THE UNIVERSITY
of EDINBURGH

Transborylation: Borane-catalysed Hydroboration and Hidden Catalysis

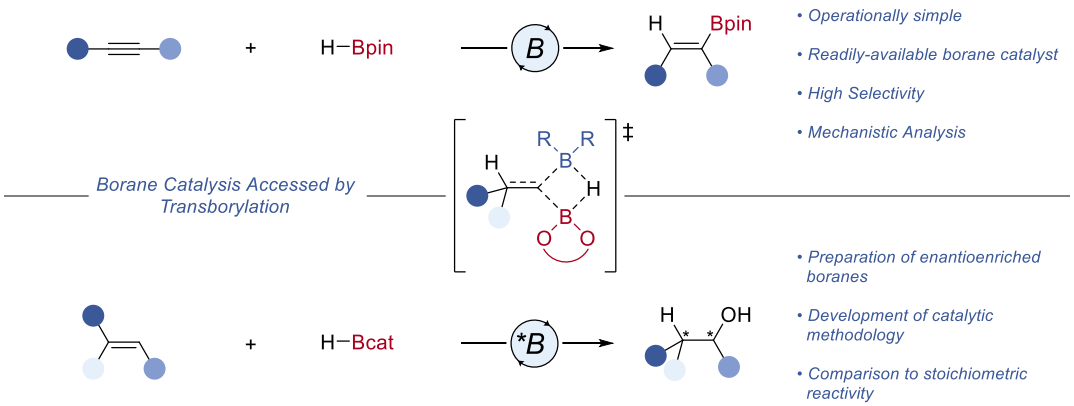
Andrew Dougal Bage

A thesis submitted for the degree of Doctor of Philosophy

2021

Abstract

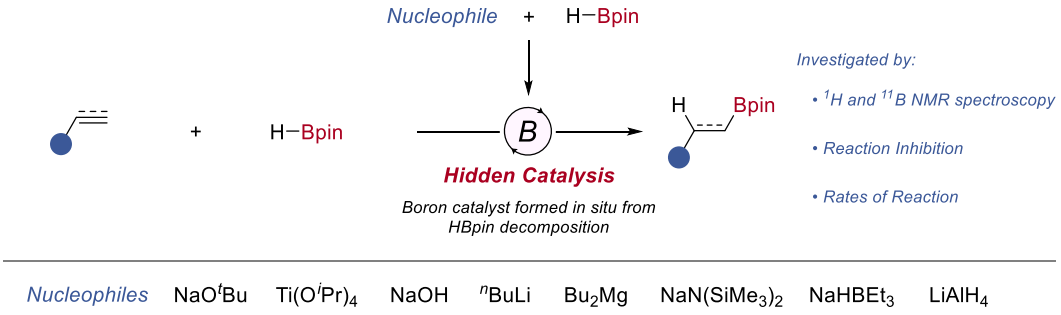
Hydroboration is a textbook reaction, finding application in total synthesis and the fine chemicals industry. The versatility of the organoborane products to be transformed into an array of different functionalities makes the reaction a valuable intermediary in multi-step syntheses. Traditionally, hydroboration was performed using stoichiometric borane reagents, but this was gradually superseded by transition metal-catalysed hydroboration systems. The established metal catalysts are typically based on scarce or expensive transition metals, of which some are toxic. When developing new catalysts for a known transformation, the system must provide a benefit over previous systems, be it through orthogonal reactivity, increased sustainability, or improved chemoselectivity, leading to increased potential to be used in late-stage functionalisation. A potential sustainable alternative to the standard transition metal catalysts is to use a catalyst based upon main-group elements. However, the traditional mechanisms of transition metal catalysis (oxidative addition and reductive elimination) cannot be easily applied to main group catalysts. Therefore, new turnover mechanisms are required to support the development of useful main-group catalysts. Transborylation is a redox-neutral turnover step that transforms stoichiometric borane reagents into catalysts, providing a platform to use the extensive knowledge base of stoichiometric borane reduction to develop new metal-free catalyst systems that could potentially rival transition metal catalysts. Transborylation has been used to develop a borane-catalysed hydroboration of alkynes with HBpin, showing impressive selectivity, and has been used to provide preliminary results for a borane-catalysed enantioselective hydroboration of alkenes (Scheme A1).



Scheme A1. The Application of Transborylation in Hydroboration Catalysis

Abstract

The importance of the hydroboration reaction has resulted in catalysed hydroboration becoming a benchmark with which to test new catalysts. Nucleophiles are abundant in catalyst architectures, as ligands and exogenous activators, and in catalysts that are inherently nucleophilic. Nucleophiles with structural similarities to known hydroboration catalysts were shown to mediate the decomposition of HBpin to active boron-based catalysts, which were the true catalysts of the hydroboration of alkynes and alkenes with HBpin. Hidden boron catalysis was shown to operate in systems for the hydroboration of alkynes and alkenes, previously proposed to be catalysed by nucleophilic catalysts (Scheme A2).



Scheme A2. Hidden Boron Catalysis

Lay Summary

A catalyst is a species that promotes a reaction that otherwise would not proceed or helps a reaction to proceed more readily, allowing the user to convert simple starting materials into valuable products. The catalyst is not destroyed in the process, leading to the potential reuse of the catalyst for subsequent reactions. Catalysis is integral to the bulk and fine chemicals industry (e.g. pharmaceutical and agrochemical companies). There are many reasons to develop new catalysts for a reaction, including reduced costs, environmental impact, and waste. The preparation of valuable products (e.g. medicines and pesticides) typically occurs over several steps, building up complexity in the product in each step. A catalyst system that can tolerate the presence of more complexity is particularly beneficial to the fine chemicals industry as it can be used in the final stages of the multi-step preparation. Therefore, this is a key focus in the development of new catalysts. Using boron-based compounds as catalysts for reactions offers a non-toxic, metal-free alternative to the standard metal-based catalysts used by industry. A boron-based catalyst system for a widely-used reaction in the fine chemicals industry has been developed, tolerating a high level of complexity, making it an attractive alternative to the standard catalysts for this reaction.

Understanding the manner in which a catalyst works is essential to the development of new catalysts. Therefore, investigations to comprehend this boron-catalysed system have been performed. In the constant drive to develop new catalysts for a reaction, understanding the way the catalyst works is sometimes overlooked. These boron catalysts can be formed accidently by other catalysts, including metal-based catalysts. Investing time and money into making a new catalyst that only works by forming the boron catalysts in the reaction can lead to a waste of resources, as the boron catalysts are commercially available. This has been shown by taking several catalysts developed for industrially-relevant reactions and investigating their role in the reaction, where they are merely acting to form boron catalysts accidently.

Declaration

I certify:

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

b) either that the work is my own, or, where I have been a member of a research group, that I have made a substantial contribution to the work, such contribution being clearly indicated, and

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

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

Andrew D. Bage

Acknowledgements

First of all, I would like to thank my supervisor Dr Stephen Thomas for his help and encouragement throughout my PhD. His confidence in me helped to increase my self-belief and his affable temperament created a supportive and stimulating work environment. I would like to thank AstraZeneca for funding my PhD and my industrial supervisor Dr Thomas Hunt for his helpful contributions to my PhD projects and his welcoming nature during my industrial placement with AZ.

The Thomas group has been a great place to work these past four years and I would like to thank everyone who has been part of the group during that time for making it so. In particular, I would like to thank Jon and Peter for involving me in football from the start of my PhD; Riaz, Alessandro, and Jamie for teaching me new experimental techniques and being my lab mates over the years; Joanne, whose friendship and incessant questions immediately made me feel part of the group; and Kieran, Dom, Luke, and Alex, who made the second half of my PhD as good as the first. Thanks again to Kieran, Dom, Luke, Joanne, and Steve for proof-reading my thesis. Thanks to the University of Edinburgh technical and analytical staff, without whom the completion of this PhD would not have been possible. Also, thanks to everyone who has ever played 5s or 11s with me, Thursday night football was often the highlight of my working week!

Thanks to my friends (and flatmates) Jack, Jacob, and Aaron. Our flat was a great place to live, the constant laughs and ridiculous moments were a brilliant tonic to the stresses of PhD life. Also, thanks to Helen, Caitlin, and Ellie, whose company during the first lockdown made a difficult time for everyone far more bearable. Thank you to all my friends who came to visit me in Edinburgh over the years: Chris, Matt, Bradley, Alex, Abby, Millard, Jack, Katy, Matt, and Karla, whose visits were welcomed distractions from my PhD.

I would not be here and would not have completed my PhD without the love and support from all of my family. My parents and my brother, Thomas, are always there for me; something I cherish and try to never take for granted.

I would like to dedicate my thesis to John S.W. Wilson (1929-2021).

Contents

Abbreviations

Ar	Aryl
Ar^F	3,5-Bis(trifluoromethyl)-phenyl
Ar_F	4-Fluorophenyl
BBN	Borabicyclo[3.3.1]nonane
BINAP	2,2′-Bis(diphenylphosphino)-1,1′-binaphthalene
calc	Calculated
cat	Catecholato
COD	1,4-Cyclooctadiene
Cy	Cyclohexyl
DFT	Density Functional Theory
DG	Directing Group
DME	Dimethoxyethane
DIOP	2,3-*O*-*iso*-Propylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
e.e.	Enantiomeric Excess
e.f.	Enantiofidelity
equiv.	Equivalents
ESI	Electrospray Ionisation
Et	Ethyl
FLP	Frustrated Lewis Pair
gem	*Geminal*
HPLC	High-Performance Liquid Chromatography
HRMS	High-Resolution Mass Spectrometry
Ipc	*iso*-Pinocampheyl
^{i}Pr	*iso*-Propyl
IR	Infrared
L	Lewis Base
Lgf	Longifolyl
Lim	Limonyl
Me	Methyl
MP	Melting Point
MS	Mass Spectrometry
NBD	Norbornadiene
^{n}Bu	*normal*-Butyl
NCTS	*N*-Cyano-*N*-phenyl-*p*-toluenesulphonamide
NMR	Nuclear Magnetic Resonance
Nu	Nucleophile
obs	Observed

Ph	Phenyl
pin	Pinacolato
Pybox	2,6-Bis(2-oxazolin-2-yl)pyridine
S_EAr	Electrophilic Aromatic Substitution
TADDOL	α,α,α,α-Tetraaryl-1,3-dioxolane-4,5-dimethanol
TBDMS	*tertiary*-Butyldimethylsilyl
^{t}Bu	*tertiary*-Butyl
Tf	Trifluoromethanesulfonate
THF	Tetrahydrofuran
TLC	Thin-Layer Chromatography
TMEDA	*N*,*N*,*N*′,*N*′-Tetramethylethylenediamine

1. Introduction

1.1 Catalysis

Catalysis is integral to organic synthesis and the fine chemicals industry, as it allows for the preparation of high-value, complex products from simple starting materials. The development of new catalytic methodologies helps to broaden chemical space through orthogonal reactivity but also serves to reduce costs, waste, and environmental impact. These factors have become increasingly pertinent in recent years, with research focused on the search for more sustainable methods of synthesis. Traditional catalytic methods typically use platinum group metals such as iridium, rhodium, and palladium. Not only are these metals scare and expensive, but their low permitted daily exposure limits also increase downstream processing requirements in fine chemical synthesis to avoid trace metal contamination.[1-3]

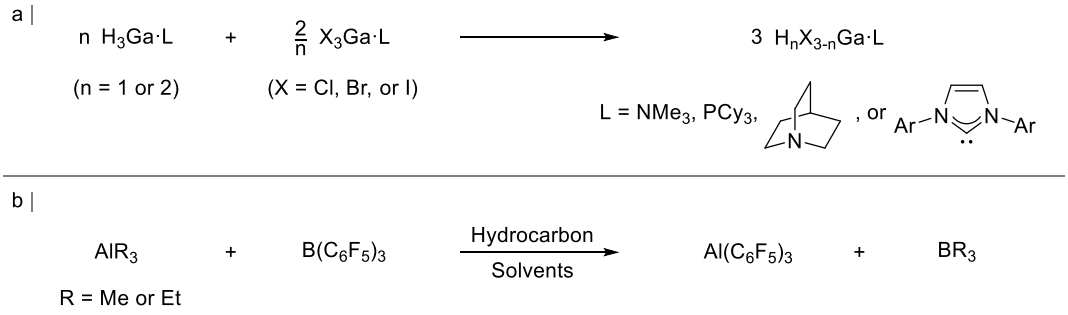
The shift to more sustainable methods of catalysis has led to exploration of alternative catalytic methodologies, including using more Earth-abundant and less toxic elements, with a focus on those from the main-group of the Periodic Table. However, new turnover mechanisms are an essential requirement in the evolution of main-group catalysis. Transition metal catalysis typically proceeds through oxidation and reduction turnover mechanisms, as multiple oxidation states are readily accessed by transition metals. Conversely, many main-group elements do not readily exist in multiple oxidation states, therefore, these turnover mechanisms are not easily translated to the main-group. Consequently, new, redox-neutral turnover mechanisms are vital for main group catalysts to rival established transition metal catalysts.

1.2 Group 13 Stoichiometric Redistribution Reactions

1.2.1 Gallium and Aluminium

The dimeric nature of neutral group 13 reagents containing two bridging 3-centre-2-electron bonds supports the redistribution of groups between the two group 13 centres. Coordinated gallanes and gallium trihalides have been shown to undergo Ga–H/Ga–X redistribution (where X = Cl, Br, or I) to form mixed halogallanes (Scheme 1-1, a).[4-7]

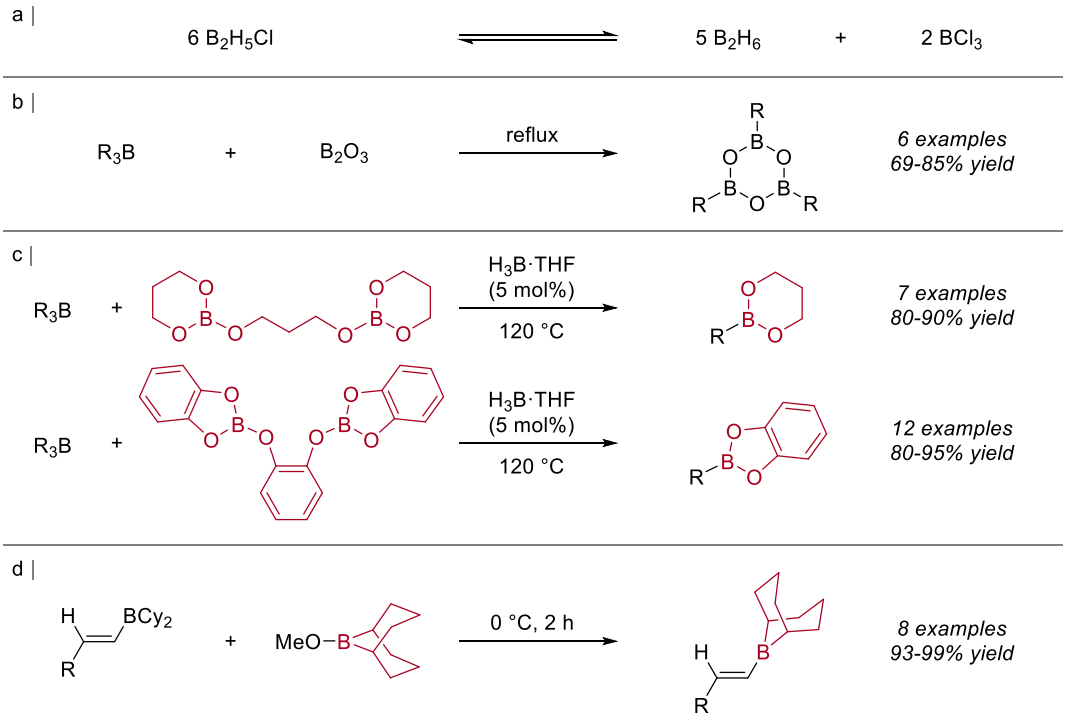
Similarly, trialkylalanes undergo Al–C(sp^3)/B–C(sp^2) redistribution with $B(C_6F_5)_3$ in hydrocarbon solvents to form $Al(C_6F_5)_3$ (Scheme 1-1, b).[8, 9] These redistribution reactions were used as foundations to develop gallium- and aluminium-catalysed hydroboration reactions.[10-12]



Scheme 1-1. a) Gallium-based Redistribution; b) Aluminium Redistribution Reactions

1.2.2 Boron

The stoichiometric redistribution of boranes has been widely studied since Schlesinger's observation that monochlorodiborane (B_2H_5Cl) would undergo B–H/B–Cl redistribution to form diborane (B_2H_6) and boron trichloride (BCl_3) at 0 °C (Scheme 1-2, a).[13] Subsequent redistribution reactions were investigated, including the B–C(sp^3)/B–H redistribution of B_2H_6 with trialkylboranes[6] and $H_3B{\cdot}L$ (L = THF or SMe_2) with trialkylboranes,[7] forming mixtures of BH_3, mono-, di-, and trialkylboranes, and homo- and heterodimers of these boranes, occurring readily at room temperature. The B–C(sp^3)/B–Cl redistribution of trialkylboranes with boron trichloride to dialkylchloroboranes could be achieved at 100 °C, but no redistribution was observed at lower temperatures.[14] Similarly, B–C(sp^3)/B–O redistribution of trialkylboranes with boron trioxide or trimethoxyboroxine occurred slowly under reflux in the absence of solvent to give the alkylboroxine products [$(RBO)_3$] (Scheme 1-2, b).[15, 16] Brown used BH_3 (5 mol%) to promote the B–C(sp^3)/B–H redistribution of trialkylboranes with trimethyleneborate in THF (Scheme 1-2, c).[17] The redistribution occurred readily at 120 °C with both straight-chain and cyclic alkenes, forming the alkyl propanediol boronic esters. After developing the novel 1,3,2-dioxaborolane catecholborane (HBcat), Brown realised the method of preparing alkyl propanediol boronic esters from B–C(sp^3)/B–H redistribution could also be used to prepare alkyl catechol boronic esters from B_2cat_3.[18] Furthermore, Hoshi showed that alkenyldicyclohexylboranes would undergo B–C(sp^2)/B–O redistribution with MeO-*B*-9-BBN (Scheme 1-2, d).[19]



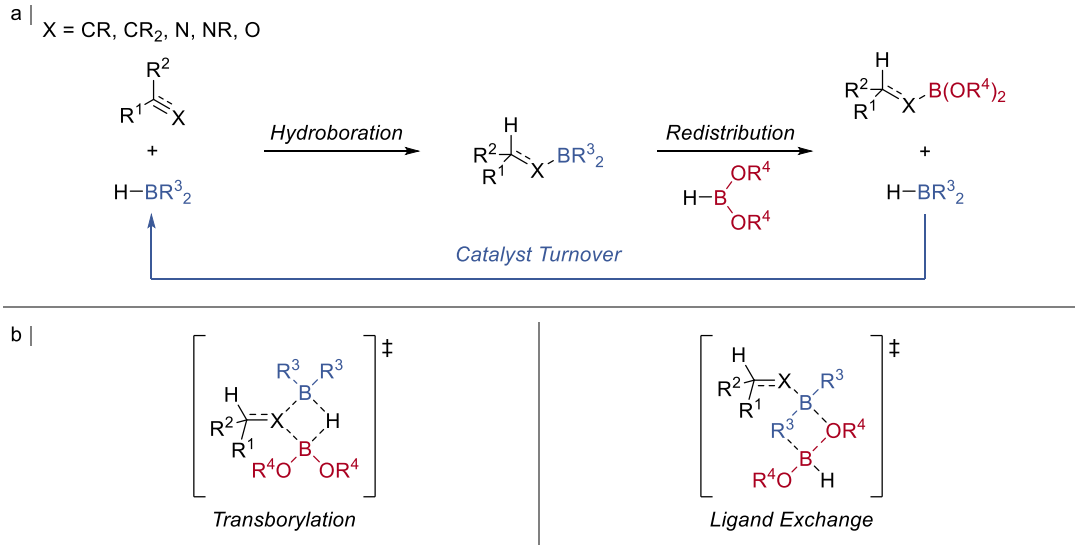
Scheme 1-2. Stoichiometric Redistribution Reactions: a) Redistribution of Monochlorodiborane; b) Preparation of Alkylboroxines; c) Preparation of Alkyl Boronic Esters; d) Redistribution Reactions of Alkenyldicyclohexylboranes with MeO-B-9-BBN

1.3 Transborylation as a Turnover Strategy

1.3.1 Concept

Evidently, stoichiometric redistribution reactions between boron compounds can be controlled to generate useful products. In many instances, the boron compounds that underwent redistribution could be prepared by stoichiometric hydroboration. Therefore, if the stoichiometric processes of hydroboration and redistribution could be combined, a catalytic system could be developed, using redistribution as a means for catalyst turnover (Scheme 1-3, a). This principle has received significant interest and the redistribution process has been referred to as transborylation when used in catalysis.[20] There are two similar but distinct redistribution processes that act as turnover mechanisms for catalysis, herein termed transborylation and ligand exchange (Scheme 1-3, b). In transborylation, the groups of interest are exchanged from boron to boron; in ligand exchange, the backbones of the catalyst and the turnover reagent are exchanged, and the groups of interest remain on the starting boron atoms. There are a small number of boron-based reactions proposed to proceed through ligand

exchange and not transborylation, including the 1,4-addition to α,β-unsaturated ketones,[21-23] and the borane-catalysed hydroboration of *N*-arylsulphonyl indoles.[24]

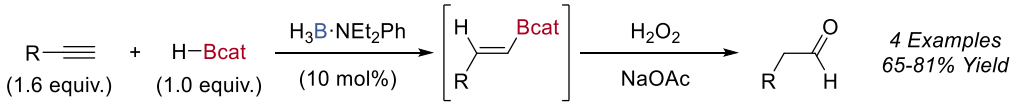


Scheme 1-3. a) Combining Hydroboration and Redistribution to Develop Borane Catalysis; b) Transborylation and Ligand Exchange

1.3.2 B–C(sp^2)/B–H Transborylation

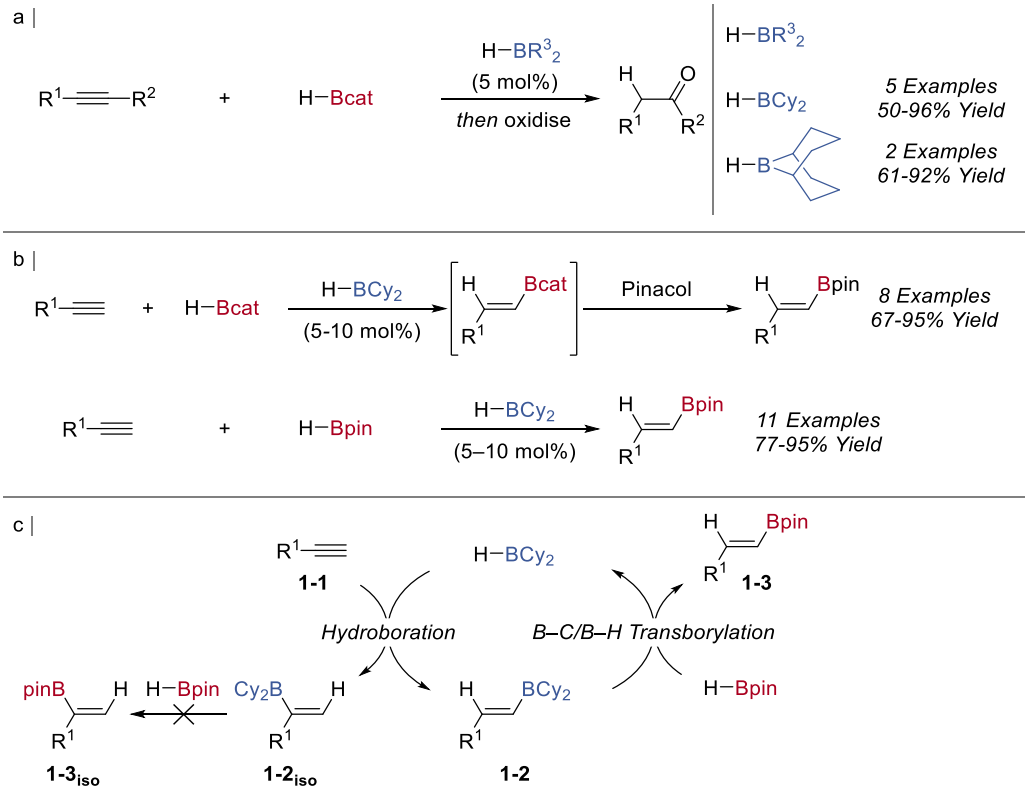
1.3.2.1 Alkyne Hydroboration

Periasamy envisaged a catalytic system which exploited the B–C(sp^2)/B–H redistribution of trialkenylboranes with HBcat to give alkenyl boronic esters. Direct hydroboration of an alkyne with HBcat will only proceed under forcing conditions (100 °C).[18] However, the hydroboration of an alkyne with BH_3 under mild conditions results in the generation of a trialkenylborane which, in the presence of HBcat, could redistribute to form the alkenyl catechol boronic ester and regenerate the catalyst, $R_nBH_{(3-n)}$ (where R = alkenyl, n = 0, 1, or 2). Further equivalents of alkyne could then undergo hydroboration by $R_nBH_{(3-n)}$. Therefore, a substoichiometric quantity of BH_3 could be used, representing the first borane-catalysed alkyne hydroboration. Periasamy showed that alkynes would undergo hydroboration with HBcat, catalysed by $H_3B{\cdot}NEt_2Ph$ (10 mol%) (Scheme 1-4).[25, 26] Oxidation of the alkenyl boronic ester resulted in the formation of aldehydes.



Scheme 1-4. $H_3B{\cdot}NEt_2Ph$-catalysed Hydroboration of Alkynes with HBcat

Similar principles were used by Hoshi to develop the dicyclohexylborane- and H-*B*-9-BBN-catalysed hydroboration of alkynes with HBcat (Scheme 1-5, a), isolating the products as aldehydes following oxidation.[27] Subsequently, Hoshi showed that alkenyl pinacol boronic esters could be formed from the dicyclohexylborane-catalysed hydroboration of alkynes with HBcat, followed by transesterification with pinacol, or by replacing HBcat with HBpin (Scheme 1-5, b).[28] The dicyclohexylborane-catalysed hydroboration of alkynes has since been used in several total syntheses, including the preparations of (-)-FR182877,[29, 30] the C1–C9 segment of dictyostatin,[31] amphidinolide V,[32] (+)-herboxidiene,[33] and mandelalide A.[34]



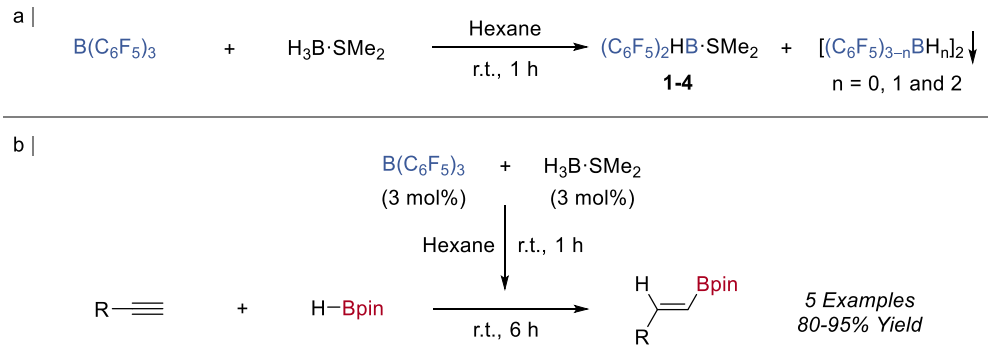
Scheme 1-5. a) Dicyclohexylborane-catalysed Hydroboration of Alkynes with HBcat; b) Dicyclohexylborane-catalysed Hydroboration of Alkynes with HBpin; c) Proposed Mechanism

Hoshi proposed that the reaction proceeds in an analogous manner to that initially postulated by Periasamy (Scheme 1-5, c). First, the alkyne **1-1** undergoes hydroboration by dicyclohexylborane to form the linear alkenylborane intermediate **1-2**; in some cases, the branched regioisomer **1-2$_{iso}$** was observed in small quantities, consistent with stoichiometric hydroboration. The alkenylborane intermediate **1-2** was prepared from stoichiometric hydroboration and used as a catalyst in place of dicyclohexylborane, giving comparable reactivity to dicyclohexylborane. This suggests that the reaction proceeds through initial hydroboration of the alkyne **1-1** with dicyclohexylborane and the alkenylborane intermediate **1-2** is an on-cycle species. The

alkenyl group of the linear alkenylborane intermediate **1-2** is subsequently exchanged with the hydride of HBcat or HBpin through B–C(sp^2)/B–H transborylation, to form the alkenyl boronic ester product **1-3** and concurrently re-form the dicyclohexylborane catalyst. The branched alkenylborane regioisomer **1-2$_{iso}$** appears to not undergo B–C(sp^2)/B–H transborylation, as no branched alkenyl boronic ester **1-3$_{iso}$** was observed. No evidence was provided to support B–C(sp^2)/B–H transborylation but it is comparable to redistribution reactions of alkylboranes with HBcat.[18] Comparable results to dicyclohexylborane were observed by Thomas when $H_3B{\cdot}L$ (L = THF or SMe_2) was used as a catalyst for the hydroboration of alkynes with HBpin (Scheme 1-6).[35]

Scheme 1-6. BH_3-catalysed Hydroboration of Alkynes with HBpin

Hoshi exploited the redistribution process to prepare a new catalyst, bis(pentafluorophenyl)borane-dimethyl sulphide complex **1-4**, from equimolar quantities of $H_3B{\cdot}SMe_2$ and tris(pentafluorophenyl)borane (Scheme 1-7, a).[36] The hydroboration of alkynes with HBpin was efficiently catalysed by bis(pentafluorophenyl)borane-dimethyl sulphide complex **1-4** (Scheme 1-7, b). Hoshi postulated that bis(pentafluorophenyl)borane-dimethyl sulphide complex **1-4** catalyses the reaction by the same mechanism as proposed for dicyclohexylborane, and successfully used the alkenylborane intermediate, formed from the hydroboration of 1-hexyne with bis(pentafluorophenyl)borane-dimethyl sulphide **1-4**, in place of the catalyst to promote the hydroboration of 1-hexyne with HBpin.



Scheme 1-7. a) Formation of Bis(pentafluorophenyl)borane-dimethyl sulphide complex **1-4** from Redistribution; b) Bis(pentafluorophenyl)borane-dimethyl sulphide complex **1-4**-catalysed Hydroboration of Alkynes with HBpin

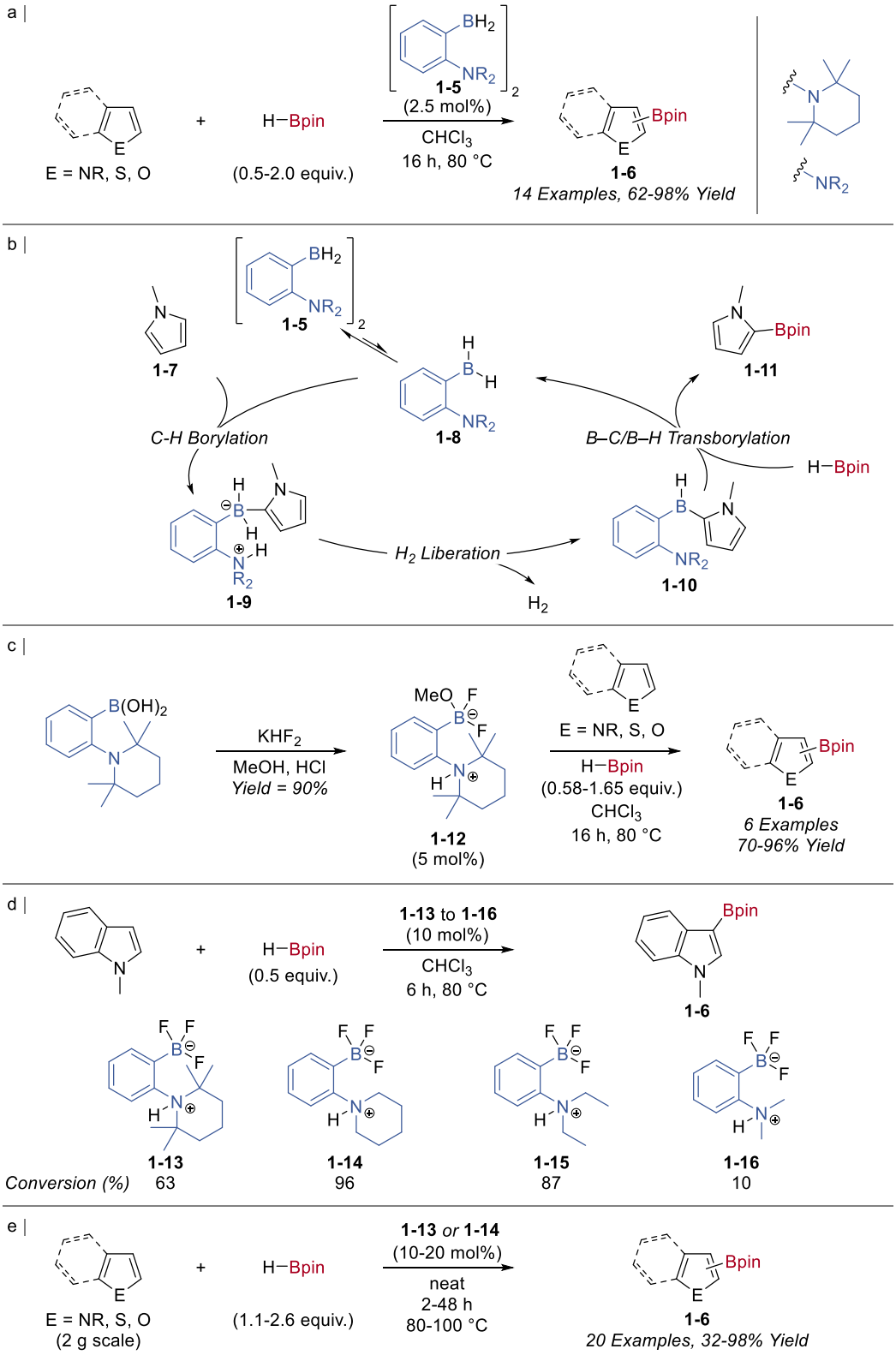
1.3.2.2 Heteroarene Borylation

The C-H borylation of arenes is an indispensable reaction to organic synthesis and the pharmaceutical industry as the products can be used in a range of transformations, including the Suzuki-Miyaura cross-coupling reaction.[37] Therefore, there is significant interest in the development of new methods to generate borylated arenes.[38] Typically catalysed by transition metals such as iridium, introducing metal-free routes to avoid trace metal contamination would represent a notable shift in borylation catalysis. Fontaine developed a boron-based Frustrated Lewis Pair (FLP) **1-5** to catalyse the C-H borylation of heteroarenes with HBpin (Scheme 1-8, a).[39] The borylation of protected pyrroles, *N*-methyl indole, thiophenes and furans proceeded in good yields to give aryl boronic esters **1-6**.

Density Functional Theory (DFT) calculations were used to propose a mechanism for catalysis (Scheme 1-8, b). The heteroarene **1-7** undergoes concerted borylation and deprotonation by the monomeric form of the catalyst **1-8**. The zwitterion **1-9** then releases H_2 to form the neutral intermediate **1-10**. HBpin reacts with the neutral intermediate **1-10** through B–C(sp^2)/B–H transborylation to give the aryl boronic ester product **1-11** and regenerate the catalyst **1-8**.

Fontaine subsequently designed a bench-stable pre-catalyst for the C-H borylation of heteroarenes, preparing a fluoroborate salt **1-12** that could be converted into the active catalyst by reaction with HBpin (Scheme 1-8, c).[40] Comparable reactivity of C-H borylation was observed when the fluoroborate pre-catalyst **1-12** was used in place of the borane catalyst **1-5**. This development increased the utility of the reaction by avoiding the use of specialist equipment, such as a Schlenk line or a glovebox.

Subsequent catalyst design refinement by Fontaine showed that varying the alkyl groups of the amine drastically altered catalyst activity.[41] Using the piperidyl-based FLP catalyst **1-14** resulted in the highest reactivity compared to the other amine substituents tested (**1-13**, **1-15**, **1-16**) (Scheme 1-8, d). Kinetic and DFT analysis suggested that the reduction in steric bulk of the amine changed the rate-determining step from C-H activation to dimer dissociation and H_2 liberation.

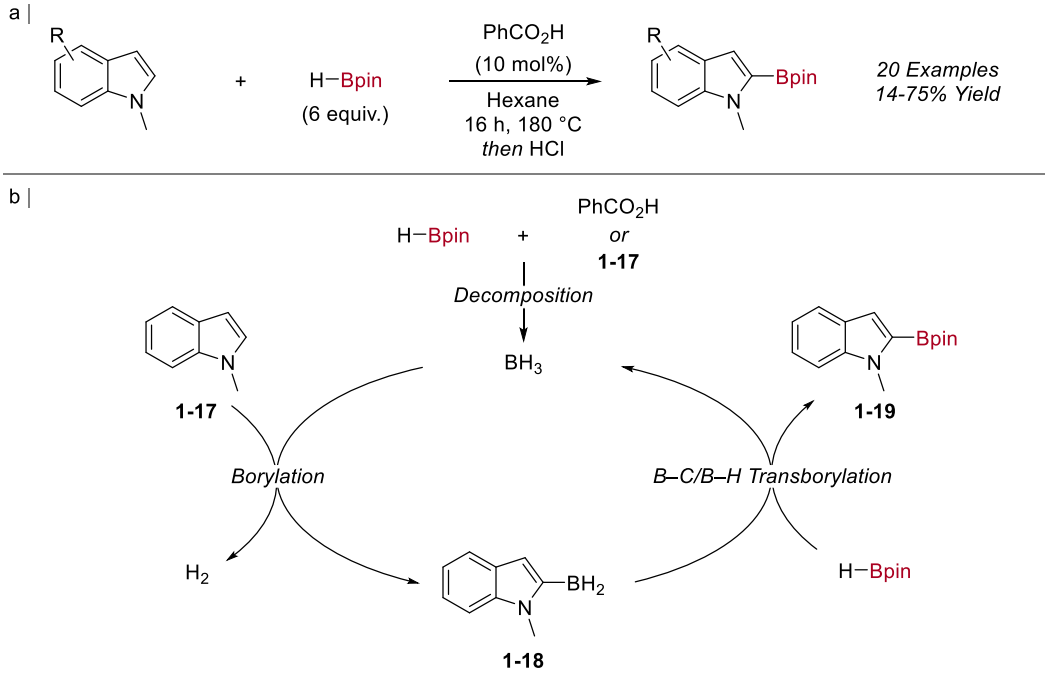


Scheme 1-8. a) Fontaine's Boron-based FLP **1-5**-catalysed C-H Borylation of Heteroarenes with HBpin; b) Proposed Mechanism of C-H Borylation; c) Fluoroborate Pre-catalyst **1-12** Synthesis and Application; d) Effect of Amine Groups on Catalyst Activity; e) Scalable FLP-catalysed C-H Borylation of Heteroarenes with HBpin

To showcase the utility of the reaction to the fine chemicals industry, Fontaine increased the scale of both the catalyst synthesis and the C-H borylation reaction.[42] The pre-catalyst **1-14** was prepared on a 100 g scale in good yield over three steps (55-

59%). An increased scope of the C-H borylation of heteroarenes (protected pyrroles, indoles, and aza-indoles, thiophenes, and furans), performed on a 2 g scale, showed that the reaction tolerated ethers, acetals, halides, and methyl-, benzyl- and silyl-protecting groups for nitrogen-based heteroarenes (Scheme 1-8, e). Nine example heteroarenes were then shown to undergo C-H borylation on a 50 g scale without reduction in reactivity. The C-H borylation of *N*-methylindole with HBpin was performed on a 1 kg scale, obtaining the aryl boronic ester in excellent yield (95%).

The C(2)-H borylation of *N*-methyl indoles **1-17** with HBpin was shown to be promoted by benzoic acid at elevated temperatures (180 °C) (Scheme 1-9, a).[43] Zhang suggested that the benzoic acid or the substrate **1-17** decomposed HBpin to BH_3, which acted as the catalyst (Scheme 1-9, b). Whilst mechanistic investigations were inconclusive, the reaction was proposed to proceed through C-H activation to form the indol-2-yl-BH_2 **1-18** and liberate H_2. B–C(sp^2)/B–H transborylation between the indol-2-yl-BH_2 **1-18** and HBpin generates the aryl boronic ester product **1-19** and re-forms the catalyst, BH_3.

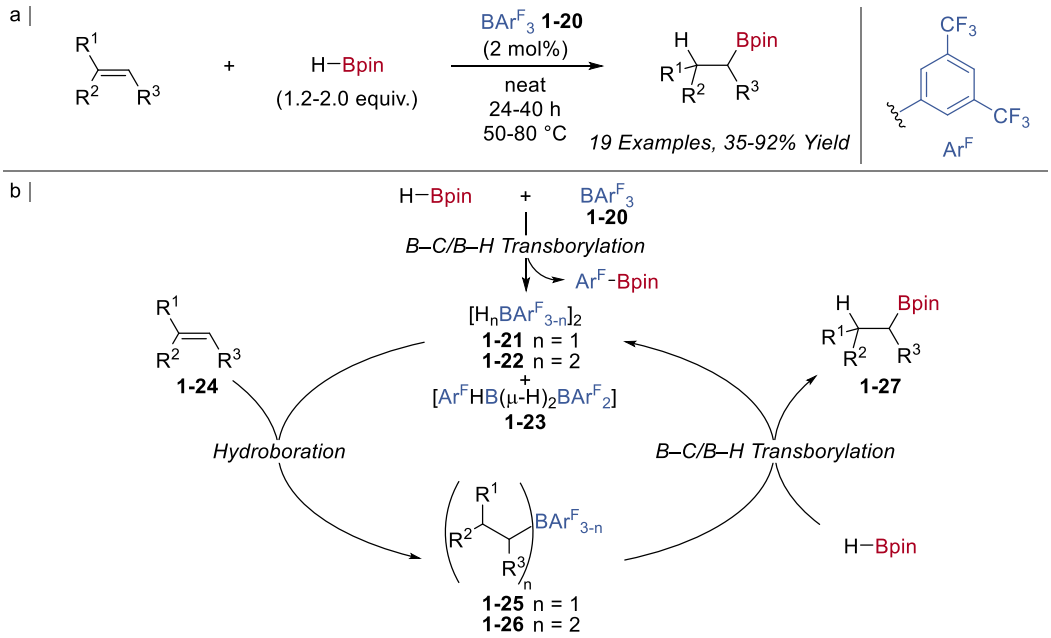


Scheme 1-9. a) Benzoic Acid-promoted C-H Borylation of *N*-Methyl Indoles with HBpin; b) Proposed Mechanism

1.3.3 B–C(sp^3)/B–H Transborylation

1.3.3.1 Alkene Hydroboration

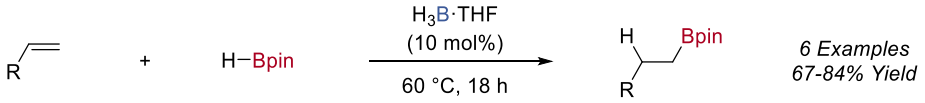
B–C(sp^3)/B–H transborylation has been used in borane-catalysed alkene hydroboration. Oestreich showed that tris[3,5-bis(trifluoromethyl)-phenyl]borane **1-20** promoted the hydroboration of alkenes with HBpin to give alkyl boronic esters in good yield (Scheme 1-10, a).[44] The reaction tolerated ether, halide, internal alkene, and silyl groups. Stoichiometric mechanistic experiments indicated that the mechanism involved two transborylation steps, B–C(sp^2)/B–H transborylation for catalyst activation and B–C(sp^3)/B–H transborylation for product formation and catalyst regeneration (Scheme 1-10, b). Oestreich proposed that B–C(sp^2)/B–H transborylation between tris[3,5-bis(trifluoromethyl)-phenyl]borane **1-20** and HBpin generated a mixture of active catalysts, the hydridoboranes bis[3,5-bis(trifluoromethyl)-phenyl]borane **1-21** and 3,5-bis(trifluoromethyl)-phenylborane **1-22** and the mixed dimer **1-23**. These undergo hydroboration of the alkene **1-24** to form alkylborane intermediates **1-25** and **1-26**, which then undergo B–C(sp^3)/B–H transborylation with HBpin to re-form the catalysts **1-21**, **1-22** and **1-23** and generate the alkyl boronic ester product **1-27**.



Scheme 1-10. a) Tris[3,5-bis(trifluoromethyl)-phenyl]borane **1-20**-promoted Hydroboration of Alkenes with HBpin; b) Proposed Mechanism

The hydroboration of alkenes with HBpin can also be catalysed by $H_3B{\cdot}L$ (L = THF or SMe_2), tolerating trialkoxysilane, ether and fluoride groups (Scheme 1-11).[35] Whilst

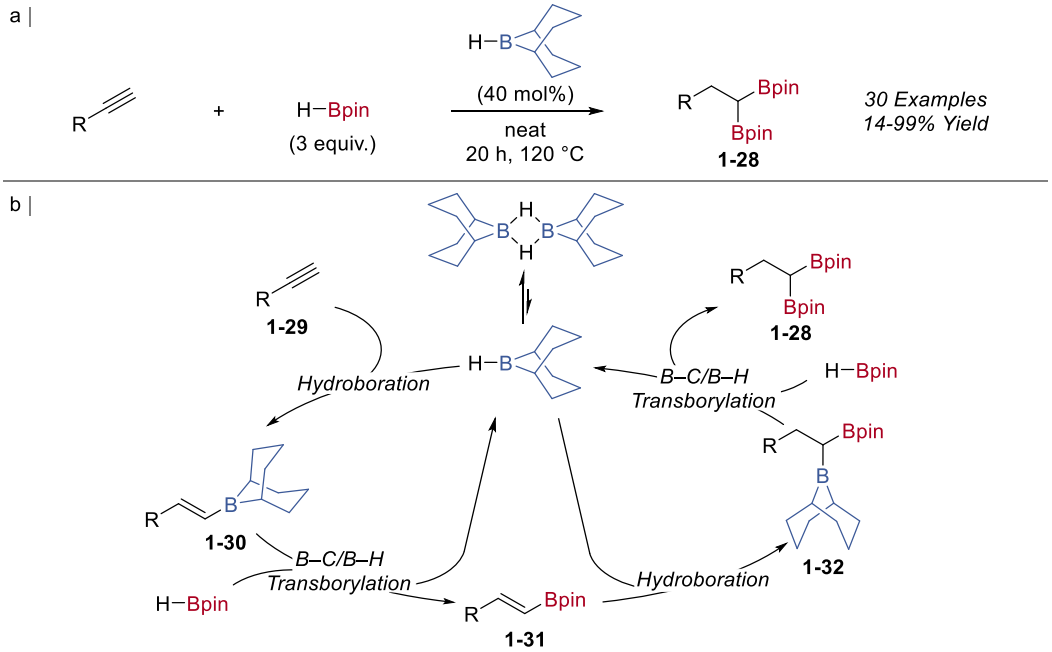
a mechanism was not proposed for the transformation, it is believed to proceed through a hydroboration and B–C(sp^3)/B–H transborylation catalytic cycle.



Scheme 1-11. BH_3-catalysed Hydroboration of Alkenes with HBpin

1.3.3.2 Alkyne Double Hydroboration

The double hydroboration of alkynes with HBpin can be catalysed by H-*B*-9-BBN at elevated temperatures (120 °C) (Scheme 1-12, a).[20] Other boranes (dicyclohexylborane, $H_3B{\cdot}THF$ and $H_3B{\cdot}SMe_2$) showed limited catalytic activity. The reaction conditions were shown to generate *gem*-diborylalkanes **1-28** in good yield and tolerated ether, amine, halide, thiophene, thioether, ferrocene, acetal, and cyclopropane functionalities. A *gem*-diborylalkane containing an ester functional group was isolated in 14% yield, but no other reducible functional groups were shown to tolerate the reaction conditions.



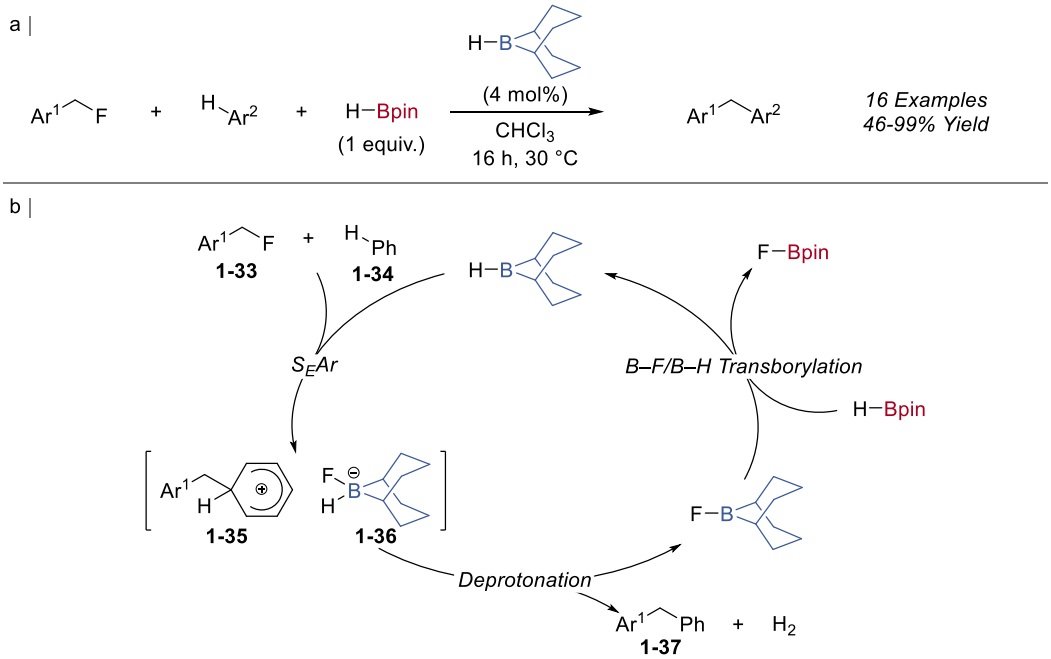
Scheme 1-12. a) H-*B*-9-BBN-catalysed Double Hydroboration of Alkynes with HBpin; b) Proposed Mechanism

Mechanistic studies, including isotopic labelling experiments, led to the proposal of a double transborylation mechanism (Scheme 1-12, b). The alkyne **1-29** undergoes hydroboration by H-*B*-9-BBN to give the alkenylborane **1-30** which then undergoes B–C(sp^2)/B–H transborylation with HBpin to form the alkenyl boronic ester **1-31**, re-

forming H-*B*-9-BBN. The hydroboration of the alkenyl boronic ester **1-31** with H-*B*-9-BBN generates the mixed *gem*-diborylalkane intermediate **1-32**, undergoing B–C(sp^3)/B–H transborylation to give the *gem*-diborylalkane product **1-28** and re-form the catalyst, H-*B*-9-BBN. The cyclic group of H-*B*-9-BBN does not undergo ligand exchange; the alkyl pinacol boronic ester group undergoes transborylation exclusively.

1.3.4 B–F/B–H Transborylation

The arylation of benzylic C-F bonds can be catalysed by H-*B*-9-BBN in the presence of stoichiometric quantities of HBpin (Scheme 1-13, a).[45] The benzyl fluorides were successfully coupled with carbo- and heteroarenes, including furan, thiophene, and *N*-methyl indole. The reaction was shown to tolerate non-benzylic aliphatic fluorides and aryl halides and displayed good regioselectivity. Through a combination of stoichiometric turnover experiments and DFT calculations, a reaction mechanism was proposed (Scheme 1-13, b). The benzyl fluoride **1-33** undergoes electrophilic aromatic substitution (S_EAr) with the aryl coupling partner **1-34**, promoted by H-*B*-9-BBN, which acts as a Lewis acid, abstracting fluoride. The newly-formed Wheland intermediate **1-35** is deprotonated by the fluoroborohydride **1-36** to release H_2 and form the benzyl arene product **1-37** and F-*B*-9-BBN. HBpin acts as the turnover reagent, undergoing B–F/B–H transborylation with F-*B*-9-BBN to regenerate the catalyst, H-*B*-9-BBN, and form FBpin as a side product.

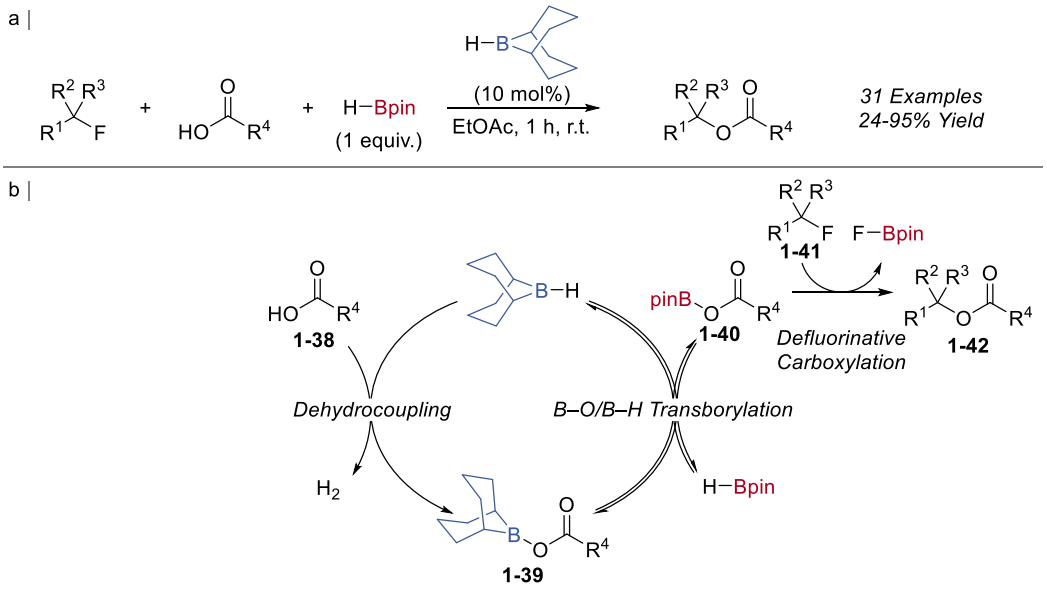


Scheme 1-13. a) H-*B*-9-BBN-catalysed Arylation of Benzylic C-F Bonds; b) Proposed Mechanism

1.3.5 B–O/B–H Transborylation

1.3.5.1 C-F Esterification

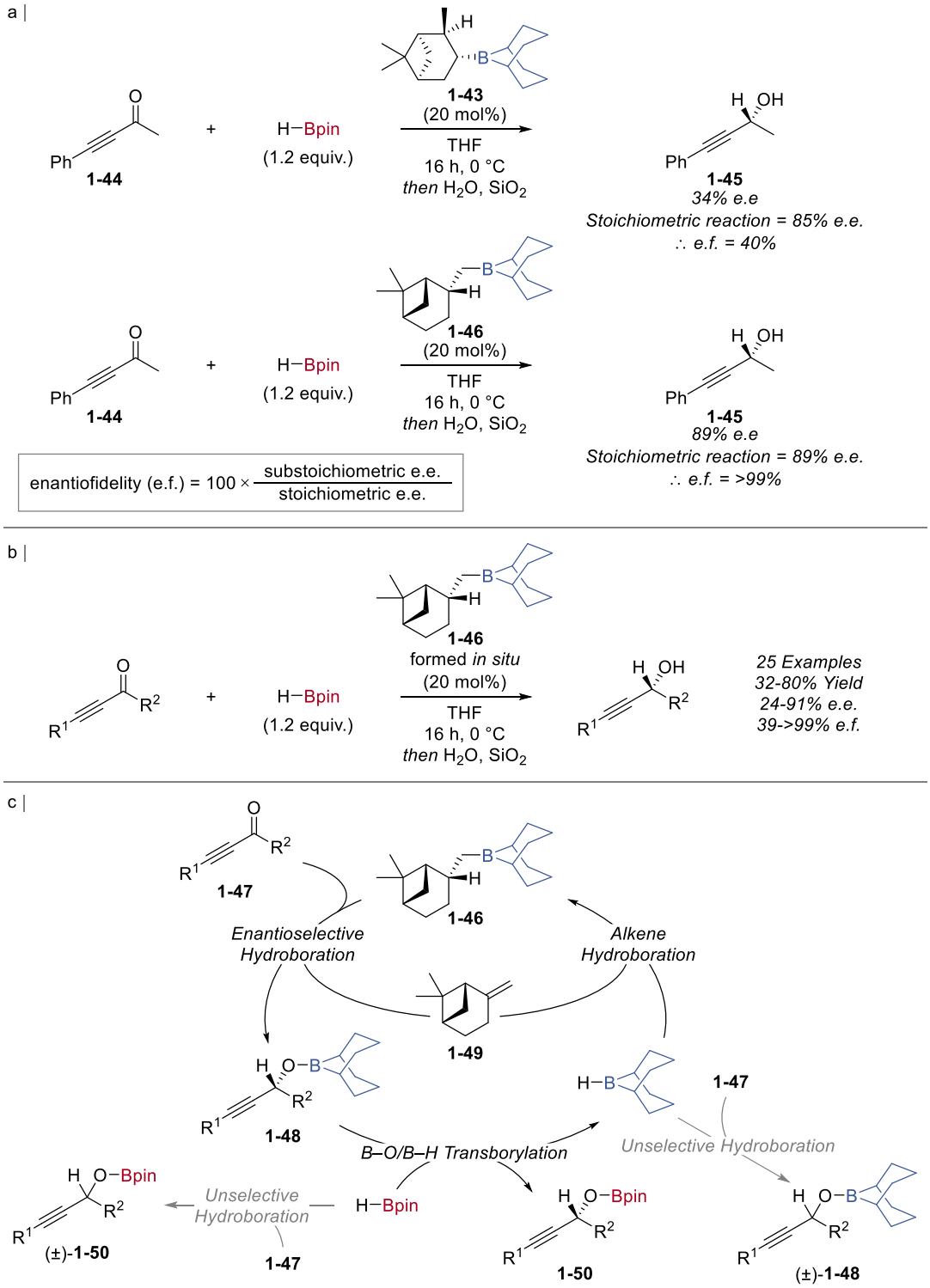
In the borane-catalysed C-F arylation, the reaction is formally proposed to proceed through a carbocation, formed from fluoride abstraction by H-*B*-9-BBN; therefore, the system was used to probe reactivity with other nucleophiles. Carboxylic acids readily reacted as nucleophiles with the alkyl fluorides to form esters in good yields and with broad functional group tolerance (Scheme 1-14, a).[45] Alkenes, alkynes, nitriles, and amides, all known to undergo stoichiometric reduction with H-*B*-9-BBN, were tolerated under reaction conditions, as well as alcohols, tertiary amines, sulphones, indoles, ethers, halides, cyclopropanes, acetals, and nitro groups. The reaction was also applied to industrially relevant targets, reacting alkyl fluorides with fifteen different acid-containing drugs. Unlike C-F arylation, which was proposed to proceed through B–F/B–H transborylation, mechanistic studies suggested that C-F esterification involves B–O/B–H transborylation (Scheme 1-14, b). H-*B*-9-BBN undergoes dehydrocoupling with the carboxylic acid **1-38** to give the acyloxy-*B*-9-BBN intermediate **1-39**, which reacts with HBpin through B–O/B–H transborylation to give the acyloxy pinacol boronic ester **1-40** and re-form the catalyst, H-*B*-9-BBN. In the absence of H-*B*-9-BBN, but under otherwise normal reaction conditions, no reactivity between the carboxylic acid **1-38** and HBpin was observed. The acyloxy pinacol boronic ester **1-40** then reacts directly with the alkyl fluoride **1-41** to form the ester product **1-42** and F-Bpin, confirmed by single-turnover experiments.



