

**Cationic Rhodium-Catalyzed Hydroboration:
Investigations into Electronic and Ligand Effects; Lewis-Acid Reaction
Acceleration and Regioselectivity Change**

by

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Abstract

Mechanistic aspects of the asymmetric rhodium catalyzed hydroboration of vinyl arenes with catecholborane (HBCat) and pinacolborane (HBPin) have been probed. Competition studies conducted with catalysts bearing asymmetric ligands Josiphos or Quinap reveal substituent effects of varying sensitivity correlating to Hammett parameter sigma. In reactions involving the Quinap ligand, rho-values of +1.97 and +1.02 are observed for HBCat and HBPin, respectively. In Josiphos-ligated systems, rho-values of +1.38 and -3.17 are observed, indicating that the reaction proceeds through differing mechanisms depending on the borane employed. Labeling experiments reveal differences in the reversibility of the hydride insertion step of reaction depending on the ligand and borane implemented in hydroboration.

A new methodology has been developed for regioselective rhodium-catalyzed hydroboration of internal olefins with pinacolborane. The addition of co-catalytic Lewis acids results in the activation of cationic rhodium catalysts in chlorinated solvents. Increased catalytic activity and regioselectivity are observed under these conditions. For internal alkyl olefins, selectivity for non-isomerized secondary boronate esters was found originate from the non-coordinating solvents employed in the reaction. For aromatic olefins, increased regioselectivity and reaction acceleration are both effects of the Lewis acid additive. Study of the reaction revealed that these properties are linked to Lewis acid-base mediated heterolytic B-H bond cleavage of pinacolborane, and suggests that the reagent is transferred to the rhodium catalyst as borenium ion and hydride moieties. Inhibition studies confirmed that Lewis acid is required throughout the reaction and does not solely act as an initiator.

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List of Abbreviations

Ac	acetyl
Ad	adamantyl
Ar	aryl
9-BBN	9-borabicyclo[3.3.1]nonane
Bdpp	2,4-bis(diphenylphosphino)pentane
Binap	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bu	butyl
°C	Celsius
cat	catalyst
COD	1,5-cyclooctadiene
Cy	cyclohexyl
D	deuterium
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DCE	dichloroethane
DCM	dichloromethane
DIOP	2,3- <i>O</i> -isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
diphos-4	1,4-bis(diphenylphosphino)butane
DMAP	4-dimethylaminopyridine
DME	dimethyl ether
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane

dppf	(diphenylphosphino)ferrocene
ee	enantiomeric excess
ent	enantiomer
Et	ethyl
eq.	equation
equiv.	equivalents
FAB	tris(pentafluorophenyl)boron
FLP	frustrated Lewis acid-base pair
GC	gas chromatography
HBPin	pinacolborane
HBCat	catecholborane
HRMS	high-resolution mass spectrometry
h	hours
Hz	Hertz
Icp ₂ BH	diisopinocampheylborane
iPr	isopropyl
<i>J</i>	coupling constant
Josiphos	1-[2-(diphenylphosphino)ferrocenyl]ethylcyclohexane
K	Kelvin
KIE	kinetic isotope effect
L	ligand
LA	Lewis acid
LB	Lewis base

LDA	lithium diisopropylamide
Me	methyl
MeOH	methanol
Mes	mesityl
nbd	2,5-norbornadiene
NMR	nuclear magnetic resonance
[O]	oxidation
OEt	ethoxy
OMe	methoxy
OTf	triflate
Ph	phenyl
PPh ₃	triphenylphosphine
ppm	parts per million
Pr	propyl
Quinap	1-(2-diphenylphosphino-1-naphthyl)isoquinoline
sBu	<i>sec</i> -butyl
T	temperature
tBu	<i>tert</i> -butyl
THF	tetrahydrofuran
PHOX	phosphino-oxazoline ligand

Chapter 1: Introduction to the Field of Catalyzed Hydroborations

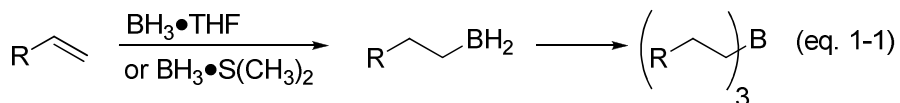
1.1: Introduction

Building molecules of high complexity from simple, cheap, and abundant precursors involves numerous obstacles and challenges. Most of the time, this process requires the introduction of heteroatoms onto an existing hydrocarbon-based template or backbone in order to create desired functional groups in the product. Just as commonly, the formation of additional carbon-carbon bonds is often required in order to build molecules of higher complexity. These two basic goals are the stuff of synthesis, and are made challenging by the constant need to control the reaction employed in terms of regiochemistry, chemoselectivity, and, depending on the requirements of the product, the stereoselectivity of each transformation. Selectivity poses problems in any synthesis, marring the straight path from starting material to pure end product, and requiring the use of various synthetic tools developed to overcome potentially undesired side reactions in an efficient manner. Thus, it is only natural that methodology development and mechanistic study of new or existing reactions are fields of chemistry irreversibly bound with that of organic synthesis.

Classical examples of such methodologies include the use of protecting groups for heteroatoms already in place on a substrate molecule ensuring the correct chemoselectivity in a subsequent reaction; the use of the Mitsunobu reaction to invert the stereochemistry of an alcohol moiety,¹ or the use of a radical initiator in the hydro-halogenation of an olefin to ensure the halide is installed in an anti-Markovnikov fashion.²

In response to the demand for general methodologies which have control over selectivity, organoboron compounds have been developed for several important transformations that can yield a variety of new functional groups including new carbon-carbon bonds. Many of these reactions utilize the unique properties of boron in order to affect stereospecific functional group transformations (see Section 1.7).^{3,4} Thus, much research and effort has been devoted to the functionalization of precursors with a boron moiety in a selective manner.³ To this end, one of the most important methods of achieving this is the hydroboration of an alkene or alkyne using a borane,^{3,4} although modern methods such as direct borylation⁵ are also becoming increasingly utilized.

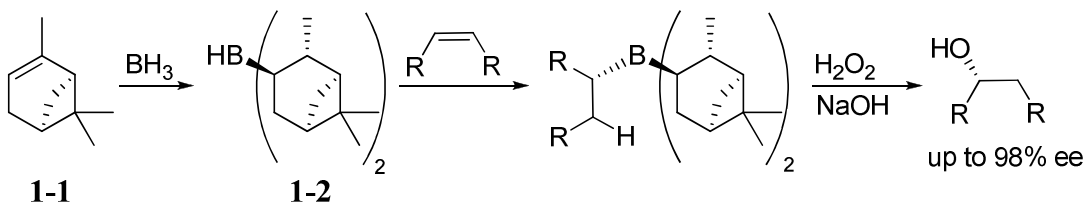
Hydroboration was originally conducted thermally, or uncatalyzed, and in its simplest form involved the addition of an adduct of borane, BH₃ (normally a reactive gas), to an olefin.³ This reaction, which proceeds via a concerted asynchronous mechanism, is selective for placement of boron in the anti-Markovnikov position, and thus is especially useful for the generation of linear alkyl boranes from terminal olefins. However, unsymmetrical internal olefins can show less selectivity for the formally anti-Markovnikov position depending on the functional groups flanking the reacting double bond.⁶ The reaction of BH₃ tends to hydroborate more than one equivalent of olefin, yielding alkylboranes as products, equation 1-1. These products are not typically air- or water-stable, and are most commonly subjected to an oxidative workup to yield the corresponding alcohol using well established conditions.⁷



The desire for hydroborating reagents which would provide a 1:1 stoichiometry of reaction while at the same time providing more stable products led to the development of

more synthetically useful compounds. Of particular note are alkyl boranes in which only one boron-hydrogen moiety is present such as 9-BBN.⁸ Chiral versions of dialkylboranes were largely developed by H.C. Brown to affect the asymmetric hydroboration of olefins through the attachment of various chiral alkyl groups to boron, yielding chiral hydroborating reagents.³ This work was summarized by Brown himself in a comprehensive review.⁹ Typically, chiral organoboranes are procured from readily available chiral alkenes in the chiral pool, perhaps the best known of which is (+)- α -pinene **1-1**.^{10,11} Preparation of the chiral borane, diisopinocampheylborane (Ipc₂BH) **1-2**, is a simple and efficient procedure, as steric bulk prevents the full reaction of 3 equivalents of **1-1** with BH₃, thus yielding a chiral dialkylborane that crystallizes in ethereal solvents. The procedure also allows essentially optically pure **1-2** to be synthesized from commercial grade α -pinene, which can only be obtained in 92% enantiomeric excess.¹² Borane **1-2** hydroborates various prochiral *cis*-olefinic compounds at low temperature with some of the highest enantioselectivities ever reported at the time (Figure 1-1). Borane **1-2** was also found to be useful in the kinetic resolution of racemic olefin-containing compounds.¹³ These achievements marked one of the first milestones in the area of hydroboration, and spurred on further advances in the field.

Figure 1-1: Typical Asymmetric Hydroboration with Ipc₂BH



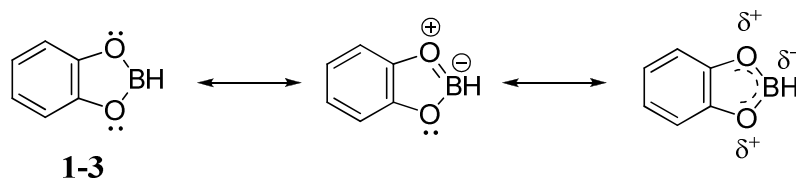
Although thermal hydroboration has been developed and is still utilized in modern synthesis, it suffers from several limitations that needed to be improved upon. Firstly, the

stability of alkylborane products is low due to the Lewis acidic nature of the boron atom. This precludes isolation of alkylboranes, which are typically oxidized *in situ* to alcohols stereospecifically, as noted above. Secondly, although effective, chiral hydroboration requires the use of one full equivalent of chiral borane and the reaction must be carried out at cryogenic temperatures to achieve high enantioselectivities. Although the chiral reagent **1-1** may be recovered and recycled,¹⁴ this process complicates an otherwise excellent chiral methodology. Thirdly, thermal hydroboration is not generally tolerant of carbonyl or imine functional groups on the reactant, since these more reactive unsaturated moieties are reduced more quickly than olefins.

1.2: Catalyzed Hydroboration

Sneddon initially reported that hydroboration of alkynes with pentaborane could be catalyzed with cobalt,¹⁵ iridium,¹⁶ and palladium¹⁷ transition metal complexes. In 1985, Mannig and Nöth¹⁸ discovered that hydroboration of alkenes with catecholborane **1-3** could be accomplished through the addition of a rhodium catalyst. Reagent **1-3**, a dioxaborole, is much less reactive than alkylboranes due to the two boron-oxygen bonds contained in the molecule. This decreases the Lewis acidity at boron through resonance overlap between the lone pairs of electrons of the oxygens and the empty p-orbital on boron (Figure 1-2). Subsequently, thermal hydroboration of alkenes with dioxaboroles requires elevated temperatures and lengthened reaction times, allowing the catalyzed variant of the reaction to proceed without any background reaction.

Figure 1-2: Resonance Stabilization of Boron p-orbital of Catecholborane (HBCat)

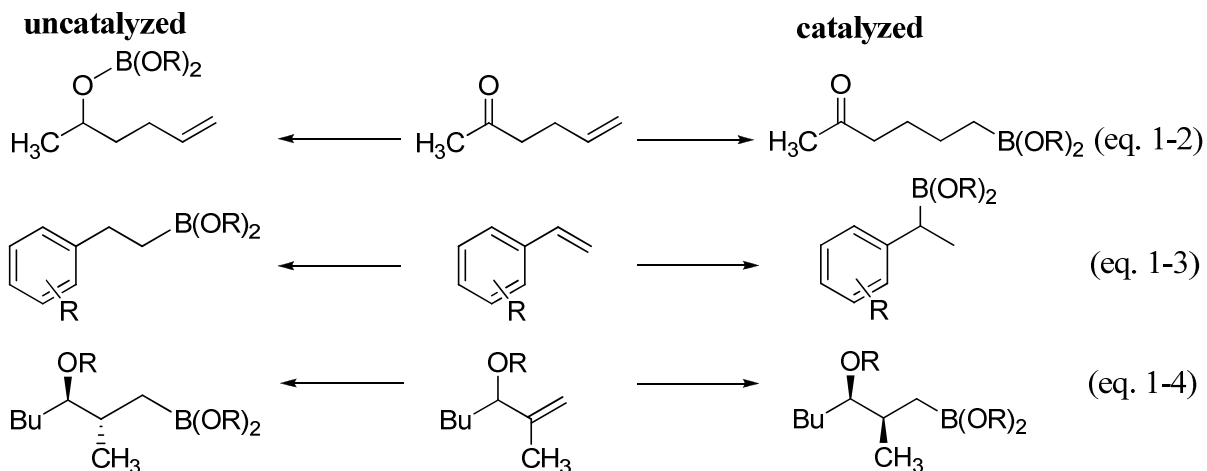


Most importantly, the rhodium-catalyzed reaction displays unique chemoselectivity compared to the thermal version. For example, under metal-catalyzed conditions, 5-hexen-2-one is hydroborated at the olefin rather than the more reactive ketone moiety (Scheme 1-1).¹⁸ This seminal paper sparked further investigation into the catalyzed hydroboration and the birth of the next generation of this important reaction.

Several developments in this newly struck field included the discovery of several novel catalysts for this reaction, based on metals other than rhodium, including Zr,^{19,20} La,^{21,22} Sm,^{23,24} Ru,²⁵ Pd and Ni,²⁶ and Ir.^{27,28,29} Of these metals, iridium has gained popularity as an analogue of similar rhodium catalysts for its complimentary regioselectivity in the hydroboration of vinyl arenes, where Ir gives essentially complete selectivity for the linear isomer under optimized conditions, equation 1-3.³⁰ Following a publication by Smith and Iverson, iridium complexes are also now utilized in the direct borylation of aromatic compounds using similar dioxaborolanes as in hydroboration.⁵ Rhodium, however, remains the most widely utilized metal for catalyzed hydroboration. Scheme 1-1 reveals the unique selectivity that can be attained by the use of a Rh catalyst compared to the conventional thermal reaction. The use of cationic Rh catalysts, which were originally developed for their application as hydrogenation catalysts,³¹ brought several expansions to the scope of the catalyzed hydroboration, including better yields, selectivity, and the ability to use less

reactive boranes than **1-3**. Additionally, highly enantioselective chiral catalysts are easily obtained via various asymmetric ligands (See Section 1.6).

