UNIVERSITY OF LIVERPOOL

The Preparation and Catalytic Ring Opening Diborylation of 1-Substituted Biphenylenes

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Doctor in Philosophy by:

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Abstract

In this work, the synthesis and palladium catalysed ring opening diborylation of 1-monosubstituted biphenylenes is discussed.

The preparation of 1-monosubstituted biphenylenes is challenging and there is no general method in which a broad range can be prepared in high yield. In the first part of this work, a series of 1-monosubstituted biphenylenes were prepared in two or three steps from commercially available reagents. Using this method, several new 1-monosubstituted biphenylenes were synthesised. Substituted biphenylenes have applications in catalysis, as spacers, and as precursors of functionalised aromatic compounds, therefore methods for their synthesis are valuable.

In the second part of this work, the development of reaction conditions for the catalytic ring opening diborylation of 1-susbstituted biphenylenes will be discussed. The scope and limitations of this reaction will then be detailed and the effect of the 1-substituent on the regioselectivity of the reaction discussed. Stoichiometric reactions between the catalyst and the reagents suggest that in the mechanism of the desired transformation C-C bond cleavage precedes B-B bond cleavage.

The sterically bulky trisubstituted biaryls which result from the ring opening diborylation of 1-substituted biphenylenes are difficult to prepare using traditional synthetic methods. These biaryls bear two boronic ester moieties in two of the *ortho* positions and are therefore amenable to post-functionalisation. The post-functionalisation of the ring opened diborylated products will be discussed in the later part of this work.

Publications

Catalytic Ring Opening Diborylation of 1-Substituted Biphenylenes

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Manuscript in Preparation

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Abbreviations

δ	Chemical Shift
Å	Angstrom
Ac	Acetate
Ad	Adamantyl
aq	Aqueous
BARF	tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
BPO	Benzoyl Peroxide
BrettPhos	2-(Dicyclohexylphosphino)3,6-dimethoxy-2′,4′,6′-triisopropyl-1,1′-biphenyl
br. s	Broad Singlet
Bu	Butyl
cal	Calorie
Cat	Catechol
C-C	carbon-carbon bond
CI	Chemical Ionaisation
cod	Cyclooctadiene
Cp	Cyclopentadienyl
CPME	Cyclopentyl methyl ether
Cy	Cyclohexyl
CyJohnPhos	2-Biphenyl)dicyclohexylphosphine
d	Doublet
dan	1,8-diaminonaphthalene
dba	Dibenzylideneacetone
DCC	N,N′-Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DCM	Dichloromethane
dd	Doublet of doublets
DFT	Density Functional Theory
dia.	Diastereomer

DIC	N,N′-Diisopropylcarbodiimide
dippe	1,2-Bis(diisopropylphosphino)ethane
DMA	Dimethylacetamide
DME	Dimethoxyethane
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DPPF	bisdiphenylphosphinoferrocene
dppp	1,3-Bis(diphenylphosphino)propane
dr	Diastereomeric Ratio
dt	Doublet of triplets
DTBB	4,4'-di-*tert*-butylbiphenyl
EI	Electron Impact
Eq.	Equivalents
ESI	Electrospray
Et	Ethyl
et al.	et alias
EtOAc	Ethyl Acetate
FG	Functional Group
FID	Flame Ionisation Detector
Fig.	Figure
FT	Film Thickness
GC	Gas Chromatography
GC-MS	Gas Chromatography Mass Spectrometry
h	Hour
HMDS	Hexamethyldisilazide
HOMO	Highest Occupied Molecular Orbital
HRMS	High Resolution Mass Spectroscopy
Hz	Hertz
ID	Inner Diameter
IMes	1,3-Dimesitylimidazol-2-ylidene

J	Coupling Constant
JohnPhos	2-(di-*tert*-butylphosphino)biphenyl
LDA	Lithium Diisopropylamine
LUMO	Lowest Unoccupied Molecular Orbital
m	Multiplet
Me	Methyl
mes	Mesitylene
MHz	MegaHertz
min	Minutes
mol	Mole
MS	Molecular Sieves
neop	Neopentyl glycolato
NHPI	*N*-Hydroxyphthalimide
nm	Nanometre
NMR	Nuclear Magnetic Resonance
o/n	Overnight
Ph	Phenyl
phen	1,10-Phenanthroline
pin	Pinacol
ppm	Parts Per Million
PPTS	Pyridinium p-toluenesulfonate
q	Quartet
quant.	Quantitative
rpm	Rotations Per Minute
rt	Room Temperature
s	Singlet
SPhos	2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl
spt	Septet
t	Triplet
TBS	*tert*-butyldimethylsilyl ether

*t*Bu	*tert*-butyl
TCNHPI	*N*-Hydroxytetrachlorophthalimide
Tf	Triflate
TFP	Tri-(2-furyl)phosphine
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMA	Tetramethylammonium
TMEDA	Tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidine
TMS	Tetramethysilane
Ts	Tosyl
UV	Ultraviolet
w/u	Work-Up
XPhos	2-dicyclohexylphosphino-2’,4’,6’-triisopropylbiphenyl
XRD	X-ray Diffraction

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Chapter 1 Introduction

1.1. C-C Bond Activation and Cleavage

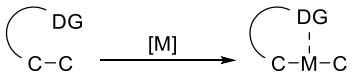
1.1.1. Strategies Towards the Activation and Cleavage of C-C Bonds

C-C bond functionalisation is highly attractive because it has the potential to convert ubiquitous C-C bonds into functional groups with high atom economy. The cleavage of C-C single bonds is particularly attractive because from one single bond, two reactive C-M bonds can be generated, giving two potential points of functionalisation. C-C bond functionalisation can therefore enable the preparation of value-added chemicals from hydrocarbons.

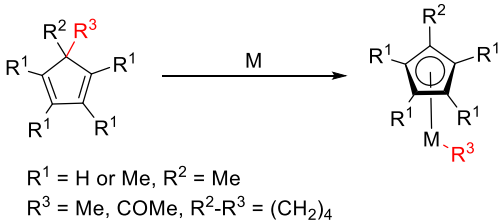
Despite its attractiveness, C-C functionalisation is much less common than the functionalisation of other bonds, such as C-H.[1,2] This is in part due to the thermodynamic stability of C-C bonds, which are in general stronger than two C-M bonds, thus making oxidative addition to C-C single bonds thermodynamically unfavourable in many instances.[3,4] In terms of kinetics, C-C bond cleavage is disfavoured by the highly directional nature of the sigma orbital along the bond axis. In contrast, the s orbital of hydrogen is spherical and does not need to distort to interact with a metal, making oxidative addition of C-H more facile.[4] Finally, C-H bonds are generally more abundant than C-C bonds and more sterically accessible because each carbon atom of a C-C bond is bonded to three other atoms, which sterically hinders the approach of a metal.[1,2] Thus, in many cases the more ubiquitous, sterically accessible, and less thermodynamically stable C-H bonds are functionalised instead of C-C bonds.

Despite the above-mentioned challenges, strategies have been developed to facilitate the functionalisation of C-C bonds. These include the use of a directing group (chelation), aromatisation, and the release of ring strain. Firstly, in chelation assisted C-C bond cleavage a Lewis basic group coordinates to the metal, bringing it into close proximity of the targetted C-C bond and making the cleavage kinetically more favourable (Scheme 1.1).[1] Chelation can also make the cleavage thermodynamically more favourable by stabilising reaction intermediates, particularly when a 5-membered metallocycle is formed.[3] In the aromatisation strategy, the energy of the products containing the cleaved C-C bond are lowered by the introduction of

aromaticity, which brings substantial stabilisation and makes the process thermodynamically more favourable (Scheme 1.2).[2,4]

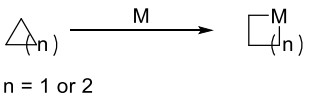


Scheme 1.1 *Chelation assisted C-C bond cleavage, in which a Lewis basic group coordinates to the metal.*



Scheme 1.2 *C-C bond cleavage driven by aromatisation of the substrates.*

Finally, the release of ring strain is a commonly used strategy to make C-C bond cleavage more favourable (Scheme 1.3).[1–4] In this approach, high energy starting materials are employed to make C-C bond cleavage more thermodynamically favourable. Three and four membered ring systems have been most used because these systems are significantly strained. As shown in figure 1.1, unsubstituted cyclopropane has a strain energy of 29.0 kcal/mol and unsubstituted cyclobutane has a strain energy of 26.3 kcal/mol, much higher than that of cyclopentane and cyclohexane.[1] It is worth noting that the strain energy is also affected by the substitution pattern on the ring.[1] The release of ring strain upon going from a three to a four membered ring or from a four to a five membered ring provides a strong driving force for C-C cleavage.



Scheme 1.3 *C-C bond cleavage facilitated by the release of ring strain.*

The employment of substrates containing ring strain can also make C-C cleavage kinetically more favourable. The HOMOs and LUMOs of cyclopropane and cyclobutane protrude away from the bond axis which enables better overlap with the metal orbitals, lowering the kinetic barrier.[2] Many examples of strain driven C-C bond

cleavage have been reported, substrates include activated cyclopropanes, cyclopropenes, cyclobutane derivatives bearing a ketone moiety, and biphenylenes.[1]

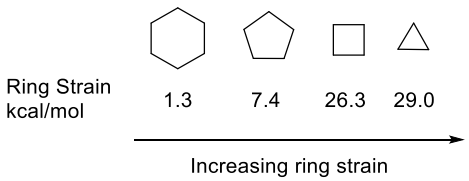
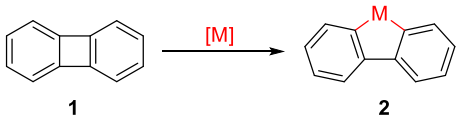


Fig. 1.1 *The ring strain associated with cyclopropane, cyclobutane, cyclopentane, and cyclohexane given in kcal/mol.*

1.1.2. C-C Bond Cleavage and Functionalisation of Biphenylene(s)

1.1.2.1. Introduction

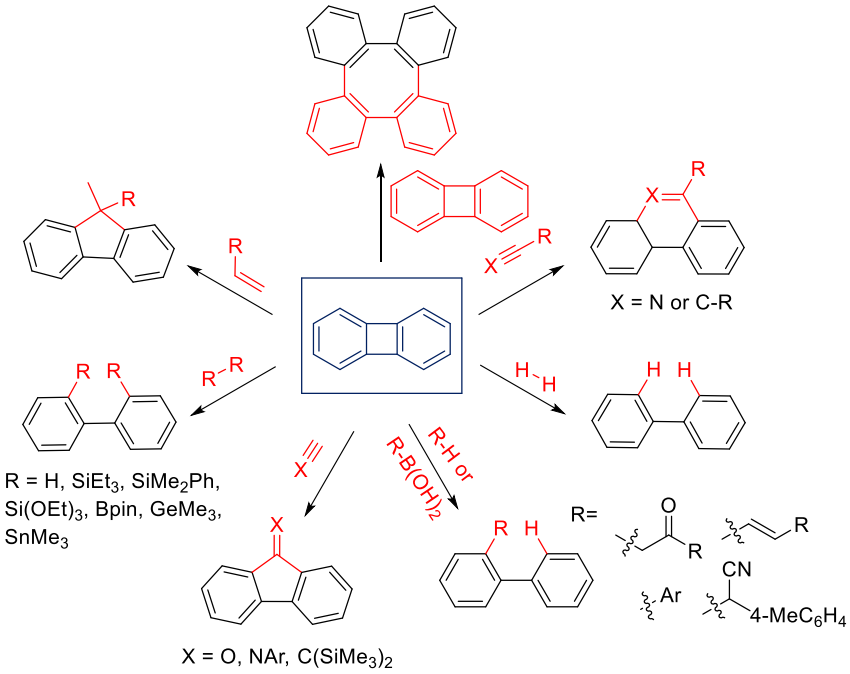
Biphenylene(s) are particularly attractive substrates for strain driven C-C bond cleavage because of their high strain energy. The C-C bond strength of biphenylene, **1**, has been estimated to be 65.4 kcal/mol, 53 kcal/mol less than the C-C bond in biphenyl, which does not experience any ring strain.[5] The weak C-C bond of biphenylene makes it an ideal target for C-C bond cleavage because two relatively strong aryl-M bonds are formed and a weak C-C bond cleaved. In addition, the π-system of biphenylene has the potential to coordinate to the catalyst, which lowers the kinetic barrier to oxidative addition.[6] As such biphenylene is known to react with a range of transition metals including: iron, iridium, nickel, chromium, ruthenium, osmium, palladium, cobalt, rhodium, platinum, and gold.[7]



Scheme 1.4 *The insertion of a transition metal into the strained C-C bond of biphenylene to give metallafluorene **2**.*

The C-C bond of biphenylene can be cleaved to give metallafluorene **2**, which can give a variety of functionalised products (Scheme 1.4). Scheme 1.5. summarises key transformations of biphenylene (and its derivatives). The majority of transformations involve the insertion of small molecules into the C-C bond. Examples include;

dimerisation,[6,8–11] [4+1] cycloaddition,[9,12–14] and [4+2] cycloaddition.[9,13,15–22] The ring opening of biphenylene (and its derivatives) to yield biaryls is also known and examples include hydrogenolysis,[9,23,24] hydrofunctionalisation,[25,26] and difunctionalisation.[26,27]

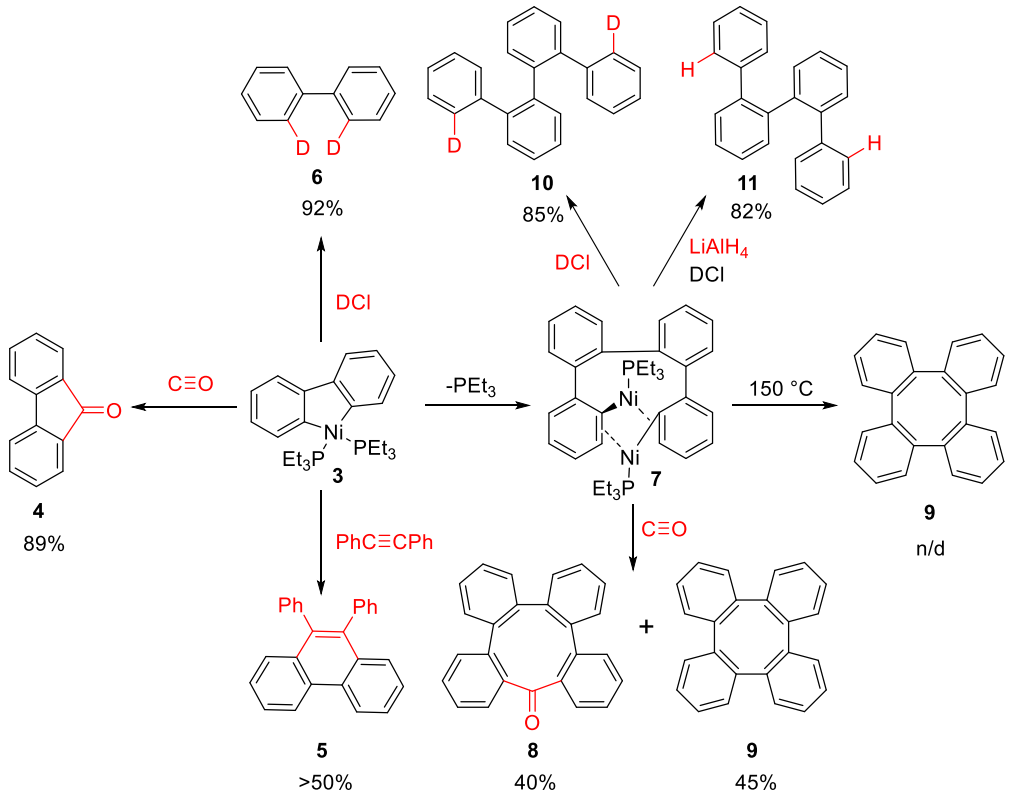


Scheme 1.5 *Key transformations of biphenylene, in which the strained C-C bond is cleaved.*

1.1.2.2. Insertion of Small Molecules into the Strained C-C Bond of Biphenylene(s)

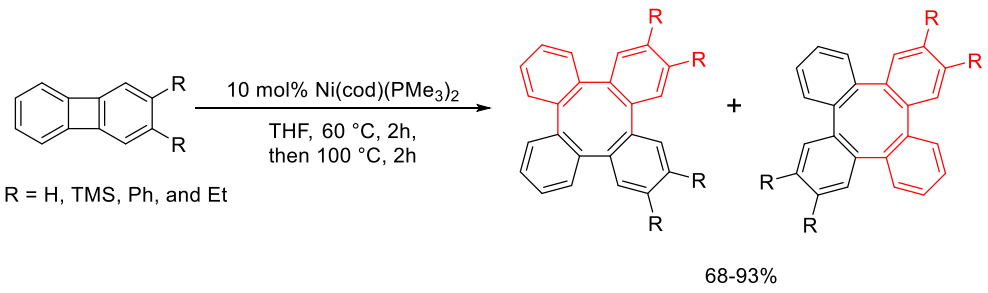
An early innovator in the C-C bond cleavage of biphenylenes was Eisch. In 1985, Eisch *et al.* reported the oxidative addition of biphenylene to nickel(0) complexes.[9] The reactivity of the nickel complexes varied substantially dependent on the ligand. It was proposed that more electron rich ligands promote oxidative addition, in part because they bond more strongly to nickel (II). Of the nickel (0) complexes tested $Ni(PEt_3)_4$ was found to be the most reactive and the resulting dibenzonickelole-bis(triethylphosphine) **3** was isolated when the reaction was conducted at approximately 0 °C. It was found that **3** reacted with CO, PhC≡CPh, and DCl to give insertion products **4** and **5** and the ring opened product **6** in high yield (Scheme 1.6). The attempted oxidation of **3** gave a mixture of different products. Over time **3**

decomposed to **7**, which reacted with CO, DCl, and $LiAlH_4$ to give the insertion products **8** and **9** and the ring opened products **10** and **11**. Upon heating to 150 °C, **7** decomposed to metallic nickel and tetraphenylene **9** (Scheme 1.6).



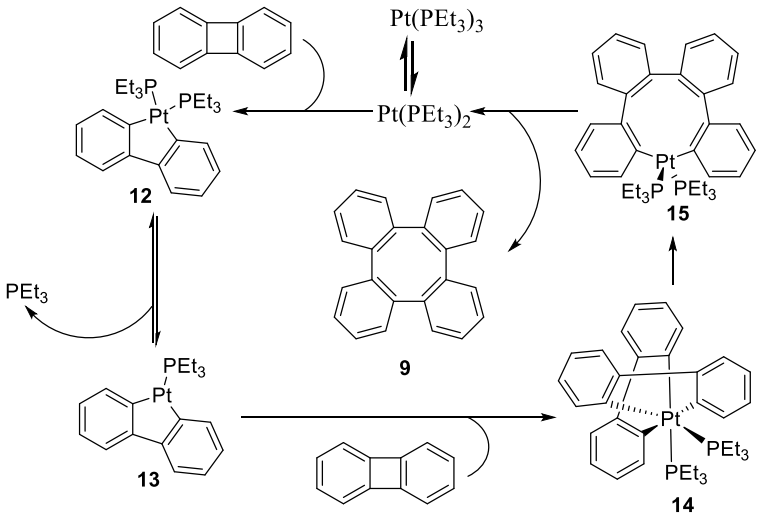
Scheme 1.6 *Different functionalisations of biphenylene achieved using stoichiometric* $Ni(PEt_3)_4$.

In the first example of the catalytic dimerisation of biphenylene, Vollhardt *et al.* later reported that $Ni(cod)(PMe_3)_2$ catalysed biphenylene dimerisation at the lower temperature of 100 °C, to give tetraphenylene in 92% yield (Scheme 1.7). Three additional substituted biphenylenes were also found to undergo catalytic dimerisation.[8]



Scheme 1.7 *The* $Ni(cod)(PMe_3)_2$ *catalysed dimerisation of biphenylene and its substituted derivatives.*

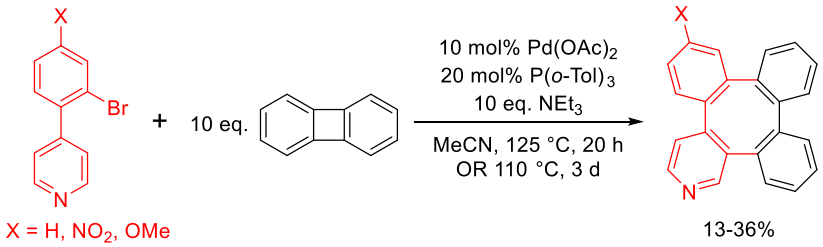
In addition, Jones *et al.* reported that $Pt(PEt_3)_3$ and $Pd(PEt_3)_3$ complexes catalyse the dimerisation of biphenylene to yield its dimer, tetraphenylene.[6] Complexes **12** and **15** were identified as intermediates when $Pt(PEt_3)_3$ was employed as the catalyst and the catalytic cycle in Scheme 1.8 was proposed. The first step is loss of PEt_3 to form $Pt(PEt_3)_2$, to which biphenylene oxidatively adds. Intermediate **12** loses PEt_3 to form **13**, to which a second molecule of biphenylene oxidatively adds. This is followed by two sequential reductive C-C couplings to form tetraphenylene. The proposed mechanism is consistent with the observation that free PEt_3 inhibits the reaction. $Pd(PEt_3)_3$ was a more effective catalyst for the dimerisation of biphenylene and the palladium analogue of **12** was observed by NMR, but not the palladium analogue of **15**. It is proposed that the catalytic cycle outlined in Scheme 1.8 is consistent with this observation and that the palladium analogue of **15** is not observed because reductive elimination from palladium complexes is more facile than that from platinum complexes.



Scheme 1.8 *Proposed mechanism for the dimerisation of biphenylene by reaction with $Pt(PEt_3)_3$ (and $Pd(PEt_3)_3$).*

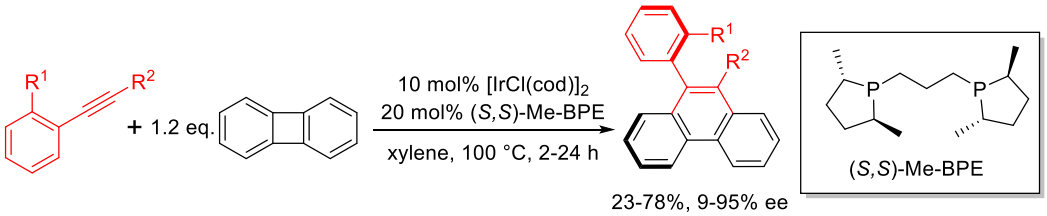
Only one example has been reported in which a heterophenylene was prepared by the C-C functionalisation of biphenylene. In this work, biphenylene was reacted with *o*-bromosubstituted biaryls to give unsymmetrical heterophenylene products in low to moderate yields (Scheme 1.9).[10] The authors propose that the *o*-bromosubstituted biaryl undergoes oxidative addition to the palladium catalyst first and not biphenylene. This is followed by C-H insertion of the adjacent *ortho* C-H bond which generates a

5-membered palladacycle, this palladacycle subsequently reacts with biphenylene to yield the heterophenylene product. This proposal was supported by a competition reaction between biphenylene and an *o*-bromosubstituted biaryl with an alkene, in which only the *o*-bromosubstituted biaryl reacted.



Scheme 1.9 *Reaction of biphenylene with o-bromosubstituted biaryls to give unsymmetrical heterophenylenes.*

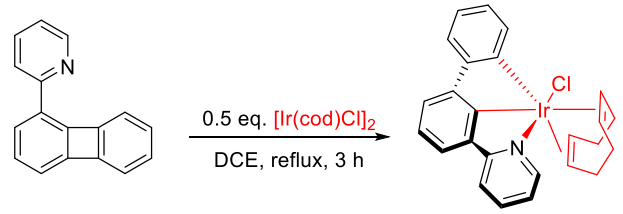
Other notable examples of C-C functionalisation of biphenylene(s) in which new C-C bonds are formed, include [4+2] cycloaddition. An interesting example of this type was reported by Shibata *et al.* who achieved the synthesis of axially chiral 9,10-di-substituted phenanthrenes by the reaction of biphenylene with *ortho*-alkynyl substituted benzenes (Scheme 1.10).[28] Enantioselectivity was achieved using a chiral iridium complex and was strongly affected by the substrate. The highest enantioselectivities were obtained with polarised alkynes bearing an electron donating group on one side of the alkyne and an electron withdrawing group on the other.



Scheme 1.10 *Enantioselective [4+2] cycloaddition of biphenylene with ortho-alkynylsubstituted benzene substrates.*

The insertion of small molecules into the C-C bond of unsymmetrical substituted biphenylenes is also known. In an unsymmetrical substituted biphenylene, the two C-C bonds are inequivalent, and the catalyst could insert into either one. Regioselective C-C bond cleavage of unsymmetrical substituted biphenylenes can be challenging, but it is highly valuable because it increases the range of products that can be prepared. One way to achieve regioselective C-C cleavage is to place a directing group in the 1-

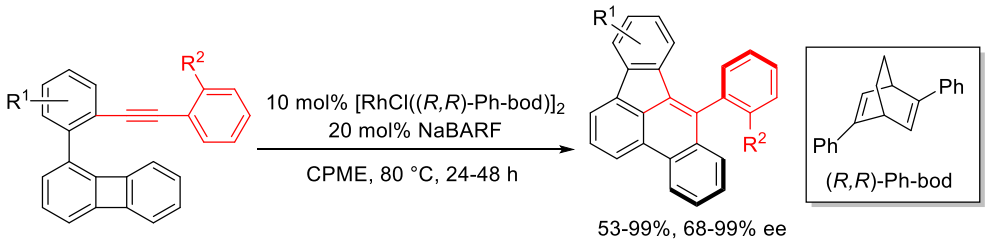
position of the biphenylene. Use of a directing group for selective C-C cleavage was reported by Matsubara *et al.* (Scheme 1.11).[29] In this reaction, $[Ir(cod)Cl]_2$ selectively inserted into the proximal C-C bond in 1-(2-pyridyl)biphenylene, **16**, and none of the product of distal C-C bond cleavage was observed. The resulting iridium complex **17** underwent reaction with conjugated aromatic compounds to give luminescent iridium complexes.



16 **17** 92%

Scheme 1.11 *The insertion of $[Ir(cod)Cl]_2$ into the more sterically hindered C-C bond of 1-(2-pyridyl)biphenylene,* ***16****.*

Regioselective C-C bond cleavage in unsymmetrical substituted biphenylenes has also been achieved catalytically using a directing group. Shibata *et al.*, who reported the enantioselective intermolecular [4+2] cycloaddition of alkynes and biphenylene, later reported the intramolecular enantioselective [4+2] cycloaddition of 1-(2-alkynylaryl)-substituted biphenylenes (Scheme 1.12).[20] In this instance, a chiral rhodium complex was found to be the most effective catalyst.

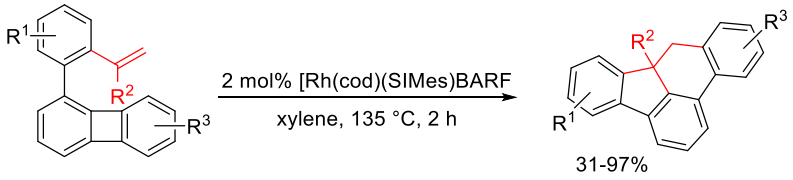


53-99%, 68-99% ee

Scheme 1.12 *Enantioselective, alkyne directed, intramolecular [4+2] cycloaddition of 1-(2-alkynylaryl) substituted biphenylenes.*

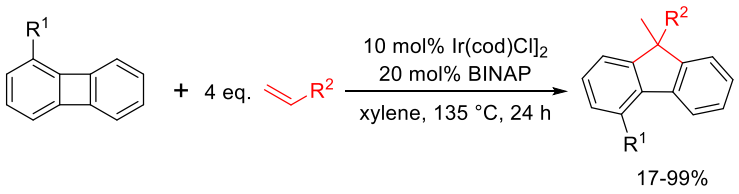
In this reaction the alkyne behaves as a directing group and the more sterically hindered C-C bond is selectively cleaved. A broad range of substrates were tolerated in the reaction, including substrates bearing two alkyne moieties and two biphenylene moieties, which underwent consecutive cycloadditions to give complex polycyclic aromatic hydrocarbons with two chiral axes. These polycyclic aromatic hydrocarbons potentially have applications as organic electronic materials.

In earlier work, the same group reported a related reaction, in which 1-(2-vinylaryl)-substituted biphenylenes underwent a rhodium catalysed intramolecular [4+2] cycloaddition reaction to give dihydrobenzofluoranthenes (Scheme 1.13).[22] Similarly to the alkyne, the alkene acts as a directing group and the sterically more hindered C-C bond is selectively cleaved. Several substrates were tolerated; however, placing a bulky group in the available *ortho*- position of the aryl ring was not.



Scheme 1.13 *Alkene directed, intramolecular [4+2] cycloaddition of 1-(2-vinylaryl)-substituted biphenylenes.*

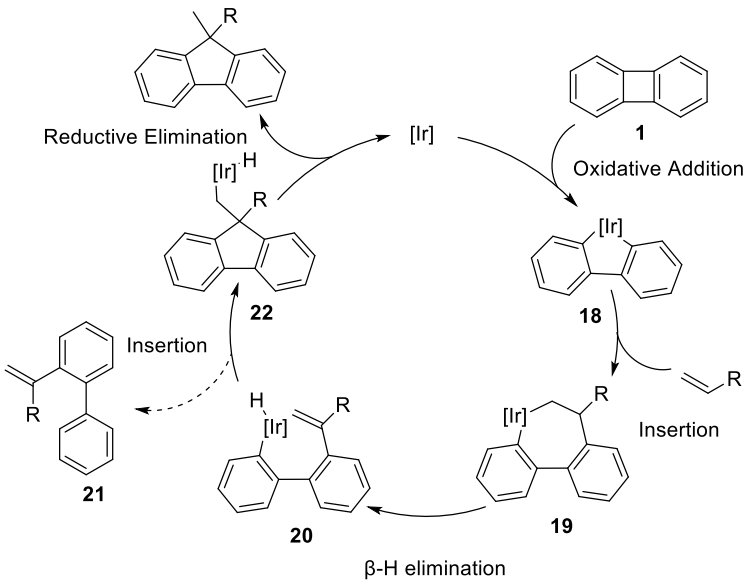
Interestingly, when biphenylene(s) were intermolecularly reacted with an alkene the [4+1] cycloaddition product was obtained instead of the [4+2] cycloaddition product (Scheme 1.14).[14] In this work it was also shown that in the absence of a directing group the catalyst cleaves the least sterically hindered C-C bond. When 1-substituted biphenylenes: 1-phenylbiphenylene, 1-methylbiphenylene, 1,8-dimethylbiphenylene, 1-(trimethylsilyl)biphenylene, and benzo[a]biphenylene were employed as substrates only the least sterically hindered C-C bond was cleaved. No fluorene product resulting from cleavage of the more sterically hindered C-C bond was detected in any instance.



Scheme 1.14 *The preparation of 9,9-disubstituted fluorenes via the [4+1] cycloaddition of biphenylenes with alkenes.*

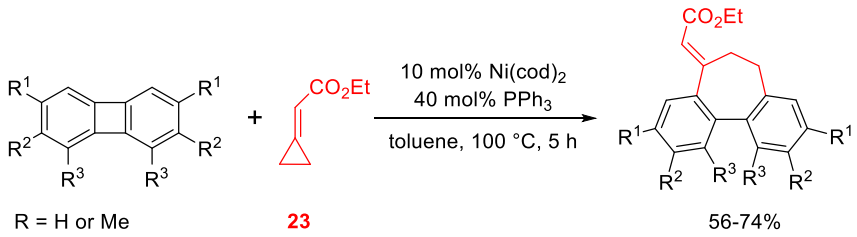
The mechanism outlined in Scheme 1.15 was proposed, in which oxidative addition of biphenylene first occurs to form the 5-membered metallocycle **18**.[14,30] Alkene insertion and subsequent β-hydride elimination generates **20**. Intermediate **20** undergoes intramolecular insertion, followed by reductive elimination to give the fluorene product. The observation of biaryl products with an *exo*-olefin moiety, **21**, supports this mechanism. In addition, DFT calculations support this mechanism because the

reductive elimination of **19** or **20** were both calculated to have higher activation energies than the reductive elimination of **22** and the preceding β-hydride elimination and intramolecular insertion steps.



Scheme 1.15 *Proposed mechanism for the intermolecular [4+1] cycloaddition of biphenylene(s) with alkenes.*

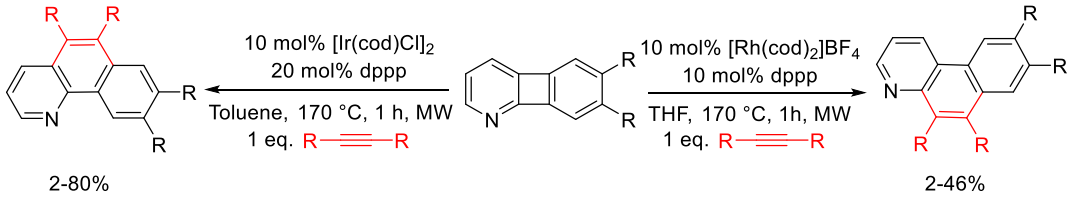
In 2010, Saito *et al.* reported that biphenylene and two substituted biphenylene derivatives underwent ring expansion by reaction with ethyl-2-cyclopropylidene acetate **23** (Scheme 1.16).[31] It was found that the E-isomer was selectively formed in all three reactions and when 1,8-dimethylbiphenylene was employed as a substrate only the least sterically hindered C-C bond was cleaved.



Scheme 1.16 *The nickel catalysed ring expansion of biphenylene(s) by insertion of ethyl-2-cyclopropylidene acetate,* ***23****.*

Finally, Kotora *et al.* reported that 1-azabiphenylenes underwent a [4+2] cycloaddition reaction with alkynes (Scheme 1.17).[18] The regioselectivity of the reaction towards distal or proximal C-C bond cleavage was catalyst controlled. A neutral iridium catalyst selectively catalysed the [4+2] cycloaddition of the distal C-C bond with

alkynes. It was also shown in one instance that a neutral rhodium catalyst similarly catalysed cleavage of the distal C-C bond. Conversely, when a cationic rhodium catalyst was employed, the proximal C-C bond underwent preferential [4+2] cycloaddition and the extent of distal C-C activation varied between substrates.



Scheme 1.17 *The [4+2] cycloaddition of 1-azabiphenylenes with alkynes.*

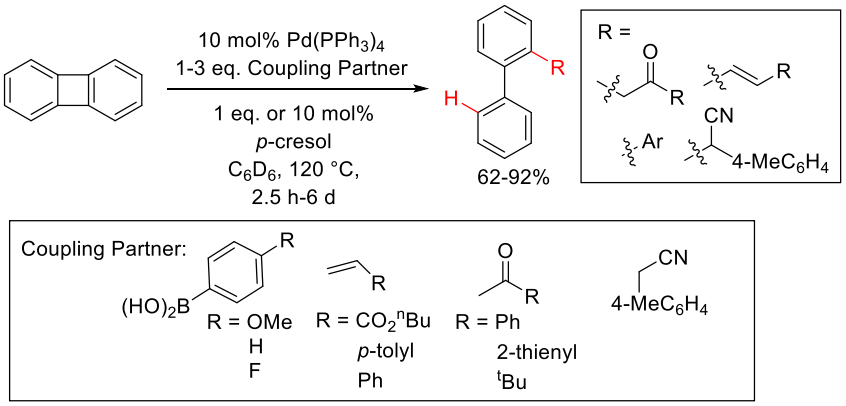
It was proposed based on DFT calculations that the selectivity for distal or proximal C-C cleavage is dictated by kinetic control of the C-C oxidative addition step. In both reactions higher yields were obtained when the R group in the six and seven positions was TMS, not hydrogen. In addition, distal C-C activation was in general found to give the cycloaddition products in higher yields than proximal C-C activation.

1.1.2.3. Ring Opening Reactions of Biphenylene(s)

Although not as prevalent as the insertion of small molecules into the strained C-C bond of biphenylene(s), examples of the ring opening of biphenylene(s) to yield *ortho*-substituted biaryls are also known. In 2001, Jones and Satoh reported the palladium catalysed hydrofunctionalisation of biphenylene with alkenes, aryl boronic acids, ketones, and a nitrile (Scheme 1.18).[25] *p*-Cresol was crucial for the desired transformation: in its absence the yield of the hydrofunctionalised product drops and tetraphenylene forms. Stoichiometric amounts of *p*-cresol gave high yields in the coupling of alkenes and aryl boronic acids, whereas catalytic amounts gave improved yields with ketone substrates. Acetic acid, a stronger acid was less effective than *p*-cresol at facilitating the desired reaction. The authors suggest that in the presence of *p*-cresol, the palladium complex, L_2Pd(2,2'-biphenylyl), resulting from the oxidative addition of biphenylene, may undergo protonolysis before further reaction with the second substrate.

Yus *et al.* reported the reductive ring opening of biphenylene by reaction with a catalytic amount of 4,4'-di-*tert*-butylbiphenyl (DTBB) and an excess of lithium: the

resulting *o,o'*-dilithiated biphenyl was treated with a range of electrophiles to give a range of *o,o'*-disubstituted biaryls (Scheme 1.19).[27] When water and deuterium oxide were employed as the electrophiles the desired product was obtained in high yield. Except for TMSCl, all other electrophiles gave moderate yields of the desired product and less than 10% of the product of monofunctionalisation. When TMSCl was employed as the electrophile, the only product of the reaction was silafluorene **24**, not the expected *o,o'*-disilylated biaryl. This is of note because the formation of carbon-element bonds other than C-C, C-H, and C-N *via* the C-C cleavage of biphenylene is relatively rare.



Scheme 1.18 *Palladium catalysed hydrofunctionalisation of biphenylene with alkenes, aryl boronic acids, ketones, and a nitrile.*

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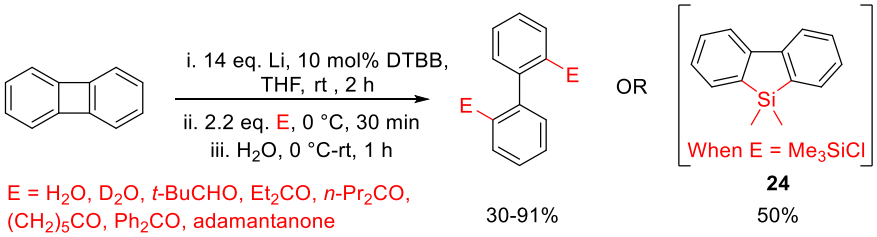
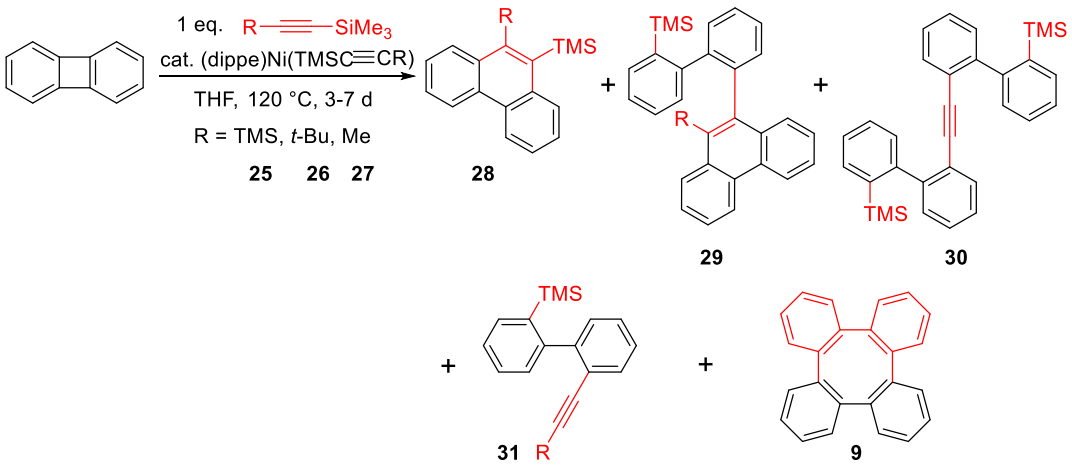


Scheme 1.19 *The preparation of o,o'-disubstituted biaryls from biphenylene by lithiation, followed by reaction with an electrophile.*

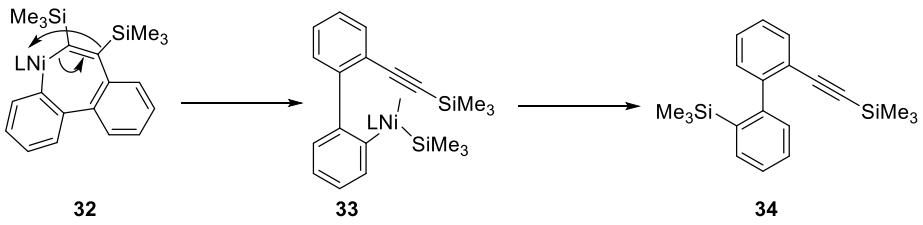
The first example of the catalytic introduction of silicon into biphenylene was reported by Edelbach *et al.* In this work, it was found that the nickel catalysed reaction of biphenylene with trimethylsilyl substituted alkynes resulted in a mixture of products (Scheme 1.20).[32] In addition to the expected [4+2] cycloaddition products **28**, products of C-Si addition across the C-C bond **29**, **30**, and **31** were also observed. The chemoselectivity of the reaction varied dependent on the alkyne substrate. When biphenylene was reacted with alkynes **26** and **27** the major product was the expected

phenanthrene product **28**. In the former instance, **29** and **31** were also isolated and the ratio of **28**:**29**:**31** was 4:1:1 by GC-MS. In the latter instance, side-product **29** was isolated and a small amount of tetraphenylene, the ratio of **28**:**29** was reported as 2:1.



Scheme 1.20 *The reaction of biphenylene with trimethylsilyl substituted alkynes to yield a mixture of products.*

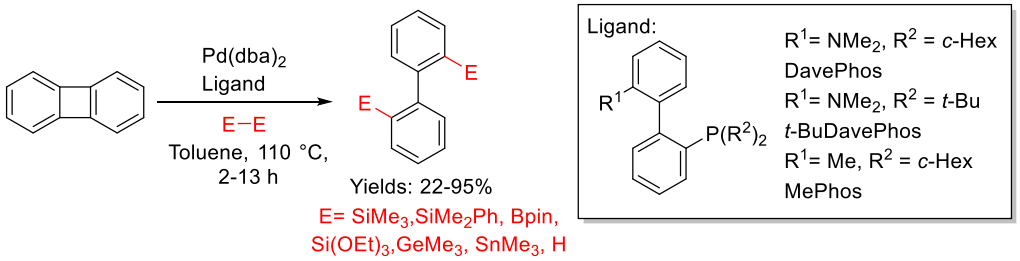
Conversely, when biphenylene was reacted with **25**, none of the [4+2] cycloaddition product **28** was isolated and the major product, **31**, was isolated in 41% yield. It was proposed that **31** is formed by 1,3-trimethylsilyl migration of intermediate **32**, which outcompetes phenanthrene reductive elimination (Scheme 1.21). In addition, **29** was isolated in 14% yield, **30** was isolated in impure form, so no yield was given, and trace amounts of tetraphenylene were observed. NMR of the reaction mixture suggested that following its formation, **31** coordinates to the nickel catalyst and undergoes further reaction to give the products **29** and **30**.



Scheme 1.21 *Proposed 1,3-trimethylsilyl migration of intermediate **32**.*

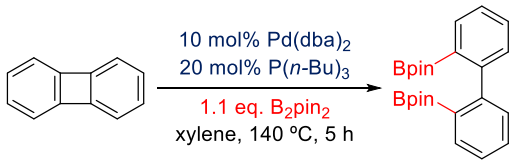
Following this work by Edelbach *et al.*, Matsuda and Kirikae reported several reactions in which biphenylene underwent palladium catalysed hydrofunctionalisation and difunctionalisation (Scheme 1.22).[26] Firstly, biphenylene underwent hydrosilylation at 110 °C with the triorganyl silanes $HSiEt_3$, $HSiMe_2Ph$, and $Si(OEt)_3$ when DavePhos was employed as the ligand, giving the products in 43-95% yield. MePhos was found

to be a better ligand for the hydroborylation of biphenylene with pinacolborane and the *ortho*-borylated product was isolated in 56% yield. Difunctionalisation was achieved using both symmetrical reagents, in which the two functional groups introduced are the same, and unsymmetrical reagents, in which two different functional groups were introduced (Scheme 1.22). The functional groups introduced were $SiMe_3$, $SiMe_2Ph$, $GeMe_3$, $SnMe_3$, and Bpin.



Scheme 1.22 *The catalytic hydrofunctionalisation and difunctionalisation of unsubstituted biphenylene.*

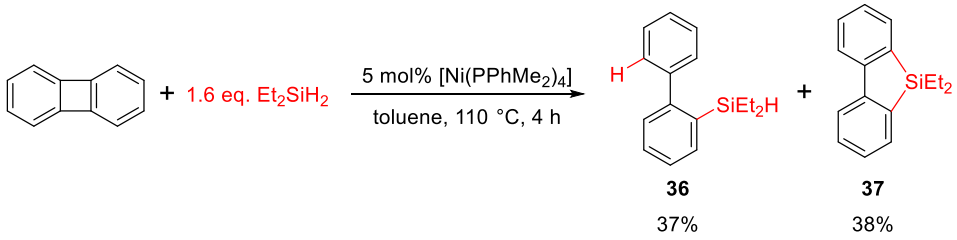
Attempted diborylation with B_2pin_2 using DavePhos as the ligand resulted in a mixture of monoborylated and diborylated product, in which the former predominated. Diborylation was achieved selectively, albeit in moderate yield when P(*n*-Bu)$_3$ was employed as the ligand and the reaction temperature was raised to 140 °C (Scheme 1.23). The difunctionalisation of biphenylenes is an atom economic method of preparing *o,o'*-difunctionalised biaryls. Diborylation is particularly appealing because boryl functional groups are known to undergo several transformations and thus several functionalised aromatic compounds could in principle be prepared from them.



Scheme 1.23 *The ring opening diborylation of unsubstituted biphenylene with B_2pin_2.*

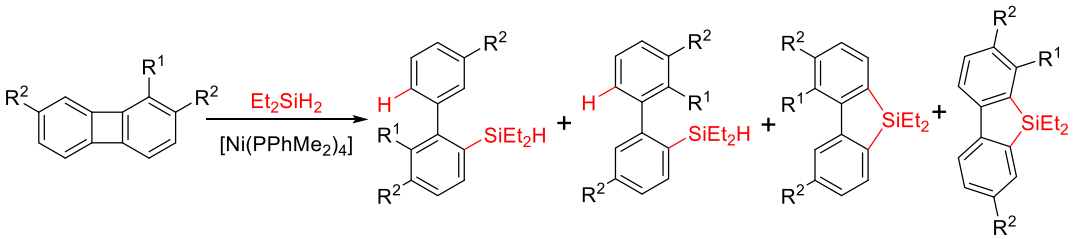
Building on from this work, Lerner *et al.* reported the reaction of biphenylene with Et_2SiH_2 (Scheme 1.24).[33] Using the conditions reported by Matsuda and Kirikae, only 20% conversion was achieved using the dialkyl silane Et_2SiH_2 in place of triorganyl silanes. [Ni(PPhMe_2)$_4$] was found to be a much more effective catalyst, giving full

conversion, but a mixture of hydrosilylated product **36** and silafluorene product **37** was obtained. Conditions were not found for the chemoselective preparation of silafluorene **37**. However, following its purification by column chromatography, the side-product **36** underwent dehydrogenation to yield the desired silafluorene **37**, using Wilkinson's catalyst.



Scheme 1.24 *The ring opening silylation and hydrosilylation of biphenylene with* $SiEt_2H_2$.

Unfortunately, when the biphenylene substrate scope was investigated 1,8-dimethylbiphenylene was found to be completely unreactive. However, the least sterically hindered C-C bond of 1-methylbiphenylene was selectively cleaved to give a mixture of silafluorene and the two regioisomers of hydrosilylation (Scheme 1.25). In contrast, 2,7-(di-*tert*-butyl)biphenylene showed no selectivity for the least hindered C-C bond and a mixture silafluorene regioisomers resulting from distal and proximal C-C bond cleavage was obtained (Scheme 1.25).



R^1= Me, R^2 = H	not given	not given	48%	0%
R^1= H, R^2= *t*Bu	0%	0%	25%	30%

When R^1= H, R^2= *t*Bu, following reaction with $[Ni(PPhMe_2)_4]$ and column chromatography the resulting product is reacted with $[Rh(PPh_3)_3Cl]$

Scheme 1.25 *The reaction of substituted biphenylenes with* Et_2SiH_2 *to give hydrosilylated and silafluorene products.*

Finally, Lerner *et al.* found that $[Ni(PPhMe_2)_4]$ also catalysed the reaction of biphenylene with triorganyl silanes to give 2-silylbiphenyls in high yield. However, triorganyl silanes bearing sterically bulky alkyl groups were not tolerated because the Si-H bond was not sterically accessible. Tetraphenylene was instead isolated as the product.

Many reactions have been reported in which the C-C bond of biphenylene is catalytically and stoichiometrically functionalised. Most of these reactions are insertion reactions, such as [4+1] cycloaddition, [4+2] cycloaddition, and dimerisation (4+4 cycloaddition). There are comparatively few examples in which *o*-substituted biaryls are prepared from biphenylenes. *o*-Monofunctionalised biaryls have been prepared by hydrofunctionalisation and *o,o'*-difunctionalised biaryls have been prepared by a sequence of lithiation and quenching with an electrophile, and by reaction with silyl, boryl, germanyl, and stannyl reagents.

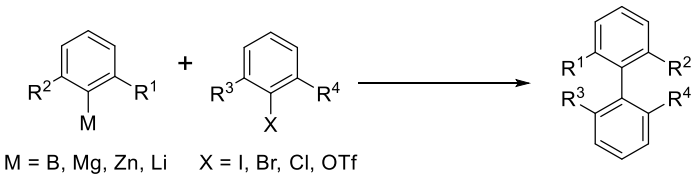
The single example of biphenylene diborylation with B_2pin_2 reported by Matsuda and Kirikae remains the only example of biphenylene diborylation. The optimisation of this reaction and its extension to 1-substituted biphenylenes has the potential to give synthetic access to a range of *o,o,o'*-trisubstituted biaryl products, which are traditionally challenging to prepare due to steric hindrance around the biaryl axis. The resulting products would contain two aryl boronate ester moieties, which as will be discussed in section 1.3.1, are valuable synthetic intermediates. In addition, the ring opening of biphenylene compounds that are only substituted in the 1-position should enable the unambiguous determination of the effect of a particular substituent on the reaction, which will enable a greater understanding of the reaction.

1.2. Preparation of Sterically Congested Tri- and Tetra- *Ortho* Substituted Biaryls

Many natural products, pharmaceuticals, and ligands contain a tri- or tetra- *ortho* substituted biaryl moiety and as such their preparation has received significant attention. Well known examples include Vancomycin, Steganacin, BINAP, and BINOL.[34,35] The majority of tri- and tetra- *ortho* substituted biaryls are axially chiral because the *ortho* substituents restrict rotation about the aryl-aryl bond, therefore much work in this area focusses on their asymmetric synthesis.[35]

The cross-coupling of *ortho* substituted aryl electrophiles and nucleophiles in which the biaryl axis is formed, is one of the most employed methods for the synthesis of sterically congested biaryls (Scheme 1.26). Of the cross-coupling reactions, the Suzuki–Miyaura cross-coupling reaction has been the most used method (Scheme

1.26, M = B). One of the biggest challenges in the Suzuki–Miyaura cross-coupling approach towards sterically congested biaryls is the lower reactivity of *ortho*-substituted aryl boronic acids in the transmetallation step compared to aryl boronic acids with no *ortho* substituents.[36] This can be exacerbated by the use of sterically bulky, electron rich ligands, which are often employed to facilitate challenging oxidative additions.[36] To address this problem a huge amount of research into new ligand systems has been conducted. In general, and somewhat counterintuitively, a number of sterically hindered ligands have been found to increase the catalytic activity, which has enabled the use of milder reaction conditions.[34,37]

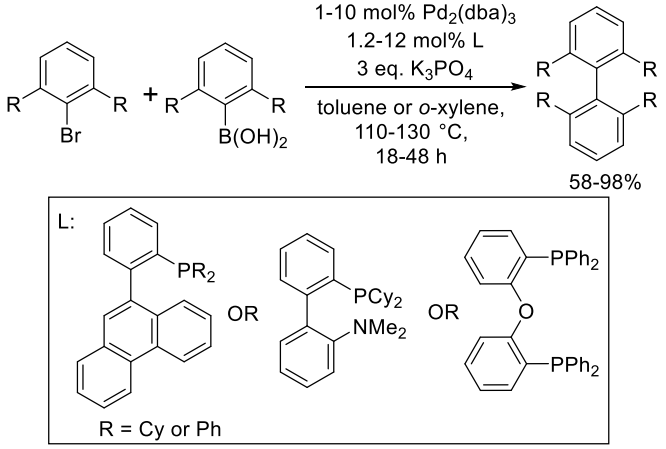


Scheme 1.26 *The cross-coupling of ortho substituted aryl electrophiles and nucleophiles to prepare tri- and tetra- ortho substituted biaryls.*

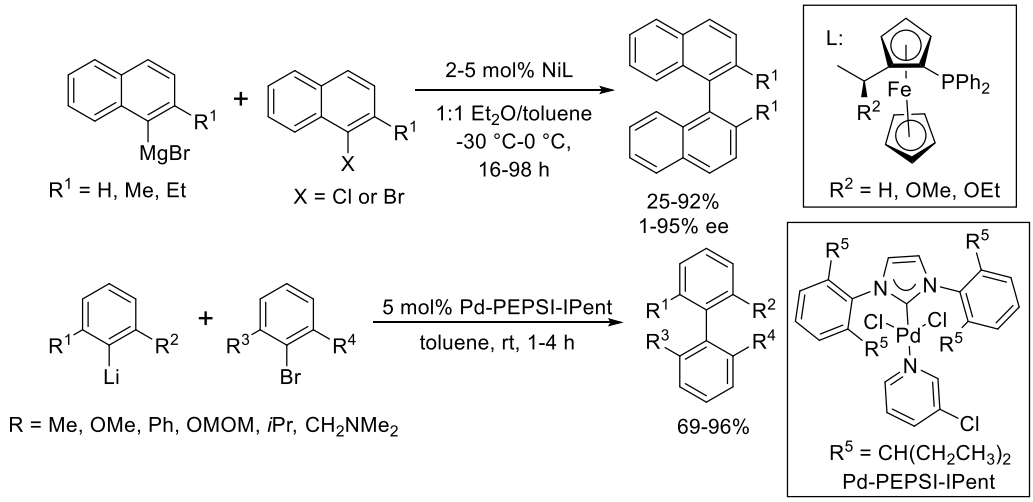
An early example of the preparation of sterically congested biaryls *via* Suzuki–Miyaura cross-coupling was reported by Buchwald *et al.* (Scheme 1.27).[38] In this work, several tetra- *ortho* substituted biaryls were prepared in moderate to high yield using one of four different ligands. In addition to the preparation of racemic biaryls, there have been many examples of enantioselective and diastereoselective Suzuki–Miyaura cross-coupling reactions to yield axially chiral biaryls. However, these reactions are generally limited either by a lack of substrate scope or the need for stoichiometric amounts of chiral reagent.[34]

Compared to the Suzuki–Miyaura cross-coupling reaction there are few examples in which sterically congested biaryls have been prepared *via* the Kumada–Tamao–Corriu cross-coupling reaction (Scheme 1.26, M= Mg). Both palladium and nickel catalysts have been employed in this reaction and sterically congested biaryls have been prepared in high yield.[34,39,40] In one example, Hayashi and Ito prepared three axially chiral binaphthyls at various temperatures using three different nickel catalysts (Scheme 1.28).[41] In 2013, Feringa *et al.* reported that aryllithium reagents could also be used to prepare sterically congested biaryls. Aryllithium reagents were cross-coupled with aryl bromides in the presence of catalytic Pd-PEPSI-IPent to yield tri-

and tetra- *ortho* substituted biaryls at room temperature (Scheme 1.28).[42] Due to the reactive nature of aryllithium and Grignard reagents, these cross-coupling reactions are limited by substrate scope.



Scheme 1.27 *The preparation of tetra- ortho substituted biaryls via Suzuki–Miyaura cross-coupling.*

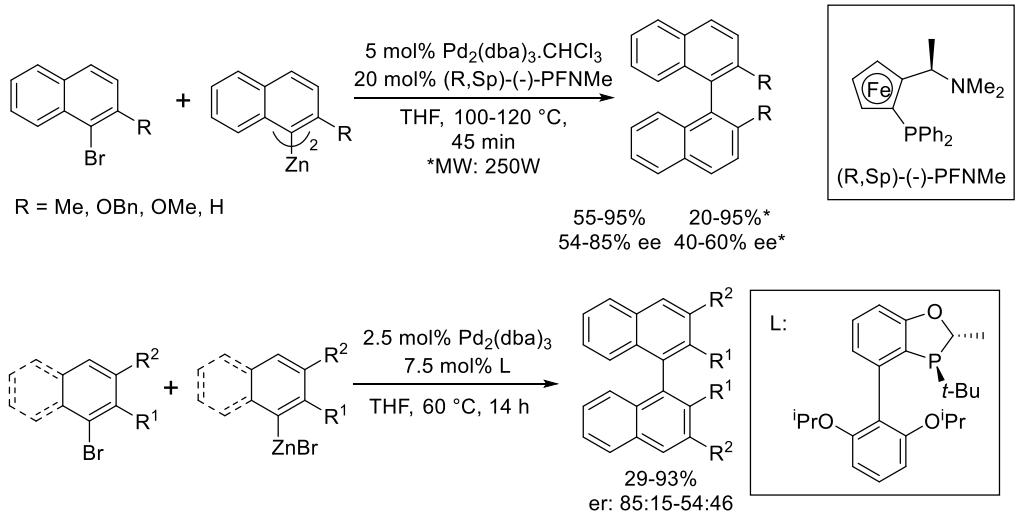


Scheme 1.28 *Examples of the preparation of sterically congested biaryls via cross-coupling reactions.*

Organozinc reagents, which have a higher functional group tolerance than aryllithium and Grignard reagents, have also been used to prepare sterically congested biaryls in Negishi cross-coupling reactions (Scheme 1.26, M = Zn).[43–47] The preparation of axially chiral biaryls *via* the Negishi reaction was first reported by Espinet *et al.*, in which binaphthalenes were synthesised in high yield with moderate to high enantioselectivities. Microwave irradiation reduced reaction times, but caused enantioselectivity to drop (Scheme 1.29).[44,45] Patel, Sieber, Kozlowski, Senanayake *et al.* later reported the enantioselective preparation of tetra- *ortho* substituted biaryls *via*

Negishi cross-coupling using slightly different reaction conditions (Scheme 1.29).[46] Despite its greater functional group tolerance, the Negishi cross-coupling reaction does still require anhydrous conditions and there are limited examples using this approach.

Cross-coupling reactions are a widely used and attractive method for the preparation of sterically hindered biaryls. However, the *ortho* substituted aryl electrophiles and nucleophiles suffer greater steric hindrance than their non *ortho* substituted counterparts rendering them less reactive. In general, cross-coupling reactions are limited by a lack of substrate scope. The Kumada–Tamao–Corriu and Negishi cross-coupling reactions are limited by the tolerance of the metal fragment towards other functional groups and there is no universal ligand that that works for all Suzuki–Miyaura cross-coupling reactions.[34]

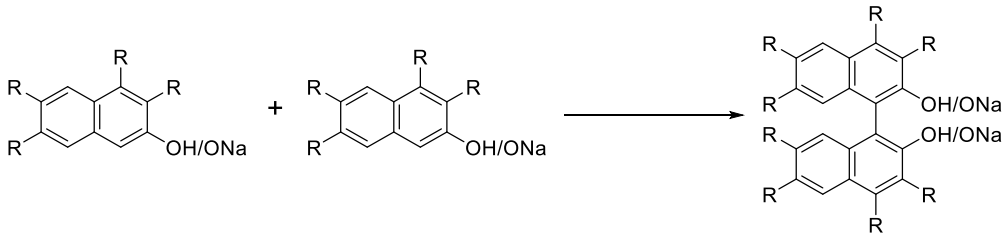


Scheme 1.29 *The preparation of sterically congested biaryls via Negishi cross-coupling.*

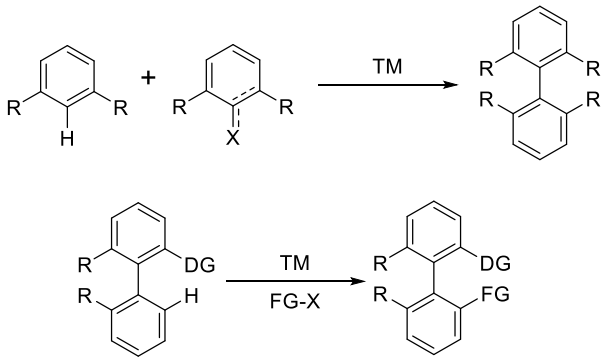
Oxidative coupling is another method that has been used to prepare sterically congested biaryls. It is predominantly limited to 1,1'-bis-2,2'-binaphthols due to generally poor regioselectivity with other substrates (Scheme 1.30).[34] Copper, vanadium, and iron catalysts have all been employed in this reaction to yield sterically congested biaryls in high yields and enantioselectivities.[34] Although an attractive method for the preparation of sterically congested biaryls, the scope of this method is limited because in many instances regioselective oxidative coupling is not possible.

Two main strategies have been employed to prepare sterically congested biaryls *via* C-H activation. In the first strategy, the biaryl axis is formed *via* C-H activation

(Scheme 1.31) and in the second, an additional *ortho* substituent is added to a di- or tri- *ortho* substituted biaryl *via* C-H activation (Scheme 1.31).[48] Both strategies have been used to synthesise sterically congested biaryls in high yield with high enantioselectivity or diastereoselectivity.[48] This type of chemistry is in its infancy and therefore there are limited examples. In addition, due to the ubiquitous nature of C-H bonds, directing groups are required to differentiate between them, which can limit the substrate scope and necessitate extra addition and removal steps.



Scheme 1.30 *The oxidative coupling of 2-naphthols to yield 1,1'-bis-2,2'-binaphthols.*

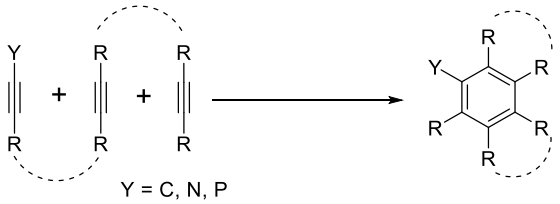


Scheme 1.31 *Strategies towards sterically congested biaryls via C-H activation.*

Finally, another more recent approach towards sterically congested biaryls is aromatic ring construction. The transition metal catalysed [2+2+2] cycloaddition reaction is one of the most common transformations of this type and has been achieved using cobalt, iridium, and rhodium catalysis (Scheme 1.32). Most commonly a 1,6-diyne is reacted with an alkyne, although the intermolecular reaction of three alkynes and the intramolecular reaction of triynes have also been reported. Using this method, sterically congested tri- and tetra- *ortho* substituted biaryls have been prepared in high yield and with high enantioselectivities.[34] One drawback of this method is the need to prepare the alkyne substrates. Other approaches which involve aromatic ring construction include the Dötz benzannelation of Fischer carbenes with alkynes and the diastereoselective reaction of an aryl Grignard reagent with an *ortho* substituted

cyclohexanone, followed by reduction. Although aromatic ring construction is an attractive and novel method for the preparation of sterically congested biaryls, these reactions are generally limited by a lack of substrate scope.[35]

To conclude, most existing methods towards sterically congested biaryls are limited by either substrate scope or the need for catalysts and ligands which are either not commercially available or expensive. The development of new methods towards this structural motif, which is present in many natural products and biologically active compounds, is therefore highly attractive. In particular, a method that enabled the synthesis of tri- and/or tetra- *ortho* substituted biaryls, with *ortho* substituents amenable to a variety of post-functionalisation reactions would be of high value.



Scheme 1.32 *Construction of an aromatic ring via [2+2+2] cycloaddition to form sterically congested biaryls.*

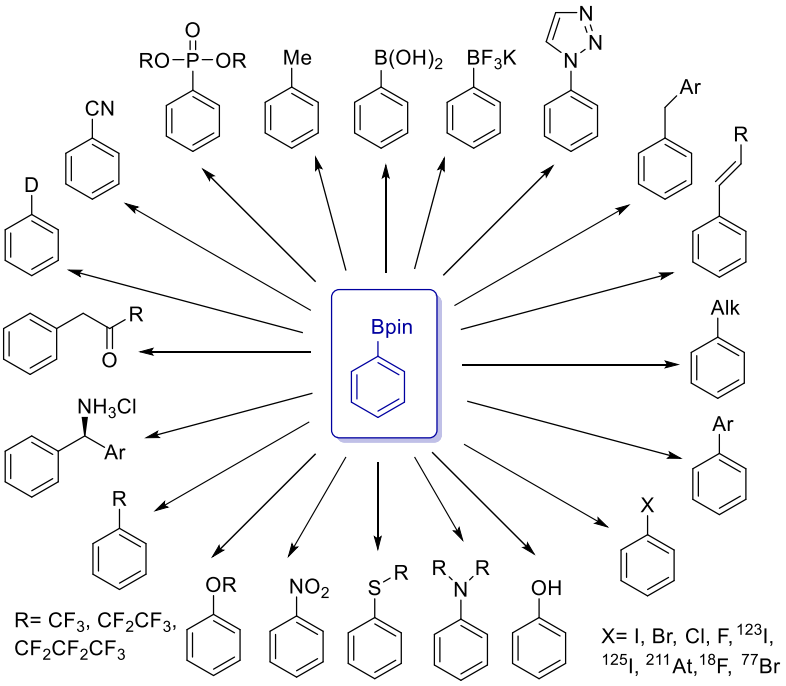
1.3. Aryl Pinacolboronate Esters

1.3.1. The Synthetic Importance of Aryl Pinacolboronate Esters

Aryl boronate esters are versatile building blocks in organic synthesis because they undergo a wide range of transformations. One of the most used types of aryl boronate esters are aryl pinacolboronate esters, which are generally more stable and easier to handle than the corresponding aryl boronic acids. In most cases they can be purified by column chromatography without decomposition and are stable in aqueous media.[49] As shown in Scheme 1.33, aryl pinacolboronate esters have been reported to undergo a large number of synthetic transformations, including C-C, C-N, C-O, C-S, C-D, C-P, and C-halogen bond formation. In the following section, representative examples of aryl pinacolboronate ester transformations will be discussed.

It is very popular due to the non-toxic nature of the boron coupling partners, in stark contrast to reagents such as stannanes, employed in the Stille cross-coupling reaction,

which are highly toxic.[49] In addition, aryl pinacolboronates are generally air and moisture stable and so can be stored and weighed in air, thus making them convenient substrates. Unlike aryl zinc and aryl magnesium reagents employed in the Negishi and Kumada–Tamao–Corriu cross-coupling reactions, aryl pinacolboronates have high functional group tolerance.[50] Therefore, a wider range of functionalised biaryls can be readily accessed.