Scheme 1-14. a) H-*B*-9-BBN-catalysed C-F Esterification; b) Proposed Mechanism

1.3.5.2 Enantioselective Reduction of Propargylic Ketones

Thomas sought to use transborylation as a turnover mechanism in an enantioselective transformation for the first time, exploring the Midland reduction of propargylic ketones.[46] The Midland reduction has been used stoichiometrically in the syntheses of several natural products, including pheromones secreted by black-tailed deer and dermestid and Japanese beetles,[47] chemicals isolated from marine sponges (lembehyne A, chondrillin and plakorin),[48, 49] the antibiotic pseudomonic acid C,[50] the fungal metabolite (−)-pestalotin,[51] and the corticosteroid hydrocortisone acetate.[52] The borane used is typically Alpine-Borane® **1-43**, formed from the hydroboration of α-pinene by H-*B*-9-BBN. The use of Alpine-Borane® **1-43** as a catalyst for the enantioselective reduction of the propargylic ketone 4-phenyl-3-butyn-2-one **1-44** with HBpin gave the corresponding alcohol **1-45** in low enantiopurity (34% e.e.), in contrast to the high enantiopurity observed for the stoichiometric reaction (85% e.e.) (Scheme 1-15, a). The reduction of the propargylic ketone by Alpine-Borane® **1-43** proceeds through a Meerwein-Ponndorf-Verley-type transition-state structure with concurrent formation of α-pinene.[53] To regenerate the Alpine-Borane® catalyst **1-43** under catalytic conditions, H-*B*-9-BBN must react chemoselectively with the newly-formed α-pinene. The reduction in enantiopurity in the catalytic system was rationalised to be caused by slow catalyst regeneration, leading to an increased effect of the direct, unselective background reactions of both H-*B*-9-BBN and HBpin with the propargylic ketone **1-44**. To decrease the effect of the background reactions on the enantiopurity of the alcohol product **1-45**, the rate of catalyst regeneration had to be increased. Replacing the trisubstituted alkene α-pinene with the 1,1-disubstituted alkene β-pinene was envisaged to increase the rate of catalyst regeneration, as the hydroboration of a 1,1-disubstituted alkene by H-*B*-9-BBN is typically faster than the hydroboration of a trisubstituted alkene;[54] this was confirmed experimentally. Myrtanyl-Borane **1-46**, formed *in situ* from β-pinene and H-*B*-9-BBN, was shown to catalyse the enantioselective reduction of 4-phenyl-3-butyn-2-one **1-44** with HBpin without reduction in enantiopurity between the stoichiometric (89% e.e.) and catalytic reactions (89% e.e.). Therefore, the increased rate of catalyst regeneration reduced the impact of the background reactions on the enantiopurity of the product **1-45**.



Scheme 1-15. a) Comparison of Stoichiometric and Catalytic Reductions of 4-Phenyl-3-butyn-2-one **1-44** with Alpine-Borane® **1-43** and Myrtanyl-Borane **1-46** b) Myrtanyl-Borane **1-46**-catalysed Enantioselective Reduction of Propargylic Ketones with HBpin; c) Proposed Mechanism

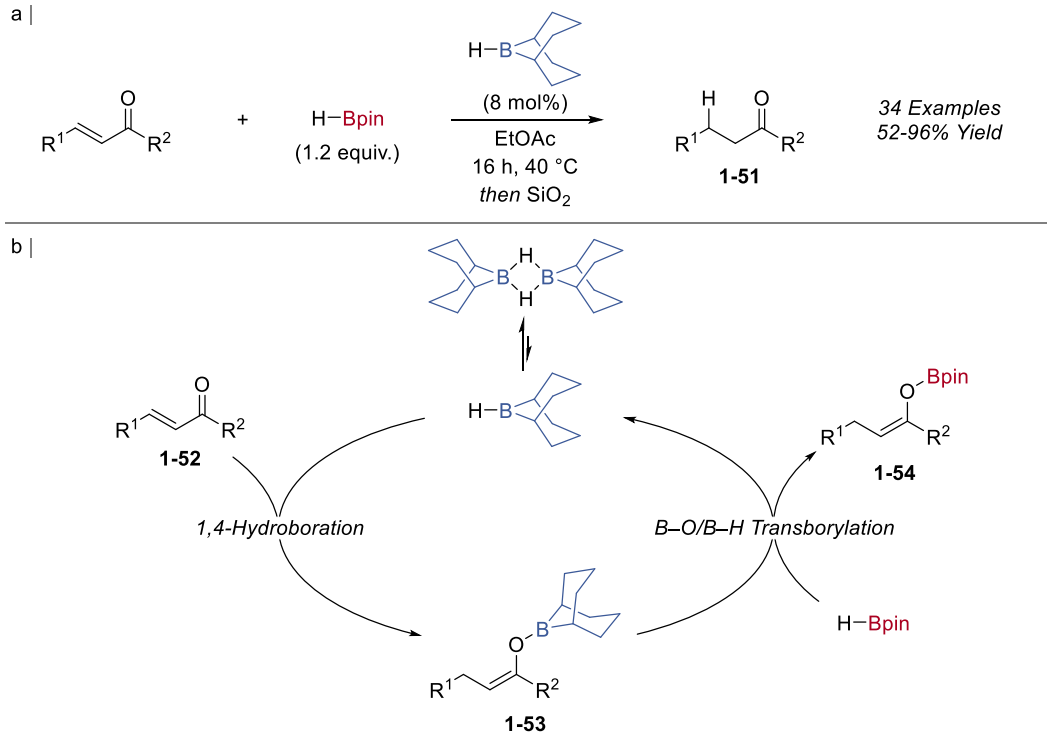
The application of this catalytic methodology to a range of propargylic ketones showed that enantioselectivity could be largely conserved when moving from the stoichiometric to the catalytic reduction (Scheme 1-15, b). Enantiofidelity was used to describe the comparison between the two reduction methods. Halides, esters, amides,

ethers, thioethers, tertiary amines, acetals, nitriles, and silyl groups were tolerated under reaction conditions. The enantioselectivity of the transformation was highly dependent on the substrate, but high enantioselectivity was observed for some substrates. Likewise, the enantiofidelity was substrate-dependent, where both increased steric bulk and the inclusion of both strong electron-donating and electron-withdrawing substituents reduced the enantiofidelity of the catalytic method, presumably caused by a decrease in the rate of hydroboration and an increase in the rate of the background reactions, respectively.

A combination of single turnover and ^{10}B-labelling experiments were used to postulate a catalytic cycle (Scheme 1-15, c). The propargylic ketone **1-47** undergoes enantioselective hydroboration with Myrtanyl-Borane **1-46** to form the borinic ester intermediate **1-48** and β-pinene **1-49**. B−O/B–H transborylation of the borinic ester intermediate **1-48** with HBpin generates the alkoxy boronic ester product **1-50** and regenerates H-*B*-9-BBN. Chemo-, regio- and stereoselective hydroboration of β-pinene **1-49** by H-*B*-9-BBN regenerates the Myrtanyl-Borane catalyst **1-46**. Side reactions of direct, unselective hydroboration of the propargylic ketone with H-*B*-9-BBN and HBpin are largely suppressed but can occur ((±)-**1-48** and (±)-**1-50**), especially with substrates that undergo hydroboration by Myrtanyl-Borane **1-46** slowly, leading to a reduction in enantiopurity of the product **1-50**.

1.3.5.3 Carbonyl Reduction

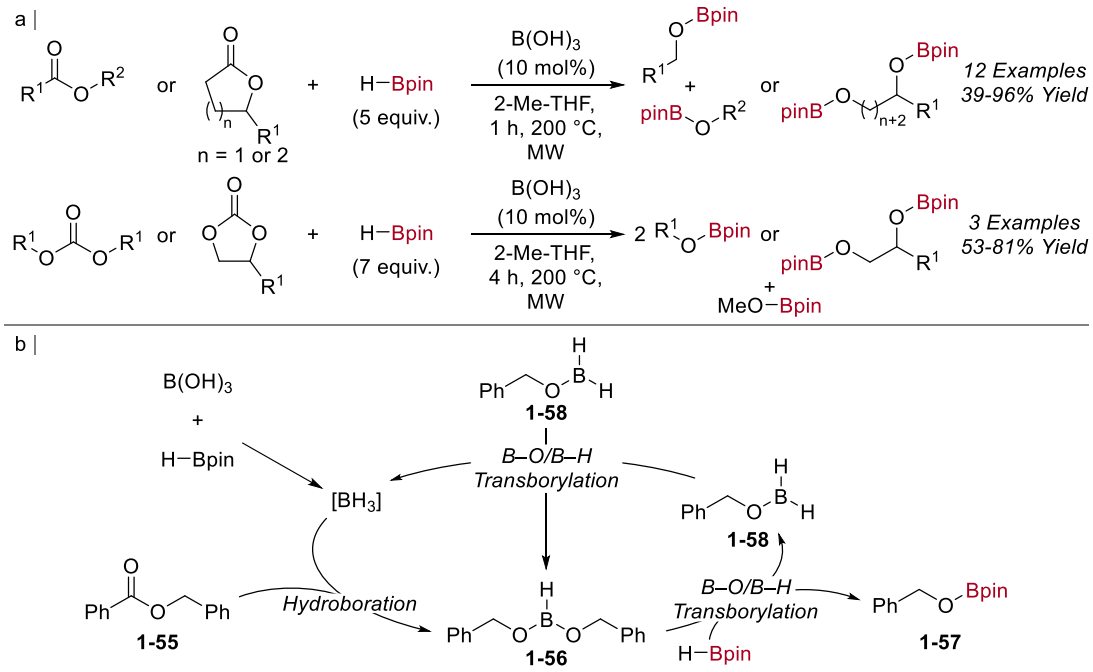
The 1,4-reduction of α,β-unsaturated ketones with HBpin was shown to be catalysed by H-*B*-9-BBN (Scheme 1-16, a).[55] The saturated ketone products **1-51** were isolated in high yields and an array of reducible functional groups were shown to be tolerated by the reaction conditions, including esters, nitriles, alkynes, alkenes, and nitro groups. Furthermore, pyridine, thiophene, furan, halide, thioether, ether, alcohol, acetal, and tertiary amine groups were tolerated. A combination of isotopic labelling and single turnover experiments were used to propose a mechanism (Scheme 1-16, b). 1,4-Hydroboration of the α,β-unsaturated ketone **1-52** with H-*B*-9-BBN forms the O-*B*-9-BBN-enolate **1-53**. HBpin undergoes B–O/B–H transborylation with the O-*B*-9-BBN-enolate **1-53** to re-form H-*B*-9-BBN and give the O-*B*-Bpin-enolate **1-54**, which undergoes hydrolysis upon work-up to give the saturated ketone product **1-51**.



Scheme 1-16. a) H-*B*-9-BBN-catalysed 1,4-reduction of α,β-unsaturated ketones with HBpin; b) Proposed Mechanism

Fontaine showed that boric acid ($B(OH)_3$) acts as a pre-catalyst for BH_3-catalysed hydroboration of esters and carbonates with HBpin.[56] Addition of $B(OH)_3$ to HBpin resulted in the formation of BH_3, confirmed by ^{11}B NMR spectroscopy. Accordingly, $B(OH)_3$ was used as a pre-catalyst for the reduction of esters, lactones, and carbonates with HBpin (Scheme 1-17, a). Under microwave irradiation, alkoxy boronic ester products were formed in good yield, and the conditions tolerated nitro, tertiary amine, and fluoride groups. Single-turnover experiments and DFT calculations supported a mechanism of hydroboration and B–O/B–H transborylation. Formation of BH_3 from $B(OH)_3$ and HBpin was suggested to be the rate-determining step, as HBpin and $B(OH)_3$ concentrations affected the rate of reaction, but ester concentration did not. Hydroboration of the ester **1-55** by BH_3 forms the dialkoxyborane **1-56**, which undergoes B–O/B–H transborylation with HBpin to form the alkoxy boronic ester product **1-57** and the monoalkoxyborane **1-58**. Redistribution of two equivalents of the monoalkoxyborane **1-58** through B–O/B–H transborylation is proposed to regenerate BH_3 and the dialkoxyborane **1-56**. Computational calculations suggested that this redistribution is kinetically and thermodynamically favoured ($\Delta G^{\ddagger}$ = 14.8 kcal mol^{-1}, ΔG^{0} = −6.1 kcal mol^{-1}). However, as the reaction was performed at 200 °C under microwave irradiation, other routes not subjected by DFT analysis are also possible, including the hydroboration of the ester **1-55** by the alkoxy- and dialkoxyboranes

1-58 and **1-56** prior to B–O/B–H transborylation, and direct reaction of the ester **1-55** with HBpin.

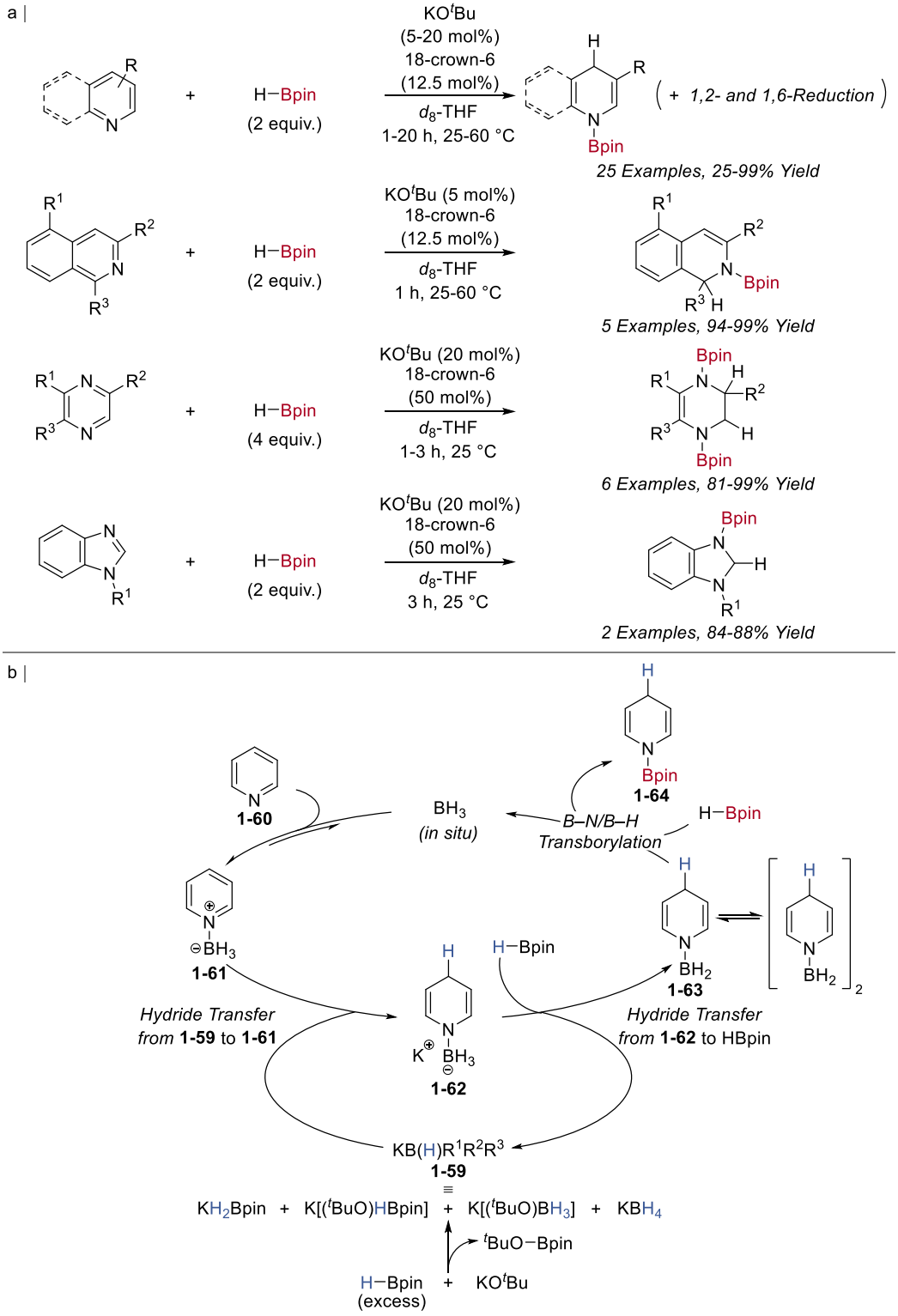


Scheme 1-17. a) Boric acid-promoted Reduction of Esters, Lactones and Carbonates; b) Proposed Mechanism

1.3.6 B–N/B–H Transborylation

1.3.6.1 Reduction of N-Heteroarenes

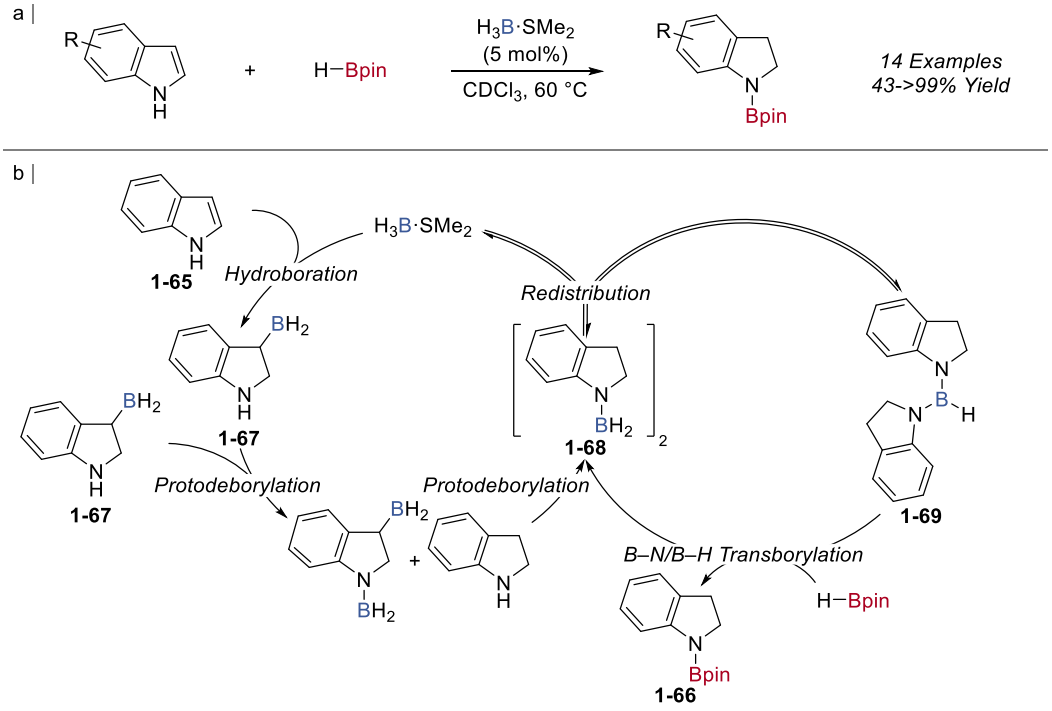
The KO^{t}Bu-promoted reduction of *N*-heteroarenes with HBpin developed by Chang was proposed to proceed through B–N/B–H transborylation (Scheme 1-18, a).[57] Pyridines, quinolines, isoquinolines, pyrazines, quinoxalines, and imidazoles were reduced under reaction conditions to form the amino boronic ester products. Mechanistic experiments showed that addition of KO^{t}Bu to HBpin resulted in the formation of several boron compounds, including several borohydride species **1-59** and BH_3 (Scheme 1-18, b). The pyridine **1-60** was proposed to form an adduct with BH_3, to form an activated pyridine **1-61**. The borohydride species **1-59** could then transfer hydride to the activated pyridine **1-60**, forming the 1,4-dihydropyridyl borohydride **1-62**. This can transfer hydride to HBpin to regenerate the borohydride catalyst **1-59** and form the neutral 1,4-dihydropyridyl borane **1-63**. B–N/B–H transborylation between HBpin and the 1,4-dihydropyridyl borane **1-63** forms the 1,4-dihydropyridyl boronic ester product **1-64** and re-forms BH_3.



Scheme 1-18. a) KO^{t}Bu-promoted Reduction of *N*-Heteroarenes; b) Proposed Mechanism

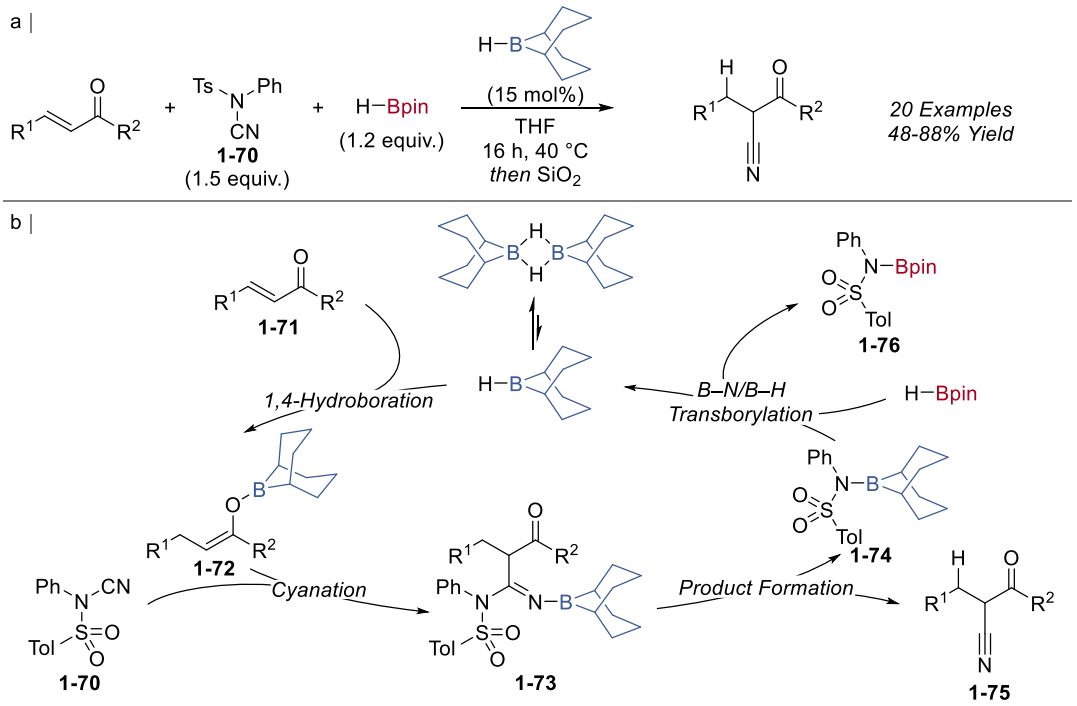
The reduction of *N*-H-indole **1-65** with HBpin was shown by Fontaine to be catalysed by $H_3B{\cdot}SMe_2$, to give the *B*-indolinyl boronic ester **1-66** only.[58] The formation of the indolin-3-yl boronic ester was not observed. The reaction conditions were applied to several substituted *N*-H-indoles, to give the *B*-indolinyl boronic ester products in good yield, tolerating halides, ethers, and nitro groups (Scheme 1-19, a). The mechanism of

this transformation was not immediately clear; therefore, thorough investigations were performed, using both experimental and computational methods to propose a mechanism (Scheme 1-19, b). The reaction of *N*-H-indole **1-65** with $H_3B{\cdot}SMe_2$ could proceed through dehydrocoupling, direct hydroboration, or hydroboration of the 3-*H*-tautomer of *N*-H-indole **1-65**. DFT calculations showed that the equilibriums of tautomerisation exist far towards the 1-H form of *N*-H-indole **1-65**, so the reaction presumably does not proceed through a tautomerisation-hydroboration pathway. Only minor quantities of H_2 were observed, and DFT analysis suggested that direct hydroboration was kinetically favoured over dehydrocoupling ($\Delta G^{\ddagger}$ (kcal mol^{-1}) = 19.6 and 26.3, respectively). Therefore, it was proposed that the first step in the mechanism was direct hydroboration of *N*-H-indole **1-65** with $H_3B{\cdot}SMe_2$ to form the indolin-3-yl-BH_2 **1-67**. Isomerisation of indolin-3-yl-BH_2 **1-67** to the *B*-indolinyl-BH_2 dimer **1-68** was proposed to proceed through protodeborylation with a minor contribution from a dehydrocoupling pathway, supported by DFT calculations. Stoichiometric experiments confirmed that the reaction proceeds through to the *B*-indolinyl-BH_2 dimer **1-68** and the *B*,*B*-bisindolinyl borane **1-69**, and that formation of the *B*-indolinyl boronic ester **1-66** occurs by the reaction of HBpin with *B*,*B*-bisindolinyl borane **1-69**. This turnover step is proposed by DFT analysis to proceed through B–N/B–H transborylation. The *B*-indolinyl-BH_2 dimer **1-68** and the *B*,*B*-bisindolinyl borane **1-69** are believed to exist in equilibrium.



Scheme 1-19. a) Borane-catalysed Reduction of *N*-H-Indoles; b) Proposed Mechanism

1.3.6.2 Hydrocyanation of α,β-Unsaturated Ketones



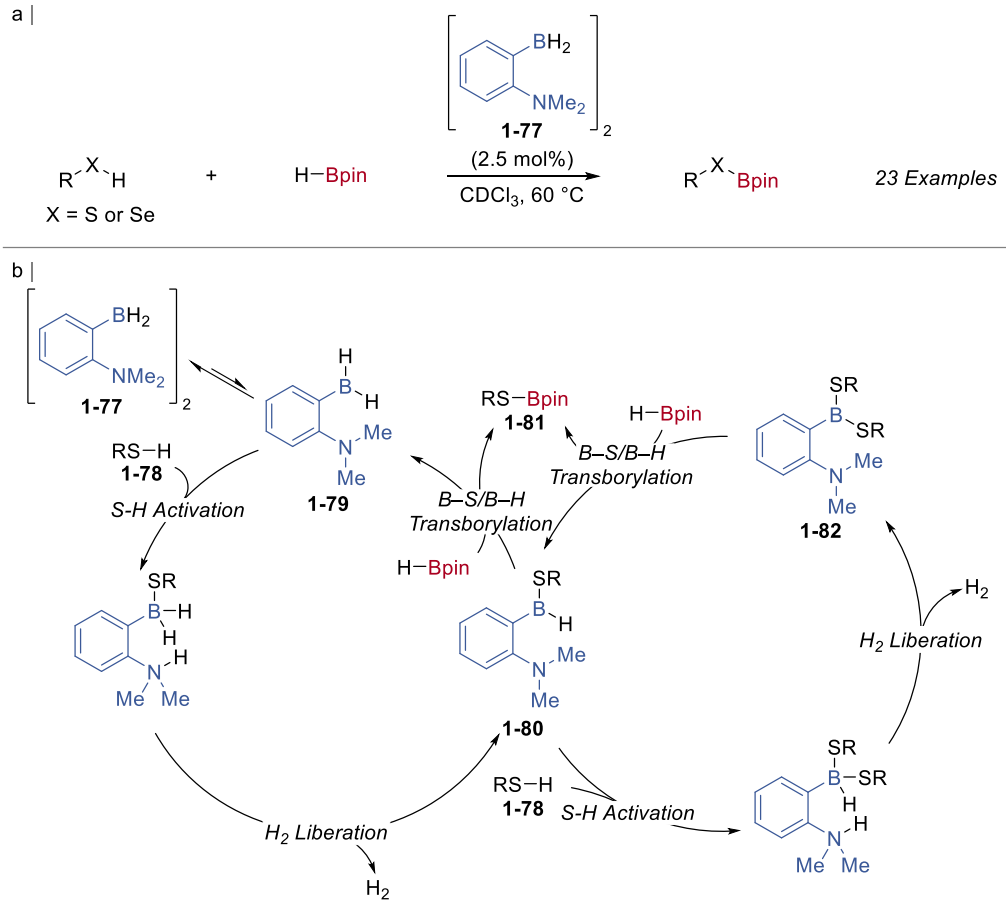
Scheme 1-20. a) H-*B*-9-BBN-catalysed Hydrocyanation of α,β-Unsaturated Ketones; b) Proposed Mechanism

The electrophilic cyanation reagent *N*-cyano-*N*-phenyl-*p*-toluenesulphonamide **1-70** (NCTS) was used by Thomas to develop a borane-catalysed hydrocyanation of α,β-unsaturated ketones (Scheme 1-20, a).[59] The reaction generated the β-ketonitrile products in good yield, tolerating a range of functional groups, including reducible functionalities such as alkynes, esters, and nitro groups. Ethers, tertiary amines, thioethers, and halides were also tolerated under reaction conditions, as well as pyrrole, thiophene, and furan-based heterocycles. Stoichiometric mechanistic experiments suggested that the reaction proceeded through B–N/B–H transborylation (Scheme 1-20, b). The α,β-unsaturated ketone **1-71** undergoes 1,4-hydroboration by H-*B*-9-BBN to form the O-*B*-9-BBN enolate **1-72**. This reacts with NCTS, resulting in the formation of the borylated β-keto-*B*-amidine **1-73** which then eliminates the amino-*B*-9-BBN **1-74** to form the β-ketonitrile product **1-75**. HBpin reacts with the amino-*B*-9-BBN **1-74** through B–N/B–H transborylation to re-form the catalyst, H-*B*-9-BBN, generating the amino boronic ester **1-76** as a side-product. The amino-*B*-9-BBN intermediate **1-74** was shown to catalyse the hydrocyanation reaction, suggesting the intermediate **1-74** is an on-cycle species. However, an alternative reaction pathway where transborylation precedes product formation could not be ruled out. Reaction of the borylated β-keto-*B*-amidine **1-73** could react with HBpin through B–N/B–H

transborylation to form the corresponding borylated pinacol β-keto-*B*-amidine, which would then undergo elimination to form the β-ketonitrile product **1-75** and the amino boronic ester side-product **1-76**.

1.3.7 B–S/B–H Transborylation

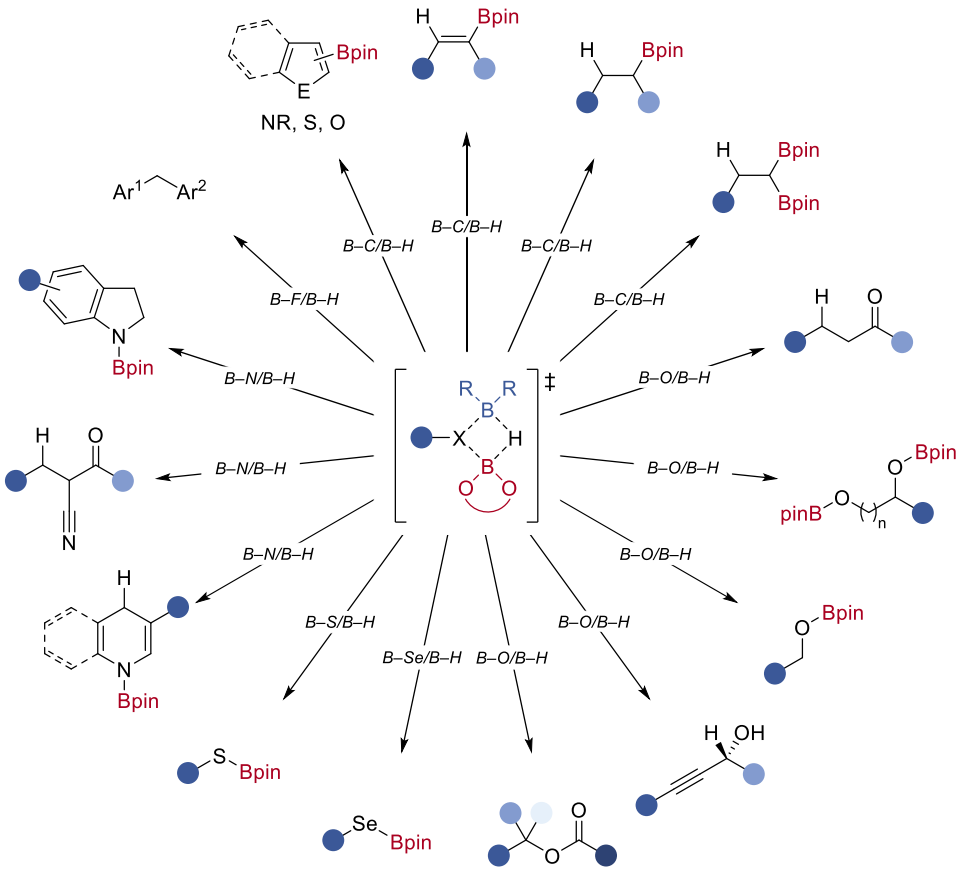
The dehydrogenative borylation of thiols with HBpin was shown by Fontaine to be catalysed by the dimethylamino-FLP **1-77** to form thiolate boronic esters (Scheme 1-21, a).[60] Ether, halide, and furan functional groups were tolerated by the reaction conditions. Selenophenol also underwent dehydrogenative borylation, representing the sole example of B–Se/B–H transborylation. The reaction mechanism was investigated by NMR spectroscopy and DFT analysis. As the FLP catalyst **1-77** contained two B-H bonds, there were two cycles proposed to be working in a complementary fashion (Scheme 1-21, b). In the first cycle, the thiol **1-78** undergoes dehydrogenative coupling with the monomeric form of the catalyst **1-79**, followed by H_2 extrusion to form the neutral intermediate **1-80**. This then undergoes B–S/B–H transborylation with HBpin to form the thiolate boronic ester product **1-81** and re-form the catalyst **1-79**. In the second cycle, a second equivalent of thiol reacts with the neutral intermediate **1-80**, then liberates H_2 to form the neutral bisthiolate intermediate **1-82**. Subsequent reaction of the neutral bisthiolate intermediate **1-82** with HBpin through B–S/B–H transborylation generates the thiolate boronic ester product **1-81** and re-forms the neutral intermediate **1-80**. DFT calculations and NMR analysis suggested that the neutral bisthiolate intermediate **1-82** was the resting state of the catalytic cycle. It was proposed that an increase in the steric bulk of the thiol increased the contribution of the first cycle to catalysis, and in the case of *tert*-butyl thiol, the resting state of the cycle was proposed to be the neutral monothiolate intermediate **1-80**. It is plausible to suggest that, instead of S-H activation across the FLP catalyst **1-79**, the thiol **1-78** undergoes a two-step process: deprotonation by **1-79** followed by nucleophilic addition of the thiolate to the borane functionality of **1-79**. Subsequent extrusion of H_2 would generate the neutral intermediate **1-80**. Alternatively, the borane group of the catalyst **1-79** could undergo dehydrocoupling with the thiol **1-78**, followed by B–S/B–H transborylation with HBpin to form the product **1-81** and regenerate the catalyst **1-79**. In this proposed mechanism, the amine functionality is redundant in catalysis; the catalyst **1-79** is merely acting as a borane and not an FLP. However, the energies associated with these alternative reaction pathways were not calculated.



Scheme 1-21. a) Dehydrogenative Borylation of Thiols with HBpin; b) Proposed Mechanism

1.4 Conclusion

Using the stoichiometric redistribution of boranes as an inspiration, several different applications of transborylation have been developed (Scheme 1-22). Transborylation has been used for both catalyst activation[44] and turnover. Boronic ester functionalities have been incorporated into molecules by both borylation[39] and hydroboration[20, 28, 44] methods, using boron-based catalysts. Transborylation has also been applied to transform stoichiometric reductions into catalytic methods, with comparable reactivity displayed.[46, 55, 59] In some instances, catalytic systems demonstrated improved functional group tolerance relative to the stoichiometric reactions, including the hydroboration[55] and hydrocyanation[59] of α,β-unsaturated ketones. However, catalytic systems that use transborylation for turnover are not limited to converting stoichiometric reactions, transformations that cannot be performed stoichiometrically have also been developed, such as C-F esterification.[45]



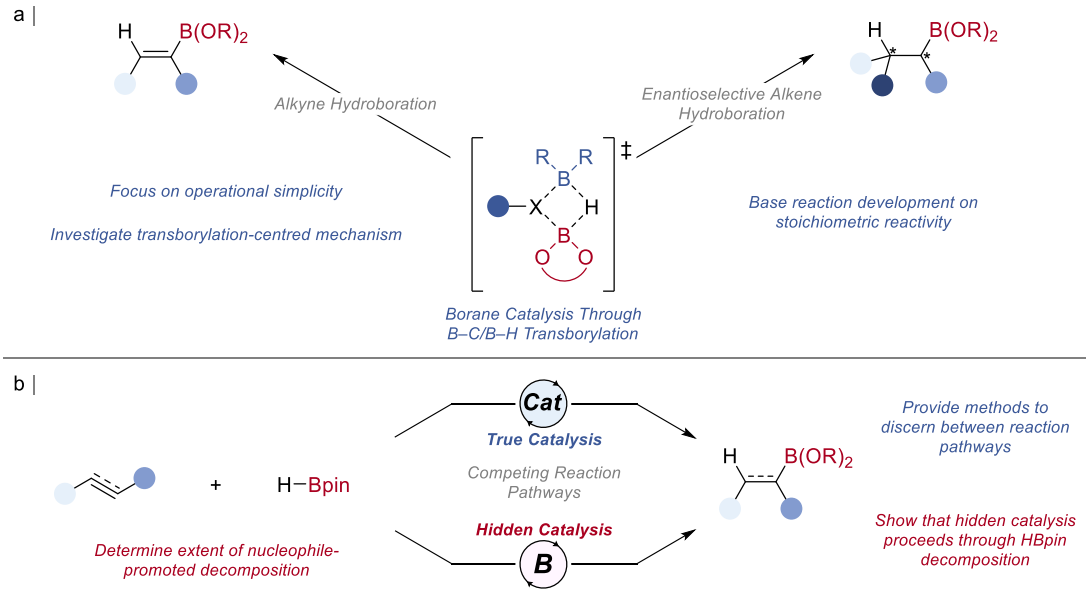
Scheme 1-22. Applications of Transborylation

1.5 General Aims

The intention of this collection of work is to showcase transborylation as a potential general turnover mechanism for catalysis, focusing on B–C/B–H transborylation (Scheme 1-23, a). An exemplar reaction of alkyne hydroboration using B–C/B–H transborylation will be developed, based on stoichiometric reactivity. Increased functional group tolerance and operational simplicity will be the focal points in the development of this transformation. General mechanistic understanding of transborylation will be explored by investigation of this catalytic protocol through single-turnover experiments and kinetic analysis. Extending transborylation to an enantioselective transformation, where transborylation occurs at a stereogenic centre, will underpin the general applicability of this turnover mechanism.

The role of boranes in hydroboration catalysis will be explored more generally, through the consideration of nucleophile-promoted HBpin decomposition to form active boron-based catalysts (Scheme 1-23, b). This decomposition process will be

shown to have broad applicability by investigating simple nucleophiles that are prevalent throughout hydroboration catalyst structures. Providing methods to differentiate between 'true' catalysis and 'catalysis' proceeding through HBpin decomposition (hidden catalysis) will be of paramount importance, as it will allow future hydroboration catalysis research to use this work as a fundamental platform for ensuring transformations proceed through 'true' catalysis.



Scheme 1-23. Aims

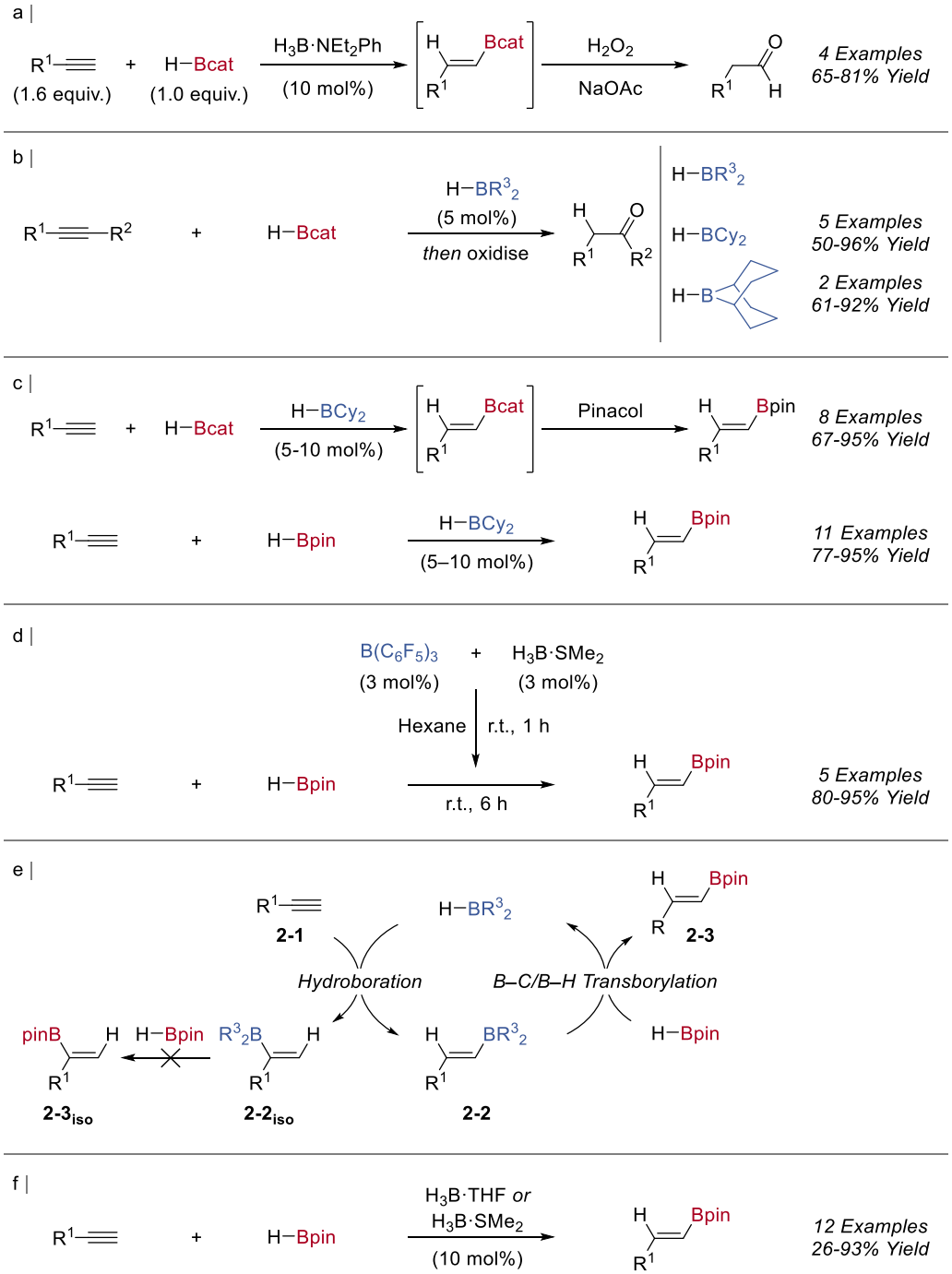
2. Dialkylborane-catalysed Hydroboration of Alkynes

2.1 Introduction

The potential application of the stoichiometric redistribution of boranes in catalysis was first realised by Periasamy, using $H_3B{\cdot}NEt_2Ph$ as a catalyst in the hydroboration of alkynes with HBcat to give aldehydes, after oxidation (Scheme 2-1, a). It was proposed that the alkyne would undergo hydroboration with $H_3B{\cdot}NEt_2Ph$ to give an alkenylborane intermediate that would react with HBcat, transferring the alkenyl group from boron to boron (B–C(sp^2)/B–H transborylation). Hoshi extended the use of redistribution in borane catalysis by using the dialkylboranes dicyclohexylborane ($HBCy_2$) and 9-borabicyclo[3.3.1]nonane (H-*B*-9-BBN) as catalysts for the hydroboration of alkynes with HBcat, isolating the products as aldehydes and ketones by oxidation of the reaction mixture (Scheme 2-1, b). Subsequently, Hoshi isolated the products as alkenyl pinacol boronic esters by transesterification of the alkenyl catechol boronic ester intermediates with pinacol (Scheme 2-1, c). Replacing the turnover reagent HBcat with HBpin also resulted in the formation of alkenyl pinacol boronic esters. Alkenyl boronic esters were formed in good yield in both systems, with some chemoselectivity displayed when HBpin was used; chloride, internal alkene, ether, acetal, and ester groups were tolerated by the system. The diarylborane bis(pentafluorophenyl)borane-dimethyl sulphide was prepared *in situ* by Hoshi from $H_3B{\cdot}SMe_2$ and tris(pentafluorophenyl)borane and used as a catalyst in alkyne hydroboration with HBpin, displaying similar reactivity to the dialkylborane-catalysed hydroboration systems (Scheme 2-1, d). In a limited substrate scope, chloride and internal alkene functionalities were tolerated.

Hoshi postulated that the dialkyl- and diarylborane-catalysed systems proceeded through an analogous mechanism to that proposed by Periasamy (Scheme 2-1, e). First, hydroboration of the alkyne **2-1** with the secondary borane would give an alkenylborane intermediate **2-2**, that would then undergo B–C(sp^2)/B–H transborylation with HBpin (or HBcat) to give the alkenyl boronic ester product **2-3**, and concomitantly re-form the secondary borane catalyst. Markovnikov hydroboration of the alkyne to give the regioisomer **2-2$_{iso}$** can occur, but **2-2$_{iso}$** does not appear to undergo B–C(sp^2)/B–H transborylation to form **2-3$_{iso}$**, leading to catalyst deactivation. $H_3B{\cdot}THF$ and $H_3B{\cdot}SMe_2$ were shown to catalyse the hydroboration of alkynes with

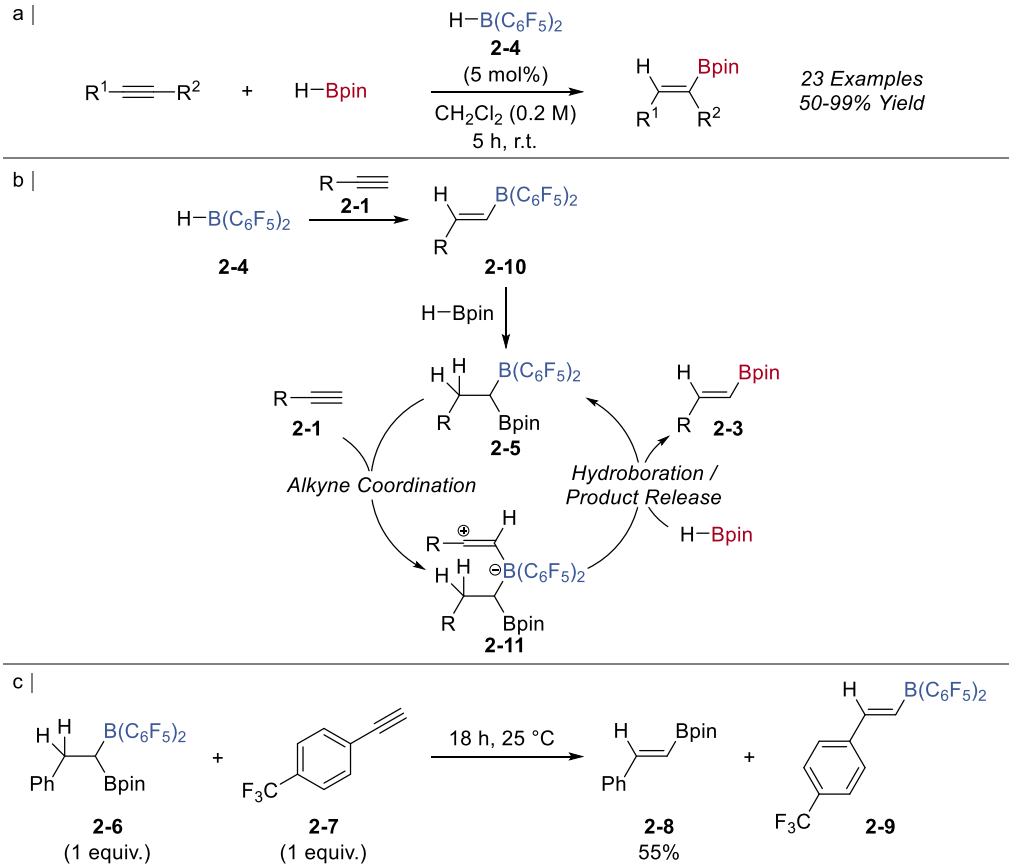
HBpin and were believed to proceed through a comparable mechanism of hydroboration and transborylation (Scheme 2-1, f). The reaction scope was limited to non-reducible functional groups, although esters were tolerated. Like the dicyclohexylborane-catalysed reaction, the system tolerated ether and chloride groups, as well as fluoride, primary amine, and cyclopropyl functionalities.



Scheme 2-1. a) $H_3B{\cdot}NEt_2Ph$-catalysed Alkyne Hydroboration with HBcat; b) Dialkylborane-catalysed Alkyne Hydroboration with HBcat; c) Dicyclohexylborane-catalysed Alkyne Hydroboration; d) Bis(pentafluorophenyl)borane-dimethyl Sulphide-catalysed Alkyne Hydroboration with HBpin; e) Proposed Mechanism for Borane-catalysed Alkyne Hydroboration; f) $H_3B{\cdot}THF$ and $H_3B{\cdot}SMe_2$-catalysed Alkyne Hydroboration with HBpin

Stephan used bis(pentafluorophenyl)borane (Piers's borane) **2-4** to promote the hydroboration of alkynes with HBpin (Scheme 2-2, a).[61] Ester, ether, nitrile, halide, phthalimide, thiophene, internal alkene and silyl functional groups were tolerated under the reaction conditions. Stephan proposed that the high Lewis acidity of Piers's borane resulted in a distinct mechanism from that postulated by Hoshi for the dicyclohexylborane- and the bis(pentafluorophenyl)borane-dimethyl sulphide complex-catalysed hydroboration reactions (Scheme 2-2, b). The mixed *gem*-diborylalkane **2-5** was observed in an endpoint analysis of the reaction, and subsequently prepared and successfully used as a catalyst in place of Piers's borane **2-4**. The mixed *gem*-diborylalkane **2-5** could catalyse the reactions in two ways, either by retro-hydroboration to regenerate Piers's borane **2-4**, which would then act as a catalyst in the same manner as dicyclohexylborane, or by acting as a Lewis acid to activate the alkyne towards hydroboration by HBpin. To exclude the retro-hydroboration pathway, the mixed *gem*-diborylalkane **2-6** was reacted with 4-ethynyl-α,α,α-trifluorotoluene **2-7**, resulting in the formation of the alkenyl boronic ester **2-8** and the alkenylborane **2-9** (Scheme 2-2, c). This reaction indicated the formation of the mixed *gem*-diborylalkane **2-5** is reversible and this reaction must proceed through a retro-hydroboration pathway. However, the rate of hydroboration is far slower than that observed under catalysis. Therefore, the retro-hydroboration pathway was rejected, and the reaction was proposed to proceed through a Lewis-acid promoted mechanism (Scheme 2-2, b). First, hydroboration of the alkyne **2-1** by Piers's borane **2-4** followed by hydroboration of the resulting alkenylborane **2-10** by HBpin results in the formation of the mixed *gem*-diborylalkane **2-5**. This reacts with another alkyne to form a zwitterionic intermediate **2-11**, which then undergoes concerted hydroboration and product release with HBpin to form the alkenyl boronic ester **2-3** and re-form the mixed *gem*-diborylalkane **2-5**. The stoichiometric formation of the mixed *gem*-diborylalkane **2-5** and its catalytic competency led Stephan to discount a mechanism that proceeded through hydroboration and transborylation, analogous to that proposed by Hoshi. However, the mixed *gem*-diborylalkane **2-5** could be an off-cycle species, acting as a sink for the true catalyst, Piers's borane **2-4**. Furthermore, whilst retro-hydroboration was excluded as the primary mode of catalysis based on the rate of reaction between the mixed *gem*-diborylalkane **2-5** and 4-ethynyl-α,α,α-trifluorotoluene **2-7**, the stoichiometry of this experiment did not match that of catalysis, where the alkyne **2-7** would be in a large excess, relative to the mixed *gem*-

diborylalkane **2-5**. Performing the reaction with stoichiometries that matched catalysis would likely increase the rate of retro-hydroboration.

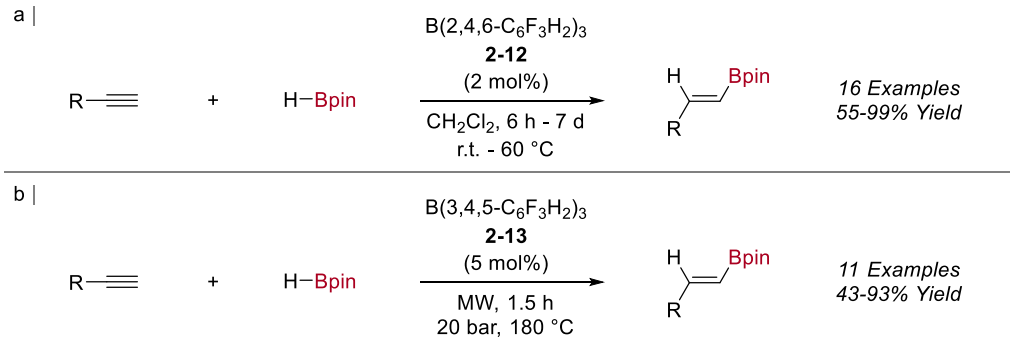


Scheme 2-2. a) Piers's Borane **2-4**-promoted Hydroboration of Alkynes with HBpin; b) Proposed Mechanism; c) Retro-hydroboration Experiment

The hydroboration of alkynes with HBpin can also be catalysed with triarylboranes. Stephan[61] and Melen[62] both showed that tris(pentafluorophenyl)borane would catalyse alkyne hydroboration and similarly Melen used tris(2,4,6-trifluorophenyl)borane **2-12** as a catalyst for the transformation (Scheme 2-3, a). Whilst no mechanistic experiments were performed, it is plausible that the reaction follows a comparable mechanism to that proposed by Hoshi for dicyclohexylborane.[28] Tris(2,4,6-trifluorophenyl)borane **2-12** could undergo redistribution with HBpin to form a diarylborane, which would then react in the same manner as dicyclohexylborane. Good functional group tolerance was displayed; the reaction tolerated ester, nitro, ether, α,β-unsaturated ester, silyl, and internal alkyne groups.

