry	Nuc.	Ligand	*T* (°C)	*t* (h)	Yield (%) (**mono**:**di**)	*ee* (%)
1	**118**	**L50**	23	48	59 (**122:127** 73:27)	38
2	**119**	**L50**	27	48	64 (**123:128** 95:5)	44
3	**119**	**L50**	27	10	67 (**123:128** 91:9)	2
4	**119**	(***R***)-**L1**	35	48	93 (**123:128** 47:53)	25
5	**120**	**L50**	28	18	18 (**124:129** 89:11)	49
6	**120**	**L50**	50	18	55 (**124:129** 73:27)	69
7	**47**	**L50**	50	40	64 (**125:130** 80:20)	55
8	**47**	(***R***)-**L8**	25	18	69 (**125:130** 84:16)	21
9	**121**	**L50**	70	20	13 (**126:131** 33:67)	40

Reagents and Conditions: bischloride **117** (1 eq.), boronate (3 eq.), $[PdCl(allyl)]_2$ (10 mol%), ligand (12 mol%), TlOH (0.4 $M_{(aq)}$, 3 eq.).

Vinyl boronic acid **118** gave the optically active monocoupled product in 38% *ee* and 43% yield with hemilabile ferrocene **L50** at room temperature. The α-methylvinylboronic acid **119** gave a much improved ratio of the monocoupled to dicoupled products with a slight enhancement in enantioselectivity to 44% (Table

2.5, entries 1-2). The authors account for this observation by citing the stereoelectronic effects of the electron-donating methyl group. Interestingly, shortened reaction times gave very poor enantioselectivity (entry 3), whilst (*R*)-BINAP **(*R*)-L1** proved to be a highly active catalyst but again selectivity was low (entry 4).[121]

Coupling of aryl boronic acids gave uniformly higher selectivities. Under identical conditions to the coupling of vinylboronic acid **118**, phenyl boronic acid **120** gave an increase to 49% *ee* though chemical yield was greatly reduced. This was prevented by raising the reaction temperature to 50 °C to achieve comparable yield and, surprisingly, an increase to 69% *ee* (entries 5-6). *Ortho*-substitution of the aryl moiety required more forceful reaction condition with an increase in temperature or reaction time necessary to achieve coupling. Application of hemilabile MeO-MOP **(*R*)-L8** failed to achieve an improvement in enantioselectivity though yields were satisfactory (entries 7-9).[121]

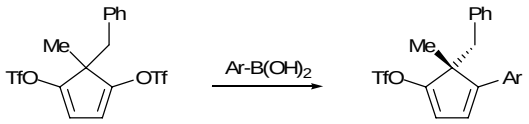
During their study Hayashi *et a*l also investigated the corresponding coupling of organotin, magnesium and zinc reagents. They found that the stannane and Grignard reagents gave racemic products, whilst zinc based nucleophiles gave enantioselectivities similar to organoboron substrates. They suggest that any enantioselectivity observed is dependent on the nature of the metal which has a direct role in determining enantioselection in the oxidative addition to one of the enantiotopic carbon-chlorine bonds. Subsequently they proposed the oxidative addition occurred enantioselectivity from a palladium/ligand/organo-metal complex, not *via* a conventional palladium/ligand complex.

3. A Desymmetrisation Protocol for the Total Synthesis of Hodgkinsine

The highlighted works demonstrate the powerful nature of asymmetric palladium catalysis and the potential for the construction of structural complexity from comparatively simple substrates. The area of palladium catalysed enantioselective desymmetrisation remains an evolving field and, following the recent development of a successful enantioselective Suzuki desymmetrisation protocol within our group, we sought to develop and apply this technique to more challenging substrates.

Research in the Willis group has demonstrated the palladium catalysed desymmetrisation of achiral bisvinyltriflate **132** by an enantioselective intermolecular Suzuki coupling. A chiral catalyst prepared from palladium acetate and (*S*)-MeO-MOP **(*S*)-L8** exhibits selectivity by differentiation of the diastereotopic faces, based on steric interactions, followed by preferential oxidative addition to one of the enantiotopic triflate groups as determined by the chiral ligand, generating a remote stereodefined sp^3 quaternary carbon centre in high enantioselectivity. A range of *ortho*, *meta* and *para* substituted boronic acids were successful in the coupling, achieving high enantioselectivity (Table 3.1).[122]

Table 3.1: Palladium catalysed enantioselective desymmetrisation of bisvinyltriflate **132**



132

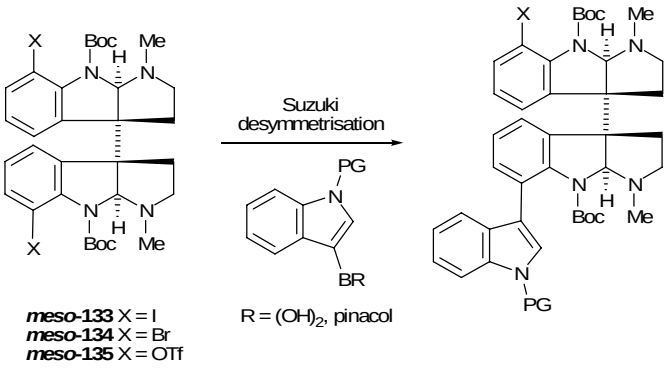
Entry	Ar	Yield (%)	*ee* (%)
1	4-$C_6H_4C(O)Me$	46	77
2	3-$C_6H_4C(O)Me$	51	86
3	4-C_6H_4CHO	47	73
4	3-C_6H_4CHO	57	80
5	2-C_6H_4CHO	41	82
6	3-C_6H_4OH	43	74
7	3-furyl	53	72
8	3-*N*-Bs-indolyl	66	85

Reagents and Conditions: bisvinyltriflate **132** (1 eq.), boronate (2 eq.), $Pd(OAc)_2$ (10 mol%), (*S*)-MeO-MOP **(*S*)-L8** (11 mol%), CsF (2 eq.), dioxane r.t.

We sought to extend our interest in the area of palladium catalysed enantioselective desymmetrisation by developing the published Suzuki protocol to desymmetrise

more complex achiral substrates. In particular, we envisaged an opportunity to achieve an improved synthesis of the trimeric pyrrolidinoindoline hodgkinsine **20**.

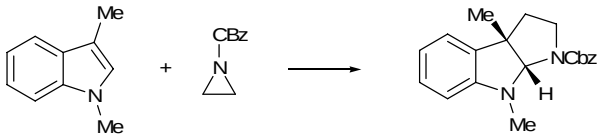
Although a considerably more complex substrate than the achiral bisvinyltriflate **132** previously investigated, we proposed that our Suzuki coupling would be applicable to the intermolecular desymmetrisation of a C-7 functionalised *meso*-chimonanthine derivative with an indole boronic acid/ester (Scheme 3.1). Suitable derivatives of *meso*-chimonanthine ***meso*-19** would include C-7 bisiodide ***meso*-133**, bisbromide ***meso*-134** and bistriflate ***meso*-135**. A synthetic route to C-7 bisiodides ***meso*-133** has already been demonstrated by Overman *et al.* in their syntheses of quadrigemine C **21**; directed *ortho*-lithiation from the carbamate generates the C-7 anion that is subsequently quenched by diiodoethane (cf. Scheme 1.8).[54] Synthesis of the bromide and triflate derivatives should be possible with the appropriate electrophilic source.



Scheme 3.1

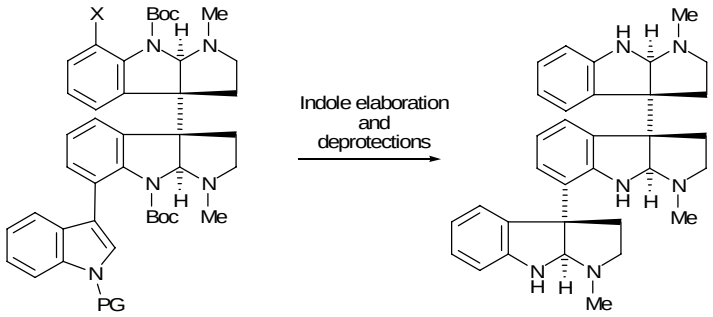
Enantioselectivity would be imparted by developing a suitable chiral catalyst to break the planar symmetry of the *meso* substrate through enantiotopic group discrimination. Optimisation of the reaction conditions through screening of palladium sources, ligands and solvent effects, high enantioselectivities should be achieved.

The indole unit could then be expanded to the third pyrrolidinoindoline motif by cyclisation with an aziridine, based on precedent by Nakagawa and Kawahara (Scheme 3.2).[123] Subsequent deprotections would complete the total synthesis of hodgkinsine **20** (Scheme 3.3).



90%

Scheme 3.2: *Reagents and Conditions*: aziridine (1 eq.), indole (2 eq.), $Sc(OTf)_3$ (2 eq.), TMSCl (1 eq.), DCM, -30 °C.



X = I, Br, OTf

hodgkinsine **20**

Scheme 3.3

This proposed synthesis would provide hodgkinsine **20** as single product in six steps from *meso*-chimonanthine ***meso*-19**, with no requirement for resolution step or inherent loss of 50% of the material. A successful enantioselective Suzuki desymmetrisation of this nature would represent a considerable advance in the field due to the complexity of the substrate, as well as overcoming the challenge of *ortho*-substitution in the coupling.

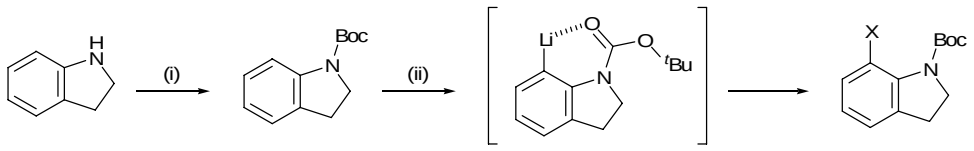
4. Suzuki Coupling of *meso*-Chimonanthine Substrates

4.1. Model Studies for the Suzuki Coupling of Aryl Halides and Triflates

4.1.1. C-7 Functionalisation

We chose to model the pyrrolidinoindoline motif by preparing *N*-protected C-7 functionalised indolines. In an identical procedure to Overman's iodination of *meso*-chimonanthine ***meso*-19**, 7-iodo-*N*-BOC-indoline **134** was prepared in 79% yield by *ortho*-lithiation of carbamate **133** and quenching of the organometallic species with diiodoethane.[54] Iodine monochloride and iodine (solution in diethyl ether)[124] were also investigated as electrophilic iodine sources but gave reduced yields and purification was significantly more problematic. Dibromoethane proved to be a suitable source of bromine, providing the C-7 bromo derivative **135**, again *via ortho*-lithiation, in 50% yield (Table 4.1).

Table 4.1: C-7 halogenation of *N*-BOC-indoline **133**



133 97%

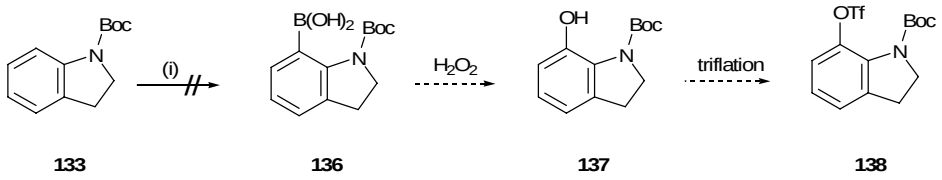
134 X = I
135 X = Br

Entry	Electrophile	Product	Yield (%)[a]
1	ICH_2CH_2I	**134**	79
2	ICl	**134**	65
3	I_2	**134**	57
4	$BrCH_2CH_2Br$	**135**	50

Reagents and Conditions: (i) indoline (1 eq.), $(Boc)_2O$, THF, r.t.; (ii) *sec*-BuLi (1.2 eq.), TMEDA (1.3 eq.), Et_2O, -78 °C, 1 h, then electrophile (3 eq.), -78 °C to r.t., 1 h. [a] Isolated yields.

To prepare a C-7 triflate derivative, we envisaged initially preparing C-7 hydroxy *N*-BOC-indoline **137** followed by a standard phenol triflation procedure to give triflate **138** (Scheme 4.1). Traditional procedures for preparation of phenols from organometallic species include quenching the anion with a trialkyl borate followed by oxidation of the organoborane with alkaline hydrogen peroxide.[125]

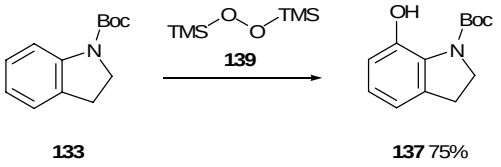
Disappointingly, attempts to quench the *ortho*-lithiation product of carbamate **133** with either trimethyl borate or boron trichloride, followed by acidic work-up, failed to furnish any of the desired intermediate boronic acid **136**, instead providing a complex mixture of starting material and numerous by-products in both instances. Variation of boron electrophile equivalents, including large excess to favour monoarylation of boron failed to alter the complex nature of the products obtained (Scheme 4.1).



133 **136** **137** **138**

Scheme 4.1: *Reagents and Conditions*: (i) carbamate **133** (1 eq.), *sec*-BuLi (1.2 eq.), TMEDA (1.3 eq.), Et_2O or THF, -78 °C, 1 h, then $B(OR)_3$ or BCl_3 (2-10 eq.), -78 °C to r.t., 2 h. Quench HCl (3 M).

Rather than develop a two-step borylation-oxidation procedure to prepare alcohol **137**, we focused on employing a direct source of electrophilic oxygen. Trimethylsilylperoxide **139** is prepared from trimethylsilyl urea and urea hydrogen peroxide in dichloromethane at reflux[126] and demonstrates efficiency in quenching a range of *ortho*, *meta*, and *para*-lithiated species to furnish phenols in good yield.[127] When employed with the *ortho*-lithiated derivative of carbamate **133**, the desired phenol was prepared in a synthetically useful 75% yield (Scheme 4.2).



133 **137** 75%

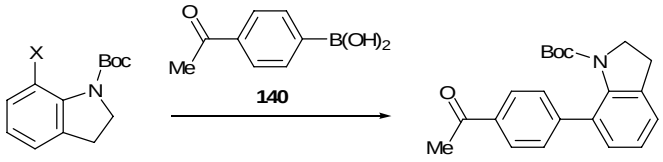
Scheme 4.2: *Reagents and Conditions*: carbamate **133** (1 eq.), *sec*-BuLi (1.2 eq.), TMEDA (1.3 eq.), Et_2O, -78 °C, 1 h, then $(TMSO)_2$ **139** (1.2 eq.), -78 °C to r.t., 2 h.

4.1.2. Model Suzuki Couplings

In a model study, 4-acetylboronic acid **140** was successfully coupled with 7-iodo-**134** and 7-bromo-N-BOC-indoline **135** to furnish biaryl **141** in low to moderate yields (Table 4.2). These results were consistent with results previously observed,[122] as expected the more reactive iodide gave a higher yield than the corresponding

bromide (39% and 27% respectively). The halide was recovered in greater than 50% in both instances, indicating catalyst inactivity or stability is a major problem, rather than substrate decomposition. Protodeboronation of the boronic acid could also be a factor though this is unlikely as there is no *ortho*-substitution of the boryl moiety to encourage such a process.

Table 4.2: Suzuki coupling of C-7 halo-indolines



134 X = I
135 X = Br

141

Entry	Halide	Yield **141** (%)[a]
1	**134**	39
2	**135**	27

Reagents and Conditions: halide (1 eq.), boronic acid **140** (1.25 eq.), $Pd(OAc)_2$ (10 mol%), PPh_3 **L32** (22 mol%), KOH (1.78 M, 1.25 eq.), THF, reflux, 48 h. [a] Isolated yields.

4.1.3. Summary

Successful C-7 bromination and hydroxylation of indoline fragments as model substrates for the pyrrolidinoindoline motif *via* an *ortho*-lithiation procedure with suitable bromine and oxygen electrophile sources has been demonstrated. C-7 iodide **134** and C-7 bromide **135** have been shown to undergo Suzuki couplings despite bulky *ortho*-substitution, suggesting a successful outcome of a Suzuki coupling with a *meso*-chimonanthine derivative will be determined by the nature of the boronic coupling partner and development of a more active catalyst system.

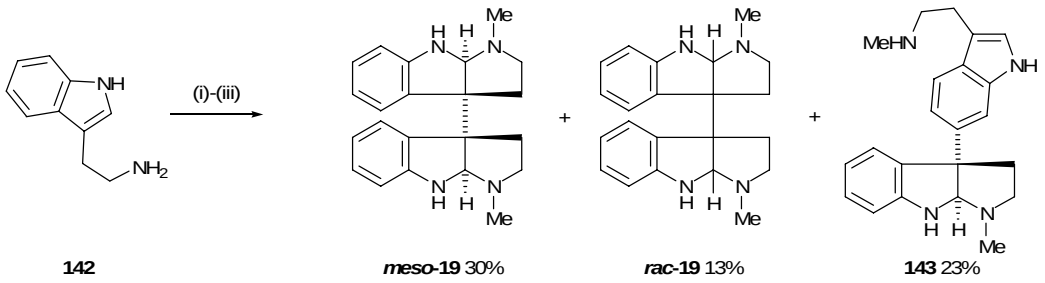
Although the coupling demonstrated is not a desymmetrisation, the results validate the viability for the Suzuki coupling of an *ortho*-*N*-substituted aryl halide. Yields achieved were moderate at best though the *meso*-chimonanthine substrates we proposed for the total synthesis are markedly more complex substrates to those employed so far. A great deal of catalyst optimisation would be required and would ultimately be expected to achieve better results. Therefore, we chose to finish our investigations of model Suzuki couplings at this stage.

4.2. Preparation of *meso*-Chimonanthine Derivatives

4.2.1. Synthesis of *meso*-Chimonanthine

Attempts to construct bisbenzylic quaternary carbon centres, as found in *meso*-chimonanthine ***meso*-19**, achieved a great deal of attention during the 1950's and 1960's as the number of isolated polypyrrolidinoindolines expanded. It was believed that biosynthetic pathways towards the pyrrolidinoindoline motif involved an oxidative dimerisation of an indole or oxindole tryptamine derivative, though it was uncertain as to which was correct. Subsequently, attempts at constructing these C-3a dimers were made using both derivatives as a starting point and were successful in preparing both the *meso* and *rac* diastereomers.[128, 129]

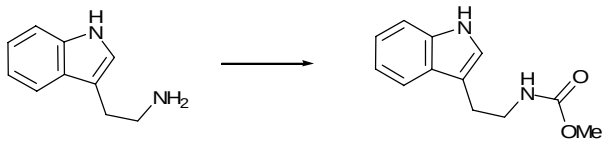
Recent interest in the use of hypervalent iodine reagents has led to the development of a broad range of reactions involving these compounds.[130] Natural product studies by Takayama *et al.* led to the development of a novel oxidative dimerisation reaction employing the hypervalent iodine reagent bis(trifluoroacetoxy)iodobenzene. Subsequent extension of this methodology achieved the synthesis of *meso*-chimonanthine ***meso*-19** and *rac*-chimonanthine ***rac*-19** in just three steps from tryptamine **142** (Scheme 4.3).[131]



Scheme 4.3: *Reagents and Conditions*: (i) tryptamine **142** (1 eq.), $ClCO_2Me$, NaOH/DCM; (ii) bis(trifluoroacetoxy)iodobenzene (0.5 eq.), CF_3CH_2OH, -30 °C, 8 h; (iii) Red-Al, toluene, reflux.

Although not as elegant a solution to the synthesis of *meso*-chimonanthine ***meso*-19** as that demonstrated by Overman *et al,*[48, 51] the hypervalent dimerisation approach allowed for rapid preparation of our proposed starting material for the development of the Suzuki coupling substrates, albeit in a relatively low yield (30%). The simplicity of this synthesis for such a complex product was the major factor in our decision to prepare *meso*-chimonanthine ***meso*-19** *via* this dimerisation.

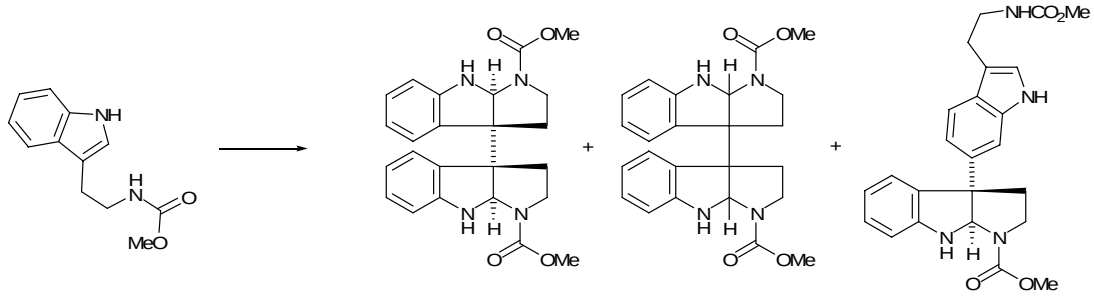
Therefore, dimerisation precursor *N*′-carbomethoxytryptamine **144** was prepared in near quantitative yield from tryptamine **142** and methyl chloroformate. Recrystallisation from *iso*propanol-hexanes gave the analytically pure product (Scheme 4.4).



142 **144** 94%

Scheme 4.4: *Reagents and Conditions*: tryptamine **142** (1 eq.), $ClCO_2Me$ (2 eq.), NaOH/DCM (1:1), 0 °C.

N′-carbomethoxytryptamine **144** was subsequently employed in the hypervalent iodine mediated oxidative dimerisation developed by Takayama *et al.* (Scheme 4.5). Initially 50 mol% of bis(trifluoroacetoxy)iodobenzene is added in two equal portions two hours apart at -30 °C. It was found that the reported reaction duration of eight hours required extending to twenty-four hours with a further 15 mol% of bis(trifluoroacetoxy)benzene added after twenty hours to force the reaction to completion. Column chromatography isolated the *meso* and *rac* diastereomers ***meso*-145** and ***rac*-145** as a mixture and the dimer **146** as a clean product. The *meso* diastereomer could then be isolated by recrystallisation from chloroform-hexanes. Unfortunately the yields attained were not consistent, achieving a maximum of 28%.



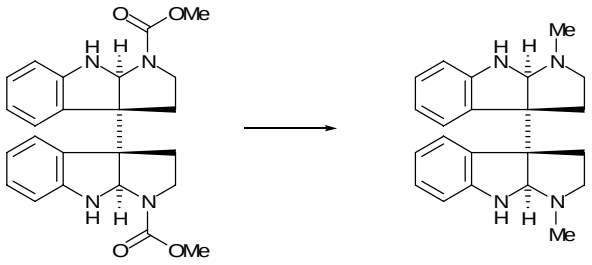
144 ***meso*-145** 28% ***rac*-145** 12% **146** 16%

Scheme 4.5: *Reagents and Conditions*: carbamate **144** (1 eq.), bis(trifluoroacetoxy)iodobenzene (0.65 eq.), CF_3CH_2OH, -30 °C, 24 h.

A recent publication states the addition of 50 mol% anhydrous sodium hydrogen carbonate to the dimerisation at the same time as the hypervalent iodine reagent achieves an increase in yield of 10% of the carbamate intermediate ***meso*-145**, presumably by quenching the by-products as they form to give a cleaner reaction.[132] However this effect was not observed in our hands, indeed the reaction did not reach

completion even after forty-eight hours with only trace quantities of the desired *meso*-dimer ***meso*-145** isolated.

Takayama *et al.* report the separation of the dimerisation products after reduction of the crude dimerisation mixture. However, the separation of the diastereomers proved to be easier as the carbamate derivatives ***meso*-145**, ***rac*-145** and **146**. Therefore, Red-Al reduction of pure *meso*-dicarbamate ***meso*-145** gave *meso*-chimonanthine ***meso*-19** in 77% yield, 20% overall yield from tryptamine **142** (Scheme 4.6).



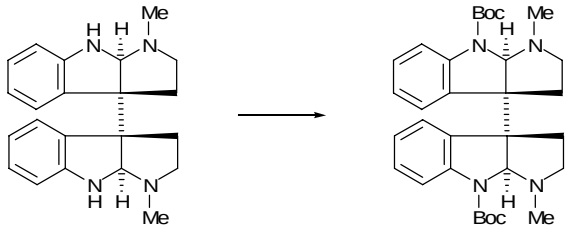
***meso*-145** ***meso*-19**

Scheme 4.6: *Reagents and Conditions*: carbamate ***meso*-145** (1 eq.), Red-Al (10 eq.), toluene, reflux, 16 h.

The preparation of *meso*-chimonanthine ***meso*-19** has been demonstrated at the multi-gram scale *via* a hypervalent iodine dimerisation approach with a modification of the reported purification process. Therefore, with a quick and efficient route to large quantities of pure starting material, investigations into C-7 functionalisation of the *meso* core were undertaken.

4.2.2. C-7 Functionalisation of *meso*-Chimonanthine

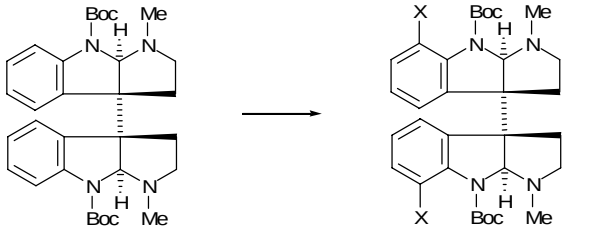
Following the C-7 functionalisation protocol of *meso*-chimonanthine ***meso*-19** detailed by Overman *et al.*, protection of ***meso*-19** as biscarbamate ***meso*-31** proceeded smoothly in 82% yield. Trace quantities of what was thought to be the monocarbamate were observed by TLC, though subsequently proved difficult to isolate and characterise. Improved yields were achieved by increasing the equivalents of sodium bis(trimethylsilyl)amide compared to the literature procedure (Scheme 4.7).



***meso*-19** ***meso*-31** 82%

Scheme 4.7: *Reagents and Conditions*: *meso*-chimonanthine ***meso*-19** (1 eq.), NaHMDS (4.5 eq.), $(Boc)_2O$ (2.2 eq.), THF, 3 h.

Ortho-lithiation of biscarbamate ***meso*-31** with *sec*-butyllithium and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine followed by quenching of the organolithium with diiodoethane furnished known bisiodide ***meso*-133** in 75% yield. Analogous quenching with dibromoethane provided bisbromide ***meso*-134** in 54% yield (Scheme 4.8).

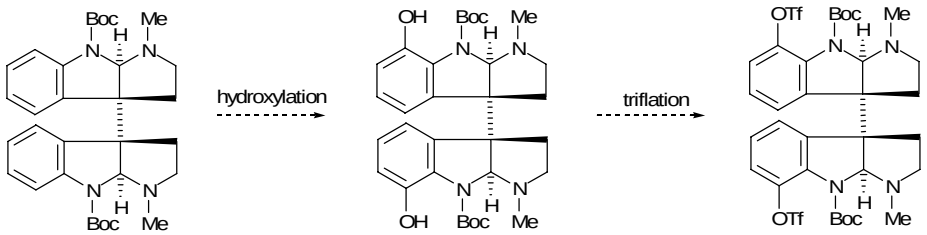


***meso*-31**

***meso*-133** X = I, 75%
***meso*-134** X = Br, 54%

Scheme 4.8: *Reagents and Conditions*: biscarbamate ***meso*-31** (1 eq.), *sec*-BuLi (4.5 eq.), TMEDA (6 eq.), Et_2O, -78 °C, then diiodoethane or dibromoethane (10 eq.), Et_2O, -78 °C to r.t.

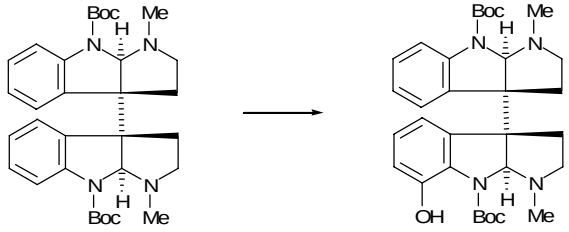
The successful synthesis of bistriflate ***meso*-135** proved more problematic. We sought to prepare the triflate moieties by initial preparation of bisphenol ***meso*-147** which would allow triflation under standard conditions to give bistriflate ***meso*-135** (Scheme 4.9).



***meso*-31** ***meso*-147** ***meso*-135**

Scheme 4.9

Previously, the successful hydroxylation of carbamate **133** with trimethylsilylperoxide **139** as the electrophilic oxygen source was described. However, under identical conditions dihydroxylation of biscarbamate ***meso*-31** was not achieved. The reaction consistently returned an approximately 1:1 ratio of starting biscarbamate ***meso*-31** to the monohydroxylated product ***rac*-148** by ^{1}H NMR spectroscopic analysis of the crude mixture (Scheme 4.10).



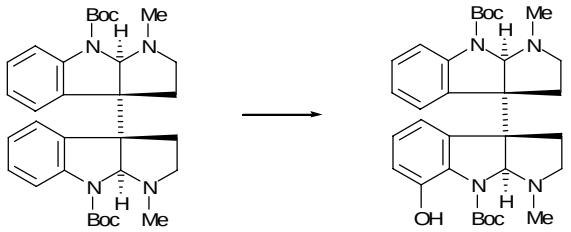
***meso*-31** ***rac*-148**

Scheme 4.10: *Reagents and Conditions*: biscarbamate ***meso*-31** (1 eq.), *sec*-BuLi (4.5 eq.), TMEDA (6 eq.), THF, -78 °C, then $(TMSO)_2$ **139** (5 eq.), THF, -78 °C to r.t.

It was also quickly established that the preparation of the organoborane with subsequent alkaline hydrogen peroxide oxidation to furnish the alcohol was again ineffective for the preparation of bisphenol ***meso*-147**. Subsequently, further investigations into electrophilic oxygen sources were conducted.

tert-Butylhydroperoxide represents a reactive source of electrophilic oxygen. Investigations by Boche *et al.* have shown the utility of this peroxide, either in combination with titanium *iso*propoxide or as its lithiated derivative, in the oxidation of a range of organometallics including *ortho*-substituted substrates.[133, 134]

Accordingly, a 1 M solution of lithium *tert*-butylhydroperoxide in tetrahydrofuran, prepared from *tert*-butylhydroperoxide and *n*-butyllithium at -78 °C, was added *via* cannula to an ethereal solution of *ortho*-lithiated biscarbamate ***meso*-31**. Acidic work-up or *in-situ* acylation with acetic anhydride quench and subsequent hydrolysis of the ester was expected to provide bisphenol ***meso*-147**. Unfortunately, bisphenol ***meso*-147** was not prepared in either instance, whether the lithiated peroxide was prepared in diethyl ether or tetrahydrofuran. Following an acidic work-up procedure, the monohydroxylated product ***rac*-148** was again prepared as the single product by ^{1}H NMR spectroscopic analysis (Scheme 4.11). No oxidation was observed when quenching the reaction with acetic anhydride.

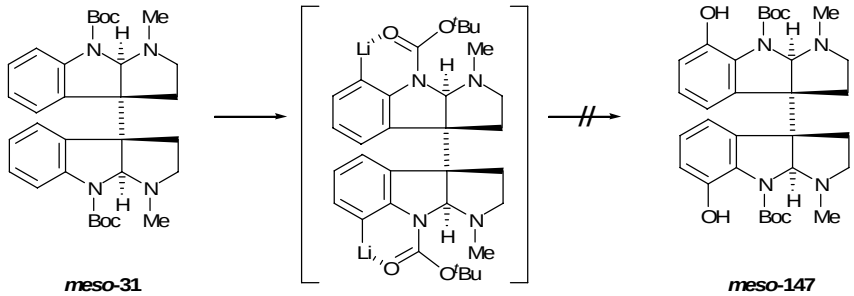


***meso*-31** ***rac*-148**

Scheme 4.11: *Reagents and Conditions*: biscarbamate ***meso*-31** (1 eq.), *sec*-BuLi (5 eq.), TMEDA (6 eq.), Et_2O, -78 °C, then lithium *tert*-butylhydroperoxide (10 eq.), THF or Et_2O, -78 °C to r.t., 3 h, then acidic work-up.

The use of titanium *iso*propoxide in such oxidations of organometallics allows the use of *tert*-butylhydroperoxide directly, rather than pre-preparation of the lithiated derivative. The peroxide is proposed to react initially with the titanium species to prepare the metallated peroxide. Although the *iso*propanol by-product is protic, the reaction of the organometallic substrate with the metallo-peroxide is proposed to be much faster than protonation by *iso*propanol therefore providing the oxidised product.[134]

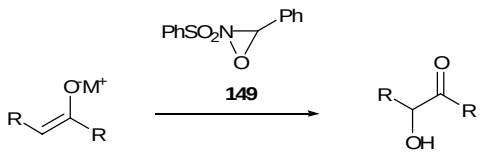
In our hands stepwise addition of titanium *iso*propoxide then *tert*-butylhydroperoxide failed to achieve oxidation of the lithiated species, returning unreacted biscarbamate ***meso*-31** with only trace quantities of the monohydroxylated species ***rac*-148** observed by ^{1}H NMR spectroscopy (Scheme 4.12). The lack of reactivity could be due to the increased stability of the lithiated species achieved by coordination with the carbonyl of the adjacent BOC group (Scheme 4.12). Subsequently the difference in reactivity between the metallo-peroxide and *iso*propanol is reduced and, in this instance, protonation is favoured. Alternatively the metallo-peroxide may simply not be reactive enough to deliver the electrophilic oxygen and protonation of the lithiated species occurs on work-up.



***meso*-31** ***meso*-147**

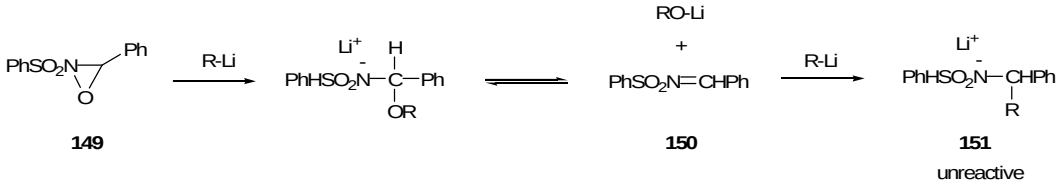
Scheme 4.12: *Reagents and Conditions*: biscarbamate ***meso*-31** (1 eq.), *sec*-BuLi (5 eq.), TMEDA (6 eq.), Et_2O, -78 °C, then titanium *iso*propoxide (4 eq.) then *tert*-butylhydroperoxide (4 eq.), THF, -78 °C, 1 h.

The lack of success with peroxides led to our consideration of oxaziridines as a suitable source of electrophilic oxygen. Davis' oxaziridine **149** has been shown to be highly efficient in delivering an oxygen atom when subjected to nucleophilic attack, particularly in the stereoselective synthesis of α-hydroxy carbonyls from ketone enolates (Scheme 4.13).[135]



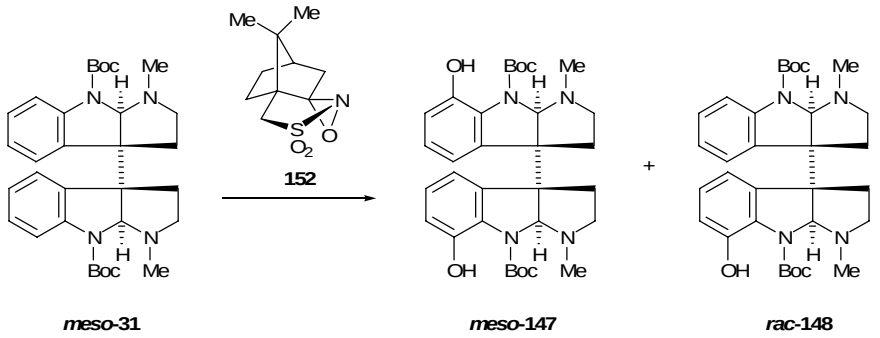
Scheme 4.13

Davis oxaziridine **149** was added to the lithiated derivative of biscarbamate ***meso*-31** *via* cannula as a solution in tetrahydrofuran after pre-cooling to -78 °C. Complete conversion of the starting material was repeatedly observed. The crude components were difficult to separate by column chromatography and the reaction products could not be isolated. Sulfonimine **150**, formed by the reduction of the oxaziridine, is susceptible to a secondary reaction with unoxidised starting material to give an unreactive by-product **151** and we believed this explained the complex nature of the crude products (Scheme 4.14).[136]



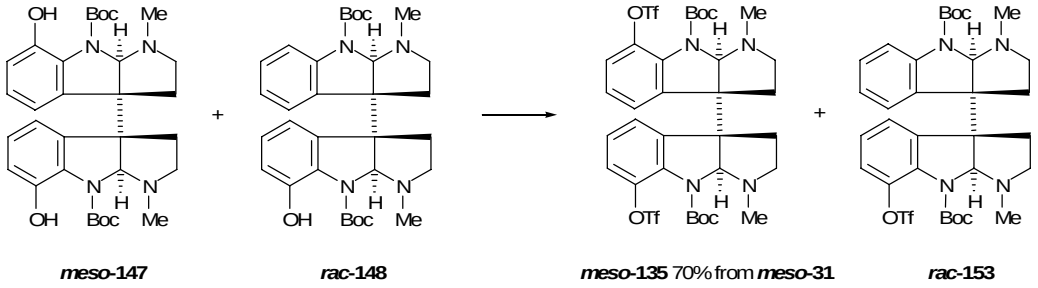
Scheme 4.14

Re-addition can be minimised by employing camphorsulfonyl oxaziridine **152**.[137, 138] The imine side product is highly sterically hindered and is therefore stable towards nucleophilic attack. Its application in our envisaged oxidation of biscarbamate ***meso*-31** resulted in a much cleaner reaction. All starting material was consumed and unreacted oxaziridine and the imine side product were removed by filtration. NMR spectroscopic analysis revealed a 3:1 ratio of the bisphenol ***meso*-147** to monohydroxylated product ***rac*-148** (Scheme 4.15). Unfortunately, the phenols could not be separated; therefore the mixture was carried through in the expectation that separation would be achieved as the triflate derivatives.



Scheme 4.15: *Reagents and Conditions*: biscarbamate ***meso*-31**, *sec*-BuLi (5 eq.), TMEDA (6 eq.), Et_2O, -78 °C, then oxaziridine **152** (6 eq.), THF, -78 °C, 1 h.

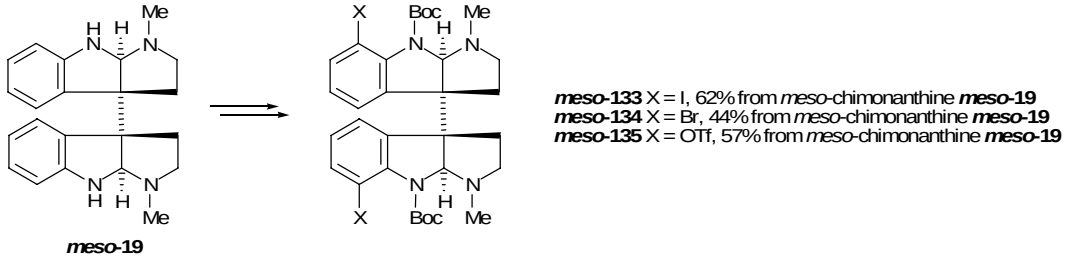
Triflation of phenols ***meso*-147** and ***rac*-148** under standard conditions with triflic anhydride and pyridine allowed separation of the compounds, furnishing the desired bistriflate ***meso*-135** in 70% yield (Scheme 4.16).[40]



Scheme 4.16: *Reagents and Conditions*: Tf_2O (4 eq.), py. (27 eq.), DCM, 0 °C, 1.5 h.

4.2.3. Summary

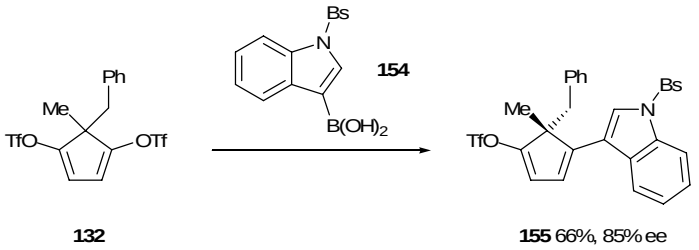
Short and reliable syntheses of the three desired *meso*-chimonanthine derivatives ***meso*-133**, ***meso*-134** and ***meso*-135** have been successfully achieved in synthetically useful and reproducible yields (Scheme 4.17). The structure and conformation of bistriflate ***meso*-135** was confirmed by X-ray crystallography (Appendix A). With these in hand, our attention focused on the development of a suitable boronic coupling partner for the proposed Suzuki couplings.



Scheme 4.17

4.3. Development of the Boronic Coupling Partner

Previous studies in the Willis group have demonstrated the successful Suzuki coupling of *N*-benzenesulfonyl indole-3-boronic acid **154** with bisvinyltriflate **132** to furnish the optically active monotriflate **155** in good yield and enantioselectivity (Scheme 4.18).[122]



132 **155** 66%, 85% ee

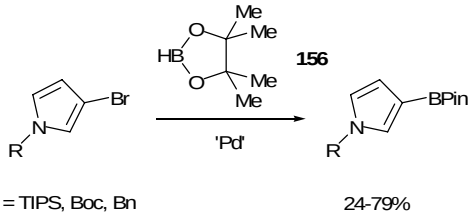
Scheme 4.18: *Reagents and Conditions*: bisvinyltriflate **132** (1 eq.), boronic acid **154** (2 eq.), $Pd(OAc)_2$ (10 mol%), (*R*)-MeO-MOP **(*R*)-L8** (10 mol%), CsF (3 eq.), dioxane, r.t., 8 h.

The commercial availability of this boronic acid initially led us to propose this substrate as the coupling partner to be used in our Suzuki couplings with *meso*-chimonanthine derivatives. However, the compound is highly susceptible to protodeboronation and inconsistencies in the quality of the product led us to consider other *N*-protected boronic acids.

The availability of indole-3-boronic acids is extremely limited, other than acid **154** only an *N*-tri*iso*propylsilyl protected derivative can be purchased in synthetically useful quantities and which is also susceptible to protodeboronation. Additionally, as part of the total synthesis, all protecting groups would ideally be cleaved in a single step. Therefore, as BOC groups are employed as protecting groups in the preparation of the *meso*-chimonanthine derivatives, we envisaged the preparation of *N*-BOC-indole-3-boronic substrate to allow for a global deprotection protocol in the synthesis of hodgkinsine **20**.

Traditionally, functionalisation of indole at C-3 involves metallation of C-3 followed by quenching with an appropriate electrophile. In the preparation of boronic acids, trialkyl borates are suitable electrophiles that are then hydrolysed to the acid. Recent publications have detailed borylation of pyrrole and indole substrates by iridium catalysed carbon-hydrogen bond activation[139, 140] or palladium catalysed coupling.

Palladium catalysed borylation to prepare pyrrole-3-pinacol boronic esters from vinyl bromides with pinacolborane **156** proceeds in low yield with a range of nitrogen protecting groups (Scheme 4.19).[141] The choice of nitrogen protecting group appeared to have no major influence on the stability of the boryl product as protodeboronation occurs with both electron donating and electron withdrawing groups. Additionally, only a tri*iso*propylsilyl derivative proved stable at elevated temperatures in subsequent Suzuki couplings. Indole-3-boronic esters were not prepared.



Scheme 4.19: *Reagents and Conditions*: pyrrole (1 eq.), $PdCl_2(MeCN)_2$ (3 mol%), S-Phos **L29** (9 mol%), pinacol borane **156** (1.5 eq.), NEt_3, toluene, 80-90 °C.

4.3.1. Synthesis of Indole-3-boronic acids and Esters

We favoured the preparation of a boronic acid moiety over an ester due to concerns over activation of the boronic ester and to minimise possible steric interactions in the proposed Suzuki couplings. Therefore, based on literature precedent for the preparation of C-3 functionalised *N*-protected indoles, indole **157** was protected as its *N*-BOC derivative to give carbamate **158**. Direct lithiation with an alkyllithium was expected to give a mixture of C-2 and C-3 lithiated products due to the directing potential of the carbamate. C-3 Bromination with *N*-bromosuccinimide to give bromide **159** allowed for lithium-halogen exchange at -100 °C to prepare the C-3 lithiated species as the sole regioisomer.[142] At this temperature, addition of a trimethyl borate followed by acidic work-up furnished *N*-BOC-indole-3-boronic acid **160** (Scheme 4.20). However, this compound was extremely unstable with protodeboronation highly favourable and the desired boronic acid could not be isolated in sufficient purity or yield, The isolation of small polar boronic acids is notoriously challenging due to their high solubility in aqueous media, even at relatively low pH.[125]

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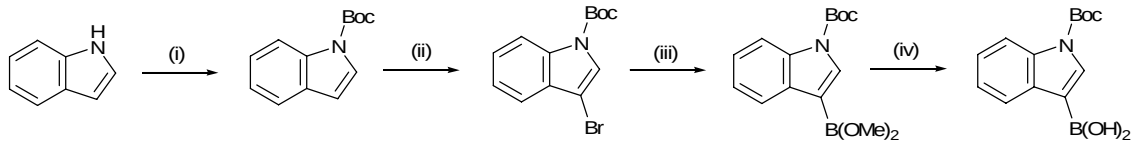
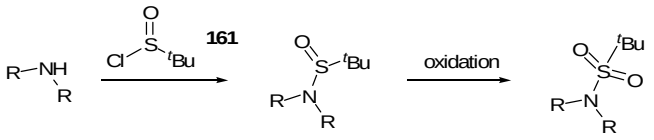


157 **158** 97% **159** 77% **160**

Scheme 4.20: *Reagents and Conditions*: indole **157** (1 eq.), $(Boc)_2O$ (1.1 eq.), DMAP (0.01 eq.), THF; (ii) NBS (1.3 eq.), THF; (iii) *tert*-BuLi (1.05 eq.), THF, -100 °C, 10 min. then $B(OMe)_3$ (2 eq.), -100 °C to r.t.; (iv) 3 M HCl.

A recent publication by Weinreb *et al.* demonstrated the application of a novel *tert*-butylsulfonyl (BUS) amine protecting group.[143] BUS protected primary and secondary amines are deprotected under acidic conditions with either triflic or trifluoroacetic acid, analogous conditions for the deprotection of *N*-BOC amines. Although explicit protection/deprotection of indoles was not demonstrated in their studies, the compatible deprotection conditions led us to attempt the synthesis of *N*-BUS indole-3-boronic acid to allow further investigation.

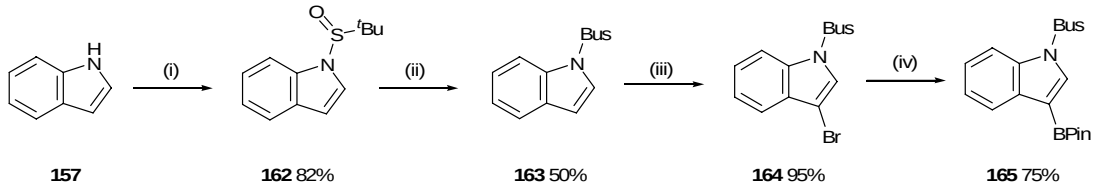
The direct introduction of the BUS group from *tert*-butylsulfonyl chloride is not possible due to rapid hydrolysis of the chloride across a broad pH range.[144] The lower oxidation level of *tert*-butylsulfinyl chloride **161** allows for nucleophilic displacement of chloride; subsequent facile oxidation with *meta*-chloroperoxybenzoic acid or sodium periodate/ruthenium trichloride furnishes the desired sulfoxide (Scheme 4.21).



