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Transition Metal Catalysed Borylation of C-H Bonds

By

Ibraheem Ahmed I. Mkhalid

A Thesis Presented to the University of Durham in Fulfillment

of the Thesis Requirement for the Degree of Doctor of

Philosophy in Chemistry

University of Durham

Ibraheem Mkhalid 2006

Dedication

To My Parents, My Wife Maha Al-haddad and My

Son Ahmed M.khalid for Their

Continual Love and Support

Declaration

The work described in this thesis was carried out in the Department of Chemistry at the University of Durham between October 2002 and May 2006, under the supervision of Prof. Todd B. Marder. All the work is my own, unless otherwise stated, and has not been submitted previously for a degree at this or any other university.

Ibraheem A. I. Mkhalid

17.07.06

Statement of Copyright

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Conferences Attended

1- 5th Anglo-Dutch Conference on Organometallic Chemistry and Catalysis Cardiff University, 14-16 April 2004.

2- 14th International Symposium on Homogeneous Catalysis, Munich, Germany, 5-9 July, 2004.

3- EUROBORON 3 Conference, Prague, Czech Republic 2005.

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Abstract

Chapter one provides a general review of the metal catalysed diboration of alkynes, 1,2- and 1,3-dienes, α,β-unsaturated carbonyl compounds, and alkenes, as well as the metal catalysed borylation of alkane and arene C-H bonds.

Chapter two is divided into two main sections. The first section introduces a high yield, highly selective catalytic synthesis of vinylboronate esters VBEs, including 1,1-disubstituted VBEs, from alkenes without significant hydrogenation or hydroboration, using the catalyst precursor, *trans*-$[RhCl(CO)(PPh_3)_2]$, and the diboron reagents B_2pin_2, B_2neop_2 and HBpin. The second section addresses the synthesis of VBEs *via* microwave-assisted catalysis and these results are compared with those from the conventional, thermal reactions.

Chapter three investigates regioselectivity in the synthesis of pyridinyl and bipyridinyl boronate esters *via* C-H activation using the catalyst precursor, $[Ir(COD)(\mu\text{-}OMe)]_2$, and 4,4'-$^tBu_2$-2,2'-bipyridine as the ligand. Several the pyridinyl and bipyridinyl boronate esters were coupled with aryl halides by Suzuki-Miyaura cross-coupling reactions *in one pot*. Examples include msiture-sensitve heteroaryl 2-boronate esters.

Chapter four shows the utility of the transition metal catalysed borylation of C-H bonds in the synthesis of biologically active retinoic acid analogs.

List of Abbreviations

Å	Angstrom	**equiv.**	equivalent
Ar	aromatic group	**Et**	ethyl
Ar-BIAN	bis(arylimino)acenaphthene	**g**	gram
acac	acetylacetone	**GC**	gas chromatography
bpy	2,2'-bipyridinyl	**h**	hour
1,2-BBE	1,2-bis(boronate)esters	**Iso. yield**	isolated yield
^{t}Bu	*tert*-butyl	**L**	ligand
cat	catecholato, (1,2-$O_2C_6H_4$)	**g**	gram
COD	cyclooctadiene	**Me**	methyl
COE	*cis*-cyclooctene	**mg**	milligram
Cp	cyclopentadienyl	**ml**	milliliter
Cp*	pentamethylcyclopentadienyl	**mmol**	millmol
Cy	cyclohexyl	**MS**	mass spectrometry
dba	dibenzylideneacetone	**m/z**	Mass to charge ratio
dcpe	1,2-bis(dicyclohexylphosphino)ethane	**nbe**	norbornene
DMF	N,N-dimethylformamide	**nbd**	norbornadiene
DMFU	But-2-enedioic acid dimethylester	**neop**	Neopentylglycolato ($OCH_2CMe_2CH_2O$)
dtbpy	4,4'-di-*tert*-butyl-2,2'-bipyridinyl	**pin**	pinacolato ($OCMe_2CMe_2O$)
dppb	1,4-bis(diphenylphosphino)butane	**Ph**	phenyl
dppe	1,4-bis(diphenylphosphino)ethane	**^{i}Pr**	*iso*-propyl
dppm	bis(diphenylphosphino)methane	**R**	alkyl
1,2,2-TBE	1,2,2-tris(boronate)ester	**TMS**	trimethylsilyl

2,2,2-TBE	2,2,2-tris(boronate)ester
THF	tetrahydrofuran
tol	tolyl
VBE	vinyl boronate ester
VBBE	vinyl bis(boronate)ester
X	halogen

Abbreviations used for NMR

d	doublet
Hz	hertz
J	coupling constant
m	multiplet
MHz	megahertz
q	quartet
s	singlet
t	triplet

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Chapter two: *Trans*-[RhCl(CO)(PPh$_3$)$_2$]-Catalysed Dehydrogenative Borylation of Vinylarenes, 1,1-Disubstituted Alkenes and other Alkenes

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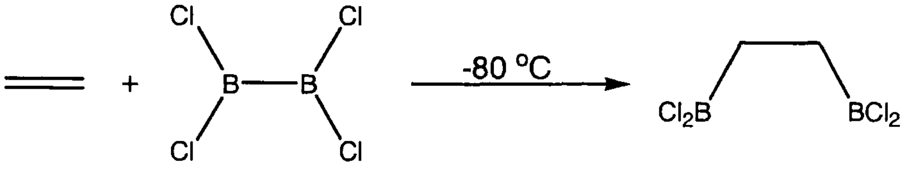
1.1 Introduction

Organoboron compounds have received attention because of their importance as intermediates in organic synthesis.[1,2] This makes the borylation of hydrocarbons an objective of much research. In general terms, when the B-C bond is formed, it can be cleaved with or without homologation to form many useful functionalised compounds.[2] One very important application of organoboron compounds is in the Suzuki-Miyaura cross-coupling reaction,[3,4] which employs boronic acids or boronate esters.

Hydroboration is the primary method for synthesis of organoboron compounds, which was developed[2] by H. C. Brown and his co-workers, and for which he earned the Nobel Prize. An interesting aspect of the hydroboration reaction is that the addition of the H-B bond occurs with anti-Markovnikov regioselectivity, which is opposite to the typical addition reactions in organic chemistry.

Diboration is another method used to prepare organoboron compounds, which involves the addition of a B-B bond across an unsaturated organic molecule. The first example of this reaction was in 1954, when Schlesinger et al.[5] added B_2Cl_4 across ethylene to form $Cl_2BC_2H_4BCl_2$, (Eq. 1.1.1).



Eq.1.1.1 Reaction of ethylene with B_2Cl_4

However, B_2Cl_4 is difficult to prepare and unstable. Subsequently, diboron reagents such as $B_2(NMe_2)_4$,[6-8] B_2pin_2 **1a**,[8-11] (pin = pinacolato = $OCMe_2CMe_2O$), B_2neop_2 **1b**,[12-14] (neop = neopentaneglycolato = $OCH_2CMe_2CH_2O$) and B_2cat_2 **1c**,[12-15] (cat = catecholato = 1,2-$O_2C_6H_4$) were developed, (Fig. 1.1.1); however, these stable diboron reagents need a transition metal catalyst,[6] which is required to cleave the B-B bond to form a metal bis-boryl complex by oxidative addition.[16,17]

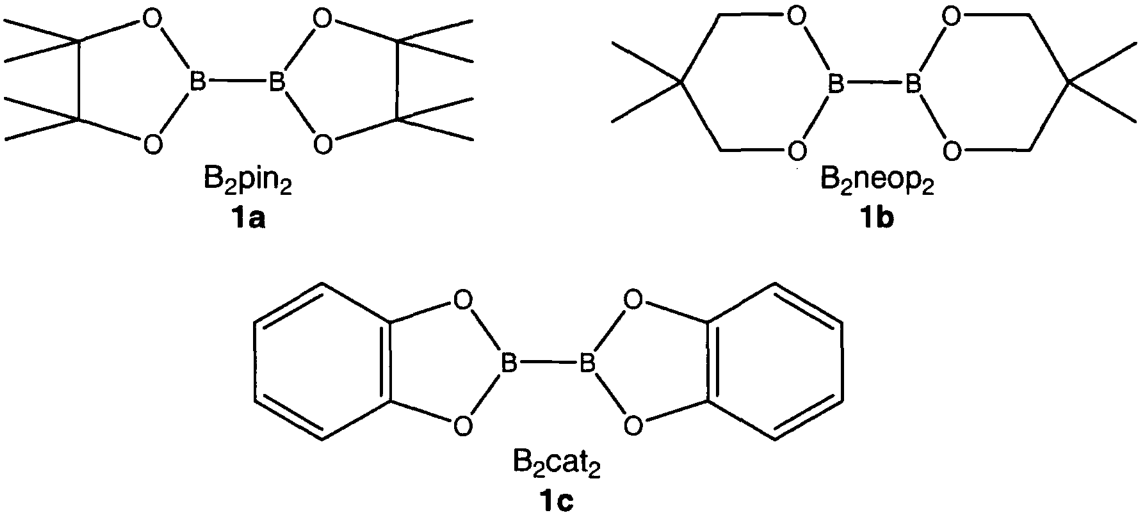
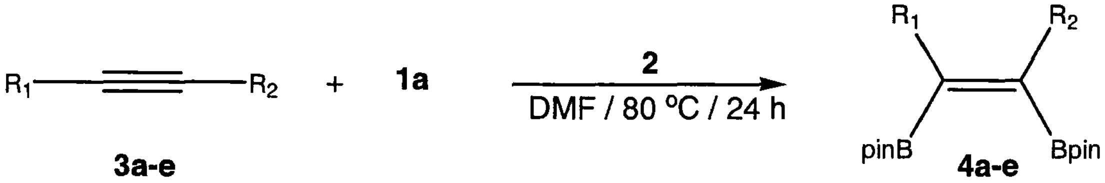


Fig. 1.1.1 The diboron reagents

Here I will introduce a general review[17-19] of the metal catalysed diboration of alkynes, 1,2- and 1,3-dienes, α,β-unsaturated carbonyl compounds, and alkenes as well as the metal catalysed borylation of alkane and arene C-H bonds.

1.2 Metal Catalysed Diboration of Alkynes

The special advantage of alkyne diboration is that there is no possibility for β-hydride elimination, which makes the diboration of alkynes better understood than that of alkenes. The earliest report was in 1993, by Miyaura *et al.*[20] They examined the catalysed diboration of terminal and internal alkynes with $[Pt(PPh_3)_4]$ **2** and found that both reactions gave *cis*-alkene bis(boronate) esters by Nuclear Overhauser Effect (NOE) NMR. Their reactions were carried out in DMF at 80 °C for 24 hours, using 3 mol% of **2** as catalyst precursor (Eq. 1.2.1), and their results are summarised in Table 1.2.1.

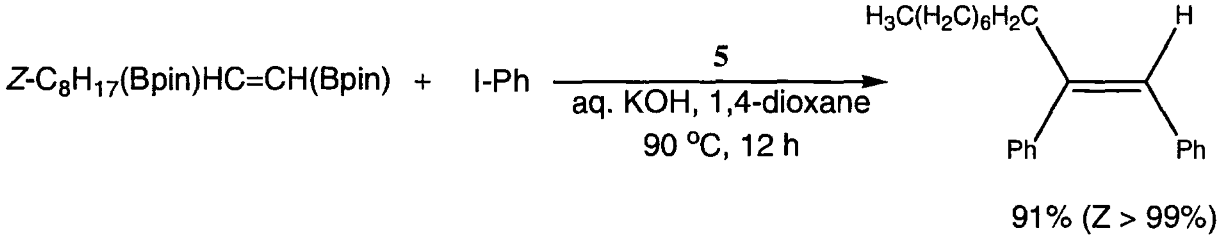


Eq. 1.2.1 Diboration of alkynes

Table 1.2.1 Diboration of alkynes

Alkyne	Product	Yield %
$C_6H_{13}C{\equiv}CH$ (**3a**)	**4a**	82
$C_8H_{17}C{\equiv}CH$ (**3b**)	**4b**	86
Cy-C≡CH (**3c**)	**4c**	78
$C_3H_7C{\equiv}CC_3H_7$ (**3d**)	**4d**	86
PhC≡CPh (**3e**)	**4e**	79

The final alkene bis(boronate) product of Eq. 1.2.1 can undergo Suzuki-Miyaura cross-coupling reactions. For example, the bis(boronate) **4b** was reacted with 3 M KOH (6 equiv.) and iodobenzene (2.4 equiv.) using the catalyst [Pd(PPh_3)$_4$], **5**, (3 mol%). The mixture was heated in 1,4-dioxane at 90 °C for 12 hours to give Z-C_8H_{17}PhC=CHPh (Eq. 1.2.2).



Eq.1.2.2 Suzuki-Miyaura cross-coupling reaction

The second report of Miyaura *et al.*[21] included spectroscopic evidence for formation of *cis*-[Pt(PPh_3)$_2$(Bpin)$_2$] **6** which results from the oxidative addition of **1a** to **2**. Moreover, this report[16] was more exhaustive and investigated the effects of a variety of catalysts, solvents and diboron reagents. They examined the reaction of 1-octyne with **1a** at 80 °C in DMF for 24 hours with a variety of catalysts including [$PtCl_2$(PPh_3)$_2$], **7**, [Pd(OAc)$_2$] (**8**) / 15 equiv. ^{t}BuCN, [RhCl(PPh_3)$_3$] **9**, [$NiCl_2$(PPh_3)$_2$] **10**, CuCN and [CoCl(PPh_3)$_3$]. The only catalysts which showed any reactivity for alkynes were **2** and [Pt(CO)$_2$(PPh_3)$_2$] **11**, both of which produced **6**. The solvent did not appear to play an important role. Furthermore, they did not observe large differences in the yield or in the reaction rate between the diboration of internal and terminal alkynes. On the other hand, the addition of $B_2(OMe)_4$ to 1-octyne in DMF in the presence of **2** at 80 °C for 24 h gave

89% of the desired product, whereas $B_2(NMe)_4$ gave only 7% yield, even at 120 °C. It was also reported that **2** was unreactive in the diboration of alkenes.

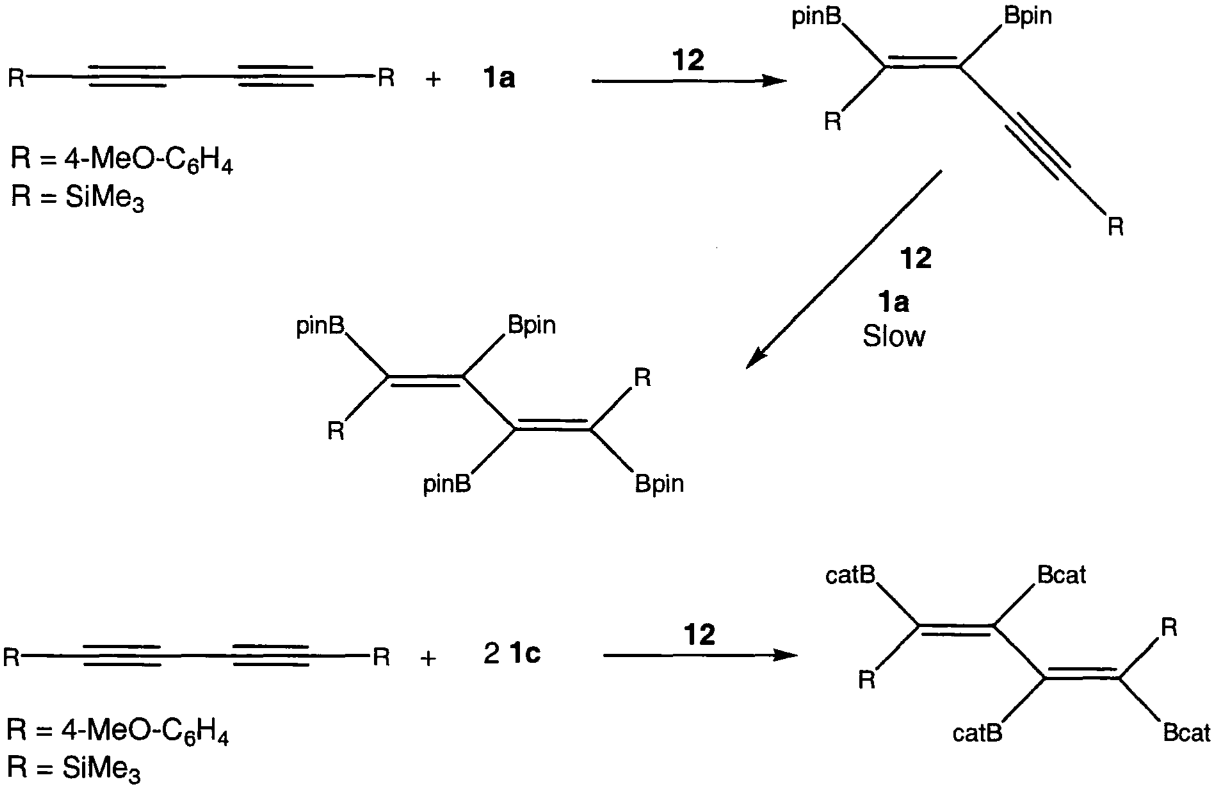
The first report of Miyaura *et al.*[20] indicated that the diboration of phenylacetylene gave a low yield of product. Marder *et al.*[22] observed that the yield could be increased by extending the time of reaction. The rate of the reactions also depends on the nature of the substitution on the *para*-positon on the phenyl ring of the terminal phenylacetylenes. Thus, they found that donor groups such as *para* MeO-, accelerated the rate of the reaction whereas withdrawing group such as CN, reduced the rate of the reaction. In contrast, Smith[23] reported that a *para* MeO- group, slightly decelerated and a *para*-CF_3 group accelerated the rate of stoicheometric diboration of internal diphenylacetylenes.

A reinvestigation by Marder *et al.*[24] showed that the rate is indeed enhanced by electron withdrawing substituents and reduced by electron donating groups for diphenylacetylenes but the reverse is true for terminal phenylacetylenes regardless of the diboron regent used.[22]

Interestingly, Siebert *et al.*[25] employed $[Pt(PPh_3)_2(\eta^2\text{-}C_2H_4)]$ (**12**) and **1c** to diborate catB-C≡C-Bcat to yield a novel tetraboronate ester $(catB)_2$-C=C-$(Bcat)_2$ (Eq. 1.2.3).

Eq. 1.2.3 Addition of B_2cat_2 to catB-≡-Bcat

The nature of the diboron reagent was examined by Marder *et al.*[22] to study its effect on the reaction rate for 1,3-diyne borylation in the presence of **12** as a catalyst (Eq. 1.2.4). The **1a** reagent was more selective than **1c**. For example, the diboration of 1,3-butadiynes with 1 equiv. of **1a** gave 1,2-diboration whereas with **1c**, a mixture of unreacted, diborated and tetraborated products was observed. The reactions were repeated with 2 equiv. of **1a** and **1c** and gave the tetraborated products with extended reaction times.



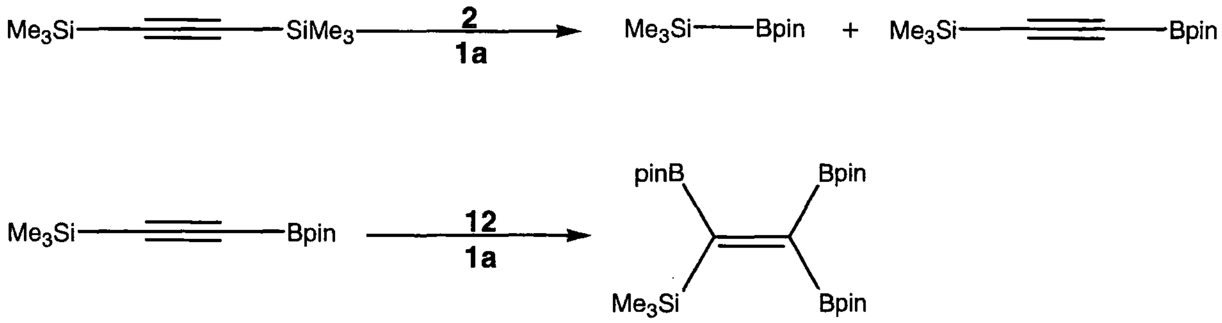
Eq. 1.2.4 Addition of **1a** and **1c** to 1,3-butadiyne

As mentioned previously in Miyaura's report,[21] the efficiency of the catalyst in the diboration of alkynes depends on formation of the Pt^0 species, which can oxidatively add B-B bonds. Thus, **6** was isolated and analysed by single-crystal X-ray diffraction;

however, the number and nature of the phosphine ligands on Pt in the active catalyst were not addressed by Miyaura.

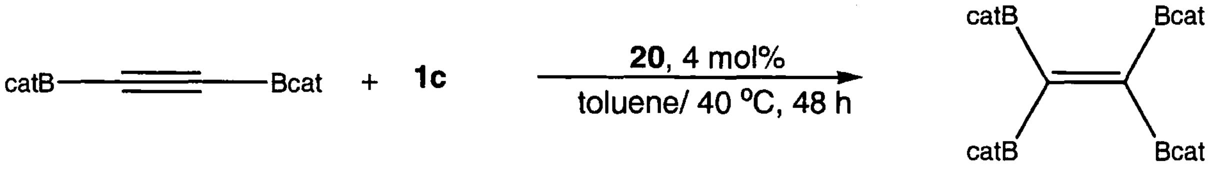
The catalyst **12** had been developed at the same time by Iverson and Smith[23,26] and Marder *et al.*[22,27] The former group reported that **12** reacts with **1c** to yield 75% of *cis*-[Pt(PPh_3)$_2$(Bcat)$_2$] **13** with rapid evolution of ethylene. In addition, the alkyne complex [Pt(PPh_3)$_2$(η^2-4-octyne)] **14** also reacts with **1c** to offer 62% of **13** with loss of alkyne. Interestingly, the reaction of **13** and alkyne give complicated mixtures; however, reaction of **13** and 4-octyne in the presence of 1.5 molar equiv. of **1c**, gave a clean conversion to the *cis*-4,5-bis(boryl)octene; perhaps the excess of **1c** prevents the decomposition of Pt(PPh_3)$_2$. Moreover, the metallacyclopentane [(PPh_3)$_2$Pt(CH_2)$_4$] **15** also reacts with 2 molar equiv. of **1c** for 8 h at 95 °C to give 68% yield of **3** and catB(CH_2)$_4$Bcat (47%).

Marder *et al.*[22,27] also studied the effects of the nature and concentration of phosphine ligands on the catalytic activity of the Pt complexes. Additionally, they prepared and characterised a series of *cis*-bis(phosphine)platinum(II)bis(boryl) complexes, such as *cis*-[(PPh_3)$_2$Pt(Bcat)$_2$].C_6D_6 **16**, *cis*-[(PPh_3)$_2$Pt(B-4-Bu^{t}cat)$_2$] **17**, *cis*-[(dppe)Pt(Bcat)$_2$] **18** (dppe = 1,2-bis(diphenylphosphino)ethane) and *cis*-[(dppb)Pt(Bcat)$_2$] **19** (dppb = 1,2-bis(diphenylphosphino)butane). They employed **12**, **13**, and **17** as catalysts for the diboration of alkynes and they found them to be more active than **2**. Furthermore, they found that it was unlikely that more than two phosphines were present on the active platinum centre in Miyaura's alkyne diboration catalyst system. Therefore, they added PPh_3 to **17** and found the activity was decreased strongly. The dichelating phosphine ligands in complex **18** and **19** greatly reduced the catalyst efficiency for all types of alkyne diboration, with the dppe system being completely inactive under the reaction conditions used. These results suggested that the active catalyst contains a single bound phosphine ligand. Consequently, $[Pt(PPh_3)_2]$ has to dissociate one of the PPh_3 ligands during the reaction. Complex **1a** was also examined and showed less reactivity than **1c**. Moreover, they employed **12** with **1a** to diborate $Me_3Si-C{\equiv}C-SiMe_3$. Me_3Si-Bpin and $Me_3Si-C{\equiv}C$-Bpin were observed; presumably the second product was then diborated to lead to the novel tris(boronate) ester product (Eq. 1.2.5).



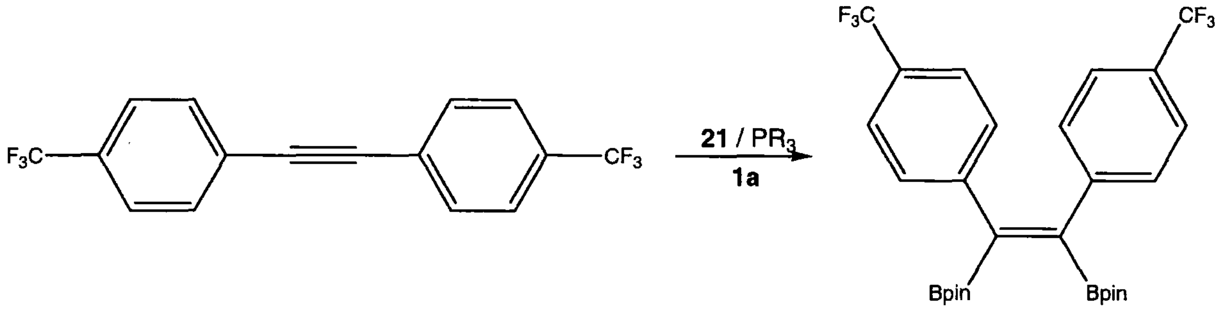
Eq. 1.2.5 Addition of B_2pin_2 to $Me_3Si-C{\equiv}C-SiMe_3$

The synthesis of tetraborylethene had been achieved by Gleiter and Siebert *et al.*[28] employing $[Pt(COD)_2]$ (**20**) (4 mol%) and B_2cat_2 to diborate bis(boryl)ethyne in the absence of phosphines (Eq. 1.2.6) (compare Eq. 1.2.3). The reaction was carried out in toluene at 40 °C for 48 hours, and the product was formed in 70% yield.



Eq. 1.2.6 Diboration of diborylethyne using **20**

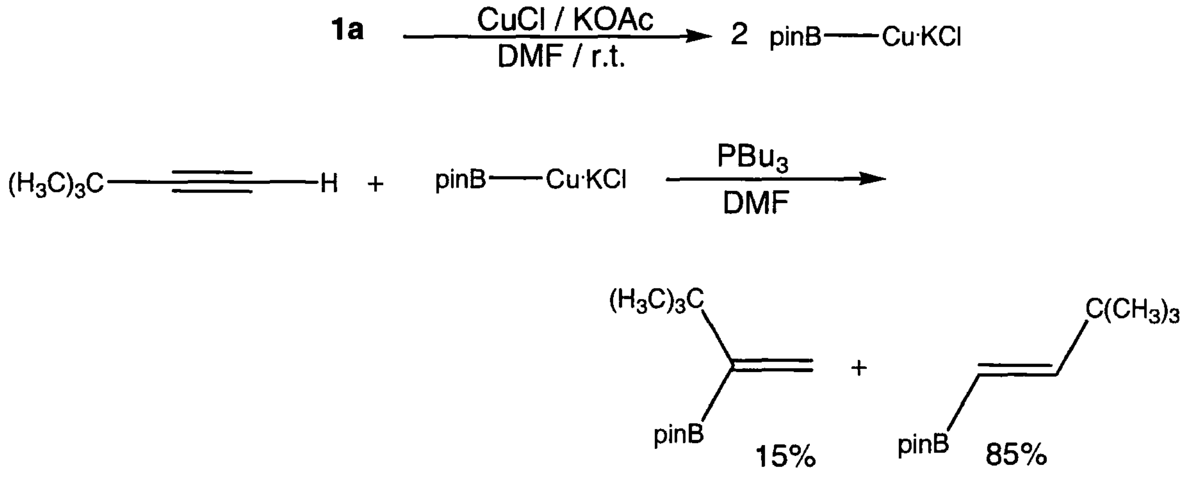
In 2001, Marder *et al.*[29] showed that the diboration of alkynes could be catalysed by [Pt(NBE)$_3$] **21** in the absence of phosphine (Eq. 1.2.7). This study investigated the effect of the concentration and nature of phosphines on the platinum catalysed diboration of alkynes.



Eq. 1.2.7 Diboration of alkyne via **21**

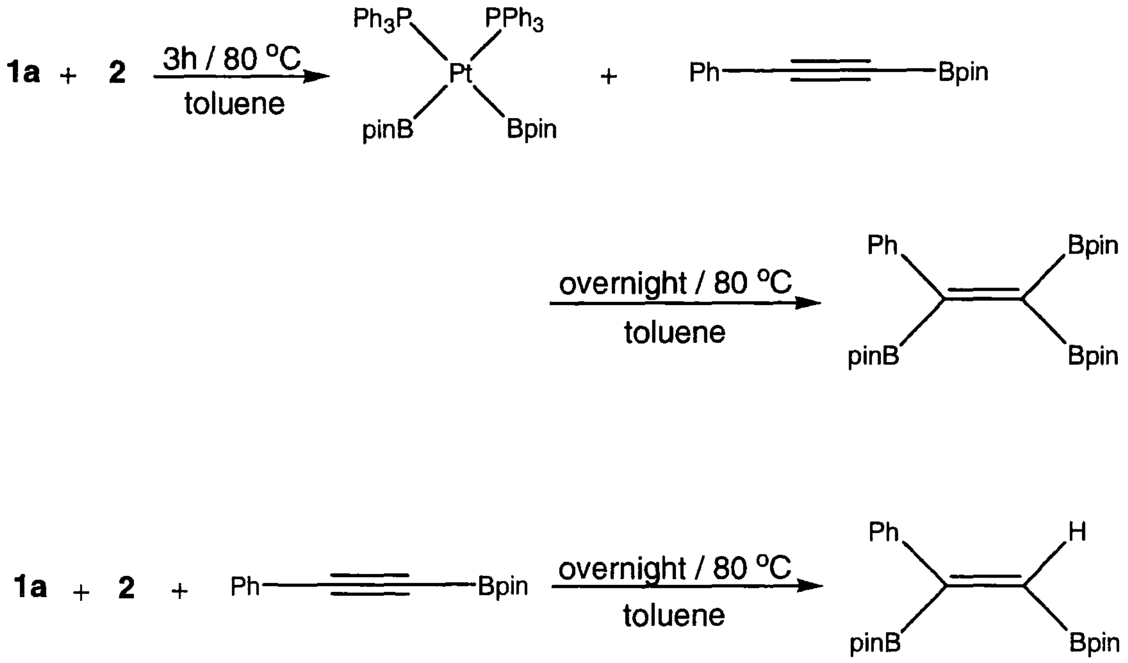
The catalyst is more active when the ratio of **21** to PPh$_3$ is 1:1, and the activity is diminished upon addition of excess phosphine. In addition, this study also showed that the efficiency of the catalyst depended on the nature of the phosphine ligand and increased in the order: Ph$_2$(*o*-Tol)P > PCy$_3$ > Bu$^n{}_3$P ≈ PMe$_2$Ph > PMePh$_2$ > PPh$_3$ > no phosphine ≈ P(C$_6$F$_6$)$_3$ ≈ P(*o*-Tol)$_3$ > ^{t}Bu$_3$P.

In 2001, Miyaura *et al.*[29] reported the synthesis of a borylcopper species from B_2pin_2 and its addition to terminal alkynes. The reactions were mediated by CuCl in the presence of AcOK and DMF at room temperature. The products were a mixture of internal and terminal alkenyl boronates. The addition of a donating phosphine ligand such as $^{t}Bu_3P$ and $^{i}Pr_3P$ improved the terminal selectivity ranging between 70 and 90%. (Eq. 1.2.8).



Eq.1.2.8 Diboration of a terminal alkyne

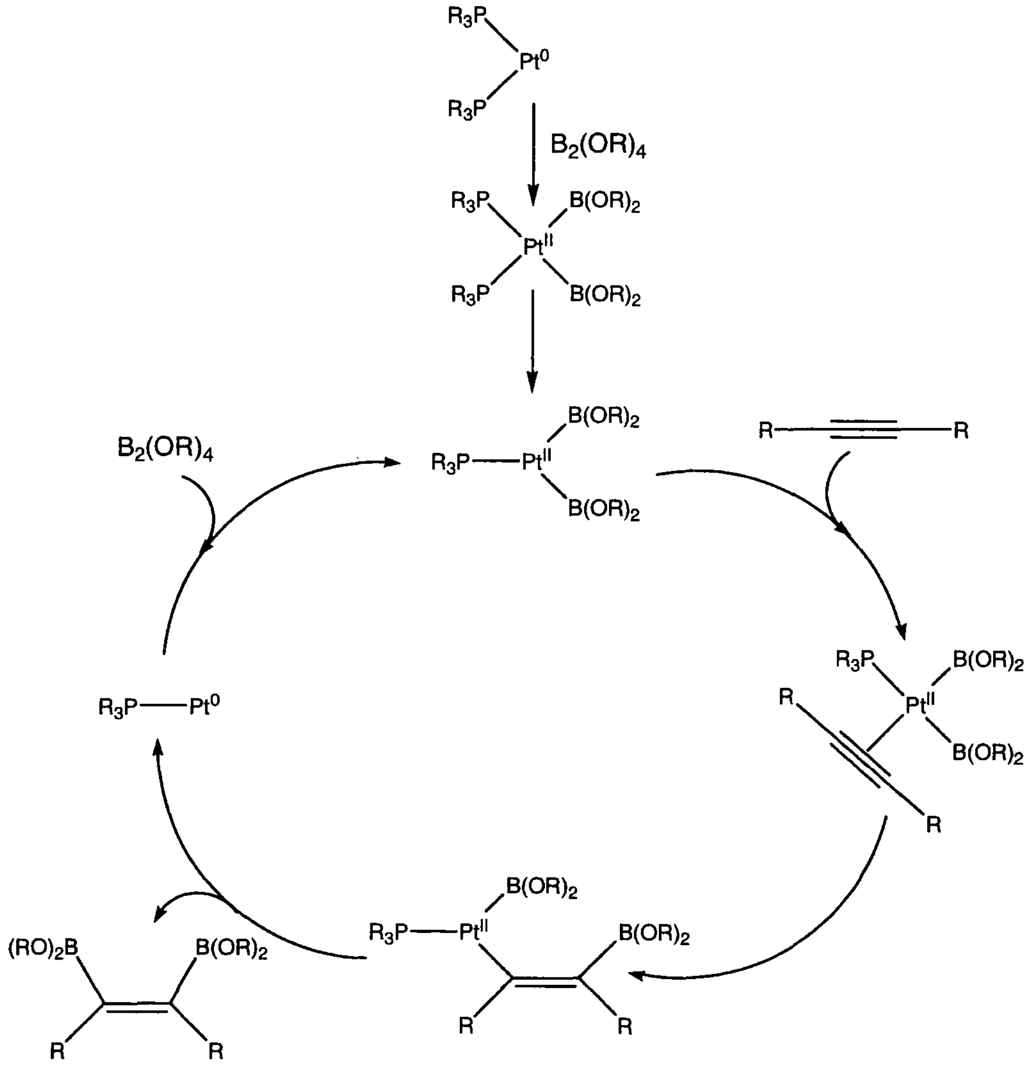
In 2002, Srebnik *et al.*[30] demonstrated the effect of differing reaction conditions on the type of boronate products obtained. They added **2** to **1a** in toluene and then stirred for 3 hours at 80 °C, followed by addition of R_1-C≡C-Bpin. The reaction mixture was heated overnight at 80 °C to afford 86-87% of tris(boronate) esters. In contrast, when the alkynylboronate was added directly to the reaction mixture of **2** and **1a** in toluene and stirred overnight at 80 °C, the *cis*-alkene-1,2-bis(boronate) was obtained in 100% conversion.



Eq. 1.2.9 Diboration of a 1-alkynylboronate ester

1.2.1 Proposed Mechanism for the Diboration of Alkynes

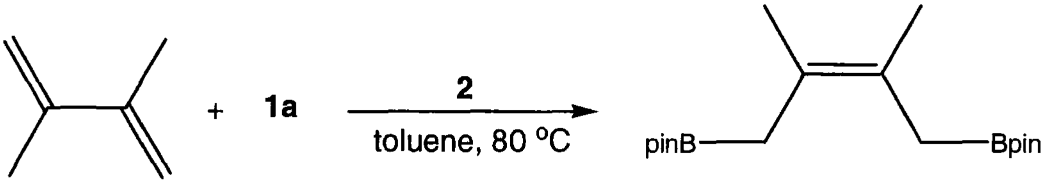
The mechanism of catalytic diboration of alkynes,[20] has been proposed to consist, firstly, of oxidative addition of $B_2(OR)_4$ to Pt^0, then dissociation of a PR_3 ligand if more than one is present to form $[Pt^{II}(PR_3)\{B(OR)_2\}_2]$ species, then coordination of alkyne to the vacant site, insertion of alkyne into the B-Pt bond to provide a vinylplatinum(II) species, followed by reductive elimination to form the diborated product and to regenerate the active catalyst (Scheme 1.2.1.1), ($B_2(OR)_4$ = **1a**).



Scheme 1.2.1.1

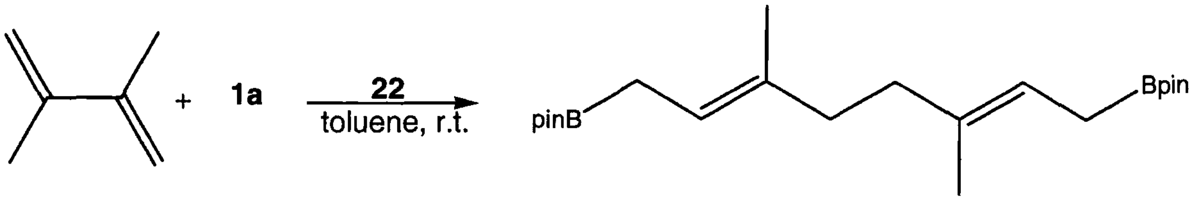
1.3 Metal Catalysed Diboration of Dienes

The diboration of both 1,3- and 1,2-dienes were investigated by Miyaura *et al.*[31] The addition of diboron to 1,3-dienes shows two different products with Pt^0, depending on the presence or absence of phosphines at the catalyst centre. The first reaction employed 3 mol% of **2** as a catalyst with 1.5 equiv. of isoprene and 1 equiv. of **1a** in DMF. The reaction mixture was heated at 80 °C for 16 hours to yield 57% of the product of 1,4-diboration. The use of toluene in place of DMF improved the yield to 93% with > 99% Z-stereochemistry (Eq. 1.3.1).



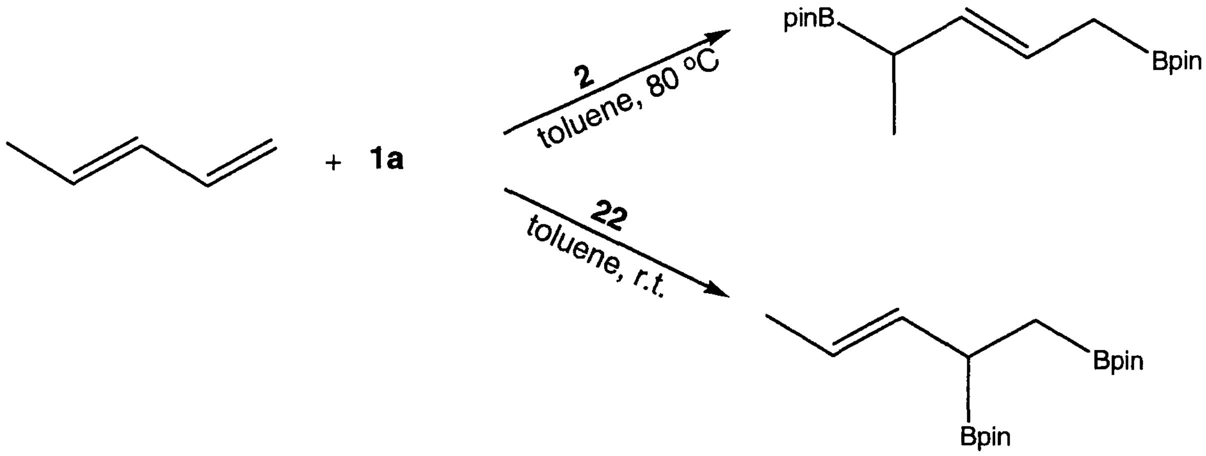
Eq. 1.3.1 Diboration of a 1,3-diene

In the second reaction, they employed $[Pt(dba)_2]$ **22** as a catalyst precursor in the presence of 3 equiv. of isoprene with 1 equiv. of **1a** in toluene at room temperature, which gave 94% of the diborated diene dimerisation product with 99% E,E-stereoselectivity (Eq. 1.3.2).



Eq. 1.3.2 Diboration of a 1,3-diene with dimerisation

Interestingly, in the following paper on the diboration of 1,3-dienes, Miyaura *et al.*[32] reported the reaction of penta-1,3-diene with **1a** in the presence of **2** and **22**. The reaction with **2** gave the 1,4-diboration product. In contrast, the reaction with **22** gave the 1,2-diboration product (Eq. 1.3.3).



Eq. 1.3.3 Diboration of penta-1,3-diene

In addition, Norman and Marder *et al.*[33] examined chiral diboron reagents such as $B_2(S\text{-}O_2CH_2CHPh)_2$ **23a**, $B_2(R,R\text{-}O_2CHPh\text{-}CHPh)_2$ **23b**, $B_2[R,R\text{-}O_2CH(CO_2Me)\text{-}CH(CO_2Me)]_2$ **23c**, $B_2(O_2C_{20}H_{12})_2$ **23d**, and (Fig. 1.3.1), in the 1,4-diboration of *trans*-penta-1,3-diene, *trans*-hexa-1,3-diene, *trans*-2-methylpenta-1,3-diene and cyclohexa-1,3-diene. Catalyst

12 (5 mol%) was used in toluene at 80 °C for 1 hour. In all cases, diastereomers of [S, R] 1,4-diborated dienes were formed in approximately equal amounts with all boron regents except **23d**. The yields were between 55 and 90%.

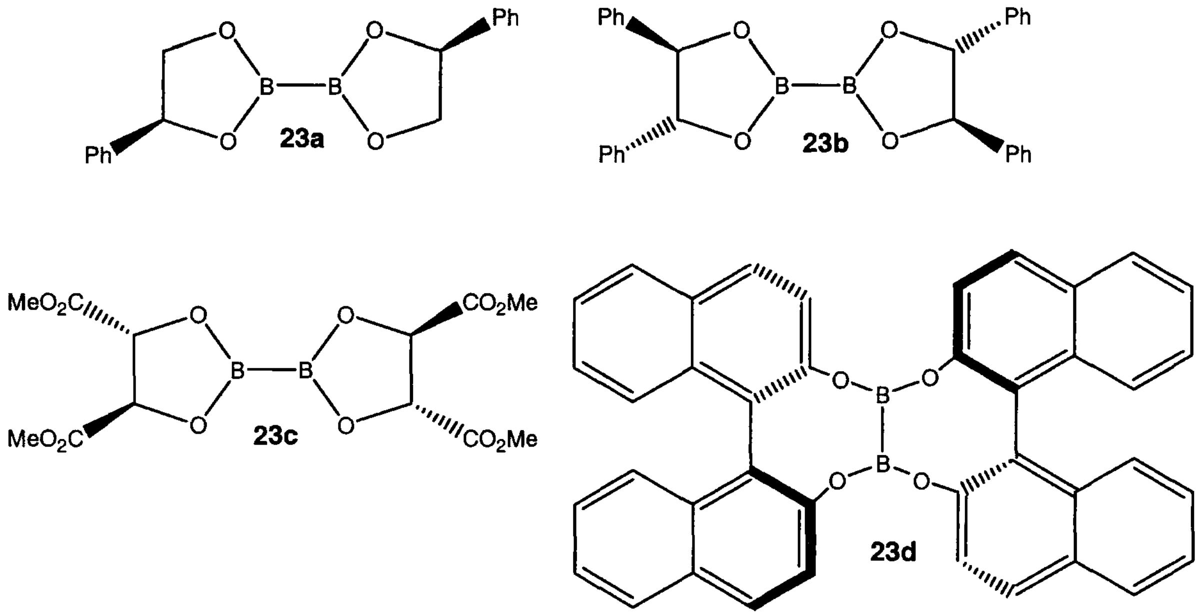
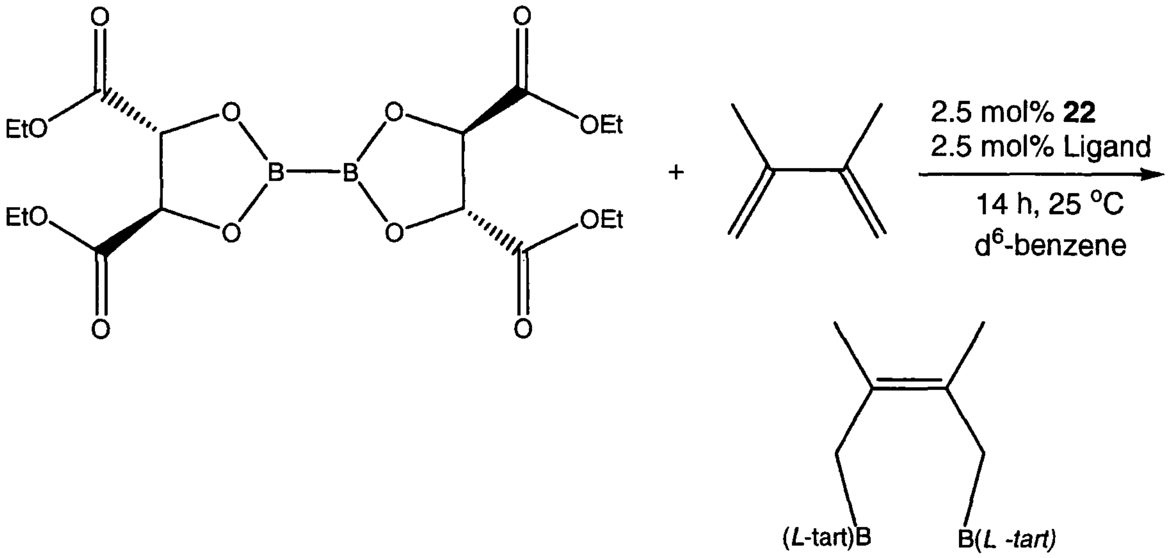


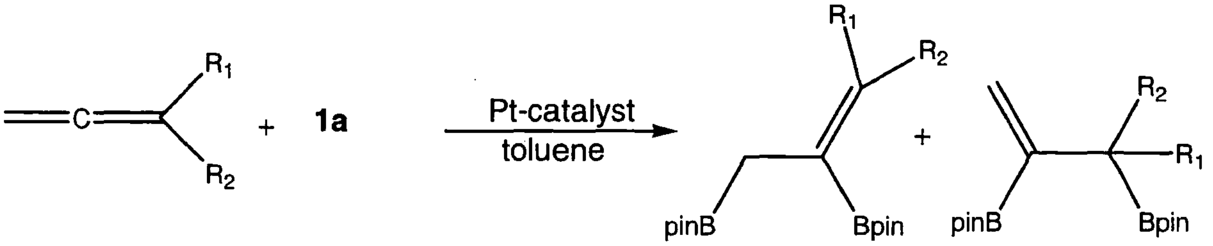
Fig 1.3.1

In 2003, Morken *et al.*[34] used **22** with phosphines ligands such as PPh_3 and PCy_3 to diborate 2,3-dimethylbuta-1,3-diene. Bis(diethyl-*L*-tartrateglycolato)diboron was chosen as the diboron reagent. The reaction was stirred at room temperature in d^6-benzene for 14 hours; the yields were 10% in the absence of phosphines and 5% with PPh_3 as a ligand but 95% when Cy_3P was used (Eq. 1.3.4).



Eq. 1.3.4 Diboration of 2,3-dimethylbuta-1,3-diene

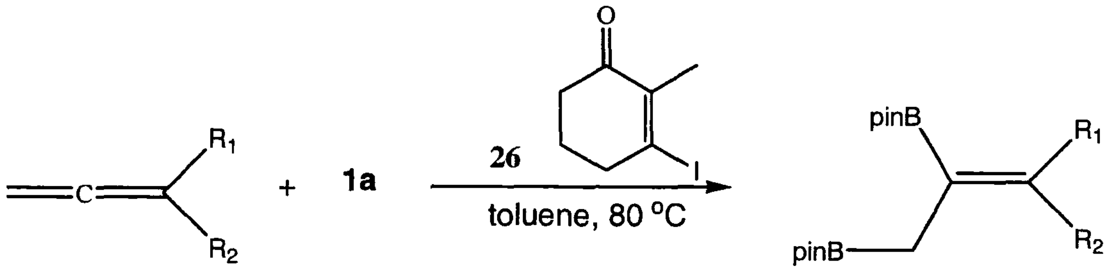
In the diboration of 1,2-dienes,[35] **2** (3 mol%) and **22** / PCy_3 (10 mol%) were employed as a catalyst with B_2pin_2 in toluene to afford the products shown in Eq. 1.3.5 and Table 1.3.1. Complex **2** catalysed the addition in toluene resulting in the corresponding products in 99% yield at 80 °C for 16 hours. The addition of **22** in toluene at 50 °C for 18 hours, gave a low yield (50%); the catalyst efficiency was improved by adding bulky phosphine ligands. The regioselectivity of the two products depends on the steric hindrance in both the allenes and the phosphine ligands. The addition of **1a** to 1,2-dienes occurs at the internal double bond when the diene is mono-substituted and the ligand on the catalyst is PPh_3. On the other hand, 1,1-disubstituted 1,2-dienes and bulky ligands such as PCy_3 force the addition of **1a** to the terminal double bond.



24 **25a** **25b**

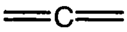
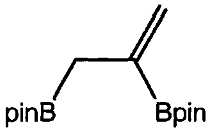
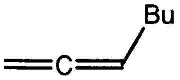
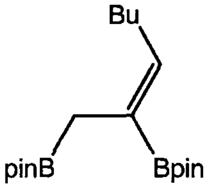
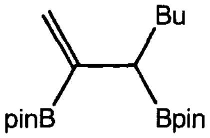
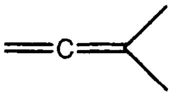
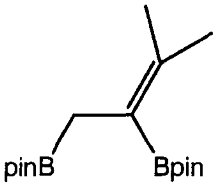
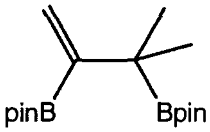
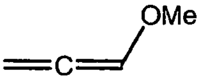
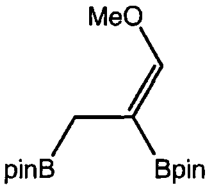
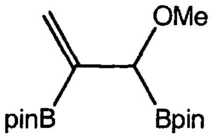
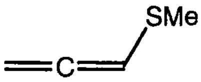
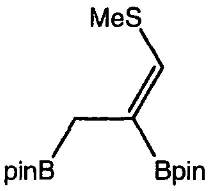
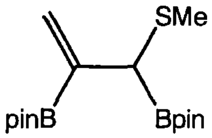
Eq. 1.3.5 Diboration of 1,2-dienes

Interestingly, in 2001 Cheng *et al.*[36] obtained a terminal diborylation from monosubstituted 1,2-dienes with high regioselectivity 92-96%. At the same time, they introduced Pd as a catalyst in this reaction which was previously inactive in diboration of alkenes, alkynes and dienes, a consequence of the reluctance of **1a** to oxidatively add to Pd. This report employed 3-iodo-2-methylcyclohex-2-en-1-one to utlise a B-I instead of a B-B bond in the oxidative addition step. The reaction was carried out at 80 °C in toluene with [Pd(dba)$_2$] **26** as a catalyst Eq. 1.3.6.

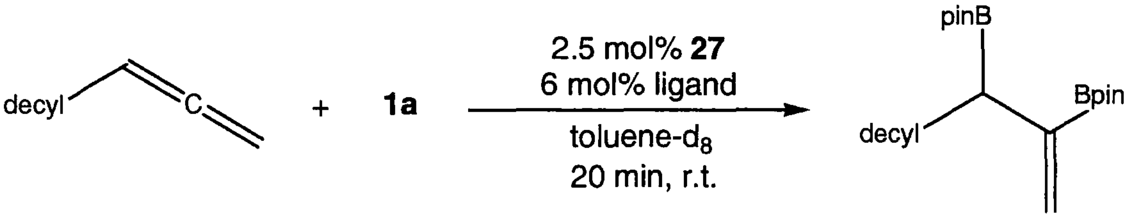


Eq. 1.3.6 Catalysed diboration of 1,2-dienes by **2**

Table 1.3.1 The Diboration of 1,2-dienes

Allene **24**	**25a**	**25b**	**2**		**22** / Cy_3P	
			25a	**25b**	**25a**	**25b**
			99		99	
			6	94	16	84
			76	24	98	2
			100	0	100	0
			50	50	82	12

Recently, Morken *et al.*[37] reported the addition of **1a** to 1,2-dienes using [$Pd_2(dba)_3$] **27** in the presence of phosphine ligands at room temperature. They studied the effect of the ligand on palladium-catalysed internal diboration of 1,2-dienes, by NMR. PCy_3 gave 100% conversion.



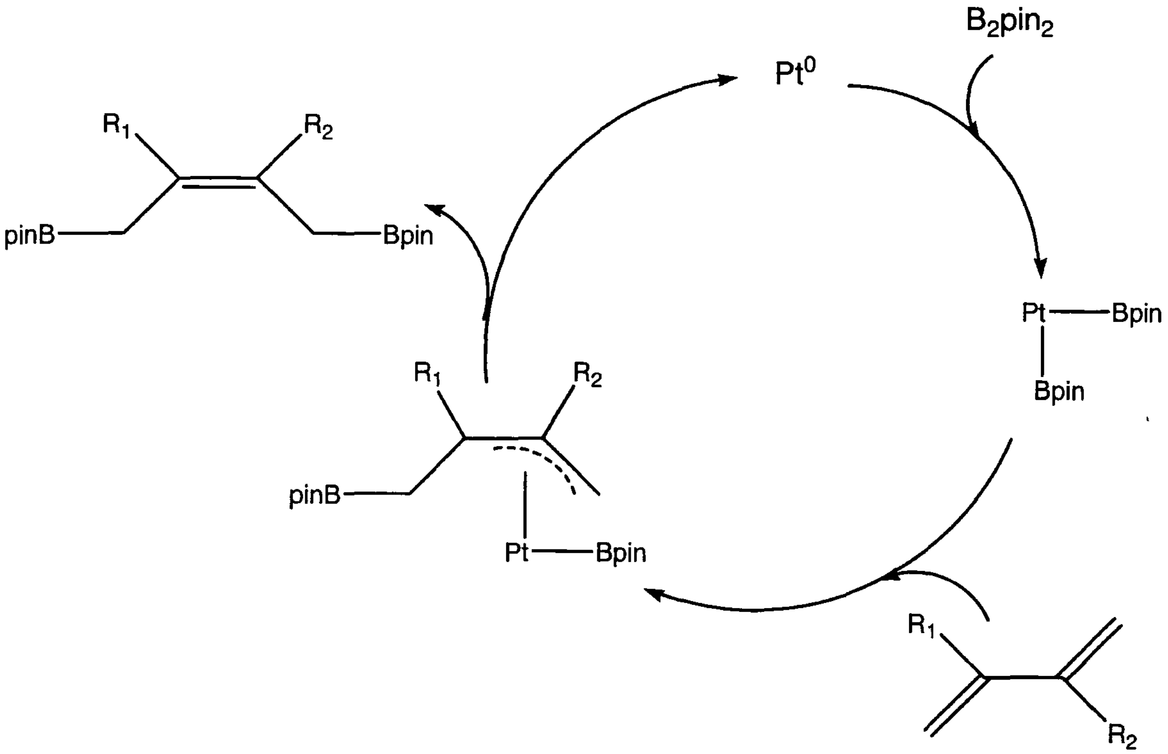
Eq. 1.3.7 Catalysed diboration of 1,2-dienes using **27**

Table 1.3.2 Effect of added ligand on the diboration of 1,2-dienes catalysed by **27**

Ligand	Conversion by ^{1}H-NMR
none	<5
PPh_3	<5
dppe	<5
PCy_3	100
PPh_2Cy	86
$P(OEt)_3$	41

1.3.1 Proposed Mechanism for the 1,4-Diboration of 1,3-Dienes

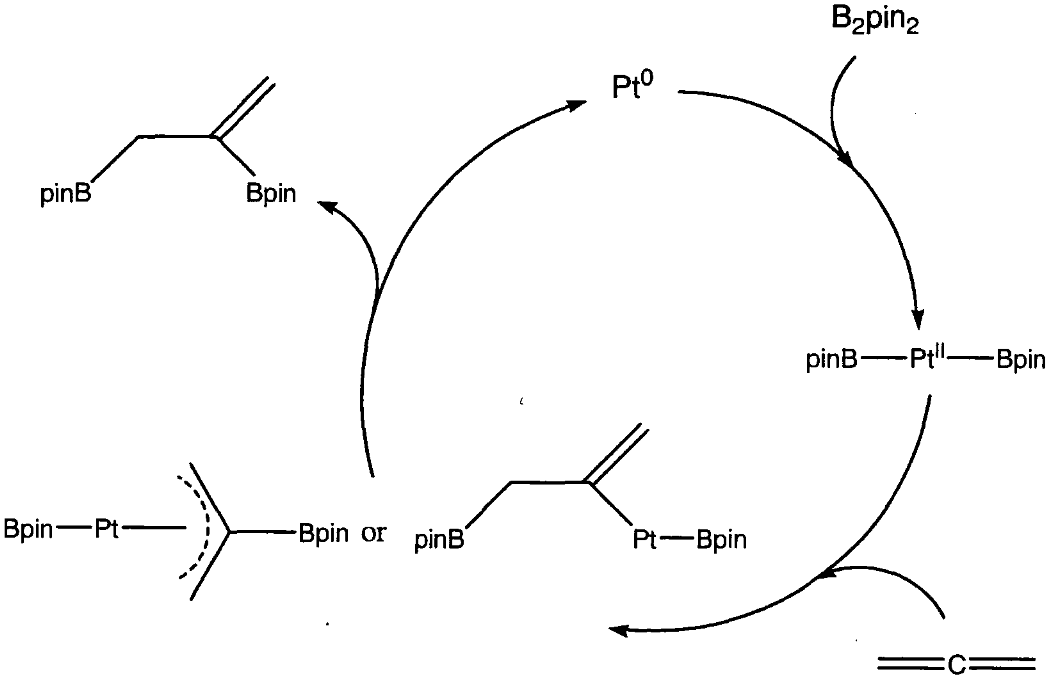
The catalytic cycle for the 1,4-diboration of 1,3-dienes may involve oxidative addition of **1a** to the platinum(0) complex which gives a bis(boryl)platinum(II) complex, then insertion of diene into the B-Pt bond to form a π-allylborylplatinum(II) intermediate, followed by reductive elimination to give 1,4-diboration,[30] and to regenerate the active catalyst (Scheme 1.3.1.1)



Scheme 1.3.1.1

1.3.2 Proposed Mechanism for the Diboration of 1,2-Dienes

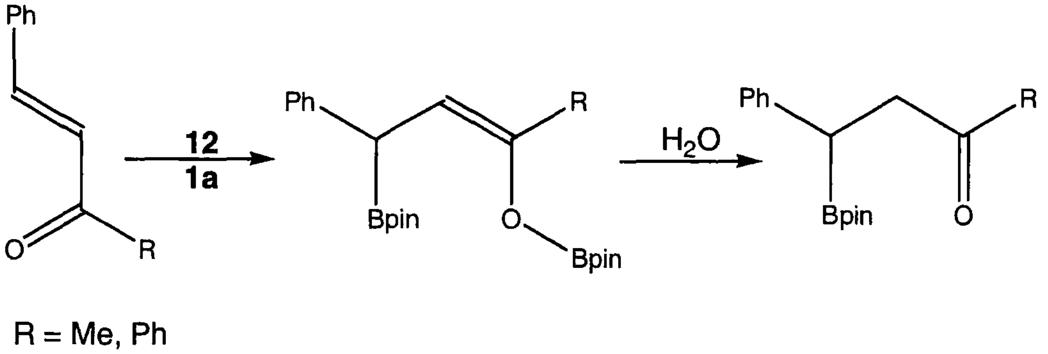
The proposed mechanism for the Pt-catalysed diboration of 1,2-dienes, involves oxidative addition of B_2pin_2 to Pt^0 to form a bis(boryl)platinum(II) intermediate, then insertion of 1,2-diene into the B-Pt bond to provide σ-vinyl or π-allyl platinum species, and in the last step, reductive elimination,[34] to regenerate the active catalyst (Scheme 1.3.2.1).



Scheme 1.3.2.1

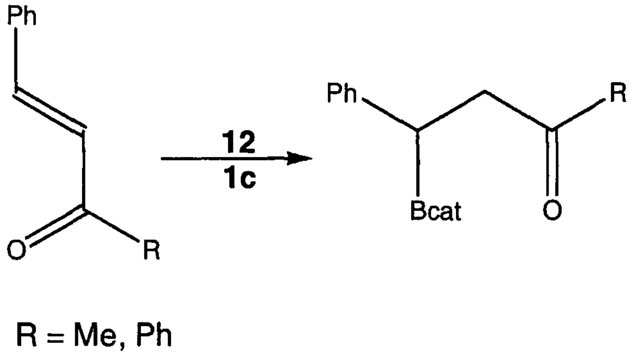
1.4 Metal Catalysed Diboration of α,β-Unsaturated Carbonyls

The earliest report of the diboration of α,β-unsaturated ketones was in 1997 by Marder and Norman *et al.*[38] They employed 5 mol% of **12** and *trans*-4-phenylbut-3-en-one and trans-1,2-diphenylprop-2-en-1-one in the presence of **1a** and **1c** in toluene at 80 °C for 12 hours. compound **1a** gave 1,4-bis(boronate)ester product (Eq. 1.4.1) and the product was identified as the Z-isomer by ^{1}H NMR using N.O.E. spectroscopy.



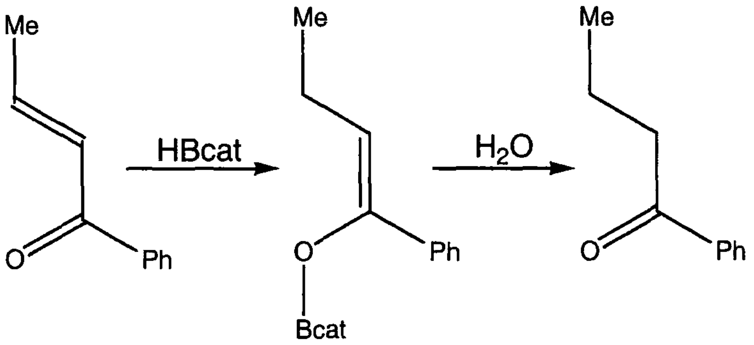
Eq. 1.4.1 Diboration of trans-4-phenylbut-3-en-one with **1a**

With **1c**, the 1,4-bis(boronate)ester was not observed but instead, the hydrolysis product was formed, as the stability to hydrolysis of the **1c** product is lower than for the Bpin analogues (Eq. 1.4.2).



Eq. 1.4.2 Diboration of trans-4-phenylbut-3-en-one with **1c**

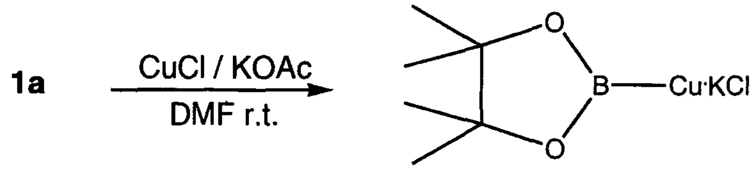
These results are related to those reported[39] for the hydroboration of similar substrates shown in Eq.1.4.3.



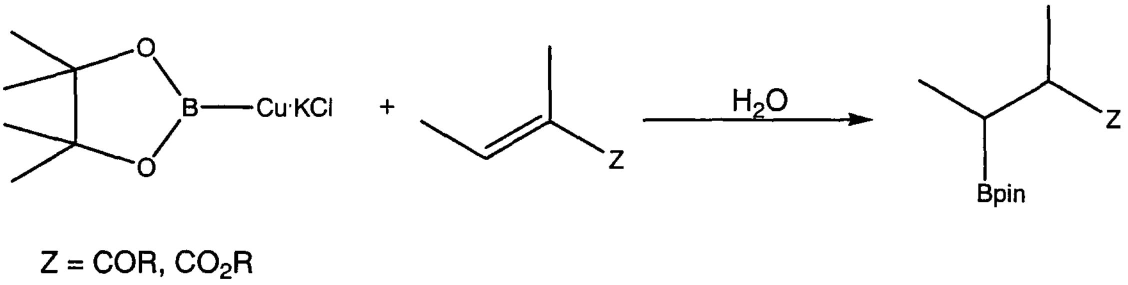
Eq. 1.4.3 Catalysed hydroboration of trans-1-phenylbut-3-en-2-one.

Srebnik *et al.*[40] and Miyaura *et al.*[41,42] reported two different conditions to diboronate α,β-unsaturated carbonyl compounds. The first group used **2** to catalyse diboration of 4-isopropylcyclohexanone, cyclopentanone, *trans*-cinnamaldehyde and *trans*-methyl cinnamate which were borylated in a 1,4-manner to give β-boryl carbonyl compounds after hydrolysis. Yields were 80, 86, 79 and 68% respectively using B_2pin_2 in toluene at 110 °C for 20 hours.

The latter group used CuCl in the present of AcOK with B_2pin_2 in DMF at room temperature to form a proposed pinB-Cu-KCl species (Eq. 1.4.4), which was employed in the borylation of α,β-unsaturated ketones (Eq. 1.4.5).

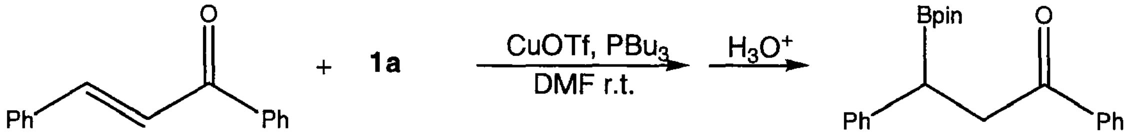


Eq. 1.4.4 Proposed Formation of pinB-Cu-KCl Species



Eq. 1.4.5 Reaction of pinB-Cu-KCl species with α,β-unsaturated ketones

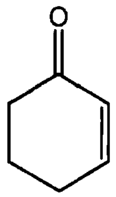
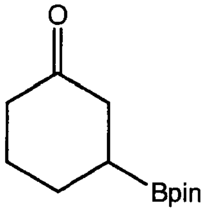
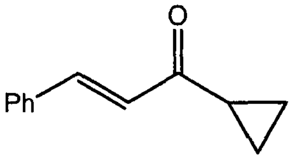
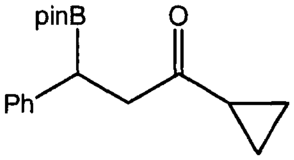
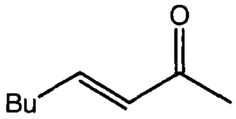
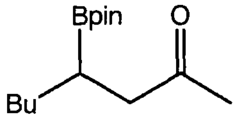
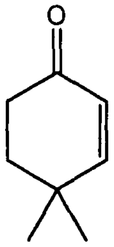
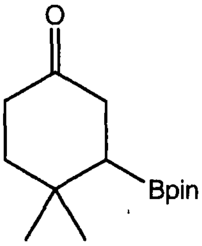
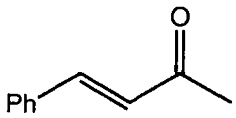
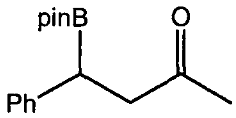
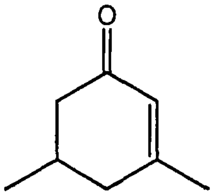
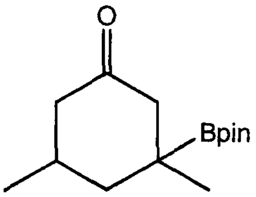
Interestingly, catalysts composed of a copper(I) salt such as CuOTf or CuCl and various phosphines were employed to diborate α,β-unsaturated ketones by Hosomi.[43] The reaction of CuOTf with α,β-unsaturated ketones at room temperature for 14 hours gave no reaction but in the presence of PBu_3, yielded 96% of the β-boryl ketone after hydrolysis, (Eq.1.4.6).



Eq. 1.4.6 CuOTf Promoted diboration of α,β-unsaturated ketones in the presence of PBu_3

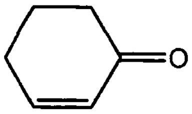
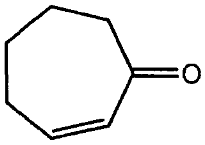
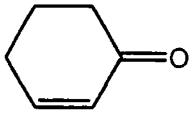
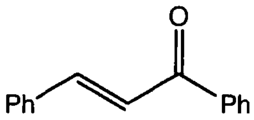
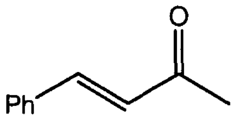
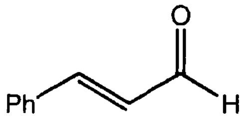
With less electron donating phosphines such as PPh_3, the yield was lower (50%). In addition, in the absence of copper salts, PBu_3 alone yielded 7% product. With excess PBu_3 in the presence of CuOTF, the yield decreased. No reaction was observed when the dichelating ligand dppp (dppp = 1,3-bis(diphenylphosphino)propane) was added as a source of phosphine at room temperature; however, the yield was increased to 36% when the temperature was raised to 50 °C. On the other hand, CuCl in the presence of PBu_3 gave 83% yield at room temperature. DMF was a good solvent for the reaction whereas less polar solvents such as THF, CH_2Cl_2 and toluene were less effective. The results for α,β-unsaturated ketones are shown in Table 1.4.1.

Table 1.4.1 CuOTf Catalysed diboration α,β-unsaturated ketones in the presence of PBu_3 in DMF

Substrate	Conditions	Product	Yield %
	r.t. 6 h		87
	r.t. 20 h		71
	r.t. 3 h		82
	r.t. 36 h		87
	r.t. 24 h		72
	80 °C 12 h		Trace

In 2002, Kabalka *et al.*[44] employed Wilkinson's catalyst, **9**, (10 mol%) with **1a** and **1b** for 1,4-diborations of α,β-unsaturated ketones and aldehydes. The reactions were carried in toluene at 80 °C, and the reported results are presented in Table 1.4.2. (yields are for the hydrolysis products). It is should be noted that attempts to reproduce some of these results by Bell and Marder have been unsuccessful.

Table 1.4.2 Catalysed diboration of α,β-unsaturated carbonyl compounds using **9**

Substrate	Boron Reagent	Time / h	Yield %
	**1a**	13	78
	**1a**	12	75
	**1b**	12	76
	**1b**	13	67
	**1b**	14	64
	**1b**	10	62

Most recently, Marder *et al.*[45] reported the use of [Pt(BIAN)(DMFU)] **28** (5 mol%) (Fig. 1.4.1) to catalyse the diboration of α,β-unsaturated carbonyl compounds (BIAN = bis(phenylimino)acenaphthene). The reactions were carried out in d_6-benzene at room temperature for 24 hours using **1a**. The results given in Eq. 1.4.7 and Table 1.4.3, show that the ketones are more selective for 1,4-addition, whereas the esters result in predominately 3,4-addition across the C=C bond.

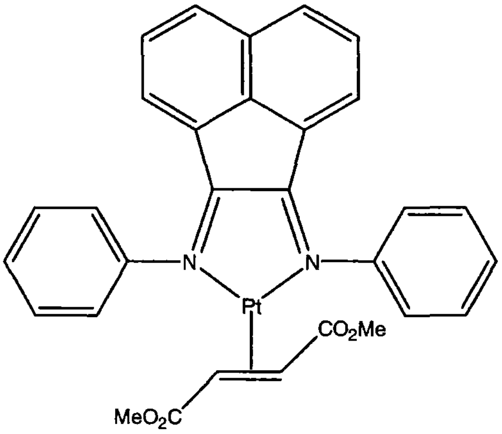
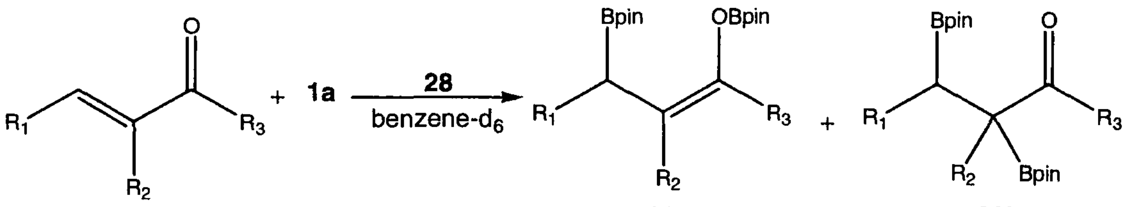


Fig. 1.4.1 [Pt(BIAN)(DMFU)] **28**



29 **30a** **30b**

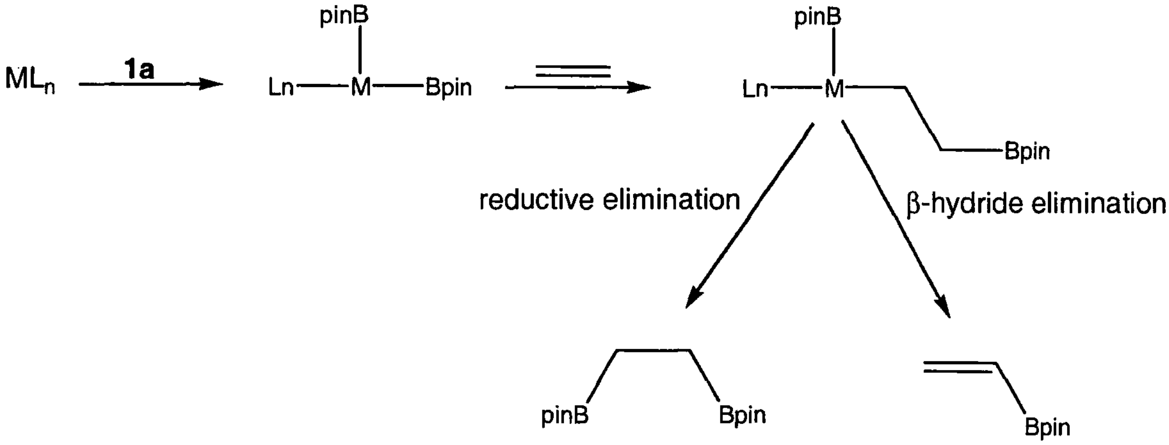
Eq. 1.4.7 Diboration of α,β-unsaturated carbonyl compounds in the presence of **28**

Table 1.4.3 Results of reactions carried out by Marder *et al.*[45]

	R_1	**R_2**	**R_3**	**Conversion 30a%**	**Conversion 30b%**
29	H	H	Me	100	0
29	Ph	H	Me	77	0
29	Ph	H	Ph	89	0
29	H	Me	OMe	0	87
29	Me	H	OEt	9	59
29	CO_2Me	H	OMe	0	93

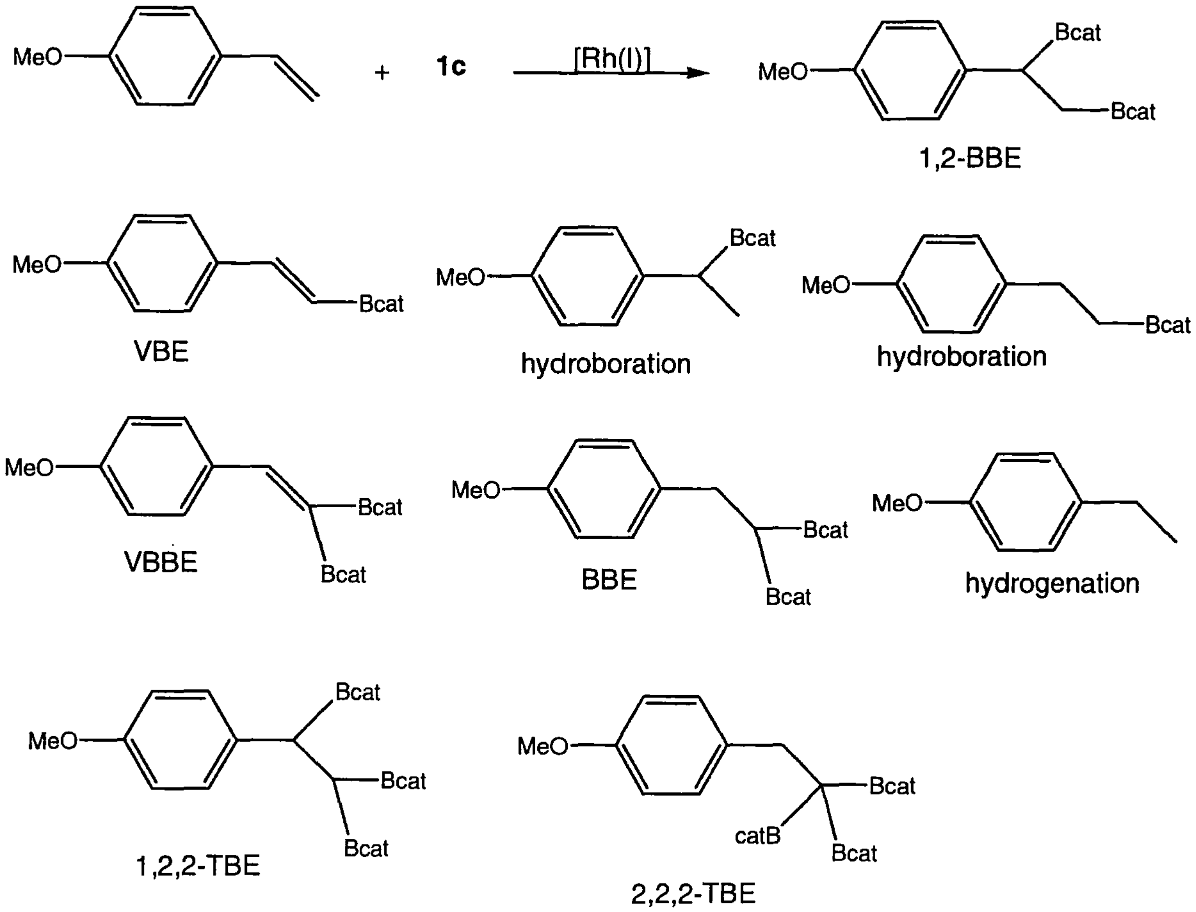
1.5 Metal Catalysed Diboration of Alkenes

Diborations of alkenes are more complicated than those of alkynes because mixtures of products are formed due to the competition between the B-C reductive elimination step, resulting in alkene diboration, and β-hydride elimination pathways, leading to dehydrogenative borylation (Eq. 1.5.1). Dehydrogenative borylation of alkenes is a useful method for the synthesis of vinylboronate, which is discussed in Section 1.6.



Eq. 1.5.1 Competition between reductive elimination and β-hydride elimination

The first report of the diboration of alkenes via several of Rh(I) catalysts was in 1995 by Marder and Baker *et al.*[46] compound **1c** and 4-vinylanisole were reacted in the presence of various catalysts in THF at room temperature. The products were mixtures of hydrogenation, and hydroboration products, bis(boronate) ester (1,2-BBE), 1,2,2-tris(boronate) ester (1,2,2-TBE), 2,2,2-tris(boronate) ester (2,2,2-TBE), vinylboronate esters (VBE) and vinyl-bis(boronate)ester (VBBE) (Eq. 1.5.2).

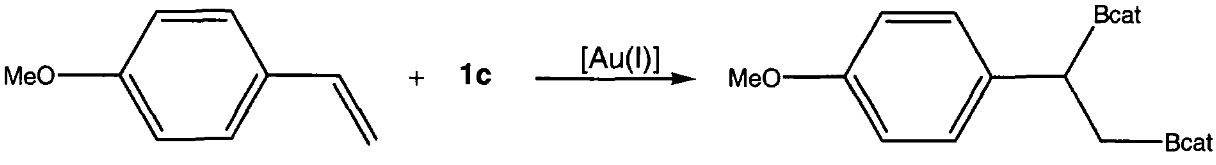


Eq. 1.5.2 Diboration of 4-vinylanisole

The desired 1,2-bis(boronate) ester product was formed in 44% yield when the zwitterionic catalyst, [Rh(dppb)(η^6-cat)B(cat)] **31**, was used. The distribution of products was formed owing to the competition between reductive elimination and β-hydride elimination.

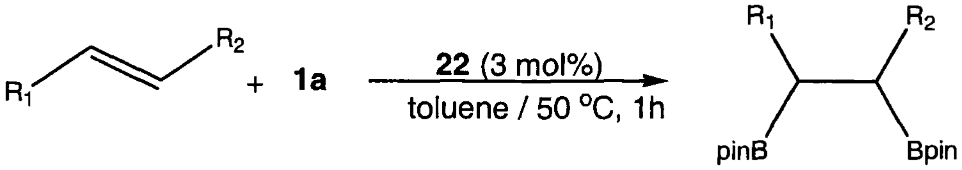
In addition, Au(I) was used to avoid the β-hydride elimination in the diboration of alkenes,[46] which is favourable when many Rh compounds are used as the catalyst. Au(I) has low energy d-orbitals likely to inhibit π-back bonding to alkenes and therefore destabilises the alkene hydride with respect to the alkyl complex.

The reaction of [AuCl(PEt$_3$)] **32** + 1,2-bis(dicyclohexylphosphino)ethane with **1c** and vinylanisole at 80 °C for 48 hours in DMF gave exclusive formation of the desired 1,2-bis(boronate)ester and shut off the β-hydride elimination (Eq. 1.5.3); however, the reaction is not practical, requiring long reaction times, elevated temperatures, high catalyst loading and excess **1c**.



Eq. 1.5.3 Diboration of vinylanisole via [Au(I)]

In 1997, Miyaura *et al.*[47] employed **22** as a catalyst to diborate terminal alkenes and strained, cyclic alkenes with B$_2$pin$_2$ to 1,2-BBE in toluene as solvent at 50 °C for 1 hour. This system was successful with 1-decene, styrene, 4-vinylanisole, cyclopentene and norbornene, and the yields ranged 76 to 86%, (Eq. 1.5.4); however, this system failed to diborate simple internal alkenes such as oct-4-ene, stilbene and cyclohexene.



Eq. 1.5.4 Diboration of alkenes using **22**

At about the same time Smith *et al.*[48] reported that the reaction of terminal alkenes, non-conjugated dienes and strained norbornene and norbornadiene with **21** and **20** in the presence of **1c** at room temperature gave the desired 1,2-bis(boronate) esters; however, this system also suffers from β-hydride elimination with internal alkenes.

In 1998, Marder *et al.*[49] reported the diboration of alkenes by the zwitterionic catalyst [Rh(dppm)(η^6-cat)B(cat)] **33**, which was generated *in situ* by reaction of [(acac)Rh(dppm)] **34** with B_2cat_3. The reactions were carried out in THF at room temperature in the presence of 4 mol% of **34** / B_2cat_3, and the alkene and **1c** in a 1:1 ratio. The results are summarised in Table 1.5.1.

In the same year, Norman and Marder *et al.*[50] employed **22** as a catalyst precursor to diborate terminal alkenes using chiral diboron reagents such as **23a**, **23b**, **23c** and **23d** (see Fig. 1.3.1) with yields reaching up to 80% but with diastereomeric excess not exceeding 60%.

In 2000, Baker *et al.*[51] employed [Pt(COD)Cl_2] **35** as a catalyst precursor to diborate the terminal alkenes 4-vinylanisole, 4-chlorostyrene and 1-octene in the presence of **1c** at room temperature for 3 hours in benzene solvent, which gave excellent yields of over 90% of the 1,2-bis(boronate)esters (Table 1.5.1).

Table 1.5.1 Catalysed diboration of alkenes by **33**

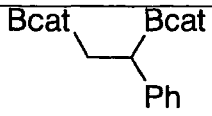
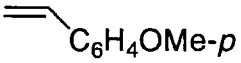
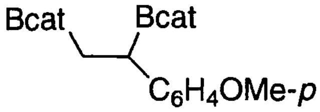
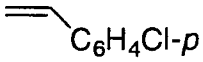
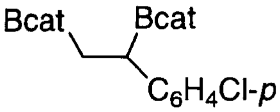
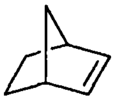
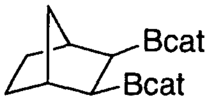
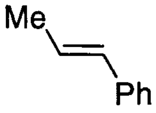
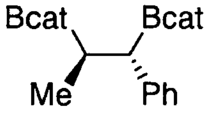
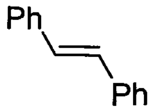
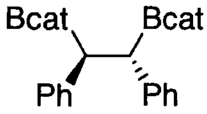
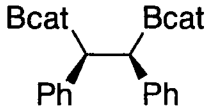
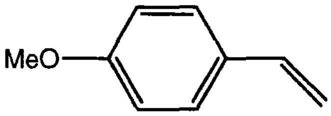
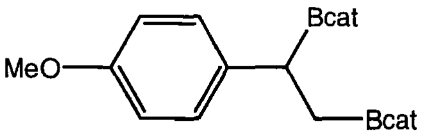
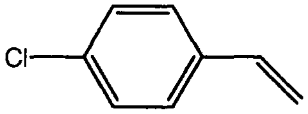
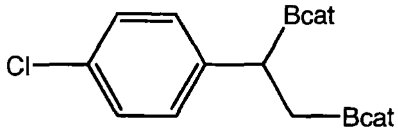
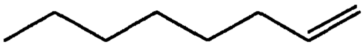
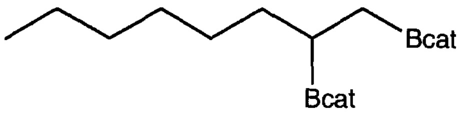
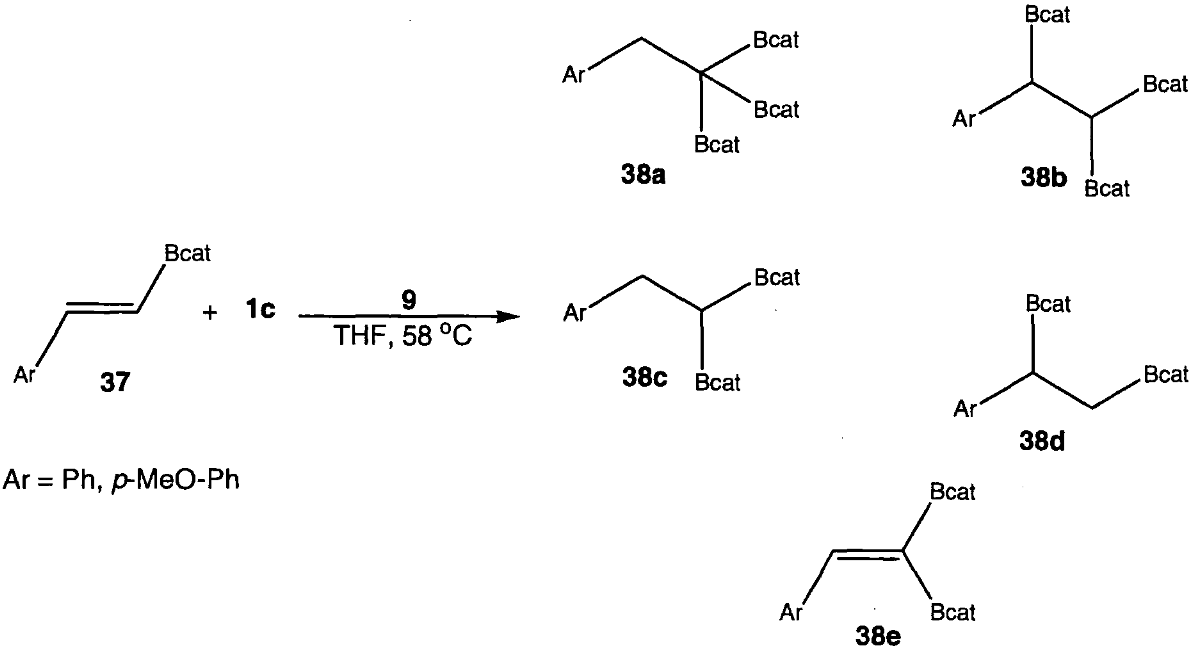
Alkene	Product	Time/ h	Yield %
		2	87
		2.5	77
		1	79
		6	>99
		30	>99
		<72	92
		<72	>99

Table 1.5.2 The diboration of alkenes using **35**

Substrate	Product	Yield %
		96
		93
		93

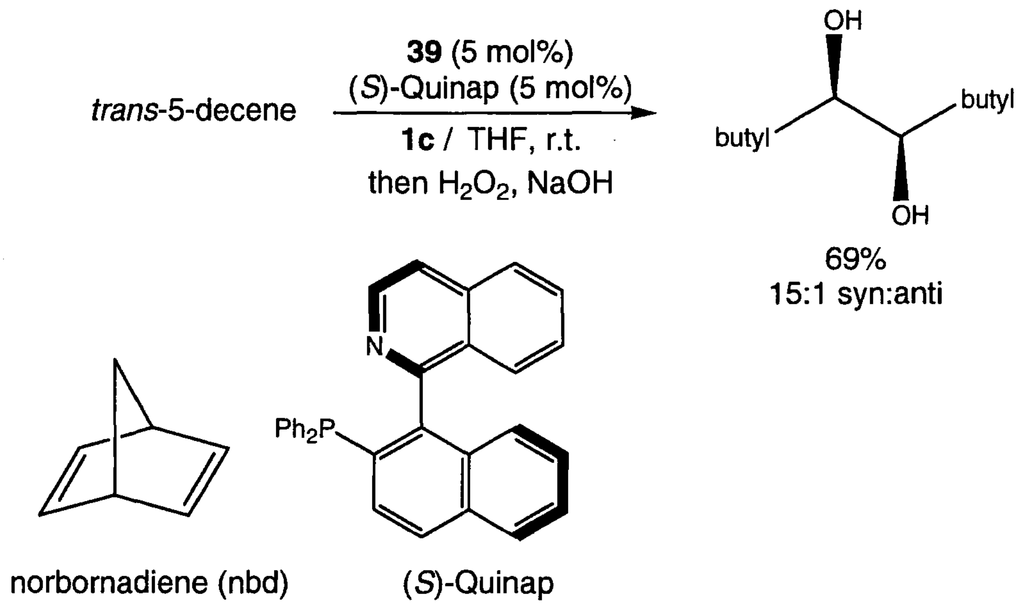
In 2002, Marder *et al.*[52] reported the diboration of (*E*)-styrylboronate esters (VBEs), which were previously prepared *via* hydroboration of the corresponding vinylbenzene with HBcat. They employed **9**, **31**, **33**, $[Rh(COE)_2(\mu\text{-}Cl)]_2$ **36** + 2 P(*o*-tol)$_3$ or 2 PCy_3 and again **9** with 10 equiv. of PPh_3 to diborate VBEs. The reactions were carried out with 1 mol% of catalyst at 58 °C for 12 hours using **1c** and THF as solvent. Scheme 1.5.1 shows the distribution of the products. Catalyst precursor **9** gave the highest selectivity for **38a**, 75%, with the reaction going to completion. Yield of **38b-e** were between 5 and 15%.



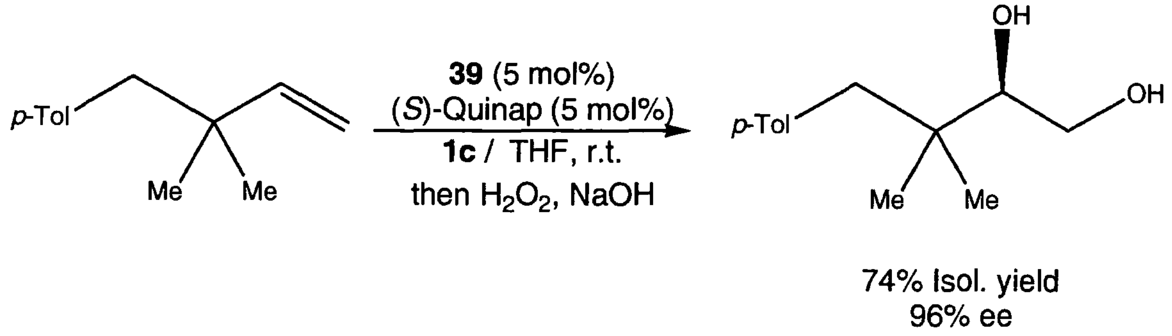
Scheme 1.6.1

In 2003, Morken *et al.*[53] reported the enantioselective 1,2-diboration of *trans*-alkenes, employing [(nbd)Rh(acac)] **39** (0.5 mol%) with (*S*)-quinap 0.5 mol% as a ligand in the presence of **1c**. The reactions were stirred at room temperature in THF for 24 hours, then followed by adding H_2O_2 and NaOH for oxidation to form the diol (Eq. 1.5.5). They observed that the diboration of *trans*-alkenes and indene gave syn-1,2-diol in high optical purity, whereas the *cis*-alkenes, for example, 1,2-dihydronaphthalene and *cis*-β-methylstyrene, provided the opposite configuration of products, i.e. anti-1,2-diol. The results are summarised in Table 1.5.3.

In 2004, this group also reported the asymmetric 1,2-diboration of terminal alkenes, and the final products were oxidized to provide 1,2-diols in good yield.[54] They employed **39** (5 mol%) with (*S*)-quinap 5 mol% as a ligand in the presence of 1.5 equiv. of **1c**. The reactions were stirred at room temperature in THF for 6 hours, then followed by adding H_2O_2 and NaOH for oxidation to form the 1,2-diol (Eq. 1.5.6). They observed that the 1,2-diboration of aliphatic and aromatic alkenes react to form diols of the same configuration, and also that aliphatic alkenes react with higher enantioselectivity than similar size aromatic alkenes (Table 1.5.4, Entries 5 and 7). The results are summarised in Table 1.5.4.

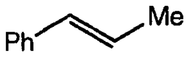
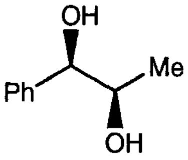
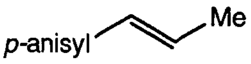
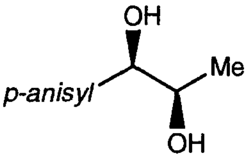
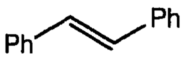
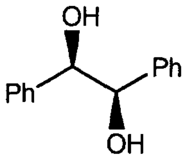
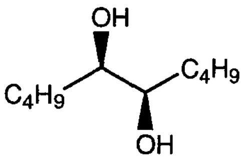
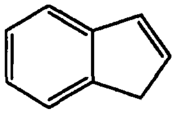
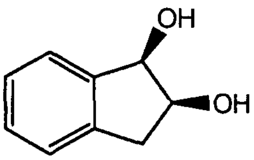
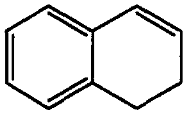
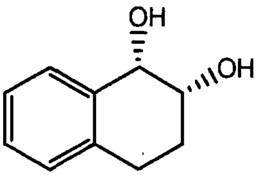
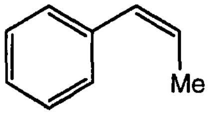
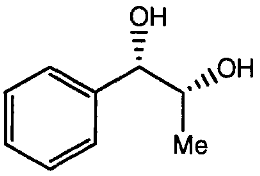


Eq. 1.5.5 Catalysed enantioselective diboration of *trans*-5-decene using **39**

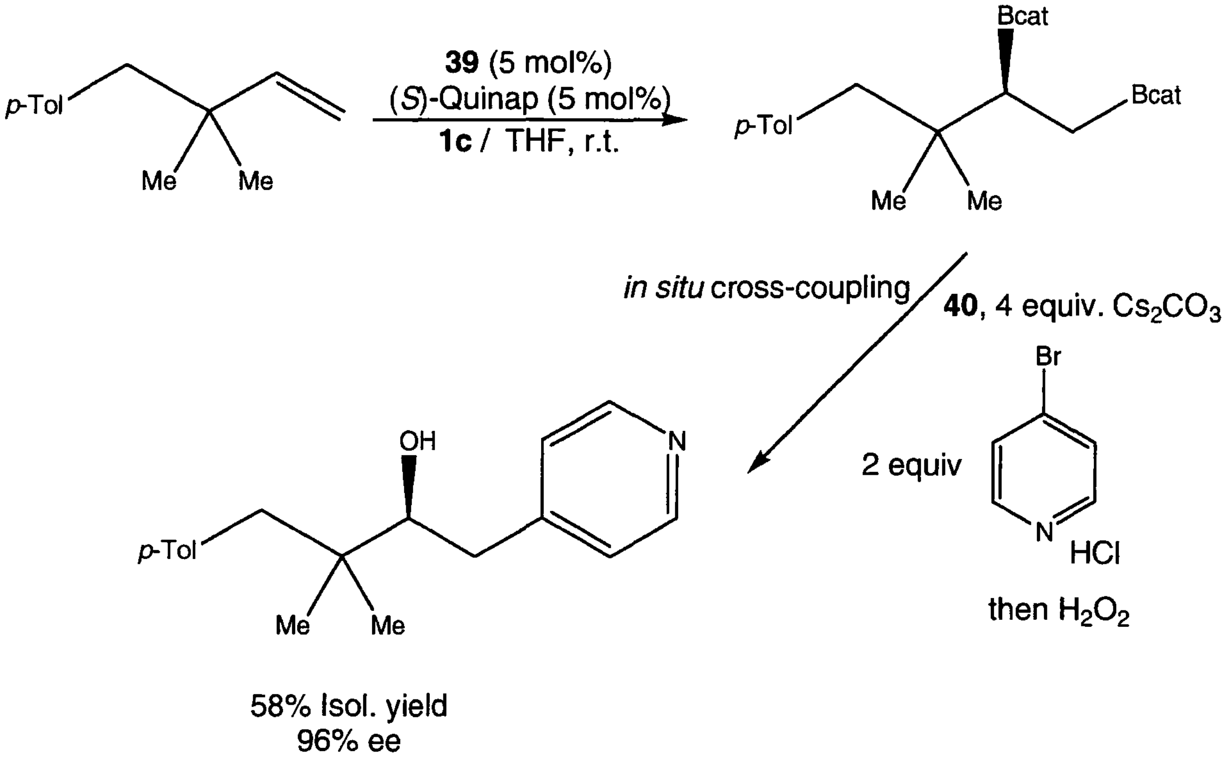


Eq. 1.5.6 Catalysed enantioselective diboration of 1,2-alkenes using **39**

Table 1.5.3 Catalysed diboration of *trans*- and *cis*-alkenes using **39**

Substrate	Product	Isol. Yield %	ee %
		71	93
		71	98
		48	98
		76	98
		68	88
		72	49
		61	49

In addition, the same 1,2-alkyl bis(boronate) intermediate was subjected to an *in situ* cross-coupling reaction. The crude mixture arising from diboration was diluted with THF and H_2O, followed by addition of 10 mol% of [(dppf)$PdCl_2$] **40**, $CsCO_3$ and 2 equiv. of aryl halide. The mixture was heated at 80 °C for 18 hours, then quenched by H_2O_2 to afford the carbohydroxylation product in 58% isolated yield (Eq. 1.5.7). They observed that the terminal C-B bond reacted faster and leaving the more hindered, secondary C-B bond available for other transformations such as oxidation. The results are summarised in Table 1.5.5.



