Palladium-catalysed enantioselective desymmetrisations

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Palladium-Catalysed Enantioselective Desymmetrisations

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Abstract

Palladium catalysed cross-coupling reactions have become extremely useful synthetic tools in organic synthesis, and when used in conjunction with an enantioselective desymmetrisation strategy, can provide rapid asymmetric synthetic routes to complex organic molecules.

Using palladium catalysed Suzuki reactions, prochiral ditriflates are coupled with a range of aromatic boronic acids to generate products containing a stereodefined quaternary carbon centre and a synthetically useful vinyl triflate functionality. This is achieved through enantiotopic group selection. The substrates possess C_S symmetry with a mirror plane bisecting the compound and consequently they contain two alkene stereofaces; one side contains a small R group (R_S), whereas the other contains a sterically bulkier R group (R_L).

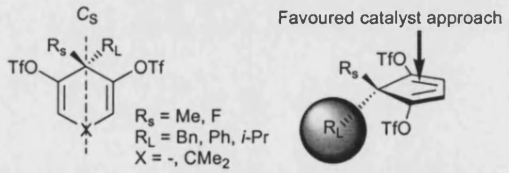
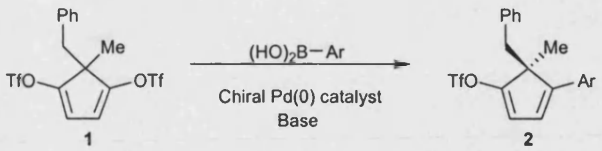


Figure 1

Using a chiral ligand in conjunction with a palladium source, a catalytic species is generated which prefers to approach the ditriflate on the least hindered side. Therefore, the catalyst obtains selectivity through enantiotopic group discrimination. The substrate contains a quaternary centre, which upon desymmetrisation becomes a stereogenic centre. In this way it is possible to undergo a cross-coupling reaction which generates a single enantiomer of the product. These transformations have been achieved with selectivities of up to 86% ee.

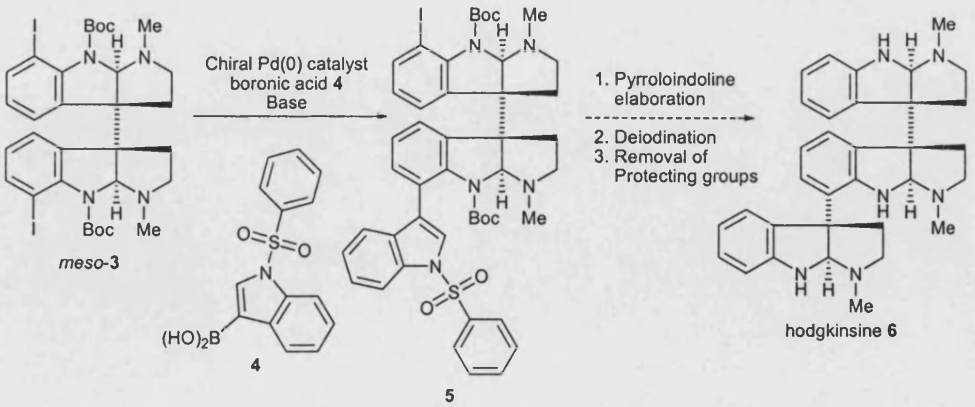


Scheme 1

A range of cyclic ditriflate compounds were synthesised in order to study the effects of steric crowding upon the enantioselectivities obtained, by increasing the bulky group (R_L) and also reducing the size of the small group (R_s).

The monocoupled products generated in these asymmetric Suzuki reactions represent versatile intermediates as they contain a synthetically useful triflate functionality. This component was used for a range of further palladium-catalysed derivatisations to generate complex, enantiomerically enriched compounds in high yield.

Finally, the utility of this desymmetrisation procedure was then tested further, by transferring the conditions developed onto the desymmetrisation of the radically different *meso*-diiodide compound **3**, for the development of a new enantioselective synthesis of the natural product hodgkinsine **6**.



Scheme 2

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Acknowledgements

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Abbreviations and Acronyms

Å	Angstrom
Ac	Acetyl
AMPHOS	(-)-2((*S*)-1-Dimethylaminoethyl)-phenyl 7-diphenyl phosphine
app	Apparent
aq	Aqueous
Ar	Aryl
Atm.	Atmosphere (unit of pressure)
β_i	Reaction rate
9-BBN	9-Borabicyclo[3.3.1]nonane
B	Generic base
BINAM	2,2'-Diamino-1,1'-binaphthyl
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BINAP(O)	2-Diphenylphosphino-2'-diphenylphosphinyl-1,1'-binaphthalene
$BINAP(O)_2$	2,2'-Bis(diphenylphosphiyl)-1,1'-binaphthyl
BINAs	2,2'-Bis(diphenylarsino)1,1'-binaphthyl
BINAPAs	2-Diphenylarsino-2'-diphenylphosphino-1,1'-binaphthyl
BINAPFu	2,2'-Bis(diphenylphosphino-3,3'-binaphtho[2,1-b]furan
BINOL	1,1'-Bi-2-naphthol
BisP*	Bis(trialkylphosphine)
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
BPPFA	(*S*)-*N*,*N*-dimethyl-1-[(*R*)-1',2-bis(diphenylphosphino)ferrocenyl]amine
BPPFOAc	1-[1-(Acetoxy)ethyl]-1',2-bisdiphenylphosphino)ferrocene
br	Broad
Bu	Butyl
t-Bu-BOX	2,2'-*iso*-Propylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline]
Bz	Benzoyl
°C	Degrees Celsius
CAM	Ceric ammonium molybdate
Cbz	Carboxybenzyl

(*S*,*S*)-CHIRAPHOS	(2*S*,3*S*)-(-)-Bis(diphenylphosphino)butane
CI	Chemical Ionisation
(*S*)-Cl-MeO-BIPHEP	(*S*)-(+)-5,5'-Dichloro-6,6'-dimethoxy-2,2'-bis(diphenylphosphino)-1,1'-biphenyl
cm	Centimetre
conc.	Concentrated
conv.	Conversion
Cy	Cyclohexyl
CSA	Camphorsulphonic acid
δ	Chemical shift in parts per million
d	Doublet
dba	(*E*,*E*)-Dibenzylideneacetone
DCE	Dichloroethane
DCM	Dichloromethane
de	Diastereomeric excess
DEAD	Diethyl azodicarboxylate
DIAMCY	1,2-Diaminocyclohexane
DIBAL	Di*iso*butyl aluminium hydride
DIOP	(-)-2,3-*ortho*-*iso*-Propylidene-2,3-dihydroxy-1,4-bis(diphenyl phosphine) propane
Dioxane	1,4-Dioxane
DIPT	Di-*iso*-propyltartrate
DMA	*N*,*N*-Dimethylacetamide
DME	1,2-Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulfoxide
DNP	2,4-Dinitrophenylhydrazine
dppb	1,4-Diphenylphosphinobutane
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dppp	1,3-Diphenylphosphinopropane
ed.	Edited by
ee	Enantiomeric excess
EI	Electron impact

eq.	Equivalent
ES	Electrospray
Et	Ethyl
Ethylene glycol	1,2-Ethanediol
Δ	Heat
g	gram
GC	Gas chromatography
h	Hour
Hal	Halide
HOMO	Highest occupied molecular orbital
(*R*)-HO-MOP	(*R*)-2'-Diphenylphosphino-1,1'-binaphthalene-2-ol
HPLC	High performance liquid chromatography
Hz	Hertz
IR	Infrared
Im	Imidazole
i	*iso*, equal
J	Coupling constant (in NMR spectrometry)
(*R*,*S*)-JOSIPHOS	(*R*)-(-)-[(*S*)-2-(Diphenylphosphino)ferrocenyl]ethyl dicyclohexylphosphine
k_i	Reaction rate
KHMDS	Potassium hexamethyldisilazide
L	Ligand
L*	Chiral ligand
LDA	Lithium di*iso*-propylamide
LHMDS	Lithium hexamethyldisilazide
LUMO	Lowest unoccupied molecular orbital
M	Molar (number of moles per litre), metal
m	Multiplet
m-	*meta*
MAP	2-Dimethylamino-2'-diphenylphosphino-1,1'-binaphthyl
Me	Methyl
(*S*)-MeO-BIPHEP	(*S*)-(+)-6,6'-Dimethoxy-2,2'-bis(diphenylphosphino)-1,1'-biphenyl

(*R*,*R*)-Me-DUPHOS	(-)-1,2-Bis((2*R*,5*R*)-2,5-dimethylphospholano)benzene
(*R*)-MeO-MOP	(*R*)-(+)-2-Diphenylphosphino-2'-methoxy-1,1'-binaphthyl
mg	Milligram
MHz	Megahertz
min	Minute
MiniPHOS	(*R*,*R*)-Bis((*tert*-butyl)methylphosphino)methane
ml	Millilitre
mmol	Millimole
MOM	Methoxymethyl ether
(*S*)-(*S*)-MOPF	(*S*)-(-)-2-(*ortho*-Anisole)-1-(dicyclohexylphosphanyl)ferrocene tetrafluoroboric acid salt
mp	Melting point
MS	Molecular sieves, mass spectrometry
MW	Molecular weight
m/z	Mass to charge ratio
N	Normal (number of equivalents per litre)
n-	*normal*
NaHMDS	Sodium hexamethyldisilazide
Naphth	Naphthyl
Nf	Nonafluorobutyl sulfonyl
Ninhydrin	1,2,3-Indantrione monohydrate
(*S*)-NMDPP	(*S*)-(+)-Neomenthyldiphenylphosphine
NMP	*N*-Methyl-2-pyrrolidinone
NMR	Nuclear magnetic resonance
nOe	Nuclear Overhauser effect
(+)-NORPHOS	(2*S*,3*S*)-(+)-2,3-bis(diphenylphosphino)bicycle[2.2.1]hept-5-ene
o-	*ortho*
p-	*para*
PFOMe	(+)-(*S*)-1-[(*R*)-2-(diphenylphosphino)ferrocenyl]ethyl methyl ether
Ph	Phenyl
(*R*)-PHANEPHOS	(*R*)-(-)-4,12-Bis(diphenylphosphino)-[2.2]paracyclophane
PHOX	Phosphinoxazoline

PIFA	Phenyliodine(III) bis(trifluoroacetate), [Bis(trifluoroacetoxy)iodo] benzene
Pin	Pinacol, 2,3-Dimethyl-2,3-butanediol
PMHS	Poly(methylhydrosiloxane)
PMP	1,2,2,6,6-Pentamethylpiperidine
PNB	*Para*-nitro benzyl
PPFA	*N*,*N*-dimethyl-1-[2-(diphenylphosphino)ferrocenyl]ethylamine
PPF-pyrrolidine	[1-(*N*-Pyrrolidino)ethyl]ferrocenyl]-2-diphenylphosphine
(*S*)-(*S*)-*i*-Pr-Phosferrox	(*S*)-2-[(*S*)-2-(diphenylphosphino)ferrocenyl]-4-(1-methylethyl)oxazoline
(*R*)-*i*-PrO-MOP	(*R*)-(+)-2-Diphenylphosphino-2'-*iso*-propoxy-1,1'-binaphthyl
Proton sponge	1,8-Bis(dimethylamino)naphthalene
Pv	Pivaloyl, trimethylacetyl
pp.	Pages
ppm	Parts per million
Pr	Propyl
q	Quartet
(*R*)-QUINAP	(*R*)-(+)-1-(2-Diphenylphosphino-1-naphthyl)isoquinoline
R	General hydrocarbon substituent
rac-	Racemic
Red-Al®	Sodium bis(2-methoxyethoxy)aluminium hydride solution
ref(s).	Reference(s)
R_f	Retention factor (in chromatography)
rt	Room temperature
s	Singlet
sec	Secondary
Selectfluor™	1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)
SEMI-ESPHOS	1-(2-Methoxyphenyl)-2-phenylhexahydropyrrolo[1,2-c][1,3,2]diazaphosphole
sept.	septet
sol.	Solution
t	Triplet

t	*tert*, Tertiary
TADDOL	(4*R*,5*R*)-(-)-2,2-Dimethyl-α,α,α',α'-tetraphenyl-1,3-dioxolane-4,5-dimethanol
TBDMS or TBS	*tert*-Butyldimethylsilyl
Tf	Trifluoromethanesulfonyl (triflyl)
THF	Tetrahydrofuran
TIPS	Tri*iso*-Propylsilyl
TLC	Thin layer chromatography
TMEDA	*N*,*N*,*N*',*N*'-Tetramethylethylenediamine
TMS	Trimethylsilyl, tetramethylsilane
TOF	Turn over frequency
Tol.	Tolyl (*para*-methyl phenyl)
(*R*)-Tol-BINAP	(*R*)-(+)-2,2'Bis-(di-*p*-tolyl-phosphino)-1,1'-binaphthyl
Ts	*p*-Toluenesulfonyl (tosyl)
triflate	Trifluromethanesulfonate
Vanillin	4-Hydroxy-3-methoxybenzaldehyde
Vol.	Volume
X	General halide substituent (also used for triflate in Suzuki couplings)
Xyl	Xylyl, 3,5-Dimethyl phenyl
(*R*)-Xyl-BINAP	(*R*)-(+)-2,2'Bis-(di(3,5-dimethyl phenylphosphino)-1,1'-binaphthyl
v	Frequency

1 Enantioselective palladium-catalysed reactions

Palladium has become one of the most useful and versatile metals used in organic chemistry.[1] The main facet of palladium catalysts is their ability to perform a variety of C-X and C-C bond forming reactions, whilst exhibiting good tolerance towards a variety of functionality. Palladium chemistry has had widespread use throughout organic synthesis, where it is shown to be extremely effective in producing single enantiomers.[2] This enantioselectivity is achieved through combining palladium sources with chiral ligands to generate enantioselective catalysts.

Over recent years the scope of enantioselective palladium chemistry has increased significantly. The most common reaction studied is the Heck reaction; first discovered simultaneously by the Heck and Mizoroki groups.[3,4] This is the reaction between an aryl or alkenyl triflate or halide and an alkene to generate a substituted (*E*)-alkene (Figure 1.1). The reaction is facilitated by the presence of a palladium(0) species and a base. Organometallic couplings have also been accomplished utilising the same aryl or alkenyl compounds in conjunction with lithium, magnesium, zinc, tin, aluminium, silicon or boron organometallic compounds.[5] The main reactions of this type are those of the Stille coupling,[6,7] using organostannane reagents of the type $RSnR'_3$; the Kumada cross-coupling,[8,9] involving organomagnesium compounds RMgX; and the Suzuki-Miyaura coupling,[10-13] which utilises an organoboron species $RB(OR')_2$ (Figure 1.1).

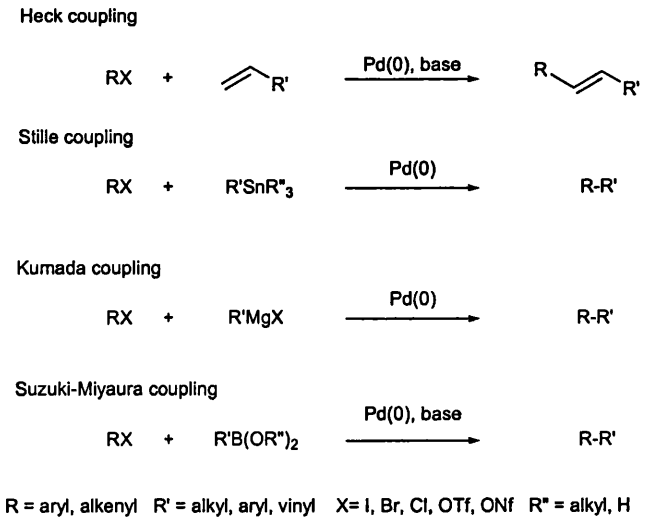


Figure 1.1

Although these reactions have been extensively studied, certain aspects of the exact mechanisms are still not fully understood.[14,15] The initial step involves creating a σ-aryl or σ-alkenyl palladium(II) bond (Figures 1.2 and 1.3) *via* the oxidative addition of the palladium(0) catalyst into the aryl or alkenyl halide or triflate unit. For the Heck reaction the subsequent reaction step involves the tandem coordination and insertion of the alkene into the C-Pd bond of the palladium(II) species followed by an internal rotation (Figure 1.2). With the organometallic species used in the Kumada, Stille and Suzuki couplings, a transmetallation step occurs transferring the alkyl, aryl or vinyl species from the metal to the palladium(II) species. It has been proposed that this transmetallation process is the rate determining step in most cross-coupling reactions.[12] The final step in the catalytic cycle is the reductive elimination of the catalyst species to create the desired product and a regenerated and fully active catalyst; although in the case of the Heck reaction the final step is the base mediated reduction of a hydridopalladium species, which regenerates the active catalyst. In the Suzuki coupling the exact nature of the boronic species which takes part in the transmetallation is unclear, however, it is likely to be a boronate species ($R\text{-}BY_3^-$) formed upon addition of the base.[16,17]

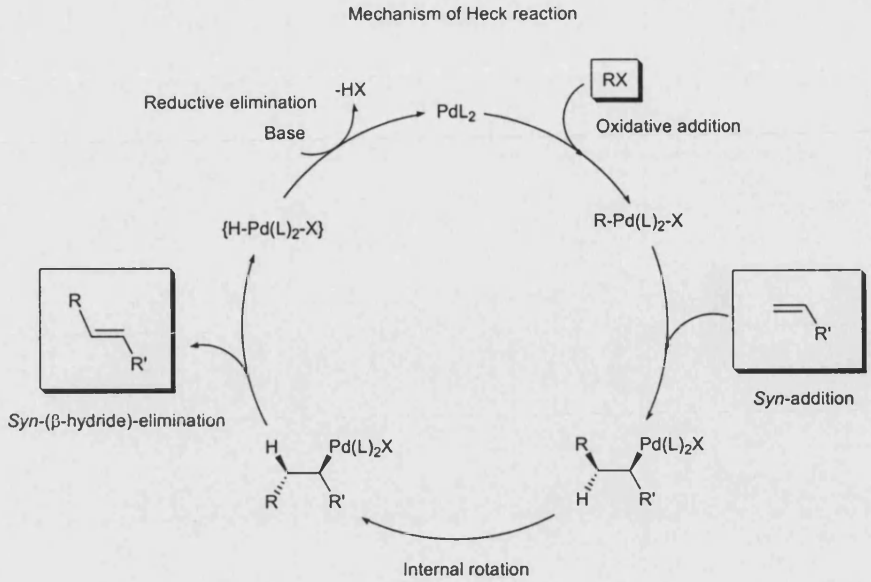


Figure 1.2

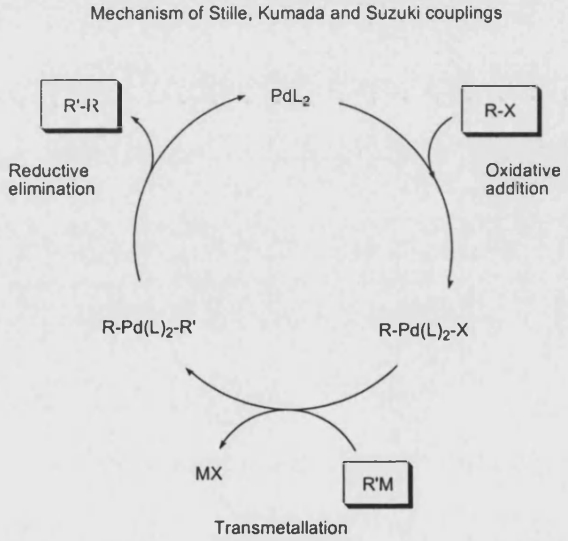


Figure 1.3

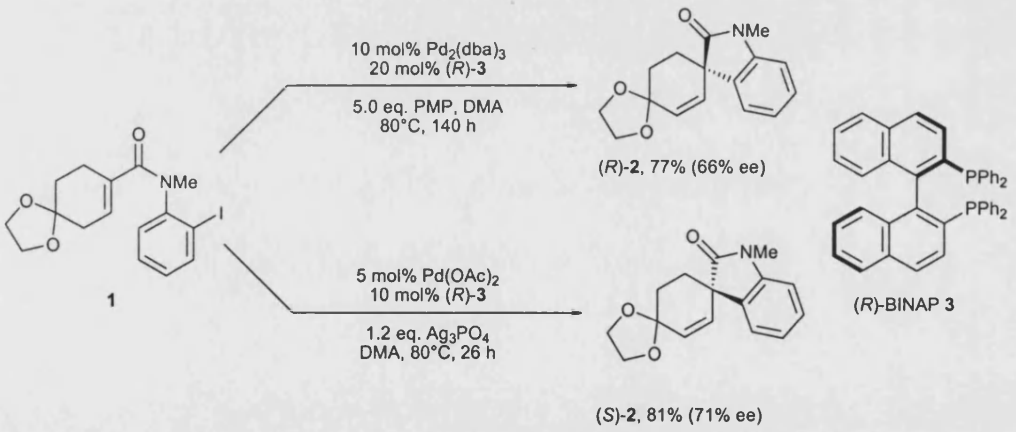
1.1 Enantioselective palladium catalysis

Enantioselective palladium catalysis is a rapidly expanding general topic and has been reviewed in detail recently.[18] The development of natural product synthesis and drug design has provided an increased desire to create stereogenic centres from palladium-catalysed C-C bond forming reactions. To facilitate asymmetric reactions chiral ligands can be added to the palladium. These ligands bind to the metal centre and mean that subsequent reactions can transfer the chiral information from the ligands to the prochiral substrates, thus producing an enantioselective coupling

reaction. There have been many chiral ligands developed for just this purpose, including bidentate diphosphines, aminophosphines, and phosphinoxazoline.[19-24]

1.2 Enantioselective Heck reactions

Enantioselective Heck reaction procedures have become increasingly important in synthesis and have recently been reviewed in detail.[25,26] The Heck reaction has been found to be extremely useful in target directed synthesis, especially during intramolecular Heck reactions. One significant breakthrough in this field was the enantioselective formation of quaternary carbon centres, which remains an important challenge for synthetic chemists.[27,28] Overman *et al.* were the first to accomplish this using a Heck reaction, although the enantioselectivity achieved was modest (45% ee).[29] In a related study the full potential of this approach was discovered when synthesising spirooxindoles (*R*) and (*S*)-**2** (Scheme 1.1).[30]

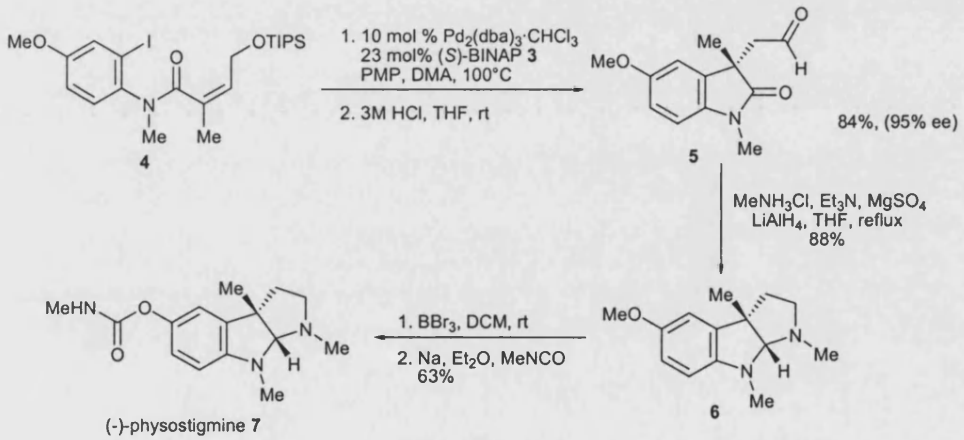


Scheme 1.1

The study used iodoanilide **1**, a catalytic amount of palladium, and the chiral ligand (*R*)-BINAP **3** to promote the intramolecular Heck reaction. It was discovered that using different types of HI scavenger led to the selective formation of either enantiomer. These scavengers are often required to encourage Heck reactions, especially silver salts, which form cationic palladium complexes as intermediates.[31]

When pentamethylpiperidine (PMP) is used in the coupling reaction the *R* enantiomer of oxindole **2** is produced in 77% yield with a 66% ee. However, when silver phosphate is used the *S* enantiomer of oxindole **2** is produced in 81% yield and 71% ee.

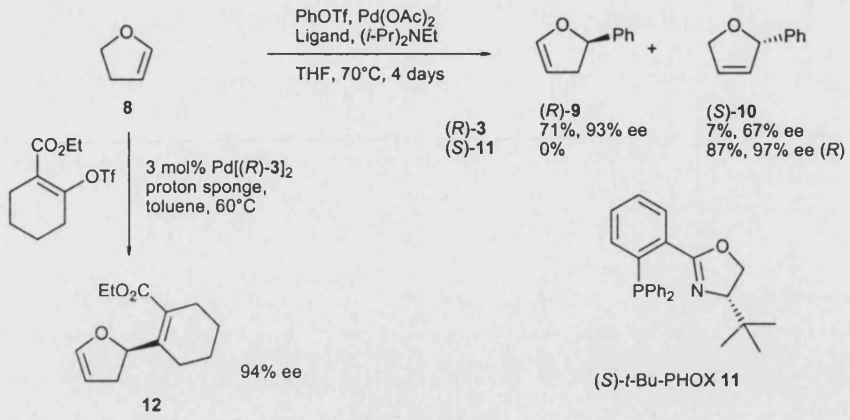
Overman *et al.* have developed useful intramolecular Heck methodology for the synthesis of a family of polypyrrolidinoindoline alkaloids.[32-34] The first example of this was used for the total synthesis of one of the simplest members of this alkaloid family, physostigmine **7** (Scheme 1.2).[32]



Scheme 1.2

The key step in this sequence was the stereocontrolled Heck cyclisation of the (*Z*)-2-methyl-2-butenalide **4** to the oxindole aldehyde (*S*)-**5**, achieved in high yield with excellent enantioselectivity. Again this process required the presence of the HI scavenger pentamethylpiperidine. Oxindole aldehyde **5** was then elaborated into pyrrolidinoindoline **6** and then through to the final natural product **7**.

A system that has been well documented is that involving asymmetric intermolecular Heck reactions of dihydrofuran **8** (Scheme 1.3).[35]

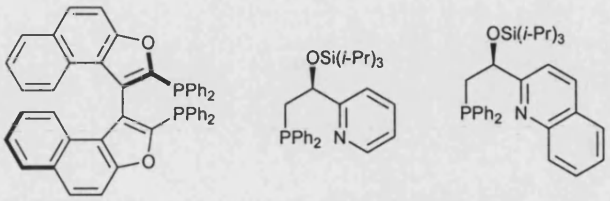


Scheme 1.3

This system was first investigated by Hayashi *et al.* and utilises a (*R*)-BINAP **3** palladium catalyst and phenyl triflate to arylate the dihydrofuran. It was noted that a small proportion of the regioisomer, dihydrofuran **10**, was produced in moderate enantioselectivity. It was suggested that this was due to the ability of the catalyst to approach from either side of the substrate, to yield one of two diastereomeric complexes. In one of these cases unfavourable steric factors caused the catalyst to leave the substrate, thus yielding dihydrofuran **10**. In the other diastereomer the palladium favours a reinsertion into the alkene followed by a second elimination, which yields the main dihydrofuran product **9**. Pfaltz *et al.* tested this by using the chiral ligand (*S*)-*t*-butylphosphinoxazoline ((*S*)-*t*-Bu-PHOX) **11** on the same system.[36] They found that when using (*S*)-*t*-Bu-PHOX **11**, no double bond isomerisation occurs, yielding dihydrofuran **10** as a single product with a 97% ee. Dihydrofuran **8** has also been successfully vinylated in a Heck reaction again using (*R*)-BINAP to give dihydrofuran **12** in high enantioselectivities (94% ee) as a single regioisomer (Scheme 1.3).[37]

The use of BINAP has been well established in enantioselective Heck reactions, but more recently *P,N*-ligands have been introduced, with ligands such as the

phosphinoxazolines yielding high ee's in asymmetric Heck reactions. The main area of recent progress in asymmetric Heck reactions has been the design of new effective chiral ligands. Recent examples include BINAPFu **13**, which has yielded dihydrofuran products with excellent enantioselectivities (Figure 1.4).[38]



BINAPFu **13** **14** **15**

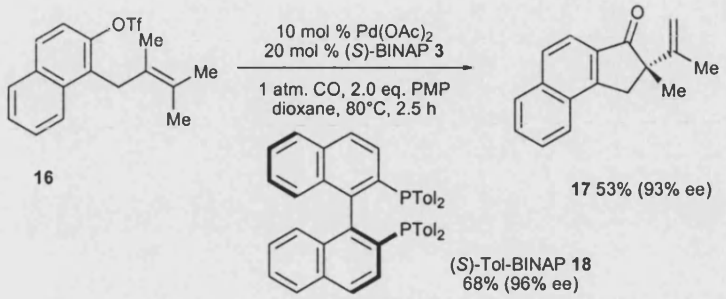
Figure 1.4

Alternative *P*,*N*-ligands have recently been developed further with the introduction of *P*,*N*-pyridine **14** and quinoline **15** type ligands (Figure 1.4).[39] These ligands have been specifically designed to have the same diphenylphosphino groups and similar coordination geometries when in metal complexes to those of the phosphinoxazoline ligands. The steric and electronic properties differ greatly from the oxazoline ligands, and the results yielded from Heck reactions have proved very interesting. Conversions of up to 100% with 97% ee on the 2,3-dihydrofuran and phenyl triflate model were observed.

1.3 Enantioselective palladium-catalysed carbonylations

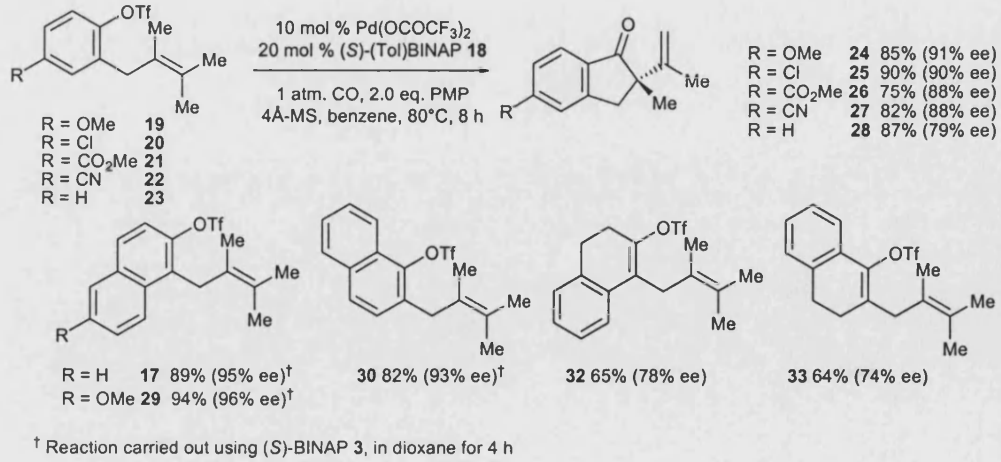
Palladium-catalysed carbonylation reactions are extremely useful methods for the homologation of organic compounds. In many organometallic coupling reactions the rate-limiting step is the transmetallation step of the catalytic cycle. However, carbonyl insertion is a more facile process than transmetallation, and is synthetically very useful as it can be applied to generating unsaturated ketones, aldehydes and esters.[40-43] There are an increasing number of investigations into asymmetric versions of these reactions, often focused upon hydroformylations.[18] However, there are

several interesting examples of note in the literature whereby halides or triflates are used to undergo asymmetric carbonylations. Hayashi *et al.* have shown the utility of this process by taking *ortho*-allylaryl triflates and subjecting them to cyclocarbonylation.[44]



Scheme 1.4

They screened a variety of ligands and found that the best results were achieved using the bidentate ligands BINAP **3** and Tol-BINAP **18**. These ligands generated moderate yields of the ketone **17** with excellent enantioselectivities (Scheme 1.4). Further optimisation of the reaction conditions revealed that using palladium(II) trifluoroacetate as the precatalyst, benzene as solvent and the addition of 4 Å molecular sieves increased the yields further. They then used these conditions and examined the substrate variation tolerated in this process (Scheme 1.5).

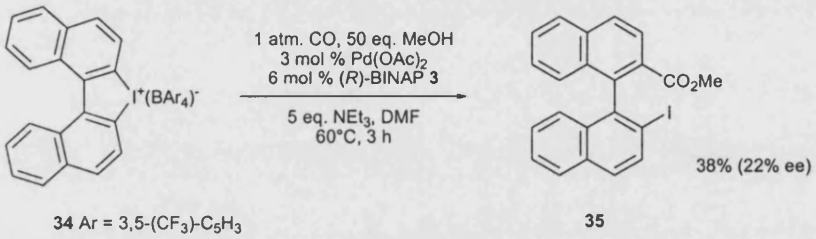


Scheme 1.5

They found that simple *para*-substituted phenyltriflates **19-23** furnished good yields and enantioselectivities, as did the 1- and 2-substituted naphthyl triflates **17**, **30**, and

especially the methoxy substituted triflate **29**. They also showed that this methodology could be applied to different types of triflate by successfully cyclising alkenyl triflates **32** and **33**, albeit in slightly lower yield and enantioselectivity.

Hayashi *et al.* have also shown that it is possible to generate functionalised binaphthyls such as iodide **35** through asymmetric carbonylation of dinaphthaleneiodonium salt **34** (Scheme 1.6).[45]

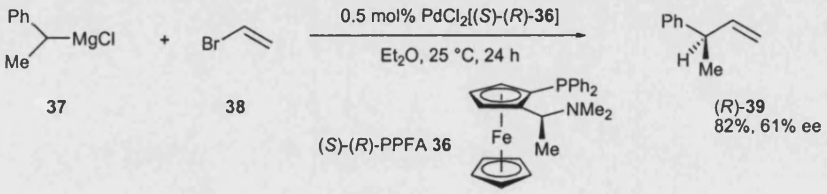


Scheme 1.6

The use of this methodology may be limited however, as the yield and enantioselectivity are low.

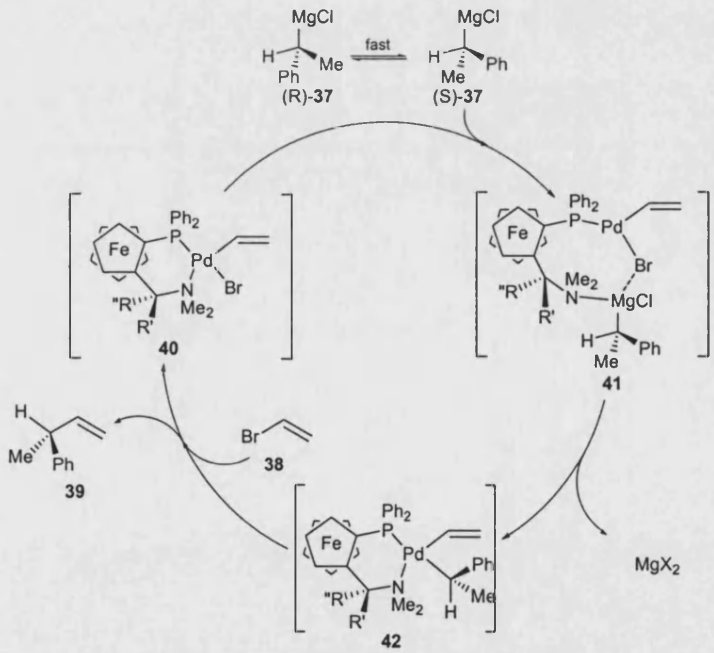
1.4 Enantioselective Kumada cross-coupling

The main breakthrough achieved with the asymmetric Kumada cross-coupling was the development of ferrocenylphosphines such as (*S*)-*N*,*N*-dimethyl-1-[(*R*)-2-(diphenylphosphino)ferrocenyl] ethyl amine **36**.[46] These proved to be effective at providing high yields (82%) with reasonable enantioselectivity (61%) for the asymmetric coupling of 1-phenyl magnesium chloride **37** with vinyl bromide **38** (Scheme 1.7).[47]



Scheme 1.7

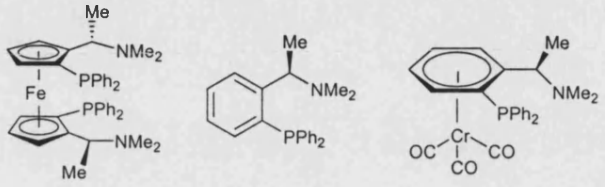
The main characteristic of these ferrocenyl ligands is the way they blend together different types of chirality and functionality. They contain planar stereochemistry in the ring systems, stereocentres and also additional functional groups such as the amine on the side chain of (*S*)-(*R*)-PPFA **36**. It has been observed in NMR experiments that the palladium (*S*)-(*R*)-PPFA **36** catalyst combines chelation through both the phosphorus and the nitrogen. It was established in a study of ferrocenyl derived ligands, that the presence of chirality in the side chain was important, and the dimethyl amino group aids considerably in imparting stereoinformation to the products. The increase in selectivity with the presence of an amino group in the ligand can be justified by the ability of the amino group to coordinate to the magnesium of the Grignard reagent **37** (intermediate **41** in Scheme 1.8).



Scheme 1.8

Oxidative addition of the catalyst into the vinyl bromide yields the first intermediate **40**. The dimethyl amino group in the ferrocenyl ligand will then dissociate from the palladium of intermediate **40**, and selectively coordinate to the magnesium of one of the rapidly interchanging enantiomers of the racemic Grignard reagent **37**, generating

the intermediate **41** (generating a dynamic kinetic resolution). The next process is transmetallation, which forms the intermediate **42**, this will then yield the chiral product **39** by reductive elimination and the cycle can continue. These ferrocenyl ligands have been shown to be highly enantioselective giving up to 95% enantiomeric excess, in good yields.



(+)-43 AMPHOS 44 (*S*)-(*R*)-45

Figure 1.5

New chiral ligands developed for Kumada cross-coupling reactions that have shown potential include: Hayashi's ferrocenyl diphosphine ligand (+)-**43**,[48] the benzene ring based (-)-2((*S*)-1-dimethylaminoethyl)-phenyl-7-diphenylphosphine **44** developed by Kreuzfeld *et al.*,[48,] and also a ligand that contains tricarbonyl chromium complexed to a phenyl ring (arene **45**)[49,50] (Figure 1.5).

1.5 Enantioselective Suzuki-Miyaura reactions

The Suzuki-Miyaura reaction has been studied comprehensively since it was first developed in 1978,[16,51,52] however, it has only recently been reported that the reaction can be performed asymmetrically. The first asymmetric Suzuki cross-coupling reactions were reported simultaneously from the groups of Buchwald and Cammidge. They described the preparation of enantiomerically enriched naphthalenes, which are an important class of atropoisomeric compounds.

Cammidge *et al.* reported the C-C coupling reaction involving naphthyl halides **46** or **47** together with the boronic acid or ester **48** or **49** to synthesise a series of axially

chiral biaryl compounds.[53] They successfully carried out the coupling reactions in both heterogeneous and homogeneous conditions utilising a variety of solvents (DME, DME/H_2O and toluene/EtOH/H_2O) and bases ($Ba(OH)_2$, CsF, Na_2CO_3 and NaOH).

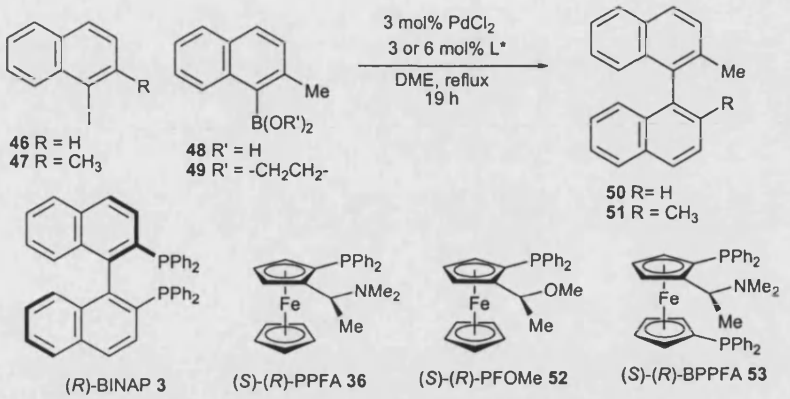


Table 1.1: Enantioselective Suzuki couplings of 1-iodonaphthalenes

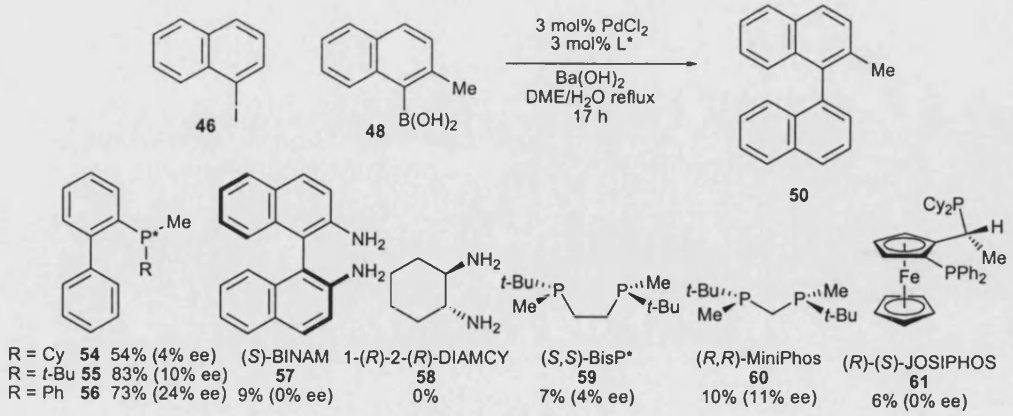
Reaction	Halide	Boronate	Base	Ligand[a]	Product	Yield (%)	ee (%)
1[b]	**46**	**48**	$Ba(OH)_2$	(*S*)-(*R*)-**36**	*R*(-)-**50**	44	63
2	**46**	**48**	CsF	(*S*)-(*R*)-**36**	*R*(-)-**50**	44	55
3	**46**	**48**	CsF	*R*-(+)-**3**	*S*(+)-**50**	43	21
4[b]	**46**	**48**	$Ba(OH)_2$	(*S*)-(*R*)-**52**	*R*(-)-**50**	74	14
5[b]	**46**	**48**	$Ba(OH)_2$	(*S*)-(*R*)-**53**	*S*(+)-**50**	73	4
6[c]	**47**	**49**	CsF	(*S*)-(*R*)-**36**	*R*(-)-**51**	50	85

[a] Reactions were carried out with 1.1-1.2 eq. of boronate in solvent heated to reflux using 3 mol% $PdCl_2$ /6 mol% monophosphine chiral ligand or 3 mol% $PdCl_2$ /3 mol% bidentate chiral ligand for 19 h. [b] Reaction was carried out in DME/ H_2O. [c] Reaction was stopped after 6 days

The highest enantioselectivity was achieved with ferrocenyl aminophosphine (*S*)-(*R*)-PPFA **36** acting as the ligand. They formed 2-methyl-1,1'-binaphthalene **50** in yields between 44-55% and ee's of 52-63%. In combining the dimethyl derivative **51** and the boronic ester **49** along with the ligand (*R*)-BINAP **3** they obtained their highest ee (85%) (Table 1.1). The best reaction rates were achieved using derivatives of the ferrocenyl monophosphine ligand **36**. Firstly, with the dimethyl amine group replaced with a methoxy group (PFOMe **52**), or by the addition of a second diphenylphosphine unit (BPPFA **53**). These conditions yielded up to 74% of the

binaphthalene product **50** after 19 hours, however, the enantioselectivities were low (entries 4 & 5).

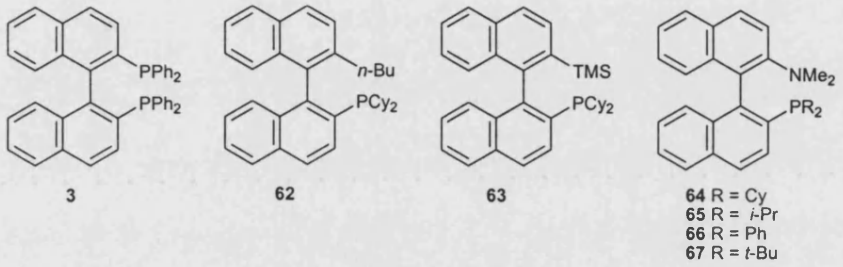
Since this initial research was carried out a full report has been published by Cammidge *et al.* in which further ligand screening and more general information about these reactions is described.[54] They indicate that these reactions suffer from competing deboronation, which seems to be accelerated by the presence of palladium.[55] Another important aspect conveyed was that boronic esters are preferred to their boronic acid counterparts, especially in hindered substrates, as higher conversions are achieved, albeit at slower rates. Interestingly, using the pinacol boronate ester yielded the opposite major enantiomer compared to using the ethylene glycol boronate ester or the parent boronic acid. The authors remarked that this implies kinetic control in this reaction, reasoning that thermodynamic control would lead to the same enantiomer regardless of boronate. They also remarked that this indicates that the enantio-determining step is transmetallation of the palladium intermediate. The further ligands tested yielded no increase in enantioselectivity (Scheme 1.9).



Scheme 1.9

They show that bidentate ligands yielded both poor yields and ee's including diamine ligands **57** and **58**. Moderate to good yields were attained using the biphenyl phosphine ligands **54**, **55** and **56**.

Buchwald *et al.* also reported their own efforts at asymmetric Suzuki reactions, synthesising axially chiral functionalised compounds. Their strategy employed a variety of bulky electron rich phosphine ligands **62-67** with similar structures to BINAP **3** (Figure 1.6).[56]



3 **62** **63**

64 R = Cy
65 R = *i*-Pr
66 R = Ph
67 R = *t*-Bu

Figure 1.6

They screened these ligands in two different Suzuki cross couplings, firstly that of 2-diethylphosphite-1-bromonaphthalene **68** with *ortho*-tolylboronic acid **69** to form the biaryl-diethylphosphite **70** (reaction A, Table 1.2). The second Suzuki coupling was between 2-nitrobromobenzene **71** and 2-phenyl-naphthylboronic acid **72** to generate the triaryl **73** (reaction B, Table 1.2).

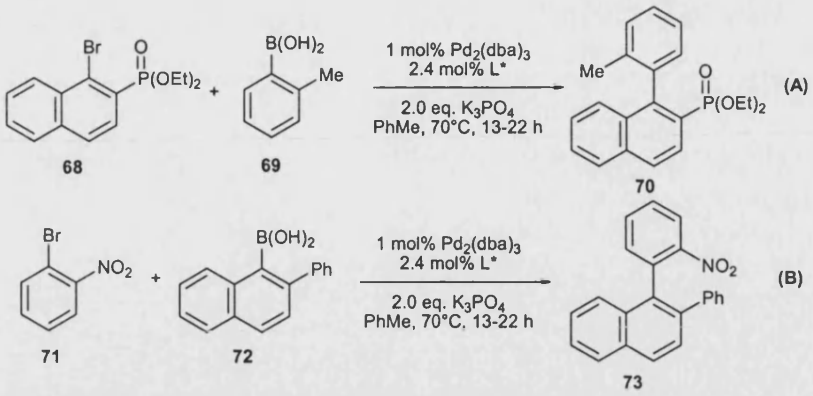


Table 1.2: Ligand screen for enantioselective Suzuki reactions

Entry	Ligand	Conversion (%) (reaction A)	ee (%)	Conversion (%) (reaction B)	ee (%)
1	BINAP **3**	trace	-	46	22
2	PCy_2 *n*-Bu **62**	100	54	100	32
3	PCy_2 TMS **63**	100	23	60	62
4	PCy_2 MAP **64**	100[a,b]	87	81[c]	73
5	PCy_2 MAP **64**	100[b,d]	87	72[d]	68
6	P*i*-Pr_2 MAP **65**	61	86	92	65
7	PPh_2 MAP **66**	76[e]	75	67	38
8	P*t*-Bu_2 MAP **67**	73[f]	81	-[g]	-

[a] 0.5 mol% $Pd_2(dba)_3$. [b] 3 eq. of K_3PO_4 used. [c] Reaction time 92 h. [d] THF used as solvent. [e] 2.5 mol% $Pd_2(dba)_3$ used. [f] Dehalogenated product: desired product 1:1 ratio. [g] No desired product observed.

From this ligand screen it was noted that the cyclohexylphosphino MAP **64** provided the highest enantioselectivities (entries 4 and 5). Replacing the cyclohexyl groups with *iso*-propyl groups (**65**) had only a slight effect, providing good enantioselectivity (entry 6). However, these levels and yields dropped further with the *tert*-butyl (**67**) and phenyl (**66**) substituted MAP ligand. By replacing the dimethyl-amino group with an *n*-butyl (**62**) or trimethylsilyl group (**63**) the enantioselectivities decreased. The bidentate bis-phosphine BINAP **3** provided only traces of the coupled product with poor enantioselectivity. It is interesting to note that when BINAP **3** was replaced with monophosphine **62** asymmetric induction was improved, as in this ligand only one heteroatom is available for co-ordination (entry 2).

From this point on they used the cyclohexylphosphino MAP **64** to screen other reaction variables. They synthesised several biaryl species from either 2-dialkylphosphite-1-bromonaphthalenes **68** or **74** and *ortho*-tolylboronic acids **69** and **75**, or from 2-nitrohalobenzenes **71** or **78** and 2-phenyl-naphthylboronic acid **72** (Table 1.3). The best results were achieved when the solvent used was toluene.

The most useful base proved to be K_3PO_4, which gave higher enantioselectivities than CsF, KO*t*-Bu or KF. They showed that for the best rate of reaction 3 eq. of base was optimal, and that this enabled the reaction time to be reduced to 24 h (from 96-140 h with 2 eq. of K_3PO_4). This also enabled the catalyst loading to be reduced, as less was lost through catalyst decomposition.

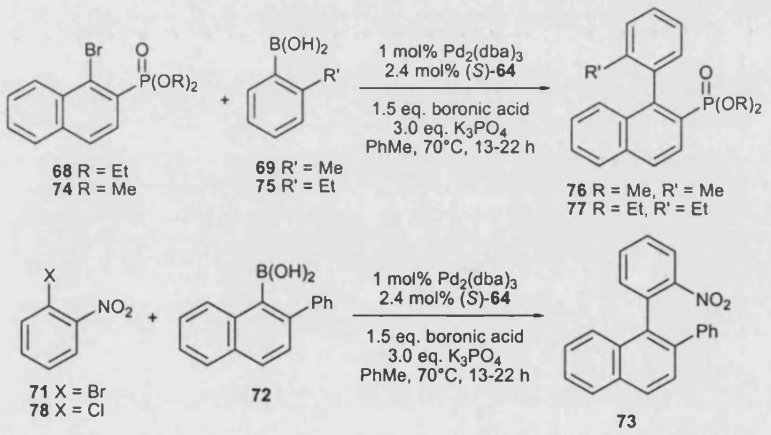


Table 1.3: Enantioselective, biaryl compound forming Suzuki reactions

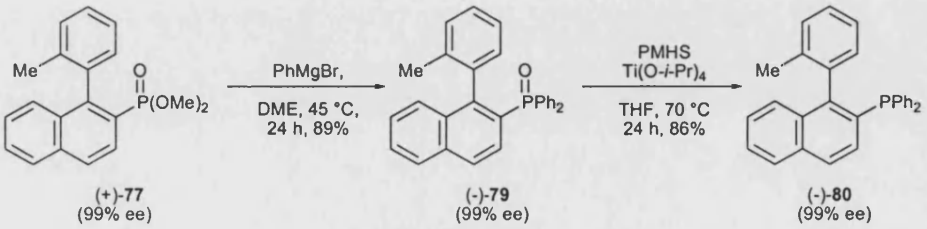
Reaction	Halide	Boronic acid	Pd (mol %)	Time (h)	Product	Yield % (ee %)
1	**68**	**75**	2	24	(+)-**77**	96 (92)[a]
2	**68**	**75**	1	24	(+)-**77**	94 (92)
3	**74**	**69**	0.3	24	(+)-**76**	95 (86)[a]
4	**74**	**69**	0.2	24	(+)-**76**	95 (86)
5	**71**	**72**	10	48	(+)-**73**	82 (72)[b]
6	**78**	**72**	4	48	(+)-**73**	83 (72)[b]

[a] 3.0 eq. of NaI added. [b] 2.0 eq. of K_3PO_4 used.

From the data above, the best result shown is the first entry, coupling 1-bromonaphthalene **68** and phenyl boronic acid **75** with 2 mol% of palladium to create the biaryl (+)-**77** in 96% yield and 92% ee. From this the catalyst loading could be reduced to 1 mol% and the yield and enantiomeric excess of the biaryl **77** were

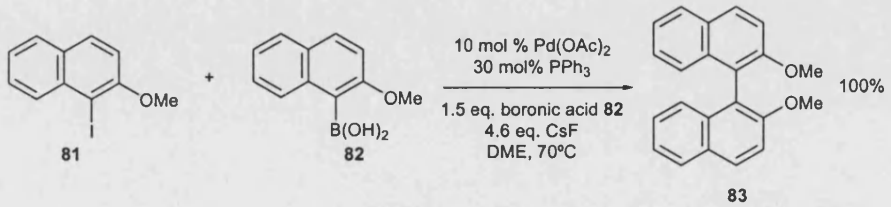
relatively unchanged. It was discovered that particularly low levels of catalyst could be successfully employed with relatively little impact on the yields and ee's. This can be seen with entry 4, where using only 0.2 mol% palladium achieved a 95% yield of biaryl-diethlylphosphite **76** with an ee of 86% (upon recrystallisation from DCM/hexane this yielded 63% of the biaryl with a 99% ee).

Also reported was the further functionalisation of biaryl compounds of the type **77** to create optically pure monophosphines that could subsequently be used as monodentate ligands in asymmetric catalysis. On heating (+)-**77** in DME with PhMgBr for 24 h at 45°C, the phosphine oxide (-)-**79** was formed in 89% yield and 99% ee (Scheme 1.10). Upon reduction, the monophosphine ligand (-)-**80** was produced in 86% yield with 99% ee.



Scheme 1.10

Since these breakthroughs several other groups have explored developing asymmetric Suzuki methodology into the synthesis of biaryls. Firstly, Colobert *et al.* utilised a range of binaphthyl ligands to synthesise the dimethoxy BINOL derivative **83** (Scheme 1.11).[57]



Scheme 1.11

After initial racemic conditions were optimised (optimal conditions shown in Scheme 1.11), enantioselective reactions were undertaken using (*R*)-BINAP **3**, (*R*)-Tol-BINAP **18** and (*R*)-BINAP(O) **84**.