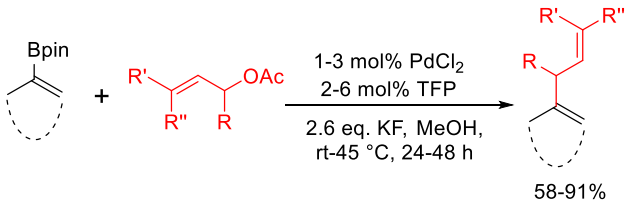
Scheme 1.33 *Known synthetic transformations of aryl pinacolboronate esters.*

If necessary, aryl pinacolboronate esters can be converted into the generally more reactive aryl boronic acids and trifluoroborates. In 2001, Falck *et al.* prepared a range of *ortho*-alkenylarylboronic acids from the corresponding alkenylaryl pinacolboronate esters, by hydrolysis of the ester.[51] Sodium periodate is added to the reaction to oxidise pinacol to acetone and thus push the equilibrium towards the boronic acid. Hartwig *et al.* later showed that crude aryl pinacolboronate esters formed by C-H borylation were hydrolysed when subjected to the conditions reported by Falck *et al.* A range of substrates were found to be compatible, and in general high yields were achieved.[52]

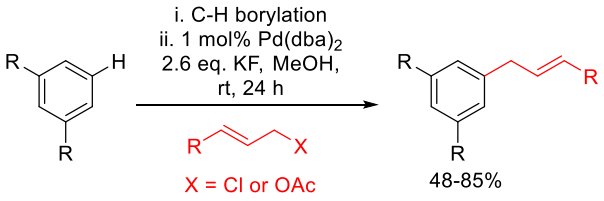
Lennox and Lloyd-Jones developed a procedure for the preparation of potassium organotrifluoroborate salts from aryl boronic acids and aryl pinacolboronate esters, without HF or KHF_2 which were necessary in prior methods.[53] The boron species is

treated with KF and a stoichiometric amount of L-(+)-tartaric acid, which drives the equilibrium towards the trifluoroborate salt by removing KOH/$C_6H_{12}O_2K_2$. The bitartrate salt is poorly soluble and easy to remove in the presence of water. By replacing KF with CsF, it was also possible to prepare caesium organotrifluoroborate salts.[53]

In addition to the Suzuki–Miyaura cross-coupling reaction, several C-C bond forming reactions of aryl pinacolboronate esters are known. Firstly, Ortar reported the palladium catalysed allylation of aryl and vinyl pinacolboronate esters with allyl acetates (Scheme 1.34).[54] The best conditions were found to be those previously reported for the allylation of aryl boronic acids by Balme *et al*.[55] Hartwig and Robbins later reported the one-pot C-H borylation of arenes, followed by allylation with a variety of allyl chlorides and allyl acetates, catalysed by $Pd(dba)_2$ (Scheme 1.35).[56]



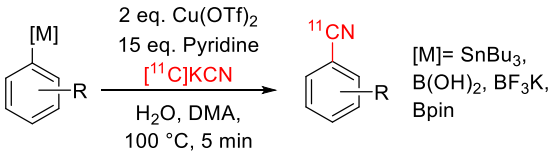
Scheme 1.34 *The allylation of aryl and vinyl pinacolboronate esters with allyl acetates.*



Scheme 1.35 *One-pot C-H borylation of 1,3-disubstituted biaryls, followed by allylation with allyl acetates or allyl chlorides.*

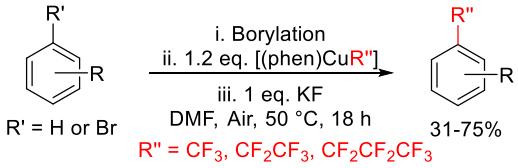
In 2010, Hartwig *et al.* reported a copper mediated oxidative cyanation of aryl pinacolboronate esters, generated *in situ* by C-H borylation. The conditions were also found to be compatible with aryl boronic acids.[57] Aromatic nitriles are themselves important synthetic intermediates, amenable to a number of post-functionalisation reactions, and therefore have the potential to give synthetic access to valuable functionalised products.[57]

Since this initial report, further cyanation reactions of aryl pinacolboronate esters have been published, two of which employ catalytic amounts of copper.[58–61] In one particularly interesting example, Sanford, Scott *et al.* reported a copper mediated [^{11}C] radiocyanation of aryl boron compounds and aryl stannanes, including aryl pinacolboronate esters (Scheme 1.36).[58] The reaction had a good substrate scope and was applied to the synthesis of the radiotracer [^{11}C] perampanel.[58] In addition to ^{11}C cyanation, ^{11}C radiolabelling of aryl pinacolboronate esters has also been achieved *via* methylation, carboxylation, and carbonylation.[62]



Scheme 1.36 *[^{11}C] Radiocyanation of aryl boron and aryl stannanes with [^{11}C]KCN.*

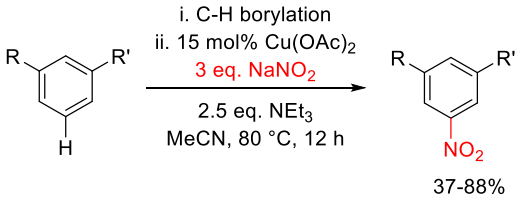
In addition, the introduction of perfluoroalkyl groups, which are present in several pharmaceutically relevant compounds, by the perfluoroalkylation of aryl pinacolboronate esters was reported by Hartwig *et al.* (Scheme 1.37). Crude aryl pinacolboronate esters generated *in situ* by the borylation of C-H or C-Br could be used without purification. The perfluoroalkyl groups introduced were trifluoromethyl, pentafluoroethyl, and heptafluoropropyl, by an oxidative Chan–Lam type reaction with [(phen)CuCF$_3$], [(phen)CuCF$_2$CF$_3$), and [(phen)CuCF$_2$CF$_2$CF$_3$], in which oxygen acted as the oxidant.[63] Shen *et al.* also reported the trifluoromethylation of aryl pinacolboronate esters in earlier work by reaction with Togni's reagent under copper catalysis.[64]



Scheme 1.37 *The perfluoroalkylation of crude aryl pinacolboronate esters.*

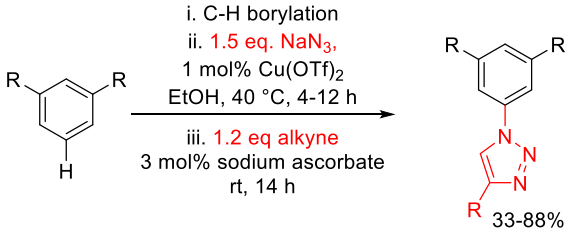
In addition to C-C bond forming reactions, C-N bond forming reactions of aryl pinacolboronate esters are also known. A one-pot nitration of 1,3-disubstituted arenes by C-H borylation and copper catalysed nitration with sodium nitrite was reported by Srinivasan *et al* (Scheme 1.38).[65] It was found that substrates bearing one or two

ortho/*para* directing groups, such as halogens gave modest to good yields, and that electron deficient heteroarenes were also tolerated. The products obtained in this reaction are either difficult to prepare or not possible to prepare using other synthetic methods.[65]



Scheme 1.38 *One-pot nitration of 1,3-disubstituted arenes by sequential C-H borylation and nitration to yield nitro-arenes.*

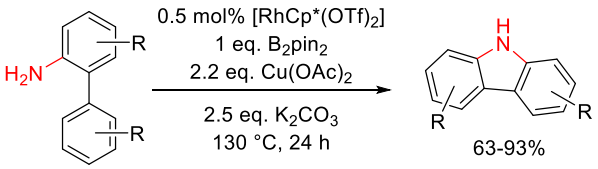
Srinivasan *et al.* were also able to prepare *N*-aryl 1,2,3-triazoles from 1,3-disubstituted arenes (Scheme 1.39). The transformation involves three sequential steps in one-pot: iridium catalysed C-H borylation, copper catalysed azidation, and a click reaction with added alkyne, which is catalysed by the same copper catalyst. The substrate scope was good, and the products were isolated in 33-88% yield. This method could be applied to the late stage functionalisation of biologically active compounds and their analogues. In addition, in one instance the azide intermediate was isolated and converted into an amine, amide, and sulfonamide to demonstrate the potential synthetic utility of this reaction in preparing more than just *N*-aryl 1,2,3-triazoles.



Scheme 1.39 *One-pot C-H borylation of arenes, followed by azidation and a click reaction to give N-aryl 1,2,3-triazoles.*

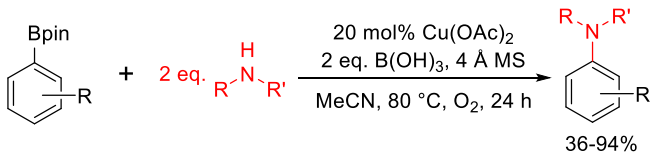
The amination of aryl pinacolboronate esters was first reported by Hartwig *et al.*, and worked reasonably well with primary amines, although lower yields were obtained with electron rich aryl pinacolboronate esters. Secondary amines worked poorly in the reaction and both aryl amines and alcohols were not tolerated at all: a boronic acid coupling partner had to employed instead.[66]

Since this initial report, directing groups have been utilised to improve the reactivity. In one particularly interesting example, Chen *et al.* reported the one-pot amino-directed C-H borylation of 2-aminobiaryls, followed by a copper mediated intramolecular amination, in which the amino directing group replaces the pinacolboronate ester to form a carbazole (Scheme 1.40).[67] Xu and Liu reported the oxidative amination of aryl pinacolboronate esters with 2-acylsubstituted anilines and Clark *et al.* reported the oxidative amination of benzylamine pinacolboronate esters with anilines.[68,69] Clark *et al.* later reported the oxidative etherification of benzylamine pinacolboronate esters with phenols using different reaction conditions.[70]



Scheme 1.40 *Preparation of carbazoles via one-pot C-H activation, followed by intramolecular amination.*

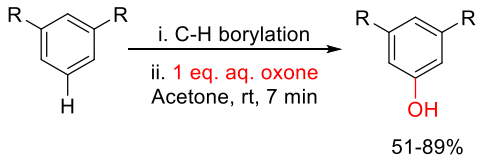
More general conditions for the Chan–Evans–Lam oxidative coupling of aryl and alkyl amines with aryl pinacolboronate esters were reported by Watson *et al.*[71] Initially, the amination reaction required stoichiometric amounts of copper catalyst. However, the same group later investigated the mechanism of the amination reaction and found that replacement of triethylamine with boric acid significantly improved the reactivity (Scheme 1.41).[72] This enabled the use of catalytic amounts of copper. The reaction had good substrate scope, and it was shown in a limited number of examples that the same reaction conditions were effective for etherification and thiolation.



Scheme 1.41 *The Chan–Evans–Lam amination of aryl pinacolboronate esters.*

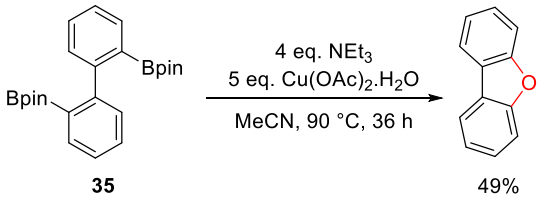
In addition to etherification, C-O bond formation has also been achieved by the oxidation of aryl pinacolboronate esters to the corresponding alcohol (Scheme 1.42).[73] In this work, conditions previously reported by Webb *et al.* for the oxidation of boronic acids, an aryl catecholboronate, and an aryl boronic acid glycol ester to alcohols were

optimised for the oxidation of crude aryl pinacolboronate esters.[74] Oxone, which is commercially available, was used as the oxidising agent and was tolerant of ester, ether, and amine functional groups. The reaction conditions were mild and the reaction went to completion at room temperature within seven minutes.[73] Due to the substitution pattern, the products of this reaction would be difficult to prepare using other synthetic methods.[73]



Scheme 1.42 *One-pot C-H borylation and oxidation of 1,3-disubstituted arenes to prepare phenols.*

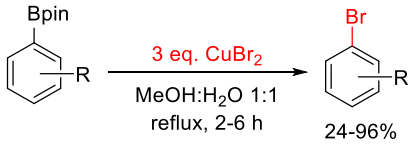
In an isolated example of C-O bond formation, Yorimitsu *et al.* reported that attempts to oxidatively aminate 2,2'-di(pinacolatoboron)biphenyl, **35**, resulted in the formation of dibenzofuran (Scheme 1.43).[75] In the same paper, oxaborin and azaborin were prepared from **35** by partial oxidative hydroxylation and amination.[75] These boracycles have been attracting growing interest because of their electrical and photophysical properties.[75]



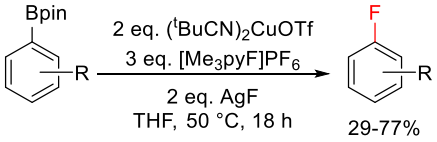
Scheme 1.43 *The formation of dibenzofuran from* ***35*** *using stoichiometric amounts of* $Cu(OAc)_2.H_2O$.

Other C-heteroatom bond forming reactions include the halogenation of aryl pinacolboronate esters. In 2004, Huffman *et al.* reported the bromination of aryl pinacolboronate esters with copper (II) bromide (Scheme 1.44).[76] Hartwig *et al.* later reported the one-pot C-H borylation of arenes, followed by bromination with copper (II) bromide. By substituting copper (II) bromide for copper (II) chloride, the method could be extended to chlorination.[77] Simply replacing the copper reagent with copper iodide did not affect the iodination of aryl pinacolboronate esters. Iodination could however be achieved by treatment with a stoichiometric amount of potassium iodide, in the presence of a catalytic amount of copper iodide and phenanthroline.[78]

Hartwig *et al.* also reported the fluorination of aryl pinacolboronate esters using $[Me_3PyF]PF_6$ as the source of fluorine, mediated by stoichiometric amounts of copper and silver fluoride (Scheme 1.45).[79] The reaction conditions were mild and the substrate scope good. More recently, Planas, Wang *et al.* reported that a rationally designed bismine complex catalysed the fluorination of aryl pinacolboronate esters, *via* a Bi(III)/Bi(V) redox cycle.[80] The substitution of transition metals, which can be both expensive and rare, with earth-abundant main group elements is very attractive and there is growing interest in this area.



Scheme 1.44 *The bromination of aryl pinacolboronate esters using copper (II) bromide.*

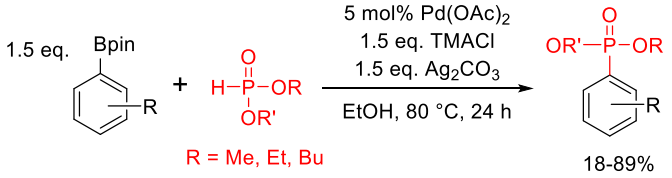


Scheme 1.45 *The fluorination of aryl pinacolboronate esters with* $[Me_3PyF]PF_6$ *to yield fluorinated arenes.*

In addition to the halogenation reactions discussed above, aryl pinacolboronate esters have been employed as substrates for radiohalogenation. Modification of the nucleophilic iodination reported by Hartwig *et al.* enabled the radio-iodination of aryl pinacolboronate esters using $[^{123}I]NaI$ and $[^{125}I]NaI$.[81–83] Utilising the same transformation radio-astatination of aryl pinacolboronate esters using $[^{211}At]NaAt$ was also achieved.[83] In addition, it has been shown that aryl pinacolboronate esters can be converted into the corresponding $[^{18}F]$ radiolabelled fluoroarenes and $[^{77}Br]$ radiolabelled bromoarenes.[62,84] The resulting radiolabelled molecules have a wide range of applications in molecular imaging.[62]

Finally, C-P bond formation was achieved by Lee *et al.*, who reported a palladium catalysed oxidative cross-coupling of aryl pinacolboronate esters with H-phosphonates (Scheme 1.46).[85] The reaction proceeds in the absence of ligand and base. This is a novel transformation and unfortunately, the substrate scope was found to be relatively

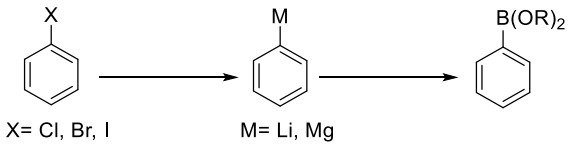
limited. A number of substrates including those that were *ortho*-substituted undergo protodeboronation, the best yields being obtained with electron rich substrates.[85]



Scheme 1.46 *Oxidative coupling reaction between aryl pinacolboronate esters and H-phosphonates.*

1.3.2. How Aryl Pinacolboronate Esters are Prepared

Due to the importance of aryl pinacolboronate esters as intermediates in organic chemistry, several methods have been developed for their synthesis. Traditionally, aryl boronate esters were prepared by the reaction of an aryl Grignard or an aryl lithium reagent, generated by metal-halogen exchange, with a trialkylborate, followed by an aqueous work-up (Scheme 1.47).[86,87] However, the scope of aryl boronates that can be prepared by this method is significantly limited because acidic, electrophilic, or base sensitive functional groups are not tolerated.



Scheme 1.47 *Preparation of aryl boronate esters by the reaction of an aryl Grignard or an aryl lithium with a trialkylborate.*

In 1995, Miyaura *et al.* reported the palladium catalysed borylation of aryl bromides and iodides with B_2pin_2 (Scheme 1.48).[88] Electron deficient substrates were found to be the most reactive, however electron donating groups were tolerated and several functional groups were found to be compatible including carbonyl, ester, cyano, and nitro groups. The improved functional group tolerance of this catalytic transformation significantly increased the number of synthetically accessible aryl pinacolboronate esters.

Since this first report, a large amount of work has been done in the area of catalytic C-B bond formation. Advances include the coupling of aryl triflates and the less reactive aryl chlorides, tosylates, and mesylates.[89] More synthetically challenging, sterically

bulky aryl boronates such as 2,6-disubstituted aryl boronates have been prepared, as well as electron-rich aryl boronates.[89] In addition, given that only one pinacol borane moiety is introduced into the molecule, the cheaper and more atom economic pinacol borane has become one of the most popular choices of coupling partner.[89] Further advances include the use of other transition metals including copper, iron, zinc, and nickel instead of the more expensive palladium and ligandless conditions.[89,90]

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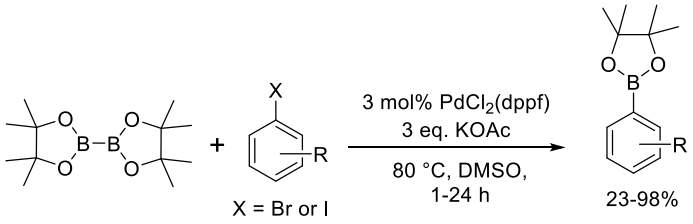


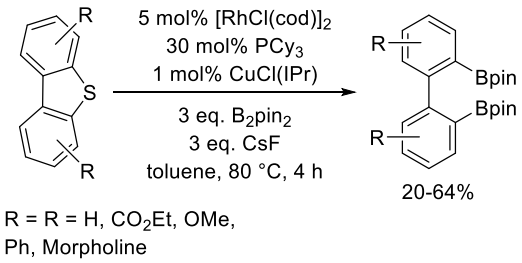
Scheme 1.48 *Preparation of aryl pinacolboronate esters by the coupling of B_2pin_2 with aryl halides.*

In addition to the catalytic borylation of halides and pseudohalides, there are limited examples of other functional groups being converted to aryl pinacolboronate esters: these include methoxy and fluorine functional groups.[91–93] These transformations are particularly valuable for late stage functionalisation, because fluorine and methoxy are relatively unreactive and could be carried through several synthetic steps.

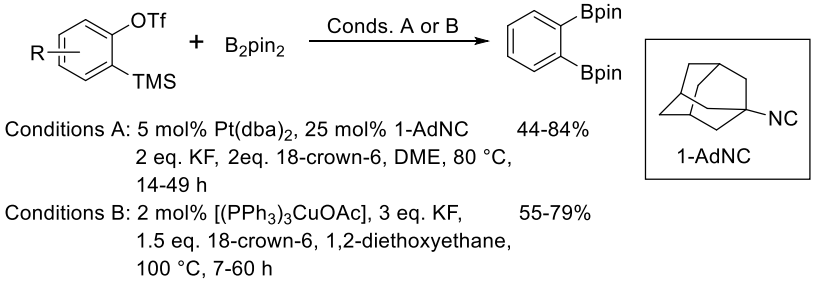
In one particularly interesting example Yorimitsu *et al.* reported the diborylation of dibenzothiophenes to give the corresponding 2,2'-diborylbiaryls (Scheme 1.49).[75] $[RhCl(cod)]_2$ and PCy_3 catalysed the reaction, but a catalytic amount of CuCl(IPr) was necessary to reduce the reaction time and prevent product decomposition. Interestingly, only B_2pin_2 was effective, both bis(neopentylglycolato)diboron (B_2neop_2) and bis(catecholato)diboron (B_2cat_2) were ineffective. Only five substrates were tested, and the yields were moderate, which was due to the formation of unidentified oligomers and poor stability of the products on silica gel. Despite this, two pinacol borane molecules are introduced into the molecule in a single step to give 2,2'-diborylbiaryls in an atom-economic fashion. Besides the diborylation of biphenylene and dibenzothiophene with B_2pin_2, 2,2'-diborylbiaryls have been prepared from the corresponding 2,2'-dihalobiaryls, most commonly *via* halogen lithium exchange and subsequent electrophilic borylation.[94–98]

Another synthetic method towards diborylated aryls, in which two boryl groups are introduced in a single step, is the diborylation of arynes generated *in situ* (Scheme

1.50). Yoshida *et al.* reported that a platinum isocyanide complex effectively facilitated this transformation and several substrates were found to be compatible (Scheme 1.50, conditions A).[99] The resulting diborylated aryls readily underwent several double Suzuki–Miyaura cross-coupling reactions to afford *ortho*-terphenyls. The same group later reported that the same transformation was catalysed by a copper-phosphine complex (Scheme 1.50, conditions. B).[100] The authors propose that copper acetate reacts with B_2pin_2 to generate a copper species, which inserts into the aryne triple bond. The resulting organocopper species undergoes σ-bond metathesis with B_2pin_2 to afford the diborylated product.



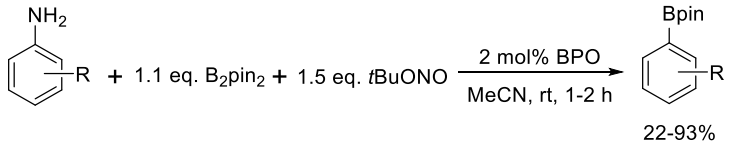
Scheme 1.49 *The diborylation of dibenzothiophenes to give the corresponding 2,2'-diborylbiaryls.*



Scheme 1.50 *The diborylation of arynes generated in situ to give o-diborylated arenes.*

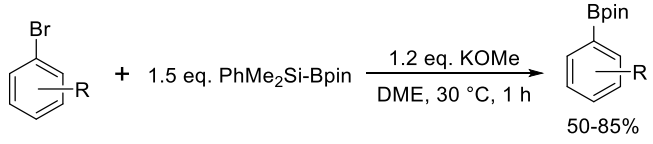
In addition to the widely used transition metal catalysed synthesis of aryl pinacolboronate esters, a significant amount of work has been done in transition metal free borylation. One example is the Sandmeyer reaction. In 2012, Mo, Wang *et al.* reported that B_2pin_2 reacted with aryl amines in the presence of *tert*-butyl nitrite, a diazotisation agent, and a catalytic amount of benzoyl peroxide, BPO, a radical initiator, in air at room temperature (Scheme 1.51).[101] In subsequent work the substrate scope was expanded and the need for BPO negated by increasing the reaction

temperature.[102] In addition to the Sandmeyer reaction of aryl amines, other transition metal free C-N borylations are known for aryldiazonium salts and aryl triazenes.[103,104]



Scheme 1.51 *The transition metal free borylation of aryl amines with B_2pin_2.*

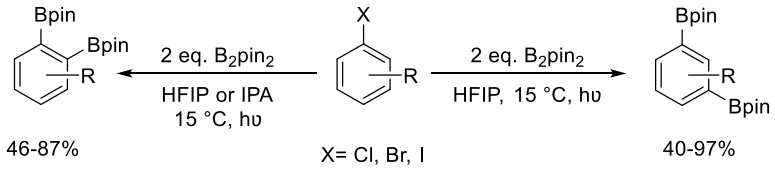
Several examples of the transition metal free borylation of aryl halides and pseudohalides have been reported.[105–107] In one example, Ito *et al.*, achieved the borylation of aryl bromides, using $PhMe_2Si$-Bpin in the presence of an alkoxy base (Scheme 1.52).[108–110] Interestingly, good selectivity was observed for the incorporation of Bpin, over $SiMe_2Ph$ using the optimum reaction conditions. A broad range of aryl and heteroaryl bromides were tested and the reaction had a good substrate scope, although some substrates including nitro, alkynyl, and ketone substituted aryls halides were not tolerated. The reaction was applied to the synthesis of precursors of two pharmaceutically relevant compounds and modification of the reaction conditions allowed for the borylation of alkenyl bromides and iodides. Subsequently, Chen *et al*. reported the photolytic borylation of aryl halides using diboron reagents including B_2pin_2, B_2neop_2, tetrahydroxydiboron, $B_2(OH)_4$, and BpinBdan, under batch and continuous flow conditions. In general, aryl iodides gave slightly better yields than aryl bromides. A broad range of functional groups were tolerated and the reaction could be conducted on gram scale.[111]



Scheme 1.52 *Transition metal free preparation of aryl pinacolboronate esters via a nucleophilic substitution reaction.*

In a particularly interesting example of transition metal free C-X borylation, Larionov *et al.* reported a regioselective photoinduced dual C-H/C-X diborylation of aryl halides (Scheme 1.53).[112] The regioselectivity of the reaction is determined by the solvent and the substituents on the aromatic ring. When isopropanol was used as the solvent the 1,2-diborylated product was preferentially formed. Whereas when HFIP was employed as the solvent the 1,3-diborylated product was preferentially formed, unless

the aryl halide bore an electron withdrawing group in the *para*-position or an electron donating group in the *meta*-position, in which case the 1,2-diborylated product was selectively formed. The diborylation reaction could be conducted on gram scale without the exclusion of air or moisture in both batch and flow.



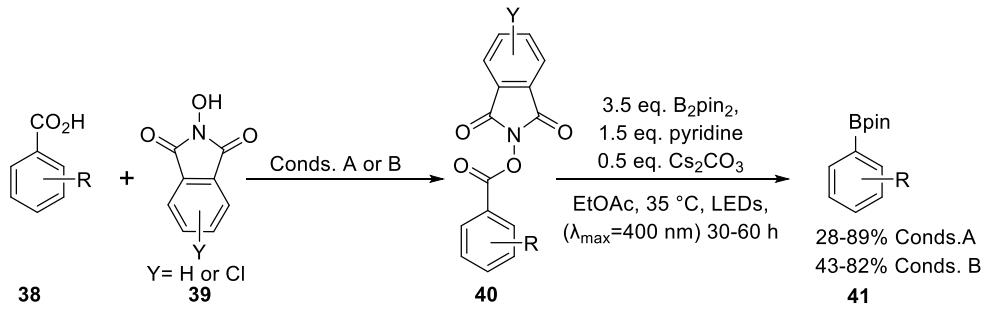
Scheme 1.53 *The solvent and substrate controlled regioselective dual C-H/C-X diborylation of aryl halides.*

Transition metal free decarboxylative borylation is also known: Glorius *et al*. reported the visible light enabled conversion of *N*-hydroxyphthalimide (NHPI) esters, **40**, prepared from cheap and abundant carboxylic acids, **38**, into the corresponding aryl pinacolboronate esters, **41** (Scheme 1.54).[113] The reaction had a broad substrate scope and electron withdrawing groups on the aryl ring were tolerated when the electron deficient *N*-hydroxytetrachlorophthalimide (TCNHPI) activator (**39**, Y = Cl) was employed, although *ortho*-substituted substrates did give lower yields. The reaction was successfully applied to the preparation of pharmaceutically relevant compounds. Later in the same year Fu and Shang reported the same transformation catalysed by isonicotinate *tert*-butylester in refluxing trifluorotoluene, without any additive, base or visible-light irradiation.[114]

Although the conversion of functional groups into pinacolboronate esters is a commonly used and valuable method for their preparation, it does rely on prefunctionalised starting material. This limits which aryl pinacolboronate esters can be prepared because the corresponding functionalised starting material must be synthetically accessible. The need for prefunctionalised starting material is obviated by C-H borylation. There have been many reports of transition metal catalysed C-H borylation of arenes, using iridium, rhodium, iron, cobalt, nickel, zinc, ruthenium, and platinum catalysis.[115]

A breakthrough in C-H borylation was the discovery by Ishiyama, Miyaura, and Hartwig that the combination of an iridium precursor and a bipyridine ligand is particularly effective for this type of transformation. In their first report, excess arene

was reacted with B_2pin_2, catalysed by $[Ir(cod)Cl]_2$ and 2,2'-bipyridine at 80 °C, to give a variety of aryl pinacolboronate esters (Scheme 1.55).[116] A large amount of work was subsequently carried out to optimise this reaction, and the reaction has since been conducted without an excess of arene, and at room temperature in some instances.[117,118] It was found that electron poor arenes were the most reactive substrates. The reaction had a good substrate scope, and the C-H bond was selectively borylated in the presence of functional groups, including halogens, nitriles, esters, amines, and ethers.



Conditions A (when NHPI ester isolated): 1 eq. DCC, EtOAc, rt
Conditions B (NHPI ester generated *in situ*): 1 eq. DIC, EtOAc, rt

Scheme 1.54 *The decarboxylative borylation of N-hydroxyphthalimide esters.*

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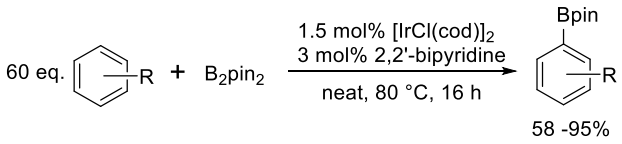
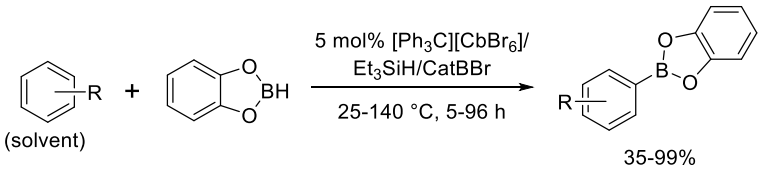


Scheme 1.55 *The C-H borylation of arenes with B_2pin_2 to yield aryl pinacolboronate esters.*

The regioselectivity of arene C-H borylation is predominantly controlled by sterics and the boryl group introduced into the most sterically accessible position. For example, mono-substituted arenes give mixtures of *meta*- and *para*- borylation and 1,3-disubstituted or 1,2,3-trisubstituted arenes selectively undergo borylation in the *meta*-position.[119] In contrast, the C-H activation of heteroarenes is largely controlled by electronics. Generally, five-membered ring heterocycles preferentially undergo borylation at the C-H bond alpha to the heteroatom, although the regioselectivity can be altered by placing a large protecting group on the heteroatom.[117–119] To access differently substituted aryl boronates, strategies towards directed C-H borylation have been investigated. A variety of directing groups have been employed in C-H

borylation, predominantly to achieve *ortho*-borylation, however *meta*- and *para*-borylation have also been reported.[115]

Finally, transition metal free C-H borylation has also been achieved. One strategy is the electrophilic aromatic substitution of arenes with electrophilic boron reagents. In 2010, the Ingleson group first developed an intermolecular electrophilic aromatic substitution reaction which afforded aryl catecholboronate esters (Scheme 1.56).[120] The reaction required high temperatures and an excess of arene, which was used as the solvent. It was proposed that a highly electrophilic boron species, which could not be clearly identified, was generated *in situ* from catalytic amounts of *B*-bromocatecholborane (CatBBr), Et_3SiH, and [*closo*-1-H-$CB_{11}H_5Br_6$]$^-$ ([$CbBr_6$]). This electrophilic species underwent electrophilic aromatic borylation, generating a Brønsted acidic by-product, which reacted with catecholborane (HBCat), liberating H_2 and re-generating the electrophilic boron species.

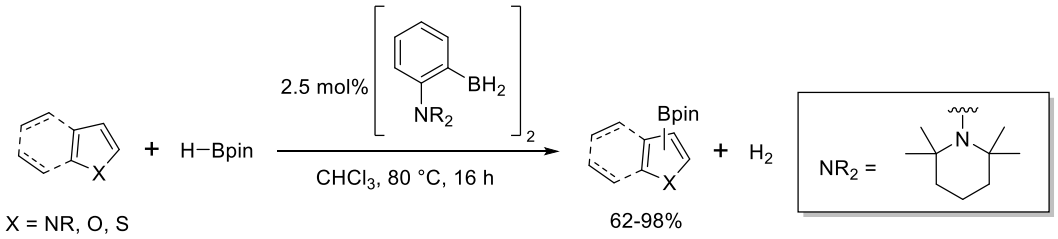


Scheme 1.56 *The catalytic borylation of arene C-H bonds to afford aryl catecholatoboronate esters.*

In subsequent work, the same group reported the stoichiometric generation of additional boron electrophiles which enabled the direct borylation of (hetero)arenes, not used in large excess, to yield aryl pinacolboronate esters, aryl MIDA boronates, and aryl neopentylboronate esters. The reaction sequence consists of borylation followed by *in situ* esterification or transesterification, dependent on the boron electrophile.[121–123] The reaction worked best for activated arenes and the regioselectivity was controlled by electronic effects, though *ortho*-borylation has been achieved using 2-phenoxypyridine as a directing group.[124]

In later work, Fontaine *et al.* reported that frustrated Lewis pairs (FLPs) catalysed the C-H borylation of heteroarenes (Scheme 1.57).[125] In this approach, a Lewis basic amine abstracts a proton from the arene and the electrons are transferred onto a Lewis acidic borane. The reaction works well for electron rich heterocycles, including *N*-protected pyrroles, thiophenes substituted with electron donating groups, and furans to

yield products in which the most nucleophilic carbon atom is borylated. In later work, the same group found that air and moisture stable fluoroborate protected analogues could be readily deprotected to the active dihydroborane, obviating difficulty with the handling and storage of the reagents.[126] More economical and active catalysts have been found and the reaction has been conducted on scales as large as 1 kg without solvent.[127,128] The same group also reported solid-supported FLP catalysed C-H borylation, but these catalysts were less active than the corresponding homogeneous FLP catalysts.[129] Like the electrophilic aromatic substitution approach, the scope of this transformation is limited to activated arenes.



Scheme 1.57 *The FLP catalysed C-H borylation of heteroarenes.*

To conclude, aryl pinacolboronate esters are important synthetic intermediates, which have been shown to undergo a wide range of transformations, and thus have the potential to give synthetic access to a wide range of functionalised products. Most existing synthetic methods towards aryl pinacolboronate esters involve the transformation of one functional group, or one C-H bond into one aryl pinacolboronate ester and there are comparatively few examples of diborylation

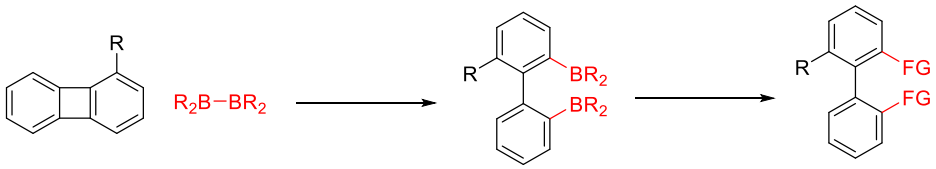
o,o'-Diborylated biphenyls have been prepared by the transition metal catalysed ring opening of biphenylene, dibenzothiophene, and substituted dibenzothiophenes. These reactions give only moderate yields and few examples have been reported. In addition, the diborylation of *o,o'*-dihalogenated biaryls is known but is limited by the need for prefunctionalised starting material. The extension and improvement of existing methods towards *o,o'*-diborylated biaryls is highly desirable because their preparation and functionalisation enables multiple bond formations to take place in one step, which is much more efficient than forming one bond in each step.

1.4. Outline and Aims of the Project

There are four key aims in this work: firstly, to develop a general method for the ring opening diborylation of the strained C-C bond in 1-substituted biphenylenes. Only a single example of the diborylation of unsubstituted biphenylene with B_2pin_2 is known. The diborylation of 1-substituted biphenylenes is significantly more challenging because of increased steric hindrance and the added problem of regioselectivity, since placing a substituent in the 1-position renders the two strained C-C bonds inequivalent.

The second and third aims are to determine which functional groups are tolerated in the ring opening diborylation reaction and investigate what effect the 1-substituent has on the regioselectivity of the reaction. To enable the unambiguous determination of the effect of a substituent on the reaction, only mono substituted biphenylene substrates bearing a substituent in the 1-position will be tested.

The products of the reaction, aryl pinacolboronate esters are highly sought-after synthetic intermediates in organic chemistry. This reaction represents an atom economic method of adding two pinacol borane substituents into the molecule in a single step. The resulting *o,o,o'*-trisubstituted biaryls are sterically bulky and are difficult to prepare using traditional synthetic methods. The fourth key aim of this work is to investigate the post-functionalisation of the pinacolboronate ester moieties to demonstrate the potential synthetic utility of the reaction (Scheme 1.58).



Scheme 1.58 *The key aims of this work: optimise the diborylation of 1-substituted biphenylenes, investigate its scope and regioselectivity, and investigate the post-functionalisation of the products.*

As will be discussed in detail in the following section, the preparation of 1-substituted biphenylenes is challenging and the scope of these reactions is limited. Therefore, in addition to the above-mentioned aims it is also necessary to develop a synthetic route towards a range of 1-monosubstituted biphenylenes.

1.5. References

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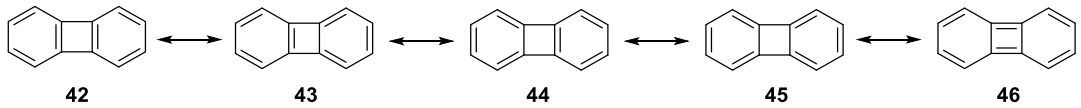
Chapter 2 Preparation of 1-Substituted Biphenylenes

2.1. Introduction

2.1.1. Biphenylene(s)

Biphenylene has a unique structure in which a four-membered ring is fused to two benzene rings. In principle, there are five possible resonance forms of biphenylene (Scheme 2.1). The X-ray crystallographic structure of biphenylene shows that the best representation of biphenylene is **45**.[1] Biphenylene has predominantly cyclobutane character, with a small cyclobutene element, and a negligible amount of cyclobutadiene.[1,2] The benzene rings are not fully delocalised, the bond distances are alternately long and short, and the bond angle in the six membered ring is distorted from 120 °.[2] The two benzene rings are joined by two bonds, 1.514 Å in length, which can be approximated to be single bonds.[1,3] There is still some debate over the extent of delocalisation and aromaticity of biphenylene, which is somewhere between unstable, anti-aromatic cyclobutadiene and stable, aromatic benzene.[4,5] However, since biphenylene is stable, its electronic properties have received considerable attention.

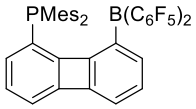


Scheme 2.1 *The five possible resonance forms of biphenylene.*

The central 4-membered ring in biphenylene has a bond angle of 90° and is therefore considerably strained.[1] This ring strain causes a weakening of the C-C bonds linking the two benzene rings. The bond strength has been estimated as 65.4 kcal/mol, significantly lower than the corresponding C-C bond in biphenyl, which has an estimated bond strength of 118.4 kcal/mol.[6] As a consequence of this lower bond strength, there has been significant interest in the cleavage of this C-C bond with transition metal complexes, as was discussed in section 1.1.2. This has enabled the preparation of functionalised aromatic compounds including: tetraphenylenes, phenanthrenes, fluorenones, and *o*-substituted biaryls, *via* catalytic and stoichiometric C-C bond functionalisation.

In addition to its unique structure and its C-C cleavage, substituted biphenylenes have been employed as both catalysts and as ligands.[7] Finally, by placing reactive functional

groups in the 1- and 8- positions of biphenylene, the biphenylene skeleton has been used as a spacer of functional groups in a variety of functional molecules.[7] For example, **47** (Fig. 2.1) has found application as a frustrated Lewis pair.[8]

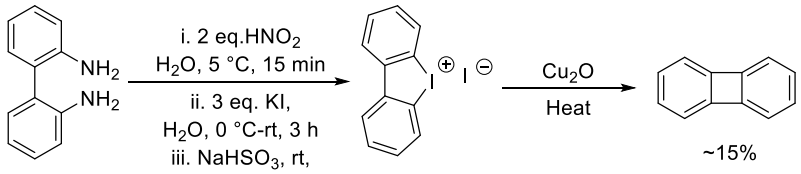


47

Fig. 2.1 *The Structure of biphenylene based frustrated Lewis pair,* ***47****.*

2.1.2. Preparation of Biphenylene(s)

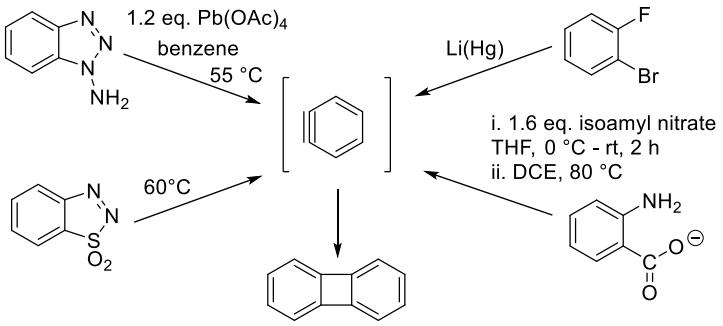
Biphenylene was first prepared by Lothrop, who showed that 2,2'-dibromobiphenyl reacted in an intramolecular Ullman reaction in the presence of cuprous oxide to form biphenylene.[9] Due to problems separating unreacted 2,2'-dibromobiphenyl from biphenylene, the starting material was changed to iodonium iodide **49**, which was prepared from 2,2'-diaminobiphenyl **48**. This improved procedure gave biphenylene in 15% yield (Scheme 2.2).



48 **49** **1**

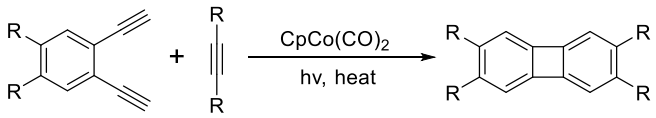
Scheme 2.2 *Preparation of biphenylene via an intramolecular Ullman reaction.*

Since this first synthesis, several methods for preparing biphenylene and its derivatives have been reported. One commonly used method is the [2+2] dimerisation of benzyne generated *in situ via* an elimination reaction: representative examples are shown in (Scheme 2.3).[10–14] In general, the yields of these reactions are quite low and several employ explosive intermediates. Higher yields of up to 83% were obtained when 1-aminobenzotriazole was employed as the precursor, which can be prepared in one step from commercially available material, albeit in low yield.[11] It has also been shown that benzyne can be generated by flash vacuum pyrolysis and subsequently dimerised: representative examples include the flash vacuum pyrolysis of *o*-diiodobenzene and phthalic anhydride.[15,16] Pyrolysis is however a limited method of accessing biphenylenes because it can only be used on small scale.[1]



Scheme 2.3 *[2+2] Dimerisation of benzyne as a method for the preparation of biphenylene.*

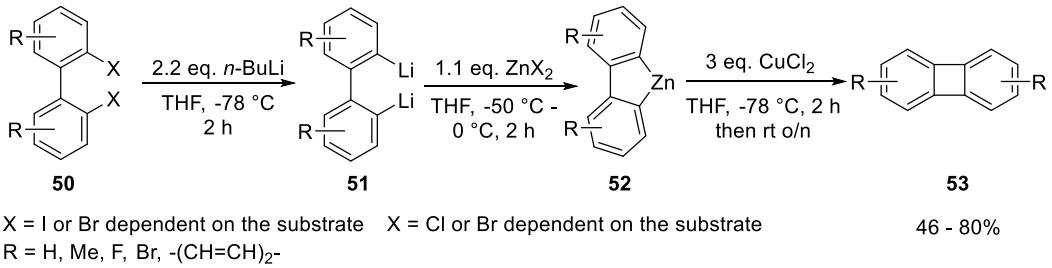
The preparation of substituted biphenylenes is also known. Vollhardt and co-workers developed a new method for the preparation of biphenylene and its substituted derivatives by the cobalt catalysed [2+2+2] cycloaddition of *o*-diethynylbenzenes with alkynes under photolysis (Scheme 2.4).[17–19] This method could be used to prepare a number of biphenylenes with substituents in the 2 and 3 positions, as well as benzobiphenylenes, poly(biphenylenes) and even heterophenylenes. This method vastly increased the number of synthetically accessible biphenylenes and is particularly attractive for the preparation of substituted biphenylenes. [18,19] However, the scope is limited by the synthetic accessibility of the diethynylbenzene starting materials and the position that the substituents can be placed in. Only the two, three, six, and seven positions have been reported to our knowledge.



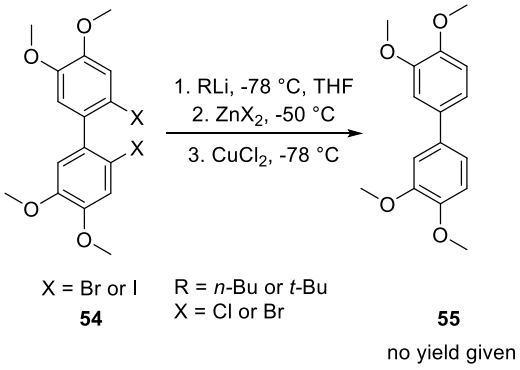
Scheme 2.4 *[2+2+2] Cycloaddition of o-diethynylbenzenes with alkynes.*

It was later reported by Iyoda *et al.* that biphenylene and its substituted derivatives could be prepared *via* the copper (II) chloride mediated intramolecular coupling of an organozinc intermediate, **52** (Scheme 2.5). The organozinc intermediate, **52**, is prepared from the corresponding 2,2'-dilithiobiaryl **51**, which in turn is obtained from the appropriate 2,2'-dihalogenated biaryl **50**.[20–22] It was found that going *via* the organozinc intermediate gave higher yields of biphenylene than directly treating the 2,2'-dilithiobiaryl intermediate **51** with $CuCl_2$.[21]

The chemoselectivity of the reaction for biphenylene or tetraphenylene was found to depend on the choice of solvent and substrate. In general, THF favoured biphenylene formation and ether favoured tetraphenylene formation.[20–22] However, when 2,2'-dibromo or 2,2'-diiodobiaryl **54** were employed as the substrates, the product of reduction, **55**, was obtained (Scheme 2.6). Upon optimisation of the reaction conditions, the authors prepared the tetraphenylene product **56**, a synthetically valuable compound (Scheme 2.7). However, conditions that favoured the formation of the biphenylene product **57** were not found. Similar reactivity was observed when the 2,2'-dibromo biaryl **58** was employed as the substrate and the tetraphenylene product **59**, not the biphenylene product **60**, was obtained.[22]



Scheme 2.5 *Intramolecular coupling of zincacyclopentadienes to synthesise biphenylenes.*

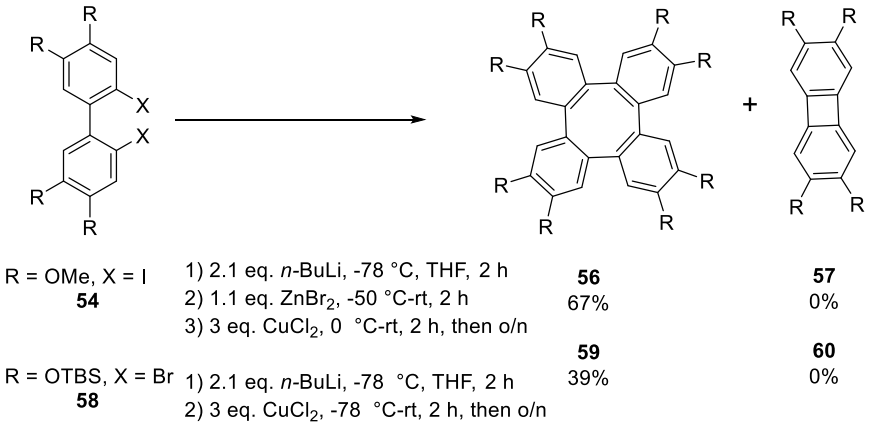


Scheme 2.6 *The reduction of 2,2'-dihalo biaryl **54** to give **55**.*

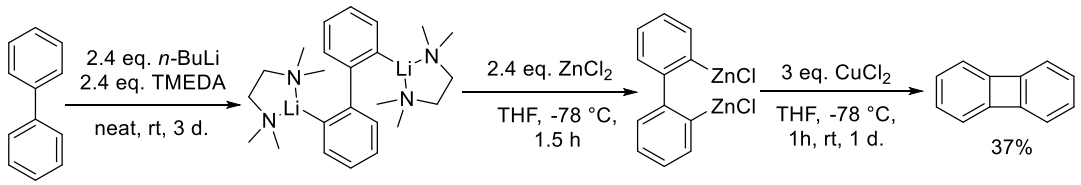
Therefore, although this is a valuable method for the preparation of biphenylene and its substituted derivatives, there are some drawbacks. The starting material needs to be pre-functionalised with the substituents desired in the product and the corresponding biaryl may be expensive or not commercially available. In addition, not all substituents are tolerated in the reaction, limiting the scope of biphenylenes that can be prepared.

A modification of this protocol for the synthesis of biphenylene in 37% yield from cheap and widely available biphenyl was later reported by Schaub and Radius (Scheme

2.8). In this modification biphenyl undergoes regioselective dilithiation of the *ortho* positions, followed by transmetallation and oxidation.[23]



Scheme 2.7 *The preparation of substituted tetraphenylenes* ***56*** *and* ***59*** *from the corresponding 2,2'-dihalo biaryls* ***54*** *and* ***58****.*



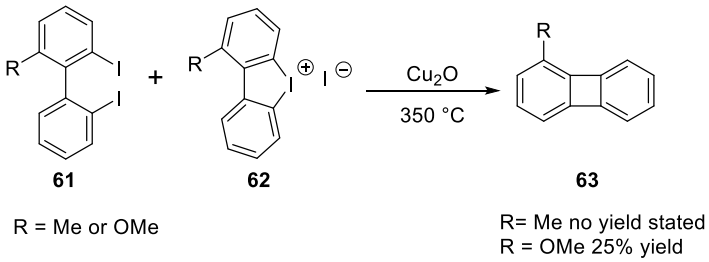
Scheme 2.8 *The 3-step preparation of biphenylene from biphenyl.*

2.1.3. The Preparation of Biphenylenes Bearing a Substituent in the 1-Position

As discussed in section 1.4, in this work the transition metal catalysed diborylation of 1-substituted biphenylenes is to be investigated. To achieve this, it is first necessary to prepare 1-substituted biphenylenes. The preparation of biphenylenes bearing a substituent in the 1-position is challenging and although some synthetic approaches have been reported, in general the substrate scope of these reactions is poor. In particular, there are a lack of methods towards 1-monosubstituted biphenylenes.

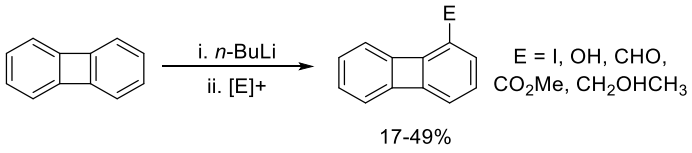
The first preparation of a 1-substituted biphenylene was reported by Baker, Barton, and McOmie, who prepared 1-methyl and 1-methoxy biphenylene by the intramolecular Ullman coupling reaction of the corresponding 2,2'-diiodo biaryls (Scheme 2.9).[24] This is a modification of the conditions originally reported by Lothrop for the synthesis of biphenylene. A mixture of **61** and **62** are heated in the presence of cuprous oxide. A mixture is used because the iodonium iodide compound **62** is a side-product in the preparation of the di-iodo biaryl **61**. The authors do not purify the

mixture because upon heating **62** converts into **61**, which is in turn converted into the corresponding biphenylene **63**. This synthetic method is limited by the substrate scope, since the starting material must be pre-functionalised with the desired 1-substituent in the *ortho*-position, which may not always be synthetically available. In addition, it is limited by the high reaction temperature of 350 °C, which is required. Some functional groups will not be stable at such high temperature and it is difficult to do reactions on large scale at such a temperature.



Scheme 2.9 *The preparation of 1-methyl and 1-methoxy biphenylene via an intramolecular Ullman coupling reaction.*

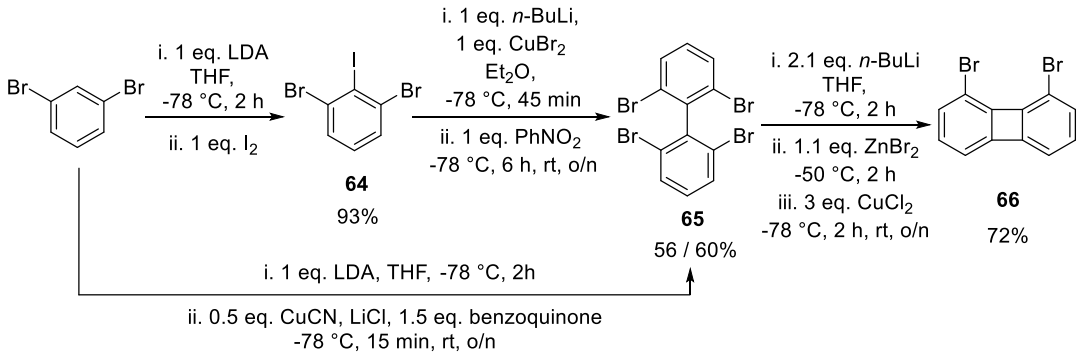
An alternative method of preparing 1-substituted biphenylenes is to lithiate biphenylene with *n*-butyllithium and treat the resulting lithiated intermediate with an electrophile (Scheme 2.10).[25–27] This reaction can be conducted at room temperature and in principle a number of different electrophiles could be introduced into the 1-position, to give a range of different 1-substituted biphenylenes from just one starting material. However, the lithiation of biphenylene is not selective. Although the 1-lithiated isomer is the major isomer, a mixture of 1- and 2-lithiated biphenylene is formed.[26] In general, the lithiation approach towards 1-substituted biphenylenes is low yielding, and difficult-to-separate mixtures are often obtained. It also requires the prior synthesis of biphenylene, which is itself challenging.



Scheme 2.10 *Lithiation of biphenylene followed by quenching with an electrophile.*

As discussed in section 2.1.2, Iyoda *et* al. reported that biphenylene and its derivatives could be prepared *via* the intramolecular coupling of zincacyclopentadienes.[20,21] This method was used to synthesise 1,8-dibromobiphenylene **66** from 2,2'-6,6'-

tetrabromobiphenyl **65** in 72 % yield (Scheme 2.11).[21,22] Tetrabromobiphenyl **65** can be prepared in two steps from 1,3-dibromobenzene in 52% overall yield.[28–30] Alternatively, it can be made in a single step from 1,3-dibromobenzene, in a higher yield of 60%, however this procedure requires the use of highly toxic CuCN.[31] The preparation of **66** is highly valuable because **66** has been used as an intermediate in the synthesis of many 1,8-disubstituted biphenylene derivatives. In addition, **66** can be treated with one equivalent of *n*-butyllithium, followed by quenching, to give synthetic access to 1-bromobiphenylene.[32] This method does however require several steps and to our knowledge this is the only example of a 1,8-disubstituted biphenylene prepared using this method.

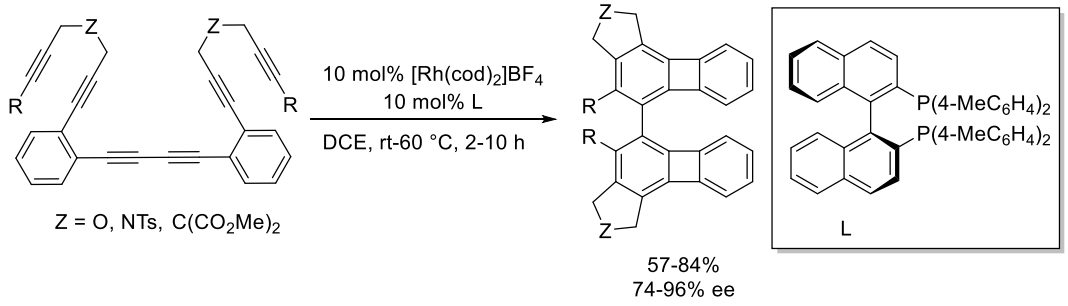


Scheme 2.11 *The preparation of 1,8-dibromobiphenylene from 1,3-dibromobenzene in two or three steps.*

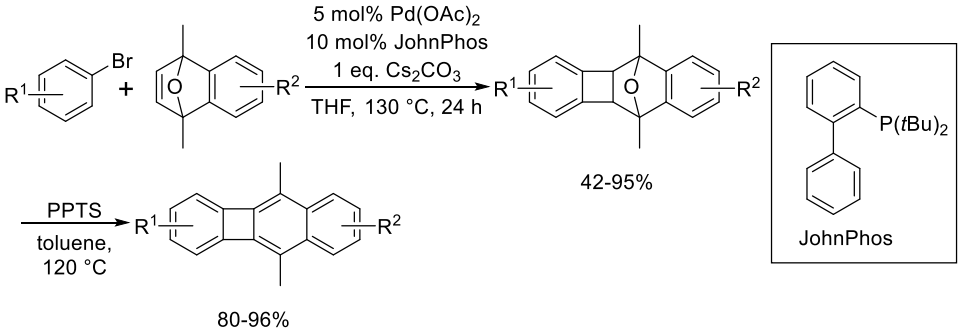
In 2011, Shibata *et al.* reported the first example of an axially chiral biphenylene derivative (Scheme 2.12). Axially chiral biphenylene derivatives were prepared *via* the enantioselective intramolecular [2+2+2] cycloaddition of hexynes, using a chiral cationic rhodium complex.[33] It was found that the highest enantioselectivities were obtained when phenyl groups were placed at the two ends of the hexyne.[33] This work is an important contribution to the area of biphenylenes, though the starting materials required are relatively complex.

A new synthetic strategy for the preparation of polycyclic conjugated biphenylenes in two steps was reported by Xia *et al.* in 2017 (Scheme 2.13).[34] The first step is a catalytic C-H activated arene-oxanorbornene annulation. In this step, the aryl bromide first adds to palladium, which is followed by coupling to the oxanorbornene, C-H activation of the *ortho*-aryl C-H bond, and reductive elimination. It was found that two methyl groups are needed in the two bridgehead positions to prevent β-oxygen

elimination competing with the desired annulation pathway. The second step is an acid catalysed aromatisation using PPTS. Besides being limited to having two methyl groups in the two bridgehead positions, this method is very valuable for the preparation of polycyclic biphenylenes, several of which can be prepared in two steps from commercially available reagents.



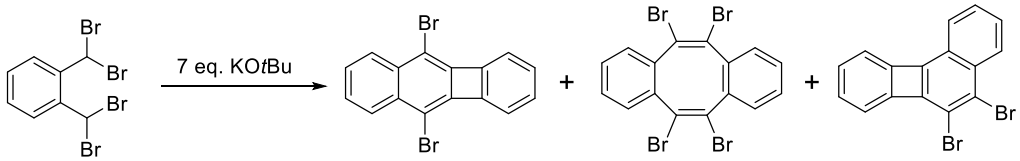
Scheme 2.12 *Preparation of axially chiral bis(biphenylene) derivatives.*



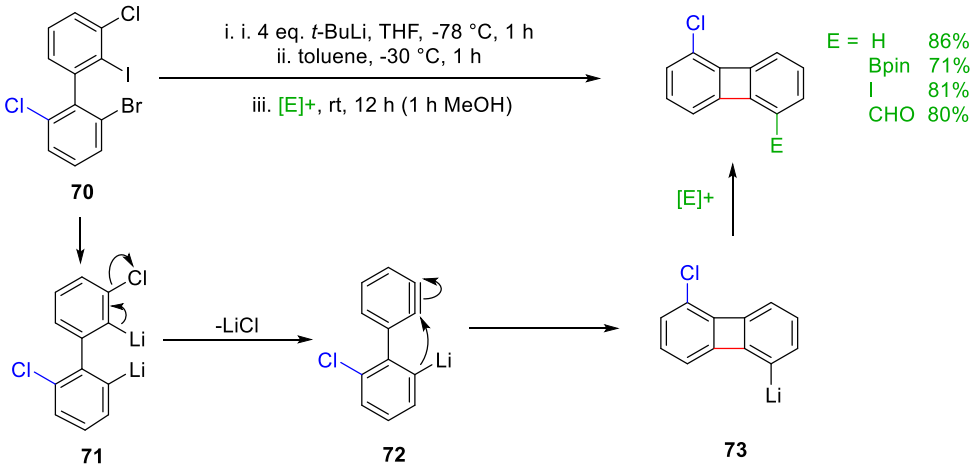
Scheme 2.13 *Preparation of polycyclic conjugated biphenylenes via catalytic C-H activated arene-oxanorbornene annulation.*

In earlier work, Jensen and Coleman reported a one-step synthetic strategy for the preparation of another polycyclic conjugated biphenylene, **67**, from α,α,α',α'-tetrabromo-*o*-xylene (Scheme 2.14). The side-product **68** was also isolated.[35] In this work, it was shown that the two bromo substituents on **67** could be converted into carboxyl groups by treatment with *n*-butyllithium, followed by carbon dioxide. The two bromo substituents could also be replaced by hydrogens when the dilithiated intermediate was instead treated with methanol. This work was later replicated by Baker *et al.* who noted the formation of product **69**, not observed by Jensen and Coleman, and reported an experimental procedure, which was not reported by Jensen and Coleman (Scheme 2.14).[36] In later work, Bunz *et al*. who were interested in the preparation of **68**, reported the synthesis of **67** in 62% yield and **68** in 33% yield when the base was changed to NaO*t*Bu.[37]

In 2017, Wu *et al.* reported a new method for the preparation of substituted biphenylenes and their π-extended derivatives *via* the cyclisation of aryne derivatives (Scheme 2.15).[38,39] Using this method, they were able to prepare 1-substituted and 1,5-disubstituted biphenylenes, including 1-chloro- and 1-fluoro-biphenylene. In this method *t*-butyllithium is reacted with the biaryl to affect a double halogen lithium exchange, which gives the dilithiated intermediate **71**. The elimination of lithium halide from **71** gives the aryne intermediate **72**, which intramolecularly cyclises to give **73**, bearing lithium in the 1-position. Intermediate **73** is then quenched with methanol, or **73** can be treated with electrophiles including isopropoxyboronic acid pinacol ester, iodine, and DMF to give the corresponding 1-substituted and 1,5-disubstituted biphenylenes in high yields.[38,39] This method is particularly attractive because it does not require high temperature or transition metals.



Scheme 2.14 *The preparation of biphenylene* ***67*** *and side-products* ***68*** *and* ***69*** *by the treatment of α,α,α',α'-tetrabromo-o-xylene with KOtBu.*

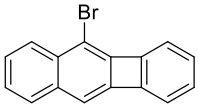


Scheme 2.15 *The preparation of 1-substituted and 1,5-disubstituted biphenylenes via the cyclisation of aryne derivatives.*

Although there are several synthetic approaches towards biphenylenes bearing a substituent in the 1-position, the scope of these reactions is limited, in most cases because only certain substrates/functional groups are tolerated under the reaction

conditions. As discussed in chapter 1, we are interested in the transition metal mediated C-C activation of 1-substituted biphenylenes in a catalytic diborylation reaction. For this work, 1-monosubstituted biphenylenes need to be prepared, so that the effect of that substituent on the reactivity and regioselectivity can be unambiguously determined. To study the effects of electronics and sterics on the reaction, a range of 1-monosubstituted biphenylene substrates including: 1-aryl, 1-halo, 1-methyl, 1-Bpin, 1-TMS, and 1-PPh_2 were needed.

Of the methods discussed, only four could be employed to prepare a range of 1-monosubstituted biphenylenes. Firstly, the lithiation of biphenylene, followed by reaction with an electrophile, which is low yielding and gives mixtures. Secondly, Iyoda's method could be used to prepare 1,8-dibromobiphenylene: the extra bromine could then be removed by reaction with one equivalent of *n*-butyllithium to give 1-bromobiphenylene in an overall yield of 32 or 37% dependent on the method employed.[32] This method would involve three to four steps, dependent on whether toxic CuCN was employed. Similarly, using the third method which employs α,α,α',α'-tetrabromo-*o*-xylene as the starting material, the extra bromine on **67** could, in principle, be removed by reaction with one equivalent of *n*-butyllithium to yield **74** (Fig. 2.2). Although this method involves fewer steps and gives higher yields than Iyoda's approach, it is limited by substrate scope because it is only possible to prepare polycyclic biphenylenes. The fourth and final method is the aryne cyclisation method, which is the most attractive. It has been used to prepare 1-chlorobiphenylene in 58% yield and 1-fluorobiphenylene in 47% yield in three steps from commercially available reagents.[38,40,41]



74

Fig. 2.2 *The structure of **74**, which could in principle be prepared from **67** by treatment with one equivalent of n-butyllithium.*

2.2. The Preparation of 1-Arylbiphenylenes *via* Suzuki–Miyaura Cross-Coupling

2.2.1. The Suzuki–Miyaura Cross-Coupling of 1-Chlorobiphenylene and Phenylboronic Acid.

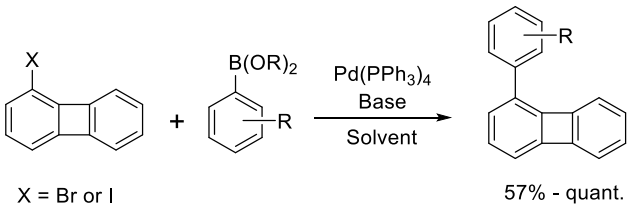
The most convenient and versatile starting materials for the preparation of various 1-substituted biphenylenes are 1-halobiphenylenes because the halogen substituent could be replaced by a variety of functional groups, for example *via* cross-coupling. The Suzuki–Miyaura cross-coupling reaction is arguably the most used cross-coupling reaction and the most common method for the construction of C-C bonds. The Suzuki–Miyaura cross-coupling reaction of a 1-halobiphenylene with an aryl boronate was therefore first investigated for the preparation of 1-arylsubstituted biphenylenes.

In the Suzuki–Miyaura cross-coupling reaction, an aryl boronic acid, aryl boronic ester, or aryl boronate is coupled with an aryl halide in the presence of palladium (0) catalyst, aqueous base, and normally in the presence of a ligand.[42] The reaction is widely used due to its broad substrate scope, high functional group tolerance, and due to the stability and non-toxic nature of the starting materials.[42] A large number of boronic acids and boronic esters are commercially available, therefore in principle it should be possible to access a wide range of 1-aryl substituted biphenylenes by the Suzuki–Miyaura cross-coupling of a 1-halobiphenylene with commercially available reagents.

As discussed in the introduction there are literature methods for the preparation of three 1-halobiphenylenes, which could undergo Suzuki–Miyaura cross-coupling: 1-iodo, 1-bromo, and 1-chlorobiphenylene. The preparation of 1-iodobiphenylene was low yielding and a mixture of the 1-substituted and 2-substituted isomers were obtained.[25,26,43] It is likely that the products of the Suzuki–Miyaura cross-coupling reaction, 1-aryl and 2-aryl substituted biphenylene, would also be inseparable and therefore could not be used as substrates in the ring opening study. 1-Chlorobiphenylene was favoured over 1-bromobiphenylene because it could be prepared without the need for toxic reagents in fewer steps and in higher yield.

The Suzuki–Miyaura cross-coupling of 1-bromo and 1-iodobiphenylene are known and were reported by Shibata *et al.* and Jones Jr *et al.* (Scheme 2.16).[25,44,45] In both

cases $Pd(PPh_3)_4$, (5-6 mol%) was used as the palladium source. The coupling of 1-bromobiphenylene is conducted in a mixture of DME/EtOH at 85 °C, using Na_2CO_3 as the base or CsF, dependent on the source of boron.[45] The coupling of 1-iodobiphenylene is conducted in a mixture of toluene and EtOH at 80 °C, using $Na_2CO_3 \cdot H_2O$ as the base.[25] In the instance of 1-iodobiphenylene, only one example is reported, the cross-coupling with phenyl boronic acid. Shibata *et al.* reported that 1-bromobiphenylene could be cross-coupled with a range of aryl boronic acids and aryl pinacolboronic esters, bearing methoxy, fluorine, chlorine, aldehyde and ketone functional groups.[45] In both cases the C-halogen bond was selectively cleaved and no competing activation of the C-C bond was reported.

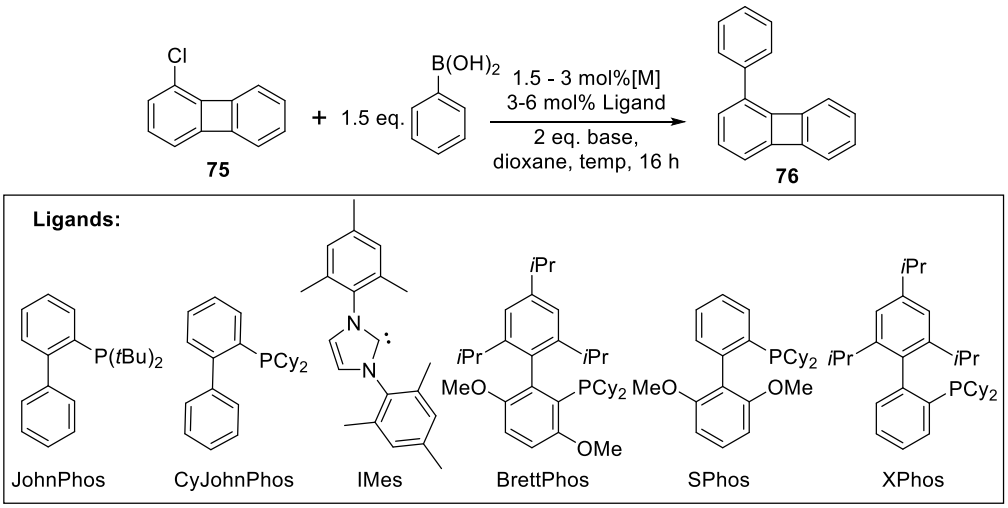


Scheme 2.16 *The Suzuki–Miyaura cross-coupling of 1-halogenated biphenylene to give 1-arylbiphenylenes.*

Aryl chlorides are traditionally more challenging to cross-couple than the corresponding aryl bromides and aryl iodides, in part due to the higher strength of C-Cl bonds, which makes the oxidative addition step less favourable.[46] The greater strength of the C-Cl bond also means that competitive activation of the C-C bond is more likely to occur. Despite their lower reactivity, a large amount of work has been done in the area of the Suzuki–Miyaura cross-coupling of aryl chlorides and they can be coupled in high yields with the appropriate conditions. Therefore, rather than trying the conditions reported for the much more reactive 1-bromo and 1-iodo biphenylene, screening was started from conditions reported for the Suzuki–Miyaura cross-coupling of less reactive aryl chlorides. Conditions for the Suzuki–Miyaura cross-coupling reaction were screened using 1-chlorobiphenylene and phenylboronic acid as the model substrates on a 0.2 mmol scale (Table 2.1).