Scheme 4.21

Our approach to the synthesis of *N*-BUS indole-3-boronic acid followed a similar protocol to that of *N*-BOC indole-3-boronic acid **160**. Indole **157** was deprotonated with *n*-butyllithium and the resultant anion quenched with *tert*-butylsulfinyl chloride **161** to give *tert*-butylsulfinylindole **162** (Scheme 4.22). Subsequent oxidation with *meta*-chloroperoxybenzoic acid in gave *N*-BUS-indole **163** in moderate yield (50%). Literature procedures conduct this oxidation in dichloromethane but with our indole substrate oxidation only occurred in tetrahydrofuran. No starting material was returned to account for the mass balance; instead a complex mixture of side-products

was observed, possibly due to over oxidation. The boronic moiety was introduced as described previously, C-3 bromination to **164** followed by lithium-halogen exchange allowed quenching of the anion with trimethyl borate. Acid hydrolysis to yield the acid again provided a highly unstable product which was difficult to extract from other side products. However, recurring stability problems were solved by preparation of pinacol boronic ester derivative **165**. The crude methyl boronic ester was stirred with pinacol in the presence of 4Å molecular sieves to remove the methanol generated by the reaction and drive it to completion.[145] Recrystallisation from acetonitrile-hexanes provided **165** in 75% yield from bromide **164**.



157 **162** 82% **163** 50% **164** 95% **165** 75%

Scheme 4.22: *Reagents and Conditions*: indole **157** (1 eq.), *n*-BuLi (1 eq.), THF, -78 °C, 1 h then *tert*-BuS(O)Cl **161** (1.2 eq.), -78 °C to r.t., 2 h; (ii) *m*-CPBA (3 eq.), THF, 18 h; (iii) NBS (3 eq.), THF, 4 h; (iv) *tert*-BuLi (2 eq.), THF, -100 °C, 10 min. then $B(OMe)_3$ (2 eq.), -100 to 0 °C, 2 h, then pinacol, 4 Å MS, 5 h.

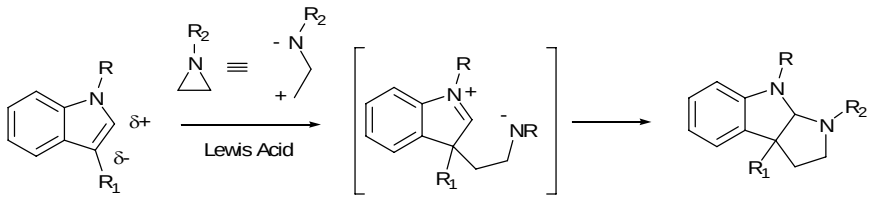
4.3.2. Summary

The synthesis of *N*-BOC or *N*-BUS-indole-3-boronic acids provided highly unstable compounds, though the stability issues were solved by the preparation of the *N*-BUS-indole-3-pinacol boronic ester **165**. Despite its increased stability, column chromatography or continued exposure of boronic ester **165** to air resulted in partial decomposition. Suzuki coupling of heteroaromatic compounds has been shown to proceed optimally in protic solvents and the propensity of indole-3-boronic acids and esters to protodeboronate may be further enhanced under such conditions. Due to our concerns with the stability of the boronic ester we sought to investigate the efficiency of the proposed indole alkylation-cyclisation sequence before focusing on the key Suzuki coupling step.

4.4. Investigations into the Indole Ring Expansion to the Pyrrolidinoindoline Motif

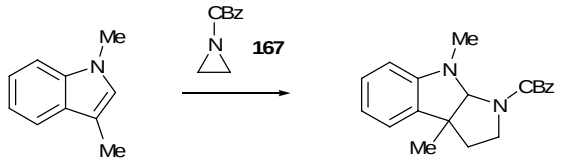
4.4.1. Aziridines

We proposed to construct the third pyrrolidinoindoline motif by a Lewis acid catalysed alkylation-cyclisation derivatisation of an indole moiety in a one-pot process. The intermolecular nucleophilic attack by the C-3 position of an indole to a Lewis acid activated aziridine would provide a C-3 disubstituted indolinium intermediate. The indolinium charge would be quenched by intramolecular attack of the resonance stabilised nucleophilic nitrogen species thus furnishing the pyrrolidinoindoline motif (Scheme 4.23). In such a reaction the aziridine effectively acts as a 1,3-dipolar, two-carbon component.



Scheme 4.23

Precedent by Nakagawa and Kawahara demonstrated the alkylation of 1,3-dimethylindole **166** with *N*-CBz aziridine **167** (Scheme 4.24).[123] The reaction required a great deal of optimisation, with scandium triflate[146] proving the most efficient Lewis acid in dichloromethane at -30 °C. Previous studies had demonstrated a rate enhancement of lanthanide triflate catalysed transformations by the addition of an equivalent trimethylsilyl chloride. Although trimethylsilyl chloride itself was not an active catalyst, trimethylsilyl triflate which may be formed *in-situ* proved to promote the alkylation although a Lewis acid was still required. Its application with indole substrates also proved beneficial in an equimolar ratio with the aziridine, significantly increasing yields.[147] Finally, optimal alkylation-cyclisation was achieved when employing a 2:1 ratio of indole to aziridine, furnishing the pyrrolidinoindoline **168** in 90% yield, based on the aziridine **167**. Additionally, the scandium triflate promoted alkylation of enols with aziridines has also been demonstrated.[148]



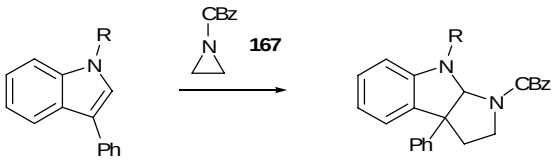
166 **168** 90% based on **167**

Scheme 4.24: *Reagents and Conditions*: indole **166** (2 eq.), aziridine **167** (1 eq.), $Sc(OTf)_3$ (2 eq.), TMSCl (1 eq.), DCM, -30 °C, 9 h.

Although we had successfully prepared the *N*-BUS protected boronic ester **165** and proposed this as the Suzuki coupling partner with our *meso*-chimonanthine derivatives, model studies into the alkylation-cyclisation procedure were conducted with a range of *N*-substituted indoles **169-174** to determine the effect of electron-donating and electron-withdrawing properties on alkylation with aziridine **167**.[149] It was expected that electron-rich indoles would favour the C-3 alkylation step due to the higher nucleophilicity of the C-2/C-3 double bond, whilst the indolinium species would be less reactive due to charge stabilisation by electron donation. Conversely, electron-poor indoles may require harsher reaction conditions to achieve C-3 alkylation though the instability of the indolinium would encourage a fast cyclisation step. Additionally, the C-3 position of the indole substrates was substituted with a phenyl group[150] to closely mimic the steric and electronic environment that would be encountered with the natural product substrate (Table 4.3).

Table 4.3: Indole alkylation-cyclisation with aziridine **167** under published conditions

169 R = H
170 R = TIPS
171 R = Bn
172 R = PMB
173 R = *tert*-BuS(O)
174 R = Bus



Entry	Indole	Products[b]
1	**169**	SM
2	**170**	SM
3	**171**	SM
4	**172**	SM
5	**173**	SM
6	**174**	SM
7[a]	**175**	90% **169**, 10% SM

Reagents and Conditions: indole (2 eq.), aziridine **167** (1 eq.), $Sc(OTf)_3$ (2 eq.), TMSCl (1 eq.), DCM, -30 °C, 12 h. [a] 48 h. [b] NMR conversion. SM = starting material.

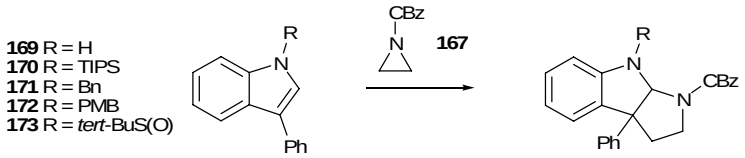
Under the optimal conditions of Nakagawa and Kawahara, no reaction was observed with any of the indole substrates (Table 4.3, entries 1-6).[123] Additionally *N*-

alkylation of the free unprotected indole **169**, an expected side reaction, was not observed and extended reaction time resulted in desilylation of indole **170** (entry 7). The formation of triflic acid under the reaction conditions has been proposed, however only trace deprotection of *N*-BUS indole **174**, known to be unstable in the presence of acid, occurred therefore suggesting that acid formation occurs slowly and therefore in low molarity.

At this point we felt further investigations into the alkylation-cyclisation reaction conditions were required, particularly with respect to the ratios of reactants as the previously tested 2:1 ratio of indole to aziridine was not appropriate for our total synthesis where the valuable indole substrate would be expected to be the limiting reagent.

4.4.2. Investigation of Alkylation-Cyclisation Conditions

Table 4.4: Variation of reaction conditions for alkylation-cyclisation of indoles with aziridine **167**

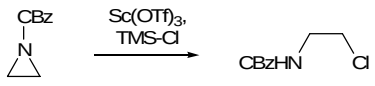


Entry	Indole (eq.)	$Sc(OTf)_3$ (eq.)	TMSCl (eq.)	**167** (eq.)	Products[c]
1[a,b]	**169** (2)	1	1	1	SM
2[a,b]	**169** (1)	1.5	1.5	1.5	SM + opened Az
3[b]	**169** (1)	1.5	1.5	1.5	SM + opened Az
4[b]	**169** (1)	0.2	1.5	1.5	SM + opened Az
5[a,b]	**170** (1.5)	1	1	1	**169**
6[a,b]	**170** (1)	1.5	1.5	1.5	**169**
7	**173** (1)	0.1	3	3	SM
8	**173** (1)	0.1	0.5	3	SM
9	**173** (1)	2	1	1	SM
10	**171** (1)	1	1	1	SM
11	**171** (1)	4	2	2	SM
12	**171** (1)	3	3	3	SM + opened Az
13	**171** (1)	0.1	1.5	1.5	SM + opened Az
14	**171** (1)	1	-	1.5	SM
15	**172** (1)	1	1	1	SM
16	**172** (1)	4	2	2	SM
17	**172** (1)	3	3	3	SM
18	**172** (1)	0.1	1.5	1.5	SM + opened Az
19	**172** (1)	0.5	-	1.5	SM

Reagents and Conditions: indole, $Sc(OTf)_3$, TMSCl, aziridine **167**, DCM, -30 °C, 12 h. SM = starting material. Az = aziridine. [a] 24 h. [b] r.t. [c] NMR analysis.

Disappointingly, broad variations in reaction conditions failed to achieve the desired pyrrolidinoindoline products with both electron-rich and electron-poor substrates (Table 4.4). Conducting the reaction with published reagent ratios at room temperature again returned starting indole **169**, with no nitrogen alkylation observed (entry 1). Employing catalytic, stoichiometric or excess quantities of scandium triflate with respect to aziridine **167** also failed to achieve the alkylation reaction at -30 °C or room temperature.

Whilst all reactions returned the indole starting material, or the desilylated product when employing silyl indole **170**, NMR spectroscopic analysis of the crude reaction mixtures suggested ring-opening of the aziridine **167** in some but not all reactions. This side reaction appears to occur when aziridine **167** and trimethylsilyl chloride are in excess of the indole and, as the indole is returned quantitatively another nucleophilic component is required. Chemical shifts of the alkyl protons suggested an electronegative heteroatom had opened aziridine ring and control experiments showed identical decomposition of aziridine **167** in the presence of trimethylsilyl chloride and scandium triflate at room temperature, without the Lewis acid no decomposition occurred. If *in-situ* formation of trimethylsilyl triflate does occur, then the chloride anion would be free to attack the electropositive carbon and would represent a more reactive nucleophile than the softer triflate anion. Therefore, although not isolated and characterised, it is proposed that the side-product observed is chloride **175** (Scheme 4.25). Intramolecular cyclisation of chloride **175** to reform aziridine **167** is plausible though literature precedent details elevated temperatures of 180 °C and reduced pressure are required.[151]



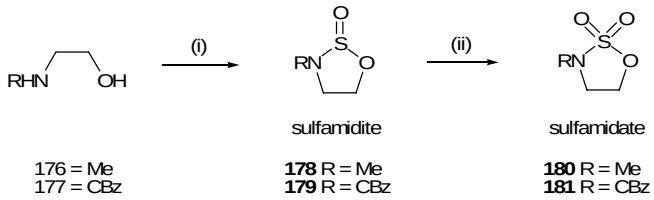
167 **175**

Scheme 4.25

4.4.3. Sulfamidites and Sulfamidates

The disappointing results observed with aziridine **167** in the alkylation-cyclisation protocol led us to consider aziridine equivalents. Cyclic sulfamidites and

sulfamidates have been shown to be highly reactive sources of electrophilic two-carbon fragments.[152] Prepared from the substituted ethanolamine and thionyl chloride, *N*-methyl and *N*-CBz sulfamidites were converted to their respective sulfamidates by ruthenium trichloride catalysed oxidation with sodium periodate (Scheme 4.26).[153]

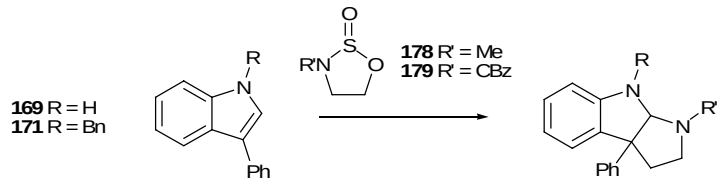


Scheme 4.26: *Reagents and Conditions*: (i) $SOCl_2$ (1.1 eq.), NEt_3 (2.2 eq.), imidazole (4 eq.), DCM; (ii) $NaIO_4$ (1.5 eq.), $RuCl_3$ (cat.), $MeCN/H_2O$ (1:1), 0 °C.

The reactivity of sulfamidites and sulfamidates is characterised by the electropositive C-2 position which, in the presence of a nucleophile, ring-opens to provide an acyclic oxo-sulphur intermediate which on acidic work-up furnishes the secondary amine. In the proposed reaction with our indole substrates, it was hoped that the secondary amine could be formed *in-situ* and subsequently spontaneously cyclise to quench the indolinium species to furnish the pyrrolidinoindoline motif in a one-pot process. However, the initial goal in these studies was to achieve C-3 alkylation of the indole substrate. Initially, alkylation of unprotected indole **169** and electron-rich *N*-benzyl indole **171** with sulfamidites **178** and **179** was investigated (Table 4.5).

We believed that sulfamidites **178** and **179** were better electrophiles than aziridine **167** due to the greater polarisation of the carbon-heteroatom bond (carbon-oxygen versus carbon-nitrogen). However C-3 alkylation did not occur under a variety of conditions (Table 4.5). In all attempted alkylations both starting materials were returned underivatised as determined by crude NMR spectroscopy. The addition of a Grignard reagent to unprotected indole **169** to increase the nucleophilicity by deprotonation of the enamine moiety prior to sulfamidite addition failed to improve the results, even at reflux (entries 9-12).[154]

Table 4.5: Alkylation-cyclisation of indoles with sulfamidites

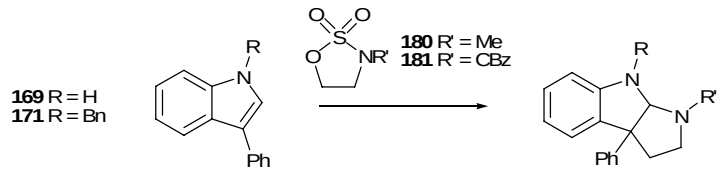


Entry	Indole	Sulfamidite (eq.)	Additive (eq.)	*t* (h)	*T* (°C)	Yield (%)[a,b]
1	**169**	**178** (2)	-	18	r.t.	-
2	**169**	**179** (2)	-	18	r.t.	-
3	**169**	**178** (2)	-	18	reflux	-
4	**169**	**179** (2)	-	18	reflux	-
5	**171**	**178** (2)	-	4	r.t.	-
6	**171**	**179** (2)	-	4	r.t.	-
7	**171**	**178** (2)	-	4	reflux	-
8	**171**	**179** (2)	-	4	reflux	-
9	**169**	**178** (1.5)	MeMgBr (1.5)	4	0 °C to r.t.	-
10	**171**	**178** (1.5)	MeMgBr (1.5)	4	0 °C to r.t.	-
11	**169**	**178** (2)	EtMgBr (1.5)	24	reflux	-
12	**169**	**179** (2)	EtMgBr (1.5)	24	reflux	-

Reagents and Conditions: indole (1 eq.), sulfamidite, additive, THF. [a] entries 1-12 returned both the starting indole and sulfamidite. [b] NMR analysis.

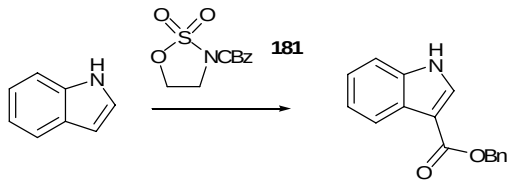
Unfortunately, the application of cyclic sulfamidates **180** and **181** also failed to achieve alkylation, with starting materials again being returned (Table 4.6, entries 1-6). As a control reaction, Grignard promoted alkylation of indole **157** was attempted under identical conditions to that of unprotected C-3 phenyl indole **169** with *N*-CBz sulfamidate **181** (entry 8). C-3 functionalisation of indole **157** was achieved, however nucleophilic attack to the CBz moiety in preference to the electropositive C-2 carbon of the sulfamidite **181** was observed in good yield (Scheme 4.27).

Table 4.6: Alkylation-cyclisation of indoles with sulfamidates



Entry	Indole	Sulfamidate	Additive (eq.)	Yield (%)[a]
1	**169**	**180**	-	-
2	**169**	**181**	-	-
3	**171**	**180**	-	-
4	**171**	**181**	-	-
5	**169**	**180**	EtMgBr (1.5)	-
6	**169**	**181**	EtMgBr (1.5)	-
7	**157**	**180**	EtMgBr (1.5)	-
8	**157**	**181**	EtMgBr (1.5)	**182** 74

Reagents and Conditions: indole (1 eq.), sulfamidate (2 eq.), additive, THF, 50 °C, 24 h. entries 1-7 returned both the starting indole and sulfamidate. [a] Isolated yields

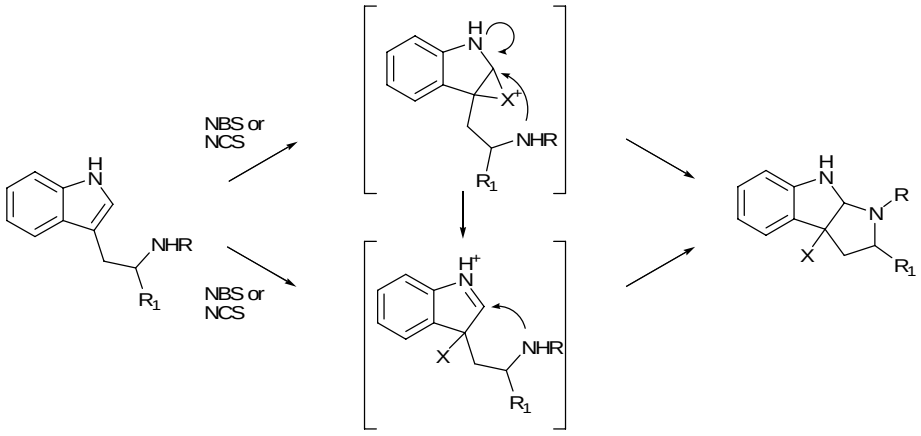


157 **182** 74%

Scheme 4.27: *Reagents and Conditions*: indole **157** (1 eq.), sulfamidate **181** (2 eq.), EtMgBr (1.5 eq.), THF, 50 °C, 24 h.

The increased reactivity of indole **157** over C-3 phenyl indole **169**, although providing an undesired product, demonstrates that C-3 phenyl-substituted indoles are less nucleophilic than their unsubstituted counterparts and that the carbamate functionality of *N*-CBz sulfamidate **181** is more electrophilic than the previously predicted C-2 position. Attempted alkylation of indole **157** with *N*-methyl sulfamidate **180** did not proceed and returned both starting materials. In conclusion, sulfamidates do not possess enough electropositive character at the C-2 position to achieve our proposed alkylation-cyclisation procedure with C-3 substituted indole nucleophiles.

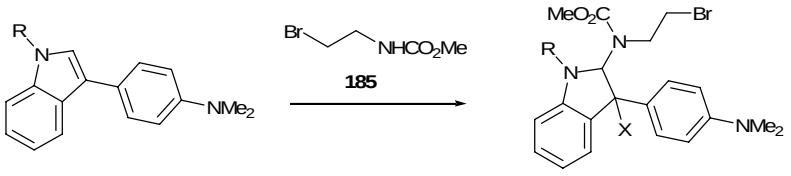
With concerns over the reactivity of C-3 phenyl indoles, it was felt further investigations into the electrophilic activation of C-3 substituted indoles were required. A survey of the Literature demonstrated the intramolecular cyclisation of tryptamine and tryptophan derivatives, examples of C-3 alkyl substituted indoles, by activation of the indole core with electrophilic heteroatom and halogen sources.[155-158] Whether the reactions proceed *via* an indolinium or bridged cationic intermediate is unclear, though intramolecular quenching of the charge results in preparation of the pyrrolidinoindoline motif. The resulting C-3a functionalised pyrrolidinoindoline can be further elaborated, or treatment with base eliminates the acid to regenerate the indole core (Scheme 4.28). Unfortunately, no examples of activations of C-3 aryl substituted indoles being activated by the methodology were found, however this protocol allows for a concise one-pot synthesis of the desired motif.



Scheme 4.28

Attempts to activate C-3 phenyl indoles **183** and **184** with *N*-chloro- or *N*-bromosuccinimide followed by trapping of the cationic intermediate with carbamate nucleophile **185** failed to achieve C-3 functionalisation (Table 4.7). NMR spectroscopic analysis of the crude mixtures showed residual carbamate and complex aryl regions which suggests halogenation of the aromatic ring. This is a plausible side reaction if the C-3 position of the indole is unreactive as conjugation of the nitrogen lone pair into the aromatic system of the indole moiety increases the nucleophilicity of the aryl ring.

Table 4.7: Activation of C-3 phenyl substituted indoles with halo-succinimides



183 R = H
184 R = Boc

Entry	Indole	Halide source (eq.)	Yield (%)[a]
1	**183**	NCS	-
2	**183**	NBS	-
3	**184**	NCS	-
4	**184**	NBS	-

Reagents and Conditions: indole (1 eq.), halide source (1 eq.), DCM, 30 min, then carbamate **185** (2 eq.), DCM, 4 h. [a] NMR analysis.

4.4.4. Summary

Investigations into C-3 phenyl-substituted indoles failed to achieve the desired alkylation-cyclisation procedure. We failed to achieve the initial alkylation step

across a range of conditions with a variety of electrophilic two-carbon fragments including aziridines, cyclic sulfamidites and sulfamidates for which literature precedent demonstrates their broad utility as an electrophilic reagent. The phenyl substituent appears to markedly decrease the nucleophilicity of the C-3 position. As well as greatly increasing the steric congestion around the carbon centre, the aryl ring markedly increases the degree of conjugation of the C-2/C-3 double bond and therefore the nucleophilicity of the latent enamine moiety, already weaker than an acyclic enamine by the nature of the aromaticity of the indole core, is further reduced. This proposed reduction in nucleophilicity is supported by the unreactive nature of C-3 phenyl indoles **183** and **184** relative to the C-3 alkyl-substituted tryptamine and tryptophan derivatives. As a result of the unsuccessful alkylation-cyclisation of the indole moiety we re-evaluated our approach to the total synthesis of hodgkinsine.

4.5. Re-evaluation of the Proposed Synthetic Route to Hodgkinsine

It was believed that the alkylation-cyclisation protocol initially proposed was unsuccessful due to the low nucleophilicity of the phenyl substituted indole core at the C-3 position. This lack of reactivity may be (i) a result of extended conjugation of the C-2/C-3 double bond with the aromatic ring or (ii) a result of increased steric hindrance due to the phenyl group.

Maintaining the desire to achieve a successful enantioselective desymmetrising Suzuki coupling, we approached the design of a new boronic coupling partner with the aim of improving the nucleophilicity of the C-3 position of the substituted indole core. Having found that the latent enamine moiety of the indole is not of sufficient nucleophilicity, we proposed that a better electron push could be achieved with the introduction of a latent enolate species. This would necessitate the introduction of a protected oxo-species at the C-2 position that could be deprotected in the presence of an electrophile to unmask a formal enolate to achieve C-3 substitution (Figure 4.1).

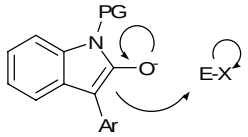
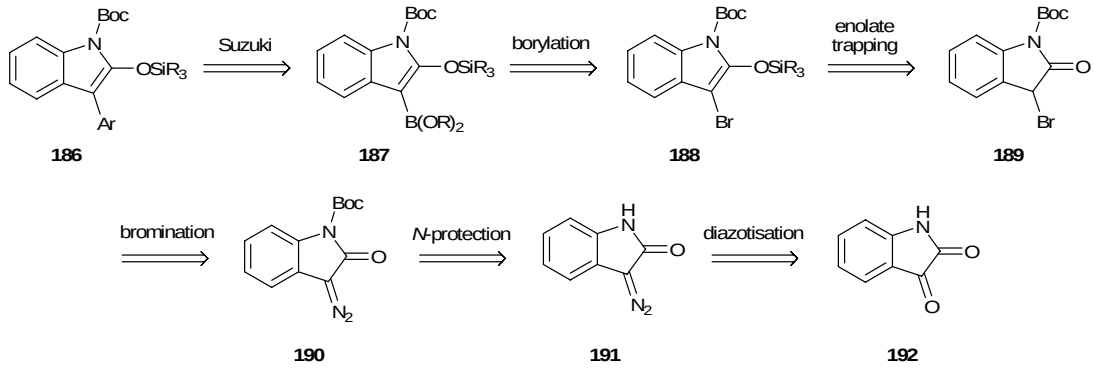


Figure 4.1

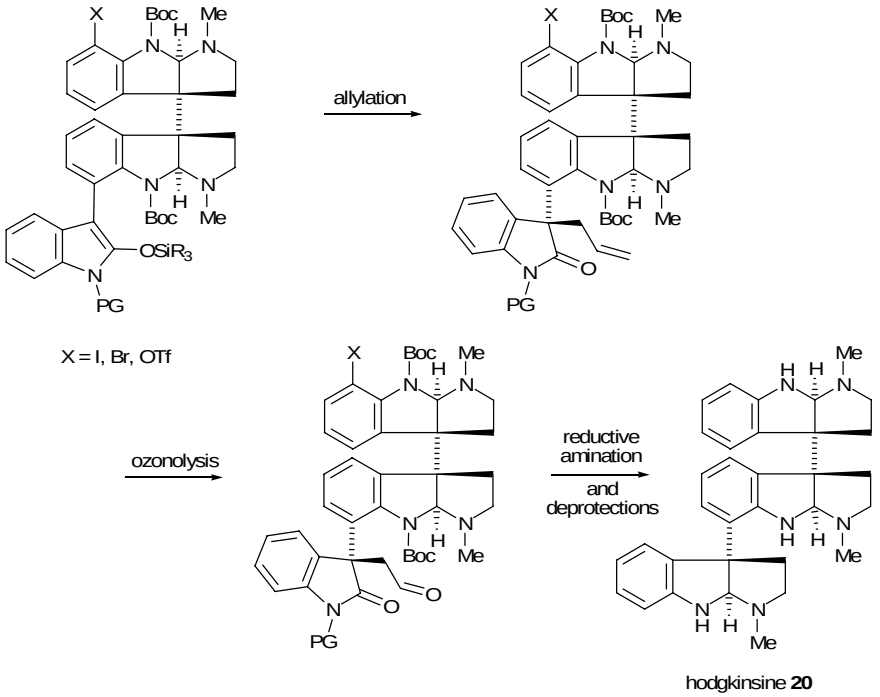
Retrosynthetic analysis reveals boronic acid or ester **187** could be prepared from vinyl bromide **188** by palladium catalysed borylation or lithium-halogen exchange (Scheme 4.29). Trapping the enolate of bromide **189** as the silyl enol ether could provide vinyl bromide **188**. Initial proposals for the preparation of bromide **189** involved enolisation of an oxindole substrate and subsequent quench with an electrophilic bromine source. However, we were aware of potential problems with over bromination due to the increased acidic nature of the product.[159] Therefore we hoped to avoid this problem by addition of hydrogen bromide to the stable α-diazocarbonyl **190** to give a single product. Although there is little precedent for such a reaction with hydrogen bromide, the analogous reaction with hydrogen chloride is well established to furnish α-chloro carbonyls. α-Diazocarbonyl **190** is

prepared from commercially available isatin **192** by literature procedures and protected to give **190**.



Scheme 4.29

The completion of the synthesis of hodgkinsine **20** from the proposed Suzuki product is outlined in Scheme 4.30. From the Suzuki product we proposed to construct the third pyrrolidinoindoline motif of hodgkinsine by employing a Trost asymmetric allylation to install a three carbon fragment, a transformation which has precedent for C-3 aryl oxindoles.[160] Subsequent ozonolysis of the allyl moiety reduces the carbon chain to a two carbon unit and reductive amination-cyclisation of the aldehyde would provide hodgkinsine **20** (Scheme 4.30). The high enantioselectivity of the allylation would allow for control of the stereochemistry of the C-3a/C-7 linkage, an aspect of the synthesis which was less defined under the previously proposed alkylation-cyclisation protocol.



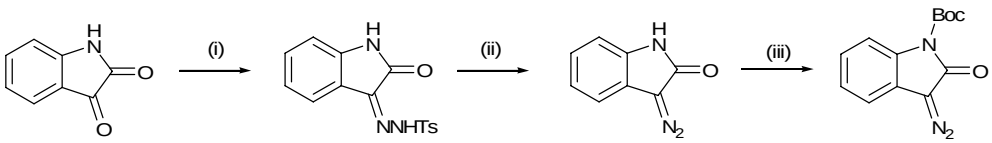
Scheme 4.30

4.6. Synthesis of Boronic Ester 200

4.6.1. Development of Latent Enolate Functionality

Exploratory investigations into the direct bromination of a protected oxindole substrate with *N*-bromosuccinimide or dibromotetrachloroethane to give bromide **189** were unsuccessful as we previously hypothesised. Due to the increased acidity of the C-3 proton in the monobromide product further reaction of bromide **189** to the C-3 dibromide was a consistent background reaction. Additionally, precedent for the rearrangement of indole-3-carboxaldehyde with *N*-bromosuccinimide to provide the *N*-H derivative of bromide **189** achieved consistently low yields with the products difficult to purify.[161]

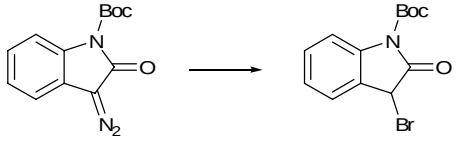
Therefore α-diazocarbonyl **191** was prepared in two high yielding steps from isatin **192** *via* the reduction of tosyl hydrazone **193**.[162] *N*-BOC protection proceeded well under standard conditions providing carbamate **190** in 76% yield over the 3 steps (Scheme 4.31).



192 **193** 98% **191** 83% **190** 93%

Scheme 4.31: *Reagents and Conditions*: (i) isatin **192** (1 eq.), $TsNHNH_2$ (1.02 eq.), MeOH, reflux, 30 min; (ii) NaOH (2 eq.), H_2O, 50 °C; (iii) $(Boc)_2O$ (2 eq.), DMAP (cat.), NEt_3 (1.5 eq.), THF, r.t.

The addition of a solution of hydrogen bromide in acetic acid to α-diazocarbonyl **190** furnished bromide **189** in 77% yield. When conducted at 0 °C competing *N*-BOC deprotection under the highly acidic conditions produced a mixture of products. This could be eliminated by reducing the reaction temperature to -78 °C to give **189** in 77% yield (Scheme 4.32).



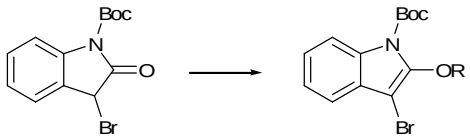
190 **189** 77%

Scheme 4.32: *Reagents and Conditions*: α-diazocarbonyl **190** (1 eq.), HBr/AcOH (1.5 eq.), DCM, -78 °C.

Having observed the over reaction of bromide **189** in previous reactions due to the increased acidity of the C-3 proton, it was hoped that the silyl enol ether moiety could be introduced under mild conditions. We hoped that bromide **189** could easily be enolised under basic conditions, driven by aromatisation to the indole moiety, which would reduce the protection to that of an alcohol which would not require the formation of a formal alkali metal enolate.[163]

The results summarised in Table 4.8 show that the tri*iso*propylsilyl or *tert*-butyldimethylsilyl enol ether formation from tri*iso*propylsilyl chloride or *tert*-butyldimethylsilyl chloride respectively did not occur under mild conditions with a range of organic or inorganic bases. Additionally, formal lithium, sodium and potassium enolates did not react with the silyl chlorides (entries 1-11). The use of the more reactive silyl triflates in conjunction with sodium bis(trimethylsilyl)amide provided the silyl enol ethers **194** and **195** in 79% and 87% yields respectively (entries 12-13). The application of silyl-triflate reagents may be efficient under the previously studied mild conditions. However, with high yielding routes in hand, these were not investigated due to time constraints.

Table 4.8: Synthesis of silyl enol ethers **194** and **195**



189 **194** R = TBDMS
195 R = TIPS

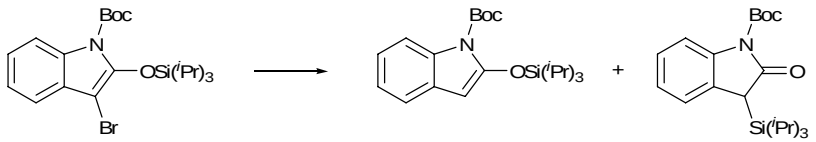
Entry	Base	Electrophile	Yield (%)[c]
1	NEt_3	TBS-Cl	-
2	NaOMe	TBS-Cl	-
3	KO^{t}Bu	TBS-Cl	-
4	NaHMDS	TBS-Cl	-
5	Imidazole	TIPS-Cl	-
6	NEt_3	TIPS-Cl	-
7	DBU	TIPS-Cl	-
8	Zn	TIPS-Cl	-
9	LDA	TIPS-Cl	-
10	NaHMDS	TIPS-Cl	trace
11	KO^{t}Bu	TIPS-Cl	deprotection of **189**
12	NaHMDS	TBS-OTf	**194** 79
13	NaHMDS	TIPS-OTf	**195** 87

Reagents and Conditions: bromide **189** (1 eq.), base (1.5 eq.), electrophile (1.2 eq.), THF, -78 °C. [a] 1.1 eq. base.[b] 1.2 eq. electrophile. [c] Isolated yields.

With high yielding routes to both the *tert*-butyldimethylsilyl and tri*iso*propylsilyl enol ethers, investigations into the borylation protocol were conducted with both substrates.

4.6.2. Palladium Catalysed Borylation

Borylation by lithium halogen exchange and quenching of the vinylic anion with *iso*propoxy-pinacolborane, effectively nucleophilic substitution of the *iso*propoxy moiety at boron, was unsuccessful with the tri*iso*propylsilyl enol ether **195**.[164] Exchange with either *n*-butyllithium or *tert*-butyllithium at -78 °C resulted in an approximately 1:1 ratio of debrominated silyl enol ether **196** and the reverse Brook rearrangement product **197** (Scheme 4.33). Attempted formation of the Grignard reagent from *iso*propylmagnesium chloride or magnesium metal was also unsuccessful, returning clean starting material.



195 **196** 32% **197** 39%

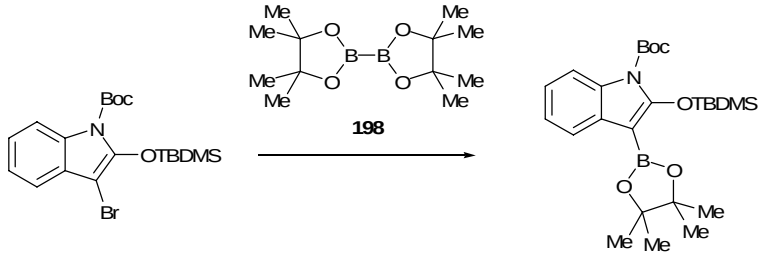
Scheme 4.33: *Reagents and Conditions*: *n*-BuLi or *tert*-BuLi (1.1 eq.), THF, -78 °C.

The palladium catalysed borylation of aryl and vinyl halides is an established method for the preparation of boronic esters, from which the corresponding acid can be prepared by hydrolysis. Typical boron sources include bispinacolato-diboron **198** and pinacolborane **156**, whilst inorganic and organic bases have been employed in a variety of solvents. Our studies initially focused on the application of established catalyst systems for the borylation of *tert*-butyldimethylsilyl enol ether **194** with bispinacolato-diboron **198** to furnish pinacol boronic ester **199** (Table 4.9).

The desired borylation of *tert*-butyldimethylsilyl enol ether **199** was not achieved with the published catalyst systems when employing bispinacolato-diboron **198** as the coupling partner.[165-167] With potassium acetate and a triphenylphosphine based catalyst in toluene, clean starting material was returned (Table 4.9, entry 1). However, when potassium phenoxide is employed partial hydrodebromination of the starting material is observed. The source of the proton to achieve the

hydrodebromination is unclear (entries 2-3). The ferrocene based catalyst system resulted in the decomposition of the starting material with both potassium acetate and potassium phenoxide. Elevated temperatures were also employed therefore the source of decomposition can not be directly attributed to a particular reaction parameter (entries 4-6).

Table 4.9: Borylation of TBDMS enol ether **194** with bispinacolato-diboron **158**



Entry	Pd source (mol%)	Base (eq.)	Solvent	*t* (h)	*T* (°C)	Products[a]
1[a]	$PdCl_2(PPh_3)_2$ (0.1)	KOAc (1.5)	Toluene	18	50	SM
2[a]	$PdCl_2(PPh_3)_2$ (0.1)	KOPh (1.5)	Toluene	1.5	50	SM + debromo **194**
3[a]	$PdCl_2(PPh_3)_2$ (0.1)	KOPh (1.5)	Toluene	24	50	SM + debromo **194**
4	$PdCl_2$(dppf) (0.05)	KOAc (3)	DMSO	4	80	dec.
5	$PdCl_2$(dppf) (0.05)	KOPh (3)	DMSO	4	80	dec.
6	$PdCl_2$(dppf) (0.05)	KOPh (3)	DMF	1	80	dec.

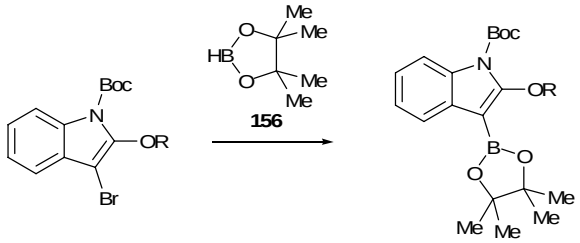
Reagents and Conditions: silyl enol ether **194** (1 eq.), bispinacolato-diboron **198** (1.2 eq.), Pd source, base, solvent Δ. [a] PPh_3 **L32** (0.2 mol%) added. SM = starting material. dec. = decomposed. [a] NMR analysis.

Our attention turned to the use of pinacolborane **156** in palladium catalysed borylation (Table 4.10). These couplings represent a more atom economic synthesis of pinacolate esters as the hydrogen of the borane is the only waste product. In contrast, couplings of bispinacolato-diboron **198** only involve one half of the dimer, losing the other half as waste.

Successful catalyst systems have been employed with palladium acetate and both the monodentate and bidentate phosphine ligands **L24** and **L40**.[168-171] Disappointingly, when employed with the *tert*-butyldimethylsilyl enol ether **194** at 80 °C both ligands failed to achieve borylation with hydrodebromination again a competing side reaction (Table 4.10, entries 1-2). Pleasingly, successful borylation of the tri*iso*propylsilyl enol ether **195** was achieved with 2-(dicyclohexylphosphino)biphenyl **L24** in excellent yield (86%) with only trace hydrodebromination observed. It was necessary to increase the reaction temperature to achieve high conversion of the starting bromide **195** (entry 3). In contrast, the

DPEphos **L40** based catalyst resulted in decomposition of the starting material to a complex mixture of product, including hydrodebrominated and desilylated derivatives (entry 4). Boronic ester **200** is highly stable and was stored at room temperature. Attempted hydrolysis of the ester to the acid under acidic, basic or oxidative conditions with an appropriate work-up was unsuccessful, providing complex mixtures of products.[172] Attempted preparation of the trihydroxyborate salt returned starting material,[173] whilst attempted synthesis of the trifluoroborate salt resulted in the expected decomposition of **200**.

Table 4.10: Borylation of silyl enol ethers with pinacolborane



194 R = TBDMS
195 R = TIPS

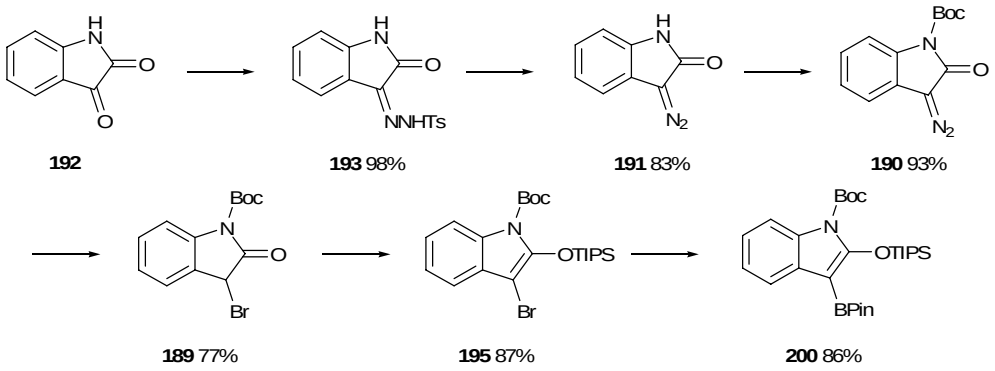
199 R = TBDMS
200 R = TIPS

Entry	Silyl Ether	Ligand	*t* (h)	*T* (°C)	Products[a]
1	**194**	**L24**	2	80	debromo **194**
2	**194**	**L40**	2	80	SM + debromo **194**
3	**195**	**L24**	1.5	100	**200** 86%[b]
4	**195**	**L40**	1.5	100	dec.

Reagents and Conditions: bromide (1 eq.), $Pd(OAc)_2$, (5 mol%), ligand (20 mol%), pinacolborane **156** (3 eq.), NEt_3 (4 eq.), dioxane, Δ, 1.5 h. SM = starting material; dec. = decomposed. [a] NMR analysis. [b] Isolated yield.

4.6.3. Summary

The successful synthesis of the stable complex boronic ester **200** which contains latent enolate functionality was achieved by the proposed retrosynthetic route on a multi-gram scale in reproducible yields. All transformations proceed in high yield furnishing boronic ester **200** in an excellent 44% yield over six steps (Scheme 4.34).



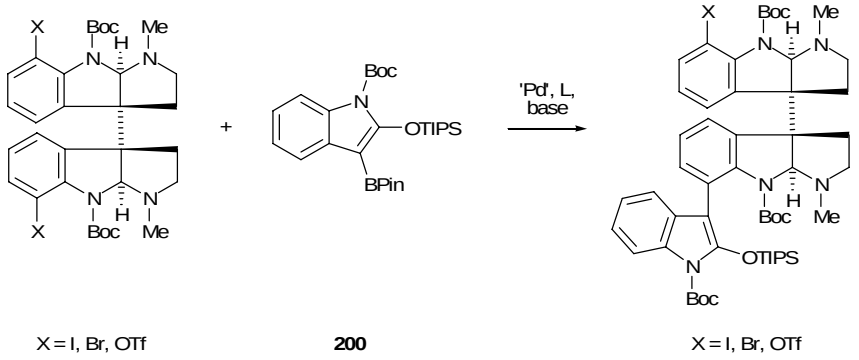
192 **193** 98% **191** 83% **190** 93%

189 77% **195** 87% **200** 86%

Scheme 4.34

4.7. Suzuki Couplings of *meso*-Chimonanthine Substrates

Having prepared stable boronic ester **200**, investigations into the crucial Suzuki coupling with *meso*-chimonanthine substrates were undertaken (Scheme 4.35). Such a coupling represents a difficult challenge in Suzuki chemistry due to the steric hindrance of the substrates, with *ortho-substitution* of the C-7 halide or triflate and a bulky silyl enol ether moiety at the C-2 position of the C-3 indole boronic ester **200**.



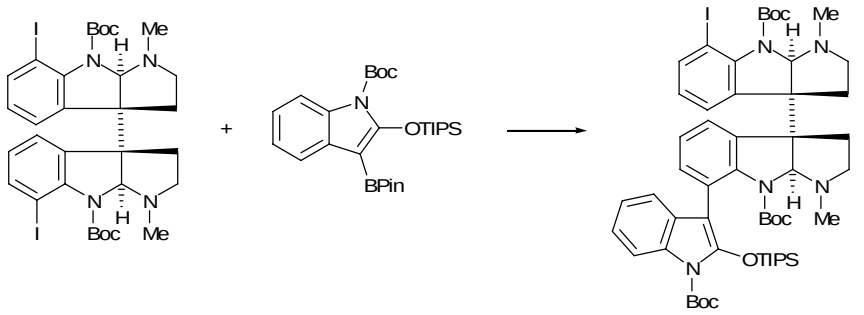
Scheme 4.35

4.7.1. Coupling of Boronic Ester 200 Under Anhydrous Conditions

The first couplings of bisiodide ***meso*-133** employed Fu's improved conditions for Suzuki cross couplings with potassium fluoride in tetrahydrofuran.[174] Although boronic ester **200** exhibits a silyl enol ether moiety which is labile in the presence of fluoride sources, we hoped that by employing one equivalent of this base the planar boron moiety would be the more reactive centre in preference to the sterically hindered silyl group. Palladium acetate in conjunction with bis-, mono and hemilabile phosphines generated the catalysts at 40 °C (Table 4.11).

The results show that all couplings were unsuccessful. Each reaction returned bisiodide ***meso*-133** whilst in each instance the boronic ester was fully decomposed to a mixture of products including protodeboronated product **196**, *N*-BOC-oxindole **203** and intriguing C-3 oxindole dimer **202** (Scheme 4.36). The exact mechanism for the formation of dimer **202** is unclear, though it's likely that the silyl enol ether is cleaved in the presence of fluoride and is the initial step in the decomposition of boronic ester **200**.

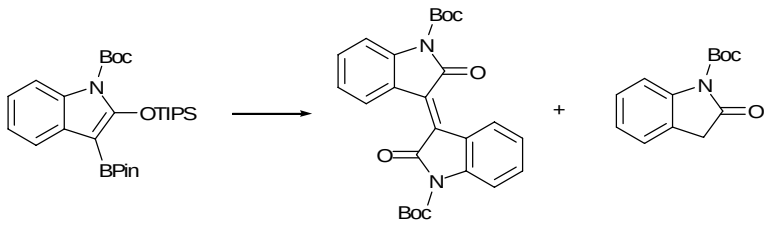
Table 4.11: Ligand screen for Suzuki coupling of bisiodide ***meso*-133** under Fu's conditions



***meso*-133** **200** ***rac*-201**

Entry	Ligand	Products[a]
1	***rac*-L1**	SM ***meso*-133** + **202**
2	**L23**	SM ***meso*-133** + **202**
3	**L40**	SM ***meso*-133** + **202**
4	**L24**	SM ***meso*-133** + **202**
5	***rac*-L8**	SM ***meso*-133** + **202**
6	**L60**	SM ***meso*-133** + **202**
7	**L69**	SM ***meso*-133** + **202**

Reagents and Conditions: bisiodide ***meso*-133** (1 eq.) boronic ester **200** (1.25 eq.), $Pd(OAc)_2$, (10 mol%), ligand (11 mol%), KF (1 eq.), THF, 40 °C. [a] NMR analysis. SM = starting material.