Scheme 1-1: Comparison of selectivity in Rh-catalyzed and non-catalyzed variants of hydroboration



1.3: Hydroborating Reagents

Although catecholborane **1-3** remains one of the most utilized reagents in hydroboration, its high reactivity carries with it several drawbacks. Firstly, although its Lewis acidity is attenuated by the catechol backbone such that its participation in thermal hydroboration is negligible at ambient temperatures, it remains quite reactive and susceptible to degradation, generating B_2Cat_3 and an equivalent of BH_3 . This undesired reaction is accelerated by the presence nucleophilic molecules such as PPh_3 , a common ligand,^{30,32} necessitating the use of an excess of **1-3** to affect full conversion of the starting material. Of course, with the use of monodentate phosphines ligands like PPh_3 in Rh catalysts, whose mechanism commonly involves preliminary dissociation of one or more phosphine, the

ability of the system to cause the degradation of **1-3** can lead to undesired thermal hydroboration by the much more reactive BH_3 that is produced. Secondly, the catechol boronate ester products generated from the hydroboration are susceptible to degradation and are neither air- nor water-stable, precluding purification after reaction. Thus, the products are typically oxidized to alcohols *in situ* or converted via trans-esterification to a more stable boronate ester. This is most commonly accomplished through the addition of pinacol to the crude reaction, generating a pinacolboronate ester (Scheme 1-2), which is both air- and water-stable, and can even be subjected to column chromatography before subsequent transformations.³³

Scheme 1-2: Pinacol Quench

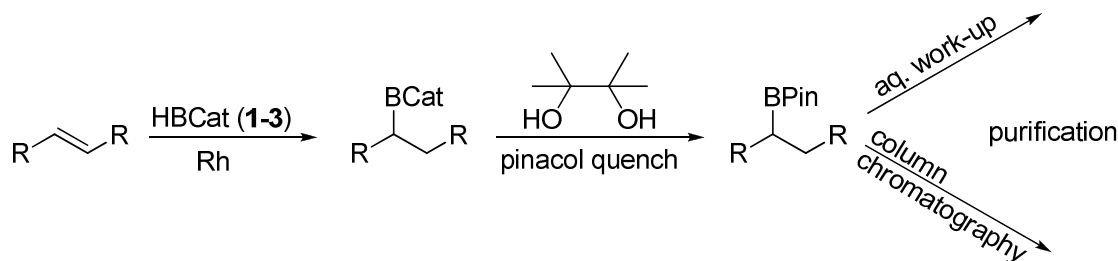
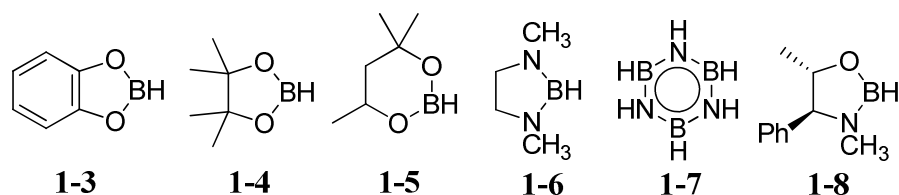


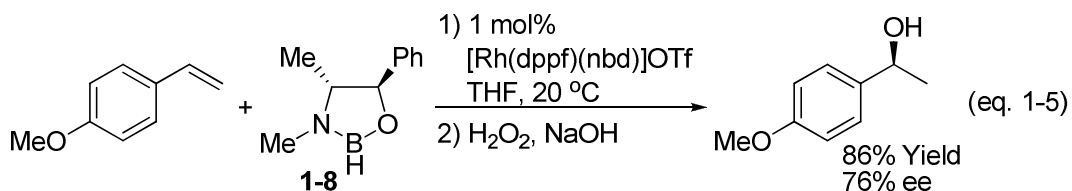
Figure 1-3: Hydroborating Reagents



Unsurprisingly, the inferior product stability in hydroborations utilizing **1-3** led to the development of alternative hydroborating reagents in an effort to balance reactivity with stability and ease of use. A brief collection of selected boranes is outlined in Figure 1-3.

Reagent **1-5** was utilized by Männig and Nöth in their seminal paper¹⁸ and found to be less

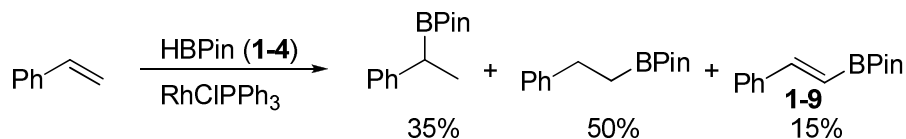
active than **1-3**. The nitrogen containing analogue 1,3-dimethyl-1,3,2-diazaborolidine **1-6** found utility in the lanthanide catalyzed hydroboration-cyclization of 1,5 and 1,6-dienes.^{23,34} Borazine **1-7** also has utility in rhodium catalyzed hydroboration,^{35,36} although the high cost of this reagent precludes practical implementation. As with thermal hydroboration, enantioselective transformations were attempted with boranes functionalized with molecules from the chiral pool. Unlike chiral boranes used in the thermal reaction, the chiral substituent is required to attenuate the reactivity of the resultant borane such that it does not participate in the non-catalyzed reaction. Borane **1-8**, which is functionalized with pseudoephedrine, was employed in this type of approach to enantioselective hydroboration.^{37,38} However, only moderate e.e.'s are reported in the reaction with the optimized substrate, *p*-vinylanisole, equation 1-5. This approach was largely abandoned, however, in lieu of the development of chiral bisphosphines, which provide a broader substrate scope and preclude the use of a full equivalent of chiral material (Section 1.6).



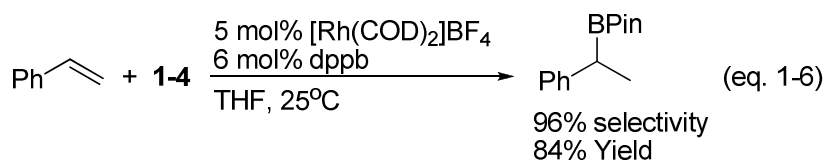
Pinacolborane **1-4** was first utilized directly in several rhodium and zirconium catalyzed hydroborations by the group of Srebnik.^{19,20,39} This reagent provided a direct one-step route to stable pinacolboronate ester products, and was successfully employed in Rh-catalyzed transformations of alkynes, vinyl arenes, and terminal olefins. However, pinacolborane **1-4** is not well tolerated in hydroborations of vinyl arenes catalyzed by neutral Rh catalysts like Wilkinson's catalyst. As shown in Figure 1-4, only a 35% yield of the secondary boronate ester product is observed, whereas when **1-3** is employed this regio-

isomer is produced selectively. Instead, the major product in 50% yield is the linear boronate, with a significant amount of alkenylboronate **1-9** present.²⁰

Figure 1-4: Products in the Catalyzed Reaction of Pinacolborane **1-4** and Styrene



This does not preclude the use of **1-4** for the hydroboration of vinyl arenes, an important substrate class for the reaction (Section 1.7). Cationic rhodium catalysts, such as that employed in equation 1-6 are now more commonly used and are much more selective for this less reactive borane.³⁰ Thus, **1-4** has become one of the most robust boranes in catalyzed hydroboration due to its stability and its utility in generating stable organoboronate products.

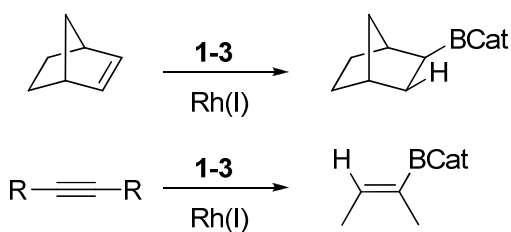


1.4: Mechanistic Investigations

Unlike the thermal hydroboration, which is generally accepted to proceed through a concerted asynchronous transition state addition across a double or triple bond, the rhodium catalyzed transformation is thought to occur in a stepwise manner. Although the mechanism of the rhodium-catalyzed reaction is not currently understood fully, perhaps the most in-depth studies have been conducted with **1-3**. Mannig and Nöth¹⁸ laid out the basics of the catalytic cycle that is still accepted today. This begins with oxidative addition of the borane

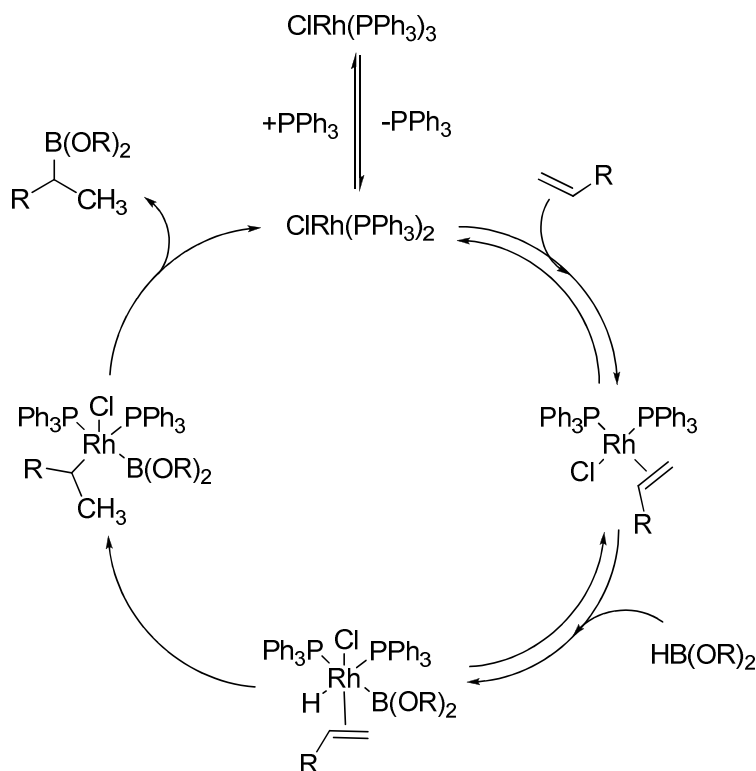
to the Rh metal center after the loss of a PPh₃ ligand in the case of Wilkinson's catalyst (RhCl(PPh₃)₃).⁴⁰ This intermediate has been observed by NMR⁴⁰ and a P(iPr)₃-analogue has been isolated and had its structure verified by X-ray crystallography.⁴¹ The reaction of **1-3** and Wilkinson's catalyst was probed mechanistically by the Evans group⁴² and also by the groups of Baker, Marder and Westcott.⁴¹ Initially, the authors showed that the reaction proceeded smoothly and was not poisoned via the addition of mercury or duroquinone, which have been shown to inhibit heterogeneous catalysts⁴³ and radical intermediates,⁴⁴ respectively. With evidence of a true homogeneous catalytic mechanism, Evans and Fu continued to explore aspects of this system. With both alkenes and alkynes, the addition of the B-H bond occurs with *syn* stereoselectivity, indicating a catalysis by a unimolecular Rh species (Figure 1-5). Several deuterium labeling studies were conducted with **1-3** in the hydroboration of a variety of olefinic substrates. Both Wilkinson's catalyst and a representative cationic analogue, [Rh(nbd)(diphos-4)]BF₄ were utilized in the study to highlight mechanistic differences in these two system types.

Figure 1-5: *Syn* Addition of **1-3** Exemplified in Catalyzed Hydroboration

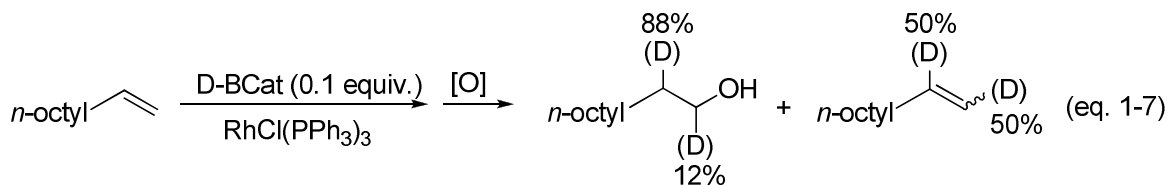


The labeling results with both catalysts in this study suggest that oxidative addition and olefin association are followed by an insertion of a hydride followed by irreversible reductive elimination of the intermediate alkyllrhodium(boryl) species to yield the boronate ester product (Scheme 1-3).⁴²

Scheme 1-3: Proposed General Catalytic Cycle for Hydroboration of Olefins



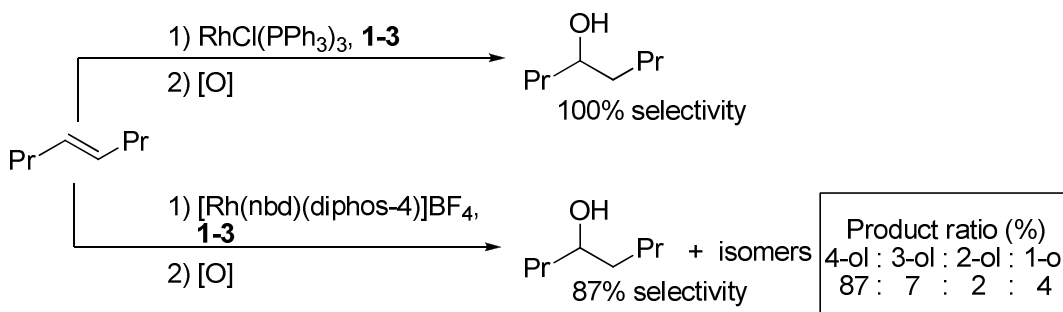
Through deuterium labeling studies, it was found that the reversibility of the hydride insertion step varied markedly depending on the olefin employed. For terminal olefins such as 1-decene in equation 1-7, linear products are formed, but deuterium is observed at both carbons of the former olefin, indicating that metal hydride addition/olefin decomplexation has some level of reversibility.⁴²