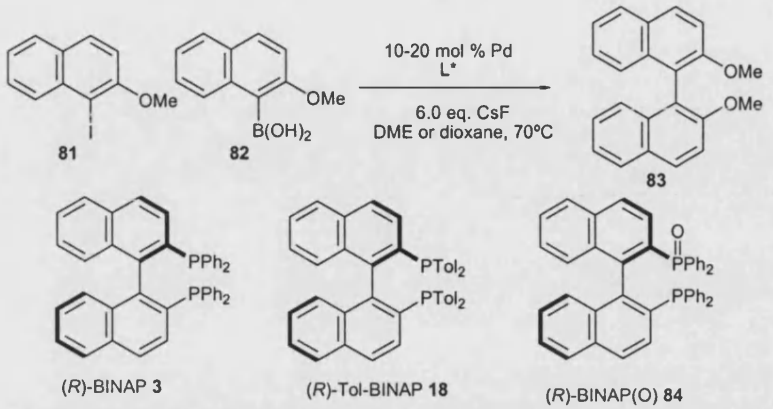


Table 1.4: Enantioselective, biaryl compound forming Suzuki reactions

Reaction	Pd Source	Ligand	Solvent	Ligand/Pd	Time (h)	Yield of 83 (%)	ee (%)
1	$Pd(OAc)_2$[a]	(*R*)-BINAP **3**	DME	0.85	6	(-)-84	22
2	$Pd(OAc)_2$[a]	(*R*)-BINAP **3**	DME	1.85	4	(+)-94	28
3	$Pd(OAc)_2$[a]	(*R*)-BINAP **3**	DME	3.1	6	(+)-19	20
4	$(\eta^3\text{-allylPdCl})_2$[b]	(*R*)-Tol-BINAP **18**	DME	0.96	12	(-)-67	22
5	$(\eta^3\text{-allylPdCl})_2$[b]	(*R*)-Tol-BINAP **18**	DME	1.93	7	(+)-50	24
6	$(\eta^3\text{-allylPdCl})_2$[a]	(*R*)-BINAP **3**	Dioxane	0.92	7	(-)-76	30
7	$Pd_2(dba)_3$[a]	(*R*)-BINAP **3**	Dioxane	1.1	7.5	(+)-46	15
8	$Pd_2(dba)_3$[a]	(*R*)-BINAP(O) **84**	Dioxane	1.1	12	(+)-22	24

[a] 10 mol % Pd. [b] 20 mol %.

It is interesting to note that when the ratio of chiral ligand to palladium was less than 1:1 the (-)-**83** enantiomer was produced as the major product (Table 1.4 entries 1, 4 and 6), whereas when more chiral ligand was added (i.e. > 1:1 ratio) the (+)-**83** enantiomer was produced as the major product (entries 2, 3, 5 and 7). This chirality reversal dependant upon ligand: Pd ratio has also been noted by Genêt *et al.* in his investigation into asymmetric allylations of Schiff bases using (+)-NORPHOS **85** or (+)-DIOP **86** with $Pd_2(dba)_3$.[58]

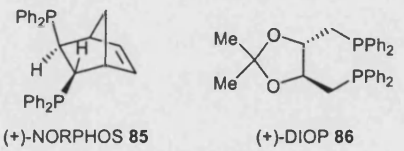
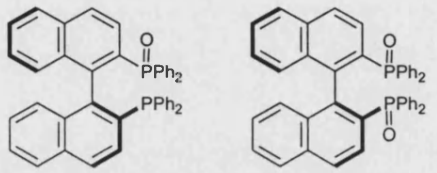


Figure 1.7

Shimizu *et al.* also noted this chirality inversion when using BINAP **3** in conjunction with $Pd(OAc)_2$ in the asymmetric elimination of allylic carbonate.[59]



(*S*)-BINAP(O) **84** (*S*)-BINAP(O)$_2$ **87**

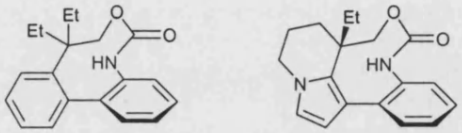
Figure 1.8

Shimizu *et al.* concluded that in generating the active catalytic species palladium acetate is reduced from Pd(II) to Pd(0). This is facilitated by the oxidation of the phosphine ligand, BINAP **3**, which would be converted to the phosphine oxide (*S*)-BINAP(O) **84** and diphosphine oxide (*S*)-BINAP(O)$_2$ **87** (Figure 1.8). Shimizu demonstrated that when the Pd(0) source $Pd_2(dba)_3$ was used there was no chirality inversion based on Pd/ligand ratio. However, when (*S*)-BINAP(O) **84** was used as a ligand with $Pd_2(dba)_3$ the opposite enantiomer of product was produced. He also demonstrated that the catalyst generated with (*S*)-BINAP(O)$_2$ **87** was inactive towards the reaction.

This conclusion was ruled out by Colobert *et al.* in their system as BINAP **3** and BINAP(O) **84** both produced the same major enantiomer of product when used with $Pd_2(dba)_3$ (Table 1.4 entries 7 & 8). The level of enantioselectivity achieved by Colobert *et al.* was generally low with a maximum ee of only 30% achieved using $(\eta^3\text{-allylPdCl})_2$ as the palladium source (Table 1.4 entry 6). It has been noted by Burgess *et al.* that when using $(\eta^3\text{-allylPdCl})_2$ with phosphine oxazoline ligands in the alkylation of allylic acetates there was a strong ligand to metal ratio effect.[60] This was attributed to the generation of two different catalytic species. When the ligand: ratio is more than one, two phosphines can coordinate to the palladium. When the

ratio is less than one, the catalytic species would contain one phosphine ligand coordinating through both the phosphorous and the nitrogen. However, it is not known what the active species is in these reactions and the possibility remains that several catalytically active species are generated including polynuclear complexes.[57]

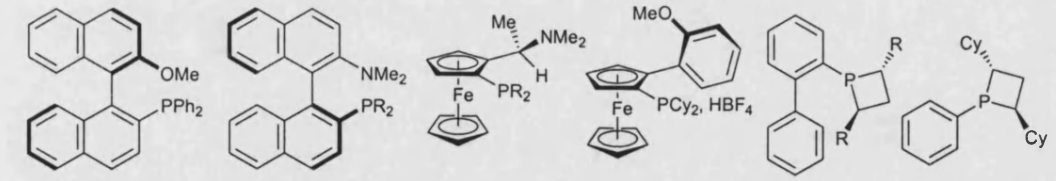
Baudoin *et al.* developed enantioselective methodology for the synthesis of carbamate **88**, a biologically interesting analogue of the alkaloid (-)-rhazinilam **89** (Figure 1.9).[61]



(-)-88 (-)-rhazinilam 89

Figure 1.9

A range of boronates, halide coupling partners and ligands were tested (Table 1.5). The ligands employed include those which were commercially available such as (*R*)-BINAP **3**, (*R*)-MeO-MOP **90**, and Hayashi's ferrocenyl (*R*)-(*S*)-PFNMe **36**; the MAP ligands **64**, **65** and **67** employed by Buchwald *et al.* and derivatives of these (**91** and **92**); derivatives of Hayashi's ferrocenyl ligands (**93** and **94**); also they developed their own biphenyl phosphetane ligands **95**, **96**, and finally, a simple phosphetane **97** developed by Genêt (Figure 1.10).[62]



(*R*)-MeO-MOP **90**

(*S*)-**64** R = Cy
(*S*)-**65** R = *i*-Pr
(*S*)-**67** R = *t*-Bu
(*S*)-**91** R = Et
(*S*)-**92** R = Me

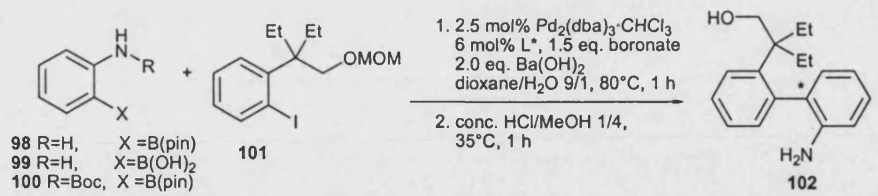
(*R*)-(*S*)-**36** R=Ph
(*S*)-(*R*)-**93** R=Cy

(*S*)-(*S*)-MOPF **94**

(*R,R*)-**95** R=Me
(*S,S*)-**96** R=Cy

(*S,S*)-**97**

Figure 1.10



98 R=H, X =B(pin)
99 R=H, X=$B(OH)_2$
100 R=Boc, X =B(pin)

101

102

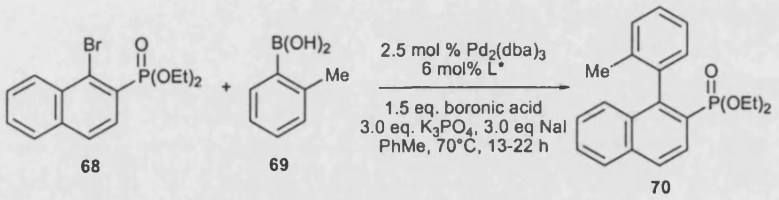
Table 1.5: Ligand and boronate screen for enantioselective Suzuki reactions

Reaction	Ligand	Boronate	Yield of 102 (%)	ee (%)
1	(*R*)-BINAP **3**	B(pin) **98**	12	0
2	(*R*)-MeO-MOP **90**	B(pin) **98**	51	(+) 7
3	(*S*)-Cy-MAP **64**	B(pin) **98**	56	(-) 40
4	(*S*)-*i*-Pr-MAP **65**	B(pin) **98**	49	(-) 41
5	(*S*)-*t*-Bu-MAP **67**	B(pin) **98**	8	(-) 3
6	(*S*)-Et-MAP **91**	B(pin) **98**	35	(-) 36
7	(*S*)-Me-MAP **92**	B(pin) **98**	35	(-) 30
8	(R)-(*S*)-Ph-PFNMe **36**	B(pin) **98**	38	(+) 5
9	(*S*)-(*R*)-Cy-PFNMe **93**	B(pin) **98**	28	(-) 8
10	(*S*)-PCy_2-MOPF **94**	B(pin) **98**	39	(-) 10
11	(*R,R*)-Me **95**	B(pin) **98**	21	(+) 6
12	(*S,S*)-Cy **96**	B(pin) **98**	37	(+) 17
13	(*S,S*)-**97**	B(pin) **98**	19	0
14	(*S*)-Cy-MAP **60**	$B(OH)_2$ **99**	31	(-) 32
15	(*S*)-Cy-MAP **60**	B(pin) **100**	38	0

Relatively moderate to low enantioselectivities were achieved throughout this study, however, they did uncover some useful information about the performance of the ligands used. BINAP **3** provided both poor yield and enantioselectivity, as did phosphetane **97** (entries 1 & 13). The remaining phosphetanes (**95** and **96**) along with the three ferrocenyl ligands (**36**, **93** and **94**) all provided low yields with low levels of enantioselectivity (up to 17% ee on the cyclohexyl-substituted phosphetane **96**). MeO-MOP **90** gave one of the highest yields (51%) however little enantioselectivity was attained. When the dimethylamino analogues of this hemi-labile ligand (Cy-MAP **64**, *i*-Pr-MAP **65**, *t*-Bu-MAP **67**, Et-MAP **91**, and Me-MAP **92**) were used, the enantioselection was improved. The results from these five analogues seem to provide useful information regarding the ideal cone angle of the phosphine. The cone angle increases with the bulkiness of the substituents on the phosphorus.[63] When the phosphine is too bulky (*t*-Bu-MAP **67**, entry 5) the palladium complex showed poor reactivity and low enantioselectivity. The optimal phosphine size appeared to be the

slightly less bulky dicyclohexylphosphino-MAP **64**. As the alkyl substituent is reduced further in size, the yield and enantioselectivity is also reduced (Cy-MAP **64** > *i*-Pr-MAP **65** > Et-MAP **91** > Me-MAP **92**) indicating that steric bulk is required to facilitate higher yields and enantioselectivities. Although, the authors also noted that the change in reactivity could be related to the basicity of the phosphine which is related to the size of the phosphine groups.[63,64]

To test the usefulness of these ligands further, Baudoin *et al.* tested them in the system developed by Buchwald for comparative purposes. However, it is important to note that they increased the palladium and ligand loadings from 1 mol % $Pd_2(dba)_3$ and 2.4 mol % ligand to 2.5 mol % $Pd_2(dba)_3$ and 6 mol % ligand.



68 69 70

Table 1.6: Ligand screen on Buchwald's system

Reaction	Ligand	Time (h)	Yield of 70 (%)	ee (%)
1	(*S*)-Cy-MAP **64**	17	93	87
2	(*S*)-*t*-Bu-MAP **67**	17	37	81
3	(*S*)-Et-MAP **91**	56	5	77
4	(R)-(*S*)-Ph-PFNMe **36**	12	60	44
5	(*S*)-(*R*)-Cy-PFNMe **93**	22	79	24
6	(*S*)-PCy_2-MOPF **94**	44	52	3
7	(*S,S*)-Cy **96**	61	10	40

This time when using the different MAP ligands (**64**, **67** and **91**, entries 1-3) the dicyclohexylphosphino MAP **64** again provided the highest yield and ee. However, the di-*tert*-butylphosphino MAP **67** provided a high ee but lower yield and the diethylphosphino MAP **91** provided a low yield, albeit in good enantioselectivity. With the ferrocenyl ligands the dicyclohexylphosphine **93** provided a higher yield than the diphenylphosphine analogue **36**, however, the ee decreased. Ferrocenyl

ligand **94** showed poor enantioselectivity and the phosphetane **96** showed moderate enantioselectivity, but with a poor yield.

Almost simultaneously to this research, Jensen and Johannsen reported developing a range of pseudo-biaryl ferrocenyl monophosphine ligands (aryl-MOPF **94**, **106** and **107**).[65] They utilised these primarily for achiral substrates, however, they then endeavoured to exploit the planar chirality present in these ligands. Therefore, they screened these in asymmetric couplings to generate the binaphthalene **105**. In their achiral studies they commented that the catalyst turn over frequency (TOF) was greatly dependant on the Pd:ligand ratio. At a ratio of 1:2 the TOF was 67 h^{-1}, when this ratio was 1:1.2 the TOF increased to 180,000 h^{-1}. This suggests the presence of a highly active monophosphine palladium complex. However, when the reaction temperature was raised, the ligand ratio needed to be increased due to the prevalence of catalyst decomposition.

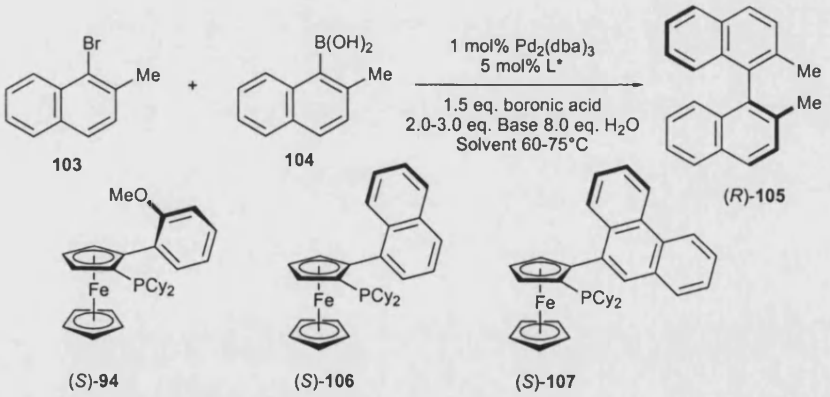
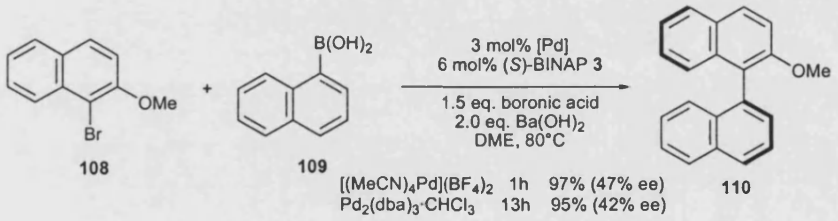


Table 1.7: Ferrocenyl ligand screen

Reaction	Ligand	Base	Solvent	Yield of 107 (%)	ee (%)
1	(*S*)-PCy_2-*o*-MeO-C_6H_4-MOPF **94**	K_3PO_4	toluene	62	43
2	(*S*)-PCy_2-*o*-MeO-C_6H_4-MOPF **94**	CsF	DME	28	46
3	(*S*)-PCy_2-*o*-MeO-C_6H_4-MOPF **94**	$Ba(OH)_2$	DME	30	46
4	(*S*)-PCy_2-Naphth-MOPF **106**	K_3PO_4	toluene	65	54
5	(*S*)-PCy_2-Phenanth-MOPF **107**	K_3PO_4	toluene	<1	-
6	(*S*)-PCy_2-Phenanth-MOPF **107**	K_3PO_4	THF	32	45

The results showed that K_3PO_4 performed as the best base, with toluene as the best solvent, although entries five and six show that with the phenanthrenyl substituted ligand THF is preferred. The highest enantioselectivity achieved was using the naphthyl substituted MOPF ligand **106** (54% ee) in fairly good yield (65%).

The most recent examples of enantioselective Suzuki couplings were reported by Mikami *et al.*, who were interested in the use of cationic chiral Pd(II) complexes in asymmetric Suzuki couplings to generate binaphthalenes **108** (Scheme 1.12).[66] They observed that when using (*S*)-BINAP **3** in conjunction with $Pd_2(dba)_3{\cdot}CHCl_3$ extended reaction times were required, however, when using $[(MeCN)_4Pd](BF_4)_2$ the reaction proceeded to completion within an hour.



Scheme 1.12

They then tried premixing the palladium source with BINAP **3** and using this for the Suzuki couplings, this improved the enantioselectivity.* They then looked at varying the ligands through changing the substituent on the phosphine with tolyl **18**, xylyl **114** and cyclohexyl **115** BINAP's (Table 1.8).

* The authors state the use of $[(MeCN)_4Pd](BF_4)_2$ as the palladium source in the text, however, the tabulated results state that the counterions are $2(SbF_6)^-$.

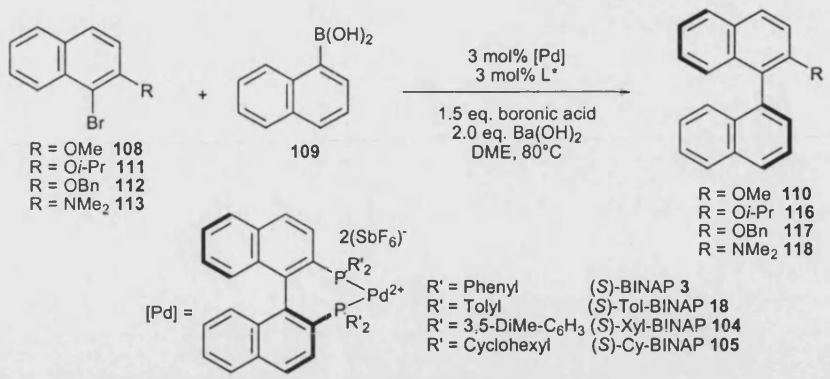


Table 1.8: Asymmetric Suzuki couplings of naphthalenes

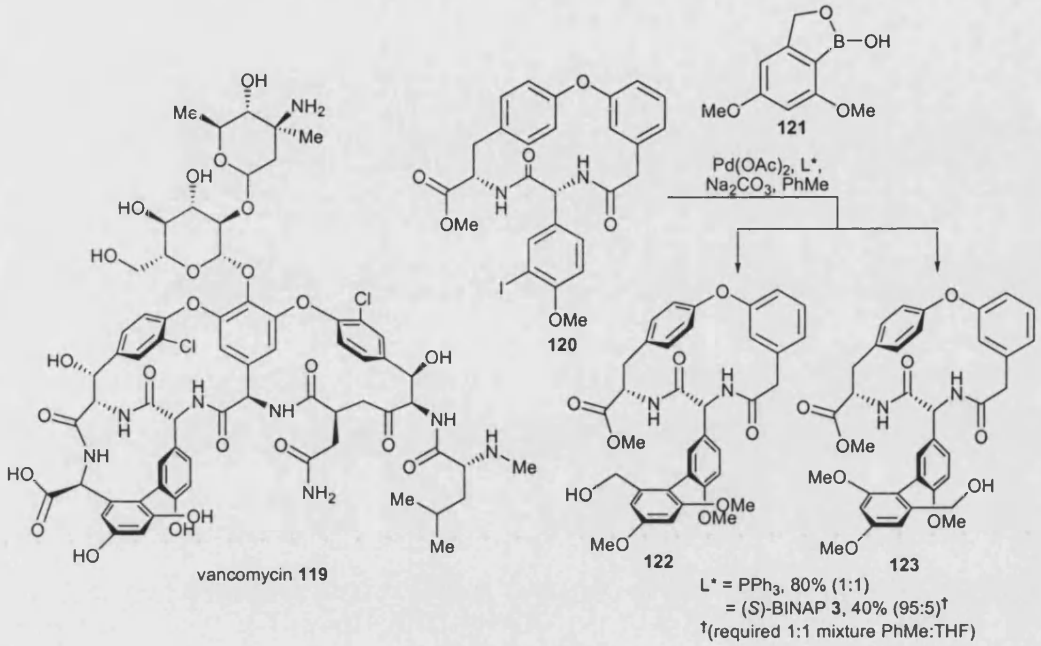
Reaction	Bromide	Ligand	Time (h)	Yield (%)	ee (%)
1	R= OMe **108**	(*S*)-BINAP **3**	0.5	91	56
2	R= OMe **108**	(*S*)-Tol-BINAP **18**	1	97	40
3	R= OMe **108**	(*S*)-Xyl-BINAP **104**	4	0	-
4	R= OMe **108**	(*S*)-Cy-BINAP **105**	1	92	70
5	R= OMe **108**	(*S*)-Cy-BINAP **105**	6	17[a]	84
6	R= O*i*-Pr **111**	(*S*)-BINAP **3**	0.5	99	50
7	R= OBn **112**	(*S*)-Cy-BINAP **105**	4	99	54
8	R= NMe_2 **113**	(*S*)-BINAP **3**	0.5	61	58

[a] Carried out at rt.

The authors demonstrated that in changing the phenyl groups on the phosphines to tolyl and xylyl groups failed to improve the enantioselectivity (entries 2 & 3). However, when the phosphine is substituted with cyclohexyl groups the enantioselectivity was improved (entry 4). The enantioselectivity could be increased further (84% ee in entry 5) when the reaction was performed at room temperature, however, the yield was dramatically reduced. They also showed that they could vary the substrate substituents and achieve good to excellent yields. However, the levels of enantioselectivity were not improved (up to 58% ee entry 8).

Although these groups have not improved upon the levels of enantioselectivity set by Buchwald *et al.*, they represent interesting studies into varying reaction conditions and especially into ligand design and catalyst effects.

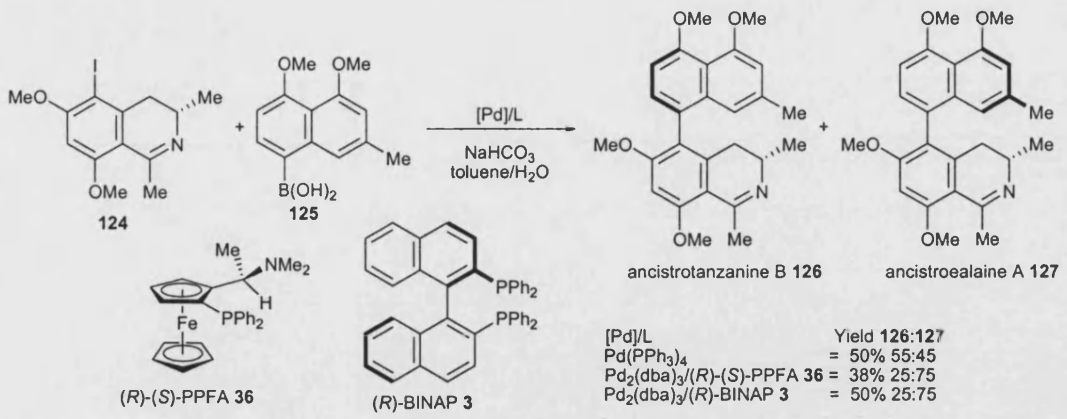
Other researchers have focused upon developing methodology to create diastereoselective Suzuki reactions. Nicolaou *et al.* utilised an asymmetric Suzuki strategy in the synthesis of vancomycin **119**.[67]



Scheme 1.13

They had hoped that they could impart some degree of stereocontrol by using a bulky chiral iodide **120** to undergo Suzuki coupling. However, this resulted in a 1:1 mixture of diastereomers (**122** & **123**). Through the use of either *R* or *S* BINAP **3** they were able to selectively generate either diastereomer in good diastereoselectivity.

Bringmann *et al.* have also employed chiral ligands to undertake diastereoselective Suzuki couplings in the synthesis of the antileishmanial naphthylisoquinoline alkaloids; ancistrotanzanine B **126** and ancistroealaine A **127**.[68]



Scheme 1.14

In this study they found that the iodide was preferred to the corresponding bromide which showed poor reactivity. They established that using $Pd(PPh_3)_4$ as the catalyst achieved little diastereoselectivity. Therefore, they moved on to the use of chiral ligands **36** and **3**, with which they achieved moderate levels of enantioselectivity. Lipshutz *et al.* have also utilised diastereoselective Suzuki reactions to generate related natural products.[69] However, they achieved this using an achiral catalyst, the use of bulky protecting groups and internal phosphine ligand coordination in the iodide coupling partners to impart stereochemistry into the biaryl products.

An alternative approach to undertaking asymmetric Suzuki reactions involves the generation of arene chromium complexes with planar chirality which then undergo diastereoselective Suzuki couplings. The chromium can then be removed from these arene complexes to provide axially chiral biaryls. The groups of both Uemura and Nelson have developed this methodology to generate simple biaryls,[70,71] phosphine ligands and axially chiral natural products, in good yields and enantiopurities.[72-77]

Another widely studied palladium-catalysed reaction is that between nucleophiles and allylic acetates. This transformation can also be achieved enantioselectively and has been extensively reviewed elsewhere.[78-80]

1.6 Conclusions

These studies have shown that enantioselective palladium-catalysed coupling reactions are capable of furnishing excellent yields with a high degree of enantioselectivity. One of the most important areas of progression is the development of new chiral ligands with enhanced performance and efficiency. Examples include the ferrocenylphosphine ligands used in asymmetric Kumada cross-coupling reactions or the *t*-butylphosphinoxazoline ligands, applied to the enantioselective Heck coupling reactions. As a consequence of the development of these coupling reactions there have been various cases where these reactions have been employed as the key steps in the synthesis of natural products.

The use of enantioselective palladium-catalysed couplings could also be exploited as a valuable tool in a different approach, that of enantioselective desymmetrisation, this will be discussed in the next chapter.

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2 Enantioselective desymmetrisations

The presence of a plane of symmetry in a bifunctional prochiral molecule (where the two halves are enantiotopic and contain potential stereocentres), means that chiral reagents or catalysts should be able to differentiate between each side, allowing chiral recognition, and therefore the opportunity for enantioselectivity. This means that an achiral or a *meso* compound could be transformed into a chiral molecule containing multiple stereogenic centres in one synthetic operation. Because of this asymmetric desymmetrisation is a useful method for the synthesis of highly enantiomerically enriched products.[1,2] The majority of catalytic desymmetrisations reported involve the use of enzymes to differentiate between enantiotopic functional groups, as enzymes by their very nature are extremely selective. The number of non-enzymatic catalysed systems is increasing,[3-5] and this strategy has also been utilised as a key step in synthesising several important target molecules.[6]

2.1 Desymmetrisation: The principle

Enantioselective desymmetrisation of a bifunctional prochiral compound *via* the use of chiral reagents leads to the favoured formation of one of the two enantiomeric products (Figure 2.1).

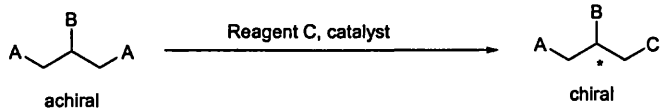


Figure 2.1

It has also been established in certain cases, due to an *in situ* kinetic resolution the enantiomeric purity of the reaction product increases as the reaction proceeds.[7,8] This feature has been well studied and utilised in asymmetric reactions of achiral-diene

substrates. Figure 2.2 illustrates the theory behind this process using a hypothetical epoxidation of a symmetrical diene substrate.

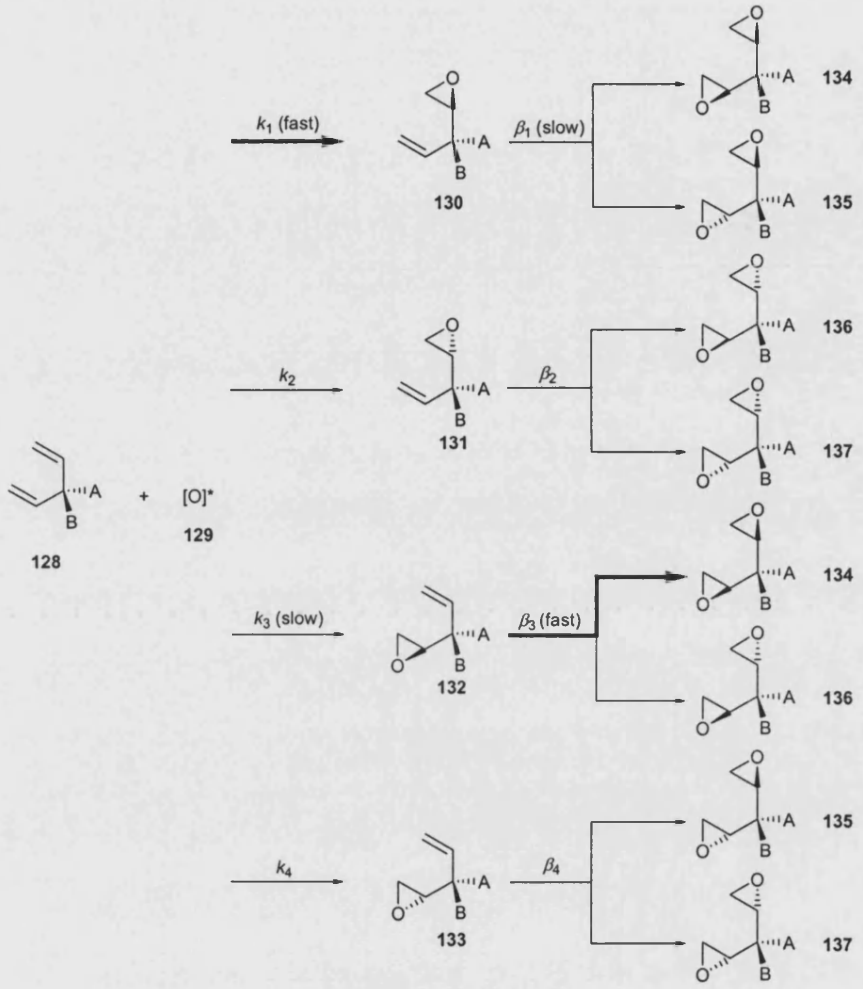


Figure 2.2

Using a chiral reagent [O]* **129** that can attack the diene **128** to form one of the four stereoisomeric products **130**, **131**, **132** and **133**, where **130** and **132** are enantiomers (as are **131** and **133**). Each of the four possible transformations will occur at a different reaction rate k_i (i = 1-4). In this case a major product would be formed as a result of double stereoselection; differentiating between two enantiotopic groups coupled with a diastereotopic face differentiation (as A ≠B in the achiral diene **128**, the four substrate faces are different, therefore, the initial reaction will produce one of four different possible products). The ee (ratio **130/132**) varies with reaction time, as a second addition can occur by epoxidising the second double bond, and

destroying the mono-epoxide. Therefore, for this example where $k_1 > k_2$, k_3 and k_4, **130** will be the major enantiomer and has an unsaturated group remaining which is "slow reacting," the minor enantiomer **132** contains the "fast reacting" unsaturated group available for successive reaction. This means that the minor enantiomer **132** is effectively being preferentially "destroyed" thus increasing the ratio of **130/132** (and therefore the ee) as the reaction proceeds. The key factor with this enhancement concept is that in order for the process to work effectively, a large difference in the rates of epoxidation (k_i) is required and there should be little influence from the first addition over the second addition. To solve this, the chiral reagent employed requires an intrinsic enantiotopic face differentiating ability and should be sensitive to the stereodirecting properties of the allylic substituents A and B (e.g. preference for addition *syn* to the B group in rotamer **128**).

Schrieber *et al.* developed a mathematical model on this principle.[9] They assumed that each reaction is first order in substrate and reagent, and produced an equation showing that the ratio of enantiomers can be as large as desired simply by achieving a conversion level that is high enough.

This process has been studied by a variety of different groups,[10] one of the first being that of Partridge *et al.* focusing on the asymmetric hydroboration of achiral 5-alkyl-1,3-cyclopentadienes.[11] Other examples include the Sharpless asymmetric epoxidation reaction, which also demonstrates this process yielding useful synthetic mono-epoxide products.[12,13] This is an interesting case, which shows reagent control by facial discrimination and substrate control *via* the sensitivity of the reagent to the structure of the substrate.

An example of this can be seen below (Table 2.1), *E,E*-divinylcarbinol **138** undergoes desymmetrisation when a catalytic amount of titanium tetra*iso*propoxide and *t*-butyl-hydroperoxide react together with either (-) or (+)-di*iso*-propyl tartrate to form either enantiomer **139** or **140** respectively.[9]

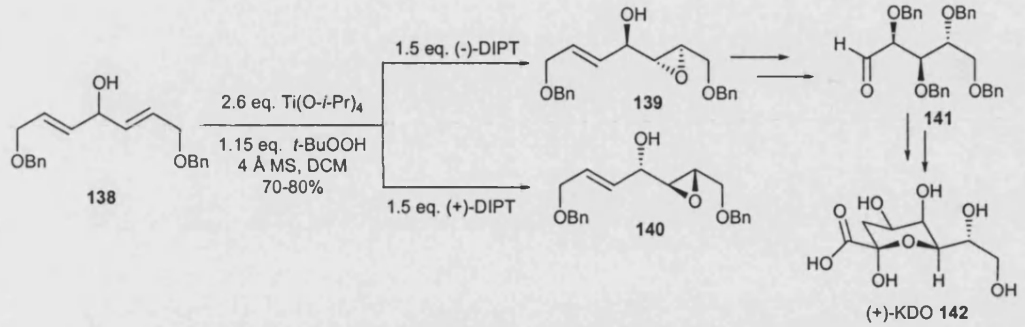


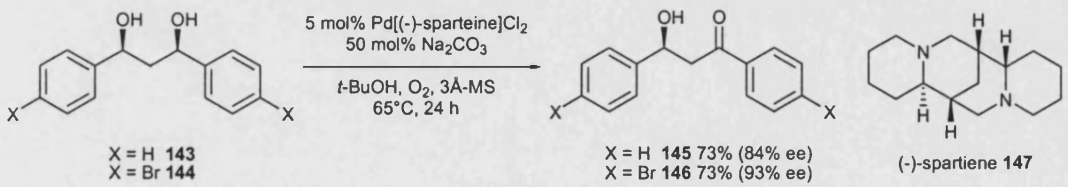
Table 2.1: Asymmetric epoxidation of 138 using L-(+)-DIPT

Entry	Conditions	ee (%) of 140	de (%) of 140
1	1 h, -25 °C	93	>97
2	3 h, -25 °C	95	>97
3	44 h, -25 °C	>97	>97

[a] 2.60 eq. *t*-BuOOH, 1.15 eq. Ti(O-*i*-Pr)$_4$, 1.50 eq. L-(+)-DIPT with powdered 4 Å MS in DCM

This data shows that when using L-(+)-di*iso*propyl tartrate the ee increases as the reaction proceeds. As an example of the usefulness of this process the chiral mono-epoxide **139** was subsequently reacted further in an enantioselective synthesis of 3-deoxy-*D-manno*-2-octulosonic acid ((+)-KDO) **142**.[14]

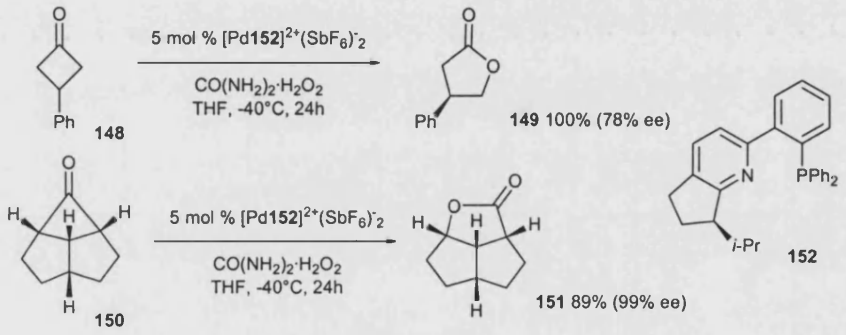
In recent years examples of palladium-catalysed desymmetrising oxidations have appeared in the literature. Sigman *et al.* showed that *meso* 1,3-diols could be oxidised to their corresponding enantiomerically enriched *β*-hydroxycarbonyls **145** and **146** using a chiral (-)-sparteine **147** derived palladium(II) catalyst (Scheme 2.1).[15,16]



Scheme 2.1

They achieved good yields in excellent enantioselectivity especially when *para*-bromophenyl substituents were present (diol **144**). However, this methodology has thus far failed to transfer well on to *meso*-1,2-diols giving a maximum ee of 37% in low yield, with the major product being the diketone resulting from over oxidation.

Katsuki and Ito *et al.* reported the palladium-catalysed asymmetric Baeyer-Villiger reaction on achiral and *meso* butanones.[17] In this study the cyclobutanones (**148** and **150**) were desymmetrised to create the corresponding enantiomerically enriched lactones (**149** and **151**) using a palladium catalyst supported by chiral phosphine ligand **152** (Scheme 2.2).



Scheme 2.2

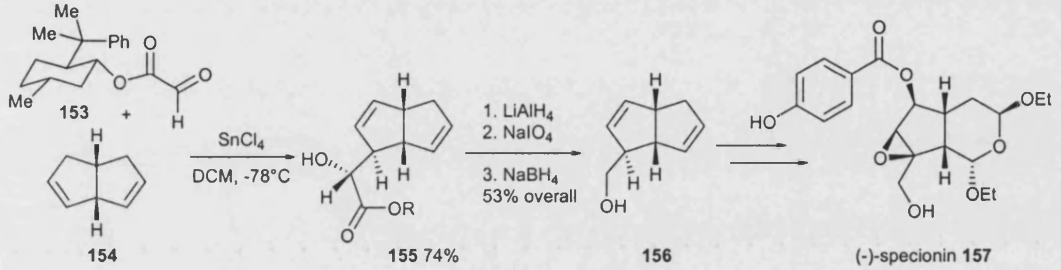
In this study it was thought that the square planar chiral palladium(II) catalyst could coordinate to the Criegee intermediate and impart asymmetric induction through steric factors.[18] Excellent yields and enantioselectivities were achieved. However, this methodology has thus far only been used on cyclobutanone substrates.

A variety of functional groups have been utilised in enantioselective desymmetrisations, including anhydride, alkene, diene and diol functionalities, creating C-O, C-N, C-S and C-Cl bonds using a range of reactions. These reactions have been carried out using both stoichiometric and catalytic quantities of reagents to

trigger these processes,[10] although catalytic desymmetrisations employing C-C forming reactions have been less well documented.

2.2 Desymmetrisations forming C-C bonds

Whitesell *et al.* provided an early example of a C-C bond forming enantioselective desymmetrisation,[19] with the novel use of chiral glyoxylate esters as enophiles in the intramolecular ene reaction.

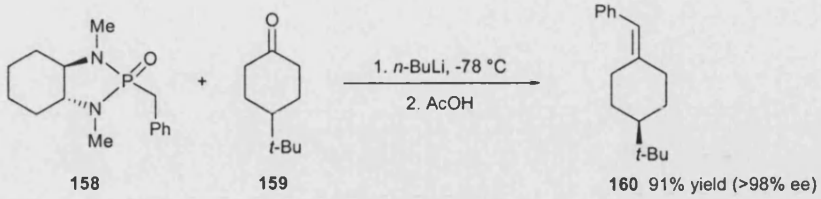


Scheme 2.3

Using the glyoxylate ester **153** (derived from 8-phenylmenthol) to attack the cyclic prochiral-diene **154** in combination with tin tetrachloride in DCM at –78 °C, the ene product **155** is produced in 74% yield as a single isomer (Scheme 2.3). The development is taken further by reductively removing the chiral auxiliary followed by oxidative cleavage to give the allylic alcohol **156**. The synthesis is completed after a further eight step sequence to produce (-)-specionin **157** as a single enantiomer.[20]

A later example of a C-C bond forming enantioselective desymmetrisation is the development of chiral phosphonates and phosphonamides, reported by Hanessian *et al.*[21] In their system they used phosphonamide **158** (which was derived from *trans*-cyclohexane-1,2-diamine), to enantioselectively desymmetrise a range of ketones in a process related to the Horner-Wadsworth-Emmons reaction. Using *n*-butyl lithium

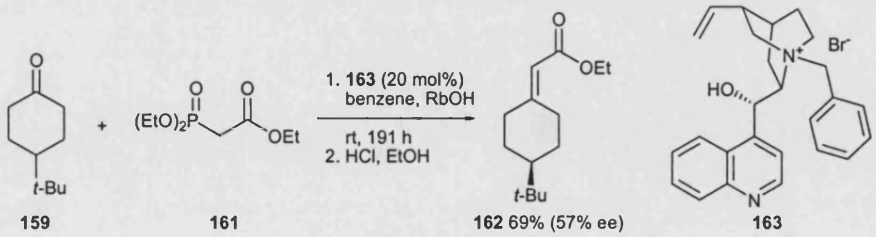
the phosphonamide **158** is deprotonated at -78 °C, and then *t*-butylcyclohexanone **159** is added; treatment with acid affords the *exo*-alkene **160** with a 91% yield at 98% ee (Scheme 2.4).[21,22]



Scheme 2.4

This method has been successfully used to synthesise optically pure allylidene alkylcyclohexane products by substituting the benzyl group for an allyl group on the phosphonamide.

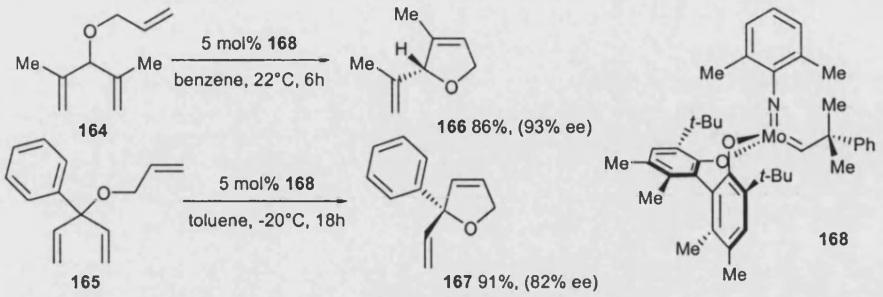
Since this advance further examples have been developed broadening the scope of the reaction.[23] A more recent example of an asymmetric Horner-Wadsworth-Emmons reaction using a catalytic amount of the quaternary ammonium salt **163** in a phase transfer reaction (a range of counterions were tested but this was found to be the best).[24] In this desymmetrisation the *t*-butylcyclohexanone **159** is attacked by the phosphonate **161** in conjunction with 20% of the ammonium salt **163** and rubidium oxide. The α,β-unsaturated product **162** was generated in 57% yield and 69% ee (Scheme 2.5).



Scheme 2.5

A key area of development is the use of sub-stoichiometric quantities of a catalyst to facilitate the desymmetrisation reaction, especially those used to generate C-C bonds.

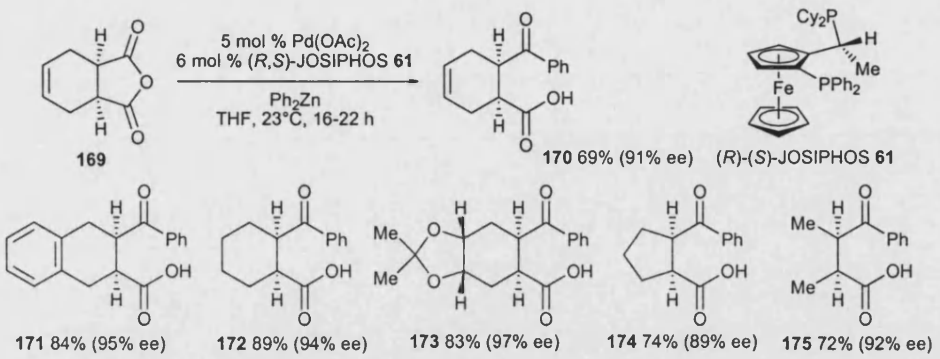
Examples include the desymmetrising ring closing metathesis work carried out by Hoveyda and Grubbs on a range of triene substrates (e.g. **164** and **165**) to generate chiral dihydrofurans (**166** and **167**) using the chiral molybdenum catalyst **168**.[25,26]



Scheme 2.6

In this methodology they have converted a standard achiral reaction procedure into an asymmetric process, generating chiral centres in high yield and excellent enantioselectivity. This is attractive, as they have achieved this in a process which would otherwise prohibit stereoselective transformations, simply by substrate and catalyst design. This shows the precedent for converting standard achiral transformations into enantioselective process able to generate stereodefined quaternary carbon centres.

A recent example of a palladium-catalysed C-C bond forming desymmetrisation has been reported by Rovis *et al.* They used diphenylzinc as a coupling partner to enantioselectively desymmetrise *meso*-succinic anhydrides (e.g. anhydride **169** Scheme 2.7).



Scheme 2.7

They reported that a range of γ-ketocarboxylic acids **170-175** could be generated in high yields with excellent enantioselectivity. The examples presented showed that a variety of substituents were tolerated with little change in yield or selectivity, although coupling into cyclic anhydrides of alternative ring sizes were not reported.

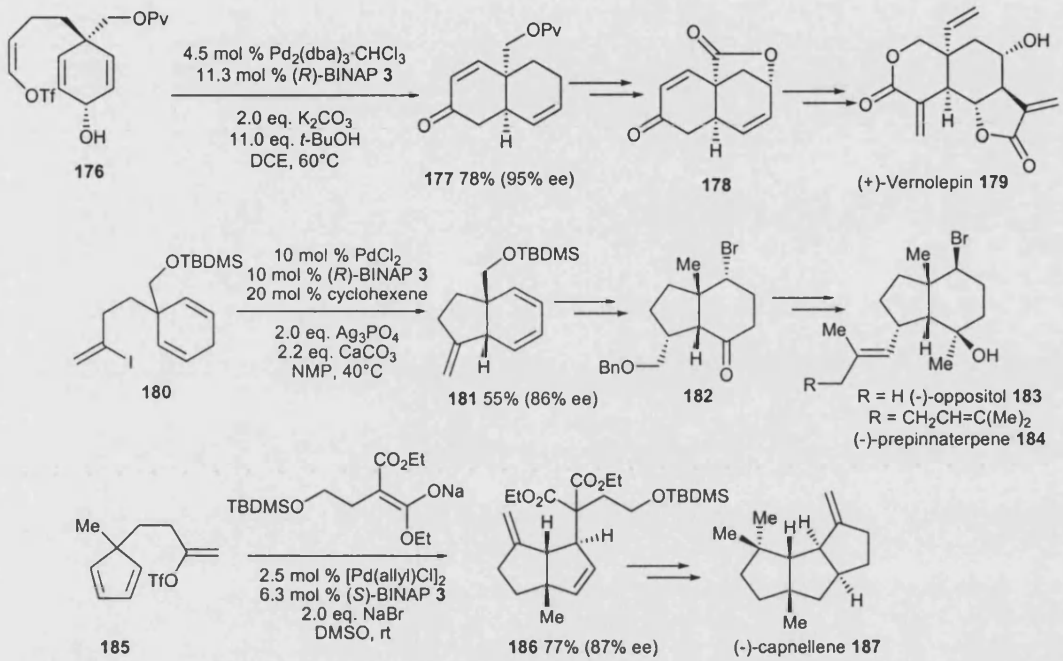
2.3 Palladium-catalysed desymmetrisations forming C-C bonds

Palladium catalysis is commonly used in C-C bond forming reactions. To successfully undergo a desymmetrisation cross-coupling procedure, an achiral or *meso* compound is needed. This compound needs two reactive enantiotopic groups, thus, using a chiral palladium species, enantiotopic discrimination can be effected and functionalisation achieved. This establishes a new technique for the generation of enantiomerically enriched and architecturally complex molecules. Despite the usefulness of this novel approach it is still relatively uncommon, with the first palladium-catalysed example of an asymmetric desymmetrisation only occurring in the last few years.

2.3.1 Heck reaction

Shibasaki *et al.* have carried out pioneering work in the field of desymmetrising intramolecular Heck reactions.[27] They developed multiple examples of vinyl triflates

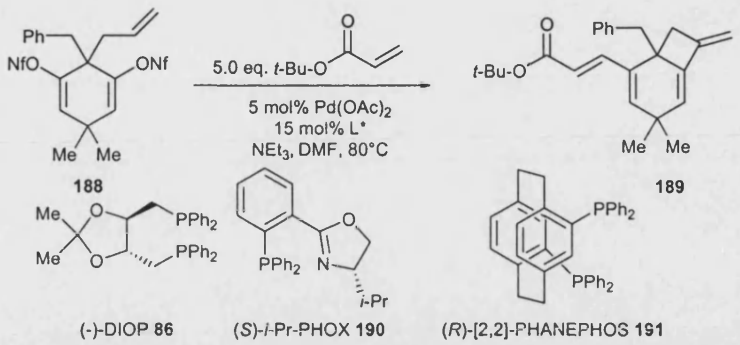
and iodides selectively cyclising onto one of the two enantiotopic alkenes, thus generating fused rings with stereodefined carbon centres.[28] They have continued to optimise these systems through the use of additives and new ligands. They have also investigated the mechanistic aspects of these reactions.[29-31]



Scheme 2.8

Furthermore they have demonstrated their synthetic utility by using these processes in the synthesis of natural products ((-)-capnellene **187**) or intermediates in natural product syntheses (**178** and **182**) (Scheme 2.8).[32-37]

The use of chiral palladium catalysis in inter- and intramolecular coupling reactions has recently attracted much interest. Bräse reported an interesting enantioselective desymmetrisating Heck reaction in 1999.[38] This involved firstly forming the achiral 1,3-bis(enolnonaflate) **188** from dimedone in four steps. Subsequent combination with *t*-butyl acrylate under Heck conditions, formed the bicyclo[4.2.0]octadiene product **189**, in moderate yield and enantioselectivity (Table 2.2).



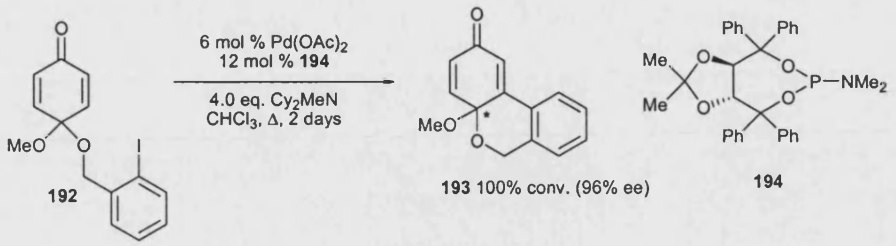
(-)-DIOP **86** (*S*)-*i*-Pr-PHOX **190** (*R*)-[2,2]-PHANEPHOS **191**

Table 2.2: Heck type Enantioselective desymmetrisation of 188

Entry	Ligand	Yield of 189 (%)	ee (%) of 189
1	(*R*)-BINAP-**3**	57	27
2	(-)-DIOP-**86**	42	18
3	(*S*)-*i*-Pr-PHOX -**190**	25	52
4	(*R*)-[2,2]-PHANEPHOS-**191**	23	37

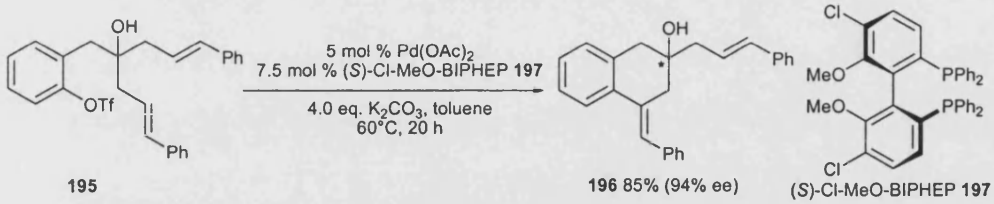
It was found that the highest ee's were obtained when *iso*-propylphosphinoxazoline ((*S*)-*i*-Pr-PHOX) **190** was used as the chiral ligand (52% ee, 25% yield) however the greatest yield was obtained when BINAP **3** was used as the chiral ligand (27% ee, 57% yield). There are several novel aspects to this reaction; it is highly unusual in Heck reactions for this kind of *exo-trig*-cyclisation to occur,[39,40] especially with the presence of a 1,5-hexadiene substrate where palladium-catalysed Cope rearrangement is generally favoured.[41]

Generally asymmetric Heck reactions involve carbon-carbon double bond transposition, resulting in the stereoselective formation of a new sp^3 centre.[42-44] There have recently been further examples where improved yields and ee's have been accomplished involving systems with novel ligands and through the use of specifically designed sterically hindered substrates.[45-47] In one such ligand investigation Feringa *et al.* showed that the TADDOL-derived phosphoramidite **194** worked well for the formation of ether **193** (Scheme 2.9).[48,49]



Scheme 2.9

More recently Oestreich *et al.* have progressed enantioselective desymmetrising Heck reactions further by demonstrating the role coordinating groups can perform in this methodology.[50]



Scheme 2.10

In the cyclisation of triflate **195** high yields were attained with excellent enantioselectivity (Scheme 2.10). However, when the hydroxyl group was protected as the trimethylsilyl ether the yield dropped and the product was essentially racemic (55% yield, 2% ee). When the hydroxyl group was replaced with a proton the yields were again lower and the highest enantioselectivity achieved was an 18% ee. Investigation into the parameters of this process revealed that generating a six-membered ring was optimal as was the position of the hydroxyl group, which it was postulated could act as a weak ligand. This report illustrates an important concept however it also highlights the limitations involved in this methodology.

2.3.2 Carbonylation reactions

Schmaltz *et al.* reported the enantioselective desymmetrisation of achiral 1,2-dichlorobenzene tricarbonylchromium **198**, using palladium to catalyse the process

of methoxycarbonylation.[51] The substrates used are unusual for use in palladium chemistry as the C-Cl bond in the chloroarene was commonly thought to be resistant to the oxidative addition step. However, in this complex the tricarbonylchromium unit withdraws electron density away from these bonds, so assisting this process.[52,53] The reaction yielded both the monocoupled product **199** and the dicoupled product **200** (results are presented in Table 2.3).

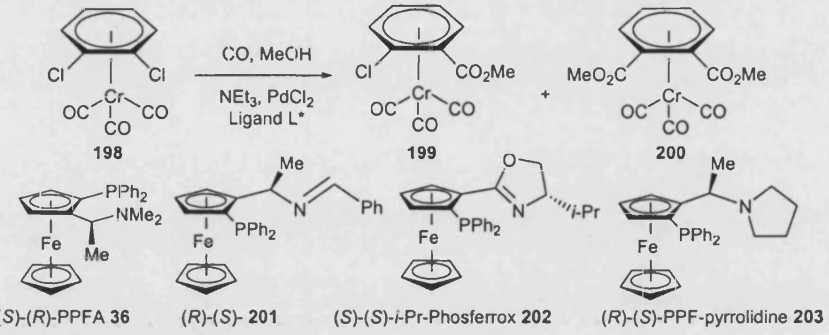


Table 2.3: Enantioselective carbonylation of 198 [a]

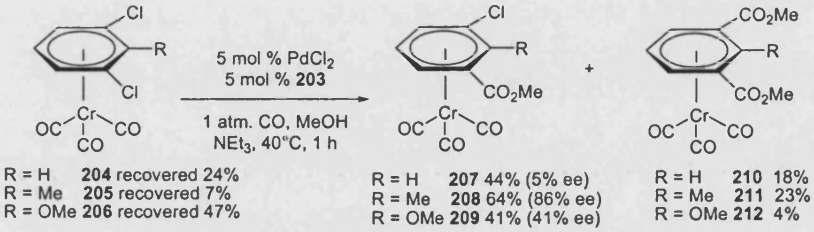
Reaction	Catalyst	Recovered 198 (%)	Yield of 199 (%)	Yield of 200 (%)	ee (%) of 199[a]
1	$PdCl_2$[(*R*)-**3**]	35	49	10	(1 *R*) 16
2	$PdCl_2$[(*R*)-(*S*)-**36**]	18	41	31	(1 *R*) 30
3	$PdCl_2$[(*R*)-(*S*)-**201**]	42	43	14	<2
4	$PdCl_2$[(*S*)-(*S*)-**202**]	76	22	1	(1 *R*) 6
5	$PdCl_2$[(*R*)-(*S*)-**203**]	24	47	23	(1 *S*) 63
6	$PdCl_2$[(*R*)-(*S*)-**203**][b]	5	31	48	(1 *S*) 95

[a] Reactions were performed on 0.5 mmol scale, 2/1 mixture of MeOH/NEt_3, 5 mol% of palladium catalyst, 1 atm. CO at 60 °C for 2 h. [b] Reaction was performed with 2 mol% of catalyst for 3 h.