Melen subsequently used tris(3,4,5-trifluorophenyl)borane **2-13** to catalyse the hydroboration of alkynes with HBpin, showing that microwave irradiation increased the yield of alkenyl boronic ester product with reduced reaction time (Scheme 2-3, b). Ethers and aryl chlorides were tolerated under reaction conditions. Without microwave

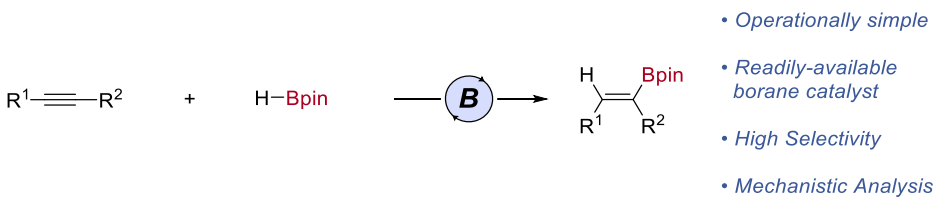
irradiation, a conversion of 40% was observed when the reaction was heated to 180 °C for 90 minutes. With microwave irradiation, and all other conditions kept constant, quantitative conversion was observed. When an increased catalyst loading (10 mol%) was used, quantitative conversion was obtained after 96 hours at 70 °C without microwave irradiation. Therefore, as the reaction displayed limited functional group tolerance, the need for microwave irradiation should be considered; irradiation evidently reduced reaction time but may have come at the cost of functional group tolerance.



Scheme 2-3. a) Tris(2,4,6-trifluorophenyl)borane **2-12**-catalysed Alkyne Hydroboration; b) Tris(3,4,5-trifluorophenyl)borane **2-13**-catalysed Alkyne Hydroboration

2.2 Project Aims

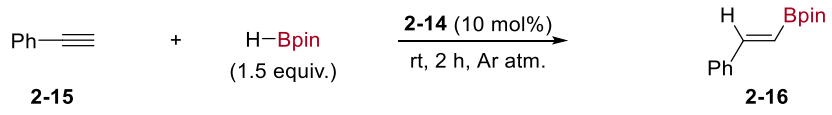
Previous borane-catalysed alkyne hydroboration systems relied on strict air- and moisture-sensitive techniques, required catalyst synthesis or purification prior to its use in catalysis, or displayed limited scope. Therefore, the key objectives of this project were to use a commercially available and easy to handle borane to develop an operationally simple borane-catalysed alkyne hydroboration reaction; to investigate the regio-, stereo-, chemoselectivity of the reaction by the completion of a substrate scope; and to study the mechanism of dialkylborane-catalysed alkyne hydroboration to support future applications of transborylation.



2.3 Reaction Optimisation

Phenylacetylene was used as a model substrate to develop reaction conditions for the borane-catalysed hydroboration of alkynes with HBpin. As borane,[63] monoalkyl-[64] and dialkylboranes[65] are all known to undergo stoichiometric hydroboration with alkynes, each were tested as catalysts for this transformation. $H_3B{\cdot}THF$ **2-14a**, the monoalkylborane thexylborane **2-14b**, and the dialkylborane H-*B*-9-BBN **2-14c** were shown to catalyse the hydroboration of phenylacetylene **2-15** with HBpin. The yield of the alkenyl boronic ester **2-16** was significantly reduced when $H_3B{\cdot}THF$ **2-14a** was used (Table 2-1, Entry 1), with thexylborane **2-14b** and H-*B*-9-BBN **2-14c** giving comparable yields (Table 2-1, Entries 2 and 3). Thexylborane **2-14b** was prepared *in situ* and cannot be stored for long periods of time as the thexyl group slowly isomerises to 2,3-dimethyl-*n*-butyl group through a retro-hydroboration and hydroboration process.[66] Unlike thexylborane, H-*B*-9-BBN **2-14c** is commercially available as both a solid and in solution and can be stored indefinitely under an inert atmosphere without decomposition, therefore, H-*B*-9-BBN **2-14c** was chosen as the catalyst for this transformation. It should be noted that H-*B*-9-BBN **2-14c** has previously been used as a catalyst for the hydroboration of alkynes with HBcat[67-71] and HBpin[72] in a limited number of total syntheses, but a thorough investigation of the transformation has not been performed.

Table 2-1. Borane Catalyst Screening



2-15 **2-16**

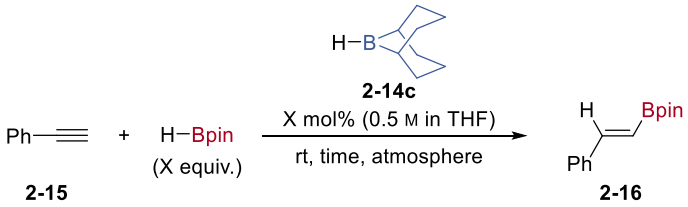
2-14a (1 M in THF) | **2-14b** (1 M in THF) | **2-14c** (0.5 M in THF)

Entry	Borane 2-14	Yield 2-16 (%)
1	**2-14a**	28
2	**2-14b**	62
3	**2-14c**	69

Conditions: Phenylacetylene **2-15** (1.0 mmol), HBpin (1.5 mmol), and borane catalyst **2-14** (0.10 mmol), r.t., 2 h, Ar atmosphere. Yields were determined by ^{1}H NMR spectroscopy using an internal standard (1,3,5-trimethoxybenzene).

Subsequent optimisation reactions were performed to improve the yield of alkenyl boronic ester **2-16**. A range of solvents were screened (Table 2-2, Entries 1-6); the highest yield of **2-16** was observed when no solvent was added to the reaction (the reaction still contained THF from the solution of H-*B*-9-BBN). Increasing the equivalents of HBpin resulted in an increase in yield of **2-16** but reached a plateau above 1.5 equivalents of HBpin (Table 2-2, Entries 6-10). An increase in reaction time did not increase the yield of **2-16** (Table 2-2, Entries 10-11), and using the H-*B*-9-BBN solid dimer in place of the solution gave a slightly lower yield (Table 2-2, Entry 12). In the interest of operational simplicity, it was decided that using the solution of H-*B*-9-BBN was a more appropriate choice. Increasing the catalyst loading resulted in an increase in yield of **2-16**, with 20 mol% giving the highest yield (Table 2-2, Entries 13-15). Performing the reaction under argon, nitrogen or air all gave comparable yields (Table 2-2, Entries 16-18), increasing the utility of the reaction.

Table 2-2. Reaction Optimisation



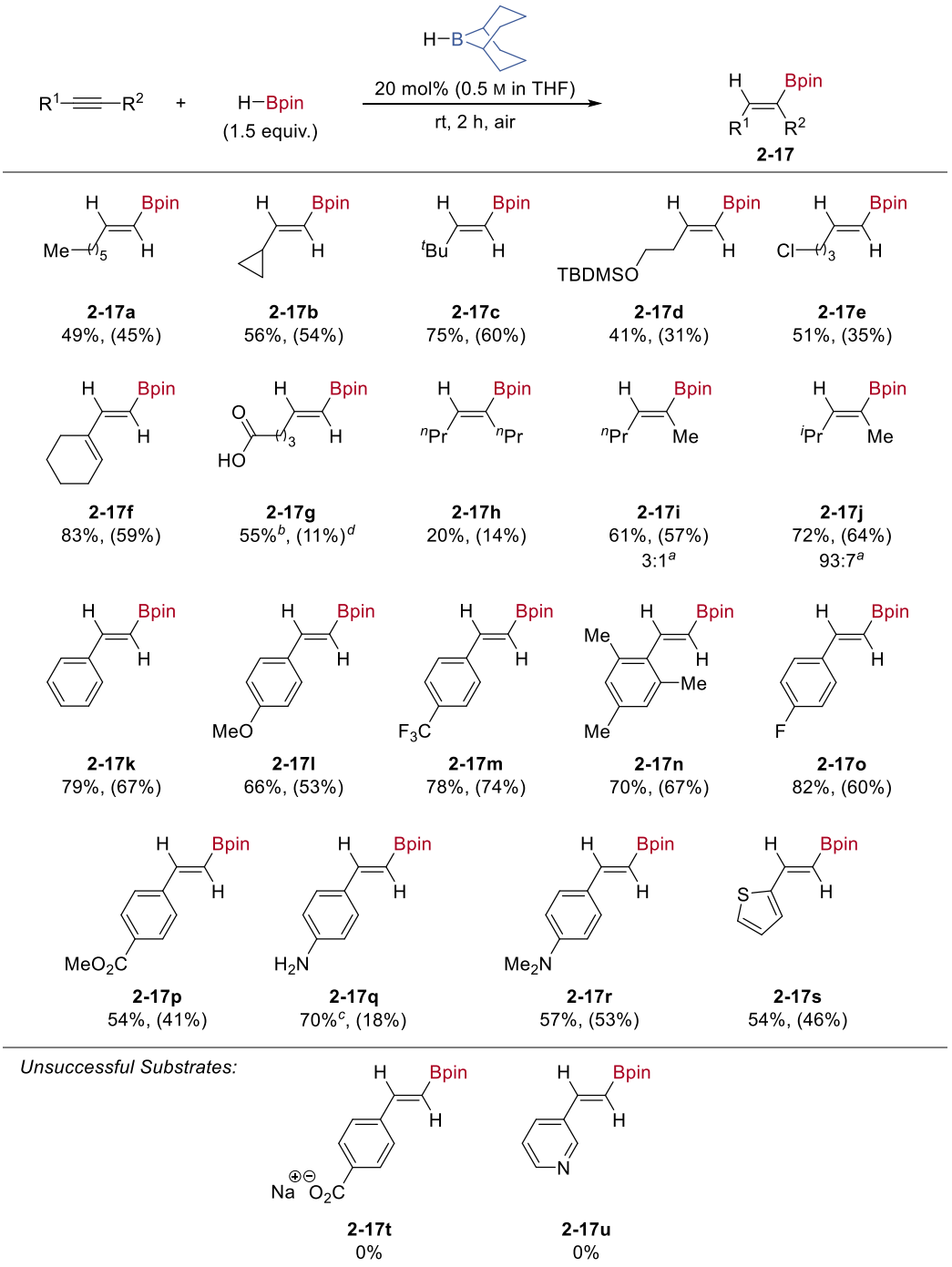
Entry	Catalyst Loading (mol%)	HBpin Equiv.	Solvent	Concentration (M)	Atmosphere	Reaction Time (h)	Yield (%)
1	10	1.1	THF	0.50	Argon	2	50
2	10	1.1	Toluene	0.50	Argon	2	51
3	10	1.1	CH_2Cl_2	0.50	Argon	2	40
4	10	1.1	Dioxane / $CHCl_3$ (100:1)	0.50	Argon	2	51
5	10	1.1	MeCN	0.50	Argon	2	17
6	10	1.1	THF[a]	5.0	Argon	2	65
7	10	1.25	THF[a]	5.0	Argon	2	68
8	10	1.5	THF[a]	5.0	Argon	2	69
9	10	2.0	THF[a]	5.0	Argon	2	70
10	10	2.0	THF[a]	5.0	Argon	2	68
11	10	2.0	THF[a]	5.0	Argon	2.5	65
12	20[b]	2.0	None	n/a	Argon	2	53
13	5.0	2.0	THF[a]	10	Argon	2	47
14	15	2.0	THF[a]	3.3	Argon	2	73
15	20	2.0	THF[a]	2.5	Argon	2	76
16	20	1.5	THF[a]	2.5	Argon	2	81
17	20	1.5	THF[a]	2.5	Nitrogen	2	78
18	20	1.5	THF[a]	2.5	Air	2	79

Conditions: Phenylacetylene **2-15** (1.0 mmol), HBpin, H-*B*-9-BBN, r.t. Yields were determined by ^{1}H NMR spectroscopy using an internal standard (1,3,5-trimethoxybenzene). [a]No further solvent added, reaction contained THF from the H-*B*-9-BBN solution. [b]Catalyst added to the reaction as a solid.

2.4 Substrate Scope

The chemo-, regio- and stereoselectivity of the reaction was probed by the exploration of a substrate scope (Scheme 2-4). In all cases, only the alkenyl boronic ester products from *cis*-hydroboration were observed and for terminal alkynes, only the linear regioisomers were observed. For aliphatic alkynes, the yield of the alkenyl boronic ester **2-17** was shown to increase with an increase in alkyl substitution, using alkynes bearing primary (**2-17a**), secondary (**2-17b**) and tertiary alkyl substituents (**2-17c**). The reaction conditions tolerated silyl-protected alcohols (**2-17d**) and alkyl chlorides (**2-17e**) and showed a preference for terminal alkynes over internal alkenes (**2-17f**). An alkyne containing a carboxylic acid group (**2-17g**) successfully underwent hydroboration after increasing the equivalents of HBpin (3.0 equiv.), but isolation was only possible after conversion of the acid to the methyl ester, during which a significant decrease in yield was observed.

A substantial reduction in yield was observed for a symmetrical internal alkyne (**2-17h**) compared to the terminal regioisomer (**2-17a**). However, unsymmetrical internal alkynes (**2-17i**, **2-17j**) showed higher yields than both the terminal and the symmetrical internal alkyne (**2-17a**, **2-17h**). It is possible that this increase in yield is caused by reduced steric hindrance from the methyl groups of **2-17i** and **2-17j** compared to the *n*-propyl group of **2-17h**. Moreover, as seen with the terminal aliphatic alkynes (**2-17a**, **2-17b**, **2-17c**), increasing the alkyl substitution from primary to secondary alkyl substituents led to an increase in boronic ester yield (**2-17i**, **2-17j**). The reaction conditions displayed impressive regioselectivity, with a high preference for reacting the boron group at the least hindered end of the alkyne (**2-17i**, **2-17j**), exemplified by a regioselectivity of 93:7 in the case of the alkenyl boronic ester **2-17j**. The regioselectivity observed for the hydroboration of 2-hexyne (**2-17i**) and 4-methyl-2-pentyne (**2-17j**) matched the ratios observed in the stoichiometric hydroboration with H-*B*-9-BBN.[65]



Scheme 2-4. Substrate scope for the H-*B*-9-BBN-catalysed hydroboration of alkynes with HBpin

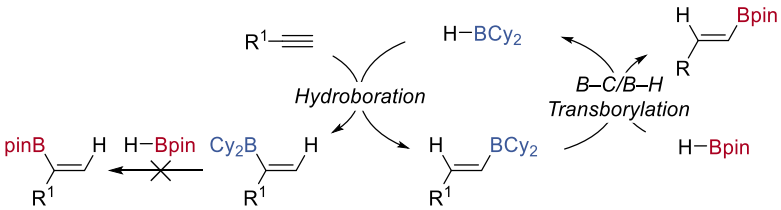
Conditions: Alkyne (1.0 mmol), HBpin (1.5 mmol), and H-*B*-9-BBN **2-14c** (0.5 M in THF, 0.20 mmol), r.t., 2 h, air. Yields determined by ^{1}H NMR spectroscopy using an internal standard (1,3,5-trimethoxybenzene). Yields in parentheses are isolated yields. [a]Ratios of regioisomers, determined by ^{1}H NMR spectroscopy; the major product is displayed. [b]Reaction used 3.0 equivalents of HBpin. [c]Reaction used 4.5 equivalents of HBpin. [d]Isolated as the methyl ester.

Several aryl substituents were tolerated; alkynes bearing anisyl (**2-17l**), *p*-trifluoromethylphenyl (**2-17m**), 2,4,6-trimethylphenyl (**2-17n**) and *p*-fluoro (**2-17o**) groups underwent hydroboration in good yield, with lower yields observed for alkynes containing ester (**2-17p**) and *p*-dimethylaminophenyl (**2-17r**) groups. 4-Ethynylaniline

underwent hydroboration to form the alkenyl boronic ester in a good yield (**2-17q**) when an additional 3.0 equivalents of HBpin were added to the reaction to protect the primary amine by dehydrocoupling with HBpin. However, isolation of the boronic ester proved challenging, resulting in a low isolated yield. Using the standard conditions resulted in trace yield of the boronic ester, presumably because the primary amine underwent dehydrocoupling reactions with both HBpin and H-*B*-9-BBN, resulting in deactivation of the catalyst. Electronic effects of the aryl substituents do not appear to have a strong influence on the yield; the highest and lowest yields are observed with electron-withdrawing groups (**2-17m**, **2-17o**). The reaction conditions were shown to tolerate thiophenes (**2-17s**) but not pyridines (**2-17u**), possibly due to catalyst deactivation. Reduction of the pyridine group was not observed. Sodium 4-ethynylbenzoate (**2-17t**) did not undergo hydroboration, possibly caused by deactivation of the catalyst by the reaction of the catalyst with the carboxylate group.

2.5 Mechanistic Studies

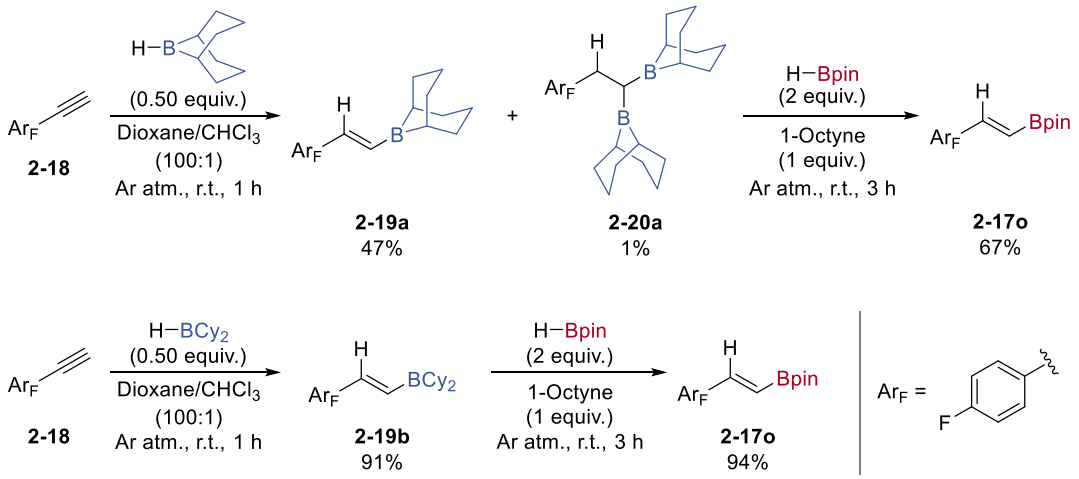
In collaboration with the Lloyd-Jones research group, the mechanism of the dialkylborane-catalysed hydroboration of alkynes with HBpin was investigated. A plausible mechanism had been previously proposed by Hoshi for the dicyclohexylborane-catalysed reaction (Scheme 2-5),[28] and although limited experimental evidence was provided, the mechanism was based on established borane reactivity.



Scheme 2-5. Hoshi's Mechanism for Dicyclohexylborane-catalysed Alkyne Hydroboration

Seeking to determine the correct mechanism for this reaction, kinetic analysis and stoichiometric single-turnover reactions were performed. Hydroboration of 4-fluorophenylacetylene **2-18** by both H-*B*-9-BBN and dicyclohexylborane resulted in the formation of the alkenylborane intermediate **2-19** and trace amounts of the *gem*-diborylalkane **2-20** (Scheme 2-6). Greater quantities of the *gem*-diborylalkane **2-20a** were formed with H-*B*-9-BBN and more 4-fluorophenylacetylene **2-18** remained unreacted. Subsequent addition of HBpin resulted in the formation of the alkenyl

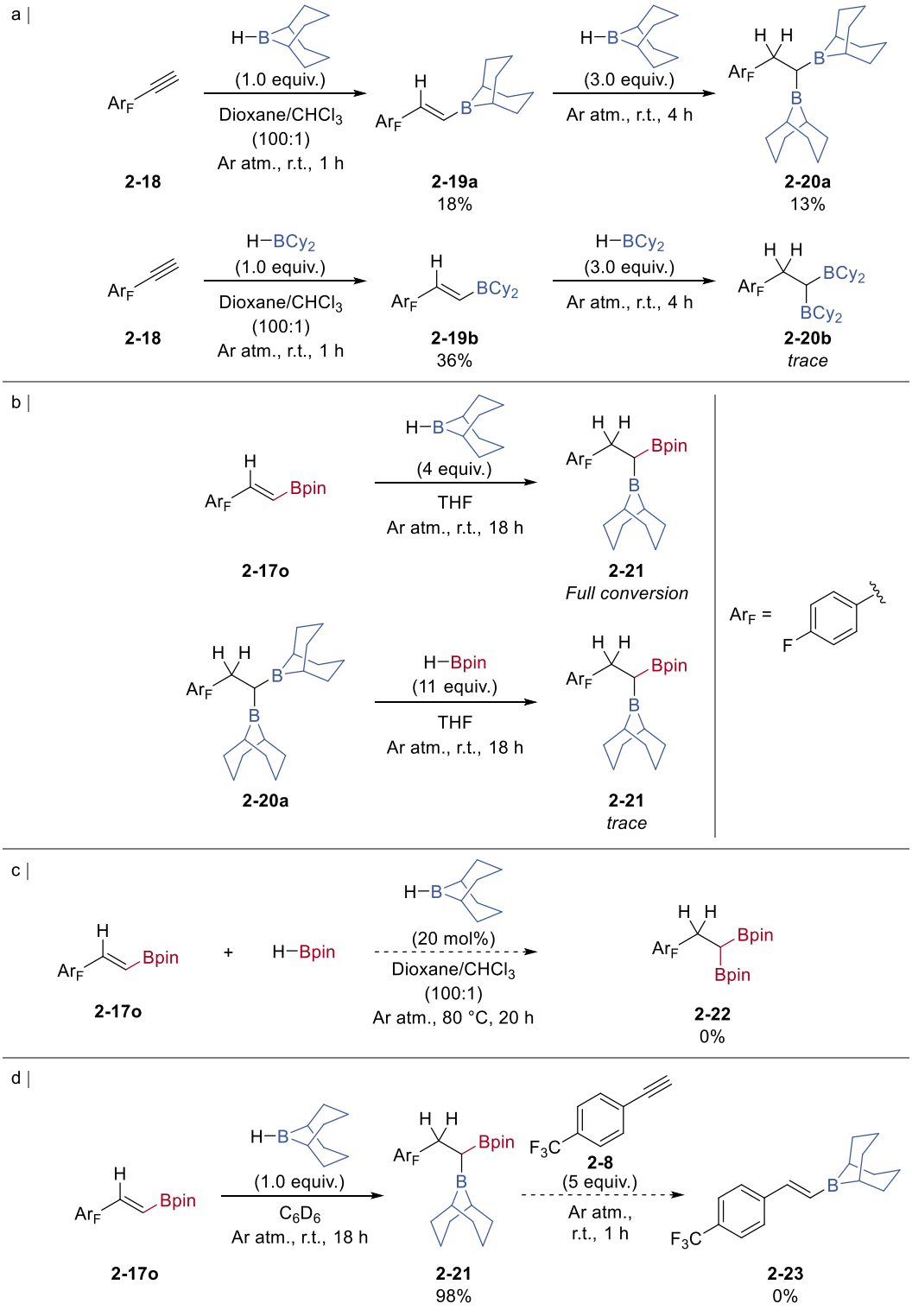
boronic ester product **2-17o**, supporting the mechanism proposed by Hoshi. Evidently, over-hydroboration to form the *gem*-diborylalkane **2-20** occurs and therefore needed both further investigation and to be considered in Hoshi's cycle.



Scheme 2-6. Single Turnover Experiments

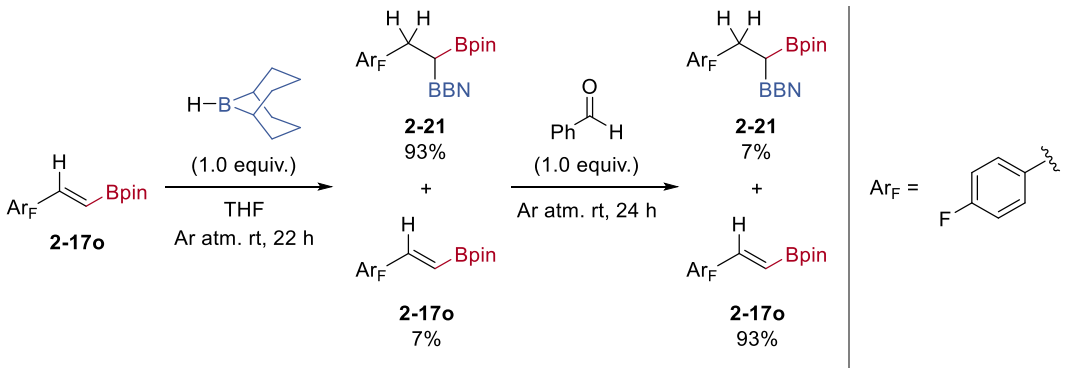
Sequential hydroboration of 4-fluorophenylacetylene **2-18** by 1.0 equivalent of H-*B*-9-BBN to form the alkenylborane intermediate **2-19a**, followed by the addition of an excess of H-*B*-9-BBN, resulted in the formation of the *gem*-diborylalkane **2-20a** (Scheme 2-7, a). The equivalent reaction with dicyclohexylborane resulted in trace amounts of the *gem*-diborylalkane **2-20b**. The stoichiometric reaction of the alkenyl boronic ester product **2-17o** with H-*B*-9-BBN resulted in the formation of the mixed *gem*-diborylalkane **2-21** (Scheme 2-7, b). Conversely, reaction of the *gem*-diborylalkane **2-20a** with HBpin resulted in trace amounts of the mixed *gem*-diborylalkane **2-21**. Therefore, formation of the mixed *gem*-diborylalkane **2-21** appears to proceed through hydroboration of the alkenyl boronic ester **2-17o** with H-*B*-9-BBN and not through reaction of the *gem*-diborylalkane **2-20a** with HBpin. Attempts to form the *gem*-diborylalkane **2-22** under catalysis were unsuccessful (Scheme 2-7, c), but subsequent work in the group has shown that the reaction will proceed at elevated temperatures in the absence of solvent.[20] To confirm that the alkenyl boronic ester product **2-17o** did not form from retro-hydroboration of the mixed *gem*-diborylalkane **2-21**, the alkenyl boronic ester **2-17o** was reacted with H-*B*-9-BBN to form the mixed *gem*-diborylalkane **2-21**, then treated with an equivalent of 4-ethynyl-α,α,α-trifluorotoluene **2-8** (Scheme 2-7, d). No formation of the alkenylborane **2-23** or change in the ratio of products was observed, suggesting the formation of the mixed *gem*-diborylalkane **2-21** is irreversible under reaction conditions. This will not only lower the isolated yield of alkenyl boronic ester but will

also deactivate the catalyst, potentially resulting in unreacted alkyne, further reducing the yield.



Scheme 2-7. a) Attempted Formation of *gem*-Diborylalkanes **2-20** from the Hydroboration of 4-Fluorophenylacetylene **2-18** with H-*B*-9-BBN and Dicyclohexylborane; b) Attempted Formation of the *gem*-Diborylalkane **2-21**; c) Attempted Formation of *gem*-Diborylalkane **2-22** under Catalysis; d) Irreversibility Experiment

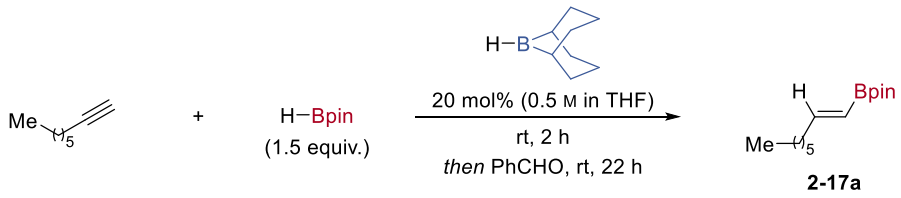
Under catalysis, the formation of the mixed *gem*-diborylalkane **2-21** is irreversible. However, addition of aldehydes to *gem*-diborylalkanes results in an oxidation where the alkenylborane is re-formed and the aldehyde is concomitantly reduced through a Midland-type reduction.[73] With the knowledge that the mixed *gem*-diborylalkane **2-21** forms under catalysis, it is possible that some of the lower yields of alkenyl boronic esters **2-17** were caused by the formation of the mixed *gem*-diborylalkanes. The alkenyl boronic ester **2-17o** was reacted with an equivalent of H-*B*-9-BBN to form the mixed *gem*-diborylalkane **2-21** (Scheme 2-8). Subsequent addition of an excess of benzaldehyde (5 equivalents) resulted in consumption of the mixed *gem*-diborylalkane **2-21** and the concomitant reformation of the alkenyl boronic ester **2-17o**.



Scheme 2-8. Benzaldehyde Reversibility Experiment

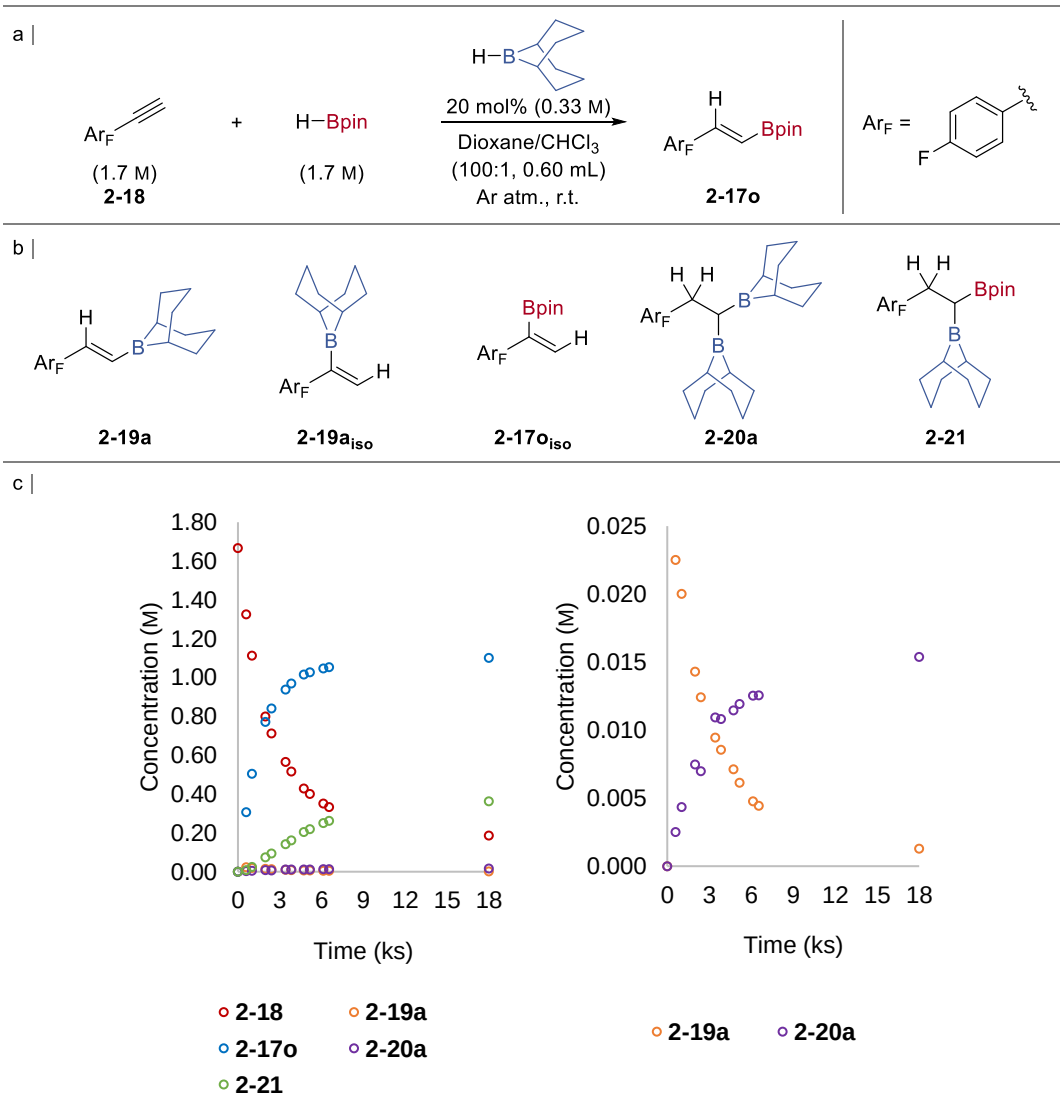
A low-yielding substrate, 1-octyne, was selected as an exemplar to determine whether the yield could be improved by addition of benzaldehyde prior to quenching (Table 2-3). Hydroboration of 1-octyne for 24 h under otherwise optimised conditions resulted in a 55% yield of alkenyl boronic ester **2-17a** (Table 2-3, Entry 1), comparable to the yield observed after 2 h (49%, Scheme 2-4, **2-17a**). Addition of an equivalent of benzaldehyde relative to catalyst loading resulted in a 6% increase in yield (Entry 2), presumably unreacted HBpin consumed most of the aldehyde. Similarly, when one equivalent of benzaldehyde (relative to the substrate) was added, an 11% increase in yield of alkenyl boronic ester **2-17a** was observed (Entry 3). As the total boron content of the reaction equates to 1.7 equivalents, an excess of benzaldehyde (2.0 equivalents) was used to ensure unreacted HBpin did not prevent benzaldehyde from reacting with the mixed *gem*-diborylalkane **2-21** (Entry 4). This resulted in an increase in yield of 18%, essentially equal to the catalyst loading of the reaction. Therefore, some of the lower yields of alkenyl boronic ester **2-17** could be improved by quenching with an excess of benzaldehyde.

Table 2-3. Benzaldehyde Quenching of 1-Octyne Hydroboration



Entry	Benzaldehyde Equivalents	Yield (%)
1[a]	0	55
2	0.20	61
3	1.0	66
4	2.0	73

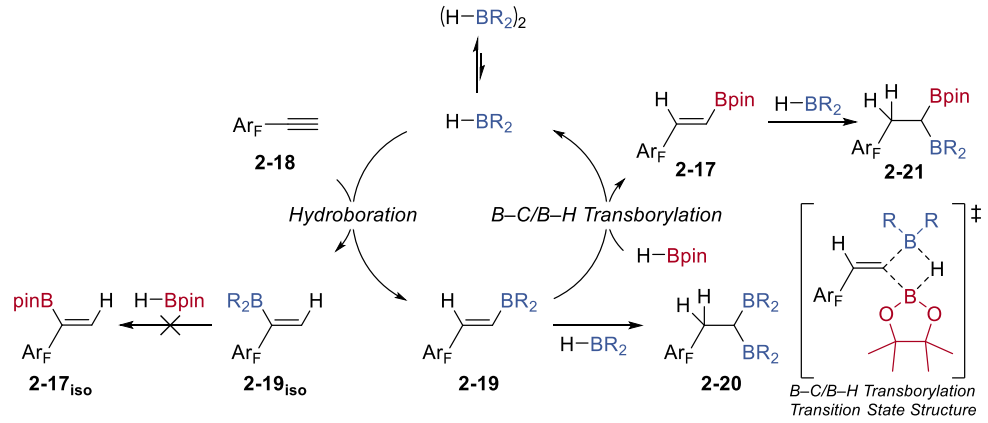
Conditions: Alkyne (1.0 mmol), HBpin (1.5 mmol), and H-*B*-9-BBN **2-14c** (0.5 M in THF, 0.20 mmol), r.t., 2 h, air, then benzaldehyde, r.t. 22 h. Yields determined by ^{1}H NMR spectroscopy using an internal standard (1,3,5-trimethoxybenzene). [a]24 h reaction time.



Scheme 2-9. a) H-*B*-9-BBN-catalysed Hydroboration of 4-Fluorophenylacetylene **2-18** with HBpin; b) Intermediates and Side-products; c) Kinetic Profile (L) and Enlarged Profile (R)

The H-*B*-9-BBN-catalysed hydroboration of 4-fluorophenylacetylene **2-18** with HBpin was monitored by ^{19}F NMR spectroscopy (Scheme 2-9). The linear regioisomer of the alkenylborane **2-19a** reaches maximum concentration (23 μM) at 0.60 ks and then decreases in concentration. The alkenyl boronic ester **2-17o** forms rapidly (υ_0 = 5.2×10^2 M s^{-1}) but slowly reacts with H-*B*-9-BBN to form the mixed *gem*-diborylalkane **2-21** until all the H-*B*-9-BBN is irreversibly consumed, resulting in unreacted 4-fluorophenylacetylene **2-18**. The branched regioisomer of the alkenylborane **2-19a$_{iso}$** is formed in very small quantities, with a selectivity of 3×10^2:1 for the linear alkenylborane **2-19a**. No branched alkenyl boronic ester product **2-17o$_{iso}$** was observed. Double hydroboration of the 4-fluorophenylacetylene **2-18** with H-*B*-9-BBN also occurs to form the *gem*-diborylalkane **2-20a** at a slow rate (4.2 M s^{-1}).

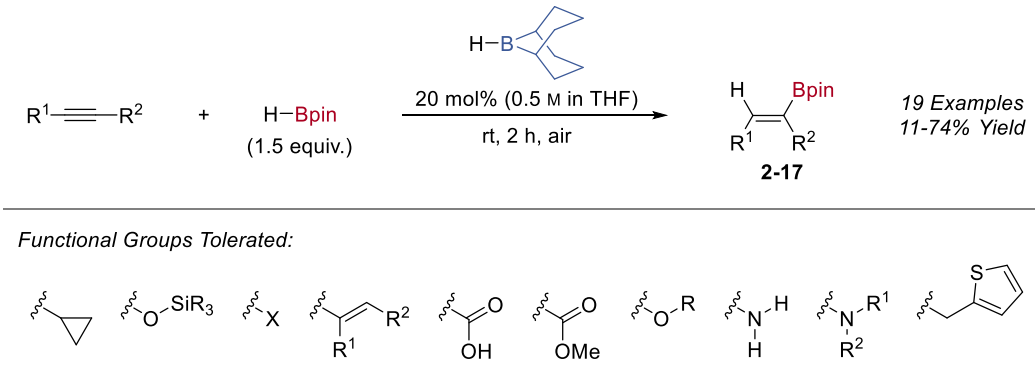
Reaction progress monitoring and single-turnover experiments, combined with isotopic-entrainment and isotopic-labelling experiments (performed by E. Nieto-Sepulveda), resulted in the postulation of a mechanism (Scheme 2-10) similar to that initially proposed by Hoshi for the dicyclohexylborane-catalysed hydroboration of alkynes with HBpin. In solution, dialkylboranes exist in equilibrium between dimers and solvent-ligated monomers. In dioxane/chloroform (100:1), H-*B*-9-BBN (0.083 M) is largely dimeric (98%), determined by ^{11}B NMR spectroscopy. Initial hydroboration of alkyne **2-18** results in the formation of the linear and branched alkenylboranes **2-19** and **2-19$_{iso}$** with high linear regioselectivity (3×10^2:1). Reaction of the alkenylborane **2-19** with HBpin results in the formation of the alkenyl boronic ester **2-17o**, proceeding through B–C(sp^2)/B–H transborylation, where the alkenyl group is transferred from boron to boron, as hypothesised by Hoshi. This was confirmed by a single-turnover experiment with the alkenylborane **2-19** and ^{10}B-labelled HBpin, resulting in the formation of ^{10}B-labelled alkenyl boronic ester product **^{10}B-2-17o** exclusively (reaction performed by E. Nieto-Sepulveda). The branched alkenyl boronic ester product **2-17o$_{iso}$** was not observed. Over-hydroboration of the alkenylborane **2-19** and the alkenyl boronic ester **2-17o** by H-*B*-9-BBN can occur, resulting in the irreversible formation of the *gem*-diborylalkanes **2-20** and **2-21**, as confirmed by stoichiometric experiments. An isotopic-entrainment experiment confirmed that the alkenylborane **2-19** exists as an on-cycle intermediate and that each step in the catalytic cycle is irreversible (performed by E. Nieto-Sepulveda).



Scheme 2-10. Mechanism for the Dialkylborane-catalysed Hydroboration of Alkynes with HBpin

2.6 Conclusions and Future Work

An H-*B*-9-BBN-catalysed hydroboration of alkynes with HBpin was developed (Scheme 2-11). Other boranes, including the commercially-available $H_3B{\cdot}SMe_2$ displayed lower reactivity compared to H-*B*-9-BBN. The relative stability of the commercially-available borane H-*B*-9-BBN and the straightforward reaction set-up makes this catalytic system accessible and operationally simple.

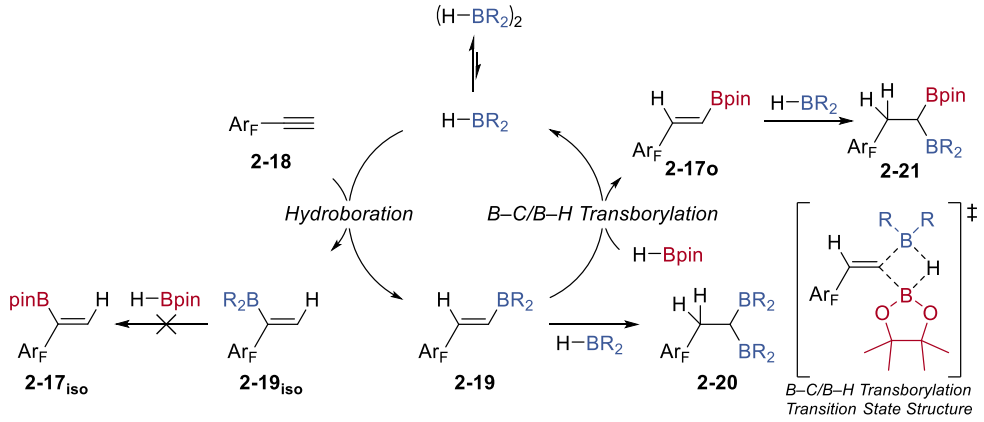


Scheme 2-11. H-*B*-9-BBN-catalysed Hydroboration of Alkynes with HBpin

The reaction conditions tolerated a large range of functional groups, including cyclopropyl, silyl ether, halide, internal alkene, acid, ether, primary and tertiary amine, and thiophene groups. The reaction resulted in *cis*-hydroboration products exclusively and exhibited high linear regioselectivity. Low to moderate yields of alkenyl boronic ester were observed for several substrates, possibly caused by over-hydroboration by H-*B*-9-BBN to form the mixed *gem*-diborylalkane, reducing the yield and inhibiting the catalyst. Other borane-catalysed systems either do not observe over-hydroboration or not to the same extent as this H-*B*-9-BBN-catalysed reaction. This limitation could be overcome in part by first quenching the reaction with excess benzaldehyde to react

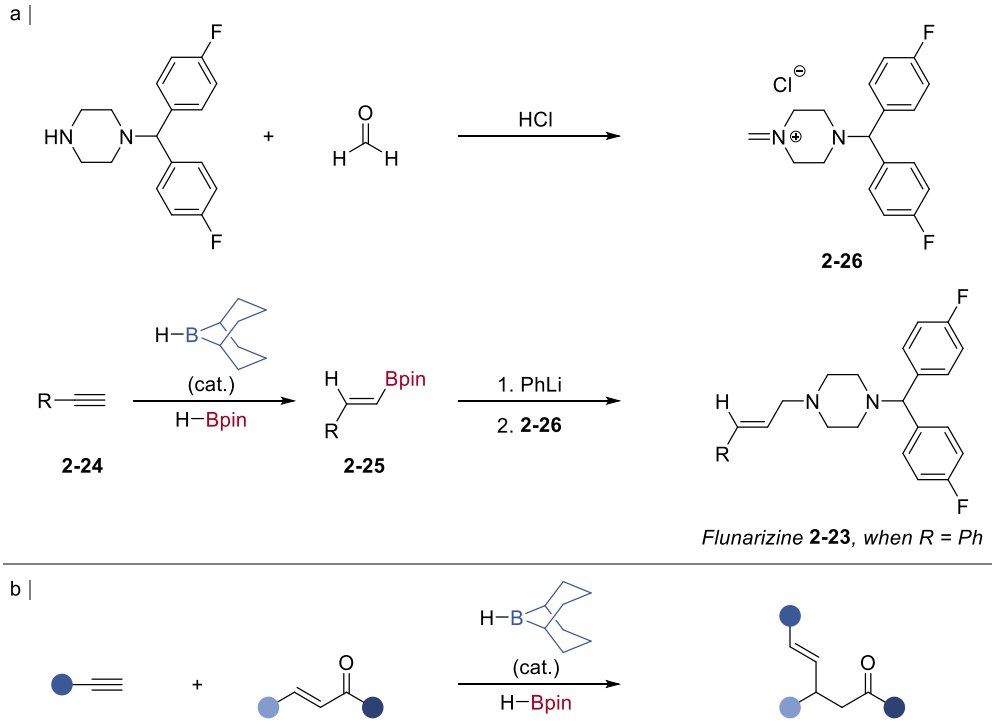
with the mixed *gem*-diborylalkane and re-form the alkenyl boronic ester. In the case of 1-octyne, the yield of alkenyl boronic ester could be increased by 18% by using this method.

Whilst the straightforward mechanism initially postulated by Hoshi was supported by kinetic analysis, and single-turnover and isotopic-labelling experiments, side reactions complicate the system, including the irreversible formation of *gem*-diborylalkanes from H-*B*-9-BBN, inhibiting the reaction (Scheme 2-12). The key turnover step is a B−C(sp^2)/B−H transborylation (alkenyl transfer from boron to boron), confirmed by a single-turnover experiment using ^{10}B-labelled HBpin (reaction performed by E. Nieto-Sepulveda). This mechanistic analysis will continue to provide a basis for future transborylation projects, having been used as such in several projects already.[20, 45, 46, 55, 59, 74]



Scheme 2-12. Proposed Mechanism

This system has already been used as a point of reference to develop a borane-catalysed double hydroboration with HBpin, giving *gem*-diborylalkane products.[20] Extending this project further, the catalytic system could be used in the preparation of the calcium antagonist flunarizine **2-23** and similar compounds, where the hydroboration of an alkyne precursor **2-24** would be a key step in the synthesis (Scheme 2-13, a). Subsequent reaction of the alkenyl boronic ester **2-25** with the iminium ion **2-26** would generate the target compound. If B−C(sp^2)/B−H transborylation can be controlled, a catalytic system for the 1,4-alkenylation of α,β-unsaturated ketones could be developed, using H-*B*-9-BBN as the catalyst and HBpin as the turnover reagent (Scheme 2-13, b).[22]

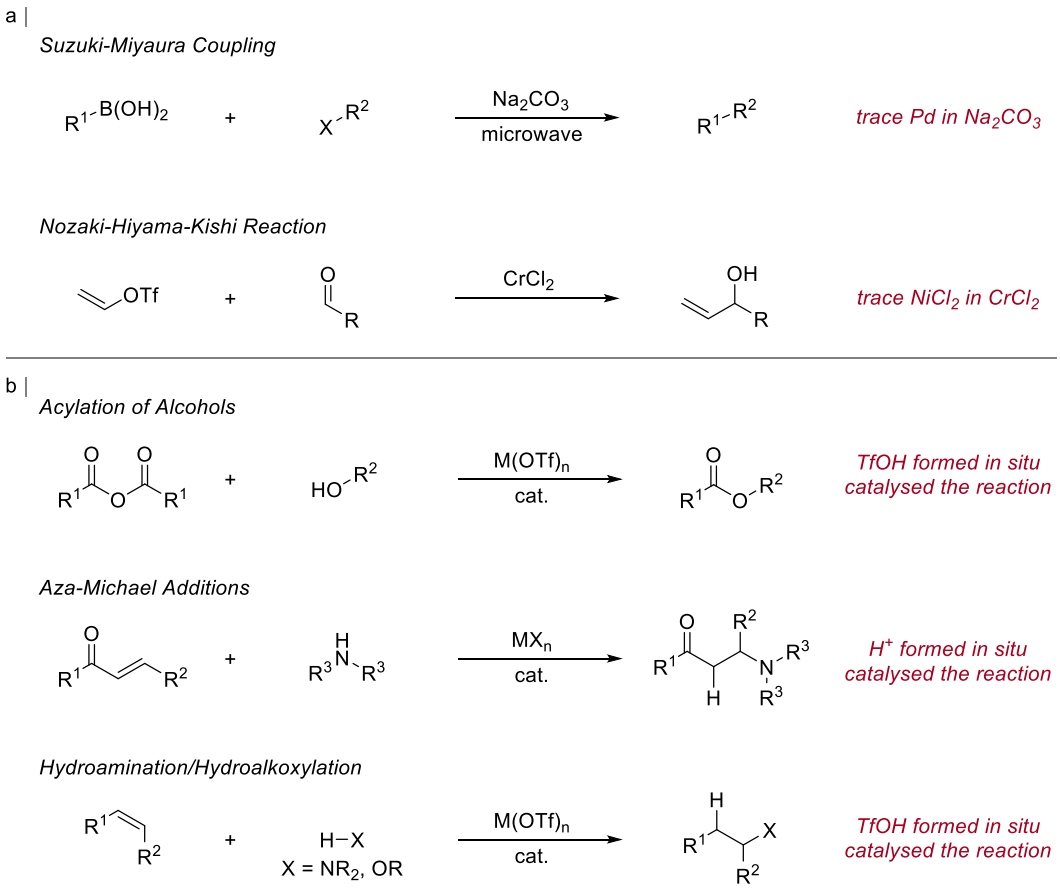


Scheme 2-13. Future Work: a) Flunarizine **2-23** Synthesis; b) Borane-catalysed 1,4-Alkenylation of α,β-Unsaturated Ketones

3. Hidden Boron Catalysis

3.1 Introduction

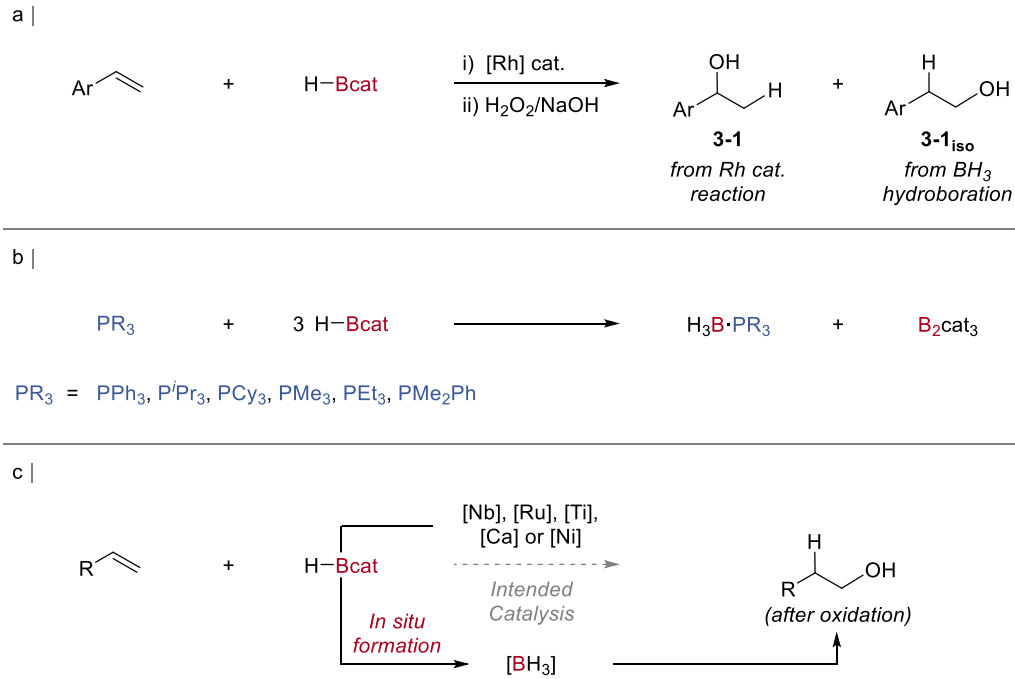
The development of new catalyst systems for organic transformations has been afflicted by hidden catalysis. Trace metal contamination continues to cause misconceptions in new systems, including in "Pd-free" Suzuki-Miyaura cross-couplings,[75] in the Nozaki-Hiyama-Kishi reaction[76] and in "Fe-catalysed" cross-couplings (Scheme 3-1, a).[77] Furthermore, several "metal-catalysed" transformations have been shown, after reassessment, to be Brønsted acid-catalysed, where the role of the metal salt was merely to form a simple or complex acid *in situ* (Scheme 3-1, b).[78] Notable examples include the acylation of alcohols,[79] aza-Michael additions,[80] and the hydroamination and hydroalkoxylation of alkenes.[81-83]



Scheme 3-1. Hidden Catalysis in Organic Transformations: a) Trace Metal Contamination; b) Hidden Brønsted Acid Catalysis

Catalysed hydroboration is not immune to hidden catalysis. The first examples of catalysed hydroboration focused on phosphine-based rhodium complexes.[84] Marder and Baker used a series of rhodium complexes, including Wilkinson's catalyst

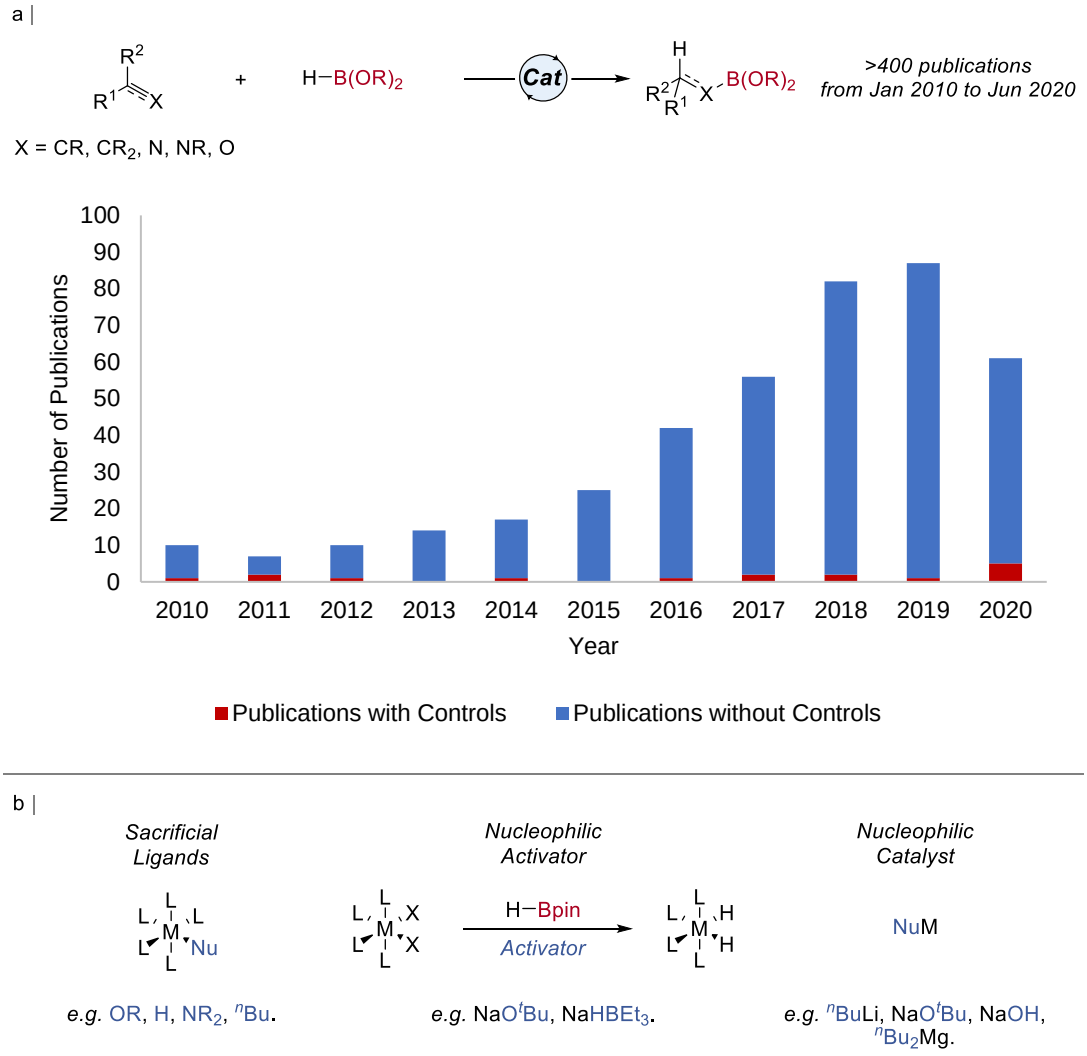
[$Rh(PPh_3)_3Cl$], in the hydroboration of alkenes with HBcat, exhibiting Markovnikov selectivity (Scheme 3-2, a).[85] With some substrates, significant quantities of the *anti*-Markovnikov regioisomer **3-1$_{iso}$** were observed. After a detailed investigation, it was determined that the phosphine ligands were labile and reacting with HBcat, resulting in the formation of BH_3 (Scheme 3-2, b).[86, 87] The hydroboration of alkenes with BH_3 is known to proceed predominantly with *anti*-Markovnikov selectivity,[88] and it was rationalised that stoichiometric BH_3 hydroboration was responsible for the formation of the *anti*-Markovnikov regioisomer **3-1$_{iso}$**. Around the same time, BH_3 was shown to catalyse the hydroboration of alkynes with HBcat,[25, 26] therefore, it is plausible that the regioisomer **3-1$_{iso}$** was formed from a BH_3-catalysed hydroboration of the alkene with HBcat, rather than from the proposed stoichiometric hydroboration.