Eq. 1.5.7 Suzuki-Miyaura cross-coupling reaction of the 1,2-bis(boronate) intermediate

Table 1.5.4 Catalysed 1,2-diboration of terminal alkenes using **39**

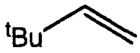
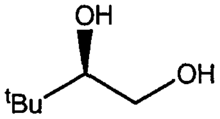
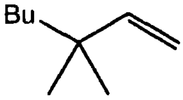
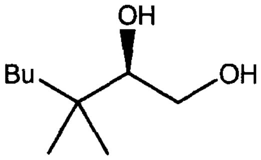
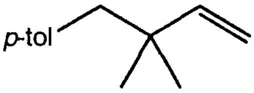
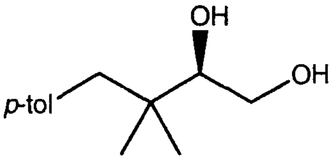
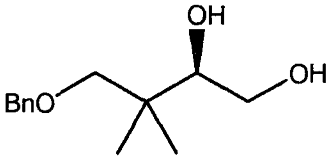
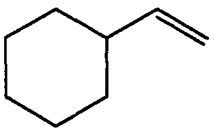
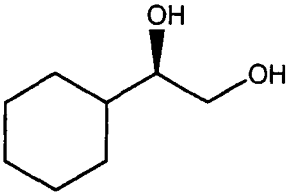
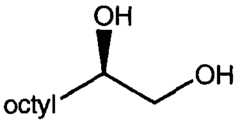
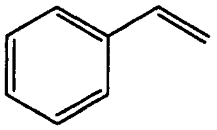
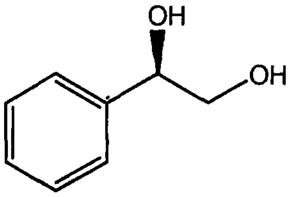
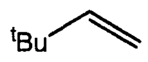
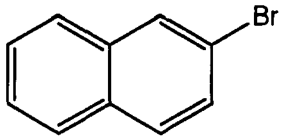
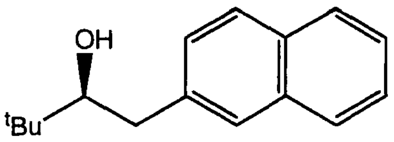
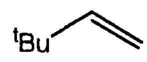
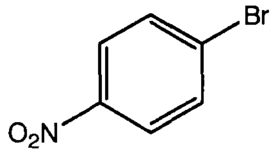
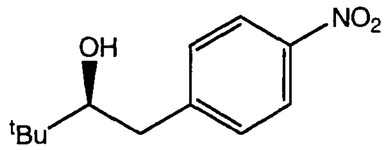
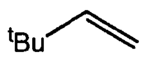
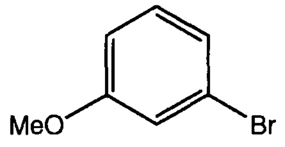
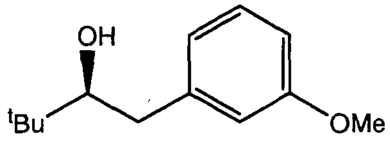
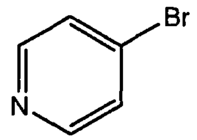
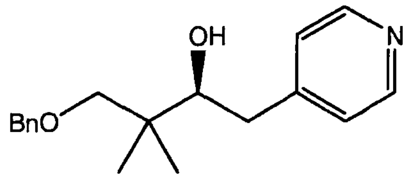
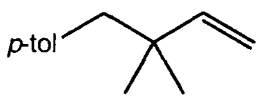
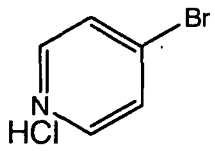
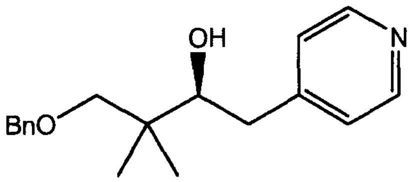
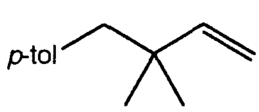
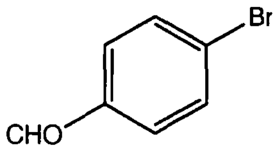
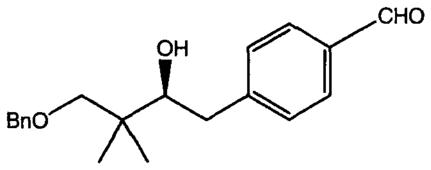
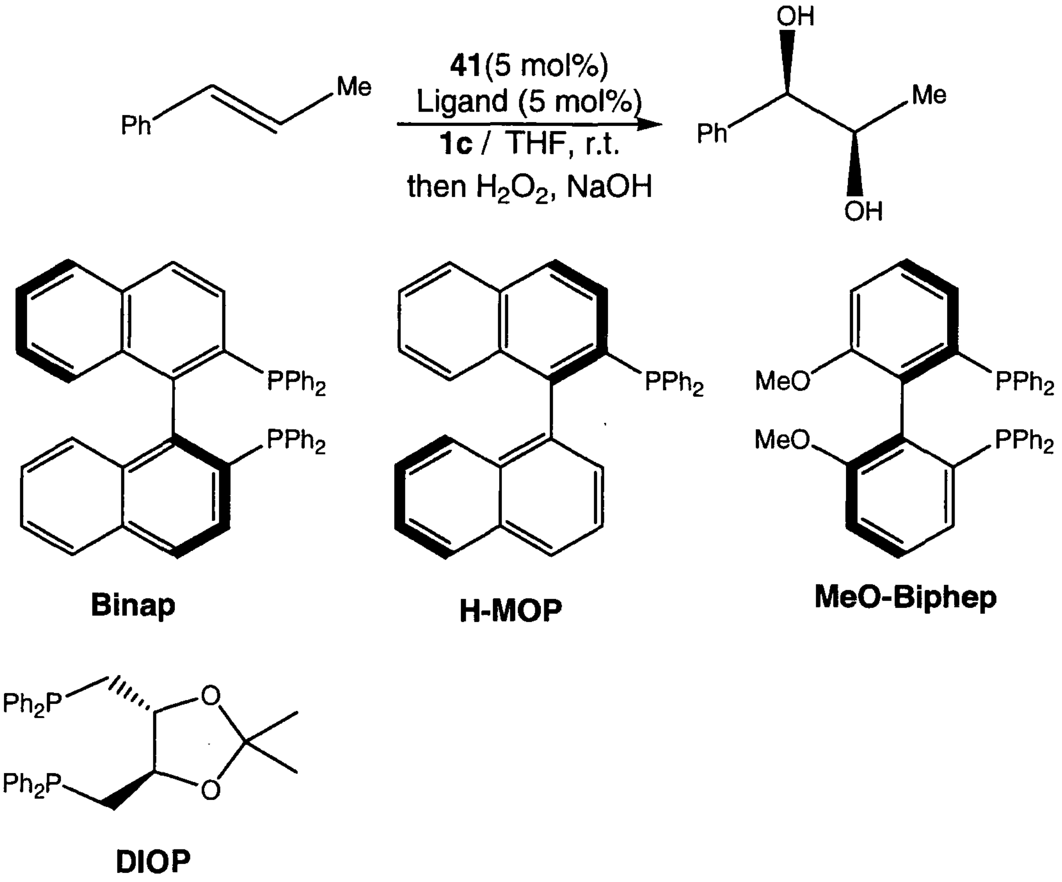
Substrate	Product	Isol. Yield %	ee %
		74	94
		82	95
		74	96
		71	93
		81	59
		68	33
		68	33

Table 1.5.5 Catalysed 1,2-diboration of terminal alkenes followed by *in situ* cross-coupling

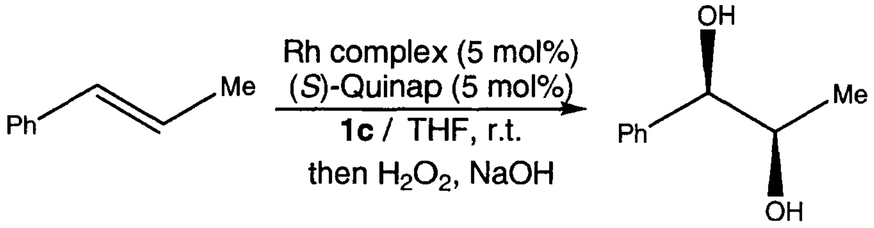
Substrate	Coupling partner	Product	Isol. Yield %	ee %
			69	92
			62	94
			77	95
			58	93
			58	96
			48	96

In the following year, Morken *et al.*[55] reported a comprehensive study of the Rh-catalysed enantioselective diboration of simple alkenes. It was more exhaustive than previous studies and investigated the effect of a variety of ligands, catalysts, solvents and diboron reagents. They examined the reaction of *trans*-2-methylstyrene with **1c** in THF at room temperature in the presence of 5 mol% of $[(COD)_2Rh]BF_4$ **41** with 5 mol% of a variety of chiral ligands such as (*S*)-Quinap, Binap, H-MOP, MeO-Biphep and Diop (Eq. 1.5.8). The only ligand which showed good reactivity was (*S*)-Quinap which afforded the highest diastereo- and enantioselectivity giving 24% yield. Binap also showed an interesting reactivity giving 25% yield; however, the reaction provided a significant amount of the anti isomer.



Eq. 1.5.8 Rh-catalysed diboration reaction in the presence of a variety of chiral ligands

Furthermore, they examined a variety of catalyst precursors including **39**, **41**, [(COD)Rh(acac)] **42**, [(ethylene)Rh(acac)] **43**, [$(nbd)_2Rh]BF_4$ **44**, and [(COD)Ir]BF_4 **45**, in the presence of (*S*)-Quinap, as this ligand gave the highest diastereo- and enantioselectivity. The reactions were carried out in THF at room temperature (Eq. 1.5.9). They found that cationic **44** and neutral **39** provided the best yields, whereas **41** and **45** provided the lowest yields (Table 1.5.6).

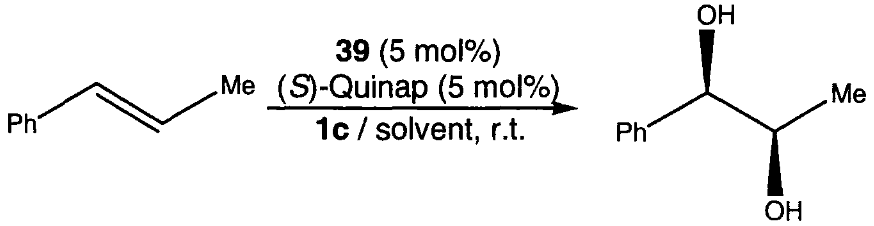


Eq. 1.5.9 Rh-catalysed asymmetric alkene diboration in the presence of (*S*)-Quinap

Table 1.5.6 Results of Rh-catalysed asymmetric alkene diboration in the presence of (*S*)-Quinap

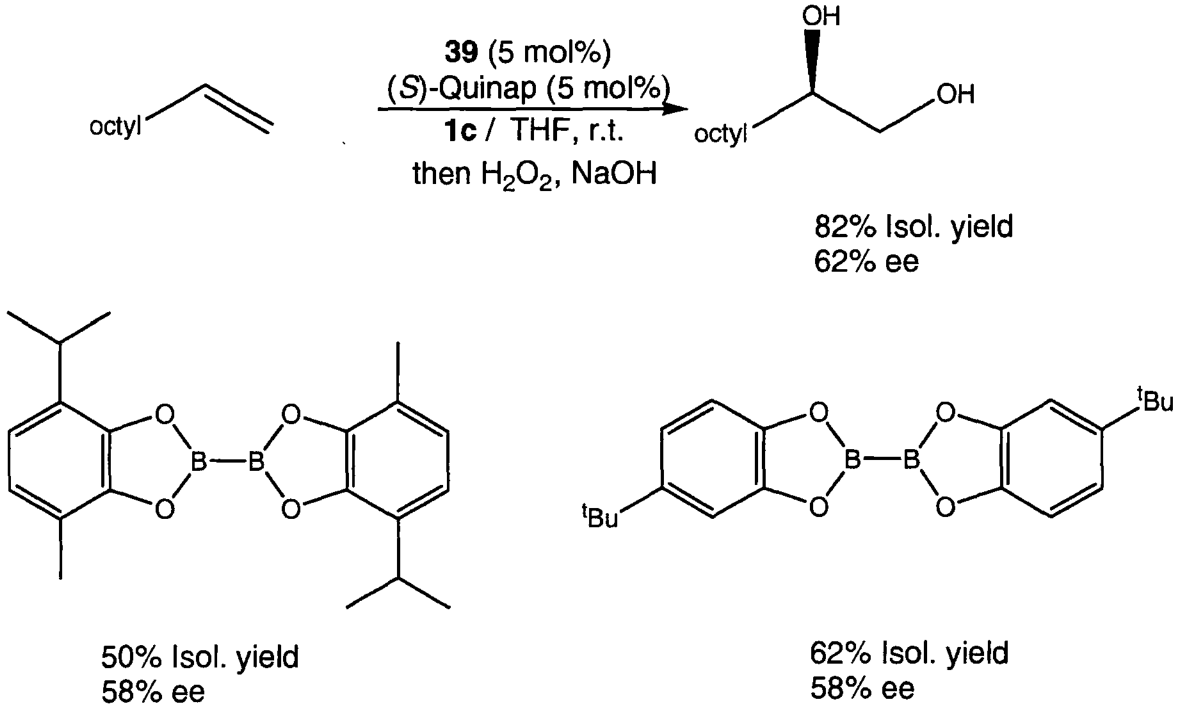
Rh salt	Isol. Yield %	ee %
39	71	93
41	24	86
42	43	93
43	50	92
44	56	95
45	<5	

In addition, they examined the effect of the solvent on the diboration of alkenes (Eq. 1.5.10). Thus, of THF, CH_2Cl_2, dichloroethane, dimethoxyethane, toluene, ether, acetonitrile, acetone and 1,4-dioxane, THF was most effective giving 71% during 12 hours, whereas toluene afforded a modest yield of 35% during 24 hours. The other solvents showed less reactivity, with yields in the range of 5 to 21%.



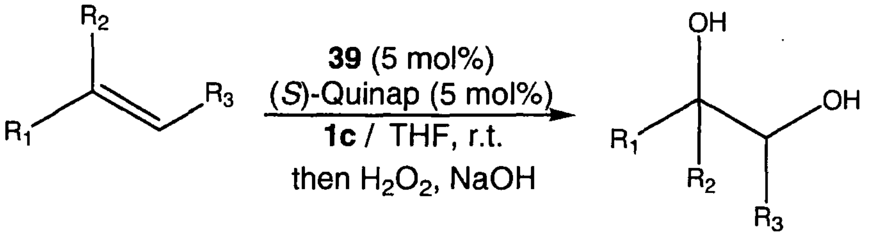
Eq. 1.5.10 Catalysed diboration of alkenes in different solvents

Furthermore, they examined alternative diboron reagents to improve the stereoselection with monosubstituted alkenes. They expected that increasing the steric hindrance adjacent to the boron atom would improve the selectivity; however, they observed that the reactivity was slightly diminished and there was no change in the selectivity (Eq. 1.5.11).



Eq. 1.5.11 Catalysed diboration of 1-decene with substituted diboron reagents

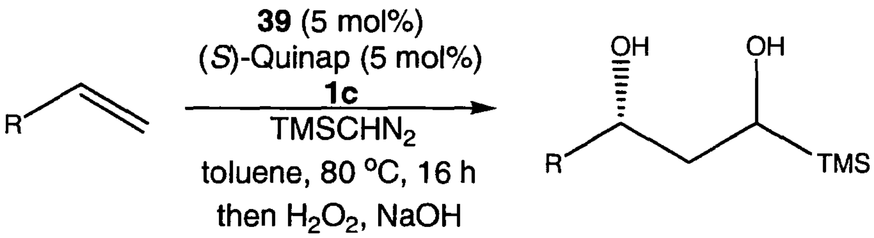
They also examined 1,1-disubstituted and trisubstituted alkenes in the presence of 5 mol% of **39** and 5 mol% of (*S*)-Quinap. The reaction was carried out in THF at room temperature (Eq. 1.5.12) and the results are summarised in Table 1.5.7



Eq. 1.5.12 Catalysed diboration of 1,1-disubstituted and trisubstituted alkenes using **39**

From the above table, both classes of alkenes gave tertiary C-B bonds in the reaction intermediate; however, the reactions of 1,1-disubstituted alkenes gave high yields with low enantioselection, whereas the trisubstituted alkenes gave low yields with high enantioselection.

In the same year, Morken *et al.*[56] reported the regioselective homologation of 1,2-bis(boronate) intermediates. The reaction was carried out with 1-octene in the presence of 5 mol% of **39** and 5 mol% of (*S*)-Quinap. The mixture was initially treated with 4 equiv. of $TMSCHN_2$ ($TMSCHN_2$ = trimethylsilyldiazomethane) in toluene, and was heated for 8 hours at 80 °C. Then, an additional 4 equiv. of $TMSCHN_2$ were added and the mixture was heated for an additional 8 hours. Oxidation of the mixture by NaOH and H_2O_2 gave an 58% yield of 1-trimethylsilyl-1,3-nonanediol Eq. 1.5.13.



Eq. 1.5.13 Homologation and oxidation of 1,2-bis(boronate) intermediates

Several alkenes were examined; all of the aliphatic alkenes gave a good yield (45-58%) with a mixture of diastereomers regardless of the substitution at the allylic carbon. Only styrene gave a low yield of 15%. The results are summarised in Table 1.5.8.

Table 1.5.7 Catalysed diboration of 1,1-disubstituted and trisubstituted alkenes using **39**

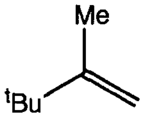
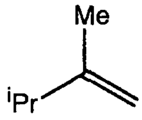
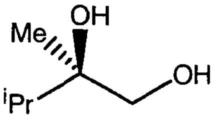
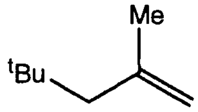
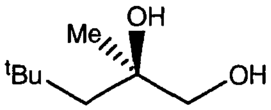
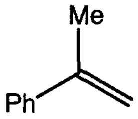
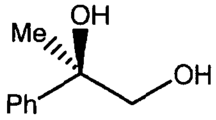
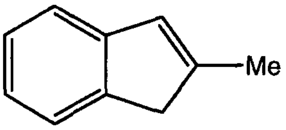
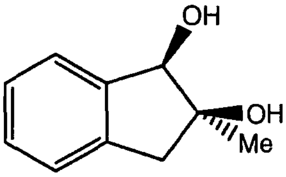
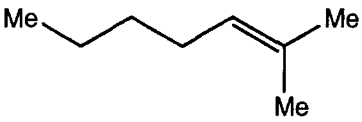
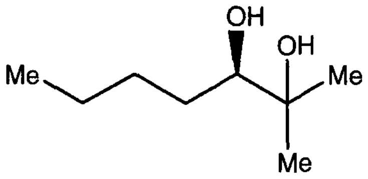
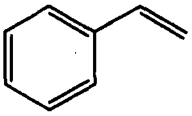
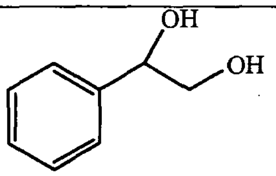
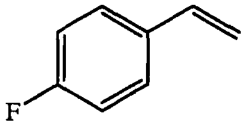
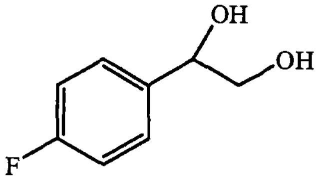
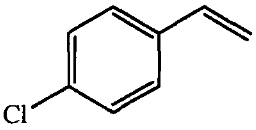
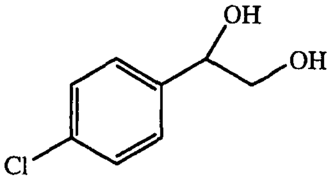
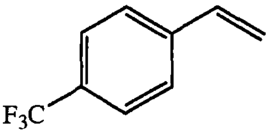
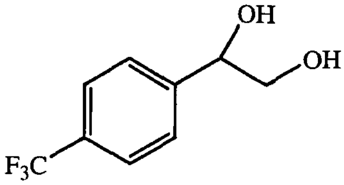
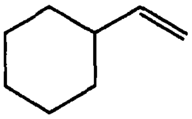
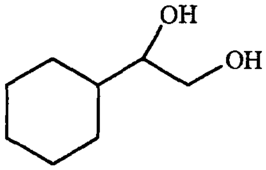
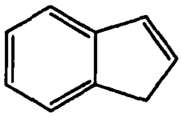
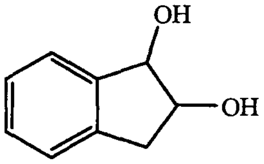
Substrate	Product	Time (h)	Yield %	ee %
	No reaction	14	<5	-
		14	58	25
		14	79	14
		24	67	46
		24	17	93
		24	8	91

Table 1.5.8 Homologation and oxidation of 1,2-bis(boronate) intermediates

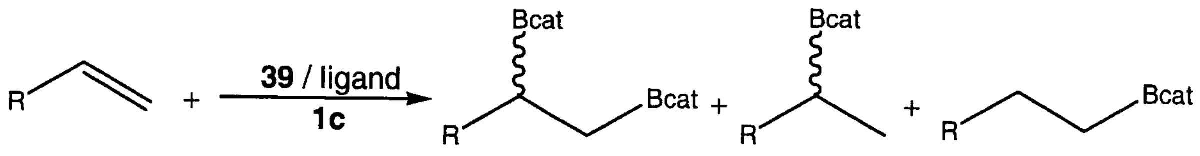
R	Isol. Yield %
hexyl	58
^{t}Bu	49
neopentyl	51
cyclohexyl	55
^{i}Bu	53
Ph	15

Peris and Fernández *et al.*[57] employed the known complex [(mentimid)$_2$Ag]AgCl$_2$ **46** (mentimid = 1-methyl-3-(+)-methylmenthoxide imidazolium chloride) for the 1,2-diboration of terminal alkenes. They used silver because it has low energy *d*-orbitals and it will minimize the π-backbonding to the alkenes which reduces the β-elimination pathway. The reactions were carried out with 5 mol% of **46**, and **1c** in THF at room temperature for 60 hours, and the conversion was determined by ^{1}H NMR spectroscopy. The mixture was quenched by H_2O_2 and NaOH to form the 1,2-diol (Table 1.5.9).

Table 1.5.9 Catalysed diboration of terminal alkenes using **46**

Substrate	Product	Diboration %	Diol %
		76	100
		12	100
		14	100
		10	100
		90	100
		20	100

The same group also studied the addition of diboranes to vinylarenes to produce the 1,2-diboration products catalysed by **39**in the presence of different ligands,[58] (Eq. 1.5.14). The conversions and selectivities were determined by ^1H NMR spectroscopy. The reactions were carried out in THF at room temperature for 15 hours, with 5 mol% of catalyst and ligand in the presence of **1c** as a source of boron. They found that the reaction with styrene in the presence of (*S*)-Quinap as a ligand gave 90% conversion with 76% selectivity for 1,2-BBE and 24% for hydroboration as a side product, whereas using (*R*)-Binap as the ligand gave 99% conversion with 21% selectivity for the desired products and 79% for the hydroboration. The results are summarised in Table 1.5.10.



47a: R = C_6H_5
47b: R = p-MeO-C_6H_4
47c: R = p-F-C_6H_4
47d: R = C_6H_{11}

48a **48b** **48c**

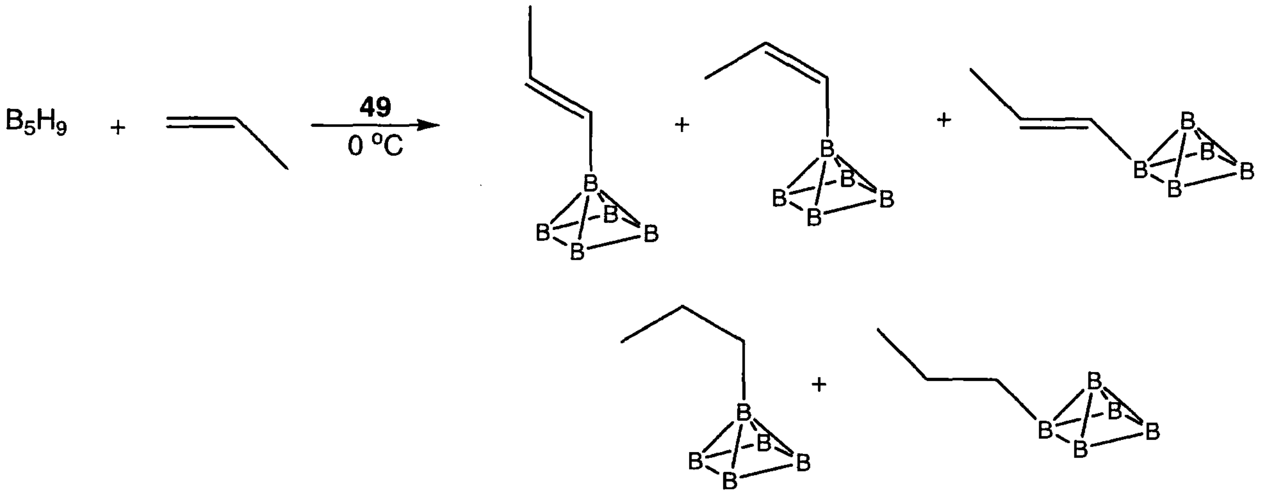
Eq. 1.5.14 Diboration of vinylarenes

Table 1.5.10 Catalysed diboration of vinylarenes using **39** in the presence of added ligand

Substrate	**Ligand**	**Conversion %**	**48a (ee) %**	**48b (ee) %**	**48c**
47a	(*S*)-Quinap	90	76 (35*R*)	24 (34*S*)	-
47a	(*R*)-Binap	99	21(21*R*)	69 (3*S*)	10
47a	(*S*,*S*)-BDPP	95	17 (16*R*)	68 (2*S*)	14
47b	(*S*)-Quinap	77	82 (26*R*)	11	7
47c	(*S*)-Quinap	58	58 (20*R*)	36 (45*S*)	6
47d	(*S*)-Quinap	100	78 (54*R*)	7	15

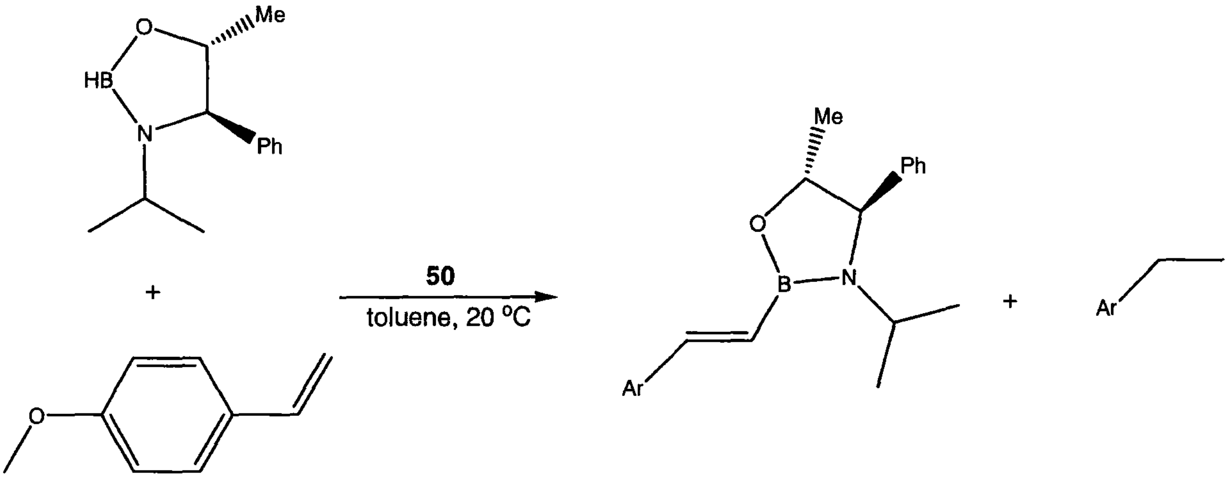
1.6 Metal Catalysed Dehydrogenative Borylation of Alkenes

The first report of the dehydrogenative borylation of alkenes was by Sneddon *et al.*,[59] who employed $PdBr_2$ **49** (1 mol%) and pentaborane to borylate ethylene, but-1-ene and propylene. The reaction with propylene gave a mixture of products consisting of 3 isomers of vinylboronate esters (VBEs) and 2 isomers of the hydroboration product; however, 50% of the alkene was consumed by hydrogenation (Eq. 1.6.1).



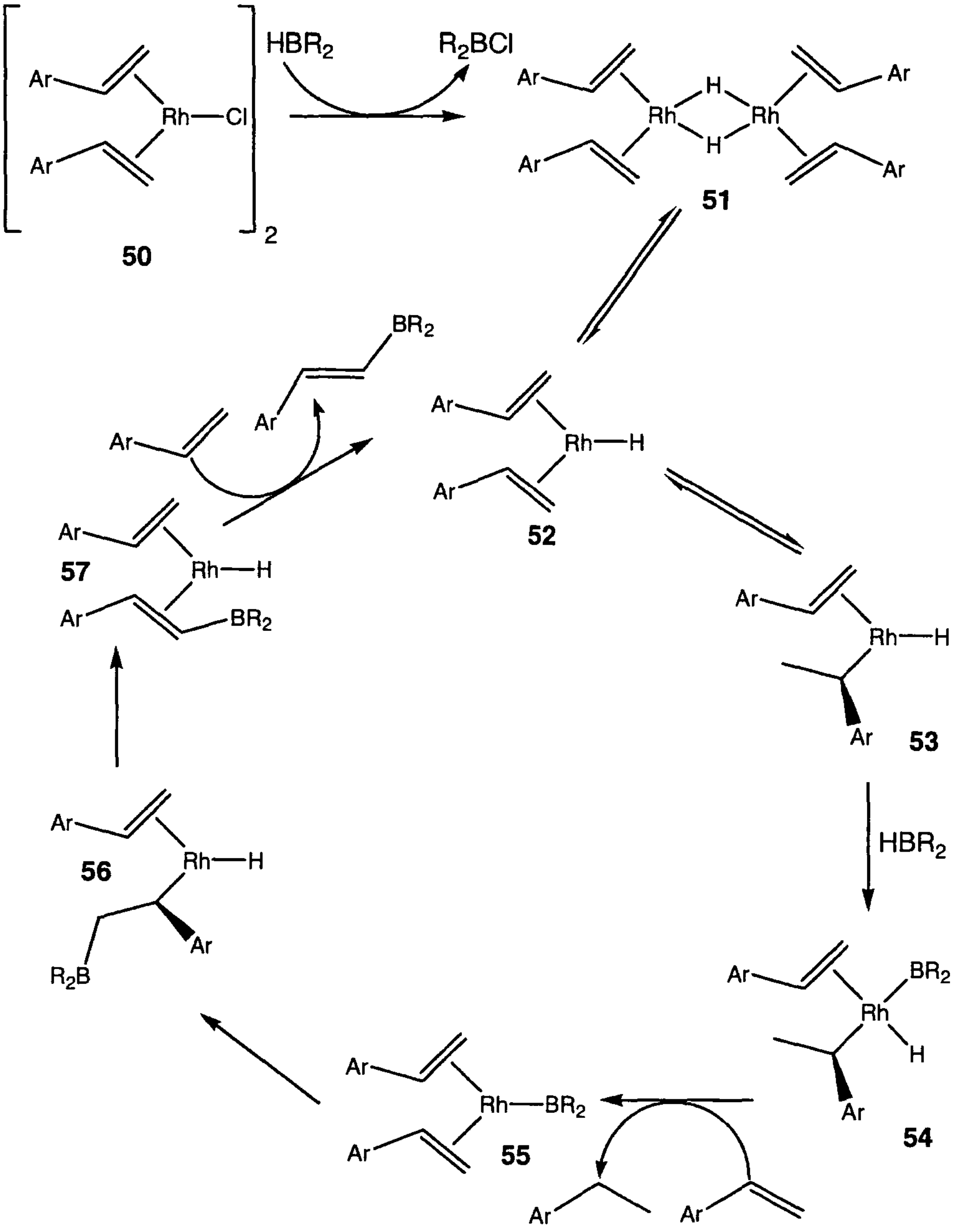
Eq.1.6.1 Catalysed dehydrogenative borylation of propylene using **49**

In 1992, Brown *et al.*[60] used an oxazaborolidine hydroborating reagent and $[Rh(\mu\text{-}Cl)(\eta^2\text{-}CH_2CHAr)_2]_2$ **50** where Ar = 4-MeO-C_6H_4 with 4-vinylanisole. The reaction was carried out in toluene at room temperature, yielding a 1:1 mixture of VBE and hydrogenation products (Eq. 1.6.2).



Eq. **1.6.2** Dehydrogenative borylation of 4-vinylanisole

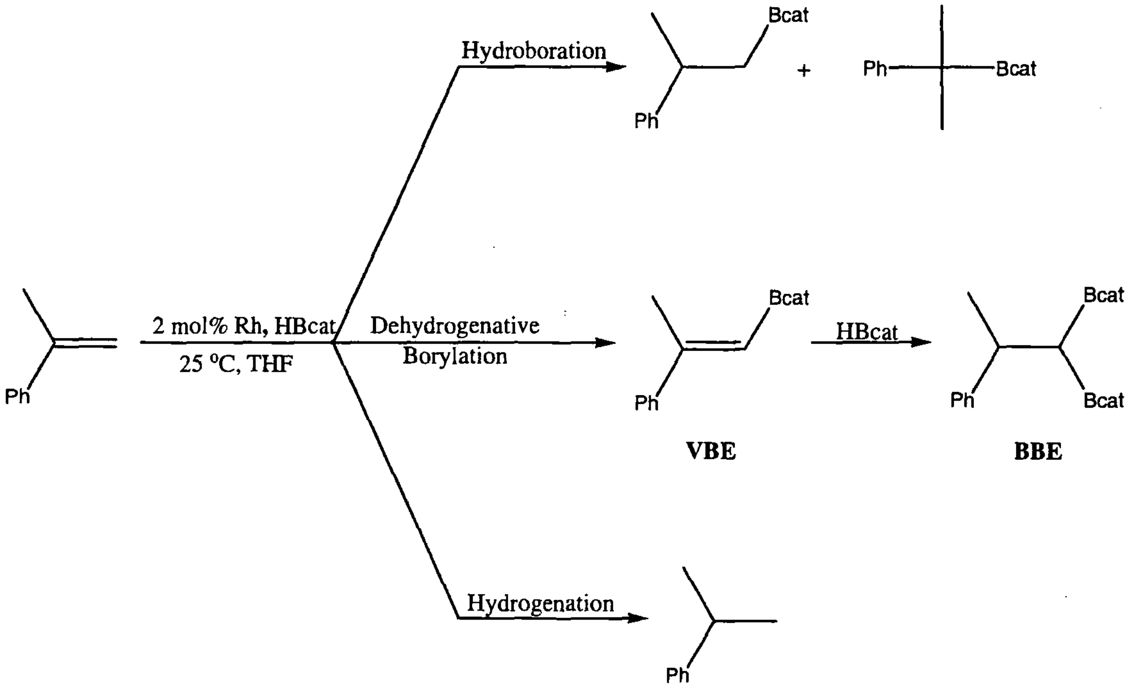
In a subsequent full paper, Brown *et al.*[61] reported additional results using 4-vinylanisole and 4-chlorostyrene, and again, they found that half of the alkene was consumed by hydrogenation with no evidence of any hydroboration. HBcat was also used to borylate the alkenes, but again, there was loss of half of the alkene substrate to hydrogenation with no evidence of hydroboration. The proposed mechanism is shown in (Scheme 1.6.1). Firstly, there is a reaction between the HBcat reagent and **50** to give the dimeric Rh hydride **51** in the preactivation step, which enters the catalytic cycle by dissociation of the dimer to give monomeric Rh hydride **52**, followed by hydride migration to give the branched alkylrhodium complex **53** which is in competition with reversible alkene association. The next step is the addition of HBcat to the intermediate **53** giving the square planar Rh complex **54**, followed by reductive elimination of the alkyl and binding of further alkene to give the Rh-boryl complex **55**, then boron migration to give the branched benzylrhodium complex **56**, and β-hydride elimination to afford the VBE coordinated to the Rh intermediate **57**. Finally, alkene exchanges with the bound VBE to regenerate the catalyst **52**.



Scheme 1.6.1

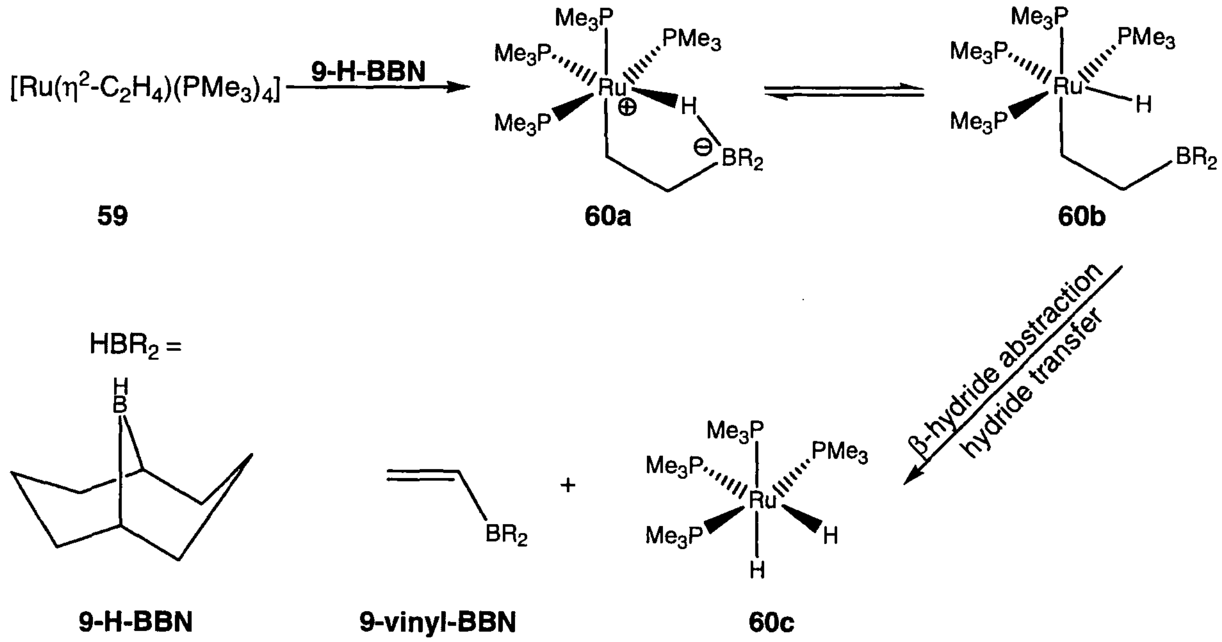
In 1993, Baker and Marder *et al.*[62] observed VBEs in their study of the stoichiometric insertion of alkenes into Rh-B bonds. They added 2 equiv. of vinylanisole to a CD_2Cl_2 solution of $[RhCl(Bcat)_2(PPh_3)_2]$ **58**. After 24 hours at room temperature, the ^1H NMR spectrum showed a mixture of 1,2-BBE, VBE and internal hydroboration products in a 3:2:2 ratio with a trace of the terminal hydroboration product.

Also in 1993, Marder and Baker *et al.*[63] introduced the first example of dehydrogenative borylation without significant hydrogenation, as well as the dehydrogenative borylation of a 1,1-disubstituted alkene. They reported that the reaction of 2-phenylpropene with HBcat in the presence of 2 mol% of **9**, carried out at 25 °C in THF, gave VBE and 1,1-bis(boronate) ester (1,1-BBE) which was produced from the subsequent hydroboration of the VBE. The total yield was 80%, with 53% selectivity for VBE and 27% BBE, 17% hydroboration, and 3% hydrogenation products (Eq. 1.6.3).



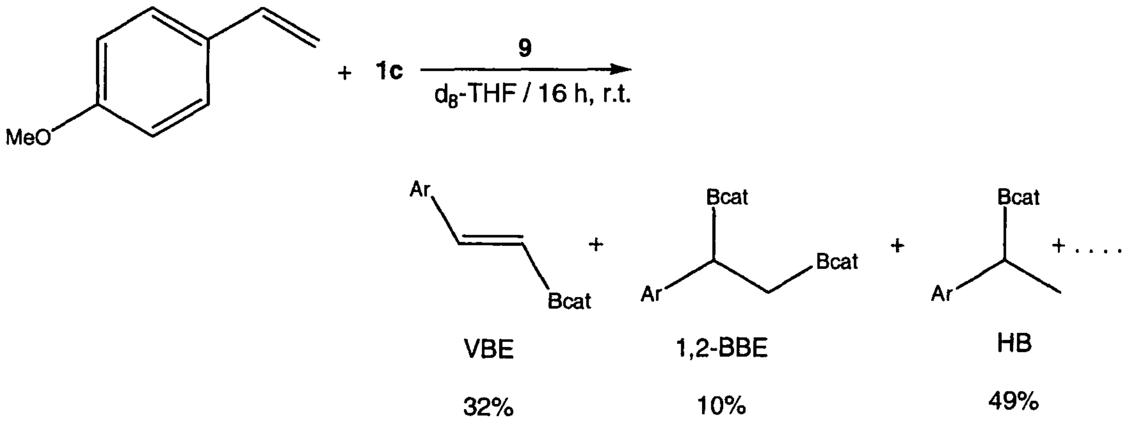
Eq. 1.6.3 Dehydrogenative borylation of 2-phenylpropene catalysed by various Rh-complex

In 1995, Baker, Marder *et al.*[64] again observed VBEs formation in the stoichiometric reaction of the organoruthenium complex $[Ru(\eta^2\text{-}C_2H_4)(PMe_3)_4]$ **59** with 9-H-BBN, (Scheme 1.6.2). The boron adds to the ethylene ligand, forming the cyclic, saturated borylalkyl zwitterionic intermediate **60a**. This intermediate undergoes cleavage of the B-H bond to give intermediate **60b**, which undergoes β-hydride elimination to give 9-vinyl-BBN and ruthenium di-hydride species **60c**.



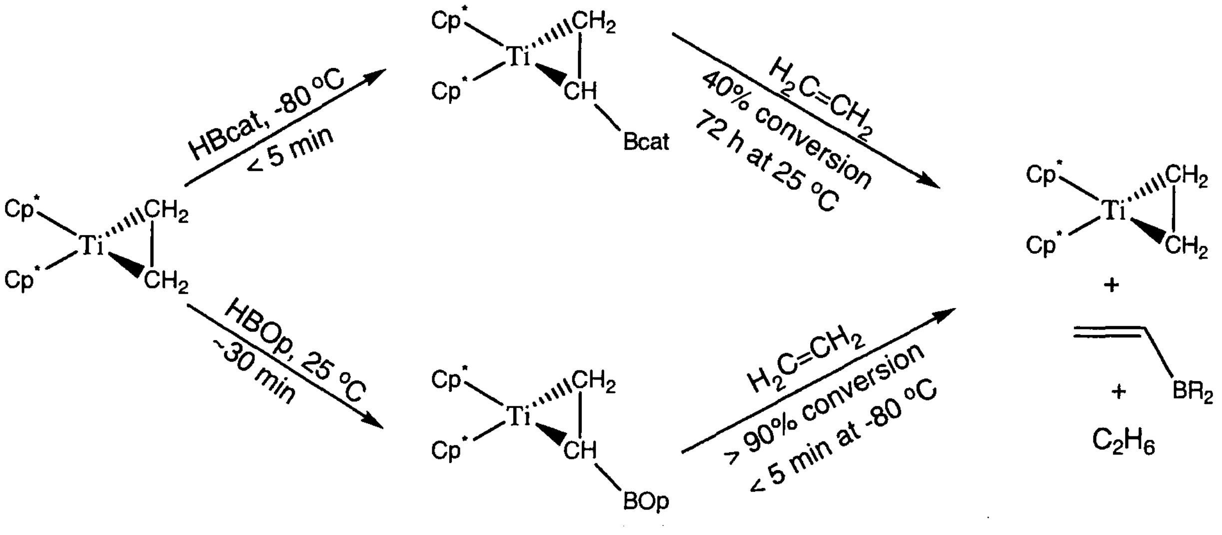
Scheme 1.6.2

About the same time, this group also observed formation of VBEs in the diboration of vinylanisole (Eq. 1.6.4). The reaction was catalysed by **9** (1 mol%) in the presence of **1c**. The reaction was carried out in d_8-THF at room temperature with stirring for 20 hours, and a mixture of products was observed.[46]



Eq. 1.6.4 Dehydrogenative borylation of vinylanisole catalysed by **9**

The next report of dehydrogenative borylation was by Smith *et al.*[65,66] who reported the titanium catalysed reaction of ethylene with HBOp (Op = benzo-1,3,2-diazaborolane) and HBcat, using $[(Cp^*)_2Ti(\eta^2\text{-}CH_2CH_2)]$ **61** (3 mol%) as a catalyst. The reaction with HBcat gave VBE and generates other active species that account for the normal hydroboration product CH_3CH_2Bcat. The reaction with HBOp was more successful than with HBcat at low temperature (Scheme 1.6.3).

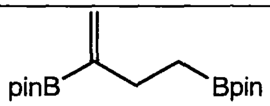
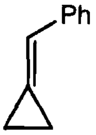
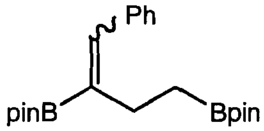
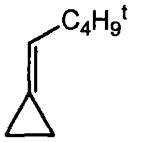
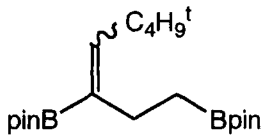
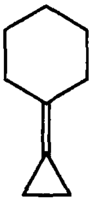
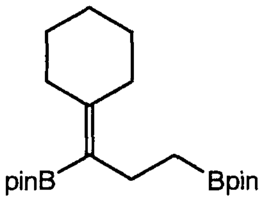


Scheme 1.6.3

Analogous to the prior work of Brown and Lloyd-Jones,[60,61] Masuda *et al.*[67,68] reported the reaction of 0.5 mol% of $[RhCl(COD)]_2$ **62** and HBpin with a variety of vinyl arenes including styrene and vinylanisole. The reactions were carried out in toluene at ambient temperature. These conditions caused dehydrogenative borylation to give a high yield and selectivity for VBEs of over 90% along with hydrogenation. In addition, the five solvents, THF, benzene, toluene, dioxane and CH_2Cl_2 were tested. It was observed that these did not have a significant impact on the yield or the selectivity. Additional catalysts, for example, **41** and [Ru(COD)(COT)] **63** as well as $[Rh_4(CO)_{12}]$ **64** were employed but were found to be less effective than **59**. Moreover, the presence of electron donating and withdrawing groups such as MeO and CO_2Me on the aryl group of the substrate did not play an important role in the reaction. However, alkane was always produced as a side product.

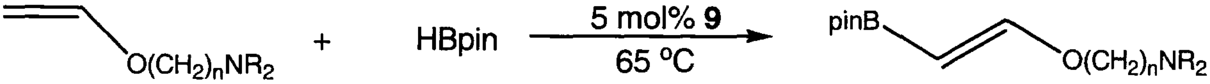
At about the same time, Miyaura *et al.*[69] reported the synthesis of VBEs from methylenecyclopropane derivatives. They employed **2** and **22** to catalyse the reactions. With **2**, the reactions were carried out in toluene at 80 °C, whereas **22** catalysed the reaction at room temperature. They observed that increasing the bulk of the groups around the double bond decreased the yield of the product. In addition, using **22** produced a low yield due to the catalyst decomposition during the reaction. Results are summarised in Table 1.6.1.

Table 1.6.1 Pt-catalysed diboration reaction of methylenecyclopropane using **2** and **22**

Compound	**Product**	**Yield % (Time / h)**	
		2	**22**
		75 (5)	71 (3)
		66 (5)	60 (2)
		60 (51)	15 (145)
		57 (34)	36 (96)

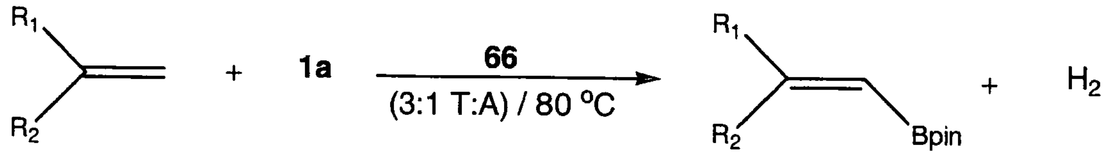
In 2000, Sneddon *et al.*[70] employed **49** and $[(H)_2Pt(Cl)_6].6H_2O$ **65** with *arachno*-6,8-$C_2B_7H_{13}$ for the dehydrogenative borylation of excess styrene, ethylene and pent-1-ene at room temperature. The reactions formed the dehydrogenative borylation products with some hydroboration.

Westcott *et al.*[71] employed 5 mol% of **9** with HBpin to borylate several alkylamino-vinyl ethers at 65 °C (Eq. 1.6.5). However, no yields were presented and the report does not provide more information about hydrogenation or hydroboration.



Eq. 1.6.5 Dehydrogenative borylation of alkylaminovinyl ethers using **9**

In 2003, Marder *et al.*[72] reported the dehydrogenative borylation of vinylarenes with high selectivities and yields for VBEs and without consumption of the half alkene substrate by hydrogenation. They employed *trans*-[Rh(Cl)(CO)(PPh_3)$_2$] **66** to catalyse dehydrogenative borylation of vinylarenes such as 4-vinylanisole and 1,1-disubstituted alkenes including α-methylstyrene, 1,1-diphenylethylene, methylene cyclopentane and methylene cyclohexane in the presence of **1a** and **1b**. The reaction was examined with a variety solvents such as toluene and THF as well as 1,4-dioxane. All of these solvents gave complicated mixture of products such as hydrogenation, hydroboration diboration, vinyl-bis(boronate) esters VBBEs and VBEs. In contrast, the reaction in CH_3CN gave a high selectivity for VBEs; however, the reaction was slow. Therefore, a mixture of toluene and acetonitrile, 3:1 (3:1 T:A), provided an excellent compromise between selectivity and rate. As a results, the reactions were carried out with 3 mol% of **66** and 0.67 equiv. of **1a** in (3:1 T:A) at 80 °C (Eq. 1.6.6) and the results are summarised in Table 1.6.2.



R_1 = Ph-OMe, R_2 = H
R_1 = Ph, R_2 = Me
R_1 = Ph, R_2 = Ph
R_1, R_2 = $(-CH_2-)_n$ n = 4, 5

Eq. 1.6.6 Dehydrogenative borylation of vinylarenes using **66**

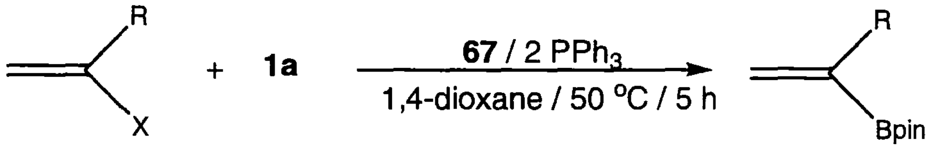
Table 1.6.2 Dehydrogenative borylation of vinylarenes using **66**

Substrate	Boron reagent	Hydroboration (hydrogenation)	Total VBE %	Total VBBE %	Time days	Yield %
4-vinylanisole	**1a**	12 (trace)	88		2	100
4-vinylanisole	**1b**	5 (22)	73		1	62
4-vinylanisole[a]	**1a**	1	14	85	5	100
α-methylstyrene	**1a**	1	99		4	68
α-methylstyrene[b]	**1a**	9	87		2	72
α-methylstyrene[c]	**1a**	trace	100		6	70
α-methylstyrene[d]	**1a**		100		3	90
α-methylstyrene[e]	**1a**		100		2	100
α-methylstyrene	**1b**	9	91		1	49
1,1-diphenylethylene	**1a**	2	98		4	48
1,1-diphenylethylene[e]	**1a**	1	100		3	100
methylene cyclopentane	**1a**		100		3	100
methylene cyclohexane	**1a**	8	92		5	80

[d] 2 equiv. of **1a** and 5 mol% of **66** was used. [b] Toluene only was used. [c] Acetonitrile was used. [d] 5 mol% of **66** was used. [e] 1 equiv. of **1a** was used.

VBEs also can be synthesised by the Suzuki-Miyaura cross-coupling reaction of alkenyl halides or by hydroboration of alkynes, as well as by diboration of alkynes which has been discussed in section (1.2).

Miyaura *et al.*[73] reported the cross-coupling reaction of alkenyl halides with **1a** in the presence of toluene as solvent and PhOK as the base. The reaction was catalysed by [$(PPh_3)_2PdCl_2$] **67** (0.03 mmol) in the presence of 2 equiv. of PPh_3 at 50 °C for 5 hours; results are summarised in Eq. 1.6.7.



68a-e

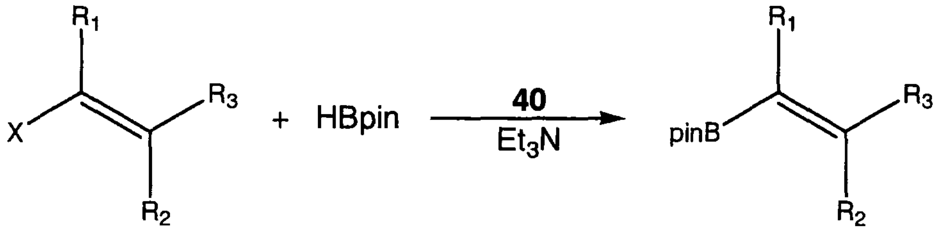
69a-e

68a: R = C_8H_{17}, X = Br
68b: R = C_8H_{17}, X = I
68c: R = *t*-C_4H_9, X = Br
68d: R = Ph, X = Br
68e: R = $(CH_2)_3CN$, X = Br

69a = 96%
69b = 65%
69c = 69%
69d = 88%
69e = 85%

Eq. 1.6.7 Cross-coupling reaction of alkenyl halides with **1a**

In the same year, Masuda *et al.*[74] reported the synthesis of VBEs from cycloalkenyl triflates and iodides using HBpin as a source of boron (Eq. 1.6.8). The cross-coupling reactions were catalysed by **40** / 4 $AsPh_3$ with triethylamine as the base. The mixture was heated in 1,4-doxane for 16 hours at 80 °C. The yield ranged between 60 and 86% and no large differences in reactivity between cycloalkenyl iodide and triflate were found.

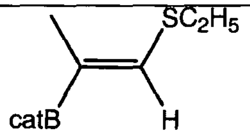
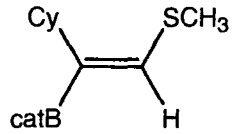
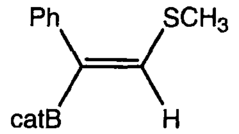


X = I, OTf

Eq. 1.6.8 Synthesis of VBEs via Masuda cross-coupling reaction

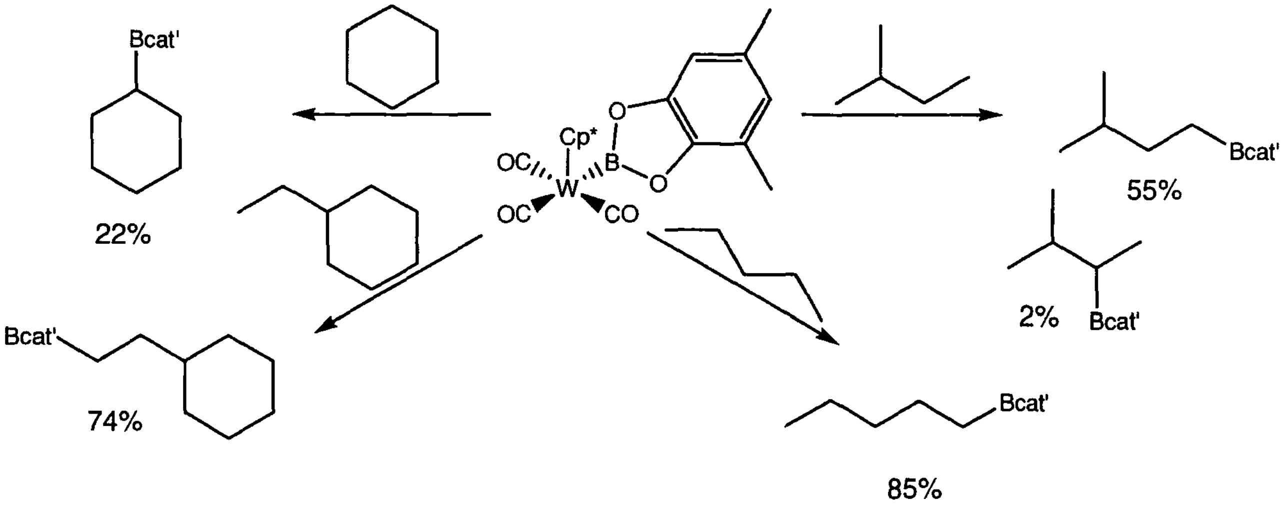
Suzuki and Miyaura *et al.*[75] reported the regioselective hydroboration of thioalkynes using HBcat and [(dppf)NiCl$_2$] **70** as a catalyst to produce the thio-VBEs. The reactions were carried out in benzene at room temperature for 5 hours and they observed that the Bcat prefers to occupy the position *trans* to the sulfur atom (Table 1.6.3).

Table 1.6.3 Ni-Catalysed hydroboration of thioalkynes using **70**

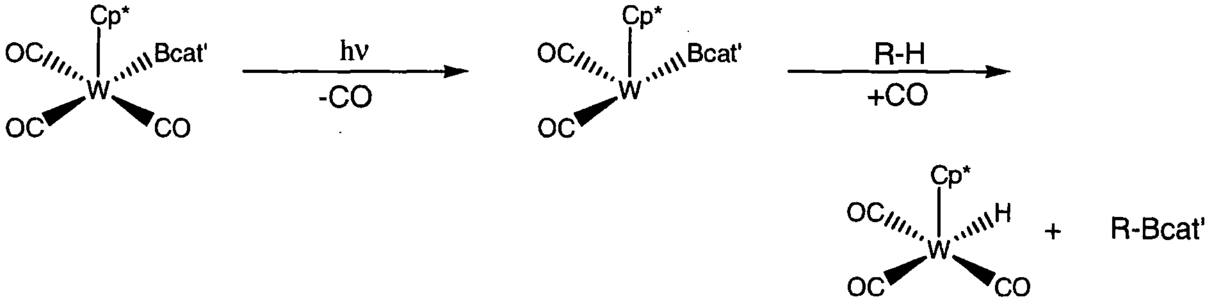
Alkyne	Product	Yield %
—≡—SC_2H_5		99
Cy—≡—SC_2H_5		92
Ph—≡—SC_2H_5		95

1.7 Metal Catalysed Borylation of Alkanes

In 1997, Hartwig *et al.*[76] reported that photolytic borylation of alkanes is selective for the terminal carbon. They employed stoichiometric [Cp*W(CO)$_2$(Bcat')] **71**, [Cp*Fe(CO)$_2$(Bcat')] **72** and [Cp*Ru(CO)$_2$(Bcat')] **73** (cat' = 1,2-$O_2C_6H_2$-3,5-Me_2) to borylate pentane. The tungsten complex **71** was more active than the others and gave 85% of alkylboronate esters, whereas the **72** and **73** complexes gave 28 and 40% of the alkylboronate esters respectively. Ethylcyclohexane and 2-methylbutane as well as cyclohexane were examined using **71**, and the results are summarised in Scheme 1.7.1, the conversions and selectivities having been determined by a combination of GC/MS and ^{1}H NMR spectroscopy. In addition, they observed that the majority of borylation occurred at the primary carbon with some of borylation at the secondary carbon especialy with cyclohexane and 2-methylbutane. The proposed mechanism of the reaction is shown in Scheme 1.7.2. The reaction proceeds *via* the photolytic loss of CO from the metal, followed by thermal reaction with R-H to yield the borylated alkane.

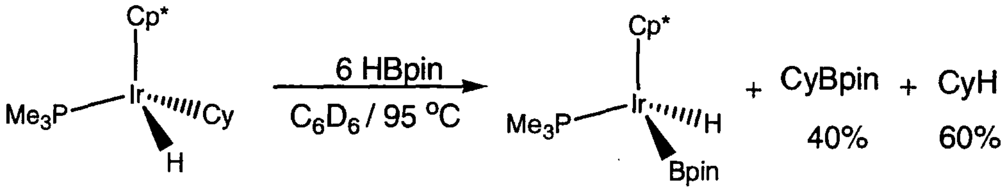


Scheme 1.7.1



Scheme 1.7.2

In 1999, Iverson and Smith *et al.*[77] reported the stoichiometric thermal borylation of cyclohexane with HBpin in the presence of [Cp*Ir(PMe$_3$)(H)(Cy)] **74** (Eq. 1.7.1). The reaction was carried out in d$_6$-benzene at 95 °C.



Eq. 1.7.1 The reaction between **74** and HBpin

Further studies of the photolytic, stoichiometric reaction were reported by Waltz and Hartwig.[78] They used 17 different complexes of the form [$Cp^*M(L)_n(BR_2)$], in order to study the effect of the boryl group and ligand. Reaction with pentane gave pentylboronate esters in 0-85% yields, indicating that many of the complexes were unreactive (Table 1.7.1).

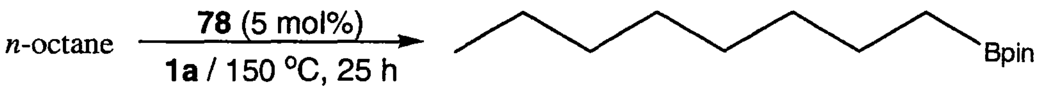
Table 1.7.1 Yields of pentylboronate esters from the photochemical reaction of metal boryl complex with pentane

Compound	Yield %	Compound	Yield %
[$CpFe(CO)_2(Bcat)$]	<1	[$Cp^*Ru(CO)_2(BMe_2)$]	<1
[$Cp^*Fe(CO)_2\{Bcat(^tBu)_2\}$]	15	[$Cp^*Ru(CO)_2(Bpin)$]	72
[$Cp^*Fe(CO)_2\{Bcat(Me)_2\}$]	20	[$Cp^*W(CO)_3\{Bcat(Me)_2\}$]	85
[$Cp^*Fe(CO)_2(Bcat)$]	<1	[$Cp^*Mo(CO)_3\{Bcat(Me)_2\}$]	7
[$CpFe(CO)_2\{Bcat(^tBu)_2\}$]	<1	[$Cp^*Fe(CO)_2BBN$]	8
[$Cp^*Ru(CO)_2\{Bcat(Me)_2\}$]	40	[$Cp^*Ru(CO)_2BBN$]	<1
[$Cp^*W(CO)_3(Bcat)$]	20	[$Cp^*Ru(CO)_2BCy_2$]	<1
[$Cp^*W(CO)_3(Bpin)$]	72	[$Cp^*Ru(CO)_2BS_2Tol$]	<1
[$Cp^*W(CO)_2(PCy_3)\{Bcat(Me)_2\}$]	59	[$Cp^*W(CO)_2(PMe_3)$ $\{Bcat(Me)_2\}$]	32

Table 1.7.2 Catalytic functionalization of alkanes by **77**

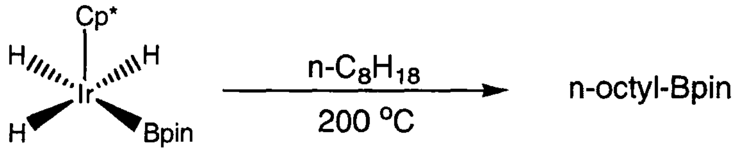
Substrate	77 (mol%)	Time / h	Yield %
n-pentane	2.4	56	95
2-methylbutane	3.4	55	83
methylcyclohexane	5	60	75
di-*n*-butyl ether	5	45	100

In 2000, Hartwig *et al.*[81] examined [Cp*Rh(C_2H_4)$_2$], [Cp*Rh($C_2H_3SiMe_3$)$_2$], [Cp*Rh(H_2)($SiEt_3$)$_2$], [Cp*Rh(η^4-C_6Me_6)] **78**, [Cp*Ir(H)$_4$] **79** and [Cp*Ir(C_2H_4)$_2$] **80** with HBpin and **1a** to borylate n-octane. They found that 10 mol% of **79** did not give more than 20% of alkylboronate esters. In contrast, the reaction with 10 mol% of **80** gave 58% of the desired products; however, the reaction was very slow, requiring 10 days at 200 °C. Complex **78** showed high activity over long periods of time (Eq. 1.7.4). The reactions were carried out with 5 mol% of the catalyst at 150 °C for 25 hours yielding 88% of n-octyl-Bpin (Table 1.7.3).



Eq. 1.7.4 Catalytic functionalization of octane by **78** in the presence of **1a**

One year later, Kawamura and Hartwig,[79] reported the stoichiometric thermal borylation of octane with [Cp*Ir $(H)_3$(Bpin)] **75** at 200 °C for 2 days to give 50% of the borylated products (Eq 1.7.2).



Eq. 1.7.2 Ir(V) Stoichiometric C-H activation

In the same year, Hartwig *et al.*[80] reported further studies on the rhenium catalysed photolytic borylation of alkanes. They employed 2.4-5 mol% of [Cp*Re$(CO)_3$] and **1a** in the presence of CO (2 atm) at room temperature to diborate methylcyclohexane, *n*-pentane, 2-methylbutane, di-n-butyl ether and t-butyl ethyl ether (Eq. 1.7.3 and Table 1.7.2). In addition, they observed that the borylations occurred predominately at the primary site. Isolation of the complex *trans*-[Cp*Re$(CO)_2$$(Bpin)_2$] **76** and subsequent reaction with pentane gave similar results to those using [Cp*Re$(CO)_3$] **77**, suggesting that the reaction proceeds with initial oxidative addition of **1a** to the metal centre.

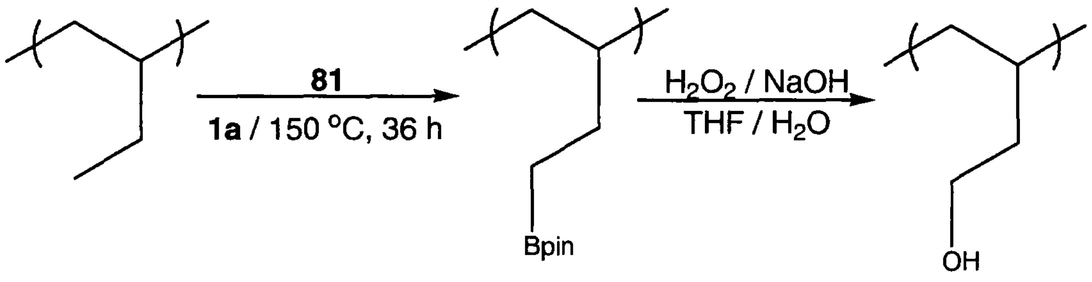
$$\text{R-H} \; + \; \mathbf{1a} \; \xrightarrow[\text{hv, CO, 25 °C}]{\mathbf{77}\text{ (2.4-5 mol\%)}} \; \text{R-Bpin} \; + \; \text{HBpin}$$

Eq. 1.7.3 C-H activation of alkanes via **76**

Table 1.7.3 Catalytic functionalisation of alkanes via **78**

Substrate	78 (mol%)	Time / h	Conversion %
n-octane	5	25	88
n-octane	1	80	72
2-methylpentane	1	60	61
methylcyclohexane	6	80	49

In 2002, following the report of Shimada and Marder *et al.*[82] that $[Cp^*RhCl_2]_2$ **81** gave similar results in the toluene borylation to those reported[83] for **78**, *vide infra*, Hartwig et al.[84] reported that **81** catalysed the borylation of alkane C-H bonds to form a polyolefin with Bpin groups at the terminal position of branches (Eq. 1.7.5).

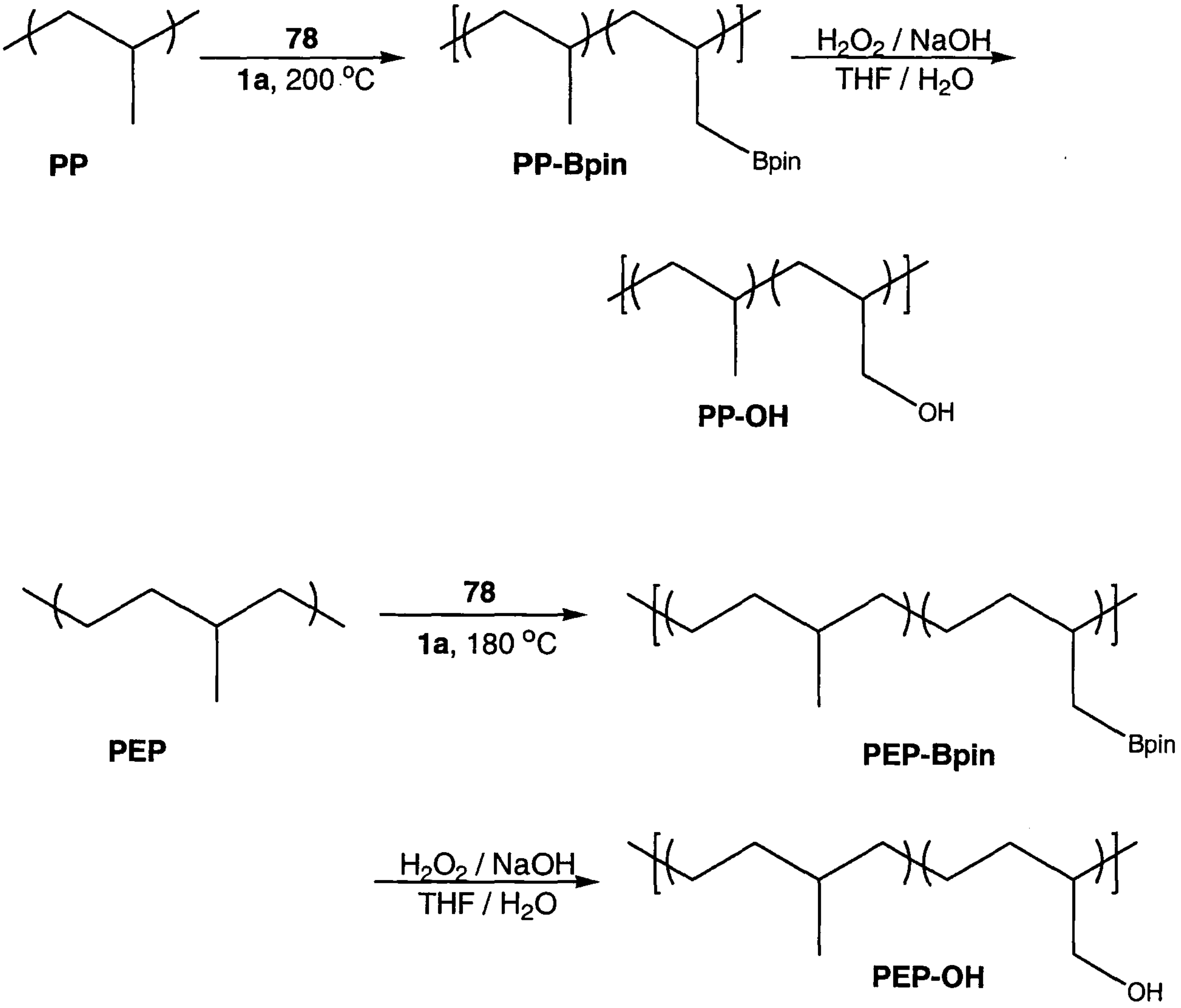


Eq. 1.7.5 Catalytic borylation and oxidation of **PEE-1**

They used a low molecular weight polymer such as polyethylethylene **PEE-1** (M_n = 1.7 Kg/mol) (M_n = Number-average molecular weight) and a high molecular weight polymer, **PEE-2** (M_n = 73 Kg/mol).

The reactions were conducted with 5 mol% of **81** and a ratio of **1a** to polymer chain **PEE-1** (**1a**:monomer = 0.2) on a gram scale at 150 °C for 36 hours. After the entire boron reagent was fully consumed, the mixture was oxidised by H_2O_2 in a mixture of THF and H_2O yielding the corresponding alcohols in 70%. The borylation of **PEE-2** was carried out at various ratios of **1a** to monomer unit (0.07, 0.3 and 1:1), with 5 mol% of **81**, at 150 °C. After 36 hours, the mixture was also oxidised by H_2O_2 in a mixture of THF and H_2O yielding the corresponding alcohols in 93, 45 and 20% respectively. The products were identified by ^1H NMR, ^{13}C NMR and IR spectroscopies and also by MALDI-MS. For example, the methylene protons α to the hydroxyl group appear at 3.7 ppm. The spectra lacked signals for the methyl groups, and the carbon α to the hydroxyl group appears at 60.15 ppm which was confirmed by DEPT ^{13}C NMR spectrum at 135 °C.

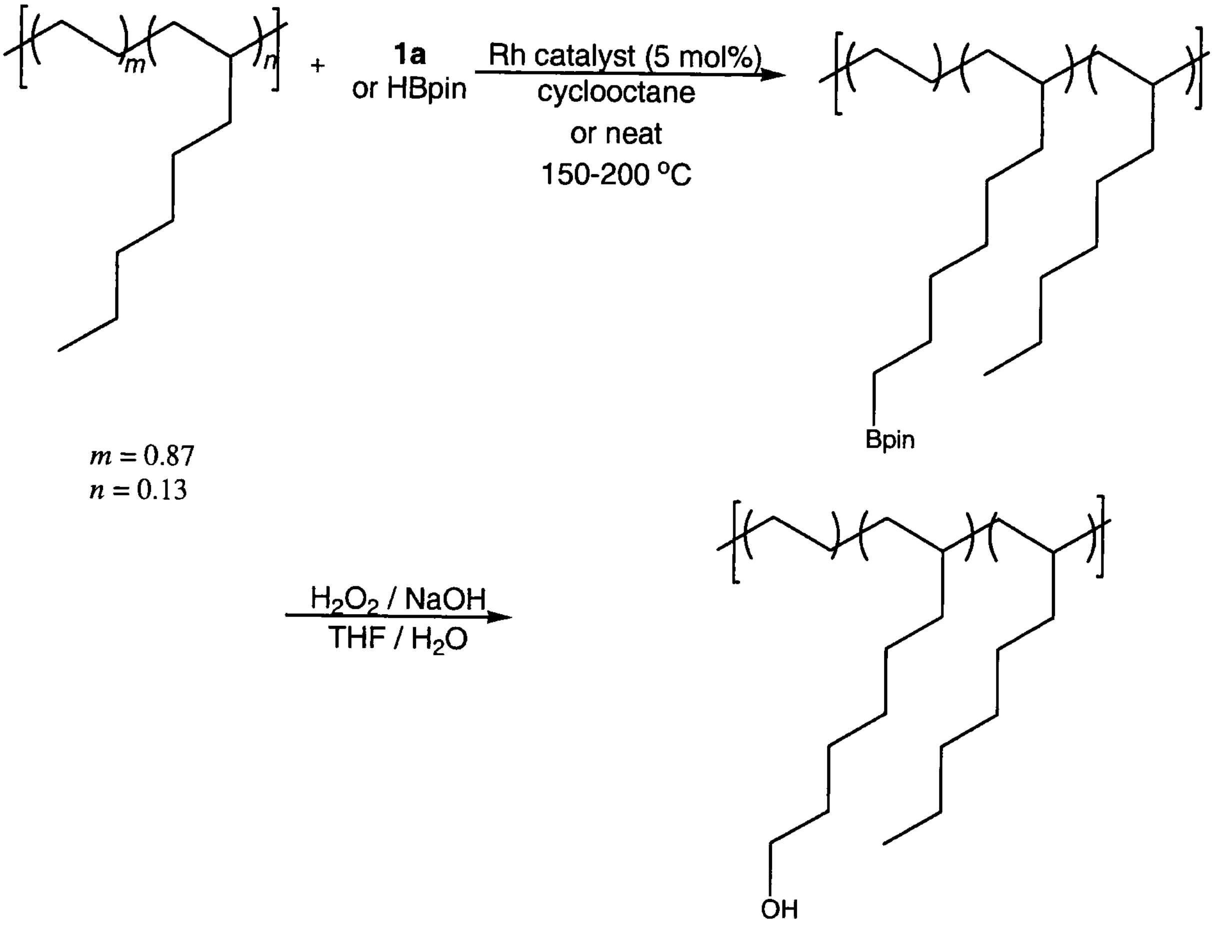
Also in the same year, Hartwig *et al.*[85] reported the borylation of polyproplylene **PP** with 1 equiv. of **1a** in the presence of 5 mol% of **78.** The reaction was conducted in neat polymer at 200 °C for 24 hours yielding the borylated polymer **PP-Bpin** in 96%. The **PP-Bpin** was oxidised by H_2O_2 in a mixture of THF and H_2O yielding the corresponding alcohols **PP-OH** (Eq. 1.7.6). At the same time, they also reported the borylation of poly(ethylene-*alt*-propylene) **PEP** in the presence of 5 mol% of **78** and **1a**. The reaction was carried out in neat of polymer at 180 °C, yielding 70-80% of borylated polymer **PEP-Bpin**; again oxidation gave the corresponding alcohols **PEP-OH** (Eq. 1.7.6)



Eq. 1.7.6 Catalytic borylation and oxidation of **PP** and **PEP**

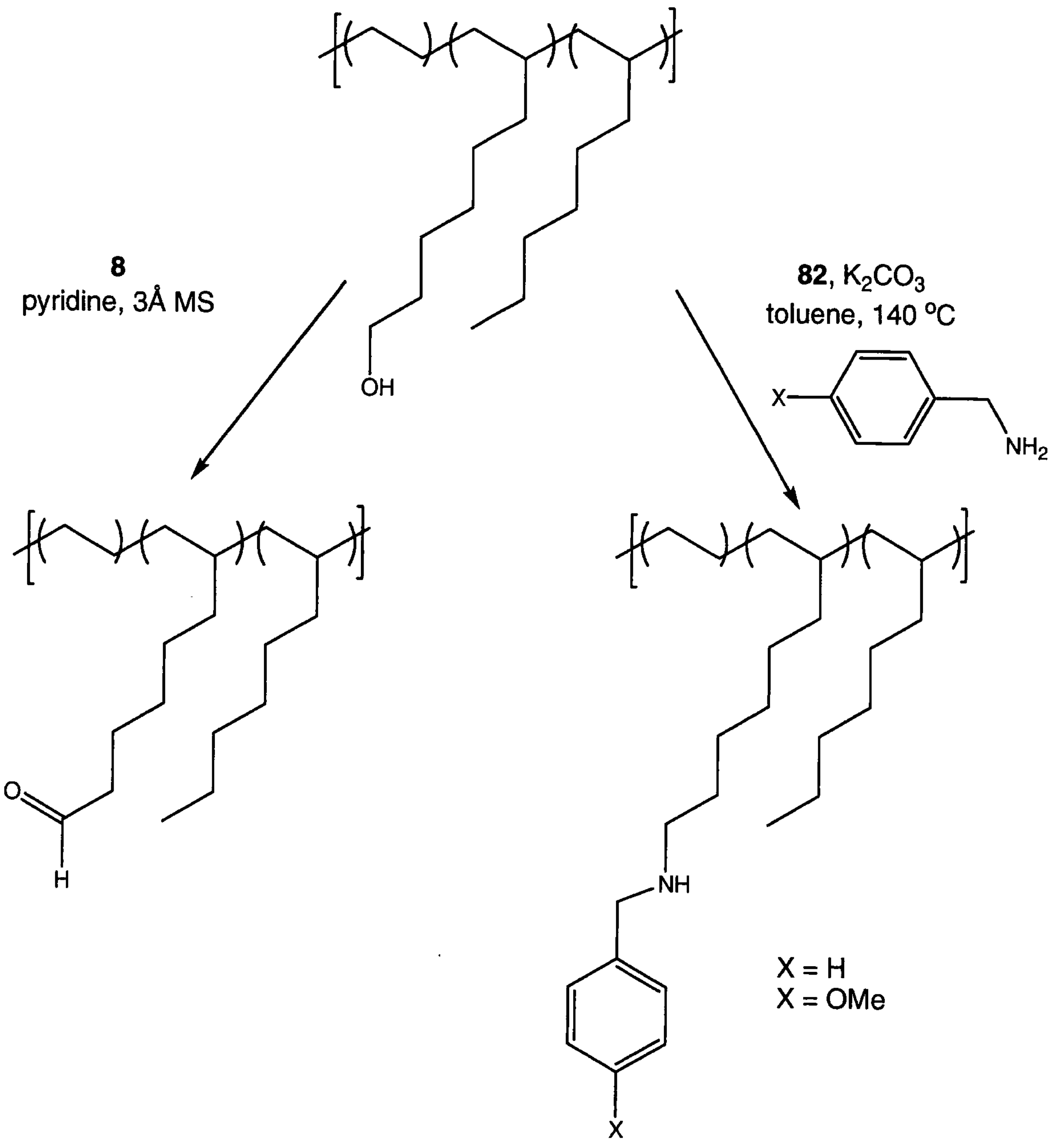
In 2005, this group reported[86] the functionalisation of the linear low density polyethylene **LLDPEs** using **1a** and HBpin in the presence of 5 mol% of various Rh catalysts such as **78** and **81**, giving the corresponding polymer with Bpin groups at the end of the side chains. The isolated Bpin-polymer was oxidized to give the corresponding alcohol with the OH groups at the end of the hexyl side chains. The reactions were carried out in cyclooctane or neat polymer at 150-200 °C (Eq. 1.7.7). The yield was 13%

of OH at the end of side chain when the boron reagent was HBpin and the catalyst was **78** and 4% with **81**. When boron reagent was **1a** and the catalyst was **78**, the yield was 34% of hydroxylated product whereas a yield of 18% was obtained with **81**.



Eq. 1.7.7 Regiospecific functionalisation and subsequent oxidation of LLDPEs

Interestingly, the final product (the hydroxylated polymer) was converted into materials with formyl and amino groups by **8** and $[Cp^*IrCl_2]_2$ **82** (Eq. 1.7.8).



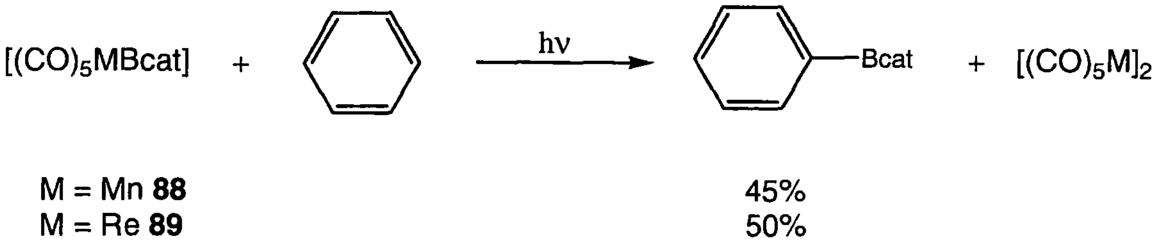
Eq. 1.7.8 Conversion of hydroxylated polymer into formyl and amino functionalised polymers

1.8 Metal Catalysed Borylation of Arenes

The earliest observation of the borylation of arenes was in 1993, when Marder *et al.*[87] noted the production of sub-stoichiometric quantities of two isomers of tolylBcat and Ar-Bcat in the synthesis of [Ir(η^6-MeC$_6$H$_5$)(Bcat)$_3$] **83** compounds from reaction [Ir(η^5-Indenyl)(COD)] **84** and excess HBcat in toluene solution. Similar observations of Ph-Bcat and C_6D_5Bcat were found when benzene or C_6D_6 were used as solvent.

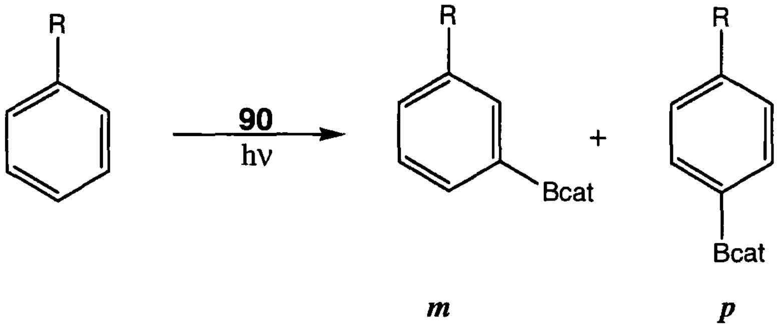
In 1995 Hartwig *et al.*[88] employed [Mn(CO)$_5$(Bcat)] **85** and [Re(CO)$_5$(Bcat)] **86** as well as [CpFe(CO)$_2$(Bcat)] **87** for the photolytic stoichiometric borylation of benzene and toluene. Reaction of **85** with benzene yielded 45% of PhBcat and reaction of **86** with toluene gave tolylBcat with *meta:para* ratio of 1.6:1, and no *ortho* product observed, whereas, the reaction with benzene yielded 50% of PhBcat. However; reaction of **87** with toluene gave tolyl Bcat with a *meta:para* ratio of 1.1:1 and no *ortho* product.

The same group also reported the photolysis of [(CO)$_5$MnBcat] **88**, [(CO)$_5$ReBcat] **89** and [CpFe(CO)$_2$(Bcat)] **90** with several arenes.[89] For the stoichiometric photolysis reactions between **88**, **89** and benzene, the yields were about 50% by NMR (Eq. 1.8.1).



Eq. 1.8.1 Reaction of **88** and **89** with benzene

Complex **90** was reacted with benzene and a series of mono substituted arenes, and was found to be more reactive than the other complexes. For example, the reaction with benzene gave 100% of the product. In addition, all of the reactions gave *meta* and *para* isomers; the *ortho* isomer appeared only with anisole. The reaction with *p*-xylene gave very low yields, whereas the yield was very high with toluene. Interestingly, *N,N*-dimethylaniline showed 30% conversion with a preference for reaction at the *para* position while anisole showed 52% conversion and gave three isomers. The results are summarised in Eq. 1.8.2 and Table 1.8.1.

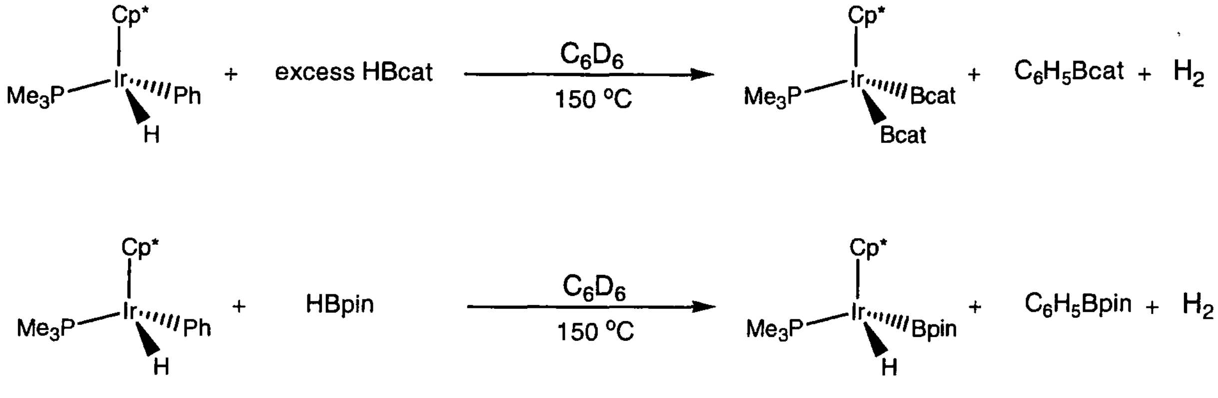


Eq. 1.8.2 C-H Activation of arenes via **90**

Table 1.8.1 Product isomer ratio from reaction of **90** with substituted arenes

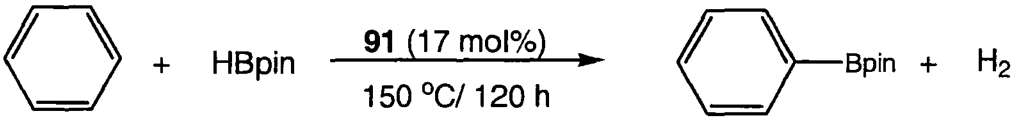
R	Product isomer ratio			Yield %
	o	*m*	*p*	
Me		1.1	1.0	70
OMe	1.0	1.6	1.1	52
Cl		1.5	1.0	55
CF_3		1.5	1.0	33
NMe_2		1.0	8.0	30

Also, in the same year, Iverson and Smith *et al.*[77] reported the stoichiometric thermal borylation of benzene using Ir complexes with HBcat and HBpin. They found, by proton NMR spectroscopy, that PhBcat or PhBpin were the major products respectively (Scheme 1.8.1).



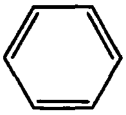
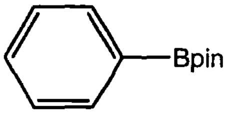
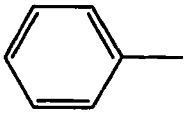
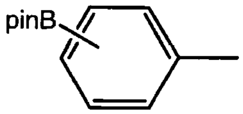
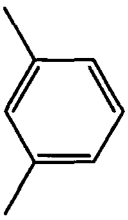
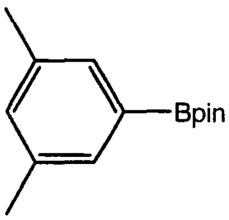
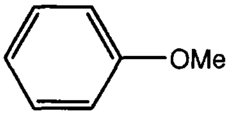
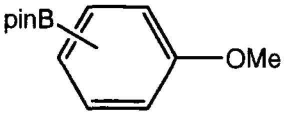
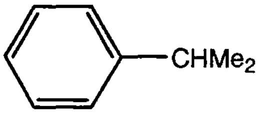
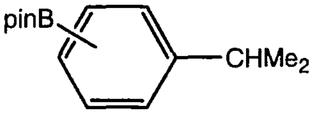
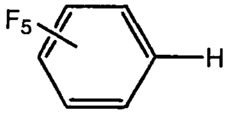
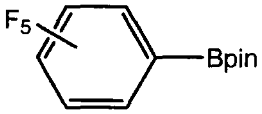
Scheme 1.8.1

In addition they reported using 17 mol% of [Cp*Ir(PMe$_3$)(H)(Bpin)] **91** or [Cp*Ir(PMe$_3$)(H)$_2$] **92** with HBpin for aromatic C-H borylation (Eq. 1.9.1). The reactions were carried out at 150 °C for 120 hours and 3 turnovers were obtained making this the first catalytic thermal borylation of arene C-H bonds. In addition, the borylation of toluene was kinetically determined, giving a statistical mixture of *meta:para* isomers (ca. 2:1). Furthermore, they found that borylation selectivity occurred at the *meta*-position for 1,3-disubstituted arenes such as 1,3-dimethylbenzene. (Table 1.8.2).



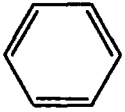
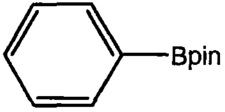
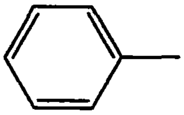
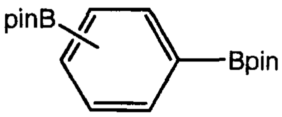
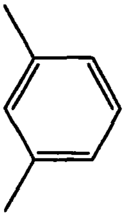
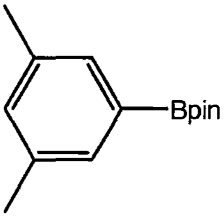
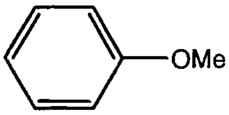
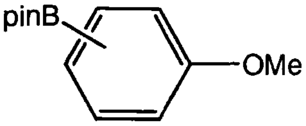
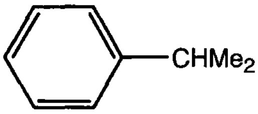
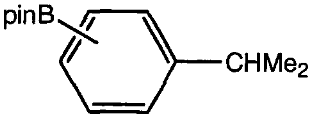
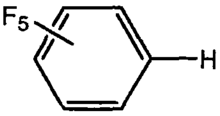
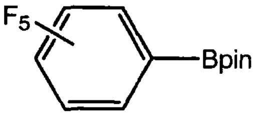
Eq. 1.8.3 C-H Activation via **91**

Table 1.8.2 C-H borylation using **91**

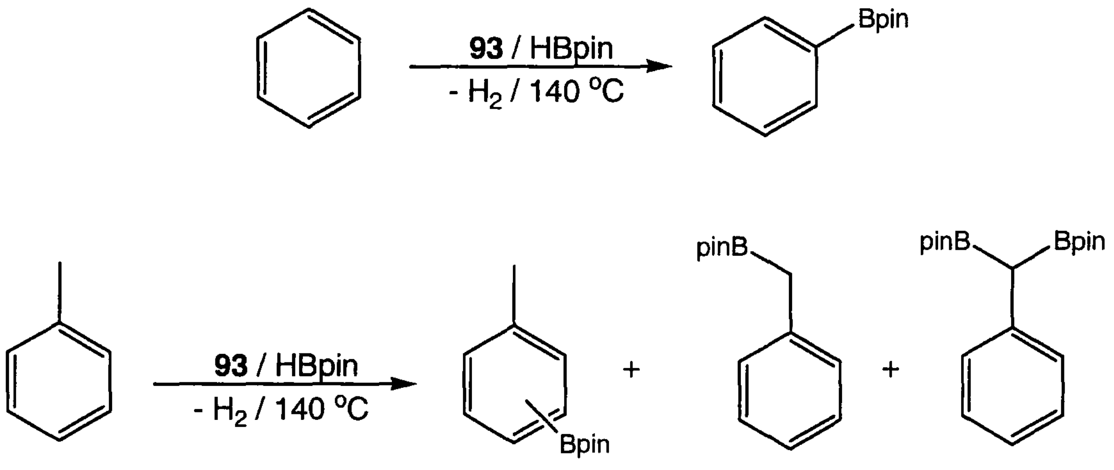
Arene	**Products**	**Yield %** (*o:m:p*)**, time**
		53, 120 h
		91 (0.12, 1.83, 1.00), 51 h
		60, 151 h
		55 (0.08, 4.06, 1), 65 h
		52 (0.03, 2.19, 1.00), 142 h
		81, 18 h

The same group also reported a related study using 2 mol% of **78** and HBpin.[83] The reactions were carried out at 150 °C and the yield ranged from 41 to 92%. They observed that benzene and *m*-xylene gave a single product while mono substituted arene such as toluene, anisole and isopropyl benzene gave three isomers with a preference for borylation at the *meta* position. The results and isolated yields are summarised in Table 1.8.3.

Table 1.8.3 Borylation of arenes catalysed by **78**

Arene	**Products**	**Yield % (*o*:*m*:*p*) / time (h)**
		92 / 2.5
		72 (0.12:1.93: 1.00) / 3.5
		73 / 4
		65 (0.30:2.63: 1.00) / 1
		67 (0.02:1.99: 1:00) / 2
		41 / 0.5

In 2001, Marder *et al.*[82] employed [Rh(Cl)(N_2)(P^iPr_3)$_2$] **93** as a catalyst for aromatic and benzylic C-H activation of benzene, toluene, *p*-xylene and mesitylene at 140 °C using HBpin. Reaction of benzene with 0.2 M HBpin and 1 mol% of **93**, gave 62% PhBpin after 14 h, and 86% after 58 h. Using (0.3 mol%) of **93**, a 67% yield of PhBpin was produced after 104 h. The effect of the concentration of HBpin was investigated and it was found that a lower concentration of HBpin can help to improve the yield. For example, the use of 1 M HBpin in benzene gave a 20% yield of PhBpin after 58 h, whereas a fourfold dilution improved the yield to 35% in the same time. Reaction with toluene gave different results. Benzylic borylation predominated over arene C-H borylation and even benzylic bis(borylation) was observed (Scheme 1.8.3). The reaction with *p*-xylene and mesitylene also gave benzylic activation products. In addition, no alkane activation was observed and the reaction using **1a** was ineffective (Table 1.8.3).



Scheme 1.8.3 Arene and benzylic activation of benzene and toluene

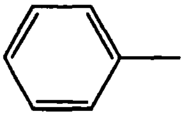
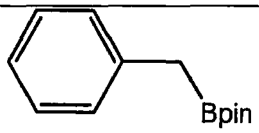
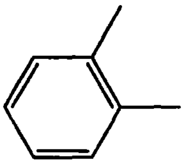
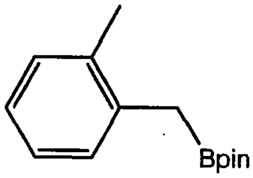
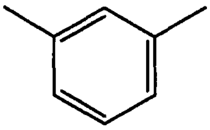
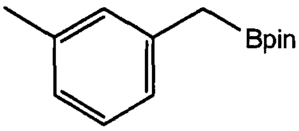
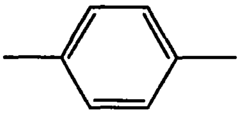
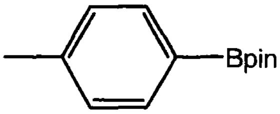
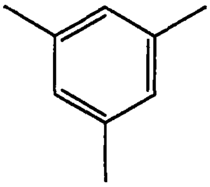
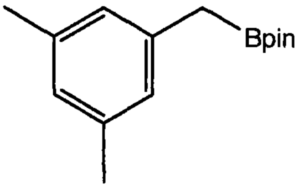
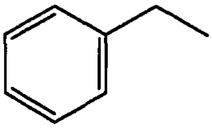
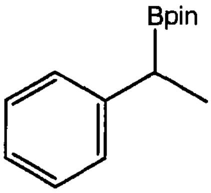
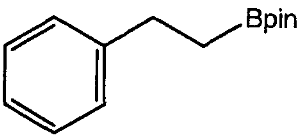
Table 1.8.4 Aromatic and benzylic C-H borylation catalysed by **93**

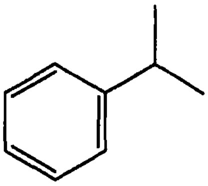
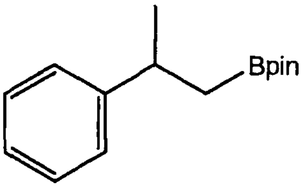
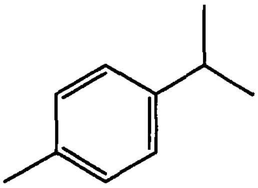
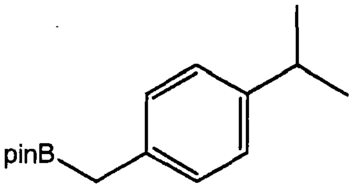
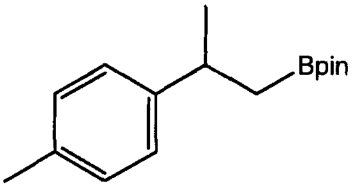
Substrate	Time (h)	Total Yield %	Product ratio $PhCH_2Bpin : 2\text{-}MeC_6H_4Bpin : 3\text{-}MeC_6H_4Bpin : 4\text{-}MeC_6H_4Bpin$
toluene	14	40	85:3:9:3
toluene	58	64	82:3:11:4
toluene	80	69	81:3:12:4
p-xylene	80	41	98:2*
mesitylene	80	17	

* Ratio of benzylic to aromatic C-H borylation

In 2001, Miyaura *et al.*[90] reported the use of 10 mol% of Pd/C as a catalyst for the reaction of HBpin and **1a** with substituted arenes at 100 °C, to yield predominantly benzylic C-H borylation products. However, ethylbenzene gave a mixture of benzylic and and terminal carbon borylation products. In addition, they found that the **1a** gave higher yields than HBpin. The results are summarised in Table 1.8.4.