200 **202** **203**

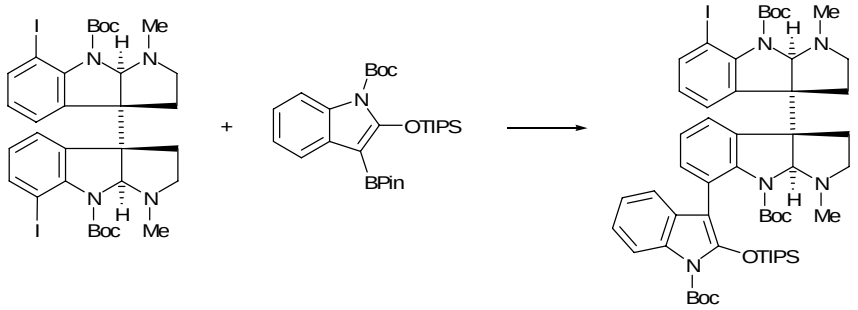
Scheme 4.36: Decomposition of boronic ester **200**

With the attribution of the boronic ester degradation to the fluoride base, a screen of a variety of organic, inorganic and aqueous bases was undertaken to determine if the degradation was indeed promoted by fluoride or whether another reaction component could be involved. The base screens were conducted in tetrahydrofuran or dioxane with a simple palladium acetate and triphenylphosphine catalyst system. The reaction temperature was maintained at 40 °C.

Again no coupling between bisiodide ***meso*-133** and boronic ester **200** occurred. The complex mixture of side-products was repeatedly observed particularly with alkoxide bases (Table 4.12, entries 1-3). Weaker bases did not decompose the boronic ester, returning both starting materials under the anhydrous conditions. The most interesting result, in both tetrahydrofuran and dioxane, was that only trace

protodeboronated product **196** was observed when employing aqueous hydroxide base with dimerisation of the substrate eliminated (entries 4 and 10). Successful literature couplings have been shown to occur under both anhydrous and mixed solvent systems although mixed aqueous/organic conditions are thought to be optimal. The reduced decomposition of the boronic ester in the presence of aqueous hydroxide encouraged us to investigate couplings of boronic ester **200** under mixed solvent conditions.

Table 4.12: Base screen for Suzuki coupling of bisiodide ***meso*-133** with Pd/triphenylphosphine catalyst



***meso*-133** **200** ***rac*-201**

Entry	Base	Products[a]
1	KOAc	SM ***meso*-133** + **202**
2	KO^{t}Bu	SM ***meso*-133** + **202**
3	KOPh	SM ***meso*-133** + **202**
4	KOH (1 M)	SM ***meso*-133**
5	NEt_3	SM ***meso*-133**
6	Cs_2CO_3	SM ***meso*-133** + **202**
7	K_3PO_4	SM ***meso*-133**
8	Na_2CO_3	SM ***meso*-133**
9	$KHCO_3$	SM ***meso*-133**
10	NaOH (1 M)	SM ***meso*-133**

Reagents and Conditions: bisiodide ***meso*-133** (1 eq.), boronic ester **200** (1.25 eq.), $Pd(OAc)_2$, (10 mol%), PPh_3 **L32** (22 mol%), base (3 eq.), THF or dioxane, 40 °C. [a] NMR analysis. SM = Starting material.

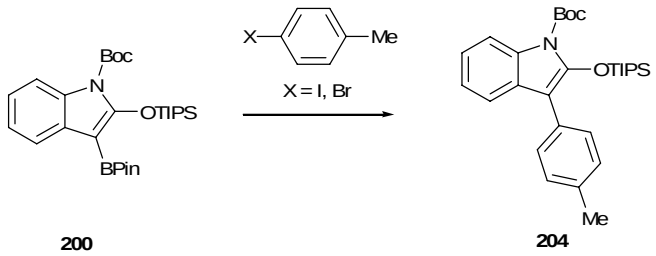
4.7.2. Couplings of Boronic Ester 200 in Aqueous Mixed Solvent Systems

With clear problems in controlling the reactivity and stability of boronic ester **200** we sought to develop conditions for its coupling with simple aryl iodides and bromides before refocusing our efforts on the more challenging *meso*-chimonanthine derivatives.

4-iodo- and 4-bromotoluene were selected as suitable aryl halides. The difference in decomposition of boronic ester **200** when aqueous hydroxide was employed

encouraged us to investigate mixed solvent systems. Successful literature conditions for the coupling of boronic esters detail palladium tetra*kis*(triphenylphosphine) as an active catalyst in a degassed toluene/ethanol/water solvent system.[175] Although a relatively poor catalyst in terms of our future ambitions, at this stage our aims were to achieve coupling and in the process to identify suitable base and solvent combinations therefore these conditions were employed.

Table 4.13: Base screen for model Suzuki couplings of boronic ester **200** with simple aryl halides



200 **204**

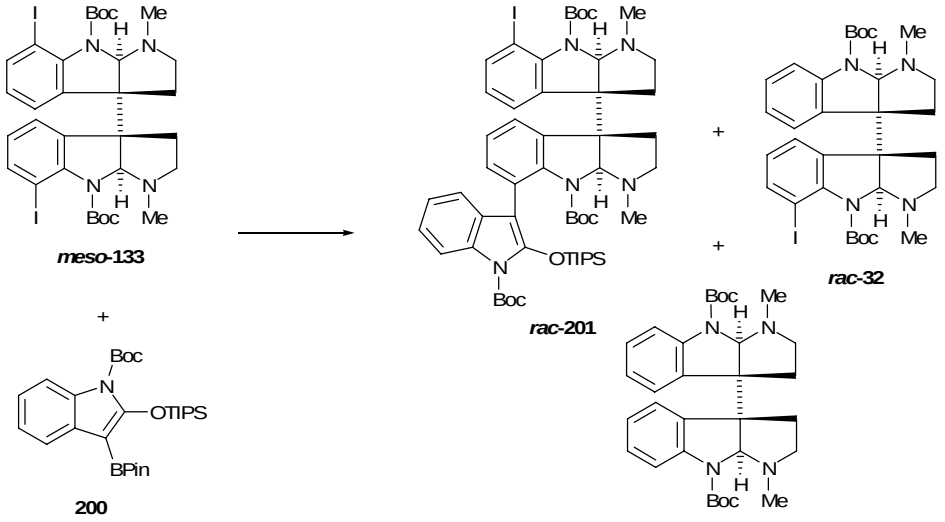
Entry	X	Base	Yield **204** (%)[a]
1	I	Na_2CO_3	45
2	I	$CsCO_3$	55
3	I	K_3PO_4	50
4	I	KF	trace
5	I	KOH	64
6	Br	KOH	36
7	I	NaOEt	-

Reagents and Conditions: arene (1 eq.), boronic ester **200** (1.25 eq.), $Pd(PPh_3)_4$, (5 mol%), base (2 $M_{(aq.)}$, 24 eq.), toluene/EtOH (4:1), 80 °C. [a] NMR conversion.

The results show successful coupling of both 4-iodo and 4-bromotoluene with a variety of bases to prepare indole **204** (Table 4.13), though inseparable from trace protodeboronated side product. Moderate yields were observed in all cases and even potassium fluoride achieved trace coupling with no formation of oxindole dimer **202** (entries 1-4). 4-Iodotoluene coupled in better yield than 4-bromotoluene as expected (entries 5-6). No boronic ester **200** remained by TLC after one hour in all conditions, even though an excess was employed. Therefore it may be expected that activation of the boron centre is readily achieved to form the 'ate' complex which is subsequently highly reactive. After reduction of the crude mixtures *in vacuo*, by-products precipitated on the re-addition of organic solvents. NMR spectroscopic analysis showed a complex mixture of products and the precipitate accounted approximately for the mass balance of the reaction, based on boronic ester **200**, in all instances.

With the knowledge of successful combinations of base and mixed solvent systems our focus returned to the coupling with bisiodide ***meso*-133** (Table 4.14).

Table 4.14: Application of successful conditions to the Suzuki coupling of bisiodide *meso*-**133**



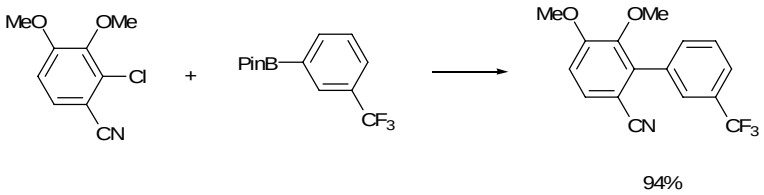
Entry	Pd source (mol%)	Ligand (mol%)	Base	*T* (°C)	Products[a]
1[a]	$Pd(PPh_3)_4$ (5)	-	KOH	80	38% SM ***meso*-133**
2	$Pd(OAc)_2$ (10)	**L32** (22)	Na_2CO_3	40	69% SM ***meso*-133**, trace rac-**32**
3	$Pd_2(dba)_3$ (5)	**L32** (22)	Na_2CO_3	40	75% SM ***meso*-133**
4	$Pd(OAc)_2$ (10)	**L32** (22)	Na_2CO_3	70	56% SM ***meso*-133**, 17% rac-**32**
5	$Pd_2(dba)_3$ (5)	**L32** (22)	Na_2CO_3	70	47% SM ***meso*-133**, 13% rac-**32**
6	$Pd(OAc)_2$ (10)	**L32** (22)	KOH	70	40% rac-**32**, 33% ***meso*-31**

Reagents and Conditions: bisiodide ***meso*-133** (1 eq.), boronic ester **200** (1.25 eq.), base (2 $M_{(aq.)}$, 24 eq.), toluene/EtOH (4:1), Δ, 24 h. [a] Isolated yields. SM = Starting material.

The conditions that proved successful for the coupling of simple aryl halides were not transferable to bisiodide ***meso*-133** (entry 1). Changing the palladium source and lowering the phosphine to palladium ratio did not improve results at 40 °C though raising the reaction temperature to 70 °C appeared to provide a more active catalyst system (entries 2-3). Although coupling with boronic ester **200** did not occur, reduction of bisiodide ***meso*-133** to monoiodide ***rac*-32** and biscarbamate ***meso*-31** was observed in the protic solvent (entries 4-6). This was indicative of oxidative addition to the aryl halide now being favourable whilst transmetallation of the boronate, which has been shown to be reactive in the presence of aqueous base, was the challenging aspect of the catalytic cycle.

Elegant examples of the Suzuki coupling of hindered substrates have been demonstrated by Buchwald *et al*. They reported a general catalyst system for the

coupling of aryl halides with boronic acids to furnish tetra-*ortho*-substituted unsymmetrical biaryls as well as conditions for the coupling of heteroaromatic boronic acids and esters with aryl chlorides.[141, 176] The use of electron-rich monophosphine ligands was crucial in achieving the desired coupling, in particular S-Phos **L29** and X-Phos **L30** proved the most generally applicable ligand and allowed catalyst loadings to be reduced to less than 1% (Scheme 4.37).



Scheme 4.37: *Reagents and Conditions*: arene (1 eq.), boronic ester (1.5 eq.), $Pd(OAc)_2$, (1 mol%), ligand **L29** (2 mol%), K_3PO_4 (2 eq.), THF/H_2O (10:1), 100 °C, 0.5 h.

The high activity of the catalyst is attributed to the η_1 palladium-carbon(*ipso*) interaction observed by X-ray crystallography (Figure 4.2).[177] The interaction imparts stability to the palladium, preventing dissociation and deposition of palladium black, though computational studies suggest the active catalyst does not retain the *ipso* interaction; rather a coordinatively unsaturated palladium centre is the highly active species. Bisligated palladium species have also been isolated, however the phosphine(1)-palladium-phosphine(2) bond angle is close to linear which would prohibit an oxidative addition process and so is not thought to be an active catalyst.

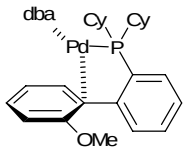
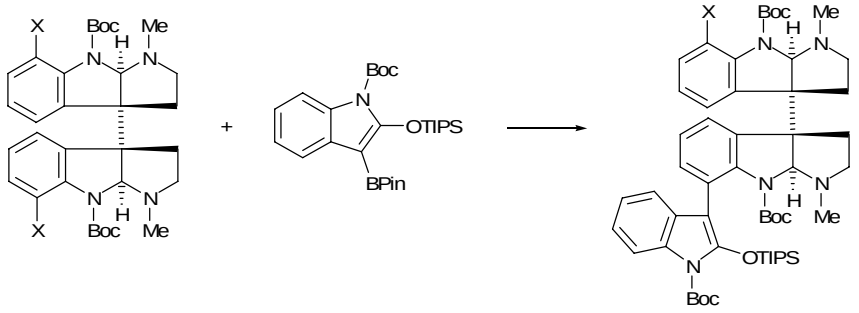


Figure 4.2 (second methoxy group omitted for clarity)

The success of electron-rich biaryl ligands in promoting sterically demanding cross-couplings encouraged us to investigate their effect in our proposed Suzuki coupling (Table 4.15). The substrate scope was also extended to bisbromide ***meso*-134**, as we believed a smaller counter-ion of the oxidative addition product may reduce steric crowding around the palladium centre thus encouraging the transmetallation of the activated boronic ester.

Table 4.15: Electron-rich biphenyl ligands in the Suzuki coupling of C-7 functionalised *meso*-chimonanthines



***meso*-133** X = I
***meso*-134** X= Br

200

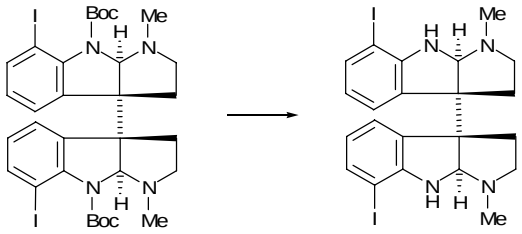
Entry	Halide	Pd source	Ligand	Base	Solvent	*T* (°C)	Products[a]
1	**133**	$Pd(OAc)_2$	**L24**	KOH	Tol/EtOH	70	trace SM ***meso*-133**, rac-**32**
2	**133**	$Pd(OAc)_2$	**L29**	KOH	Tol/EtOH	70	trace SM ***meso*-133**, rac-**32**
3	**133**	$Pd(OAc)_2$	**L30**	KOH	Tol/EtOH	70	trace SM ***meso*-133**, rac-**32**
4	**133**	$Pd(OAc)_2$	**L29**	K_3PO_4	Tol/EtOH	70	SM ***meso*-133**, rac-**32**
5	**133**	$Pd(OAc)_2$	**L29**	K_3PO_4	BuOH	100	SM ***meso*-133**
6	**133**	$Pd(OAc)_2$	**L30**	K_3PO_4	BuOH	100	SM ***meso*-133**
7	**133**	$Pd_2(dba)_3$	**L29**	K_3PO_4	BuOH	100	SM ***meso*-133**
8	**133**	$Pd_2(dba)_3$	**L30**	K_3PO_4	BuOH	100	SM ***meso*-133**
9	**134**	$Pd(OAc)_2$	**L29**	K_3PO_4	BuOH	100	SM ***meso*-134**
10	**134**	$Pd_2(dba)_3$	**L29**	K_3PO_4	BuOH	100	SM ***meso*-134**

Reagents and Conditions: arene (1 eq.), boronic ester **200** (1.25 eq.), Pd source (10 mol% Pd), ligand (20 mol%), KOH (2 $M_{(aq.)}$, 24 eq.) or K_3PO_4 (2 eq.), Toluene/EtOH (4:1) or *n*-BuOH/H_2O (8:1), Δ, 24 h. [a] NMR analysis.

The results in Table 4.15 show that no coupling between boronic ester **200** and the *meso*-chimonanthine substrates occurred with electron-rich biaryl monophosphines, with either the conditions we had previously found successful or the general conditions published by Buchwald *et al.* employing potassium phosphate in *n*-butanol. The palladium/monophosphine catalysts were active as reduction of the aryl halide was observed (entries 1-4), though interestingly the reduction of the aryl halide was inhibited in *n*-butanol even at increased temperatures (entries 5-10). Boronic ester **200** decomposed to a mixture of protodeboronated material **196** and *N*-BOC-oxindole **203** in all reactions.

4.7.3. Reducing Steric Interactions

With consistent problems with the transmetallation process we chose to reduce the steric interactions between the substrates by deprotection of bisiodide ***meso*-133** with trimethylsilyl triflate to bisamine ***meso*-205** in 94% yield (Scheme 4.38).

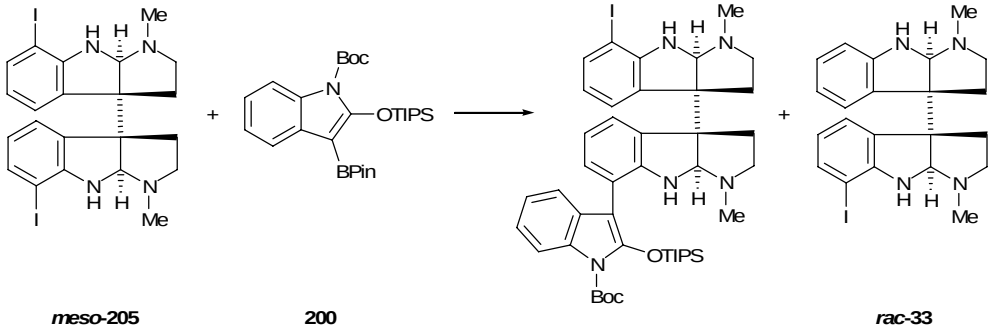


***meso*-133** ***meso*-205** 94%

Scheme 4.38: *Reagents and Conditions*: TMS-OTf (4.4 eq.), DCM, 3 h, r.t.

Bisamine ***meso*-205** was subsequently employed in Suzuki coupling reactions with boronic ester **200** under the conditions published by Buchwald *et al.* for the coupling of *N*-protected heterocyclic boronic esters. Excess base was employed to allow for deprotonation of the chimonanthine amine moieties in addition to boronic ester activation (Table 4.16).

Table 4.16: Suzuki coupling of bisamine *meso*-**205** with electron-rich biphenyl ligands



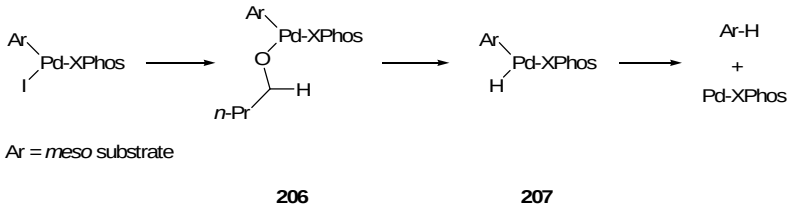
***meso*-205** **200** ***rac*-33**

Entry	Pd source	Ligand	Solvent	Products[a]
1	$Pd(PPh_3)_4$	-	Tol/EtOH/H_2O	30% SM ***meso*-205**, 60% ***rac*-33**
2	$Pd(OAc)_2$	**L29**	*n*-BuOH	SM ***meso*-205**, trace ***rac*-33**
3	$Pd(OAc)_2$	**L30**	*n*-BuOH	SM ***meso*-205**, ***rac*-33**
4	$Pd_2(dba)_3$	**L29**	*n*-BuOH	SM ***meso*-205**, trace ***rac*-33**
5	$Pd_2(dba)_3$	**L30**	*n*-BuOH	SM ***meso*-205**, ***rac*-33**

Reagents and Conditions: bisamine ***meso*-205** (1 eq.), boronic ester **200** (1.25 eq.), Pd source (10 mol% Pd), ligand (20 mol%), K_3PO_4 (4 eq.), *n*-BuOH/H_2O (8:1), 100 °C, 14 h. [a] NMR analysis.

A complex mixture of products was observed in the attempted couplings though the predominant reaction products were unreacted starting material bisamine ***meso*-205** and hydrodehalogenated product monoiodide ***rac*-33** (Table 4.16). Monoiodide product ***rac*-33** was unexpected as halide reduction did not occur in previous couplings in *n*-butanol but was favoured when X-Phos **L30** was employed as ligand. The common decomposition of boronic ester **200** to silyl enol ether **196** and *N*-BOC-oxindole **203** was also observed.

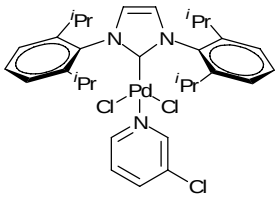
A mechanism for hydrodehalogenation is suggested in Scheme 4.39. As transmetallation of the boronate is unfavourable, substitution of halide by butanol in the palladium coordination sphere allows for β-hydride elimination from the oxo-palladium intermediate **206** to give palladium hydride species **207**. Reductive elimination furnishes the hydrodehalogenated product. In the specific instance of bisamine ***meso*-205**, the smaller steric interactions in comparison to bisiodide ***meso*-133** allows for faster oxidative addition. The bulky *iso*propyl groups of X-Phos **L30** create a sterically congested environment in the oxidative addition complex, thus favouring a rapid elimination process from the palladium centre.



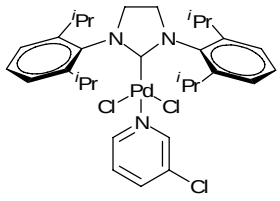
Scheme 4.39

With recurring problems in coupling boronic ester **200**, further model studies were conducted into the coupling with simple aryl halides. Particular focus was put upon water/organic solvent combinations and developing a more versatile catalyst system than palladium tetrakis(triphenylphosphine) which had previously shown limited success (Table 4.17).

Even when employing halides with no *ortho*-substitution, no coupling was achieved with decomposition to *N*-BOC-oxindole **203** the predominant reaction with conventional palladium/phosphine catalysts in biphasic solvent systems (entries 1-5). Saturated and unsaturated *N*-heterocyclic carbene based palladium sources **208** and **209** (Figure 4.3), found to be highly active in cross coupling chemistry,[178, 179] also failed to promote the Suzuki coupling though decomposition of the boronic ester was reduced (entries 6-9).



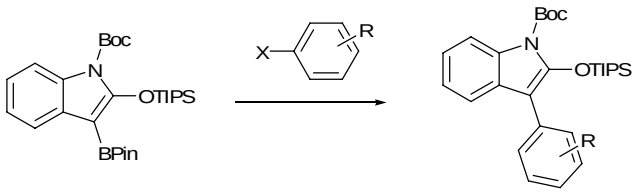
208 PEPPSI-IPr



209 PEPPSI-sIPr

Figure 4.3

Table 4.17: Further model studies into Suzuki coupling of boronic ester **200** with simple aryl halides



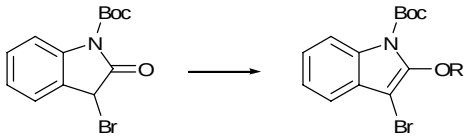
200

Entry	X	R	Pd source	Solvent	*T* (°C)	Products
1	Br	4-OMe	$Pd_2(dba)_3$	BuOH/H_2O (2.5:1)	100	oxindole **203**
2	I	4-Me	$Pd(OAc)_2$	Tol/H_2O (10:1)	80	oxindole **203**
3	Br	4-OMe	$Pd(OAc)_2$	Tol/H_2O (10:1)	80	oxindole **203**
4	I	4-Me	$Pd(OAc)_2$	THF/H_2O (10:1)	60	oxindole **203**
5	Br	4-OMe	$Pd(OAc)_2$	THF/H_2O (10:1)	60	oxindole **203**
6[a,c]	I	4-Me	PEPPSI-s^{i}Pr	Tol	80	BE **200**
7[a,c]	Br	4-OMe	PEPPSI-s^{i}Pr	Tol	80	67% BE **200**, 33% oxindole **203**
8[b,c]	I	4-Me	PEPPSI-^{i}Pr	Tol/EtOH	80	BE **200**
9[a,c]	I	4-Me	PEPPSI-^{i}Pr	*n*-BuOH	80	oxindole **203**

Reagents and Conditions: arene (1 eq.), boronic ester **200** (1.25 eq.), Pd source (5 mol% Pd), S-Phos **L29** (10 mol%), K_3PO_4 (3 eq.), 12 h. [a] K_3PO_4 (2 $M_{(aq.)}$, 3 eq.) as base. [b] Na_2CO_3 (2 $M_{(aq)}$, 3 eq.) as base. [c] no added ligand. [d] NMR analysis. BE = boronic ester

With repeated failure to coupling boronic ester **200**, we attempted to further reduce steric interactions in the transmetallation process by trapping the latent enolate functionality of the boronic ester with a smaller protecting group (Table 4.18). At high concentrations (>0.15 M) in tetrahydrofuran at -78 °C dimerisation of the potassium and sodium enolates of bromide **189** to the previously observed dimer **202** was rapid and quantitative, however at reduced concentrations (<0.1 M) this dimerisation was remedied. The preparation of the preferred methyl enol ether **210** was unsuccessful when trapping the sodium or potassium enolate of bromide **189** with the hard electrophilic methyl sources dimethyl sulfate and Meerwein's salt (Table 4.18, entries 1-6). However, the sodium enolate was trapped with methyl chloroformate to yield bromo-carbonate **211** in 87% yield (entry 7).

Table 4.18: Investigation of enol ether protecting groups from bromide **189**

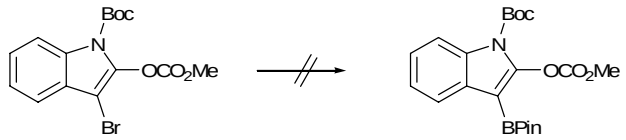


189 **210** R = Me
211 R = CO_2Me

Entry	Base	Electrophile	*T* (°C)	Yield (%)[a]
1	NaHMDS	MeI	0	-
2	NaHMDS	Me_2SO_4	-78	-
3	NaHMDS	Me_2SO_4	-78	-
4	KHMDS	Me_2SO_4	-78	-
5	NaHMDS	$(MeO)_3BF_4$	-78	-
6	KHMDS	$(MeO)_3BF_4$	-78	-
7	NaHMDS	$ClCO_2Me$	-78	**211** 87

Reagents and Conditions: bromide **189** (1 eq.), base (1.5 eq.), electrophile (2 eq.), THF, 1 h. [a] Isolated yields.

Unfortunately, conversion of bromo-carbonate **211** to boronic ester **212** by the previously successful conditions employing a palladium acetate/2-(dicyclohexylphosphino)biphenyl **L24** catalyst resulted in the decarboxylation and debromination of the starting material. No desired boronic ester **212** was observed (Scheme 4.40).



211 **212**

Scheme 4.40: *Reagents and Conditions*: bromide **211** (1 eq.), $Pd(OAc)_2$, (5 mol%), ligand **L24** (20 mol%), pinacolborane **156** (3 eq.), NEt_3 (4 eq.), dioxane, 100 °C, 1.5 h.

4.8. Conclusions

It was clear that the Suzuki coupling of boronic ester **200** was an extremely difficult transformation, with very limited success achieved with simple aryl halide substrates. No coupling was observed with *N*-8 protected or *N*-8 deprotected *meso*-chimonanthine substrates across a broad range of reaction conditions identical to, or based on, successful literature reports. Reactions in anhydrous conditions resulted in the formation of oxindole dimer **202** as the predominant product whilst the application of aqueous conditions promoted the decomposition of the ester to the protodeboronated silyl enol ether **196** or *N*-BOC-oxindole **203** at elevated temperatures. We attribute this lack of desired reactivity to the relatively high steric interactions of the tri*iso*propylsilyl protecting group of the latent enolate functionality which makes the transmetallation process of the activated boronic ester unfavourable. Hydrodehalogenation of *meso* substrates when reactions were conducted in protic solvents was a consistent side-reaction, providing a greater conversion than the palladium catalyst loading, thus indicating reduction was occurring under the reaction conditions and not from protonation of a palladated oxidative addition intermediate upon work-up. This provides further evidence that the transmetallation process was the problematic step of the catalytic cycle.

The repeatedly unsuccessful coupling of silyl boronic ester **200** and the difficulty in preparing analogous, less sterically hindered derivatives led to further reconsideration of our synthetic approach to the preparation of the C-3/C-7 carbon-carbon bond of hodgkinsine **20**.

5. Alternative Approaches for the Palladium Catalysed Preparation of the C-3/C-7 Bond

We conducted preliminary investigations into four new synthetic approaches towards the preparation of the C-3/C-7 carbon-carbon bond, though all were based on palladium mediated enantiotopic discrimination of the functional groups of the *meso*-chimonanthine core (Figure 5.1); (i) asymmetric borylation of the *meso*-chimonanthine core would allow for reversal of the coupling partners in a Suzuki coupling with a functionalised C-3 bromoindole; (ii) asymmetric desymmetrisation *via* C-7 hydrodehalogenation of the functionalised *meso*-chimonanthine; (iii) asymmetric arylation of a tryptamine derivative *via* enamine activation to prepare the new C-3 benzylic quaternary carbon centre in one step; and (iv) asymmetric desymmetrisation with the enolate of an *N*-protected oxindole which would allow further elaboration by the previously highlighted Trost asymmetric allylation protocol.[180]

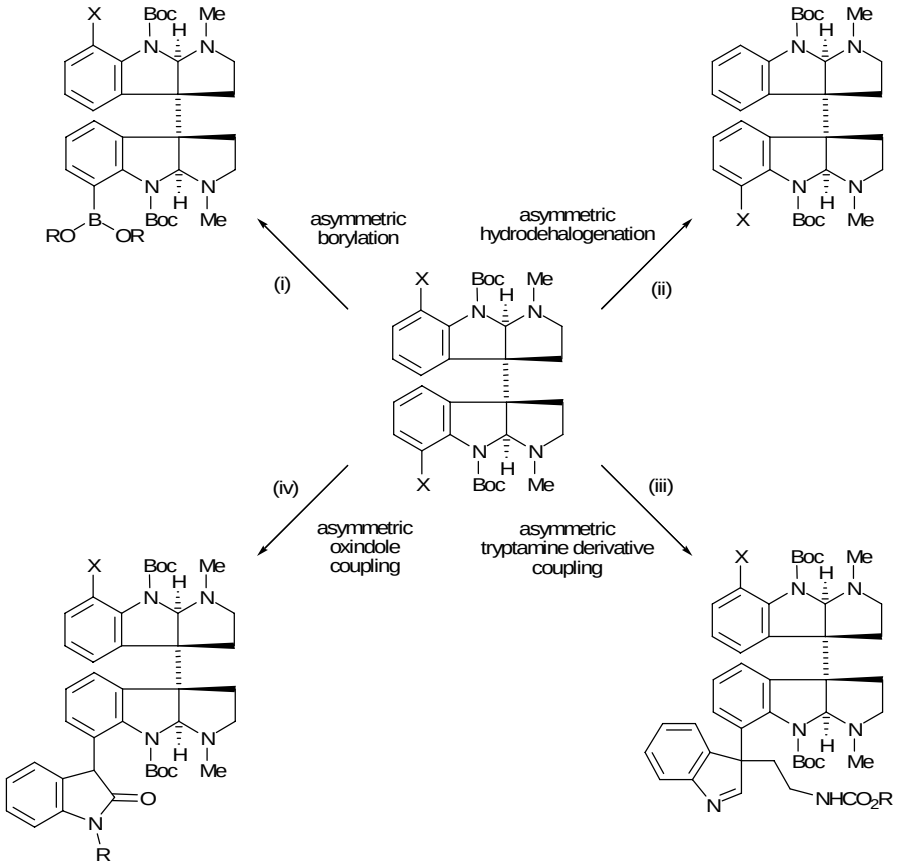
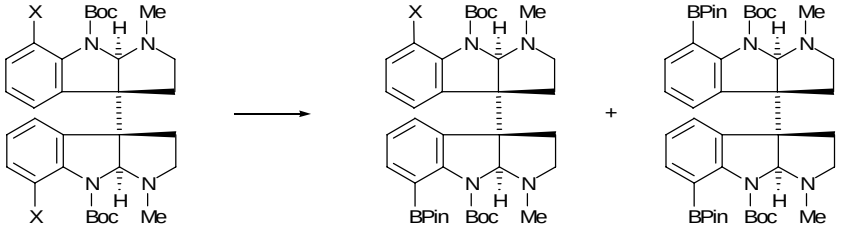


Figure 5.1

5.1. Borylation of *meso*-Chimonanthine Derivatives

Table 5.1: Reaction development for the borylation of C-7 functionalised *meso*-chimonanthines



***meso*-133** X = I
***meso*-134** X=Br

***rac*-213** X = I
***rac*-214** X=Br

***meso*-215**

Entry	Halide	Pd source (mol%)	Ligand (mol%)	Base	Boron source	Products
1	**133**	$Pd(OAc)_2$ (2)	**L40** (3)	NEt_3	**156**	44% ***meso*-215**,[c] trace ***rac*-213**
2[a]	**133**	$Pd(OAc)_2$ (2)	**L24** (3)	NEt_3	**156**	70% ***meso*-215**,[c] trace ***rac*-213**
3	**134**	$Pd(OAc)_2$ (6)	**L24** (12)	NEt_3	**156**	SM ***meso*-134**[d]
4	**134**	$PdCl_2$(dppf) (3)	-	KOAc	**198**	100% SM ***meso*-134**[d]
5[b]	**134**	$Pd(OAc)_2$ (5)	**L30** (10)	KOAc	**198**	100% SM ***meso*-134**[d]

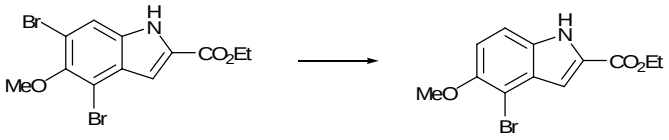
Reagents and Conditions: arene (1 eq.), boron source (2 eq.), Pd source, ligand, base (2.5 eq.), dioxane, 85 °C, 2 h. [a] 3 eq. pinacolborane. [b] 3 eq. base. [c] Isolated yields. [d] NMR conversion. SM = Starting material.

The monoborylation of bisiodide ***meso*-133** with pinacolborane **156** under racemic conditions with DPEphos **L40** was difficult to control, with further coupling to bisboronic ester ***meso*-215** a highly favourable process and only trace quantities of the desired product ***rac*-213** observed. Mono-phosphine 2-(dicyclohexylphosphino)-biphenyl **L24** provided near quantitative conversion based on the boron source to bisboryl ***meso*-215** (Table 5.1, entry 2). Borylation of bisbromide ***meso*-134** with pinacolborane **156** did not occur to any extent, instead resulting in reduction of the aryl bromide moiety (entry 3). When bispinacolato-diboron **198** was employed as the boron source no desired coupling or halide reduction was observed, with bisbromide returned quantitatively (entries 4-5).

These results highlight a much greater reactivity of bisiodide ***meso*-133** towards borylation than bisbromide ***meso*-134**, an effect which may be attributable to counter-ion effects whereby the oxidative addition product of the iodide results in a more dissociated and reactive palladium(II) complex from the iodide counter-ion in comparison to the equivalent oxidative addition product of bisbromide ***meso*-134** (though the overall reactivity is likely to be influenced by solvent effects).

5.2. C-7 Hydrodehalogenation of *meso*-Chimonanthine Derivatives

The palladium catalysed hydrodehalogenation of aryl halides is well established with a variety of hydride sources.[181-183] Conditions for the reduction of aryl bromides have been reported by Buchwald *et al*. The palladium catalysed reduction of dibromide **216** with sodium borohydride showed high chemoselectivity to furnish bromide **217** (Scheme 5.1).[184]

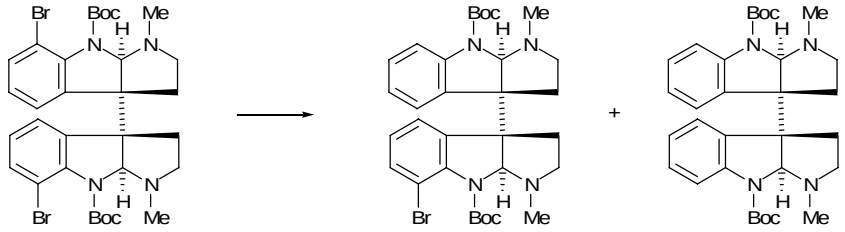


216 **217**

Scheme 5.1: *Reagents and Conditions*: dibromide **216** (1 eq.), $Pd(OAc)_2$, (5 mol%), *rac*-BINAP ***rac*-L1** (5.5 mol%), TMEDA (1.5 eq.), $NaBH_4$ (1 eq., 0.5 M in diglyme), THF, 50 °C, 24 h.

The efficiency of the *rac*-BINAP ***rac*-L1** in conjunction with sodium borohydride offers the potential for the development of conditions with chiral ligands to achieve an asymmetric reduction of achiral substrates. Therefore the reduction of bisbromide ***meso*-134** under identical racemic conditions was investigated (Table 5.2).

Table 5.2: Reduction of bisbromide *meso*-**134** with borohydride



***meso*-134** ***rac*-218** ***meso*-31**

Entry	$NaBH_4$ (eq.)	*t* (h)	*T* (°C)	Products[b]
1[a]	1.05	24	50	16% SM ***meso*-134**, 50% ***rac*-218**, 10% ***meso*-31**
2	1.1	36	50	76% SM ***meso*-134**, trace ***rac*-218**
3	2	15	65	33% SM ***meso*-134**, 63% ***rac*-218**
4	2	36	65	19% SM ***meso*-134**, 81% ***rac*-218**
5	3	24	65	unknown products

Reagents and Conditions: bisbromide ***meso*-134** (1 eq.), $Pd(OAc)_2$, (5 mol%), *rac*-BINAP ***rac*-L1** (5.5 mol%), TMEDA (1.5 eq.), $NaBH_4$ (0.5 M in diglyme), THF, Δ. [a] $NaBH_4$ solid. [b] Isolated yields.

Hydrodehalogenation of bisbromide ***meso*-134** was successfully achieved under modified conditions of those developed by Buchwald *et al*. The direct addition of sodium borohydride as a solid rather than a solution in diglyme yielded 50% of the

monobromide ***rac*-218** with 76% of the mass balance accounted for (Table 5.2, entry 1). Direct application of the published conditions achieved only trace reduction (entry 2). Increasing the reaction temperature in conjunction with an increase in hydride equivalents led to the optimal yield of 81% of monobromide ***rac*-218** after thirty-six hours with an excellent mass balance (entries 3-4). Further hydrodehalogenation of the monobromide ***rac*-218** was not observed. Increasing the hydride equivalents resulted in the complete conversion of bisbromide ***meso*-134** to unknown products (entry 5).

The asymmetric hydrodebromination of biscarbamate ***meso*-134** in 81% yield employing *rac*-BINAP ***rac*-L1** as the ligand shows a great deal of promise for the development of an asymmetric variant. Due to time constraints and the desire to investigate the viability of a direct arylation protocol, further investigations into asymmetric hydrodebromination were not conducted

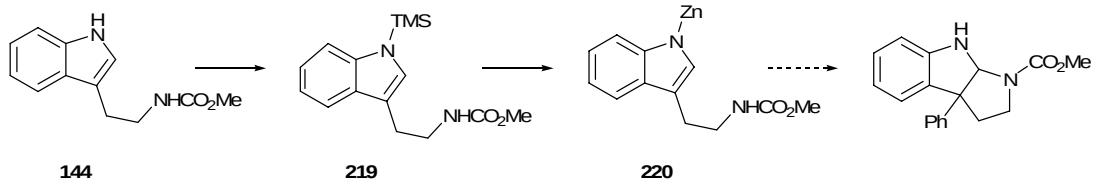
5.3. Arylation of Tryptamine Derivatives *via* Enamine Activation

Metal mediated arylation of enamines is a relatively undeveloped field, with the coupling of such substrates with stoichiometric aryl lead triacetates the only major published works.[185] The lack of development in the field is presumably due to the relatively low nucleophilicity of the enamine functionality. The development of an efficient catalyst system would therefore necessitate the preparation of a highly electrophilic metal centre or utilise an additive to increase the 'electron push' of the enamine by activation of the nitrogen atom.

We attempted to increase the nucleophilicity of *N*′-carbomethoxytryptamine **144**, based on an analogous process developed by Hartwig *et al.* for the arylation of esters and imides.[79] Carbamate **144** was protected as the trimethylsilyl derivative **219** and it was expected that, in the presence of a metal fluoride, *in-situ* cleavage of the silyl group would generate the metalated anion **220** (Scheme 5.2).

Tri-*tert*-butyl phosphine **L35** was employed with either palladium acetate or palladium bis(dibenzylidene)acetone to favour a monoligated palladium centre,

whilst dimethylformamide was chosen as solvent to allow for greater ion solvation and to create a more dissociated ion pair from the oxidative addition. Unfortunately, with zinc fluoride as additive, no arylation of carbamate **144** occurred though the yield of desilylated material was proportional to the amount of zinc fluoride employed. Therefore it can be concluded that the silyl group was cleaved as expected but the palladium centre did not exhibit sufficient electrophilicity for nucleophilic attack of the metalated enamine which was protonated on work-up.



144 **219** **220**

Scheme 5.2: *Reagents and Conditions*: carbamate **144** (1 eq.), bromobenzene 1.1 (eq.), $Pd(OAc)_2$ or $Pd(dba)_2$ (5-10 mol%), P^tBu_3 **L35** (L/Pd 2:1), ZnF (0.5-1 eq.), DMF, 80 °C.

The arylation of tryptamine derivatives of the type **144** is an extremely challenging transformation, not least due to the inherent requirement to form a quaternary carbon centre. A successful coupling with *meso*-chimonanthine derivatives would therefore not only require a chiral catalyst that could differentiate between the enantiotopic groups of the *meso* substrate but also generate the new benzylic quaternary carbon centre with the desired *R* absolute configuration.

With this in mind, and the problems associated with the asymmetric borylation and asymmetric reduction protocols, we focused on achieving a successful general C-3 arylation protocol of oxindoles with simple aryl halides which could be extended to our *meso*-chimonanthine substrates.

5.4. C-3 Arylation of Oxindoles

5.4.1. Introduction

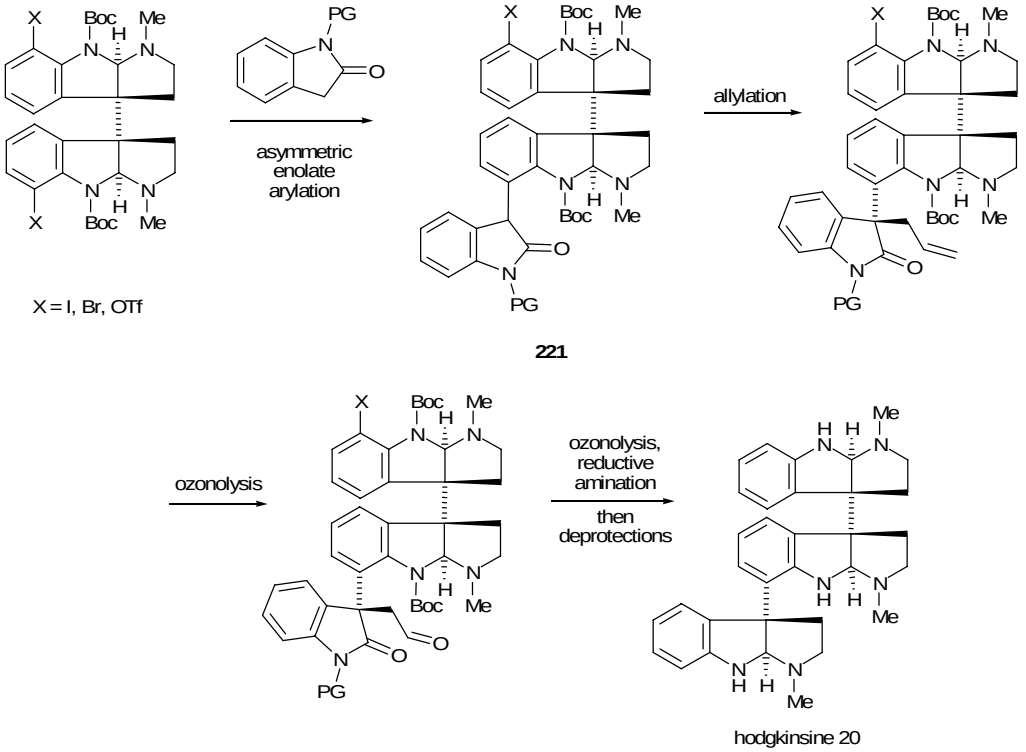
The intramolecular palladium catalysed α-arylation of substituted acyclic amides is an established protocol for the preparation of C-3 substituted oxindoles.[186] In contrast, the intermolecular variant is less well developed. Acyclic amides have been shown to be viable substrates though chemical yields are variable,[85] whilst the direct α-arylation of cyclic amides exhibits catalyst dependency on the individual amide and is limited to piperidinone substrates. Elegant work utilising transmetallation of lithium to the corresponding zinc enolates has broadened the scope of the process, however examples of the direct arylation of cyclic amides remain rare.[187]

Oxindoles, specifically those with C-3 functionalisation, represent an important motif in a number of natural products and pharmaceutical targets.[188] They display biological activity against a number of neurodegenerative disorders and exhibit anti-tumor[189] and anti-HIV properties.[190] C-3 Aryl oxindoles specifically maintain an important role in potassium channel modulation for the treatment of post-stroke patients.[191] Traditional methods for their preparation include reduction of a parent isatin, and palladium catalysed asymmetric intramolecular cyclisation. However, there remains a need for an efficient, catalytic process for direct intermolecular arylation of the C-3 position.

The arylation of amide enolates represents the most challenging of carbonyl compounds due to the high pK_a of the substrates. The development of an intermolecular palladium catalysed α-arylation of oxindoles would also have to overcome issues of substrate dependency and tolerate a broad scope of oxindole substrates and substituted arenes, particularly heteroaromatics and those with *ortho*-substitution.

Such a coupling would represent an important advance in the arylation of carbonyl compounds as well as provide a rapid route into pharmaceutically important compounds. The extension of the reaction scope from simple arenes to our *meso*-chimonanthine substrates with a chiral catalyst to achieve enantiotopic group

discrimination could intercept Trost asymmetric allylation precursor **221**, the desilylated analogue of the previously proposed allylation substrate **193** (Scheme 5.3).

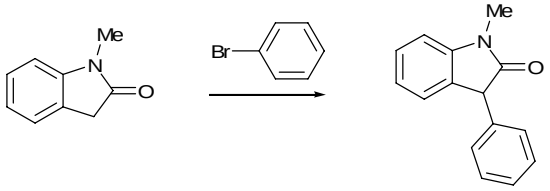


Scheme 5.3

5.4.2. Initial Investigations

We selected the coupling of *N*-methyl oxindole **222** and bromobenzene as our test system; our optimisation study is summarised in Table 5.3. Initial conditions were based on those used successfully for the α-arylation of amides, however the use of the ligands *rac*-BINAP ***rac*-L1**, P^{t}Bu$_3$ **L35**, PCy$_3$ **L33** or dppf **L64** in combination with potassium bis(trimethylsilyl)amide as base were unsuccessful (entries 1-4). We switched attention to the electron-rich biphenyl-based phosphine ligands **L29** and **L30**. A reaction employing S-Phos **L29** delivered the expected arylated product in 20% yield, however a significant improvement was achieved when the more sterically demanding X-Phos **L30** was employed and the product was isolated in 91% yield (entries 5 and 6). We also established that the equivalents of base employed could be reduced from 2.0 to 1.1 with only minimal effect on reaction efficiency (entry 7), whilst coupling did not proceed at room temperature (entry 8).

Table 5.3: Ligand screen for the arylation of oxindole enolates



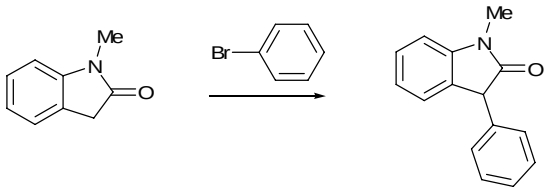
222 **223**

Entry	Base (eq.)	Ligand	Yield **223** (%)[b]
1	KHMDS (2.0)	***rac*-L1**	0
2	KHMDS (2.0)	**L35.HBF$_4$**	<2
3	KHMDS (2.0)	**L33**	0
4	KHMDS (2.0)	**L64**	0
5	KHMDS (2.0)	**L29**	20
6	KHMDS (2.0)	**L30**	91
7	KHMDS (1.1)	**L30**	90
8[a]	KHMDS (1.1)	**L30**	0

Reagents and Conditions: oxindole **222** (1 eq.), bromobenzene 1.1 (eq.), Pd(dba)$_2$ (2 mol%), ligand (3 mol%), base, THF, 70 °C, 3 h. [a] reaction performed at 25 °C. [b] Isolated yields.