The degree of reversibility of the hydride insertion has implications in regioselectivity, as indicated in the hydroboration of internal olefin *trans*-4-octene catalyzed by either neutral or cationic rhodium catalysts (Scheme 1-4). With Wilkinson's catalyst,

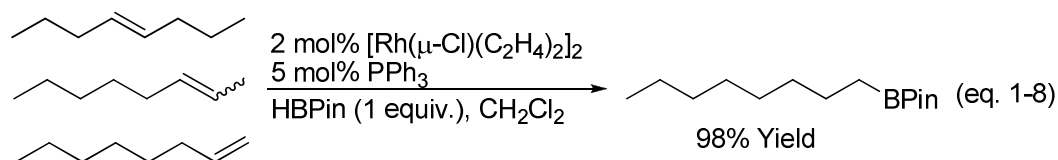
hydroboration proceeds regioselectively, affording the 4-octanol product after oxidative workup. In contrast, $[\text{Rh}(\text{nbd})(\text{diphos-4})]\text{BF}_4$ yields a mixture of isomers, indicative of olefin migration due to the same reversible hydride insertion and β -hydride elimination steps observed for 1-decene.⁴²

Scheme 1-4: Catalyzed Hydroboration of *trans*-4-octene



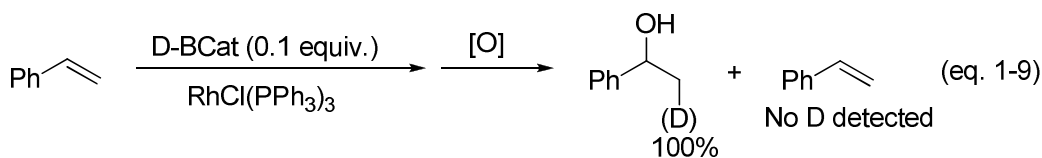
The reactivity of the borane is important in the regioselectivity of hydroboration as well. In catalyzed reactions that employ HBPIn **1-4** as a reagent, *trans*-4-octene and other internal olefinic substrates are converted cleanly to the linear boronate ester product, equation 1-8.^{20,45} This is due, in part, to the greater steric demand by the pinacol backbone of **1-4**, hindering reductive elimination at a secondary carbon. Thus, the reduced rate of reductive elimination of boron from the rhodium catalyst relative to facile insertion and β -hydride elimination reactions lead to olefin migration such that the boron-carbon bond is formed kinetically at the least hindered terminal carbon. The hindered reductive elimination step can also be attributed to the decreased Lewis acidity of **1-4** relative to **1-3**. Lone pair electrons on oxygen may donate into the empty p-orbital on boron in **1-4** more effectively than with HBCat, where they also donate into the phenyl ring. Analogous research conducted by Hartwig displayed increasing rates of reductive elimination in Pd-catalyzed C-

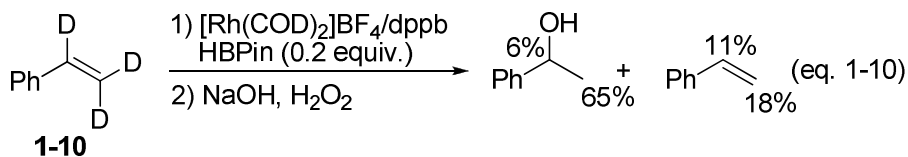
N bond forming reactions as one of the coupling partners is made more electron-withdrawing.⁴⁶



Although alkyl olefins are accessible substrates, it is vinyl arenes that have received the most attention in rhodium catalyzed hydroboration. Typically, these substrates are reduced with Markovnikov selectivity in Rh catalyzed system to yield a secondary boronate ester product. This selectivity is atypical of hydroboration, and proves useful in generating products of chirality (Section 1.6).

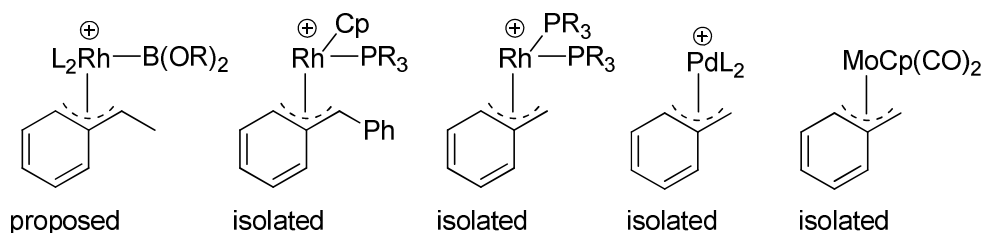
Mechanistic differences with this substrate class are also apparent. In the deuterium labeling study of the catalyzed hydroboration of styrene with **1-3**, the label is selectively incorporated into the β -position of the olefin, and no deuterium is observed in un-reacted starting material, equation 1-9.⁴² This suggests irreversible hydride insertion or regioselective (but reversible) hydride insertion and irreversible olefin complexation. In equation 1-10, a similar labeling experiment conducted with deuterated styrene **1-10** and limiting HBPin reveal that label is incorporated into terminal and benzylic positions in both the product and recovered starting material.⁴⁷ This indicates a higher degree of reversibility of the initial steps, which may have its origin in the reduced propensity for reductive elimination of the pinacol boronates. It should be apparent by this point that the mechanism is extremely sensitive to changes in substrate, hydroborating reagent, and the catalyst species employed.





The Markovnikov regioselectivity observed in the case of vinyl arenes (and other aromatic olefins) was first attributed by Hayashi⁴⁸ to the stabilization of the rhodium catalyst via a π -benzylic interaction between the secondary organometallic and the adjacent aromatic, which is not possible in the linear isomer (Figure 1-6). Although such an interaction is only proposed in the hydroboration reaction,⁴⁸ examples of π -benzylic interactions have been isolated with other catalytic metals^{49,50,51,52} including rhodium.^{53,54}

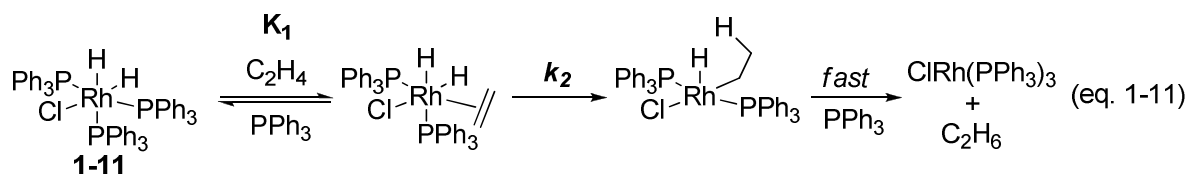
Figure 1-6: Proposed and isolated π -benzylic interactions; descriptor of regiochemistry



The insertion of alkenes into rhodium-hydrogen bonds has been the subject of considerable study in related catalytic systems. Complex **1-11** catalyzes the hydrogenation of olefins via rate-determining insertion of the olefin into a rhodium-hydride bond followed by fast reductive elimination in equation 1-11.⁵⁵ By studying the hydrogenation of a series of para-substituted vinyl arenes Halpern found an electronic effect on hydride insertion,⁵⁶ where the migratory insertion is facilitated by resonance electron donating groups (Table 1-1). It was postulated that electron donation to the coordinatively unsaturated metal aids hydride insertion. However, the reverse trend is observed with respect to the equilibrium

constant of olefin binding to the catalyst, indicating the complexity that can arise from the study of a multistep reaction. This illustrates how the hydride insertion can be affected by the electronics of the olefin, which has implications in the selectivity of hydroboration as well as related rhodium catalyzed hydroformylation.⁵⁷

Table 1-1: Rate and Equilibrium Data for the Hydrogenation of Vinyl Arenes⁵⁶

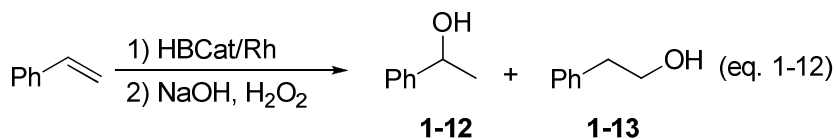


Olefin	K ₁ (10 ³)	k ₂ (s ⁻¹)
Cyclohexene	0.34	0.20
<i>p</i> -Cl-styrene	2.53	0.097
Styrene	1.72	0.11
<i>p</i> -F-styrene	1.04	0.22
<i>p</i> -CH ₃ -styrene	0.69	0.23
<i>p</i> -CH ₃ O-styrene	0.34	0.50

There are other factors that can affect the reactivity of the metal-catalyzed hydroboration. The presence of oxygen in the system can greatly degrade the regioselectivity of reaction, as shown conclusively by Evans and Fu,⁴² settling a debate in the literature with respect to hydroborations catalyzed by Wilkinson's catalyst, equation 1-12.⁵⁸ The presence of oxygen oxidizes this catalyst, degrading it to triphenylphosphine oxide and [Rh(μ-Cl)(PPh₃)₂]₂ and [RhCl(O₂)(PPh₃)₂]₂ which react with different selectivity than the original catalyst.⁵⁹ The usually selectivity for **1-12** is greatly deteriorated, with the linear product **1-**

13 being produced in almost equal proportions (Table 1-2), and different deuterium labeling results are also obtained.^{32,42,48}

Table 1-2: Effect of Oxygenation on Catalyst Regioselectivity in Hydroboration of Styrene

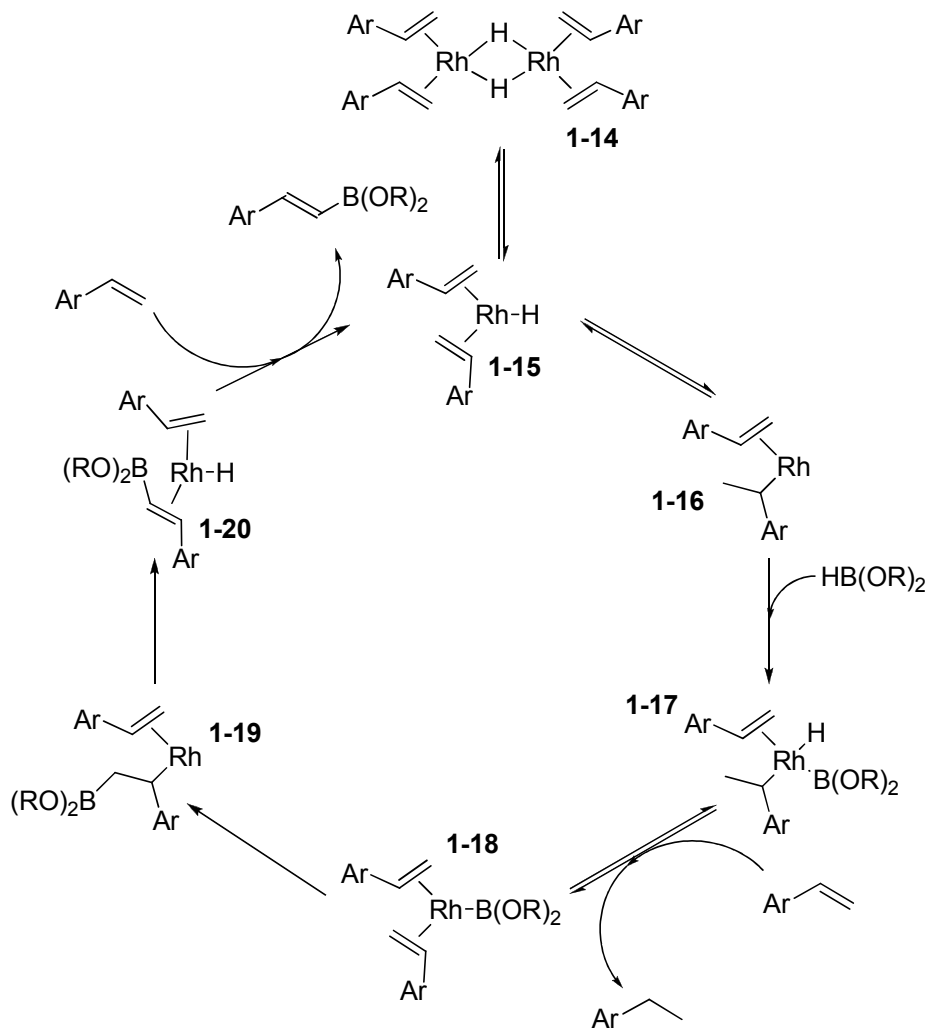


Entry	Catalyst	Treatment	1-12	1-13	Ref.
1	RhCl(PPh ₃) ₃	O ₂ treated	60	40	48
2	RhCl(PPh ₃) ₃	Fresh	99	<1	42
3	RhCl(PPh ₃) ₃	O ₂ treated, then 2 equiv. PPh ₃ added	99	<1	42,48

In the complete absence of phosphine ligands, rhodium complexes catalyze both hydrogenation and dehydrogenative borylation.³⁸ In this case, vinylboronate esters and hydrogenated products are observed in equal proportion as major species of the reaction. This suggests a catalytic cycle, depicted in Scheme 1-5, in which the production of these two species is linked.³⁸ Here, the precursor **1-14** is observed to be half-order in the reaction, suggesting the active rhodium hydride species is monomeric (**1-15**). Subsequent hydride insertion into one of the ligated olefins yields **1-16** which may then undergo oxidative addition of the borane yielding **1-17**. Facile reduction elimination of a molecule of alkane yields boryl-rhodium complex **1-18**. Boryl insertion is then proposed to give alkyl-rhodium(I) complex **1-19** which undergoes fast β-hydride elimination to yield vinylboronate ester ligated rhodium(I) intermediate **1-20** that regenerates catalyst **1-15**, by displacement of

product. This proposed mechanism is supported by detailed kinetic studies, and accounts for the production of equimolar amounts of vinylboronate and hydrogenated starting material.