Scheme 3-2. a) Rh-catalysed Hydroboration of Alkenes with HBcat; b) Phosphine-promoted Decomposition of HBcat to BH_3 c) Other Catalysts Shown to Decompose HBcat

Subsequent catalysed hydroboration reactions with HBcat would routinely test for the formation of BH_3 to exclude hidden catalysis (Scheme 3-2, c).[89-93] However, as hydroboration catalysis switched from using HBcat to the more stable HBpin, these decomposition studies were largely overlooked, even though BH_3 is known to catalyse the hydroboration of alkynes and alkenes with HBpin.[35] Hydroboration has become an exemplar reaction with which to test new catalysts; there has been a surge in new systems for catalysed hydroboration with 1,3,2-dioxaborolanes (e.g. HBcat and HBpin), with over 400 papers published between January 2010 and June 2020 (Scheme 3-3, a). Nucleophiles are abundant in new catalyst architectures as sacrificial

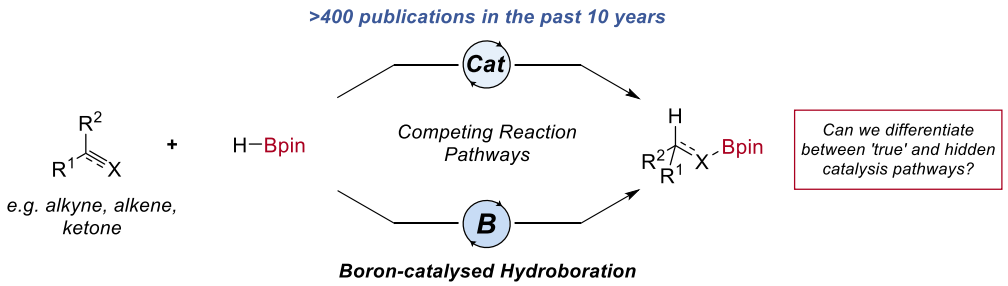
ligands, catalyst activators and in inherently nucleophilic catalysts (Scheme 3-3, b). Therefore, there is significant potential for these nucleophilic species to decompose HBpin to BH_3, and the potential that the catalyst systems are merely proceeding through a hidden boron-catalysed pathway. Less than 5% of the publications between January 2010 and June 2020 performed suitable control reactions to exclude the formation of BH_3 and hidden boron catalysis (Scheme 3-3, a).



Scheme 3-3. a) Catalysed Hydroboration Publications Between January 2010 and June 2020, and Publications With (Red) and Without (Blue) Suitable Controls; b) Nucleophiles in Catalysed Hydroboration Systems

3.2 Project Aims

The aims of this project were to illustrate the propensity of simple nucleophiles to decompose HBpin to catalytically-active boranes and borohydrides, quantifying the amounts formed; to show that BH_3 forms under 'catalysis'; and to discern 'true' from hidden catalysis.

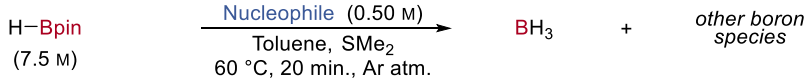


3.3 Nucleophile-Promoted Decomposition of HBpin

As nucleophiles are ubiquitous in catalysed hydroboration systems, as pre-catalyst activators, sacrificial ligands, and inherent 'catalysts', it was deemed necessary to explore the potential of simple nucleophiles to decompose HBpin and to record and quantify the amounts of any new boron species formed by ^{11}B NMR spectroscopy (Table 3-1). Burgess added Ti(O^{i}Pr)$_4$ to HBcat to show that BH_3 would form, and therefore was not a 'true' alkene hydroboration catalyst.[91] Comparably, Ti(O^{i}Pr)$_4$ (0.50 M in toluene) will decompose HBpin (7.5 M) to form BH_3 (monomer ligated to SMe_2 or HBpin) in significant quantities (0.30 M) (Table 3-1, Entry 1). Sodium and potassium *tert*-butoxide have been used as activators in hydroboration catalysis and have previously been shown to decompose HBpin to BH_3.[57, 94-96] The reactions of potassium, sodium, and lithium *tert*-butoxide with HBpin all gave similar quantities of BH_3 formation (0.02-0.03 M) (Entries 2-4), suggesting the anion, and not the cation, is largely responsible for decomposition. In the case of lithium *tert*-butoxide, trace quantities of borohydride ($[BH_4]^-$) and [(^{t}BuO)HBpin]$^-$ were formed. The poor solubility of metal borohydrides in toluene may have lowered this observed concentration, however, mass balance calculations suggested that any effect from decreased solubility was negligible. Hydroboration pre-catalysts have been activated by the addition of organolithium and Grignard reagents.[97, 98] Both MeLi and MeMgBr promoted BH_3 formation from HBpin (0.02 and 0.01 M) (Entries 5-6). MeLi also formed $[BH_4]^-$ (0.01 M), formed from hydride transfer to BH_3, and MeBpin (0.27 M) and Me_3B (0.03 M), which are by-products of decomposition. Nucleophilic addition of MeLi to HBpin results in the formation of Li[(Me)HBpin], which can transfer hydride to another molecule of HBpin, promoting decomposition and forming MeBpin. Further addition would result in the formation of Me_3B and B_2pin_3. Similarly, MeMgBr formed MeBpin (0.09 M) and Me_3B (<0.01 M), albeit in much smaller quantities. Trace quantities of [(Me)HBpin]$^-$ (<0.01 M) were also observed, supporting

the hypothesis that decomposition proceeds through this intermediate. Triethylborohydride has been used as both an activator[99, 100] and a hydroboration catalyst.[101-103] $NaHBEt_3$ was shown to decompose HBpin to BH_3 (0.03 M) (Entry 7), forming significant quantities of Et_3B (0.37 M) and EtBpin (0.21 M), as well as small amounts of $[B_2H_4Et_3]^-$ (0.03 M) (a dimer of BH_3 and $[HBEt_3]^-$), $[(Et)HBpin]^-$ (0.02 M) and $EtH_2B{\cdot}SMe_2$ (0.01 M). The amides $[N(SiMe_3)_2]^-$ and $[N^iPr_2]^-$ have been used as spectator and sacrificial ligands in hydroboration catalysis.[104-109] Both $Na[N(SiMe_3)_2]$ and LiN^iPr_2 promoted BH_3 formation (0.02 and 0.06 M) (Entries 8 and 9). LiN^iPr_2 also formed $[BH_4]^-$ (0.02 M) and trace quantities of $[(^iPr_2N)HBpin]^-$ (<0.01 M). NaOH has been proposed as an active hydroboration catalyst but promoted decomposition to form BH_3 (0.01 M) (Entry 10).[110] The *n*-butyl anion has been proposed as a sacrificial ligand in hydroboration pre-catalysts;[111-115] upon reaction with HBpin, a metal-hydride catalyst is formed along with ^{n}BuBpin. $^nBu_2Mg$ and ^{n}BuLi have also been proposed as active hydroboration catalysts,[116-120] but both formed BH_3 (0.07 and 0.04 M, respectively) along with several other decomposition products (Entries 11 and 12). $^nBu_2Mg$ formed $[BH_4]^-$ (0.04 M), $^nBu_3B$ (0.08 M), $[B_2H_7]^-$ (0.01 M), ^{n}BuBpin (0.20 M) and trace quantities of $[(^nBu)HBpin]^-$ (<0.01 M). ^{n}BuLi formed $[BH_4]^-$ (0.01 M), $^nBu_3B$ (0.06 M), ^{n}BuBpin (0.16 M), $^nBuH_2B{\cdot}SMe_2$ (0.01 M) and $^nBuH_2B$ (0.02 M) as a mixed dimer coordinated to $^nBu_2HB$ (peak obscured by HBpin). The same reaction was analysed again after 2 hours and the same concentrations were observed for most species (Entry 13), although [$^nBu_3B$] and [HBpin] had decreased (0.04 and 7.20 M) with a concomitant increase in [^{n}BuBpin] (0.19 M), a result of B−C/B−H transborylation. $LiAlH_4$ has been used to catalyse the hydroboration of alkenes,[12] but decomposition of HBpin to BH_3 was observed (0.18 M), along with significant quantities of $[BH_4]^-$ (0.36 M) (Entry 14). Similarly, $LiBH_4$ has been used to promote the hydroboration of alkenes with HBcat.[121] When reacted with HBpin (Entry 15), $LiBH_4$ promotes formation of BH_3 (0.01 M) but the solubility of $LiBH_4$ reduced the concentration of $LiBH_4$ observed (0.01 M). This should be considered when evaluating the concentrations of other metal borohydrides. Triflate has been used as a sacrificial ligand in hydroboration catalysis.[122] When sodium triflate was added to HBpin, no decomposition was observed (Entry 16), presumably because triflate is a weak nucleophile.

Table 3-1. Quantifying Boron Species Formation from the Reaction of Nucleophiles with HBpin with Associated ^{11}B NMR Signals



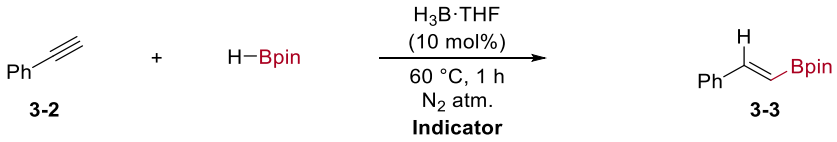
Entry	Nucleophile	HBpin (M)	B_2pin_3 and ROBpin (M)	$L{\cdot}BH_3$ (M)[a]	$[BH_4]^-$ (M)	R_3B (M)	$[B_2H_7]^-$ and $[B_2H_4Et_3]^-$ (M)	$[(R)HBpin]^-$ (M)	$RH_2B{\cdot}SMe_2$ (M)	$[RBH_2][R_2BH]$ (M)	RBpin (M)	Total (M)
1	$Ti(O^iPr)_4$	5.66	1.59	0.30	-	-	-	-	-	-	-	7.55
2	KO^tBu	7.19	0.25	0.02	-	-	-	-	-	-	-	7.46
3	NaO^tBu	7.29	0.14	0.02	-	-	-	-	-	-	-	7.45
4	LiO^tBu	7.25	0.21	0.03	<0.01	-	-	<0.01	-	-	-	7.49
5	MeLi	7.15	0.03	0.02	0.01	0.03	-	-	-	-	0.27	7.51
6	MeMgBr	7.33	0.08	0.01	-	<0.01	-	<0.01	-	-	0.09	7.51
7	$NaHBEt_3$	7.22	0.15	0.03	-	0.37	0.03	0.02	0.01	-	0.21	8.04
8	$Na[N(SiMe_3)_2]$	7.24	0.18	0.02	-	-	-	-	-	-	-	7.44
9	LiN^iPr_2	7.25	0.15	0.06	0.02	-	-	<0.01	-	-	-	7.48
10	NaOH	7.41	0.06	0.01	-	-	-	-	-	-	-	7.48
11	$^nBu_2Mg$	7.00	0.12	0.07	0.04	0.08	0.01	<0.01	-	-	0.20	7.52
12	^{n}BuLi	7.23	0.04	0.04	0.01	0.06	-	-	0.01	0.02	0.16	7.55
13	^{n}BuLi[b]	7.20	0.04	0.04	0.01	0.04	-	-	0.01	0.02	0.19	7.53
14	$LiAlH_4$	6.84	0.05	0.18	0.36	-	-	-	-	-	-	7.43
15	$LiBH_4$	7.36	0.12	0.01	0.01	-	-	<0.01	-	-	-	7.50
16	NaOTf	7.46	0.02	0.00	-	-	-	-	-	-	-	7.48
^{11}B NMR Signals (δ)		28 (d, J = 173 Hz)	22 (s)	−12 (q, J = 98 Hz),[56] −20 (q, J = 97 Hz)[123]	−39 (p, J = 81 Hz)[124]	~85 (s)[124]	−27 (q, J = 75 Hz)[125]	R ≠ H ~5 (s)[95], R = H −6 (t, J = 99 Hz)[5]	~−8 (t, J = 104 Hz)[126]	17 (s)[126]	~34 (s)[6]	

- = not observed. [a]L = HBpin or SMe_2. [b]After 2 hours.

3.4 BH_3 Formation in Catalysis

Evidently, nucleophiles will readily decompose HBpin to BH_3. However, it was not clear that the nucleophiles would mediate a hydroboration reaction with HBpin or that BH_3 was forming under reaction conditions, and if BH_3 was formed was it in a sufficient quantity to catalyse the reaction. A BH_3 indicator, observable after work-up, would confirm that BH_3 was forming under catalysis. Inhibition of BH_3 catalysis by coordination of the indicator would provide a qualitative assessment in support of hidden catalysis.

Table 3-2. Optimisation of Indicators for BH_3 Formation under Catalysis



Entry	Indicator	Yield 3-3 (%)	Diagnostic NMR Signal
1	-	60	-
2	1,3-Cyclohexadiene	33	×
3	1,5-Hexadiene	39	×
4	PPh_3	36	✓
5	Triallylamine	11	✓
6	TMEDA	2	✓

Conditions: Phenylacetylene **3-2** (1.0 mmol), $H_3B{\cdot}THF$ (0.10 mmol), HBpin (1.1 mmol) and indicator (0.10 mmol). Yields were determined by ^1H NMR spectroscopy using an internal standard (1,3,5-trimethoxybenzene).

Using phenylacetylene **3-2** as an example substrate, a range of indicators were tested (Table 3-2). Hydroboration of phenylacetylene with HBpin, catalysed by $H_3B{\cdot}THF$, gave the alkenyl boronic ester **3-3** in good yield (60%) (Entry 1). Dienes react with BH_3 to form polymeric materials.[127] Addition of the dienes, 1,3-cyclohexadiene and 1,5-hexadiene (Entries 2 and 3), to the reaction reduced hydroboration (33 and 39%, respectively) but did not provide a suitable diagnostic peak to confirm BH_3 formation under catalysis. Excess PPh_3 has been shown to reduce the activity of BH_3 in rhodium-catalysed alkene hydroboration[86] and PPh_3 reduced the yield of alkenyl boronic ester (36%, Entry 4) and the Lewis acid-Lewis base adduct was observable by ^{11}B NMR spectroscopy. Triallylamine has been shown to undergo hydroboration with BH_3 to form a tricyclic compound.[128] Whilst this was not observed in the example hydroboration reaction, diagnostic signals of various adducts were observed.

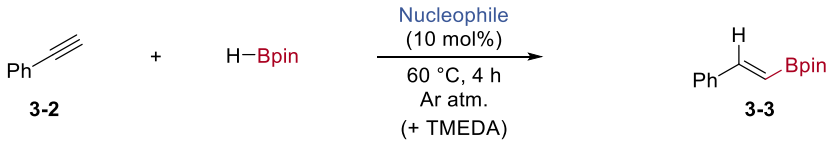
Triallylamine also reduced the yield of alkenyl boronic ester significantly (11%, Entry 5). *N*,*N*,*N*′,*N*′-Tetramethylethylenediamine (TMEDA) forms mono- and bis-adducts with BH_3 that are air- and moisture-stable.[129] Inhibition of the hydroboration reaction by TMEDA was observed (2%, Entry 6) and $(H_3B)_2$·TMEDA and H_3B·TMEDA were observable by ^{11}B NMR spectroscopy (δ −10). Moreover, no interaction between TMEDA and HBpin nor any HBpin decomposition were observed by ^{11}B NMR spectroscopy after heating at 60 °C, so TMEDA would not be responsible for any potentially observed HBpin decomposition. Therefore, TMEDA was used as the indicator for BH_3 formation under catalysis conditions.

$H_3B{\cdot}SMe_2$ efficiently catalyses the hydroboration of phenylacetylene **3-2** with HBpin, forming the alkenyl boronic ester **3-3** in good yield (94%) (Table 3-3, Entry 1).[35] Addition of TMEDA results in inhibition of the reaction (10%) and the formation of $(H_3B)_2$·TMEDA and H_3B·TMEDA, as observed by ^{11}B NMR spectroscopy (δ −10). $(H_3B)_2$·TMEDA was prepared and used as a catalyst, resulting in a low yield of alkenyl boronic ester **3-3** (5%) (Entry 2). However, at 80 °C, $(H_3B)_2$·TMEDA will catalyse the reaction (Entry 3). This suggests inhibition of the reaction by TMEDA occurs by the formation of a strong Lewis acid-Lewis base adduct between BH_3 and TMEDA, which is sufficiently labile above 60 °C, allowing BH_3 to catalyse the reaction at 80 °C.

A selection of the nucleophiles tested in the decomposition studies were used to mediate the hydroboration of phenylacetylene **3-2** with HBpin (Entries 4-12). All of the nucleophiles tested were found to mediate the hydroboration reaction to form the alkenyl boronic ester **3-3**. Likewise, all of the nucleophile-mediated reactions were inhibited by the addition of TMEDA, and TMEDA adducts of BH_3 were observed in all cases. $NaHBEt_3$ mediated the formation of the alkenyl boronic ester **3-3** in good yield (61%) but required more TMEDA (0.60 equivalents) to inhibit the reaction (Entry 4). This may be due to the formation of Et_3B in large quantities (Table 3-1, Entry 7), which can act as a pre-catalyst for hydroboration (B–C(sp^3)/B–H transborylation of Et_3B with HBpin would result in the formation of diethyl- and monoethylborane, which could catalyse hydroboration in an analogous manner to H-*B*-9-BBN). The increased steric bulk from the ethyl groups of Et_3B, compared to the hydrides of BH_3, may reduce the interaction between the Et_3B and TMEDA, in turn reducing the efficacy of TMEDA to inhibit the reaction. $LiAlH_4$, previously used as a catalyst for alkene hydroboration, promoted the hydroboration of phenylacetylene **3-2**

with HBpin (51%) and the reaction was inhibited effectively by TMEDA (3%) (Entry 5). NaOH, NaO^{t}Bu, Na[N(SiMe$_3$)$_2$] and MeMgBr all promoted the formation of the alkenyl boronic ester **3-3** (41%, 59%, 29%, 60%) (Entries 6-9) and all of the reactions were inhibited by the addition of TMEDA. ^{n}BuLi, Ti(O^{i}Pr)$_4$, and ^{n}Bu$_2$Mg mediated the hydroboration of phenylacetylene **3-2** with HBpin (53%, 51%, 81%) (Entries 10-12). These nucleophiles required greater quantities of TMEDA to inhibit the reaction (0.30 equivalents). From the decomposition studies, ^{n}BuLi and ^{n}Bu$_2$Mg both formed ^{n}Bu$_3$B and ^{n}BuLi also formed ^{n}Bu$_2$BH and ^{n}BuBH$_2$ (Table 3-1, Entries 11 and 12). These may have reduced interactions with TMEDA, as proposed for Et$_3$B formed from NaHBEt$_3$. Furthermore, TMEDA is known to form complexes with Mg and Li,[130-133] potentially reducing the amount of TMEDA available to coordinate to BH$_3$.

Table 3-3. Nucleophile-mediated Alkyne Hydroboration with HBpin and Inhibition by TMEDA



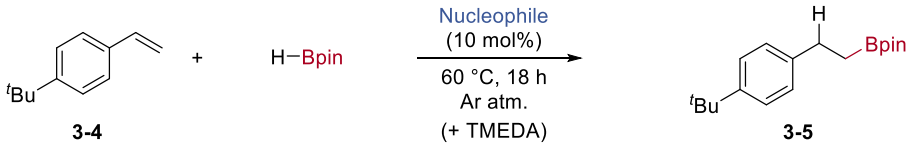
Entry	Nucleophile[a]	Yield 3-3 (%)	
		Without TMEDA	With TMEDA[c]
1	$H_3B{\cdot}SMe_2$	94	10
2	$(H_3B)_2{\cdot}$TMEDA	5	n/a
3	$(H_3B)_2{\cdot}$TMEDA	85[b]	n/a
4	NaHBEt$_3$	61	3[c]
5	LiAlH$_4$	51	3
6	NaOH	41	1
7	NaO^{t}Bu	59[e]	1[e]
8	Na[N(SiMe$_3$)$_2$]	29	0
9	MeMgBr	60	1
10	^{n}BuLi	53	1[f]
11	Ti(O^{i}Pr)$_4$	51	5[f]
12	^{n}Bu$_2$Mg	81	11[f]

Conditions: Phenylacetylene **3-2** (1.0 mmol), nucleophile (0.10 mmol) and HBpin (1.5 mmol). Yields were determined by ^{1}H NMR spectroscopy using an internal standard (1,3,5-trimethoxybenzene). [a]Samples of nucleophiles used as purchased, i.e., without removal or exchange of solvent. [b]80 °C, 18 h. [c]With 0.10 mmol of TMEDA (10 mol%), unless otherwise noted. [d]With 0.60 mmol of TMEDA. [e]18 h. [f]With 0.30 mmol of TMEDA.

As the hydroboration of alkenes with HBpin can be catalysed by BH$_3$ (Table 3-4, Entry 1),[35] it was necessary to investigate the ability of the same nucleophiles to mediate the hydroboration of an example alkene, *tert*-butylstyrene **3-4**. Similar results to alkyne hydroboration were observed (Entries 2-10). TMEDA successfully inhibited the

reaction and the TMEDA adducts of BH_3 were observed by ^{11}B NMR spectroscopy. $NaHBEt_3$ promoted the formation of the alkyl boronic ester **3-5** in good yield (81%) (Entry 2) and was inhibited by TMEDA (0.20 equivalents), reducing the yield of alkyl boronic ester **3-5** (43%). $LiAlH_4$, NaOH, NaO^tBu, $Na[N(SiMe_3)_2]$ and MeMgBr all mediated the hydroboration of *tert*-butylstyrene **3-4** with HBpin (81%, 28%, 71%, 72% and 55%) (Entries 3-7) and all were inhibited by the addition of TMEDA. The alkyl boronic ester **3-5** was formed in the ^{n}BuLi-promoted hydroboration of *tert*-butylstyrene **3-4** (30%) (Entry 8), but the reaction was inhibited slightly by the addition of TMEDA (0.20 equivalents). As with the ^{n}BuLi-promoted hydroboration of phenylacetylene **3-2**, it is likely that the other boranes that were formed in the decomposition of HBpin (i.e. $^nBu_3B$, $^nBu_2BH$ and $^nBuBH_2$) were not inhibited effectively by TMEDA. $Ti(O^iPr)_4$ and $^nBu_2Mg$ mediated the formation of the alkyl boronic ester **3-5** (73% and 85%) (Entries 9 and 10) and were inhibited by the addition of TMEDA.

Table 3-4. Nucleophile-mediated Alkene Hydroboration with HBpin and Inhibition by TMEDA



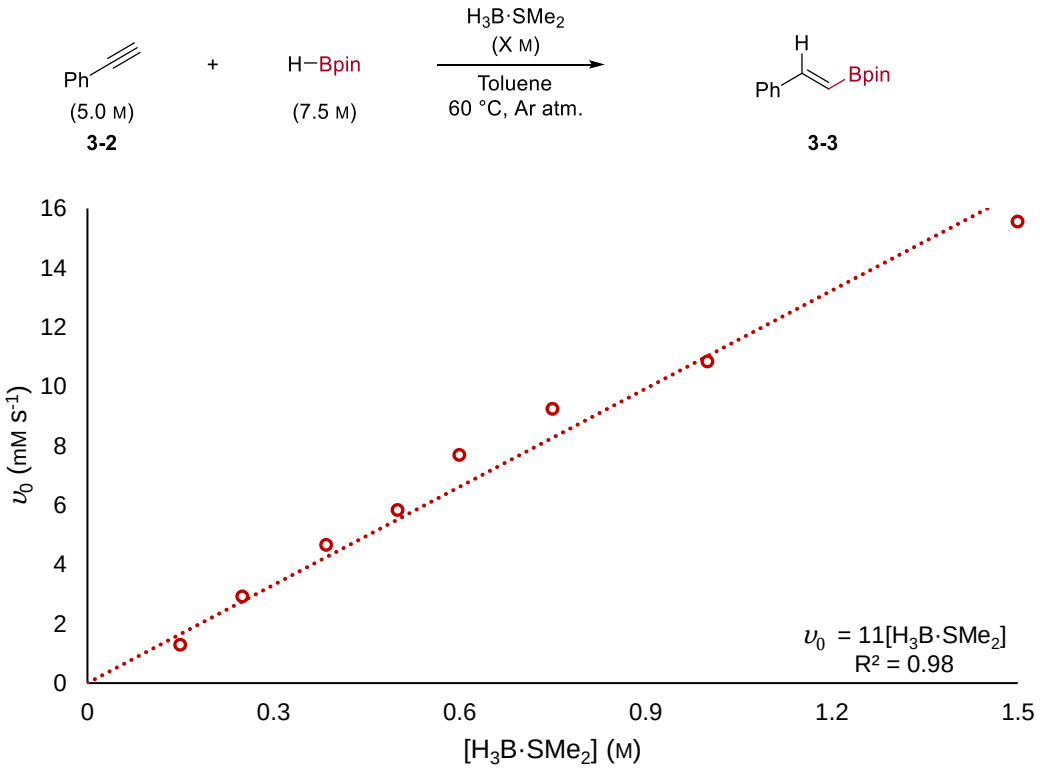
3-4 **3-5**

Entry	Nucleophile[a]	Yield 3-5 (%)	
		Without TMEDA	With TMEDA[b]
1	$H_3B{\cdot}SMe_2$	67	5
2	$NaHBEt_3$	81	43
3	$LiAlH_4$	81	5
4	NaOH	28	7
5	NaO^tBu	71	10
6	$Na[N(SiMe_3)_2]$	72	12
7	MeMgBr	55	21
8	^{n}BuLi	30	26
9	$Ti(O^iPr)_4$	73	10
10	$^nBu_2Mg$	85	22

Conditions: *tert*-Butylstyrene **3-4** (1.0 mmol), nucleophile (0.10 mmol), and HBpin (1.5 mmol). Yields were determined by ^1H NMR spectroscopy using an internal standard (1,3,5-trimethoxybenzene). [a]Samples of nucleophiles used as purchased, i.e., without removal or exchange of solvent. [b]With 0.20 mmol of TMEDA (20 mol %).

3.5 Rates of Reaction

Whilst TMEDA inhibition confirmed BH_3 was forming under catalysis, it only provided a qualitative assessment of BH_3 formation; it did not confirm the reaction proceeded through BH_3 catalysis only. TMEDA may also be inhibiting 'true' catalysis pathways as TMEDA is known to coordinate metals and affect the aggregation states of organometallic reagents.[130-134] Therefore, to distinguish between competing pathways of 'true' and 'hidden' catalysis, a quantitative assessment needed to be designed. By comparing the initial rate of reaction of a nucleophile-promoted hydroboration to the initial rate of reaction for the corresponding BH_3-catalysed reaction, where the concentration of BH_3 used matched the concentration observed in the decomposition studies, it would be possible to distinguish between these two reaction pathways.



Scheme 3-4. Calibration Gradient for the Initial Rate of Reaction (υ_0) Plotted Against [$H_3B{\cdot}SMe_2$] (in M) for the Hydroboration of Phenylacetylene **3-2** with HBpin

A plot of varying concentrations of $H_3B{\cdot}SMe_2$ against initial rate of reaction for the hydroboration of phenylacetylene **3-2** with HBpin provided a calibration gradient to be used to compare to the nucleophile-promoted hydroboration of phenylacetylene **3-2** (SMe_2 added to the nucleophile-promoted reactions to ensure that all other variables were kept constant) (Scheme 3-4). Using the initial rates for the nucleophile-promoted

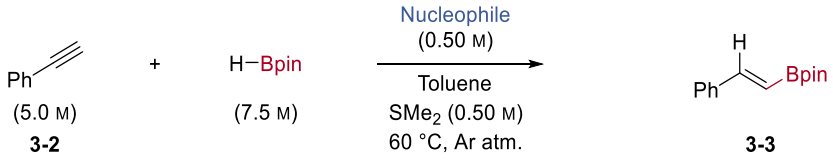
reactions and the calibration gradient, it was possible to calculate a BH_3 concentration ($[BH_3]_{calc}$). If the observed BH_3 concentration ($[BH_3]_{obs}$) matched the calculated BH_3 concentration ($[BH_3]_{calc}$), the nucleophiles must only mediate the decomposition of HBpin to BH_3 and the reaction proceeds through BH_3 catalysis only. Conversely, if the concentrations of $[BH_3]_{obs}$ and $[BH_3]_{calc}$ are different, true catalysis may be operating but does not conclusively exclude hidden boron catalysis, as other boron-based catalysts may be formed alongside BH_3 and would not be accounted for in this comparison of BH_3 concentrations. By maintaining consistent reagent concentrations between the decomposition studies (Table 3-1, $[BH_3]_{obs}$) and the initial rates of reaction (Table 3-5, $[BH_3]_{calc}$) and by adding the substrate after 20 minutes (the same time point for $[BH_3]_{obs}$), direct comparison between experiments was possible.

For the nucleophiles NaO^tBu, $Na[N(SiMe_3)_2]$ and $LiAlH_4$, the rates of phenylacetylene **3-2** hydroboration resulted in $[BH_3]_{calc}$ that were comparable to $[BH_3]_{obs}$ from the decomposition studies (Table 3-5, Entries 2, 3 and 4). Therefore, these nucleophiles are not acting as catalysts in the hydroboration of alkynes but are merely decomposing HBpin to BH_3.

The $^nBu_2Mg$-promoted hydroboration of phenylacetylene **3-2** with HBpin gave a higher $[BH_3]_{calc}$ than $[BH_3]_{obs}$, initially suggesting that $^nBu_2Mg$ is an active catalyst. However, BH_3 was not the only boron species formed in the decomposition of HBpin by $^nBu_2Mg$, $^nBu_3B$ (0.09 M) was also formed (Table 3-1, Entry 11). Whilst trialkylboranes have not been reported to catalyse hydroboration previously, dialkyl- and monoalkylboranes are known to form from the redistribution of trialkylboranes with $H_3B{\cdot}SMe_2$,[126] and are known hydroboration catalysts.[135] It was proposed that trialkylboranes could act as a pre-catalyst undergoing redistribution with HBpin to form the active catalysts, dialkyl- and monoalkylboranes, *in situ*.[28, 135] Therefore, Et_3B was used as an example trialkylborane to mediate the hydroboration of phenylacetylene **3-2** with HBpin (Entry 7), but the rate of reaction (υ_0) was much lower than when $H_3B{\cdot}SMe_2$ was used (Entry 1). As $^nBu_2Mg$ formed BH_3 (0.07 M) and $^nBu_3B$ (0.09 M), a mimic of this system was made from a mixture of $H_3B{\cdot}SMe_2$ (0.07 M) and Et_3B (0.09 M) (Entry 8). This was used to catalyse the hydroboration of phenylacetylene **3-2** with HBpin and the initial rate (υ_0 = 2.0 mM s^{-1}) matched that of $^nBu_2Mg$. Therefore, $^nBu_2Mg$ is not a 'true' active catalyst for alkyne hydroboration but only mediates the decomposition of HBpin. The differences in initial rate between

Et_3B (0.50 M) (Entry 7) and the mixture of $H_3B{\cdot}SMe_2$ (0.07 M) and Et_3B (0.09 M) (Entry 8) suggests that the redistribution (or transborylation) between HBpin and Et_3B occurs less readily than the redistribution between $H_3B{\cdot}SMe_2$, Et_3B and HBpin. Redistribution of trialkylboranes with HBcat has been shown to be catalysed by $H_3B{\cdot}THF$.[18] It is likely that this proceeds through initial redistribution between the trialkylborane and $H_3B{\cdot}THF$, explaining the increased rate of reaction observed for the $H_3B{\cdot}SMe_2$ and Et_3B mixture-catalysed hydroboration, compared to the Et_3B-catalysed hydroboration.

Table 3-5. Comparison of Calculated and Observed BH_3 Concentrations for Phenylacetylene **3-2** Hydroboration



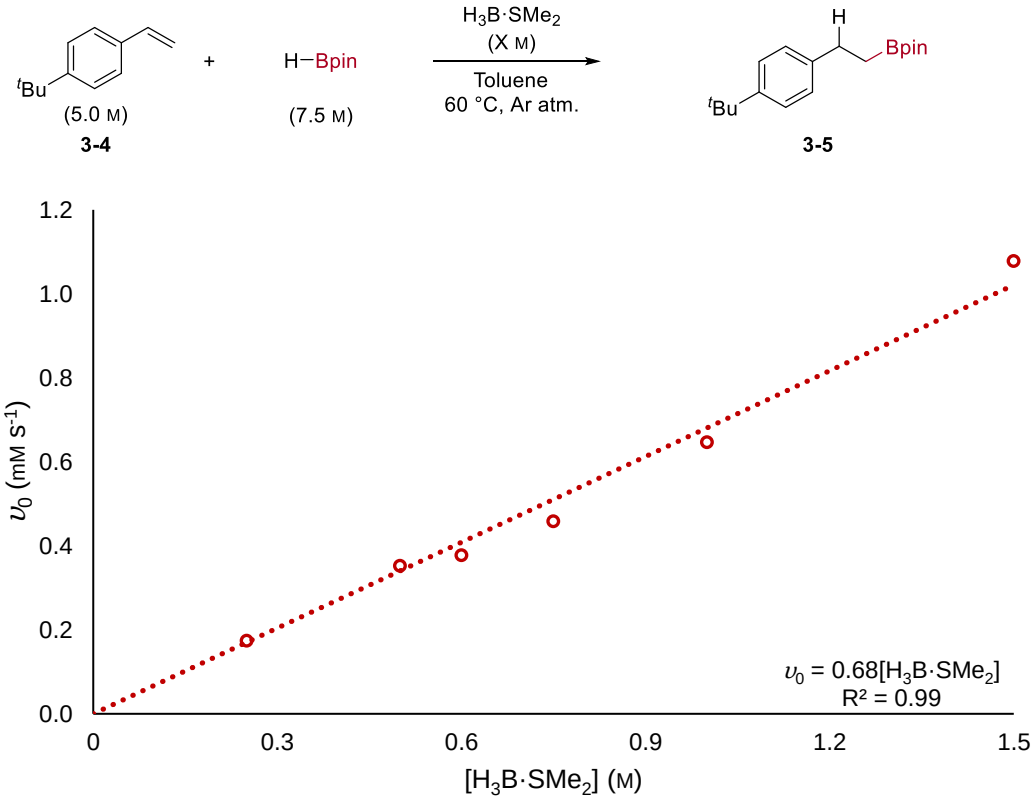
Entry	Nucleophile / Catalyst	v_0 (mM s^{-1})	$[BH_3]_{calc}$ (M)	$[BH_3]_{obs}$ (M)[a]
1[b]	$H_3B{\cdot}SMe_2$	5.8	n/a	n/a
2	NaO^tBu	0.15	0.01	0.02
3	$Na[N(SiMe_3)_2]$	0.15	0.01	0.02
4	$LiAlH_4$	2.1	0.19	0.18
5	$^nBu_2Mg$	2.0	0.18	0.07
6	^{n}BuLi	3.6	0.33	0.04
7	Et_3B	1.7	0.15	n/a
8	Et_3B and $H_3B{\cdot}SMe_2$[c]	2.0	0.18	n/a
9	H-*B*-9-BBN	>32	n/a	n/a

Conditions: Phenylacetylene **3-2** (2.0 mmol, 5.0 M), nucleophile (0.20 mmol, 0.50 M, 10 mol%), HBpin (3.0 mmol, 7.5 M), SMe_2 (0.20 mmol, 0.50 M), toluene (0.40 mL), 60 °C, 20 minutes prior to the addition of phenylacetylene **3-2**. Yields were determined by ^{1}H NMR spectroscopy using an internal standard (1,3,5-trimethoxybenzene, 0.10 mmol). [a]From Table 3-1. [b]No SMe_2 added. [c]Et_3B (0.09 M) and $H_3B{\cdot}SMe_2$ (0.07 M).

The $[BH_3]_{calc}$ for the ^{n}BuLi-promoted hydroboration of phenylacetylene **3-2** far surpasses the $[BH_3]_{obs}$ (Entry 6). As with $^nBu_2Mg$, the ^{n}BuLi-promoted decomposition of HBpin resulted in the formation of several boron species. As well as BH_3, $^nBu_3B$ (0.06 M), $^nBuH_2B{\cdot}SMe_2$ (0.01 M) and $[^nBu_2BH][^nBuBH_2]$ (0.02 M, based on $^nBuBH_2$ only) were formed during decomposition. All of these species are active hydroboration catalysts or pre-catalysts (Entries 1, 7 and 9). Furthermore, in the decomposition of HBpin by ^{n}BuLi, ^{13}C and ^{7}Li NMR spectroscopy showed that the ^{n}BuLi was fully consumed and the only Li species present was $LiBH_4$. Therefore, the reaction is not

^{n}BuLi-catalysed, nor can it be Li-catalysed. However, the decomposition was too complex to create a mimic like the one used for $^{n}Bu_2Mg$, but it appears to be clear that ^{n}BuLi merely decomposes HBpin to a mixture of boron species that catalyse the reaction.

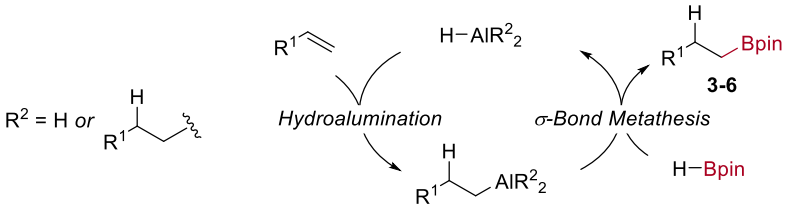
The hydroboration of alkenes was subjected to the same analysis. Using *tert*-butylstyrene as an exemplar, a calibration gradient for the initial rate of reaction (υ_0) against $H_3B{\cdot}SMe_2$ concentration was generated (Scheme 3-5).



Scheme 3-5. Calibration Gradient for the Initial Rate of Reaction (υ_0) Plotted Against $[H_3B{\cdot}SMe_2]$ (in M) for the Hydroboration of *tert*-Butylstyrene **3-4** with HBpin

Again, the nucleophiles NaO^{t}Bu and Na[N(SiMe$_3$)$_2$] were shown to only decompose HBpin to BH_3, giving comparable values of $[BH_3]_{calc}$ and $[BH_3]_{obs}$ (Table 3-6, Entries 2 and 3). $LiAlH_4$ gave a higher initial rate (υ_0) than expected, with a higher $[BH_3]_{calc}$ than $[BH_3]_{obs}$ (Entry 4). Unlike $^{n}Bu_2Mg$ and ^{n}BuLi, which formed multiple boron species that can catalyse alkyne and alkene hydroboration, the only boron-based hydroboration catalyst $LiAlH_4$ formed during decomposition was BH_3 (Table 3-1, Entry 14). Therefore, the difference in $[BH_3]_{calc}$ and $[BH_3]_{obs}$ cannot be explained by the formation of other boron-based catalysts. The transfer of hydride from $LiAlH_4$ to HBpin to initiate decomposition would also result in the formation of AlH_3. In the

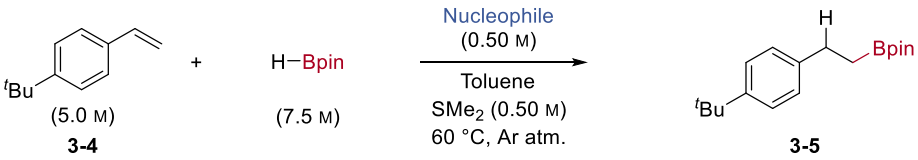
$LiAlH_4$-promoted hydroboration of alkenes with HBpin,[12] $LiAlH_4$ is proposed to be a pre-catalyst, forming the catalyst, a neutral alane species ($HAlR_2$), *in situ*. The alkene undergoes hydroalumination with an alane species, followed by σ-bond metathesis with HBpin to reform the catalyst and form the alkyl boronic ester product **3-6** (Scheme 3-6). Therefore, as BH_3 is evidently formed (from the decomposition studies) but not the only active catalyst in the reaction (based on v_0), it is plausible to propose two complementary reaction pathways, one boron-catalysed and the other aluminium-catalysed, which both form the same alkyl boronic ester product.



Scheme 3-6. Aluminium-catalysed Hydroboration of Alkenes with HBpin

Whilst both ^{n}BuLi and ^{n}Bu$_2$Mg gave higher values of $[BH_3]_{calc}$ than the $[BH_3]_{obs}$ (Entries 5 and 6), it is likely that these species are not catalysts for alkene hydroboration but form other boron-based catalysts upon HBpin decomposition which inflate the rate of reaction (v_0) above the $[BH_3]_{obs}$, as seen with alkyne hydroboration.

Table 3-6. Comparison of Calculated and Observed BH_3 Concentrations for *tert*-Butylstyrene **3-4** Hydroboration



Entry	Nucleophile / Catalyst	v_0 (μM s^{-1})	$[BH_3]_{calc}$ (M)	$[BH_3]_{obs}$ (M)[a]
1[b]	$H_3B{\cdot}SMe_2$	350	n/a	n/a
2	NaO^{t}Bu	13	0.02	0.02
3	Na[N(SiMe$_3$)$_2$]	22	0.03	0.02
4	$LiAlH_4$	220	0.32	0.18
5	^{n}Bu$_2$Mg	110	0.16	0.07
6	^{n}BuLi	130	0.19	0.04
7	H-*B*-9-BBN	180	n/a	n/a

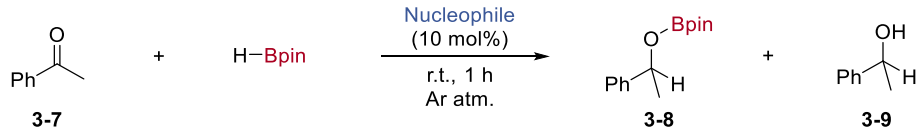
Conditions: *tert*-Butylstyrene **3-4** (2.0 mmol, 5.0 M), nucleophile (0.20 mmol, 0.50 M, 10 mol%), HBpin (3.0 mmol, 7.5 M), SMe_2 (0.20 mmol, 0.50 M), toluene (0.40 mL), 60 °C, 20 minutes prior to the addition of *tert*-butylstyrene **3-4**. Yields were determined by ^{1}H NMR spectroscopy using an internal standard (1,3,5-trimethoxybenzene, 0.10 mmol). [a]From Table 3-1. [b]No SMe_2 added.

3.6 Ketone Hydroboration

A recent surge in catalysed carbonyl hydroboration publications highlights that this has become a testing ground for new catalysts (125 publications between January 2019 and June 2020). However, as nucleophiles are ubiquitous in catalyst architectures, it seemed sensible to consider the existence of hidden boron catalysis in catalysed carbonyl hydroboration.

$H_3B{\cdot}SMe_2$ was shown to mediate the hydroboration of acetophenone **3-7** with HBpin giving the reduction products **3-8** and **3-9** in low yield (32%) after 1 h (Table 3-7, Entry 1). Conversely, the yield of products **3-8** and **3-9** was essentially quantitative for most of the nucleophile-mediated hydroboration reactions (Table 3-7, Entries 2-10). The only nucleophile which gave a similar yield to $H_3B{\cdot}SMe_2$ was $Ti(O^iPr)_4$ (Entry 9). The significant difference in yields between the nucleophile-mediated reactions and the $H_3B{\cdot}SMe_2$-mediated reaction indicated that hydroboration must not proceed through a BH_3-catalysed pathway. In fact, when NaO^tBu was used as a model nucleophile, the reaction was shown to be complete after just 2 minutes (>95%).

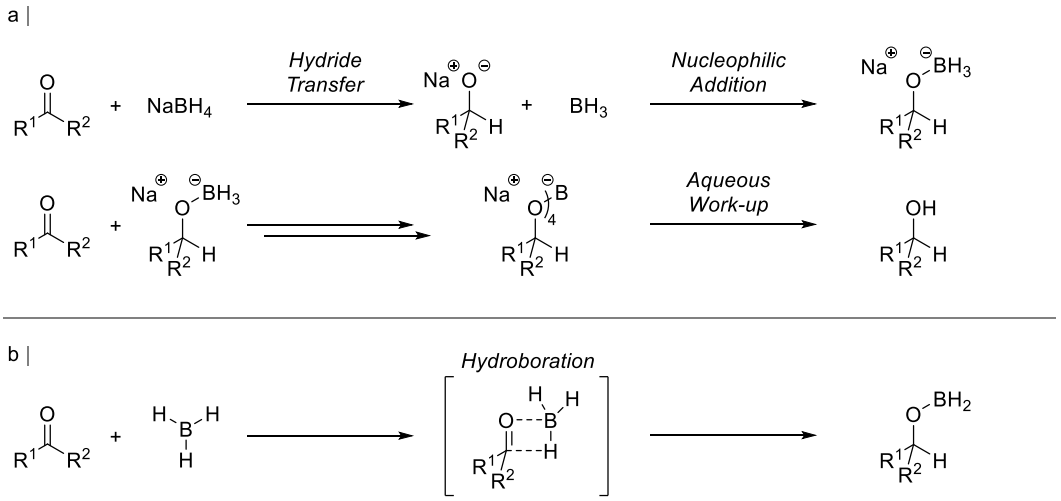
Table 3-7. Nucleophile-mediated Ketone Hydroboration with HBpin



Entry	Nucleophile / Catalyst[a]	Yield 3-8 and 3-9 (%)
1	$H_3B{\cdot}SMe_2$	32
2	$NaHBEt_3$	>95
3	$LiAlH_4$	>95
4	NaOH	92
5	NaO^tBu	>95
6	$Na[N(SiMe_3)_2]$	>95
7	MeMgBr	>95
8	^{n}BuLi	93
9	$Ti(O^iPr)_4$	29
10	$^nBu_2Mg$	>95

Conditions: Acetophenone **3-7** (1.0 mmol), nucleophile (0.10 mmol), and HBpin (1.5 mmol). Yields were determined by ^{1}H NMR spectroscopy using an internal standard (1,3,5-trimethoxybenzene). [a]Samples of nucleophiles used as purchased, i.e., without removal or exchange of solvent.

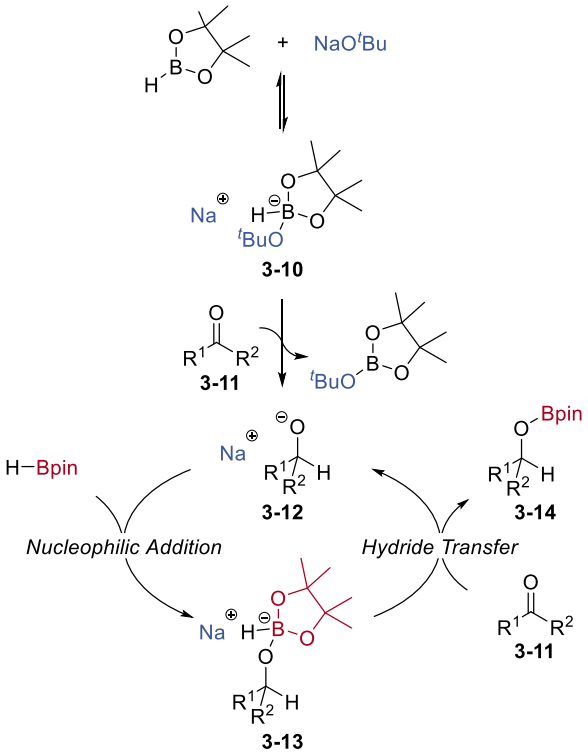
In the decomposition studies, many of the nucleophiles formed borohydride species in addition to BH_3. Stoichiometric reduction of carbonyls with borohydrides is well established[136] and triethylborohydride-catalysed reductions of carbonyl derivatives have been developed.[101-103] Whilst the exact mechanism of stoichiometric borohydride carbonyl reductions remains contested,[137-140] the consensus is that the reaction proceeds through hydride transfer from the borohydride to the carbonyl, forming an alkoxide (or amide) and a neutral boron species (Scheme 3-7, a).[139-148] The alkoxide then undergoes nucleophilic addition to the neutral boron species to reform a negatively charged boron species, making the hydride nucleophilic. This can then transfer hydride to another carbonyl molecule. Whilst some publications believe otherwise,[137, 138] the reaction does not proceed through hydroboration, in which there is a concerted transition state where all of the bonds are broken and formed concurrently (Scheme 3-7, b).



Scheme 3-7. a) Hydride Transfer in the Stoichiometric Reduction of Ketones by Borohydride; b) Hydroboration of Ketones by BH_3

The mechanisms of the triethylborohydride-catalysed reductions were postulated to proceed through a hydroboration/transborylation mechanism,[101-103] the same mechanism through which BH_3 would proceed. However, as stoichiometric borohydride reductions do not proceed through hydroboration, it is unlikely that borohydride-catalysed reductions would behave differently. The distinction between hydroboration and hydride transfer mechanisms is incredibly important when relayed to borohydride-catalysed carbonyl reductions; after hydride transfer there is a nucleophile formed (e.g. the alkoxide) that can react with either the newly formed neutral boron species or HBpin. Therefore, if borohydride species could be formed *in situ* by the addition of any nucleophile to HBpin, the nucleophile-mediated reactions could proceed through this mechanism, where the catalyst is really the nucleophilic

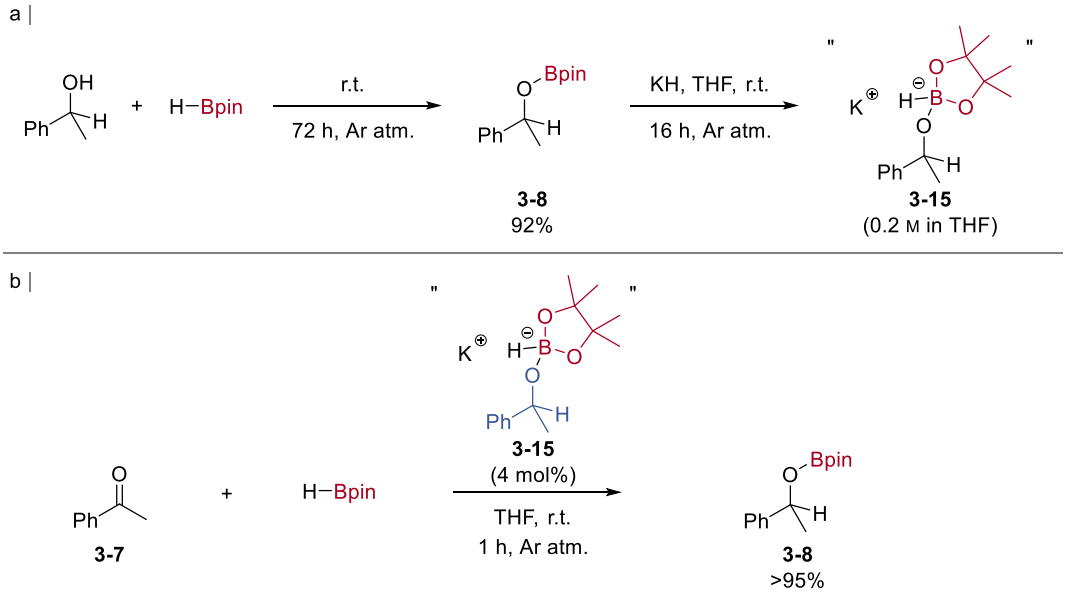
form of the product (e.g. the alkoxide). This was the mechanism postulated by Clark for the NaO^{t}Bu-mediated reduction of ketones with HBpin (Scheme 3-8).[95] NaO^{t}Bu coordinates to HBpin forming a trialkoxyborohydride **3-10** which can reduce a ketone molecule **3-11** by hydride transfer. This forms an alkoxide **3-12** and ^{t}BuOBpin. The alkoxide **3-12** can then undergo nucleophilic addition with another molecule of HBpin, resulting in the formation of a new trialkoxyborohydride **3-13**. This can transfer hydride to another ketone molecule **3-11**, forming the product **3-14** and reforming the alkoxide **3-12**, propagating the reaction.



Scheme 3-8. Clark's Proposed Mechanism for the NaO^{t}Bu-mediated Hydroboration of Ketones with HBpin

The trialkoxyborohydride **3-13**, formed from the alkoxide product **3-12** and HBpin, is key to this mechanism. Clark observed formation of the trialkoxyborohydride **3-10**, formed from the addition of NaO^{t}Bu to HBpin, by ^{11}B NMR spectroscopy. This was confirmed by Clark through the preparation of an analogous trialkoxyborohydride by addition of KH to ^{i}PrOBpin, leading Clark to propose the alkoxide-catalysed mechanism. However, the trialkoxyborohydride species **3-10** and **3-13** were not tested as potential on-cycle species in hydroboration. Therefore, 1-phenylethanol and HBpin were reacted to form the alkoxyboronic ester product **3-8** and subsequently treated with KH to form a solution of the trialkoxyborohydride **3-15** in THF (Scheme 3-9, a). Whilst the data for the trialkoxyborohydride **3-15** were in agreement with previous reports of trialkoxyborohydride formation, the ^{11}B NMR spectra suggested that three

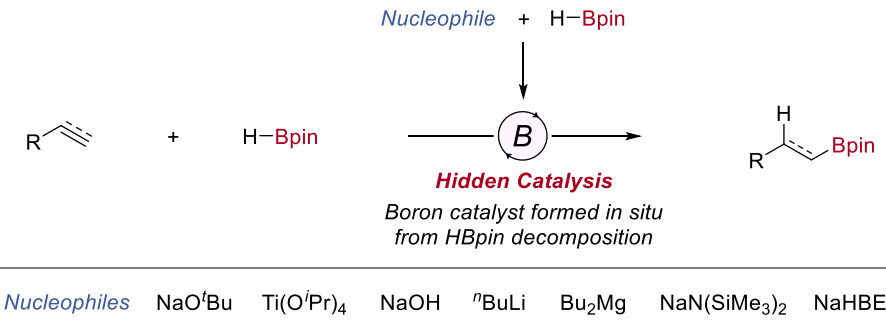
boron species were present, including $[Bpin_2]^-$ and another unknown species.[149] This should be taken into consideration when evaluating the results of the following experiments. This was then used as a catalyst for the hydroboration of acetophenone with HBpin (Scheme 3-9, b), resulting in a quantitative yield (>95%) of the alkoxyboronic ester product **3-8**, comparable to the nucleophile-mediated hydroboration reactions. This suggests this species is on-cycle, supporting the mechanism proposed by Clark. The nucleophile-HBpin adduct $[(Nu)HBpin]^-$ was proposed to be the initial species formed in the decomposition of HBpin, this could continue to decompose HBpin to other boron species or react with the carbonyl derivative to initiate the product-mediated catalytic cycle. Any borohydride species could initiate this process; therefore, it is probable that the product-mediated catalytic cycle is applicable to other nucleophiles.



Scheme 3-9. a) Preparation of the Trialkoxyborohydride **3-15**; b) Trialkoxyborohydride **3-15**-mediated Hydroboration of Acetophenone with HBpin

3.7 Conclusions and Future Work

Simple nucleophiles, based on motifs similar to those seen in hydroboration catalysts, were shown to decompose HBpin to multiple boron species, including BH_3 (Scheme 3-10). In many instances, borohydride species were also formed, and some organometallic reagents reacted with HBpin to form trialkyl-, dialkyl- and monoalkylboranes.



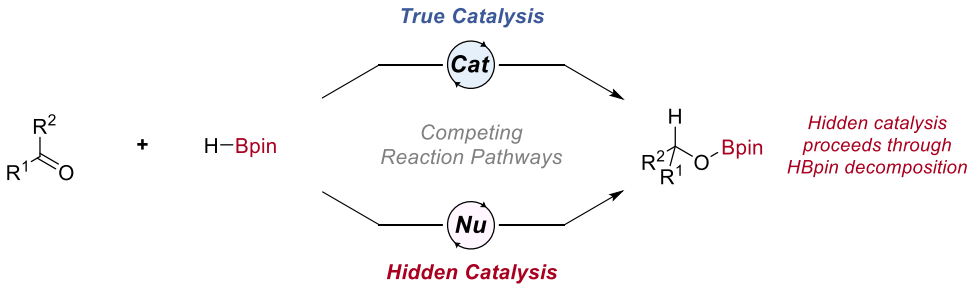
Scheme 3-10. Hidden Catalysis Mediated by Simple Nucleophiles

Alkyne, alkene, and ketone hydroboration reactions with HBpin were shown to be mediated by nucleophiles. For alkynes and alkenes, TMEDA was used to indicate the formation of BH_3 in hydroboration catalysis, forming mono- and bis-adducts with BH_3 that were observable after work-up by ^{11}B NMR spectroscopy. Furthermore, TMEDA inhibited reactivity, suggesting BH_3 was essential to catalysis. However, TMEDA could also be inhibiting 'true' catalysis by acting as a ligand or changing the aggregation state of the catalyst.

The nucleophiles NaO^{t}Bu, Na[N(SiMe$_3$)$_2$], ^{n}BuLi and ^{n}Bu$_2$Mg do not catalyse the hydroboration of alkynes and alkenes, but merely decompose HBpin to active boron-based hydroboration catalysts. This was supported by the comparison of initial rates of reaction for the nucleophile-mediated reactions with the observed BH_3 concentrations from the decomposition studies and the corresponding BH_3-catalysed initial rate of reaction. In the cases of ^{n}BuLi and ^{n}Bu$_2$Mg, other decomposition products needed to be considered to discern 'true' from hidden catalysis. $LiAlH_4$ merely acts as a nucleophile in the $LiAlH_4$-mediated hydroboration of alkynes with HBpin, but in the hydroboration of alkenes it appeared that complementary aluminium- and boron-catalysed pathways were operating.

