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Development of Earth-Abundant Metal Catalysts for Carbon-Boron and Carbon-Carbon Bond Forming Reactions

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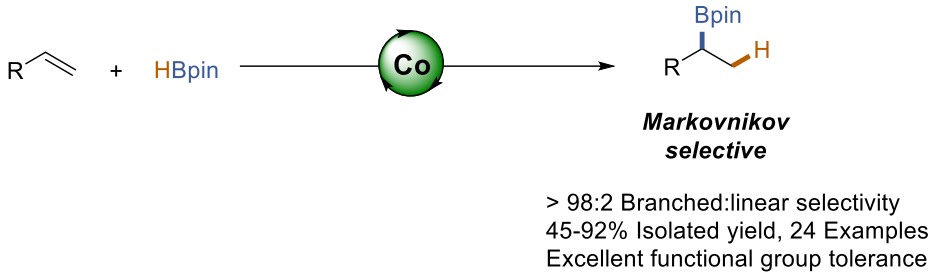
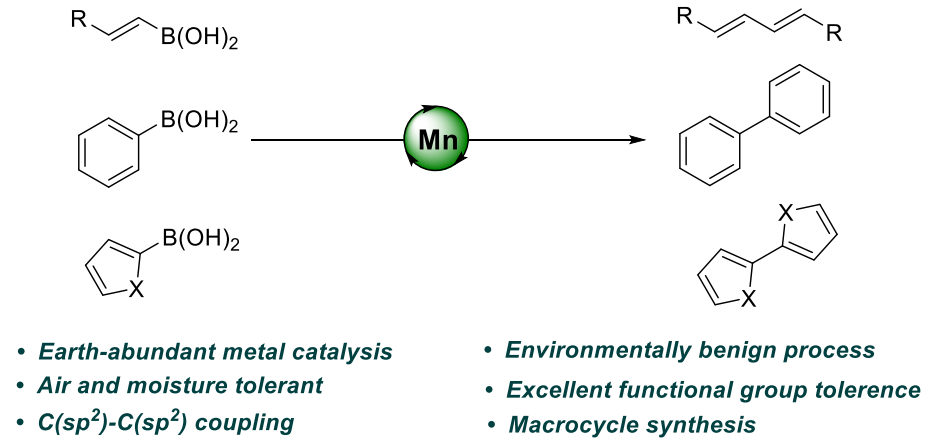
Abstract

We have developed a Markovnikov-selective cobalt-catalysed hydroboration of alkenes with pinacolborane at ambient temperature, using a bench-stable bipyridyl-oxazoline catalyst $_{t\text{Bu}}$BPOCoCl$_2$ and NaOtBu as the *in situ* activator. This strategy has been applied to a variety of electronically and sterically differentiated styrene derivatives, bearing a range of functional groups, to give the secondary boronic esters in both high yield and regioselectivity.



Scheme A1: Cobalt-catalysed Markovnikov selective hydroboration of alkenes

We have developed a manganese-catalysed homo-coupling of aryl-, alkenyl- and heterocyclic boronic acids across a range of electronically and sterically differentiated coupling partners. This mild and operationally simple coupling reaction uses commercially available and inexpensive manganese(III) acetylacetonate, ethanol as the solvent, and air as the terminal oxidant. This represents the first-stage in developing a new manganese-catalysed cross-coupling reaction for the synthesis biaryl compounds.



Scheme A2: Manganese-catalysed homo-coupling of boronic acids

Lay summary

Catalysis is a powerful method for the manufacture of products used in daily life, such as plastics, fabrics and pharmaceuticals, providing the ability to synthesis molecules in a controlled manner. With ever-growing global chemical demand and energy consumption, the development of sustainable synthetic processes that address the minimisation of environmental impact is of paramount importance. The low cost, ready availability, comparatively low toxicity and greater sustainability are all factors leading to an increase of the development of Earth-abundant metal-catalysed transformations.

This work contained herein has focussed on the development of novel cobalt and manganese catalysts for carbon-boron and carbon-carbon bond forming reactions and mechanistic investigation. These reactions have been developed with aim of simplifying the procedure and providing reaction that can be performed by chemist who are non-experts. These novel discoveries using Earth-abundant metal catalysts will offer an entry point for the development of sustainable and environmentally benign chemistry.

Declaration

I certify:

a) that the thesis has been composed by the student, and

b) either that the work is the student's own, or, if the student has been a member of a research group, that the student has made a substantial contribution to the work, such contribution being clearly indicated, and

c) that the work has not been submitted for any other degree or professional qualification except as specified, and

d) that any included publications are the student's own work, except where indicated throughout the thesis and summarised and clearly identified on the declarations page of the thesis.

Jingying Peng

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Abbreviations

Ac	Acetyl
acac	Acetylacetonate
Ar	Aryl
BIP	Bis(imino)pyridine
Bn	Benyl
BPO	Bipyridiyl-oxazoline
BOX	Bis(oxazoline)
Bu	Butyl
cat	Catacholate
COT	1,3,5,7-cyclooctatetraene
Cp	Cyclopentadienyl
Cy	Cyclohexyl
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCT	Dibenzo[*a*,*e*]cyclooctatetraene
DIPP	2,6-Di*iso*propylphenyl
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
DPPF	1,1'-Bis(diphenylphosphino)ferrocene
ee	Enantiomeric excess
equiv.	Equivalents
ESI	Electrospray ionisation
Et	Ethyl
HFA	Hexafluoroacetylacetonate
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
ICP-MS	Inductively coupled plasma mass spectrometry
IMes·HCl	1,3-Bis(2,4,6-trimethylphenyl)imidazolinium chloride
IPO	Iminopyridine oxazoline
IPr·HCl	1,3-Bis(2,6-diisopropylphenyl)imidazolium Chloride
IR	Infrared
J	Coupling constant in Hz

L	Ligand
m.p.	Melting point
M	Metal
MD'M	1,1,1,3,3,5,5-Heptamethyltrisiloxane
Me	Methyl
Mes	Mesityl
NHC	*N*-heterocyclic carbene
NMR	Nuclear magnetic resonance
n.r	No reactivity
Ph	Phenyl
pin	Pinacolate
ppb	Parts per billion
ppm	Parts per million
Pr	Propyl
py	Pyridine
r.t.	Room temperature
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
Terpy	Terpyridine
Tf	Trifluoromethanesulfonyl
THF	Tetrahydrofuran
TMEDA	*N*,*N*,*N*',*N*'-Tetramethylethylenediamine
TMHD	2,6,6-tetramethyl-3,5-heptanedionato
TOF	Turnover frequency
TON	Turnover number
Ts	*para*-Toluenesulfonyl
SIPr·HCl	1,3-Bis-(2,6-diisopropylphenyl)imidazolinium chloride
UV	Ultraviolet

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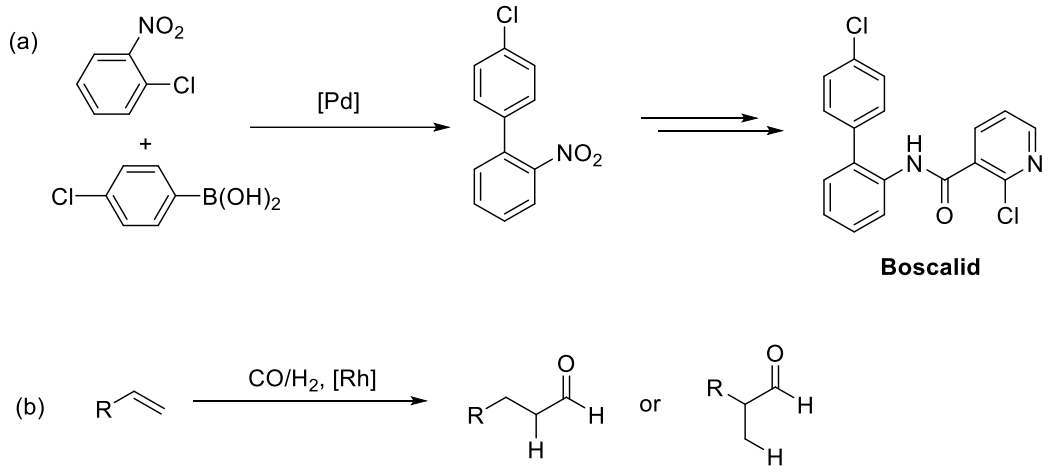
Chapter 1 Introduction

1.1 Catalysis

The field of chemical catalysis has a pivotal role in modern synthetic chemical transformations. It has been estimated that more than 90% of the products of the chemical industry are prepared using catalytic processes.[1] A catalyst is a chemical species that can lower the activation energy required to perform a chemical reaction while not being consumed. Catalysts are necessary for the production of a large number of bulk chemicals, pharmaceuticals and agrochemicals. A catalyst can offer an alternative, energetically favourable mechanism compared to the uncatalysed process, thus, enabling reactions to be carried out at industrially feasible conditions of pressure and temperature.

Transition metal-catalysed reactions are routinely applied in many synthetic schemes. Precious metals such as palladium[2] and rhodium[3] are among the most widely used transition metals in homogeneous catalysis. These noble metal catalytic systems have resulted in the development of a wide range of robust processes with excellent chemo-, regio- and stereoselectivity.[4] For example, palladium-catalysed Suzuki-Miyaura cross-coupling reactions have become ubiquitous for compound discovery in medicinal chemistry. An example of the application of the Suzuki-Miyaura reaction is the large scale synthesis of Boscalid on >1000 tonnes/year scale (Scheme 1.01a).[5] Another example of the use of platinum group metals on an industrial scale is the widely used rhodium-catalysed olefin hydroformylation reaction (Scheme 1.01b).[6] It is a vital reaction for the production of aldehydes from alkenes, with the formed aldehydes being versatile intermediates in the synthesis of bulk chemicals such as alcohols, esters and amines. This transformation represents one of the largest applications of homogenous catalysis in the chemical industry.



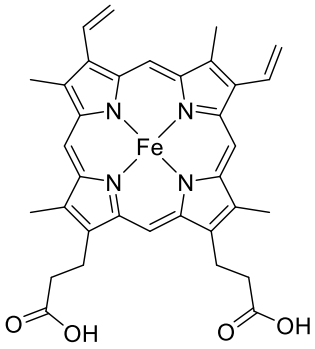
Scheme 1.01 (a) Palladium-catalysed Suzuki-Miyaura cross-coupling reaction. (b) Rhodium-catalysed hydroformylation of alkenes.

1.2 Earth-Abundant Metal Catalysis

Modern synthetic chemistry has been profoundly influenced by the use of organometallic catalysts and catalyst development has been dominated by systems based on platinum-group metals. Despite the huge success of precious metal systems and their contributions to synthetic organic chemistry, these catalytic processes have sustainability issues. Firstly, the terrestrial deposits of platinum-group metals are rare, with major mines in Russia, South Africa and Montana, leading to price volatility and a lack of supply security.[7] The quantity of platinum-group metal exploitation has declined by 20% between 2010 to 2015.[8] Secondly, platinum-group metals are extremely toxic and the cost of removing these metals to low ppm level from active pharmaceutical intermediates can be considerable.[9] These limitations in the existing precious metal catalytic systems have inspired the search for more sustainable and environmentally benign catalysts focused on the Earth-abundant first-row transition metals such as iron, cobalt and manganese.

Iron is the fourth most abundant element in the Earth's crust, accounting for 6% of its mass. The abundance of iron makes it a readily available and inexpensive metal, and the price is less volatile compared with many precious metals.[10] In heterogeneous catalysis, iron has been used in several large-scale industrial processes such as the Haber-Bosch ammonia synthesis[11] and the Fischer-Tropsch hydrocarbon preparation.[12] Iron salts have been further used as Lewis acids for the carbon-carbon and carbon-heteroatom bond formation reactions.[13] Iron forms the basis for several metalloproteins in living cells which play a major role in metabolism[14] and for example, iron is found in haemoglobin, the carrier of oxygen in red blood cells (Scheme 1.02). Although the abundance of cobalt is lower than that of iron in the Earth's crust, it is

significantly higher than that of platinum group metals. For organisms, cobalt is a trace dietary element to mammals, and it occurs in metalloenzymes, such as coenzyme B_{12}-dependent enzymes, methionine aminopeptidase and nitrile hydratase.[15] Manganese is also less toxic and more environmentally benign compared to platinum group metals. Trace manganese species in human body help promote healthy bone structure, bone metabolism and create essential enzymes for building bones.[16]



Scheme 1.02 Selected example: iron-containing haem b in haemoglobin.

In recent years, Earth-abundant metal catalysis for fine chemical synthesis has received huge interest academically and industrially. The number of chemical transformations catalysed by using Earth-abundant metal catalysts has expanded dramatically in the last half-century (Figure 1.01). Numerous applications using Earth-abundant metal catalysts, such as iron, cobalt and manganese, rely on the use of low oxidation-state complexes or *in situ* reductive activation procedures.[17-20]

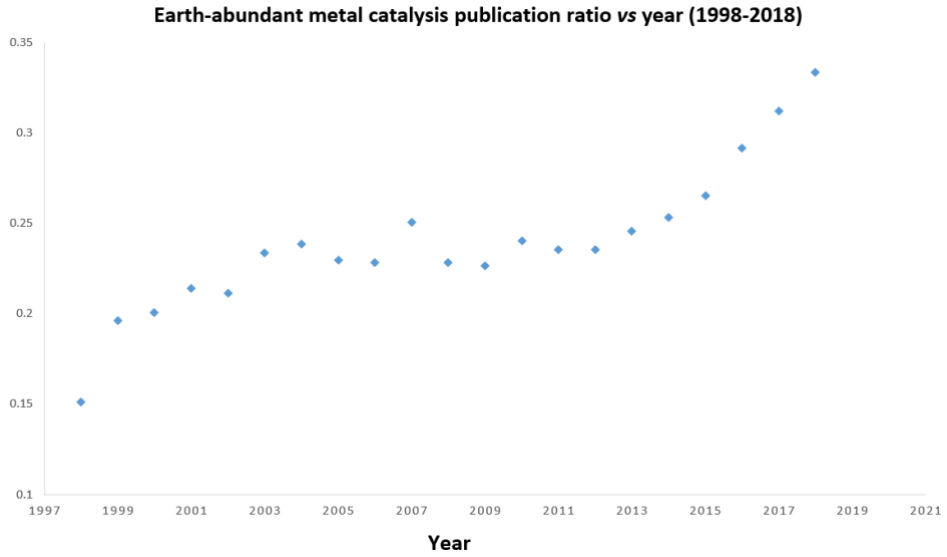
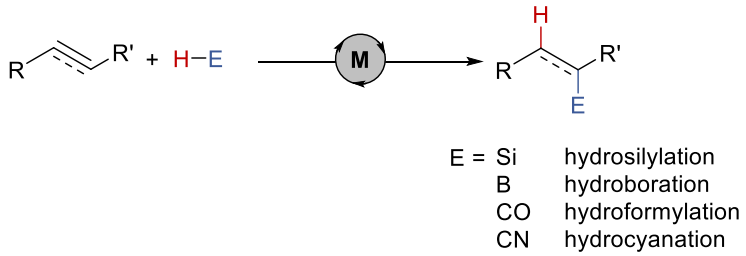


Figure 1.01 Scopus search for the ratio of 'Earth-abundant metal catalysed reactions' in 'metal catalysed reactions', from 1998 to 2018.

1.2.1 Hydrofunctionalisation

Alkenes are a substrate class which are simple, readily available and inexpensive. Reactions that can functionalise carbon-carbon double bonds selectively are of high importance in synthetic organic chemistry. Such reagents make the transformation of bench-stable and commercially available starting materials into valuable products and provide the opportunity of building complexity at a late stage of synthesis. A hydrofunctionalisation reaction is defined by the addition of a hydrogen atom and another moiety, 'E' which can be either electrophilic or nucleophilic, across an unsaturated bond (Scheme 1.03). A large number of examples of late transition metal pre-catalysts are suitable for alkene hydrofunctionalisation, which are widely used in both bulk chemical and fine chemical industry. For example, Wilkinson's catalyst [$Rh(PPh_3)_4Cl$] and Crabtree's catalyst [$Ir(COD)(PCy_3)(py)PF_6$] are effective and commercially available catalysts for alkene hydrogenation.[21, 22] Karstedt's catalyst $Pt_2[(Me_2SiCH{=}CH_2)_2O]_3$ is used for alkene hydrosilylation to produce cross-linked polymers.[23]



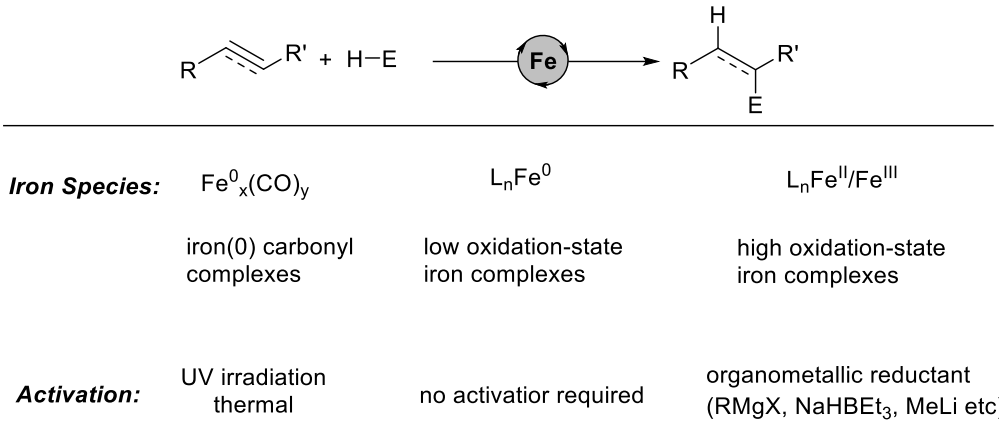
Scheme 1.03 Transition metal-catalysed hydrofunctionalisation of alkenes or alkynes.

Hydrofunctionalisation reactions are a class of reactions in which low oxidation-state Earth-abundant metal catalysts have been used as sustainable alternatives to late transition metal catalysts.[17-20, 24, 25] This introduction will explore the progress towards developing activation strategies for low oxidation-state Earth-abundant metal catalysis.

1.2.2 Low Oxidation-State Earth-Abundant Metal Catalysis

Earth-abundant metal species, with a formal oxidation-state below +2 are usually highly reactive species and have been applied in a variety of alkene hydrofunctionalisation reactions. Using iron-catalysed hydrofunctionalisation as an example, general strategies for accessing low oxidation-state catalytically active species can be divided into the following three categories depending on the pre-catalyst activation approach used: firstly the use of stable iron(0) carbonyl species as pre-catalysts; secondly the use of well-defined iron(0) complexes;

and thirdly the use of high oxidation-state iron(II/III) pre-catalysts, *in situ* activated by reducing agents (Scheme 1.04).



Scheme 1.04 Strategies for accessing low oxidation-state iron catalyst for hydrofunctionalisation reactions.

The first strategy utilises iron(0) carbonyl complexes as precursors to access low oxidation-state iron species. The majority of iron complexes in low oxidation-states are air- and moisture sensitive and therefore tend to be oxidised to iron(II) and iron(III) species. Iron(0) carbonyl complexes are stable low oxidation-state pre-catalysts and they have been investigated for more than a century. However, carbon monoxide is well known to form strong bonds to metal centres due to the formation of strong σ-bonds, stabilised by π-back-bonding, making the iron(0) carbonyl complexes thermodynamically stable and catalytically inert. Active iron(0) species are generated by reagent induced ligand dissociation or by photo- or thermal-irradiation.[26] When activated in this way, a coordinatively unsaturated iron(0) carbonyl species can be generated through carbon monoxide dissociation and the vacant site on the metal complex facilitates reactivity.

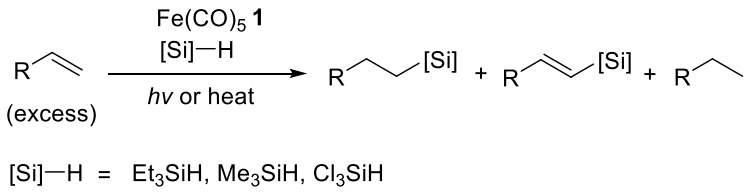
The second strategy to access low oxidation-state iron catalysts is to prepare well-defined iron(0) pre-catalysts, which can subsequently undergo facile catalyst activation. This strategy generally requires a strong reducing agent such as sodium amalgam to reduce an iron(II) halide pre-catalyst in the presence of dinitrogen to give the corresponding low oxidation-state iron dinitrogen complex.[27] Redox-active ligands have been commonly used to accept electron density from the iron centre and therefore stabilise the low oxidation-state iron species. Although these iron(0) complexes are usually highly air- and moisture sensitive, they be can fully characterised by NMR spectroscopy and crystallography, and therefore can be beneficial for mechanistic studies.

The third strategy uses iron(II) halide pre-catalysts which can be activated *in situ* by the addition of reducing organometallic reagents. This strategy allows the use of more stable pre-catalysts, which are usually formed *in situ* from free ligand and iron(II) salts. However, the standard electrode potential (E^o) for Fe(II)/Fe(0) is -0.44 V. This is a thermodynamically unfavourable process, meaning that Fe(0) cannot be readily generated from Fe(II) and this process requires considerable energy input.[28] The *in situ* generation of low oxidation-state iron species therefore requires the use of strong organometallic reducing agents, such as *n*-butyllithium, sodium triethylborohydride and Grignard reagents.[29]

1.3 Accessing Low Oxidation-State Earth-Abundant Metal Catalysis

1.3.1 Metal Carbonyl Complexes

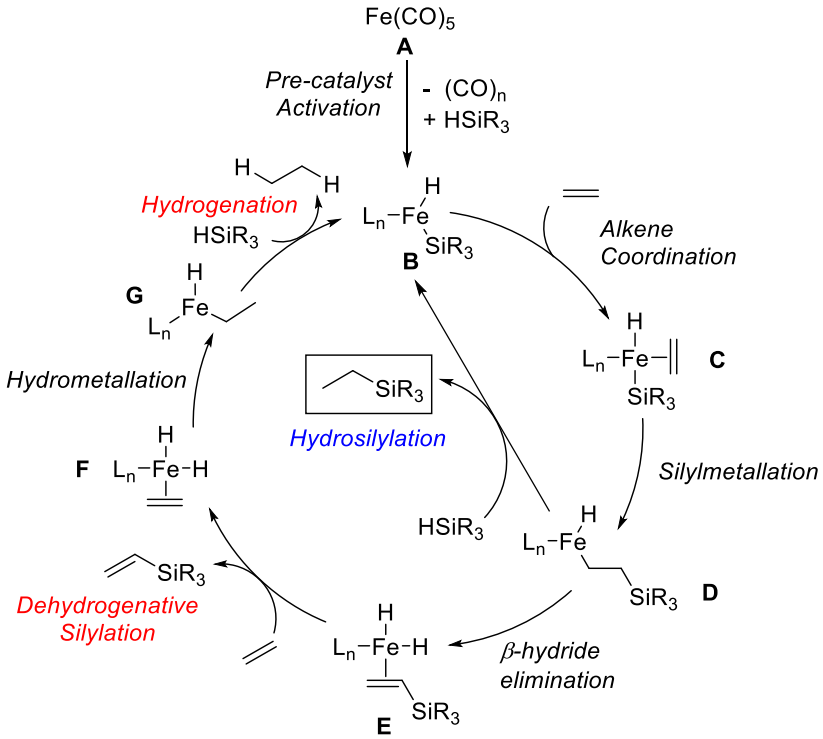
Many strategies have been reported to access low oxidation-state Earth-abundant metal species and enable successful hydrofunctionalisation reactions. The earliest examples used metal-carbonyl complexes as pre-catalysts, which were thermally activated. The first example of Fe-catalysed alkene hydrosilylation involved the addition of tertiary silanes to alkenes, using [$Fe(CO)_5$] as the pre-catalyst (Scheme 1.05).[30] The pre-catalyst activation required photo-irradiation or thermolysis at high temperature. A limitation of this process is the poor selectivity. Side products can result from dehydrogenative silylation and alkene hydrogenation.



Scheme 1.05 General overview of $Fe(CO)_5$-catalysed hydrosilylation of alkenes.

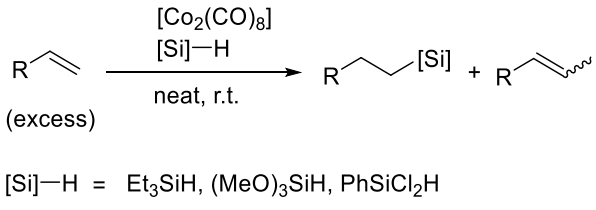
The mechanism of $Fe(CO)_5$-catalysed hydrosilylation has been investigated. The intermediate species [$Fe(CO)_3$] and [$Fe(CO)_4$] were generated through the dissociation of CO ligands and characterised. Previous mechanistic studies carried out by Chalk and Harrod, indicated a hydrometallation step to give a metal-silyl-alkyl complex.[31, 32] Due to the formation of both alkenyl silane and alkane products, Wrighton proposed the modified Chalk-Harrod mechanism (Scheme 1.06).[33-36] Thermal or photochemical activation of [$Fe(CO)_5$] **A** followed by oxidative addition of a silane gave the iron-silyl-hydride species **B**. Reversible alkene coordination and subsequent silyl-metallation gave intermediate **D**, followed by carbon-hydrogen bond reductive elimination to generate intermediate **B** and hydrosilylation product. In an alternative

pathway, β-hydride elimination from intermediate **D** gave an iron dihydride species **E** and ligand exchange of a second equivalent alkene gave alkenyl silane, the dehydrogenative silylation product. Hydrometallation of the newly coordinated alkene **F** gave intermediate **G**, followed by metathesis with another equivalent hydrosilane gave an alkane, the hydrogenation product, and the corresponding iron hydride species **B**.



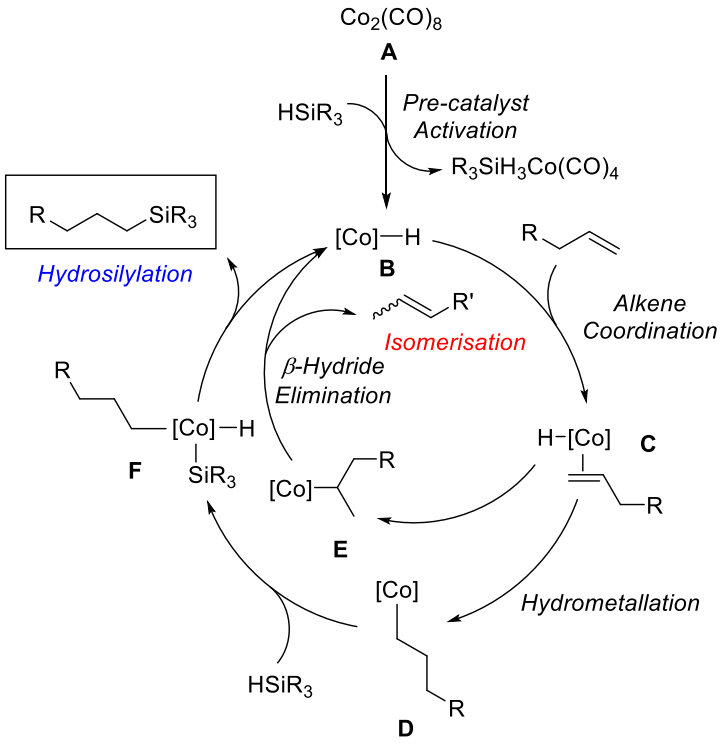
Scheme 1.06 Proposed activation of $Fe(CO)_5$ and modified Chalk-Harrod mechanism for $Fe(CO)_5$-catalysed hydrosilylation of alkene, which leads to dehydrogenative silylation and alkene hydrogenation products

Cobalt carbonyl clusters were also used as catalysts for alkene hydrosilylation, firstly developed by Chalk and Harrod (Scheme 1.07).[19] $[Co_2(CO)_8]$ was an effective pre-catalyst for hydrosilylation of terminal alkyl alkenes with a series of tertiary silanes. The reaction gave *anti*-Markovnikov products in high yields at room temperature. However, this system also generated alkene isomerisation side products.[31, 32]



Scheme 1.07 General overview of $Co_2(CO)_8$-catalysed alkene hydrosilylation.

Mechanistic studies indicated that a Chalk-Harrod mechanism was operational, which explained the observed alkene isomerisation. It was proposed that the pre-catalyst [$Co_2(CO)_8$] **A** initially reacted with hydrosilane to generate cobalt-silyl species and active cobalt-hydride species **B**. Alkene coordination to **B** produced intermediate **C**, from which hydrometallation could give either the cobalt-alkyl species **D** or **E**. Further interaction of cobalt-alkyl species **D** with hydrosilane produced the oxidative addition product **F** that underwent reductive elimination to generate the hydrosilylation product and regenerate cobalt hydride species **B**. Alternatively, β-hydride elimination from cobalt alkyl species **E** gave the alkene isomerisation product along with the regeneration of cobalt hydride species **B** (Scheme 1.08).[31, 32, 37]



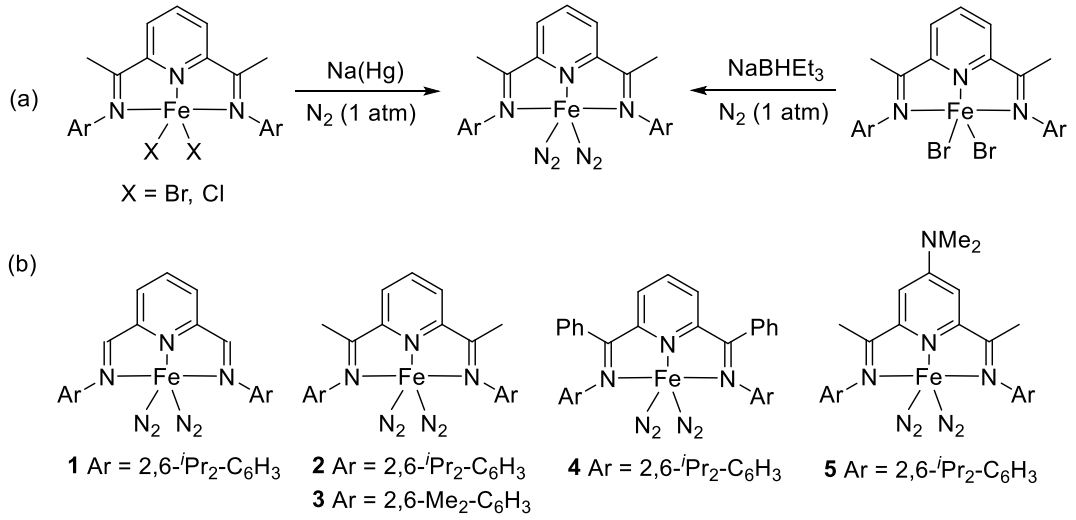
Scheme 1.08 Proposed Chalk-Harrod mechanism for $Co_2(CO)_8$-catalysed hydrosilylation of alkenes, which leads to alkene isomerisation products

1.3.2 Well-Defined Low Oxidation-State Complexes

Several well-defined low oxidation-state iron and cobalt complexes have been developed for use as hydrofunctionalisation pre-catalysts. A key strategy that underlies all the application of low oxidation-state iron and cobalt catalysis is stabilisation by their corresponding ligands. Redox-active ligands, such as bis(imino)pyridine, are capable of both accepting and donating electron density, therefore they are used to increase the stability and catalyst lifetime in low-oxidation state Earth-abundant metal complexes.

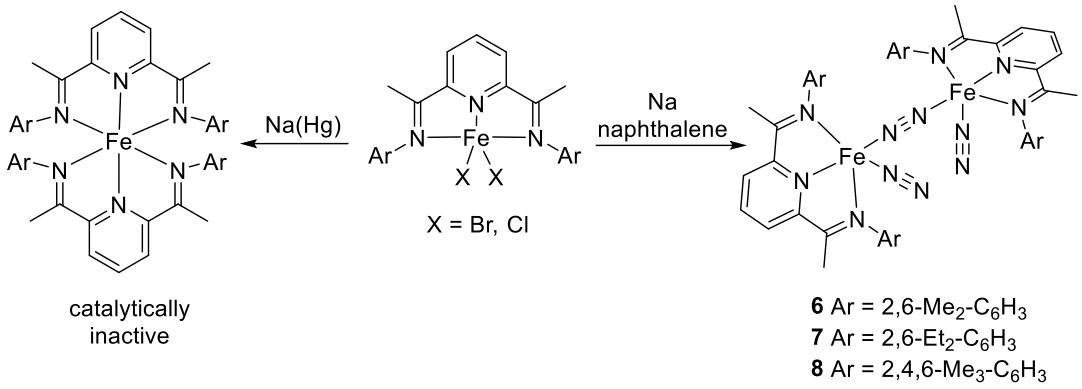
1.3.2.1 Metal Dinitrogen Complexes

Chirik reported a variety of well-defined bis(imino)pyridine iron(0) dinitrogen complexes capable of catalytic transformations of alkenes including: hydrosilylation, hydroboration, hydrogenation and [2+2] cycloaddition.[27, 38-40] These low oxidation-state complexes are prepared by the reduction of corresponding iron(II) complexes with strong reducing agents primarily: sodium amalgam, sodium triethylborohydride and sodium naphthalene, under an atmosphere of nitrogen (**1-5**, Scheme 1.09).[27] Upon the solvation of these low oxidation-state iron complexes, it was found that one of the N_2 ligands rapidly dissociate, giving the 4-coordinate [BIPFe(N_2)] species.[41]



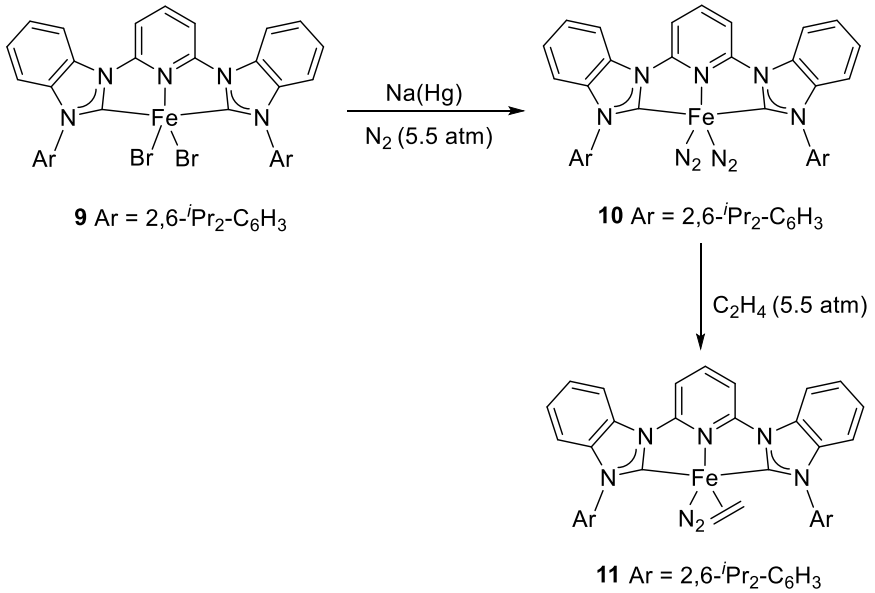
Scheme 1.09 (a) Preparation of bis(imino)pyridine iron(0) dinitrogen complexes, using sodium amalgam or sodium triethylborohydride. (b) A series of bis(imino)pyridine iron(0) dinitrogen complexes **1-5** used in alkene hydrofunctionalisation reactions developed by Chirik.

Complexes bearing less bulky substituent on the imine-nitrogen formed coordinatively saturated complexes when using sodium amalgam as the reductant. The formation of coordinatively saturated complexes were inhibited by performing the reduction with sodium naphthalene, which produced pre-catalyst iron dimers (**6-8**, Scheme 1.10), with two iron centres linked by a μ_2-N_2 bridging ligand.[42]



Scheme 1.10 Reduction of bis(imino)pyridine iron(II) precursors with different reducing agents. Sterically unencumbered bis(imino)pyridine iron(0) complexes **6**-**8** present a greater synthetic challenge due to the potential formation of coordinatively saturated species.

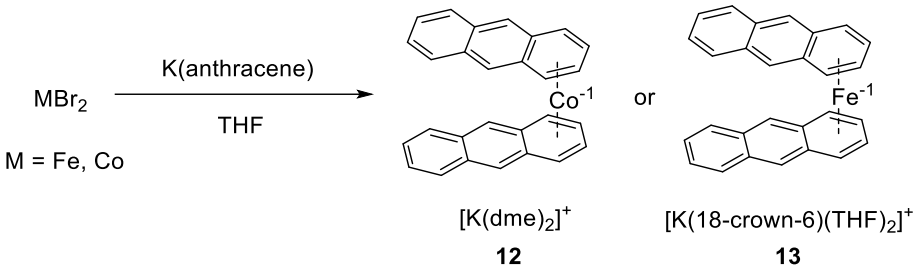
Similarly, Danopoulos prepared a bis-*N*-heterocyclic carbene (NHC) iron dinitrogen complex **10** by the reduction of bis-NHC iron(II) dibromide **9** with sodium amalgam under an atmosphere of nitrogen (Scheme 1.11).[43] Reaction of the bis-NHC pyridine iron(0) dinitrogen complex **10** with ethene resulted in facile substitution of one dinitrogen ligand and the formation of complex **11**, which may be critical to its reactivity in alkene hydrosilylation.



Scheme 1.11 Preparation of a bis-NHC pyridine iron(0) dinitrogen complexes by the reduction of bis-NHC pyridine iron(II) complexes with sodium amalgam.

Ellis reported that reduction of either iron dibromide or cobalt dibromide with potassium anthracene (3 equiv.) resulted in low oxidation-state iron and cobalt anthracene complexes (Scheme 1.12, **12**-**13**).[44] Wolf used these complexes as low oxidation-state pre-catalysts for

the cross-coupling between aryl bromide and aryl Grignard reagents, where they gave moderate yield for the product, and the author proposed this to be due to a labile coordination environment.[45]



Scheme 1.12 Preparation of bis(anthracene)Co$_{-1}$ complex **12** and bis(anthracene)Fe$_{-1}$ complex **13**.

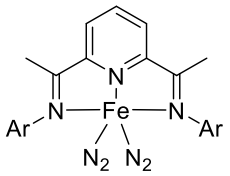
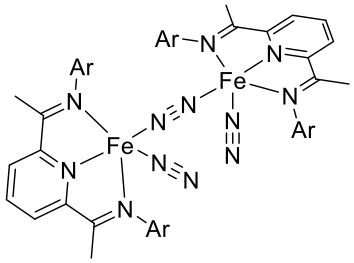
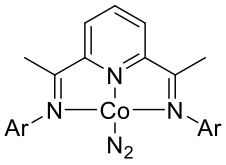
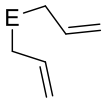
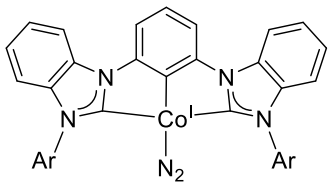
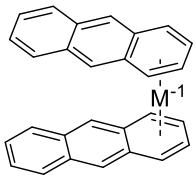
Low oxidation-state Earth-abundant metal dinitrogen complexes have demonstrated high versatility of these complexes in a wide range of catalytic transformations (Table 1.01). It was reported that bis(imino)pyridine iron(0) dinitrogen complexes $_{i\text{Pr}}$BIPFe(N$_2$)$_2$ **2** served as an effective pre-catalyst for the hydrogenation of a range of alkenes and alkynes, with extremely low catalyst loadings at ambient temperature (Entry 1).[27] Both $_{i\text{Pr}}$BIPFe(N$_2$)$_2$ **2** and [$_{\text{Me}}$BIPFe(N$_2$)]$_2$(μ_2-N$_2$) **6** promoted the *anti*-Markovnikov hydroboration of terminal and internal alkenes in high yield and regioselectivity using pinacolborane **16** (Entry 2).[46] Chirik reported that $_{i\text{Pr}}$BIPFe(N$_2$)$_2$ **2** was also active for the hydrosilylation of terminal alkene (Entry 3).[27] Both 1-hexene and styrene underwent *anti*-Markovnikov hydrosilylation with phenylsilane **17** in the presence of 0.3 mol% $_{i\text{Pr}}$BIPFe(N$_2$)$_2$ **2** at room temperature, with no dehydrogenative silylation or alkene isomerisation by-products observed. Chirik also reported that [$_{\text{Me}}$BIPFe(N$_2$)]$_2$(μ_2-N$_2$) **6** was effective for the hydrosilylation of 1-octene with the triethylsilane **18**, triethoxysilane **19** and MD'M **20**, along with the hydrosilylation of styrene with MD'M **20** (Entry 4).[47]

Beyond hydrofunctionalisation reactions, Chirik reported that bis(imino)pyridine cobalt(I) nitrogen complex **14** was active for [2+2] cycloaddition of 1,6-dienes (Entry 5).[48] It was shown that more sterically hindered substituents on the ligand, such as 2,4,6-tricyclopentyl, gave higher yield of cyclobutane product.

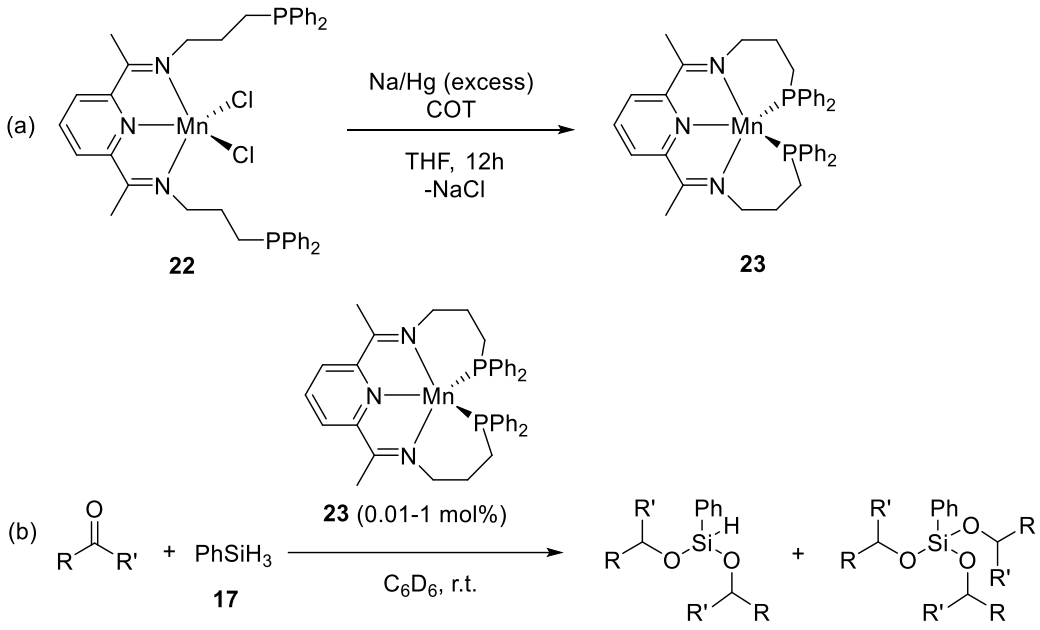
Low oxidation-state cobalt(I) nitrogen complexes were also used in hydrofunctionalisation reactions. Fout reported a highly chemoselective hydroboration protocol with terminal alkyl alkenes and aryl alkenes using a bis-NHC pyridine cobalt(I) nitrogen complex **15**. The catalytic process gave exclusive formation of *anti*-Markovnikov hydroboration products, tolerating functional groups such as amines, esters and epoxides (Entry 6).[49] This cobalt

complex **15** also showed excellent reactivity for olefin hydrosilylation with MD'M **20** and dimethylphenylsilane **21** (Entry 7).[50] Wolf and Jacobi von Wangelin showed that both bis(anthracene)Co^{-1} **12** and bis(anthracene)Fe^{-1} **13** were effective for the reduction of alkenes (Entry 8).[51] Bis(anthracene)Co^{-1} **12** was highly active in the hydrogenation of alkenes, alkynes, ketones and imines whereas iron complex **13** was only active for a limited selection of terminal aryl alkenes.

Table 1.01 Applications of low oxidation-state iron and cobalt nitrogen complexes in a wide range of reactions

Entry	Pre-catalyst	Reagent	Reaction Type
1	 **2** Ar = 2,6-*i*Pr$_2$-C$_6$H$_3$	H_2	Hydrogenation, 0.3 mol%, 8 Examples, Up to 98% yield
2		HBpin **16**	Hydroboration, *anti*-Markovnikov 1-5 mol%, 9 Examples, Up to 98% yield
3		PhSiH$_3$ **17**	Hydrosilylation, *anti*-Markovnikov 0.3 mol%, 8 Examples, Up to 98% yield
4	 **6** Ar = 2,6-Me$_2$-C$_6$H$_3$	(EtO)$_3$SiH **18** Et$_3$SiH **19** MD'M **20**	Hydrosilylation, *anti*-Markovnikov Using industrially relevant tertiary silanes 0.3 mol%, 5 Examples, Up to 98% yield
5	 **14** Ar = 2,4,6-(C$_5$H$_9$)$_3$-C$_6$H$_3$ C$_5$H$_9$ = cyclopentyl		Intramolecular [2+2] cycloaddtion 1-10 mol%, 10 Examples, Up to 99% yield
6	 **15** Ar = 2,6-*i*Pr$_2$-C$_6$H$_3$	HBpin **16**	Hydroboration, *anti*-Markovnikov 2.5 mol%, 14 Examples, Up to 97%
7		MD'M **20** Me$_2$PhSiH **21**	Hydrosilylation, *anti*-Markovnikov Using industrially relevant tertiary silanes 5 mol%, 16 Examples, Up to 99% yield
8	 M = Co **12** M = Fe **13**	H_2	[Fe], Hydrogenation, 1 mol%, 9 Examples, Up to 100% yield [Co], Hydrogenation, 1 mol%, 43 Examples, Up to 100% yield

Trovitch reported that the reduction of bis(imino)pyridine manganese(II) dichloride **22** using excess sodium amalgam in the presence of 1,3,5,7-cyclooctatetraene (COT) afforded the formally zerovalent complex **23** (Scheme 1.13a). This pentadentate bis(imino)pyridine complex **23** bearing σ-donor phosphine groups was effective for the hydrosilylation of ketones and esters. Complex **23** gave a TOF of 76800 h^{-1} for the hydrosilylation of ketones in the absence of reaction solvent (Scheme 1.13b).[52]

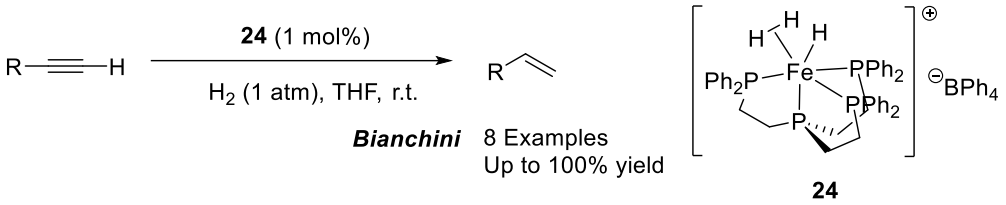


Scheme 1.13 (a) Preparation of pentadentate bis(imino)pyridine manganese complex **23** (b) Hydrosilylation of ketones with a bis(imino)pyridine manganese complex **23**.

1.3.2.2 Metal Hydride Complexes

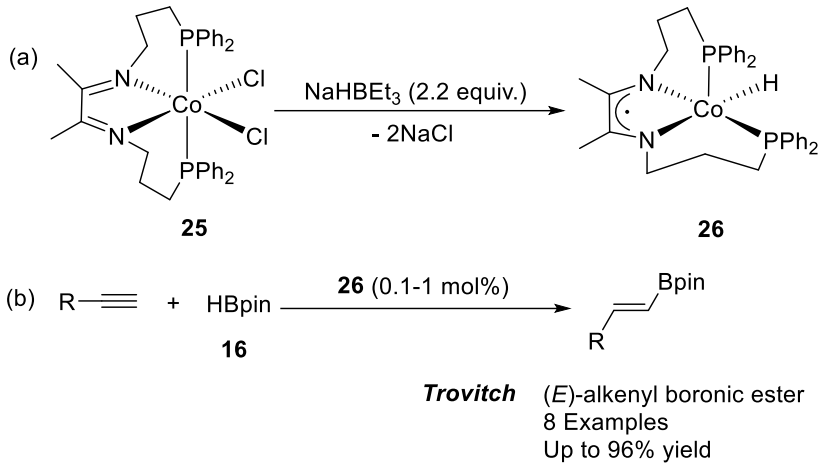
Several high oxidation-state iron and cobalt hydride complexes have been reported to catalyse hydrofunctionalisation reactions. Metal hydride complexes are typically prepared from their corresponding metal dichloride or dibromide complexes.

Bianchini reported the preparation of iron(II) dihydride complex **24** supported by tetradentate ligand, by the reaction of corresponding Fe-Cl species with sodium borohydride.[53] **24** was effective for the selective reduction of terminal alkynes to alkenes under mild reaction conditions, with excellent yields (Scheme 1.14).[54, 55]



Scheme 1.14 Iron-catalysed hydrogenation of alkynes using multidetate phosphine ligands reported by Bianchini.

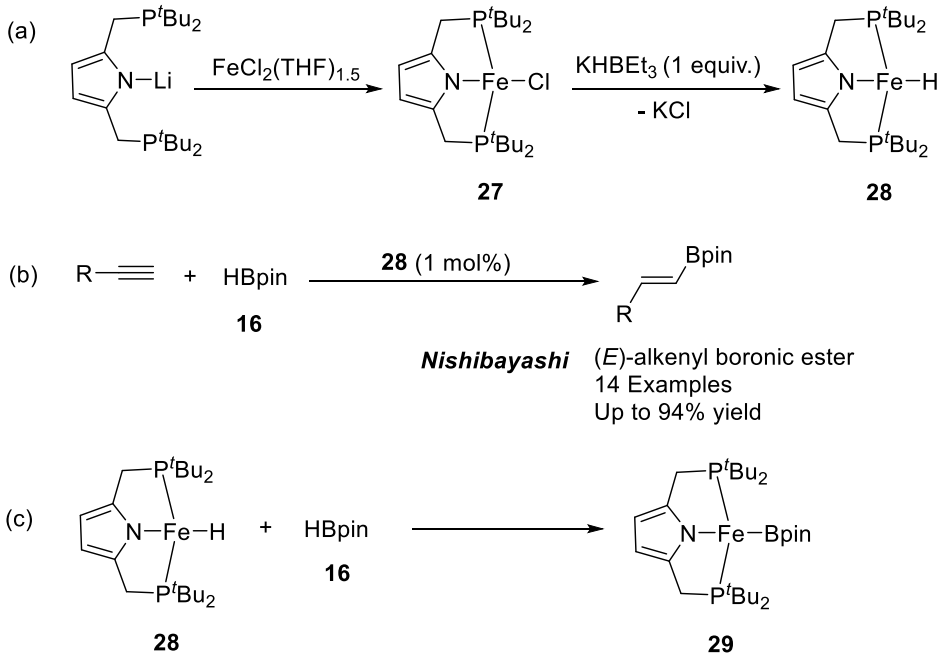
Trovitch reported the reaction of a cobalt dichloride complex **25** with excess sodium triethylborohydride to give cobalt hydride complex **26** bearing a tetradentate PNNP α-diimine ligand (Scheme 1.15a).[56] This complex was capable of catalysing the hydroboration of terminal alkynes under mild conditions. A number of corresponding (*E*)-alkenyl boronic esters were generated in high yields (Scheme 1.15b). DFT calculcations and XRD analysis showed that this cobalt hydride complex was a low spin cobalt(II) centre and a radical monoanionic diimine chelate.



Scheme 1.15 (a) Reaction of cobalt(II) dichloride complex with $NaHBEt_3$ to give cobalt hydride complex. (b) Application of cobalt(II) hydride complex in catalytic hydroboration of terminal alkynes.

Nishibayashi reported the preparation of iron(II) hydride complex **28** bearing a pyrrolide-based PNP pincer ligand from the corresponding iron(II) dichloride complex **27** (Scheme 1.16a).[57] This iron(II) hydride complex **28** was effective for hydroboration of both alkyl alkynes and aryl alkynes under ambient temperature (Scheme 1.16b).[58] In exploring the reaction mechanism, the reaction between bisphosphine pyrrole iron(II) hydride complex **28** and superstoichiometric pinacolborane **16** led to the formation of iron(II) boryl complex **29**, which was also capable of catalysing alkyne hydroboration reactions (Scheme 1.16c). Previously, Webster proposed an alkyne hydroboration pathway through the reaction of an iron hydride complex with an alkyne (hydrometallation) and subsequent σ-bond metathesis

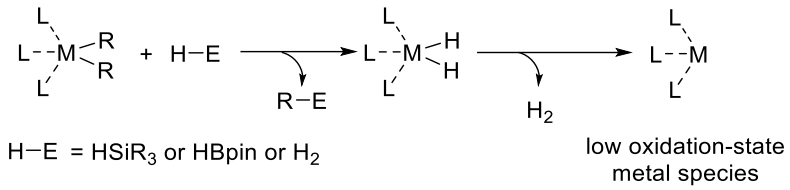
with pinacolborane **16**.[59] Due to insufficient evidence such a mechanism could not be ruled out in this case. However, the high reactivity of iron boryl complex indicated an alternative pathway in which the reaction of iron boryl complexes with alkyne (borometallation) and subsequent σ-bond metathesis with pinacolborane **16**. It was also possible that the iron hydride complex showed reactivity by allowing facile reductive elimination to give dihydrogen and a coordinatively unsaturated iron species.



Scheme 1.16 (a) Preparation of PNP iron(II) hydride complex **28**. (b) Application of iron(II) hydride **28** complex to catalytic hydroboration of terminal alkynes (c) Generation a of iron-boryl species **29**.

1.3.2.3 Metal Alkyl Complexes

Despite the success of several Earth-abundant metal dinitrogen and hydride pre-catalysts in hydrofunctionalisation reactions, these complexes have limited practical use owing to air- and moisture-sensitivity and challenging preparation. This has inspired the hunt for more easily accessible alternatives. A number of metal alkyl complexes have been used as precursors that form an active species upon reaction with a hydrofunctionalisation reagent (H-E) (Scheme 1.17). These iron or cobalt alkyl complexes are usually prepared by the reaction of metal dihalide precursors with alkyl lithium or alkyl Grignard reagents.

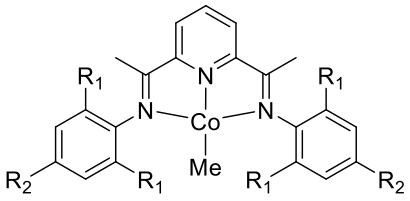
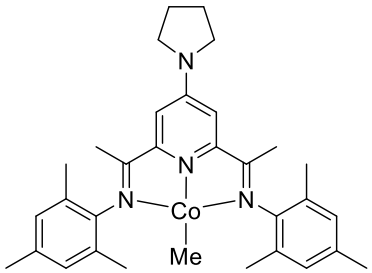
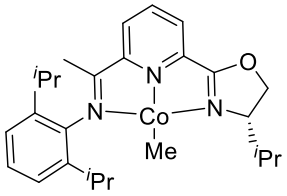
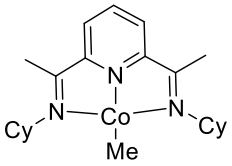
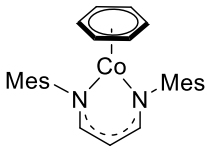


Scheme 1.17 Metal pre-catalysts bearing alkyl groups that undergo reactions with hydrofunctionalisation reagent (H-E) to generate active species.

Further investigation of a series of cobalt(I) methyl complexes have shown the versatility of these complexes (Table 1.02). Chirik reported bis(imino)pyridine cobalt(I) methyl pre-catalyst $^{i\text{Pr}}$BIPCoMe **30** and $^{\text{Me}}$BIPCoMe **31** were used for the hydroboration of both alkyl alkenes and aryl alkenes with *anti*-Markovnikov selectivity and excellent yields (Entry 1).[60] Mechanistic studies showed that pinacolborane **16** interacted with bis(imino)pyridine cobalt(I) complex to generate an active cobalt(I) hydride species. When using a bis(imino)pyridine ligands with a 4-pyrrolidinyl substituted pyridine, pre-catalyst **32** was able to catalyse the isomerisation-hydroboration of more sterically hindered internal alkenes with high yield, giving the product of terminal hydroboration (Entry 2).[60] Huang reported that the enantiopure iminopyridine oxazoline cobalt(I) methyl complex **33** was used for asymmetric hydroboration of 1,1-disubstituted aryl alkenes with pinacolborane **16** (Entry 3).[61] The reaction gave the *anti*-Markovnikov product with exclusive regioselectivity in high yields with up to 99% *ee*. Chirik showed the applicability of *N*-cyclohexyl bis(imino)pyridine cobalt(I) methyl complex **34** as a pre-catalyst in the hydroboration of terminal alkynes, giving (*Z*)-vinylboronic esters in excellent yield and stereoselectivity (Entry 4).[62] Stoichiometric experiments and deuterium labelling experiments indicated that the pre-catalyst **4** participating the catalytic cycle by reacting with a terminal alkyne to generate an active cobalt acetylide species.