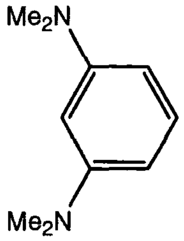
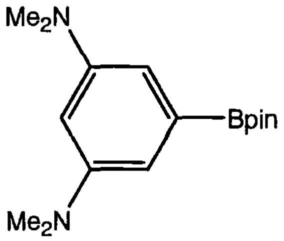
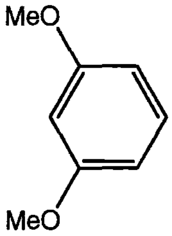
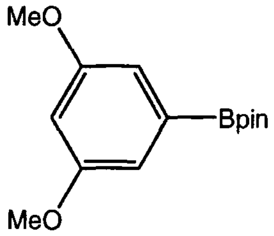
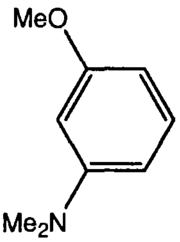
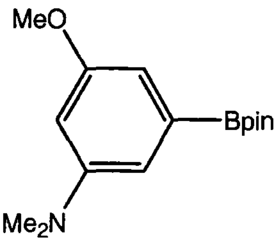
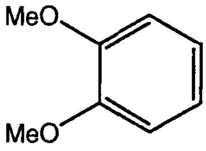
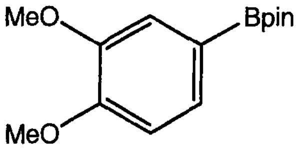
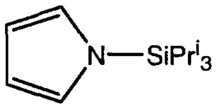
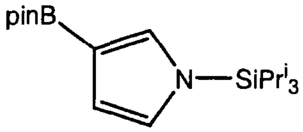
Table 1.8.5 Borylation of benzylic C-H bonds catalysed by Pd/C

Arenes	**Product**	**Yield % using B_2pin_2**	**Yield % using HBpin**
		74	52
		77	-
		79	-
		72	51
		64	45
		39	15
		15	6

		38	13
		39	42
		9	5

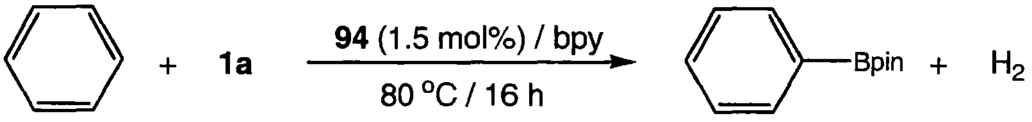
Also in the same year, Smith *et al.*[91] reported that cyclohexane could be used as an inert solvent in the reaction of disubstituted arenes and HBpin in the presence of 2 mol% of **78**. They found that the borylation took place at the 5 position of 1,3-disubstituted arenes and that it occurred at the 4-position of 1,2-disubstituted arenes (Table 1.8.6).

Table 1.8.6 Catalytic borylation of arenes in the presence of 2 mol% of **78**

Arene	Product	Yield %
		69
		62
		75
		82
		81

1.9 Ir-Catalysed Borylation of Arenes

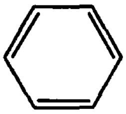
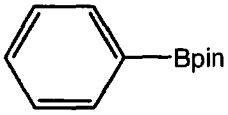
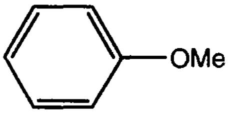
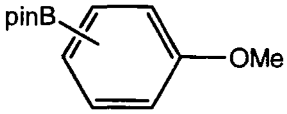
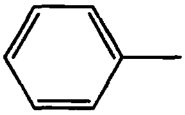
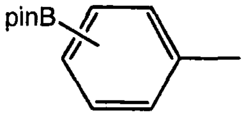
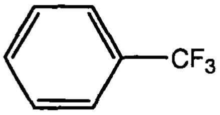
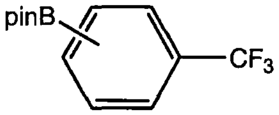
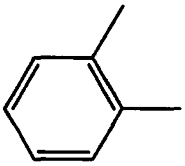
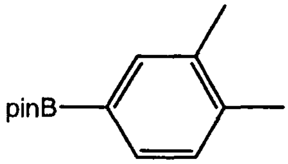
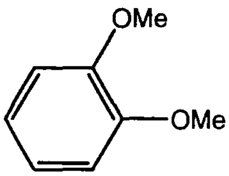
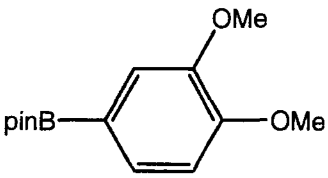
In 2002, Hartwig and Miyaura *et al.*[92] and Smith *et al.*[93] reported the use of iridium-based catalysts for arene C-H activation. Hartwig and Miyaura *et al.*[92] employed [IrCl(COD)]$_2$ **94** (1.5 mol%) with 2,2-bipyridine (bpy) and **1a** for aryl borylation. The reactions were carried out at 80 °C for 16 hours without solvent, (Eq. 1.9.1).

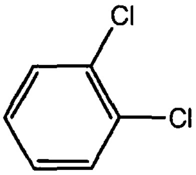
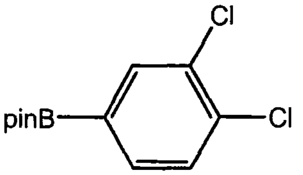
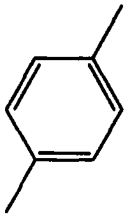
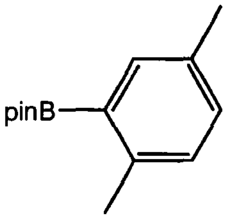
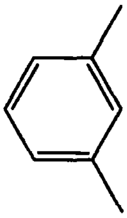
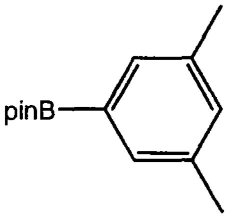


Eq. 1.9.1 C-H Arene borylation using **94**

In addition, they found that both electron-rich and electron-poor monosubstituted arenes underwent reaction to give regioisomeric mixtures of the *meta* and *para* borylation products in statistical ratios (ca. 2:1). The *ortho* isomer was not observed due to the effect of steric hindrance. In contrast, the regioselective borylation of 1,3- and 1,2-disubstituted arenes gave only one isomer, because the substituents block the ortho position, with borylation of 1,3-disubstituted arenes occurring only at the mutually *meta* position. The results are summarised in Table 1.9.1. Furthermore, they also studied the relative reactivity of electron-poor and electron-rich arenes. The reactions of an equimolar mixture of trifluoromethylbenzene and toluene, trifluoromethylbenzene and anisole as well as toluene and anisole, gave the arylboronate esters in the respective ratios of 90:10, 85:15 and 40:60. These results indicate that electron-poor arenes are more reactive than electron-rich arenes and those inductive effects are important.

Table 1.9.1 Catalysed borylation of arenes using **94** / bpy in the presence of **1a**

Arene	Products	Yield % (*o:m:p*)
		95
		95 (1: 74: 25)
		82 (0: 69:31)
		80 (0: 70: 30)
		83
		86

		83
		58
		86

Building on the results of Marder *et al.*,[87] Smith *et al.*[93] employed 2 mol% of the iridium catalysts [Ir(η^6-Mes)(Bpin)$_3$] **95** (Mes = mesitylene), and **84** with HBpin in the presence of phosphine ligands, such as PMe$_3$, dmpe (dmpe = 1,2-bis(dimethylphosphino)ethane and dppe (dppe = 1,2-bis(diphenylphosphino)ethane for arene borylation. The reactions were carried out in the presence of B$_2$pin$_2$ at 100-150 °C in neat arene. They found that the bidentate phosphine ligands showed high efficiency for the borylation reactions giving turnover numbers as high as 5000. In addition, C-H borylation was effective even in the presence of F, Cl, Br, or I groups. Again, they observed that the borylation of mono substituted arenes gave statistical mixtures of *meta:para* isomers (ca. 2:1) and that the borylation of 1,3-disubstituted arenes occurred at the mutually *meta*-position. The results are summarised in Table 1.9.2.

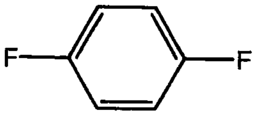
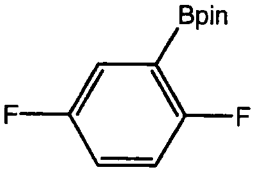
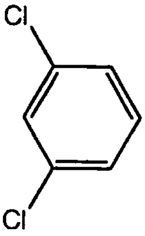
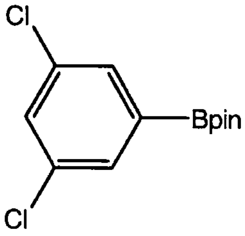
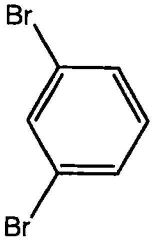
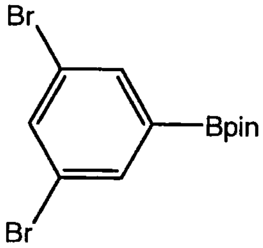
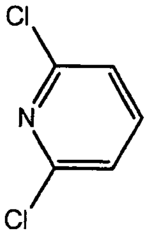
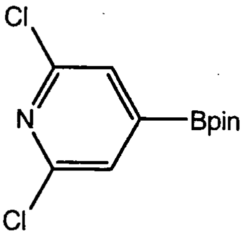
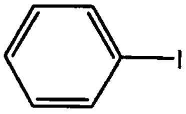
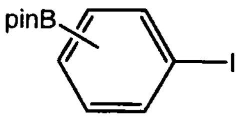
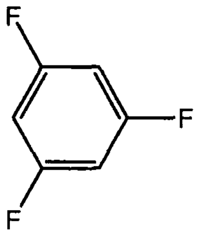
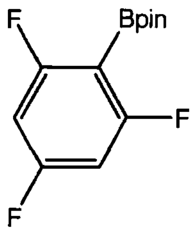
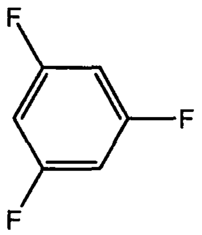
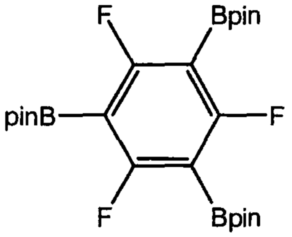
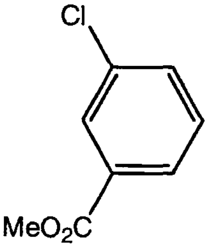
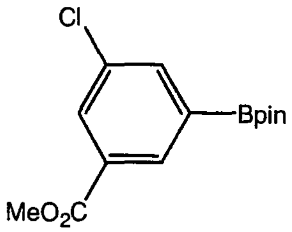
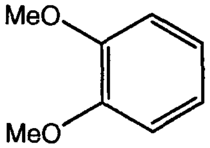
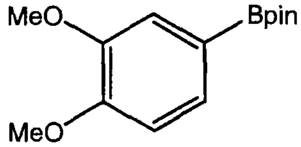
		4:1	**84**	dppe	81
		1:1.5	**84**	dppe	89
		1:1.5	**84**	dppe	92
		1:2	**84**	dppe	69
		10:1	**84**	dppe	77

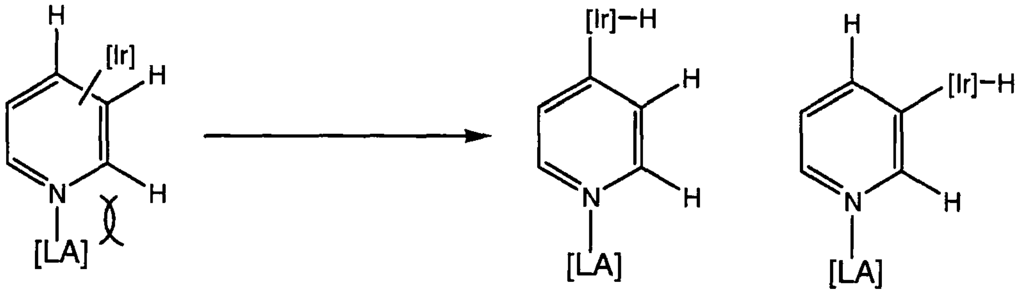
Table 1.9.2 C-H borylation of arenes using **84** / L_2 and related systems

Arene	Product	Arene:HBpin	Catalyst	Ligand	Yield %
C_6H_6	C_6H_5-Bpin	16:1	**95**	$2PMe_3$	98
C_6H_6	C_6H_5-Bpin	16:1	**84**	$2PMe_3$	88
C_6H_6	C_6H_5-Bpin	16:1	**84**	dppe	95
C_6H_6	C_6H_5-Bpin	16:1	**84**	dmpe	84
C_6H_6	C_6H_5-Bpin	16:1	0.02 mol% **84**	dmpe	90
C_6H_6	C_6H_5-Bpin	16:1	**94**	dmpe	74
		4:1	**84**	dmpe	63
		1:5	**84**	dmpe	76

		1:2	**84**	dppe	95
		1:3	**84**	dmpe	62

In 2002, Ishiyama and Miyaura *et al.*[94] reported the C-H borylation of heteroaromatic compounds with **1a** in the presence of **94** and 4,4'-di-tert-butyl-[2,2']bipyridine (dtbpy). The reactions were carried out in octane at 80-100 °C with 1.5 mol% of $[Ir(Cl)(COD)]_2$ and 3 mol% of dtbpy. Several heteroaromatic compounds were investigated as shown in Table 1.9.4. In all cases, the borylation took place at the 2-position of the five membered arenes because the heteroatom activates this position. Moreover, they found that five-membered heteroarenes such as thiophene, furan and pyrrole gave a slightly lower yield than those of benzo-fused derivatives. Additionally, octane was used as a solvent to reduce the concentration of substrates (**1a** : heteroarenes = 1:4-10).

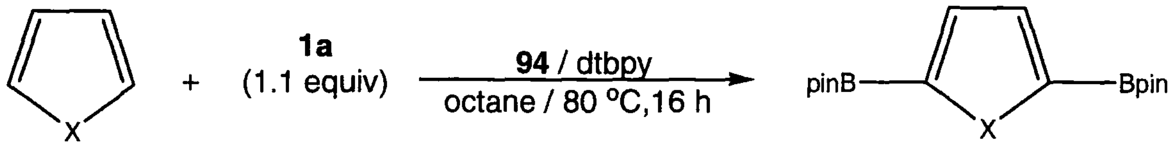
Interestingly, six-membered heteroarenes such as pyridine and quinoline showed lower reactivity and different regioselectivity than those of five membered heteroarenes. Quinoline yielded 3-borylquinoline in 84% yield, whereas, pyridine gave a mixture of 3- and 4-borylpyridine in a statistical ratio of (ca. 2:1) with a significantly lower yield 42%. Because the pyridine has a strong coordination affinity for Lewis acids (Scheme 1.9.1), it was suggested that the Ir metal centre or a B atom could bind reversibly to the basic nitrogen and that the coordination activates the pyridine ring for oxidative addition and blocks borylation at the α-position.



LA = Ir or B compounds

Scheme 1.9.1

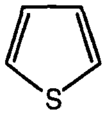
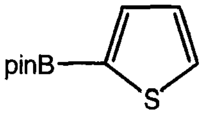
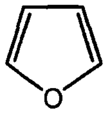
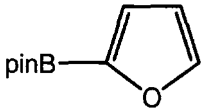
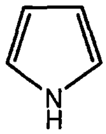
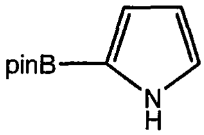
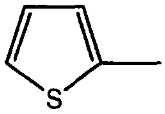
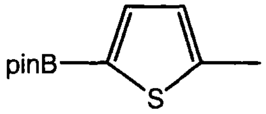
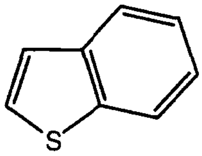
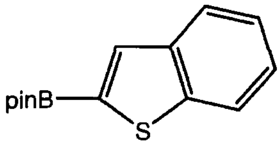
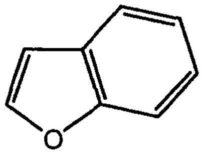
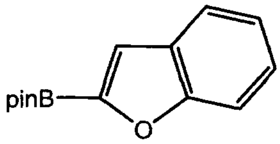
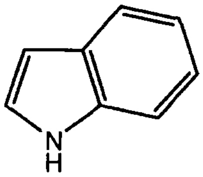
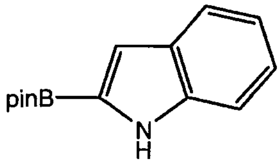
In addition, the synthesis of bis(boryl)heteroarenes has been achieved with thiophene, furan and pyrrole. All of the five-membered heteroarenes were converted to the corresponding 2,5-diborylated products with excellent regioselectivity in the presence of 1.1 equiv. of **1a** (Eq. 1.9.2).

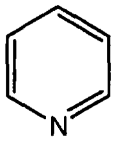
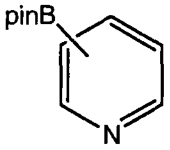
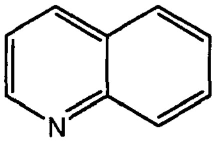
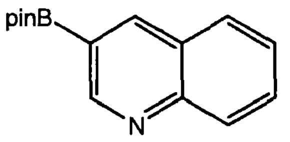


X = S 80%
O 71%
NH 80%

Eq. 1.9.2 Synthesis of 2,5-bis(boryl)heteroarenes via using **94** / dtbpy

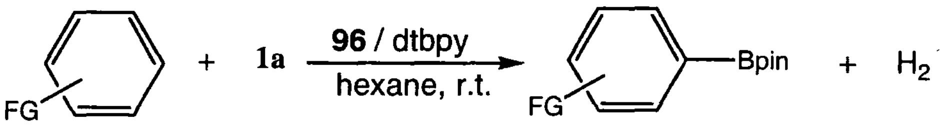
Table 1.9.3 Catalytic borylation of heteroarenes and benzo-fused heteroarenes via using **94** / dtbpy

Heteroarene (H)	Product	H : B_2pin_2	Temperature °C	Yield %
		10 : 1	80	83[a]
		10 : 1	80	83[a]
		10 : 1	80	67[a]
		10 : 1	80	91
		4 : 1	80	89
		4 : 1	80	91
		4 : 1	80	92

		2 : 1	100	42[a] (67:33)[b]
		10 : 1	100	84

[a] Diborylated products were also observed (12-17%). [b] Ratio of 3- and 4-borypyridine.

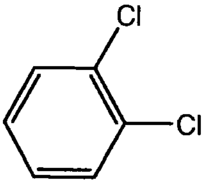
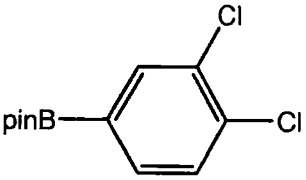
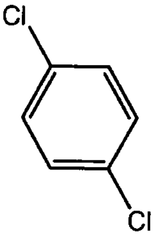
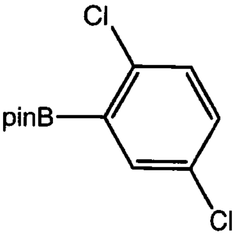
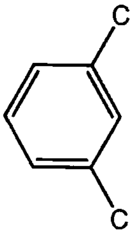
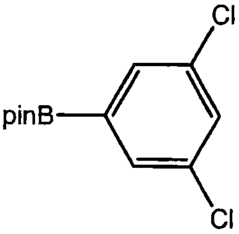
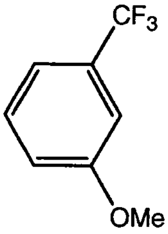
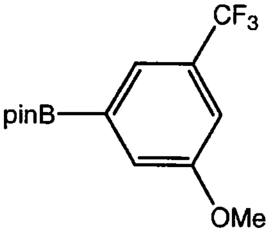
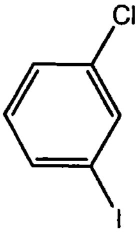
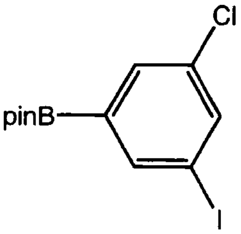
Also in the same year, Miyaura and Hartwig *et al.*[95] reported the development of catalysts that allow for the direct borylation of arenes and heteroarenes at room temperature in an inert solvent. They found that the combination of $[Ir(\mu\text{-}OMe)(COD)]_2$ **96** and dtbpy exhibited high catalyst activity at room temperature (Eq. 1.9.3).

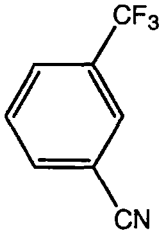
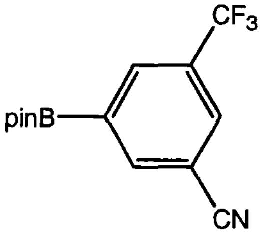
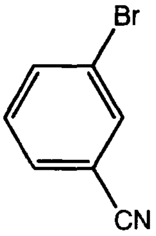
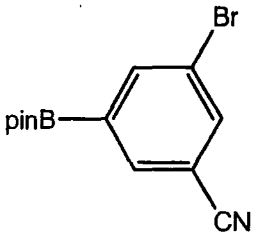
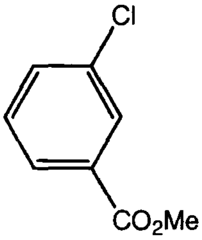
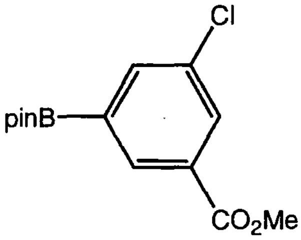
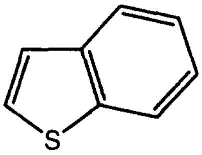
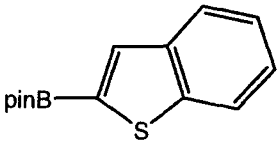
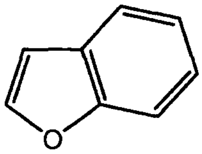
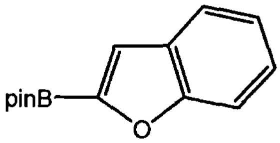
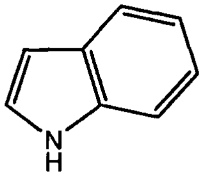
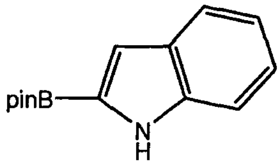


Eq. 1.9.3 Aromatic C-H borylation at room temperature

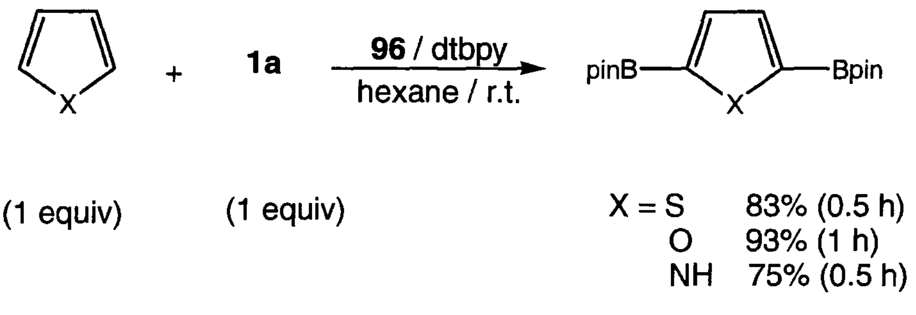
In addition, they observed that the effect of varying the anionic ligand (X) (X = OMe, OH, OPh, Cl, OAc) respectively on iridium(I) precursors $[Ir(X)(COE)_2]_2$ provides a good effect on catalyst activity, with X = OMe being the most active precursor. Moreover, the steric and electronic effects of substituents in 2,2'-bipyridine were examined. No large difference was found between the efficiency of catalysts bearing 4,4'- and 5,5'-dimethyl substituents on the 2,2'-bipyridine. In contrast, the ligands bearing 6,6'-dimethyl substituents did not promote the reaction at all due to the steric congestion around the iridium centre, whereas, the catalyst bearing 3,3'-dimethyl substituents was less active and gave only a moderate yield. They employed 1.5 mol% of **96** and 3 mol% of dtbpy with **1a** to borylate several arenes at room temperature (Table 1.9.4). The reaction conditions were suitable for a wide variety of functional groups such as Cl, Br, I, CF_3, OMe, CO_2Me and CN. Again, they found that the borylation prefers to occur at the C-H bond *para* or *meta* to a substituent and does occur readily at sterically hindered *ortho* positions. With 1,2-dichlorobenzene, the yield was 82% of a single isomer, whereas with 1,4-dichlorobenzene the borylation can only occur at a carbon *ortho* to a substituent, giving only 53% conversion, due to the steric hindrance of the substituent. They also observed that the borylation of 1,3-dichlorobenzene only occurred at the common *meta* position. Moreover, they found that the borylation of benzo-fused 5-membered hetroaromatics in hexane occurred selectivity at the 2-position because the C-H bond at the 2-position is activated by the heteroatom.

Table 1.9.4 C-H borylation of arenes and Benzo-Fused heteroarenes using **96** / dtbpy

Arene	Product	Time h	Yield %
		8	82
		24	53
		2	84
		8	81
		4	82

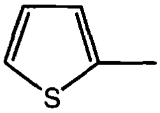
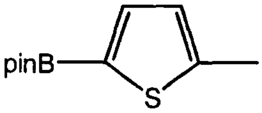
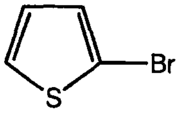
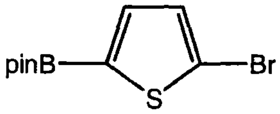
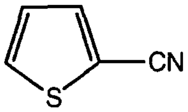
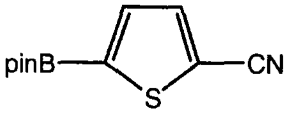
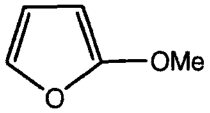
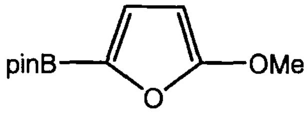
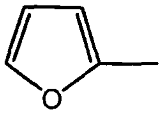
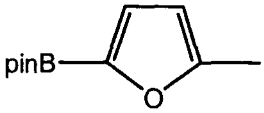
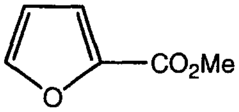
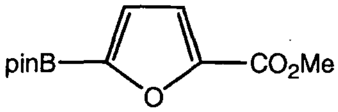
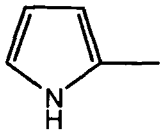
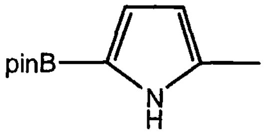
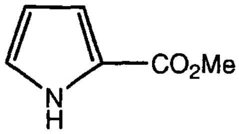
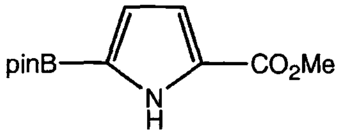
		2	84
		2	83
		8	80
		2	81
		4	83
		0.5	88

In 2003, Ishiyama and Miyaura *et al.*[96] developed an efficient method for the borylation of 5-membered heteroarenes at room temperature with equimolar amount of diboron reagents and heteroarenes. The reactions were catalysed by a combination of dimer **96** (1.5 mol%) and dtbpy (3 mol%) with 1 mmol of **1a** in 6 ml of hexane at room temperature. They observed that the electronegative heteroatom activates the C-H bonds at the α-position allowing regioselective borylation this position. The results are summarised in Table 1.9.5. Thiophene, pyrrole and furan were converted into 2,5-bis(boryl)heteroarenes at room temperature, with excellent yields and regioselectivities (Eq. 1.9.4).

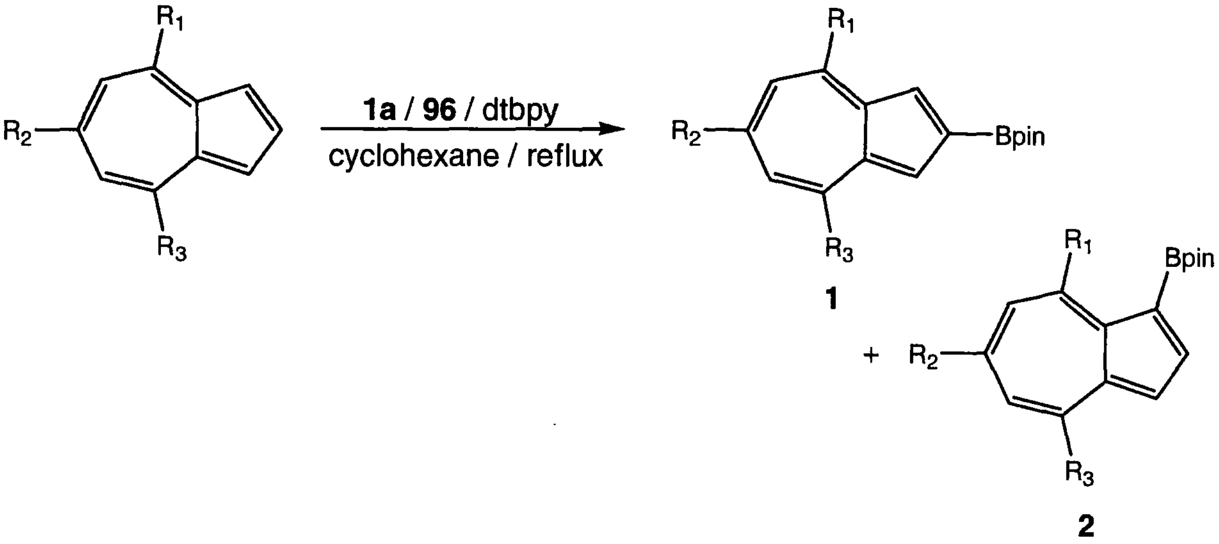


Eq. 1.9.4 Synthesis of 2,5-bis(boryl)heteroarenes

Table 1.9.5 Borylation of 5-membred heteroarenes at room temperature using **96** / dtbpy

Heteroarene (H)	Product	H : B_2pin_2	Time h	Yield %
		2 : 1	2	95
		2 : 1	2	91
		2 : 1	24	60
		2 : 1	2	90
		2 : 1	2	85
		2 : 1	2	80
		2 : 1	1	96
		2 : 1	1	99

In 2003, Murafuji and Sugihara *et al.*[97] reported the borylation of the 2-position of substituted azulenes using the Miyaura methodology.[96] The reactions were catalysed by **96** and dtbpy with **1a** in cyclohexane at reflux (Eq. 1.9.5). The yields ranged between 24% and 70%.

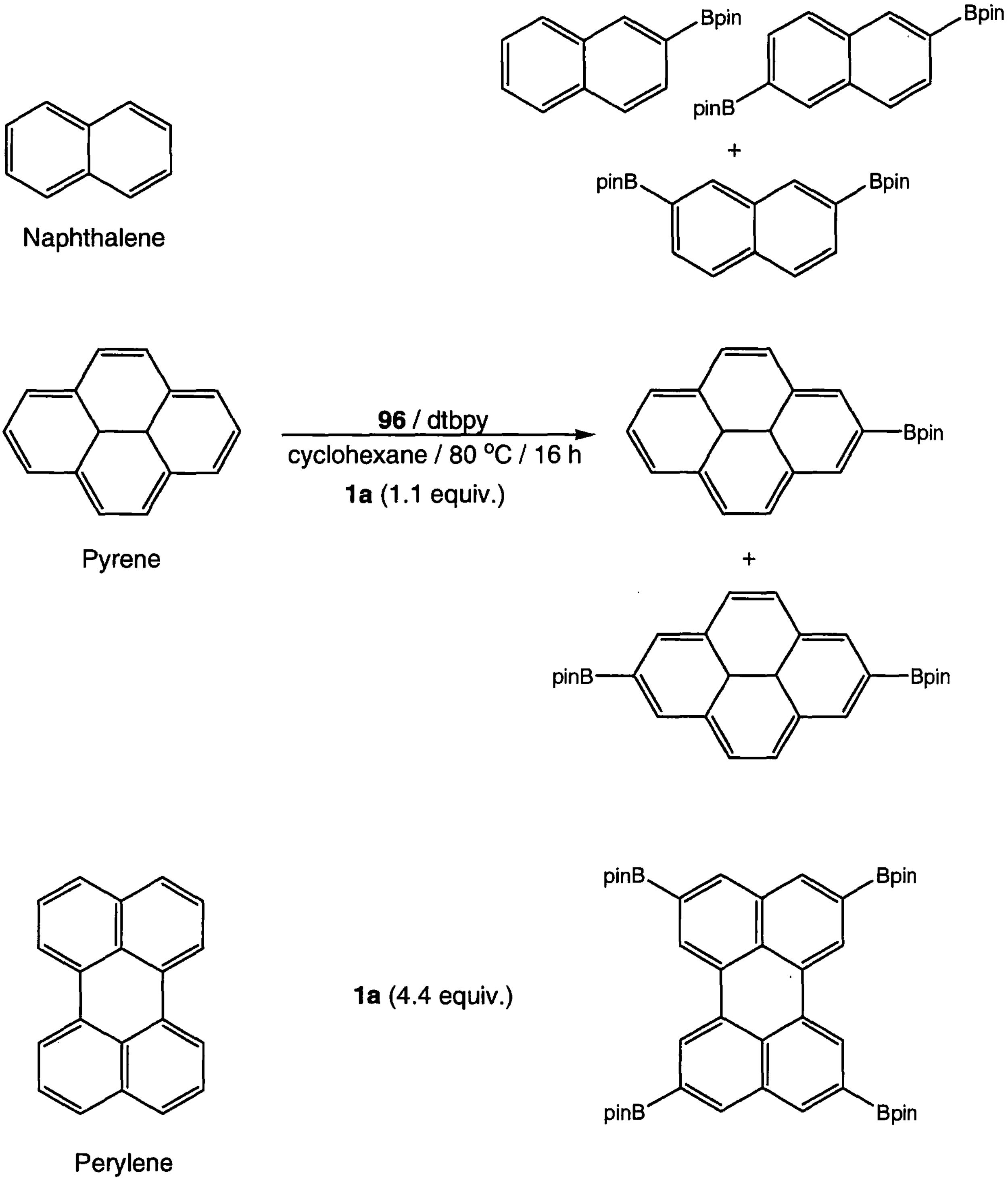


R_1, R_2, R_3 = H 70% (**1**) 10% (**2**) (14 h)
R_1, R_2, R_3 = Me 32% (**2**) (24 h)

Eq. 1.9.5 Synthesis of borylazulene

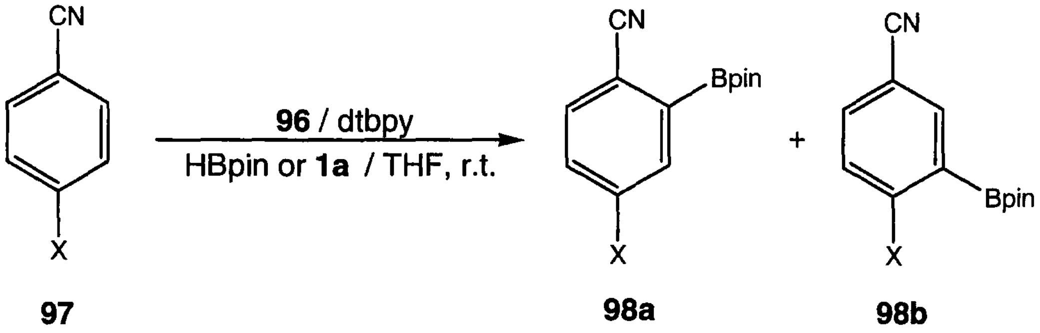
Interestingly, Plenio *et al.*[98] also reported an application of the Miyaura methodology[96] to borylate ferrocenes and half-sandwich compounds. The reactions were carried out in octane with 0.5 equiv. of **1a** and were catalysed by combination of **96** and dtbpy at 126 °C for 24 hours. The yields ranged between 35-83%.

Recently, Marder *et al.*[99] reported the borylation of polycyclic aromatic hydrocarbons. They proved that the borylation of C-H bonds avoids positions *ortho* to a ring junction when other sites are available. Naphthalene and pyrene as well as perylene were reacted with 1.1 equiv. of **1a** in the presence of **96** (5 mol%) and dtbpy (10 mol%) in cyclohexane at 80 °C for 16 hours (Eq 1.9.7). They found that the borylation of naphthalene produced a mixture of one monoboryl (49%) and two bis(boryl)naphthalene isomers (22%). The boryl group of the monoboryl product was found by NMR spectroscopy to be at the 2-position. The two bis(boryl) products were shown by NMR spectroscopy to be 2,6- and 2,7-bis(boryl)naphthalenes in nearly equal amounts. Interestingly, increasing the concentration of **1a** to 2.2 equiv. gave only the two bis(boryl)naphthalenes in 93% overall yield. Reaction of pyrene with 1.1 equiv. of **1a** yields 68% and 6% of monoboryl pyrene and bis(boryl)pyrene respectively. Increasing the concentration of **1a** to 2.2 equiv. yielded only 2,7-bis(boryl)pyrene in 97% yield which characterized by X-ray diffraction. The reaction of perylene under the same conditions gave a complicated mixture containing monoboryl perylene, three isomer of bis(boryl)perylene, one isomer of tris(boryl)perylene and one isomer of tetrakis(boryl)perylene. Increasing the concentration of **1a** to 4.4 equiv. yielded 2,5,8,11-tetrakis(boryl)perylene as the major product in 83% yield, which was characterised by X-ray diffraction.



Eq. 1.9.6 Borylation of polycyclic aromatic hydrocarbon compounds

As discussed previously, the borylation of substituted arenes tends to avoid positions *ortho* to any substituent. However, Smith *et al.*[100] reported that the borylation of 1,4-disubstituted arenes can occur with a good regioselectivity and in good yields. They studied the borylation of 4-halobenzonitriles and found that the C-H borylation occurs predominately at the position adjacent to the cyano group, if the 4-substitutent is larger than the cyano group and in the opposite sense if the 4-substitutent group is smaller than the cyano group. For example, the borylation of 4-fluorobenzonitrile gave a 71% yield with 8% selectivity for **98a** product and 92% selectivity for **98b**, which means that the cyano group is bigger than the fluorine group. In contrast, the iodide group gave a 70% yield with 99% selectivity for **98a** product and 1% for **98b** product which means that the cyano group is smaller than the iodide group. Several 1,4-disubstituted arenes were examined THF with HBpin or **1a** in the presence of **96** (1.5 mol%) and dtbpy (3 mol%). All results are summarised in Scheme 1.9.2 and Table 1.9.6.



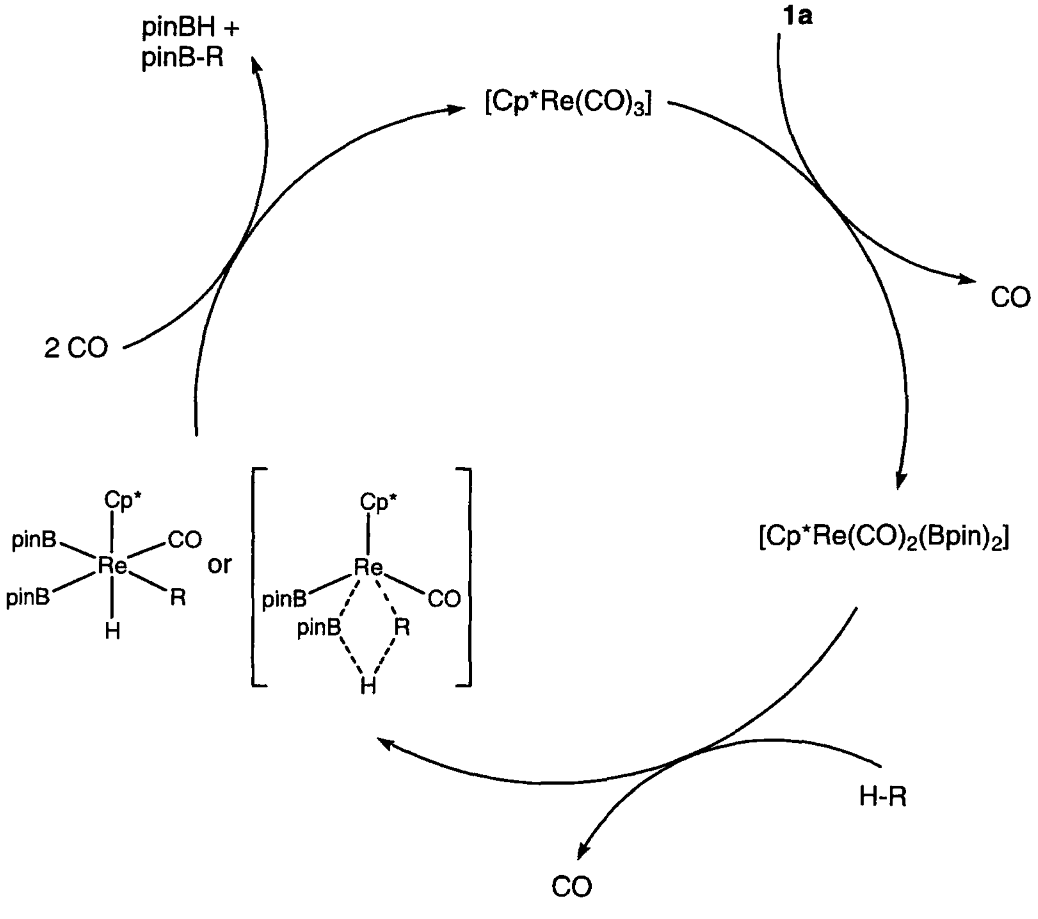
Scheme 1.9.2

Table 1.9.6 Borylation of 4-substituted benzonitriles using **96** / dtbpy

97-X	**Borane (equiv.)**	**Time h**	**Yield %**	**%98a:%98b**
F	HBpin (0.25)	8	71	8:92
Cl	HBpin (0.25)	36	76	81:19
Br	HBpin (0.25)	48	73	97:3
I	B_2pin_2 (1.0)	40	70	99:1
CH_3	HBpin (0.25)	72	64	92:8
OMe	HBpin (0.25)	24	65	67:33
SMe	B_2pin_2 (0.25)	18	55	87:13
NMe_2	B_2pin_2 (1.0)	72	58	99:1
CO_2Me	B_2pin_2 (0.8))	48	65	99:1
NHAc	B_2pin_2 (1.6)	18	62	99:1
CF_3	HBpin (1.1)	24	68	99:1

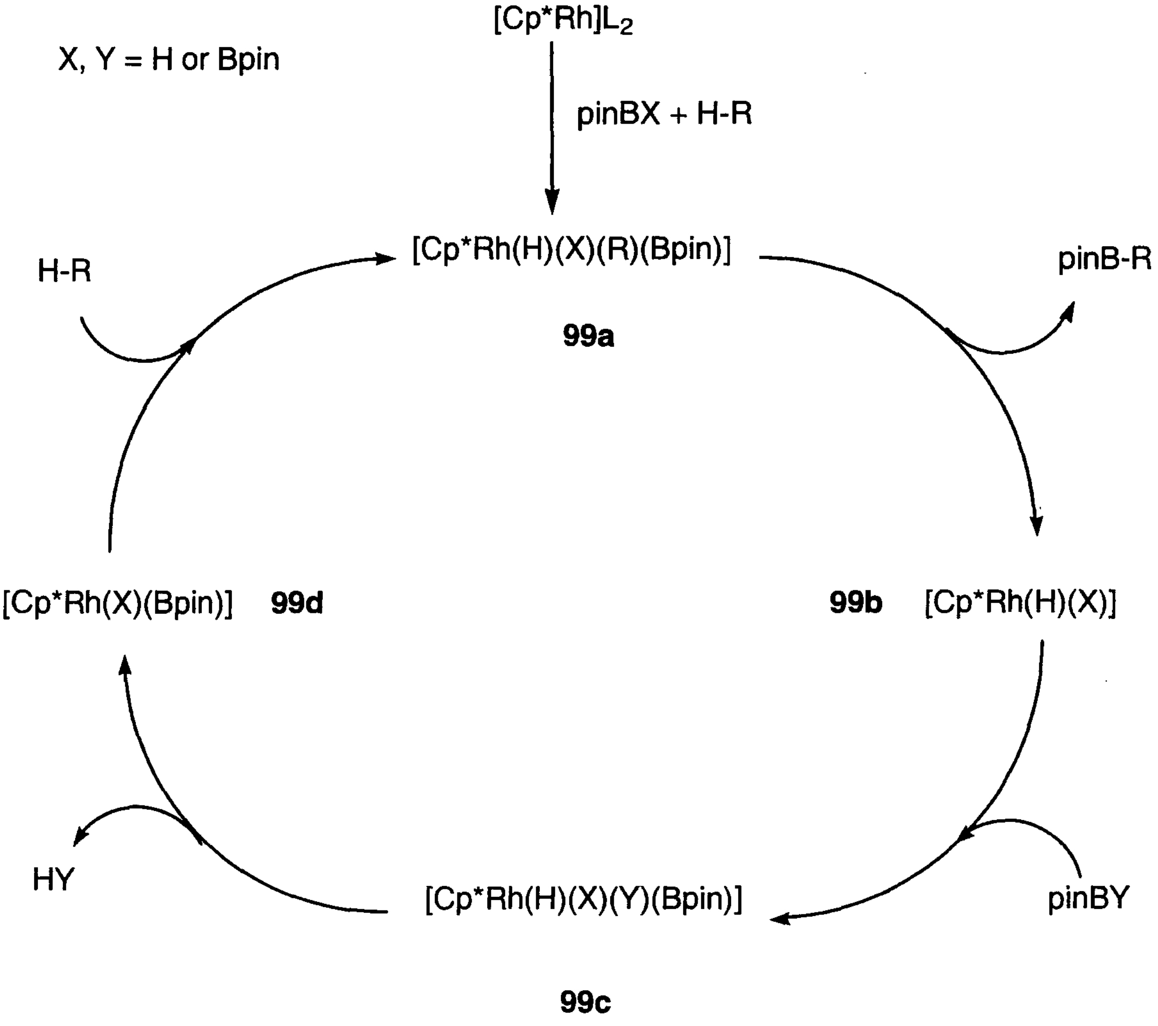
1.10 Proposed Mechanism for the Borylation of Alkanes and Arenes

In 1999, Hartwig *et al.*[80] proposed a mechanism for aliphatic C-H borylation, which involves oxidative addition of **1a** to **77** with dissociation of CO to form [Cp*Re(CO)$_2$(Bpin)$_2$]. This is followed by oxidative addition of an alkane C-H bond to form Re(V) or by σ-bond metathesis involving Re^{III} with dissociation of CO, and finally reductive elimination of the borylation product with association of CO to regenerate the catalyst (Scheme 1.10.1). In addition, a theoretical study by the same group suggested that the formation of the B-C bond occurs through a σ-bond metathesis followed by elimination of borylated product, which is thermodynamically favorable.[101]



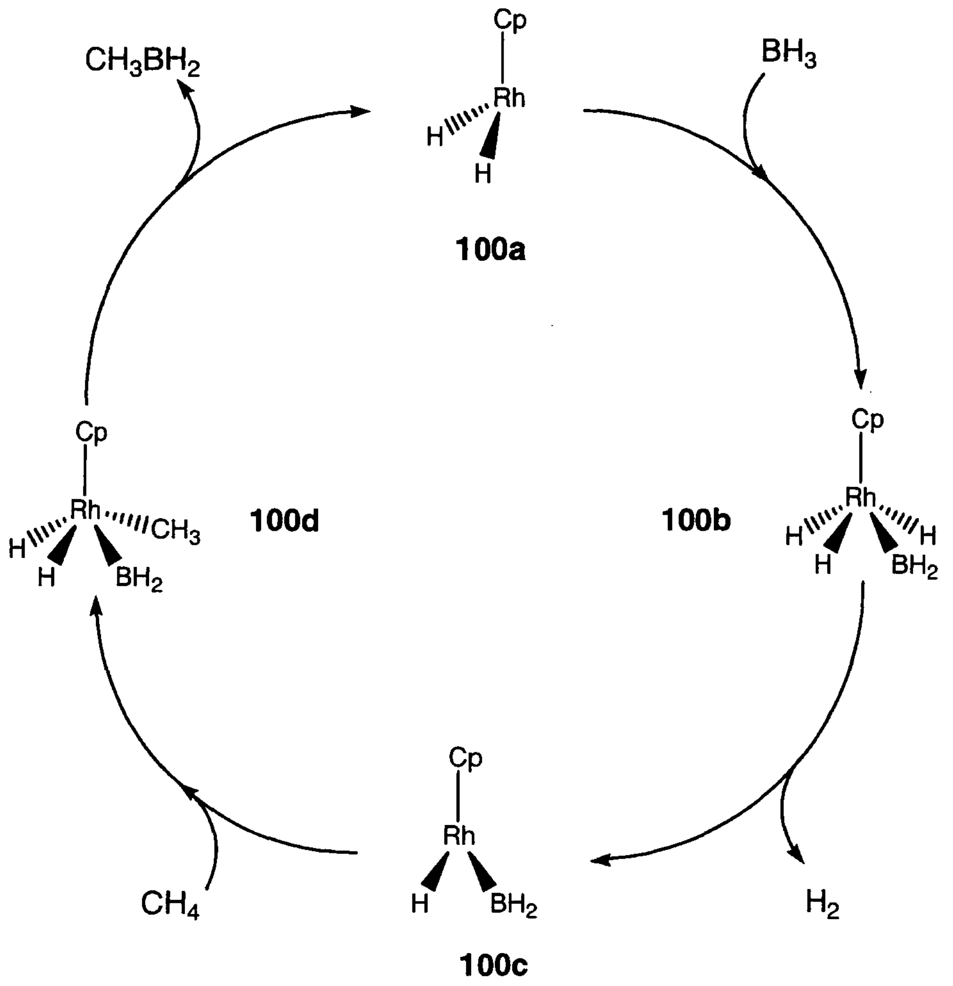
Scheme 1.10.1

In 2000, Hartwig *et al.*[81] reported a proposed mechanism for the borylation of alkanes by complex **78**. They suggested that precatalyst **78** loses the hexamethylbenzene ligand to form the intermediate [Cp*Rh(H)$_2$(Bpin)$_2$] V, which is the active species for the catalytic reaction. The mechanism involves an oxidative addition for HBpin or **1a** to form the hydridorhodium boryl complex or bis(boryl)Rh(V) complex After reductive elimination of H_2 or HBpin to create a vacant site, the complex could react with alkane rapidly giving Rh(V) complex **99a** leading to the borylation product. An oxidative addition of HBpin or **1a** to Rh(III) complex **99b** gave the intermediate **99c**, followed by reductive elimination of HBpin or H_2 to form **99d**, and then oxidative addition of alkane intermediate **99a**, which reductive elimination to form the borylation product regenerating the active species, **99b** (Scheme 1.10.2).



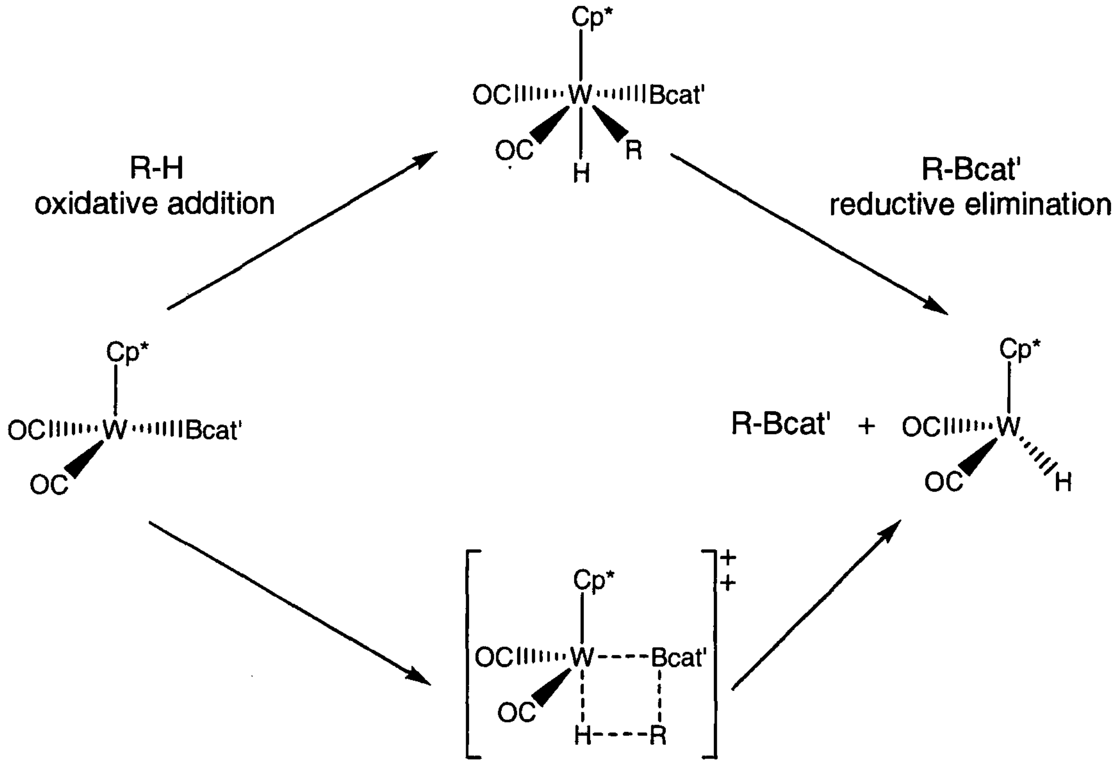
Scheme 1.10.2

The mechanism was examined by Miyamoto *et al.*[102] in a theoretical study employing BH_3 in place of HBpin Scheme 1.10.3. They found that the borylation reaction pathways proceed by oxidative addition of BH_3 to **100a**, formation of the reactive boryl complex **100c** by elimination of H_2 from the trihydride complex **100b**, then oxidative addition of alkane to form the alkyl boryl dihydride complex **100d**, and finally, reductive elimination to form the borylated product regenerating **100a**.



Scheme 1.10.3

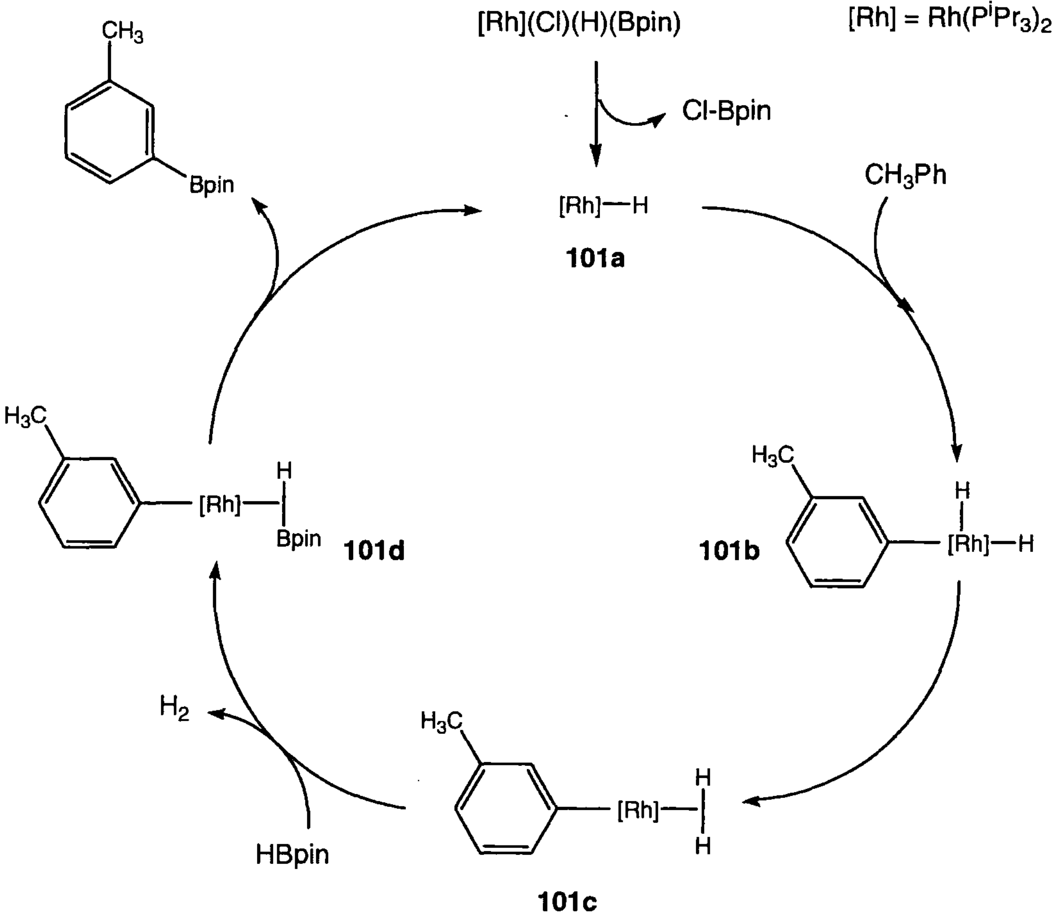
In 2003, Lin *et al.*[103] reported a theoretical study of the mechanism of methane and benzene functionalisation borylation by **71** and **72**. They found that the Fe complex is reactive towards aromatic C-H bonds and unreactive towards alkane C-H bond activation. The proposed mechanism involves oxidative addition of alkane to form an 16-electron Fe(IV) complex followed by reductive elimination to give the borylation product and metal hydride [Cp*Fe(CO)$_2$(H)]. By contrast, the W complex was reactive for both alkane and arene C-H bonds. The mechanism may involve two possible pathways. One possibility is an oxidative addition of the alkane to form the 18-electron W(IV) complex, followed by reductive elimination to form the borylation product and metal hydride [Cp*W(CO)$_2$(H)]. The other possibility is a one-step mechanism which involves a σ-bond metathesis via a four-centre transition state (Scheme 1.10.4). Both possible mechanisms are acceptable for the early transition metal system.



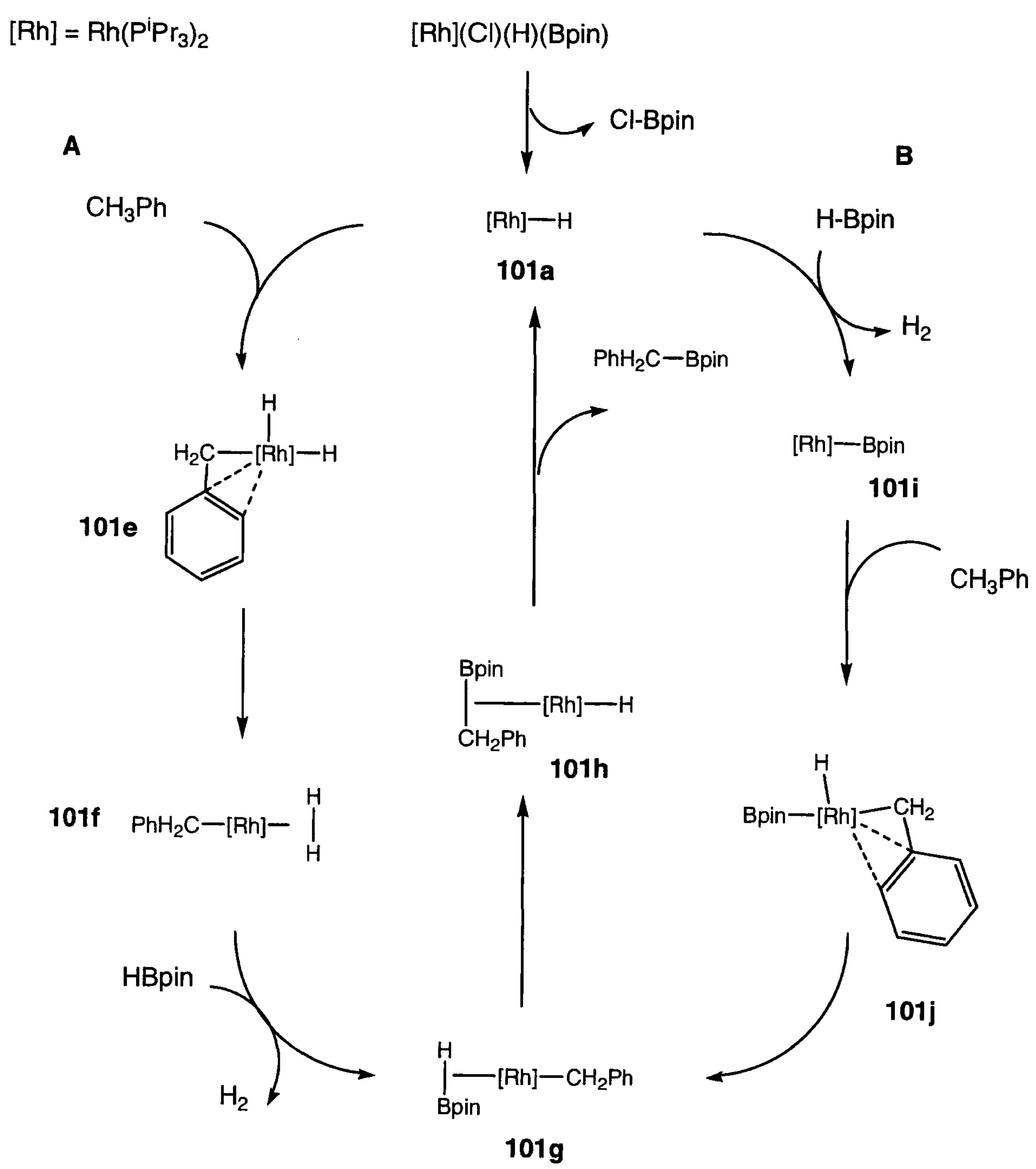
Scheme 1.10.4

Moreover, they found that the [Rh(PR_3)$_2$H] is the active species leading to an η^3-benzyl complex which is the key step for the C-H benzylic activation. In addition, they suggested that the mechanism could consist of two possible pathways (Scheme 1.10.6). In path **A**, oxidative addition of the C-H benzylic to give an η^3-benzyl intermediate {[Rh](H)$_2$(η^3-CH_2Ph)]} **101e** is followed by a reductive coupling of the two metal hydrides to form an η^2-H_2 σ-complex **101f**, and elimination of the dihydrogen ligand by coordination of HBpin to give σ-borane complex [Rh](CH_2Ph)$_2$(η^2-H-HBpin] **101g** and finally, reductive elimination of the borylation product from intermediate **101h** to form PhH_2C-Bpin regenerating the active species **101a**. In path **B**, the first step is coordination of the HBpin to the [Rh(PR_3)$_2$H] complex to form the σ-borane complex {[Rh](H)(η^2-H-Bpin)} **101i**, which undergoes oxidative addition of B-H and reductive elimination of H_2 to give Rh$^{(I)}$-boryl complex. The next step is C-H bond activation of toluene {[Rh](H)(Bpin)} to form the {[Rh](H)(Bpin)(η^3-CH_2Ph)]} **101j**, which could also lead to **101g**. The final step is the reductive elimination of the borylation product to form PhC H_2-Bpin regenerating the active species **101a**. The calculations suggest that path **A** predominates the important point is that the C-H addition takes place from the rhodium hydride rather than the rhodium boryl complex as the very strong *trans* influence of the boryl ligand makes coordination of C-H bond *trans* to it very unfavorable.

In 2004, Marder *et al.*[104] reported a theoretical study for the mechanism reaction of the rhodium phosphine catalysed borylation of arenes and methyl substituted arenes. They suggested that the arene C-H bond undergoes oxidative addition to a Rh hydride complex to give the intermediate $\{[Rh](H_2)(C_6H_4\text{-3-Me})\}$ followed by a reductive coupling of the hydrides to form an η^2-H_2 σ-complex **101b**. Substitution of the η^2-H_2 ligand by HBpin in the intermediate **101c** gives $\{[Rh](C_6H_4\text{-3-Me})(\eta^2\text{-H-Bpin})\}$ **101d** Finally, B-H oxidative addition and elimination of the borylated product, 3-Me-C_6H_4Bpin, from **101d** regenerate the catalysts **101a**, Scheme 1.10.5.

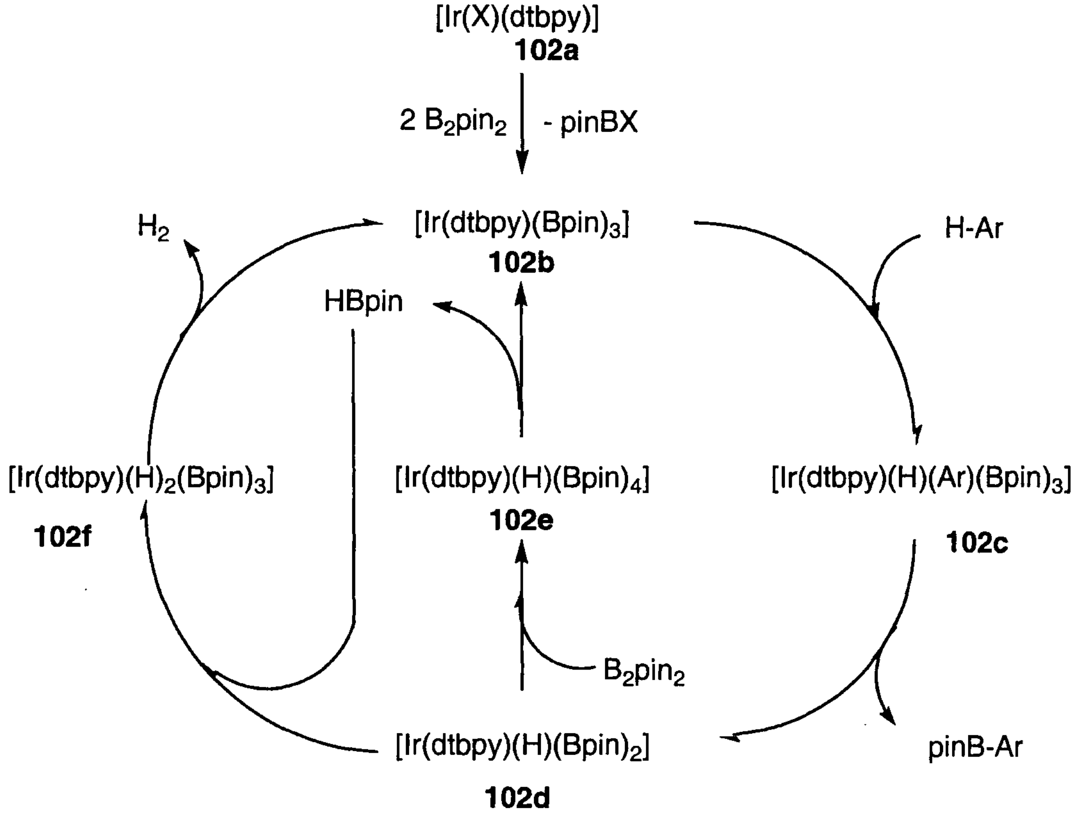


Scheme 1.10.5


[Rh] = Rh(P^{i}Pr$_3$)$_2$
[Rh](Cl)(H)(Bpin)
Cl-Bpin
A
B
CH$_3$Ph
[Rh]—H
101a
H-Bpin
H$_2$
PhH$_2$C—Bpin
101e
[Rh]—Bpin
101i
CH$_3$Ph
Bpin
[Rh]—H
CH$_2$Ph
101h
101f
PhH$_2$C—[Rh]—
H
H
Bpin—[Rh]
CH$_2$
101j
HBpin
H$_2$
H
[Rh]—CH$_2$Ph
Bpin
101g

Scheme 1.10.6

It had been suggested by Miyaura *et al.*[92] that [Ir(dtbpy)(Bpin)$_3$] could be an intermediate in the catalytic process, related to other isolated tris(boryl)Ir(III) complexes.[87,93] The proposed mechanism may involve reaction of **1a** with Ir(I) complex [Ir(X)(dtbpy)] to generate the tris(boryl)Ir(III) intermediate **102b**, followed by oxidative addition of the arene to yield Ir(V) species **102c**, then reductive elimination of a borylarene to give a bis(boryl)Ir(III)(H) complex **102d**. This intermediate undergoes oxidative addition of B_2pin_2 and reductive elimination of HBpin to regenerate the tris(boryl)Ir(III) complex **102b** (Scheme 1.10.7).[90] The proposed pathways had been supported by experimental mechanistic studies as well as a theoretical study (*vide infra*).[105,106]



Scheme 1.10.7

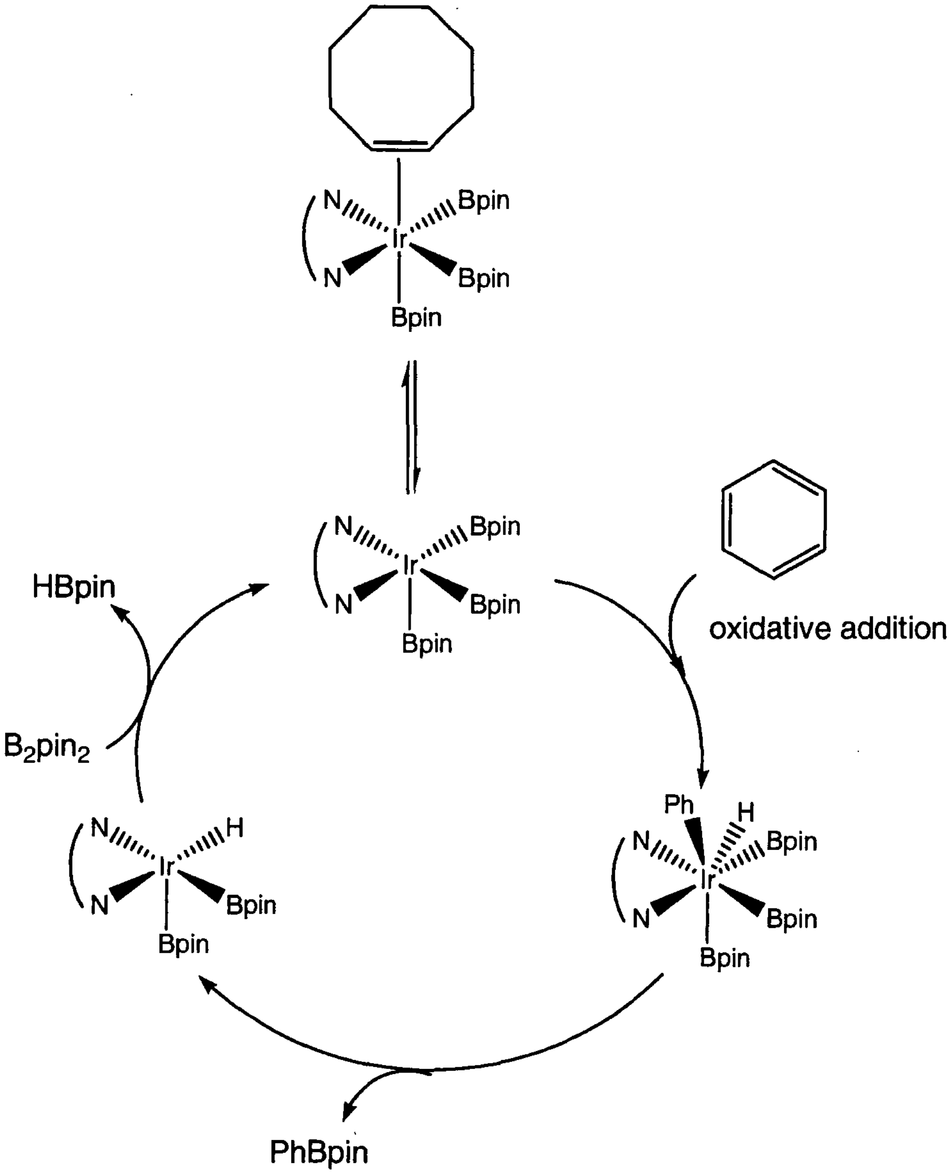
In 2003, Sakaki *et al.*[105] reported a theoretical study of the mechanism of the iridium-catalysed borylation of benzene, which supports the previous proposal.

They found that the tris(boryl)iridium(III) complex [Ir(bpy)(Bpin)$_3$] is the active species. The C-H bond of benzene was added to the above complex by oxidative addition to form the Ir(V) complex [Ir(bpy)(H)(Ph)(Bpin)$_3$] which is the key step. Reductive elimination gave the borylation product and bis(boryl)hydride iridium(III) complex [Ir(bpy)(H)(Bpin)$_2$]. Again, a reaction takes place between the diboron reagent **1a** and [Ir(bpy)(H)(Bpin)$_2$] to form HBpin and the active species [Ir(bpy)(Bpin)$_3$]. In addition, after complete consumption of **1a** the [Ir(bpy)(H)(Bpin)$_2$] will react with HBpin to form H_2 and regenerate the active species [Ir(bpy)(Bpin)$_3$].

Moreover, they noted several factors which make the catalytic reaction successful. One is the used of **1a** giving Bpin ligand which are exceptionally strong σ-bonds which can thus stabilise the iridium(V) complex, and secondly, the bpy ligand is a strong electrons donor which also helps to stabilise the high oxidation state of the metal. Also, the structure of bpy is planar, minimising steric hindrance seven-coordinate Ir(V) intermediate **102c**.

In addition, since the seven-coordinate, Ir(V) complex is very hindered, borylation at less hindered aromatic C-H bonds is favored.

In 2005, Hartwig *et al.*[106] reported experimental studies which support the above mechanism. They isolated the species [Ir(COE)(dtbpy)(Bpin)$_3$] (COE = cyclooctene) in high yield by reacting **96** with dtbpy, COE and HBpin. A kinetic study shows that this complex [Ir(COE)(dtbpy)(Bpin)$_3$] reacts with arenes after reversible dissociation of COE. This is apparently followed by cleavage of C-H bond arenes by oxidative addition and then reductive elimination to form the borylation product and regenerating of the active species (Scheme 1.10.8).



Scheme 1.10.8

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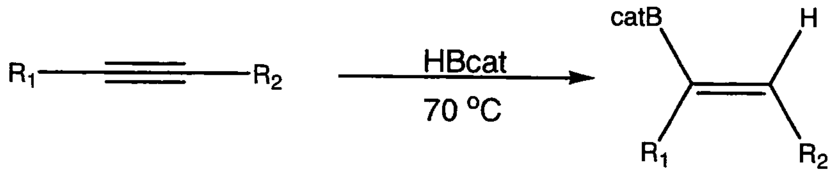
Trans-[RhCl(CO)(PPh$_3$)$_2$]-Catalysed Dehydrogenative Borylation of Vinylarenes, 1,1-Disubstituted Alkenes and other Alkenes

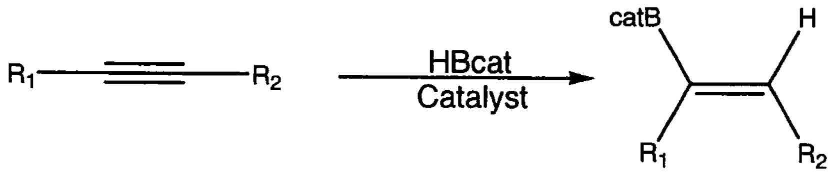
2.1 Introduction

Vinylboronate esters (VBEs) are useful intermediates which are widely employed in organic reactions such as the formation of C-C bonds via Pd-catalysed Suzuki-Miyaura,[1,2] and Heck cross-coupling reactions,[3] additions of (α-chloroallyl)boronates to aldehydes,[4] Diels-Alder reactions,[5,6] in multicomponent chiral amine synthesis,[7,8] and in the preparation of chiral cyclopropanones.[9]

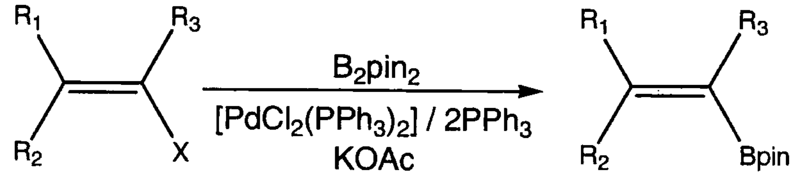
VBEs can be prepared by uncatalysed,[10,11] (Eq. 2.1.1), or transition metal catalysed hydroboration of alkynes,[12-16] (Eq. 2.1.2). They can also be prepared via Pd-catalysed cross-coupling reactions of 1-alkenylhalides or triflates with B$_2$pin$_2$,[17,18] (Eq. 2.1.3), by reaction of 1-halo-1-lithioalkenes and B$_2$pin$_2$ at −110 °C,[19] (Eq. 2.1.4), by Pt-catalysed 1,2-diboration of alkynes,[20-24] giving *cis*-alkene bis(boronate)esters (VBBEs) (Eq. 2.1.5), by Pd-catalysed diboration of methylenecyclopropanes,[25] (Eq. 2.1.6) which gives vinyl boronates with ring opening, by Pd-catalysed borylsilylation or borylstannylation of 1,2-dienes,[26] (Eq. 2.1.7), by ruthenium-catalysed olefin cross-metathesis of vinyl boronates and alkene,[27,28] (Eq. 2.1.8), by catalytic boryl group transfer from a vinyl boronate to an alkene,[29] (Eq. 2.1.9), and by enyne cross metathesis reaction between borylated alkynes and terminal alkenes,[30] (Eq. 2.1.10).



Eq. 2.1.1 Synthesis of VBE in the absence of catalyst

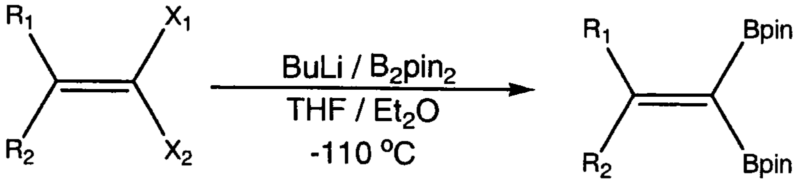


Eq. 2.1.2 Synthesis of VBE in the presence of catalyst



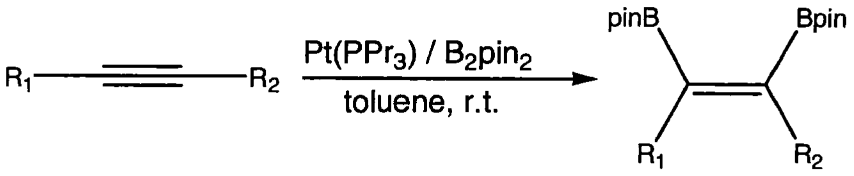
X = Br, OTf

Eq. 2.1.3 Synthesis of VBE via cross-coupling reaction

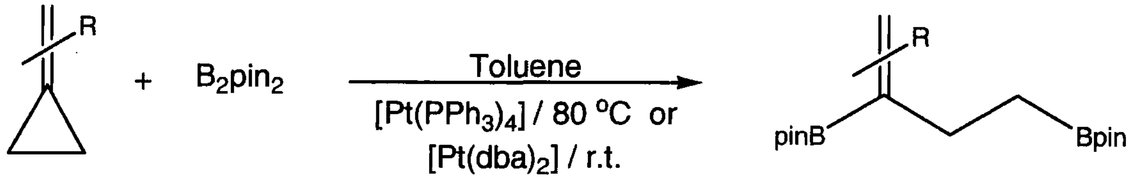


X_1 = halogen, X_2 = X_1 or H

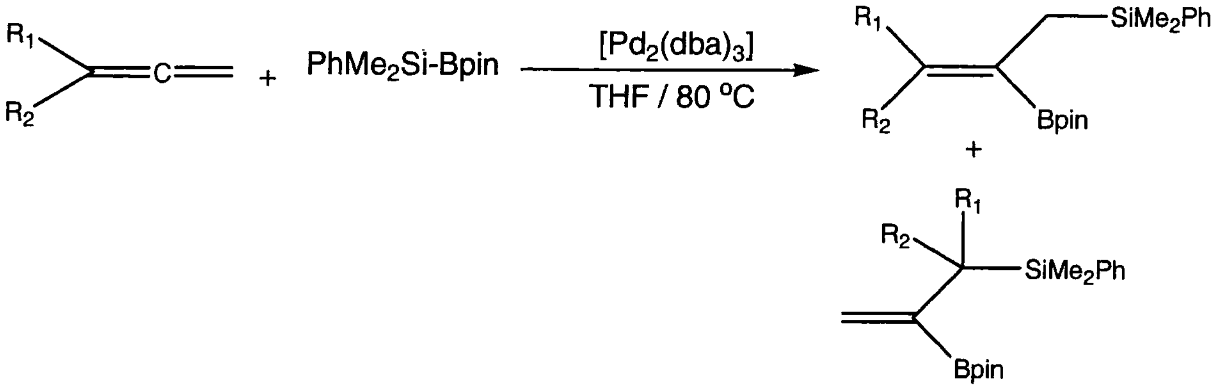
Eq.2.1.4 Synthesis of vinyl-bis(boronate) esters, VBBE, by reaction of 1-halo-1-lithioalkenes with B_2pin_2



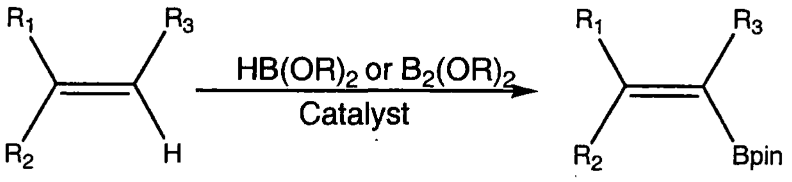
Eq. 2.1.5 Synthesis of VBBE by 1,2-diboration of alkynes



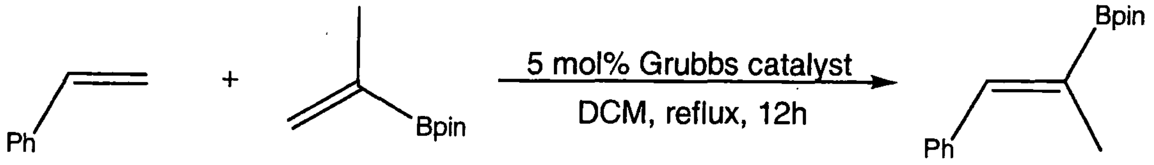
Eq. 2.1.6 Synthesis of VBE via Pt-catalysed diboration of methylenecyclopropane

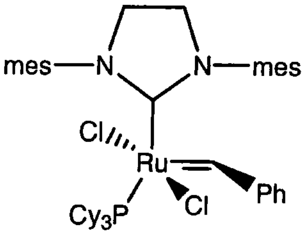


Eq. 2.1.7 Pd-catalysed borylsilylation of 1,2-dienes



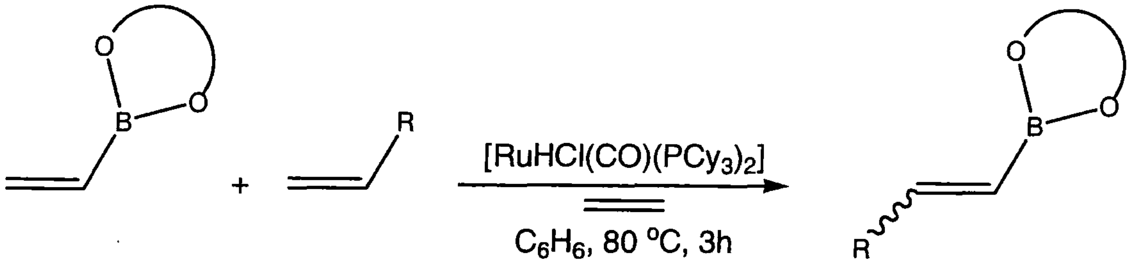
Eq. 2.1.8 Dehydrogenative borylation of alkenes



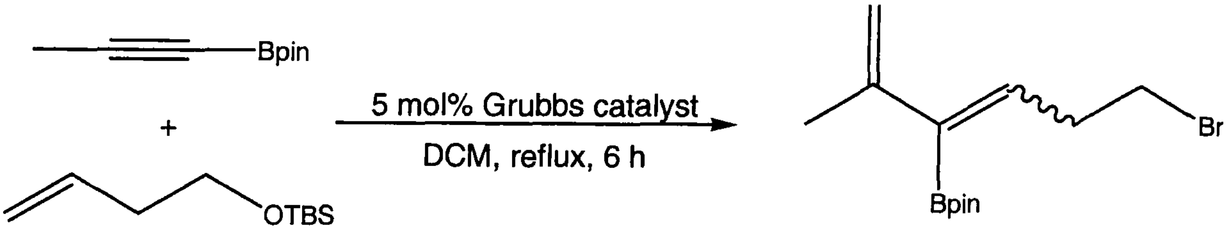


Grubbs catalyst

Eq. 2.1.9 Synthesis of VBE by cross-metathesis



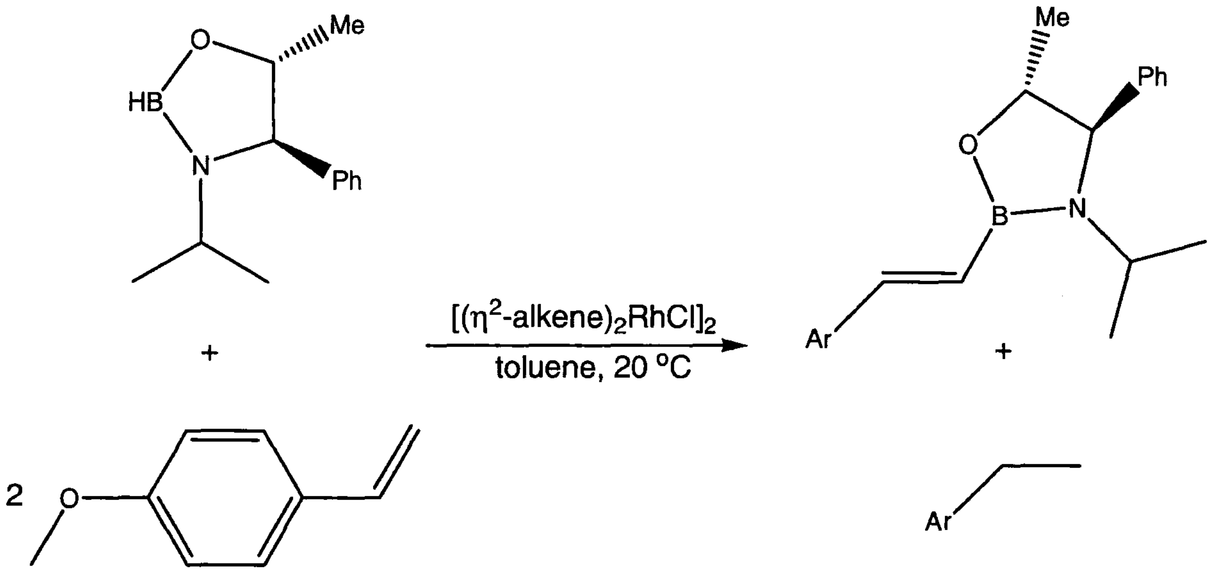
Eq. 2.1.10 Boryl group transfer from VBE to alkene



Eq. 2.1.11 Synthesis of VBE-containing 1,3-dienes

All VBEs, mentioned above, were synthesised by hydroboration or diboration of alkyne or by indirect reaction. An alternative method is the catalytic dehydrogenative borylation of alkenes,[13,31-38] (Eq. 2.1.8), which would allow the direct synthesis of 1,1-disubstituted VBEs that cannot be made by hydroboration of alkynes. However, conditions must be found wherein the H_2 produced is not consumed *via* hydrogenation of half of the alkene substrate.

A *trans*-VBE was synthesised in 1992 by Brown *et al.*[31,33] *via* reaction of 4-vinylanisole (VA) with N-isopropyl oxazaborolidine in the presence of $[(\eta^2\text{-alkene})_2RhCl]_2$, with 50% hydrogenation of alkene (Eq.2.1.12).



Eq. 2.1.12 Dehydrogenative borylation of 4-vinylanisole with accompanying alkene hydrogenation

Several reports followed using Rh,[13,32,37-39] Ti,[34,36] Ru,[35,40] Pd,[39] and Pt,[39] catalysts, all with significant alkene hydrogenation. In one case only, VBEs were synthesised without significant of hydrogenation and 1,1-disubstituted alkenes were employed.[33] **(for more details and discussion see Chapter 1, section 1.6)**

Here, we introduce a high yield, highly selective catalytic synthesis of VBEs, including 1,1-disubstituted VBEs, from alkenes without significant hydrogenation or hydroboration using the simple catalyst *trans*-[RhCl(CO)(PPh$_3$)$_2$] **(1)** and the diboron reagents B$_2$pin$_2$ **2a** or B$_2$neop$_2$ **2b** (neop = neopentylglycolato, OCH$_2$CMe$_2$CH$_2$O) or HBpin all of which are commercially available. In addition, all of the selectivities and conversions were determined by a combination of *in situ* GC/MS and ^{1}H NMR spectroscopy.

Furthermore, synthesis of VBEs *via* microwave-assisted catalysis will be addressed, and these results will compared with those from conversional thermal reactions.

Preliminary thermal studies on this system were carried out by F. E. S. Souza[41] and R. B. Coapes.[42] This chapter introduces more detailed and a re-examination of this system along with the use of new substrates and boron reagents, as well as the microwave-assisted reactions.

2.2 Results and Discussion

In the course of our studies on alkene diboration,[43-45] we examined the reaction of VA with B_2pin_2 catalysed by **1** in a variety of solvents. Toluene, THF and 1,4-dioxane all gave complicated mixtures containing dehydrogenative borylation VBE, diboration, hydroboration and hydrogenation products and, in some cases, vinyl-bis(boronate) esters (VBBEs). In contrast, reaction in CH_3CN was clean, giving 93% VBE, but the rate was much slower than that in e.g. toluene. We therefore examined the reaction in 3:1 toluene:acetonitrile (3:1 T:A) which proved an excellent compromise between selectivity and rate,[46] giving 98% selectivity towards VBE. In the beginning, the yields and selectivities were determined by GC/MS where response factors for the starting materials and products have not been determined. In order to improve the accuracy of our measurements of yields and selectivities, an alternative approach was required which does not depend upon relative response factors. In this regard, NMR spectroscopy is an excellent choice provided that sufficiently long relaxation delays are used. However, the reaction must be carried out in deuterated solvents in order to obtain *in situ* spectra of the crude reaction mixtures. To this end, we chose to examine these reactions in 3:1 C_6D_6:CD_3CN (3:1 d_6:d_3). However, we re-ran the reactions in regular benzene:acetonitrile (3:1) and compared these results to those which were obtained from the reactions in toluene:acetonitrile (3:1 T:A), and we found no difference between toluene and benzene as solvents.

Firstly, we examined the mono substituted alkenes, styrene and VA. The reaction of styrene with **2a** (0.67) equiv. and 3 mol% of **1** in 2 ml of (3:1 d_6:d_3) at 80 °C gave 100% conversion in 5 days by NMR spectroscopy (Table 1, Entry 1) with 86% selectivity for

VBE with 11 and 3% selectivity for VBBE and hydroboration respectively, (Fig. 2.2.1). On the other hand, the conversion by GC/MS (Table 2, Entry 1) was 100% with 66% selectivity for VBE, 19% and 4% selectivity for two hydroboration isomers and 11% selectivity for VBBE. Thus, the hydroboration products appear to have high response factor than VBE or VBBE in the GC/MS.

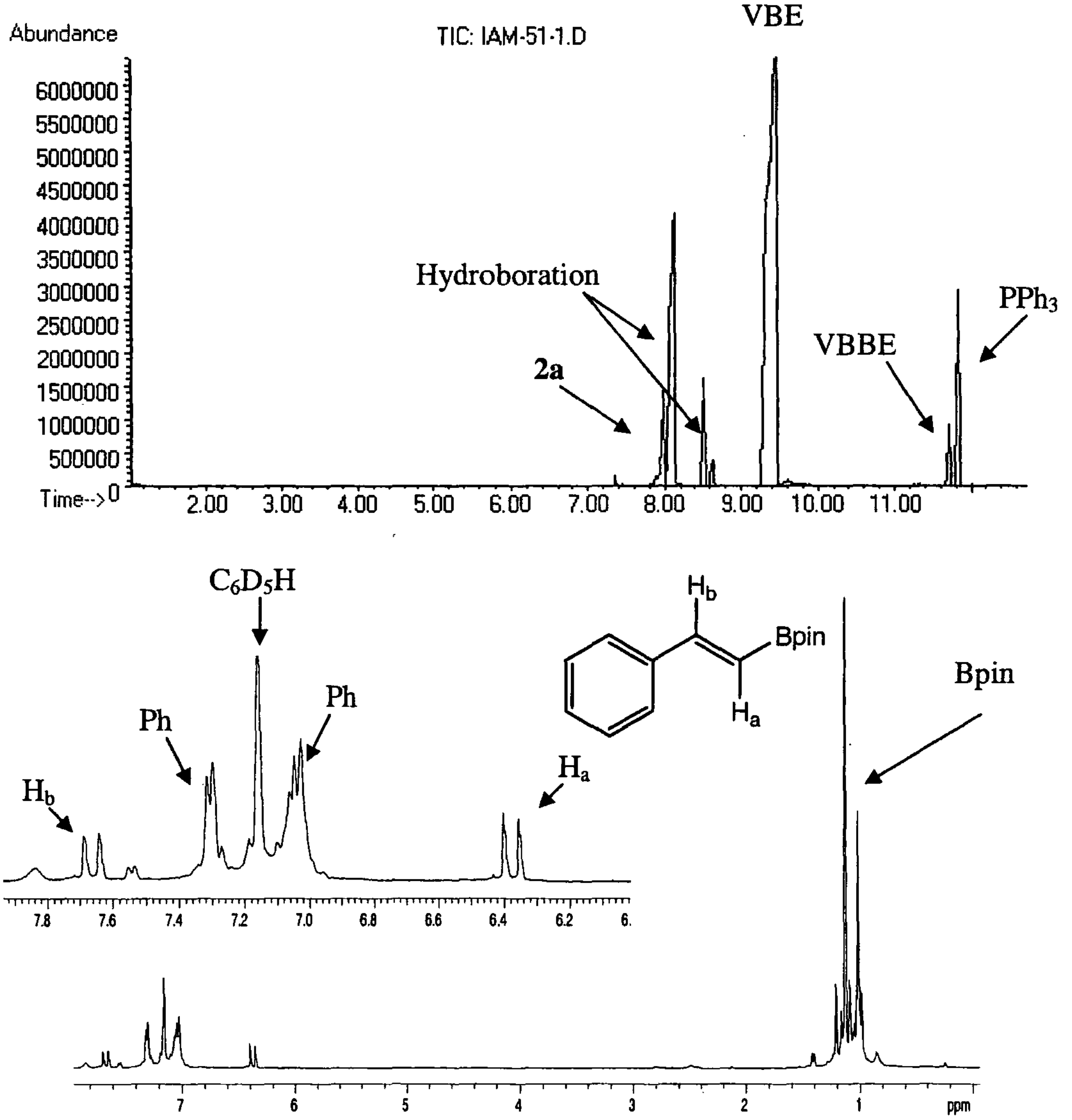


Fig. 2.2.1 Top: GC (TIC) of the reaction of styrene with 0.67 equiv. of **2a**. Bottom: *In situ* ^{1}H NMR spectrum of VBE {(E)-(Ph)CH=CHBpin}

The reaction of VA with 0.67 equiv. of **2a** and 3 mol% of **1** in 2 ml of (3:1 d_6:d_3) at 80 °C gave 99% conversion during 2 days by NMR spectroscopy with 93% selectivity for VBE and 7% hydroboration. It appears from ^{1}H NMR spectroscopy that hydroboration isomers, terminal and internal are produced but, the internal one predominates. (Table 1, Entry 2). The GC/MS shows 100% conversion with 81% selectivity for VBE and 19% hydroboration with 4% of an isomeric hydroboration product (Table 2, Entry 2).