Scheme 1-5: Proposed phosphine free catalytic cycle



1.5: Scope of the Catalyzed Reaction

The catalyzed hydroboration is generally capable of converting simple alkyl substituted alkenes into alkylboronates, although the rate of this reaction is highly substrate dependent. Typically, the greater the degree of substitution about the olefin, the slower the rate, in which the general trend follows that of hydrogenation: mono-substituted alkenes > 1,1-disubstituted alkenes > 1,2-disubstituted alkenes >> tri- and tetra-substituted alkenes.⁶⁰ With tri- and tetra-substituted olefins, the reaction becomes difficult, as steric bulk hinders olefin association and insertion into the rhodium complex. Because of this, these substrates tend to give a mixture of products that include dehydrogenative borylation and hydrogenation of the substrate, and can also yield isomerized products via initial isomerizations to yield a less substituted olefin followed by hydroboration. Typically, low conversions and yields can be expected from such hindered alkenes. Even 1,2-disubstituted alkenes can yield isomerized boronate ester products depending on the borane employed, as previously discussed in the hydroboration of *trans*-4-octene **1-21** with HBCat **1-3** or HBPIn **1-4** (Scheme 1-6). As noted previously, the bulkier and less Lewis acidic pinacolborane yields the terminal alcohol after oxidation due the relatively slow rate of reductive elimination of boron from the rhodium catalyst compared to the fast and reversible hydride insertion and β -hydride elimination. This leads to isomerization of the olefin to the terminal position of the alkyl chain, where reductive elimination is less sterically hindered. Although isomerization is a complication that must be addressed, the low rate of hydroboration for tri- and tetra-substituted alkenes presents the opportunity for selective reduction of less hindered olefins in the presence of more substituted olefins, without the need for protection. This is exemplified

in the hydroboration-oxidation of limonene **1-24** in Figure 1-7, where product **1-25** is obtained selectively, leaving the tri-substituted olefin of the molecule unreacted.⁶⁰

Scheme 1-6: Differences in regioselectivity of hydroboration of *trans*-4-octene

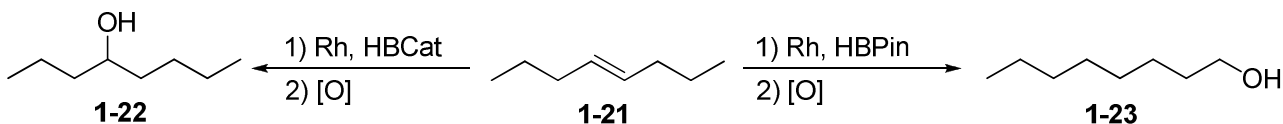
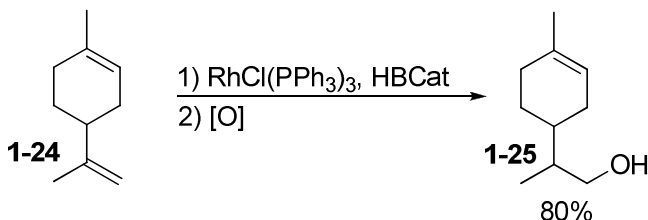


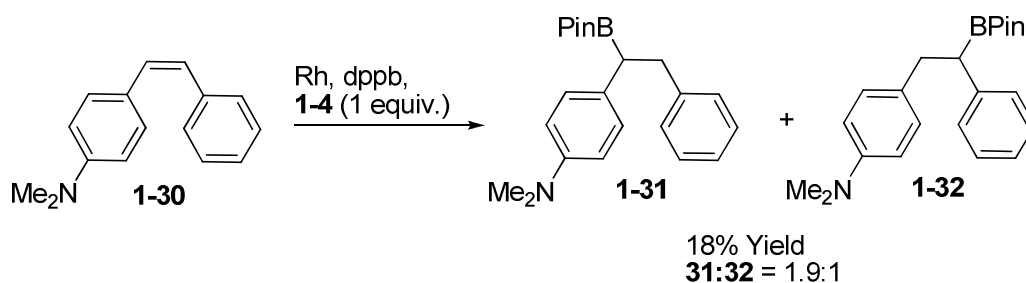
Figure 1-7: Chemo selectivity in the catalyzed hydroboration of limonene



The anti-Markovnikov selectivity observed with simple alkyl-substituted olefins is similar to that of the conventional hydroboration and is especially typical with terminal or 1,1-disubstituted olefins. However, in more complex olefinic substrates, which tend to yield more valuable products, a variety of selectivity changes are observed. The regioselectivity of hydroboration in terminal olefins bearing perfluorinated alkyl substituents is one such example (Scheme 1-7). Again a difference in the placement of the C-B bond is observed depending on which borane is implemented, where HBPin yields the expected linear alcohol after oxidation and HBCat yields the secondary 2-alcohol.⁶¹ Both methods provide regioselectivities greater than 92%.

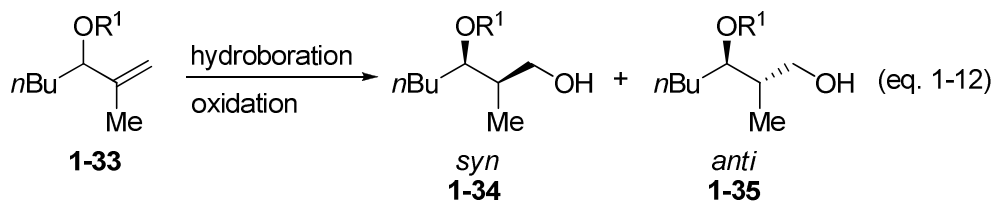
Simple protection of N-H and O-H bonds precludes the need for such excesses of borane. However, these heteroatoms may still act as ligands to the catalyst employed, potentially lowering yields or slowing the rate of reaction. One such example is shown in Figure 1-8, where methyl protection of the amino group in **1-30** prevents borylation at the nitrogen, but the yield of the two regio-isomeric products **1-31** and **1-32** is obviously impacted in the hydroboration with HBPIn.⁴⁷

Figure 1-8: Hydroboration of Amine-Functionalized *cis*-stilbene



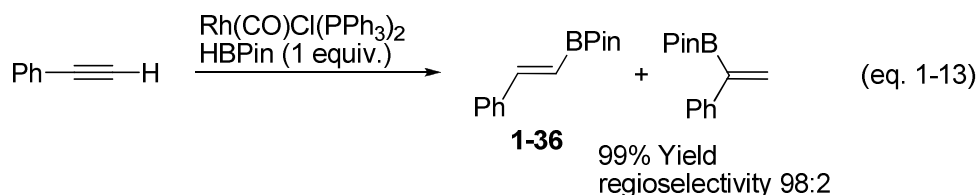
Heteroatoms protected with bulkier substituents are more easily tolerated, and can act as directing groups in catalyzed hydroboration. This is evident in the reaction of allylic ethers of 1,1-disubstituted alkenes **1-33** (Table 1-3). Whereas typical thermal hydroboration reactions tend to yield *anti*-isomers with these compounds, the Rh-catalyzed variant of the reaction gives the complimentary *syn*-isomer as the major product, equation 1-12.⁶³ Here, sufficiently bulky protecting groups prevent insertion of Rh catalyst into the olefin on the same face as the protected ether, leading to a net *syn* relative stereochemistry in the major product **1-34** after oxidation. By contrast, association of the oxygen heteroatom to 9-BBN favours hydroboration on the same face as the ether moiety, leading to *anti* relative stereochemistry products **1-35** predominantly.

Table 1-3: Complimentary Stereochemistry in Catalyzed and Thermal Hydroboration⁶³



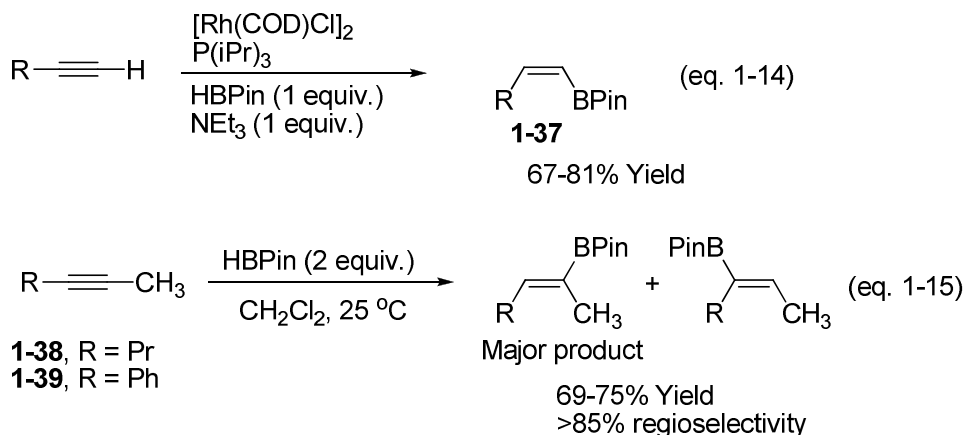
R^1	Conditions	<i>Syn</i> -isomer	<i>Anti</i> -isomer
CO ^t Bu	9-BBN	4	96
	Rh / HBCat	87	13
COCF ₃	9-BBN	7	93
	Rh / HBCat	88	12

Of course, hydroboration is not merely limited to olefins. Alkynes, too, are available substrates for the Rh-catalyzed hydroboration. The products of these reactions, vinylboronate esters, can be utilized as substrates in subsequent carbon-carbon bond forming cross coupling reactions (See Section 1.7), making them useful precursors for the synthesis of value-added products. Phenylacetylene may be hydroborated with HBPin **1-4** and a commercially available catalyst, Rh(CO)Cl(PPh₃)₂ to yield the *trans*-product **1-36** with high regioselectivity, indicating the B-H bond reduces the alkyne in a *syn* fashion, equation 1-13.²⁰

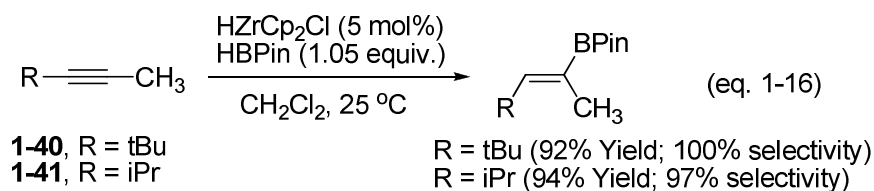


Interestingly, a change in the catalyst precursor employed and the addition of a good base, NEt₃, in this reaction yields the *cis*-vinylboronate ester product **1-37**, equation 1-14.⁶⁴ The mechanism of this reaction is thought to involve an intermediate rhodium-vinylidene species that favours this stereochemistry. Due to the increased reactivity of the triple bond,

the thermal hydroboration of terminal alkynes with pinacolborane has also been reported by Knochel, mild conditions furnish the *trans*-vinylboronate ester in moderate to good yields, although only a limited reaction scope was displayed.⁶⁵ Internal alkynes **1-38** and **1-39** were also reported to undergo selective thermal hydroboration, placing the boron group at the least hindered carbon of the alkyne with reasonable selectivity, equation 1-15.⁶⁵

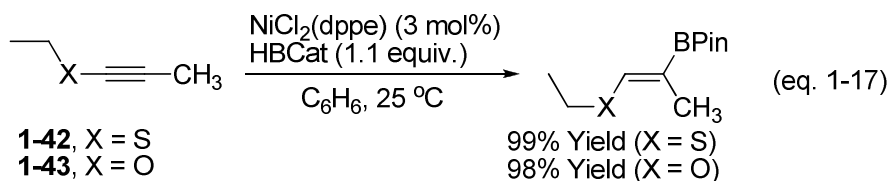


In the Rh-catalyzed variant of the reaction, the hydroboration of internal alkynes have not been extensively studied. However, other metals have found utility in this application. HZrCp₂Cl catalyzes the reaction of dialkyl substituted alkynes with HBPin **1-4**, yielding good regioselectivity if the two substituents about the triple bond differ significantly in steric bulk.¹⁹ As shown in equation 1-16, alkynes **1-40** and **1-41** are converted to their respective vinylboronates in good yield and regioselectivity.



Internal alkynes directly substituted with ether and thioether functional groups are hydroborated by HBCat **1-3** in room temperature reactions catalyzed by NiCl₂(dppe).²⁵ Functionalized alkynes **1-42** and **1-43** are converted in good yield using only 3 mol% of

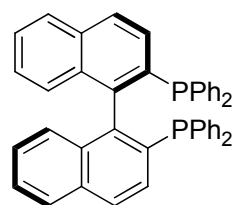
NiCl₂(dppe), equation 1-17. The vinylic sulfide products are particularly useful in that they provide a handle for additional Ni-catalyzed cross-coupling with Grignard reagents.