The results show that the bidentate ligand (*R*)-BINAP **3** again performed moderately in the coupling reaction yielding 49% of the monocoupled product **199** but only giving a 16% ee. The bidentate ferrocenyl ligand (*S*)-(*R*)-PPFA **36** performed similarly, with a moderate yield and a 30% ee, it also furnished a notable quantity of the dicoupled product **200**. Several further derivatives of the chiral ferrocenyl ligands were also tested as to their ability to aid the catalysis of this methoxycarbonylation. The chiral *P,N* ferrocene ligands **201** and **202** provided modest yields of the monocoupled product and very little dicoupled product. However, the enantioselectivity was particularly low.[54,55] A more hindered analogue of the PPFA

ligand (*R*)-(*S*)-PPF-pyrrolidine **203** was also used and delivered a fairly high enantioselectivity (63% ee) with a moderate yield (47%).[56] Repeating this reaction with a lower catalyst loading of 2% and extending the reaction time to three hours, produced 31% **199** with a 95% ee along with 48% of the dicoupled product **200**.

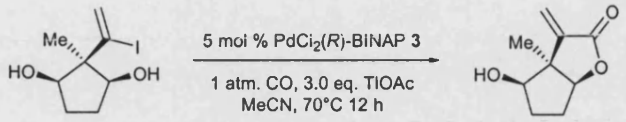
Schmaltz *et al.* have recently followed up this research by investigating into the carbonylative desymmetrisation of 1,3-dichloroarenes.[57] They varied the substituent in an *ortho*-position to both of the enantiotopic chlorines (Scheme 2.11).



Scheme 2.11

They showed that without an additional functional group in an *ortho*-position to the two chlorines (**204**) little enantioselection was realised. This is probably due to the similar steric environment of each of the enantiotopic chlorines. With the methyl substituted substrate **205** excellent enantioselectivity was attained. It was found that the enantiopurity could be increased further by extending the reaction time by 30 minutes (at 90 minutes 53% **208**, 90% ee). However, the yield was reduced as more of the material was converted to the dicoupled material (44% **211**). This suggests that kinetic resolution is important in achieving high levels of enantioselectivity. The presence of the methoxy group yielded a relatively small amount of dicarbonylated material (4% **212**) with much of the material unreacted (47% **206**), the ee of the monocarbonylated material **209** was moderate (41% ee).

Shibasaki *et al.* have generated stereodefined quaternary carbon centres utilising a desymmetrisation strategy.[58] Using a simple *meso*-diol **213** they were able to carboxylate the vinyl iodide and selectively cylclise into one of the alcohol substituents to generate the lactone **214** (Scheme 2.12).



213 **214** 74% (50% ee)

Using 5 mol % $Pd(OAc)_2$, 10 mol % (*R*)-BINAP **3** 3 eq. Ag_2O, 18 h gave 44% (57% ee)

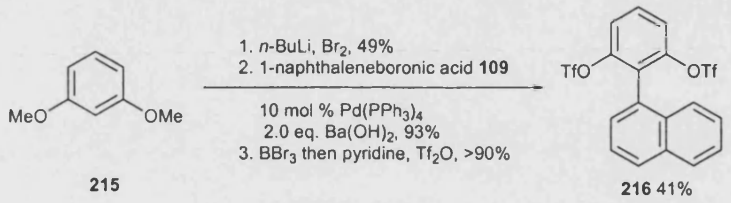
Scheme 2.12

They found that the base used was important in generating high levels of enantioselectivity, with a complete loss of asymmetric induction when K_2CO_3 was used. They suggested that this may be due to coordination of the hydroxyl group to the catalyst causing the bidentate ligand to partially dissociate to give a 16-electron species, thus producing a racemic product **214**. Therefore, silver and thallium salts were used in an effort to remove the halide from the palladium to generate a cationic palladium species. Although the enantioselectivities achieved were modest, the concept illustrated is of significance.

2.3.3 Kumada cross-coupling reactions

1,1'-Binaphthyl compounds represent an important class of compound which have found a great deal of use in asymmetric synthesis. The axial chirality required is usually generated *via* the coupling of two biaryl units.[59,60] The first reported palladium-catalysed synthesis was by Hayashi *et al.*, when they prepared axially chiral biaryls *via* enantiotopic group discrimination.[61] The catalyst used selectively reacts with one of the two enantiotopic triflate groups on the achiral biaryl bis-triflate. To prepare the achiral biaryl bis-triflate, 1,3-dimethoxybenzene **215** is *ortho*-

lithiated then brominated and subsequently the bromobenzene was coupled with 1-naphthylboronic acid **109** using barium hydroxide and 10 mol % of $Pd(PPh_3)_4$. The methyl ester groups are removed using boron tribromide creating phenol groups; these are then triflated using trifluoromethanesulfonic anhydride, producing the bis-triflates **216** in a 41% overall yield (Scheme 2.13).



Scheme 2.13

The achiral-bis-triflate **216** undergoes the enantioselective Kumada cross-coupling reaction using phenylmagnesium bromide, lithium bromide and a chiral palladium complex. The monosubstituted biaryl compounds (**217**) produced were obtained in good yield and excellent stereoselectivities (Table 2.4).

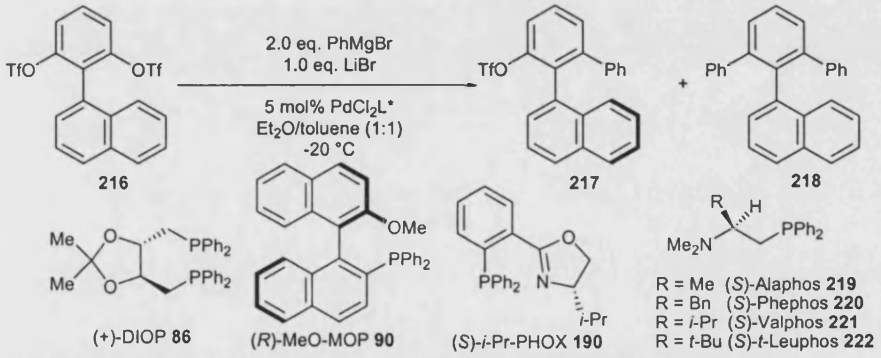


Table 2.4: Enantioselective desymmetrisation of bis-triflates 216

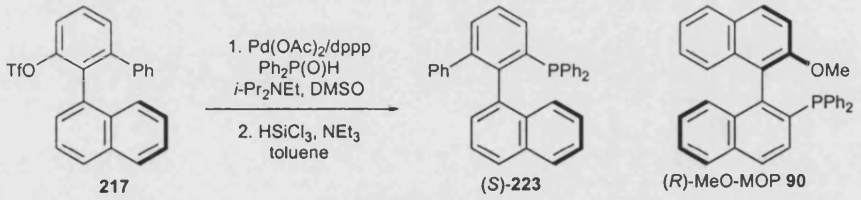
Reaction	Catalyst	Recovered 216 (%)	Yield of 217 (%)	Yield of 218 (%)	ee (%) of 217[a]
1	$PdCl_2$[(*R*)-MeOMOP **90**]$_2$	85	7	0	(*R*) 40
2	$PdCl_2$[(+)-DIOP **86**]	82	6	0	(*R*) 46
3	$PdCl_2$[(*S*)-*i*-Pr-PHOX **190**]	47	26	11	(*S*) 52
4	$PdCl_2$[(*S*)-Alaphos **219**]	0	84	10	(*S*) 90
5	$PdCl_2$[(*S*)-Phephos **220**]	0	87	12	(*S*) 86
6	$PdCl_2$[(*S*)-Valphos **221**]	28	56	0	(*S*) 78
7	$PdCl_2$[(*S*)-*t*-Leuphos **222**]	64	24	11	(*S*) 52

[a] Determined *via* HPLC analysis of phenol obtained by alkaline hydrolysis of triflate **217**.

It can be seen from the data in Table 2.5 that the chiral aminophosphines (*S*)-Alaphos **219** and (*S*)-Phephos **220** (which are derived from natural amino acids) generate extremely effective palladium catalysts: These *P,N* ligands produce yields of up to 87% and ee's of 90%; although (*S*)-Valphos **221**, (*S*)-*t*-Bu-Leuphos **222** and (*S*)-*i*-Pr-PHOX **190**, which are similar chiral aminophosphine *P,N* ligands, produced less effective catalysts. The reaction proceeded very slowly using the ligands DIOP **3** and (*R*)-MeO-MOP **90** and the ee produced was also lower.[62] They then further optimised the reaction conditions and found that changing the additive from lithium bromide to lithium iodide and increasing the temperature to -10 °C successfully increased the yield and enantioselectivity (90%, ee 94%). They have also successfully changed other criteria in these Kumada coupling reactions including the use of alternative coupling partners such as triphenylsilylethynylmagnesium bromide and 3-methylphenylmagnesium bromide. This methodology also transferred well to other simple biaryl bis-triflates. These alterations still delivered highly enantiomerically enriched products in good yields (up to 88% yield with a 99% ee).[63,64]

Kinetic resolution effects were also monitored in these reactions showing that the optical purity of **217** depends upon the yield of the diphenyl product **218**. When a racemic mixture of **217** was subjected to the asymmetric Kumada cross-coupling conditions, the reaction was stopped at 20% conversion, and the diphenyl product **218** was separated from the montriflate **217**. It was found that monotriflate **217** had been enantiomerically enriched (17% ee of the (*S*)-isomer). This indicates the emergence of a kinetic process in which the (*R*)-isomer of **217** reacts around five times faster than the (*S*)-isomer in the Kumada process.

The monotriflate product **217** was also further functionalised by coupling a phosphine group into the triflate thus generating a new chiral triaryl monophosphine (*S*)-**223** (Scheme 2.14). When used as a ligand for the palladium-catalysed asymmetric hydrosilylation of styrene using trichlorosilane, phosphine **223** was found to be more effective than all other phosphine ligands screened including MeO-MOP **90** (with which its structure bears a close resemblance) giving a 91% ee.



217 (*S*)-**223** (*R*)-MeO-MOP **90**

Scheme 2.14

2.3.4 Suzuki cross-coupling reactions

Uemura, Hayashi *et al.* carried out desymmetrisation reactions on arene-chromium complex **198**, using both aryl and alkenyl boronic acids, in Suzuki reactions.[65] In the reaction, the alkenyl or aryl unit is delivered into one of the two enantiotopic C-Cl bonds on the achiral chromium complex **198**. The tricarbonyl (η^6-arene)chromium complex produced has an arene ring containing an *ortho*-substituted group and a chlorine, creating two enantiomers due to the planar chirality: Dicoupled material is also produced in small amounts. A range of chiral ligands were evaluated as to their ability, in combination with palladium, to catalyse this Suzuki reaction enantioselectively (Table 2.5).

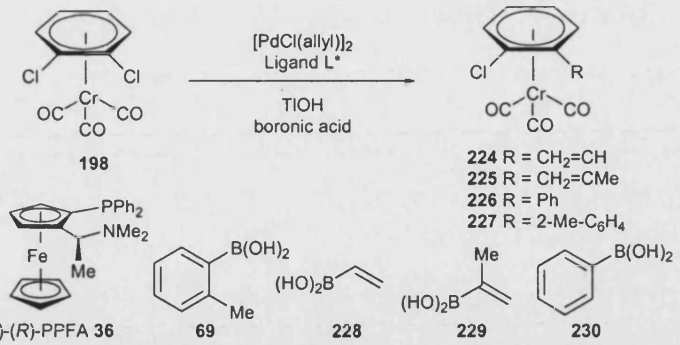


Table 2.5: Enantioselective desymmetrisation of achiral chromium complex 198

Reaction	Boronic acid[a]	Ligand	Temperature (°C)	Monosubstituted Product	Yield (%)	ee (%)
1[b]	**228**	(*S*)-(*R*)-PPFA **36**	23	(1*S*,2*R*)-**224**	43	38
2[b]	**229**	(*S*)-(*R*)-PPFA **36**	27	(1*S*,2*R*)-**225**	61	44
3[b]	**229**	(*R*)-BINAP **3**	35	(1*S*,2*R*)-**225**	44	25
4[c]	**230**	(*S*)-(*R*)-PPFA **36**	28	(1*S*,2*R*)-**226**	16	49
5[c]	**230**	(*S*)-(*R*)-PPFA **36**	50	(1*S*,2*R*)-**226**	40	69
6[d]	**69**	(*S*)-(*R*)-PPFA **36**	50	(1*S*,2*R*)-**227**	52	55

[a] molar ratio complex **198**/boronic acid/chiral ligand L*/palladium = 1.0 / 3.0 / 0.12 / 0.10. [b] Reaction time 48 h. [c] Reaction time 18 h. [d] Reaction time 40 h.

The ferrocene derivative ligand (*S*)-(*R*)-PPFA **36** shows the greatest selectivity as a ligand in the Suzuki coupling especially in conjunction with the phenylboronic acid **230**. This furnished the monosubstituted product in up to 69% ee, the highest overall yield (61%) was obtained with the alkenyl boronic acid **229** obtained with the same catalyst conditions. It is interesting to note that in changing from phenyl boronic acid **230** to the more hindered boronic acid **69**, which required a longer reaction time, also resulted in a lower ee (entries 5 and 6).

In addition to the Suzuki couplings Uemura, Hayashi *et al.* attempted other organometallic cross-coupling reactions on the same achiral chromium arene complex **198**. A significant feature established was that the enantioselectivity was largely dependant upon the metal of the arylating or vinylating reagents; organozinc reagents produced moderate enantioselectivities (up to 42% ee) in the coupling products, whilst organostannane reagents produced racemic mixtures. The authors suggested that this implies oxidative addition occurs enantioselectively, and that this

enantioselectivity is determined by a complex, which is a combination of the chiral catalyst and the organometallic reagent.

Shibasaki *et al.* utilised an enantioselective desymmetrisation strategy in an intramolecular Suzuki cross-coupling reaction.[66] They utilised prochiral alkylboron reagents with either a bromine or a triflate group present (bromide **231** and triflates **232** and **233** Figure 2.3).

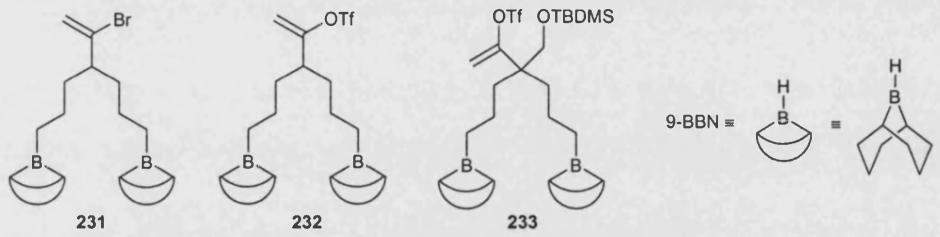
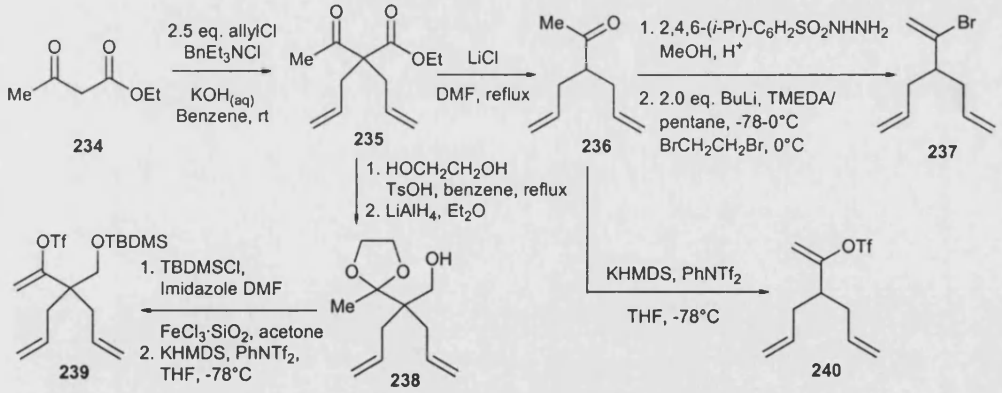


Figure 2.3

These were all generated by the hydroboration of the corresponding alkenes (**237**, **239** and **240**), which were all generated in a straightforward manner from ethyl acetoacetate **234** (Scheme 2.15).



Scheme 2.15

Enantiotopic group selective ring closure was achieved by palladium-catalysed asymmetric reaction of the prochiral alkylboron species **231**, **232** and **233**. These were generated *in situ* from achiral dienes **236**, **239** and **240** upon treatment with 9-BBN. The reaction is completed by oxidative work-up and protection of the alcohol group, to provide the chiral cyclopentane derivatives **241** or **242**. With optimised

reaction conditions in hand a range of chiral ligands were screened in the intramolecular Suzuki step (Figure 2.4, Table 2.6).

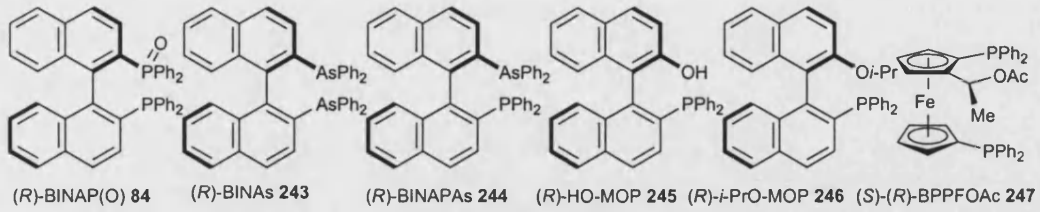


Figure 2.4

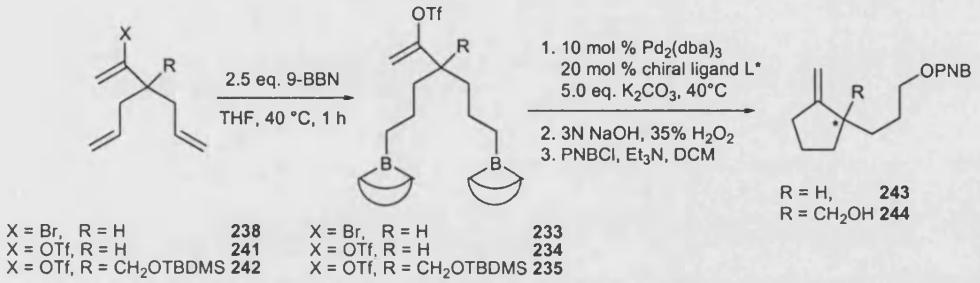


Table 2.6: Enantioselective desymmetrisation of prochiral dienes 236, 239 & 240

Reaction	Substrate[a]	Chiral Ligand L*	Yield of 241/242 (%)	ee (%) of 241/242
1	**236**	(*R*)-BINAP **3**	Trace	-
2	**236**	(*R*)-BINAs **243**	37	0
3	**236**	(*R*)-BINAPAs **244**	10	(*R*) 2
4	**236**	(*S*)-(*R*)-BPPFOAc **247**	41	(*S*) 10
5	**239**	(*R*)-BINAP **3**	-	-
6	**239**	(*R*)-MeO-MOP **90**	67	(*S*) 14
7	**239**	(*R*)-HO-MOP **245**	59	(*S*) 6
8	**239**	(*S*)-(*R*)-PPFA **36**	48	(*S*) 20
9	**239**	(*S*)-(*R*)-BPPFOAc **247**	58	(*R*) 28
10	**240**	(*R*)-BINAPAS **244**	57	(*S*) 11
11	**240**	(*S*)-(*R*)-BPPFOAc **247**	65	(*S*) 2
12	**240**	(*S*)-(*R*)-PPFA **36**	42	(*R*) 31
13	**240**	(*R*)-*i*-PrO-MOP **246**	90	(*R*) 9
14[a]	**240**	(*R*)-BINAP(O) **84**	60	(*S*) 16

[a] 20 mol % $Pd(OAC)_2$, 20 mol % chiral ligand L*.

The bromide **236** produced disappointing results, with a maximum enantiopurity of 10% ee of the protected alcohol **241** achieved using bidentate ferrocenyl ligand (*S*)-(*R*)-BPPFOAc **247**.[67] Improved yields were achieved with the triflate substrates (up to 90%). Triflate **239** yielded higher enantioselectivities particularly with the ferrocenyl ligands (*S*)-(*R*)-PPFA **36** and (*S*)-(*R*)-BPPFOAc **235** (although these were still low, up to 28% ee). Triflate **240** contains a quaternary carbon centre which is

stereodefined upon desymmetrisation to yield protected alcohol **242**. This provided better yields, however, enantioselectivities were low. This time the diphosphine **247** produced essentially racemic material and monophosphine **36** generated the highest enantioselectivity (31% ee). Bidentate ligand (*R*)-BINAP **3** performed poorly throughout, as did the arsine ligands (*R*)-BINAs **243** and (*R*)-BINAPAs **244**. The hemi-labile MOP ligands **90**, **245** and **246** produced good yields, but showed poor enantioselectivities (up to 14% ee).[68] Although the enantioselectivities achieved were low, it is important to note that this represents the first time Suzuki methodology has been used to generate stereodefined sp^3 carbon centres.

2.4 Generating stereogenic carbon centres through enantioselective desymmetrisations

Many of the enantioselective desymmetrisations established so far have generated chirality through chiral planes or axes. Our aim is to develop enantioselective desymmetrisation methods which will generate stereogenic carbon centres, particularly quaternary centres, as these would have extremely useful synthetic applications. The strategy envisaged involves preparing these highly enantiomerically enriched products through the use of palladium-catalysed chemistry.

In designing our starting material, several factors were considered; two identical enantiotopic leaving groups are required. These could be halogen or triflate groups, which must be capable of being differentiated through enantiotopic discrimination. Thus, the substrate can undergo selective oxidative addition with a palladium(0) species which is then open to further functionalisation, therefore producing an

enantioselective coupling reaction. For example if this substrate were to undergo Suzuki cross-coupling then an enantiomerically enriched product will be generated. It has been shown that the oxidative addition step is sensitive to the steric environment.[69] Therefore, if a bulky intermediate substituent is present close to the reactive groups then enantiotopic discrimination can be effected between the two. It was also important to be able to prepare the compounds for the palladium-catalysed desymmetrisation reactions in a relatively short synthetic process.

We envisioned the use of substrates of the class 2,2-disubstituted-1,4-divinyltriflates with one small alkyl substituent (R_s) and one large group (R_L) (as seen in Figure 2.5). There is a plane of symmetry running down the centre of the compound with a quaternary carbon centre in the middle, which upon desymmetrisation will become a stereodefined quaternary carbon centre. The main distinction is the size of the groups attached to this quaternary centre on the ring-system, as this will play an important role in the enantioselectivity of the catalysed reactions (Figure 2.5).

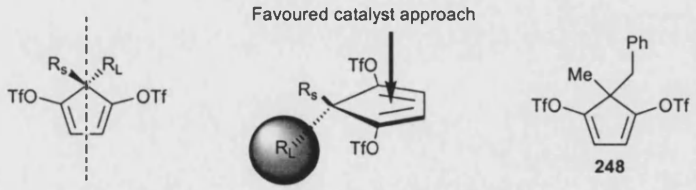


Figure 2.5

With a bulky R substituent present on one side of the molecule (R_L) and a comparatively small group (R_s) on the opposite side, the face with the small group would appear less hindered and so more accessible than the alternative face. The initial substrate chosen was bis-triflate **248**, which is substituted with a large benzyl substituent (R_L) and a small methyl substituent (R_s).

Making use of this enantiotopic group discrimination, the monosubstituted products obtained from palladium cross-coupling reaction would be useful as intermediates for further transformations. After the first coupling reaction the remaining triflate group could be coupled to with an alternative group, or simply reduced to the alkene from where it can be further functionalised, for example though ozonolysis, hydroboration, epoxidation or hydroxylation (Figure 2.6).

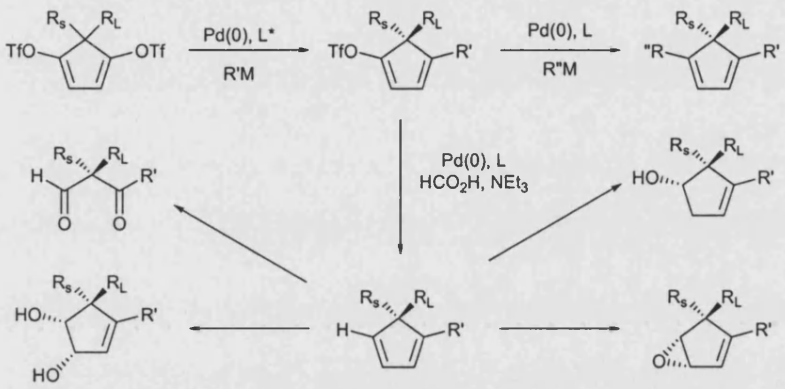


Figure 2.6

In this way a variety of compounds can be created easily, varying the composition of the substituents in the 2 position of the ring, changing the boronic acids, or altering the size of the ring would all result in creating a wide range of functionalities, and would also provide useful information on enantioselectivites achievable in the asymmetric palladium-catalysed reactions.

2.5 Conclusions

Using a desymmetrisation strategy it is possible to generate compounds with one or more chiral stereocentres in a single step. Another advantage is that it is possible to achieve this over a variety of substrates, and can be used to produce synthetically important compounds. Combining this approach with asymmetric palladium catalysis has proved effective and we wish to use this process to enantioselectively desymmetrise achiral cyclic 1,4-divinyltriflate compounds.

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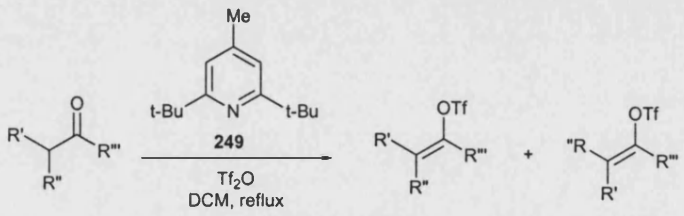
3 Initial Investigations

3.1 Preparation of bis-triflates

Triflates are widely employed as synthetic precursors in organic synthesis for generating vinyl cations and alkylidene substrates,[1,2] and since the discovery that vinyl or aryl triflates can also be used in cross-coupling reactions with organometallics they have become well established reagents. These cross-coupling reactions can provide high regioselectivity and generally proceed under mild conditions, tolerating the presence of numerous other functional groups.[3] Triflate groups are useful in synthesis due to their ability to undergo the oxidative insertion of metal catalysts. The use of vinyl and aryl triflates in palladium mediated coupling reactions has become commonplace, yielding coupling products from many organometallic compounds including organoboron, -zinc, -aluminium and -tin species. They have also been used in carbonylations, aminations and Heck reactions, and these coupling reactions often feature as key steps in natural product and drug syntheses.[4]

There are several methods available for generating vinyl triflates, the first method developed involved the direct treatment of a carbonyl unit with triflic anhydride in the presence of a non-nucleophilic base. The base typically used is the sterically hindered 2,6-di-*t*-butyl-4-methylpyridine **249**, which will not react with the triflic anhydride itself but acts as an acid scavenger (Scheme 3.1).[2]



Scheme 3.1

For acyclic carbonyl compounds the more thermodynamically stable *E*-vinyl triflate is the main product although mixtures of *E* and *Z*-vinyl triflates are often produced. Another method for generating vinyl triflates is by direct treatment of the carbonyl compound with a base and trapping the enolate produced with an electrophillic source of triflate (Figure 3.1). Bases typically utilised are LDA, NaHMDS or (*i*-Pr)$_2$NMgBr.[5,6]

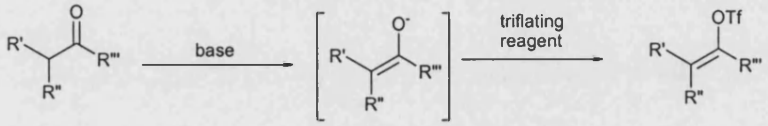
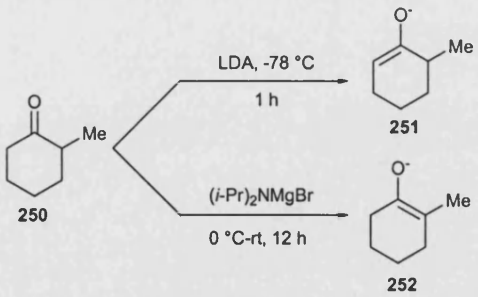


Figure 3.1

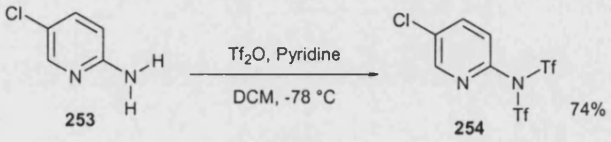
Cyclic compounds are often employed as substrates for triflate studies due to the more straightforward stereocontrol obtained. It is possible to selectively generate either of the two possible enolates of α-substituted cyclohexanones such as 2-methylcyclohexanone **250**. When using lithium di*iso*propylamide at –78 °C for 1 hour, the more accessible site is deprotonated, which gives the kinetically derived enolate **251** with a regioselectivity of 95:5. The thermodynamic enolate **252** can be obtained when bromomagnesium di*iso*propylamide is used at 0 °C and allowed to equilibrate to room temperature over a 12 hour period (Scheme 3.2).



Scheme 3.2

To prepare bis-triflates required for our investigations it was found that the use of relatively reactive triflating reagents was required. From previous work performed within the group, it was found that the best results were achieved through the use of

N-(5-chloro-2-pyridyl)triflimide **254**.[7] *N*-Phenyltriflimide was first reported in 1983 and is often used in the preparation of triflates,[8] however the most effective reagents were synthesised by Comins *et al.* who introduced the pyridine ring and the chlorine substituent.[9] This reagent is available commercially but due to cost was synthesised in a simple one step reaction from 5-chloro-2-aminopyridine **253** and triflic anhydride (Scheme 3.3).



Scheme 3.3

These structural modifications increased the reactivity of the triflating agent due to the electron poor pyridine ring creating very powerful electrophiles, which are consequently more reactive towards enolates. There is also the possibility that the reaction can be activated through chelation *via* the pyridyl nitrogen to the metal of the metallo-enolate (as seen in Figure 3.2).

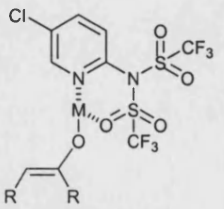
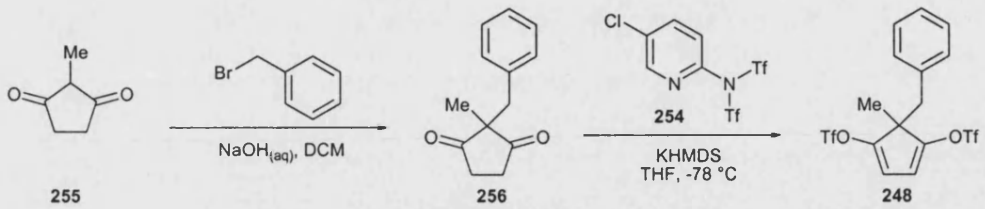


Figure 3.2

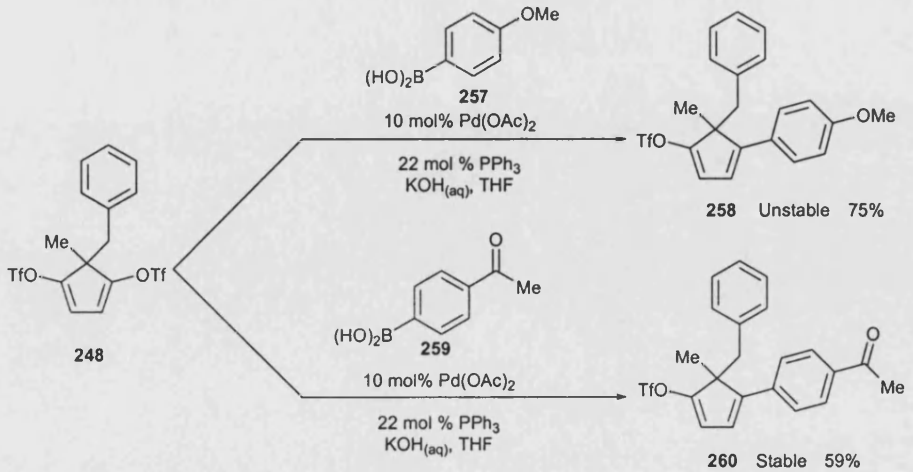
The initial bis-triflate substrate was prepared in two steps from 2-methyl-1,3-cyclopentandione **255**. The first step introduces the benzyl group *via* alkylation with the use of benzyl bromide in 75% yield (Scheme 3.4).[10] This yielded the diketone **256** which was then converted to the bis-triflate. This was found to be best achieved using *N*-(5-chloro-2-pyridyl)triflimide **254** followed by the strong base potassium hexamethyldisilazane in THF at –78 °C, yielding 61% of the bis-triflate **248**.



Scheme 3.4

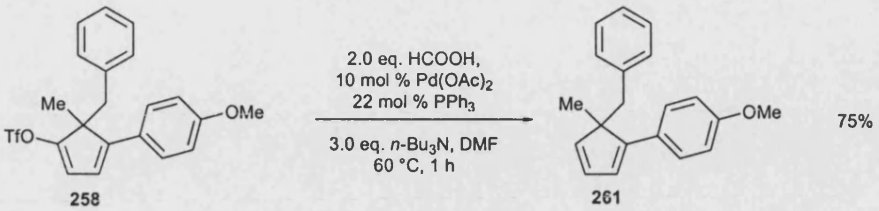
3.2 Achiral Suzuki cross-coupling reactions of the bis-triflate 248

With bis-triflate **248** in hand, its suitability as a substrate for Suzuki reactions was then tested. The achiral Suzuki reactions were carried out using palladium(II) acetate with triphenylphosphine as the ligand, and aqueous potassium hydroxide as the base in THF. It was previously shown within the group that these conditions are successful in yielding monocoupled products in good to moderate yields.[7] Previous work has also shown that the use of 4-methoxyphenylboronic acid **257** generated an unstable product **258** which decomposed on standing. Whilst, the use of 4-acetylphenylboronic acid **259** yielded a comparatively stable monocoupled product **260** in 59% yield (Scheme 3.5). This was accredited to the electron withdrawing effect of the acetyl group which seemed to stabilise the monocoupled product. With the *para*-methoxyphenyl substituents the electron donating effect seemed to destabilise the monocoupled product leading to decomposition.



Scheme 3.5

Thus, from this previous work, monocoupled product **258** needed to be reduced by hydrogenation to form a stable product **261**, enabling full spectroscopic analysis (Scheme 3.6).



Scheme 3.6

From this information it was decided to screen various boronic acids as to their ability to undergo the cross-coupling reaction. The main focus of these reactions investigated the use of coupling partners featuring phenyl rings substituted with electron withdrawing groups, in an attempt to generate more stable products, although a variety of other boronic acids were also screened.

The results from screening various boronic acids can be separated into three categories; firstly, those which showed little or no reactivity; those which reacted but which could not be separated from the starting material *via* flash chromatography; and finally those which reacted and were more easily separated from the starting material.

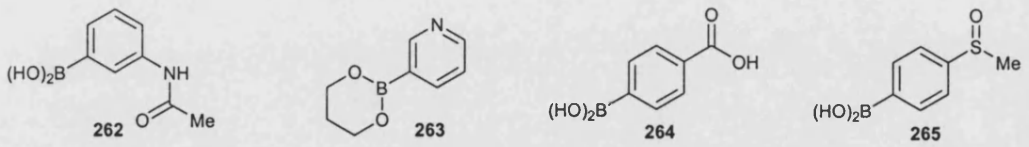


Figure 3.3

The first set of boronic acids/ester which did not react under the given conditions are shown in Figure 3.3. With both 3-acetamidobenzeneboronic acid **262** and pyridine-3-boronic ester **263** the reactions appeared to react at a slow rate, yielding only traces of product. With boronic acid **262** this could be due to incompatibility of the

comparatively acidic *N-H* on the acetamido group. Compound **263** was the only boronic ester tested and the low reaction rate may show that different reaction conditions are required for this type of compound. Although, it must also be noted that whilst halopyridines are widely used in cross-coupling reactions the use of pyridylboronic acids or esters has been limited.[11] Another explanation for this lack of reactivity may be that the boronic ester interferes with the catalyst, as pyridylboronic acids have also been used in the assembly of polynuclear metal complexes acting as bifunctional ligands; coordinating through the N and O atoms.[12,13] Using 4-carboxyphenylboronic acid **264,** material precipitated out of solution upon the addition of the base. This would seem to suggest instability towards the aqueous potassium hydroxide, with the carboxylic acid forming an insoluble carboxylate salt, this may be resolved through the use of a different base. Alternatively the carboxyl unit may be incompatible with general basic conditions. In this case, protecting the acid as an ester may provide a solution. The presence of the extremely polar sulfoxide functionality in boronic acid **265** may be too electron withdrawing to facilitate a coupling reaction. It is known that electron deficient boronic acids can be poor coupling partners due to a lack of nucleophilicity and slower rates of transmetallation.[14]

The second set of boronic acids which all showed evidence of having successfully reacted are shown in Figure 3.4. These compounds proved to have similar polarities as the bis-triflate starting material **248**. This meant that purification was extremely difficult, providing the product combined with varied amounts of unreacted starting material. It was considered important to be able to isolate pure compounds to allow accurate HPLC assays to be established.

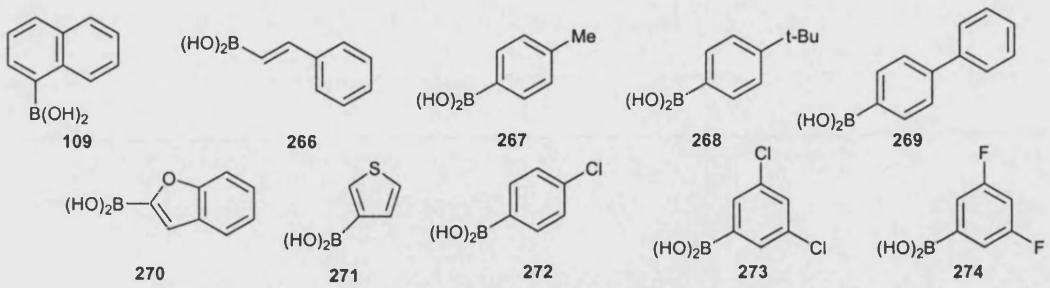


Figure 3.4

As these reactions were part of a large screening process, and these compounds proved difficult to isolate cleanly it was felt that it was unnecessary to fully characterise them. The main evidence for their reaction is from TLC and ^{1}H NMR (300 MHz), which shows the introduction of an aromatic group in the δ_H 7.00-7.50 ppm chemical shift region. More conclusively, the desymmetrisation has split the signal corresponding to the vinylic hydrogens in the cyclopentadiene unit into two doublets, as they became inequivalent. Also hydrogen signals corresponding to the benzyl CH_2 unit (δ_H 3.30-2.80 ppm), were split into two doublets as they became diastereotopic.

The final set of boronic acids all produced a change in the polarity of the product thus allowing easier purification (Figure 3.5).

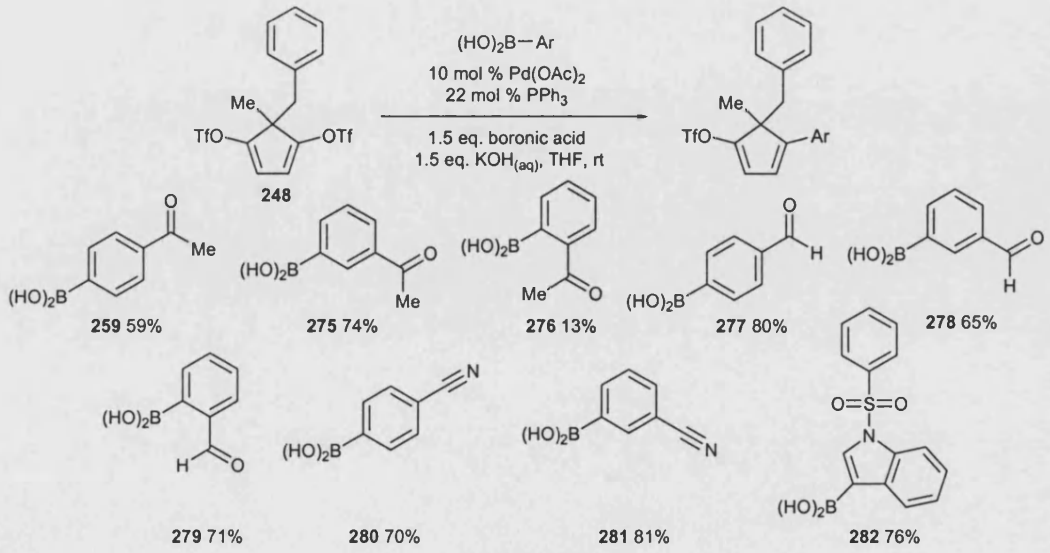
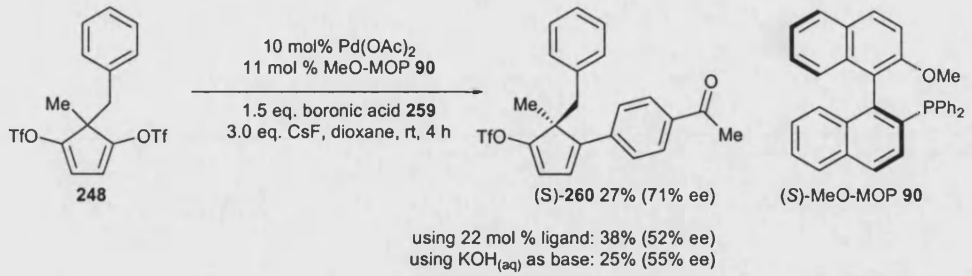


Figure 3.5

The reactions were monitored by TLC for the conversion of starting material. typically these reactions also yielded 0-10% of recovered starting material and generally 5-10% of what was thought to be dicoupled material although these compounds proved difficult to isolate. Many of the reactions yielded unidentified by-products which could not be isolated cleanly especially using boronic acid **276**. Indeed it has been noted in the literature that the presence of electron withdrawing substituents on boronic acids can lead to competitive homocoupling and hydrolytic deboronation, thus often giving unsatisfactory results.[15-18] The presence of the mono-coupled product was confirmed by ^{1}H NMR analysis. It was soon established that the products are in many cases heat sensitive, rapidly decomposing upon mild warming, highlighting the instability of these triflates. It was also noted that the aldehydes produced using boronic acids **277**, **278** and **279** all suffered from rapid decomposition in the deuterated chloroform solvent used for NMR analysis. This is thought to be due to the acidity of the chloroform. They appeared more stable in either benzene or dichloromethane.

3.3 Enantioselective desymmetrisation of bis-triflate 248

After it was established that these Suzuki cross-coupling reactions were able to proceed with reasonable yield, it was decided that the potential for enantioselective reactions should be assessed. A chiral ligand screen of commercially available ligands was previously carried out for this reaction within the Willis group (the best results obtained with the remaining chiral ligands are depicted in Figure 3.6).[7] The screening reactions utilised either aqueous potassium hydroxide in THF, or cesium fluoride in dioxane as the base and solvent. Ligand loadings were also examined, with the most successful ligand screened being MeO-MOP **90** (see Scheme 3.7).



Scheme 3.7

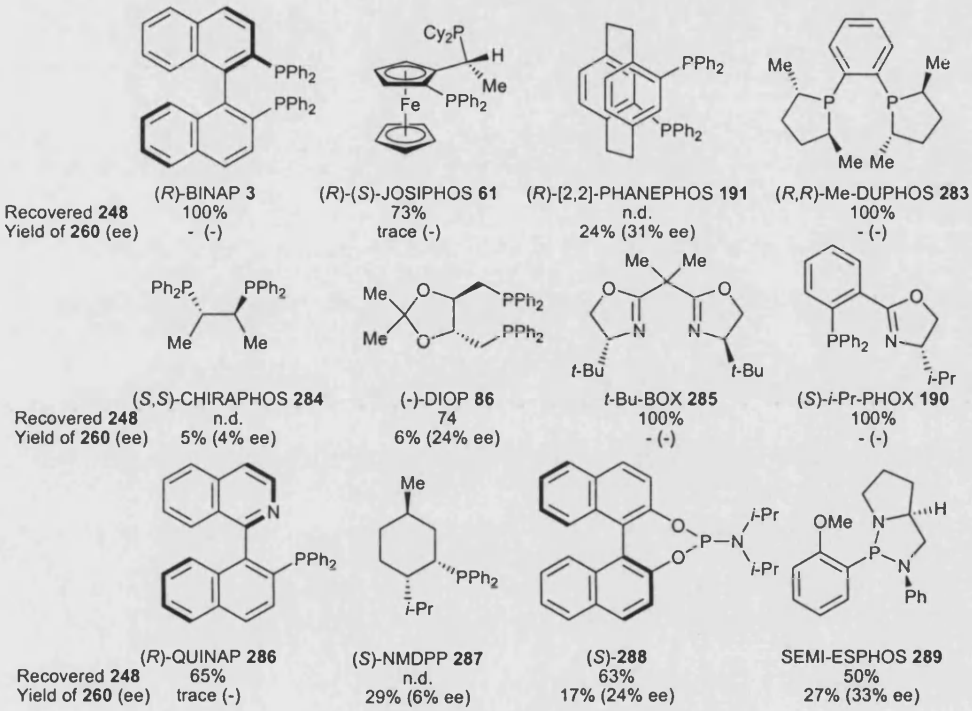


Figure 3.6

It was concluded from this ligand screening that coupling reactions using diphosphine ligands generally showed poor reactivity, and that the monophosphines showed poor enantioselectivity. However, the more complex monophosphine chiral ligand (*S*)-MeO-MOP **90** yielded the monocoupled material in moderate yields with high enantioselectivity. It has been suggested that the MeO-MOP **90**, may have hemilabile properties either through coordination of the oxygen in the methoxy group or directly to the π-system of the naphthalene itself.[19,20] This added facet means that it could interact with the metal centre of the catalyst in the intermediates of the catalytic cycle. This, could aid its ability to relay stereoinformation, more effectively

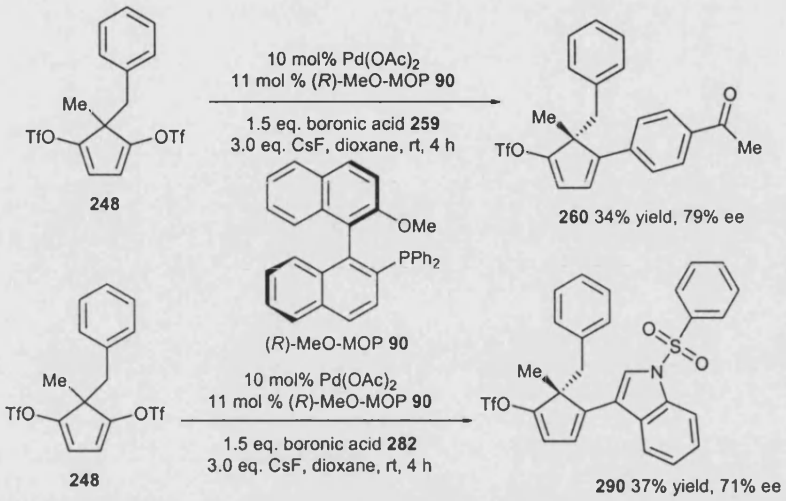
than the simple monophosphines, without the constraining nature of the diphosphines.

Interestingly the ligand loading of 11 mol % gave the best enantioselectivity in this reaction thus suggesting that the active catalyst was only mono-ligated corresponding to what would be expected in a bidentate ligand. Indeed the groups of both Buchwald and Baudoin have noted that in their asymmetric Suzuki reactions a 1:1 ratio of ligand (PCy_2 MAP **64**) to palladium was the likely catalytic species in their systems where changing the palladium:ligand ratio had no effect on enantioselectivity.[21,22]

The use of an 11 mol % loading of MeO-MOP **90** yielded a 71% ee of the monocoupled material, which upon x-ray analysis of recrystallised material (99% ee) determined the reaction to be in favour of generating the *S* enantiomer. The best results in terms of enantioselectivity were obtained in dioxane with cesium fluoride as the base. Therefore, it was decided to utilise these conditions to further investigate the enantioselective desymmetrisation of bis-triflate **248**.

Two different boronic acids have been examined so far: 4-Acetylphenyl boronic acid **259**, (which had previously been used within in the group with positive results) and 1-(phenylsulfonyl)-3-indoleboronic acid **291** (which had shown a rapid rate of reaction, providing the mono-coupled product in high yield). The solid base cesium fluoride was chosen so to avoid the presence of water, which we reasoned may interfere with the enantioselectivity of the reaction, especially with the ligand (*R*)-MeO-MOP **90** which is known to be air sensitive. The solvent used was 1,4-dioxane,

which had been degassed to remove oxygen prior to the reaction. The reactions were carried out at room temperature over four hours.



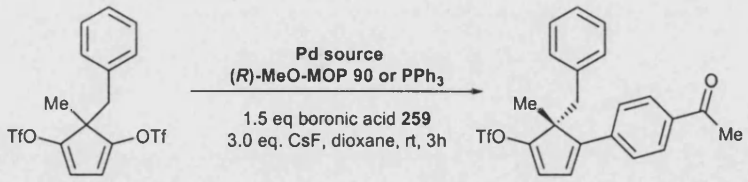
Scheme 3.8

The reactions produced positive results, yielding 34% of **260** and 37% of **290**, which is a drop from those obtained under the achiral conditions, however, the ee's obtained were very good; 79% and 71% respectively (Scheme 3.8). Before further screening of substrates could take place, we embarked on the optimisation of reaction conditions.

3.4 Optimisation of reaction conditions

The reaction of 4-acetylphenyl boronic acid **259** with the bis-triflate **248** was chosen as the procedure to optimise the conditions upon, because this had yielded the best enantioselectivities and full analytical characterisation was available. The first criterion focused upon was the catalyst. The conditions chosen were first tested using triphenyl phosphine as the ligand to compare the yields obtained with (*R*)-MeO-MOP **90**. (*R*)-MeO-MOP **90** was then used throughout the rest of the optimisations. The palladium source was examined to judge which pre-catalyst source would generate the most useful catalyst. The yields attained thus far had been moderate. One way to

try to improve them was to increase the catalyst loading to 20 mol % (these optimisation results are shown in Table 3.1).



248 260

Table 3.1: Optimisation of catalyst

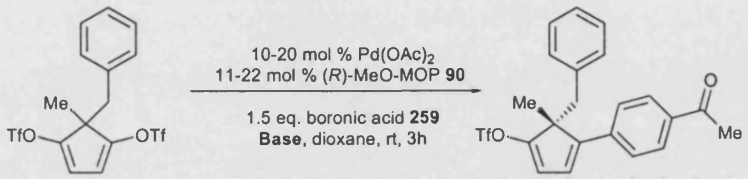
Reaction	Catalyst	Recovered 248 (%)	Yield of 260 (%)	ee (%)
1	10 mol % $Pd(OAc)_2$ 22 mol % PPh_3	48	33	0
2	10 mol % $Pd(OAc)_2$ 11 mol % (*R*)-MeO-MOP **90**	63	34	74
3	5 mol % $Pd_2(dba)_3$ 11 mol % (*R*)-MeO-MOP **90**	63	30	51
4	10 mol % $PdCl_2$ 11 mol % (*R*)-MeO-MOP **90**	88	-	-
5	20 mol % $Pd(OAc)_2$ 22 mol % (*R*)-MeO-MOP **90**	70	22	73

The first entry shows that in changing the base and solvent from the racemic conditions of aqueous potassium hydroxide in THF to cesium fluoride in dioxane yielded 33% of the desired monotriflate. Interestingly, this was similar to that attained under the same conditions when using MeO-MOP **90** as the ligand (entry 2). Entry 3 shows that in changing the pre-catalyst source from palladium acetate to palladium dibenzylideneacetone (dba), the enantioselectivity is lowered. This could be due to dba acting as a spectator ligand, interfering with the active catalyst or possibly due to generation of an alternate catalytic species. This type of effect has been noted previously by Amatore and Jutand and also Pregossin *et al.*[23-25] Fu *et al.* also found that $Pd(OAc)_2$ performed better than $Pd_2(dba)_3$ as the palladium source in the Suzuki coupling of vinyl triflates.[26] When the palladium source is changed to palladium chloride (Entry 4) the reaction shuts down and the majority of the starting material is recovered presumably due to failure to generate an active catalyst. From the final entry it is interesting to note that increasing the catalyst loading did not

improve the yield of monocoupled material. However, the level of enantioselectivity stayed roughly the same. Buchwald has also noted this in investigations into generating hindered biaryls.[27]

The next criterion examined was the choice of base. The base is thought to help generate a reactive boronate anion, which then undergoes transmetallation. Suzuki and Miyaura discovered that by increasing the strength of the base used in their coupling reactions, from Na_2CO_3 to aqueous NaOH or $Ba(OH)_2$, accelerated the rate of the reaction rapidly.[28] However triflates are known to hydrolyse when used in conjunction with strong bases especially when moisture is present. Coudret and Mazenc found that triflate hydrolysis could be minimised through the use of potassium phosphate in dioxane. This also helped to reduce the deboronation of electron deficient boronic acids.[29] Fluoride bases have also shown great use as alternatives to hydroxides especially where functional group compatibility is an issue. Fluoride ions have a high affinity for boron, thus easily generating an active boronate for transmetallation, whilst at the same time they are only weakly basic and poor nucleophiles, tolerating a wider range of functionalities. It is also noted that fluorine only forms weak bonds to palladium thus limiting interference on the catalyst.[30] The base used in the racemic conditions was aqueous potassium hydroxide which produced good yields, so this was tested to see if yields of the mono-coupled product could be improved. It had been noted by Colobert *et al.* that the use of aqueous bases encouraged deboronation of the boronic acid and that anhydrous solvents and bases were therefore preferred.[31] Other bases chosen were cesium carbonate and potassium phosphate, which have both been known to catalyse Suzuki reactions.[27,32]

In the optimisations carried out thus far it was felt that the reaction rate was initially high but quickly declined (as monitored by TLC) resulting in moderate yields. This hinted that the catalyst may be deteriorating thus effectively shutting the reaction down after only a few hours. A way to counterbalance this would be to add the pre-catalyst portion-wise during the reaction, thus ensuring that catalyst availability was increased. It has been suggested that the base also plays an important part of the catalytic cycle by activating the boron reagent, so an extra three equivalents of the base were also added portion-wise (optimisation results are shown in Table 3.2).