Given the increased acidity of oxindoles derivatives relative to simple amides,[192] we explored the use of weaker bases (Table 5.4). However a variety of organic and inorganic alternatives were all unsuccessful and delivered only trace amounts of the product at best (entries 1-5). These observations suggested that the formation of a formal alkali metal enolate was necessary for efficient reaction. In addition to potassium, sodium enolates could also be employed, although these resulted in lower yielding reactions (entries 6 and 7). Finally, we established that the reaction time could be reduced from the initial 3 hours to only 30 minutes, with the product still being isolated in an impressive 95% yield (entry 9).

Table 5.4: Base screen for the arylation of oxindole enolates



222 **223**

Entry	Base	*t* (h)	Yield **223** (%)[a]
1	$CsCO_3$	3	-
2	K_3PO_4	3	-
3	NEt_3	3	-
4	DBU	3	trace
5	KOAc	3	trace
6	NaHMDS	3	81
7	NaH	3	44
8	KHMDS	1	90
9	KHMDS	0.5	95

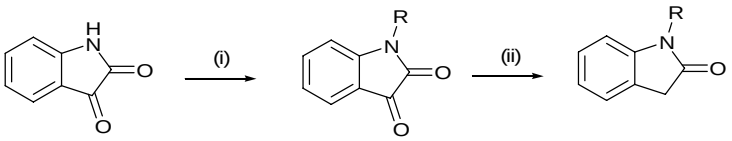
Reagents and Conditions: oxindole **222** (1 eq.), bromobenzene (1.1 eq.), Pd(dba)$_2$ (2 mol%), X-Phos **L30** (3 mol%), base (1.1 eq.), THF, 70 °C. [a] Isolated yield.

The arylation of *N*-methyl oxindole **222** with bromobenzene was also demonstrated on a 20 mmol scale (~ 3 g), providing the C-3 aryl oxindole in 85% yield in just thirty minutes.

Unfortunately, arylation of 1,3-dimethyl oxindole to prepare a quaternary carbon centre was not successful with the palladium/X-Phos **L30** catalyst system in tetrahydrofuran, returning the starting oxindole. Additionally, attempts to lower the catalyst loading from 2% to 0.2% gave no arylated product. This is due to an enforced reduction in the molarity of the reaction with respect to palladium as the lower limit of reaction volume is limited by addition of the alkali metal base as a 0.5 molar solution in toluene. The reaction proceeds optimally when tetrahydrofuran is also present, which further increases the solvent volume to palladium ratio.

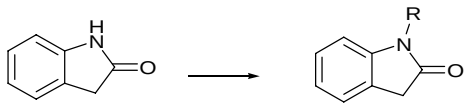
5.4.3. Expansion of Reaction Scope – Protecting Groups

With successful arylation conditions developed for *N*-methyl oxindole, we sought to extend the arylation protocol to oxindoles with an easily cleaved nitrogen protecting group. *N*-benzyl and *N*-*para*-methoxybenzyl oxindole **226**-**227** were prepared by reduction of the parent *N*-protected isatins with hydrazine monohydrate (Scheme 5.4). Acyl, pivalic and *N*-BOC derivatives **229**-**231** were prepared directly from oxindole **228** (Scheme 5.5).[193]



192 **224** R = Bn, **225** R = PMB **226** R = Bn, **227** R = PMB

Scheme 5.4: *Reagents and Conditions*: (i) isatin (1 eq.), NaH (1.05 eq.), 0 °C, DMF, 30 min then alkyl bromide (1.2 eq.), 45 min; (ii) $N_2H_4.H_2O$ neat, reflux.

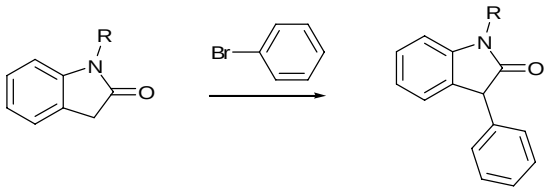


228 **229** R = Boc, **230** R = Piv, **231** R = Ac

Scheme 5.5: *Reagents and Conditions*: oxindole **228** (1 eq.), anhydride (2.5 eq.), DMAP (cat.), Na_2CO_3, THF, 70 °C, reflux.

Investigation of the nitrogen protecting group gave mixed results (Table 5.5). Electron-rich groups reacted faster than electron-poor. *N*-Methyl and *N*-benzyl oxindole performed well, though *para*-methoxybenzyl oxindole gave no arylated product; all starting material was rapidly consumed to an intractable mixture, possibly due to the enolate being too unstable (entries 1-3). Electron-withdrawing groups were less successful; *N*-BOC-oxindole proved applicable to the conditions, whilst the pivolyl protected substrate suffered from competing deprotection (entries 4-5). The acyl group was unstable under the strong basic conditions and deprotected fully, presumably *via* deprotonation of the terminal methyl group (entry 6). Arylation of the free *N*-H compound, employing two equivalents of base, was unsuccessful (entry 7). A precipitate formed during the reaction, likely to be the oxindole potassium salt.

Table 5.5: Protecting group screen for the arylation of oxindole enolates



Entry	R	Yield (%)[a]
1	Me **222**	95
2	Benzyl **226**	91
3	PMB **227**	-
4	Boc **228**	60
5	Pivolyl **230**	34
6	Acyl **231**	-
7[a]	H **228**	-

Reagents and Conditions: oxindole (1 eq.), bromobenzene (1.1 eq.), $Pd(dba)_2$ (2 mol%), X-Phos **L30** (3 mol%), KHMDS (1.1 eq.), THF, 70 °C. [a] Isolated yields.

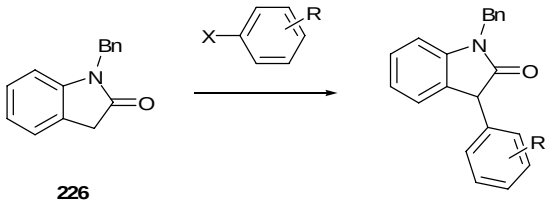
5.4.4. Expansion of Reaction Scope – Arenes

We next explored variation in both the oxindole and aryl halide coupling partners (Table 5.6). *N*-Benzyl oxindole **226** was used as the standard oxindole substrate: As well as aryl bromides, both aryl chlorides and aryl triflates are also effective substrates (entries 1-2). Functionalisation of the aryl halide is tolerated well; both electron-rich and electron-poor groups can be accommodated, and substituents *ortho*, *meta* or *para* to the halide group can all be included (entries 3-12). When both

bromo- and chloro-substituents were present in the arene, selective reaction at the bromo-substituent was always observed (entries 13 and 14). It is notable that this selectivity was preserved when 2-MeO-5-Cl-bromobenzene, which features a hindered bromo-substituent, was employed as a substrate, allowing the efficient introduction of the 2-MeO-5-Cl-arene unit found in the biologically active compound MaxiPost (entry 15). Competition between a triflate and a chloro group resulted in selective functionalisation of the triflate substituent (entry 16).

Unfortunately, cyano and nitro substitution of the aryl halide was not tolerated under the strongly basic conditions whilst aldehyde derivatives gave the expected complex mixture of products due to the potential for aldol condensation with the oxindole enolate (entries 17-19). Heteroaromatic bromides did not perform well; 3-bromo-thiophene gave the arylated oxindole in low yield while 3-bromo-indole failed to couple (entries 20 and 21).

Table 5.6: Arene scope in the arylation of oxindole enolates



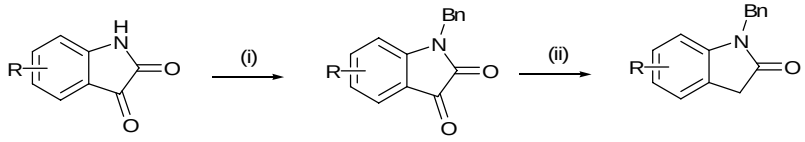
226

Entry	Arene	Yield (%)[a]
1	Cl-C_6H_5	70
2	TfO-C_6H_5	85
3	1-Br-4-^{t}Bu-C_6H_4	79
4	1-Br-4-MeO-C_6H_4	85
5	1-Cl-4-MeO-C_6H_4	70
6	1-Br-4-F_3C-C_6H_4	80
7	1-Cl-4-F_3C-C_6H_4	66
8	1-Br-3-Me-C_6H_4	77
9	1-Br-3-MeO-C_6H_4	85
10	1-Br-2-Me-C_6H_4	74
11	1-Cl-2-Me-C_6H_4	60
12	1-Br-naphthyl	80
13	1-Br-4-Cl-C_6H_4	70[b]
14	1-Br-3-Cl-C_6H_4	73[b]
15	1-Br-2-MeO-5-Cl-C_6H_3	77[b]
16	1-Cl-4-TfO-C_6H_4	70[c]
17	1-Br-4-CN-C_6H_4	0
18	1-Br-4-NO_2-C_6H_4	0
19	2-Br-benzaldehyde	
20	3-Br-thiophene	20
21	3-Br-*N*-Bn-indole	0

Reagents and Conditions; oxindole **226** (1.0 equiv.), arene (1.1 equiv), $Pd(dba)_2$ (2 mol%), X-Phos **L30** (3 mol%), KHMDS (1.1 equiv), THF, 70 °C, 30 mins. [a] Isolated yields. [b] Product from coupling at Br-substituent. [c] Product from coupling at TfO-substituent.

5.4.5. Expansion of Reaction Scope – Oxindole Substitution

Employing *N*-benzyl protected oxindoles, we sought to investigate the versatility of the oxindole substrates. The substituted oxindoles **242**-**246** were prepared by reduction of the parent *N*-benzyl isatins **237**-**241**, all in good yield (Scheme 5.6).[162]



232 R = 5,7-dimethyl
233 R = 5-OMe
234 R = 6-Cl
235 R = 5-Cl
236 R = 4-Cl

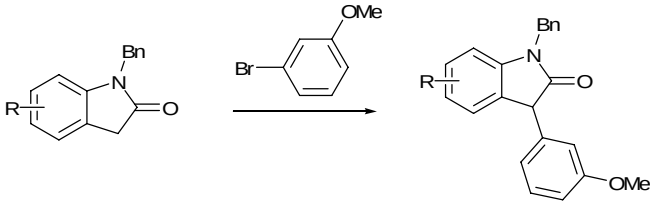
237 R = 5,7-dimethyl, 86%
238 R = 5-OMe, 92%
239 R = 6-Cl, 80%
240 R = 5-Cl, 92%
241 R = 4-Cl, 84%

242 R = 5,7-dimethyl, 66%
243 R = 5-OMe, 62%
244 R = 6-Cl, 46%
245 R = 5-Cl, 70%
246 R = 4-Cl, 69%

Scheme 5.6: *Reagents and Conditions*: (i) isatin (1 eq.), NaH (1.05 eq.), 0 °C, DMF, 30 min then alkyl bromide (1.2 eq.), 45 min; (ii) $N_2H_4.H_2O$ neat, reflux.

Dialkyl and electron-rich oxindoles **242** and **243** coupled with similar efficiency to unsubstituted oxindoles though yields were slightly lower in comparison (Table 5.7, entries 1 and 2). It is possible to retain a synthetically useful aryl chloride group on the oxindole during the coupling process, utilising the previously observed catalyst selectivity for bromo over chloro, though slightly extended reaction times were required (entries 3-5).

Table 5.7: Oxindole backbone substitution in enolate arylation

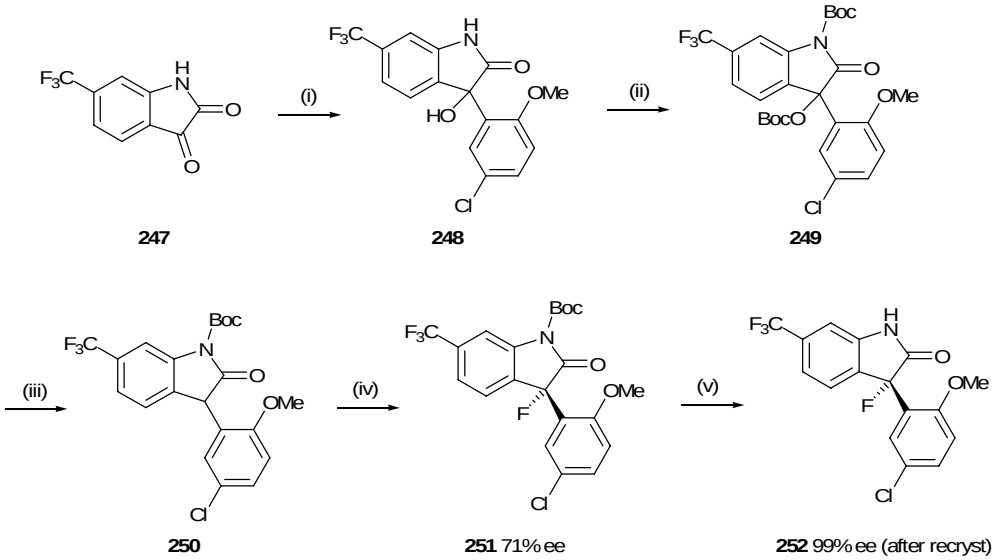


Entry	Oxindole	Yield (%)[a]
1	5,7-dimethyl **242**	67
2	5-OMe **243**	76
3	6-Cl **244**	70
4	5-Cl **245**	66
5	4-Cl **246**	61

Reagents and Conditions: oxindole (1.0 equiv.), arene (1.1 equiv), $Pd(dba)_2$ (2 mol%), X-Phos **L30** (3 mol%), KHMDS (1.1 equiv), THF, 70 °C, 30 min. [a] Isolated yields.

5.4.6. Synthesis of a MaxiPost Intermediate

MaxiPost **252** is a potent potassium channel regulator. and potential treatment for post stroke patients. A modern synthesis of MaxiPost **252** involves enantioselective fluorination of the C-3 aryl species **250**, which itself is prepared by nucleophilic addition of the Grignard derivative of 2-MeO-5-Cl-bromobenzene to isatin **247**, with subsequent di-BOC protection and C-3 reduction (Scheme 5.7).[194]

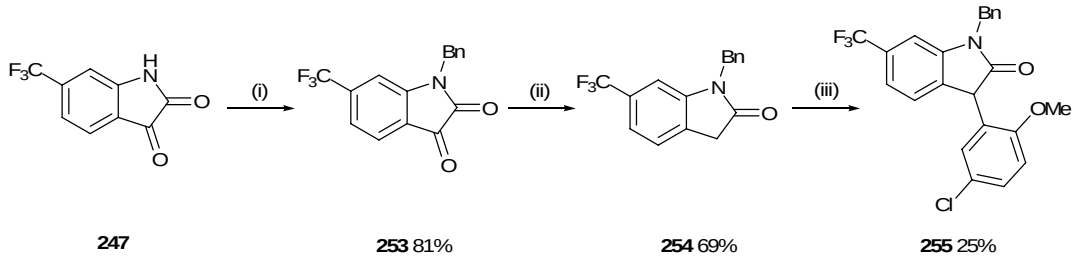


Scheme 5.7: *Reagents and Conditions*: (i) isatin **247** (1 eq.), aryl-MgBr (2 eq.), THF, -40 °C; (ii) $(Boc)_2O$ (2 eq.), DMAP (0.1 eq.), DCM; (iii) $Pd(OH)_2$, H_2, MeOH-EtOAc; (iv) $[PdOH((S)$-DM-BINAP) **(*S*)-L3**$]_2$ (2.5 mol%), NFSI (1.5 eq.), acetone, 0 °C; (v) TFA, DCM.

Having previously demonstrated the preferential bromo coupling of 2-MeO-5-Cl-bromobenzene with *N*-benzyl oxindole, we proposed to achieve direct arylation of an *N*-protected 6-CF_3 oxindole **254** with the same arene. The product would intercept enantioselective fluorination substrate **250** and from which the fluorination product could be deprotected to furnish MaxiPost **252**.[194]

Attempts to prepare the *N*-BOC-6-CF_3-oxindole were unsuccessful, by direct *N*-BOC protection of the free oxindole with triethylamine/DMAP or protection and subsequent reduction of the corresponding isatin. Synthesis of the *N*-benzylated derivative was more encouraging. Accordingly, 6-CF_3 isatin **247** was benzylated under standard conditions to give isatin **253** which was subsequently reduced to give oxindole **254**, both steps in good yield (Scheme 5.8). Arylation under the established conditions proceeded to give the desired C-3 aryl oxindole **255** in a poor yield of

25%, though all starting material was consumed. It was noticeable that upon addition of the base at 70 °C the mixture turned purple, a feature not observed with previous oxindole substrates. This alternative reaction was attributed to the trifluoromethyl group of the oxindole and represented an inherent reactivity issue with this particular oxindole substrate under the established conditions. The synthesis of MaxiPost **252** is beyond the aims of this project therefore we did not optimise the arylation of oxindole **254**.



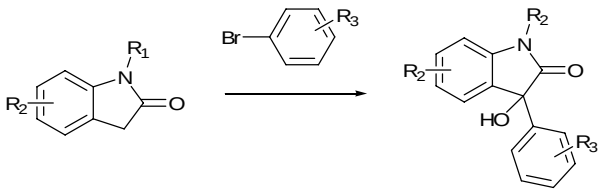
247 **253** 81% **254** 69% **255** 25%

Scheme 5.8: *Reagents and Conditions*: (i) isatin **247** (1 eq.), NaH (1.05 eq.), 0 °C, DMF, 30 min then BnBr (1.2 eq.), 45 min; (ii) $N_2H_4.H_2O$ neat, reflux; (iii) arene (1.1 equiv), $Pd(dba)_2$ (2 mol%), X-Phos **L30** (3 mol%), KHMDS (1.1 equiv), THF, 70 °C, 30 mins.

5.4.7. Arylation-hydroxylation

When originally exploring the conditions needed to achieve smooth α-arylation reactions we observed small amounts of products resulting from α-oxidation of the arylated compounds. This was conveniently remedied by the use of de-gassed solvents. If the C-3 oxidised compounds were the desired products they could be isolated in excellent yield by conducting the arylation as normal, followed by opening the reaction flask to air for an additonal five minutes (Table 5.8).

Table 5.8: Arylation-hydroxylation of oxindole derivatives



Entry	R_1	R_2	R_3	Yield (%)[a]
1	Me	H	4-OMe	97
2	Bn	5,7-dimethyl	3-OMe	94
3	Bn	7-Cl	3-OMe	89

Reagents and Conditions; oxindole (1.0 equiv.), arene (1.1 equiv), $Pd(dba)_2$ (2 mol%), X-Phos **L30** (3 mol%), KHMDS (1.1 equiv), THF, 70 °C, 30 mins then open to air 5 mins. [a] Isolated yields.

The origin of the oxidation process of the aryl oxindoles could not be precisely determined. Control reactions with *N*-methyl-3-phenyloxindole showed partial oxidation in the individual presence of the alkali metal base, bis(trimethylsilyl)amine, palladium source and the palladium source with X-Phos **L30**. It is therefore likely that a combination of mechanisms achieve the observed oxidation as air oxidation of alkali metal enolates and C-3 oxidation of oxindole in the presence of a palladium catalyst have been separately reported.[195, 196]

5.5. Conclusions

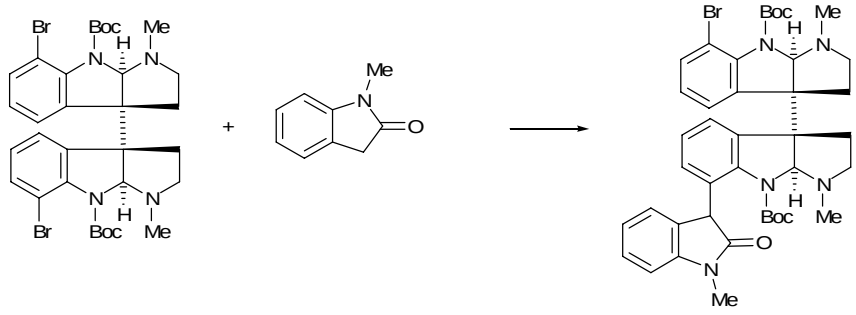
We have successfully demonstrated a versatile palladium catalysed C-3 arylation protocol of a variety of *N*-protected oxindoles. A range of electron-rich and electron-poor bromides, chlorides and triflates with *ortho*, *meta* and *para* substitution can be employed with a catalyst formed from palladium bis(dibenzylidene)acetone and the electron-rich monodentate biphenyl X-Phos **L30**. Substitution of the oxindole ring is also well tolerated, and the arylation proceeds well at larger scales with no loss of reaction rate. Extension of the reaction methodology provides biologically active C-3 aryl-hydroxy oxindoles in excellent yield by exposure of the arylation mixture to air to allow *in-situ* oxidation.

6. C-3 Arylation of Oxindoles with *meso*-Chimonanthine Substrates

6.1.1. Arylations

Having successfully developed an efficient C-3 oxindole arylation protocol which tolerates *ortho*-substitution, we sought to extend the coupling to our *meso*-chimonanthine derivatives. Therefore, investigations into the racemic coupling of bisbromide ***meso*-134** with *N*-methyl oxindole **222** were conducted (Table 6.1).

Table 6.1: Screen of conditions for the arylation of oxindoles with bisbromide *meso*-**134**



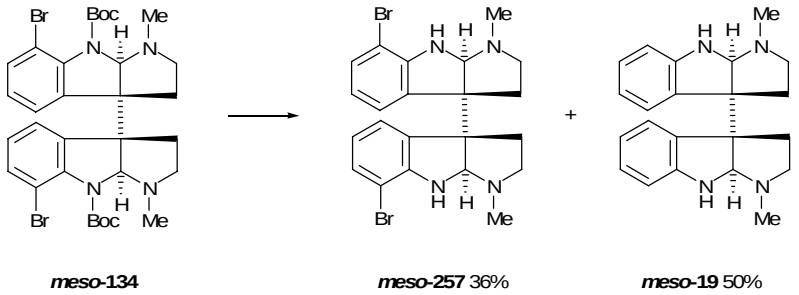
***meso*-134** **222** ***rac*-256**

Entry	Pd (mol %)	Ligand (mol%)	T (°C)	Products
1	2	**L30** (3)	70	SM, ***meso*-134**
2	10	**L30** (15)	90	SM, ***meso*-134**
3	5	***rac*-L1** (7.5)	70	SM, ***meso*-134**
4	5	**L29** (7.5)	70	SM, ***meso*-134**
5	5	**L31** (7.5)	70	SM, ***meso*-134**

Reagents and Conditions: bisbromide ***meso*-134** (1.0 equiv.), oxindole **222** (1.1 equiv), $Pd(dba)_2$, ligand (L:Pd 1.5:1), KHMDS (1.1 equiv), THF, 70 °C, 30 mins. SM = starting material.

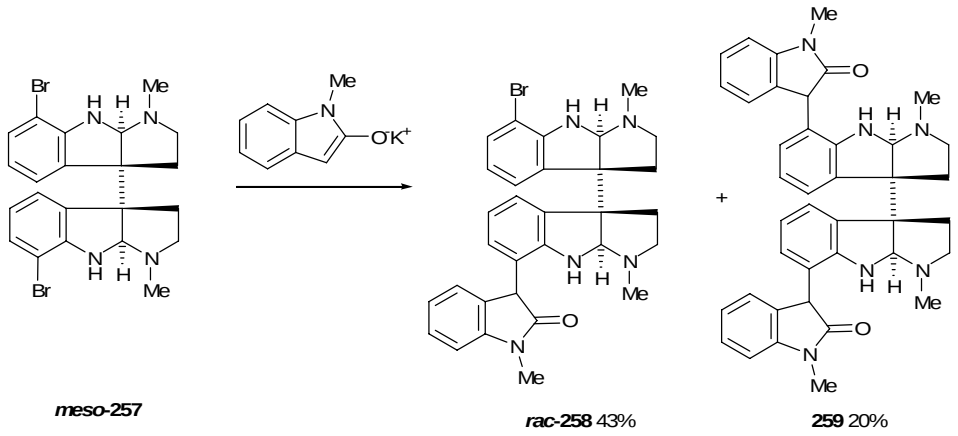
With the *N*-protected bisbromide ***meso*-134** no coupling was achieved despite increased catalyst loadings, elevated temperatures and variation of the ligand. Starting material was returned quantitatively and no hydrodehalogenation was observed. With the previous success of simple arenes under the same catalyst system, we proposed that again steric interactions of the *ortho N*-BOC protecting group were inhibiting the coupling rather than slow oxidative addition to the aryl halide. Therefore the free amine derivative bisamine ***meso*-257** was prepared in analogous fashion to the iodide derivative by deprotection with trimethylsilyl triflate (Scheme 6.1). Bisamine ***meso*-257** was prepared in a disappointing 36% yield, with

competing hydrodebromination a major side reaction giving *meso*-chimonanthine ***meso*-19** in 50% yield.



Scheme 6.1: *Reagents and Conditions*: TMS-OTf (4.4 eq.), DCM, 8 h, r.t.

With bisamine ***meso*-257** in hand, the arylation of *N*-methyl oxindole **22** was attempted (Scheme 6.2). Initially, the free amine moieties were protected as the sodium salt by deprotonation with sodium hydride at 70 °C in tetrahydrofuran. The solvent was evaporated under positive argon pressure to ensure no solvated hydrogen would be present when the palladium was added which could promote hydrodehalogenation. Subsequently, the palladium catalyst, X-Phos **L30** and redistilled tetrahydrofuran were added consecutively and heated to 70 °C at which point a tetrahydrofuran solution of the potassium enolate of *N*-methyl oxindole was added in one portion. After twenty minutes the reaction was quenched with saturated ammonium chloride solution.



Scheme 6.2: *Reagents and Conditions*: oxindole **222** (1.0 equiv.), bisamine ***meso*-257** (2.0 equiv), NaH (4.05 eq.), $Pd(dba)_2$ (2 mol%), X-Phos **L30** (3 mol%), KHMDS (1.1 equiv), THF, 70 °C.

The coupling of bisamine ***meso*-257** with *N*-methyl oxindole proceeded well under the racemic catalyst conditions developed previously to give the desired desymmetrised product ***rac*-258** in 43% yield based on the oxindole, with the dicoupled product **259** observed in 20% yield. The preparation of the sodium salt of

the chimonanthine substrate appears to be vital to achieving a successful coupling as steric interactions are greatly reduced and allowing for rapid catalyst turnover with the limiting oxindole reagent fully consumed in twenty minutes.

The mono and dicoupled products proved difficult to separate and were identified primarily by mass spectrometry and infra-red analysis. NMR spectroscopic analysis was inconclusive even when conducted at 100 °C. The spectra for both the mono and dicoupled products were complicated by the presence of severe rotameric effects and diastereomers at the C-3 position of the oxindole moiety and as such could not be used as an analytical tool in these instances (Appendix B).

6.1.2. Summary

Preliminary investigations into the arylation of oxindoles with the more sterically hindered biscarbamate ***meso*-134** derivative did not proceed, returning starting material in each instance. Employing the sodium salt of bisamine ***meso*-257**, successful unification with *N*-methyl oxindole **222** was achieved, providing the monoarylated product ***rac*-258** in 43% yield and the diarylated product **259** in 20% yield. This represents an 83% conversion based on the oxindole as the limiting reagent. Analysis of the desymmetrised products is heavily dependent of mass spectrometry, due to highly complicated NMR spectra.

7. Summary and Conclusions

Our initial proposals to prepare the C-3/C-7 bond of hodgkinsine **20** focused on developing an enantioselective Suzuki coupling between a C-7 functionalised *meso*-chimonanthine core and a C-3 boryl indole derivative. Preliminary model Suzuki couplings indicated *ortho*-substitution of an aryl halide was tolerated therefore the appropriate C-7 functionalised *meso*-chimonanthine substrates were prepared by directed *ortho*-lithiation with quenching by an appropriate electrophile. Bisiodide ***meso*-133**, bisbromide ***meso*-134** and bistriflate ***meso*-135** were prepared reproducibly in 62%, 44% and 57% yields respectively from *meso*-chimonanthine ***meso*-19**.

The indole coupling partner was difficult to prepare, with facile protodeboronation of the *N*-BOC boronic acid and *N*-BUS boronic ester continually observed. This prompted investigations into viability of the proposed indole elaboration protocol. It was quickly established that the latent enamine moiety of a 3-phenylindole core was not of sufficient nucleophilicity to achieve an intermolecular alkylation with aziridines or cyclic sulfamidites and sulfamidates. It was concluded the lack of reactivity was due to a combination of steric interactions and increased conjugation of the indole double bond with the C-3 phenyl moiety. Subsequently, the highly functionalised boronic ester **200**, which exhibits stronger electron push by a latent enolate functionality, was synthesised in an excellent 44% yield over six steps from isatin.

Unfortunately, under a broad range of conditions, Suzuki coupling of boronic ester **200** with *meso*-chimonanthine derivatives was not achieved. The failure to achieve coupling and the accompanying extensive decomposition of the ester was attributed to a highly unfavourable transmetallation step of the boronate due to extensive steric interactions, particularly of the silyl enol ether moiety in boronic ester. Attempts to synthesise less sterically encumbered boronic esters were also unsuccessful.

The repeated problems with steric interactions in the investigated Suzuki couplings led us to consider other potential palladium catalysed processes for the synthesis of

the C-3/C-7 bond. Borylation of the *meso* coupling partner or a hydrodebromination protocol showed promise, however we focused on the enolate arylation of oxindoles which would allow for a Trost allylation protocol as the second key transformation in a total synthesis of hodgkinsine **20**.

Therefore a new approach to the construction of the C-3a/C-7 bond of hodgkinsine **20** has been developed with the optimisation of a novel palladium catalysed protocol for the C-3 arylation of oxindoles; aryl bromides, chlorides and triflates are all suitable coupling partners, whilst a broad range of *ortho*, *meta* and *para* functionalised arenes are well tolerated providing C-3 aryl oxindoles in high yield.

Preliminary extension of the reaction to the racemic C-3 arylation of *N*-methyl oxindole **222** with biscarbamate ***meso*-134** again demonstrated the detrimental effects of steric interactions of the carbamate moiety. Deprotection of biscarbamate ***meso*-134** to bisamine ***meso*-257** and subsequent arylation under the standard conditions gave successful arylation of the oxindole enolate, providing the desired monoarylated product ***rac*-258** in 43% yield with the diarylated product **259** furnished in 20% yield, thus achieving 83% conversion of the limiting oxindole reagent. This result provides great encouragement for the development of an enantioselective variant by achieving enantiotopic group discrimination of the *meso* substrate.

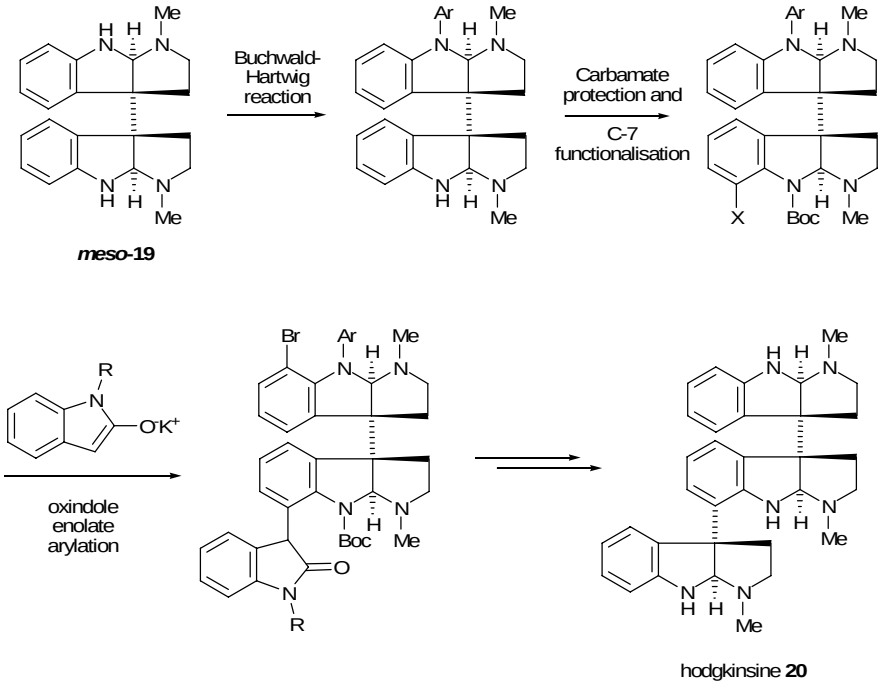
8. Future Work

The success of preliminary investigations into the arylation of oxindoles with bisamine ***meso*-257** provides great optimism for the future enantioselective total synthesis of hodgkinsine **20**. Synthetic development should focus on the optimisation of this arylation protocol, either with bisamine ***meso*-257** or novel *meso* chimonanthine derivatives exhibiting smaller *N*-8 protecting moieties such as formyl or trifluoromethyl acetyl groups. Such groups also maintain a directing effect for an *ortho*-lithiation procedure and therefore may be introduced at an early stage of the synthesis.

The potential for variation of the arylation partners is vast. The nature of the protecting groups of both substrates is crucial, particularly as we wish to consider a global deprotection strategy to minimise the number of synthetic steps. The nature of C-7 functionalisation of the *meso*-chimonanthine substrate may also play a part in the activity of the palladium catalyst by virtue of counter-ion effects therefore as well as our initial demonstration of bromide coupling, iodides, triflates and even chlorides warrant further investigation.

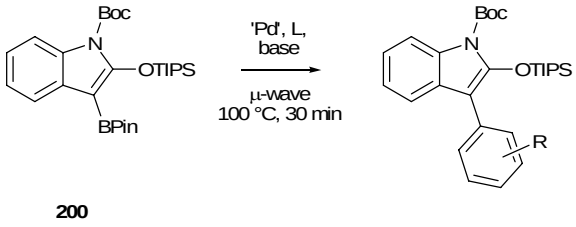
To ultimately achieve the synthesis in an enantioselective fashion, the arylation conditions must be extended from the currently utilised biphenyl X-Phos **L30** to employ a chiral ligand for enantiotopic discrimination of the *meso*-chimonanthine substrate. Initial investigations into this area should focus on binaphthyl monophosphines of the type developed by Hiyashi bearing C-2′ alkyl substitution.[197]

An alternative synthetic route could involve an asymmetric protection strategy of *meso*-chimonanthine ***meso*-19**, whereby enantiotopic selection of the free amine moieties would allow for preferential arylation by a Buchwald-Hartwig reaction protocol.[198] Subsequently, the residual free amine moiety could be protected as the carbamate to allow for C-7 functionalisation and arylation of an oxindole enolate, from which elaboration to hodgkinsine **20** would follow the allylation/ozonolysis/reductive-amination sequence described previously (Scheme 8.1).



Scheme 8.1

Additionally, the borylation and hydrodebromination protocols that were shown to be viable in preliminary investigations could be investigated more thoroughly whilst the recent discovery in our group of the Suzuki coupling of boronic ester **200** under microwave conditions certainly warrants further investigation (Scheme 8.2). Examples of such heavily *ortho*-substituted substrates in Suzuki chemistry are rare and its development would represent an important advance in the field.[199]



Scheme 8.2

Overall, it is clear that whilst we have demonstrated the potential of an oxindole enolate arylation protocol for our proposed total synthesis, there is still a great deal of research required to make an efficient synthesis of hodgkinsine **20** a reality.

9. Experimental

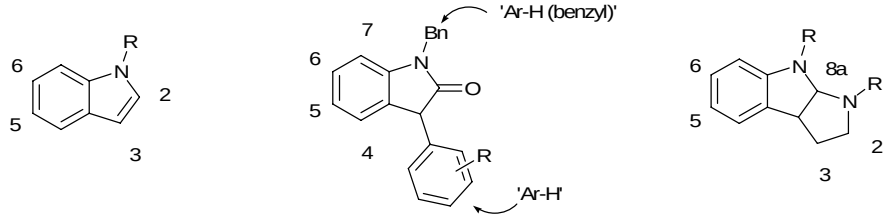
9.1. General Information

Experiments were conducted at the University of Oxford unless otherwise stated.
* denotes experiments conducted at the University of Bath.

Reactions were conducted with continuous magnetic stirring under an inert nitrogen or argon atmosphere with dry solvents unless otherwise stated. Nitrogen and argon were passed through a Drierite® filled drying tube before use. Glassware was either oven-dried at >200 °C or dried employing a heat-gun, and allowed to cool to room temperature under a positive nitrogen pressure or vacuum. Cooling of reaction vessels to 0 °C was achieved by an ice-water slush bath, cooling to -78 °C was achieved by a dry ice-acetone bath and cooling to -100 °C was achieved by a dry ice-diethyl ether-N_2(l) bath.

Reagents were purchased from Sigma-Aldrich Chemical Co. Ltd., Acros Organics Ltd, Avocado, Fluorochem or Lancaster Synthesis Ltd. and used as supplied. The following chemicals were distilled prior to use: pyridine (dist. KOH), triethylamine (dist. and stored over KOH), *N,N,N′,N′*-tetramethylethylenediamine (dist. sodium), dioxane (dist. Na/benzophenone), methanol (dist. magnesium), ethanol (dist. magnesium), *tert*-butanol (dist. magnesium), dimethyl sulfoxide (dist. calcium hydride).

Compounds are characterised in a uniform manner herein. Numbers, according to IUPAC nomenclature, are utilised to assign the structural core of indoles, oxindoles and pyrrolidinoindolines where possible/required, with the aid of 2D NMR spectroscopy techniques.



9.1.1. General Information for Experiments Conducted at the University of Oxford

Dry dimethylformamide was purchased from Romil and stored as received over molecular sieves. Tetrahydrofuran, purchased from Rathburn (HPLC grade), was distilled from Na/benzophenone and stored over 4Å molecular sieves prior to use. Diethyl ether, dichloromethane and toluene were collected fresh from an Innovative Technology Inc. PS-400-7 solvent purification system having been passed through anhydrous alumina columns.

Reactions were monitored by TLC until deemed complete using aluminium backed silica plates (Merck Kieselgel 60 F_{254}). Plates were visualised under ultraviolet light (254 nm) and/or by staining with $KMnO_4$, vanillin or ceric ammonium molybdate (CAM). Flash column chromatography was carried out using Zeochem ZEOprep hyd. 40-63 micron silica with pre-absorption of the crude product onto silica. Pressure was applied at the column head *via* hand bellows.

^{1}H, ^{13}C, ^{11}B and ^{19}F nuclear magnetic resonance experiments were carried out using Bruker DPX-200, DPX-250, DQX-400 or AVC-500 MHz NMR spectrometers. Chemical shifts were reported in parts per million from the residual solvent peak. Chemical shifts (δ) are given in parts per million (ppm) and coupling constants (*J*) in Hertz (Hz). Proton multiplicity is assigned using the following abbreviations: singlet (s), doublet (d), triplet (t), quartet (q), septet (sep), multiplet (m), broad (br), apparent (app.), overlapping (o) and aryl (Ar). Where required, proton assignment was achieved using 2D NMR spectroscopy techniques, predominantly COSY and HMQC spectroscopy.

Melting points were determined using a Leica Galen III hot-stage microscope and are reported uncorrected. Infrared measurements were carried out as a thin film on a NaCl disc using a Bruker Tensor 27 FT-IR with internal calibration in the range 4000-600 cm^{-1}. Accurate mass measurements were carried out on a Bruker MicroTOF mass spectrometer by the internal service at the Department of Organic Chemistry, University of Oxford.

9.1.2. General Information for Experiments Conducted at the University of Bath

Anhydrous dichloromethane, tetrahydrofuran, diethyl ether, toluene and acetonitrile were collected fresh from an Innovative Technologies 'Grubbs Apparatus' solvent purification system.[200] All water was previously distilled. Where necessary, deoxygenated solvents were purged with nitrogen prior to use. 'Petrol' refers to petroleum ether fraction in the boiling range 40-60 °C. 4Å molecular sieves were activated by drying in an oven at >150°C, powdered molecular sieves were activated by heating with a heat gun for 5 minutes.

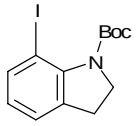
Reactions were followed by thin layer chromatography (TLC) which was performed using commercially available Merck or Macherey-Nagel aluminium backed plates coated with a 0.20 mm layer of silica gel 60 with fluorescent indicator UV_{254}. These plates were visualised with UV light of 254 nm and stained using potassium permanganate, vanillin or ceric ammonium molybdate (CAM) as appropriate. Flash column chromatography was carried out using Davisil LC 60Å silica gel (35-70 μm) purchased from Fluorochem. Samples were pre-absorbed on silica unless soluble in an appropriately minimal quantity of the eluent. Pressure was applied at the column head *via* hand bellows.

^{1}H and ^{13}C NMR spectra were recorded as dilute solutions on either a Bruker Avance 400 spectrometer (at 400.1 and 100.6 MHz respectively) or a Bruker Avance AC-300 spectrometer (300.2 and 75.5 MHz respectively) in $CDCl_3$ or $(CD_3)_2SO$ with tetramethylsilane (TMS) (δ_H 0 ppm) and/or the residual solvent as internal standards. ^{11}B NMR spectra were recorded on a Bruker Avance AC-300 spectrometer (at 96.3 MHz) with $BF_3{\cdot}OEt_2$ as an external standard. Proton multiplicities were assigned as previously described (page 120).

Capillary melting points were determined on a Buchi 535 melting point apparatus. Readings were taken from an in-glass mercury thermometer and reported un-corrected as the meniscus point, rounded to the nearest 1 °C. Infra-red spectra were recorded on a Perkin-Elmer 1600 Series FT-IR spectrometer with an internal background calibration in the range 4000-600 cm^{-1} using KBr discs (KBr disc). Mass

spectroscopy, including high resolution spectra, were recorded by the EPSRC National Mass Spectrometry Service Centre, Swansea, using either electron impact (EI), chemical ionisation (CI) or electrospray (ES) techniques. Analyses were performed in positive ionisation mode. For low resolution measurements ammonia was used as the CI reagent gas on a Micromass Quantro II triple quadrupole. Elemental analyses were performed by the microanalysis service at the Department of Chemistry at the University of Bath, using an Exeter Analytical Inc CE-440 elemental analyser.

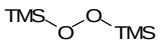
tert-Butyl 7-iodoindoline-1-carboxylate, 134[124] *



134

sec-Butyllithium (1.3 M in cyclohexane, 1.37 mL, 1.78 mmol) was added dropwise to a stirred solution of *N*-BOC-indoline **133** (300 mg, 1.48 mmol) and *N,N,N′,N′*-tetramethylethylenediamine (0.30 mL, 2.00 mmol) in diethyl ether (5 mL) at -78 °C. After 1 h a solution of diiodoethane (1.13 g, 4.45 mmol) in diethyl ether (10 mL) was added dropwise. After a further 15 minutes the reaction was warmed to 0 °C for 1 h. The reaction was quenched with saturated sodium thiosulphate (10 mL) and diluted with water (5 mL). The phases were separated and the aqueous phase extracted with diethyl ether (3 × 10 mL). The combined organic phases were dried ($MgSO_4$) and reduced *in vacuo*. Purification by flash column chromatography (SiO_2, petrol/diethyl ether 10 : 1) gave 7-iodo-*N*-BOC-indoline **134** (286 mg, 79%) as a white crystalline powder; ν_{max} (KBr disc)/cm^{-1} 3005, 2971, 2923, 1709 (C=O), 1639, 1442, 1359, 1333, 1312, 1243, 1165, 1033, 858, 761; ^{1}H NMR (300 MHz, $CDCl_3$) 7.64 (1H, dd, *J* 7.8 and 1.0, H-6), 7.16 (1H, dd, *J* 7.6 and 1.0, H-4), 6.74 (1H, dd, *J* 7.8 and 7.6, H-5), 4.10 (2H, t, *J* 7.6, 2 × H-2), 3.05 (2H, t, *J* 7.6, 2 × H-3), 1.56 (9H, s, $C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 153.5, 146.8, 138.6, 137.1, 126.2, 124.6, 85.9, 82.0, 51.8, 30.9, 28.8. Data consistent with the literature.[124]

Peroxybis(trimethylsilane), 139[126] *

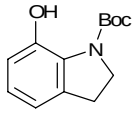


139

Bistrimethylsilyl urea (4.86 g, 21.3 mmol) and urea hydrogen peroxide complex (2 g, 21.3 mmol) were heated to reflux in dichloromethane (20 mL) for 12 h. After cooling to room temperature all volatiles were distilled over into a dry ice trap under reduced pressure. The volatiles collected were transferred to a pear flask and dichloromethane distilled off through a short Vigreux column at atmospheric pressure. Finally, distillation (48 °C at 50 mmHg) into a dry ice trap, again through a short Vigreux column, gave trimethylsilyl peroxide **139** as a colourless oil (1.70 g,

45%); ^{1}H NMR (400 MHz, $CDCl_3$) 0.19 (18H, s, 2 × (Si(CH_3)$_3$)); ^{13}C NMR (100 MHz, $CDCl_3$) -1.29. Data consistent with the literature.[126]

***tert*-Butyl 7-hydroxyindoline-1-carboxylate, 137 ***



137

sec-Butyllithium (1.4 M in cyclohexane, 0.65 mL, 0.91 mmol) was added dropwise to a stirred solution of *N*-BOC-indoline **133** (200 mg, 0.91 mmol) and *N,N,N,N*-tetramethylethylenediamine (0.19 mL, 1.23 mmol) in diethyl ether (5 mL) at -78 °C. After 1 h trimethylsilyl peroxide (185 mg, 1.04 mmol) was added dropwise, and the reaction stirred at -78 °C for 30 minutes before warming to room temperature for 2.5 h. After quenching with saturated ammonium chloride (10 mL), the phases were separated and the aqueous phase extracted with diethyl ether (3 × 10 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and reduced *in vacuo*. Purification by flash column chromatography (SiO_2, dichloromethane/petrol 1 : 1) gave 7-hydroxy-*N*-BOC-indoline **137** (160 mg, 75%) as a white powder; ν_{max} (KBr disc)/cm^{-1} 3436 (OH), 2978, 2864, 1657 (C=O), 1598, 1483, 1350, 1261, 1164, 1028, 774; ^{1}H NMR (300 MHz, $CDCl_3$) 11.10 (1H, br s, OH, D_2O exchangeable), 6.92 (1H, dd, *J* 7.8 and 7.5, H-5), 6.77 (1H, d, *J* 7.8, H-4), 6.66 (1H, d, *J* 7.5, H-6), 3.96 (2H, t, *J* 8.5, 2 × H-2), 3.05 (2H, t, *J* 8.5, 2 × H-3), 1.54 (9H, s, C(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 154.3, 145.2, 133.7, 127.8, 125.6, 117.2, 115.8, 82.7, 48.7, 28.3, 28.1; *m/z* LRMS (EI$^+$) 179.0 (20%, [*M* - ^{t}Bu + H]$^+$), 134.0 (80%, [*M* – $CO_2{}^t$Bu]$^+$); HRMS (ESI$^+$, [*M* + H]$^+$) $C_{13}H_{18}NO_3$ requires 236.1282, found 236.1281.