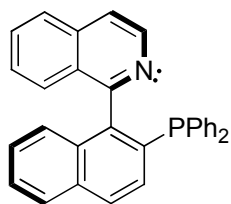
1.6: Enantioselective Hydroboration

Following the work on chiral thermal hydroboration with enantio-enriched boranes,⁹ attention was turned to the use of catalytic amounts of chiral ligand to effect the enantioselective reduction of alkenes. This variant of the reaction is superior to hydroboration with chiral boranes such as **1-8** since full equivalencies of the chiral element are not required. Furthermore, since organoboron products are most commonly used as reagents for subsequent reactions to generate higher value organic compounds (see Section 1.7), the preclusion of the necessity for chiral boranes presents a much less wasteful methodology in terms of total synthesis. A number of chiral ligands have been developed and employed in various rhodium complexes to achieve a high level of enantioselectivity in a limited number of substrates. Several notable ligands are given in Figure 1-9.^{30,66-76}

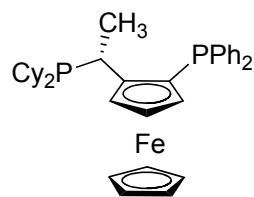
Figure 1-9: Commonly used chiral ligands in rhodium-catalyzed hydroboration



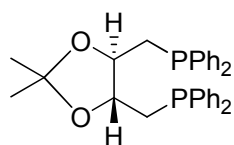
Binap **1-44**



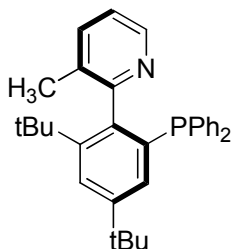
Quinap **1-45**



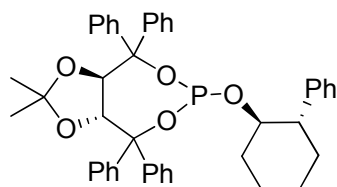
Josiphos **1-46**



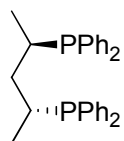
DIOP **1-47**



Pyphos **1-48**



1-49



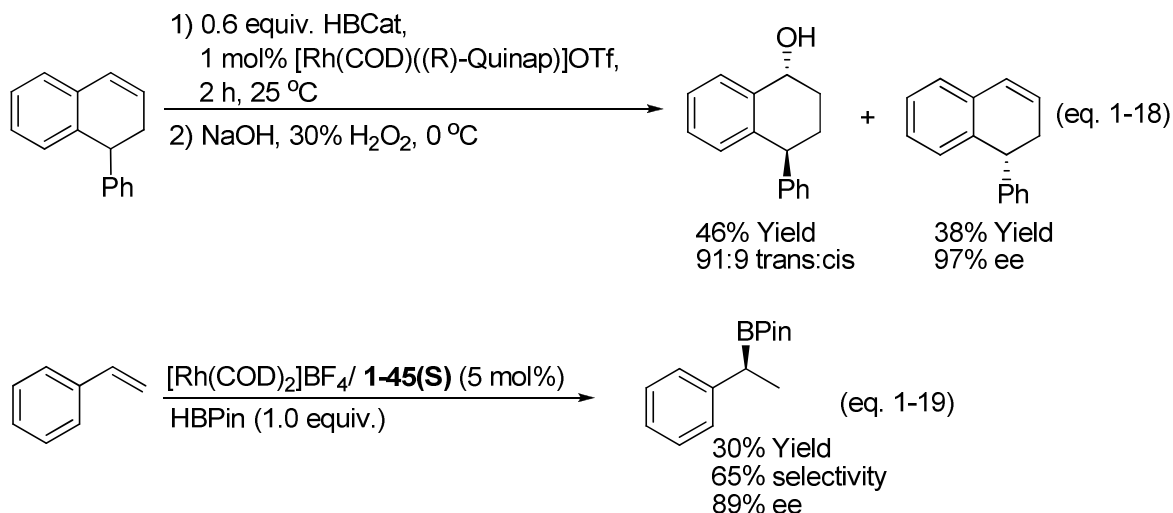
BDPP **1-50**

A common feature of many of these ligands is their bidentate nature and C_2 -symmetry. Bidentate ligands aid in chirality transfer by reducing the ability of the ligand to dissociate from the catalyst. C_2 symmetric ligands have an advantage over C_1 ligands in that they decrease the number of potential diastereomeric transition states by a factor of two.

As already expressed, vinyl arenes are the most attractive substrates for chiral hydroboration, as the resultant products can be obtained with high regio and enantioselectivity. As such, many of the chiral ligands employed in this catalysis are targeted to these substrates. One of the earliest successful reports involves the use of Binap **1-44**.⁶⁶ Using a cationic rhodium precatalyst, $[\text{Rh}(\text{COD})_2]\text{BF}_4$ and **1-3** as the borane, excellent yields

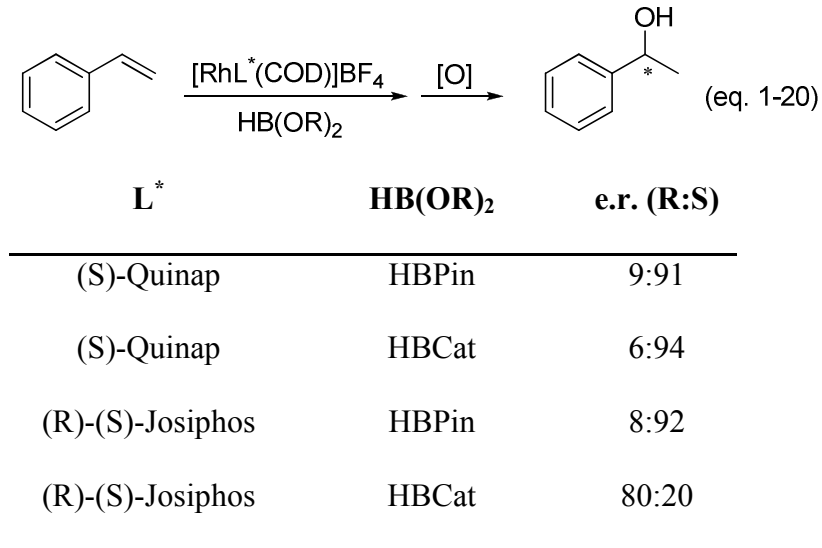
and selectivity are obtained, with e.e.'s in the 90s after oxidation to the corresponding alcohols. However, one drawback of the method is the requirement of cryogenic temperatures, which obviates the use of less reactive boranes like HBPIn **1-4**.

C₂-symmetric *ortho*-substituted biaryl ligands similar to **1-44** were examined in order to optimize the enantioselective hydroboration. In particular, a more active catalyst was desired in order to forego cryogenic conditions and widen the substrate scope. Quinap **1-45**,⁶⁷ developed by J.M. Brown, proved highly enantioselective at ambient temperature, where vinyl arenes are successfully converted to chiral products. Furthermore, internal β-substituted versions of these substrates are hydroborated with extremely good enantioselectivities.⁶⁸ Substrates already possessing a chiral center, such as 1-phenyl-1,2-dihydronaphthalenes can be resolved using this catalyst, yielding both boronate ester product and starting olefin with high enantioselectivity, as shown in Equation 1-18.⁶⁹ Additionally, due to the higher catalytic activity of rhodium catalysts ligated with **1-45**, HBPIn **1-4** can also be utilized in the reaction, albeit with a loss in yield as well as the selectivity for the chiral product, equation 1-19.³⁰ However, in a separate publication, Fernandez obtains near quantitative yields under similar conditions by utilizing Rh catalysts pre-ligated with Quinap.⁷⁰ Of particular note is the electronic dependence on enantioselectivity, where electron-rich vinyl arenes react with higher enantioselectivities.⁶⁸ This is hypothesized to be due to a stronger *trans* binding influence of the vinyl arene to the catalyst with respect to the nitrogen atom of **1-45**, allowing better transfer of chirality to the olefin.^{68,71} Similar results are obtained with analogous rhodium catalysts ligated with Pyphos **1-48**, another *P,N*-type ligand. When Pyphos-based catalysts are employed, the temperature of reaction had to be cooled to 0°C to obtain enantioselectivities similar to those observed with **1-45**.⁷¹

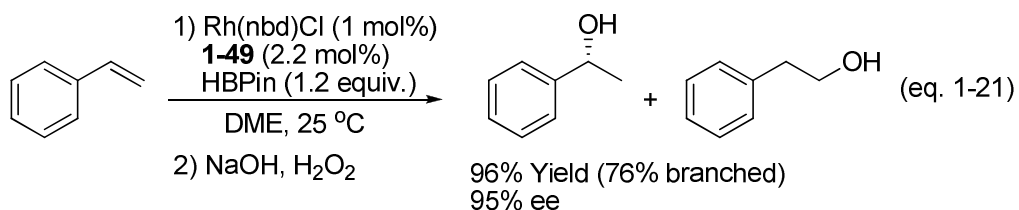


Chiral ferrocenyl derivatives such as Josiphos **1-46** also effect hydroboration of aromatic olefins at ambient temperature.³⁰ This ligand, which was developed in the Togni research group,⁷² proved effective in generating products of high enantioselectivity in systems employing either **1-3** or **1-4**. Interestingly, Josiphos, unlike Quinap, yields the opposite enantiomer product depending on the borane employed in the reaction (Table 1-4).³⁰ In equation 1-20, the use of either HBPIn or HBCat for a given antipode of the ligand yields products of opposite enantioselectivity when the catalyst is ligated with **1-46**. Ligand **1-46** is also more enantioselective at ambient temperature in hydroborations with HBPIn **1-4** than HBCat **1-3**.³⁰

Table 1-4: Enantioselectivity of Hydroboration with **1-3** and **1-4** with Chiral Catalysts³⁰



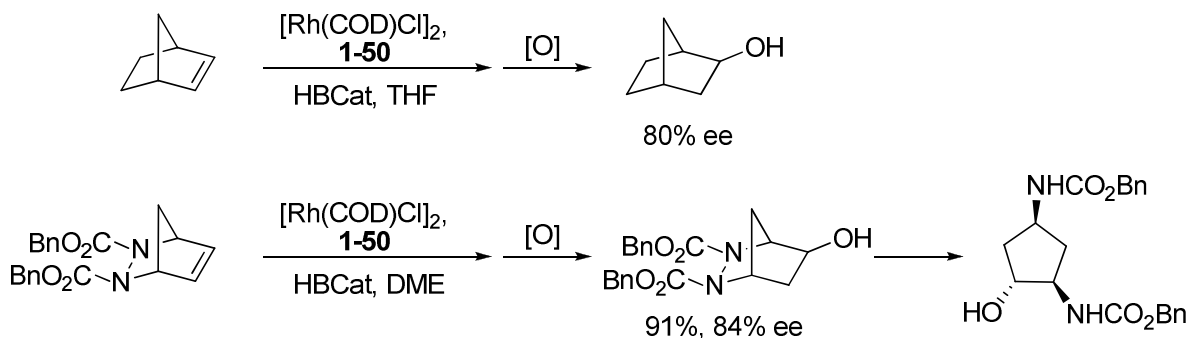
One well known exception to the typical C_2 -symmetric bidentate class of ligand is **1-49**, a monodentate TADDOL-derived phosphite ligand, which has been developed by the Takacs group for the hydroboration of vinyl arenes in high enantiomeric excess.⁷³ Interestingly, both neutral and cationic rhodium complexes are effective with this ligand. Perhaps most notable is that HBPIn **1-4** is more effective than HBCat **1-3** in this reaction with regard to enantioselectivity.⁷³ However, as with **1-45** ligated systems, there is a loss of regioselectivity, such that a significant quantity of linear boronate ester is produced. The hydroboration of styrene, one of the best substrates in terms of product enantioselectivity and yield, only 76% of the chiral alcohol is obtained, equation 1-21.



Of course, enantioselective hydroboration reactions have been developed for substrates other than aromatic olefins. More classical chiral ligands such as DIOP **1-47** and

BDPP **1-50** are capable of generating products with moderate enantioselectivity. For example, norbornene can be hydroborated with HBCat with a moderate e.e. of 55% using Rh catalysts of ligand **1-47**. However, the reaction must be conducted at -40°C and is less enantioselective than the corresponding reaction with rhodium catalysts of **1-44**, which react with an e.e. of 64% at -25°C .⁷⁴ Ligand **1-50** is better yet, generating chiral alcohol in 80% e.e. after oxidation.^{75,76} Higher value chiral products can be generated with the use of this ligand in the catalytic hydroboration of diazaonorborene analogues, where subsequent ring opening furnishes enantio-enriched poly-substituted diaminocyclopentanes (see Scheme 1-9). It should be noted that these substrates are symmetrical olefins, and thus regioselectivity of hydroboration does not pose a problem.

Scheme 1-9: Asymmetric hydroboration of norbornene and azanorborene⁷⁶



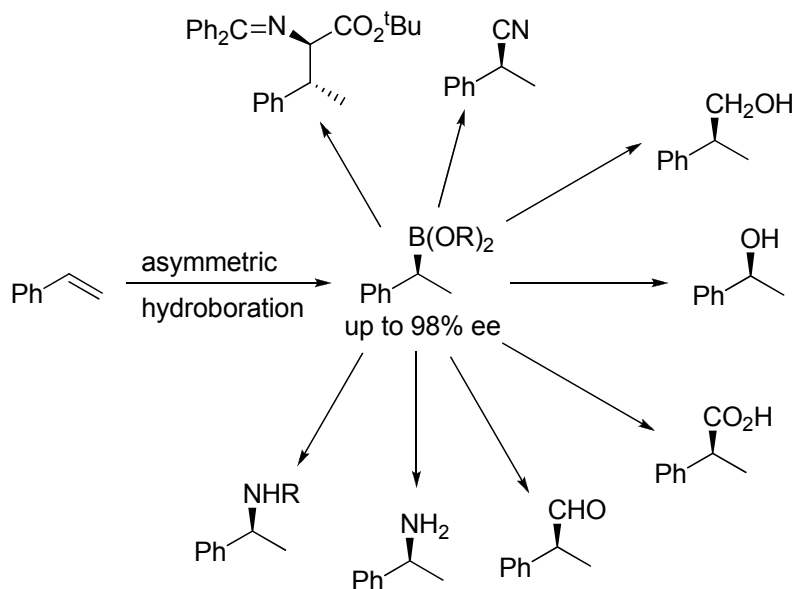
Unfortunately, the level of enantio-induction in the hydroboration of alkyl-substituted olefinic substrates is typically low in Rh catalyzed reactions.⁷⁷ Terminal aliphatic olefins are also problematic in that the linear isomer is formed preferentially or exclusively, and thus chiral alcohols are generally not accessible from these substrates.

1.7: Functional Group Transformation of the C-B Bond

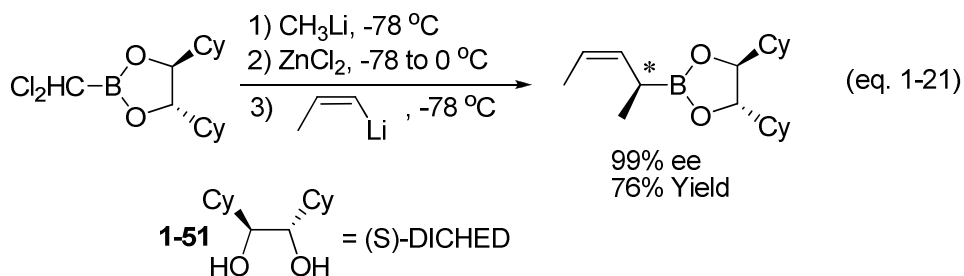
Rarely is the boronate ester of catalyzed hydroboration of an olefin desired as an end product. Much more common is the use of such compounds in derivative reactions to yield more typical organic species of higher value. These subsequent transformations are not merely limited to simple stereospecific oxidation to the corresponding alcohol.⁷⁸ This reaction presents in the literature so commonly following hydroboration due to its simple procedure, quantitative nature, and ease of characterization of products and their chirality in the case of asymmetric catalysis.⁷⁸

Fortunately, numerous other transformations to more complex functional groups can be obtained stereospecifically from the products of olefin hydroboration. A collection of representative transforms is shown in Scheme 1-10.