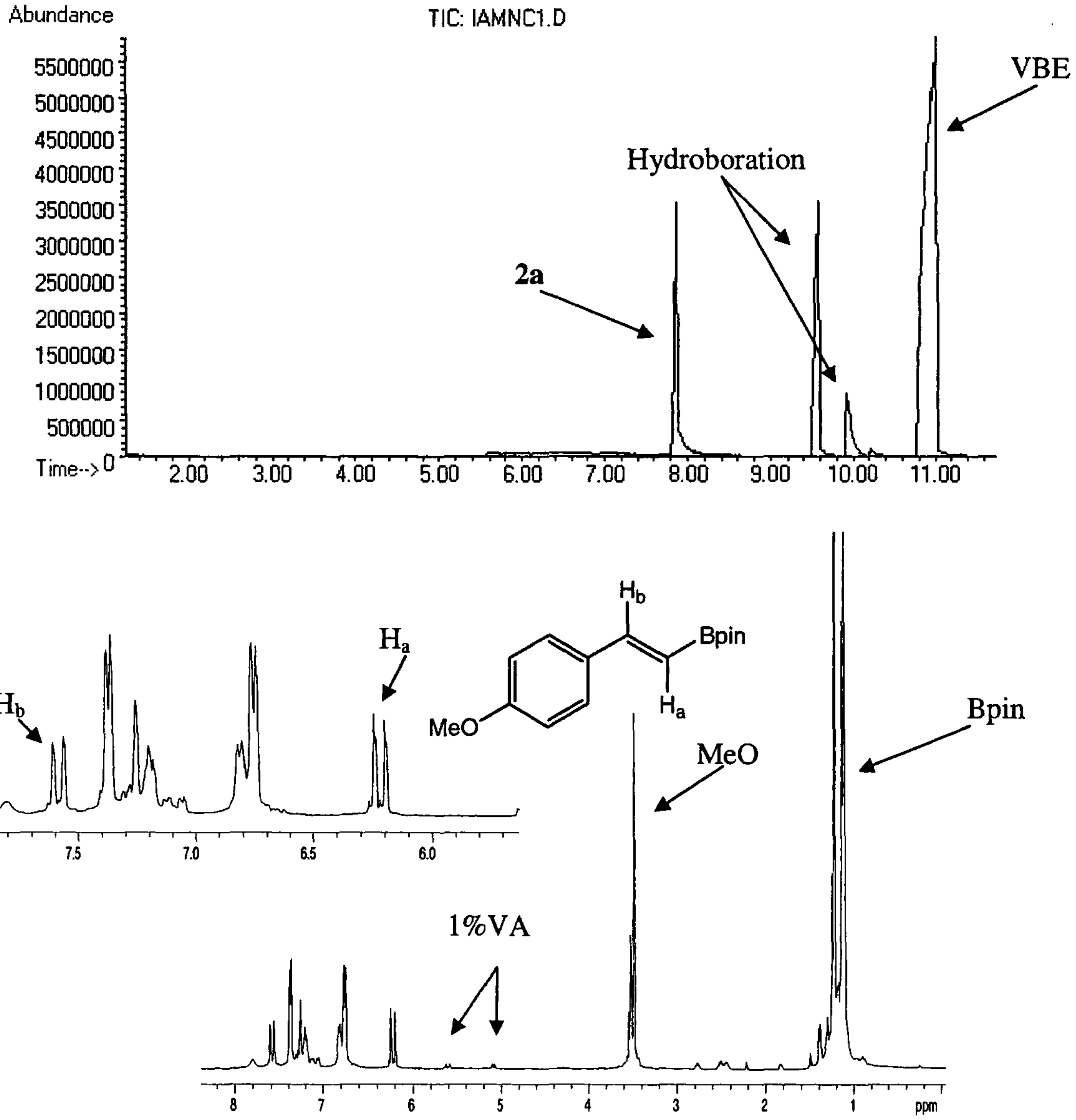


Fig. 2.2.2 Top: GC (TIC) of the reaction of VA with 0.76 equiv. of **2a**. Bottom: *In situ* ^{1}H NMR spectrum of VBE {(E)-4-MeO-C_6H_4-CH=CHBpin}

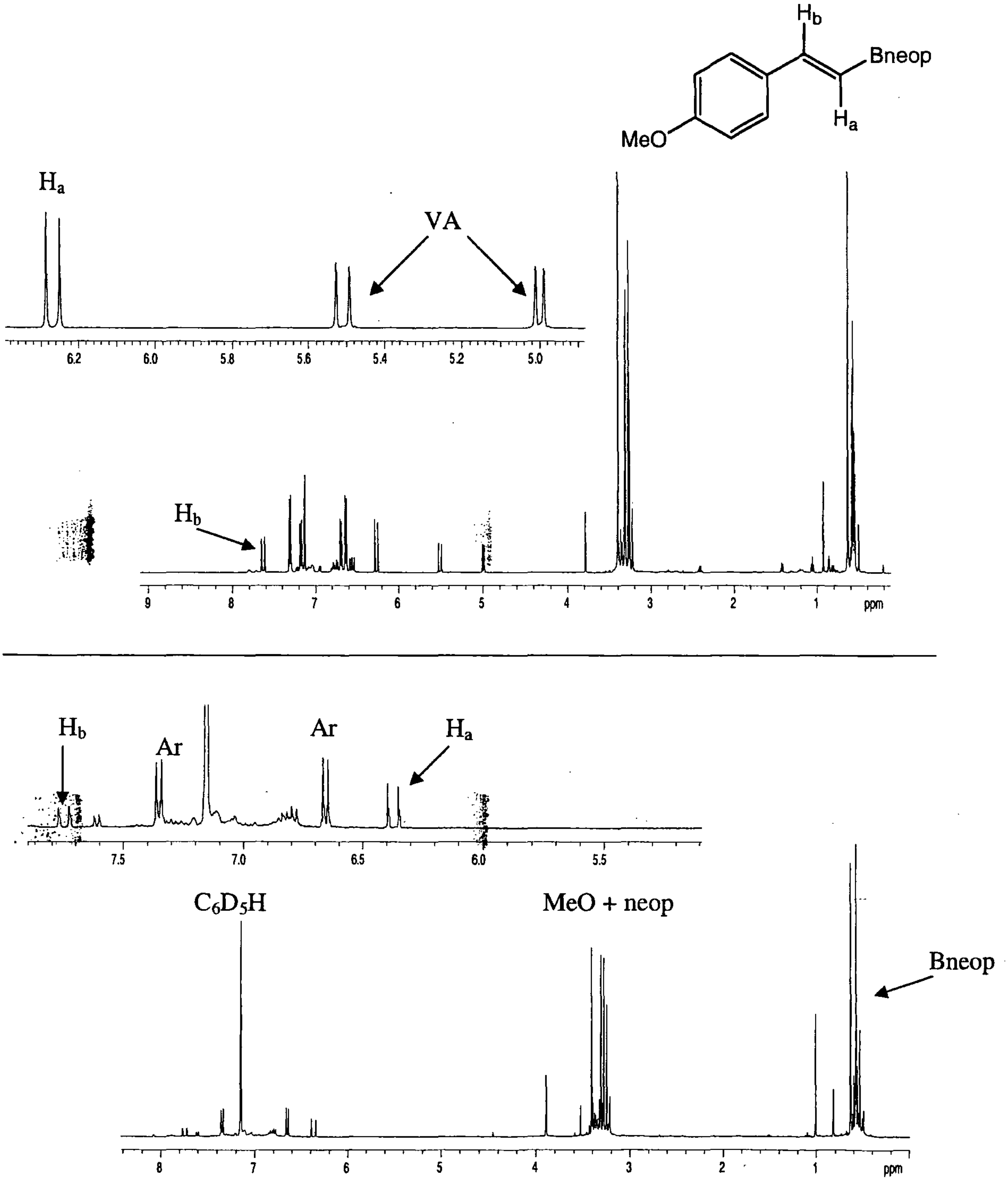


Fig. 2.2.4 Top: *In situ* ^{1}H NMR spectrum of the reaction of VA with 0.67 equiv. of **2b** after 4 days. Bottom: *In situ* ^{1}H NMR spectrum of the reaction of VA with 1 equiv. of **2b** after 2 days

In an investigation of **2b** as a source of boron, the VA was reacted with 0.67 equiv of **2b** and 3 mol% of **1** in 2 ml of (3:1 d_6:d_3) at 80 °C, the yield was 44% during 2 days and 65% during 4 days by NMR spectroscopy with complete selectivity for VBE (Table 1, Entry 3 and 4, Fig. 2.2.3 and Fig. 2.2.4 Top). The GC/MS shows 66 and 77% conversion during 2 and 4 days respectively with 10% hydroboration as a side product (Table 2, Entry 3 and 4). The concentration of **2b** was increased to 1 equiv. under the above condition, after 2 days the NMR spectroscopy shows complete reaction giving 100% for conversion and selectivity for VBE (Table 1, Entry 5, Fig. 2.2.4 Bottom). On the other hand, the GC/MS also shows complete reaction with 10% hydroboration and 90% selectivity for VBE (Table 2, Entry 5).

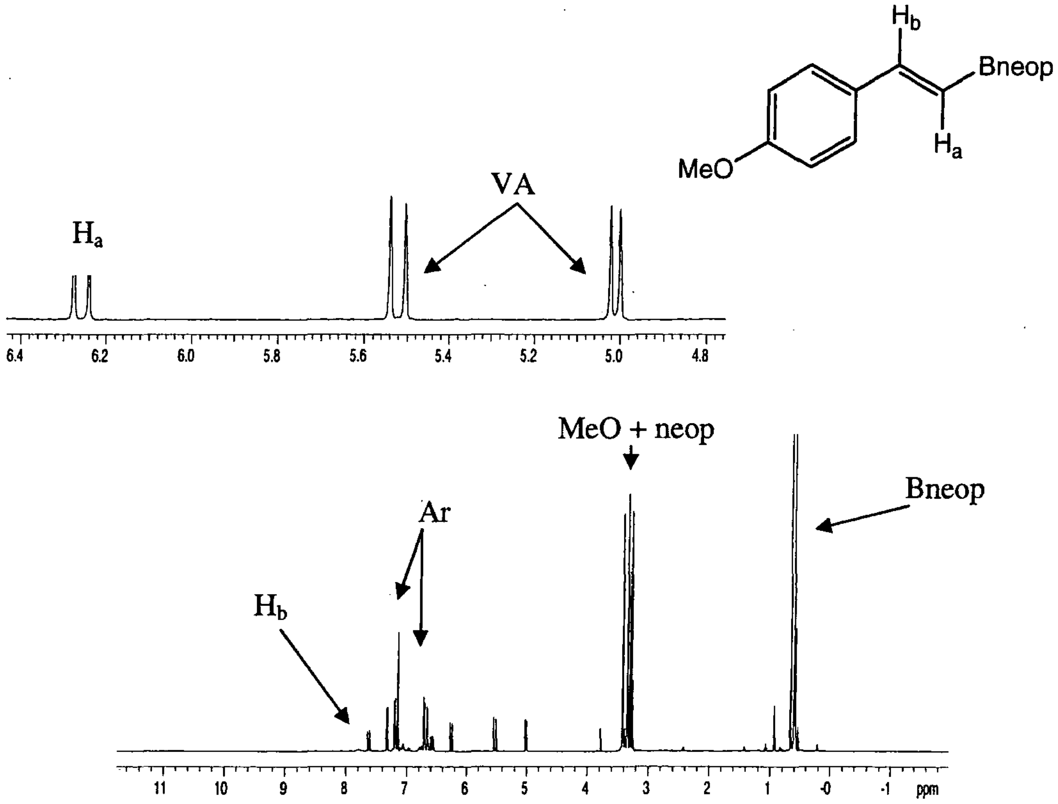


Fig. 2.2.3 Top: *In situ* ^{1}H NMR spectrum of the reaction of VA with 0.67 equiv. of **2b** after 2 days.

Reaction of VA with 2 equiv. of **2a** and 5 mol% of **1** in 2 ml (3:1 d_6:d_3) (Table 1, Entry 6) gave 93% selectivity for VBBE and 7% VBE by NMR spectroscopy (Fig. 2.2.5). Thus both hydrogens of the $=CH_2$ group were replaced by Bpin in a single catalytic reaction. Also the GC/MS shows 100% conversion with 88% selectivity for VBBE and 12% for VBE (Table 2, Entry 6).

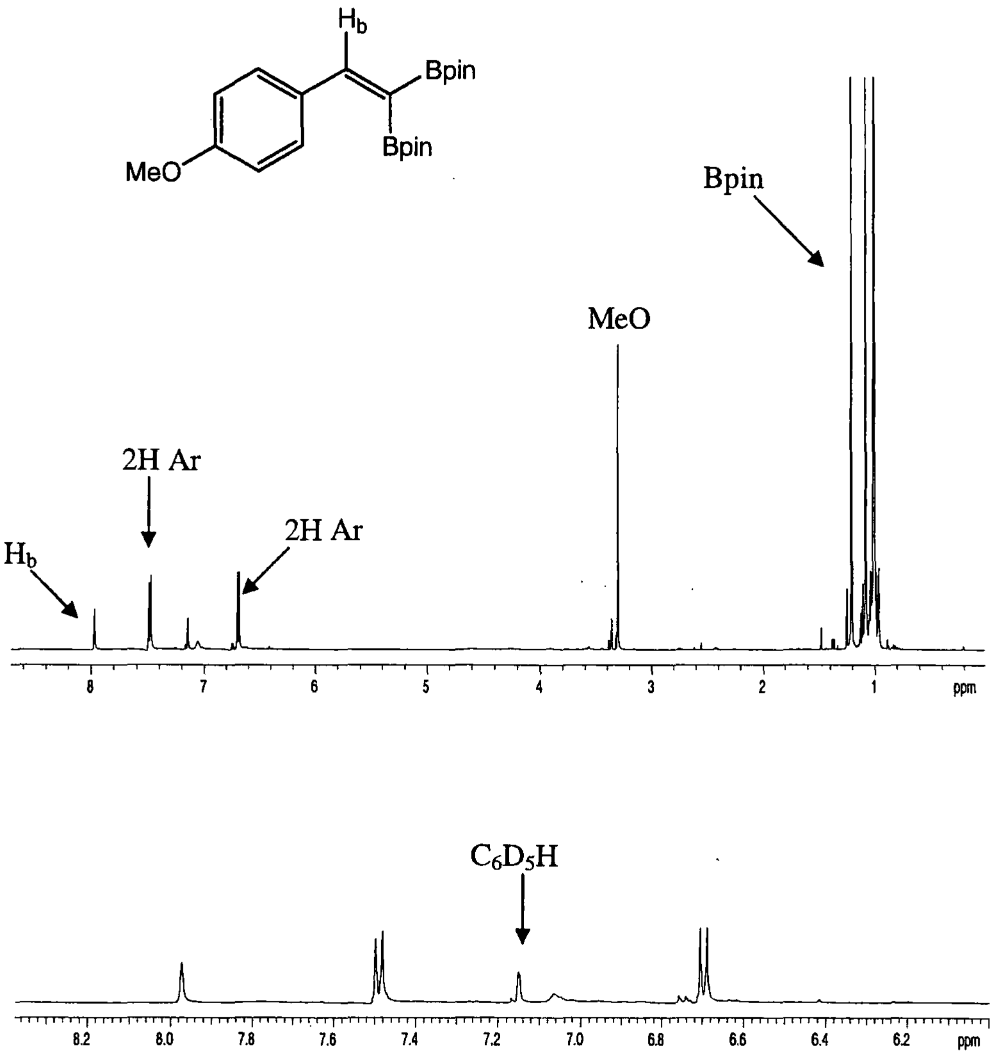


Fig. 2.2.5 Top: *In situ* ^1H NMR spectrum of VBBE {(E)-4-MeO-C_6H_4-CH=C(Bpin)$_2$}.

Bottom: Expansion of the spectrum

Interestingly, the reaction of 1-octene with 0.67 equiv. of **1a** and 3 mol% catalyst in 2 ml of (3:1 d_6:d_3) (Table 1, Entry 7) gave 100% conversion with 67% selectivity for VBBEs with 33% dehydrogenative borylation. The GC/MS showed 100% conversion with 66% selectivity for VBBEs of which 60% is the $C_6H_{13}CH=C(Bpin)_2$ isomer, with 34% VBE, 54% an isomeric of VBE (Table 2, Entry 7). This distribution of products likely result from the isomerisation of the double bond along the hydrocarbon chain.

The 1,2-disubstituted alkene, indene, and the 1,1,2-trisubstituted alkenes 2-methyl-2-butene and 3,4,4-trimethyl-2-pentene were examined under the above conditions. Indene showed lower reactivity than the mono-substituted alkenes giving 100% selectivity for VBE with 19% but only conversion by NMR spectroscopy after 6 days (Table 1, Entry 8). The GC/MS gave 21% conversion and 95% selectivity for VBE with 5% of hydroboration (Table 2, Entry 8). No reaction at all was observed with either 2-methyl-2-butene or 3,4,4-trimethyl-2-pentene. Consequently, this system appears to be generally unsuitable for dehydrogenative borylation of 1,1,2-trisubstituted alkenes.

By contrast, the reactions of 1,1-disubstiuted alkenes such as α-methylstyrene and 1,1-diphenylethylene shows higher activity than for the 1,2-disubstituted and 1,1,2-trisubstituted alkenes. The reaction of 0.67 equiv. of **2a** with α-methylstyrene and 1,1-diphenylethylene, in the presence of 3 mol% of **1** in 2 ml (3:1 d_6:d_3) at 80°C gave by NMR spectroscopy 100% of (E)-VBE (Table 1, Entry 9) with 90% conversion during 4 days, and also 90% conversion by GC/MS with 95% selectivity for VBE with 5% of hydroboration (Table 2, Entry 9), (Fig. 2.2.6).

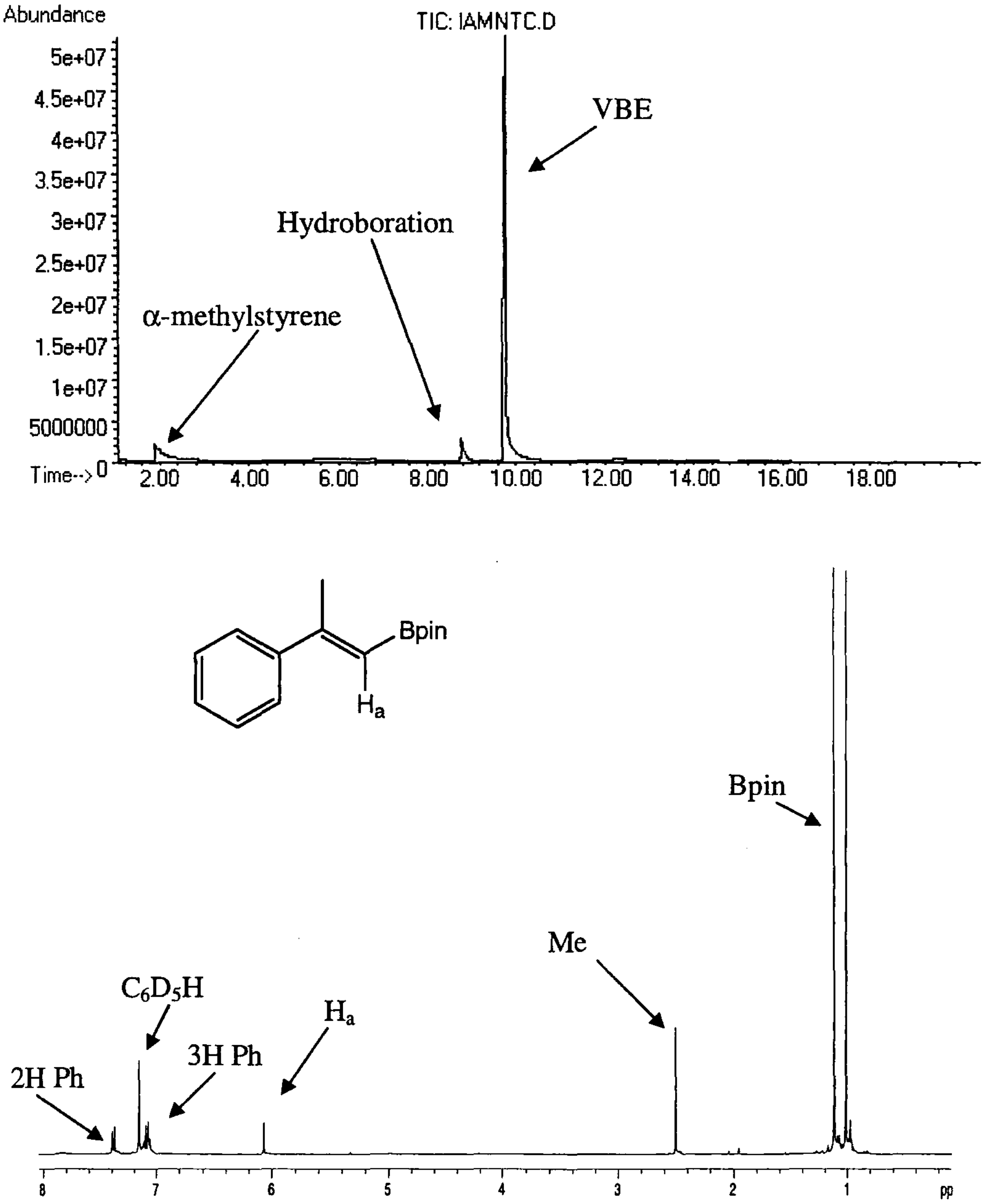


Fig. 2.2.6 Top:. GC (TIC) of the reaction of α-methylstyrene with 0.67 equiv. of **2a**

Bottom: *In situ* ^{1}H NMR spectrum of VBE {(E)-(Ph)C(Me)=CHBpin}

Under the same reaction conditions, 1,1-diphenylethylene proved less reactive than α-methylstyrene, most likely due to increased steric bulk, giving 67% conversion during 4 days (Fig. 2.2.7) with 100% selectivity for VBE in both techniques (GS/MS and ^{1}H NMR spectroscopy) with traces of hydroboration (Table 1 and 2, Entry 18 and 18).

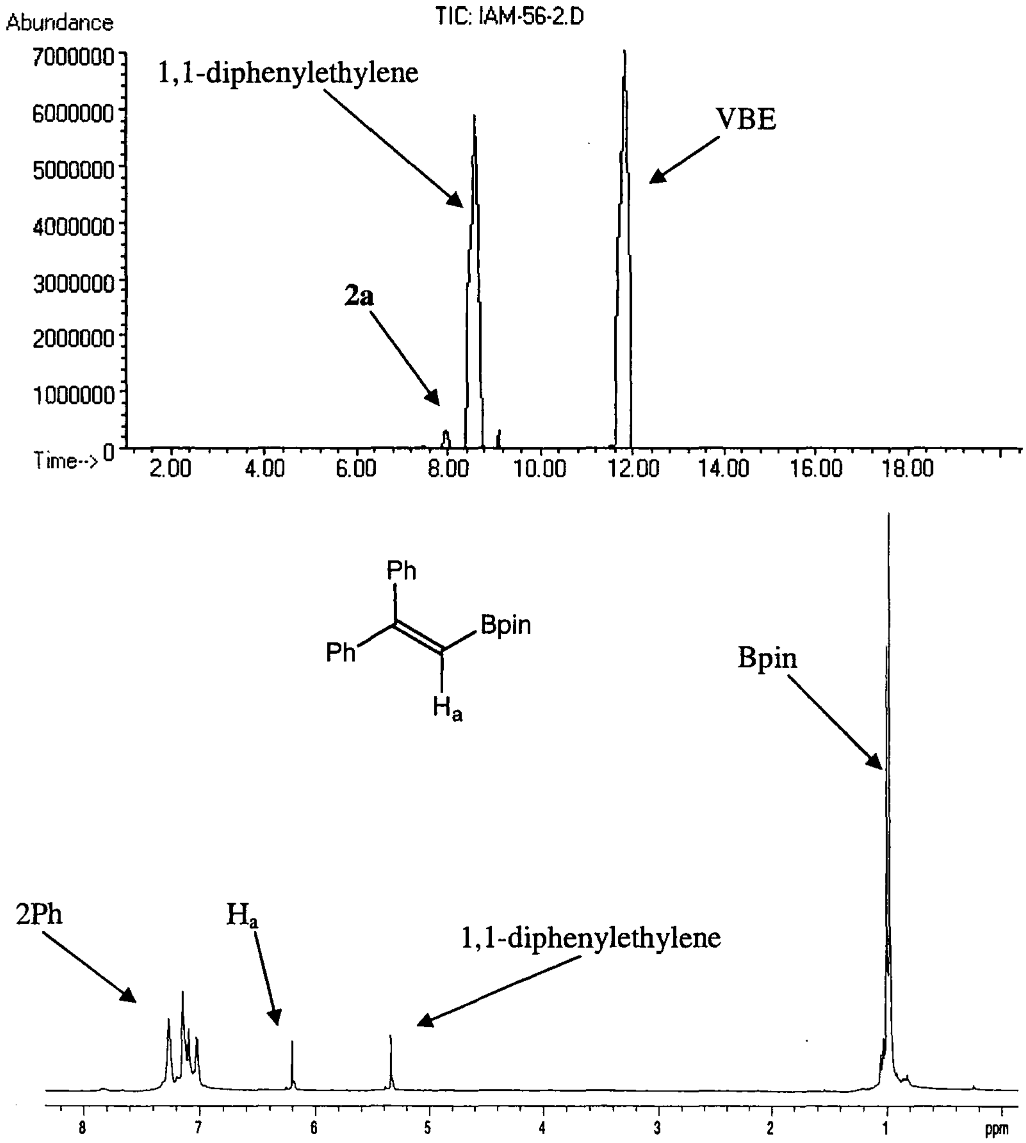
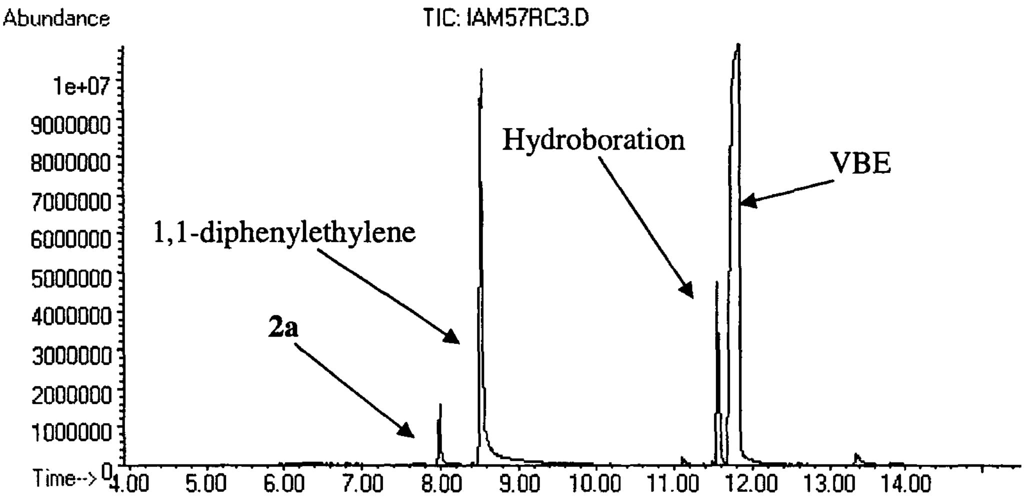


Fig. 2.2.7 Top: GC (TIC) of the reaction of 1,1-diphenylethylene with 0.67 equiv. of **2a**. Bottom: *In situ* ^{1}H NMR spectrum of VBE {$Ph_2C{=}CHBpin$}

Investigation of solvents effects on the reaction of 1,1-diphenylethylene and α-methylstyrene using neat benzene-d_6 or acetonitrile-d_3 shows that the reaction in benzene-d_6 was fast, giving 71% conversion by NMR spectroscopy during 1 day, with 94% selectivity for VBE and 6% of hydroboration side product (Table 1, Entry 19) and 76% conversion by GC/MS with 91% selectivity for VBE and 9% hydroboration (Table 2, Entry 19, Fig. 2.2.8 Top). On the other hand, the reaction in acetonitrile-d_3 was very clean, giving 100% selectivity for VBE with 48% conversion during 4 days by the two techniques (Table 1 and 2, Entry 20), (Fig. 2.2.8 Bottom). In addition, α-methylstyrene gave 54% conversion during 2 days when benzene-d_6 was used with 94% selectivity for VBE and 6% of the side product of hydroboration (Table 1 and 2, Entry 9). The reaction in acetonitrile-d_3 gave 52% conversion during 6 days with 100% selectivity for VBE (Table 1 and 2, Entry 10).



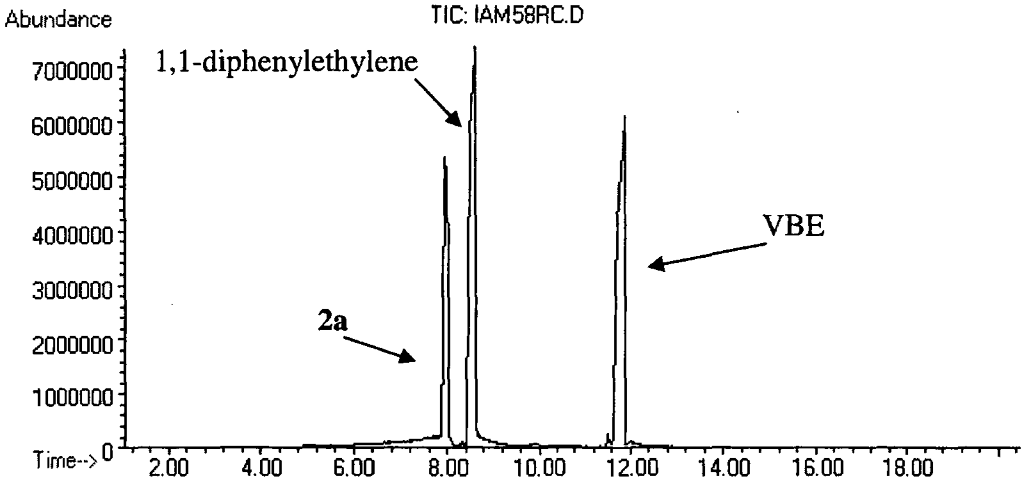


Fig. 2.2.8 Top: GC (TIC) of the reaction of 1,1-diphenylethylene with 0.67 equiv. of **2a** in benzene-d_6. Bottom: GC (TIC) of the reaction of 1,1-diphenylethylene with 0.67 equiv. of **2a** in acetonitrile-d_3

The substrate 1,1-diphenylethylene was reacted with 1 equiv. of **2a** in the presence of 3 mol% of **1** and (3:1 d_6:d_3) to examine the high loading of **2a**, and to ensure the reaction went to completion. After 3 days the selectivity was 100% for both VBE and conversion and all the 1,1-diphenylethylene was converted to product by NMR spectroscopy (Table 1, Entry 22). Interestingly, the GC/MS shows 100% conversion with 96% and 1% selectivity for VBE and hydroboration respectively with a small side product being the VBBE (Table 2, Entry 22), (Fig. 2.2.9). These results indicate that the [Rh(Bpin)$_2$] species is more reactive than [Rh(H)(Bpin)] species which is resulting after the consumption of the first boron.

To investigate HBpin as a source of boron and also the behaviour of the proposed [Rh(H)(Bpin)] species, both of the alkenes 1,1-diphenylethylene and α-methylstyrene were reacted with 1.34 equiv. of HBpin instead of **2a** under the above conditions. All the reactions gave VBE with modest amounts of hydroboration. The reaction of 1,1-diphenylethylene gave 44% conversion during 2 days with 90% selectivity for VBE and 10% for hydroboration (Table 1, Entry 23). On the other hand, the GC/MS shows 49% conversion with 84% selectivity for VBE and 16% for hydroboration (Fig. 2.2.10). The reaction of α-methylstyrene gave 55% conversion by NMR spectroscopy during 2 days with 95% selectivity for VBE and 5% of hydroboration (Table 1, Entry 13). These experiments indicated that the [Rh(H)(Bpin)] species has a lower reactivity than [Rh(Bpin)$_2$] species and leads to some degree of hydroboration.

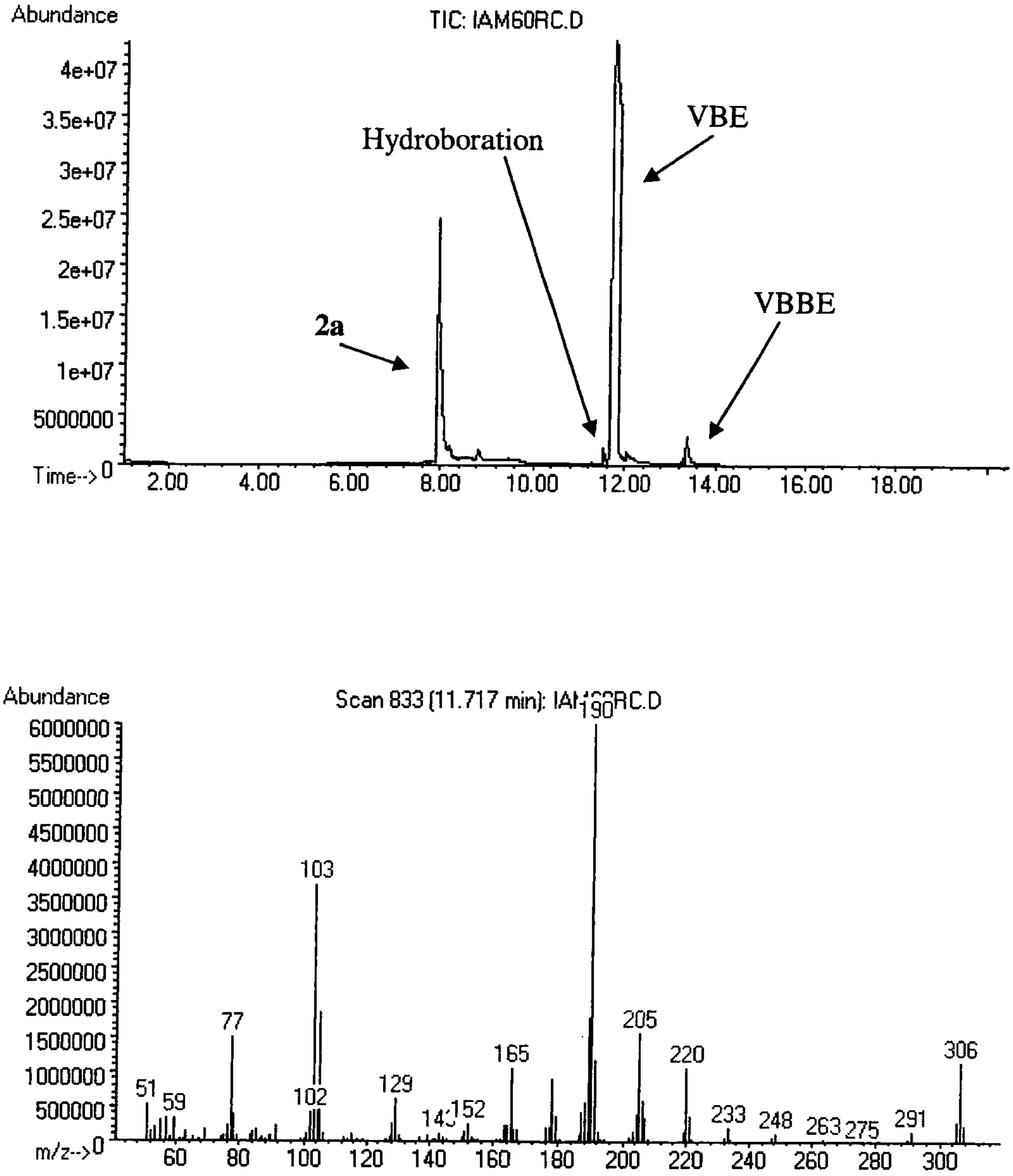


Fig. 2.2.9 Top: GC (TIC) of the reaction of 1,1-diphenylethylene with 1 equiv. of **2a**

Bottom: Mass spectrum of the VBE

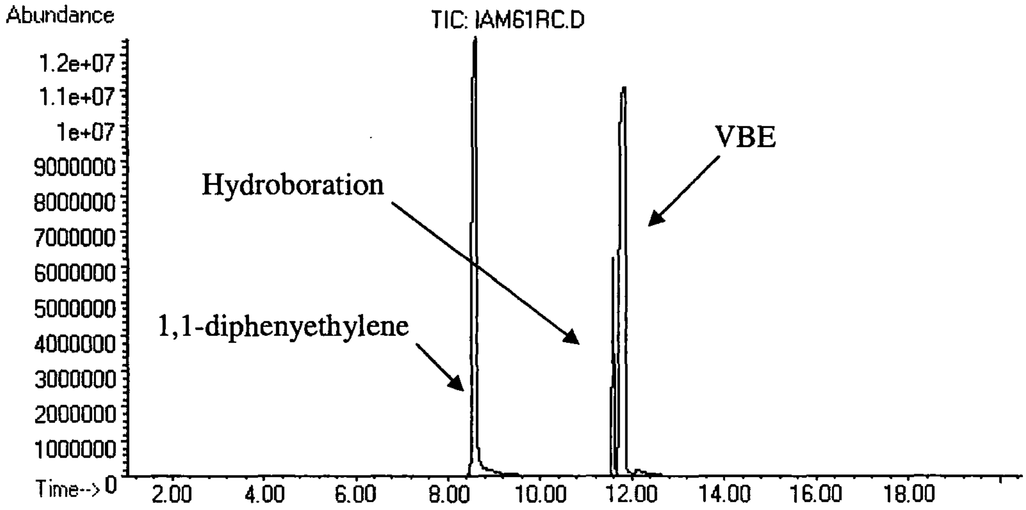


Fig. 2.2.10 GC (TIC) of the reaction of 1,1-diphenylethylene with 1.34 equiv. of HBpin

In addition, the reaction of 1,1-diphenylethylene was examined with 5 mol% of catalyst and 0.67 equiv. of B_2pin_2, (Table 1 and 2, Entry 21), which gave 70% conversion during 3 days with 100% selectivity for VBE (Fig. 2.2.11). No significant effect of the higher catalyst loading was observed for this system, so the key factor is increasing the amount of B_2pin_2 to 1 equiv.

Diboron compound **2b** was then investigated as a source of boron with the substrates 1,1-diphenylethylene and α-methylstyrene. The reaction was carried with 0.67 equiv. of **2b** in the presence of 1,1-diphenylethylene which gave 29% conversion during 2 days by the two techniques (GC/MS, ^{1}H NMR spectroscopy) with 100% selectivity for VBE (Table 1 and 2, Entry 24). On the other hand, the reaction with α-methylstyrene gave 42% conversion during 2 days with 100% selectivity for VBE (Table 1, Entry 14). The

GC/MS shows 49% conversion with 100% selectivity for VBE (Table 2, Entry 14). This result shows that **2b** has a lower reactivity than **2a** in this reaction.

In order to optimise the conditions for the reaction of α-methylstyrene with **2b**, the reaction was carried out under the above conditions and the conversion was increased to 53% with the same selectivity for VBE when the reaction time was extended to 4 days. Again, increasing the concentration of **2b** to 1 equiv. instead of 0.67 equiv. gave 96% conversion of α-methylstyrene with 100% selectivity for VBE during 2 days and 100% conversion after 3 days (Table 1 and 2, Entries 16 and 17).

Methylene cyclopentane and methylene cyclohexane were examined as 1,1-disubstituted alkenes without aromatic substituents. The borylation methylene cyclopentane was achieved during 3 days with 0.67 equiv. of **2a** giving 96% conversion with 91% selectivity for VBE and 9% being an isomeric VBE (Table 1, Entry 25). The GC/MS shows the same results except that the VBE consist of 3 isomers, one of which constitute 92% of the total VBE; 5% and 3% (Table 2, Entry 25), (Fig. 2.2.12). This distribution of products might be accorded to the isomerisation of the double bond into the hydrocarbon ring. Because the two mono VBE isomers total less than 9% and the aliphatic protons resonances are overlapped, it was not possible to identify these isomers in the ^{1}H NMR spectrum.

Finally, ethylene cyclohexane was reacted with 0.67 and 1 equiv. of **2a** giving 86% and 96% conversions respectively during 5 days with complete selectivity for a single VBE (Table 1 and 2, Entry 26 and 27).

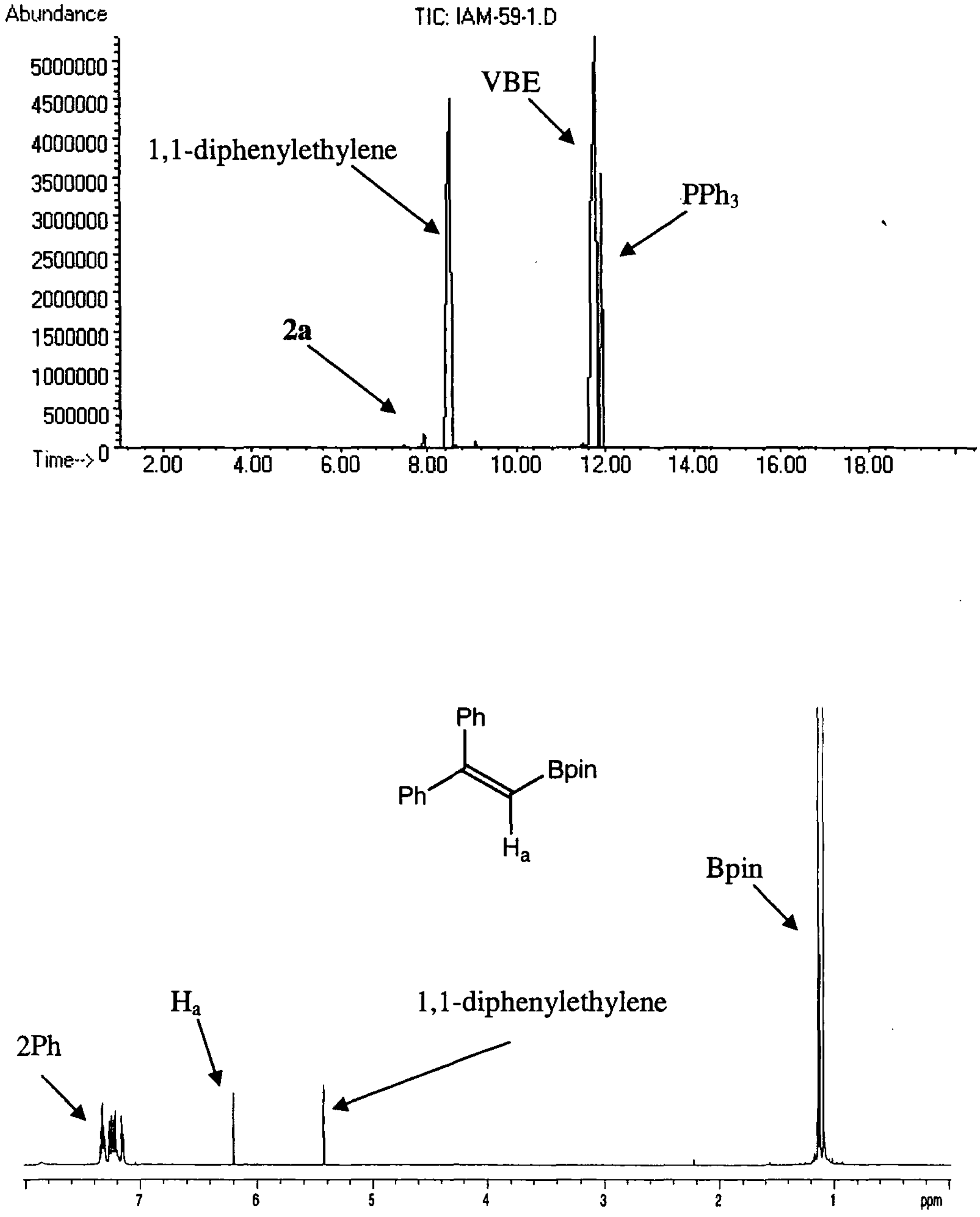


Fig. 2.2.11 Top: GC (TIC) of the reaction of 1,1-diphenylethylene with 0.67 equiv of **2a** in the presence of 5 mol% of **1**. Bottom: ^{1}H NMR spectrum of VBE {$Ph_2C{=}CHBpin$}

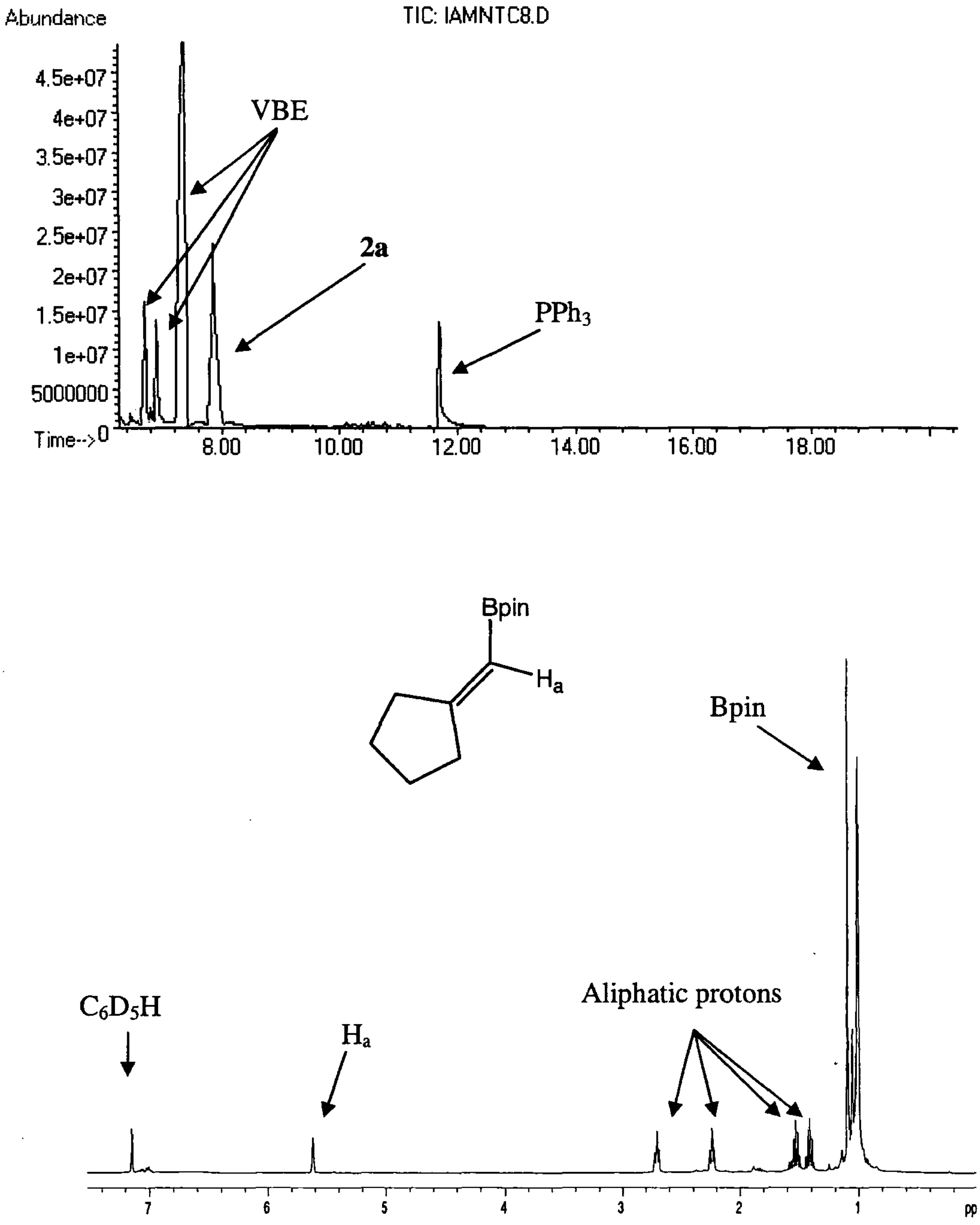
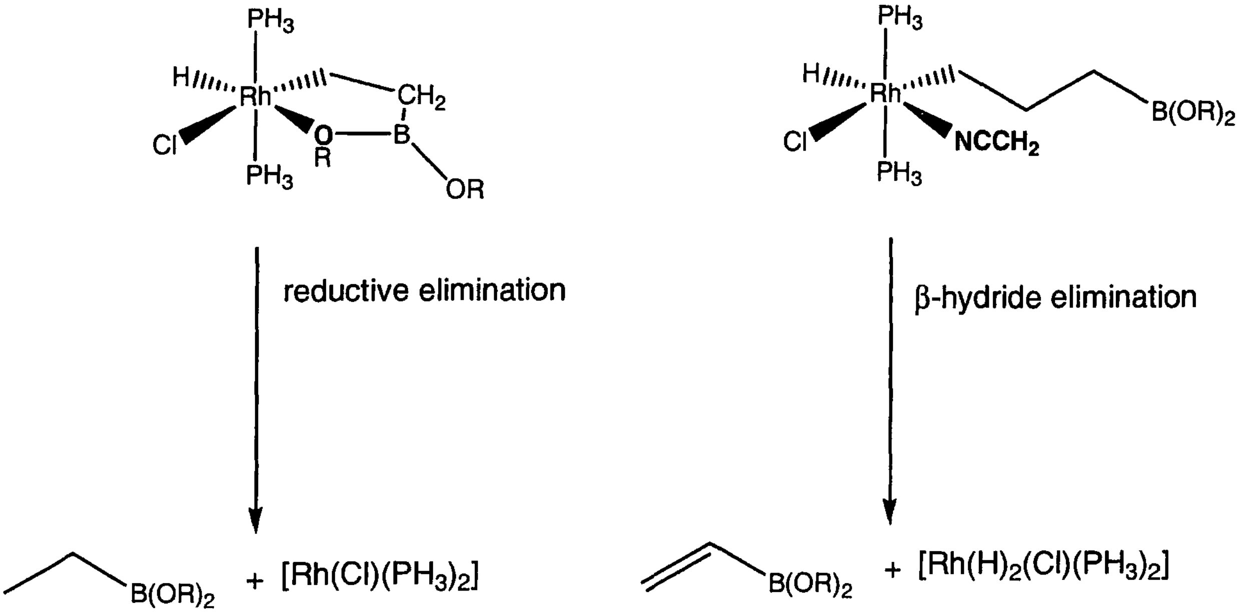


Fig. 2.2.12 Top: GC (TIC) of the reaction of methylene cyclopentane with 0.67 equiv. of **2a**. Bottom: ^{1}H NMR spectrum of VBE {C_5H_8=CHBpin}

2.3 Proposed Mechanism[46]

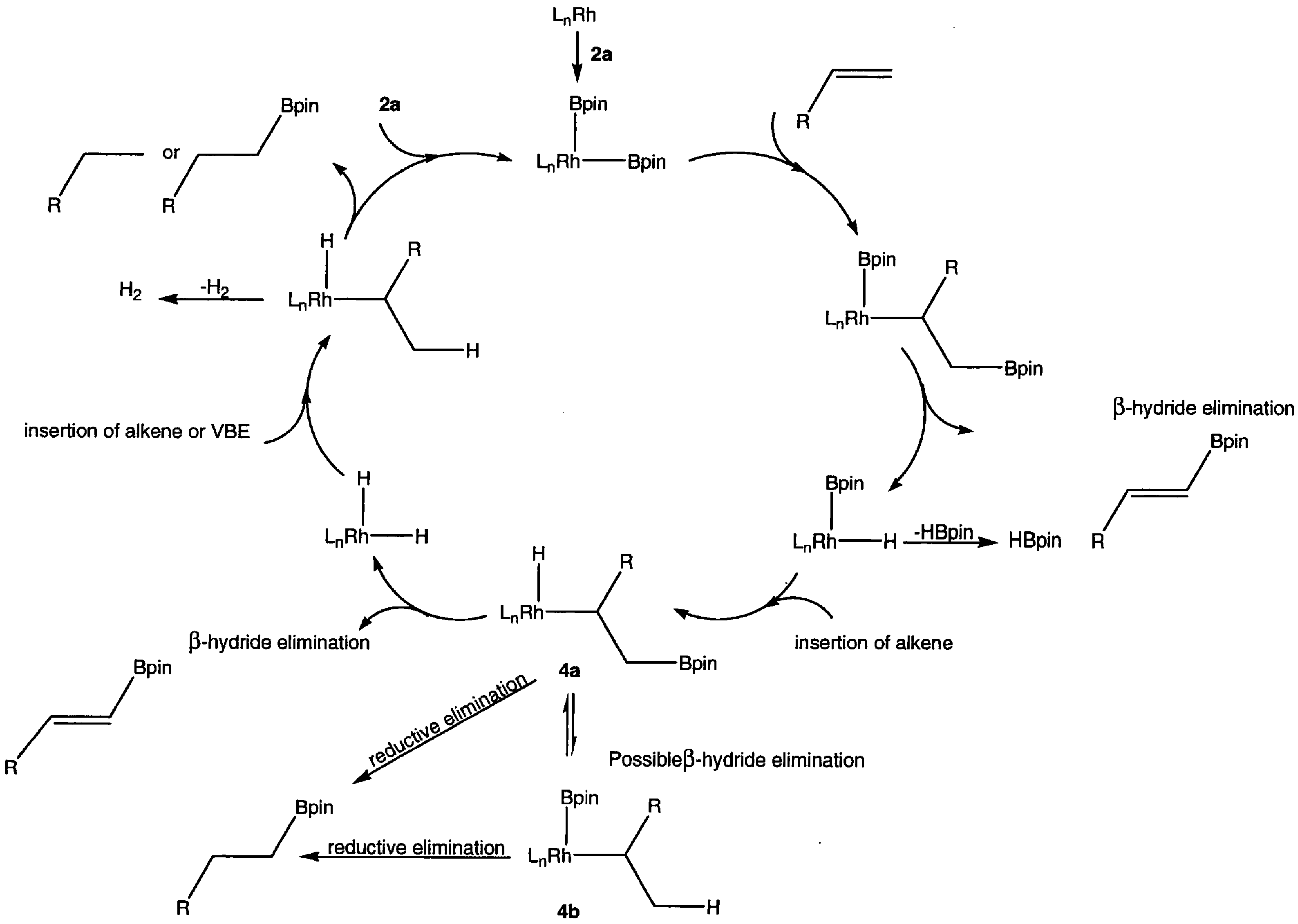
The previous results indicate that the reaction is very selective in acetonitrile solvent; however, the reaction rate is slow. Theoretical studies[47] suggested that there is an intramolecular interaction between the oxygen of Bpin and the vacant site on the Rh intermediate in the model $[(PH_3)_2Rh(Cl)(H)(CH_2CH_2BOR(OR)]$, with the ring strain leading to reductive elimination and formation of the hydroboration product (Scheme 2.3.1, **3a**). However, in the presence of a strongly coordinating solvent such as acetonitrile, the reductive elimination rate, relative to β-hydride elimination is apparently inhibited by CH_3CN, allowing β-hydride elimination to predominate to form the VBEs and the dihydridorhodium complex (Scheme 2.3.1, **3b**). This coordination of acetonitrile to the active site could also decrease the overall reactivity of the Rh intermediate. As a *cis*-vacant site is also required for β-hydride elimination as well as for "O" coordination, so we do not yet understand fully the role of acetonitrile in controlling selectivity.

The mechanism may involve an oxidative addition of **2a** to the Rh-complex to form the bis(boryl)Rh(III) complex, followed by insertion of the alkene, and then β-hydride elimination to produce the VBE and [Rh(Bpin)(H)] species. Further insertion of alkene into the [Rh(Bpin)(H)] species, which can lead to intermediate **4a** or intermediate **4b**. Intermediate **4b** can lead to hydroboration after reductive elimination, whereas intermediate **4a** can lead to VBE after β-hydride elimination, and then give a $Rh(H)_2$ species. This species presumably hydrogenates the VBE or the alkene giving the hydroboration and hydrogenation products (Scheme 2.3.2).



3a **3b**

Scheme 2.3.1



Scheme 2.3.2 Possible mechanism for formation of VBE

Table 1 Product distributions and conversions by ^{1}H NMR spectroscopy for the dehydrogenative borylation of alkenes.[a]

Entry	Substrate	Boron Reagent	Hydroboration %	Total VBE[b] (Maj.isomer) %	Total VBBE[c] (Maj.isomer) %	Time /days	Solvent[d]	Conversion %
1	Styrene	B_2pin_2	3	86	11	5	3:1 B:A	100
2	4-vinyl anisole	B_2pin_2	7	93		2	3:1 B:A	99
3	4-vinyl anisole	B_2neop_2		100		2	3:1 B:A	44
4	4-vinyl anisole	B_2neop_2		100		4	3:1 B:A	65
5	4-vinyl anisole[e]	B_2neop_2		100		2	3:1 B:A	100
6	4-vinyl anisole[f]	B_2pin_2		7	93	4	3:1 B:A	100
7	octene	B_2pin_2		33	67	3	3:1 B:A	100
8	indene	B_2pin_2		100		6	3:1 B:A	19
9	α-methyl styrene	B_2pin_2		100		4	3:1 B:A	90
10	α-methyl styrene	B_2pin_2	4	96		2	B	54
11	α-methyl styrene	B_2pin_2		100		6	A	52
12	α-methyl styrene[g]	B_2pin_2	3	97		2	3:1 B:A	86
13	α-methyl styrene	HBpin	5	95		2	3:1 B:A	55
14	α-methyl styrene	B_2neop_2		100		2	3:1 B:A	42
15	α-methyl styrene	B_2neop_2		100		4	3:1 B:A	53
16	α-methyl styrene[e]	B_2neop_2		100		2	3:1 B:A	96
17	α-methyl styrene[e]	B_2neop_2		100		3	3:1 B:A	100
18	1,1-diphenylethylene	B_2pin_2		100		4	3:1 B:A	67
19	1,1-diphenylethylene	B_2pin_2	6	94		1	B	71
20	1,1-diphenylethylene	B_2pin_2		100		4	A	48
21	1,1-diphenylethylene[h]	B_2pin_2		100		3	3:1 B:A	70
22	1,1-diphenylethylene[g]	B_2pin_2		100		3	3:1 B:A	100
23	1,1-diphenylethylene	HBpin	10	90		2	3:1 B:A	44
24	1,1-diphenylethylene	B_2neop_2		100		2	3:1 B:A	29
25	methylene cyclopentane	B_2pin_2		100 (91)		3	3:1 B:A	96
26	methylene cyclohexane	B_2pin_2		100		5	3:1 B:A	86
27	methylene cyclohexane[g]	B_2pin_2		100		5	3:1 B:A	96

[a] For detailed reaction conditions, see experimental section. Reactions were carried out in deuterated solvents. Conversions and product distributions were determined by *in situ* ^{1}H-NMR spectroscopy (see text). [b] VBE = vinylboronate ester. [c] VBBE = vinyl-bis(boronate) ester. [d] B = benzene-d_6, A = acetonitrile-d_3. [e] 1 equiv. of B_2neop_2 used. [f] 2 equiv. of B_2pin_2 and 5 mol% of catalyst used. [g] 1 equiv. of B_2pin_2 used. [h] 5 mol% of catalyst used

Table 2 Product distributions and conversions by GC/MS for the dehydrogenative borylation of alkenes.[a]

Entry	Substrate	Boron Reagent	Hydroboration %	Total VBE[b] (Maj.isomer) %	Total VBBE[c] (Maj.isomer) %	Time /days	Solvent[d]	Conversion %
1	Styrene	B_2pin_2	19 (4)	66	11	5	3:1 B:A	100
2	4-vinyl anisole	B_2pin_2	19	81		2	3:1 B:A	100
3	4-vinyl anisole	B_2neop_2	5 (5)	90 (99)		2	3:1 B:A	66
4	4-vinyl anisole	B_2neop_2	5 (6)	89 (98)		4	3:1 B:A	77
5	4-vinyl anisole[e]	B_2neop_2	10	90 (99)		2	3:1 B:A	100
6	4-vinyl anisole[f]	B_2pin_2		12	88 (98)	4	3:1 B:A	100
7	octene	B_2pin_2		34 (54)	66 (60)	3	3:1 B:A	100
8	indene	B_2pin_2	5	95		6	3:1 B:A	21
9	α-methyl styrene	B_2pin_2		100 (94)		4	3:1 B:A	90
10	α-methyl styrene	B_2pin_2	4	96		2	B	54
11	α-methyl styrene	B_2pin_2		100		6	A	52
12	α-methyl styrene[g]	B_2pin_2	6	94		2	3:1 B:A	89
13	α-methyl styrene	HBpin	5	95		2	3:1 B:A	55[i]
14	α-methyl styrene	B_2neop_2		100 (98)		2	3:1 B:A	49
15	α-methyl styrene	B_2neop_2	2	98 (99)		4	3:1 B:A	66
16	α-methyl styrene[e]	B_2neop_2	trace	100		2	3:1 B:A	98
17	α-methyl styrene[e]	B_2neop_2	trace	100		3	3:1 B:A	100
18	1,1-diphenylethylene	B_2pin_2		100		4	3:1 B:A	67
19	1,1-diphenylethylene	B_2pin_2	9	91		1	B	76
20	1,1-diphenylethylene	B_2pin_2		100		4	A	48
21	1,1-diphenylethylene[h]	B_2pin_2		100		3	3:1 B:A	70
22	1,1-diphenylethylene[g]	B_2pin_2	1	96	3	3	3:1 B:A	100
23	1,1-diphenylethylene	HBpin	16	84		2	3:1 B:A	49
24	1,1-diphenylethylene	B_2neop_2		100		2	3:1 B:A	29
25	methylene cyclopentane	B_2pin_2		100 (92, 5, 3)		3	3:1 B:A	96[i]
26	methylene cyclohexane	B_2pin_2		100		5	3:1 B:A	86[i]
27	methylene cyclohexane[g]	B_2pin_2		100		5	3:1 B:A	96[i]

[a] For detailed reaction condition, see experimental section. Reactions were carried out in deuterated solvents. Conversion and product distributions were determined by in situ GC/MS spectroscopy. [b] VBE = vinylboronate ester. [c] VBBE = vinyl-bis(boronate) ester. [d] B = benzene-d_6, A = acetonitrile-d_3. [e] 1 equiv. of B_2neop_2 used. [f] 2 equiv. of B_2pin_2 and 5 mol% of catalyst used. [g] 1 equiv. of B_2pin_2 used. [h] 5 mol% of catalyst used. [i] conversion determined by ^{1}H-NMR.

2.4 VBEs from Microwave-Assisted Synthesis

The application of microwave irradiation in organic synthesis has increased recently.[48] This source of energy can be optimised to synthesise a variety of organic and drug compounds,[49-51] which have been synthesised previously by thermal methods. In addition, microwave technology can be used in polymer synthesis,[52] alkene decomposition,[53] hydrolysis of proteins and peptides,[54] and in inorganic and solid state synthesis.[55,56]

In the thermal reactions, the reactants are slowly activated by the external heating source. The heat passes the walls of the glass container, and then reaches the solvent and reactants. This method requires time to reach the required temperature.

In microwave technology, the microwave energy excites the solvent and/or the reactants, leading to a rapid rise in temperature. The time of transfer of this energy to the entering solvent and reactants is less than a nanosecond (10^{-9} s). Building on the results that have been obtained over the last fifteen years, it has been found that microwave heating reaction rates are faster than thermal heating by a factor of 1000.[48]

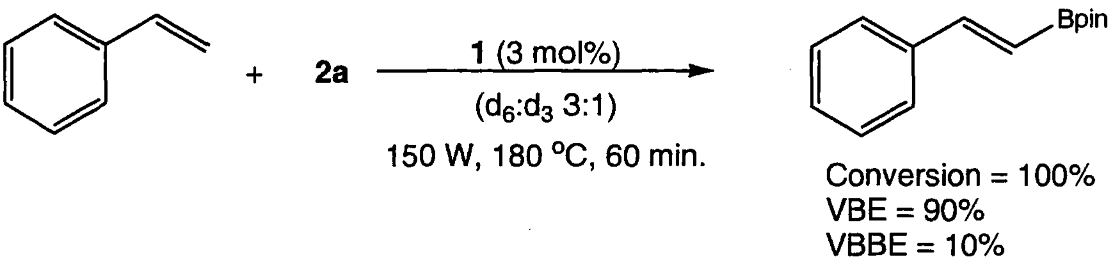
Increasing the polarity of the solvents or reactants, causes increasing absorption of the microwave energy, which allows reaching high temperatures, often exceeding more than the boiling point of the solvents. In general term, microwave irradiation can directly activate most molecules that have a dipole moment or are ionic.

Here, the synthesis of VBEs *via* microwave heating will be addressed. All the thermal reactions (discussed in section 2.2) were re-examined using microwave heating with the same conditions, unless otherwise stated. The reactions were carried out in the presence of alkenes and 3 mol% of **1** with 0.67 equiv. of **2a** in a mixture of deuterated solvents

(3:1 d_6:d_3) under a variety conditions. Again, the use of deuterated solvents allowed the selectivities and conversions to be measured by *in situ* ^{1}H NMR spectroscopy, and these are compared to those obtained from conventional thermal reactions which were also examined by *in situ* ^{1}H NMR spectroscopy. It should be noted that the reactions of styrene, 1-octene, indene and 1,1-diphenylethylene were carried out in a CEM microwave reactor maximum at 150 W microwave power and 150 °C, unless otherwise stated. On the other hand, the reactions of 4-vinylanisole and α-methylstyrene were carried out in Biotage Personal Chemistry Optimizer Exp. Microwave reactor with a maximum input power 300 W to reach the required temperature of 150 °C. Once the required temperature was reached, monitored internally by an infrared sensor, the reactor automatically adjust the microwave input power to maintain the setpoint temperature.

2.5 Results and Discussion

The reaction of styrene (Table 3, Entry 1) with 0.67 equiv. of **2a** and 3 mol% of **1** in 2 ml of (3:1 d_6:d_3) was carried out 150 W at 180 °C (Eq. 2.5.1). The conversion was 100%, with 90% selectivity for VBE and 10% for VBBE after 60 minutes (Fig 2.5.1).



Eq. 2.5.1 Reaction of styrene with 0.67 equiv. of **2a**

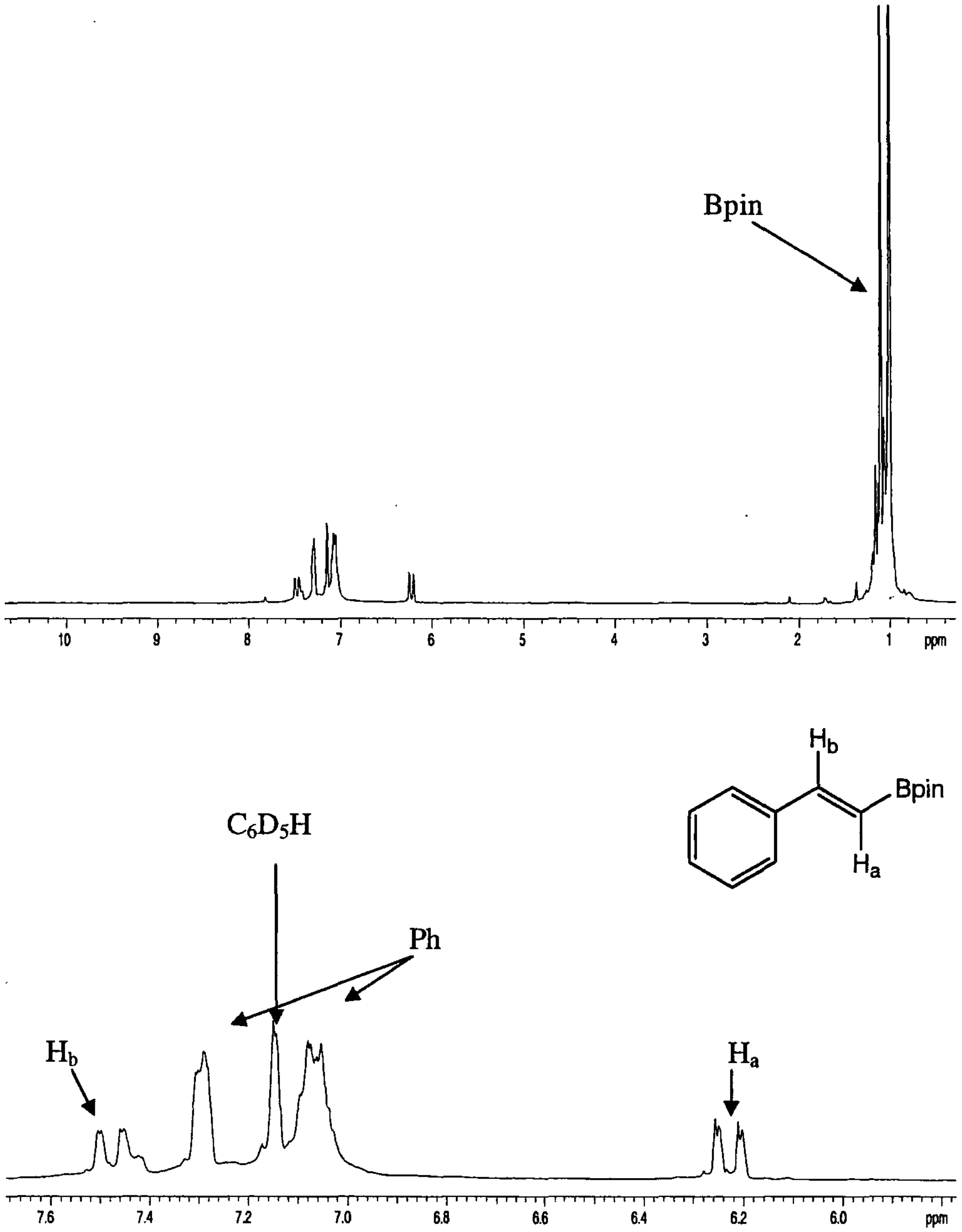
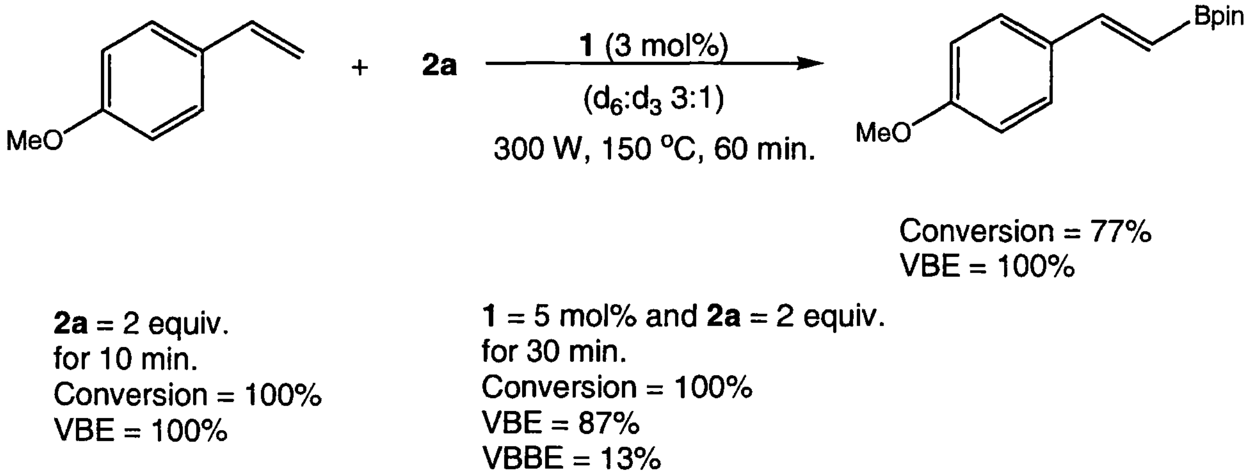


Fig. 2.5.1 Top: *In situ* ^{1}H NMR spectrum of the reaction of styrene with 0.67 equiv. of **2a**. Bottom: Expansion of the spectrum of VBE {(E)-(Ph)CH=CHBpin}

On the other hand, the reaction of VA (300 W) at 150 °C gave 77% conversion after 1 hour, with 100% selectivity for VBE (Eq. 2.5.2, Table 3, Entry, 2, Fig. 2.5.2 Top). Again, the reaction was examined with 2 equiv. of **2a** to improve the selectivity for VBBE. However, the reaction reached 100% conversion within 10 minutes giving 100% selectivity for VBE (Fig. 2.5.2 Bottom, Table 3, Entry 3). Increasing the time of the reaction to 30 and 60 minutes, using 5 mol% of **1**, gave 13% VBBE and 87% VBE with 100% conversion (Table 3, Entry 4). No difference was found between reaction turn of 30 or 60 minutes.



Eq. 2.5.2 Reaction VA with 0.67 and 2 equiv. of **2a**

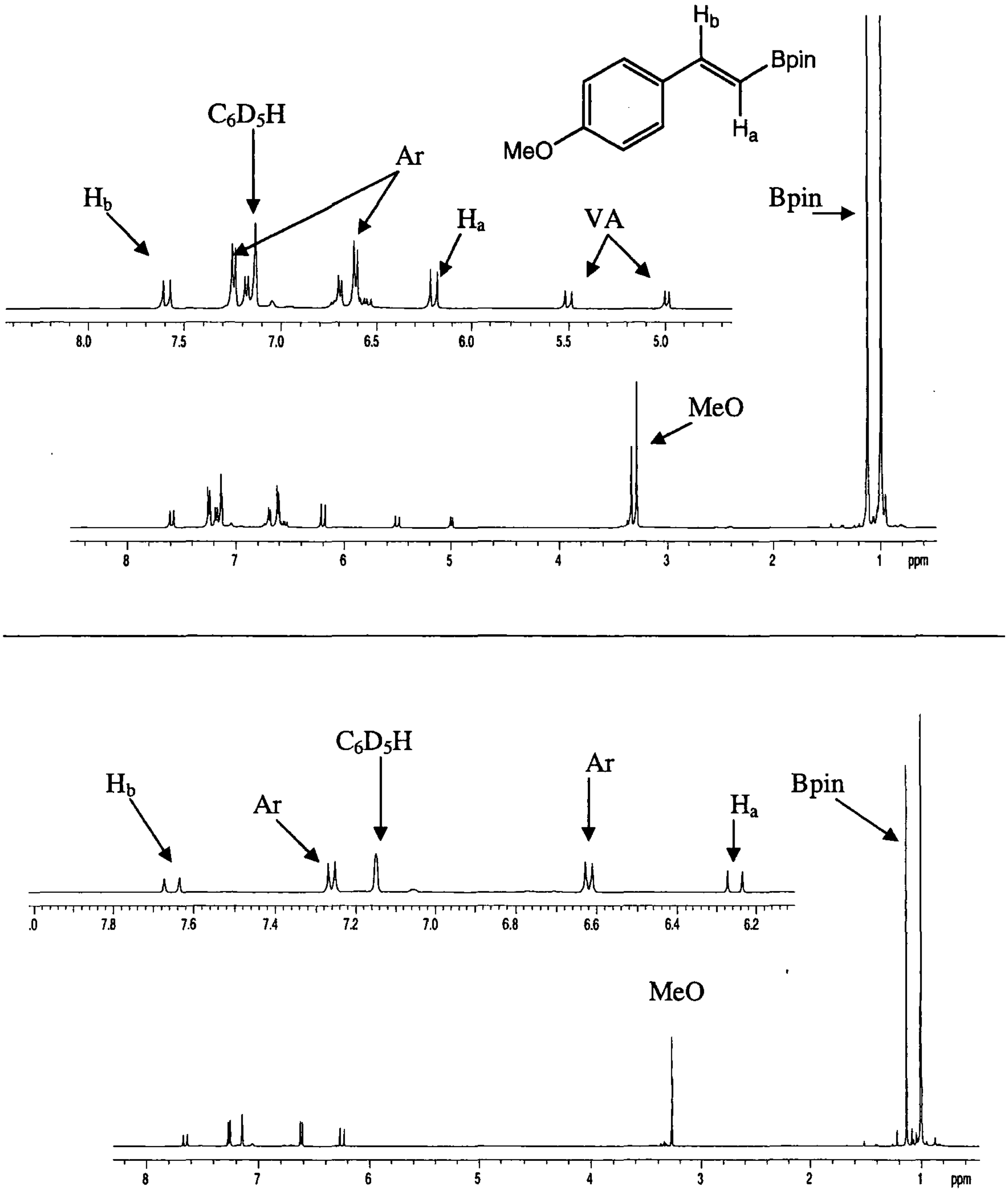


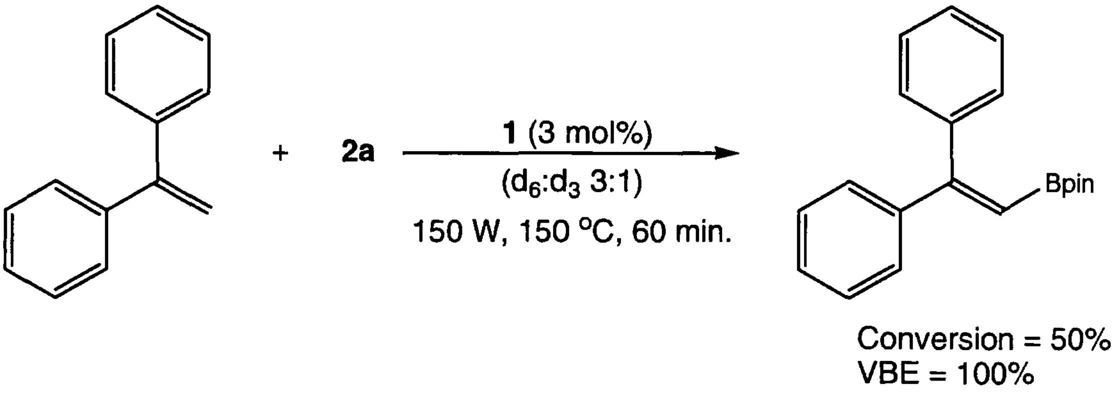
Fig. 2.5.2 Top: *In situ* ^{1}H NMR spectrum of the reaction of VA with 0.67 equiv. of **2b** after 60 minutes. Bottom: *In situ* ^{1}H NMR spectrum of the reaction of VA with 2 equiv. of **2b** after 10 minutes

The reaction of 1-octene with 0.67 equiv. of **2a** (150 W) at 150 °C for 10 minutes gave 100% conversion, with 35% VBE and 65% VBBE (Table 3, Entry 5).

The 1,2-disubstituted alkene, indene, is less reactive under microwave heating, gave only 5% conversion during 1 hour, but with 100% selectivity for VBE.

The 1,1-disubstituted alkenes, 1,1-diphenylethylene and α-methylstyrene were also examined using microwave heating, and again proved less reactivity than monosubstituted alkenes.

The reaction of 1,1-diphenylethylene was examined with 0.67 equiv. of **2a** in the presence of 3 mol% of **1** (150 W) at 150 °C for 60 minutes. The conversion was 50% with 100% selectivity for VBE (Table 3, Entry 7, Fig. 2.5.3 Top). Using 1 equiv. of **2a**, under the above conditions gave 83% conversion with 100% selectivity for VBE (Table 1, Entry 10, Fig. 2.5.3 Bottom). Increasing the concentration of catalyst to 5 mol%, with 0.67 equiv. of **2a** and (3:1 d_6:d_3), gave only 62% conversion (Table 3, Entry 11, Fig. 2.5.4).



Eq. 2.5.3 Reaction of 1,1-diphenylethylene with 0.67 equiv. of **2a**

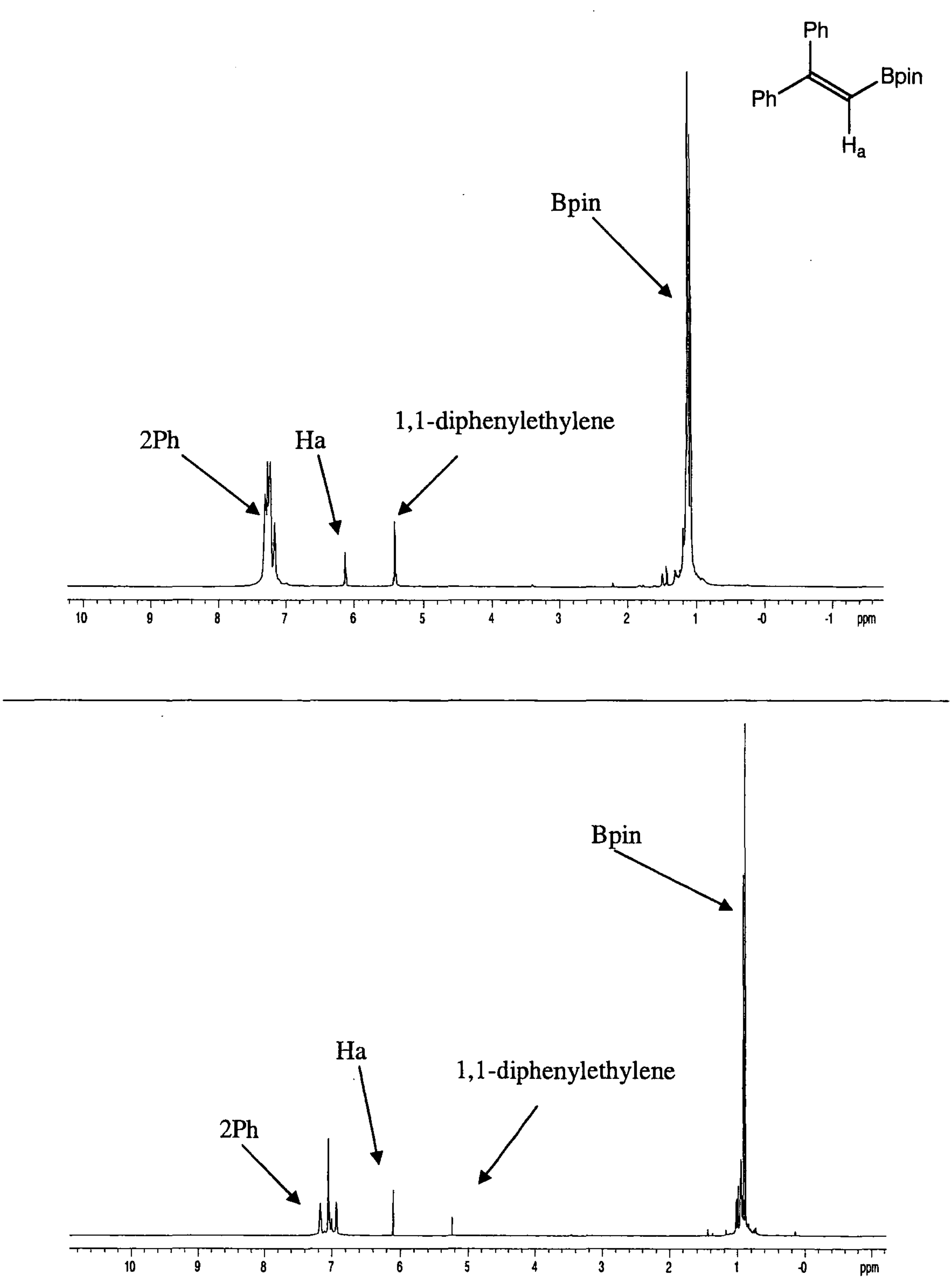


Fig. 2.5.3 Top: ^{1}H NMR spectrum of the reaction of 1,1-diphenylethylene with 0.67 equiv. of **2a** after 60 minutes. Bottom: ^{1}H NMR spectrum of the reaction of 1,1-diphenylethylene with 1 equiv. of **2a** after 60 minutes

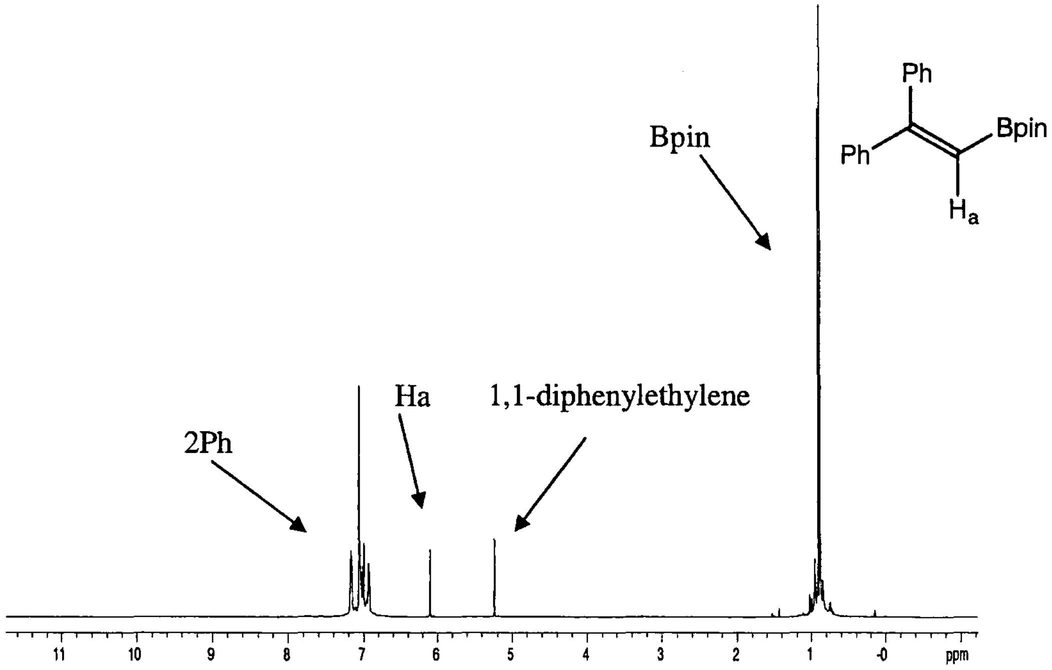
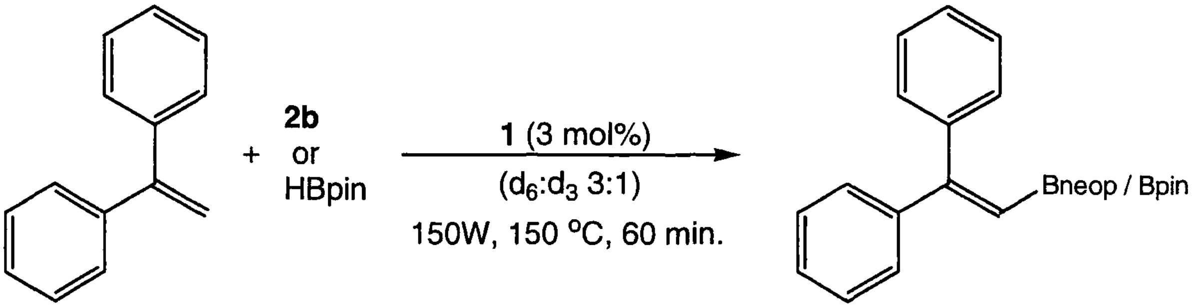


Fig. 2.5.4 ^{1}H NMR spectrum of the reaction of 1,1-diphenylethylene with 0.67 equiv. of **2a** in the presence of 5 mol% of **1** after 60 minutes

To investigate the solvent effect on the dehydrogenative borylation of 1,1-diphenylethylene, the reaction was carried out in neat benzene-d_6 and neat acetonitrile-d_3 (150 W) at 150 °C for 1 hour. The reaction in neat benzene-d_6 gave 95% selectivity for VBE with 5% of the common side product from hydroboration and 48% conversion (Table 3, Entry 8). On the other hand, the reaction in acetonitrile gave 44% conversion with 100% selectivity for VBE (Table 3, Entry 9). Using 1.34 equiv. of HBpin in place of B_2pin_2 the reaction gave only 39% conversion after 1 hour with 100% selectivity for VBE (Table 3, Entry 12), whereas using 0.67 equiv. of **2b** gave 29% conversion after 1 hour with 100% selectivity for VBE (Table 3, Entry 13).

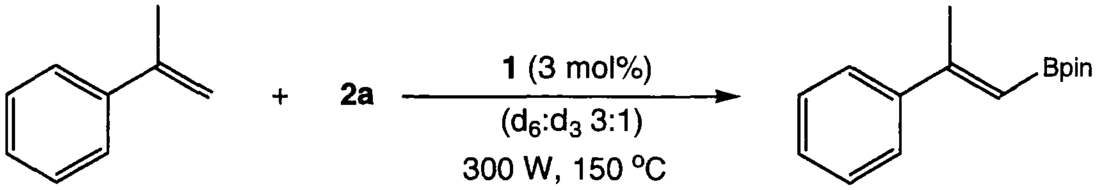


1.34 equiv. of HBpin
Conversion = 39%
VBE = 100%

0.67 equiv. of **2b**
Conversion = 29%
VBE = 100%

Eq. 2.5.4 Reaction of 1,1-diphenylethylene with 0.67 equiv. of **2b** and 1.34 equiv. of HBpin

Finally, the reaction of α-methylstyrene was examined (300 W) at 150 °C with 0.67 equiv. of **2a** in the presence of 3 mol% of **1**. After 1 hour, the reaction gave 100% selectivity for VBE with 55% conversion (Fig. 2.6.3 Top, Table 3, Entry 14). Using 2 equiv. of **2a**, increased the conversion slightly to 65% after 30 minutes with 100% selectivity for VBE (Table 3, Entry15). Similar conversion and selectivity were observed when the time of the reaction was extended to 60 minutes.



2 equiv. of **2a** for 30 min.
Conversion =65%
VBE = 100%

0.67 equiv. **2a** for 60 min.
Conversion = 55%
VBE = 100%

Eq. 2.5.5 Reaction of α-methylstyrene with 0.67 and 2 equiv. of **2a**

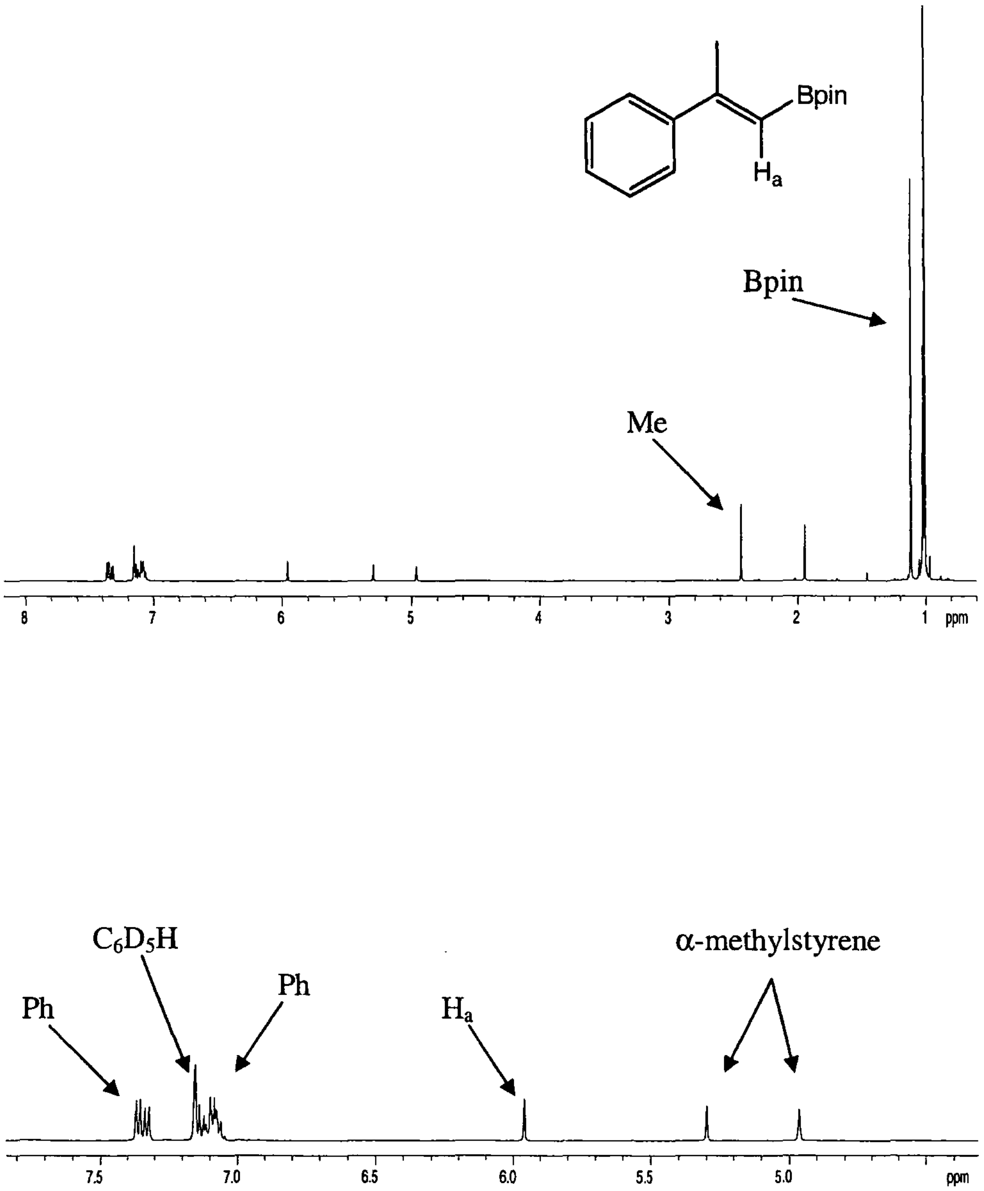


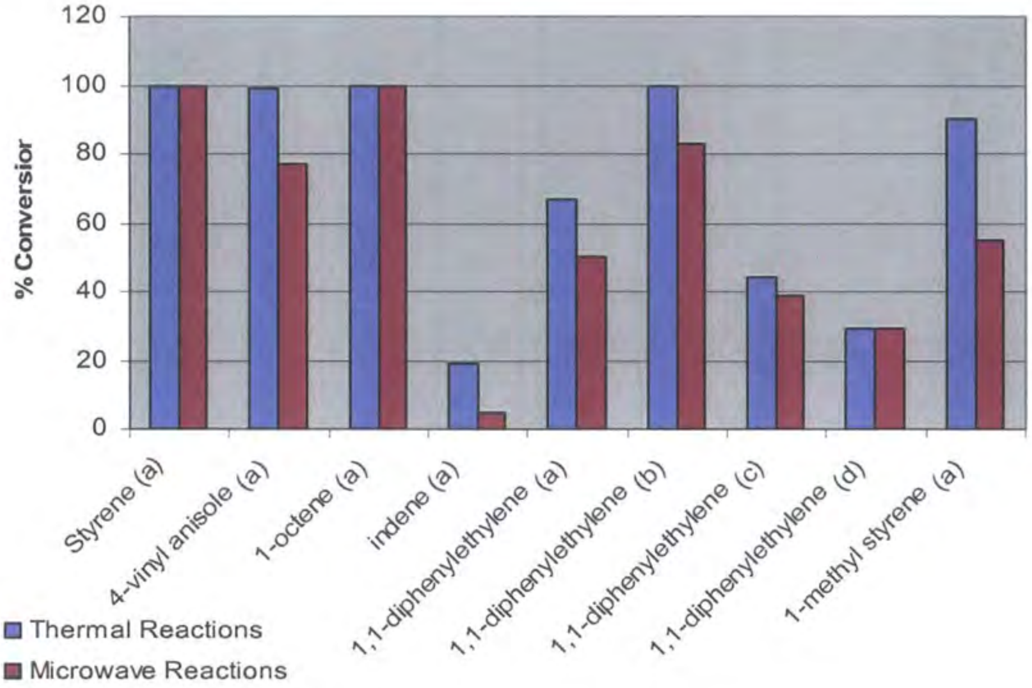
Fig. 2.5.3 Top: ^{1}H NMR spectrum of the reaction of α-methylstyrene with 0.67 equiv. of **2a** Bottom: expansion of NMR spectrum of VBE {(E)-(Ph)C(Me)=CHBpin}

Table 3 Product distributions and conversions for the dehydrogenative borylation of alkenes using microwave heating.[a]

Entry	Substrate	Boron Reagent	Hydroboration %	Total VBE (Maj.isomer) %	Total VBBE (Maj.isomer) %	Solvent[b]	Conversion %
1	styrene[c]	B_2pin_2		90	10	3:1 B:A	100
2	4-vinyl anisole	B_2pin_2		100		3:1 B:A	77
3	4-vinyl anisole[d,e]	B_2pin_2		100		3:1 B:A	100
4	4-vinyl anisole[d,f,g]	B_2pin_2		87	13	3:1 B:A	100
5	1-octene[e]	B_2pin_2		35	65	3:1 B:A	100
6	indene	B_2pin_2		100		3:1 B:A	5
7	1,1-diphenylethylene	B_2pin_2		100		3:1 B:A	50
8	1,1-diphenylethylene	B_2pin_2	5	95		B	48
9	1,1-diphenylethylene	B_2pin_2		100		A	44
10	1,1-diphenylethylene[g]	B_2pin_2		100		3:1 B:A	62
11	1,1-diphenylethylene[h]	B_2pin_2		100		3:1 B:A	83
12	1,1-diphenylethylene	HBpin		100		3:1 B:A	39
13	1,1-diphenylethylene	B_2neop_2		100		3:1 B:A	29
14	α-methyl styrene	B_2pin_2		100		3:1 B:A	55
15	α-methyl styrene[d,f]	B_2pin_2		100		3:1 B:A	65

[a] The reaction conditions:- in a nitrogen-filled glove box, a mixture of boron reagent (0.4 mmol total boron) and alkene (0.3 mmol) in 1 ml of solvent was added to a solution of *trans*-$[Rh(Cl)(CO)(PPh_3)_2]$ (3 mol%) in 1 ml of solvent (2 ml total solvent volume). The mixture was shaken vigorously to ensure complete mixing, transferred to microwave tubes (5 ml), and then heated (150 W) at 150 °C for 60 min. Reactions were carried out in deuterated solvents. Conversion and product distributions were determined by *in situ* ^1H NMR. [b] B = benzene-d_6, A = acetonitrile-d_3. [c] 180 °C used. [d] 2 equiv. of B_2pin_2 used. [e] 10 min heating. [f] 30 min heating. [g] 5 mol% of catalyst used. [h] 1 equiv. of B_2pin_2 used. Reactions of styrene, 1-octene, indene and 1,1-diphenylethylene were carried out in a CEM microwave reactor (150 W) at 150 °C, unless otherwise stated. Reactions of 4-vinylanisole and α-methylstyrene were carried out in a Biotage Personal Chemistry Optimizer Exp., (300 W) at 150 °C.

2.6 Comparison between thermal and microwave results



a = 0. 67 equiv. of **2a** used, b = 1 equiv. of **2a** used, c = 1.34 equiv. of HBpin used, d = 0. 67 equiv. of **2b** used

Chart 2.6.1 Comparison between the conversion of some of thermal reactions and microwave reactor reactions

The conversions of styrene by thermal or microwave heating were similar, and the distribution was 90% VBE and 10% VBBE by microwave heating at 180 °C and 86% VBE, 11% for VBBE and 3% hydroboration under conventional heating at 80 °C. Thus in this case, the microwave reactions were cleaner than the thermal reaction.

The reaction of VA with 0.67 equiv. of **2a** at 80 °C gave 99% conversion with 98% selectivity for VBE in 2 days. On the other hand, the microwave reaction gave 77% conversion with 100% selectivity for VBE at 150 °C in 60 minutes but went to completion in only 10 minutes using 2 equiv. of **2a**. In contrast, 93% selectivity for VBBE was observed in the thermal reaction of VA with 2 equiv. of **2a** and 5 mol% of **1** at 80 °C with 7% VBE and 100% conversion. In spite of the presence of 2 equiv. of **2a** and 5 mol% of **1**, the microwave reaction gave only 13% VBBE, with 87% VBE and 100% conversion in 1 hour.

The reaction of 1-octene with 0.67 equiv. of **2a** gave the same conversion (100%) and the same selectivities for VBE and VBBE by both (thermal and microwave heating). However, thermal reaction at 80 °C took 3 days, whereas only 10 minutes were required at 150 °C using the microwave reactor.

Indene showed even less reactivity in the microwave reaction, giving only 5% conversion after 1 hour, whereas 19% conversion was observed at 80 °C after 6 days.

The reaction of 1,1-diphenylethylene with 0.67 equiv. of **2a** gave 67% conversion after 3 days at 80 °C and 50% conversion by the microwave reaction after 1 hour with the same selectivity for VBE. Moreover, increasing the amount of **2a** to 1 equiv. with 1,1-diphenylethylene in the microwave reaction gave 83% conversion after 1 hour. On the other hand, 1 equiv. of **2a** was sufficient to obtain complete reaction, with 100% selectivity for VBE at 80 °C in 3 days. The reaction of 1,1-dipheneylethylene with 0.67 equiv. of **2a** in the presence of 5 mol% of **1** gave 70% conversion after 3 days at 80 °C, but 62% in the microwave reaction after 1 hour.

In addition, the reactions of 1,1-diphenylethylene in neat benzene-d_6 and acetonitrile-d_3, were compared. In acetonitrile-d_3 the conversion and selectivity were similar with 48% conversion thermally after 4 days, and 44% conversion during 1 hour by microwave reacting. On the other hand, the conversion in benzene-d_6 is higher by the thermal technique being 71% during 1 day but 48% by microwave reactor during 1 hour.

Similar conversion and selectivity was observed in the reaction of 1,1-diphenylethylene with **2b** by microwave reactor and thermal reaction. The conversions for the thermal reaction at 80 °C of 1,1-diphenylethylene with HBpin and **2b** were 44% and 29% respectively, and 39% and 29% respectively using microwave reactor.