It is worth noting that all the ligands employed in the screening were electron rich, sterically bulky ligands. This is because sterically bulky ligands tend to favour LPd(0) over $L_2Pd(0)$. The mono-ligated complexes are more reactive, making the oxidative addition step, which is often the rate limiting step with aryl chlorides,

Table 2.1 Screening the Suzuki–Miyaura cross-coupling reaction of phenylboronic acid with 1-chlorobiphenylene.



Entry	[M]	Ligand /mol%	Base	T/°C	Conversion (%)	GC Yield (%)
1[a]	$Pd(OAc)_2$	6 JohnPhos	KF	80	28	7
2[b]	$Pd(OAc)_2$	6 CyJohnPhos	K_3PO_4	80	26	7
3	$Pd_2(dba)_3$	3 IMes	Cs_2CO_3	80	2	2
4	$Pd_2(dba)_3$	3 P(Cy)$_3$	Cs_2CO_3	80	20	12
5	$Pd_2(dba)_3$	3 P(*t*-Bu)$_3$	Cs_2CO_3	80	23	10
6	$Pd_2(dba)_3$	3 P(n-Bu)$_3$	Cs_2CO_3	80	0	0
7	$Pd_2(dba)_3$	3 JohnPhos	Cs_2CO_3	80	33	28
8	$Pd_2(dba)_3$	3 CyJohnPhos	Cs_2CO_3	80	75	58
9	$Pd_2(dba)_3$	3 CyJohnPhos	Cs_2CO_3	100	86	55
10	$Pd_2(dba)_3$	6 CyJohnPhos	Cs_2CO_3	100	100	54
11	$Pd_2(dba)_3$	6 CyJohnPhos	Cs_2CO_3	80	96	58
12	$Pd_2(dba)_3$	6 CyJohnPhos	Cs_2CO_3	60	52	34
13	$Pd_2(dba)_3$	3 BrettPhos	Cs_2CO_3	80	100	95
14	$Pd_2(dba)_3$	3 BrettPhos	Cs_2CO_3	80	100	102
15	$Pd_2(dba)_3$	3 XPhos	Cs_2CO_3	80	100	93
16	$Pd_2(dba)_3$	3 XPhos	Cs_2CO_3	80	100	95
17	$Pd_2(dba)_3$	3 SPhos	Cs_2CO_3	80	29	17

All conversions and yields are based on GC analysis using n-dodecane as the internal standard (0.2 mmol scale). [a] Solvent is THF, [b] Solvent is toluene, [M] = $Pd(OAc)_2$: 3 mol%, [M] = $Pd_2(dba)_3$: 1.5 mol%

more favourable.[42] The use of electron rich ligands makes the palladium complex more electron rich, which facilitates the challenging oxidative addition step.[42]

The first conditions tested were taken from two papers published by Buchwald *et al.* on the Suzuki–Miyaura cross-coupling of aryl chlorides, in which $Pd(OAc)_2$ was used as the palladium source.[47,48] Two sets of conditions were tried from these papers, the first employed JohnPhos as the ligand, KF as the base, and THF as the solvent (Table 2.1, Entry 1).[47,48] The second, employed CyJohnPhos as the ligand, K_3PO_4 as the base, and toluene as the solvent (Table 2.1, Entry 2).[47] Both sets of conditions gave comparable and low conversions of 28% and 26% respectively, and only a 7% GC yield of the desired product, **76**, was obtained.

Given that the first set of conditions tried were not particularly promising, conditions reported by the group of Nolan were next investigated.[49] In these conditions, $Pd_2(dba)_3$ was used as the palladium source, the *N*-heterocyclic carbene, 1,3-Dimesitylimidazol-2-ylidene (IMes) was employed as the ligand, Cs_2CO_3 as the base, and dioxane as the solvent (Table 2.1, Entry 3).[49] Using these conditions an even poorer conversion of 2% was obtained and only a trace amount of the desired product **76** was observed. *N*-Heterocyclic carbene ligands were therefore not investigated any further.

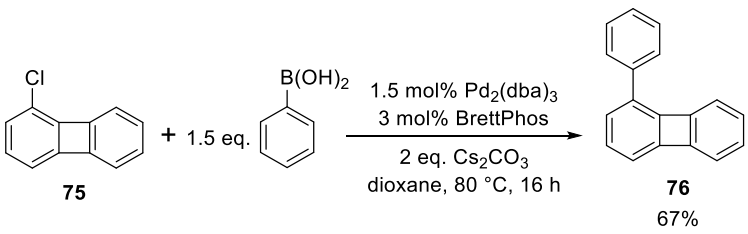
The final set of conditions that were tried from the literature were reported by Littke and Fu.[50] Littke and Fu screened the Suzuki–Miyaura cross-coupling of 4-chlorotoluene with phenylboronic acid, using $Pd_2(dba)_3$ as the palladium source and dioxane as the solvent. In their screening they found P(*t*-Bu)$_3$ to be the most effective ligand followed by P(Cy)$_3$, and they found Cs_2CO_3 to be the most effective base, closely followed by K_3PO_4.[50] Both P(*t*-Bu)$_3$ and P(Cy)$_3$ were tested with Cs_2CO_3. Both gave low conversions of 23 and 20% respectively and less than 15% GC yield of **76** (Table 2.1, Entries 4 and 5). Another trialkylphosphine ligand, P(*n*-Bu)$_3$, not tried by Fu and Littke was screened, but was completely ineffective, most probably because it is not electron rich or sterically bulky enough (Table 2.1, Entry 6).

JohnPhos and CyJohnPhos, the ligands reported by Buchwald *et al.*, were next tried using the conditions of Littke and Fu. JohnPhos gave an improved conversion of 33% and the GC yield of **76** was 28% (Table 2.1, Entry 7). CyJohnPhos, was significantly more effective and gave by far the highest conversion of 75% and the highest GC yield of **76**, 58% (Table 2.1, Entry 8). The temperature and ligand loadings were next varied.

Decreasing the temperature caused a significant decrease in the conversion and GC yield (Table 2.1, Entry 12). Conversely, increasing the temperature did not change the GC yield, although a slightly higher conversion of 86% was observed (Table 2.1, Entry 9). No additional signals were present in the GC chromatogram, however. Increasing the ligand loading also gave slightly improved conversions, but not improved GC yields (Table 2.1, Entries 10 and 11). A very small additional peak was observed in the GC chromatogram of the run using 6 mol% ligand loading at 100 °C: the most likely competing process being C-C bond activation (Table 2.1, Entry 10).

Given that CyJohnPhos gave the most promising results, other Buchwald ligands were next screened. SPhos gave a low conversion of 29% and a poor GC yield, 17% (Table 2.1, Entry 17). However, both BrettPhos and XPhos gave high conversions and high GC yields, significantly higher than CyJohnPhos (Table 2.1, Entries 13-16). It is interesting to note that the three ligands that worked the best are very similar in structure: all three are electron rich Buchwald ligands with $P(Cy)_2$ in the *ortho* position. XPhos and BrettPhos, the most effective ligands differ only by two methoxy groups. The *i*-Pr groups in the two *ortho* positions are believed to help promote the formation of PdL, rather than PdL_2, and improve the stability of the catalyst, which may account for the improved GC yields in these cases.[51]

Of the catalyst and ligand combinations screened, the optimal combination was found to be $Pd_2(dba)_3$ and BrettPhos (Table 2.1, Entries 13 and 14). This reaction was scaled up to 1.5 mmol, from 0.2 mmol (Scheme 2.17). Using the same conditions as in the screening reactions, 9% starting material was recovered and **76** was isolated in a good 67% yield.

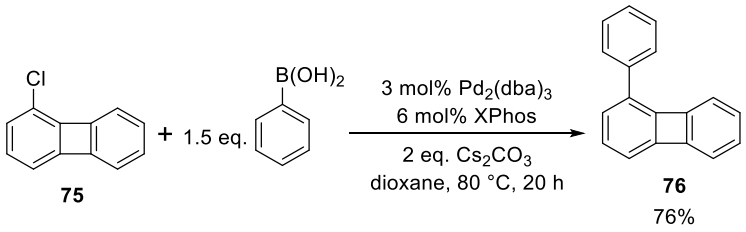


Scheme 2.17 *Suzuki–Miyaura cross-coupling of 1-chlorobiphenylene with phenylboronic acid, using BrettPhos as the ligand.*

BrettPhos is an expensive choice of ligand. At the time of writing £132/1g from Sigma Aldrich and for this reason it was not an ideal choice. XPhos is significantly cheaper

than BrettPhos: at the time of writing £33.6/1g from Sigma Aldrich and is therefore a preferable choice of ligand. XPhos was found to be the second-best ligand when employed in combination with $Pd_2(dba)_3$ (Table 2.1, Entries 15 and 16) and gave only marginally lower GC yields of **76** than the combination of BrettPhos and $Pd_2(dba)_3$ (93% vs 95%).

The reaction was therefore next tried on large scale using XPhos as the ligand instead of BrettPhos (Scheme 2.18). Given that when the reaction with BrettPhos was scaled up it did not go to completion, the reaction with XPhos was conducted for the slightly longer time of twenty hours and with double the catalyst loading. XPhos is significantly cheaper than BrettPhos, thus even using double the catalyst loading of XPhos it is still cheaper than BrettPhos. With the higher catalyst loading and longer reaction time, the reaction did go to completion and the desired product was isolated in 76% yield. A second product was also isolated, but GC-MS showed that this consisted of a mixture of around twenty different components and this was therefore not investigated further.

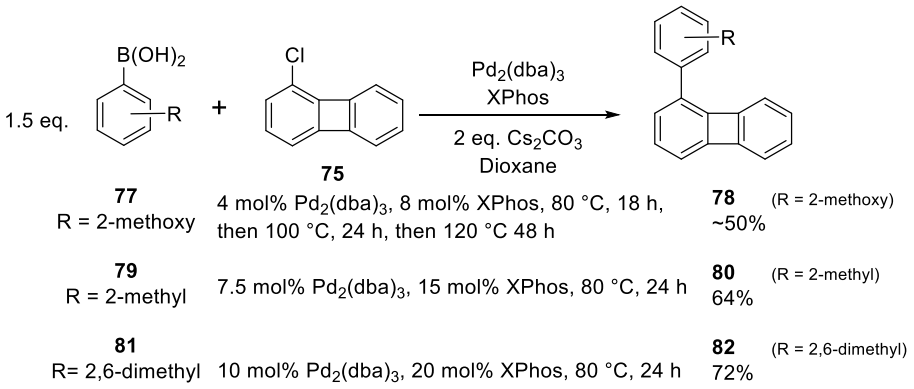


Scheme 2.18 *Suzuki–Miyaura cross-coupling of 1-chlorobiphenylene with phenylboronic acid, using XPhos as the ligand.*

2.2.2. The Scope of the Suzuki–Miyaura Cross-Coupling of 1-Chlorobiphenylene

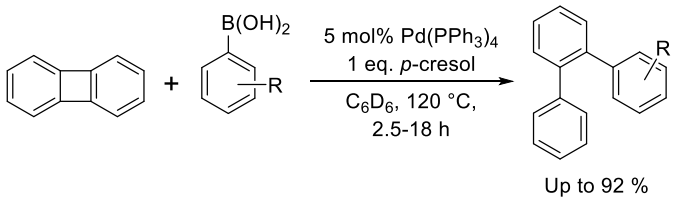
With optimised conditions for the Suzuki–Miyaura cross-coupling reaction of 1-chlorobiphenylene with phenylboronic acid in hand, the scope of the reaction was next investigated. When 2-methoxyphenyl boronic acid **77** was employed as the coupling partner, 19% starting material was recovered. This was despite a higher catalyst loading of 4 mol% $Pd_2(dba)_3$ and 8 mol% XPhos being used and the temperature being increased from 80 °C to 120 °C (Scheme 2.19, R = 2-methoxy). Lower reactivity is most probably a consequence of **77** being more sterically bulky than phenylboronic

acid. Although it is also possible that the methoxy group coordinates to palladium, which would slow the transmetallation step. The desired product was isolated in approximately 50% yield; however, it was contaminated with a small impurity.



Scheme 2.19 *Preparation of 1-aryl substituted biphenylenes by the Suzuki–Miyaura cross-coupling reaction of 1-chlorobiphenylene.*

It was found that when the temperature of the reaction was increased from 100 °C to 120 °C a side-product began to form. One possible side-reaction is cleavage of the strained C-C bond, which as discussed in section 1.1.2.3, has been reported by Jones *et al.* under similar reaction conditions (Scheme 2.20). In this work, the $Pd(PPh_3)_4$ catalysed coupling of unsubstituted biphenylene with aryl boronic acids at 120 °C yielded *o*-aryl substituted biaryls in the presence of 1 equivalent of *p*-cresol. In the absence of *p*-cresol, the *o*-aryl substituted biaryl was obtained in lower yield and tetraphenylene was also isolated.



Scheme 2.20 *The coupling of biphenylene with aryl boronic acids.*

However, the side-product(s) could not be identified, and NMR did not look consistent with C-C cleavage. Given that the aim of this work was to access 1-monosubstituted biphenylenes, this side-reaction was not explored further. All subsequent Suzuki–Miyaura cross-coupling reactions were conducted at 80 °C to avoid the competing side-reaction that occurred when the reaction temperature was increased to 120 °C.

The next substrate to be investigated was 2-methylphenyl boronic acid **79**. Since the reaction in which **77** was employed as a substrate did not go to completion, the catalyst and ligand loadings were increased from 4 mol% $Pd_2(dba)_3$ to 7.5 mol% and from 8 mol% XPhos to 15 mol%. Using these reaction conditions, only trace amounts of starting material remained after the reaction mixture was heated at 80 °C for twenty-four hours and the desired product, **80**, was isolated in 64% yield (Scheme 2.19, R = 2-methyl). Both the yield and conversion are significantly better than when **77** was employed as the coupling partner.

Finally, when 2,6-dimethylphenyl boronic acid **81** was cross-coupled with 1-chlorobiphenylene, the catalyst and ligand loadings were increased again, from 7.5 mol% $Pd_2(dba)_3$ to 10 mol% and from 15 mol% XPhos to 20 mol%. This was done to try to push the reaction to completion. Despite the higher catalyst and ligand loadings, trace amounts of starting material remained after the reaction mixture was heated at 80 °C for twenty-four hours (Scheme 1.19, R = 2,6-dimethyl). The desired product, **82**, was however isolated in a high 72% yield.

Using the optimised reaction conditions, four 1-arylbiphenylenes were prepared in moderate to high yield. This was despite the Suzuki–Miyaura cross-coupling reaction not going to completion when three of the substrates were employed. In principle, higher yields should be obtained if these reactions could be pushed to completion. To address this, much more reactive 1-iodobiphenylene could be employed as a substrate.

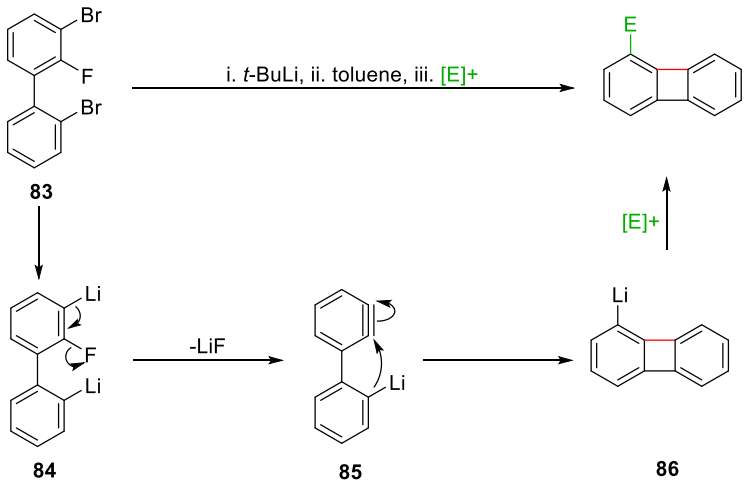
2.3. Preparation of 1-Iodobiphenylene

2.3.1. Proposal

The aryne cyclisation strategy reported by Wu *et al*. only gives synthetic access to two 1-monosubstituted biphenylenes: 1-fluoro- and 1-chloro-biphenylene. 1-Arylbiphenylenes can be prepared from 1-chlorobiphenylene, but dependent on the substrate the reaction does not always go to completion. For our study of the transition metal catalysed ring-opening diborylation of 1-substituted biphenylenes it is necessary to prepare several different 1-monosubstituted biphenylenes. Here, a different starting material for the aryne cyclisation strategy is proposed, **83**. Aryne cyclisation of **83**

could provide synthetic access to a wider range of 1-monosubstituted biphenylenes, including 1-iodobiphenylene.

As discussed in section 2.1.3, Wu *et al.* demonstrated that the 1-lithiated intermediate **73** could be intercepted with various electrophiles to yield 1,5-disubstituted biphenylenes (Scheme 2.15). It was envisaged that by changing the choice of starting material from that reported by Wu *et al.* to **83**, 1-lithiobiphenylene **86** could be generated *in situ* (Scheme 2.21). In principle, the treatment of **86** with different electrophiles could give synthetic access to a broader range of 1-monosubstituted biphenylenes. As will be discussed in the next section, it was thought that the biaryl starting material **83** could be prepared in one-step from commercially available starting materials *via* a Suzuki–Miyaura cross-coupling reaction. This synthetic strategy would therefore be one step quicker than the preparation of 1-chlorobiphenylene and 1-fluorobiphenylene. This method is particularly attractive, because using the same two starting materials, several different 1-monosubstituted biphenylenes could be prepared in two steps from commercially available reagents.



Scheme 2.21 *Proposed synthesis of 1-monosubstituted biphenylenes.*

Using iodine as the electrophile, it should be possible to prepare 1-iodobiphenylene in two steps. This is one step quicker than the preparation of 1-chlorobiphenylene and would save time. In addition, aryl iodides are generally more reactive than the corresponding aryl bromides and significantly more reactive than the corresponding aryl chlorides. This is at least in part due to their relative bond strengths, with C-I bonds being the weakest and C-Cl bonds being the strongest.[46] This has two possible benefits: 1) synthetic access to 1-(2-pyridyl)biphenylene, which would be challenging

to prepare starting from 1-chlorobiphenylene and 2) 1-iodobiphenylene should be more reactive in the Suzuki–Miyaura cross-coupling reaction. Given that the Suzuki–Miyaura cross-coupling reactions of 1-chlorobiphenylene and sterically bulky boronic acids did not always go to completion, substitution of 1-chlorobiphenylene with 1-iodobiphenylene could give higher yields of the desired 1-arylsubstituted biphenylenes.

2.3.2. Preparation of 2',3-Dibromo-2-fluoro-1,1'-biphenyl, 83

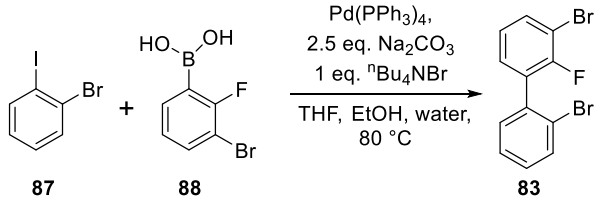
To realise the proposed synthetic route towards 1-iodobiphenylene it was first necessary to prepare the biaryl starting material **83**. Biaryl **83** could in principle be prepared by the Suzuki–Miyaura cross-coupling of 2-bromoiodobenzene **87** and (3-bromo-2-fluorophenyl) boronic acid **88**. As a starting point, reaction conditions reported by Wu *et al.* for the preparation of biaryls were tested (Table 2.2, Entry 1) .[38] However, on a 3 mmol scale in the presence of 5 mol% $Pd(PPh_3)_4$, 2.5 eq. of Na_2CO_3, and 1 eq. of $^nBu_4NBr$ after twenty hours at 80 °C, the reaction proceeded with 58% conversion to give the desired biaryl product **83** in 45% yield.

Due to the amount of **83** required for future chemistry the scale of the reaction was increased to 9 mmol. In addition, because the reaction had not gone to completion when it was conducted on a 3 mmol scale, the catalyst loading was increased to 10 mol% and the reaction time was increased to 64 hours. Unfortunately, even using these more forcing conditions **83** was isolated in only 38% yield (Table 2.2, Entry 2). When the scale of the reaction was increased further to 20 mmol and 30 mmol, **83** was isolated in even lower yields of 31% and 33% respectively (Table 2.2, Entries 5 and 7). These results suggest that the reaction works best on a smaller scale, but once a certain point is reached, i.e. going from 20 to 30 mmol scale there is no significant change.

With the aim of determining the effect of time on the conversion and yield of the reaction, the reactions on 20 and 30 mmol scale were both repeated and the reaction stopped after 24 hours (Table 2.2, Entries 6 and 8). It was found in both cases that the difference in yield and conversion was negligible, thus it is not necessary to heat the reaction for 64 hours. Finally, with the intention of minimising the amount of palladium catalyst required, the reaction was also conducted on a 9 mmol scale using

5 mol% catalyst loading, instead of 10 mol% (Table 2.2, Entry 3). It was found that the difference in the yield of **83** was negligible, therefore increasing the catalyst loading from 5 to 10 mol% does not improve the yield of **83**.

Table 2.2 Suzuki–Miyaura cross-coupling of 2-bromoiodobenzene **87** with (3-bromo-2-fluorophenyl) boronic acid **88**.



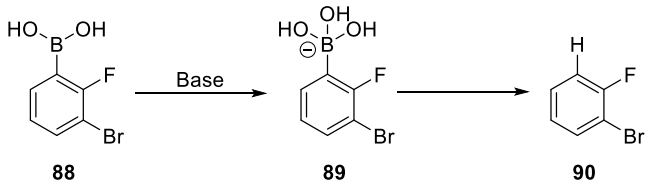
87 88 83

Entry	Scale/ mmol	Catalyst Loading/ mol%	Boronic Acid eq.	Time/h	Conversion	83 Yield (%)
1	3	5	1.2	20	58	45
2	9	10	1.2	64	59	38
3	9	5	1.2	64	60	34
4	9	10	2	64	56	31
5	20	10	1.2	64	71	31
6	20	10	1.2	24	n/d	35
7	30	10	1.2	64	n/d	33
8	30	10	1.2	24	n/d	30

Yields are isolated yields and conversions are based on the recovery of 2-bromoiodobenzene **87**.

The relatively modest conversions and yields observed in the Suzuki–Miyaura cross-coupling reaction might be explained by the base-catalysed protodeboronation of **88** under the reaction conditions (Scheme 2.22). Protodeboronation of **88** could compete with transmetallation, which might be slowed down by the *ortho*-substituent and the electron poor character of **88**. In addition, consumption of **88** *via* protodeboronation would mean that the amount of **88** present in the reaction mixture was insufficient for the desired transformation to go to completion. It is known that having a fluorine substituent *ortho* to the boronic acid moiety significantly accelerates the rate of base catalysed protodeboronation.[52] In addition, 12% of the protodeboronated starting material, **90**, was isolated after column chromatography. It is important to note however that this does not definitively prove that protodeboronation takes place during the reaction because it could have taken place on the column.

To investigate whether protodeboronation of **88** was the cause of the low conversions and yields in the Suzuki–Miyaura cross-coupling reaction, the equivalents of **88** were increased from 1.2 to 2 on the 9 mmol scale (Table 2.2, Entry 4). It was hoped that if protodeboronation was taking place, having higher equivalents of **88** would mean a higher conversion could be achieved before complete protodeboronation had taken place. Unfortunately, increasing the equivalents of **88** to 2 did not improve the yield of the reaction: the desired product was isolated in a slightly lower yield of 31%. In addition, 20% of protodeboronated **90** was isolated.

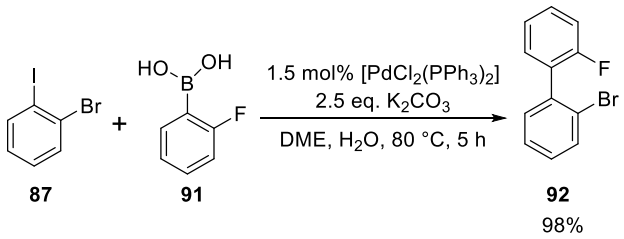


88 **89** **90**

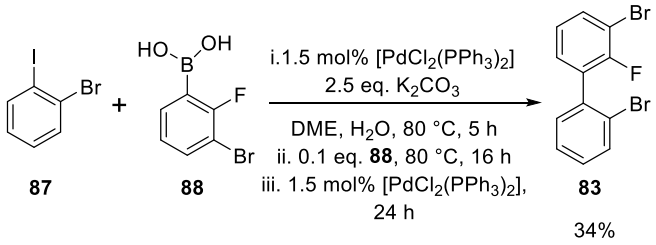
Scheme 2.22 *Base-catalysed protodeboronation of boronic acid starting material **88**.*

This result suggests that protodeboronation may not be the reason for the reaction not going to completion. As well as protodeboronation, other possible side-reactions that could take place and suppress the desired transformation are homo-coupling and oxidation of **88** to the corresponding phenol, however no evidence of these processes was observed.[42] It is therefore most probable that slow transmetallation, caused by the steric bulk and electron deficiency of **88**, is the reason for the low conversions and yields. Transmetallation is known to be slower for electron-poor substrates.[42]

Larsen *et al.* reported the Suzuki–Miyaura cross-coupling of **87** with 2-fluorophenylboronic acid **91**, in which they isolated the cross-coupled product **92** in 98% yield (Scheme 2.23).[53] It was hoped that since the aryl halide coupling partner **87** was the same, and the boronic acid coupling partner differed only by a bromo substituent in the *meta* position, that these conditions would work well for the desired transformation. However, on a 9 mmol scale the conversion was 50% and the desired product was isolated in a 34% yield (Scheme 2.24). This was after increasing the equivalents of **88** to from 1 eq. to 1.1 eq. and doubling the catalyst loading to 3 mol%. The additional bromo substituent on the aryl boronic acid **88** makes the substrate more electron poor, which would make the transmetallation step less favourable. This could slow the rate of the reaction, though the difference in reactivity between the aryl boronic acids **88** and **91** is greater than would be expected.



Scheme 2.23 *The Suzuki–Miyaura cross-coupling reaction between 2-bromoiodobenzene* ***87*** *and 2-fluorophenylboronic acid* ***91****.*



Scheme 2.24 *The Suzuki–Miyaura cross-coupling reaction between 2-bromoiodobenzene* ***87*** *and (3-bromo-2-fluorophenyl) boronic acid* ***88****.*

The conditions reported by Larsson *et al.* and the conditions reported by Wu *et al.* gave comparable yields of the desired biaryl **83.** In the interests of time, the preparation of **83** was not optimised further. However, had more time been available a screening of catalysts, ligands, solvents, and bases would have been conducted. With **83** in hand, its utility in the aryne cyclisation reaction was next investigated.

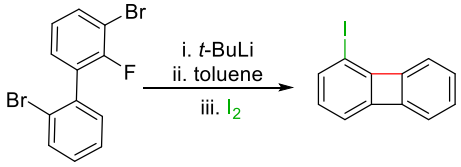
2.3.3. Preparation of 1-Iodobiphenylene *via* Aryne Cyclisation

The second and final step in the proposed synthetic route towards 1-iodobiphenylene is the one pot aryne cyclisation of biaryl **83** and subsequent treatment with iodine. In the literature precedent for the aryne cyclisation method, three different sets of conditions were employed dependent on the substrate. Since it was not known which of the three sets of conditions reported by Wu *et al.* would work best with biaryl **83**, three small scale test reactions were conducted, in which **83** was subjected to the three different sets of conditions (Table 2.3).

In the reactions in which ether was employed as the solvent, 1-iodobiphenylene was isolated in low yields (Table 2.3, Entries 1 and 2). No starting material was recovered

from either reaction, so the conversion is 100%. In both cases a significant amount of brown gum was flushed off the column. NMR shows that in both cases this material is the same, but the NMR is not conclusive. There are no peaks in the aliphatic region, but a significant number of peaks in the aromatic region. It is therefore most likely that polymerisation has taken place.

Table 2.3 The isolated yields of 1-iodobiphenylene following the aryne cyclisation of biaryl **83** using three different sets of conditions reported in the literature for aryne cyclisation.



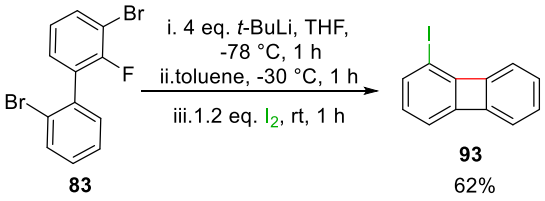
83 **93**

Entry	Reaction Conditions	93 Yield
1	i. 3 eq. *t*-BuLi, Et_2O, -100 °C, 1h ii. -78 °C, 1 h iii. Toluene, -50 °C, 1h iv. 1.5 eq. I_2, rt, 1h	25%
2	i. 3 eq. *t*-BuLi, Et_2O, -100 °C, 1h ii. -78 °C, 1 h iii. Toluene, -30 °C, 1h iv. 1.5 eq. I_2, rt, 1h	18%
3	i. 4 eq. *t*-BuLi, THF, -78 °C, 1h ii. Toluene, -30 °C, 1h iii. 1.2 eq. I_2, rt, 1h	42%

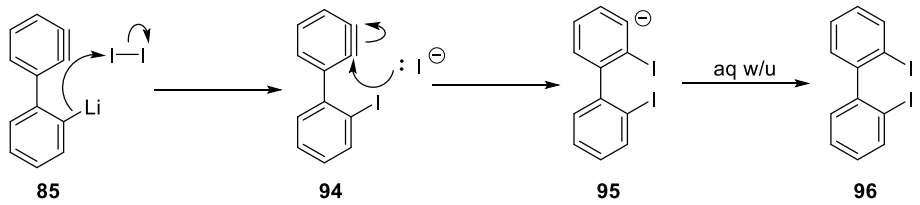
Yields are isolated yields.

The best yield, 42% was obtained when the solvent was changed from ether to THF, the equivalents of *t*-butyllithium increased from three to four, and the halogen lithium exchange step conducted at -78 °C, not -100 °C (Table 2.3, Entry 3). Given that this reaction gave the best result, it was scaled up to 6.4 mmol from 0.45 mmol (Scheme 2.25). A significantly improved yield of 62% was achieved on the larger scale. Several side-products were produced in the reaction, many of these came off the column together and so it was difficult to determine the exact amounts of each.

The side-products include less than 2% biphenylene, **1**. Formation of **1** is most likely because of the incomplete reaction of 1-lithiobiphenylene **86** with iodine, unreacted **86** would be protonated during the aqueous work-up to give **1**. 2,2'-diiodo-1,1'-biphenyl **96** was also identified as a side-product by proton NMR. It is most likely that **96** forms *via* the reaction of uncyclised **85** with iodine (Scheme 2.26). Interestingly, its isomer resulting from addition of iodine to the other end of the triple bond was not observed.

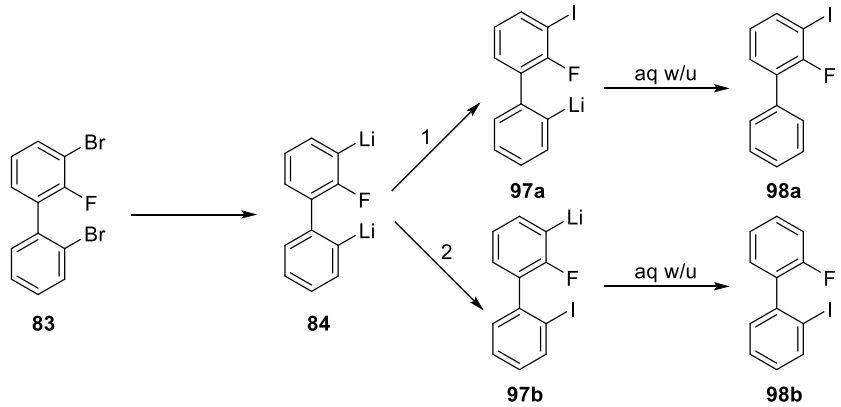


Scheme 2.25. *The preparation of 1-iodobiphenylene via aryne cyclisation of* ***83****.*



Scheme 2.26 *Potential mechanism for the formation of the side-product* ***96****.*

In addition to **1** and **96,** which could be clearly identified by NMR, an ion with m/z 298 g/mol is observed by GC-MS. This is most likely fluoroiodobiphenyl, and in principle two isomers are possible: **98a** or **98b**. Fluoroiodobiphenyl is most probably formed due to incomplete elimination of LiF from **84**. Unreacted **84** could react with iodine to give two possible regioisomers, as shown in Scheme 2.27. From the NMR it was not possible to determine which regioisomer is formed.

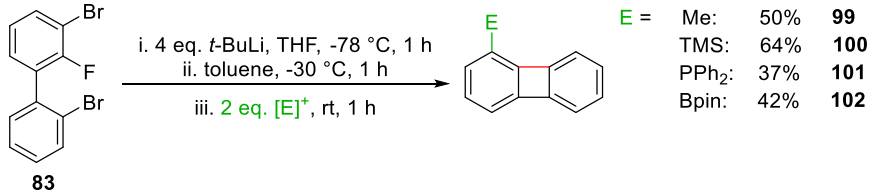


Scheme 2.27 *Potential mechanism for the formation of regioisomers* ***98a*** *and* ***98b****, a potential side-product in the preparation of 1-iodobiphenylene.*

2.4. The Scope of the Aryne Cyclisation

The conditions that worked best for the preparation of 1-iodobiphenylene, from **83**, were next employed to prepare other 1-substituted biphenylenes, from **83**, by employing different electrophiles in the quenching step (Scheme 2.28). The same reaction conditions were employed because the same 1-lithiobiphenylene intermediate **86** is formed, the only thing that has been changed is the final quenching step. Four additional electrophiles were found to be compatible with the reaction conditions and gave the desired 1-substituted biphenylenes in good to moderate yields. The equivalents of electrophile were increased from 1.2 to 2 to push the final step to completion, since trace amounts of biphenylene were observed when 1-iodobiphenylene was prepared.

It was necessary to determine the effect of the steric bulk of the 1-substituent on the ring opening diborylation reaction. Therefore, the first 1-substituted biphenylene investigated was 1-methylbiphenylene **99** because the steric bulk of methyl is between that of fluorine and phenyl. Using the aryne cyclisation strategy, **99** was isolated in a moderate yield of 50% (Scheme 2.27, $[E]^+ = CH_3I$) and 22% yield over two steps from commercially available reagents.

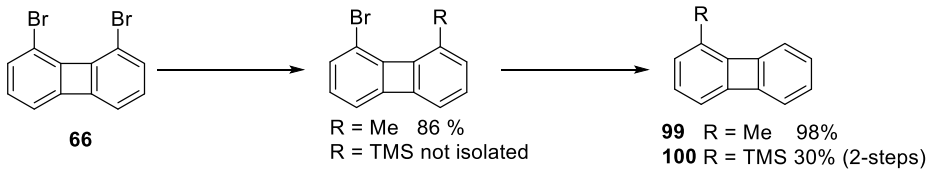


Scheme 2.28. *The preparation of 1-monosubstituted biphenylenes.*

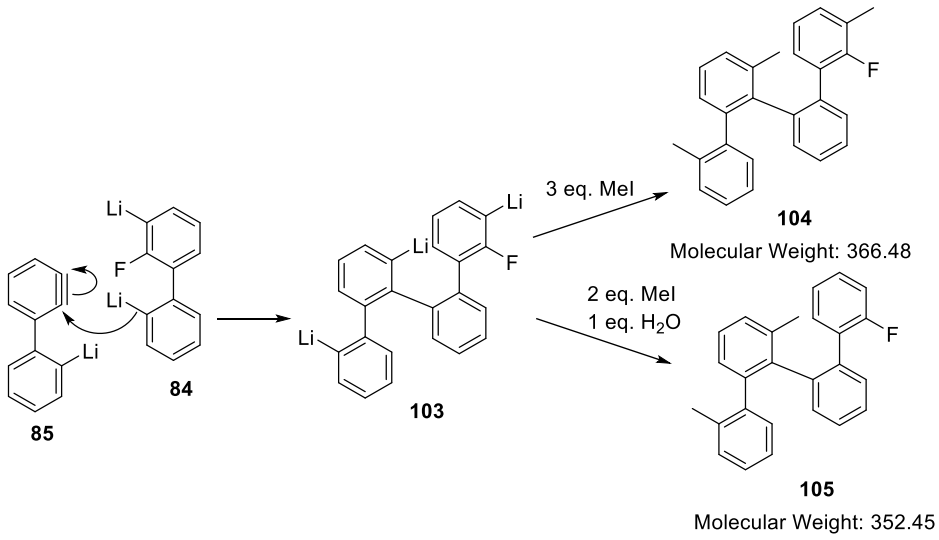
1-Methylbiphenylene **99** has previously been prepared using several different methods, these include by intramolecular Ullman coupling and lithiation of biphenylene, followed by treatment with iodomethane.[24,54] Using the first method, high temperatures of 350 °C are needed and no yield for **99** was given. Using the second method, clean **99** could not be isolated and no yield for **99** was given.[54]1-Methylbiphenylene **99** has also been prepared from 1,8-dibromobiphenylene **66** in 84% yield (Scheme 2.29, R = Me).[55] Therefore, using this method **99** can be prepared from commercially available reagents in 32% yield over five steps without CuCN, or in 36% yield over four steps with CuCN. This method is slightly higher yielding than

the aryne cyclisation method developed in this work, however it is much less time efficient because it requires two or three additional purification and isolation steps.

In addition to the desired product **99**, eight side-products were formed in the aryne cyclisation reaction. GC-MS showed that ions with m/z: 366, 352, 332, 318, 262, and 276 g/mol were present. For z=1, 366 and 352 g/mol corresponds to the molecular weights of **104** and **105** or their isomers (Scheme 2.30). One possible mechanism for their formation is outlined in Scheme 2.30, in which intermediate **84** first adds to intermediate **85** to form **103**. Intermediate **103** can then react with either three equivalents of iodomethane to give **104** or two equivalents of iodomethane and one equivalent of water to form **105**. Multiple isomers are possible dependent on whether the *ortho*-lithium or the *meta*-lithium in **84** adds across the benzyne and whether it adds to the *ortho*-carbon or the *meta*-carbon of the benzyne. From GC-MS data alone it is not possible to determine which isomer forms.



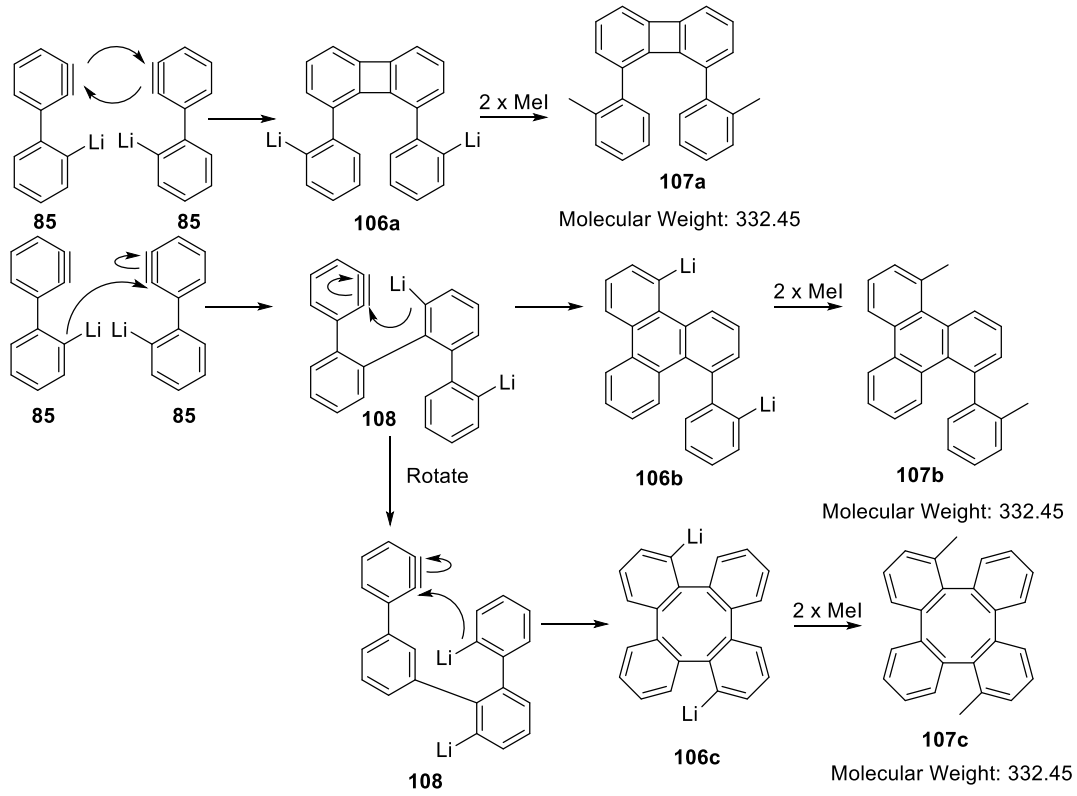
Scheme 2.29 *The preparation of 1-methylbiphenylene from 1,8-dibromobiphenylene.*



Scheme 2.30 *Dimerisation of **83** followed by reaction with iodomethane (and water).*

Three ions with m/z 332 g/mol were observed by GC-MS. For z =1, 332 g/mol could be attributed to the isomers **107a** - **107c** (Scheme 2.31). These side-products could be formed by the dimerisation of the benzyne intermediate **85**, to give cyclised

intermediates, followed by double reaction with iodomethane (Scheme 2.31). A product with the molecular weight 318 g/mol (**108**) would result if one of the cyclised intermediates **106a** - **106c** reacted with one equivalent of iodomethane and one equivalent of water, instead of two equivalents of iodomethane. Finally, no obvious side-products could be attributed to the ions with m/z 262 g/mol and 276 g/mol.



Scheme 2.31 *Potential mechanisms for the formation of regioisomers* ***107a*** *–* ***107c****.*

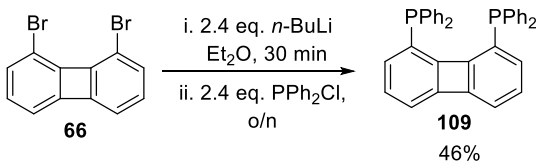
The next 1-substituted biphenylene investigated was 1-(trimethylsilyl)biphenylene **100** (Scheme 2.28, $[E]^+$ = TMSCl). 1-(Trimethylsilyl)biphenylene **100** was chosen as a substrate for the ring opening diborylation reaction because the steric bulk of trimethylsilyl is between that of phenyl and methyl. Therefore, investigation of the ring opening diborylation of **100** would provide more information about the effect of steric bulk on this reaction. Using the aryne cyclisation strategy, **100** was isolated in a good yield of 64% and no side-products were isolated.

Using the aryne cyclisation strategy, **100** was prepared in two steps from commercially available reagents in an overall yield of 29%. 1-(Trimethylsilyl)biphenylene **100** has previously been prepared using different synthetic routes. Firstly, it has been prepared by the lithiation of biphenylene (which can be prepared in up to 81% yield), followed by treatment with TMSCl, which gave **100** in 42% yield, 34% overall yield.[20,56]

Secondly, it has been prepared from 1,8-dibromobiphenylene **66** in 30% yield (Scheme 2.29, R = TMS).[44] Therefore, using this method **100** can be prepared from commercially available reagents in 11% yield over five steps without CuCN or in 13% yield over four steps with CuCN. The first literature method gives a higher yield of **100**, however, optimisation of the aryne cyclisation route could make this a better route in the future.

1-Diphenylphosphinobiphenylene **101** was next prepared for the ring opening diborylation study, to determine if diphenylphosphine could act as a directing group and favour addition of the catalyst to the adjacent C-C bond. When diphenylchlorophosphine was employed as the electrophile in the aryne cyclisation reaction, **101** was isolated in 37% yield (Scheme 2.28, $[E]^+ = PPh_2Cl$). The yield is slightly lower than with other electrophiles due to difficulties with the purification of **101**. Following purification by column chromatography, the product was approximately 90% pure, and the crude yield was approximately 57%. There were five other small phosphorus environments present by ^{31}P NMR. Following recrystallisation with ethanol, the pure product was obtained, but the yield dropped significantly to 37%.

1-Diphenylphosphinobiphenylene, **101**, is a new compound, which demonstrates the potential of this synthetic strategy for the preparation of new 1-substituted biphenylenes. The related compound 1,8-diphenylphosphinobiphenylene **109** has been prepared in 46% yield by the treatment of 1,8-dibromobiphenylene **66** with *n*-butyllithium, followed by reaction with two equivalents of diphenylchlorophosphine (Scheme 2.32).[57] It was shown that **109** could be used as a bidentate ligand for late transition metal chlorides. Therefore, in addition to serving as a substrate for the ring opening diborylation reaction, **101** may also have some application as a monodentate ligand.[57]



Scheme 2.32 *The preparation of 1,8-diphenylphosphinobiphenylene,* ***109.***

Finally, when isopropoxyboronic acid pinacol ester was employed as the electrophile, 1-Bpinbiphenylene, **102**, was obtained in a moderate yield of 42% (Scheme 2.28, $[E]^+$

= *i*-PrOBpin). 1-Bpinbiphenylene **102** was prepared as a substrate for the ring opening diborylation reaction to determine if the reaction tolerates a Bpin functional group. The yield of **102** is lower than other 1-substituted biphenylenes because of difficulty with its purification. The crude product was purified by silica column twice and the recovery of **102** after flash column chromatography was poor.

Poor recovery is a relatively common problem encountered in the purification of aryl boronic esters by column chromatography. One explanation for poor recovery is uneven over-adsorption of the aryl boronic ester, which is the most probable explanation for the moderate yield of **102**.[58] This is supported by two observations: firstly, when the second column was flushed with EtOAc following chromatographic purification **102** was isolated. Presumably, some **102** would also have remained on the first column which was not flushed with EtOAc and would account for some of the missing mass balance. Secondly, **102** tailed by TLC, which is consistent with uneven over-adsorption of **102.** This also causes **102** to come off the column over a long period of time, making separation from side-products challenging.

Since it was not possible to cleanly isolate **102**, it was used as it was following the second column in subsequent chemistry. Although **102** was prepared in moderate yield this is the first ever report of its synthesis. As discussed in detail in section 1.3.1, aryl pinacol boronate esters are versatile building blocks in organic synthesis that can undergo a wide range of synthetic transformations. Therefore, **102** could provide synthetic access to several 1-substituted biphenylenes not previously prepared.

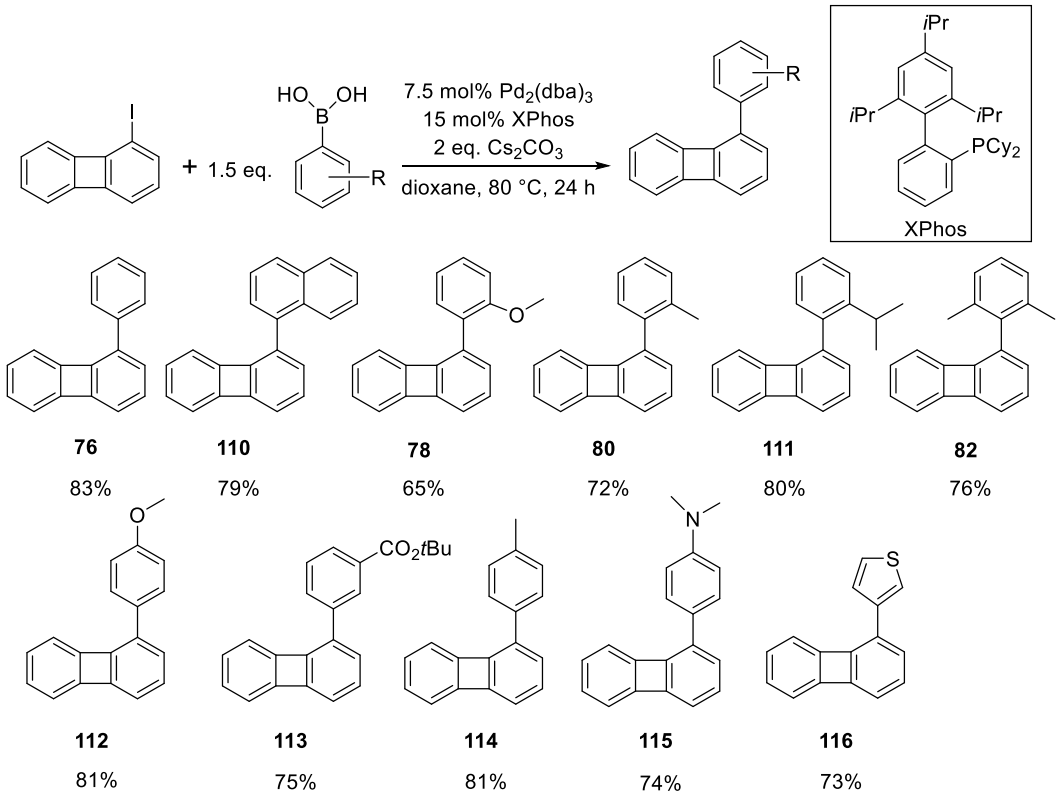
If more time had been available, the purification of **102** would have been further investigated. For example, it has been shown that impregnating silica with boric acid has improved the separation of some aryl boronic esters by TLC.[58] This is thought to be because uneven over-adsorption is caused by interactions of the empty p-orbital on boron with nucleophilic sites on silica gel, which are capped by boric acid. If a better method of purification were found this would give **102** in higher yield.

Although in some instances the yields could be improved on, this is mainly due to problems with purification. If more time were spent on this project, it may be possible to find better methods of purification and isolate some of the products in higher yields. Overall, this is a very attractive method of accessing a range of 1-substituted biphenylene substrates in only two steps starting from commercially available

reagents. Several different 1-substituted biphenylenes can be prepared from the same starting material, simply by changing the choice of electrophile.

2.5. Scope of the Suzuki–Miyaura Cross-Coupling Reaction

The method developed for the preparation of 1-iodobiphenylene was, advantageously, one step quicker than the preparation of 1-chlorobiphenylene and 1-iodobiphenylene is much more reactive than 1-chlorobiphenylene. 1-Iodobiphenylene was therefore used as the starting material for subsequent Suzuki–Miyaura cross-coupling reactions. The Suzuki–Miyaura cross-coupling reaction of 1-iodobiphenylene with aryl boronic acids was achieved using the catalyst, ligand, solvent, and base combination of $Pd_2(dba)_3$, XPhos, dioxane, and Cs_2CO_3 that had been identified from the screening of 1-chlorobiphenylene and phenylboronic acid (Scheme 2.33). The catalyst loading was kept at 7.5 mol% $Pd_2(dba)_3$ and 15 mol% XPhos, and the reaction time was kept at twenty-four hours. This was in the interests of time, since it had been found that some of the more sterically bulky substrates were sluggish in the reaction with 1-chlorobiphenylene.



Scheme 2.33. *1-Arylbiphenylenes prepared by the Suzuki–Miyaura cross-coupling of 1-iodobiphenylene and various arylboronic acids. Yields are isolated yields.*

Using these conditions all the reactions went to completion within twenty-four hours and so all the necessary starting material could be accessed quickly and straightforwardly. Firstly, 1-phenylbiphenylene **76** was prepared in 83% yield (Scheme 2.33). This is higher than the 76% yield, which was obtained from the Suzuki–Miyaura cross-coupling of 1-chlorobiphenylene using lower catalyst loadings of 3 mol% $Pd_2(dba)_3$ and 6 mol% XPhos.

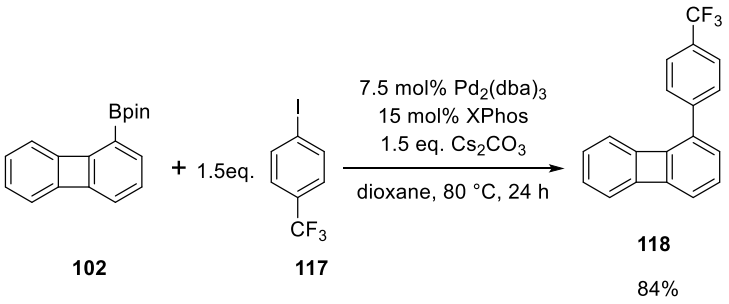
To effectively investigate the effect of the 1-substituent on the ring opening diborylation reaction it was necessary to prepare a wide range of 1-arylbiphenylenes with varying steric and electronic properties. 1-Arylbiphenylenes bearing *ortho*-substituents with varying degrees of steric bulk were required to investigate the effect of steric bulk on the ring opening diborylation reaction. Sterically bulky 1-arylbiphenylenes **78**, **80**, **82**, **110**, and **111** were prepared in moderate to high yield (Scheme 2.33).

It is of note that when 1-iodobiphenylene is used as the aryl halide coupling partner instead of 1-chlorobiphenylene 1-(*o*-tolyl)biphenylene **80** was isolated in 72% yield, a marked improvement on the previous 64% yield. The yield of 1-(2,6-dimethylphenyl)biphenylene **82**, improved negligibly from 72 to 76%, using a slightly lower catalyst loading. 1-(2-Methoxy)phenyl biphenylene **78** was isolated in 65% yield, this is a significant improvement on the 50% yield obtained when 1-chlorobiphenylene was employed as the coupling partner and a lower catalyst loading of 4 mol% $Pd_2(dba)_3$ and 8 mol% XPhos was employed. The yield is slightly lower than other 1-arylbiphenylenes, not because the reaction did not work well, but because the product could not be separated from XPhos by flash column chromatography and some product was lost when the crude product was recrystallised.

1-Arylbiphenylenes which have electron-donating and electron-withdrawing substituents were required to investigate the effect of electronics on the ring opening diborylation reaction. 1-Arylbiphenylenes **112** and **114**-**116**, bearing electron donating substituents were prepared in high yields as was 1-arylbiphenylene **113**, which contains an electron withdrawing ester moiety. It was found that methoxy, ester, alkyl, thiophene, and amine functional groups were all tolerated in the reaction. Except for 1-phenylbiphenylene all these 1-arylbiphenylenes are new compounds. This demonstrates the potential of the three-step sequence of Suzuki–Miyaura cross-

coupling, aryne cyclisation, and Suzuki–Miyaura cross-coupling as a method for the preparation of a broad range of 1-arylsubstituted biphenylenes.

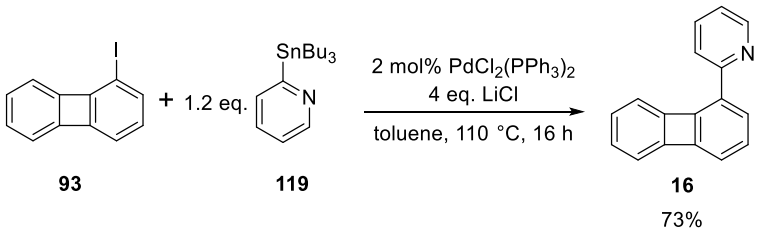
It was a concern that 4-trifluoromethylphenylboronic acid, required for the preparation of 1-(4-trifluoromethylphenyl)biphenylene **118** was particularly electron poor. Electron poor boronic acids are poorer nucleophiles than electron neutral or electron rich aryl boronic acids, and therefore the transmetallation step is less likely to work well.[59] Therefore, **117** was instead prepared by the Suzuki–Miyaura cross-coupling of 1-Bpinbiphenylene **102** with 4-iodobenzotrifluoride **117** (Scheme 2.34). The reaction worked well giving the desired product **118** in 84% yield. The potential to use the biphenylene moiety as either the aryl halide coupling partner or as the aryl boronate coupling partner further adds to the versatility of this synthetic approach because it increases the scope of coupling partners that can be used. For example, if a particular aryl group is not commercially available as the aryl boronic acid, it may be commercially available as the aryl halide.



Scheme 2.34 *Preparation of 1-(4-trifluoromethylphenyl)biphenylene **118** via Suzuki–Miyaura cross-coupling of **102** and **117**.*

Finally, it was necessary to prepare biphenylene substrates bearing a directing group in the 1-position to determine if pre-coordination of a directing group to the catalyst could affect the regioselectivity of the ring opening diborylation reaction. As discussed in the introduction, it has been shown that placing a pyridyl group in the 1-position of biphenylene directs the transition metal complex to the adjacent C-C bond. For this reason, it was necessary to prepare 1-(2-pyridyl)biphenylene **16**. The preparation of **16** by Suzuki–Miyaura cross-coupling was not attempted because 2-pyridylboronic acid would most likely undergo protodeboronation.[52] 1-(2-Pyridyl)biphenylene **16** was instead prepared by the Stille cross-coupling reaction of 1-iodobiphenylene with 2-tributylstannylpyridine **119**, to give **16** in 73% yield (Scheme 2.35). The reaction was

conducted using conditions reported by Matsubara *et al.* for the Stille cross-coupling of 1-bromobiphenylene with **119**.[60]



Scheme 2.35 *Preparation of 1-(2-pyridyl)biphenylene* ***16*** *via Stille cross-coupling of* ***93*** *with* ***119****.*

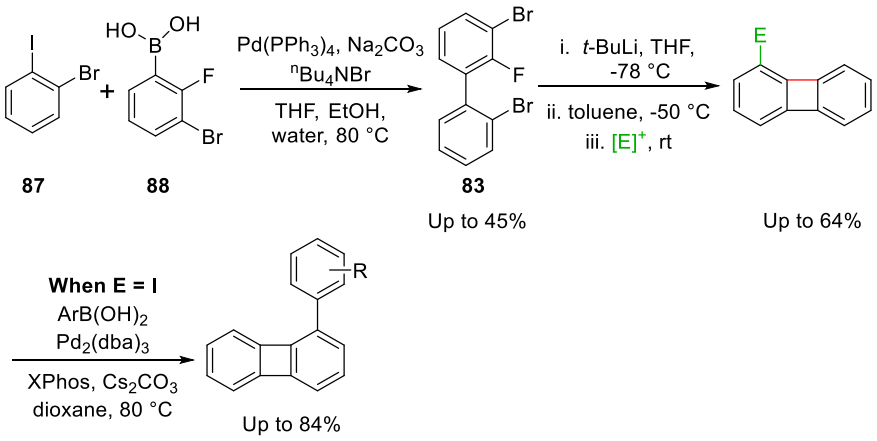
2.6. Summary and Future Work

Biphenylene and its substituted derivatives are attractive synthetic targets which have a range of applications. These applications include: 1) acting as spacers of functional molecules, 2) serving as a backbone for catalysts and ligands, and 3) as precursors to functionalised aromatic compounds, prepared by C-C activation. Despite this, the preparation of 1-monosubstituted biphenylenes is still challenging.

In this work, the recently published procedure of Wu *et al.*, in which biphenylenes bearing a substituent in the 1-position were prepared *via* an aryne cyclisation reaction, has been modified to prepare a wider range of 1-monosubstituted biphenylenes (Scheme 2.36). It was found that the biaryl **83** could be prepared in moderate yield *via* the Suzuki–Miyaura cross-coupling reaction of **87** and **88**. Biaryl **83** underwent aryne cyclisation and subsequent reaction with an electrophile to yield five 1-monosubstituted biphenylenes in good to moderate yields, in two steps from commercially available reagents.

In addition, conditions were found for the selective Suzuki–Miyaura cross-coupling reaction of 1-chloro, 1-iodo, and 1-Bpin biphenylene, in the presence of a strained C-C bond, with a variety of aryl boronic acids (and an aryl halide) in moderate to high yields. This gave synthetic access to a range of 1-arylsubstituted biphenylenes with varying steric and electronic properties in three or four steps starting from commercially available material.

In terms of further work it would be valuable to conduct a screening of conditions for the Suzuki–Miyaura cross-coupling reaction of **87** with **88**, since being able to access the biaryl **83** in higher yield would make this strategy much more attractive. $Pd(dba)_2$ and $Pd_2(dba)_3$ are commonly used sources of palladium (0), which would be worth investigating and different classes of ligand should be screened, to see if any are particularly effective. In addition, the use of anhydrous conditions with organic soluble bases would also be valuable to determine if water is the cause of the moderate yield.



Scheme 2.36 *Two-step preparation of different 1-monosubstituted biphenylenes, and three step preparation of 1-arylbiphenylenes.*

If appropriate conditions could not be found, it would also be advisable to investigate the use of an alternate boronate species. This would likely involve an additional step, since all but the corresponding pinacol boronic ester, which is significantly more expensive than **88,** are not commercially available. Boronate species that act as a slow release of boronic acid under the reaction conditions may give increased yields due to the suppression of potential side-reactions. Alternatively, the boronic acid **88** could be added portion-wise to the reaction mixture to avoid the need for an additional step.

In addition to optimising the Suzuki–Miyaura cross-coupling reaction, it would also be valuable to increase the scope of electrophiles that can be used in the aryne cyclisation reaction. This approach has the potential to give synthetic access to a range of 1-monosubstituted biphenylenes, which would otherwise be difficult to prepare. Other electrophiles that could be investigated include: DMF,[26,38] acetaldehyde,[27] carbon tetrabromide, and oxygen.[26]

2.7. Experimental

2.7.1. General Methods

All air sensitive reactions were conducted under an atmosphere of argon using standard Schlenk techniques or in an Innovative Technologies glovebox. Argon (Pureshield, >99.998%) was purchased from BOC and used as received. All glassware was heated to 120 °C in an oven and cooled under vacuum prior to use.

Nuclear Magnetic Resonance (NMR) spectra were recorded on Bruker AVIII HD 500 MHz, Bruker AVI 400 MHz, and Bruker AVIII HD 400 MHz spectrometers at ambient temperature. Chemical shifts are reported in ppm relative to a residual solvent peak ($CDCl_3$, δ 7.26 ppm for ^{1}H and 77.16 ppm for ^{13}C); 0.0 ppm chemical shifts of $CFCl_3$ and H_3PO_4 were used for referencing of ^{19}F and ^{31}P, respectively. The splitting patterns are reported as follows s (singlet), d (doublet), t (triplet), q (quartet), spt (septet), m (multiplet), dd (doublet of doublets), dt (doublet of triplets), br. s (broad singlet). The coupling constants *J* are given in Hertz.

HRMS were recorded using the analytical service in the Chemistry Department at the University of Liverpool. HRMS were conducted on either an Agilent QTOF 7200 or an Agilent QTOF 6540 using chemical ionisation (CI) or electrospray (ESI), respectively.

Gas chromatography analyses for the Suzuki–Miyaura cross-coupling of 1-chlorobiphenylene were conducted on an Agilent 7890 Gas chromatograph fitted with a HP-5 column (length: 30 m, ID: 0.32 mm, FT: 0.25 µm) and an FID detector. The carrier gas used was helium. The following GC oven temperature programme was used: 80 °C hold for 5 min, ramp 40 °C/min to a final temperature of 150 °C and hold for 5 min, ramp 15 °C/min to a final temperature of 250 °C and hold for 10 min.

Gas chromatography-Mass Spectra (GCMS) analyses were conducted on a Thermo Scientific ISQ single quadrupole instrument equipped with a HP-1 column (length: 30m, ID: 0.32 mm, FT: 0.25 µm). The carrier gas used was helium and the ionisation mode was EI. The following GC oven temperature programme was used: 80 °C hold for 2 min, ramp 20 °C/min to a final temperature of 250 °C and hold for 7 min.

Analytical thin-layer chromatography (TLC) was performed on Merck F254 TLC silica gel 60 TLC plates (visualising with UV light (254 nm)). Column chromatography was performed using VWR silica gel 40-63 μm.

Unless otherwise stated, all chemicals were obtained from commercial suppliers and used without further purification. $Pd_2(dba)_3$, $Pd(PPh_3)_4$, (3-bromo-2-fluorophenyl) boronic acid, 2-bromoiodobenzene, and XPhos were obtained from Fluorochem. 1-Chlorobiphenylene was prepared according to the literature procedure.[38,40] Iodomethane and n-dodecane were degassed by freeze-pump thaw technique (3 cycles) and stored over molecular sieves.

Dry dioxane was purchased from Acros. Unless otherwise stated all other solvents were dried over the appropriate drying agent and distilled under argon. THF, ether and toluene were refluxed over sodium, using benzophenone as an indicator. All distilled solvents were stored in either Sure-Store flasks under argon or in an Innovative Technologies glovebox. Unless otherwise noted the stated reaction temperature is the temperature of the oil bath.

2.7.2. Screening Conditions for the Suzuki–Miyaura Cross-Coupling Reaction of 1-Chlorobiphenylene with Phenylboronic Acid

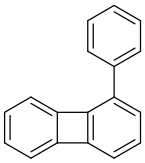
General Procedure

When the screening was begun, 1-phenylbiphenylene was not available. The GC yields were therefore calculated assuming that the response factor of 1-phenylbiphenylene is 1.

A stock solution of 1-chlorobiphenylene (0.2 mmol) and n-dodecane (internal standard for GC, 0.1 mmol) in dioxane (0.6 mL) was added to a 4 mL vial that had been charged with the metal precursor (1.5 - 3 mol%), ligand (3 - 6 mol%), base (0.4 mmol), and phenylboronic acid (0.3 mmol). The reaction mixture was stirred (600 rpm) at the stated temperature for 16 h. The reaction mixture was cooled to room temperature, filtered through celite, and washed through with EtOAc until no compound was visible by UV on a TLC plate. The filtrate was analysed by GC.

2.7.3. Synthesis of 1-Arylbiphenylenes *via* the Suzuki–Miyaura Cross-Coupling of 1-Chlorobiphenylene

Synthesis of 1-Phenylbiphenylene 76 from 1-Chlorobiphenylene 75, Using BrettPhos as the Ligand



A Schlenk bomb was charged with $Pd_2(dba)_3$ (20.6 mg, 0.0225 mmol), BrettPhos (24.4 mg, 0.0455 mmol), Cs_2CO_3 (0.984 g, 3.02 mmol), and phenylboronic acid (276.0 mg, 2.263 mmol). The Schlenk bomb was evacuated and backfilled with argon. To the Schlenk bomb was added a solution of 1-chlorobiphenylene (282.0 mg, 1.511 mmol) in dioxane (4.5 mL). The reaction mixture was stirred (600 rpm) at 80 °C for 16 h. The reaction mixture was cooled to room temperature, filtered through celite, and washed through with EtOAc until no compound was visible by UV on a TLC plate. The solvent was removed under reduced pressure to give the crude product. The crude product was purified by flash column chromatography (silica gel, hexane) to give **76** as a yellow oil (230 mg, 1.01 mmol, 67%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.5 Hz, 2H, CH), 7.45 (t, *J* = 7.5 Hz, 2H, CH), 7.35 (t, *J* = 7.2 Hz, 1H, CH), 7.00 (d, *J* = 8.4 Hz, 1H, CH), 6.87 – 6.84 (m, 1H, CH), 6.79 – 6.76 (m, 3H, CH), 6.70 – 6.66 (m, 1H, CH), 6.62 (d, *J* = 6.7 Hz, 1H, CH). The ^{1}H NMR data was consistent with that reported in the literature.[44]

General Procedure for the Synthesis of 1-Arylbiphenylenes from 1-Chlorobiphenylene, Using XPhos as the Ligand

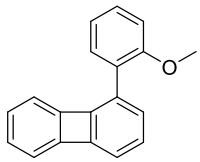
A Schlenk bomb was charged with $Pd_2(dba)_3$ (3-10 mol%), XPhos (6-20 mol%), Cs_2CO_3 (2 eq.), and arylboronic acid (1.5 eq.). The Schlenk bomb was evacuated and backfilled with argon. To the Schlenk bomb was added a solution of 1-chlorobiphenylene (1 eq.) in dioxane (0.33 M). The reaction mixture was stirred (600 rpm) at the stated temperature for the stated time. The reaction mixture was cooled to room temperature, filtered through celite, and washed through with EtOAc until no compound was visible by UV on a TLC plate. The solvent was removed under reduced

pressure to give the crude product. The crude product was purified by flash column chromatography.

Synthesis of 1-Phenylbiphenylene, 76

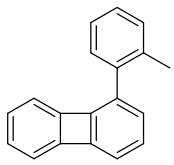
The reaction was conducted according to the general procedure using $Pd_2(dba)_3$ (35.5 mg, 0.0388 mmol), XPhos (37.0 mg, 0.0776 mmol), Cs_2CO_3 (0.850 g, 2.61 mmol), phenylboronic acid (238.0 mg, 1.951 mmol), 1-chlorobiphenylene (241.0 mg, 1.291 mmol), and dioxane (3.9 mL). The reaction mixture was stirred (600 rpm) at 80 °C for 20 h. The crude product was purified by flash column chromatography (silica gel, 0-5% EtOAc in hexane) to give **76** as a yellow oil (224 mg, 0.981 mmol, 76%). A yellow gum was isolated (33 mg). The NMR spectrum was inconclusive, and GC-MS showed that a mixture of around 20 different components were present.

Attempted Synthesis of 1-(2-Methoxyphenyl)biphenylene, 78



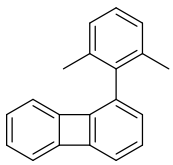
The reaction was conducted according to the general procedure using $Pd_2(dba)_3$ (21.4 mg, 0.0234 mmol), XPhos (23.0 mg, 0.0482 mmol), Cs_2CO_3 (0.390 g, 1.20 mmol), 2-methoxyphenylboronic acid (137.0 mg, 0.9016 mmol), 1-chlorobiphenylene (112.0 mg, 0.6001 mmol), and dioxane (1.8 mL). The reaction mixture was stirred (600 rpm) at 80 °C for 18 h. Upon heating reaction mixture turned from dark brown to green. The reaction mixture was stirred (600 rpm) at 100 °C for 24 h. The reaction mixture was stirred (600 rpm) at 120 °C for 48 h. The crude product was purified by flash column chromatography (2.5% EtOAc in hexane) to give **78** as a yellow solid (83 mg). Also contained a small impurity, ~50% yield. For NMR see page 98. A yellow oil was isolated (22 mg, 0.12 mmol, 19%) and was consistent with starting material. An orange oil was isolated (29 mg). The NMR spectrum of this oil was inconclusive.