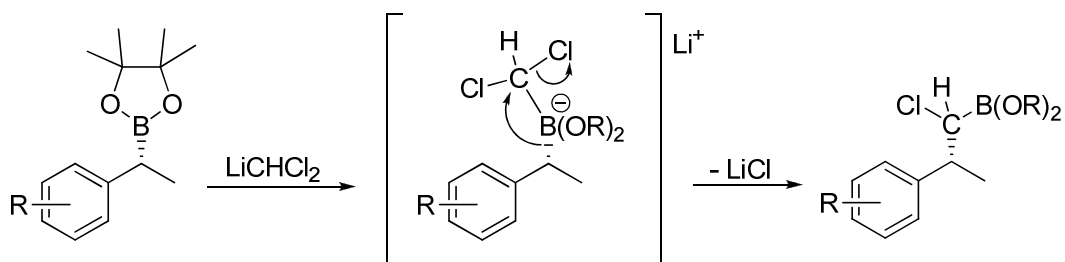
Scheme 1-10: Stereospecific Functional Group Access from Chiral Alkylboronate Esters⁷⁹



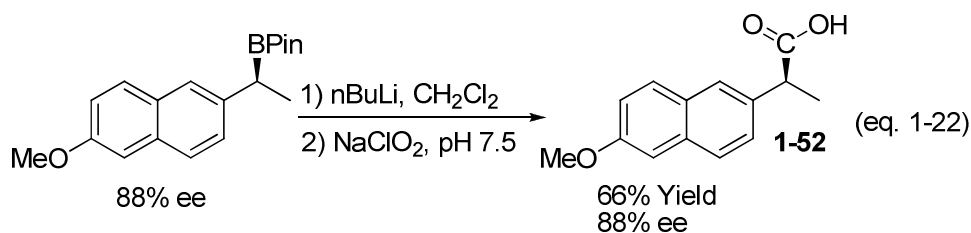
Many of the transformations shown in Scheme 1-10 are obtained through the initial homologation of the boronate ester. This involves the generation of a one-carbon nucleophile such as LiCHCl_2 from the slow addition of butyllithium or LDA to dichloromethane.³³ The reaction of this nucleophile with a boronate ester results in a stereospecific one-carbon insertion between the C-B bond as shown in Scheme 1-11. The functional group on boron is crucial to the success of the homologation, and catechol boronates are too unstable to be subjected to the conditions of the reaction.^{33,80} Thus, if catechol boronate products are to be implemented, they must first be converted into less reactive species such as pinacol boronates via pinacol quench.³³ Alternatively, the hydroboration can be carried out with HBPi_n, precluding this extra step. Additionally, ZnCl_2 is sometimes required to facilitate the bond migration and loss of chloride leaving group,⁸¹ but is not strictly necessary for 1-arylpinacolboronate esters.⁸² If stereoselective homologation is desired, a boronate ester is prepared with a chiral diol group instead of pinacol or catechol.⁸³ With a chiral auxiliary such as (S)-DICHED **1-51**, which was first used in asymmetric homologations by Matteson⁸³, the reaction can be carried out with extremely good enantiomeric excess. Thus, the reaction is extremely valuable and was utilized by Hoffman en route to a total synthesis of a natural antibiotic, equation 1-21.⁸⁴ This methodology is well characterized and is summarized by Matteson in a review.⁸⁵



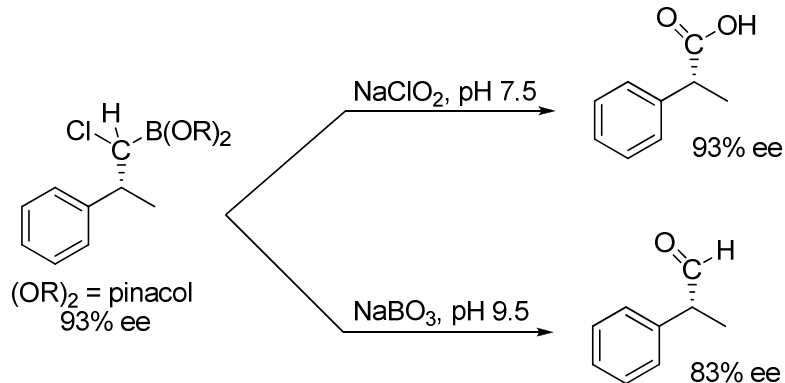
Scheme 1-11: Mechanism of homologation of chiral boronates with LiCHCl₂



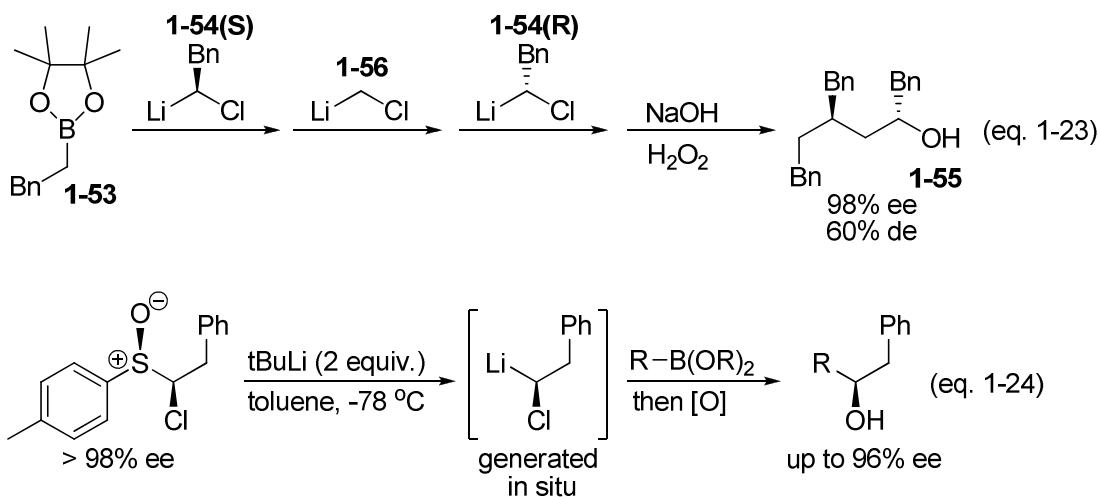
Following the homologation with LiCHCl₂, the resultant *alpha*-chloro-boronates can be converted to molecules of higher complexity. Oxidants may be applied to generate either a carboxylic acid or aldehyde moiety (Scheme 1-12),^{30,33,78} or the addition of nucleophiles, which result in the displacement of the chloride to yield more complex boronates, which can then be subjected again to homologation or oxidation.⁸⁶ The controlled oxidation of the homologated boronate ester to an aldehyde in Scheme 1-12 exemplifies utility as a carbon monoxide-free enantioselective hydroformylation.³⁰ Full oxidation to the carboxylic acid has been utilized after hydroboration and homologation in the synthesis of the anti-inflammatory drug NaproxenTM **1-52** in 66% total yield over three steps, equation 1-22.³⁰ Both oxidations require the careful control of solvent acidity, as the products are sensitive to racemization.⁸⁰



Scheme 1-12: Post-Homologation Oxidation Protocols for *alpha*-chloro-boronates³³



In one recent example by Blakemore and Surge, a terminal boronate ester **1-53** was subjected to three sequential homologation steps, equation 1-23.⁸⁶ Two of these reactions involved homologating nucleophiles bearing stereocenters **1-54**, which are prepared by lithium-sulfoxide exchange of enantiomerically enriched α -chloro sulfoxides, equation 1-24.^{86,87} The resulting product **1-55** incorporates these two chiral centers with high enantioselectivity.



As equation 1-23 reveals, the products of homologation need not be *alpha*-chloro-boronates. If a simple -CH₂ insertion is desired, one needs only to change the homologation reagent. Treatment of BrCH₂Cl with n-butyllithium results in a metal-bromine exchange to

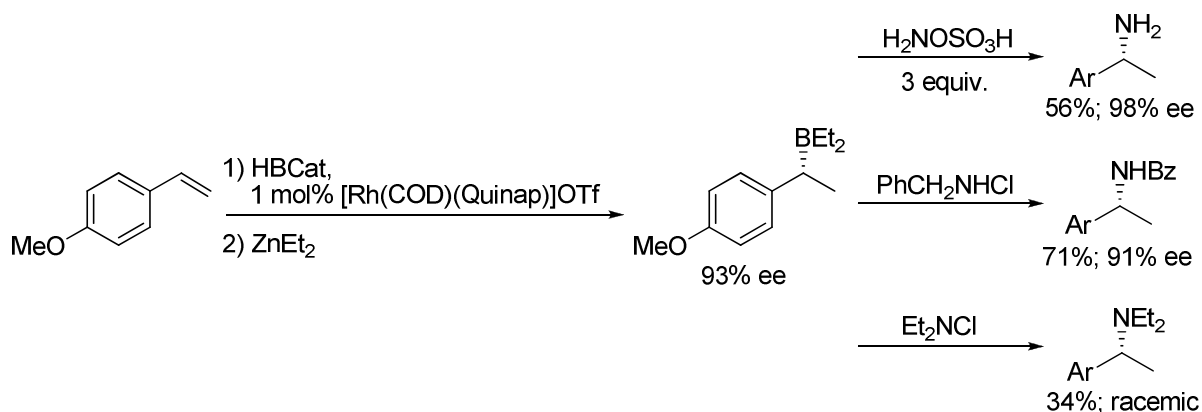
yield lithium methylene chloride **1-56**.³³ The corresponding reaction with a boronate results in a one-carbon chain extension, equation 1-25. This methodology has also been utilized after chiral hydroboration in producing 2-arylpropanols in high enantiomeric excess (Table 1-5).³³

Table 1-5: Hydroxymethylation via LiCH₂Cl Homologation of Chiral Boronate Esters³³

Ar	Conversion (%)	Yield (%)	e.e. (%)
Ph	98	78	95 (R)
Ph (ent)	88	68	88 (S)
<i>p</i> -MePh	87	69	96 (R)
<i>p</i> -ClPh	70	69	91 (R)

Conversion of boronate products to amines proceeds in a similar fashion to homologation, where the nucleophile amine requires a good leaving group to affect the alkyl group transfer from boron.⁸⁸ However, these relatively weaker nucleophiles require that the boronate first be converted into a more reactive alkylborane species via treatment with ZnEt₂ or EtMgBr before the reaction may proceed (Scheme 1-13).^{71,88} Primary and secondary amine products are accessible with good retention of stereochemistry, albeit moderate yields, whereas tertiary amines are not produced in good yield and become racemized.

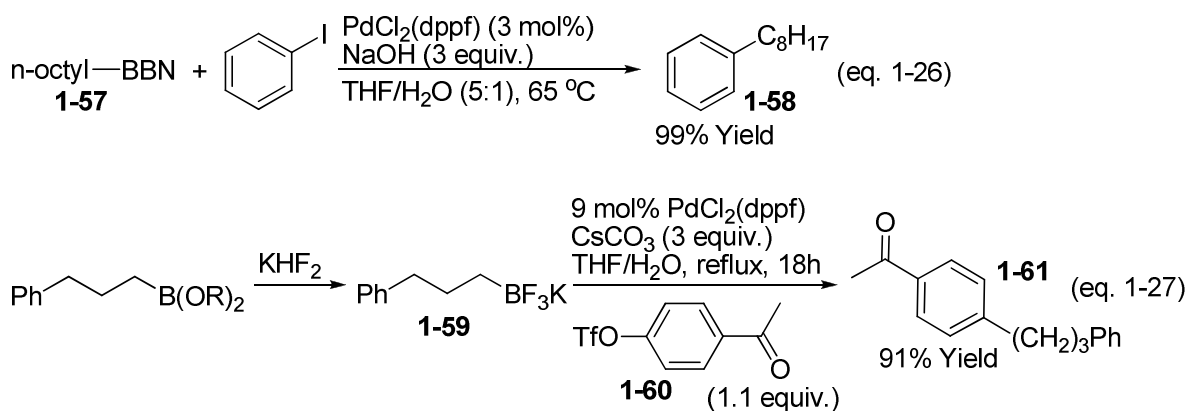
Scheme 1-13: Amination of Chiral Trialkylboranes



The products of alkyne hydroboration find utility in the now ubiquitous Suzuki-Miyaura cross-coupling reaction.^{89,90} This well-established methodology can be used reliably to form new carbon-carbon bonds between two cross-coupling partners. This reaction is generally employed to couple two sp²-hybridized carbons, one bearing a halide or triflate, and the other a boron substituent. Because of the importance of this transformation, this Pd-catalyzed reaction is now arguably the most commonly used reaction for the synthesis of carbon-carbon bonds in fine chemical synthesis⁹¹. Vinylboronates have been utilized extensively in this reaction to generate a variety of aromatic olefins for various applications including fluorescent dyes⁹² and natural products.