248 260

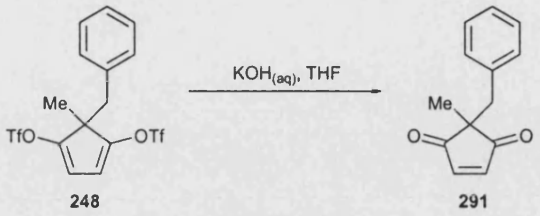
Table 3.2: Optimisation of base

Reaction	Base	Catalyst	Recovered 248 (%)	Yield of 260 (%)	ee (%)
1	3 eq. CsF	10 mol % $Pd(OAc)_2$ 11 mol % (*R*)-MeO-MOP **90**	63	34	74
2	2 eq. $KOH_{(aq)}$	10 mol % $Pd(OAc)_2$, 11 mol % (*R*)-MeO-MOP **90**	27	35	51
3	3 eq. Cs_2CO_3	10 mol % $Pd(OAc)_2$, 11 mol % (*R*)-MeO-MOP **90**	67	-	-
4	3 eq. K_3PO_4	10 mol % $Pd(OAc)_2$, 11 mol % (*R*)-MeO-MOP **90**	83	-	-
5[a]	6 eq. CsF	20 mol % $Pd(OAc)_2$, 22 mol % (*R*)-MeO-MOP **90**	68	22	75
6[b]	6 eq. CsF	20 mol % $Pd(OAc)_2$, 22 mol % (*R*)-MeO-MOP **90**	72	24	74

[a] $Pd(OAc)_2$, (*R*)-MeO-MOP **90** and CsF added in 2 portions, half at the start and half after 1 h. [b] 3.0 eq. boronic acid **259** used, $Pd(OAc)_2$, (*R*)-MeO-MOP **90**, boronic acid **259** and CsF added in 2 portions, half at the start and half after 1 h.

The second entry shows that in changing to the aqueous base the yield does not seem to have been improved, however, the enantioselectivity is decreased. This is possibly due to water interfering with the coordination between the palladium and the ligand. When cesium carbonate or potassium phosphate were used the reaction did not proceed to yield the desired product, although a reasonable amount of the starting material was unaccounted for in both reactions. This may simply be due to the

decomposition of the starting bis-triflate which, from previous work carried out within the group, is known to be converted to the unsaturated diketone **291** (Scheme 3.9).[7]

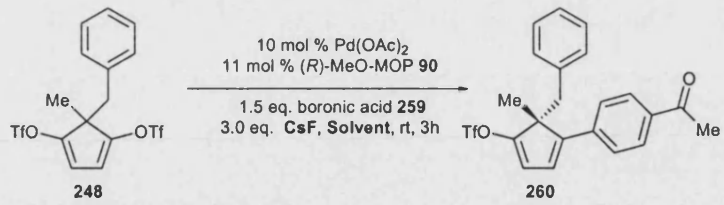


248 291

Scheme 3.9

When the base and catalyst were added in two portions the reaction proceeded disappointingly, yielding 22% of the desired product, with good enantioselectivity (Entry 5). It was thought that the lower yield achieved could be due to an imbalance in the basicity caused by the six equivalents of base used. Thus, a second portion-wise addition experiment was investigated whereby a further portion of boronic acid was added along with the extra catalyst and base. This however gave an almost identical result (entry six) as the previous effort. The low conversion observed may be attributed to the fact that the reaction is inevitably exposed to air upon the addition of the extra components, thus interfering with the reaction.

One main observation of the reactions performed thus far was that the cesium fluoride base used was largely insoluble in the solvent. This lack of solubility could well impair the ability of this component to participate fully in the reaction. Therefore, alternative solvent systems were investigated as to their suitability in this reaction (Table 3.3).



248 260

Table 3.3: Optimisation of solvent

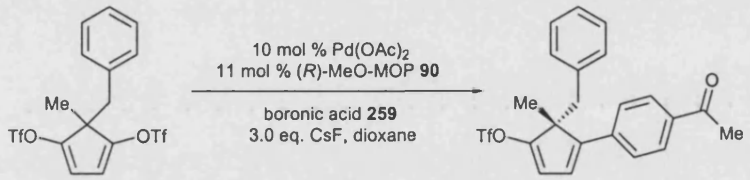
Reaction	Solvent	Recovered 248 (%)	Yield of 260 (%)	ee (%)
1	dioxane	63	34	74
2[a]	toluene	55	-	-
3[b]	THF	35	30	72
4[c]	DME	53	13	70
5	dioxane/DCM	43	34	75
6	toluene/DCM	54	30	77

[a] Starting materials failed to dissolve. [b] Several by-products detected but could not be isolated.
[c] Gave a mixture of unidentified products.

When the solvent was changed to toluene the solubility was not improved and the reaction failed to proceed to the desired product. When THF was used as the solvent a mixture of unidentified products was produced along with the desired product, this propensity to obtain alternative products occurred more so when the solvent was changed to DME. It was thought that maybe the use of solvent mixtures may aid the solubility therefore DCM was used as a co-solvent. When DCM was used in conjunction with dioxane (entry 5) there appeared to be an improvement in the solubility however this made no real difference to the results attained, except that less starting material was recovered. The toluene-DCM mixture (entry 6) improved the solubility. However, the result was very similar to that achieved previously when dioxane was used (entry 1).

Another parameter examined was the temperature of the reaction, although it was known that both the bis-triflate starting material, and the mono-coupled product were temperature sensitive, decomposing readily at elevated temperatures. It was apparent from TLC analysis that the coupling reaction proceeded rapidly at first, however, the rate of reaction deteriorated rapidly after an hour. The ideal reaction time was also

investigated, to see what effect extended reaction time would have on the yield and enantioselectivity of the mono-coupled product. Finally the amount of boronic acid **259** used was investigated. It was initially thought that 1.5 equivalents should be sufficient for the coupling to produce a high proportion of mono-coupled material, whilst being low enough to prevent over-reaction to generate dicoupled material. However it was apparent from our results that over-reaction was not a problem; with the majority of the material accounted for in recovered starting material and mono-coupled material. Therefore, increasing the quantity of boronic acid was investigated (results shown in Table 3.4).



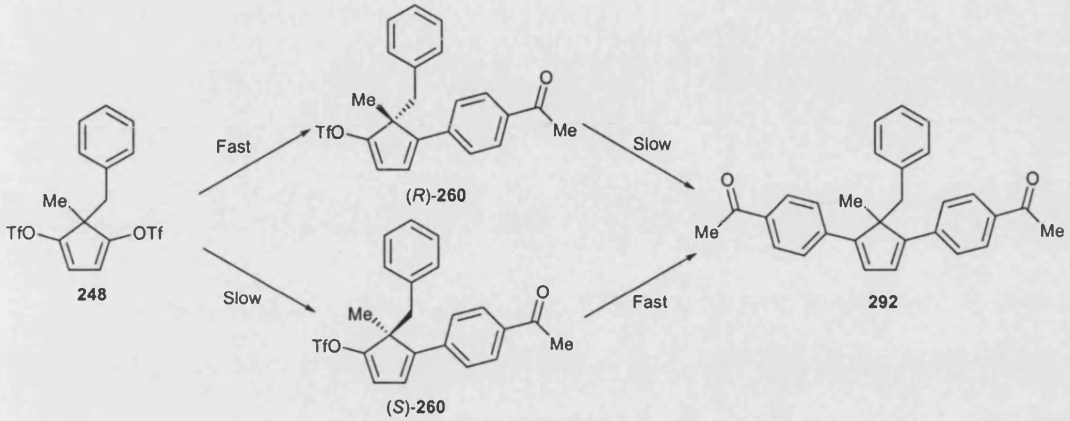
248 260

Table 3.4: Optimisation of conditions

Reaction	eq. 259	Temperature (°C), Time (h)	Recovered 248 (%)	Yield of 260 (%)	ee (%)
1	1.5	rt, 3	63	34	74
2	1.5	40°C, 3	56	35	72
3	1.5	rt, 24	25	56	67
4	2.0	rt, 3	55	37	74
5	3.0	rt, 3	34	8	77
6	2.0	rt, 8	32	46	77

The second entry shows that when the reaction is heated the yield and enantioselectivity remain unchanged. This indicates that this small increase in temperature has little effect on the reactivity. As both the starting material and desired product were known to be thermally unstable this study was not pursued at higher temperature. The highest yield obtained (56%) was achieved by leaving the reaction mixture for 24 hours at room temperature (entry 3). The enantiomeric excess however was reduced to 67%. This result was disappointing as it was hoped that extending the reaction time should enrich the enantiopurity of the material yielded

through kinetic resolution; whereby the undesired isomer should be more selectively converted into dicoupled material **292** (Scheme 3.10). This result may also suggest that an alternative catalytic species is formed and takes prevalence over longer reaction times.

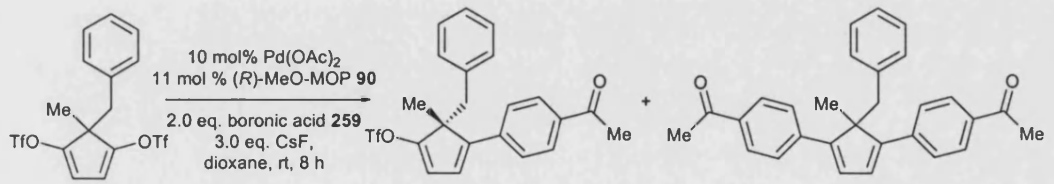


Scheme 3.10

When the quantity of boronic added was altered (entries 4 and 5) it was interesting to note that the yield of mono-coupled material improved slightly with two equivalents of boronic acid to 37%. However, when this was increased to three equivalents, the yield dropped to 8%. This could possibly be explained due to a subtle balance in the acidity of the reaction conditions being upset by the addition of more boronic acid. Another explanation of this could be due to the now very concentrated solution (0.72 M compared with the standard reaction at 0.57 M) becoming saturated and interfering with the catalysis of the reaction. At this point it was decided that two equivalents of boronic acid was the optimal amount to use along with three equivalents of cesium fluoride in anhydrous degassed dioxane. The reaction time was extended slightly to eight hours to see how the enantioselectivity was affected. Pleasingly the yield was increased slightly to 46% with no adverse effect on the enantioselectivity which was recorded as 77% ee.

3.4.1 Summary

When MeO-MOP **90** was used as the ligand the enantiomeric excess was generally shown to stay around 70-75% for most of the featured reactions. The main reductions in enantioselectivity occurred when $Pd_2(dba)_3$ was used as the palladium source, or when aqueous potassium hydroxide was used as the base. In the reactions where 20 mol % catalyst was used the yield of the product also diminished. And where twice the amount of boronic acid **259** was used the yield dropped to 8%. It was found that during the reactions a second minor product would appear on the TLC plate. It was presumed to be the dicoupled product **292** (Scheme 3.11). However, this proved difficult to isolate as pure material and so could not be fully characterised. Extended reaction times helped to increase the yields, however, when overnight reaction times are used the enantioselectivity is decreased.



Scheme 3.11

3.5 Screening of boronic acids

At this point it was decided we should investigate a range of boronic acids using the best enantioselective conditions as described above, to see what functionality was tolerated and how these affected the yields and enantioselectivities. The conditions selected for this screening process were; 10 mol % palladium acetate 11 mol % (*R*)-MeO-MOP **90** two equivalents of boronic acid and three equivalents of cesium fluoride in dioxane at room temperature. The reaction times were limited to 8 hours or until the starting material had disappeared. The time limit was installed to try to optimise any beneficial effect from kinetic resolution, shorter reaction times were

found to give slightly lower yields, prolonged reaction times gave higher yields but with lower enantioselectivities.

With these conditions in hand a range of boronic acids were tested. These were chosen based on the criteria set out so far i.e. preferably containing electron withdrawing groups to aid with separation by chromatography.

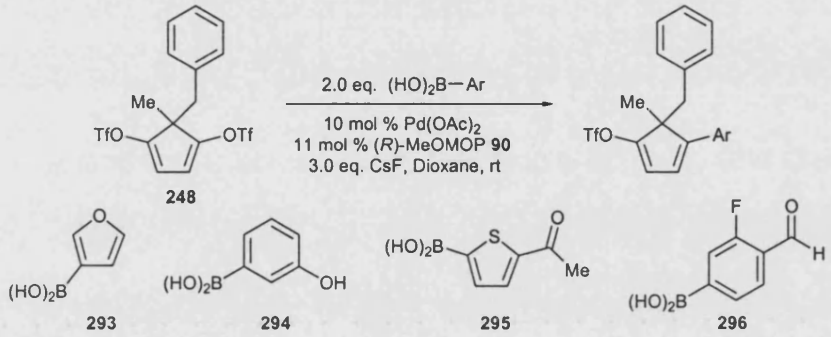


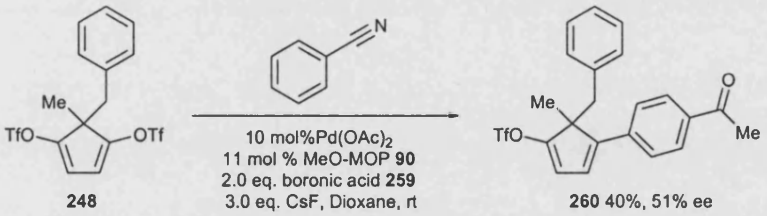
Table 3.5: Boronic acid screen

Reaction	Boronic acid	Time (h)	Recovered 248 (%)	Monotriflate product (%)	ee (%)
1	4-$C_6H_4C(O)Me$ **259**	8	32	46	77
2	3-$C_6H_4C(O)Me$ **275**	8	35	51	86
3	2-$C_6H_4C(O)Me$ **276**	8	30	5	-
4	4-C_6H_4CHO **277**	8	30	47	73[a]
5	3-C_6H_4CHO **278**	8	23	57	80[b]
6	2-C_6H_4CHO **279**	6	20	41	82
7	4-C_6H_4CN **280**	8	53	27	55
8	3-C_6H_4CN **281**	8	34	22	45
9	3-*N*-$PhSO_2$-indolyl **282**	8	8	66	85
10	3-Furyl **293**	8	27	53	72
11	3-C_6H_4OH **294**	8	45	43	74
12	2-(5-C(O)Me)-thiophenyl **295**	7	23	40	53
13	4-(2-F)-C_6H_3CHO **296**	8	56	5	-

[a] ee determined by derivatisation of monotriflate, as detailed in chapter 4. [b] ee determined by derivatisation of monotriflate, as detailed below.

The results showed that the conditions chosen worked fairly well on the majority of the substrates with moderate to good yields and excellent enantioselectivities of up to 86% ee. However, some substrates proved problematic; the *ortho*-acetylphenyl boronic acid was poor yielding, (entry 3). This was presumably due to the steric hindrance generated by the acetyl substituent. Interestingly this is not the case for the

formyl equivalent. Another interesting feature was that using cyano-substituted phenyl boronic acids the reaction produced lower yields and lower enantioselectivities. This was unexpected and is postulated to be due to interference with the catalyst. Experimental information to support this was to add benzonitrile to one of the reactions where high levels of enantioselectivity occurs. Thus benzonitrile was added to the reaction of the bis-triflate with *para*-acetylphenyl boronic acid (Scheme 3.12).



Scheme 3.12

The presence of benzonitrile in the reaction did indeed lower the enantioselectivity of the reaction to the same level as seen when cyano-substituted boronic acids are used. The use of the acetylthiophene boronic acid **295** also showed lowered enantioselectivity this may also be due to interference with the catalyst.

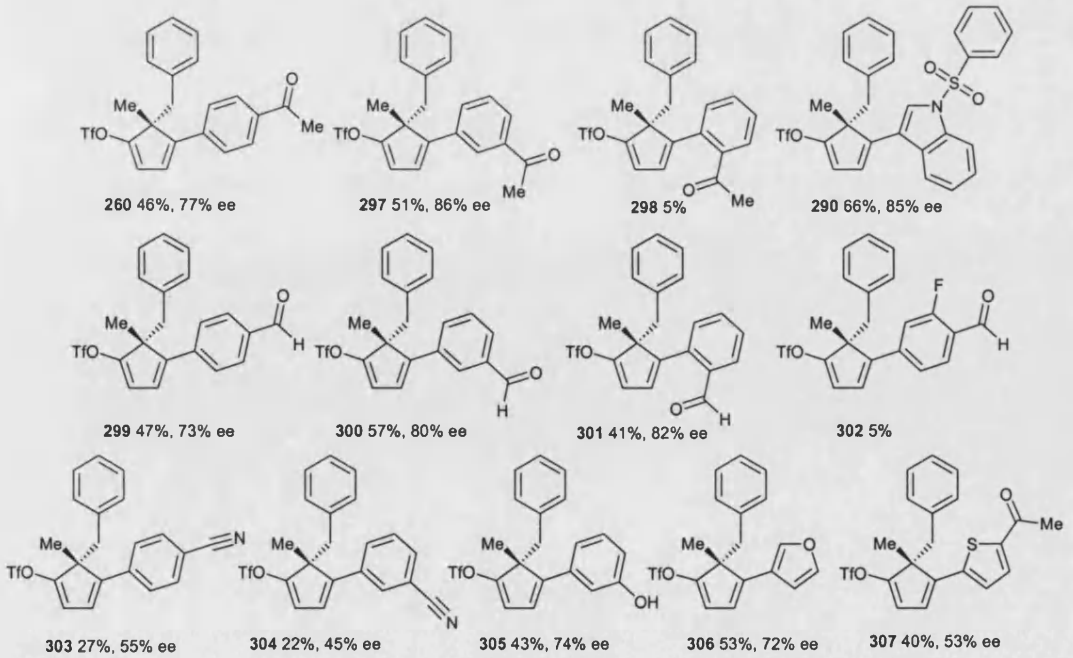
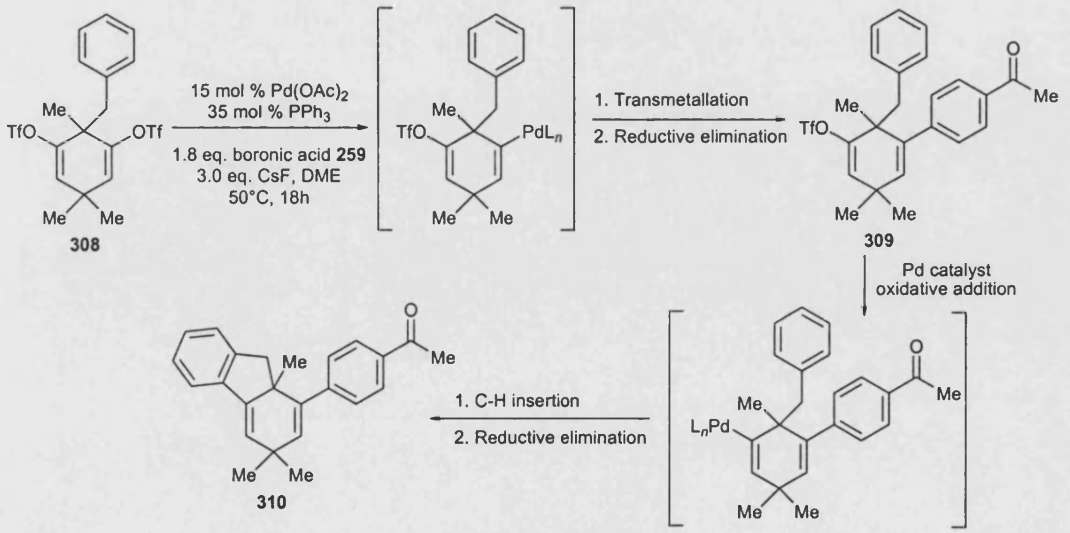


Figure 3.7

An interesting development was noticed in the coupling reactions of the formyl-substituted boronic acids; an alternative product was also being produced. ^{1}H NMR analysis clearly showed that it was not the dicoupled material as it showed a loss of symmetry. Instead it appeared to be similar to that of the monocoupled product, with two doublets appearing corresponding to the two vinyl protons. However, these were shifted more downfield and had smaller coupling constants to those of the monocoupled products. The peaks corresponding to the benzylic and methyl positions were also changed in the alternative material, moving more upfield. The splitting pattern corresponding to the aromatic region was also more complicated and only integrated to eight protons rather than the nine seen in the monocoupled material.

In previous work carried out within the group using achiral Suzuki methodology on cyclohexyl-derived bis-triflates, it was noted that after the coupling to generate the monotriflate a second reaction occurred. It was thought that the palladium catalyst inserts into the remaining triflate functionality promoting cyclisation onto the phenyl ring of the benzyl unit *via* a C-H activation process (Scheme 3.13).



Scheme 3.13

C-H activation chemistry is known to occur with many transition metals,[33-35] and in a variety of substrates, it has been noted that the reactions occur best in electron rich substrates and often require high temperatures and catalyst loadings to proceed.[36-42] This reaction had not been previously observed in the equivalent cyclopentyl-derived bis-triflates, but was confirmed through high resolution mass spectrometry. This was especially convenient for the formylsubstituted monotriflates as these were unstable and decomposed fairly rapidly at room temperature, in air and also when deuterated chloroform was used as an NMR solvent, even when base washed. This instability led to a failure to identify the formylphenylsubstituted monotriflates by mass spectrometry. This C-H activation seemed to occur in many of the substrates to a varying degree, although it typically yielded too little material for full characterisation, but this process was especially prevalent in the formyl or acetyl substituted compounds (Table 3.1).

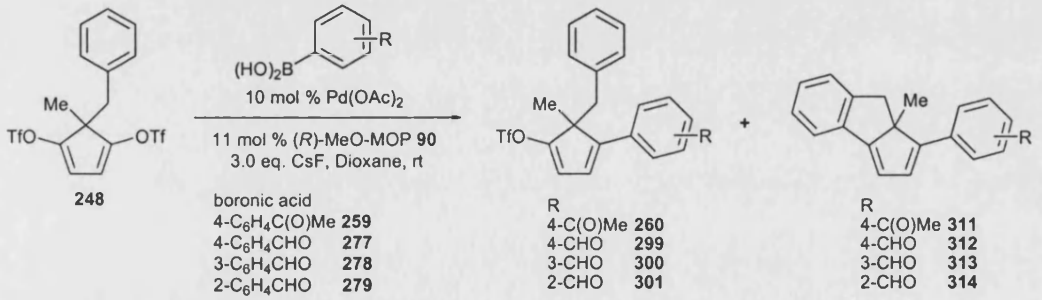
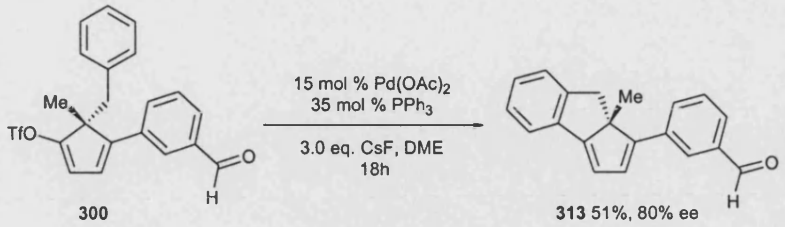


Table 3.6: Yields of cyclised material

Reaction	Boronic acid	Recovered 248 (%)	Monotriflate Product (%)	ee (%)	Cyclised material (%)
1	4-$C_6H_4C(O)Me$ **259**	32	46	77	11
2	4-C_6H_4CHO **277**	30	47	72	18
3	3-C_6H_4CHO **278**	23	57	80	17
4	2-C_6H_4CHO **279**	20	41	81	10

This is an interesting development showing that when an aryl unit is coupled and especially one containing an electron withdrawing substituent, the catalyst will insert into the remaining triflate functionality and that the intramolecular C-H insertion is more favoured than a second intermolecular Suzuki coupling.

Using a modification of the conditions used for the tandem coupling and cyclisation of the cyclohexyl derived bis-triflate **308**, monotriflate **300** was successfully cyclised to generate tricyclicdiene **313** (Scheme 3.14).



300 **313** 51%, 80% ee

Scheme 3.14

This was useful for the characterisation of the formylphenyl substituted monotriflates, as they exhibited poor stability and could be more accurately assessed after conversion to their corresponding tricyclicdienes.

3.6 Conclusions

This work has demonstrated that it is possible to perform enantioselective palladium catalysed cross-couplings on a simple achiral bis-triflate. Using the chrial ligand MeO-MOP **90** in conjunction with palladium acetate, enantioselective desymmetrisations can be achieved. Moderate to good yields of monocoupled material containing a stereodefined quaternary carbon centre have been produced, in up to 86% ee. It has been demonstrated that it is possible to use a wide range of boronic acids as coupling partners, particularly those with polar functionality, with little influence on the enantioselectivity. Although the acetyl-thiophenyl and nitrile substituted phenylboronic acids gave slightly reduced enantioselectivities.

In the Suzuki reactions utilising acetyl- and formyl-substituted boronic acids, varying amounts of cyclised material were produced, through what is thought to be an intramolecular palladium-catalysed C-H activation process. This is achieved under

extemely mild conditions, and represents a remarkable transformation to generate an interesting core structure.

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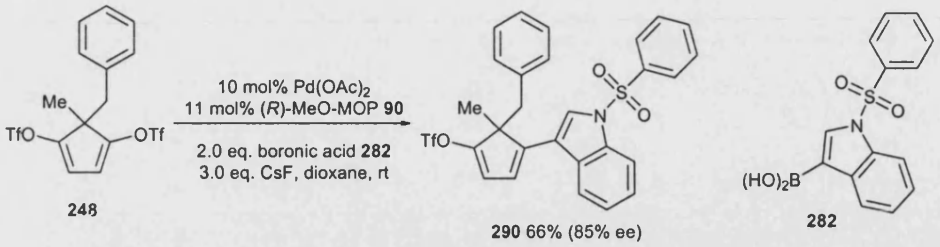
4 Developing alternative substrates



Scheme 4.1

Having shown that it is possible to achieve an enantioselective Suzuki coupling on the bis-triflate substrate **248** yielding up to 66% of product **290** with an 85% ee (Scheme 4.1), further investigation of this methodology was envisioned. It was reasoned that the enantioselectivity was gained from enantiotopic group discrimination between the two triflate groups; however, the first differentiation is made between the two alkene stereofaces of the cyclopentadiene. We reasoned that the catalyst would choose the least hindered face of the molecule; thus discriminating between the steric bulk of the methyl group and the benzyl substituent. However, the steric difference between these two groups is not large as the phenyl ring can orientate away from the face of the molecule and thus, away from the approaching catalyst. This is evident when comparing the relevant *A* values (*A* value; CH_3 ≈1.74, CH_2Ph ≈1.76).[1]

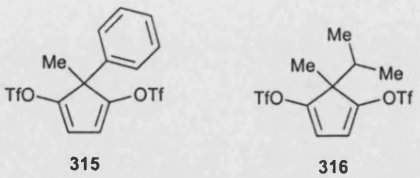


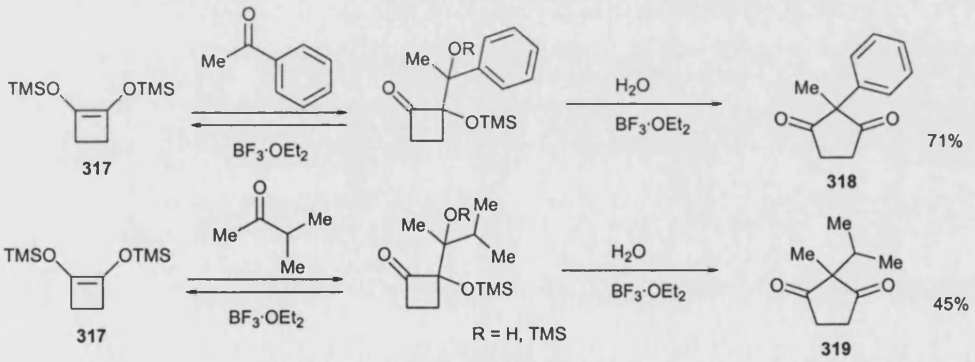
Figure 4.1

In view of this it was reasoned that if a bulkier substituent was introduced in place of the benzyl group, steric differentiation of the alkene stereofaces could be improved. Consequently it was decided to replace the benzyl unit with a phenyl ring (compound

315) and an isopropyl unit (compound **316**, Figure 4.1) (*A* values; phenyl = 2.7, *i*-Pr = 2.15), with the aim of inducing more enantioselectivity in the reaction.

4.1 Synthesis of more sterically hindered diketones

Substrates **315** and **316** were prepared from the corresponding known diketones **318** and **319**, which were in turn generated according to literature procedures.[2] In these procedures Jenkins and Burnell used 1,2-bis-((trimethylsilyl)oxy)cyclobutene **317** which underwent a Lewis acid catalysed aldol type reaction with a range of ketones to yield the corresponding alkylated cyclobutanones. Upon addition of water and more Lewis acid these cyclobutanones then rearranged in a pinacol-type process to yield the 2,2-disubstituted-1,3-pentanediones (Scheme 4.2).



Scheme 4.2

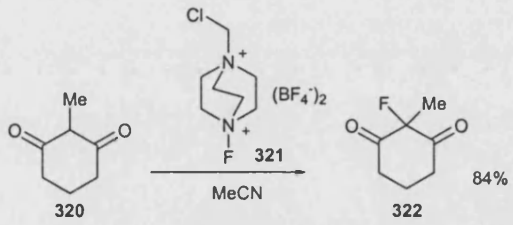
Thus using acetophenone as the ketone, the dione **318** was produced in good yield, 71% (literature 83%), and using 3-methylbutanone the dione **319** was produced in moderate yield, 45% (literature 52%).

In a parallel approach, it was thought that replacement of the methyl group with a smaller substituent could also generate increased enantioselectivity by again increasing the steric differentiation between the two stereofaces. However, replacement of the methyl group with a proton would be difficult due to the acidity

of this easily enolisable position making the preparation of this bis-triflate substrate unfeasible.

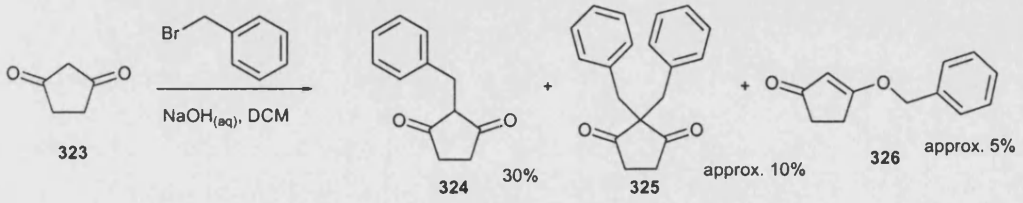
4.2 Synthesis of fluorinated diketones

As a solution to this problem the attachment of a fluorine in the 2-position would create a sterically smaller stereoface than that of the methyl substituent in bis-triflate **248** (*A* value; F = 0.25). There was literature precedent for the fluorination of 1,3-diones using the electrophillic fluorine source Selectfluor **321**. This was used by Banks *et al.* to produce the fluorinated cyclic 1,3-dione in good yield (Scheme 4.3).[3]



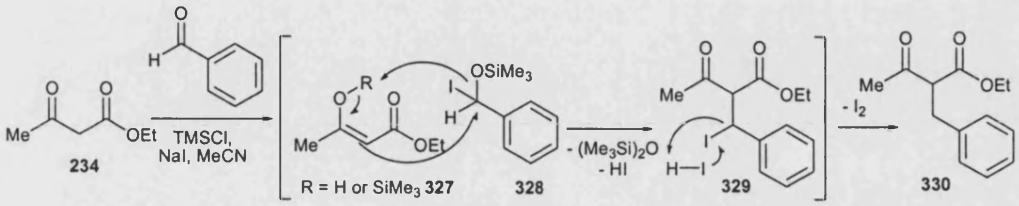
Scheme 4.3

The first step towards this substrate was the benzylation of cyclopentane-1,3-dione **323**. Initial attempts using benzyl bromide and sodium hydroxide in DCM, produced a mixture of monoalkylated diketone **324**, dialkylated diketone **325** and also significant quantity of the *O*-alkylated product **326** (Scheme 4.4). Several other routes were attempted including the use of phase transfer agents, and alternative solvents, however, all yielded similarly low yields of the desired monoalkylated diketone **324**.[4]



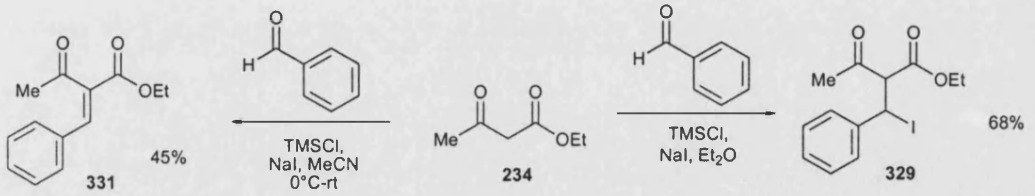
Scheme 4.4

Sakai *et al.* have detailed an alternative method of alkylating 1,3-diones and β-keto-esters, using benzaldehyde in conjunction with trimethylsilyl chloride and sodium iodide in acetonitrile, (as detailed in Scheme 4.5) including their proposed mechanism.[5]



Scheme 4.5

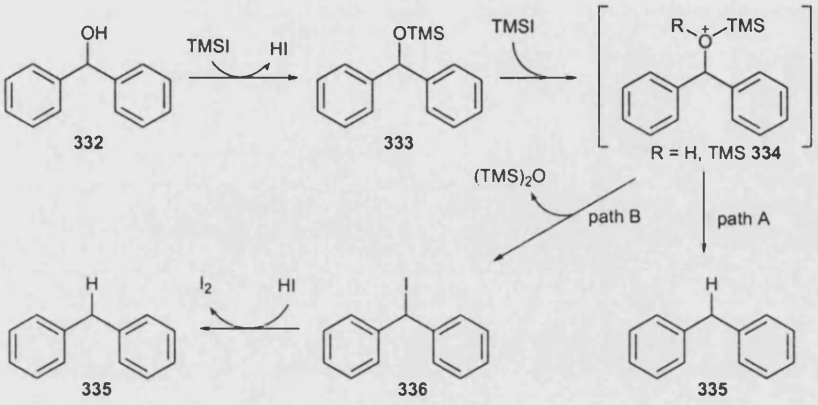
In this mechanism the enol or silyl enol ether **327** reacts with iodinated silyl ether **328** to form a 2-(α-iodobenzyl)-3-butanoate **329**. They stated that this could then be reduced by hydrogen iodide generated *in situ* to produce the desired monoalkylated β-keto-esters **330**. They supported this mechanistic view by the observation that when the reaction was carried out on ethyl acetoacetate **234** at a lower temperature (0°C-room temperature) the unsaturated product **331** was isolated in 45% yield. This could be formed from elimination of hydrogen iodide from the 2-(α-iodobenzyl)-3-butanoate intermediate **329** (Scheme 4.6). Also, when the solvent was replaced with diethyl ether, 2-(α-iodobenzyl)-3-butanoate **329** was isolated as the major product in 68% yield. This product being an assumed intermediate in their original process.



Scheme 4.6

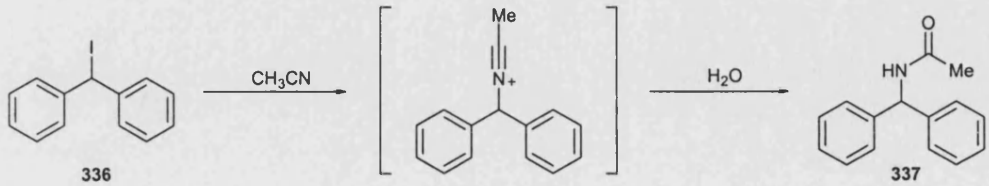
This mechanistic outlook seems questionable hence more details were investigated in associated literature procedures. In related methodology by Stoner *et al.* on benzylation *via* tandem Grignard reaction and iodotrimethylsilane mediated

reductions, they attempted to analyse this type of reduction mechanism by studying the conversion of benzhydrol **332** to diphenyl methane **335** (Scheme 4.7).[6]



Scheme 4.7

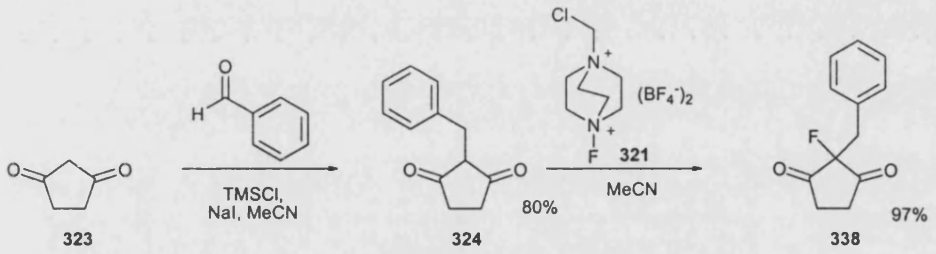
They proposed that the alcohol would be converted into the silyl ether **333**, which could be reduced through either displacement of an activated silyl group to directly form the reduced compound **335** (path A); or by iodide substitution to form iodide **336** with subsequent reduction by HI to yield iodine and diphenyl methane **335** (path B). They suggest that trimethylsilyl iodide (TMSI) is involved in the reductive step and that at least three equivalents are required for the reaction to proceed in good yield. Upon investigation of the two proposed intermediates, silyl ether **333** and iodide **336** it was found that silyl ether **333** required two equivalents of TMSI and one equivalent of HI for reduction. Conversely, iodide **336** performed poorly, yielding substantial amounts of by-product amide **337** (thought to be formed in a Ritter type process (Scheme 4.8)).



Scheme 4.8

From all this evidence they suggested that the iodide pathway (path B) was not the preferred reaction pathway. However, ^{1}H NMR studies revealed the rapid conversion

of the alcohol into either the iodide **336** or the reduced compound **335**, with no silyl ether **333** detected. Stoner *et al.* suggested that the reduction site would form a cation, which was supported by evidence of racemisation of optically active alcohols into racemic hydrocarbons.[7] They also suggest that the TMSI reduction pathway was more favourable than the HI process due to the formation of a carbonium ion species, from a silyl activated intermediate **334**; concluding that the oxophillic TMSI acts as a Lewis acid facilitating ionisation and therefore reduction; however, they do not yield a definite conclusion. There is also evidence in other TMSCl/NaI/MeCN mediated transformations whereby a radical pathway is suggested for the reductive removal of halides from aryl units.[8]



Scheme 4.9

Using the methodology developed by Sakai *et al.* to generate our chosen substrate proved successful at furnishing the mono *C*-alkylated product **324** in high yield (80%). This was then fluorinated in excellent yield (97%) to generate the disubstituted diketone **338** (Scheme 4.9).

4.3 Synthesis of cyclohexyldiketone analogues

In order to investigate the scope of our desymmetrisation process, the reaction was also attempted on the cyclohexadiene equivalents. However, from previous work within the group it was known that the cyclohexadiene equivalent **339** was a problematic coupling substrate in Suzuki couplings, presumably due to the acidity of

the protons in the methylene unit on the ring.[9] Therefore the two methylene protons in **339** were substituted with a geminal-dimethyl unit **308** (Figure 4.2).

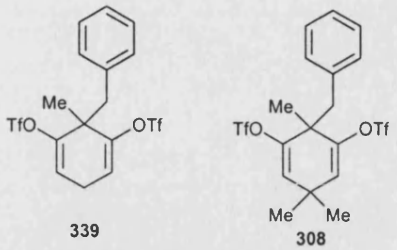
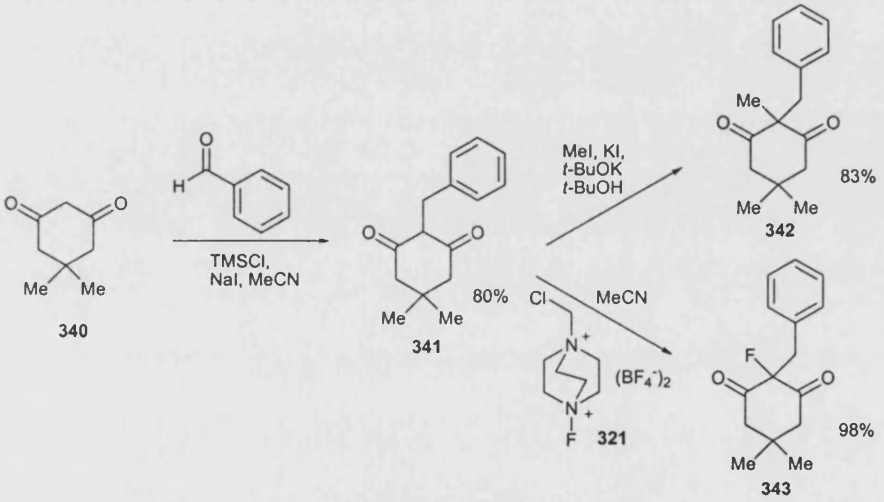


Figure 4.2

The benzylation conditions developed by Sakai *et al.* translated well onto this substrate, which was then methylated to generate the diketone **342** using methyl iodide, potassium iodide and potassium *t*-butoxide in *t*-butanol in good yield.[10] The benzylated product **341** was also fluorinated in excellent yield (Scheme 4.10).

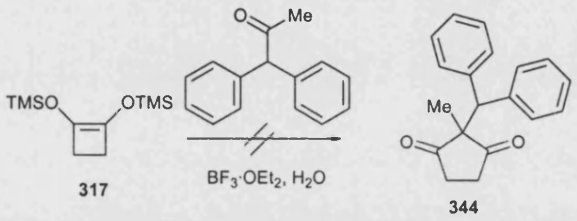


Scheme 4.10

It was reasoned that in the existing substrates that the benzyl substituents may orientate away from the face therefore limiting the steric influence on any approaching catalyst. Thus a final substrate was designed whereby the benzyl unit was swapped for a benzhydryl unit, in an attempt to further increase the difference between the two stereofaces. In this substrate even if the phenyl rings were orientated away from the ring face they should still be close enough to hinder the catalyst approach.

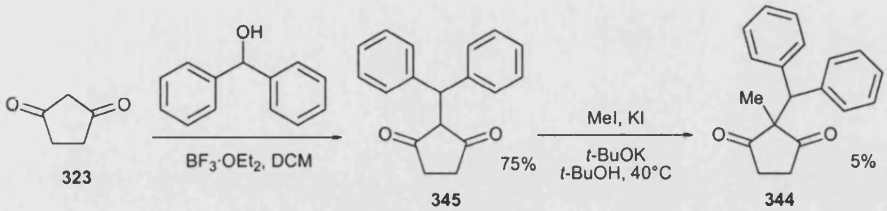
4.4 Synthesis of a benzhydryl substituted cyclopentanedione

Several methods were attempted to prepare the benzhydryl diketone **344**. Firstly, the method previously used to generate the phenyl and isopropyl substituted diketones **318** and **319** using 1,2-bis-((trimethylsilyl)oxy)cyclobutene **317** and 1,1-dipenylacetone was attempted. This method however, only yielded the ketone starting material (Scheme 4.11).



Scheme 4.11

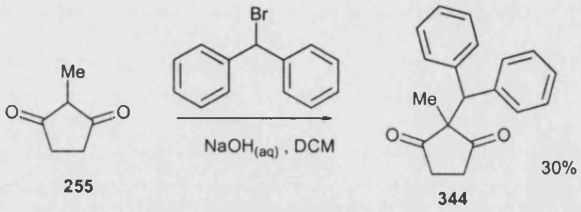
An alternative method was found in the literature showing that it was possible to add a benzhydryl unit to the activated methylene unit in pentane-2,4-dione in high yield using benzhydrol and boron trifluoride etherate.[11] This could be used on cyclopentane-1,3-dione **323** to yield the mono-substituted product **345** which could be subsequently methylated using the conditions used previously to yield the desired diketone **344**.



Scheme 4.12

Using this methodology the diketone was successfully benzhydrylated. However, attempts to methylate diketone **345** proved unsuccessful, yielding a mixture of unidentified products and only a small proportion of the desired product **344** (5%) (Scheme 4.12). A final method to generate the desired diketone **344** was carried out by using the 2-methylcyclopenatendione **255** with benzhydryl bromide in aqueous

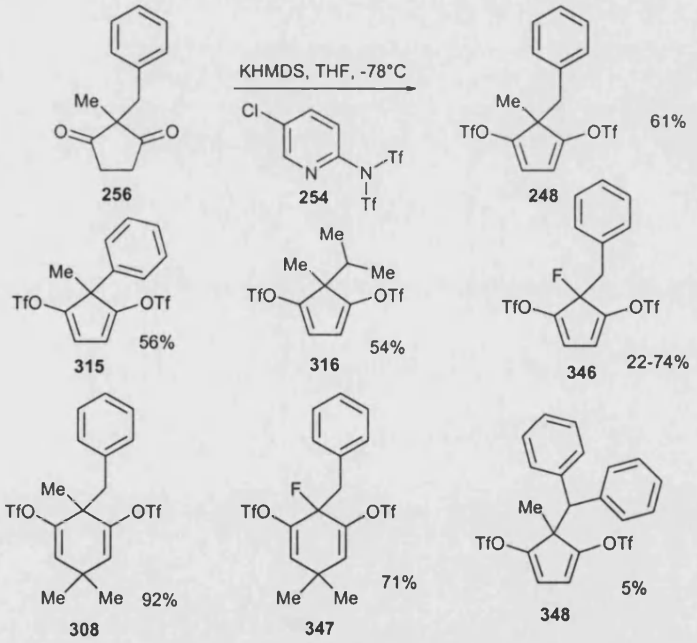
sodium hydroxide and DCM. However, this reaction required a prolonged reaction period of seven days and only yielded 30% diketone **344** (Scheme 4.13).



Scheme 4.13

4.5 Triflation of diketones

With a range of diketones in hand, the subsequent ditriflations were performed. We used the conditions which had previously been developed to successfully generate the original bis-triflate **248**, using chloropyridyltriflimide **254** with KHMDS in THF (Scheme 4.14).

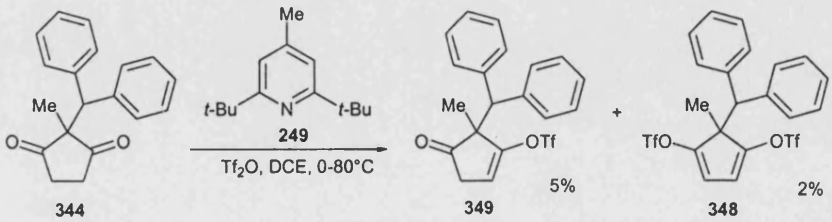


Scheme 4.14

These triflations gave good to excellent yields of the desired materials, except in the case of the benzhydryl diketone **344**. In this case, a complex mixture of unidentified products was formed, these proved difficult to purify *via* flash chromatography, with the product being inseparable from the excess triflimide **254**. The second

troublesome substrate was the fluorinated pentadione **338**, which worked well at the first attempt giving 74% of the desired product **346**, whilst on subsequent attempts yields only reached 22%. One possible explanation could be the presence of impurities of KOH in the KHMDS of the original reaction, although this was not experimentally verified.

A second attempt was made to create the benzhydryl bis-triflate **348** in a stepwise fashion by first generating the monotriflate **349** using triflic anhydride in conjunction with 2,6-di-*t*-butyl-4-methylpyridine **249** as the base in DCE (Scheme 4.15). From work carried out within the group this was known to work well for the generation of monotriflates from diketones.[12] The monotriflates could then be transformed into their corresponding bis-triflates using similar conditions as previously seen with the *N*-(5-chloro-2-pyridyl)triflimide **254** and KHMDS. However, when this was attempted on the benzhydryl diketone **344**, a mixture of rearrangement products were formed, with the monotriflate **349** and bis-triflate **348** being formed in a disappointing 5% and 2% yield respectively (from ^{1}H NMR estimations), neither of which could be separated from the rest of the reaction mixture, for full characterisation. This propensity for generating rearrangement products was thought to be due to the increased steric bulk involved favouring a less hindered conformation.



Scheme 4.15

4.6 Substrate screening

With these substrates in hand, investigation began into performing the Suzuki couplings. The conditions chosen were those which had proved successful in the racemic and enantioselective reactions described previously. It was decided to carry out these reactions using the boronic acid that had previously been the most successful. Hence, the (phenylsulfonyl)indoleboronic acid **282** was used despite the purification difficulties encountered previously (results can be seen in Table 4.1).

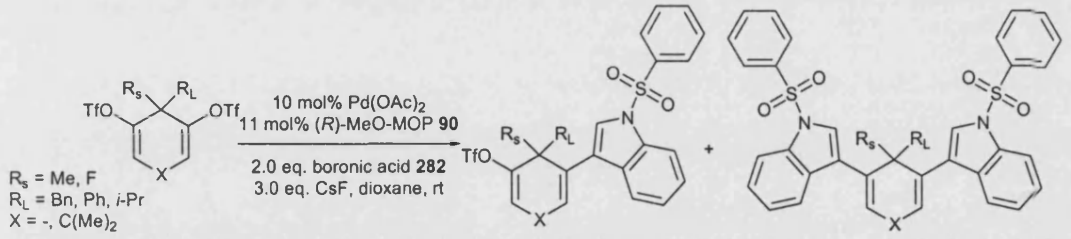


Table 4.1: Enantioselective reaction screening

Substrate	Reaction time (h)	Recovered starting material (%)	Monotriflate product (%)	ee (%)	Dicoupled product (%)
Me/Bn-**248**	8	8	66	85	12
Me/Ph-**315**	8	36	20	59	44
Me/*i*-Pr-**316**	8	12	33	58	50
F/Bn-**346**	8	23	14	45	61
6-Me/Bn-**308**	1	-	45	46	36
6-F/Bn-**347**	3	11	59[a]	16	32

[a] obtained a rearranged product as a 4:1 mixture of regioisomers

The results show that the enantioselective reaction conditions can be transferred to a range of bis-triflates. However, the selectivity has been reduced in all cases. The phenyl substituted substrate **315** produced the best enantioselectivity for the new substrates, with an ee of 59%. This shows that the concept is transferable, although the selectivity was not improved by increasing the steric difference between the substituents of the cyclopentadiene. The amount of dicoupled material and recovered starting material **315** was increased, showing that the second coupling reaction had become more favourable. The isopropyl substituted compound **316** showed high reactivity leaving relatively little recovered starting material **316**, and a better yield of the monocoupled material (33%). This substrate exhibited a good level of

enantioselectivity (58%), showing that a similar steric bulk is produced to that of the phenyl substituent in bis-triflate **315**. However, the amount of dicoupled material produced (50%) was even greater than that of the phenyl substituted bis-triflate **315**, showing that the second coupling reaction is increasingly favoured. This was also noticed in the fluorinated cyclopentyl derived bis-triflate **346**, which only yielded 14% monocoupled material, with the bulk of the material being converted to the dicoupled material (61%). This may be due to the major change in the electronic set-up of the molecule with the fluorine imposing its electronegativity upon the vinyltriflate functionalities. Enantioselectivity is still being achieved (45% ee) but to a lesser extent.

The reactivity of the cyclohexenyl substrates **308** and **347** was increased from that of the cyclopentenyl equivalents **248** and **346**, with significantly shorter reaction times required. The standard substrate **308** was consumed in less than an hour, however, this increased reactivity came with decreased enantioselectivity, with the faster reactions being less selective. Once again, a significant amount of the material was being converted to the dicoupled product. The lowering of enantioselectivity may be ascribed to the presence of the geminal dimethyl group imposing upon the stereofaces making catalyst approach more hindered.

This increase in reactivity was seen to a lesser extent in the fluorinated compound **347**. Upon inspection of the coupling product of the fluorinated bis-triflate **347**, it was noted that the signals corresponding to the diastereotopic benzylic protons lacked the characteristic coupling to fluorine. ^{19}F NMR analysis revealed the presence of a triflate functionality, and the absence of the expected C-F signal.

Accurate mass spectroscopy confirmed the loss of hydrogen fluoride from the mass of the expected product. 2D NMR analysis revealed the expected vinylic protons were absent, more revealing was a distinct nOe signal between one of the methyl substituents and the protons in the two and four position of the indole unit. The remaining methyl substituent lacked this interaction but displayed an nOe signal to an aromatic singlet (Figure 4.3, see spectra in appendix).

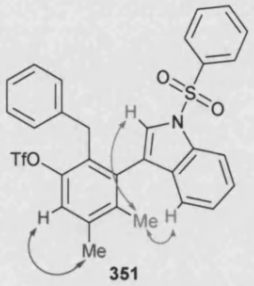
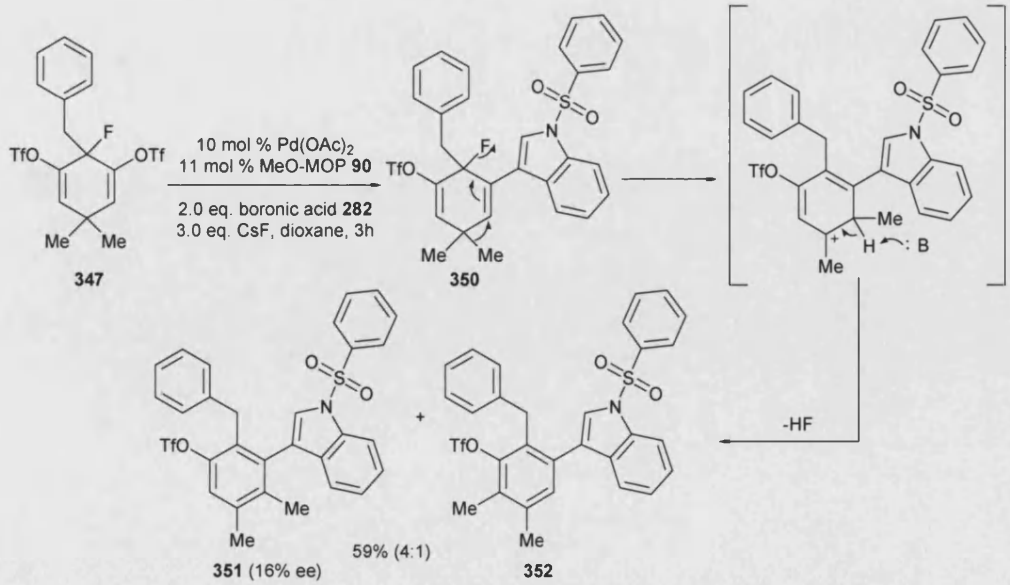


Figure 4.3

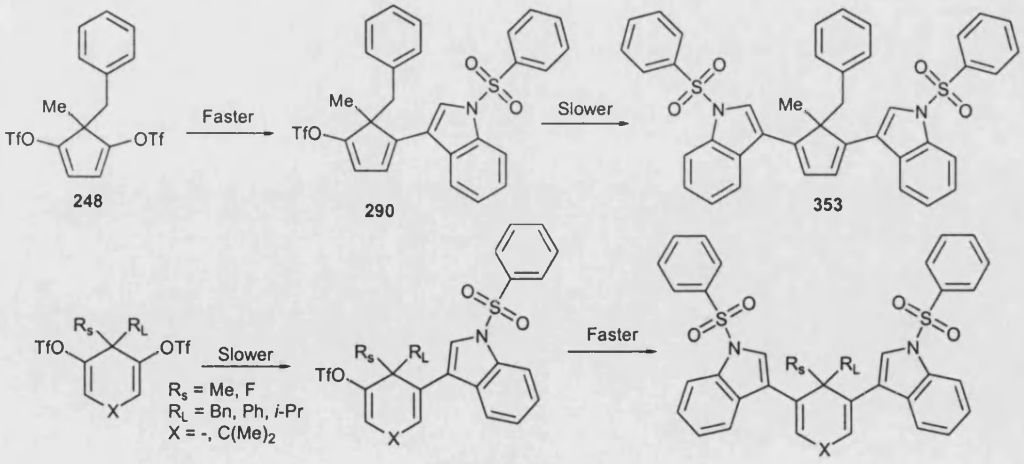
This information is consistent with the structure of triflate **351**, NMR data also suggests the presence of a small amount the regioisomer **352**, (ratio of products 4:1 **351**:**352**). The two regioisomers remained inseparable. Both of these structures could be generated by a methyl shift and elimination of fluoride from the coupled product **350**, followed by proton loss to generate an aromatic system (Scheme 4.16).