The reaction of α-methylstyrene with 0.67 equiv. of **2a** gave 90% conversion thermally after 2 days with 100% selectivity for VBE. The microwave reaction, gave only 55% conversion with 0.67 equiv. of **2a** and only 65% conversion when the amount of **2a** was increased to 2 equiv.

From chart 2.6.1, and Tables 1,2, and 3, it can be seen that the distributions of products were fairly similar but the overall conversions often significantly higher in the thermal reactions compared to the microwave ones. However, the microwave technique was a useful way to reduce the reactions times from days to minutes.

2.7 Conclusion

In conclusion, mono and 1,1-disubstituted alkenes can be converted into VBEs in high yield and with excellent selectivity by dehydrogenative borylation of C-H bonds using the simple catalyst, **1**, and commercially available boron reagents, **2a** and **2b**.

Proton NMR spectroscopy, which was used to determine the conversions of the reactions, was more accurate than GC/MS (Table 1) due to the fact that the NMR technique does not depend on a response factor for each compound; however, it is difficult to estimate, by ^{1}H NMR, the side products such as those arising from hydroboration and hydrogenation if they are present in very small quantities. The GC/MS is a useful technique and depends on the ability of the volatile organic molecules to travel along the column. Table 2 shows somewhat higher conversions than measured by NMR and also shows more of some of the small side products, which were not always observed by NMR spectroscopy. To improve the accuracy, of the GC/MS method, it is necessary to obtain response factors for the starting materials and every product; however, this is not always practical, especially when many different substrates are employed, as it would entail isolation of every possible product and isomer. What is clear, however, is that, in this study, closely related isomeric products have very similar response factors, and that hydroboration products have larger response factors than VBEs, which in turn have larger response factors than the hydrocarbons. In any event, the differences are not very large, and for this chemistry, GC/MS, even without predetermined response factors, provides reasonable quality data which can be considered as at least semi-quantitative.

Microwave heating is a useful technique to reduce the time of the reaction from days to minutes. Noting that the temperatures used in the two types of reactions were 80 ^{o}C and

150 °C, and that, as a rule of thumb, one may expect an approximate doubling of reaction rates with every 10 °C increase in temperature, so we might expect rate increases of ca. $2^7 = 128$ in the microwave reactions. Thus, 60 minutes at 150 °C is roughly comparable to 5 days at 80 °C. With this in mind, we can suggest that there is nothing unusual about the microwave results to imply any special effect rather than the ability to safely and rapidly heat the sample to 150 °C, well above the solvent boiling points and, in a sealed system, allowing for convenient, rapid reactions. However, two important points are worth noting. First, as these are carried out in sealed tubes, the higher temperature results in a much higher pressure which could well inhibit the reactions, especially, those producing gaseous products such as H_2. Obviously, care needs to be taken to calculate the maximum potential pressure to avoid explosions, if possible, although the reactor monitors pressure *in situ* and shuts off heating when a preselected maximum (safe) pressure is reached. In addition, the reactor is designed to withstand explosion of the special thick walled glass reaction tubes. Secondly, we must also consider the possibility that catalyst deactivation becomes important at 150 °C such that reluctant substrates may give even lower overall conversions at this temperature.

The distributions of products were usually very similar to the thermal reactions. Mono substituted alkenes such as styrene and VA can reach completion with good selectivity for VBEs with styrene or increasing the concentration of **2a** with VA. On the other hand, 1,1-disubstituted alkenes such as 1,1-diphenylethylene and α-methylstyrene did not reach completion in the microwave reaction; however, half of the alkenes were converted to the VBE without any significant amount of side products such as hydroboration or hydrogenation. Therefore, synthesis of VBEs using the microwave reactor as a source of the energy is possible.

2.8 Experimental section

All reactions were carried out under a dry nitrogen atmosphere using standard Schlenk techniques or in an Innovative Technology, Inc. System 1 glove box. Glassware was oven dried before transfer into the glove box. Toluene was dried and deoxygenated by passage through columns of activated alumina and BASF-R311 catalyst under Ar pressure using a locally modified version of the Innovative Technology, Inc. SPS-400 solvent purification system. The solvents CH_3CN, CD_3CN, C_6D_6 and $CDCl_3$ were dried over calcium hydride, and 1,4-dioxane, THF and C_7D_8 were dried over sodium/benzophenone; all were distilled under nitrogen. B_2pin_2 and B_2neop_2 supplied as a gift by Frontier Scientific Inc. and NetChem Inc. All other compounds were obtained from Aldrich Chemical Company, tested for purity by GC/MS and used without further purification. The catalyst precursor *trans*-[RhCl(CO)(PPh_3)$_2$] was prepared using published procedures and checked for purity by NMR.[58,59] NMR spectra were recorded at 25°C on Varian Inova 500 (^1H, $^{13}C\{^1H\}$, HSQC), Varian C 500 (^1H, $^{13}C\{^1H\}$, HSQC), Varian Unity 300 (^{11}B and $^{11}B\{^1H\}$) and Bruker AC200 ($^{13}C\{^1H\}$) instruments. Proton and carbon spectra were referenced to external $SiMe_4$ via residual protons in the deuterated solvents or solvent resonances respectively. ^{11}B chemical shifts were referenced to external $BF_3{\cdot}OEt_3$. Elemental analyses were conducted in the Department of Chemistry at the University of Durham using an Exeter Analytical Inc. CE-440 Elemental Analyzer. GC/MS analyses were performed on a Hewlett-Packard 5890 Series II gas chromatograph equipped with a 5971A mass selective detector and a 7673 autosampler. A fused silica capillary column (10m or 12m cross-linked 5% phenylmethylsilicone) was used, and the oven temperature was ramped from 50°C to 280°C at a rate of 20°C/min. UHP grade helium was used as the carrier gas. The screw-cap autosampler vials used were supplied by Thermoquest Inc. and were fitted with teflon/silicone/teflon septa and 0.2 ml micro inserts. Microwave reactions were carried out in a CEM Corporation and Biotage Personal Chemistry Optimizer Exp., which using liquid handling system / autosampler reactors. The reactions carried in thick-walled glass reaction tubes with septum seals specifically designed to with stand the pressures generated.

General Procedures

Thermal Reactions:

To a solution of *trans*-[Rh(Cl)(CO)(PPh_3)$_2$] (3 mol%) in 1 ml of solvent was added a mixture of boron reagent (0.4 mmol total boron) and alkene (0.3 mmol) in 1 ml of solvent (2 ml total solvent volume). The mixture was shaken vigorously to ensure complete mixing, transferred to ampoules sealed with a Teflon Young's tap and then heated to 80 °C. The reaction was monitored by either GC-MS or a combination of GC-MS and NMR spectroscopy.

Microwave Reactions:

Solutions were prepared as a above. The mixture was shaken vigorously to ensure complete mixing, transferred thick-walled glass reaction tubes (Microwave Tubes) and then heated to 150 °C. The reaction was monitored by either NMR or a combination of GC/MS and NMR spectroscopy. Reactions of styrene, 1-octene, indene and 1,1-diphenylethylene were carried out in a CEM microwave reactor (150 W) at 150 °C, unless otherwise stated. Reactions of 4-vinylanisole and α-methylstyrene were carried out in Biotage Personal Chemistry Optimizer Exp., (300 W) at 150 °C.

(E)-(Ph)CH=CH(Bpin): ^{1}H NMR (400 MHz, C_6D_6): δ 1.17 (s, 12H; **Bpin**), 6.39 (d, ^{3}J(H,H) = 18 Hz, 1H; =**CH**Bpin), 7.08 (m, 3H; $C_6\mathbf{H_5}$), 7.31 (m, 2H; $C_6\mathbf{H_5}$), 7.68 (d, ^{3}J(H,H) = 18 Hz, 1H; Ph**CH=**); ^{13}C{^{1}H} NMR (100 MHz, C_6D_6): δ 24.42 (s, $BO_2C_2(CH_3)_4$), 83.43 (s, $BO_2\mathbf{C_2}(CH_3)_4$), 127.22, 128.81, 129.33, 137.81 (s, $\mathbf{C_6}H_5$), 149.83 (s, PhCH=), the resonance for the carbon attached to boron was not observed; ^{11}B{^{1}H} NMR (128.4 MHz, C_6D_6): δ 30.30 (s, br); MS (EI): m/z : 230 [M^{+}], 215 [M-Me^{+}].

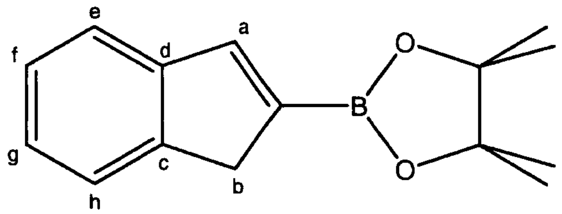
(E)-CH$_3$O-C$_6$H$_4$CH=CH(Bpin): ^{1}H NMR (500 MHz, C_6D_6): δ 1.24 (s, 12H; Bpin), 3.37 (s, 3H; **CH$_3$**O), 6.25 (d, ^{3}J(H,H) = 18 Hz, 1H; =**CH**Bpin), 6.75 (d, ^{3}J(H,H) = 9 Hz, 2H; *o*-$C_6\mathbf{H_4}$), 7.41 (d, ^{3}J(H,H) = 9 Hz, 2H; *m*-$C_6\mathbf{H_4}$), 7.60 (d, ^{3}J(H,H) = 18 Hz, 1H; Ar**CH=**); ^{13}C{^{1}H} NMR (100 MHz, C_6D_6): δ 24.82 (s, $BO_2C_2(CH_3)_4$), 54.63 (s, **C**H$_3$O), 83.42 (s, $BO_2\mathbf{C_2}(CH_3)_4$), 127.19, 128.78, 129.27, 137.82 (s, $\mathbf{C_6}H_4$), 145.11 (s, ArCH=), the resonance for the carbon attached to boron was not observed; ^{11}B{^{1}H} NMR (128.4 MHz, C_6D_6): δ 30.30 (s, br); MS (EI): m/z: 260 [M^{+}], 246 [M-Me^{+}].

4-MeO-C$_6$H$_4$CH=C(Bpin)$_2$: ^{1}H NMR (500 MHz, C_6D_6): δ 1.24 (s, 24H; Bpin), 3.31 (s, 3H; **CH$_3$**O), 6.70 (d, ^{3}J(H,H) = 8 Hz, 2H; *o*-$C_6\mathbf{H_4}$), 7.49 (d, ^{3}J(H,H) = 8 Hz, 2H; *m*-$C_6\mathbf{H_4}$), 7.98 (s, 1H; Ar**CH=**); ^{13}C{^{1}H} NMR (100 MHz, C_6D_6): δ 24.83 (s, $BO_2C_2(CH_3)_4$), 54.62 (s, **C**H$_3$O), 83.42 (s, $BO_2C_2(CH_3)_4$), 127.21, 128.83, 129.33, 137.83 (s, $\mathbf{C_6}H_4$), 145.12 (s, ArCH=), the resonance for the carbon attached to boron was not observed; ^{11}B{^{1}H} NMR (128.4 MHz, C_6D_6): δ 30.25 (s, br); MS (EI): m/z : 364 [M^{+}], 349 [M-Me^{+}].

(E)-4-MeO-C_6H_4CH=CH(Bneop): ^{1}H NMR (400 MHz, C_6D_6): δ 0.64 (s, 6H; Bneop-CH_3), 3.32 (s, 4H; Bneop-CH_2), 3.41 (s, 3H; CH_3O), 6.39 (d, ^3J(H,H) = 18 Hz, 1H; =CHBneop), 6.54 (d, ^3J(H,H) = 8 Hz, 2H; *o*-C_6H_4), 7.35 (d, ^3J(H,H) = 8 Hz, 2H; *m*-C_6H_4) 7.75 (d, ^3J(H,H) = 18 Hz, 1H; ArCH=); $^{13}C\{^1H\}$ NMR (100 MHz, C_6D_6): δ 21.52 (s, Bneop-CH_3), 31.62 (s, neop-CMe_2), 71.65 (s, Bneop-CH_2), 72.22 (s, CH_3O), 116.11, 128.79, 132.22 (s,C_6H_4), 147.87 (s, ArCH=), 161 (s, C_6H_4), the resonance for the carbon attached to boron was not observed; $^{11}B\{^1H\}$ NMR (128.4 MHz, C_6D_6): δ 27.11 (s, br); MS (EI): m/z (rel. int.): 256 [M^+], 231 [M-Me^+].

$CH_3(CH_2)_5CH=C(Bpin)_2$: ^{1}H NMR (400 MHz, C_6D_6): δ 0.76 (t, $^3J_{H-H}$ = 7 Hz, 3H, CH_3), 0.89-1.13 (m, 32H, $(Bpin)_2$ +$(CH_2)_4$), 2.25 (q, $^3J_{H-H}$ = 7, 2H, =CH$CH_2(CH_2)_4$), 6.62 (m, 1H, CH=C$(Bpin)_2$); $^{13}C\{^1H\}$ NMR (100 MHz, C_6D_6): δ 14.10 (s, CH_3), 22.67 (s, $CH_3CH_2(CH)_4$), 24.61 (s, $C_3H_6CH_2CH_3$), 24.67, 24.81 (s, $BO_2C_2(CH_3)_4$), 29.42 (s, $C_3H_6CH_2CH_3$), 31.56 (s, $C_3H_6CH_2CH_3$), 32.78 (s, $CH_2CH=C(Bpin)_2$), 83.10 (s, $BO_2C_2(CH_3)_4$), 163.72 (s, $CH_2CH=C(Bpin)$, the resonance for the carbon attached to boron was not observed; $^{11}B\{^1H\}$ NMR (128.4 MHz, C_6D_6): δ 28.30 (s, br); MS (EI): m/z: 364 [M^+], 349 [M-Me^+].

2-indenyl(Bpin):



^{1}H NMR (400 MHz, C_6D_6): δ 1.26 (s, 12H, Bpin), 3.28 (s, 2H, **b**), 7.14-7.42 (m, 4H, **e**, **f**, **g**, **h**), 8.14 (s, 1H, **a**); ^{13}C{^{1}H} NMR (100 MHz, C_6D_6): δ 22.67 (s, $BO_2C_2(CH_3)_4$), 38.19 (s, **b**), 83.21, 83.33 (s, $BO_2C_2(CH_3)_4$), 124.56, 125.80, 126.12, 126.32 (s, **e**, **f**, **g**, **h**) 134.21, 134.78 (s, **c**, **d**), 149.4 (s, **a**); the resonance for the carbon attached to boron was not observed ^{11}B{^{1}H} NMR (128.4 MHz, C_6D_6): δ 28.30 (s, br); MS (EI): m/z: 242 [M^+], 227 [$M-Me^+$].

(E)-(Ph)C(Me)=CH(Bpin):^{1}H NMR (400 MHz, C_6D_6): δ 1.20 (s, 12H; Bpin), 2.49 (s, 3H; **CH_3**PhC=), 6.15 (s, 1H; =**CH**Bpin), 7.17 (m, 3H; C_6**H_5**), 7.44 (m, 2H; C_6**H_5**), ^{13}C{^{1}H} NMR (100 MHz, C_6D_6): δ 21.82 (s, **CH_3**PhC=), 24.81 (s, $BO_2C_2(CH_3)_4$), 83.41 (s, $BO_2C_2(CH_3)_4$), 127.21, 128.81, 129.32, 137.78 (s, **C_6**H_5), 157.78 (s, CH_3PhC=), the resonance for the carbon attached to boron was not observed; ^{11}B{^{1}H} NMR (128.4 MHz, C_6D_6): δ 30.25 (s, br); MS (EI): m/z (rel. int.): 244 (89) [M^+], 230 (24) [$M-Me^+$].

(E)-PhC(Me)=CH(Bneop): ^{1}H NMR (400 MHz, C_6D_6): δ 0.60 (s, 6H; Bneop-**CH_3**), 2.56 (s, 3H; **CH_3**PhC=), 3.31 (s, 4H; Bneop-**CH_2**), 6.14 (s 1H; =**CH**Bneop), 7.10 (m, 3H; C_6**H_5**), 7.47 (d, ^3J(H,H) = 8 Hz, 2H; *o*-C_6**H_4**); ^{13}C{^{1}H} NMR (100 MHz, C_6D_6): δ 21.41

(s, $CH_3PhC=$); 21.89 (s, Bneop-CH_3); 31.56 (s, neop-CMe_2); 73.21 (s, Bneop-CH_2); 126.27, 128.21, 128.56, 143.60, (C_6H_5); 156.10 (s, MePhC=), the resonance for the carbon attached to boron was not observed; $^{11}B\{^1H\}$ NMR (128.4 MHz, C_6D_6): δ 27.10 (s, br); MS (EI): m/z: 230 [M^+], 215 [$M\text{-}Me^+$].

$Ph_2C=CH(Bpin)$: ^1H NMR (400 MHz, C_6D_6): δ 1.1 (s, 12H, Bpin), 6.22 (s, 1H, =**CH**Bpin), 7.16-7.38 (m, 10H, Ph); $^{13}C\{^1H\}$ NMR (100 MHz, C_6D_6): δ 24.5 (s, $BO_2C_2(CH_3)_4$), 83.10 (s, $BO_2C_2(CH_3)_4$), 119.06 (s, br, =CHBpin) 128.21, 128.33, 130.32, 143.23 (s, Ph), 160.31 (s, $Ph_2C=$); $^{11}B\{^1H\}$ NMR (128.4 MHz, C_6D_6): δ 30.20 (s, br); MS (EI): m/z: 306 [M^+], 291 [$M\text{-}Me^+$].

$Ph_2C=CH(Bneop)$: ^1H NMR (400 MHz, C_6D_6): δ 0.50 (s, 6H, neop-CH_3), 3.15 (s, 4H, neop-CH_2), 5.96 (s, 1H, =**CH**Bneop) 6.91-7.11 (m, 10H, Ph); $^{13}C\{^1H\}$ NMR (100 MHz, C_6D_6): δ 21.71 (s, neop-CH_3), 31.42 (s, neop-$C(CH_3)_2$), 71.60 (s, neop-CH_2), 122.10 (s, br, =CHBneop) 128.60, 128.71, 130.30, 143.10 (s, Ph), 158.41 (s, $Ph_2C=$); $^{11}B\{^1H\}$ NMR (128.4 MHz, C_6D_6): δ 26.80 (s, br); MS (EI): m/z: 292 [M^+], 277 [$M\text{-}Me^+$].

$C_5H_8=CH(Bpin)$: ^1H NMR (500 MHz, C_6D_6): δ 1.09 (s, 12H; Bpin), 1.41 (m, 2H; CH_2), 1.51 (m, 2H; CH_2), 2.24 (t, $^3J_{H\text{-}H}$ = 7 Hz, 2H; CH_2), 2.69 (t, $^3J_{H\text{-}H}$ = 7 Hz, 2H; CH_2), 5.58 (s, 1H; =**CH**Bpin); $^{13}C\{^1H\}$ NMR (126 MHz, C_6D_6): δ 25.14 (s, $BO_2C_2(CH_3)_4$), 26.34 (s, CH_2), 27.34 (s, CH_2), 33.87 (s, CH_2), 37.39 (s, CH_2), 82.64 (s, $BO_2C_2(CH_3)_4$), 110.10 (s, br, =CHBpin), 171.67 (s, C=CHBpin); $^{11}B\{^1H\}$ NMR (128.4 MHz, C_6D_6): δ 30.20 (s, br); MS (EI): m/z: 208 [M^+], 194 [$M\text{-}Me^+$].

C_6H_{10}=CH(Bpin): ^{1}H NMR (500 MHz, C_6D_6): δ 1.24 (s, 12H; Bpin), 1.35 (m, 2H; **CH_2**), 1.43 (m, 2H; **CH_2**), 1.51 (m, 2H; **CH_2**), 2.10 (t, $^3J_{H\text{-}H}$ = 6 Hz, 2H; **CH_2**), 2.68 (t, $^3J_{H\text{-}H}$ = 6 Hz, 2H; **CH_2**), 5.29 (s, 1H; =**C**HBpin); ^{13}C{^{1}H} NMR (126 MHz, C_6D_6): δ 25.20 (s, $BO_2C_2(CH_3)_4$), 26.80 (s, **CH_2**), 28.89 (s, **CH_2**), 29.10 (s, **CH_2**), 33.52 (s, **CH_2**), 40.51 (s, **CH_2**), 83.52 (s, $BO_2C_2(CH_3)_4$), 112.20 (s, br, =**C**HBpin), 167.12 (s, **C**=CHBpin); ^{11}B{^{1}H} NMR (128.4 MHz, C_6D_6): δ 30.20 (s, br); MS (EI): m/z: 222 [M$^+$], 208 [M-Me$^+$].

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Iridium-Catalysed Borylation of C-H Bonds in Nitrogen-Containing Heterocycles: Regioselectivity in the Synthesis of Heteroarylboronate Esters

3.1 Introduction

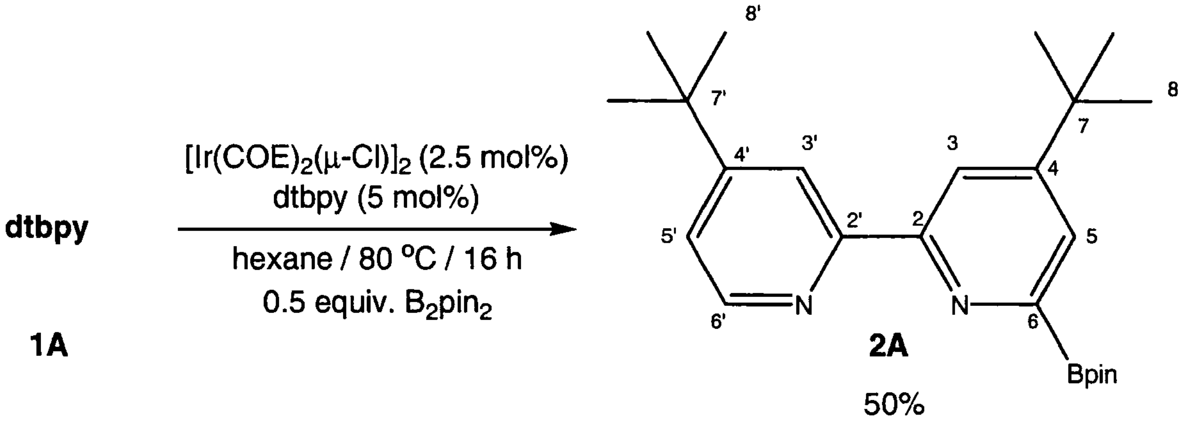
Aryl- and heteroaryl boronates are very important, especially as intermediates for Suzuki-Miyaura cross-coupling reactions,[1-7] for the Cu-catalysed C-O and C-N coupling reactions developed by Chan and Lam,[8] and for Rh-catalysed conjugate additions to carbonyl compounds.[9-10] The most attractive potential synthesis of these boronate esters would be the direct borylation of C-H bonds in the arenes or heteroarenes themselves. A very exciting recent advance has been the development, by Ishiyama, Miyaura and Hartwig, *et al.*,[11,12] and by Smith, *et al.*,[13] of *in situ*-prepared, suitably ligated analogues of the iridium tris(boryl) complexes discovered[14] by our group, which catalyse the borylation of aromatic C-H bonds under mild conditions. DFT calculations by Sakaki *et al.*,[15] in agreement with proposals by the experimental teams, suggest that the key catalytic intermediate leading to C-H activation is the sterically encumbered, 5-coordinate $[L_2Ir(Bpin)_3]$ species. This accounts for the selectivity observed in that borylation typically avoids positions *ortho* to either substituents or to ring junctions. Marder et al.[16] have taken advantage of this selectivity to prepare novel pyrene-2,6-bis(boronate) and perylene-2,5,8,11-tetra(boronate) esters amongst other polycyclic arylboronates. During the course of our studies using the Ishiyama/Miyaura/Hartwig system (L_2 = 4,4'-^{t}Bu$_2$-2,2'-bipyridine = dtbpy = **1A**), we were intrigued that *in situ* GC/MS analysis of the borylation reaction mixtures did not show any borylation of the ligand, **1A**, although we were able to detect **1A** itself. We envisaged three possible reasons for this: (1) the ligand is firmly attached to the Ir centre via the nitrogens at all times; (2) it is simply not a suitable substrate for the catalyst even if it were to dissociate; or (3) we would be unable to detect the borylated dtbpy using our GC/MS method. We noted that pyridine itself is a 'poor' substrate for the borylation reaction,[17,18] whereas pyrrole and quinoline are readily borylated;[19,20] however, 2,6-Cl$_2$-pyridine and 2,6-dimethylpyridine were effectively borylated at the 4-position,[13,21,22] and 5-bromo-2-cyanopyridine was borylated at the 3- and 4-positions in a 2:1 ratio.[23]

Herein, the synthesis of pyridinyl and bipyridinyl boronate esters will be addressed and the product will be coupled by Suzuki-Miyaura cross-coupling reaction *in one pot.*

3.2 Results and Discussion

3.2.1 Synthesis of 4,4'-^{t}Bu$_2$-6-(Bpin)-2,2'-bipyridine and 4,4'-^{t}Bu$_2$-6,6'-(Bpin)$_2$-2,2'-bipyridine

To investigate the question of the borylation of **1A** further, rather than adding a stoichiometric amount of **1A** with respect to Ir, we considered the ligand as a substrate, and added 1 equiv. of **1A** and 0.5 equiv. of B_2pin_2 in hexane (5 ml) to [Ir(COE)$_2$(μ-Cl)]$_2$ 2.5 mol%. After heating at 80 °C for 16 hours, *in situ* GC/MS analysis of the reaction mixture showed borylation of **1A** with 40-50% conversion of the starting material to 4,4'-^{t}Bu$_2$-6-(Bpin)-2,2'-bipyridine **2A**, with only trace of bis(borylation), **3A**, (Eq. 3.2.1, Fig. 3.2.1).



Eq. 3.2.1 The reaction of **1A** with 0.5 equiv. of B_2pin_2

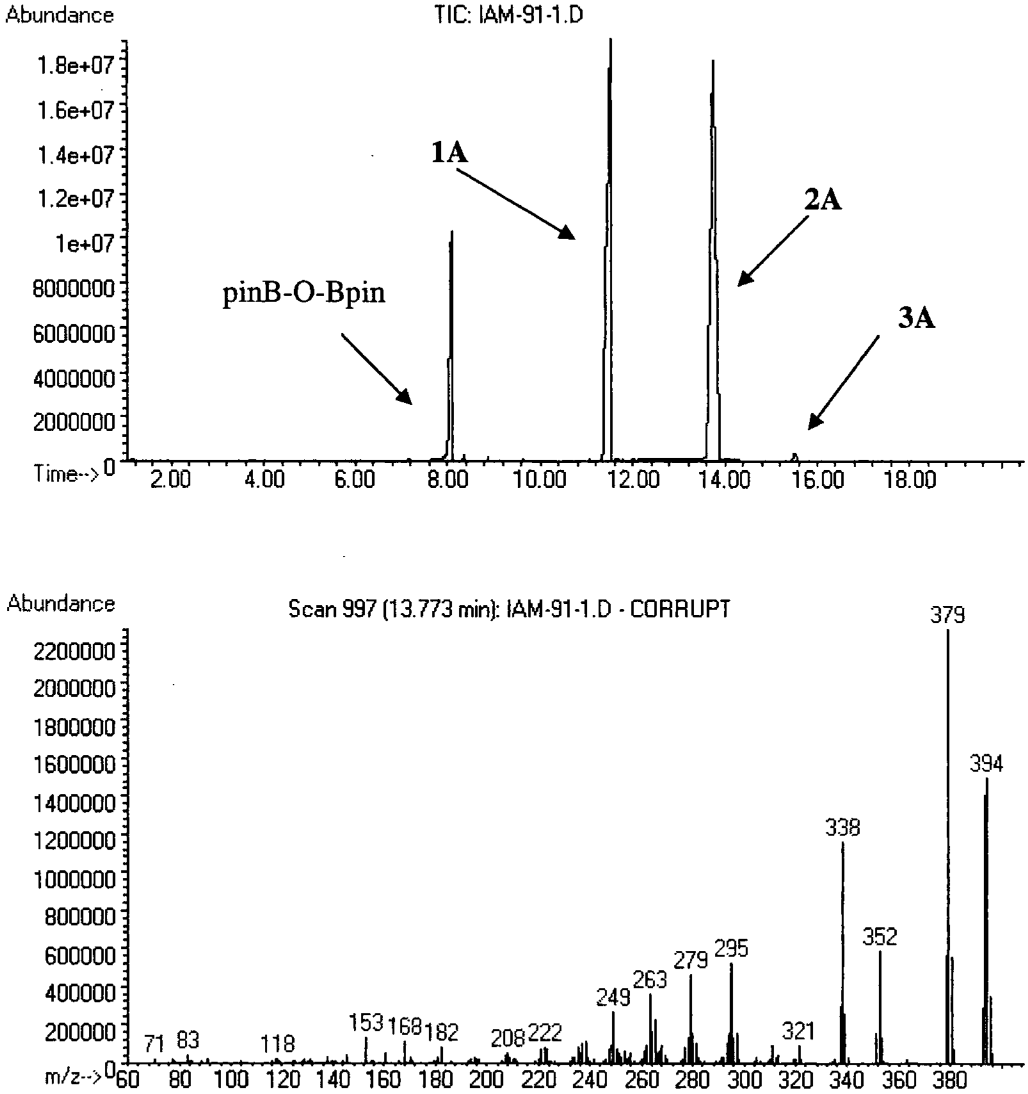


Fig. 3.2.1 Top: GC (TIC) of the reaction of **1A** with 0.5 equiv. of B_2pin_2.

Bottom: Mass spectrum of the product **2A**

The crude mixture was analysed by ^{1}H and 2D NMR (COSY) experiments (Fig. 3.2.2), to assign the position of the Bpin group. The results indicated that the borylation took place α to the N atom. The ^{1}H spectrum shows a singlet at 1.13 ppm which represents twelve protons of the Bpin moiety, two singlets at 1.15 and 1.16 ppm exhibiting nine protons each of two ^{t}Bu groups (8, 8'), a doublet of doublets at 6.90 ppm ($^{3}J_{H,H}$ = 2.0 Hz) representing one proton (H5'), another doublet at 8.26 ppm ($^{3}J_{H,H}$ = 2.0 Hz) indicating one proton (H5), and a doublet at 8.63 ppm ($^{3}J_{H,H}$ = 5.0 Hz) representing one proton (H6'); however, this proton over lapped with 2 protons of the starting material **1A**. A slightly broadened singlet at 9.14 ppm which is due to H3', (coupling to H5' was not resolved) and a doublet at 9.16 ppm ($^{3}J_{H,H}$ = 2.0 Hz) representing one proton (H3) are also observed. The ^{1}H COSY spectrum shows a correlation between H5' and H3', and H5 also correlates with H3.

The ^{13}C NMR spectrum shows four resonances in the aliphatic region. The first one at 24.94 ppm results from the methyl groups of the Bpin moiety, the resonances at 30.50 and 30.52 ppm representing methyls of two ^{t}Bu groups (8, 8') and the last one is the quarternary carbon of ($C(CH_3)_3$) at 34.5 ppm (7,7'), whereas the quarternary carbon of the Bpin group appears at 84.12 ppm. The aromatic region shows nine resonances at 118.89, 120.30, 128.35, 128.67, 149.35, 157.36, 157.86, 159.17, 160.59 ppm representing carbons of the dipyridyl rings. C6 was not observed due to broadening by quadrupolar boron. The ^{11}B spectrum shows a broad peak at 31.17 ppm. The EI-MS spectra exhibited molecular ion at *m/z* at 394, with a fragment ion 379 indicating the loss of a methyl group.

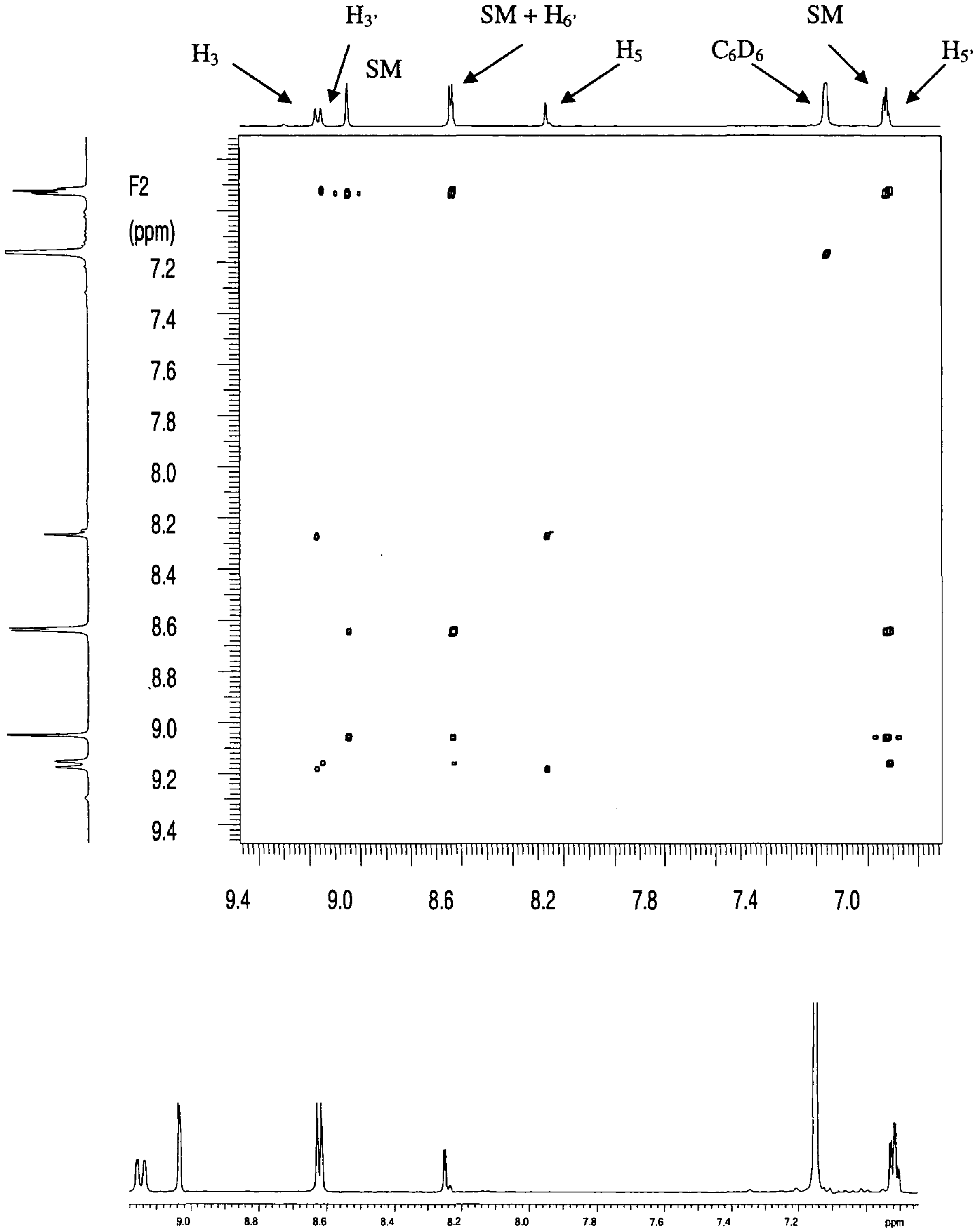


Fig. 3.2.2 ^{1}H COSY and ^{1}H NMR spectra for **2A** in the aromatic region

To attempt to reach 100% conversion of **1A**, 1 equiv. of B$_2$pin$_2$ was used instead of 0.5 equiv., under the same conditions. *In situ* GC/MS analysis of the reaction mixture showed 82% conversion of **1A**, giving 2 borylation products (Fig. 3.2.3), one of which is **2A**, with 46% selectivity, the second product being the bis(borylated) species 4,4’-^{t}Bu$_2$-6,6’-(Bpin)$_2$-2,2’-bipyridine, **3A**, with 54% selectivity, (Fig. 3.2.4).

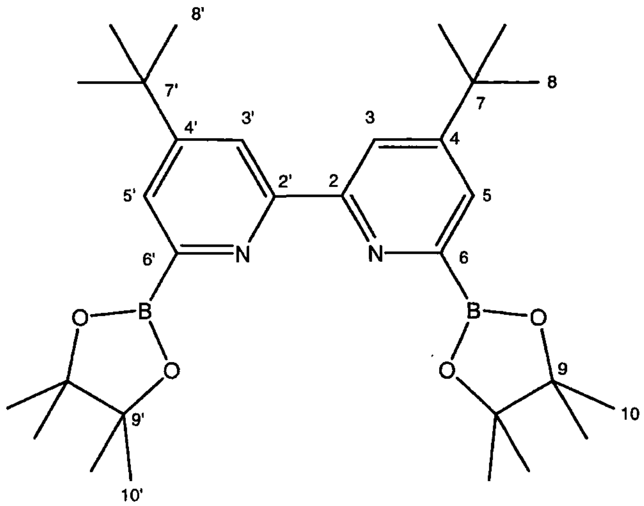


Fig. 3.2.3 Structure of 4,4’-^{t}Bu$_2$-6,6’-(Bpin)$_2$-2,2’-bipyridine **3A**, showing the numbering system used for the NMR assignment

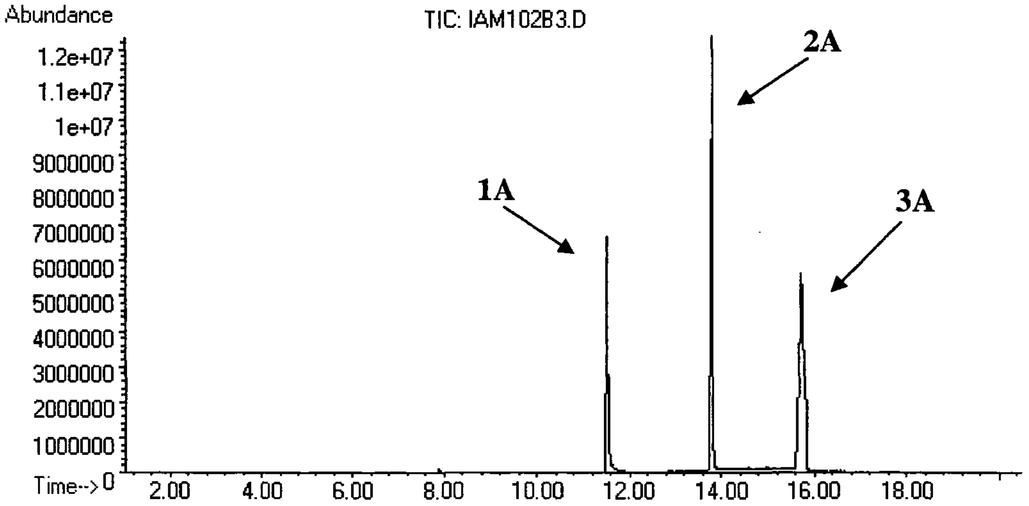


Fig. 3.2.4 GC (TIC) of the reaction of **1A** with 1 equiv. of B$_2$pin$_2$

These results suggest that higher concentrations of B_2pin_2 favour the bis-borylation over mono-borylation.

Recently, it had been shown that a combination of $[Ir(COD)(\mu\text{-}OMe)]_2$, **I**, and dtbpy in a 1:2 ratio is active for the borylation of arenes and hetero arenes at room temperature.[11] To explore this analog, 2.5 mol% of **I** was used to borylate **1A** using 0.5 or 1 equiv. of B_2pin_2. The mixtures were stirred at room temperature in hexane and also were heated at 80 °C for 16 hours. *In situ* GC/MS analysis of the reaction mixtures showed similar results to those obtained previously, (Figs. 3.2.5 and 3.2.6); however, the borylation products were observed at room temperature, which was not the case with the $[Ir(COE)_2(\mu\text{-}Cl)]_2$ complex.

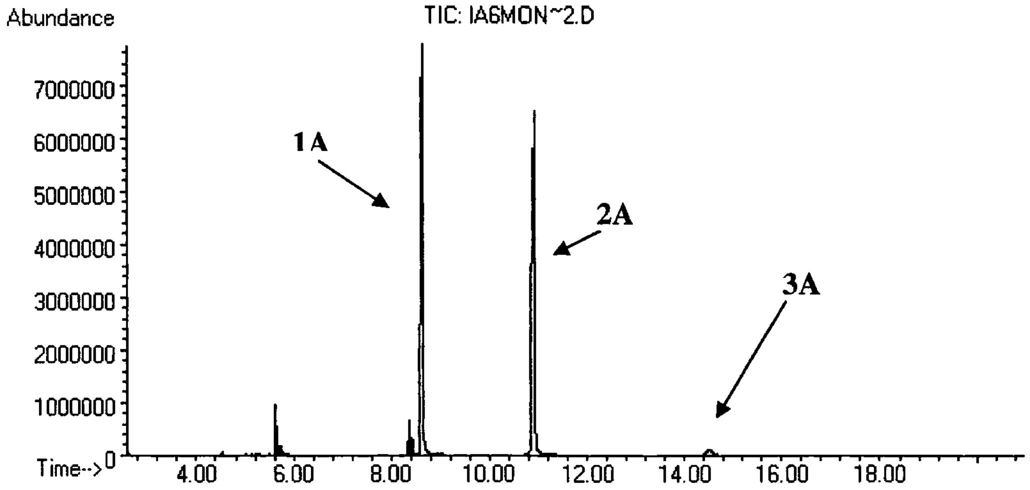


Fig. 3.2.5 GC (TIC) of the Reaction of 1A with 0.5 equiv. of B_2pin_2 in the presence of **I**

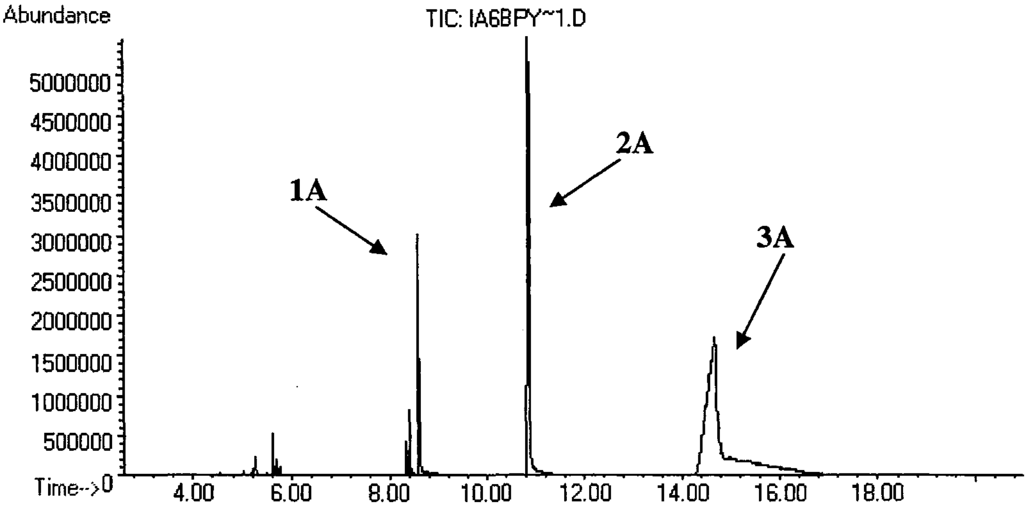
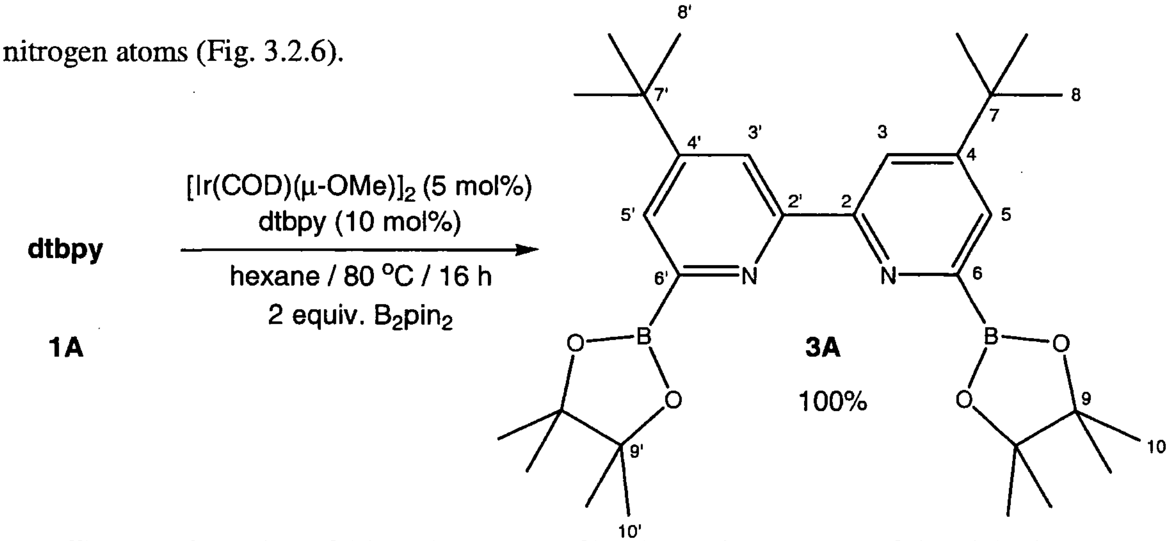


Fig. 3.2.6 GC (TIC) of the Reaction of 1A with 1 equiv. of B_2pin_2 in the presence of I

Complex **I** showed a high efficiency when the reaction was conducted with 2 equiv. of B_2pin_2 and 5 mol% catalyst loading in hexane at 80 °C for 16 hours. *In situ* GC/MS analysis of this reaction mixture showed that the borylation of **1A** was complete (Eq. 3.2.2) and (Fig 3.2.7) giving rise to a single product which ^1H, ^{13}C and 2D NMR experiments indicated to be **3A**, with the two boryl groups on the carbons adjacent to the nitrogen atoms (Fig. 3.2.6).



Eq. 3.2.2 Reaction of **1A** with 2 equiv. of B_2pin_2 in the presence of 5 mol% of **I**

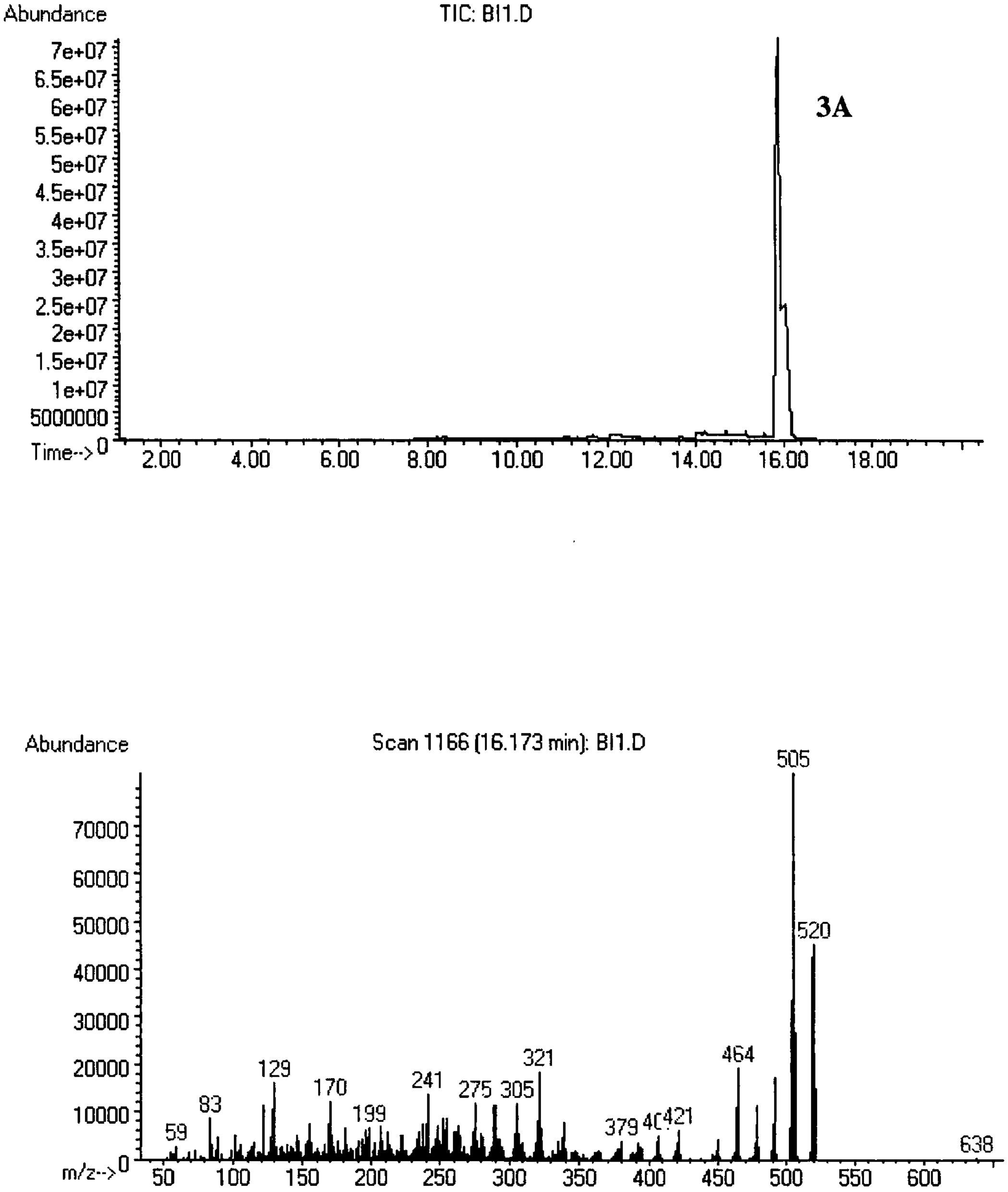


Fig. 3.2.7 Top: GC (TIC) of the reaction of **1A** with 2 equiv. of B_2pin_2. Bottom: Mass spectrum of the product **3A**

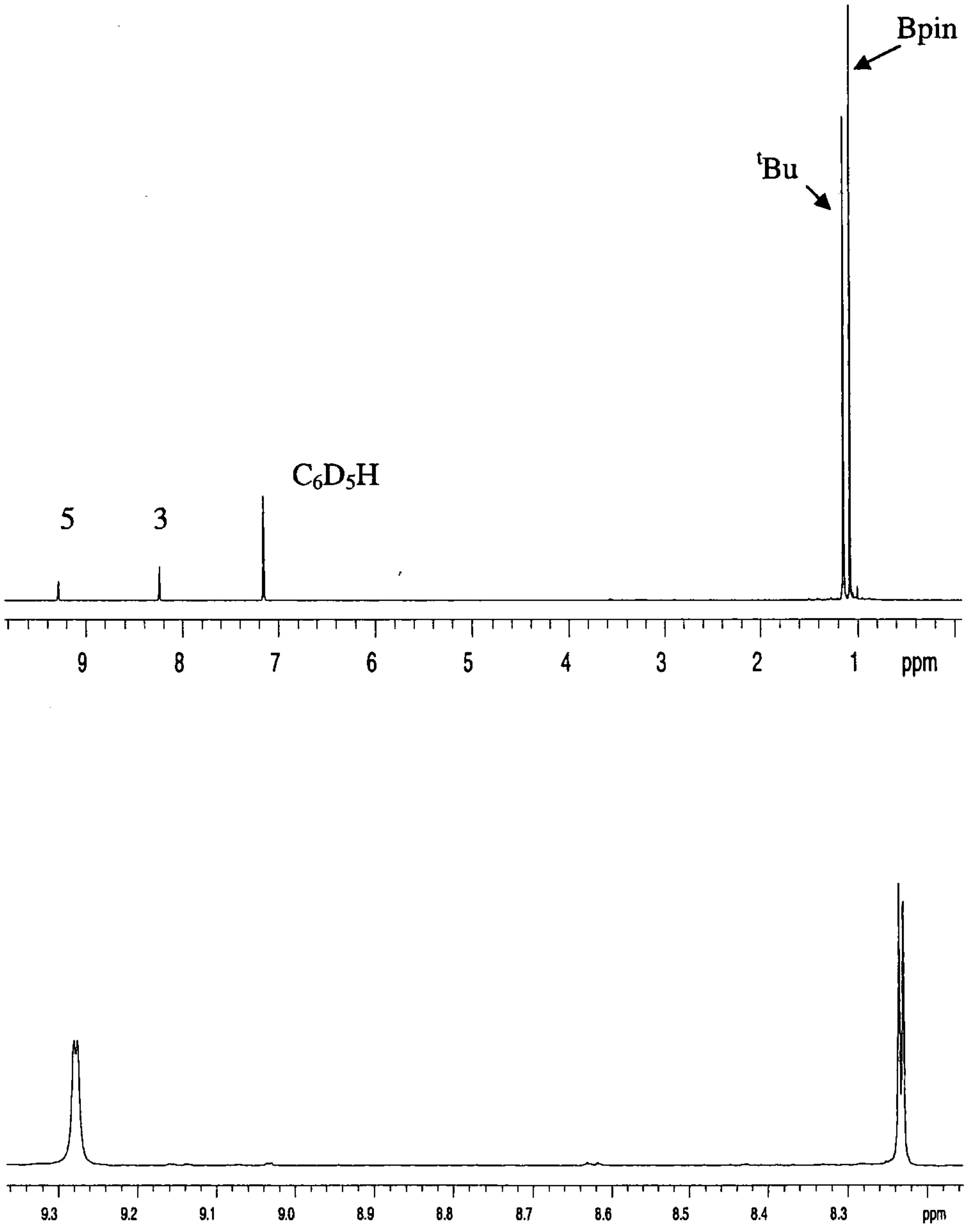
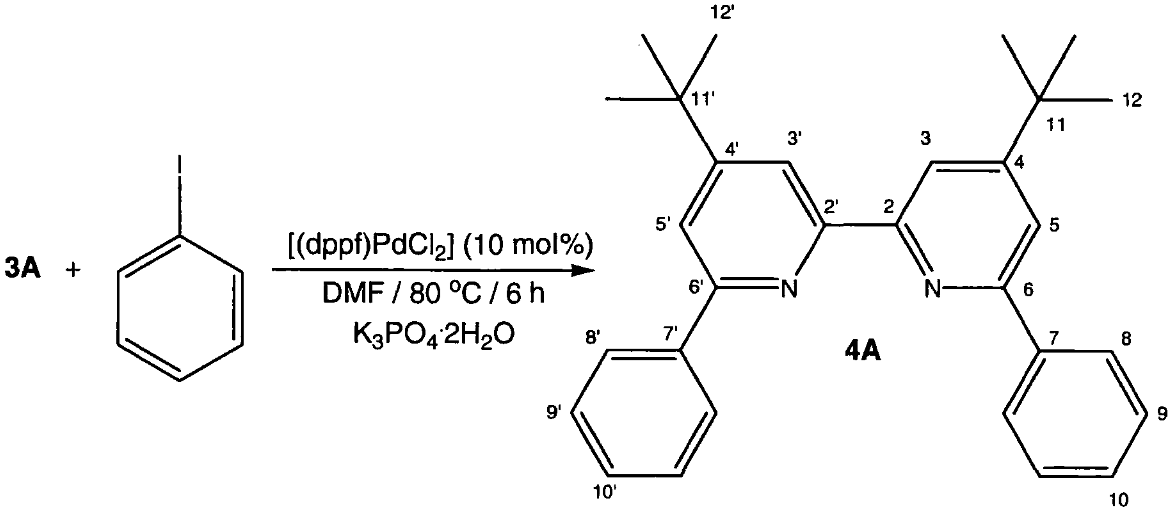


Fig. 3.2.8 Top: ^{1}H NMR spectrum of the product **3A**. Bottom: Expansion of the spectrum showing the aromatic region

dry DMF (Eq. 3.2.3). The product was extracted with hexane, dried over $MgSO_4$, and chromatographed on silica gel eluting with hexane:diethylether, (9:1) to yield 66.6% of 4,4'-$^tBu_2$-6,6'-Ph_2-2,2'-bipyridine **4A** (Eq. 3.2.3).



Eq. 3.2.3 The cross-coupling reaction of **3A** with 3 equivalents of 1-iodobenzene

The ^1H NMR spectrum exhibited a singlet at 1.47 ppm indicating nine protons of three methyl groups, a triplet at 7.45 ppm ($^3J_{H,H}$ = 7.6 Hz) representing one proton (H10), and another triplet at 7.53 ppm ($^3J_{H,H}$ = 7.6 Hz) indicating two protons (H9), a doublet at 7.78 ppm ($^3J_{H,H}$ = 1.5 Hz) representing one proton (H5), another doublet at 8.17 ppm ($^3J_{H,H}$ = 7.6 Hz) indicating two protons (H8), and the last doublet at 8.61 ppm ($^3J_{H,H}$ = 1.5 Hz) represents one proton (H3). The ^{13}C NMR spectrum contains resonances at 29.76 and 34.17 ppm arising from the three methyl groups and the quarternary ^tBu carbon respectively, while the aromatic region contains nine peaks from 116.89 to 161.68 ppm representing all of the aromatic carbons. The EI-MS spectrum exhibited the molecular

The ^{1}H NMR spectrum shows a singlet at 1.10 ppm representing 24 protons of two Bpin groups, another singlet at 1.14 ppm representing 18 protons of two ^{t}Bu groups (8, 8'), a doublet at 8.24 ppm ($^{3}J_{H,H}$ = 2.0 Hz) representing two protons (H5, 5'), and another doublet at 9.28 ppm ($^{3}J_{H,H}$ = 2.0 Hz) representing two protons (H3, 3'). The ^{13}C NMR spectrum showed three resonances in the aliphatic region, at 25.01 ppm for the Bpin methyl groups, at 30.50 ppm for ^{t}Bu methyl groups and a third at 34.75 ppm for the quarternary ^{t}Bu carbon. The quarternary carbon of the Bpin group resonates at 84.12 ppm. Three resonances at 120.63, 158.00, and 159.16 ppm are attributed to carbons (3, 5), 2 and 4, respectively. The ^{11}B spectrum showed a broad peak at 31.24 ppm. The EI-MS spectrum exhibited the molecular ion at *m/z* = 520, with the largest fragment ion indicating the loss of one methyl group. This compound is very sensitive, undergoing hydrolysis of the C-Bpin bond during all attempts at purification, including column chromatography, recrystallisation and extraction. The proximity of the Bpin to the nitrogen increases hydrolytic sensitivity.

An *in situ* Suzuki-Miyaura cross-coupling reaction on **3A** was investigated using catalyst precursors such as $[Pd(PPh_3)_4]$, $[Pd(OAc)_2]$ and $[Pd(PPh_3)_2Cl_2]$, a variety of solvents such as 1,4-dioxane, THF, benzene and toluene, and the bases NaOH, K_2CO_3 and K_3PO_4. However, all of these conditions gave only the hydrolysis product without any evidence of cross-coupling. In contrast, a combination of $[(dppf)PdCl_2]$ and $K_3PO_4 \cdot 2H_2O$ in dry DMF was found to be very effective. Thus, after **1A** had been converted to the bis(borylation) product, **3A,** (100% conversion, Fig. 3.2.8), the solvent was removed *in vacuo* followed by addition of 3 equiv. of PhI, 4 equiv. of $K_3PO_4 \cdot 2H_2O$ as base and 10 mol% of $[(dppf)PdCl_2]$ as catalyst, and the mixture was heated at 80 °C for 6 h in 8 ml of ion at *m/z* = 420 with a fragment ion = 405 *m/z* indicating the loss of a CH_3 group. The molecular structure of **4A** was confirmed by single-crystal X-ray diffraction (Fig. 3.2.9), *vide infra*.

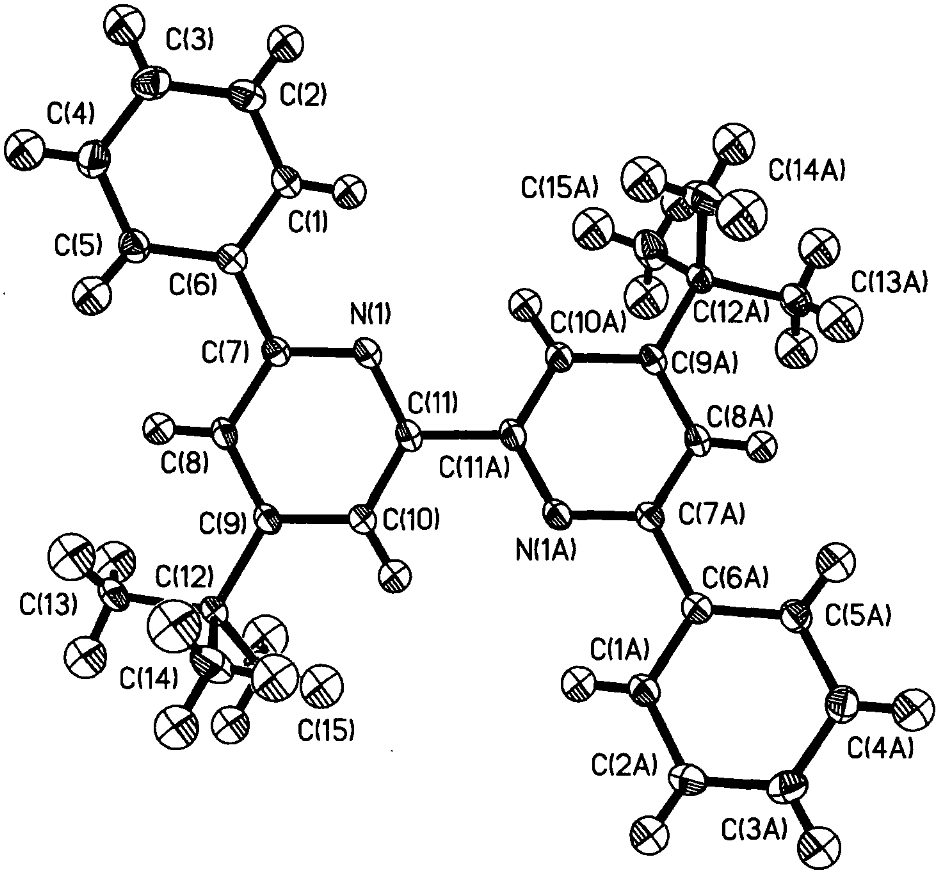
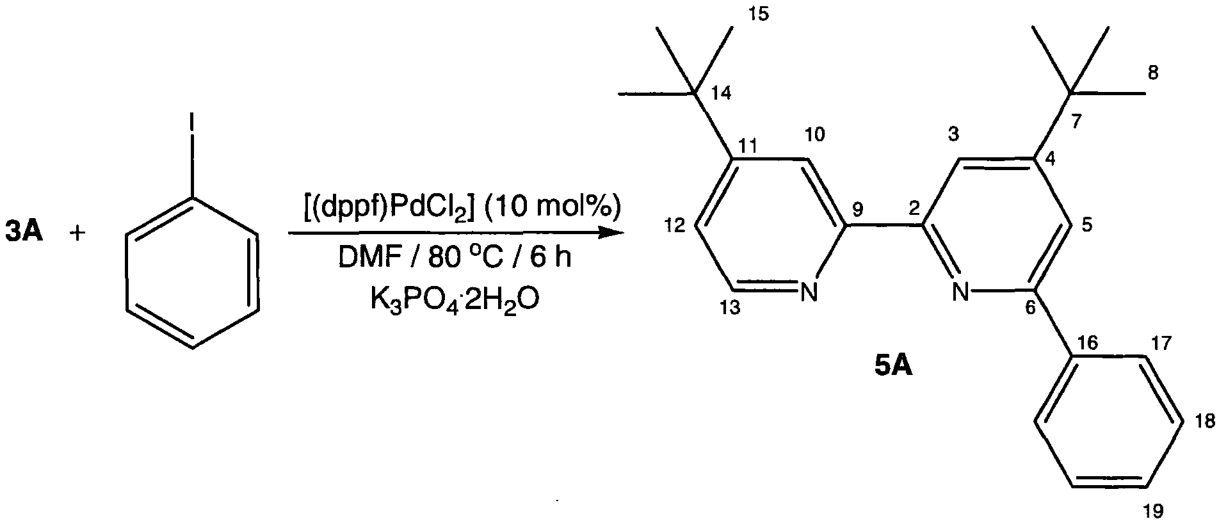


Fig. 3.2.9 Molecular structure of **4A**

Interestingly, the same bis(borylated) dtbpy **3A** could be converted cleanly to the mono-phenyl product **5A** under the same conditions but using only 1.2 equiv. of PhI and 2 equiv. of $K_3PO_4 \cdot 2H_2O$ as base (Eq. 2.2.4), indicating that: (1) cross-coupling took place initially at one ring; and (2) when the PhI was depleted, hydrolysis of the remaining C-B bond was relatively facile under the reactions conditions. The yield was 31% and the structure of **5A** was confirmed by single-crystal X-ray diffraction (Fig. 3.2.10).



Eq. 3.2.4 The cross-coupling reaction of **3A** with 1.2 equivalent of 1-iodobenzene

The ^{1}H NMR spectrum of **5A** shows two singlets at 1.17 and 1.20 ppm indicating nine protons for each ^{t}Bu group (8, 15), a doublet of doublet at 6.96 ppm ($^{3}J_{H,H}$ = 2.0, 5.0 Hz) representing one proton (H12), a triplet at 7.23 ppm ($^{3}J_{H,H}$ = 7.0 Hz) representing H19, a triplet at 7.35 ppm ($^{3}J_{H,H}$ = 7.0 Hz) representing two protons (H18), a duplet at 7.71 ppm ($^{3}J_{H,H}$ = 2.0 Hz) for H5, a doublet at 8.31 ppm ($^{3}J_{H,H}$ = 7.0 Hz) for H17, a doublet at 8.66 ppm ($^{3}J_{H,H}$ = 5.0 Hz) representing H13, a doublet at 9.01 ppm ($^{3}J_{H,H}$ = 2.0 Hz) for H3, and a doublet at 9.08 ppm (^{3}J(H,H) = 2.0 Hz) representing H10. The ^{1}H COSY spectrum (Fig. 3.2.12) shows that H12 correlates with H13 and 10, H18 correlates with H17 and 19, whereas H3 correlates with H5. The ^{13}C spectrum showed four resonances in the aliphatic region, at 30.32, 30.40, 34.60 and 34.90 ppm, representing the methyl and quarternary carbons of each ^{t}Bu group. Fourteen peaks were observed in the aromatic region, six of them appearing at 117.70, 117.90, 118.68, 121.18, 141.11 and 149.70 ppm representing carbons 5, 3, 10, 12, 16 and 13 respectively. Three peaks at 127.79, 128.54 and 129.17 ppm represent three of the phenyl carbons, C17, 18 and 19, and the remaining five peaks at 157.24, 157.33, 157.51, 160.72 and 161.86 ppm representing the other aromatic carbons C2, 9, 6, 4 and 11. The (^{1}H, ^{13}C) HSQC spectrum showed that C5 is connected to H5, and C3 to H3, whereas C10 and 12 correlated with H10 and 12 respectively. Phenyl carbons 17, 18 and 19 correlate with H17, 18 and 19 respectively, and C13 is connected to H13. The EI-MS spectrum exhibited the molecular ion at *m/z* at 344 with the fragment ion = 329 *m/z* indicating the loss of a methyl group. The structure of **5A** was confirmed by single-crystal X-ray diffraction (Fig. 3.2.10).

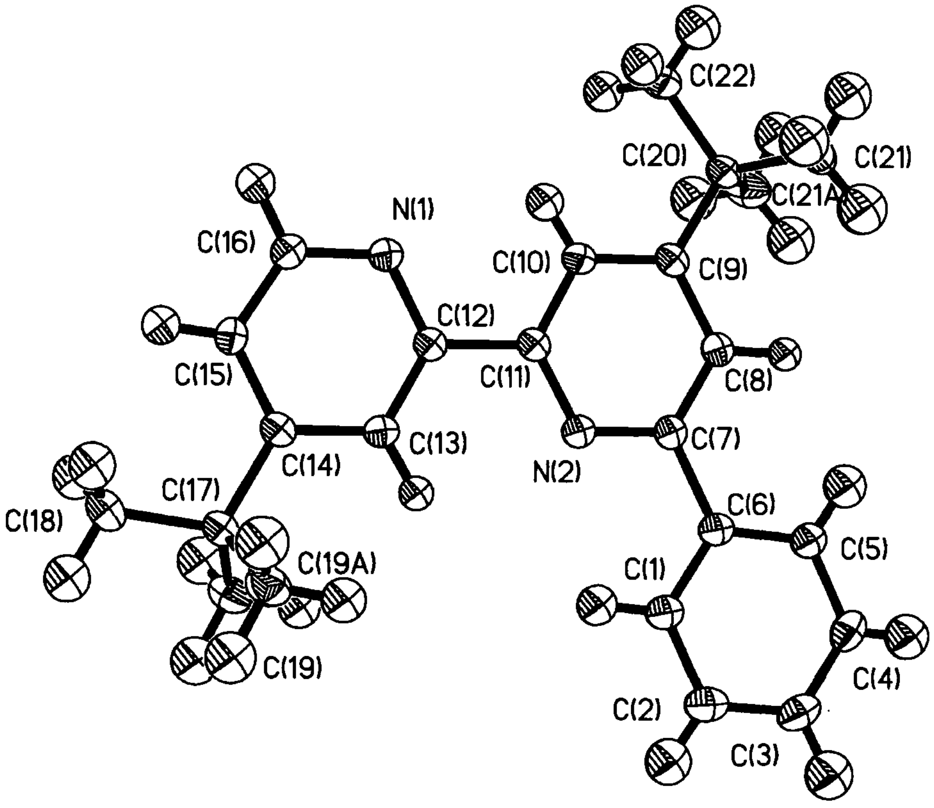


Fig. 3.2.10 Molecular structure of **5A**

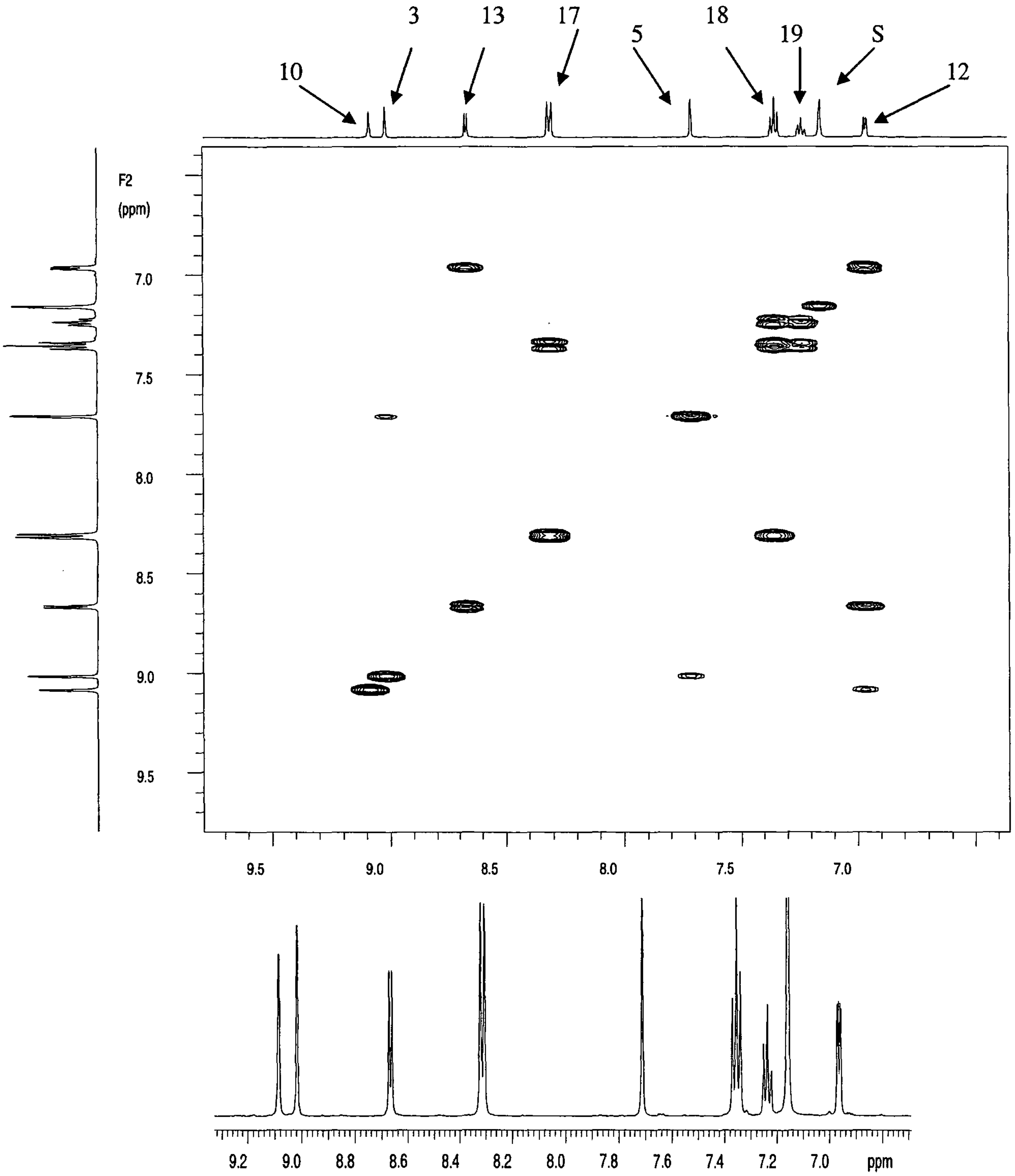


Fig. 3.2.11 Top: ^{1}H COSY spectrum for the product **3A**. Bottom: Expansion of the ^{1}H NMR spectrum showing the aromatic region

It had been mentioned by Miyaura *et al.*[12] that the catalytic borylation rate decreased in coordinating solvents such as DME and DMF. We examined the reaction of **1A** with B_2pin_2 in the presence of 2.5 mol% of $[Ir(COE)_2(\mu\text{-}Cl)]_2$ and 5 mol% of dtbpy in THF at 80 °C. After 16 hours, *in situ* GC/MS analysis showed that the mono borylation product was formed as expected and along with a small amount of another boron compound. This peak only appeared in the TIC when THF was used as the solvent. In addition, the same substance appeared in the *in situ* GC/MS TIC of other borylation conducted in THF using $[Ir(COE)_2(\mu\text{-}Cl)]_2$. The formation of the catalytically active Ir-tris(boryl) complex presumably requires reductive elimination of Cl-Bpin from Ir using this precursor. As Cl-Bcat is well known to cleave ethers, it seems likely that Cl-Bpin would react readily with THF causing ring opining.[23,24] We observed a peak with $m/z = 268$ with fragment m^+-15 (CH_3), m^+-57 (C_4H_9), m^+-73 ($-C_4H_9O$), 127 = Bpin

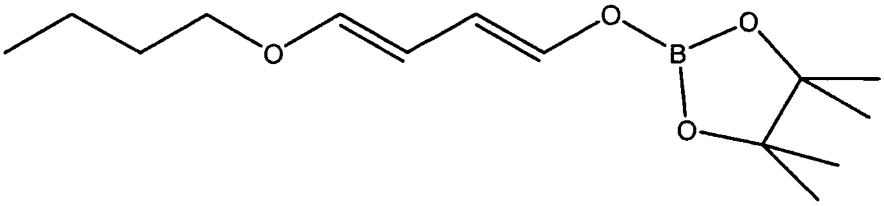


Fig. 3.2.12 Borylation product producing by ring opining of THF by Cl-Bpin produced during catalyst activation

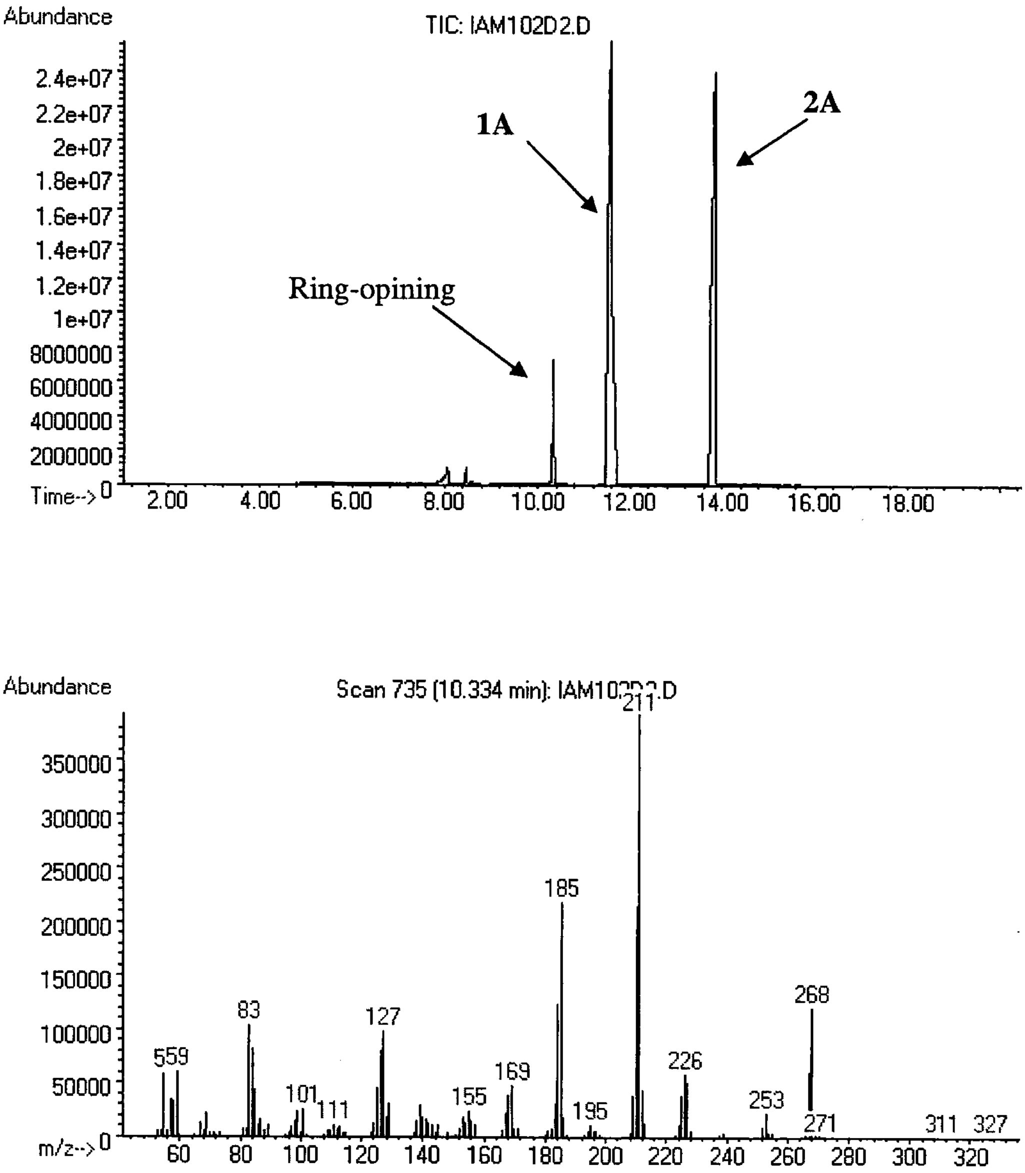
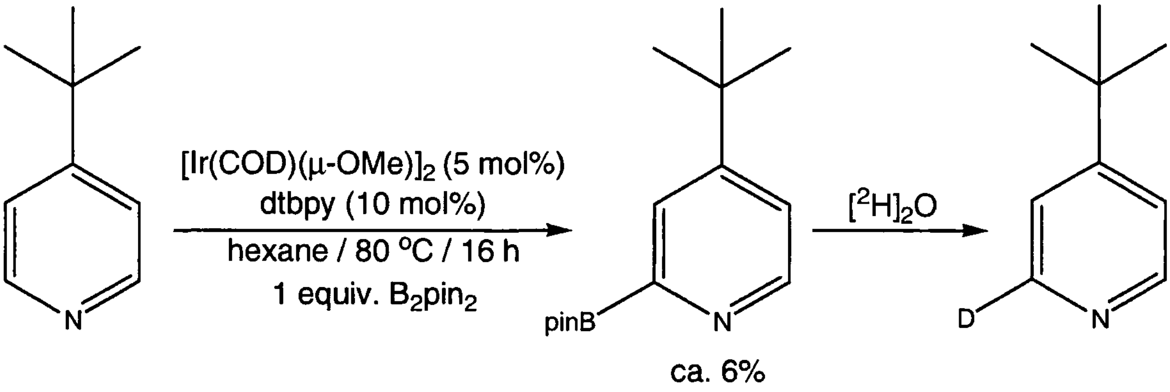


Fig 3.2.13 Top: GC (TIC) of the reaction of **1A** with 0.5 equiv. of B_2pin_2 in the presence of $[Ir(COE)_2(\mu\text{-}Cl)]_2$ in THF. Bottom: Mass spectrum of the borylation product (ring-opining)

3.2.2 Attempted borylation of 4-^{t}Bu-pyridine

Given the observed reactivity of dtbpy, we decided to examine the analogous reaction of 4-^{t}Bu-pyridine. Interestingly, no borylation product was observed for the reaction of 4-*tert*-butyl-pyridine with 1 equiv. of B_2pin_2 in the presence of 2.5 mol% of $[Ir(COD)(\mu\text{-}OMe)]_2$, + 2 (4,4'-^{t}Bu$_2$-2,2'-bipyridine = dtbpy = **1A**) even after 2 days at 80 °C in hexane. Five mol% of **I** was required to get up to ca. 6% conversion to the C-H borylation product (Eq. 4.2.5). Interestingly, the ^{2}H NMR spectrum following quench with $[^2H]_2O$ showed that borylation had taken place *ortho* to the nitrogen atom, as the borylated product was readily hydrolysed and the deuterated product displayed a ^{2}H-resonance at 8.45 ppm.



Eq. 3.2.5 The borylation reaction of 4-tert-butyl-pyridine

Presumably, 4-^{t}Bu-pyridine binds to iridium strongly *via* nitrogen, blocking the site needed for C-H activation (see Chapter 1, scheme 1.8.1).[18]

3.2.3 Synthesis of 4,4'-(MeO)$_2$-5-(Bpin)-2,2'-bipyridine and 4,4'-(MeO)$_2$-5,5'-(Bpin)$_2$-2,2'-bipyridine

As the borylation of 4-*tert*-butyl-pyridine gave a low conversion, 4,4'-MeO$_2$-2,2'-bipyridine, **1B** was selected, due its similarity with **1A**. The reaction was carried out under the same conditions used for the borylation of **1A**. Using [Ir(COE)$_2$(μ-Cl)]$_2$ (2.5 mol%) and 0.5 or 1 equiv. of B$_2$pin$_2$ with heating for 16 hours in hexane, the reactions gave a similar conversion of ca. 50% to that observed with **1A**. In addition, when 1 equiv. of B$_2$pin$_2$ was used, a similar distribution between products, giving 86% selectivity for mono borylated 4,4'-MeO$_2$-5-(Bpin)-2,2'-bipyridine, **2B**, and 14% selectivity for bis(borylated) 4,4'-MeO$_2$-5,5'-(Bpin)$_2$-2,2'-bipyridine, **3B**, products were observed by *in situ* GC/MS (Fig 3.2.14).

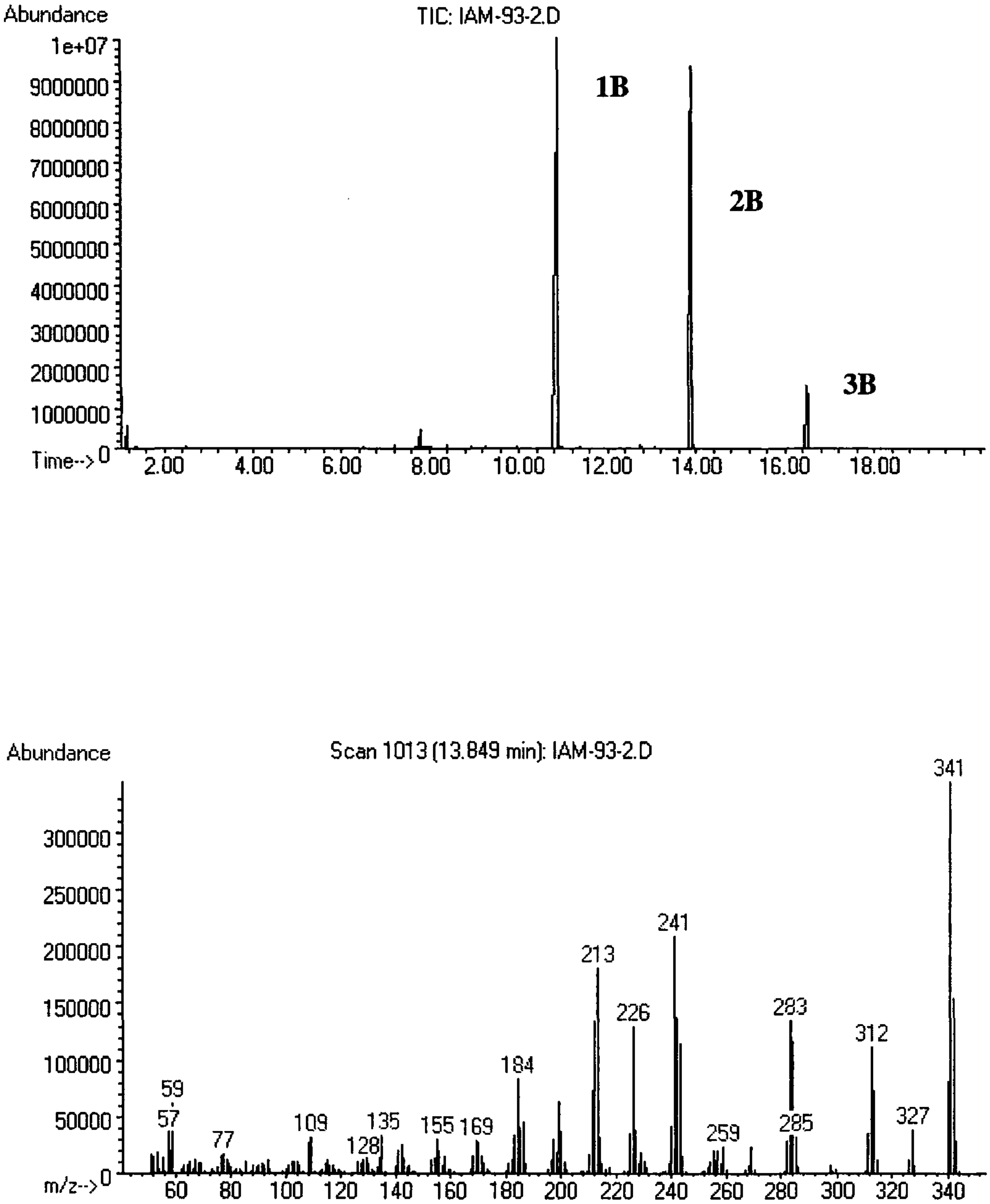
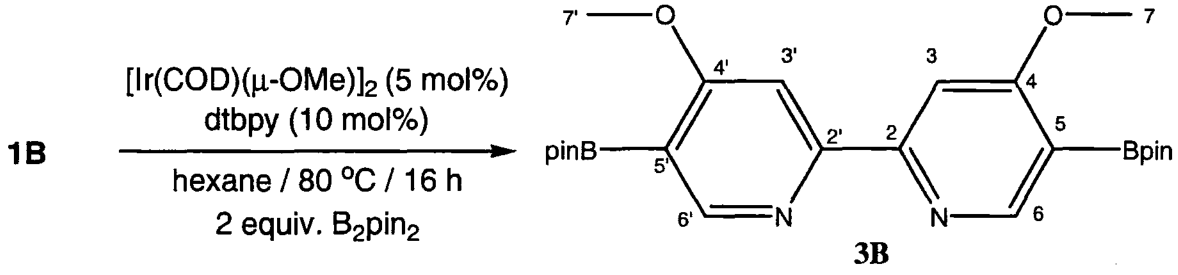


Fig 3.2.14 Top: GC (TIC) of the reaction of **1B** with 1 equiv. of B_2pin_2 in the presence of $[Ir(COE)_2(\mu\text{-}Cl)]_2$. Bottom: Mass spectrum of the product **3B**

Using 2 equiv. of B_2pin_2 in hexane (5 ml), **I** (5 mol%) and **1A** (10 mol%) at 80 °C, *in situ* GC/MS after 16 hours showed complete reaction giving 85% of the bis(boronate) ester, **3B** with 15% of **2B**. proton, ^{13}C and 2D NMR experiments indicated that borylation took place at the position *ortho* to the MeO groups and *meta* to the nitrogen, in complete contrast with the dtbpy borylation (Eq. 3.2.6).



Eq. 3.2.6 The reaction of **1B** with 2 equiv. of B_2pin_2 in the presence of 5 mol% of **I**

The ^{1}H NMR spectrum shows a singlet at 1.10 ppm representing twelve protons of the Bpin group, and another singlet at 3.36 ppm for the methoxy group. Two singlets in the aromatic region, at 8.49 and 9.51 ppm, are assigned to H3 and 6, respectively. The ^{13}C NMR spectrum displayed resonances at 24.57 ppm for the four methyl groups on the Bpin moiety, and at 55.83 ppm for the methoxy group. A resonance at 83.82 ppm represents the quarternary carbon of the Bpin group. In the aromatic region, four resonances at 111.11, 150.05, 156.70 and 167.73 ppm represent carbons 3, 6, 2 and 4 respectively. The resonance for C3, attached to the Bpin group, was too broad to be observed. The EI-MS spectrum exhibited the molecular ion at *m/z* at 467, with a fragment ion = 453 *m/z*, indicating the loss of one CH_2 group. The structure of **3B** was confirmed by a single crystal X-ray diffraction (Fig. 3.2.15).

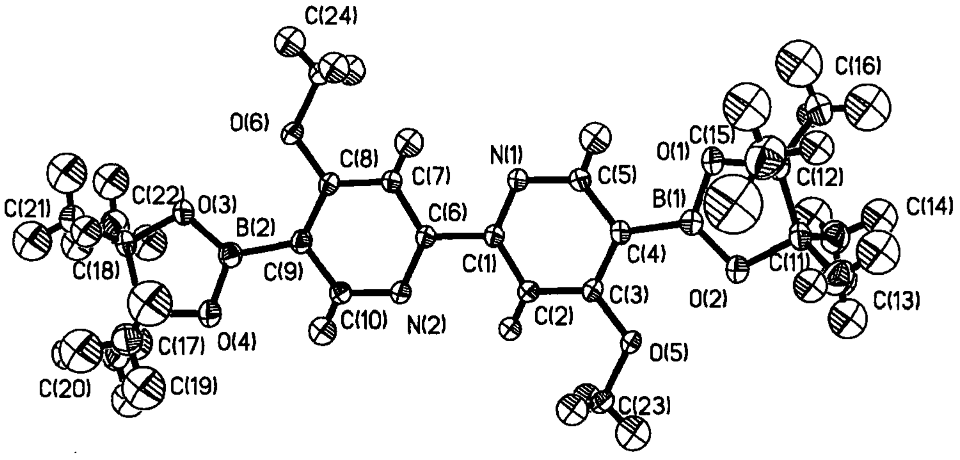
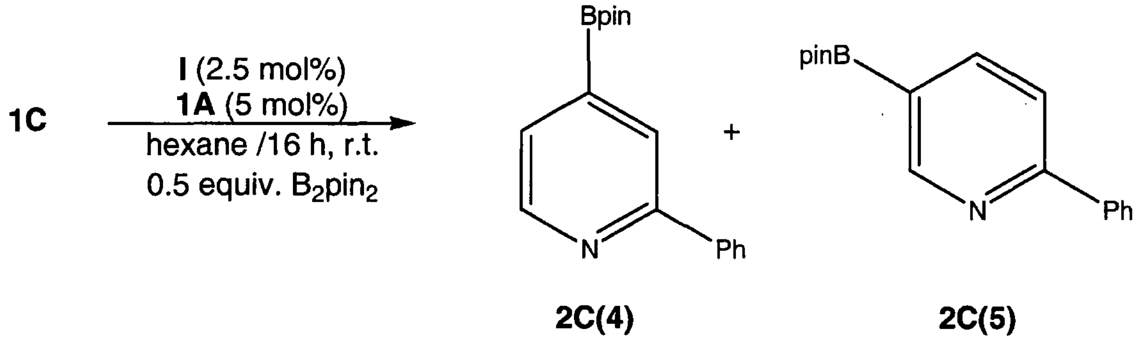


Fig. 3.2.15 Molecular structure of **3B**

It would thus appear that, for electronic reasons, the borylation reactions will avoid positions *ortho* to N in a pyridine ring unless extreme steric hindrance makes other positions inaccessible. Results of DFT calculation (B3LYP, 6-31G*) show that charges on C *ortho* to N, and the HOMOs and LUMOs of the **1A** and **1B** are very similar. This is the first example wherein purely electronic control leads to exclusive aromatic borylation *ortho* to a substituent, for example OMe. For a recent discussion of substitutent effects in the borylation of cyanoarenes,[25] **see Chapter 1, Section 1.9**. Even though the regioselectivity of borylation of the two 4,4'-disubstituted bpys was different, what they have in common is that bpy can be considered to be a 2-pyridyl substituted pyridine, i.e., that there is a bulky py-substituent *ortho* to N which blocks N-coordination of **either** ring due to the steric constraints of the key $[(dtbpy)Ir(Bpin)_3]$ intermediate. It cannot act as a bidentate ligand because the iridium is already 5-coordinate, and it cannot act as a monodentate py ligand, because the *ortho* py substitutent is too big to allow coordination at N. With that model in mind, we decided to examine 2-phenylpyridine **1C** which, along with its derivatives, has received considerable attention as a C,N-chelate on Ir for electroluminescence in OLED devices.[25-28] We wondered whether a single 2-Ph group would also inhibit N-coordination allowing borylation of the pyridine ring, and whether pyridine or phenyl ring borylation would predominate.

3.2.4 Synthesis of 2-Ph-4-(Bpin)-pyridine and 2-Ph-5-(Bpin)-pyridine

Indeed, the borylation of 2-Phpy was successful after 16 hours at room temperature with 0.5 equiv. of B_2pin_2 using 2.5 mol% of **I** and 5 mol% of **1A**, giving rise to equal amounts of 2-Ph-4-(Bpin)-pyridine **2C(4)** and 2-Ph-5-(Bpin)-pyridine **2C(5)** with over 90% conversion (Eq. 3.2.7 and Fig. 3.2.15). Interestingly, we found that borylation of the pyridine ring takes place in preference to the phenyl ring.



Eq. 3.2.7 The reaction of 2-phenylpyridine with 0.5 equiv. of B_2pin_2

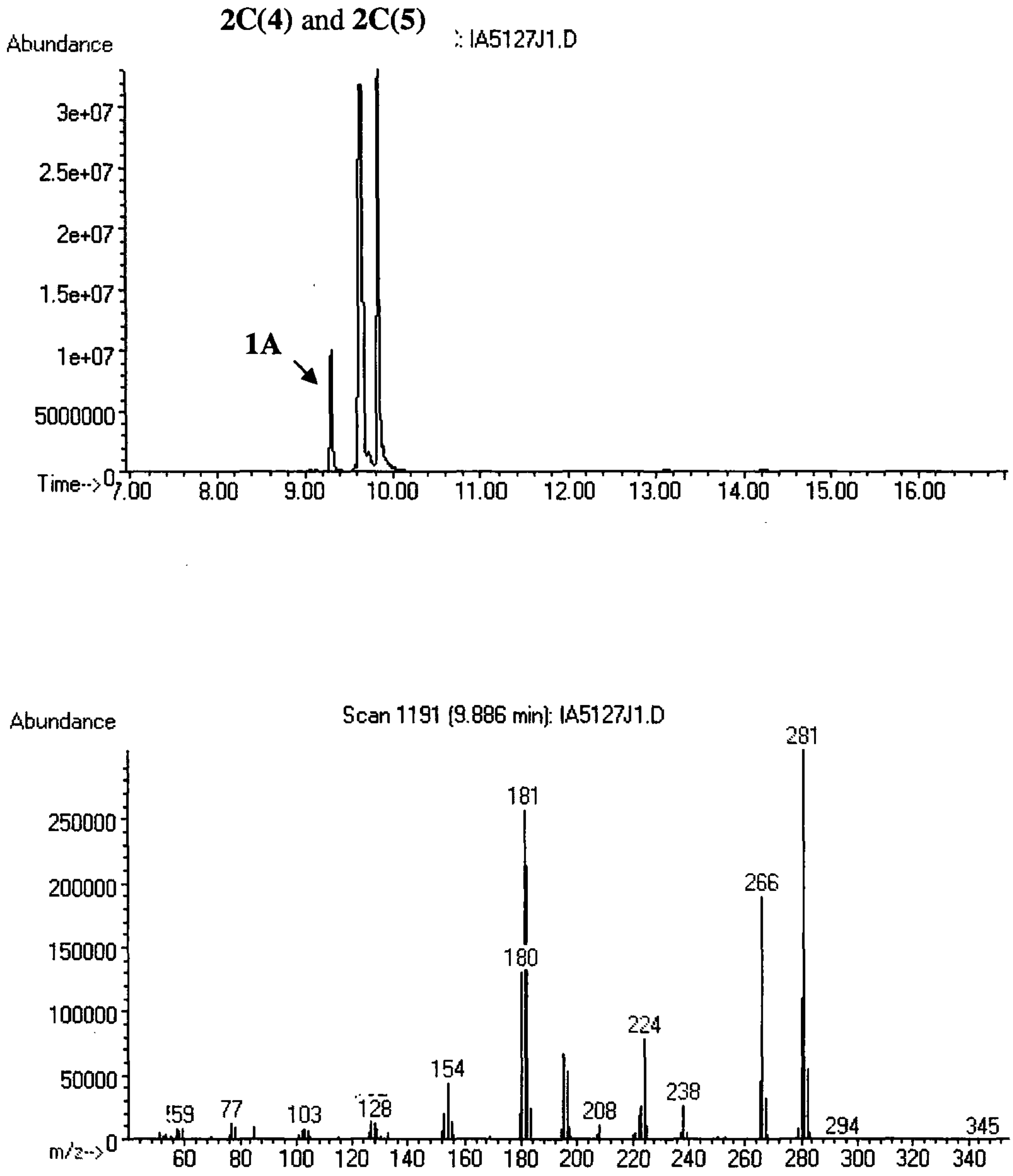
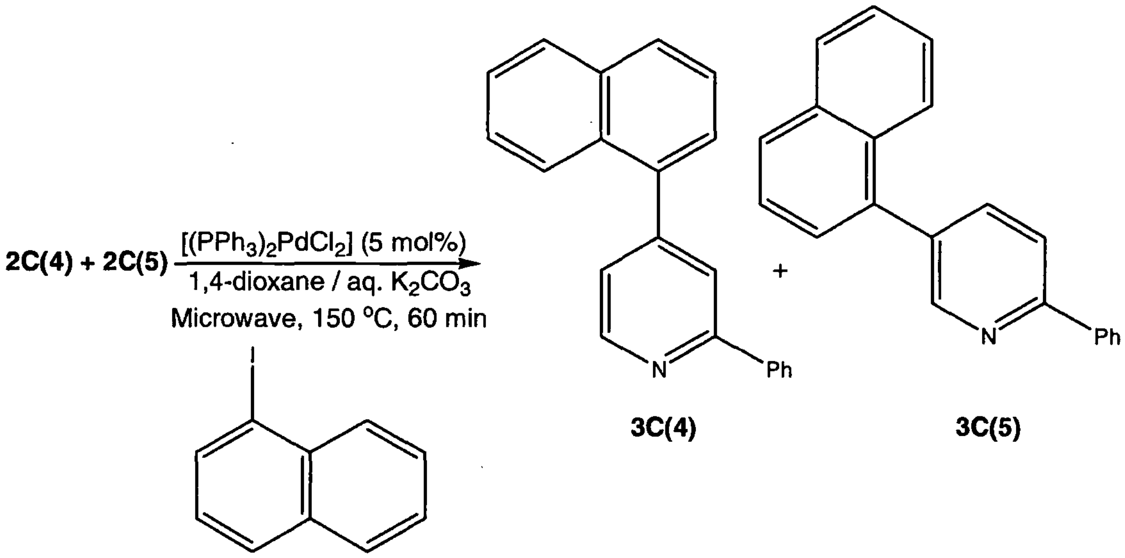


Fig. 3.2.15 Top: GC (TIC) The reaction of **1C** with 0.5 equiv. of B_2pin_2 in the presence of $[Ir(COD)(\mu\text{-}OMe)]_2$. Bottom: Mass spectrum of the product **2C(4)** or **2C(5)**

Because of the difficulty encountered in separating the isomers **2C(4)** and **2C(5)** and the fact that the pyridinyl boronic acids and esters are not stable to the column chromatography, we preferred to run a Suzuki-Miyaura cross-coupling reaction directly without isolating or purifying the boronate products. Once the borylation products formed, as shown by GC/MS, the solvent was removed *in vacuo* and the crude mixture was redissolved in 1,4-dioxane, followed by addition of 2 equiv. of aq. K_2CO_3 and $[(PPh_3)_2PdCl_2]$ (5 mol%). This mixture was treated with 1-iodonaphthalene in a 20 ml crimp-top sealed glass reaction vessel and was heated to 150 °C for 1 h in a Biotage-Personal Chemistry microwave reactor. The product was extracted with ethylacetate, dried over $MgSO_4$, and chromatographed on silica gel (hexane : ethylacetate, 95:5) to yield a mixture of the two isomers in 67% combined isolated yield, with 45% selectivity (isolated) for 2-Ph-4-(1-Np)-pyridine **3C(4)** and 55% selectivity (isolated) for 2-Ph-5-(1-Np)-pyridine **3C(5)**, (Eq. 3.2.8).