Except these cobalt(I) methyl complexes, Weix and Holland used potassium graphite for the reduction of *β*-aldiminate cobalt(II) dichloride precursor in benzene to give *β*-aldiminate cobalt(I) benzene complex **35**. This complex was effective for the hydrosilylation of terminal alkyl alkene using phenylsilane **17** and triethoxysilane **18** with *anti*-Markovnikov selectivity (Entry 5).[63]

Table 1.02 Applications of bis(imino)pyridine cobalt(I) alkyl complexes in a wide range of reactions

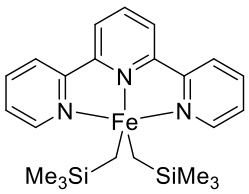
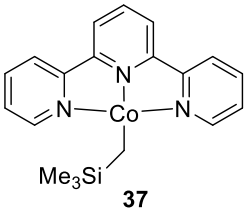
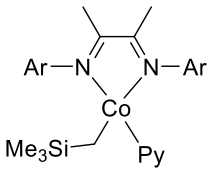
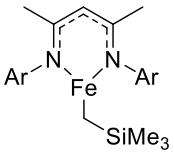
Entry	Pre-catalyst	Reagent	Reaction Type
1	 **30** R_1 = ^{i}Pr, R_2 = H **31** R_1 = R_2 = Me	HBpin **16**	Hydroboration, *anti*-Markovnikov 1 mol%, 11 Examples, Up to 98% yield
2	 **32**	HBpin **16**	Isomerisation-hydroboration Internal alkenes gave terminal product 1 mol%, 8 Examples, Up to 98% yield
3	 **33**	HBpin **16**	Enantioselective hydroboration 0.5 mol%, 24 Examples, Up to 98% yield Up to 99% ee
4	 Cy = cyclohexyl **34**	HBpin **16**	(*Z*)-selective alkyne hydroboration 3 mol%, 12 Examples, Up to 91% yield
5	 **35** Mes = 2,4,6-Me_3-C_6H_2	$PhSiH_3$ **17** $(EtO)_3SiH$ **18**	Hydrosilylation, *anti*-Markovnikov 0.5-2 mol%, 15 Examples, Up to 94% yield

A number of metal methylene trimethylsilane (CH_2SiMe_3) complexes were also used in hydrofunctionalisation reactions (Table 1.03). Metal methylene trimethylsilane complexes exhibit enhanced air- and moisture- stability than metal dihydrogen and metal hydride complexes, representing an alternative protocol of harnessing the powerful reactivity obtained with dinitrogen complexes.[17] These metal methylene trimethylsilane complexes are typically

prepared by the reaction of their corresponding metal dichloride precursors with (trimethylsilyl)methyllithium.

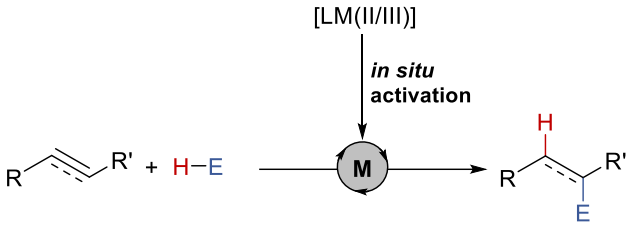
Chirik reported that terpyridine iron complex **36** promoted the effective hydrosilylation of vinylcyclohexene oxide, using MD'M **20**, with no observed ring opening of the epoxide. This protocol can be applied in a variety of industrial applications, including the high-performance coating for glass, wood and leather (Entry 1).[64] It was postulated that the mechanism of the generation of the active catalyst is through formation of a dihydride complex followed by reductive elimination to give an iron(0) complex. Attempted hydrosilylation of vinylcyclohexene oxide using Karstedt's catalyst with MD'M **20** resulted in 50% decomposition of platinum complex, owing to the incompatibility with the epoxide functional group.[65] Terpyridine supported cobalt(I) methylene trimethylsilane complex **37** and *N*-di*iso*propylphenyl substituted diimine supported cobalt(I) methylene trimethylsilane complex **38** were shown to be effective for the isomerisation-hydroboration of di-, tri- and tetra substituted alkenes, giving the terminal hydroboration product in high yields (Entry 2).[66] Webster used 1,3-diketimine (NacNac) iron(II) methylene trimethylsilane complex **39** for the hydroboration of both terminal and internal alkenes (Entry 3).[59] A stoichiometric reaction of **39** and pinacolborane **16** resulted in the formation of pinBCH_2SiMe_3. It was proposed that an iron(II) hydride was the key intermediate, although Webster did not rule out a radical mechanism. It was also possible that iron(II) hydride underwent reductive elimination to give a coordinatively unsaturated iron(I) species.

Table 1.03 Applications of metal methylene trimethylsilane complex in hydrofunctionalisation reactions

Entry	Pre-catalyst	Reagent	Reaction Type
1	 **36**	MD'M **20** Et_3SiH **19**	Hydrosilylation, *anti*-Markovnikov Using industrially relevant tertiary silanes 1 mol%, 3 Examples, Up to 95% yield
2	 **37**	HBpin **16**	Isomerisation-hydroboration Internal alkenes gave terminal product 1 mol%, 24 Examples, Up to 98% yield
	 **38** Ar = 2,6-$^{i}Pr_2$-C_6H_3		
3	 **39** Ar = 2,6-$^{i}Pr_2$-C_6H_3	HBpin **16**	Hydroboration, *anti*-Markovnikov terminal alkenes and internal alkenes 1 mol%, 15 Examples, Up to 99% yield

1.3.3 *in situ* Activation of High Oxidation-State Complexes

Despite the high reactivity achieved by using the well-defined low oxidation-state iron and cobalt complexes, these systems are not applicable for large-scale use. These Earth-abundant metal complexes are highly air- and moisture-sensitive, requiring specialist techniques for their preparation and handling. To overcome these limitations, *in situ* activation strategies have been developed. This entails the use of iron(II) or cobalt(II) dihalide complexes and addition of strongly reducing reagents to generate low oxidation-state species *in situ* which can then catalyse the reaction (Scheme 1.18). This has provided an easier and more powerful method for accessing active iron and cobalt species.

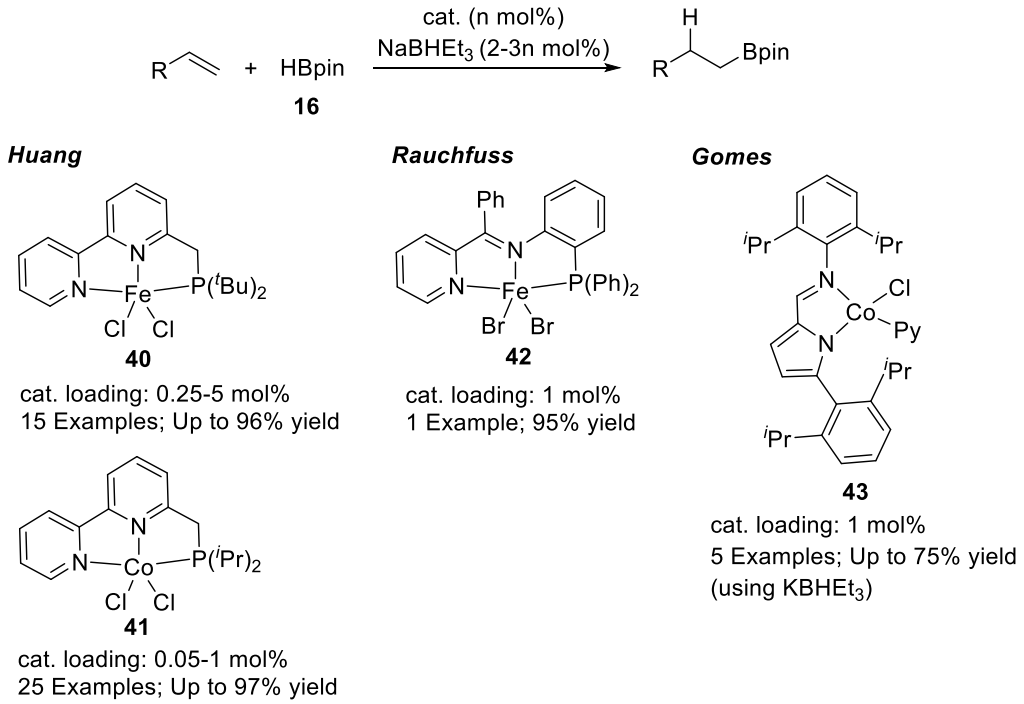


Scheme 1.18 *in situ* reduction of high oxidation-state metal pre-catalysts

1.3.3.1 Organometallic Activating Reagents

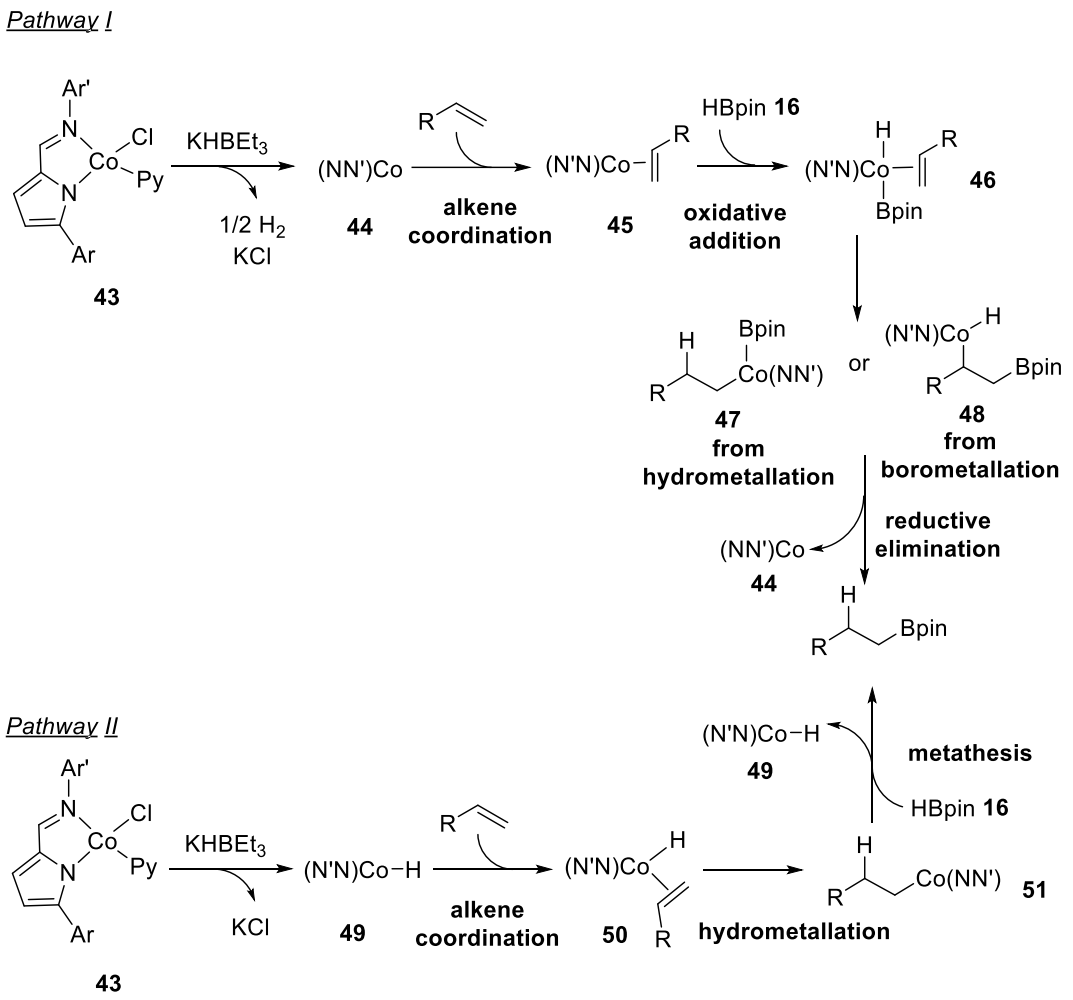
Alkali metal salts of triethylborohydride are one of the most widely used activators in the generation of low oxidation-state iron and cobalt catalysts.[67] Numerous alkene hydroboration reactions have been achieved by making use of *in situ* activation strategies.

Huang developed the bipyridyl-phosphine cobalt(II) and iron(II) dichloride complexes (**40**-**41**) for the hydroboration of both aryl alkenes and alkyl alkenes using pinacolborane **16**.[68, 69] These high oxidation-state pre-catalysts required the addition of sodium triethylborohydride for *in situ* activation. A wide range of terminal alkenes underwent hydroboration, giving the *anti*-Markovnikov product with excellent regioselectivity, chemoselectivity and functional group tolerance. Other complexes using alkali metal salts of triethylborohydride as an activator include the phosphine-imine-pyridine iron(II) dibromide pre-catalyst **42** developed by Rauchfuss[70] and mono(2-iminopyrrolyl)cobalt(II) dichloride pre-catalyst **43** developed by Gomes (Scheme 1.19).[71]



Scheme 1.19 Iron- and cobalt-catalysed hydroboration of alkenes, *in situ* activated by $NaHBEt_3$ or $KHBEt_3$.

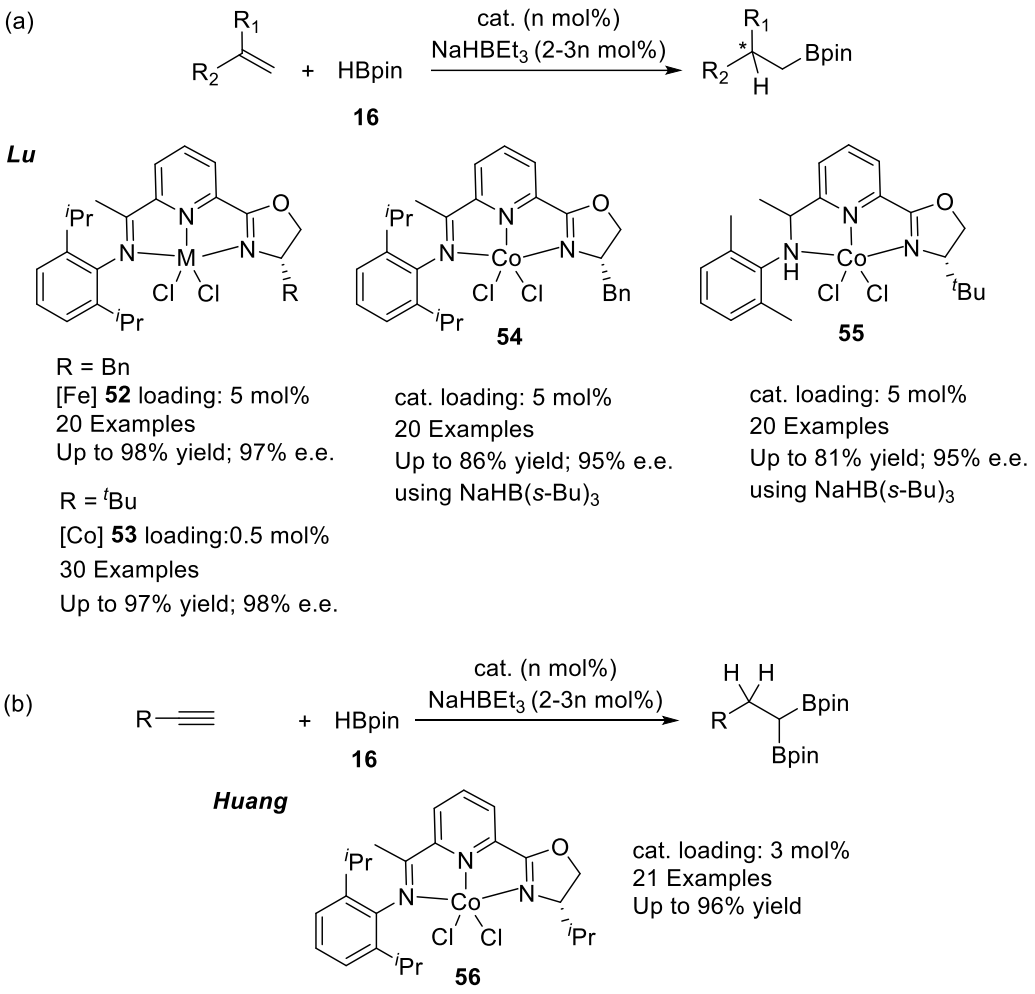
Gomes proposed two possible mechanisms for the potassium triethylborohydride activation (Scheme 1.20).[71] In one pathway, it was postulated that the reduction of cobalt(II) pre-catalyst **43** to give a 'naked' cobalt(I) species **44** through reductive elimination of H_2. The cobalt(I) species **44** underwent alkene coordination to give **45** and subsequent oxidative addition of pinacolborane **16** to give **46**, followed by hydrometallation or borometallation to give **47** or **48**. Finally, a reductive elimination reaction generated the hydroboration product and regenerated the active 'naked' cobalt(I) species **44**. In the other pathway, it was proposed that the hydride transfer gave a cobalt(II) hydride species **49**, which underwent alkene coordination to give **50** and hydrometallation to generate the cobalt-alkyl intermediate **51**. The intermediate **51** reacted with pinacolborane **16** through σ-bond metathesis, giving the boronic ester product and regenerating the active cobalt hydride species **49**.



Scheme 1.20 Proposed reaction pathways of the cobalt-catalysed alkene hydroboration, *in situ* activated by KHBEt3

A number of iron and cobalt complexes have also been reported for enantioselective alkene hydroboration, *in situ* activated with alkali metal salts of triethylborohydride. Lu reported that iminopyridine-oxazoline iron or cobalt complexes (**52-54**) were able to catalyse the hydroboration of 1,1-disubstituted alkenes with excellent yield, regioselectivity and enantioselectivity (Scheme 1.21a).[72, 73] An interesting observation was that aminopyridine-oxazoline complex **55** gave the opposite enantiomer of hydroboration products.[74] The reason for the enantiodivergent hydroboration reaction was not fully investigated, but the flexibility and steric bulk of aminopyridine-oxazoline ligand had an effect on the selectivity. The enantiodivergent hydroboration reaction was proposed to proceed through different pathways, with less bulky iminopyridine-oxazoline cobalt complex undergoing hydrometallation before the oxidative addition of pinacolborane **16**. For the more sterically encumbered aminopyridine-oxazoline cobalt complex, oxidative addition of pinacolborane **16** was followed by borometallation, adding to the opposite face. Huang reported the synthesis of 1,1-

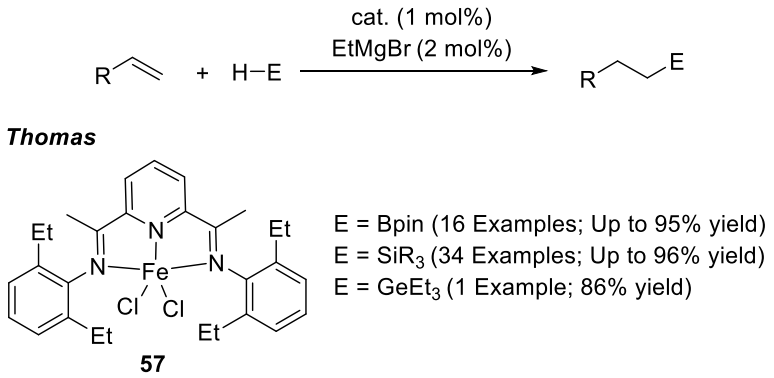
diboronate esters from terminal alkynes using an enantiopure iminopyridine-oxazoline cobalt complex **56**, in which sodium triethylborohydride was used for pre-catalyst *in situ* activation (Scheme 1.21b).[75] The reaction proceeded under mild reaction conditions, giving the 1,1-diboronate esters with excellent yield and broad functional group tolerance.



Scheme 1.21 (a) Iron and cobalt-catalysed enantioselective alkene hydroboration, *in situ* activated by $NaHBEt_3$. (b) Cobalt-catalysed sequential hydroboration of terminal alkynes, *in situ* activated by $NaHBEt_3$.

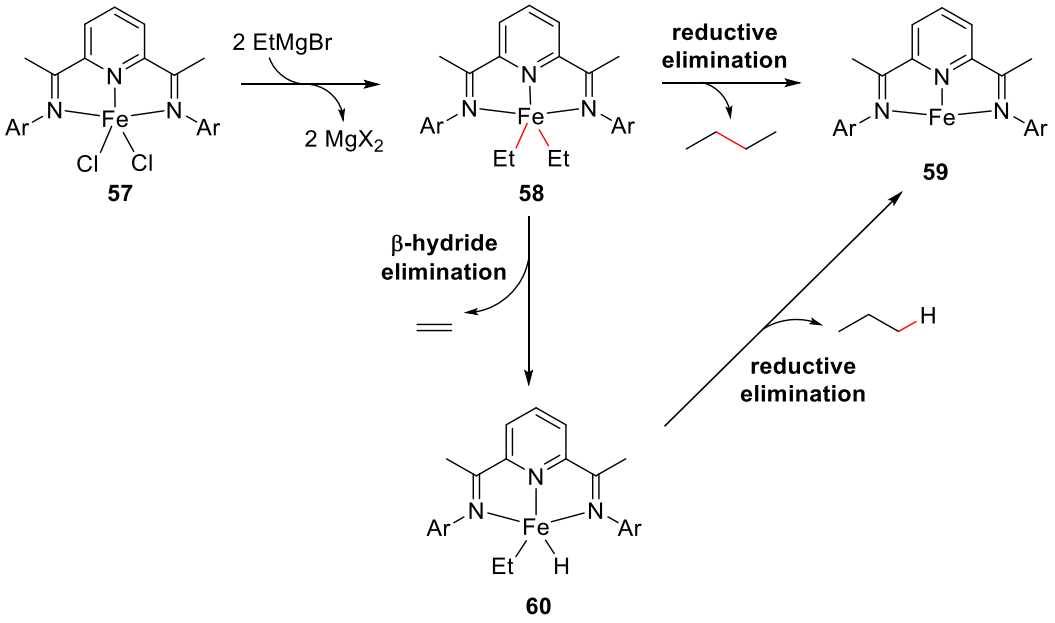
High oxidation-state iron and cobalt complexes have also been reduced *in situ* by Grignard reagents, and this represents another useful method for the generation of low oxidation-state Earth-abundant metals species.

Thomas found that bis(imino)pyridine iron(II) dichloride **57** could be readily prepared from air- and moisture-stable precursors, and subsequently activated *in situ* using ethylmagnesium bromide. This activation strategy was shown to be applicable to the iron-catalysed alkene hydrosilylation, hydroboration and the first example of hydrogermylation (Scheme 1.22).[76, 77]



Scheme 1.22 Iron-catalysed hydroboration, hydrosilylation and hydrogermylation, *in situ* activated by EtMgBr.

The reduction of iron(II) complex **57** by Grignard reagents is proposed by the following mechanism (Scheme 1.23). Alkylation of the iron(II) pre-catalyst **57** gave the iron(II) dialkyl intermediate **58**. The intermediate **58** underwent a reductive elimination, performing a 2-electron reduction of the metal centre to give low oxidation-state active iron(0) species **59** and generating an equivalent of dimerised Grignard reagent as a by-product.[77] In an alternative pathway, when the Grignard reagent having *β*-hydrogens, iron(II) dialkyl intermediate **58** underwent *β*-hydride elimination reaction and generated iron(II) hydride species **60**, which following reductive elimination to produce **59**, along with an equivalent of alkene and an equivalent of alkane.[78-80]

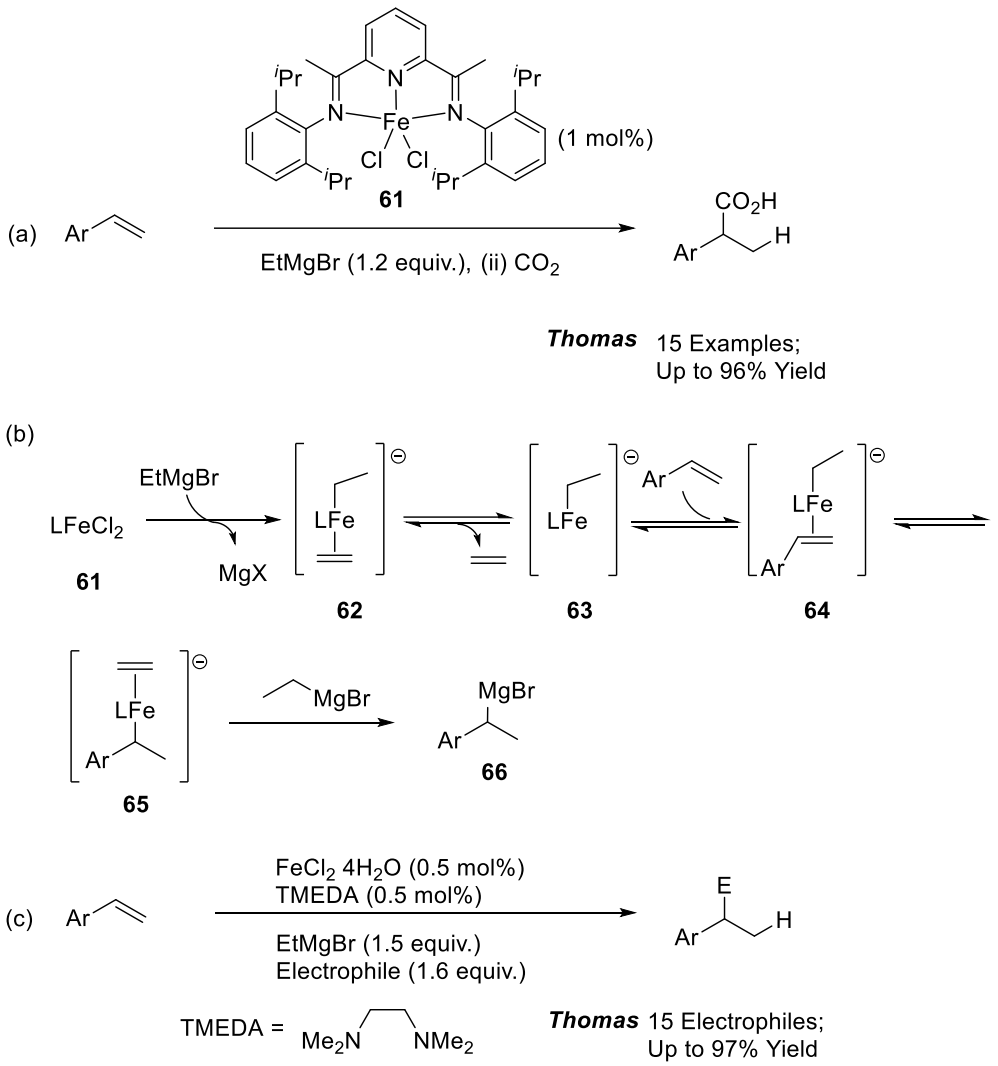


Scheme 1.23 Proposed pathways for the *in situ* activation of bis(imino)pyridine iron(II) dichloride **57** using EtMgBr.

Thomas reported the iron-catalysed hydrocarboxylation of styrenes using bis(imino)pyridine ligand and stoichiometric ethylmagnesium bromide, which proceeded by the hydromagnesiation of styrene derivatives to form a nucleophilic benzylic Grignard reagent intermediate (Scheme 1.24a).[80] The reaction gave the carboxylic acid products in excellent yields. Similarly, Shirakawa and Hayashi reported an iron- and copper-cocatalysed hydromagnesiation of terminal alkyl alkenes with linear selectivity.[81] Nakumura reported the hydromagnesiation of diaryl alkynes.[82]

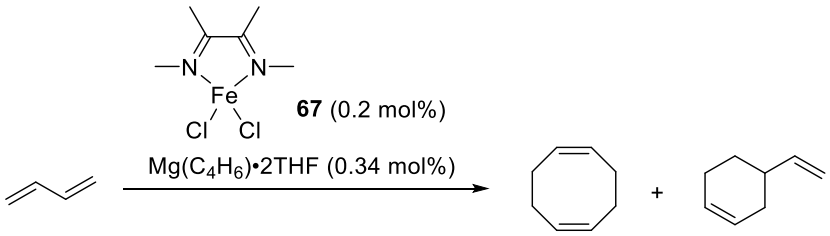
Iron-catalysed hydromagnesiation has been investigated in detail (Scheme 1.24b).[80, 83] After much effort, a formally Fe(0) 'ate' species [$_{i\text{Pr}}$BIPFe(Et)(ethene)]$^{-1}$ **62** was identified as the resting state in the hydromagnesiation. In contrast to our originality proposed iron-hydride intermediate, it was determined that a *β*-hydride of an ethyl ligand was the active hydrometallation species. The [$_{i\text{Pr}}$BIPFe(Et)(ethene)]$^{-1}$ complex **62** could loss ethene to give [$_{i\text{Pr}}$BIPFe(Et)]$^{-1}$ **63** and transiently coordinate the styrene derivative and mediate a rapid and reversible direct *β*-hydride transfer to give the benzylic iron species **65**, negating the necessity of a discrete iron hydride intermediate. Catalyst turnover was achieved by transmetallation with ethylmaganesium bromide to regenerate [$_{i\text{Pr}}$BIPFe(Et)(ethene)]$^{-1}$ **62** and the benzylic Grignard reagent **66**.

Hydromagnesiation of styrene derivatives was also an effective method for the introduction of new functional groups onto styrene derivatives. The key intermediate benzylic Grignard reagent generated *in situ* was able to react with 18 unique electrophiles. Using tetramethylethylenediamine (TMEDA) instead of bis(imino)pyridine ligand, the reaction proceeded with extremely high regioselectivity, excellent functional group tolerance and high yield (Scheme 1.24c).[84]



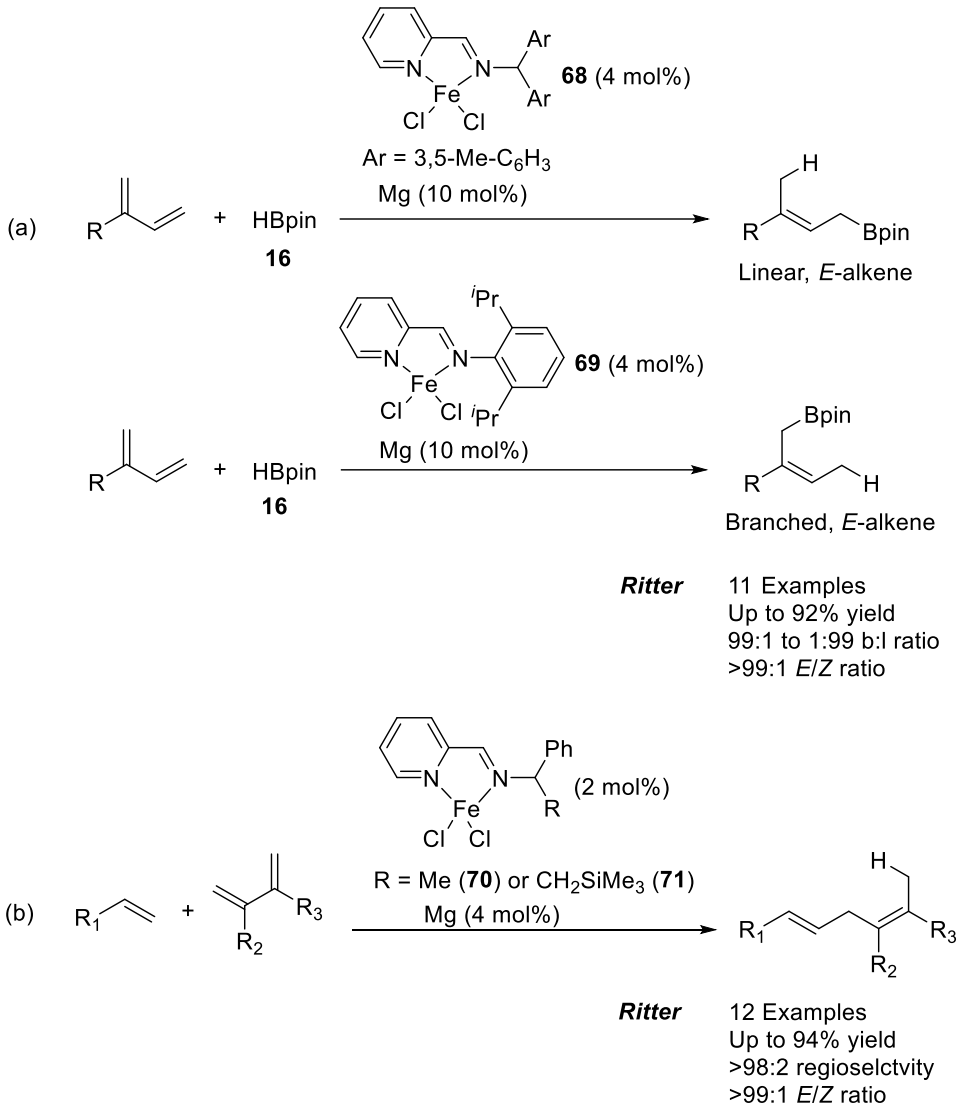
Scheme 1.24 (a) Iron-catalysed aryl alkene hydrocarboxylation, using stoichiometric EtMgBr as hydride donor and activator. (b) Proposed reaction mechanism for the bis(imino)pyridine iron(II) complex-catalysed hydromagnesiation of styrene derivatives. (c) The application of hydromagnesiation: hydrofunctionalisation of aryl alkenes with different electrophiles.

Tom Dieck reported the synthesis bidentate iron(II) complex **67** by the reaction of diimine ligand and iron(II) dichloride.[85] The complex was activated *in situ* by butadienemagnesium ($Mg(C_4H_6)\cdot 2THF$) to generate an active catalyst for butadiene dimerisation, however the yields for these reactions were not reported (Scheme 1.25).[86]



Scheme 1.25 Dimerisation of butadiene using diimine iron(II) complex and butadienemagnesium.

Activated magnesium has also been used for generating low oxidation-state species. Ritter reported a series of iminopyridine iron(II) chloride complexes (**68**-**69**), *in situ* activated with highly reactive Reike magnesium, effective for the 1,4-hydroboration of 1,3-dienes using pinacolborane **16** (Scheme 1,26a).[87] It was proposed that bidentate iminopyridine ligand offered a vacant site for diene coordination, and thus this system was selective for dienes over terminal alkenes. Ligand could be used to switch the branched/linear selectivity of the reaction. When using diarylmethane substituted imine, the reaction gave the linear 1,4-hydroboration product. An aryl substituent on the ligand gave the branched 1,4-hydroboration product. Ritter also developed the 1,4-hydrovinylation reaction of diene using iminopyridine iron(II) dichloride complexes (**70**-**71**) that were *in situ* activated using Reike magnesium (Scheme 1.26b).[88] Both regioselectivity and alkene geometry of the addition product could be controlled. Two structurally different iminopyridine iron complexes (**70**-**71**) gave high yield of the non-conjugated diene products and the iron(II) pre-catalyst bearing trimethylsilyl group demonstrated improved regioselectivity in several examples.

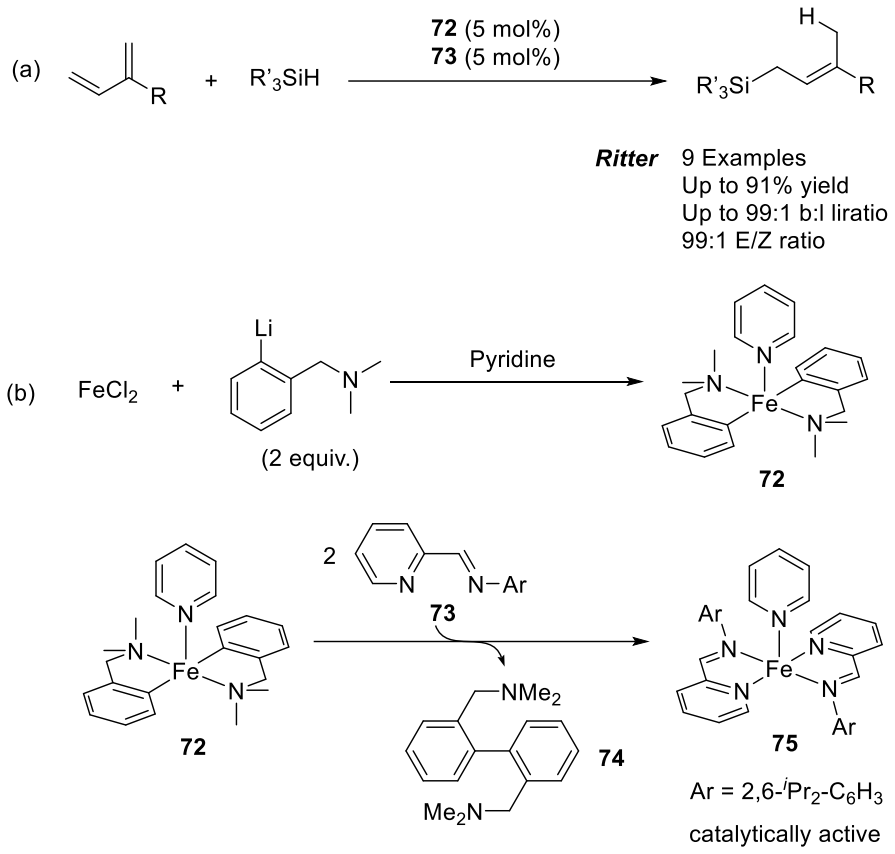


Scheme 1.26 (a) Iron-catalysed regiodivergent 1,4-hydroboration of 1,3-dienes, *in situ* activated by Reike magnesium. (b) Iron-catalysed 1,4-hydrovinylation of 1,3-dienes with alkyl and aryl alkenes, *in situ* activated by Reike magnesium.

1.3.3.2 Non-Organometallic Activating Reagents

Many *in situ* activation strategies, using organometallic reagents to access low oxidation-state iron or cobalt species, were described in the previous section. However, the air and moisture instability of these organometallic activators limit adoption by synthetic chemists. Ideally, the development of activation strategies using readily available, bench stable and easily-handled reagents as activators instead of pyrophoric organometallic reagents would allow access to low oxidation-state Earth-abundant metal catalysts in a highly operationally simple and safe manner.

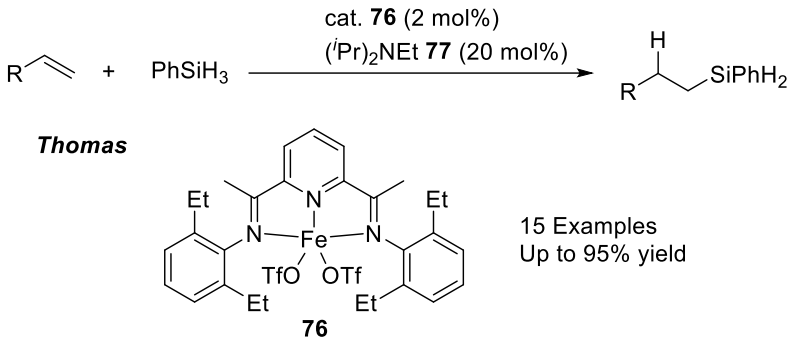
Ritter reported that iron-catalysed regio- and stereoselective 1,4-hydrosilylation of 1,3-dienes with a range of tertiary silanes, using iron complex **72** and iminopyridine ligand **73** as an *in situ* activator (Scheme 1.27a).[89] In this case, a well-defined bis(aryl) iron(II) pyridine complex **72** was prepared from the reaction between iron(II) dichloride and aryl lithium reagent (2 equiv.). The bis(aryl) iron(II) pyridine complex **72** underwent reductive elimination by the addition of activating reagent iminopyridine **73** to generate the catalytically active bis(iminopyridine) iron(0) pyridine complex **75,** accompanied by an equivalent biaryl by-product **74** (Scheme 1.27b).



Scheme 1.27 (a) Iron-catalysed 1,4-hydroboration of 1,3-dienes, *in situ* activated by iminopyridine ligand. (b) *in situ* Activation of bis(aryl) iron(II) pyridine complex by the reductive elimination.

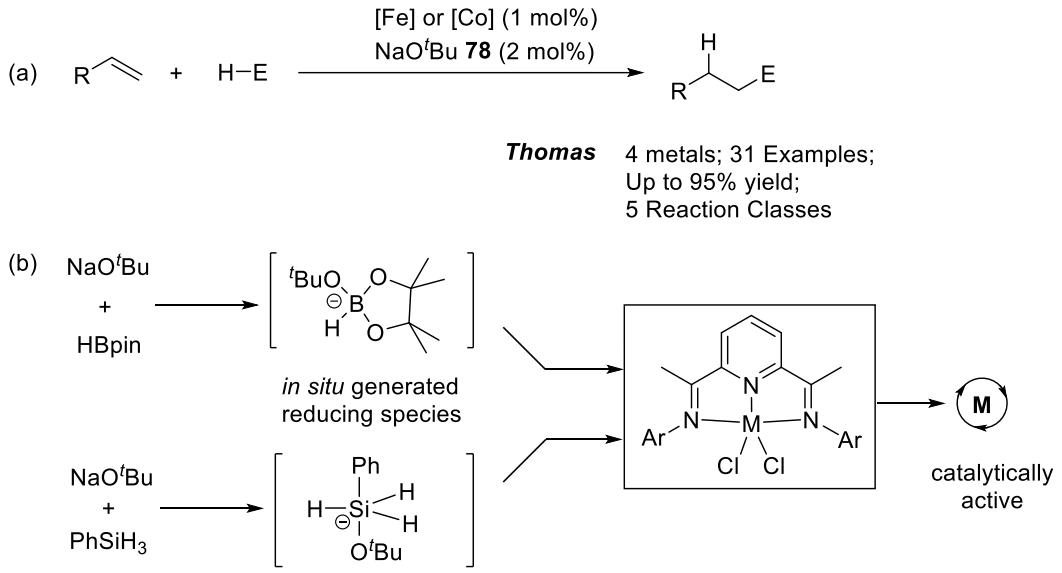
Thomas reported that bis(imino)pyridine iron(II) triflate pre-catalyst **76**, *in situ* activated with the tertiary amine Hünig's base **77**, was capable of catalysing the hydrosilylation of alkenes and alkynes (Scheme 1.28).[90] Equal reactivity in air and under inert atmospheres was found applicable for gram-scale hydrosilylation reactions. The use of weakly coordinating triflate counterions was demonstrated to be critical for catalysis to occur. Amines have been reported to reduce late transition metal complexes by coordination and *β*-hydride elimination.[91, 92] However, the possible by-products such as aldehydes and imines were not observed in the

reaction. In addition, no direct evidence for the formation of a silicon ‘ate’ complexes was obtained.



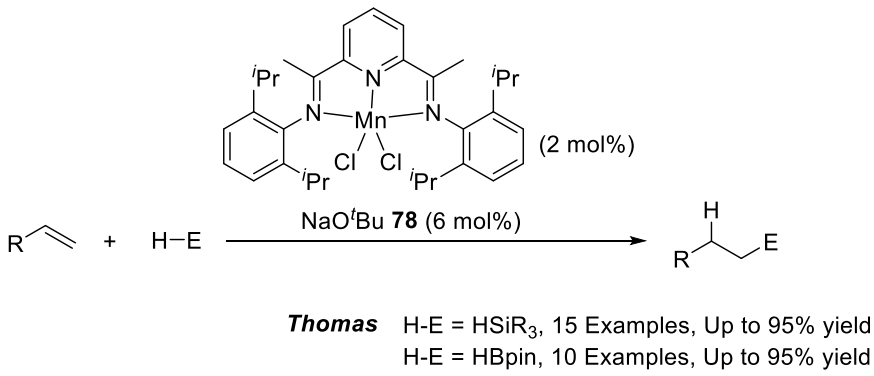
Scheme 1.28 Iron-catalysed hydrosilylation reaction, *in situ* activated by amine.

Thomas also reported that the use of commercially available, bench-stable and non-toxic alkoxide salt sodium *tert*-butoxide **78** as a generic activation strategy for Earth-abundant metal complexes to catalyse a range of transformations, including hydroboration and hydrosilylation (Scheme 1.29a).[93] The activation was shown to proceed through the *in situ* generation of hypervalent boron or silicon ‘ate’ complexes, which were observed by ^{11}B and ^{29}Si NMR respectively. These ‘ate’ complexes are well-known to act as nucleophilic reagents in literature.[94-96] In this scenario, the boron or silicon ‘ate’ complex acted as *in situ* hydride donor, transferring hydride to a pre-catalyst, generating a metal hydride complex. This was followed by reductive elimination to generate the low oxidation-state active species, along with dihydrogen (Scheme 1.29b).



Scheme 1.29 (a) Earth-abundant metal-catalysed hydrofunctionalisation reactions, *in situ* activated by NaO*t*Bu. (b) Proposed pre-catalyst activation pathway, by the generation of catalytically active boron 'ate' species or silcon 'ate' species.

Based on the mechanistic investigations, a number of reactions have been developed following the discovery and development of sodium *tert*-butoxide **78** activation. The key mechanistic finding was that the combination of sodium *tert*-butoxide **78** and stoichiometric pinacolborane **16** produced a boron 'ate' complex, which could react with iron(II) or cobalt(II) complexes, generating a low oxidation-state species that can be used to catalyse other transformations. Therefore, hydrovinylation, hydrogenation and [2+2] cycloaddition reactions were developed using sodium *tert*-butoxide activation.[93] This simplified activation strategy was later applied in manganese-catalysed, *anti*-Marknovnikov selective hydrosilylation and hydroboration of alkenes (Scheme 1.30).[97]



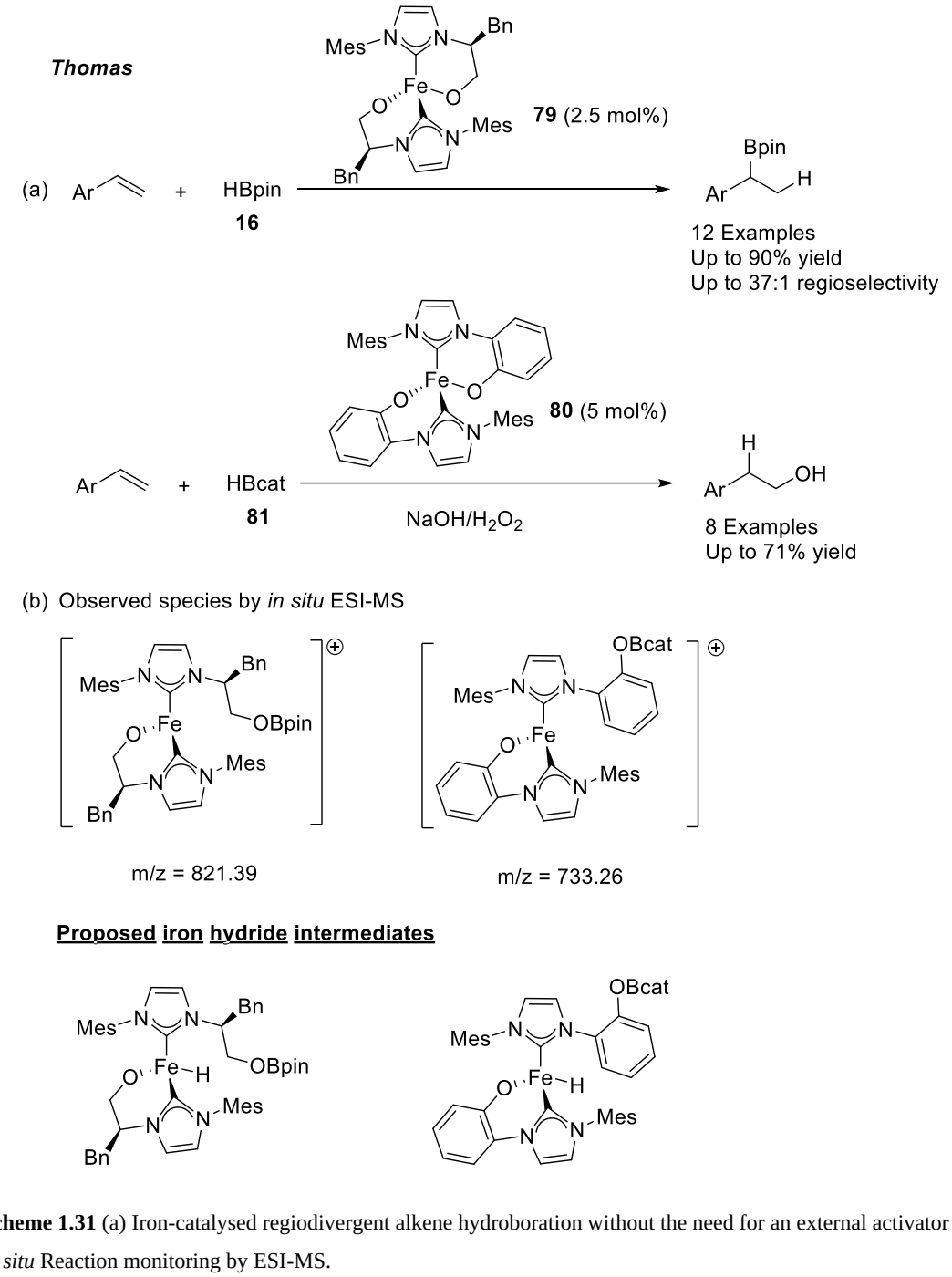
Scheme 1.30 Manganese-catalysed hydrosilylation and hydroboration of alkenes, *in situ* activated by NaO*t*Bu.

1.3.4 'Activator-Free' Systems

'Activator-free' hydrofunctionalisation systems have also been established, in which high oxidation-state Earth-abundant metal complexes undergo activation without the need for external activators. This represents an emerging state-of-the-art for Earth-abundant metal catalysis and demonstrates the potential of more extensive use of these metal complexes. Metal complexes bearing ligands with tethered bonds and metal carboxylate complexes are usually used in these 'activator-free' systems.

Thomas reported that regioselective alkene hydroboration using two alkoxy-tethered *N*

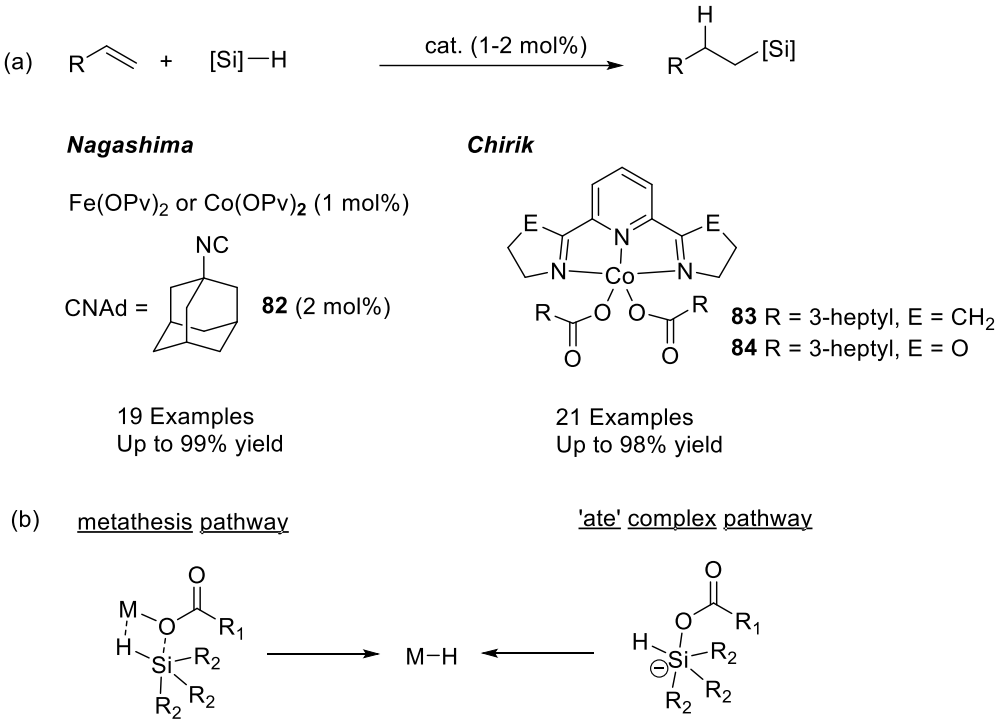
-heterocyclic carbene iron(II) complexes (Scheme 1.31a, **79**-**80**).[98] Markovnikov selective alkene hydroboration with pinacolborane **16** was achieved for the first time using an iron catalyst **79**. *anti*-Markovnikov selective alkene hydroboration was also achieved using catecholborane **81** with the modification of ligand backbone. These iron(II) complexes **79**-**80** were designed bearing carbon-oxygen which was proposed to react with pinacolborane **16** or catecholborane **81** to give an iron-hydride species. This was supported by *in situ* reaction monitoring using mass spectrometry, in which the borylated iron complexes **79**·Bpin, and **80**·Bcat were observed (Scheme 1.31b). It was proposed that these species were derived from the corresponding iron hydride complexes.



Scheme 1.31 (a) Iron-catalysed regiodivergent alkene hydroboration without the need for an external activator (b) *in situ* Reaction monitoring by ESI-MS.

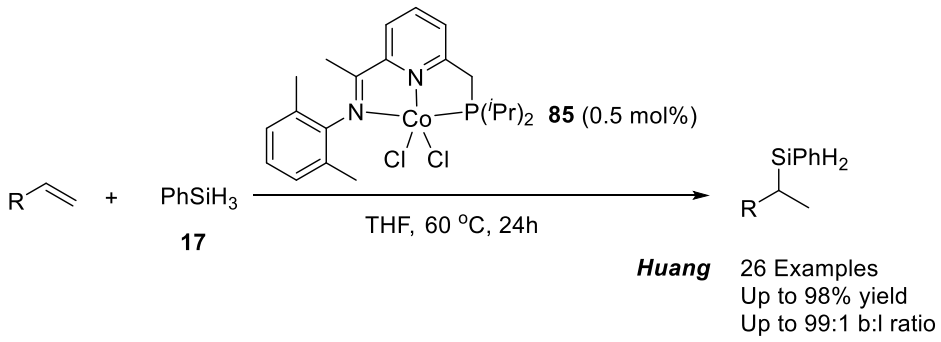
Earth-abundant metal-carboxylate complexes have been used as pre-catalysts which were proposed to undergo reaction with hydrofunctionalisation reagents (H-ER$_3$) to give reactive metal hydride species (Scheme 1.32a). Nagashima developed a novel 'activator-free' system for alkene hydrosilylation with a range of tertiary silanes, using a mixture of cobalt or iron pivalate salts and isocyanide ligand **82**.[99] Similarly, Chirik reported that bench-stable pyridine diimine cobalt(II) bis(carboxylate) complexes (**83**-**84**) were highly effective for the hydrosilylation of alkenes using tertiary silanes.[100] In comparison with metal halide pre-

catalysts, these metal carboxylate salts have less commercial availability and are air- and moisture-sensitive. The reactivity of these 'activator-free' systems and activation ability of carboxylate counterions was shown to be dependent on the hydrofunctionalisation reagent (H-ER3). This transformation likely proceeded *via* a σ-bond metathesis pathway, where a metal hydride complex was formed through a 4-membered transition state. Alternatively it was also possible that the reaction occurred through a silicon 'ate' complex formed by the combination of weekly coordinating counterion carboxylate and tertiary silane. The silcon 'ate' complex reacted with iron(II) or cobalt(II) complexes, giving a low oxidation-state species that can be used to catalyse the alkene hydrosilylation reaction (Scheme 1.32b).



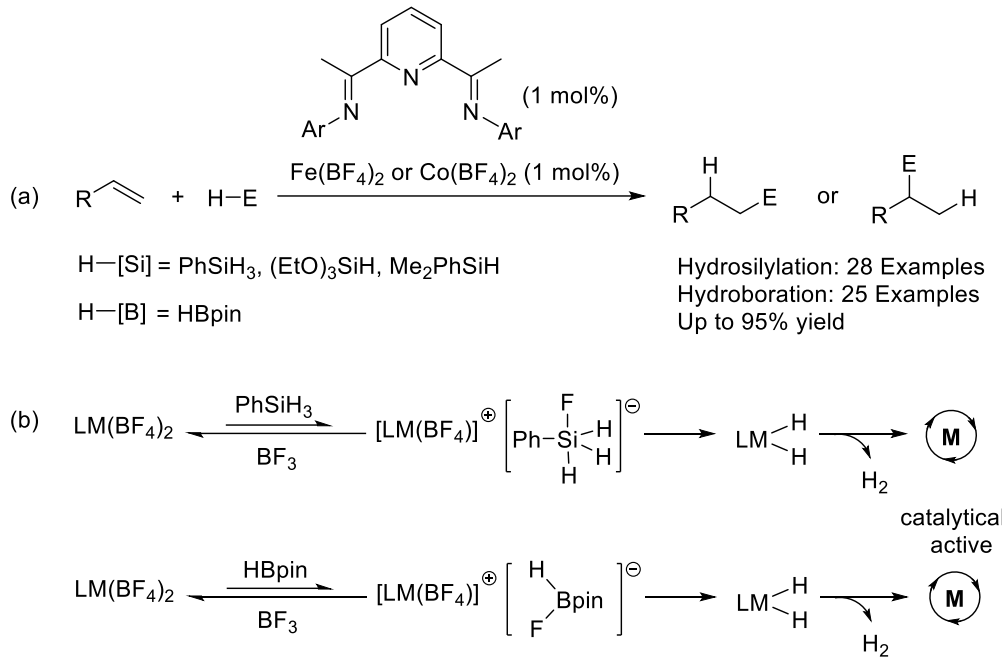
Scheme 1.32 (a) Iron- or cobalt-catalysed alkene hydrosilylation with tertiary silanes, using carboxylate counterion. (b) Proposed reaction pathway in the 'activator-free' systems: metathesis pathway or 'ate' complex pathway.

Huang reported that phosphinite-iminopyridine cobalt(II) dichloride pre-catalyst **85** was effective for the hydrosilylation of terminal alkenes without the use of external activating reagents. The hydrosilylation products were obtained in high yields and Markovnikov selectivity (Scheme 1.33).[101] Control reactions demonstrated that the use of sodium triethylborohydride was not required for the activation of the cobalt(II) pre-catalyst, but the activator-free reaction proceeded at a relatively slower rate. It was subsequently found that reactivity was enhanced at elevated temperatures.



Scheme 1.33 Cobalt-catalysed Markovnikov selective hydrosilylation of terminal alkyl and aryl alkenes without the use of an external activating reagent.