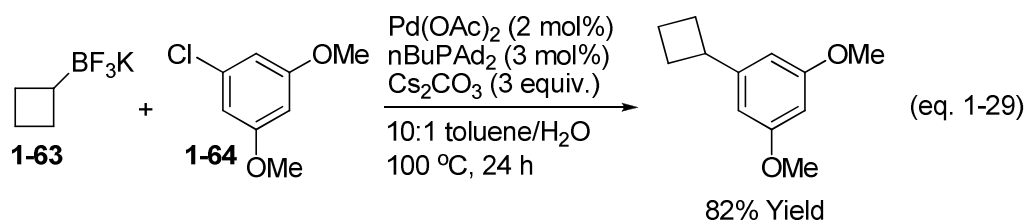
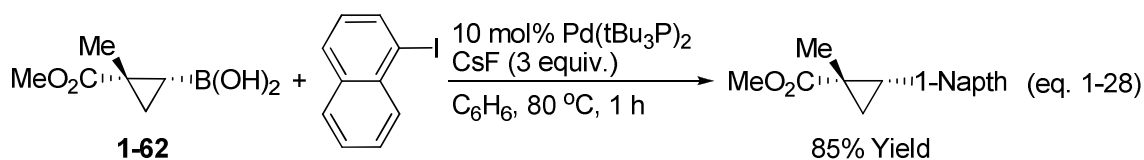
Coupling of sp³-hybridized alkylboronates presents a challenge in this reaction due to the facile β-hydride elimination that can occur after the transmetalation step in the catalytic cycle. However, relatively recent developments with this methodology have shown that certain alkylboronates can be employed successfully in this reaction.⁷⁹ Primary organoboron compounds, which are generally favoured in the hydroboration of terminal olefins, have been extensively utilized for cross-coupling in the Suzuki reaction, as shown in equation 1-26

where species such as **1-57** couples with iodobenzene to give product **1-58** in 99% yield.⁹³ Additionally, boronate ester products may be converted into potassium trifluoroborate, or Molander, salts prior to the reaction.⁹⁴ This air stable salt provides a convenient method to the coupling of terminal sp^3 carbons, as shown in an example in equation 1-27. Treatment of a terminal boronate ester with KHF_2 yield the borate **1-59**, which is cross-coupled to the aryl triflate **1-60** to yield product **1-61** in 91% yield.⁹⁴



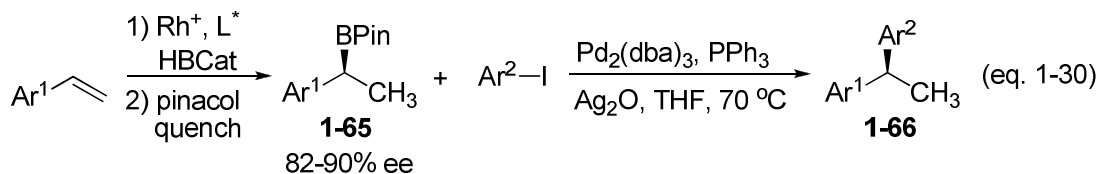
Secondary sp^3 -boronates are much more difficult substrates, as they transmetallate poorly, and are much more sensitive to β -hydride elimination on the Pd catalyst. Specialized substrates, including cyclopropylboronic acids such as **1-62**, which can be obtained by hydroboration of the corresponding cyclopropene, are coupled reasonably well with aryl iodides in a methodology developed by Gevorgyan, equation 1-28.⁹⁵ However, it is likely that the substantial ring strain of the cyclopropyl group imparts sp^2 character to the transmetallated carbon and prevents β -hydride elimination. Molander expanded the scope of substrates that can be employed in this cross-coupling methodology to include cyclobutyl boronates and aryl chlorides, which are typically the most difficult aryl halides to couple, although only symmetrical, unsubstituted examples are given. In equation 1-29, potassium

cyclobutyltrifluoroborate **1-63** is cross-coupled with aryl chloride **1-64** in 82% yield under similar conditions employed by Gevorgyan.⁹⁶



Very recently, the scope of secondary sp^3 - sp^2 Suzuki cross coupling was expanded to include 1-arylethylboronates **1-65**.⁹⁷ These compounds, which are the typical products of Rh catalyzed hydroboration of vinyl arenes, can be coupled to various aryl iodides (Table 1-6).⁹⁷ Additionally, as the hydroboration can be carried out asymmetrically, chiral secondary boronates may be used in this method, and levels of enantio-retention over 90% can be achieved in the cross-coupled product **1-66**, equation 1-30. Although the scope of boronates that can be employed is still limited, the use of these particular boronates marks an important advance in the field of Suzuki cross-coupling and an expansion in the potential applications for Rh catalyzed hydroboration.

Table 1-6: Suzuki-Miyaura Cross-Coupling of Secondary Boronate Esters⁹⁷



Ar ¹	Ar ²	Yield (%)	Stereo-retention
Ph	3,5-diMePh	86	93%
Ph	p-MePh	86	92%
p-ClPh	Ph	84	84%
p-MePh	Ph	54	94%

1.8: Conclusions

The rhodium catalyzed hydroboration has developed significantly in terms of reaction scope and application to synthesis since its initial discovery by Mannig and Nöth.¹⁸ Significant advances in the understanding of the mechanism of this transformation have been made, although the reaction appears to differ appreciably depending on the specific conditions employed.⁴² The catalyzed reaction can provide complimentary chemo, regio, and stereoselectivity to the conventional thermal hydroboration, marking a general expansion of reaction scope in the field of hydroboration. With the ability to stereospecifically convert the C-B bond to a wide variety of functional groups, catalyzed hydroboration provides the key step to the generation of enantiomeric value-added products, and can be considered a cornerstone of diversity-based synthesis.⁷⁸ Furthermore, with the advent of the Suzuki-Miyaura reaction and its ever-broadening substrate scope, the products of hydroboration, and therefore the reaction itself, remain increasingly valuable.⁷⁹

1.9: References

-
- ¹ Mitsunobu, O. *Synthesis* **1981**, 40, 1-28.
- ² Carey, F.A.; Sundberg, R.J. *Advanced Organic Chemistry Part A: Structures and Mechanisms* 5th Edition, **2007**, Springer-Science: New York.
- ³ Brown, H.C., *Organic Syntheses via Boranes*. **1975**, John Wiley and Sons: London.
- ⁴ Burkhardt, E.R.; Matos, K. *Chem. Rev.* **2006**, 106, 2617-2650.
- ⁵ Smith, M.R.; Iverson, C.R. *J. Am. Chem. Soc.* **1999**, 121, 7696-7697.
- ⁶ Brown, H.C.; Prasad, J.V.N.; Zee, S.-H. *J. Org. Chem.* **1986**, 51, 439-445.
- ⁷ Smith, M.B.; March, J. *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure* 6th Edition, **2006**, Wiley-Interscience.
- ⁸ Dhillon, R.S. *Hydroboration and Organic Synthesis: 9-Boracyclo[3.3.1]Nonane (9-BBN)*, **2007**, Springer: New York.
- ⁹ Brown, H.C.; Jadhav, P.K.; Mandal, A.K. *Tetrahedron* **1981**, 37, 3547-3587.
- ¹⁰ Brown, H.C.; Yoon, N.M. *Israel J. Chem.* **1977**, 15, 12.
- ¹¹ Mandal, A.K.; Yoon, N.M. *J. Organomet. Chem.* **1978**, 156, 183-190.
- ¹² Brown, H.C.; Joshi, N.N. *J. Org. Chem.* **1988**, 53, 4059-4062.
- ¹³ Brown, H.C.; Ayyangar, N.R.; Zweifel, G. *J. Am. Chem. Soc.* **1964**, 86, 397-403.
- ¹⁴ Brown, H.C.; Jadhav, P.K.; Desai, M.C. *J. Am. Chem. Soc.* **1982**, 104, 4303-4304.
- ¹⁵ Wilczynski, R.; Sneddon, L.G. *J. Am. Chem. Soc.* **1980**, 103, 2857-2858.
- ¹⁶ Wilczynski, R.; Sneddon, L.G. *Inorg. Chem.* **1981**, 20, 3955-3962.
- ¹⁷ Davan, T.; Corcoran, E.W.(Jr.); Sneddon, L.G. *Organometallics* **1983**, 2, 1693-1694.
- ¹⁸ Männig, D. and Nöth, H. *Angew. Chem. Int. Ed.* **1985**, 24, 878-879.
- ¹⁹ Pereira, S. and Srebnik, M. *Organometallics* **1995**, 14, 3127-3128.

-
- ²⁰ Pereira, S. And Srebnik, M. *J. Am. Chem. Soc.* **1996**, 118, 909-910.
- ²¹ Harrison, K.N. and Marks, T.J. *J. Am. Chem. Soc.* **1992**, 114, 9220-9221.
- ²² Horino, Y.; Livinghouse, T.; Magdalena, S. *Synlett* **2001**, 14, 2639-2641.
- ²³ Molander, G.A. and Pfeiffer, D. *Org. Lett.* **2001**, 3, 361-363.
- ²⁴ Evans, D.A.; Muci, A.R.; Stürmer, R. *J. Org. Chem.* **1993**, 53, 5307-5309.
- ²⁵ Burgess, K. and Jaspars, M. *Organometallics* **1993**, 12, 4197-4200.
- ²⁶ Gridnev, I.D.; Miyaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, 58, 5351-5354.
- ²⁷ Mirabelli, M.G.L. and Sneddon, L.G. *J. Am. Chem. Soc.* **1988**, 110, 449-453.
- ²⁸ Knorr, J.R. and Merola, J.S. *Organometallics* **1990**, 9, 3008-3010.
- ²⁹ Evans, D.A. and Fu, G.C. *J. Am. Chem. Soc.* **1991**, 113, 4042-4043.
- ³⁰ Crudden, C.M.; Hleba, Y.B.; Chen, A.C. *J. Am. Chem. Soc.* **2004**, 126, 9200-9201.
- ³¹ Schrock, R.R.; Osborn, J.A. *J. Am. Chem. Soc.* **1976**, 98, 2134-2143.
- ³² Burgess, K.; Van Der Donk, W.A.; Westcott, S.A.; Marder, T.B.; Baker, R.T.; Calabrese, J.C. *J. Am. Chem. Soc.* **1992**, 114, 9350-9359.
- ³³ Chen, A.; Ren, L.; Crudden, C.M. *J. Org. Chem.* **1999**, 64, 9704-9710.
- ³⁴ Merriam, J.S. and Niedenzu, K. *Inorg. Synth.* **1972**, 44, 162.
- ³⁵ Fazen, P.J. and Sneddon, L.G. *Organometallics* **1994**, 13, 2867-2877.
- ³⁶ Lynch, A.T. and Sneddon, L.G. *J. Am. Chem. Soc.* **1989**, 111, 6201-6209.
- ³⁷ Brown, J.M. and Lloyd-Jones, G.C. *Tetrahedron: Asymm.* **1990**, 12, 869-872.
- ³⁸ Brown, J.M. and Lloyd-Jones, G.C. *Chem. Commun.* **1992**, 710-712.
- ³⁹ Pereira, S. and Srebnik, M. *Tet. Lett.* **1996**, 37, 3283-3286.
- ⁴⁰ Kono, H.; Itoi, K.; Nagai, Y. *Chem. Lett.* **1975**, 1095-1096.
- ⁴¹ Westcott, S.A.; Taylor, N.J.; Marder, T.B.; Baker, R.T.; Jones, N.J.; Calabrese, N.J. *Chem. Commun.* **1991**, 304-305.

-
- ⁴² Evans, D.A.; Fu, G.C.; Anderson, B.A. *J. Am. Chem. Soc.* **1992**, 114, 6679-6685.
- ⁴³ Anton, D.R.; Crabtree, R.H. *Organometallics* **1983**, 2, 855-859.
- ⁴⁴ Albertia, A.; Chatgililoglu, C. *Tetrahedron* **1990**, 46, 3963-3972.
- ⁴⁵ Edwards, D.R.; Crudden, C.M.; Yam, K. *Adv. Synth. Catal.* **2005**, 347, 50-54.
- ⁴⁶ Shen, Q, and Hartwig, J.F. *J. Am. Chem. Soc.* **2007**, 129, 7734-7735.
- ⁴⁷ Edwards, D.E.; Hleba, Y.B.; Lata, C.J.; Calhoun, L.A.; Crudden, C.M. *Angew. Chem. Int. Ed.* **2007**, 46, 7799-7802.
- ⁴⁸ Hayashi, T.; Matsumoto, Y.; Ito, Y. *Tetrahedron: Asymm.* **1991**, 2, 601-612.
- ⁴⁹ Cotton, F.A.; Marks, T.J. *J. Am. Chem. Soc.* **1969**, 91, 1339-1346.
- ⁵⁰ Cotton, F.A.; LaPrade, M.D. *J. Am. Chem. Soc.* **1968**, 90, 5418-5422.
- ⁵¹ Becker, Y.; Stille, K. *J. Am. Chem. Soc.* **1978**, 100, 845-850.
- ⁵² Craswell, L.E.; Lister, S.A.; Redhouse, A.D.; Spencer, J.L. *J. Organomet. Chem.* **1990**, C35-C38.
- ⁵³ Fryzuk, M.D.; McConville, D.H.; Rettig, S.J. *J. Organomet. Chem.* **1993**, 445, 245-256.
- ⁵⁴ Bleuel, E.; Schwab, P.; Laubender, M.; Werner, H. *J. Chem. Soc., Dalton Trans.* **2001**, 266-273.
- ⁵⁵ Halpern, J.; Okamoto, T.; Zakhariev, A. *J. Mol. Catal.* **1976**, 2, 65.
- ⁵⁶ Halpern, J.; Okamoto, T. *Inorg. Chim. Acta.* **1984**, 89, L53-L54.
- ⁵⁷ Watkins, A.L.; Hashiguchi, B.G.; Landis, C.R. *Org. Lett.* **2008**, 10, 4553-4556.
- ⁵⁸ Burgess, K.; Donk, W.A.; Kook, A.M. *J. Org. Chem.* **1991**, 56, 2949-2951.
- ⁵⁹ Bennet, M.J. and Donaldson, P.B.K. *Inorg. Chem.* **1977**, 16, 1581-
- ⁶⁰ Evans, D.A.; Fu, G.C.; Hoveyda, A.H. *J. Am. Chem. Soc.* **1992**, 114, 6671-6679.
- ⁶¹ Ramachandran, P.V.; Jennings, M.P.; Brown, H.C. *Org. Lett.* **1999**, 1, 1399-1402.
- ⁶² Vogels, C.M.; Decken, A; Westcott, S.A.; *Tet. Lett.* **2006**, 47, 2419-2422.