Nucleophile-mediated ketone hydroboration with HBpin does not proceed through BH_3 catalysis. The Clark mechanism of product-mediated hydroboration appears to be applicable to other nucleophiles. The alkoxide product undergoes nucleophilic addition, promoting subsequent hydride transfer. This mechanism will be the focus of future work to confirm that hidden catalysis is prevalent in the catalysed hydroboration of carbonyl derivatives (Scheme 3-11). There will be several challenges associated with this project, including finding suitable conditions to monitor the reaction; currently the rate of reaction is too high to measure on an NMR spectroscopy time scale. The rate of reduction for each borohydride species (e.g. mono-, di-,

trialkoxyborohydride) observed in the decomposition studies should be determined and the alkoxide product should be used in varying concentrations to monitor the effect it has on the rate of reaction. The investigation should include other carbonyl derivatives and any group that will undergo stoichiometric reduction by borohydride species.



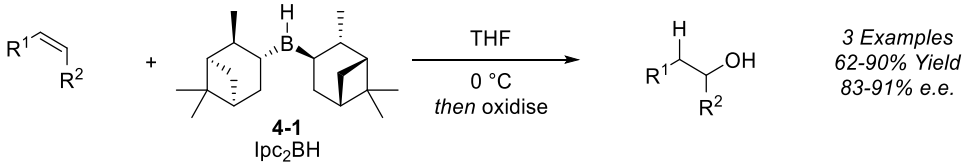
Scheme 3-11. Potential Reaction Pathways in ‘Catalysed’ Carbonyl Hydroboration

4. Borane-catalysed Enantioselective Hydroboration of Alkenes

4.1 Introduction

4.1.1. Stoichiometric Hydroboration

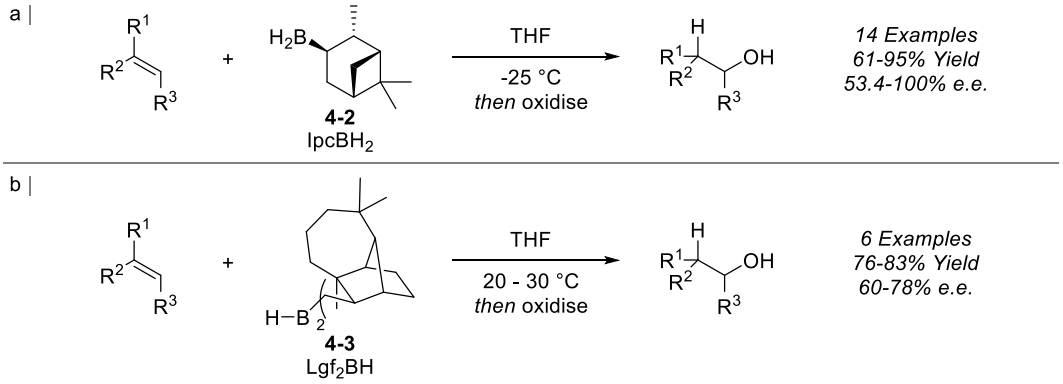
A new era in organic synthesis began when Brown developed the enantioenriched borane diisopinocampheylborane (Ipc_2BH) **4-1** to obtain enantioenriched alcohols.[150] The hydroboration of (+)-α-pinene with BH_3 resulted in the formation of Ipc_2BH **4-1**, which underwent enantioselective hydroboration with prochiral *cis*-alkenes to form alcohols of high enantiopurity (83-91% enantiomeric excess (e.e.)), after oxidation (Scheme 4-1). As the enantiomeric excess of the (+)-α-pinene used was approximately 90%, the transformation appeared to proceed with almost complete enantioselectivity. Refinement of the synthesis allowed for the isolation of Ipc_2BH **4-1** in high enantiopurity (99.1% e.e.) from (+)-α-pinene (92% e.e.).[151] Accordingly, this increased the enantiopurity of the alcohols obtained from the hydroboration reaction (e.g. *cis*-2-butene, from 87% to 98% e.e.). Unfortunately, the system was limited to *cis*-alkenes only, therefore, Brown developed further enantioenriched boranes to target other classes of prochiral alkenes.



Scheme 4-1. Stoichiometric Enantioselective Hydroboration of *cis*-Alkenes with Ipc_2BH **4-1**

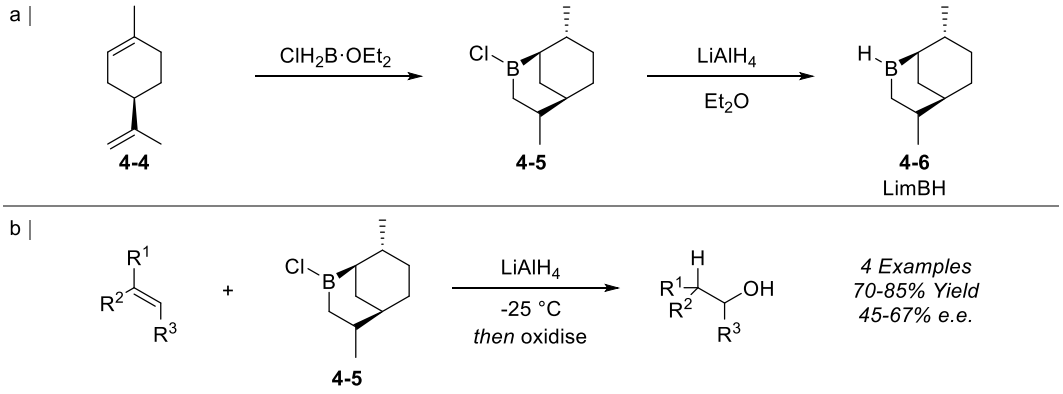
Monoisopinocampheylborane ($IpcBH_2$) **4-2** was developed by Brown for the asymmetric hydroboration of trisubstituted and *trans*-disubstituted alkenes (Scheme 4-2, a).[152-154] For aliphatic trisubstituted alkenes, moderate enantioselectivities were observed (53.4-72.4% e.e.),[152] the hydroboration of *trans*-alkenes gave alcohols of slightly higher enantiopurity (70-92% e.e.),[154] and for phenyl-substituted trisubstituted alkenes, alcohols of high enantiopurity were formed (81-100% e.e.).[153] Seeking to develop new enantioenriched boranes, Brown investigated using alternative terpenes to (+)-α-pinene. The sesquiterpene (+)-longifolene was used by Brown to prepare dilongifolylborane (Lgf_2BH) **4-3**.[155] The hydroboration of prochiral alkenes by Lgf_2BH **4-3** gave, after oxidation, alcohols of moderate enantiopurity (Scheme 4-2, b).

Trisubstituted alkenes and *cis*-disubstituted alkenes were tested, giving alcohols of moderate enantiopurity (60-78% e.e.).



Scheme 4-2. Stoichiometric Enantioselective Hydroboration of Prochiral Alkenes: a) with $IpcBH_2$ **4-2**; b) with Dilongifolylborane **4-3**

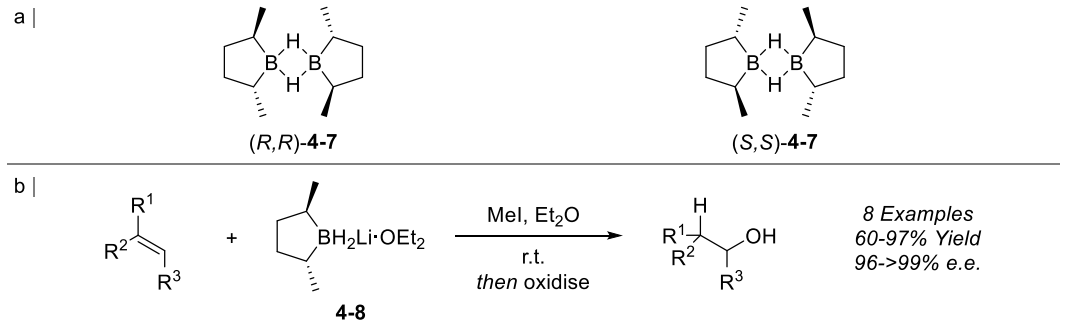
The first cyclic enantioenriched borane, limonyl borane (LimBH) **4-6**, was developed by Jadhav from the hydroboration of (+)-limonene **4-4** (Scheme 4-3, a).[156] LimBH **4-6** was formed *in situ* from the reaction of *B*-chlorolimonyl borane **4-5** with $LiAlH_4$ and underwent hydroboration with prochiral alkenes to give alcohols of moderate enantiopurity (45-67% e.e.), after oxidation (Scheme 4-3, b). Similar enantioselectivities were observed for *cis*-, *trans*-, and trisubstituted alkenes. However, the 1,1-disubstituted alkene 2-methyl-1-butene underwent hydroboration essentially without any enantioselectivity (5.2% e.e.).



Scheme 4-3. a) Preparation of LimBH **4-6**; b) Stoichiometric Enantioselective Hydroboration of Alkenes with LimBH **4-6**

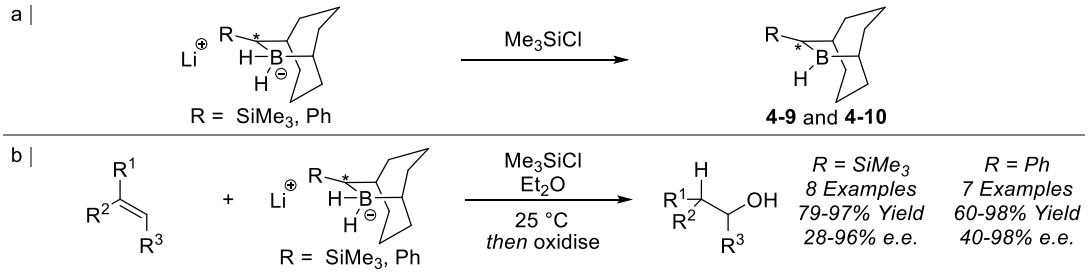
(*R*,*R*)- and (*S*,*S*)-2,5-dimethylborolane **4-7** were developed by Masamune for the enantioselective hydroboration of prochiral alkenes (Scheme 4-4, a).[157] The 2,5-dimethylborolanes (*R*,*R*)-**4-7** and (*S*,*S*)-**4-7** were prepared *in situ* from the reaction of the lithium borohydride monoetherate **4-8** with iodomethane. After oxidation of the reaction mixture, alcohols of high enantiopurity were obtained from the hydroboration of trisubstituted and *cis*- and *trans*-1,2-disubstituted alkenes (Scheme 4-4, b).

However, the hydroboration of a 1,1-disubstituted alkene, 2,3-dimethyl-1-butene, proceeded with essentially no enantioselectivity (1.5% e.e.).



Scheme 4-4. a) (*R*,*R*)- and (*S*,*S*)-2,5-dimethylborolane (*R*,*R*)-**4-7** and (*S*,*S*)-**4-7**; b) Stoichiometric Enantioselective Hydroboration of Prochiral Alkenes with 2,5-Dimethylborolane **4-7**

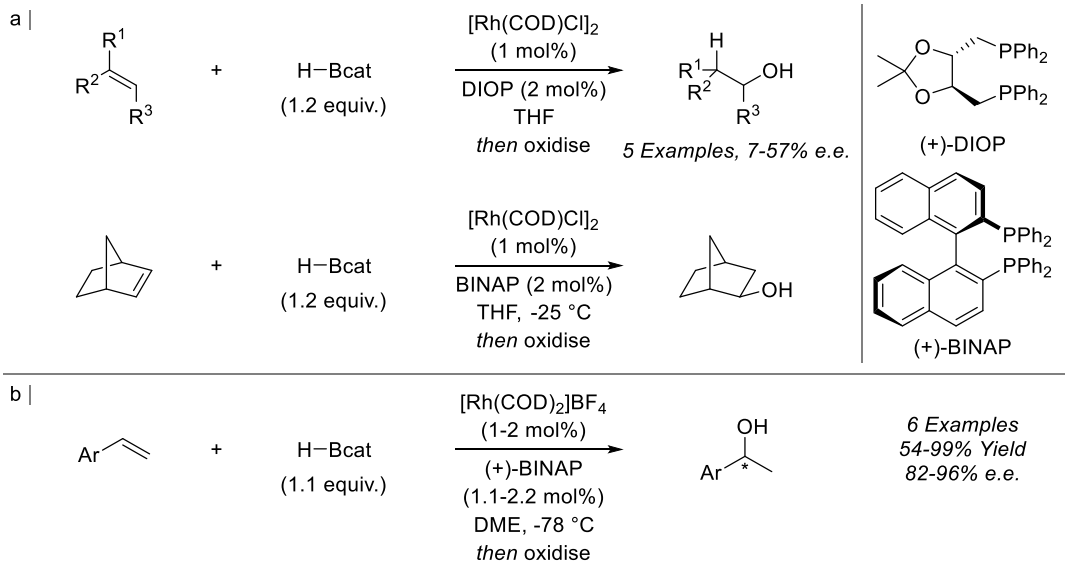
1,1-Disubstituted alkenes were the only class of alkene that underwent hydroboration with low enantioselectivity with all of the enantioenriched chiral boranes. Therefore, Soderquist targeted the enantioselective hydroboration of 1,1-disubstituted alkenes when devising new chiral boranes. The 10-substituted 9-borabicyclo[3.3.2]decanes **4-9** and **4-10** were developed by Soderquist and tested in enantioselective hydroboration, activating the catalysts by reaction with Me_3SiCl (Scheme 4-5, a).[158] Good enantioselectivity was observed when *cis*- and *trans*-alkenes underwent hydroboration with (*R*)-10-trimethylsilyl-9-borabicyclo[3.3.2]decane (*R*)-**4-9** (84-95% e.e.); (*S*)-10-phenyl-9-borabicyclo[3.3.2]decane (*S*)-**4-10** gave good enantioselectivity for *trans*-alkenes (96% e.e.) but proceeded with low enantioselectivity when *cis*-2-butene was used (32% e.e.) (Scheme 4-5, b). 1,1-Disubstituted alkenes underwent hydroboration with good enantioselectivity when 10-phenyl-9-borabicyclo[3.3.2]decane **4-10** was used (28-92% e.e.). Increasing the difference in steric bulk between the two substituents of the 1,1-disubstituted alkene increased the enantioselectivity. The reaction of (*R*)-10-trimethylsilyl-9-borabicyclo[3.3.2]decane (*R*)-**4-9** with 1,1-disubstituted alkenes followed a similar trend of increasing enantioselectivity with an increased difference in steric bulk (40-98% e.e.).



Scheme 4-5. a) Activation of 10-Substituted 9-Borabicyclo[3.3.2]decanes **4-9** and **4-10**; b) Stoichiometric Enantioselective Hydroboration of Alkenes with **4-9** and **4-10**

4.1.2 Catalysed Hydroboration

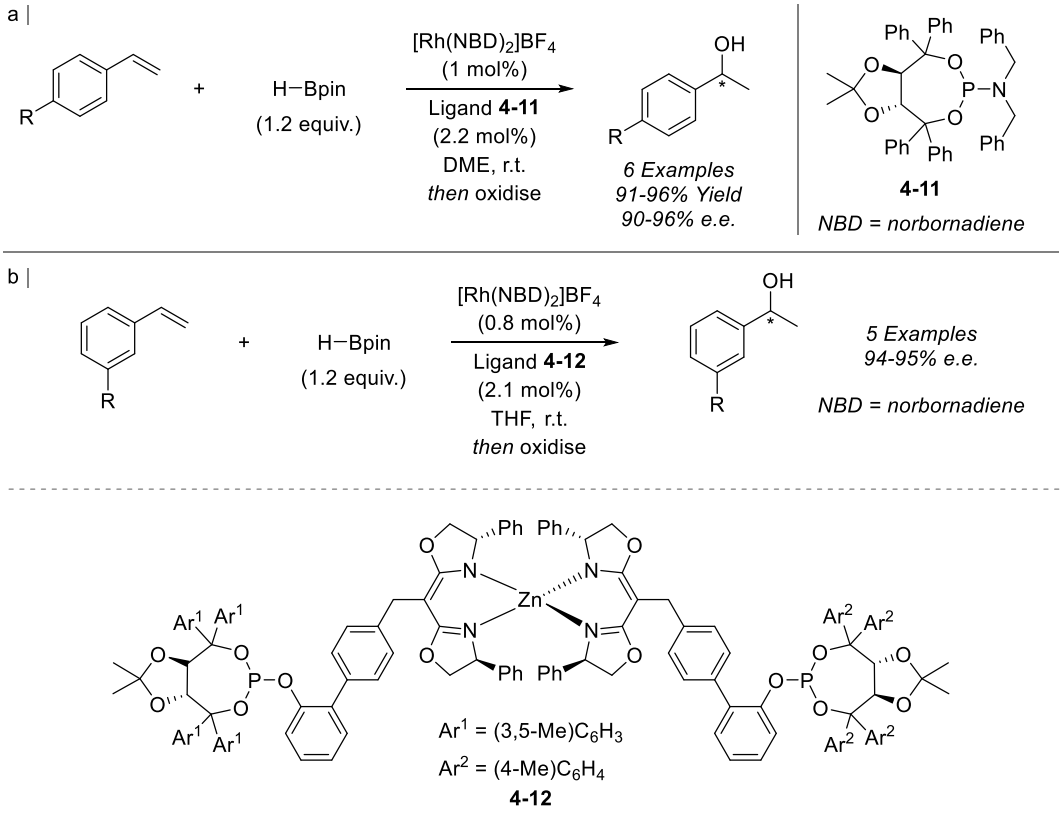
From Nöth's seminal report of rhodium-catalysed alkene hydroboration with HBcat,[84] enantioselective counterparts quickly followed. Burgess developed the first catalysed enantioselective hydroboration of alkenes, using $[Rh(COD)Cl]_2$·$(DIOP)_2$ and $[Rh(COD)Cl]_2$·$(BINAP)_2$, formed *in situ*, and HBcat as the borane reagent (Scheme 4-6, a).[159] $[Rh(COD)Cl]_2$·$(DIOP)_2$ catalysed the hydroboration of *cis*-, *trans*- and 1,1-disubstituted alkenes in low to moderate enantioselectivity (7-76% e.e.). $[Rh(COD)Cl]_2$·$(BINAP)_2$ was tested on norbornene only, forming *exo*-norborneol in 64% e.e. Hayashi and Ito subsequently used $[Rh(COD)_2]BF_4$·$(BINAP)_2$ to catalyse the enantioselective hydroboration of styrenes with Markovnikov selectivity (Scheme 4-6, b).[160] At −78 °C, high enantioselectivity was achieved (85-96% e.e.). α- and β-Substituted styrene derivatives would not undergo hydroboration at −30 °C; at room temperature, low enantioselectivity was observed – the hydroboration of (*E*)-β-methylstyrene gave (*S*)-1-phenylpropanol in 41% e.e.



Scheme 4-6. a) Rhodium-catalysed Enantioselective Aliphatic Alkene Hydroboration; b) Rhodium-catalysed Enantioselective Hydroboration of Styrenes

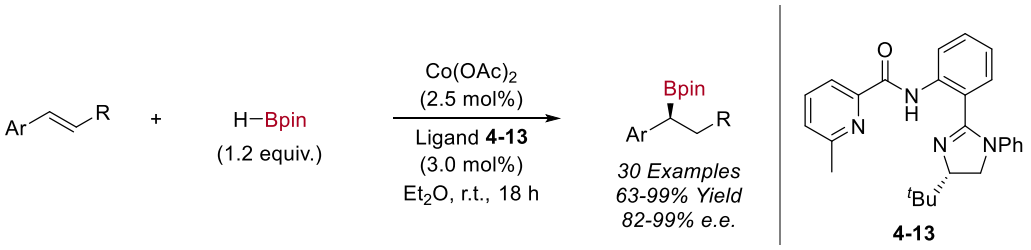
Current state-of-the-art methods for catalysed enantioselective alkene hydroboration are still based on transition metal complexes. Often systems rely on directing groups,[161-165] target only one or two classes of alkene, focus largely on styrene derivatives, use large designer ligands, and do not explore functional group tolerance. Metal-catalysed enantioselective hydroboration of unsubstituted styrene derivatives proceeds with Markovnikov selectivity, the opposite regioselectivity to stoichiometric hydroboration,[166] which would not induce enantioselectivity. Takacs developed two

rhodium-based systems for the enantioselective hydroboration of *para*- and *meta*-substituted styrenes (Scheme 4-7, a and b), which proceeded with high enantioselectivity (90-96% e.e.), using large designer TADDOL-based phosphorous ligands **4-11** and **4-12**.[167, 168]



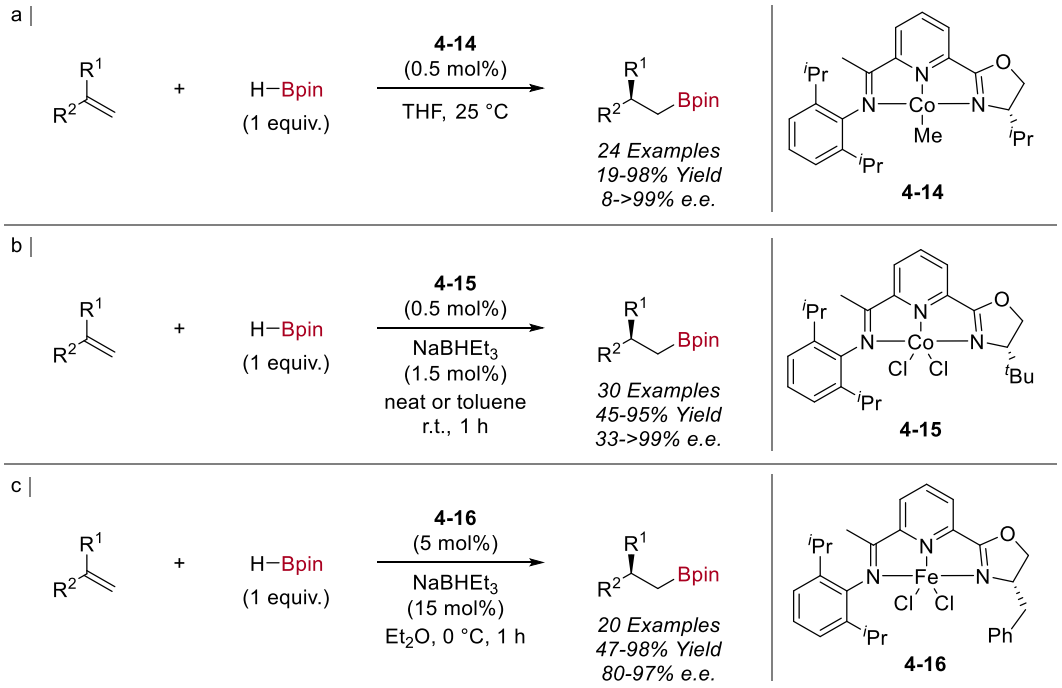
Scheme 4-7. Rhodium-catalysed Enantioselective Hydroboration of (a) *para*- and (b) *meta*-Substituted Styrenes

Unlike unsubstituted styrene derivatives, β-substituted styrene derivatives undergo stoichiometric enantioselective hydroboration[153] and catalysed systems have since been developed. Lu developed a cobalt-catalysed system, which gave alkyl pinacol boronic esters in high enantioselectivity (82-99% e.e.) (Scheme 4-8).[169] The hydroboration of both styrenes and β-substituted styrenes proceeded with Markovnikov regioselectivity. Halides, esters, alcohols, ethers, pyridines, and sulphides were tolerated under reaction conditions.



Scheme 4-8. Cobalt-catalysed Enantioselective Hydroboration of Styrenes and β-Substituted Styrenes

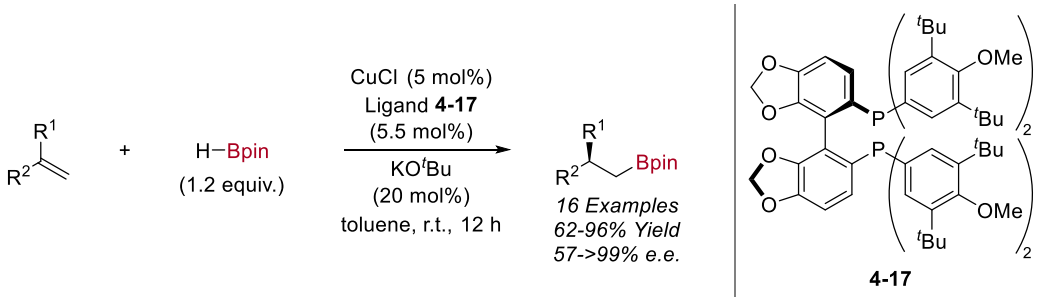
Huang used a cobalt-Pybox catalyst **4-14** for the enantioselective hydroboration of α-alkyl substituted styrenes to form alkyl pinacol boronic esters in high enantioselectivity (77->99% e.e.) (Scheme 4-9, a).[170] Low enantioselectivities were observed for α-aryl substituted styrenes (8-54% e.e.) and for the aliphatic 1,1-disubstituted alkene 2-methyl-4-phenyl-1-butene (14% e.e.), but norbornene underwent hydroboration with high enantioselectivity (94% e.e.). Halides, esters, acetals, and ethers were tolerated under reaction conditions. Lu used a very similar system for enantioselective hydroboration, using a cobalt-Pybox pre-catalyst **4-15** that was activated *in situ* with $NaBHEt_3$ (Scheme 4-9, b).[171] The hydroboration of α-alkyl substituted styrenes proceeded with high enantioselectivity (53->99% e.e.) and the reaction tolerated ethers, tertiary amines, silyl-protected alcohols, sulphides, halides, and acetals. Lower enantioselectivities were observed for aliphatic 1,1-disubstituted alkenes (33-70% e.e.). Lu also used an iron-Pybox pre-catalyst **4-16** for the enantioselective hydroboration of α-alkyl substituted vinyl arenes to give alkyl pinacol boronic esters in high enantioselectivity (80-97% e.e.), tolerating ether, tertiary amine, silyl-protected alcohol, sulphide, halide and ferrocenyl groups (Scheme 4-9, c).[172]



Scheme 4-9. Metal-Pybox Catalysts for the Enantioselective Hydroboration of Alkenes: a) Huang's Cobalt-catalysed Enantioselective Hydroboration; b) Lu's Cobalt-catalysed Enantioselective Hydroboration; c) Iron-catalysed Enantioselective Hydroboration

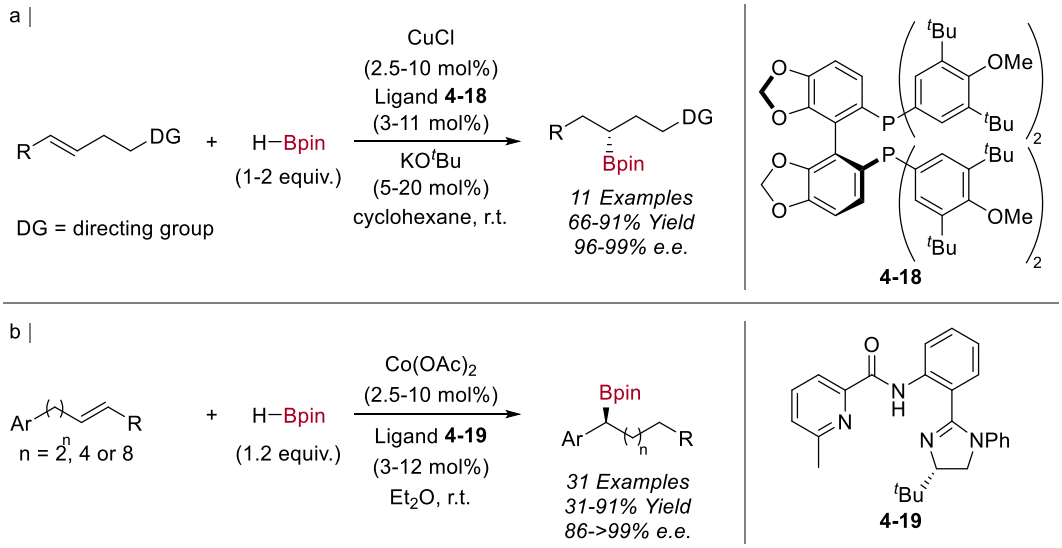
Yun developed a copper-phosphine complex for the enantioselective hydroboration of 1,1-disubstituted alkenes (Scheme 4-10).[173] The hydroboration of aliphatic 1,1-disubstituted alkenes proceeded with moderate to good enantioselectivity (60-98%

e.e.) and high enantioselectivities were observed when allyl acetals, protected allyl alcohols, vinyl silanes and vinyl amines were used as substrates (82->99% e.e.).



Scheme 4-10. Copper-catalysed Enantioselective Hydroboration of 1,1-Disubstituted Alkenes

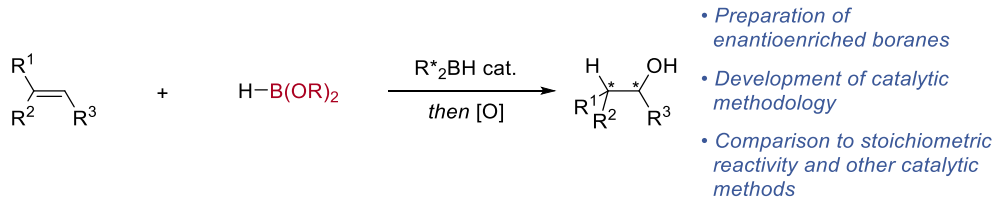
Unlike substituted styrenes, where a range of different catalytic systems have been developed, systems that target aliphatic alkenes remain underexplored. A scope of unbiased aliphatic 1,2-disubstituted alkenes has yet to be shown to undergo catalysed hydroboration with high enantioselectivity. Hartwig used a copper-phosphine complex for the directed enantioselective hydroboration of aliphatic alkenes in high enantioselectivity (96-99% e.e.), using tertiary amines and ethers to direct hydroboration (Scheme 4-11, a).[161] The unbiased aliphatic alkene *trans*-4-octene underwent hydroboration in low yield (34%) but high enantioselectivity (98% e.e.). Lu used isomerisation-hydroboration to generate benzyl pinacol boronic esters from aliphatic alkenes, catalysed by a cobalt-imidazoline complex (Scheme 4-11, b).[174] The reaction proceeded with high enantioselectivity (86->99% e.e.) and tolerated ethers, halides, pyridines, thiophenes, acetals, esters, amides, alcohols, phthalimides, and tri-substituted alkenes.



Scheme 4-11. Enantioselective Hydroboration of Aliphatic Alkenes: a) Hartwig's Copper-catalysed Directed Enantioselective Hydroboration; b) Lu's Cobalt-catalysed Isomerisation-Hydroboration

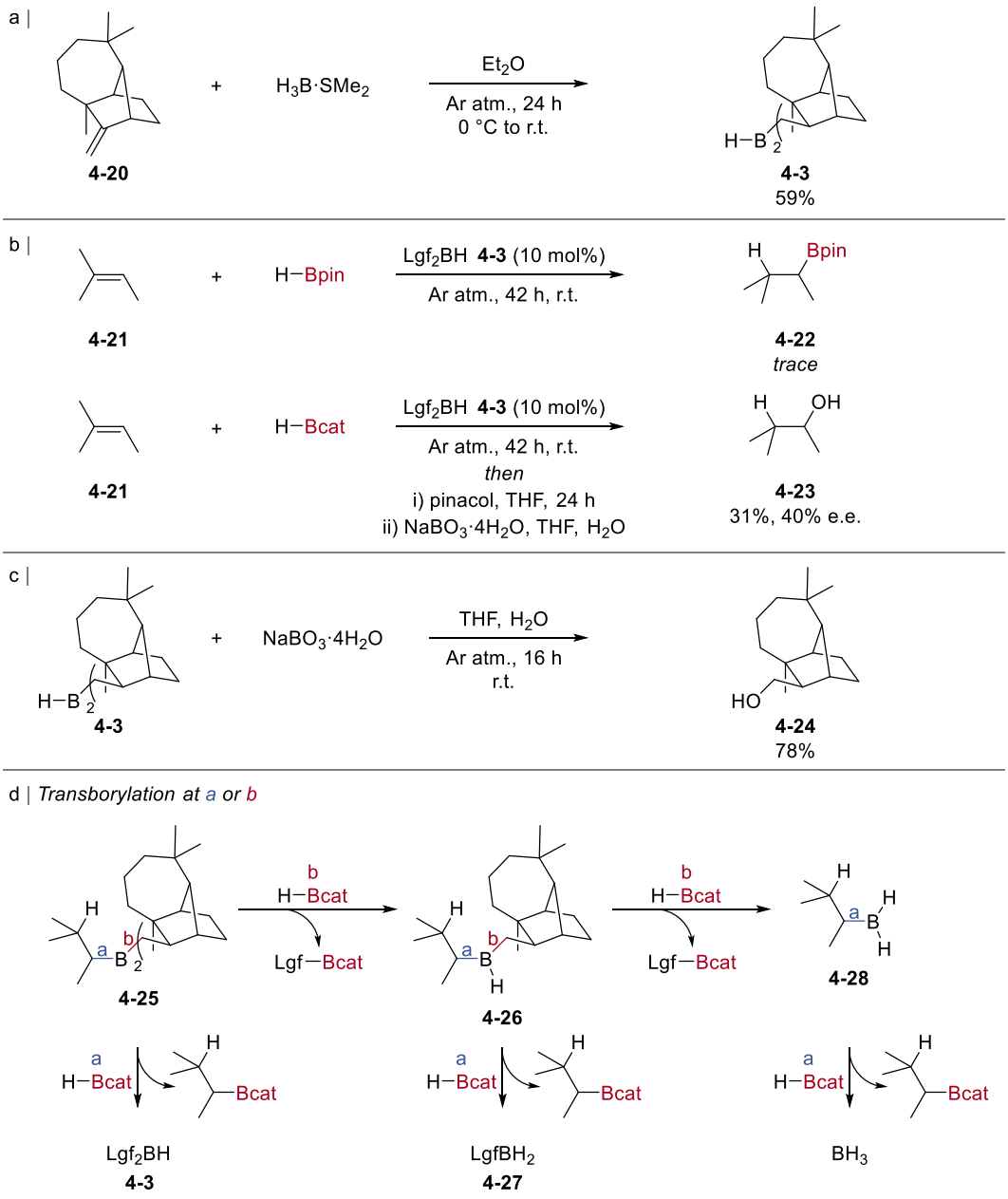
4.2 Project Aims

The motivation for this chapter was to extend the use of transborylation to an enantioselective transformation, using an enantioenriched borane as a catalyst for the enantioselective hydroboration of prochiral alkenes. Furthermore, the ease of catalyst synthesis and utility was considered.



4.3 Dilongifolylborane

The enantioenriched borane Lgf_2BH **4-3** is easily prepared in one step from commercially-available reagents.[155] Therefore, it provided a sensible starting point to test the use of transborylation in enantioselective alkene hydroboration. Lgf_2BH **4-3** was prepared from (+)-longifolene **4-20** and $H_3B{\cdot}SMe_2$ in Et_2O in good yield (59%, Scheme 4-12, a). To test Lgf_2BH **4-3** under catalysis, the hydroboration of 2-methyl-2-butene **4-21** was used as an exemplar; when Lgf_2BH **4-3** was used stoichiometrically, Brown achieved an e.e. of 70%. A substoichiometric quantity (10 mol%) of Lgf_2BH **4-3** was used for the hydroboration of 2-methyl-2-butene **4-21** with HBpin at room temperature. Trace quantities of the alkyl boronic ester **4-22** were observed (Scheme 4-12, b). It was thought that the increased reactivity and Lewis acidity of HBcat, compared to HBpin, would increase the rate of transborylation. Therefore, the reaction was repeated, replacing HBpin with HBcat. After transesterification of the alkyl catechol boronic ester to the pinacol ester **4-22**, and subsequent oxidation by sodium perborate, the yield of the alcohol **4-23** was 31%, indicating some turnover had occurred. The alcohol **4-23** was reacted with (+)-Mosher's acid to determine the enantiopurity; the alcohol **4-23** had an e.e. of 40%, by ^{19}F NMR spectroscopy. This value is far lower than was observed for stoichiometric hydroboration (70% e.e.).



Scheme 4-12. a) Preparation of Lgf_2BH **4-3**; b) Lgf_2BH **4-3** in Catalysis; c) Preparation of Longifolol **4-24**; d) Lack of Selectivity in Transborylation

The observed reduction in enantiopurity between the stoichiometric and substoichiometric reactions could be caused by unselective transborylation between alkyl groups in the exchange step, a lack of stereospecificity in transborylation, or by direct, unselective hydroboration of the alkene with HBcat. In the absence of Lgf_2BH **4-3**, only trace quantities (<5%) of the alcohol **4-23** were observed, after oxidation. Therefore, the background reaction between 2-methyl-2-butene **4-21** and HBcat was not responsible for the reduction in observed enantiopurity. Attempts to show that transborylation was stereospecific proved inconclusive; a sample of the trialkylborane formed from the hydroboration of 2-methyl-2-butene **4-21** with Lgf_2BH **4-3** was split into two samples, HBcat was added to one of the samples, then oxidised to form the

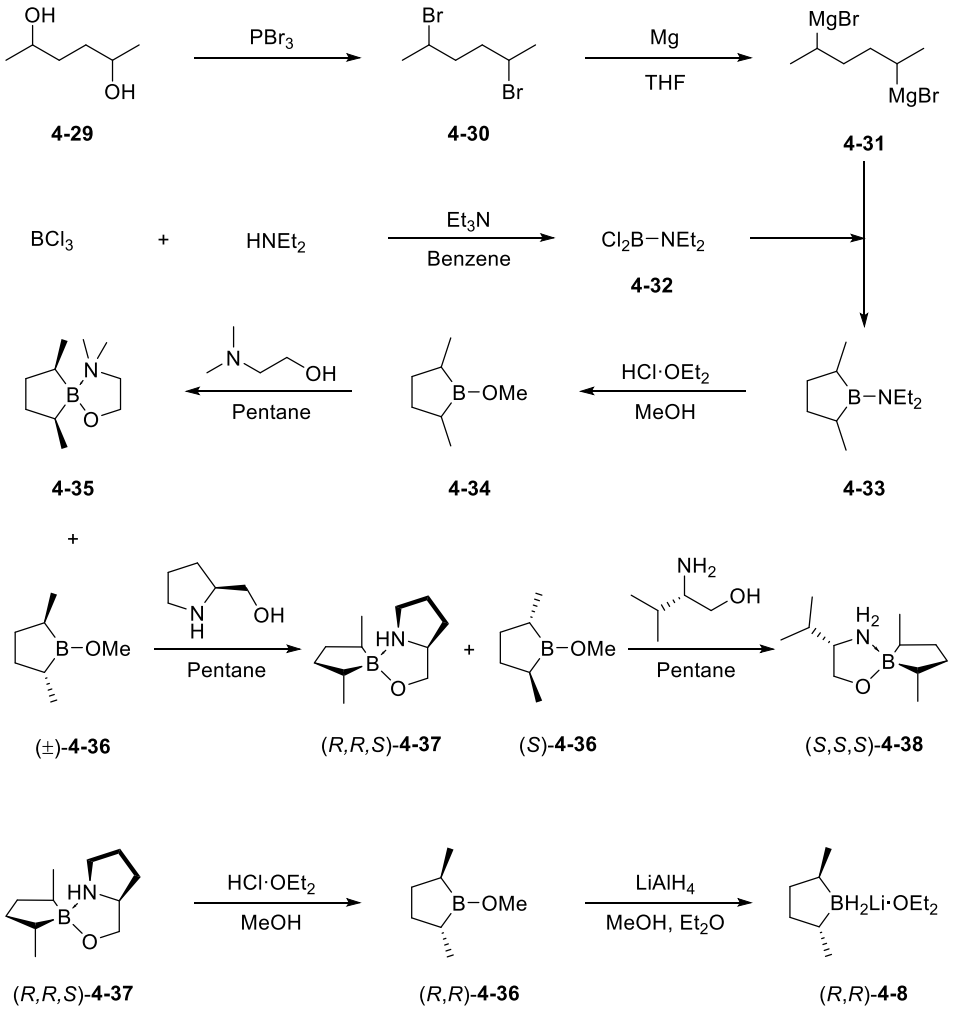
alcohol **4-23**, the other sample was oxidised directly. A comparison between the enantiopurities of the two samples of alcohol **4-23** would have provided a measure of the stereospecificity of transborylation. However, the subsequent addition of (+)-Mosher's acid to the crude oxidation reaction mixture to derivatise the alcohol **4-23** formed a mixture of species, and the discernment of enantiopurity and was not possible. Longifolol **4-24** was prepared separately (Scheme 4-12, c) and compared to the ^{1}H NMR spectra of the crude oxidation catalysis reaction mixtures. Shifts corresponding to longifolol **4-24** were observed, suggesting that transborylation is unselective in exchange of the alkyl groups on the hydroboration intermediate **4-25** (Scheme 4-12, d). This in turn would lead to different borane catalysts **4-26**, **4-27**, **4-28** and BH_3, that could undergo hydroboration with subsequent alkene molecules. These new catalysts would have different enantioselectivity in the hydroboration step; in the case of BH_3, hydroboration would have no stereoselectivity. This conclusion is based on the assumption that Lgf_2BH **4-3** and any longifolyl-containing boranes formed in the reaction (e.g. **4-25**, **4-26**, **4-27**, and not LgfBpin) underwent protodeborylation during the work-up procedure and were therefore not present during the oxidation reaction. If these boranes were present during oxidation, longifolol would be formed regardless of the selectivity of transborylation. Similar observations of potential unselective transborylation were made for Ipc_2BH **4-1**; the formation of α-pinanyl pinacol boronic ester was observed (reactions performed J. Dunne). To overcome this perceived lack of selectivity in transborylation, it was thought that a cyclic enantioenriched borane would not undergo transborylation on the catalyst backbone, avoiding catalyst decomposition.

4.4 2,5-Dimethylborolane

4.4.1 Preparation

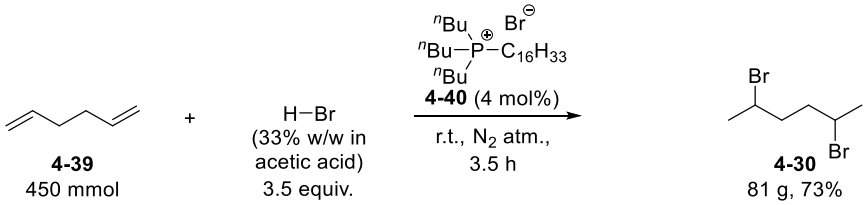
The synthesis of (*R*,*R*)- and (*S*,*S*)-2,5-dimethylborolane (*R*,*R*)-**4-7** and (*S*,*S*)-**4-7** is non-trivial, time-consuming, and contains a diastereomeric resolution and two enantiomeric resolutions (Scheme 4-13).[157] The first step in the route was the preparation of 2,5-dibromohexane **4-30**. Whilst Masamune prepared 2,5-dibromohexane **4-30** from 2,5-hexanediol **4-29**, our attempts to prepare 2,5-dibromohexane **4-30** by an Appel reaction using 2,5-hexanediol **4-29**, PPh_3 and CBr_4 were unsuccessful. Instead, 2,5-dibromohexane **4-30** was prepared by the

hydrobromination of 1,5-hexadiene **4-39** with HBr, catalysed by tributylhexadecylphosphonium bromide **4-40** (Scheme 4-14). 2,5-Dibromohexane **4-30** was synthesised on a 450 mmol scale with yields of up to 73%.



Scheme 4-13. Masamune's Route for the Synthesis of (*R*,*R*)- and (*S*,*S*)-2,5-Dimethylborolane (*R*,*R*)-**4-7** and (*S*,*S*)-**4-7**

Preparation of the Grignard reagent, hexane-2,5-di(magnesium bromide) **4-31**, proved more challenging. Initially, test reactions were performed to optimise the yield of the reaction (Table 4-1).

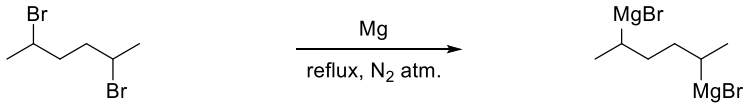


Scheme 4-14. Hydrobromination of 1,5-Hexadiene **4-39**

Performing the Grignard preparation on a 22 mmol scale with 1.1 equivalents of magnesium per bromide and in THF at a concentration of 0.22 M, resulted in a yield

of only 11%, determined by titration against *N*-salicylaldehyde phenylhydrazone (Table 4-1, Entry 1). Increasing the number of equivalents of magnesium (1.5 equivalents) and the concentration of the reaction (1.3 M) resulted in an increase in yield (23%) (Entry 2). It was thought that the low yield could have been caused by incomplete activation of the magnesium turnings, therefore, Rieke magnesium was prepared[175] and used in place of the turnings, however the yield did not improve (18%) (Entry 3). Increasing the scale of the reaction (40 mmol) in conjunction with increasing the equivalents of magnesium (3 equivalents), resulted in an increase in yield (37%) (Entry 4). Masamune prepared hexane-2,5-di(magnesium bromide) **4-31** in a solution of THF from a THF-solvated reaction, however Whitesides prepared hexane-2,5-di(magnesium bromide) **4-31** in a solution of THF from a Et_2O-solvated reaction.[176] Therefore, Et_2O was used in place of THF but this did not change the yield (35%) (Entry 5). The final conditions for Grignard formation (350 mmol of 2,5-dibromohexane **4-30**, 2.75 equivalents of magnesium, reaction concentration 1.2 M in THF) gave a yield of 41% (Entry 6), with repeats giving yields between 35 and 41%.

Table 4-1. Optimisation of the Preparation of Hexane-2,5-di(magnesium bromide) **4-31**



4-30 **4-31**

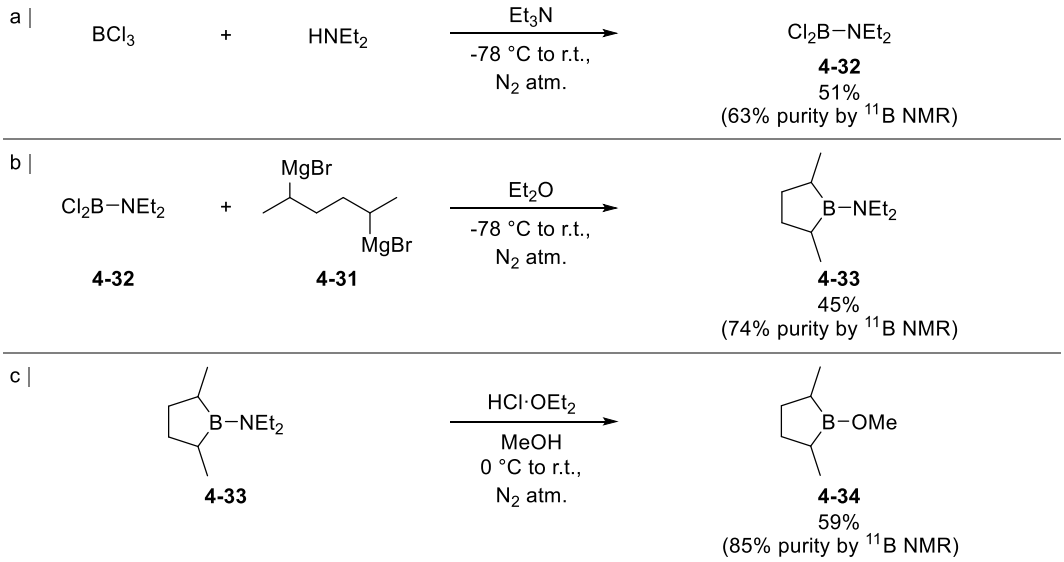
Entry	2,5-Dibromohexane (mmol)	Magnesium (Equivalents)	Reaction Solvent	Reaction Concentration (M)	Yield 4-31 (%)[a]
1	22	1.1	THF	0.22	16
2	20	1.5	THF	1.3	23
3	10	1.25[b]	THF	0.67	18
4	40	3.0	THF	0.50	37
5	100	2.75	Et_2O	1.1	35
6	350	2.75	THF	1.2	41

[a]Determined by titration against *N*-salicylaldehyde phenylhydrazone in THF; [b]Rieke Magnesium.

N,*N*-Diethylaminodichloroborane **4-32** was prepared from the reaction of boron trichloride with diethylamine in approximately 51% yield and used without purification (Scheme 4-15, a) (sample contaminated with bis(*N*,*N*-diethylamino)chloroborane[177]).* The subsequent reaction of hexane-2,5-

*Estimated percentage yields were based on isolated masses then scaled by the molar ratio of the boron species present in the ^{11}B NMR spectra (referred to as purity) and not the masses of the species and are therefore only estimated guides that are there to provide the reader with context.

di(magnesium bromide) **4-31** with *N*,*N*-diethylaminodichloroborane **4-32** resulted in the formation of *B*-(*N*,*N*-diethylamino)-2,5-dimethylborolane **4-33** in a yield of approximately 45% (Scheme 4-15, b) (distillation performed by J. Dunne, sample contaminated with unreacted bis(*N*,*N*-diethylamino)chloroborane and *B*,*B*-bis(*N*,*N*-diethylamino)alkylborane[177]).* The formation of *B*-methoxy-2,5-dimethylborolane **4-34** could be achieved by the methanolysis of 1-(*N*,*N*-diethylamino)-2,5-dimethylborolane **4-33** (Scheme 4-15, c) (reaction performed by J. Dunne). The yield of this reaction was approximately 59% and contaminated with an unknown by-product that co-distilled with the *B*-methoxy-2,5-dimethylborolane **4-34** (approximately 85% pure by ^{11}B NMR spectroscopy).*



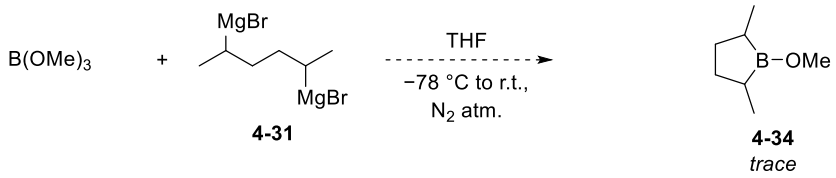
Scheme 4-15.* a) Preparation of *N*,*N*-Diethylaminodichloroborane **4-32**; b) Preparation of *B*-(*N*,*N*-Diethylamino)-2,5-dimethylborolane **4-33**; c) Preparation of *B*-Methoxy-2,5-dimethylborolane **4-34**

The low yields obtained for the first five steps in the synthesis of 2,5-dimethylborolane **4-7**, particularly the Grignard formation, and inconsistencies in the yield of the methanolysis reaction, meant that multiple reactions were required to obtain the quantities of *B*-methoxy-2,5-dimethylborolane **4-34** needed. This route is synthetically challenging and extremely time-consuming, typically taking at least five weeks to reach sufficient quantities of *B*-methoxy-2,5-dimethylborolane **4-34**.

*Estimated percentage yields were based on isolated masses then scaled by the molar ratio of the boron species present in the ^{11}B NMR spectra (referred to as purity) and not the masses of the species and are therefore only estimated guides that are there to provide the reader with context.

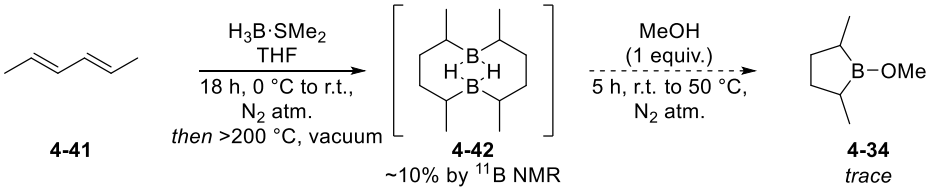
4.4.2 Alternative Routes

As the synthesis of 2,5-dimethylborolane **4-7** is difficult, shorter, alternative routes were sought. First, the preparation of *N*,*N*-diethylaminodichloroborane **4-32** was considered. If a commercially-available boron source could be used in its place, the route would be shortened. When hexane-2,5-di(magnesium bromide) **4-31** was reacted with trimethyl borate, many different boron species were formed, including the open-chained dialkyl borinic ester, the alkyl boronic ester, a trialkylborane and trace quantities of the *B*-methoxy-2,5-dimethylborolane **4-34** (Scheme 4-16). Varying the reaction conditions, including varying concentration and the temperature of addition only resulted in changing the major species between the open-chained dialkyl borinic ester and the alkyl boronic ester; *B*-methoxy-2,5-dimethylborolane **4-34** was still only formed in trace quantities.



Scheme 4-16. Attempted Preparation of *B*-Methoxy-2,5-Dimethylborolane **4-34** from Trimethyl Borate and Hexane-2,5-Di(magnesium Bromide) **4-31**

The hydroboration of 1,3-butadiene with $H_3B{\cdot}SMe_2$ was shown by Brown to form 1,6-diboracyclodecane, which could react with methanol to form *B*-methoxyborolane.[178] Therefore, it was thought that 2,4-hexadiene **4-41** could undergo the analogous reaction with $H_3B{\cdot}SMe_2$ to form 1,6-dibora-2,5,7,10-tetramethylcyclodecane **4-42** which could then undergo methanolysis to form *B*-methoxy-2,5-dimethylborolane **4-34** (Scheme 4-17). The reaction of 2,4-hexadiene **4-41** with $H_3B{\cdot}SMe_2$, followed by reaction with MeOH only formed trace quantities of *B*-methoxy-2,5-dimethylborolane **4-34**.



Scheme 4-17. Attempted Preparation of *B*-Methoxy-2,5-Dimethylborolane **4-34** from the Hydroboration of 2,4-Hexadiene **4-41** by BH_3

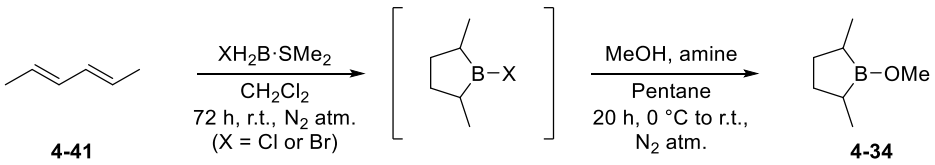
Masamune used a similar route to prepare *B*-methoxy-2,5-di*iso*propylborane. Hydroboration of 2,7-dimethyl-2,6-octadiene with $H_3B{\cdot}THF$, followed by

methanolysis, resulted in the formation of *B*-methoxy-2,5-di*iso*propylborane in excellent yield (96%).[179] Instead of using $H_3B{\cdot}THF$, Hodgetts used monohaloborane dimethyl sulphide complexes for the hydroboration of 2,7-dimethyl-2,6-octadiene to form *B*-methoxy-2,5-di*iso*propylborane, after methanolysis.[180] It was thought that using monohaloboranes could give more control over the hydroboration of 2,4-hexadiene **4-41**, reducing the formation of other boron species. Therefore, a test reaction using $ClH_2B{\cdot}SMe_2$ and 2,4-hexadiene **4-41** on a 10 mmol scale was performed. Methanolysis in the presence of diethylamine formed *B*-methoxy-2,5-dimethylborolane **4-34** in insufficient quantities to distil (Table 4-2, Entry 1). Both $ClH_2B{\cdot}SMe_2$ and $BrH_2B{\cdot}SMe_2$ are commercially-available, however samples of $ClH_2B{\cdot}SMe_2$ were contaminated with significant quantities of $Cl_2HB{\cdot}SMe_2$. Therefore, $BrH_2B{\cdot}SMe_2$ was used in the hydroboration reaction on a 5 mmol scale, resulting in the formation of *B*-methoxy-2,5-dimethylborolane **4-34** in a 6% estimated yield after methanolysis and distillation (Entry 2), in approximately 18% purity by ^{11}B NMR spectroscopy (yield determined after scaling for ^{11}B purity).* Scaling-up the reaction to 25 mmol to make the distillation easier and changing the amine from diethylamine to *sym*-collidine (the amine used by Hodgetts)[180] formed *B*-methoxy-2,5-dimethylborolane **4-34** in an 11% estimated yield after distillation, in approximately 60% purity by ^{11}B NMR spectroscopy (Entry 3).* Repeating this reaction on a 260 mmol scale gave *B*-methoxy-2,5-dimethylborolane **4-34** in 14% yield in approximately 48% purity by ^{11}B NMR spectroscopy (Entry 4).* Reducing the reaction concentration to 0.50 M and performing the reaction on a 20 mmol scale gave *B*-methoxy-2,5-dimethylborolane **4-34** in an 18% estimated yield in approximately 60% purity by ^{11}B NMR spectroscopy (Entry 5).* Reducing the concentration further to 0.25 M, reduced both the estimated yield (14%) and purity (40%) of the *B*-methoxy-2,5-dimethylborolane **4-34** (Entry 6).* Scaling up the reaction to 167 mmol at 0.50 M concentration resulted in the formation of *B*-methoxy-2,5-dimethylborolane **4-34** in a 28% estimated yield and 41% purity by ^{11}B NMR spectroscopy (Entry 7).* Whilst this estimated yield is still fairly low, the yield over four steps achieved from Masamune's route to reach *B*-methoxy-2,5-dimethylborolane **4-34** was only 2.8% (although Masamune achieved a yield of 28%). More importantly, the reaction takes less than two weeks from set-up to isolation, compared with a minimum of five weeks to reach

*Estimated percentage yields were based on isolated masses then scaled by the molar ratio of the boron species present in the ^{11}B NMR spectra (referred to as purity) and not the masses of the species and are therefore only estimated guides that are there to provide the reader with context.

the same point using Masamune's route. The impurities present in the product could not be properly identified.