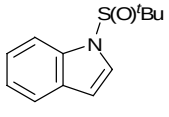
General procedure for the Suzuki coupling of the monohalide *N*-BOC-indolines

***tert*-Butyl 7-(4-acetylphenyl)indoline-1-carboxylate, 141 ***

141

To a screw-cap tube was added 7-iodo-*N*-BOC-indoline **134** (100 mg, 0.29 mmol), 4-acetylphenylboronic acid **140** (82 mg, 0.36 mmol), palladium acetate (9 mg, 0.029 mmol) and triphenylphosphine **L32** (23 mg, 0.064 mmol). The solids were taken up in tetrahydrofuran (2 mL) and stirred for 30 minutes, after which aqueous potassium hydroxide (1.78 M, 0.20 mL, 0.36 mmol) was added *via* syringe. The flask was sealed and stirred for 48 h. The mix was diluted with water (6 mL) and ethyl acetate (6 mL), the phases separated and the aqueous phase extracted with ethyl acetate (2 × 10 mL). The combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), and reduced *in vacuo*. Purification by flash column chromatography (SiO_2, gradient elution 5-20% ethyl acetate/petrol) gave tri-cycle **141** (38 mg, 39%) as an orange powder; m.p. 120-121 °C (hexane); ν_{max} (film)/cm^{-1} 3055, 2976, 2931, 1710 (C=O), 1683 (C=O), 1436, 1367, 1267, 1161, 1003, 838, 767; ^{1}H NMR (400 MHz, $CDCl_3$) 7.97 (2H, d, *J* 8.3, 2 × Ar-H), 7.64 (2H, d, *J* 8.3, 2 × Ar-H), 7.23 (2H, m, H-6 and H-4), 7.13 (1H, dd (app. t), *J* 7.5, H-5), 4.19 (2H, t, *J* 7.7, 2 × H-2), 3.07 (2H, t, *J* 7.7, 2 × H-3), 2.61 (3H, s, C(O)CH_3), 1.10 (9H, s, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) 197.8, 153.0, 146.4, 140.3, 135.6, 135.2, 129.9, 129.0, 128.6, 127.2, 124.7, 124.3, 81.0, 50.6, 29.3, 27.9, 26.7; *m/z* HRMS (ESI$^+$, [*M* + Na]$^+$) $C_{21}H_{23}NNaO_3$ requires 360.1570, found 360.1570.

1-(*tert*-Butylsufinyl)-1*H*-indole, 162 *

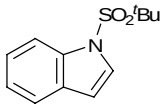


162

n-Butyllithium (2.5 M in hexanes, 1.71 mL, 4.27 mmol) was added dropwise to a stirred solution of indole **157** (500 mg, 4.27 mmol) in tetrahydrofuran (5 mL) at -78 °C. After 30 minutes the reaction was warmed to 0 °C for a further 1 h, before re-

cooling to -78 °C when *tert*-butyl sulfinyl chloride (0.59 mL, 5.13 mmol) was added dropwise and the internal temperature maintained below -70 °C. After 30 minutes the reaction was warmed to room temperature over 1 h. The reaction was quenched with saturated sodium hydrogen carbonate (10 mL) and the phases separated. The aqueous phase was extracted with diethyl ether (3 × 10 mL), the combined organic phases washed with brine (15 mL), dried ($MgSO_4$) and reduced *in vacuo*. Purification by flash column chromatography (SiO_2, dichloromethane/petrol 1 : 1) gave *tert*-butyl sulfinyl indole **162** (770 mg, 82%) as a white powder; m.p. 53-55 °C; ν_{max} (KBr disc)/cm^{-1} 3118, 3099, 2975, 2925, 1601, 1473, 1446, 1268, 1130, 1104 (S=O), 972, 769, 738, 640; ^{1}H NMR (400 MHz, $CDCl_3$) 7.61 (1H, d, *J* 7.2, H-4), 7.54 (1H, d, *J* 8.0, H-7), 7.47 (1H, d, *J* 3.5, H-2), 7.25 (1H, dd, *J* 8.0 and 7.6, H-6), 7.19 (1H, dd, *J* 7.6 and 7.2, H-5), 6.71 (1H, d, *J* 3.5, H-3), 1.29 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) 138.0, 129.5, 123.3, 123.2, 121.8, 121.4, 111.5, 106.8, 61.0, 22.6; *m/z* LRMS (CI^+) 239.1 (35%, $[M + NH_4]^+$), 222.1 (25%, $[M]^+$), 118.0 (100%, $[M - S(O)^tBu]^+$); HRMS (ESI^+, $[M + H]^+$) $C_{12}H_{16}NOS$ requires 222.0947, found 222.0947.

1-(*tert*-Butylsulfonyl)-1*H*- indole, 163 *

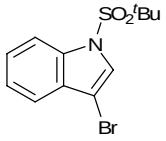


163

m-Chloroperoxybenzoic acid (77% by weight, 2.40 g, 10.4 mmol) was added in one portion to a stirred solution of *tert*-butyl sulfinyl indole **162** (850 mg, 3.80 mmol) in tetrahydrofuran (50 mL) at room temperature. After 18 h, the reaction was quenched with saturated sodium hydrogen carbonate (20 mL) and saturated sodium hydrogen sulphate (20 mL). The phases were separated and the aqueous phase extracted with dichloromethane (3 × 10 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and reduced *in vacuo*. Purification by flash column chromatography (SiO_2, petrol/dichloromethane 5 : 1) gave *N*-BUS-indole **163** (450 mg, 50%) as a white powder; m.p. 96-97 °C; ν_{max} (KBr disc)/cm^{-1} 3134, 3066, 2980, 1668, 1530, 1478, 1347, 1266, 1140 (S=O), 1125 (S=O), 998, 777, 683; ^{1}H NMR (400 MHz, $CDCl_3$) 7.97 (1H, d, *J* 8.2, H-7), 7.59 (1H, d, *J* 7.8, H-4), 7.39 (1H, d, *J*

3.7, H-2), 7.30 (1H, dd, *J* 8.2 and 7.1, H-6), 7.24 (1H, dd, *J* 7.8 and 7.1, H-5), 6.66 (1H, d, *J* 3.7, H-3), 1.41 (9H, s, C(C*H*$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) 136.6, 130.0, 128.1, 124.3, 122.9, 121.2, 114.3, 107.3, 63.9, 24.7; *m/z* LRMS (CI$^+$) 237.3 (25%, [*M*]$^+$), 116.1 (100%, [*M* – $SO_2{}^tBu$]$^+$); HRMS (ESI$^+$ [*M* + NH_4]$^+$) $C_{12}H_{19}N_2O_2S$ requires 255.1162, found 255.1163.

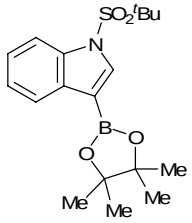
3-Bromo-1-(*tert*-butylsulfonyl)-1*H*-indole, 164 *



164

N-Bromosuccinimide (750 mg, 4.22 mmol) was added in one portion to a stirred solution of *N*-BUS-indole **163** (400 mg, 1.69 mmol) in tetrahydrofuran (8 mL). After 4 h the reaction was quenched with saturated sodium hydrogen sulphite (10 mL). The phases were separated and the aqueous phase extracted with dichloromethane (3 × 10 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and reduced *in vacuo*. Purification by flash column chromatography (SiO_2, petrol/ethyl acetate 9 : 1) gave 3-bromo-*N*-BUS-indole **164** (380 mg, 95%) as a white powder; m.p. 109-111 °C; ν_{max} (KBr disc)/cm^{-1} 3136, 3054, 2979, 1606, 1529, 1478, 1338, 1266, 1136 (S=O), 1125 (S=O), 998, 776, 686; ^{1}H NMR (300 MHz, $CDCl_3$) 7.96 (1H, dd, *J* 6.9 and 1.2, H-7), 7.58 (1H, dd, *J* 6.0 and 1.2, H-4), 7.46 (1H, s, H-2), 7.34 (2H, m, H-6 and H-5), 1.43 (9H, s, C(C*H*$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 136.0, 128.9, 126.5, 125.5, 123.5, 119.8, 114.3, 97.9, 64.1, 24.6; *m/z* LRMS (CI$^-$) 236.2 (30%, [*M* – ^{79}Br]$^-$), 196.0 (100%, [*M* – ^{t}Bu]$^-$); HRMS (EI$^+$, [*M*]$^+$) $C_{12}H_{14}{}^{79}BrNO_2S$ requires 314.9923, found 314.9932.

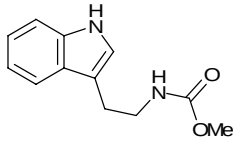
1-(*tert*-Butylsulfonyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole, 165 *



165

tert-Butyllithium (1.4 M in hexanes, 0.90 mL, 1.27 mmol) was added dropwise to a stirred solution of 3-bromo-*N*-BUS-indole **164** (200 mg, 0.63 mmol) in tetrahydrofuran (5 mL) at -100 °C, maintaining the internal temperature below -80 °C. After 5 minutes, trimethyl borate (0.14 mL, 1.27 mmol) was added dropwise and the solution stirred for a further 15 minutes after which it was warmed to 0 °C for 2 h. The reaction was quenched with methanol (5 mL) and immediately concentrated. (Note: continued exposure to air results in the clear solution turning purple, a possible indication of the instability of the methyl ester). The white residue was immediately placed under a nitrogen atmosphere and dissolved in tetrahydrofuran (3 mL). Pinacol (746 mg, 3.16 mmol) and 4Å molecular sieves (150 mg) were added in one portion and the mixture stirred for 5 h. The reaction was diluted with diethyl ether (10 mL) and water (10 mL). The phases were separated and the aqueous phase extracted with diethyl ether (3 × 10 mL). The combined organic phases were washed with brine (15 mL), dried ($MgSO_4$) and reduced *in vacuo*. Recrystallisation of the crude white solid from acetonitrile-hexane gave the *N*-BUS-indole-3-pinacol boronic ester **165** (170 mg, 75%) as a white powder; m.p. 186-187 °C; ν_{max} (KBr disc)/cm^{-1} 3118, 3073, 2986, 2933, 1606, 1550, 1350 (SO_2-N), 1143 (S=O), 1125 (S=O), 1039, 946, 752 and 695; ^{1}H NMR (300 MHz, $CDCl_3$) 8.03-7.98 (1H, m, H-7), 7.95-7.90 (1H, m, H-4), 7.81 (1H, s, H-2), 7.31-7.26 (2H, m, H-6 and H-5), 1.43 (9H, s, $C(CH_3)_3$), 1.37 (12H, s, 4 × CH_3 (pinacol)); ^{13}C NMR (75 MHz, $CDCl_3$) 137.3, 137.0, 133.0, 124.3, 123.1, 122.9, 114.0, 83.5, 63.8, 24.9, 24.6, (one carbon signal not observed); *m/z* LRMS (CI^+) 381.3 (35%, $[M + NH_4]^+$), 244.2 (80%, $[M - S(O)^tBu + 2H]^+$); HRMS (ESI^+, $[M + H]^+$) $C_{18}H_{27}BNO_4S$ requires 364.1748, found 364.1748.

Methyl 2-(1*H*-indol-3-yl)ethylcarbamate, 144 *



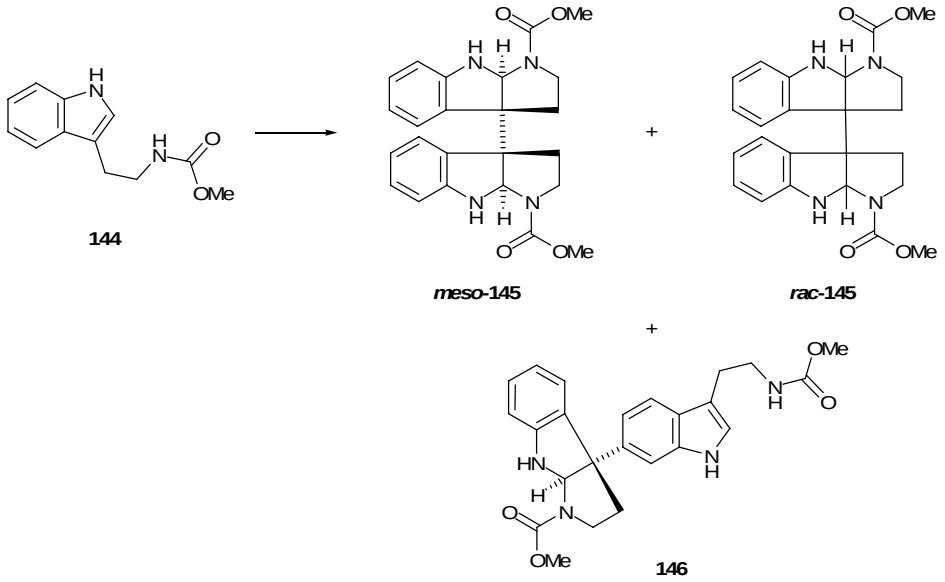
144

Tryptamine **142** (12.0 g, 75 mmol) was suspended in a 1 : 1 v/v mixture of 2 M aqueous sodium hydroxide (110 mL, 225 mmol) and dichloromethane (110 mL). After cooling to 0 °C, methyl chloroformate (11.6 mL, 150 mmol) was added dropwise. Once addition was complete the mixture was warmed to room temperature. After 2 h, the phases were separated and the aqueous phase extracted with dichloromethane (3 × 50 mL). The combined organic phases were washed with brine (75 mL), dried ($MgSO_4$) and reduced *in vacuo*. Repeated recrystallisation from diethyl ether/hexanes gave *N*′-carbomethoxytryptamine **144** (overall yield 15.1 g, 92%) as beige crystals; m.p. 79-81 °C (lit. 79 °C); ν_{max} (KBr disc)/cm^{-1} 3401 (NH), 3284 (NH), 3075, 2960, 2850, 1687 (C=O), 1550, 1457, 1290, 1149, 998, 740; ^{1}H NMR (300 MHz, $CDCl_3$) 8.23 (1H, br s, H-1), 7.62 (1H, d, *J* 7.8, H-4), 7.37 (1H, d, *J* 8.0, H-7), 7.22 (1H, dd, *J* 7.8 and 7.0, H-6), 7.14 (1H, dd, *J* 8.0 and 7.0, H-5), 7.00 (1H, s, H-2), 4.82 (1H, br s, H-1′), 3.68 (3H, s, OCH_3), 3.52-3.48 (2H, m, H-2′), 2.98 (2H, t, *J* 6.8, H-3′); ^{13}C NMR (75 MHz, $CDCl_3$) 157.6, 136.9, 127.7, 122.9, 122.5, 119.9, 119.1, 113.2, 111.7, 52.5, 41.7, 26.2; *m/z* LRMS (CI^+) 236.1 (100%, [*M* + NH_4]$^+$), 219.0 (65%, [*M* + H]$^+$), 187.0 (90%, [*M* – OMe]$^+$); Anal. calc. for $C_{12}H_{14}N_2O_2$, requires C: 66.04%; H: 6.47%; N: 12.84%, found C: 65.8%; H: 6.35%; N: 12.8%.

rac-Dimethyl 3,3a,3′,3′a,8,8a,8′,8′a-octahydro-3a,3′a-bipyrrolo[2,3-*b*]indole-1,1′(2*H*,2′*H*)-dicarboxylate, _rac_-145[58] *

meso-Dimethyl 3,3a,3′,3′a,8,8a,8′,8′a-octahydro-3a,3′a-bipyrrolo[2,3-*b*]indole-1,1′(2*H*,2′*H*)-dicarboxylate, _meso_-145[58] *

(3a*S)-Methyl 3a-(3-(2-(methoxycarbonylamino)ethyl)-1*H*-indol-5-yl)-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole-1(2*H*)-carboxylate, 146 ***



Under an inert argon atmosphere, *N*′-carbomethoxytryptamine **144** (5 g, 23 mmol) was dissolved in trifluoroethanol (80 mL) and cooled to -30 °C. Bis(trifluoroacetoxy)iodobenzene (5 g, 11.5 mmol) was added in two equal portions 2 h apart. After 18 h, a further portion of bis(trifluoroacetoxy)iodobenzene (1.5 g, 3.5 mmol) was added. After a further 4 h the reaction was quenched with saturated sodium hydrogen carbonate (30 mL) and diluted with chloroform (100 mL). The phases were separated and the aqueous phase extracted with chloroform (5 × 25 mL). The combined organic phases were washed with brine (100 mL), dried ($MgSO_4$) and reduced *in vacuo*. Purification by flash column chromatography (SiO_2, gradient elution 5-30% ethyl acetate/chloroform) gave, in order of elution, the *rac* and *meso* carbomethoxychimonanthines, ***rac*-145** and ***meso*-145** respectively, as a mixture, and the monopyrrolidinoindoline dimer **146** (800 mg, 16%) as a pale yellow foam. The *meso* and *rac* diastereomers were separated by recrystallisation from chloroform/hexane to give *meso*-carbomethoxychimonanthine ***meso*-145** (1.38 g,

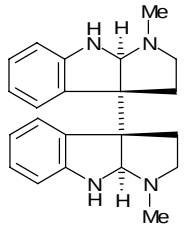
28%) as a white powder, and *rac*-carbomethoxychimonanthine ***rac*-145** (620 mg, 12%) as a pale yellow foam.

***rac*-145:** m.p. 187-188 °C (lit. 191 °C); ν_{max} (KBr disc)/cm^{-1} 3358 (NH), 3045, 2954, 2880, 1695 (C=O), 1453, 1385, 1202, 1117, 885, 749; ^{1}H NMR (400 MHz, d_6-DMSO, 120 °C) 7.24 (2H, d, *J* 7.5, 2 × H-4), 7.03 (2H, ddd, *J* 7.6, 7.5 and 1.0, 2 × H-6), 6.65 (2H, ddd (app td), *J* 7.5 and 1.0, 2 × H-5), 6.60 (2H, d, *J* 7.6, 2 × H-7), 6.04 (2H, br s, 2 × H-8), 4.96 (2H, s, 2 × H-8a), 3.61-3.54 (8H, m, 2 × OC*H*$_3$ and 2 × H-2), 2.81-2.74 (2H, m, 2 × H-2), 2.58-2.50 (2H, m, 2 × H-3), 2.16-2.09 (2H, dd, *J* 12.6 and 5.9, 2 × H-3); ^{13}C NMR (100 MHz, d_6-DMSO, 120 °C) 154.5, 151.4, 129.1, 129.0, 124.9, 118.0, 109.2, 78.5, 60.0, 52.2, 45.2, 32.9. Data consistent with the literature.[58]

***meso*-145:** m.p. 279-280 °C (lit. 276 °C); ν_{max} (KBr disc)/cm^{-1} 3356 (NH), 3056, 2956, 2894, 1691 (C=O), 1454, 1390, 1248, 1200, 1066, 890, 749; ^{1}H NMR (400 MHz, d_6-DMSO, 120 °C) 6.99 (2H, dd, *J* 7.6 and 7.5, 2 × H-6), 6.63 (2H, d, *J* 7.3, 2 × H-4), 6.53-6.46 (4H, m, 2 × H-7 and 2 ×H-5), 5.91 (2H, br s, 2 × H-8), 5.35 (2H, d, *J* 1.2, 2 × H-8a), 3.68-3.62 (8H, m, 2 × OC*H*$_3$ and 2 × H-2), 2.89-2.81 (2H, m, 2 × H-2), 2.34-2.18 (4H, m, 4 × H-3); ^{13}C NMR (100 MHz, d_6-DMSO, 120 °C) 154.6, 151.3, 129.5, 128.9, 124.2, 117.8, 108.8, 77.6, 62.5, 52.3, 45.3, 34.3; *m/z* LRMS (CI$^+$) 435.3 (50%, $[M + H]^+$), 217.1 (65%, $[M / 2]^+$); Anal. calc. for $C_{24}H_{26}N_4O_4$, requires C: 66.34%, H: 6.03%; N: 12.89%, found C: 66.0%, H: 5.97%, N: 12.7%. Data consistent with the literature.[58]

monopyrrolidinoindoline 146: m.p. 131-133 °C; ν_{max} (KBr disc)/cm^{-1} 3403 (NH), 3335 (NH), 3051, 2954, 1696 (C=O), 1525, 1457, 1388, 1202, 1047, 748; ^{1}H NMR (400 MHz, d_6-DMSO, 120 °C) 10.39 (1H, br s, H-1″), 7.46 (1H, d, *J* 8.3, H-4′), 7.30 (1H, s, H-7`), 7.09-6.98 (4H, m, H-4, H-6, H-2′ and H-5′), 6.69-6.54 (3H, m, H-5, H-7 and H-1′), 6.11 (1H, br s, H-8), 5.49 (1H, s, H-8a), 3.84-3.77 (1H, m, H-2), 3.68 (3H, s, OC*H*$_3$), 3.56 (3H, s, OC*H*$_3$), 3.33-3.26 (2H, m, 2 × H-2″), 3.09-3.01 (2H, m, 2 × H-2), 2.87-2.81 (2H, m, 2 × H-3″), 2.72-2.57 (2H, m, 2 × H-3); ^{13}C NMR (100 MHz, d_6-DMSO, 120 °C) 156.1, 153.8, 149.0, 136.9, 136.0, 132.6, 127.3, 125.6, 123.2, 122.3, 117.7, 117.5, 116.0, 111.3, 108.7, 107.9, 82.5, 59.0, 51.3, 50.4, 45.3, 40.9, 36.3, 25.0.

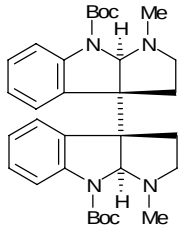
meso-1,1′-Dimethyl-1,1′,2,2′,3,3a,3′,3′a,8,8a,8′,8′a-dodecahydro-3a,3′a-bipyrrolo[2,3-*b*]indole, _meso_-19[49] *



***meso*-19**

Red-Al® (65% (~3.5 M) in toluene, 7.7 mL, 25.3 mmol) was added to a suspension of *meso*-*N*-carbomethoxychimonanthine ***meso*-145** (1.1 g, 2.53 mmol) in toluene (240 mL) at room temperature. The reaction was heated to reflux for 16 h then cooled to room temperature before quenching with 5% sodium hydroxide (30 mL). After filtration through celite, the phases were separated and the aqueous phase extracted with chloroform (3 × 30 mL). The combined organic phases were washed with brine (50 mL), dried ($MgSO_4$), and reduced *in vacuo*. Purification by flash column chromatography (SiO_2, chloroform/methanol/ammonia 9 : 1 : 0.15) and subsequent recrystallisation from dichloromethane/ethyl acetate gave *meso*-chimonanthine ***meso*-19** as a white crystalline solid (680 mg, 77%); m.p. 198-199 °C (lit. 196-197 °C); ν_{max} (KBr disc)/cm^{-1} 3400 (NH), 3047, 2959, 2860, 1602, 1487, 1347, 1321, 1157, 1022, 987, 748; ^{1}H NMR (400 MHz, d_6-DMSO, 120 °C) 6.87 (2H, dd, *J* 7.6 and 7.5, 2 × H-6), 6.55 (2H, br s, 2 × H-4), 6.40-6.34 (4H, m, 2 × H-7 and 2 × H-5), 5.49 (2H, s, 2 × H-8), 4.58 (2H, s, 2 × H-8a), 2.70 (2H, m, 2 × H-2), 2.52-2.43 (2H, m, 2 × H-2), 2.37-2.29 (8H, m, 2 × CH_3 and 2 × H-3), 1.92-1.86 (2H, m, 2 × H-3); ^{13}C NMR (100 MHz, d_6-DMSO, 120 °C) 153.1, 133.5, 127.8, 124.3, 116.7, 107.8, 83.6, 63.7, 52.2, 35.9, 22.6; *m/z* LRMS (CI^+) 346.2 (80%, $[M]^+$); Anal. calc. for $C_{22}H_{26}N_4$, requires C: 76.27%; H: 7.56%, N: 16.2%, found C: 75.9%, H: 7.55%, N: 16.1%. Data consistent with the literature.[49]

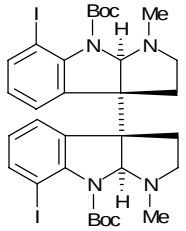
meso-Di-_tert_-butyl 1,1′-dimethyl-1,1′,2,2′,3,3a,3′,3′a-octahydro-3a,3′a-bipyrrolo[2,3-_b_]indole-8,8′(8a_H_,8a′_H_)-dicarboxylate, _meso_-31[52] *



***meso*-31**

Sodium bis(trimethylsilyl)amide (1.0 M in THF, 6.5 mL, 6.50 mmol) was added dropwise *via* syringe pump over 30 minutes to a stirred solution of *meso*-chimonanthine ***meso*-19** (500 mg, 1.45 mmol) and di-*tert*-butyl dicarbonate (787 mg, 3.61 mmol) in tetrahydrofuran (20 mL). After 2 h the solution was partitioned between saturated ammonium chloride (10 mL) and dichloromethane (15 mL) and the phases separated. The aqueous phase was extracted with dichloromethane (3 × 10 mL) and the combined organic phases dried ($MgSO_4$) and reduced *in vacuo*. Purification by flash column chromatography (SiO_2, ethyl acetate/petrol 4 : 1) gave biscarbamate ***meso*-31** (645 mg, 82%) as a white foam; ν_{max} (KBr disc)/cm^{-1} 3038, 2975, 2938, 1706 (C=O), 1483, 1366, 1170, 1022, 758; ^{1}H NMR (400 MHz, d_6-DMSO, 120 °C) 7.53 (2H, d, *J* 8.0, 2 × H-7), 7.14 (2H, dd, *J* 8.0 and 7.5, 2 × H-6), 6.82 (2H, dd, *J* 7.5 and 7.2, 2 × H-5), 6.55 (2H, br s, 2 × H-4), 4.92 (2H, s, 2 × H-8a), 2.76-2.70 (2H, m, 2 × H-2), 2.47-2.36 (10H, m, 2 × CH_3, 2 × H-2 and 2 × H-3), 2.07-2.00 (2H, m, 2 × H-3), 1.44 (18H, s, 2 × C(CH_3)$_3$); ^{13}C NMR (100 MHz, d_6-DMSO, 120 °C) 152.2, 143.9, 134.9, 128.3, 124.1, 122.7, 115.7, 85.4, 80.8, 61.3, 53.3, 37.4, 34.9, 28.4; Anal. calc. for $C_{32}H_{42}N_4O_4$, requires C: 70.3%, H: 7.74%, N: 10.25%, found C, 70.2%, H, 7.75%, N: 10.2%. Data consistent with the literature.[52]

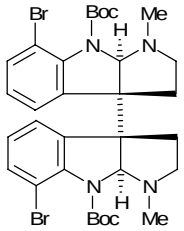
meso-Di-_tert_-butyl 7,7′-diiodo-1,1′-dimethyl-1,1′,2,2′,3,3a,3′,3′a-octahydro-3a,3′a-bipyrrolo[2,3-_b_]indole-8,8′(8a_H_,8a′_H_)-dicarboxylate, _meso_-133[52] *



***meso*-133**

sec-Butyllithium (1.4 M in cyclohexane, 0.52 mL, 0.73 mmol) was added dropwise to a stirred solution of biscarbamate ***meso*-31** (100 mg, 0.18 mmol) and *N,N,N′,N′*-tetramethylethylenediamine (0.17 mL, 1.10 mmol) in diethyl ether (2 mL) at -78 °C. After 1 h, diiodoethane (154 mg, 0.55 mmol) in diethyl ether (2 mL) was added dropwise. After 10 minutes at -78 °C, the reaction was warmed to 0 °C and stirred for 2 h then quenched with saturated sodium dithionite (10 mL) and saturated sodium hydrogen carbonate (10 mL). The phases were separated and the aqueous phase extracted with diethyl ether (3 × 10 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and reduced *in vacuo*. Purification by flash column chromatography (SiO_2, ethyl acetate/petrol 1 : 1) and subsequent recrystallisation of the solid from hot toluene gave bisiodide ***meso*-133** (545 mg, 75%) as colourless plates; m.p. 211-213 °C (toluene) (lit. 215-220 °C); ν_{max} (KBr disc)/cm^{-1} 3064, 2979, 2939, 1714 (C=O), 1570, 1442, 1350, 1338, 1288, 1160, 1030, 758; ^{1}H NMR (400 MHz, d_6-DMSO, 120 °C) 7.61 (2H, d, *J* 7.8, 2 × H-6), 6.82 (2H, br s, 2 × H-4), 6.72 (2H, dd, *J* 7.8 and 7.6, 2 × H-5), 4.95 (2H, s, 2 × H-8a), 2.75-2.69 (2H, m, 2 × H-2), 2.44 (6H, s, 2 × CH_3), 2.40-2.33 (2H, m, 2 × H-2), 2.24-2.16 (2H, m, 2 × H-3), 1.96-1.90 (2H, m, 2 × H-3), 1.44 (18H, s, 2 × C(CH_3)$_3$); ^{13}C NMR (100 MHz, d_6-DMSO, 120 °C) 152.0, 146.9, 139.3, 139.1, 126.3, 124.4, 87.7, 85.3, 81.6, 62.2, 52.3, 36.4, 36.1, 28.2. Data consistent with the literature.[52]

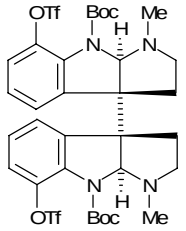
meso-Di-_tert_-butyl-7,7′-dibromo-1,1′-dimethyl-1,1′,2,2′,3,3a,3′,3′a-octahydro-3a,3′a-bipyrrolo[2,3-_b_]indole-8,8′(8a_H_,8′a_H_)-dicarboxylate, _meso_-134 *



***meso*-134**

sec-Butyllithium (1.4 M in cyclohexane, 0.52 mL, 0.73 mmol) was added dropwise to a stirred solution of biscarbamate ***meso*-31** (100 mg, 0.18 mmol) and *N,N,N′,N′*-tetramethylethylenediamine (0.17 mL, 1.10 mmol) in diethyl ether (2 mL) at -78 °C. After 1 h, dibromoethane (0.16 mL, 1.83 mmol) was added dropwise. After 10 minutes at -78 °C, the reaction was warmed to 0 °C and stirred for 2 h then quenched with water (10 mL) and saturated sodium hydrogen carbonate (10 mL). The phases were separated and the aqueous phase extracted with diethyl ether (3 × 10 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and reduced *in vacuo*. Purification by flash column chromatography (SiO_2, ethyl acetate/petrol 1 : 1) and subsequent recrystallisation of the solid from hot toluene gave the bisbromide ***meso*-134** (70 mg, 54%) as colourless plates; m.p. 203-205 °C (toluene); ν_{max} (KBr disc)/cm^{-1} 3042, 2978, 2947, 2798, 1716 (C=O), 1574, 1460, 1352, 1244, 1163, 1030, 758; ^{1}H NMR (400 MHz, d_6-DMSO, 120 °C) 7.40 (2H, d, *J* 7.7, 2 × H-6), 6.92 (2H, dd, *J* 7.7 and 7.7, 2 × H-5), 6.82 (2H, br s, 2 × H-4), 4.96 (2H, s, 2 × H-8a), 2.76-2.70 (2H, m, 2 × H-2), 2.45 (6H, s, 2 × CH_3), 2.44-2.37 (2H, m, 2 × H-2), 2.28-2.20 (2H, m, 2 × H-3), 1.97 (2H, ddd, *J* 12.0, 5.4 and 2.9, 2 × H-3), 1.43 (18H, s, 2 × C(CH_3)$_3$); ^{13}C NMR (100 MHz, d_6-DMSO, 120 °C) 152.7, 143.7, 140.0, 133.4, 126.6, 124.1, 112.5, 88.5, 81.9, 62.5, 52.6, 36.7, 36.5, 28.4; *m/z* LRMS $(CI)^+$ 705.2 (75%, $[M + H]^+$), 625.3 (100%, $[M - {}^{79}Br]^+$); HRMS (ESI^+, $[M + H]^+$) $C_{32}H_{41}{}^{79}Br_2N_4O_4$ requires 703.1489, found 703.1487.

meso-Di-_tert_-butyl-1,1′-dimethyl-7,7′-bis(trifluoromethylsulfonyloxy)-1,1′,2,2′,3,3a,3′,3′a-octahydro-3a,3′a-bipyrrolo[2,3-_b_]indole-8,8′(8a_H_,8′a_H_)-dicarboxylate, _meso_-135 *



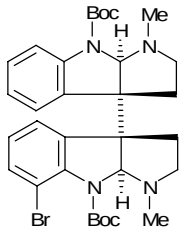
***meso*-135**

sec-Butyllithium (1.4 M in cyclohexane, 0.65 mL, 0.92 mmol) was added dropwise to a stirred solution of biscarbamate ***meso*-31** (100 mg, 0.18 mmol) and *N,N,N′,N′*-tetramethylethylenediamine (0.11 mL, 0.73 mmol) in diethyl ether (2 mL) at -78 °C. After 1 h, camphorsulfonyl oxaziridine **152** (201 mg, 0.88 mmol) in tetrahydrofuran (2 mL) was added *via* cannula over 5 minutes. After 30 minutes at -78 °C, the reaction was warmed to 0 °C and stirred for 1 h before quenching with saturated ammonium chloride (5 mL). The phases were separated and the aqueous phase extracted with diethyl ether (3 × 10 mL). The combined organics were washed with brine (20 mL), dried ($MgSO_4$) and reduced. Purification by flash column chromatography (SiO_2, ethyl acetate/petrol 3:1) gave an inseparable mixture of the mono and bisphenol ***rac*-148** and ***meso*-147** as a white solid (106 mg).

A mixture of the mono and bisphenols ***rac*-148** and ***meso*-147** (106 mg, 0.183mmol) was taken up in dichloromethane (3 mL) and cooled to 0 °C in a foil wrapped round-bottomed flask. Freshly distilled pyridine (0.4 mL, 4.95 mmol) and a solution of triflic anhydride (0.13 mL, 0.73 mmol) in dichloromethane (1 mL) were added consecutively. After 30 minutes the reaction was allowed to warm to room temperature, and after a further 30 minutes the reaction was re-cooled to 0 °C and quenched with saturated citric acid solution (5 mL). The phases were separated and the aqueous phase extracted with ethyl acetate (3 × 10 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and reduced *in vacuo*. Purification by flash column chromatography (SiO_2, gradient elution ethyl acetate/hexane 2 : 1 to 4 : 1) and subsequent recrystallisation of the white powder from hot toluene gave bistriflate ***meso*-135** (108 mg, 70%) as colourless plates; m.p. 174-176 °C (toluene); ν_{max} (KBr disc)/cm^{-1} 3013, 2982, 2949, 2814, 1719, 1478,

1358, 1250, 1162, 1032, 935, 821; ^{1}H NMR (250 MHz, d_6-DMSO, 120 °C) 7.18-7.09 (4H, m, 2 × H-6 and 2 × H-5), 6.85 (2H, br s, 2 × H-4), 4.98 (2H, br s, 2 × H-8a), 2.83-2.75 (2H, m, 2 × H-2), 2.46 (6H, s, 2 × CH_3), 2.47-2.40 (2H, m, 2 × H-2), 2.37-2.27 (2H, m, 2 × H-3), 2.08-1.99 (2H, m, 2 × H-2), 1.40 (18H, s, 2 × C(CH_3)$_3$); ^{13}C NMR (62.5 MHz, d_6-DMSO, 120 °C) 151.1, 139.2, 136.7, 135.2, 124.9, 123.8, 121.5, 87.1, 81.1, 61.0, 50.9, 35.1, 34.3, 26.8. CF_3 signal not observed; *m/z* LRMS (EI$^+$) 842.3 (100%, [*M*]$^+$), 769.2 (65%, [*M* - O^{t}Bu]$^+$), 694.3 (10%, [*M* – OTf + H]$^+$); HRMS (EI$^+$, [*M*]$^+$) $C_{34}H_{40}F_6N_4O_{10}S_2$ requires 842.2085, found 842.2083. (Crystal structure – Appendix A).

(3a*R*,3′a*S*,8a*S*,8′a*R*)-Di-*tert*-butyl-7-bromo-1,1′-dimethyl-1,1′,2,2′,3,3a,3′,3′a-octahydro-3a,3′a-bipyrrolo[2,3-*b*]indole-8,8′(8a*H*,8′a*H*)-dicarboxylate, *rac*-218

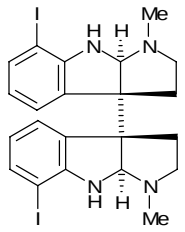


***rac*-218**

A screw cap tube was charged with palladium acetate (1 mg, 0.0045 mmol), *rac*-BINAP ***rac*-L1** (3.1 mg, 0.0049 mmol), bisbromide ***meso*-134** (63 mg, 0.09 mmol) then tetrahydrofuran (0.2 mL). After stirring for 20 minutes at room temperature, *N,N,N′,N′*-tetramethylethylenediamine (20 μL, 0.13 mmol) and extra tetrahydrofuran (0.2 mL) were added. After a further 20 minutes sodium borohydride (0.5 M in diglyme, 0.2 mL, 0.10 mmol) was added in one portion and the reaction heated at 65 °C for 36 h. After cooling to room temperature, the mixture was diluted with diethyl ether (10 mL) and water (10 mL). The phases were separated and the aqueous phase extracted with diethyl ether (3 × 10 mL). The combined organic phases were washed with brine (10 mL), dried ($MgSO_4$) and reduced *in vacuo*. Purification by flash column chromatography (SiO_2, ethyl acetate/petrol 2 : 1) gave monobromide ***rac*-218** (44 mg, 79%) as a white powder; m.p. 91-93 °C; ν_{max} (film)/cm^{-1} 3064, 2975, 2941, 2796, 1722 (C=O), 1705 (C=O), 1482, 1386, 1290, 1166, 1066, 823; ^{1}H NMR (250 MHz, d_6-DMSO, 100 °C) 7.49 (1H, d, *J* 8.0, H-7′), 7.35 (1H, d, *J* 8.0, H-6),

7.17 (1H, dd, *J* 8.0 and 6.8, H-6′), 6.94-6.79 (3H, m, H-5, H-4, H-5′), 6.52 (1H, br s, H-4′), 4.96 (1H, br s, H-8a), 4.91 (1H, br s, H-8a′), 2.75-2.66 (2H, m, H-2 and H-2′), 2.47-2.38 (9H, m inc. 2.45 (3H, s, NCH_3) and 2.41 (3H, s, NCH_3), H-2, H-2′ and H-3), 2.27-2.20 (1H, m, H-3′), 2.12-2.04 (1H, m, H-3), 1.88 (1H, ddd, *J* 11.8, 5.1 and 2.8, H-3′), 1.43 (9H, s, C(CH_3)$_3$), 1.42 (9H, s, C(CH_3)$_3$); ^{13}C NMR (62.5 MHz, d_6-DMSO, 100 °C) 151.3, 150.8, 142.8, 142.1, 133.7, 131.9, 131.8, 131.6, 127.4, 124.7, 123.3, 122.2, 122.0, 115.1, 110.7, 86.9, 84.1, 80.1, 79.9, 61.3, 59.7, 51.9, 51.3, 35.8, 35.3, 35.0, 34.2, 27.1; *m/z* HRMS (ESI$^+$, [*M* + H]$^+$) $C_{32}H_{42}{}^{79}BrN_4O_4$ requires 625.2384, found 625.2386.

meso-7,7′-Diiodo-1,1′-dimethyl-1,1′,2,2′,3,3a,3′,3′a,8,8a,8′,8′a-dodecahydro-3a,3′a-bipyrrolo[2,3-*b*]indole, _meso_-205[52]

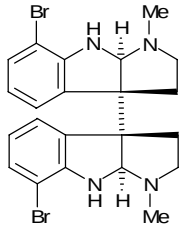


***meso*-205**

Trimethylsilyl trifluoromethanesulfonate (0.20 mL, 1.10 mmol) was added dropwise to a solution of *meso* bisiodide ***meso*-133** (200 mg, 0.25 mmol) in dichloromethane (7 mL) at room temperature. The septum was removed (to allow the formation of small quantities of triflic acid) and after 3 h the reaction was quenched with saturated sodium hydrogen carbonate, the phases separated and the aqueous phase extracted with dichloromethane (3 × 10 mL). The combined organic phases were dried ($MgSO_4$) and reduced *in vacuo*. Purification by flash column chromatography (SiO_2, dichloromethane/methanol/triethylamine 9 : 1 : 0.1) gave the deprotected bisamine ***meso*-205** (485 mg, 94%) as a pale brown solid; ν_{max} (film)/cm^{-1} 3385 (NH), 3040, 2811, 1601, 1474, 1246, 1029, 642; ^{1}H NMR (250 MHz, d_6-DMSO, 100 °C) 7.29 (2H, d, *J* 8.0, 2 × H-6), 6.52 (2H, br s, 2 × H-4), 6.24 (2H, m, 2 × H-5), 5.44 (2H, br s, 2 × N*H*), 4.63 (2H, br s, 2 × H-8a), 2.81-2.76 (2H, m, 2 × H-2), 2.48-2.42 (8H, m, 2 × CH_3 and 2 × H-2), 2.38-2.34 (2H, m, 2 × H-3), 1.94-1.89 (2H, m, 2 × H-3); ^{13}C NMR (62.5 MHz, d_6-DMSO, 100 °C) 152.0, 136.1, 132.3, 122.9, 118.2, 81.3, 72.9,

64.2, 51.2, 35.8, 34.7; *m/z* HRMS (ESI^+, $[M + H]^+$) $C_{22}H_{24}I_2N_4$ requires 599.0163, found 599.0168. Data consistent with the literature.[52]

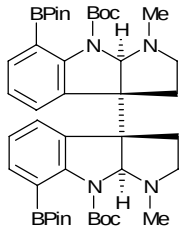
meso-7,7′-Dibromo-1,1′-dimethyl-1,1′,2,2′,3,3a,3′,3′a,8,8a,8′,8′a-dodecahydro-3a,3′a-bipyrrolo[2,3-*b*]indole, _meso_-257



***meso*-257**

Trimethylsilyl trifluoromethanesulfonate (2.2 mL, 12.1 mmol) was added dropwise to a solution of bisbromide ***meso*-134** (1.9 g, 2.70 mmol) in dichloromethane (50 mL) at room temperature. The septum was removed to allow the formation of small quantities of triflic acid. After 4 h a further portion of trimethylsilyl trifluoromethanesulfonate (0.5 mL, 2.70 mmol) was added dropwise and the solution stirred for 12 h. The reaction was quenched with saturated sodium hydrogen carbonate, the phases separated and the aqueous phase extracted with dichloromethane (3 × 20 mL). The combined organic phases were dried ($MgSO_4$) and reduced *in vacuo*. Purification by flash column chromatography (SiO_2, dichloromethane/methanol/triethylamine 9 : 1 : 0.1) gave bisamine ***meso*-257** (485 mg, 36%) as a beige solid; m.p. 208 °C (dec.); ν_{max} (film)/cm^{-1} 3407 (NH), 3062, 2934, 2861, 1601, 1475, 1246, 1169, 1029, 735; ^1H NMR (250 MHz, d_6-DMSO, 100 °C) 7.14 (2H, d, *J* 8.5, 2 × H-6), 6.50 (2H, br s, 2 × H-4), 6.39 (2H, dd, *J* 8.5 and 7.8, 2 × H-5), 5.80 (2H, br s, 2 × N*H*), 4.69 (2H, br s, 2 × H-8a), 3.01-2.91 (2H, m, 2 × H-2), 2.88-2.80 (2H, m, 2 × H-2), 2.45-2.32 (8H, m, 2 × CH_3 and 2 × H-3), 2.02-1.94 (2H, m, 2 × H-3); ^{13}C NMR (62.5 MHz, d_6-DMSO, 100 °C) 150.9, 134.7, 131.4, 123.8, 119.1, 101.7, 83.5, 65.0, 52.6, 37.1, 36.2; *m/z* HRMS (ESI^+, $[M + H]^+$) $C_{22}H_{24}{}^{79}Br_2N_4$ requires 503.0450, found 503.0440.

meso-Di-_tert_-butyl-1,1′-dimethyl-7,7′-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,1′,2,2′,3,3a,3′,3′a-octahydro-3a,3′a-bipyrrolo[2,3-_b_]indole-8,8′(8a_H_,8′a_H_)-dicarboxylate, _meso_-215

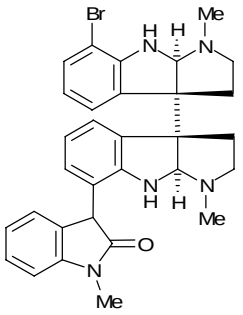


***meso*-215**

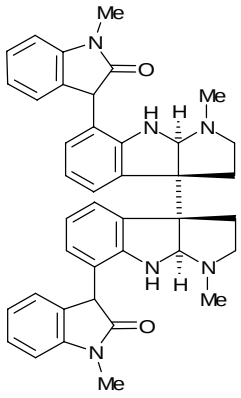
A screw cap tube was charged with palladium acetate (1.7 mg, 0.008 mmol), 2-(dicyclohexylphosphino)biphenyl **L24** (3.9 mg, 0.011 mmol) and bisiodide ***meso*-133** (300 mg, 0.38 mmol). Dioxane (1.5 mL) was added and the solution freeze-thaw degassed three times under argon. Pinacolborane (82 μL, 0.56 mmol) and triethylamine were added sequentially and the mixture heated at 85 °C for 20 h. After cooling to room temperature the solution was diluted with dichloromethane (10 mL) and washed with water (3 × 10 mL) and brine (10 mL). The organic phase was dried ($MgSO_4$) and reduced *in vacuo*. Purification by flash column chromatography (SiO_2, ethyl acetate/petrol 3 : 1) gave bisboryl ***meso*-215** (224 mg, 75%) as a white foam; m.p. 128-131 °C; ν_{max} (film)/cm^{-1} 3054, 2975, 2798, 1699 (C=O), 1481, 1438, 1366, 1167, 1097, 852, 792, 701; ^{1}H NMR (250 MHz, d_6-DMSO, 100 °C) 7.20 (2H, d, *J* 7.3, 2 × H-6), 6.88-6.78 (2H, m, 2 × H-5), 6.60 (2H, br s, 2 × H-4), 4.87 (2H, br s, 2 × H-8a), 2.76-2.68 (2H, m, 2 × H-2), 2.46-2.35 (10H, m, 2 × CH_3, 2 × H-3 and 2 × H-2), 2.14-1.96 (2H, m, 2 × H-3), 1.40 (18H, s, 2 × C(CH_3)$_3$), 1.29 (12H, s, 4 × CH_3), 1.27 (12H, s, 4 × CH_3); ^{13}C NMR (62.5 MHz, d_6-DMSO, 100 °C) 152.2, 145.2, 133.3, 131.4, 125.1, 123.7, 121.9, 84.1, 81.8, 80.1, 60.3, 51.8, 35.5, 34.5, 27.3, 24.6, 24.3; *m/z* HRMS (ESI$^+$, [*M* + H]$^+$) $C_{44}H_{65}B_2N_4O_8$ requires 799.4983, found 799.4998.