Eq. 3.2.8 The cross-coupling reaction of **2C(4)** and **2C(5)** with 1 equiv. of 1-iodonaphthalene

The ^{1}H NMR spectra of **3C(4)** and **3C(5)** each contain resonances for fifteen protons in the aromatic region, with overlapping of some signals observed in both spectra. For the **3C(4)**, their are three areas showing overlapped peaks. Firstly, a doublet of doublet appears at 6.49 ppm ($^3J_{H,H}$ = 4.9, $^4J_{H,H}$ = 1.5 Hz) representing H5. Between 7.02 and 7.07 ppm, we observed complex multiplets integrating to three protons and with additional complex multiplets a appearing between 7.23 and 7.28 ppm, integrating to four protons, along with doublets at 7.65 ppm ($^3J_{H,H}$ = 8 Hz) representing one proton, and 7.67 ppm ($^3J_{H,H}$ = 8.0 Hz) again representing one proton. A singlet at 7.69 ppm represents one proton. A doublet at 7.76 ppm ($^3J_{H,H}$ = 8.0 Hz) indicates one proton, whereas two overlapped doublet appear at 8.19 ppm ($^3J_{H,H}$ = 7.0 Hz), and a doublet at 8.67 ppm ($^3J_{H,H}$ = 5.0 Hz) is assigned to H6. The ^{1}H NMR spectrum of **3C(5)** also shows a similarity to the **3C(4)** spectrum in term of overlapping peaks. Again, there are fifteen protons in the aromatic region by the integration, with two overlapped regions at 7.17-7.28, 7.32 and an abx multiplet at 7.40-7.45 ppm representing five, two and two protons respectively. Three doublets at 7.64, 7.68 and 7.83 ppm ($^3J_{H,H}$ = 8.0, 8.0 and 9.0 Hz) indicate three protons. A doublet at 8.28 ppm ($^3J_{H,H}$ = 8.0 Hz) indicates one proton and d doublet of doublet at 8.90 ppm ($^3J_{H,H}$ = 1.0, 2.0 Hz) integrates to one proton. The EI-MS spectra for the two compounds exhibited the molecular ion at *m/z* at 281. The ^{13}C NMR spectra for the two products each show nineteen aromatic peaks between 119.46 and 157.70 ppm. The structures of **3C(4)** and **3C(5)** were confirmed by two separate single-crystal X-ray diffraction studies (Fig. 3.2.16 and Fig. 3.2.17).

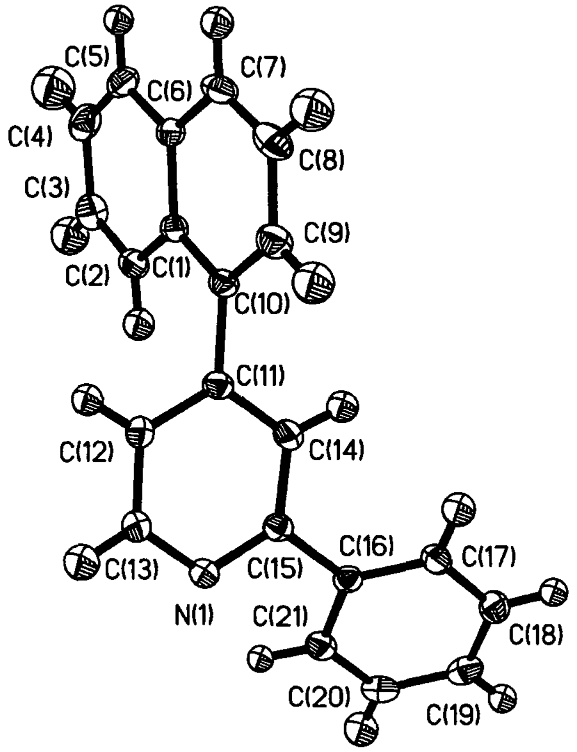


Fig. 3.2.16 Molecular structure of **3C(4)**

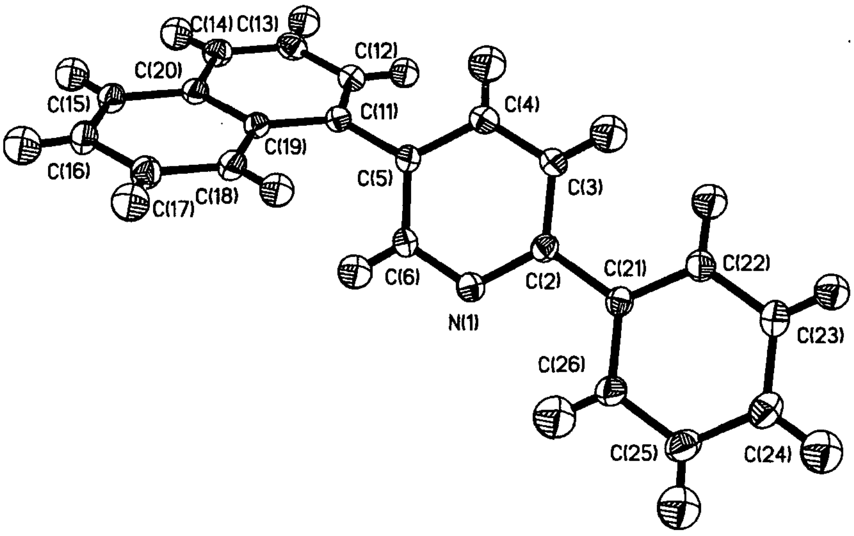


Fig. 3.2.17 Molecular structure of **3C(5)**

The reaction shows high efficiency for the mono borylation but we did notice a trace of the bis(borylation) products. The reaction was re-examined with 1 equiv. of B_2pin_2 at room temperature for 16 h. The reaction went to completion and showed, 45 and 55% selectivity for the bis(borylation) and mono borylation products, respectively.

These results indicate that the reaction depends on the ratio of starting material to B_2pin_2. When the mono borylation products have formed completely and no starting material remains, the excess boron will start to borylate the products, whereas if there is excess starting material, the reaction will afford only the mono borylation products. In addition, it is not clear whether the site of the second borylation would be the pyridine ring or the phenyl ring. Therefore, If the second Bpin prefers to borylate the **2C(4)** product, the Bpin group will adjunct *ortho* to the nitrogen atom **II** (Fig 3.2.18), which is not favorable for electronic reasons. As a result the borylation reactions will avoid the positions *ortho* to N in a pyridine ring and in the same time it is possible but it will not be the major product. In contrast, if the phenyl ring shows activity for the second borylation, the products will consist of five isomers including **III**, **IV**, **V** and **VI** (Fig. 3.2.18), with preference for the *meta* position in the phenyl ring.[11]

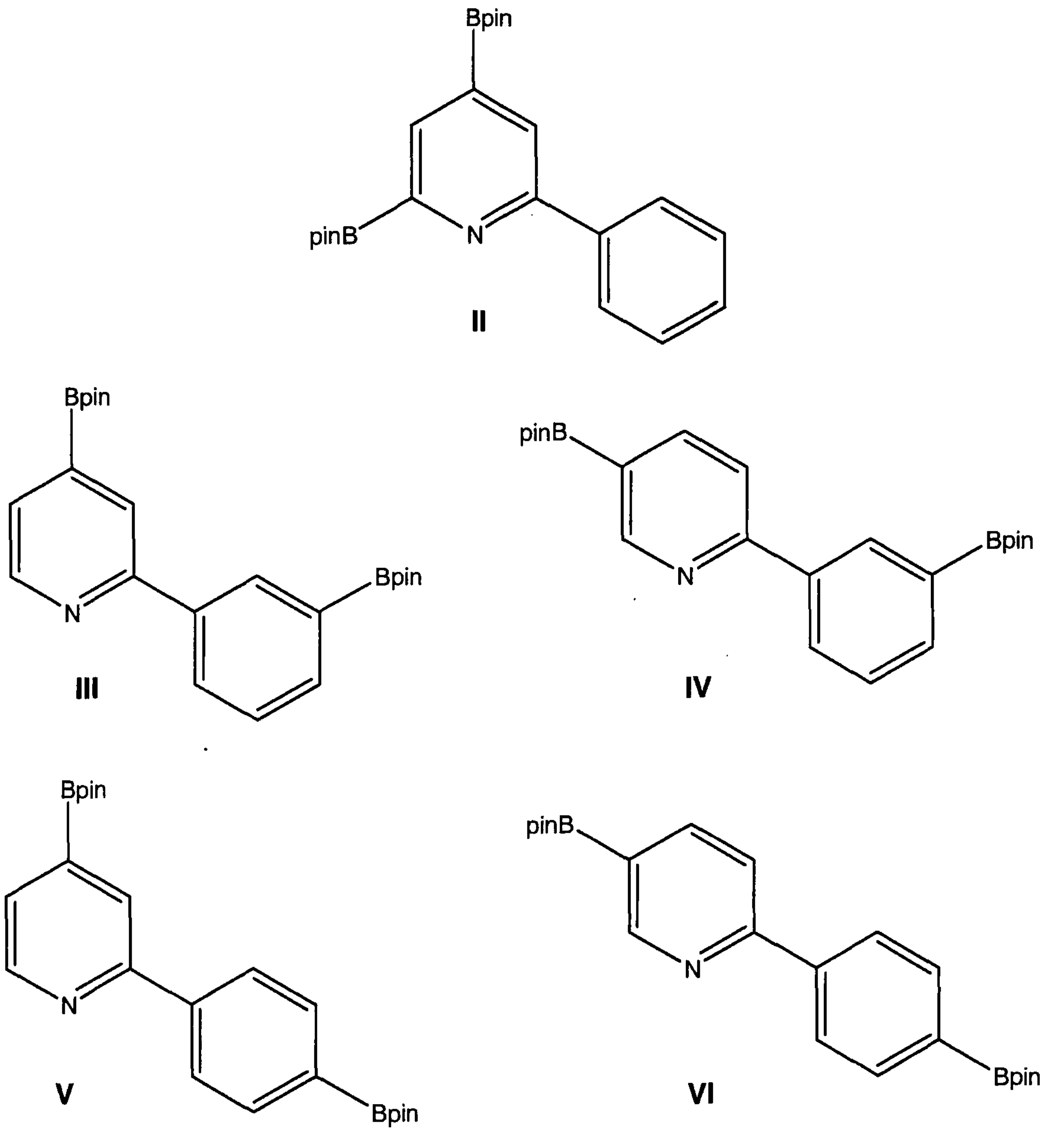


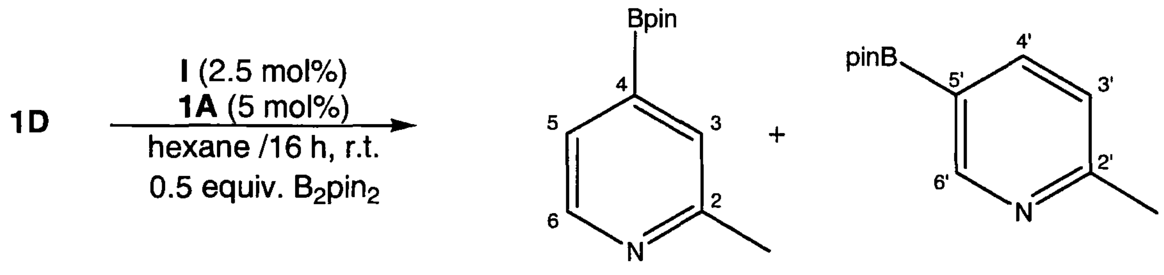
Fig. 3.2.18 The possible isomers of the bis(borylation) products

For this reason, the reaction was examined with 2 equiv. of B_2pin_2 and 5 mol% of **I** / **1A**. The mixture was heated in hexane at 80 °C for 16 hours; *in situ* GC/MS analysis showed five isomers of the bis(borylation) products, (Fig. 3.2.19, 3.2.20), two of which dominate the mixture. Given the results of the mono-borylation, it is assumed that **2C(4)** and **2C(5)**

For **2C(4)**, borylation at the 6-position on the pyridine ring *ortho* to nitrogen, is also possible, but as this position is apparently deactivated, we expect the 4,6-$(Bpin)_2$ product to be a minor one.

3.2.5 Synthesis of 2-Me-4-(Bpin)-pyridine and 2-Me-5-(Bpin)-pyridine

To test whether a single CH_3 group is sufficient to block N-coordination, and allow the borylation reaction to occur, 2-methylpyridine, **1D**, was examined, in which the methyl group is *ortho* to the nitrogen atom. The reaction was carried out under the same condition as for **1C**, with 0.5 equiv. of B_2pin_2. After 16 hours, *in situ* GC/MS analysis showed complete reaction with (85-90%) selectivity for mono borylation and 10-15% selectivity for bis(borylation) products. Two isomers of mono borylation product were observed, 2-methyl-4-(Bpin)-pyridine **2D(4)** and 2-methy-5-(Bpin)-pyridine **2D(5)**, with 54% selectivity for **2D(4)** and 46% selectivity for **2D(5)** by ^1H NMR spectroscopy, (Eq. 3.2.8 and Fig. 3.2.21).



2D(4) **2D(5)**

Eq. 3.2.8 The reaction of **1D** with 0.5 equiv. of B_2pin_2

are formed eventually. The most likely site of secondary borylation would be the *meta* position of the phenyl ring, followed by the *para* position of phenyl ring.

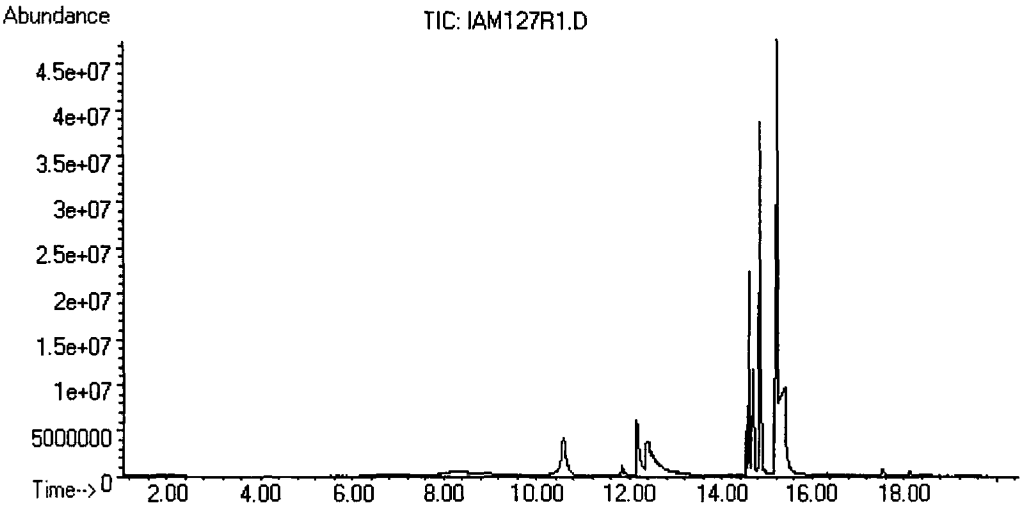


Fig. 3.2.19 GC (TIC) the reaction of **1C** with 2 equiv. of B_2pin_2 at 80 °C

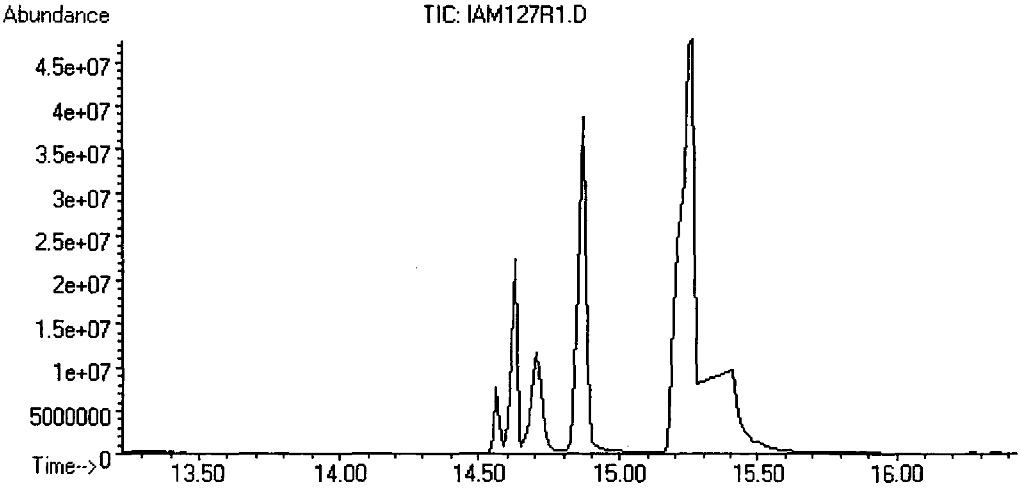


Fig. 3.2.20 GC (TIC) expansion for Fig. 3.2.19

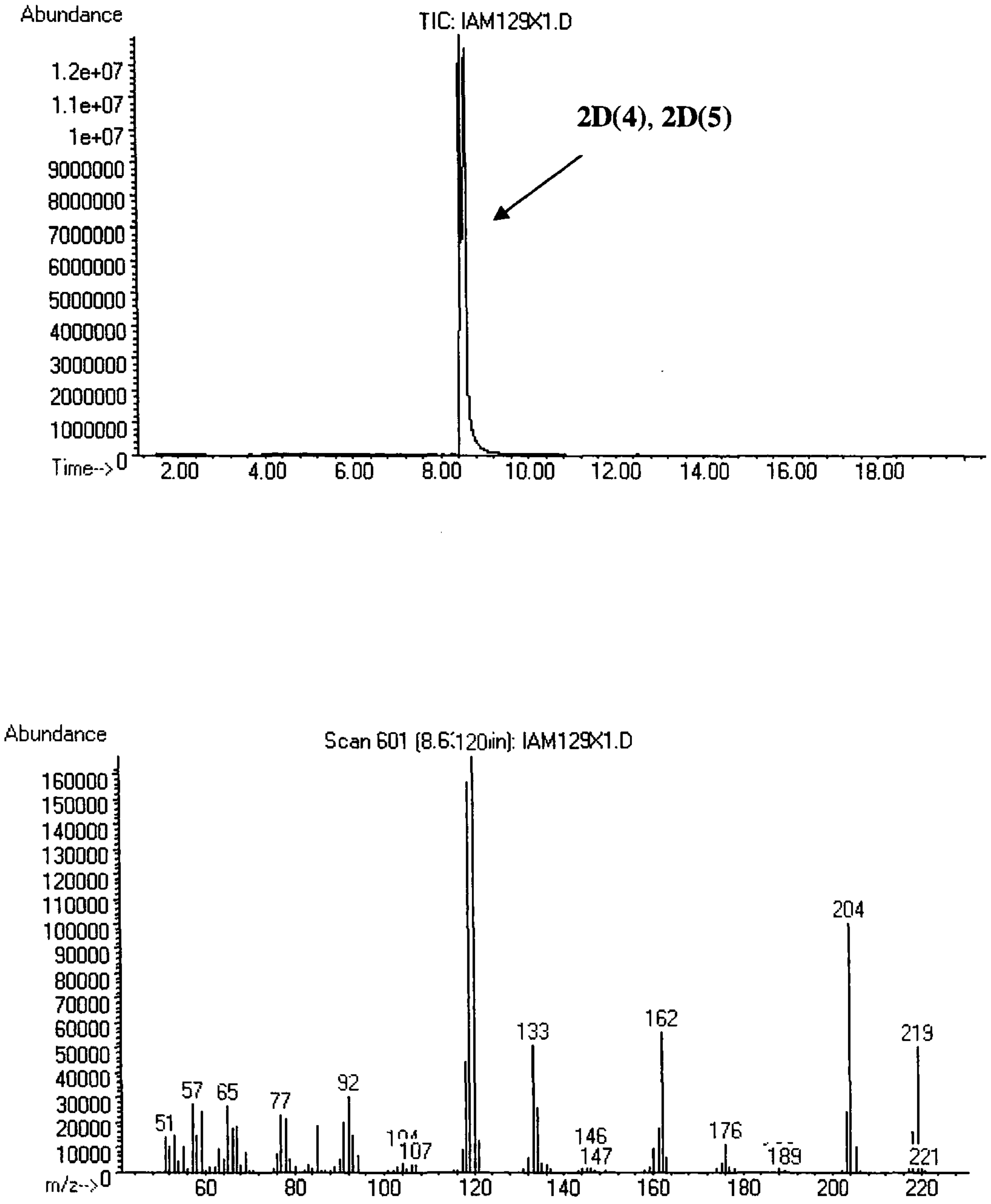


Fig. 3.2.21 Top: GC (TIC) The reaction of **1D** with 0.5 equiv. of B_2pin_2. Bottom: Mass spectrum of the product **2D(4)/2D(5)**

The ^{1}H NMR spectrum of the mixture contains well-separated resonances for all of the protons of the two isomers, **2D(4)** and **2D(5)**. The spectrum of **2D(4)** showed a singlet at 1.31 ppm representing twelve Bpin protons and another singlet at 2.53 ppm indicating the methyl group of the picoline. A doublet at 7.40 ppm ($^3J_{H,H}$ = 4.8 Hz) for H5, a singlet at 7.49 ppm for H3, and a doublet at 8.48 ppm ($^3J_{H,H}$ = 4.8 Hz) for H6 complete the spectrum. The ^{13}C NMR spectrum shows the picoline methyl resonance at 23.81 ppm followed by the methyl groups of Bpin at 25.02 ppm, and the quarternary carbons of Bpin at 83.73 ppm. The aromatic region contains four resonances at 125.32, 128.17, 148.18 and 157.27 ppm representing carbons 5, 3, 6 and 2 respectively. In the ^{1}H-^{13}C HSQC spectrum, H3 correlates with C3, H 5 correlates with C5, and H6) correlates with C6. From the ^{1}H-^{13}C HMBC spectrum, the picoline methyl group correlates with a singlet proton signal, i.e., (H 3). For **2D(5)**, a singlet at 1.32 ppm indicates twelve Bpin protons, another singlet at 2.54 ppm represents the picoline methyl group. A doublet at 7.11 ppm ($^3J_{H,H}$ = 7.8 Hz) is assigned to H3', which is coupled to H4', the later appearing as a doublet at 7.91 ppm ($^3J_{H,H}$ = 7.8). A singlet at 8.80 ppm is assigned to H6' which is *ortho* to the nitrogen atom. The ^{13}C NMR spectrum shows three resonances in the aliphatic region at 24.78, 25.03 and 84.64 ppm representing the picoline methyl group, the methyl groups of Bpin and the quarternary carbons of Bpin, the aromatic resonances at 122.90, 142.84, 155.12 and 161.17 ppm representing carbons 3', 4', 6' and 2', respectively. From the ^{1}H-^{13}C HSQC spectrum, H3' correlates with C3', H4' correlates with C4', and H 6' correlates with C6'. The ^{1}H-^{13}C HMBC spectrum identifies the isomer, as the picoline methyl signal correlates with the doublet proton resonance at 7.11 ppm which belongs to

H3'. The EI-MS spectra of both isomers exhibited the molecular ions at *m/z* = 219 with fragment ions at 204 indicating the loss of a CH_3 group.

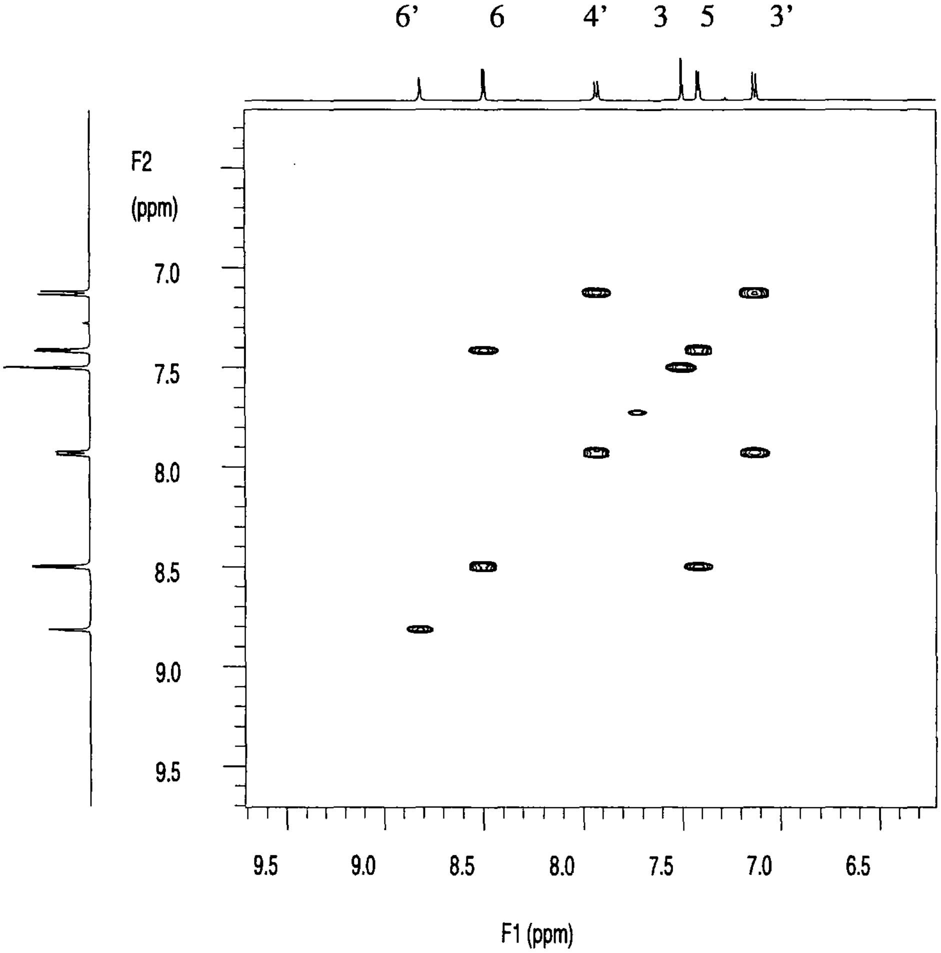
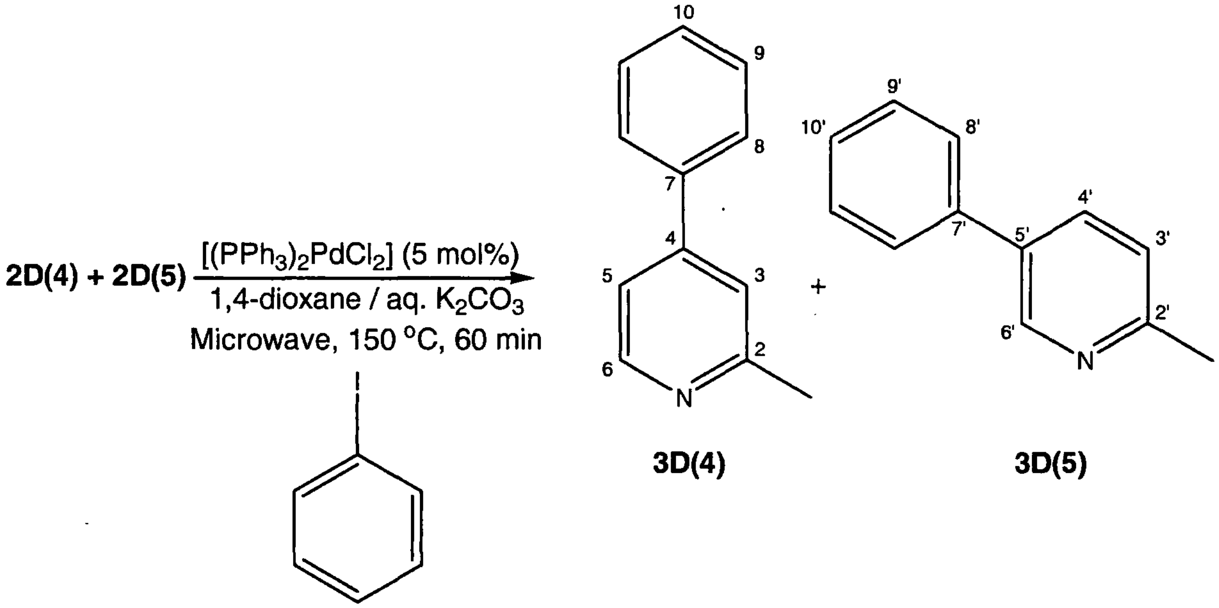


Fig. 3.2.22 Top: ^1H COSY spectrum for the product **2D**

The cross-coupling reaction was carried out *in situ* for the mixture of **2D(4)** and **2D(5)**. Once the borylation reaction was complete, the solvent was removed *in vacuo*, followed by addition of 20 ml of 1,4-dioxane, 5 mol% of $[(PPh_3)_2PdCl_2]$ and 1 equiv. of iodobenzene, with aq. K_2CO_3 as the base. The mixture was heated in the microwave reactor at 150 °C for 1 hour, giving 2-Me-4-(Ph)-pyridine **3D(4)** and 2-Me-5-(Ph)-pyridine **3D(5)** (Eq. 3.2.9), which were separated chromatographically to give a 67% total isolated yield of phenylated picolines, with 51% selectivity for **3D(5)**, identified spectroscopically, and 49% for **3D(4)**, confirmed by a single-crystal X-ray diffraction study (Fig. 3.2.23).



Eq. 3.2.9 The cross-coupling reaction of **2D** with iodobenzene

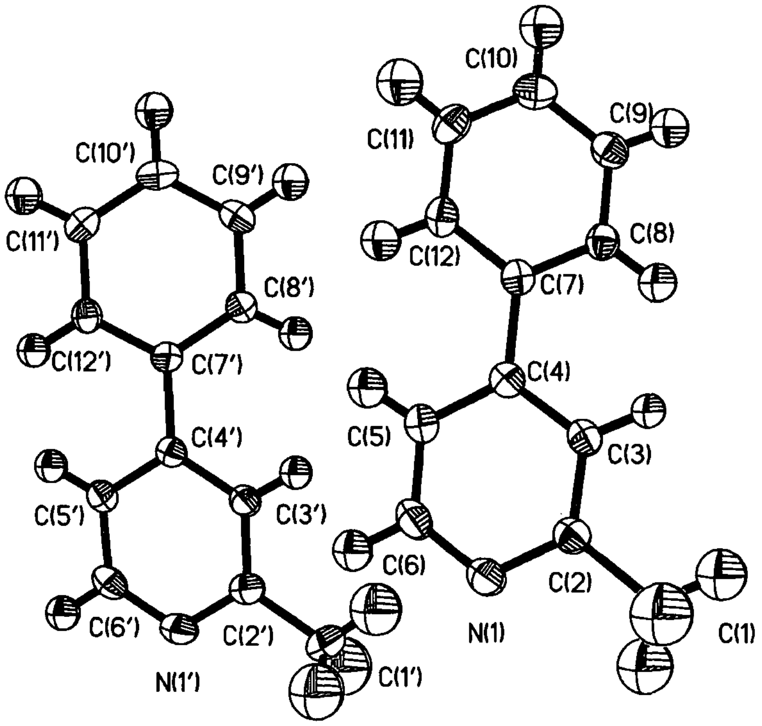


Fig 3.2.23 Molecular structure of **3D(4)** showing the two independent molecules in the asymmetric unit

The ^{1}H NMR spectrum of **3D(5)** shows a singlet at 2.47 ppm representing the methyl group, a doublet at 6.72 ppm ($^3J_{H,H}$ = 8.0 Hz) indicating H3', an overlapped multiplet from 7.10 to 7.14 ppm integrating to three protons of the phenyl ring (9', 10'), another doublet at 7.29 ppm ($^3J_{H,H}$ = 8.0 Hz) representing H4', a multiplet at 7.34 ppm indicating the H8 proton of the phenyl ring, and a singlet at 8.78 ppm for H6'. From the COSY spectrum, H3 correlates with the methyl group and H4. The ^{13}C NMR spectrum shows resonance at 22.83 ppm for CH_3 and at 121.56, 125.76, 137.22 146.82 and 156.74 ppm representing the pyridine carbons 3', 4', 5', 6' and 2' respectively, whereas the phenyl carbons appear at 126.32, 127.87, 132.43 and 133.15 ppm. The EI-MS spectrum for each of the two isomers exhibited molecular ions at *m/z* = 169 with fragment ions = 154 *m/z* indicating the loss of a CH_3 group.

As mentioned previously in Eq. 3.2.8, we had observed ca. 10% of bis(borylation) products. This small amount of diboration can be stopped by using a deficiency of B_2pin_2 **1D** (Fig. 3.2.24).

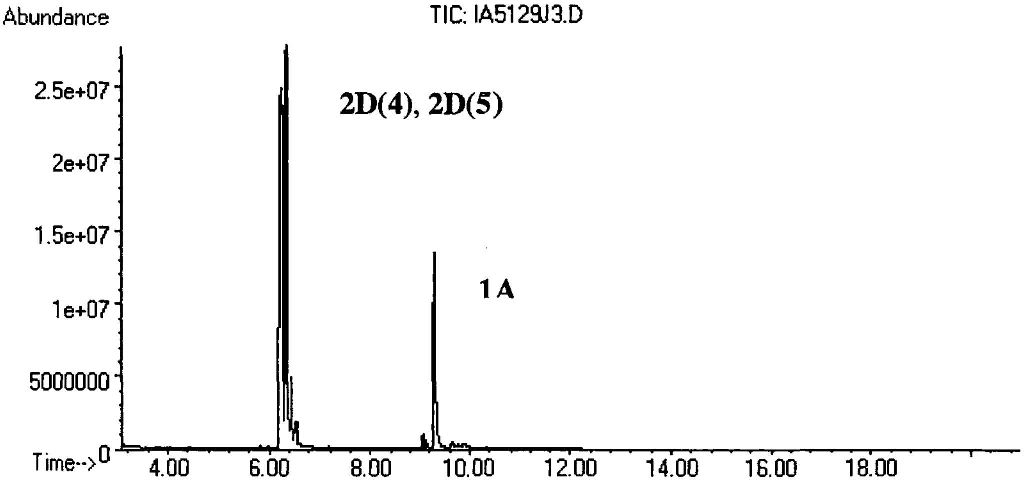


Fig. 3.2.24 GC (TIC) of the reaction of 1 equiv. of **1D** with 0.5 equiv. of B_2pin_2

To explore the reaction of **1D** with excess B_2pin_2, the reaction was re-examined under the same conditions except that the concentration of B_2pin_2 was increased to 1 equiv. After 16 hour, the GC/MS showed 55% mono borylation products and 45% bis(borylation) products. Only one isomer of the bis(borylation) product was observed. Most likely, the second borylation occurs at the position *ortho* to the nitrogen atom in **2D(4)** (Fig. 3.2.25).

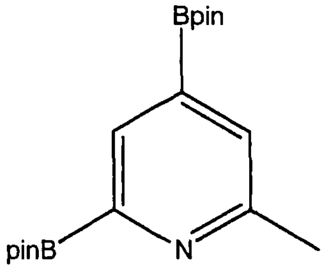
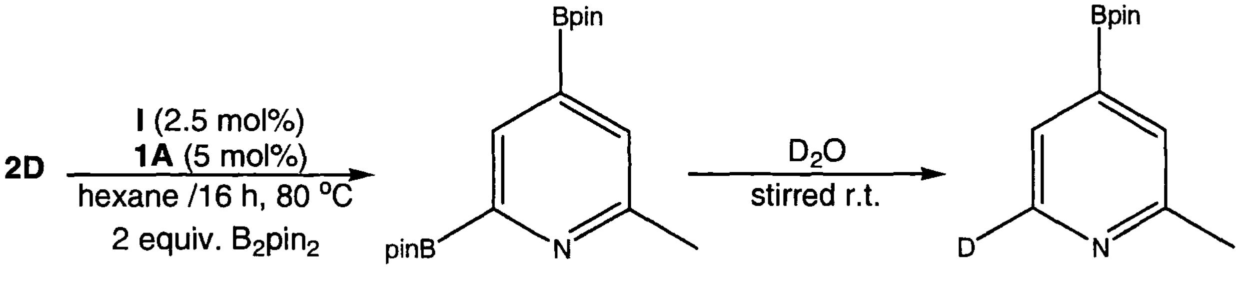


Fig. 3.2.25 Possible isomer of bis(borylation)product

To confirm this hypothesis, the reaction was carried out with 2 equiv. of B_2pin_2 in 6 ml of hexane. The mixture was heated for 16 hours at 80 °C, after which *in situ* GC/MS analysis indicated one peak of bis(borylation), (Fig. 3.2.26).

Interestingly, the mixture was quenched with a few drops of D_2O, and was stirred at room temperature, *in situ* GC/MS of the crude mixture showed that the peak in the total ion chromatogram (TIC) for which m/z = 345 [M^+ for the 4,6-bis(boronate)], disappears after D_2O quench, and is replaced with a signal in the TIC corresponding to 2-Me-4-Bpin-6-D-pyridine, with m/z = 220 [M^+].The ^2H NMR spectrum showed that the second borylation had taken place *ortho* to the nitrogen atom (Eq. 3.2.10), as the borylated product was readily hydrolysed, and the deuterated product displayed a ^2H-resonance at 8.44 ppm.



Eq. 3.2.10 The reaction of **2D** with 2 equiv. of B_2pin_2 at 80 °C

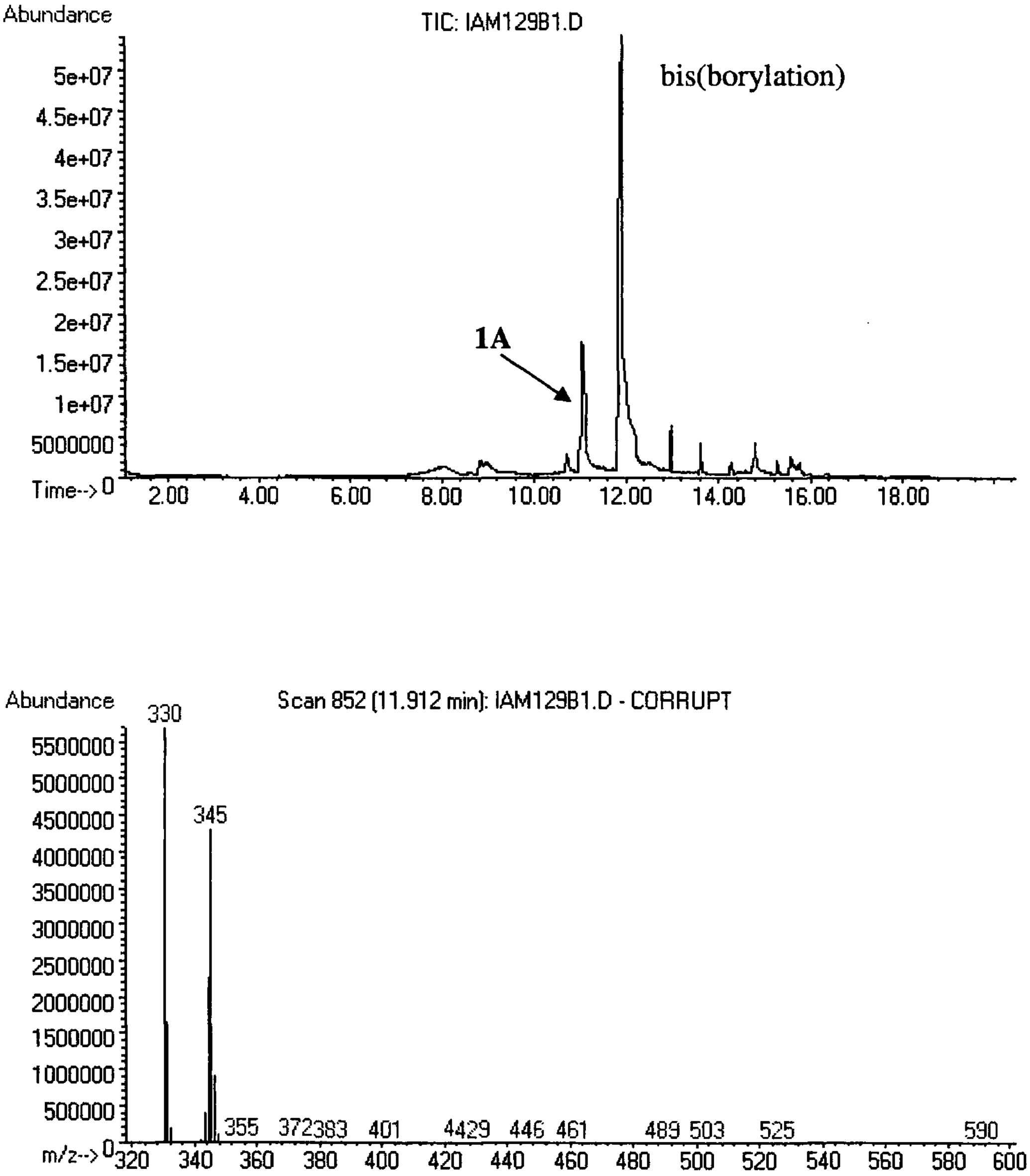
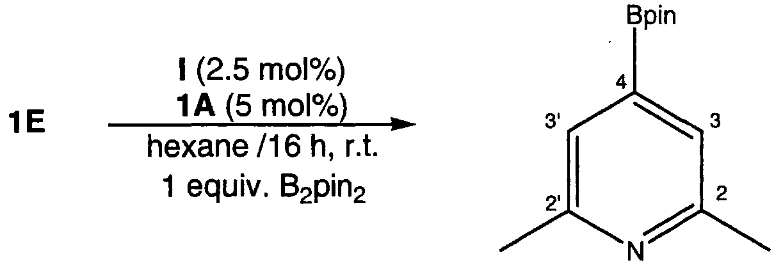


Fig.3.2.26 Top: GC (TIC) of the reaction of **1D** with 2 equiv. of B_2pin_2 in the presence of 5 mol% of **I**. Bottom: Mass spectrum of the product

3.2.6 Synthesis of 2,6-dimethyl-4-(Bpin)-pyridine



2E

Eq. 3.2.11 The reaction of 2,6-dimethylpyridine with 1 equiv. of B_2pin_2

The reaction of 2,6-dimethylpyridine, **1E**, worked smoothly, and a single regioselective borylation occurred at the *para*-position (Eq. 3.2.11), as reported by Smith *et al.*[21] who obtained the borylated product in 40% yield using 2 mol% of $[(Cp^*)Rh(\eta^4\text{-}C_6Me_6)]$ at 150 °C for 16 hours. Because the positions *ortho* to the nitrogen are substituted by two methyl groups, N-coordination is blocked and the borylation proceeds readily. The methyl groups also provide steric hindrance to prevent borylation at the *meta*-positions.The reaction was carried out under standard conditions using 2.5 mol% of **I** + 5 mol% of **1A** in the presence of 1 equiv. of B_2pin_2 and 1 equiv. of 2,6-dimethylpyridine, in hexane at room temperature. The GC/MS showed complete reaction after 16 hours, giving only 2,6-dimethyl-4-(Bpin)-pyridine, **2E**. The solvent was removed *in vacuo*, and then Kugelrohr distillation (100-170 °C, 3 x 10^{-4} torr) gave **2E** as a white solid in 86% yield. Slow evaporation of a CH_2Cl_2 solution of **2E** gave a suitable single crystal for X-ray diffraction studies (Fig. 3.2.27).

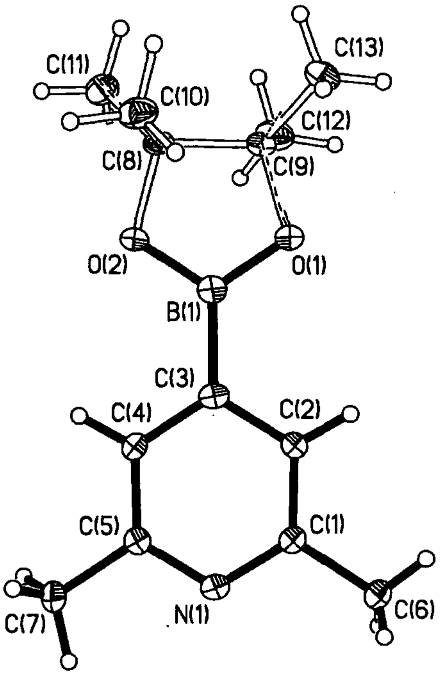


Fig. 3.2.27 Molecular structure of **2E**

A Suzuki-Miyaura cross-coupling reaction was also carried out *in situ* for compound **2E**. Once **2E** had formed completely by GC/MS analysis, the solvent was removed *in vacuo* followed by addition of 20 ml of 1,4-dioxane and 1 equiv. 1-iodonaphthalene. Two equiv. of aq. K_2CO_3 was added as base, followed by 5 mol% of $[(PPh_3)_2PdCl_2]$. The mixture was transferred to a microwave tube (20 ml volume) as above, then sealed and heated for 1 hour at 150 °C. The product was extracted with ethylacetate, dried over $MgSO_4$, and chromatographed on a short column of silica gel (hexane:ethylacetate, 9:1), to afford a 92% yield of 2,6-dimethyl-4-naphthalen-1-yl-pyridine, **3E**. The slow evaporation of a diethylether solution of **3E** gave a suitable single crystal for X-ray diffraction studies (Fig. 3.2.28).

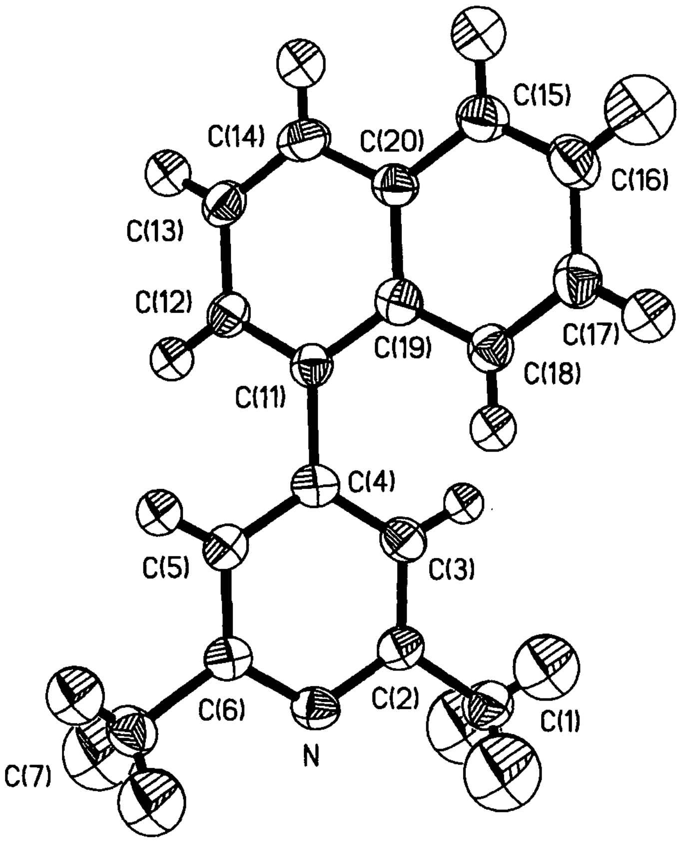
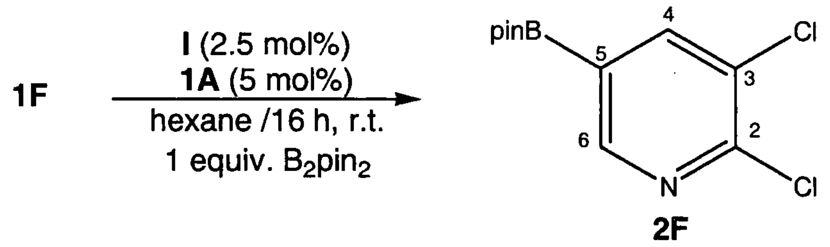


Fig 3.2.28 Molecular structure of **3E**

3.2.7 Synthesis of 2,3-dichloro-5-(Bpin)-pyridine

Synthesis of halopyridinyl boronate esters is an attractive goal for organic researchers.[3-7, 29,30] These can be prepared by reaction of organolithium or magnesium intermediates, generated by deprotonation or halogen-metal exchange, with trialkylborates.[31,32,33] Here, we examined 2,3-dichloropyridine, **1F**, to explore whether or not a single chlorine *ortho* to nitrogen is sufficient to block the coordination of pyridine and promote borylation of a C-H bond. Again, the reaction was carried out under the standard conditions at room temperature. The GC/MS showed that the reaction worked smoothly to give 2,3-dichloro-5-(Bpin)-pyridine, **2F** (Eq. 3.2.12).



Eq. 3.2.12 The reaction of **1F** with 1 equiv. of B_2pin_2

The solvent was removed *in vacuo*, and then Kugelrohr distillation (100-170 °C, 3 x 10^{-4} torr) gave the product as a white solid in 88.7% yield. The structure of **2F** was confirmed by single-crystal X-ray diffraction analysis (Fig. 3.2.29).

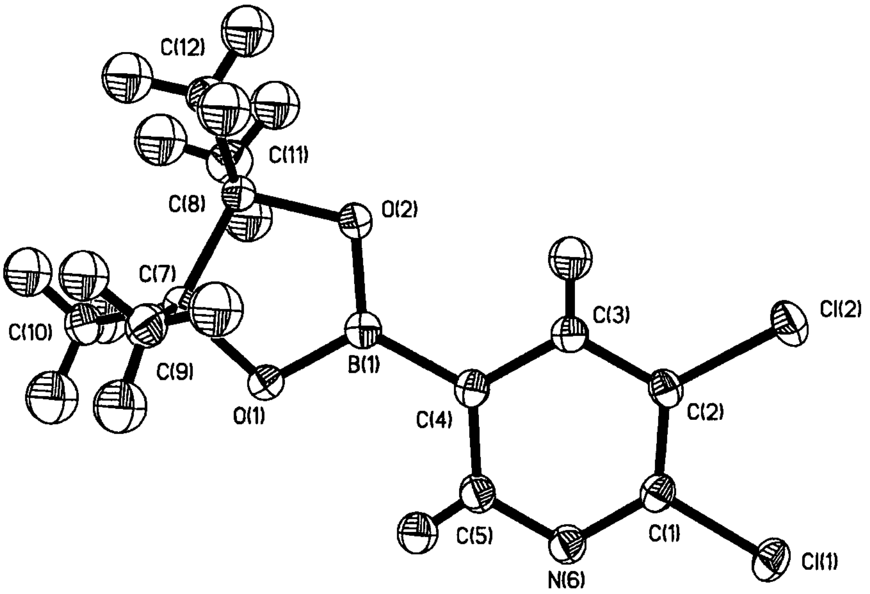
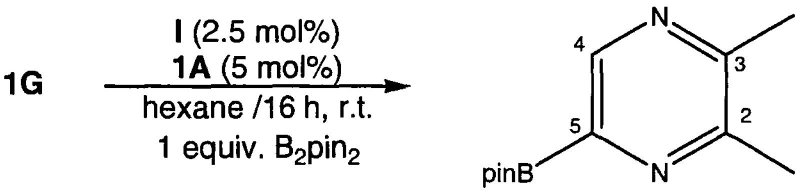


Fig. 3.2.29 Molecular structure of **2F**

3.2.8 Synthesis of 2,3-dimethyl-5-(Bpin)-pyrazine

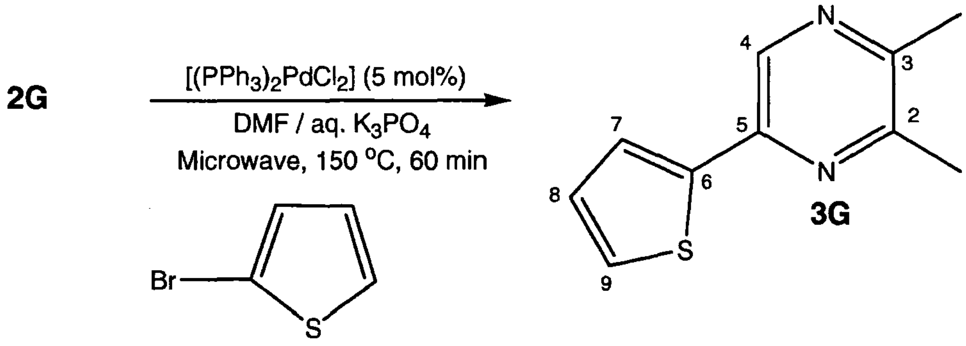
Heterocyclic pyrazine derivatives have applications in many area of chemistry, including use as ligands for coordination to metals centres.[34] We examined the borylation of 2,3-dimethylpyrazine **1G**, which has two nitrogen atoms and, at the same time, has methyl groups *ortho* to each nitrogen (Eq. 3.2.13). The reaction was carried out under the same conditions as for **1F**. After 16 hour, the product, 2,3-dimethyl-5-(Bpin)-pyrazine, **2G**, formed with 80% conversion. The ^1H NMR spectrum of the crude reaction mixture showed a single aromatic proton at 8.65 ppm, and the ^{11}B NMR spectrum displayed one signal at 30.86 ppm.



2G

Eq. 3.2.13 The reaction of **1G** with 1 equiv. of B_2pin_2

The solvent was removed *in vacuo*, followed by addition of 1-bromothiophene and 5 mol% of $[(PPh_3)_2PdCl_2]$ in 20 ml of DMF with K_3PO_4 as the base. The mixture was heated in the microwave reactor at 150 °C for 1 hour to afford a 34% yield of 2,3-dimethyl-5-thiophen-2-yl-pyrazine, **3G** (Eq. 3.2.14),[32] the structure of which is shown in Fig. 3.2.30.



Eq. 3.2.14 The cross-coupling reaction of **2G** with 2-bromothiophene

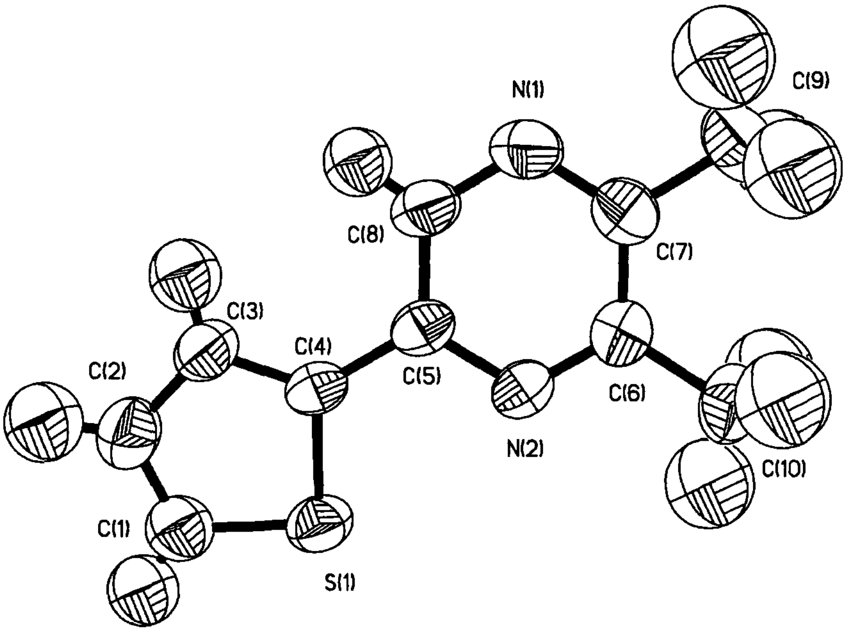
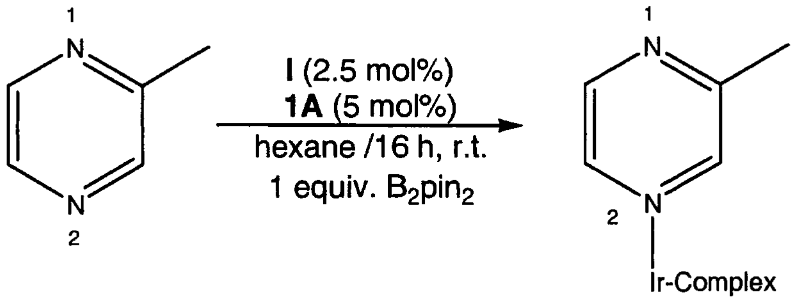


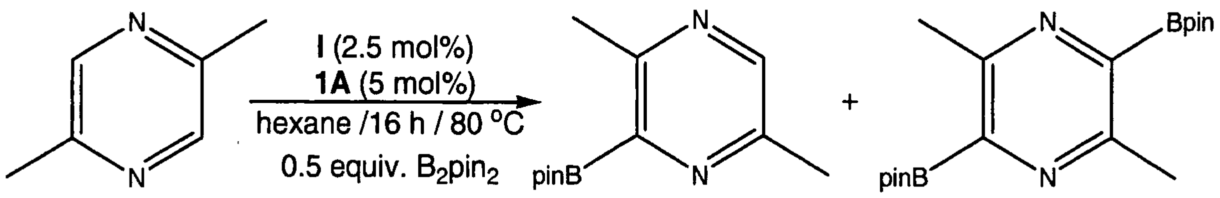
Fig. 3.2.30 Molecular structure of **3G**

Extending our studies of pyrazine derivatives to see if one methyl group is sufficient to block the coordination of both nitrogen atoms allowing the borylation to proceed, we attempted the borylation of 2-methypyrazine under the above conditions. No borylation reaction was observed at room temperature or after heating for 24 hours. Thus, a substituent is required *ortho* to each nitrogen in order to stop coordination and allow the C-H activation step to proceed (Eq. 3.2.15).



Eq. 3.2.15 The reaction of 2-methypyrazine with 1 equiv. of B_2pin_2

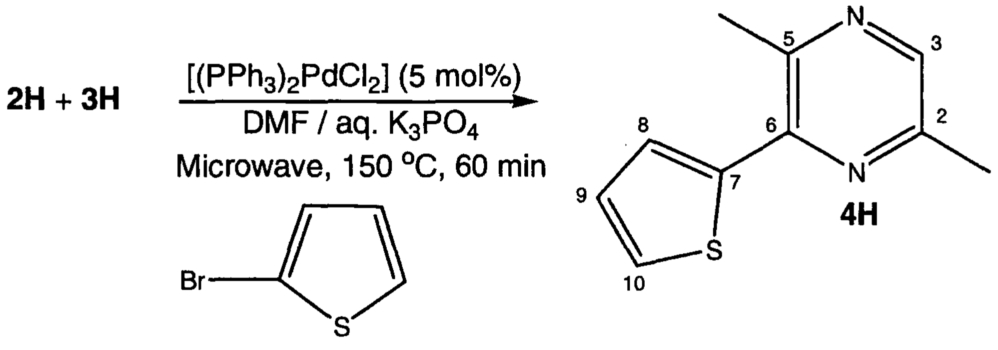
With this in mind, 2,5-dimethypyrazine **1H**, was chosen in which the two methyl groups are *ortho* to one nitrogen each and are in mutually *para* positions. The reaction was carried under the above conditions with 0.5 equiv. of B_2pin_2. After stirring at room temperature for 16 hours, no product was observed. Heating to 80 °C for 16 hours, *in situ* GC/MS analysis of the reaction mixture *in situ* GC/MS analysis of the reaction mixture showed borylation of **1H** with 55% conversion of the starting material giving 85% selectivity for the mono borylation product, 2,5-dimethy-6-(Bpin)-pyrazine, **2H**, and 15% for the bis(borylation) product, 2,5-dimethy-3,6-$(Bpin)_2$-pyrazine, **3H**, (Eq. 3.2.16).



1H **2H** **3H**

Eq. 3.2.16 The reaction of **1H** with 0.5 equiv. of B_2pin_2

The solvent was removed *in vacuo*, followed by addition of 1-bromothiophene and 5 mol% of $[(PPh_3)_2PdCl_2]$ in 20 ml of DMF with K_3PO_4 as the base. The mixture was heated in the microwave reactor at 150 °C for 1 hour to afford a 17% isolated yield of 2,5-dimethy-6-thiophen-2-yl-pyrazine, **3H** (Eq. 3.2.17).

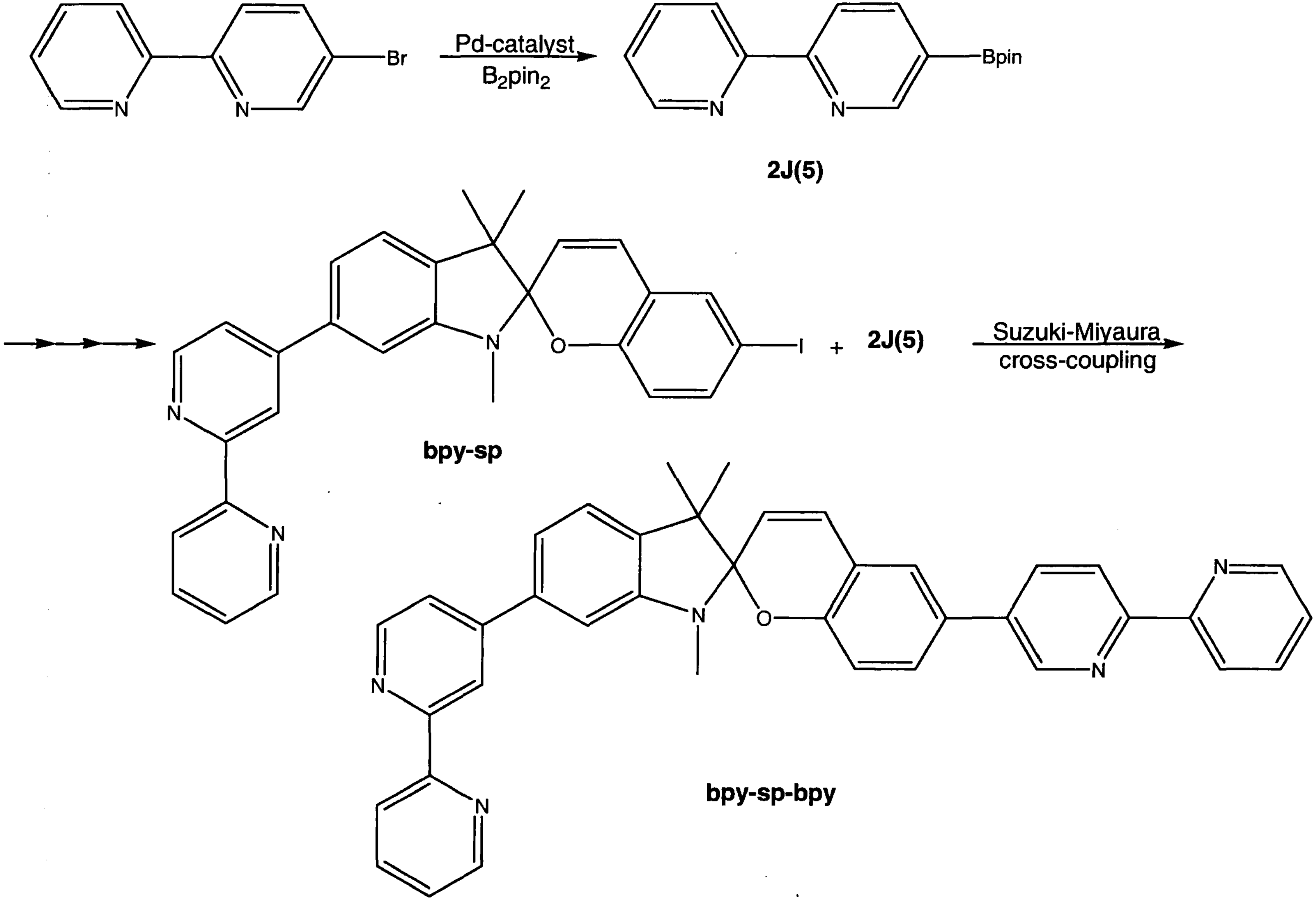


Eq. 3.2.17 The cross-coupling reaction of **2H** with 2-bromothiophene

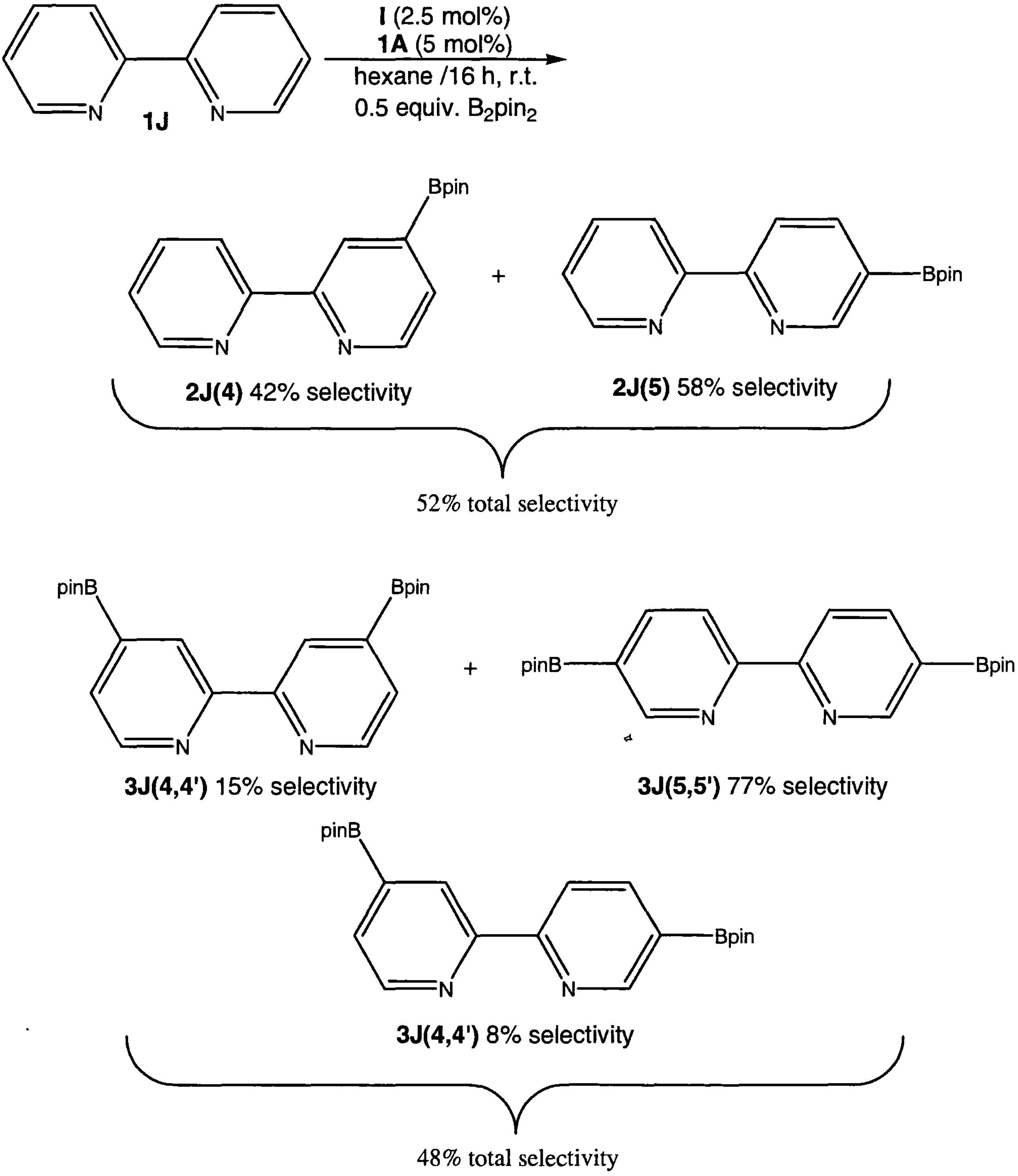
The ^1H NMR spectrum of **4H** shows singlets at 2.12 and 2.54 ppm representing the two methyl groups, a doublet of doublets at 6.78 ppm ($^3J_{H,H}$ = 4.0, 1.0 Hz) indicating H9, a doublet of doublets at 6.98 ppm ($^3J_{H,H}$ = 5.0, $^4J_{H,H}$ = 1 Hz) representing H8, an additional doublet of doublets at 7.24 ppm ($^3J_{H,H}$ = 4.0, $^4J_{H,H}$ = 1 Hz) for H10, and a singlet at 7.92 ppm for H3. The ^{13}C NMR spectrum shows resonance at 20.72 and 24.10 ppm for two CH_3 and at 127.65, 127.92 and 128.61 ppm representing the thiophene carbons 8, 9 and 10, resonances at 141.38 and 144.35 ppm for C 3 and 7, and the last three resonances appear at 146.22, 146.38 and 150.15 ppm for C 2, 5 and 6 respectively; The EI-MS spectrum exhibited molecular ions at *m/z* = 190 with fragment ions = 108 *m/z* indicating the loss of a $C_4H_2S^+$ group.

3.2.9 Syntheses of 4-(Bpin)-2,2'-bipyridine and 5-(Bpin)-2,2'-bipyridine

Syntheses of 4-(Bpin)-2,2'-bipyridine, **2J(4)**, and 5-(Bpin)-2,2'-bipyridine, **2J(5)**, are receiving attention because they are an important intermediates for the synthesis of new spiropyran systems attached to bipyridine moieties (Scheme 3.2.1). In addition, the spiropyran system can be used as a wire-type bridging ligand in heteronuclear metal complexes.[35] The compound **2J(5)** had been prepared by a Suzuki-Miyaura cross-coupling reaction in the presence of 5-Br-2,2'-bipyridine using B_2pin_2 with a Pd-catalyst in 74% yield.[36]



Scheme 3.2.1 Synthesis of spiropyran (bpy-sp-bpy)



Eq. 3.2.18 The reaction of **1J** with 0.5 equiv. of B_2pin_2

We thus examined the borylation of 2,2-bipyridine, and found that it takes place at both the 4- and 5-position in **1J**, giving **2J(4)** and **2J(5)**. At the same time, three isomers of the bis(borylation) product were observed by GC/MS, i.e. 4,4'-$(Bpin)_2$-2,2'-bipyridine, **3J(4,4')**, 5,5'-$(Bpin)_2$-2,2'-bipyridine **3J(5,5')**, and 4,5-$(Bpin)_2$-2,2'-bipyridine **3J(4,5)**. The reaction was carried out under the same condition as for **1C**, with 0.5 equiv. of B_2pin_2 (Eq. 3.2.18). After 16 hours, *in situ* GC/MS analysis showed complete consumption of B_2pin_2 with 85% conversion of **1J**, giving two main products. The two isomeric mono borylation products were formed in 52% overall selectivity, of which 42% was **2J(4)** and 58% was **2J(5)**. On the other hand, the GC/MS showed that the three isomeric bis(borylated) species constitute 48% of the overall products, with 77% selectivity for **3J(5,5')**, 15% selectivity for **3J(4,4')**, and 8% selectivity for **3J(4,5)**. However, the NMR spectrum showed only sets of resonances directly attributable to **3J(4,4')** and **3J(5,5')**, in a ca. 30/70 ratio, but it is likely that the resonances for **3J(4,5)** are those of **3J(4,4')** and **2J(5,5')**. The structure of **3J(4,4')** was confirmed by single crystal X-ray diffraction (Fig. 3.2.31).

We did notice, from the borylation reaction of **1C**, that borylation takes place first at pyridine ring and, if there is an excess of B_2pin_2, phenyl ring will subsequently be borylated. In this case, due to the asymmetric in compound **1J**, the two pyridine rings were borylated randomly giving mixture of mono and bis(borylation) products.

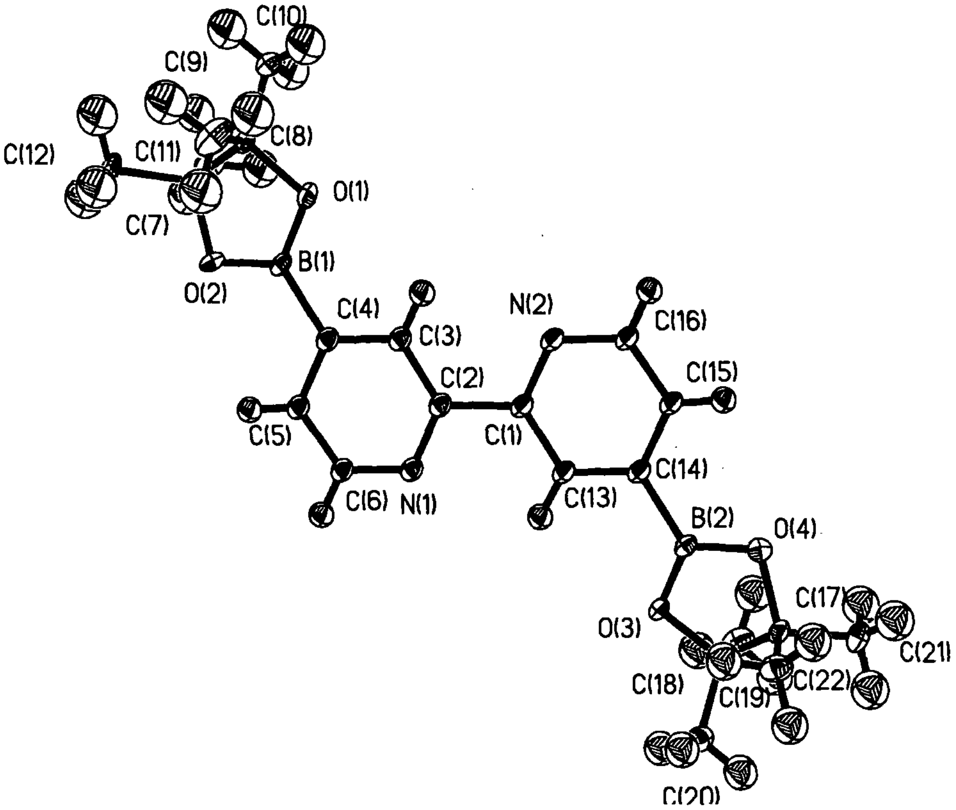
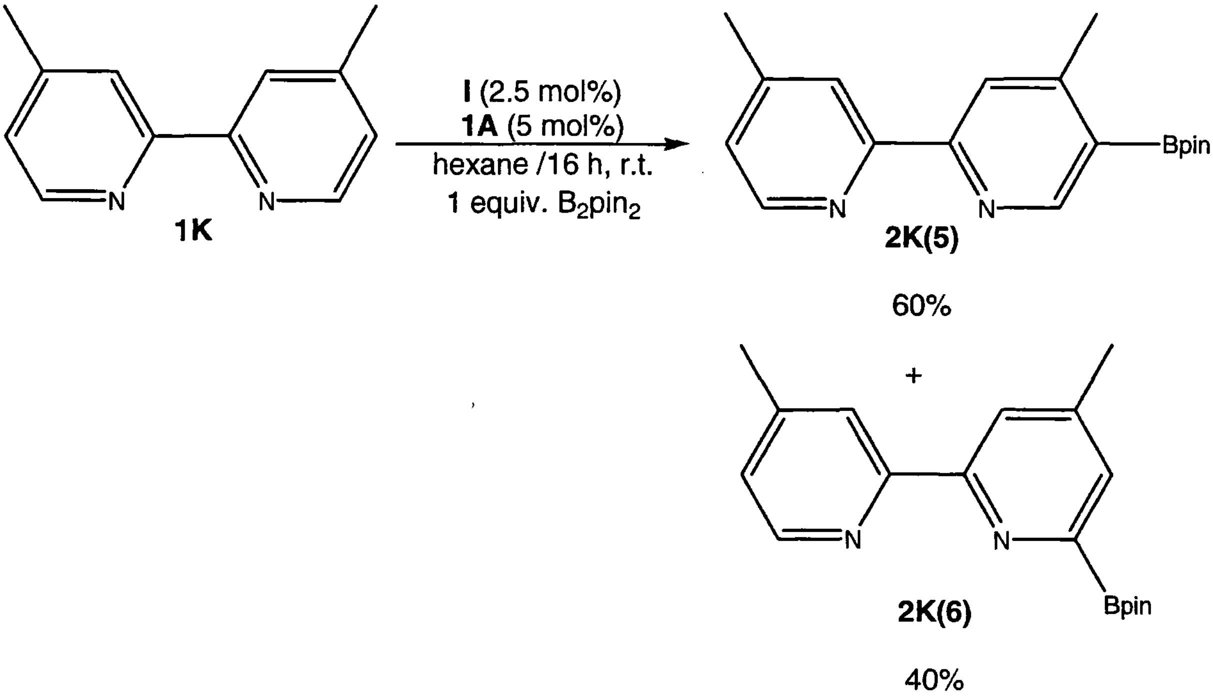


Fig. 3.2.31 Molecular structure of **2J(4,4')**

3.2.10 Borylation of 4,4'-Me_2-2,2'-bipyridine to give 4,4'-Me_2-5-(Bpin)-2,2'-bipyridine and 4,4'-Me_2-6-(Bpin)-2,2'-bipyridine

Here, 4,4'-Me_2-2,2'-bipyridine, **1K**, was examined, due its similarity with **1A** and **1B**, to see whether the Me group is able to direct borylation to take place *ortho* to the nitrogen as in the reaction of **1A**, or it will avoid this position and occur *ortho* to the substituent, as in the reaction of **1B**.

The reaction was carried out under the same conditions used for the borylation of **1A**. Using **I** (2.5 mol%) and 1 equiv. of B_2pin_2 in 5 ml hexane, the mixture was stirred for 16 hours at room temperature (Eq. 3.2.19). Interestingly, *in situ* GC/MS analysis of the reaction mixture showed borylation of **1K** with 44% conversion of the starting material, giving 4,4'-Me_2-5-(Bpin)-2,2'-bipyridine **2K(5)** with 60% selectivity, and 40% selectivity for 4,4'-Me_2-6-$(Bpin)_2$-2,2'-bipyridine **2K(6)**, Fig. 3.2.32.



Eq. 3.2.19 The reaction of **1K** with 1 equiv. of B_2pin_2 in the presence of 2.5 mol% of **I**

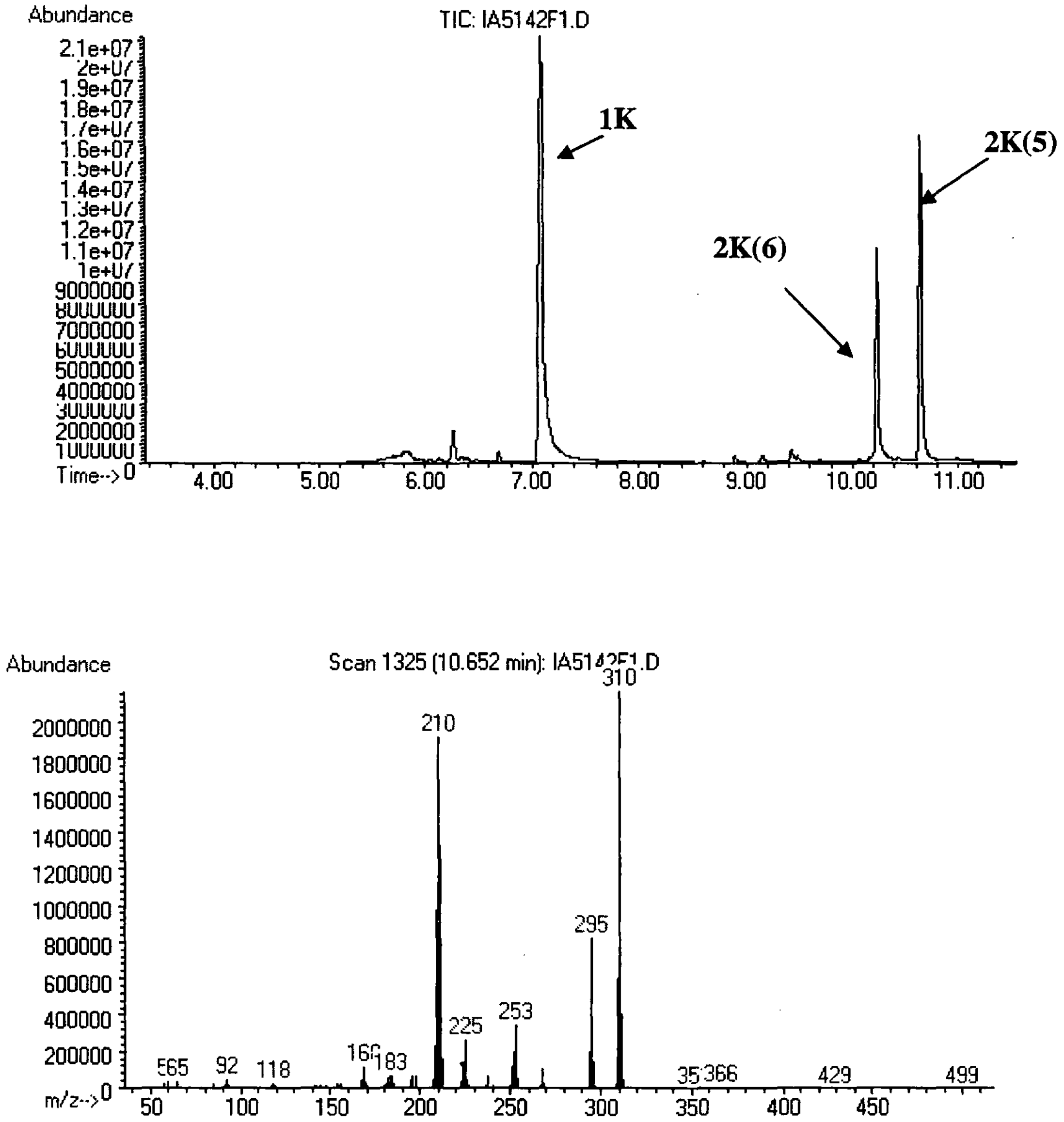


Fig. 3.2.32 Top: GC (TIC) of the reaction of **1K** with 1 equiv. of B_2pin_2 in the presence of 2.5 mol% of **I**. Bottom: Mass spectrum of the product

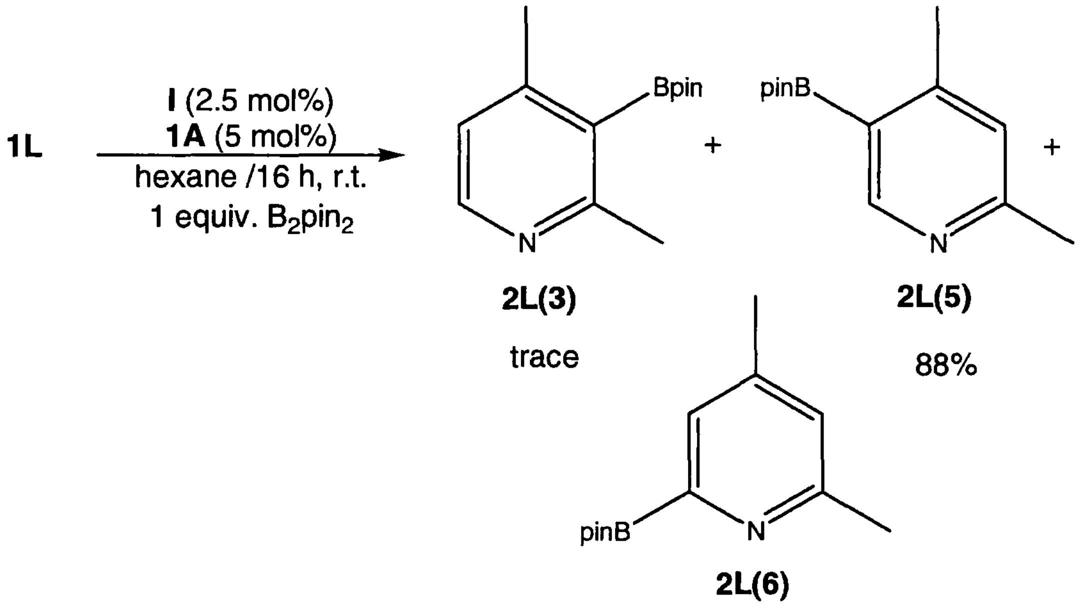
This mixture of isomers indicated that in spite of steric hindrance, the borylation avoids the position *ortho* to the nitrogen atom for an electronic reason. Moreover, the Me group in **1K** exerts more hindrance than the MeO group in **1B**, but less hindrance than the ^{t}Bu group in **1A**, thus giving mixture of products. We do not understand why borylation tends to avoid the position next to the nitrogen; M.O. calculations are being conducted by Prof. Z. Lin's group at HKOST to examine this point.

The crude mixture was used in a Suzuki-Miyaura cross-coupling reaction. However, no evidence for coupling with [Pd(PPh$_3$)$_4$] or [Pd(PPh$_3$)$_2$Cl$_2$] in variety solvents such as DMF, 1,4-dioxane and base K_2CO_3 and $K_3PO_4 \cdot 2H_2O$ was obtained; and a trace of product was observed by GC/MS when [(dppf)PdCl$_2$] and $K_3PO_4 \cdot 2H_2O$ in DMF was used.

For this reason, once the borylation product was formed as shown by *in situ* GC/MS analysis, the mixture was quenched a small amount of D_2O and then stirred at room temperature. Interestingly, *in situ* GC/MS analysis showed that the first peak, with retention time of 10.24 minutes in the GC (TIC) disappeared and this must represent **2K(6)**. On the other hand, the second peak, with a retention time of 10.65 minutes was still present in the TLC. The ^{2}H NMR spectrum for the same solution showed that the hydrolysis had taken place *ortho* to the nitrogen atom, and the deuterated product displayed a ^{2}H-resonance at 8.30 ppm.

3.2.11 Borylation of 2,4-Me$_2$-pyridine to give 2,4-Me$_2$-5-(Bpin)- pyridine and 2,4-Me$_2$-6-(Bpin)- pyridine

2,4-Me$_2$-pyridine **1L**, was examined under the above conditions (Eq. 3.2.21). We know, from the reaction of **1D**, that a single Me group *ortho* to the nitrogen atom is enough to block the coordination to the Ir metal giving borylation products. However, in this case, the 4-position is also blocked by a Me group. *In situ* GC/MS analysis of the reaction mixture showed borylation of **1L** with 52% conversion of the starting material, giving a trace of 2,4-Me$_2$-3-(Bpin)-pyridine **2L(3)**, 2,4,-Me$_2$-5-(Bpin)-pyridine **2L(5)** (88% selectivity), and 2,4-Me$_2$-6-(Bpin)-pyridine **2L(6)** (12% selectivity) as shown in Fig. 3.2.33.



2L(3)
trace

2L(5)
88%

2L(6)
12%

Eq. 3.2.20 The reaction of **1L** with 1 equiv. of B$_2$pin$_2$ in the presence of 2.5 mol% of **I**

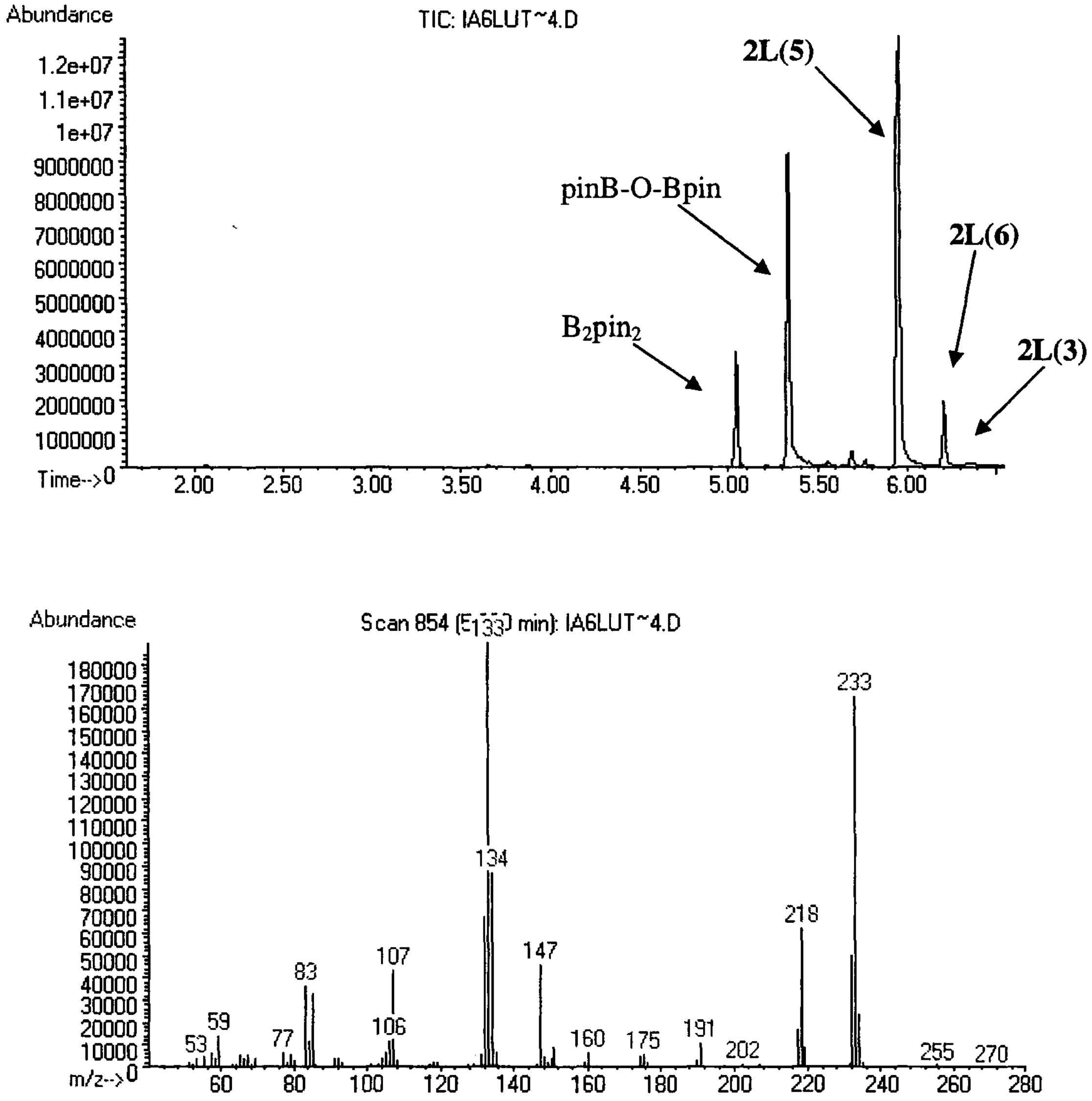


Fig. 3.2.33 GC (TIC) of the reaction of **1L** with 1 equiv. of B_2pin_2 in the presence of 2.5 mol% of **I**. Bottom: Mass spectrum of the product

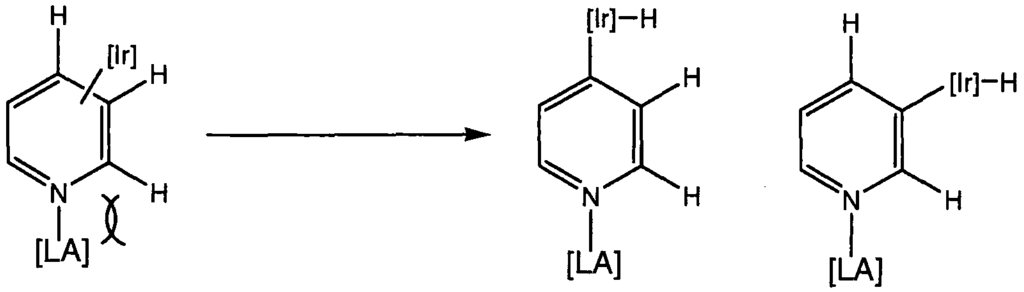
This example indicated that the α-position to the nitrogen atom is not a favorable location for the borylation to take place. Again, once the borylation product was formed as evidenced by *in situ* GC/MS analysis, the mixture was quenched with few drops of D_2O and then stirred at room temperature. Interestingly, *in situ* GC/MS analysis showed that the major peak, **2L(5)**, still remains and the minor component, **2L(6)** was hydrolysed. The ^{2}H NMR spectrum of the same solution showed that the hydrolysis had taken place *ortho* to the nitrogen atom, and the deuterated product displayed a ^{2}H-resonance at 8.26 ppm.

3.2.12 Does the pyridine ring coordinate to the Ir-centre or to a boron atom

As mentioned in Chapter 1, section 1.9, Ishiyama and Miyaura et al.[17] found that pyridine shows less reactivity than benzene for C-H borylation, and we found very low reactivity in the reaction of 4-^{t}Bu-pyridine. They have suggested that the pyridine has a strong coordination affinity for Lewis acids (Scheme 3.2.2), so perhaps the Ir centre or a B atom in B_2pin_2 binds reversibly to the basic nitrogen and the coordination activates the pyridine ring for oxidative addition and blocks borylation at the α-position.

To investigate the binding of 4-^{t}Bu-pyridine to a boron atom, we examined the interaction of 4-^{t}Bu-pyridine with B_2pin_2 by conducting the following ^{11}B NMR spectroscopic study, noting that any significant binding would result in a large upfield shift consistent with 4-coordinate boron, as Marder *et al.*[37,38] found for the more Lewis acidic B_2cat_2.

A solution of 70 mg of B_2pin_2 in 0.7 ml of benzene-d_6 was examined by ^{11}B NMR. It exhibited the typical singlet at the position expected for 3-coordinate boron (31.27 ppm), and then 3 solutions containing the same concentration of B_2pin_2 + 41 mg (1 equiv.), 208 mg (5 equiv.) or 405 mg (10 equiv.) of 4-^{t}Bu-pyridine were examined. No change in the ^{11}B NMR shift was observed in any of the samples. These experiments indicated that pyridine does not coordinate to B_2pin_2 to any measurable extent, even in very concentrated solution.



LA = Ir or B compounds

Scheme 3.2.2

As discussed in chapter 1, section 1.10, the active species [Ir(bpy)(Bpin)$_3$], has one vacant site on iridium for the C-H borylation to occur (Fig. 3.2.34). It possible that pyridine and 4-^{t}Bu-pyridine coordinate strongly at this site, and inhibits the C-H activation. To examine this issue, the following experiments were conducted.

The compound 2,6-Me$_2$-pyridine (**2E**) was chosen because it is borylated easily whereas 4-^{t}Bu-pyridine is not borylated at all at room temperature. We thus examined the effect of added 4-^{t}Bu-pyridine on the borylation of **2E** using 2.5 mol% **I** and 5 mol% of **1A** as catalyst in hexane at room temperature for 16 hours with different amounts of B_2pin_2 present (Table 3.2.1).

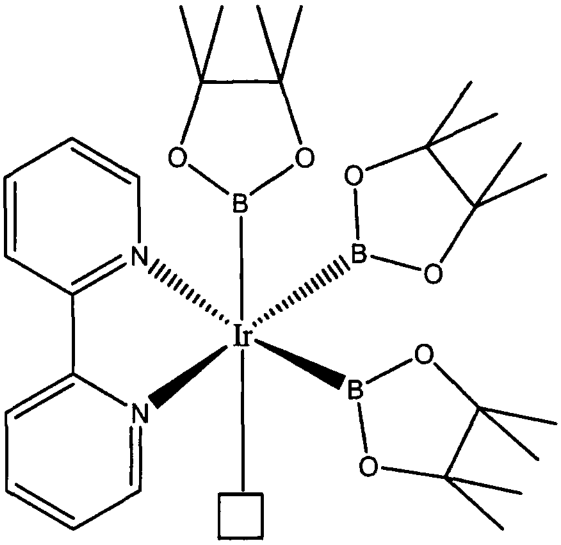


Fig. 3.2.34 [Ir(bpy)(Bpin)$_3$]

Table 3.2.1 Reactions of **2E** and 4-^{t}Bu-pyridine with B$_2$pin$_2$ in the presence of **I** / **1A**

Entry	**2E** equiv.	4-^{t}Bu-pyridine equiv	B$_2$pin$_2$ equiv.	Result
1	1	-	1	100% borylation of **2E**
2.	1	1	0.5	Trace borylation of **2E**
3.	1	1	1	Trace borylation of **2E**
4	1	1	2	Trace borylation of **2E**
5	1	0.1	1.1	Trace borylation of **2E**

Trace:- Detected by GC/MS but less than 3%.

From above table, the borylation of **2E** was inhibited in the presence 4-^{t}Bu-pyridine. Even when there is enough boron to borylate both pyridines, (Entry 4), the presence of 4-

^{t}Bu-pyridine inhibits borylation of **2E**. Indeed, even 0.1 equiv. of 4-^{t}Bu-pyridine (relative to **2E**) was enough to inhibit catalytic activity almost completely.

Therefore, pyridine binding to Ir inhibits catalysis by blocking the site needed for C-H activation.