Scheme 4.16

This process generates a biaryl system which, in the case of triflate **351** contains two *ortho*-substituents on the phenyl ring restricting free rotation and generating axial chirality. This would help to explain the observed splitting of the diastereotopic benzylic protons seen in the ^{1}H NMR. The product was analysed by HPLC where distinct peaks were observed providing a 16% ee, however, the presence of both regioisomers in the sample hinders the accuracy of these measurements. A second product was also noticed in these reactions, this appeared to contain diastereotopic benzylic protons and two separate indole units, although purification was again difficult. It was assumed that this material was dicoupled material, which had also undergone this elimination and aromatisation.

The general trend observed was that the rate of the second coupling had increased and that the selectivity was reduced from the original system. This suggested that either changing the steric environment had been detrimental to the enantioselectivity or that changing the conformation has effected the electronic environments of the vinyltriflate functionalities, thus altering reactivity.



Scheme 4.17

In the original substrate **248**, after the initial coupling to form **290**, a subsequent coupling was a less favoured process than what is observed in the new substrates

(Scheme 4.17). This indicates that for these new compounds the triflate group in the coupled material seems to be more reactive than either of those present in the starting material.

4.6.1 Reduced reaction times

Due to the prevalence of dicoupled material in the reactions carried out with the new substrates, it was rationalised that the optimised reaction time for the original substrate was not ideal for the new substrates. The reactions were followed closely by TLC, this however, proved to be ineffective at quantifying the amount of dicoupled material being produced due to the presence of other by-products with similar R_f values. Therefore, reactions were run for a set period of time or until the starting material had either disappeared, or significantly reduced in quantity.

Thus reduced reaction times were attempted. At first, three hour reaction times were performed, however, these again yielded mainly dicoupled material. This was also observed when thirty minute reaction times were attempted as seen in Table 4.2.

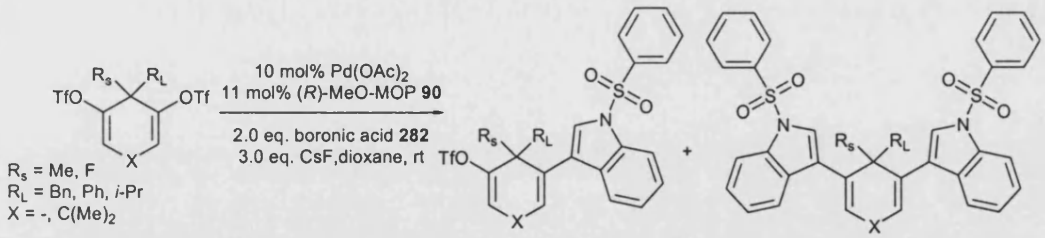


Table 4.2: Reduced Reaction Times

Substrate	Reaction time (h)	Recovered starting material (%)	Monotriflate Product (%)	ee (%)	Dicoupled Product (%)
Me/Bn-**248**	0.5	40	51	66	7
Me/Ph-**315**	0.5	55	16	50	29
Me/*i*-Pr-**316**	0.5	27	20	48	45
F/Bn-**346**	0.5	33	8	43	58
6-Me/Bn-**308**	0.5	20	33	22	29
6-F/Bn-**347**[a]	0.5	23	16[b]	15	22

[a] Reaction yielded several other unidentified products. [b] Monotriflate product yielded as a 4:1 mixture of regioisomers **351**:**352**.

As it can be seen this strategy was not successful and resulted in no improvement in the proportion of monocoupled material. In all cases, the majority of the isolated material was either starting material or dicoupled product. The exception was the original substrate **248** which delivered mainly monocoupled material **290** or recovered starting material **248**. Interestingly all of the reactions had progressed rapidly with a large proportion of the material already processed to coupled or dicoupled material suggesting that the rate of the reaction was fairly rapid at first and decreased as the catalyst progresses through successive turnovers.

This progressive decrease in reaction rate as the reaction proceeds seems to be linked to the enantioselectivity generated, with up to a 20% increase in ee when longer reaction periods were used. This supports the proposed kinetic resolution reasoning, showing that the initial reaction is more rapid and less selective. The selectivity is increased as the reaction progresses, whereby the favoured enantiomer is preferentially created whilst the opposite enantiomer is preferentially converted to the dicoupled material. This seemingly requires time to establish itself as the optimal system, when the reactive species become increasingly scarce.

4.6.2 Changing the coupling partner

The increased reaction rate observed could be affected by the reactivity of the coupling partner, as we had chosen the most reactive boronic acid for the original substrate. Therefore an alternative boronic acid was tested on the phenyl and isopropyl substrates. The boronic acid chosen was the meta-acetylphenyl boronic acid **275**, as this substrate had provided good reactivity with excellent enantioselectivity when using the original bis-triflate **248**.

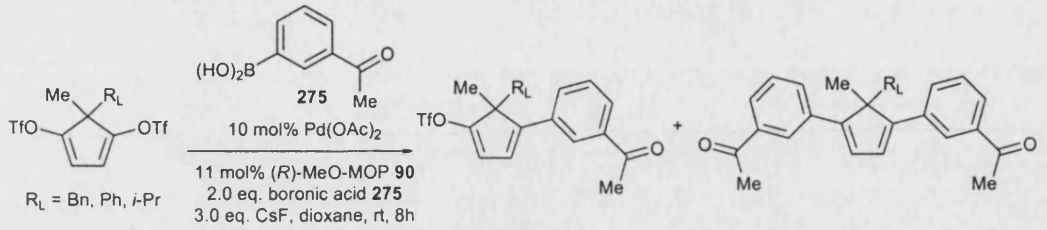


Table 4.3: Effect of changing boronic acid

Substrate	Recovered starting material (%)	Monotriflate product (%)	ee (%)	Dicoupled product (%)
Me/Bn-**248**	35	51	86	9
Me/Ph-**315**	17	16	61	51
Me/*i*-Pr-**316**	19	32	46	37

The results obtained were shown to be similar to those attained using the (phenylsulfonyl)indole boronic acid **282**. Very similar enantioselectivities and proportions of mono and dicoupled material were produced, although the yields were slightly lower using this less reactive boronic acid, mirroring the results shown previously. It appears that changing the coupling partner has little effect on the reaction (products shown in Figure 4.4).

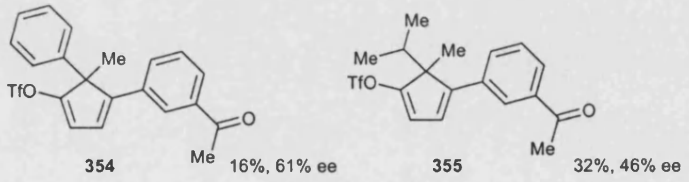
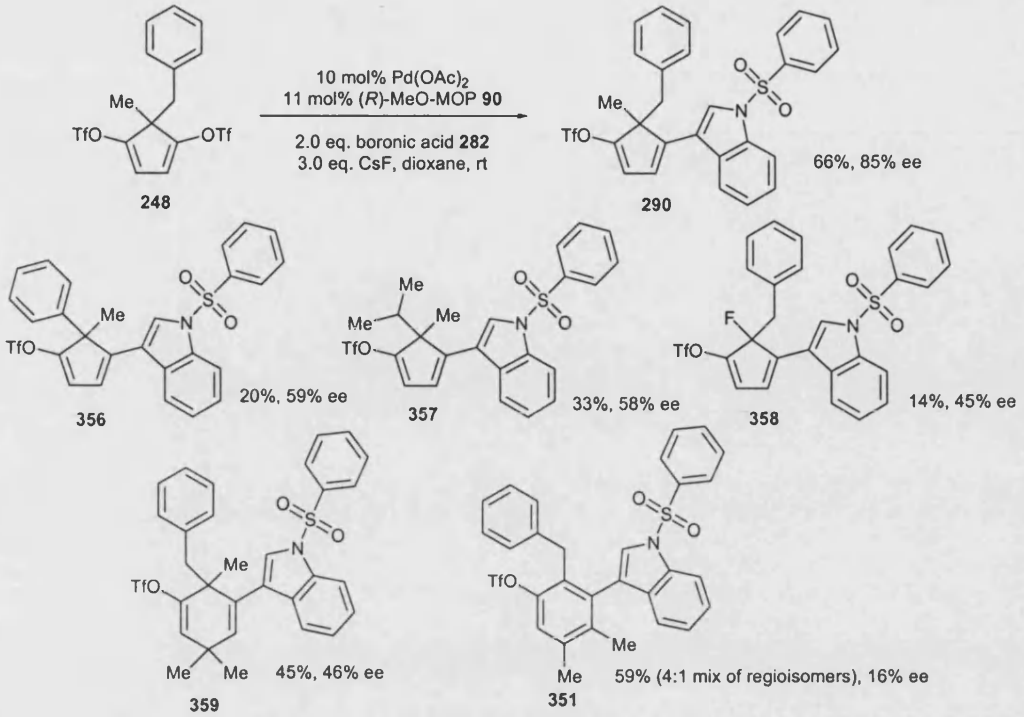


Figure 4.4

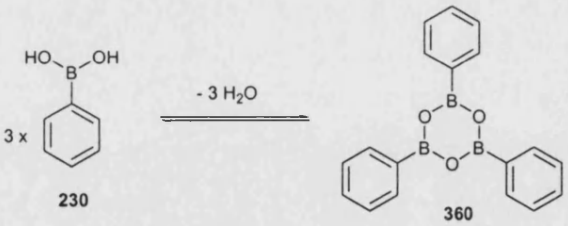
In summary the new substrates demonstrated moderate to good enantioselectivity but lower than those levels established on the original substrate **248** (Scheme 4.18). In addition, once the new substrates were arylated, the second triflate functionality became more activated to a second substitution when using this catalyst, and consequently a higher level of dicoupled material is observed.



Scheme 4.18

4.6.3 Boronic acid alternatives

The use of boronic acids as coupling partners is well-established and advantageous due to their stability, low toxicity, and tolerance of substituents. However, boronic acids contain an inherent level of a trimerised boroxine material **360** the formation of which releases water (Scheme 4.19).[13,14]



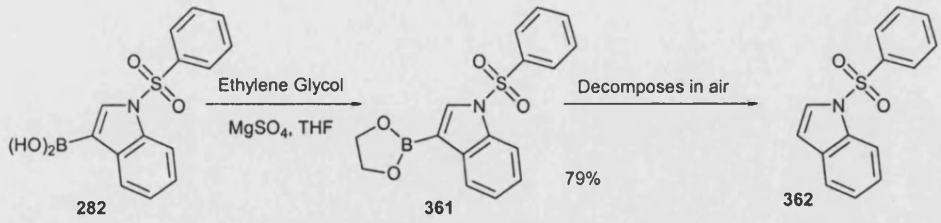
Scheme 4.19

Therefore, when a boronic acid is used a certain level of water is likely to be present. For Suzuki reactions this is often not a problem as most systems are tolerant to water, indeed, in some cases water may even be necessary to form a reactive borate species. However, in our enantioselective system for Suzuki couplings, an aqueous base was found to produce lower enantioselectivities. Consequently, the hygroscopic base

cesium fluoride was used as a suspension to good effect. In view of this, it was thought that it might be possible to increase the enantioselectivity of the reaction if an anhydrous equivalent of the boronic acid was employed.

One strategy to limit this trimerisation was to use a boronic ester as a coupling partner. Indeed, it had been noted by Baudoin, in his groups synthesis of axially chiral natural products using a Suzuki methodology, that the use of boronic esters improved both the yield and ee of the products generated (as discussed previously, Chapter 1 Table 1.5).[15]

Ethylene glycol was chosen as the diol to form the ester as this would form a five membered boracycle providing the boron more sp^3 character and consequently creating a more reactive species. This substrate **361** was easily generated from the boronic acid **282** by simply adding ethylene glycol in the presence of magnesium sulphate (Scheme 4.20). However, it showed poor stability, turning a brown colour upon exposure to air and showing appreciable amounts of a deboronated species **362** by ^{1}H NMR analysis.

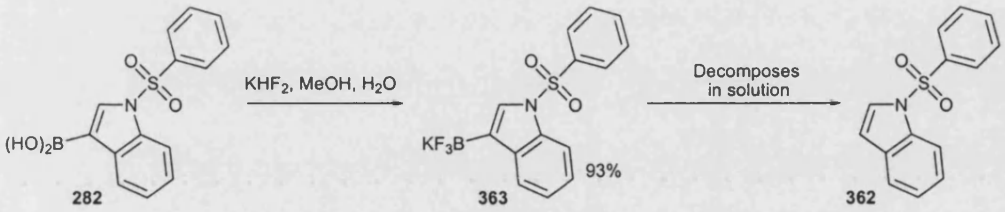


Scheme 4.20

A second strategy consisted of the use of an aryltrifluoroborate salt **363**, which have recently shown excellent reactivity as boronic acid equivalents in both rhodium and palladium catalysed processes.[16] These substrates have exhibited excellent stability and can potentially be generated in an anhydrous fashion. The aryltrifluoroborates

could be easily synthesised from their corresponding boronic acids using potassium hydrogen difluoride according to literature precedent.[17,18]

The conversion of the boronic acid **282** to the boronic salt **363** proceeded in excellent yield (Scheme 4.21). This boronate **363** appeared to be more air stable than the previous boronic ester **361**, however, it proved difficult to remove all traces of water. When a sample was analysed by ^{1}H NMR deboronation to form indole **362** slowly occurred resulting in a purple hue to the solution.

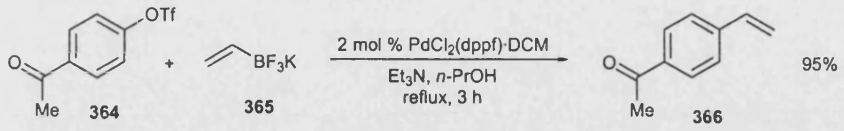


Scheme 4.21

Particular care was taken so as to ensure the purity of these boron reagents before they were then tested under the enantioselective Suzuki conditions. However, the potassium trifluoroborate **363** showed poor reactivity. It has been suggested that these types of salts could act as intermediates in Suzuki couplings when fluoride bases are used in conjunction with boronic acids (such as in our case),[19] however, this methodology proved unsuccessful for our substrate. Recent examples of aryltrifluoroborate salts failing to react in such a manner have also been noted in the literature.[20,21]

Examination of the established literature of these species found, that when used in palladium catalysed transformations, these aryl trifluoroborate salts often required water or simple alcohols in order for the reactions to proceed stating that the possible reactive species could be an aryl difluorohydroxyborate intermediate.[21-24] Therefore,

as we were developing anhydrous conditions, instead of water, propan-1-ol was used as a solvent and triethylamine as the base. Molander *et al.* had demonstrated these conditions showed good reactivity with triflate **364** (Scheme 4.22).[22,23]



Scheme 4.22

In a slight modification to their conditions the reaction temperature was maintained at room temperature to aid comparison with the original substrate. These conditions were then used to assess the reactivity of the trifluoroborate salt **363**

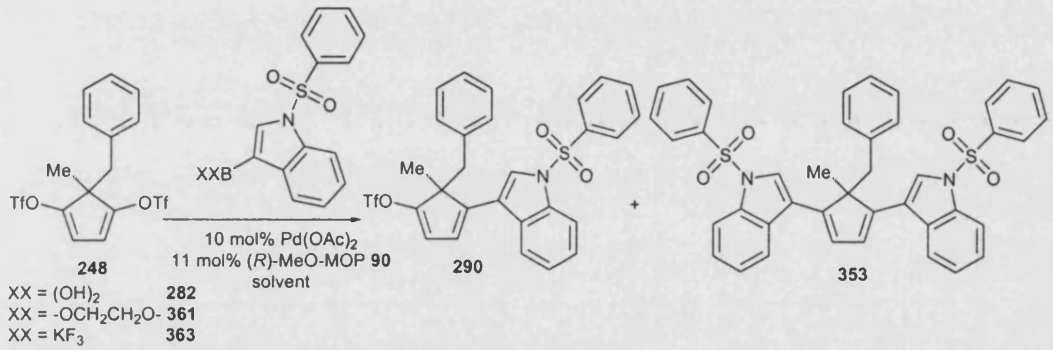


Table 4.4: Testing boronic acid equivalents

Boron reagent	Reaction time (h)	Recovered 248 (%)	Yield of 290 (%)	ee (%)	Yield of 353 (%)
Acid-**282**[a]	8	8	66	85	12
Ester-**361**[a]	8	10	60	66	22
Salt-**363**[a]	36	78	5		5
Salt-**363**[b]	8	68	22	62	9

[a] 10 mol % $Pd(OAc)_2$, 11 mol % MeO-MOP **90**, 3.0 eq. CsF, 2.0 eq. boron reagent, dioxane, rt.
[b] 10 mol % $Pd(OAc)_2$, 11 mol % MeO-MOP **90**, 1.0 eq. NEt_3, 2.0 eq. boron reagent, propan-1-ol, rt.

As shown in Table 4.4, the boronic ester **361** showed very similar reactivity to that of the boronic acid **282** yielding 60% of the desired product **290**, however, the ee induced was lower. This lowering of the enantioselectivity could be related to the lower stability of the boronic ester. The potassium trifluoroborate **363** showed poor reactivity even when using similar conditions to those described in the literature. The majority of the material recovered was starting material **248**, and the enantioselectivity was again lower than that of the boronic acid **282**. This lower

reactivity could be ascribed to the fact that a lower reaction temperature than that used in the literature was used, and that activation occurs upon heating. This could obviously be countered by heating the reaction, however, we were looking for mild reaction conditions and so it was decided to avoid this. Another possible explanation for this lowered reactivity could be that the catalytic system is simply not transferable to these coupling partners. This has been demonstrated by Fu *et al.* when using his versatile catalyst system in the coupling of aryl bromides.[20] In the course of their investigation, they attempted to couple an equivalent potassium aryltrifluoroborate, which failed to couple under conditions which had proven effective in a wide range of couplings.

In conclusion, this information seemed to suggest that the reaction conditions would need to be optimised further for the use of the potassium salt **363**. In the case of the boronic ester **361**, stability problems may have hindered its performance as a coupling partner. This may be improved through generating a more stable boronic ester using either a pinacol ester **367**, which are often stable to column chromatography.[25] Alternatively a propane-1,3-diol derived boronic ester **368** could be used, these have shown improved stability due to the wider boron bond angles involved in a six-membered boracycle, giving more sp^2 character(Figure 4.5).[26,27]

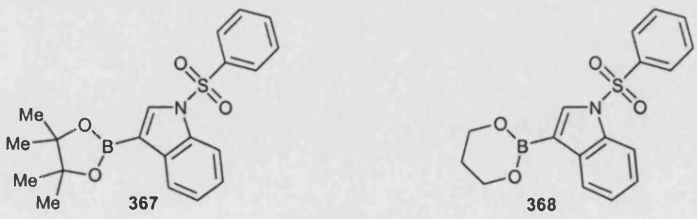
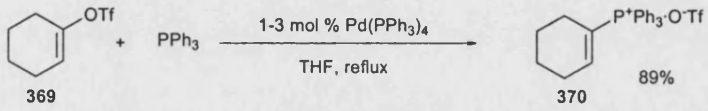


Figure 4.5

4.6.4 Effects on the reaction rate

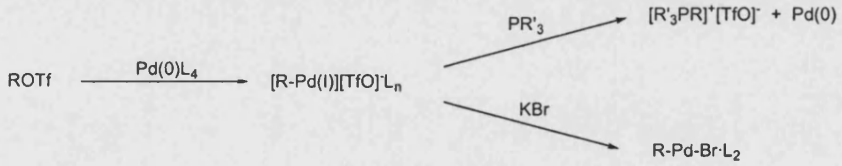
Other variables tested in the standard reaction included lowering the temperature in an attempt to slow the reaction down and thus, try to make it more selective. Indeed, the reaction proceeded slowly at -20°C, and even proceeded to a limited extent at -50°C. At this point the use of $Pd_2(dba)_3$ was also revisited for comparative purposes to investigate whether changing the palladium source could help generate a more active catalyst at lower temperatures.

Another aspect considered was the fact that it appeared our catalytic system was deteriorating with successive catalyst turnovers meaning little yield was gained from extended reaction periods, and that enantioselectivity was not improved when overnight reactions were tried. This suggested that a less selective reaction began to dominate, when the initial catalytic species expired. This could be due to the formation of phosphonium salts similar to salt **370**, formed by the reaction of the phosphine ligand with the triflate group (Scheme 4.23).[28]



Scheme 4.23

In this regard, the use of alkali metal halide additives had been shown to combat this process and extend the life of palladium catalysts in the coupling of triflates, promoting the reaction and preventing premature catalyst decomposition (Scheme 4.24).[29]



Scheme 4.24

These variables were then tested using the standard enantioselective coupling conditions. The results of these reactions have are summarised in Table 4.5.

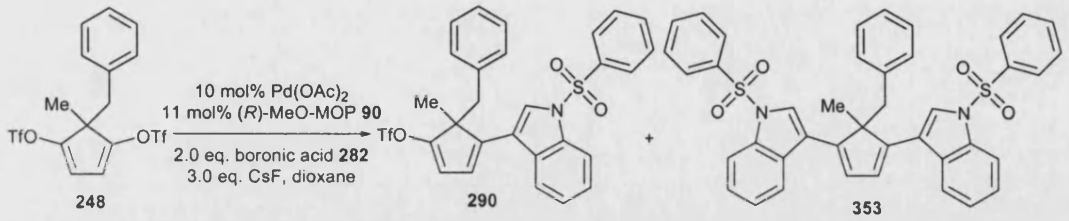


Table 4.5: Changing reaction temperature, Pd source and use of additives

Entry	Temperature (°C)	Reaction Time (h)	Recovered 248 (%)	Yield of 290 (%)	ee (%)	Yield of 353 (%)
1[a]	-50°C	30	75	15	81	7
2[a]	-20 °C	20	53	33	81	14
3[a]	-20 °C	8	71	24	75	2
4[b]	-20 °C	20	88	-	-	-
5[c]	rt	6	5	50	62	40

[a] 10 mol % $Pd(OAc)_2$, 11 mol % MeO-MOP **90**, 3.0 eq. CsF, 2.0 eq. **282**, THF. [b] 5 mol % $Pd_2(dba)_3$, 11 mol % MeO-MOP **90**, 3 eq. CsF, 2.0 eq. boronic acid **282**, THF. [c] 10 mol % $Pd(OAc)_2$, 11 mol % MeO-MOP **90**, 3.0 eq. CsF, 2.0 eq. boronic acid **282**, 1.1 eq. KBr, dioxane.

The results show that the reaction was slowed dramatically when cooled. After eight hours at -20°C, the main component observed was still the starting material **248** (71%), with very little dicoupled product **353** being isolated. This result indicated that the formation of the monotriflate product **290** was the most favoured reaction at this point. The enantioselectivity however, was shown to be slightly lower (75% ee) than the highest achieved on the original system (85% ee). When the reaction time was extended to 20 h the reaction progressed further yielding 33% of the monocoupled material **290** (compared to 24% after eight h) showing the catalyst to still be active, although the main component was still the bis-triflate starting material **248** (53%). The enantioselectivity had increased slightly (81% ee) with the extended reaction time but failed to improve on that of the established system. This increase in enantioselectivity when using extended reaction times provides further evidence for kinetic resolution occurring as discussed previously, albeit over an increased time period. It was found that the reaction will even proceed at -50°C to a limited degree. However, the enantioselectivity was not increased and the main component

recovered was the starting bis-triflate **248** (75%). It was felt that extending the reaction period further was not desirable. When $Pd_2(dba)_3$ was used as the palladium source at -20°C, the reaction failed to proceed.

The use of potassium bromide as an additive increased the rate of reaction, however, this resulted in generating more dicoupled product and lowering the enantioselectivity of the monocoupled material **290**. This could be used to help increase the rate of the cold reactions and thus generate more of the monocoupled material **290**. However, the increased rate of reaction may again decrease the enantioselectivity and this loss could negate any improvement gained from cooling the reaction.

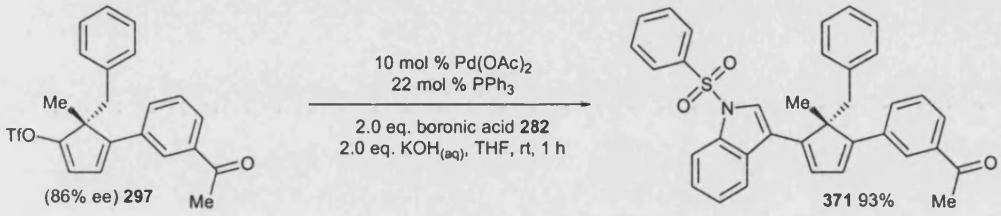
At this point, due to time constraints, further development and optimisation of these asymmetric Suzuki reactions on the bis-triflate substrates was halted. There is a clear need to further investigate how enantioselectivity is attained in these systems; it appears steric factors can only partially account for the levels achieved. One possibility is that in the original bis-triflate **248**, instead of the benzyl substituent hindering the catalyst approach to one face of the molecule, catalyst coordination could occur through π-stacking interactions on the phenyl ring, thus directing the catalyst into one face.

4.7 Derivatisations of monotriflates

The enantioselective generation of quaternary carbon centres remains a significant challenge;[30-32] The presence of such centres in the monocoupled products, together with the fact that they contain a synthetic handle in the remaining triflate group

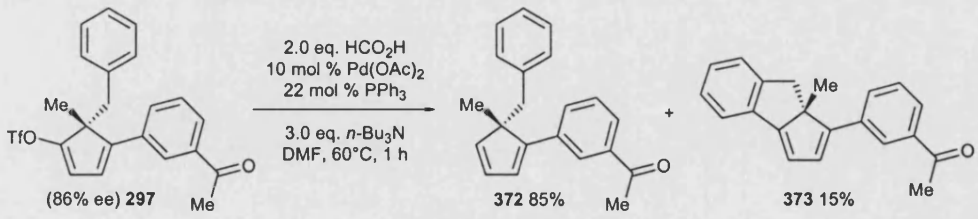
means that these compounds represent useful synthetic intermediates. To demonstrate their synthetic utility a series of palladium catalysed reactions were carried out. These reactions were initially tested using racemic material (**297**) and subsequently with the enantiomerically enriched material (**297**, with an 86% ee).

The first reaction carried out was a second Suzuki coupling using the phenylsulfonylindolyl boronic acid under the racemic conditions utilised previously. This was very successful yielding 93% of the desired product (**371**) in an hour at room temperature (Scheme 4.25).



Scheme 4.25

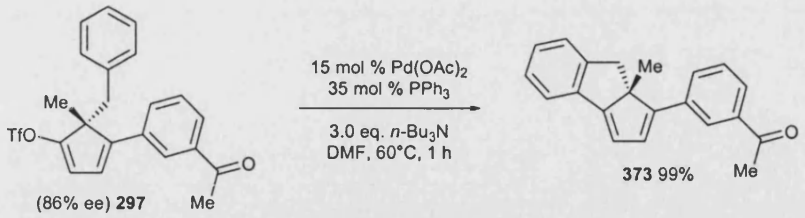
The second derivatisation was the palladium catalysed reduction of the monotriflate **297** to produce the alkene **372**. This was achieved in a 99% yield in the racemic material, however when applied to the enantiomerically enriched material 85% of the desired material was produced the remaining 15% of material isolated was cyclised material **373**, this could be due to the speed of addition of the formic acid to the reaction mixture (Scheme 4.26).



Scheme 4.26

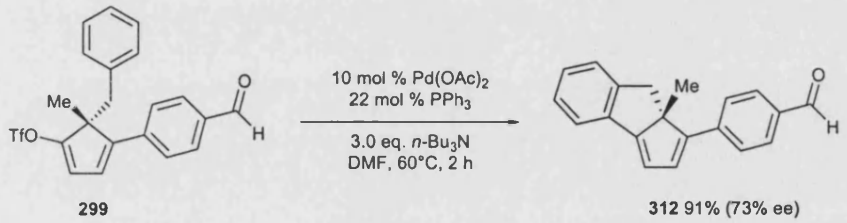
Finally, as cyclisation to form tricyclicdiene **373** occurred readily using the reduction conditions these were then transferred minus the formic acid reductant, into this

transformation. Pleasingly the reaction occurred quantitatively in under an hour, showing that this process is very favourable (Scheme 4.27).



Scheme 4.27

A slight modification of this process was utilised for the conversion of the unstable 4-formylphenyl substituted monotriflate **299** into the relatively more stable tricyclic diene **312**, in high yield (Scheme 4.28). Full spectroscopic analysis could then be obtained on tricyclic diene **312**, this was useful as the unstable monotriflate **299** had failed to provide adequate spectroscopic data.



Scheme 4.28

4.8 Conclusions

This work has shown that it is possible to perform enantioselective palladium catalysed cross-couplings on a variety of simple achiral vinyl triflates. It has been demonstrated that changing the boronic acids coupling partners has little influence on the enantioselectivity. However, changing the bis-triflate substrate had a more significant impact on the rate of reaction, affecting the yields and enantioselectivities achieved to varying degrees. The use of a fluorine substituted cyclohexyl derived bis-triflate (**347**) in these Suzuki couplings resulted in a rearrangement and aromatisation of the material, to generate a mixture of regiosiomers, one of which contained atropisomers in low ee.

It appears that simple steric factors can not account for the levels of enantioselectivity achieved, there remains the possibility of directing affects. Although changes in the electronic environment of the triflate functionalities are also important in governing the yields and enantioselectivity of the monotriflates produced. However, it is envisioned that these yields and enantioselectivities could be improved further with optimisation of reaction conditions.

In terms of investigating how enantioselectivity is being achieved there are several routes which could be investigated to enable further understanding of this asymmetric process. Firstly, by adding an electron withdrawing or donating groups onto the phenyl ring of the original substrate, any possible electronic interaction with the catalytic species would be affected and possibly tuned (**Figure 4.6**). Alternatively, if it is indeed steric factors which account for the enantioselectivity, replacement of the phenyl ring of the benzyl substituent for a similarly sized cyclohexyl substituent (**374**) should yield comparable levels of enantioselectivity. In this case there is no possibility for the catalyst to coordinate through π-interactions, thus providing an indication of any such directing affect in the original substrate.

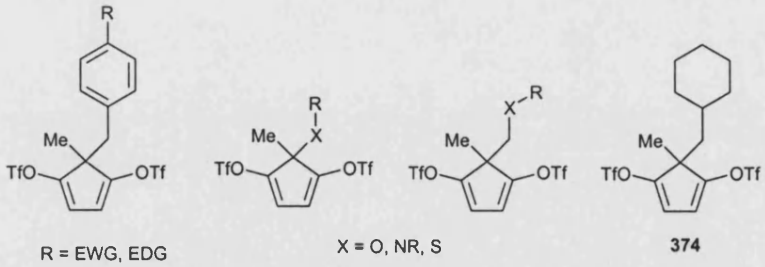


Figure 4.6

The main area for future development of this project will be to focus on improving the catalytic species through investigating both alternative classes of ligands and a second generation of hemi-labile binaphthyl ligands. Examples include the various

MAP and MOP ligands, and their derivatives, which have been shown to be effective in examples detailed in the introduction.

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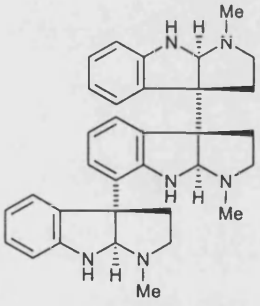
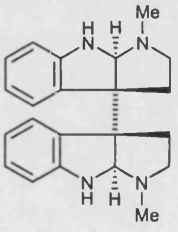
5 Towards the total synthesis of hodgkinsine

Hodgkinsine **375** is a member of a family of polypyrrolidinoindoline alkaloids (see examples depicted in Figure 5.1), which have demonstrated various forms of biological activity including antibiotic activity, human platelet aggregation inhibition, cytotoxicity and activity upon the central nervous system.[1-3] Hodgkinsine **375** was first isolated from the leaves of *Hodgkinsonia frutescens*, a shrub which grows in the coastal and tableland region of Queensland in Australia.[4] It is also found in the extracts of numerous members of the *Psychotria* genus,[5-10] including the plant *P. colorata*, which has been traditionally used in the Amazon region of Brazil as a remedy for pain.[11] Recently, hodgkinsine **375** has been shown to be a micromolecular agonist of the μ-opiod receptor and a potent dose-dependent analgesic against capsaicin-induced pain.[12]


hodgkinsine **375**


meso-chimonanthine **376**

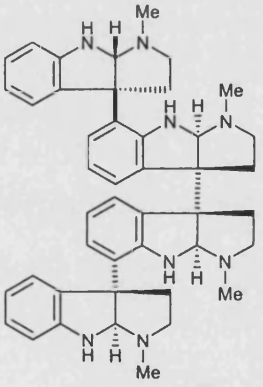
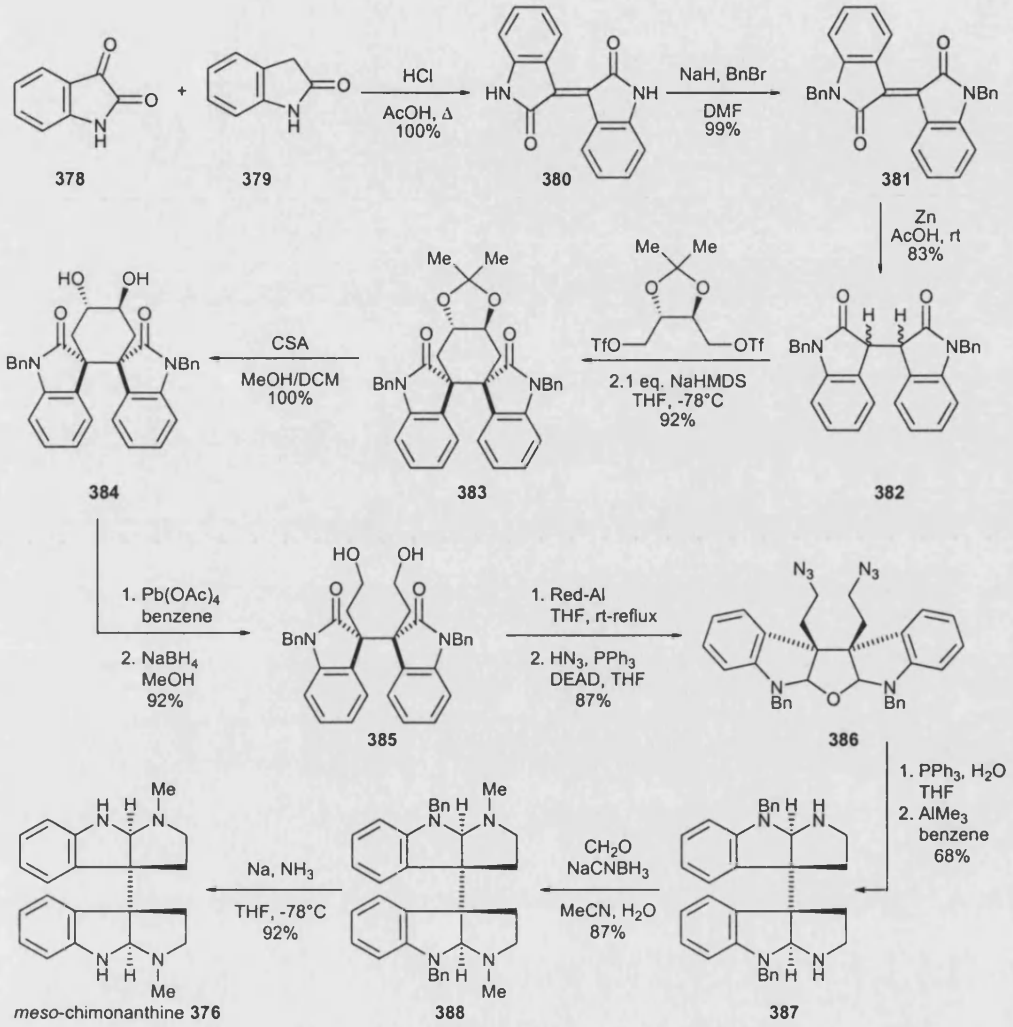

quadrigemine **377**

Figure 5.1

5.1 Overman's synthesis of *meso*-chimonanthine

Overman *et al.* have developed syntheses for several members of this family of polypyrrolidinoindoline alkaloids, including hodgkinsine **375**. All these syntheses involve the initial synthesis of the *meso*-chimonanthine **376** core structure, to which side chain are attached and subsequently elaborated into pyrrolidinoindoline units to

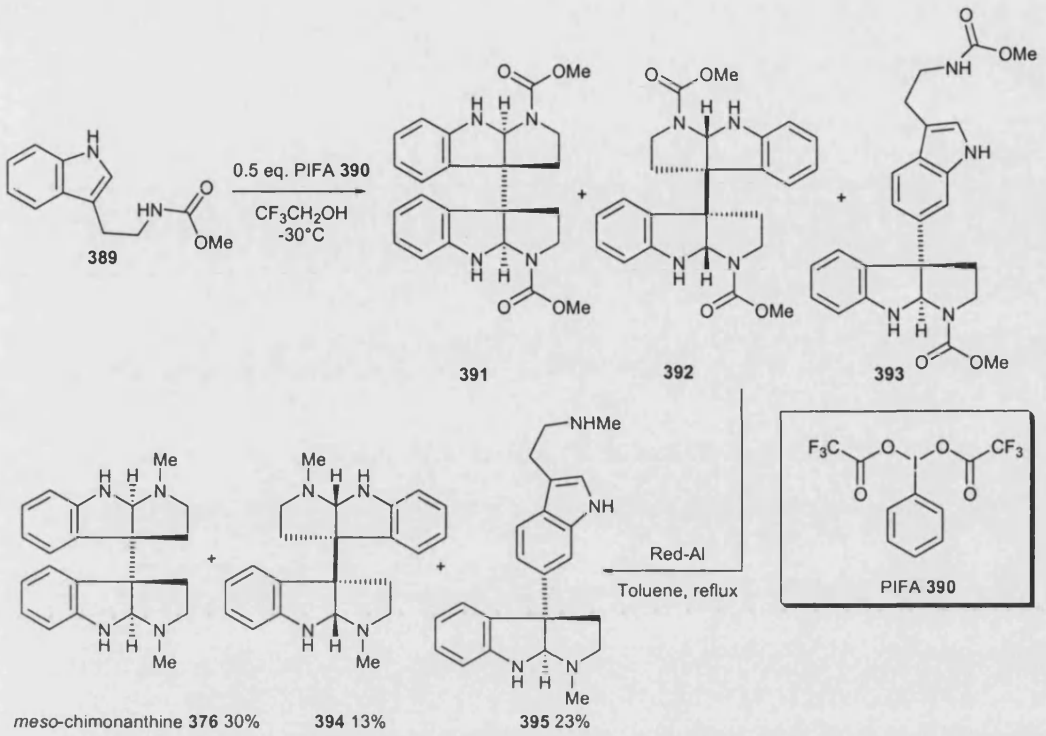
generate the desired compounds. The stereocontrolled synthesis of *meso*-chimonanthine **376** was achieved in a 35% overall yield over 13 steps (Scheme 5.1).[13]



Scheme 5.1

This approach employs extremely elegant tethering methodology to express stereocontrol, the core structure was then elaborated further through multiple high-yielding transformations to generate the desired *meso*-chimonanthine **376**. However, Takayama *et al.* have recently reported the synthesis of *meso*-chimonanthine **376** in a two-step stereorandom process from carbamate protected tryptamine **389** in 30% overall yield (Scheme 5.2).[14] This method employs the hypervalent iodine reagent

phenyliodine(III) bis(trifluoroacetate) (PIFA **390**) to cyclise and dimerise a simple tryptamine derivative.

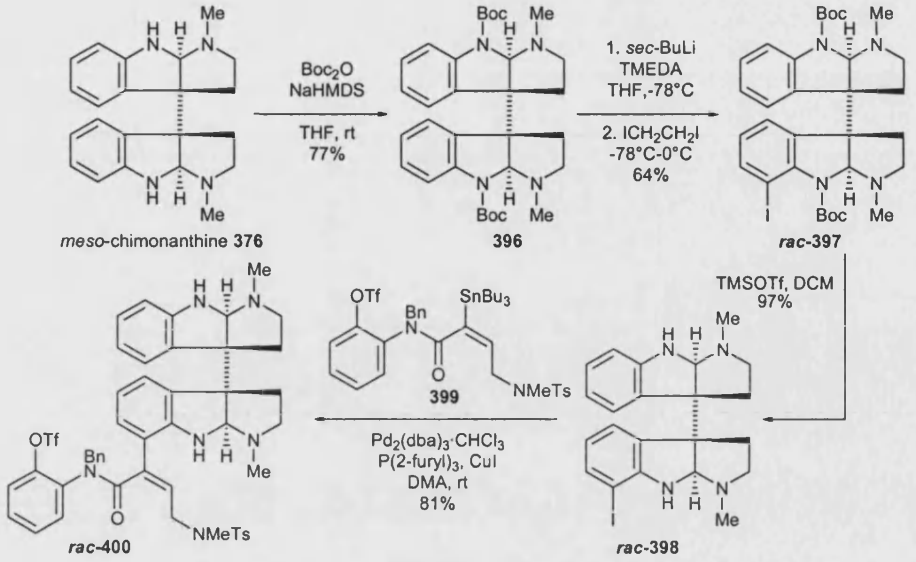


Scheme 5.2

Although the yield for the formation of *meso*-chimonanthine **376** was low, the ability of PIFA **390** to generate this unit in a single synthetic operation represents a very practical approach to the formation of such a complex structure.

5.2 Overman's synthesis of hodgkinsine

For their synthesis of hodgkinsine **375**, Overman *et al.* employed *meso*-chimonanthine **376** as their starting point and functionalised this further (see Scheme 5.3).[15] Firstly, *meso*-chimonanthine **376** was Boc-protected to yield pyrrolidinoindoline **396**. Pyrrolidinoindoline **396** was then desymmetrised by mono-*ortho*-lithiation and subsequent treatment with diiodoethane to form the *rac*-monoiodide **397**. *rac*-Monoiodide **397** was then deprotected and subjected to a Stille coupling with stannane **399** to give the heptacyclic triflate **400**.



Scheme 5.3

The racemic heptacyclic triflate **400** obtained from this coupling was then used in a stereocontrolled intramolecular Heck cyclisation as a means of resolution, affording the diastereomeric compounds **401** and **402**. A variety of ligands were screened for this reaction (shown in Table 5.1). Octacyclic oxindole **401** was the desired diastereoisomer for the synthesis of hodgkinsine **375**.

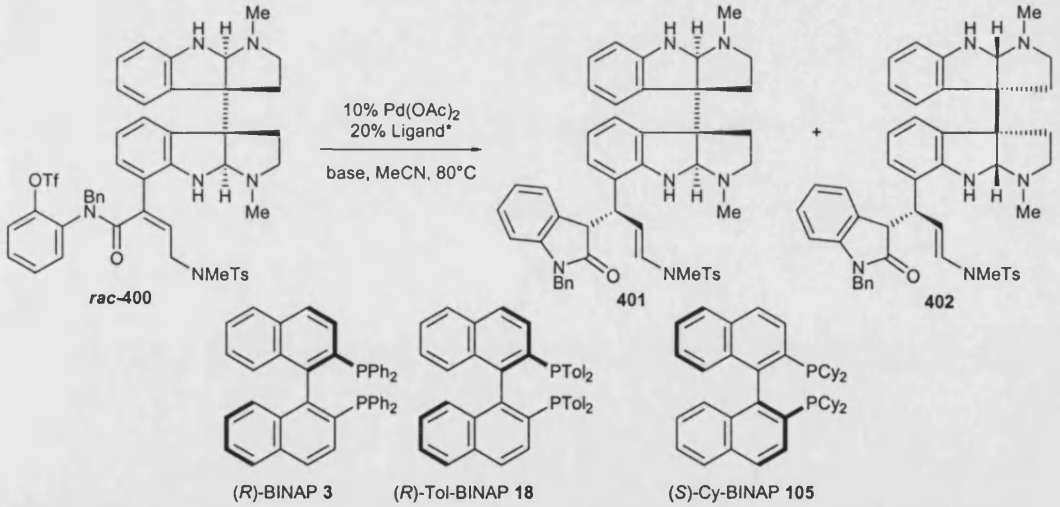
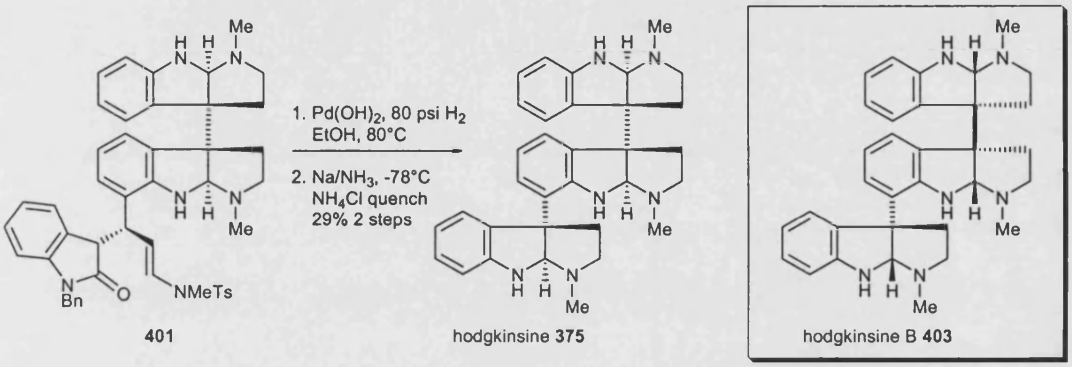


Table 5.1: Enantioselective intramolecular Heck reaction of triflate (*rac*)-400

Reaction	Ligand	Yield of 401 (%)	ee (%)	Yield of 402 (%)	ee (%)
1[a]	dppb	50	-	24	-
2[a]	(*R*)-BINAP **3**	40	68	38	69
3[a]	(R)-Tol-BINAP **18**	37	78	37	82
4[a]	(S)-Cy-BINAP **105**	7	11	6	6
5[b]	(R)-Tol-BINAP **18**	48	79	45	83

[a] Reaction carried out with 4.0 eq. proton sponge. [b] Reaction carried out with 4.0 eq. PMP.

Initially, the authors investigated the possibility of substrate-controlled diastereoselection. However, the use of achiral ligands such as dppb gave poor diastereocontrol (entry 1). The use of chiral binaphthyl ligands generated the desired products in high enantiomeric excess. It was also found that changing the base from proton sponge to PMP resulted in higher yields (entry 5).



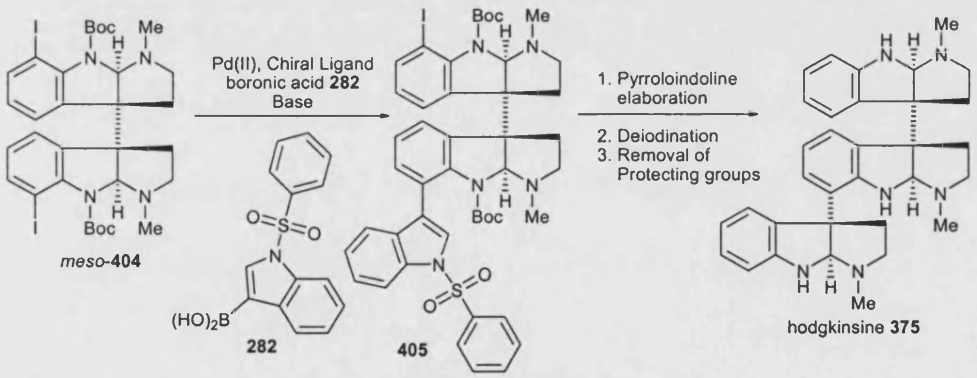
Scheme 5.4

The enamine moiety of the octacyclic oxindole **401** was then reduced, followed by a reductive deprotection-cyclisation in a low yielding two step procedure, to yield hodgkinsine **375** in a 1.5% overall yield with around 80% ee (Scheme 5.4). The other diastereoisomer, octacyclic oxindole **402**, was used for the formation of hodgkinsine B **403**.

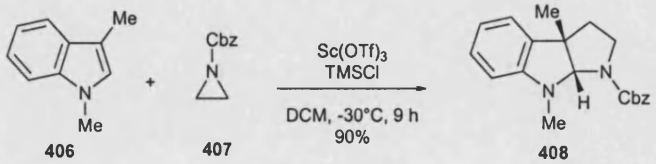
5.3 Desymmetrising *meso*-chimonanthine

In the synthesis reported by Overman *et al.*, the desymmetrisation of *meso*-chimonanthine **376** was carried out racemically to generate both enantiomers of the iodide **397**, and thus the products thereafter. A resolution strategy was then used to separate the stereoisomers by means of an intramolecular Heck reaction as diastereoisomers **401** and **402**. Using this strategy it was possible to generate both hodgkinsine **375** and its stereoisomer hodgkinsine B **403**. However, as this is a

resolution strategy the overall yield is limited to a maximum of 50%. It was envisaged that the use of our enantioselective desymmetrisation methodology could result in a more efficient procedure. The strategy to be used would consist of first creating *meso*-chimonanthine **376** which could be converted to *meso*-diiodide **404** using methodology developed by Overman. *meso*-Diiodide **404** could then be subjected to an enantioselective desymmetrisation using a chiral palladium catalyst, which would selectively insert into one of the two enantiotopic iodines in the oxidative addition step. Subsequently, this intermediate would be coupled with an indole unit. The pyrrolidinoindoline unit could then be generated using methods such as that developed by Nakagawa and Kawahara involving the addition of an aziridine unit to an indole followed by cyclisation (Scheme 5.6).[16] Subsequent deiodination and removal of protecting groups would provide hodgkinsine **375** in fewer steps and without the need to diverge half of the material.



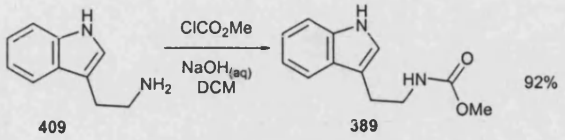
Scheme 5.5



Scheme 5.6

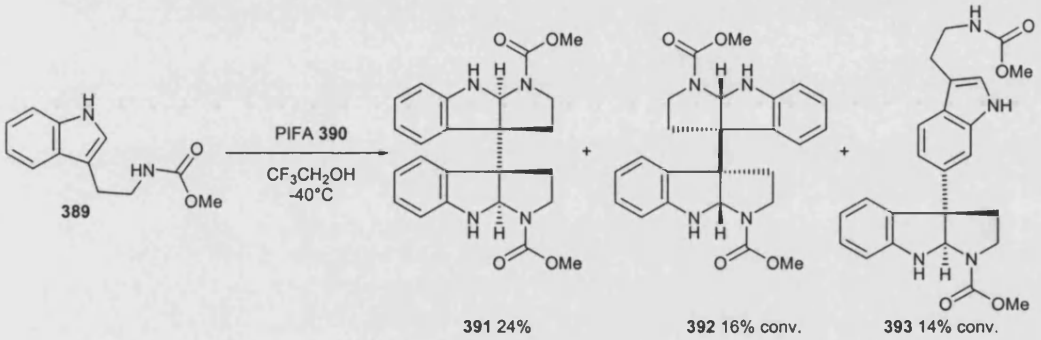
It was decided to generate *meso*-chimonanthine **376** using the hypervalent iodine chemistry developed by Takayama *et al*. This substrate would then be converted into *meso*-diiodide **404** using the transformations established by Overman *et al*.[17]

Our initial investigations focused on the hypervalent iodine dimerisation. For this purpose, carbomethoxytryptamine **389** was easily synthesised from tryptamine **409** and methyl chloroformate in good yield (92%) (Scheme 5.7). Carbomethoxytryptamine **389** could be readily recrystallised from diethyl ether.



Scheme 5.7

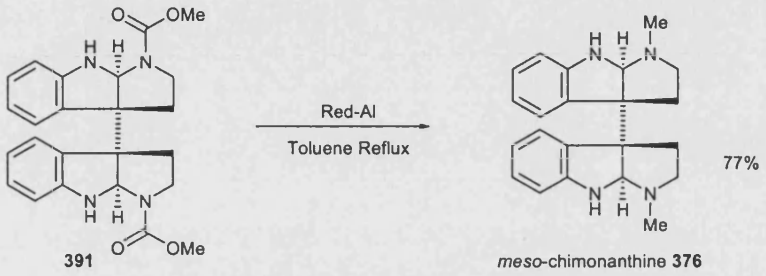
Carbomethoxytryptamine **389** was then dimerised by adaptation of a procedure developed by Takayama *et al.* using PIFA **390** (Scheme 5.8).[18]



Scheme 5.8

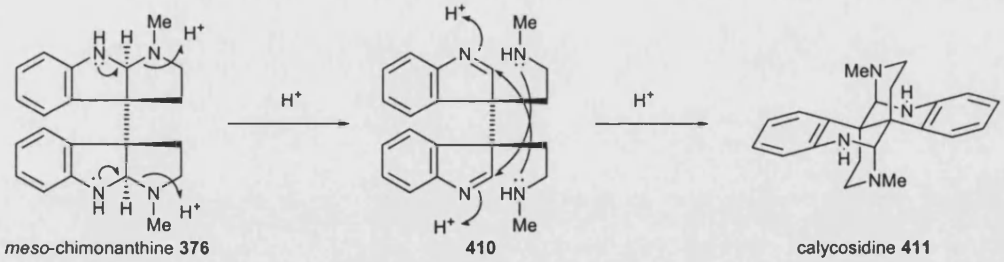
It was found that in order to drive the reaction to completion, the reaction time needed to be extended from the reported 8 hours to 20 hours, and an extra 25 mol % of PIFA **390** added after 16 hours. This reaction yielded several unidentified products, which were difficult to separate *via* flash chromatography. The diastereomeric compounds **391** and **392**, as well as the dimer **393**, also failed to separate appreciably. However, it was found that the *meso*-dimer **391** had a greater tendency to crystallise out of solution than either the C_2-isomer **392** or the dimer **393**. This fact was exploited to crystallise the desired *meso*-isomer **391** from chloroform and ethyl acetate in a 24% yield.

In their report, Takayama *et al.* stated that they took the dimerisation mixture through the subsequent reduction to yield both diastereomers of chimonanthine (**376** and **394**) and the other dimer (**395**) (Scheme 5.2). However, **376**, **394** and **395** proved more difficult to separate than their carbamate equivalents **391**, **392** and **393**, consequently, purification was realised before the reduction step.