3-(7′-Bromo-1,1′-dimethyl-1,1′,2,2′,3,3a,3′,3′a,8,8a,8′,8′a-dodecahydro-3a,3′a-bipyrrolo[2,3-*b*]indol-7-yl)-1-methylindolin-2-one, *rac*-258

3,3′-(1,1′-dimethyl-1,1′,2,2′,3,3a,3′,3′a,8,8a,8′,8′a-dodecahydro-3a,3′a-bipyrrolo[2,3-*b*]indole-7,7′-diyl)bis(1-methylindolin-2-one), 259



***rac*-258**

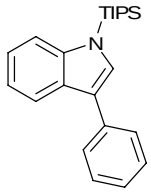


259

Under argon, bisamine ***meso*-257** (70 mg, 0.14 mmol) and sodium hydride (60% weight dispersion in mineral oil, 11.4 mg, 0.147 mmol) were taken up in degassed tetrahydrofuran (0.2 mL) and heated at 70 °C for 5 minutes. The tetrahydrofuran was carefully evaporated off and the residual salt cooled to room temperature. Palladium bis(dibenzylideneacetone) (2 mg, 0.0035 mmol) and X-Phos **L30** (2.5 mg, 0.0052 mmol) were added and the solids taken up in tetrahydrofuran (0.10 mL). After heating to 70 °C, a solution of the potassium enolate of *N*-methyl oxindole ((10.3 mg, 0.07 mmol oxindole; 0.14 mL, 0.07 mmol potassium bis(trimethylsilyl)amide (0.5 M solution in toluene); 0.05 mL tetrahydrofuran)) preformed at room temperature was added in one portion. After 20 minutes the reaction was quenched with saturated ammonium chloride (5 mL) and diluted with dichloromethane (10 mL). The phases were separated and the aqueous phase extracted with dichloromethane (3 × 10 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and reduced *in vacuo*. Purification by flash column chromatography (SiO_2, dichloromethane/methanol/triethylamine 19 : 1 : 0.1) gave, in order of elution, the monobromide ***rac*-258** as a pale yellow powder (17 mg, 43%); ν_{max} (film)/cm^{-1} 3374 (N-H), 3356 (N-H), 3055, 2932, 2854, 2793, 1700 (C=O), 1613, 1472, 1348, 1126, 1028, 799; *m/z* HRMS (ESI$^+$, $[M + H]^+$) $C_{31}H_{32}{}^{79}BrN_5O$ requires 570.1863, found 570.1864; and dicoupled product **259** (9 mg, 20%) as a pale yellow film; ν_{max} (film)/cm^{-1} 3382 (N-H), 3054, 2938, 2793, 1709 (C=O), 1612, 1469, 1348, 1159, 1032, 753; *m/z* HRMS (ESI$^+$, $[M + H]^+$) $C_{40}H_{41}N_6O_2$ requires

637.3286, found 637.3278. ^{1}H NMR data for these compounds were obtained at 100 °C in DMSO but resonances are unassignable due to the presence of rotamers and diastereomers (for spectra, see Appendix B).

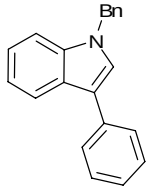
3-Phenyl-1-(tri*iso*propylsilyl)-1*H*-indole, 170 *



170

n-Butyllithium (2.5 M in hexanes, 2.7 mL, 6.78 mmol) was added dropwise to a solution of 3-phenyl indole (1 g, 5.18 mmol) in tetrahydrofuran (25 mL) at -78 °C. After 1 h, tri*iso*propylsilyl chloride (1.45 mL, 6.78 mmol) was added dropwise and the reaction slowly warmed to 0 °C and then to room temperature over 1 h. The reaction was diluted with water (20 mL) and diethyl ether (30 mL), the phases separated and the aqueous phase extracted with diethyl ether (3 × 15 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and reduced *in vacuo*. Purification by flash column chromatography (SiO_2, hexane/diethyl ether 200 : 1) gave 3-phenyl-*N*-TIPS-indole **170** (1.36 g, 79%) as a white powder; m.p. 75-76 °C (hexane); ν_{max} (KBr disc)/cm^{-1} 3027, 2948, 2868, 1606, 1451, 1239, 1143, 997, 883, 741, 698; ^{1}H NMR (250 MHz, $CDCl_3$) 8.02-7.97 (1H, m, H-4), 7.77-7.71 (2H, m, 2 × Ar-H), 7.64-7.59 (1H, m, H-7), 7.51 (2H, dd (app. t), *J* 7.5, 2 × Ar-H), 7.45 (1H, s, H-2), 7.38-7.22 (3H, m, Ar-H, H-6, H-5), 1.80 (3H, sep, *J* 7.6, 3 × C*H*$(CH_3)_2$), 1.24 (18H, d, *J* 7.5, 3 × (CH(C*H*$_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) 142.2, 136.2, 129.7, 129.3, 129.1, 128.0, 126.3, 122.1, 120.6, 120.5, 120.0, 114.6, 18.6, 13.3; *m/z* LRMS (EI$^+$) 349.2 (100%, $[M]^+$), 306.2 (90%, $[M - {}^{i}Pr]^+$), 192.0 (20%, $[M - Si({}^{i}Pr)_3]$); HRMS (ESI$^+$, $[M + H]^+$) $C_{23}H_{32}NSi$ requires 350.2299, found 350.2300.

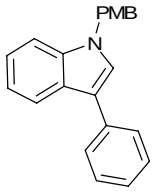
1-Benzyl-3-phenyl-1*H*-indole, 171 *



171

Sodium hydride (60% weight dispersion in mineral oil, 161 mg, 4.03 mmol) was added in small portions to a solution of 3-phenyl indole (647 mg, 3.35 mmol) and benzyl bromide (0.80 mL, 6.70 mmol) in tetrahydrofuran (20 mL). After stirring at 40 °C for 18 h, the reaction was allowed to stir open to air then filtered through $MgSO_4$ and reduced *in vacuo*. Purification by flash column chromatography (SiO_2, diethyl ether/hexane 1 : 1) gave *N*-benzyl-3-phenyl indole **171** (790 mg, 83 %) as a white powder; m.p. 58-59 °C (hexane); ν_{max} (KBr disc)/(cm^{-1}) 3056, 3024, 2924, 1541, 1469, 1391, 1186, 748, 738; ^{1}H NMR (300 MHz, $CDCl_3$) 7.97 (1H, d, *J* 7.5, H-4), 7.66 (2H, d, *J* 7.8, 2 × Ar-H), 7.42 (2H, dd, *J* 7.8 and 7.5, 2 × Ar-H), 7.34-7.13 (10H, m, H-7, H-6, H-5, H-2, Ar-H, 5 × Ar-H (benzyl)), 5.34 (2H, s, C*H*$_2$ (benzyl)); ^{13}C NMR (75 MHz, $CDCl_3$) 137.7, 137.6, 136.0, 129.3, 129.2, 128.2, 127.8, 127.4, 126.9, 126.3, 126.2, 122.6, 120.6, 120.5, 117.8, 110.5, 50.6; *m/z* LRMS (EI^+) 283.1 (45%, $[M]^+$), 192.0 (30%, $[M - CH_2Ph]^+$), 91.0 (100%, CH_2Ph); HRMS (ESI^+, $[M + H]^+$) $C_{21}H_{18}N$ requires 284.1434, found 284.1432.

1-(4-Methoxybenzyl)-3-phenyl-1*H*-indole, 172 *

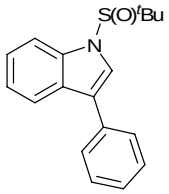


172

Sodium hydride (60% weight dispersion in mineral oil, 161 mg, 4.03 mmol) was added in small portions to a solution of 3-phenyl indole (647 mg, 3.35 mmol) and *para*-methoxybenzyl chloride (0.54 mL, 4.03 mmol) in tetrahydrofuran (20 mL). After stirring at 40 °C for 18 h, the reaction was allowed to stir open to air then filtered through $MgSO_4$ and reduced *in vacuo*. Purification by flash column chromatography (SiO_2, chloroform/hexane 1 : 1) gave 3-phenyl-*N*-PMB-indole **172**

(739 mg, 71%) as a colourless oil; ν_{max} (KBr disc)/cm^{-1} 3024, 2953, 2932, 1610, 1513, 1463, 1253, 1177, 1033, 770, 698; ^{1}H NMR (400 MHz, $CDCl_3$) 7.96 (1H, d, *J* 7.6, H-4), 7.64 (2H, d, *J* 7.7, 2 × Ar-H), 7.40 (2H, dd (app. t), *J* 7.7, 2 × Ar-H), 7.32 (1H, d, *J* 7.2, H-7), 7.27-7.14 (4H, m, H-6, H-5, H-2 and Ar-H), 7.08 (2H, d, *J* 8.5, Ar-H (PMB)), 6.80 (2H, d, *J* 8.5, 2 × Ar-H (PMB)), 5.21 (2H, s, C*H*$_2$ (PMB)), 3.72 (3H, s, OC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) 159.3, 137.1, 135.7, 129.2, 128.8, 128.5, 127.4, 126.5, 125.8, 122.1, 120.1, 120.0, 117.3, 114.3, 110.1, 55.4, 49.7, (one carbon signal not observed); *m/z* LRMS (EI$^+$) 313.2 (20%, [*M*]$^+$), 121.0 (100%, $CH_2(C_6H_4)OMe$); HRMS (ESI$^+$, [*M* + H]$^+$) $C_{22}H_{20}NO$ requires 314.1539, found 314.1537.

1-(*tert*-Butylsulfinyl)-3-phenyl-1*H*-indole, 173 *

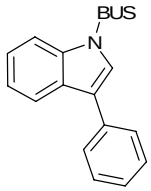


173

n-Butyllithium (2.5 M, 2.7 mL, 6.78 mmol) was added dropwise to a solution of 3-phenyl indole (1 g, 5.18 mmol) in tetrahydrofuran (25 mL) at -78 °C. After 1 h, *tert*-butylsulfinyl chloride (0.84 mL, 6.78 mmol) was added dropwise and the reaction slowly warmed to 0 °C and then room temperature over 1 h. The reaction was diluted with water (20 mL) and diethyl ether (30 mL), the phases separated and the aqueous phase extracted with diethyl ether (3 × 15 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and reduced *in vacuo*. Purification by flash column chromatography (SiO_2, hexane/diethyl ether 1 : 1) followed by recrystallisation from dichloromethane/hexane gave 3-phenyl-*N*-*tert*-butylsulfinyl-indole **173** (1.39 g, 90%) as white needles; m.p. 160-161 °C (dichloromethane/hexane); ν_{max} (KBr disc)/cm^{-1} 3076, 3056, 2974, 1609, 1443, 1163, 1029, 773, 699; ^{1}H NMR (300 MHz, $CDCl_3$) 7.90 (1H, d, *J* 7.8, H-4), 7.67 (2H, d, *J* 7.7, 2 × Ar-H), 7.63 (1H, s, H-2), 7.60 (1H, d, *J* 8.0, H-7), 7.47 (2H, dd, *J* 7.7 and 7.3, 2 × Ar-H), 7.37 (1H, d, *J* 7.3, Ar-H), 7.30 (2H, m, H-6 and H-5), 1.35 (9H, s, C(C*H*$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 139.3, 134.5, 130.3, 129.3, 128.2,

128.1, 127.4, 124.0, 122.5, 120.8, 120.6, 112.1, 61.5, 23.0; *m/z* LRMS (EI^+) 297.1 (10%, $[M]^+$), 241 (40%, $[M - {}^t\text{Bu} + H]^+$), 193.1 (100%, $[M - S(O){}^t\text{Bu}]^+$); HRMS ($ESI^+$, $[M + H]^+$) $C_{18}H_{20}NOS$ requires 298.1260, found 298.1262.

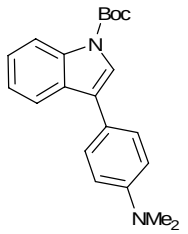
1-(*tert*-Butylsulfonyl)-3-phenyl-1*H*-indole, 174 *



174

m-Chloroperoxybenzoic acid (77% by weight, 490 mg, 2.18 mmol) was added in one portion to a solution of 3-phenyl-*N*-*tert*-butylsulfinyl-indole **173** (500 mg, 1.68 mmol) in dichloromethane (15 mL). After 6 h the reaction was quenched with saturated sodium hydrogen carbonate (20 mL) and saturated sodium hydrogen sulfite (20 mL). The phases were separated and the aqueous phase extracted with dichloromethane (3 × 20 mL). The combined organics were washed with brine (30 mL), dried ($MgSO_4$) and reduced. Purification by flash column chromatography (SiO_2, hexane/dichloromethane 2 : 1) gave 3-phenyl-*N*-BUS indole **174** (262 mg, 50%) as a white powder; m.p. 148-150 °C (hexane); ν_{max} (KBr disc)/cm^{-1} 3123, 3101, 2989, 2972, 1606, 1447, 1347, 1168, 1014, 932, 774, 669; ^1H NMR (300 MHz, $CDCl_3$) 8.05 (1H, d, *J* 7.6, H-4), 7.85 (1H, d, *J* 7.8, H-7), 7.66 (2H, d, *J* 7.6, 2 × Ar-H), 7.54 (1H, s, H-2), 7.49 (2H, dd, *J* 7.6 and 7.2, 2 × Ar-H), 7.42-7.29 (3H, m, H-6, H-5, and Ar-H), 1.47 (9H, s, $C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 137.7, 133.6, 129.3, 128.9, 128.4, 127.9, 125.3, 125.1, 123.6, 122.6, 120.6, 115.0, 64.5, 25.2; *m/z* LRMS (EI^+) 313.2 (10%, $[M]^+$), 193.2 (65%, $[M - SO_2{}^t\text{Bu} + H]^+$), 57.2 (100%, $[{}^t\text{Bu}]^+$); HRMS (ESI^+, $[M + NH_4]^+$) $C_{18}H_{23}N_2O_2S$ requires 331.1475, found 331.1469.

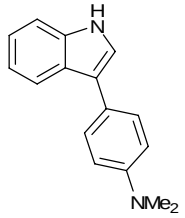
tert-Butyl 3-(4-(dimethylamino)phenyl)-1*H*-indole-1-carboxylate, 184 *



184

3-Bromo-*N*-BOC-indole (1.26 g, 4.26 mmol), palladium (tetrakis) triphenylphosphine (98 mg, 0.09 mmol) and (4-dimethylamino)phenyl boronic acid (699 mg, 4.26 mmol) were added sequentially to a Schlenk tube. After purging three times with nitrogen, the solids were taken up in dimethoxyethane (30 mL). A solution of sodium carbonate (590 mg, 5.54 mmol) in distilled water (25 mL) was added in one portion and the reaction heated at 90 °C for 24 h. After cooling to room temperature the reaction was diluted with dichloromethane (50 mL), the phases separated, and the aqueous phase extracted with dichloromethane (3 × 10 mL). The combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and reduced *in vacuo*. Purification by flash column chromatography (SiO_2, hexane/ethyl acetate 15 : 1) gave 3-((4-dimethylamino)phenyl)-*N*-BOC-indole **184** (1.21 g, 84%) as a white powder; m.p. 146-147 °C; ν_{max} (KBr disc)/cm^{-1} 3051, 3006, 2976, 2891, 1726 (C=O), 1618, 1520, 1452, 1375, 1243, 1157, 1106, 1050, 822, 749; ^{1}H NMR (300 MHz, $CDCl_3$) 8.13 (1H, d, *J* 6.8, H-7), 7.74 (1H, d, *J* 7.4, H-4), 7.54 (1H, s, H-2), 7.46 (2H, d, *J* 8.8, 2 × Ar-H), 7.30-7.17 (2H, m, H-6 and H-5), 6.76 (2H, d, *J* 8.7, 2 × Ar-H), 2.92 (6H, s, N(CH_3)$_2$), 1.60 (9H, s, C(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 150.3, 150.2, 136.3, 129.9, 129.2, 124.8, 123.1, 122.8, 122.3, 122.0, 120.6, 115.8, 113.3, 84.0, 41.1, 28.7; *m/z* LRMS (EI^+) 336.2 (15%, $[M]^+$), 280.1 (60%, $[M - {}^t\text{Bu} + H]^+$), 236.2 (100%, $[M - CO_2{}^t\text{Bu} + H]^+$); HRMS ($ESI^+$, $[M + H]^+$) $C_{21}H_{25}N_2O_2$ requires 337.1911, found 337.1912.

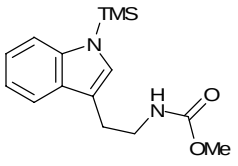
4-(1*H*-Indol-3-yl)-*N*,*N*-dimethylbenzenamine, 183 *



183

Trifluoroacetic acid (0.91 mL, 12 mmol) was added in one portion to a solution of 3-((4-dimethylamino)phenyl)-*N*-BOC-indole **184** (400 mg, 1.2 mmol) in dichloromethane (4 mL). After 2 h, the reaction was quenched with saturated sodium hydrogen carbonate (5 mL) and diluted with dichloromethane (15 mL). The phases were separated and the aqueous phase extracted with dichloromethane (3 × 10 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and reduced *in vacuo*. Purification by flash column chromatography (SiO_2, hexane/ethyl acetate 5 : 1) gave 3-((4-dimethylamino) phenyl)indole **183** (276 mg, 98%) as a white powder; m.p. 118-119 °C; ν_{max} (KBr disc)/cm^{-1} 3409 (NH), 3031, 2977, 2882, 1623, 1556, 1456, 1359, 1228, 1113, 802, 746; ^{1}H NMR (300 MHz, $CDCl_3$) 8.19 (1H, br s, H-1), 7.94 (1H, d, *J* 7.8, H-4), 7.59 (2H, d, *J* 8.6, 2 × Ar-H), 7.41 (1H, d, *J* 7.4, H-7), 7.28-7.16 (3H, m, H-6, H-5, H-2), 6.93 (2H, d, *J* 8.6, 2 × Ar-H), 3.02 (6H, s, 2 × NCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 148.7, 136.6, 128.4, 126.0, 122.2, 120.9, 120.0, 119.9, 118.3, 113.7, 113.7, 111.3, 41.2; *m/z* LRMS (EI^+) 236.0 (100%, $[M]^+$); HRMS (ESI^+, $[M + H]^+$) $C_{16}H_{17}N_2$ requires 237.1386, found 237.1384.

Methyl 2-(1-(trimethylsilyl)-1*H*-indol-3-yl)ethylcarbamate, 219 *

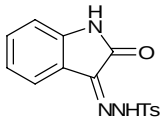


219

Chlorotrimethylsilane (2.80 mL, 22.0 mmol) was added in one portion to a solution of *N*′-carbomethoxytryptamine **144** (4 g, 18.3 mmol) in tetrahydrofuran (80 mL) at -78 °C. After 5 minutes potassium bis(trimethylsilyl)amide (1 M in toluene, 36.7 mL, 36.7 mmol) was added dropwise over 15 minutes. After 3 h the reaction was quenched with saturated ammonium chloride (100 mL). The phases were separated and the aqueous phase extracted with ethyl acetate (3 × 30 mL). The combined

organic phases were washed with brine (100 mL), dried ($MgSO_4$) and reduced *in vacuo*. Purification by flash column chromatography (SiO_2, hexane/ethyl acetate 4 : 1) gave *N*-TMS-*N*′-carbomethoxytryptamine **219** (3.2 g, 60%) as a white powder; m.p. 88-89 °C; ν_{max} (KBr disc)/cm^{-1} 3330 (NH), 3077, 3060, 2963, 1691 (C=O), 1540, 1452, 1318, 1166, 1046, 839, 760; ^{1}H NMR (300 MHz, $CDCl_3$) 7.62 (1H, d, *J* 7.4, H-4), 7.49 (1H, d, *J* 8.1, H-7), 7.25-7.13 (2H, m, H-6 and H-5), 7.00 (1H, s, H-2), 4.82 (1H, br s, H-1′), 3.69 (3H, s, CH_3), 3.54 (2H, m, 2 × H-2′), 2.97 (2H, t, *J* 6.8, 2 × H-3′), 0.56 (9H, s, Si(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 157.1, 140.8, 131.0, 127.7, 121.7, 119.7, 119.0, 114.7, 113.1, 52.1, 41.3, 26.0, 0.03; *m/z* (EI^+) 202.1 (35%, $[M - CH_2NHCO_2Me]^+$), 130.0 (100%, $[M - CH_2NHCO_2Me - SiMe_3 + H]^+$); HRMS ($EI^+$, $[M]^+$) $C_{15}H_{22}N_2O_2Si$ requires 290.1445, found 290.1445.

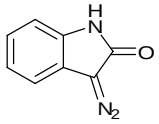
(*Z*)-4-Methyl-*N*′-(2-oxoindolin-3-ylidene)benzenesulfonohydrazide, 193[162] *



193

Tosyl hydrazine (7.75 g, 41.6 mmol) was added in one portion to a refluxing solution of isatin **192** (6.0 g, 40.8 mmol) in methanol (180 mL). After 30 minutes the solution was allowed to cool to room temperature over 90 minutes and the precipitate filtered and washed with ice cold methanol (2 × 50 mL) to give the tosylhydrazone **193** (12.5 g, 98%) as yellow needles; m.p 190-191 °C (dec.) (lit. 190-200 °C, MeOH); ν_{max} (KBr disc)/cm^{-1} 3352 (NH), 3159 (NH), 3060, 2821, 1717 (C=O), 1620, 1467, 1170, 1081, 863, 758, 676; ^{1}H NMR (300 MHz, d_6-DMSO) 10.77 (1H, br s, N*H*), 7.90-7.82 (3H, m, H-4 and 2 × Ar-H (tosyl)), 7.44 (2H, d, *J* 8.0, 2 × Ar-H (tosyl)), 7.38 (1H, dd (app. t), *J* 7.7, H-6), 7.06 (1H, dd (app. t), *J* 7.7, H-5), 6.85 (1H, d, *J* 7.8, H-7), 2.38 (3H, s, CH_3); ^{13}C NMR (75 MHz, d_6-DMSO) 164.1, 144.5, 144.3, 135.6, 133.5, 130.0, 128.3, 127.0, 122.1, 115.6, 111.0, 110.9, 21.4; *m/z* LRMS (EI^+) 159.1 (60%, $[M - H - tosyl]^+$). Data consistent with the literarture.[162]

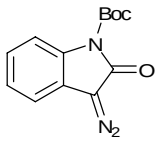
3-Diazoindolin-2-one, 191[162] *



191

Sodium hydroxide (1.14 g, 28.6 mmol) in water (60 mL) was added *via* dropping funnel to a solution of tosylhydrazone **193** (3.00 g, 9.52 mmol) in water (40 mL). The mixture was warmed to 50 °C for 20 h then allowed to cool to room temperature before quenching with dry ice. The resulting suspension was filtered and the product washed with ice cold water. The solid was taken up in acetone (50 mL), dried ($MgSO_4$) and reduced *in vacuo* to give 3-diazooxindole **191** (1.25 g, 83 %) as an orange powder; m.p. 171-173 °C (lit. 171-173.5 °C); ν_{max} (KBr disc)/cm^{-1} 3126 (NH), 3022, 2895, 2802, 2089 (N≡N), 1678 (C=O), 1617, 1465, 1212, 1096, 747, 662; ^{1}H NMR (300 MHz, $CDCl_3$) 9.15 (1H, br s, N*H*) 7.19 (1H, d, *J* 7.8, H-4), 7.16-7.05 (2H, m, H-6 and H-5), 7.01 (1H, d, *J* 7.8, H-7); ^{13}C NMR (75 MHz, $CDCl_3$) 169.3, 131.9, 125.6, 122.2, 118.4, 117.3, 110.8. C=N_2 signal not observed; *m/z* LRMS (EI^+) 159.1 (42%, $[M]^+$), 131.0 (45%, $[M - N_2]^+$); HRMS (EI^+, $[M]^+$) $C_8H_5N_3O$ requires 159.0427, found 159.0428. Data consistent with the literature.[162]

***tert*-Butyl 3-diazo-2-oxoindoline-1-carboxylate, 190 ***

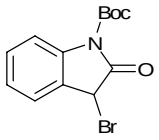


190

Triethylamine (0.79 mL, 5.66 mmol) was added in one portion to a solution of 3-diazooxindole **191** (600 mg, 3.77 mmol), 4-dimethylaminopyridine (34 mg, 0.28 mmol) and di-*tert*-butyl dicarbonate (1.65 g, 7.55 mmol) in tetrahydrofuran (12 mL). After 15 minutes the reaction was diluted with water (15 mL) and ethyl acetate (15 mL). The phases were separated and the aqueous phase extracted with ethyl acetate (3 × 10 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and reduced *in vacuo*. Purification by flash column chromatography (SiO_2, hexane/ethyl acetate 100 : 1) gave *N*-BOC-3-diazooxindole **190** (909 mg, 93%) as a red powder; m.p. 54-56 °C; ν_{max} (KBr disc)/ cm^{-1} 3055, 2982, 2934, 2101 (N≡N), 1778 (C=O), 1734 (C=O), 1687, 1462, 1343, 1320, 1149, 843, 737; ^{1}H NMR (300

MHz, $CDCl_3$) 7.90 (1H, dd, *J* 6.3 and 2.4, H-7), 7.25-7.14 (3H, m, H-6, H-5 and H-4), 1.66 (9H, s, $(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 165.3, 149.4, 131.2, 126.5, 124.9, 118.0, 116.3, 116.0, 85.1, 28.5. C=N_2 signal not observed; *m/z* LRMS (EI^+) 259.1 (10%, $[M]^+$), 159.1 (30%, $[M - CO_2{}^tBu + H]^+$), 131.1 (30%, $[M - CO_2{}^tBu - N_2 + H]^+$), 57.2 (100%, ^tBu); HRMS (EI^+, $[M]^+$) $C_{13}H_{13}N_3O_3$ requires 259.0951, found 259.0947.

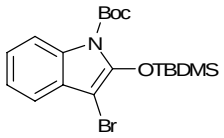
tert-Butyl 3-bromo-2-oxoindoline-1-carboxylate, 189 *



189

A solution hydrogen bromide in acetic acid (33% weight, 0.62 mL, 3.44 mmol) was added dropwise to a solution of *N*-BOC-3-diazooxindole **190** (892 mg, 3.44 mmol) in dichloromethane (60 mL) at -78 °C. After 45 minutes a further portion of hydrogen bromide in acetic acid (0.30 mL) was added dropwise. After 1 h the reaction was quenched with saturated sodium hydrogen carbonate (30 mL) and allowed to warm to room temperature. The phases were separated and the aqueous phase extracted with dichloromethane (3 × 20 mL). The combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and reduced *in vacuo*. Purification by flash column chromatography (SiO_2, hexane/ethyl acetate 12 : 1) gave 3-bromo-*N*-BOC-oxindole **189** (825 mg, 77%) as a red oil that solidified on standing; m.p. 99-101 °C; ν_{max} (KBr disc)/cm^{-1} 3120, 3052, 2983, 2971, 1774 (C=O), 1730 (C=O), 1477, 1372, 1288, 1089, 843, 750; ^1H NMR (300 MHz, $CDCl_3$) 7.84 (1H, d, *J* 8.1, H-7), 7.43 (1H, d, *J* 7.5, H-4), 7.38 (1H, dd, *J* 8.1 and 7.8, H-6), 7.21 (1H, dd, *J* 7.8 and 7.5, H-5), 5.37 (1H, s, H-3), 1.65 (9H, s, $(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 170.5, 149.2, 140.3, 131.1, 126.4, 125.5, 125.3, 116.0, 85.5, 39.5, 28.5; *m/z* LRMS (CI^+) 329.2 (62%, $[M + NH_4]^+$), 251.2 (100%, $[M - {}^{79}Br + NH_3 + H]^+$), 195.1 (100%, $[M - {}^{79}Br - {}^tBu + NH_3 + 2H]^+$), 151.1 (100%, $[M - {}^{79}Br - CO_2{}^tBu + NH_3 + 2H]^+$); HRMS ($ESI^+$, $[M + NH_4]^+$) $C_{13}H_{18}{}^{79}BrN_2O_3$ requires 329.0495, found 329.0494.

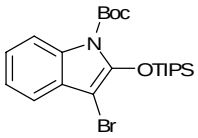
tert-Butyl 3-bromo-2-(_tert_-butyldimethylsilyloxy)-1_H_-indole-1-carboxylate, 194 *



194

A solution of 3-bromo *N*-BOC-oxindole **189** (825 mg, 2.64 mmol) in tetrahydrofuran (80 mL) was cooled to -78 °C. Sodium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 3.96 mL, 3.96 mmol) was added dropwise. After 50 minutes *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.21 mL, 5.29 mmol) was added dropwise. After a further 1 h the reaction was quenched with saturated sodium hydrogen carbonate (20 mL) and diluted with dichloromethane (40 mL). The phases were separated and the aqueous phase extracted with dichloromethane (3 × 20 mL). The combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and reduced *in vacuo*. Purification by flash column chromatography (SiO_2, hexane/ethyl acetate 100 : 1) gave TBDMS enol ether **194** (893 mg, 79 %) as a viscous colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$) 7.81 (1H, dd, *J* 6.6 and 1.5, H-7), 7.38 (1H, dd, *J* 5.8 and 1.4, H-4), 7.25 (1H, ddd, *J* 7.3, 6.6 and 1.4, H-6), 7.20 (1H, ddd, *J* 7.3, 5.8 and 1.7, H-5), 1.68 (9H, s, O(CH_3)$_3$), 1.08 (9H, s, (CH_3)$_3$), 0.31 (6H, s, 2 × (CH_3)); ^{13}C NMR (75 MHz, $CDCl_3$) 149.0, 145.3, 130.8, 127.7, 123.5, 123.4, 118.4, 114.9, 84.6, 80.8, 28.7, 26.2, 18.9, -3.30; *m/z* LRMS (EI$^+$) 427.1 (100%, [*M*(^{81}Br)]$^+$), 425.1 (95%, [*M*(^{79}Br]$^+$), 312.0 (32%, [*M* - 2 × ^{t}Bu + H]$^+$), 57.0 (100%, C(CH_3)$_3$); HRMS (EI$^+$, [*M*]$^+$) $C_{19}H_{28}{}^{79}BrNO_3Si$ requires 425.1016, found 425.1013.

tert-Butyl 3-bromo-2-(tri_iso_propylsilyloxy)-1_H_-indole-1-carboxylate, 195 *

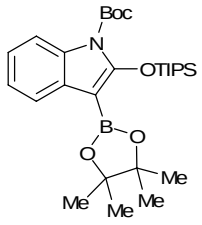


195

A solution of 3-bromo *N*-BOC-oxindole **189** (1.5 g, 4.8 mmol) in tetrahydrofuran (80 mL) was cooled to -78 °C. Sodium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 7.5 mL, 7.2 mmol) was added dropwise. After 50 minutes tri*iso*propylsilyl trifluoromethanesulfonate (2.7 mL, 9.6 mmol) was added dropwise.

After a further 1 h the reaction was quenched with saturated sodium hydrogen carbonate (30 mL) and diluted with dichloromethane (60 mL). The phases were separated and the aqueous phase extracted with dichloromethane (3 × 20 mL). The combined organic phases were washed with brine (40 mL), dried ($MgSO_4$) and reduced *in vacuo*. Purification by flash column chromatography (SiO_2, hexane/ethyl acetate 100 : 1) gave TIPS enol ether **195** (1.96 g, 87%) as a viscous colourless oil that solidified on standing to give a white powder; m.p. 78-80 °C; ν_{max} (KBr disc)/cm^{-1} 3053, 2943, 2868, 1749 (C=O), 1618, 1454, 1369, 1215, 1134, 1001, 954, 741; ^{1}H NMR (300 MHz, $CDCl_3$) 7.68 (1H, dd, *J* 7.3 and 1.8, H-7), 7.28 (1H, dd, *J* 6.0 and 1.6, H-4), 7.14 (1H, ddd, *J* 7.3, 6.0 and 1.8, H-5), 7.10 (1H, dd (app. t), *J* 7.3, H-6), 1.60 (9H, s, O(C*H*$_3$)$_3$), 1.43 (3H, sep, 3 × (C*H*(CH$_3$)$_2$)), 1.08 (18H, d, *J* 7.5, 3 × (CH(C*H*$_3$)$_2$)); ^{13}C NMR (75 MHz, $CDCl_3$) 148.8, 145.8, 130.3, 127.7, 123.4, 123.2, 118.3, 114.8, 84.4, 79.8, 28.6, 18.3, 14.3; *m/z* LRMS (CI^+) 468.2 (25%, [*M*(^{79}Br)]$^+$), 412.2 (15%, [*M* – ^{t}Bu + H]$^+$), 390.4 (15%, [*M* – ^{79}Br + H]$^+$), 290.3 (100%, [*M* – $CO_2{}^t$Bu – ^{79}Br + 2H]$^+$); HRMS (ESI^+, [*M* + H]$^+$) $C_{22}H_{35}{}^{79}BrNO_3Si$ requires 468.1564, found 468.1567.

tert-Butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(tri*iso*propylsilyloxy)-1*H*-indole-1-carboxylate, 200 *

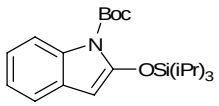


200

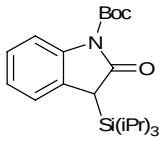
A screw capped vial was charged with TIPS enol ether **195** (400 mg, 0.85 mmol), palladium acetate (9.6 mg, 0.043 mmol) and 2-(dicyclohexylphosphino)biphenyl **L24** (60 mg, 0.17 mmol). After purging three times with nitrogen, dioxane (8 ml), pinacolborane **156** (328 mg, 2.56 mmol) and triethylamine (0.48 mL, 3.42 mmol) were added sequentially. After heating at 100 °C for 90 minutes, the reaction was cooled to room temperature and diluted with ethyl acetate (25 mL) and water (25 mL). The phases were separated and the organic phase washed with water (3 × 25 mL), brine (30 mL), dried ($MgSO_4$) and reduced *in vacuo*. Purification by flash

column chromatography (SiO_2, hexane/ethyl acetate 100 : 1) gave boronic ester **200** (375 mg, 86%) as white plates; m.p. 89-91 °C; ν_{max} (KBr disc)/cm^{-1} 3049, 2977, 2867, 1749 (C=O), 1568, 1466, 1322, 1143, 1003, 885, 686; ^{1}H NMR (300 MHz, $CDCl_3$) 7.92 (1H, d, *J* 7.3, H-7), 7.69 (1H, d, *J* 8.0, H-4), 7.16-7.13 (2H, m, H-6 and H-5), 1.68 (9H, s, C(CH_3)$_3$), 1.34 (12H, s, 2 × (C(CH_3)$_2$)), 1.59 (3H, sep, *J* 7.5, 3 × (C*H*(CH_3)$_2$)), 1.14 (18H, d, *J* 7.5, 3 × (CH(CH_3)$_2$)); ^{13}C NMR (75 MHz, $CDCl_3$) 156.2, 148.9, 131.8, 131.7, 122.6, 121.5, 121.3, 113.5, 83.5, 82.6, 28.2, 24.9, 18.1, 13.7 (one carbon signal not observed); ^{11}B NMR (96 MHz, $CDCl_3$) 30.9; *m/z* LRMS (CI^+) 516.4 (50%, $[M + H]^+$), 416.4 (65%, $[M - CO_2{}^tBu + H]^+$), 290.3 (100%, $[M - CO_2{}^tBu - B(Pin) + H]^+$); HRMS ($ESI^+$, $[M + H]^+$) $C_{28}H_{47}BNO_3Si$ requires 516.3311, found 516.3314.

tert-Butyl 2-(tri*iso*propylsilyloxy)-1*H*-indole-1-carboxylate 196 and _tert_-butyl 2-oxo-3-(tri*iso*propylsilyl)indoline-1-carboxylate, 197 *



196



197

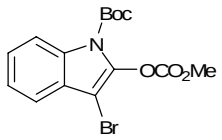
tert-Butyllithium (1.6 M in hexane, 73 μL, 0.12 mmol) was added dropwise to a solution of TIPS enol ether **195** (50 mg, 0.11 mmol) in tetrahydrofuran (1 ml) at -78 °C. After 30 minutes trimethyl borate (24 μL, 0.21 mmol) was added dropwise. After a further 30 minutes the reaction was allowed to warm to room temperature and the solution reduced *in vacuo*. Purification by flash column chromatography (SiO_2, hexane/ethyl acetate 50 : 1) gave the debrominated product **196** (13 mg, 32%) as a colourless oil and the reverse Brook rearrangement product **197** (16 mg, 39%) as a white solid;

tert-Butyl 2-(tri*iso*propylsilyloxy)-1*H*-indole-1-carboxylate, 196: ^{1}H NMR (300 MHz, $CDCl_3$) 7.87 (1H, m, H-7), 7.30 (1H, m, H-4), 7.15-7.08 (2H, m, H-6 and H-5), 5.61 (1H, s, H-3), 1.66 (9H, s, C(CH_3)$_3$), 1.39 (3H, sep, *J* 7.3, 3 × (C*H*(CH_3)$_2$)), 1.16 (18H, d, *J* 7.3, 3 × (CH(CH_3)$_2$)); ^{13}C NMR (75 MHz, $CDCl_3$) 149.2, 148.8, 131.3, 128.3, 122.5, 121.3, 118.5, 114.4, 86.8, 83.3, 28.3, 17.8, 12.7; *m/z* LRMS (CI^+) 390.4 (85%, $[M + H]^+$), 334.3 (35%, $[M - {}^tBu + 2H]^+$), 290.3 (100%, [*M* –

$CO_2{}^tBu + H]^+$); HRMS (ESI^+, $[M + H]^+$) $C_{22}H_{36}NO_3Si$ requires 390.2459, found 390.2456.

***tert*-Butyl 2-oxo-3-(tri*iso*propylsilyl)indoline-1-carboxylate, 197**: ν_{max} (KBr disc)/cm^{-1} 2943 and 2866 (saturated CH), 1745 (C=O), 1730 (C=O), 1604, 1478, 1348, 1294, 1147, 1046, 846, 778; ^1H NMR (300 MHz, $CDCl_3$) 7.85 (1H, d, *J* 7.9, H-7), 7.22 (1H, dd, *J* 7.9 and 7.6, H-6), 7.15 (1H, d, *J* 7.2, H-4), 7.07 (1H, dd, *J* 7.6 and 7.2, H-5), 3.74 (1H, s, H-3), 1.63 (9H, s, $C(CH_3)_3$), 1.41 (3H, sep, *J* 7.5, 3 × $CH(CH_3)_2$), 1.13 (18H, d, *J* 7.5, 3 × ($CH(CH_3)_2$)); ^{13}C NMR (75 MHz, $CDCl_3$) 175.3, 149.6, 139.6, 127.3, 126.4, 123.6, 122.8, 114.7, 83.8, 37.5, 28.2, 18.3, 10.9; *m/z* LRMS (CI^+) 390.4 (10%, $[M + H]^+$), 334.3 (25%, $[M - {}^tBu + 2H]^+$), 290.3 (100%, $[M - CO_2{}^tBu + H]^+$); HRMS (ESI^+, $[M + H]^+$) $C_{22}H_{36}NO_3Si$ requires 390.2459, found 390.2459.

tert-Butyl 3-bromo-2-(methoxycarbonyloxy)-1*H*-indole-1-carboxylate, 211

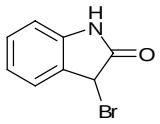


211

A solution of 3-bromo-*N*-BOC-oxindole **189** (650 mg, 2.1 mmol) in tetrahydrofuran (40 mL) was cooled to -78 °C. Sodium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 2.43 mL, 2.43 mmol) was added dropwise. After 50 minutes methyl chloroformate (0.63 mL, 8.10 mmol) was added dropwise. After a further 1 h the reaction was quenched with saturated sodium hydrogen carbonate (30 mL) and diluted with dichloromethane (60 mL). The phases were separated and the aqueous phase extracted with dichloromethane (3 × 20 mL). The combined organic phases were washed with brine (40 mL), dried ($MgSO_4$) and reduced *in vacuo*. Purification by flash column chromatography (SiO_2, hexane/ethyl acetate 100 : 1) gave carbonate **211** (1.96 g, 87%) as a viscous colourless oil that solidified on standing to give colourless plates; m.p. 113-115 °C; ν_{max} (film)/cm^{-1} 3057, 2982, 2934, 1786 (C=O), 1743 (C=O), 1615, 1451, 1322, 1242, 1161, 941, 751; ^1H NMR (400 MHz, $CDCl_3$) 8.13 (1H, d, *J* 7.5, H-7), 7.52 (1H, d, *J* 7.4 and 1.3, H-4), 7.38 (1H, ddd, *J* 7.5, 7.4 and 1.3, H-6), 7.33 (1H, ddd (app t), *J* 7.4 and 1.3, H-5), 4.00 (3H, s, OCH_3), 1.66 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) 152.0, 148.1, 138.3, 131.7, 125.7,

125.5, 123.7, 119.2, 115.4, 88.2, 85.2, 56.3, 28.0; *m/z* HRMS (ESI^+, $[M + Na]^+$) $C_{15}H_{16}{}^{79}BrNNaO_5$ requires 392.0104, found 392.0102.

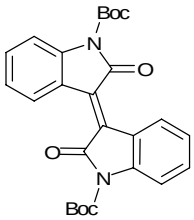
3-Bromoindolin-2-one, *N*-H 189 *



***N*-H 189**

A solution of hydrogen bromide in acetic acid (33% weight, 1.03 mL, 5.66 mmol) was added dropwise to a solution of 3-diazooxindole **191** (600 mg, 3.77 mmol) in dichloromethane (45 mL) at 0 °C. After 15 minutes the reaction was quenched with saturated sodium hydrogen carbonate (20 mL). The phases were separated and the organic phase washed with 10% sodium thiosulphate solution (20 mL), brine (20 mL), dried ($MgSO_4$) and reduced *in vacuo*. Purification by flash column chromatography (SiO_2, hexane/ethyl acetate 5 : 1) gave 3-bromooxindole ***N*-H 189** (689 mg, 86%) as a pale yellow powder; m.p. 153-154 °C (dec); ν_{max} (KBr disc)/cm^{-1} 3374 (NH), 3085, 3037, 2972, 1706 (C=O), 1621, 1472, 1336, 1199, 1097, 845, 674; ^{1}H NMR (300 MHz, d_6-DMSO) 10.76 (1H, br s, N*H*), 7.33 (1H, d, *J* 7.5, H-4), 7.27 (1H, dd, *J* 7.8 and 7.2, H-6), 7.01 (1H, dd, *J* 7.5 and 7.2, H-5), 6.86 (1H, d, *J* 7.8, H-7), 5.70 (1H, s, H-3); ^{13}C NMR (75 MHz, d_6-DMSO) 173.9, 142.7, 130.6, 127.4, 126.4, 122.6, 110.5. 40.9; *m/z* LRMS (EI^+) 211.0 (10%, $[M(^{79}Br)^+]$), 133.1 (100%, $[M - {}^{79}Br + H]^+$); HRMS (ESI^+, $[M + NH_4]^+$) $C_8H_{10}{}^{79}BrN_2O$ requires 228.9972, found 228.9971.

***N*,*N'*-di(*tert*-butoxycarbonyl)isoindigo, 202**



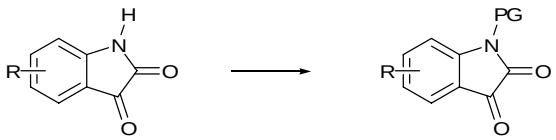
202

Anhydrous sodium carbonate (564 mg) was added in one portion to a solution of 3-bromo-oxindole ***N*-H 189** (200 mg, 0.94 mmol) and di-*tert*-butyl dicarbonate (467

mg, 2.36 mmol) in tetrahydrofuran (5 mL). After 1 h at room temperature the reaction was heated at 40 °C for 24 h. The mixture was diluted with dichloromethane (20 mL) and water (20 mL) and the phases separated. The organic phase was washed successively with saturated sodium thiosulphate (10 mL), water (20 mL) and brine (20 mL), then dried ($MgSO_4$) and reduced *in vacuo*. Purification by flash column chromatography (SiO_2, hexane/diethyl ether 6 : 1) gave dimer **202** (131 mg, 60%) as a red powder; m.p. 152-153 °C; ν_{max} (film)/cm^{-1} 2980, 2934, 1783 (C=O), 1738 (C=O), 1600, 1339, 1153, 774, 660; ^{1}H NMR (400 MHz, $CDCl_3$) 8.96 (2H, d, *J* 7.8, 2 × H-7), 7.81 (2H, d, *J* 7.8, 2 × H-4), 7.43 (2H, ddd (app. td), *J* 7.8 and 1.3, 2 × H-5), 7.18 (2H, ddd (app. td), 7.8 and 1.3, 2 × H-6), 1.68 (18H, s, 2 × C(C*H*$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) 165.8, 148.7, 141.1, 133.1, 132.6, 129.1, 124.0, 121.7, 114.2, 84.8, 28.1; *m/z* HRMS (ESI$^+$, [*M* + MeOH + Na]$^+$) $C_{27}H_{30}N_2NaO_7$ requires 493.1969, found 493.1970.

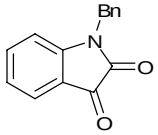
N.B. *N*,*N*′-di(*tert*-butoxycarbonyl)isoindigo **202** was also prepared under anhydrous Suzuki coupling conditions (section 4.7.1.) and by enolisation of *tert*-Butyl 3-bromo-2-oxoindoline-1-carboxylate **189** with alkali metal bases (section 4.7.3.).

General procedure A: *N*-protection of isatins with benzylic bromides



Based on a procedure by Marti and Carreira;[162] A solution of the appropriate isatin (6.80 mmol) in dimethylformamide (12.5 mL) was added dropwise to a suspension of sodium hydride (60% dispersion in mineral oil, 290 mg, 7.14 mmol) in dimethylformamide (12.5 mL) at 0 °C. After 30 minutes benzyl or *para*-methoxybenzyl bromide (8.16 mmol) was added dropwise to the purple solution. After a further 45 minutes the reaction was quenched at 0 °C by the addition of water (50 mL) upon which time the product precipitated from the solution. The desired *N*-protected isatin (appearance as described) was isolated by filtration, washed with water and hexane, and dried over P_2O_5 under high vacuum.

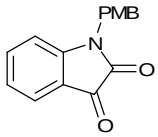
1-Benzylindoline-2,3-dione, 224[162]



224

Prepared according to the general procedure **A**; Isolated as a red powder (96%); m.p. 131-133 °C (H_2O) (lit. 133-135 °C); ^{1}H NMR (200 MHz, $CDCl_3$) 7.61 (1H, d, *J* 7.5, H-4), 7.50 (1H, ddd (app td), *J* 7.8 and 1.3, H-6), 7.40-7.32 (5H, m, 5 × Ar-H (benzyl)), 7.10 (1H, dd, *J* 7.8 and 7.5, H-5), 6.79 (1H, d, *J* 7.8, H-7), 4.95 (2H, s, CH_2 (benzyl)). Data consistent with the literature.[162]

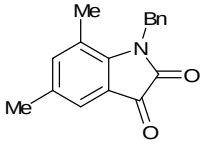
1-(4-Methoxybenzyl)indoline-2,3-dione, 225[201]



225

Prepared according to the general procedure **A**; Isolated as a tan powder (70%); m.p. 171-172 °C (H_2O) (lit. 171-172 °C (EtOH)); ν_{max} (film)/cm^{-1} 2958, 2854, 1735 (C=O), 1611, 1468, 1313, 1179, 1003, 761; ^{1}H NMR (400 MHz, $CDCl_3$) 7.59 (1H, d, *J* 7.3, H-4), 7.49 (1H, ddd (app td), *J* 7.8 and 1.2, H-6), 7.28 (2H, d, *J* 8.6, 2 × Ar-H (PMB)), 7.08 (1H, dd (app. t), *J* 7.8, H-5), 6.88 (2H, d, *J* 8.6, 2 × Ar-H (PMB)), 6.81 (1H, d, *J* 7.8, H-7), 4.86 (2H, s, CH_2 (PMB)), 3.78 (3H, s, OCH_3 (PMB)); ^{13}C NMR (100 MHz, $CDCl_3$) 183.3, 159.3, 158.2, 150.7, 138.2, 128.9, 126.4, 125.3, 123.7, 117.6, 114.3, 111.0, 55.2, 43.5. Data consistent with the literature.[201]

1-Benzyl-5,7-dimethylindoline-2,3-dione, 237

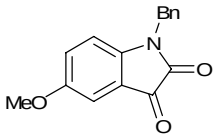


237

Prepared according to the general procedure **A**; Isolated as brown powder (86%); m.p. 209-210 °C (H_2O); ν_{max} (film)/cm^{-1} 3031, 2923, 1731 (C=O), 1602, 1488, 1344,

1165, 779, 698; ^{1}H NMR (400 MHz, $CDCl_3$) 7.36-7.26 (4H, m, H-4 and 3 × Ar-H (benzyl)), 7.20 (2H, d, *J* 7.8, 2 × Ar-H (benzyl)), 7.08 (1H, s, H-6), 5.17 (2H, s, CH_2 (benzyl)), 2.27 (3H, s, CH_3), 2.21 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 183.9, 159.6, 146.3, 143.0, 136.3, 133.8, 129.0, 127.6, 125.6, 123.8, 121.7, 118.8, 45.2, 20.3, 18.4; *m/z* (ESI$^+$, [*M* + Na]$^+$) $C_{17}H_{15}NNaO_2$ requires 288.0995, found 288.0997.