Table 4-2. Optimisation of the Preparation of *B*-Methoxy-2,5-Dimethylborolane **4-34** from 2,4-Hexadiene **4-41** Hydroboration



4-41 **4-34**

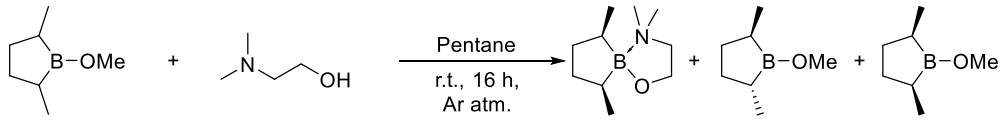
Entry	2,4-Hexadiene 4-41 (mmol)	Monohalo-borane	Amine	Reaction Concentration (M)	Estimated Yield 4-34 (%)[a]	Estimated Purity (%)[b]
1	10	$ClH_2B{\cdot}SMe_2$	Diethylamine	1.0	Trace	n/a
2	5	$BrH_2B{\cdot}SMe_2$	Diethylamine	1.0	6	18
3	25	$BrH_2B{\cdot}SMe_2$	*sym*-Collidine	1.0	11	60
4	260	$BrH_2B{\cdot}SMe_2$	*sym*-Collidine	1.0	14	48
5	20	$BrH_2B{\cdot}SMe_2$	*sym*-Collidine	0.50	18	60
6	20	$BrH_2B{\cdot}SMe_2$	*sym*-Collidine	0.25	14	40
7	167	$BrH_2B{\cdot}SMe_2$	*sym*-Collidine	0.50	28	41

[a]Estimated Yields based on isolated yields then scaled for ^{11}B purity from ^{11}B NMR spectroscopy.* [b]Estimated Purities by ^{11}B NMR spectroscopy.*

At this point in the synthesis the two routes converge. However, the samples of *B*-methoxy-2,5-dimethylborolane **4-34** from the 2,4-hexadiene **4-41** route were impure, which led to new challenges in the diastereomeric and enantiomeric resolutions. The first resolution is to remove the *meso*-isomer, *cis*-*B*-methoxy-2,5-dimethylborolane **4-43** from the two *trans*-isomers (±)-**4-36**. Addition of *N*,*N*-dimethylaminoethanol (0.44 equivalents) to *B*-methoxy-2,5-dimethylborolane **4-34** resulted in the formation of (*R*,*S*)-1-(2-*N*,*N*-dimethylaminoethoxy)-2,5-dimethylborolane **4-35**. The *trans*-*B*-methoxy-2,5-dimethylborolane (±)-**4-36** was then distilled from the reaction mixture. Using this method, *trans*-*B*-methoxy-2,5-dimethylborolane (±)-**4-36** was obtained in 54% yield over two fractions. The first fraction (15% of total yield of (±)-**4-36**) was distilled without heating (8 mbar) to give *B*-methoxy-2,5-dimethylborolane (±)-**4-36** in low purity (25% by ^{11}B NMR spectroscopy)* but in a high ratio of *trans*- to *cis*-isomers (91:9 by ^{1}H NMR spectroscopy). Most of the *trans*-*B*-methoxy-2,5-dimethylborolane (±)-**4-36** was obtained in the second fraction (85% of total yield of

*Estimated percentage yields were based on isolated masses then scaled by the molar ratio of the boron species present in the ^{11}B NMR spectra (referred to as purity) and not the masses of the species and are therefore only estimated guides that are there to provide the reader with context.

(±)-**4-36**) by heating the oil bath to 55 °C, in a higher purity (50% by ^{11}B NMR spectroscopy)* but in lower ratio of *trans*- to *cis*-isomers (74:26). Kim stated that the barrier for equilibrium between *N*,*N*-dimethylaminoethanol complexation of *cis*- and *trans*-isomers was low,[181] therefore, heating the *trans*-*B*-methoxy-2,5-dimethylborolane (±)-**4-36** in the presence of (*R*,*S*)-1-(2-*N*,*N*-dimethylaminoethoxy)-2,5-dimethylborolane **4-35** would result in a reduction in the ratio of *trans*- to *cis*-isomers. Therefore, when this reaction was repeated, the *trans*-*B*-methoxy-2,5-dimethylborolane (±)-**4-36** was separated from the reaction mixture by static vacuum transfer, achieving a yield of 85% in a ratio of 90:10 (*trans*- to *cis*-isomer) and in a similar purity (55% by ^{11}B NMR spectroscopy)* (Scheme 4-18).



4-34
25 mmol
(51% purity by ^{11}B NMR)

0.44 equiv.

4-35

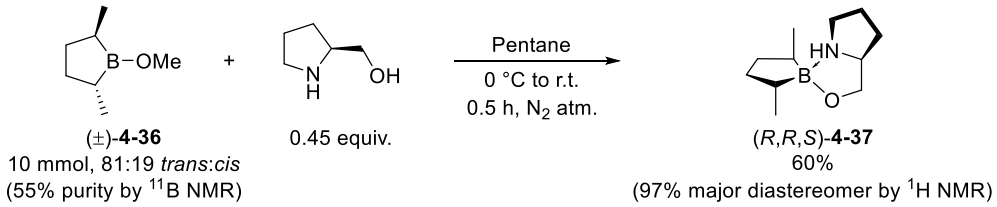
(±)-**4-36**
85%
(55% purity by ^{11}B NMR)

4-43
9%

Scheme 4-18.* Reaction of *N*,*N*-Dimethylaminoethanol with *B*-Methoxy-2,5-Dimethylborolane **4-34**

The lack of purity of the distillate in the previous steps of the synthesis was not considered an issue providing prolinol was selective for *B*-methoxy-2,5-dimethylborolane **4-34**, as the impurities could be removed in the enantiomeric resolution. Addition of a solution of (*S*)-prolinol (0.45 equivalents) in Et_2O to an impure sample of *trans*-*B*-methoxy-2,5-dimethylborolane (±)-**4-36** (55% purity by ^{11}B NMR spectroscopy, 81:19 *trans*- to *cis*-isomer)* in pentane, resulted in the immediate precipitation of (*R*,*R*)-*B*-[(*S*)-2-pyrrolidinemethoxy]-2,5-dimethylborolane (*R*,*R*,*S*)-**4-37** (97% major diastereomer by ^{1}H NMR spectroscopy) in good yield (60%) (Scheme 4-19). Subsequent repeat reactions of this enantiomeric resolution gave slightly lower yields (46-53%) and diastereomeric purities (90-93% major diastereomer by ^{1}H NMR spectroscopy). This reduction in diastereomeric purity may have been caused by the error in measuring sample purity by ^{11}B NMR spectroscopy only, causing an overestimation of the yield of **4-34** and the addition of more than 0.45 equivalents of (*S*)-prolinol. This would result in some complexation of the other isomers of **4-36** (i.e. (*S*,*S*)-**4-36** and *cis*-**4-36**) and lead to a reduction in diastereomeric purity.

*Estimated percentage yields were based on isolated masses then scaled by the molar ratio of the boron species present in the ^{11}B NMR spectra (referred to as purity) and not the masses of the species and are therefore only estimated guides that are there to provide the reader with context.



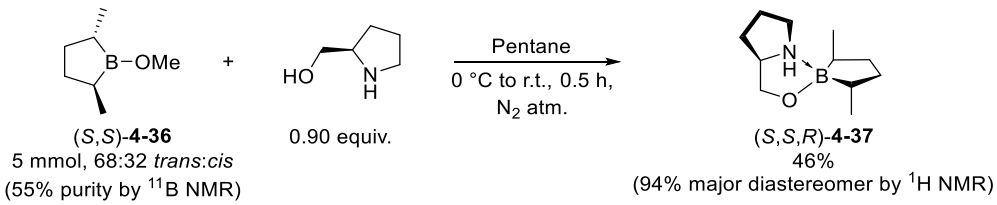
(±)-**4-36**
10 mmol, 81:19 *trans*:*cis*
(55% purity by ^{11}B NMR)

0.45 equiv.

(*R*,*R*,*S*)-**4-37**
60%
(97% major diastereomer by ^{1}H NMR)

Scheme 4-19. Preparation of (*R*,*R*)-*B*-[(*S*)-2-Pyrrolidinemethoxy]-2,5-Dimethylborolane (*R*,*R*,*S*)-**4-37**

After the addition of (*S*)-prolinol to remove (*R*,*R*)-*B*-methoxy-2,5-dimethylborolane (*R*,*R*)-**4-36** from solution, Masamune used (*S*)-valinol to selectively remove (*S*,*S*)-*B*-methoxy-2,5-dimethylborolane (*S*,*S*)-**4-36**. However, in our hands, precipitation of (*S*,*S*)-*B*-[(*S*)-2-amino-3-methyl-1-butoxy]-2,5-dimethylborolane (*S*,*S*,*S*)-**4-38** proved challenging (reactions performed by J. Dunne). Instead, as (*R*)-prolinol is commercially-available and the prolinol complexes readily precipitate from solution, it was decided that (*R*)-prolinol would be used to selectively remove (*S*,*S*)-*B*-methoxy-2,5-dimethylborolane (*S*,*S*)-**4-36** from solution. The addition of a solution of (*R*)-prolinol (0.90 equivalents) in Et_2O to the distillate of the (*S*)-prolinol reaction resulted in the formation of (*S*,*S*)-*B*-[(*R*)-2-pyrrolidinemethoxy]-2,5-dimethylborolane (*S*,*S*,*R*)-**4-37** in moderate yield (46%) and good diastereopurity (94% major diastereomer by ^{1}H NMR spectroscopy) (Scheme 4-20). Furthermore, unlike the corresponding valinol complex (*S*,*S*,*S*)-**4-38**, (*S*,*S*)-*B*-[(*R*)-2-pyrrolidinemethoxy]-2,5-dimethylborolane (*S*,*S*,*R*)-**4-37** readily precipitated from solution. The repeat reactions of (*R*)-prolinol with the distillates of the (*S*)-prolinol complexation reactions gave (*S*,*S*)-*B*-[(*R*)-2-pyrrolidinemethoxy]-2,5-dimethylborolane (*S*,*S*,*R*)-**4-37** in similar yields (42-46%) but in lower diastereomeric purity (74-89% major diastereomer by ^{1}H NMR spectroscopy). However, increasing the diastereopurity by recrystallisation was possible. The sample of (*S*,*S*)-*B*-[(*R*)-2-pyrrolidinemethoxy]-2,5-dimethylborolane (*S*,*S*,*R*)-**4-37** with 74% diastereopurity (by ^{1}H NMR spectroscopy) was recrystallised from dichloromethane to give (*S*,*S*)-*B*-[(*R*)-2-pyrrolidinemethoxy]-2,5-dimethylborolane (*S*,*S*,*R*)-**4-37** in much higher diastereopurity (97% major diastereomer by ^{1}H NMR spectroscopy).



(*S*,*S*)-**4-36**
5 mmol, 68:32 *trans*:*cis*
(55% purity by ^{11}B NMR)

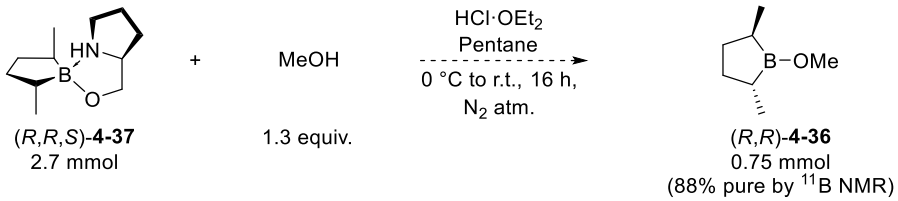
0.90 equiv.

(*S*,*S*,*R*)-**4-37**
46%
(94% major diastereomer by ^{1}H NMR)

Scheme 4-20. Preparation of (*S*,*S*)-*B*-[(*R*)-2-Pyrrolidinemethoxy]-2,5-Dimethylborolane (*S*,*S*,*R*)-**4-37**

As (*S*)- and (*R*)-prolinol appeared to have selectivity for the *trans*-isomers over the *cis*-isomer and precipitate from solutions of pentane, it was thought that prolinol could be added first, in place of *N*,*N*-dimethylaminoethanol, to precipitate one diastereomer of *trans*-*B*-methoxy-2,5-dimethylborolane (±)-**4-36** preferentially. However, the addition of (*S*)-prolinol to a sample of *B*-methoxy-2,5-dimethylborolane **4-34** (30% pure by ^{11}B NMR spectroscopy, 48:52 *trans*- to *cis*-isomer) resulted in the reaction of (*S*)-prolinol with both the *cis*- and *trans*-isomers. Unreacted *B*-methoxy-2,5-dimethylborolane **4-34** remained in the supernatant, in the same ratio (47:53 *trans*- to *cis*-isomer) as was seen in the starting material. Therefore, the diastereomeric resolution to remove *cis*-*B*-methoxy-2,5-dimethylborolane **4-43** by reaction with *N*,*N*-dimethylaminoethanol, prior to the addition of prolinol, was necessary.

The final step in the synthesis was to convert (*R*,*R*)-*B*-[(*S*)-2-pyrrolidinemethoxy]-2,5-dimethylborolane (*R*,*R*,*S*)-**4-37** or (*S*,*S*)-*B*-[(*R*)-2-pyrrolidinemethoxy]-2,5-dimethylborolane (*S*,*S*,*R*)-**4-37** back into the resolved (*R*,*R*)- or (*S*,*S*)-*B*-methoxy-2,5-dimethylborolane (*R*,*R*)-**4-36** and (*S*,*S*)-**4-36** by methanolysis (Scheme 4-21). However, all attempts to isolate (*R*,*R*)-*B*-methoxy-2,5-dimethylborolane (*R*,*R*)-**4-36** from methanolysis of the prolinol complex (*R*,*R*,*S*)-**4-37** were unsuccessful. Distillation of the reaction mixture resulted in contaminated samples of (*R*,*R*)-*B*-methoxy-2,5-dimethylborolane (*R*,*R*)-**4-36**, which did not increase in purity upon re-distillation. The contaminant was a boron species that could not be properly identified (but is thought to be a decomposition product of the formula R_2BOH or R_2BOBR_2).

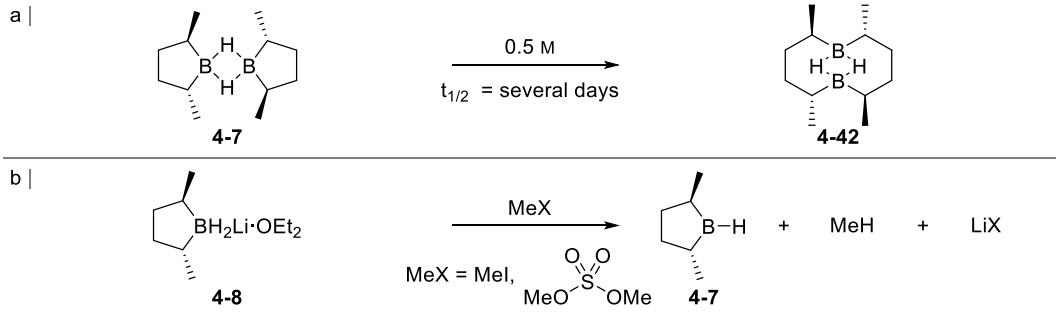


Scheme 4-21. Attempted Methanolysis of (*R*,*R*)-*B*-[(*S*)-2-Pyrrolidinemethoxy]-2,5-Dimethylborolane (*R*,*R*,*S*)-**4-37**

4.4.3 Catalyst Activation

2,5-Dimethylborolane **4-7** is unstable, slowly rearranging to form the 1,6-dibora-2,5,7,10-tetramethylcyclodecane **4-42** (Scheme 4-22, a).[157] Therefore, Masamune used the methylating reagents iodomethane and dimethyl sulphate to convert the lithium borohydride monoetherate **4-8** into the borolane **4-7** *in situ* for the enantioselective

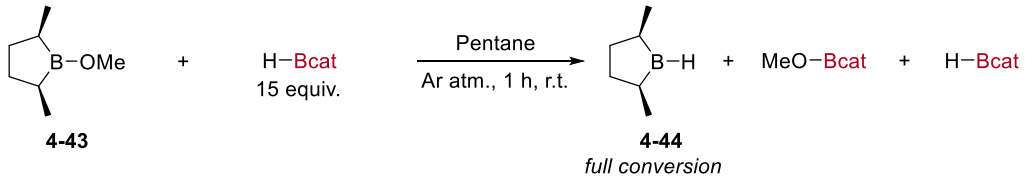
hydroboration of alkenes and ketones,[182] respectively (Scheme 4-22, b). Instead of isolating the borolane **4-7** to use as a catalyst, the lithium borohydride monoetherate **4-8** could be used as a pre-catalyst, forming the active borolane catalyst **4-7** *in situ* upon reaction with an activator such as iodomethane or dimethyl sulphate. However, incomplete activation would result in residual lithium borohydride monoetherate **4-8**; in the presence of HBpin or HBcat, the borohydride **4-8** would promote decomposition of the dioxaborolanes, forming BH_3.[74] This would lead to non-enantioselective hydroboration catalysed by BH_3 and concomitant reduction in the enantiopurity of the product. Activation by iodomethane was inconsistent, often resulting in incomplete activation (reactions performed by J. Dunne). Whilst dimethyl sulphate cleanly formed the borolane catalyst **4-7** (reactions performed by J. Dunne), the reagent is very toxic and the addition of further reagents to the catalyst system reduces the atom economy and utility of the reaction. Furthermore, lithium methyl sulphate is formed as a side-product during activation which could promote decomposition of the dioxaborolane to BH_3,[74] resulting in non-enantioselective hydroboration.



Scheme 4-22. a) Rearrangement of 2,5-Dimethylborolane **4-7**; b) Masamune's *in situ* Formation of 2,5-Dimethylborolane **4-7**

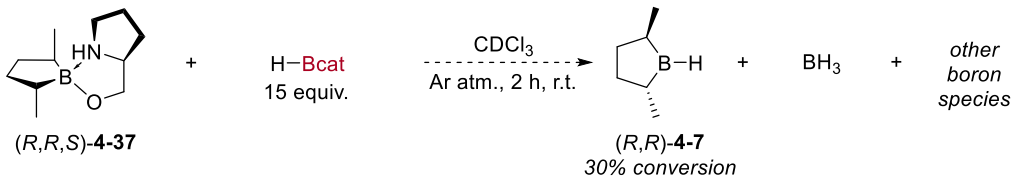
Alternatively, transborylation could be used to generate the active catalyst. This could not be used with the lithium borohydride monoetherate **4-8** as the borohydride would react through hydride transfer rather than transborylation, resulting in the decomposition of the dioxaborolane to form BH_3.[74] However, it may be possible to use the *B*-methoxy-2,5-dimethylborolane **4-34** as a pre-catalyst; a B–O/B–H transborylation of *B*-methoxy-2,5-dimethylborolane **4-34** with a dioxaborolane (e.g. HBcat) would result in the formation of the catalyst, 2,5-dimethylborolane **4-7**. The reaction of *cis*-*B*-methoxy-2,5-dimethylborolane **4-43** (**4-43** prepared by J. Dunne) with an excess of HBcat (to mimic catalytic conditions) resulted in full consumption of *cis*-*B*-methoxy-2,5-dimethylborolane **4-43** and formation of *cis*-2,5-dimethylborolane **4-44** by ^{11}B NMR spectroscopy (Scheme 4-23). Therefore, transborylation could be used as the activation method for catalysis. This avoids the

addition of further reagents and reduces the number of steps in the catalyst synthesis, as the lithium borohydride monoetherate **4-8** is prepared from the resolved (*R*,*R*)- or (*S*,*S*)-*B*-methoxy-2,5-dimethylborolane (*R*,*R*)-**4-36** and (*S*,*S*)-**4-36**.



Scheme 4-23. Activation of *cis*-*B*-methoxy-2,5-dimethylborolane **4-43** by B–O/B–H Transborylation

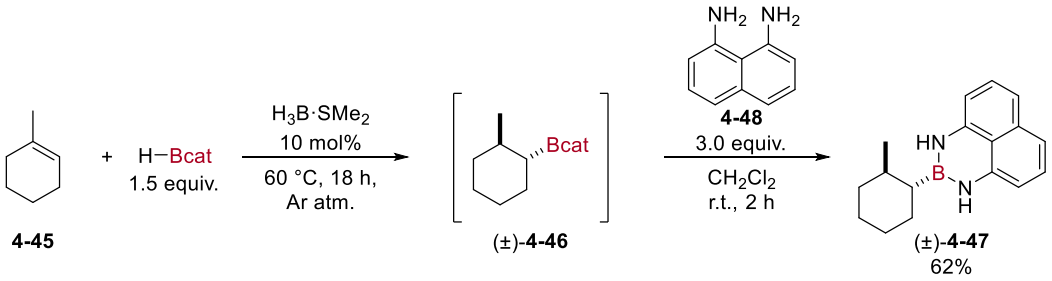
Using the prolinol complex (*R*,*R*,*S*)-**4-37** as a pre-catalyst would further reduce the number of steps and simplify the reaction setup as the prolinol complexes are air-stable. However, the reaction of HBcat with the prolinol complex (*R*,*R*,*S*)-**4-37** led to incomplete activation and the formation of BH_3, therefore, this is not a viable method of activation (Scheme 4-24).



Scheme 4-24. Incomplete Activation of Prolinol Complex (*R*,*R*,*S*)-**4-37** by HBcat and BH_3 Formation

4.4.4 Catalysis

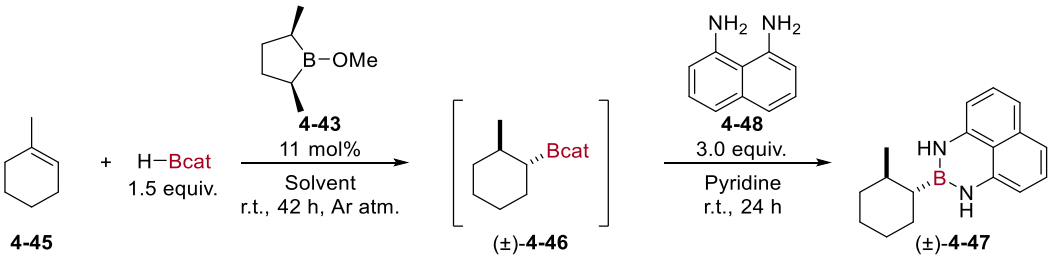
The use of transborylation to form 2,5-dimethylborolane **4-7** *in situ* from *B*-methoxy-2,5-dimethylborolane **4-36** was tested in catalysis. Catalyst turnover in the Lgf_2BH-catalysed hydroboration reactions was achieved with HBcat, but no turnover was observed with HBpin. Therefore, HBcat was selected as the turnover reagent in 2,5-dimethylborolane **4-7** catalysis. A model reaction, using 1-methylcyclohexene **4-45** as the substrate, was used to test reaction conditions. This alkene was shown by Masamune to undergo stoichiometric hydroboration slowly (96 h) to give the corresponding alcohol, 2-methylcyclohexanol, after oxidation, in good yield (60%) and high enantiopurity (95.6% e.e.) As the alkyl catechol boronic ester product **4-46** was not air-stable, it was converted *in situ* to the alkyl diazaborinine **4-47**, which could be analysed by ^{1}H NMR spectroscopy. The alkyl diazaborinine **4-47** was prepared independently (Scheme 4-25) to provide diagnostic ^{1}H NMR signals for the determination of product yield, by comparison against an internal standard.



Scheme 4-25. Preparation of the Alkyl 2,3-Dihydro-1H-Naphtho[1,8-de]-1,3,2-Diazaborinine **4-47**

1-Methylcyclohexene **4-45** underwent hydroboration with HBcat, promoted by *cis*-*B*-methoxy-2,5-dimethylborolane **4-43** (**4-43** prepared by J. Dunne) in a range of solvents to optimise the yield of the reaction (Table 4-3). By using the *meso*-isomer **4-43** the yield of the reaction could be optimised without using valuable enantioenriched (*R*,*R*)- or (*S*,*S*)-*B*-methoxy-2,5-dimethylborolane (*R*,*R*)-**4-36** and (*S*,*S*)-**4-36**. When the reaction was performed without solvent (Table 4-3, Entry 1), the highest yield of alkyl diazaborinine **4-47** product was observed (40%). A marginally lower yield (38%) was obtained with the addition of the Lewis base dimethyl sulphide (Entry 2), added under the premise that the Lewis base would reduce dimerisation of the active catalyst, increasing the rate of hydroboration. The same yield (38%) was obtained when dichloromethane was used as the solvent (Entry 3). When pentane and toluene were used as the reaction solvent, slightly lower yields (32 and 33%) were observed (Entries 4 and 5).

Table 4-3. Solvent Screen for the 2,5-Dimethylborolane **4-7**-catalysed Hydroboration of 1-Methylcyclohexene **4-45**

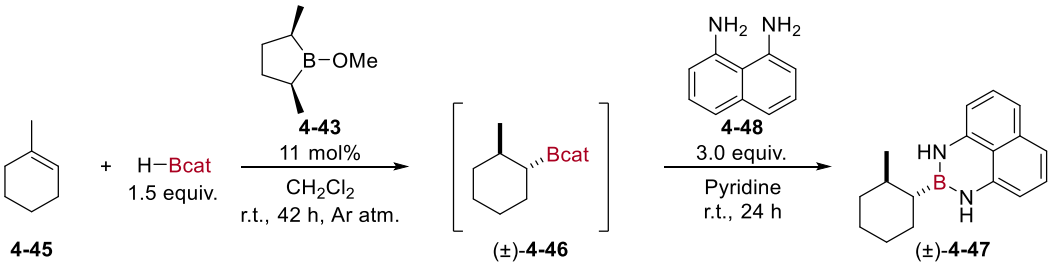


Entry	Reaction Solvent	Yield 4-47 (%)
1	Neat	40
2	Dimethyl sulphide[a]	38
3	Dichloromethane	38
4	Pentane	32
5	Toluene	33

Conditions: 1-Methylcyclohexene **4-45** (0.50 mmol), HBcat (0.75 mmol), solvent (25 µL) and *cis*-B-methoxy-2,5-dimethylborolane **4-43** (0.055 mmol), r.t., 42 h, Ar atmosphere, then 1,8-diaminonaphthalene **4-48** (1.5 mmol) in pyridine (2 mL), r.t., 24 h. Yields were determined by ^{1}H NMR spectroscopy using an internal standard (1,3,5-trimethoxybenzene). [a]10 µL.

As the yields of the alkyl diazaborinine **4-47** product were essentially the same when the reaction was performed neat or in dichloromethane (Table 4-3, Entries 1 and 3), the effect of the reaction concentration on yield was tested by increasing the volume of dichloromethane added to the reaction (Table 4-4, **4-43** prepared by J. Dunne). A reduction in yield of alkyl diazaborinine **4-47** was observed with decreasing reaction concentration (Entries 1-5), with a large reduction in yield observed above 100 µL of dichloromethane (5 M reaction concentration). Therefore, it was decided that performing the reaction without solvent was the optimum solvent conditions for yield. The observed reduction in yield with decreasing concentration could be explained by the requirement for high concentrations to promote the formation of the heterodimeric transborylation transition-state structure.

Table 4-4. Concentration Screen for the 2,5-Dimethylborolane **4-7**-catalysed Hydroboration of 1-Methylcyclohexene **4-45**



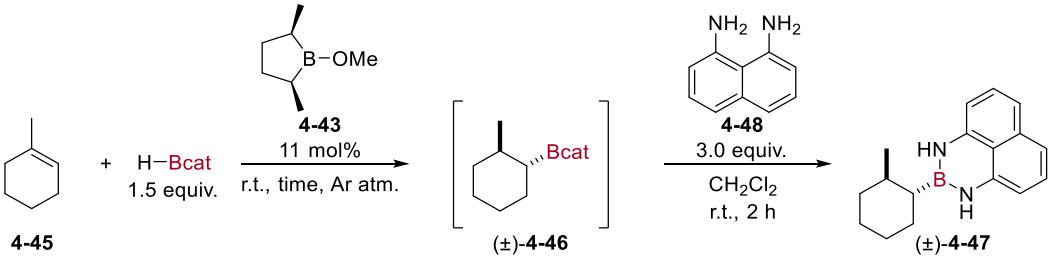
Entry	Dichloromethane Volume (µL)	Yield 4-47 (%)
1	25	38
2	50	29
3	100	25
4	200	6
5	500	4

Conditions: 1-Methylcyclohexene **4-45** (0.50 mmol), HBcat (0.75 mmol), dichloromethane (X µL) and *cis*-B-methoxy-2,5-dimethylborolane **4-43** (0.055 mmol), r.t., 42 h, Ar atmosphere, then 1,8-diaminonaphthalene **4-48** (1.5 mmol) in pyridine (2 mL), r.t., 24 h. Yields were determined by ^{1}H NMR spectroscopy using an internal standard (1,3,5-trimethoxybenzene).

Masamune obtained the alcohol, 2-methylcyclohexanol, in a 60% yield after oxidation, from the stoichiometric hydroboration of 1-methylcyclohexene **4-45** over 96 h. As 1-methylcyclohexene evidently undergoes hydroboration slowly, the reaction time of catalysis was extended to 96 h (Table 4-5, **4-43** prepared by J. Dunne), to match that of Masamune's stoichiometric hydroboration. A slight increase in yield of the alkyl diazaborinine **4-47** product (52%) was observed (Entry 2) compared to 42 h (40%, Entry 1). This result was significant as, with regards to yield, catalytic conditions were close to matching stoichiometric conditions. Unfortunately, subsequent optimisation

of yield and enantioselectivity was not possible as no further *B*-methoxy-2,5-dimethylborolane **4-34** has been isolated free from impurities.

Table 4-5. Time Screen for the 2,5-Dimethylborolane **4-7**-catalysed Hydroboration of 1-Methylcyclohexene **4-45**

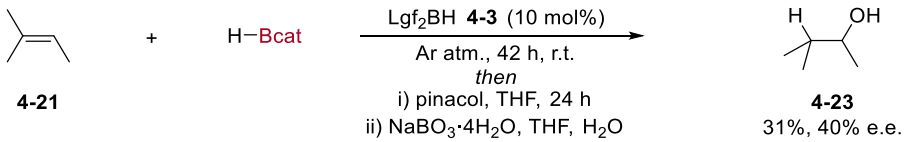


Entry	Reaction Time (h)	Yield 4-47 (%)
1	42	40
2	96	52

Conditions: 1-Methylcyclohexene **4-45** (0.50 mmol), HBcat (0.75 mmol) and *cis*-B-methoxy-2,5-dimethylborolane **4-43** (0.055 mmol), r.t., Ar atmosphere, then 1,8-diaminonaphthalene **4-48** (1.5 mmol) in dichloromethane (1 mL), r.t., 2 h. Yields were determined by ^{1}H NMR spectroscopy using an internal standard (1,3,5-trimethoxybenzene).

4.5 Conclusions and Future Work

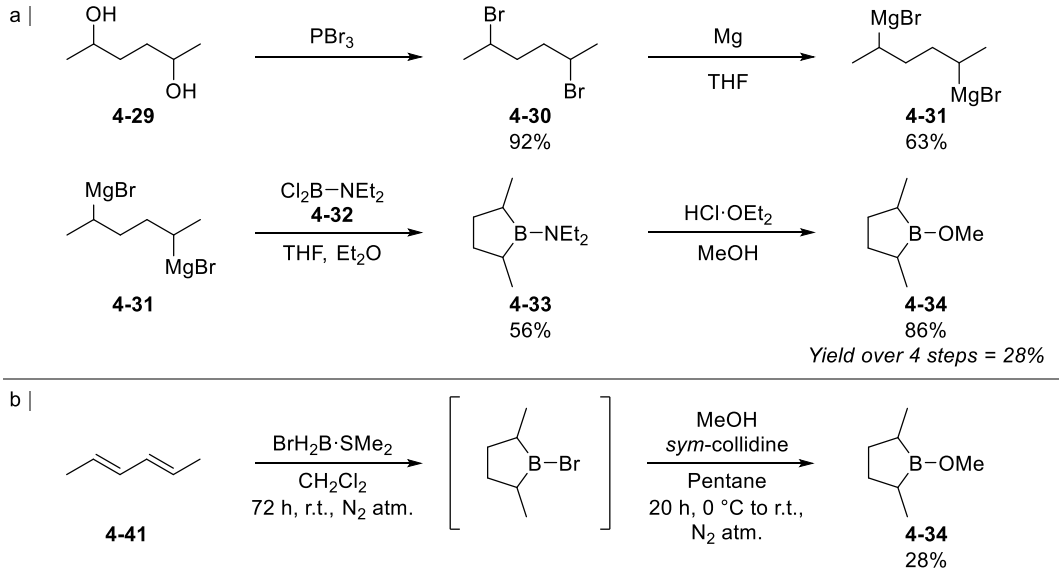
Transborylation was tested as a means for developing a borane-catalysed enantioselective hydroboration of prochiral alkenes. The acyclic enantioenriched borane Lgf_2BH **4-3**-catalysed the hydroboration of 2-methyl-2-butene **4-21** with HBcat in low yield (31%) and enantioselectivity (40% e.e.) (Scheme 4-26) but showed that turnover was possible. The reduction in enantioselectivity relative to the stoichiometric reaction (70% e.e.) appeared to be caused by a lack of selectivity in the transborylation step, supported by the observation of longifolol **4-24** in the reaction mixture, after oxidation.



Scheme 4-26. Lgf_2BH **4-3**-catalysed Hydroboration of 2-Methyl-2-Butene **4-21** with HBcat

It was proposed that a cyclic borane may improve selectivity in the transborylation step. However, the original synthesis for the cyclic enantioenriched borane 2,5-dimethylborolane **4-7**, designed by Masamune, is very challenging and time-consuming (Scheme 4-27, a).[157] Therefore, an alternative route was developed (Scheme 4-28, b), achieving the same yield at the point at which the two syntheses

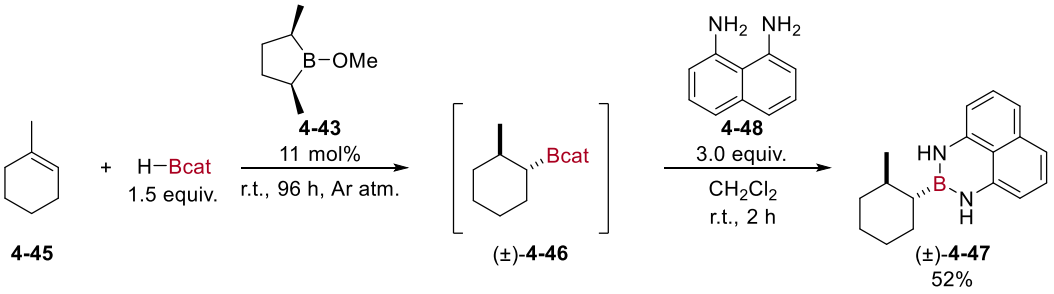
converge, forming *B*-methoxy-2,5-dimethylborolane **4-34** (28%) over a much shorter timescale (less than two weeks). The new route to *B*-methoxy-2,5-dimethylborolane **4-34** requires more refinement to achieve a higher yield and cleaner samples. Performing the reactions under an argon atmosphere may improve the yield, as the yields of *B*-methoxy-2,5-dimethylborolane **4-34** increased after the drying column for the nitrogen was refreshed. Furthermore, using more specialist distillation equipment, such as a Vigreux, Widmer, or Raschig ring-packed column to increase the theoretical number of plates in the distillation, may help to improve the yield and purity of the distillate, especially on the small scale reactions. Reducing the path length of distillation by using apparatus such as a Hickman still would be particularly useful for the final stages of the synthesis, where the volume of distillate is less than 1 mL. These refinements may also provide a solution for the isolation of (*R*,*R*)-*B*-methoxy-2,5-dimethylborolane (*R*,*R*)-**4-36** from the methanolysis reaction.



Scheme 4-27. a) Masamune's Preparation of *B*-Methoxy-2,5-Dimethylborolane **4-34**; b) New Route to *B*-Methoxy-2,5-Dimethylborolane **4-34**

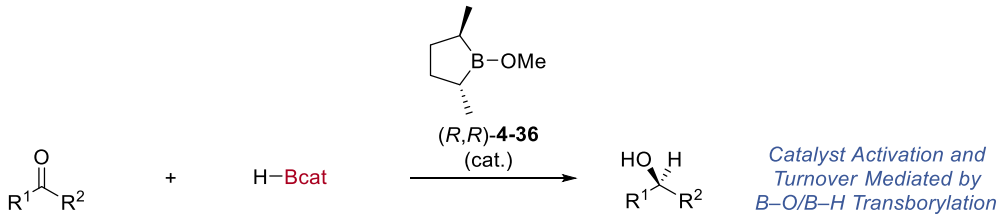
Transborylation was successfully used as a method for catalyst activation, by converting the pre-catalyst *B*-methoxy-2,5-dimethylborolane **4-34** into 2,5-dimethylborolane **4-7** *in situ* upon reaction with HBcat. *cis*-*B*-Methoxy-2,5-dimethylborolane **4-43** was used as a pre-catalyst to optimise the yield for the hydroboration of prochiral alkenes with HBcat. 1-Methylcyclohexene **4-45** was used as an exemplar, the alkyl diazaborinine **4-47** was obtained in moderate yield (52%) but this was comparable to stoichiometric reactivity (Scheme 4-28). Therefore, catalytic conditions were close to equalling stoichiometric conditions, with respect to yield. Further optimisation is required, including varying HBcat equivalents, reaction

temperature and pre-catalyst loading. Once enantioenriched *trans*-*B*-methoxy-2,5-dimethylborolane (*R*,*R*)-**4-36** or (*S*,*S*)-**4-36** has been isolated, optimisation of enantioselectivity will be necessary. After reaction optimisation, a substrate scope should be completed. The alkenes used by Masamune should be tested under catalytic conditions to compare the enantioselectivities of the stoichiometric and catalysed hydroboration reactions. Subsequently, a range of prochiral alkenes should be investigated, with a particular focus on substrates with reducible functional groups and industrially-relevant targets. As the enantioenriched chiral boranes previously developed undergo stoichiometric hydroboration with aliphatic alkenes, and there has been limited exploration of aliphatic alkenes in catalysed enantioselective hydroboration, aliphatic alkenes should also receive significant attention.



Scheme 4-28. *cis*-2,5-Dimethylborolane **4-7**-catalysed Hydroboration of 1-Methylcyclohexene **4-45** with HBcat

Once this project is complete, other stereoselective transformations using (*R*,*R*)- and (*S*,*S*)-2,5-dimethylborolane (*R*,*R*)-**4-7** and (*S*,*S*)-**4-7** as a catalyst should be developed, taking inspiration from stoichiometric examples.[183, 184] The (*R*,*R*)- and (*S*,*S*)-2,5-dimethylborolane (*R*,*R*)-**4-7** and (*S*,*S*)-**4-7**-catalysed enantioselective reduction of ketones (Scheme 4-29) should receive particular attention.

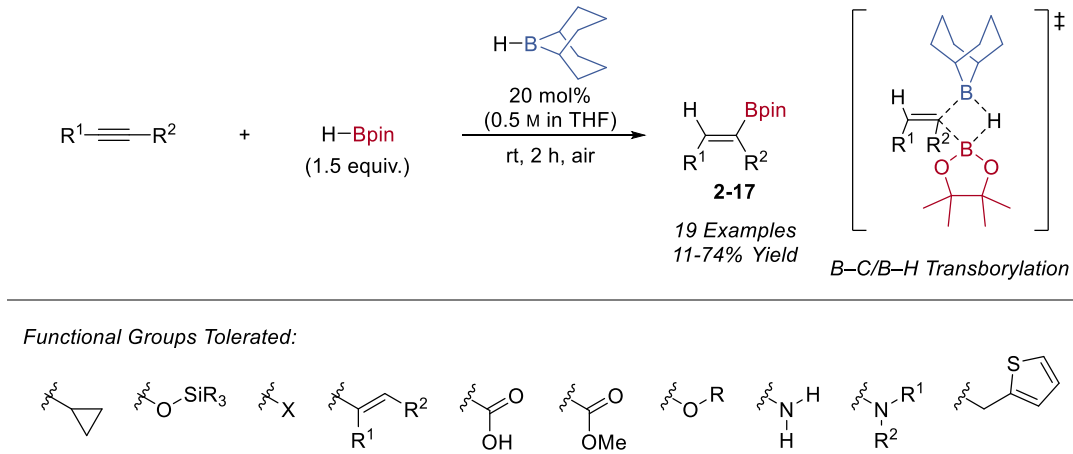


Scheme 4-29. Future Work: Catalysed Enantioselective Reduction of Ketones

5. Conclusion and Outlook

The application and understanding of B–C/B–H transborylation have been expanded through the course of this work. The development of new borane catalysis alongside mechanistic analysis of borane-catalysed hydroboration has presented a platform for future transborylation projects and provided fundamental knowledge that will underpin the future of the field of hydroboration catalysis.

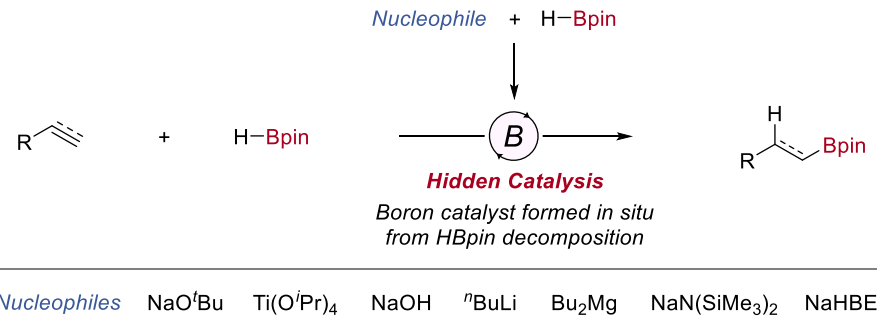
A new catalytic methodology for alkyne hydroboration with HBpin was developed, using the commercially-available H-*B*-9-BBN as a catalyst (Scheme 5-1). The mild reaction conditions showed broad functional group tolerance, but the yield of alkenyl boronic ester product can be affected by hydroboration of the product by H-*B*-9-BBN, leading to catalyst deactivation and a reduction in yield. Kinetic analysis and single-turnover experiments supported the proposal of a mechanism based on that first postulated by Hoshi.[28] The key step in the catalytic cycle was shown to be B–C(sp^2)/B–H transborylation, enabling re-formation of the catalyst, H-*B*-9-BBN, and generation of the alkenyl boronic ester product. The mechanistic understanding and knowledge-base acquired during this work has been applied to subsequent transborylation projects.[20, 45, 46, 55, 59, 74]



Scheme 5-1. H-*B*-9-BBN-catalysed Hydroboration of Alkynes with HBpin

Hidden boron catalysis was shown to exist in the ‘catalysed’ hydroboration of alkynes and alkenes with HBpin (Scheme 5-3). Simple nucleophiles, prevalent in hydroboration catalyst architectures, promoted the decomposition of HBpin to active boron-based catalysts. The addition of TMEDA to nucleophile-promoted hydroboration reactions resulted in reaction inhibition. The observation of $H_3B{\cdot}$TMEDA adducts supported the proposal of a hidden catalysis mechanism but did

not completely exclude a contribution from true catalysis, as this could have also been inhibited by TMEDA. This qualitative experiment has already become a standard technique used to investigate the presence of hidden catalysis in catalysed hydroboration reactions.[43, 185-191] The initial rates of reaction were investigated, comparing the nucleophile-promoted reactions to the corresponding BH_3-catalysed hydroboration, using the concentrations of BH_3 observed in the decomposition studies. Ultimately, hydroboration was shown to proceed through hidden catalysis for the nucleophiles tested in this study. This work has general implications in hydroboration catalysis and will be relevant as long as new catalysed hydroboration systems are developed.

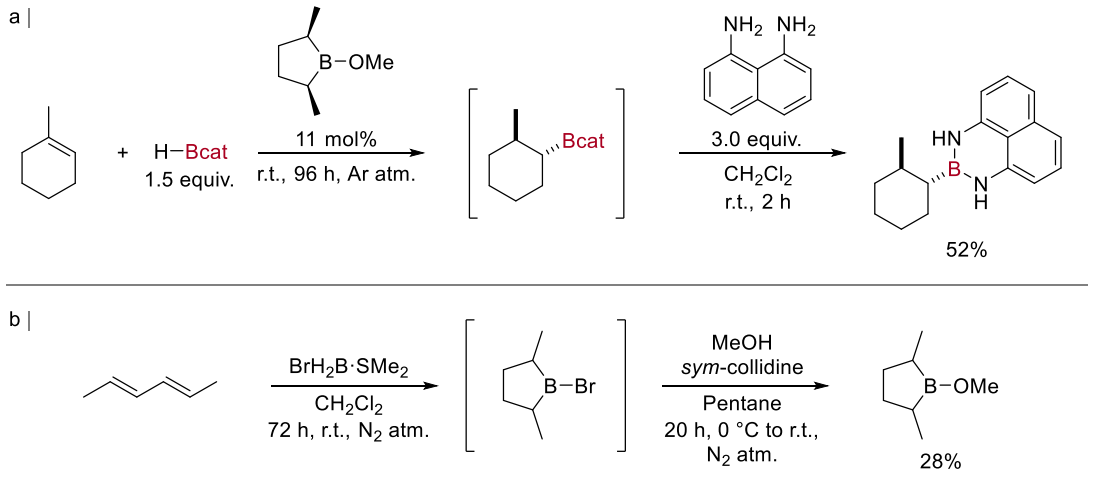


Scheme 5-3. Hidden Boron Catalysis

B-Methoxy-2,5-dimethylborolane has been used as a pre-catalyst for the hydroboration of alkenes with HBcat; activation of *B*-methoxy-2,5-dimethylborolane was achieved by B–O/B–H transborylation with HBcat (Scheme 5-2, a). Initial results suggest that B–C/B–H transborylation could be applied to the enantioselective hydroboration of prochiral alkenes. A new route to *B*-methoxy-2,5-dimethylborolane has been developed, matching the yield of the original route (28%), and reducing the amount of time required to prepare the borolane (Scheme 5-2, b). Future work on this project includes the preparation of the enantiopure (*R*,*R*)- or (*S*,*S*)-*B*-methoxy-2,5-dimethylborolane to complete the optimisation of reaction conditions, and the completion of a substrate scope to compare the new catalytic methodology to both the stoichiometric method and current state-of-the-art catalytic systems.

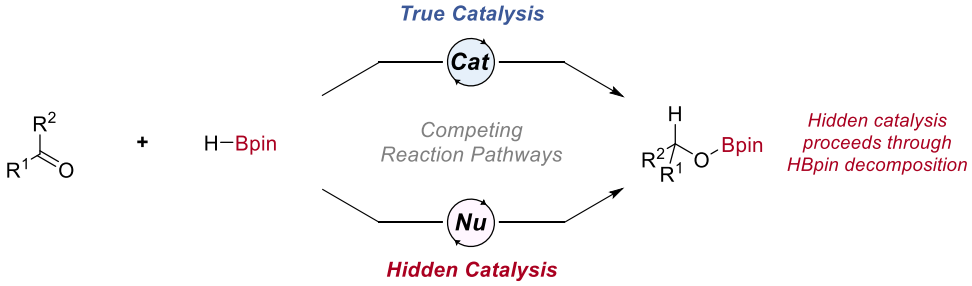
Stoichiometric hydroboration continues to offer potential applications of transborylation in catalysis, but more holistic considerations of borane catalysis are required to increase the utility of transborylation. Transborylation beyond using a B-H bond in the turnover step (i.e. B–X/B–Y transborylation, where X and Y = C, F, O, N, S, etc. and ≠ H) could introduce the next generation of transborylation reactions,

but to do so would require a focus on stoichiometric redistribution reactions that do not involve a B-H bond.



Scheme 5-2. a) 2,5-Dimethylborolane-catalysed Hydroboration of 1-Methylcyclohexene; b) New route to *B*-Methoxy-2,5-Dimethylborolane

Hidden catalysis in carbonyl hydroboration still requires further understanding to determine the true reaction pathway in the catalysed hydroboration of carbonyl derivatives (Scheme 5-4). Research into the discernment of the nucleophile-promoted carbonyl hydroboration mechanism would likely become integral to future hydroboration catalysis publications. The formation of different borohydride species should be considered during the decomposition process, along with the nucleophilicities of the carbonyl group, HBpin and the other neutral boron species formed. The effect of the cation on the rates of reaction and HBpin decomposition should also be investigated by kinetic analysis.



Scheme 5-4. Hidden Catalysis in Carbonyl Hydroboration

6. Experimental

6.1 General Experimental

Reaction Setup: All reactions were performed in oven (180 °C) and/or flamed-dried glassware under an atmosphere of anhydrous argon or nitrogen, unless otherwise indicated. All air- and moisture sensitive reactions were carried out using standard vacuum line and Schlenk techniques, or in a glovebox with a purified argon atmosphere. All glassware was cleaned using base (KOH, ^{i}PrOH) and acid (HCl_{aq}) baths. All reported reaction temperatures correspond to external oil bath temperatures. Room temperature (r.t.) was approximately 20 °C.

NMR Spectroscopy: ^{1}H, ^{7}Li, ^{13}C, ^{11}B and ^{19}F NMR spectra were recorded on Bruker Avance III 400 and 500 MHz; Bruker Avance I 600 MHz spectrometers. Chemical shifts are reported in parts per million (ppm). ^{1}H NMR spectra were referenced to the residual protonated solvent peak ($CDCl_3$: 7.26 ppm; C_6D_6: 7.16 ppm). ^{13}C NMR spectra were referenced to the solvent peak ($CDCl_3$ 77.00 ppm; C_6D_6: 128.06 ppm; h_8-toluene: 137.84 ppm) and are ^{1}H decoupled, unless stated. Multiplicities are indicated by br. (broad), s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), sext. (sextet), sept. (septet), m (multiplet), app. (apparent). Coupling constants, *J*, are reported in Hertz and rounded to the nearest 0.1 Hz.

Infrared Spectroscopy: Infra-red (IR) spectra were recorded on a Perkin-Elmer Spectrum One FT-IR or Shimadzu IRAffinity-1 spectrometer. Peaks are reported in cm^{-1} with indicated relative intensities: s (strong, 0-33% T), m (medium, 34-66% T), w (weak, 67- 100% T), and br. (broad).

Chromatography: Flash column chromatography was performed on silica gel (Geduran Si 60). Thin layer chromatography was performed on aluminium-backed silica TLC plates (Silica Gel 60 F_{254}). Staining with $KMnO_4$ was used to view spots, where necessary.

Mass Spectrometry: Mass spectrometry (MS) was performed by the University of Edinburgh, School of Chemistry, Mass Spectrometry Laboratory. High resolution mass spectra were recorded on a VG autospec, or Thermo/Finnigan MAT 900, mass spectrometer. Electrospray Ionization (ESI^{+}) spectra were performed using a time-of-flight (TOF) mass analyzer. Data are reported in the form of m/z (intensity relative to the base peak = 100).

Melting Points: Melting points were determined using a Stuart Scientific

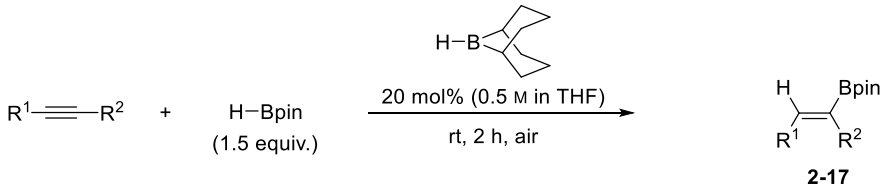
SMP10 or Griffin Gallankamp and are uncorrected.

Solvents: All solvents for air- and moisture sensitive techniques were obtained from an anhydrous solvent system (Innovative Technology). Reaction solvents tetrahydrofuran (THF) (Fisher, HPLC grade), diethyl ether (Et_2O) (Fisher, BHT stabilized ACS grade), and dichloromethane (CH_2Cl_2) (Fisher, unstabilised HPLC grade) were dried by percolation through two columns packed with neutral alumina under a positive pressure of argon. Toluene (ACS grade) and pentane (Fisher, unstabilised HPLC grade) were dried by percolation through a column packed with neutral alumina and a column packed with Q5 reactant (supported copper catalyst for scavenging oxygen) under a positive pressure of argon. Solvents for filtration, transfers, chromatography, and recrystallisation were dichloromethane (CH_2Cl_2) (ACS grade), diethyl ether (Et_2O) (Fisher, BHT stabilised ACS grade), ethyl acetate (EtOAc) (Fisher, ACS grade), hexane (Optima), methanol (MeOH) (ACS grade), pentane (ACS grade), and petroleum ether (40–60 °C, ACS grade).

Chemicals: All reagents were purchased from Sigma Aldrich, Alfa Aesar, Acros organics, Tokyo Chemical Industries UK, Fluorochem, Fisher Scientific and Apollo Scientific, or synthesised within the laboratory.

6.2 Dialkylborane-catalysed Hydroboration of Alkynes

6.2.1 General Procedure for the Hydroboration of Alkynes

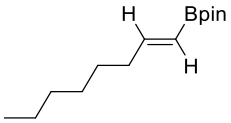


2-17

The alkyne (1.0 mmol), HBpin (0.22 mL, 1.5 mmol), and H-*B*-9-BBN (0.5 M in THF, 0.40 mL, 0.20 mmol) were added to a reaction vial in air. The reaction mixture was stirred at room temperature for 2 hours, then quenched with Et_2O (1 mL) and water (1 mL). The organic phase was extracted with Et_2O (3 × 5 mL), concentrated *in vacuo*, and purified by flash column chromatography (3.5 g SiO_2, 15 mm Ø).

6.2.2 Preparation and Characterisation of Hydroboration Products

(*E*)-4,4,5,5-Tetramethyl-2-(oct-1-enyl)-1,3,2-dioxaborolane, 2-17a



According to the general procedure, 1-octyne (0.15 mL, 1.0 mmol), HBpin (0.22 mL, 1.5 mmol), and H-*B*-9-BBN (0.5 M in THF, 0.40 mL, 0.20 mmol) were reacted. The crude reaction mixture was purified by flash column chromatography (hexane/ethyl acetate 98:2) to give the boronic ester **2-17a** (108 mg, 0.45 mmol, 45%) as a colourless oil.

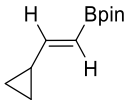
^{1}H NMR: (500 MHz, $CDCl_3$)
6.63 (dt, *J* = 17.9, 6.4 Hz, 1H, *H*C=CHBpin), 5.42 (dt, *J* = 18.0, 1.6 Hz, 1H, HC=C*H*Bpin), 2.18-2.11 (m, 2H, H_2C-C=C), 1.44-1.37 (m, 2H, H_2C), 1.26 (m, 18H, $(CH_2)_3$ and 4×CH_3), 0.88 (t, *J* = 7.0 Hz, 3H, H_3C-CH_2).

^{13}C NMR: (126 MHz, $CDCl_3$)
154.8, 118.2 (br.), 83.0, 35.8, 31.7, 28.9, 28.2, 24.8, 22.6, 14.1.

^{11}B NMR: (160 MHz, $CDCl_3$)
29.89.

Data were in accordance with those previously reported.[192]

(*E*)-4,4,5,5-Tetramethyl-2-(cyclopropyl-1-ethenyl)-1,3,2-dioxaborolane, 2-17b



According to the general procedure, cyclopropylacetylene (0.085 mL, 1.0 mmol), HBpin (0.22 mL, 1.5 mmol), and H-*B*-9-BBN (0.5 M in THF, 0.40 mL, 0.20 mmol) were reacted. The crude reaction mixture was purified by flash column chromatography (hexane/ethyl acetate 98:2) to give the boronic ester **2-17b** (104 mg, 0.54 mmol, 54%) as a colourless oil.

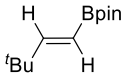
^{1}H NMR: (500 MHz, $CDCl_3$)
6.08 (dd, *J* = 17.8, 9.3 Hz, 1H, *H*C=CHBpin), 5.49 (d, *J* = 17.8 Hz, 1H, HC=C*H*Bpin), 1.57-1.48 (m, 1H, CH), 1.25 (s, 12H, 4×CH_3), 0.82-0.78 (m, 2H, CH_2), 0.55-0.52 (m, 2H, CH_2).

^{13}C NMR: (126 MHz, $CDCl_3$)
158.6, 115.2 (br.), 82.9, 24.7, 17.0, 7.9.

^{11}B NMR: (128 MHz, $CDCl_3$)
29.69.

Data were in accordance with those previously reported.[193]

(*E*)-2-4,4,5,5-Tetramethyl-2-(3,3-dimethylbut-1-enyl)-1,3,2-dioxaborolane, 2-17c



According to the general procedure, 3,3-dimethyl-1-butyne (0.123 mL, 1.0 mmol), HBpin (0.22 mL, 1.5 mmol), and H-*B*-9-BBN (0.5 M in THF, 0.40 mL, 0.20 mmol) were reacted. The crude reaction mixture was purified by flash column chromatography (hexane/ethyl acetate 98:2) to give the boronic ester **2-17c** (125 mg, 0.60 mmol, 60%) as a colourless oil.