Synthesis of 1-(2-Methylphenyl)biphenylene, 80



The reaction was conducted according to the general procedure using $Pd_2(dba)_3$ (41.2 mg, 0.0450 μmol), XPhos (42.5 mg, 0.0892 mmol), Cs_2CO_3 (0.390 g, 1.20 mmol), 2-methylphenylboronic acid (122.0 mg, 0.8973 mmol), 1-chlorobiphenylene (112.0 mg, 0.6001 mmol), and dioxane (1.8 mL). The reaction mixture was stirred (600 rpm) at 80 °C for 24 h. The crude product was purified by flash column chromatography (silica gel, hexane) to give **80** as a yellow solid (93 mg, 0.38 mmol, 64%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.29 – 7.24 (m, 4H, CH), 6.81 (t, *J* = 7.5 Hz, 1H, CH), 6.74 – 6.61 (m, 5H, CH), 6.39 (d, *J* = 6.6 Hz, 1H, CH), 2.37 (s, 3H, CH_3), **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 151.7 (C), 151.4 (C), 151.1 (C), 149.4 (C), 137.8 (C), 135.7 (C), 132.0 (C), 130.6 (CH), 130.0 (CH), 129.1 (CH), 128.6 (CH), 128.3 (CH), 128.3 (CH), 127.8 (CH), 126.0 (CH), 117.9 (CH), 117.3 (CH), 116.1 (CH), 20.0 (CH_3). **HRMS** (CI^+) m/z: calculated for $(C_{19}H_{14}+H)^+$ 243.1174, found 243.1178.

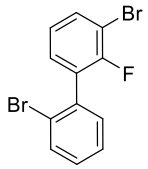
Synthesis of 1-(2,6-Dimethylphenyl)biphenylene, 82



The reaction was conducted according to the general procedure using $Pd_2(dba)_3$ (54.8 mg, 0.0598 mmol), XPhos (56.3 mg, 0.0120 mmol), Cs_2CO_3 (0.390 g, 1.20 mmol), 2,6-dimethylphenylboronic acid (135.0 mg, 0.9001 mmol), 1-chlorobiphenylene (113.0 mg, 0.6054 mmol), and dioxane (1.8 mL). The reaction mixture was stirred (600 rpm) at 80 °C for 24 h. The crude product was purified by flash column chromatography (silica gel, hexane) to give **82** as a yellow oil (112 mg, 0.437 mmol, 72%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.17 – 7.09 (m, 3H, CH), 6.82 – 6.78 (m, 1H, CH), 6.74 – 6.63 (m, 4H, CH), 6.56 (d, *J* = 6.7 Hz, 1H, CH), 6.24 (d, *J* = 6.7 Hz, 1H, CH), 2.21 (s, 6H, CH_3), **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 151.7 (C), 151.5 (C), 151.3 (C), 149.6 (C), 137.3 (C), 136.2 (2C), 130.8 (C), 130.3 (CH), 128.6 (CH), 128.4 (CH), 128.3 (CH), 127.5 (2CH), 127.4 (CH), 117.5 (CH), 117.4 (CH), 116.1 (CH), 20.6 ($2CH_3$). **HRMS** (CI^+) m/z: calculated for $(C_{20}H_{16}+H)^+$ 257.1330, found 257.1332.

2.7.4. Preparation of 2',3-Dibromo-2-fluoro-1,1'-biphenyl, 83

Representative Procedure for the Preparation of 2',3-Dibromo-2-fluoro-1,1'-biphenyl, 83



THF, water, and ethanol were degassed by bubbling argon through them for 15 min and the reaction was conducted under an atmosphere of argon.

A round bottom flask fitted with a condenser was charged with $Pd(PPh_3)_4$ (0.520 g, 0.450 mmol), Na_2CO_3 (2.383 g, 22.48 mmol), $^nBu_4NBr$ (2.904 g, 9.008 mmol), (3-bromo-2-fluorophenyl) boronic acid (2.359 g, 10.78 mmol), and 2-bromoiodobenzene (2.576 g, 9.106 mmol). To the round bottom flask was next added THF (30 mL), EtOH (15 mL), and water (15 mL) to give a yellow suspension. The reaction mixture was stirred (600 rpm) at 80 °C for 44 h. The reaction mixture was beige in colour. Additional $Pd(PPh_3)_4$ (0.520 g, 0.450 mmol) was added to the reaction mixture. The reaction mixture was stirred (600 rpm) at 80 °C for a further 20 h. The reaction mixture was cooled to room temperature and the organic solvent was removed under reduced pressure. The resulting residue was diluted with water (60 mL) and EtOAc (60 mL). The two phases were separated. The aqueous phase was extracted with EtOAc (2 x 60 mL). The combined organic layers were washed with water (2 x 60 mL), dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexane) to give **83** as a colourless oil (1.130 g, 3.424 mmol, 38 %). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.0 Hz, 1H, CH), 7.60 (t, *J* = 7.2 Hz, 1H, CH), 7.38 (t, *J* = 7.5 Hz, 1H, CH), 7.30 – 7.21 (m, 3H, CH), 7.1 (t, *J* = 7.8 Hz, 1H, CH). **^{19}F{^{1}H} NMR** (377 MHz, $CDCl_3$) δ -107.26. **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 156.0 (d, *J* = 248.3 Hz, C), 136.3 (C), 133.5 (CH), 133.0 (CH), 131.6 (CH), 130.8 (d, *J* = 2.5 Hz, CH), 130.3 (d, *J* = 17.2 Hz, C), 130.0 (CH), 127.4 (CH), 124.8 (d, *J* = 4.6 Hz, CH), 123.7 (C), 109.6 (d, *J* = 21.7, C). **HRMS** (CI^+) m/z: calculated for $(C_{12}H_7Br_2F+H)^+$ 328.8977, found 328.8972. A mixture of 2-bromoiodobenzene **87** (41%) and 2-fluorobromobenzene **90** (11% relative to **88**) was isolated as a colourless oil (1.27 g). **90 ^{1}H NMR** (400 MHz, $CDCl_3$)

δ 7.57-7.53 (m, 1H), 7.31-7.27 (m, 1H), 7.14-7.10 (m, 1H), 7.05-7.01 (m, 1H). The ^{1}H NMR data was consistent with that reported by Sigma Aldrich.

It is of note that in all the reactions listed in the table 2.2, starting material remained at the end of the reaction by TLC. Since we were interested in the desired product, time was not spent isolating the starting material to determine the conversion in some of the later reactions, which is why not determined (n/d) is given for the conversion in some cases.

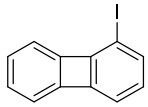
Synthesis of 2',3-Dibromo-2-fluoro-1,1'-biphenyl 83 Using the Method of Larsen *et al.* [53]

DME and water were degassed by bubbling argon through them for 15 min.

A round bottom flask fitted with a condenser was charged with $[PdCl_2(PPh_3)_2]$ (95.0 mg, 0.135 mmol), K_2CO_3 (3.118 g, 22.56 mmol), (3-bromo-2-fluorophenyl) boronic acid (1.968 g, 8.994 mmol), and 2-bromoiodobenzene (2.557 g, 9.039 mmol). To the round bottom flask was next added DME (27 mL) and water (3.6 mL). The reaction mixture was pale yellow in colour. The reaction mixture was stirred (600 rpm) at 80 °C for 3 h. Additional (3-bromo-2-fluorophenyl) boronic acid (198 mg, 0.905 mmol) was added to the reaction mixture. The reaction mixture was stirred (600 rpm) at 80 °C for a further 16 h. Additional $[PdCl_2(PPh_3)_2]$ (95.0 mg, 0.135 mmol) was added to the reaction mixture. The reaction mixture was stirred (600 rpm) at 80 °C for a further 24 h. DME was removed under reduced pressure. The resulting residue was diluted with water (40 mL) and extracted with ether (3 x 40 mL). The combined organic layers were washed with brine (40 mL), dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexane) to give **83** as a colourless oil (1.015 g, 3.076 mmol, 34%). A mixture of 2-bromoiodobenzene **87** (50%) and 2-fluorobromobenzene **90** (13% relative to **88**) was isolated as a colourless oil (1.500 g).

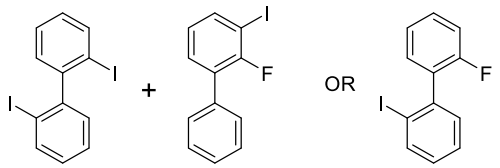
2.7.5. Preparation of 1-Iodobiphenylene 93 *via* Aryne Cyclisation

1-Iodobiphenylene 93



Large Scale Synthesis of 1-Iodobiphenylene 93 from 2',3-Dibromo-2-fluoro-1,1'-biphenyl 83

A round bottom flask was charged with 2',3-dibromo-2-fluoro-1,1'-biphenyl (2.097 g, 6.355 mmol) and THF (32 mL). The resulting solution was cooled to -78 °C and a 1.7 M solution of *t*-BuLi in pentane (15.0 mL, 25.4 mmol) was added dropwise over a period of 40 min to give a yellow reaction mixture. The reaction mixture was stirred (500 rpm) at -78 ºC for 1 h. To the reaction mixture at -78 ºC was slowly added toluene (95 mL) over a period of 25 min. The reaction mixture was then warmed to -30 ºC and stirred (500 rpm) at that temperature for 1 h. To the reaction mixture was added iodine (1.940 g, 7.644 mmol), following the addition the reaction mixture turned orange. The reaction mixture was warmed to room temperature and stirred (500 rpm) at that temperature for 1 h. To the reaction mixture was added a solution of sodium thiosulfate (60 mL, 1M). The reaction mixture turned pale yellow in colour. The two phases were separated. The aqueous phase was extracted with EtOAc (2 x 60 mL). The combined organic layers were washed with water (2 x 60 mL), dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexane) to give **93** as a pale-yellow oil (1.100 g, 3.956 mmol, 62 %), which was contaminated with <2% biphenylene. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.95 (d, *J* = 8.6 Hz, 1H, CH), 6.84 – 6.73 (m, 3H, CH), 6.67 – 6.65 (m, 1H, CH), 6.58 (d, *J* = 6.7 Hz, 1H, CH), 6.45 (dd, *J* = 9.1, 6.8 Hz, 1H, CH), **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 156.8 (C), 152.9 (C), 151.2 (C), 149.7 (C), 136.3 (CH), 129.9 (CH), 129.3 (CH), 128.8 (CH), 117.9 (CH), 116.6 (2CH), 80.8 (C). **HRMS** (CI^+) m/z calculated for $(C_{12}H_7I+H)^+$ 278.9671, found 278.9661. The ^{1}H NMR data was consistent with that reported in the literature.[25]



96 **98a** **98b**

A white solid (136 mg) was also isolated and was found to predominantly contain **96**. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.0 Hz, 2H, CH), 7.45-7.40 (m, 2H, CH), 7.20 (dd, *J* = 7.4, 1.6 Hz, 2H, CH), 7.10 (t,d, *J* = 7.7, 1.6 Hz, 2H, CH). The ^{1}H NMR data was consistent with that reported in the literature.[61] An ion with a m/z consistent with **98** was observed by GC-MS.

Small Scale Synthesis of 1-Iodobiphenylene 93 from 2',3-Dibromo-2-fluoro-1,1'-biphenyl 83 General Procedure (Table 2.3, Entries 1 and 2).

A round bottom flask was charged with 2',3-dibromo-2-fluoro-1,1'-biphenyl (0.40 mmol) and ether (2 mL). The resulting solution was cooled to -100 °C and a 1.7 M solution of *t*-BuLi in pentane (1.2 mmol) was added dropwise to give a pale-yellow solution. The reaction mixture was stirred (600 rpm) at -100 °C for 1 h. The reaction mixture was warmed to -78 °C and stirred (600 rpm) at that temperature for 1 h. To the reaction mixture was added toluene (2 mL). The reaction mixture was warmed to the stated temperature and stirred (600 rpm) at that temperature for 1 h. To the reaction mixture was added iodine (0.60 mmol). The reaction mixture was warmed to room temperature and stirred at that temperature for 1 h. To the reaction mixture was added water (4 mL) and EtOAc (4 mL). The two phases were separated. The aqueous phase was extracted with EtOAc (2 x 4 mL). The combined organic layers were washed with water (2 x 4 mL), dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography.

Table 2.3, Entry 1

The reaction was conducted according to the general procedure using 2',3-dibromo-2-fluoro-1,1'-biphenyl (131 mg, 0.397 mmol), ether (2 mL), 1.7 M solution of *t*-BuLi in pentane (0.70 mL, 1.2 mmol), toluene (2 mL), and iodine (151 mg, 0.595 mmol). The temperature was increased to -50 °C following stirring at -78 °C for 1 h. The crude product was purified by flash column chromatography (silica gel, hexane) to give **93** as a yellow oil (28 mg, 0.10 mmol) in 25% yield. An orange gum (53 mg) was also isolated, and NMR of this gum was inconclusive.

Table 2.3, Entry 2

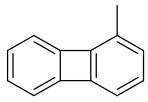
The reaction was conducted according to the general procedure using 2',3-dibromo-2-fluoro-1,1'-biphenyl (131 mg, 0.397 mmol), ether (2 mL), 1.7 M solution of *t*-BuLi in pentane (0.70 mL, 1.2 mmol), toluene (2 mL), and iodine (151 mg, 0.595 mmol). The temperature was increased to -30 °C following stirring at -78 °C for 1 h. The crude product was purified by flash column chromatography (silica gel, hexane) to give impure **93** as a yellow oil (20 mg, 70 μmol, ~18%). An orange solid (52 mg) was also isolated, and NMR of this solid was inconclusive.

Small Scale Synthesis of 1-Iodobiphenylene from 2',3-Dibromo-2-fluoro-1,1'-biphenyl (Table 2.3, Entry 3)

A round bottom flask was charged with 2',3-dibromo-2-fluoro-1,1'-biphenyl (147 mg, 0.445 mmol) and THF (2.2 mL). The resulting solution was cooled to -78 °C and a 1.7 M solution of *t*-BuLi in pentane (1.06 mL, 1.80 mmol) was added dropwise to give a yellow reaction mixture. The reaction mixture was stirred (600 rpm) at -78 ºC for 1 h. To the reaction mixture at -78 ºC was slowly added toluene (6.7 mL). The reaction mixture was then warmed to -30 ºC and stirred (600 rpm) at that temperature for 1 h. To the reaction mixture was added iodine (137 g, 0.540 mmol), following the addition the reaction mixture turned orange. The reaction mixture was warmed to room temperature and stirred (500 rpm) at that temperature for 1 h. To the reaction mixture was added water (5 mL). The reaction mixture turned pale yellow in colour. The two phases were separated. The aqueous phase was extracted with EtOAc (2 x 60 mL). The combined organic layers were washed with water (2 x 5 mL), dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexane) to give **93** as a pale-yellow oil (53 mg, 0.19 mmol, 42 %).

2.7.6. Preparation of 1-Monosubstituted Biphenylenes *via* Aryne Cyclisation

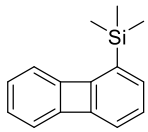
1-Methylbiphenylene, 99



A round bottom flask was charged with 2',3-dibromo-2-fluoro-1,1'-biphenyl (495 mg, 1.50 mmol) and THF (7.5 mL). The resulting solution was cooled to -78 °C and a 1.7 M solution of *t*-BuLi in pentane (3.5 mL, 6.0 mmol) was added dropwise to give a yellow reaction mixture. The reaction mixture was stirred (600 rpm) at -78 ºC for 1 h. To the reaction mixture at -78 ºC was slowly added toluene (22.5 mL) over a period of 10 min. The reaction mixture was warmed to -30 ºC and stirred (600 rpm) at that temperature for 1 h. The reaction mixture turned dark green in colour. At -30 ºC iodomethane (187 μL, 3.00 mmol) was added dropwise. The reaction mixture was warmed to room temperature and stirred (600 rpm) at that temperature for 1 h. To the reaction mixture was added water (15 mL). The two phases were separated. The aqueous phase was extracted with EtOAc (2 x 15 mL). The combined organic layers were washed with water (2 x 15 mL), dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexane) to give **99** as a yellow oil (126 mg, 0.758 mmol, 50%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.75 – 6.59 (m, 5H, CH), 6.54 (d, *J* = 8.3 Hz, 1H, CH), 6.48 (d, *J* = 6.7 Hz, 1H, CH), 2.1 (s, 3H, CH_3). The ^{1}H NMR data was consistent with that reported in the literature.[55]

A yellow gum (46 mg) was also isolated. By GC-MS this contained **104**, **105**, **107**, and **108**.

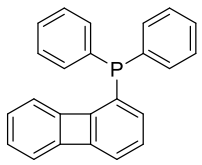
1-(Trimethylsilyl)biphenylene, 100



A round bottom flask was charged with 2',3-dibromo-2-fluoro-1,1'-biphenyl (331 mg, 1.00 mmol) and THF (5 mL). The resulting solution was cooled to -78 °C and a 1.7 M solution of *t*-BuLi in pentane (2.4 mL, 4.0 mmol) was added dropwise to give a yellow

reaction mixture. The reaction mixture was stirred (600 rpm) at -78 ºC for 1 h. To the reaction mixture at -78 ºC was slowly added toluene (15 mL) over a period of 5 min. The reaction mixture was warmed to -30 ºC and stirred (600 rpm) at that temperature for 1 h. The reaction mixture turned dark green in colour. To the reaction mixture was added TMSCl (254 μL, 2.00 mmol) dropwise, the reaction mixture remained dark green. The reaction mixture was warmed to room temperature and stirred (600 rpm) at that temperature for 1 h. To the reaction mixture was added water (10 mL). The two phases were separated. The aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with water (2 x 10 mL), dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexane) to give **100** as a yellow oil (145 mg, 0.646 mmol, 64 %). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.82 (d, *J* = 8.0 Hz, 1H, CH), 6.74 - 6.69 (m, 3H, CH), 6.66 - 6.60 (m, 3H, CH), 0.26 (s, 9H, CH_3). The ^{1}H NMR data was consistent with that reported in the literature.[44]

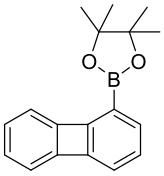
1-Diphenylphosphinebiphenylene, 101



A round bottom flask was charged with 2',3-dibromo-2-fluoro-1,1'-biphenyl (497 mg, 1.51 mmol) and THF (7.5 mL). The resulting solution was cooled to -78 °C and a 1.7 M solution of *t*-BuLi in pentane (3.5 mL, 6.0 mmol) was added dropwise over a period of 10 min to give a yellow reaction mixture. The reaction mixture was stirred (600 rpm) at -78 ºC for 1 h. To the reaction mixture at -78 ºC was slowly added toluene (22.5 mL) over a period of 10 min. The reaction mixture was warmed to -30 ºC and stirred (600 rpm) at that temperature for 1 h. At -30 ºC diphenylchlorophosphine (0.55 mL, 3.0 mmol) was added dropwise to give a dark brown reaction mixture. The reaction mixture was warmed to room temperature and stirred (600 rpm) at that temperature for 1 h. To the reaction mixture was added water (15 mL). The two phases were separated. The aqueous phase was extracted with EtOAc (2 x 15 mL). The combined organic layers were washed with water (2 x 15 mL), dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 1% EtOAc in hexane) followed

by recrystallisation in EtOH to give **101** as a yellow solid (186 mg, 0.553 mmol, 37 %). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51- 7.46 (m, 4H, CH), 7.38 – 7.36 (m, 6H, CH), 6.72 – 6.57 (m, 5H, CH), 6.50 (t, *J* = 5.0 Hz, 1H, CH), 5.32 (d, *J* = 6.9 Hz, 1H, CH), **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 155.7 (d, *J* = 12.0 Hz, C), 151.7 (C), 151.65 (C), 151.6 (C), 151.0 (C), 136.3 (d, *J* = 10.2 Hz, 2C), 133.9 (d, *J* = 19.9 Hz, 4CH), 132.5 (d, *J* = 20.7 Hz, CH), 129.0 (2CH), 128.8 (d, *J* = 7.2 Hz, 4CH), 128.5 (2CH), 128.3 (CH), 118.9 (CH), 117.2 (CH), 116.9 (CH), **^{31}P{^{1}H} NMR** (162 MHz $CDCl_3$) δ -12.0. **HRMS** (CI^+) m/z: calculated for $(C_{24}H_{17}P+H)^+$ 337.1146, found 337.1154.

1-Bpinbiphenylene, 102



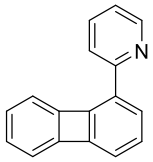
A round bottom flask was charged with 2',3-dibromo-2-fluoro-1,1'-biphenyl (990 mg, 3.00 mmol) and THF (15 mL). The resulting solution was cooled to -78 °C and a 1.7 M solution of *t*-BuLi in pentane (7.0 mL, 12 mmol) was added dropwise to give a yellow reaction mixture. The reaction mixture was stirred (600 rpm) at -78 ºC for 1 h. To the reaction mixture at -78 ºC was slowly added toluene (45 mL) over a period of 15 min. The reaction mixture was warmed to -30 ºC and stirred (600 rpm) at that temperature for 1 h. At -30 ºC isopropoxyboronic acid pinacol ester (1.3 mL, 6.4 mmol) was added dropwise to give a brown reaction mixture. The reaction mixture was warmed to room temperature and stirred (600 rpm) at that temperature for 1 h. To the reaction mixture was added water (30 mL). The two phases were separated. The aqueous phase was extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with water (2 x 30 mL), dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 4% EtOAc in hexane) to give **102** as a yellow oil (276 mg, 0.992 mmol, 42%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.05 (d, *J* = 8.1 Hz, 1H, CH), 6.85 (d, *J* = 6.2 Hz, 1H, CH), 6.79 – 6.70 (m, 3H, CH), 6.66 (d, *J* = 6.5 Hz, 1H, CH), 6.63 (d, *J* = 6.3 Hz, 1H, CH), **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 159.9 (C), 152.6 (C), 152.0 (C), 151.0 (C), 132.7 (CH), 128.7 (CH), 128.5 (CH), 127.5 (CH), 119.1 (CH), 119.0 (CH), 117.5 (CH), 83.8 (2C), 25.1 (CH_3). One quaternary carbon signal is not

observed. **HRMS** (CI^+) m/z: calculated for $(C_{18}H_{19}BO_2+H)^+$ 279.1556, found 279.1553.

On a silica TLC plate, substantial tailing of **102** was observed. TLC was also run using alumina TLC plates; however, this gave no improvement over silica, which is why purification using an alumina column was not attempted. Following purification by silica flash column chromatography some impurities were still present in the product by proton NMR. The crude product was therefore purified by silica column a second time, using a less polar eluent to try to improve the separation. During the second column it became clear that spots that had been removed during the first column were present by TLC. This is most likely because of uneven over-adsorption of **102**.

2.7.7. Cross-Coupling Reactions of 1-Iodobiphenylene and 1-BpinBiphenylene

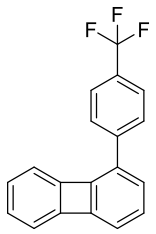
1-(2-Pyridyl)biphenylene, 16



A Schlenk bomb was charged with $PdCl_2(PPh_3)_2$ (11.5 mg, 0.0164 mmol), LiCl (135 mg, 3.18 mmol), 1-iodobiphenylene (222.5 mg, 0.8001 mmol), and toluene (4 mL). To this suspension was added 2-(tributylstannyl)pyridine (0.31 mL, 0.96 mmol) to give a dark brown reaction mixture. The Schlenk bomb was sealed and the reaction mixture stirred (600 rpm) at 110 °C for 16 h. The reaction mixture was cooled to room temperature. To the reaction mixture was added a saturated solution of KF (4 mL). The reaction mixture was stirred (600 rpm) at room temperature for 30 min. The reaction mixture was filtered and washed with DCM (2 x 4 mL). The two phases were separated. The aqueous phase was extracted with DCM (2 x 4 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 5% EtOAc in hexane) to give **16** as a yellow oil (135 mg, 0.589 mmol, 73%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.72 – 8.70 (m, 1H, CH), 7.76 (td, *J* =7.6, 3.4 Hz, 1H, CH), 7.63 (d, *J* = 7.9 Hz, 1H, CH), 7.41 (d, *J* = 8.5 Hz, 1H, CH), 7.22 (dd, *J*

= 7.5, 1.9 Hz, 1H, CH), 6.95 – 6.93 (m, 1H, CH), 6.88 (dd, *J* = 8.5, 5.1 Hz, 1H, CH), 6.80 (dd, *J* = 5.2, 2.6 Hz, 2H, CH), 6.70 – 6.68 (m, 1H, CH), 6.66 (d, *J* = 6.6 Hz, 1H, CH). The ^{1}H NMR data was consistent with that reported in the literature.[60]

1-(4-(Trifluoromethyl)phenyl)biphenylene, 118



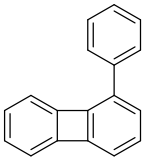
A Schlenk bomb was charged with $Pd_2(dba)_3$ (53.6 mg, 0.0585 mmol), Cs_2CO_3 (381 mg, 1.17 mmol), XPhos (56.0 mg, 0.117 mmol), and 4-iodotrifluoromethylbenzene (175 µL, 1.17 mmol). To the Schlenk bomb was added a solution of 1-Bpinbiphenylene (217 mg, 0.780 mmol) in dioxane (1.8 mL) to give a brown suspension. The Schlenk bomb was sealed and the reaction mixture stirred (600 rpm) at 80 °C for 24 h. The reaction mixture was cooled to room temperature. The reaction mixture was filtered through celite and washed through with EtOAc (~200 mL) until no compound was visible by UV on a TLC plate. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (silica gel, hexane) to give **118** as a yellow solid (195 mg, 0.658 mmol, 84 %). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71 – 7.67 (m, 4H, CH), 6.98 (d, *J* = 8.5 Hz, 1H, CH), 6.88 (t, *J* = 7.6 Hz, 1H, CH), 6.82 – 6.73 (m, 3H, CH), 6.69 (d, *J* = 6.2 Hz, 1H, CH), 6.66 (d, *J* = 6.8 Hz, 1H, CH), **^{19}F{^{1}H} NMR** (377 MHz, $CDCl_3$) δ -62.45, **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 151.8 (C), 151.3 (C), 150.9 (C), 148.7 (C), 141.1 (C), 130.0 (C), 129.8 (q, *J* = 32.6 Hz, C), 129.7 (CH), 129.0 (CH), 128.6 (CH), 126.9 (CH), 126.8 (2CH), 125.9 (q, *J* = 3.8 Hz, 2CH), 139.3 (q, *J* = 272.0 Hz, C), 118.1 (CH), 117.8 (CH), 117.0 (CH). **HRMS** (CI^+) m/z: calculated for $(C_{19}H_{11}F_3+H)^+$ 297.0891, found 297.0887.

General Procedure for the Preparation of 1-Aryl Substituted Biphenylenes from 1-Iodobiphenylene

A Schlenk bomb was charged with $Pd_2(dba)_3$ (7.5 mol%), XPhos (15 mol%), Cs_2CO_3 (1.5 – 2 eq.), and arylboronic acid (1.5 eq.). The Schlenk bomb was evacuated and backfilled with argon. To the Schlenk bomb was added a solution of 1-

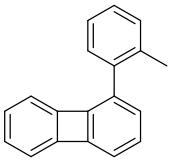
iodobiphenylene (1 eq.) in dioxane. The Schlenk bomb was sealed and the reaction mixture stirred (600 rpm) at 80 °C for 24 h. The reaction mixture was cooled to room temperature. The reaction mixture was filtered through celite and washed through with EtOAc (~200 mL) until no compound was visible by UV on a TLC plate. The solvent was removed under reduced pressure to give the crude product. The crude product was purified by flash column chromatography.

1-Phenylbiphenylene, 76



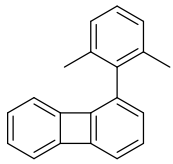
The reaction was conducted according to the general procedure, using $Pd_2(dba)_3$ (41.5 mg, 0.0453 mmol), XPhos (43.2 mg, 0.0906 mmol), Cs_2CO_3 (391 mg, 1.20 mmol), phenylboronic acid (110.3 mg, 0.9046 mmol), 1-iodobiphenylene (167.0 mg, 0.6005 mmol), and dioxane (1.4 mL). The crude product was purified by flash column chromatography (silica gel, hexane). Compound **76** was isolated as a pale-yellow oil (114 mg, 0.499 mmol, 83%). Characterisation data is as was reported on page 83.

1-(*o*-Tolyl)biphenylene, 80



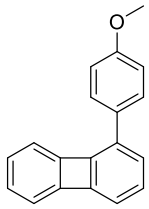
The reaction was conducted according to the general procedure, using $Pd_2(dba)_3$ (55.0 mg, 0.0601 mmol), XPhos (56.5 mg, 0.119 mmol), Cs_2CO_3 (522 mg, 1.60 mmol), *o*-tolylboronic acid (162.0 mg, 1.192 mmol), 1-iodobiphenylene (223.0 mg, 0.8019 mmol), and dioxane (2.4 mL). The crude product was purified by flash column chromatography (silica gel, 2% EtOAc in hexane). Compound **80** was isolated as a yellow solid (140 mg, 0.578 mmol, 72%). Characterisation data is as was reported on page 85.

1-(2,6-Dimethylphenyl)biphenylene, 82



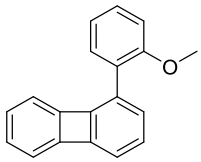
The reaction was conducted according to the general procedure, using $Pd_2(dba)_3$ (54.9 mg, 0.0600 mmol), XPhos (57.2 mg, 0.120 mmol), Cs_2CO_3 (388 mg, 1.19 mmol), (2,6-dimethyl)phenylboronic acid (137.0 mg, 0.9135 mmol), 1-iodobiphenylene (225.0 mg, 0.8091 mmol), and dioxane (1.8 mL). The crude product was purified by flash column chromatography (silica gel, hexane). Compound **82** was isolated as a yellow oil (156 mg, 0.609 mmol, 76 %). Characterisation data is as was reported on page 85.

1-(4-Methoxyphenyl)biphenylene, 112



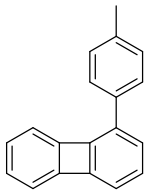
The reaction was conducted according to the general procedure, using $Pd_2(dba)_3$ (55.1 mg, 0.0602 mmol), XPhos (57.0 mg, 0.120 mmol), Cs_2CO_3 (390 mg, 1.20 mmol), 4-methoxyphenyl boronic acid (182.0 mg, 1.198 mmol), 1-iodobiphenylene (225.0 mg, 0.8091 mmol), and dioxane (1.8 mL). The crude product was purified by flash column chromatography (silica gel, 2% EtOAc in hexane). Compound **112** was isolated as a yellow solid (168 mg, 0.650 mmol, 81%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.6 Hz, 2H, CH), 7.00 (d, *J* = 8.7 Hz, 2H, CH), 6.97 (d, *J* = 8.6 Hz, 1H, CH), 6.86 – 6.84 (m, 1H, CH), 6.79 – 6.76 (m, 3H, CH), 6.69 – 6.68 (m, 1H, CH), 6.60 (d, *J* = 6.8 Hz, 1H, CH), 3.86 (s, 3H, CH_3), **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 159.4 (C), 151.6 (C), 151.5 (C), 151.3 (C), 147.2 (C), 131.2 (C), 129.9 (C), 129.4 (CH), 128.4 (CH), 128.2 (CH), 127.7 (2CH), 126.8 (CH), 117.7 (CH), 117.3 (CH), 115.7 (CH), 114.3 (2CH), 55.4 (CH_3). **HRMS** (CI^+) m/z: calculated for $(C_{19}H_{14}O+H)^+$ 259.1123, found 259.1128.

1-(2-Methoxyphenyl)biphenylene, 78



The reaction was conducted according to the general procedure, using $Pd_2(dba)_3$ (55.0 mg, 0.0601 mmol), XPhos (57.2 mg, 0.120 mmol), Cs_2CO_3 (392 mg, 1.20 mmol), 2-methoxyphenyl boronic acid (183.0 mg, 1.204 mmol), 1-iodobiphenylene (225.0 mg, 0.8091 mmol), and dioxane (1.8 mL). The crude product was purified by flash column chromatography (silica gel, 1% EtOAc in hexane) and recrystallised in hexane. Compound **78** was isolated as a yellow solid (134 mg, 0.519 mmol, 65%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 7.5, 1.7 Hz, 1H, CH), 7.35 – 7.31 (m, 1H, CH), 7.03 (td, *J* = 7.5, 3.2 Hz, 1H, CH), 6.99 (d, *J* = 3.7 Hz, 1H, CH), 6.97 (d, *J* = 3.8 Hz, 1H, CH), 6.81 (dd, *J* = 8.4, 6.8 Hz, 1H, CH), 6.75 – 6.69 (m, 2H, CH), 6.66 – 6.65 (m, 1H, CH), 6.61 (d, *J* = 6.8 Hz, 1H, CH), 6.48 – 6.47 (m, 1H, CH), 3.85 (s, 3H, CH_3), **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 156.8 (C), 152.4 (C), 151.5 (C), 151.2 (C), 149.9 (C), 129.9 (CH), 129.8 (CH), 129.2 (CH), 128.5 (C), 128.4 (CH), 128.2 (CH), 128.1 (CH), 126.7 (C), 120.8 (CH), 118.1 (CH), 117.1 (CH), 116.0 (CH), 111.1 (CH), 55.5 (CH_3). **HRMS** (CI^+) m/z: calculated for $(C_{19}H_{14}O+H)^+$ 259.1123, found 259.1128.

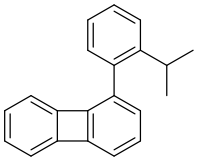
1-(*p*-Tolyl)biphenylene, 114



The reaction was conducted according to the general procedure, using $Pd_2(dba)_3$ (55.0 mg, 0.0601 mmol), XPhos (57.0 mg, 0.120 mmol), Cs_2CO_3 (521 mg, 1.60 mmol), *p*-tolylboronic acid (163.0 mg, 1.199 mmol), 1-iodobiphenylene (226.0 mg, 0.8127 mmol), and dioxane (2.4 mL). The crude product was purified by flash column chromatography (silica gel, hexane). Compound **114** was isolated as a yellow solid (157 mg, 0.648 mmol, 81 %). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.9 Hz, 2H, CH), 7.24 – 7.22 (m, 2H, CH), 6.96 (d, *J* = 8.5 Hz, 1H, CH), 6.81 (t, *J* = 7.6 Hz, 1H, CH), 6.74 – 6.73 (m, 3H, CH), 6.65 – 6.64 (m, 1H, CH), 6.57 (d, *J* = 6.7 Hz, 1H, CH), 2.38 (s, 3H, CH_3), **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 151.6 (2C), 151.4 (C), 147.7

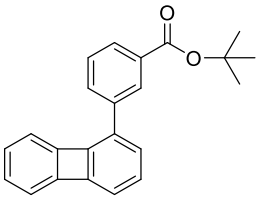
(C), 137.7 (C), 134.6 (C), 131.5 (C), 129.6 (2CH), 129.3 (CH), 128.5 (CH), 128.3 (CH), 127.0 (CH), 126.5 (2CH), 117.9 (CH), 117.4 (CH), 116.0 (CH), 21.4 (CH_3). **HRMS** (CI^+) m/z: calculated for $(C_{19}H_{14}+H)^+$ 243.1174, found 243.1160.

1-(2-Isopropylphenyl)biphenylene, 111



The reaction was conducted according to the general procedure, using $Pd_2(dba)_3$ (55.0 mg, 0.0601 mmol), XPhos (57.4 mg, 0.120 mmol), Cs_2CO_3 (521 mg, 1.60 mmol), (2-*iso*propyl)phenyl boronic acid (197.0 mg, 1.201 mmol), 1-iodobiphenylene (225.0 mg, 0.8091 mmol), and dioxane (2.4 mL). The crude product was purified by flash column chromatography (silica gel, hexane - 1.5 % EtOAc in hexane). Compound **111** was isolated as a yellow oil (174 mg, 0.644 mmol, 80 %). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 – 7.41 (m, 1H, CH), 7.38 – 7.36 (m, 1H, CH), 7.25 – 7.21 (m, 2H, CH), 6.82 (dd, *J* = 8.6, 6.8 Hz, 1H, CH), 6.77 – 6.64 (m, 5H, CH), 6.39 – 6.37 (m, 1H, CH), 3.29 (spt, *J* = 6.8 Hz, 1H, CH), 1.21 (d, *J* = 6.9 Hz, 6H, CH_3), **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 151.6 (C), 151.4 (C), 151.2 (C), 149.3 (C), 146.6 (C), 136.9 (C), 132.0 (C), 130.3 (CH), 129.3 (CH), 128.4 (CH), 128.3 (CH), 128.3 (CH), 128.2 (CH), 125.7 (CH), 125.7 (CH), 117.6 (CH), 117.5 (CH), 116.1 (CH), 29.5 (CH), 24.2 ($2CH_3$). **HRMS** (CI^+) m/z: calculated for $(C_{21}H_{18}+H)^+$ 271.1487, found 271.1477.

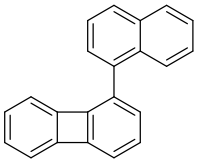
***Tert*-butyl 3-(biphenylen-1-yl)benzoate, 113**



The reaction was conducted according to the general procedure, using $Pd_2(dba)_3$ (54.9 mg, 0.0600 mmol), XPhos (57.2 mg, 0.120 mmol), Cs_2CO_3 (392 mg, 1.20 mmol), (3-*tert*butoxycarbonyl)phenyl boronic acid (266.0 mg, 1.198 mmol), 1-iodobiphenylene (225.0 mg, 0.8091 mmol), and dioxane (1.8 mL). The crude product was purified by flash column chromatography (silica gel, 2.5 % EtOAc in hexane). Compound **113** was isolated as a yellow oil (201 mg, 0.612 mmol, 75 %). **^{1}H NMR** (400 MHz, $CDCl_3$)

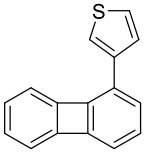
δ 8.26 (t, *J* = 1.6 Hz, 1H, CH), 7.98 (dt, *J* = 8.0, 1.4 Hz, 1H, CH), 7.76 – 7.74 (m, 1H, CH), 7.50 (t, *J* = 7.7 Hz, 1H, CH), 7.05 (d, *J* = 8.4 Hz, 1H, CH), 6.90 – 6.84 (m, 2H, CH), 6.80 – 6.78 (m, 2H, CH), 6.70 – 6.67 (m, 1H, CH), 6.62 (d, *J* = 6.7 Hz, 1H, CH), 1.64 (s, 9H, CH_3), **$^{13}C\{^1H\}$ NMR** (100 MHz, $CDCl_3$) δ 165.7 (C), 151.7 (C), 151.3 (2C), 148.3 (C), 137.2 (C), 132.7 (C), 130.4 (C), 129.9 (CH), 129.5 (CH), 128.9 (CH), 128.7 (2CH), 128.4 (CH), 127.6 (CH), 126.5 (CH), 118.2 (CH), 117.5 (CH), 116.5 (CH), 81.4 (C), 28.4 ($3CH_3$). **HRMS** (ESI^+) m/z: calculated for $(C_{23}H_{20}O_2+Na)^+$ 351.1361, found 351.1357.

1-(Naphthalen-1-yl)biphenylene, 110



The reaction was conducted according to the general procedure, using $Pd_2(dba)_3$ (56.0 mg, 0.0612 mmol), XPhos (57.2 mg, 0.120 mmol), Cs_2CO_3 (521 mg, 1.60 mmol), naphthalene boronic acid (206.0 mg, 1.198 mmol), 1-iodobiphenylene (223.0 mg, 0.8019 mmol), and dioxane (2.4 mL). The crude product was purified by flash column chromatography (silica gel, hexane). Compound **110** was isolated as a yellow oil (177 mg, 0.636 mmol, 79 %). **^1H NMR** (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 7.8 Hz, 1H, CH), 7.95 – 7.88 (m, 2H, CH), 7.56 – 7.53 (m, 4H, CH), 6.99 – 6.91 (m, 2H, CH), 6.74 – 6.73 (m, 3H, CH), 6.65 – 6.61 (m, 1H, CH), 6.02 (d, *J* = 6.8 Hz, 1H, CH), **$^{13}C\{^1H\}$ NMR** (100 MHz, $CDCl_3$) δ 151.6 (C), 151.4 (C), 151.3 (C), 150.1 (C), 136.1 (C), 134.0 (C), 130.7 (C), 130.6 (C), 130.5 (CH), 129.0 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 128.3 (CH), 126.5 (CH), 126.4 (CH), 126.1 (CH), 126.0 (CH), 125.6 (CH), 118.6 (CH), 117.4 (CH), 116.3 (CH). **HRMS** (CI^+) m/z: calculated for $(C_{22}H_{14}+H)^+$ 279.1174, found 279.1179.

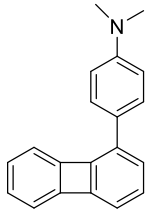
1-(3-Thienyl)biphenylene, 116



The reaction was conducted according to the general procedure, using $Pd_2(dba)_3$ (54.7 mg, 0.0597 mmol), XPhos (57.0 mg, 0.120 mmol), Cs_2CO_3 (388 mg, 1.19 mmol), 3-

thiophene boronic acid (153.5 mg, 1.200 mmol), 1-iodobiphenylene (225.0 mg, 0.8091 mmol), and dioxane (1.8 mL). The crude product was purified by flash column chromatography (silica gel, hexane). Compound **116** was isolated as a yellow solid (137 mg, 0.585 mmol, 73%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 – 7.44 (m, 1H, CH), 7.41 – 7.39 (m, 1H, CH), 7.36 – 7.35 (m, 1H, CH), 6.97 (d, *J* = 8.5 Hz, 1H, CH), 6.83 – 6.77 (m, 4H, CH), 6.69 – 6.66 (m, 1H, CH), 6.57 (d, *J* = 6.7 Hz, 1H, CH), **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 151.5 (C), 151.3 (C), 151.1 (C), 147.2 (C), 138.9 (C), 129.3 (CH), 128.5 (CH), 128.4 (CH), 126.8 (CH), 126.5 (C), 126.3 (CH), 126.2 (CH), 121.4 (CH), 117.8 (CH), 117.4 (CH), 116.0 (CH), **HRMS** (CI^+) m/z: calculated for $(C_{16}H_{10}S+H)^+$ 235.0581, found 235.0586.

1-(4-(Dimethylamino)phenyl)biphenylene, 115



The reaction was conducted according to the general procedure, using $Pd_2(dba)_3$ (41.0 mg, 0.0448 mmol), XPhos (43.0 mg, 0.0902 mmol), Cs_2CO_3 (391 mg, 1.20 mmol), *p*-dimethylaminophenyl boronic acid (149.0 mg, 0.9033 mmol), 1-iodobiphenylene (162.0 mg, 0.5825 mmol), and dioxane (1.4 mL). The crude product was purified by flash column chromatography (silica gel, 5% EtOAc in hexane). Compound **115** was isolated as an orange solid (117 mg, 0.431 mmol, 74%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 – 7.49 (m, 2H, CH), 6.98 (d, *J* = 8.4 Hz, 1H, CH), 6.84 – 6.74 (m, 6H, CH), 6.66 – 6.65 (m, 1H, CH), 6.55 (d, *J* = 6.7 Hz, 1H, CH), 3.01 (s, 6H, CH_3), **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 152.0 (C), 151.5 (C), 151.4 (C), 150.2 (C), 146.6 (C), 131.8 (C), 129.2 (CH), 128.2 (CH), 128.1 (CH), 127.4 (2CH),126.6 (CH), 125.2 (C), 117.6 (CH), 117.1 (CH), 115.1 (CH), 112.6 (2CH), 40.6 ($2CH_3$). **HRMS** (ESI^+) m/z: calculated for $(C_{20}H_{17}N+H)^+$ 272.1439, found 272.1440.

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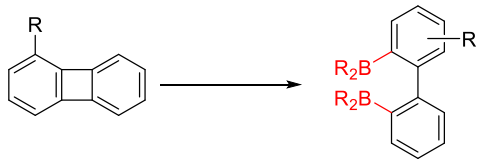
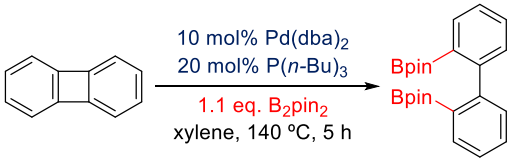
Chapter 3 Catalytic Ring Opening Diborylation of Biphenylenes

3.1. Optimisation of the Ring Opening Diborylation of 1-Fluorobiphenylene

As outlined in the introduction, there are four key aims in this work, the first of which is to optimise the ring opening diborylation of the strained C-C bond in 1-substituted biphenylenes (Scheme 3.1). As discussed in the introduction, only one example of the ring opening diborylation of a biphenylene is known: using biphenylene itself (Scheme 3.2).[1] The reaction conditions reported by Matsuda and Kirikae were therefore used as a starting point for the desired diborylation reaction.



Scheme 3.1 *The ring opening diborylation of 1-substituted biphenylenes.*



35

57 %

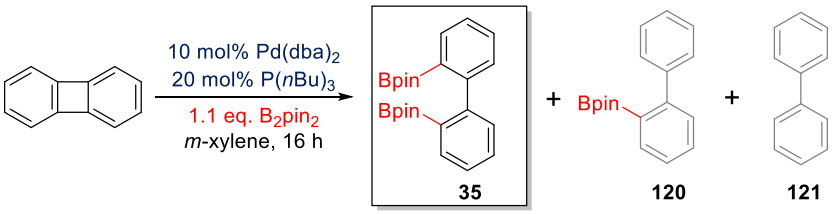
Scheme 3.2 *The ring opening diborylation of unsubstituted biphenylene with B_2pin_2.*[1]

When the reaction mixture was heated at 140 °C for sixteen hours rather than five, the reaction went to completion and the desired product was obtained in a GC yield of 70% (Table 3.1, Entry 1). This is significantly higher than the 57% isolated yield reported in the literature. To determine if the reaction occurred at temperatures below 140 °C, the reaction was next attempted at 110 °C and 80 °C. At 110 °C, the conversion dropped significantly, as did the GC yield of **35** to 4% (Table 3.1, Entry 2). Changing the solvent from *m*-xylene to toluene at 110 °C caused a small drop in the conversion of biphenylene and the GC yield of **35** (Table 3.1, Entry 3). Finally, when the reaction temperature was dropped to 80 °C, no conversion was observed (Table 3.1, Entry 4).

The optimisation of C-C diborylation in 1-substituted biphenylenes was begun by using 1-fluorobiphenylene as the model substrate. This substrate was chosen because

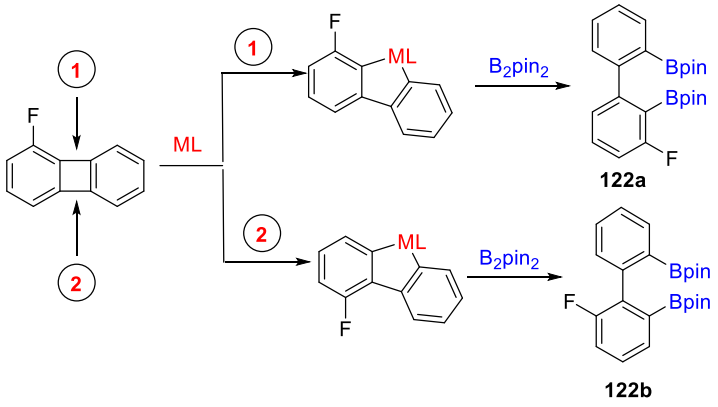
it could be readily synthesised in the lab using the reported literature procedure and fluorine has an A-value of between 0.28 and 0.36 kcal/mol, therefore the increase in substrate steric bulk when the substrate is changed from biphenylene to 1-fluorobiphenylene is minimised.[2–4] It is of note that when a 1-monosubstituted biphenylene is employed as the substrate instead of biphenylene, the two C-C bonds become inequivalent and the catalyst can insert into either one. This gives rise to two possible regioisomers of the diborylated product, **122a** and **122b** (Scheme 3.3).

Table 3.1 Screening results for the ring opening diborylation of biphenylene with B_2pin_2.



Entry	Temperature/ °C	Biphenylene Conversion	GC Yield 35 (%)	GC Yield 120 (%)	GC Yield 121 (%)
1	140	99	70	6	4
2	110	12	4	2	<1
3[a]	110	5	1	1	<1
4	80	0	0	0	0

All conversions and yields are based on GC analysis using n-dodecane as the internal standard (0.1 mmol scale). [a] Reaction was conducted in toluene.

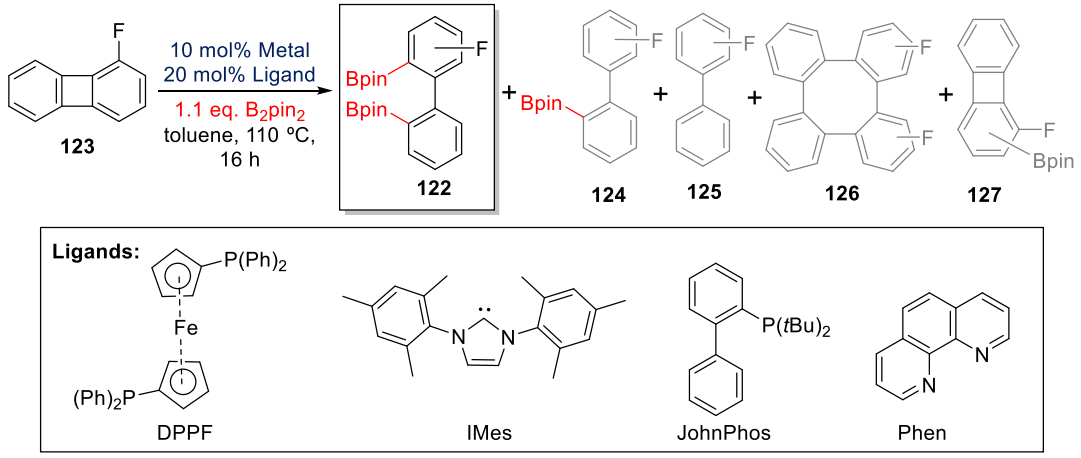


Scheme 3.3 *The two regioisomers* ***122a*** *and* ***122b*** *that it is possible to form, from the ring opening diborylation of 1-fluorobiphenylene.*

Given the results obtained from the small screening conducted with biphenylene, 110 °C was chosen as the screening temperature, with the aim of keeping the temperature

as low as possible, whilst still maintaining reactivity. Toluene was the preferred solvent because it is more convenient: in terms of the work-up it is much easier to remove. Therefore, the ring opening diborylation of 1-fluorobiphenylene with 1.1 eq. of B_2pin_2 was screened at 110 °C in toluene for 16 h, using a 0.1 mmol scale with respect to 1-fluorobiphenylene (Table 3.2).

Table 3.2 Screening results for the ring opening of 1-fluorobiphenylene with B_2pin_2.



Entry	Metal	Ligand	Conversion of 123 (%)	122 (%)	124 (%)	125 (%)	126 (%)
1	$Pd(dba)_2$	P(*n*-Bu)$_3$	5	1	1	<1	0
2[a]	$Pd(dba)_2$	P(*n*-Bu)$_3$	11	5	1	<1	0
3	$Pd(dba)_2$	DPPF	4	0	<1	<1	0
4[b]	$Pd(dba)_2$	IMes	80	8	10	16	0
5	$Pd(dba)_2$	JohnPhos	99	7	4	<1	77
6	$Pd(dba)_2$	Phen	4	2	0	<1	0
7	$[Ir(cod)Cl]_2$	DPPF	13	<1	<1	<1	0
8[b]	$[Ir(cod)Cl]_2$	IMes	56	0	10	20	0
9	$[Ir(cod)Cl]_2$	JohnPhos	24	<1	3	3	0
10	$[Ir(cod)Cl]_2$	Phen	29	0	0	0	0
11	$[Ir(cod)Cl]_2$	P(*n*-Bu)$_3$	1	0	0	0	0
12	$Ni(cod)_2$	DPPF	11	0	<1	2	0
13[b]	$Ni(cod)_2$	IMes	99	<1	5	18	59
14	$Ni(cod)_2$	JohnPhos	1	0	0	0	0

All conversions and yields are based on GC analysis using n-dodecane as the internal standard (0.1 mmol scale). [a] Reaction was conducted in *m*-xylene. [b] IMes was generated *in situ* by the treatment of the chloride salt with 22 mol% KO^{t}Bu.

Firstly, the combination of $Pd(dba)_2$ and P(*n*-Bu)$_3$ reported by Matsuda and Kirikae was employed and the desired diborylated product was obtained in 5% GC yield (Table 3.2, Entry 2). Changing the solvent from *m*-xylene to toluene gave a slightly worse GC yield of 1% (Table 3.2, Entry 1). Despite the poorer yield the difference is not large and as mentioned previously toluene was the favoured solvent because it is more convenient. In both reactions, reduced products **125** and monoborylated products **124** were observed and were identified by GC-MS. There are two possible regioisomers of the reduced product: 3-fluoro-1,1'-biphenyl **125a** and 2-fluoro-1,1'-biphenyl **125b** (Fig. 3.1), dependent on which C-C bond was cleaved, both were observed. The reduced products **125** could be formed either by protodeboronation of 2,2'-diborylated **122** under the reaction conditions; or could be formed by trace amounts of water in the reaction mixture, which could protonate a palladium intermediate in the catalytic cycle.

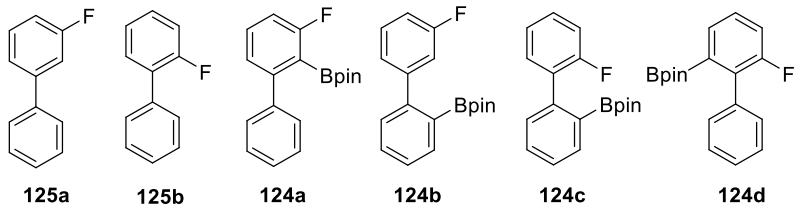
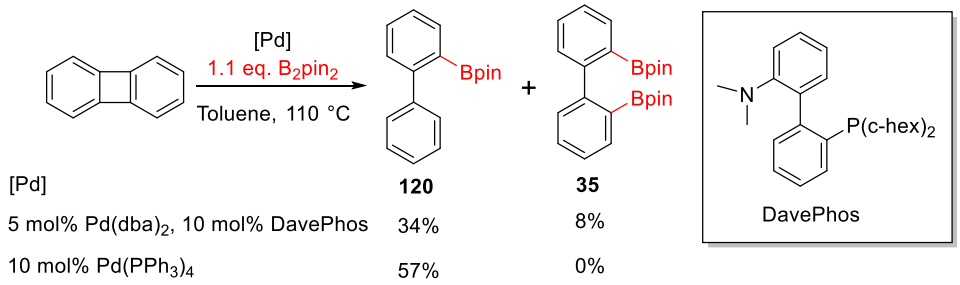


Fig. 3.1 *The structure of the reduced side-products* ***125a*** *and* ***125b*** *and the monoborylated side-products* ***124a-124d****.*

Four regioisomers of the monoborylated product are possible: **124a-124d** (Fig. 3.1). Only three signals were observed in the GC chromatogram, presumably because two of the isomers have the same retention time using this GC method. Monoborylated product **124** could be formed in the same two ways as **125**. Matsuda and Kirikae reported the monoborylation of unsubstituted biphenylene when $Pd(dba)_2$ was used in combination with DavePhos, and when $Pd(PPh_3)_4$ was used in the absence of ligand (Scheme 3.4). They reported that protodeboronation of **122** under the reaction conditions was negligible and that therefore monoborylation most probably results from adventitious water protonating a palladium intermediate in the catalytic cycle.[1]

Given that the combination of $Pd(dba)_2$ and P(*n*-Bu)$_3$ did not work well at 110 °C, a broader scope of metal precursors and ligands were next investigated. Four different ligand classes: diphosphine, carbene, nitrogen, and monophosphine, including a Buchwald ligand were tested to determine if one ligand class was particularly effective

for the desired transformation. Only monophosphine ligands were tested by Matsuda and Kirikae.[1] It was found that the combination of $Pd(dba)_2$ and DPPF or 1,10-phenanthroline gave low conversions of 4% (Table 3.2, Entries 3 and 6).



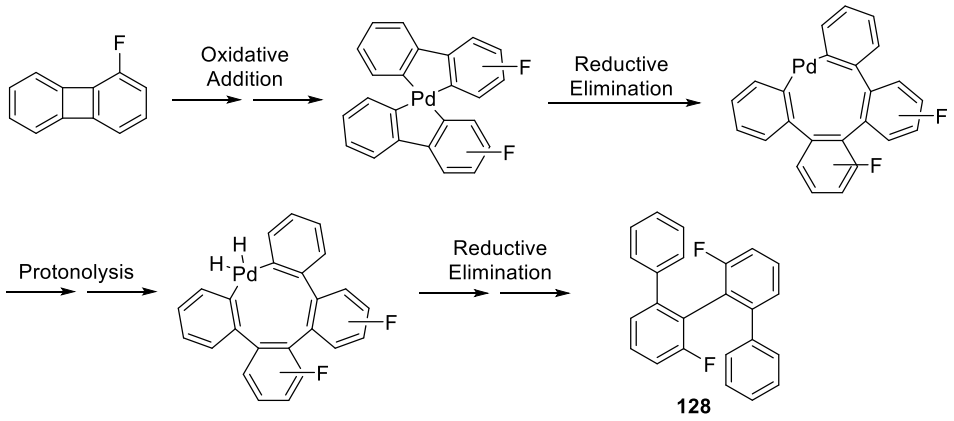
Scheme 3.4 *The monoborylation of biphenylene using B_2pin_2 observed by Matsuda and Kirikae.*[1]

The combination of $Pd(dba)_2$ and IMes gave a high conversion of 80%, but only 8% GC yield of the desired product **122**. The reduced products **125a** and **125b** were formed in 16% GC yield, and 10% of the monoborylated products **124a** – **124d** were also observed (Table 3.2, Entry 4). In addition, difluorotetraphenyl **128**, of which there are eight possible regioisomers, one of which is shown in Scheme 3.5, was identified by GC-MS. Difluorotetraphenyl most likely forms by the oxidative addition of two biphenylene molecules, followed by one reductive elimination, in which a C-C bond is formed, followed by two sequential palladium protonations and C-H bond forming reductive eliminations. Despite the identification of these products, a significant amount of the mass balance is still unaccounted for. It is most likely that this is due to the formation of a polymer or an oligomer, which is too heavy to be observed by GC. ^{19}F NMR of the crude reaction mixture was consistent with biphenylene polymerisation because several fluorine environments were present.

When $Pd(dba)_2$ and JohnPhos were employed, the reaction was highly chemoselective for the tetraphenylene product **126** obtained in 77% GC yield as a mixture of isomers (Table 3.2, Entry 5). Similarly, when $Ni(cod)_2$ and IMes were employed, the reaction was reasonably chemoselective for the dimerised product **126**, which was obtained in 59% GC yield as a mixture of isomers (Table 3.2, Entry 13). $Ni(cod)_2$ was tested because other nickel based catalysts have been used in the catalytic functionalisation of biphenylenes.[5–9]

Dimerisation of biphenylene using both nickel and palladium catalysis is known, as discussed in section 1.1.2.2.[6,9–11] There are five possible regioisomers of

tetraphenylene: **126a** – **126e** (Fig. 3.2). Different regioisomers result dependent on which two C-C single bonds in 1-fluorobiphenylene **123** undergo oxidative addition to palladium. The tetraphenylene side-products were identified by GC-MS.



Scheme 3.5 *Potential mechanism for the formation of difluorotetraphenyl* ***128****, of which there are eight possible regioisomers, one of which is shown.*

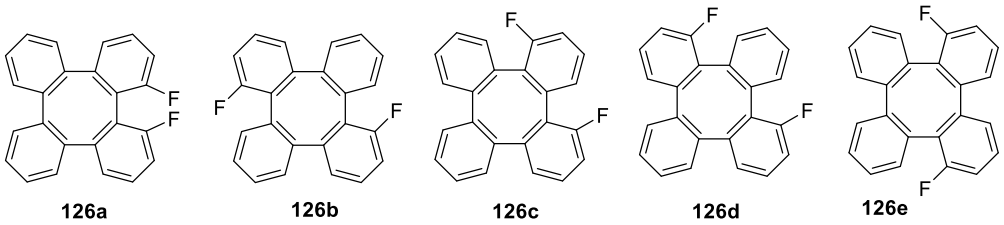


Fig. 3.2 *The structures of the five possible tetraphenylene side-products* ***126a*** *–* ***126e****.*

It was also found that the combination of $Ni(cod)_2$ and either DPPF or JohnPhos gave low conversions of 11% and 1% respectively (Table 3.2, Entries 12 and 14). In both reactions, none of the desired product **122** was observed. For this reason, $Ni(cod)_2$ was not further investigated as a metal precursor.

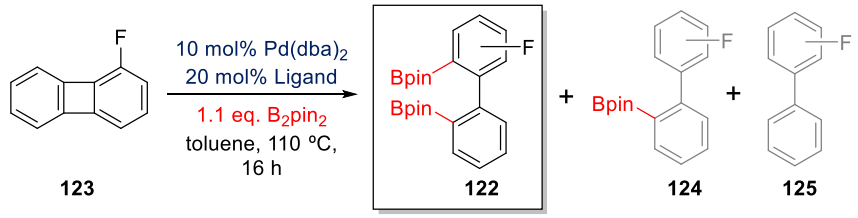
$[Ir(cod)Cl]_2$ was next investigated as a metal precursor. This precursor was chosen because it has been shown to insert into the strained C-C bond of biphenylene and has been employed in the catalytic addition of alkynes and alkenes across the strained C-C bond in substituted biphenylene derivatives.[12–14] Unfortunately, in almost every instance in which $[Ir(cod)Cl]_2$ was employed as the metal precursor, unselective C-H borylation of both 1-fluorobiphenylene and the solvent, toluene, was observed by GC-MS to give **127** (Table 3.2, Entries 7-11). C-H borylation of 1-fluorobiphenylene accounts for the missing mass balance in all the reactions in which $[Ir(cod)Cl]_2$ was employed as the metal precursor.

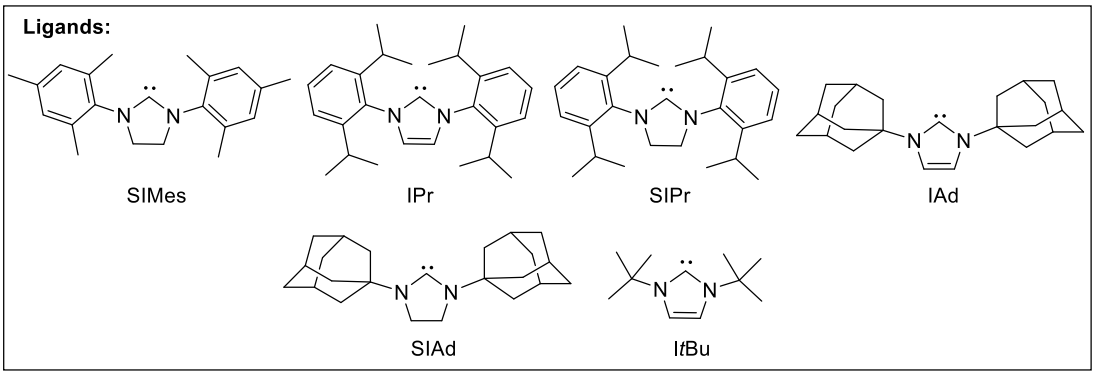
Iridium catalysed C-H borylation of aromatic C-H bonds with B_2pin_2 in the presence of $[Ir(cod)Cl]_2$ and a bidentate nitrogen ligand is known.[15] In one example, 1,10-phenanthroline, tested as a ligand in this screening (Table 3.2, Entry 10), gave the C-H borylated product in a high yield of 89%. Therefore, the observation of C-H borylation is in agreement with what has been reported in the literature.[15] The aim of this work was to achieve chemoselective C-C diborylation, therefore due to the extent of unselective C-H borylation observed when $[Ir(cod)Cl]_2$ was employed as the metal precursor, this was not further investigated.

Of the precursors and ligands tested, the combination of $Pd(dba)_2$ and the carbene ligand IMes was the most chemoselective for the desired product **122**, which was obtained in 8% GC yield. Building upon this result, a range of different carbene ligands were next screened using $Pd(dba)_2$ as the metal precursor (Table 3.3).

For comparison, the carbene ligands are shown alongside their Tolman electronic parameter (TEP) determined from IR spectroscopy of $[IrCl(CO)_2(NHC)]$ complexes.[16] TEP is a measure of the π-donating ability of the metal centre. In principle, the more electron donating the NHC, the higher the electron density on the metal, and the greater the π-back bonding into the π^*_{CO} anti-bonding orbital. Greater π-back bonding weakens the C-O triple bond and gives a lower TEP value. TEP is not a measure of the absolute electron density on the metal centre and is therefore not the best method to compare ligands in which the nature of M-L bonding is different, such as saturated NHCs and unsaturated NHCs.[16] However, it is a good method for the comparison of saturated NHCs with saturated NHCs and unsaturated NHCs with unsaturated NHCs. The carbene ligands are also shown alongside their percent buried volume ($\%V_{bur}$) determined from [AuCl(NHC)] complexes when the M-NHC bond length was 2.00 Å.[17,18] $\%V_{bur}$ is the percentage of a sphere, with a 3.5 Å radius around the metal centre that is filled by a given ligand. It is a useful metric for evaluating NHC steric properties.[18]

Table 3.3 Screening results for the ring opening of 1-fluorobiphenylene with B_2pin_2, using carbene ligands.





Entry	Ligand	TEP /cm^{-1}	%V_{bur}	Conversion 123 (%)	Conversion B_2pin_2 (%)	122 (%)	124 (%)	125 (%)
1	IMes	2049.6	36.5	80	16	8	10	16
2	SIMes	2050.8	36.9	61	42	0	16	20
3	IPr	2050.2	44.5	85	41	2	23	8
4	SIPr	2051.1	47.0	99	87	<1	24	11
5	IAd	2048.3	39.8	99	99	64	9	2
6	SIAd	-	-	15	4	1	11	2
7	I^{t}Bu	2048.9	39.6	51	72	27	10	2
8[a]	IAd	2048.3	39.8	100	99	58	12	12
9[b]	IAd	2048.3	39.8	100	71	85	8	2

All carbenes were generated *in situ* by the treatment of the tetrafluoroborate salt or the chloride salt with 22 mol% KO^{t}Bu. All conversions and yields are based on GC analysis using n-dodecane as the internal standard (0.1 mmol scale).[a] Reaction was conducted at 100 °C, [b] 2 eq. B_2pin_2.

SIMes, the saturated analogue of IMes, the best ligand in the first screening, was first investigated (Table 3.3, Entry 2). Unfortunately, none of the desired product **122** was observed, although both the reduced products **125a** and **125b**, and the monoborylated products **124a** – **124d** were observed. The most sterically bulky carbene ligands tested in this study by %V_{bur}, IPr and SIPr, were not very effective for the desired

transformation.[17] Despite high conversions of 85 and 99%, low GC yields of <2% of the desired product **122** were obtained (Table 3.3, Entries 3 and 4).

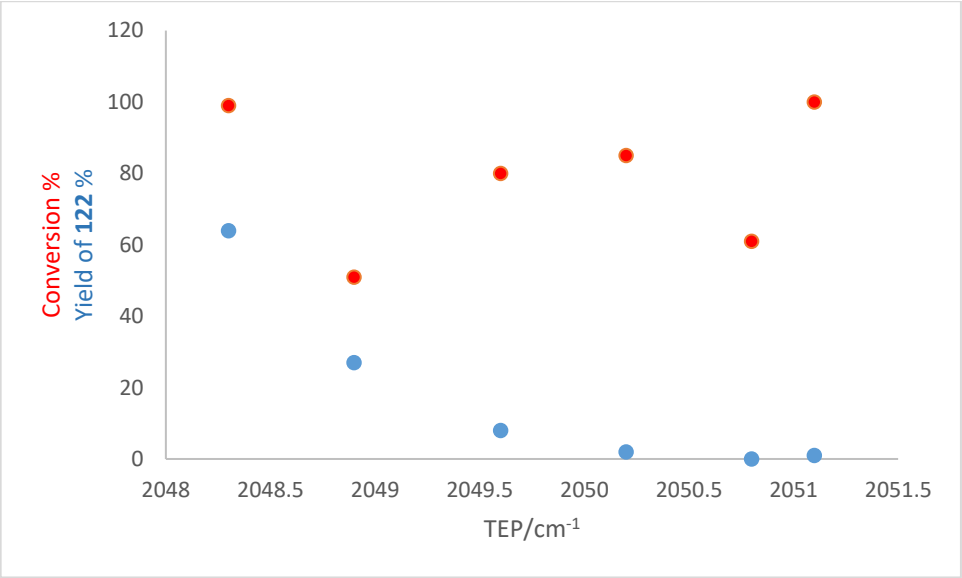
Of the carbene ligands screened, IAd was found to be the most effective: only a trace amount of starting material remained, and the desired product **122** was obtained in 64% GC yield (Table 3.3, entry 5). Surprisingly, when the saturated analogue of IAd, SIAd, was employed a huge difference in both the reactivity and chemoselectivity was observed (Table 3.3, entry 6). In the case of SIAd, the conversion was only 15% and the major product was instead the monoborylated products **125a** – **125d**, observed in 11% GC yield. Only a trace amount of **122** was observed.