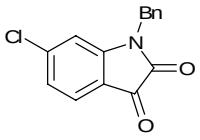
1-Benzyl-5-methoxyindoline-2,3-dione, 238



238

Prepared according to the general procedure **A**; Isolated as brown powder (92%); m.p. 120-121 °C (H_2O); ν_{max} (film)/cm^{-1} 2924, 1731 (C=O), 1489, 1340, 1274, 1176, 1017, 822, 773, 699; ^{1}H NMR (400 MHz, $CDCl_3$) 7.36-7.26 (5H, m, 5 × Ar-H (benzyl)), 7.12 (1H, d, *J* 2.7, H-4), 7.01 (1H, dd, *J* 8.6 and 2.7, H-6), 6.67 (1H, d, *J* 8.6, H-7), 4.89 (2H, s, CH_2 (benzyl)), 3.76 (3H, s, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 183.6, 158.3, 156.5, 144.5, 134.5, 129.0, 128.0, 127.3, 124.6, 118.0, 112.0, 109.5, 55.9, 44.0; *m/z* (ESI$^+$, [*M* + Na]$^+$) $C_{16}H_{13}NNaO_3$ requires 290.0788, found 290.0790.

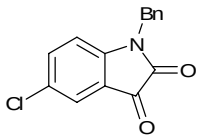
1-Benzyl-6-chloroindoline-2,3-dione, 239



239

Prepared according to the general procedure **A**; Isolated as red plates after column chromatography (SiO_2, petrol/diethyl ether 2 : 1; 80%); m.p. 174-175 °C (hexane); ν_{max} (film)/cm^{-1} 3073, 2925, 1736 (C=O), 1611, 1435, 1369, 1350, 1105, 1073, 878, 793 699; ^{1}H NMR (400 MHz, $CDCl_3$) 7.54 (1H, d, *J* 8.0, H-4), 7.40-7.30 (5H, m, 5 × Ar-H (benzyl)), 7.07 (1H, dd, *J* 8.0 and 1.6, H-5), 6,78 (1H, d, *J* 1.6, H-7), 4.91 (2H, s, CH_2 (benzyl)); ^{13}C NMR (100 MHz, $CDCl_3$) 181.6, 158.2, 151.6, 144.7, 134.0, 129.1, 128.3, 127.4, 126.4, 124.1, 115.9, 111.6, 44.2; *m/z* (ESI$^+$, [*M* + Na]$^+$) $C_{15}H_{10}ClNNaO_2$ requires 294.0292, found 294.0287.

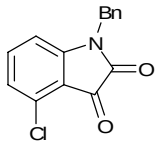
1-Benzyl-5-chloroindoline-2,3-dione, 240



240

Prepared according to the general procedure **A**; Isolated as a brown powder (92%); m.p. 140-142 °C (H_2O); ν_{max} (film)/cm^{-1} 3093, 2924, 1739 (C=O), 1607, 1473, 1446, 1328, 1173, 1176, 823, 697; ^1H NMR (400 MHz, $CDCl_3$) 7.55 (1H, s, H-4), 7.42 (1H, d, *J* 8.4, H-7), 7.38-7.28 (5H, m, 5 × Ar-H (benzyl)), 6.73 (1H, d, *J* 8.4, H-6), 4.92 (2H, s, CH_2 (benzyl)); ^{13}C NMR (100 MHz, $CDCl_3$) 182.3, 157.7, 148.9, 137.7, 134.0, 129.7, 129.2, 128.4, 127.4, 125.3, 118.5, 112.4, 44.2; *m/z* (ESI^+, $[M + Na]^+$) $C_{15}H_{10}ClNNaO_2$ requires 294.0292, found 294.0282.

1-Benzyl-4-chloroindoline-2,3-dione, 241



241

Prepared according to the general procedure **A**; Isolated as red plates after column chromatography (SiO_2, petrol/diethyl ether 2 : 1; 84%); m.p. 153-155 °C (hexane); ν_{max} (film)/cm^{-1} 3095, 2925, 1739 (C=O), 1600, 1452, 1330, 1234, 1150, 865, 780; ^1H NMR (400 MHz, $CDCl_3$) 7.41-7.27 (6H, m, H-6 and 5 × Ar-H (benzyl)), 7.01 (1H, d, *J* 8.2, H-5), 6.69 (1H, d, *J* 8.0, H-7), 4.93 (2H, s, CH_2 (benzyl)); ^{13}C NMR (100 MHz, $CDCl_3$) 180.1, 157.4, 151.7, 138.5, 134.2, 133.9, 129.1, 128.3, 127.4, 125.4, 114.7, 109.3, 44.2; *m/z* (ESI^+, $[M + Na]^+$) $C_{15}H_{10}ClNNaO_2$ requires 294.0292, found 294.0292.

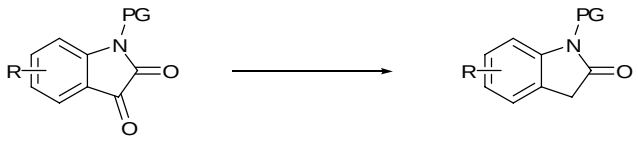
Preparation of Oxindoles

The *N*-protected oxindoles were prepared by one of two methods, either by reaction of the free oxindole with the appropriate anhydride and sodium carbonate or by reduction of the parent *N*-protected isatin with hydrazine monohydrate.

General Procedure B: The direct protection of oxindoles (representative)

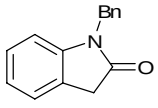
Pivalic anhydride (0.76 mL, 3.75 mmol) was added in one portion to a solution of oxindole (200 mg, 1.5 mmol), DMAP (approx 5 mg) and anhydrous sodium carbonate (900 mg) in tetrahydrofuran (8 mL). After 20 h at 70 °C the reaction was diluted with dichloromethane (20 mL) and water (10 mL), the phases separated and the aqueous phase extracted with dichloromethane (3 × 10 mL). The combined organic phases were dried ($MgSO_4$) and reduced *in vacuo*. Purification by column chromatography (SiO_2, petrol/diethyl ether 4 : 1) gave the desired protected oxindole.

General procedure C: The reduction of *N*-protected isatins to oxindoles



Based on a procedure by Marti and Carreira; A suspension of the protected isatin (1.88 mmol) in hydrazine hydrate (2 mL) was heated to reflux for 1.5 h. After cooling to room temperature, the reaction was diluted with water (20 mL) and ethyl acetate (20 mL), the phases separated and the aqueous phase extracted with ethyl acetate (3 × 10 mL). The combined organics were dried ($MgSO_4$) and reduced *in vacuo*. Purification by flash column chromatography (SiO_2, petrol/diethyl ether 2 : 1) and subsequent recrystallisation from diethyl ether gave the desired *N*-benzyl oxindole (appearance as described).

1-Benzylindolin-2-one, 226[162]

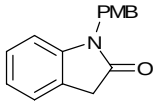


226

Prepared according to the general procedure **C**; Isolated as white needles (88%); ν_{max} (film)/cm^{-1} 1710 (C=O); ^1H NMR (400 MHz, $CDCl_3$) 7.35-7.24 (6H, m, H-4 and 5 ×

Ar-H (benzyl)), 7.18 (1H, dd, *J* 7.8 and 7.7, H-6), 7.02 (1H, dd, *J* 7.7 and 7.4, H-5), 6.74 (1H, d, *J* 7.8, H-7), 4.94 (2H, s, CH_2 (benzyl)), 3.64 (2H, s, 2 × H-3); ^{13}C NMR (100 MHz, $CDCl_3$) 175.1, 144.2, 135.8, 128.7, 127.8, 127.6, 127.3, 124.4, 124.3, 122.3, 109.0, 43.7, 35.7. Data consistent with the literature.[162]

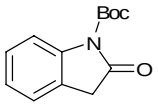
1-(4-Methoxybenzyl)indolin-2-one, 227[202]



227

Prepared according to the general procedure **C**; Isolated as white needles (75%); ν_{max} (film)/cm^{-1} 3056, 2932, 2835, 1711 (C=O), 1613, 1513, 1353, 1248, 1032, 749; ^{1}H NMR (400 MHz, $CDCl_3$) 7.28-7.23 (3H, m, H-4 and Ar-H (PMB)), 7.18 (1H, dd, *J* 7.8 and 7.7, H-6), 7.01 (1H, dd, *J* 7.8 and 7.7, H-5), 6.85 (2H, d, *J* , Ar-H (PMB)), 6.76 (1H, d, *J* 7.8, H-7), 4.86 (2H, s, CH_2 (PMB)), 3.78 (3H, s, OCH_3), 3.61 (2H, s, 2 × H-3); ^{13}C NMR (100 MHz, $CDCl_3$) 175.1, 159.0, 144.3, 128.8, 128.0, 127.8, 124.5, 124.4, 122.3, 114.1, 109.1, 55.3, 43.2, 35.8. Data consistent with the literature.[202]

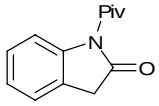
***tert*-Butyl 2-oxoindoline-1-carboxylate, 229[203]**



229

Prepared according to the general procedure **B**; employing di-*tert*-butyl dicarbonate as the electrophile at room temperature. The product was isolated as a white powder (73%); ^{1}H NMR (300 MHz, $CDCl_3$) 7.79 (1H, d, *J* 8.1, H-7), 7.30 (1H, dd, *J* 8.1 and 7.7, H-6), 7.24 (1H, d, *J* 7.6, H-4), 7.13 (1H, dd, *J* 7.7 and 7.4, H-5), 3.65 (2H, s, 2 × H-3), 1.65 (9H, s, C(CH_3)$_3$); Data consistent with the literature.[203]

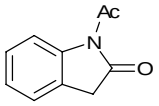
1-pivaloylindolin-2-one, 230[163]



230

Prepared according to the general procedure **B**; employing pivalic anhydride as the electrophile. The product was isolated as a purple powder (48%); ν_{max} (film)/cm^{-1} 3021, 2986, 2947, 2875, 1773 (C=O), 1698 (C=O), 1474, 1307, 1232, 1117, 865, 761; ^{1}H NMR (400 MHz, $CDCl_3$) 7.46 (1H, d, *J* 8.1, H-7), 7.31-7.24 (2H, m, H-6 and H-4), 7.13 (1H, dd (app. t), *J* 7.5, H-5), 3.67 (2H, s, 2 × H-3), 1.44 (9H, s, C(C*H*$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) 182.7, 174.0, 142.4, 127.9, 124.5, 124.2, 124.0, 114.2, 43.3, 36.6, 26.8; *m/z* (FI, [*M*]$^+$) $C_{13}H_{15}NO_2$ requires 217.1103, found 217.1103. Data consistent with the literature.[163]

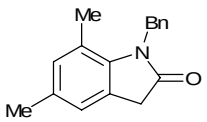
1-Acetylindolin-2-one, 231[192]



231

Prepared according to the general procedure **B**; employing acetic anhydride as the electrophile. The product was isolated as a white powder (92%); m.p. 125-127 °C (lit. 127-128 °C); ^{1}H NMR (400 MHz, $CDCl_3$) 8.23 (1H, d, *J* 8.0, H-7), 7.39-7.14 (3H, m, H-6, H-5 and H-4), 3.73 (2H, s, 2 × H-3), 2.69 (3H, s, C(O)C*H*$_3$); Data consistent with the literature.[192]

1-benzyl-5,7-dimethylindolin-2-one, 242

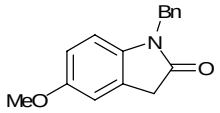


242

Prepared according to the general procedure **C**; Isolated as white needles (66%); m.p. 138 °C (Et_2O); ν_{max} (film)/cm^{-1} 3030, 2923, 1693 (C=O), 1483, 1358, 1212, 1017, 899, 712; ^{1}H NMR (400 MHz, $CDCl_3$) 7.28 (2H, dd (app. t), *J* 7.3, 2 × Ar-H

(benzyl)), 7.21 (1H, t, *J* 7.3, Ar-H (benzyl)), 7.13 (2H, d, *J* 7.3, 2 × Ar-H (benzyl)), 6.94 (1H, s, H-6), 6.73 (1H, s, H-4), 5.15 (2H, s, CH_2 (benzyl)), 3.60 (2H, s, 2 × H-3), 2.25 (3H, s, CH_3), 2.20 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 176.0, 139.8, 137.6, 132.0, 131.8, 128.7, 127.0, 125.5, 125.1, 123.0, 119.4, 44.8, 35.5, 20.6, 18.4; *m/z* (ESI$^+$, [*M* + Na]$^+$) $C_{17}H_{17}NNaO$ requires 274.1202, found 274.1206.

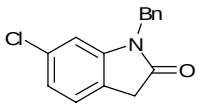
1-Benzyl-5-methoxyindolin-2-one, 243



243

Prepared according to the general procedure **C**; Isolated as white needles (62%); m.p. 50-52 °C (Et_2O); ν_{max} (film)/cm^{-1} 3062, 3031, 2938, 1706 (C=O), 1602, 1494, 1344, 1219, 1037, 804, 706; ^{1}H NMR (400 MHz, $CDCl_3$) 7.30-7.19, (5H, m, 5 × Ar-H (benzyl), 6.84 (1H, d, *J* 2.5, H-4), 6.65 (1H, dd, *J* 8.5 and 2.5, H-6), 6.56 (1H, d, *J* 8.5, H-7) 4.85 (2H, s, CH_2 (benzyl)), 3.71 (3H, s, OCH_3), 3.57 (2H, s, 2 × H-3); ^{13}C NMR (100 MHz, $CDCl_3$) 174.7, 155.8, 137.8, 135.9, 128.7, 127.5, 127.3, 125.8, 112.1, 111.9, 109.3, 55.7, 43.8, 36.1; *m/z* (ESI$^+$, [*M* + Na]$^+$) $C_{16}H_{15}NNaO_2$ requires 276.0995, found 276.0992.

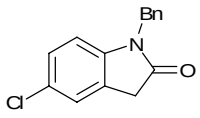
1-Benzyl-6-chloroindolin-2-one, 244



244

Prepared according to the general procedure **C**; Isolated as white needles (46%); m.p. 115 °C (Et_2O); ν_{max} (film)/cm^{-1} 3062, 3029, 2973, 1707 (C=O), 1614, 1489, 1367, 1221, 950, 917, 893; ^{1}H NMR (400 MHz, $CDCl_3$) 7.36-7.28 (5H, m, 5 × Ar-H (benzyl)), 7.15 (1H, d, *J* 7.9, H-4), 6.98 (1H, dd, *J* 7.9 and 1.8, H-5), 6.71 (1H, d, *J* 1.8, H-7), 4.88 (2H, s, CH_2 (benzyl)), 3.59 (2H, s, 2 × H-3); ^{13}C NMR (100 MHz, $CDCl_3$) 175.0, 145.5, 135.3, 133.6, 128.9, 127.8, 127.3, 125.3, 122.7, 122.3, 109.6, 43.9, 35.3; *m/z* (ESI$^+$, [*M* + Na]$^+$) $C_{15}H_{12}ClNNaO$ requires 280.0500, found 280.0499.

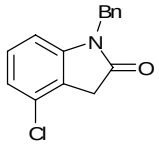
1-Benzyl-5-chloroindolin-2-one, 245



245

Prepared according to the general procedure **C**; Isolated as white needles (70%); m.p. 103 °C (Et_2O; lit: 103-104 °C); ν_{max} (film)/cm^{-1} 3064, 3031, 2923, 1711 (C=O), 1484, 1338, 1196, 1074, 808, 732, 699; ^1H NMR (400 MHz, $CDCl_3$) 7.30-7.21 (5H, m, 5 × Ar-H (benzyl)), 7.18 (1H, d, *J* 2.4, H-4), 7.08 (1H, dd, *J* 8.3 and 2.4, H-6), 6.57 (1H, d, *J* 8.3, H-7), 4.85 (2H, s, CH_2 (benzyl)), 3.57 (2H, s, 2 × H-3); ^{13}C NMR (100 MHz, $CDCl_3$) 174.4, 142.8, 135.4, 128.8, 127.7, 127.7, 127.2, 126.0, 124.8, 109.9, 43.8, 35.6, (one carbon signal not observed); *m/z* (ESI^+, $[M + Na]^+$) $C_{15}H_{12}ClNNaO$ requires 280.0500, found 280.0497.

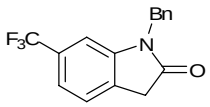
1-benzyl-4-chloroindolin-2-one, 246



246

Prepared according to the general procedure **C**; Isolated as white needles (69%); m.p. 121 °C (Et_2O); ν_{max} (film)/cm^{-1} 3033, 3008, 2929, 1703 (C=O), 1608, 1480, 1358, 1159, 771, 706; ^1H NMR (400 MHz, $CDCl_3$) 7.35-7.24 (5H, m, 5 × Ar-H (benzyl)), 7.11 (1H, dd, *J* 8.0 and 8.0, H-6), 6.98 (1H, d, *J* 8.0, H-5), 6.61 (1H, d, *J* 7.0, H-7), 4.90 (2H, s, CH_2 (benzyl)), 3.62 (2H, s, 2 × H-3); ^{13}C NMR (100 MHz, $CDCl_3$) 174.1, 145.3, 135.4, 130.4, 129.2, 128.8, 127.7, 127.3, 123.0, 122.5, 107.3, 44.0, 35.3; *m/z* (ESI^+, $[M + Na]^+$) $C_{15}H_{12}ClNNaO$ requires 280.0500, found 280.0497.

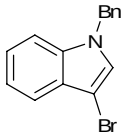
1-Benzyl-6-(trifluoromethyl)indolin-2-one, 254



254

Prepared according to the general procedure **C**; Isolated as white needles (69%); m.p. 120-122 °C (Et_2O); ν_{max} (film)/cm^{-1} 3073, 2916, 1698 (C=O), 1623, 1457, 1319, 1116, 1057, 842, 699; ^{1}H NMR (400 MHz, $CDCl_3$) 7.37-7.27 (7H, m, H-5, H-4 and 5 × Ar-H (benzyl)), 6.95 (1H, s, H-7), 4.95 (2H, s, CH_2 (benzyl)), 3.67 (2H, s, 2 × H-3); ^{13}C NMR (100 MHz, $CDCl_3$) 174.5, 144.8, 135.1, 130.4 (q, *J* 32.5), 128.8, 128.3, 127.8, 127.3, 124.5, 123.83, (q, *J* 272.3), 119.4 (q, *J* 4.1), 105.4 (q, *J* 3.9), 43.8, 35.5; *m/z* (ESI^+, $[M + Na]^+$) $C_{16}H_{12}F_3NNaO$ requires 314.0763, found 314.0765.

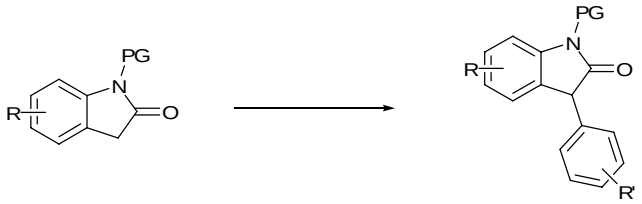
1-benzyl-3-bromo-1*H*-indole, (Table 5.6, entry 21, coupling partner)



3-bromoindole was alkylated according to the general procedure **A**; the reaction was quenched at 0 °C by the addition of water (50 mL) and diluted with dichloromethane (100 mL). The phases were separated and the organic phase washed with water (3 × 100 mL) and brine (50 mL). Purification by flash column chromatography (SiO_2, petrol/diethyl ether 20 : 1) gave indole 3-bromo-*N*-benzyl indole (90%) as a white powder; m.p. 68-69 °C; ν_{max} (film)/cm^{-1} 3115, 3059, 3030, 2925, 1612, 1456, 1324, 1195, 1164, 946, 730, 695; ^{1}H NMR (400 MHz, $CDCl_3$) 7.63 (1H, dd, *J* 6.9 and 1.8, H-4), 7.37-7.29 (4H, m, H-7, H-6 and 2 × Ar-H (benzyl)), 7.28-7.21 (2H, m, H-5 and Ar-H (benzyl)), 7.17-7.13 (3H, m, H-2 and 2 × Ar-H (benzyl)), 5.30 (2H, s, CH_2 (benzyl)); ^{13}C NMR (100 MHz, $CDCl_3$) 136.7, 135.8, 128.8, 127.8, 127.4, 127.0, 126.9, 122.8, 120.3, 119.4, 109.9, 90.2, 50.3; *m/z* (ESI^+, $[M + Na]^+$) $C_{15}H_{12}{}^{79}BrNNa$ requires 308.0045, found 308.0045.

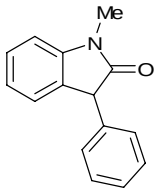
Oxindole Arylation

General procedure D: C-3 arylation of oxindoles



A small reaction tube (diameter 12 mm, depth 84 mm) was charged with the oxindole (0.25 mmol), $Pd(dba)_2$ (0.005 mmol, 2.9 mg) and X-Phos **L30** (0.07 mmol, 3.3 mg), sealed with a rubber septum, then vacuum purged three times with argon. Anhydrous, deoxygenated tetrahydrofuran (0.4 mL) and the aryl bromide/triflate/chloride (0.275 mmol) were added sequentially and the mixture heated to 70 °C. Potassium bis(trimethylsilyl)amide (0.5 M solution in toluene, 0.55 mL, 0.275 mmol) was added in one portion and the reaction stirred for 30 minutes. After quenching with saturated ammonium chloride (1 mL), the mixture was diluted with dichloromethane (10 mL) and water (10 mL), the phases separated and the aqueous phase extracted with further dichloromethane (2 × 10 mL). The combined organic phases were dried ($MgSO_4$) and the solvents reduced *in vacuo*. Purification by flash column chromatography (as described) gave the desired C-3 aryl oxindole.

1-Methyl-3-phenylindolin-2-one, 223[180]

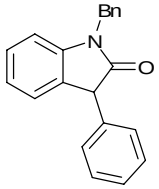


223

Prepared according to the general procedure **D**; Flash column chromatography (petrol/diethyl ether 5 : 1) and subsequent recrystallisation from hexane gave the oxindole as white crystalline needles (95%); m.p. 119-120 °C (hexane) (lit. 119-120 °C, hexane); ^{1}H NMR (400 MHz, $CDCl_3$) 7.36-7.28 (4H, m, H-6 and 3 × Ar-H), 7.22-7.16 (3H, m, H-5 and 2 × Ar-H), 7.07 (1H, ddd (app. td), *J* 7.5 and 0.8, H-4),

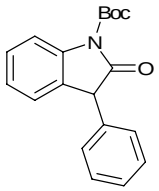
6.91 (1H, d, *J* 7.8, H-7), 4.62 (1H, s, H-3), 3.26 (3H, s, NCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 175.9, 144.4, 136.5, 128.8, 128.7, 128.3, 127.5, 125.0, 122.6, 108.1, 51.9, 26.4, (one carbon signal not observed). Data consistent with the literature.[180]

1-Benzyl-3-phenylindolin-2-one, (Table 5.5, entry 2 and Table 5.6, entries 1-2)[180]



Prepared according to the general procedure **D**; Flash column chromatography (petrol/diethyl ether 5 : 1) and subsequent recrystallisation from hexane gave the oxindole as white needles (89%); m.p. 108-109 °C (hexane) (lit. 115-116 °C (hexane); ν_{max} (film)/cm^{-1} 3060, 3030, 2923, 1713 (C=O), 1612, 1488, 1349, 1183, 1080, 892, 696; ^{1}H NMR (400 MHz, $CDCl_3$) 7.39-7.19 (11H, m, H-6, 5 × Ar-H (benzyl) and 5 × Ar-H), 7.17 (1H, d, *J* 7.4, H-4), 7.03 (1H, dd, *J* 7.5 and 7.4, H-5), 6.80 (1H, d, *J* 7.8, H-7), 5.01 (1H, d, *J* 15.6, C*H* (benzyl), 4.91 (1H, d, *J* 15.6, C*H* (benzyl)), 4.72 (1H, s, H-3); ^{13}C NMR (100 MHz, $CDCl_3$) 176.1, 143.6, 136.7, 135.9, 129.0, 128.9, 128.8, 128.5, 128.3, 127.7, 127.6, 127.4, 125.1, 122.8, 109.2, 58.1, 44.0. Data consistent with the literature.[180]

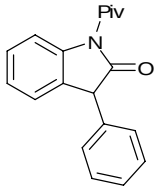
***tert*-Butyl 2-oxo-3-phenylindoline-1-carboxylate, (Table 5.5, entry 4)**



Prepared according to the general procedure **D**; Flash column chromatography (petrol/diethyl ether 5 : 1) and subsequent recrystallisation from hexane gave the oxindole as white needles (60%); m.p. 108-109 °C (hexane); ν_{max} (film)/cm^{-1} 3060, 3030, 2981, 2933, 1769 (C=O), 1729 (C=O), 1495, 1370, 1291, 1148, 848, 722; ^{1}H NMR (500 MHz, $CDCl_3$) 7.94 (1H, d, *J* 8.2, H-7), 7.40-7.29 (4H, m, H-6 and 3 × Ar-H), 7.24-7.16 (4H, m, H-5, H-4 and 2 × Ar-H), 4.74 (1H, s, H-3), 1.64 (9H, s, C(CH_3)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) 173.9, 149.4, 140.5, 136.3, 128.9, 128.6,

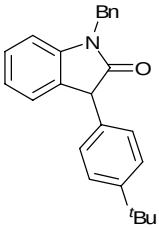
127.9, 127.4, 125.1, 124.6, 115.1, 84.4, 52.6, 28.1, (one carbon signal not observed); *m/z* (ESI^+, $[M + Na]^+$) $C_{19}H_{19}NNaO_3$ requires 332.1257, found 332.1260.

3-Phenyl-1-pivaloylindolin-2-one, (Table 5.5, entry 5)



Prepared according to the general procedure **D**; Flash column chromatography (petrol/diethyl ether 5 : 1) and subsequent recrystallisation from hexane gave the oxindole as white needles (34%); m.p. 94-95 °C; ν_{max} (film)/cm^{-1} 3062, 3030, 2967, 2872, 1748 (C=O), 1708 (C=O), 1607, 1480, 1267, 1113, 1085, 893, 724; ^1H NMR (400 MHz, $CDCl_3$) 7.56 (1H, d, *J* 8.2, H-7), 7.38-7.31 (4H, m, H-6 and 3 × Ar-H)), 7.21-7.19 (2H, m, 2 × Ar-H), 7.16-7.14 (2H, m, H-5 and H-4), 4.74 (1H, s, H-3), 1.40 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) 182.7, 175.1, 141.7, 136.3, 129.0, 128.7, 128.5, 128.4, 127.9, 125.1, 124.5, 114.2, 52.7, 43.4, 26.8; *m/z* (ESI^+, $[M + Na]^+$) $C_{19}H_{19}NNaO_2$ requires 316.1308, found 316.1306.

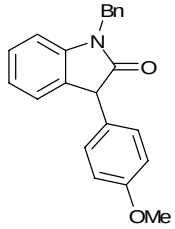
1-Benzyl-3-(4-*tert*-butylphenyl)indolin-2-one, (Table 5.6, entry 3)



Prepared according to the general procedure **D**; Flash column chromatography (petrol/diethyl ether 5 : 1) and subsequent recrystallisation from hexane gave the oxindole as white needles (79%); m.p. 116 °C (hexane); ν_{max} (film)/cm^{-1} 3031, 2962, 2903, 2868, 1714 (C=O), 1611, 1516, 1488, 1347, 1203, 1182, 750, 697; ^1H NMR (400 MHz, $CDCl_3$) 7.38 (2H, d, *J* 8.3, 2 × Ar-H), 7.36-7.26 (5H, m, 5 × Ar-H (benzyl)), 7.23-7.16 (4H, m, H-6, H-4 and 2 × Ar-H), 7.03 (1H, dd (app. t), *J* 7.5, H-5), 6.79 (1H, d, *J* 7.7, H-7), 5.01 (1H , d, *J* 15.6, C*H* (benzyl)), 4.92 (1H, d, *J* 15,6, C*H* (benzyl)), 4.71 (1H, s, H-3), 1.32 (9H, s, $(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$)

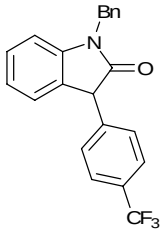
176.3, 150.3, 143.5, 135.9, 133.5, 129.0, 128.7, 128.2, 128.0, 127.6, 127.3, 125.9, 125.1, 122.6, 109.1, 51.6, 43.9, 34.5, 31.3; *m/z* (ESI^+, $[M + H]^+$) $C_{25}H_{26}NO$ requires 356.2009, found 356.2003.

1-Benzyl-3-(4-methoxyphenyl)indolin-2-one, (Table 5.6, entries 4-5)



Prepared according to the general procedure **D**; Flash column chromatography (petrol/diethyl ether 5 : 1) and subsequent recrystallisation from hexane gave the oxindole as white needles (85%); m.p. 109 °C (hexane); ν_{max} (film)/cm^{-1} 3032, 2928, 1712 (C=O), 1611, 1512, 1488, 1466, 1347, 1249, 1179, 1031, 751, 698; ^1H NMR (400 MHz, $CDCl_3$) 7.35-7.26 (5H, m, 5 × Ar-H (benzyl)), 7.21 (1H, dd, *J* 7.8 and 7.5, H-6), 7.18-7.13 (3H, m, 2 × Ar-H and H-4), 7.03 (1H, dd (app. t), *J* 7.5, H-5), 6.89 (2H, d, *J* 8.6, 2 × Ar-H), 6.79 (1H, d, *J* 7.8, H-7), 5.00 (1H, d, *J* 15.6, C*H* (benzyl)), 4.90 (1H, d, *J* 15.6, C*H* (benzyl)), 4.66 (1H, s, H-3), 3.80 (3H, s, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 176.4, 159.0, 143.5, 135.9, 129.4, 129.1, 128.7, 128.7, 128.2, 127.6, 127.3, 125.0, 122.7, 114.4, 109.1, 55.3, 51.2, 43.9; *m/z* (ESI^+, $[M + Na]^+$) $C_{22}H_{19}NNaO_2$ requires 352.1308, found 352.1301.

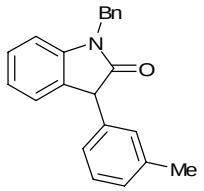
1-Benzyl-3-(4-(trifluoromethyl)phenyl)indolin-2-one, (Table 5.6, entries 6-7)



Prepared according to the general procedure **D**; Flash column chromatography (petrol/diethyl ether 5 : 1) and subsequent recrystallisation from hexane gave the oxindole as white needles (80%); m.p. 120-121 °C (hexane); ν_{max} (film)/cm^{-1} 3061, 3034, 2925, 1714 (C=O), 1612, 1326, 1165, 1069, 752, 699; ^1H NMR (400 MHz,

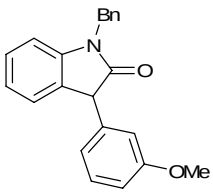
$CDCl_3$) 7.62 (2H, d, *J* 8.1, 2 × Ar-H), 7.37 (2H, d, *J* 8.1, 2 × Ar-H), 7.35-7.27 (5H, m, 5 × Ar-H (benzyl)), 7.25 (1H, dd, *J* 7.8 and 7.5, H-6), 7.16 (1H, d, *J* 7.5, H-4), 7.06 (1H, dd (app. t), *J* 7.5, H-5), 6.84 (1H, d, *J* 7.8, H-7), 5.00 (1H, d, *J* 15.6, C*H* (benzyl)), 4.91 (1H, d, *J* 15.6, C*H* (benzyl)), 4.78 (1H, s, H-3); ^{13}C NMR (100 MHz, $CDCl_3$) 175.2, 143.5, 140.7, 135.6, 129.9 (q, *J* 32.5), 128.8, 128.8, 128.7, 127.8, 127.7, 127.3, 125.8, 125.1, 124.0 (q, *J* 272.2), 122.9, 109.4, 51.7, 44.0; ^{19}F NMR (376.5 MHz, $CDCl_3$) -62.5; *m/z* (ESI$^+$, $[M + H]^+$) $C_{22}H_{17}F_3NO$ requires 368.1257, found 368.1260.

1-Benzyl-3-*m*-tolylindolin-2-one, (Table 5.6, entry 8)



Prepared according to the general procedure **D**; Flash column chromatography (petrol/diethyl ether 5 : 1) gave the oxindole as a viscous pale yellow oil (77%); ν_{max} (film)/cm^{-1} 3032, 2921, 1715 (C=O), 1612, 1488, 1348, 1182, 1081, 752, 695; ^{1}H NMR (400 MHz, $CDCl_3$) 7.38-7.27 (5H, m, 5 × Ar-H (benzyl)), 7.25-7.21 (3H, m, H-6, H-5 and H-4), 7.14 (1H, d, *J* 7.6, Ar-H), 7.08-7.01 (3H, m, 3 × Ar-H), 6.82 (1H, d, *J* 7.8, H-7), 5.03 (1H, d, *J* 15.6, C*H* (benzyl)), 4.93 (1H, d, *J* 15.6, C*H* (benzyl)), 4.69 (1H, s, H-3), 2.36 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 176.2, 143.4, 138.5, 136.6, 135.9, 129.1, 129.0, 128.7, 128.6, 128.4, 128.2, 127.6, 127.3, 125.4, 125.0, 122.7, 109.1, 52.0, 43.9, 21.4; *m/z* (ESI$^+$, $[M + Na]^+$) $C_{22}H_{19}NNaO$ requires 336.1359, found 336.1361.

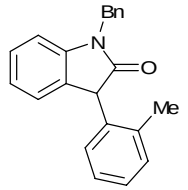
1-Benzyl-3-(3-methoxyphenyl)indolin-2-one, (Table 5.6, entry 9)



Prepared according to the general procedure **D**; Flash column chromatography (petrol/diethyl ether 5 : 1) and subsequent recrystallisation from hexane gave the

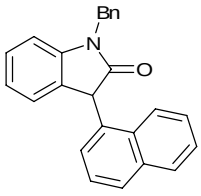
oxindole as pale yellow needles (85%); m.p. 69-70 °C (hexane); ν_{max} (film)/cm^{-1} 3058, 3031, 2835, 1714 (C=O), 1612, 1489, 1244, 1047, 752, 693; ^{1}H NMR (400 MHz, $CDCl_3$) 7.35-7.25 (6H, m, 5 × Ar-H (benzyl) and Ar-H), 7.24-7.16 (2H, m, H-6 and H-4), 7.02 (1H, ddd (app. td), *J* 7.5 and 0.9, H-5), 6.87-6.77 (4H, m, H-7 and 3 × Ar-H), 5.01 (1H, d, *J* 15.6, C*H* (benzyl)), 4.90 (1H, d, *J* 15.6, C*H* (benzyl)), 4.68 (1H, s, H-3), 3.78 (3H, s, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 175.9, 159.9, 143.5, 138.1, 135.9, 129.9, 128.7, 128.7, 128.3, 127.6, 127.3, 125.1, 122.7, 120.7, 114.2, 113.0, 109.2, 55.2, 52.0, 43.9; *m/z* (ESI$^+$, [*M* + Na]$^+$) $C_{22}H_{19}NNaO_2$ requires 352.1308, found 352.1307.

1-Benzyl-3-*o*-tolylindolin-2-one, (Table 5.6, entries 10-11)



Prepared according to the general procedure **D**; Flash column chromatography (petrol/diethyl ether 5 : 1) and subsequent recrystallisation from hexane gave the oxindole as white crystalline needles (74%); m.p. 85-86 °C (hexane); ^{1}H NMR (250 MHz, d_6-DMSO, 90 °C) 7.42-7.02 (9H, m, 5 × Ar-H (benzyl) and 4 × Ar-H), 7.02-6.94 (3H, m, 3 × Ar-H), 6.91 (1H, d, *J* 7.2, H-7), 5.10 (1H, s, H-3), 4.96 (2H, s, CH_2 (benzyl)), 2.26 (3H, s, CH_3); ^{13}C NMR (62.5 MHz, d_6-DMSO, 90 °C) 176.4, 144.2, 137.8, 137.4, 136.9, 131.5, 130.3, 129.8, 129.4, 128.8, 128.3, 128.2, 128.1, 126.9, 125.0, 123.2, 109.9, 50.6, 44.1, 19.9; *m/z* (ESI$^+$, [*M* + H]$^+$) $C_{22}H_{20}NO$ requires 314.1539, found 314.1539.

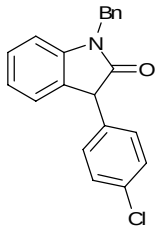
1-Benzyl-3-(naphthalen-1-yl)indolin-2-one, (Table 5.6, entry 12)



Prepared according to the general procedure **D**; Flash column chromatography (petrol/diethyl ether 3 : 1) and subsequent recrystallisation from hexane gave the

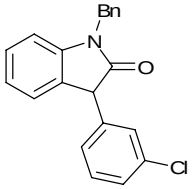
oxindole as pale yellow plates (80%); m.p. 63-65 °C (hexane); ν_{max} (film)/cm^{-1} 3058, 2924, 1712 (C=O), 1611, 1487, 1346, 1170, 899, 751, 698; ^{1}H NMR (250 MHz, d_6-DMSO, 100 °C) 7.96-7.88 (3H, m, 3 × Ar-H (naphthyl)), 7.56-7.12 (10H, m, H-6, 5 × Ar-H (benzyl) and 4 × Ar-H (naphthyl), 7.06 (1H, d, *J* 7.8, H-5), 7.09-6.90 (2H, m, H-7 and H-4), 5.65 (1H, s, H-3), 5.07 (1H, d, *J* 15.6, C*H* (benzyl)), 4.99 (1H, d, *J* 15.6, C*H* (benzyl)); ^{13}C NMR (62.5 MHz, d_6-DMSO, 100 °C) 176.5, 143.9, 137.4, 137.3, 134.9, 134.7, 132.7, 130.7, 130.6, 129.5, 129.4, 129.4, 128.9, 128.3, 128.2, 127.0, 126.6, 126.3, 125.1, 125.0, 123.2, 110.1, 44.2; *m/z* (ESI$^+$, $[M + Na]^+$) $C_{25}H_{19}NNaO$ requires 372.1359, found 372.1357.

1-Benzyl-3-(4-chlorophenyl)indolin-2-one, (Table 5.6, entries 13 and 16)



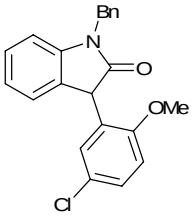
Prepared according to the general procedure **D**; Flash column chromatography (petrol/diethyl ether 5 : 1) and subsequent recrystallisation from hexane gave the oxindole as white needles (70%); m.p. 126-127 °C (hexane); ν_{max} (film)/cm^{-1} 3061, 1712 (C=O), 1612, 1488, 1408, 1201, 1015, 892, 751, 697; ^{1}H NMR (400 MHz, $CDCl_3$) 7.37-7.26 (7H, m, 5 × Ar-H (benzyl) and 2 × Ar-H), 7.24 (1H, dd (app. t), *J* 7.8, H-6), 7.20-7.15 (3H, m, H-4 and 2 × Ar-H), 7.05 (1H, dd (app. t), *J* 7.8, H-5), 6.82 (1H, d, *J* 7.8, H-7), 5.00 (1H, d, *J* 15.6, C*H* (benzyl)), 4.91 (1H, d, *J* 15.6, C*H* (benzyl)), 4.70 (1H, s, H-3); ^{13}C NMR (100 MHz, $CDCl_3$) 175.6, 143.6, 135.8, 135.2, 133.6, 129.8, 129.1, 128.8, 128.6, 128.3, 127.7, 127.4, 125.1, 122.9, 109.4, 51.4, 44.0; *m/z* (ESI$^+$, $[M + H]^+$) $C_{21}H_{17}ClNO$ requires 334.0993, found 334.0987.

1-Benzyl-3-(3-chlorophenyl)indolin-2-one, (Table 5.6, entry 14)



Prepared according to the general procedure **D**; Flash column chromatography (petrol/diethyl ether 5 : 1) and subsequent recrystallisation from hexane gave the oxindole as white needles (73%); m.p. 81-82 °C (hexane); ν_{max} (film)/cm^{-1} 3060, 2923, 1713 (C=O), 1612, 1488, 1347, 1201, 1080, 778, 721; ^{1}H NMR (400 MHz, $CDCl_3$) 7.35-7.27 (7H, m, 5 × Ar-H (benzyl) and Ar-H), 7.26-7.20 (2H, m, H-6 and Ar-H), 7.18-7.13 (2H, m, Ar-H and H-4), 7.05 (1H, dd, *J* 7.5 and 7.5, H-5), 6.82 (1H, d, *J* 7.8, H-7), 4.99 (1H, d, *J* 15.6, C*H* (benzyl)), 4.92 (1H, d, *J* 15.6, C*H* (benzyl)), 4.69 (1H, s, H-3); ^{13}C NMR (100 MHz, $CDCl_3$) 175.4, 143.5, 138.6, 135.7, 134.7, 130.1, 128.8, 128.6, 128.5, 128.0, 127.9, 127.7, 127.3, 126.8, 125.1, 122.9, 109.3, 51.5, 44.0; *m/z* (ESI$^+$, $[M + Na]^+$) $C_{21}H_{16}ClNNaO$ requires 356.0813, found 356.0813.

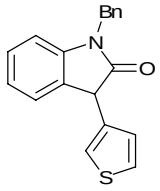
1-Benzyl-3-(5-chloro-2-methoxyphenyl)indolin-2-one, (Table 5.6, entry 15)



Prepared according to the general procedure **D**; Flash column chromatography (SiO_2, petrol/diethyl ether 4 : 1) and subsequent recrystallisation from hexane gave the oxindole as pale yellow needles (77%); m.p. 123-125 °C (hexane); ν_{max} (film)/cm^{-1} 3059, 2940, 2838, 1714 (C=O), 1612, 1489, 1358, 1153, 1027, 809, 650; ^{1}H NMR (400 MHz, $CDCl_3$) 7.41 (2H, d, *J* 7.6, 2 × Ar-H (benzyl)), 7.35 (2H, dd, *J* 7.6 and 7.1, 2 × Ar-H (benzyl)), 7.30 (1H, d, *J* 7.1, Ar-H (benzyl)), 7.25 (1H, dd, *J* 8.8 and 2.6, Ar-H), 7.17 (1H, dd, *J* 7.9 and 7.4, H-6), 7.12 (1H, br s, Ar-H), 7.05 (1H, d, *J* 7.4, H-4), 6.96 (1H, dd (app. t), *J* 7.4, H-5), 6.83 (1H, d, *J* 8.8, Ar-H), 6.80 (1H, d, *J* 7.9, H-7), 5.09 (1H, d, *J* 15.6, C*H* (benzyl)), 4.90 (1H, d, *J* 15.6, C*H* (benzyl)), 4.88

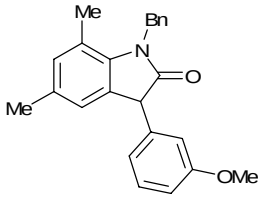
(1H, s, H-3), 3.62 (3H, s, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) 175.9, 156.1, 143.3, 136.0, 130.2, 128.8, 128.6, 128.6, 127.9, 127.5, 127.5, 127.3, 125.5, 124.0, 122.5, 112.5, 108.9, 55.8, 48.0, 43.9; *m/z* (ESI$^+$, [*M* + Na]$^+$) $C_{22}H_{18}ClNNaO_2$ requires 386.0918, found 386.0911.

1-Benzyl-3-(thiophen-3-yl)indolin-2-one, (Table 5.6, entry 20)



Prepared according to the general procedure **D**; Flash column chromatography (petrol/diethyl ether 5 : 1) gave the oxindole as a colourless film (20%); ν_{max} (film)/cm^{-1} 3104, 3057, 2923, 1712 (C=O), 1612, 1488, 1355, 1180, 1081, 849, 752, 697; ^{1}H NMR (500 MHz, $CDCl_3$) 7.36-7.27 (7H, m, H-4, H-5 (thiophene), 5 × Ar-H (benzyl)), 7.23 (1H, dd, *J* 7.9 and 7.6, H-6), 7.20-7.18 (1H, m, H-2 (thiophene)), 7.09 (1H, dd, *J* 5.0 and 1.3, H-4 (thiophene)), 7.06 (1H, ddd (app. td), *J* 7.6 and 1.0, H-5), 6.79 (1H, d, *J* 7.9, H-7), 4.99 (1H, d, *J* 15.8, C*H* (benzyl)), 4.93 (1H, d, *J* 15.8, C*H* (benzyl)), 4.84 (1H, s, H-3); ^{13}C NMR (125 MHz, $CDCl_3$) 175.4, 143.3, 135.9, 135.8, 128.8, 128.4, 128.3, 127.6, 127.3, 127.2, 126.4, 125.0, 122.7, 122.6, 109.3, 47.4, 43.9; *m/z* (ESI$^+$, [*M* + Na]$^+$) $C_{19}H_{15}NNaOS$ requires 328.0767, found 328.0770.

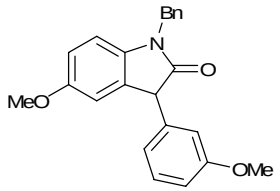
1-Benzyl-3-(3-methoxyphenyl)-5,7-dimethylindolin-2-one, (Table 5.7, entry 1)



Prepared according to the general procedure **D**; Flash column chromatography (SiO_2, petrol/diethyl ether 2 : 1) gave the oxindole as a viscous pale yellow oil (67%); ν_{max} (film)/cm^{-1} 3060, 3030, 2935, 1710 (C=O), 1600, 1481, 1342, 1263, 1177, 1039, 728, 698; ^{1}H NMR (400 MHz, $CDCl_3$) 7.35-7.25 (4H, m, 3 × Ar-H (benzyl) and Ar-H), 7.21 (2H, d, *J* 7.1, 2 × Ar-H (benzyl)), 6.91-6.89 (2H, m, Ar-H), 6.88-6.86 (1H, m, H-4), 6.85-6.83 (1H, m, H-6), 6.82 (1H, s, Ar-H), 5.28 (1H, d, *J* 16.8, C*H*

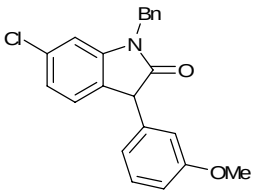
(benzyl)), 5.20 (1H, d, *J* 16.8, C*H* (benzyl)), 4.69 (1H, s, H-3), 3.81 (3H, s, OCH_3), 2.31 (3H, s, CH_3), 2.26 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 177.0, 160.0, 139.2, 138.8, 137.9, 132.7, 132.4, 129.9, 129.7, 128.9, 127.2, 125.8, 123.9, 120.9, 119.6, 114.4, 113.0, 55.3, 51.9, 45.2, 20.8, 18.7; *m/z* (ESI$^+$, [*M* + MeCN + NH_4]$^+$) $C_{26}H_{30}N_3$ requires 416.2333, found 416.2330.