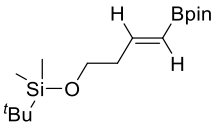
^{1}H NMR: (500 MHz, $CDCl_3$)
6.62 (d, *J* = 18.3 Hz, 1H, *H*C=CHBpin), 5.33 (d, *J* = 18.3 Hz, 1H, HC=C*H*Bpin), 1.25 (s, 12H, 4×CH_3), 1.00 (s, 9H, 3×CH_3).

^{13}C NMR: (126 MHz, $CDCl_3$)
164.4, 112.5 (br.) 83.0, 35.0, 28.9, 24.8.

^{11}B NMR: (128 MHz, $CDCl_3$)
30.29.

Data were in accordance with those previously reported.[28]

(*E*)-(*tert*-Butyl)dimethyl{[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-yl]oxy}silane, 2-17d



According to the general procedure, 4-(*tert*-butyldimethylsilyloxy)-1-butyne (0.21 mL, 1.0 mmol), HBpin (0.22 mL, 1.5 mmol), and H-*B*-9-BBN (0.5 M in THF, 0.40 mL, 0.20 mmol) were reacted. The crude reaction mixture was purified by flash column chromatography (hexane/ethyl acetate 95:5) to give the boronic ester **2-17d** (96 mg, 0.31 mmol, 31%) as a colourless oil.

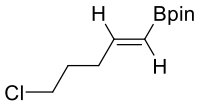
^{1}H NMR: (500 MHz, $CDCl_3$)
6.59 (dt, *J* = 18.0, 6.7 Hz, 1H, *H*C=CHBpin), 5.48 (dt, *J* = 18.0, 1.5 Hz, 1H, HC=C*H*Bpin), 3.68 (t, *J* = 7.0 Hz, 2H, O-C*H*$_2$-CH_2), 2.38 (app. qd, *J* = 6.9, 1.5 Hz, 2H, H_2C-C*H*$_2$-CH), 1.25 (s, 12H, 4×CH_3), 0.88 (s, 9H, 3×CH_3), 0.04 (s, 6H, 2×CH_3).

^{13}C NMR: (126 MHz, $CDCl_3$)
150.7, 120.9 (br.), 83.0, 62.2, 39.4, 25.9, 24.7, 18.4, -5.3.

^{11}B NMR: (160 MHz, $CDCl_3$)
29.78.

Data were in accordance with those previously reported.[192]

(*E*)-2-(5-Chloropent-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, 2-17e



According to the general procedure, 5-chloropentyne (0.11 mL, 1.0 mmol), HBpin (0.22 mL, 1.5 mmol), and H-*B*-9-BBN (0.5 M in THF, 0.40 mL, 0.20 mmol) were reacted. The crude reaction mixture was purified by flash column chromatography (hexane/ethyl acetate 98:2) to give the boronic ester **2-17e** (81 mg, 0.35 mmol, 35%) as a colourless oil.

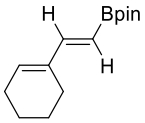
^{1}H NMR: (500 MHz, $CDCl_3$)
6.57 (dt, *J* = 18.0, 6.4 Hz, 1H, *H*C=CHBpin), 5.48 (d, *J* = 18.0 Hz, 1H, HC=C*H*Bpin), 3.52 (t, *J* = 6.7 Hz, 2H, H_2CCl), 2.33-2.27 (m, 2H, C*H*$_2$$CH_2Cl$), 1.89 (p, *J* = 7.0, 2H, CH_2), 1.25 (s, 12H, 4×CH_3).

^{13}C NMR: (126 MHz, $CDCl_3$)
152.0, 120.0 (br.), 83.1, 44.3, 32.7, 31.0, 24.7.

^{11}B NMR: (160 MHz, $CDCl_3$)
29.72.

Data were in accordance with those previously reported.[192]

(*E*)-4,4,5,5-Tetramethyl-2-(2-cyclohexenyl-1-enyl)-1,3,2-dioxaborolane, 2-17f



According to the general procedure, 1-ethynylcyclohexene (0.12 mL, 1.0 mmol), HBpin (0.22 mL, 1.5 mmol), and H-*B*-9-BBN (0.5 M in THF, 0.40 mL, 0.20 mmol) were reacted. The crude reaction mixture was purified by flash column chromatography (hexane/ethyl acetate 98:2) to give the boronic ester **2-17f** (138 mg, 0.59 mmol, 59%) as a light yellow oil.

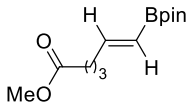
^{1}H NMR: (500 MHz, $CDCl_3$)
7.02 (d, *J* = 18.3 Hz, 1H, *H*C=CHBpin), 5.98-5.94 (m, 1H, *H*C=C), 5.42 (d, *J* = 18.3 Hz, 1H, HC=C*H*Bpin), 2.18-2.11 (m, 4H, 2×CH_2), 1.69-1.55 (m, 4H, 2×CH_2), 1.27 (s, 12H, 4×CH_3).

^{13}C NMR: (126 MHz, $CDCl_3$)
153.2, 137.2, 134.2, 111.9 (br.), 83.0, 26.2, 24.8, 23.7, 22.4, 22.3.

^{11}B NMR: (160 MHz, $CDCl_3$)
30.30.

Data were in accordance with those previously reported.[28]

(*E*)-6-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)hex-5-enoic acid methyl ester, 2-17g



According to a modified general procedure, 5-hexynoic acid (0.11 mL, 1.0 mmol), HBpin (0.44 mL, 3.0 mmol), and H-*B*-9-BBN (0.5 M in THF, 0.40 mL, 0.20 mmol) were reacted. The crude reaction mixture was diluted with methanol (0.5 mL) and treated with trimethylsilyldiazomethane (2.0 mL, 4 mmol, 2.0 M in hexanes) at 0 °C, then allowed to warm to room temperature once nitrogen evolution had stopped and left to stir for 1 h. The reaction was then diluted with Et_2O (1 mL) and water (1 mL), the organic phase was extracted with Et_2O and purified by flash column chromatography (hexane/ethyl acetate 7:3) to give the boronic ester **2-17g** (27 mg, 0.11 mmol, 11%) as a colourless oil.

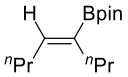
^{1}H NMR: (500 MHz, $CDCl_3$)
6.58 (dt, *J* = 18.0, 6.4 Hz, 1H, *H*C=CHBpin), 5.45 (dt, *J* = 18.0, 1.6 Hz, 1H, HC=C*H*Bpin), 3.66 (s, 3H, OCH_3), 2.32 (t, *J* = 7.5 Hz, 2H, H_2CC=O), 2.19 (tdd, *J* = 7.6, 6.4, 1.6 Hz, 2H, H_2C(H)C=), 1.76 (p, *J* = 7.5 Hz, 2H, CH_2), 1.26 (s, 12H, 4×CH_3).

^{13}C NMR: (126 MHz, $CDCl_3$)
173.9, 152.9, 119.7 (br.), 83.1, 51.5, 34.9, 33.4, 24.8, 23.4.

^{11}B NMR: (160 MHz, $CDCl_3$)
29.87.

Data were in accordance with those previously reported.[194]

(*Z*)-4,4,5,5-Tetramethyl-2-(oct-4-enyl)-1,3,2-dioxaborolane, 2-17h



According to the general procedure, 4-octyne (0.15 mL, 1.0 mmol), HBpin (0.22 mL, 1.5 mmol), and H-*B*-9-BBN (0.5 M in THF, 0.40 mL, 0.20 mmol) were reacted. The crude reaction mixture was purified by flash column chromatography (hexane/ethyl acetate 98:2) to give the boronic ester **2-17h** (33 mg, 0.14 mmol, 14%) as a colourless oil.

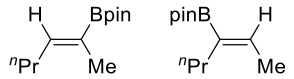
^{1}H NMR: (500 MHz, $CDCl_3$)
6.29 (t, J = 7.2 Hz, 1H, HC=CBpin), 2.13-2.08 (m, 4H, 2×CH_2), 1.45-1.39 (m, 2H, CH_2), 1.38-1.31 (m, 2H, CH_2), 1.25 (s, 12H, 4×CH_3), 0.91 (t, J = 7.4 Hz, 3H, CH_2CH_3), 0.88 (t, J = 7.4 Hz, 3H, CH_2CH_3).

^{13}C NMR: (126 MHz, $CDCl_3$)
146.0, 82.9, 30.6, 30.6, 24.7, 23.3, 22.4, 14.1, 14.1, (*C*-B not observed).

^{11}B NMR: (160 MHz, $CDCl_3$)
30.66.

Data were in accordance with those previously reported.[61]

(*Z*)-4,4,5,5-Tetramethyl-2-(hex-2-en-2-yl)-1,3,2-dioxaborolane, 2-17i (A) and (*Z*)-4,4,5,5-Tetramethyl-2-(hex-2-en-3-yl)-1,3,2-dioxaborolane, 2-17i (B)



A **B**

According to the general procedure, 2-hexyne (0.11 mL, 1.0 mmol), HBpin (0.22 mL, 1.5 mmol), and H-*B*-9-BBN (0.5 M in THF, 0.40 mL, 0.20 mmol) were reacted. The crude reaction mixture was purified by flash column chromatography (hexane/ethyl acetate 98:2) to give the boronic ester **2-17i** (120 mg, 0.57 mmol, 57%) as a colourless oil. Ratio of isomers A:B was 3:1.

Isomer A:

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

6.31 (td, *J* = 6.9, 1.7 Hz, 1H, HC=CBpin), 2.13-2.06 (m, 2H, CH_2, overlapping signals of isomers A and B), 1.67 (m, 3H, C*H*$_3$CH), 1.42 (sext., *J* = 7.4 Hz, 2H, $CH_2C\mathit{H}_2CH_3$), 1.25 (s, 12H, 4×CH_3), 0.91 (t, *J* = 7.4 Hz, 3H, C*H*$_3$$CH_2$).

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

146.4, 126.8 (br.), 83.0, 30.7, 24.8, 22.0, 14.0, 13.9.

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

30.32.

Isomer B:

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

6.41 (q, *J* = 6.8 Hz, 1H, HC=CBpin), 2.13-2.06 (m, 2H, CH_2, overlapping signals of isomers A and B), 1.70 (d, *J* = 6.8 Hz, 3H, C*H*$_3$CH), 1.36 (sext., *J* = 7.4 Hz, 2H, $CH_2C\mathit{H}_2CH_3$), 1.24 (s, 12H, 4×CH_3), 0.87 (t, *J* = 7.4 Hz, 3H, C*H*$_3$$CH_2$).

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

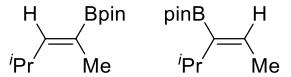
140.2, 133.2 (br.), 83.0, 30.0, 24.7, 23.0, 14.2, 14.0.

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

30.32.

Ratio of regioisomers determined by the relative integration of the peaks at 6.31 (A) and 6.41 (B) in ^{1}H NMR spectrum. Data were in accordance with those previously reported.[11]

(*Z*)-4,4,5,5-Tetramethyl-2-(4-methyl-pent-2-en-2-yl)-1,3,2-dioxaborolane, 2-17j (A) and (*Z*)-4,4,5,5-Tetramethyl-2-(4-methyl-pent-2-en-3-yl)-1,3,2-dioxaborolane, 2-17j (B)



A **B**

According to the general procedure, 4-methyl-2-pentyne (0.12 mL, 1.0 mmol), HBpin (0.22 mL, 1.5 mmol), and H-*B*-9-BBN (0.5 M in THF, 0.40 mL, 0.20 mmol) were reacted. The crude reaction mixture was purified by flash column chromatography (hexane/ethyl acetate 98:2) to give the boronic ester **2-17j** (134 mg, 0.64 mmol, 64%) as a colourless oil. Ratio of isomers A/B was 93:7.

Isomer A:

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

6.12 (dq, *J* = 9.1, 1.7 Hz, 1H, HC=CBpin), 2.68 (dsept., *J* = 9.0, 6.7 Hz, 1H, *H*C-CH=), 1.67 (d, *J* = 1.8 Hz, 3H, =C-C*H*$_3$), 1.25 (s, 12H, 4×CH_3), 0.96 (d, *J* = 6.7 Hz, 6H, HC(C*H*$_3$)$_2$).

^{13}C NMR: (126 MHz, $CDCl_3$)

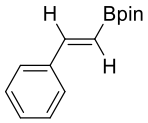
153.3, 123.9 (br.) 83.0, 27.4, 24.8, 22.2, 13.7.

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

30.43.

Ratio of regioisomers determined by the relative integration of the peaks at 6.12 (A) and 6.25 (B) in ^{1}H NMR spectrum. Data were in accordance with those previously reported.[195]

(*E*)-4,4,5,5-Tetramethyl-2-(styryl)-1,3,2-dioxaborolane, 2-17k



According to the general procedure, phenylacetylene (0.11 mL, 1.0 mmol), HBpin (0.22 mL, 1.5 mmol), and H-*B*-9-BBN (0.5 M in THF, 0.40 mL, 0.20 mmol) were reacted. The crude reaction mixture was purified by flash column chromatography (hexane/ethyl acetate 98:2) to give the boronic ester **2-17k** (155 mg, 0.67 mmol, 67%) as a colourless oil.

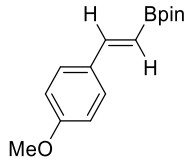
^{1}H NMR: (400 MHz, $CDCl_3$)
7.51-7.47 (m, 2H, 2×Ar*H*), 7.40 (d, *J* = 18.4 Hz, 1H, Ar*H*), 7.36-7.27 (3H, m, 2×Ar*H* and *H*C=CHBpin), 6.17 (d, *J* = 18.4 Hz, 1H, HC=C*H*Bpin), 1.32 (s, 12H, 4×CH_3).

^{13}C NMR: (126 MHz, $CDCl_3$)
149.5, 137.5, 128.9, 128.5, 127.0, 116.4 (br.), 83.3, 24.8.

^{11}B NMR: (160 MHz, $CDCl_3$)
30.30.

Data were in accordance with those previously reported.[193]

(*E*)-4,4,5,5-Tetramethyl-2-(4-methoxystyryl)-1,3,2-dioxaborolane, 2-17l



According to the general procedure, 4-ethynylanisole (0.13 mL, 1.0 mmol), HBpin (0.22 mL, 1.5 mmol), and H-*B*-9-BBN (0.5 M in THF, 0.40 mL, 0.20 mmol) were reacted. The crude reaction mixture was purified by flash column chromatography (hexane/ethyl acetate 98:2) to give the boronic ester **2-17l** (137 mg, 0.53 mmol, 53%) as orange cuboids.

MP 36-38 °C (from hexane/ethyl acetate); (lit.,[196] 55 °C).

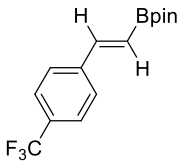
^{1}H NMR: (400 MHz, $CDCl_3$)
7.45-7.41 (m, 2H, 2×Ar*H*), 7.35 (d, *J* = 18.4 Hz, 1H, *H*C=CHBpin), 6.88-6.82 (m, 2H, 2×Ar*H*), 5.99 (d, *J* = 18.4 Hz, 1H, HC=C*H*Bpin), 3.79 (s, 3H, OCH_3), 1.30 (s, 12H, 4×CH_3).

^{13}C NMR: (126 MHz, $CDCl_3$)
160.3, 149.0, 130.4, 128.5, 114.0, 83.2, 55.3, 24.8, (*C*-B not observed).

^{11}B NMR: (128 MHz, $CDCl_3$)
30.47.

Data were in accordance with those previously reported.[196]

(*E*)-4,4,5,5-Tetramethyl-2-[4-(trifluoromethyl)styryl]-1,3,2-dioxaborolane, 2-17m



According to the general procedure, 4-trifluoromethylphenylacetylene (0.16 mL, 1.0 mmol), HBpin (0.22 mL, 1.5 mmol), and H-*B*-9-BBN (0.5 M in THF, 0.40 mL, 0.20 mmol) were reacted. The crude reaction mixture was purified by flash column chromatography (hexane/ethyl acetate 98:2) to give the boronic ester **2-17m** (222 mg, 0.77 mmol, 74%) as white cuboids.

MP 58-59 °C (from hexane/ethyl acetate); (lit.,[197] 60 °C from hexane/ethyl acetate).

^{1}H NMR: (500 MHz, $CDCl_3$)
7.58-7.52 (m, 4H, 4×Ar*H*), 7.39 (d, *J* = 18.4 Hz, 1H, *H*C=CHBpin), 6.25 (d, *J* = 18.4 Hz, 1H, HC=C*H*Bpin), 1.29 (s, 12H, 4×CH_3).

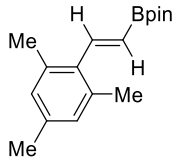
^{13}C NMR: (126 MHz, $CDCl_3$)
147.6, 140.8, 130.4 (q, *J* = 32.4 Hz), 127.1, 125.5 (q, *J* = 3.8 Hz), 124.1 (q, *J* = 272.0 Hz), 119.6 (br.), 83.5, 24.7.

^{11}B NMR: (128 MHz, $CDCl_3$)
30.10.

^{19}F NMR: (376 MHz, $CDCl_3$)
−62.65.

Data were in accordance with those previously reported.[61]

(*E*)-4,4,5,5-Tetramethyl-2-(2,4,6-trimethylstyryl)-1,3,2-dioxaborolane, 2-17n



According to the general procedure, 2,4,6-trimethylphenylacetylene (0.16 mL, 1.0 mmol), HBpin (0.22 mL, 1.5 mmol), and H-*B*-9-BBN (0.5 M in THF, 0.40 mL, 0.20 mmol) were reacted. The crude reaction mixture was purified by flash column chromatography (hexane/ethyl acetate 98:2) to give the boronic ester **2-17n** (182 mg, 0.67 mmol, 67%) as orange plates.

MP 81-82 °C (from hexane/ethyl acetate).

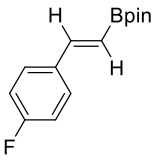
^{1}H NMR: (500 MHz, $CDCl_3$)
7.44 (d, *J* = 18.8 Hz, 1H, *H*C=CHBpin), 6.86 (s, 2H, 2×Ar*H*), 5.68 (d, *J* = 18.8 Hz, 1H, HC=C*H*Bpin), 2.30 (s, 6H, 2×ArCH_3), 2.27 (s, 3H, ArCH_3), 1.33 (s, 12H, 4×CH_3).

^{13}C NMR: (126 MHz, $CDCl_3$)
148.5, 136.7, 135.9, 135.2, 128.7, 123.0 (br.), 83.2, 24.8, 20.9, 20.9.

^{11}B NMR: (160 MHz, $CDCl_3$)
30.13.

Data were in accordance with those previously reported.[61]

(*E*)-4,4,5,5-Tetramethyl-2-(4-fluorostyryl)-1,3,2-dioxaborolane, 2-17o



According to the general procedure, 4-fluorophenylacetylene (120 mg, 1.0 mmol), HBpin (0.22 mL, 1.5 mmol), and H-*B*-9-BBN (0.5 M in THF, 0.40 mL, 0.20 mmol) were reacted. The crude reaction mixture was purified by flash column chromatography (hexane/ethyl acetate 98:2) to give the boronic ester **2-17o** (148 mg, 0.60 mmol, 60%) as white needles.

MP 64-66 °C (from hexane/ethyl acetate); (lit.,[35] 63.5-65.3 °C (from hexane/ethyl acetate).

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

7.50-7.41 (m, 2H, 2×Ar*H*), 7.35 (d, *J* = 18.4 Hz, 1H, *H*C=CHBpin), 7.06-6.98 (m, 2H, 2×Ar*H*), 6.07 (dd, *J* = 18.4 Hz, 1H), 1.31 (s, 12H, 4×CH_3).

^{13}C NMR: (126 MHz, $CDCl_3$)

163.1 (d, *J* = 248.4 Hz), 148.1, 133.7 (d, *J* = 3.2 Hz), 128.7 (d, *J* = 8.3 Hz), 115.9 (br.), 115.5 (d, *J* = 21.6 Hz), 83.4, 24.8.

^{11}B NMR: (128 MHz, $CDCl_3$)

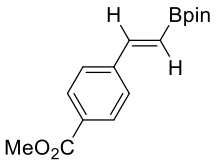
30.29.

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

−112.44 (ddd, *J* = 14.0, 8.6, 5.4 Hz).

Data were in accordance with those previously reported.[11]

Methyl 4-[(*E*)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-vinyl]benzoate, 2-17p



According to the general procedure, methyl 4-ethynylbenzoate (160 mg, 1.0 mmol), HBpin (0.22 mL, 1.5 mmol), and H-*B*-9-BBN (0.5 M in THF, 0.40 mL, 0.20 mmol) were reacted. The crude reaction mixture was purified by flash column chromatography (hexane/ethyl acetate 95:5) to give the boronic ester **2-17p** (119 mg, 0.41 mmol, 41%) as pale yellow cuboids.

MP 91-94 °C (from hexane/ethyl acetate); (lit.,[196] 79-80 °C).

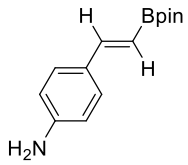
^{1}H NMR: (500 MHz, $CDCl_3$)
8.02-7.98 (m, 2H, 2×Ar*H*), 7.54-7.52 (m, 2H, 2×Ar*H*), 7.41 (d, *J* = 18.4 Hz, 1H, *H*C=CHBpin), 6.27 (d, *J* = 18.4 Hz, 1H, HC=C*H*Bpin), 3.91 (s, 3H, OCH_3), 1.32 (s, 12H, 4×CH_3).

^{13}C NMR: (126 MHz, $CDCl_3$)
166.8, 148.1, 141.7, 130.1, 129.9, 126.9, 119.5 (br.), 83.6, 52.1, 24.8.

^{11}B NMR: (160 MHz, $CDCl_3$)
30.26.

Data were in accordance with those previously reported.[61]

(*E*)-4-[2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl]aniline, 2-17q



According to a modified general procedure, 4-ethynylaniline (117 mg, 1.0 mmol), HBpin (0.65 mL, 4.5 mmol), and H-*B*-9-BBN (0.5 M in THF, 0.40 mL, 0.20 mmol) were reacted. The crude reaction mixture was purified by flash column chromatography (CH_2Cl_2/MeOH 99:1) to give the boronic ester **2-17q** (45 mg, 0.18 mmol, 18%) as orange cuboids.

MP 144-145 °C (from hexane/MeOH).

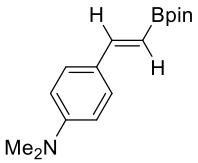
^{1}H NMR: (500 MHz, $CDCl_3$)
7.34-7.28 (m, 3H, 2×Ar*H* and *H*C=CHBpin), 6.65-6.61 (m, 2H, 2×Ar*H*), 5.93 (d, *J* = 18.4 Hz, 1H, HC=C*H*Bpin), 3.78 (s (br.), 2H, NH_2), 1.30 (s, 12H, 4×CH_3).

^{13}C NMR: (126 MHz, $CDCl_3$)
149.6, 147.3, 128.6, 128.3, 114.8, 111.5 (br.), 83.1, 24.8.

^{11}B NMR: (160 MHz, $CDCl_3$)
30.53.

Data were in accordance with those previously reported.[35]

(*E*)-*N*,*N*-Dimethyl-4-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl]aniline, 2-17r



According to the general procedure, 4-ethynyl-*N*,*N*-dimethylaniline (145 mg, 1.0 mmol), HBpin (0.22 mL, 1.5 mmol), and H-*B*-9-BBN (0.5 M in THF, 0.40 mL, 0.20 mmol) were reacted. The crude reaction mixture was purified by flash column chromatography (hexane/ethyl acetate 98:2) to give the boronic ester **2-17r** (187 mg, 0.53 mmol, 53%) as red plates.

MP 85-86 °C (from hexane/ethyl acetate); (lit.,[196] 83-87 °C).

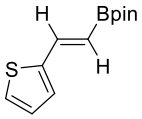
^{1}H NMR: (500 MHz, $CDCl_3$)
7.42-7.37 (m, 2H, 2×Ar*H*), 7.33 (d, *J* = 18.4 Hz, 1H, *H*C=CHBpin), 6.68-6.65 (m, 2H, 2×Ar*H*), 5.92 (d, *J* = 18.3 Hz, 1H, HC=C*H*Bpin), 2.98 (s, 6H, N(CH_3)$_2$), 1.30 (s, 12H, 4×CH_3).

^{13}C NMR: ($CDCl_3$)
151.0, 149.8, 128.4, 125.9, 111.9, 110.62 (br.), 83.0, 40.3, 24.8.

^{11}B NMR: ($CDCl_3$)
29.90.

Data were in accordance with those previously reported.[196]

(*E*)-4,4,5,5-Tetramethyl-2-[2-(thiophen-2-yl)vinyl]-1,3,2-dioxaborolane, 2-17s



According to the general procedure, 2-ethynylthiophene (0.11 mL, 1.0 mmol), HBpin (0.22 mL, 1.5 mmol), and H-*B*-9-BBN (0.5 M in THF, 0.40 mL, 0.20 mmol) were reacted. The crude reaction mixture was purified by flash column chromatography (hexane/ethyl acetate 9:1) to give the boronic ester **2-17s** (107 mg, 0.46 mmol, 46%) as a yellow oil.

^{1}H NMR: (500 MHz, $CDCl_3$)
7.47 (d, *J* = 18.1 Hz, 1H, *H*C=CHBpin), 7.24 (d, *J* = 5.0 Hz, 1H, Ar*H*), 7.08 (d, *J* = 3.5 Hz, 1H, Ar*H*), 6.98 (dd, *J* = 5.0, 3.6 Hz, 1H, Ar*H*), 5.91 (d, *J* = 18.1 Hz, 1H, HC=C*H*Bpin), 1.30 (s, 12H, 4×CH_3).

^{13}C NMR: (126 MHz, $CDCl_3$)
143.9, 141.8, 127.7, 127.6, 126.3, 115.9 (br.), 83.4, 24.8.

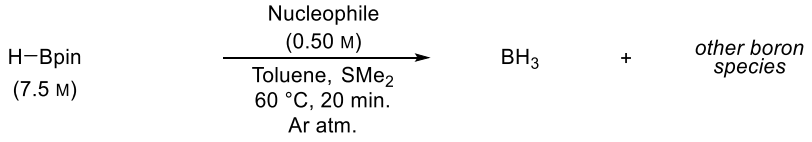
^{11}B NMR: (160 MHz, $CDCl_3$)
30.06.

Data were in accordance with those previously reported.[198]

6.3 Hidden Boron Catalysis

6.3.1 Experimental Procedures

6.3.1.1 Quantifying the Nucleophile-Promoted Decomposition of HBpin by ^{11}B NMR Spectroscopy



For solid and liquid nucleophiles:

A stock solution of HBpin (5.20 mL, 36.0 mmol) and dimethyl sulphide (176 µL, 2.40 mmol) in toluene (4.80 mL) was prepared under N_2. A sample of the stock solution (0.50 mL, 1.8 mmol HBpin) was added to an NMR tube under argon. A ^{11}B NMR spectrum was recorded to give a baseline spectrum, then the nucleophile (0.12 mmol) was added to the NMR tube under argon. The reaction was heated to 60 °C for 20 minutes, then a second ^{11}B NMR spectrum was recorded. Comparison between the two spectra gave concentrations of ^{11}B species (see Table 3-1).

For solution-based nucleophiles:

The solvent was removed under reduced pressure to give solid samples for MeLi, MeMgBr and LDA. These were used in the same procedure as for the other solid nucleophiles (see Table 3-1). ^{n}BuLi, $^{n}Bu_2Mg$ and $NaHBEt_3$ were redissolved in toluene to give 1.0 M solutions (see Note). For these nucleophiles, a modified procedure was used:

A stock solution of HBpin (2.60 mL, 18.0 mmol) and dimethyl sulphide (88 µL, 1.2 mmol) in toluene (1.20 mL) was prepared under N_2. A sample of the stock solution (0.38 mL, 1.8 mmol HBpin) was added to an NMR tube under argon. A nucleophile (1.0 M in toluene, 0.12 mL, 0.12 mmol) was added to the NMR tube under argon. A control sample was prepared by the same method except toluene (0.12 mL) was added in place of the nucleophile. The samples were heated to 60 °C for 20 minutes, then ^{11}B NMR spectra were recorded. Comparison between the two spectra gave concentrations of ^{11}B species (see Table 3-1). For the reaction which used ^{n}BuLi, ^{13}C and ^{7}Li NMR

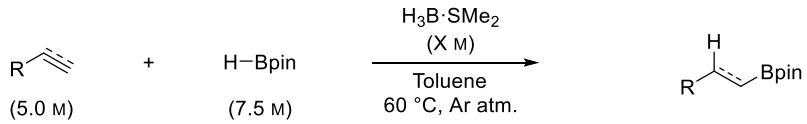
spectra were also recorded, and a second ^{11}B NMR spectrum was recorded after 2 hours (see Table 3-1).

Note

- Concentration was determined by titration against *N*-salicylaldehyde phenylhydrazone.[199]

6.3.1.2 Initial Rates of Reaction

6.3.1.2.1 BH_3-catalysed Hydroboration



Representative Procedure:

A stock solution of 1,3,5-trimethoxybenzene in toluene (1.0 M) was prepared under argon and a portion of this (0.20 mL, 0.20 mmol) was added to a reaction vial. Toluene (0.20 mL) and HBpin (0.44 mL, 3.0 mmol) were added to the reaction vial, followed by the substrate [phenylacetylene **3-2** (0.22 mL, 2.0 mmol) or *tert*-butylstyrene **3-4** (0.37 mL, 2.0 mmol)]. $H_3B{\cdot}SMe_2$ (10.2 M, X mol%) was added to the reaction vial. The reaction was heated to 60 °C with stirring, and aliquots were taken at the given time intervals, quenching in Et_2O. ^1H NMR spectra of the aliquots were recorded in $CDCl_3$. A minimum of two runs for each catalyst loading were used to determine average yields. The rate of reaction at the first time point was used as the initial rate of reaction (υ_0).

Alkyne Hydroboration:

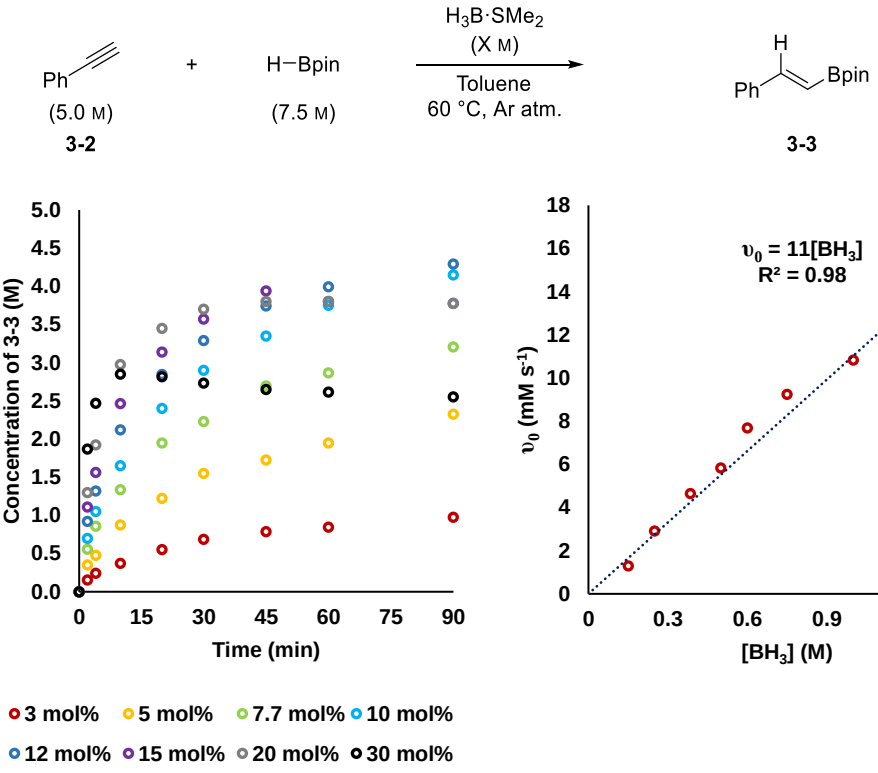


Figure 6-1. Left – Kinetic profiles for varied BH_3 loadings; Right – Calibration gradient of initial rate of reaction (υ_0) plotted against BH_3 concentration.

Alkene Hydroboration

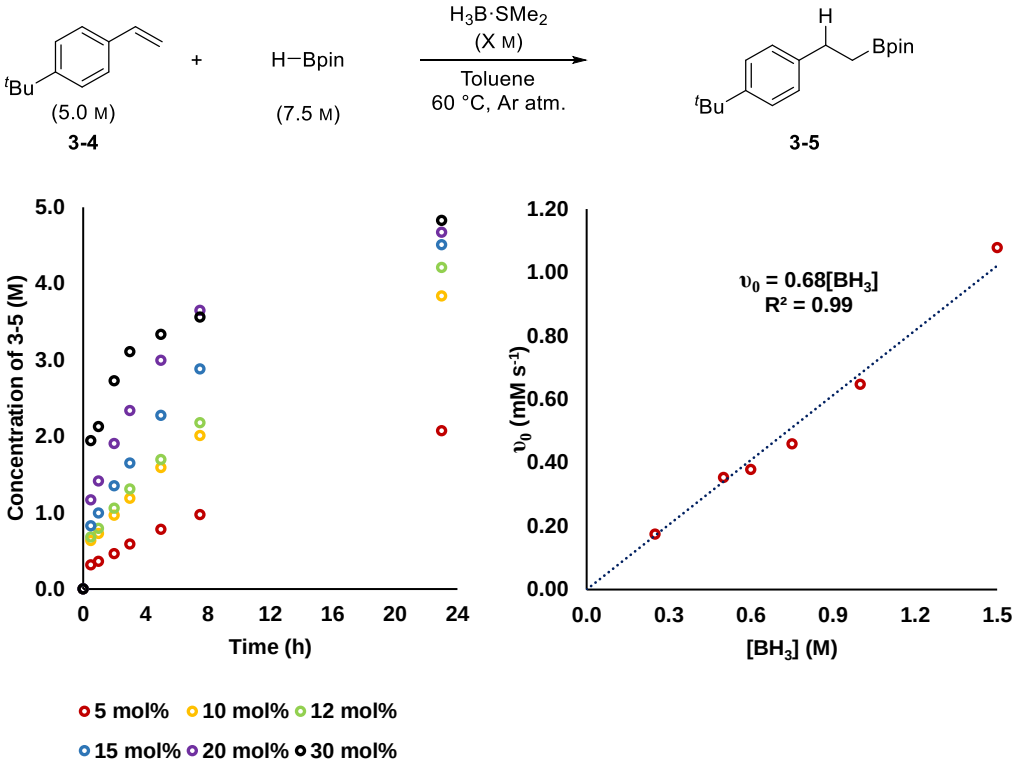
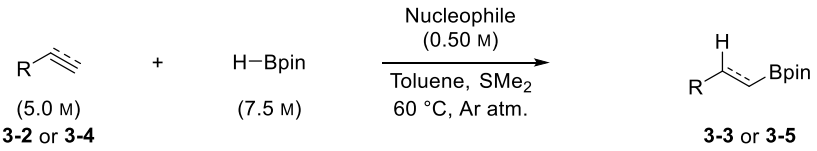


Figure 6-2. Left – Kinetic profiles for varied BH_3 loadings; Right – Calibration gradient of initial Rate of reaction (υ_0) plotted against BH_3 concentration.

6.3.1.2.2 Nucleophile-Promoted Hydroboration



For solid nucleophiles (NaO^tBu, $Na[N(SiMe_3)_2]$, $LiAlH_4$):

A stock solution of 1,3,5-trimethoxybenzene in toluene (1.0 M) was prepared under argon and a portion of this (0.20 mL, 0.20 mmol) was added to a reaction vial containing the nucleophile (0.20 mmol). Toluene (0.20 mL) and HBpin (0.44 mL, 3.0 mmol) were added to the reaction vial, followed by dimethyl sulphide (15 µL, 0.20 mmol). The reaction was heated to 60 °C for 20 minutes with stirring, followed by the substrate [phenylacetylene **3-2** (0.22 mL, 2.0 mmol) or *tert*-butylstyrene **3-4** (0.37 mL, 2.0 mmol)]. Aliquots were taken at the given time intervals, quenching in Et_2O. ^1H NMR spectra of the aliquots were recorded in $CDCl_3$. A minimum of two runs for each catalyst loading were used to determine average yields. The rate of reaction at the first time point was used as the initial rate of reaction (υ_0).

For nucleophiles in solution (^nBuLi and $^nBu_2Mg$):

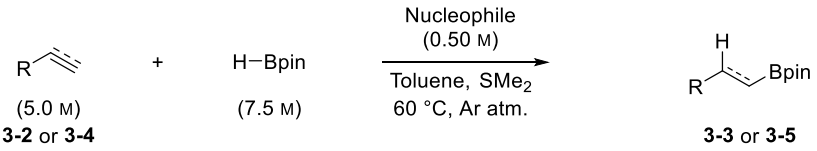
A stock solution of 1,3,5-trimethoxybenzene in toluene (1.0 M) was prepared under argon and a portion of this (0.20 mL, 0.20 mmol) was added to a reaction vial. HBpin (0.44 mL, 3.0 mmol) was added to the reaction vial, followed by dimethyl sulphide (15 µL, 0.20 mmol) and the nucleophile (1.0 M in toluene (see Note), 0.20 mL, 0.20 mmol). The reaction was heated to 60 °C for 20 minutes with stirring, followed by the substrate [phenylacetylene **3-2** (0.22 mL, 2.0 mmol) or *tert*-butylstyrene **3-4** (0.37 mL, 2.0 mmol)]. Aliquots were taken at the given time intervals, quenching in Et_2O. ^1H NMR spectra of the aliquots were recorded in $CDCl_3$. A minimum of two runs for each catalyst loading were used to determine average yields. The rate of reaction at the first time point was used as the initial rate of reaction (υ_0).

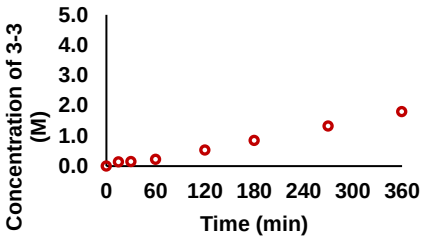
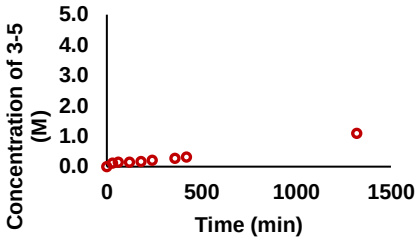
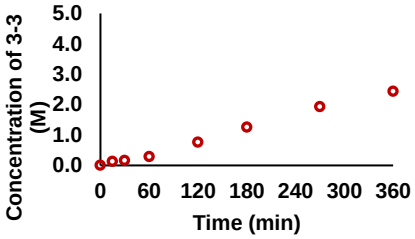
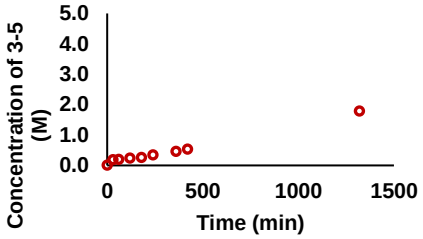
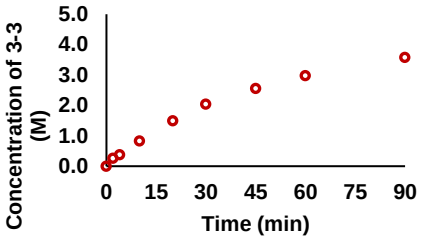
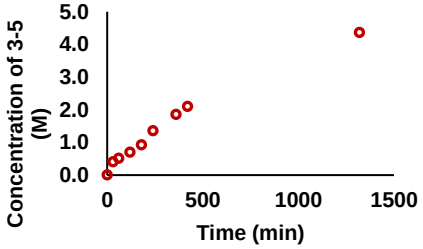
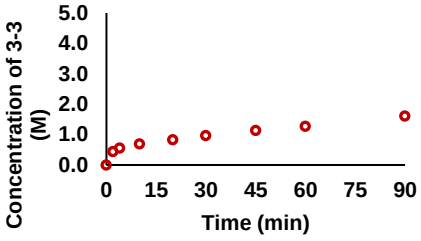
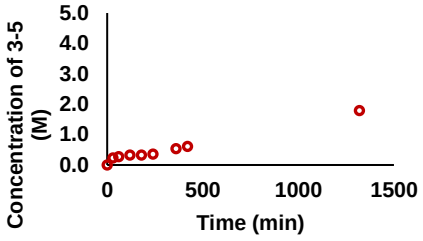
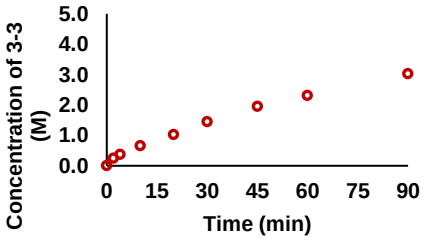
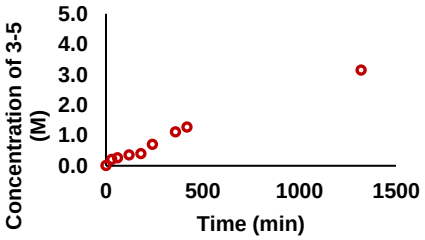
Note

- Concentration was determined by titration against *N*-salicylaldehyde phenylhydrazone.[199]

Kinetic Profiles

Table 6-1. Kinetic profiles for the nucleophile-mediated hydroboration of phenylacetylene **3-2** and *tert*-butylstyrene **3-4**

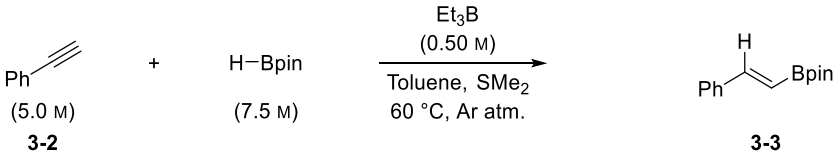


Nucleophiles	Hydroboration of **3-2**	Hydroboration of **3-4**
NaO^tBu		
$Na[N(SiMe_3)_2]$		
$LiAlH_4$		
^nBuLi		
$^nBu_2Mg$		

6.3.1.2.3 Triethylborane-catalysed Hydroboration

Triethylborane is commercially available as a solution in hexanes (1.0 M). To make a solution of triethylborane in toluene, triethylborane (1.0 M in hexanes, 10 mL, 10 mmol) was dissolved in toluene (10 mL). The hexanes were removed under reduced pressure to give a 1.2 M solution, determined by ^{11}B NMR spectroscopy.

For triethylborane (10 mol%):



A stock solution of 1,3,5-trimethoxybenzene in toluene (1.0 M) was prepared under argon and a portion of this (0.20 mL, 0.20 mmol) was added to a reaction vial. Toluene (0.03 mL) and HBpin (0.44 mL, 3.0 mmol) were added to the reaction vial, followed by dimethyl sulphide (15 µL, 0.20 mmol) and phenylacetylene **3-2** (0.22 mL, 2.0 mmol). Triethylborane (1.2 M in toluene, 0.17 mL, 0.20 mmol) was added to the reaction vial. The reaction was heated to 60 °C with stirring, and aliquots were taken at the given time intervals, quenching in Et_2O. ^{1}H NMR spectra of the aliquots were recorded in $CDCl_3$. Two runs were used to determine average yields. The rate of reaction at the first time point was used as the initial rate of reaction (υ_0 = 1.7 mM s^{-1}).

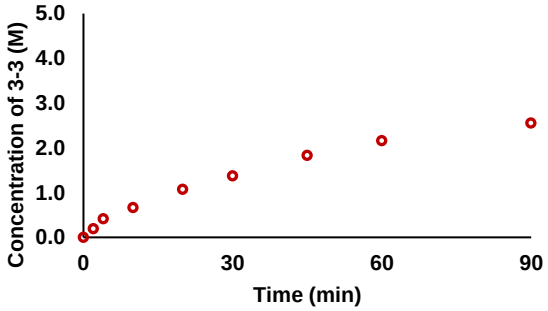
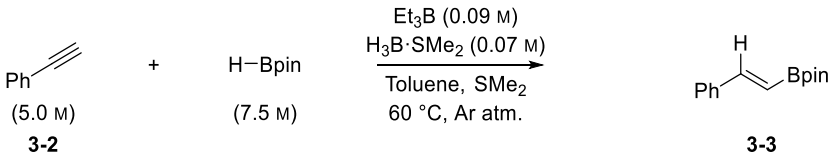


Figure 6-3. Kinetic profile for the triethylborane-mediated hydroboration of phenylacetylene **3-2**

For $^{n}Bu_2Mg$ mimic (Triethylborane 1.8 mol% and $H_3B{\cdot}SMe_2$ 1.4 mol%):



A stock solution of 1,3,5-trimethoxybenzene in toluene (1.0 M) was prepared under argon and a portion of this (0.20 mL, 0.20 mmol) was added to a reaction vial. Toluene (0.20 mL) and HBpin (0.44 mL, 3.0 mmol) were added to the reaction vial, followed by dimethyl sulphide (13 µL, 0.17 mmol) and phenylacetylene **3-2** (0.22 mL, 2.0 mmol). A stock solution of triethylborane (1.2 M in toluene, 0.75 mL, 0.90 mmol) and $H_3B{\cdot}SMe_2$ (10.2 M, 69 µL, 0.70 mmol) was prepared. A portion of this stock solution (30 µL, Et_3B 0.036 mmol, $H_3B{\cdot}SMe_2$ 0.028 mmol) was added to the reaction vial. The reaction was heated to 60 °C with stirring, and aliquots were taken at the given time intervals, quenching in Et_2O. ^1H NMR spectra of the aliquots were recorded in $CDCl_3$. Two runs were used to determine average yields. The rate of reaction at the first time point was used as the initial rate of reaction (υ_0 = 2.0 mM s^{-1}).

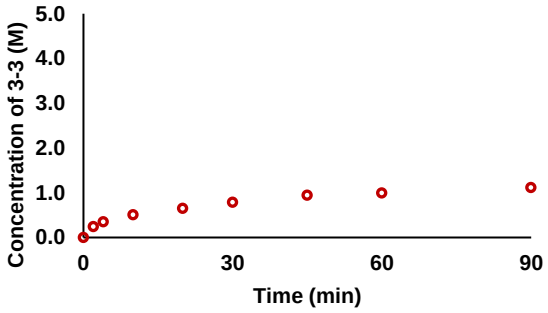
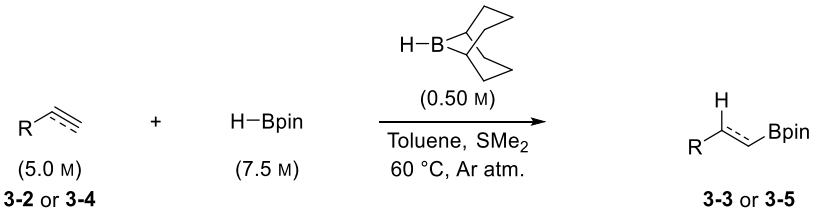


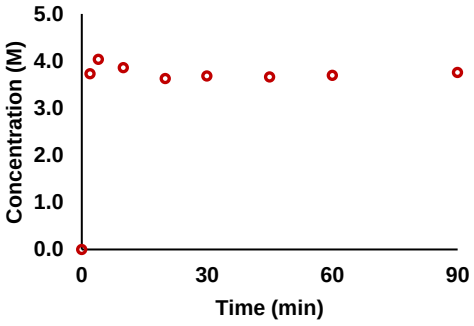
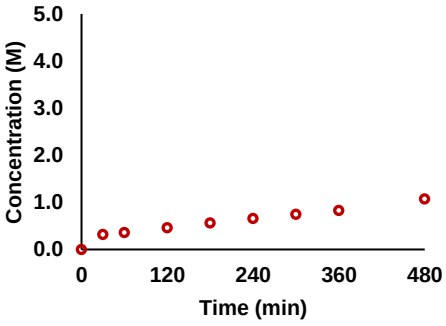
Figure 6-4. Kinetic profile for the '$^{n}Bu_2Mg$ mimic'-mediated hydroboration of phenylacetylene **3-2**

6.3.1.2.4 H-*B*-9-BBN-catalysed Hydroboration



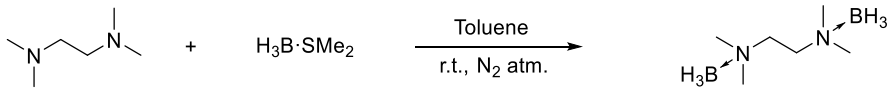
A stock solution of 1,3,5-trimethoxybenzene in toluene (1.0 M) was prepared under argon and a portion of this (0.20 mL, 0.20 mmol) was added to a reaction vial containing 9-borabicyclo[3.3.1]nonane (24 mg, 0.20 mmol). Toluene (0.20 mL) and HBpin (0.44 mL, 3.0 mmol) were added to the reaction vial, followed by dimethyl sulphide (15 µL, 0.20 mmol). The solution was heated to 60 °C and the substrate (phenylacetylene **3-2** or *tert*-butylstyrene **3-4**) (2.0 mmol) was added with stirring. Aliquots were taken at the given time intervals, quenching in Et_2O. ^1H NMR spectra of the aliquots were recorded in $CDCl_3$. A minimum of two runs for each catalyst loading were used to determine average yields. The rate of reaction at the first time point was used as the initial rate of reaction.

Table 6-2. Kinetic profiles and initial rates of reaction for the H-*B*-9-BBN-catalysed hydroboration of phenylacetylene **3-2** and *tert*-butylstyrene **3-4**

Hydroboration of **3-2**	Hydroboration of **3-4**
	
$\upsilon_0 > 32$ mM s^{-1}	$\upsilon_0 = 0.18$ mM s^{-1}
For reference BH_3 (10 mol%): $\upsilon_0 = 5.8$ mM s^{-1}	For reference BH_3 (10 mol%): $\upsilon_0 = 0.35$ mM s^{-1}

6.3.2 Preparation and Characterisation of Products

Bis-borane Tetramethylethylenediamine Complex, $(H_3B)_2$·TMEDA



N,*N*,*N*′,*N*′-Tetramethylethylenediamine (TMEDA) (3.0 mL, 20 mmol) was added dropwise to a solution of $H_3B{\cdot}SMe_2$ (1.9 mL, 20 mmol) in toluene (5 mL) under N_2. A white precipitate rapidly formed. The toluene and dimethyl sulphide were removed under reduced pressure to give $(H_3B)_2$·TMEDA (1.5 g, 10 mmol, 52%) as a white amorphous solid.

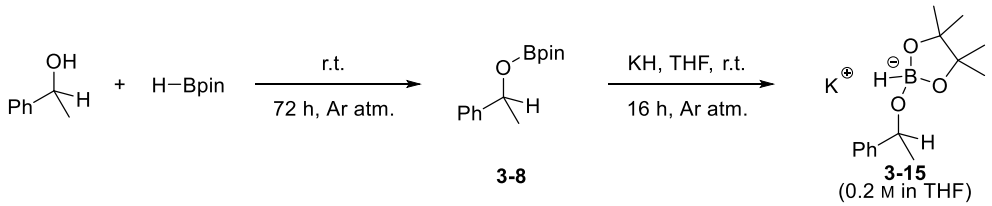
^{1}H NMR: (500 MHz, $CDCl_3$)
3.16 (s, 4H, 2×CH_2), 2.64 (s, 12H, 4×CH_3), 1.57 (app. q, J = 190.9, 85.8 Hz, 6H, 2×BH_3).
Mono-adduct: 2.86 (dd, J = 8.1, 6.1 Hz, 4H, 2×CH_2), 2.62 (s, 6H, H_3B-NC(CH_3)$_2$), 2.24 (s, 6H, 2×CH_3).
[Free TMEDA: 2.37 (s, 4H, 2×CH_2), 2.23 (s, 12H, 2×CH_3).]

^{13}C NMR: (126 MHz, $CDCl_3$)
58.9, 52.8.
Mono-adduct: 61.8, 54.2, 51.9, 45.7.
[Free TMEDA: 57.6, 45.8]

^{11}B NMR: (160 MHz, $CDCl_3$)
−10.62 (q, J = 98.4 Hz).

Data were in accordance with those previously reported.[129, 200]

Potassium 4,4,5,5-tetramethyl-2-(1-phenylethoxy)-1,3,2-dioxaborolan-2-uide, 3-15



1-Phenylethanol (1.20 mL, 10.0 mmol) was added dropwise to a flask of HBpin (2.04 mL, 14.0 mmol) under argon with stirring. The reaction was left to stir at room temperature for 72 hours. Excess HBpin was removed under reduced pressure to give 4,4,5,5-tetramethyl-2-(1-phenylethoxy)-1,3,2-dioxaborolane **3-8** (2.29 g, 9.23 mmol, 92.3%) as a colourless oil and was used without purification.

^{1}H NMR: (500 MHz, C_6D_6)
7.40 – 7.34 (m, 2H, 2×Ar*H*), 7.17 – 7.11 (m, 2H, 2×Ar*H*), 7.07 – 7.03 (m, 1H, Ar*H*), 5.42 (q, *J* = 6.5 Hz, 1H, *H*C-CH_3), 1.46 (d, *J* = 6.5 Hz, 3H, HC-C*H*$_3$), 1.03 (s, 6H, 2×CH_3), 1.00 (s, 6H, 2×CH_3).

^{13}C NMR: (126 MHz, C_6D_6)
145.4, 128.6, 127.4, 125.7, 82.5, 73.0, 25.8, 24.7, 24.6.

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

Data were in accordance with those previously reported.[201]

Using a modified procedure based on the method of Docherty *et al.*,[10] a sample of 4,4,5,5-tetramethyl-2-(1-phenylethoxy)-1,3,2-dioxaborolane **3-8** (25 mg, 0.10 mmol) was dissolved in THF (0.50 mL) under argon and reacted with potassium hydride (40 mg, 1.0 mmol), heating at 60 °C for 16 hours. The reaction was allowed to cool to room temperature and filtered through glass wool to give a solution of potassium 4,4,5,5-tetramethyl-2-(1-phenylethoxy)-1,3,2-dioxaborolan-2-uide **3-15** (0.20 M in THF).

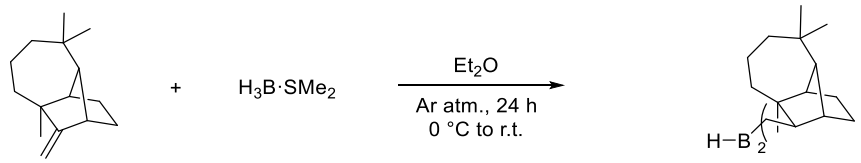
^{11}B NMR: (160 MHz, h_8-THF)
20.63 (br. s), 6.23 (s) ([$Bpin_2$]$^-$), 5.26 (s).

Data were in accordance with those previously reported.[94, 95]

6.4 Boron-catalysed Enantioselective Hydroboration of Alkenes

6.4.1 Preparation and Characterisation of Boranes

*6.4.1.1 Dilongifolylborane, **4-3***

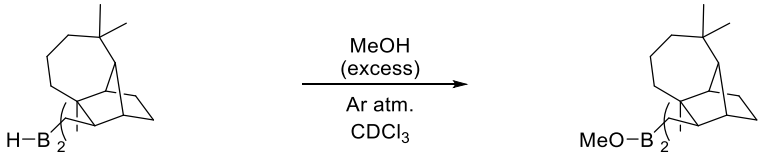


4-20 **4-3**

According to the procedure of Jadhav and Brown,[155] (+)-longifolene **4-20** (4.4 mL, 20 mmol) was dissolved in Et_2O (20 mL) in a Schlenk flask under an argon atmosphere. $H_3B{\cdot}SMe_2$ (0.95 mL, 10 mmol) was added dropwise to the solution at 0 °C with stirring. The reaction mixture allowed to warm to room temperature and left stirring for 24 hours, during which a white precipitate formed. The supernatant was removed by cannula filtration, and the white precipitate was washed with Et_2O (3 × 20 mL), removing the supernatant by cannula filtration. The remaining solvent was removed under reduced pressure to give dilongifolylborane **4-3** (2.5 g, 5.9 mmol, 59%) a white amorphous solid.

IR ν_{max} (neat) 2950 (m), 2864 (m), 1573 (m).

As per the procedure detailed by Jadhav and Brown,[155] dilongifolylborane **4-3** is insoluble in all common solvents, therefore, to analyse the sample, dilongifolylborane **4-3** was methanolysed in an NMR tube with excess MeOH to form *B*-methoxy-dilongifolylborane **6-1**.



4-3 **6-1**

^{1}H NMR: (500 MHz, $CDCl_3$)
3.49 (s, 3H, OCH_3), 1.98 (d, *J* = 4.5 Hz, 2H, 2×CH), 1.77-1.34 (m, 20H, 5×CH_2), 1.30-1.23 (m, 4H, 2×CH_2B), 1.17 (ddd, *J* = 10.8, 9.0, 4.2 Hz, 2H, 2×C*H*CH_2B), 1.07-0.99 (m, 4H, 4×CH), 0.98 (s, 6H, 2×CH_3), 0.96 (s, 6H, 2×CH_3), 0.92 (s, 6H, 2×CH_3).