There are some differences between unsaturated NHCs, of which IAd is an example, and saturated NHCs, of which SIAd is an example, which may account for the large difference in the reactivity and chemoselectivity. Firstly, unsaturated NHCs are partially aromatic and are therefore more stable.[16] Secondly, saturated NHCs tend to be slightly more sterically bulky.[17,18] Thirdly, saturated NHCs bind more strongly to the metal centre because they are both stronger σ-donors and stronger π-acceptors than unsaturated NHCs. This makes the metal centre more electron rich overall and makes the metal complex more stable.[16,19] The stronger binding of saturated NHCs to the metal could make the metal a worse σ-acceptor and a worse π-donor to other ligands, which may be why their TEP values are higher despite being more electron rich.[16,19] This may also lower the reactivity of the metal complex due to weaker interaction with some substrates.[19] This is one potential explanation for the difference in reactivity observed when the ligand was changed from IAd to SIAd.

When I^{t}Bu was employed as the ligand the reaction was chemoselective for the desired product **122**, which was obtained in 27% GC yield (Table 3.3, Entry 7). This was the second highest GC yield of **122** after the yield obtained with IAd. However, the conversion was significantly lower than when IAd was employed as the ligand and a significant amount of monoborylated product, 10% GC yield, was obtained.

A graph of the TEP values of the ligands investigated *vs* the yield of the desired product shows that there is a correlation between how electron rich the ligand is and the yield of the desired product (Graph 3.1) Of the ligands investigated those that were more electron rich gave higher yields of the desired product. There was no correlation between the TEP value of the ligands and the conversion (Graph 3.1). The most

effective carbene ligand tested, IAd, was the second most electron rich with a TEP value of 2048.3 cm^{-1}, and the second most effective carbene ligand tested, I*t*Bu, was the third most electron rich with a TEP value of 2048.9 cm^{-1}.[16] Both carbene ligands have very similar steric properties with $\%V_{bur}$ values of 39.8 and 39.6. More sterically bulky NHCs and less sterically bulky NHCs gave lower yields of the desired product **122**. This could be because this is the optimum window for steric bulk or because these ligands were less electron rich. It is not possible from these results to compare steric bulk and electronics in isolation.



Graph 3.1 *A plot of ligand's TEP values vs conversion and the yield of the desired product* ***122****.*

IAd was the most effective ligand of those screened and therefore a couple of iterations were tried using this ligand to see if the GC yield could be improved further. Firstly, the temperature was decreased to 100 °C, to establish if higher chemoselectivity for **122** could be achieved by conducting the reaction at lower temperature. Unfortunately, this had the opposite effect: the GC yield of the diborylated product dropped from 64% to 58% (Table 3.3, entries 5 and 8). In addition, the GC yield of the monoborylated side-product increased from 9% to 12% and the GC yield of unborylated side-product increased from 2% to 12%.

Secondly, it was noticed that when IAd was employed as the ligand, B_2pin_2 was nearly completely consumed during the reaction. It was therefore thought that B_2pin_2 was being consumed in a side-reaction, which prevented there from being sufficient B_2pin_2

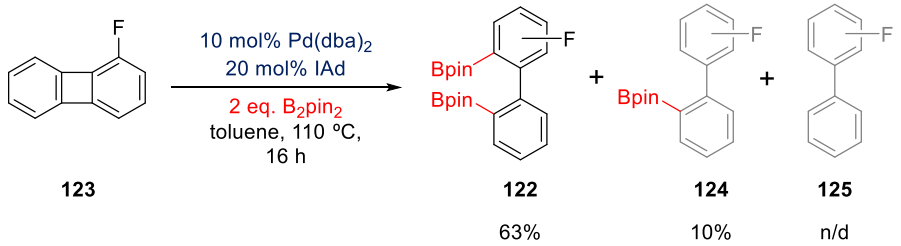
for the desired transformation. When the equivalents of B_2Pin_2 were increased from 1.1 to 2, the GC yield of **122** did increase significantly to 85% and the GC yields of the side-products remained the same (Table 3.3, Entry 9). It is most likely that B_2pin_2 adds across the double bond in dba, as 20 mol% of free dba would be present in the reaction mixture, following the complexation of IAd. Though it is also possible that B_2pin_2 is consumed by reaction with the carbene ligand, for example by borylating the double bond in the five-membered ring. This may alter the catalytic activity of the ligand and is another possible explanation for the large difference in reactivity when SIAd, which differs from IAd only by the absence of this double bond, is employed as the ligand.

The conditions of 10 mol% $Pd(dba)_2$, 20 mol% IAd, 2 eq. B_2pin_2, in toluene at 110 °C for sixteen hours were therefore taken forward as the optimum conditions. Using the optimised reaction conditions, the reaction using 1-fluorobiphenylene as the substrate was scaled up to 0.5 mmol from 0.1 mmol (Scheme 3.6). The reaction scale was increased for two reasons: firstly, because the desired product **122** is a new compound and reasonable quantities of it were needed so that it could be fully characterised. Secondly, GC yields were approximate because the response factor of **122** was not known, and it was therefore necessary to obtain isolated yields to confirm the validity of the best GC screening result.

The desired diborylated product **122** was isolated in 63% yield as a 1:1 mixture of two regioisomers. This is slightly less than the 85% GC yield obtained on 0.1 mmol scale (Table 3.3, Entry 9). This is in part due to losses during purification as **122** was columned twice to try to separate the two regioisomers. In addition, the monoborylated product **124** was isolated in 10% yield, slightly higher than the 8% GC yield and the reduced product **125** was not isolated because it could not be separated from several other compounds (Table 3.3, Entry 9).

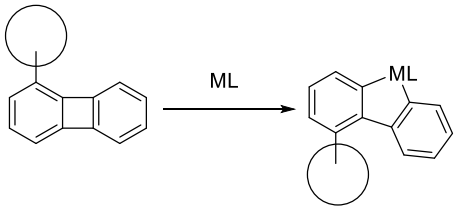
To conclude, it was found that in general more electron rich carbene ligands (IAd and I^tBu) were the most effective for the desired transformation. Although the regioselectivity of the reaction was not 1:1 in every screening reaction, the combination of $Pd(dba)_2$ and IAd yielded the desired diborylated product as a 1:1 mixture of regioisomers. This transformation had good chemoselectivity for the

desired diborylated product, which was isolated in 63% yield. The focus of the work next shifted to improving the regioselectivity of the ring opening diborylation reaction.



Scheme 3.6 *0.5 mmol Scale ring opening diborylation of 1-fluorobiphenylene with B_2pin_2.*

As discussed in the introduction, it has been found with other catalytic systems that in the absence of a directing group the catalyst preferentially inserts into the least sterically hindered C-C bond, when the 1-substituent is phenyl, methyl or TMS.[7,12,20] Fluorine has an A-value of between 0.28 and 0.36 kcal/mol and is thus only slightly more sterically bulky than hydrogen.[3,4] Therefore, the lack of regioselectivity might be because fluorine is too small to significantly bias which C-C bond the catalyst adds across. Alternatively, fluorine has been shown to have a weak *ortho* directing effect in the iridium catalysed tritiation of fluorinated aryls and might also act as a weak directing group in the ring opening diborylation reaction.[21] This would favour cleavage of the most sterically hindered C-C bond, which could offset the effect of fluorine's steric bulk resulting in a 1:1 mixture of regioisomers. It was therefore next investigated whether placing a more sterically bulky group in the 1-position would hinder addition of the catalyst to the adjacent C-C bond and therefore bias the regioselectivity (Scheme 3.7).

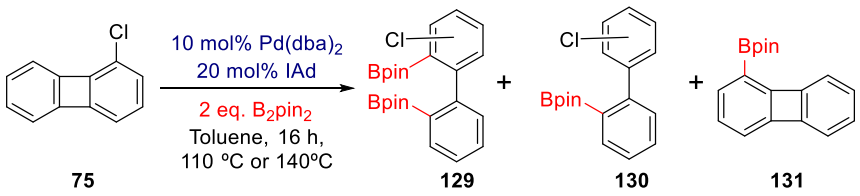


Scheme 3.7 *Proposed ring opening of biphenylenes, substituted with sterically bulky groups in the 1-position.*

3.2. Biphenylene Scope in the Ring Opening Diborylation Reaction, Part One

The first 1-substituted biphenylene investigated after 1-fluorobiphenylene was 1-chlorobiphenylene. Chlorine has an A-value of between 0.51 and 0.53 kcal/mol, which is significantly higher than that of fluorine.[3,4] Therefore, looking only at the effect of steric bulk, the ring opening diborylation of 1-chlorobiphenylene should be more regioselective than that of 1-fluorobiphenylene. As discussed in section 2.2, 1-chlorobiphenylene contains a potentially reactive C-Cl bond, which was selectively activated using a combination of $Pd_2(dba)_3$ and either BrettPhos or XPhos. Despite the risk of C-Cl bond activation, it is ultimately necessary to determine which functional groups are tolerated in the ring opening diborylation reaction.

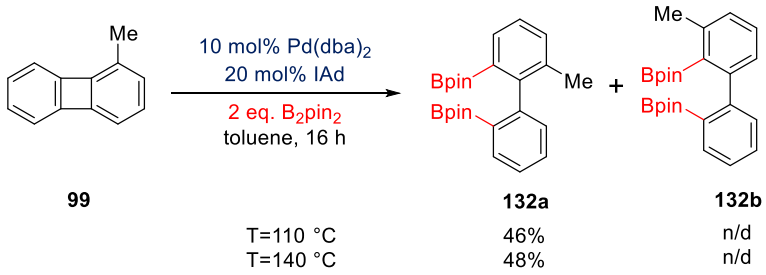
1-Chlorobiphenylene was poorly reactive under the optimised reaction conditions (Scheme 3.8). The conversion was 23% by GC and none of the desired product **129** was observed. Although it was not possible to determine GC yields, by GC-MS the major product was the monoborylated product **130**, which was a mixture of regioisomers. In addition, a small amount of the C-Cl cross-coupled product **131** was also observed.



Scheme 3.8 *The reaction of 1-chlorobiphenylene with* B_2pin_2.

The temperature of the reaction was increased from 110 °C to 140 °C to try to improve the conversion. At the higher temperature, the conversion was 21% by GC and a trace amount of the desired product **129** was observed (Scheme 3.8). By GC-MS, the major product was again the monoborylated product **130** and there was also a small amount of the C-Cl cross-coupled product **131**. Given that no improvement in conversion was observed upon raising the temperature from 110 °C to 140 °C, the reaction was not attempted at higher temperatures. It is most likely that the poor conversion of 1-chlorobiphenylene is caused by conversion of the catalyst into an unreactive intermediate *via* oxidative addition of the C-Cl bond. This is supported by the observation of **131** as a side-product.

The next substrate to be investigated was 1-methylbiphenylene. Methyl has an A-value of between 1.50 and 1.74 kcal/mol, around five times that of 1-fluorobiphenylene and is significantly more inert than chlorine.[22,23] When the optimised reaction conditions were used, the major regioisomer, **132a** was isolated in 46% yield (Scheme 3.9). A second product was isolated, which was a mixture of at least two different compounds by proton and carbon NMR. HR-MS was consistent with the desired product **132**. There were no peaks in the HR-MS that corresponded to the products of reduction, monoborylation, or dimerisation. Proton, DEPT-90, and DEPT-135 NMR showed that there were two methyl groups, one of which is from the diborylated product **132b**. The observation of a second methyl group rules out the possibility that the second compound in the mixture results from benzylic C-H borylation.



Scheme 3.9 *The ring opening diborylation of 1-methylbiphenylene at 110 and 140 °C.*

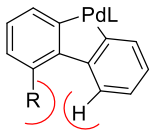
Although it was not possible to determine what the second compound in the mixture was from the HR-MS and NMR spectra, the regioselectivity can be estimated to be 5.5:1 from the crude NMR spectrum. This is based on the assumption that the major product in the mixture is **132b**. This is a significant improvement in regioselectivity compared to when 1-fluorobiphenylene was ring opened at 110 °C and a 1:1 mixture of regioisomers was obtained.

The chemoselectivity of the ring opening diborylation of 1-fluorobiphenylene was better at 110 °C than at 100 °C. Therefore, the ring opening diborylation of 1-methylbiphenylene was conducted at 140 °C to determine if raising the reaction temperature would prevent the formation of unwanted side-product(s). At the higher temperature, the major regioisomer **132a** was isolated in 48% yield and the minor regioisomer **132b** was contaminated with more of the same impurity/impurities (Scheme 3.9). The ratio of the methyl groups was 1.7:1 opposed to 3:1 at 110 °C. It was not possible to estimate the regioselectivity because there were no clean signals

in the crude NMR spectrum. However, if it is assumed that the second product is pure **132b**, the regioselectivity is 3.1:1. Therefore, the regioselectivity of the reaction is better than 3.1:1, which is significantly better than when 1-fluorobiphenylene was employed as the substrate and a 1:1 mixture of regioisomers was obtained.

The results of the ring opening diborylation of 1-fluoro and 1-methyl biphenylene suggest that increasing the steric bulk of the 1-substituent on biphenylene improves the regioselectivity of the reaction. Therefore, trimethylsilyl, which is more sterically bulky than methyl, with an A-value of between 2.4 and 2.6 kcal/mol, opposed to between 1.5 and 1.74 kcal/mol was next investigated as the 1-susbtituent on biphenylene to determine if the regioselectivity could be further improved.[22,23]

It was expected that 1-(trimethylsilyl)biphenylene would be less reactive than 1-methyl and 1-fluoro biphenylene. This is because the C-C bond adjacent to the trimethylsilyl group should be less reactive because the trimethylsilyl group hinders the approach of the catalyst. The distal C-C bond should be less reactive because the expected intermediate **133** (Fig. 3.3), should be higher in energy when R is trimethylsilyl than when R is fluorine or methyl. This is due to the greater steric clash between the trimethylsilyl group and the hydrogen atom on the adjacent benzene ring. For this reason, the reaction was initially conducted at 140 °C opposed to the standard temperature of 110 °C (Scheme 3.10). Under these conditions only starting material was recovered (60%).

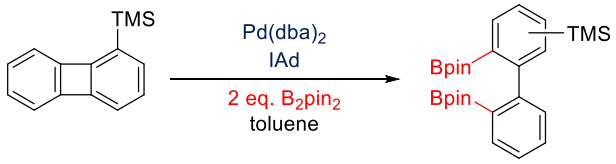


133

Fig. 3.3 *Proposed intermediate **133**, formed by the addition of palladium across the distal C-C bond in 1-substituted biphenylene.*

When the catalyst loading was doubled to 20 mol% $Pd(dba)_2$ and 40 mol% IAd and the reaction mixture heated to 180 °C for 40 hours, the reaction did go to completion (Scheme 3.10). The desired diborylated product was isolated in 39% yield. By NMR it looked as though only one regioisomer was present, however, it was not possible to unambiguously determine which regioisomer from the NMR spectra alone. It is most likely that the regioisomer resulting from cleavage of the least sterically hindered C-C

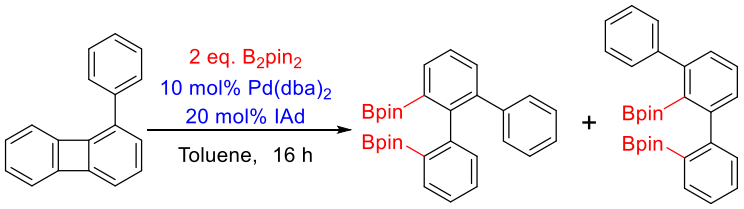
bond would be favoured. Although other compounds were flushed off the column, by NMR, these contained predominantly aliphatic signals and did not account for the missing mass balance. It is most likely that at the high temperature required for the desired transformation some decomposition of the starting material takes place.



100		134
10 mol% $Pd(dba)_2$, 20 mol% IAd, T=140 °C, t = 16 h		0%
20 mol% $Pd(dba)_2$, 40 mol% IAd, T=180 °C, t = 40 h		39%

Scheme 3.10 *The ring opening diborylation of 1-(trimethylsilyl)biphenylene at 140 and 180 °C.*

The effect of placing a chemically benign, sterically bulky substituent in the 1-position was next investigated in the hope that good regioselectivity and chemoselectivity could be achieved simultaneously. Phenyl is generally accepted as having an A-value of between 2.6 and 3.0 kcal/mol and is therefore more sterically bulky than trimethysilyl.[23–25] Hence, the ring opening diborylation of 1-phenylbiphenylene was next investigated (Scheme 3.11). After sixteen hours at 110 °C, the reaction did not go to completion. 22% Starting material was recovered and the desired product **135** was isolated as a mixture of regioisomers in 44% yield. The ring opening diborylation of 1-phenylbiphenylene was next conducted at 140 °C in an attempt to push the reaction to completion. After sixteen hours at 140 °C, the reaction did go to completion and the diborylated product was isolated as a mixture of regioisomers in 81% yield (Scheme 3.11).



76		135a	135b
	110 °C	40%	4%
	140 °C	69%	12%

Scheme 3.11 *The ring opening diborylation of 1-phenylbiphenylene at 110 °C and 140 °C.*

In both reactions, two regioisomers of the desired diborylated product, **135a** and **135b**, were isolated. Although it was not possible to differentiate between the two regioisomers by NMR, the structure of the major regioisomer, **135a**, was confirmed by XRD (Fig. 3.4). The major regioisomer **135a** was obtained in 40% yield and the minor regioisomer **135b** was obtained in 4% yield when the reaction was conducted at 110 °C. Proton NMR of the crude product showed that the regioisomers were present in a ratio of 10:1, in favour of **135a**, which is consistent with the isolated yields.

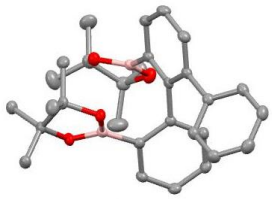


Fig. 3.4 *Single crystal structure of regioisomer* ***135a****.*

The regioselectivity of the ring opening diborylation of 1-phenylbiphenylene at 110 °C is better than the regioselectivity estimated for the ring opening diborylation of 1-methylbiphenylene at 110 °C, which was 5.5:1. This is consistent with an increase in the steric bulk of the 1-substituent of biphenylene making distal C-C bond cleavage more favourable. Although the chemoselectivity was much better than the ring opening diborylation of 1-(trimethylsilyl)biphenylene, the regioselectivity was not as good because only one diborylated regioisomer was isolated when 1-(trimethylsilyl)biphenylene was ring opened.

When 1-phenylbiphenylene reacted with B_2pin_2 at 140 °C, the regioselectivity was 5.8:1, in favour of the major regioisomer **135a**, using isolated yields, and 5.3:1 using the crude NMR. This is lower than the regioselectivity obtained when 1-phenylbiphenylene was ring opened at 110 °C and is comparable to the regioselectivity estimated for the ring opening diborylation of 1-methybiphenlene at 110 °C.

The aliphatic region of the NMR spectra differed between the two regioisomers. In the NMR spectrum of the minor regioisomer **135b**, were two Bpin methyl signals, which each integrated to 12: this was expected because there are two different Bpin environments in **135b**. Conversely, in the NMR spectrum of regioisomer **135a** were four Bpin methyl signals, which each integrated to 6. This is most likely because the two Bpin groups in regioisomer **135a** are in a sterically crowded environment and

rotation about the two C-B bonds is restricted. Restricted rotation about the C-B bonds could render the four methyl groups on each Bpin moiety inequivalent. Inequivalence of methyl groups on Bpin moieties in similarly sterically crowded environments have been reported. In the related tri-*ortho* substituted biaryls **136** – **138,** two Bpin methyl environments were observed, despite there being one Bpin environment (Fig. 3.5).[26] The tetra-*ortho* substituted biaryl **139** has a plane of symmetry and therefore the two Bpin moieties are equivalent, despite this two Bpin methyl environments are observed in the NMR spectrum.[27]

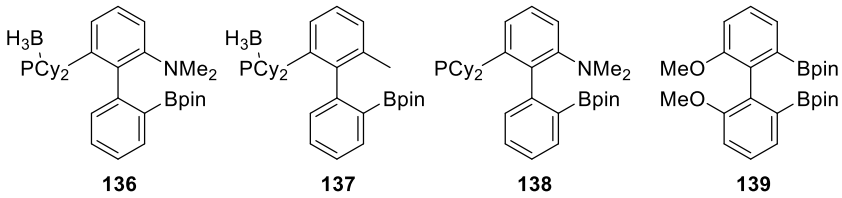


Fig. 3.5 *The structure of* ***136*** *-* ***139*** *which have Bpin groups in similar steric environments to* ***135a****.*

To conclude, it was found that a chloro substituent was not tolerated in the ring opening diborylation reaction and that 1-methyl and 1-trimethylsilyl biphenylene gave lower yields of the desired diborylated products than 1-fluorobiphenylene. Despite the poorer chemoselectivity obtained with these substrates relative to 1-fluorobiphenylene, both showed an improvement in regioselectivity. 1-Phenylbiphenylene gave the desired diborylated product in high 82% yield when the reaction was conducted at 140 °C, however higher regioselectivity was obtained when the reaction was conducted at 110 °C. It was hoped that further screening reactions would yield a more reactive metal precursor and ligand combination that would enable the reaction of more sterically bulky substrates to occur at lower temperature with higher regioselectivity.

3.3. Optimisation of the Ring Opening Diborylation of 1-Phenylbiphenylene

A small screening of the ring opening diborylation of 1-phenylbiphenylene was conducted using $[Rh(cod)Cl]_2$ as the metal precursor at 110 °C. The aim of this screening was to find conditions which enabled full conversion of 1-

phenylbiphenylene to the desired diborylated product at the milder temperature of 110 °C. $[Rh(cod)Cl]_2$ was chosen as the metal precursor because it has previously been shown to catalyse the [4+2] cycloaddition of nitriles and of alkenes into the C-C bond of biphenylene.[13,28] In addition, Shibata *et al.* used [Rh(cod)(SIMes)]BARF as a catalyst for the [4+2] cycloaddition of alkenes.[29]

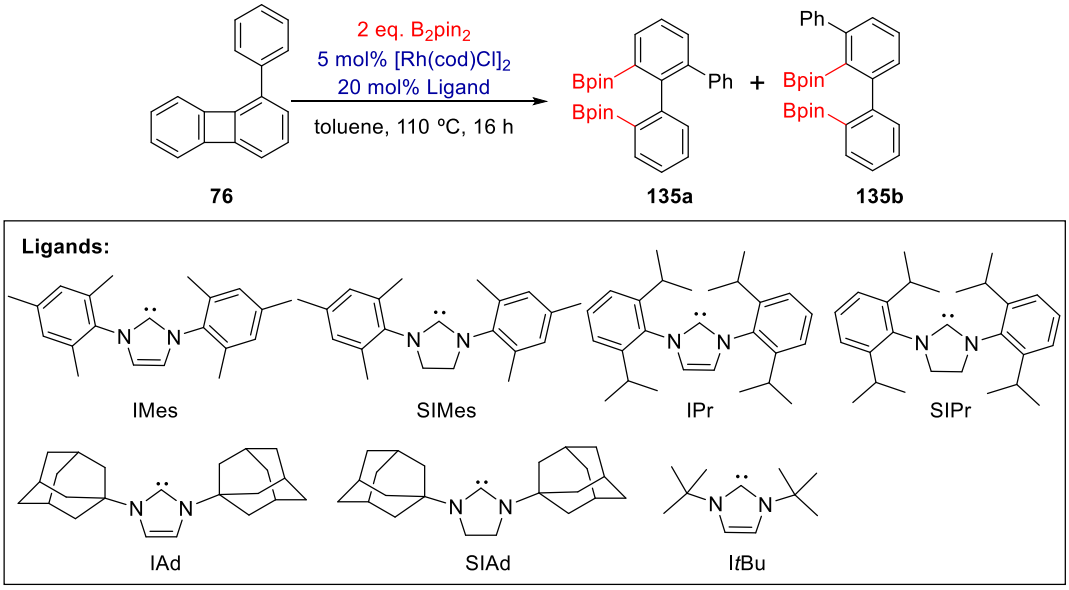
In this small screening, the same seven carbene ligands that were tested with $Pd(dba)_2$ were tested with $[Rh(cod)Cl]_2$ (Table 3.4). Given that the two desired products of the ring opening diborylation **135a** and **135b** had been isolated and characterised by NMR, the conversions and yields were calculated from NMR spectra, not from GC chromatograms. Similarly to the screening reactions with $Pd(dba)_2$ and 1-fluorobiphenylene, the highest NMR yield, 14%, was obtained when IAd was employed as the carbene ligand (Table 3.4, Entry 2). Unfortunately, this is significantly lower than the 44% isolated yield of **135** achieved when $Pd(dba)_2$ was employed as the metal precursor and therefore was not pursued further. The next best NMR yield, 4%, was obtained with IMes (Table 3.4, Entry 1): all the other carbene ligands gave negligible yields of **135** (Table 3.4, Entries 3-7).

Despite the poor NMR yields of **135**, low to moderate conversions of 27-70% were obtained. Additional peaks which did not correspond to 1-phenylbiphenylene starting material or **135** were observed in the NMR spectra of every screening reaction, however the products could not be identified from the NMR spectra alone. It is most probable that these signals correspond to the products of reduction, monoborylation, dimerisation or C-H borylation that were identified when the ring opening diborylation of 1-fluorobiphenylene was screened. However, since the aim of this work is to achieve the ring opening diborylation of 1-monosubstituted biphenylenes, these side-products were not investigated further.

To conclude, when $[Rh(cod)Cl]_2$ was employed as the metal precursor with the seven ligands listed in Table 3.4, the desired diborylated product **135** was obtained in low yields. Therefore, the best ligand and metal precursor combination found for the ring opening diborylation of 1-substituted biphenylenes is $Pd(dba)_2$ and IAd. Given the large difference in both reactivity and regioselectivity observed when the biphenylene substrate was changed, the diborane scope in the ring opening diborylation reaction was next investigated. It was expected that like different biphenylenes, different

diboranes would have different reactivities and regioselectivities and that the correct choice of diborane could facilitate the regioselective diborylation of 1-phenylbiphenylene at 110 °C.

Table 3.4 Screening results for the ring opening of 1-phenylbiphenylene with B_2pin_2, using $[Rh(cod)Cl]_2$ with different carbene ligands.



Entry	Carbene	Conversion of 76 (%)	135a Yield (%)	135b Yield (%)
1	IMes	57	4	0
2	IAd	70	14	0
3	SIMes	65	0	0
4	IPr	27	0	0
5	SIPr	60	0	0
6	SIAd	40	<1	0
7	I*t*Bu	43	<1	0

All carbenes were generated *in situ* by the treatment of the tetrafluoroborate salt or the chloride salt with 22 mol% KO^{t}Bu. All conversions and yields are based on NMR analysis using 1,3,5-trimethoxybenzene as the internal standard (0.1 mmol scale).

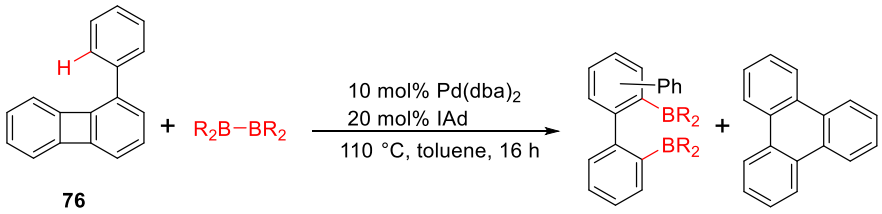
3.4. Diborane Scope in the Ring Opening Diborylation Reaction

The ring opening diborylation of 1-phenylbiphenylene with different diboranes was conducted using the optimal reaction conditions found when the ring opening diborylation of 1-fluorobiphenylene with B_2pin_2 was screened (Table 3.5). A range of diboranes with differing steric and electronic properties were investigated to determine what affect this had on the reaction. As discussed in section 3.2, when B_2pin_2 was employed as the diborane, the reaction does not go to completion at 110 °C and the desired diborylated product **135** was isolated in 44% yield (Table 3.5, Entry 1).

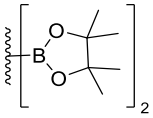
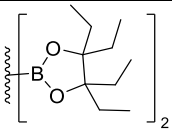
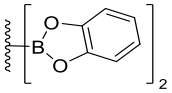
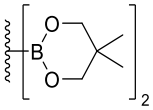
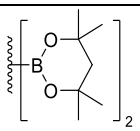
The second diborane to be investigated was 4,4,4',4',5,5,5',5'-octaethyl-2,2'-bi(1,3,2-dioxaborolane) (Epin), **140**. Diborane **140** is more sterically bulky than B_2pin_2 and it was hoped that it would therefore give improved regioselectivities in the ring opening diborylation reaction. Unfortunately, when **140** was employed as the diborane the conversion was approximately 30%, none of the desired diborylated product was isolated, and triphenylene **148** was isolated in approximately 8% yield. (Table 3.5, Entry 2). The greater steric bulk of **140** compared to B_2pin_2 is the most likely reason for its lower reactivity in the ring opening diborylation reaction. This is because a similar reduction in the reactivity of 1-monosubstituted biphenylenes was observed upon changing the substituent from fluorine to a more sterically bulky phenyl or trimethylsilyl group.

Catecholborane (B_2cat_2) **141** and bis(neopentylglycolato)diboron (B_2neop_2) **142** were next tested and both were found to be unreactive using the optimised reaction conditions (Table 3.5, Entries 3 and 4). Finally, diborane **143** was found to be the most reactive of the diboranes tested and the reaction went to completion (Table 3.5, Entry 5). However, the desired diborylated product **147** was isolated in a slightly lower yield of 39% than when B_2pin_2 was employed as the diborane (Table 3.5, Entry 1). It was not possible to separate the two regioisomers resulting from proximal and distal C-C cleavage by column chromatography, nor was it possible to unambiguously determine which regioisomer was which. However, the regioselectivity was estimated to be 3.8:1 from the NMR spectrum. This is significantly worse than the regioselectivity of 10:1 which was achieved with B_2pin_2. Although it could not be confirmed, it is most likely that the least sterically hindered C-C bond was preferentially cleaved as was observed with B_2pin_2.

Table 3.5 The ring opening diborylation of 1-phenylbiphenylene with different diboranes.



76 A 135 + 144-147 148

Entry	Diborane	Conversion of 76 (%)	A (%)	148 (%)	Selectivity (%) A Yield/Conversion
1		78	44	0	56
2	 140	~32	0	~8	n/a
3	 141	8	0	0	n/a
4	 142	28	0	0	n/a
5	 143	100	39	14	39

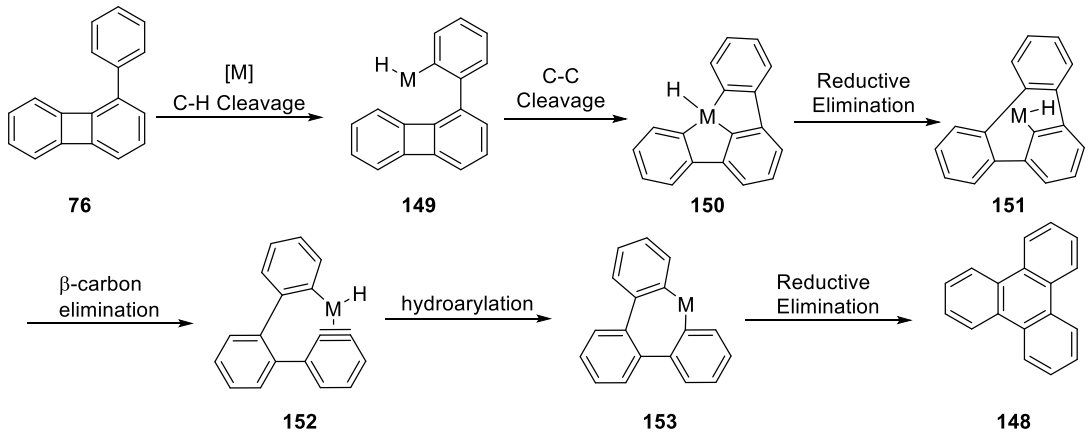
IAd was generated *in situ* by the treatment of 1,3-bis(1-adamantyl)imidazolium tetrafluoroborate with 22 mol% KO^{t}Bu. Yields are isolated yields.

Although **143** gave a higher conversion than B_2pin_2 the reaction was much less chemoselective. The side-product, triphenylene **148**, was isolated in 14% yield and a further 47% of the mass balance is unaccounted for. A significant amount of a sticky gum was flushed off the column, so it is most likely that the remaining mass balance is accounted for by either oligomerisation or polymerisation of 1-phenylbiphenylene under the reaction conditions.

A likely mechanism for the formation of triphenylene from 1-phenylbiphenylene is outlined in Scheme 3.12. Firstly, C-H activation of the *ortho* proton on the phenyl ring

and C-C cleavage of the most sterically hindered C-C bond takes place to give intermediate **150**. In principle, either C-C cleavage or C-H cleavage could occur first. C-H cleavage is probably kinetically faster because the C-H bond is more sterically accessible. In addition, prior C-H cleavage would bring the catalyst into close proximity of the most sterically hindered C-C bond, making this step more favourable.

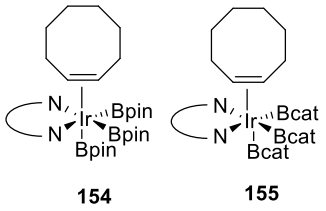
Reductive elimination from **150** can either return intermediate **149** or form the seven-membered ring complex **151**. β-Carbon elimination of **151** generates the unstable benzyne complex **152**, which would rapidly undergo hydroarylation to give the seven-membered metallocycle **153**. Although the aryne intermediate **152** would be highly unstable, the reaction was conducted at high temperature, 110 °C, and its formation may relieve the ring strain present in the seven-membered ring complex **151**. In addition, the benzyne fragment is probably stabilised by coordination to the palladium catalyst, as shown, which has been previously reported in other systems.[30] Finally, reductive elimination of **153** generates triphenylene, this step, in which a six-membered aromatic ring is formed, should be irreversible and is presumably the driving force of the reaction.



Scheme 3.12 *Proposed mechanism for the formation of triphenylene from 1-phenylbiphenylene.*

The reactivity and chemoselectivity varied dramatically between the different diboranes. Large differences in the reactivity of different diboranes have previously been reported: for example, Hartwig *et al.* found that there was a significant difference in reactivity towards C-H borylation between B_2pin_2 and **141** (B_2cat_2).[31] B_2pin_2 was found to be far more reactive and the trisboryl complex **154** (Fig. 3.6), believed to be an intermediate, reacted with benzene at room temperature, whereas the trisboryl

complex **155** (Fig. 3.6) is stable for several hours at room temperature. IR stretching frequencies showed that the iridium trisboryl complex **154** was significantly more electron rich than **155** and it was found that oxidative addition of benzene to complex **154** was more facile. In the ring opening diborylation reaction, the two most electron poor diboranes **141** and **142** were found to be the least reactive and it is therefore likely that the electronic properties of the diborane have a significant effect. However, detailed mechanistic studies would be necessary to fully understand the differences in reactivity.



154 **155**

Fig. 3.6 *The structures of trisboryl complexes **154** and **155**, which are intermediates in the C-H borylation of benzene.*

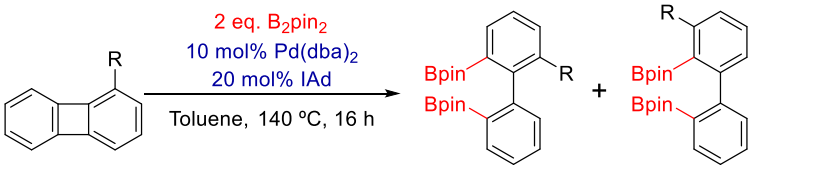
Unfortunately, none of the four diboranes (**140** – **143**) tested gave improved results in the ring opening diborylation of 1-phenylbiphenylene at 110 °C compared to B_2pin_2. When the ring opening diborylation of 1-phenylbiphenylene was conducted with B_2pin_2 at 140 °C, the desired product **135** was isolated in a high yield of 81%, with high chemoselectivity. Therefore, in the absence of reaction conditions that enabled the ring opening diborylation of 1-phenylbiphenylene at 110 °C, these conditions were taken forward as the optimum conditions.

3.5. Biphenylene Scope of the Ring Opening Diborylation Reaction, Part Two

3.5.1. The Effect of Steric Bulk and Electronics on the Regioselectivity

The results of the ring opening diborylation reaction discussed in section 3.2 showed that the nature of the 1-substituent in 1-monosubstituted biphenylenes strongly affects the regioselectivity of the reaction. Therefore, the effect of the 1-substituent on the regioselectivity of the ring opening diborylation reaction with B_2pin_2 was next investigated in more detail.

Firstly, the effect of further increasing the steric bulk of the 1-substituent on the regioselectivity of the ring opening diborylation reaction was investigated. This was done by employing 1-aryl substituted biphenylenes which bore substituents in the *ortho*-positions of the phenyl ring as substrates (Scheme 3.13). These biphenylenes would be expected to be at least as sterically bulky, if not more sterically bulky than unsubstituted 1-phenylbiphenylene. The alteration of the 1-substituent also allowed the scope of 1-substituted biphenylenes that are tolerated in the ring opening diborylation reaction to be explored.



R:							
Substrate	**76**	**76**	**80**	**82**	**110**	**78**	**111**
Product	**135**	**135**	**156**	**157**	**158**	**159**	**160**
Yield	82%	76%[a]	81%	74%	61%	70%*	78%
Ratio **a**:**b**	5.8:1	4.8:1	3:1	2.7:1	2.5:1	6.7:1	3:1

[a] reaction conducted at 180 °C, 20 mol% $Pd(dba)_2$, and 40 mol% IAd

Scheme 3.13 *The ring opening diborylation of 1-arylsubstituted biphenylenes, with a substituent in the ortho-position. Yields are isolated yields.*

1-Arylsubstituted biphenylenes which bore methyl, methoxy, *iso*propyl, and naphthalene substituents in the *ortho* position of the phenyl ring underwent the desired ring opening diborylation reaction. The sterically hindered products were isolated in 61-81% yield, demonstrating the potential of this method for the preparation of trisubstituted biaryls.

In contrast to what was expected, the introduction of an *ortho* substituent lead to a decrease in the regioselectivity of the ring opening diborylation reaction. When the *ortho* substituent was methyl or *iso*-propyl, substrates **80** and **111**, the regioselectivity was 3:1. This is lower than the regioselectivity of 5.8:1 that was obtained with 1-phenylbiphenylene. Lower regioselectivities of 2.5:1 and 2.7:1, were obtained when *o*-naphthalene and *o,o*-dimethyl substituted 1-arylbiphenylene substrates **110** and **82** were employed, respectively. Of the *ortho* substituted 1-arylbiphenylenes tested, *o*-methoxy substituted **78** was the only substrate which gave better regioselectivity than

1-phenylbiphenylene, 6.7:1 vs 5.8:1. Substrate **78** was also the least reactive *ortho* substituted substrate and the temperature had to be increased to 180 °C to push the reaction to completion.

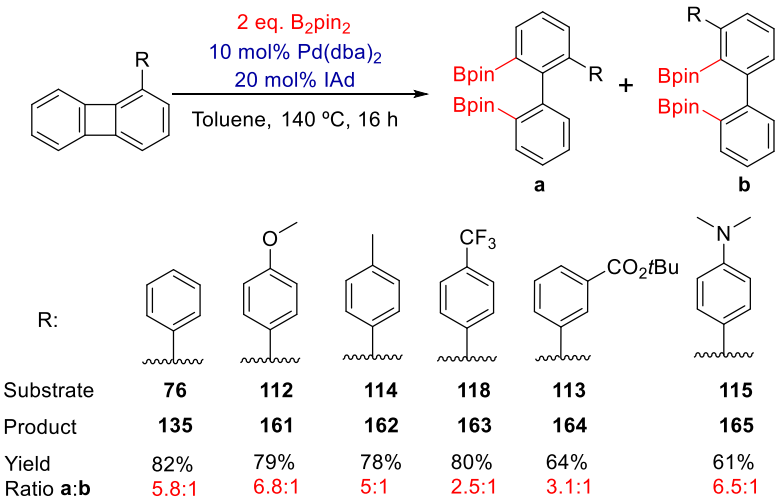
As discussed in section 3.2, it was found that the ring opening diborylation of 1-phenylbiphenylene was more regioselective when the reaction was conducted at 110 °C, than when the reaction was conducted at 140 °C. To determine whether increasing the reaction temperature from 140 °C to 180 °C is detrimental to the regioselectivity of the reaction, the ring opening diborylation of 1-phenylbiphenylene was conducted at 180 °C. At 180 °C the yield of **135** dropped slightly from 82% to 76% and the regioselectivity dropped slightly from 5.8:1 to 4.8:1 (Scheme 3.13). Thus, increasing the temperature from 140 °C to 180 °C does cause a drop in regioselectivity, but not as substantial a drop as when the temperature is increased from 110 °C to 140 °C. These results suggest that **135a** is both the kinetic product and the thermodynamic product and that as the temperature is increased equilibrium is being approached.

The drop in regioselectivity of the ring opening diborylation of 1-phenylbiphenylene, observed upon increasing the reaction temperature from 140 to 180 °C, makes the relatively high regioselectivity obtained in the ring opening diborylation of **78** at 180 °C more unexpected. Of all the *ortho* substituents tested, methoxy was the most electron donating (by resonance), which is the most likely reason for the improved regioselectivity.

The large variability in regioselectivity which does not correlate with the steric bulk of the 1-substituent shows that steric bulk alone does not dictate the regioselectivity of the ring opening diborylation reaction. Therefore, the effect of the electronic properties of the 1-substituent were next investigated (Scheme 3.14). To effectively investigate the effect of electronics on the regioselectivity, substituents were placed in the *meta* and *para* positions so that there was no steric contribution.

Firstly, *p*-methyl **114** and *p*-methoxy **112** substrates were tested (Scheme 3.14). A *p*-methoxy group has a Hammett sigma constant of -0.268 and a methyl group has a Hammett sigma constant of -0.17.[32] A Hammett sigma constant is a measure of how electron donating or withdrawing a substituent is relative to hydrogen: it is the pK_a of benzoic acid minus the pK_a of benzoic acid with the given substituent. Therefore, a

substituent with a negative Hammett sigma constant is electron donating and the more negative the Hammett sigma constant the more electron donating the substituent.



Scheme 3.14 *The ring opening diborylation of 1-arylsubstituted biphenylenes, bearing meta and para substituents with varying electronic properties. Yields are isolated yields.*

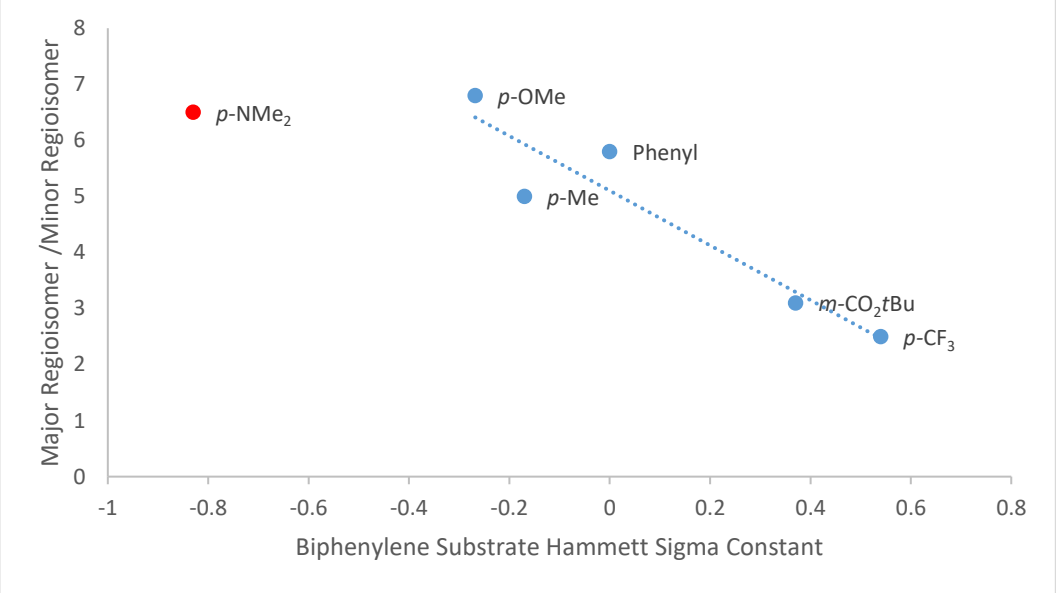
Pleasingly, *p*-methyl substrate **114** and *p*-methoxy substrate **112** underwent the desired transformation to give the desired diborylated products in 79% and 78% yield, respectively. The ring opening diborylation of *p*-methyl substrate **114**, which is slightly more electron rich than 1-phenylbiphenylene, had a regioselectivity of 5:1. This is slightly worse than the 5.8:1 regioselectivity achieved with 1-phenylbiphenylene. The regioselectivity of the ring opening diborylation of the *p*-methoxy substrate **112** was better than 1-phenylbiphenylene, at 6.8:1.

Biphenylene **115**, which contains a strongly electron donating *p*-dimethylamino substituent, Hammett sigma constant -0.83, was next investigated (Scheme 3.14).[32] This substrate was tested to determine whether a further increase in the electron donating ability of the substituent would further improve the regioselectivity of the reaction. Gratifyingly, **115** underwent the desired reaction and the diborylated product was isolated in 61% yield. The regioselectivity of the reaction was 6.5:1, which is better than the regioselectivity of 5.8:1 obtained with 1-phenylbiphenyelene. However, it is slightly lower than the regioselectivity obtained with the *p*-methoxy substrate **112**, which is significantly less electron rich than the *p*-NMe_2 substrate **115**.

Substrates **118** and **113**, which contain strongly electron withdrawing substituents, *p*-CF_3 and *m*-CO_2tBu, were next employed (Scheme 3.14). The Hammett sigma constant

of *p*-CF_3 is 0.54 and the Hammett sigma constant of the related *m*-$CO_2C_2H_5$ is 0.37.[32] Both substrates underwent the desired transformation to give the desired diborylated products **163** and **164** in 80% and 64% yield, respectively. No substantial side-products were isolated in either reaction. The ring opening of *p*-CF_3 biphenylene **118**, the most electron poor substrate, gave the lowest regioselectivity of the substrates tested, 2.5:1, which is significantly lower than the 5.8:1 regioselectivity that was obtained with 1-phenylbiphenylene. The ring opening of *m*-CO_2tBu biphenylene **113**, the second most electron poor substrate tested gave a regioselectivity of 3.1:1, which is higher than *p*-CF_3 substrate **118**, but lower than 1-phenylbiphenylene.

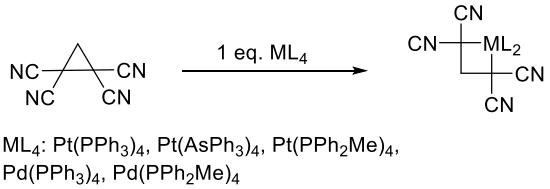
A graph of the biphenylene substrate's Hammett sigma constant *vs* major regioisomer/ minor regioisomer isolated following the ring opening diborylation of these six substrates was plotted (Graph 3.1). The general trend is that substrates bearing more electron withdrawing groups give poorer regioselectivities in the ring opening diborylation reaction.



Graph 3.1 *A plot of Hammett sigma constants vs major regioisomer/ minor regioisomer obtained following the ring opening diborylation reaction of substrates* ***118*** *and* ***112*** *-* ***115****.*

One probable explanation for the lower regioselectivity obtained with electron poor substrates is that an electron withdrawing substituent removes electron density from the C-C bond, causing it to be weaker. A weaker C-C bond is easier to break, rendering it more reactive. An increase in the reactivity of both C-C bonds could cause a drop in

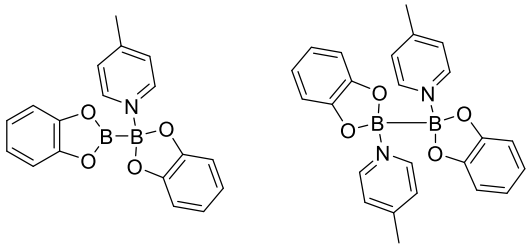
regioselectivity. In addition, the C-C bond closest to the electron withdrawing group, the most sterically hindered one, should be weakened most significantly which is consistent with what is observed. Electron withdrawing groups are known to weaken C-C bonds in related cyclic systems. For instance, when cyclopropyl derivatives bearing electron donating, non-coordinating substituents were reacted with a metal, the least sterically hindered C-C bond was cleaved.[33] Conversely, when 1,1,2,2-tetracyanopropane was reacted with a metal, C-C cleavage occurred at the most sterically hindered C-C bond (Scheme 3.15).[34] This substrate contains four strongly electron withdrawing cyano substituents next to the most sterically hindered C-C bond, which is consistent with electron withdrawing groups activating the adjacent C-C bond towards cleavage.



Scheme 3.15 *The selective cleavage of the most sterically hindered C-C bond in 1,1,2,2-tetracyanopropane.*

Surprisingly, *p*-NMe_2 substrate **115**, which is significantly more electron rich than *p*-methoxy substrate **112**, underwent less regioselective ring opening diborylation than *p*-methoxy substrate **112**. It is possible that increasing the electron richness of the biphenylene substrate improves the regioselectivity up to a point, but that increasing the electron richness of the biphenylene substrate beyond this point does not further benefit the regioselectivity. Alternatively, the comparable regioselectivity obtained with *p*-methoxy substrate **112** and *p*-NMe_2 substrate **115** could be explained by excess B_2pin_2 in the reaction mixture coordinating to the nitrogen lone pair. This would make the lone pair unavailable for donation into biphenylene and thus the dimethylamino substituent would not be strongly electron donating.

In a related example, Marder *et al.* showed that when one equivalent of picoline was added to B_2cat_2, complex **166** formed and when two equivalents of picoline were added to B_2cat_2, complex **167** was formed (Fig. 3.7).[35] Although B_2pin_2 is a weaker Lewis acid than B_2cat_2 and did not coordinate to picoline, it may coordinate to the nitrogen atom in biphenylene **115**.



166 167

Fig. 3.7 *The structures of compounds **166** and **167** prepared by the reaction of B_2cat_2 with picoline.*

The products of the ring opening diborylation reaction contain a sterically congested biaryl axis and therefore have the potential to be axially chiral. An axially chiral biaryl compound is one which has different substituents on each side of a rotationally stable biaryl axis (Fig. 3.8 where A ≠ B).[36] In general, tri-*ortho* or tetra-*ortho* substituted biaryls form stable atropisomers.[36] It is therefore very likely that the major regioisomer of the ring opening diborylation reaction, **168** (Fig. 3.9), is rotationally stable. Di-*ortho* substituted biaryls can also be axially chiral, but only if both substituents are bulky, therefore it is possible that the minor regioisomer **169** (Fig. 3.9), which has two bulky Bpin groups in two of the *ortho* positions is axially chiral.[36]

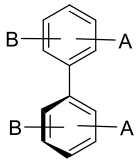
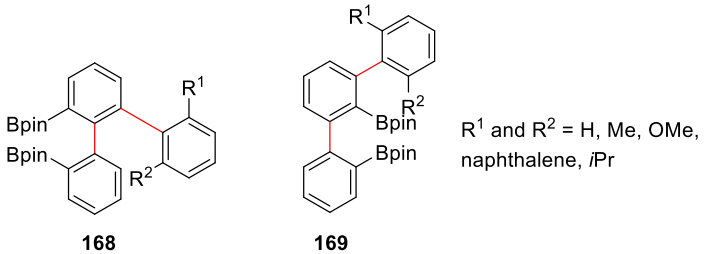


Fig. 3.8 *An axially chiral biaryl, where A ≠ B and the biaryl axis is rotationally stable.*



168 169

Fig. 3.9 *The structure of the two possible regioisomers **168** and **169** resulting from the ring opening diborylation of 1-(o-substitutedphenyl)biphenylenes.*

Rotational stability was confirmed in the major regioisomers **156a**, **158a**, and **160a**, which were isolated as a mixture of two diastereomers. The observation of two diastereomers is consistent with the two biaryl axes, highlighted in red in **168** (Fig.

3.9), both being axially chiral. The diastereoselectivity varied from substrate to substrate: **156a**: 3:1, **158a**: 2.3:1, and **160a**: 1.8:1. The difference in diastereoselectivity between substrates might be due to the relative stability of the diastereomers or could be controlled by kinetics. When R^1=R^2, the biaryl axis adjacent to R^1 and R^2 is not axially chiral and therefore diastereomers were not observed in the NMR spectra of **135a**, **157a** and **161a**-**165a** (Fig. 3.9). The steric environment of the second biaryl axis (adjacent to the two Bpin groups) is very similar to that in regioisomers **156a**, **158a**, and **160a** and is therefore likely to be rotationally stable. Thus, although it was not definitively proven, regioisomers **135a**, **157a**, and **161a**-**165a** likely exist as a mixture of enantiomers.

Somewhat surprisingly, unlike **156a**, **158a**, and **160a**, **159a** was not isolated as a mixture of diastereomers. Only one product was visible in the proton and carbon NMR spectra. This could be explained by one of the lone pairs on the methoxy oxygen interacting with the empty p-orbital on the adjacent Bpin moiety, which could make one diastereomer more thermodynamically stable than the other (Fig. 3.10).

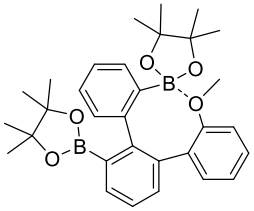


Fig. 3.10. *The structure of **159a**, in which the potential interaction between oxygen on the methoxy group and boron on the Bpin group is highlighted.*

The NMR spectrum of **159a** was also unusual because the methoxy signal, one of the Bpin methyl signals, and three of the aromatic proton signals were broadened (Fig. 3.11 and Fig. 3.12). One potential explanation for the broad signals observed at room temperature is the emergence of weak interactions between the methoxy and Bpin groups, limiting rotation about the C-O and C-B bonds (Fig. 3.10). It was thought that by lowering the temperature, the rotation about these bonds would be further impacted producing sharper NMR signals.

When the sample was cooled down in 25 °C intervals to -25 °C, the methoxy signal became increasingly sharp as did the three aromatic proton signals (Fig. 3.11 and Fig. 3.12). This is consistent with rotation being restricted and only the most stable conformer being observed. As the temperature was lowered two of the Bpin methyl

signals merged into one: this is most probably due to a change in the populations of different conformations in solution causing a change in the chemical shift. Further lowering of the temperature to -50 °C resulted in subsequent broadening of the signals due to a large change in the viscosity of the solution. Despite its unusual NMR spectrum, the structure of **159a** was confirmed by XRD (Fig. 3.13).

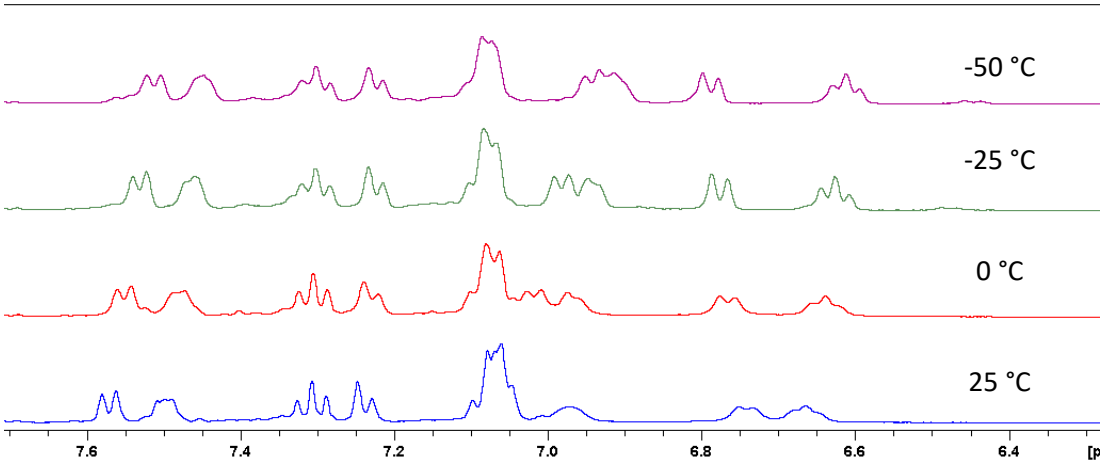


Fig. 3.11 *Aromatic region of the NMR spectrum of* ***159a*** *at 25 °C, 0 °C, -25 °C, and -50 °C.*

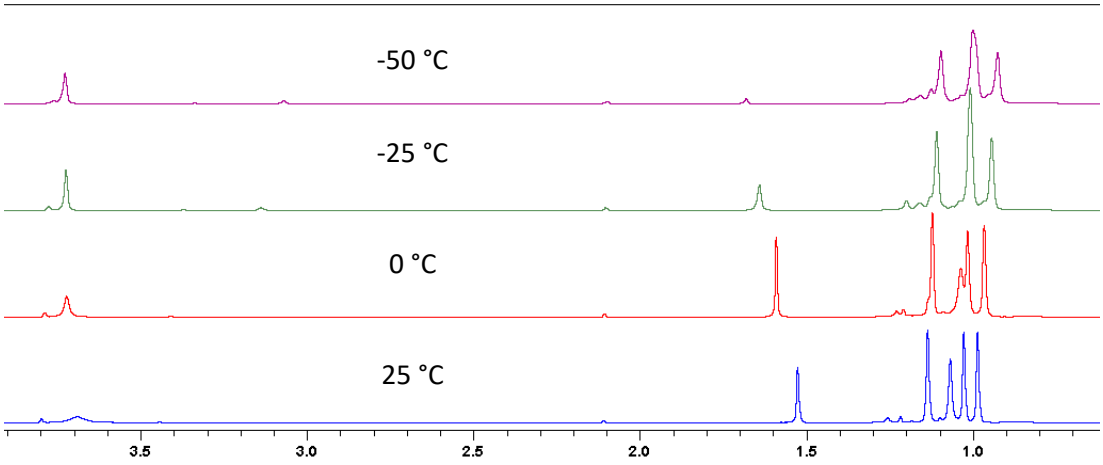


Fig. 3.12 *Aliphatic region of the NMR spectrum of* ***159a*** *at 25 °C, 0 °C, -25 °C, and -50 °C.*

A mixture of diastereomers was not observed in the NMR spectra of any of the minor regioisomers (**169** Fig. 3.9) resulting from the ring opening diborylation of 1-arylsubstituted biphenylenes. Thus, there are two possibilities, firstly, the reaction is highly diastereoselective, which is unlikely given the high reaction temperature of 140 °C. Secondly, and most probably, one of, or both biaryl axes highlighted in red in **169**

are not axially chiral, i.e. their rotation at room temperature is faster than the NMR time scale (Fig. 3.9).

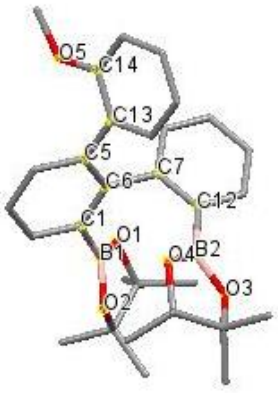


Fig. 3.13. *Single crystal structure of regioisomer* ***159a****.*

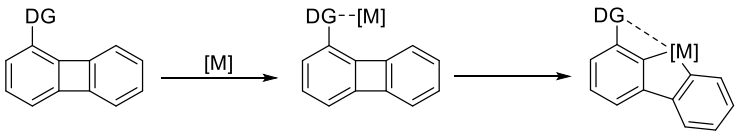
To conclude, it was shown that a range of functional groups were tolerated in the ring opening diborylation of biphenylenes. Although good regioselectivity for the least sterically hindered C-C bond was achieved in the ring opening diborylation of 1-arylsubstituted biphenylenes, there was still some cleavage of the more sterically hindered C-C bond. Therefore, it was next investigated whether placing a directing group in the 1-position could improve the regioselectivity of the ring opening diborylation reaction.

3.5.2. The Investigation of the Use of Pyridine and Diphenylphosphine as Directing Groups

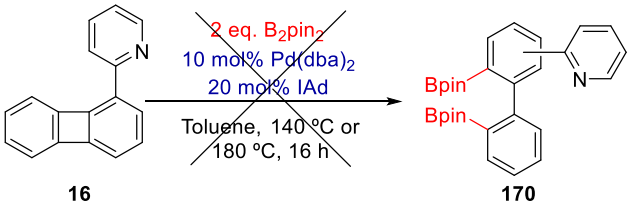
As discussed in the introduction, it has been reported that placing an alkene or alkyne bearing aryl ring, or a pyridyl in the 1-position of biphenylene can direct the transition metal complex to the adjacent C-C bond (Scheme 3.16). It was hoped that a similar directing effect would be observed in the ring opening diborylation reaction. Alkene and alkyne based directing groups were not investigated because B_2pin_2 would most likely react with these functional groups instead of the strained biphenylene C-C bond. Instead, the first directing group to be investigated was pyridine.

When 1-(2-pyridyl)biphenylene **16** was employed as the substrate, no conversion was observed after sixteen hours at 140 °C (Scheme 3.17). The reaction was next conducted

at 180 °C, but even at this higher temperature none of the desired product was isolated and only starting material was recovered. It is most likely that the nitrogen atom coordinates to the catalyst to form an unreactive complex, which prevents the desired transformation from taking place.



Scheme 3.16 *Directed cleavage of the most sterically hindered C-C bond in 1-substituted biphenylenes.*

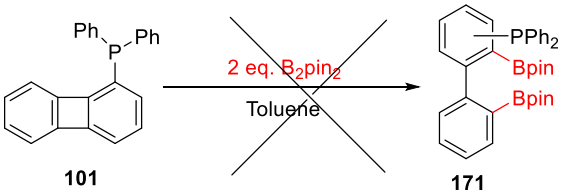


Scheme 3.17 *The attempted ring opening diborylation of 1-(2-pyridyl)biphenylene.*

The second directing group to be tested was diphenylphosphine. Like the nitrogen atom in pyridine, the phosphorus atom in diphenylphosphine has a lone pair which could coordinate to the catalyst and direct it to the adjacent C-C bond. The reaction was first conducted using the optimised reaction conditions at 140 °C (Scheme 3.18). The conversion was approximately 50% but none of the desired product was obtained: instead two side-products that could not be identified were isolated. NMR and mass-spectra of the first product were not consistent with the products of reduction, dimerisation, monoborylation, or oxidation. The second product is most likely oxidised starting material because the shift of phosphorus in the phosphorus NMR was 24.7 ppm, which is consistent with phosphine oxide. However, oxidised starting material was not observed by GC-MS. It was not possible to estimate a yield for this side-product because it was not clean.

The reaction was next conducted at 180 °C to try to push it to completion (Scheme 3.18). After forty hours of heating, the reaction went to completion, but none of the desired product was obtained. The same, first side-product that was isolated when the reaction was conducted at 140 °C was isolated and accounted for approximately 30% of the mass balance. Two further products were also isolated but could not be

identified. This chemistry was not pursued any further because none of the desired product was isolated and the reaction was not chemoselective for any product. It is likely that at 180 °C decomposition of the starting material starts to take place.



Conditions A: 10 mol% $Pd(dba)_2$, 20 mol% IAd, 140 °C, 16 h
Conditions B: 20 mol% $Pd(dba)_2$, 40 mol% IAd, 180 °C, 40 h

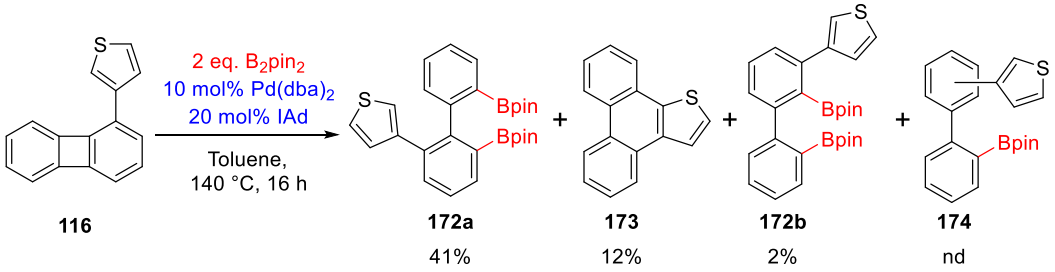
Scheme 3.18 *The attempted ring opening diborylation of 1-(diphenylphosphine)biphenylene.*

3.5.3. The Investigation of 1-BpinBiphenylene and 1-(3-Thiophene) Biphenylene as Substrates

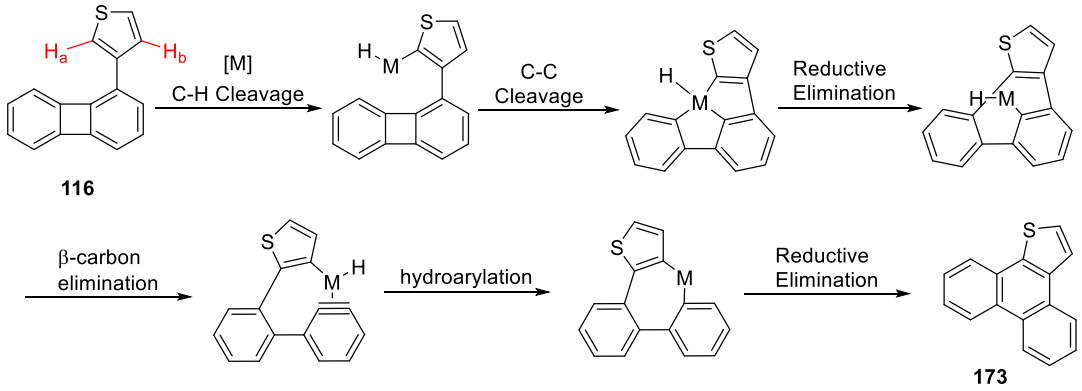
With the aim of further investigating the scope of the ring opening diborylation reaction, biphenylene substrates bearing sulfur and boron heteroatoms were next investigated. 1-(3-Thiophene)biphenylene was first tested using the optimised reaction conditions (Scheme 3.19). The major product of the reaction was the desired diborylated product **172a**, which was isolated in 41% yield. The regioisomer, **172b** was also isolated in approximately 2% yield. Estimating the regioselectivity of the reaction by adding standard to the isolated product **172** gave a regioselectivity of 20:1, whereas the regioselectivity from the crude NMR spectrum was 10:1, both are approximate due to a lack of clean signals in the NMR spectra. Although the regioselectivity is approximate, the ring opening diborylation of 1-(3-thiophene)biphenylene is better than when 1-phenylbiphenylene underwent ring opening diborylation: 5.8:1. Thiophene is an electron rich heterocycle because of the electron donating ability of the sulfur atom and this result is therefore fitting with electron rich substrates giving higher regioselectivities in the ring opening diborylation reaction.

The side-product phenanthro[9,10-*b*]thiophene **173** was isolated in 12% yield. This is the same side-reaction that was observed when the ring opening of 1-phenylbiphenylene was attempted with the diboranes **140** and **143**. The most likely

mechanism is as described in section 3.4 and is outlined in Scheme 3.20. Unlike when 1-phenylbiphenylene was the substrate, there are two different C-H bonds which could undergo C-H activation, highlighted in red: **173** is formed when the C-H bond adjacent to sulfur, CH_a, undergoes C-H activation. Interestingly, none of the regioisomer resulting from the C-H activation of CH_b was observed. Finally, monoborylated product **174** was also identified by HR-MS and could account for some of the missing mass balance in this ring opening reaction.



Scheme 3.19 *The ring opening diborylation of 1-(3-thiophene)biphenylene.*

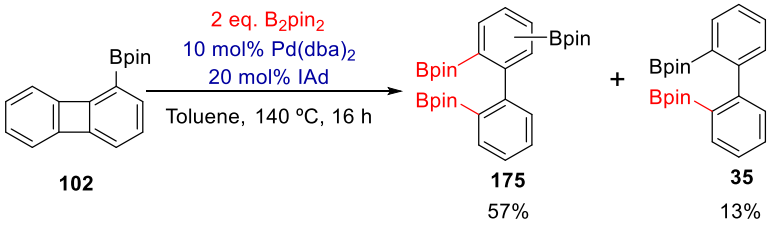


Scheme 3.20 *Proposed mechanism for the formation of phenanthro[9,10-b]thiophene* ***173*** *from 1-(3-thiophene)biphenylene* ***116****.*

1-Bpinbiphenylene was next tested in the ring opening diborylation reaction and the desired diborylated product, **175**, was isolated in 57% yield (Scheme 3.21). By NMR, a single regioisomer was present although it could not be determined from the NMR spectrum alone which regioisomer had formed. Attempts to grow crystals of this product were unsuccessful. It is most probable that this is the product resulting from cleavage of the least sterically hindered C-C bond because this bond was cleaved preferentially in other 1-substituted biphenylenes tested in this study.