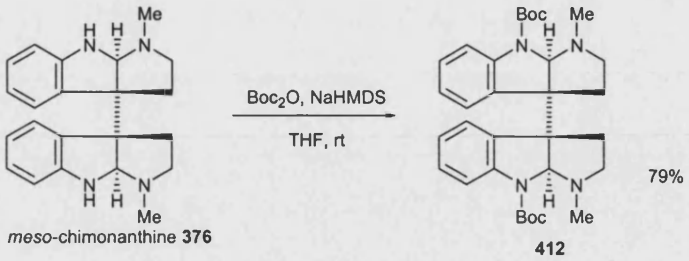
Scheme 5.9

The reduction proceeded smoothly to yield the natural product *meso*-chimonanthine **376** in 77% yield, which seemed to be light sensitive, with the compound turning from a cream colour to a light orange/yellow colour when kept out on the bench. This could be a result of the oxidation of the amine substituents, alternatively, it was also known that this substrate was susceptible to acid catalysed rearrangement to yield the resultant natural product calycosidine **411** (Scheme 5.10).[19]



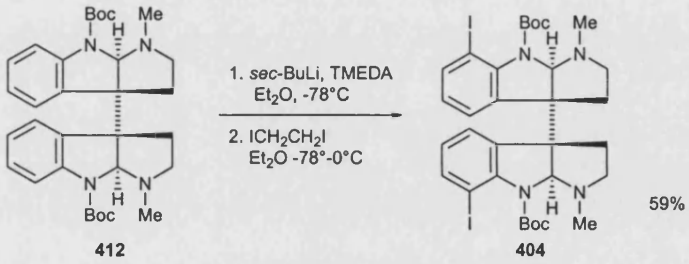
Scheme 5.10

The Boc-protection detailed by Overman *et al.* was first attempted on the crude reduced material, however, the presence of unknown by-products made purification difficult. Thus chimonanthine **376** was purified and then protected (Scheme 5.11)



Scheme 5.11

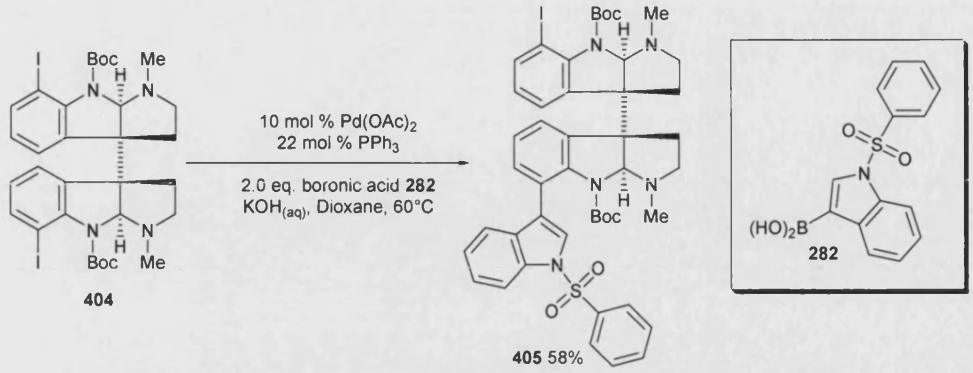
When pure material was used the reaction proceeded in good yield (79%) with a small amount of what was thought to be mono-Boc protected material being present, although this could be not isolated cleanly. The di-Boc-protected compound **412** was subsequently *ortho*-lithiated using five equivalents of *sec*-butyl lithium, which was then treated with diiodoethane to furnish diiodide **404** in good yield (59%) (Scheme 5.12).



Scheme 5.12

With *meso*-diiodide **404** in hand, the desymmetrisation was then attempted using the standard racemic conditions which had previously been successfully used on the bis-triflate substrates. The initial trial reaction using these conditions was carried out on a small scale (~40 mg diiodide **404**), and isolation *via* flash chromatography, yielded mainly recovered starting material, which co-eluted with a small amount of unidentified desymmetrised product. It had been shown by work carried out previously within the group that when iodides were used in Suzuki couplings heating of the reaction to 60°C was also required for the reaction to proceed.[20] Thus, the reaction was scaled up and repeated at 60°C. This accelerated the progress of the

reaction, and although purification was difficult, the product was generated in a 58% yield.



Scheme 5.13

^{1}H NMR spectroscopic analysis revealed that desymmetrisation of the diiodide **404** had occurred, as indicated by the resonances corresponding to the protons in the aminal positions, which were inequivalent (δ_H 4.90-4.80 and δ_H 4.70 ppm Figure 5.2). This inequivalency was also observed when comparing monoiodide **397** and diiodide **404** as reported by Overman.

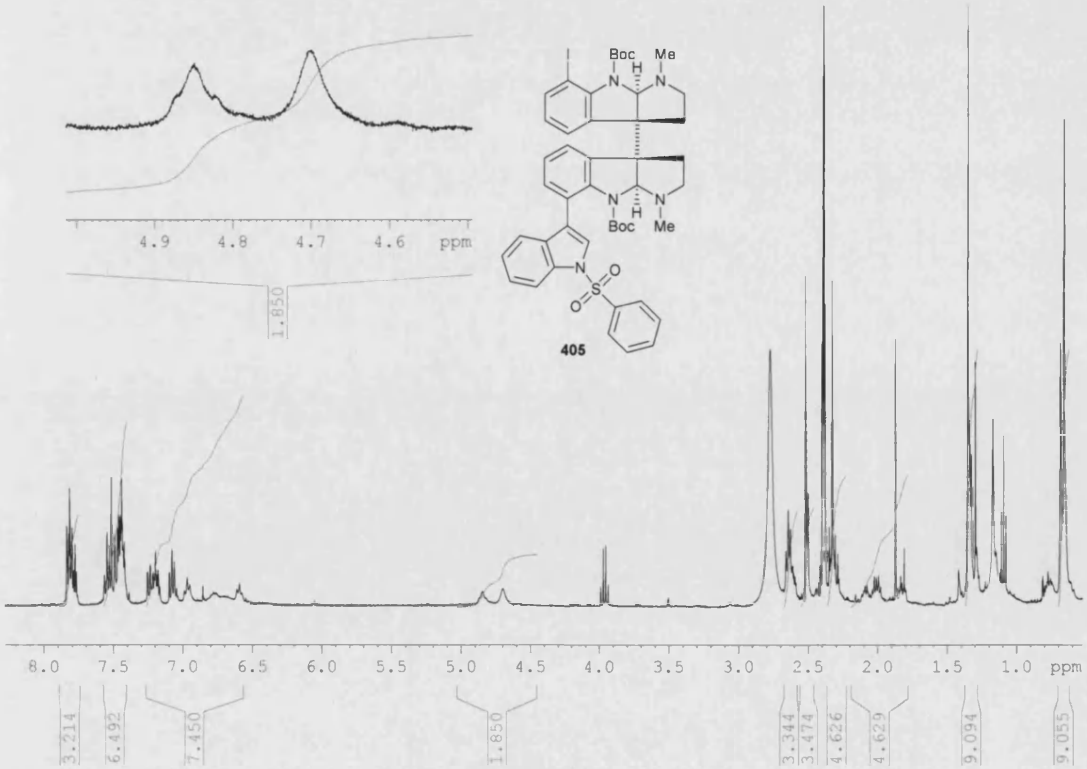


Figure 5.2

Further analysis of the ^{1}H NMR data showed that the region corresponding to the aromatic protons was much more complex than that seen in either monoiodide **397** or diiodide **404**. When examining the integration of this region it was found to correspond to 16 protons, in accordance with number of protons in the predicted product monoiodide **405**. A resonance at δ_H 1.35 ppm integrating to nine protons was in accordance with corresponding to a single Boc-group. Another resonance integrating to nine protons appeared at δ_H 0.67 ppm, which seemed fairly highfield to correspond to the second Boc-group. However, when simple computational energy minimisation models were carried out using MM2 modelling of the structure for monoiodide **405**, these showed that the Boc-group on the more congested pyrrolidinoindoline ring system positioned itself above the planes of the indole and phenyl sulfonyl substituents (Figure 5.3). This could account for the observed shielding of this group in ^{1}H NMR analysis.

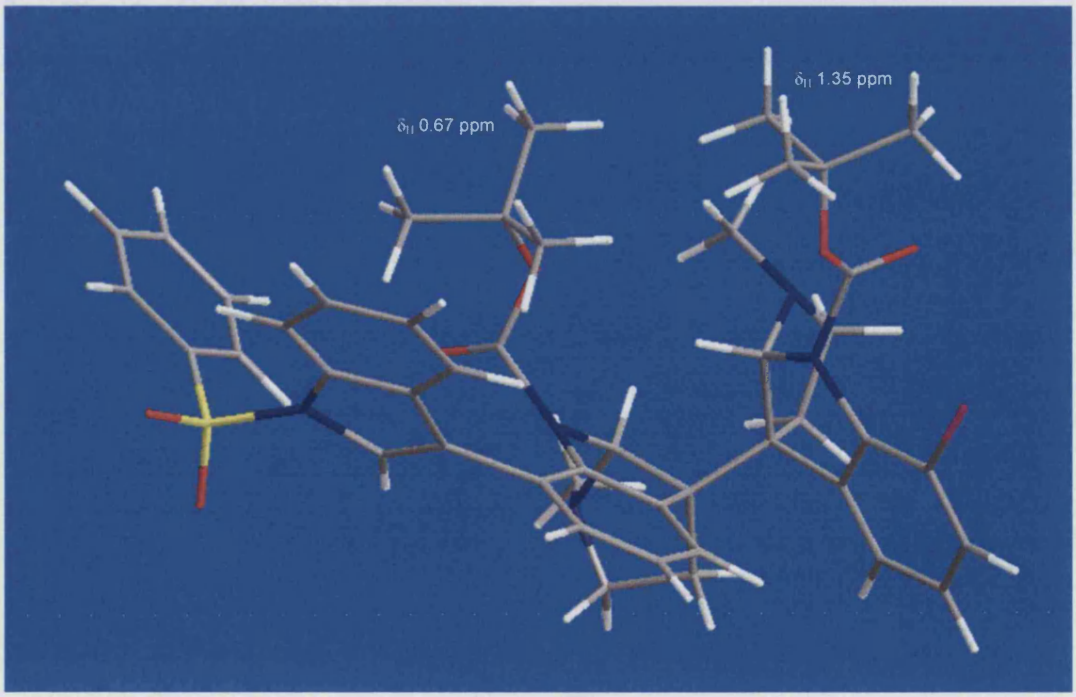
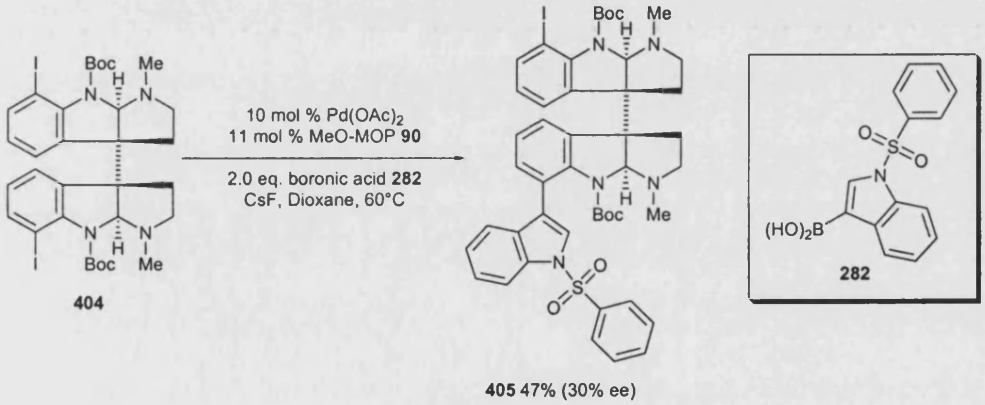


Figure 5.3

Further evidence for the formation of monoiodide **405** was provided by confirmation of the exact mass ion through high resolution mass spectrometry.

No dicoupled material was observed, although these Suzuki reactions also generate many other by-products. Indeed, if no dicoupled material was produced, this might be a result of the extra steric bulk of the phenylsulfonyl indole forcing the Boc groups to sterically shield the remaining iodide functionality, thus hindering catalyst approach to this position. If this is the case then this could aid the yields attained in this process as there is no destruction of the product.

The diiodide **404** was then subjected to the enantioselective Suzuki procedure using the established conditions for the bis-triflate substrates, with the temperature again raised to 60°C.



Scheme 5.14

This reaction mixture was again difficult to purify, with the product and starting material co-eluting. However, the desired product **405** was successfully generated in a 47% yield, with a 30% ee.

5.4 Conclusions

This shows that using an enantioselective desymmetrisation strategy it is possible to effect the generation of this key intermediate. From this point it should be possible to expand the indole group to the pyrrolidinoindoline unit on iodide **405**, for which

there has been literature precedent. Then deiodination and deprotection would afford hodgkinsine **375**. This result also shows that the methodology developed is transferable between radically different substrates; the bis-triflates in which enantiotopic discrimination occurs between the two vinyl triflate functionalities three bonds apart and the aromatic diiodides, in which the reactive enantiotopic groups are eight bonds apart.

Thus, although it has been proved that our developed methodology can be used for the preparation of the key compound **405**, this methodology needs further optimisation in order to improve both the yield and the enantioselectivity of the reaction. With this aim, different chiral ligands and coupling partners, such as a boronic acid containing a protecting group on the indole, which could be easily removed along with the Boc-protecting groups already present, are currently being investigated within the Willis research group. This would help to minimise the number of reaction steps. The use of triflates or bromides is also envisaged for comparison with the reactivity of diiodide **404** to provide information on the ideal substrate and generality of this coupling methodology.

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6 Conclusions and Future work

6.1 Conclusions

The project presented in this thesis has produced some very encouraging results, developing asymmetric Suzuki methodology to generate stereodefined quaternary carbon centres. Firstly, using an enantioselective desymmetrisation strategy, which utilises a chiral palladium species, a range of bis-triflate substrates have undergone asymmetric Suzuki couplings. This has been shown to generate useful monotriflate products in yields of up to 66%, and enantiopurities of up to 86% ee. This methodology has been shown to work well for a wide variety of boronic acids, particularly those containing polar functionality. It has also been demonstrated that the enantioenriched monotriflate products formed can be easily derivatised using palladium catalysis, furnishing chiral products of increased complexity in excellent yields. Furthermore, the methodology developed also translated onto the desymmetrisation of the highly complex intermediate diiodide **404** as the key step for the proposed total synthesis of hodgkinsine **375**.

The investigation into the use of bulkier substituents on the ring system to increase enantiotopic discrimination, indicated that other factors are involved in achieving enantioselection. Further investigation is needed in this context in order to determine the factors governing enantioselection. Substrate variations are currently being investigated within the Willis research group.

From the analysis of the results presented it can be concluded that the enantioselectivity did not vary greatly when using different boronic acids, although

there was a slight drop observed with the presence of certain functional groups. This suggests that the enantioselective process is the oxidative addition of the palladium catalyst. Therefore, it should be possible to accomplish other asymmetric palladium catalysed transformations using this desymmetrisation strategy. Thus if developed further this strategy could become a valuable tool for the use of palladium catalysis in asymmetric synthesis.

6.2 Future work

The project has concentrated upon commercially available ligands, showing that using the ligand MeO-MOP **90** enantioselectivities of up to 86% ee are achievable in good yield. Thus the primary aim is to improve these levels further, focusing upon the investigation of alternative ligands, particularly those which display hemilabile characteristics. There are notable analogues of MeO-MOP **90** to be investigated;[1-3] including replacing the methoxy substituent for other ether groups to create MOP derivatives; replacement of the methoxy group for substituted amines to create the MAP derivatives; the use of other substituted weakly coordinating heteroatoms (such as S) to generate further analogues. Also as Baudoin *et al.* demonstrated in their enantioselective Suzuki studies, variation of the phosphine substituents to generate the ideal cone angle and electronic set up can have a great impact on yield and enantioselectivity.[4] *P*-Chirogenic analogues of these are also known and provide the possibility of two different types of asymmetric induction.[5,6] Other ligands of interest are the various ferrocenyl derived ligands and the phosphoramidites (Figure 6.1). Although many of these ligands are not commercially available, they are known in the literature and possess powerful synthetic potential.

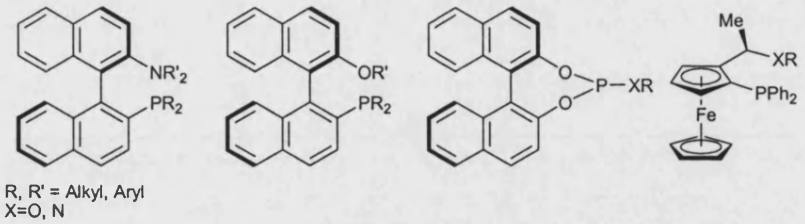


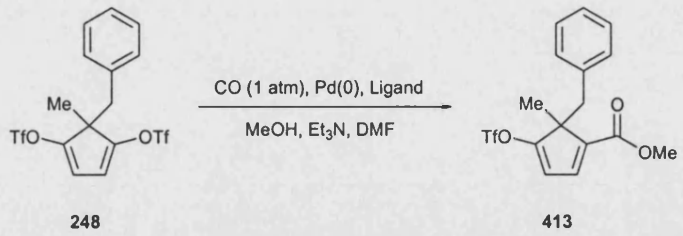
Figure 6.1

Investigation into the mechanism of enantioselectivity should also be examined, to see if the selectivity obtained in the original system was due to π-stacking interactions directing the catalyst into one face of the substrate. By adding varied electron withdrawing and donating groups onto the phenyl ring, any possible electronic interaction with the catalytic species could be affected and possibly tuned. This investigation would help to increase our understanding of the system and to aid the development a model for the mode of enantioselection.

Finally, future work should involve transferring this chemistry onto a wider range of substrates including halide equivalents to compare the reactivity. It has been shown that a wide variety of functional groups are tolerated on the coupling partners, therefore, they should also be permitted in the substrate. Furthermore as it appears that enantioselectivity is attained by the oxidative addition of the catalyst into one of the triflate groups alternative palladium coupling reactions can be investigated to apply this concept to a wider range of transformations.

There are various other palladium catalysed reactions which could be attempted, including aminations and *O*-arylations, which have been developed on achiral systems within the group.[7,8] Also of interest are palladium catalysed reductions and the further development of the C-H activation process with a view with to

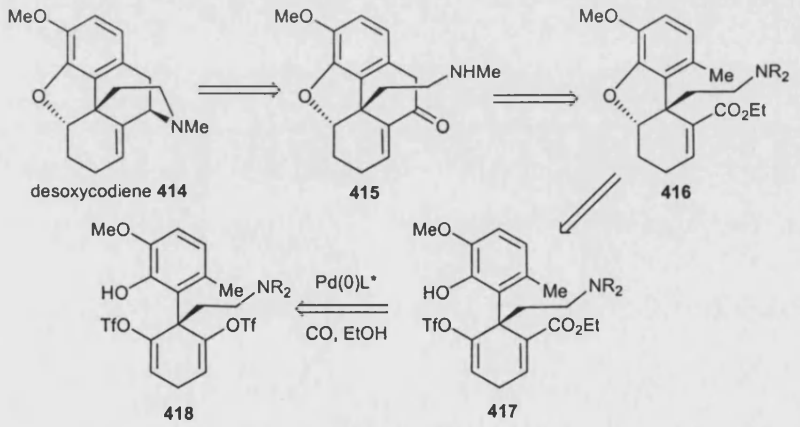
development in this desymmetrisations process. One of the most interesting reactions to develop is the carbonylation of bis-triflate **248** to create ester **413** (Scheme 6.1).



248 413

Scheme 6.1

It is envisaged that this methodology could be utilised as the key step for the natural product synthesis of desoxycodiene **414**, starting from a symmetrical bis-triflate **418** (Figure 6.2). This retrosynthesis provides a highly concise route to the codeine core structure. This strategy could be used for the synthesis of various natural products or drugs.



desoxycodiene **414** **415** **416**

418 **417**

Figure 6.2

References

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Experimental

7.1 General Experimental

7.1.1 Apparatus

^{19}F NMR spectra were recorded on a Bruker Avance 400 spectrometer (at 376.5 MHz). ^{11}B NMR spectra were recorded on a Bruker Avance AC-300 spectrometer (at 96.3 MHz). ^{1}H and ^{13}C NMR spectra were recorded on either a Bruker Avance 400 spectrometer (at 400.1 and 100.6 MHz respectively), a Bruker Avance AC-300 spectrometer (at 300.2, 75.5 MHz respectively) or a Bruker AV400 spectrometer (at 400.1 and 100.6 MHz respectively) in $CDCl_3$, CD_3OD, C_6D_6, $(CD_3)_2CO$, $(CD_3)_2SO$ or CD_2Cl_2, using tetramethylsilane (TMS) (δ_H 0 ppm) and/or the residual solvent signal as internal standards, CCl_3F as an external standard for ^{19}F NMR and boron trifluoride etherate as external standard for ^{11}B NMR. Chemical shifts (δ) are given in parts per million and coupling constants (J) in Hz. All the following ^{1}H NMR data use the abbreviations as follows: singlet (s), doublet (d), triplet (t), quartet (q), septet (sept), multiplet (m), broad (br), apparent (app) and aryl (Ar). In certain instances structural assignments of the ^{1}H and ^{13}C NMR spectra were elucidated with the aid of COSY, HMBC, HMQC, NOESY and PENDANT experiments. The characterisation of compounds utilises numbers to represent specific positions, these were assigned in a uniform manner in all the compounds described herein. The diketones, bis-triflates monotriflates and their derivatives are all labelled starting at the ketone/triflate functionality and then proceeding through the disubstituted position into the second triflate or substituted position, for comparative purposes. Hence, the numbers that appear in the diagrams may not correspond to the numbers which appear in the compound name.

Capillary melting points were determined on a Büchi 535 melting point apparatus. The readings were taken from a mercury-in-glass thermometer and are reported uncorrected as the meniscus point, rounded to the nearest 1°C. Where the sample changed colour or evolved gas during or after the melt, thermal decomposition (dec.) is noted.

Infrared spectra were recorded on Avatar 360 FT-IR ESP, a Nicolet Nexus^{TM} FT-IR spectrometer or a Perkin Elmer 1600 Series FT-IR spectrometer with internal background calibration in the range 600-4000 cm^{-1}, either neat (neat), using thin films on NaCl plates (film), or KBr discs (KBr disc) as stated. Absorption maxima are recorded in wavenumbers (cm^{-1}).

Mass spectra including high resolution spectra were recorded by the EPSRC National Mass Spectrometry Service Centre, Swansea, or at Novartis Pharmaceuticals, Horsham, using electron impact (EI), chemical ionisation (CI) or electrospray (ES). Analyses were performed in positive ionisation mode. For low resolution measurements ammonia was used as the CI reagent gas, on a Micromass Quattro II triple quadrupole (Swansea). For high resolution measurements, heptacosa (perfluorotributylamine) was used as the EI and CI reference compound, and polyethylenimine for ES, using either a Finnigan MAT95 high resolution double focussing mass spectrometer, or a MAT900 high resolution double focussing mass spectrometer with tandem ion trap or a Micromass LCT spectrometer (Novartis).

Elemental analyses were performed by the microanalysis service of the Department of Chemistry of the University of Bath, using an Exeter Analytical Inc CE-440 elemental analyser.

High performance liquid chromatography was performed either on a TSP Thermo Separation Products spectra series system, or a Agilent 1100 series system, using different chiral columns, flow rates, and *n*-hexane/*i*-PrOH solvent systems, as specified.

Basic MM2 calculations were made using the Chem3D Ultra computational package.

7.1.2 Chemicals

All solvents were reagent grade. Water was distilled. Where dry solvents were required, they were freshly distilled under nitrogen prior to use. CH_2Cl_2 was distilled from calcium hydride, whilst THF was distilled from sodium wire. Solvents and reagents were deoxygenated where necessary by purging with nitrogen. 'Petroleum ether' refers to light petroleum, the fraction of petroleum ether boiling in the range of 40-60 °C. Organic layers were dried over $MgSO_4$ or Na_2SO_4. All reagents were used as supplied without prior purification unless otherwise stated, and obtained from Acros Organics Ltd, Avocado, Fluka, Strem, Lancaster Synthesis Ltd and Sigma-Aldrich Chemical Co Ltd. Thin layer chromatography 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 using either ultraviolet light of 254 nm wavelength, or by staining

the plates with vanillin, 2,4-dinitrophenylhydrazine (DNP), ceric ammonium molybdate (CAM) or ninhydrin solution followed by gentle warming. Flash column chromatography was carried out using Davisil LC 60A silica gel (35-70 μm) purchased from Flurochem. Samples were pre-absorbed on silica. Reactions requiring anhydrous conditions were performed under nitrogen in oven dried glassware. 4 Å molecular sieves (powdered and beads) were activated by drying in an oven at 150 °C or alternatively, by heating with a heat gun *in vacuo* (powdered molecular sieves).

7.2 Preparation of diketones

Preparation of 2-benzyl-2-methyl-1,3-cyclopentadione 256

255 256

2-Methyl-1,3-cyclopentadione **255** (10.09 g, 90 mmol) was added to a stirred aqueous 1 M NaOH solution (90 mL, 90 mmol), and the resultant orange suspension was stirred at room temperature for 1 h. Benzyl bromide (16.03 mL, 135 mmol) was then added dropwise over 1 h, and this solution was stirred for 48 h. After this time the aqueous phase was extracted with DCM (4 × 100 mL), and the combined organic phases were then washed with brine (200 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified *via* flash chromatography (20% EtOAc/petroleum ether) to give the *diketone* **256** (13.63 g, 75%) as a white crystalline solid. mp 50-51°C (lit. 42-43°C); R_f(petroleum ether:EtOAc 4:1) 0.25; δ_H (300 MHz, $CDCl_3$) 7.19-7.12 (3H, m, H-4', H-5', H-6'), 7.01-6.94 (2H, m, H-3', H-7'), 2.90 (2H, s, H-1'), 2.56-2.34 (2H, m, 1 × H-4, 1 × H-5), 2.08-1.87 (2H, m, 1 × H-4, 1 × H-5), 1.15 (3H, s, Me); δ_C (75 MHz, $CDCl_3$) 217.5 (2 × C, C=O, C-1, C-3), 136.1 (C, C-2'), 129.9 (2 × CH, C-4', C-6'), 128.9 (2 × CH, C-3', C-7'), 127.5 (CH, C-5'), 58.5 (C, C-2), 36.1 (CH_2, C-1'), 44.2 (2 × CH_2, C-4, C-5), 20.3 (CH_3, Me); (Found C, 77.40; H, 7.01%. $C_{13}H_{14}O_2$ requires C, 77.20; H, 6.98%); data consistent with literature.[1]

Preparation of 2-methyl-2-phenylcyclopentane-1,3-dione 318

317 318

To a stirred solution of acetophenone (2.34 mL, 20 mmol) in dry DCM (100 mL), boron trifluoride etherate (3.01 mL, 24 mmol) was added followed by bistrimethylsilylcyclobutene **317** (7.71 mL, 30 mmol) at room temperature, under a nitrogen atmosphere. After 2.5 h water (3.13 mL) was added, and after a further 10 minutes boron trifluoride etherate (38.02 mL, 300 mmol) was added. The reaction mixture was then stirred for an additional 1 h. The reaction mixture was washed with water (2 × 60 mL) and the combined aqueous phases were then extracted with DCM (2 × 60 mL), the combined organic layers were washed with brine (60 mL), dried ($MgSO_4$) and concentrated under vacuum, to provide a brown oil. The resulting crude mixture was redissolved in diethyl ether (50 mL) and decolourising charcoal (6 g) added. The mixture was then filtered through a plug containing more charcoal (12 g) and Fluorisil (36 g), an additional 200 mL of diethyl ether was passed through the plug and resulting filtrate was concentrated under reduced pressure to provide the *diketone* **318** (2.69 g, 71%) as an orange oil. R_f (petroleum ether:EtOAc 9:1) 0.27; δ_H (300 MHz, $CDCl_3$) 7.39-7.26 (3H, m, H-4', H-5', H-6'), 7.24-7.17 (2H, m, H-3', H-7'), 2.96-2.67 (4H, m, H-4, H-5), 1.43 (3H, s, Me); δ_C (75 MHz, $CDCl_3$) 213.5 (2 × C, C=O, C-1, C-3), 137.4 (C, C-1'), 129.7 (2 × CH, C-2', C-6'), 128.4 (CH, C-4'), 126.8 (2 × CH, C-3', C-5'), 62.4 (C, C-2), 35.7 (2 × CH_2, C-4, C-5), 20.2 (CH_3, Me); data consistent with literature.[2]

Preparation of 2-*iso*-propyl-2-methylcyclopentane-1,3-dione 319

317 319

To 3-methylbutanone (2.86 mL, 27 mmol) was added boron trifluoride etherate (4.01 mL, 32 mmol) followed by bistrimethylsilylcyclobutene **317** (10.28 mL, 40 mmol) and the resulting solution stirred at room temperature under an atmosphere of nitrogen. After 2 h, water (4.17 mL) was added, and after a further 10 minutes boron trifluoride etherate (56.77 mL, 400 mmol) was added. The reaction was then stirred for an additional 1 h. The reaction mixture was washed with water (2 × 80 mL) and extracted with DCM (2 × 80 mL), the combined organic layers were then washed with brine (80 mL), dried ($MgSO_4$) and concentrated under vacuum, to provide a brown oil. The resulting residue was then redissolved in diethyl ether (50 mL) and decolourising charcoal (8 g) added. The mixture was then filtered through a plug containing more charcoal (16 g) and Fluorisil (48 g), an additional 200 mL of diethyl ether was passed through the plug and the resulting filtrate concentrated under reduced pressure to provide the *diketone* **319** (1.84 g, 45%) as an orange oil; δ_H (400 MHz, CD_2Cl_2) 2.72-2.54 (4H, m, H-4, H-5), 1.90 (1H, sept, *J* 7.1, H-1'), 0.93 (3H, s, Me), 0.82 (6H, d, *J* 7.1, Me-2'); δ_C (100 MHz, CD_2Cl_2) 217.4 (2 × C, C=O, C-1, C-3), 60.2 (C, C-2), 36.4 (2 × CH_2, C-4, C-5), 34.5 (CH, C-1'), 17.9 (CH_3, Me), 15.7 (2 × CH_3, 2 × Me-2'); data consistent with literature.[1]

Preparation of 2-benzylcyclopentane-1,3-dione 324

323 324

To a stirred solution of trimethysilylchloride (634.6 μL, 5.0 mmol), sodium iodide (749 mg, 5.0 mmol) and 1,3-cyclopentanedione **323** (98 mg, 1.0 mmol) in acetonitrile (5 mL), benzaldehyde (102 μL, 1.0 mmol) was added at 0°C. The mixture was allowed to warm to room temperature and stirred for 6 h. The reaction mixture was then heated up to 60°C for 10 h. Water (10 mL) was then added and the reaction mixture extracted with diethyl ether (30 mL). The organic layer was then washed with aqueous $Na_2S_2O_3$ (10 mL) to remove liberated iodine, acidified with hydrochloric acid (10 mL, 2 M), and extracted with potassium carbonate (20 mL, 1 M). The aqueous layer was then re-acidified with hydrochloric acid (10 mL, 3 M) and extracted with diethyl ether (30 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield the *C-alkylated diketone* **324** (150 mg, 80%) as a cream coloured powder. mp 186-188°C (lit. 196°C); NMR data shows compound in enol form; δ_H (300 MHz, $CDCl_3$) 7.19-7.11 (4H, m, H-3', H-4', H-6', H-7'), 7.04 (1H, t, *J* 7.1, H-5'), 3.41 (2H, s, H-1'), 2.38 (4H, s, H-4, H-5); (300 MHz, CD_3OD) 7.10-7.07 (4H, m, H-3', H-4', H-6', H-7'), 7.04-6.96 (1H, m, H-5'), 3.32 (2H, s, H-1'), 2.40 (4H, s, H-4, H-5); δ_C (75 MHz, CD_3OD) 207.0 (C, C-1), 199.1 (C, C-3), 142.0 (C, C-2'), 129.8 (2 × CH, C-3, C-5), 129.5 (2 × CH, C-4', C-6'), 127.1 (CH, C-5'), 118.4 (C, C-2), 31.8 (2 × CH_2, C-4, C-5), 28.0 (C, C-1'); data consistent with literature.[3]

Preparation of 2-benzyl-5,5-dimethylcyclohexane-1,3-dione 341

340 341

To a stirred solution of trimethysilylchloride (6.35 mL, 50.0 mmol), sodium iodide (7.49 g, 50.0 mmol) and 5,5-dimethyl-1,3-cyclohexanedione **340** (1.40 g, 10.0 mmol) in acetonitrile (50 mL), benzaldehyde (1.02 mL, 10.0 mmol) was added at 0°C. The mixture was allowed to warm to room temperature and stirred for 6 h. The reaction mixture was then heated up to 60°C for 10 h. Water (25 mL) was then added and the reaction mixture extracted with diethyl ether (50 mL). The organic layer was then washed with aqueous $Na_2S_2O_3$ (15 mL) to remove liberated iodine, acidified with hydrochloric acid (10 mL 2 M), and extracted with potassium carbonate (25 mL, 1 M). The aqueous layer was then re acidified with hydrochloric acid (25 mL, 3 M) and extracted with diethyl ether (50 mL). The organic layer was then dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield the *C-alkylated diketone* **341** (1.83 g, 80%) as a cream coloured powder. mp 141°C (lit. 154-155°C); NMR data shows compound in enol form; δ_H (300 MHz, CD_3OD) 7.09-7.05 (4H, m, H-3', H-4', H-6', H-7'), 7.00-6.95 (1H, m, H-5'), 3.46 (2H, s, H-1'), 2.22 (4H, s, H-4, H-5), 0.95 (6H, s, 2 × Me); δ_C (75 MHz, CD_3OD) 208.3 (C, C-1), 176.3 (C, C-3), 143.4 (C, C-2'), 129.9 (2 × CH, C-3, C-5), 129.3 (2 × CH, C-4', C-6'), 126.7 (CH, C-5'), 115.8 (C, C-2), 52.8 (CH_2, C-6), 46.6 (CH_2, C-4), 28.9 (2 × CH_3, 2 × Me), 28.7 (C, C-5), 28.4 (C, C-1'); data consistent with literature.[4]

Preparation of 2-benzyl-2,5,5-trimethylcyclohexane-1,3-dione 342

341 342

Iodomethane (0.94 mL, 15.2 mmol) was added *via* syringe to a solution of diketone **341** (3.00 g, 13.04 mmol) and KI (230 mg, 1.38 mmol) in 1 M *t*-BuOK solution (15.2 mL, in *t*-BuOH). The mixture was gently refluxed for 20 h, the reaction was then allowed to cool to room temperature and extracted with diethyl ether (4 × 20 mL). The combined organic extracts were then washed with NaOH (0.5 M, 30 mL), washed with water (30 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (25% diethyl ether/petroleum ether) to give the *C-alkylated diketone* **342** (2.65 g, 83%) as a white solid, mp 52-53°C (lit. 49-50°C); R_f (petroleum ether:EtOAc 66:33) 0.45; ν_{max} (film)/cm^{-1} 3030 (unsaturated CH), 2955 and 2871 (saturated CH), 1726 (C=O), 1496 (aromatic C=C); δ_H (400 MHz, $CDCl_3$) 7.21-7.18 (3H, m, H-4', H-5', H-6'), 7.17-7.03 (2H, m, H-3', H-7'), 3.07 (2H, s, H-1'), 2.47 (2H, d, *J* 15.0, 1 × H-4, 1 × H-6), 2.35 (2H, d, *J* 15.0, 1 × H-4, 1 × H-6), 1.26 (3H, s, Me) 0.87 (3H, s, Me), 0.79 (3H, s, Me); δ_C (100 MHz, $CDCl_3$) 210.4 (2 × C, C=O, C-1, C-3), 135.9 (C, C-2'), 130.1 (2 × CH, C-4', C-6'), 128.2 (2 × CH, C-3', C-7'), 126.9 (CH, C-5'), 64.7 (C, C-2), 52.8 (CH_2, C-1'), 44.2 (2 × CH_2, C-4, C-6), 30.2 (C, C-5), 29.2 (CH_3, Me), 28.2 (CH_3, Me), 20.8 (CH_3, Me); data consistent with literature.[5]

Preparation of 2-benzyl-2-fluorocyclopentane-1,3-dione 338

324 338

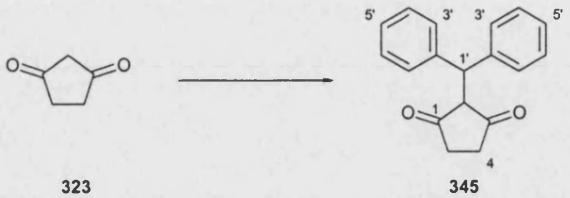
Diketone **324** (745 mg, 4 mmol) was stirred with Selectfluor **321** (1.42 g, 4 mmol) in dry acetonitrile (40 mL) at room temperature for 24 h. The reaction mixture was then concentrated *in vacuo*. The residue was partitioned between water (50 mL) and DCM (50 mL), the organic layer was then washed with water (2 × 25 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure, to yield the *fluorinated diketone* **338** (801 mg, 97%) as a cream coloured crystalline solid. mp 128-130°C; R_f (petroleum ether:EtOAc 9:1) 0.11; ν_{max} (KBr disc)/cm^{-1} 3031 (unsaturated CH), 2977 and 2927 (saturated CH), 1736 (C=O), 1603 (aromatic C=C) 1035 (CF); δ_H (300 MHz, $CDCl_3$) 7.36-7.28 (3H, m, H-4', H-5', H-6'), 7.17-7.06 (2H, m, H-3', H-7'), 3.28 (2H, d, *J* 14.3, H-1'), 2.74-2.52 (2H, m, 1 × H-4, 1 × H-5) 2.44-2.19 (2H, m, 1 × H-4, 1 × H-5); δ_C (75 MHz, $CDCl_3$) 207.1 (2 × C, C=O, d *J* 14.9, C-1, C-3), 130.3 (d, *J* 9.3, C-2'), 130.0 (2 × CH, C-4', C-6'), 129.1 (2 × CH, C-3', C-7'), 128.3 (CH, C-5'), 93.1 (CF, d, *J* 207.2, C-2), 40.7 (CH_2, d, *J* 26.1, C-1'), 34.3 (2 × CH_2, d, *J* 2.5, C-4, C-5); δ_F (376 MHz, $CDCl_3$) -168.00 (t, *J* 14.4); *m/z* (ES^+) 224.1 (100%, $M+NH_4)^+$; (Found $(M+NH_4)^+$, 224.1079. $C_{12}H_{15}NO_2F$ requires 224.1081); (Found C, 69.5; H. 5.36%. $C_{12}H_{11}O_2F$ requires C, 69.89; H, 5.38%).

Preparation of 2-Benzyl-2-fluoro-5,5-dimethylcyclohexane-1,3-dione 343

341 343

Diketone **341** (921 mg, 4 mmol) was stirred with Selectfluor **321** (1.42 g, 4 mmol) in dry acetonitrile (40 mL) at room temperature for 24 h. The reaction mixture was then concentrated *in vacuo*. The residue was partitioned between water (50 mL) and DCM (50 mL), the organic layer was then washed with water (2 × 25 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure, to yield the *fluorinated diketone* **343** (971 mg, 98%) as a brown/cream coloured crystalline solid. mp 102-104°C; R_f (petroleum ether:EtOAc 9:1) 0.19; ν_{max} (KBr disc)/cm^{-1} 3030 (unsaturated CH), 2958 and 2877 (saturated CH), 1715 (C=O), 1497 (aromatic C=C), 1192 (CF); δ_H (300 MHz, $CDCl_3$) 7.35-7.28 (3H, m, H-4', H-5', H-6'), 7.21-7.16 (2H, m, H-3', H-7'), 3.33 (2H, d, *J* 23.7, H-1'), 2.81 (2H, app d, *J* 13.9, 1 × H-4, 1 × H-6) 2.66-2.65 (2H, m, 1 × H-4, 1 × H-6) 1.11 (3H, Me) 0.97 (3H, Me); δ_C (75 MHz, $CDCl_3$) 200.6 (2 × C, C=O, d *J* 16.7, C-1, C-3), 131.8 (C, C-2'), 129.9 (2 × CH, C-4', C-6'), 128.8 (2 × CH, C-3', C-7'), 128.1 (CH, C-5'), 102.6 (CF, d, *J* 205.3, C-2), 52.3 (2 × CH_2, d, *J* 1.2, C-4, C-6), 41.9 (CH_2, d, *J* 23.0, C-1'), 31.1 (C, C-5), 30.0 (CH_3, Me), 26.7 (CH_3, Me); δ_F (376 MHz, $CDCl_3$) -171.49 (t, *J* 23.8); *m/z*; (ES^+) 266.2 (100%, $M+NH_4)^+$; (Found $(M+NH_4)^+$, 266.1550. $C_{15}H_{21}NO_2F$ requires 266.1550).

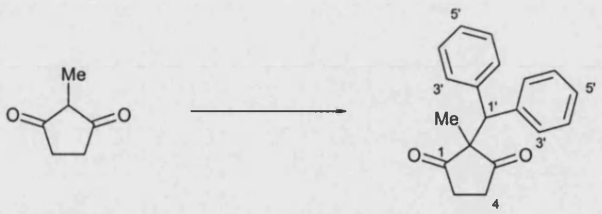
Preparation of 2-benzhydrylcyclopentane-1,3-dione 345



323 345

To a stirred suspension of benzhydryl alcohol (2.03 g, 11 mmol) and cyclopentanedione **323** (981 mg, 10 mmol) in DCM (200 mL), under nitrogen, boron trifluoride etherate (1.52 mL, 12 mmol) was added at room temperature. The mixture was stirred for 1 h before saturated $NaHCO_3$ (100 mL) was added. The aqueous layer was extracted using DCM (100 mL), and the organic layer washed with brine (50 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was then recrystalised from diethyl ether/hexane to yield the *diketone* **345** (1.98 g, 75%) as a cream/white solid, mp 205°C(dec.). ν_{max} (KBr Disc)/cm^{-1} 3025 (unsaturated CH), 3003 and 2923 (saturated CH), 1653 (C=O), 1559 (aromatic C=C), 1457 (saturated CH); NMR data shows compound in enol form; δ_H (300 MHz, $CDCl_3$) 7.33-7.17 (6H, m, 2 × H-4', 2 × H-6', 2 × H-5'), 7.13-7.07 (4H, m, 2 × H-3', 2 × H-7') 5.21 (1H, s, H-1'), 2.44 (4H, s, 2 × H-4, 2 × H-5); δ_C (75 MHz, $(CD_3)_2SO$) 194.7 (2 × C, C=O, br s, C-1, C-3), 143.3 (2 × C, 2 × C-2'), 129.0 (4 × CH, 2 × C-4', 2 × C-6'), 128.3 (4 × CH, 2 × C-3', 2 × C-7'), 126.2 (2 × CH, 2 × C5'), 118.5 (C, C-2), 44.6 (CH, C-1'), 30.6 (2 × CH_2, C-4, C-5), ; *m/z* (CI^+) 265.2 (100%, M+H)$^+$; (Found (M+H)$^+$ 265.1223. $C_{18}H_{17}O_2$ requires 265.1223).

Preparation of 2-benzhydryl-2-methylcyclopentane-1,3-dione 344



255 344

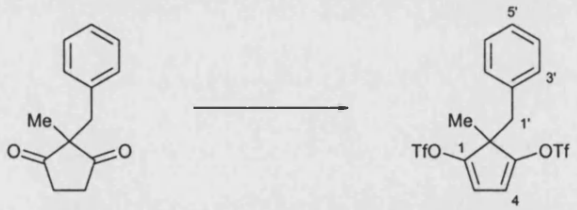
To a solution of benzhydryl bromide (24.71 g, 100 mmol) and 2-methyl-1,3-cyclopentadione **255** (11.21 g, 100 mmol) was added 1 M sodium hydroxide solution (100 mL, 100 mmol). The resultant solution was stirred at room temperature under air for 48 h. The aqueous phase was extracted with DCM (4 × 100 mL) and the combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified *via* flash chromatography (20% EtOAc/petroleum ether) to give the *diketone* **344** (5.91 g, 21%) as a white crystalline solid, mp 125-126°C (lit. 120-121°C). R_f (petroleum ether:EtOAc 9:1) 0.25; ν_{max} (KBr Disc)/cm^{-1} 3035 (unsaturated CH), 2964 and 2911 (saturated CH), 1720 (C=O), 1495 (aromatic C=C), 1447 (saturated CH); δ_H (300 MHz, $CDCl_3$) 7.48-7.41 (4H, m, 2 × H-4', 2 × H-6'), 7.41-7.20 (6H, m, 2 × H-3', 2 × H-7', 2 × H-5') 2.71-2.49 (2H, m, 1 × H-4, 1 × H-5), 2.22-2.01 (2H, m, 1 × H-4, 1 × H-5), 1.11 (3H, s, Me); δ_C (75 MHz, $CDCl_3$) 218.1 (2 × C, C=O, C-1, C-3), 140.0 (2 × C, 2 × C-2'), 130.0 (4 × CH, 2 × C-4', 2 × C-6'), 129.0 (4 × CH, 2 × C-3', 2 × C-7'), 127.5 (2 × CH, 2 × C5'), 60.7 (C, C-2), 58.7 (CH, C-1'), 36.3 (2 × CH_2, C-4, C-5), 20.5 (CH_3, Me); *m/z* (EI^+) 278.2 (70%, M^+), (Found (M^+) 278.1303. $C_{19}H_{18}O_2$ requires 278.1301); (Found C, 82.0; H, 6.54%. $C_{19}H_{18}O_2$ Requires C, 81.99; H, 6.52%); data consistent with literature.[6]

7.3 Preparation of bis-triflates

All of the bis-triflates were prepared using the following standard procedure.

To a stirred solution of diketone (14.1 mmol) and 2-[*N,N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine **254** (12.0 g, 30.8 mmol) in dry THF (120 mL) under nitrogen at -78°C, KHMDS (0.5 M in toluene 59.34 mL, 29.7 mmol) was added over 1 h, and the solution stirred at -78°C for 17 h. The reaction mixture is then allowed to warm to room temperature over 2 h. Hexane (500 mL) was added and washed with water (300 mL), 10% aqueous sodium hydroxide (300 mL) and brine (300 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a dark oil. The residue was purified by flash chromatography (gradient elution 5-30% DCM/petroleum ether) to produce the *bis-triflate.*

Preparation of 5-benzyl-5-methyl-4-((trifluoromethylsulfonyl)oxy)-1,3-cyclopentadien-1-yl trifluoromethanesulfonate 248

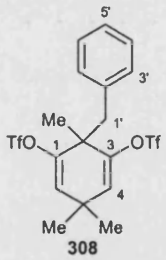


256 248

Using 2.88 g (14.1 mmol) of the diketone **256**, 12.0 g (30.8 mmol) of the triflimide **254** and 59.34 mL (29.7 mmol) KHMDS (0.5 M in toluene) in dry THF (120 mL) produced the *bis-triflate* **248** (4.01 g, 61%) as a white solid. mp 37-37.5°C from MeOH (lit. 37-37.5°C); R_f(petroleum ether:EtOAc 9:1) 0.80, (petroleum ether:DCM 8:2) 0.45; ν_{max} (film)/cm^{-1} 3034 (unsaturated CH), 2982 and 2938 (saturated CH), 1631 (C=C), 1497 (aromatic C=C), 1429 (O-SO_2), 1328 (O-SO_2), 1311 (SO_2), 1140

(SO_2); δ_H (400 MHz, $CDCl_3$) 7.25-7.20 (3H, m, H-4', H-5', H-6'), 7.07-7.06 (2H, m, H-3', H-7'), 5.81 (2H, s, H-4, H-5), 2.97 (2H, s, 2 × H-1'), 1.41 (3H, s, Me); δ_C (100 MHz, $CDCl_3$) 151.9 (2 × C, C-1, C-3), 134.0 (C, C-2'), 128.9 (2 × CH, C-4', C-6'), 128.0 (2 × CH, C-3', C-7'), 127.2 (CH, C-5'), 118.3 (q, *J* 319, 2 × CF_3), 111.9 (2 × CH, C-4, C-5), 54.2 (C, C-2), 39.7 (CH_2, C-1'), 18.5 (CH_3, Me); δ_F (376 MHz, $CDCl_3$) -73.80; (Found C, 38.4; H, 2.65%. $C_{15}H_{12}O_6S_2F_6$ requires C, 38.6; H, 2.60%); data consistent with literature.[7]

6-Benzyl-3,3,6-trimethyl-5-((trifluoromethylsulfonyl)oxy)-1,4-cyclohexadien-1-yl triflouromethanesulfonate 308

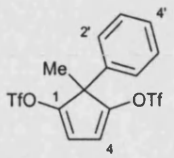


308

Using 1.50 g (6.15 mmol) of the diketone **342**, 5.54 g (14.1 mmol) of the triflimide **254** and 28.3 mL (14.1 mmol) KHMDS (0.5 M in toluene) in dry THF (50 mL) produced the *bis-triflate* **308** (2.86 g, 92%) purified as a colourless oil; R_f(petroleum ether:EtOAc 9:1) 0.86; ν_{max} (neat)/cm^{-1} 3034 (unsaturated CH), 2968 and 2942 (saturated CH), 1602 (C=C), 1422 (O-SO_2), 1213 (O-SO_2), 1142 (SO_2); δ_H (400 MHz, $CDCl_3$) 7.29-7.18 (3H, m, H-4', H-5', H-6'), 7.06-7.03 (2H, m, H-3', H-7'), 5.48 (2H, s, H-4, H-6), 2.85 (2H, s, 2 × H-1'), 1.52 (3H, s, Me) 1.09 (3H, s, Me) 0.34 (3H, s, Me); δ_C (100 MHz, $CDCl_3$) 145.6 (2 × C, C-1, C-3), 135.7 (C, C-2'), 130.1 (2 × CH, C-4', C-6'), 128.3 (2 × CH, C-3', C-7'), 127.3 (CH, C-5'), 124.3 (2 × CH, C-4, C-6), 118.6 (q, *J* 319, 2 × CF_3), 46.1 (C, C-2), 41.8 (CH_2, C-1'), 35.5 (C, C-5), 30.2 (CH_3, Me) 28.7 (CH_3, Me) 23.2 (CH_3, Me); δ_F (376 MHz, $CDCl_3$) -74.70; *m/z*

(EI^+) 508 (100%, M^+); (Found $(M+NH_4)^+$, 526.0796. $C_{18}H_{22}NO_6S_2F_6$ requires 526.0793); data consistent with literature.[7]

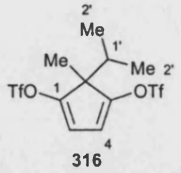
5-Phenyl-5-methyl-4-((trifluoromethylsulfonyl)oxy)-1,3-cyclopentadien-1-yl trifluoromethanesulfonate 315



315

Using 264 mg (1.4 mmol) of the diketone **318**, 1.22 g (3.1 mmol) of the triflimide **254** and 6 mL (3.0 mmol) KHMDS (0.5 M in toluene) in dry THF (15 mL) produced the *bis-triflate* **315** as a colourless oil (408 mg, 64%); R_f(petroleum ether:EtOAc 9:1) 0.77; ν_{max} (Film)/cm^{-1} 3030 (unsaturated CH), 2990 and 2946 (saturated CH), 1631 (C=C), 1499 (aromatic C=C), 1426 (O-SO_2), 1324 (O-SO_2), 1282 (SO_2), 1253 (C-F), 1133 (SO_2); δ_H (300 MHz, $CDCl_3$) 7.39-7.29 (3H, m, H-3', H-4', H-5'), 7.24-7.15 (2H, m, H-2', H-6'), 6.14 (2H, s, H-4, H-5), 1.72 (3H, s, Me); δ_C (75 MHz, $CDCl_3$) 154.7 (2 × C, C-1, C-3), 132.2 (C, C-1'), 129.2 (2 × CH, C-3', C-5'), 128.7 (CH, C-4'), 126.0 (2 × CH, C-2', C-6'), 118.3 (q, *J* 321, 2 × CF_3), 111.7 (2 × CH, C-4, C-5), 56.2 (C, C-2), 16.8 (CH_3, Me); δ_F (376 MHz, $CDCl_3$) -73.27; *m/z* (ES^+) 452.1 (100%, M^+); (Found $(M+NH_4)^+$, 470.0164. $C_{14}H_{14}NO_6S_2F_6$ requires 470.0161).

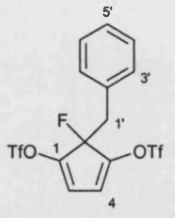
5-*iso*-Propyl-5-methyl-4-((trifluoromethylsulfonyl)oxy)-1,3-cyclopentadien-1-yl trifluoromethanesulfonate 316



316

Using 154 mg (1.0 mmol) of the diketone **319**, 824 mg (2.1 mmol) of the triflimide **254** and 4.4 mL (2.2 mmol) KHMDS (0.5 M in toluene) in dry THF (10 mL) produced the *bis-triflate* **316** as a colourless oil (227 mg, 54%); R_f(petroleum ether:EtOAc 9:1) 0.86; ν_{max} (Film)/cm^{-1} 2977 (unsaturated CH), 2942 and 2892 (saturated CH), 1626 (C=C), 1426 (O-SO_2), 1353 (O-SO_2), 1318 (SO_2), 1210 (C-F), 1144 (SO_2); δ_H (300 MHz, C_6D_6) 5.42 (2H, s, H-4, H-5), 1.53 (1H, sept, *J* 6.7, CH-1'), 0.92 (3H, s, Me) 0.63 (6H, d, *J* 6.7, Me-2'); δ_C (75 MHz, C_6D_6) 152.9 (2 × C, C-1, C-3), 118.9 (q, *J* 320, 2 × CF_3), 112.2 (2 × CH, C-4, C-5), 56.1 (C-2), 31.6 (C-H, C-1'), 16.7 (CH_3, Me), 16.6 (2 × CH_3, Me-2'); δ_F (376 MHz, $CDCl_3$) -73.49; *m/z* (EI) 418.1 (34%, M^+); (Found (M^+), 417.9973. $C_{11}H_{12}O_6S_2F_6$ requires 417.9974).

5-Fluoro-5-benzyl-4-((trifluoromethylsulfonyl)oxy)-1,3-cyclopentadien-1-yl trifluoromethanesulfonate 346

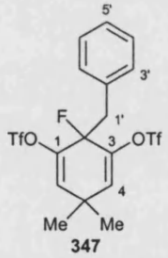


346

Using 144 mg (0.7 mmol) of the diketone **338**, 577 mg (1.47 mmol) of the triflimide **254** and 3.1 mL (1.54 mmol) KHMDS (0.5 M in toluene) in dry THF (7 mL) produced the *bis-triflate* **346** as a white solid (245 mg, 74%), mp 66-68°C; R_f(petroleum ether:EtOAc 9:1) 0.73; ν_{max} (KBr Disc)/cm^{-1} 3116 (unsaturated CH),

3035 (saturated CH), 2930 (saturated CH), 1657 (C=C), 1594 (aromatic C=C), 1430 (O-SO_2), 1341 (O-SO_2), 1249 (SO_2), 1235 (CF) 1135 (SO_2); δ_H (300 MHz, $CDCl_3$) 7.27-7.20 (3H, m, H-4', H-5', H-6'), 7.12-7.09 (2H, m, H-3', H-7'), 5.80 (2H, d, *J* 1.5, H-4, H-5), 3.25 (2H, d, *J* 11.7, 2 × H-1'); δ_C (75 MHz, $CDCl_3$) 145.8 (2 × C, d, *J* 16.7, C-1, C-3), 131.1 (C, d, *J* 10.5, C-2'), 130.1 (2 × CH, C-4', C-6'), 129.0 (2 × CH, C-3', C-7'), 128.5 (CH, C-5') 118.8 (q, *J* 321, 2 × CF_3), 115.7 (2 × CH, d, *J* 5.0, C-4, C-5), 97.0 (d, *J* 196.6, C-F), 37.5 (CH_2, d, *J* 27.3, C-1'); δ_F (376 MHz, $CDCl_3$) -72.82 (d, *J* 5.4, 2 × Tf), -182.25 (br sept, *J* 5.4, C-F); failed to provide mass ion.