3.3 Conclusion

In conclusion, we have shown that the catalyst is capable of borylating dtbpy unless it is already coordinated to iridium. Moreover, we note that a single substituent *ortho* to the nitrogen atom is sufficient to inhibit nitrogen coordination to iridium, thus "activating" the 6-membered heteroarenes to C-H borylation, providing a design criterion for substrates for selective borylation. Complete regioselectivity has been achieved via either electronic or steric control, allowing, for the first time, borylation of pyridine derivatives *ortho* to nitrogen or *ortho* to a MeO substituent (i.e. *meta* to N).

The compound 2-Ph-pyridine, important in the design of triplet emitting Ir complexes for OLEDs,[26-28] can be further derivatised at the 4- and 5-positions of the pyridine ring in preference to the phenyl ring, leading to useful 4-(or 5-)-Ar'-2-Ph-pyridine derivatives.

The compound 2-methylpyridine was examined, in which the methyl group is *ortho* to the nitrogen atom. We found that a single CH_3 group is sufficient to block N-coordination to Ir, allowing the borylation reaction to occur at the 4- and 5-positions.

The compound 2,6-dimethylpyridine is borylated readly at room temperature and gave a high yield compared to that reported by Smith *et al.* using Hartwig's Rh-catalyst. [21]

The borylation of 2,3-dichloropyridne is an attractive reaction for organic synthesis.[3-7, 29,30] and we found that one chlorine *ortho* to the nitrogen atom is also enough to block the nitrogen coordination to Ir and enhance the borylation reaction to occur at room temperature.

The compound 2,3-dimethylpyrazine was borylated *ortho* to nitrogen and cross-coupled with the electron-rich heteroarene 2-bromothiophene. In addition, 2,5-dimethylpyrazine was showed activity for borylation under our conditions.

The unsubstituted compound, 2,2'-bipyridine shows high reactivity giving mixture of mono- and bis(borylation) products, whereas 2-phenylpyridine gave mono-substituted products on pyridine ring unless an excess of B_2pin_2 was present.

Borylation of 4,4'-Me_2-2,2'-bipyridine and 2,4-Me_2-pyridine, each gave two isomeric product; in both cases, the Bpin group tends to avoid the position *ortho* to the nitrogen.

Some of the aryl pyridines, such as **3a** and **4a**, have been used previously as ligands in Ru and luminescent Ir and Pt complexes,[39-41] having been prepared *via* addition of PhLi to dtbpy, followed by hydrolysis and oxidation. Our route is more general, and inherently more functional-group tolerant, not requiring highly reactive ArLi reagents. We expect this route to be of use in applications ranging from pharmaceuticals to new optical and electronic materials.

Finally, pyridine derivatives are also suitable substrates for catalytic C-H borylation, if their binding *via* nitrogen to the critical catalytic site on Ir can be inhibited by suitable substitution at the 2-position. Indeed, the pyridines are inherently more reactive than benzene, as shown by the "internal competition" reaction using 2-Phpy, or quinoline.

Sterics play a major role in determining the selectivities of arene and heteroarene borylation reactions. However, the influence of electronic effects on selectivity is not yet understood.

3.4 Discussion of crystal structures

3.4.1 Molecular structure of 4,4'-^{t}Bu$_2$-6,6'-(Ph)$_2$-2,2'-bipyridine, 4A·2C_6F_6

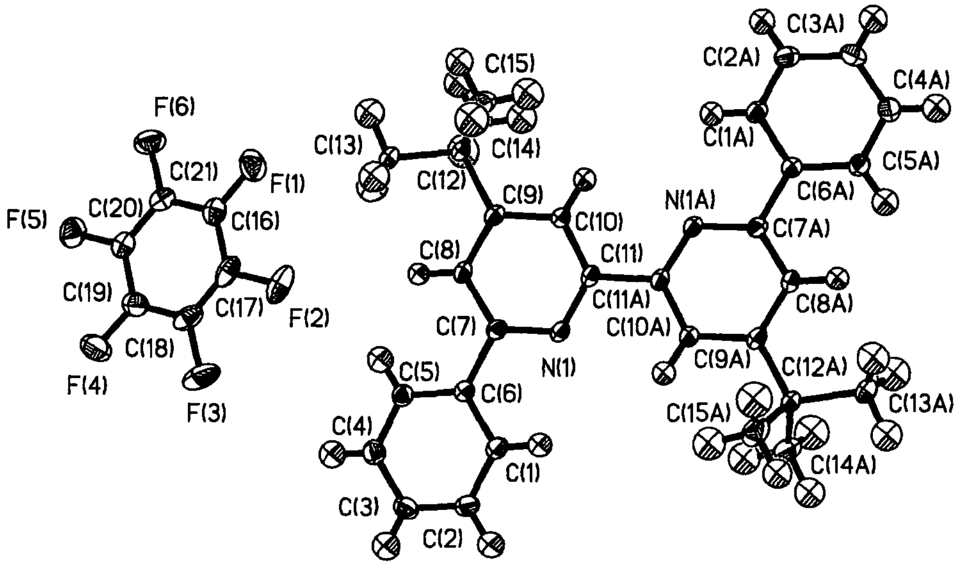


Fig. 3.4.1 Molecular structure of **4A**

Crystals of 4,4'-^{t}Bu$_2$-6,6'-(Ph)$_2$-2,2'-bipyridine·2C_6F_6 **4A** were grown by slow evaporation of a C_6F_6 solution of **4A**. The compound crystallises in the orthorhombic space group *Pccn*, with Z = 4. The asymmetric unit contains one half of a molecule of **4A**, and one molecule of C_6F_6. The molecular centroid of **4A** is coincident with a crystallographic centre of inversion. The angle between the mean planes of the phenyl ring and the pyridyl ring is 11.6° and the angle between the mean planes of the two pyridyl rings is 19.2 °.

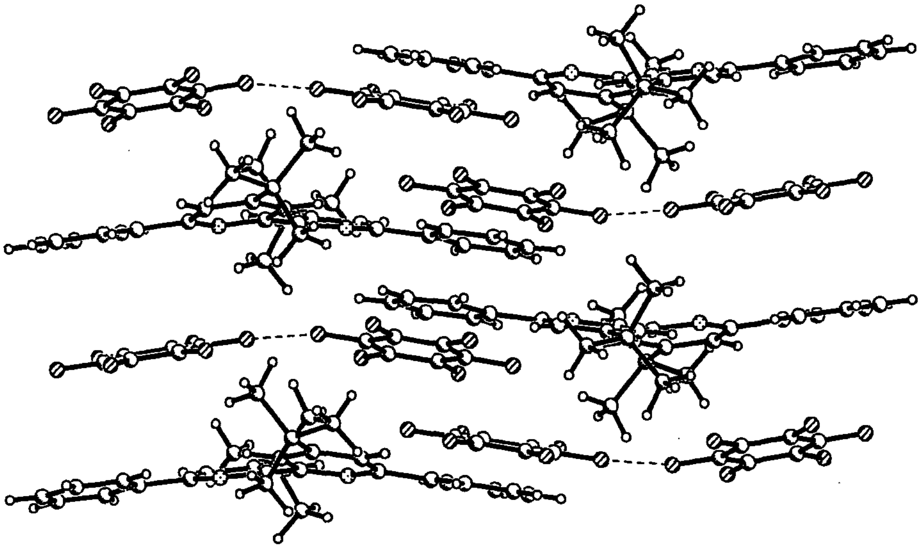


Fig. 3.4.2 Packing of **4A**

The molecules of **4A** and two molecules of HFB alternate in infinite stacks. The HFB molecules are offset so that they each lie above one half of the molecules of **4A**. The mean plane of the HFB molecule and the mean plane of half of the **4A** molecule that it lies above form an angle of 6.9°. The shortest distance between the mean plane of the HFB molecule and the mean plane of half of the adjacent **4A** molecule is 3.38 Å. This is comparable to those in other HFB complexes.[42]

There is a close intermolecular contact between two F atoms of the adjacent HFB molecules. The F⋯F distance is 2.82 Å, which is slightly shorter than the sum the van der Waals radii of F – 2.90 Å.[43]

3.4.2 Molecular structure of 4,4'-^{t}Bu$_2$-6-(Ph)-2,2'-bipyridine 5A (as complex with C_6F_6)

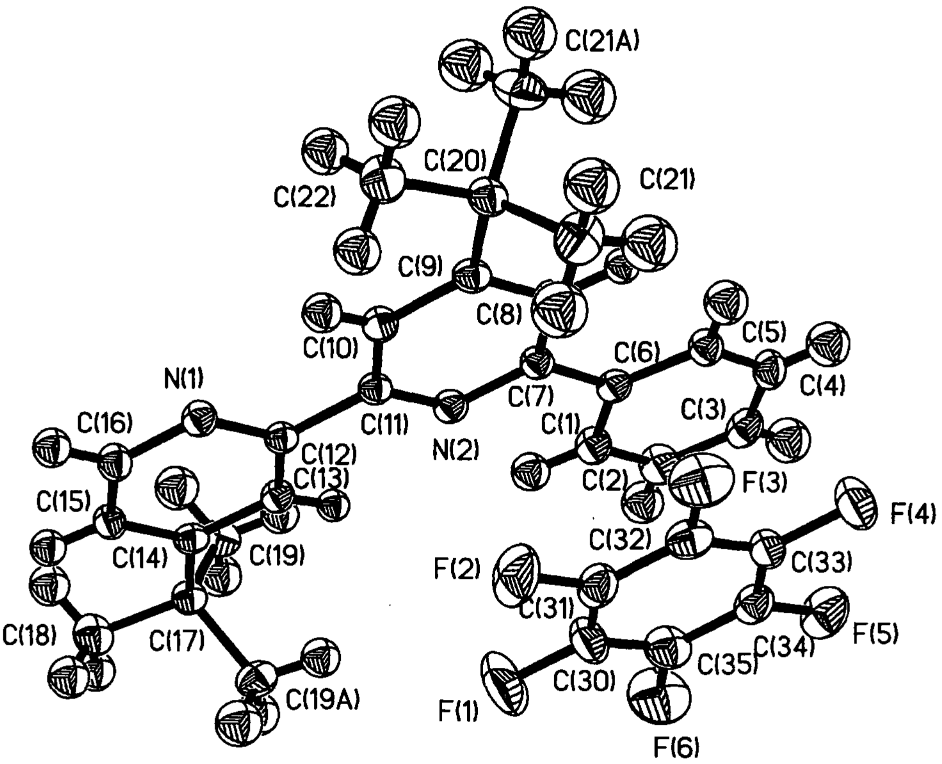


Fig. 3.4.3 Molecular structure of **5A**

Crystals of 4,4'-^{t}Bu$_2$-6,6'-(Ph)-2,2'-bipyridine **5A** were grown by slow evaporation of a C_6F_6 solution of **5A**. The compound crystallises produce in the orthorhombic space group Pnma, with Z = 4. The asymmetric unit contains one molecule of **5A** and one molecule of C_6F_6. The molecules of **5A** are exactly planar. The molecules of **5A** and HFB alternate in infinite stacks with their mean planes both being exactly parallel. The shortest distance between the mean planes of adjacent **5A** and HFB molecules is 3.37 Å, comparable to those in other HFB complexes.[42] There is considerable offset of the HFB molecules with respect to the phenyl rings of **5A**. All of the molecules in each stack are parallel, so the structure is said to be laminar.

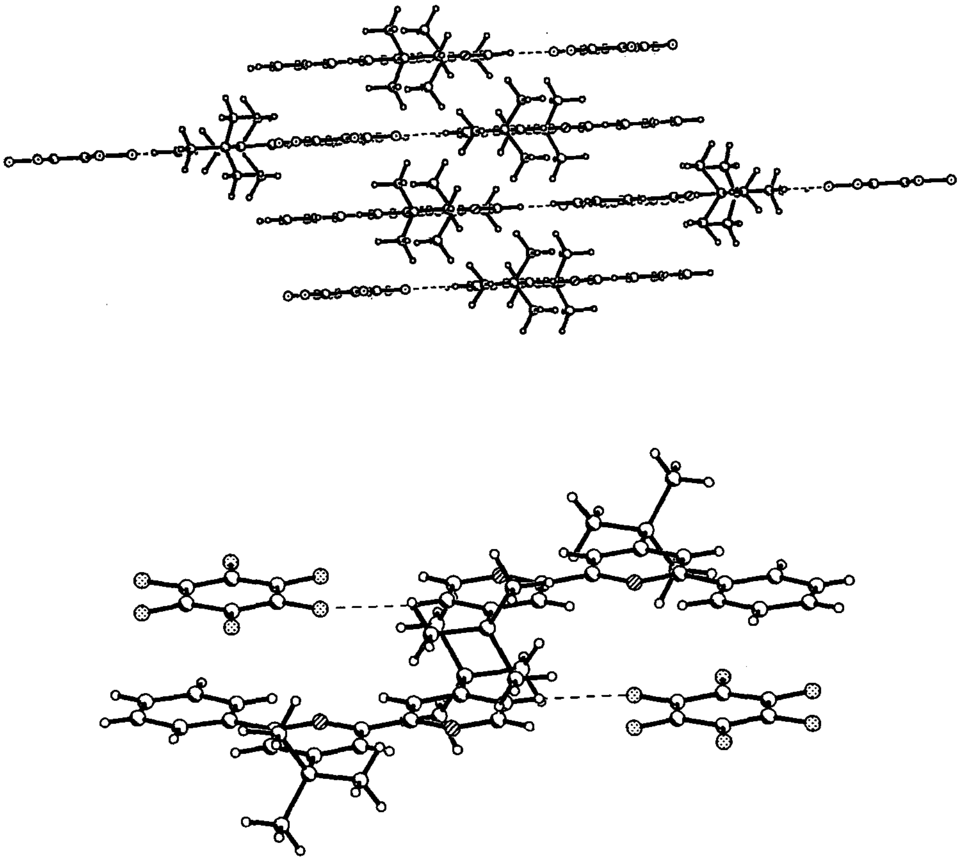


Fig. 3.4.4 Packing of **5A** with dashed lines indicating short intermolecular H···F contacts

There is a close intermolecular contact between the H atom in the *meta* position on the pyridyl ring and one of the F atoms of the HFB. The H···F distance is 2.35 Å (with the C-H bond length being set to that typically obtained from neutron diffraction (1.08 Å).[44] This is considerably shorter than the sum the van der Waals radii of H and F (2.56 Å),[43] and may be a weak hydrogen bond.

3.4.3 Molecular structure of 4,4'-MeO_2-6,6'-$(Bpin)_2$-2,2'-bipyridine 3B

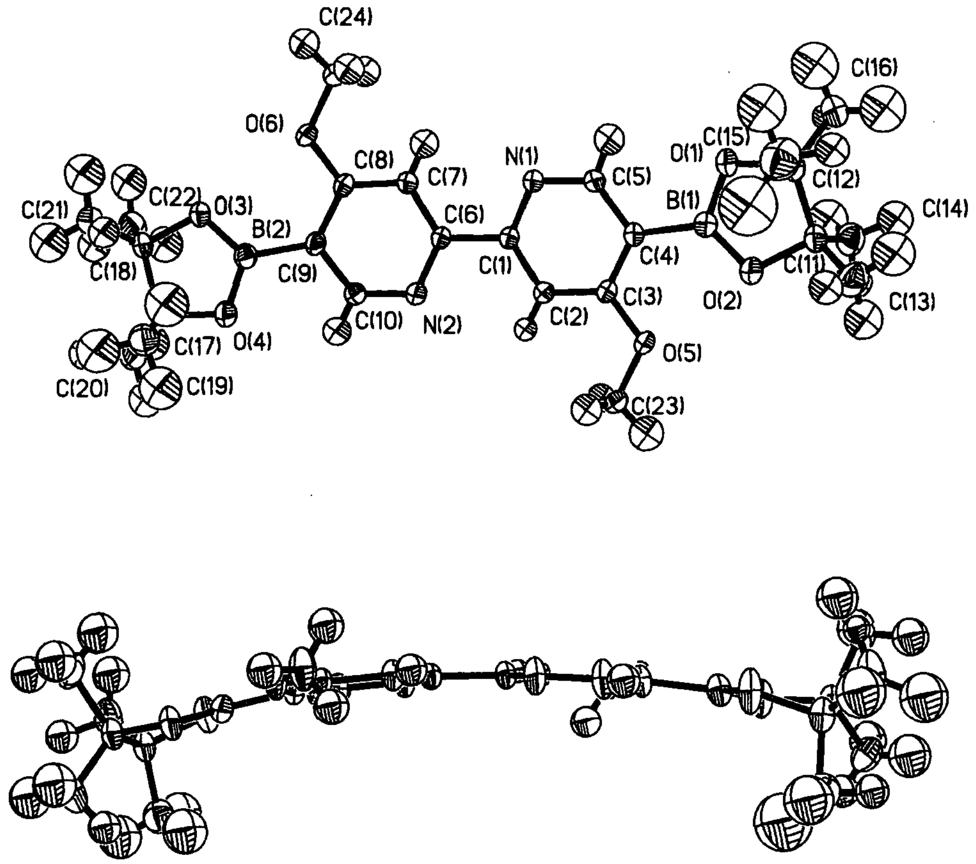


Fig. 3.4.5 Molecular structure of **3B**

Monoclinic crystals of 4,4'-MeO_2-6,6'-$(Bpin)_2$-2,2'-bipyridine **3B** (space group $P2_1/n$, with Z = 4), were grown by slow evaporation of a DCM solution (Fig. 3.3.5). The two C-B bond lengths are 1.560(3) and 1.566(3) Å. The angles between the mean planes of the boryl groups and the pyridyl rings {[B(1), O(1), O(2), C(11), C(12) and N(1), C(1), C(2), C(3), C(4), C(5)]; B(2), O(3), O(4), C(18), C(19) and N(2), C(6), C(7), C(8), C(9), C(10)]} are 7.1° and 11.4°, respectively, and the dihedral angles C(23) O(5) C(3) C(2) and C(24) O(6) C(8) C(7) are -7.6(3) and 2.8(3) respectively, so the methoxy groups are nearly coplanar with the pyridine rings. The dihedral angle between the planes of the two pyridyl rings is 9.5°.

3.4.4 Molecular structure of 2-Ph-4-(1-Np)-pyridine 3C(4)

Monoclinic crystals of 2-Ph-4-(1-Np)-pyridine **3C(4)** (space group $P2_1$, with Z = 2), were grown by slow evaporation of a DCM solution. The angle between the mean planes of the naphthalene ring and the pyridyl ring is 77.6° and between the mean planes of the phenyl ring and the pyridyl ring is 33.9°.

3.4.5 Molecular structure of 2-Ph-5-(1-Np)-pyridine 3C(5)

Monoclinic crystals of 2-Ph-4-(1-Np)-pyridine **3C(5)** (space group $P2_1$, with Z = 2), were grown by slow evaporation of a DCM solution. The angles between the mean planes of the naphthalene ring and the pyridyl ring and between the phenyl ring and the pyridyl ring are 48.7 and 10.2°, respectively.

3.4.6 Molecular structure of 2-Me-4-Ph-pyridine 3D(4)

Orthorhombic crystals of 2-Me-4-(Ph)-pyridine **3D(4)** (space group Pbca, with Z = 16) were grown by slow evaporation of a DCM solution. The asymmetric unit contains two independent molecules. The angles between the mean planes of phenyl ring and the pyridyl ring are 24.7° in molecule 1 and 28.6° in molecule 1'.

3.4.7 Molecular structure of 2,6-dimethyl-4-(Bpin)-pyridine 2E

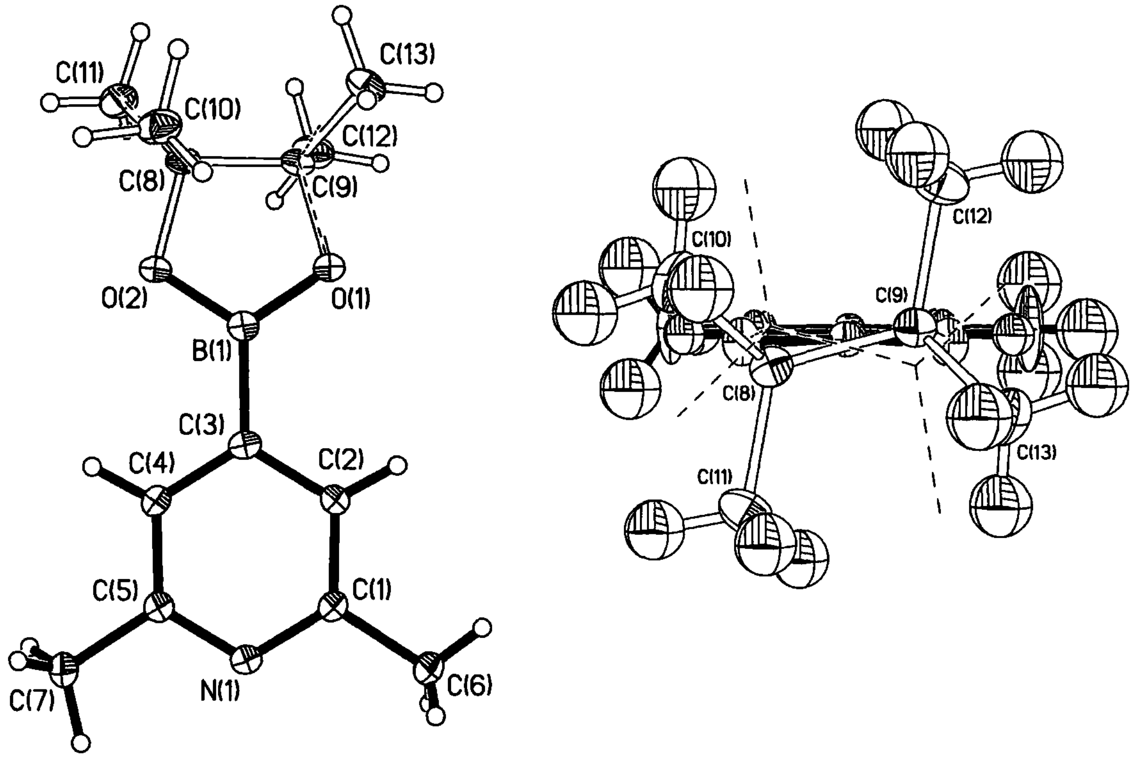


Fig. 3.4.6 Molecular structure of **2E** (left), with an edge-on view (right) showing disorder in the pinacolate moiety

Monoclinic crystals of 2,6-dimethyl-4-(Bpin)-pyridine **2E** (space group $P2_1/m$ with Z = 4), were grown by slow evaporation of a DCM solution. The C-B bond length is 1.559(3) Å. The angle between the mean planes of the BO_2 unit and the pyridyl ring is 0.0°. The pinacolate group is disordered over two crystallographically independent positions, each with 50% occupancy.

3.4.8 Molecular structure of 2,6-dimethyl-4-naphthalen-1-yl-pyridine 3E

Monoclinic crystals of 2,6-dimethyl-4-naphthalen-1-yl-pyridine **3E** (space group $P2_1/c$, with Z = 4), were grown by slow evaporation of a diethylether solution. The angle between the mean planes of the naphthalene ring and the pyridyl ring is 51.2°.

3.4.9 Molecular structure of 2,3-dichloro-5-(Bpin)-pyridine 2F

Monoclinic crystals of 2,3-dichloro-5-(Bpin)-pyridine **2F** (space group $P2_1/n$, with Z = 4), were grown from slow evaporation of a DCM solution. The C-B bond length is 1.560(2) Å. The angle between the mean planes of the BO_2C_2 unit and the pyridyl ring is 13.3°.

3.4.10 Molecular structure of 2,3-dimethy-5-thiophen-2-yl-pyrazine 3G

Monoclinic crystals of 2,3-dimethy-5-thiophen-2-yl-pyrazine **3G** (space group $P2_1/c$ with Z = 4), were grown by slow evaporation of a DCM solution of **3G**. The angle between the mean planes of the thiophene ring and the pyrazine ring is 10.3°.

3.4.11 Molecular structure of 4,4'-(Bpin)$_2$-2,2'-bipyridine 3J(4,4)

Orthorhombic crystals of 4,4'-(Bpin)$_2$-2,2'-bipyridine **3J(4,4')** (space group $Pna2_1$, with Z = 4), were grown by slow evaporation of a DCM solution. The C(4)-B(1) and C(14)-B(2) bond lengths are 1.572(3) and 1.574(3) Å, respectively. The angles between the mean planes of the boryl groups and the pyridyl rings {[B(1), O(1), O(2), C(7), C(8) and N(1), C(2), C(3), C(4), C(5), C(6),)]; [B(2), O(3), O(4), C(17), C(18) and N(2), C(1), cross-linked 5% phenylmethylsilicone) was used, and the oven temperature was ramped from 50 °C to 280 °C at a rate of 20 °C/min. UHP grade helium was used as the carrier gas. The screw-cap autosampler vials used were supplied by Thermoquest Inc. and were fitted with Teflon / silicone / Teflon septa and 0.2 ml micro inserts. Microwave reaction were carried out in a Biotage Personal Chemistry Optimizer Exp. reactor using thick-walled glass reaction tubes with septum seals specifically designed to with stand the pressures generated.

General Procedure for Catalytic Borylations:-

In a nitrogen-filled glove box, to a premixed solution of $[Ir(\mu\text{-}OMe)COD]_2$ (X mol%) and dtbpy (X mol%) in 2 ml of solvent was added a mixture of boron reagent (Y mmol) and pyridine derivatives (Z mmol) in 3 ml of hexane (5 ml total solvent volume). The mixture was shaken vigorously to ensure complete mixing, and then the mixture was stirred at room temperature or transferred to ampoules sealed with a Teflon Young's tap and heated to 80 °C. The reactions were monitored by GC/MS.

General Procedure for Suzuki-Miyaura Cross-Coupling Reaction:-

Once the borylation product formed, as shown by *in situ* GC/MS analysis, the solvent was removed *in vacuo*, followed by addition of arylhalide (X mmol), K_2CO_3 (aq.) (Y equiv., (aq. = each 1 ml water = 4.5-5 ml solvent), $[(PPh_3)_2PdCl_2]$ (Z mmol, 5 mol%) and 1,4-dioxane (15-20 ml). The mixture was transferred to a microwave reaction tube (20 ml volume), then sealed and heated for 1 h at 150 °C.

C(13), C(14), C(15), C(16)]} are 11.2° and 15.8° respectively. The angle between the planes of the two pyridyl rings is only 0.7°.

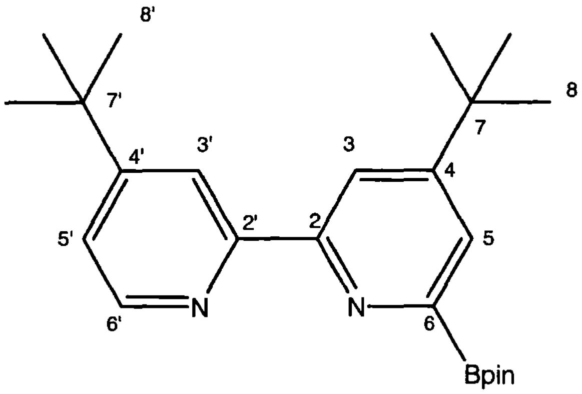
3.5 Experimental

All reactions were carried out under a dry nitrogen atmosphere using standard Schlenk techniques or in an Innovative Technology Inc. System 1 double-length glove box. Glassware was oven dried before transfer into the glove box. Hexane was dried over sodium / benzophenone and distilled under nitrogen; 2-picoline, 2-phenylpyridine, 2,3'-dimethylpyrazine and 2,5-dimethylpyrazine were dried over CaH_2. $[Ir(\mu\text{-}OMe)(COD)]_2$ was synthesised by a literature procedure,[45] and $IrCl_3 \cdot 3H_2O$ and $PdCl_2$ were obtained from Precious Metals Online. B_2pin_2 was supplied as a gift by Frontier Scientific Inc. and Netchem Inc. All other compounds were obtained from Aldrich Chemical Company, tested for purity by GC/MS and used without further purification. NMR spectra were recorded at ambient temperature on Varian Inova 500 (^1H, $^{13}C\{1H\}$, HSQC, HMBC), Varian C500 (^1H, $^{13}C\{^1H\}$, HSQC, HMBC), Varian Unity 300 (^{11}B and $^{11}B\{^1H\}$) and Bruker AC200 ($^{13}C\{^1H\}$) instruments. Proton and carbon spectra were referenced to external $SiMe_4$ via residual protons in the deuterated solvents or solvent resonance respectively. Elemental analyses were conducted in the Department of Chemistry at the University of Durham using an Exeter Analytical Inc. CE-440 Elemental Analyser. GC/MS analyses were performed on a Hewlett-Packard 5890 Series II gas chromatograph equipped with a 5971 mass selective detector and a 7673 autosampler or on an Agilent 6890 Plus GC equipped with a 5973N MSD and an Anatune Focus robotic liquid handling system / autosampler. A fused silica capillary column (10 m or 12 m

General Procedure for Suzuki-Miyaura Cross-Coupling Reaction for Compound 4A and 5A:-

In a nitrogen-filled glove box, once the borylated compound **3A** was formed as shown by *in situ* GC/MS analysis, the solvent was removed *in vacuo* followed by addition of PhI (X mmol), $K_3PO_4 \cdot 2H_2O$ (Y mmol, Y equiv.), [(dppf)PdCl$_2$] (Z mmol, 10 mol%) and dry DMF (8 ml). The reaction was heated at 80 °C for 5 h. The product was extracted into hexane, dried ($MgSO_4$), and chromatographed on silica gel (hexane:diethylether, 9:1) to give the desired product.

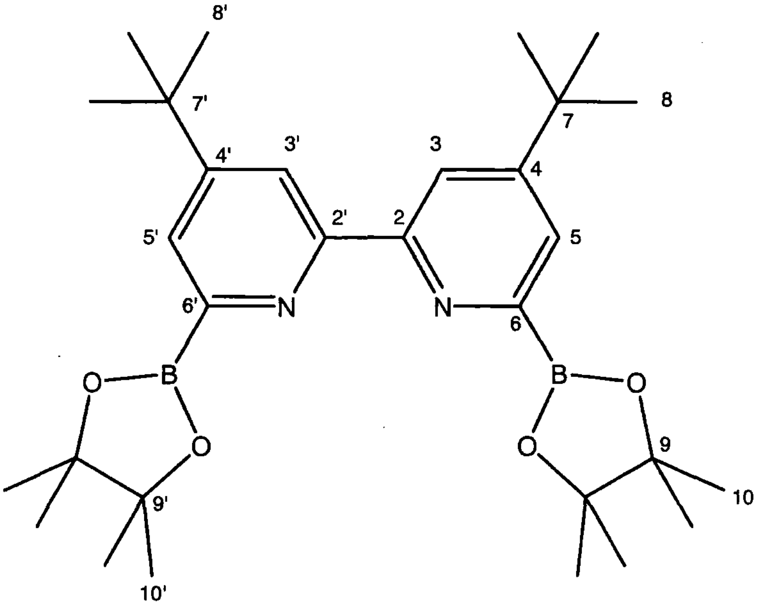
3.5.1- Synthesis of 4,4'-$^{t}Bu_2$-6-(Bpin)-2,2'-bipyridine 2A



In a nitrogen-filled glove box, to a solution of [Ir(μ-OMe)COD]$_2$ (3.1 mg, 4.7 x 10^{-3} mmol, 2.5 mol%) and dtbpy (2.5 mg, 9.3 x 10^{-3} mmol, 5 mol%) in 2 ml of hexane was added a mixture of B_2pin_2 (23.7 mg, 93.3 x 10^{-3} mmol) and additional dtbpy (50 mg, 186.6 x 10^{-3} mmol) in 3 ml of hexane (5 ml total volume). The mixture was shaken vigorously to ensure complete mixing, and then stirred at room temperature. After 16 h the mixture was analysed by GC/MS, then the solvent was removed *in vacuo*, dry C_6D_6 was added, and the mixture was analysed again by GC/MS and NMR spectroscopy.

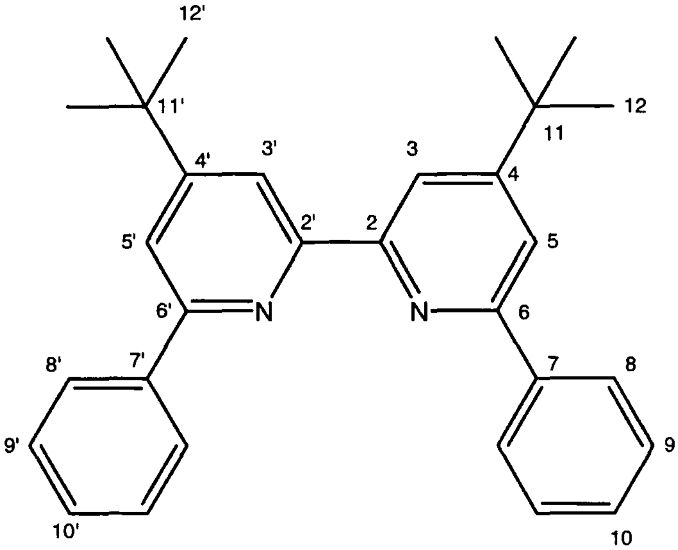
^{1}H NMR (500 MHz, C_6D_6): δ 1.13 (s, 12H; **Bpin**), 1.15 (s, 9H; **8**), 1.16 (s, 9H; **8'**), 6.90 (d, ^3J(H,H) = 2.0 Hz, 1H; **5'**), 8.26 (d, ^3J(H,H) = 2.0 Hz, 1H; **3**), 8.63 (d, overlapped with 2H of dtbpy (starting material) ^3J(H,H) = 5.0 Hz, 1H; **6'**), 9.14 (s, 1H; **3'**), 9.16 (d, ^3J(H,H) = 2.0 Hz, 1H; **3**); ^{13}C{^{1}H} NMR (125 MHz, C_6D_6): δ 24.94 (s, $BO_2C_2(CH_3)_4$), 30.50 (s, **8**), 30.52 (s, **8'**), 34.5 (s, **7**), 84.12 (s, $BO_2C_2(CH_3)_4$), 118.89, 120.30, 128.35, 128.67, 149.35, 157.36, 157.86, 159.17, 160.59; ^{11}B{^{1}H} NMR (128.4 MHz, C_6D_6): δ 31.17 (s, br); MS (EI) m/z: 394 [M^+], 379 [$M-Me^+$].

3.5.2- Synthesis of 4,4'-^{t}Bu$_2$-6,6'-(Bpin)$_2$-2,2'-bipyridine 3A



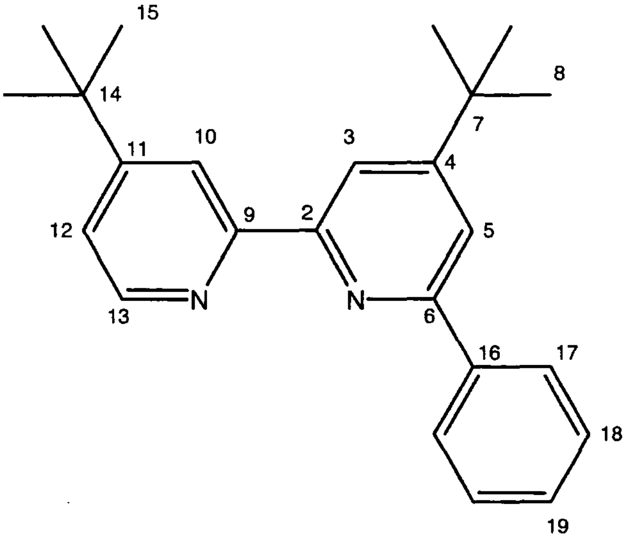
In a nitrogen-filled glove box, to a solution of [Ir(μ-OMe)COD]$_2$ (6.2 mg, 9.3 x 10^{-3} mmol, 5 mol%) and dtbpy (5 mg, 18.66 x 10^{-3} mmol, 10 mol%) in 2 ml of hexane was added a mixture of B$_2$pin$_2$ (94.7 mg, 0.373 mmol, 2 equiv.) and dtbpy (50 mg, 186.6 x 10^{-3} mmol,) in 3 ml of hexane (5 ml total volume). The mixture was shaken vigorously to ensure complete mixing, transferred to an ampoule sealed with a Teflon Young's tap and heated at 80 °C. After 16 h, the mixture was analyzed by GC/MS, then the solvent was removed *in vacuo*, dry C_6D_6 was added, and the mixture was analysed by NMR spectroscopy. ^{1}H NMR (500 MHz, C_6D_6): δ 1.10 (s, 24H; **10**, **10'**), 1.14 (s, 18H; **8**, **8'**), 8.24 (d, ^3J(H,H) = 2.0 Hz, 2H; **5**, **5'**), 9.28 (d, ^3J(H,H) = 2.0 Hz, 2H; **3**, **3'**); ^{13}C{^{1}H} NMR (125 MHz, C_6D_6): δ 25.01 (s, **10**), 30.50 (s, **8**), 34.75 (s, 7), 84.12 (s, **9**), 120.63 (s, **3**, **5**), 158.00 (s, **2**), 159.16 (s, **4**); ^{11}B{^{1}H} NMR (128.4 MHz, C_6D_6): δ 31.24 (s, br); MS (EI) m/z: 520 [M$^+$], 505 [M-Me$^+$].

3.5.3- Synthesis of 4,4'-^{t}Bu$_2$-6,6'-Ph$_2$-2,2'-bipyridine 4A



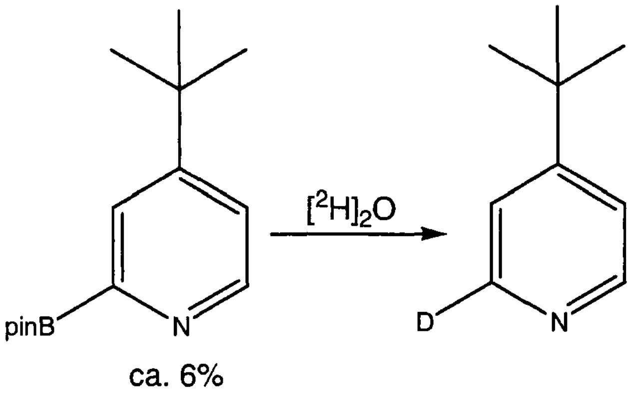
Once the **3A** product formed, as shown by *in situ* GC/MS analysis, the solvent was removed *in vacuo*, followed by addition of PhI (114 mg, 55.9 x 10^{-3} mmol, 3 equiv.), $K_3PO_4 \cdot 2H_2O$ (185 mg, 745 x 10^{-3} mmol, 4 equiv.), [(dppf)PdCl$_2$] (15 mg, 18.3 x 10^{-3} mmol, 10 mol%) and dry DMF (8 ml). The mixture was heated at 80 °C for 5 h. The product was extracted into hexane, dried (MgSO$_4$), and chromatographed on silica gel (hexane:diethylether, 9:1) to yield 52 mg (0.098 mmol, 67%) of product; ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.47 (s, 9H; **12**), 7.45 (t, ^3J(H,H) = 7.6 Hz, 1H; **10**), 7.53 (t, ^3J(H,H) = 7.6 Hz, 2H; **9**), 7.78 (d, ^3J(H,H) = 1.5 Hz, 1H; **5**), 8.17 (d, ^3J(H,H) = 7.6 Hz, 2H; **8**), 8.61 (d, ^3J(H,H) = 1.5 Hz, 1H; **3**). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 29.76 (s, **12**), 34.17 (s, **11**), 117.13, 117.63 (s, **3**, **5**), 127.26, 128.82 (s, **8**, **10**), 128.87 (s, **9**), 140.07 (s, **7**), 156.57 (s, overlapped, **2**, **6**), 161.68 (s, **4**); MS (EI) m/z: 420 [M$^+$], 405 [M-Me$^+$]; Anal. Calcd. for $C_{30}H_{32}N_2$: C 85.76, H 7.67, N 6.66; found C 85.61, H 7.66, N 6.55; m.p. 182-184 °C.

3.5.4- Synthesis of 4,4'-^{t}Bu$_2$-6,6'-Ph-2,2'-bipyridine 5A



Borylated compound **3A** was prepared as above. The solvent was removed *in vacuo* followed by addition of PhI (45.7 mg, 224 x 10^{-3} mmol, 0.025 ml, 1.2 equiv.), $K_3PO_4 \cdot 2H_2O$ (92.5 mg, 372 x 10^{-3} mmol, 2 equiv.), [(dppf)PdCl$_2$] (15 mg, 18.3 x 10^{-3} mmol, 10 mol%) and dry DMF (8 ml). The reaction was heated at 80 °C for 5 h. The product was extracted into hexane, dried (MgSO$_4$), and chromatographed on silica gel (hexane:diethylether, 9:1) to give 20 mg (0.098 mmol, 31%) of product; ^{1}H NMR (500 MHz, C_6D_6): δ 1.17, 1.20 (s, 18H; **8**, **15**), 6.96 (dd, ^3J(H,H) = 1.7, 5.2 Hz, 1H; **12**), 7.23 (t, ^3J(H,H) = 7.3 Hz, 1H; **19**), 7.35 (t, ^3J(H,H) = 7.3 Hz, 2H; **18**), 7.71 (d, ^3J(H,H) = 1.7 Hz, 1H; **5**), 8.31 (d, ^3J(H,H) = 7.3 Hz, 1H; **17**), 8.66 (d, ^3J(H,H) = 5.2 Hz, 1H; **13**), 9.01 (d, ^3J(H,H) = 1.7 Hz, 1H; **3**), 9.08 (d, ^3J(H,H) = 1.7 Hz, 1H; **10**). ^{13}C{^{1}H} NMR (100 MHz, C_6D_6): δ = 30.32, 30.40 (s, **8**, **15**), 34.60, 34.90 (s, **7**, **14**), 117.70 (s, **5**), 117.90 (s, **3**), 118.68 (s, **10**), 121.18 (s, **12**), 127.79, 128.54, 129.17 (s, **17**, **18**, **19**), 141.11 (s, **16**), 149.70 (s, **13**), 157.24, 157.33, 157.51 160.72 161.86, (s, **2**, **9**, **6**, **4**, **11**); MS (EI) m/z: 344 [M$^+$], 329 [M-Me$^+$]; Anal. Calcd. for $C_{24}H_{28}N_2$: C 83.68, H 8.19, N 8.13; found C 83.49, H 8.12, N 8.10; m.p. 107-109 °C

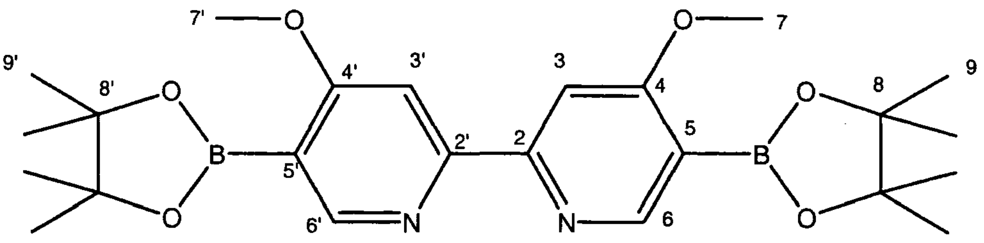
3.5.5- Attempted borylation of 4-^{t}Bu-pyridine



In a nitrogen-filled glove box, to a solution of [Ir(μ-OMe)COD]$_2$ (24.5 mg, 37.1 x 10^{-3} mmol, 5 mol%) and dtbpy (19.8 mg, 74 x 10^{-3} mmol, 10 mol%) in 2 ml of hexane was added a mixture of B_2pin_2 (188 mg, 740 x 10^{-3} mmol, 1 equiv.) and 4-^{t}Bu-pyridine (100 mg, 740 x 10^{-3} mmol,) in 3 ml of hexane (5 ml total volume). The mixture was shaken vigorously to ensure complete mixing, transferred to an ampoule sealed with a Teflon Young's tap and heated at 80 °C. After 16 h, the mixture was analyzed by GC/MS, then quenched by D_2O with stirred at room temperature. The mixture was analysed by ^2H NMR spectroscopy.

^2H NMR (76 MHz, D_2O): δ 8.45 (s, 1D).

3.5.6- Synthesis of 4,4'-dimethoxy-5,5'-(Bpin)$_2$ bipyridine 3B



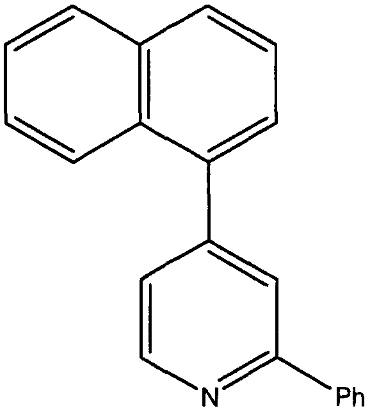
In a nitrogen-filled glove box, to a solution of [Ir(μ-OMe)COD]$_2$ (7.7 mg, 11.6 x 10^{-3} mmol, 5 mol%) and dtbpy (6.2 mg, 23.1 x 10^{-3} mmol, 10 mol%) in 2 ml of hexane was added a mixture of B$_2$pin$_2$ (117.6 mg, 465 x 10^{-3} mmol, 2 equiv.) and 4,4'-MeO$_2$-2,2'-bipyridine (50 mg, 231 x 10^{-3} mmol) in 3 ml of hexane (5 ml total volume). The mixture was shaken vigorously to ensure complete mixing, transferred to an ampoule sealed with a Teflon Young's tap and heated at 80 °C for 16 h. The mixture was analysed by GC/MS. The solvent was removed *in vacuo*, and the residue was redissolved in 10 ml of hexane, and then filtered through a celite pad, and the solvent was evaporated. Single crystals were grown by slow evaporation of a CH_2Cl_2 solution.

^{1}H NMR (400 MHz, C_6D_6): δ 1.10 (s, 12H; **8**), 3.36 (s, 3H; **7**), 8.49 (s, **3**), 9.51 (s, **6**); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 24.57 (s, **9**), 55.83 (s, **7**), 83.82 (s, **8**), 111.11, 150.05, 156.70, 167.73 (s, **Ar**); MS (EI) m/z: 467 [M$^+$], 453 [M-CH$_2^+$].

3.5.7- Synthesis of 4-naphthalen-1-yl-2-phenyl-pyridine and 5-naphthalen-1-yl-2-phenyl-pyridine

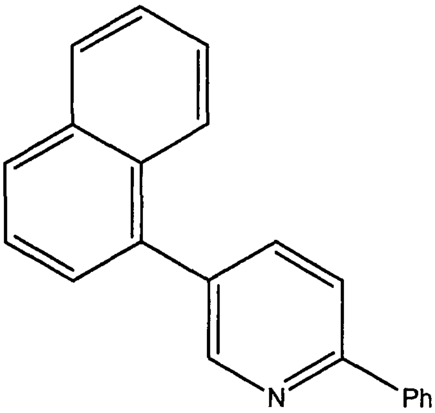
In a nitrogen-filled glove box, to a solution of [Ir(μ-OMe)COD]$_2$ (21.3 mg, 32.2 x 10^{-3} mmol, 2.5 mol%) and dtbpy (17.3 mg, 64.5 x 10^{-3} mmol, 5 mol%) in 2 ml of hexane was added a mixture of B$_2$pin$_2$ (163.8 mg, 645.1 x 10^{-3} mmol, 0.5 equiv.) and 2-phenylpyridine (200 mg, 1.3 mmol) in 3 ml of hexane (5 ml total volume). The mixture was stirred at room temperature for 16 h. The solvent was removed *in vacuo* followed by addition of 1-iodonaphthalene (328 mg, 1.3 mmol, 1 equiv.), K_2CO_3 (aq.) (359 mg, 2.6 mmol, 2 equiv.), [(PPh$_3$)$_2$PdCl$_2$] (45.3 mg, 65 x 10^{-3} mmol, 5 mol%) and 1,4-dioxane (20 ml). The mixture was transferred to a microwave reaction tube (20 ml volume), then sealed and heated for 1 h at 150 °C. The product was extracted with ethylacetate, dried ($MgSO_4$), and chromatographed on silica gel (hexane:ethylacetate, 95:5) to yield the two isomers, 4-naphthalen-1-yl-2-phenyl-pyridine **3C(4)** (100 mg, 356 x 10^{-3} mmol, 30%), and 5-naphthalen-1-yl-2-phenyl-pyridine **3C(5)** (120 mg, 427 x 10^{-3} mmol, 37%).

4-Naphthalen-1-yl-2-phenyl-pyridine 3C(4)



Yield: 100 mg (0.356 mmol, 30%); ^{1}H NMR (500 MHz, C_6D_6): δ = 6.94 (dd, ^3J H,H) = 4.9, ^4J(H,H) = 1.5 Hz, 1H), 7.02-7.07 (m, 3H), 7.23-7.28 (m, 4H), 7.65 (d, ^3J(H,H) = 8.3 Hz, 1H), 7.67 (d, ^3J(H,H) = 7.8 Hz, 1H), 7.69 (s, 1H), 7.76 (d, ^3J(H,H) = 8.3 Hz, 1H), 8.19 (2 overlapped d, ^3J(H,H) = 6.8 Hz, 2H), 8.67 (d, ^3J(H,H) = 4.9 Hz, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, C_6D_6): δ 119.50, 123.57, 125.52, 125.79, 126.34, 126.87, 127.04, 127.39, 128.72, 128.91, 128.94, 129.62, 131.53, 134.26, 138.36, 139.69, 149.42, 150.09, 157.70 (s); MS (EI) m/z: 281 [M$^+$]; Anal. Calcd. for $C_{21}H_{15}N$: C 89.65, H 5.37, N 4.89; found C 89.41, H 5.56, N 4.98; m.p. 80-82 °C.

5-Naphthalen-1-yl-2-phenyl-pyridine 3C(5)

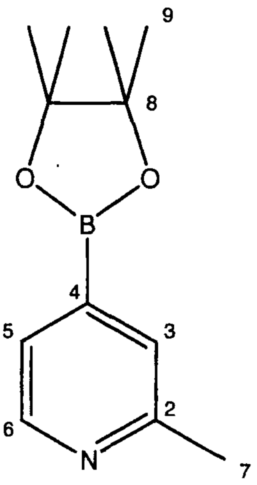


Yield: 120 mg (0.427 mmol, 37%); ^{1}H NMR (500 MHz, C_6D_6): δ = 7.17-7.28 (m, 5H), 7.32 (m, 2H), 7.40-7.45 (m, 2H), 7.64 (d, ^3J(H,H) = 8.3 Hz, 1H), 7.68 (d, ^3J(H,H) = 7.8 Hz, 1H), 7.83 (d, ^3J(H,H) = 8.8 Hz, 1H), 8.28 (2 overlapped d, ^3J(H,H) = 8.3 Hz, 1H), 8.90 (s, 1H). ^{13}C{^{1}H} NMR (125 MHz, C_6D_6): δ = 119.46, 125.66, 125.82, 126.26, 126.71, 127.27, 127.57, 128.55, 128.57, 128.74, 129.15, 129.25, 134.40, 134.92, 136.89, 137.95, 139.56, 150.82, 156.32 (s); MS (EI) m/z: 281 [M$^+$]; Anal. Calcd. for $C_{21}H_{15}N$: C 89.65, H 5.37, N 4.89; found C 89.42, H 5.52, N 4.79; m.p. 130-132 °C.

3.5.8- Synthesis of 2-Methyl-4-(Bpin)-pyridine 2D(4) and 2-Methyl-5-(Bpin)-pyridine 2D(5)

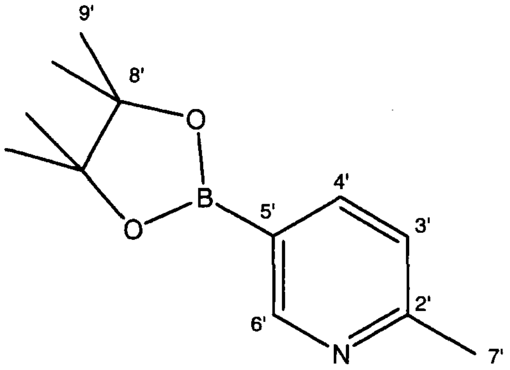
In a nitrogen-filled glove box, to a solution of $[Ir(\mu\text{-}OMe)COD]_2$ (17.8 mg, 26.9 x 10^{-3} mmol, 2.5 mol%) and dtbpy (14.4 mg, 51.5 x 10^{-3} mmol, 5 mol%) in 2 ml of hexane was added a mixture of B_2pin_2 (130.9 mg, 515.3 x 10^{-3} mmol, 0.5 equiv.) and 2-picoline (100 mg, 1.07 mmol) in 3 ml of hexane (5 ml total volume). The mixture was stirred at room temperature for 16 h. The solvent was removed *in vacuo* and Kugelrohr distillation (100-170 °C, 3 x 10^{-4} torr) gave a mixture of the two isomers, 2-methyl-4-(Bpin)-pyridine and 2-methyl-5-(Bpin)-pyridine 57% total yield. Anal. Calcd. for $C_{24}H_{36}N_2B_2O_4$: C 65.79, H 8.28, N 6.39; found C 66.02, H 8.39, N 6.19.

2-methyl-4-(Bpin)-pyridine 2D(4)



^{1}H NMR (500 MHz, CDCl$_3$): δ 1.31 (s, 12H; **9**), 2.53 (s, **7**), 7.40 (d, ^{3}J(H,H) = 4.8 Hz, 1H; **5**), 7.49 (s, 1H; **3**), 8.48 (d, ^{3}J(H,H) = 4.8 Hz, 1H; **6**). ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$): δ 23.81 (s, **7**), 25.02 (s, **9**), 83.73 (s, **8**), 125.32 (s, **5**), 128.17 (s, **3**), 148.18 (s, **6**), 157.27 (s, **2**), From HSQC, the following correlations were observed (H3 - C3), (H5 – C5), and (H6 – C6). From HMBC, ^{13}C of Me on the 2-picoline correlates with (H 3). The resonance for the carbon attached to boron was not observed; ^{11}B{^{1}H} NMR (128.4 MHz, CDCl$_3$): δ 30.86 (s, br); MS (EI) m/z : 219 [M$^+$], 204 [M-CH$_3$$^+$].

2-methyl-5-(Bpin)-pyridine 2D(5)

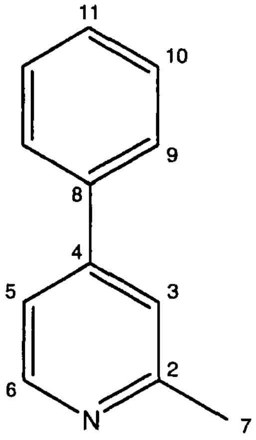


^{1}H NMR (500 MHz, CDCl$_3$): δ 1.32 (s, 12H; **9'**), 2.54 (s, 3H; **7'**), 7.11 (d, ^3J(H,H) = 7.8 Hz, 1H; **3'**), 7.91 (d, ^3J(H,H) = 7.8 Hz, 1H; **4'**), 8.80 (s, 1H; **6'**). ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$): δ 24.78 (s, **7'**), 25.03 (s, **9'**), 84.64 (s, **8'**), 122.90 (s, **3'**), 142.84 (s, **4'**), 155.12 (s, **6'**), From HSQC, the following correlation were observed, (H3' - C3'), (H4' - C4'), (H6' – C6'). From HMBC, ^{13}C of Me on the 2-picoline correlates with (H 3'). The resonance for the carbon attached to boron was not observed; ^{11}B{^{1}H} NMR (128.4 MHz, CDCl$_3$): δ 30.86 (s, br); MS (EI) m/z: 219 [M$^+$], 204 [M- CH$_3^+$].

3.5.9- Synthesis of 2-methyl-4-phenyl-pyridine and 2-methyl-5-phenyl-pyridine

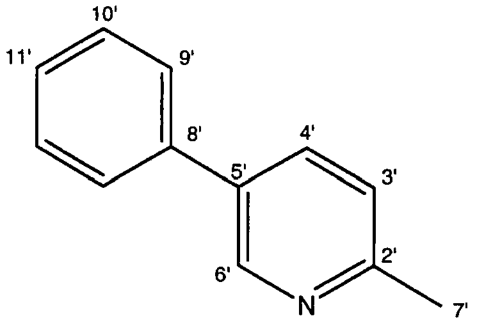
Once the borylation product **2D(4)** and **2D(5)** formed, as shown by GC/MS, the solvent was removed *in vacuo* followed by addition of 1-iodobenzene (219 mg, 1.07 mmol, 1 equiv.), K_2CO_3 (aq.) (279 mg, 2.02 mmol, 2 equiv.), $[(PPh_3)_2PdCl_2]$ (37.7 mg, 53.7 x 10^{-3} mmol, 5 mol%) and 1,4-dioxane (20 ml). The mixture was transferred to a microwave tube (20 ml volume), then sealed and heated for 1 h at 150 °C. The product was extracted into ethylacetate, dried ($MgSO_4$), and chromatographed on silica gel (hexane:diethylether, 50:50) to yield 2-methyl-4-phenyl-pyridine **3D(4)** (120 mg, 0.71 mmol, 32%) and 2-methyl-5-phenyl-pyridine **3D(5)** (123 mg, 0.73 mmol, 34%).

2-methyl-4-phenyl-pyridine 3D(4)



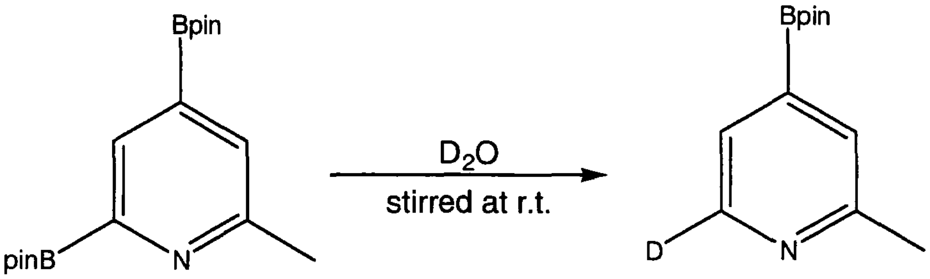
Yield: 120 mg (0.71 mmol, 32%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.63 (s, 3H; **7**), 7.31 (d, ^3J(H,H) = 5.4 Hz, 1H; **5**), 7.37 (s, 1H; **3**), 7.41-7.48 (m, 3H; **10, 11**), 7.62 (d, ^3J(H,H) = 7.7 Hz, 2H; **9**), 8.54 (d, ^3J(H,H) = 5.4 Hz, 1H; **6**); from COSY (H **3**) correlates with Me, and (H **5**) correlates with (H **6**); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 24.11 (s, **7**), 118.56 (s, **5**), 120.93 (s, **3**), 126.69 (s, **9**), 128.61, 128.72 (s, **10**, **11**), 138.13 (s, **8**), 148.51 (s, **4**), 149.12 (s, **6**), 158.45 (s, **2**), from HSQC, the following correlations were observed (H3 – C3), (H**5** – C5), (H6 – C6), (H10 – C10), and (H11 – C11); MS (EI) m/z: 169 [M^+], 155 [$M-CH_2^+$]. Anal. Calcd. for $C_{12}H_{11}N$: C 85.17, H 6.55, N 8.28; found C 85.04, H 6.60, N 8.25; m.p. 42-44 °C.

2-methyl-5-phenyl-pyridine 3D(5)



Yield: 123 mg (0.73 mmol, 34%); ^{1}H NMR (500 MHz, C_6D_6): δ 2.47 (s, 3H; **7'**), 6.72 (d, $^3J(H,H)$ = 7.7 Hz, 1H; **3'**), 7.10-7.14 (m, 3H; **10'**, **11'**), 7.29 (d, $^3J(H,H)$ = 7.7 Hz, 1H; **4'**), 7.34 (m, 2H; **8'**), 8.78 (s, 1H; **6'**), from COSY, (H 3') correlates with Me and (H 4'); $^{13}C\{^1H\}$ NMR (100 MHz, C_6D_6): δ 22.83 (s, **7'**), 121.56 (s, **3'**), 125.76 (s, **4'**), 126.32, 127.87, 132.43, 133.15 **(Ph)**, 137.22 (s, **5'**), 146.82 (s, **6'**), 156.47 (s, **2'**), HSQC correlations: (H3' – C3'), (H4' – C4'), and (H6' – C6'); MS (EI) m/z: 169 [M^+], 155 [M-CH_2^+]. Anal. Calcd. for $C_{12}H_{11}N$: C 85.17, H 6.55, N 8.28; found C 84.89, H 6.56, N 8.15; m.p. 82-84 °C.

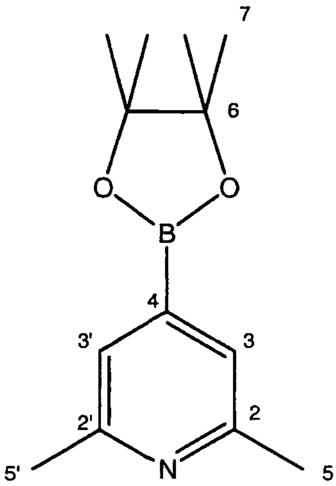
3.5.10- Reaction of 1D with 2 equiv. of B_2pin_2



In a nitrogen-filled glove box, to a solution of [Ir(μ-OMe)COD]$_2$ (15.5 mg, 23.4 x 10^{-3} mmol, 2.5 mol%) and dtbpy (14.4 mg, 53.7 x 10^{-3} mmol, 5 mol%) in 2 ml of hexane was added a mixture of B_2pin_2 (546 mg, 2.15 mmol, 2 equiv.) and 2-picoline (100 mg, 1.07 mmol) in 3 ml of hexane (5 ml total volume). The mixture was heated at 80 °C for 16 h, *in situ* GC/MS analysis showed that one major peak assign to a bis(borylation) product. The mixture was quenched with a few drop of D_2O with stirred at room temperature, and then analysed by ^2H NMR spectroscopy and GC/MS.

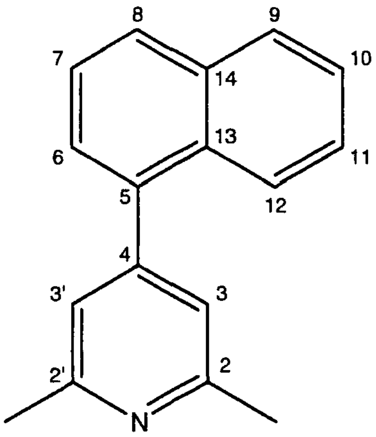
^2H NMR (76 MHz, D_2O): δ 8.44 (s, 1D). The peak in the total ion chromatogram (TIC) for which m/z = 345 [M^+ for the 4,6-bis(boronate)], disappears after D_2O quench, and is replaced with a signal in the TIC corresponding to 2-Me-4-Bpin-6-D-pyridine, with m/z = 220 [M^+].

3.5.11- Synthesis of 2,6-dimethyl-4-(Bpin)-pyridine 2E



In a nitrogen-filled glove box, to a solution of [Ir(μ-OMe)COD]$_2$ (30.7 mg, 46.3 x 10^{-3} mmol, 2.5 mol%) and dtbpy (25.1 mg, 93.5 x 10^{-3} mmol, 5 mol%) in 2 ml of hexane was added a mixture of B$_2$pin$_2$ (475 mg, 1.87 mmol, 1 equiv.) and 2,6-dimethylpyridine (200 mg, 1.87 mmol) in 3 ml of hexane (5 ml total volume). The mixture was stirred at room temperature for 16 h. The solvent was removed *in vacuo* and Kugelrohr distillation (100-170 °C, 3 x 10^{-4} torr) gave an analytically pure sample 375 mg (1.61 mmol, 86%). Slow evaporation of a DCM solution gave white crystals suitable for X-ray diffraction. ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.33 (s, 12H; **7**), 2.52 (s, 6H; **5**, **5'**), 7.31 (s, 2H; **3**, **3'**); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 23.78 (s, **5**), 24.50 (s, **7**), 84.03 (s, **6**), 125.09 (s, **3**), 156.50 (s, **2**), the resonance for the carbon attached to boron was not observed; ^{11}B{^{1}H} NMR (128.4 MHz, CDCl$_3$): δ 30.38 (s, br); MS (EI) m/z: 233 [M$^+$], 218 [M-CH$_3$$^+$]. Anal. Calcd. for $C_{13}H_{20}BNO_2$: C 66.98; H 8.65; N 6.01; found C 66.71; H 8.69; N 5.85; m.p. 80-82 °C.

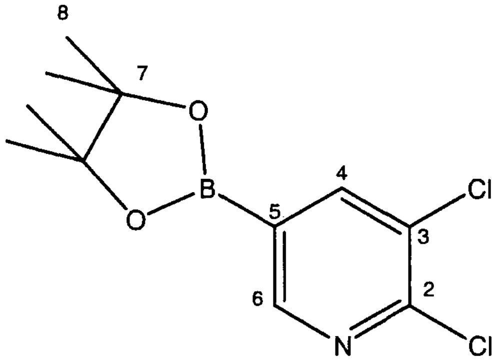
3.5.12- Synthesis of 2,6-dimethyl-4-naphthalen-1-yl-pyridine 3E



Once compound **2E** had formed completely, as shown by *in situ* GC/MS analysis, the solvent was removed *in vacuo*, followed by addition of 1-iodonaphthalene (474 mg, 1.87 mmol, 1 equiv.), K_2CO_3 (aq.) (517 mg, 3.75 mmol, 2 equiv.), $[(PPh_3)_2PdCl_2]$ (65.5 mg, 93 x 10^{-3} mmol, 5 mol%) and 1,4-dioxane (20 ml). The mixture was transferred to a microwave tube (20 ml volume) as above, then sealed and heated for 1 h at 150 °C. The product was extracted into ethylacetate, dried ($MgSO_4$), and chromatographed on silica gel (hexane:ethylacetate, 90:10) to yield 400 mg (1.72 mmol, 92%) of product. Slow evaporation of a diethylether solution gave white crystals suitable for X-ray diffraction. ^{1}H NMR (500 MHz, C_6D_6): δ 2.20 (s, 6H; 2 **Me**), 6.51 (s, 2H; **3**), 6.86-6.92 (m, 2H; **7**, **8**), 6.97 (t, ^3J(H,H) = 8 Hz, 2H; **10**,**11**), 7.36 (d, ^3J(H,H) = 8 Hz, 1H; **9**), 7.39 (d, ^3J(H,H) = 7.8 Hz, 1H; **6**), 8.30 (d, ^3J(H,H) = 8 Hz, 1H; **12**), from NOESY, (H 6) correlates with (H 3), from COSY, (H 3) correlates with Me; $^{13}C\{^1H\}$ NMR (100 MHz, C_6D_6): δ 24.58, (s, 2**CH_3**), 121.55 (s, **3**), 125.50, 125.97 (s, **10**, **11**), 126.24 (s, **6**) 126.63, 126.86 (s, **7**, **8**), 131.61 (s, **9**, **12**), 131.61, 134.29 (s, **13**, **14**), 138.67 (s, **5**), 149.20 (s, **4**), 158.14 (s, **2**);

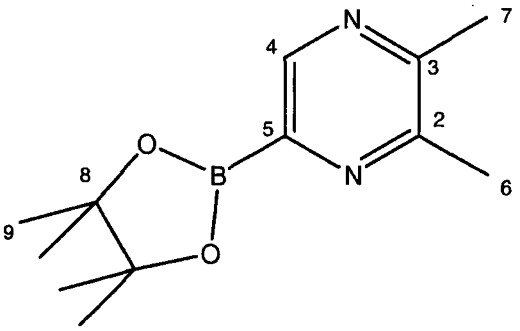
from HSQC, the following correlations were observed, (H15 – C15), (H3 – C3), (H6 - C6), (H8 - C8) (H9 - C9), and (H10 – C10); MS (EI) m/z : 233 [M$^+$], 218 [M-CH$_3$]$^+$. Anal. Calcd. For $C_{17}H_{15}N$, C 87.52, H 6.48, N 6.00; found C, 87.37, H, 6.45, N, 6.14; m.p. 90-92 °C.

3.5.13- Synthesis of 2,3-dichloro-5-(Bpin)-pyridine 2F



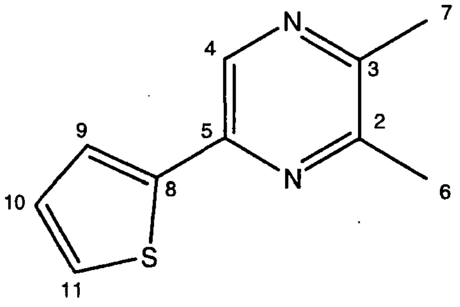
In a nitrogen-filled glove box, to a solution of [Ir(μ-OMe)COD]$_2$ (22.4 mg, 33.7 x 10^{-3} mmol, 2.5 mol%) and dtbpy (18.1 mg, 67.5 x 10^{-3} mmol, 5 mol%) in 2 ml of hexane was added a mixture of B$_2$pin$_2$ (342 mg, 1.35 mmol, 1 equiv.) and 2,3-dichloro-pyridine (200 mg, 1.35 mmol) in 3 ml of hexane (5 ml total volume). The mixture was stirred at room temperature for 16 h. The solvent was removed *in vacuo* and Kugelrohr distillation (100-170 °C, 3 x 10^{-4} torr) gave an analytically pure sample (332 mg, 1.21 mmol, 88.7%). Slow evaporation of a DCM solution gave white crystals suitable for X-ray diffraction. ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.34 (s, 12H; **8**), 8.11 (s, 1H; **4**), 8.60 (s, 1H; **6**). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 24.50 (s, **8**), 84.48 (s, **7**), 130.06 (s, **4**), 144.4 (s, **3**), 151.4 (s, **6**), 152.43 (s, **2**); the resonance for the carbon attached to boron was not observed; ^{11}B{^{1}H} NMR (128.4 MHz, CDCl$_3$): δ 30.11 (s, br); MS (EI): m/z (rel. int.): 273 [M$^+$], 258 [M-CH$_3$]$^+$. Anal. Calcd. For $C_{11}H_{14}BCl_2NO_2$, C 48.23, H 5.15, N 5.11; found C, 48.10, H, 5.15, N, 4.99; m.p. 48-50 °C.

3.5.14- Synthesis of 2,3-dimethyl-5-(Bpin)-pyrazine 2G



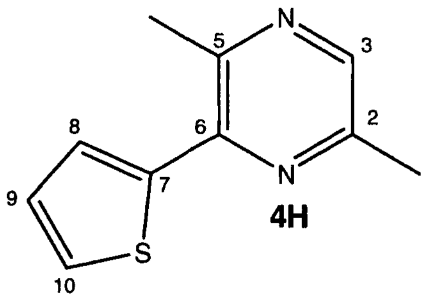
In a nitrogen-filled glove box, to a solution of $[Ir(OMe)COD]_2$ (30.7 mg, 46.3 x 10^{-3} mmol, 2.5 mol%) and dtbpy (24.8 mg, 92.5 x 10^{-3} mmol, 5 mol%) in 2 ml of hexane was added a mixture of B_2pin_2 (470 mg, 1.85 mmol, 1 equiv.) and 2,3-dimethyl-pyrazine (200 mg, 1.85 mmol) in 3 ml of hexane (5 ml total volume). The mixture was stirred at room temperature. After 16 h, the mixture was analysed by GC/MS, then the solvent was removed *in vacuo*, dry C_6D_6 was added and the mixture was analysed by NMR spectroscopy. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.36 (s, 12H; **9**), 2.54, 2.59 (s, 6H; **6**, **7**), 8.65 (s, 1H; **4**). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 22.40 (s, **6**, **7**), 24.78 (s, **9**), 84.70 (s, **8**), 147.47 (s, **4**), 154.18 (s, **2**, **3**); the resonance for the carbon attached to boron was not observed; $^{11}B\{^1H\}$ NMR (128.4 MHz, $CDCl_3$): δ 30.86 (s, br); MS (EI) m/z: 234 [M^+], 219 [$M-CH_3^+$].

3.5.15- Synthesis of 2,3-dimethy-5-thiophen-2-yl-pyrazine 3G



Once compound **2G** had formed, as shown by *in situ* GC/MS analysis, the solvent was removed *in vacuo*, followed by addition of 2-bromothiophene (300 mg, 1.84 mmol, 1 equiv.), K_3PO_4 (aq.) (785 mg, 3.70 mmol, 2 equiv.), $[(PPh_3)_2PdCl_2]$ (65 mg, 93 x 10^{-3} mmol, 5 mol%) and DMF (20 ml). The reaction mixture was transferred to a microwave tube (20 ml volume), crimp sealed with a septum cap, and heated for 1 h at 150 °C. The product was extracted into ethylacetate, dried ($MgSO_4$), and chromatographed on silica gel (hexane:ethylacetate, 9:1) to yield 120 mg of product (0.632 mmol, 34%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.52, 2.54 (s, 6H; **6**, **7**), 7.10 (dd, ^3J(H,H) = 4.0, 5.1 Hz, 1H; **10**), 7.39 (dd, ^3J(H,H) = 5.1, ^4J(H,H) = 1.0 Hz, 1H; **9**), 7.59 (dd, ^3J(H,H) = 4.0, ^4J (H,H) = 1.0 Hz, 1H; **11**), 8.62 (s, 1H; **4**); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 21.59, 21.98 (s, **6**, **7**), 124.63, 127.61, 128.15 (s, **9**, **10**, **11**), 136.64 (s, **4**), 141.82 (s, **8**), 145.10 (s, **5**), 150.15, 151.67 (s, **2**, **3**); MS (EI) m/z: 190 [M^+], 108 [$M-C_4H_2S^+$]. Anal. Calcd. For $C_{10}H_{10}N_2S$, C 63.13, H 5.30, N 14.72; found C, 63.18, H, 5.34, N, 14.50; m.p. 50-52 °C.

3.5.16- Synthesis of 2,5-dimethy-6-thiophen-2-yl-pyrazine 4H



4H

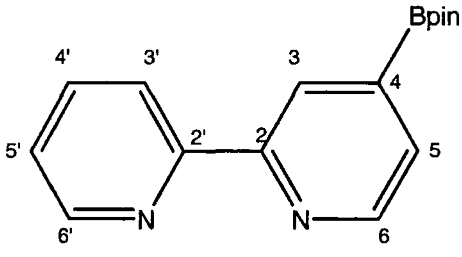
In a nitrogen-filled glove box, to a solution of [Ir(OMe)COD]$_2$ (30.7 mg, 46.3 x 10^{-3} mmol, 2.5 mol%) and dtbpy (24.8 mg, 92.5 x 10^{-3} mmol, 5 mol%) in 2 ml of hexane was added a mixture of B$_2$pin$_2$ (235 mg, 925 x 10^{-3} mmol, 0.5 equiv.) and 2,5-dimethyl-pyrazine (200 mg, 1.85 mmol) in 3 ml of hexane (5 ml total volume). The mixture was heated at 80 °C. After 16 h, *in situ* GC/MS analysis showed that the conversion was 55%, with 85% selectivity for the mono borylation product 2,5-dimethy-6-(Bpin)-pyrazine **2H**, and 15% for bis(borylation) products **3H**. The solvent was removed *in vacuo* followed by addition of 2-bromothiophene (300 mg, 1.84 mmol, 1 equiv.), K_3PO_4 (aq.) (785 mg, 3.70 mmol, 2 equiv.), [(PPh$_3$)$_2$PdCl$_2$] (65 mg, 93 x 10^{-3} mmol, 5 mol%) and DMF (20 ml). The reaction mixture was transferred to a microwave tube (20 ml volume), crimp sealed with a septum cap, and heated for 1 h at 150 °C. The product was extracted into ethylacetate, dried (MgSO$_4$), and chromatographed on silica gel (hexane:ethylacetate, 9:1) to yield 15.3 mg of product (158 x 10^{-3} mmol, 15%); ^{1}H NMR (400 MHz, C_6D_6): δ 2.12, 2.54 (s, 6H; 2 **Me**), 6.78 (dd, ^3J(H,H) = 4.0, 1.0 Hz, 1H; **9**), 6.98 (dd, ^3J(H,H) = 5.1, ^4J(H,H) = 1.0 Hz, 1H; **8**), 7.24 (dd, ^3J(H,H) = 4.0, ^4J (H,H) = 1.1 Hz, 1H; **10**), 7.92 (s, 1H; **3**); ^{13}C{^{1}H} NMR (100 MHz, C_6D_6): δ 20.72, 24.10 (s, 2 **Me**), 127.65, 127.92, 128.61 (s, **8**, **9**, **10**), 141.38 (s, **3**), 144.35 (s, **7**), 146.22, 146.38 (s, **2**, **5**) 150.15 (s, **6**); MS (EI) m/z: 190 [M^+], 108 [$M-C_4H_2S^+$]. Anal. Calcd. For $C_{10}H_{10}N_2S$, C 63.13, H 5.30, N 14.72; found C, 62.96, H, 5.12, N, 14.56; m.p. 44-46 °C.

3.5.17- Synthesis of 4-(Bpin)-2,2'-bipyridine 2J(4), 5-(Bpin)-2,2'-bipyridine 2J(5), 4,4'-(Bpin)$_2$-2,2'-bipyridine 3J(4,4) and 5,5'-(Bpin)$_2$-2,2'-bipyridine 3J(5,5)

In a nitrogen-filled glove box, to a solution of [Ir(μ-OMe)COD]$_2$ (10.6 mg, 16.0 x 10^{-3} mmol, 2.5 mol%) and dtbpy (8.6 mg, 33.2 x 10^{-3} mmol, 5 mol%) in 2 ml of hexane was added a mixture of B_2pin_2 (82 mg, 322 x 10^{-3} mmol, 0.5 equiv.) and 2,2'-bipyridine (100 mg, 641 x 10^{-3} mmol) in 3 ml of hexane (5 ml total volume). The mixture was stirred at room temperature for 16 h. *In situ* GC/MS analysis showed that all of the B_2pin_2 was consumed.

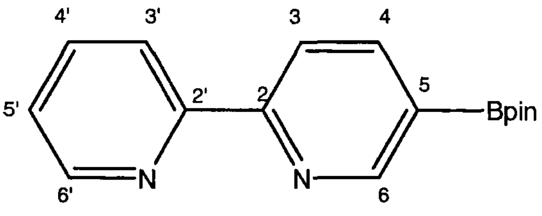
Kugelrohr distillation (100-220 °C, 3 x 10^{-4} torr), with gradually increasing temperature yielded several fractions.

The two isomers of mono borylation products sublimed first giving an analytically pure sample (44 mg, 156 x 10^{-3} mmol, 24%), followed by analytically bis(borylation) products (36 mg, 88 x 10^{-3} mmol, 20%).



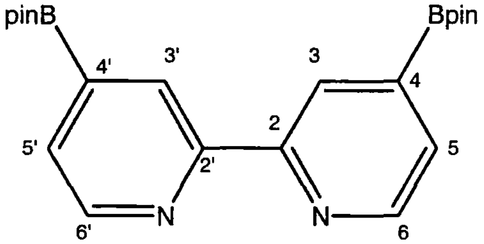
2J(4)

+



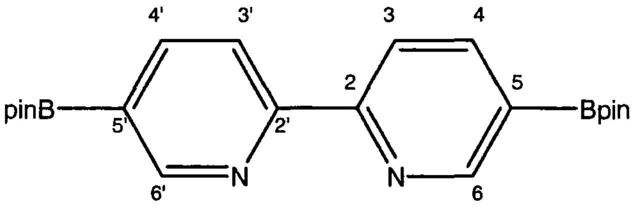
2J(5)

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.37 (s, 24H; **Bpin**), 7.29 (m, 2H), 7.63 (d, ^3J(H,H) = 4.6 Hz, 1H; **5** (**2J**(**4**)), 7.579 (m, 2H), 8.18 (d, ^3J(H,H) = 7.7, 1.7 Hz, 1H; **4** (**2J**(**5**)), 8.35 (t, ^3J(H,H) = 7.7 Hz, 2H), 8.42 (d, ^3J(H,H) = 7.7 Hz, 1H), 8.67 (dd, ^3J(H,H) = 4.6 Hz, 3H), 8.71 (s, 1H; 6, (**2J**(**4**)), 9.00 (s, 1H, 6, (**2J**(**5**)).^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 25.11, 84.46, 84.75, 120.48, 121.41, 121.85, 123.83, 124.20, 126.62, 128.97, 137.11, 137.21, 143.55, 148.87, 149.40, 149.44, 155.30, 155.68, 156.31, 156.55, 158.20. MS (EI) m/z: 282 [M$^+$], 267 [M-CH_3^+]. Anal. Calcd. For $C_{16}H_{19}N_2BO_2$, C 68.11, H 6.79, N 9.93; found C, 67.94, H, 6.57, N, 9.66.



3J(4,4')

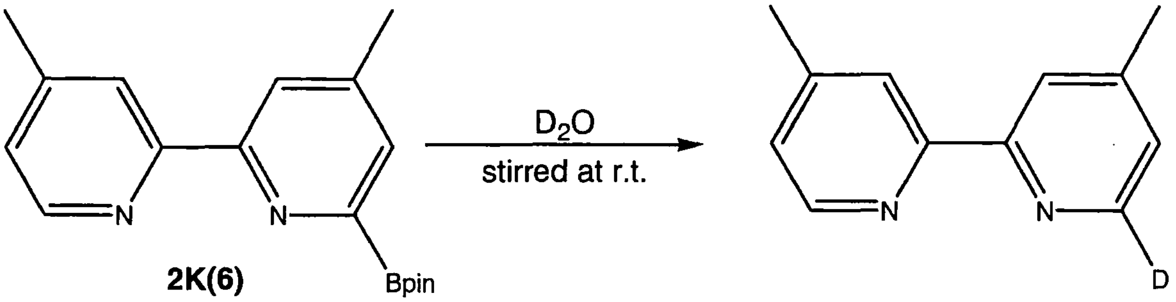
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.37 (s, 24H; **Bpin**), 7.46 (d, ^3J(H,H) = 5.0 Hz, 2H; **5,5'**), 8.70 (s, **3,3'**), 8.73 (d, ^3J(H,H) = 5.0 Hz, 2H; **6,6'**).



3J(5,5')

^{1}H NMR (500 MHz, CDCl$_3$): δ 1.37 (s, 24H; **Bpin**), 8.19 (dd, ^3J(H,H) = 8.0 Hz,^4J(H,H) = 1.7, 2H; **4,4'**), 8.42 (dd, ^3J(H,H) = 8.0 Hz, ^5J(H,H) = 1.0 Hz, 2H; **3,3'**), 9.01 (dd, ^5J(H,H) = 1.0 Hz, ^4J(H,H) = 1.7, 2H; **6,6'**).^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) for both compounds (**3J(4,4')** and **3J(5,5')**): δ 25.02, 84.38, 84.64, 120.80, 126.52, 128.74, 143.43, 148.84, 155.24, 158.13. MS (EI) m/z: 408 [M$^+$], 393 [M-CH$_3$$^+$]. Anal. Calcd. For $C_{22}H_{30}N_2B_2O_4$, C 64.75, H 7.41, N 6.86; found C, 64.64, H, 7.31, N, 6.60.

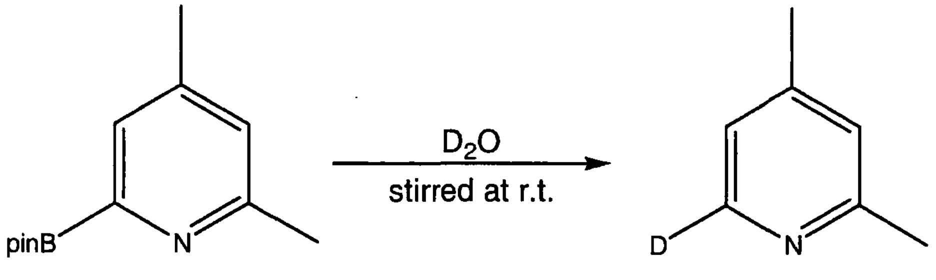
3.5.18- Borylation of 4,4'-Me_2-2,2'-bipyridine to give 4,4'-Me_2-5-(Bpin)-2,2'-bipyridine and 4,4'-Me_2-6-(Bpin)-2,2'-bipyridine



In a nitrogen-filled glove box, to a solution of $[Ir(\mu\text{-}OMe)COD]_2$ (9.01 mg, 13.6 x 10^{-3} mmol, 2.5 mol%) and dtbpy (7.3 mg, 27.2 x 10^{-3} mmol, 5 mol%) in 2 ml of hexane was added a mixture of B_2pin_2 (138 mg, 543 x 10^{-3} mmol, 1 equiv.) and 4,4'-$(Me)_2$-2,2'-bipyridine (100 mg, 543 x 10^{-3} mmol,) in 3 ml of hexane (5 ml total volume). The mixture was stirred at room temperature. After 16 h, *in situ* GC/MS showed 44% conversion of the starting material with 60% selectivity for 4,4'-Me_2-5-(Bpin)-2,2'-bipyridine **2K(5)** and 40% selectivity for 4,4'-Me_2-6-$(Bpin)_2$-2,2'-bipyridine **2K(6)**. The mixture was quenched with few drops of D_2O, and stirred at room temperature, and then analysed by ^2H NMR spectroscopy.

^2H NMR (76 MHz, D_2O): δ 8.30 ppm (s, 1D).

3.5.19- Borylation of 2,4-Me_2-pyridine to give 2,4-Me_2-5-(Bpin)- pyridine and 2,4-Me_2-6-(Bpin)- pyridine



2L(6)

In a nitrogen-filled glove box, to a solution of [Ir(μ-OMe)COD]$_2$ (23.2 mg, 35 x 10^{-3} mmol, 2.5 mol%) and dtbpy (18.8 mg, 70 x 10^{-3} mmol, 5 mol%) in 2 ml of hexane was added a mixture of B_2pin_2 (356 mg, 1.40 mmol, 1 equiv.) and 2,4-dimethylpyridine (150 mg, 1.40 mmol,) in 3 ml of hexane (5 ml total volume). The mixture was stirred at room temperature. After 16 h, *in situ* GC/MS showed 52% conversion of the starting material. The product consist of 3 isomers, trace of 2,4-Me_2-3-(Bpin)-pyridine **2L(3)**, and 88% selectivity for 2,4,-Me_2-5-(Bpin)-pyridine **2L(5)**, and 12% selectivity for 2,4-Me_2-6-(Bpin)-pyridine **2L(6)**.

The mixture was quenched with few drops of D_2O, stirred at room temperature, and then analysed by ^{2}H NMR spectroscopy

^{2}H NMR (76 MHz, D_2O): δ 8.30 ppm (s, 1D).

3.5.20 Spectroscopic search for interaction between 4-^{t}Bu-pyridine and verity amount of B_2pin_2

In a nitrogen-filled glove box, to three different vials, each containing a solution of B_2pin_2 (70 mg, 276 x 10^{-3} mmol) and 0.7 ml of benzene-d_6 were added respectively, a (41 mg, 304 x 10^{-3} mmol, 1 equiv.), (208 mg, 1.54 mmol, 5 equiv.), (405 mg, 2.25 mmol, 10 equiv.) of 4-^{t}Bu-pyridine. The mixtures were shaken vigorously to ensure complete mixing, transferred to three NMR tubes with Teflon Young's taps.

^{11}B NMR 31.27 ppm.

3.5.21 Competition reactions between 2,6-Me_2-pyridine and 4-^{t}Bu-pyridine in the presence of I / 1A with varying amounts of B_2pin_2

In a nitrogen-filled glove box, to four different vials, each containing a solution of [Ir(μ-OMe)COD]$_2$ (15 mg, 22.6 x 10^{-3} mmol, 2.5 mol%) and dtbpy (12 mg, 44.8 x 10^{-3} mmol, 5 mol%) in 2 ml of hexane were added 3 ml of the following mixtures (total volume 5 ml):-

Entry	2,6-Me_2-pyridine (equiv., mg, mmol)	4-^{t}Bu-pyridine (equiv., mg, mmol)	B_2pin_2 (equiv., mg, mmol)
1	1, 100, 0.935	-	1, 237, 0.933
2	1, 100, 0.935	1, 100, 0.741	0.5, 119, 0.469
3	1, 100, 0.935	1, 100, 0.741	1, 237, 0.933
4	1, 100, 0.935	1, 100, 0.741	2, 475, 1.87
5	1, 100, 0.935	0.1, 12, 0.088	1.1, 261, 1.03

The mixtures were stirred at room temperature. After 16, *in situ* GC/MS showed only a trace of borylation of **2E** when any amount of 4-^{t}Bu-pyridine was present (Entry 2-5). On other hand, in the absence of 4-^{t}Bu-pyridine, the borylation reaction went completion (Entry 1).

3.5.22 Crystallography

The X-ray diffraction data for compounds **4A**, **2E** were collected on a Bruker Apex CCD diffractometers and **3C(5)** and **3D(4)** with Bruker SMART 6000 CCD detector, and **3C(4)** and **3G** with SMART 1K, and **5A**, **3B** and **2F** with SMART 6K with CCD area detectors, using graphite-monochromated sealed-tube Mo-K_α radiation λ = 0.71073 Å. The data collections were carried out at 120(2) K for all using cryostream (Oxford cryosystem) open flow N_2 cryostats. Reflection intensities were crystals integrated using the *SAINT* program.[46] The crystal structures were solve using direct-methods and refined by full matrix least-squares against F^2 of all data using *SHELXTL* software.[47] Crystal data and experimental details are listed in Table 3.5.1.

The CCDC deposition numbers for compounds **4A**, **5A**, **3B**, **3C(4)**, **3C(5)** and **3G** are 279973 to 279978. The other data remain to be deposited.

Table 3.5.1

Compound	**4A**	**5A**	**3B**
Empirical formula	$C_{30}H_{32}N_2 \cdot 2C_6F_6$	$C_{24}H_{28}N_2 \cdot C_6F_6$	$C_{24}H_{34}B_2N_2O_6$
Formula weight	792.70	530.54	468.15
Temperature / K	120(2)	120(2)	120(2)
Crystal system	Orthorhombic	Orthorhombic	Monoclinic
Space group	Pccn	Pnma	$P2_1/n$
a / Å	14.021(2)	27.2125(17)	9.3567(6)
b / Å	19.509(3)	6.7353(5)	22.0270(13)
c / Å	13.2267(19)	14.3175(10)	12.2764(8)
α / β / γ / deg.	90	90	90 / 98.213(3) / 90
Volume / Å^3	3618.1(9)	2624.2(3)	2504.2(3)
Z	4	4	4
D_c / Mg · m^{-3}	1.455	1.343	1.242
μ / mm^{-1}	0.128	0.108	0.087
Crystal size / mm^3	0.50 x 0.16 x 0.10	0.40 x 0.20 x 0.08	0.34 x 0.20 x 0.14
Theta range / deg.	1.79 - 30.49	1.61 - 30.51	1.85 - 30.50
Reflections collected	35508	24307	30071
Independent reflections	5474	4319	7652
Goodness-of-fit on F^2	1.297	1.010	1.037
$R_{(int)}$	0.0550	0.0508	0.0697
$wR(F^2)$(all data)	0.1583	0.1346	0.2025
R[I>2σ (I)]	0.0550	0.0508	0.0697
Refined parameters	317	291	317
Largest diff. peak and hole / e^{-} Å^{-3}	0.538 and -0.338	0.344 and -0.266	0.500 and -0.281

Table 3.5.1 (Cont'd)

Compound	**3C(4)**	**3C(5)**	**3D(4)**
Empirical formula	$C_{21}H_{15}N$	$C_{21}H_{15}N$	$C_{12}H_{11}N$
Formula weight	281.34	281.34	169.22
Temperature / K	120(2)	120(2)	120(2)
Crystal system	Monoclinic	Monoclinic	Orthorhombic
Space group	$P\,2_1$	$P\,2_1$	Pbca
a / Å	6.7020(8)	7.099(1)	7.4760(6)
b / Å	7.6743(9)	12.943(2)	20.8897(14)
c / Å	14.6965(17)	7.928(1)	23.5283(17)
α / β / γ / deg.	90 / 97.980(3) / 90	90 / 100.02(1) / 90	90
Volume / $Å^3$	748.57(15)	717.33(18)	3674.4(5)
Z	2	2	16
D_c / Mg · m^{-3}	1.248	1.303	1.224
μ / mm^{-1}	0.072	0.075	0.072
Crystal size / mm^3	0.45 x 0.40 x 0.35	0.36 x 0.30 x 0.05	0.44 x 0.16 x 0.02
Theta range / deg.	1.40 - 29.99	2.61- 29.98	1.73 - 27.50
Reflections collected	7457	9586	30673
Independent reflections	3523	2163	4220
Goodness-of-fit on F^2	0.645	1.069	1.006
$R_{(int)}$	0.0426	0.0423	0.0381
$wR(F^2)$(all data)	0.1261	0.1188	0.1036
$R[I>2\sigma(I)]$	0.0426	0.0423	0.0381
Refined parameters	260	259	323
Largest diff. peak and hole / $e^- Å^{-3}$	0.327 and -0.188	0.326 and -0.199	0.278 and -0.192

Table 3.5.1 (Cont'd)

Compound	2E	3E	2F
Empirical formula	$C_{13}H_{20}BNO_2$	$C_{17}H_{15}N$	$C_{11}H_{14}BCl_2NO_2$
Formula weight	233.11	233.30	273.94
Temperature / K	120(2)	120(2)	120(2)
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1/m$	P2(1)/c	P2(1)/n
a / Å	7.9952(15)	11.2252(16)	6.5381(4)
b / Å	6.8431(13)	15.438(2)	21.3579(12)
c / Å	12.251(2)	7.6917(12)	9.4192(5)
α / β / γ / deg.	90 / 93.085(4) / 90	90 / 107.874(4) / 90	90 / 93.137(2) / 90
Volume / Å^3	669.3(2)	1268.6(3)	1313.33(13)
Z	4	4	4
D_c / Mg · m^{-3}	1.157	1.222	1.385
µ / mm-1	0.076	0.071	0.482
Crystal size / mm^3	0.46 x 0.42 x 0.10	0.35 x 0.06 x 0.05	0.24 x 0.20 x 0.12
Theta range / deg.	2.97 - 30.57	1.91 - 25.00	2.37 - 30.50
Reflections collected	5166	11358	18635
Independent reflections	2164	2236	4008
Goodness-of-fit on F^2	1.133	0.886	1.052
$R_{(int)}$	0.0797	0.0435	0.0313
$wR(F^2)$(all data)	0.2047	0.1142	0.0835
$R[I>2\sigma(I)]$	0.0797	0.0435	0.0313
Refined parameters	119	223	210
Largest diff. peak and hole / e$^-$ Å^{-3}	0.489 and -0.392	0.207 and -0.185	0.363 and -0.168

Table 3.5.1 (Cont'd)

Compound	3G	3J(4,4')
Empirical formula	$C_{10}H_{10}N_2S$	$C_{22}H_{30}B_2N_2O_4$
Formula weight	190.26	408.10
Temperature / K	120(2)	120(2)
Crystal system	Monoclinic	Orthorhombic
Space group	$P2_1/c$	$Pna2_1$
a / Å	7.1352(19)	20.849(4)
b / Å	12.292(3)	6.6532(12)
c / Å	11.175(3)	15.874
α / β / γ / deg.	90 / 94.168(4) / 90	90
Volume / $Å^3$	977.5(4)	2201.9(7)
Z	4	4
D_c / Mg · m^{-3}	1.293	1.231
μ / mm^{-1}	0.283	0.082
Crystal size / mm^3	0.45 x 0.40 x 0.35	0.20 x 0.08 x 0.06
Theta range / deg.	2.47 - 29.89	1.95 to 30.39°
Reflections collected	9294	14651
Independent reflections	2618	3139
Goddness-of-fit on F^2	1.062	1.048
$R_{(int)}$	0.0464	0.0926
$wR(F^2)$(all data)	0.1293	0.1960
$R[I>2\sigma(I)]$	0.0464	0.0926
Refined parameters	142	195
Largest diff. peak and hole / $e^- Å^{-3}$	0.248 and -0.194	0.902 and -0.374

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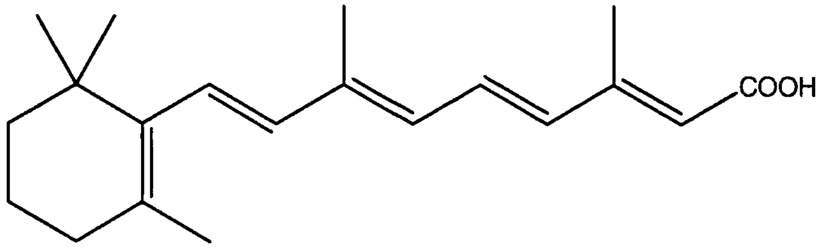
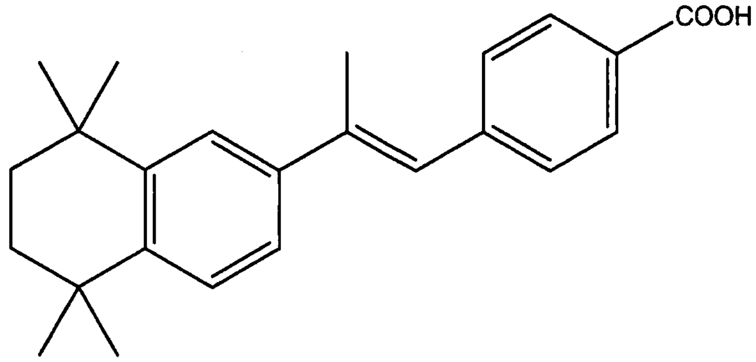
Application of Aromatic C-H Borylation, Suzuki-Miyaura Cross-Coupling and Alkene Dehydrogenative Borylation via Transition Metal Catalysis

4.1 Introduction

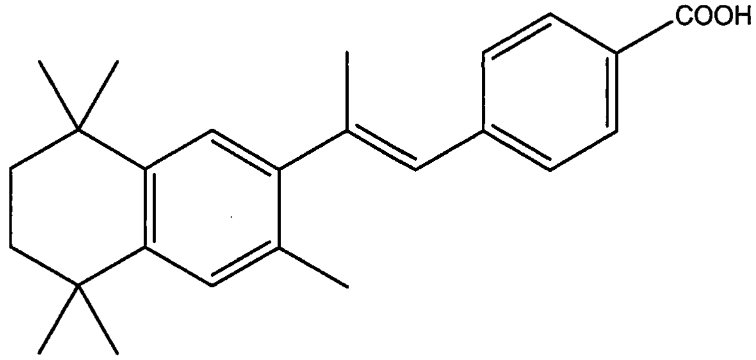
Retinoids or vitamin A derivatives are of interest because of their wide range of biological activities,[1,2] (Fig. 4.1.1). They play important roles in embryonic development, vision and cellular differentiation,[3] proliferation and apoptosis. Retinoid derivatives can be used to control the growth of bacteria and fungi, the mediation of cell growth and differentiation, and also for the treatment of dermatological diseases such as psoriasis, as well as cancer, including chemotherapeutic and chemopreventative applications.[4-12] The administration of retinoic acids at high concentration can create side effects ranging from skin irritation through to toxicity and teratogenicity. These effects of retinoids are mediated by the retinoid nuclear receptors (RARs and RXRs).[13-15] There is much interest in the synthesis of effective and selective retinoids, which can activate the receptors required to elicit the desired response without any undesirable side effects. Retinoids can be defined as molecules related to all *trans*-retinoic acid, and because of their biological activities are classified into two types, retinoic acid receptor (RAR) and retinoid X receptor (RXR).[16-18]



all-*trans*-retinoic acid **1**



TTNPB **2**



3-MeTTNPB **3**

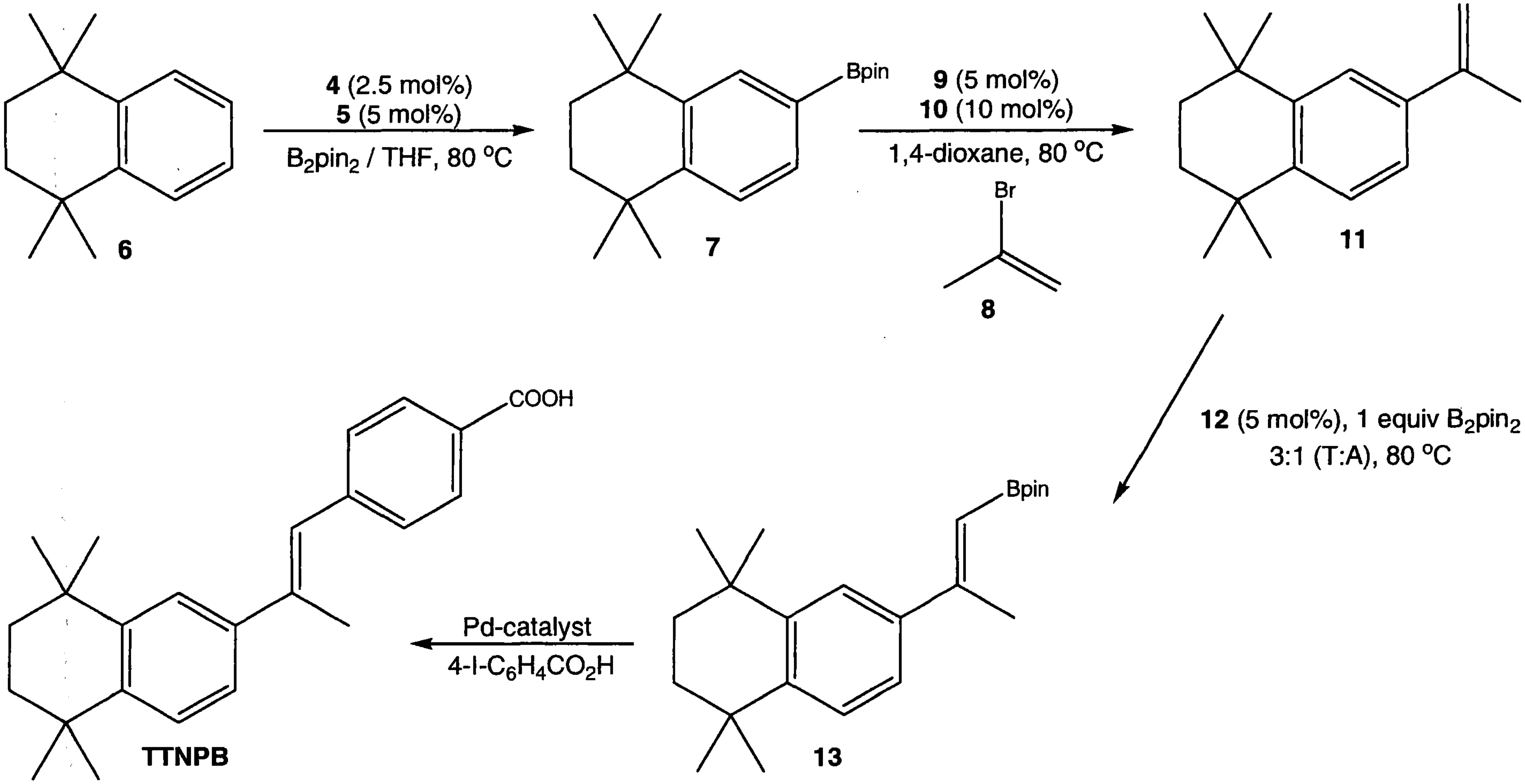
Fig. 4.1.1 Retinoic acid derivatives

Two examples of synthetic retinols which have been shown to exhibit significant biological activity are displayed in Fig. 4.1.1. TTNPB, **2**,[19] 4-(E)-[2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)-propenyl] benzoic acid is cytotoxic and a strong inducer of apoptosis, being 500-times more active than the natural metabolite, all-*trans*- retinoic acid,[20-22] **1**, making it a suitable compound for cancer therapy.