Thomas reported a novel and operationally simple endogenous activation method, using commercially available tetrafluroborate iron and cobalt salts and bis(imino)pyridine ligands. Catalytic regiodivergent hydrosilylation and *anti*-Markovnikov hydroboration reactions were carried out without the addition of any external activator, thus highly simplifying the procedure of hydrofunctionalisation reactions (Scheme 1.34a).[102, 103] Except bis(imino)pyridine ligand, the use of other ligands such as bisphosphine, xantphos and dppf in combination of cobalt(II) tetrafluroborate effectively catalysed the hydrosilylation of 1-octene with phenylsilane **17**. This endogenous activation was shown to proceed by the dissociation of fluoride from the metal tetrafluoroborate pre-catalysts, which led to the formation of catalytically active hydridic boron or silicon 'ate' complex. The 'ate' complex activated a metal complex by hydride transfer, generating a metal hydride complex, which was followed by reductive elimination to generate the low oxidation-state species to catalyse the reaction (Scheme 1.34b).



Scheme 1.34 (a) Iron- or cobalt-catalysed regiodivergent hydrosilylation and hydroboration of alkenes, using tetrafluroborate metal salts and bis(imino)pyridine ligands. (b) Proposed tetrafluroborate activation: hydridic 'ate' complex formation to reduce metal complex.

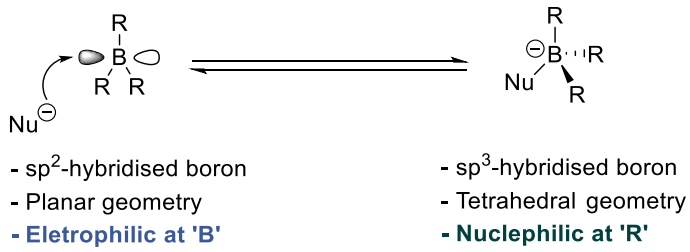
The use of the tetrafluoroborate activation as a general platform to access low oxidation-state, catalytically active species, was also investigated. The combination of tetrafluoroborate pre-catalysts and stoichiometric hydrofunctionalisation reagents, such as phenylsilane **17** and pinacolborane **16**, produced a hydridic 'ate' complex, which would give a low oxidation-state species that would be applicable to other reaction classes beyond hydrosilylation and hydroboration. Therefore, hydrogenation, [2+2] cycloaddtion and C-H borylation were also developed using tetrafluroborate activation.[102]

Chapter 2 Cobalt-Catalysed Alkene Hydroboration Reactions

2.1 State-of-the-Art at the Outset of the Project

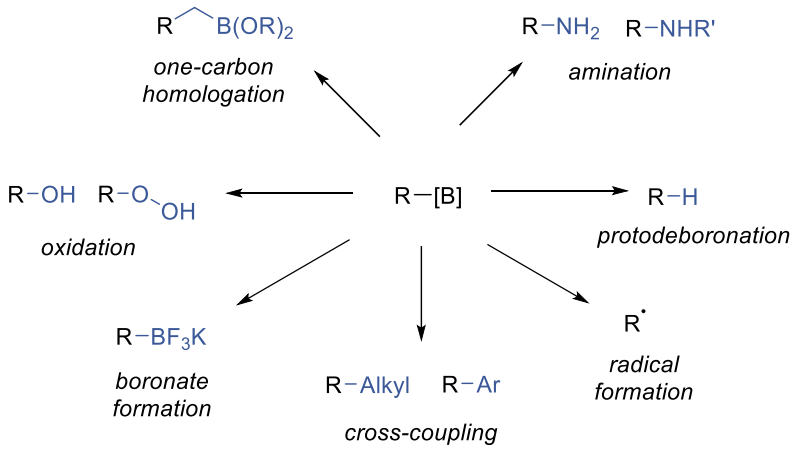
2.1.1 General Background

Organoboranes are versatile reagents in organic synthesis.[104, 105] The boron atom of an organoboron compound usually adopts an oxidation-state of +3, and forms three bonds to neighbouring atoms through sp^2-hybridised orbitals. With only six valence electrons and a consequent deficit of two electrons, the sp^2-hybridised boron atom has a vacant *p*-orbital that is ready to accept a pair of electrons and therefore many organoboron compounds are Lewis acidic. Addition of a nucleophile into this vacant *p*-orbital forms a sp^3-hybridised and tetrahedral boron 'ate' complex. The sp^3-hybridised boronate complexes generated are nucleophilic on the group coordinating boron.[106] The switchable properties between electrophilic and nucleophilic character makes boron compounds ubiquitous in organic synthesis (Scheme 2.01)



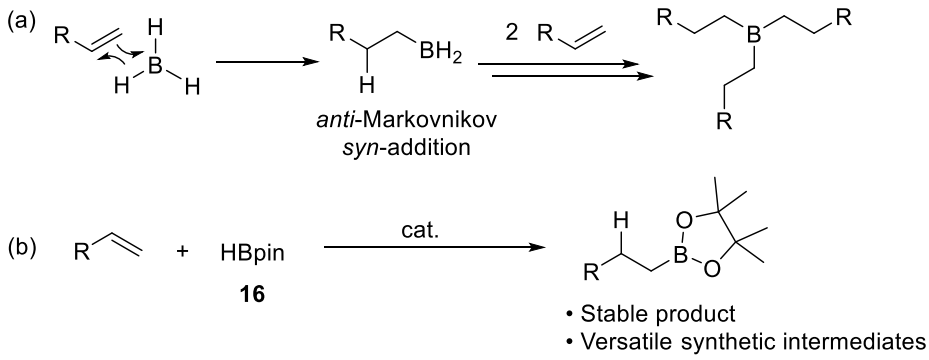
Scheme 2.01 The switchable properties between electrophilic and nucleophlic of organoboranes

Organoboranes can be used in a wide range of organic transformations, including oxidation to alcohols and peroxides,[107] protonolysis, the generation of alkyl and aryl radicals,[108-110] direct amination reactions,[111] homologation reactions[112] and protodeboronation (Scheme 2.02).[113] Perhaps mostly importanly, oraganoboranes are widely used as pro-nucleophilies in Suzuki-Miyaura cross-coupling reacions.[95] The palladium-catalysed Suzuki-Miyaura coupling reaction between aryl boronic acid derivatives and aryl halides has become one of the most significant accomplishments in homogenous catalysis, which has been recognised by the 2010 Nobel Prize in Chemistry.[114] This ubiquitous reaction has found wide applications in the large-scale synthesis of many bulk chemicals, fine chemicals, agrochemicals and pharmaceutials.[115]



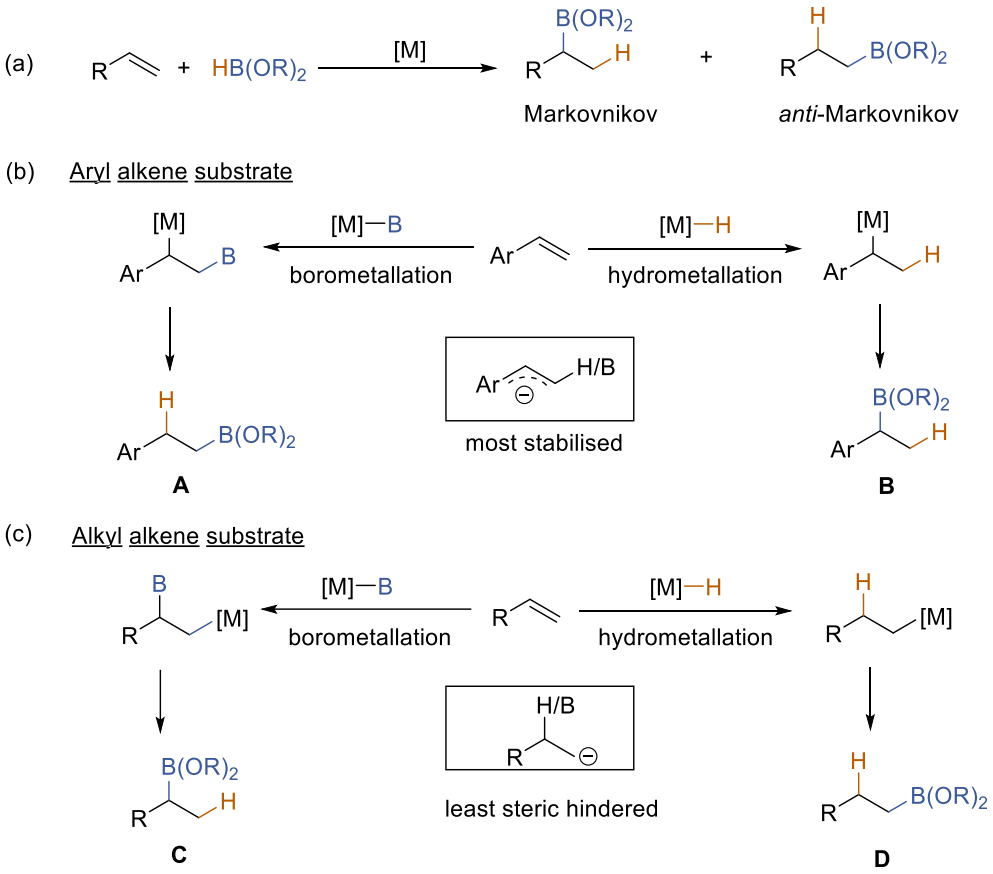
Scheme 2.02 Selected synthetic transformations of organoboranes.

Alkene hydroboration refers to the addition of H-B bond across a carbon-carbon double bond and it is a powerful strategy for the introduction of boron to organic molecules. Hydroboration is also a member of the family of hydrofunctionalisation reactions (Chapter 1). Unlike most electrophilic additions to alkenes, which occur in a stepwise manner through charged intermediates, hydroboration is concerted so that both new bonds are formed at the same time (Scheme 2.03a). With highly reactive boranes such as diborane (B_2H_6), borane-tetrahydrofuran complex ($H_3B{\cdot}THF$) and 9-borabicyclo[3.3.1]nonane (9-BBN), these hydroboration reactions are highly exothermic and typically do not require a catalyst.[116, 117] However, the resulting hydroboration products are unstable and are usually oxidised prior to purification due to the high air and moisture sensitivity of the borane intermediates. The synthesis of bench-stable and isolable hydroboration products requires the use of boronic ester reagents. Pinacolborane **16**, a reagent capable of performing transition metal-catalysed hydroboration reactions for the preparation of alkyl boronic esters, which are compatible with purifications such as flash chromatography and distillation (Scheme 2.03b).[118, 119]



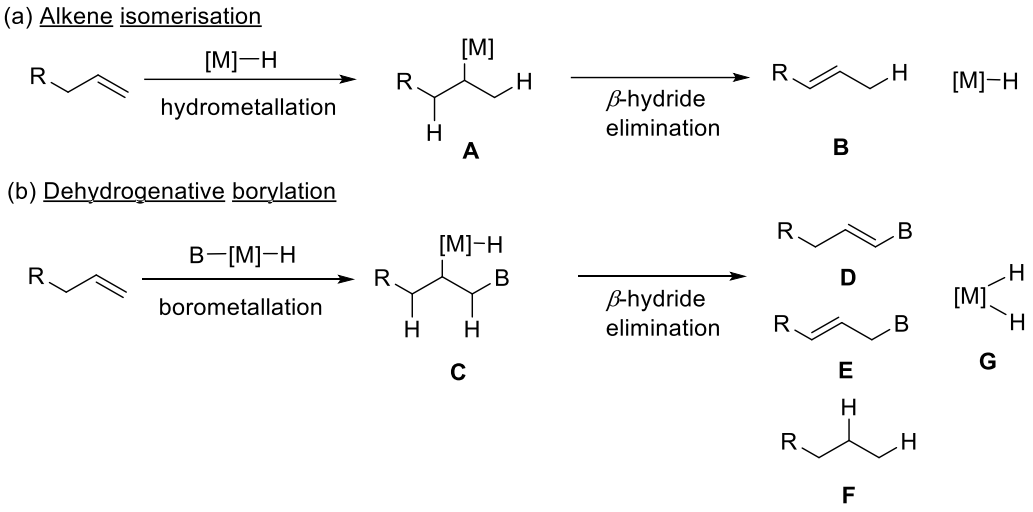
Scheme 2.03 (a) Mechanism for uncatalysed alkene hydroboration using BH_3 (b) Catalytic alkene hydroboration reaction using pinacolborane **16**

Alkene hydroboration reactions can proceed with either *anti*-Markovnikov or Markovnikov selectivity (Scheme 2.04a). The crucial step for determining product regioselectivity is the selectivity between hydrometallation and borometallation to generate an alkylmetal intermediate. The regioselectivity in forming the alkylmetal intermediate has a dependence on substrate. Substrates where an alkylanion can be stabilised, such as arylalkenes, have a selectivity for forming the alkylanion at an electronically stabilised benzylic position, which give product **A** and **B** (Scheme 2.04b). Alkyl alkenes are more likely to generate alkyl intermediate at the least sterically hindered position, as primary alkyl organometallic reagents are more stable than secondary alkyl organometallic reagents, giving product **C** and **D** (Scheme 2.04c). Therefore, the regioselectivity of alkene hydroboration is determined by two factors. One is the regioselectivity of metalation step which is dependent on substrate, and the other is the selectivity for hydrometallation or borometallation which is dependent on hydroboration reagent and catalyst properties.



Scheme 2.04 (a) Markovnikov-selective and *anti*-Markovnikov-selective alkene hydroboration (b) Selectivity for the formation of alkylmetal intermediates leads to product selectivity in aryl alkene substrates (c) Selectivity for the formation of alkylmetal intermediates leads to product selectivity in alkyl alkene substrates

Even though a large number of catalysts have shown excellent yield and selectivity for alkene hydroboration, side reactions can also be observed. Alkene isomerisation product **B** can occur by β-hydride elimination from the alkyl-metal intermediate **A** (Scheme 2.05a). β-hydride elimination from the alkyl-metal intermediate **C** gives the dehydrogenative borylation product; alkenylboron species **D** or allylicboron species **E** along with a stoichiometric quantity of a dihydrometal species **G**. The dihydrometal species **G** is an active catalyst in hydrogenation reactions, indicating that dehydrogenative borylation products are possibly accompanied by hydrogenation product **F** (Scheme 2.05b).



Scheme 2.05 Potential side reaction: (a) Alkene isomerisation to generate internal alkenes from terminal alkenes (b) Dehydrogenative borylation to give alkeneylboron, allylicboron products and hydrogenation product.

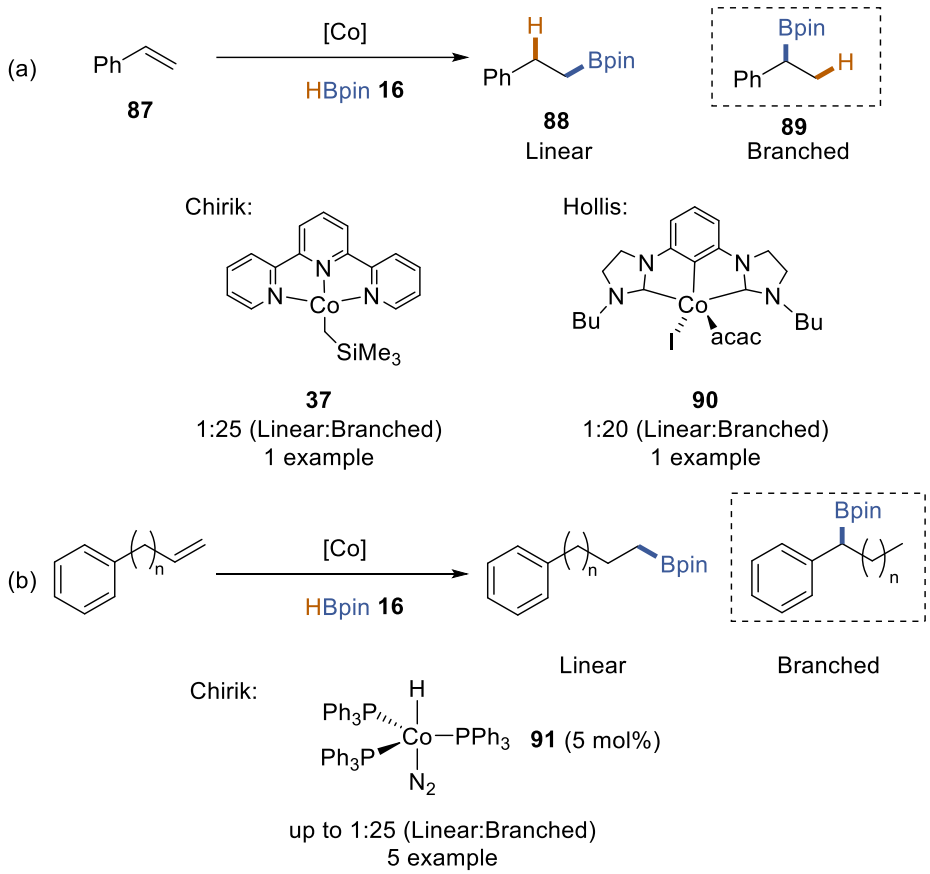
2.1.2 Markovnikov Selective Hydroboration of Alkenes

The majority of metal-catalysed alkene hydroboration reactions involve complexes of late transition metals, such as rhodium, palladium and ruthenium.[120-122] Although high chemoselectivity, regioselectivity and enantioselectivity can be achieved, the low abundance and environmental concerns associated with these metals has driven investigations into Earth-abundant metal alternatives.

In recent years, a number of examples of cobalt-catalysed alkene hydroboration have been reported (Section 1.3). These reactions have been achieved using either well-defined low oxidation state complexes or *in situ* activation of cobalt(II) pre-catalysts using external activating reagents. In most cases, these reactions are either highly *anti*-Markovnikov selective or give a mixture of both Markovnikov and *anti*-Markovnikov products.[49, 56, 60, 66, 68, 70, 71] There

are very few examples of cobalt-catalysed alkene hydroboration with Markovnikov selectivity.[66, 123, 124]

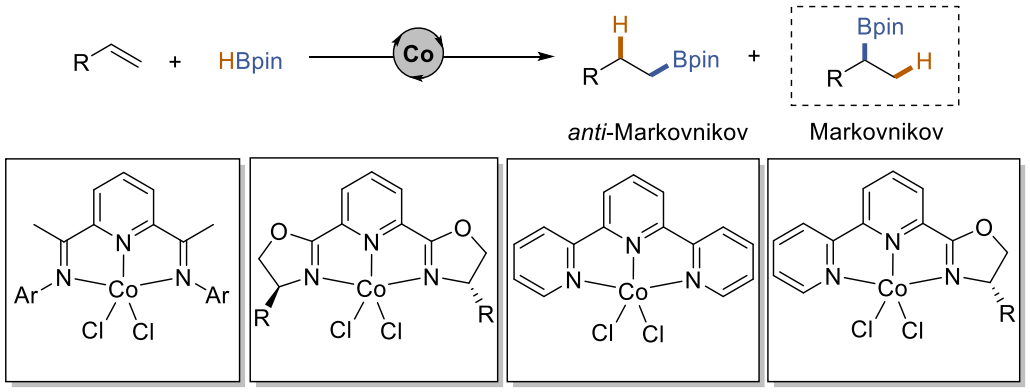
Chirik showed that terpyridine cobalt(I) methylene trimethylsilane was effective for Markovnikov selective hydroboration of styrene **87** with a 25:1 ratio of branched **88** to linear product **89**.[66] Hollis also demonstrated that an air stable CCC-NHC pincer cobalt complex was selective for the formation of Markovnikov product in the hydroboration of styrene **87**, and the highest Markovnikov:*anti*-Markovnikov selectivity was 20:1 (Scheme 2.06a).[123] Isomerisation–hydroboration using cobalt catalyst **91** has also been reported by Chirik, which served as an orthogonal procedure for the generation of branched boronic esters from aliphatic terminal alkenes, with a 25:1 ratio branched to linear product (Scheme 2.06b).[124]



Scheme 2.06 State-of-the-art cobalt-catalysed Markovnikov selective cobalt-catalysed hydroboration of alkenes: (a) Markovnikov hydroboration of styrene **87** using Chirik's and Hollis' cobalt complexes (b) Isomerisation–hydroboration of terminal alkene to give branched boronic esters using Chirik's cobalt complex

2.2 Project Aims

At the outset of the project, there was no general reaction protocol with broad scope using a cobalt catalyst for the direct Markovnikov selective hydroboration of alkenes. This project aimed to build upon the previously developed cobalt-catalysed *anti*-Markovnikov selective alkene hydroboration (Chapter 1) and develop a novel methodology for the cobalt-catalysed Markovnikov selective hydroboration of alkenes, which would proceed under simple reaction conditions, with easily handled reagents and without the need for organometallic activators. We focused on screening a series of cobalt complexes for alkene hydroboration and *in situ* activating reagents (Scheme 2.07).



Scheme 2.07 Overview of the cobalt-catalysed hydroboration of alkenes with potential pre-catalysts

2.3 Results and Discussion

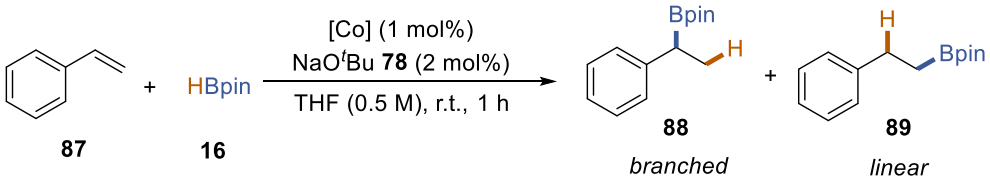
2.3.1 Methodology and Development

2.3.1.1 Initial Results and Optimisation

The sodium *tert*-butoxide activation method has successfully been used for the activation of a series of cobalt(II) pre-catalysts for alkene hydrofunctionalisation reactions.[93] Given the established reactivity in anhydrous THF for *anti*-Markovnikov selective hydroboration reactions using bis(imino)pyridine cobalt(II) dichloride complexes, these conditions could also be tested for Markovnikov selective hydroboration of vinylarenes.

Chirik reported that the *N*-aryl substituents on bis(imino)pyridine ligands had a profound impact on the activity and selectivity of the pre-catalyst.[48, 125] Initial studies focused on the hydroboration of styrene **87** with pinacolborane **16** (1.1 equiv.) using a range of sterically differentiated cobalt complexes (1 mol%, **92**-**96**) and sodium *tert*-butoxide **78** (2 mol%) as the *in situ* activator in anhydrous THF at room temperature (Table 2.01). All the bis(imino)pyridine cobalt(II) pre-catalysts (**92**-**96**) that were tested showed good reactivity, giving moderate to high yield of a mixture of both branched and linear products (Entry 1-5). A general trend showed that bis(imino)pyridine ligands bearing sterically hindered *N*-aryl substituents showed higher selectivity for the branched product. The *N*-*iso*propylsubstituted pre-catalyst $^{i\text{Pr}}$BIPCoCl$_2$ **96** gave the best selectivity for branched product. Terpyridine cobalt(II) dichloride TerpyCoCl$_2$ **97** was also assessed for the hydroboration of styrene **87** and it gave the hydroboration product in moderate yield, with 88:12 branched:linear selectivity (Entry 6). Cobalt complexes bearing pyridine bis(oxazoline) ligands were also investigated. Hydroboration of styrene **87** using $^{\text{Ph}}$PyBOXCoCl$_2$ **98** and $^{i\text{Pr}}$PyBOXCoCl$_2$ **99** gave the product in moderate yield and with 65:35 and 70:30 branched:linear regioselectivity, respectively (Entry 7-8). These results presented the possibility of conducting an enantioselective hydroboration of styrene **87**.

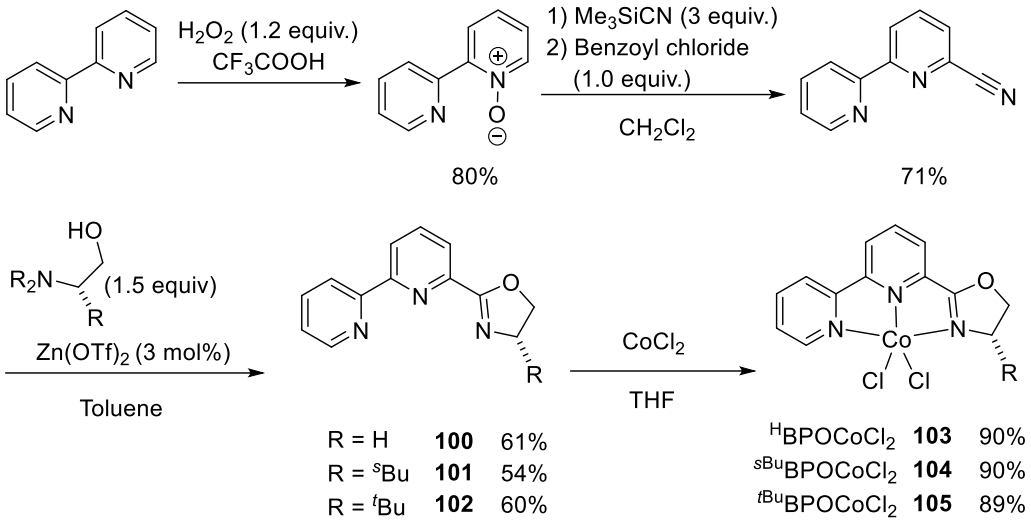
Table 2.01 Screening of ligands for the hydroboration of styrene[a]



Entry	Catalyst	Concentration	Yield[b] (%)	Branched:Linear
1	$_{H}$BIPCoCl$_2$ **92**	0.5 M	40	30:70
2	$_{Me}$BIPCoCl$_2$ **93**	0.5 M	76	28:72
3	$_{Et}$BIPCoCl$_2$ **94**	0.5 M	92	10:90
4	$_{Mes}$BIPCoCl$_2$ **95**	0.5 M	84	40:60
5	$_{iPr}$BIPCoCl$_2$ **96**	0.5 M	89	54:46
6[c]	TerpyCoCl$_2$ **97**	0.5 M	62	88:12
7[d]	$_{Ph}$PyBOXCoCl$_2$ **98**	0.5 M	45	68:32
8[e]	$_{iPr}$PyBOXCoCl$_2$ **99**	0.5 M	39	70:20

[a] Reaction conditions: Styrene **87** (0.5 mmol), HBpin **16** (1.1 mmol), [Co] (1 mol%), NaO$_t$Bu **78** (2 mol%), anhydrous THF (1 mL), room temperature is 20 °C, 1 h. [b] NMR yield determined by $_1$H NMR of crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard. [c] 10% hydrogenation product observed. [d] 35% hydrogenation product observed. [e] 40% hydrogenation product observed.

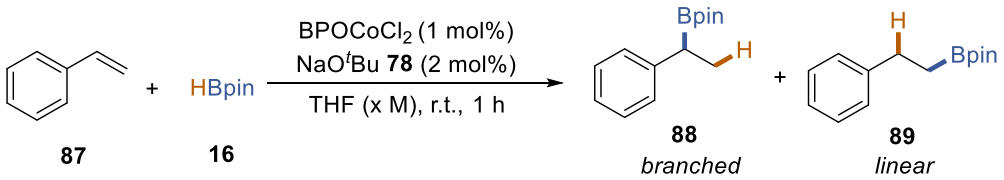
It was shown that terpyridine and bis(oxazoline) cobalt(II) complexes were relatively effective at producing the Markovnikov hydroboration product **88**, and therefore we focused on the synthesis of novel bipyridyl-oxazoline ligands (**100**-**102**). Reaction of 2,2′-bipyridine with hydrogen peroxide and trifluoroacetic acid gave 2,2′-bipyridine-1-oxide, which was reacted with trimethylsilyl cyanide and benzoyl chloride to give the bipyridyl-carbonitrile compound.[126] Condensation of the bipyridyl-carbonitrile with various enantiopure amino alcohols in the presence of Zn(OTf)$_2$ produced the bipyridyl-oxazoline ligands **100**-**102** in good yields.[61] The neutral bipyridyl–oxazoline cobalt(II) dichloride complexes **103**-**105** were formed in high yield by the addition of the corresponding ligand to anhydrous cobalt dichloride in anhydrous THF (Scheme 2.08). These cobalt complexes showed paramagnetically broadened and shifted resonances in the $_1$H NMR spectra.



Scheme 2.08 Preparation of bipyridyl-oxazoline cobalt(II) dichloride complexes

Investigations focused on the hydroboration of styrene **87** with pinacolborane **16** (1.1 equiv.) using a range of bipyridyl-oxazoline cobalt(II) pre-catalysts (1 mol%, **103**-**105**) and sodium *tert*-butoxide **78** (2 mol%) as the *in situ* activator in anhydrous THF at room temperature (Table 2.02). Hydroboration of styrene **87** using $_{H}$BPOCoCl$_2$ **103** and $_{sBu}$BPOCoCl$_2$ **104** gave the branched hydroboration product in good yield, with 70:30 and 82:18 branched:linear regioselectivity, respectively (Entry 1-2). When the more bulky $_{tBu}$BPOCoCl$_2$ **105** was used, hydroboration of styrene **87** proceeded in excellent yield and with 95:5 branched:linear regioselectivity (Entry 3). Reaction concentration investigations showed that a low reaction concentration gave a slight increase in the regioselectivity and yield (Entry 4-6). Increasing reaction concentration to 1 M gave both decreased yield and decreased Markovnikov regioselectivity (Entry 7). It was found that a dilute reaction concentration of 0.16 M was optimal for the hydroboration of styrene using $_{tBu}$BPOCoCl$_2$ **105**, giving the highest yield and Markovnikov regioselectivity (97:3).

Table 2.02 Screening of bipyridyl-oxazoline cobalt(II) pre-catalysts and reaction concentration for the hydroboration of styrene **87**[a]

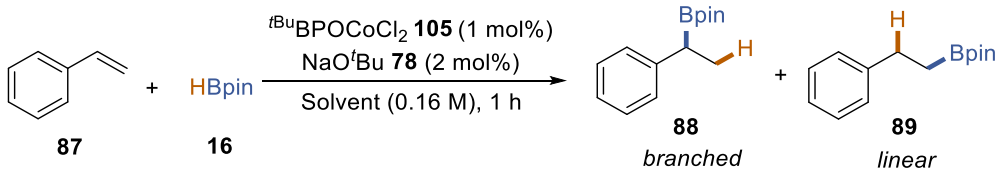


Entry	Catalyst	Concentration (M)	Yield[b] (%)	Branched:Linear
1	$_{H}$BPOCoCl$_2$ **103**	0.5	70	70:30
2	$_{s\mathrm{Bu}}$BPOCoCl$_2$ **104**	0.5	81	82:18
3	$_{t\mathrm{Bu}}$BPOCoCl$_2$ **105**	0.5	86	95:5
4	$_{t\mathrm{Bu}}$BPOCoCl$_2$ **105**	0.25	89	97:3
5	$_{t\mathrm{Bu}}$BPOCoCl$_2$ **105**	0.16	97	97:3
6	$_{t\mathrm{Bu}}$BPOCoCl$_2$ **105**	0.12	91	97:3
7	$_{t\mathrm{Bu}}$BPOCoCl$_2$ **105**	1	75	92:8

[a] Reaction conditions: Styrene **87** (0.5 mmol), HBpin **16** (1.1 mmol), [Co] (1 mol%), NaO$_t$Bu (2 mol%), anhydrous THF (X mL), room temperature is 20 °C, 1 h. [b] NMR yield determined by $_1$H NMR of crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard.

A screen of reaction solvent, temperature and catalyst loading for the hydroboration of styrene **87** with pinacolborane **16** was performed (Table 2.03) Except where otherwise mentioned, all solvents were either purchased in an anhydrous and degassed condition or obtained from a solvent purification system. No solvent was found to give a higher yield or Markovnikov regioselectivity than anhydrous THF under these conditions (Entry 1-7). Non-purified reagent grade THF showed slightly diminished yield (Entry 8), indicating that the reaction intermediate generated was possibly sensitive either to air and moisture or to the stabilisers and impurities present in commercially available THF. Increasing the reaction temperature to 40 °C, 60 °C and 80 °C gave a decreased yield of 64%, 37% and 11% respectively, possibly owing to catalyst decomposition at higher temperatures (Entry 9-11). By reducing the catalyst loading to 0.5 mol%, the yield was also reduced to 84% (Entry 12). Increasing the catalyst loading to 2 mol% and 5 mol% had only a small impact on the yield, with 92% and 96% yield of the product being obtained respectively and Markovnikov regioselectivity being unchanged (Entry 13-14).

Table 2.03 Screening of reaction solvent, temperature and catalyst loadings for the hydroboration of styrene **87**[a]



87 **16** **88** *branched* **89** *linear*

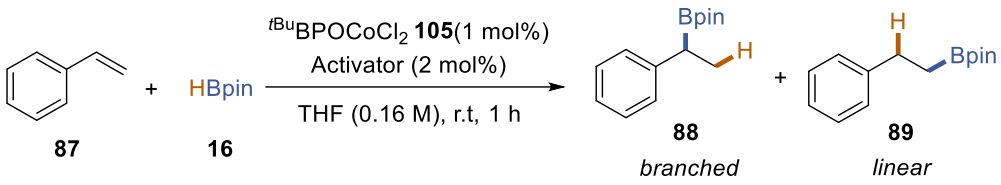
Entry	Catalyst Loading (mol%)	Solvent	Temp. (°C)	Yield[b] (%)	Branched:Linear
1	1	THF	20	97	97:3
2	1	Et_2O	20	59	80:20
3	1	DCM	20	0	*n.d*
4[c]	1	MTBE	20	40	90:10
5	1	Toluene	20	95	95:5
6	1	EtOAc	20	77	96:4
7	1	MeCN	20	0	*n.d*
8	1	THF[d]	20	82	97:3
9	1	THF	40	64	95:5
10	1	THF	60	37	90:10
11	1	THF	80	11	*n.d*
12	0.5	THF	20	84	97:3
13	2	THF	20	92	97:3
14	5	THF	20	96	97:3

[a] Reaction conditions: Styrene **87** (0.5 mmol), HBpin **16** (1.1 mmol), $_{t\text{Bu}}$BPOCoCl$_2$ **105** (1 mol%), activator (2 mol%), solvent (3 mL), room temperature is 20 °C, 1 h. [b] NMR yield determined by $_1$H NMR of crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard. [c] 8% hydrogenation product observed. [d] Reagent-grade THF not dried or degassed

A screen of activating reagents for the hydroboration of styrene with pinacolborane **16** was performed (Table 2.04). Using lithium *tert*-butoxide gave the branched boronic ester in low yield (Entry 2). Using potassium *tert*-butoxide showed comparable reactivity to that of sodium *tert*-butoxide **78**, giving 88% yield of the product and 97:3 branched:linear regioselectivity (Entry 3). Cobalt(II) pre-catalyst activation *in situ* with ethylmagnesium bromide, *n*-butyllithium and sodium triethylborohydride all gave lower yields and regioselectivities compared to the activation using sodium *tert*-butoxide **78** (Entry 4-6). The reaction initiated by sodium methoxide and sodium phenylmethanolate showed low activity for the hydroboration of styrene **87**, giving trace yield of branched boronic ester product (Entry 7-8). Interestingly sodium carbonate also initiated catalysis to give a low yield of the hydroboration product (Entry 9). Unfortunately, Hünig's base[90] was not effective for the activation of

cobalt(II) dichloride pre-catalyst **105** (Entry 10). According to results from activating reagents screening, sodium *tert*-butoxide gave the best yield and Markovnikov selectivity and therefore was used for further reactions.

Table 2.04 Screening of the activating reagent for the hydroboration of styrene **87**[a]



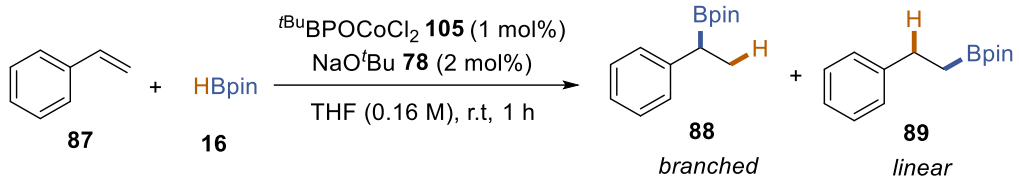
Entry	Activating reagent	Yield[b] (%)	Branched:Linear
1	NaO*t*Bu	97	97:3
2	LiO*t*Bu	9	*n.d*
3	KO*t*Bu	88	97:3
4	EtMgBr	85	90:10
5	*n*-BuLi	54	88:12
6	$NaHBEt_3$	63[c]	86:14
7	NaOMe	<5	*n.d*
8	NaOBn	<5	*n.d*
9	Na_2CO_3	10	*n.d*
10	$(iPr)_2NEt$	0	*n.d*

[a] Reaction conditions: Styrene **87** (0.5 mmol), HBpin **16** (1.1 mmol), $_{t\text{Bu}}$BPOCoCl$_2$ **105** (1 mol%), activating reagent (2 mol%), anhydrous THF (3 mL), room temperature is 20 °C, 1 h. [b] NMR yield determined by $_1$H NMR of crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard. [c] 5% hydrogenation product observed.

2.3.1.2 Control Reactions

Control reactions were also performed to ensure the validity of the methodology (Table 2.05). The hydroboration of styrene **87** gave the secondary boronic ester **88** in excellent yield, and a 97:3 branched:linear selectivity, using $_{t\text{Bu}}$BPOCoCl$_2$ **105** (1 mol%), sodium *tert*-butoxide **78** (2 mol%) and pinacolborane **16** (Entry 1). A reaction using non-ligated anhydrous cobalt(II) dichloride under the initial reaction conditions, showed no catalytic activity (Entry 2). Similarly, the reaction did not proceed in the absence of the cobalt(II) pre-catalyst **105** or without added sodium *tert*-butoxide **78** (Entry 3-4). These results indicates both cobalt(II) pre-catalyst **105** and sodium *tert*-butoxide **78** are critical to the success of the reaction.

Table 2.05 Control reactions[a]



Entry	Catalyst	Activating Reagent	Yield[b] (%)	Branched:Linear
1	$_{t\text{Bu}}$BPOCoCl$_2$ **105**	NaOtBu	97	97:3
2	CoCl$_2$	NaOtBu	0	*n.d*
3	$_{t\text{Bu}}$BPOCoCl$_2$ **105**	-	3	*n.d*
4	-	NaOtBu	0	*n.d*

[a] Reaction conditions: Styrene **87** (0.5 mmol), HBpin **16** (1.1 mmol), $_{t\text{Bu}}$BPOCoCl$_2$ **105** (1 mol%), NaOtBu (2 mol%), anhydrous THF (3 mL), room temperature is 20 °C, 1 h. [b] NMR yield determined by $_1$H NMR of crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard.

A large number of alkene hydroboration reactions have been reported using second- and third-row transition metal catalyst, such as ruthenium, rhodium and palladium.[120-122] Trace metals contained within the cobalt complex, activator or alkene would possibly have an effect on the reaction outcome or even dominate it, and therefore analytical techniques should be applied for identifying or quantifying trace metal impurities in the reagents.[127]

The ICP-MS technique was used to analyse the quantity of trace metal contaminants, which has a sensitivity of ppb concentration for metal contaminants. The standard reaction used included: styrene **87** (0.5 mmol), pinacolborane **16** (0.55 mmol), $_{t\text{Bu}}$BPOCoCl$_2$ **105** (1 mol%) and NaOtBu **78** (2 mol%). A portion of the reaction mixture was analysed by ICP-MS and the concentrations of trace elements determined by comparison against a standard solution (Table 2.06, *ICP-Ms analysis performed and data provided by Dr Lorna Eades*). These results showed the concentration of these late transition metals in the reaction mixture was dramatically lower than the concentration of cobalt catalyst. Taken together with previous control reactions (Table 2.05), this implied that the reactivity observed was the result of successful reduction of $_{t\text{Bu}}$BPOCoCl$_2$ **105** with sodium *tert*-butoxide **78** and not related to trace metal contaminants.

Table 2.06 ICP-MS analysis of cobalt-catalysed hydroboration of styrene **87**[a]

Element	Mass	Concentration (ppb)	Relative to Co
Al	29	4.100	2.09×10^{-3}
Mn	55	1.400	7.16×10^{-4}
Fe	57	0.200	1.02×10^{-4}
Co	59	1955	1.00
Ni	60	1.900	9.71×10^{-4}
Cu	63	0.323	1.65×10^{-4}
Ru	101	0.003	1.53×10^{-6}
Rh	103	0.009	4.60×10^{-6}
Pd	105	0.008	4.09×10^{-6}
Ag	107	0.015	7.67×10^{-6}
Ir	193	0.021	1.07×10^{-5}
Pt	195	0.007	3.58×10^{-6}
Au	197	0.002	1.02×10^{-6}

[a] Nitric acid (1 mL, Conc.) Aristar ultra high purity was carefully added dropwise to a mixture of styrene **87** (0.5 mmol), HBpin **16** (0.55 mol), $_{t\text{Bu}}$BPOCoCl$_2$ **105** (1 mol%) and NaO*t*Bu **78** (2 mol%). Water (9 mL, ultrapure) was added to the mixture and a 1 mL portion was diluted to a total volume of 10 mL. Analysis of the resulting solution was performed using an Agilent 7500ce ICP-MS calibrated against a multi-element standard solution.

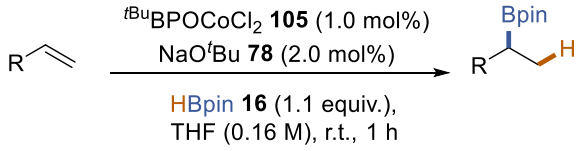
2.3.2 Substrate Scope

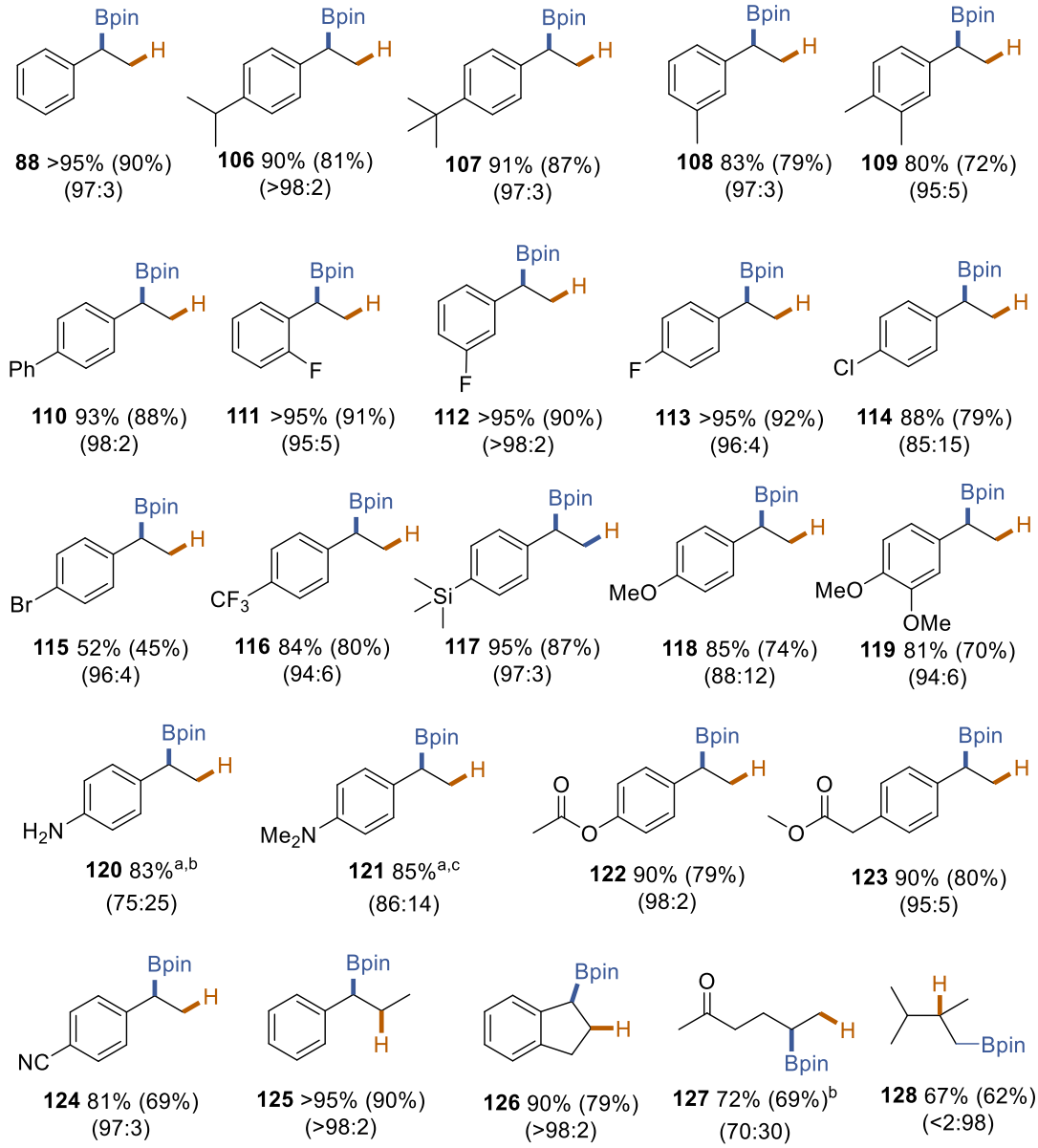
Using the optimised reaction conditions, the substrate scope of the Markovnikov selective hydroboration was explored using a range of electronically and sterically differentiated styrene derivatives, BPOCoCl$_2$ **105** (1 mol%), sodium *tert*-butoxide **78** (2 mol%) and pinacolborane **16** (1.1 equiv.) (Table 2.07).

Hydroboration of styrene **87** gave the secondary boronic ester in excellent isolated yield, and a 97:3 branched:linear selectivity (**88**, 90%) under optimised reaction conditions. Styrene derivatives bearing electron-donating groups such as *iso*-propyl, *tert*-butyl and methyl underwent successful hydroboration in excellent yield and regioselectivity (**106**-**109**, 72-87%). 4-Phenylstyrene gave the secondary boronic ester in good yield and regioselectivity (**110**, 88%). Styrene derivatives bearing electron-withdrawing substituents including fluoro-, chloro-, bromo- and trifluoromethyl groups also underwent successful hydroboration, giving the secondary boronic esters in moderate to excellent yields, with no cleavage of aryl-halide bond observed (**111**-**116**, 79-92%).[128, 129] Styrene derivatives bearing trialkylsilyl- and ether substituents also underwent successful hydroboration in good yields and selectivity to give the branched boronic esters (**117**-**119**, 70-87%). Hydroboration of primary and tertiary amine

substituted substrate both gave the secondary boronic ester in good regioselectivity and yield (**120**-**121**, 83-85%). Styrene derivatives containing more than one unsaturated group, such as ester and nitrile substituents, underwent chemoselective hydroboration at the alkene in excellent yield and regioselectivity, with no observed carbon-oxygen or carbon-nitrogen bond cleavage, or reduction (**122**-**124**, 69-80%).[130] Styrene derivatives bearing substituents at the *β*-position, such as *trans*-β-methylstyrene and indene were reactive under the developed conditions, giving the branched boronic esters with complete control of regioselectivity and in excellent yield (**125**-**126,** 79-90%). For an alkyl alkene, 5-hexen-2-one successfully gave the branched boronic ester in both moderate yield and regioselectivity, without ketone reduction (**127**, 69%). Hydroboration of 2,3-dimethyl-1-butene gave the linear boronic ester **128** in good yield. Presumably the increased steric bulk of the 1,1-disubtituted alkene led to the formation of the *anti*-Markovnikov regioisomer.

Table 2.07 Substrate scope of cobalt-catalysed Markovnikov selective hydroboration of styrene derivatives



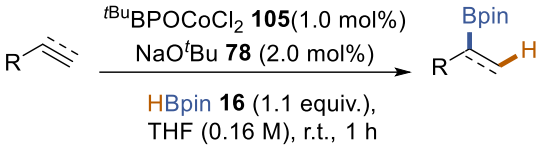


88 >95% (90%) (97:3)
106 90% (81%) (>98:2)
107 91% (87%) (97:3)
108 83% (79%) (97:3)
109 80% (72%) (95:5)
110 93% (88%) (98:2)
111 >95% (91%) (95:5)
112 >95% (90%) (>98:2)
113 >95% (92%) (96:4)
114 88% (79%) (85:15)
115 52% (45%) (96:4)
116 84% (80%) (94:6)
117 95% (87%) (97:3)
118 85% (74%) (88:12)
119 81% (70%) (94:6)
120 83%[a,b] (75:25)
121 85%[a,c] (86:14)
122 90% (79%) (98:2)
123 90% (80%) (95:5)
124 81% (69%) (97:3)
125 >95% (90%) (>98:2)
126 90% (79%) (>98:2)
127 72% (69%)[b] (70:30)
128 67% (62%) (<2:98)

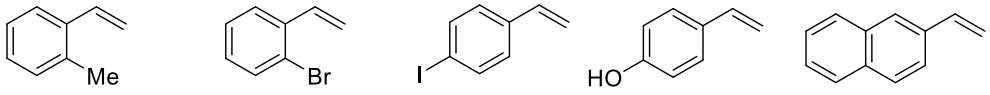
Conditions: alkene (0.5 mmol), HBpin **16** (1.1 equiv.), $_{t\text{Bu}}$BPOCoCl$_2$ **105** (1.0 mol%) and NaOtBu **78** (2.0 mol%) in anhydrous THF (3 mL), room temperature is 20 °C, 1 h. Yield was determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. Isolated yields in parentheses. Branched:linear ratios determined from integrals of product peaks in ^{1}H NMR of crude reaction mixtures. [a] Product decomposed on SiO$_2$. [b] 10% alkene hydrogenation product observed in the crude reaction mixture. [c] 8% Alkene hydrogenation product observed in the crude reaction mixture.

A number of other classes of substrates were also investigated under the optimised reaction conditions (Table 2.08). *ortho*-Substituted styrenes, such as 2-methyl styrene **129** and 2-bromostyrene **130** were not compatible with the optimised reaction conditions, and only a trace amount of product was detected. 4-Iodostyrene **131** did not undergo hydroboration, with some protodeboronation product observed in the crude reaction mixture. The hydroboration of 4-hydroxylstyrene **132** did not procced, leading to complete destruction of starting material. 2-Vinylnaphthalene **133** also proved unreactive, perhaps due to the poor solubility of the vinylarene substrate in THF. Styrene derivatives bearing substituents on the alkenyl group, including α-methylstyrene **134**, α-bromostyrene **135** and and β-methylstyrene **136** were all unreactive, presumably owing to steric bulk proximal to the carbon-carbon double bond. Cyclic styrene derivatives such as benzofuran **137**, thianaphthene **138** and coumarin **139** were tested and they were shown to be unreactive under the reaction conditions. Hydroboration of 3-vinylpyridine **140** and 4-vinylpyridine **141** under reaction conditions led to complete distruction of starting materials. Conjugated 1,3-dienes, myrcene **142** and isoprene **143** gave trace yields of hydroboration product. Phenylacetylene **144** gave an unidentifiable mixture of polymerisation products.

Table 2.08 Unsuccessful cobalt-catalysed Marknovnikov selective hydroboration of alkenes and alkynes

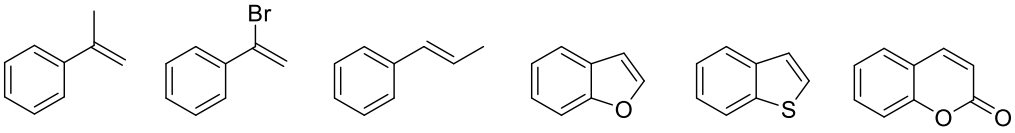


Styene derivatives:



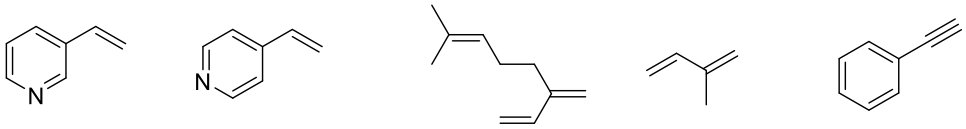
129 trace product | **130** trace product | **131** n.r. | **132** n.r. | **133** n.r.

Substituted styrene derivatives:



134 n.r. | **135** n.r. | **136** n.r. | **137** n.r. | **138** n.r. | **139** n.r.

Vinyl pyridine derivatives: | Conjugated 1,3-dienes | Phenylacetylene:



140 SM destruction | **141** SM destruction | **142** trace product | **143** trace product | **144** polymerisation

Conditions: alkene (0.5 mmol), HBpin **16** (1.1 equiv.), $_{t\text{Bu}}$BPOCoCl$_2$ **105** (1.0 mol%) and NaOtBu **78** (2.0 mol%) in anhydrous THF (3 mL), room temperature is 20 °C, 1h. Yield was determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard.

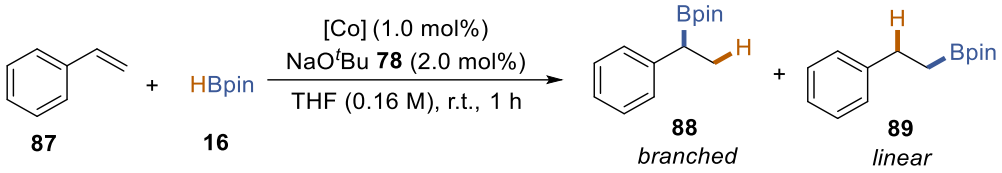
2.3.3 Attempted Enantioselective Reactions

Both Lu and Huang reported that iminopyridine-oxazoline cobalt(II) pre-catalysts were effective for the enantioselective hydroboration of 1,1-disubstituted alkenes.[18, 73] Assuming high yield and regioselectivity for the Markovnikov product could be achieved, we proposed the introduction of chiral units as stereo-directing elements in order to perform an enantioselective Markovnikov hydroboration.

We focused on investigating the ability of enantiopure bipyridine-oxazoline cobalt(II) dichloride to induce enantioselectivity in the Markovnikov selective hydroboration of styrene under the optimised reaction conditions. Hydroboration using $_{t\text{Bu}}$BPOCoCl$_2$ **105** proceeded in excellent yield and with Markovnikov selectivity but unfortunately gave a racemic mixture of

the branched regioisomer (Entry 1). The hydroboration of styrene using $_{s\text{Bu}}$BPOCoCl$_2$ **104**, $_{\text{Ph}}$PyBOXCoCl$_2$ **98** and $_{i\text{Pr}}$PyBOXCoCl$_2$ **99** proceeded in moderate yield and with Markovnikov regioselectivity, but again with extremely low enantiomeric ratios (Entry 2-4). The maximum enantiomeric excess observed was 16%.

Table 2.09 Cobalt-catalysed enantioselective hydroboration and hydrosilylation of styrene **87**[a]



Entry	Catalyst	Yield[b] (%)	Branched:Linear	*e.r.*[c]
1	$_{t\text{Bu}}$BPOCoCl$_2$ **105**	97	97:3	50:50
2	$_{s\text{Bu}}$BPOCoCl$_2$ **104**	87	82:18	45:55
3	$_{\text{Ph}}$PyBOXCoCl$_2$ **98**	52	70:30	47:53
4	$_{i\text{Pr}}$PyBOXCoCl$_2$ **99**	45	75:25	42:58

[a] Reaction conditions: Styrene **87** (0.5 mmol), HBpin **16** (1.1 mmol), [Co] (1 mol%), NaOtBu (2 mol%), THF (3 mL), room temperature is 20 °C, 1h. [b] NMR yield determined by $_1$H NMR of crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard. [c] Determined by HPLC of the secondary alcohol following NaOH/H$_2$O$_2$ oxidation.

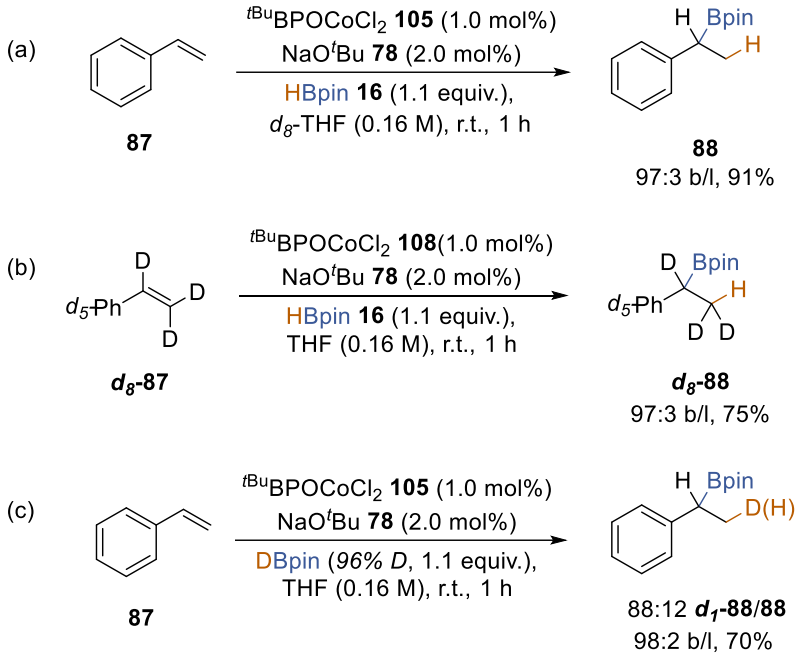
2.3.4 Mechanistic Investigations

2.3.4.1 Deuterium Labelling Experiments

In order to gain insight into the mechanism of the Markovnikov selective hydroboration of vinylarenes with pinacolborane **16**, deuterium labelling experiments were performed.