The product of monoborylation of the least sterically hindered C-C bond, **35**, was isolated in 13% yield. Biaryl **35** is a known compound, and its structure was confirmed by NMR, however, interestingly none of the other three possible monoborylated

isomers were observed. The isolation of only this regioisomer supports the theory that the least sterically hindered C-C bond is preferentially cleaved and that the diborylated isomer obtained is that resulting from cleavage of the least sterically hindered C-C bond. Although the yield of the ring opening diborylation of 1-Bpinbiphenylene was moderate, besides the ring opening diborylation of 1-(trimethylsilyl)biphenylene, this is the only ring opening diborylation reaction in which a single regioisomer of the desired diborylated product was isolated.



Scheme 3.21 *The ring opening diborylation of 1-BpinBiphenylene with B_2pin_2.*

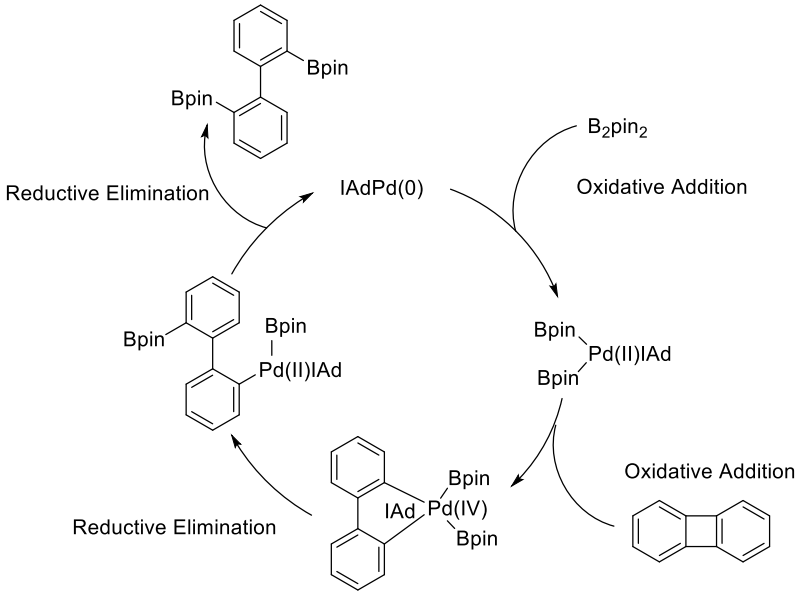
To conclude, sterically bulky trisubstituted biaryls were prepared in high yields *via* the ring opening diborylation of a range of 1-substituted biphenylenes with B_2pin_2. Functional groups tolerated in the reaction included Bpin, 3-thiophene, alkyl, methoxy, ester, amine, and CF_3. It is clear from the results of these reactions that the regioselectivity of the reaction is substrate dependent, however, to fully understand the regioselectivities observed investigation of the reaction mechanism is necessary.

3.6. Mechanistic Insight

To rationalise the different regioselectivities obtained with different substrates in the ring opening diborylation reaction, investigation of the reaction mechanism is necessary. Several different mechanisms are plausible, but for simplicity in this section the focus will be on the two main types of mechanism for C-C diborylation in biphenylenes.

The first of these mechanisms is outlined in Scheme 3.22. In this mechanism, the B-B bond in B_2pin_2 is cleaved first and the strained C-C bond in biphenylene is cleaved second. Braga, Navarro, Spencer *et al.* who reported the diborylation of alkynes catalysed by **176** (Fig. 3.14), proposed based on DFT calculations that cleavage of the B-B bond in B_2pin_2 occurs before cleavage of the C-C triple bond of the alkyne.[37] Two

sequential reductive eliminations would follow the two oxidative additions to yield the desired diborylated product. In the second mechanism, the strained C-C bond in biphenylene is cleaved first and the B-B bond in B_2pin_2 is cleaved second as depicted in Scheme 3.23. Similarly, two subsequent sequential reductive eliminations yield the desired diborylated product.



Scheme 3.22 *Potential mechanism for the ring opening diborylation reaction.*

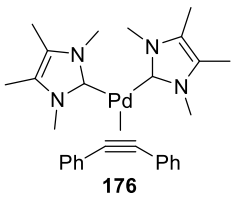
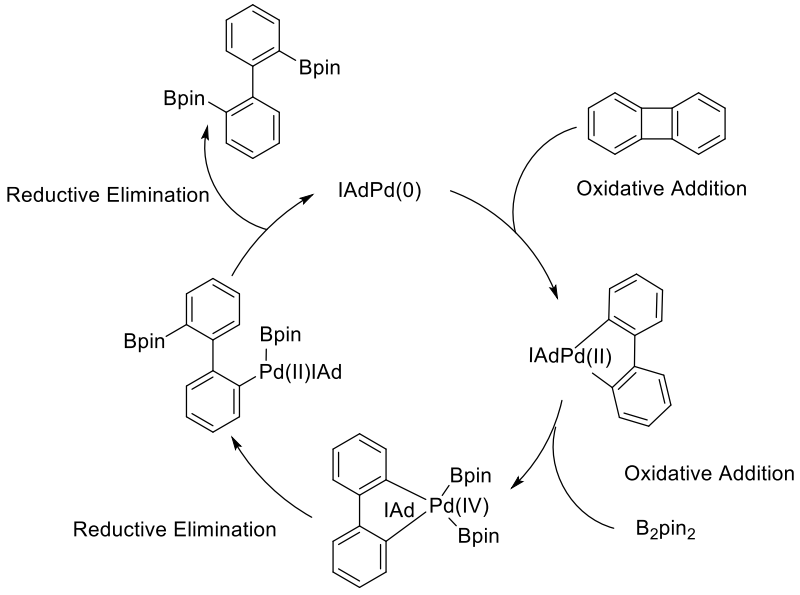


Fig. 3.14 *The structure of N-heterocyclic carbene bearing catalyst* ***176****.*

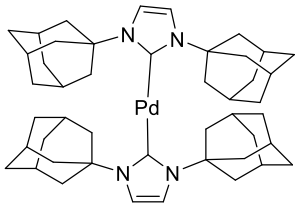


Scheme 3.23 *Potential mechanism for the ring opening diborylation reaction.*

To distinguish between the two most probable mechanisms described in Scheme 3.22 and Scheme 3.23, it is necessary to determine whether B-B or C-C cleavage occurs quicker. To do this, it is necessary to conduct two reactions: one in which the biphenylene substrate is reacted with a stoichiometric amount of catalyst and one in which B_2pin_2 is reacted with a stoichiometric amount of catalyst. The reactions should initially be conducted at room temperature and the temperature increased in increments until one of the substrates is consumed to determine which reagent, B_2pin_2 or biphenylene, reacts most quickly with the palladium catalyst.

In the ring opening diborylation reaction, $Pd(dba)_2$ is employed as the metal precursor and IAd is employed as the ligand. It was a concern that free dba, formed following the complexation of IAd and which contains two alkene moieties, could react with B_2pin_2, and that this would give inconclusive results. This was not a problem in the catalytic reaction because 10 mol% catalyst was used and therefore only 20 mol% dba was generated, which is less than the one equivalent excess of B_2pin_2 that was employed.

$Pd(IAd)_2$ (Fig. 3.15) was chosen as a cleaner alternative source of the active palladium catalyst. This is because it was expected that $Pd(IAd)_2$ is formed *in situ* from the reaction of $Pd(dba)_2$ and IAd and that this is the starting complex in the catalytic cycle. Using $Pd(IAd)_2$ directly is much cleaner than generating it *in situ* because it avoids the formation of unnecessary side-products such as dba.

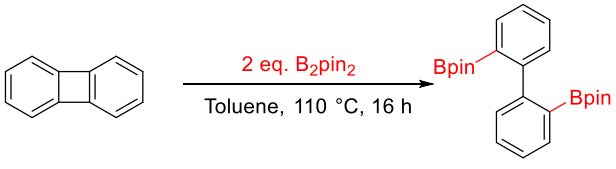


$Pd(IAd)_2$

Fig. 3.15 *The structure of $Pd(IAd)_2$ believed to be the catalytically active starting complex in the ring opening diborylation reaction of biphenylenes.*

$Pd(IAd)_2$ could be readily prepared in the lab using the literature procedure.[38] However, before any mechanistic studies could be conducted with $Pd(IAd)_2$, it was first necessary to confirm that it did catalyse the ring opening diborylation of biphenylenes. This was done by conducting two reactions, one in which biphenylene was subjected to the standard ring opening diborylation conditions and one in which

$Pd(dba)_2$ and IAd were replaced by $Pd(IAd)_2$ (Scheme 3.24). As expected, using the standard conditions the reaction worked well and the desired diborylated product **35** was isolated in 89% yield, which is a significant improvement on the previous 57% literature yield.[1] When $Pd(IAd)_2$ was employed as the catalyst, the reaction worked similarly well and the desired product **35** was again isolated in 89% yield. This result is consistent with $Pd(IAd)_2$ being generated *in situ* from $Pd(dba)_2$ and IAd, and with $Pd(IAd)_2$ being the catalytically active starting complex.



35

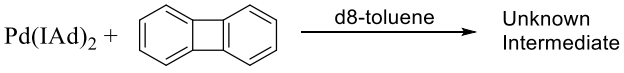
Conditions A: 10 mol% $Pd(dba)_2$, 20 mol% IAd — 89%
Conditions B: 10 mol% $Pd(IAd)_2$ — 89%

Scheme. 3.24 *The ring opening diborylation of biphenylene catalysed by a combination of $Pd(dba)_2$ and IAd, and $Pd(IAd)_2$.*

Therefore $Pd(IAd)_2$ was chosen as the catalyst for the model reaction and, as the only diborane that was found to work in the ring opening diborylation reaction, B_2pin_2 was chosen as the diborane substrate. Biphenylene was chosen as the model biphenylene substrate for two reasons. Firstly, biphenylene has the simplest NMR spectrum of all the biphenylene substrates tested in the ring opening diborylation reaction and none of the proton signals overlapped with either toluene or $Pd(IAd)_2$, therefore the reaction could be followed by proton NMR. Secondly, biphenylene was the only symmetrical substrate tested, therefore the ring opening diborylation of biphenylene does not produce regioisomers and the NMR spectra of the intermediates and products of the reaction will be simpler and easier to interpret, thus making the reaction easier to follow.

Firstly, biphenylene was reacted with a stoichiometric amount of $Pd(IAd)_2$ in d8-toluene and the reaction monitored by NMR spectroscopy (Table 3.6). After two hours at 80 °C, 42% biphenylene had been consumed (Table 3.6, Entry 4). The reaction was significantly accelerated at 110 °C and after twenty minutes at this temperature biphenylene had been fully consumed (Table 3.6, Entry 6).

Table 3.6 The reaction of $Pd(IAd)_2$ with biphenylene in d8-toluene, which was followed by NMR spectroscopy.



Entry	T/°C	Time	Biphenylene Conversion (%)
1	50	2 h	0
2	80	10 min	5
3	80	1 h	18
4	80	2 h	42
5	110	10 min	88
6	110	20 min	100

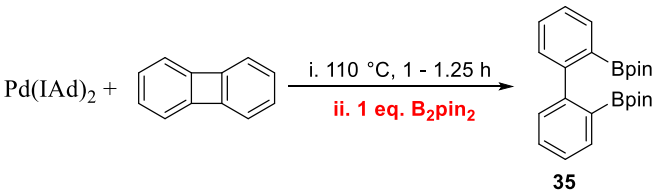
Conversions are based on NMR analysis using 1,3,5-trimethoxybenzene as the internal standard (6 μmol scale).

To determine if the product of the reaction of $Pd(IAd)_2$ and biphenylene was an intermediate in the catalytic cycle, it was treated with a stoichiometric amount of B_2pin_2 and the formation of the desired product **35** was monitored by NMR spectroscopy (Table 3.7). Upon addition of B_2pin_2 at room temperature, the desired product **35** was formed in 74-80% NMR yield after two hours (Table 3.7, Entries 1, 7, and 12). It was found that leaving the reaction mixture at room temperature for more than two hours did not improve the NMR yield (Table 3.7, Entries 2-4). Pleasingly, upon raising the reaction temperature to 50 °C a slight increase in the NMR yield of the desired product **35** was observed from 74-80% to 83-84%, but extended heating at 50 °C did not give a further increase in the NMR yield (Table 3.7, Entries 8, 9, 13, and 14). The $Pd(IAd)_2$ complex was regenerated, which is consistent with the process being catalytic.

Although the NMR yield of the desired product **35** was good (83-84%), the isolated yield in the catalytic reaction was slightly higher (89%). It was thought that the difference in yield might be because two equivalents of B_2pin_2 were used in the catalytic reaction opposed to the one used in the stoichiometric reactions. As discussed in section 3.1, in the screening reactions with 1-fluorbiphenylene, the GC yield of the desired diborylated product **122** improved significantly from 64% to 85% when the

equivalents of B_2pin_2 were increased from 1.1 to 2. Therefore, the stoichiometric reaction of biphenylene with $Pd(IAd)_2$ was repeated, using two equivalents of B_2pin_2 in the second step (Table 3.8).

Table 3.7 The reaction of biphenylene with $Pd(IAd)_2$ followed by reaction with 1 eq. B_2pin_2 to yield **35**. The reaction was run three times, to check reproducibility.

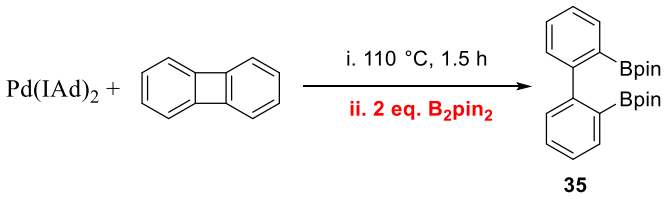


35

Run 1: 2nd Step (addition of B_2pin_2)			
Entry	**T/ °C**	**Time**	**35 Yield (%)**
1	25	2 h	74
2	25	3 h	77
3	25	4 h	77
4	25	5 h	77
Run 2: 2nd Step (addition of B_2pin_2)			
Entry	**T/ °C**	**Time**	**35 Yield (%)**
5	25	10 min	32
6	25	1 h	74
7	25	2 h	80
8	50	30 min	83
9	50	1.5 h	84
Run 3: 2nd Step (addition of B_2pin_2)			
Entry	**T/ °C**	**Time**	**35 Yield (%)**
10	25	10 min	34
11	25	1 h	78
12	25	2 h	77
13	50	30 min	81
14	50	1.5 h	83

Yields are based on NMR analysis using 1,3,5-trimethoxybenzene as the internal standard (6 μmol scale).

Table 3.8 The reaction of biphenylene with $Pd(IAd)_2$ followed by reaction with 2 eq. B_2pin_2 to yield **35**.



35

2nd Step (addition of B_2pin_2)			
Entry	**T/°C**	**Time**	**35 yield (%)**
1	25	10 min	53
2	25	1 h	77
3	25	2 h	78
4	50	30 min	79
5	50	1.5 h	81

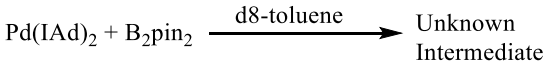
Yields are based on NMR analysis using 1,3,5-trimethoxybenzene as the internal standard (6 μmol scale).

Unfortunately, doubling the equivalents of B_2pin_2 did not improve the NMR yield of the desired diborylated product **35**, which was comparable to the yield obtained when only one equivalent of B_2pin_2 was added to the reaction mixture (Table 3.8, Entry 5). This is consistent with an excess of B_2pin_2 being needed in the reactions with $Pd(dba)_2$ because B_2pin_2 adds across the double bond of dba, which is formed upon complexation of IAd. The results from these reactions suggest that C-C bond cleavage followed by B-B bond cleavage is a feasible reaction pathway. This is because this sequence was catalytic with respect to $Pd(IAd)_2$, the reaction time was shorter than that used for the catalytic reactions, and the yield of diborylated product **35** was comparable.

To determine if B-B bond cleavage followed by C-C bond cleavage is a feasible reaction pathway, a stoichiometric amount of $Pd(IAd)_2$ was next reacted with B_2pin_2 (Table 3.9). After two hours at 80 °C, 24% B_2pin_2 had been consumed (Table 3.9, Entry 4) and at 110 °C the reaction was significantly accelerated. After two hours at 110 °C, 58% B_2pin_2 had been consumed and after sixteen hours (as in the standard reaction conditions) 98% B_2pin_2 had been consumed (Table 3.9, Entries 7 and 8). The rate of reaction was substantially slower than that observed in the corresponding

reaction with biphenylene, which went to completion within one and a half hours at 110 °C.

Table 3.9 The reaction of $Pd(IAd)_2$ with B_2pin_2 in d8-toluene, which was followed by NMR spectroscopy.



Entry	T/°C	Time	B_2pin_2 Conversion (%)
1	50	2 h	0
2	80	10 min	8
3	80	1 h	16
4	80	2 h	24
5	110	10 min	27
6	110	1 h	45
7	110	2 h	58
8	110	16 h	98

Conversions are based on NMR analysis using 1,3,5-trimethoxybenzene as the internal standard (6 μmol scale).

After heating the mixture of B_2pin_2 and $Pd(IAd)_2$ at 80 °C for two hours a black solid crashed out. It was considered likely that this was a consequence of the instability of $Pd(IAd)_2$ in d8-toluene at elevated temperature for extended periods of time. To confirm this, $Pd(IAd)_2$ was subjected to the same conditions as the mixture of $Pd(IAd)_2$ and B_2pin_2 and monitored by NMR spectroscopy (Table 3.10). It was found that after heating the solution at 80 °C for two hours, the $Pd(IAd)_2$ complex began to decompose and upon heating to 110 °C, a black solid crashed out. After sixteen hours at 110 °C in d8-toluene, 53% of the $Pd(IAd)_2$ complex had decomposed (Table 3.10, Entry 8). This experiment shows that $Pd(IAd)_2$ is not stable for the duration of the reaction.

Table 3.10 The decomposition of $Pd(IAd)_2$ upon heating, which was followed by NMR spectroscopy.

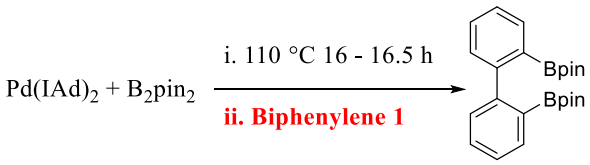
Entry	T/°C	Time	$Pd(IAd)_2$ Conversion (%)
1	50	2 h	0
2	80	10 min	0
3	80	1 h	3
4	80	2 h	12
5	110	10 min	12
6	110	1 h	20
7	110	2 h	34
8	110	16 h	53

Conversions are based on NMR analysis using 1,3,5-trimethoxybenzene as the internal standard (6 μmol scale).

The reaction of B_2pin_2 with a stoichiometric amount of $Pd(IAd)_2$ was next repeated and after sixteen hours at 110 °C, one equivalent of biphenylene was added to the reaction mixture (Table 3.11). This was to determine whether the product resulting from this reaction would react with biphenylene to produce the desired product **35**. Following the addition of biphenylene and after two hours at 80 °C, formation of the desired product **35** was observed (Table 3.11, Entries 3, 9, and 16). However, the NMR yield was not reproducible and varied significantly from 18-55% between different reactions (Table 3.11, Entries 6, 13, and 18).

This can be explained by the reaction of B_2pin_2 and $Pd(IAd)_2$ not going to completion after sixteen hours at 110 °C. The $Pd(IAd)_2$ which remains after the first step reacts with biphenylene at 80 °C and the intermediate resulting from this reaction reacts with B_2pin_2 which was not consumed in the first step, to yield the desired product **35**. This is supported by the observation that the highest yields of **35** were obtained in the reactions in which the greatest amount of B_2pin_2 remained after sixteen hours of heating at 110 °C (Table 3.11, Entries 6, 13, and 18). In none of the reactions was $Pd(IAd)_2$ regenerated, which shows that the pathway in which B_2pin_2 reacts with the catalyst before biphenylene is not catalytic with respect to $Pd(IAd)_2$.

Table 3.11 The reaction of B_2pin_2 with $Pd(IAd)_2$ followed by reaction with 1 eq. biphenylene to yield **35**. The reaction was run three times to check reproducibility.



35

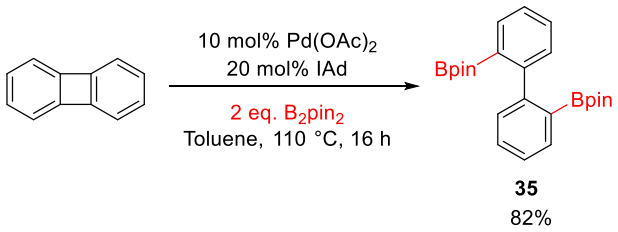
Run 1: 2nd Step (addition of **1**), B_2pin_2 after 1st Step: 2.7 µmol				
Entry	**T/ °C**	**Time**	**Conversion of 1**	**35 Yield (%)**
1	50	2 h	0	0
2	80	1 h	11	0
3	80	2 h	27	16
4	80	4 h	58	54
5	110	0.5 h	97	55
6	110	1 h	100	55
Run 2: 2nd Step (addition of **1**), B_2pin_2 left after 1st Step: 0.12 µmol				
Entry	**T/ °C**	**Time**	**Conversion of 1**	**35 Yield (%)**
7	50	2 h	0	0
8	80	1 h	9	0
9	80	2 h	18	3
10	80	4 h	42	13
11	110	0.5 h	78	17
12	110	1 h	91	17
13	110	1 h 15	94	18
Run 3: 2nd Step (addition of **1**), B_2pin_2 left after 1st Step: 1.55 µmol				
Entry	**T/°C**	**Time**	**Conversion of 1**	**35 yield (%)**
14	50	2 h	0	0
15	80	1 h	40	27
16	80	2 h	60	37
17	80	4 h	76	39
18	110	0.5 h	100	39

Yields are based on NMR analysis using 1,3,5-trimethoxybenzene as the internal standard (6 µmol scale).

The results of these reactions suggest that C-C bond cleavage occurs before B-B bond cleavage in the reaction pathway. This is supported by two observations, firstly, the

reaction in which C-C bond cleavage occurs first was found to be catalytic with respect to $Pd(IAd)_2$. Secondly, the reaction in which C-C bond cleavage occurs first occurred at the same temperature as the catalytic reaction in shorter time and gave the desired product **35** in comparable yield.

One final reaction was conducted in which $Pd(OAc)_2$ was used as the palladium precursor instead of $Pd(dba)_2$ (Scheme 3.25). This was to determine if palladium (II), which is in general more stable than palladium (0), could instead be used as a source of palladium in the reaction. The reaction worked well giving the desired diborylated product **35** in 82% yield. This is only slightly lower than the 89% yield which was obtained when palladium (0) was used as the palladium source. In the literature it has been shown that heating several $[LPd(OAc)_2]$ complexes with B_2pin_2 at 70 °C resulted in their reduction to palladium (0).[39] Therefore, it is most likely that B_2pin_2 reduces palladium (II) to palladium (0), which is the catalyst.



Scheme 3.25 *The ring opening diborylation of biphenylene using $Pd(OAc)_2$ as the palladium source.*

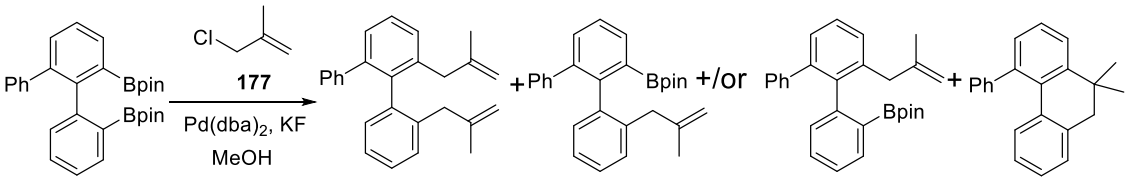
3.7. Post-Functionalisation of the Ring Opened Products

3.7.1. Allylation of the Ring Opened Products

The tri *ortho* substituted biaryl products which result from the ring opening diborylation of 1-monosubstituted biphenylenes contain two pinacolboronate ester moieties. As discussed in section 1.3.1, aryl pinacolboronate esters are important synthetic intermediates because they can undergo several transformations. The ring opened products therefore have the potential to give synthetic access to a wide range of functionalised aromatic products. Of the possible functionalisations, C-C bond forming reactions are particularly attractive because they help to increase the complexity of the carbon framework. Therefore, in this work post-functionalisation reactions in which a C-C bond is formed were investigated.

The first post-functionalisation of the ring opened diborylated products to be investigated was diallylation. Diallylation was investigated because allyl groups are themselves versatile functional groups that could undergo several post-functionalisation reactions to yield new and potentially useful products.[40] The allylation of aryl pinacolboronate esters has been reported by both Hartwig *et al.* and Ortar using different, less sterically hindered substrates, as discussed in section 1.3.1.[41,42] The conditions reported by Hartwig were chosen as a starting point for the diallylation of **135** for two reasons. Firstly, Hartwig *et al.* tested a wider range of substrates, including both allyl chlorides and allyl acetates. Secondly, Hartwig's conditions were ligandless and therefore more synthetically attractive.

The diallylation of **135** was first attempted using 3-chloro-2-methylpropene **177** as the coupling partner (Scheme 3.26, Conditions A). More forcing conditions were required than those reported by Hartwig *et al.*, presumably because **135** is much more sterically hindered than the substrates tested by Hartwig *et al.* Despite this, in the presence of 12 mol% $Pd(dba)_2$ (6 mol% per Bpin) complete consumption of the starting material was achieved following heating at 50 °C.



135 **178** **179a** **179b** **180a (OR 180b)**

Conditions A: i. 4 mol% $Pd(dba)_2$, 4 eq. **177**, 4 eq. KF, MeOH, rt, 24 h, then 50 °C, 24 h **ii.** 8 mol% $Pd(dba)_2$, 50 °C, 20 h — ~ 34 % — ~34 % — Trace

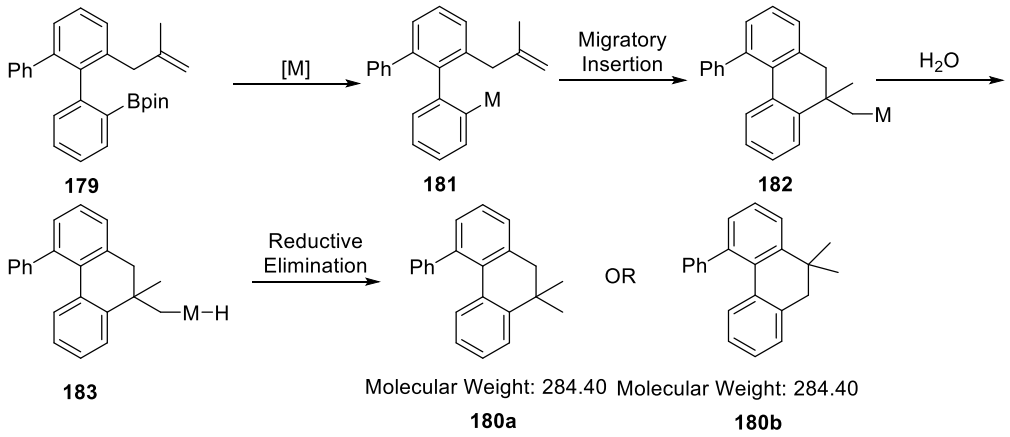
Conditions B: i. 15 mol% $Pd(dba)_2$, 4 eq. **177**, 4 eq. KF, MeOH, 70 °C, 18 h **ii.** 15 mol% $Pd(dba)_2$, 2 eq. **177**, 2 eq. KF, 70 °C, 18 h — ~54 % — ~12 %

Scheme 3.26 *Attempts to diallylate biaryl* ***135*** *with 3-chloro-2-methyl-1-propene* ***177****.*

Three inseparable products were isolated. The two major components of the mixture were consistent with the desired diallylated product **178** and the monoallylated product **179**. It was not possible to determine which isomer of the monoallylated product was present or if it was a mixture of both, although NMR suggests that it is likely one regioisomer. The yield of the monoallylated produced was estimated to be 34% and

the yield of the diallylated product was estimated to be 34% from the integration of the Bpin Me signals, alkene Me signals, and CH_2 signals in the proton NMR spectrum.

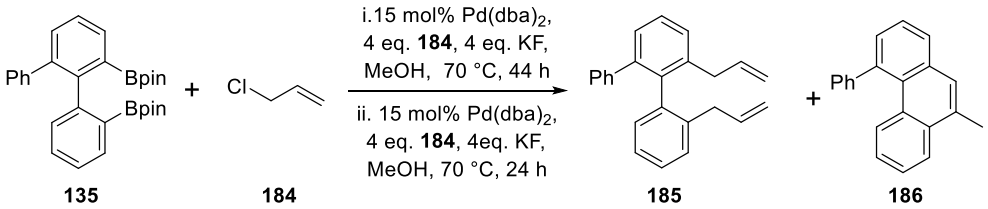
Only a trace amount of the third compound was present. By HR-MS, an ion with m/z 285 g/mol was observed. This is most probably **180a** or its regioisomer **180b**, which could be formed from the monoallylated product by the mechanism outlined in Scheme 3.27, if trace amounts of water were present. The necessity for water would explain why only trace amounts of **180** were isolated. Both isomers are equally plausible, i.e. either monoallylated regioisomer could undergo the reaction and it was not possible to tell from the GC-MS spectrum alone whether one isomer or a mixture of both had been formed.



Scheme 3.27 *Likely mechanism for the formation of side-product **180** observed in the attempted diallylation of **135**.*

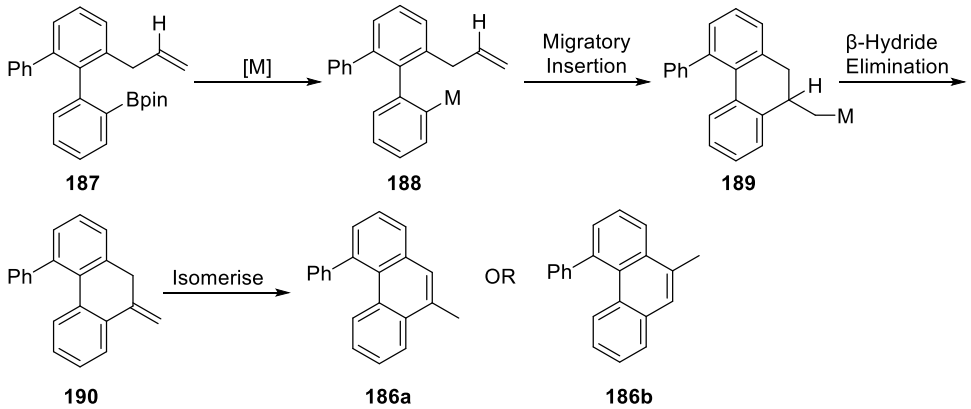
The reaction was repeated using more forcing conditions in an attempt to push it to completion (Scheme 3.26, Conditions B). The temperature was raised from 50 °C to 70 °C, the catalyst loading increased from 12 mol% to 30 mol% (15 mol% per Bpin), and the equivalents of **177** and KF were increased from four to six. After thirty-six hours, monoallylated product remained. Diallylated product **178** was isolated in approximately 54% yield and impure monoallylated product **179** was isolated in approximately 12% yield. Although the more forcing conditions did push the reaction towards the diallylated product, the reaction did not go to completion and the reaction was significantly less clean. For this reason, more forcing conditions were not investigated.

The diallylation of **135** was next investigated using the less sterically bulky allyl chloride **184** in place of 3-chloro-2-methyl-1-propene **177** in the hope that the reduced steric bulk of the alkene would make the reaction more favourable (Scheme 3.28). In the presence of 30 mol% (15 mol% per Bpin) of $Pd(dba)_2$ all the starting material was consumed following heating at 70 °C for sixty-eight hours.



Scheme 3.28 *Attempted diallylation of* ***135*** *with allyl chloride* ***184****.*

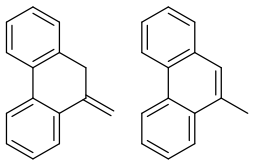
A mixture of two inseparable products was obtained: GC-MS was consistent with a mixture of the desired diallylated product **185** and cyclised product **186**. Cyclised product, **186**, is likely formed from the monoallylated product **187** by the mechanism outlined in Scheme 3.29. This is a similar mechanism to that proposed for the formation **180**, which was observed in trace amounts when 3-chloro-2-methyl-1-propene **177** was employed as the coupling partner. However, unlike intermediate **182**, intermediate **189** possesses a β-hydrogen and can thus undergo β-hydride elimination instead of reacting with water.



Scheme 3.29 *Proposed mechanism for the formation of the potential side-product* ***186****.*

Although **190** is not a known compound, the related compound **191** (Fig. 3.16) is. **191** has a distinctive CH_2 signal, at 3.7 ppm, which was not visible in the NMR spectrum of the mixture. However, there was a very strong singlet at 2.73 ppm, this is consistent

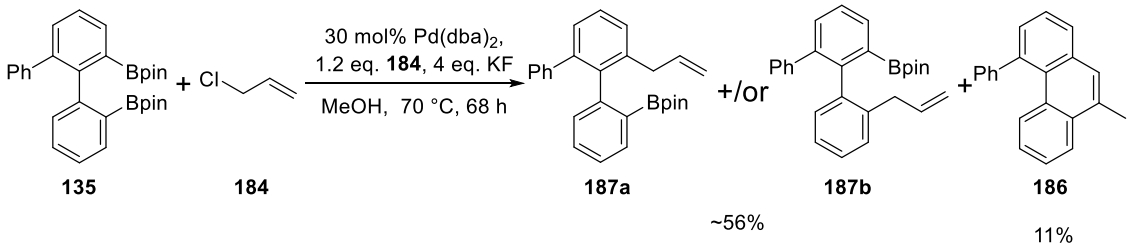
with **186**, because the related compound **192** (Fig. 3.16) has a distinctive CH_3 signal at 2.73 ppm.[43] It was reported that heating **191** to 80 °C resulted in its isomerisation to **192** and that reacting **191** with potassium *t*-butoxide also resulted in its isomerisation to **192**.[43] Thus, it is most probable that **190** is first formed by the mechanism outlined in Scheme 3.29 and under the reaction conditions, in which high temperature (70 °C) and a large excess of KF are employed, isomerises to the more stable **186**. It was not possible to estimate the approximate yields by NMR because there were no clean signals for each compound. The mixture of **185** and **186** accounted for approximately 70% of the mass balance and the uncorrected ratio from the GC-MS spectrum was 2.5:1 in favour of the cyclised product.



191 **192**

Fig. 3.16 *The structure of isomers **191** and **192** structurally related to **186** and **190** believed to be formed in the attempted diallylation of **135**.*

This was the only post-functionalisation reaction in which both Bpin moieties in the starting material had undergone complete conversion. The reaction was next conducted using 1.2 eq. of allyl chloride opposed to 8 eq. using otherwise identical reaction conditions (Scheme 3.30). It was hoped that lowering the equivalents of the allyl chloride would suppress the formation of the diallylated product **185** and it might be possible to chemoselectively form the cyclised product **186**.



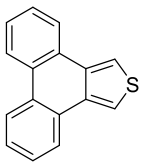
Scheme 3.30 *The attempted monoallylation and cyclisation of **135**.*

Reducing the equivalents of allyl chloride did disfavour the formation of the diallylated product as expected and none was isolated. By NMR, the major product was the monoallylated product **187**. By NMR it is likely that a single regioisomer is formed, although this could not be unambiguously determined. The desired cyclised product

was also isolated, but in relatively low 11% yield. Since chemoselectivity was not observed for any one product, the reaction was not pursued further.

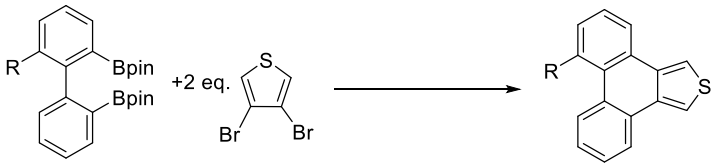
3.7.2. Suzuki–Miyaura Cross-Coupling of the Ring Opened Products

The second post-functionalisation of the ring opened diborylated products to be investigated was the Suzuki–Miyaura cross-coupling reaction. The preparation of phenanthrene fused thiophenes was first investigated. Phenanthrene fused thiophenes, such as phenanthro[9,10-c]thiophene **193** (Fig. 3.17) have potential application in the preparation of conjugated polymers because of their aromatic stabilisation energies.[44] Phenanthrene fused thiophene **193** was shown to undergo polymerisation to yield a conducting polymer which was shown to undergo electrochemical oxidation, reduction, and chemical oxidative polymerisation to yield conducting polymers.[45] It was envisaged that unusually substituted phenanthrene fused thiophenes could be prepared *via* the double Suzuki–Miyaura cross-coupling reaction of the ring opened diborylated products with 3,4-dibromothiophene (Scheme 3.31).



193

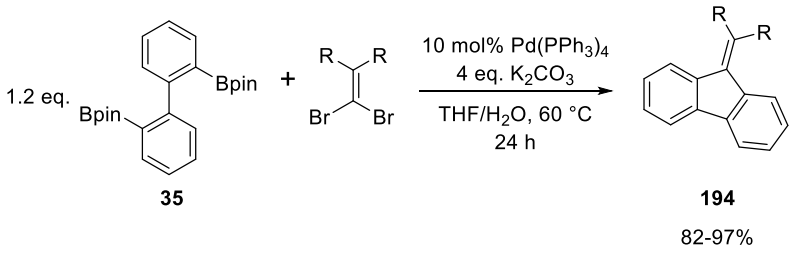
Fig. 3.17 *The structure of phenanthro[9,10-c]thiophene **193**.*



Scheme 3.31 *Proposed preparation of phenanthrene fused thiophenes from the tri-ortho substituted ring opened products.*

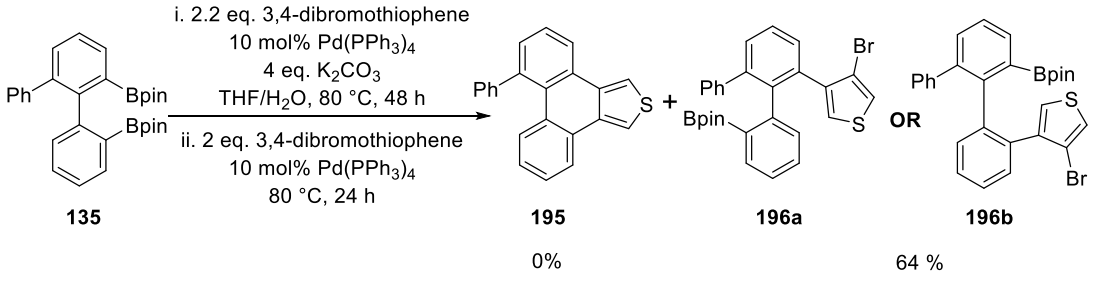
Yorimitsu *et al.* who, as discussed in section 1.3.2, prepared the 2,2'-diborylated biaryl **35** reported the related double Suzuki–Miyaura cross-coupling reaction of **35** with *gem*-dibromoethylenes to give fulvenes, **194** (Scheme 3.32). These conditions were used as a starting point for the desired double Suzuki–Miyaura cross-coupling reaction.

It was thought that this transformation was more likely to go to completion than other transformations of aryl pinacolboronate esters reported in the literature because 2,2'-diborylbiphenyl **35**, which is sterically very similar to the substrates in this work, was successfully used as a substrate in the related literature reaction.



Scheme 3.32 *Double Suzuki–Miyaura cross-coupling of 2,2'-diborylbiphenyl* ***35*** *with gem-dibromoethylenes to give fulvenes.*

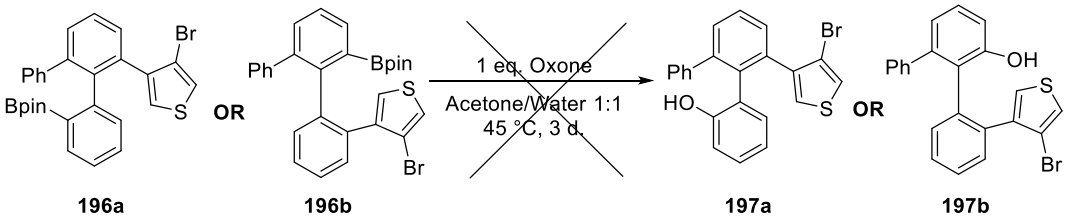
It was found that more forcing conditions were required than those reported by Yorimitsu *et al.* In the presence of 20 mol% (10 mol% per Bpin) $Pd(PPh_3)_4$ all the starting material was consumed following heating at 80 °C for three days (Scheme 3.33). None of the expected phenanthro[9,10-c]thiophene product **195** was isolated. A single product was isolated from the reaction mixture, which by NMR and HR-MS is the product of a single Suzuki–Miyaura cross-coupling reaction. There are two possible regioisomers **196a** and **196b**, however by NMR a single regioisomer was present and it was not possible to determine which. The product was an oil and so it was not possible to obtain crystals for XRD.



Scheme 3.33 *The attempted double Suzuki–Miyaura cross-coupling reaction of 3,4-dibromothiophene with* ***135****.*

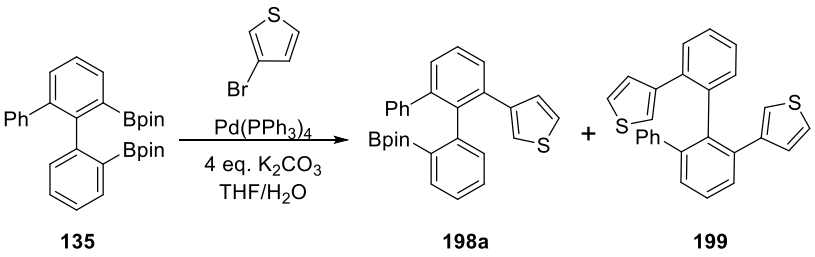
The oxidation of **196** to **197** was attempted using reaction conditions reported by Maleczka, Smith *et al.* for the oxidation of aryl pinacolboronate esters (Scheme 3.34).[46] It was thought that the product of oxidation **197** was more likely to be a solid and that it might therefore be possible to obtain XRD of **197** to determine which

pinacol boronate moiety underwent Suzuki–Miyaura cross-coupling. Unfortunately, even when the reaction temperature was increased, none of the desired product was obtained and only starting material was recovered.



Scheme 3.34 *The attempted oxidation of the pinacol boronate ester moiety on* ***196*** *to a hydroxy group.*

It was thought that the Suzuki–Miyaura cross-coupling reaction does not go to completion because both the biaryl **135** and 3,4-dibromothiophene are too sterically bulky. The double Suzuki–Miyaura cross-coupling reaction of **135** was therefore next attempted with the less sterically bulky 3-bromothiophene (Scheme 3.35, Conditions A). Using 10 mol% catalyst loading (5 mol% per Bpin), the reaction went to completion within twenty-four hours. The major product was **198a**, the product of a single Suzuki–Miyaura cross-coupling reaction, which was isolated in 53% yield. By NMR only one regioisomer of the single Suzuki–Miyaura cross-coupling reaction was present. The regioisomer was unambiguously determined as **198a** by XRD (Fig. 3.18).



Conditions A: 10 mol% $Pd(PPh_3)_4$, 2.4 eq. 3-bromothiophene, 80 °C, 24 h	~54%	~28%
Conditions B: i. 20 mol% $Pd(PPh_3)_4$, 4 eq. 3-bromothiophene, 100 °C, 48 h **ii.** 20 mol% $Pd(PPh_3)_4$, 4 eq. 3-bromothiophene, 100 °C, 24 h	~59%	~35%

Scheme 3.35 *The attempted double Suzuki–Miyaura cross-coupling reaction of* ***135*** *with 3-bromothiophene.*

Isolation of regioisomer **198a** is consistent with what would be expected because this regioisomer results from cross-coupling of the pinacol borane moiety which is on the

same aryl ring as the phenyl group. This pinacol borane is less sterically hindered than the pinacol borane on the adjacent aryl ring and should therefore be more reactive. Although it could not be definitively proven by XRD, it is most likely that the same pinacol borane moiety was selectively functionalised when **135** was reacted with 3,4-dibromothiophene. In addition to the monoarylated product **198a**, the desired diarylated product **199** was also isolated in 28% yield.

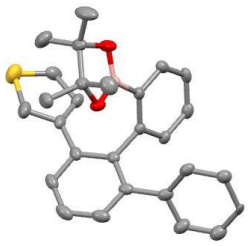


Fig. 3.18 *Single crystal structure of regioisomer* ***198a****.*

The reaction with 3-bromothiophene was repeated using more forcing conditions in an attempt to push it to completion (Scheme 3.35, Conditions B): the temperature was raised from 80 °C to 100 °C, the catalyst loading increased from 10 mol% to 40 mol% (20 mol% per Bpin), and the equivalents of 3-bromothiophene were increased from 2.4 to 8. Using the more forcing conditions the reaction did not go to completion, the monoarylated product was isolated in 59% yield, and the diarylated product was isolated in 35% yield. Although the desired diallylated product was obtained in a slightly higher yield using the more forcing reaction conditions, the reaction was less clean and both products were contaminated with small impurities, which could not be clearly identified. For this reason, the reaction was not attempted at higher temperature.

To conclude, two different post-functionalisations of the ring opened diborylated products were investigated: the Suzuki–Miyaura cross-coupling reaction and diallylation. Attempts to chemoselectively diallylate the ring opened diborylated products were unsuccessful, presumably due to the steric bulk of the starting material. When allyl chloride was employed as the cross-coupling partner an unexpected, cyclised product was also isolated.

When 3,4-dibromothiophene was employed as the coupling partner in the Suzuki–Miyaura cross-coupling reaction, one of the pinacol boronate ester moieties selectively

underwent reaction and when the steric bulk of the cross-coupling partner was reduced, a mixture of diarylated and monoarylated product were isolated, in which the monoarylated product predominated. This shows that the chemoselectivity of this reaction is strongly affected by the steric bulk of the cross-coupling partner and that it is possible to selectively functionalise one of the aryl pinacolboronate ester moieties. Thus, sequential functionalisation of the aryl pinacol boronate esters is, in principle possible. Had more time been available the sequential functionalisation of the ring opened diborylated product would have been investigated. In addition, a full screening of conditions for both the Suzuki–Miyaura cross-coupling reaction and the diallylation reaction would have been conducted.

3.8. Summary and Future Work

In this work a screening of reaction conditions for the ring opening diborylation of 1-fluorobiphenylene with B_2pin_2 was conducted and the combination of $Pd(dba)_2$ and IAd was found to be optimum. The desired product was obtained in good yield with high chemoselectivity as a mixture of regioisomers. Upon increasing the reaction temperature, these reaction conditions were successfully employed for the ring opening diborylation of a range of 1-substituted biphenylenes with B_2pin_2 to form sterically bulky trisubstituted biaryls in high yields. None of these trisubstituted biaryl products have been prepared before and they would be challenging to prepare using other synthetic methods. It was shown that a variety of functional groups were tolerated in the ring opening diborylation reaction, including Bpin, fluorine and 1-arylbiphenylenes which bore alkyl, methoxy, ester, amine and CF_3 functional groups. B_2pin_2 was the only diborane tested that underwent the ring opening diborylation reaction with high chemoselectivity.

It was found that the steric bulk of the substituent placed in the 1-position does affect the regioselectivity of the ring opening diborylation reaction to an extent. Increasing the steric bulk from fluorine to methyl to phenyl does improve the regioselectivity, however ring opening reactions with *ortho*-substituted 1-arylbiphenylenes demonstrated that steric bulk alone does not determine the regioselectivity of the reaction. Interestingly, the substrates 1-(3-thiophene)biphenylene **116**, 1-Bpinbiphenylene **102**, and 1-(trimethylsilyl)biphenylene **100** were found to undergo

less chemoselective diborylation but gave the highest regioselectivities of all the substrates tested. The results of this work suggest that electron poor substrates give lower regioselectivities in the reaction. In addition, it was found that increasing the reaction temperature caused a decrease in the regioselectivity of the reaction. Finally, attempts to direct the catalyst to the most sterically hindered C-C bond using directing groups in the 1-position were unsuccessful.

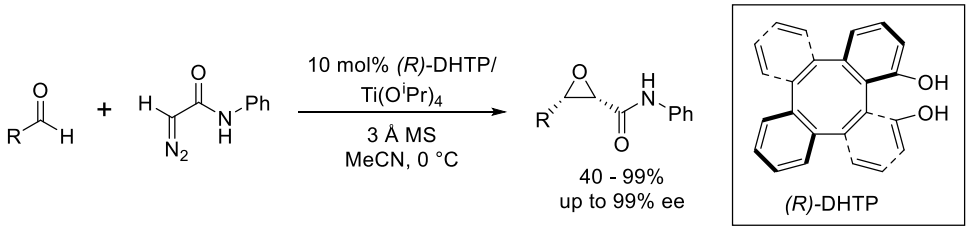
Stoichiometric reactions of $Pd(IAd)_2$ with biphenylene and B_2pin_2 suggest that C-C bond cleavage of biphenylene precedes B-B bond cleavage of B_2pin_2. Finally, it was shown that the ring opened diborylated products underwent Suzuki–Miyaura cross-coupling and allylation to an extent. However, due to the steric bulk of the substrates it was not possible to push the reactions to completion. Of particular note, in one example with 3,4-dibromothiophene it was shown that selective monoarylation of one of the Bpin moieties was possible.

Much of this work focussed on investigating the biphenylene scope of this reaction. Although five diboranes were tested, it would be interesting to investigate if other reagents can be reacted with biphenylenes in a similar manner. In their paper Matsuda and Kirikae reported that unsubstituted biphenylene underwent a similar reaction with disilanes, a digermane, and a distannane.[1] Therefore, it would be of value to investigate whether the reaction conditions used in this work could also be employed with these reagents.

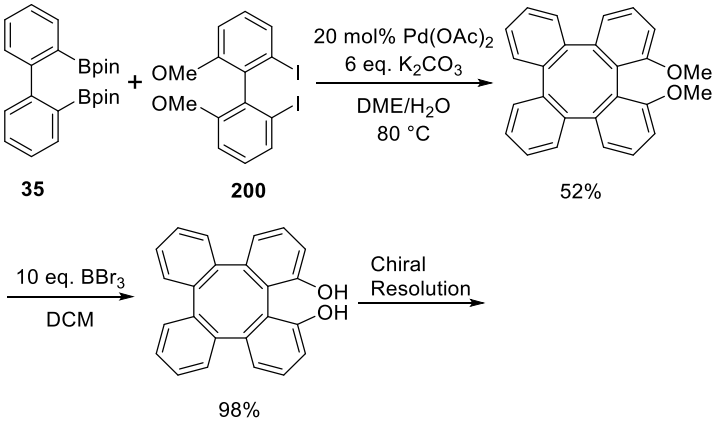
In addition to increasing the scope of the reaction it would also be valuable to further investigate the reaction mechanism to fully understand the different regioselectivities obtained with different substrates. Of most value would be isolation of the intermediate generated following the reaction of biphenylene and $Pd(IAd)_2$. Characterisation of this intermediate would help to clarify what the first step in the mechanism is.

Finally, further work on the post-functionalisation of the ring opened diborylated products would also be of value. Most importantly, a full screening of reaction conditions for the Suzuki–Miyaura cross-coupling and allylation reactions may enable functionalisation of both pinacol boronate ester moieties. In addition, it would be valuable to investigate other post-functionalisation reactions to demonstrate the potential synthetic utility of the ring opening diborylation reaction.

For example, the preparation of tetraphenylenes from the ring opened diborylated products could be investigated. Axially chiral tetraphenylene compounds have been applied to asymmetric synthesis, for example, the chiral tetraphenylene ligand hydroxytetraphenylene *(R)*-DHTP (Scheme 3.36) was employed in an asymmetric Darzens reaction of aldehydes and diazo-*N*,*N*-dimethylacetamide to give *cis*-glycidic amides with high enantioselectivity (Scheme 3.37).[47–49] *(R)*-DHTP was prepared by the double Suzuki–Miyaura cross-coupling reaction of **35** with **200**, followed by demethylation, and chiral resolution. In principle, it should be possible to prepare unusually substituted analogues *(R)*-DHTP from the products of the ring opening diborylation reaction: these analogues may be useful in asymmetric synthesis.



Scheme 3.36 *The asymmetric Darzens reaction of aldehydes and diazo-N,N-dimethylacetamide to give cis-glycidic amides.*



Scheme 3.37 *The preparation of (R)-DHTP from the 2,2'-diborylated biaryl* ***35****.*

3.9. Experimental

3.9.1. General Methods

All air sensitive reactions were conducted under an atmosphere of argon using standard Schlenk techniques or in an Innovative Technologies glovebox. Argon (Pureshield, >99.998%) was purchased from BOC and used as received. All glassware was heated to 120 °C in an oven and cooled under vacuum prior to use.

Nuclear Magnetic Resonance (NMR) spectra were recorded on Bruker AVIII HD 500 MHz, Bruker AVI 400 MHz and Bruker AVIII HD 400 MHz spectrometers at ambient temperature. Chemical shifts are reported in ppm relative to a residual solvent peak ($CDCl_3$, δ 7.26 ppm for ^{1}H and 77.16 ppm for ^{13}C. CD_2Cl_2 δ 5.32 ppm for ^{1}H. 0.0 ppm chemical shifts of $CFCl_3$ and H_3PO_4 were used for referencing of ^{19}F and ^{31}P, respectively. The splitting patterns are reported as follows s (singlet), d (doublet), t (triplet), q (quartet), spt (septet), m (multiplet), dd (doublet of doublets), dt (doublet of triplets), br. s (broad singlet). The coupling constants, *J* are given in Hertz.

HRMS were recorded using the analytical service in the Chemistry Department at the University of Liverpool. HRMS were conducted on either an Agilent QTOF 7200 or an Agilent QTOF 6540 using chemical ionisation (CI) or electrospray (ESI), respectively.

Gas chromatography analyses for the ring opening diborylation of biphenylene were conducted on an on an Agilent 7890 Gas chromatograph fitted with a HP-5 column (length: 30 m, ID: 0.32 mm, FT: 0.25 μm) and an FID detector. The carrier gas used was helium. The following GC oven temperature programme was used: 50 °C hold for 3 min, ramp 20 °C/min to 100 °C, hold for 3 min, ramp 15 °C/min to a final temperature of 250 °C and hold for 10 min.

Gas chromatography analyses for the ring opening diborylation of 1-fluorobiphenylene were conducted on an Agilent 6890N Gas chromatograph fitted with a ZB-WAX column (length: 30 m, ID: 0.25 mm, FT: 0.25 μm) and an FID detector. The carrier gas was nitrogen. The following GC oven temperature programme was used: 60 °C hold for 8 min, ramp 20 °C/min to a final temperature of 230 °C and hold for 17 min. Tetraphenylene products were too heavy to come off using this method. Reactions in which tetraphenylene was observed, used the following GC

temperature programme: 60 °C hold for 8 min, ramp 20 °C/min to a final temperature of 230 °C and hold for 17 min, ramp 20 °C/min to a final temperature of 250 °C and hold for 20 min.

Gas chromatography analyses for the ring opening diborylation of 1-chlorobiphenylene were conducted on an Agilent 7890 Gas chromatograph fitted with a HP-5 column (length: 30 m, ID: 0.32 mm, FT: 0.25 μm) and an FID detector. The carrier gas used was helium. The following GC oven temperature programme was used: 80 °C hold for 5 min, ramp 40 °C/min to a final temperature of 150 °C and hold for 5 min, ramp 15 °C/min to a final temperature of 250 °C and hold for 10 min.

Gas chromatography-Mass Spectra (GC-MS) analyses were conducted on a Thermo Scientific ISQ single quadrupole instrument equipped with a HP-1 column (length: 30m, ID: 0.32 mm, FT: 0.25 μm). The carrier gas used was helium and the ionisation mode was EI. The following GC oven temperature programme was used: 80 °C hold for 2 min, ramp 20 °C/min to a final temperature of 250 °C and hold for 7 min.

Analytical thin-layer chromatography (TLC) was performed on Merck F254 TLC silica gel 60 TLC plates (visualising with UV light (254 nm)). Column chromatography was performed using VWR silica gel 40-63 μm.

Unless otherwise stated, all chemicals were obtained from commercial suppliers and used without further purification. $Pd(dba)_2$ was obtained from Fluorochem and 1,3-bisadamantylimidazolium tetrafluoroborate was obtained from Alfa Aesar and Sigma Aldrich. B_2pin_2 was obtained from Fluorochem. Biphenylene was prepared using the procedure of Schaub and Radius or obtained from Sigma Aldrich.[50] 1-Flurobiphenylene and 1-chlorobiphenylene were prepared according to the literature procedure.[2,51] The diborane **140** was prepared according to the literature procedure.[52] IAd and $Pd(IAd)_2$ were prepared according to the literature procedure.[38,53]

m-Xylene was purchased as 'extra dry' from Acros Organics and used as received. n-Dodecane and deuterated toluene were degassed by freeze-pump-thaw technique (3 cycles) and stored over molecular sieves. Unless otherwise stated all other solvents were dried over the appropriate drying agent and distilled under argon. THF and toluene were refluxed over sodium, using benzophenone as an indicator. Methanol was distilled over CaH_2. All distilled solvents were stored in either Sure-Store flasks under

argon or in an Innovative Technologies glovebox. Unless otherwise noted the stated reaction temperature is the temperature of the oil bath.

3.9.2. Screening Conditions for the Ring Opening Diborylation of Biphenylene, 1-Fluorobiphenylene, and 1-Phenylbiphenylene

General Procedure for Screening the Ring Opening Diborylation of Biphenylene

Under an atmosphere of argon, a stock solution of biphenylene (0.1 mmol/mL) and n-dodecane (internal standard for GC, 0.05 mmol/mL) was prepared in the stated solvent. Under an atmosphere of argon, a 4 mL vial was charged with $Pd(dba)_2$ (10 µmol), P*n*Bu_3 (20 µmol), and B_2pin_2 (0.11 mmol). To the 4 mL vial was added 1 mL of stock solution. The 4 mL vial was sealed, and the reaction mixture stirred at room temperature for 10 min. The reaction mixture was then stirred at the stated temperature for 16 h. The reaction mixture was cooled to room temperature, filtered through celite, and washed through with EtOAc, until no compound was visible by UV on a TLC plate. The filtrate was analysed by GC. The GC yields were calculated assuming that the response factor for **35** was 0.8, that the response factor for **120** was 0.9, and that the response factor of **121** was 1.16, the response factor calculated for biphenylene.

General Procedure for Screening the Ring Opening Diborylation of 1-Fluorobiphenylene

Under an atmosphere of argon, a stock solution of 1-fluorobiphenylene (0.1 mmol/mL) and n-dodecane (internal standard for GC, 0.05 mmol/mL) was prepared in the stated solvent. A Schlenk bomb was charged with catalyst (10 µmol for $Pd(dba)_2$ and $Ni(cod)_2$, 5 µmol for $[Ir(cod)Cl]_2$), ligand (20 µmol), and B_2pin_2 (0.11 – 0.2 mmol). All carbene ligands were used as either the chloride or the tetrafluoroborate salt and were free-based *in-situ* by adding a slight excess of KO*t*Bu (22 µmol). To the Schlenk bomb was added 1 mL of stock solution. The Schlenk bomb was sealed and the reaction mixture stirred at room temperature for 10 min. The reaction mixture was then stirred at the stated temperature for 16 h. The reaction mixture was cooled to room temperature, filtered through celite, and washed through with EtOAc, until no compound was visible by UV on a TLC plate. The filtrate was analysed by GC.

When the screening was begun the desired product **122,** and the side-products **124a** – **124d**, **125a**, **125b**, and **126a** – **126e** were not available. The GC yields were therefore

calculated assuming that the response factor of the reduced products **125a** and **125b** and of the tetraphenylene products **126a** – **126e** were the same as 1-fluorobiphenylene. That the response factor of the mono-borylated products **124a** – **124d** were 0.9 and that the response factor of the desired diborylated product **122** was 0.8.

General Procedure for Screening the Ring Opening Diborylation of 1-Phenylbiphenylene With B_2pin_2

Under an atmosphere of argon, a Schlenk bomb was charged with ligand (20 μmol), KO*t*Bu (22 μmol), and B_2pin_2 (0.2 mmol). All carbene ligands were used as either the chloride or the tetrafluoroborate salt. To the Schlenk bomb was next added $[Rh(cod)Cl]_2$ (2.5 mg, 5.0 μmol) as a solution in toluene (0.25 mL), followed by 1-phenylbiphenylene (22.8 mg, 0.0999 mmol) as a solution in toluene (0.75 mL). The Schlenk bomb was sealed and the reaction mixture stirred at room temperature for 10 min. The reaction mixture was then stirred at 110 °C for 16 h. The reaction mixture was cooled to room temperature, filtered through celite, and washed through with EtOAc, until no compound was visible by UV on a TLC plate. The solvent was removed under reduced pressure and a known amount of 1,3,5-trimethoxybenzene was added to determine the NMR yield.

3.9.3. Ring Opening Diborylation of Biphenylene(s)

General Procedure for 1-Chlorobiphenylene

Under an atmosphere of argon, a Schlenk bomb was charged with $Pd(dba)_2$ (10 μmol), 1,3-bis(1-adamantylimidazolium)tetrafluoroborate (20 μmol), KO*t*Bu (22 μmol), and B_2pin_2 (0.2 mmol). To the Schlenk bomb was next added a solution of biphenylene (0.1 mmol) and n-dodecane (internal standard for GC, 30 μmol) in toluene (1 mL) to give a wine-red suspension. The Schlenk bomb was sealed and the reaction mixture stirred at room temperature for 10 min. The reaction mixture was then stirred at the stated temperature (110 °C or 140 °C) for 16 h, following heating the reaction mixture turned dark brown. The reaction mixture was cooled to room temperature, filtered through celite, and washed through with EtOAc, until no compound was visible by UV on a TLC plate. The filtrate was analysed by GC and GC-MS.

110 °C

The reaction was conducted according to the general procedure, using 1-chlorobiphenylene (18.6 mg, 0.0997 mmol), n-dodecane (5.4 mg, 30 μmol) B_2pin_2 (50 mg, 0.20 mmol), KO*t*Bu (2.6 mg, 23 μmol), 1,3-bis-(1-adamantylimidazolium) tetrafluoroborate (8.6 mg, 20 μmol), $Pd(dba)_2$ (5.9 mg, 10 μmol), and toluene (1 mL). The reaction mixture was heated to 110 °C. By GC, the conversion was 23%. The GC-MS spectrum and mass spectra are reported in the appendix.

140 °C

The reaction was conducted according to the general procedure, using 1-chlorobiphenylene (18.6 mg, 0.0997 mmol), n-dodecane (5.4 mg, 30 μmol) B_2pin_2 (50 mg, 0.20 mmol), KO*t*Bu (2.5 mg, 23 μmol), 1,3-bis-(1-adamantylimidazolium) tetrafluoroborate (8.4 mg, 20 μmol), $Pd(dba)_2$ (5.9 mg, 10 μmol), and toluene (1 mL). The reaction mixture was heated to 140 °C. By GC, the conversion was 21%. The GC-MS spectrum and mass spectra are reported in the appendix.

General Procedure for 1-Monosubstituted Biphenylenes and Biphenylene

Under an atmosphere of argon, a Schlenk bomb was charged with $Pd(dba)_2$ (40 μmol), 1,3-bis-(1-adamantylimidazolium)tetrafluoroborate (80 μmol), KO*t*Bu (88 μmol), and B_2pin_2 (0.8 mmol). The Schlenk bomb was evacuated and backfilled with argon. To the Schlenk bomb was added a solution of biphenylene (0.4 mmol) in toluene (4 mL). The reaction mixture was stirred (600 rpm) at room temperature for 10 minutes. The Schlenk bomb was sealed and the reaction mixture stirred (600 rpm) at the specified temperature for 16 h. The reaction mixture was filtered through celite and washed through with EtOAc until no compound was visible by UV on a TLC plate. The solvent was removed under reduced pressure to give the crude product. The crude product was purified by flash column chromatography.

Unless otherwise stated, in all the ring opening diborylation reactions a wine-red suspension is observed following the addition of toluene at room temperature. When the reaction mixture is heated it turns khaki green.

When the substrate was a 1-arylbiphenylene, except for 1-(3-thiophene)biphenylene and 1-(4-methoxyphenyl)biphenylene, both regioisomers had a similar R_f and could

not be completely separated by column chromatography. The main regioisomer could be obtained in pure form and was fully characterised. A mixture of regioisomers was also obtained and the yields of the two regioisomers was calculated from the ratio of the two regioisomers determined from proton integrals. In most cases, the minor regioisomer which had been separated from the major regioisomer contained small impurities and the accurate yield was calculated by adding a known amount of standard, either 1,3,5-trimethoxybenzene or durene. The minor regioisomer was clean enough to be fully characterised. The yields are presented as follows: observational properties of the pure major regioisomer (weight, moles, % yield), observational properties of the pure minor regioisomer (weight, moles, % yield), observational properties of the mixture of regioisomers (weight, moles of major regioisomer, moles of minor regioisomer, % yield of major regioisomer, % yield of minor regioisomer).

The ratio of regioisomers was determined from the isolated yields, but where possible, i.e. when there were non-overlapping signals in the crude NMR spectrum, the ratio determined from isolated yields was checked against the ratio determined from the crude NMR spectrum to ensure that there were no significant differences.

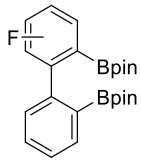
The identity of the regioisomers resulting from the ring opening diborylation of all 1-arylbiphenylenes and 1-methylbiphenylene were assigned by proton NMR spectroscopy. The structure of the tri-*ortho* substituted regioisomer **135a**, resulting from the ring opening diborylation of 1-phenylbiphenlene, was confirmed by XRD. Regioisomer **135a** had four Bpin methyl environments, whereas the di-*ortho* substituted regioisomer **135b** had two Bpin methyl environments. The identity of the regioisomers resulting from all other 1-arylbiphenylene reactions and 1-methylbiphenylene were therefore assigned based on the number of Bpin methyl environments.

In all the products of the ring opening diborylation of 1-aryl, 1-TMS, 1-Bpin, 1-F, and 1-Me biphenylenes two quaternary carbon signals were not observed in ^{13}C NMR spectra. These are the quaternary carbon atoms attached to boron, they are not observed because of the rapid quadrupolar relaxation of ^{11}B.

1-Fluorobiphenylene

The reaction was conducted according to the general procedure, using 1-fluorobiphenylene (85.1 mg 0.500 mmol), B_2pin_2 (251 mg, 0.988 mmol), KO*t*Bu (12.3

mg, 0.110 mmol), 1,3-bis-(1-adamantylimidazolium)tetrafluoroborate (42.3 mg, 0.100 mmol), $Pd(dba)_2$ (28.5 mg, 0.0496 mmol), and toluene (5 mL). The reaction mixture was heated to 110 °C. The crude product was purified by flash column chromatography (silica gel, 5% EtOAc in hexane) and (silica gel, 20-50% DCM in Hexane).



122

Compound **122** was isolated as a white solid (99 mg, 0.23 mmol, 47%) and a colourless oil (35 mg, 0.083 mmol, 17%) as a mixture of two regioisomers (r = 1:1) using signals at 6.96 ppm and 7.10 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 7.4, 1.0 Hz, 1H reg. 1, CH), 7.73 – 7.71 (m, 1H reg. 2, CH), 7.44 – 7.37 (m, 2H reg. 1, 1H reg. 2, CH), 7.34 – 7.23 (m, 3H reg. 1, 3H reg. 2, CH), 7.10 (t, *J* = 8.9 Hz, 1H reg. 1, CH), 7.04 (d, *J* = 7.4 Hz, 1H reg. 2, CH), 6.96 (t, *J* = 8.5 Hz, 1H reg. 2, CH), 1.14 (s, 12H reg. 2, CH_3), 1.11 (s, 6H reg. 1, CH_3), 1.07 – 1.05 (m, 18H reg. 1, 12H reg. 2, CH_3), **^{19}F{^{1}H} NMR** (377 MHz, $CDCl_3$) δ -107.0 (reg. 2), -115.7 (reg. 1), **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 165.2 (d, *J* = 242.6 Hz, reg.2, C), 160.0 (d, *J* = 243.4 Hz, reg.1, C), 150.4 (d, *J* = 9.0 Hz, reg.2, C), 148.1 (reg.2, C), 142.5 (reg.1, C), 136.1 (d, *J* = 16.2 Hz, reg.1, C), 134.5 (reg. 2, CH), 134.4 (reg. 1, CH), 130.1 (d, *J* = 8.5 Hz, reg. 2, CH), 130.0 (reg. 1, CH), 129.7 (reg. 2, CH), 129.6 (reg. 1, CH), 129.3 (reg. 2, CH), 129.2 (d, *J* = 3.5 Hz, reg. 1, CH), 127.9 (d, *J* = 7.8 Hz, reg. 1, CH), 126.6 (reg. 1, CH), 126.4 (reg. 2, CH), 124.9 (d, *J* = 2.8 Hz, reg. 2, CH), 116.7 (d, *J* = 23.2 Hz, reg. 1, CH), 112.7 (d, *J* = 24.2 Hz, reg. 2, CH), 83.3 (reg. 1, 2C), 83.4 (reg. 2, 2C), 83.5 (reg. 1, 2C), 83.8 (reg. 2, 2C), 24.5 (reg. 1, $2CH_3$), 24.6 (reg. 1, $2CH_3$, reg. 2, $4CH_3$), 24.7 (reg. 1, $2CH_3$), 24.8 (reg. 2, $4CH_3$), 24.9 (reg. 1, $2CH_3$). **HRMS** (ESI^+) m/z: calculated for $(C_{24}H_{31}B_2O_4F+Na)^+$ 447.2290, found 447.2304.