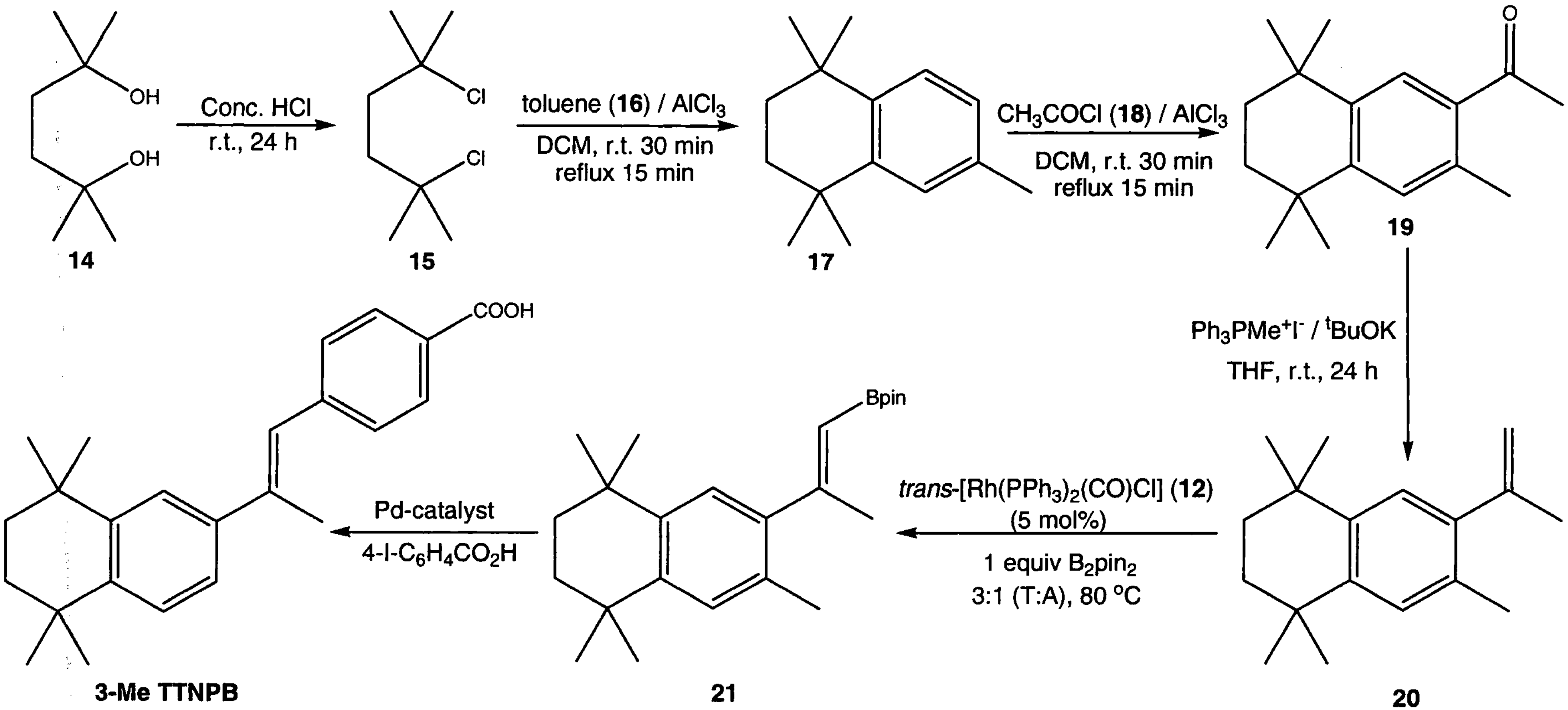
TTNPB is a highly teratogenic pan-RAR agonist, whereas 3-Me TTNPB,[19,23] **3**, 4-(E)-[2-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)-propenyl] benzoic acid selectivity activates RAR-β and –γ in addition to RXR-α.[17,24,25] Binding affinity and consequently, toxicity are decreased by 100-fold compared to TTNPB.

Here, we show the utility of the transition metal catalysed borylation of C-H bonds in the synthesis of biologically active retinoic acid analogs. In the first step, to prepare the retinoid precursor for compound, **2**, aromatic C-H borylation using $[Ir(\mu\text{-}Cl)(COE)_2]_2$,[26] **4** and 4,4'-$^tBu_2$-2,2'-bipyridine **5**, in the presence of 1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphthalene, **6**, and B_2pin_2 should give 6-(2-Bpin-1-methyl-vinyl)-1,1,4,4-tetramethyl-1,2,3,4-tetrahydro-naphthalene, **7**. Suzuki-Miyaura cross-coupling of **7** with 2-Br-propene, **8**, using $Pd(OAc)_2$, **9**, and PPh_3 **10**,[27,28] should afford 6-isopropenyl-1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphthalene, **11**. Selective dehydrogenative borylation of the resulting alkene C-H bond in the α-methylstyrene derivative, **11** using *trans*-$[Rh(Cl)(CO)(PPh_3)_2]$ **12**,[29] would give 6-(2-Bpin-1-methyl-vinyl)-1,1,4,4-tetramethyl-1,2,3,4-tetrahydro-naphthalene, **13**, Scheme 4.1.1. Finally, cross-coupling with 4-iodobenzoic acid would give TTNPB.

The second target is compound **3**. Starting with the conversion of 2,5-dimethyl-hexane-2,5-diol, **14**, into 2,5-dichloro-2,5-dimethylhexane,[17,30] **15**, which is subsequently reacted with toluene, **16**, to give 1,1,4,4,6-pentamethyl-1,2,3,4-tetrahydronaphthalene,[17] **17** via Friedel-Crafts alkylation, Friedel-Crafts acylation with acetylchloride **18** would give 1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)-ethanone, **19**. Then, methylenation of the ketone via a Wittig reaction would provide 6-isopropenyl-1,1,4,4,7-pentamethyl-1,2,3,4-tetrahydronaphthalene,[31] **20**. Rh-catalysed dehydrogenative borylation of **20** would be expected to yield 6-(2-Bpin-1-methyl-vinyl)-1,1,4,4,7-pentamethyl-1,2,3,4-tetrahydronaphthalene, **21**, (Scheme 4.1.2), which again would be cross coupled with 4-iodobenzoic acid to give 3-MeTTNPB.


6
4 (2.5 mol%)
5 (5 mol%)
B_2pin_2 / THF, 80 °C
Bpin
7
9 (5 mol%)
10 (10 mol%)
1,4-dioxane, 80 °C
Br
8
11
12 (5 mol%), 1 equiv B_2pin_2
3:1 (T:A), 80 °C
Bpin
13
Pd-catalyst
4-I-$C_6H_4CO_2H$
COOH
TTNPB

Scheme 4.1.1

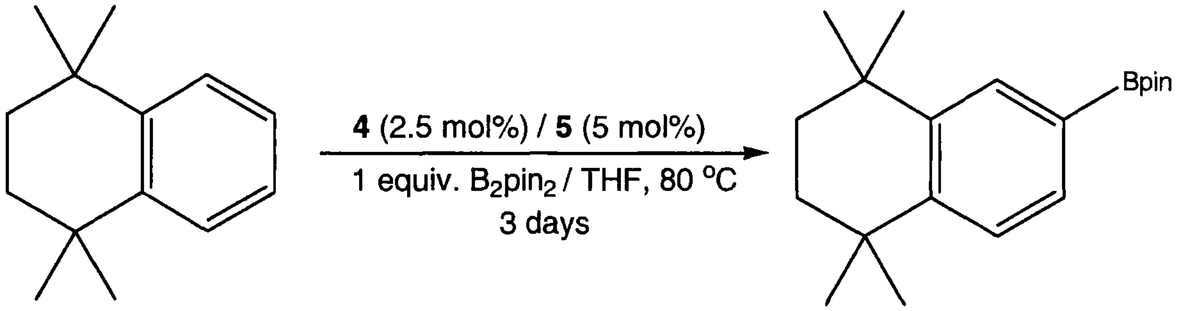

OH
OH
14
Conc. HCl
r.t., 24 h
Cl
Cl
15
toluene (16) / AlCl3
DCM, r.t. 30 min
reflux 15 min
17
O
CH3COCl (18) / AlCl3
DCM, r.t. 30 min
reflux 15 min
19
Ph3PMe+I- / tBuOK
THF, r.t., 24 h
20
trans-[Rh(PPh3)2(CO)Cl] (12)
(5 mol%)
1 equiv B2pin2
3:1 (T:A), 80 °C
Bpin
21
Pd-catalyst
4-I-C6H4CO2H
COOH
3-Me TTNPB

Scheme 4.1.2

4.2 Results and Discussion

4.2.1 Synthesis of 6-(2-Bpin-1-methyl-vinyl)-1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphthalene, 13

The first step in the preparation of compound **13** is the synthesis of 6-Bpin-1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphthalene **7** by C-H borylation Eq. 4.2.1. It should be noted that this compound had been prepared previously by the Pd-catalysed Suzuki-Miyaura cross-coupling reaction of 6-Br-1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphthalene with B_2pin_2.[32]



6

7

Eq. 4.2.1 Reaction of 1,1,4,4-tetramethyl-1,2,3,4-tetrahydro-naphthalene with 1 equiv. of B_2pin_2 in the presence of **4**

The reaction was carried out using 2.5 mol% of **4** and 5 mol% of **5** in the presence of 1 equiv. of B_2pin_2 and 1 equiv. of 1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphthalene **6** in (5 ml) THF at 80 °C. After 3 days, *in situ* GC/MS shows consumption of all B_2pin_2 and the conversion was 72% (Fig. 4.2.1).

The conversion can be improved to reach completion during 24 hours by using a high catalyst loading 20 mol% and 2 equiv. of B_2pin_2.

The solvent was removed *in vacuo* and the product was purified by sublimation at 100 °C x 0.2 torr to yield 72% of **7** as a white powder. The slow evaporation of a hexane solution of **7** gave a suitable single crystal for X-ray diffraction studies (Fig. 4.2.2). Moreover, the product can be purified by column chromatography eluting with hexane : DCM (50:50).

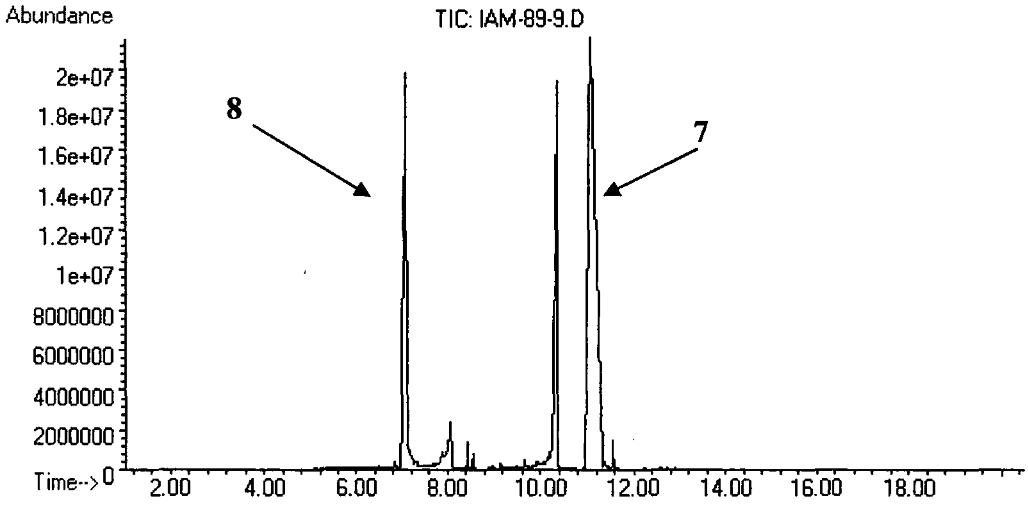


Fig. 4.2.1 Reaction of **6** with 1 equiv. of B_2pin_2 in the presence of 2.5 mol% of **4**

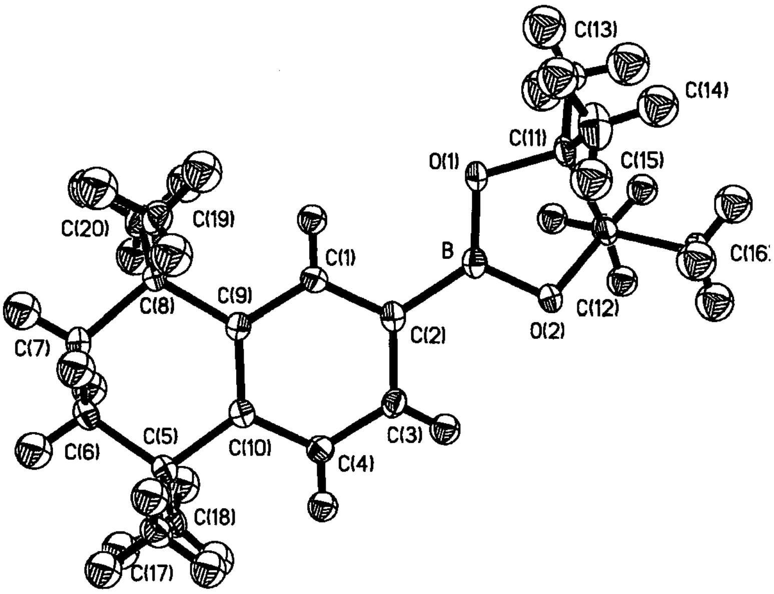
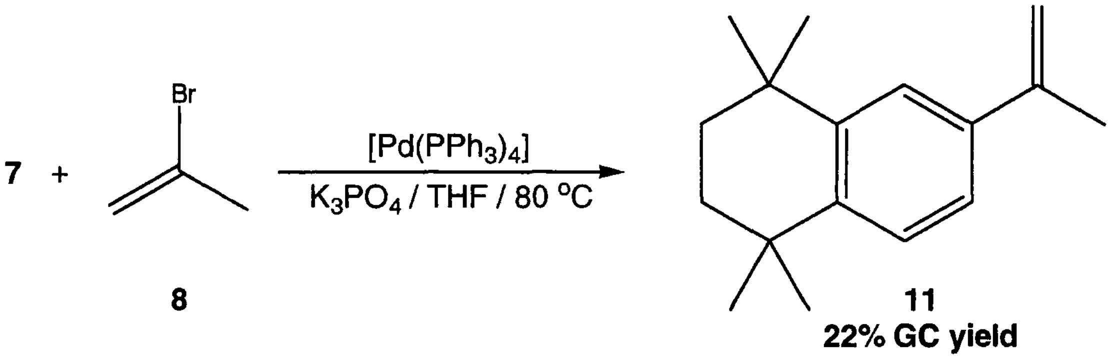


Fig. 4.2.2 Molecular structure of **7**

Selected bond distances (Å): B(1)–C(2) 1.557(3),C(2)–C(3) 1.401(3), C(9)–C(10) 1.405(3) and C(6)–C(7) 1.519(3); dihedral angles (°): O(1)BC(2)C(1) 8, O(1)BC(2)C(3) 171, O(2)BC(2)C(3) 7.7, O(2)BC(2)C(1) 173, C(1)C(9)C(10)C(4) 1.9 and C(8)C(9)C(10)C(5) 0.9. The angle between the mean planes of the arene ring and the Bpin group is 3.7°, and between the planes of the arene ring and cyclohexyl rings is 5.4°.

The Suzuki-Miyaura cross-coupling reaction was the next step employed to couple compound **7** with **8** to give compound **11**. A variety of conditions were explored to form the C-C bond. When a combination of [Pd(PPh$_3$)$_4$] and ^{t}BuOK in THF was used, after refluxing for 6 hours, no product was observed. Under the same condition, except using aq. K$_2$CO$_3$ as base, a trace of coupling was observed. In contrast, 22% of **11** was observed when K$_3$PO$_4$ was used as the base Fig. 4.2.3.



Eq. 4.2.2 Suzuki-Miyaura cross-coupling of 7 with 2-Br-propene

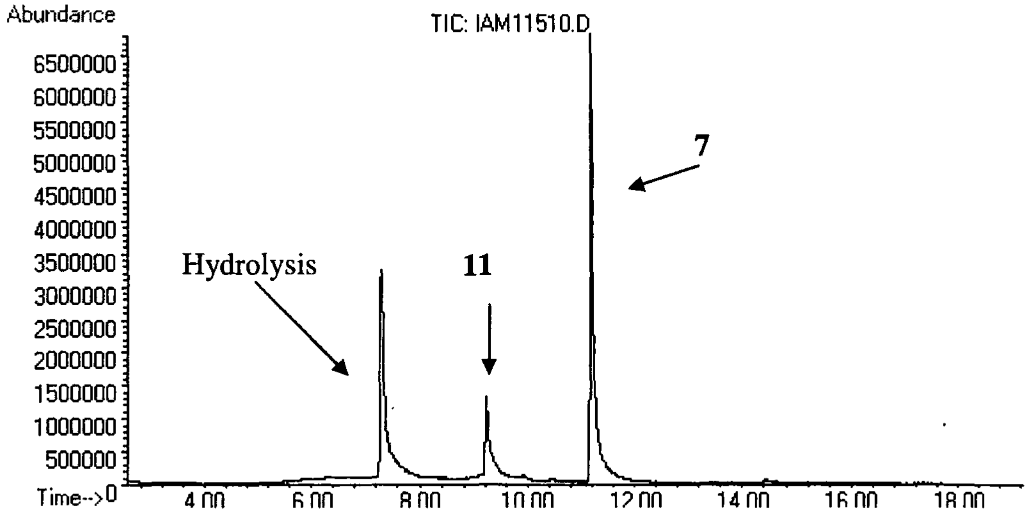


Fig. 4.2.3 GC (TIC) Suzuki-Miyaura coupling of 7 with 2-Br-propene

When compound **9**, with ≤ 2 equiv. of **10**, was used to catalyse the coupling in 1,4-dioxane with 3 equiv. of aqueous K_3PO_4 (2 ml water) at 80 °C, the reaction was successful within 3 hours giving 99% conversion, but with a significant a mount of a side product, shown to be the homo-coupling biphenyl derivative 5,5,8,8,5',5',8',8'-octamethyl-5,6,7,8,5',6',7',8'-octahydro-2,2'-binaphthayl **22** (Fig. 4.2.4).[33] The selectivity for the desired product **11** was 60% (Fig. 4.2.5) with 32% of **22** being produced. The reaction also suffered from a small amount of hydrolysis of boronate esters giving 8% of compound **6**.

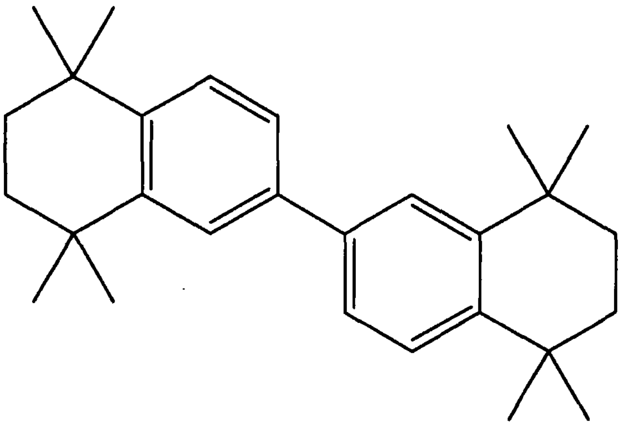


Fig. 4.2.4 5,5,8,8,5',5',8',8'-octamethyl-5,6,7,8,5',6',7',8'-octahydro-[2,2']-binaphthalenyl

22

The conditions were optimised to reduce the homocoupling. Under the same conditions except reducing the volume of aqueous base, by dissolving 3 equiv. of K_3PO_4 in 1 ml of water, *in situ* GC/MS after 3 hours showed 99% conversion of compound **7**. The selectivities were 90% for the desired product **11** and 9% of the hydrolysis byproduct with less than 1% of the homo-coupled product **22** (Fig. 4.2.6). Interestingly, the reaction only worked well on a small scale (50 mg) and showed different conversion and selectivity when it scaled up.

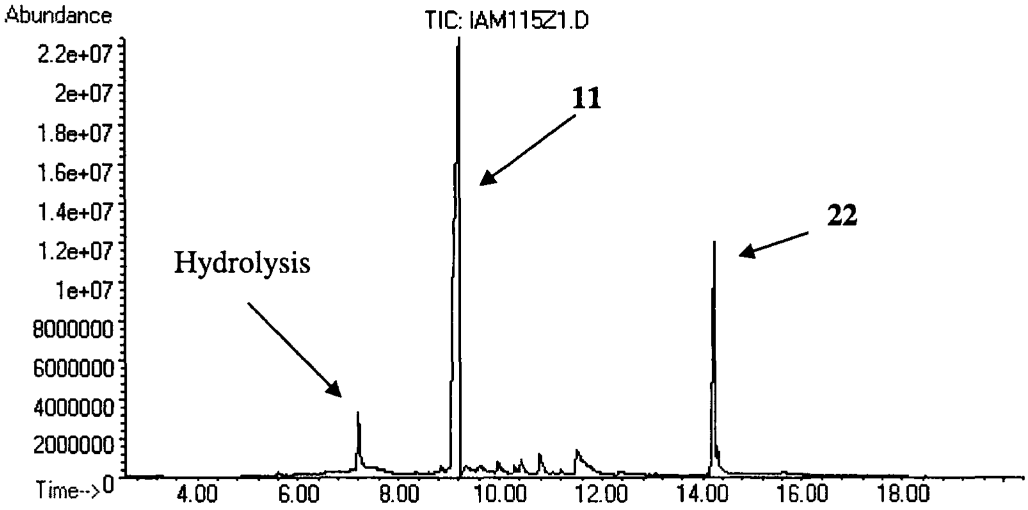


Fig. 4.2.5 GC (TIC) Suzuki-Miyaura coupling of **7** with **8** in the presence of aq. K_3PO_4 (2 ml)

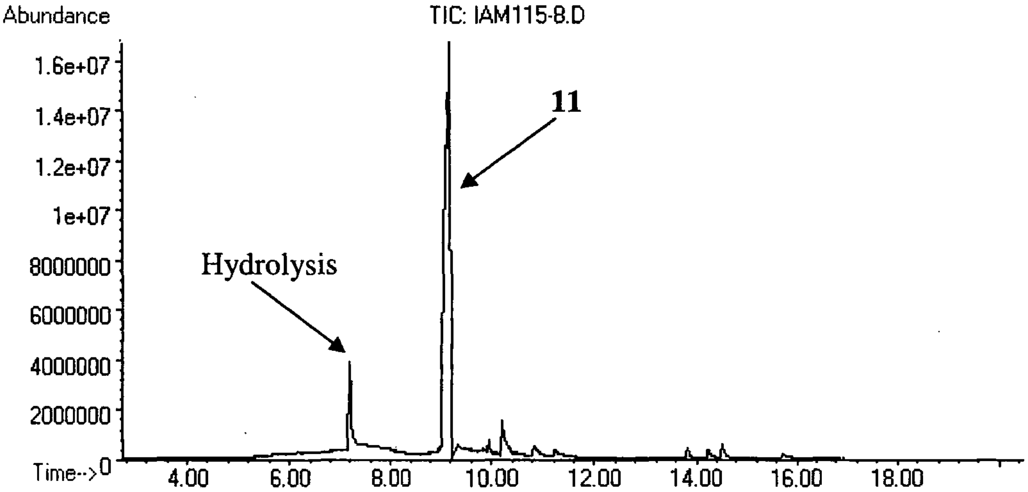
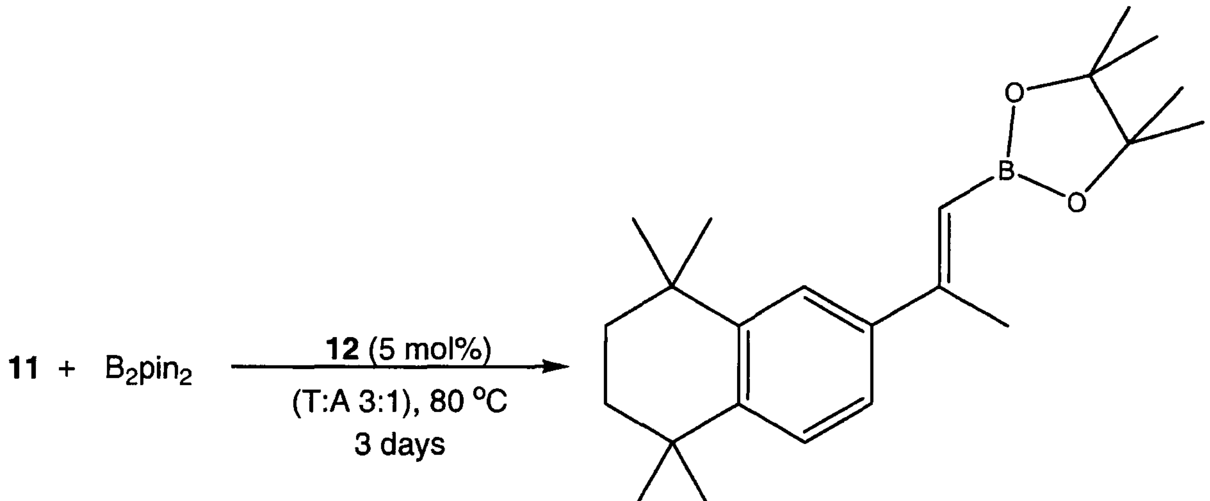


Fig. 4.2.6 GC (TIC) Suzuki-Miyaura coupling of **7** with **8** in the presence of aq. K_3PO_4 (1 ml)

The last step to prepare compound **13** is the dehydrogenative borylation of the alkene **11**. Compound **11** was reacted with 1 equiv. of B_2pin_2 in the presence of 5 mol% of **12** in a mixture of toluene : acetonitrile (3:1 T:A) Eq. 4.2.3. The reaction went to completion during 3 days giving 100% conversion with 90% selectivity for *E*-VBE (VBE = vinylboronate ester) and 10% selectivity for *Z*-VBE by GC/MS. The solvent was removed in *vacuo*, and the reaction was chromatographed on silica gel eluting with Hexane : DCM (60:40) to yield 80% of *E*-VBE **13**. Recrystalisation of **13** from a mixture of ethyl acetate and methanol (1:2) gave a suitable single crystal for X-ray diffraction studies (Fig. 4.2.7).



13

Eq. 4.2.3 Reaction of **11** with 1 equiv. of B_2pin_2 in the presence of 5 mol% of **12**

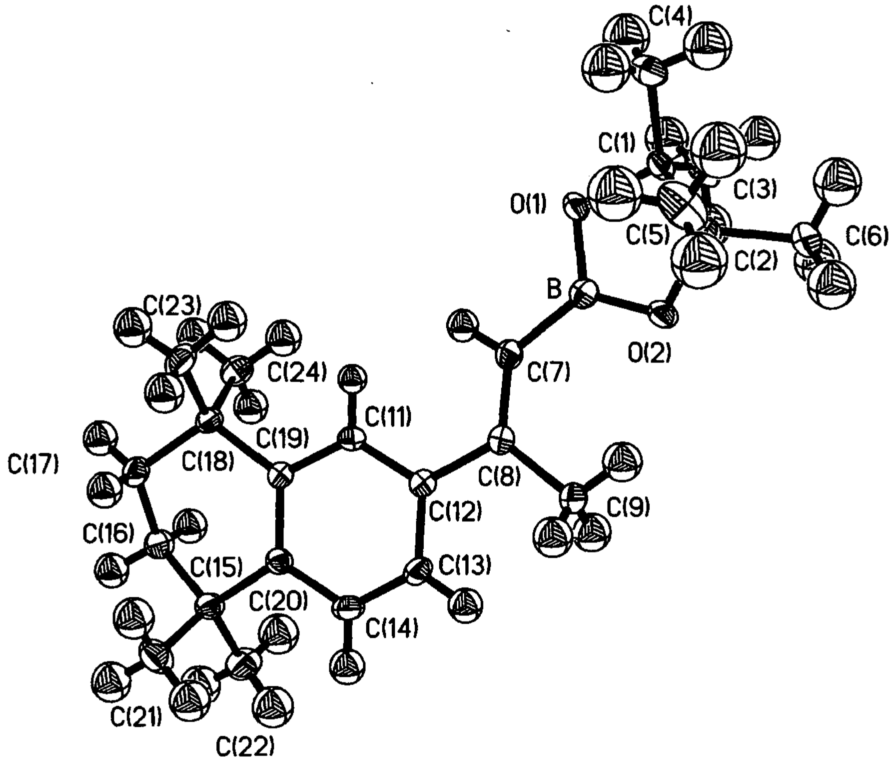
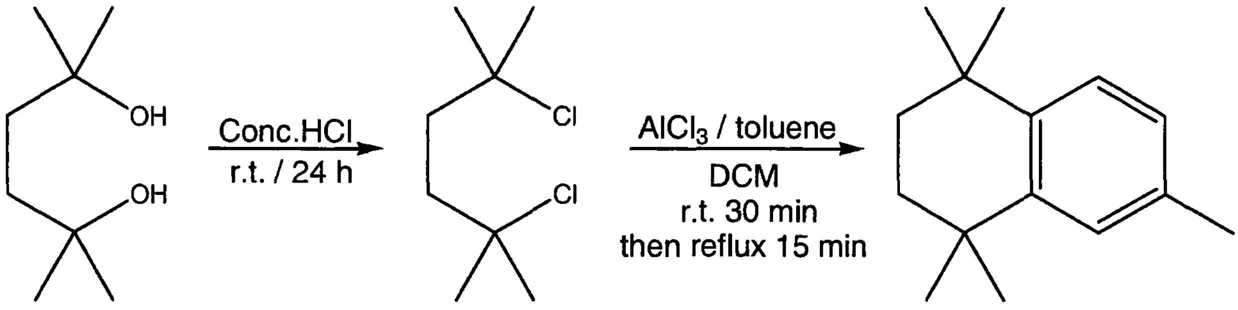


Fig. 4.2.7 Molecular structure of **13**

Selected bond distances (Å): B(1)–C(7) 1.544(19), C(7)–C(8) 1.339(18), C(8)–C(9) 1.509(18), C(8)–C(12) 1.493(17), C(12)–C(13) 1.395(18), C(19)–C(20) 1.407(18) and C(16)–C(17) 1.507(19); dihedral angles (°): O(2)BC(7)C(8) 3.5, O(1)BC(7)C(8) 176.9, BC(7)C(8)C(9) 2.5, BC(7)C(8)C(12) 178.2, C(7)C(8)C(12)C(13) 173.9, C(7)C(8)C(12)C(11) 6.9, C(9)C(8)C(12)C(13) 5.5, C(9)C(8)C(12)C(11) 173.7, C(11)C(19)C(20)C(14) 3.6, and C(18)C(19)C(20)C(15) 3. The angle between the mean planes [B O(1) O(2) C(1) C(2) and C(7) C(8) C(9)], and [B O(1) O(2) C(1) C(2) and C(7) C(8) C(12)]} are 11.2 and 10.6° respectively. The boryl moiety is disordered between two orientations: O(1), O(2), C(1), C(2), C(3) with 90% occupancies and O(1'), O(2'), C(1'), C(2'), C(3') with 10% occupancies. The positions of B, C(4), C(5) and C(6) in both orientations coincide. The dihedral angle between the planes of the disordered boryl groups is 40.7°.

4.2.2 Synthesis 6-(2-Bpin-1-methyl-vinyl)-1,1,4,4,7-pentamethyl-1,2,3,4-tetrahydronaphthalene 21

The first step to synthesise compound **21** is the preparation of compound **17** *via* Friedel-Crafts alkylation (Eq. 4.2.4). Followed by Friedel-Crafts acylation to give **19** (Eq. 4.2.5). Then, methylenation of the ketone *via* Wittig reaction gave **20** Eq. 4.2.6, and finally, Rh-catalysed dehydrogenative borylation yielded **21** (Eq. 4.2.7).



14 **15** **17**

Eq. 4.2.4 Preparation of compound **17** by Friedel-Crafts alkylation

The preparation of **15** employed a procedure which was a modification of those described by Bruson et al.[30] and Heyman et al.[17]

Thus, we employed conc. HCl instead of dry HCl gas to convert **14** into **15**. After 24 hours stirring at room temperature, a white precipitate formed. After work-up the yield was 50%, which is similar to those published.[17]

The next step was the Friedel-Crafts reaction of **15** with **16**, as previously described.[21] The reaction was conducted with $AlCl_3$ in DCM at room temperature for 30 minutes, followed by refluxing for an additional 15 minutes. After extraction into hexane, concentration *in vacuo* followed by Kugelrohr distillation gave **17** in 92%. The slow evaporation of a hexane solution of **17** gave a suitable single crystal for X-ray diffraction studies (Fig. 4.2.8).

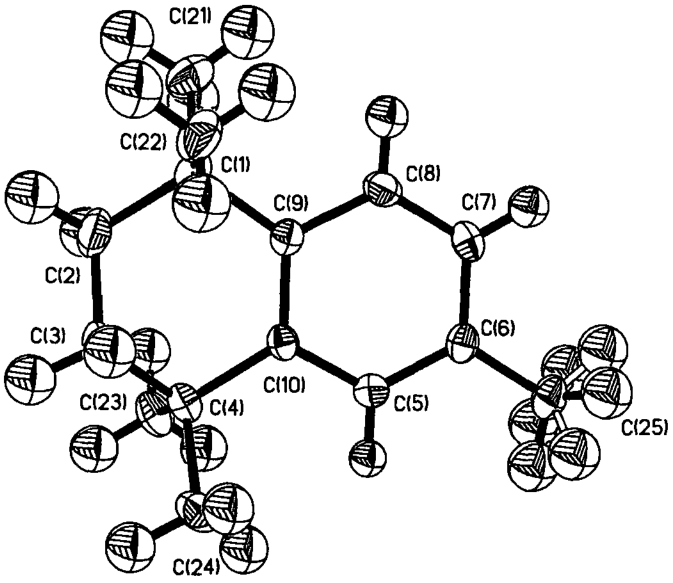


Fig. 4.2.8 Molecular structure of **17** showing the disorder in one Me group (C25) Selected bond distances (Å): C(2)–C(3) 1.518(2), C(6)–C(25) 1.505(16), and C(9)–C(10) 1.403(16); dihedral angles (°): C(8)C(9)C(10)C(5) 1.5, C(1)C(9)C(10)C(4) 3 and C(8)C(7)C(6)C(5) 0.6.

Interestingly, using a GPR (General Purpose Reagent, obtained from Fisher Scientific company) toluene to prepare compound **17**, led to a competing reaction between a trace of *ortho* xylene and toluene (Fig. 4.2.9). Clearly, the activating effect of the additional methyl group in *ortho*-xylene is very large so that even small amount of xylene reacts in preference to toluene. Therefore, the use of high purity toluene was necessary.

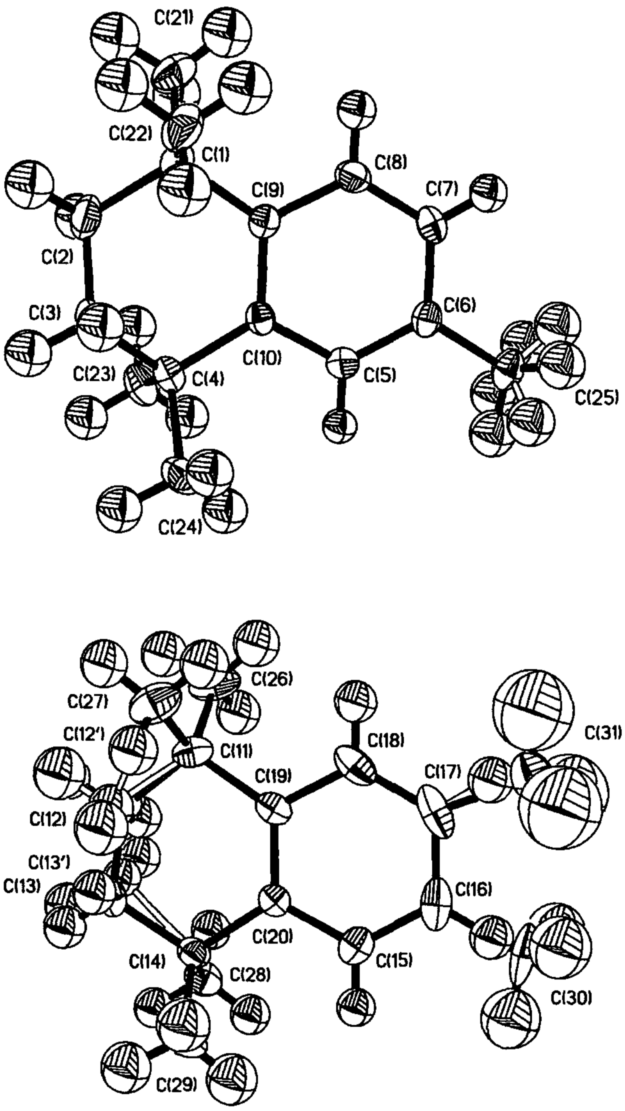
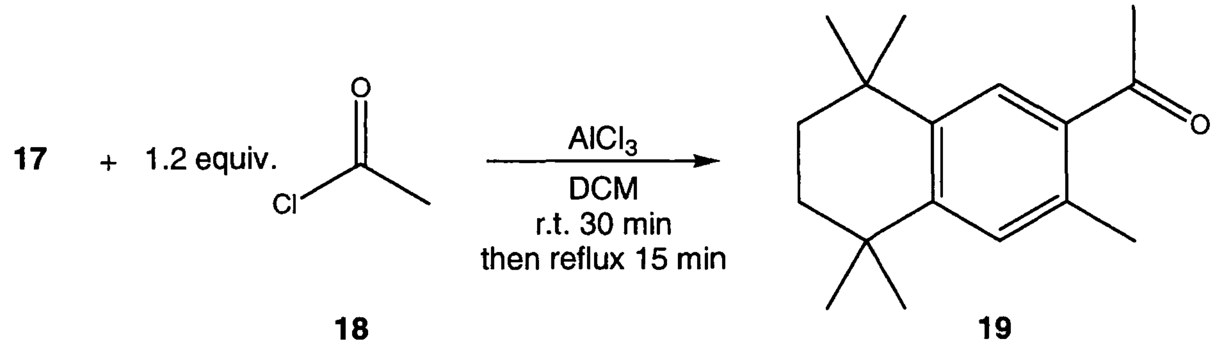


Fig. 4.2.9 Molecular structure of **17** containing small amounts of 1,1,4,4,6,7-hexamethyl-1,2,3,4-tetrahydronaphthalene from *ortho*-xylene impurities in the toluene

The crystals are composed of an mixture of approx. 87% of **17** and 13% of 1,1,4,4,6,7-hexamethyl-1,2,3,4-tetrahydronaphthalene impurity. The asymmetric unit contains two independent molecular sites. One of the sites contains no disorder apart from the aryl methyl group ($C(25)H_3$), which is rotationally disordered over two positions with occupancies of 50%. At the other site there is much disorder, and one in four of the molecules at this site is a 1,1,4,4,6,7-hexamethyl-1,2,3,4-tetrahydronaphthalene molecule. The aromatic methyl groups at C30 and C31 have occupancies of 75% and 50% respectively. The C17-H17 bond is not parallel to the C17-C31 bond. Part of the cyclohexyl ring without the methyl groups is disordered over two positions with occupancies of 92% and 8%.

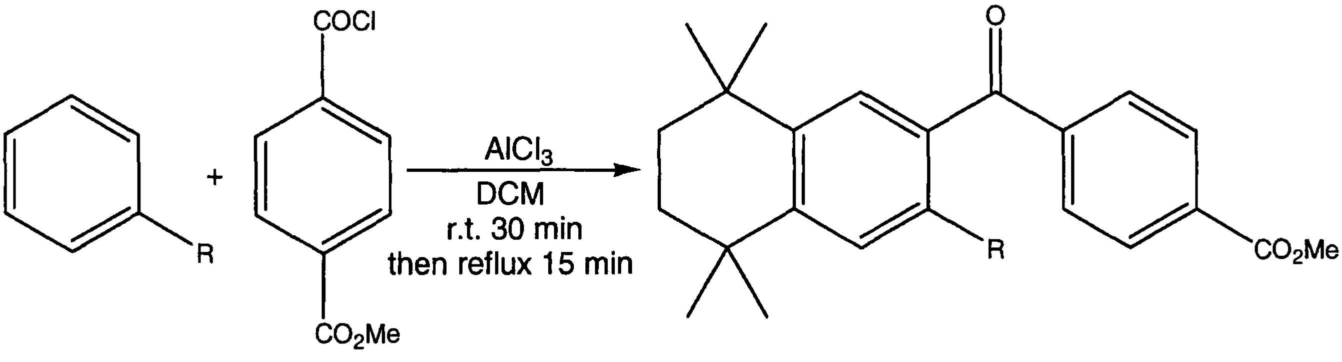
C-H borylation of compound **17** was attempted using 2.5 mol% of **4** and 5 mol% of **5**, with 1 equiv. of B_2pin_2 in hexane at 80 °C. After 3 days, *in situ* GC/MS analysis showed only a trace amount of the desired borylation product. The low reactivity was expected because the aromatic C-H bonds in **17** are α to a methyl group and/or α to the ring junction, both of which are sterically deactivated.[34-36]

Synthesis of compound **19** was achieved by Friedel-Crafts acylation (Eq. 4.2.5). The procedure employed was that published (Eq. 4.2.6).[17] However, the starting materials (**18**) and the product are different.



Eq. 4.2.5 Preparation of compound **19** by Friedel-Crafts acylation

The reaction was carried out with 1 equiv. of **17** and 1.2 equiv. of **18** in the presence of ca. 2 equiv. of $AlCl_3$. The reaction was stirred for 30 minutes in DCM at room temperature followed by an additional 15 minutes at reflux. *In situ* GC/MS showed 100% conversion with 99% selectivity for **19** with 1% of an isomeric byproduct (Fig. 4.2.10) After extraction into ethyl acetate, and then concentration *in vacuo*, Kugelrohr distillation (80-120 °C, 3 x 10^{-4} torr) gave 5.31 g (88% yield) of **19**. Slow evaporation of a hexane solution of **19** gave a suitable single crystal for X-ray diffraction (Fig. 4.2.11).[37]



R = H, Me, Et, ^{i}Pr, F, Cl, Br, OH, OMe

Eq. 4.2.6 Preparation of ketones derivatives by Friedel-Crafts acylation

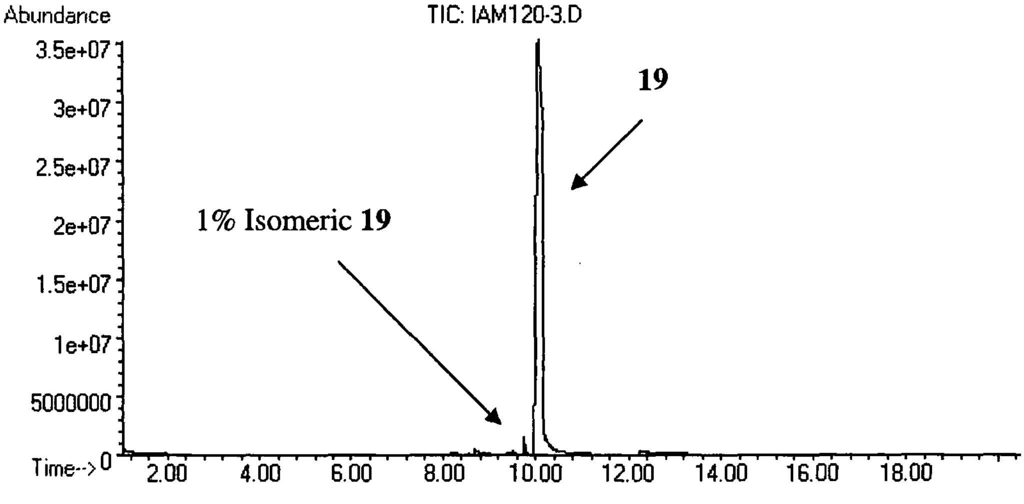


Fig. 4.2.10 GC (TIC) preparation of compound **19** by Friedel-Crafts acylation

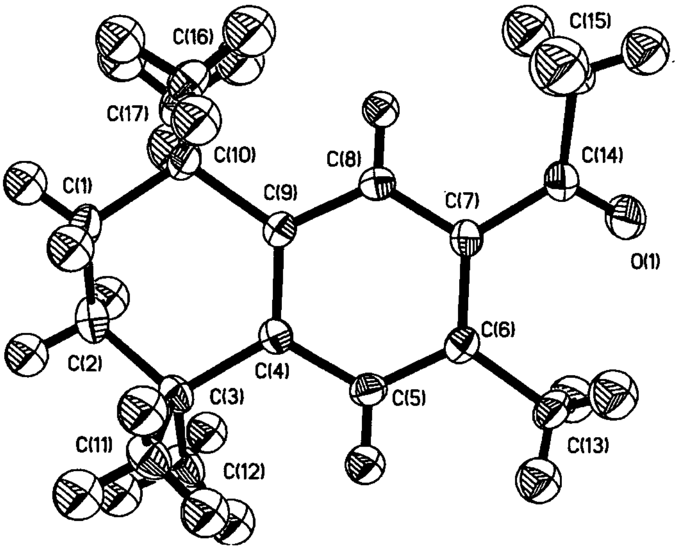
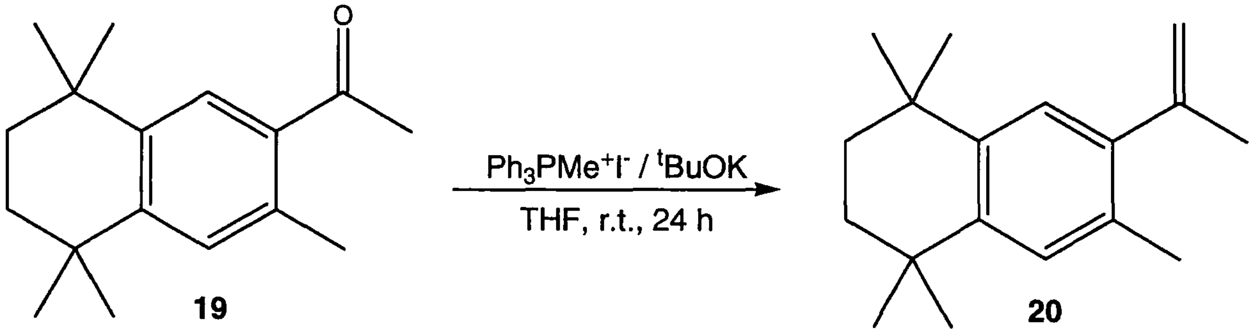


Fig. 4.2.11 Molecular structure of **19**

Selected bond distances (Å): O(1)–C(14) 1.219(4), C(14)–C(15) 1.503(17), C(7)–C(14) 1.495(15), C(6)–C(7) 1.409(15), C(4)–C(9) 1.403(15) and C(1)–C(2) 1.519(18), dihedral angles (°): O(1)C(14)C(7)C(6) 22.9, O(1)C(14)C(7)C(8) 154.3, C(15)C(14)C(7)C(6) 158.3, C(15)C(14)C(7)C(8) 24.6, C(14)C(7)C(6)C(13) 5.3, C(8)C(7)C(6)C(5) 2, C(8)C(9)C(4)C(5) 2.9 and C(10)C(9)C(4)C(3) 0.5.

A Wittig reaction of compound **19** with $Ph_3PMe^+I^-$ / ^tBuOK gave compound **20** in a good yield (Eq. 4.2.7).[31] The reaction was carried out in a nitrogen-filled glove box glove, using 1 equiv. of **19** with 1.5 equiv. of $Ph_3PMe^+I^-$ and 1.5 equiv. of ^tBuOK in THF. The mixture was stirred for 24 hours at room temperature and the reaction worked smoothly. *In situ* GC/MS showed a complete conversion of ketone into alkene (Fig. 4.2.12).



Eq. 4.2.7 Preparation of alkene derivatives by Wittig reaction

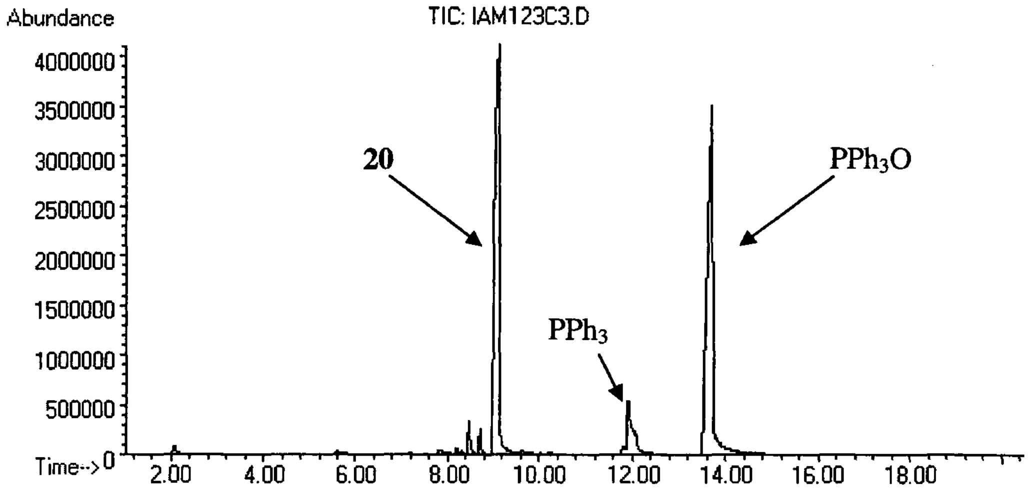
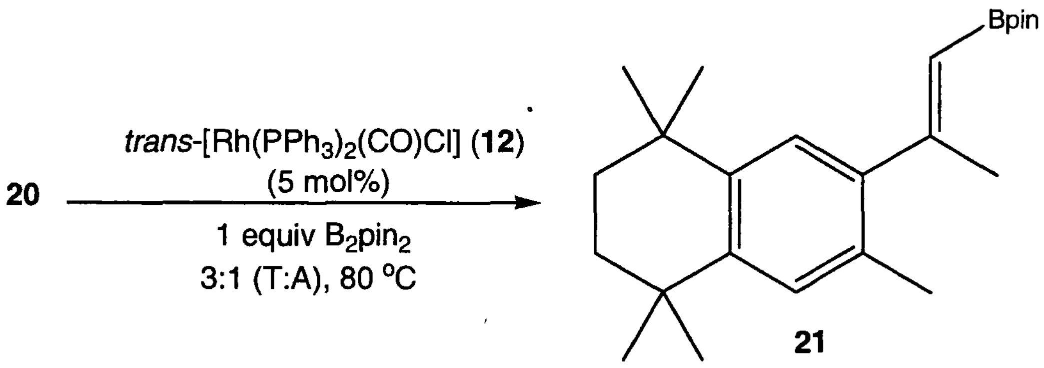


Fig. 4.2.12 GC (TIC) condensation of compound **20** with Wittig reagent

After removal of the salt by filtration, removal of PPh_3O proved difficult. Column chromatography failed to remove PPh_3O. Recrystallisation of PPh_3O from hexane was a solution; however, it required at least 4 crystallisations to remove all of the PPh_3O, and loss of some of the product is possible. On the other hand, Kugelrohr distillation (100-140 °C, 3 x 10^{-4} torr) proved to be the best way to purify the product, giving an analytically pure sample (396 mg, 80%).

Dehydrogenative borylation of compound **20** was carried out with 1 equiv. of B_2pin_2 and 5 mol% of **12** in (T:A 3:1). The mixture was heated at 80 °C for 3 days (Eq. 4.2.8). *In situ* GC/MS analysis showed 70% conversion with 93% selectivity for isomer *E*-**21** and 7% of an isomeric compound (Fig. 4.213), formed, presumably *via* borylation of the terminal C-H bond *trans* to the CH_3 group.



Eq. 4.2.8 Reaction of **20** with 1 equiv. of B_2pin_2 in the presence of 5 mol% of **21**

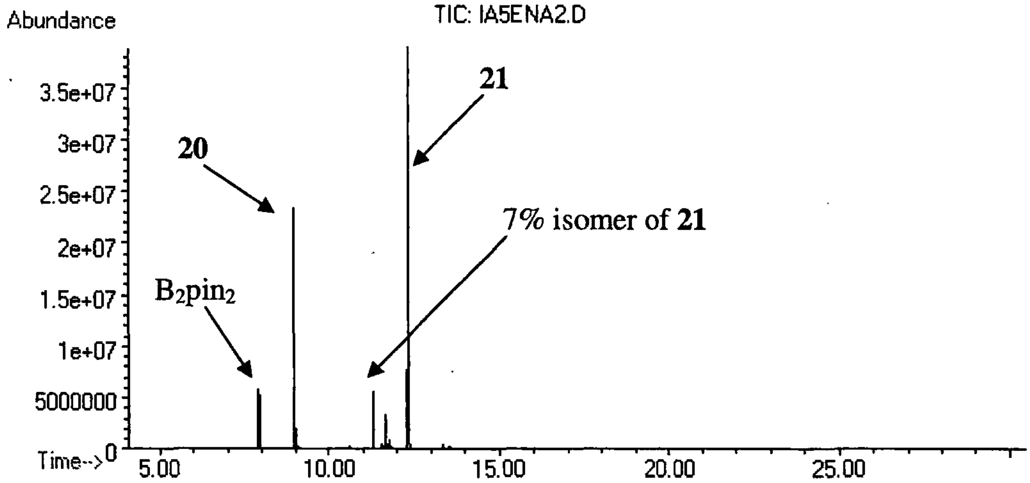


Fig. 4.2.13 GC (TIC) Dehydrogenative borylation of compound **13**

After column chromatography, recrystalisation of compound **21** from a mixture of ethyl acetate and methanol (1:2) yielded a white solid in 50% yield.

Slow evaporation of a DCM solution of **21** gave a suitable single crystal for X-ray diffraction studies (Fig. 4.2.14).

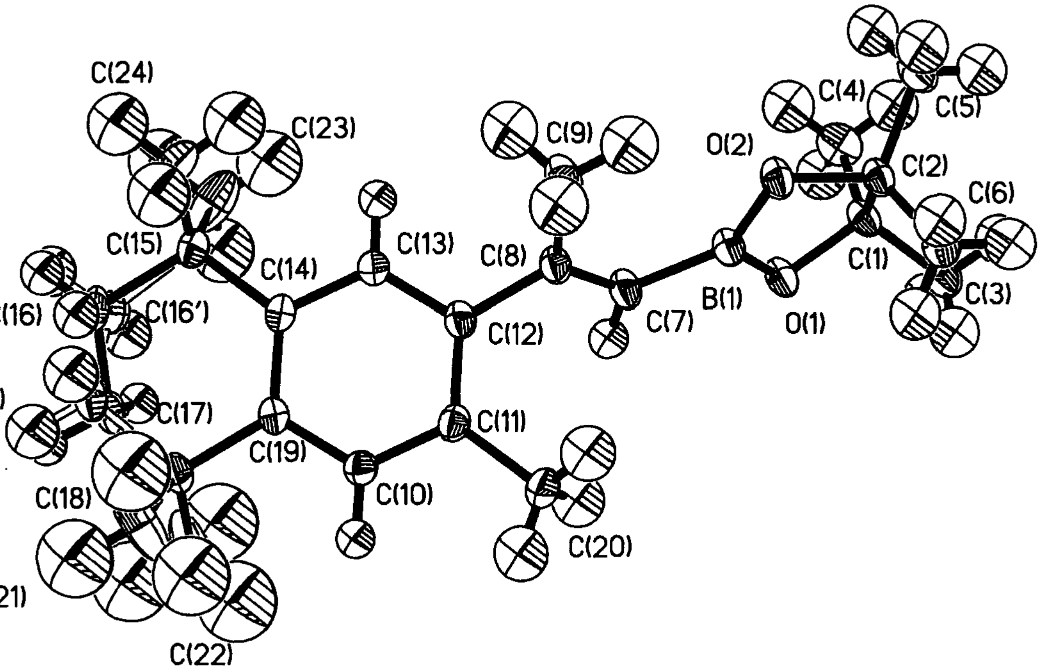


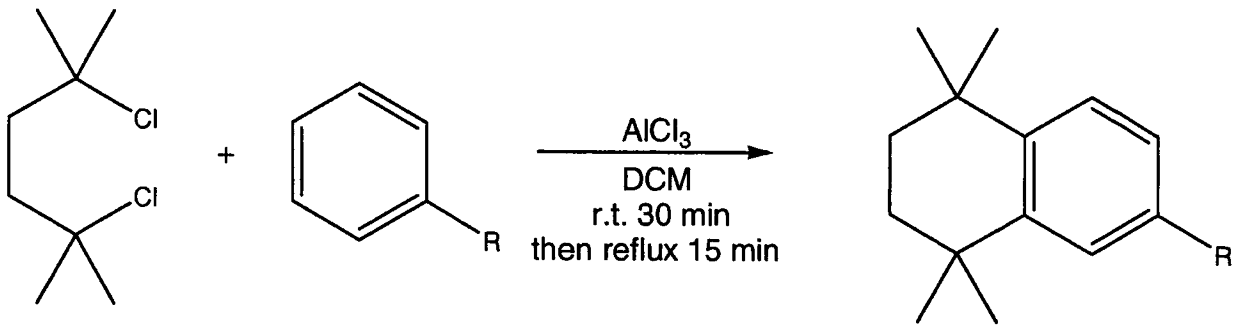
Fig. 4.2.14 Molecular structure of **21**

Selected bond distances (Å): C(11)–C(20) 1.5080(16), B(1)–C(7) 1.5489(17), C(7)–C(8) 1.3407(16), C(8)–C(12) 1.4957(15), and C(16)–C(17) 1.561(5); dihedral angles (°): O(1)B(1)C(7)C(8) 176, O(2)B(1)C(7)C(8) 5.7, B(1)C(7)C(8)C(12) 176.6, B(1)C(7)C(8)C(9) 3.4, C(7)C(8)C(12)C(11) 61.9, C(7)C(8)C(12)C(13) 120.2, C(9)C(8)C(12)C(11) 118.1, C(9)C(8)C(12)C(13) 59.8, C(8)C(12)C(11)C(20) 1.2, C(13)C(14)C(19)C(10) 1.2 and C(15)C(14)C(19)C(18) 2.1. The angle between the mean planes of [B O(1) O(2) C(1) C(2) and C(7) C(8) C(9)], and [B O(1) O(2) C(1) C(2) and C(7) C(8) C(12)]} are 13.2 and 13.1°, respectively.

Part of the cyclohexyl ring (without the methyl substituents) is disordered over two positions with occupancies of 62% and 38%. The C-B bond length is 1.5489(17) Å.

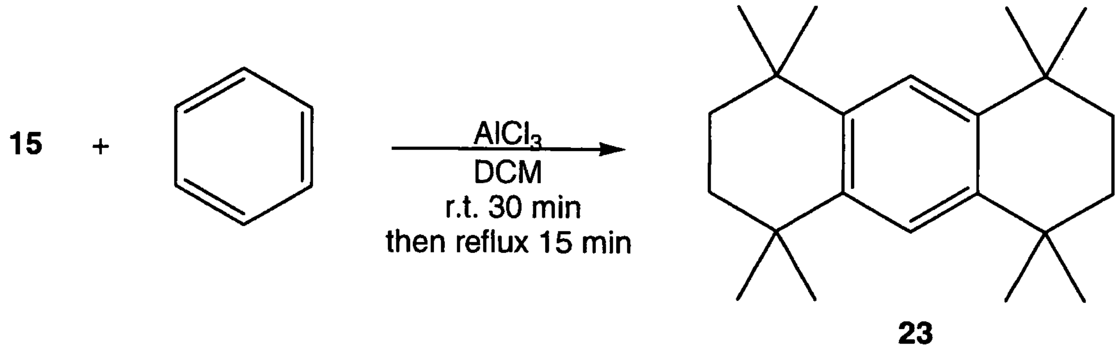
4.2.3 Synthesis of 1,1,4,4,5,5,8,8-octamethyl-1,2,3,4,5,6,7,8-octahydro-anthracene 23

During attempted preparation of compound **6** by using published method by Heyman *et al.*,[17] (Eq. 4.2.9), starting from 1 equiv. of **15** with 1 equiv. of benzene in the presence of $AlCl_3$ in DCM, *in situ* GC/MS analysis showed complete different results than what published, the remaining compound **6** was only formed in 8%, with 92% selectivity for compound **23**, (Eq. 4.2.10), [38-42] this compound **23** was formed arising from Friedel-Crafts alkylation of the initial product. Clearly, **6** is highly activated by the electron donating substituents, and reacts much faster than benzene. Presumably, the reaction needs to be carried out at high dilution. So that the relative concentration of **6**/benzene remains very low. This time, the reaction was reexamined in neat benzene to stop the competition between **6** and **23**, under above condition, *in situ* GC/MS analysis showed that compound **6** was formed in 58%; however with 42% for compound **23** in spite of the neat benzene. This indicated that substituted benzene has a higher efficiency than benzene for Friedel-Crafts alkylation. Slow evaporation of a DCM solution of **23** gave a suitable single crystal for X-ray diffraction studies (Fig. 4.2.15).



R = H, Me, Et, ^{i}Pr, F, Cl, Br, OH, OMe

Eq. 4.2.7 Preparation of compound **6** as suggested by Heyman



Eq. 4.2.8 Synthesis of **23** by Friedel-Crafts alkylation

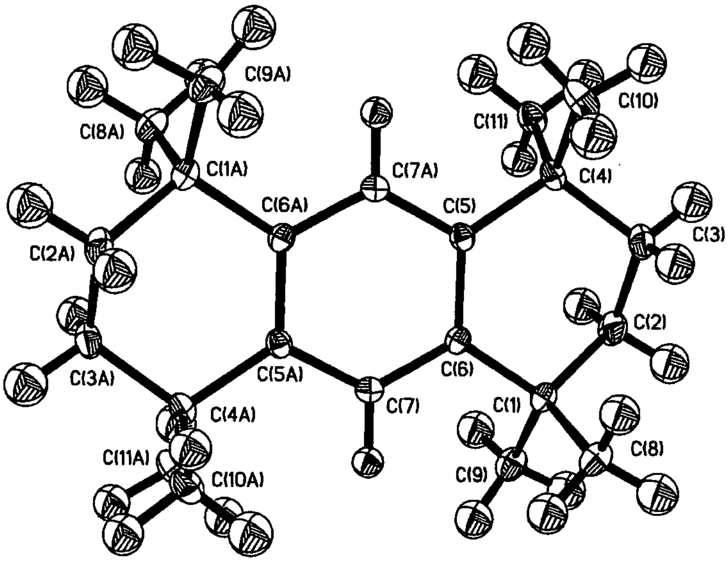


Fig. 4.2.15 Molecular structure of **23**

Selected bond distances (Å): C(2)–C(3) 1.518(13) and C(5)–C(6) 1.406(11); dihedral angles (°): C(7A)C(6A)C(5A)C(7) 1.4°, C(1A)C(6A)C(5A)C(4A) 0.3°, C(7A)C(5)C(6)C(7) 1.3°, C(4)C(5)C(6)C(1) 0.3°.The molecules lie on a crystallographic inversion centre so that the asymmetric unit contains one half of a molecule.

4.3 Conclusion

We introduced the application of transition metal catalysed borylation of two types of C-H bonds to synthesise biologically active molecules. In other words, this chapter represents some application of the work outlined in Chapters 2 and 3. The synthesis of two retinoid precursors were described. Increasing the substitution on the aromatic ring, such as in compound **20**, reduced the yield of the dehydrogenative borylation reaction compared with compound **11**. By contrast with compound **13**, the dehydrogenative borylation of alkene **20** did not reach the completion.

4.4 Experimental

All reactions were carried out under a dry nitrogen atmosphere using standard Schlenk techniques or in an Innovative Technology Inc. System 1 double-length glove box. Glassware was oven dried before transfer into the glove box. Hexane and THF were dried over sodium / benzophenone and acetonitrile was dried over CaH_2 and all were distilled under nitrogen. The solvent 1,4-dioxane was degassed by 3 freeze-pump-low-cycles. Toluene was dried and deoxygenated by passage through columns of activated alumina and BASF-R311 catalyst under Ar pressure using a locally modified version of the Innovative Technology, Inc. SPS-400 solvent purification system. The compound 1,1,4,4-tetramethyl-1,2,3,4-tetrahydro-naphthalene was purchase from Avocado Chemical Company and was dried over CaH_2 and distilled. $[Ir(\mu\text{-}Cl)(COE)_2]_2$,[43] *trans*-$[Rh(Cl)(CO)(PPh_3)_2]$[44,45] and Wittig reagent ($Ph_3PMe^+I^-$),[31] were synthesised by literature, B_2pin_2 was supplied as gifts by Frontier Scientific Inc. and NetChem Inc. Hydrochloric acid was obtained from Fisher Scientific and all other compounds were obtained from Aldrich Chemical Company, tested for purity by GC/MS and used without further purification. NMR spectra were recorded at ambient temperature on Varian Inova 500 (^1H, $^{13}C\{1H\}$, HSQC), Varian C500 (^1H, $^{13}C\{^1H\}$, HSQC),. Varian C500 (^1H, $^{13}C\{^1H\}$, HMBC), Varian Unity 300 (^{11}B and $^{11}B\{^1H\}$) and Bruker AC200 ($^{13}C\{^1H\}$) instruments. Proton and carbon spectra were referenced to external $SiMe_4$ via residual protons in the deuterated solvents or solvent resonance respectively ^{11}B NMR spectra were referenced to external $BF_3{\cdot}OEt_3$. Elemental analyses were conducted in the Department of Chemistry at the University of Durham using an Exeter Analytical Inc. CE-440 Elemental Analyser. GC-MS analyses were performed on a Hewlett-Packard

5890 Series II gas chromatograph equipped with a 5971 mass selective detector and a 7673 autosampler or on an Agilent 6890 Plus GC equipped with a 5973N MSD and an Anatune Focus robotic liquid handling system / autosampler. A fused silica capillary column (10 m or 12 m cross-linked 5% phenylmethylsilicone) was used, and the oven temperature was ramped from 50 °C to 280 °C at a rate of 20 °C/min. UHP grade helium was used as the carrier gas. The screw-cap autosampler vials used were supplied by Thermoquest Inc. and were fitted with Teflon / silicone / Teflon septa and 0.2 ml micro inserts.

4.4.1 Synthesis of 6-Bpin-1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphthalene 7

In a nitrogen-filled glove box, to a solution of $[Ir(Cl)(COE)_2]_2$ (23.8 mg, 26.6 x 10^{-3} mmol, 2.5 mol%) and dtbpy (14.3 mg, 53.2 x 10^{-3} mmol, 5 mol%) in 2 ml of THF was added a mixture of B_2pin_2 (270 mg, 1.06 mmol, 1 equiv.) and 1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphthalene (200 mg, 1.06 mmol) in 3 ml of THF (5 ml total volume). The mixture was shaken vigorously to ensure complete mixing, transferred to ampoules sealed with a Teflon Young's tap and heated at 80 °C. After 3 d, the mixture was analyzed by GC/MS, and then the solvent was removed *in vacuo*.

Two possible methods to purify the product:-

The product can be chromatographed on silica gel (hexane:DCM, 50:50) or purified by sublimation or Kugelrohr distillation (80-140 °C, 3 x 10^{-4} torr) to yield 242 mg (0.771 mmol, 72%) of product.

^1H NMR (500 MHz,C_6D_6): δ 1.14 (s, 12H; **Bpin**), 1.18 (s, 6H; **$(CH_3)_2$**), 1.22 (s, 6H; **$(CH_3)_2$**), 1.54 (s, 4H; **$(CH_2)_2$**), 7.29 (d, 1H; d, $^3J(H,H)$ = 8 Hz, 1H; **Ar**), 8.04 (d, 1H; d, $^3J(H,H)$ = 8 Hz, 1H; **Ar**), 8.25 (s, 1H; **Ar**); $^{13}C\{^1H\}$ NMR (125 MHz, C_6D_6): δ 24.86 (s, BO_2C_2**$(CH_3)_4$**), 31.72, 31.84 (s, **$(CH_3)_2$**), 34.16, 34.45 (s, ($-C(CH_3)_2)_2$), 35.26, 35.41 (s, $(CH_2)_2$), 83.46 (s, $BO_2C_2(CH_3)_4$), 126.33, 132.62, 133.89, 144.14, 148.27 (s, **Ar**), the resonance of the carbon attached to boron was not observed; $^{11}B\{^1H\}$ NMR (128.4 MHz, C_6D_6): δ 31.40 (s, br); MS (EI): m/z: 314 [M^+], 299 [M-Me^+]; Anal. Calcd. for $C_{20}H_{31}BO_2$: C 76.44, H 9.94; found C 76.22, H 9.73; m.p. = 104-106 °C.

4.4.2 Synthesis of 6-isopropenyl-1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphthalene 11

In a nitrogen-filled glove box, to an ampoule sealed with a Teflon Young's tap containing a solution of 6-Bpin-1,1,4,4-tetramethyl-1,2,3,4-tetrahydro-naphthalene (50 mg, 159 x 10^{-3} mmol), and 2-bromopropene (19.1 mg, 159 x 10^{-3} mmol) in 1 ml of 1,4-dioxane was added a solution of $Pd(OAc)_2$ (1.78 mg, 7.95 x 10^{-3} mmol, 5 mol%) and PPh_3 (4.15 mg, 15.9 x 10^{-3} mmol, 2 equiv.) (2 ml total volume) of 1,4-dioxane. To this mixture, 1 ml of aq. K_3PO_4 (101 mg, 477.5 x 10^{-3} mmol, 3 equiv.) was added under nitrogen, and then the reaction mixture was heated at 80 °C. After 3 h, *in situ* GC/MS shows conversion of the boronate ester compound to the alkene product. The product was extracted with ethyl acetate, dried over $MgSO_4$, and chromatographed on silica gel (hexane:DCM 60:40) to yield 66 mg (289 x 10^{-3} mmol, 90%). This experiment was run 10 times on a small scale, by preparing a standard solution {10 ml of solvent containing boronate ester compound and 2-bromopropene, and the other solution (10 ml) containing $[Pd(OAc)_2]$ and PPh_3} the base was added 1 ml to each 2 ml of the mixture.

^{1}H NMR (500 MHz,$CDCl_3$): δ 1.29 (s, 6H; **$(CH_3)_2$**), 1.31 (s, 6H; **$(CH_3)_2$**), 1.69 (s, 4H; **$(CH_2)_2$**), 2.15 (s, 3H; Ar**CH_3**$C=CH_2$), 5.08 (s, 1H; $ArCH_3C=$**CH_2**), 5.35 (s, 1H; $ArCH_3C=$**CH_2**), 7.26 (d, ^3J(H,H) = 2 Hz, 1H; **Ar**), 7.27 (s, 1H; **Ar**), 7.41 (d, (H,H) = 2 Hz, 1H; **Ar**); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 21.96 (s, $ArCH_3C=CH_2$), 31.94 (s, **CH_3**), 32.01 (s, **CH_3**), 34.23 (s, $(CH_3)_2$**C**-), 34.44 (s, $(CH_3)_2$**C**-), 35.18 (s, **CH_2**), 35.32 (s, **CH_2**), 111.63 (s, $ArCH_3C=CH_2$), 123.00, 123.65, 126.51, 138.43, 143.52, 144.37 (s, **Ar**), 144.68 (s, $ArCH_3C=CH_2$); MS (EI): m/z: 228 [M^+], 213 [$M-Me^+$]; Anal. Calcd. for $C_{17}H_{24}$: C 89.41, H 10.59; found C 89.52, H 10.66.

4.4.3 Synthesis of 6-(2-Bpin-1-methyl-vinyl)-1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphthalene 13

In a nitrogen-filled glove box, to a solution of *trans*-[Rh(Cl)(CO)(PPh_3)$_2$] (12.1 mg, 17.5 x 10^{-3} mmol, 5 mol%) in 2 ml of a mixture of toluene / acetonitrile (3:1) was added 89.2 mg (351 x 10^{-3} mmol, 1 equiv.) of B_2pin_2 and 6-isopropenyl-1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphthalene (80 mg, 0.350 mmol) in 2 ml of 3:1 toluene / acetonitrile solvent (4 ml total solvent volume). The mixture was shaken vigorously to ensure complete mixing, transferred to ampoules sealed with a Teflon Young's tap and then heated to 80 °C. The reaction was monitored by GC/MS. After 3 d, the solvent was removed *in vacuo* and redissolved in a mixture of hexane / DCM (60:40), and then chromatographed on silica gel (hexane / DCM, 60:40) to yield 98 mg (277 x 10^{-3} mmol, 80%) of **13**.

^{1}H NMR (400 MHz,C_6D_6): δ 1.13 (s, 12H; **Bpin**), 1.18 (s, 6H; **CH_3**), 1.20 (s, 6H; **CH_3**), 1.58 (s, 4H; **CH_2**), 2.70 (s, 3H; **CH_3**), 6.30 (s, 1H; =**CH**Bpin), 7.14 (s, 1H; **Ar**), 7.32 (d, $^3J(H,H)$ = 2 Hz, 1H; **Ar**), (d, $^3J(H,H)$ = 2 Hz, 1H; **Ar**); $^{13}C\{^1H\}$ NMR (100 MHz, C_6D_6): δ 20. 55 (s, =C**CH_3**), 25.10 (s, $BO_2C_2(CH_3)_4$), 31.95 (s, **CH_3**), 31.98 (s, **CH_3**), 34.44 (s, $C(CH_3)_2$), 34.39 (s, **C**$(CH_3)_2$), 35.48 (s, **CH_2**), 35.62 (s, **CH_2**), 82.84 (s, $BO_2C_2(CH_3)_4$), 123.89, 124.44, 126.79, 130.17, 144.87, 144.92 (s, **Ar**), 159.10 (s, $ArCH_3C{=}CHBpin$); the resonance for the carbon attached to boron was not observed; $^{11}B\{^1H\}$ NMR (128.4 MHz, C_6D_6): δ 31.15 (s, br); ; MS (EI): m/z: 354 [M^+], 339 [$M\text{-}Me^+$]; Anal. Calcd. for $C_{23}H_{35}BO_2$: C 77.96, H 9.96; found C 77.84, H 9.77; m.p. = 128-130 °C.

4.4.4 Synthesis of 2,5-dichloro-2,5-dimethylhexane 15

The preparation of this material was different than those described by Bruson et al.[30] and Heyman et al.[17]

Conc. HCl (37% v/v, d = 1.18, 250 ml) was added carefully to 2,5-dimethyl-2,5-hexanediol (20 g, 137 mmol) in a 500 ml conical flask. The mixture was stirred for 24 h and then filtered and the precipitate was washed 3 x 200 ml with water. The white crystals were redissolved in diethylether and washed with 100 ml water, and then dried over $MgSO_4$. The solvent was removed *in vacuo* to give 12.9 g (70.8 mmol, 50%) of product as a white solid. ^1H NMR (400 MHz,$CDCl_3$):): δ 1.58 (s, 12H; **CH_3**), 1.98 (s, 4H; **CH_2**); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 29. 55 (s, **CH_3**), 37.66 (s, **CH_2**), 52.95 (s, $C(CH_3)_2$); Anal. Calcd. for $C_8H_{16}Cl_2$: C 52.47, H 8.81; found C 52.55, H 8.97; m.p. = 62-64 °C.

4.4.5 Synthesis of 1,1,4,4,6-pentamethyl-1,2,3,4-tetrahydronaphthalene 17

This compound was synthesised as described.[17] To a 250 ml round bottomed flask fitted with a magnetic stirring bar and reflux condenser were added of 2,5-dichloro-2,5-dimethylhexane (10 g, 54.5 mmol), toluene (10 g, 110 mmol), and 50 ml of DCM. To this vigorously stirred solution was slowly added $AlCl_3$ (100 mg 0.75 mmol) which resulted in rapid evolution of gaseous HCl. The reaction mixture was stirred at room temperature for 30 min followed by reflux for an additional 15 min to give a red solution. After cooling, 10 ml of 20% aqueous HCl was added to the stirred solution, and the reaction mixture turned clear / white. The organic layer was washed with water and extracted with 2 x 100 ml of hexane, dried over $MgSO_4$, filtered, and concentrated. Kugelrohr distillation (40-100 °C, 3 x 10^{-4} torr) gave an analytically pure sample (10.5 g, 51.9 mmol, 92%).

^1H NMR (400 MHz, $CDCl_3$): δ 1.46 (s, 6H; $\mathbf{(CH_3)_2}$), 1.47 (s, 6H; $\mathbf{(CH_3)_2}$), 1.86 (s, 4H; $\mathbf{(CH_2)_2}$), 2.49 (s, 3H; Ar-$\mathbf{CH_3}$), 7.15 (d, ^3J(H,H) = 8 Hz, 1H; **Ar**), 7.30 (s, 1H, **Ar**), 7.39 (d, ^3J(H,H) = 8 Hz, 1H; **Ar**); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 20.82 (s, Ar-CH_3), 31.55 (s, $\mathbf{CH_3}$), 31.66 (s, $\mathbf{CH_3}$), 33.78 ($\mathbf{CH_2}$), 33.82 ($\mathbf{CH_2}$), 34.89 (s, $(CH_3)_2$**C**-), 34.94 (s, $(CH_3)_2$**C**-), 126.07, 126.24, 126.64, 134.36, 141.48, 144.33 (s, **Ar**); MS (EI): m/z: 202 [M^+], 187 [$M\text{-}Me^+$]; Anal. Calcd. for $C_{15}H_{22}$: C 89.04, H 10.96; found C 89.02, H 11.13; m.p. 30-32 °C

4.4.6 Synthesis of 1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalene-2-yl)-ethanone 19

To a 250 ml three-necked round bottomed flask fitted with a magnetic stirring bar and a reflux condenser containing acetyl chloride (2.3 g, 29.7 mmol, 1.2 equiv.) and 50 ml of DCM was added 1,1,4,4,6-pentamethyl-1,2,3,4-tetrahydronaphthalene (5 g, 24.8 mmol, 1 equiv.) followed by slow addition (Ca. 0.5 portions) of $AlCl_3$ (7.5 g, 56.2 mmol). The brown mixture was stirred for 30 min and then heated at reflux for 15 min. Additional $AlCl_3$ (1-2 g) was necessary to effect the completion of the reaction. The cooled reaction mixture was poured into 200 ml of vigorously stirred ice water followed by acidification with 20% aqueous hydrochloric acid 50 ml and addition of 100 ml of ethyl acetate. Stirring was continued until the organic layer was yellow 15 min. The organic layer was extracted with ethylacetate (2 x 100 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Kugelrohr distillation (80-120 °C, 3×10^{-4} torr) gave an analytically pure sample 5.31 g (21.8 mmol, 88%) as a white solid.

^1H NMR (400 MHz, C_6D_6): δ 1.16 (s, 3H; **CH_3**), 1.17 (s, 3H; **CH_3**) 1.54 (s, 4H; **$(CH_2)_2$**), 2.21 (s, 3H; $ArCH_3CO$**CH_3**), 2.59 (s, 3H; Ar-**CH_3**), 7.08 (s, 1H; **Ar**), 7.56 (s, 1H; **Ar**); $^{13}C\{^1H\}$ NMR (100 MHz, C_6D_6): δ 21.43 (s, Ar-**CH_3**), 28.67 ($ArCO$**CH_3**), 31.34 (s, CH_3), 31.64 (s, CH_3), 33.69 (s, $(CH_3)_2C$-), 34.10 (s, $(CH_3)_2C$-), 35.02 (s, CH_2), 35.12 (s, CH_2) 130.07, 130.23, 135.48, 135.76, 141.96, 148.36 (s, **Ar**), 199.64 (s, $ArCOCH_3$); MS (EI): m/z: 244 [M^+], 229 [$M\text{-}Me^+$]; Anal. Calcd. for $C_{17}H_{24}O$: C 83.55, H 9.90, O 6.55; found C 83.57, H 9.97; m.p. 54-56 °C.

4.4.7 Synthesis of 6-isopropenyl-1,1,4,4,7-pentamethyl-1,2,3,4-tetrahydronaphthalene 20

In a nitrogen-filled glove box, to 250 ml round bottomed flask fitted with a magnetic stirring bar containing 1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalene-2-yl)-ethanone (0.5 g, 2.05 mmol, 1 equiv.) and 50 ml of dry THF was added [$^{+}PPh_3MeI^{-}$] (1.24 g, 3.07 mmol, 1.5 equiv.), followed by ^{t}BuOK (343 g, 3.06 mmol, 1.5 equiv.). The mixture was stirred at room temperature. After 24 h, *in situ* GC/MS analysis showed a complete conversion of the carbonyl compound to the alkene product. The mixture was filtered to remove the salt. The solvent was removed *in vacuo* and the resulting solid was redissolved in hexane and then cooled in the refrigerator for 24 h to crystallise the PPh_3O. The mixture was filtered and cooled again crystallisation to remove additional PPh_3O. This step has to be repeated at least 4 times to remove all of the PPh_3O. Finally, the solvent was removed *in vacuo* to obtain the pure alkene. Alternatively, a faster method of purification, after removal of the salt by filtration, involves concentrated *in vacuo* and then Kugelrohr distillation (100-140 °C, 3 x 10^{-4} torr), which gave an analytically pure sample (396 mg, 1.64 mmol, 80%). ^{1}H NMR (400 MHz,C_6D_6): δ 1.25 (s, 12H; **$(CH_3)_4$**), 1.59 (s, 4H; **$(CH_2)_2$**), 1.94 (s, 3H; Ar**CH_3**$C=CH_2$), 2.25 (s, 3H; Ar-**CH_3**), 4.91 (s, 1H; $ArCH_3C=$**CH_2**), 5,13 (s, 1H; $ArCH_3C=$**CH_2**), 7.13 (s, 1H; **Ar**), 7.21 (s, 1H; **Ar**); $^{13}C\{^{1}H\}$ NMR (100 MHz, C_6D_6): δ 19.48 (s, Ar-CH_3), 24.31 (s, $ArCH_3C=CH_2$), 31.80 (s, CH_3), 31.84 (s, CH_3), 33.78 (s, $(CH_3)_2C$), 33.81 (s, $(CH_3)_2C$), 35.89 (s, CH_2), 35.92 (s, CH_2), 35.89 (s, CH_2), 114.33 (s, $ArCH_3C=CH_2$), 125.91, 133.71, 134.71, 141.43, 142.23 143.24 (s, **Ar**) 146.45 (s, $ArCH_3C=CH_2$); MS (EI): m/z: 242 [M^{+}], 228 [$M-Me^{+}$]; Anal. Calcd. for $C_{18}H_{26}$: C 89.19, H 10.81; found C 89.11, H 10.76; m.p. 39-40 °C.

4.4.8 Synthesis of 6-(2-Bpin-1-methyl-vinyl)-1,1,4,4,7-pentamethyl-1,2,3,4-tetrahydronaphthalene 21

In a nitrogen-filled glove box, to a solution of *trans*-[Rh(Cl)(CO)(PPh$_3$)$_2$] (28.5 mg, 41.3 x 10^{-3} mmol, 5 mol%) in 2 ml of a mixture of toluene / acetonitrile (3:1) was added B$_2$pin$_2$ (201 mg, 0.79 mmol, 1 equiv.) and 6-isopropenyl-1,1,4,4,7-pentamethyl-1,2,3,4-tetrahydronaphthalene (200 mg, 826 x 10^{-3} mmol) in 2 ml of 3:1 toluene / acetonitrile (4 ml total solvent volume). The mixture was shaken vigorously to ensure complete mixing, transferred to ampoules sealed with a Teflon Young's tap and then heated to 80°C. The reaction was monitored by *in situ* GC/MS. After 3 d, the solvent was removed *in vacuo* and the resulting solid was redissolved in a mixture of hexane / DCM (60:40), and then chromatographed on silica gel eluting with hexane / DCM (60:40) to yield 151 mg (410 x 10^{-3} mmol, 50%) of product as a white solid.

^{1}H NMR (400 MHz,C$_6$D$_6$): δ 1.11 (s, 12H; **Bpin**), 1.21 (s, 3H; **CH$_3$**), 1.24 ((s, 3H; **CH$_3$**), 1.58 (s, 4H; **CH$_2$**), 2.25 (s, 3H; **CH$_3$**), 2.55 (s, 3H; **CH$_3$**), 5.80 (s, 1H; ArCH$_3$C=**CH**Bpin), 7.11 (s, 1H; **Ar**), 7.23 (s, 1H; **Ar**); ^{13}C{^{1}H} NMR (100 MHz, C$_6$D$_6$): δ 19. 83 (s, **CH$_3$**), 23.56 (s, **CH$_3$**), 25.10 (s, BO$_2$C$_2$(**C**H$_3$)$_4$), 32.10 (s, **CH$_3$**), 32.22 (s, **CH$_3$**), 34.10 (s, **CH$_2$**), 34.33 (s, **CH$_2$**), 35.72 (s, **C**(CH$_3$)$_2$), 35.89 (s, **C**(CH$_3$)$_2$), 82.84 (s, BO$_2$**C$_2$**(CH$_3$)$_4$), 125.50, 128.72, 129.35, 142.16, 143.41, 144.93 (s, **Ar**), 162.58 (s, ArCH$_3$**C**=CHBpin); the resonance for the carbon attached to boron was not observed; ^{11}B{^{1}H} NMR (128.4 MHz, C$_6$D$_6$): δ 31.64 (s, br); ; MS (EI): m/z: 368 [M$^+$], 353 [M-Me$^+$]; Anal. Calcd. for C$_{24}$H$_{37}$BO$_2$: C 78.25, H 10.12; found C 78.12, H 9.98; m.p. = 78-80 °C.

4.4.9 Synthesis of 1,1,4,4,5,5,8,8-octamethyl-1,2,3,4,5,6,7,8-octahydro-anthracene 23

To a 250 ml round bottomed flask fitted with a magnetic stirring bar and reflux condenser were added 2,5-dichloro-2,5-dimethylhexane (10 g, 55 mmol, 2 equiv.), benzene (caution: carcinogen) (4.3 g, 55 mmol, 1 equiv.), and 50 ml of DCM. To this vigorously stirred solution was slowly added $AlCl_3$ (100 mg, 0.75 mmol) which resulted in rapid evolution of gaseous HCl. The reaction mixture was stirred at room temperature for 30 min followed by reflux for an additional 15 min to give a red solution. After cooling, 10 ml of 20% aqueous hydrochloric acid was added to the stirred solution, and the reaction mixture turned cloudy white. The organic layer was washed with water and extracted with 2 x 100 ml hexane, dried over $MgSO_4$, and the solvent was removed *in vacuo* to give the product (14.5 g, 48.6 mmole, 44.2%). A small amount of product was sublimed using Kugelrohr distillation apparatus (200-260 °C, 3×10^{-4} torr) for elemental analysis. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1,33 (s, 24H; **$(CH_3)_4$**), 1.73 (s, 8H; **$(CH_2)_2$**), 7.20 (s, 2H; Ar); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 32 (s, CH_3) 33.98 (s, CH_2), 35.41 (s, $(CH_3)_2C$), 124.03, 141.69 (s, **Ar**); MS (EI): m/z: 298 [M^+], 283 [$M\text{-}Me^+$]; Anal. Calcd. for $C_{22}H_{34}$: C 88.52, H 11.48; found C 88.41, H 11.43; m.p. 202-204°C.

4.4.10 Reaction of 2,5-dichloro-2,5-dimethylhexane with benzene in neat benzene

To a 150 ml round bottomed flask fitted with a magnetic stirring bar and reflux condenser were added 2,5-dichloro-2,5-dimethylhexane (2 g, 11 mmol) and benzene (caution: carcinogen) 50 ml. To this vigorously stirred solution was slowly added $AlCl_3$ (28 mg, 0.217 mmol) which resulted in rapid evolution of gaseous HCl. The reaction mixture was stirred at room temperature for 30 min followed by reflux for an additional 15 min to give a red solution. *In situ* GC/MS showed 52% selectivity for compound **6** and 48% selectivity for **23**.

4.4.11 *In situ* formation of 6-isopropenyl-1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphthalene 11, by Suzuki-Miyaura cross coupling reaction

In a nitrogen-filled glove box, to an ampoule sealed with a Teflon Young's tap containing a solution of 6-Bpin-1,1,4,4-tetramethyl-1,2,3,4-tetrahydro-naphthalene (100 mg, 0.318 mmol), and 2-bromopropene (38.2 mg, 0.318 mmol) in 2 ml of THF was added a solution of $[Pd(PPh_3)_4]$ (18 mg, 15.6×10^{-3} mmol, 5 mol%) 4 ml total volume of THF. To this mixture, K_3PO_4 (135 mg, 0.636 mmol, 2 equiv.) was added under nitrogen, and then the reaction mixture was heated at 80 °C. After 24 h, *in situ* GC/MS shows 22% conversion of the boronate ester compound to alkene.

4.5 Crystallography

The X-ray data sets for compounds **7**, **19** were collected on a SMART 1K, **17** and **21** with SMART 6K with CCD area detectors, **13** and **23** APEX with CCD area detectors, using graphite-monochromated sealed-tube Mo-K_α radiation λ = 0.71073 Å. The data collections were carried out at 120(2) K for all using cryostream (Oxford cryosystem) open flow N_2 cryostats. Reflection intensities were crystals integrated using the *SAINT* program.[46] The crystal structures were solve using direct-methods and refined by full matrix least-squares against F^2 of all data using *SHELXTL* software.[47] All non-hydrogen atoms were refined anisotropicaly. All hydrogen atoms were placed in calculated positions and refined using a riding model. Crystal data and experimental details are listed in Table 1.

4.5.1 Molecular structure of 6-Bpin-1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphthalene 7

Monoclinic crystals of 6-Bpin-1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphthalene **7** (space group $P2_1/n$ with Z = 4), were grown by slow evaporation of a hexane solution.

4.4.2 Molecular structure of 6-(2-Bpin-1-methyl-vinyl)-1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphthalene 13

Orthorhombic crystals of 6-(2-Bpin-1-methyl-vinyl)-1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphthalene **6** (space group Pbca with Z = 8), were grown by recrystalisation of compound **6** from a mixture of ethyl acetate and methanol (1:2).

4.4.3 Molecular structure of 1,1,4,4,6-Pentamethyl-1,2,3,4-tetrahydronaphthalene 17

Monoclinic crystals of 1,1,4,4,6-pentamethyl-1,2,3,4-tetrahydronaphthalene (space group $P2_1/c$ with Z = 8), were grown from slow evaporation of a DCM solution.

4.4.4 Molecular structure 1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)-ethanone 19

Monoclinic crystals of 1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)-ethanone (space group $P2_1/c$ with Z = 4), were grown from slow evaporation of a hexane solution.

4.4.5 Molecular structure of 6-(2-Bpin-1-methyl-vinyl)-1,1,4,4,7-pentamethyl-1,2,3,4-tetrahydronaphthalene 21

Triclinic crystals of 6-(2-Bpin-1-methyl-vinyl)-1,1,4,4,7-pentamethyl-1,2,3,4-tetrahydronaphthalene (space group P-1 with Z = 2), were grown from slow evaporation of a DCM solution.

4.4.6 Molecular structure of 1,1,4,4,5,5,8,8-octamethyl-1,2,3,4,5,6,7,8-octahydro-anthracene 23

Monoclinic crystals of of 1,1,4,4,5,5,8,8-octamethyl-1,2,3,4,5,6,7,8-octahydro-anthracene (space group $P2_1/n$ with Z = 2), were grown from slow evaporation of a DCM solution. The molecules lie on a crystallographic inversion centre so that the asymmetric unit contains one half of a molecule.

Table 4.4.1

Compound	**7**	**13**	**17**
Empirical formula	$C_{20}H_{31}BO_2$	$C_{23}H_{35}BO_2$	7/8 ($C_{15}H_{22}$) · 1/8($C_{16}H_{24}$)
Formula weight	314.26	354.32	204.08
Temperature / K	120(2)	120(2)	120(2)
Crystal system	Monoclinic	Orthorhombic	Monoclinic
Space group	$P2_1/n$	Pbca	$P2_1/c$
a / Å	15.673(3)	12.590(3)	10.251(3)
b / Å	6.067(1)	16.372(4)	23.035(6)
c / Å	20.061(4)	20.447(5)	11.836(3)
α / β / γ / deg.	90 / 101.81(1) / 90	90 / 90 / 90	90 / 112.59(1) / 90
Volume / Å^3	1867.2(6)	4214.6(18)	2580.4(12)
Z	4	8	8
D_c / Mg · m^{-3}	1.118	1.117	1.051
μ / mm^{-1}	0.069	0.068	0.058
Crystal size / mm^3	0.4 × 0.12 × 0.04	0.26 x 0.15 x 0.12	0.60 x 0.32 x 0.25
Θ range / deg.	1.51 to 27.50	2.27 to 27.49	1.77 to 29.00
Reflections collected	19576	39296	31662
Independent reflections	4285	4833	6840
Goodness-of-fit on F^2	1.055	0.950	1.025
$R_{(int)}$	0.0579	0.0442	0.0495
wR(F^2) (all data)	0.1367	0.1168	0.1515
R[I>2σ(I)]	0.0579	0.0442	0.0495
Refined parameters	224	269	308
Largest diff. peak and hole / e$^-$ Å^{-3}	0.354 and -0.259	0.313 and -0.226	0.387 and -0.259

Table 4.4.1 (Cont'd)

Compound	**19**	**21**	**23**
Empirical formula	$C_{17}H_{24}O$	$C_{24}H_{37}BO_2$	$C_{22}H_{34}$
Formula weight	244.36	368.35	298.49
Temperature / K	120(2)	120(2)	120(2)
Crystal system	Monoclinic	Triclinic	Monoclinic
Space group	$P2_1/c$	P-1	$P2_1/n$
a / Å	10.0785(12)	9.9972(6)	9.5088(9)
b / Å	13.9074(17)	10.4850(7)	9.7796(9)
c / Å	10.5905(13)	11.2430(8)	10.4057(10)
α / β / γ / deg.	90 / 95.808(2) / 90	96.524(2) / 97.066(2) / 102.994(2)	90 / 110.163(4) / 90
Volume / Å^3	1476.8(3)	1127.37(13)	908.35(24)
Z	4	2	2
D_c / Mg · m^{-3}	1.099	1.085	1.091
μ / mm^{-1}	0.066	0.066	0.060
Crystal size / mm^3	0.45 x 0.40 x 0.35	0.45 x 0.40 x 0.15	0.32 x 0.27 x 0.16
Θ range / deg.	2.03 to 30.24	1.84 to 30.54	2.95 to 30.03
Reflections collected	10343	15730	10555
Independent reflections	4006	6848	2653
Goodness-of-fit on F^2	4006	1.072	1.064
$R_{(int)}$	0.0451	0.0559	0.0417
$wR(F^2)$(all data)	0.1249	0.1649	0.1164
$R[I>2\sigma(I)]$	0.0451	0.0559	0.0417
Refined parameters	259	272	168
Largest diff. peak and hole / e$^-$ Å^{-3}	0.375 and -0.167	0.571 and -0.555	0.450 and -0.178

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