^{13}C NMR: (126 MHz, $CDCl_3$)

64.7, 53.3, 51.5, 45.8, 45.7, 44.8, 39.4, 37.3, 34.4, 33.0, 32.3, 31.6, 31.1, 25.1, 22.7 (br.), 21.5.

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

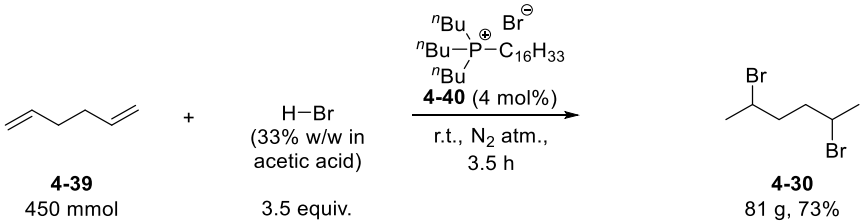
54.86.

Data were in accordance with those previously reported.[155]

*6.4.1.2 B-Methoxy-2,5-Dimethylborolane, **4-34***

6.4.1.2.1 Original Route

2,5-Dibromohexane, 4-30

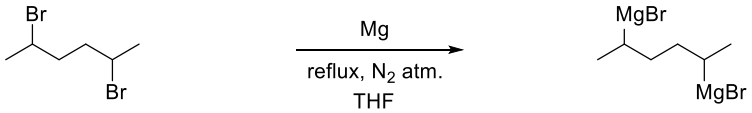


Using a modified procedure based on the method of Landini and Rolla,[202] a solution of hydrogen bromide in acetic acid (33% w/w, 270 mL, 1.6 mol) was added dropwise through a dropping funnel to a flask containing tributylhexadecylphosphonium bromide **4-40** (9.1 g, 18 mmol) and 1,5-hexadiene **4-39** (54 mL, 450 mmol) under a nitrogen atmosphere with stirring. The reaction was stirred at room temperature for 3.5 hours, then slowly diluted with $NaHCO_3$ (150 mL). The organic phase was extracted with Et_2O (150 mL) and the aqueous phase was washed with Et_2O (2 × 150 mL). The organic phases were combined and the Et_2O was removed *in vacuo*. Two phases formed, and the organic phase was extracted with Et_2O (2 × 75 mL) and washed with $NaHCO_3$ (75 mL). The organic phase was concentrated *in vacuo* and the product was purified by vacuum distillation (8 mbar, 74-76 °C) to give 2,5-dibromohexane **4-30** (81 g, 330 mmol, 73%) as a colourless oil.

^{1}H NMR: (500 MHz, $CDCl_3$)
4.21- 4.06 (m, 2H, 2×CH), 2.12-1.85 (m, 4H, 2×CH_2), 1.74 (dd, J = 6.7, 1.2 Hz, 6H, 2×CH_3).

^{13}C NMR: (126 MHz, $CDCl_3$)
50.8, 50.4, 39.5, 38.7, 26.6, 26.5.

Hexane-2,5-di(magnesium bromide), 4-31



4-30 **4-31**

Using a modified procedure based on the method of McDermott *et al.*,[176] magnesium turnings (47 g, 1.9 mol) were stirred vigorously under vacuum for 5 hours in a three-necked round-bottomed flask, fitted with a reflux condenser and a nitrogen bubbler. Stirring was stopped and the magnesium turnings were placed under a nitrogen atmosphere. THF (30 mL) was added to the flask, followed by the dropwise addition of 2,5-dibromohexane **4-30** (2.5 mL, 16 mmol, 4.6% of **4-30**). Once the reaction began to reflux, the reaction was stirred and THF (270 mL) and 2,5-dibromohexane **4-30** (51.5 mL, 334 mmol, 95.4% of **4-30**) were added in ten sequential portions. The reaction was left to stir overnight, then the supernatant was transferred to a receiver flask using a frit funnel, washing with THF (3 × 20 mL) to give a solution of hexane-2,5-di(magnesium bromide) **4-31** in THF (0.48 M (see Note), 140 mmol, 41%).

Note

- Concentration was determined by titration against *N*-salicylaldehyde phenylhydrazone.[199]

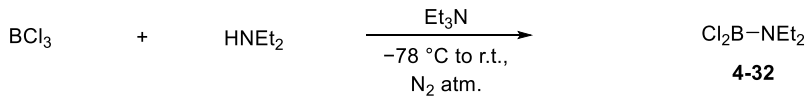
Titration against *N*-salicylaldehyde phenylhydrazone

Using a modified procedure based on the method of Love and Jones,[199] an accurate quantity of *N*-salicylaldehyde phenylhydrazone (typically 50-60 mg, 0.24-0.28 mmol) was dissolved in THF (1 mL) under an argon atmosphere with stirring. At room temperature with stirring, the solution of Grignard reagent **4-31** was added to the flask using a purged syringe. The solution immediately turned yellow upon addition, and the endpoint was indicated when the solution changed from yellow to orange.

Notes

- The concentration was calculated with consideration of the dianionic nature of **4-31**.
- Addition of excess Grignard reagent turned the solution dark red.

N,*N*-Diethylaminodichloroborane, 4-32



Using a modified procedure based on the method of Niedenzu and Dawson,[203] diethylamine (21 mL, 200 mmol) was added dropwise to a stirred solution of boron trichloride (1.0 M in hexanes, 200 mL, 200 mmol) at −78 °C under a nitrogen atmosphere. The reaction was allowed to warm to room temperature and triethylamine (28 mL, 200 mmol) was added dropwise and the reaction was stirred for 2 hours. Stirring was stopped and the supernatant was transferred to a receiver flask by cannula filtration, washing with hexane (3×10 mL). The solvent was removed *in vacuo* to give *N*,*N*-diethylaminodichloroborane **4-32** (25 g, 102 mmol, 51%, 63% purity by ^{11}B NMR)* as a yellow oil that was used without further purification (sample contaminated with bis(*N*,*N*-diethylamino)chloroborane).

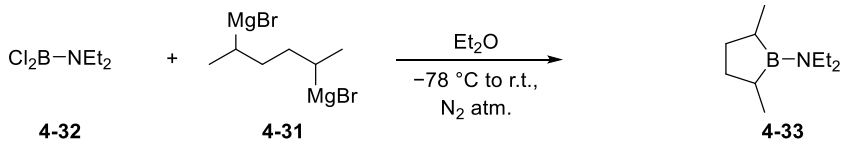
^{1}H NMR: (500 MHz, $CDCl_3$)
2.98-2.94 (m, 4H, 2×CH_2), 0.92 – 0.80 (m, 6H, 2×CH_3).

^{11}B NMR: (160 MHz, $CDCl_3$)
30.79.

Data were in accordance with those previously reported.[204]

*Estimated percentage yields were based on isolated masses then scaled by the molar ratio of the boron species present in the ^{11}B NMR spectra (referred to as purity) and not the masses of the species and are therefore only estimated guides that are there to provide the reader with context.

_B_-(_N_,_N_-Diethylamino)-2,5-dimethylborolane, 4-33



Using a modified procedure based on the method of Masamune *et al.*,[157] a solution of hexane-2,5-di(magnesium bromide) **4-31** in THF (0.44 M, 120 mmol, 270 mL) was added dropwise to a stirred solution of *N*,*N*-diethylaminodichloroborane **4-32** (25 g, 102 mmol, 51%, 63% purity by ^{11}B NMR) in Et_2O (340 mL) at −78 °C under a nitrogen atmosphere. The reaction was allowed to warm to room temperature and then stirred for 16 hours. Stirring was stopped to allow the precipitate to settle and the supernatant was transferred to a receiver flask by cannula filtration. The solvent was removed *in vacuo* and the residue was transferred to a receiver flask by vacuum transfer (200 °C). The product was purified by vacuum distillation (distillation performed by J. Dunne, 103 °C, 55 mbar) to give *B*-(*N*,*N*-diethylamino)-2,5-dimethylborolane **4-33** (104 g, 46 mmol, 45%, 74% purity by ^{11}B NMR)* as a colourless oil.

^{1}H NMR: (500 MHz, $CDCl_3$)
3.15-3.04 (m, 4H, NCH_2), 1.40-1.18 (m, 6H, NCH_2CH_3), 1.08 (td, J = 7.1, 2.3 Hz, 6H, 2×CH_2 and 2×CH), 0.96 (d, J = 7.6 Hz, 3H, CH_3), 0.87 (d, J = 7.8 Hz, 3H, CH_3).

^{13}C NMR: (126 MHz, $CDCl_3$)
42.5, 42.2, 34.1, 33.6, 23.3, 16.5, 15.7, 15.6, 15.4.

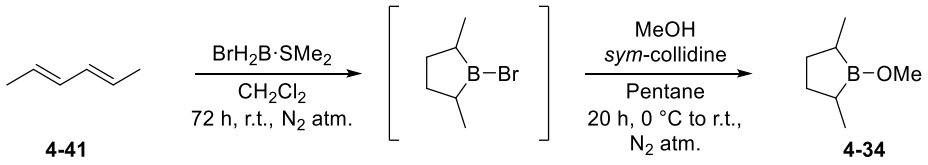
^{11}B NMR: (160 MHz, $CDCl_3$)
49.77.

Data were in accordance with those previously reported.[157]

*Estimated percentage yields were based on isolated masses then scaled by the molar ratio of the boron species present in the ^{11}B NMR spectra (referred to as purity) and not the masses of the species and are therefore only estimated guides that are there to provide the reader with context.

6.4.1.2.2 Alternate Route

***B*-Methoxy-2,5-dimethylborolane, 4-34**



Using a modified procedure based on the methods of Short *et al.*[179] and Laschober *et al.*,[180] monobromoborane dimethyl sulphide complex (1.0 M in dichloromethane, 167 mL, 167 mmol, 1.0 eq.) was diluted with dichloromethane (167 mL) in a three-necked 1 L flask under a nitrogen atmosphere. 2,4-Hexadiene (19.1 mL, 167 mmol, 1.0 eq.) was added dropwise to the flask with stirring, and the reaction was left to stir at room temperature for 72 hours. The reaction was cooled to 0 °C and methanol (13.5 mL, 334 mmol, 2.0 eq.) and *sym*-collidine (22.1 mL, 167 mmol, 1.0 eq.) were added dropwise simultaneously to the flask with vigorous stirring over a period of 45 minutes (see note 1). The reaction was kept at 0 °C for 30 minutes, then allowed to warm to room temperature and left to stir for 20 hours, then stirring was stopped to allow the white precipitate to settle. Pentane (20 mL) was added to the flask, then the supernatant was transferred to a receiver flask by cannula filtration (see note 2), washing the residue with pentane (3 × 60 mL). The solvent was removed at atmospheric pressure (see note 3), then the residue dissolved in pentane (20 mL) and the supernatant was transferred to a receiver flask by cannula filtration, washing the residue with pentane (2 × 20 mL, 1 × 10 mL). The pentane was removed under atmospheric pressure. The residue was purified by distillation (8 mbar, 22 °C) (see note 4) to give *B*-methoxy-2,5-dimethylborolane **4-34** as a colourless oil (13.7 g, ~47 mmol, ~28%, 53:47 *trans*/*cis* ratio)* that was approximately 41% pure by ^{11}B NMR spectroscopy and was used without further purification.

^{1}H NMR: (400 MHz, $CDCl_3$)
3.82 (s, 3H, *trans*-OCH_3) [3.80 (s, 3H, *cis*-OCH_3), 2.04-1.82 (m, 4H, 2×CH_2), 1.15-1.04 (m, 2H, 2×CH), 0.97 (s (br.), 6H, 2×CH_3).

^{11}B NMR: (128 MHz, $CDCl_3$)
58.01.

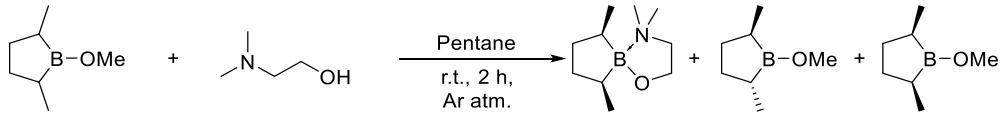
*Estimated percentage yields were based on isolated masses then scaled by the molar ratio of the boron species present in the ^{11}B NMR spectra (referred to as purity) and not the masses of the species and are therefore only estimated guides that are there to provide the reader with context.

Ratio of isomers determined by the relative integration of the peaks at 3.82 and 3.80 in ^{1}H NMR spectrum, respectively. Data were in accordance with those previously reported.[157]

Notes

1. Addition of MeOH and collidine results in the formation of a 'white cloud' – add at a rate that allows the cloud to settle.
2. Cannula can get blocked – make sure there's an oil bubbler attached to the outlet needle.
3. Using normal distillation apparatus.
4. Using microdistillation kit without stirring, oil bath temperature was 115-125 °C. Collection flask immersed in dry-ice acetone bath.

***trans*-*B*-Methoxy-2,5-dimethylborolane, (±)-4-36**



4-34
25 mmol
(51% purity by ^{11}B NMR)

0.44 equiv.

4-35

(±)-**4-36**

4-43

Using a modified procedure based on the method of Masamune *et al.*,[157] an impure sample of *cis*- and *trans*-*B*-methoxy-2,5-dimethylborolane **4-34** (~25 mmol, 50% by ^{11}B NMR spectroscopy, 52:48 trans/cis ratio) was dissolved in pentane (22 mL) under an argon atmosphere. *N*,*N*-dimethylaminoethanol (0.88 mL, 11 mmol, 0.44 eq.) was added dropwise to the flask with stirring. The reaction was left to stir at room temperature for 2 hours, then the solvent was removed under reduced pressure (see note 1). The volatiles were transferred to a receiver flask by vacuum transfer (see note 2) to give a colourless oil of *B*-methoxy-2,5-dimethylborolane (~14 mmol, 45% pure by ^{11}B NMR spectroscopy, 75:25 trans/cis ratio)*. This oil was redissolved in pentane (3 mL) and *N*,*N*-dimethylaminoethanol (0.28 mL, 3.5 mmol) was added dropwise to the flask with stirring. The reaction was left to stir at room temperature for 2 hours and the volatiles were transferred to a receiver flask by vacuum transfer (see note 2) to give a solution of *trans*-*B*-methoxy-2,5-dimethylborolane (±)-**4-36** in pentane (5.01 g, 55% by ^{11}B NMR spectroscopy, 1:2 methoxyborolane/pentane, 90:10 trans/cis ratio, 1.45 g *B*-methoxy-2,5-dimethylborolane, 1.31 g *trans*-isomer, 11 mmol *trans*-isomer, 85%)* and was used without further purification.

^{1}H NMR: (400 MHz, $CDCl_3$)
3.82 (s, 3H, *trans*-OCH_3), 2.01-1.82 (m, 4H, 2×CH_2), 1.14-1.08 (m, 2H, 2×CH), 0.97 (s (br.), 6H, 2×CH_3).

^{11}B NMR: (128 MHz, $CDCl_3$)
57.94.

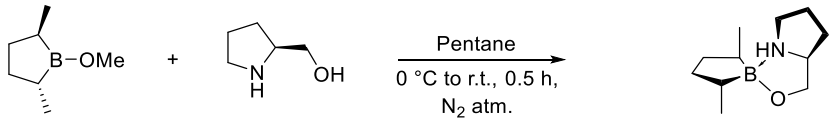
Ratio of isomers determined by the relative integration of the peaks at 3.82 and 3.80 in ^{1}H NMR spectrum, respectively. Data were in accordance with those previously reported.[157]

*Estimated percentage yields were based on isolated masses then scaled by the molar ratio of the boron species present in the ^{11}B NMR spectra (referred to as purity) and not the masses of the species and are therefore only estimated guides that are there to provide the reader with context.

Notes

1. Down to 200 mbar at room temperature, do not heat.
2. Do not heat, equilibrium constant of cis/trans complexation by *N*,*N*-dimethylaminoethanol is low.

(*R*,*R*)-*B*-[(*S*)-2-Pyrrolidinemethoxy]-2,5-dimethylborolane, (*R*,*R*,*S*)-4-37



(±)-**4-36** 0.45 equiv. (*R*,*R*,*S*)-**4-37**

Using a modified procedure based on the method of Masamune *et al.*,[157] a solution of (*S*)-prolinol (0.44 mL, 4.5 mmol) in Et_2O (0.45 mL) was added dropwise to a solution of *trans*-*B*-methoxy-2,5-dimethylborolane (±)-**4-36** (2.2 g, 55% purity by ^{11}B NMR, ~10 mmol *trans*) in pentane (10 mL) at 0 °C under a nitrogen atmosphere with stirring. An off-white precipitate formed immediately. The reaction was allowed to warm to room temperature and left to settle for 30 minutes. The supernatant was transferred to a receiver flask by cannula filtration, washing the precipitate with pentane (10 mL), to give the product (*R*,*R*,*S*)-**4-37** (530 mg, 97% major diastereomer by ^1H NMR, 2.7 mmol, 60%) as an off-white amorphous solid. The volatiles were removed from the supernatant by transferring to a receiver flask by vacuum transfer, to give a solution of *trans*-*B*-methoxy-2,5-dimethylborolane (±)-**4-36** in pentane.

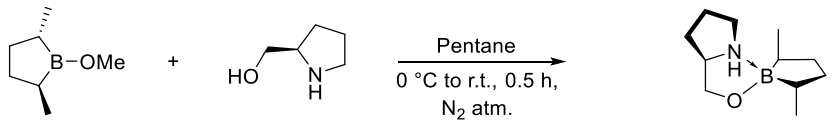
^{1}H NMR: ($CDCl_3$)
4.19 (s (br.), 1H, NH), 3.93 (dd, *J* = 9.2, 6.5 Hz, 1H, *H*C(O)H-CH), 3.69 (pd, *J* = 7.4, 3.4 Hz, 1H, CH), 3.58 (dd, *J* = 9.2, 3.4 Hz, 1H, *H*C(O)H-CH), 3.16-2.90 (m, 2H, CH_2), 2.20-1.97 (m, 2H, CH_2), 1.83-1.65 (m, 4H, 2×CH_2), 0.91 (d, *J* = 7.3 Hz, 6H, 2×CH_3), 0.60 (dt, *J* = 10.4, 7.0 Hz, 2H, 2×CH), (NCH_2 not observed).

^{13}C NMR: ($CDCl_3$)
67.4, 61.5, 48.7, 36.6, 31.2, 27.2, 25.7 (br.), 18.0 (br.).

^{11}B NMR: ($CDCl_3$)
11.46.

Ratio of diastereomers determined by the relative integration of the peaks at 3.93, 4.02, and 4.06 in ^1H NMR spectrum. Data were in accordance with those previously reported.[157]

(*S*,*S*)-*B*-[(*R*)-2-Pyrrolidinemethoxy]-2,5-dimethylborolane, (*S*,*S*,*R*)-4-37



(*S*,*S*)-**4-36** 0.90 equiv. (*S*,*S*,*R*)-**4-37**

Using a modified procedure based on the method of Kim,[181] a solution of (*R*)-prolinol (0.44 mL, 4.5 mmol) in Et_2O (0.45 mL) was added dropwise to a solution of *trans*-*B*-methoxy-2,5-dimethylborolane (±)-**4-36** (~5 mmol, 55% purity by ^{11}B NMR) in pentane (10 mL) at 0 °C under a nitrogen atmosphere with stirring. An off-white precipitate formed immediately. The reaction was allowed to warm to room temperature and left to settle for 2 hours. The supernatant was transferred to a receiver flask by cannula filtration, washing the precipitate with pentane (2 × 5 mL), to give the product (*S*,*S*,*R*)-**4-37** (400 mg, 94% major diastereomer, 2.05 mmol, 46%) as an off-white amorphous solid.

^{1}H NMR: (500 MHz, $CDCl_3$)
4.17 (s, 1H, NH), 3.94 (dd, *J* = 9.3, 6.5 Hz, 1H, *H*C(O)H-CH), 3.69 (pd, *J* = 7.4, 3.3 Hz, 1H, CH), 3.58 (dd, *J* = 9.3, 3.4 Hz, 1H, *H*C(O)H-CH), 3.15-2.91 (m, 2H, CH_2), 2.19-1.98 (m, 2H, CH_2), 1.83-1.64 (m, 4H, 2×CH_2), 0.92 (d, *J* = 7.3 Hz, 6H, 2×CH_3), 0.66-0.55 (m, 2H, 2×CH).

^{13}C NMR: ($CDCl_3$)
67.4, 61.5, 48.6, 36.6, 31.2, 27.2, 25.8 (br.), 18.0 (br.).

^{11}B NMR: ($CDCl_3$)
11.51.

Ratio of diastereomers determined by the relative integration of the peaks at 3.93, 4.02, and 4.06 in ^{1}H NMR spectrum. Data were in accordance with those previously reported.[157]

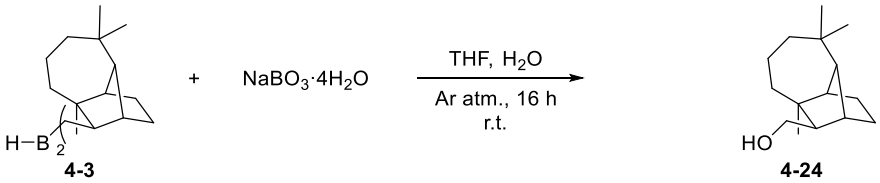
Recrystallisation of Prolinol Complexes

Recrystallisation of the prolinol complexes from dichloromethane (37 mL g^{-1}) can improve the diastereopurity of the complexes and to give **4-37** as white needles:

- (*R*,*R*,*S*)-**4-37**: **MP** 214-216 °C (from dichloromethane); (lit.,[157] 225-226 °C from dichloromethane).
- (*S*,*S*,*R*)-**4-37**: **MP** 221-223 °C (from dichloromethane); (lit.,[157] 225-226 °C, from dichloromethane).

6.4.2 Preparation and Characterisation of Products

Longifolol, 4-24



Using a modified procedure based on the method of Kabalka *et al.*,[205] dilongifolylborane **4-3** (84 mg, 0.20 mmol) and sodium perborate tetrahydrate (307 mg, 2.0 mmol) were suspended in THF (2 mL) under an argon atmosphere. H_2O (2 mL) was added dropwise, and the reaction was stirred at room temperature for 16 hours, then extracted with Et_2O (3 mL). The aqueous phase was washed with Et_2O (3 × 5 mL) and the organic phases were combined. The organic phase was washed with brine (2 × 10 mL), dried with $MgSO_4$, filtered and the solvent was removed *in vacuo* to give longifolol **4-24** (70 mg, 0.31 mmol, 78%) as a white amorphous solid.

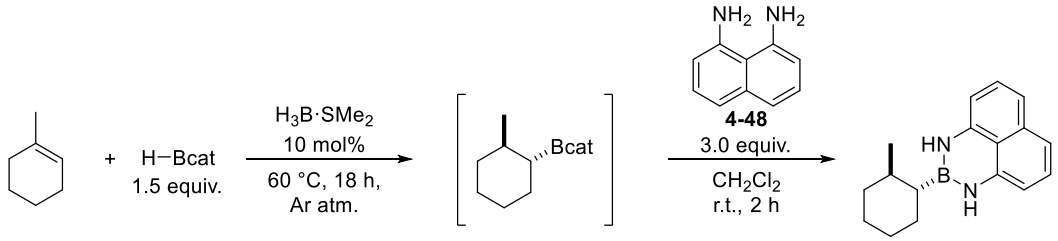
^{1}H NMR: (600 MHz, $CDCl_3$)
3.84 (dd, *J* = 10.4, 6.8 Hz, 1H, *H*CHOH), 3.73 (dd, *J* = 10.4, 8.5 Hz, 1H, *H*CHOH), 2.03 (d, *J* = 4.4 Hz, 1H, CH), 2.00 (d, *J* = 4.5 Hz, 1H, CH), 1.73-1.54 (m, 4H, 2×CH_2), 1.46-1.24 (m, 8H, 3×CH_2, CH and OH), 1.16 (ddd, *J* = 11.3, 9.1, 4.4 Hz, 1H, C*H*CH_2OH), 1.07 (s, 3H, CH_3), 0.99 (s, 3H, CH_3), 0.93 (s, 3H, CH_3).

^{13}C NMR: (151 MHz, $CDCl_3$)
64.6, 64.5, 59.7, 45.1, 44.7, 41.2, 39.3, 36.8, 34.0, 33.0, 32.4, 32.3, 31.1, 25.0, 21.3.

IR ν_{max} (neat) 3292 (w, br.), 2942 (m), 2869 (m).

MS (HRMS-ESI$^+$)
Found 245.1876 ($C_{15}H_{26}O^{23}Na$), required 245.1876.

(±)-2-(2-Methylcyclohexyl)-2,3-dihydro-1*H*-naphtho[1,8-*de*][1,3,2]diazaborinine, 4-47



1-Methylcyclohexene **4-45** (118 μL, 1.0 mmol), HBcat (160 μL, 1.5 mmol) and $H_3B{\cdot}SMe_2$ (10 μL, 0.10 mmol) were added to a reaction vial under an argon atmosphere. The reaction was stirred at 60 °C for 18 hours, then allowed to cool to room temperature. A solution of 1,8-diaminonaphthalene **4-48** (475 mg, 3.0 mmol) in dichloromethane (2.0 mL) was added to the reaction and was left to stir for 2 hours at room temperature. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (Teledyne ISCO CombiFlash NextGen 300+, Redi*Sep* R_f normal phase 12 g SiO_2 flash column, petrol/ethyl acetate 0-30%, flow rate 20 mL min^{-1}) to give the alkyl diazaborinine **4-47** (164 mg, 0.62 mmol, 62%) as colourless needles.

MP 155-157 °C (from petrol/ethyl acetate).

^{1}H NMR: (400 MHz, $CDCl_3$)
7.10 (dd, *J* = 8.3, 7.3 Hz, 2H, 2×*meta*-Ar*H*), 7.00 (dd, *J* = 8.3, 1.0 Hz, 2H, 2×*ortho*-Ar*H*), 6.30 (dd, *J* = 7.3, 1.0 Hz, 2H, 2×*para*-Ar*H*), 5.58 (s, 2H, 2×NH), 1.82-1.69 (m, 4H, 2×CH_2), 1.43-1.12 (m, 4H, 2×CH_2), 1.03-0.94 (m, 1H, CH), 0.92 (d, *J* = 6.5 Hz, 3H, CH_3), 0.55 (td, *J* = 11.6, 2.9 Hz, 1H, B-CH).

^{13}C NMR: (126 MHz, $CDCl_3$)
141.3, 136.3, 127.5, 119.7, 117.3, 105.4, 36.4, 34.8 (br.), 34.3, 29.7, 27.1, 26.8, 22.9.

^{11}B NMR: (128 MHz, $CDCl_3$)
32.56.

IR ν_{max} (neat) 3396 (w), 3049 (w), 2903 (w), 1592 (m).

MS (HRMS-ESI$^+$)
Found 264.1800 ($C_{17}H_{21}{}^{11}BN_2$), required 264.1792.

7. Appendix

7.1 Publications

1. E. Nieto-Sepulveda,[†] **A. D. Bage,**[†] L. A. Evans, T. A. Hunt, A. G. Leach, S. P. Thomas and G. C. Lloyd-Jones, *J. Am. Chem. Soc.*, 2019, **141**, 18600–18611. [†]Equal contribution.

2. **A. D. Bage,** T. A. Hunt and S. P. Thomas, *Org. Lett.*, 2020, **22**, 4107–4112.

3. **A. D. Bage,** K. Nicholson, T. A. Hunt, T. Langer and S. P. Thomas, *ACS Catal.*, 2020, **10**, 13479–13486.

4. K. Nicholson, J. Dunne, P. DaBell, A. Beaton Garcia, **A. D. Bage,** J. H. Docherty, T. A. Hunt, T. Langer and S. P. Thomas, *ACS Catal.*, 2021, **11**, 2034–2040.

8. Bibliography

1. I. Iavicoli and V. Leso, in *Handbook on the Toxicology of Metals (Fourth Edition)*, eds. G. F. Nordberg, B. A. Fowler and M. Nordberg, Academic Press, San Diego, 2015, pp. 855-878.
2. I. Iavicoli and V. Leso, in *Handbook on the Toxicology of Metals (Fourth Edition)*, eds. G. F. Nordberg, B. A. Fowler and M. Nordberg, Academic Press, San Diego, 2015, pp. 1143-1174.
3. T. Umemura, K. Sato, Y. Kusaka and H. Satoh, in *Handbook on the Toxicology of Metals (Fourth Edition)*, eds. G. F. Nordberg, B. A. Fowler and M. Nordberg, Academic Press, San Diego, 2015, pp. 1113-1123.
4. N. N. Greenwood and A. Storr, *J. Chem. Soc.*, 1965, 3426-3433.
5. F. M. Elms, G. A. Koutsantonis and C. L. Raston, *J. Chem. Soc., Chem. Commun.*, 1995, 1669-1670.
6. B. Luo, V. G. Young Jr and W. L. Gladfelter, *Chem. Commun.*, 1999, 123-124.
7. M. L. Cole, S. K. Furfari and M. Kloth, *J. Organomet. Chem.*, 2009, **694**, 2934-2940.
8. J. Klosin, G. R. Roof, E. Y. X. Chen and K. A. Abboud, *Organometallics*, 2000, **19**, 4684-4686.
9. J. Chen and E. Y. X. Chen, *Dalton Trans.*, 2016, **45**, 6105-6110.
10. A. J. Blake, A. Cunningham, A. Ford, S. J. Teat and S. Woodward, *Org. Biomol. Chem.*, 2000, **6**, 3586-3594.
11. A. Bismuto, S. P. Thomas and M. J. Cowley, *Angew. Chem. Int. Ed.*, 2016, **55**, 15356-15359.
12. A. Bismuto, M. J. Cowley and S. P. Thomas, *ACS Catal.*, 2018, **8**, 2001-2005.
13. H. I. Schlesinger and A. B. Burg, *J. Am. Chem. Soc.*, 1931, **53**, 4321-4332.
14. P. A. McCusker, G. F. Hennion and E. C. Ashby, *J. Am. Chem. Soc.*, 1957, **79**, 5192-5194.
15. G. F. Hennion, P. A. McCusker, E. C. Ashby and A. J. Rutkowski, *J. Am. Chem. Soc.*, 1957, **79**, 5194-5196.
16. P. A. McCusker and J. H. Bright, *J. Org. Chem.*, 1964, **29**, 2093-2094.
17. H. C. Brown and S. K. Gupta, *J. Am. Chem. Soc.*, 1970, **92**, 6983-6984.
18. H. C. Brown and S. K. Gupta, *J. Am. Chem. Soc.*, 1971, **93**, 1816-1818.
19. M. Hoshi, K. Shirakawa and A. Arase, *Chem. Commun.*, 1998, 1225-1226.
20. J. H. Docherty, K. Nicholson, A. P. Dominey and S. P. Thomas, *ACS Catal.*, 2020, **10**, 4686-4691.

21. T. R. Wu and J. M. Chong, *J. Am. Chem. Soc.*, 2005, **127**, 3244-3245.
22. T. R. Wu and J. M. Chong, *J. Am. Chem. Soc.*, 2007, **129**, 4908-4909.
23. H. M. Turner, J. Patel, N. Niljianskul and J. M. Chong, *Org. Lett.*, 2011, **13**, 5796-5799.
24. A. Jayaraman, L. C. Misal Castro, V. Desrosiers and F.-G. Fontaine, *Chem. Sci.*, 2018, **9**, 5057-5063.
25. Y. Suseela, A. S. B. Prasad and M. Periasamy, *J. Chem. Soc., Chem. Commun.*, 1990, 446-447.
26. Y. Suseela and M. Periasamy, *J. Organomet. Chem.*, 1993, **450**, 47-52.
27. A. Arase, M. Hoshi, A. Mijin and K. Nishi, *Synth. Commun.*, 1995, **25**, 1957-1962.
28. K. Shirakawa, A. Arase and M. Hoshi, *Synthesis*, 2004, 1814-1820.
29. D. A. Evans and J. T. Starr, *Angew. Chem. Int. Ed.*, 2002, **41**, 1787-1790.
30. D. A. Evans and J. T. Starr, *J. Am. Chem. Soc.*, 2003, **125**, 13531-13540.
31. J. Jägel and M. E. Maier, *Synlett*, 2006, **2006**, 0693-0696.
32. A. Fürstner, S. Flügge, O. Larionov, Y. Takahashi, T. Kubota and J. i. Kobayashi, *Chem. Eur. J.*, 2009, **15**, 4011-4029.
33. M. Pellicena, K. Krämer, P. Romea and F. Urpí, *Org. Lett.*, 2011, **13**, 5350-5353.
34. H. Lei, J. Yan, J. Yu, Y. Liu, Z. Wang, Z. Xu and T. Ye, *Angew. Chem. Int. Ed.*, 2014, **53**, 6533-6537.
35. N. W. J. Ang, C. S. Buettner, S. Docherty, A. Bismuto, J. R. Carney, J. H. Docherty, M. J. Cowley and S. P. Thomas, *Synthesis*, 2018, **50**, 803-808.
36. M. Hoshi, K. Shirakawa and M. Okimoto, *Tetrahedron Lett.*, 2007, **48**, 8475-8478.
37. D. G. Brown and J. Boström, *J. Med. Chem.*, 2016, **59**, 4443-4458.
38. L. Xu, G. Wang, S. Zhang, H. Wang, L. Wang, L. Liu, J. Jiao and P. Li, *Tetrahedron*, 2017, **73**, 7123-7157.
39. M.-A. Légaré, M.-A. Courtemanche, É. Rochette and F.-G. Fontaine, *Science*, 2015, **349**, 513-516.
40. M.-A. Légaré, É. Rochette, J. Légaré Lavergne, N. Bouchard and F.-G. Fontaine, *Chem. Commun.*, 2016, **52**, 5387-5390.
41. J. Légaré Lavergne, A. Jayaraman, L. C. Misal Castro, É. Rochette and F.-G. Fontaine, *J. Am. Chem. Soc.*, 2017, **139**, 14714-14723.
42. A. Jayaraman, L. C. Misal Castro and F.-G. Fontaine, *Org. Process Res. Dev.*, 2018, **22**, 1489-1499.

43. Y. Zou, B. Zhang, L. Wang and H. Zhang, *Org. Lett.*, 2021, **23**, 2821-2825.
44. Q. Yin, S. Kemper, H. F. T. Klare and M. Oestreich, *Chem. Eur. J.*, 2016, **22**, 13840-13844.
45. D. R. Willcox, G. S. Nichol and S. P. Thomas, *ACS Catal.*, 2021, **11**, 3190-3197.
46. K. Nicholson, J. Dunne, P. DaBell, A. B. Garcia, A. D. Bage, J. H. Docherty, T. A. Hunt, T. Langer and S. P. Thomas, *ACS Catal.*, 2021, **11**, 2034-2040.
47. M. M. Midland and A. Tramontano, *Tetrahedron Lett.*, 1980, **21**, 3549-3552.
48. N. Murakami, T. Nakajima and M. Kobayashi, *Tetrahedron Lett.*, 2001, **42**, 1941-1943.
49. P. H. Dussault, C. T. Eary and K. R. Woller, *J. Org. Chem.*, 1999, **64**, 1789-1797.
50. J. C. Barrish, H. L. Lee, T. Mitt, G. Pizzolato, E. G. Baggiolini and M. R. Uskokovic, *J. Org. Chem.*, 1988, **53**, 4282-4295.
51. M. M. Midland and R. S. Graham, *J. Am. Chem. Soc.*, 1984, **106**, 4294-4296.
52. W. S. Johnson, B. Frei and A. S. Gopalan, *J. Org. Chem.*, 1981, **46**, 1512-1513.
53. M. M. Midland, A. Tramontano and S. A. Zderic, *J. Am. Chem. Soc.*, 1977, **99**, 5211-5213.
54. H. C. Brown, E. F. Knights and C. G. Scouten, *J. Am. Chem. Soc.*, 1974, **96**, 7765-7770.
55. K. Nicholson, T. Langer and S. P. Thomas, *Org. Lett.*, 2021, **23**, 2498-2504.
56. J. Légaré Lavergne, H.-M. To and F.-G. Fontaine, *RSC Adv.*, 2021, **11**, 31941-31949.
57. E. Jeong, J. Heo, S. Park and S. Chang, *Chem. Eur. J.*, 2019, **25**, 6320-6325.
58. A. Jayaraman, H. Powell-Davies and F.-G. Fontaine, *Tetrahedron*, 2019, **75**, 2118-2127.
59. K. Benn, K. Nicholson, T. Langer and S. P. Thomas, *Chem. Commun.*, 2021, **57**, 9406-9409.
60. É. Rochette, H. Boutin and F.-G. Fontaine, *Organometallics*, 2017, **36**, 2870-2876.
61. M. Fleige, J. Möbus, T. vom Stein, F. Glorius and D. W. Stephan, *Chem. Commun.*, 2016, **52**, 10830-10833.
62. J. R. Lawson, L. C. Wilkins and R. L. Melen, *Chem. Eur. J.*, 2017, **23**, 10997-11000.
63. H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, 1961, **83**, 3834-3840.
64. G. Zweifel and H. C. Brown, *J. Am. Chem. Soc.*, 1963, **85**, 2066-2072.

65. H. C. Brown, C. G. Scouten and R. Liotta, *J. Am. Chem. Soc.*, 1979, **101**, 96-99.
66. E.-i. Negishi and H. C. Brown, *Synthesis*, 1974, **1974**, 77-89.
67. K. A. Scheidt, A. Tasaka, T. D. Bannister, M. D. Wendt and W. R. Roush, *Angew. Chem. Int. Ed.*, 1999, **38**, 1652-1655.
68. K. A. Scheidt, T. D. Bannister, A. Tasaka, M. D. Wendt, B. M. Savall, G. J. Fegley and W. R. Roush, *J. Am. Chem. Soc.*, 2002, **124**, 6981-6990.
69. K. C. Nicolaou, K. C. Fylaktakidou, H. Monenschein, Y. Li, B. Weyershausen, H. J. Mitchell, H.-x. Wei, P. Guntupalli, D. Hepworth and K. Sugita, *J. Am. Chem. Soc.*, 2003, **125**, 15433-15442.
70. C. C. Chrovian, B. Knapp-Reed and J. Montgomery, *Org. Lett.*, 2008, **10**, 811-814.
71. G. Minne, L. Verlinden, A. Verstuyf and P. J. De Clercq, *Molecules*, 2009, **14**, 894-903.
72. J. Gagnepain, E. Moulin, C. Nevado, M. Waser, A. Maier, G. Kelter, H.-H. Fiebig and A. Fürstner, *Chem. Eur. J.*, 2011, **17**, 6973-6984.
73. J. C. Colberg, A. Rane, J. Vaquer and J. A. Soderquist, *J. Am. Chem. Soc.*, 1993, **115**, 6065-6071.
74. A. D. Bage, T. A. Hunt and S. P. Thomas, *Org. Lett.*, 2020, **22**, 4107-4112.
75. R. K. Arvela, N. E. Leadbeater, M. S. Sangi, V. A. Williams, P. Granados and R. D. Singer, *J. Org. Chem.*, 2005, **70**, 161-168.
76. K. Takai, M. Tagashira, T. Kuroda, K. Oshima, K. Utimoto and H. Nozaki, *J. Am. Chem. Soc.*, 1986, **108**, 6048-6050.
77. S. L. Buchwald and C. Bolm, *Angew. Chem. Int. Ed.*, 2009, **48**, 5586-5587.
78. T. T. Dang, F. Boeck and L. Hintermann, *J. Org. Chem.*, 2011, **76**, 9353-9361.
79. R. Dumeunier and I. E. Markó, *Tetrahedron Lett.*, 2004, **45**, 825-829.
80. T. C. Wabnitz, J.-Q. Yu and J. B. Spencer, *Chem. Eur. J.*, 2004, **10**, 484-493.
81. D. C. Rosenfeld, S. Shekhar, A. Takemiya, M. Utsunomiya and J. F. Hartwig, *Org. Lett.*, 2006, **8**, 4179-4182.
82. M. J. L. Tschan, C. M. Thomas, H. Strub and J.-F. Carpentier, *Adv. Synth. Catal.*, 2009, **351**, 2496-2504.
83. J. G. Taylor, L. A. Adrio and K. K. Hii, *Dalton Trans.*, 2010, **39**, 1171-1175.
84. D. Männig and H. Nöth, *Angew. Chem. Int. Ed. Engl.*, 1985, **24**, 878-879.
85. S. A. Westcott, H. P. Blom, T. B. Marder and R. T. Baker, *J. Am. Chem. Soc.*, 1992, **114**, 8863-8869.

86. K. Burgess, W. A. Van der Donk, S. A. Westcott, T. B. Marder, R. T. Baker and J. C. Calabrese, *J. Am. Chem. Soc.*, 1992, **114**, 9350-9359.
87. S. A. Westcott, H. P. Blom, T. B. Marder, R. T. Baker and J. C. Calabrese, *Inorg. Chem.*, 1993, **32**, 2175-2182.
88. H. C. Brown and B. C. S. Rao, *J. Am. Chem. Soc.*, 1959, **81**, 6428-6434.
89. K. Burgess and M. Jaspars, *Tetrahedron Lett.*, 1993, **34**, 6813-6816.
90. K. Burgess and M. Jaspars, *Organometallics*, 1993, **12**, 4197-4200.
91. K. Burgess and W. A. van der Donk, *Organometallics*, 1994, **13**, 3616-3620.
92. S. Harder and J. Spielmann, *J. Organomet. Chem.*, 2012, **698**, 7-14.
93. M. Zaidlewicz and J. Melier, *Main Group Met. Chem.*, 2000, **23**, 765-772.
94. J. H. Docherty, J. Peng, A. P. Dominey and S. P. Thomas, *Nature Chem.*, 2017, **9**, 595-600.
95. I. P. Query, P. A. Squier, E. M. Larson, N. A. Isley and T. B. Clark, *J. Org. Chem.*, 2011, **76**, 6452-6456.
96. J. Wu, H. Zeng, J. Cheng, S. Zheng, J. A. Golen, D. R. Manke and G. Zhang, *J. Org. Chem.*, 2018, **83**, 9442-9448.
97. M. D. Greenhalgh and S. P. Thomas, *Chem. Commun.*, 2013, **49**, 11230-11232.
98. Z. Zuo and Z. Huang, *Org. Chem. Front.*, 2016, **3**, 434-438.
99. S. R. Tamang and M. Findlater, *J. Org. Chem.*, 2017, **82**, 12857-12862.
100. S. Mandal, P. K. Verma and K. Geetharani, *Chem. Commun.*, 2018, **54**, 13690-13693.
101. K. Kuciński and G. Hreczycho, *Green Chem.*, 2019, **21**, 1912-1915.
102. D. Bedi, A. Brar and M. Findlater, *Green Chem.*, 2020, **22**, 1125-1128.
103. Z. Du, B. Behera, A. Kumar and Y. Ding, *J. Organomet. Chem.*, 2021, **950**, 121982.
104. V. L. Weidner, C. J. Barger, M. Delferro, T. L. Lohr and T. J. Marks, *ACS Catal.*, 2017, **7**, 1244-1247.
105. C. J. Barger, R. D. Dicken, V. L. Weidner, A. Motta, T. L. Lohr and T. J. Marks, *J. Am. Chem. Soc.*, 2020, **142**, 8019-8028.
106. A. Baishya, S. Baruah and K. Geetharani, *Dalton Trans.*, 2018, **47**, 9231-9236.
107. P. Ghosh and A. Jacobi von Wangelin, *Org. Chem. Front.*, 2020, **7**, 960-966.
108. P. Ghosh and A. Jacobi von Wangelin, *Angew. Chem. Int. Ed.*, 2021, **60**, 16035-16043.
109. J. Liu, Y. Xie, C. Wu, Y. Shao, F. Zhang, Y. Shi, Q. Liu and J. Chen, *Org. Chem. Front.*, 2021, **8**, 3802-3808.

110. Y. Wu, C. Shan, J. Ying, J. Su, J. Zhu, L. L. Liu and Y. Zhao, *Green Chem.*, 2017, **19**, 4169-4175.
111. M. Arrowsmith, T. J. Hadlington, M. S. Hill and G. Kociok-Köhn, *Chem. Commun.*, 2012, **48**, 4567-4569.
112. M. Arrowsmith, M. S. Hill and G. Kociok-Köhn, *Chem. Eur. J.*, 2013, **19**, 2776-2783.
113. C. Weetman, M. S. Hill and M. F. Mahon, *Chem. Commun.*, 2015, **51**, 14477-14480.
114. C. Weetman, M. D. Anker, M. Arrowsmith, M. S. Hill, G. Kociok-Köhn, D. J. Liptrot and M. F. Mahon, *Chem. Sci.*, 2016, **7**, 628-641.
115. C. Weetman, M. S. Hill and M. F. Mahon, *Chem. Eur. J.*, 2016, **22**, 7158-7162.
116. M. Magre, B. Maity, A. Falconnet, L. Cavallo and M. Rueping, *Angew. Chem. Int. Ed.*, 2019, **58**, 7025-7029.
117. Z. Zhu, X. Wu, X. Xu, Z. Wu, M. Xue, Y. Yao, Q. Shen and X. Bao, *J. Org. Chem.*, 2018, **83**, 10677-10683.
118. D. Yan, X. Wu, J. Xiao, Z. Zhu, X. Xu, X. Bao, Y. Yao, Q. Shen and M. Xue, *Org. Chem. Front.*, 2019, **6**, 648-653.
119. Z.-C. Wang, M. Wang, J. Gao, S.-L. Shi and Y. Xu, *Org. Chem. Front.*, 2019, **6**, 2949-2953.
120. S. J. Yang, A. K. Jaladi, J. H. Kim, S. Gundeti and D. K. An, *Bull. Korean Chem. Soc.*, 2019, **40**, 34-38.
121. A. Arase, Y. Nunokawa, Y. Masuda and M. Hoshi, *J. Chem. Soc., Chem. Commun.*, 1991, 205-206.
122. R. Thenarukandiyil, V. Satheesh, L. J. W. Shimon and G. de Ruiter, *Chem. Asian J.*, 2021, **16**, 999-1006.
123. N. J. Gilmore and S. Jones, *Tetrahedron: Asymmetry*, 2003, **14**, 2115-2118.
124. T. Onak, H. Landesman, R. Williams and I. Shapiro, *J. Phys. Chem.*, 1959, **63**, 1533-1535.
125. D. F. Gaines, *Inorg. Chem.*, 1963, **2**, 523-526.
126. R. Contreras and B. Wrackmeyer, *Spectrochim. Acta A*, 1982, **38**, 941-951.
127. H. C. Brown and E. Negishi, *J. Am. Chem. Soc.*, 1971, **93**, 6682-6683.
128. N. N. Greenwood, J. H. Morris and J. C. Wright, *J. Chem. Soc.*, 1964, 4753-4761.
129. A. R. Gatti and T. Wartik, *Inorg. Chem.*, 1966, **5**, 329-330.
130. M. H. Gitlitz and W. J. Considine, *J. Organomet. Chem.*, 1970, **23**, 291-292.

131. G. L. Soloveichik, M. Andrus and E. B. Lobkovsky, *Inorg. Chem.*, 2007, **46**, 3790-3791.
132. M. A. Nichols and P. G. Williard, *J. Am. Chem. Soc.*, 1993, **115**, 1568-1572.
133. N. D. R. Barnett, R. E. Mulvey, W. Clegg and P. A. O'Neil, *J. Am. Chem. Soc.*, 1993, **115**, 1573-1574.
134. G. J. Palenik, *Acta Cryst.*, 1964, **17**, 1573-1580.
135. E. Nieto-Sepulveda, A. D. Bage, L. A. Evans, T. A. Hunt, A. G. Leach, S. P. Thomas and G. C. Lloyd-Jones, *J. Am. Chem. Soc.*, 2019, **141**, 18600-18611.
136. H. C. Brown and S. Krishnamurthy, *Tetrahedron*, 1979, **35**, 567-607.
137. O. Eisenstein, H. B. Schlegel and M. M. Kayser, *J. Org. Chem.*, 1982, **47**, 2886-2891.
138. M. M. Kayser, S. Eliev and O. Eisenstein, *Tetrahedron Lett.*, 1983, **24**, 1015-1018.
139. D. C. Wigfield, *Tetrahedron*, 1979, **35**, 449-462.
140. C. Adams, V. Gold and D. M. E. Reuben, *J. Chem. Soc., Perkin Trans. 2*, 1977, 1466-1472.
141. W. M. Jones and H. E. Wise, *J. Am. Chem. Soc.*, 1962, **84**, 997-1001.
142. B. Rickborn and M. T. Wuesthoff, *J. Am. Chem. Soc.*, 1970, **92**, 6894-6904.
143. D. C. Wigfield and F. W. Gowland, *J. Org. Chem.*, 1977, **42**, 1108-1109.
144. D. C. Wigfield and F. W. Gowland, *Can. J. Chem.*, 1978, **56**, 786-788.
145. M. J. S. Dewar and M. L. McKee, *J. Am. Chem. Soc.*, 1978, **100**, 7499-7505.
146. H. C. Brown, E. J. Mead and B. C. Subba Rao, *J. Am. Chem. Soc.*, 1955, **77**, 6209-6213.
147. H. C. Brown, O. H. Wheeler and K. Ichikawa, *Tetrahedron*, 1957, **1**, 214-220.
148. H. C. Brown and K. Ichikawa, *J. Am. Chem. Soc.*, 1962, **84**, 373-376.
149. M. Bishop, N. Shahid, J. Yang and A. R. Barron, *Dalton Transactions*, 2004, 2621-2634.
150. H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, 1961, **83**, 486-487.
151. H. C. Brown, M. C. Desai and P. K. Jadhav, *J. Org. Chem.*, 1982, **47**, 5065-5069.
152. H. C. Brown and N. M. Yoon, *J. Am. Chem. Soc.*, 1977, **99**, 5514-5516.
153. A. K. Mandal, P. K. Jadhav and H. C. Brown, *J. Org. Chem.*, 1980, **45**, 3543-3544.
154. H. C. Brown and P. K. Jadav, *J. Org. Chem.*, 1981, **46**, 5047-5048.
155. P. K. Jadhav and H. C. Brown, *J. Org. Chem.*, 1981, **46**, 2988-2990.
156. P. K. Jadhav and S. U. Kulkarni, *Heterocycles*, 1982, **18**, 169-173.

157. S. Masamune, B. M. Kim, J. S. Petersen, T. Sato, S. J. Veenstra and T. Imai, *J. Am. Chem. Soc.*, 1985, **107**, 4549-4551.
158. A. Z. Gonzalez, J. G. Román, E. Gonzalez, J. Martinez, J. R. Medina, K. Matos and J. A. Soderquist, *J. Am. Chem. Soc.*, 2008, **130**, 9218-9219.
159. K. Burgess and M. J. Ohlmeyer, *J. Org. Chem.*, 1988, **53**, 5178-5179.
160. T. Hayashi, Y. Matsumoto and Y. Ito, *J. Am. Chem. Soc.*, 1989, **111**, 3426-3428.
161. Y. Xi and J. F. Hartwig, *J. Am. Chem. Soc.*, 2016, **138**, 6703-6706.
162. V. M. Shoba, N. C. Thacker, A. J. Bochat and J. M. Takacs, *Angew. Chem. Int. Ed.*, 2016, **55**, 1465-1469.
163. S. Chakrabarty and J. M. Takacs, *J. Am. Chem. Soc.*, 2017, **139**, 6066-6069.
164. G. L. Hoang, S. Zhang and J. M. Takacs, *Chem. Commun.*, 2018, **54**, 4838-4841.
165. X.-Y. Bai, W. Zhao, X. Sun and B.-J. Li, *J. Am. Chem. Soc.*, 2019, **141**, 19870-19878.
166. G. Zweifel, N. R. Ayyangar and H. C. Brown, *J. Am. Chem. Soc.*, 1963, **85**, 2072-2075.
167. S. A. Moteki, D. Wu, K. L. Chandra, D. S. Reddy and J. M. Takacs, *Org. Lett.*, 2006, **8**, 3097-3100.
168. S. A. Moteki, K. Toyama, Z. Liu, J. Ma, A. E. Holmes and J. M. Takacs, *Chem. Commun.*, 2012, **48**, 263-265.
169. X. Chen, Z. Cheng and Z. Lu, *ACS Catal.*, 2019, **9**, 4025-4029.
170. L. Zhang, Z. Zuo, X. Wan and Z. Huang, *J. Am. Chem. Soc.*, 2014, **136**, 15501-15504.
171. J. Chen, T. Xi, X. Ren, B. Cheng, J. Guo and Z. Lu, *Org. Chem. Front.*, 2014, **1**, 1306-1309.
172. J. Chen, T. Xi and Z. Lu, *Org. Lett.*, 2014, **16**, 6452-6455.
173. W. J. Jang, S. M. Song, J. H. Moon, J. Y. Lee and J. Yun, *J. Am. Chem. Soc.*, 2017, **139**, 13660-13663.
174. X. Chen, Z. Cheng, J. Guo and Z. Lu, *Nat. Commun.*, 2018, **9**, 3939.
175. R. D. Rieke, P. T.-J. Li, T. P. Burns and S. T. Uhm, *J. Org. Chem.*, 1981, **46**, 4323-4324.
176. J. X. McDermott, J. F. White and G. M. Whitesides, *J. Am. Chem. Soc.*, 1976, **98**, 6521-6528.
177. P. Y. Chavant and M. Vaultier, *J. Organomet. Chem.*, 1993, **455**, 37-46.
178. E. Breuer and H. C. Brown, *J. Am. Chem. Soc.*, 1969, **91**, 4164-4169.
179. R. P. Short, Ph.D., Massachusetts Institute of Technology, 1989.

180. G. Laschober, M. Zorzi and K. J. Hodgetts, *Molecules*, 2001, **6**.
181. B. Kim, Ph.D., Massachusetts Institute of Technology, 1988.
182. S. Masamune, R. M. Kennedy, J. S. Petersen, K. N. Houk and Y. D. Wu, *J. Am. Chem. Soc.*, 1986, **108**, 7404-7405.
183. T. Imai, T. Tamura, A. Yamamuro, T. Sato, T. A. Wollmann, R. M. Kennedy and S. Masamune, *J. Am. Chem. Soc.*, 1986, **108**, 7402-7404.
184. R. P. Short and S. Masamune, *J. Am. Chem. Soc.*, 1989, **111**, 1892-1894.
185. M. K. Bisai, K. Gour, T. Das, K. Vanka and S. S. Sen, *J. Organomet. Chem.*, 2021, **949**, 121924.
186. M. K. Bisai, K. Gour, T. Das, K. Vanka and S. S. Sen, *Dalton Trans.*, 2021, **50**, 2354-2358.
187. N. N. H. Ton, B. K. Mai and T. V. Nguyen, *J. Org. Chem.*, 2021, **86**, 9117-9133.
188. S. Garhwal, A. A. Kroeger, R. Thenarukandiyil, N. Fridman, A. Karton and G. de Ruiter, *Inorg. Chem.*, 2021, **60**, 494-504.
189. L. Liu, S.-K. Lo, C. Smith and J. M. Goicoechea, *Chem. Eur. J.*, 2021, **n/a**.
190. R. Kumar, M. K. Bisai, S. Jain, K. Vanka and S. S. Sen, *Chem. Commun.*, 2021, **57**, 10596-10599.
191. A. M. Poitras, L. K. Oliemuller, G. P. Hatzis and C. M. Thomas, *Organometallics*, 2021, **40**, 1025-1031.
192. H. Yoshida, I. Kageyuki and K. Takaki, *Org. Lett.*, 2014, **16**, 3512-3515.
193. J. Zhao, Z. Niu, H. Fu and Y. Li, *Chem. Commun.*, 2014, **50**, 2058-2060.
194. M. Fujita, H. J. Lee and T. Okuyama, *Org. Lett.*, 2006, **8**, 1399-1401.
195. H.-Y. Wang and L. L. Anderson, *Org. Lett.*, 2013, **15**, 3362-3365.
196. W. B. Reid, J. J. Spillane, S. B. Krause and D. A. Watson, *J. Am. Chem. Soc.*, 2016, **138**, 5539-5542.
197. J. A. Souto, R. Benedetti, K. Otto, M. Miceli, R. Álvarez, L. Altucci and A. R. de Lera, *ChemMedChem*, 2010, **5**, 1530-1540.
198. C. Feng, H. Wang, L. Xu and P. Li, *Org. Biomol. Chem.*, 2015, **13**, 7136-7139.
199. B. E. Love and E. G. Jones, *J. Org. Chem.*, 1999, **64**, 3755-3756.
200. A. Bugarin and B. T. Connell, *J. Org. Chem.*, 2009, **74**, 4638-4641.
201. S. Khoo, J. Cao, F. Ng and C.-W. So, *Inorg. Chem.*, 2018, **57**, 12452-12455.
202. D. Landini and F. Rolla, *J. Org. Chem.*, 1980, **45**, 3527-3529.
203. K. Niedenzu and J. W. Dawson, *J. Am. Chem. Soc.*, 1959, **81**, 3561-3564.
204. H. Nöth and B. Wrackmeyer, *Chem. Ber.*, 1981, **114**, 1150-1156.

205. G. W. Kabalka, T. M. Shoup and N. M. Goudgaon, *J. Org. Chem.*, 1989, **54**, 5930-5933.