When the hydroboration of styrene **87** was carried out in d_8-THF, only the fully protio-boronic ester **88** was obtained, indicating that both H and Bpin originate from pinacolborane **16** (Scheme 2.09a). When the hydroboration of d_8-styrene **87** with pinacolborane **16** was performed in THF, the mono-protioboronic ester d_8-**88** was formed exclusively with 'H' at the terminal methyl group (Scheme 2.09b). When DBpin (96%D) was used in the hydroboration of styrene, a mixture of mono-deuterated boronic ester d_1-**88** and fully protio-boronic ester **88** was formed, in a ratio of 88:12 D/H (Scheme 2.09c). The presence of fully protio-boronic ester **88** presumably arises from either β-hydride elimination of an intermediate organo-cobalt species, to generate a cobalt hydride that serves to add 'H' to styrene **87**, or H/D exchange with extraneous water, either present in the reaction medium or on work-up. It should be noted

that we were unable to observe any products of H/D scrambling consistent with this scenario (*e.g.* d_n-styrene **87**) in the crude reaction mixtures, but this may be due to loss of these low boiling point products on work-up.



Scheme 2.09 Deuterium labelling studies of Markovnikov selective styrene hydroboration; isolated yields following flash column chromatography

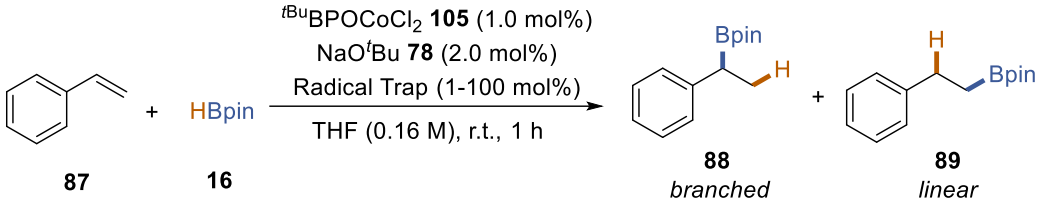
2.3.4.2 Radical Inhibition Experiments

Oxidation of the secondary boronic ester product **88**, followed by chiral HPLC analysis indicated no enantioenrichment of the secondary alcohol product, despite the presence of an enantioenriched bipyridyl-oxazoline ligand. While the lack of any enantioenrichment in the product was likely due to the remoteness of the chiral group on the ligand, it could also indicate that the reaction proceeded through a radical mechanism.

In order to probe a potential radical mechanism, the catalytic hydroboration of styrene **87** with pinacolborane **16** was performed in the presence of different radical traps (Table 2.10). Under the optimised reaction conditions, hydroboration of styrene **87** gave the secondary boronic ester **88** in excellent yield, and a 97:3 branched:linear selectivity (Entry 1). The addition of low amounts of 2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO, 1-2 mol%) had almost no effect on the yield of the product (Entry 2-3). When the amount added was increased to 10 mol% and above, decreased reactivity was observed (Entry 4-5). When 100 mol% TEMPO was added, the reaction was not inhibited, and 21% hydroboration product was observed

(Entry 6). However, the formation of neither styrene-TEMPO nor catalyst-TEMPO adducts was observed. The use of an alternative radical trap gavinoxyl led to complete inhibition of cobalt catalyst activity (Entry 7-11) Although these results suggested that the radical traps were able to quench active radical intermediates, it was also feasible that these radical traps were coordinating to the cobalt catalyst, leading to the decreased catalytic activity. Moreover, it has also been reported that radical traps are able to interact with metal hydride species in reactions which are known to proceed by two-electron processes.[131]

Table 2.10 Cobalt-catalysed Markovnikov selective hydroboration of styrene in the presence of radical traps[a]



Entry	Radical trap	Mol (%)	Yield (%)[b]	Branched:Linear
1	-	-	97	97:3
2	TEMPO	1	90	97:3
3	TEMPO	2	87	97:3
4	TEMPO	10	70	95:5
5	TEMPO	50	44	*n.d*
6	TEMPO	100	21	*n.d*
7	Galvinoxyl	1	0	*n.d*
8	Galvinoxyl	2	0	*n.d*
9	Galvinoxyl	10	0	*n.d*
10	Galvinoxyl	50	0	*n.d*
11	Galvinoxyl	100	0	*n.d*

[a] Reaction conditions: Styrene **87** (0.5 mmol), HBpin **16** (1.1 mmol), $_{t\text{Bu}}$BPOCoCl$_2$ **105** (1 mol%), NaOtBu **78** (2 mol%), anhydrous THF (3 mL), room temperature is 20 °C, 1 h. [b] NMR yield determined by $_1$H NMR of crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard.

2.3.4.3 Proposed Reaction Mechanism

The determination of reaction mechanism and active species for reactions catalysed by low oxidation-state iron and cobalt species remains elusive, even in the case of well-defined low oxidation-state species, where the isolated metal complex is likely an off-cycle intermediate or pre-catalyst rather than the active catalyst.[132]

In the majority of cobalt-catalysed hydrofunctionalisation reactions, either a pre-formed cobalt(I) complex or high oxidation-state cobalt(II) precursor that is reduced *in situ* to form a cobalt(I) species are used. $^{t\text{Bu}}$BPOCoCl$_2$ **105** exhibited paramagnetic ^{1}H NMR behaviour and displayed signals over a wide chemical shift range (Figure 2.01a). A stoichiometric quantity of cobalt complex $^{t\text{Bu}}$BPOCoCl$_2$ **105** was reacted with pinacolborane **16** and sodium *tert*-butoxide **78** (1:2:2 ratio) in anhydrous THF. The reaction mixture turned dark brown quickly and produced a mixture of diamagnetic cobalt species (Figure 2.01b), presumably a low spin d_8 complex. The analogous cobalt(II) and cobalt(0) species would have d_7 and d_9 electronic structures respectively and therefore would exist as paramagnetic complexes. However, the reduced mixture was too messy and was not fully assigned at this stage.

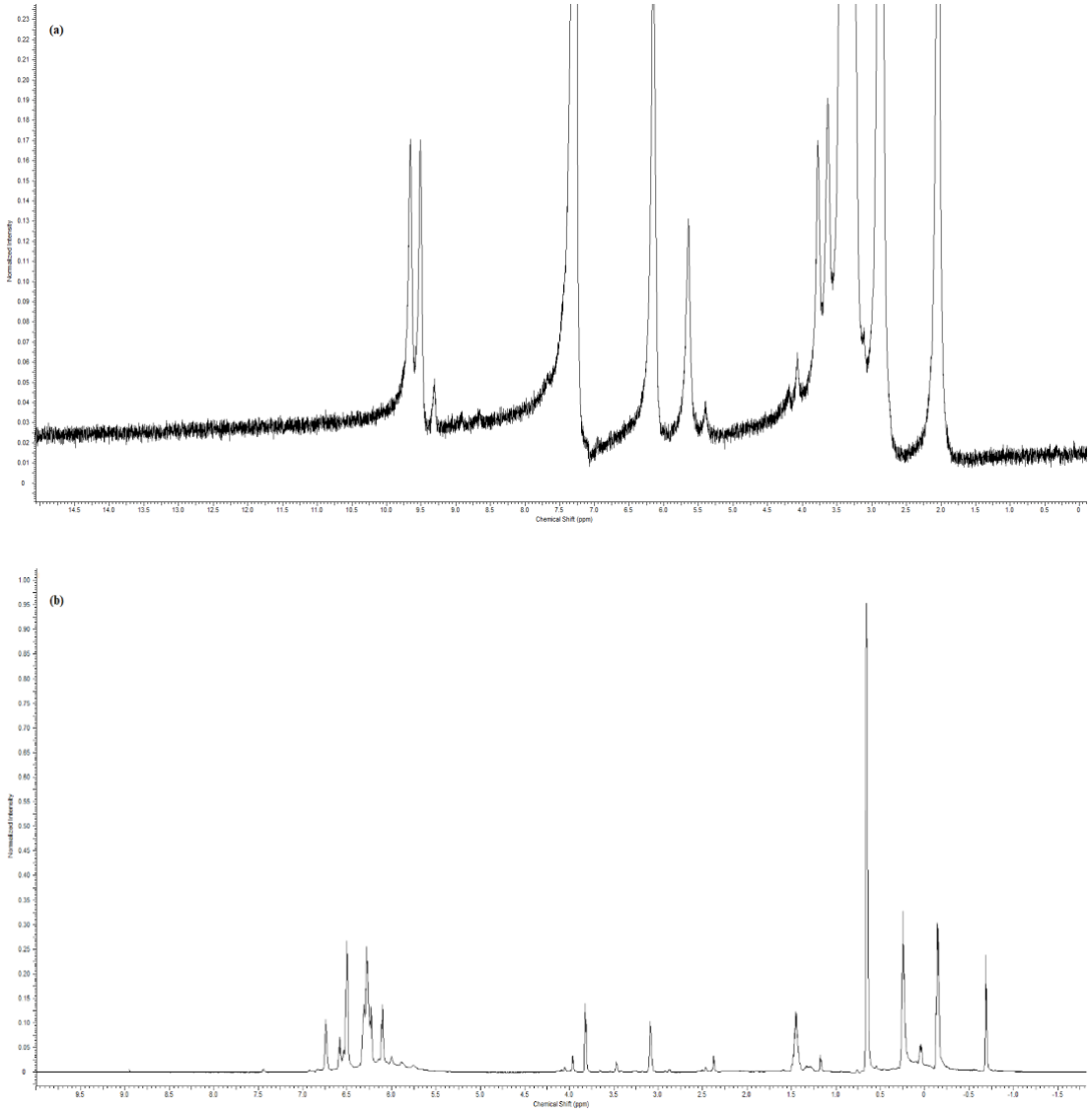
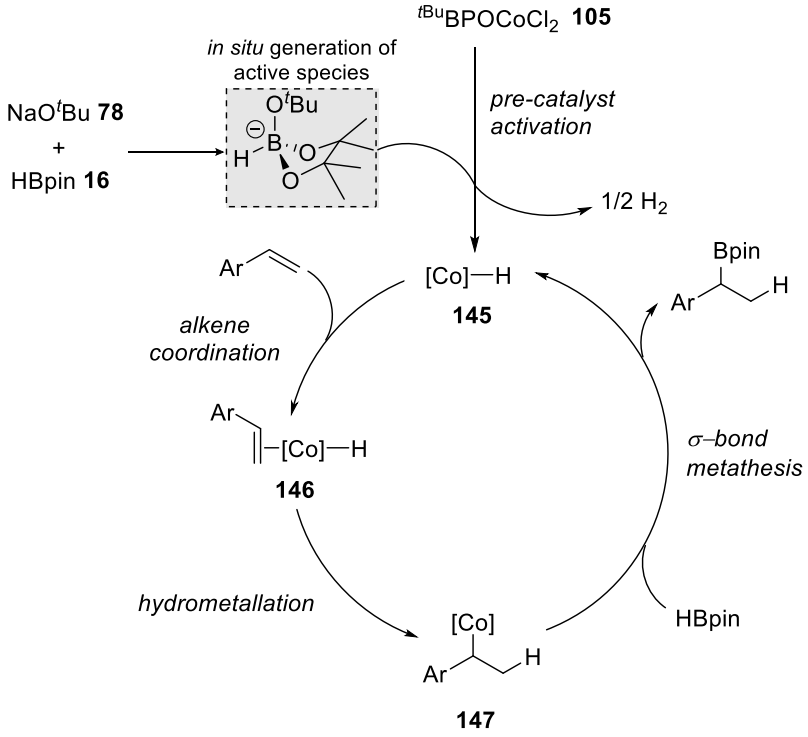


Figure 2.01 (a) $^{t\text{Bu}}$BPOCoCl$_2$ **105** in d_8-THF. (b) Reaction of $^{t\text{Bu}}$BPOCoCl$_2$ **105** with pinacolborane **16** (2 equiv.) and sodium *tert*-butoxide **78** (2 equiv.).

We proposed the Markovnikov selective hydroboration of vinylarenes using $_{t\text{Bu}}$BPOCoCl$_2$ **105**, may proceed by the formation of a boron 'ate' complex, with hydride transfer to the cobalt pre-catalyst followed by reductive elimination of dihydrogen.[93] This would give a low oxidation-state cobalt(I) hydride species **145**. The cobalt(I) hydride species **145** would undergo alkene coordination to give **146** and subsequent hydrometallation to give **147**. The benzylic cobalt species **147** would react with pinacolborane **16** through σ-bond metathesis to give the branched product and regenerate cobalt(I) hydride species **145**, which could participate in another catalytic cycle (Scheme 2.10).

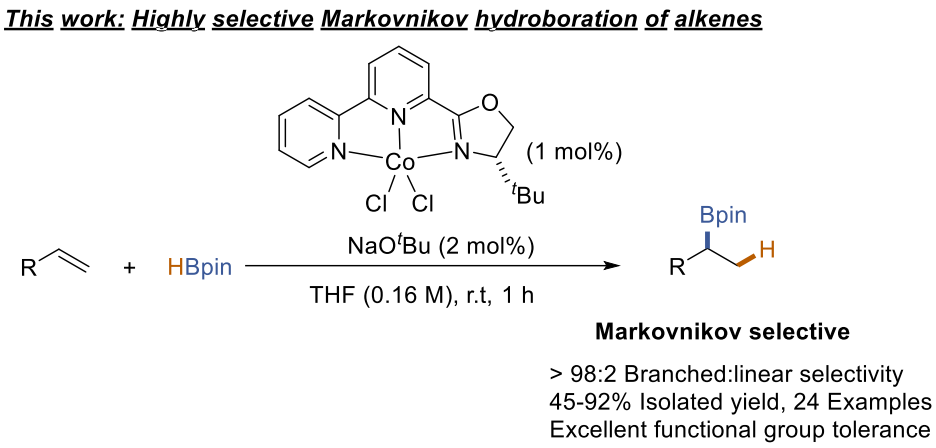


Scheme 2.10 Proposed reaction mechanism for the Markovnikov selective hydroboration of vinylarenes by $_{t\text{Bu}}$BPOCoCl$_2$ **105**.

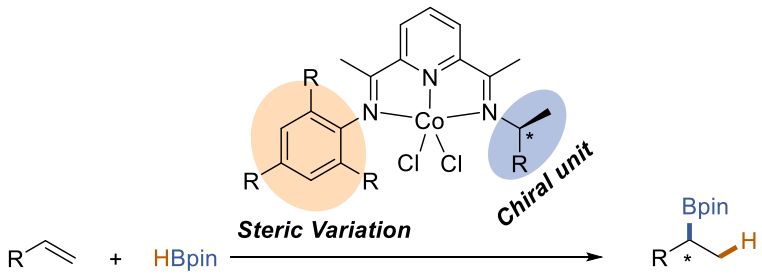
2.4 Conclusions and Future Work

In conclusion, we have developed a Markovnikov selective cobalt-catalysed hydroboration of alkenes with pinacolborane at ambient temperature, using a bench-stable cobalt pre-catalyst bearing a bipyridyl-oxazoline ligand. This strategy has been applied to a variety of electronically and sterically differentiated styrene derivatives, bearing a range of functional groups, to give the secondary boronic esters in both high yields and regioselectivities.

Future work should focus on gaining understanding of the reaction mechanism, allowing modification and refinement of the ligand to further optimise the reaction. The reduced diamagnetic cobalt(I) should be fully characterised by using $_{1}$H and $_{13}$C NMR spectroscopy in combination with COSY, HSQC and HMBC. Further reaction optimisation should be performed to increase substrate scope to include both alkyl alkenes and greater functional group tolerance. Meanwhile, this project has only explored a very small number of possible variants of steric and electronic bulk around bipyridyl-oxazoline ligands and it would be interesting to develop conditions for enantioselective hydroboration of alkenes.



This work has been published in Chemical Communications (*Chem.Comm.*, 2017, **53**, 4276)



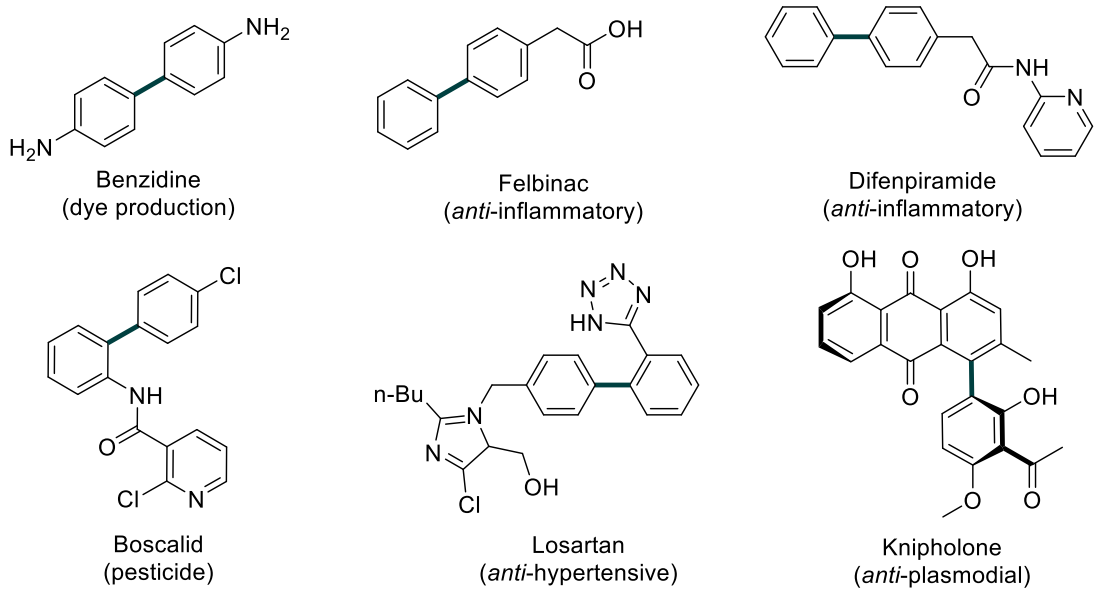
Scheme 2.11 Future work: Enantioselective hydroboration of alkenes

Chapter 3 Manganese-Catalysed Coupling Reactions of Boronic Acids

3.1 State-of-the-Art at the Outset of the Project

3.1.1 General Background

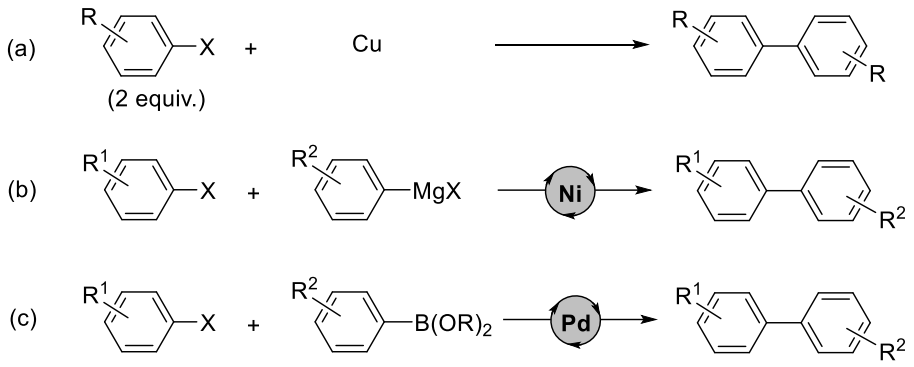
The synthesis of biaryl compounds has been studied for more than a century and is one of the most important tools in modern organic synthesis.[133-135] The versatility and importance of the biaryl scaffold is marked by its occurrence in numerous natural products, bioactive compounds, pharmaceuticals, agrochemicals and ligands (Scheme 3.01)[136, 137]



Scheme 3.01 Selected examples of industrially relevant compounds bearing the biaryl structures.

In general, biaryl compounds have been synthesised using Ullmann coupling reactions, using stoichiometric copper to promote reductive homo-coupling of aryl halides (Scheme 3.02a).[138] The major disadvantage associated with Ullmann homo-coupling is the use of elevated temperatures and poor functional group tolerance. The coupling of Grignard reagents with aryl halide electrophiles (Kumada coupling) has been achieved using several metal catalysts, with nickel catalysts dominating the field (Scheme 3.02b).[139, 140] However, nickel catalysts pose considerable issues due to their acute toxicity, limiting their use for large-scale industrial processes. Alternatively, palladium-catalysed cross-coupling between arylboronic acid derivatives and aryl halides has proved to be a highly versatile strategy for biaryl compound preparation (Scheme 3.02c).[141] Suzuki-Miyaura cross-coupling has become increasingly

popular mainly due to the compatibility with a wide range of functional groups and the extremely low catalyst loadings that can be used. More importantly, and in contrasts to other classes of organometallic coupling partners, boronic acid derivatives are inexpensive, easily prepared and transported.[106]



Scheme 3.02 (a) Ullmann coupling for biaryl compound synthesis. (b) Nickel-catalysed Kumada coupling of aryl halides with aryl Grignard reagents. (c) Palladium-catalysed Suzuki-Miyaura coupling of aryl halides with aryl boronic esters.

Although palladium catalysts are ubiquitous in the Suzuki-Miyaura reactions, the global supply of palladium is highly limited and therefore expensive alongside a high environmental footprint for extraction and purification.[7] Moreover, there are extremely strict regulatory requirements in the pharmaceutical industry to remove palladium to low ppm levels. Therefore, there is a growing impetus to develop novel or orthogonal aryl-aryl coupling strategies with more sustainable Earth-abundant metal alternatives. Iron and manganese are well suited to be potential replacements for palladium due to their relatively low cost, low toxicity and high abundance in the Earth's crust.

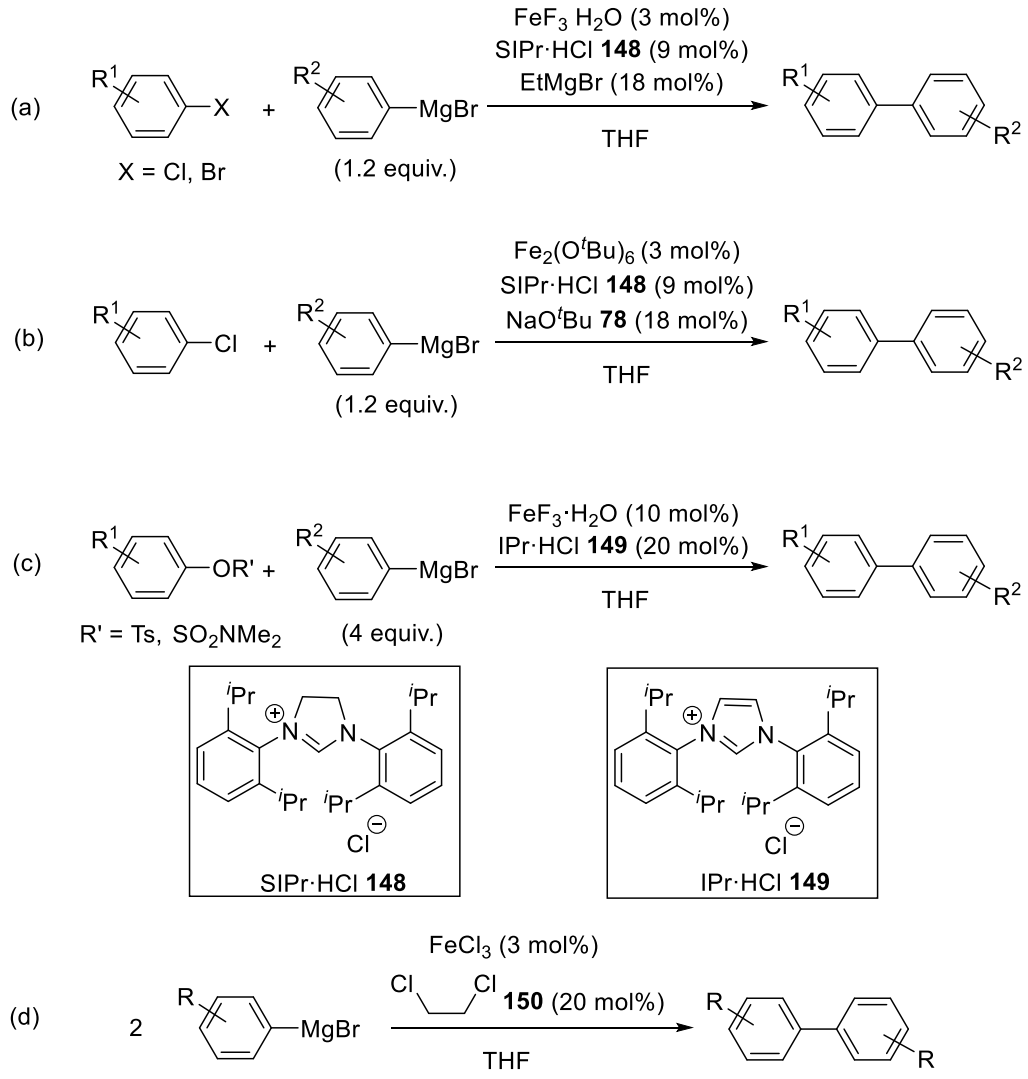
3.1.2 Aryl-Aryl Coupling Reaction Using Iron and Cobalt Catalysts

3.1.2.1 Using Organometallic Reagents

In contrast to palladium-based and nickel-based catalysts, iron and cobalt catalysts for aryl-aryl coupling are relatively uncommon. In recent years, comparatively few examples of Earth-abundant metal-catalysed aryl-aryl coupling reactions have been reported, using aryl Grignard reagents and aryl halides or pseudohalides.[142-147]

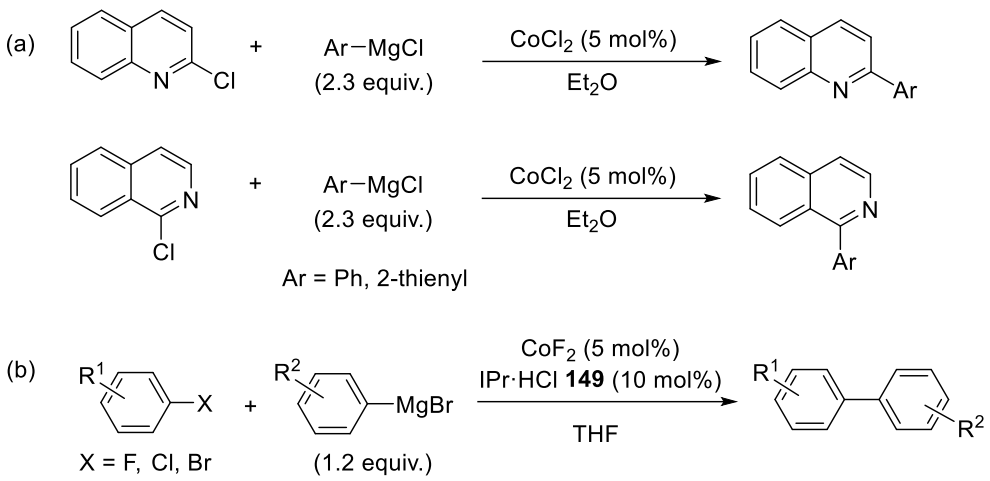
Nakamura reported that an iron(III) trifluoride catalyst supported by an *N*-heterocyclic carbene ligand **148** was effective for the Kumada biaryl coupling reaction (Scheme 3.03a).[142] It was found that the *N*-heterocyclic carbene ligand SIPr·HCl **148** and fluoride counterion were

critical to achieving high yields and selectivity. It was proposed that the fluoride ligands enhanced selectivity for the cross-coupled product by inhibiting the formation of ferrate complexes bearing excess aryl groups that led to the undesired homo-coupled products. Similarly, Duong developed a novel iron(III) alkoxide catalyst system utilising *N*-heterocyclic carbene ligand SIPr·HCl **148** for the cross-coupling of aryl chloride and arylmagnesium bromide (Scheme 3.03b).[143] Amongst the alkoxides investigated, sodium *tert*-butoxide **78** was found to inhibit the homo-coupling of aryl maganesium bromide and enabled efficient synthesis of a wide range of biaryl compounds in high yield. Cook reported the cross-coupling of aryl pseudohalides with superstoichiometric amount of aryl Grignard reagents in the presence of iron(III) fluoride and *N*-heterocyclic carbene ligand IPr·HCl **149** (Scheme 3.03c).[144] Cahiez reported an iron-catalysed oxidative homo-coupling reaction of aryl Grignard reagents using 1,2-dichloroethane **150** as a terminal oxidant for turnover of the iron catalyst (Scheme 3.03d).[145] However, the stoichiometric demand for a highly flammable and carcinogenic chemical oxidant limits the sustainability of this procedure and its applicability for large-scale industrial syntheses.



Scheme 3.03 Iron-catalysed aryl-aryl homo- and cross-coupling reactions using aryl Grignard reagents and aryl halides or pseudohalides.

Knochel reported the cobalt-catalysed cross-coupling of heteroaryl chlorides and heteroaryl- and arylmagnesium halides in high yields (Scheme 3.04a).[146] Similar to the previously reported iron-catalysed Kumada biaryl coupling reactions, Nakamura also reported a cobalt-catalysed cross-coupling reaction from non-activated aryl chlorides or heteroaryl bromides and aryl Griganard reagents (Scheme 3.04b).[147] This biaryl coupling reaction was performed in the presence of cobalt(II) fluoride and an *N*-heterocyclic carbene ligand IPr·HCl **149**.

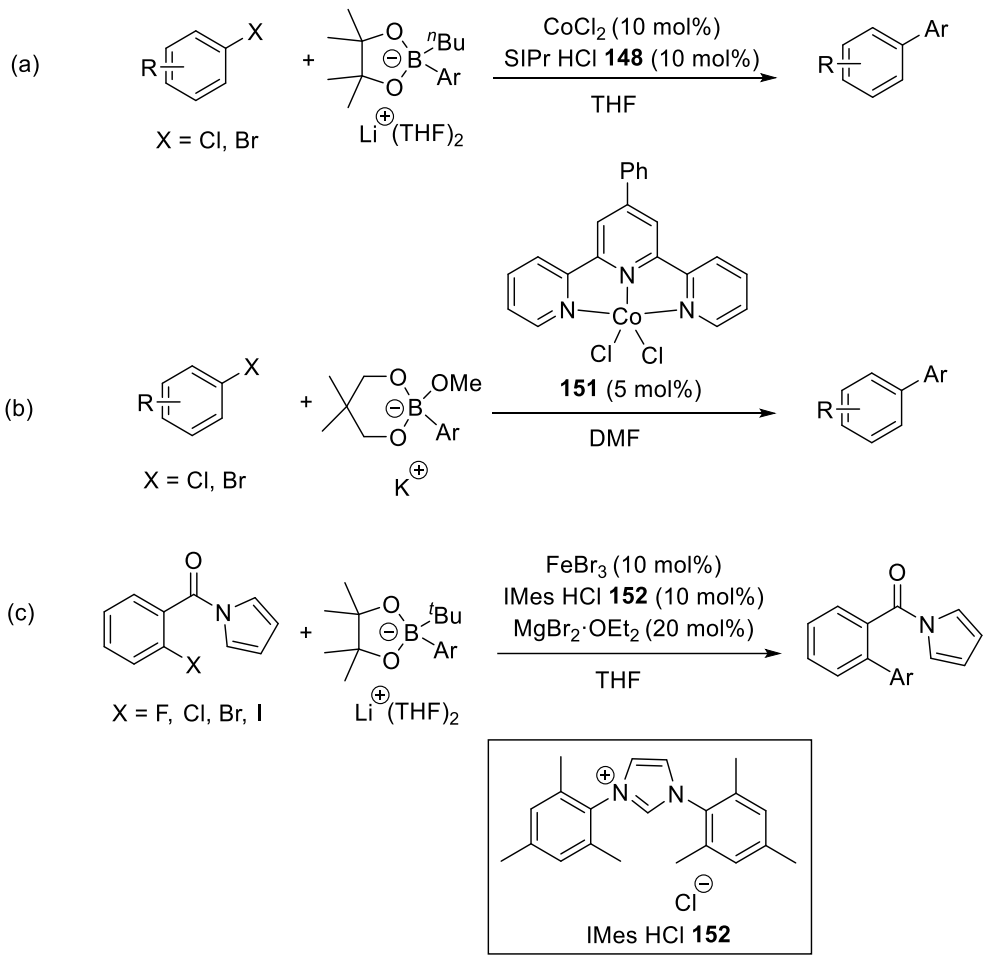


Scheme 3.04 Cobalt-catalysed cross-coupling between heteroaryl halides/aryl halides and Grignard reagents.

3.1.2.1 Using Boronic Acid Derivatives

Despite the notable rise in reports of iron and cobalt-catalysed Kumada biaryl coupling reactions, only few examples of iron- and cobalt-catalysed cross-coupling reactions between aryl halides and arylboronic acid derivatives have been developed.[148-150] Arylboronic acid derivatives present several advantages over organometallic coupling partners, such as good functional group tolerance, low toxicity, low cost and ease of handling.

Bedford reported that a cobalt(II) dichloride complex bearing a *N*-heterocyclic carbene ligand SIPr·HCl **148** was capable of catalysing the coupling of aryl chlorides and bromides with alkyllithium-activated arylboronic pinacol ester (Scheme 3.05a).[148] Duong reported the cross-coupling of alkoxide-activated aryl neopentyl glycol boronic esters and aryl halides, using terpyridine cobalt(II) chloride **151** (Scheme 3.05b).[149] Bedford also reported a substrate-directed biaryl cross-coupling reaction under mild conditions using a *N*-heterocyclic carbene ligand IMes·HCl **152** and iron(II) dichloride. Key to this breakthrough development was the observation that an *N*-acyl pyrroles substituent on the aryl halide can act as transient π-coordination motif for the reactive iron catalyst species (Scheme 3.05c).[150]

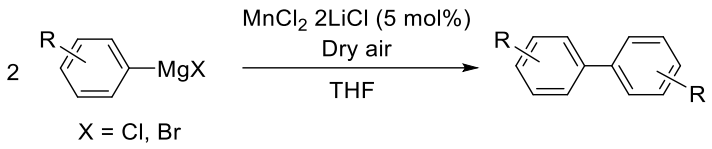


Scheme 3.05 Iron- and cobalt-catalysed aryl-aryl coupling reactions using arylboronic esters, activated by organolithium reagents or an alkoxide base.

3.1.3 Aryl-Aryl Coupling Reactions Using Manganese Catalysts

The use of iron and cobalt catalysts for aryl-aryl coupling to replace palladium-based catalysts has emerged as a very promising area for sustainable development. From both an economical and environmental point of view, manganese catalysis is also a valuable alternative to palladium catalysis. However, examples of manganese-catalysed aryl-aryl coupling reactions are very rare.

Cahiez reported an oxidative homo-coupling reaction using manganese(II) dichloride to homo-couple aryl Grignard reagents (Scheme 3.06).[151] Importantly, this procedure used dry air to enable catalyst regeneration, by re-oxidising the catalyst, eliminating the need for a chemical oxidant. Notably, the high efficiency of manganese catalyst was underlined by its faster rate of the reaction with Grignard reagents than the very fast reaction of a Grignard reagent with O_2 itself to produce the corresponding alcohols.[152]

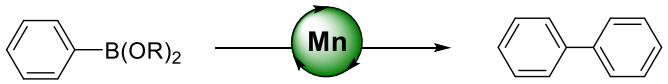


Scheme 3.06 Manganese-catalysed aryl-aryl coupling reactions using aryl Grignard reagents.

3.2 Project Aims

Cobalt-catalysed Suzuki biaryl coupling is developing rapidly, but it is highly limited to the coupling of arylboronic esters. These procedures require arylboronic esters pre-activated with either highly air- and moisture sensitive organolithium reagents or alkoxide bases. Despite growing success in iron-catalysed Suzuki biaryl couplings, aryl-aryl coupling under mild conditions remains limited to aryl halide substrates bearing directing groups that can induce aryl halide activation. However, in all of these cases, the parent boronic acid has not been used. Different from iron and cobalt, manganese-catalysed biaryl coupling has not undergone the same development. To the best of our knowledge, a general reaction protocol with broad scope using a manganese catalyst for the coupling of arylboronic acids or arylboronic esters has not been developed.

This project aimed to discover and develop a manganese catalyst for both cross-coupling and homo-coupling reactions of arylboronic acids or arylboronic esters (Scheme 3.07). Ideally the biaryl coupling reaction would be performed under mild and environmentally benign conditions and that the system would tolerate a wide range of functional groups. After the methodology has been established, further investigation would be focused on mechanistic studies.



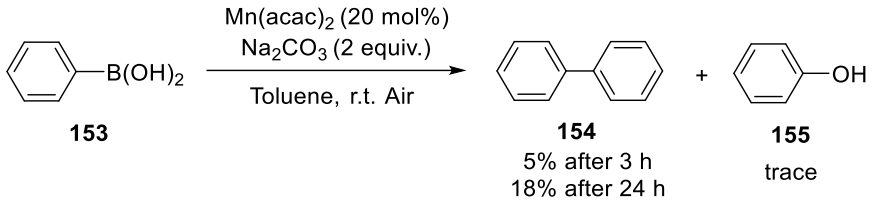
Scheme 3.07 Manganese-catalysed aryl-aryl coupling reactions using arylboronic acids or arylbornic esters

3.3 Results and Discussion

3.3.1 Methodology and Development

3.3.1.1 Initial Homo-Coupling Reactivity

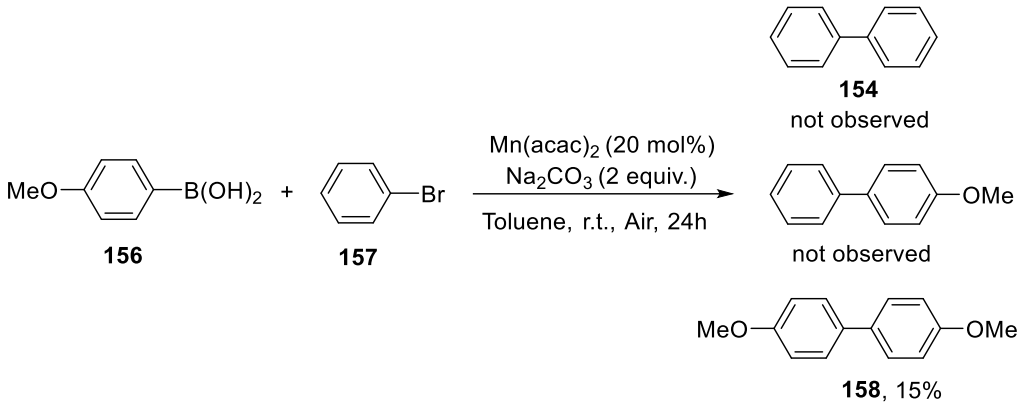
Previous work within the Thomas group had found initial reactivity for the homo-coupling of phenylboronic acid **153** in the presence of manganese(II) acetylacetonate as the catalyst.



Scheme 3.08 Initial hit for the manganese-catalysed homo-coupling of phenylboronic acid **153**.

The initial reaction was repeated to give 5% yield of biphenyl **154** after 3 hours and 18% yield of biphenyl **154** after 24 hours, along with trace phenol **155** (Scheme 3.08). The reactivity of manganese(II) acetylacetonate with phenylboronic acid **153** was extremely promising as a first stage in eventually developing a sustainable cross-coupling system. The classic Suzuki biaryl cross-coupling systems couple a nucleophilic partner, usually a boronic ester, with an electrophilic partner, usually an organic halide. The manganese catalyst was applied to an arylboronic acid and an aryl halide to assess whether a cross-coupling reaction was feasible between these two reagents.

The cross-coupling reaction between 4-methoxyphenylboronic acid **156** and bromobenzene **157** using manganese(II) acetylacetonate showed that only 4-methoxyphenylboronic acid **156** underwent homo-coupling to give the 4,4'-dimethoxybiphenyl **158** in 15% yield. Bromobenzene **157** was unreactive as the starting material was still observable and fully recovered in the crude reaction mixture (Scheme 3.09).



Scheme 3.09 Attempted cross-coupling reaction conditions: 4-methoxyphenylboronic acid **156** (0.5 mmol), bromobenzene **157** (0.5 mmol), Na_2CO_3 (1 mmol), $Mn(acac)_2$ (20 mol%) and toluene (2 mL) in a reaction vial open to air, room temperature is 20 °C, 24 h.

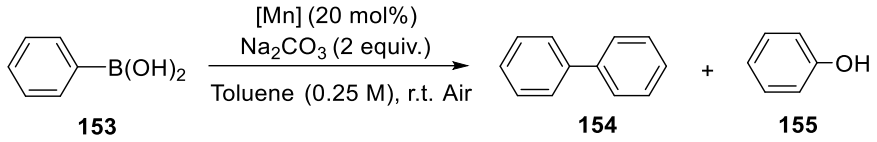
At this stage, the decision was taken to simplify the manganese system. The cross-coupling reaction between arylboronic acid and aryl halide was left one side to concentrate on optimising the reaction conditions of manganese-catalysed homo-coupling of arylboronic acids.

3.3.1.2 Reaction Optimisation

Reaction optimisation of the manganese-catalysed homo-coupling of arylboronic acids was performed using phenylboronic acid **153** as a model substrate and sodium carbonate as an additive in toluene. Initially, we turned our attention to the efficacy of a wide range of manganese(II) and manganese(III) salts (Table 3.01). This showed that the counterion had an important effect on the outcome of the reaction. Manganese(II) salts bearing halides, carbonate, acetate and nitrate counterions proved to be catalytically inert (Entry 1-7). Both manganese(II) acetylacetonate and manganese(III) acetylacetonate were effective catalysts (Entry 8-9), suggesting that the acetylacetonate ligand might be critical but that the initial oxidation-state of the manganese catalyst was not. Perhaps both manganese catalysts form the same catalytically active species in the reaction regardless of the initial oxidation states. Homo-coupling of phenylboronic acid **153** using manganese(III) acetylacetonate gave a moderate yield of biphenyl **154** (48%). Increasing the steric parameters of the manganese counterion to 2,2,6,6-tetramethyl-3,5-heptanedionato (TMHD) had little effect on the yield of biphenyl **154**, the only discernible difference being the increased quantity of phenol **155** side-product (Entry 10). Changing the electronic parameters of manganese counterion to hexafluoroacetylacetonate (HFA) gave a significantly decreased yield of biphenyl **154** (Entry 11). Other commercially available manganese(III) salts such as manganese(III) acetate and

manganese(III) fluoride also proved catalytically inactive (Entry 12-13). Additionally, various cobalt and iron acetylacetonate salts were also assessed for the homo-coupling of phenylboronic acid, but unfortunately no biphenyl **154** and phenol **155** were observed in these cases (Entry 14-17).

Table 3.01 Screening for metal salts for the homo-coupling of phenylboronic acid.



153 **154** **155**

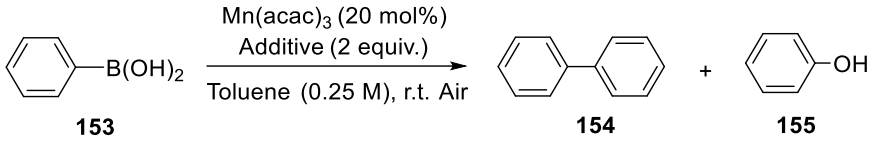
Entry	[Mn] species	Yield (**154**) (%)[b]	Yield (**155**) (%)[b]
1	MnF_2	-	-
2	$MnCl_2$	-	-
3	$MnBr_2$	-	-
4	MnI_2	-	-
5	$MnCO_3$	-	-
6	$Mn(NO_3)_2$	-	-
7	$Mn(OAc)_2$	-	-
8	$Mn(acac)_2$	18	3
9	$Mn(acac)_3$	48	6
10	$Mn(TMHD)_3$	39	15
11	$Mn(HFA)_3$	9	-
12	$Mn(OAc)_3$	-	-
13	MnF_3	-	-
14	$Co(acac)_2$	-	-
15	$Co(acac)_3$	-	-
16	$Fe(acac)_2$	-	-
17	$Fe(acac)_3$	-	-

[a] Reaction conditions: phenylboronic acid **153** (0.5 mmol), [Mn] (20 mol%), additive (1 mmol) and toluene (2 mL) in a reaction vial open to air, room temperature is 20 °C, 24 h. [b] NMR yield determined by ^1H NMR of crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard.

Subsequently, manganese(III) acetylacetonate (20 mol%) was chosen as the catalyst for the homo-coupling reaction. A survey of various additives was performed to in order to obtain a high yield of the homo-coupling product (Table 3.02). Using lithium carbonate showed a low yield of homo-coupling product, presumably owing to the poor solubility of this additive in toluene (Entry 1). Using sodium carbonate and potassium carbonate as the additive, the reaction gave 48% and 69% yield of biphenyl **154**, respectively (Entry 2-3). Other

commercially available potassium salts were also screened. Most of these salts gave a low to moderate yield of biphenyl **154**, however, potassium hydride and potassium hydroxide proved ineffective, leading to the protodeboronation of phenylboronic acid **153** (Entry 4-11). Unfortunately, organic base additives showed no reactivity in the homo-coupling reactions (Entry 12-16).

Table 3.02 Screening for additives for the homo-coupling of phenylboronic acid.



153 **154** **155**

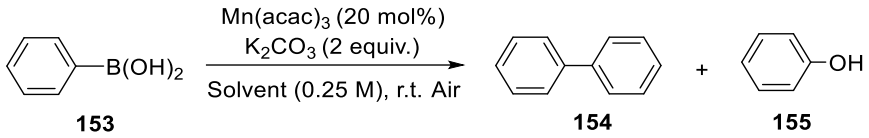
Entry	Additive	Yield (**154**) (%)[b]	Yield (**155**) (%)[b]
1	Li_2CO_3	12	-
2	Na_2CO_3	48	6
3	K_2CO_3	69	4
4	KH	-	-
5	K_2HPO_4	10	-
6	K_3PO_4	16	-
7	KOH	-	-
8	KOMe	24	3
9	KO*t*Bu	31	7
10	KF	25	3
11	KI	29	6
12	pyridine	-	-
13	Et_3N	-	-
14	piperidine	-	-
15	DMAP	-	-
16	DBU	-	-

[a] Reaction conditions: phenylboronic acid **153** (0.5 mmol), $Mn(acac)_3$ (20 mol%), additive (1 mmol) and toluene (2 mL) in a reaction vial open to air, room temperature is 20 °C, 24 h. [b] NMR yield determined by ^{1}H NMR of crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard.

Using manganese(III) acetylacetonate (20 mol%) as the catalyst and potassium carbonate (1 equiv.) as an additive, a selection of solvents were tested for the homo-coupling of phenylboronic acid **153** (Table 3.03). Except where otherwise mentioned, all solvents were used as received from commercial vendors, without drying or purification. Homo-coupling of phenylboronic acid **153** using apolar solvents such as toluene, hexane and heptane gave 69%, 19% and 34% biphenyl **154** respectively (Entry 1-3). Biphenyl **154** was obtained in excellent

yields, when using benzene, dichloromethane and chloroform as the reaction solvents (Entry 4-6). The polar aprotic solvents diethyl ether and tetrahydrofuran were found to give low yields of biphenyl **154** (Entry 7-8). Sustainable 'green' alternatives such as methyl *tert*-butylether (MTBE) and ethyl acetate did not improve these results (Entry 9-10). The polar protic solvents were also effective for the homo-coupling of phenylboronic acid **153** and when using ethanol, biphenyl **154** was obtained in 78% yield, along with 5% phenol **155** (Entry 11-12). Acetonitrile and acetone were found to be incompatible with this system (Entry 13-14). Interestingly, water was also compatible in the system and 19% biphenyl **154** was obtained (Entry 15). Due to the carcinogenicity and toxicity of benzene, further reaction optimisation was performed using ethanol as the solvent.

Table 3.03 Screening for reaction solvent for the homo-coupling of phenylboronic acid **153**.



153 **154** **155**

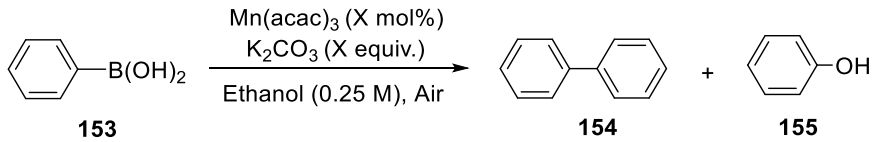
Entry	Solvent	Yield (**154**) (%)[b]	Yield (**155**) (%)[b]
1	Toluene	69	4
2	Hexane	19	-
3	Heptane	34	7
4	Benzene	80	5
5	CH_2Cl_2	77	6
6	$CHCl_3$	76	5
7	Et_2O	18	-
8	THF	20	2
9	MTBE	20	7
10	EtOAc	16	-
11	MeOH	51	10
12	EtOH	78	5
13	MeCN	3	-
14	Acetone	4	-
14	H_2O	19	-

[a] Reaction conditions: phenylboronic acid **153** (0.5 mmol), $Mn(acac)_3$ (20 mol%), K_2CO_3 (1 mmol) and solvent (2 mL) in a reaction vial open to air, room temperature is 20 °C, 24 h. [b] NMR yield determined by ^1H NMR of crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard.

With the optimal manganese salt, additive and solvent established, these reaction parameters were used to access different reaction temperatures and catalyst loadings (Table 3.04). Lower

temperature resulted in significantly decreased yield of biphenyl **154** (Entry 1-2). The reaction temperature was elevated in order to obtain a higher yield of the homo-coupling product, and the reaction gave the highest yield of biphenyl **154** at 45 °C (Entry 3-5). When the reaction was heated under reflux overnight, a significantly decreased yield of biphenyl **154** was observed and along with 16% phenol **155** (Entry 6). Decreasing the manganese salt loading to 10 mol% and potassium carbonate to 1 equivalent led to no decrease in the yield of biphenyl **154** (Entry 7). Reducing the catalyst loading to 5 mol% and 1 mol% gave considerably reduced yields (Entry 8-9).

Table 3.04 Screening for temperature, catalyst loading and base loading.



153 **154** **155**

Entry	Cat. Loading (mol%)	Base Loading (equiv.)	Temp. (°C)	Yield (**154**) (%)[b]	Yield (**155**) (%)[b]
1	20	2	0	29	3
2	20	2	10	45	6
3	20	2	35	69	10
4	20	2	45	90	5
5	20	2	65	55	15
6	20	2	100	15	16
7	10	1	45	**85**	4
8	5	1	45	49	10
9	1	1	45	20	-

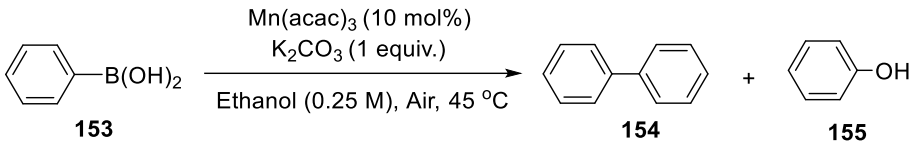
[a] Reaction conditions: phenylboronic acid **153** (0.5 mmol), $Mn(acac)_3$ (X mol%), K_2CO_3 (X equiv.) and ethanol (2 mL) in a reaction vial open to air, 24 h. [b] NMR yield determined by $_1H$ NMR of crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard.

3.3.1.3 Control Reactions

A series of control reactions were performed to ensure the validity of the methodology (Table 3.05). Homo-coupling of phenylboronic acid **153** gave biphenyl **154** in excellent yield, using manganese(III) acetylacetonate (10 mol%) and potassium carbonate (1 equiv.) in ethanol (Entry 1). The reaction did not proceed in the absence of manganese salt and additive (Entry 2). A reaction with no manganese(III) acetylacetonate gave no yield of biphenyl **154**, demonstrating that the manganese catalyst was required for successful catalysis (Entry 3). When the potassium carbonate was omitted from the system, a considerably diminished yield

was observed, indicating that potassium carbonate was not critical but helped increase the yield (Entry 4). Under an argon atmosphere, the yield of biphenyl **154** was almost equal to the catalyst loading (Entry 5). Biphenyl **154** was obtained in 85% yield under optimised reaction conditions, which equates to approximately eight catalyst turnovers of the manganese catalyst. Therefore, oxygen, in the air, was presumed to be involved in the oxidation of manganese to initiate another catalyst cycle. No phenol was observed under an argon atmosphere and the phenol **155** might come from the oxidation of phenylboronic acid **153** from peroxide species.[153] Phenol is often a by-product in the palladium-catalysed homo-coupling of arylboronic acids in the presence of dioxygen.[154, 155]

Table 3.05 Control reactions[a]



Entry	Catalyst	Additive	Yield (**154**) (%)[b]	Yield (**155**) (%)[b]
1	$Mn(acac)_3$	K_2CO_3	85	4
2	-	-	-	-
3	-	K_2CO_3	-	-
4	$Mn(acac)_3$	-	35	7
5[c]	$Mn(acac)_3$	K_2CO_3	11	-

[a] Reaction conditions: phenylboronic acid **153** (0.5 mmol), $Mn(acac)_3$ (10 mol%), K_2CO_3 (1 equiv.) and ethanol (2 mL) in a reaction vial open to air, 24 h. [b] NMR yield determined by ^1H NMR of crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard. [c] The reaction was performed under an argon atmosphere.

There are a number of reports in which the homo-coupling of boronic acids has been catalysed by late transition metals, such as palladium[156] and rhodium,[157] with extremely low catalyst loadings. Therefore, any trace metal contained within the manganese salt, additive or phenylboronic acid would have an effect on the reaction outcome.

Modern analytical strategies should be applied in this scenario for identifying and quantifying trace metal impurities in these reagents, to unambiguously show whether manganese is the responsible metal for productive catalysis. The ICP-MS was used to analyse the quantity of trace metal contaminants as this has sensitivity for ppb concentration of metal contaminants. The standard reaction used included phenylboronic acid **153** (0.5 mmol), potassium carbonate (0.5 mmol) and manganese(III) acetylacetonate (10 mol%). A portion of the reaction mixture was analysed by ICP-MS and the concentrations of trace elements determined by comparison

against a standard solution (Table 3.06, ICP-MS analysis performed and data provided by Dr Lorna Eades). These results indicated the concentration of these metals in the reaction mixture was dramatically lower than the concentration of manganese catalyst. Taken together with previous control reactions (Table 3.05), this implied the reactivity observed was not related to trace metal contaminants.

Table 3.06 Elemental concentration for selected elements in manganese(III) acetylacetonate[a]

Element	Mass	Concentration (ppb)	Relative to [Mn]
Al	29	1.880	1.9×10^{-4}
Cr	53	0.910	9.1×10^{-5}
Mn	55	9974	1
Fe	57	0.190	1.9×10^{-5}
Co	59	0.240	2.4×10^{-5}
Ni	60	1.100	1.1×10^{-4}
Cu	63	1.003	1.0×10^{-4}
Ru	101	0.013	1.3×10^{-6}
Rh	103	0.019	1.9×10^{-6}
Pd	105	0.920	9.2×10^{-5}
Ag	107	0.015	1.5×10^{-6}
Ir	193	0.081	8.1×10^{-6}
Pt	195	0.017	1.7×10^{-6}
Au	197	0.608	6.1×10^{-5}

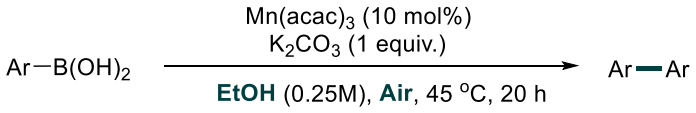
[a] Nitric acid (1 mL, Conc.) Aristar ultra high purity was carefully added dropwise to a mixture of phenylboronic acid **153** (0.5 mmol), K_2CO_3 (0.5 mol), $Mn(acac)_3$ (10 mol%). Water (9 mL, ultrapure) was added to the mixture and a 1 mL portion was diluted to a total volume of 10 mL. Analysis of the resulting solution was performed using an Agilent 7500ce ICP-MS calibrated against a multi-element standard solution.

3.3.2 Substrate Scope

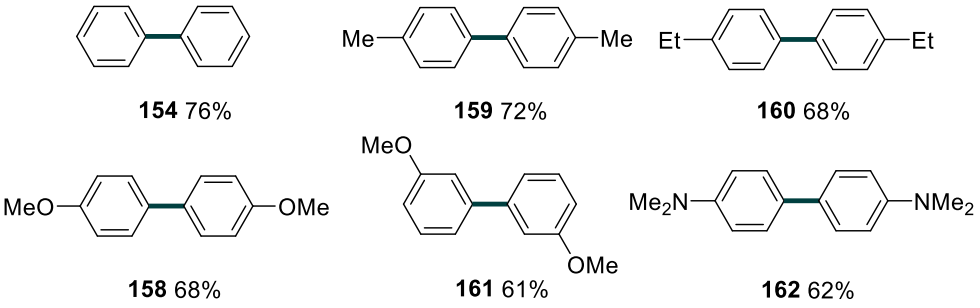
The substrate scope of this catalytic system was explored using manganese(III) acetylacetonate (10 mol%) as the catalyst and potassium carbonate (1 equiv.) in ethanol (2 mL) at 45 °C (Table 3.07). Homo-coupling of phenylboronic acid **153** gave biphenyl in high yield (**154**, 76%). Phenylboronic acid derivatives bearing electron-donating groups such as methyl, ethyl, methoxy and a tertiary amine group all underwent successful homo-coupling reactions in good isolated yield (**158**-**162**, 61-72%). Phenylboronic acid derivatives with electron-withdrawing substituents such as fluoride, chloride, bromide, iodide and trifluoromethyl were all tolerated, giving the homo-coupled products in excellent yield (**163**-**168**, 77-90%), with no cleavage of the aryl-halide bond observed. Phenylboronic acid derivatives containing

unsaturated groups, such as nitrile, aldehyde, ketone and ester substituents, were all chemoselectively homo-coupled in good yield (**169**-**172**, 52-87%). Homo-coupling of 4-(bromomethyl)phenylboronic acid gave good yield without reaction at the benzylic bromide (**173**, 71%). 4-Vinylphenylboronic acid was successfully homo-coupled to give the diene product in a good yield (**174**, 69%). Homo-coupling of 2-napthylboronic acid gave a moderate yield of binaphthyl, potentially due to the low solubility of staring material in ethanol (**175**, 50%).