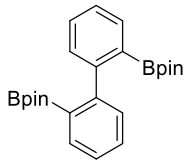
A colourless oil (16 mg, 0.054 mmol, 10%) was isolated. GC was consistent with a mixture of regioisomers resulting from monoborylation **124**.

A colourless oil (2 mg) was isolated and was found to contain **125** by GC.

Biphenylene, 1

The reaction was conducted according to the general procedure, using biphenylene (60.9 mg 0.400 mmol), B_2pin_2 (205 mg, 0.807 mmol), KO*t*Bu (10.0 mg, 0.0891

mmol), 1,3-bis-(1-adamantylimidazolium)tetrafluoroborate (34.1 mg, 0.0804 mmol), $Pd(dba)_2$ (23.1 mg, 0.0402 mmol), and toluene (4 mL). The reaction mixture was heated to 110 °C. The crude product was purified by flash column chromatography (silica gel, 4% EtOAc in hexane).



35

Compound **35** was isolated as a white solid (144 mg, 0.353 mmol, 89%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.66 (dd, *J* = 7.4, 2.8 Hz, 2H, CH), 7.38 (td, *J* = 7.5, 3.3 Hz, 2H, CH), 7.31 – 7.25 (m, 4H, CH), 1.09 (s, 24H, CH_3). The ^{1}H NMR data was consistent with that reported in the literature.[47,54]

Biphenylene Using $Pd(IAd)_2$ as the Catalyst

A Schlenk bomb was charged with $Pd(IAd)_2$ (29.8 mg, 0.0381 mmol) and B_2pin_2 (192 mg, 0.756 mmol). To the Schlenk bomb was added a solution of biphenylene (58.0 mg, 0.382 mmol) in toluene (3.8 mL) to give a bright yellow solution. The reaction mixture was stirred (600 rpm) in a sealed Schlenk bomb at room temperature for 10 min. The reaction mixture was stirred (600 rpm) at 110 °C for 16 h. Upon heating the reaction mixture turned dark brown in colour. The reaction mixture was filtered through celite and washed through with EtOAc until no compound was visible by UV on a TLC plate. The solvent was removed under reduced pressure and the crude product purified by flash column chromatography (silica gel, 5% EtOAc in hexane). Compound **35** was isolated as a white solid (137 mg, 0.337 mmol, 89%).

Biphenylene Using $Pd(OAc)_2$/IAd

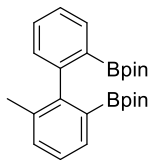
A Schlenk bomb was charged with $Pd(OAc)_2$ (8.3 mg, 0.036 mmol), 1,3-bis(1-adamantylimidazolium)tetrafluoroborate (30.1 mg, 0.0709 mmol), KO*t*Bu (9.0 mg, 0.078 mmol), and B_2pin_2 (181 mg, 0.713 mmol). To the Schlenk bomb was added a solution of biphenylene (54.0 mg, 0.355 mmol) in toluene (3.6 mL) to give a light brown suspension. The reaction mixture was stirred (600 rpm) in a sealed Schlenk bomb at room temperature for 10 min. The reaction mixture was stirred (600 rpm) at 110 °C for 16 h. Upon heating the reaction mixture turned dark brown in colour. The

reaction mixture was filtered through celite and washed through with EtOAc until no compound was visible by UV on a TLC plate. The solvent was removed under reduced pressure and the crude product purified by flash column chromatography (silica gel, 5% EtOAc in hexane). Compound **35** was isolated as a white solid (118 mg, 0.291 mmol, 82%).

1-Methylbiphenylene, 99

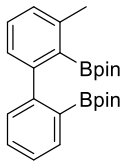
110 °C

The reaction was conducted according to the general procedure, using 1-methylbiphenylene (66.8 mg 0.402 mmol), B_2pin_2 (203 mg, 0.799 mmol), KO*t*Bu (10.2 mg, 0.0909 mmol), 1,3-bis-(1-adamantylimidazolium)tetrafluoroborate (34.1 mg, 0.0804 mmol), $Pd(dba)_2$ (23.2 mg, 0.0403 mmol), and toluene (4 mL). The reaction mixture was heated to 110 °C. The crude product was purified by flash column chromatography (silica gel, 2-4% EtOAc in hexane).



132a

Compound **132a** was isolated as a white solid (77 mg, 0.19 mmol, 46%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.3 Hz, 1H, CH), 7.47 (d, *J* = 7.0 Hz, 1H, CH), 7.37 (td, *J* = 7.5, 3.3 Hz, 1H, CH), 7.28 (td, *J* = 7.5, 2.8 Hz, 1H, CH), 7.23 – 7.22 (d, *J* = 6.8 Hz, 1H, CH), 7.18 (t, *J* = 7.4 Hz, 1H, CH), 7.14 (d, *J* = 7.5 Hz, 1H, CH), 2.02 (s, 3H, CH_3), 1.06 (s, 6H, CH_3), 1.02 (s, 6H, CH_3), 1.01 (s, 6H, CH_3), 1.00 (s, 6H, CH_3), **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 148.8 (2C), 135.6 (C), 133.9 (CH), 131.1 (CH), 130.9 (CH), 129.4 (CH), 129.3 (CH), 126.0 (CH), 125.6 (CH), 83.0 (4C), 24.8 ($4CH_3$), 24.5 ($2CH_3$), 24.4 ($2CH_3$), 20.8 (CH_3). **HRMS** (ESI^+) m/z: calculated for $(C_{25}H_{34}B_2O_4+Na)^+$ 443.2541, found 443.2546.



132b

A pale-yellow oil (30 mg) which contained **132b** was isolated. **HR-MS** (ESI^+) m/z: calculated for $(C_{25}H_{34}B_2O_4+Na)^+$ 443.2541, found 443.2545. It was not possible to calculate the yield of **132b** or fully assign the NMR spectrum because the product was too impure. The ratio of major regioisomer: minor regioisomer is 5.5:1 from the crude NMR spectrum assuming that **132b** is the major component in the mixture.

140 °C

The reaction was conducted according to the general procedure, using 1-methylbiphenylene (66.5 mg 0.400 mmol), B_2pin_2 (205 mg, 0.807 mmol), KO*t*Bu (10.0 mg, 0.0891 mmol), 1,3-bis-(1-adamantylimidazolium)tetrafluoroborate (34.3 mg, 0.0808 mmol), $Pd(dba)_2$ (23.0 mg, 0.0400 mmol), and toluene (4 mL). The reaction mixture was heated to 140 °C. The crude product was purified by flash column chromatography (silica gel, 2-4% EtOAc in hexane). Compound **132a** was isolated as a white solid (81 mg, 0.18 mmol, 48%).

A pale-yellow oil (26 mg) which contained **132b** was isolated. It was not possible to calculate the yield of **132b** or fully assign the NMR spectrum because the product was too impure.

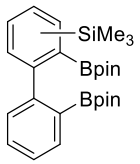
1-(Trimethylsilyl)biphenylene, 100 (140 °C)

The reaction was conducted according to the general procedure, using 1-(trimethylsilyl)biphenylene (90.0 mg, 0.401 mmol), B_2pin_2 (203 mg, 0.799 mmol), KO*t*Bu (9.9 mg, 0.088 mmol), 1,3-bis-(1-adamantylimidazolium)tetrafluoroborate (34.0 mg, 0.0801 mmol), $Pd(dba)_2$ (23.0 mg, 0.0400 mmol), and toluene (4 mL). The reaction mixture was heated to 140 °C. The crude product was purified by flash column chromatography (silica gel, hexane). The starting material, **100**, was isolated as a yellow oil (54 mg, 0.24 mmol, 60%).

1-(Trimethylsilyl)biphenylene, 100 (180 °C)

The reaction was conducted according to the general procedure, using 1-(trimethylsilyl)biphenylene (88.0 mg, 0.392 mmol), B_2pin_2 (200 mg, 0.788 mmol), KO*t*Bu (9.4 mg, 0.086 mmol), 1,3-bis-(1-adamantylimidazolium)tetrafluoroborate (33.1 mg, 0.0780 mmol), $Pd(dba)_2$ (22.6 mg, 0.393 mmol), and toluene (3.9 mL). The reaction mixture was heated to 180 °C for 16 h. To the reaction mixture was added KO*t*Bu (9.8 mg, 0.086 mmol), 1,3-bis-(1-adamantylimidazolium)tetrafluoroborate

(33.4 mg, 0.0787 mmol), and $Pd(dba)_2$ (22.6 mg, 0.0393 mmol). The reaction mixture was stirred (600 rpm) at 180 °C for a further 24 h. The crude product was purified by flash column chromatography (silica gel, 0-20% EtOAc in hexane).

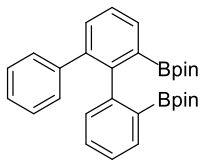


134

Compound **134** was isolated as a pale-yellow oil (75.0 mg, 1.57 mmol, 40%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.3 Hz, 1H, CH), 7.58 (d, *J* = 7.7 Hz, 2H, CH), 7.34 (td, *J* = 7.5, 1.5 Hz, 1H, CH), 7.29 – 7.24 (m, 2H, CH), 7.20 (d, *J* = 7.5 Hz, 1H, CH), 1.05 (s, 6H, CH_3), 1.02 (s, 12H, CH_3), 0.98 (s, 6H, CH_3), -0.10 (s, 9H, CH_3), **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 155.0 (C), 150.4 (C), 137.8 (C), 135.4 (CH), 133.6 (CH), 133.5 (CH), 130.4 (CH), 128.8 (CH), 125.9 (CH), 124.9 (CH), 83.0 (2C), 82.9 (2C), 24.8 ($2CH_3$), 24.6 ($4CH_3$), 24.4 ($2CH_3$), 0.7 ($3CH_3$), **HR-MS** (ESI^+) m/z: calculated for $(C_{27}H_{40}B_2O_4+Na)^+$ 501.2780, found 501.2779.

1-Phenylbiphenylene, 76 (110 °C)

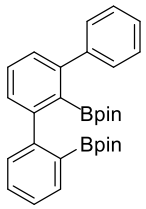
The reaction was conducted according to the general procedure, using 1-phenylbiphenylene (45.6 mg 0.200 mmol), B_2pin_2 (102 mg, 0.402 mmol), KO*t*Bu (4.9 mg, 0.044 mmol), 1,3-bis-(1-adamantylimidazolium)tetrafluoroborate (17.2 mg, 0.0405 mmol), $Pd(dba)_2$ (11.5 mg, 0.0200 mmol), and toluene (2 mL). The reaction mixture was heated to 110 °C. The crude product was purified by flash column chromatography (silica gel, 8% EtOAc in hexane). Starting material (10 mg, 0.044 mmol, 22%).



135a

Compound **135a** was isolated as a white solid (36 mg, 0.075 mmol, 37%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.62 – 7.59 (m, 2H, CH), 7.39 – 7.35 (m, 2H, CH), 7.18 – 7.07 (m, 7H, CH), 6.92 – 6.91 (m, 1H, CH), 1.15 (s, 6H, CH_3), 1.08 (s, 6H, CH_3), 1.06 (s, 6H, CH_3), 1.02 (s, 6H, CH_3), **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 148.4 (C), 147.4

(C), 142.6 (C), 140.6 (C), 133.8 (CH), 132.3 (CH), 131.3 (CH), 130.4 (CH), 130.1 (2CH), 129.0 (CH), 127.3 (2CH), 126.1 (CH), 125.9 (CH), 125.3 (CH), 83.3 (2C), 83.2 (2C), 25.1 ($2CH_3$), 25.0 ($2CH_3$), 24.6 ($2CH_3$), 24.4 ($2CH_3$). **HRMS** (ESI^+) m/z: calculated for $(C_{30}H_{36}B_2O_4+Na)^+$ 505.2697, found 505.2706. Crystals for XRD analysis were grown by slow evaporation of a concentrated solution of hexane at room temperature.



135b

Compound **135b** was isolated as a colourless oil (1.0 mg, 2.1 μmol, 1%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.7 Hz, 1H, CH), 7.70 – 7.65 (m, 3H, CH), 7.56 – 7.52 (m, 2H, CH), 7.44 -7.38 (m, 3H, CH), 7.34 – 7.30 (m, 3H, CH), 1.11 (s, 12H, CH_3), 1.06 (m, 12H, CH_3), **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 150.2 (C), 149.5 (C), 141.7 (C), 141.4 (C), 134.4 (CH), 133.7 (CH), 129.3 (2CH), 128.8 (2CH), 128.3 (CH), 127.4 (CH), 127.3 (2CH), 125.9 (CH), 124.5 (CH), 83.3 (4C), 24.7 ($8CH_3$). **HRMS** (ESI^+) m/z: calculated for $(C_{30}H_{36}B_2O_4+Na)^+$ 505.2697, found 505.2704.

A mixture of **135a** and **135b** was isolated as a colourless oil (6.0 mg, 6.2 μmol **135a**, 6.2 μmol **135b**, 3% **135a**, 3% **135b**).

1-Phenylbiphenylene, 76 (140 °C)

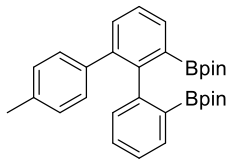
The reaction was conducted according to the general procedure, using 1-phenylbiphenylene (126.2 mg 0.5528 mmol), B_2pin_2 (279 mg, 1.10 mmol), KO*t*Bu (13.6 mg, 0.0121 mmol), 1,3-bis-(1-adamantylimidazolium)tetrafluoroborate (46.8 mg, 0.0110 mmol), $Pd(dba)_2$ (31.6 mg, 0.0550 mmol), and toluene (5.5 mL). The reaction mixture was heated to 140 °C. The crude product was purified by flash column chromatography (silica gel, 5% EtOAc in hexane). Compound **135a** was isolated as a white solid (177 mg, 0.367 mmol, 66%). Compound **135b** was isolated as a colourless oil (28 mg, 0.053 mmol, 10% yield). A mixture of **135a** and **135b** was isolated as a colourless oil (20 mg, 0.016 mmol **135a**, 0.015 mmol **135b**, 3% **135a**, 3% **135b**). The second two yields were calculated by adding a known amount of 1,3,5-trimethoxybenzene due to the impurity of the samples.

1-Phenylbiphenylene, 76 (180 °C)

The reaction was conducted according to the general procedure, using 1-phenylbiphenylene (91.3 mg 0.400 mmol), B_2pin_2 (204 mg, 0.803 mmol), KO*t*Bu (9.9 mg, 0.088 mmol), 1,3-bis-(1-adamantylimidazolium)tetrafluoroborate (33.9 mg, 0.0799 mmol), $Pd(dba)_2$ (23.3 mg, 0.0405 mmol), and toluene (4 mL). The reaction mixture was heated to 180 °C. The crude product was purified by flash column chromatography (silica gel, 5% EtOAc in hexane). Compound **135a** was isolated as a white solid (106 mg, 0.220 mmol, 54%). Compound **135b** was isolated as a colourless oil (9 mg, 0.02 mmol, 5%). The yield was calculated by adding a known amount of 1,3,5-trimethoxybenzene due to the impurity of the sample. A mixture of **135a** and **135b** was isolated as a colourless oil (31 mg, 0.034 mmol **135a**, 0.030 mmol **135b**, 9% **135a**, 8% **135b**).

1-(*p*-Tolyl)biphenylene, 114

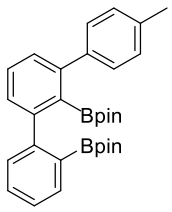
The reaction was conducted according to the general procedure, using 1-(*p*-tolyl)biphenylene (97.0 mg 0.400 mmol), B_2pin_2 (204 mg, 0.803 mmol), KO*t*Bu (10.2 mg, 0.0909 mmol), 1,3-bis-(1-adamantylimidazolium)tetrafluoroborate (34.2 mg, 0.0806 mmol), $Pd(dba)_2$ (23.1 mg, 0.402 mmol), and toluene (4 mL). The reaction mixture was heated to 140 °C. The crude product was purified by flash column chromatography (silica gel, 4% EtOAc in hexane).



162a

Compound **162a** was isolated as a white solid (124 mg, 0.250 mmol, 62%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.64 – 7.59 (m, 2H, CH), 7.38 – 7.33 (m, 2H, CH), 7.15 – 7.13 (m, 2H, CH), 7.08 (d, *J* = 7.9 Hz, 2H, CH), 6.96 – 6.93 (m, 3H, CH), 2.24 (s, 3H, CH_3), 1.15 (s, 6H, CH_3), 1.09 (s, 6H, CH_3), 1.07 (s, 6H, CH_3), 1.03 (s, 6H, CH_3), **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 148.6 (C), 147.4 (C), 140.5 (C), 139.6 (C), 135.3 (C), 133.8 (CH), 132.1 (CH), 131.4 (CH), 130.4 (CH), 129.9 (2CH), 129.0 (CH), 128.1 (2CH), 126.0 (CH), 125.2 (CH), 83.2 (2C), 83.1 (2C), 25.1 ($2CH_3$), 25.0 ($2CH_3$), 24.6

($2CH_3$), 24.4 ($2CH_3$), 21.2 (CH_3). **HRMS** (ESI^+) m/z: calculated for $(C_{31}H_{38}B_2O_4+Na)^+$ 519.2854, found 519.2861.



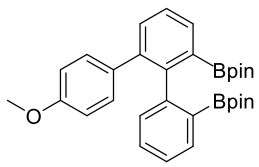
162b

Compound **162b** was isolated as a colourless gum (27 mg, 0.048 mmol, 12%). The yield was calculated by adding a known amount of 1,3,5-trimethoxybenzene due to the impurity of the sample. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.7 Hz, 1H, CH), 7.69 (d, *J* = 7.2 Hz, 1H, CH), 7.57 – 7.51 (m, 4H, CH), 7.41 – 7.38 (m, 1H, CH), 7.33 (m, 2H, CH), 7.24 (d, 7.9 Hz, 2H, CH), 2.39 (s, 3H, CH_3), 1.15 (s, 12H, CH_3), 1.07 (s, 12H, CH_3), **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 150.1 (C), 149.6 (C), 141.7 (C), 138.5 (C), 137.2 (C), 134.4 (CH), 133.7 (CH), 129.5 (2CH), 129.3 (2CH), 128.0 (CH), 127.2 (2CH), 125.9 (CH), 124.3 (CH), 83.3 (4C), 24.7 ($8CH_3$), 21.2 (CH_3). **HRMS** (ESI^+) m/z: calculated for $(C_{31}H_{38}B_2O_4+Na)^+$ 519.2854, found 519.2865.

A mixture of **162a** and **162b** was isolated as a colourless oil (11 mg, 0.012 mmol **162a**, 0.0032 mmol **162b**, 3% **162a**, 1% **162b**). The yield was calculated by adding a known amount of 1,3,5-trimethoxybenzene due to the impurity of the sample.

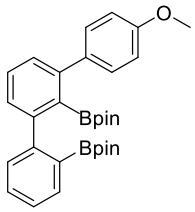
<u>1-(4-Methoxyphenyl)biphenylene, 112</u>

The reaction was conducted according to the general procedure, using 1-(4-methoxyphenyl)biphenylene (103.5 mg 0.4007 mmol), B_2pin_2 (205 mg, 0.807 mmol), KO*t*Bu (10.2 mg, 0.909 mmol), 1,3-bis-(1-adamantylimidazolium)tetrafluoroborate (33.9 mg, 0.0799 mmol), $Pd(dba)_2$ (23.0 mg, 0.0400 mmol), and toluene (4 mL). The reaction mixture was heated to 140 °C. The crude product was purified by flash column chromatography (silica gel, 6-10% EtOAc in hexane).



161a

Compound **161a** was isolated as a white solid (139 mg, 0.271 mmol, 68%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.62 – 7.60 (m, 1H, CH), 7.57 (dd, *J* = 6.8, 2.1 Hz, 1H, CH), 7.37 – 7.31 (m, 2H, CH), 7.14 – 7.12 (m, 2H, CH), 7.09 -7.07 (m, 2H, CH), 6.93 – 6.91 (m, 1H, CH), 6.67 – 6.65 (m, 2H, CH), 3.72 (s, 3H, CH_3), 1.14 (s, 6H, CH_3), 1.07 (s, 6H, CH_3), 1.06 (s, 6H, CH_3), 1.01 (s, 6H, CH_3), **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 157.9 (C), 148.6 (C), 147.4 (C), 140.2 (C), 135.0 (C), 133.8 (CH), 132.0 (CH), 131.4 (CH), 131.1 (2CH), 130.4 (CH), 129.0 (CH), 126.1 (CH), 125.3 (CH), 121.8 (2CH), 83.2 (4C), 55.1 (CH_3), 25.1 ($2CH_3$), 24.9 ($2CH_3$), 24.6 ($2CH_3$), 24.3 ($2CH_3$). **HRMS** (ESI^+) m/z: calculated for $(C_{31}H_{38}B_2O_5+Na)^+$ 535.2803, found 535.2793.

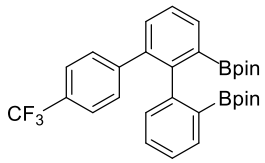


161b

Compound **161b** was isolated as a pale-yellow oil (33 mg, 0.040 mmol, 10%). The yield was calculated by adding a known amount of durene due to the impurity of the sample. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.7 Hz, 1H, CH), 7.69 – 7.68 (m, 1H, CH), 7.61 – 7.58 (m, 2H, CH), 7.52 – 7.50 (m, 1H, CH), 7.48 – 7.47 (m, 1H, CH), 7.41 – 7.37 (m, 1H, CH), 7.32 – 7.30 (m, 2H, CH), 7.97 – 7.95 (m, 2H, CH), 3.84 (s, 3H, CH_3), 1.11 (s, 12H, CH_3), 1.06 (s, 12H, CH_3), **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 159.3 (C), 150.1 (C), 149.5 (C), 141.3 (C), 134.5 (CH), 133.9 (C), 133.7 (CH), 129.3 (CH), 129.2 (CH), 128.3 (2CH), 127.8 (CH), 125.9 (CH), 124.0 (CH), 114.2 (2CH), 83.3 (4C), 55.4 (CH_3), 24.7 ($8CH_3$). **HRMS** (ESI^+) m/z: calculated for $(C_{31}H_{38}B_2O_5+Na)^+$ 535.2803, found 532.2799.

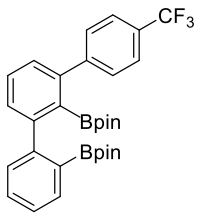
1-(4-(Trifluoromethyl)phenyl)biphenylene, 118

The reaction was conducted according to the general procedure, using 1-(4-trifluoromethyl)phenylbiphenylene (117.5 mg, 0.3966 mmol), B_2pin_2 (206 mg, 0.811 mmol), KO*t*Bu (10.0 mg, 0.0891 mmol), 1,3-bis-(1-adamantylimidazolium)tetra fluoroborate (34.2 mg, 0.0806 μmol), $Pd(dba)_2$ (23.2 mg, 0.0403 mmol), and toluene (4 mL). The reaction mixture was heated to 140 °C. The crude product was purified by flash column chromatography (silica gel, 5% EtOAc in hexane).



163a

Compound **163a** was isolated as a white solid (101 mg, 0.184 mmol, 46%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.65 – 7.61 (m, 2H, CH), 7.40 – 7.28 (m, 6H, CH), 7.15 – 7.13 (m, 2H, CH), 6.91 (m, 1H, CH), 1.15 (s, 6H, CH_3), 1.08 (s, 6H, CH_3), 1.06 (s, 6H, CH_3), 1.02 (s, 6H, CH_3), **^{19}F NMR** (377 MHz, $CDCl_3$) δ -62.32, **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 147.8 (C), 147.4 (C), 146.3 (C), 139.3 (C), 134.0 (CH), 133.0 (CH), 131.1 (CH), 130.3 (3CH), 129.2 (CH), 128.1 (q, *J* = 32.0 Hz, C), 126.3 (CH), 125.7 (CH), 124.3 (q, *J* = 3.8 Hz, 2CH), 124.5 (q, *J* = 272.0 Hz, CF_3), 83.4 (2C), 83.3 (2C), 25.1 (2CH_3), 24.9 (2CH_3), 24.5 (2CH_3), 24.4 (2CH_3). **HRMS** (ESI^+) m/z: calculated for $(C_{31}H_{35}B_2O_4F_3+Na)^+$ 573.2571, found 573.2579.



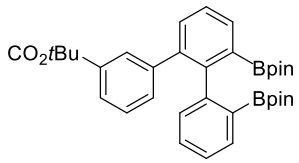
163b

Compound **163b** was isolated as a pale-yellow oil (24 mg, 0.044 mmol, 11%). The yield was calculated by adding a known amount of 1,3,5-trimethoxybenzene due to the impurity of the sample. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.79 – 7.74 (m, 3H, CH), 7.72 – 7.66 (m, 3H, CH), 7.56 – 7.53 (m, 2H, CH), 7.42 – 7.39 (m, 1H, CH), 7.34 (m, 2H, CH), 1.11 (s, 12H, CH_3), 1.06 (s, 12H, CH_3), **^{19}F NMR** (377 MHz, $CDCl_3$) δ -62.38, **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 150.4 (C), 149.2 (C), 145.0 (C), 140.1 (C), 134.5 (CH), 133.9 (CH), 129.4 (CH), 129.4 (q, *J* = 32.6 Hz, C), 129.2 (CH), 128.3 (CH), 127.6 (2CH), 126.1 (CH), 125.7 (q, *J* = 3.7 Hz, 2CH), 124.5 (CH), 124.5 (q, *J* = 271.6 Hz, CF_3), 83.5 (2C), 83.3 (2C), 24.7 (8CH_3). **HRMS** (ESI^+) m/z: calculated for $(C_{31}H_{35}B_2O_4F_3+Na)^+$ 573.2571, found 573.2577.

A mixture of **163a** and **163b** was isolated as a colourless oil (56 mg, 0.044 mmol **163a**, 0.050 mmol **163b**, 11% **163a**, 13% **163b**). The yield was calculated by adding a known amount of 1,3,5-trimethoxybenzene due to the impurity of the sample.

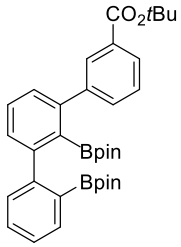
***Tert*-butyl-3-(biphenylen-1-yl)benzoate, 113**

The reaction was conducted according to the general procedure, using *tert*-butyl-3-(biphenylen-1-yl)benzoate (131.0 mg 0.3989 mmol), B_2pin_2 (203 mg, 0.799 mmol), KO*t*Bu (10.0 mg, 0.0891 mmol), 1,3-bis-(1-adamantylimidazolium)tetrafluoroborate (34.0 mg, 0.0801 mmol), $Pd(dba)_2$ (22.8 mg, 0.0397 mmol), and toluene (4 mL). The reaction mixture was heated to 140 °C. The crude product was purified by flash column chromatography (silica gel, 6% EtOAc in hexane).



164a

Compound **164a** was isolated as a white solid (103 mg, 0.177 mmol, 44%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.81 (br. s, 1H, CH), 7.72 (d, *J* = 7.8 Hz, 1H, CH), 7.63 (dd, *J* = 6.6, 1.8 Hz, 1H, CH), 7.59 (d, *J* = 6.7 Hz, 1H, CH) , 7.40 – 7.35 (m, 2H, CH), 7.28 (d, *J* = 7.7 Hz, 1H, CH), 7.16 – 7.09 (m, 3H, CH), 6.97 (d, *J* = 3.7 Hz, 1H, CH), 1.54 (s, 9H, CH_3), 1.14 (s, 6H, CH_3), 1.05 (s, 6H, CH_3), 1.04 (s, 6H, CH_3), 1.01 (s, 6H, CH_3), **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 166.1 (C), 148.1 (C), 147.5 (C), 142.5 (C), 139.9 (C), 134.3 (CH), 134.0 (CH), 132.6 (CH), 131.2 (CH), 131.1 (CH), 130.5 (CH), 129.1 (CH), 127.1 (2CH), 126.2 (CH), 125.5 (CH), 83.3 (2C), 83.1 (2C), 80.7 (C), 28.3 ($3CH_3$), 25.1 ($2CH_3$), 24.9 ($2CH_3$), 24.5 ($2CH_3$), 24.4 ($2CH_3$). Three quaternary carbon signals are not observed. **HRMS** (ESI^+) m/z: calculated for $(C_{35}H_{44}B_2O_6+Na)^+$ 605.3222, found 605.3232.



164b

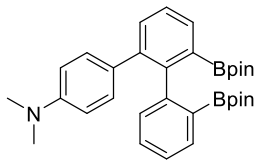
Compound **164b** was isolated as a yellow oil (26 mg, 0.024 mmol, 6%). The yield was calculated by adding a known amount of 1,3,5-trimethoxybenzene due to the impurity of the sample. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.26 (br. S, 1H, CH), 7.95 (d, *J* = 7.8 Hz, 1H, CH), 7.80 (d, *J* = 8.1 Hz, 1H, CH), 7.77 (d, *J* = 7.7 Hz, 1H, CH), 7.70 – 7.69 (m, 1H, CH), 7.57 (dd, *J* = 7.8, 1.7 Hz, 1H, CH), 7.53 – 7.52 (m, 1H, CH), 7.46 (t, *J* =

7.7 Hz, 1H, CH), 7.40 (td, *J* = 7.4, 1.4 Hz, 1H, CH), 7.33 – 7.29 (m, 2H, CH), 1.61 (s, 9H, CH_3), 1.10 (s, 12H, CH_3), 1.06 (s, 12H, CH_3), **$^{13}C\{^1H\}$ NMR** (126 MHz, $CDCl_3$) δ 166.0 (C), 150.3 (C), 149.4 (C), 141.5 (C), 140.9 (C), 134.5 (CH), 133.8 (CH), 132.6 (C), 131.3 (CH), 129.3 (2CH), 128.7 (CH), 128.4 (CH), 128.2 (2CH), 126.0 (CH), 124.5 (CH), 83.4 (2C), 83.3 (2C), 81.3 (C), 28.4 ($3CH_3$), 25.2 ($4CH_3$), 24.7 ($4CH_3$). **HRMS** (ESI^+) m/z: calculated for $(C_{35}H_{44}B_2O_6+Na)^+$ 605.3222, found 605.3231.

A mixture of **164a** and **164b** was isolated as a pale-yellow oil (48 mg, 0.030 mmol **164a**, 0.038 mmol **164b**, 8% **164a**, 10% **164b**). The yield was calculated by adding a known amount of 1,3,5-trimethoxybenzene due to the impurity of the sample.

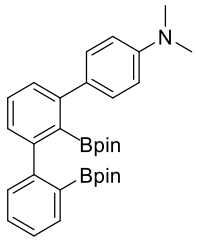
1-(4-(Dimethylamino)phenyl)biphenylene, 115

The reaction was conducted according to the general procedure, using 1-(4-(dimethylamino)phenyl)biphenylene (108.0 mg 0.3980 mmol), B_2pin_2 (204 mg, 0.803 mmol), KO*t*Bu (9.8 mg, 0.088 mmol), 1,3-bis-(1-adamantylimidazolium)tetrafluoro borate (33.6 mg, 0.0792 mmol), $Pd(dba)_2$ (23.1 mg, 0.0402 mmol), and toluene (4 mL). The reaction mixture was heated to 140 °C. The crude product was purified by flash column chromatography (silica gel, 8% EtOAc in hexane).



165a

Compound **165a** was isolated as a white solid (87 mg, 0.17 mmol, 42%). **^1H NMR** (500 MHz, $CDCl_3$) δ 7.65 – 7.63 (m, 1H, CH), 7.55 (dd, *J* = 7.3, 1.4 Hz, 1H, CH), 7.38 (dd, *J* = 7.8, 1.4 Hz, 1H, CH), 7.32 (t, *J* = 7.5 Hz, 1H, CH), 7.17 – 7.12 (m, 2H, CH), 7.06 – 7.04 (m, 2H, CH), 6.97 – 6.95 (m, 1H, CH), 6.53 – 6.51 (m, 2H, CH), 2.86 (s, 6H, CH_3), 1.15 (s, 6H, CH_3), 1.09 (s, 6H, CH_3), 1.07 (s, 6H, CH_3), 1.03 (s, 6H, CH_3), **$^{13}C\{^1H\}$ NMR** (126 MHz, $CDCl_3$) δ 149.0 (C), 148.8 (C), 147.3 (C), 140.5 (C), 133.8 (CH), 131.6 (CH), 131.5 (CH), 130.9 (C), 130.7 (2CH), 130.4 (CH), 129.1 (CH), 126.0 (CH), 125.1 (CH), 111.8 (2CH), 83.1 (4C), 40.7 ($2CH_3$), 25.1 ($2CH_3$), 25.0 ($2CH_3$), 24.6 ($2CH_3$), 24.3 ($2CH_3$). **HRMS** (ESI^+) m/z: calculated for $(C_{32}H_{41}B_2O_4N+H)^+$ 526.3300, found 526.3315.



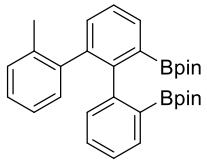
165b

Compound **165b** was isolated as a pale-yellow solid (22 mg, 0.012 mmol, 3%). The yield was calculated by adding a known amount of 1,3,5-trimethoxybenzene due to the impurity of the sample. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 7.7 Hz, 1H, CH), 7.67 – 7.65 (m, 1H, CH), 7.58 – 7.56 (m, 2H, CH), 7.51 (dd, *J* = 7.9, 1.7 Hz, 1H, CH), 7.48 – 7.47 (m, 1H, CH), 7.39 – 7.35 (m, 1H, CH), 7.31 – 7.29 (m, 2H, CH), 6.79 – 6.77 (m, 2H, CH), 2.98 (s, 6H, CH_3), 1.10 (s, 12H, CH_3), 1.06 (s, 12H, CH_3), **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 150.2 (C), 150.1 (C), 149.8 (C), 141.7 (C), 134.5 (CH), 133.5 (CH), 129.3 (C), 129.3 (CH), 129.2 (CH), 127.9 (2CH), 127.2 (CH), 125.8 (CH), 123.5 (CH), 112.8 (2CH), 83.3 (2C), 83.1 (2C), 40.7 ($2CH_3$), 25.15 ($8CH_3$). **HRMS** (ESI^+) m/z: calculated for $(C_{32}H_{41}B_2O_4N+H)^+$ 526.3300, found 526.3315 $(M+H)^+$.

A mixture of **165a** and **165b** was isolated as a colourless oil (40 mg, 0.043 mmol **165a**, 0.019 mmol **165b**, 11% **165a**, 5% **165b**). The yield was calculated by adding a known amount of 1,3,5-trimethoxybenzene due to the impurity of the sample.

1-(*o*-Tolyl)biphenylene, 80

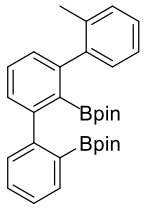
The reaction was conducted according to the general procedure, using 1-(*o*-tolyl)biphenylene (97.0 mg 0.400 mmol), B_2pin_2 (204 mg, 0.803 mmol), KO*t*Bu (10.0 mg, 0.0891 mmol), 1,3-bis-(1-adamantylimidazolium)tetrafluoroborate (34.0 mg, 0.0801 mmol), $Pd(dba)_2$ (23.0 mg, 0.0400 mmol), and toluene (4 mL). The reaction mixture was heated to 140 °C. The crude product was purified by flash column chromatography (silica gel, 4% EtOAc in hexane).



156a

Compound **156a** was isolated as a white solid (108 mg, 0.218 mmol, 54%). A mixture of two inseparable diastereomers (dr = 3:1), dia.1 = major diastereomer, dia.2 = minor diastereomer, **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.63 – 7.56 (m, 2H dia.1, 2H dia.2, CH),

7.33 – 7.29 (m, 1H dia.1, 1H dia.2, CH), 7.25 – 7.23 (m, 1H dia.1, CH), 7.17 – 7.15 (m, 1H dia.2, CH), 7.09 – 7.03 (m, 4H dia.1, 6H dia.2, CH), 6.98 – 6.95 (m, 1H dia.1, CH), 6.94 – 6.92 (m, 1H dia.2, CH), 6.86 – 6.80 (m, 2H dia.1, CH), 2.21 (s, 3H dia.1, CH_3), 1.97 (s, 3H dia.2, CH_3), 1.18 (s, 6H dia.1, CH_3), 1.13 (s, 6H dia.2, CH_3), 1.11 (br.s, 6H dia.1, 6H dia.2, CH_3), 1.06 (br.s, 6H, dia.1, 6H dia.2, CH_3), 1.01 (s, 6H dia.1, CH_3), 1.00 (s, 6H dia.2, CH_3), **$^{13}C\{^1H\}$ NMR** (126 MHz, $CDCl_3$) δ 148.5 (C dia.1), 148.0 (C dia.2), 147.6 (C dia.1), 147.0 (C dia.2), 141.9 (C dia.1), 141.7 (C dia.2), 140.4 (C dia.2), 139.7 (C dia.1), 136.5 (C dia.2), 135.6 (C dia.1), 134.8 (CH dia.2), 133.8 (CH dia.1), 132.3 (CH dia.2), 132.2 (CH dia.1), 131.5 (2CH dia.2), 131.4 (CH dia.1), 131.2 (CH dia.2), 130.6 (CH, dia.1), 129.5 (CH dia.2), 129.3 (CH dia.1), 129.0 (CH dia.1), 128.6 (CH dia.1), 128.5 (CH dia.2), 126.6 (CH dia.2), 126.3 (CH dia.1), 125.7 (CH dia.2), 125.5 (CH dia.1), 125.3 (CH dia.1, CH dia.2), 124.7 (CH dia.1), 124.2 (CH dia.2), 83.3-83.2 (4C dia.1, 4C dia.2), 25.3 ($2CH_3$ dia.2), 25.1 ($2CH_3$ dia.1, $2CH_3$ dia.2), 25.0 ($2CH_3$ dia.1), 24.6 ($2CH_3$ dia.1, $2CH_3$ dia.2), 24.3 ($2CH_3$ dia.1), 24.2 ($2CH_3$ dia.2), 20.7 (CH_3 dia.1), 20.6 (CH_3 dia.2). **HRMS** (ESI^+) m/z: calculated for $(C_{31}H_{38}B_2O_4+Na)^+$ 519.2854, found 519.2853.



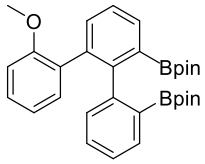
156b

Compound **156b** was isolated as a colourless oil (40 mg, 0.072 mmol, 18%). The yield was calculated by adding a known amount of 1,3,5-trimethoxybenzene due to the impurity of the sample. **^1H NMR** (500 MHz, CD_2Cl_2) δ 7.69 (d, *J* = 7.6 Hz, 1H, CH), 7.65 (dd, *J* = 7.4, 2.8 Hz, 1H, CH), 7.38 (td, *J* = 7.6, 1.5 Hz, 1H, CH), 7.30 (td, *J* = 7.5, 1.2 Hz, 1H, CH), 7.27 – 7.20 (m, 6H, CH), 7.17 – 7.16 (m, 1H, CH), 2.28 (s, 3H, CH_3), 1.11 (s, 12H, CH_3), 1.07 (s, 12H, CH_3), **$^{13}C\{^1H\}$ NMR** (126 MHz, $CDCl_3$) δ 149.7 (C), 149.6 (C), 142.8 (C), 142.2 (C), 135.6 (C), 133.8 (CH), 133.5 (CH), 130.3 (CH), 130.0 (CH), 129.8 (CH), 129.4 (CH), 129.0 (CH), 127.3 (CH), 126.7 (CH), 125.9 (CH), 125.7 (CH), 83.3 (4C), 24.7 ($8CH_3$), 20.6 (CH_3). **HRMS** (ESI^+) m/z: calculated for $(C_{31}H_{38}B_2O_4+Na)^+$ 519.2854, found 519.2855.

A mixture of **156a** and **156b** was isolated as a colourless oil (20 mg, 0.024 mmol **156a**, 0.0092 mmol **156b**, 6% **156a**, 2% **156b**). The yield was calculated by adding a known amount of 1,3,5-trimethoxybenzene due to the impurity of the sample.

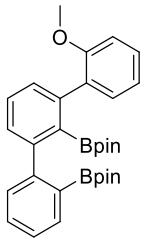
1-(2-Methoxyphenyl)biphenylene, 78

The reaction was conducted according to the general procedure, using 1-(2-methoxyphenyl)biphenylene (103.5 mg 0.4007 mmol), B_2pin_2 (203 mg, 0.799 mmol), KO*t*Bu (10.1 mg, 0.0900 mmol), 1,3-bis-(1-adamantylimidazolium)tetrafluoroborate (34.0 mg, 0.0801 mmol), $Pd(dba)_2$ (23.1 mg, 0.0402 mmol), and toluene (4 mL). The reaction mixture was heated to 160 °C for 16 h. To the reaction mixture was added $Pd(dba)_2$ (22.8 mg, 0.0397 mmol), 1,3-bis-(1-adamantylimidazolium)tetrafluoroborate (34.0 mg, 0.0801 mmol), and KO*t*Bu (9.7 mg, 0.086 mmol). The reaction mixture was heated to 160 °C for 6 h. The reaction mixture was heated to 180 °C for 16 h. The crude product was purified by flash column chromatography (silica gel, 6% EtOAc in hexane).



159a

Compound **159a** was isolated as a white solid (91 mg, 0.18 mmol, 44%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 6.2, 2.3 Hz, 1H, CH), 7.54 – 7.52 (m, 1H, CH), 7.34 – 7.30 (m, 2H, CH), 7.08 – 7.04 (m, 5H, CH), 6.70 – 6.67 (m, 2H, CH), 3.67 (br.s, 3H, CH_3), 1.15 (s, 6H, CH_3), 1.10 (s, 6H, CH_3), 1.05 (s, 6H, CH_3), 1.01 (s, 6H, CH_3), **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 156.7 (C), 148.6 (C), 148.1 (C), 137.3 (C), 133.5 (CH), 132.4 (CH), 132.0 (CH), 131.8 (CH), 131.5 (C), 129.3 (CH), 128.5 (CH), 127.8 (CH), 125.5 (CH), 125.1 (CH), 119.6 (CH), 110.1 (CH), 83.1 (4C), 55.2 (CH_3), 25.1 ($2CH_3$), 25.0 ($2CH_3$), 24.6 ($2CH_3$), 24.3 ($2CH_3$). **HRMS** (CI^+) m/z: calculated for $(C_{31}H_{38}B_2O_5+NH_4)^+$ 530.3249, found 530.3249. Crystals for XRD analysis were grown by slow evaporation of a concentrated solution of methanol at room temperature.



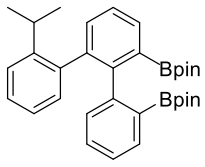
159b

Compound **159b** was isolated as a colourless oil (15 mg, 0.0080 mmol, 2%). The yield was calculated by adding a known amount of durene due to the impurity of the sample. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.7 Hz, 1H, CH), 7.67 – 7.65 (m, 1H, CH), 7.50 (dd, *J* = 7.7, 1.7 Hz, 1H, CH), 7.40 (d, *J* = 1.5 Hz, 1H, CH), 7.38 – 7.34 (m, 2H, CH), 7.32 – 7.27 (m, 3H, CH), 7.00 (td, *J* = 7.5, 1.0 Hz, 1H, CH), 6.96 (d, *J* = 8.3 Hz, 1H, CH), 3.77 (s, 3H, CH_3), 1.10 (s, 12H, CH_3), 1.07 (s, 12H, CH_3), **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 156.8 (C), 149.7 (C), 149.4 (C), 139.5 (C), 133.5 (2CH), 131.2 (C), 131.1 (CH), 130.4 (CH), 129.3 (CH), 129.2 (CH), 128.6 (CH), 127.2 (CH), 125.8 (CH), 120.9 (CH), 111.7 (CH), 83.2 (4C), 55.8 (CH_3), 24.7 (8CH_3). **HRMS** (CI^+) m/z: calculated for $(C_{31}H_{38}B_2O_5+NH_4)^+$ 530.3249, found 530.3298.

A mixture of **159a** and **159b** was isolated as a colourless oil (54 mg, 0.067 mmol **159a**, 0.029 mmol **159b**, 17% **159a**, 7% **159b**). The yield was calculated by adding a known amount of 1,3,5-trimethoxybenzene due to the impurity of the sample.

1-(2-*Iso*propylphenyl)biphenylene, 111

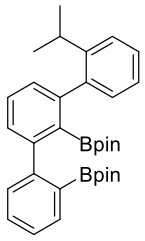
The reaction was conducted according to the general procedure, using 1-(2-*iso*propylphenyl)biphenylene (108.0 mg 0.3994 mmol), B_2pin_2 (204 mg, 0.803 mmol), KO*t*Bu (10.0 mg, 0.0891 mmol), 1,3-bis-(1-adamantylimidazolium)tetrafluoroborate (33.8 mg, 0.0797 mmol), $Pd(dba)_2$ (23.0 mg, 0.0400 mmol), and toluene (4 mL). The reaction mixture was heated to 140 °C. The crude product was purified by flash column chromatography (silica gel, 4-6% EtOAc in hexane).



160a

Compound **160a** was isolated as a white solid (54 mg, 0.10 mmol, 26%). A mixture of two inseparable diastereomers (dr = 1.8:1, based on integrals of 7.64 ppm and 6.8

ppm), dia.1 = major diastereomer, dia.2 = minor diastereomer, un = unassigned **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.64 (dd, J = 7.5, 2.8 Hz, 0.35H dia.2, CH), 7.61 – 7.56 (m, 1.52H un, CH), 7.33 – 7.28 (m, 0.97H un, CH), 7.25 – 7.22 (m, 1.25H un, CH), 7.18 – 7.14 (m, 1.35H un, CH), 7.11 – 7.00 (m, 4H un, CH), 6.94 – 6.89 (m, 1H un, CH), 6.80 (td, J = 7.5, 3.2 Hz, 0.62H dia.1, CH), 3.04 – 2.96 (m, 1H dia.1 and dia.2, CH), 1.19 – 1.17 (m, 11.9H un, CH_3), 1.11 – 1.089 (m, 5.6H un, CH_3), 1.05 (s, 3.5H un, CH_3), 1.00 (s, 5.9H un, CH_3), 0.87 (d, J = 6.8 Hz, 1.1H un, CH_3), 0.51 (d, J = 6.8 Hz, 1.1H un, CH_3), **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 148.5 (C dia.1), 147.9 (C dia.2), 147.7 (C dia.1), 147.1 (C dia.2), 146.7 (C dia.2), 146.5 (C, dia.1), 140.7 (C dia.2), 140.6 (C dia.1), 140.5 (C dia.2), 139.7 (C dia.1), 135.0 (CH dia.2), 133.9 (CH dia.1), 132.6 (CH dia.2), 132.1 (CH dia.1), 131.9 (CH dia.2), 131.6 (CH dia.2), 131.5 (CH, dia.1), 130.6 (CH dia.1, CH dia.2), 129.1 (CH dia.1), 128.9 (CH dia.1), 128.6 (CH dia.2), 127.2 (CH dia.2), 126.8 (CH dia.1), 125.7 (CH dia.2), 125.3 (2CH dia.1, CH dia.2), 124.9 (CH dia.2), 124.8 (CH dia.1), 124.3 (CH dia.1, CH dia.2), 83.3 (C un), 83.2 (C un), 29.9 (CH dia.1), 28.8 (CH dia.2), 25.7 (CH_3 un), 25.5 (CH_3 un), 25.2 (CH_3 un), 25.1 (CH_3 un), 25.0 (CH_3 un), 24.6 (CH_3 un), 24.2 (CH_3 un), 24.1 (CH_3 un), 23.3 (CH_3 un), 22.6 (CH_3 un), **HRMS** (ESI^+) m/z: calculated for $(C_{33}H_{42}B_2O_4+Na)^+$ 547.3167, found 547.3178.



160b

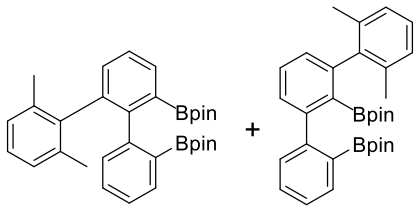
Compound **160b** was isolated as a colourless oil (12 mg, 0.016 mmol, 4%). The yield was calculated by adding a known amount of 1,3,5-trimethoxybenzene due to the impurity of the sample. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.70 – 7.68 (m, 2H, CH), 7.40 – 7.36 (m, 2H, CH), 7.33 – 7.27 (m, 3H, CH), 7.24 (dd, *J* = 7.7, 1.6 Hz, 1H, CH), 7.21 – 7.20 (m, 2H, CH), 7.16 – 7.15 (m, 1H, CH), 3.18 (spt, *J* = 6.9 Hz, 1H, CH), 1.15 (d, *J* = 6.9 Hz, 6H, CH_3), 1.10 (s, 12H, CH_3), 1.09 (s, 12H, CH_3), **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 149.8 (C), 149.6 (C), 146.5 (C), 143.0 (C), 141.5 (C), 133.8 (CH), 133.3 (CH), 130.0 (CH), 129.9 (CH), 129.4 (CH), 129.0 (CH), 127.6 (CH), 126.8 (CH), 125.9 (CH), 125.5 (CH), 125.3 (CH), 83.3 (2C), 83.2 (2C), 29.3 (CH), 24.8

($4CH_3$), 24.7 ($4CH_3$), 24.5 ($2CH_3$). **HRMS** (ESI^+) m/z: calculated for $(C_{33}H_{42}B_2O_4+Na)^+$ 547.3167, found 547.3179.

A mixture of **160a** and **160b** was isolated as a colourless oil (101 mg, 0.131 mmol **160a**, 0.0615 mmol **160b**, 33% **160a**, 15% **160b**).

1-(2,6-Dimethylphenyl)biphenylene 337

The reaction was conducted according to the general procedure, using 1-(2,6-dimethylphenyl)biphenylene (102.0 mg 0.3979 mmol), B_2pin_2 (203 mg, 0.799 mmol), KO*t*Bu (9.8 mg, 0.087 mmol), 1,3-bis-(1-adamantylimidazolium)tetrafluoroborate (34.0 mg, 0.0801 mmol), $Pd(dba)_2$ (23.5 mg, 0.0409 mmol), and toluene (4 mL). The reaction mixture was heated to 140 °C. The crude product was purified by flash column chromatography (silica gel, 5% EtOAc in hexane).



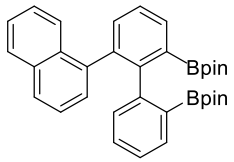
157a **157b**

Compound **157** was isolated as a pale-yellow solid (150 mg, 0.294 mmol, 74%). A mixture of two inseparable regioisomers (r = 2.7:1), reg.1 = **157b**, minor regioisomer, reg.2 = **157a**, major regioisomer, un = unassigned. **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 7.68 (d, *J* = 7.5 Hz, 1H reg. 1, CH), 7.67 – 7.61 (m, 1H reg. 1, 2H reg. 2, CH), 7.38 (td, *J* = 7.5, 1.5 Hz, 1H reg. 1, CH), 7.35 (t, *J* = 7.5 Hz, 1H reg. 2, CH), 7.29 (td, *J* = 7.4, 1.9 Hz, 1H reg. 1, CH), 7.24 – 7.23 (m, 1H reg. 1, CH), 7.13 – 7.07 (m, 4H reg. 1, 2H reg. 2, CH), 7.03 (td, *J* = 7.5, 1.6 Hz, 1H reg. 2, CH), 7.00 – 6.99 (m, 1H reg. 1, 1H reg. 2, CH), 6.96 (t, *J* = 7.5 Hz, 1H reg. 2, CH), 6.88 (d, *J* = 7.4 Hz, 1H reg. 2, CH), 6.76 (d, *J* = 7.3 Hz, 1H reg. 2, CH), 2.10 (s, 3H reg. 2, CH_3), 2.08 (s, 6H reg. 1, CH_3), 1.84 (s, 3H reg. 2, CH_3), 1.14 (s, 6H reg. 2, CH_3), 1.12 (s, 6H reg. 2, CH_3), 1.09 (s, 12H reg. 1, CH_3), 1.08 (s, 12H reg. 1, CH_3), 1.06 (s, 6H reg. 2, CH_3), 0.99 (s, 6H reg. 2, CH_3), **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 150.1 (C reg.1), 150.0 (C reg.1), 148.1 (C reg.2), 146.4 (C reg.2), 142.2 (2C reg.1), 141.4 (C reg.2), 139.0 (C reg.2), 136.9 (C reg.2), 136.6 (C reg.2), 136.1 (C reg.1), 134.9 (CH un), 134.0 (CH reg.1), 133.7 (CH reg.1), 132.5 (CH un), 131.2 (CH un), 129.5 (CH reg.1), 129.4 (CH reg.1), 128.8 (CH reg.1), 128.7 (2CH un), 127.2 (CH un), 127.0 (CH reg.1), 126.9 (CH un), 126.6 (CH

un), 126.5 (CH reg.1, CH un), 126.1 (CH, un), 125.9 (CH reg.1), 125.4 (CH un), 83.3 (4C reg.1), 83.2 (4C reg.2), 25.2 (CH_3 un), 24.9 (CH_3 un), 24.7 (CH_3 un), 24.1 (CH_3 un), 21.6 (CH_3 reg.2), 21.2 (CH_3 reg.2), 21.0 (CH_3 reg.1). Three quaternary carbon signals are not observed for regioisomer 1. Of the 11 unassigned CH signals, 10 correspond to reg.2 and 1 corresponds to two reg.1 CHs. **HRMS** (ESI^+) m/z: calculated for $(C_{32}H_{40}B_2O_4+Na)^+$ 533.3010, found 533.3019.

1-(Naphthalen-1-yl)biphenylene, 110

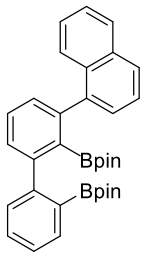
The reaction was conducted according to the general procedure, using 1-(naphthalen-1-yl)biphenylene (111.2 mg 0.3995 mmol), B_2pin_2 (203 mg, 0.799 mmol), KO*t*Bu (9.9 mg, 0.088 mmol), 1,3-bis-(1-adamantylimidazolium)tetrafluoroborate (33.9 mg, 0.0799 mmol), $Pd(dba)_2$ (23.2 mg, 0.0403 mmol), and toluene (4 mL). The reaction mixture was heated to 140 °C. The crude product was purified by flash column chromatography (silica gel, 7.5% Et_2O in hexane).



158a

Compound **158a** was isolated as a white solid (73 mg, 0.14 mmol, 34%). A mixture of two inseparable diastereomers (dr = 2.3:1, based on integrals of 7.99 ppm and 6.8 ppm), dia.1 = major diastereomer, dia.2 = minor diastereomer, un = unassigned. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.5 Hz, 0.32H dia.2, CH), 7.78 – 7.77 (m, 1.44H un, CH), 7.71 – 7.64 (m, 1.56H, CH), 7.60 (d, *J* = 8.2 Hz, 0.68H dia.1, CH), 7.56 (d, *J* = 7.3 Hz, 0.68H dia.1, CH), 7.48 (d, *J* = 7.4 Hz, 0.29H dia.2, CH), 7.44 – 7.36 (m, 4.14H un, CH), 7.32 - 7.27 (m, 0.9H un, CH), 7.19 – 7.13 (m, 1.39H un, CH), 7.02 – 6.92 (m, 1.47H un, CH), 6.80 (t, *J* = 7.4 Hz, 0.75H dia.1, CH), 6.72 (d, *J* = 7.6 Hz, 0.75H dia.1, CH), 1.27 (s, 1.8H dia.2, CH_3), 1.23 (s, 3.9H dia.1, CH_3), 1.17 - 1.16 (m, 6.2H dia.1 and dia.2, CH_3), 1.09 - 1.08 (m, 6.3H dia.1 and dia.2, CH_3), 1.03 - 1.02 (m, 6.3H dia.1 and dia.2, CH_3), **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 148.5 (C dia.1), 148.3 (C dia.1), 147.9 (C dia.2), 147.8 (C dia.2), 140.2 (C dia.2), 139.9 (C dia.1), 139.2 (C dia.2), 138.4 (C dia.1), 134.8 (CH dia.2), 133.7 (CH dia.1), 133.3 (C dia.1, C dia.2), 133.2 (C dia.1), 132.7 (CH dia.2), 132.6 (CH dia.1), 132.5 (CH dia.2), 132.3 (CH dia.1), 130.9 (CH dia.2), 128.8 (CH dia.1), 128.7 (CH dia.2), 128.5 (CH dia.1), 128.4

(CH dia.2), 128.3 (CH dia.2), 128.0 (CH dia.1), 127.9 (CH dia.1), 127.4 (CH dia.2), 127.0 (CH dia.2), 126.8 (CH dia.1), 126.6 (CH dia.1), 125.6 (CH dia.2), 125.5 (CH dia.1), 125.4 (CH dia.1), 125.3 (2CH dia.2), 125.2 (2CH dia.1), 125.0 (CH dia.1), 124.8 (CH dia.2), 124.5 (CH dia.2), 83.3 (4C dia.1, 2C dia.2), 83.2 (2C dia.2), 25.5 ($2CH_3$ dia.2), 25.2 ($2CH_3$ dia.1), 25.1 ($2CH_3$ dia.1), 25.0 ($2CH_3$ dia.2), 24.7 ($2CH_3$ dia.1), 24.6 ($2CH_3$ dia.2), 24.3 ($2CH_3$ dia.1), 24.2 ($2CH_3$ dia.2). Three quaternary carbon signals are not observed for the minor diastereomer. **HRMS** (ESI^+) m/z: calculated for $(C_{34}H_{38}B_2O_4+Na)^+$ 555.2854, found 555.2864.



158b

Compound **158b** was isolated as a colourless gum (36 mg, 0.060 mmol, 15%). Compound **158b** was contaminated with 12% of **158a**. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.5 Hz, 1H, CH), 7.89 (d, *J* = 8.1 Hz, 1H, CH), 7.85 (d, *J* = 7.9 Hz, 1H, CH), 7.81 (d, *J* = 7.5 Hz, 1H, CH), 7.73 (d, *J* = 7.4 Hz, 1H, CH), 7.54 – 7.44 (m, 5H, CH), 7.41 – 7.38 (m, 2H, CH), 7.33 – 7.26 (m, 2H, CH), 1.14 (s, 12H, CH), 1.12 (m, 12H, CH), **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 149.7 (2C), 141.5 (C), 140.7 (C), 133.9 (C), 133.8 (2CH), 131.0 (C), 130.9 (CH), 129.4 (CH), 128.9 (CH), 128.2 (CH), 127.6 (CH), 127.5 (CH), 126.8 (CH), 126.5 (CH), 126.0 (CH), 125.9 (CH), 125.8 (CH), 125.4 (CH), 83.4 (2C), 83.3 (2C), 24.8 ($4CH_3$), 24.7 ($4CH_3$). **HRMS** (ESI^+) m/z: calculated for $(C_{34}H_{38}B_2O_4+Na)^+$ 555.2854, found 555.2864.

A mixture of **158a** and **158b** was isolated as a colourless oil (39 mg, 0.054 mmol **158a**, 0.020 mmol **158b**, 13% **158a**, 5% **158b**).

1-(2-Pyridyl)biphenylene, 16 (140 °C)

The reaction was conducted according to the general procedure using 1-(2-pyridyl)biphenylene (92.0 mg, 0.401 mmol), B_2pin_2 (206 mg, 0.811 mmol), KO*t*Bu (9.9 mg, 0.088 μmol), 1,3-bis-(1-adamantylimidazolium)tetrafluoroborate (35.5 mg, 0.0837 mmol), $Pd(dba)_2$ (22.5 mg, 0.0391 mmol), and toluene (4 mL). The reaction mixture was heated to 140 °C. The crude product was purified by flash column

chromatography (silica gel, 5% EtOAc in hexane). Starting material was isolated as a yellow oil (82 mg, ~85%), which was contaminated with a small amount of B_2pin_2.

1-(2-Pyridyl)biphenylene, 16 (180 °C)

The reaction was conducted according to the general procedure using 1-(2-pyridyl)biphenylene (92.0 mg, 0.401 mmol), B_2pin_2 (203 mg, 0.799 mmol), KO*t*Bu (9.9 mg, 0.088 mmol), 1,3-bis-(1-adamantylimidazolium)tetrafluoroborate (33.0 mg, 0.0778 mmol), $Pd(dba)_2$ (22.5 mg, 0.0391 mmol), and toluene (4 mL). The reaction mixture was heated to 180 °C. The crude product was purified by flash column chromatography (silica gel, 5% EtOAc in hexane). Starting material was isolated as a yellow oil (72 mg, ~75%), which was contaminated with a small amount of B_2pin_2.

1-Diphenylphosphinobiphenylene, 101 (140 °C)

The reaction was conducted according to the general procedure using 1-diphenylphosphinobiphenylene (123.0 mg, 0.3657 mmol), B_2pin_2 (186 mg, 0.732 mmol), KO*t*Bu (9.2 mg, 0.082 mmol), 1,3-bis-(1-adamantylimidazolium)tetrafluoro borate (31.0 mg, 0.0731 mmol), $Pd(dba)_2$ (21.0 mg, 0.0366 mmol), and toluene (3.7 mL). The reaction mixture was heated to 140 °C. The reaction mixture was dark brown in colour at room temperature and remained dark brown when heated. The crude product was purified by flash column chromatography (silica gel, 1-20% EtOAc in hexane). A yellow oil (70 mg) was isolated. This oil contained starting material (~50%) and an unknown side-product . An orange gum (46 mg) was also isolated, but could not be identified.

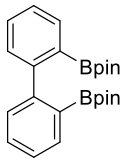
1-Diphenylphosphinobiphenylene, 101 (180 °C)

The reaction was conducted according to the general procedure using 1-diphenylphosphinobiphenylene (134.0 mg, 0.3984 mmol), B_2pin_2 (203 mg, 0.799 mmol), KO*t*Bu (9.9 mg, 0.088 mmol), 1,3-bis-(1-adamantylimidazolium)tetrafluoro borate (34.3 mg, 0.0808 mmol), $Pd(dba)_2$ (23.0 mg, 0.0400 mmol), and toluene (4 mL). The reaction mixture was heated to 180 °C for 16 h. The reaction mixture was dark brown in colour at room temperature and remained dark brown when heated. To the reaction mixture was added KO*t*Bu (10.0 mg, 0.0891 mmol), 1,3-bis-(1-adamantylimidazolium)tetrafluoroborate (40.0 mg, 0.0943 mmol), and $Pd(dba)_2$ (23.2 mg, 0.0403 mmol). The reaction mixture was heated to 180 °C for 24 h. The crude

product was purified by flash column chromatography (silica gel, 0.5-0.75% EtOAc in hexane). A yellow solid (33 mg) was isolated and could not be identified. A white solid (12 mg) was isolated and could not be identified. A brown oil (116 mg) was isolated and could not be identified.

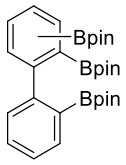
1-BpinBiphenylene, 102

The reaction was conducted according to the general procedure using 1-Bpinbiphenylene (111.3 mg, 0.4001 mmol), B_2pin_2 (204 mg, 0.803 mmol), KO*t*Bu (10.2 mg, 0.0909 mmol), 1,3-bis-(1-adamantylimidazolium)tetrafluoroborate (33.9 mg, 0.0799 mmol), $Pd(dba)_2$ (22.6 mg, 0.0393 mmol), and toluene (4 mL). The reaction mixture was heated to 140 °C. The crude product was purified by flash column chromatography (silica gel, 3-8% EtOAc in hexane).



35

Compound **35** was isolated as a white solid (13 mg, 0.032 mmol, 8%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 2.7 Hz, 2H, CH), 7.38 (td, *J* = 7.6 Hz, 1.38 Hz, 2H, CH), 7.29 (td, *J* = 7.5 Hz, 1.06 Hz, 2H, CH), 7.26 (d, *J* = 7.7 Hz, 2H, CH). The ^{1}H NMR data is consistent with that reported in the literature.[47,54]



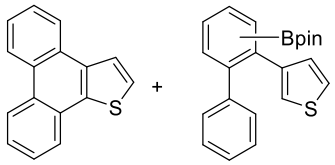
175

Compound **175** was isolated as a white solid (44 mg, 0.083 mmol, 21%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.4 Hz, 2H, CH), 7.64 (d, *J* = 7.2 Hz, 1H, CH), 7.29 – 7.21 (m, 3H, CH), 7.14 (d, *J* = 7.4 Hz, 1H, CH), 1.03 (s, 12H, CH_3), 1.02 (s, 12H, CH_3), 1.01 (s, 12H, CH_3). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 154.9 (C), 150.6 (C), 134.9 (2CH), 133.1 (CH), 129.9 (CH), 128.4 (CH), 125.2 (CH), 124.8 (CH), 83.0 (4C), 82.7 (2C), 24.7 ($4CH_3$), 24.6 ($4CH_3$), 24.4 ($4CH_3$). Three quaternary carbon signals are not observed. **HRMS** (ESI^+) m/z: calculated for $(C_{30}H_{43}B_3O_6+K)^+$ 571.2976, found 571.2992.

A mixture of **35** and **175** was isolated as a colourless oil (84 mg, 0.019 mmol **35**, 0.14 mmol **175**, 5% **35**, 36% **175**).

1-(3-Thiophene)biphenylene, 116

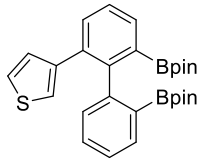
The reaction was conducted according to the general procedure using 1-(3-thiophene)biphenylene (88.0 mg 0.376 mmol), B_2pin_2 (191 mg, 0.752 mmol), KO*t*Bu (9.3 mg, 0.083 mmol), 1,3-bis-(1-adamantylimidazolium)tetrafluoroborate (31.9 mg, 0.0752 mmol), $Pd(dba)_2$ (21.6 mg, 0.0376 mmol), and toluene (3.8 mL). The reaction mixture was heated to 140 °C. The crude product was purified by flash column chromatography (silica gel, 0.5 – 50% EtOAc in hexane).



173 **174**

Compound **173** was isolated as a white solid (17 mg, 0.038 mmol, 10%). The yield was calculated by adding a known amount of 1,3,5-trimethoxybenzene due to the impurity of the sample. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.71 – 8.68 (m, 2H, CH), 8.33-8.31 (m, 1H, CH), 8.16-8.14 (m, 1H, CH), 7.97 (d, *J* = 5.3 Hz, 1H, CH), 7.68-7.62 (m, 4H, CH), 7.56 (d, *J* = 5.3 Hz, 1H, CH). The ^{1}H NMR data was consistent with that reported in the literature.[55]

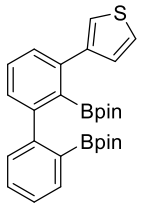
Compound **173** was isolated as a yellow oil (13 mg, 0.0075 mmol, 2%). The yield was calculated by adding a known amount of 1,3,5-trimethoxybenzene due to the impurity of the sample. Compound **173** was contaminated with compound **174**, **HRMS** (CI) m/z: calculated for $(C_{22}H_{23}BO_2S+H)^+$ 363.1590, found 363.1575. It was not possible to estimate a yield or determine which regioisomer(s) because there were no clean signals in the NMR spectrum.



172a

Compound **172a** was isolated as a yellow oil (94 mg, 0.15 mmol, 41%). The yield was calculated by adding a known amount of 1,3,5-trimethoxybenzene due to the impurity

of the sample. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.65-7.63 (m, 1H, CH), 7.58 (dd, *J* = 7.5 Hz, 1.1 Hz, 1H, CH), 7.46 (dd, *J* = 7.7 Hz, 1.2 Hz, 1H, CH), 7.32 (t, *J* = 7.5 Hz, 1H, CH), 7.20 – 7.19 (m, 2H, CH), 7.02-7.00 (m, 1H, CH), 6.99-6.97 (m, 1H, CH), 6.87 (m, 1H, CH), 6.82 (d, *J* = 5.0 Hz, 1H, CH), 1.11 (s, 6H, CH_3), 1.05 (s, 12H, CH_3), 1.02 (s, 6H, CH_3), **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 148.6 (C), 147.4 (C), 142.8 (C), 135.4 (C), 133.8 (CH), 132.3 (CH), 130.9 (CH), 130.0 (CH), 129.6 (CH), 129.2 (CH), 126.1 (CH), 125.6 (CH), 123.6 (CH), 123.0 (CH), 83.2 (2C), 83.1 (2C), 25.0 ($2CH_3$), 24.9 ($2CH_3$), 24.5 ($2CH_3$), 24.4 ($2CH_3$), **HRMS** (ESI^+) m/z: calculated for $(C_{28}H_{34}B_2O_4S+H)^+$ 489.2442, found 489.2453.