1-Benzyl-5-methoxy-3-(3-methoxyphenyl)indolin-2-one, (Table 5.7, entry 2)



Prepared according to the general procedure **D**; Flash column chromatography (SiO_2, petrol/diethyl ether 1 : 1) gave the oxindole as a viscous pale yellow oil (76%); ν_{max} (film)/cm^{-1} 3030, 2938, 2835, 1708 (C=O), 1600, 1492, 1279, 1177, 777, 696; ^{1}H NMR (400 MHz, $CDCl_3$) 7.35-7.26 (6H, m, 5 × Ar-H (benzyl) and Ar-H), 6.89-6.83 (2H, m, 2 × Ar-H), 6.82-6.79 (2H, m, H-4 and Ar-H), 6.75 (1H, dd, *J* 8.5 and 2.4, H-6), 6.69 (1H, d, *J* 8.5, H-7), 5.00 (1H, d, *J* 15.6, C*H* (benzyl)), 4.89 (1H, d, *J* 15.6, C*H* (benzyl)), 4.68 (1H, s, H-3), 3.79 (3H, s, C(aryl)-OCH_3), 3.72 (3H, s, C(5)-OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 175.6, 159.8, 156.0, 138.1, 136.6, 135.9, 130.0, 129.9, 128.7, 127.5, 127.2, 120.7, 114.1, 113.0, 112.8, 112.1, 109.5, 55.6, 55.1, 52.4, 43.9; *m/z* (ESI$^+$, [*M* + Na]$^+$) $C_{23}H_{21}NNaO_3$ requires 382.1414, found 382.1410.

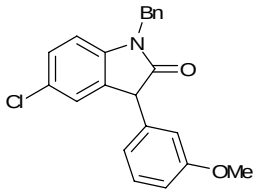
1-Benzyl-6-chloro-3-(3-methoxyphenyl)indolin-2-one, (Table 5.7, entry 3)



Prepared according to the general procedure **D**; Reaction time: 1 h; Flash column chromatography (SiO_2, petrol/diethyl ether 4 : 1) and subsequent recrystallisation from hexane gave the oxindole as white needles (66%); m.p. 90-91 °C (hexane); ν_{max} (film)/cm^{-1} 3064, 3032, 2937, 1716 (C=O), 1609, 1489, 1369, 1184, 1080, 779, 700;

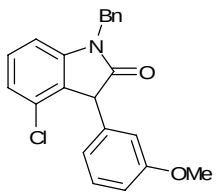
^{1}H NMR (400 MHz, $CDCl_3$) 7.38-7.28 (6H, m, 5 × Ar-H (benzyl) and Ar-H), 7.10 (1H, d, *J* 7.9, H-4), 7.01 (1H, dd, *J* 7.9 and 1.8, H-5), 6.87 (1H, dd, *J* 8.3 and 1.9, Ar-H), 6.82-6.79 (2H, m, H-7 and Ar-H), 6.76-6.74 (1H, m, Ar-H), 4.99 (1H, d, *J* 15.7, C*H* (benzyl)), 4.87 (1H, d, *J* 15.7, C*H* (benzyl)), 4.66 (1H, s, H-3), 3.79 (3H, s, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 175.8, 159.9, 144.6, 137.5, 135.3, 134.0, 130.0, 128.9, 127.8, 127.2, 127.1, 126.0, 122.7, 120.6, 114.1, 113.2, 109.7, 55.2, 51.5, 44.0; *m/z* (ESI$^+$, [*M* + Na]$^+$) $C_{22}H_{18}ClNNaO_2$ requires 386.0918, found 386.0917.

1-Benzyl-5-chloro-3-(3-methoxyphenyl)indolin-2-one, (Table 5.7, entry 4)



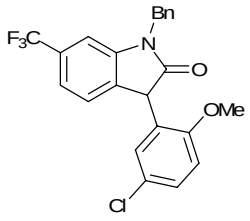
Prepared according to the general procedure **D**; Reaction time: 1 h; Flash column chromatography (SiO_2, petrol/diethyl ether 1 : 1) gave the oxindole as a viscous pale yellow oil (70%); ν_{max} (film)/cm^{-1} 3063, 3031, 2936, 1717 (C=O), 1608, 1485, 1339, 1183, 1081, 742, 695; ^{1}H NMR (400 MHz, $CDCl_3$) 7.37-7.28 (6H, m, 5 × Ar-H (benzyl) and Ar-H), 7.18 (1H, dd, *J* 8.3 and 2.4, H-6), 7.17-7.15 (1H, m, H-4), 6.88 (1H, dd, *J* 7.9 and 1.9, Ar-H), 6.80 (1H, d, *J* 7.6, Ar-H), 6.77-6.75 (1H, m, Ar-H), 6.71 (1H, d, *J* 8.3, H-7), 5.01 (1H, d, *J* 15.6, C*H* (benzyl)), 4.89 (1H, d, *J* 15.6, C*H* (benzyl)), 4.68 (1H, s, H-3), 3.80 (3H, s, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 175.4, 160.0, 141.9, 137.3, 135.4, 130.4, 130.0, 128.9, 128.3, 128.1, 127.8, 127.2, 125.4, 120.6, 114.2, 113.1, 110.1, 55.2, 52.0, 44.0; *m/z* (ESI$^+$, [*M* + Na]$^+$) $C_{22}H_{18}ClNNaO_2$ requires 386.0918, found 386.0921.

1-Benzyl-4-chloro-3-(3-methoxyphenyl)indolin-2-one, (Table 5.7, entry 5)



Prepared according to the general procedure **D**; Reaction time: 2.5 h; Flash column chromatography (SiO_2, petrol/diethyl ether 3 : 1) and recrystallisation from hexane gave the oxindole as red plates (61%); m.p. 130-131 °C (hexane); ν_{max} (film)/cm^{-1} 3029, 2935, 1719 (C=O), 1606, 1459, 1332, 1138, 772, 695; ^{1}H NMR (400 MHz, $CDCl_3$) 7.37-7.27 (6H, m, 5 × Ar-H (benzyl) and Ar-H), 7.19 (1H, dd (app. t), *J* 8.1 and 7.9, H-6), 7.01 (1H, d, *J* 8.1, H-5), 6.87 (1H, dd, *J* 8.3 and 2.4, Ar-H), 6.79 (1H, d, *J* 7.7, Ar-H), 6.76-6.74 (1H, m, Ar-H), 6.71 (1H, d, *J* 7.9, H-7), 5.00 (1H, d, *J* 15.6, C*H* (benzyl)), 4.86 (1H, d, *J* 15.6, C*H* (benzyl)), 4.71 (1H, s, H-3), 3.80 (3H, s, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 175.1, 159.8, 145.1, 136.2, 135.4, 131.5, 129.8, 129.7, 128.8, 127.7, 127.3, 126.2, 123.3, 120.4, 114.0, 113.0, 107.5, 55.2, 51.9, 44.1; *m/z* (ESI^+, [*M* + Na]$^+$) $C_{22}H_{18}ClNNaO_2$ requires 386.0918, found 386.0920.

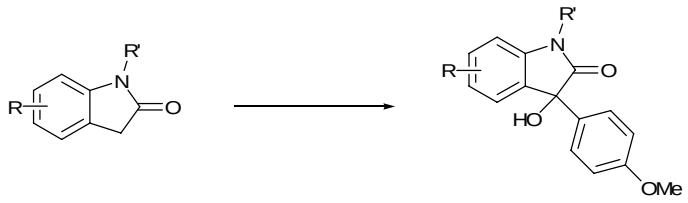
1-Benzyl-3-(5-chloro-2-methoxyphenyl)-6-(trifluoromethyl)indolin-2-one, 255



255

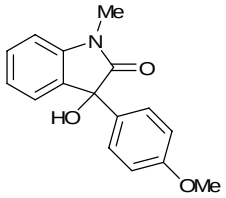
Prepared according to the general procedure **D**; Flash column chromatography (SiO_2, petrol/diethyl ether 5 : 1) gave the oxindole as white plates (25%); m.p. 125-126 °C (hexane); ν_{max} (film)/cm^{-1} 3066, 2941, 2841, 1722 (C=O), 1624, 1493, 1317, 1123, 933, 812, 700; ^{1}H NMR (400 MHz, $CDCl_3$) 7.43-7.35 (4H, m, 4 × Ar-H (benzyl)), 7.32 (1H, d, *J* 6.9, Ar-H (benzyl)), 7.28 (1H, dd, *J* 8.8 and 2.6, Ar-H), 7.25 (1H, d, *J* 7.8, H-5), 7.16 (1H, s, Ar-H), 7.13 (1H, d, *J* 7.8, H-4), 7.01 (1H, s, H-7), 6.82 (1H, d, *J* 8.8, Ar-H), 5.12 (1H, d, *J* 15.6, C*H* (benzyl)), 4.91 (1H, d, *J* 15.6, C*H* (benzyl)), 4.84 (1H, s, H-3), 3.57 (3H, s, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 175.6, 155.9, 143.9, 135.4, 132.7, 130.6, 130.3, 129.1, 128.9, 127.9, 127.6, 126.3, 125.8, 124.1, 123.1 (q, *J* 272.1), 119.6 (q, *J* 4.0), 112.6, 105.2, 55.8, 48.2, 44.1; *m/z* (ESI^+, [*M* + Na]$^+$) $C_{23}H_{17}ClF_3NNaO_2$ requires 454.0792, found 454.0787.

General Procedure E: One-Pot C-3 Arylation-Hydroxylation of Oxindoles



Prepared according to the general procedure **E**; A small reaction tube (diameter 12 mm, depth 84 mm) was charged with the oxindole (0.25 mmol), $Pd(dba)_2$ (0.005 mmol, 2.9 mg) and X-Phos **L30** (0.07 mmol, 3.3 mg), sealed with a rubber septum and vacuum purged three times with argon. Anhydrous, deoxygenated tetrahydrofuran (0.4 mL) and 4-bromoanisole (34 μL, 0.275 mmol) were added sequentially and the mixture heated to 70 °C. Potassium bis(trimethylsilyl)amide (0.5 M solution in toluene, 0.55 mL, 0.275 mmol) was added in one portion and the reaction stirred for 30 minutes. The reaction was then carefully purged with air and the rubber septum removed. After a further 5 minutes the reaction was cooled to room temperature, diluted with dichloromethane (10 mL) and filtered through a celite pad. Purification by flash column chromatography (SiO_2, petrol/diethyl ether 1 : 1) and subsequent recrystallisation from diethyl ether/hexane gave the desired product as described.

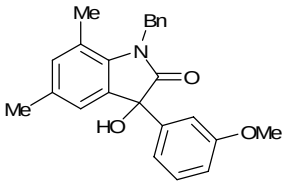
3-Hydroxy-3-(4-methoxyphenyl)-1-methylindolin-2-one, (Table 5.8, entry 1)



Prepared according to the general procedure **E**; Isolated as white needles (97%); m.p. 147-148 °C (Et_2O/hexane); ν_{max} (film)/cm^{-1} 3385 (OH), 3058, 2936, 2837, 1707 (C=O), 1612, 1510, 1470, 1251, 1174, 1030, 826, 756; ^1H NMR (400 MHz, $CDCl_3$) 7.35 (1H, ddd (app. td), *J* 7.7 and 1.2, H-6), 7.33-7.29 (3H, m, H-4 and 2 × Ar-H), 7.10 (1H, ddd (app. td), *J* 7.7 and 0.7, H-5), 6.89 (1H, d, *J* 7.7, H-7), 6.84 (2H, d, *J* 8.9, 2 × Ar-H), 3.83 (1H, br s, O*H*, D_2O exchangable), 3.77 (3H, s, OCH_3), 3.21 (3H, s, NCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 177.7, 159.5, 143.3, 132.1, 131.6, 129.7,

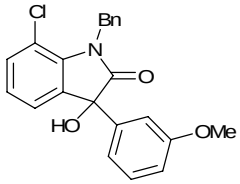
126.8, 124.8, 123.4, 113.9, 108.6, 77.5, 55.2, 26.4; *m/z* (ESI^+, $[M + Na]^+$) $C_{16}H_{15}NNaO_3$ requires 292.0944, found 292.0943.

1-Benzyl-3-hydroxy-3-(3-methoxyphenyl)-5,7-dimethylindolin-2-one, (Table 5.8, entry 2)



Prepared according to the general procedure **E**; Isolated as white needles (94%); m.p. 67-69 °C (Et_2O/hexane); ν_{max} (film)/cm^{-1} 3385 (OH), 3029, 2936, 1701 (C=O), 1641, 1483, 1346, 1257, 1127, 1046, 862, 698; ^1H NMR (400 MHz, $CDCl_3$) 7.35-7.24 (4H, m, 3 × Ar-H (benzyl) and Ar-H), 7.20 (2H, d, *J* 7.1, 2 × Ar-H (benzyl)), 7.08-7.06 (1H, m, Ar-H), 6.97-6.95 (2H, m, H-6 and Ar-H), 6.87 (1H, dd, *J* 8.2 and 2.5, Ar-H) 6.81 (1H, s, Ar-H), 5.21 (1H, d, *J* 17.7, C*H* (benzyl)), 5.17 (1H, d, *J* 17.7, C*H* (benzyl)), 3.80 (3H, s, OCH_3), 3.53 (1H, s, O*H*, D_2O exchangeable), 2.26 (3H, s, CH_3), 2.23 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 178.6, 159.7, 142.2, 138.0, 137.2, 134.2, 133.3, 132.3, 129.7, 128.9, 127.3, 125.7, 123.6, 120.1, 117.5, 113.6, 111.1, 77.4, 55.2, 45.2, 20.7, 18.6; *m/z* HRMS (ESI^+, $[M + Na]^+$) $C_{24}H_{23}NNaO_3$ requires 396.1570, found 396.1571.

1-Benzyl-7-chloro-3-hydroxy-3-(3-methoxyphenyl)indolin-2-one, (Table 5.8, entry 3)



Prepared according to the general procedure **E**; Isolated as white needles (89%); m.p. 128-129 °C (Et_2O/hexane); ν_{max} (film)/cm^{-1} 3396 (OH), 3064, 3031, 2938, 1714 (C=O), 1609, 1489, 1371, 1257, 1073, 871, 699; ^1H NMR (400 MHz, $CDCl_3$) 7.39-7.22 (6H, m, 5 × Ar-H (benzyl) and H-6), 7.19 (1H, dd, *J* 7.9 and 4.4, Ar-H), 7.04-6.98 (2H, m, 2 × Ar-H), 6.91-6.83 (2H, m, H-5 and H-4), 6.80-6.77 (1H, m, Ar-H),

5.03 (1H, d, *J* 15.7, C*H* (benzyl)), 4.77 (1H, d, *J* 15.7, C*H* (benzyl)), 3.79 (1H, br s, O*H*, D_2O exchangable), 3.77 (3H, s, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 177.5, 159.8, 143.7, 141.2, 135.5, 134.8, 130.0, 129.8, 129.0, 128.0, 127.2, 125.9, 123.5, 117.3, 114.0, 110.8, 110.3, 77.5, 55.2, 44.1; *m/z* HRMS (ESI^+, $[M + Na]^+$) $C_{22}H_{18}ClNNaO_3$ requires 402.0867, found 402.0867.

10. References

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Appendix A – X-ray Crystallography Data for Bistriflate *meso*-135

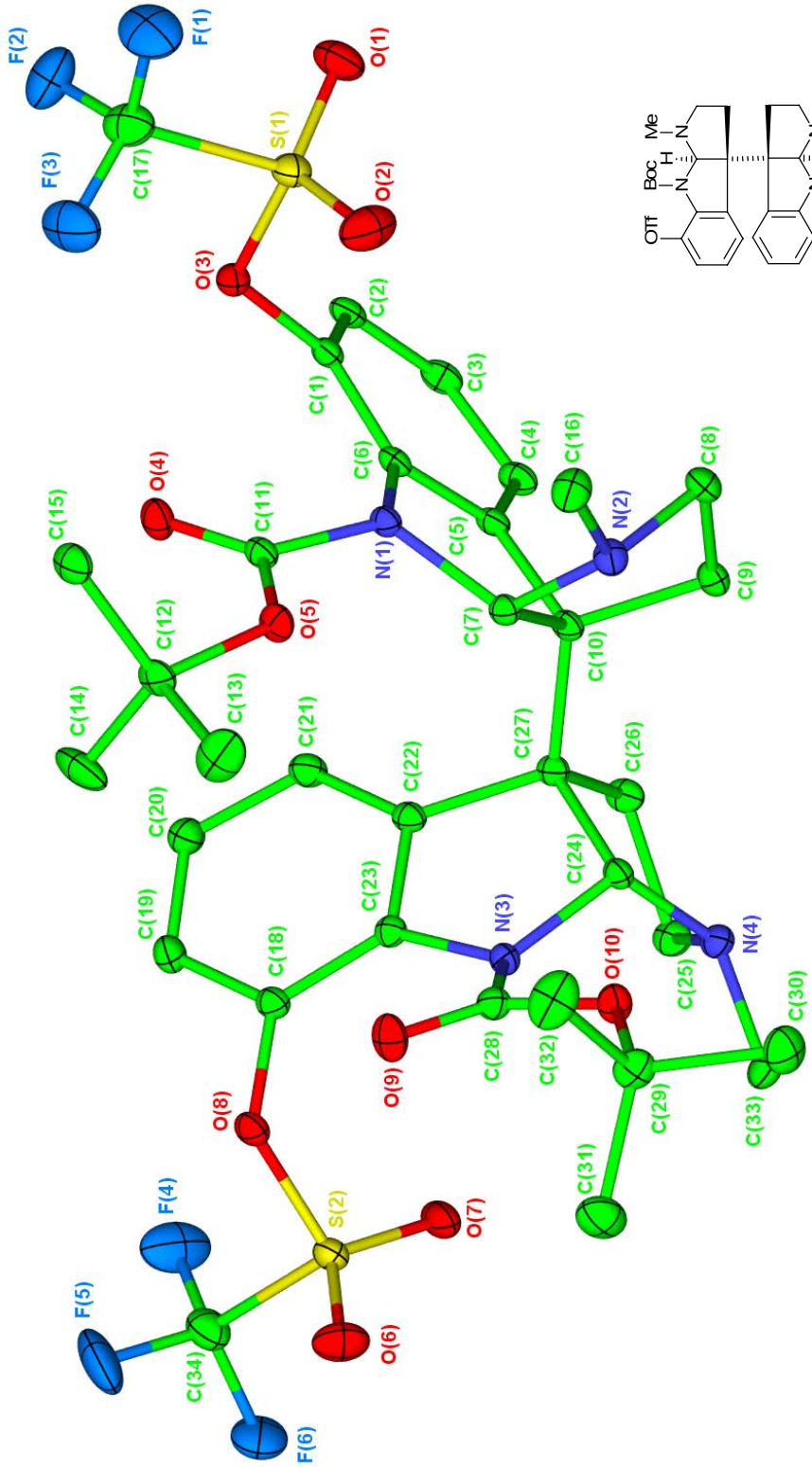


Table 1: Crystal data and structure refinement for k06mcw1.

Identification code	k06mcw1
Empirical formula	$C_{41} H_{48} F_6 N_4 O_{10} S_2$
Formula weight	934.95
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 10.2080(2)Å α = 102.782(1)^o
	b = 12.0500(2)Å β = 98.713(1)^o
	c = 18.9640(3)Å γ = 99.508(1)^o
Volume	2200.34(7) Å^3
Z	2
Density (calculated)	1.411 Mg/m^3
Absorption coefficient	0.207 mm^{-1}
F(000)	976
Crystal size	0.22 x 0.12 x 0.12 mm
Theta range for data collection	3.54 to 27.51^o
Index ranges	-13<=h<=13; -15<=k<=15; -24<=l<=24
Reflections collected	38154
Independent reflections	10072 [R(int) = 0.0593]
Reflections observed (>2σ)	8058
Data Completeness	0.994
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.96 and 0.88
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	10072 / 0 / 578
Goodness-of-fit on F^2	1.067
Final R indices [I>2σ(I)]	R^1 = 0.0566 wR_2 = 0.1385
R indices (all data)	R^1 = 0.0792 wR_2 = 0.1493
Largest diff. peak and hole	0.761 and -0.628 eÅ^{-3}

Note: asymmetric unit also contains one molecule of toluene.

Table 2: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for k06mcw1. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
S(1)	5387(1)	3275(1)	5545(1)	33(1)
S(2)	10120(1)	-1764(1)	1497(1)	30(1)
F(1)	6549(2)	4769(2)	6753(1)	74(1)
F(2)	6107(2)	3002(2)	6860(1)	67(1)
F(3)	7770(2)	3577(2)	6377(1)	69(1)
F(4)	9580(2)	-3600(2)	1995(1)	74(1)
F(5)	11682(2)	-2976(2)	2051(1)	79(1)
F(6)	10391(2)	-3870(2)	1013(1)	63(1)
O(1)	4073(2)	3279(2)	5671(1)	49(1)
O(2)	5967(2)	3977(2)	5110(1)	57(1)
O(3)	5632(1)	1995(1)	5325(1)	28(1)
O(4)	7980(2)	1647(1)	4889(1)	33(1)
O(5)	8943(1)	2686(1)	4165(1)	30(1)
O(6)	11251(2)	-1268(2)	1244(1)	51(1)
O(7)	8790(2)	-2009(2)	1087(1)	45(1)
O(8)	10233(1)	-1050(1)	2309(1)	28(1)
O(9)	10383(2)	1160(1)	2231(1)	36(1)
O(10)	9000(1)	1794(1)	1416(1)	29(1)
N(1)	6705(2)	2074(1)	3922(1)	22(1)
N(2)	6313(2)	3134(2)	2942(1)	27(1)
N(3)	8124(2)	341(2)	1868(1)	23(1)
N(4)	5992(2)	-119(2)	928(1)	28(1)
C(1)	4960(2)	1305(2)	4609(1)	24(1)
C(2)	3764(2)	531(2)	4556(1)	27(1)
C(3)	3051(2)	-123(2)	3869(1)	30(1)
C(4)	3509(2)	15(2)	3236(1)	28(1)
C(5)	4740(2)	759(2)	3298(1)	23(1)
C(6)	5494(2)	1387(2)	3988(1)	23(1)
C(7)	6633(2)	2106(2)	3131(1)	23(1)
C(8)	4840(2)	2961(2)	2732(1)	31(1)
C(9)	4472(2)	1713(2)	2261(1)	28(1)
C(10)	5410(2)	1103(2)	2692(1)	23(1)
C(11)	7911(2)	2093(2)	4379(1)	24(1)
C(12)	10360(2)	2755(2)	4531(1)	33(1)
C(13)	11162(3)	3417(3)	4089(2)	57(1)
C(14)	10640(3)	1547(3)	4452(2)	52(1)
C(15)	10589(2)	3438(2)	5325(1)	36(1)
C(16)	7008(3)	4242(2)	3444(1)	37(1)
C(17)	6538(3)	3668(3)	6444(2)	48(1)
C(18)	9040(2)	-977(2)	2608(1)	26(1)
C(19)	8852(2)	-1560(2)	3147(1)	31(1)
C(20)	7677(2)	-1582(2)	3432(1)	34(1)
C(21)	6669(2)	-1056(2)	3153(1)	30(1)
C(22)	6884(2)	-440(2)	2633(1)	24(1)
C(23)	8106(2)	-348(2)	2378(1)	23(1)
C(24)	6721(2)	548(2)	1649(1)	23(1)

C(25)	5300(2)	-1237(2)	1007(1)	31(1)
C(26)	4730(2)	-860(2)	1695(1)	28(1)
C(27)	5898(2)	103(2)	2202(1)	23(1)
C(28)	9287(2)	1121(2)	1872(1)	26(1)
C(29)	10104(2)	2553(2)	1220(1)	34(1)
C(30)	9317(3)	3089(2)	680(2)	42(1)
C(31)	10976(3)	1802(3)	830(2)	49(1)
C(32)	10912(3)	3473(3)	1891(2)	54(1)
C(33)	6722(2)	-180(2)	320(1)	34(1)
C(34)	10458(3)	-3144(2)	1653(2)	44(1)
C(35)	6399(4)	4445(4)	1577(2)	67(1)
C(36)	6018(4)	5514(4)	1720(2)	74(1)
C(37)	4844(4)	5660(3)	1287(2)	59(1)
C(38)	4078(3)	4750(2)	720(1)	42(1)
C(39)	4504(3)	3702(2)	606(2)	46(1)
C(40)	5647(4)	3563(3)	1022(2)	58(1)
C(41)	2841(3)	4872(4)	229(2)	70(1)

Table 3: Bond lengths [Å] and angles [^{o}] for k06mcw1.

S(1)-O(1)	1.3987(18)	S(1)-O(2)	1.427(2)
S(1)-O(3)	1.5768(15)	S(1)-C(17)	1.834(3)
S(2)-O(7)	1.4071(17)	S(2)-O(6)	1.4095(18)
S(2)-O(8)	1.5654(15)	S(2)-C(34)	1.830(3)
F(1)-C(17)	1.324(3)	F(2)-C(17)	1.315(3)
F(3)-C(17)	1.303(3)	F(4)-C(34)	1.303(3)
F(5)-C(34)	1.317(3)	F(6)-C(34)	1.315(3)
O(3)-C(1)	1.427(2)	O(4)-C(11)	1.205(3)
O(5)-C(11)	1.340(2)	O(5)-C(12)	1.488(2)
O(8)-C(18)	1.427(2)	O(9)-C(28)	1.207(2)
O(10)-C(28)	1.342(3)	O(10)-C(29)	1.478(3)
N(1)-C(11)	1.387(2)	N(1)-C(6)	1.408(2)
N(1)-C(7)	1.500(2)	N(2)-C(7)	1.436(3)
N(2)-C(16)	1.454(3)	N(2)-C(8)	1.464(3)
N(3)-C(28)	1.385(3)	N(3)-C(23)	1.406(3)
N(3)-C(24)	1.507(2)	N(4)-C(24)	1.442(3)
N(4)-C(33)	1.460(3)	N(4)-C(25)	1.464(3)
C(1)-C(2)	1.384(3)	C(1)-C(6)	1.387(3)
C(2)-C(3)	1.383(3)	C(3)-C(4)	1.387(3)
C(4)-C(5)	1.390(3)	C(5)-C(6)	1.392(3)
C(5)-C(10)	1.522(3)	C(7)-C(10)	1.567(3)
C(8)-C(9)	1.523(3)	C(9)-C(10)	1.546(3)
C(10)-C(27)	1.551(3)	C(12)-C(14)	1.509(4)
C(12)-C(15)	1.511(3)	C(12)-C(13)	1.515(4)
C(18)-C(19)	1.381(3)	C(18)-C(23)	1.390(3)
C(19)-C(20)	1.386(3)	C(20)-C(21)	1.392(3)
C(21)-C(22)	1.382(3)	C(22)-C(23)	1.401(3)
C(22)-C(27)	1.522(3)	C(24)-C(27)	1.568(3)
C(25)-C(26)	1.517(3)	C(26)-C(27)	1.548(3)
C(29)-C(32)	1.511(4)	C(29)-C(31)	1.525(4)

C(29)-C(30)	1.525(3)	C(35)-C(40)	1.347(5)
C(35)-C(36)	1.388(6)	C(36)-C(37)	1.407(5)
C(37)-C(38)	1.382(4)	C(38)-C(39)	1.385(4)
C(38)-C(41)	1.499(4)	C(39)-C(40)	1.362(4)
O(1)-S(1)-O(2)	121.18(13)	O(1)-S(1)-O(3)	111.14(10)
O(2)-S(1)-O(3)	111.71(10)	O(1)-S(1)-C(17)	107.82(12)
O(2)-S(1)-C(17)	106.82(14)	O(3)-S(1)-C(17)	94.63(11)
O(7)-S(2)-O(6)	122.74(12)	O(7)-S(2)-O(8)	112.16(9)
O(6)-S(2)-O(8)	106.84(10)	O(7)-S(2)-C(34)	106.43(12)
O(6)-S(2)-C(34)	105.63(12)	O(8)-S(2)-C(34)	100.61(11)
C(1)-O(3)-S(1)	116.53(12)	C(11)-O(5)-C(12)	119.84(16)
C(18)-O(8)-S(2)	119.98(12)	C(28)-O(10)-C(29)	120.25(16)
C(11)-N(1)-C(6)	119.52(16)	C(11)-N(1)-C(7)	122.14(16)
C(6)-N(1)-C(7)	108.90(15)	C(7)-N(2)-C(16)	116.76(17)
C(7)-N(2)-C(8)	108.40(16)	C(16)-N(2)-C(8)	116.41(18)
C(28)-N(3)-C(23)	120.99(16)	C(28)-N(3)-C(24)	122.88(16)
C(23)-N(3)-C(24)	109.26(15)	C(24)-N(4)-C(33)	117.40(17)
C(24)-N(4)-C(25)	107.43(16)	C(33)-N(4)-C(25)	115.66(18)
C(2)-C(1)-C(6)	120.83(19)	C(2)-C(1)-O(3)	117.66(18)
C(6)-C(1)-O(3)	121.50(18)	C(3)-C(2)-C(1)	119.64(19)
C(2)-C(3)-C(4)	120.41(19)	C(3)-C(4)-C(5)	119.3(2)
C(4)-C(5)-C(6)	120.67(19)	C(4)-C(5)-C(10)	128.98(18)
C(6)-C(5)-C(10)	110.15(17)	C(1)-C(6)-C(5)	118.77(18)
C(1)-C(6)-N(1)	130.02(18)	C(5)-C(6)-N(1)	111.13(17)
N(2)-C(7)-N(1)	116.54(16)	N(2)-C(7)-C(10)	104.89(15)
N(1)-C(7)-C(10)	104.80(15)	N(2)-C(8)-C(9)	101.60(16)
C(8)-C(9)-C(10)	102.48(16)	C(5)-C(10)-C(9)	108.68(15)
C(5)-C(10)-C(27)	114.37(16)	C(9)-C(10)-C(27)	114.43(16)
C(5)-C(10)-C(7)	103.04(15)	C(9)-C(10)-C(7)	104.10(16)
C(27)-C(10)-C(7)	111.13(15)	O(4)-C(11)-O(5)	126.91(18)
O(4)-C(11)-N(1)	123.82(18)	O(5)-C(11)-N(1)	109.27(17)
O(5)-C(12)-C(14)	109.85(18)	O(5)-C(12)-C(15)	109.30(17)
C(14)-C(12)-C(15)	112.9(2)	O(5)-C(12)-C(13)	101.73(18)
C(14)-C(12)-C(13)	111.3(2)	C(15)-C(12)-C(13)	111.2(2)
F(3)-C(17)-F(2)	109.4(3)	F(3)-C(17)-F(1)	108.3(2)
F(2)-C(17)-F(1)	110.1(2)	F(3)-C(17)-S(1)	111.72(19)
F(2)-C(17)-S(1)	110.16(18)	F(1)-C(17)-S(1)	107.1(2)
C(19)-C(18)-C(23)	120.96(19)	C(19)-C(18)-O(8)	116.71(18)
C(23)-C(18)-O(8)	122.33(18)	C(18)-C(19)-C(20)	119.8(2)
C(19)-C(20)-C(21)	119.9(2)	C(22)-C(21)-C(20)	119.9(2)
C(21)-C(22)-C(23)	120.51(19)	C(21)-C(22)-C(27)	129.12(18)
C(23)-C(22)-C(27)	110.09(17)	C(18)-C(23)-C(22)	118.42(18)
C(18)-C(23)-N(3)	130.35(18)	C(22)-C(23)-N(3)	111.07(17)
N(4)-C(24)-N(3)	115.45(16)	N(4)-C(24)-C(27)	105.05(15)
N(3)-C(24)-C(27)	104.96(15)	N(4)-C(25)-C(26)	101.56(17)
C(25)-C(26)-C(27)	102.97(16)	C(22)-C(27)-C(26)	109.78(17)
C(22)-C(27)-C(10)	113.66(16)	C(26)-C(27)-C(10)	113.73(16)
C(22)-C(27)-C(24)	103.40(15)	C(26)-C(27)-C(24)	103.61(15)
C(10)-C(27)-C(24)	111.73(16)	O(9)-C(28)-O(10)	126.41(19)
O(9)-C(28)-N(3)	123.80(19)	O(10)-C(28)-N(3)	109.78(17)
O(10)-C(29)-C(32)	111.06(19)	O(10)-C(29)-C(31)	109.05(19)
C(32)-C(29)-C(31)	112.8(2)	O(10)-C(29)-C(30)	101.70(18)

C(32)-C(29)-C(30)	111.3(2)	C(31)-C(29)-C(30)	110.4(2)
F(4)-C(34)-F(6)	109.2(2)	F(4)-C(34)-F(5)	108.9(2)
F(6)-C(34)-F(5)	108.8(2)	F(4)-C(34)-S(2)	111.20(18)
F(6)-C(34)-S(2)	108.97(19)	F(5)-C(34)-S(2)	109.83(19)
C(40)-C(35)-C(36)	119.7(3)	C(35)-C(36)-C(37)	119.5(3)
C(38)-C(37)-C(36)	120.4(3)	C(37)-C(38)-C(39)	117.5(3)
C(37)-C(38)-C(41)	122.4(3)	C(39)-C(38)-C(41)	120.1(3)
C(40)-C(39)-C(38)	122.1(3)	C(35)-C(40)-C(39)	120.8(3)

Symmetry transformations used to generate equivalent atoms:

Table 4: Anisotropic displacement parameters ($Å^2$ x 10^3) for k06mcw1. The anisotropic displacement factor exponent takes the form: $-2\ gpi^2\ [\ h^2\ a^{*2}\ U11 + ... + 2\ h\ k\ a^*\ b^*\ U$

Atom	U11	U22	U33	U23	U13	U12
S(1)	35(1)	33(1)	32(1)	3(1)	8(1)	13(1)
S(2)	25(1)	36(1)	30(1)	6(1)	6(1)	12(1)
F(1)	75(1)	50(1)	71(1)	-23(1)	-4(1)	12(1)
F(2)	76(1)	77(1)	40(1)	18(1)	1(1)	1(1)
F(3)	34(1)	85(1)	68(1)	-9(1)	-5(1)	11(1)
F(4)	109(2)	41(1)	92(1)	26(1)	54(1)	22(1)
F(5)	72(1)	74(1)	89(1)	15(1)	-19(1)	43(1)
F(6)	85(1)	48(1)	58(1)	-3(1)	17(1)	34(1)
O(1)	35(1)	53(1)	58(1)	3(1)	10(1)	18(1)
O(2)	90(2)	41(1)	51(1)	16(1)	32(1)	18(1)
O(3)	29(1)	29(1)	24(1)	4(1)	4(1)	11(1)
O(4)	23(1)	41(1)	36(1)	16(1)	2(1)	8(1)
O(5)	15(1)	41(1)	31(1)	9(1)	1(1)	3(1)
O(6)	48(1)	54(1)	55(1)	12(1)	30(1)	9(1)
O(7)	35(1)	60(1)	33(1)	-4(1)	-3(1)	24(1)
O(8)	20(1)	34(1)	30(1)	5(1)	3(1)	9(1)
O(9)	22(1)	41(1)	42(1)	17(1)	-2(1)	0(1)
O(10)	25(1)	34(1)	32(1)	15(1)	6(1)	4(1)
N(1)	17(1)	25(1)	23(1)	4(1)	2(1)	5(1)
N(2)	29(1)	23(1)	28(1)	4(1)	2(1)	5(1)
N(3)	18(1)	27(1)	23(1)	6(1)	3(1)	5(1)
N(4)	24(1)	34(1)	21(1)	2(1)	1(1)	7(1)
C(1)	21(1)	26(1)	26(1)	4(1)	3(1)	10(1)
C(2)	23(1)	30(1)	35(1)	11(1)	11(1)	12(1)
C(3)	19(1)	29(1)	43(1)	8(1)	10(1)	5(1)
C(4)	18(1)	29(1)	33(1)	0(1)	3(1)	5(1)
C(5)	18(1)	25(1)	27(1)	4(1)	6(1)	8(1)
C(6)	17(1)	23(1)	29(1)	5(1)	5(1)	8(1)
C(7)	20(1)	25(1)	22(1)	3(1)	3(1)	6(1)
C(8)	30(1)	32(1)	33(1)	9(1)	6(1)	13(1)
C(9)	22(1)	33(1)	29(1)	7(1)	2(1)	9(1)
C(10)	17(1)	24(1)	24(1)	3(1)	2(1)	5(1)
C(11)	19(1)	25(1)	27(1)	3(1)	3(1)	7(1)
C(12)	14(1)	46(1)	33(1)	2(1)	-1(1)	7(1)

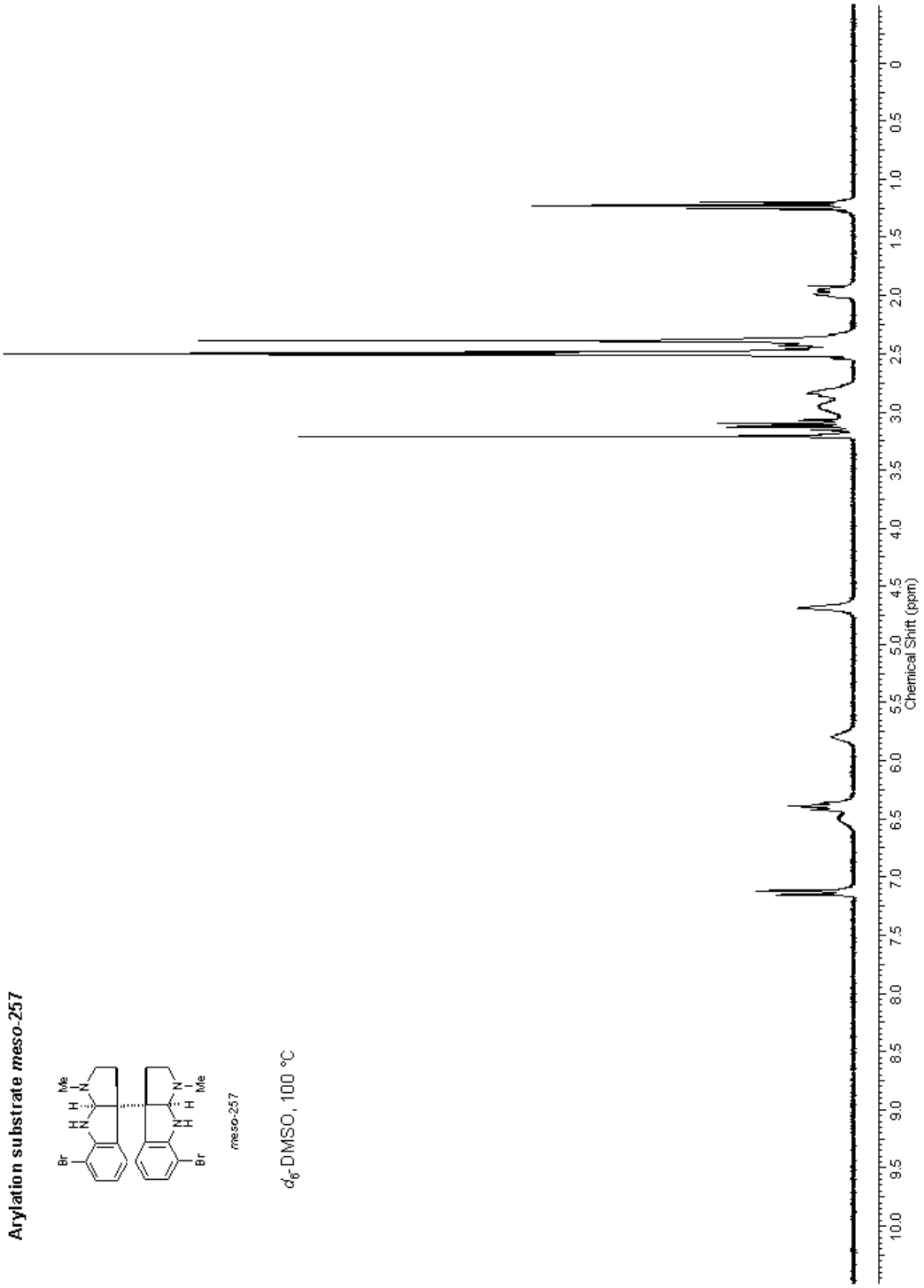
C(13)	22(1)	95(2)	50(2)	20(2)	5(1)	-3(1)
C(14)	29(1)	50(2)	67(2)	-9(1)	-3(1)	20(1)
C(15)	26(1)	40(1)	36(1)	-1(1)	-5(1)	7(1)
C(16)	48(1)	25(1)	32(1)	5(1)	2(1)	4(1)
C(17)	40(1)	48(2)	46(2)	-3(1)	6(1)	5(1)
C(18)	21(1)	29(1)	25(1)	3(1)	4(1)	6(1)
C(19)	33(1)	32(1)	30(1)	10(1)	3(1)	12(1)
C(20)	40(1)	37(1)	31(1)	14(1)	12(1)	14(1)
C(21)	29(1)	31(1)	33(1)	10(1)	11(1)	9(1)
C(22)	22(1)	23(1)	24(1)	2(1)	4(1)	5(1)
C(23)	22(1)	23(1)	21(1)	3(1)	3(1)	3(1)
C(24)	19(1)	26(1)	23(1)	4(1)	2(1)	8(1)
C(25)	27(1)	30(1)	28(1)	-2(1)	1(1)	4(1)
C(26)	23(1)	27(1)	30(1)	-1(1)	3(1)	3(1)
C(27)	19(1)	24(1)	22(1)	2(1)	3(1)	4(1)
C(28)	24(1)	29(1)	25(1)	6(1)	6(1)	6(1)
C(29)	30(1)	35(1)	37(1)	13(1)	11(1)	0(1)
C(30)	46(1)	43(1)	44(1)	23(1)	12(1)	8(1)
C(31)	46(2)	56(2)	59(2)	28(1)	29(1)	18(1)
C(32)	61(2)	42(2)	48(2)	12(1)	2(1)	-12(1)
C(33)	33(1)	47(1)	21(1)	6(1)	3(1)	11(1)
C(34)	46(2)	39(1)	47(1)	6(1)	6(1)	18(1)
C(35)	70(2)	96(3)	43(2)	30(2)	16(2)	23(2)
C(36)	79(2)	79(3)	41(2)	-6(2)	14(2)	-20(2)
C(37)	78(2)	36(2)	64(2)	8(1)	33(2)	6(1)
C(38)	45(1)	45(2)	43(1)	16(1)	24(1)	5(1)
C(39)	52(2)	40(1)	48(2)	8(1)	26(1)	4(1)
C(40)	74(2)	56(2)	59(2)	28(2)	31(2)	22(2)
C(41)	47(2)	101(3)	79(2)	44(2)	28(2)	20(2)

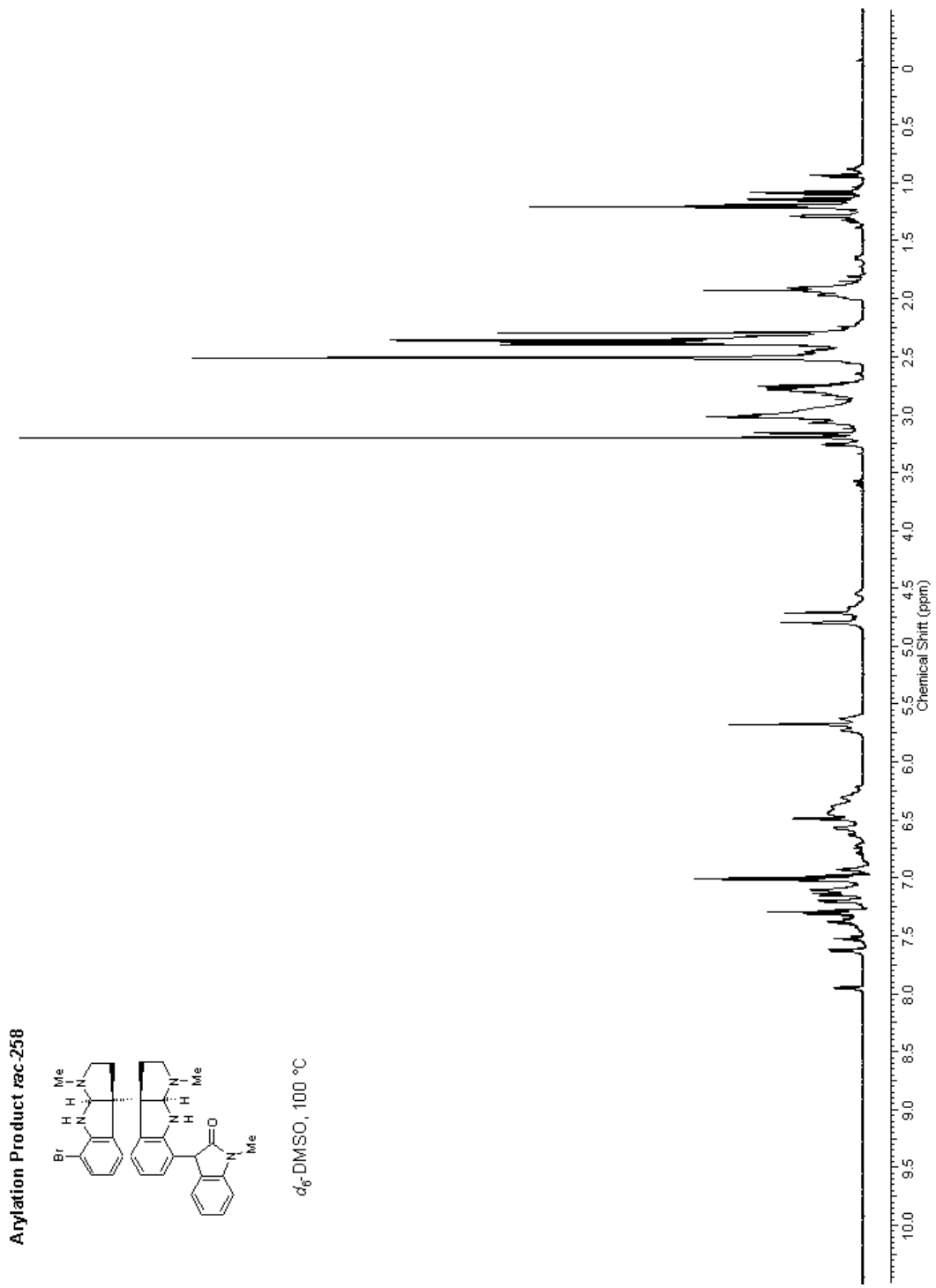
Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for k06mcw1.

Atom	x	y	z	U(eq)
H(2)	3433	450	4987	33
H(3)	2243	-671	3832	36
H(4)	2987	-395	2763	34
H(7)	7488	1952	2970	28
H(8A)	4578	3511	2445	37
H(8B)	4409	3047	3169	37
H(9A)	4660	1669	1759	34
H(9B)	3506	1367	2222	34
H(13A)	10954	2976	3571	86
H(13B)	12132	3524	4284	86
H(13C)	10918	4178	4126	86
H(14A)	10094	1135	4734	79
H(14B)	11603	1600	4640	79
H(14C)	10406	1123	3930	79
H(15A)	10322	4188	5346	54
H(15B)	11549	3571	5550	54

H(15C)	10043	2999	5595	54
H(16A)	6729	4305	3921	55
H(16B)	6774	4878	3238	55
H(16C)	7989	4292	3511	55
H(19)	9525	-1946	3322	37
H(20)	7561	-1956	3816	40
H(21)	5836	-1120	3321	36
H(24)	6750	1396	1699	27
H(25A)	5942	-1754	1078	37
H(25B)	4571	-1637	575	37
H(26A)	4513	-1513	1923	34
H(26B)	3904	-550	1582	34
H(30A)	8769	2470	264	63
H(30B)	9953	3609	499	63
H(30C)	8723	3533	930	63
H(31A)	11405	1403	1170	73
H(31B)	11676	2295	671	73
H(31C)	10406	1225	399	73
H(32A)	10296	3879	2147	81
H(32B)	11549	4031	1737	81
H(32C)	11416	3105	2224	81
H(33A)	7107	609	297	51
H(33B)	6096	-589	-145	51
H(33C)	7453	-600	399	51
H(35)	7186	4335	1869	80
H(36)	6546	6142	2108	89
H(37)	4576	6389	1384	70
H(39)	3982	3060	226	55
H(40)	5917	2836	920	70
H(41A)	2677	5659	390	105
H(41B)	2058	4303	258	105
H(41C)	2979	4733	-281	105

Appendix B – High Temperature NMR Spectra




Arylation Product rac-258
d_6-DMSO, 100 °C
Chemical Shift (ppm)