Table 3.07 Substrate scope of manganese-catalysed homo-coupling of arylboronic acids



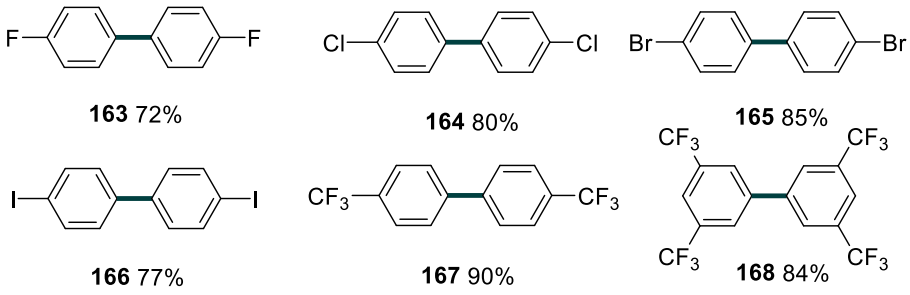
Substrates with electron-donating substituents



154 76% **159** 72% **160** 68%

158 68% **161** 61% **162** 62%

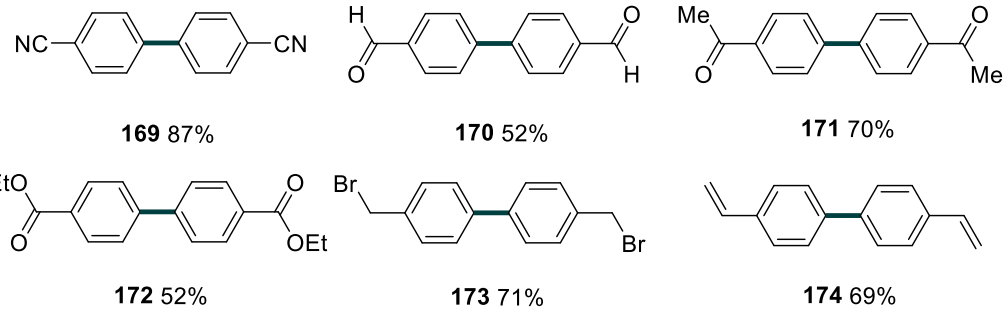
Substrates with electron-withdrawing substituents



163 72% **164** 80% **165** 85%

166 77% **167** 90% **168** 84%

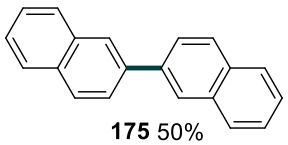
Substrates with reducible functional groups



169 87% **170** 52% **171** 70%

172 52% **173** 71% **174** 69%

Substrate with fused benzene

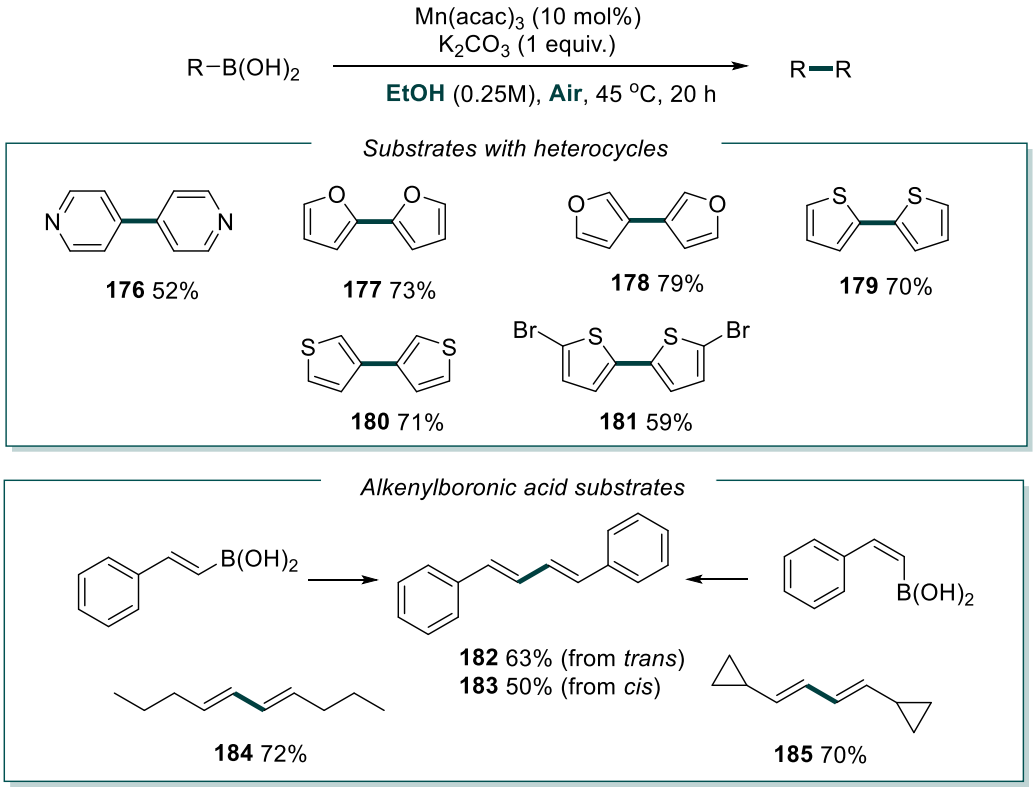


175 50%

[a] Reaction conditions: boronic acid (0.5 mmol), $Mn(acac)_3$ (10 mol%), K_2CO_3 (1 equiv.) and ethanol (2 mL) in reaction vial open to air, 24 h, isolated yield.

A series of unsaturated heterocyclic boronic acids were also investigated under modified reaction conditions (Table 3.08). Homo-coupling of 4-pyridinylboronic acid gave a moderate yield of bipyridine (**176**, 52%), presumably pyridine binding the catalyst deactivates the manganese catalyst. 2-Furanylboronic acid, 3-furanylboronic acid, 2-thienylboronic acid and 3-thienylboronic acid were successfully homo-coupled to give the product in excellent yields (**177**-**180**, 71-79%). 5-Bromo-2-thienyl-boronic acid was also homo-coupled successfully, giving the product in good yield, without any dehalogenation observed (**181**, 59%). In addition, both *trans*-2-phenylvinylboronic acid and *cis*-2-phenylvinylboronic acid were homo-coupled with the same diastereoselectivity, giving the product (1*E*,3*E*)-1,4-diphenylbuta-1,3-diene in moderate yield (**182**-**183**, 50-63%). Alkenylboronic acids with an alkyl chain or strained cyclopropane were both homo-coupled successfully, giving dienes in yields of 72% and 70%, respectively, with no ring-opening reactions observed (**184**-**185**, 70-72%).

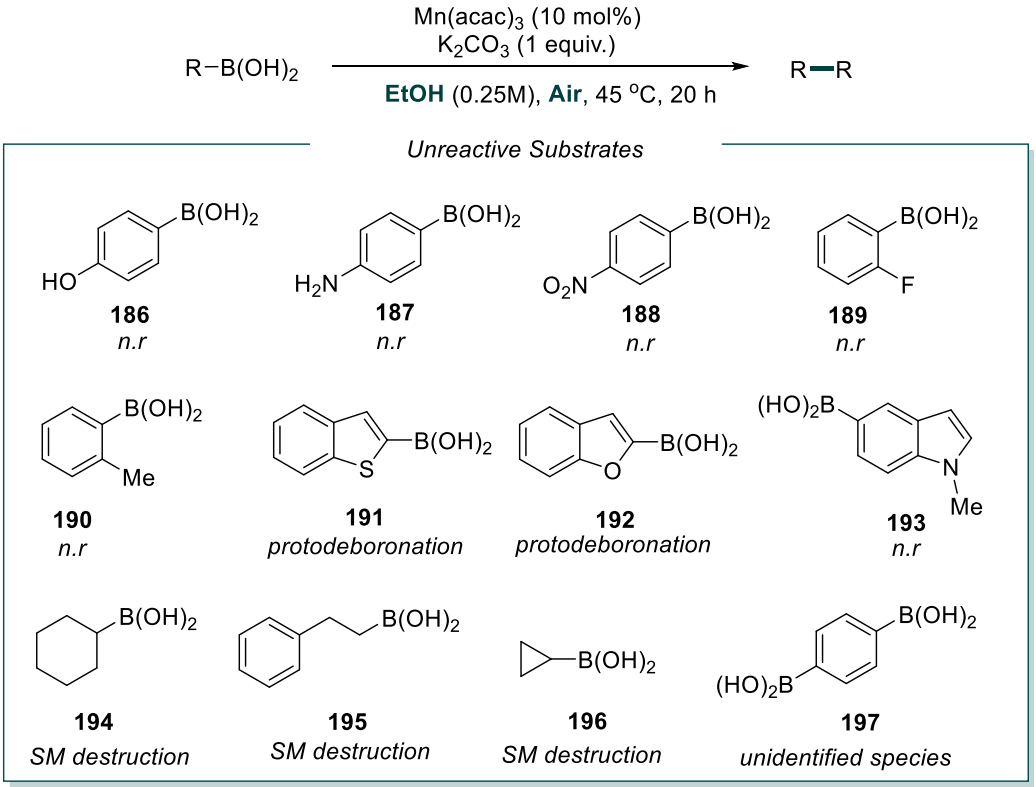
Table 3.08 Substrate scope of manganese-catalysed homo-coupling of heterocyclic boronic acids and alkenylboronic acids



[a] Reaction conditions: boronic acid (0.5 mmol), $Mn(acac)_3$ (10 mol%), K_2CO_3 (1 equiv.) and ethanol (2 mL) in reaction vial open to air, 24 h, isolated yield. [b] For the homo-coupling of heterocyclic boronic acids and alkenyl boronic acids, the reaction temperature was 0°C

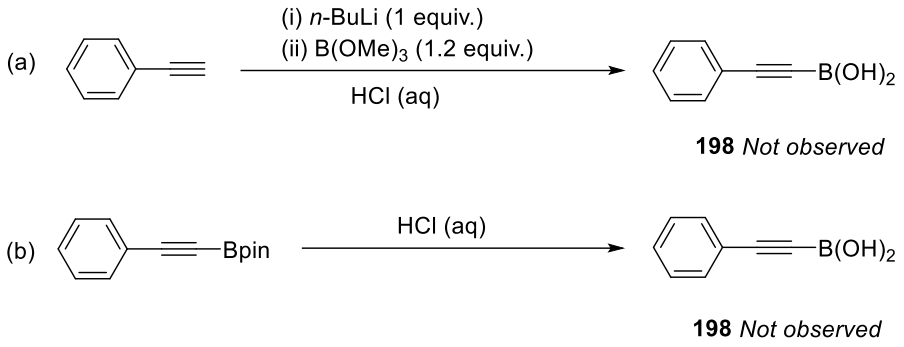
Despite a number of boronic acids were successfully homo-coupled with excellent yields, in general it was found that substrates bearing functional groups with a good affinity to coordinate to manganese and inhibits reactivity (Table 3.09). Arylboronic acids containing a free alcohol, primary amine and nitro group are examples of such substrates (**186**-**188**), with no homo-coupling product obtained under optimised reaction conditions. This was possible due to the interaction between these functional groups and manganese species, leading to the deactivation of manganese catalyst. It was also found that *ortho*-substituted arylboronic acids (**189**-**190**) were not homo-coupled under the reaction conditions, possibly due to the steric hindrance. Benzothienylboronic acid **191** and benzofuranylboronic acid **192** underwent protodeboronation under optimisation reaction conditions, with no homo-coupling products observed. Homo-coupling of *N*-Methylindole-5-boronic acid **193** did not proceed under reaction conditions. Unfortunately, a number of alkylboronic acids (**194**-**196**) did not undergo homo-coupling using the developed reaction conditions. Homo-coupling of benzene-1,4-diboronic acid **197** giving a mixture of unidentified species.

Table 3.09 Unsuccessful substrates: maganese-catalysed homo-coupling of boronic acids[a]



[a] Reaction conditions: Boronic acid (0.5 mmol), $Mn(acac)_3$ (10 mol%), K_2CO_3 (1 equiv.) and ethanol (2 mL) in reaction vial open to air, 24 h.

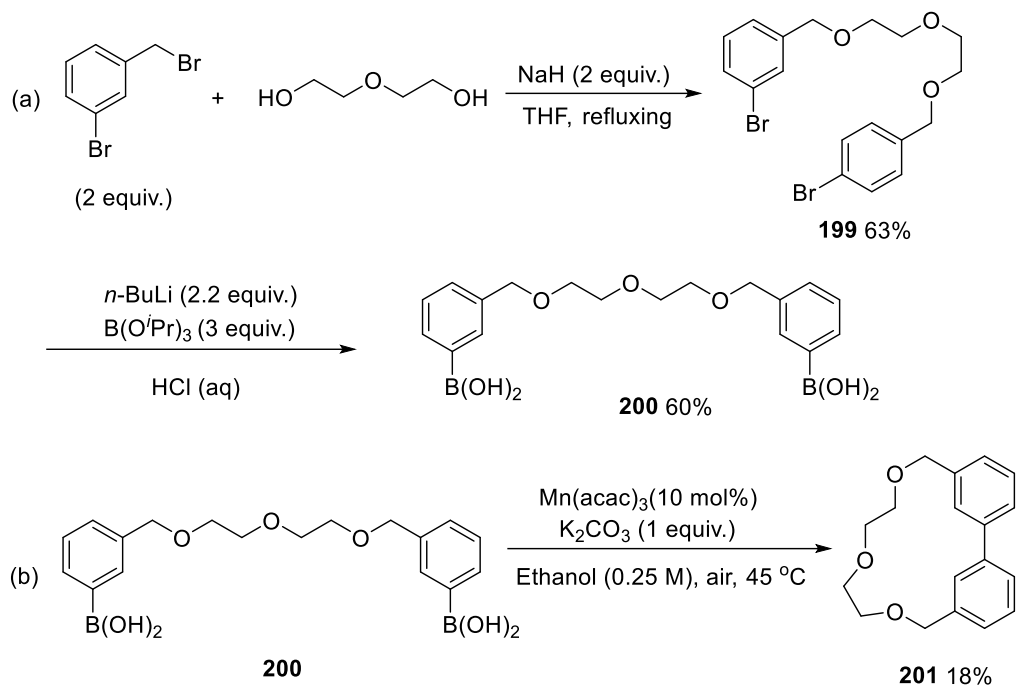
Cahiez have developed a procedure for the manganese-catalysed oxidative cross-coupling between aryl Grignard reagent and alkynyl magnesium chloride,[158] and therefore we aimed to investigate the cross-coupling of an arylboronic acid and an alkynylboronic acid. However, alkynylboronic acids are not commercially available and the preparation of phenylethynylboronic acid **198** from phenylacetylene was not successful (Scheme 3.10a).[159, 160] Alternatively, hydrolysis of the commercially available 2-phenyl-1-ethynylboronic acid pinacol ester led to protodeboronation, with no alkynylboronic acid observed (Scheme 3.10b).[106] As we were not able to prepare any alkynylboronic acid, cross-coupling reaction between an alkynylboronic acid and an arylboronic acid was not performed.



Scheme 3.10 Preparation of alkynylboronic acids.

3.3.3 Intramolecular Homo-Coupling Reactions

In order to demonstrate the synthetic utility of the methodology, we synthesised the diboronic acid **200** from **199** by metal-halogen exchange, quenched with electrophilic tri*iso*propyl borate and subsequently hydrolysis (Scheme 3.11a).[106] The diboronic acid **200** was assessed for an intramolecular homo-coupling reaction under the optimised reaction conditions, giving the corresponding macrocycle **201** in moderate yield (Scheme 3.11b).



Scheme 3.11 Manganese-catalysed intramolecular homo-coupling of a diboronic acid.

3.3.4 Mechanistic Investigations

3.3.4.1 ^{11}B NMR studies

In order to gain mechanistic insight of the homo-coupling of boronic acids, the reaction was monitored by ^{11}B NMR in *d*$_6$-benzene to identify any changes in the phenylboronic acid **153** starting material with or without the catalyst manganese(III) acetylacetonate. The ^{11}B NMR of phenylboronic acid **153** (without manganese catalyst) showed a resonance at 28.7 ppm, corresponding to the starting material (Figure 3.01a). The ^{11}B NMR of the mixture of phenylboronic acid **153** and manganese(III) acetylacetonate (10 mol%) showed two peaks at 28.7 ppm and 3.3 ppm. The peak at 28.7 ppm was consistent with starting material phenylboronic acid **153**, and the peak at 3.3 ppm was proposed to be a boron 'ate' complex (Figure 3.01b). The ^{11}B NMR of the mixture of phenylboronic acid **153**, potassium carbonate (1 equiv.) and manganese(III) acetylacetonate (10 mol%) gave the same peaks at 28.7 ppm and 3.3 ppm (Figure 3.01c). The proposed intermediate has been postulated in the catalytic cycle of the Suzuki-Miyaura cross-coupling reaction, in which a negatively-charged boron 'ate' species is used for the transmetallation.[95, 96] Previous work from the Thomas group has also observed an analogous boron 'ate' complex formed from a boronic ester at 4.7 ppm.[93] Even though the boron 'ate' formation happened in the reaction, it is clear if it played a role in the formation of homo-coupled biphenyl product **154**.

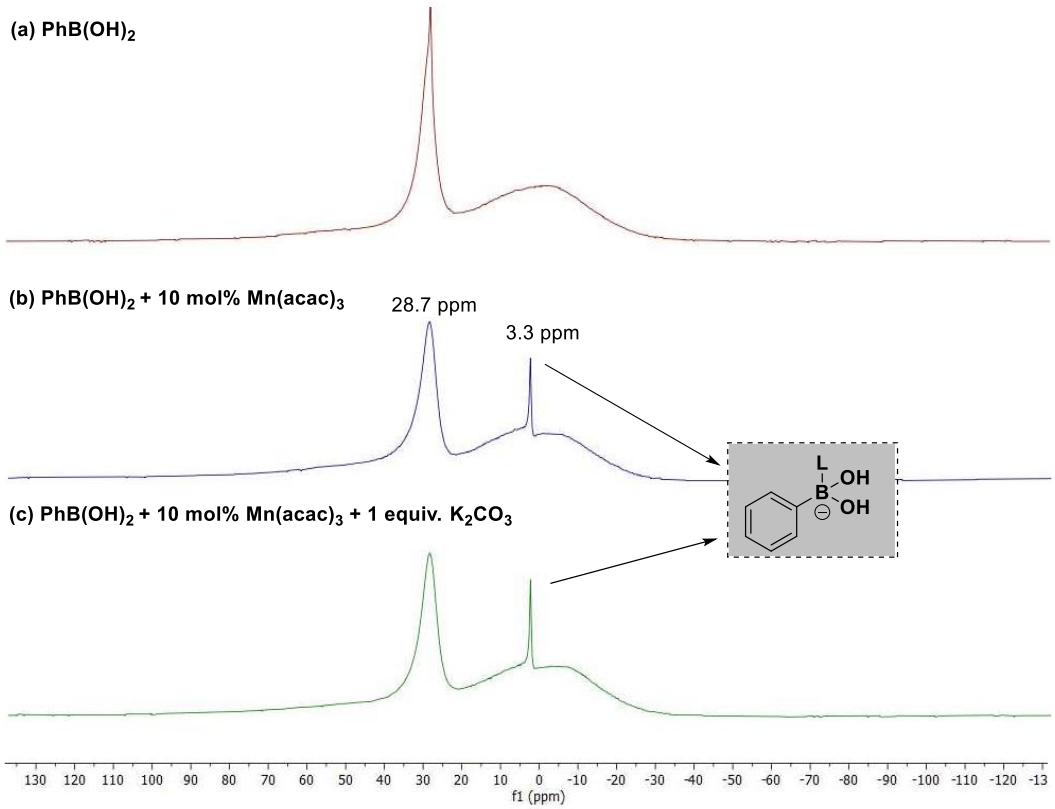
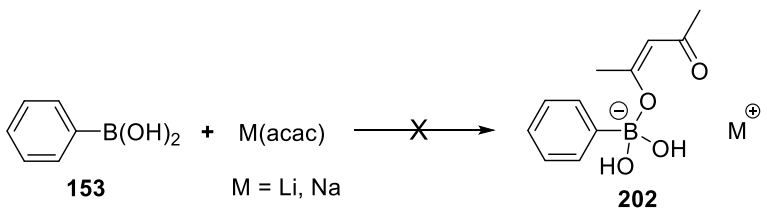


Figure 3.01 (a) ^{11}B NMR of phenylboronic acid **X** in C_6D_6 (b) ^{11}B NMR of phenylboronic acid **X** and manganese(III) acetylacetonate (10 mol%) in C_6D_6 (c) ^{11}B NMR of the mixture of phenylboronic acid **X**, potassium carbonate (1 equiv.) and manganese(III) acetylacetonate (10 mol%) in C_6D_6.

In order to identify the proposed boron 'ate' complex, we attempted to independently synthesis and fully characterise it. We proposed the boron 'ate' complex formed though the reaction of phenylboronic acid **153** and stoichiometric lithium acetylacetonate or sodium acetylacetonate. Unfortunately, we were not able to prepare the target complex **202** due to the extremely low solubility of lithium acetylacetonate and sodium acetylacetonate in the reaction solvent (Scheme 3.12). Further reaction between boron 'ate' and manganese catalyst was not performed.



Scheme 3.12 Attempted preparation of the proposed boron 'ate' complex by the reaction of phenylboronic acid **153** and stoichiometric metal acetylacetonate salt.

3.3.4.2 Reaction Kinetics

In order to gain greater insight into the manganese-catalysed homo-coupling reaction of boronic acids, a number of reaction monitoring experiments were performed. Homo-coupling of 4-fluorophenylboronic acid **203** was performed in the presence of manganese(III) acetylacetonate (20 mol%) and potassium carbonate (1 equiv.), monitored by the removal of aliquots from the reaction mixture at predetermined time points (Figure 3.02). The aliquots were analysed by ^{19}F NMR. Manganese(III) acetylacetonate at 20 mol% loading resulted in extremely rapid consumption of 4-fluorophenylboronic acid **203** in the early part of the reaction (*ca* 40 mins), before a second phase of reaction in which slower homo-coupling occurred. A second-order kinetic dependence on the substrate 4-fluorophenylboronic acid **203** was observed (Figure 3.03-3.04).

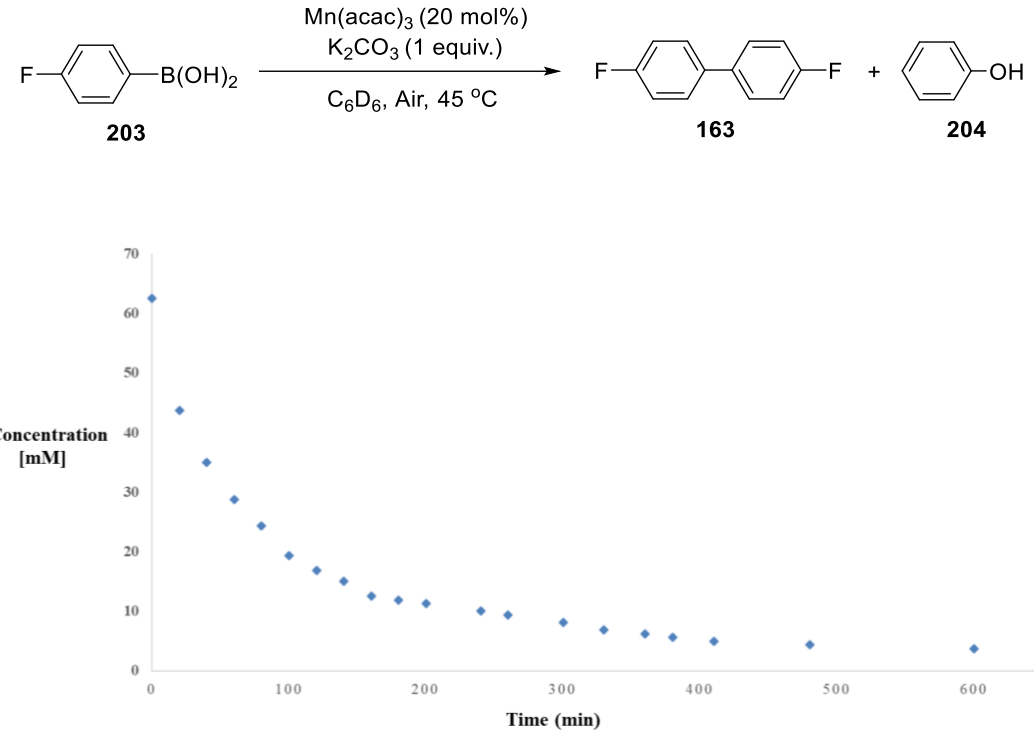


Figure 3.02 Reaction monitoring of 4-flurophenylboronic acid **203** in the presence of $Mn(acac)_3$ (20 mol%), K_2CO_3 (1 equiv.) in *d*$_6$-benzene (8 mL). Yield determined by ^{19}F NMR of aliquots from reaction mixture using fluorobenzene as an internal standard.

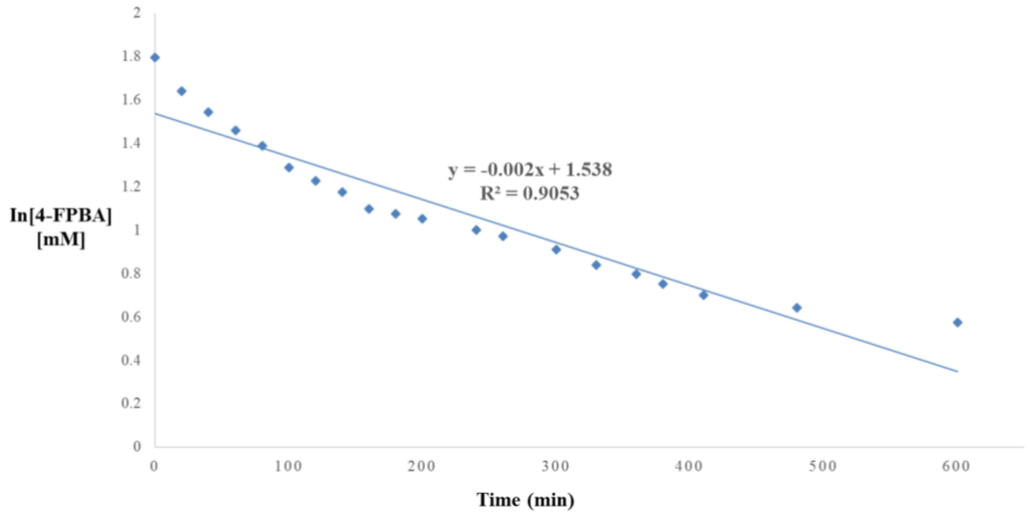


Figure 3.03 First order kinetics: Graphical plot of In[4-FPBA] (mM) *vs* time (min)

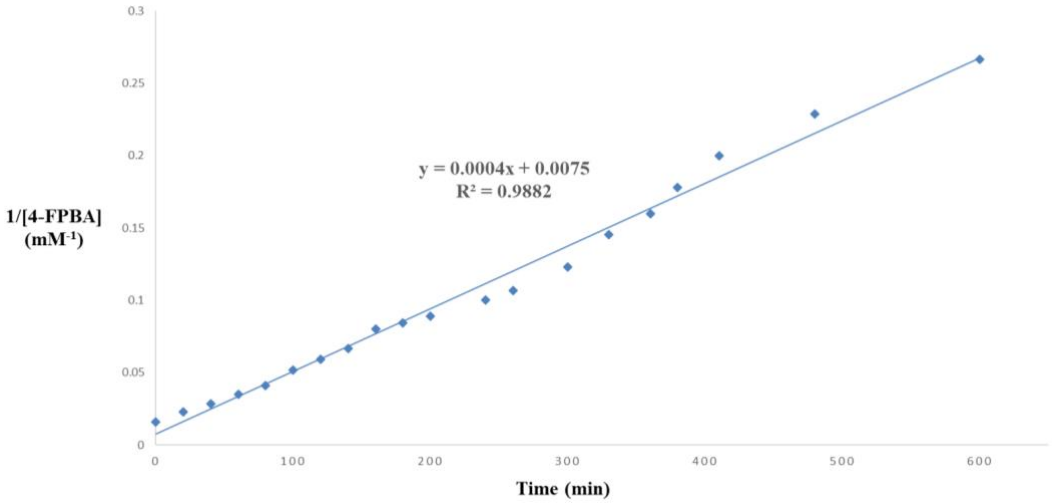


Figure 3.04 Second order kinetics: Graphical plot of 1/[4-FPBA] (mM^{-1}) *vs* time (min)

Further investigation focused on the reaction order with respect to the manganese catalyst. Homo-coupling of 4-fluorophenylboronic acid **203** was performed using different catalyst concentrations *in situ* monitoring by ^{19}F NMR (Figure 3.05). We used graphical analysis method[161] and plotted the primary data of the yield of 4,4'-difluorobiphenyl **163** against a normalised time scale $t[cat]_n$, which adjusted the entire reaction profile based on concentration data. Clear overlay of the normalised time plots to the first order (n = 1), with mismatching when plotting 0.5 and 2, suggesting the reaction was first order in manganese(III) acetylacetonate (Figure 3.06).

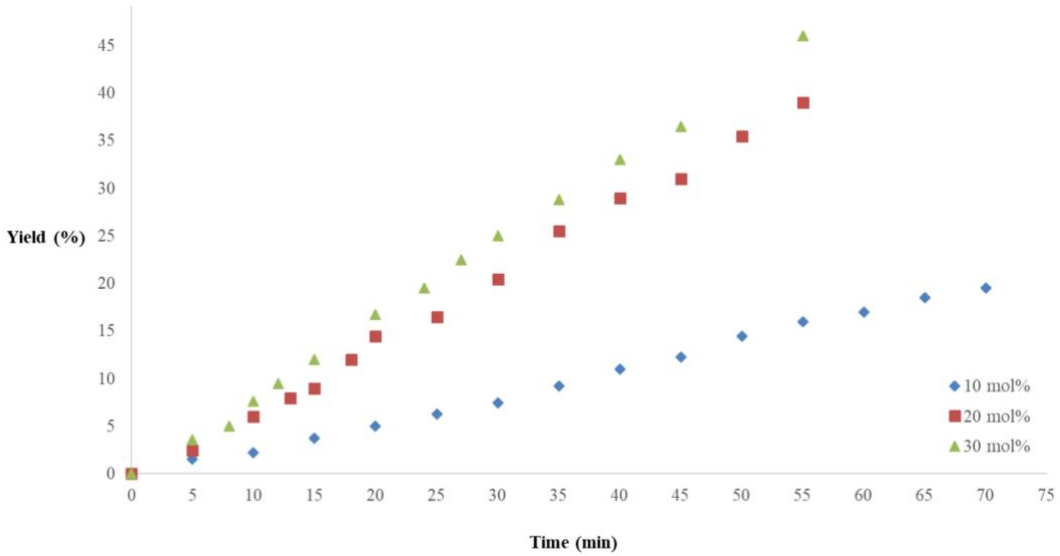


Figure 3.05 Yield monitoring of homo-coupling of 4-fluorophenylboronic acid **203** using 10 mol%, 20 mol% and 30 mol% manganese(III) acetylacetonate. Yield determined by ^{19}F NMR of aliquots from reaction mixture using fluorobenzene as an internal standard.

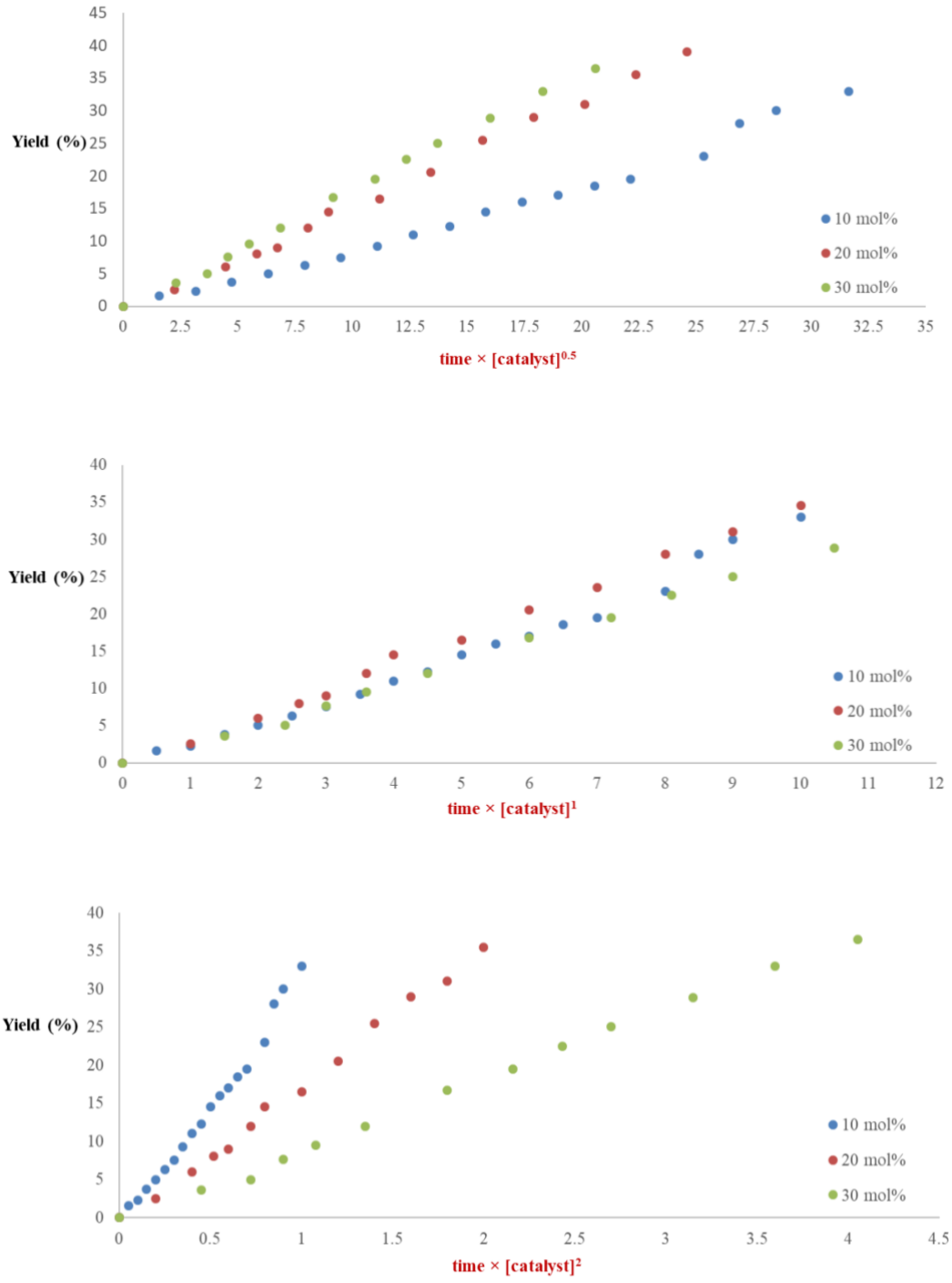


Figure 3.06 Graphical plot of the yield of 4,4'-difluorobiphenyl **163** *vs* normalised time t[Mn(acac)$_3$]$_n$

3.3.4.3 Hammett Analysis

Hammett analysis of the manganese-catalysed homo-coupling of arylboronic acids was carried out under the optimised reaction conditions, aiming to investigate whether there was an electronic bias in the catalytic system (Figure 3.07). The logarithm of initial reaction rate from

selected substrates were correlated to their respective Hammett *para* substituent constants (σ_p). The correlation showed that substrates with electron-withdrawing substituents at the *para* position had a relatively high initial rate of reaction compared to those with electron-donating substituents. The Hammett plot showed a positive reaction constant (positive ρ), suggesting that the mechanism was likely to involve an increase of electron density at boron atom during the forward reaction transition state. Hammett correlation showed that an increase in electron density at boron would support the previously proposed boron 'ate' complex formation during the reaction.

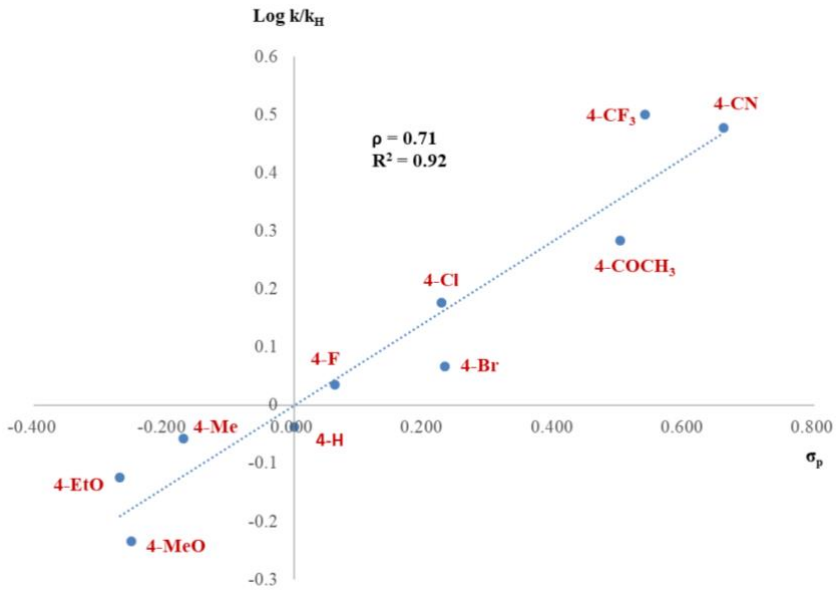


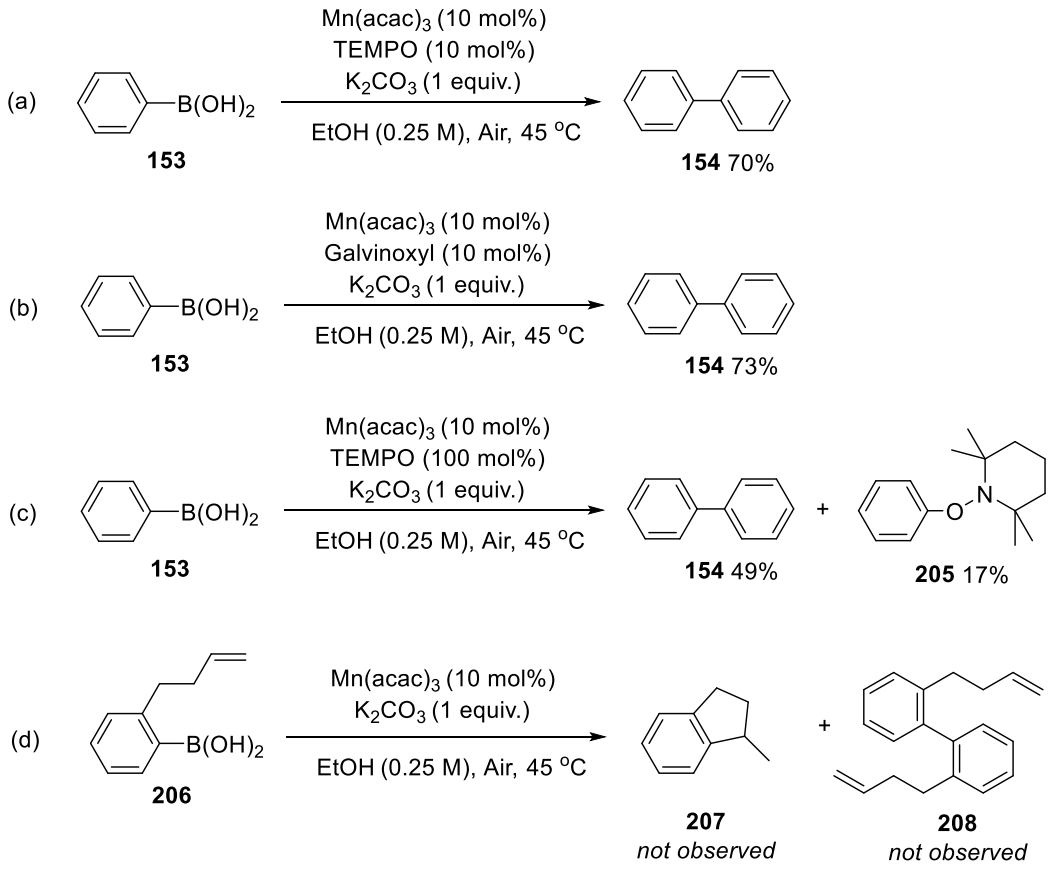
Figure 3.07 Hammett analysis of manganese-catalysed homo-coupling of phenylboronic acid derivatives

3.3.4.4 Trapping and Poisoning Experiments

As the paramagnetic nature of manganese species prohibit direct observation by ^{1}H and ^{13}C. We carried out a variety of poisoning and trapping experiments to gain further information of the homo-coupling reaction.

In order to probe a potential radical mechanism, the homo-coupling of phenylboronic acid **153** was performed in the presence of different radical traps. Under the optimised reaction conditions, homo-coupling of phenylboronic **153** gave the product biphenyl **154** in 85% yield. Arylboronic acids have been reported to decompose into aryl radical through single-electron transfer mechanism in the presence of an oxidant.[162-166] However, experiments involving the addition of stoichiometric amounts of 2,2,6,6-tetramethyl-piperidine-1-oxy (TEMPO) and galvinoxyl with respect to the manganese catalyst gave no significant change in the yield of

biphenyl **154**. The formation of aryl-TEMPO or aryl-galvinoxyl adducts were also not observed (Scheme 3.13a-b). When using stoichiometric TEMPO with respect to phenylboronic acid **153**, the reaction afforded biphenyl **154** and phenyl-TEMPO adduct **205**, with the approximate ratio 3:1 (Scheme 3.13c). Radical clock experiment using tethered alkene substrate **206** did not give any radical cyclisation product **207** or homo-coupling product **208** (Scheme 3.13d). Taking these results together, a radical pathway was presumed to be unlikely.



Scheme 3.13 Radical trapping experiments

Kinetic experiments with selective poisons were performed for the distinction between homogeneous and heterogeneous catalysts. Dibenzo[a,e]cyclooctatetraene (DCT) has been reported as selective poison/ligand of homogenous metal species due to its tub-like structure and π-acceptor properties.[167] Upon addition of 50 mol% DCT (5 equiv. per [Mn]) to the homo-coupling of 4-fluorophenylboronic acid **203** after 1 h, the catalyst activity was not significantly inhibited and a slightly decreased yield was obtained compared with the reaction under optimised conditions (Figure 3.08a). However, this DCT test has only proved indicative in limited examples with low oxidation-state palladium, rhodium, iron and manganese catalysts.[97, 167, 168] A similar poisoning experiment with superstoichiometric mercury (10 equiv.

per [Mn]) was performed (Figure 3.08b). A potential amalgam formation was not observed and no decreased yield of homo-coupling product was observed in comparison with the control reaction, indicating the manganese species was not a heterogenous catalyst.

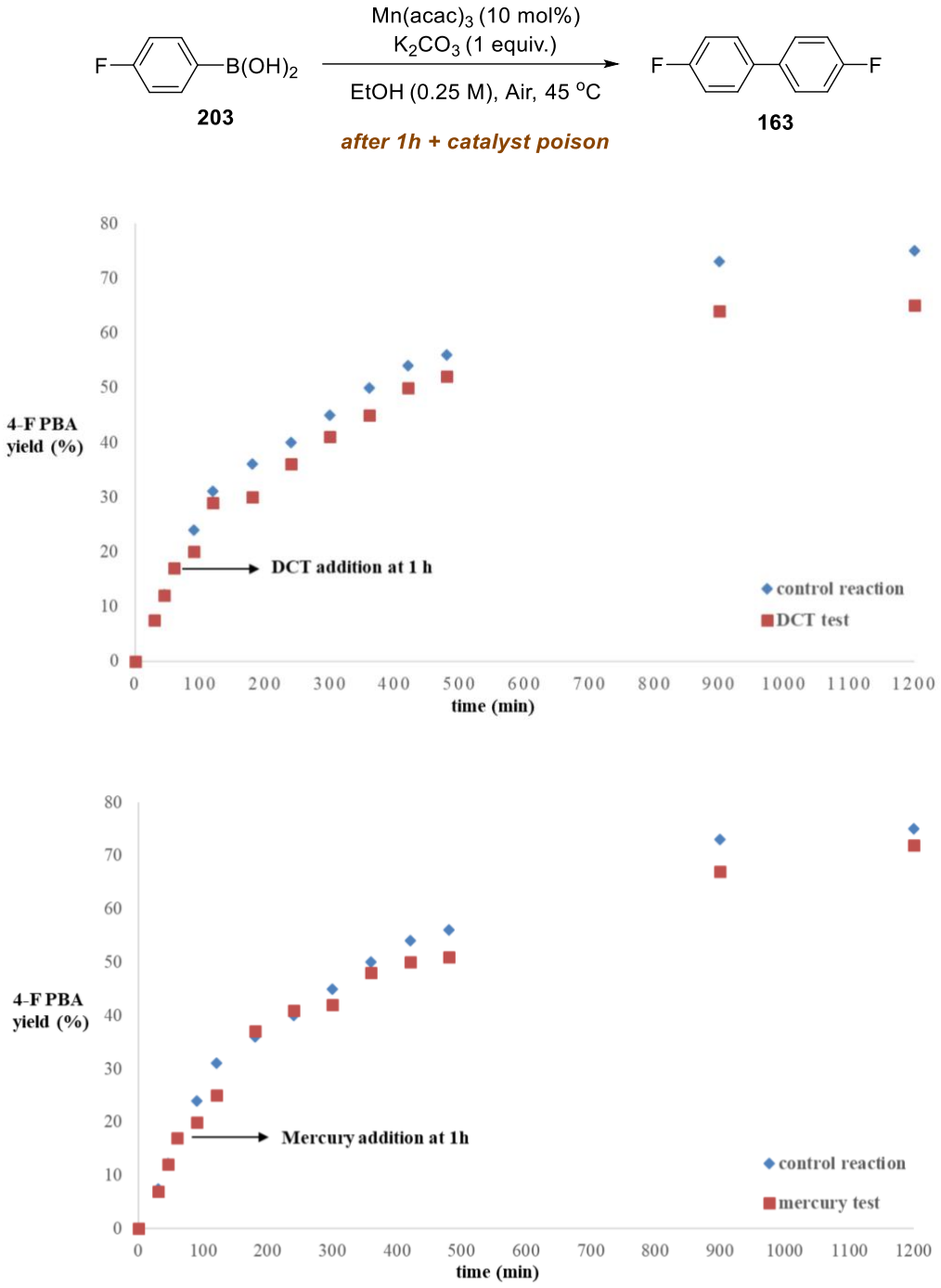
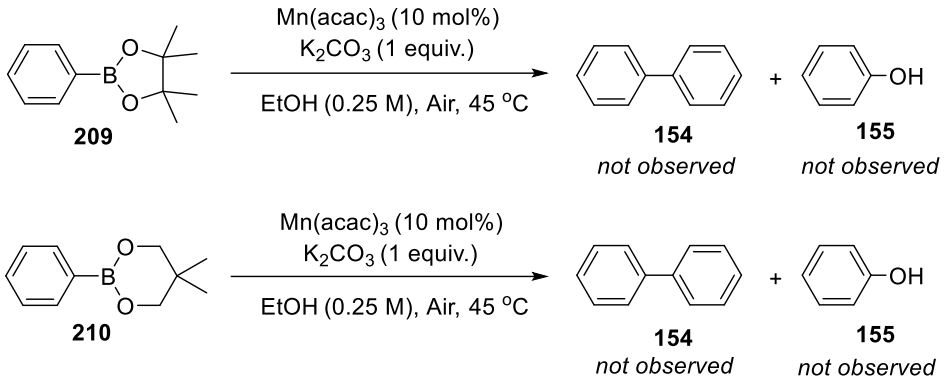


Figure 3.08 (a) Poisoning experiment with DCT (50 mol%) *vs* control reaction. (b) Poisoning experiment with superstoichiometric mercury (10 equiv.) *vs* control reaction.

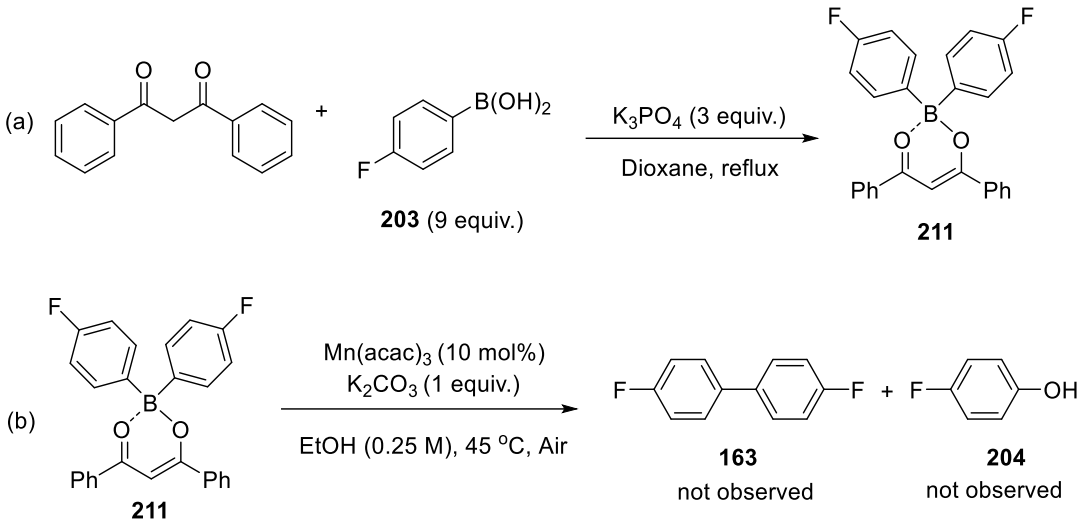
3.3.4.5 Boron 'Ate' Complex Investigations

We questioned whether other boron reagents would give biaryl formation under the optimised reaction conditions. Homo-coupling of phenylboronic acid pinacol ester **209** and phenyl neopentyl glycol boronic ester **210** did not proceed, giving only unreacted starting materials (Scheme 3.14).



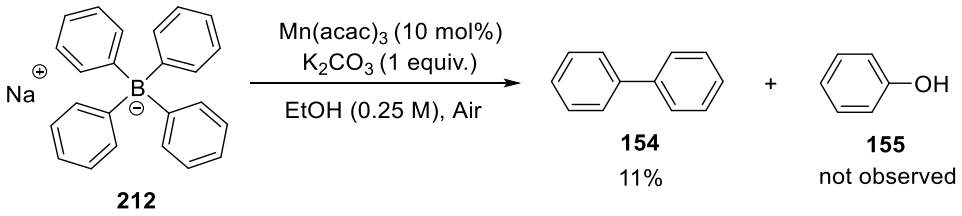
Scheme 3.14 Homo-coupling of phenylboronic acid pinacol ester **209** and phenyl neopentyl glycol boronic ester **210** under optimised reaction conditions.

Initially, the neutral four-coordinate boron(III) complex **211** was prepared using 1,3-diphenyl-1,3-propanedione and excess 4-fluorophenylboronic acid **203** according to the method developed by Lee (Scheme 3.15a).[169] This complex contains two aryl units, an acetylacetonate-type structure and has a 8.7 ppm shift in ^{11}B NMR. Therefore, it was possible that a similar reaction intermediate was generated in the manganese-catalysed homo-coupling reaction. However, reaction of the pre-formed neutral boron complex **211** under optimised reaction conditions gave no homo-coupling product **163** or corresponding phenol **204**, but only unreacted starting material was observed in the crude reaction mixture (Scheme 3.15b).



Scheme 3.15 (a) Preparation of neutral four-coordinate boron complex **211**. (b) Homo-coupling of the pre-formed neutral four-coordinate boron complex **211** under optimised reaction conditions.

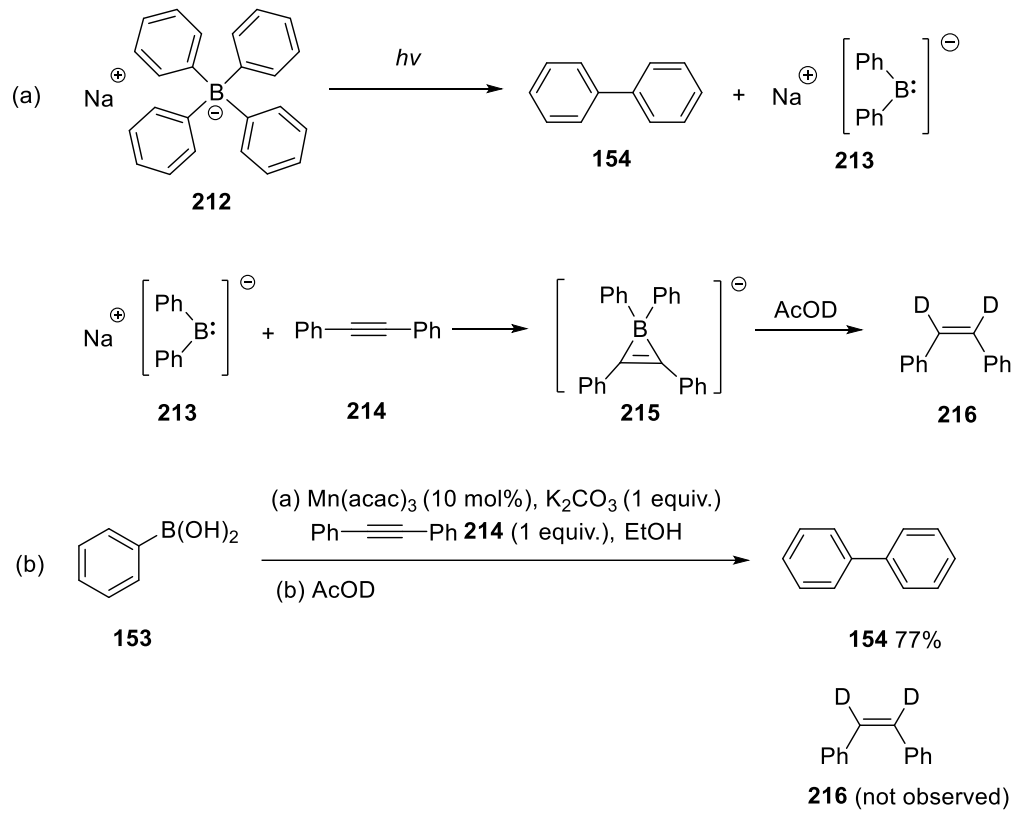
Further investigations focused on the homo-coupling reaction of anionic boronate complexes. The commercially available sodium tetraphenylborate salt **212** and derivatives were reported to liberate biaryls under irradiation with UV light[170-175] or in the presence of single-electron oxidants.[176] Homo-coupling of sodium tetraphenylborate **212** was performed under optimised reaction conditions, giving the biphenyl **154** in only 11% yield (Scheme 3.16).



Scheme 3.16 Manganese-catalysed homo-coupling of sodium tetraphenylborate **212**.

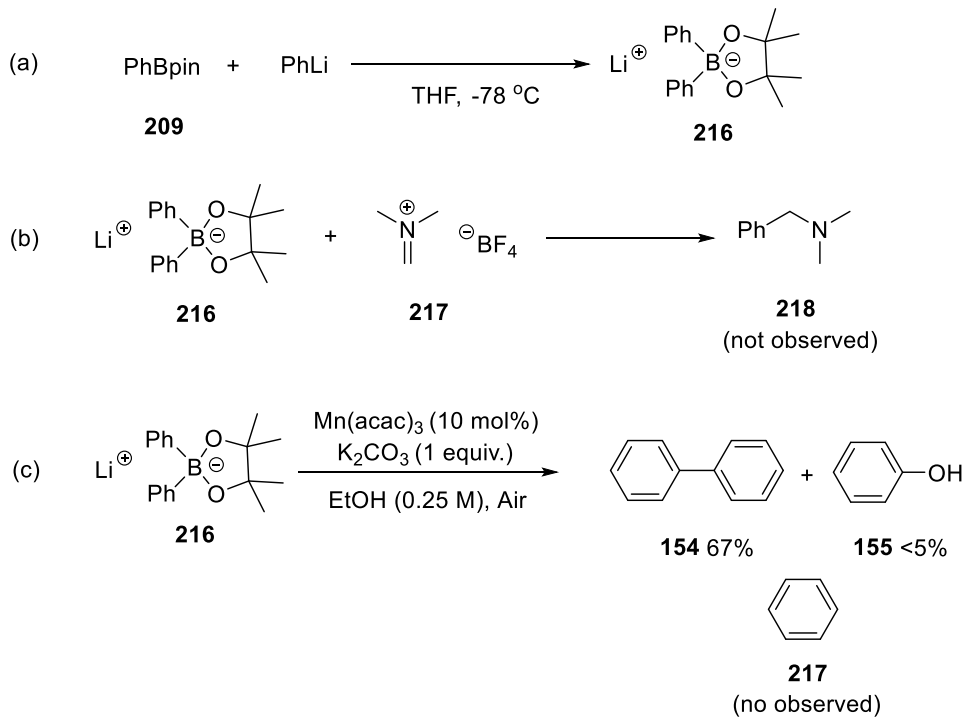
Eisch performed the irradiation of tetraphenylborate **212** under inert atmosphere in aprotic solvents containing diphenyl acetylene **214** as a presumsed trap for borene.[170, 172] Treatment of the crude reaction mixture with deuterioacetic acid gave biphenyl **154** and dideuterated stilbene **216**. The latter product **216** was proposed to arise from the reaction of a boracyclopropene intermediate **215** formed from capture of a borene anion **213** by the acetylene **214** (Scheme 3.17a). We performed the homo-coupling of phenylboronic acid **153** with borene trap diphenyl acetylene **214** (1 equiv.) using and the deuterioacetic acid in the reaction work-up. However, a slightly decrease yield of biphenyl **154** and unreacted diphenyl acetylene **214** were observed in the crude reaction mixture, with no observed dideuterated

stilbene **216** (Scheme 3.17b). These results ruled out the generation of diphenylborate intermediate in the manganese-catalysed homo-coupling reaction.