172b

Compound **172b** was isolated as a pale-yellow oil (10 mg, 0.0075 mmol, 2%). The yield was calculated by adding a known amount of 1,3,5-trimethoxybenzene due to the impurity of the sample. **HR-MS** (ESI^+) m/z: calculated for $(C_{28}H_{34}B_2O_4S+Na)^+$ 511.2262, found 511.2270. It was not possible to fully assign the NMR spectrum because the product was too impure. Characteristic Bpin methyl signals: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.10 and 1.07. The ratio of major regioisomer: minor regioisomer 1:0.1 (internal standard/isolated yields), 1:0.05 (crude NMR).

3.9.4. Ring Opening Diborylation of 1-Phenylbiphenylene With Diboranes Other Than B_2pin_2

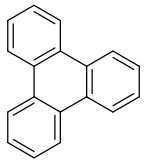
General Procedure

Under an atmosphere of argon, a Schlenk bomb was charged with $Pd(dba)_2$ (10 mol%), 1,3-di-1-(adamantyl)imidazolium tetrafluoroborate (20 mol%), KO*t*Bu (22 mol%), and diborane (2 eq.). The Schlenk bomb was evacuated and backfilled with argon. To the Schlenk bomb was added a solution of 1-phenylbiphenylene (1 eq.) in toluene. The reaction mixture was stirred (600 rpm) at room temperature for 10 min. The reaction mixture was stirred (600 rpm) at 110 °C for 16 h. The reaction mixture was filtered through celite and washed through with EtOAc until no compound was visible by UV

on a TLC plate. The solvent was removed under reduced pressure and the crude product purified by flash column chromatography.

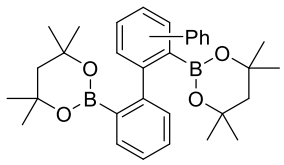
4,4,4',4',6,6,6',6'-Octamethyl-2,2'-bi(1,3,2-dioxaborinane), 143

The reaction was conducted according to the general procedure using $Pd(dba)_2$ (23.3 mg, 0.0405 mmol), 1,3-di-1-(adamantyl)imidazolium tetrafluoroborate (34.0 mg, 0.0801 mmol), KO*t*Bu (9.9 mg, 0.088 mmol), 4,4,4',4',6,6,6',6'-Octamethyl-2,2'-bi(1,3,2-dioxaborinane) (226 mg, 0.801 mmol), 1-phenylbiphenylene (91.0 mg, 0.399 mmol), and toluene (4 mL). At room temperature the reaction mixture was wine-red in colour, upon heating the reaction mixture turned dark brown. The crude product was purified by flash column chromatography (silica gel, 0-2% EtOAc in hexane).



148

Compound **148** was isolated as a white solid (13 mg, 57 μmol, 14%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.68 – 8.67 (m, 6H, CH), 7.68 – 7.66 (m, 6H, CH). The ^{1}H NMR data was consistent with that reported by Sigma Aldrich.



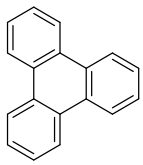
147

Compound **147** was isolated as a white solid (78 mg, 0.15 mmol, 39%). A mixture of two inseparable regioisomers (r = 3.8:1, based on the integrals of 1.71 ppm and 1.68 ppm). Major regioisomer = reg.1, minor regioisomer = reg.2, un = unassigned. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.7 Hz, 0.21H reg.2, CH), 7.70 (dd, *J* = 7.2, 1.2 Hz, 0.21H reg.2, CH), 7.65 – 7.57 (m, 2.13H un, CH), 7.51 (dd, *J* = 7.9, 1.8 Hz, 0.23H reg.2, CH), 7.45 – 7.39 (m, 0.92H un, CH), 7.33 – 7.30 (m, 1.95H un, CH), 7.23 – 7.17 (m, 1.66H un, CH), 7.15 – 7.02 (m, 4.25H un, CH), 6.86 (m, 0.8H reg.1, CH), 1.71 (s, 1.5H reg.1, CH2), 1.68 (s, 0.38H reg.2, CH2), 1.65 (s, 0.38H reg.2, CH2), 1.63 (s, 1.5H reg.1, CH2), 1.17 (s, 4H un, CH3), 1.11 – 1.05 (m, 20H un, CH3), **^{13}C{^{1}H}**

NMR (100 MHz, $CDCl_3$) δ 151.0 (C reg.2), 150.3 (C reg.2), 148.6 (C reg.1), 147.8 (C reg.1), 143.2 (C, reg.1), 141.9 (C reg.2), 140.8 (C reg.2), 140.3 (C reg.1), 133.7 (CH reg.2), 133.3 (CH reg.1), 133.1 (CH reg.2), 131.9 (CH reg.1), 130.4 (CH reg.1), 130.3 (CH reg.1), 130.1 (2CH reg.1), 129.1 (CH reg.2), 128.7 (2CH reg.2), 127.7 (CH reg.2), 127.6 (CH reg.2), 128.0 (CH reg.1), 127.3 (2CH reg.2), 127.2 (2CH reg.1), 127.0 (CH reg.2), 125.6 (CH reg.1), 125.5 (CH reg.1), 125.2 (CH reg.2), 124.8 (CH reg.1), 123.9 (CH reg.2), 70.4 (2C reg.1, 2C reg.2), 70.3 (2C reg.1, 2C reg.2), 48.9 (CH_2 reg.1), 48.8 (CH_2 reg.1, $2CH_2$ reg.2), 31.7, 31.6, 31.5 ($8CH_3$ reg.1, $8CH_3$ reg.2), **HRMS** (ESI^+) m/z: calculated for $(C_{32}H_{40}B_2O_4+Na)^+$ 533.3010, found 533.3025.

4,4,4',4',5,5,5',5'-Octaethyl-2,2'-bi(1,3,2-dioxaborolane), 140

The reaction was conducted according to the general procedure using $Pd(dba)_2$ (21.8 mg, 0.0379 mmol), 1,3-di-1-(adamantyl)imidazolium tetrafluoroborate (32.2 mg, 0.0759 mmol), KO*t*Bu (9.5 mg, 0.084 mmol), 4,4,4',4',5,5,5',5'-octaethyl-2,2'-bi(1,3,2-dioxaborolane) (278 mg, 0.759 mmol), 1-phenylbiphenylene (86.8 mg, 0.380 mmol), and toluene (3.8 mL). At room temperature the reaction mixture was wine-red in colour, upon heating the reaction mixture turned dark brown. The crude product was purified by flash column chromatography (silica gel, 0-5% EtOAc in hexane). Starting material (43 mg, 0.19 mmol, 50%) was recovered.



148

A yellow oil (26 mg) was isolated, which contained starting material (18%) and triphenylene, **148** (~8%). The oil was also contaminated with a small aliphatic impurity, which is most probably a decomposition product of the carbene ligand.

Bis(catecholato)diboron, 141

The reaction was conducted according to the general procedure using $Pd(dba)_2$ (11.3 mg, 0.0197 mmol), 1,3-di-1-(adamantyl)imidazolium tetrafluoroborate (16.6 mg, 0.0391 mmol), KO*t*Bu (5.0 mg, 0.044 mmol), bis(catecholato)diboron (95.0 mg, 0.399 mmol), 1-phenylbiphenylene (44.8 mg, 0.196 mmol), and toluene (2 mL). At room

temperature the reaction mixture was dark brown in colour, upon heating a black solid crashed out. The crude product was purified by silica column (0-30% EtOAc in Hexane). Starting material (41 mg, 0.18 mmol, 92%) was recovered.

Bis(neopentylglycolato)diboron, 142

The reaction was conducted according to the general procedure using $Pd(dba)_2$ (11.6 mg, 0.0202 mmol), 1,3-di-1-(adamantyl)imidazolium tetrafluoroborate (17.1 mg, 0.0403 mmol), KO*t*Bu (5.2 mg, 0.044 mmol), bis(neopentylglycolato)diboron (92.0 mg, 0.407 mmol), 1-phenylbiphenylene (45.8 mg, 0.201 mmol), and toluene (2 mL). At room temperature the reaction mixture was wine-red in colour, upon heating the reaction mixture turned dark brown. The crude product was purified by silica column (0-5% EtOAc in Hexane). Starting material (33 mg, 0.14 mmol, 72%) was recovered.

3.9.5. Stoichiometric Reactions for Investigation of the Mechanism

Stoichiometric Reactions of Biphenylene and B_2pin_2 with $Pd(IAd)_2$

Stoichiometric Reaction of Biphenylene and $Pd(IAd)_2$

A stock solution of 1,3,5-trimethoxybenzene (15.5 mg, 92.2 μmol) in d8-toluene (0.5 mL) was prepared.

A stock solution of biphenylene (15.0 mg, 98.7 μmol) in d8-toluene (0.6 mL) was prepared.

A J Young tube was charged with $Pd(IAd)_2$ (4.7 mg, 6.0 μmol), d8-toluene (0.7 mL), biphenylene stock solution (37 μL), and 1,3,5-trimethoxybenzene stock solution (15 μL) to give a pale-yellow reaction mixture. The reaction mixture was heated at the temperatures listed in Table 3.6 and the NMR spectrum recorded at the time-points listed.

Stoichiometric Reaction of B_2pin_2 and $Pd(IAd)_2$

A stock solution of 1,3,5-trimethoxybenzene (14.8 mg, 88.0 μmol) in d8-toluene (0.5 mL) was prepared.

A stock solution of B_2pin_2 (15.0 mg, 59.2 μmol) in d8-toluene (0.3 mL) was prepared.

A J Young tube was charged with $Pd(IAd)_2$ (4.7 mg, 6.0 μmol), d8-toluene (0.7 mL), B_2pin_2 stock solution (31 μL), and 1,3,5-trimethoxybenzene stock solution (15 μL) to give a pale-yellow reaction mixture. The reaction mixture was heated at the temperatures listed in Table 3.9 and the NMR spectrum recorded at the time-points listed.

$Pd(IAd)_2$ Heating Test

A stock solution of 1,3,5-trimethoxybenzene (15.1 mg, 89.8 μmol) in d8-toluene (0.5 mL) was prepared.

A J Young tube was charged with $Pd(IAd)_2$ (4.9 mg, 6.3 μmol), d8-toluene (0.7 mL), and 1,3,5-trimethoxybenzene stock solution (15 μL) to give a pale-yellow solution. The solution was heated at the temperatures listed in Table 3.10 and the NMR spectrum recorded at the time-points listed in Table 3.10.

Two Step Stoichiometric Reactions of Biphenylene and B_2pin_2 with $Pd(IAd)_2$

General Procedure for the Reaction of $Pd(IAd)_2$ with Biphenylene, followed by B_2pin_2

A stock solution of 1,3,5-trimethoxybenzene (15.0 mg, 89.1 μmol) in d8-toluene (0.5 mL) was prepared.

A stock solution of biphenylene (15.0 mg, 98.7 μmol) in d8-toluene (0.5 mL) was prepared.

A stock solution of B_2pin_2 (15.0 mg, 59.1 μmol) in d8-toluene (0.3 mL) was prepared.

A J Young tube was charged with $Pd(IAd)_2$ (4.7 mg, 6.0 μmol), d8-toluene (0.7 mL), 1,3,5-trimethoxybenzene stock solution (15 μL), and biphenylene stock solution (31 μL). The reaction mixture was heated at 110 °C for the stated time. To the reaction mixture was added B_2pin_2 stock solution (31 μL). The reaction mixture was heated to the stated temperature for the stated time.

Table 3.7, Run 1

The reaction was conducted according to the general procedure using 1,3,5-trimethoxybenzene (15.0 mg, 89.2 μmol), biphenylene (15.0 mg, 98.7 μmol), B_2pin_2 (15.0 mg, 59.3 μmol), and $Pd(IAd)_2$ (4.8 mg, 6.2 μmol). The starting reaction mixture

was pale-yellow in colour. The reaction mixture was heated at 110 °C for 1 h 30 min. The reaction mixture remained pale-yellow in colour after heating and after the addition of B_2pin_2. Following the addition of B_2pin_2, the reaction mixture was heated at the temperatures listed in Table 3.7, Run 1 and the NMR spectrum recorded at the time-points listed.

Table 3.7, Run 2

The reaction was conducted according to the general procedure using 1,3,5-trimethoxybenzene (14.9 mg, 88.6 μmol), biphenylene (15.1 mg, 99.3 μmol), B_2pin_2 (15.0 mg, 59.1 μmol), and $Pd(IAd)_2$ (4.6 mg, 5.9 μmol). The starting reaction mixture was pale-yellow in colour. The reaction mixture was heated at 110 °C for 1h. The reaction mixture remained pale-yellow in colour after heating and after the addition of B_2pin_2. Following the addition of B_2pin_2, the reaction mixture was heated at the temperatures listed in Table 3.7, Run 2 and the NMR spectrum recorded at the time-points listed.

Table 3.7, Run 3

The reaction was conducted according to the general procedure using 1,3,5-trimethoxybenzene (14.9 mg, 88.6 μmol), biphenylene (15.2 mg, 100.0 μmol), B_2pin_2 (15.1 mg, 59.5 μmol), and $Pd(IAd)_2$ (4.6 mg, 5.9 μmol). The starting reaction mixture was pale-yellow in colour. The reaction mixture was heated at 110 °C for 1 h 15 min. The reaction mixture remained pale-yellow in colour after heating and after the addition of B_2pin_2. Following the addition of B_2pin_2, the reaction mixture was heated at the temperatures listed in Table 3.7, Run 3 and the NMR spectrum recorded at the time-points listed.

Table 3.8

The reaction was conducted according to the general procedure using 1,3,5-trimethoxybenzene (15.2 mg, 90.4 μmol), biphenylene (15.1 mg, 99.3 μmol), B_2pin_2 (30.7 mg, 120.9 μmol), and $Pd(IAd)_2$ (4.7 mg, 6 μmol). The starting reaction mixture was pale-yellow in colour. The reaction mixture was heated at 110 °C for 1 h 30 min. The reaction mixture remained pale-yellow in colour after heating and after the addition of B_2pin_2. Following the addition of B_2pin_2, the reaction mixture was heated

at the temperatures listed in Table 3.8 and the NMR spectrum recorded at the time-points listed.

General Procedure for the Reaction of $Pd(IAd)_2$ with B_2pin_2, followed by Biphenylene

A stock solution of 1,3,5-trimethoxybenzene (15.0 mg, 89.1 μmol) in d8-toluene (0.5 mL) was prepared.

A stock solution of biphenylene (15.0 mg, 98.7 μmol) in d8-toluene (0.5 mL) was prepared.

A stock solution of B_2pin_2 (15.0 mg, 59.1 μmol) in d8-toluene (0.3 mL) was prepared.

A J Young tube was charged with $Pd(IAd)_2$ (4.7 mg, 6.0 μmol), d8-toluene (0.7 mL), 1,3,5-trimethoxybenzene stock solution (15 μL), and B_2pin_2 stock solution (31 μL). The reaction mixture was heated at 110 °C for the stated time. To the reaction mixture was added biphenylene stock solution (31 μL). The reaction mixture was heated to the stated temperature for the stated time.

Table 3.11

In all three runs there were no clean signals for the desired diborylated product **35** in the proton NMR spectra and so the actual yields of **35** are lower than that estimated from the NMR spectra.

Table 3.11, Run 1

The reaction was conducted according to the general procedure using 1,3,5-trimethoxybenzene (15.1 mg, 89.8 μmol), biphenylene (15.0 mg, 98.7 μmol), B_2pin_2 (15.1 mg, 59.5 μmol), and $Pd(IAd)_2$ (4.6 mg, 5.9 μmol). The starting reaction mixture was pale-yellow in colour. The reaction mixture was heated at 110 °C for 16 h. Upon heating, a small amount of black precipitate crashed out and the reaction mixture remained pale-yellow in colour. Following the addition of the biphenylene stock solution, the reaction mixture remained pale-yellow in colour. The reaction mixture was heated at the temperatures listed in Table 3.11, Run 1 and the NMR spectrum recorded at the time-points listed.

Table 3.11, Run 2

The reaction was conducted according to the general procedure using 1,3,5-trimethoxybenzene (14.8 mg, 88.0 μmol), biphenylene (14.9 mg, 98.0 μmol), B_2pin_2 (15.0 mg, 59.1 μmol), and $Pd(IAd)_2$ (4.7 mg, 6.0 μmol). The starting reaction mixture was pale-yellow in colour. The reaction mixture was heated at 110 °C for 16 h. Upon heating, a small amount of black precipitate crashed out and the reaction mixture remained pale-yellow in colour. Following the addition of biphenylene stock solution, the reaction mixture remained pale-yellow in colour. The reaction mixture was heated at the temperatures listed in Table 3.11, Run 2 and the NMR spectrum recorded at the time-points listed.

Table 3.11, Run 3

The reaction was conducted according to the general procedure using 1,3,5-trimethoxybenzene (15.0 mg, 89.2 μmol), biphenylene (15.0 mg, 98.7 μmol), B_2pin_2 (15.0 mg, 59.1 μmol), and $Pd(IAd)_2$ (4.6 mg, 5.9 μmol). The starting reaction mixture was pale-yellow in colour. The reaction mixture was heated at 110 °C for 16 h. Upon heating, a small amount of black precipitate crashed out and the reaction mixture remained pale-yellow in colour. Following the addition of biphenylene stock solution, the reaction mixture remained pale-yellow in colour. The reaction mixture was heated at the temperatures listed in Table 3.11, Run 3 and the NMR spectrum recorded at the time-points listed.

3.9.6. Post-Functionalisation Reactions of the Ring Opened Products

3.9.6.1. Allylation of the Ring Opened Products

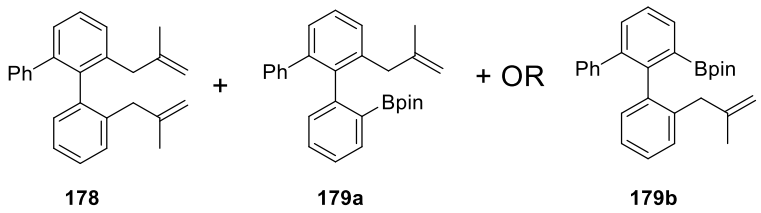
General Procedure for the Allylation of Ring Opened Product 135

A Schlenk bomb was charged with $Pd(dba)_2$ (stated amount), **135** (0.3 mmol), allyl chloride (stated amount) and MeOH (1.4 mL). The reaction mixture was stirred (600 rpm) at room temperature for 10 min. To the reaction mixture was added KF (1.2 mmol). The Schlenk bomb was sealed and the reaction mixture stirred (600 rpm) at the stated temperature for the stated time. The reaction mixture was cooled to room temperature. The reaction mixture was filtered through silica gel and washed through with EtOAc until no compound was visible by UV on a TLC plate. The solvent was

removed under reduced pressure and the crude product was purified by flash column chromatography.

Attempted Diallylation of 135 with 3-Chloro-2-methyl-propene, Conditions A

The reaction was conducted according to the general procedure using $Pd(dba)_2$ (6.9 mg, 12 μmol), **135** (144.6 mg, 0.2999 mmol), 3-chloro-2-methyl-propene (120 μL, 1.23 mmol), MeOH (1.4 mL), and KF (69.8 mg, 1.20 mmol). The reaction mixture was stirred (600 rpm) at room temperature for 24 h. The reaction mixture was pale-yellow in colour. The reaction mixture was stirred (600 rpm) at 50 °C for 24 h. Upon heating, a yellow solid crashed out of the reaction mixture. To the Schlenk bomb was added $Pd(dba)_2$ (13.8 mg, 24.0 μmol) and the reaction mixture was stirred (600 rpm) at 50 °C for 20 h. The crude product was purified by flash column chromatography (silica gel, 0-2% EtOAc in hexane).



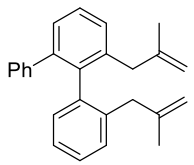
178 **179a** **179b**

A 1:1 mixture of diallylated product **178** and monoallylated product **179** was isolated as a colourless oil (76 mg, 0.10 mmol **178**, 0.10 mmol **179**, 34% **178**, 34% **179**). **HRMS** (CI^+) m/z: calculated for $(C_{28}H_{31}BO_2+H)^+$ 411.2495, found 411.2505, m/z: calculated for $(C_{26}H_{26}+H)^+$ 339.2113, found 339.2061, m/z calculated for $(C_{22}H_{20}+H)^+$ 285.1643, found 285.1635. The yield was determined from the ratio of CH_2 and CH_3 signals from the allyl group to CH_3 signals on the Bpin group in the NMR spectrum. See the NMR spectrum in the appendix.

Attempted Diallylation of 135 with 3-Chloro-2-methyl-propene, Conditions B

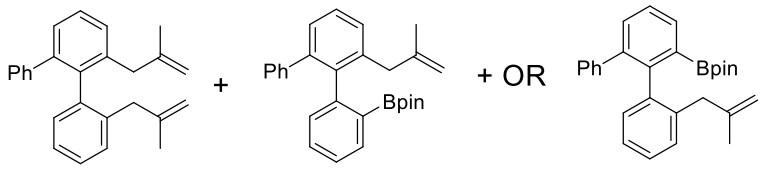
The reaction was conducted according to the general procedure using $Pd(dba)_2$ (26.0 mg, 45.2 μmol), **135** (143.0 mg, 0.2965 mmol), 3-chloro-2-methyl-propene (120 μmol, 1.23 mmol), MeOH (1.4 mL), and KF (69.0 mg, 1.19 mmol). The reaction mixture was heated to 70 °C for 18 h. The reaction mixture was pale-yellow in colour. To the reaction mixture was added $Pd(dba)_2$ (25.5 mg, 44.3 μmol), 3-chloro-2-methyl-propene (60 μL, 0.61 mmol), and KF (35.0 mg, 0.602 mmol). The reaction mixture was stirred (600 rpm) at 70 °C for a further 18 h. The reaction mixture remained pale-

yellow in colour. The crude product was purified by flash column chromatography (silica gel, 0.5 – 1% EtOAc in hexane).



178

Compound **178** was isolated as a colourless oil (30 mg, 0.086 mmol, 29%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.5 Hz, 1H, CH), 7.30 – 7.26 (m, 1H, CH), 7.19 – 7.09 (m, 8H, CH), 7.03 – 7.01 (m, 1H, CH), 4.80 (s, 1H, CH_2), 4.68 (s, 1H, CH_2), 4.54 (s, 1H, CH_2), 4.40 (s, 1H, CH_2), 3.07 (d, *J* = 15.6 Hz, 1H, CH_2), 3.51 (d, *J* = 15.6 Hz, 1H, CH_2), 2.86 (d, *J* = 15.5 Hz, 1H, CH_2), 2.70 (d, *J* = 15.5 Hz, 1H, CH_2), 1.60 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 145.0 (C), 143.8 (C), 141.9 (C), 141.7 (C), 139.5 (C), 139.3 (C), 138.4 (C), 137.4 (C), 131.6 (CH), 129.9 (2CH), 128.6 (2CH), 128.1 (CH), 127.4 (3CH), 127.2 (CH), 126.3 (CH), 125.2 (CH), 113.1 (CH_2), 112.7 (CH_2), 42.0 (CH_2), 41.4 (CH_2), 22.7 (CH_3), 22.0 (CH_3).



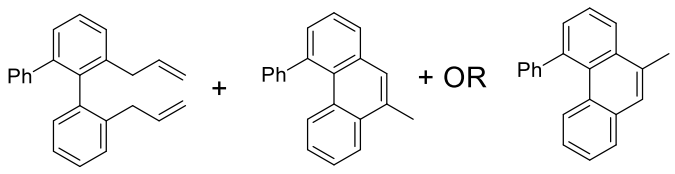
178 **179a** **179b**

A 2:1 mixture of diallylated product **178** and monoallylated product **179** was isolated as a colourless oil (42 mg, 0.074 mmol **178**, 0.036 mmol **179**, 25% **178**, 12% **179**). The yields were determined from the ratio of CH_2 and CH_3 signals from the allyl group to CH_3 signals on the Bpin group in the NMR spectrum. See the NMR spectrum in the appendix. The sample does contain some impurities.

Attempted Diallylation of 135 with Allyl Chloride

The reaction was conducted according to the general procedure using $Pd(dba)_2$ (25.9 mg, 0.0450 mmol), **135** (144.5 mg, 0.2996 mmol), allyl chloride (100 μL, 1.23 mmol), MeOH (1.4 mL), and KF (69.8 mg, 1.20 mmol). The reaction mixture was a brown suspension. The reaction mixture was heated to 70 °C for 44 h. There was no colour change upon heating. To the reaction mixture was added allyl chloride (100 μL, 1.23 mmol), KF (70.0 mg, 1.21 mmol), and $Pd(dba)_2$ (25.9 mg, 0.0450 mmol). The reaction

mixture was heated to 70 °C for a further 24 h. The crude product was purified by flash column chromatography (silica gel, 1-4% EtOAc in hexane).

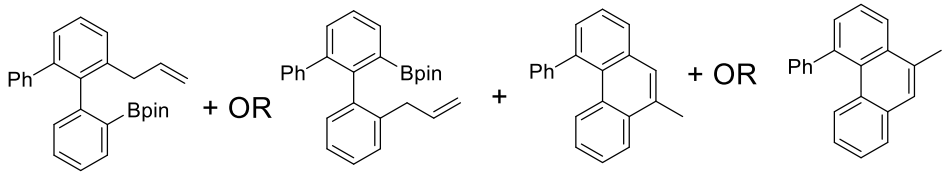


185 **186a** **186b**

A mixture of **185** and **186** was isolated as a pale-yellow oil (60 mg). **185 HRMS** (CI^+) m/z: calculated for $(C_{24}H_{22}+H)^+$ 311.1800, found 311.1779. **186 HRMS** (CI^+) m/z: calculated for $(C_{21}H_{16}+H)^+$ 269.1330, found 269.1322. It was not possible to estimate the yield from the NMR spectrum because there were not clean signals for both products. The uncorrected ratio from the GC-MS spectrum was 2.5:1 in favour of the cyclised product and accounted for approximately 70% of the mass balance. Please see the GC-MS spectrum in the appendix. A pale-yellow oil (4 mg) was also isolated but could not be identified and a pale-yellow oil (6 mg) was isolated and contained doubly reduced dba and two other components that could not be identified.

<u>Attempted Monoallylation of 135 Followed by Cyclisation</u>

The reaction was conducted according to the general procedure using $Pd(dba)_2$ (51.5 mg, 89.6 μmol), **135** (137.7 mg, 0.2855 mmol), allyl chloride (29.3 μL, 0.360 mmol), MeOH (1.4 mL), and KF (139.6 mg, 2.403 mmol). The reaction mixture was a brown suspension. The reaction mixture was heated to 70 °C for 68 h. The crude product was purified by flash column chromatography (silica gel, 0-10% EtOAc in hexane).



187a **187b** **186a** **186b**

Compound **186** was isolated as a colourless oil (2.0 mg, 7.4 μmol, 2%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.3 Hz, 1H, CH), 7.80 (d, *J* = 8.5 Hz, 2H, CH), 7.62 (br. s, 1H, CH), 7.55 (t, *J* = 7.5 Hz, 1H, CH), 7.49 – 7.39 (m, 7H, CH), 7.12 – 7.09 (m, 1H, CH), 2.74 (s, 3H, CH_3). A mixture of **186** and **187** was isolated as a yellow oil (70 mg, 0.026 mmol **186**, 0.16 mmol **187**, 9% **186**, 56% **187**). **187 HRMS** (CI^+) m/z: calculated

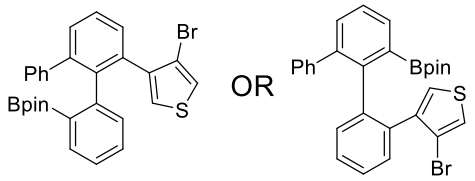
for $(C_{27}H_{29}BO_2+H)^+$ 397.2339, found 397.2351. **186 HRMS** (CI^+) m/z: calculated for $(C_{21}H_{16}+H)^+$ 269.1330, found 269.1316. The ratio of **186** and **187** was determined from the integration of the respective CH_3 signals in the NMR spectrum. Please see the NMR spectrum in the appendix. A pale-yellow oil (14 mg) was also isolated and could not be identified.

3.9.6.2. Suzuki–Miyaura Cross-Coupling of the Ring Opened Products

Reaction of 135 with 3,4-Dibromothiophene

3,4-Dibromothiophene and water were degassed by bubbling argon through them for 5 min.

A Schlenk bomb was charged with **135** (144.5 mg, 0.2996 mmol), 3,4-dibromothiophene (39.8 μL, 0.360 mmol), $Pd(PPh_3)_4$ (34.0 mg, 29.4 μmol), K_2CO_3 (165 mg, 1.19 mmol), water (0.6 mL), and THF (2.4 mL) to give an orange suspension. The Schlenk bomb was sealed and the reaction mixture stirred (600 rpm) at 80 °C for 48 h. Upon heating the reaction mixture turned pale yellow in colour. To the reaction mixture was added 3,4-dibromothiophene (33.0 μL, 0.298 mmol) and $Pd(PPh_3)_4$ (34.5 mg, 29.9 μmol). The reaction mixture was stirred (600 rpm) in a sealed Schlenk bomb at 80 °C for a further 24 h. The reaction mixture was diluted with water (90 mL), aqueous HCl (2M, 3mL), and EtOAc (90 mL). The two phases were separated. The aqueous phase was extracted with EtOAc (2 x 90 mL). The combined organics were dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 1-2% EtOAc in hexane).



196a 196b

Compound **196** was isolated as a colourless oil (99 mg, 0.19 mmol, 64%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.45 (t, *J* = 7.6 Hz, 2H, CH), 7.40-7.38 (m, 1H, CH), 7.33-7.32

(m, 1H, CH), 7.15 (td, *J* = 7.5 Hz, 1.3 Hz, 1H, CH), 7.12 (d, *J* = 3.5 Hz, 1H, CH), 7.10-7.06 (m, 6H, CH), 7.03 (t, *J* = 7.4 Hz, 1H, CH), 6.85 (d, *J* = 3.5 Hz, 1H, CH), 1.13 (s, 6H, CH_3), 1.12 (s, 6H, CH_3), **$^{13}C\{^1H\}$ NMR** (126 MHz, $CDCl_3$) δ 145.9 (C), 142.2 (C), 141.8 (C), 141.7 (2C), 135.0 (C), 134.4 (CH), 130.8 (CH), 130.2 (2CH), 129.6 (CH), 129.4 (CH), 129.3 (CH), 127.3 (2CH), 126.4 (CH), 126.2 (CH), 125.7 (CH), 124.9 (CH), 121.9 (CH), 112.8 (C), 83.2 (2C), 25.0 ($2CH_3$), 24.9 ($2CH_3$). One quaternary carbon signal is not observed. **HRMS** (ESI^+) m/z: calculated for $(C_{28}H_{26}BBrO_2S+H)^+$ 517.1008, found 517.1002.

Attempted Oxidation of Suzuki–Miyaura Cross-Coupled Product 196

Under air, a vial was charged with **196** (82.0 mg, 0.156 mmol) and acetone (0.5 mL). To the stirred solution was added a solution of oxone (48.7 mg, 0.157 mmol) in water (0.5 mL) dropwise at room temperature to give a white suspension. The reaction mixture was stirred (500 rpm) for 6 h at room temperature. The reaction mixture was stirred (500 rpm) at 45 °C for 60 h. The reaction mixture was pale yellow with a white precipitate. The reaction mixture was quenched with $NaHSO_3$ (97 mg, 0.94 mmol) in water (0.2 mL). To the reaction mixture was added water (3 mL) and ether (4 mL). The two phases were separated. The aqueous phase was extracted with ether (2 x 4 mL). The combined organics were washed with brine (4 mL), water (4 mL), dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to give starting material as a yellow oil (66 mg, 0.127 mmol, 65%).

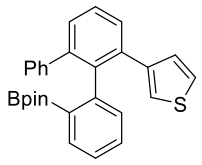
General Procedure for the Reaction of 135 with 3-Bromothiophene

3-Bromothiophene and water were degassed by bubbling argon through them for 5 min.

A Schlenk bomb was charged with **135** (0.3 mmol), aryl halide (stated amount), $Pd(PPh_3)_4$ (stated amount), K_2CO_3 (1.2 mmol), water (0.6 mL), and THF (2.4 mL). The Schlenk bomb was sealed and the reaction mixture stirred (600 rpm) at the stated temperature for the stated time. The reaction mixture was diluted with water (90 mL), aqueous HCl (2M, 3mL), and EtOAc (90 mL). The two phases were separated. The aqueous phase was extracted with EtOAc (2 x 90 mL). The combined organics were dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography.

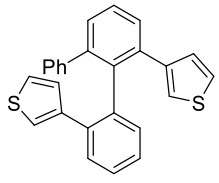
Reaction of 135 with 3-Bromothiophene at 80 °C

The reaction was conducted according to the general procedure using **135** (145.0 mg, 0.3007 mmol), 3-bromothiophene (67.5 μL, 0.720 mmol), $Pd(PPh_3)_4$ (34.5 mg, 29.9 μmol), K_2CO_3 (165 mg, 1.19 mmol), water (0.6 mL), and THF (2.4 mL). The reaction mixture was heated to 80 °C for 24 h. Upon heating the reaction mixture turned dark green in colour. The crude product was purified by flash column chromatography (silica gel, 2% EtOAc in hexane).



198a

Compound **198a** was isolated as a white solid (51 mg, 0.12 mmol, 39%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.2 Hz, 1H, CH), 7.47 (d, *J* = 6.8 Hz, 1H, CH), 7.42 (t, *J* = 7.6 Hz, 1H, CH), 7.35 (d, *J* = 7.3 Hz, 1H, CH), 7.19-7.09 (m, 7H, CH), 7.02-6.99 (m, 2H, CH), 6.80 (d, *J* = 1.8 Hz, 1H, CH), 6.71 (d, *J* = 4.8 Hz, 1H, CH), 1.11 (s, 12H, CH_3), **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 146.4 (C), 142.5 (C), 142.3 (C), 142.0 (C), 140.7 (C), 136.5 (C), 134.8 (CH), 131.5 (CH), 130.1 (2CH), 129.8 (CH), 129.4 (CH), 128.8 (CH), 128.3 (CH), 127.3 (2CH), 126.9 (CH), 126.1 (CH), 125.8 (CH), 123.7 (CH), 123.2 (CH), 83.1 (2C), 24.9 ($2CH_3$), 24.8 ($2CH_3$). One quaternary carbon signal is not observed. **HRMS** (CI^+) m/z: calculated for $(C_{28}H_{27}BO_2S+H)^+$ 439.1903, found 439.1914. Crystals for XRD analysis were grown by slow evaporation of a concentrated solution of hexane at room temperature.



199

Compound **199** was isolated as a colourless oil (8.0 mg, 20 μmol, ~6%). Compound **199** was contaminated with an unknown impurity that could not be removed. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.45-7.42 (m, 2H, CH), 7.31 (dd, *J* = 5.9, 2.8 Hz, 1H, CH), 7.22 (d, *J* = 7.5 Hz, 1H, CH), 7.17 (t, *J* = 7.5 Hz, 1H, CH), 7.10 – 6.99 (m, 7H, CH), 6.84 (d, *J* = 6.8 Hz, 2H, CH), 6.68-6.67 (m, 1H, CH), 6.58 (d, *J* = 5.0 Hz, 1H, CH), 6.53-6.51 (m, 2H, CH), **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 142.3 (C), 142.1 (C), 141.7

(C), 141.5 (C), 138.3 (C), 137.8 (C), 136.9 (C), 136.3 (C), 132.8 (CH), 129.7 (CH), 129.5 (2CH), 129.2 (CH), 129.0 (CH), 128.8 (CH), 128.1 (CH), 127.9 (CH), 127.4 (3CH), 126.6 (CH), 126.2 (CH), 123.9 (2CH), 122.9 (CH), 122.4 (CH), **HRMS** (CI^+) m/z: calculated for $(C_{26}H_{18}S_2+H)^+$ 395.0928, found 395.0931.

A mixture of compounds **198a** and **199** was isolated as a colourless oil (45 mg, 0.045 mmol **198a**, 0.066 mmol **199**, 15% **198a**, 22% **199**).

Reaction of 135 with 3-Bromothiophene at 100 °C

The reaction was conducted according to the general procedure using **135** (144.7 mg, 0.3001 mmol), 3-bromothiophene (112 μL, 1.20 mmol), $Pd(PPh_3)_4$ (70.0 mg, 60.6 μmol), K_2CO_3 (167 mg, 1.21 mmol), water (0.6 mL), and THF (2.4 mL). The reaction mixture was stirred (600 rpm) at 100 °C for 48 h. Upon heating the reaction mixture turned black in colour. Additional 3-bromothiophene (112 μL, 1.21 mmol) and $Pd(PPh_3)_4$ (68.0 mg, 58.8 μmol) were added to the reaction mixture and the reaction mixture was heated to 100 °C for a further 24 h. The crude product was purified by flash column chromatography (silica gel, 1-1.5% EtOAc in hexane). Compound **198a** was isolated as a white solid (50 mg, 0.11 mmol, 38%), which was contaminated with a small impurity. Compound **199** was isolated as a yellow solid (14 mg, 0.033 mmol, 11%), which was contaminated with a small impurity. A mixture of compounds **198a** and **199** was isolated as a pale-yellow solid (58 mg, 0.063 mmol **198a**, 0.072 mmol **199**, 21% **198a**, 24% **199**).

3.9.7. XRD Table for Complexes 135a, 159a, and 198a

Table 3.12 Crystallographic data and structure refinement for complexes **135a**, **159a**, and **198a**

Compound	**135a**	**159a**	**198a**
Chemical formula	$2(C_{30}H_{36}B_2O_4)$	$C_{31}H_{38}B_2O_5$	$C_{28}H_{27}BO_2S$
Molecular Weight	482.23 g/mol	512.23	438.36
Crystal system	Monoclinic	Monoclinic	Triclinic
Space group	P $2_1/c$	$P2_1/n$	P-1
a (Å)	16.7584(3)	9.89480(10)	10.07110(10)

b c	1.10627(14) 30.4034(4)	9.67430(10) 31.4455(4)	15.4308(4) 15.5265(4)
α (°) β γ	90 104.5462(14) 90	90 98.7050(10) 90	80.181(2) 89.585(2) 88.706(2)
Cell Volume ($Å^3$)	5477.39	2975.45(6)	2376.93(9)
Z	4	4	4
T (K)	99.8(6)	290.9(10)	100.01(10)
μ (mm^{-1})	0.587	0.593	1.372
ρ Calc (g/cm^3)	1.169	1.143	1.225
Crystal size (mm)	0.163 × 0.129 × 0.046	0.171 × 0.11 × 0.085	0.181 × 0.137 × 0.07
F(000)	2064.0	1096.0	928.0
Radiation	CuKα (λ = 1.54184)	CuKα (λ = 1.54184)	Cu Kα (λ = 1.54184)
2Θ range for data collection (°)	7.024 to 153.018	9.058 to 152.738	7.468 to 160.024
Index ranges	-21 ≤ h ≤ 20, -13 ≤ k ≤ 13, -38 ≤ l ≤ 38	-12 ≤ h ≤ 12, -12 ≤ k ≤ 8, -39 ≤ l ≤ 38	-10 ≤ h ≤ 12, -19 ≤ k ≤ 19, -18 ≤ l ≤ 19
Reflections collected	43554	25908	21645
Independent Reflections	11301 [R_{int} = 0.0380, R_{sigma} = 0.0316]	6134 [R_{int} = 0.0386, R_{sigma} = 0.0233]	9275 [R_{int} = 0.0281, R_{sigma} = 0.0323]
Data/restraints/parameters	11301/0/665	6134/41/411	9275/30/585
Goodness-of-fit on F2: 1.189	1.041	1.037	1.058
Final R indexes [I>=2σ (I)]	R_1 = 0.0454, wR_2 = 0.1126	R_1 = 0.0481, wR_2 = 0.1359	R_1 = 0.0892, wR_2 = 0.2524
Final R indexes [all data]	R_1 = 0.0553, wR_2 = 0.1180	R_1 = 0.0543, wR_2 = 0.1432	R_1 = 0.1032, wR_2 = 0.2692

Largest diff. peak/hole ($eÅ^{-3}$)	0.28/-0.28	0.24/-0.22	1.30/-1.09

R1= Σ ||Fo|-|Fc| / Σ |Fo|; wR2 = [Σ (w(Fo2 – Fc2)2 / Σ w(Fo2)2]1/2

3.10. References

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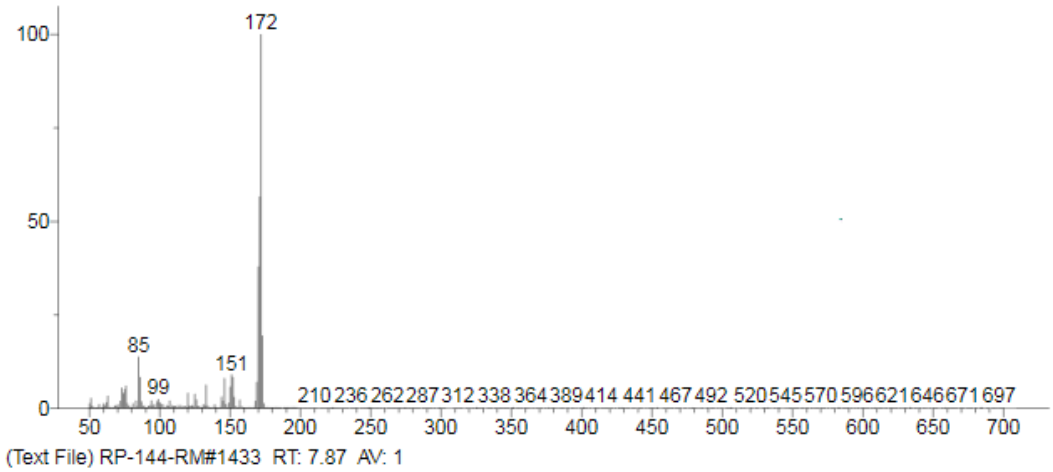
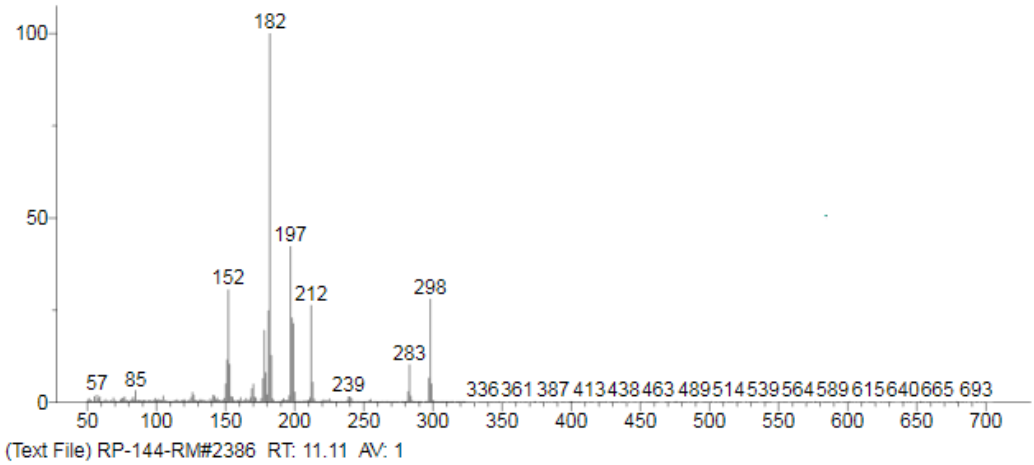
3.11. Appendix

Side-Products Observed by GCMS When the Ring Opening Diborylation of 1-Fluorobiphenylene was Screened.

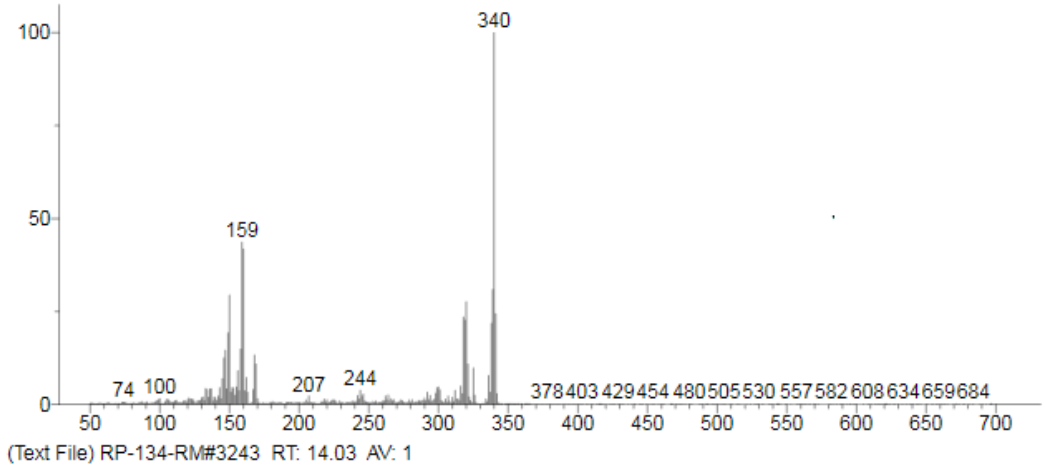
Mass Spectrum of Reduced Product 125



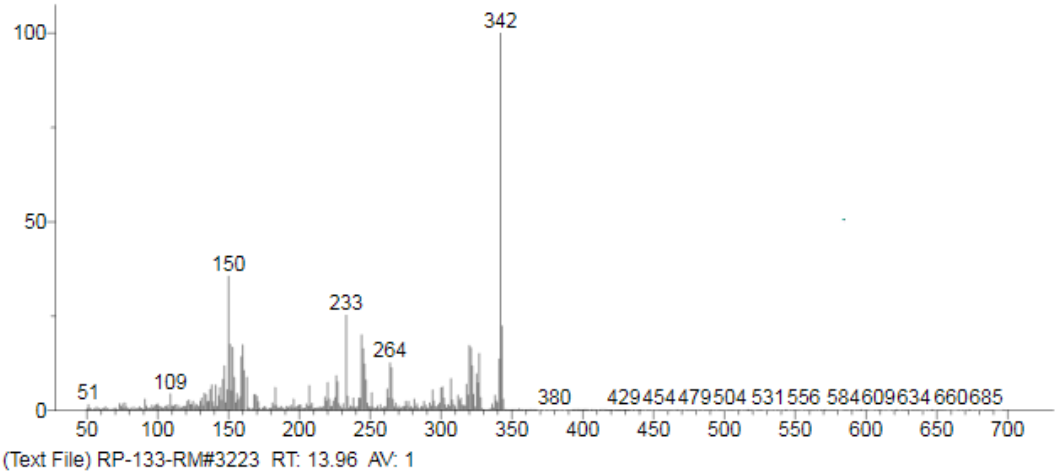
Mass Spectrum of Monoborylated Product 124



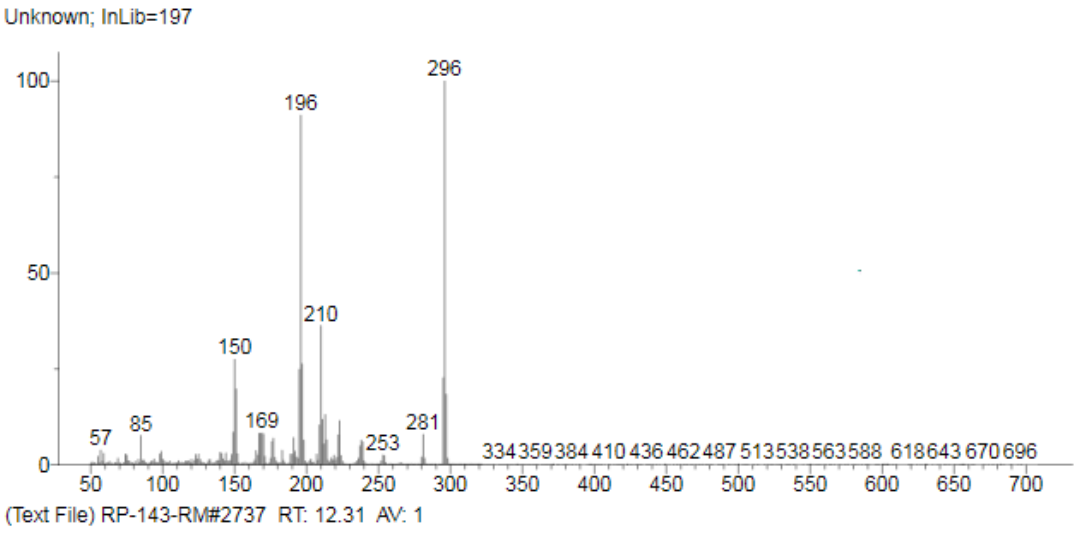
Mass Spectrum of Dimerised Product 126



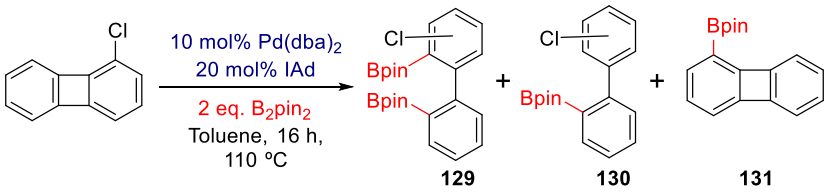
Mass Spectrum of Difluorotetraphenyl Product 128

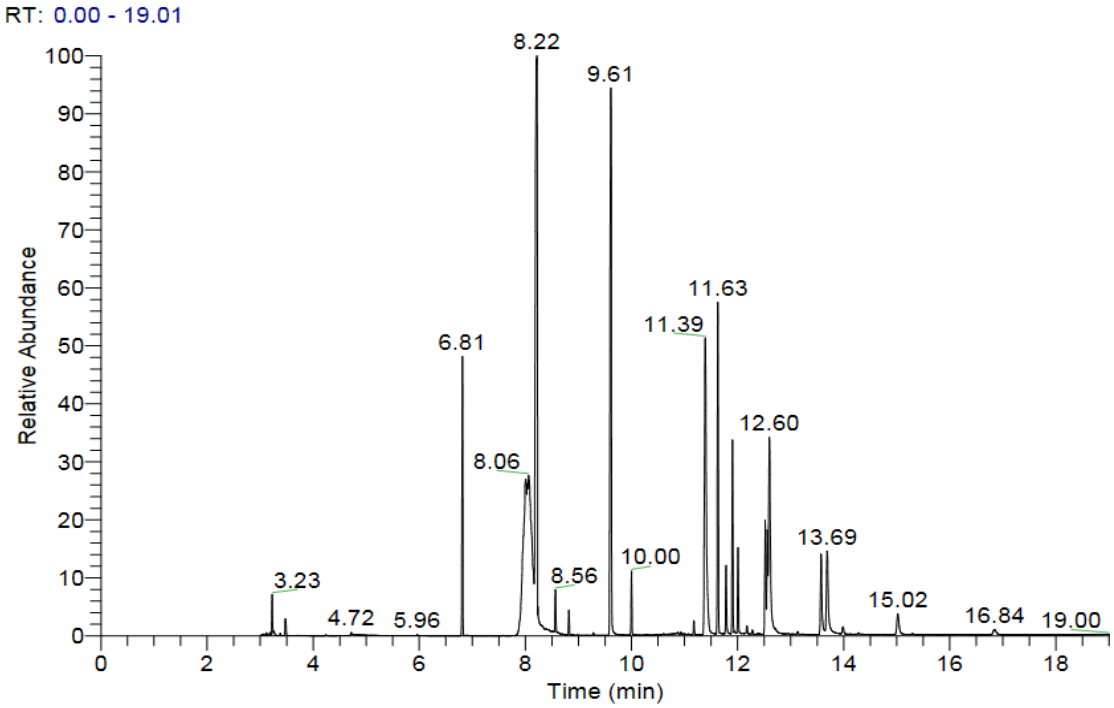


Mass Spectrum of CH Activated Product 127



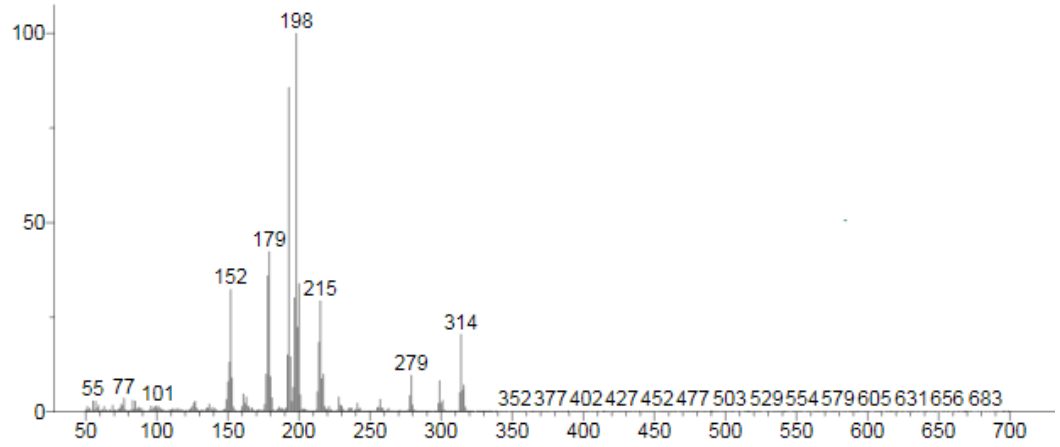
Attempted Ring Opening Diborylation of 1-Chlorobiphenylene





Time (min)	Compound	Time (min)	Compound
3.23	Pinacol alcohol	11.63	**130**
6.81	n-Dodecane (standard)	11.78	1,5-diphenylpentan-3-one (doubly reduced dba)
8.06	Grease	12.01	**130**
8.22	B_2pin_2	12.56	**131**
8.56	Biphenylene	12.60	Grease
9.61	1-Chlorobiphenylene	13.57	dba
10.00	Dichlorobiphenyl (impurity from SM)	13.69	Grease
11.39	Grease		

Mass Spectrum of 130 (GCMS)



(Text File) RP-164-RM#2536 RT: 11.62 AV: 1

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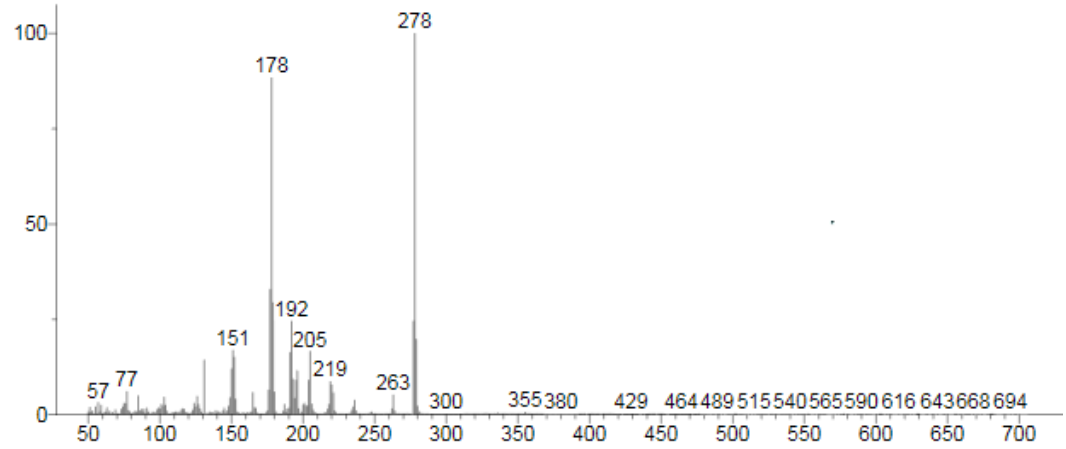
Comment: T: + c EI Full ms [50.00-700.00]
10 largest peaks:
198 999 | 193 855 | 179 423 | 178 358 | 200 337 | 152 323 | 197 300 | 215 292 | 199 222 | 314 205 |

Mass Spectrum of 131 (GCMS)



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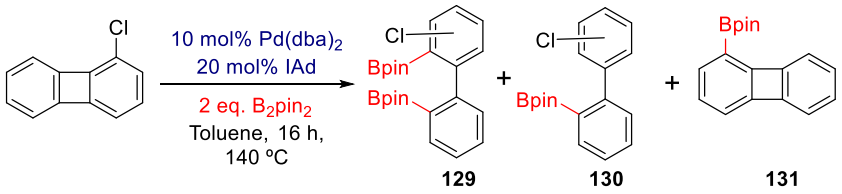
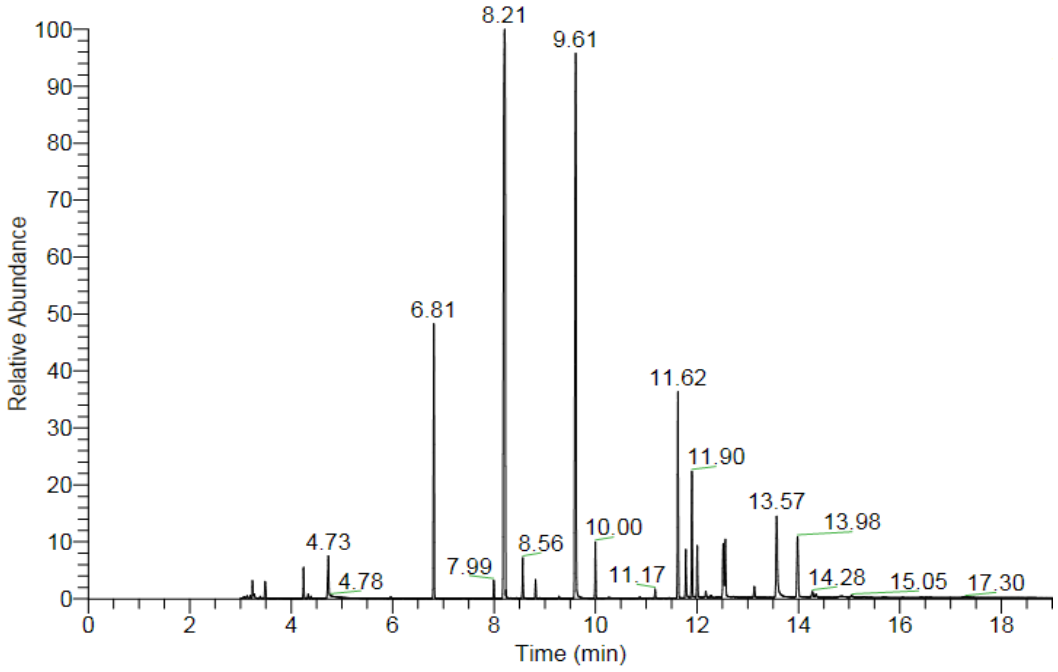
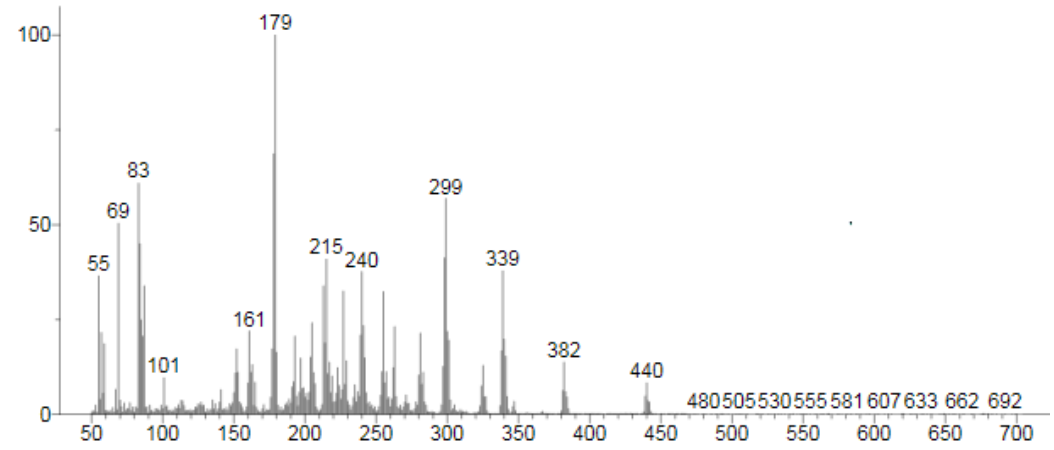




Time (min)	Compound	Time (min)	Compound
6.81	n-Dodecane (standard)	11.78	1,5-diphenylpentan-3-one (doubly reduced dba)
7.99	Biphenyl	11.90	**130**
8.21	B_2pin_2	12.00	**130**
8.56	Biphenylene	12.56	**131**
9.61	1-Chlorobiphenylene	13.57	dba
10.00	Dichlorobiphenyl (impurity from SM)	13.98	**129**
11.62	**130**		

Mass Spectra of 130 and 131 are the same as above.

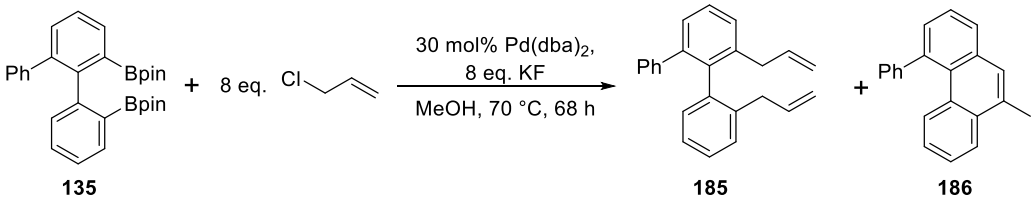
Mass Spectrum of 129 (GCMS)



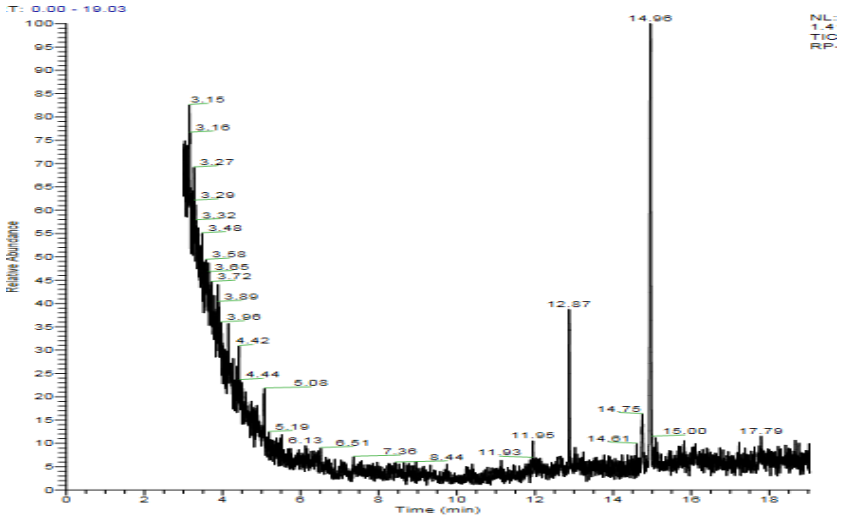
(Text File) RP-165-RM#3229 RT: 13.98 AV: 1

Name: RP-165-RM#3229 RT: 13.98 AV: 1
MW: N/A ID#: 42 DB: Text File
Comment: T: + c EI Full ms [50.00-700.00]
10 largest peaks:
179 999 | 178 685 | 83 609 | 299 568 | 69 504 | 84 448 | 298 411 | 215 409 | 339 378 | 240 376 |

Attempted Diallylation of 135

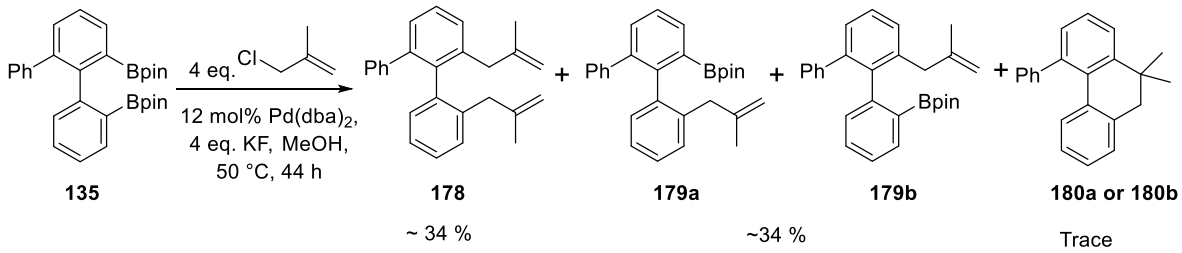


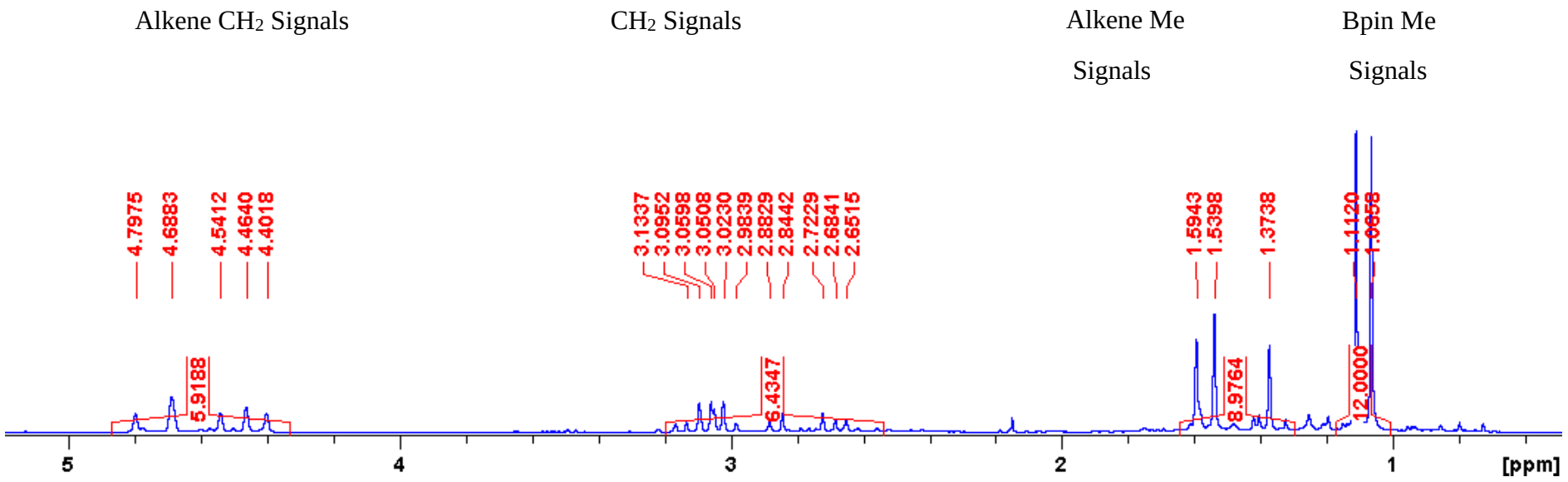
135 **185** **186**



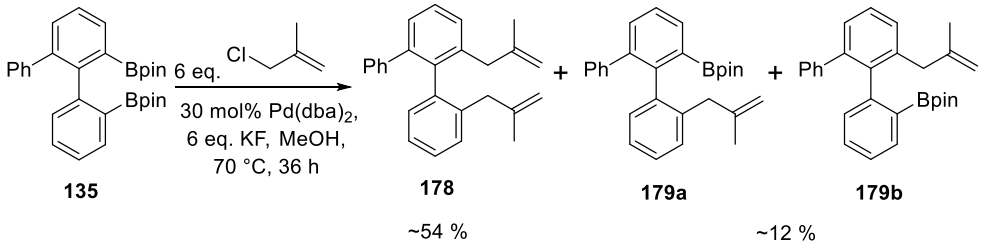
Time (min)	Compound
12.87	Diallylated **185**
14.96	Cyclised **186**

Aliphatic Region of the NMR spectrum of 178 and 179 used to estimate the yields of 178 and 179.





Aliphatic Region of the NMR spectrum of 178 and 179 used to estimate the yields of 178 and 179.

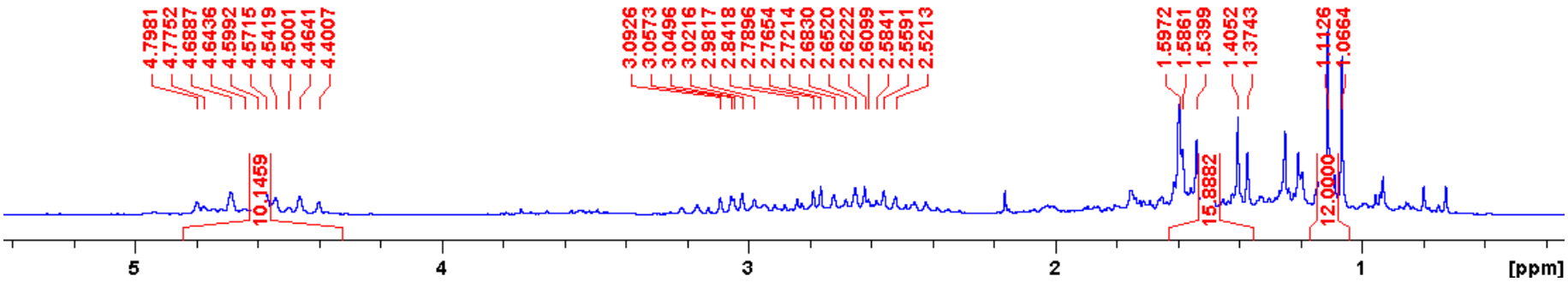


Alkene CH Signals

CH_2 Signals

Alkene Me Signals

Bpin Me Signals



CH_2 signals not used because they over-integrate substantially.

Aliphatic Region of the NMR spectrum of 186 and 187 used to estimate the yields of 186 and 187.