6-Flouro-6-benzyl-3,3-dimethyl-5-((trifluoromethylsulfonyl)oxy)-1,4-cyclohexadien-1-yl triflouromethanesulfonate 347

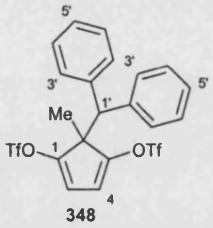


347

Using 497 mg (2.0 mmol) of the diketone **343**, 1.65 g (4.2 mmol) of the triflimide **254** and 8.8 mL (4.4 mmol) KHMDS (0.5 M in toluene) in dry THF (20 mL) produced the *bis-triflate* **347** as a white solid (725 mg, 71%) mp 78-80°C; R_f(petroleum ether:EtOAc 9:1) 0.84; ν_{max} (KBr Disc)/cm^{-1} 3058 (unsaturated CH), 2972 (saturated CH), 1617 (C=C), 1500 (aromatic C=C), 1420 (O-SO_2), 1353 (O-SO_2), 1251 (CF) 1211 (SO_2), 1140 (SO_2); δ_H (300 MHz, $CDCl_3$) 7.31-7.23 (3H, m, H-4', H-5', H-6'), 7.17-7.10 (2H, m, H-3', H-7'), 5.82 (2H, s, H-4, H-5), 3.33 (2H, d, *J* 5.7, 2 × H-1') 1.18 (3H, s, Me) 0.40 (3H, s, Me); δ_C (75 MHz, $CDCl_3$) 139.8 (2 × C, d, *J* 19.2, C-1, C-3), 132.8 (C, d, *J* 12.5, C-2'), 131.1 (2 × CH, d, *J* 4.3, C-4, C-6) 130.5 (2 × CH, C-4', C-6') 129.0 (2 × CH, C-3', C-7'), 128.3 (CH, C-5') 118.9 (q, *J*

320, 2 × CF_3), 89.4 (d, *J* 183.6, C-F), 38.8 (CH_2, d, *J* 32.3, C-1'), 36.5 (C, d, *J* 3.7, C-5), 28.0 (d, *J* 6.8, Me), 27.5 (d, *J* 6.8, Me); δ_F (376 MHz, $CDCl_3$) -73.27 (d, *J* 7.5, Tf), -137.50 (br sept, *J* 7.5, CF); *m/z* (ES^+) 530.1 (33%, $(M+NH_4)^+$; (Found $(M+NH_4)^+$, 530.0531. $C_{17}H_{19}NO_6S_2F_7$ requires 530.0537).

5-Benzhydryl-5-methyl-4-((trifluoromethylsulfonyl)oxy)-1,3-cyclopentadien-1-yl trifluoromethanesulfonate 348



348

Using 696 mg (2.5 mmol) of the diketone **344**, 2.08 g (5.3 mmol) of the triflimide **254** and 11 mL (5.5 mmol) KHMDS (0.5 M in toluene) in dry THF (25 mL) produced the *bis-triflate* **348** as a yellow/brown oil (54 mg, 4%), ν_{max} (film)/cm^{-1} 3032 (unsaturated CH), 2925 and 2855 (saturated CH), 1629 (C=C), 1494 (aromatic C=C), 1432 (O-SO_2), 1378 (O-SO_2), 1219 (SO_2), 1140 (SO_2); δ_H (300 MHz, CD_2Cl_2) 7.32-7.22 (4H, m, 2 × H-4', 2 × H-6'), 7.21-7.09 (6H, m, 2 × H-5', 2 × H-3', 2 × H-7'), 5.88 (2H, s, H-2, H-3), 4.09 (1H, s, H-1'), 1.27 (3H, s, Me); δ_C (75 MHz, CD_2Cl_2) 153.6 (2 × C-1, C-3), 138.9 (2 × C, 2 × C-2'), 129.8 (4 × CH, 2 × C-4', 2 × C-6'), 129.0 (4 × CH, 2 × C-3', 2 × C-7'), 127.9 (2 × CH, 2 × C-5'), 119.3 (q, *J* 319, 2 × CF_3), 113.5 (2 × CH, C-4, C-5), 57.1 (C, C-2), 56.9 (CH, C-1'), 20.2 (CH_3, Me).; failed to provide accurate mass data due to presence of impurities.

7.4 General procedure for Suzuki coupling reaction on bis-triflate

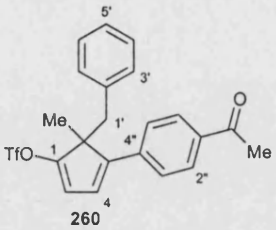
Procedure A - achiral conditions

Dry THF (2 mL) was added to a mixture of bis-triflate **248** (93.20 mg, 0.20 mmol), boronic acid (0.4 mmol), $Pd(OAc)_2$ (4.50 mg, (0.02 mmol, 10 mol %) and PPh_3 (11.50 mg, 0.044 mmol, 22 mol %) and the resulting solution stirred under nitrogen for 10 min. Aqueous potassium hydroxide (1.78 M, 0.11 mL, 0.20 mmol) was subsequently added, and the reaction mixture stirred for 8 h at room temperature. EtOAc (10 mL) and water (8 mL) were added and the aqueous layer extracted using EtOAc (2 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (gradient elution 1-40% ether:hexane) to give the *monotriflate.*

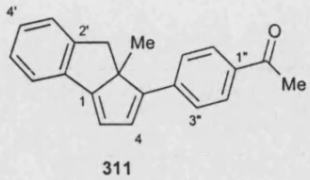
Procedure B - enantioselective conditions

Dry, degassed 1,4-dioxane (2 mL) was added to a mixture of bis-triflate **248** (93.20 mg, 0.20 mmol), boronic acid (0.4 mmol), $Pd(OAc)_2$ (4.50 mg, (0.02 mmol, 10 mol%), (*R*)-MeO-MOP (10.30 mg, 0.022 mmol 11 mol%) and cesium fluoride (91.4 mg 0.60 mmol). The reaction mixture was stirred for 8 h at room temperature. EtOAc (10 mL) and water (8 mL) were added and the aqueous layer extracted using EtOAc (2 × 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (gradient elution1-40% ether:hexane) to give the *monotriflate.*

Preparation of 4-(4-acetylphenyl)-5-benzyl-5-methylcyclopenta-1,3-dienyl trifluoromethanesulfonate 260 and 1-(4-(8,8a-dihydro-8a-methylcyclopenta[a]inden-1-yl)phenyl)ethanone 311



260



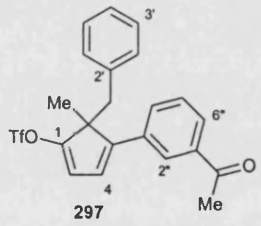
311

Using general procedure B produced in order of elution; the *tricyclic diene* **311** as a yellow solid (6.3 mg, 11%); mp 45-47°C (dec.); R_f(petroleum ether:EtOAc 9:1) 0.54; ν_{max} (KBr disc)/cm^{-1} 2956 (unsaturated CH), 2923 and 2861 (saturated CH), 1676 (C=O), 1598 (C=C); δ_H (300 MHz, $CDCl_3$) 7.92 (2H, d, *J* 8.3, H-2", H-6"), 7.59 (2H, d, *J* 8.3, H-3", H-5"), 7.42 (1H, d, *J* 7.5, H-6'), 7.27-7.09 (3H, m, H-3', H-4', H-5'), 6.95 (1H, d, *J* 2.3, H-4), 6.37 (1H, d, *J* 2.3, H-5), 3.10 (1H, d, *J* 13.9, 1 × H-1'), 2.81 (1H, d, *J* 13.9, 1 × H-1'), 2.56 (3H, s, MeC=O), 1.22 (3H, s, Me); δ_C (100 MHz, CD_2Cl_2) 197.9 (C, C=O), 169.1 (C, C-1), 153.0 (C, C-3), 151.2 (C, C-2'), 140.1 (C, C-4"), 136.1 (C, C-7'), 135.7 (C, C-1"), 132.1 (CH, C-4), 129.6 (2 × CH, C-2", C-6"), 128.0 (CH, C-5'), 127.7 (CH, C-3'), 127.0 (CH, C-4'), 126.2 (2 × CH, C-3", C-5"), 122.6 (CH, C-6'), 119.8 (CH, C-5), 57.6 (C, C-2), 41.4 (CH_2, C-1'), 30.5 (CH_3, MeC=O), 27.2 (CH_3, Me); *m/z* (ES^+) 286.2 (100%, M^+); (Found (*M*+H), 287.1446. $C_{21}H_{19}O$ requires 287.1436); and the *monotriflate* **260** as an orange yellow solid (40.2 mg, 46%); mp 107-108°C; R_f(petroleum ether:EtOAc 9:1) 0.36; ν_{max} (film)/cm^{-1} 3033 (unsaturated CH), 2936 and 2840 (saturated CH), 1674 (C=O), 1600 (C=C), 1427 (O-SO_2), 1138 (SO_2); δ_H (300 MHz, $CDCl_3$) 7.95 (2H, d, *J* 8.3, H-2", H-6"), 7.57 (2H, d, *J* 8.6, H-3", H-5"), 7.03-6.95 (3H, m, H-4', H-5', H-6'), 6.76-6.69 (2H, m, H-3', H-7'), 6.50 (1H, d, *J* 3.0, H-4), 5.95 (1H, d, *J* 3.0, H-5), 3.22 (1H, d, *J* 13.9, 1 × H-1'), 3.00 (1H, d, *J* 13.6, 1 × H-1'), 2.58 (3H, s, MeC=O), 1.55 (3H, s, Me); δ_C

(75 MHz, $CDCl_3$) 197.8 (C, C=O), 159.8 (C, C-1), 145.3 (C, C-3), 139.5 (C, C-4"), 136.0 (C, C-1"), 135.6 (C, C-2'), 129.3 (2 × CH, C-2", C-6"), 129.3 (2 × CH, C-3', C-7'), 128.0 (2 × CH, C-4', C-6'), 127.2 (2 × CH, C-5', C-4), 126.0 (2 × CH, C-3", C-5"), 118.9 (q, *J* 319, CF_3), 114.1 (CH, C-5), 56.4 (C, C-2), 41.5 (CH_2, C-1'), 27.0 (CH_3, MeC=O), 21.6 (CH_3, Me); *m/z* (EI^+) 436.1 (100%, M^+); (Found $(M+H)^+$, 437.10039. $C_{22}H_{20}O_4SF_3$ requires 437.1034).

The enantiomers of **260** were separated by HPLC using Chiracel OD column (97:3 hexane:*iso*propanol), 0.8 mL/min; t_r = 14.5 min and t_r = 18.2 min, 77% ee.

4-(3-Acetylphenyl)-5-benzyl-5-methylcyclopenta-1,3-dienyl trifluoromethanesulfonate 297



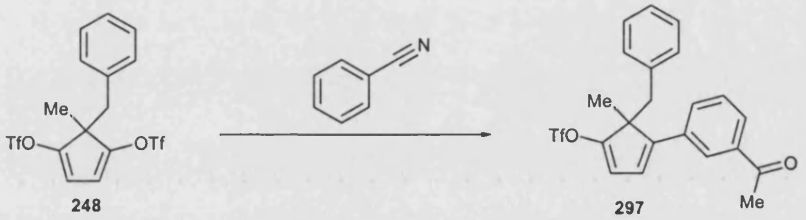
297

Using general procedure B the *monotriflate* **297** was produced as an orange yellow solid (44.5mg, 51%); mp 48-50°C; R_f(petroleum ether:EtOAc 9:1) 0.35; ν_{max} (KBr disc)/cm^{-1} 3032 (unsaturated CH), 2980and 2919 (saturated CH), 1683 (C=O), 1620 (C=C), 1433 (O-SO_2), 1226 (CF), 1134 (SO_2); δ_H (300 MHz, $CDCl_3$) 8.07 (1H, s, H-2"), 7.79 (1H, d, *J* 7.5, H-6"), 7.68 (1H, d, *J* 7.9, H-4"), 7.45 (1H, t, *J* 7.9, H-5"), 7.04-6.93 (3H, m, H-4', H-5', H-6'), 6.76-6.69 (2H, m, H-3', H-7'), 6.42 (1H, d, *J* 3.0, H-4), 5.92 (1H, d, *J* 3.0, H-5), 3.21 (1H, d, *J* 13.6, 1 × H-1'), 3.00 (1H, d, *J* 13.9, 1 × H-1'), 2.57 (3H, s, MeC=O), 1.55 (3H, s, Me); δ_C (100 MHz, CD_2Cl_2) 198.4 (C, C=O), 159.8 (C, C-1), 146.4 (C, C-3), 138.4 (C, C-1"), 136.5 (C, C-3"), 136.0 (C, C-2'), 131.0 (CH, C-4"), 129.8 (2 × CH, C-4', C-6'), 129.7 (CH, C-5"), 128.3 (2 × CH, C-3', C-7'), 128.1 (CH, C-6"), 127.4 (CH, C-5'), 126.2(CH, C-2"), 125.9 (CH,

C-4), 120.1 (q, *J* 320, CF_3), 114.5 (CH, C-5), 56.8 (C, C-2), 41.7 (CH_2, C-1'), 27.3 (CH_3, MeC=O), 21.9 (CH_3, Me); *m/z* (ES^+) 436.5 (100%, M^+); (Found $(M+NH_4)^+$, 454.1293. $C_{22}H_{24}NO_4SF_3$ requires 454.1300).

The enantiomers of **297** were separated by HPLC using Chiracel AD column (99:1 hexane:*iso*propanol), 1.0 mL/min; t_r = 22.3 min and t_r = 30.1 min, 86% ee.

4-(3-Acetylphenyl)-5-benzyl-5-methylcyclopenta-1,3-dienyl trifluoromethanesulfonate 297

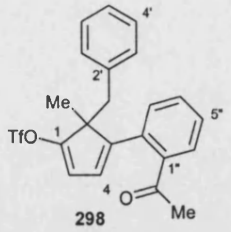


248 297

Using a variation on general procedure B: Dry, degassed 1,4-dioxane (1.5 mL) was added to a mixture of bis-triflate **248** (70.0 mg, 0.15 mmol), 3-acetylphenylboronic acid (49.2 mg. 0.3 mmol), $Pd(OAc)_2$ (3.4 mg, (0.015 mmol, 10 mol%), (*R*)-MeO-MOP (7.7 mg, 0.0165 mmol 11 mol%), cesium fluoride (68.4 mg 0.45 mmol) and benzonitrile (30.6 μL, 0.3 mmol). The reaction mixture was stirred for 8 h at room temperature. EtOAc (7.5 mL) and water (6 mL) were added and the aqueous layer extracted using EtOAc (2 × 7.5 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (gradient elution1-40% ether:hexane) to give the *monotriflate* **297** (25.9 mg, 40%); data consistent with above.

The enantiomers of **297** were separated by HPLC using Chiracel AD column (99:1 hexane:*iso*propanol), 1.0 mL/min; t_r = 22.3 min and t_r = 30.1 min, 51% ee.

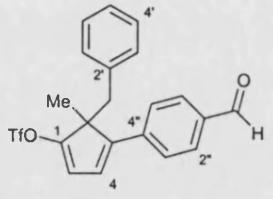
4-(2-Acetylphenyl)-5-benzyl-5-methylcyclopenta-1,3-dienyl trifluoromethanesulfonate 298



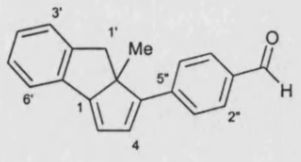
298

Using general procedure B the *monotriflate* **298** was produced as an orange yellow solid (4.4 mg, 5%); ν_{max} (KBr disc)/cm^{-1} 3029 and 2955 (unsaturated CH), 2926 and 2855 (saturated CH), 1712 (C=O), 1604 (C=C), 1454 (O-SO_2), 1214 (CF), 1119 (SO_2); δ_H (300 MHz, $CDCl_3$) 7.52-7.45 (1H, m, H-6"), 7.44-7.39 (1H, m, H-3"), 7.39-7.29 (2H, m, H-4", H-5"), 7.08-7.01 (3H, m, H-4', H-5', H-6'), 6.93-6.85 (2H, m, H-3', H-7'), 6.07 (1H, d, *J* 3.0, H-4,) 6.00 (1H, d, *J* 3.0, H-4), 3.14 (1H, d, *J* 13.9, 1 × H-1"), 2.98 (1H, d, *J* 13.9, 1 × H-1"), 1.96 (3H, s, MeC=O), 1.38 (3H, s, Me); sample failed to provide clear ^{13}C data due to lack of material; *m/z* (ES^+) 436.1 (100%, M^+); (Found $(M+NH_4)^+$, 454.1296. $C_{22}H_{24}NO_4SF_3$ requires 454.1300).

5-Benzyl-4-(4-formylphenyl)-5-methylcyclopenta-1,3-dienyl trifluoromethanesulfonate 299 and 4-(8,8a-dihydro-8a-methylcyclopenta[a]inden-1-yl)benzaldehyde 312



299



312

Using general procedure B produced in order of elution; the *tricyclic diene* **312** as a yellow solid (9.8 mg, 18%); mp 76-79°C (dec.); ν_{max} (KBr disc)/cm^{-1} 2959 (unsaturated CH), 2924 and 2853 (saturated CH), 1692 (C=O), 1599 (C=C); δ_H (300 MHz, C_6D_6) 9.79 (1H, s, HC=O), 7.68 (2H, d, *J* 8.6, H-2", H-6"), 7.38 (1H, d, *J* 7.2,

6'), 7.28 (2H, d, *J* 8.3, H-3", H-5"), 7.13-6.95 (3H, m, H-4', H-3', H-5'), 6.68 (1H, d, *J* 2.3, H-4), 6.25 (1H, d, *J* 2.3, H-5), 2.68 (1H, d, *J* 13.9, 1 × H-1'), 2.52 (1H, d, *J* 14.3, 1 × H-1'), 1.17 (3H, s, Me); δ_C (75 MHz, C_6D_6) 191.0 (C, C=O), 169.3 (C, C-1), 152.7 (C, C-3), 151.0 (C, C-2'), 140.8 (C, C-4"), 136.0 (C, C-7'), 135.5 (C, C-1"), 132.5 (CH, C-4), 130.6 (2 × CH, C-2", C-6"), 128.1 (CH, C-5'), 128.0 (CH, C-3'), 126.8 (CH, C-4'), 126.4 (2 × CH, C-3", C-5"), 122.6 (CH, C-6'), 119.6 (CH, C-5), 65.2 (C, C-2), 40.9 (CH_2, C-1'), 26.9 (CH_3, Me); *m/z* (EI^+) 272.2 (100%, M^+); (Found $(M)^+$, 272.1203. $C_{20}H_{16}O$ requires 272.1201); and the *monotriflate* **299** as a red orange solid (39.7 mg, 47%); mp 74-75°C (dec.); R_f(petroleum ether:EtOAc 9:1) 0.38; ν_{max} (KBr disc)/cm^{-1} 2978 (unsaturated CH), 2931 and 2802 (saturated CH), 1704 (C=O), 1600 (C=C), 1420 (O-SO_2), 1207 (CF), 1141 (SO_2); δ_H (300 MHz, $CDCl_3$) 9.99 (1H, s, HC=O), 7.89 (2H, d, *J* 8.3, H-2", H-6"), 7.65 (2H, d, *J* 8.7, H-3", H-5"), 7.09-6.95 (3H, m, H-3', H-7', H-5'), 6.77-6.68 (2H, m, H-4', H-6'), 6.58 (1H, d, *J* 3.0 H-4), 5.98 (1H, d, *J* 3.0, H-5), 3.25 (1H, d, *J* 13.6, 1 × H-1'), 3.06 (1H, d, *J* 13.6, 1 × H-1'), 1.55 (3H, s, Me); δ_C (75 MHz, C_6D_6) 190.9 (C, C=O), 160.2 (C, C-1), 145.2 (C, C-3), 140.4 (C, C-4"), 136.0 (C, C-2'), 135.9 (C, C-1"), 130.5 (2 × CH, C-2", C-6"), 129.5 (2 × CH, C-4', C-6'), 128.1 (2 × CH, C-3', C-7'), 127.9 (CH, C-4), 127.6 (CH, C-5'), 126.3 (2 × CH, C-3", C-5"), 119.5 (q, *J* 320, CF_3), 114.4 (CH, C-5), 56.4 (C, C-2), 41.5 (CH_2, C-1'), 21.3 (CH_3, Me). *m/z* (EI^+) 422.1 (80%, M^+); failed to provide accurate mass data due to instability.

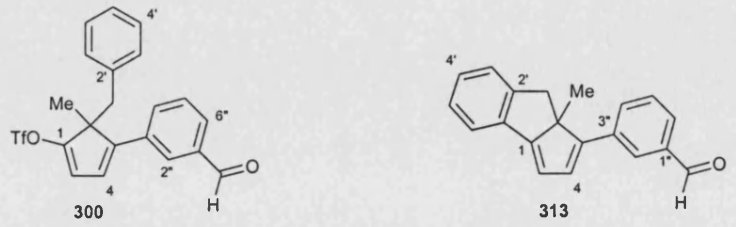
4-(8,8a-dihydro-8a-methylcyclopenta[a]inden-1-yl)benzaldehyde 312

299 312

Tri-*n*-butylamine (40.7 μL, 0.17 mmol) was added to a solution of the monotriflate **299** (produced using general procedure B) (24.1 mg, 0.057 mmol), $Pd(OAc)_2$ (1.3 mg, 0.0057 mmol, 10 mol %) and triphenylphosphine (3.3 mg, 0.0125 mmol, 22 mol %) in dry DMF (1 mL). The reaction mixture was then stirred at 60°C for 1 h under argon. The reaction mixture was partitioned between EtOAc (10 mL) and water (10 mL). The organic layer was then washed with water (3 × 5 mL), dried (Na_2SO_4), filtered, and then concentrated under reduced pressure. The residue was then purified by flash chromatography (5% diethyl ether/hexane) to yield the *tricyclic diene* **312** as a yellow solid (14.2 mg, 91%); data consistent with above.

The enantiomers of **312** were separated by HPLC using Chiracel AD column (99:1 hexane:*iso*propanol), 1.0 mL/min; t_r = 13.7 min and t_r = 14.9 min, 73% ee.

5-Benzyl-4-(3-formylphenyl)-5-methylcyclopenta-1,3-dienyl trifluoromethanesulfonate 300 and 3-(8,8a-dihydro-8a-methylcyclopenta[a]inden-1-yl)benzaldehyde 313



300 313

Using general procedure B produced in order of elution; the *tricyclic diene* **313** as a yellow solid (9.3mg, 17%); mp 82°C (dec.); ν_{max} (KBr disc)/cm^{-1} 2963 (unsaturated

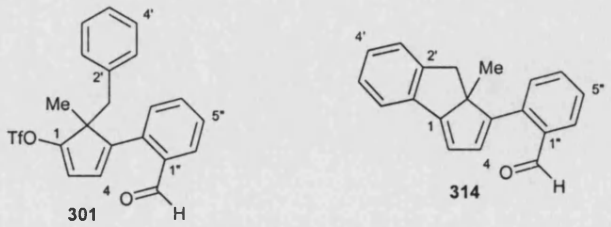
CH), 2926 and 2851 (saturated CH), 1700 (C=O), 1598 (C=C); (300 MHz, $CDCl_3$) 10.01 (1H, s, HC=O) 7.91 (1H, s, H-2"), 7.73-7.66 (2H, m, H-4", H-6"), 7.52-7.41 (2H, m, H-5", H-6'), 7.31-7.10 (3H, m, H-3', H-4', H-5'), 6.91 (1H, d, *J* 2.6, H-4), 6.39 (1H, d, *J* 2.2, H-5), 3.15 (1H, d, *J* 13.9, 1 × H-1'), 2.85 (1H, d, *J* 13.9, 1 × H-1'), 1.21 (3H, s, Me); δ_C (75 MHz, C_6D_6) 191.5 (C, C=O), 166.3 (C, C-1), 150.8 (C, C-3), 149.2 (C, C-2'), 135.8 (C, C-1"), 135.1 (C, C-3"), 134.4 (C, C-7'), 130.4 (CH, C-4"), 128.9 (CH, C-4), 128.3 (CH, C-5"), 127.1 (CH, C-5'), 126.2 (CH, C-4'), 126.1 (CH, C-3'), 125.3 (CH, C-6"), 125.1 (CH, C-2"), 120.8 (CH, C-6'), 117.9 (CH, C-5), 63.7 (C, C-2), 39.6 (CH_2, C-1'), 25.4 (CH_3, Me). *m/z* (EI^+) 422.1 (60%, M^+); failed to provide accurate mass, failed provide mass ion; and the *monotriflate* **300** as a red orange solid (48.1 mg, 57%); mp 87°C (dec.); R_f(petroleum ether:EtOAc 9:1) 0.41; ν_{max} (KBr disc)/cm^{-1} 3084 (unsaturated CH), 2984 and 2931 (saturated CH), 1705 (C=O), 1618 (C=C), 1419 (O-SO_2), 1213 (CF), 1137 (SO_2); δ_H (300 MHz, $CDCl_3$) 10.07 (1H, s, HC=O) 8.05 (1H, t, *J* 1.5, H-2"), 7.88-7.77 (2H, m, H-4", H-6"), 7.68-7.52 (1H, m, H-5''), 7.14-7.03 (3H, m, H-4', H-5', H-6'), 6.84-6.79 (2H, m, H-3', H-7'), 6.55 (1H, d, *J* 3.0, H-4), 6.06 (1H, d, *J* 3.0, H-5), 3.26 (1H, d, *J* 13.9, 1 × H-1'), 3.10 (1H, d, *J* 13.9 1 × H-1'), 1.62 (3H, s, Me); δ_C (75 MHz, $CDCl_3$) 191.6 (C, C=O), 159.4 (C, C-1), 145.3 (C, C-3), 137.2 (C, C-1"), 136.2 (C, C-3"), 135.7 (C, C-2'), 132.0 (CH, C-4"), 129.9 (CH, C-5"), 129.4 (CH, C-6"), 129.3 (2 × CH, C-3', C-7'), 128.0 (2 × CH, C-4', C-6'), 127.2 (CH, C-2"), 126.8 (CH, C-5'), 126.2 (CH, C-4), 119.0 (q, *J* 320, CF_3), 114.0 (CH, C-5), 56.4 (C, C-2), 41.5 (CH_2, C-1'), 21.6 (CH_3, Me). *m/z* (EI^+) 422.1 (50%, M^+); failed to provide accurate mass due to instability.

3-(8,8a-dihydro-8a-methylcyclopenta[a]inden-1-yl)benzaldehyde 313

Dry degassed DME (4.4 mL) was added to a mixture of the monotriflate **300** (44.4 mg, 0.11 mmol), $Pd(OAc)_2$ (3.7 mg, 0.0165 mmol, 15 mol %), triphenylphosphine (10.1 mg, 0.0385 mmol, 35 mol %) and cesium fluoride (50.1 mg, 3.3 mmol). The reaction mixture was then stirred at rt for 18 h under argon. The reaction mixture was partitioned between EtOAc (10 mL) and water (10 mL). The organic layer was then washed with water (3 × 5 mL), dried (Na_2SO_4), filtered, and then concentrated under reduced pressure. The residue was then purified by flash chromatography (5% diethyl ether/hexane) to yield the *tricyclic diene* **313** as a yellow solid (15.3 mg, 51%); data consisten with above.

The enantiomers of **313** were separated by HPLC using Chiracel OJ column (99:1 hexane:*iso*propanol), 1.0 mL/min; t_r = 22.3 min and t_r = 30.1 min, 80% ee.

5-Benzyl-4-(2-formylphenyl)-5-methylcyclopenta-1,3-dienyl trifluoromethanesulfonate 301 and 2-(8,8a-dihydro-8a-methylcyclopenta[a]inden-1-yl)benzaldehyde 314

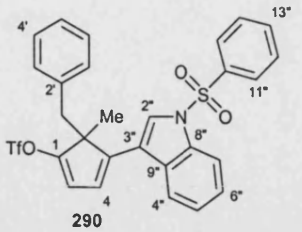


Using general procedure B produced in order of elution; the *tricyclic diene* **314** as a yellow solid (5.4mg, 10%); mp 87°C; R_f(petroleum ether:EtOAc 9:1) 0.59; ν_{max} (KBr disc)/cm^{-1} 2963 (unsaturated CH), 2906 and 2830 (saturated CH), 1699 (C=O), 1652

(C=C); δ_H (400 MHz, CD_2Cl_2) 10.06 (HC=O), 7.87 (1H, d, *J*, 7.8, H-6"), 7.57-7.53 (1H, m, H-4"), 7.48-7.39 (2H, m, H-3", H-6'), 7.37-7.33 (1H, m, H-5"), 7.26 (1H, d, *J* 7.4, H-4') 7.22-7.18 (1H, m, H-5'), 7.15-7.09 (1H, m, H-3'), 6.42 (1H, d, *J* 2.2, H-4), 6.32 (1H, d, *J* 2.3, H-5), 3.03 (1H, d, *J* 13.8, 1 × H-1'), 2.87 (1H, d, *J* 13.8, 1 × H-1'), 1.04 (3H, s, Me); δ_C (100 MHz, CD_2Cl_2) 192.8 (C, C=O), 167.5 (C, C-1), 151.4 (C, C-3), 148.7 (C, C-2'), 146.8 (C, C-7') 140.5 (C, C-7), 137.8 (CH, C-4"), 135.9 (C, C-1"), 133.9 (CH, C-6"), 129.9 (CH, C-4), 128.6 (CH, C-5"), 128.0 (CH, C-4') 128.0 (CH, C-3'), 127.9 (CH, C-3"), 126.9 (CH, C-5'), 122.6 (CH, C-6'), 119.9 (CH, C-5), 67.4 (C, C-2), 41.7 (CH_2, C-1'), 21.0 (CH_3, Me); *m/z* (ES^+) 273.1 (100%, M^+); (Found $(M+H)^+$, 273.1270. $C_{20}H_{17}O$ requires 273.1274); and the *monotriflate* **301** was produced as an orange brown solid (34.6 mg, 41%); mp 46-48°C; R_f(petroleum ether:EtOAc 9:1) 0.44; ν_{max} (KBr disc)/cm^{-1} 3060 (unsaturated CH), 2919 and 2878 (saturated CH), 1682 (C=O), 1595 (C=C), 1423 (O-SO_2), 1223 (CF), 1136 (SO_2); δ_H (300 MHz, $CDCl_3$) 8.89 (1H, s, HC=O), 7.90 (1H, d, *J* 7.2, H-6"), 7.60-7.52 (2H, m, C-3", C-4"), 7.43-7.36 (1H, m, C-5") 7.12-7.00 (3H, m, H-4', H-5', H-6'), 6.74-6.70 (2H, m, H-3', H-7'), 6.16 (1H, d, *J* 3.0, H-4), 5.92 (1H, d, *J* 3.0, H-5), 3.03 (1H, d, *J* 13.9, 1 × H-1'), 2.84 (1H, d, *J* 13.9, 1 × H-1'), 1.58 (3H, s, Me); δ_C (75 MHz, C_6D_6) 191.2 (C, C=O), 158.7 (C, C-1), 149.1 (C, C-3), 142.9 (C, C-1"), 139.1 (C, C-2"), 136.3 (C, C-2'), 135.6 (CH, C-4"), 132.7 C, C-1"), 132.2 (CH, C-6"), 129.8 (CH, C-5"), 129.1 (2 × CH, C-4', C-6'), 128.7 (2 × CH, C-3', C-7'), 127.5 (CH, C-3") 127.17 (CH, C-5'), 125.9 (CH, C-4), 119.0 (q, *J* 320, CF_3), 114.1 (CH, C-5), 56.8 (C, C-2), 40.3 (CH_2, C-1'), 21.2 (CH_3, Me); *m/z* (EI^+) 422.1 (80%, M^+); failed to provide accurate mass due to instability.

The enantiomers of **301** were separated by HPLC using Chiracel OD column (99:1 hexane:*iso*propanol), 1.0 mL/min; t_r = 8.3 min and t_r = 9.6 min, 82% ee

5-Benzyl-5-methyl-4-(1-(phenylsulfonyl)-1*H*-indol-3-yl)cyclopenta-1,3-dienyl trifluoromethanesulfonate 290

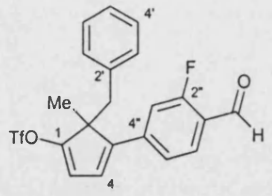


290

Using general procedure B the *monotriflate* **290** was produced as a red-brown solid (75.6 mg, 66%); mp 55-56°C (dec.); R_f(petroleum ether:EtOAc 9:1) 0.40; ν_{max} (KBr disc)/cm^{-1} 2979 (unsaturated CH), 2929 and 2858 (saturated CH), 1616 (C=C), 1447 (O-SO_2), 1373 (SO_2-N), 1175 (SO_2-N), 1175 (CF), 1129 (SO_2); δ_H (400 MHz, CD_2Cl_2) 8.02 (1H, d, *J* 8.4, H-7"), 7.89-7.84 (2H, m, H-11", H-15"), 7.75 (1H, s, H-2"), 7.55 (1H, d, *J* 8.0, H-4") 7.52-7.46 (1H, m, H-13"), 7.42-7.35 (2H, m, H-12", H-14"), 7.34-7.30 (1H, m, H-6"), 7.23-7.19 (1H, m, H-5"), 7.00-6.95 (1H, m, H-5'), 6.89 (2H, m, H-4', H-6'), 7.64 (2H, d, *J* 7.3, H-3', H-7'), 6.45 (1H, d, *J* 3.0, H-4), 5.95 (1H, d, *J* 3.0, H-5), 3.06 (1H, d, *J* 13.7, 1 × H-1"), 3.00 (1H, d, *J* 13.7, 1 × H-1"), 1.50 (3H, s, Me); δ_C (75 MHz, $CDCl_3$) 158.2 (C-1), 139.4 (C-3), 137.8 (C-2'), 135.2 (C-10"), 135.2 (C-8"), 134.1 (CH, C 13"), 129.7 (C-9"), 129.4 (2 × CH, C-12"), 128.9 (2 × CH, C-3'), 127.6 (2 × CH, C-4'), 126.7 (2 × CH, C-11"), 126.7 (CH, C-5'), 125.7 (CH, C-6"), 125.5 (CH, C-4), 124.0 (CH, C-5"), 122.7 (CH, C-2"), 121.33 (CH, C-4"), 118.6 (q, *J* 321, CF_3), 117. 6 (C-3"), 114.2 (CH, C-7"), 113.9 (CH, C-5), 57.4 (C-2), 42.4 (C-1'), 22.3 (C-H_3); *m/z* (ES^-) 572.2 (100%, *M-H*); (Found (*M*-H), 572.0814. $C_{28}H_{21}NO_5S_2F_3$ requires 572.0813).

The enantiomers of **290** were separated by HPLC using Chiracel AD column (99:1 hexane:*iso*propanol), 0.8 mL/min; t_r = 19.1 min and t_r = 22.4 min, 85% ee.

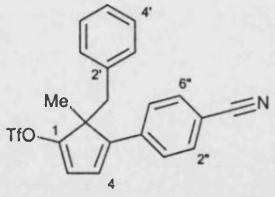
5-Benzyl-4-(3-fluoro-4-formylphenyl)-5-methylcyclopenta-1,3-dienyl trifluoromethanesulfonate 302



302

Using general procedure B the *monotriflate* **302** was produced as an orange solid (4.5 mg, 5%); mp 68-69°C; R_f(petroleum ether:EtOAc 9:1) 0.46; ν_{max} (KBr disc)/cm^{-1} 3030 and 2993 (unsaturated CH), 2944 and 2852 (saturated CH), 1697 (C=O), 1614 (C=C), 1428 (O-SO_2), 1227 (CF), 1139 (SO_2); δ_H (300 MHz, CD_2Cl_2) 10.24 (1H, s, HC=O), 7.79 (1H, t, *J* 8.0, H-6"), 7.39 (1H, dd, *J* 8.3, 1.1, H-5"), 7.16 (1H, dd, *J* 12.4, 1.9, H-3"), 7.03-6.94 (3H, m, H-4', H-5', H-6'), 6.74-6.70 (2H, m, H-3', H-7'), 6.60 (1H, d, *J* 3.0 H-4), 5.97 (1H, d, *J* 3.0, H-5), 3.19 (1H, d, *J* 13.9, 1 × H-1'), 3.03 (1H, d, *J* 13.9, 1 × H-1'), 1.52 (3H, s, Me); δ_C (75 MHz, CD_2Cl_2) 185.5 (C, d, *J* 6, C=O), 164.0 (d, *J* 257, C-F), 159.6 (C, C-1), 143.1 (C, d, *J* 3, C-3), 141.8 (C, d, *J* 9, C-4"), 134.5 (C, C-2'), 128.3 (CH, d, *J* 3, C-6"), 128.0 (2 × CH, C-4', C-6'), 128.0 (CH, C-4), 126.9 (2 × CH, C-3', C-7'), 126.0 (CH, C-5'), 121.8 (C, d, *J* 9, C-1"), 121.0 (CH, d, *J* 3, C-5"), 117.8 (q, *J* 321, CF_3), 112.8 (CH, C-5), 112.1 (CH, *J* 22, C-3"), 55.4 (C, C-2), 40.1 (CH_2, C-1'), 20.2 (CH_3, Me); *m/z* (EI^+) 440.1 (5%, M^+); (Found (M^+), 440.0700. $C_{21}H_{16}O_4SF_4$ requires 440.0700).

5-Benzyl-4-(4-cyanophenyl)-5-methylcyclopenta-1,3-dienyl trifluoromethanesulfonate 303

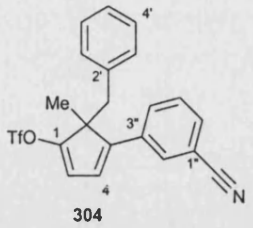


303

Using general procedure B the *monotriflate* **303** was produced as an orange yellow solid (22.7 mg, 27%); mp 59-61°C; R_f(petroleum ether:EtOAc 9:1) 0.44; ν_{max} (KBr disc)/cm^{-1} 3069 and 3032 (unsaturated CH), 2974 and 2935 (saturated CH), 2224 (CN), 1602 (C=C), 1411 (O-SO_2), 1223 (CF), 1141 (SO_2); δ_H (300 MHz, $CDCl_3$) 7.61 (2H, d, *J* 8.3, H-2", H-6"), 7.57 (2H, d, *J* 8.7, H-3", H-5"), 7.09-6.99 (3H, m, H-3', H-7', H-5'), 6.72-6.65 (2H, m, H-4', H-6'), 6.54 (1H, d, *J* 3.0, H-4), 5.98 (1H, d, *J* 3.0, H-5), 3.18 (1H, d, *J* 13.6, 1 × H-1'), 3.05 (1H, d, *J* 13.9, 1 × H-1'), 1.54 (3H, s, Me); δ_C (75 MHz, $CDCl_3$) 160.2 (C, C-1), 144.7 (C, C-3), 139.4 (C, C-4"), 135.4 (C, C-2'), 133.0 (2 × CH, C-2", C-6"), 129.2 (2 × CH, C-4', C-6'), 128.1 (CH, C-4), 128.1 (2 × CH, C-3', C-7'), 127.3 (CH, C-5'), 126.4 (2 × CH, C-3", C-5"), 119.2 (C, CN), 119.0 (q, J 321, CF_3), 114.0 (CH, C-5), 111.0 (C, C-1"), 56.5 (C, C-2), 41.5 (CH_2, C-1'), 21.5 (CH_3, Me); *m/z* (EI^+) 419.1 (20%, M^+); (Found $(M+NH_3)^+$, 419.0801. $C_{21}H_{16}NO_3SF_3$ requires 419.0803).

The enantiomers of **303** were separated by HPLC using Chiracel AD column (99:1 hexane:*iso*propanol), 1.0 mL/min; t_r = 11.6 min and t_r = 13.3 min, 55% ee.

5-Benzyl-4-(3-cyanophenyl)-5-methylcyclopenta-1,3-dienyl trifluoromethanesulfonate 304

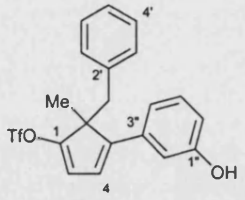


304

Using general procedure B the *monotriflate* **304** was produced as a yellow solid (18.2 mg, 22%); mp 52-53°C; R_f(petroleum ether:EtOAc 9:1) 0.44; ν_{max} (KBr disc)/cm^{-1} 3082 and 3032 (unsaturated CH), 2933 and 2872 (saturated CH), 2236 (CN), 1617 (C=C), 1419 (O-SO_2), 1215 (CF), 1137 (SO_2); δ_H (300 MHz, $CDCl_3$) 7.68 (1H, s, H-2"), 7.67-7.64 (1H, m, H-6"), 7.58-7.50 (1H, m, H-4"), 7.48-7.40 (1H, m, H-5"), 7.09-6.97 (3H, m, H-4', H-5', H-6'), 6.73-6.68 (2H, m, H-3', H-7'), 6.41 (1H, d, *J* 3.0, H-4), 5.97 (1H, d, *J* 3.0, H-5), 3.12 (1H, d, *J* 13.9, 1 × H-1'), 3.00 (1H, d, *J* 13.6, 1 × H-1'), 1.52 (3H, s, Me); δ_C (75 MHz, $CDCl_3$) 159.6 (C, C-1), 144.5 (C, C-3), 136.5 (C, C-3"), 135.5 (C, C-2'), 131.0 (CH, C-6"), 130.3 (CH, C-4"), 130.1 (CH, C-2"), 129.6 (CH, C-5"), 129.2 (2 × CH, C-4', C-6'), 128.1 (2 × CH, C-3', C-7'), 127.3 (CH, C-4), 127.0 (CH, C-5'), 119.1 (C, CN), 119.0 (q *J* 321, CF_3), 113.9 (CH, C-5), 113.5 (C, C-1"), 56.4 (C, C-2), 41.4 (CH_2, C-1'), 21.4 (CH_3, Me); *m/z* (EI^+) 419.2 (78%); (Found $(M+NH_4)^+$, 437.1147. $C_{21}H_{20}N_2O_3SF_3$ requires 437.1147).

The enantiomers of **304** were separated by HPLC using Chiracel AD column (99:1 hexane:*iso*propanol), 1.0 mL/min; t_r = 7.8 min and t_r = 8.2 min, 44% ee.

5-Benzyl-4-(3-hydroxyphenyl)-5-methylcyclopenta-1,3-dienyl trifluoromethanesulfonate 305

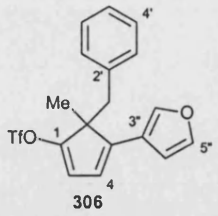


305

Using general procedure B the *monotriflate* **305** was produced as a blue solid (35.3 mg, 43%); mp 82°C (dec.); ν_{max} (KBr disc)/cm^{-1} 3414 (OH), 2969 (unsaturated CH), 2931 and 2860 (saturated CH), 1602 (C=C), 1426 (O-SO_2), 1214 (Aromatic C-OH), 1139 (SO_2); δ_H (300 MHz, $CDCl_3$) 7.22-7.14 (1H, m, H-5"), 7.08-7.04 (1H, m, H-4"), 7.02-6.95 (3H, m, H-4', H-5', H-6'), 6.92 (1H, s, H-2") 6.81-6.74 (2H, m, H-3', H-7'), 6.72-6.67 (1H, m, H-6"), 6.30 (1H, d, *J* 3.0, H-4), 5.85 (1H, d, *J* 3.0, H-5), 4.85 (1H, br s, OH), 3.19 (1H, d, 1 × H-1'), 2.93 (1H, d, 1 × H-1'), 1.58 (3H, s, Me); δ_C (100 MHz, CD_2Cl_2) 159.3 (C, C-1"), 156.8 (C, C-1), 146.8 (C, C-3), 137.2 (C, C-3"), 136.7 (C, C-2'), 130.7 (CH, C-5"), 129.8 (2 × CH, C-4', C-6'), 128.3 (2 × CH, C-3', C-7'), 127.3 (CH, C-5'), 125.2 (CH, C-4), 119.4 (q, *J* 322, CF_3), 119.2 (CH, C-4"), 115.3 (CH, C-6"), 114.4 (CH, C-5), 113.4 (CH, C-2"), 56.7 (C, C-2), 41.7 (CH_2, C-1'), 22.0 (CH_3, Me); *m/z* (EI^+) 410.2 (100%, M^+); (Found $(M)^+$, 410.0795. $C_{20}H_{17}O_4SF_3$ requires 410.0794).

The enantiomers of **305** were separated by HPLC using Chiracel OD column (99:1 hexane:*iso*propanol), 0.7 mL/min; t_r = 97.7 min and t_r = 106.4 min, 74% ee.

5-Benzyl-4-(furan-3-yl)-5-methylcyclopenta-1,3-dienyl trifluoromethanesulfonate 306

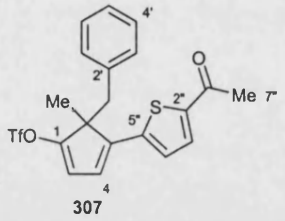


306

Using general procedure B the *monotriflate* **306** was produced as a brown solid (40.7 mg, 53%); R_f(hexane:DCM 9:1) 0.52; ν_{max} (KBr disc)/cm^{-1} 3138 and 3025 (unsaturated CH), 2963 and 2925 (saturated CH), 1559 (C=C), 1420 (O-SO_2), 1223 (Aromatic C-O-C), 1213 (CF), 1140 (SO_2);); δ_H (300 MHz, CD_2Cl_2) 7.61 (1H, s, H-2"), 7.42 (1H, t *J* 1.7, H-4"), 7.05-6.95 (3H, m, H-4', H-5', H-6'), 6.84-6.78 (2H, m, H-3', H-7'), 6.52 (1H, dd, *J* 1.9, 0.9, H-5"), 6.11 (1H, d, *J* 3.0, H-4), 5.87 (1H, d, *J* 3.0, H-5), 2.97 (2H, app s, 2 × H-1'), 1.37 (3H, s, Me); δ_C (75 MHz, CD_2Cl_2) 158.8 (C, C-1), 144.2 (CH, C-5"), 140.6 (C, C-3), 137.9 (CH, C-2"), 136.5 (C, C-2'), 129.7 (2 × CH, C-4', C-6'), 128.3 (2 × CH, C-3', C-7'), 127.4 (CH, C-5'), 122.3 (C, C-3"), 121.5 (CH, C-4), 119.2 (q, *J* 318, CF_3), 109.2 (CH, C-4"), 56.2 (C, C-2), 42.5 (CH_2, C-1'), 22.3 (CH_3, Me); *m/z* (EI^+) 384.2 (100%, M^+); (Found $(M)^+$, 384.0633. $C_{18}H_{15}O_4SF_3$ requires 384.0638).

The enantiomers of **306** were separated by HPLC using Chiracel OJ column (99:1 hexane:*iso*propanol), 0.5 mL/min; t_r = 14.2 min and t_r = 16.0 min, 72% ee.

4-(5-Acetylthiophen-2-yl)-5-benzyl-5-methylcyclopenta-1,3-dienyl trifluoromethanesulfonate 307

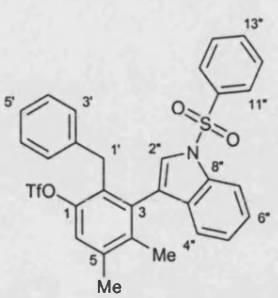


307

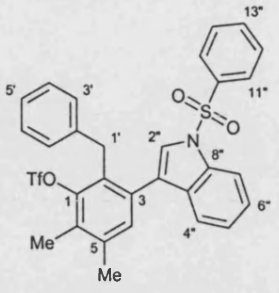
Using general procedure B the *monotriflate* **307** was produced as a purple solid (35.1 mg, 40%); mp 102-103°C; ν_{max} (KBr disc)/cm^{-1} 3065 and 3032 (unsaturated CH), 2982 and 2926 (saturated CH), 1653 (C=O), 1612 (C=C), 1420 (O-SO_2), 1227 (CF), 1133 (SO_2); δ_H (400 MHz, C_6D_6) 7.17 (1H, d, *J* 4.0, H-3"), 7.09-6.98 (5H, m, H-3', H-4', H-5', H-6', H-7'), 6.74 (1H, d, *J* 4.0, H-4"), 5.98 (1H, d, *J* 3.0, H-4), 5.68 (1H, d, *J* 3.0, H-5), 3.06 (1H, d, *J* 13.6, 1 × H-1'), 2.86 (1H, d, *J* 13.6, 1 × H-1'), 2.18 (3H, s, Me-7") 1.32 (3H, s, Me); δ_C (100 MHz, C_6D_6) 189.4 (C, C=O), 159.9 (C, C-1), 146.0 (C, C-2"), 143.3 (C, C-5"), 141.0 (C, C-3), 135.9 (C, C-2'), 132.97 (CH, C-3"), 129.5 (2 × CH, C-3', C-7'), 128.6 (2 × CH, C-4', C-6'), 127.7 (CH, C-4"), 126.8 (CH, C-5'), 124.3 (CH, C-4), 119.5 (q, *J* 321, CF_3), 114.8 (CH, C-5), 56.7 (C, C-2), 41.8 (CH_2, C-1'), 26.6 (CH_3, Me-7"), 21.5 (CH_3, Me); *m/z* (ES^+) 443.1 (100%, M^+); (Found $(M+H)^+$, 443.0592. $C_{20}H_{18}O_4S_2F_3$ requires 443.0593).

The enantiomers of **307** were separated by HPLC using Chiracel AD column (97:3 hexane:*iso*propanol), 1.0 mL/min; t_r = 7.7 min and t_r = 8.9 min, 53% ee.

2-Benzyl-4,5-dimethyl-3-(1-(phenysulfonyl)-1*H*-indol-3-yl)phenyl trifluoromethanesulfonate 351 and 2-benzyl-5,6-dimethyl-3-(1-(phenylsulfonyl)-1*H*-indol-3-yl)phenyl trifluoromethanesulfonate 352



351



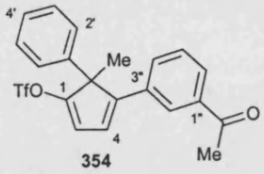
352

Using general procedure on bis-triflate **347** (51.2 mg, 0.1 mmol) B the *monotriflates* **351** and **352** (35.5 mg, 59% 4:1) were produced as an inseparable mixture of regioisomers as a brown viscous oil; R_f(petroleum ether:EtOAc 9:1) 0.61; ν_{max} (KBr disc)/cm^{-1} 3064 (unsaturated CH), 2927 and 2849 (saturated CH), 1604 (C=C), 1448 (O-SO_2), 1373 (SO_2-N), 1245 and 1215 (CF), 1187 (SO_2-N), 1131 (SO_2); NMR analysis of major regioisomer **351** only, δ_H (300 MHz, $CDCl_3$) 7.02 (1H, dt, *J* 8.3, 0.8, H-7"), 7.65-7.61 (2H, m, H-11", H-15"), 7.45-7.39 (1H, m, H-13"), 7.27-7.18 (4H, m, H-12", H-14", H-6", H-2") 7.13 (1H, s, H-6), 7.07-7.01 (1H, m, H-5"), 7.00-6.97 (3H, m, H-4', H-5', H-6'), 6.81 (1H, app ddd, *J* 7.9, 1.1, 0.7, H-4"), 6.56-6.52 (2H, m, H-3', H-7'), 3.78 (1H, d, *J* 15.8, 1 × H-1"), 3.47 (1H, d, *J* 15.8, 1 × H-1"), 2.29 (3H, s, Me-5) 1.80 (3H, s, Me-4); δ_C (100 MHz, $CDCl_3$) 146.7 (C, C-1), 139.5 (C, C-2'), 138.3(C, C-10"), 138.2 (C, C-3), 138.0 (C, C-5), 135.1 (C, C-8"), 135.1 (C, C-2), 134.3 (CH, C-13"), 131.1 (C, C-9"), 130.8 (C, C-4), 129.7 (2 × CH, C-12", C-14"), 128.5 (2 × CH, C-3', C-7'), 128.2 (2 × CH, C-4', C-6'), 127.1 (2 × CH, C-11", C-15"), 126.4 (CH, C-5'), 125.6 (CH, C-6"), 124.7 (CH, C-2"), 124.2 (CH, C-5"), 122.7 (CH, C-6), 121.6 (C, C-3"), 119.2 (q, *J* 320, CF_3), 114.2 (CH, C-7"), 34.2 (CH_2, C-1'), 21.1 (CH_3, Me-5), 17.6 (CH_3, Me-4); δ_F (376 MHz, $CDCl_3$) -73.89; *m/z*

(CI^+) 617.2 (20%, M+NH_4)$^+$; (Found (M+NH_4)$^+$, 617.1389. $C_{30}H_{28}O_5N_2F_3S_2$ requires 617.1386).

The enantiomers of **351** were separated by HPLC using Chiracel AD column (99:1 hexane:*iso*propanol), 1.0 mL/min; t_r = 8.8 min and t_r = 10.2 min, 16% ee.

4-(3-Acetylphenyl)-5-methyl-5-phenylcyclopenta-1,3-dienyl trifluoromethanesulfonate 354

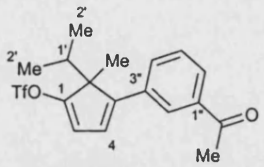


354

Using general procedure B on bis-triflate **315** (90.5 mg, 0.2 mmol) the *monotriflate* **354** (13.6 mg, 16%) was produced as a clear/yellow oil; R_f(petroleum ether:EtOAc 9:1) 0.38; ν_{max} (Film)/cm^{-1} 3063 and 2981 (unsaturated CH), 2938 and 2877 (saturated CH), 1684 (C=O), 1617 (C=C), 1425 (O-SO_2), 1215 (CF), 1141 (SO_2); δ_H (300 MHz, $CDCl_3$) 7.78-7.74 (1H, m, H-6"), 7.72-7.70 (1H, m, H-2"), 7.38-7.24 (7H, m, H-4', H-5" H-3', H-5', H-4", H-2', H-6'), 6.90 (1H, d, *J* 3.0, H-4), 6.28 (1H, d, *J* 3.0, H-5), 2.39 (3H, s, MeC=O), 1.71 (3H, s, Me); δ_C (75 MHz, $CDCl_3$) 198.2 (C, C=O), 162.3 (C, C-1), 149.7 (C, C-3), 137.6 (C, C-1"), 136.4 (C, C-1'), 134.0 (C, C-3"), 130.6 (CH, C-4"), 129.6 (2 × CH, C-3', C-5'), 129.2 (CH, C-4'), 128.3 (CH, C-5"), 127.5 (CH, C-6"), 126.5 (2 × CH, C-2', C-6'), 126.2 (CH, C-2"), 124.6 (CH, C-4), 118.7 (q, *J* 321, CF_3), 113.3 (CH, C-5), 57.9 (C, C-2), 26.8 (CH_3, MeC=O), 18.9 (CH_3, Me); *m/z* (ES^+) 440.2 (52%, M+NH_4)$^+$, (Found (M+NH_4)$^+$, 440.1135. $C_{21}H_{21}NO_4SF_3$ requires 440.1138).