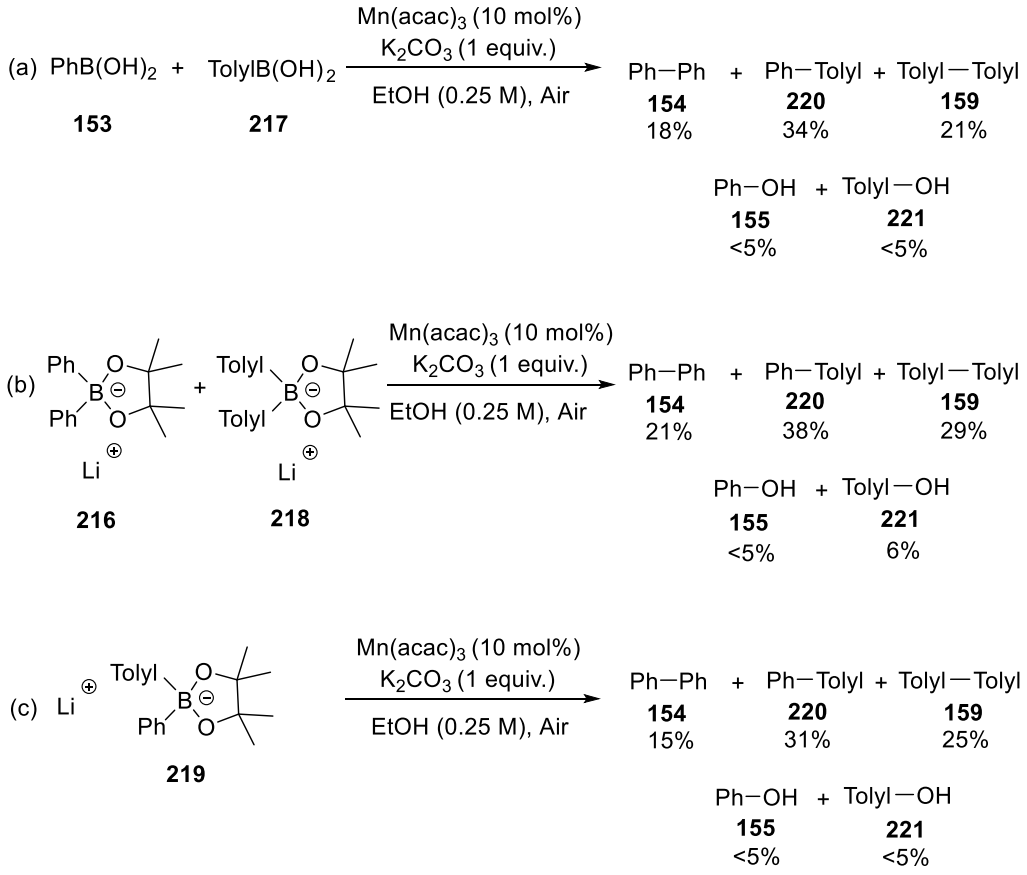
Scheme 3.17 (a) Eisch's trradiation of tetraphenylborate generated a borene anion **213** (b) Manganese-catalysed homo-coupling of phenylboronic acid **153** in the presence of borene trap diphenyl acetylene **214**.

A range of pre-activated arylboronic esters have been used in iron- and cobalt-catalysed aryl-aryl coupling reactions, in which strong organometallic reagents were used for the generation of highly reactive tetrahedral boronate complexes.[148, 150, 177, 178] We prepared the diphenylboronate complex [Li][$(Ph)_2$B(pin)] **216** by the treatment of stoichiometric phenyllithium to phenylboronic acid pinacol ester **209** using a modification of Nakamura's method (Scheme 3.18a).[177] In contrast to these previously reported activated arylboronic esters, the diphenylboronate complex [Li][$(Ph)_2$B(pin)] **216** was stable in protic solvents under an argon atmosphere and was fully characterised in d_4-methanol. The reaction of [Li][$(Ph)_2$B(pin)] **216** and stoichiometric Eschenmoser's salt **217** did not give any benzylamine **218**, indicating the phenyl group of [Li][$(Ph)_2$B(pin)] **216** was not highly nucleophilic (Scheme 3.18b). Homo-coupling of the diphenylboronate complex [Li][$(Ph)_2$B(pin)] **216** was performed under optimised reaction conditions, giving biphenyl **154** in 67% yield, trace phenol **155** and no benzene **217** (Scheme 3.18c).



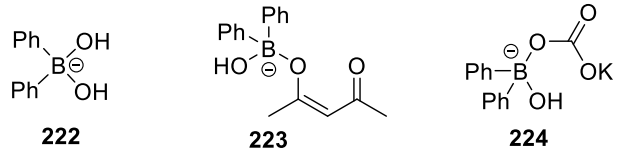
Scheme 3.18 (a) The preparation of [Li][(Ph)$_2$B(pin)] **216** using phenylboronic acid pinacol ester **209** and phenyllithium (b) Nucleophlicity test: the reaction of [Li][(Ph)$_2$B(pin)] **216** and Eschenmoser's salt (c) Manganese-catalysed homo-coupling of [Li][(Ph)$_2$B(pin)] **216** gave biphenyl **154** product.

We proposed that a tetrahedral diarylboronate complex was a key intermediate in the homo-coupling reaction, but we were not able to prepare or isolate it at this stage. In order to gain more mechanistic insights, the homo-coupling of a 1:1 mixture of phenylboronic **153** and 4-methylphenylboronic acid **217** was performed under optimised reaction conditions. The reaction gave the cross-coupling product 4-phenyltoluene **220** with the yield 34% predominately, along with biphenyl **154** and 4,4'-dimethylbiphenyl **159** in 18% and 21% yield respectively (Scheme 3.19a). When we performed the reaction using a 1:1 mixture of [Li][(Ph)$_2$B(pin)] **216** and [Li][(Tolyl)$_2$B(pin)] **218**, 4-phenyltoluene **220,** biphenyl **154** and 4,4'-dimethylbiphenyl **159** were obtained in 38%, 21% and 29% respectively (Scheme 3.19b). When the homo-coupling of [Li][(Ph)(Tolyl)B(pin)] **219** was performed, the 31% cross-coupling product **220** was not formed exclusively, with 15% biphenyl **154** and 25% 4,4'-dimethylbiphenyl **159** also observed in the reaction mixture (Scheme 3.19c).



Scheme 3.19 (a) Homo-coupling of a 1:1 mixture of phenylboronic acid **153** and 4-methylphenylboronic acid **217**. (b) Homo-coupling of a 1:1 mixture of [Li][(Ph)$_2$B(pin)] **216** and [Li][(Tolyl)$_2$B(pin)] **218**. (c) Homo-coupling of [Li][(Ph)(Tol)B(pin)] **219**.

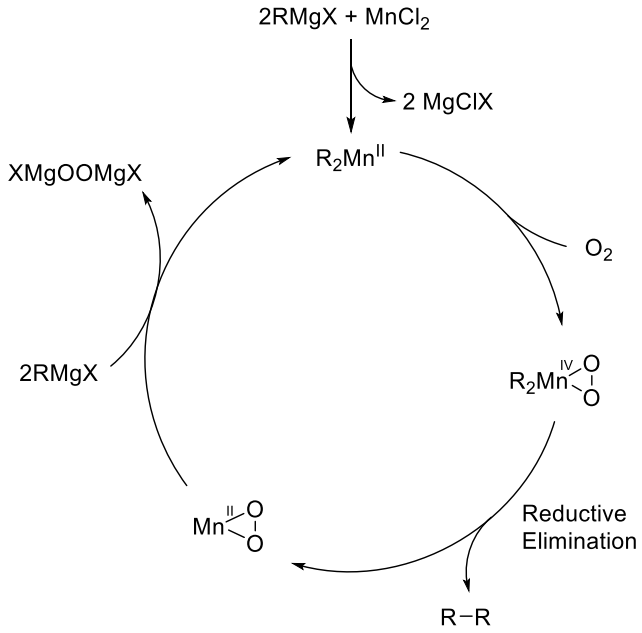
It was found that homo-coupling of 1:1 mixture of [Li][(Ph)$_2$B(pin)] **216** and [Li][(Tolyl)$_2$B(pin)] **218** (Scheme 3.19b) and homo-coupling of [Li][(Ph)(Tolyl)B(pin)] **219** (Scheme 3.19c) gave extremely similar product yields and product ratios compared with the results from standard reaction (Scheme 3.20a). Therefore, we proposed that the diarylboronate complex was a key intermediate in manganese-catalysed homo-coupling of arylboronic acids. However, the possible key intermediates (**222**-**224**) might contain acetylacetonate, carbonate or hydroxide (Scheme 3.20).



Scheme 3.20 Possible diarylboronate complexes in the manganese-catalysed homo-coupling of arylboronic acids

3.3.4.6 Proposed Reaction Mechanism

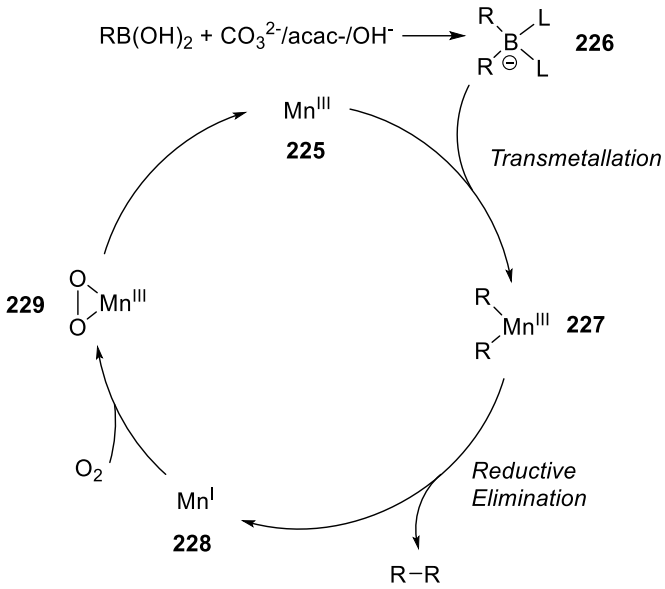
Cahiez provided mechanistic insights into the previously discussed manganese-catalysed homo-coupling of aryl Grignard reagents using dry air as an oxidant (Scheme 3.21).[158] It was proposed that key step was the oxidation of diarylmanganese(II) to a manganese(IV) peroxo species, which underwent reductive elimination to give the homo-coupled product. In the absence of air, Cahiez's system gave only trace amount of homo-coupling product. It was proposed that oxidative addition of molecular oxygen to manganese catalyst occurred before the reductive elimination and increasing the oxidation state of manganese catalyst favoured the reductive elimination. However, due to the observed stoichiometric reaction when our homo-coupling was performed under an atmosphere of argon, we proposed that oxygen must be involve later in the catalytic cycle: after the homo-coupling product has already formed.



Scheme 3.21 Cahiez's proposed reaction mechanism of manganese-catalysed homo-coupling of Grignard reagents

Based upon mechanistic studies completed thus far, a proposed reaction mechanism for the manganese-catalysed homo-coupling of boronic acids was developed (Scheme 3.22). We propose that the catalytic cycle begins with manganese in the +3 oxidation state **225**. A diarylboronate complex **226** is generated through the coordination of a ligand in the system and subsequent ligand exchange. Transmetallation between the tetrahedral diarylboronate complex **226** and the manganese complex **225** give a manganese complex bearing two aryl groups **227**. This complex **227** subsequently undergoes reductive elimination to give the homo-coupling product, reducing the manganese from Mn(III) to Mn(I) complex **X**. Oxygen

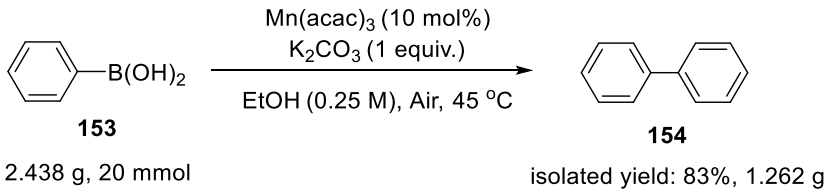
then oxidised the Mn(I) back to its Mn(III) oxidation state to give a manganese(III) peroxo species, which undergoes metathesis to give the intial manganese active species **225**.



Scheme 3.22 Proposed reaction mechanism of manganese-catalysed homo-coupling of boronic acids.

3.3.5 Gram-Scale Reaction

Importantly, and of industrial and practical relevance, the gram-scale manganese-catalysed homo-coupling reaction of phenylboronic acid **153** was carried out under optimised reaction condition (Scheme 3.23). The product biphenyl **154** was obtained in high yield.



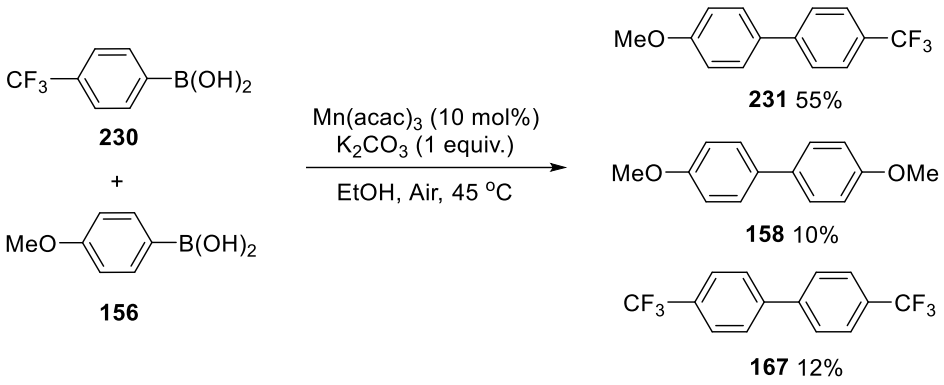
Scheme 3.23 Gram-scale manganese-catalysed homo-coupling of phenylboronic acid **X**.

3.3.6 Manganese-Catalysed Cross-Coupling of Boronic Acids

The reactivity shown from the manganese catalyst reported herein is a promising step toward developing a manganese-catalysed cross-coupled reaction. The Cahiez system showed chemoselectivity for the hetero-coupled product from aryl Grignard reagents and alkynyl Grignard reagents. As the preparation of alkynylboronic acid was not successful (See section 3.3.2), we focused on performing a manganese-catalysed coupling reaction using a 1:1 mixture

of two different arylboronic acids. We proposed that the formation of hetero-coupled product would be controlled by reaction optimisation.

Manganese-catalysed coupling reaction between 4-trifluromethylphenylboronic acid **230** and 4-methoxyphenylboronic acid **156** was investigated (Scheme 3.24). After a series of reaction optimisation, cross-coupling of 4-trifluoromethylphenylboronic acid **230** and 4-methoxyphenylboronic acid **156** gave 1-(4-methoxyphenyl)-4-(trifluoromethyl)benzene **231** with the yield 55% predominately, and homo-coupling product 4,4'-dimethoxybiphenyl **158** and 4,4'-bis(trifluoromethyl)biphenyl **167** were observed in 10% and 12% yield respectively.

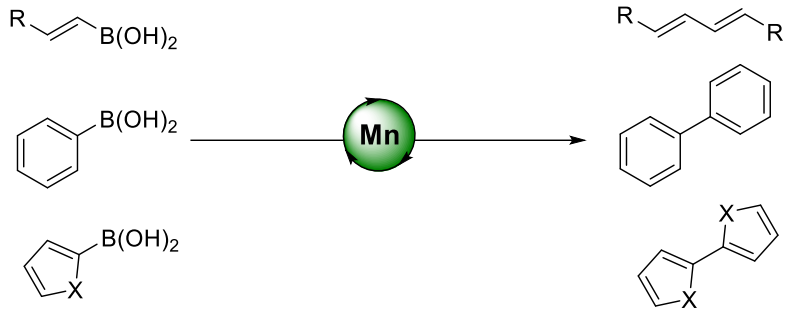


Scheme 3.24 Manganese-catalysed cross-coupling of 4-trifluoromethylphenylboronic acid **230** and 4-methoxyphenylbronic acid **156**.

3.4 Conclusions and Future Work

We have developed the manganese-catalysed homo-coupling of aryl-, alkenyl- and heterocyclic boronic acids across a range of electronically and sterically differentiated coupling partners (30 examples, 50-90%). This mild and operationally simple coupling reaction uses commercially available manganese(III) acetylacetonate, ethanol as the solvent, and air as the terminal oxidant. This represents the first-stage in developing a new manganese-catalysed cross-coupling reaction for the synthesis biaryl compounds.

***This work*: Manganese-catalysed coupling of boronic acids**



- ***Earth-abundant metal catalysis***
- ***Air and moisture tolerant***
- ***C(sp^2)-C(sp^2) coupling***
- ***Environmental benign process***
- ***Excellent functional group tolerence***
- ***Macrocycle synthesis***

The coupling reaction between two electronically differentiated arylboronic acids was performed and the hetero-coupled product was obtained in 55% yield. However, we were not able to isolate three different products though flash chromatography and recrystallization. The catalytic system could be also biased with excess of one arylboronic acid to possibly direct chemoselectivity towards the hetero-coupled product. Therefore, cross-coupling reactions using different quantities of two different boronic acids should be investigated in the future. Moreover, it would be interesting to develop a cross-coupling between arylboronic acid and alkenylbornic acids or heterocyclic boronic acids. The homo-coupling substrate scope is highly limited to C(sp_2)-C(sp_2) coupling, it would be interesting to expand the substrate scope to homo-couple alkyl boronic acids.

Future work could also be focused on developing a novel aryl-aryl coupling system using a manganese catalyst wherein oxidative cross-coupling could be achieved between different nucleophilic carbon sources, such as aryl silane and arylboronic acid.

With regard to the reaction mechanism, we were not able to prepare any possible intermediate independently. We proposed that a diarylboronate complex was a key intermediate in the

homo-coupling reaction, reaction progress monitoring of the homo-coupling of a 1:1 mixture of diarylboronate complexes [Li][$(Ph)_2$B(pin)] and [Li][$(Tolyl)_2$B(pin)] would be extremely useful compared with the monitoring of homo-coupling a 1:1 mixture of phenylboronic and 4-methylphenylboronic acid.

Chapter 4 Experimental

4.1 General Experimental

Reaction Setup: All reactions were performed in oven (185 °C) and/or flamed-dried glassware under an atmosphere of anhydrous nitrogen or argon, unless otherwise indicated. All air- and moisture sensitive reactions were carried out using standard vacuum line and Schlenk techniques, or in a glovebox with a purified argon atmosphere. All glassware was cleaned using base (KOH, $_i$PrOH) and acid (HCl_{aq}) baths and subsequent acetone washes. All reported reaction temperatures correspond to external bath temperatures. Room temperature (r.t.) was approximately 20-22 °C. Brine refers to a saturated solution of sodium chloride in H_2O.

NMR Spectroscopy: ^1H, ^{11}B, ^{13}C, ^{19}F and ^{29}Si NMR spectra were recorded on Bruker Avance III 400 and 500 MHz and Bruker Avance I 600 MHz spectrometers. Chemical shifts are reported in parts per million (ppm). ^1H and ^{13}C Spectra were referenced relative to the solvent peaks ($CDCl_3$ 7.27 ppm, 77.2 ppm; CD_2Cl_2 5.32 ppm, 53.8 ppm; C_6D_6 7.16 ppm, 128.1 ppm; *d*$_8$-THF 3.58, 1.72 ppm, 67.2, 25.3 ppm; *d*$_4$-methanol: 3.35 ppm and 4.78 ppm, 49.3 ppm) Multiplicities are indicated by app. (apparent), br. (broad), s (singlet), d (doublet), t (triplet), q (quartet), quin. (quintet), sext. (sextet), sept. (septet), non. (nonet). Coupling constants, *J*, are reported in Hertz and rounded to the nearest 0.1 Hz. ^1H and ^{13}C assignments are corroborated through DEPT 135 and 2D NMR experiments (COSY, HSQC, HMBC, included where appropriate).

Infrared Spectroscopy: Infra-red spectra were obtained using a Shimadzu IRAffinity-1 spectrometer (serial no. A213747). Peaks are reported in cm^{-1}.

Mass Spectrometry: Mass spectrometry (MS) was performed by the University of Edinburgh, School of Chemistry, Mass Spectrometry Laboratory. High resolution mass spectra were recorded on a VG autospec, or Thermo/Finnigan MAT 900, mass spectrometer. Electron Ionisation (EI^+) spectra were performed at 70 eV using methane as the carrier gas, with either a double focusing sector field (DFSF) or time-of-flight (TOF) mass analyser. Chemical Ionization (CI^+) spectra were performed with methane reagent gas, with either a double focusing sector field (DFSF) or time-of-flight (TOF) mass analyser. Electrospray Ionization (ESI^+) spectra were performed using a time-of-flight (TOF) mass analyser. Data are reported in the form of m/z (intensity relative to the base peak = 100).

Melting Points: Melting points (mp) were determined on a Stuart Scientific SMP10, or Griffin Gallankamp, melting point apparatus in capillary tubes.

Chromatography: Analytical thin-layer chromatography was performed on aluminium-backed silica plates (Merck 60 F_{254}). Pet. ether refers to petroleum ether 40-60. Product spots were visualised by UV light at 254 nm, and subsequently developed using potassium permanganate solution if appropriate. Flash column chromatography was performed on silica gel (Merck Kielselgel 60, 40-63 μm) unless otherwise stated.

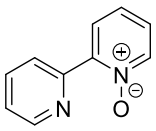
Solvents: All solvents for air- and moisture sensitive techniques were obtained from an anhydrous solvent system (Innovative Technology). Tetrahydrofuran (Fisher, HPLC grade) was dried by percolation through two columns packed with neutral alumina under a positive pressure of argon. Toluene (ACS grade) was dried by percolation through a column packed with neutral alumina and a column packed with Q5 reactant (supported copper catalyst for scavenging oxygen) under a positive pressure of argon. Ethanol (absolute, VWR) was used as received. Anhydrous d_8-tetrahydrofuran and d_6-benzene was prepared by distillation from sodium/benzophenone. Solvents for filtrations, transfers, chromatography and recrystallisation not performed using air- and moisture sensitive techniques were of ACS grade and used without further purification.

Chemicals: All reagents were purchased from Sigma Aldrich, Alfa Aesar, Acros organics, Tokyo Chemical Industries UK, Fluorochem and Apollo Scientific or synthesised within the laboratory according to literature protocols. Cobalt(II) dichloride (>98%) was purchased from Sigma Aldrich (product number 60818. Lot 19226310). Cobalt(II) dichloride was purchased from was purchased from Strem chemical Inc.UK (product number 93-2721. Lot A6262018). Sodium *tert*-butoxide (97%) was purchased from Sigma Aldrich (product number 359270. Lot 45612018). Manganese(III) acetylacetonate was purchased from Strem chemical Inc.UK (product number 25-1000. Lot A6921329).

HPLC: Chiral HPLC separations were performed on a Shimadzu LC-20AT equipped with an SPD-20A UV-Vis detector and Daicel Chiralpak IB column (250 mm length × 4.6 mm Ø, particle size 5 μm), solvent systems and retention times are reported in the text.

4.2 Preparation of Bipyridyl Oxazoline Ligands

2,2′-Bipyridine-1-oxide



Prepared according to a literature procedure.[126]

2,2′-Bipyridine (2.00 g, 12.8 mmol) was dissolved in trifluoroacetic acid (15 mL) at 10 °C, then 30% solution hydrogen peroxide (2 mL, 15.50 mmol) was added and the mixture was stirred at room temperature for 3 h. The solution was diluted with chloroform (25 mL) and washed with aqueous sodium hydroxide solution (3M, 3 x 20 mL). The aqueous phase was extracted twice with chloroform (2 x 10 mL), and the combined organic phases were dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude reaction product was purified by flash column chromatography (40 g SiO_2, 30 mm Ø, petroleum ether/dichloromethane 10:1) to give 2,2′-bipyridine-1-oxide (1.76 g, 10.2 mmol, 80%) as a pale yellow solid.

m.p 57-59 °C (dichloromethane) Lit:[126] 58-60 °C (dichloromethane)

^{1}H NMR: (500 MHz, $CDCl_3$)

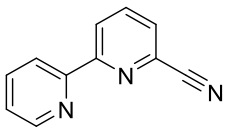
8.92 (d, *J* = 8.1 Hz, 1H), 8.74 (d, *J* = 4.0 Hz, 1H), 8.32 (d, *J* = 6.3 Hz, 1H), 8.20 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.84 (app. td, *J* = 7.9, 1.8 Hz, 1H), 7.41-7.34 (m, 2H), 7.30-7.25 (m, 1H).

^{13}C NMR: (125 MHz, $CDCl_3$)

149.7, 149.4, 147.4, 140.7, 136.2, 127.9, 125.6, 125.5, 125.2, 124.3.

The spectroscopic data were in accordance with those reported in the literature.[126]

2,2′-Bipyridyl-6-carbonitrile



Prepared according to a literature procedure.[126]

Trimethylsilyl cyanide (2.61 g, 26.3 mmol) was added to a stirred mixture of 2,2′-bipyridine-1-oxide (1.76 g, 10.2 mmol) in anhydrous dichloromethane (30 mL) at 0 °C. Benzoyl chloride (1.23 mL, 10.2 mmol) was added dropwise and the mixture warmed to room temperature and stirred for 20 h under nitrogen. Aqueous sodium carbonate solution (2 M, 10 mL) was added, and the resulting mixture extracted with dichloromethane (3 x 10 mL), dried over $MgSO_4$, filtered, and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (30 g SiO_2, 30 mm Ø, dichloromethane/ethyl acetate 7:1) to give 2,2′-bipyridyl-6-carbonitrile (1.31 g, 7.24 mmol, 71%) as a colourless solid.

m.p 129-131 °C (dichloromethane) Lit:[126] 130-132 °C (dichloromethane)

^{1}H NMR: (500 MHz, $CDCl_3$)

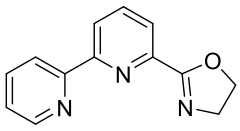
8.71-8.66 (m, 2H), 8.46 (d, *J* = 8.0 Hz, 1H), 7.95 (t, *J* = 7.9 Hz, 1H), 7.85 (td, *J* = 7.8, 1.8 Hz, 1H), 7.70 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.37 (ddd, *J* = 7.5, 4.8, 1.1 Hz, 1H).

^{13}C NMR: (125 MHz, $CDCl_3$)

157.8, 154.1, 149.3, 137.9, 137.2, 133.5, 128.2, 124.2, 124.2, 121.6, 117.4.

The spectroscopic data were in accordance with those reported in the literature.[126]

2,2′-Bipyridyl-6-oxazoline



Prepared according to a modified literature procedure.[61]

To an oven-dried 50 mL two-necked flask fitted with a reflux condenser was charged with 2,2′-bipyridyl-6-carbonitrile (300 mg, 1.64 mmol) and zinc triflate (16 mg, 0.05 mmol). The system was purged with nitrogen and anhydrous toluene (5 mL) was added. A solution of ethanolamine (150 mg, 2.46 mmol) in anhydrous toluene (10 ml) was added the flask. The resulting mixture was heated under reflux for 48 h, cooled to room temperature, diluted with ethyl acetate (20 mL) and then washed with saturated aqueous sodium hydrogen carbonate (3 x 10 mL) and water (20 mL), dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. The crude mixture was purified by flash column chromatography (40 g SiO_2, 30 mm Ø, petroleum ether/EtOAc 10:1) to give 2,2′-bipyridyl-6-[(*S*)-*iso*-butyloxazoline] (222 mg, 0.99 mmol, 61%) as a colourless solid.

m.p 87-89 °C (petroleum ether/EtOAc)

MS: (HRMS - EI^+)

Found 225.25617 ($C_{13}H_{11}O_1N_3$), requires 225.25673.

IR: *vmax* (*neat*)

3055 (w), 1712 (s), 1699 (s), 1612 (m), 1511 (m), 1011 (m).

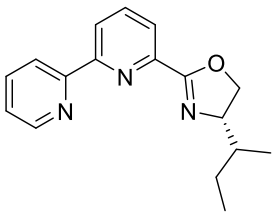
$_1$H NMR: (500 MHz, $CDCl_3$)

8.76-8.71 (m, 1H), 8.55 (dd, *J* = 7.9, 1.0 Hz, 1H), 8.38-8.35 (m, 1H), 8.24 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.99 (t, *J* = 7.8 Hz, 1H), 7.85 (td, *J* = 7.6, 1.8 Hz, 1H), 7.37 (ddd, *J* = 7.5, 4.8, 1.2 Hz, 1H), 3.94-3.90 (m, 2H), 3.76-3.71 (m, 2H).

$_{13}$C NMR: (125 MHz, $CDCl_3$)

167.6, 156.3, 155.9, 146.9, 146.6, 140.0, 137.9, 126.1, 124.0, 123.5, 122.0, 68.8, 55.1.

2,2′-Bipyridyl-6-((*S*)-*iso*-butyloxazoline)



Prepared according to a modified literature procedure.[61]

To an oven-dried 50 mL two-necked flask fitted with a reflux condenser was charged with 2,2′-bipyridyl-6-carbonitrile (300 mg, 1.64 mmol) and zinc triflate (16 mg, 0.05 mmol). The system was purged with argon and anhydrous toluene (5 mL) was added. A solution of (*S*)-(+)-isoleucinol (290 mg, 2.46 mmol) in anhydrous toluene (10 mL) was added the flask. The resulting mixture was heated under reflux for 48 h, cooled to room temperature, diluted with ethyl acetate (20 mL) and then washed with saturated aqueous sodium hydrogen carbonate (3 x 10 mL) and water (20 mL), dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. The crude mixture was purified by flash column chromatography (40 g SiO_2, 30 mm Ø, petroleum ether/EtOAc 10:1) to give 2,2′-bipyridyl-6-[(*S*)-*sec*-butyloxazoline] (248 mg, 0.98 mmol, 54%) as a colourless solid.

m.p 110-112 °C (petroleum ether/EtOAc)

MS: (HRMS - EI^+)

Found 281.15277 ($C_{17}H_{19}O_1N_3$), requires 281.15228.

IR: *vmax* (*neat*)

3055 (w), 1612 (s), 1499 (s), 1457 (s), 1433 (m), 1111 (s), 1022 (m).

^{1}H NMR: (500 MHz, $CDCl_3$)

8.71-8.68 (m, 1H), 8.57-8.52 (m, 2H), 8.13 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.92 (t, *J* = 7.9 Hz, 1H), 7.84 (td, *J* = 7.8, 1.8 Hz, 1H), 7.37 (ddd, *J* = 7.5, 4.8, 1.2 Hz, 1H), 4.55 (dd, *J* = 9.0, 7.4 Hz, 1H), 4.38-4.25 (m, 2H), 1.86-1.77 (m, 1H), 1.74-1.65 (m, 1H), 1.61-1.52 (m, 1H), 1.00 (t, *J* = 7.4 Hz, 3H), 0.92 (d, *J* = 7.5 Hz, 3H).

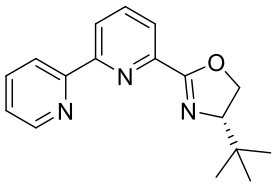
^{13}C NMR: (125 MHz, $CDCl_3$)

164.9, 156.1, 155.8, 147.9, 146.1, 139.4, 138.9, 124.7, 124.4, 123.8, 121.7, 76.9, 73.0, 33.8, 25.8, 15.7, 12.6.

***ee*:** *ee* was not obtained due to time constraints of the project

$[\alpha]_{20D}$ = 54.1 (c = 0.25, $CHCl_3$)

2,2′-Bipyridyl-6-((*S*)-*tert*-butyloxazoline)



Prepared according to a modified literature procedure.[61]

To an oven-dried 50 mL two-necked flask fitted with a reflux condenser was charged with 2,2′-bipyridyl-6-carbonitrile (300 mg, 1.64 mmol) and zinc triflate (16 mg, 0.05 mmol). The system was purged with argon and anhydrous toluene (5 mL) was added. A solution of L-*tert*-leucinol (290 mg, 2.46 mmol) in anhydrous toluene (10 ml) was added to the flask. The resulting mixture was heated under reflux for 48 h, cooled to room temperature, diluted with ethyl acetate (20 mL) and then washed with saturated aqueous sodium hydrogen carbonate (3 x 10 mL) and water (20 mL), dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. The crude mixture was purified by flash column chromatography (40 g SiO_2, 30 mm Ø,

petroleum ether/EtOAc 10:1) to give 2,2′-bipyridyl-6-[(*S*)-*tert*-butyloxazoline] (276mg, 0.98 mmol, 60%) as a colourless solid.

m.p 138-139 °C (petroleum ether/EtOAc)

MS: (HRMS - EI^+)

Found 281.15264 ($C_{17}H_{19}O_1N_3$), requires 281.15226.

IR: *vmax* (*neat*)

3013 (w), 1640 (s), 1524 (s), 1497 (s), 1433 (m), 1250 (m), 1059 (m).

^{1}H NMR: (500 MHz, $CDCl_3$)

8.70-8.68 (m, 1H), 8.65-8.52 (m, 2H), 8.16 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.91 (t, *J* = 7.9 Hz, 1H), 7.84 (td, *J* = 7.5, 1.8 Hz, 1H), 7.33 (ddd, *J* = 7.5, 4.7, 1.2 Hz, 1H), 4.52 (dd, *J* = 10.2, 8.7 Hz, 1H), 4.38 (app. t, *J* = 8.4 Hz, 1H), 4.17 (dd, *J* = 10.1, 8.4 Hz, 1H), 1.02 (s, 9H).

^{13}C NMR: (125 MHz, $CDCl_3$)

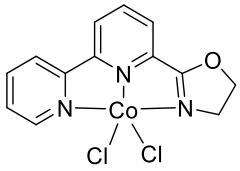
162.7, 156.1, 155.5, 149.1, 146.6, 137.4, 136.9, 124.2, 124.0, 122.8, 121.7, 76.4, 69.4, 34.1, 26.0.

***ee*:** *ee* was not obtained due to time constraints of the project

$[\alpha]_{20D}$ = 49.8 (c = 0.25, $CHCl_3$)

4.3 Preparation of Cobalt Complexes

$_{H}$BPOCoCl$_2$



2,2′-Bipyridyl-6-oxazoline (79 mg, 0.35 mmol) and cobalt(II) chloride (32 mg, 0.35 mmol) were stirred in anhydrous THF (15 mL) for 24 h at room temperature. The mixture was concentrated *in vacuo*, anhydrous diethyl ether (20 mL) was added, the precipitate collected by filtration and washed with anhydrous diethyl ether (20 mL) to give $_{H}$BPOCoCl$_2$ (111 mg, 0.32 mmol, 90%) as a light blue amorphous solid.

MS: (HRMS - EI$^+$)

Found 355.08456 ($C_{13}H_{11}O_1N_3CoCl_2$), requires 355.08581.

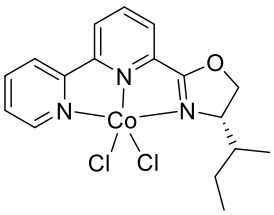
IR: *vmax* (*neat*)

3043 (w), 1633 (m), 1598 (m), 1562 (w), 1541 (m), 1477 (w). 1433 (m), 1370 (w), 1299 (w).

^{1}H NMR: (500 MHz, d_6-THF)

39.95 (br. s), 8.20 (br. s), 5.55 (br. s), 5.37 (br. s), 3.71 (br. s), 2.13 (br. s), 1.61 (br. s), -9.85 (br. s), -18.86 (br. s).

$_{s\text{Bu}}$BPOCoCl$_2$



2,2′-Bipyridyl-6-[(*S*)-*sec*-butyloxazoline] (100 mg, 0.35 mmol) and anhydrous cobalt(II) chloride (32 mg, 0.35 mmol) were stirred in anhydrous THF (15 mL) for 24 h at room temperature. The mixture was concentrated *in vacuo*, anhydrous diethyl ether (20 mL) was added, the precipitate collected by filtration and washed with anhydrous diethyl ether (20 mL) to give $_{s\text{Bu}}$BPOCoCl$_2$ (117 mg, 0.32 mmol, 90%) as a light blue amorphous solid.

MS: (HRMS - EI^+)

Found 410.02499 ($C_{17}H_{19}O_1N_3CoCl_2$), requires 410.02426.

IR: *vmax* (*neat*)

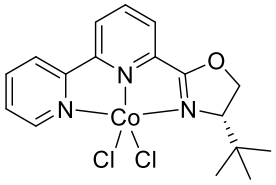
3223 (w), 1733 (m), 1590 (m), 1560 (w), 1501 (w), 1431 (m). 1403 (w), 1350 (w).

$_1$H NMR: (500 MHz, d_6-THF)

24.41 (br. s), 20.08 (br. s), 11.60 (br. s), 8.77 (br. s), 8.13 (br. s), 5.60 (br. s), 5.26 (br. s), 4.86 (br. s), -14.06 (br. s).

***ee*:** *ee* was not determined as the cobalt complex decomposed in HPLC

$_{t\text{Bu}}$BPOCoCl$_2$



2,2′-Bipyridyl-6-[(*S*)-*tert*-butyloxazoline] (100 mg, 0.35 mmol) and anhydrous cobalt(II) chloride (32 mg, 0.35 mmol) were stirred in anhydrous THF (15 mL) for 24 h at room temperature. The mixture was concentrated *in vacuo*, anhydrous diethyl ether (20 mL) was added, the precipitate collected by filtration and washed with anhydrous diethyl ether (20 mL) to give $_{t\text{Bu}}$BPOCoCl$_2$ (114 mg, 0.29 mmol, 89%) as a light blue amorphous solid.

MS: (HRMS - EI^+)

Found 410.02248 ($C_{17}H_{19}O_1N_3CoCl_2$), requires 410.02426.

IR: *vmax* (*neat*)

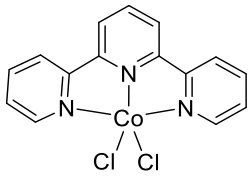
3011 (w), 1803 (m), 1794 (w), 1610 (w), 1566 (m), 1456 (w).

$_1$H NMR: (500 MHz, d_6-THF)

87.30 (br. s), 73.4 (br. s), 66.5 (br. s), 29.57 (br. s), 13.15 (br. s), 9.54 (br. s), -5.66 (br. s), -7.46 (br. s), -17.64 (br. s), -20.61(br. s).

***ee*:** *ee* was not determined as the cobalt complex decomposed in HPLC

TerpyCoCl$_2$



Terpyridine (82 mg, 0.35 mmol) and anhydrous cobalt (II) chloride (32 mg, 0.35 mmol) were stirred in anhydrous THF (15 mL) for 24 h at room temperature. The mixture was concentrated *in vacuo*, anhydrous diethyl ether (20 mL) was added, the precipitate collected by filtration and washed with anhydrous diethyl ether (20 mL) to give terpyridine cobalt(II) dichloride (107 mg, 0.32 mmol, 95%) as a light blue amorphous solid.

MS: (HRMS - EI$^+$)

Found 361.97214 ($C_{15}H_{11}N_3CoCl_2$), requires 361.97287.

IR: *vmax* (*neat*)

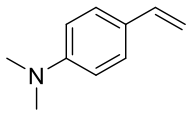
3011 (w), 1803 (m), 1794 (m), 1610 (m), 1566 (w), 1456 (w).

^{1}H NMR: (500 MHz, *d*$_6$-THF)

8.92 (br. s), 7.30 (br. s), 4.09 (br. s), 3.48 (br. s), 3.25 (br. s), 2.05 (br. s).

4.4 Preparation of Styrene Derivatives

_N,N_-Dimethylamino-4-vinylbenzene



Prepared according to a literature procedure.[179]

n-BuLi (1.6 M in hexanes, 5.60 mL, 8.95 mmol), was added dropwise to a solution of methyltriphenylphosphonium bromide (3.20 g, 8.95 mmol) in THF (20 mL) at room temperature under the atmosphere of nitrogen. After stirring for 15 min, a solution of 4-dimethylaminobenzaldehyde (1.14 g, 7.65 mmol) in THF (10 mL) was added dropwise and the resulting mixture was stirred at room temperature for 16 h. Water (30 mL) and diethyl ether (30 mL) were added and two layers were separated. The aqueous solution was extracted with diethyl ether for three times and the combined organic extracts were dried over $MgSO_4$ filtered, and concentrated *in vacuo*. The crude reaction product was purified by flash column chromatography (SiO_2 50 g, 30 mm Ø, petroleum ether/diethyl ether 10:1) to provide *N*,*N*-dimethylamino-4-vinylbenzene as a pale yellow oil (934 mg, 6.35 mmol, 83%).

^{1}H NMR: (500 MHz, $CDCl_3$)

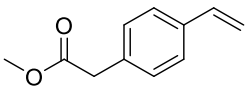
7.34 (d, *J* = 8.5 Hz, 2H), 6.71 (d, *J* = 8.4 Hz, 2H), 6.65 (dd, *J* = 10.9, 17.5 Hz, 1H), 5.56 (d, *J* = 17.5 Hz, 1H), 5.04 (d, *J* = 10.8 Hz, 1H), 3.0 (s, 6H).

^{13}C NMR: (125 MHz, $CDCl_3$)

150.3, 136.3, 127.2, 126.3, 112.4, 109.4, 40.5.

The spectroscopic data were in accordance with those reported in the literature.[179]

4-Vinyl(phenyl)acetic acid methyl ester



Prepared according to a literature procedure.[180]

1,8-Diazabicycloundec-7-ene (1.71 g, 7.69 mmol) was added to a magnetically stirred solution of 2-(4-vinylphenyl)acetic acid (0.95 g, 5.92 mmol) in THF (10 mL) at 0 °C. The solution was treated in one portion with methyl iodide (0.47 mL, 1.09 g, 7.69 mmol) and the mixture was

stirred at room temperature for 3h before being diluted with diethyl ether (20 mL). The mixture was then washed with H_2O (10 mL), HCl (1M, 10 mL), NaOH (1M, 10 mL), HCl (1M, 10 mL), and H_2O (10 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude reaction product was purified by flash column chromatography (SiO_2 30 g, 30 mm Ø, petroleum ether/diethyl ether 20:1) to provide 4-vinyl(phenyl)acetic acid methyl ester as a colourless oil (520 mg, 2.96 mmol, 50%).

^{1}H NMR: (500 MHz, $CDCl_3$)

7.39 (d, *J* = 8.1 Hz, 2H), 7.27 (d, *J* = 8.1 Hz, 2H), 6.73 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.76 (d, *J* = 17.6 Hz, 1H), 5.26 (d, *J* = 10.9 Hz, 1H), 3.72 (s, 3H), 3.64 (s, 2H).

^{13}C NMR: (125 MHz, $CDCl_3$)

171.9, 136.5, 136.4, 133.5, 129.5, 126.4, 113.9, 52.1, 40.9.

The spectroscopic data were in accordance with those reported in the literature.[180]

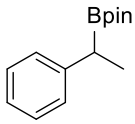
4.5 Alkene Hydroboration: Isolated Products

General procedure A: Markovnikov hydroboration of alkenes using cobalt complexes

A reaction vial was charged with cobalt pre-catalyst (5.0 μmol, 1 mol%) and activator (10.0 μmol, 2 mol%) in an argon atmosphere glovebox and the vial sealed with parafilm. The reaction vial was removed from the glovebox and anhydrous THF (3 mL), pinacolborane (80 μL, 0.55 mmol, 1.1 equiv) and alkene (0.5 mmol, 1 equiv.) were sequentially added and the resulting mixture was stirred at room temperature for 1 h, diluted with diethyl ether (2 mL) and washed with water (2 mL).

1,3,5-Trimethoxybenzene (0.1 M solution in diethyl ether, 1 mL, 0.1 mmol), as an internal standard, was added and the organic phase of the mixture was sampled. The NMR yield and branched:linear regioselectivity of the reaction were determined from integrals of product peaks in ^{1}H NMR of crude reaction mixtures. The hydroboration product was purified following column chromatography.

2-(1-Phenylethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



Using the general procedure A, styrene (57 μL, 0.5 mmol), pinacolborane (80 μL, 0.55 mmol), bipyridiyl-oxazoline cobalt(II) dichloride [$^{t\text{Bu}}$BPOCoCl$_2$] (2.0 mg, 5.0 μmol, 1 mol%) and sodium *tert*-butoxide (1.0 mg, 10.0 μmol, 2 mol%) were reacted in THF (3 mL) to give the crude product mixture. The mixture was purified by flash column chromatography (20 g SiO_2, 30 mm Ø, petroleum ether/diethyl ether 15:1) to give 2-(1-phenylthyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (104 mg, 0.45 mmol, 90%) as a colourless oil , with the regioselectivity of 97:3 (B/L).

^{1}H NMR: (500 MHz, $CDCl_3$)

7.30-7.22 (m, 3H), 7.18-6.13 (m, 2H), 2.46 (q, J = 7.5 Hz, 1H), 1.35 (d, J = 7.5 Hz, 3H), 1.24 (s, 6H), 1.23 (s, 6H).

^{13}C NMR: (125 MHz, $CDCl_3$)

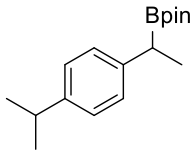
145.0, 128.3, 127.8, 125.1, 83.3, 24.6, 24.5, 16.9.

^{11}B NMR: (160 MHz, $CDCl_3$)

33.5.

The spectroscopic data were in accordance with those reported in the literature.[98]

2-(1-(4-*iso*-Propylphenyl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



Using the general procedure A, 4-*iso*-propylstyrene (73 mg, 0.5 mmol), pinacolborane (80 µL, 0.55 mmol), bipyridiyl-oxazoline cobalt(II) dichloride [^{t}BuBPOCoCl$_2$] (2.0 mg, 5.0 µmol, 1 mol%) and sodium *tert*-butoxide (1.0 mg, 10.0 µmol, 2 mol%) were reacted in THF (3 mL) to give the crude product mixture which was purified by flash column chromatography (20 g SiO_2, 30 mm Ø, petroleum ether/diethyl ether 15:1) to give 2-(1-(4-*iso*-propylphenyl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (111 mg, 0.41 mmol, 81%) as a colourless oil, with the regioselectivity of 99:1 (B/L).

MS: (HRMS - EI$^+$)

Found 274.20977 ($C_{17}H_{27}B_1O_2$), requires 274.20986

IR: *vmax* (*neat*)

2958 (w), 1512 (s), 1352 (w), 1319 (s), 1269 (w), 1213 (w), 1143 (w), 1062 (w).

^{1}H NMR: (500 MHz, $CDCl_3$)

7.18-7.13 (m, 4H), 2.88 (sept, *J* = 6.9 Hz, 1H), 2.42 (q, *J* = 7.5 Hz, 1H), 1.34 (d, *J* = 7.5 Hz, 3H), 1.26 (s, 3H), 1.25 (s, 3H), 1.24 (s, 6H), 1.23 (s, 6H).

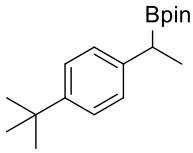
^{13}C NMR: (125 MHz, $CDCl_3$)

145.4, 142.1, 127.6, 126.3, 83.2, 33.6, 24.8 24.7, 24.6, 24.0, 17.3.

^{11}B NMR: (160 MHz, $CDCl_3$)

33.7.

2-(1-(4-*tert*-Butylphenyl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



Using the general procedure A, 4-*tert*-butylstyrene (92 µL, 0.5 mmol), pinacolborane (80 µL, 0.55 mmol), bipyridiyl-oxazoline cobalt(II) dichloride [$_{t\text{Bu}}$BPOCoCl$_2$] (2.0 mg, 5.0 µmol, 1 mol%) and sodium *tert*-butoxide (1.0 mg, 10.0 µmol, 2 mol%) were reacted in THF (3 mL) to give the crude product mixture. The mixture was purified by flash column chromatography (20 g SiO_2, 30 mm Ø, petroleum ether/diethyl ether 15:1) to give 2-(1-(4-*tert*-butylphenyl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (127 mg, 0.44 mmol, 87%) as a colourless oil, with the regioselectivity of 97:3 (B/L).

$_1$H NMR: (500 MHz, $CDCl_3$)

7.32-7.27 (m, 2H), 7.19-7.14 (m, 2H), 2.43 (q, *J* = 7.5 Hz, 1H) 1.34 (d, *J* = 7.5 Hz, 3H), 1.33 (s, 9H), 1.25 (s, 6H), 1.24 (s, 6H).

$_{13}$C NMR: (125 MHz, $CDCl_3$)

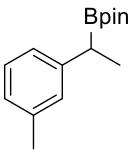
147.6, 141.7, 127.4, 125.2, 83.2, 34.2, 31.5, 24.7, 24.6, 17.2.

$_{11}$B NMR: (160 MHz, $CDCl_3$)

33.6.

The spectroscopic data were in accordance with those reported in the literature.[98]

2-(1-(3-Methylphenyl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



Using the general procedure A, 3-methylstyrene (66 µL, 0.5 mmol), pinacolborane (80 µL, 0.55 mmol), bipyridiyl-oxazoline cobalt(II) dichloride [$_{t\text{Bu}}$BPOCoCl$_2$] (2.0 mg, 5.0 µmol, 1 mol%) and sodium *tert*-butoxide (1.0 mg, 10.0 µmol, 2 mol%) were reacted in THF (3 mL) to give the crude product mixture which was purified by flash column chromatography (20 g SiO_2, 30 mm Ø, petroleum ether/diethyl ether 15:1) to give 2-(1-(3-methylphenyl)ethyl)-

4,4,5,5-tetramethyl-1,3,2-dioxaborolane (97 mg, 0.40 mmol, 79%) as a colourless oil, with the regioselectivity of 97:3 (B/L).

MS: (HRMS - EI^+)

Found 246.18590 ($C_{15}H_{23}B_1O_2$), requires 246.18639

IR: *vmax* (*neat*)

2999 (m), 1371 (s), 1350 (s), 1319 (m), 1100 (w).

$_1$H NMR: (500 MHz, $CDCl_3$)

7.19-7.15 (m, 1H), 7.07-7.02 (m, 2H), 6.99-6.95 (m, 1H), 2.42 (q, *J* = 7.5 Hz, 1H), 2.23 (s, 3H), 1.34 (d, *J* = 7.6 Hz, 3H), 1.24 (s, 6H), 1.23 (s, 6H).

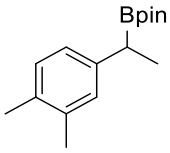
$_{13}$C NMR: (125 MHz, $CDCl_3$)

144.9, 137.7, 128.6, 128.1, 125.8, 124.8, 83.4, 83.3, 24.6, 24.6, 21.5, 17.1.

$_{11}$B NMR: (160 MHz, $CDCl_3$)

33.6.

2-(1-(3,4-Dimethylphenyl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



Using the general procedure A, 3,4-dimethylstyrene (73 µL, 0.5 mmol), pinacolborane (80 µL, 0.55 mmol), bipyridiyl-oxazoline cobalt(II) dichloride [$_{t\text{Bu}}$BPOCoCl$_2$] (2.0 mg, 5.0 µmol, 1 mol%) and sodium *tert*-butoxide (1.0 mg, 10.0 µmol, 2 mol%) were reacted in THF (3 mL) to give the crude product mixture which was purified by flash column chromatography (20 g SiO_2, 30 mm Ø, petroleum ether/diethyl ether 15:1) to give 2-(1-(3,4-dimethylphenyl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (94 mg, 0.36 mmol, 72%) as a colourless oil, with the regioselectivity of 95:5 (B/L).

MS: (HRMS - EI^+)

Found 260.19113 ($C_{16}H_{25}B_1O_2$), requires 260.19563

IR: *vmax* (*neat*)

2922 (m), 1472 (s), 1411 (s), 1369 (m), 1287 (w), 1171 (w), 1120 (w).

^{1}H NMR: (500 MHz, $CDCl_3$)

6.83-6.76 (m, 3H), 3.89 (s, 3H), 3.87 (s, 3H), 2.39 (q, *J* = 7.5 Hz, 1H), 1.33 (d, *J* = 7.5 Hz, 3H), 1.24 (s, 6H), 1.23 (s, 6H).

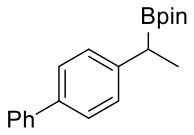
^{13}C NMR: (125 MHz, $CDCl_3$)

148.7, 146.7, 137.6, 119.4, 111.4, 111.3, 83.2, 24.4, 24.4, 19.8, 19.2, 17.4

^{11}B NMR: (160 MHz, $CDCl_3$)

33.5.

2-(1-(1,1'-Biphenyl)-4-ylethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



Using the general procedure A, 4-vinylbiphenyl (90 mg, 0.5 mmol), pinacolborane (80 µL, 0.55 mmol), bipyridiyl-oxazoline cobalt(II) dichloride [$^{t\text{Bu}}$BPOCoCl$_2$] (2.0 mg, 5.0 µmol, 1 mol%) and sodium *tert*-butoxide (1.0 mg, 10.0 µmol, 2 mol%) were reacted in THF (3 mL) to give the crude product mixture which was purified by flash column chromatography (20 g SiO_2, 30 mm Ø, petroleum ether/diethyl ether 10:1) to give 2-(1-(1,1'-biphenyl)-4-ylethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (136 mg, 0.44 mmol, 88%) as a colourless oil, with the regioselectivity of 98:2 (B/L).

^{1}H NMR: (500 MHz, $CDCl_3$)

7.63-7.58 (m, 2H), 7.55-7.51 (m, 2H), 7.46-7.41 (m, 2H), 7.35-7.29 (m, 3H), 2.51 (q, *J* = 7.5 Hz, 1H), 1.39 (d, *J* = 7.5 Hz, 3H), 1.25 (s, 6H), 1.24 (s, 6H).

^{13}C NMR: (125 MHz, $CDCl_3$)

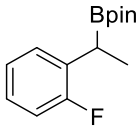
144.1, 141.2, 137.9, 128.6, 128.2, 127.0, 126.9, 126.8, 83.4, 24.8, 24.7, 24.6, 17.1.

^{11}B NMR: (160 MHz, $CDCl_3$)

33.7.

The spectroscopic data were in accordance with those reported in the literature.[181]

2-(1-(2-Fluorophenyl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



Using the general procedure A, 2-fluorostyrene (60 µL, 0.5 mmol), pinacolborane (80 µL, 0.55 mmol), bipyridiyl-oxazoline cobalt(II) dichloride [$_{t\text{Bu}}$BPOCoCl$_2$] (2.0 mg, 5.0 µmol, 1 mol%) and sodium *tert*-butoxide (1.0 mg, 10.0 µmol, 2 mol%) were reacted in THF (3 mL) to give the crude product mixture. The crude was purified by flash column chromatography (20 g SiO_2, 30 mm Ø, petroleum ether/diethyl ether 15:1) to give 2-(1-(2-fluorophenyl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (114 mg, 0.46 mmol, 91%) as a colourless oil, with the regioselectivity of 95:5 (B/L).

MS: (HRMS - EI$^+$)

Found 250.14530 ($C_{14}H_{20}O_2B_1F_1$), requires 250.14326

IR: *vmax* (*neat*)

2978 (w), 1489 (s), 1452 (s), 1321 (m), 1167 (w), 1006 (w).

$_1$H NMR: (500 MHz, $CDCl_3$)

7.27-7.23 (m, 1H), 7.17-7.11 (m, 1H), 7.10-7.05 (m, 1H), 7.03-6.97 (m, 1H), 2.59 (q, *J* = 7.6 Hz, 1H), 1.34 (d, *J* = 7.6 Hz, 3H), 1.26 (s, 6H), 1.25 (s, 6H).

$_{13}$C NMR: (125 MHz, $CDCl_3$)

160.8 (d, *J* = 243.8 Hz), 132.2 (d, *J* = 15.5 Hz), 129.5 (d, *J* = 5.0 Hz), 126.6 (d, *J* = 8.0 Hz), 124.0 (d, *J* = 3.5 Hz), 114.9 (d, *J* = 22.4 Hz), 83.4, 24.7, 24.6, 15.9.

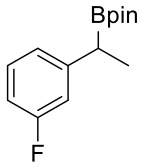
$_{19}$F NMR: (470 MHz, $CDCl_3$)

-117.5.

$_{11}$B NMR: (160 MHz, $CDCl_3$)

33.5.

2-(1-(3-Fluorophenyl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



Using the general procedure A, 3-fluorostyrene (60 µL, 0.5 mmol), pinacolborane (80 µL, 0.55 mmol), bipyridiyl-oxazoline cobalt(II) dichloride [$_{t\text{Bu}}$BPOCoCl$_2$] (2.0 mg, 5.0 µmol, 1 mol%) and sodium *tert*-butoxide (1.0 mg, 10.0 µmol, 2 mol%) were reacted in THF (3 mL) to give the crude product mixture. The crude mixture was purified by flash column chromatography (20 g SiO_2, 30 mm Ø, petroleum ether/diethyl ether 15:1) to give 2-(1-(3-fluorophenyl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (113 mg, 0.45 mmol, 90%) as a colourless oil, with the regioselectivity of 99:1 (B/L).

$_{1}$H NMR: (500 MHz, $CDCl_3$)

7.26-7.20 (m, 1H), 7.03-6.99 (m, 1H), 6.98-6.93 (m, 1H), 6.87-6.81 (m, 1H), 2.47 (q, *J* = 7.4 Hz, 1H), 1.35 (d, *J* = 7.5 Hz, 3H), 1.24 (s, 6H), 1.23 (s, 6H).

$_{13}$C NMR: (125 MHz, $CDCl_3$)

163.2 (d, *J* = 244.8 Hz), 147.7 (d, *J* = 7.0 Hz), 129.5 (d, *J* = 8.5 Hz), 123.5 (d, *J* = 2.5 Hz), 114.5 (d, *J* = 21.4 Hz), 111.9 (d, *J* = 20.9 Hz), 83.4, 24.7, 24.6, 15.9.

$_{19}$F NMR: (470 MHz, $CDCl_3$)

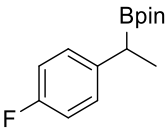
-114.3.

$_{11}$B NMR: (160 MHz, $CDCl_3$)

33.6.

The spectroscopic data were in accordance with those reported in the literature.[182]

2-(1-(4-Fluorophenyl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



Using the general procedure A, 4-fluorostyrene (60 µL, 0.5 mmol), pinacolborane (80 µL, 0.55 mmol), bipyridiyl-oxazoline cobalt(II) dichloride [$_{t\text{Bu}}$BPOCoCl$_2$] (2.0 mg, 5.0 µmol, 1 mol%) and sodium *tert*-butoxide (1.0 mg, 10.0 µmol, 2 mol%) were reacted in THF (3 mL) to give the crude product mixture. The mixture was purified by flash column chromatography (20 g SiO_2, 30 mm Ø, petroleum ether/diethyl ether 15:1) to give 2-(1-(4-fluorophenyl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (115 mg, 0.46 mmol, 92%) as a colourless oil, with the regioselectivity of 96:4 (B/L).

^{1}H NMR: (500 MHz, $CDCl_3$)

7.21-7.16 (m, 2H), 6.99-6.94 (m, 2H), 2.43 (q, *J* = 7.5 Hz, 1H), 1.33 (d, *J* = 7.6 Hz, 3H), 1.23 (s, 6H), 1.22 (s, 6H)

^{13}C NMR: (125 MHz, $CDCl_3$)

160.9 (d, *J* = 242.3 Hz), 140.5 (d, *J* = 3.0 Hz), 129.0 (d, *J* = 7.5 Hz), 114.9 (d, *J* = 20.9 Hz), 83.4, 24.6, 24.5, 17.2.

^{19}F NMR: (470 MHz, $CDCl_3$)

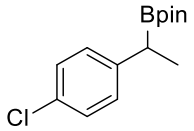
-119.1.

^{11}B NMR: (160 MHz, $CDCl_3$)

33.5.

The spectroscopic data were in accordance with those reported in the literature.[182]

2-(1-(4-Chlorophenyl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



Using the general procedure A, 4-chlorostyrene (60 µL, 0.5 mmol), pinacolborane (80 µL, 0.55 mmol), bipyridiyl-oxazoline cobalt(II) dichloride [$_{t\text{Bu}}$BPOCoCl$_2$] (2.0 mg, 5.0 µmol, 1 mol%) and sodium *tert*-butoxide (1.0 mg, 10.0 µmol, 2 mol%) were reacted in THF (3 mL) to give the crude product mixture. The mixture was purified by flash column chromatography (20 g SiO_2, 30 mm Ø, petroleum ether/diethyl ether 15:1) to give 2-(1-(4-fluorophenyl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (105 mg, 0.40 mmol, 79%) as a colourless oil, with the regioselectivity of 85:15 (B/L).

^{1}H NMR: (500 MHz, $CDCl_3$)

7.26-7.22 (m, 2H), 7.18-7.15 (m, 2H), 2.42 (q, *J* = 7.5 Hz, 1H), 1.33 (d, *J* = 7.5 Hz, 3H), 1.23 (s, 6H), 1.22 (s, 6H).

^{13}C NMR: (125 MHz, $CDCl_3$)

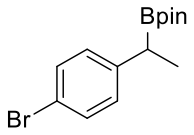
143.6, 130.8, 129.2, 128.5, 83.6, 24.7, 24.6 17.1.

^{11}B NMR: (160 MHz, $CDCl_3$)

33.5.

The spectroscopic data were in accordance with those reported in the literature.[182]

2-(1-(4-Bromophenyl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



Using the general procedure A, 4-bromostyrene (65 µL, 0.5 mmol), pinacolborane (80 µL, 0.55 mmol), bipyridiyl-oxazoline cobalt(II) dichloride [$^{t\text{Bu}}$BPOCoCl$_2$] (2.0 mg, 5.0 µmol, 1 mol%) and sodium *tert*-butoxide (1.0 mg, 10.0 µmol, 2 mol%) were reacted in THF (3 mL) to give the crude product mixture. The mixture was purified by flash column chromatography (20 g SiO_2, 30 mm Ø, petroleum ether/diethyl ether 15:1) to give 2-(1-(4-brophenyl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (70 mg, 0.23 mmol, 45%) as a colourless oil, with the regioselectivity of 96:4 (B/L).

^{1}H NMR: (500 MHz, $CDCl_3$)

7.41-7.37 (m, 2H), 7.13-7.09 (m, 2H), 2.41 (q, *J* = 7.5 Hz, 1H), 1.32 (d, *J* = 7.5 Hz, 3H), 1.23 (s, 6H), 1.22 (s, 6H).

^{13}C NMR: (125 MHz, $CDCl_3$)

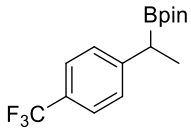
144.0, 131.3, 129.5, 118.7, 83.4, 24.6, 24.5, 16.8.

^{11}B NMR: (160 MHz, $CDCl_3$)

33.4.

The spectroscopic data were in accordance with those reported in the literature.[182]

2-(1-(4-Trifluromethylphenyl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



Using the general procedure A, 4-(trifluoromethyl)styrene (74 µL, 0.5 mmol), pinacolborane (80 µL, 0.55 mmol), bipyridiyl-oxazoline cobalt(II) dichloride [$_{t\text{Bu}}$BPOCoCl$_2$] (2.0 mg, 5.0 µmol, 1 mol%) and sodium *tert*-butoxide (1.0 mg, 10.0 µmol, 2 mol%) were reacted in THF (3 mL) to give the crude product mixture. The mixture was purified by flash column chromatography (20 g SiO_2, 30 mm Ø, petroleum ether/diethyl ether 15:1) to give 2-(1-(4-trifluoromethylphenyl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (120 mg, 0.4 mmol, 80%) as a colourless oil, with the regioselectivity of 94:6 (B/L).

$_1$H NMR: (500 MHz, $CDCl_3$)

7.53 (d, *J* = 8.1 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 2.53 (q, *J* = 7.4 Hz, 1H), 1.37 (d, *J* = 7.6 Hz, 3H), 1.24 (s, 6H), 1.23 (s, 6H).

$_{13}$C NMR: (125 MHz, $CDCl_3$)

149.3, 127.9, 125.1 (q, *J* = 3.5 Hz), 83.3, 24.6, 24.5, 16.7.

$_{19}$F NMR: (470 MHz, $CDCl_3$)

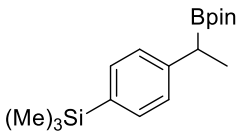
-62.3.

$_{11}$B NMR: (160 MHz, $CDCl_3$)

33.2.

The spectroscopic data were in accordance with those reported in the literature.[182]

2-(1-(4-Trimethylsilylphenyl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



Using the general procedure A, 4-trimethylsilylstyrene (88 mg, 0.5 mmol), pinacolborane (80 µL, 0.55 mmol), bipyridiyl-oxazoline cobalt(II) dichloride [$_{t\text{Bu}}$BPOCoCl$_2$] (2.0 mg, 5.0 µmol, 1 mol%) and sodium *tert*-butoxide (1.0 mg, 10.0 µmol, 2 mol%) were reacted in THF (3 mL) to give the crude product mixture. The mixture was purified by flash column chromatography

(20 g SiO_2, 30 mm Ø, petroleum ether/diethyl ether 10:1) to give 2-(1-(4-trimethylsilylphenyl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (132 mg, 0.41 mmol, 80%) as a colourless oil, with the regioselectivity of 97:3 (B/L).

^{1}H NMR: ($CDCl_3$)

7.46-7.42 (m, 2H), 7.25-7.21 (m, 2H), 2.44 (q, *J* = 7.5 Hz, 1H), 1.35 (d, *J* = 7.6 Hz, 3H), 1.25 (s, 6H), 1.23 (s, 6H), 0.27 (s, 9H).

^{13}C NMR: (125 MHz, $CDCl_3$)

145.6, 136.3, 133.4, 127.8, 83.3, 24.6, 24.6, 17.1, -1.1

^{29}Si NMR: (99 MHz, $CDCl_3$)

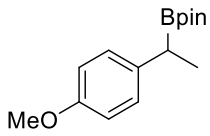
-4.6.

^{11}B NMR: (160 MHz, $CDCl_3$)

33.7.

The spectroscopic data were in accordance with those reported in the literature.[98]

2-(1-(4-Methoxylphenyl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



Using the general procedure A, 4-methoxylstyrene (67 µL, 0.5 mmol), pinacolborane (80 µL, 0.55 mmol), bipyridiyl-oxazoline cobalt(II) dichloride [$^{t\text{Bu}}$BPOCoCl$_2$] (2.0 mg, 5.0 µmol, 1 mol%) and sodium *tert*-butoxide (1.0 mg, 10.0 µmol, 2 mol%) were reacted in THF (3 mL) to give the crude product mixture which was purified by flash column chromatography (20 g SiO_2, 30 mm Ø, petroleum ether/diethyl ether 15:1) to give 2-(1-(4-methoxylphenyl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (97 mg, 0.37 mmol, 74%) as a colourless oil, with the regioselectivity of 88:12 (B/L).

^{1}H NMR: ($CDCl_3$)

7.09 (dt, *J* = 8.7, 2.5 Hz, 2H), 6.80 (dt, *J* = 8.7, 2.5 Hz, 2H), 3.76 (s, 3H), 2.32 (q, *J* = 7.5 Hz, 1H), 1.26 (d, *J* = 7.5 Hz, 3H), 1.20 (s, 6H), 1.19 (s, 6H).

^{13}C NMR: (125 MHz, $CDCl_3$)

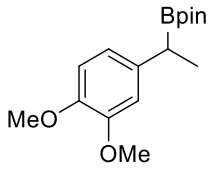
157.6, 137.3, 128.6, 113.6, 83.2, 55.1, 24.6, 17.1.

^{11}B NMR: (160 MHz, $CDCl_3$)

33.6.

The spectroscopic data were in accordance with those reported in the literature.[182]

2-(1-(3,4-Dimethoxylphenyl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



Using the general procedure A, 3,4-dimethoxystyrene (74 µL, 0.5 mmol), pinacolborane (80 µL, 0.55 mmol), bipyridiyl-oxazoline cobalt(II) dichloride [$_{t\text{Bu}}$BPOCoCl$_2$] (2.0 mg, 5.0 µmol, 1 mol%) and sodium *tert*-butoxide (1.0 mg, 10.0 µmol, 2 mol%) were reacted in THF (3 mL) to give the crude product mixture which was purified by flash column chromatography (20 g SiO_2, 30 mm Ø, petroleum ether/diethyl ether 10:1) to give 2-(1-(3,4-dimethoxyphenyl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (102 mg, 0.35 mmol, 70%) as a colourless oil, with the regioselectivity of 94:6 (B/L).

MS: (HRMS - EI$^+$)

Found 292.18539 ($C_{16}H_{25}O_4B_1$), requires 292.18404

IR: *vmax* (*neat*)

3000 (w), 1514 (s), 1456 (m), 1370 (m), 1351 (w), 1249 (w), 1234 (w), 1169 (w), 1028 (w).

^{1}H NMR: (500 MHz, $CDCl_3$)

6.82-6.75 (m, 3H), 3.88 (s, 3H), 3.86 (s, 3H), 2.39 (q, J = 7.5 Hz, 1H), 1.33 (d, J = 7.5 Hz, 3H), 1.24 (s, 6H), 1.22 (s, 6H)

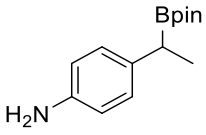
^{13}C NMR: (125 MHz, $CDCl_3$)

145.1, 144.2, 125.9, 125.5, 124.3, 124.2, 83.3, 55.8, 55.7, 24.8, 24.6, 17.3.

^{11}B NMR: (160 MHz, $CDCl_3$)

33.5.

4-(1-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)benzenamine



Using the general procedure A, 4-aminostyrene (74 µL, 0.5 mmol), pinacolborane (80 µL, 0.55 mmol), bipyridiyl-oxazoline cobalt(II) dichloride [$^{t\text{Bu}}$BPOCoCl$_2$] (2.0 mg, 5.0 µmol, 1 mol%) and sodium *tert*-butoxide (1.0 mg, 10.0 µmol, 2 mol%) were reacted in THF (3 mL) to give the crude product mixture. The crude mixture was extracted with ether (5 mL), and the organic phase were dried over $MgSO_4$, filtered and evaporated *in vacuo* to give 4-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)benzenamine (103 mg, 0.42 mmol, 83%) as a colourless oil, with the regioselectivity of 75:25 (B/L).

^{1}H NMR: (500 MHz, $CDCl_3$)

7.05-7.01 (m, 2H), 6.67-6.62 (m, 2H), 3.56 (brs, 2H), 2.33 (q, *J* = 7.5 Hz, 1H), 1.30 (d, *J* = 7.5 Hz, 3H), 1.23 (s, 6H), 1.22 (s, 6H)

^{13}C NMR: (125 MHz, $CDCl_3$)

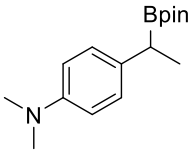
143.5, 135.1, 128.5, 115.5, 83.1, 24.6, 24.5, 17.3.

^{11}B NMR: (160 MHz, $CDCl_3$)

33.8.

The spectroscopic data were in accordance with those reported in the literature.[183]

4-(1-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)-*N*,*N*-dimethylbenzenamine



Using the general procedure A, *N*,*N*-dimethylamino-4-vinylbenzene (74 mg, 0.5 mmol), pinacolborane (80 µL, 0.55 mmol), bipyridiyl-oxazoline cobalt(II) dichloride [$^{t\text{Bu}}$BPOCoCl$_2$] (2.0 mg, 5.0 µmol, 1 mol%) and sodium *tert*-butoxide (1.0 mg, 10.0 µmol, 2 mol%) were reacted in THF (3 mL) to give the crude product mixture. The crude mixture was extracted with ether (5 mL), and the organic phase were dried over $MgSO_4$, filtered and evaporated *in vacuo* to give 4-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)-*N*,*N*-

dimethylbenzenamine (113 mg, 0.42 mmol, 83%) as a colourless oil, with the regioselectivity of 86:14 (B/L).

MS: (HRMS - EI^+)

Found 275.20540 ($C_{16}H_{26}O_2B_1N_1$), requires 275.20511

IR: *vmax* (*neat*)

2976 (w), 1517 (s), 1452 (m), 1321 (w), 1217 (w).

$_1$H NMR: (500 MHz, $CDCl_3$)

7.16-7.05 (m, 2H), 6.76-6.67 (m, 2H), 2.91 (s, 6H), 2.34 (q, *J* = 7.5 Hz, 1H), 1.30 (d, *J* = 7.6 Hz, 3H), 1.23 (s, 6H), 1.22 (s, 6H).

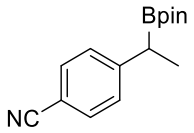
$_{13}$C NMR: (125 MHz, $CDCl_3$)

155.2, 139.8, 117.1, 109.1, 83.7, 41.9, 24.7, 24.6, 19.1.

$_{11}$B NMR: (160 MHz, $CDCl_3$)

33.7.

2-(1-(4-Cyanophenyl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



Using the general procedure A, 4-cyanostyrene (64 mg, 0.5 mmol), pinacolborane (80 µL, 0.55 mmol), bipyridiyl-oxazoline cobalt(II) dichloride [$_{t\text{Bu}}$BPOCoCl$_2$] (2.0 mg, 5.0 µmol, 1 mol%) and sodium *tert*-butoxide (1.0 mg, 10.0 µmol, 2 mol%) were reacted in THF (3 mL) to give the crude product mixture. The mixture was purified by flash column chromatography (20 g SiO_2, 30 mm Ø, petroleum ether/diethyl ether 15:1) to give 2-(1-(4-cyanophenyl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (85 mg, 0.34 mmol, 69%) as a colourless oil, with the regioselectivity of 99:1 (B/L).

MS: (HRMS - EI^+)

Found 257. 15899 ($C_{15}H_{20}B_1O_2N_1$), requires 257.15816

IR: *vmax* (*neat*)

2225 (s), 1373 (s), 1346 (s), 1144 (m), 1016 (m).

$_{1}$H NMR: (500 MHz, $CDCl_3$)

7.58-7.54 (m, 2H), 7.35-7.30 (m, 2H), 2.53 (q, *J* = 7.4 Hz, 1H), 1.36 (d, *J* = 7.4 Hz, 3H), 1.22 (s, 6H), 1.21 (s, 6H).

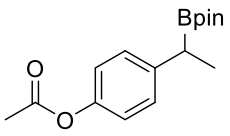
$_{13}$C NMR: (125 MHz, $CDCl_3$)

150.9, 132.0, 128.5, 119.3, 108.9, 83.7, 24.6, 24.5, 16.3.

$_{11}$B NMR: (160 MHz, $CDCl_3$)

33.2.

2-(1-(4-Acetoxyphenyl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



Using the general procedure A, 4-acetoxystyrene (76 µL, 0.5 mmol), pinacolborane (80 µL, 0.55 mmol), bipyridiyl-oxazoline cobalt dicholoride [$_{t\text{Bu}}$BPOCoCl_2] (2.0 mg, 5.0 µmol, 1 mol%) and sodium *tert*-butoxide (1.0 mg, 10.0 µmol, 2 mol%) were reacted in THF (3 mL) to give the crude product mixture. The mixture was purified by flash column chromatography (20 g SiO_2, 30 mm Ø, petroleum ether/diethyl ether 10:1) to give 2-(1-(4-acetoxyphenyl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (114 mg, 0.39 mmol, 79%) as a colourless oil, with the regioselectivity of 98:2 (B/L).

$_{1}$H NMR: (500 MHz, $CDCl_3$)

7.26-7.21 (m, 2H), 7.02-6.97 (m, 2H), 2.45 (q, *J* = 7.5 Hz, 1H), 2.30 (s, 3H), 1.34 (d, *J* = 7.6 Hz, 3H), 1.23 (s, 6H), 1.22 (s, 6H).

$_{13}$C NMR: (125 MHz, $CDCl_3$)

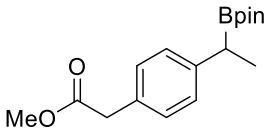
169.8, 148.2, 142.5, 128.6, 121.2, 83.4, 24.7, 24.6, 21.2, 17.1.

$_{11}$B NMR: (160 MHz, $CDCl_3$)

33.6.

The spectroscopic data were in accordance with those reported in the literature.[182]

2-(1-(4-(Acetic acid methyl ester)phenyl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



Using the general procedure A, 4-vinyl(phenyl)acetic acid methyl ester (88 mg, 0.5 mmol), pinacolborane (80 µL, 0.55 mmol), bipyridiyl-oxazoline cobalt dicholoride [$_{t\text{Bu}}$BPOCoCl$_2$] (2.0 mg, 5.0 µmol, 1 mol%) and sodium *tert*-butoxide (1.0 mg, 10.0 µmol, 2 mol%) were reacted in THF (3 mL) to give the crude product mixture. The mixture was purified by flash column chromatography (20 g SiO_2, 30 mm Ø, petroleum ether/diethyl ether 10:1) to give 2-(1-(4-(acetic acid methyl ester)phenyl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (122 mg, 0.4 mmol, 80%) as a colourless oil, with the regioselectivity of 95:5 (B/L).

MS: (HRMS - EI$^+$)

Found 304.18448 ($C_{17}H_{25}B_1O_4$), requires 304.18404

IR: *vmax* (*neat*)

1735 (s), 1319 (s), 1255 (m), 1160 (m), 1018 (w), 1004 (w).

$_1$H NMR: (500 MHz, $CDCl_3$)

7.19 (s, 4H), 3.70 (s, 3H), 3.60 (s, 2H), 2.44 (q, *J* = 7.6 Hz, 1H), 1.34 (d, *J* = 7.6 Hz, 3H), 2.30 (s, 3H), 1.23 (s, 6H), 1.22 (s, 6H).

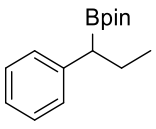
$_{13}$C NMR: (125 MHz, $CDCl_3$)

172.3, 143.82, 130.54, 129.15, 128.0, 83.3, 51.9, 40.8, 24.7, 24.6, 17.1, 15.3.

$_{11}$B NMR: (160 MHz, $CDCl_3$)

33.6.

4, 4, 5, 5-Tetramethyl-2-(1-phenyl-propyl)-1,3,2-dioxaborolane



Using the general procedure A, trans-β-methylstyrene (65 µL, 0.5 mmol), pinacolborane (80 µL, 0.55 mmol), bipyridiyl-oxazoline cobalt dicholoride [$_{t\text{Bu}}$BPOCoCl$_2$] (2.0 mg, 5.0 µmol, 1 mol%) and sodium *tert*-butoxide (1.0 mg, 10.0 µmol, 2 mol%) were reacted in THF (3 mL) to

give the crude product mixture which was purified by flash column chromatography (20 g SiO_2, 30 mm Ø, petroleum ether/diethyl ether 15:1) to give the single regioisomer 4, 4, 5, 5-tetramethyl-2-(1-phenyl-propyl)-1,3,2-dioxaborolane (110 mg, 0.45 mmol, 90%) as a colourless oil.

^{1}H NMR: (500 MHz, $CDCl_3$)

7.30-7.21 (m, 4H), 7.17-7.13 (m, 1H), 2.24 (t, *J* = 7.9 Hz, 1H), 1.95-1.85 (m, 1H), 1.75-1.65 (m, 1H), 1.24 (s, 6H), 1.22 (s, 6H), 0.93 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$)

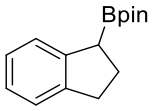
143.4, 128.4, 128.2, 125.1, 83.2, 25.8, 24.7, 24.6, 13.9

^{11}B NMR: (160 MHz, $CDCl_3$)

33.5.

The spectroscopic data were in accordance with those reported in the literature.[59]

2-(2,3-Dihydro-1*H*-inden-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



Using the general procedure A, indene (58 µL, 0.5 mmol), pinacolborane (80 µL, 0.55 mmol), bipyridiyl-oxazoline cobalt(II) dicholoride [$^{t\text{Bu}}$BPOCoCl$_2$] (2.0 mg, 5.0 µmol, 1 mol%) and sodium *tert*-butoxide (1.0 mg, 10.0 µmol, 2 mol%) were reacted in THF (3 mL) to give the crude product mixture which was purified by flash column chromatography (20 g SiO_2, 30 mm Ø, petroleum ether/diethyl ether 15:1) to give the single regioisomer 2-(2,3-dihydro-1*H*-inden-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (96 mg, 0.39 mmol, 79%) as a colourless oil.

^{1}H NMR: (500 MHz, $CDCl_3$)

7.33-7.29 (m, 1H), 7.25-7.21 (m, 1H), 7.16-7.09 (m, 2H), 3.03-2.89 (m, 2H), 2.75 (t, *J* = 8.5 Hz, 1H), 2.29-2.21 (m, 1H), 2.17-2.07 (m, 1H), 1.28 (s, 6H), 1.27 (s, 6H).

^{13}C NMR: (125 MHz, $CDCl_3$)

145.1, 144.2, 125.9, 125.5, 124.4, 124.2, 83.3, 33.3, 27.8, 24.9, 24.7.

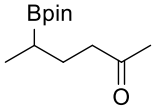
No signal was observed for the carbon attached to boron.

^{11}B NMR: ($CDCl_3$, 160 MHz)

33.6.

The spectroscopic data were in accordance with those reported in the literature.[182]

5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)hexan-2-one



Using the general procedure A, 5-hexen-2-one (58 µL, 0.5 mmol), pinacolborane (80 µL, 0.55 mmol), bipyridiyl-oxazoline cobalt(II) dichloride [$_{t\text{Bu}}$BPOCoCl$_2$] (2.0 mg, 5.0 µmol, 1 mol%) and sodium *tert*-butoxide (1.0 mg, 10.0 µmol, 2 mol%) were reacted in THF (3 mL) to give the crude product mixture which was purified by flash column chromatography (20 g SiO_2, 30 mm Ø, petroleum ether/diethyl ether 10:1) to give 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexan-2-one (78 mg, 0.34 mmol, 69%) as a colourless oil, with the regioselectivity of 75:25 (B/L).

^{1}H NMR: ($CDCl_3$, 500 MHz)

2.43 (t, *J* = 7.6 Hz, 2H), 2.12 (s, 3H), 1.71-1.53 (m, 2H), 1.64-1.38 (m, 2H), 1.25 (s, 12H), 1.01-0.97 (m, 2H).

^{13}C NMR: ($CDCl_3$, 125 MHz)

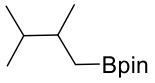
209.5, 83.0, 43.2, 29.8, 27.2, 24.8, 24.7, 15.4.

^{11}B NMR: ($CDCl_3$, 160 MHz)

34.0.

The spectroscopic data were in accordance with those reported in the literature.[184]

2-(2,3-Dimethylbutyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



Using the general procedure A, 2,3-dimethyl-1-butene (62 µL, 0.5 mmol), pinacolborane (80 µL, 0.55 mmol), bipyridiyl-oxazoline cobalt(II) dichloride [$_{t\text{Bu}}$BPOCoCl$_2$] (2.0 mg, 5.0 µmol,

1 mol%) and sodium *tert*-butoxide (1.0 mg, 10.0 µmol, 2 mol%) were reacted in THF (3 mL) to give the crude product mixture which was purified by flash column chromatography (20 g SiO_2, 30 mm Ø, petroleum ether/diethyl ether 10:1) to give 2-(2,3-dimethylbutyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (78 mg, 0.34 mmol, 69%) as a colourless oil.

^{1}H NMR: (500 MHz, $CDCl_3$)

1.64-1.56 (m, 1H), 1.53-1.45 (m, 1H), 1.24 (2 overlapping singlets, 12H), 0.85-0.79 (overlapping doublets, 10H), 0.61 (dd, *J* = 15.2, 9.8 Hz, 1H).

^{13}C NMR: (125 MHz, $CDCl_3$)

82.9, 35.2, 34.3, 25.1, 24.8, 19.9, 18.8, 18.7.

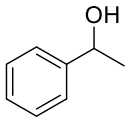
^{11}B NMR: (160 MHz, $CDCl_3$)

33.9.

The spectroscopic data were in accordance with those reported in the literature.[60]

4.6 Oxidation of Hydroboration Product

1-Phenylethanol



Using the general procedure A, styrene (57 µL, 0.5 mmol), pinacolborane (80 µL, 0.55 mmol), bipyridiyl-oxazoline cobalt(II) dichloride [$_t$BuBPOCoCl$_2$] (2.0 mg, 5.0 µmol, 1 mol%) and sodium *tert*-butoxide (1.0 mg, 10.0 µmol, 2 mol%) were reacted in THF (3 mL) to give the crude product mixture. The mixture was oxidised with 30% solution hydrogen peroxide (1 mL) sodium hydroxide solution (1 M, 1 mL) and purified by flash column chromatography (20 g SiO_2, 30 mm Ø, petroleum ether/diethyl ether 20:1) to give 1-phenylethanol as a colourless oil (49 mg, 0.4 mmol, 80%). The purified alcohol was analysed by chiral HPLC and showed no enantioselectivity.

$_1$H NMR: (500 MHz, $CDCl_3$)

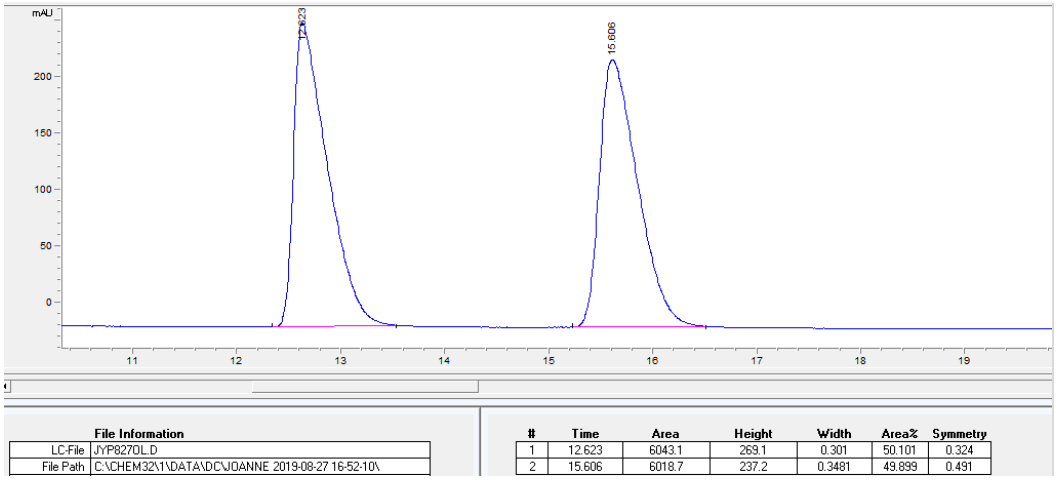
7.36 (m, 4H), 7.28 (t, *J* = 6.1 Hz, 1H), 4.92 (q, *J* = 6.3 Hz, 1H), 1.77 (br. s, 1H), 1.53 (d, *J* = 6.4 Hz, 3H).

$_{13}$C NMR: (125 MHz, $CDCl_3$)

145.8, 128.5, 127.5, 125.4, 70.4. 25.2.

The spectroscopic data were in accordance with those reported in the literature.[185]

HPLC conditions: hexanes/$_i$PrOH, 95:5 v/v; 0.5 mL/min; R_f 12.6 min (50.1%), 15.6 min (49.9%). Assigned by comparison with an authentic sample of 1-phenylethanol.[185]



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File Path	C:\CHEM32\1\DATA\DC\JOANNE 2019-08-27 16-52-10\

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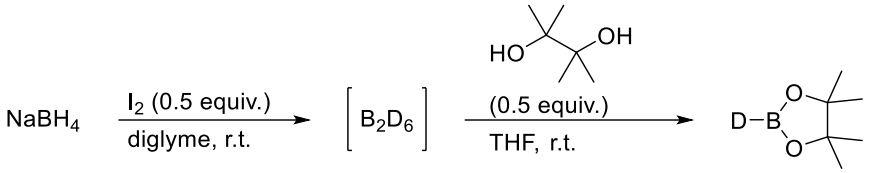
2	15.606	6018.7	237.2	0.3481	49.899	0.491

4.7 Alkene Hydroboration: Deuterium Labelling Experiments

***d*1-Pinacolborane (DBpin)**



Prepared according to a modified literature procedure.[186]

Safety Concern: This reaction liberates pyrophoric and toxic polydeuterated diborane gas, this should be quenched in a controlled manner. Additionally flammable D_2 gas is liberated.

The reaction and purification procedures were carried out in Schlenk glassware under a nitrogen atmosphere. A solution of iodine (5.08 g, 20 mmol) in diethylene glycol dimethyl ether (20 mL) was added dropwise at room temperature over 3 h to a solution of sodium borodeuteride (1.674 g, 40 mmol) in diethylene glycol dimethyl ether (20 mL). The resulting gas was vented, through a plastic cannula, into a solution of pinacol (2.36 g, 20 mmol) in THF (10 mL). After completion of addition of the iodine solution, a stream of nitrogen gas was applied to the diethylene glycol dimethyl ether solution for 2 h, such that any residual gasses were bubbled through the THF solution. Volatiles were removed from resulting THF solution of *d*1-pinacolborane *in vacuo* (200 mbar, 30-40 °C). Following vacuum distillation (50 mbar, 40 °C), *d*1-pinacolborane was isolated (0.266 g, 2.06 mmol, 10%).

^{1}H NMR: (500 MHz, C_6D_6)

0.99 (s, 12H).

^{13}C NMR: (125 MHz, C_6D_6)

83.4, 25.3.

^{11}B NMR: (160 MHz, C_6D_6)

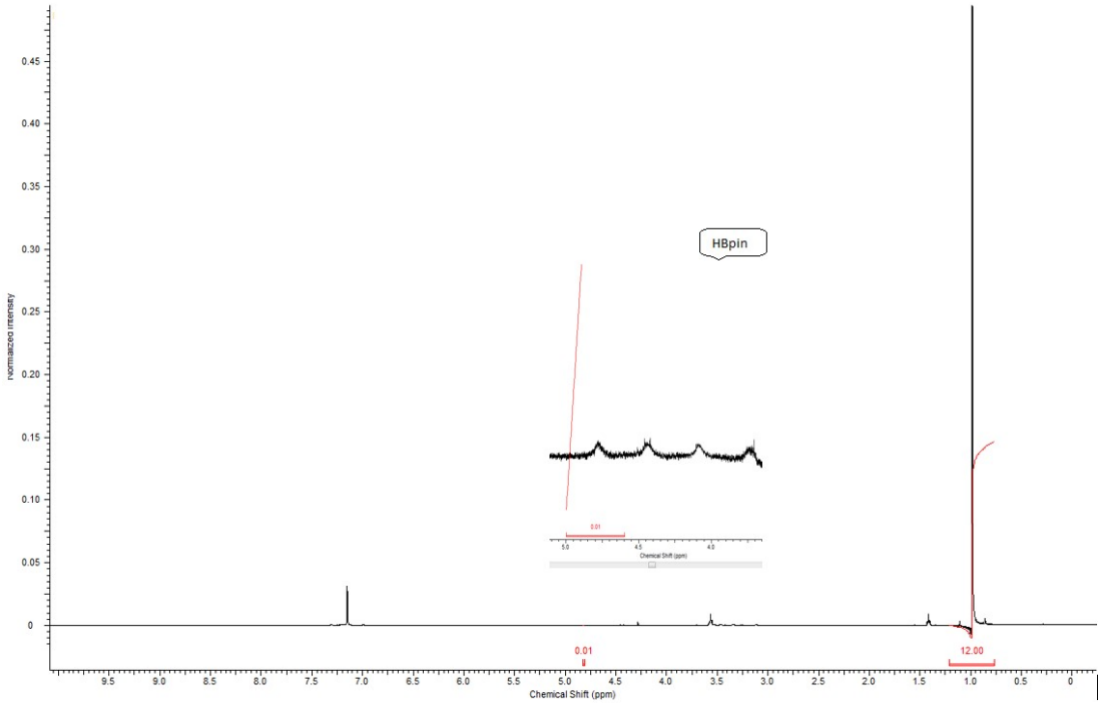
28.4.

^{2}H NMR: (77 MHz, C_6D_6)

5.12-3.71 (br. m).

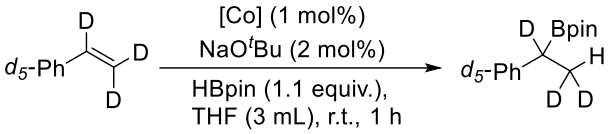
The spectroscopic data were in accordance with those reported in the literature.[186]

^{1}H NMR (500 MHz, C_6D_6) of *d*1-Pinacolborane (DBpin)



We observed 4% HBpin in the prepared d_1-pinacolborane (DBpin), which was confirmed by the observation of its characteristic resonance of H-B by ^{1}H NMR at 3.4-4.9 as a broadening quartet, which was identical to that of anthentic sample in d_6-benzene.

2-[1-(d_5-Phenyl)-1-d_1-2-d_2-ethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



Using the general procedure A, d_8-styrene (56 mg, 0.5 mmol), pinacolborane (80 µL, 0.55 mmol), bipyridiyl-oxazoline cobalt dicholoride [^{t}BuBPOCoCl$_2$] (2.0 mg, 5.0 µmol, 1.0 mol%) and sodium *tert*-butoxide (1.0 mg, 10.0 µmol, 2 mol%) were reacted in THF (3 mL) to give the crude product mixture. The mixture was purified by flash column chromatography (20 g SiO_2, 30 mm Ø, petroleum ether/diethyl ether 15:1) to give 2-[1-(d_5-phenyl)-1-d_1-2-d_2-ethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (89 mg, 0.37 mmol, 75%) as a colourless oil, with the regioselectivity of 97:3 (B/L).

^{1}H NMR: (500 MHz, $CDCl_3$)

1.34-1.30 (br. m, 1H), 1.24 (s, 6H), 1.22 (s, 6H).

^{13}C NMR: (125 MHz, $CDCl_3$)

144.8, 127.8 (t, *J* = 24.2 Hz), 127.3 (t, *J* = 23.7 Hz), 124.5 (t, *J* = 24.2 Hz), 83.3, 24.6, 24.6, 16.3 (quint., *J* = 19.3 Hz).

^{11}B NMR: (160 MHz, $CDCl_3$)

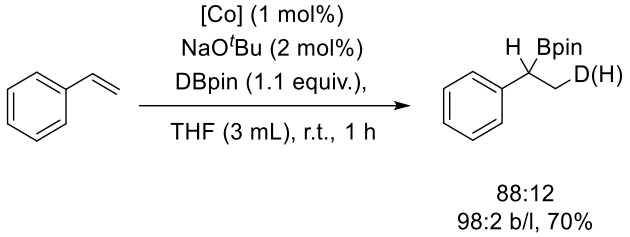
33.6.

^{2}H NMR: (77 MHz, $CDCl_3$)

7.31 (br. s), 7.28 (br. s), 7.19 (s), 2.42 (br. s), 1.32 (br. d, *J* = 1.8 Hz).

The spectroscopic data were in accordance with those reported in the literature.[98]

2-(1-Phenyl-2-*d*$_1$-ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



Using the general procedure A, styrene (57 mg, 0.5 mmol), *d*$_1$-pinacolborane (80 µL, 0.55 mmol), bipyridiyl-oxazoline cobalt(II) dichloride [$_{t\text{Bu}}$BPOCoCl$_2$] (2.0 mg, 5.0 µmol, 1.0 mol%) and sodium *tert*-butoxide (1.0 mg, 10.0 µmol, 2 mol%) were reacted in THF (3 mL) to give the crude product mixture. The reaction mixture was purified by flash column chromatography (20 g SiO_2, 30 mm Ø, petroleum ether/diethyl ether 15:1) to give 2-(1-phenyl-2-*d*$_1$-ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (77 mg, 0.35 mmol, 70%) as a colourless oil, in a 88:12 mixture with fully protio-boronic ester, with the regioselectivity of 98:2 (B/L).

^{1}H NMR: (500 MHz, CD_2Cl_2)

7.31-7.26 (m, 2H), 7.23-7.20 (m, 2H), 7.16 (tt, *J* = 7.3, 1.3 Hz, 1H), 2.42 (t, *J* = 7.4 Hz, 1H), 1.35-1.30 (m, 2.12H, 88:12 mixture of CH_2D and CH_3), 1.24 (s, 6H), 1.23 (s, 6H).

^{13}C NMR: (125 MHz, CD_2Cl_2)

145.0, 128.0, 128.4, 125.1, 83.3, 25.0, 17.4 (s, CH_3, from protonated product), 17.2 (t, *J* = 19.5 Hz, CH_2D from mono-deuterated product).

^{11}B NMR: (160 MHz, CD_2Cl_3)

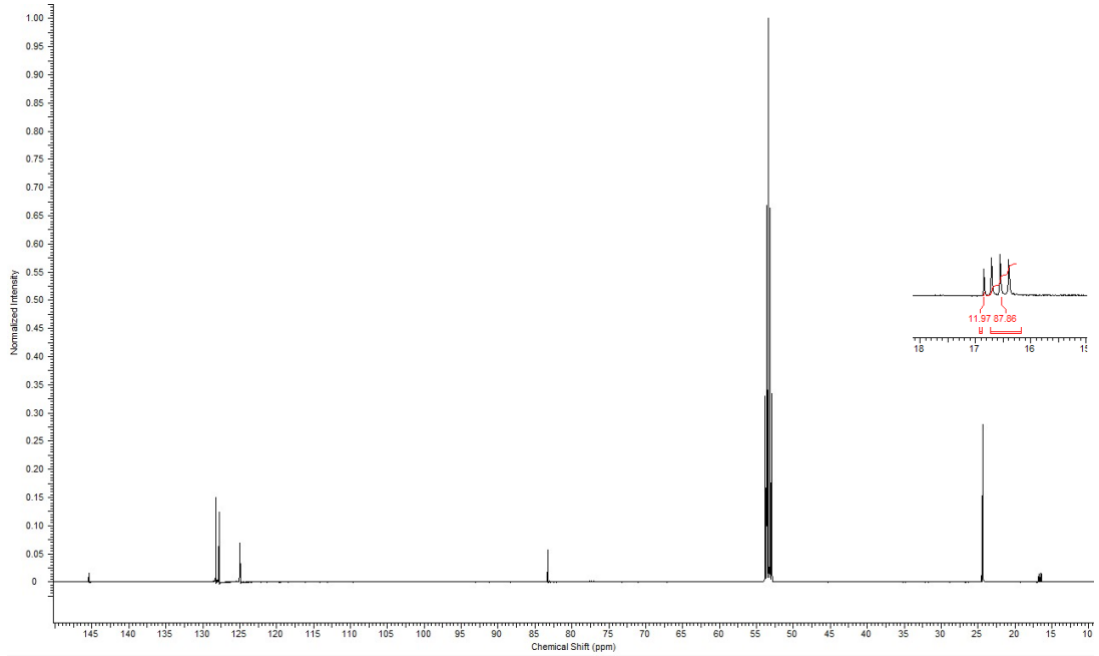
33.6.

$_2$H NMR: (77 MHz, CD_2Cl_3)

1.37-1.25 (br, m)

The spectroscopic data were in accordance with those reported in the literature.[98]

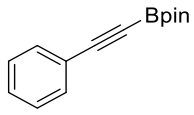
$_{13}$C NMR (125 MHz, CD_2Cl_2) of 2-(1-Phenyl-2-*d*$_1$-ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



The mono-deuterated boronic ester and fully protio-boronic ester was formed in a ratio of 88:12 D/H, which was determined by both $_1$H NMR and quantitative $_{13}$C NMR.

4.8 Preparation of Boronic Acids

4,4,5,5-Tetramethyl-2-(phenylethynyl)-1,3,2-dioxaborolane



Prepared according to a literature procedure.[187]

n-BuLi in hexanes (8.0 mL, 2.5 M, 20 mmol) was added dropwise to a solution of phenylacetylene (2.2 mL, 20 mmol) in THF (25 mL) at -78 °C. After stirring for 1 h in the atmosphere of nitrogen, 4,4,5,5-tetramethyl-2-(1-methylethoxy)-1,3,2-dioxaborolane (22 mmol, 4.5 mL) was added to the reaction mixture at -78 °C. After being stirred for 4 h, the reaction mixture was quenched with 2.0 M HCl/Et_2O and warmed to room temperature with additional 1 h stirring. The mixture was filtrated and the solvent was evaporated to give a pale yellow oil (3.88 g, 17.8 mmol, 89%).

^{1}H NMR: (500 MHz, $CDCl_3$)

7.54-7.51 (m, 2H), 7.38-7.28 (m, 3H), 1.32 (s, 12H).

^{13}C NMR: (125 MHz, $CDCl_3$)

132.4, 129.3, 128.1, 121.7, 84.4, 24.7.

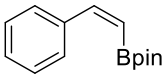
The carbon signals of triple bond were not observed due to low intensity.

^{11}B NMR: (160 MHz, $CDCl_3$)

24.3.

The spectroscopic data were in accordance with those reported in the literature.[187]

(*Z*)-4,4,5,5-Tetramethyl-2-styryl-1,3,2-dioxaborolane



Prepared according to a literature procedure.[188]

A solution of 4,4,5,5-tetramethyl-2-(phenylethynyl)-1,3,2-dioxaborolane (2.28 g, 10 mmol) in anhydrous THF (10 mL) was added to a stirred suspension of Schwartz reagent $Cp_2ZrCl(H)$ (2.58 g, 10 mmol) in 30 ml anhydrous THF at 25 °C under an atmosphere of nitrogen. The reaction was stirred for an additional 2 h until it turned clear and became orange in colour. Addition of excess H_2O to the reaction mixture led to the disappearance of the colour. After

stirring for an additional 1 h, the reaction mixture was extracted with diethyl ether (3 x 10 mL) and dried over $MgSO_4$. Evaporation of the solvent and the mixture was purified by flash chromatography (20 g SiO_2, 30 mm Ø, pentane/diethyl ether 40:1) to give (*Z*)-4,4,5,5-tetramethyl-2-styryl-1,3,2-dioxaborolane as a pale yellow oil (912 mg, 4.0 mmol, 40%).

$_1$H NMR: (500 MHz, $CDCl_3$)

7.57 (d, *J* = 8.4 Hz, 2H), 7.36-7.27 (m, 3H), 7.24 (d, *J* = 14.7 Hz, 1H), 5.62 (d, *J* = 14.8 Hz, 1H), 1.32 (s, 12H).

$_{13}$C NMR: (125 MHz, $CDCl_3$)

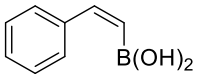
148.2, 138.5, 128.7, 128.0, 127.9, 118.7 (C-B, low intensity), 83.5, 24.8.

$_{11}$B NMR: (160 MHz, $CDCl_3$)

30.3.

The spectroscopic data were in accordance with those reported in the literature.[188]

***(Z)*-2-Phenylvinylboronic acid**



Prepared according to a literature procedure.[188]

Sodium metaperiodate (636 mg, 3 mmol) and ammonium acetate (231 mg, 3 mmol) were added to a solution of (*Z*)-4,4,5,5-tetramethyl-2-styryl-1,3,2-dioxaborolane (230 mg, 1 mmol) in a mixture of acetone and water (30 mL, 2:1). The resulting cloudy solution was stirred at room temperature. After 48 h, the reaction mixture was evaporated under reduced pressure to remove acetone, diluted with ethyl acetate (5 mL) and the phases separated. The aqueous layer was extracted with ethyl acetate (2 x 5 mL) and the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and filtered. The solution was concentrated under reduced pressure to provide (*Z*)-phenylvinyl boronic acid as a colourless oil (104 mg, 0.7 mmol, 70%).

$_1$H NMR: (500 MHz, $(CD_3)_2CO$)

7.52-7.48 (m, 2H), 7.34-7.29 (m, 2H), 7.27-7.22 (m, 1H), 7.02-6.88 (m, 3H), 5.71 (d, *J* = 15.0 Hz, 1H).

$_{13}$C NMR: (125 MHz, $(CD_3)_2CO$)

141.8, 139.2, 128.1, 127.8, 127.3.

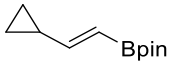
No signal was observed for the carbon attached to boron.

^{11}B NMR: (160 MHz, $(CD_3)_2CO$)

29.5

The spectroscopic data were in accordance with those reported in the literature.[188]

(*E*)-4,4,5,5-Tetramethyl-2-(cyclopropyl-1-ethenyl)-1,3,2-dioxaborolane



Prepared according to a literature procedure.[189]

Schwartz reagent Cp_2ZrHCl (258 mg, 1 mmol) was added to a two-necked round bottom flask under an atmosphere of nitrogen. Cyclopropylacetylene (661 mg, 10 mmol), pinacolborane (1.4 g, 11 mmol) and trimethylamine (101 mg, 10 mmol) were added to the flask. The reaction mixture was heated at 60 °C for 13 h. The crude reaction mixture was directly purified flash chromatography (20 g SiO_2, 30 mm Ø, petroleum ether/ethyl acetate 20:1) to give (*E*)-4,4,5,5-tetramethyl-2-(cyclopropyl-1-ethenyl)-1,3,2-dioxaborolane as a colourless liquid (1.7 g, 8.8 mmol, 88%).

^{1}H NMR: (500 MHz, $CDCl_3$)

6.10 (dd, *J* = 17.8, 9.3 Hz, 1H), 5.51 (d, *J* = 17.8 Hz, 1H), 1.56-1.50 (m, 1H), 1.27 (s, 12H), 0.84-0.80 (m, 2H), 0.57-0.54 (m, 2H).

^{13}C NMR: (125 MHz, $CDCl_3$)

158.5, 82.9, 24.8, 17.0, 7.9.

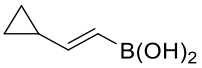
No signal was observed for the carbon attached to boron.

^{11}B NMR: (160 MHz, $CDCl_3$)

29.8.

The spectroscopic data were in accordance with those reported in the literature.[189]

(*E*)-(2-Cyclopropylvinyl)boronic acid



Prepared according to a literature procedure.[189]

Sodium metaperiodate (636 mg, 3 mmol) and ammonium acetate (231 mg, 3 mmol) were added to a solution of (*E*)-4,4,5,5-tetramethyl-2-(cyclopropyl-1-ethenyl)-1,3,2-dioxaborolane (193 mg, 1 mmol) in a mixture of acetone and water (30 mL, 2:1). The resulting cloudy solution was stirred at room temperature. After 48 h, the reaction mixture was evaporated under reduced pressure to remove acetone, diluted with ethyl acetate (5 mL) and the phases separated. The aqueous layer was extracted with ethyl acetate (2 x 5 mL) and the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and filtered. The solution was concentrated under reduced pressure to provide (*E*)-(2-cyclopropylvinyl)boronic acid as an amorphous colourless powder (90 mg, 0.8 mmol, 80%).

^{1}H NMR: ($CDCl_3$)

6.38 (dd, *J* = 17.5, 9.4 Hz, 1H), 5.56 (d, *J* = 17.5 Hz, 1H), 1.61-1.55 (m, 1H), 0.89-0.85 (m, 2H), 0.61-0.58 (m, 2H).

^{13}C NMR: ($CDCl_3$)

161.6, 17.0, 8.4.

No signal was observed for the carbon attached to boron.

^{11}B NMR: ($CDCl_3$)

28.8.

The spectroscopic data were in accordance with those reported in the literature.[189]

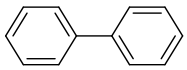
4.9 Homo-Coupling of Boronic Acids: Isolated Products

General Procedure B: Manganese-catalysed homo-coupling of boronic acids

Boronic acid (0.5 mmol, 1 equiv.), manganese(III) acetylacetonate (17 mg, 0.05 mmol, 10 mol%) and potassium carbonate (69 mg, 0.5 mmol, 1 equiv.) were added to ethanol (2 mL) in a reaction vial. The reaction was left to stir under air atmosphere at 45 °C for 20 h, diluted with diethyl ether (3 mL) and washed with sodium hydroxide solution (1M, 3 mL) and water (3 mL).

1,3,5-Trimethoxybenzene (0.1 M solution in diethyl ether, 1 mL, 0.1 mmol), as an internal standard, was added and the organic phase of the mixture was sampled. The NMR yield of the reaction were determined from integrals of product peaks in ^{1}H NMR of crude reaction mixtures. The homo-coupling product was purified following column chromatography.

Biphenyl



Using the general procedure B, phenylboronic acid (61 mg, 0.5 mmol), manganese(III) acetylacetonate (17 mg, 0.05 mmol) and potassium carbonate (69 mg, 0.5 mmol) were reacted in ethanol (2 mL) to give a crude reaction mixture which was purified by flash column chromatography (40 g SiO_2, 30 mm Ø, petroleum ether/diethyl ether 10:1) to give biphenyl (30 mg, 0.191 mmol, 75%) as a colourless microcrystalline solid.

m.p 71-72 °C (petroleum ether/EtOAc) Lit:[190] 70-72 °C (EtOAc)

^{1}H NMR: (500 MHz, $CDCl_3$)

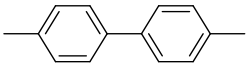
7.62 (d, *J* = 7.2 Hz, 4H), 7.47 (t, *J* = 7.8 Hz, 4H), 7.37 (t, *J* = 7.4 Hz, 2H).

^{13}C NMR: (125 MHz, $CDCl_3$)

141.3, 128.8, 127.3, 127.2.

The spectroscopic data were in accordance with those reported in the literature.[190]

4,4'-Dimethylbiphenyl



Using the general procedure B, 4-methylphenylboronic acid (67 mg, 0.5 mmol), manganese(III) acetylacetonate (17 mg, 0.05 mmol) and potassium carbonate (69 mg, 0.5 mmol) were reacted in ethanol (2 mL) to give a crude reaction mixture which was purified by flash column chromatography (40 g SiO_2, 30 mm Ø, petroleum ether/diethyl ether 10:1) to give 4,4'-dimethylbiphenyl (33 mg, 0.179 mmol, 72%) as a colourless microcrystalline solid.

m.p 120-121 °C (petroleum ether/EtOAc)

Lit:[191] 118-121 °C (petroleum ether/EtOAc)

$_1$H NMR: (500 MHz, $CDCl_3$)

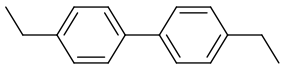
7.50 (d, *J* = 8.2 Hz, 4H), 7.26 (d, *J* = 7.8 Hz, 4H), 2.41 (s, 6H).

$_{13}$C NMR: (125 MHz, $CDCl_3$)

138.3, 136.7, 129.4, 126.8, 21.1.

The spectroscopic data were in accordance with those reported in the literature.[190]

4,4'-Diethylbiphenyl



Using the general procedure B, 4-ethylphenylboronic acid (70 mg, 0.5 mmol), manganese(III) acetylacetonate (17 mg, 0.05 mmol) and potassium carbonate (69 mg, 0.5 mmol) were reacted in ethanol (2 mL) to give a crude reaction mixture which was purified by flash column chromatography (40 g SiO_2, 30 mm Ø, petroleum ether/diethyl ether 10:1) to give 4,4'-diethylbiphenyl (36 mg, 0.170 mmol, 68%) as a colourless microcrystalline solid.

m.p 77-79 °C (petroleum ether/EtOAc) Lit:[190] 76-79 °C (petroleum ether/EtOAc)

$_1$H NMR: (500 MHz, $CDCl_3$)

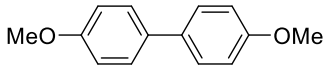
7.55 (d, *J* = 8.2 Hz, 4H), 7.30 (d, *J* = 8.1 Hz, 4H), 2.73 (q, *J* = 7.7 Hz, 4H), 1.32 (t, *J* = 7.7 Hz, 6H).

$_{13}$C NMR: (125 MHz, $CDCl_3$)

143.1, 138.6, 128.2, 126.9, 28.5, 15.6.

The spectroscopic data were in accordance with those reported in the literature.[190]

4,4'-Dimethoxybiphenyl



Using the general procedure B, 4-methoxylphenylboronic acid (76 mg, 0.5 mmol), manganese(III) acetylacetonate (17 mg, 0.05 mmol) and potassium carbonate (69 mg, 0.5 mmol) were reacted in ethanol (2 mL) to give a crude reaction mixture which was purified by flash column chromatography (40 g SiO_2, 30 mm Ø, petroleum ether/diethyl ether 10:1) to give 4,4'-dimethoxybiphenyl (37 mg, 0.173 mmol, 68%) as a colourless microcrystalline solid.

m.p 176-178 °C (petroleum ether/EtOAc) Lit:[192] 174-175 °C (methanol)

^{1}H NMR: (500 MHz, $CDCl_3$)

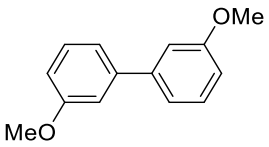
7.50 (d, *J* = 8.8 Hz, 4H), 6.98 (d, *J* = 8.8 Hz, 4H), 3.87 (s, 6H).

^{13}C NMR: (125 MHz, $CDCl_3$)

158.7, 133.5, 127.7, 114.2, 55.4.

The spectroscopic data were in accordance with those reported in the literature.[190]

3,3'-Dimethoxybiphenyl



Using the general procedure B, 3-methoxylphenylboronic acid (75 mg, 0.5 mmol), manganese(III) acetylacetonate (17 mg, 0.05 mmol) and potassium carbonate (69 mg, 0.5 mmol) were reacted in ethanol (2 mL) to give a crude reaction mixture which was purified by flash column chromatography (40 g SiO_2, 30 mm Ø, petroleum ether/diethyl ether 10:1) to give 3,3'-dimethoxybiphenyl (32 mg, 0.152 mmol, 61%) as a colourless oil.

^{1}H NMR: (500 MHz, $CDCl_3$)

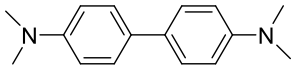
7.39-7.36 (m, 2H), 7.22-7.19 (m, 2H), 7.16-7.14 (m, 2H), 6.95-6.91 (m, 2H), 3.89 (s, 6H).

^{13}C NMR: (125 MHz, $CDCl_3$)

159.9, 142.9, 129.7, 119.7, 112.9, 112.8, 55.3.

The spectroscopic data were in accordance with those reported in the literature.[193]

***N*,*N*,*N'*,*N'*-Tetramethylbenzidine**



Using the general procedure B, 4-(dimethylamino)phenylboronic acid (83 mg, 0.5 mmol), manganese(III) acetylacetonate (17 mg, 0.05 mmol) and potassium carbonate (69 mg, 0.5 mmol) were reacted in ethanol (2 mL) to give a crude reaction mixture which was purified by flash column chromatography (40 g SiO_2, 30 mm Ø, petroleum ether/diethyl ether 10:1) to give *N*,*N*,*N'*,*N'*-tetramethylbenzidine (41 mg, 0.170 mmol, 68%) as a colourless microcrystalline solid.

m.p 189-191 °C (petroleum ether/EtOAc) Lit:[194] 188-193 °C (methanol)

^{1}H NMR: (500 MHz, $CDCl_3$)

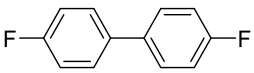
7.48 (d, *J* = 8.9 Hz, 4H), 6.83 (d, *J* = 8.9 Hz, 4H), 3.00 (s, 12H).

^{13}C NMR: (125 MHz, $CDCl_3$)

149.3, 129.9, 127.0, 113.1, 40.8.