The enantiomers **354** were separated by HPLC using Chiracel AD column (99:1 hexane:*iso*propanol), 0.7 mL/min; t_r = 13.3 min and t_r = 15.7 min, 61% ee

4-(3-Acetylphenyl)-5-*iso*-propyl-5-methylcyclopenta-1,3-dienyl trifluoromethanesulfonate 355

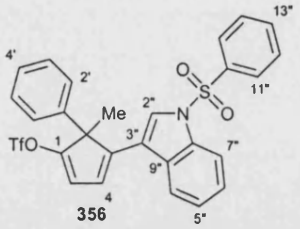


355

Using general procedure B on bis-triflate **316** (83.6 mg, 0.2 mmol) the *monotriflate* **355** (24.8 mg, 32%) was produced as a clear/yellow oil; R_f(petroleum ether:EtOAc 9:1) 0.50; ν_{max} (Film)/cm^{-1} 2968 (unsaturated CH), 2932 and 2878 (saturated CH), 1685 (C=O), 1617 (C=C), 1424 (O-SO_2), 1216 (CF), 1141 (SO_2); δ_H (300 MHz, $CDCl_3$) 8.00 (1H, t, *J* 1.9, H-2"), 7.87 (1H, ddd, *J* 7.2, 1.9, 1.1, H-6"), 7.61 (1H, ddd, *J* 7.8, 1.9, 1.2, H-4"), 7.50-7.41 (1H, td, *J* 7.8, 0.4, H-5"), 6.50 (1H, d, *J* 3.0, H-4), 6.24 (1H, d, *J* 3.0, H-5), 2.62 (3H, s, MeC=O), 2.03 (1H, m, H-1'), 1.56 (3H, s, Me), 1.07 (3H, d, *J* 7.2, Me-2'), 0.52 (3H, d, *J* 6.8, Me-2'); δ_C (75 MHz, $CDCl_3$) 198.3 (C, C=O), 159.0 (C, C-1), 149.1 (C, C-3), 137.8 (C, C-1"), 136.8 (C, C-3"), 131.7 (CH, C-4"), 129.2 (CH, C-5"), 127.9 (CH, C-6"), 126.8 (CH, C-2"), 125.7 (CH, C-4), 118.9 (q, *J* 320, CF_3), 114.4 (CH, C-5), 59.0 (C, C-2), 32.9 (CH, C-1'), 27.1 (CH_3, MeC=O), 19.4 (CH_3, Me), 17.7 (CH_3, Me-2') 17.4 (CH_3, Me-2'); *m/z* (EI^+) 388.2 (14%, M^+); (Found $(M)^+$, 388.0950. $C_{18}H_{19}O_4SF_3$ requires 388.0951).

The enantiomers of **355** were separated by HPLC using Chiracel OD-H column (99:1 hexane:*iso*propanol), 0.7 mL/min; t_r = 13.2 min and t_r = 16.3 min, 46% ee.

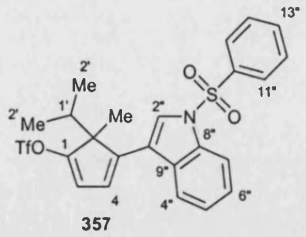
5-Phenyl-5-methyl-4-(1-(phenylsulfonyl)-1*H*-indol-3-yl)cyclopenta-1,3-dienyl trifluoromethanesulfonate 356



Using general procedure B on bis-triflate **315** (90.5 mg, 0.2 mmol) the *monotriflate* **356** (22.3 mg, 20%) was produced as a red-brown solid; mp 72-74°C; ν_{max} (KBr disc)/cm^{-1} 3063 (unsaturated CH), 2964 and 2919 (saturated CH), 1615 (C=C), 1447 (O-SO_2), 1370 (SO_2-N), 1213 (CF), 1176 (SO_2-N), 1139 (SO_2); δ_H (300 MHz, $CDCl_3$) 7.95-7.90 (1H, m, H-7"), 7.76-7.70 (1H, m, H-4"), 7.48-7.36 (3H, m, H-11", H-13", H-15"), 7.32-7.23 (7H, m, H-4', H-3', H-5', H-6", H-5", H-12", H-14"), 7.18-7.11 (2H, m, H-2', H-6'), 6.81 (1H, d, *J* 2.6, H-4), 6.71 (1H, s, H-2"), 6.25 (1H, d, *J* 3.0, H-5), 1.67 (3H, s, Me); δ_C (75 MHz, $CDCl_3$) 161.7 (C, C-1), 144.7 (C, C-3), 137.9 (C, C-10"), 137.0 (C, C-1'), 135.5 (C, C-8"), 134.2 (C-H, C-13"), 129.7 (C, C-9"), 129.5 (2 × CH, C-3', C-5'), 129.5 (2 × CH, C-12", C-14"), 128.3 (CH, C-4'), 127.1 (2 × CH, C-11", C-15"), 126.7 (2 × CH, C-2', C-6'), 125.6 (CH, C-6"), 124.4 (CH, C-5"), 123.8 (CH, C-4), 123.8 (CH, C-2"), 121.4 (CH, C-4"), 118.8 (q, *J* 321, CF_3), 116.4 (C-3"), 114.4 (CH, C-7"), 113.9 (CH, C-5), 58.7 (C, C-2), 20.1 (CH_3, Me); *m/z* (ES^-) 558.2 (100%, *M-H*); (Found (*M*-H), 558.0651. $C_{27}H_{19}NO_5S_2F_3$ requires 558.0662).

The enantiomers of **356** were separated by HPLC using Chiracel AD column (99:1 hexane:*iso*propanol), 1.0 mL/min; t_r = 19.8 min and t_r = 23.1 min, 59% ee.

5-*iso*-Propyl-5-methyl-4-(1-(phenylsulfonyl)-1*H*-indol-3-yl)cyclopenta-1,3-dienyl trifluoromethanesulfonate 357

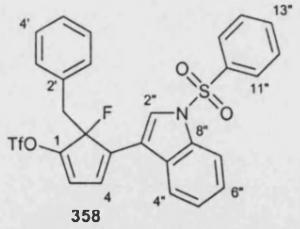


357

Using general procedure B on bis-triflate **316** (41.8 mg, 0.1 mmol) the *monotriflate* **357** (17.4 mg, 33%) was produced as a red-brown solid; mp 56-58°C (dec.); R_f(petroleum ether:EtOAc 9:1) 0.45; ν_{max} (KBr disc)/cm^{-1} 2962 (unsaturated CH), 2926 and 2855 (saturated CH), 1619 (C=C), 1449 (O-SO_2), 1373 (SO_2-N), 1173 (SO_2-N), 1132 (SO_2); δ_H (300 MHz, CD_2Cl_2) 7.93 (1H, d, *J* 8.1, H-7"), 7.81 (2H, d, *J* 7.91, H-11", H-15"), 7.65- (1H, d, *J* 7.9, H-4"), 7.55 (1H, s, H-2") 7.54-7.46 (1H, m, H-13"), 7.43-7.36 (2H, m, H-12", H-14"), 7.34-7.13 (2H, m, H-6", H-5"), 6.57 (1H, d, *J* 3.0, H-4), 6.22 (1H, d, *J* 3.0, H-5), 2.04-1.90 (1H, m, H-1'), 1.40 (3H, s, Me), 1.01 (3H, d, *J* 6.9, 1 × Me-2'), 0.52 (3H, d, *J* 6.8, 1 × Me-2'); δ_C (75 MHz, CD_2Cl_2) 159.1 (C, C-1), 142.5 (C, C-3), 138.1 (C, C-10"), 135.7 (C, C-8"), 134.9 (CH, C-13"), 130.8 (C, C-9"), 130.2 (2 × CH, C-12", C-14"), 127.5 (2 × CH, C-11", C-15"), 126.3 (CH, C-6"), 126.0 (CH, C-4), 124.6 (CH, C-5"), 123.1 (CH, C-4"), 121.7 (CH, C-2"), 118.2 (C-3"), 115.5 (CH, C-5), 114.4 (CH, C-7"), 59.7 (C, C-2), 34.3 (CH, C-1'), 19.8 (CH_3, Me), 18.0 (CH_3, Me-2') 17.5 (CH_3, Me-2'); *m/z* (ES^+) 526.2 (100%, *M*+H); (Found $(M+NH_4)^+$, 543.1227. $C_{24}H_{26}N_2O_5S_2F_3$ requires 543.1230).

The enantiomers of **357** were separated by HPLC using Chiracel OD-H column (99:1 hexane:*iso*propanol), 1.0 mL/min; t_r = 9.4 min and t_r = 10.5 min, 58% ee.

5-Benzyl-5-fluoro-4-(1-(phenylsulfonyl)-1*H*-indol-3-yl)cyclopenta-1,3-dienyl trifluoromethanesulfonate 358

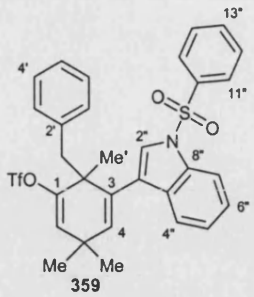


358

Using general procedure B on bis-triflate **346** (47.0 mg, 0.1 mmol) the *monotriflate* **358** (7.8 mg, 14%) was produced as a purple brown solid; mp 67-69°C; R_f(petroleum ether:EtOAc 9:1) 0.29; ν_{max} (KBr disc)/cm^{-1} 3058 (unsaturated CH), 2923 and 2843 (saturated CH), 1631 and 1606 (C=C diene), 1449 (O-SO_2), 1372 (SO_2-N), 1219 (CF), 1176 (SO_2-N), 1136 (SO_2); δ_H (300 MHz, $CDCl_3$) 8.04 (1H, app dt, *J* 8.3, 0.9, H-7"), 7.89-7.84 (2H, m, H-11", H-15"), 7.81 (1H, d, *J* 1.1, H-4"), 7.49-7.23 (5H, m, Ar), 7.27-7.23 (1H, m, Ar), 7.11-7.04 (1H, m, Ar), 7.01-6.94 (2H, m, H-4', H-6'), 6.73-6.68 (2H, m, H-3', H-7'), 6.23 (1H, app t, *J* 2.7, H-4), 5.92 (1H, dd, *J* 3.0, 1.0, H-5), 3.35 (1H, app dd, *J* 12.5, 11.0, 1 × H-1'), 3.21 (1H, app dd, *J* 12.5, 10.3, 1 × H-1'); sample failed to provide clear ^{13}C data due to lack of material; failed to provide mass ion.

The enantiomers of **358** were separated by HPLC using Chiracel AD column (99:1 hexane:*iso*propanol), 1.0 mL/min; t_r = 17.9 min and t_r = 22.1 min, 45% ee.

6-Benzyl-3,3,6-trimethyl-5-(1-(phenylsulfonyl)-1*H*-indol-3-yl)cyclohexa-1,4-dienyl trifluoromethanesulfonate 359



359

Using general procedure B on bis-triflate **308** (101.7 mg, 0.2 mmol) the *monotriflate* **359** (54.8 mg, 45%) was produced as a white solid; mp 142-144°C; ν_{max} (KBr disc)/cm^{-1} 3063 (unsaturated CH), 2956 and 2858 (saturated CH), 1696 (C=C), 1604 (Ar), 1411 (O-SO_2), 1377 (SO_2-N), 1251 (CF), 1185 (SO_2-N), 1130 (SO_2); δ_H (300 MHz, CD_2Cl_2) 7.95 (1H, m, H-7"), 7.88-7.83 (2H, m, H-11", H-15"), 7.65 (1H, s, H-2"), 7.53-7.48 (1H, m, H-13") 7.45-7.39 (2H, m, H-12", H-14"), 7.33-7.26 (2H, m, H-6", H-4"), 7.20-7.15 (1H, m, H-5"), 7.15-7.09 (3H, m, H-5', H-4', H-6'), 7.00-6.95 (2H, m, H-3', H-7'), 5.50 (1H, d, *J* 1.9, H-4), 5.49 (1H, d, *J* 1.9, H-6), 2.83 (1H, d, *J* 14.1, 1 × H-1'), 2.77 (1H, d, *J* 14.1, 1 × H-1'), 1.23 (3H, s, Me') 1.05 (3H, s, Me) 0.40 (3H, s, Me); δ_C (75 MHz, CD_2Cl_2) 150.3 (C, C-1), 139.5 (CH, C-4), 138.6 (C, C-3), 137.8 (C, C-10"), 135.5 (C, C-2'), 134.9 (CH, C-13"), 132.9 (C, C-9"), 131.0 (2 × CH, C-3', C-7'), 130.2 (2 × CH, C-12", C-14"), 128.7 (C, C-8"), 128.6 (2 × CH, C-4', C-6'), 127.5 (2 × CH, C-11", 15"), 127.4 (CH, C-5'), 126.0 (CH, C-6"), 125.3 (CH, C-6), 124.3 (CH, C-5"), 123.6 (CH, C-2"), 122.4 (C, C-3"), 121.8 (CH, C-4"), 119.2 (q, *J* 318, CF_3), 114.3 (CH, C-7"), 45.8 (C, C-2), 43.4 (CH_2, C-1'), 36.7 (C, C-5), 31.0 (CH_3, Me), 28.9 (CH_3, Me), 25.9 (CH_3, Me'); *m/z* (ES^+) 615.1 (100%, M^+); (Found $(M+NH_4)^+$, 633.1699. $C_{31}H_{32}N_2O_5S_2F_3$ requires 633.1699).

The enantiomers of **359** were separated by HPLC using Chiracel AD column (99:1 hexane:*iso*propanol), 1.0 mL/min; t_r = 7.1 min and t_r = 8.0 min, 46% ee.

Preparation of 1-(3-(5-benzyl-5-methylcyclopenta-1,3-dienyl)phenyl)ethanone 372

Formic acid (7.5 μL, 0.2 mmol), was added to a stirred solution of monotriflate **297** (43.6 mg, 0.1 mmol), tri-*n*-butylamine (71.5 μL, 0.3 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 10 mol %) and triphenylphosphine (5.8 mg, 0.022 mmol, 22 mol %) in dry DMF (1 mL). The reaction mixture was then stirred at 60°C for 1 h under argon. The reaction mixture was partitioned between EtOAc (10 mL) and water (10 mL).The organic layer was then washed with water (3 × 5 mL), dried (Na_2SO_4), filtered, and then concentrated under reduced pressure. The residue was then purified by flash chromatography (5% diethyl ether/hexane) to yield the *cyclopentadiene* **372** as a pale yellow viscous oil (24.5 mg, 85%) R_f(petroleum ether:EtOAc 9:1) 0.50; ν_{max} (neat)/cm^{-1} 3056 and 3021(unsaturated CH), 2951 and 2925 (saturated CH), 1683 (C=O), 1596 (C=C); δ_H (400 MHz, CD_2Cl_2) 8.06 (1H, s, H-2"), 7.76 (1H, d, *J* 7.0, H-6"), 7.70 (1H, d, *J* 7.0, H-4"), 7.40 (1H, t, *J* 7.8, H-5"), 7.05-6.98 (3H, m, H-4', H-5', H-6'), 6.87-6.82 (2H, m, H-3', H-7'), 6.59 (1H, app t, *J* 1.8, H-4) 6.35 (1H, dd, *J* 5.4, 1.5, H-1), 6.17 (1H, dd, *J* 5.4, 2.3, H-5), 3.05 (1H, d, *J* 13.3, 1 × H-1'), 2.91 (1H, d, *J* 13.3, 1 × H-1'), 2.53 (3H, s, MeC=O), 1.36 (3H, s, Me); δ_C (100 MHz, CD_2Cl_2) 198.6 (C, C=O), 152.6 (C, C-3), 148.4 (CH, C-4), 138.9 (C, C-2'), 138.3 (C, C-1"), 137.2 (C, C-3"), 133.3 (CH, C-4"), 130.5 (2 × CH, C-3', C-7'), 129.7 (CH, C-1), 129.5 (CH, C-5"), 128.8 (CH, C-5), 128.1 (2 × CH, C-4', C-6'), 127.1 (CH, C-6"), 126.8 (CH, C-2"), 126.6 (CH, C-3'), 58.3 (C, C-2), 43.6 (CH_2, C-1'), 27.3 (CH_3,

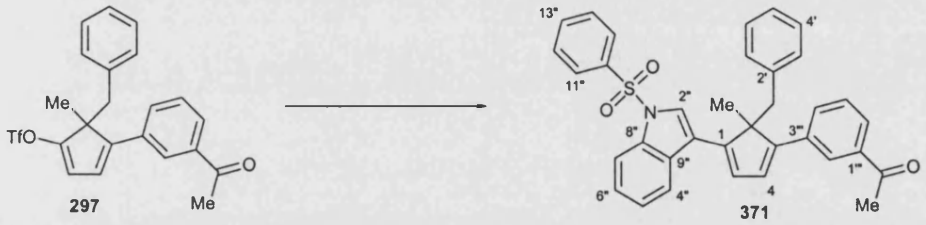
MeC=O), 22.2 (CH_3, Me); *m/z* (ES^+) 289.3 (100%, $M+H^+$); (Found $(M+H)^+$, 289.1624. $C_{21}H_{21}O$ requires 289.1624).

Preparation of 1-(3-(8,8a-dihydro-8a-methylcyclopenta[a]inden-1-yl)phenyl)ethanone 373

Tri-*n*-butylamine (71.5 μL, 0.3 mmol) was added to a solution of the monotriflate **297** (43.6 mg, 0.1 mmol), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol, 15 mol %) and triphenylphosphine (9.2 mg, 0.035 mmol, 35 mol %) in dry DMF (1 mL). The reaction mixture was then stirred at 60°C for 1 h under argon. The reaction mixture was partitioned between EtOAc (10 mL) and water (10 mL). The organic layer was then washed with water (3 × 5 mL), dried (Na_2SO_4), filtered, and then concentrated under reduced pressure. The residue was then purified by flash chromatography (5% diethyl ether/hexane) to yield the *tricyclic diene* **373** as a yellow solid (28.4 mg, 99%); mp 65°C; R_f(petroleum ether:EtOAc 9:1) 0.38; ν_{max} (neat)/cm^{-1} 3061 (unsaturated CH), 2966 and 2912 (saturated CH), 1681(C=O), 1590 (C=C); δ_H (400 MHz, C_6D_6) 8.30 (1H, s, H-2"), 7.73 (1H, d, *J* 7.6, H-6"), 7.57 (1H, d, *J* 7.8, H-4"), 7.50 (1H, d, *J* 7.4, H-5"), 7.27-7.11 (4H, m, H-3', H-4', H-5', H-6'), 6.80 (1H, d, *J* 2.2, H-4), 6.41 (1H, d, *J* 2.2, H-5), 3.02 (1H, d, *J* 14.1, 1 × H-1'), 2.78 (1H, d, *J* 14.1, 1 × H-1'), 2.30 (3H, s, MeC=O), 1.36 (3H, s, Me); δ_C (100 MHz, C_6D_6) 197.0 (C, C=O), 167.7 (C, C-1), 153.2 (C, C-3), 151.0 (C, C-2'), 138.6 (C, C-1"), 136.4 (C, C-3"), 136.3 (C, C-7'), 130.4 (CH, C-4"), 130.1 (CH, C-4), 129.4 (CH, C-5"), 127.9 (CH, C-5'), 127.7 (CH, C-4'), 127.2 (CH, C-3'), 126.9 (CH, C-6"), 126.0 (CH, C-

2"), 122.5 (CH, C-6'), 119.6 (CH, C-5), 65.5 (C, C-2), 41.2 (CH_2, C-1'), 26.9 (CH_3, MeC=O), 26.6 (CH_3, Me); *m/z* (ES^+) 286.1 (100%, M^+); (Found $(M+H)^+$, 287.1445. $C_{21}H_{19}O$ requires 287.1436).

Preparation of 1-(3-(5-benzyl-5-methyl-4-(1-(phenylsulfonyl)-1*H*-indol-3-yl)cyclopenta-1,3-dienyl)phenyl)ethanone 371



The Suzuki coupling was carried out using the standard racemic conditions described in procedure A using monotriflate **297** (43.6 mg, 0.1 mmol). This yielded the *dicoupled* **371** material as an orange yellow solid (50.7 mg, 93%); mp 86°C; R_f(petroleum ether:EtOAc 9:1) 0.11; ν_{max} (neat)/cm^{-1} 3024 (unsaturated CH), 2921 and 2855 (saturated CH), 1682 (C=O), 1574 (C=C) 1372 (SO_2-N), 1171 (SO_2-N), 1132 (SO_2); δ_H (400 MHz, CD_2Cl_2) 8.16 (1H, s, H-2"'), 8.02 (1H, d, *J* 8.2, H-7") 7.88-7.82 (3H, m, H-11", H-15", H-2"), 7.79-7.75 (2H, m, H-6"', H-4"'), 7.60 (1H, d, *J* 8.0, H-4"), 7.47-7.39 (2H, m, H-5"', H-13"), 7.37-7.28 (3H, m, H-12", H-14", H-6"), 7.20 (1H, app q, *J* 8.1, H-5"), 6.83 (1H, t, *J* 8.0, H-5') 6.73 (2H, app s, H-4, H-5) 6.67 (2H, t, *J* 7.7, H-4', H-6'), 6.38 (2H, d, *J* 7.2, H-3', H-7'), 3.39 (1H, d, *J* 13.9, 1 × H-1'), 3.25 (1H, d, *J* 14.0, 1 × H-1'), 2.54 (3H, s, MeC=O), 1.67 (3H, s, Me); δ_C (100 MHz, CD_2Cl_2) 198.6 (C, C=O), 153.5 (C, C-3), 148.5 (C, C-1), 138.5 (C, C-3"'), 138.4 (C, C-2'), 137.6 (C, C-1"'), 136.9 (C, C-8"), 136.1 (C, C-10"), 134.9 (CH, C-13"), 131.3 (CH, C-4"'), 131.1 (C, C-9"), 130.3 (2 × CH, C-12", C-14"), 130.0 (CH, C-5"'), 129.7 (CH, Ar), 129.5 (2 × CH, C-3', C-7'), 127.9 (2 × CH, C-4', C-6'), 127.6 (CH, Ar), 127.5 (2 × CH, C-11", C-15"), 127.5 (CH, C-5'), 126.9

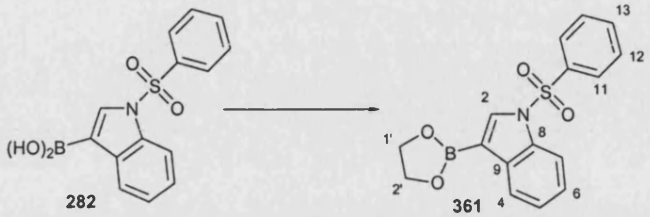
(CH, C-2'''), 126.6 (CH, C-6''), 126.1 (CH, C-5''), 124.7 (CH, C-2''), 122.7 (CH, C-6'''), 122.5 (CH, C-4''), 119.2 (C, C-3''), 114.6 (CH, C-7''), 60.2 (C, C-2), 44.0 (CH_2, C-1'), 27.4 (CH_3, MeC=O), 25.2 (CH_3, Me); *m/z* (ES^+) 543.3 (100%, M^+); (Found $(M+H)^+$, 544.1962. $C_{35}H_{29}NO_3S$ requires 544.1946).

Potassium 1-(phenylsulfonyl)-1-*H*-indol-3-yl-trifluoroborate 363

To a solution of 1-(phenylsulfonyl)-2-indoleboronic acid **282** (500 mg, 1.65 mmol) in methanol (8.0 mL) and water (2.0 mL) in a teflon vessel, KHF_2 (425 mg, 5.45 mmol) was added and stirred. After 10 minutes a white precipitate was formed, the solvent was then removed under vacuum and the white crystalline solid was extracted with acetone twice at room temperature and then once with boiling acetone. The combined extracts were filtered and the solvent removed under reduced pressure to yield a white solid which was then recrystalised from acetone/diethyl ether to give the *potassium organofluoroborate* **363** as a white crystalline solid (555 mg, 93%), mp 180-185°C (dec.); $_{max}$ (KBr disc)/cm^{-1} 3066 (aromatic CH), 1355 (SO_2-N), 1175 (SO_2-N), 1122 (SO_2); δ_H (300 MHz, $(CD_3)_2CO$) 7.92-7.85 (3H, m, H-11, H-15, H-7), 7.61 (1H, d, *J* 7.9, H-4), 7.43-7.32 (3H, m, H-13, H-12, H-14), 7.15 (1H, s, H-2), 7.03-6.87 (2H, m, H-6, H-5); δ_C (75 MHz, $(CD_3)_2CO$) 140.4 (C, C-10), 138.0 (C, C-9), 137.3 (C, C-8), 134.7 (CH, C-13), 130.9 (C, C-3), 130.5 (2 × CH, C-12, C-14), 128.2 (CH, C-2), 127.8 (2 × CH, C-11, C-15), 125.2 (CH, C-4), 123.9 (CH, C-6), 123.2 (CH, C-5), 113.9 (CH, C-7); δ_B (96 MHz, $(CD_3)_2CO$) 3.61 (q, *J* 49); *m/z* (ES^+)

324.1 (100%, *M-K*)$^-$; (Found (*M*+K)$^+$, 401.9752, $C_{14}H_{10}NO_2BSF_3K_2$ requires 401.9746).

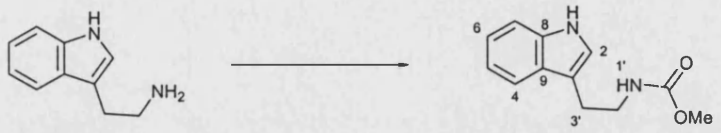
3-(1,3,2-Dioxaborolan-2-yl)-1-(phenylsulfonyl)-1*H*-indole 361



To a stirred suspension of 1-(phenylsulfonyl)-2-indoleboronic acid **282** (500 mg, 1.65 mmol) and $MgSO_4$ (600 mg, 5 mmol) in THF (5 mL), ethylene glycol was added (9.2 μL, 1.65 mmol), and stirred overnight. The suspension was then filtered and the solvent removed under vacuum, to yield the *boronic ester* **361** (426 mg, 79%) as a cream/white solid which decomposed upon exposure to air; mp 80°C (dec.); $_{max}$ (KBr disc)/cm^{-1} 2971 (aromatic CH), 1205 (saturated CH), 1386 (SO_2-N), 1365 (B-O), 1176 (SO_2-N), 1131 (SO_2); δ_H (300 MHz, ($CDCl_3$) 7.96 (1H, s, H-2), 7.88 (1H, d, *J* 7.88, H-4), 7.85-7.79 (3H, m, H-11, H-15, H-7), 7.47-7.40 (1H, m, H-13), 7.34 (2H, m, H-12, H-14) 7.20 (2H, m, H-5, H-6) 4.30 (4H, s, 2 × H-1', 2 × H-2'); δ_C (75 MHz, $(CD_3)_2CO$) 139.4 (C, C-10), 136.9 (C, C-9), 136.6 (CH, C-2), 135.9 (CH, C-13) 134.8 (C, C-8), 130.9 (2 × CH, C-12, C-14), 128.2 (2 × CH, C-11, C-15), 125.6 (CH, C-5), 124.9 (CH, C-6), 124.6 (CH, C-4), 114.5 (CH, C-7) 67.0 (2 × CH_2, C-1', C-2'); δ_B (96 MHz, $(CD_3)_2CO$) 31.96; failed to provide mass ion.

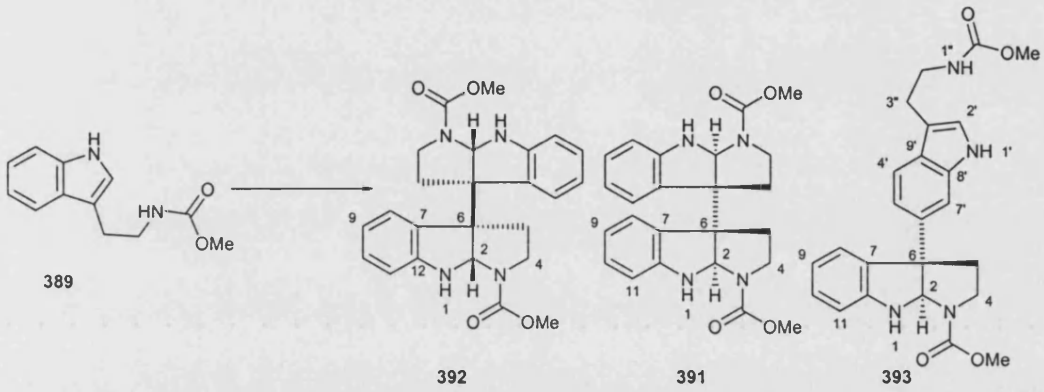
7.5 Towards the synthesis of hodgkinsine

Preparation of methyl 2-(1*H*-indol-3-yl)ethylcarbamate 389



Methyl chloroformate (8.50 mL, 110 mmol) was added to a stirred mixture of tryptamine **409** (16.02 g, 100 mmol) and 1 M sodium hydroxide (100 mL, 100 mmol) in DCM (200 mL), under nitrogen, this was stirred for 2 h. This was then extracted with DCM (200 mL), washed with 2% HCl (50 mL), washed with brine (100 mL), dried ($MgSO_4$), and reduced *in vacuo*. The residue was then recrystalised from diethyl ether to yield the *carbamate* **389** (19.80 g, 92%) as a brown crystalline solid; mp 80-82°C from diethyl ether (lit. 79°C); ν_{max} (KBr disc)/cm^{-1} 3400 (NH), 3056 (unsaturated CH), 2941 and 2850 (saturated CH), 1687 (C=O), 1550 (CO-NH), 1290 (C-O); δ_H (300 MHz, $CDCl_3$) 8.05 (1H, bs, NH-1), 7.61 (1H, d, *J* 7.9, H-7), 7.38 (1H, d, *J* 8.3, H-4), 7.25-7.19 (1H, m , H-6) 7.17-7.11 (1H, m, H-5), 7.05 (1H, s, H-2), 4.74 (1H, br s, NH-1'), 3.67 (3H, s, OMe), 3.59-3.42 (2H, m, 2 × H-2'), 2.88 (2H, t, *J* 6.8, 2 × H-3'); δ_C (75 MHz, $CDCl_3$) 157.2 (C, C=O), 136.8 (C, C-8), 127.7 (C-9), 122.6 (CH, C-6), 122.4 (CH, C-2), 119.9 (CH, C-5), 119.1 (CH, C-7), 113.3 (C, C-3), 111.5 (CH, C-7), 52.4 (CH_3, OMe), 41.6 (CH_2, C-2'), 26.2 (CH_2, C-3'); *m/z* (ES^+) 219.2 (37%, $(M+H)^+$; Found $(M+H)^+$, 219.1129. $C_{12}H_{15}N_2O_2$ requires 219.1128; (Found C, 65.9; H, 6.46; N, 12.84%. $C_{12}H_{14}N_2O_2$ requires C, 66.04; H, 6.47; N, 12.84%); data consistent with literature.[8]

(±)-Methyl 3a-(1-(methoxycarbonyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indol-3a-yl)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1(2*H*)-carboxylate 392, *meso*-methyl 3a-(1-(methoxycarbonyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indol-3a-yl)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1(2*H*)-carboxylate 391 and methyl 2-(6-(1-(methoxycarbonyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indol-3a-yl)-1*H*-indol-3-yl)ethylcarbamate 393

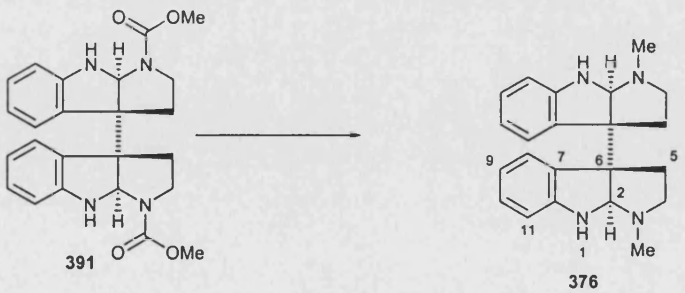


A mixture of the tryptamine methylformate **389** (5.43 g, 24.9 mmol) and PIFA **390** (5.33 g, 12.4 mmol) was dissolved in trifluoroethanol (100 mL) at -30°C under an atmosphere of argon, this was stirred for 16 h at which point a further portion of PIFA **390** (2.67 g, 6.2 mmol) was added and stirred for a further 4 h. The reaction mixture was then brought up to room temperature and washed with saturated $NaHCO_3$ solution (100 mL), this was then extracted three times with chloroform (3 × 100 mL). The combined organic extracts were then washed with brine (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The oil was then purified by flash chromatography (gradient elution 5-30% EtOAc/chloroform) and recrystalisation (chloroform/hexane) to yield the three dimerised products in order of elution; *rac-dimer* **392** (16%, based on NMR conversion) as a brown solid; mp 182-183°C from chloroform/hexane (lit. 191°C); ν_{max} (KBr disc)/cm^{-1} 3357 (NH), 3054 (unsaturated CH), 2954 and 2880 (saturated CH), 1694 (C=O) 1451 and 1383 (saturated CH), 1202 (C-O); NMR data appears to show rotomers of the above

quoted compounds, δ_H (300 MHz, $CDCl_3$) 7.16-6.99 (4H, m, H-8, 2 × H-10), 6.77-6.64 (2H, m, 2 × H-9), 6.58 (2H, t, *J* 7.6, 2 × H-11), 5.03-4.75 (2H, m, 2 × H-2), 3.62-3.54 (6H, m, 2 × OMe), 3.62-3.41 (2H, m, 2 × H-4), 2.89-2.75 (2H, m, 2 × H-4), 2.62-2.45 (2H, m, 2 × H-5), 2.12-1.93 (2H, m, 2 × H-5); δ_C (75 MHz, $CDCl_3$) 155.6 and 254.7 (C, C=O), 150.9 and 150.6 (C, C-12), 129.7 and 129.6 (CH, C-10), 128.7 and 128.5 (C, C-7), 125.7 and 125.6 (CH, C-8), 119.6, 119.4, 119.2 and 118.9 (CH, C-9), 110.4 (CH, C-11), 79.6, 79.4 and 78.8 (CH, C-2), 62.2, 61.2 and 61.1 (C, C-6), 53.0 and 52.7 (CH_3, OMe), 46.0 and 45.7 (CH_2, C-4), 32.0, 31.9 and 31.7 (CH_2, C-5); *m/z* (ES^+) 435.3 (48%, M+H)$^+$; (Found (M+H)$^+$, 435.2033. $C_{24}H_{27}N_4O_4$ requires 435.2027); data consistent with literature;[8] the *meso-pyrrolidinoindoline dimer* **391** (1.31 g, 24%) as a white powdered solid; mp 279-281°C from chloroform/hexane (lit. 276°C); ν_{max} (KBr disc)/cm^{-1} 3356 (NH), 3056 (unsaturated CH), 2983 and 2895 (saturated CH), 1691 (C=O) 1453 and 1389 (saturated CH), 1200 (C-O); NMR data shows apparent rotomers of the compound; δ_H (300 MHz, $CDCl_3$) 7.08 (2H, t, *J* 7.5, 2 × H-8), 6.80-6.46 (6H, m, 2 × H-10, 2 × H-9, 2 × H-11), 5.49-5.31 (2H, m, 2 × H-2), 3.83-3.54 (8H, m, 2 × OMe, 2 × H-4), 3.08-2.88 (2H, m, 2 × H-4), 2.38-2.12 (4H, m, 4 × H-5); δ_C (75 MHz, $CDCl_3$) 155.7 (C, C=O), 150.8 (C, C-12), 129.5 (CH, C-10), 129.4 and 129.2 (C, C-7), 124.5 (CH, C-8), 119.2 and 119.1 (CH, C-9), 109.9, 109.7 and 109.6 (CH, C-11), 78.2 (CH, C-2), 61.2 (C, C-6), 53.1 and 52.7 (CH_3, OMe), 45.7 and 45.6 (CH_2, C-4), 33.8 and 33.4 (CH_2, C-5); *m/z* (ES^+) 435.3 (11%, M+H)$^+$; (Found (M+H)$^+$, 435.2024. $C_{24}H_{27}N_4O_4$ requires 435.2027); (Found C, 65.90; H, 5.97; N, 12.5%. $C_{24}H_{26}N_4O_4$ requires C, 66.34; H, 6.03; N, 12.89%); data consistent with literature;[8] and the *mono-pyrrolidinoindoline dimer* **393** (14%, based on NMR conversion) as a yellow/brown viscous oil; ν_{max} (KBr disc)/cm^{-1} 3338 (NH), 3051 (unsaturated CH), 2953 and 2881 (saturated CH),

1693 (C=O) 1524 (CO-NH), 1454 and 1386 (saturated CH), 1249 and 1201(C-O); NMR data shows apparent rotomers of the compound δ_H (300 MHz, $CDCl_3$) 8.10 (1H, br s, NH-1'), 7.43 (1H, d, *J* 8.3, H-4'), 7.16 (1H, s, H-7'), 7.15-7.05 (1H, m, H-5'), 7.04-6.96 (2H, m, H-8, H-10), 6.83 (1H, bs, H-2'), 6.71-6.63 (1H, m, H-9), 6.62-6.54 (1H, m, H-11), 5.50-5.38 (1H, m, H-2), 4.70 (1H, bs, NH-1"), 3.89-3.50 (7H, m, H-4, OMe-1, OMe-2), 3.42-3.28 (2H, m, H-2"), 3.13-3.01 (1H, m, H-4), 2.82 (2H, t, *J* 6.4, H-3"), 2.72-2.47 (2H, m, H-5); δ_C (75 MHz, $CDCl_3$) 157.5 (C, C=O-2), 155.7 and 155.0 (C, C=O-1), 149.4 and 149.1 (C, C-12), 138.2 (C, C-6'), 138.0 (C, C-8'), 133.2 and 133.1 (C, C-7), 128.9 and 128.9 (CH, C-8), 126.5 (C, C-9'), 124.6 and 124.5 (CH, C-10), 122.9 (CH, C-2'), 119.9 and 119.3 (CH, C-9), 119.7 (CH, C-4'), 117.8 (C-5'), 113.0 (C, C-3'), 110.5 and 110.3 (CH, C-11), 109.1 (CH, C-7'), 83.8 and 83.5 (CH, C-2), 62.2 and 61.0 (C, C-6), 53.1 and 52.4 (CH_3, OMe-1), 52.8 (CH_3, OMe-2), 47.0 and 46.6 (CH_2, C-4), 41.6 (CH_2, C-2"), 37.2 and 37.0 (CH_2, C-5), 26.2 (CH_2, C-3"); *m/z* (ES^+) 435.3 (100%, $M+H)^+$; (Found $(M+H)^+$, 435.2023. $C_{24}H_{27}N_4O_4$ requires 435.2027).

meso-(3aS,8aS)-1,2,3,3a,8,8a-Hexahydro-3a-((3aR,8aR)-1,2,3,3a,8,8a-hexahydro-1-methylpyrrolo[2,3-b]indol-3a-yl)-1-methylpyrrolo[2,3-b]indole (_meso_-chimonanthine) 376



To a stirred solution of the *meso-pyrrolidinoindoline dimer* **391** (2.17 g, 5 mmol) in toluene (550 mL) was added Red-Al (14.75 mL, 65% solution in toluene, 49.25

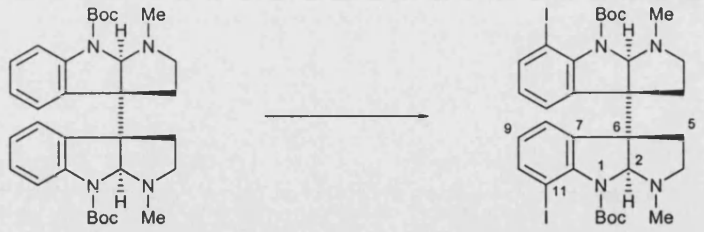
mmol). This was then heated under reflux, under nitrogen, for 18 h. The solution was then cooled to rt, at which point 5% aqueous sodium hydroxide (200 mL) was added and this mixture was filtered through celite (30 g) with chloroform (200 mL). The filtrate was then extracted with chloroform (3 × 300 mL), and the combined organic extracts were washed with brine (200 mL), dried over $MgSO_4$, and concentrated under vacuum. The resulting residue was purified *via* flash chromatography in chloroform/methanol/ammonia (9:1:0.15), and then recrystalised from DCM/ EtOAc to yield *meso-chimonanthine* **376** (1.34 g, 77%) as a cream solid which turns yellow upon exposure to light, mp 198-199°C (lit. 194-196°C, 199-201°C); ν_{max} (KBr disc)/cm^{-1} 3399 (NH), 3042 and 2959 (unsaturated CH), 2909 and 2859 (saturated CH), 2819 (N-Me), 1601 (ArC), 1485 and 1342 (saturated CH); δ_H (300 MHz, CD_3OD) 6.84 (2H, br s, H-10), 6.35 (2H, d, *J* 7.9, H-11), 4.49 (2H, br s, NH-1), 2.69-2.58 (2H, m, H-4), 2.47-2.14 (10H, m, 2 × H-5, 2 × H-4, 2 × Me), 2.02-1.89 (2H, m, H-5), δ_H (400 MHz, $(CD_3)_2SO$, 100 °C) 6.89 (2H, t, *J* 7.5, 2 × H-10), 6.54 (2H, br s, 2 × H-9), 6.38 (2H, d, *J* 7.7, 2 × H-11), 5.53 (2H, s, 2 × H-8), 4.59 (2H, s, 2 × H-2), 2.69 (2H, m, 2 × H-4), 2.50-2.40 (2H, m, 2 × H-4), 2.45-2.38 (8H, m, 2 × H-5, 2 × Me), 1.92-1.84 (2H, m, 2 × H-5); δ_C (75 MHz, CD_3OD) 153.9 (C, br s, C-12), 134.2 (C, br s, C-7), 129.6 (CH, C-10), 125.8 (CH, C-8), 119.0 (CH, C-9), 109.9 (CH, br s, C-11), 84.7 (CH, C-2), 65.2 (C, C-6), 53.9 (CH_2, C-4), 37.5 (CH_2, br, C-5), 36.7(CH_3, Me); *m/z* (ES^+) 346.3 (39%, $M)^+$; (Found $(M+H)^+$, 347.2235. $C_{22}H_{27}N_4$ requires 347.2230); data consistent with literature.[8,9]

meso-1,1'-Dimethyl-1,2,3,8a,1',2',3',8a'-octahydro-[3a,3a']-bi[pyrrolo[2,3-_b_]indolyl]-8,8'-diacrboxylic acid di-_tert_-butyl ester 412

376 412

To a stirred solution of the *meso*-chimonanthine **376** (103.9 mg, 0.3 mmol) Boc-anhydride (144.0 mg, 0.66 mmol) in THF (4.5 mL), at r.t. was added NaHMDS (1.35 mL, 1 M in THF, 1.35 mmol) dropwise. The resulting solution was stirred under nitrogen for 1 h. The reaction was then partitioned between aqueous NH_4Cl (10 mL) and DCM (15 mL). The aqueous layer was then extracted with DCM (3 × 15 mL), the combined organics were dried over $MgSO_4$, filtered and concentrated. The residue was then purified by flash chromatography (gradient elution 33-60% EtOAc/petroleum ether) to afford the *dicarbamate* **412** (129.3 mg, 79%) as a colourless foam. ν_{max} (KBr disc)/cm^{-1} 3074 and 2975 (unsaturated CH), 2942 and 2794 (saturated CH), 1707 (C=O) 1483 and 1389 (saturated CH), 1168 (C-O); δ_H (400 MHz, $(CD_3)_2SO$, 100 °C) 7.45 (2H, d, *J* 8.1, 2 × H-11), 7.06 (2H, app t, *J* 7.5, 2 × H-10), 6.73 (2H, br s, 2 × H-9), 6.46 (2H, br s, 2 × H-8), 4.81(2H, br s, 2 × H-2), 2.67-2.57 (2H, m, 2 × H-4), 2.39-2.27 (10H, m, 2 × H-4, 2 × Me, 2 × H-5), 1.97-1.89 (2H, m, 2 ×H-5), 1.35 (18H, s, 2 × $OC(Me)_3$); δ_C (100 MHz, $(CD_3)_2SO$, 100 °C) 152.1 (C, C=O), 143.9 (C, C-7), 134.8 (C, C-12), 128.4 (CH, C-10), 124.1 (CH, C-8), 122.8 (CH, C-9), 115.7 (CH, C-11), 85.3 (CH, C-2), 80.8 (C, O*C*$(Me)_3$), 61.3 (C, C-6), 53.3 (CH_2, C-4), 37.4 (CH_3, Me), 34.9 (CH_2, C-5), 28.4 (3 × CH_3, OC(*Me*)$_3$); *m/z* (ES^+) 547.4 (100%, $(M+H)^+$; (Found $(M+H)^+$, 547.3281. $C_{32}H_{43}N_4O_4$ requires 547.3279); data consistent with literature.[10]

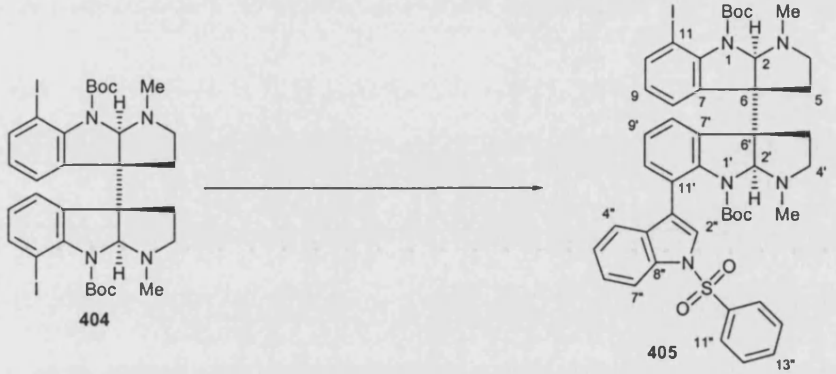
meso-7,7'-Diiodo-1,1'-dimethyl-1,2,3,8a,1',2',3',8a'-octahydro-[3a,3a']-bi[pyrrolo[2,3-_b_]indolyl]-8,8'-diacrboxylic acid di-_tert_-butyl ester 404



A solution of *s*-BuLi (0.7 mL, 1.3 M) in pentane was added dropwise to a solution of the dicarbamate **412** (109.3 mg, 0.2 mmol), *N*,*N*,*N*',*N*'-tetramethyletheylenediamine (181 μL, 1.2 mmol) in diethyl ether (2.0 mL) at -78°C. After 54 min, a solution of diiodoethane (563.7 mg, 2.0 mmol) in Diethyl ether (1.5 mL) was added to the reaction mixture dropwise, the reaction mixture was maintained at -78°C for a further 10 min and then warmed to 0°C for a 30 min period. Saturated aqueous $Na_2S_2O_4$ (10 mL) and saturated aqueous $NaHCO_3$ (30 mL) were then added to the reaction mixture which was then extracted with EtOAc (3 × 50 mL). The combined organics were then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was then purified *via* flash chromatography and subsequently recrystalised from DMSO/DCM to yield the *diiodide* **404** (93 mg, 59%) as a colourless solid, mp 207-208°C from DMSO/DCM (lit. 215-220°C). ν_{max} (KBr disc)/cm^{-1} 3064 and 2978 (unsaturated CH), 2940 and 2795 (saturated CH), 1715 (C=O) 1442 and 1368 (saturated CH), 1159 (C-O); δ_H (400 MHz, $(CD_3)_2SO$, 120 °C) 7.62 (2H, d, *J* 7.8, 2 × H-10), 6.83 (2CH, br s, 2 × H-8), 6.73 (2H, app t, *J* 7.4, 2 × H-9), 4.96 (2H, br s, 2 × H-2), 2.78-2.69 (2H, m, 2 × H-4), 2.46 (6H, s, 2 × Me), 2.45-2.35 (2H, m, 2 × H-4), 2.26- 2.16 (2H, m 2 × H-5). 1.98-1.90 (2H, m, 2 × H-5), 1.44 (18H, s, 2 × $OC(Me)_3$); δ_C (100 MHz, $(CD_3)_2SO$, 120 °C) 152.0 (C, C=O), 147.0 (C, C-12), 139.3 (C, C-7), 139.1 (CH, C-10), 126.3 (CH, C-9), 124.4 (CH, C-8), 87.7 (CI, C-11), 85.4 (CH, C-

2), 81.6 (C, O*C*(Me)$_3$), 62.2 (C, C-6), 52.3 (CH_2, C-4), 36.4 (CH_3, Me), 36.1 (CH_2, C-5), 28.3 (3 × CH_3, OC(*Me*)$_3$); *m/z* (ES^+) 798.2 (100%, M^+); (Found $(M+H)^+$, 799.1211. $C_{32}H_{41}N_4O_4I_2$ requires 799.1212); data consistent with literature.[10]

tert-Butyl 3a-(8-_tert_-butoxycarbonyl-1,2,3,3a,8,8a-hexahydro-1-methyl-7-(1-(phenylsulfonyl)-1*H*-indol-3-yl)pyrrolo[2,3-*b*]indol-3a-yl)-1,2,3,3a-tetrahydro-7-iodo-1-methylpyrrolo[2,3-*b*]indole-8(8a*H*)-carboxylate 405



Dry degassed dioxane (1.5 mL) was added to a mixture of diiodide **404** (119.7 mg, 0.15 mmol), 1-(phenylsulfonyl)-3-indoleboronic acid **282** (90.3 mg, 0.3 mmol), palladium acetate (3.4 mg, 0.015 mmol), MeO-MOP **90** (7.7 mg, 0.0165 mmol) and cesium fluoride (68.3 mg, 0.45 mmol). This was then heated up to 60°C under argon for 8 h. EtOAc (10 mL) was then added and the mixture was partitioned with water (8 mL), the aqueous layer was washed with EtOAc (2 × 10 mL). The combined organics are dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was then purified by flash chromatography (20-40% EtOAc/Hexane) to yield the *monoiodide* **405** (65.6 mg, 47%) as a white solid; mp 118°C (from DMSO/DCM); ν_{max} (KBr disc)/cm^{-1} 2956 and 2924 (unsaturated CH), 2853 and 2791 (saturated CH), 1720 and 1712 (C=O) 1449 and 1367 (saturated CH), 1171 (C-O), 1139 (SO_2); δ_H (400 MHz, $(CD_3)_2SO$, 120 °C) 7.85-7.76 (3H, m, H-11", H-15", H-7"), 7.58-7.39 (6H, m, H-13", H-2", H-10, H-4", H-12", H-14"), 7.26-7.16 (2H,

m, H-10', H-6"), 7.11-7.04 (1H, m, H-5"), 7.00-6.93 (1H, app t, *J* , H-9'), 6.87-6.53 (3H, m, H-8, H-8', H-9), 4.90-4.80 (1H, br m, H-2), 4.70 (1H, br s, H-2'), 2.67-2.58 (3H, m, 2 × H-4, 1 × H4'), 2.53 (3H, s, Me), 2.37-2.27 (4H, m, Me', 1 × H5), 2.18-1.80 (3H, m, 1 × H5, 2 × H-5'), 1.35 (9H, s, 2 × $OC(Me)_3$) 0.67 (9H, s, 2 × $OC(Me)_3$); δ_C (100 MHz, $(CD_3)_2SO$, 120 °C) 151.9 (C, C=O), 151.8 (C, C=O), 147.0 (C, C-12), 146.1 (C, Ar), 141.4 (C, Ar), 139.1 (2 × C, 2 × Ar), 138.5 (CH, C-10), 135.6 (C, Ar), 135.1 (C, Ar), 134.5 (CH, C-13"), 130.4 (CH, C-10'), 129.9 (2 × CH, C-12", C-14"), 129.5 (C, C-9"), 126.9 (2 × CH, C-11", C-15"), 126.2 (CH, C-9), 125.2 (CH, C-Ar), 124.8 (CH, C-6"), 124.5 (C, C-3"), 124.2 (CH, C-Ar), 123.9 (CH, C-9'), 123.1 (CH, C-5"), 122.6 (CH, C-2"), 121.6 (CH, C-4"), 113.5 (CH, C-7"), 88.3 (CH, C-2'), 88.2 (CI, C-11), 87.5 (CH, C-2), 81.4 (C, $OC(Me)_3$), 80.4 (C, $OC(Me)_3$), 62.3 (C, C-6), 52.8 (CH_2, C-4), 52.1 (CH_2, C-4'), 37.6 (CH_3, Me'), 36.5 (CH_2, C-5), 36.1 (CH_3, Me), 35.9 (CH_2, C-5'), 28.4 (3 × CH_3, $OC(Me)_3$) 27.3 (3 × CH_3, $OC(Me')_3$); *m/z* (ES^+) 927.4 (100%, M^+); (Found $(M+H)^+$, 928.2592. $C_{46}H_{51}N_5O_6IS$ requires 928.2599).

The enantiomers of **406** were separated by HPLC using Chiracel AD column (97:3 hexane:*iso*propanol), 1.0 mL/min; t_r = 14.1 min and t_r = 17.0 min, 30% ee.

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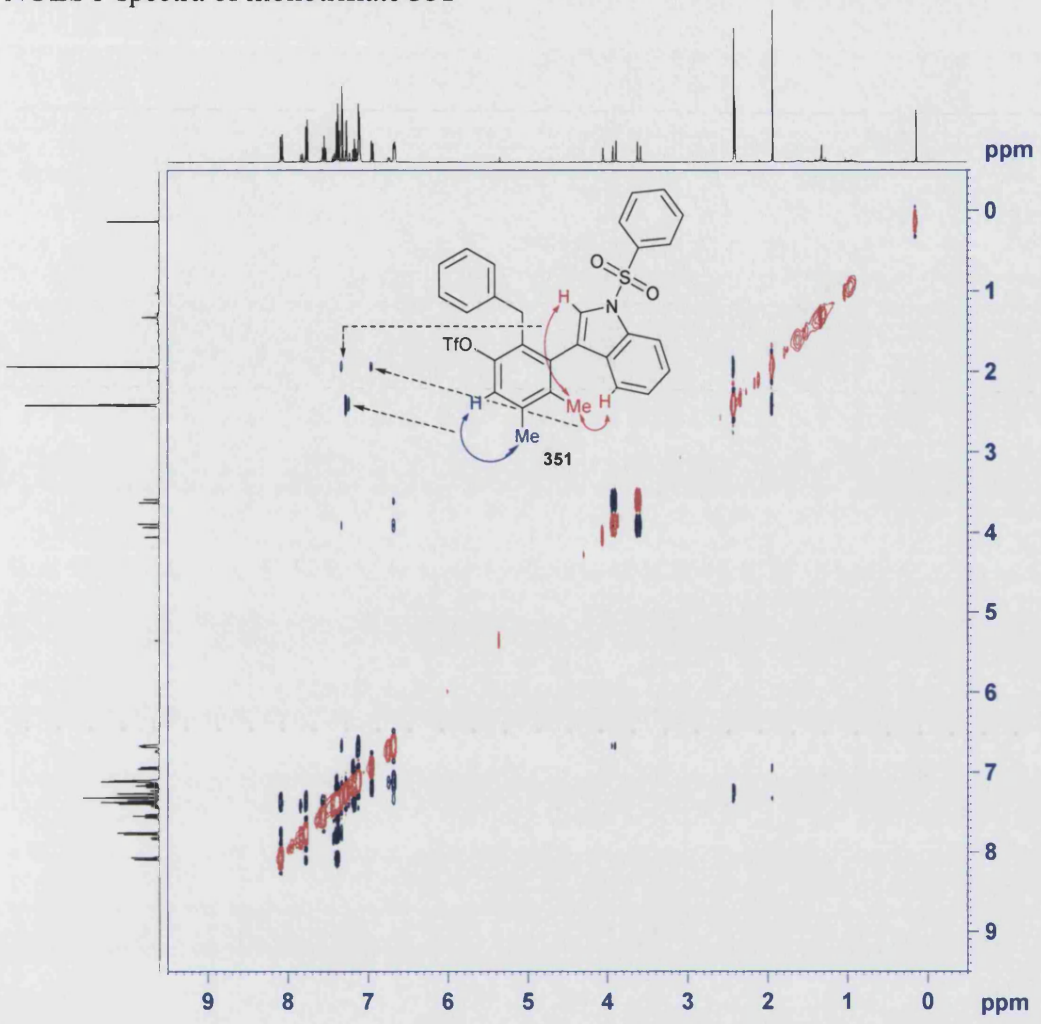
Appendix

NOESY spectra of monotriflate **351**



^{1}H NMR spectra of iodide **405**