The spectroscopic data were in accordance with those reported in the literature.[195]

4,4'-Difluorobiphenyl



Using the general procedure B, 4-fluorophenylboronic acid (70 mg, 0.5 mmol), manganese(III) acetylacetonate (17 mg, 0.05 mmol) and potassium carbonate (69 mg, 0.5 mmol) were reacted in ethanol (2 mL) to give a crude reaction mixture which was purified by flash column chromatography (40 g SiO_2, 30 mm Ø, petroleum ether/diethyl ether 10:1) to give 4,4'-difluorobiphenyl (34 mg, 0.181 mmol, 72%) as a colourless microcrystalline solid.

m.p 96-98 °C (petroleum ether/EtOAc) Lit:[190] 97-98 °C (petroleum ether/EtOAc)

^{1}H NMR: (500 MHz, $CDCl_3$)

7.51 (dd, *J* = 8.8 Hz, 5.3 Hz, 4H), 7.14 (t, *J* = 8.7 Hz, 4H).

^{13}C NMR: (125 MHz, $CDCl_3$)

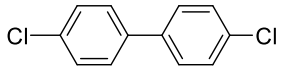
162.5 (d, *J* = 246.3 Hz), 136.4, 128.6 (d, *J* = 8.4 Hz), 115.7 (d, *J* = 21.4 Hz).

^{19}F NMR: (470 MHz, $CDCl_3$)

-115.8.

The spectroscopic data were in accordance with those reported in the literature.[190]

4,4'-Dichlorobiphenyl



Using the general procedure B, 4-chlorophenylboronic acid (78 mg, 0.5 mmol), manganese(III) acetylacetonate (17 mg, 0.05 mmol) and potassium carbonate (69 mg, 0.5 mmol) were reacted in ethanol (2 mL) to give a crude reaction mixture which was purified by flash column chromatography (40 g SiO_2, 30 mm Ø, petroleum ether/diethyl ether 10:1) to give 4,4'-dichlorobiphenyl (45 mg, 0.201 mmol, 80%) as a colourless microcrystalline solid.

m.p 145-147 °C (petroleum ether/EtOAc)

Lit:[190]148-149 °C (petroleum ether/EtOAc)

^{1}H NMR: (500 MHz, $CDCl_3$)

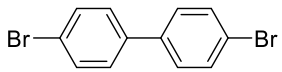
7.50 (d, *J* = 8.6 Hz, 4H), 7.43 (d, *J* = 8.6 Hz, 4H).

^{13}C NMR: (125 MHz, $CDCl_3$)

138.5, 133.8, 129.1, 128.2.

The spectroscopic data were in accordance with those reported in the literature.[190]

4,4'-Dibromobiphenyl



Using the general procedure B, 4-bromophenylboronic acid (100 mg, 0.5 mmol), manganese(III) acetylacetonate (17 mg, 0.05 mmol) and potassium carbonate (69 mg, 0.5 mmol) were reacted in ethanol (2 mL) to give a crude reaction mixture which was purified by flash column chromatography (40 g SiO_2, 30 mm Ø, petroleum ether/diethyl ether 10:1) to give 4,4'-dibromobiphenyl (66 mg, 0.214 mmol, 85%) as a colourless microcrystalline solid.

m.p 162-164 °C (petroleum ether/EtOAc)

Lit:[190] 162-163 °C (petroleum ether/EtOAc)

^{1}H NMR: (500 MHz, $CDCl_3$)

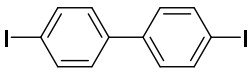
7.59 (d, *J* = 8.5 Hz, 4H), 7.43 (d, *J* = 8.5 Hz, 4H).

^{13}C NMR: (125 MHz, $CDCl_3$)

138.9, 132.0, 128.5, 121.9.

The spectroscopic data were in accordance with those reported in the literature.[190]

4,4'-Diiodobiphenyl



Using the general procedure B, 4-iodophenylboronic acid (124 mg, 0.5 mmol), manganese(III) acetylacetonate (17 mg, 0.05 mmol) and potassium carbonate (69 mg, 0.5 mmol) were reacted in ethanol (2 mL) to give a crude reaction mixture which was purified by flash column chromatography (40 g SiO_2, 30 mm Ø, petroleum ether/diethyl ether 10:1) to give 4,4'-diiodobiphenyl (78 mg, 0.194 mmol, 77%) as a colourless microcrystalline solid.

m.p 202-203 °C (petroleum ether/EtOAc)

Lit:[196] 200-201 °C (petroleum ether/EtOAc)

^{1}H NMR: (500 MHz, $CDCl_3$)

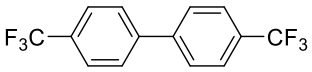
7.50 (d, *J* = 8.6 Hz, 4H), 7.43 (d, *J* = 8.6 Hz, 4H).

^{13}C NMR: (125 MHz, $CDCl_3$)

138.5, 133.8, 129.1, 128.2.

The spectroscopic data were in accordance with those reported in the literature.[197]

4,4'-Bis(trifluoromethyl)biphenyl



Using the general procedure B, 4-trifluoromethylphenylboronic acid (95 mg, 0.5 mmol), manganese(III) acetylacetonate (17 mg, 0.05 mmol) and potassium carbonate (69 mg, 0.5 mmol) were reacted in ethanol (2 mL) to give a crude reaction mixture which was purified by flash column chromatography (40 g SiO_2, 30 mm Ø, petroleum ether/diethyl ether 10:1) to give 4,4'- bis(trifluoromethyl)biphenyl (65 mg, 0.225 mmol, 90%) as a colourless microcrystalline solid.

m.p 99-101 °C (petroleum ether/EtOAc) Lit:[198] 97-98 °C (petroleum ether/EtOAc)

^{1}H NMR: (500 MHz, $CDCl_3$)

7.75-7.69 (m, 8H).

^{13}C NMR: (125 MHz, $CDCl_3$)

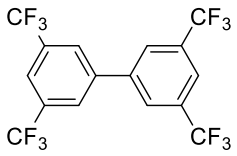
143.2, 130.3 (q, J = 32.6 Hz), 127.6, 125.9 (q, J = 3.8 Hz), 124.10 (q, J = 272.2 Hz).

^{19}F NMR: (470 MHz, $CDCl_3$)

-62.6.

The spectroscopic data were in accordance with those reported in the literature.[198]

3,3',5,5'-Tetrakis(trifluoromethyl)biphenyl



Using the general procedure B, 3,5-bis(trifluoromethyl)phenylboronic acid (129 mg, 0.5 mmol), manganese(III) acetylacetonate (17 mg, 0.05 mmol) and potassium carbonate (69 mg, 0.5 mmol) were reacted in ethanol (2 mL) to give a crude reaction mixture which was purified by flash column chromatography (40 g SiO_2, 30 mm Ø, petroleum ether/diethyl ether 10:1) to give 3,3',5,5'-tetrakis(trifluoromethyl)biphenyl (90 mg, 0.211 mmol, 84%) as a colourless microcrystalline solid.

m.p 78-80 °C (petroleum ether/EtOAc) Lit:[199] 82-83 °C (EtOAc)

$_{1}$H NMR: (500 MHz, $CDCl_3$)

8.05 (s, 4H), 8.01 (s, 2H).

$_{13}$C NMR: (125 MHz, $CDCl_3$)

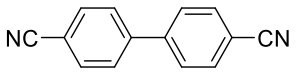
140.4, 132.9 (q, *J* = 33.4 Hz), 127.4 (d, *J* = 3.0 Hz), 123.0 (q, *J* = 273.2 Hz), 122.6 (quin, *J* = 3.99 Hz).

$_{19}$F NMR: (470 MHz, $CDCl_3$)

-62.9.

The spectroscopic data were in accordance with those reported in the literature.[157]

4,4'-Dicyanobiphenyl



Using the general procedure B, 4-cyanophenylboronic acid (82 mg, 0.5 mmol), manganese(III) acetylacetonate (17 mg, 0.05 mmol) and potassium carbonate (69 mg, 0.5 mmol) were reacted in ethanol (2 mL) to give a crude reaction mixture which was purified by flash column chromatography (40 g SiO_2, 30 mm Ø, petroleum ether/diethyl ether 10:1) to give 4,4'-dicyanobiphenyl (44 mg, 0.218 mmol, 87%) as a colourless microcrystalline solid.

m.p 230-231 °C (petroleum ether/EtOAc) Lit:[200] 238-239 °C (tetrahydrofuran)

$_{1}$H NMR: (500 MHz, $CDCl_3$)

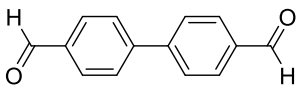
7.81 (d, *J* = 8.3 Hz, 4H), 7.72 (d, *J* = 8.3 Hz, 4H).

$_{13}$C NMR: (125 MHz, $CDCl_3$)

143.5, 132.9, 127.9, 118.4, 112.5.

The spectroscopic data were in accordance with those reported in the literature.[190]

1,1'-Biphenyl-4,4'-dicarbaldehyde



Using the general procedure B, 4-formylphenylboronic acid (75 mg, 0.5 mmol), manganese(III) acetylacetonate (17 mg, 0.05 mmol) and potassium carbonate (69 mg, 0.5 mmol) were reacted in ethanol (2 mL) to give a crude reaction mixture which was purified by flash column chromatography (40 g SiO_2, 30 mm Ø, petroleum ether/diethyl ether 10:1) to give 1,1'-biphenyl-4,4'-dicarbaldehyde (27 mg, 0.139 mmol, 52%) as a colourless microcrystalline solid.

m.p 139-141 °C (petroleum ether/EtOAc) Lit:[200]135-136 °C (hexane/EtOAc).

^{1}H NMR: (500 MHz, $CDCl_3$)

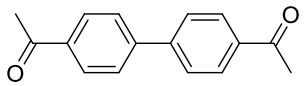
10.1 (s, 2H), 8.03 (d, *J* = 8.2 Hz, 4H), 7.83 (d, *J* = 8.2 Hz, 4H).

^{13}C NMR: (125 MHz, $CDCl_3$)

191.8, 145.6, 136.0, 130.4, 128.1.

The spectroscopic data were in accordance with those reported in the literature.[201]

4,4'-Diacetylbiphenyl



Using the general procedure B, 4-acetylphenylboronic acid (82 mg, 0.5 mmol), manganese(III) acetylacetonate (17 mg, 0.05 mmol) and potassium carbonate (69 mg, 0.5 mmol) were reacted in ethanol (2 mL) to give a crude reaction mixture which was purified by flash column chromatography (40 g SiO_2, 30 mm Ø, petroleum ether/diethyl ether 10:1) to give 4,4'-diacetylbiphenyl (41 mg, 0.175 mmol, 70%) as a colourless microcrystalline solid.

m.p 147-148 °C (petroleum ether/EtOAc) Lit:[200]145-146 °C (hexane/EtOAc).

^{1}H NMR: (500 MHz, $CDCl_3$)

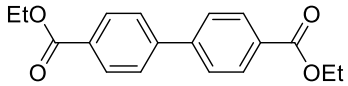
8.09 (d, *J* = 8.6 Hz, 4H), 7.75 (d, *J* = 8.6 Hz, 4H), 2.68 (s, 6H).

^{13}C NMR: (125 MHz, $CDCl_3$)

197.9, 140.5, 135.9, 133.8, 127.6, 26.8.

The spectroscopic data were in accordance with those reported in the literature.[202]

Diethyl (1,1'-biphenyl)-4,4'-dicarboxylate



Using the general procedure B, 4-ethoxycarbonylphenylboronic acid (97 mg, 0.5 mmol), manganese(III) acetylacetonate (17 mg, 0.05 mmol) and potassium carbonate (69 mg, 0.5 mmol) were reacted in ethanol (2 mL) to give a crude reaction mixture which was purified by flash column chromatography (40 g SiO_2, 30 mm Ø, petroleum ether/diethyl ether 10:1) to give diethyl (1,1'-biphenyl)-4,4'-dicarboxylate (38 mg, 0.131 mmol, 52%) as a colourless microcrystalline solid.

m.p 111-113 °C (petroleum ether/EtOAc) Lit:[203] 107-108 °C (hexane/EtOAc)

$_1$H NMR: (500 MHz, $CDCl_3$)

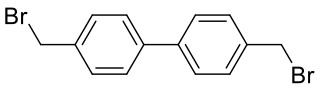
8.15 (d, *J* = 8.2 Hz, 4H), 7.71 (d, *J* = 8.2 Hz, 4H), 4.42 (q, *J* = 7.0 Hz, 4H), 1.43 (t, *J* = 7.0 Hz, 6H).

$_{13}$C NMR: (125 MHz, $CDCl_3$)

166.3, 144.3, 130.1, 129.9, 127.1, 61.0, 14.3.

The spectroscopic data were in accordance with those reported in the literature.[204]

4,4'-Bis(bromomethyl)biphenyl



Using the general procedure B, 4-bromophenylboronic acid (100 mg, 0.5 mmol), manganese(III) acetylacetonate (17 mg, 0.05 mmol) and potassium carbonate (69 mg, 0.5 mmol) were reacted in ethanol (2 mL) to give a crude reaction mixture which was purified by flash column chromatography (40 g SiO_2, 30 mm Ø, petroleum ether/diethyl ether 10:1) to give 4,4'-bis(bromomethyl)biphenyl (61 mg, 0.178 mmol, 71%) as a colourless microcrystalline solid.

m.p 162-163 °C (petroleum ether/EtOAc)

Lit:[205] 157-160 °C (petroleum ether/EtOAc)

$_1$H NMR: (500 MHz, $CDCl_3$)

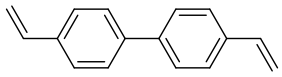
7.61-7.54 (m, 4H), 7.52-7.48 (m, 4H), 4.57 (s, 4H).

^{13}C NMR: (125 MHz, $CDCl_3$)

140.6, 137.1, 129.6, 127.5, 33.2.

The spectroscopic data were in accordance with those reported in the literature.[205]

4,4'-Divinyl-1,1'-biphenyl



Using the general procedure B, 4-vinylphenylboronic acid (74 mg, 0.5 mmol), manganese(III) acetylacetonate (17 mg, 0.05 mmol) and potassium carbonate (69 mg, 0.5 mmol) were reacted in ethanol (2 mL) to give a crude reaction mixture which was purified by flash column chromatography (40 g SiO_2, 30 mm Ø, petroleum ether/diethyl ether 10:1) to give 4,4'-divinyl-1,1'-biphenyl (35 mg, 0.173 mmol, 69%) as a colourless microcrystalline solid.

m.p 140-142 °C (petroleum ether/EtOAc)

Lit:[201] 140-142 °C (petroleum ether/EtOAc)

^{1}H NMR: (500 MHz, $CDCl_3$)

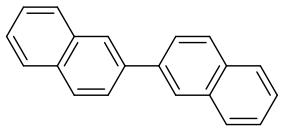
7.61 (d, *J* = 8.4 Hz, 4H), 7.51 (d, *J* = 8 Hz, 4H), 6.79 (dd, *J* = 10.9, 17.6 Hz, 2H), 5.82 (d, *J* = 17.6 Hz, 2H), 5.30 (d, *J* = 10.8 Hz, 2H).

^{13}C NMR: (125 MHz, $CDCl_3$)

140.0, 136.7, 136.4, 127.0, 126.7, 113.9.

The spectroscopic data were in accordance with those reported in the literature.[201]

2,2'-Binaphthalene



Using the general procedure B, 2-naphthylboronic acid (86 mg, 0.5 mmol), manganese(III) acetylacetonate (17 mg, 0.05 mmol) and potassium carbonate (69 mg, 0.5 mmol) were reacted in ethanol (2 mL) to give a crude reaction mixture which was purified by flash column chromatography (40 g SiO_2, 30 mm Ø, petroleum ether/diethyl ether 10:1) to give 2,2'-binaphthalene (31 mg, 0.125 mmol, 50%) as a colourless microcrystalline solid.

m.p 186-189 °C (petroleum ether/EtOAc) Lit:[206] 187-188 °C (hexane).

$_1$H NMR: (500 MHz, $CDCl_3$)

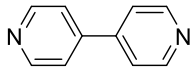
8.21 (s, 2H), 8.03-7.90 (m, 8H), 7.59-7.51 (m, 4H).

$_{13}$C NMR: (125 MHz, $CDCl_3$)

138.4, 133.7, 132.7, 128.5, 128.2, 127.7, 126.4, 126.1, 126.0, 125.7

The spectroscopic data were in accordance with those reported in the literature.[201]

4,4'-Bipyridine



Using the general procedure B, 4-pyridinylboronic acid (61 mg, 0.5 mmol), manganese(III) acetylacetonate (17 mg, 0.05 mmol) and potassium carbonate (69 mg, 0.5 mmol) were reacted in ethanol (2 mL) at 0 °C to give a crude reaction mixture which was purified by flash column chromatography (40 g SiO_2, 30 mm Ø, petroleum ether/diethyl ether 10:1) to give 4,4'-bipyridine (21 mg, 0.130 mmol, 52%) as a colourless microcrystalline solid.

m.p 108-111 °C (pnetroleum ether/EtOAc) Lit:[190] 107-109 °C (hexane)

$_1$H NMR: (500 MHz, $CDCl_3$)

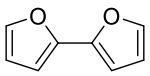
8.78-8.75 (m, 4H), 7.58-7.54 (m, 4H).

$_{13}$C NMR: (125 MHz, $CDCl_3$)

150.7, 145.6, 121.4.

The spectroscopic data were in accordance with those reported in the literature.[190]

2,2'-Bifuran



Using the general procedure B, 2-furanylboronic acid (56 mg, 0.5 mmol), manganese(III) acetylacetonate (17 mg, 0.05 mmol) and potassium carbonate (69 mg, 0.5 mmol) were reacted in ethanol (2 mL) at 0 °C to give a crude reaction mixture which was purified by flash column chromatography (40 g SiO_2, 30 mm Ø, hexane/diethyl ether 50:1) to give 2,2'-bifuran (24 mg, 0.183 mmol, 73%) as a pale yellow oil liquid.

$_1$H NMR: (500 MHz, $CDCl_3$)

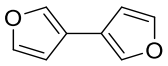
7.44-7.42 (m, 2H), 6.58-6.56 (m, 2H), 6.49-6.46 (m, 2H).

$_{13}$C NMR: (125 MHz, $CDCl_3$)

146.6, 141.8, 111.3, 105.1.

The spectroscopic data were in accordance with those reported in the literature.[207]

3,3'-Bifuran



Using the general procedure B, 3-furanylboronic acid (56 mg, 0.5 mmol), manganese(III) acetylacetonate (17 mg, 0.05 mmol) and potassium carbonate (69 mg, 0.5 mmol) were reacted in ethanol (2 mL) at 0 °C to give a crude reaction mixture which was purified by flash column chromatography (40 g SiO_2, 30 mm Ø, petroleum ether/diethyl ether 10:1) to give 3,3'-bifuran (26 mg, 0.196 mmol, 79%) as a pale yellow solid.

m.p 43 °C (petroleum ether/EtOAc)

$_1$H NMR: (500 MHz, $CDCl_3$)

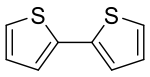
7.60 (s, 2H), 7.46 (s, 2H), 6.54 (s, 2H).

$_{13}$C NMR: (125 MHz, $CDCl_3$)

143.5, 138.3, 117.6, 109.1.

The spectroscopic data were in accordance with those reported in the literature.[208]

2,2'-Thiophene



Using the general procedure B, 2-thienylboronic acid (64 mg, 0.5 mmol), manganese(III) acetylacetonate (17 mg, 0.05 mmol) and potassium carbonate (69 mg, 0.5 mmol) were reacted in ethanol (2 mL) at 0 °C to give a crude reaction mixture which was purified by flash column chromatography (40 g SiO_2, 30 mm Ø, petroleum ether/diethyl ether 10:1) to give 2,2'-thiophene (29 mg, 0.175 mmol, 70%) as a yellow solid.

m.p 37-39 °C (petroleum ether/EtOAc) Lit:[209] 33-34 °C (hexane)

$_1$H NMR: (500 MHz, $CDCl_3$)

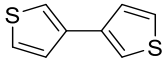
7.23 (dd, *J* = 5.1, 1.1 Hz, 2H), 7.20 (dd, *J* = 3.6, 1.1 Hz, 2H), 7.04 (dd, *J* = 5.1, 3.6 Hz, 2H).

$_{13}$C NMR: (125 MHz, $CDCl_3$)

137.4, 127.8, 124.4, 123.8.

The spectroscopic data were in accordance with those reported in the literature.[210]

3,3'-Thiophene



Using the general procedure B, 3-thienylboronic acid (64 mg, 0.5 mmol), manganese(III) acetylacetonate (17 mg, 0.05 mmol) and potassium carbonate (69 mg, 0.5 mmol) were reacted in ethanol (2 mL) at 0 °C to give a crude reaction mixture which was purified by flash column chromatography (40 g SiO_2, 30 mm Ø, petroleum ether/diethyl ether 10:1) to give 3,3'-thiophene (30 mg, 0.177 mmol, 71%) as a pale yellow solid.

m.p 130-131 °C (petroleum ether/EtOAc)

Lit:[201] 130-131 °C (petroleum ether/EtOAc)

$_1$H NMR: (500 MHz, $CDCl_3$)

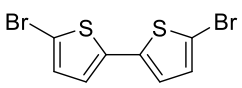
7.43-7.34 (m, 6H).

$_{13}$C NMR: (125 MHz, $CDCl_3$)

137.2, 126.4, 126.1, 119.8.

The spectroscopic data were in accordance with those reported in the literature.[210]

5,5'-Dibromo-2,2'-bithiophene



Using the general procedure B, 5-bromo-2-thienylboronic acid (103 mg, 0.5 mmol), manganese(III) acetylacetonate (17 mg, 0.05 mmol) and potassium carbonate (69 mg, 0.5 mmol) were reacted in ethanol (2 mL) at 0 °C to give a crude reaction mixture which was purified by flash column chromatography (40 g SiO_2, 30 mm Ø, petroleum ether/diethyl ether 10:1) to give 5,5'-dibromo-2,2'-bithiophene (48 mg, 0.147 mmol, 59%) as a pale yellow solid.

m.p 87-90 °C (petroleum ether/EtOAc) Lit:[211] 81-82°C (hexane).

^{1}H NMR: (500 MHz, $CDCl_3$)

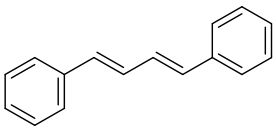
6.98 (d, *J* = 3.9 Hz, 2H), 6.87 (d, *J* = 3.8 Hz, 2H).

^{13}C NMR: (125 MHz, $CDCl_3$)

137.8, 130.7, 124.2, 111.6.

The spectroscopic data were in accordance with those reported in the literature.[201]

(1*E*,3*E*)-1,4-Diphenylbuta-1,3-diene



Using the general procedure B, *trans*-2-phenylvinylboronic acid (74 mg, 0.5 mmol), manganese(III) acetylacetonate (17 mg, 0.05 mmol) and potassium carbonate (69 mg, 0.5 mmol) were reacted in ethanol (2 mL) at 0 °C to give a crude reaction mixture which was purified by flash column chromatography (40 g SiO_2, 30 mm Ø, petroleum ether/diethyl ether 10:1) to give (1*E*,3*E*)-1,4-diphenylbuta-1,3-diene (32 mg, 0.158 mmol, 63%) as a colourless microcrystalline solid.

m.p 152-155 °C (petroleum ether/EtOAc) Lit:[212] 151-153 °C (pentane)

^{1}H NMR: (500 MHz, $CDCl_3$)

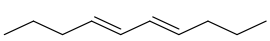
7.47 (dd, *J* = 8.2, 1.4 Hz, 4H), 7.36 (t, *J* = 6.3 Hz, 4H), 7.26 (tt, *J* = 7.3, 1.2 Hz, 2H), 7.02-6.96 (m, 2H), 6.74-6.68 (m, 2H).

^{13}C NMR: (125 MHz, $CDCl_3$)

137.4, 132.8, 129.3, 128.7, 127.6, 126.4.

The spectroscopic data were in accordance with those reported in the literature.[213]

(*E*,*E*)-4,6-decadiene



Using the general procedure B, 1-pentenylboronic acid (57 mg, 0.5 mmol) and manganese(III) acetylacetonate (17 mg, 0.05 mmol) and potassium carbonate (69 mg, 0.5 mmol) were reacted in ethanol (2 mL) at 0 °C to give a crude reaction mixture which was purified by flash column chromatography (40 g SiO_2, 30 mm Ø, petroleum ether/diethyl ether 50:1) to give (*E*,*E*)-4,6-decadiene (99 mg, 0.36 mmol, 72%) as a colourless oil liquid.

$_1$H NMR: (500 MHz, $CDCl_3$)

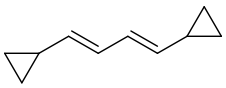
6.07-5.89 (m, 2H), 5.64-5.53 (m, 2H), 2.05 (q, *J* = 7.3 Hz, 4H), 1.42 (sextet, *J* = 7.4 Hz, 4H), 0.92 (t, *J* = 7.3 Hz, 6H).

$_{13}$C NMR: (125 MHz, $CDCl_3$)

132.1, 130.5, 34.7, 22.6, 13.7.

The spectroscopic data were in accordance with those reported in the literature.[214]

1,1'-(1,3-butadiene-1,4-diyl)biscyclopropane



Using the general procedure B, (*E*)-(2-cyclopropylvinyl)boronic acid (56 mg, 0.5 mmol) and manganese(III) acetylacetonate (17 mg, 0.05 mmol) and potassium carbonate (69 mg, 0.5 mmol) were reacted in ethanol (2 mL) at 0 °C to give a crude reaction mixture which was purified by flash column chromatography (40 g SiO_2, 30 mm Ø, petroleum ether/diethyl ether 50:1) to give (*E*,*E*)-4,6-decadiene (99 mg, 0.36 mmol, 70%) as a colourless oil liquid.

$_1$H NMR: (500 MHz, $CDCl_3$)

6.14-6.04 (m, 2H), 5.19-5.09 (m, 2H), 1.44-1.35 (m, 2H), 0.78-0.70 (m, 4H), 0.42-0.36 (m, 4H).

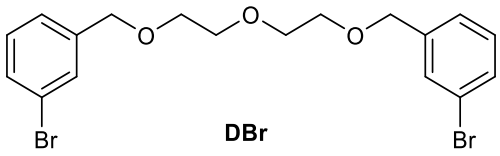
$_{13}$C NMR: (125 MHz, $CDCl_3$)

135.1, 127.9, 13.9, 7.1.

The spectroscopic data were in accordance with those reported in the literature.[215]

4.10 Intramolecular Homo-Coupling of Diboronic Acid

DBr: 3,3'-(2,2'-oxybis(ethane-2,1-diyl)bis(oxy))bis(methylene)bis(bromobenzene)



DBr

Solid 60% NaH (0.764 g, 19.1 mmol) was added in a 100 mL two-necked round-bottom flask. The flask was placed in an ice bath and a solution of di(ethylene glycol) (0.81 g, 7.63 mmol) in 5 mL THF was added dropwise. After the addition was complete, the reaction mixture was stirred at 0°C for 1 h, followed by slow addition of 3-bromobenzyl bromide (4 g, 16.0 mmol) in 10 mL THF. The reaction was allowed to warm to room temperature, and then heated under reflux overnight. After cooling to room temperature, the reaction was quenched with H_2O and diluted with diethyl ether. The layers were separated and the aqueous phase was re-extracted with diethyl ether. The combined diethyl ether layers were washed with brine and dried over anhydrous $MgSO_4$. Filtration and removal of the solvent gave an oily residue that was purified by flash column chromatography (60 g SiO_2, 30 mm Ø, hexane/ethyl acetate 4:1) to give DBr as a colourless oil liquid (2.13 g, 4.80 mmol, 63%).

MS: (HRMS - EI^+)

Found 441.97551 ($C_{18}H_{20}O_3Br_2$), requires 441.97737.

IR: *vmax* (*neat*)

3002 (s), 1649 (m), 1533 (m), 1354 (w), 1201 (w).

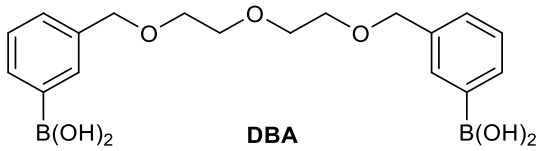
^{1}H NMR: (500 MHz, $CDCl_3$)

7.55-7.52 (m, 2H), 7.45-7.40 (m, 2H), 7.31-7.26 (m, 2H), 7.22 (t, *J* = 7.7 Hz, 2H), 4.57 (s, 4H), 3.74-3.66 (m, 8H).

^{13}C NMR: (125 MHz, $CDCl_3$)

140.7, 130.6, 130.5, 129.9, 126.1, 122.54, 72.4, 70.7, 69.7.

DBA: 3,3'-(2,2'-oxybis(ethane-2,1-diyl)bis(oxy))bis(methylene)bis(phenylboronic acid)



DBA

n-BuLi in hexanes (7 mL, 1.6 M, 10.8 mmol) was added dropwise to a solution of **DBr** (2 g, 4.5 mmol) in THF (20 mL) at -78 °C. After stirring for 2 h in the atmosphere of nitrogen, $B(O_iPr)_3$ (2.5 mL, 2.03 g, 10.8 mmol) was added slowly and the mixture was stirred at -78 °C for 5 hrs. The mixture was allowed to warm to room temperature then 1M HCl was added (40 mL) to quench the reaction. The mixture was transferred to a separation funnel with the aid of THF (40 mL). After phase separation, the organic layer was washed with water and dried over anhydrous $MgSO_4$. Filtration and removal of the solvent gave an oily residue that was washed by hexane for three times. Boiling water (20 mL) was added to the residue. After cooling to 0 °C, mixture was filtered to give **DBA** as a colourless solid (0.99 g, 60% yield).

m.p 90 °C (petroleum ether/EtOAc)

MS: (HRMS - EI^+)

Found 374.17764 ($C_{18}H_{24}O_7B_2$), requires 374.17699.

IR: *vmax* (*neat*)

3033 (br, s), 2903 (m), 1800 (m), 1710 (s), 1511 (w).

^{1}H NMR: (500 MHz, *d*$_6$-DMSO)

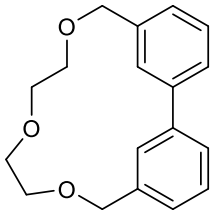
8.02 (s, 4H), 7.75-7.68 (m, 4H), 7.37-7.27 (m, 4H), 4.48 (s, 4H), 3.60-3.54 (m, 8H).

^{13}C NMR: (125 MHz, *d*$_6$-DMSO)

137.7, 134.0, 133.7, 129.9, 127.7, 72.9, 70.2, 69.5.

^{11}B NMR: (160 MHz, *d*$_6$-DMSO)

30.9.



Following the general procedure B, **DBA** (220 mg, 0.5 mmol) and manganese(III) acetylacetonate (17 mg, 0.05 mmol) and potassium carbonate (69 mg, 0.5 mmol) were reacted in ethanol (10 mL) to give a crude reaction mixture which was purified by flash column chromatography (40 g SiO_2, 30 mm Ø, petroleum ether/dichloromethane 2:1) to give the macrocycle (26 mg, 0.09 mmol, 18%) as a colourless solid.

m.p 290-292 °C (dichloromethane)

MS: (HRMS - EI^+)

Found 284.14778 ($C_{18}H_{20}O_3$), requires 284.14608.

IR: *vmax* (*neat*)

2933 (s), 1899 (s), 1800 (m), 1710 (m), 1511 (w), 1000 (w).

^{1}H NMR: (500 MHz, CD_2Cl_2)

7.58-7.55 (m, 2H), 7.48-7.44 (m, 2H), 7.33-7.30 (m, 2H), 7.28-7.24 (m, 2H)

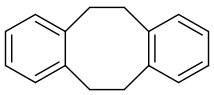
4.56 (s, 4H), 3.72-3.66 (m, 8H).

^{13}C NMR: (125 MHz, CD_2Cl_2)

141.2, 130.5, 130.4, 129.9, 126.1, 122.3, 72.2, 70.6, 69.9.

4.11 Preparation of DCT

5,6,11,12-Tetrahydrodibenzo[a,e]cyclooctene



Prepared according to a literature procedure.[216]

α,α'-Dibromo-*o*-xylene (5.3 g, 20 mmol) in anhydrous THF (10 mL) was added for 1h to a suspension of granular lithium (350 mg, 50 mmol) in anhydrous THF (20 mL). The reaction was heated under reflux for an additional 2 h. The reaction was cooled, filtered and concentrated *in vacuo*. Dichloromethane (50 mL) was added to the residue and stirred for 2 minutes. The suspension was filtered through a plug of silica, which washed subsequently washed with dichloromethane (2 × 50 mL). The filtrate was dried over $MgSO_4$ and concentrated *in vacuo* to give a pale yellow solid, which was purified by flash silica chromatography (pet. ether) to give 5,6,11,12-tetrahydrodibenzo[a,e]cyclooctene as colourless plates (621 mg, 2.98mmol, 30%).

m.p 108-109 °C (petroleum ether/EtOAc)

$_1$H NMR: (500 MHz, $CDCl_3$)

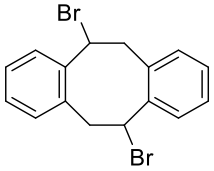
7.04-6.98 (m, 8H), 3.08 (s, 8H).

$_{13}$C NMR: (125 MHz, $CDCl_3$)

140.6, 129.7, 126.1, 35.2.

The spectroscopic data were in accordance with those reported in the literature.[216]

5,11-Dibromo-5,6,11,12-tetrahydrodibenzo[a,e]cyclooctene



Prepared according to a literature procedure.[216]

N-Bromosuccinimide (766 mg, 4.3 mmol) was added to a solution of 5,6,11,12-tetrahydrodibenzo[a,e]cyclooctene (416 mg, 2 mmol) in tetrachloromethane (10 mL) under a

nitrogen atmosphere. The reaction was heated under reflux for 2 h. The reaction mixture was filtered through a sinter, which was washed with tetrachloromethane (5 mL). The solvent was removed *in vacuo* and the yellow residue washed on a sinter using water (2 × 5 mL), and dried under vacuum. The crude product (668 mg) was determined to be approximately 95% pure by ^{1}H NMR spectroscopy, and was used without further purification.

m.p 178-180 °C (ethanol)

^{1}H NMR: (500 MHz, $CDCl_3$)

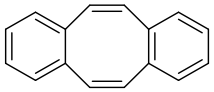
7.14 (td, *J* = 7.5, 1.5 Hz, 2H), 7.09 (dd, *J* = 7.5, 1.5 Hz, 2H), 7.05 (td, *J* = 7.5, 1.5 Hz, 2H), 6.99 (dd, *J* = 7.5, 1.5 Hz, 2H), 5.35 (dd, *J* = 11.0, 8.5 Hz, 2H), 4.30 (dd, *J* = 14.0, 11.0 Hz, 2H), 3.67 (dd, *J* = 14.0, 8.5 Hz, 2H).

^{13}C NMR: (125 MHz, $CDCl_3$)

138.4, 136.4, 131.0, 130.8, 129.1, 127.9, 53.0, 43.7.

The spectroscopic data were in accordance with those reported in the literature.[216]

Dibenzo[a,e]cyclooctene



Prepared according to a literature procedure.[216]

5,11-Dibromo-5,6,11,12-tetrahydrodibenzo[a,e]cyclooctene (2g, ~5.1 mmol) in anhydrous tetrahydrofuran (10 mL) was added over 13 minutes to a solution of potassium *tert*-butoxide **755** (2.45 g, 21.6 mmol) in anhydrous tetrahydrofuran (8 mL) at 0 °C, under a nitrogen atmosphere. The reaction was allowed to warm to room temperature and was stirred for an additional 2 hours. Water (1 mL) was added and the mixture filtered through a silica plug (wetted with diethyl ether), and washed with diethyl ether (2 × 30 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give a brown solid, which was purified by flash silica chromatography (pet. ether) to give dibenzo[a,e]cyclooctene as colourless plates (701 mg, 3.43 mmol, 67%).

m.p 105-106 °C (ethanol)

^{1}H NMR: (500 MHz, $CDCl_3$)

7.19-7.14 (m, 4H), 7.09-7.05 (m, 4H), 6.77 (s, 4H).

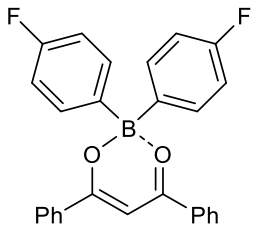
^{13}C NMR: (125 MHz, $CDCl_3$)

137.1, 133.2, 129.1, 126.8.

The spectroscopic data were in accordance with those reported in the literature.[216]

4.12 Preparation Neutral Boron Complex

(*Z*)-3-((Bis(4-fluorophenyl)boryl)oxy)-1,3-diphenylprop-2-en-1-one



Prepared according to a modified literature procedure.[169]

To a 100 mL round bottom flask equipped with magnetic stirring bar and reflux condenser, were added sequentially 1,3-diphenyl-1,3-propanedione (224 mg, 1.0 mmol), 4-fluorophenylboronic acid (1.259 g, 9.0 mmol), K_3PO_4 (636 mg, 3.0 mmol) and 1,4-dioxane (50 mL). The mixture was heated under reflux for 20 h under the atmosphere of nitrogen and the solvent was evaporated under reduced pressure. The resulting crude product was dissolved in ethyl acetate (20 mL) and washed with water (20 mL). The separated organic layer was then washed with KOH solution (1M, 3 x 10 mL) and brine (10 mL), dried over $MgSO_4$, and evaporated to dryness under reduced pressure. The residue was purified by flash column chromatography (40 g SiO_2, 30 mm Ø, hexane/EtOAc 20:1) to give (Z)-3-((Bis(4-fluorophenyl)boryl)oxy)-1,3-diphenylprop-2-en-1-one (99 mg, 0.8 mmol, 80%) as a yellow solid.

m.p 216-217 °C (dichloromethane)

MS: (HRMS - EI^+)

Found 424.14328 ($C_{27}H_{19}O_2BF_2$), requires 424.14407.

^{1}H NMR: (500 MHz, $CDCl_3$)

8.23-8.17 (m, 4H), 7.71 (t, *J* = 7.5 Hz, 2H), 7.61-7.54 (m, 8H), 7.05 (s, 1H), 7.02-6.97 (m, 4H)

^{13}C NMR: (125 MHz, $CDCl_3$)

141.2, 130.5, 130.4, 129.9, 126.1, 122.3, 72.2, 70.6, 69.9.

No signal was observed for the carbon attached to boron.

^{11}B NMR: (160 MHz, $CDCl_3$)

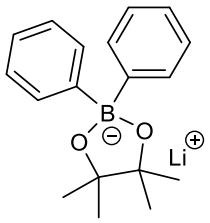
8.7

^{19}F NMR: (99 MHz, $CDCl_3$)

-116.7

4.13 Preparation of Boron 'ate' complexes

[Li][(Ph)$_2$B(pin)]



Prepared according to a modified literature procedure.[177]

To a THF solution (5 mL) of phenylboronic acid pinacol ester (204 mg, 1.0 mmol) was added phenyllithium in dibutyl ether (526 µL, 1.9 M, 1.0 mmol) at -78 ℃ under a nitrogen atmosphere. The reaction mixture was stirred at -78 ℃ for 1h. The solvent was removed *in vacuo* at room temperature, and the product was wash with anhydrous hexane (3 x 5 mL) under an argon atmosphere to give [Li][(Ph)$_2$B(pin)] (273 mg, 0.95 mmol, 95%) as a colourless solid.

m.p: decomposed when heated above 200 °C (tetrahydrofuran).

$_1$H NMR: (500 MHz, CD_3OD)

7.53-7.50 (m, 4H), 7.01 (t, *J* = 7.5 Hz, 4H), 6.87 (tt, *J* = 7.3, 1.4 Hz, 2H), 1.08 (s, 12H)

$_{13}$C NMR: (125 MHz, CD_3OD)

131.9, 125.3, 122.7, 77.9, 25.1

No signal was observed for the carbon attached to boron.

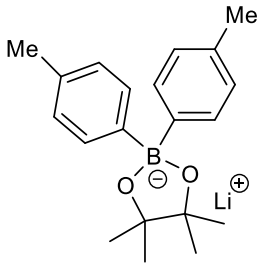
$_{11}$B NMR: (160 MHz, CD_3OD)

6.2

$_7$Li NMR: (155 MHz, CD_3OD)

-0.4

[Li][(*p*-tol)$_2$B(pin)]



Prepared according to a modified literature procedure.[177]

To a THF solution (10 mL) of 4-bromotoluene (171 mg, 1.0 mmol) was added n-BuLi in hexanes (400 µL, 2.5 M, 1.0 mmol) at -78 ℃ under a nitrogen atmosphere, and the reaction mixture was stirred for 1h at -78 ℃. 4-Methylphenylboronic acid pinacol ester (218 mg, 1.0 mmol) in anhydrous THF (5 mL) was added, and the resulting mixture was stirred for another 1h. The solvent was removed *in vacuo* at room temperature, and the product was wash with anhydrous hexane (3 x 5 mL) under an argon atmosphere to give [Li][(*p*-tol)$_2$B(pin)] (284 mg, 0.90 mmol, 90%) as a colourless solid.

m.p: decomposed when heated above 200 °C (tetrahydrofuran).

$_1$H NMR: (500 MHz, CD_3OD)

7.39 (d, *J* = 7.8 Hz, 4H), 6.84 (d, *J* = 7.4 Hz, 4H), 2.21 (s, 6H), 1.07 (s, 12H)

$_{13}$C NMR: (125 MHz, CD_3OD)

132.6, 132.0, 131.27, 77.9, 23.6, 19.9.

No signal was observed for the carbon attached to boron.

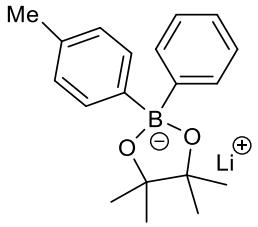
$_{11}$B NMR: (160 MHz, CD_3OD)

6.2

$_7$Li NMR: (155 MHz, CD_3OD)

-0.4

[Li][(Ph)(*p*-tol)B(pin)]



Prepared according to a modified literature procedure.[177]

To a THF solution (5 mL) of 4-methylphenylboronic acid pinacol ester (218 mg, 1.0 mmol) was added phenyllithium in dibutyl ether (526 µL, 1.9 M, 1.0 mmol) at -78 °C under a nitrogen atmosphere. The reaction mixture was stirred at -78 °C for 1h. The solvent was removed *in vacuo* at room temperature, and the product was wash with anhydrous hexane (3 x 5 mL) under an argon atmosphere to give [Li][(Ph)(*p*-tol)B(pin)] (286 mg, 0.95 mmol, 95%) as a colourless solid.

m.p: decomposed when heated above 200 °C (tetrahydrofuran).

$_{1}$H NMR: (500 MHz, CD_3OD)

7.52-7.51 (m, 2H), 7.40 (d, *J* = 7.9 Hz, 2H), 7.02-6.98 (m, 2H), 6.88-6.83 (m, 3H), 2.21 (s, 3H), 1.08 (s, 6H), 1.07 (s, 6H)

$_{13}$C NMR: (125 MHz, CD_3OD)

132.1, 131.9, 131.3, 126.1, 125.3, 122.6, 77.8, 25.1, 25.0

No signal was observed for the carbon attached to boron.

$_{11}$B NMR: (160 MHz, CD_3OD)

6.1

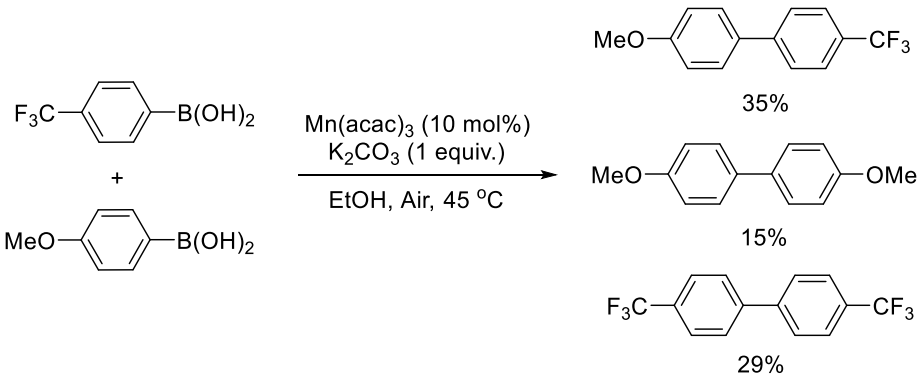
$_{7}$Li NMR: (155 MHz, CD_3OD)

-0.4

4.14 Manganese-Catalysed Cross-Coupling Reactions

Standard cross-coupling reactions

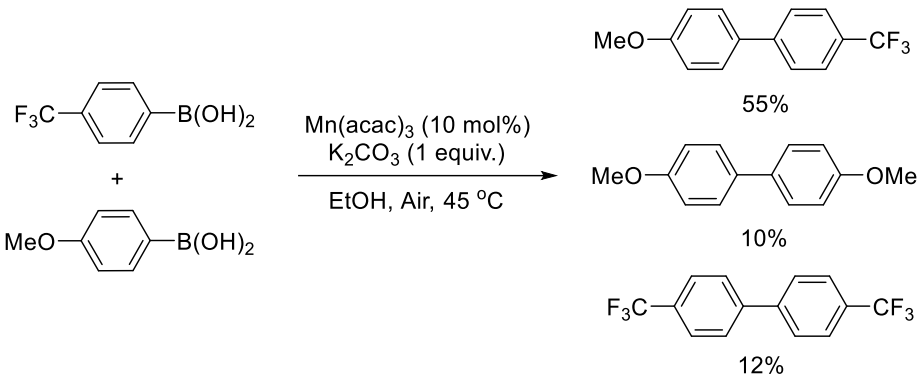
4-methoxyphenylboronic acid (0.25 mmol, 38 mg), 4-(trifluoromethyl)phenylboronic acid (0.25 mmol, 47 mg), manganese(III) acetylacetonate (17 mg, 0.05 mmol, 10 mol%) and potassium carbonate (69 mg, 0.5 mmol, 1 equiv.) were added to ethanol (2 mL) in a reaction vial. The reaction was left to stir under air atmosphere at 45 °C for 20 h, diluted with diethyl ether (3 mL) and washed with sodium hydroxide solution (1M, 3 mL) and water (3 mL). The organic phase was directly through silica plug (5 g SiO_2, 10 mm Ø, hexane) and the solvent removed *in vacuo*. 1,3,5-Trimethoxybenzene (16.8 mg, 0.1 mmol), as an internal standard, was added to the product. The NMR yield of products were determined by quantitative ^{13}C NMR.



Scheme 4.01 Manganese-catalysed cross-coupling of 4-trifluoromethylphenylboronic acid and 4-methoxyphenylbronic acid under standard reaction conditions

Optimised cross-coupling reactions

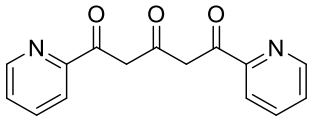
Manganese(III) acetylacetonate (17 mg, 0.05 mmol, 10 mol%) and potassium carbonate (69 mg, 0.5 mmol, 1 equiv.) were added to ethanol (2 mL) in a reaction vial. A solution of 4-methoxyphenylboronic acid (0.25 mmol, 38 mg) in ethanol (5 mL) was dropwisely added to the mixture for 1h. A solution of 4-(trifluoromethyl)phenylboronic acid (0.25 mmol, 47 mg) in ethanol (5 mL) was dropwisely added to the mixture for 5h. The resulting mixture was left to stir under air atmosphere at 45 °C for 20 h, diluted with diethyl ether (10 mL) and washed with sodium hydroxide solution (1M, 3 mL) and water (3 mL). The organic phase was directly through silica plug (5 g SiO_2, 10 mm Ø, hexane) and the solvent removed *in vacuo*. 1,3,5-Trimethoxybenzene (16.8 mg, 0.1 mmol), as an internal standard, was added to the product. The NMR yield of products were determined by quantitative ^{13}C NMR.



Scheme 4.01 Manganese-catalysed cross-coupling of 4-trifluoromethylphenylboronic acid and 4-methoxyphenylbronic acid under optimised reaction conditions

4.14 Self-Activating Catalysis

1,5-Bis(2′-bipyridyl)pentane-1,3,5-trione



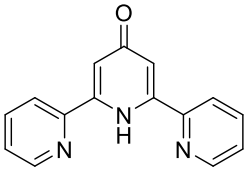
Prepared according to a modified literature procedure.[217]

To NaH (1.50 g, 60% dispersion in oil, 37.5 mmol) in anhydrous THF (50 mL) heated to reflux under a nitrogen atmosphere was added a solution of ethyl 2-pyridine-carboxylate (5 mL, 37.5 mmol) in anhydrous THF (10 mL) and acetone (900 µL, 12.5 mmol) in anhydrous THF (10 mL), dropwise over 2h, and the reaction mixture was then heated for 2h, giving an orange solution. The reaction mixture was then cooled, the solvent removed under reduced pressure and the residue dissolved in water (100 mL). After filtration through Celite, the solution was neutralised by the addition of 5% acetic acid, precipitating a yellow powder, which was recrystallised from ethanol to give 1,5-bis(2′-bipyridyl)pentane-1,3,5-trione (2.35 g, 8.75 mmol, 70%) as a light yellow powder.

m.p 116-117 °C (ethanol)

Because of the presence of different keto-enol tautomers the ^{1}H-NMR spectrum was not interpreted.

(2,2':6',2''-Terpyridin)-4'(1'*H*)-one



Prepared according to a modified literature procedure.[217]

Excess ammonium acetate (4.0 g, 50 mmol) and 1,5-bis(2′-bipyridyl)pentane-1,3,5-trione (2.0 g, 7.46 mmol) were dissolved in EtOH (50 mL) and heated to reflux. After 6 h the resultant brown solution was concentrated to ca. 8 mL and cooled to 0 °C, precipitating the product as colourless powder which was crystallised from ethanol to give (2,2':6',2''-terpyridin)-4'(1'*H*)-one (1.67g, 6.7 mmol, 90%) as colourless crystals.

m.p 169-171 °C (ethanol)

^{1}H NMR: (500 MHz, $CDCl_3$)

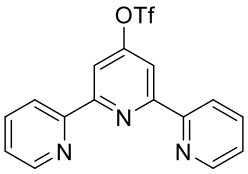
12.1 (br, 1H), 8.84-8.80 (m, 2H), 8.02-7.96 (m, 2H), 7.92 (dt, *J* = 1.7, 7.5 Hz, 2H), 7.47 (ddd, *J* = 7.4, 4.8, 1.1 Hz, 2H), 7.28 (s, 2H)

^{13}C NMR: (125 MHz, $CDCl_3$)

181.6, 149.5, 148.6, 144.5, 137.7, 125.2, 120.5, 113.6

The spectroscopic data were in accordance with those reported in the literature.[217]

4'-(((Trifluoromethyl)sulfonyl)oxy)-2,2':6',2''-terpyridine



Prepared according to a modified literature procedure.[218]

Terpyridone (1.25 g, 5 mmol) was dissolved in anhydrous pyridine (30 mL) and the reaction mixture was cooled down to 0 °C. Trifluoromethanesulfonic anhydride (833 µL, 5 mmol) was added and the mixture was stirred overnight at room temperature. Ice (10 g) was then added and the reaction mixture was stirred for 1h. The white precipitate was filtered and washed with cold water to give 4'-(((trifluoromethyl)sulfonyl)oxy)-2,2':6',2''-terpyridine (1.81 g, 4.75 mmol, 95%) as a white solid.

m.p 104-105 °C (ethanol)

^{1}H NMR: (500 MHz, $CDCl_3$)

8.75 (dq, *J* = 4.7, 0.8 Hz, 2H), 8.65 (dq, *J* = 8.0, 1.0 Hz, 2H), 8.45 (s, 2H), 7.9 (td, *J* = 7.8, 1.8 Hz, 2H), 7.42 (ddd, *J* = 7.4. 4.7. 1.1 Hz, 2H).

^{13}C NMR: (125 MHz, $CDCl_3$)

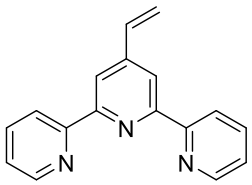
158.8 (d, *J* = 2.5 Hz), 158.5 (*J* = 2.5 Hz), 154.3 (*J* = 2.5 Hz), 149.4 (*J* = 2.0 Hz), 137.0 (*J* = 2.0 Hz), 124.7 (*J* = 2.0 Hz), 121.4 (*J* = 2.0 Hz), 113.2 (*J* = 1.5 Hz).

^{19}F NMR: (99 MHz, $CDCl_3$)

-72.9

The spectroscopic data were in accordance with those reported in the literature.[218]

4'-Vinyl-2,2':6',2''-terpyridinyl



Prepared according to a modified literature procedure.[219]

A mixture of 4'-(((trifluoromethyl)sulfonyl)oxy)-2,2':6',2''-terpyridine (955 mg, 2.5 mmol), vinyltributyltin (1.11 g, 3.5 mmol), triethylamine (1.5 mL, 11 mmol), and bis(triphenylphosphine)palladium dichloride (50 mg, 70 µmol) in anhydrous DMF (10 mL) was stirred at 90 °C for 4 h under the atmosphere of nitrogen. The reaction mixture was then diluted with ice water (50 mL), stirred for 1 h, and filtered. The light-yellow solid was washed several times with water and dried. The crude product was dissolved in diethyl ether (100 mL) and the insoluble material removed by filtration. Evaporation of the ether under reduced pressure resulted in a pale yellow solid that was crystallised from *n*-hexane to give give 4'-vinyl-2,2':6',2''-terpyridinyl (188 mg, 0.75 mmol, 30%) as colourless cream rosettes.

m.p 90-91 °C (hexane)

$_1$H NMR: (500 MHz, $CDCl_3$)

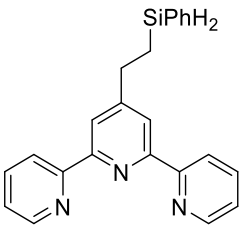
8.74 (dq, *J* = 4.8, 0.8 Hz, 2H), 8.65 (dt, *J* = 8.0, 1.0 Hz, 2H), 8.50 (s, 2H), 7.89 (td, *J* = 7.8, 1.8 Hz, 2H), 7.37 (ddd, *J* = 7.4, 4,8, 1.1 Hz, 2H), 6.90 (dd, *J* = 17.7, 10.9 Hz, 1H), 6.26 (d, *J* = 17.7 Hz, 1H), 5.59 (d, *J* = 17.7 Hz, 1H).

$_{13}$C NMR: (125 MHz, $CDCl_3$)

156.2, 155.8, 149.1, 146.9, 136.9, 135.2, 123.8, 121.3, 118.9, 118.2

The spectroscopic data were in accordance with those reported in the literature.[220]

4'-(2-(Phenylsilyl)ethane)-2,2':6',2''-terpyridinyl

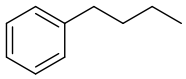


$_1$H NMR: (500 MHz, $CDCl_3$)

8.64 (dq, *J* = 4.6, 0.8 Hz, 2H), 8.65 (dt, *J* = 8.0, 1.0 Hz, 2H), 8.15 (s, 2H), 7.69 (td, *J* = 7.8, 1.8 Hz, 2H), 7.53-7.4 (m, 5H), 7.21 (ddd, *J* = 7.4, 4,8, 1.1 Hz, 2H), 4.15 (t, *J* = 3.6 Hz, 2H), 2.98-2.76 (m, 2H), 1.33-1.25 (m, 2H).

Attempts to purify the product resulted in decomposition.

1-Butylbenzene



Prepared according to a modified literature procedure.[93]

In an autoclave, 4-phenyl-1-butene (156 µL, 1.0 mmol) was added to a mixture of 4'-(2-(Phenylsilyl)ethane)-2,2':6',2''-terpyridinyl (3.7 mg, 10 µmol, 1 mol%) and iron(II) dichloride (0.7 mg, 10 µmol, 1 mol%) and sodium *tert*-butoxide (2.0 mg, 20 µmol, 2 mol%). Phenylsilane (5 µL, 40 µmol, 4 mol%) and anhydrous THF (0.2 mL) were sequentially added, and the autoclave pressurised with H_2 (15 bar). The resulting mixture was stirred at room temperature for 24 h, diluted with diethyl ether (2 mL) and sulfate buffer (2 mL). 1,3,5-Trimethoxybenzene, as an internal standard, was added and the organic phase of the mixture was sampled. The yield for the reaction was determined by integration of product $_1$H NMR resonances.

The crude reaction product was purified by flash column chromatography (25 g SiO_2, 30 mm Ø, pentane) and the pentane removed *in vacuo* (400 mbar, 35°C) to give the volatile product 1-butylbenzene (14 mg, 0.11 mmol, 11%) as a colourless oil.

$_1$H NMR: (500 MHz, $CDCl_3$)

7.35-7.28 (m, 2H), 7.26-7.17 (m, 3H), 2.65 (t, *J* = 7.8 Hz, 2H), 1.68-1.61 (m, 2H), 1.44-1.36 (m, 2H), 0.97 (t, *J* = 7.5 Hz, 3H)

$_{13}$C NMR: (125 MHz, $CDCl_3$)

142.9, 128.4, 128.2, 125.6, 35.7, 33.7, 22.4, 14.0

The spectroscopic data were in accordance with those reported in the literature.[93]

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Chapter 6 Appendix: Publications

Journal Publications (chronological order):

1. J. H. Docherty, **J. Peng**, A. P. Dominey and S. P. Thomas. Activation and Discovery of Earth-Abundant Metal Catalysts Using Sodium *tert*-Butoxide. *Nature Chemistry* 2017, **9**, 595-600.

2. **J. Peng**, J. H. Docherty, A. P. Dominey and S. P. Thomas. Cobalt-Catalysed Markovnikov Selective Hydroboration of Vinylarenes. *Chemical Communications* 2017, **53**, 4726-4729.

3. **J. Peng** and S. P. Thomas. Activation Strategies for Earth-abundant Metal Catalysis. *Synlett* (Manuscript submitted)

4. **J. Peng**, J. E. Bennington, P. G. N. Neate and S. P. Thomas. Manganese-Catalysed Homo-Coupling of Boronic Acids. (Manuscript in preparation)