-
- ⁶³ Burgess, K.; van der Donk, W.A.; Jarstfer, M.B.; Ohlmeyer, M.J. *J. Am. Chem. Soc.* **1991**, 113, 6139-6144.
- ⁶⁴ Ohmura, T.; Yamamoto, Y.; Miyaura, N. *J. Am. Chem. Soc.* **2000**, 122, 4990-4991.
- ⁶⁵ Tucker, C.E.; Davidson, J.; Knochel, P. *J. Org. Chem.* **1992**, 57, 3482-3485.
- ⁶⁶ Hayashi, T.; Matsumoto, Y.; Ito, Y. *J. Am. Chem. Soc.* **1989**, 111, 3426-3428.
- ⁶⁷ Alcock, N.W.; Brown, J.M.; Hulmes, D.I. *Tetrahedron: Asymm.* **1993**, 4, 743-756.
- ⁶⁸ Doucet, H.; Fernandez, E.; Layzell, T.P.; Brown, J.M. *Chem. Eur. J.* **1999**, 5, 1320-1330.
- ⁶⁹ Maeda, K. and Brown, J.M. *Chem. Commun.* **2002**, 310-311.
- ⁷⁰ Segarra, A.M.; Daura-Oller, E.; Claver, C.; Poblet, J.M.; Bo, C.; Fernández, E. *Chem. Eur. J.* **2004**, 10, 6456-6467.
- ⁷¹ Kwong, F.Y.; Yang, Q.; Mak, T.C.W.; Chan, A.S.C.; Chan, K.S. *J. Org. Chem.* **2002**, 67, 2769-2777.
- ⁷² Togni, A.; Breutel, C.; Schnyder, A.; Spindler, F.; Landert, H.; Tijani, A. *J. Am. Chem. Soc.* **1994**, 116, 4062-4066.
- ⁷³ Moteki, S.A.; Wu, D.; Chandra, K.L.; Reddy, S.; Takacs, J.M. *Org. Lett.* **2006**, 8, 3097-3100.
- ⁷⁴ Burgess, K. and Ohlmeyer, M.J. *J. Org. Chem.* **1988**, 53, 5178-5179.
- ⁷⁵ Burgess, K.; Van der Donk, W.A.; Ohlmeyer, M.J. *Tetrahedron: Asymm.* **1991**, 2, 613-621.
- ⁷⁶ Luna, A.P.; Bonin, M.; Micouin, L.; Husson, H.P. *J. Am. Chem. Soc.* **2002**, 124, 12098-12099.
- ⁷⁷ Carroll, A. -M.; O'Sullivan, T.P.; Guiry, P.J. *Adv. Synth. Catal.* **2005**, 347, 609-631.
- ⁷⁸ Crudden, C.M.; Edwards, D. *Eur. J. Org. Chem.* **2003**, 4695-4712.
- ⁷⁹ Crudden, C.M.; Glasspoole, B.G.; Lata, C.J. *Chem. Commun.* **2009**, in press
- ⁸⁰ Chen, A.C.; Ren, L.; Crudden, C.M. *Chem. Commun.* **1999**, 611-612.
- ⁸¹ Matteson, D.S.; Sadhu, K.M. *J. Am. Chem. Soc.* **1983**, 105, 2077-2078.
- ⁸² Matteson, D.S.; Majumdar, D. *Organometallics* **1983**, 2, 1529-1535.

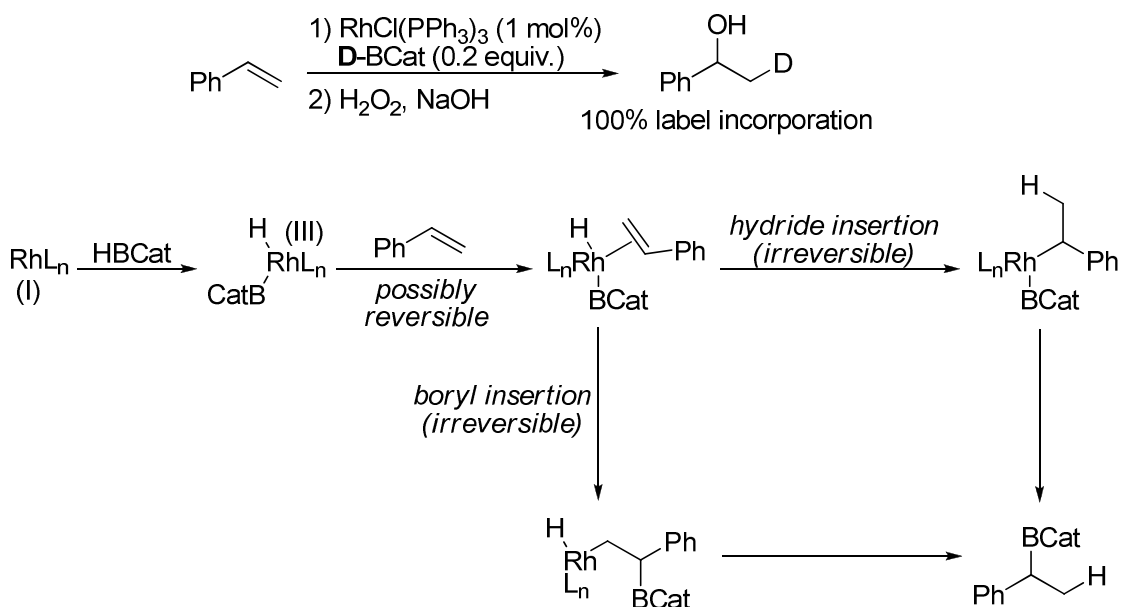
-
- ⁸³ Sadhu, K.M.; Matteson, D.S.; Hurst, G.D.; Kurosky, J.M. *Organometallics* **1984**, 3, 804-806.
- ⁸⁴ Ditrich, K.; Bube, T.; Stürmer, R., Hoffmann, R.W. *Angew. Chem. Int. Ed.* **1986**, 25, 1028-1030.
- ⁸⁵ Matteson, D.S. *Tetrahedron* **1998**, 54, 10555-10607.
- ⁸⁶ Blakemore, P.R.; Surge, M.S. *J. Am. Chem. Soc.* **2007**, 129, 3068-3069.
- ⁸⁷ Blakemore, P.R.; Marsden, S.P.; Vater, H.D. *Org. Lett.* **2006**, 8, 773-776.
- ⁸⁸ Fernandez, E.; Maeda, K.; Hooper, M.W.; Brown, J.M. *Chem. Eur. J.* **2000**, 6, 1840-1946.
- ⁸⁹ Miyaura, N. and Suzuki, A. *Chem. Rev.* **1995**, 95, 2457-2483.
- ⁹⁰ Bellina, F; Carpita, A.; Rossi, R. *Synlett* **2004**, 15, 2419-2440.
- ⁹¹ Rouhi, A.M. *Chem. Eng. News* **2004**, 82, 49-58.
- ⁹² Itami, K.; Tonogaki, K.; Ohashi, Y.; Yoshida, J. *Org. Lett.* **2004**, 6, 4093-4096.
- ⁹³ Chemler, S.R.; Trauner, D.; Danishefsky, S.J. *Angew. Chem. Int. Ed.* **2001**, 40, 4544-4568.
- ⁹⁴ Molander, G.A. and Ito, T. *Org. Lett.* **2001**, 3, 393-396.
- ⁹⁵ Rubina, M.; Rubin, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2003**, 125, 7198-7199.
- ⁹⁶ Molander, G.A.; Gormisky, P.E. *J. Org. Chem.* **2008**, 73, 7481-7485.
- ⁹⁷ Imao, D.; Glasspoole, B.W.; Laberge, V.S.; Crudden, C.M. *J. Am. Chem. Soc.* **2009**, 131, 5024-5025.

Chapter 2 – Mechanistic Studies on Asymmetric Cationic Rhodium Catalyzed Hydroboration of Para-Substituted Vinyl Arenes

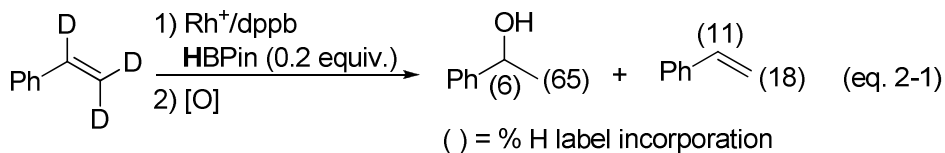
2.1 Introduction

The rhodium catalyzed hydroboration of olefins provides access to different products than would be obtained in the thermal uncatalyzed variant of the reaction in terms of chemo, regio, and stereoselectivity. Perhaps the most beneficial substrates to be utilized in catalyzed hydroboration are vinyl arenes, which yield boronate ester products with Markovnikov selectivity rather than the typical linear alkylboron species obtained via non-catalyzed hydroborations. Thus, the products of hydroboration of vinyl arenes can be synthesized enantioselectively by adorning the Rh catalyst with various chiral ligands.¹ Unfortunately, this useful reaction has not been studied in great detail with respect to the origins of the unique regioselectivity observed.² Labeling studies conducted with styrene and catecholborane (HBCat) in Wilkinson's catalyzed hydroboration have established that hydride insertion into the olefin is not reversible, but this does not conclusively disprove the possibility that the reaction proceeds via boryl insertion (Scheme 2-1).³

Scheme 2-1: Possible Catalyst Pathways in Styrene Hydroboration with HBCat



Additionally, the mechanism of hydroboration appears to be sensitive to the reagent employed, as a similar deuterium labeling study conducted with deuterated styrene and pinacolborane (HBPin) reveals that label is incorporated without complete selectivity in both the olefin starting material and product, equation 2-1.⁴ Thus, little is known about the mechanistic details of the reaction and the reaction steps that may give rise to the branched selectivity that is observed.

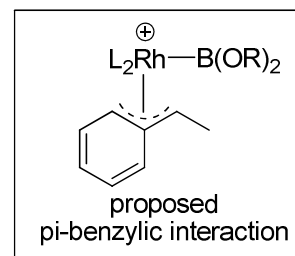


Hayashi hypothesized that the Markovnikov addition to vinyl arenes occurs because of stabilization of the Rh-intermediate via a π -benzylic interaction with the aryl ring.

Although this complex is only proposed,⁵ other Rh species have been observed bearing ligands of this nature (see right).^{6,7} Indirect evidence of such an

interaction in controlling the regiochemistry is observed in the comparative selectivity for the benzylic product in the

hydroboration of styrene or its naphthyl derivative **2-1**.⁸ In



equation 2-2, styrene is hydroborated with HBPin, catalyzed by a cationic rhodium complex to produce the benzylic branched boronate ester product with 72% regioselectivity.

Correspondingly, when **2-1** is subjected to the same treatment, the benzylic product is

produced with 95% selectivity, equation 2-3.⁸ Based on steric effects alone, it would, if

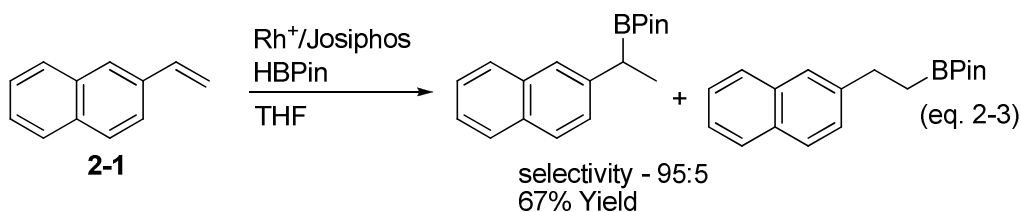
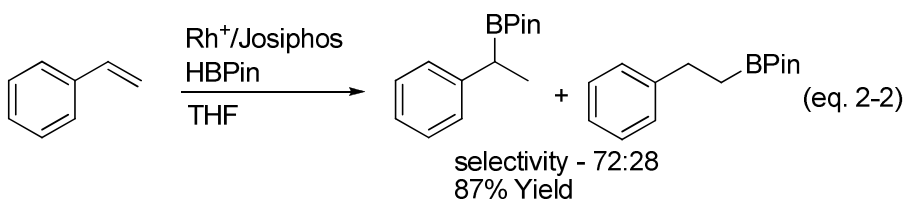
anything, be expected that **2-1** would be hydroborated with equal or less selectivity than

styrene. However, if a stabilizing π -benzylic interaction is formed on the catalytic cycle, the

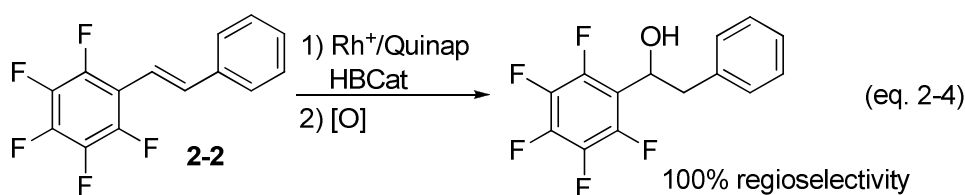
larger aromatic system of **2-1** would be expected to have a stronger electronic effect. This

interaction formally breaks the aromaticity of the ring, which requires less energy for larger

rings. Thus, a π -benzylic interaction would be expected to be more easily formed with **2-1**.



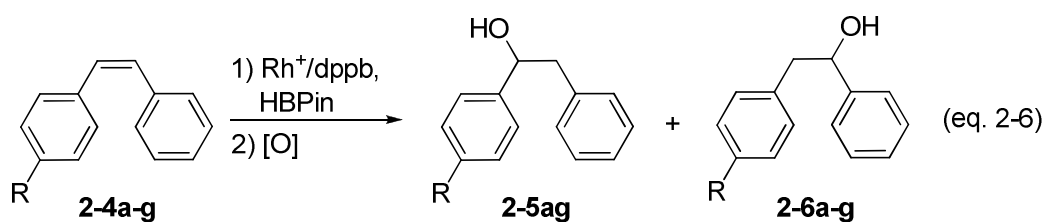
Although this is not clear evidence of the presence of a pi-benzyl interaction which affects the selectivity, it does suggest that a marked electronic effect controls selectivity in the hydroboration of these substrates. This is further exemplified in the hydroboration of various 1,2-diaryl substituted alkenes **2-2** and **2-3**, equations 2-4 and 2-5. In the reaction of these substrates with HBCat catalyzed by Quinap-ligated cationic Rh catalysts, boron is preferentially incorporated in the benzylic position proximal to the more electron withdrawn aromatic ring.⁹ However, the strength of the electronic effect in regioselectivity is apparently ligand dependent. The same substrates and reaction conditions applied in hydroborations catalyzed by dppb-ligated Rh catalysts yield products with weak selectivity in which boron is preferentially installed at the least sterically hindered benzylic position.⁹



If HBPIn is employed, a different, more complex electronic effect is observed, equation 2-6. As shown in Table 2-1, unsymmetrical *para*-substituted *cis*-stilbenes applied in this reaction are preferentially hydroborated to place the boron moiety at the benzylic position proximal to the aryl ring rather than the phenyl ring, regardless of whether the aryl ring contains either electron donating or withdrawing groups.⁴ Furthermore, the strength of regio-directing electronic effect correlates strongly with the Hammett parameter, σ . Plotting

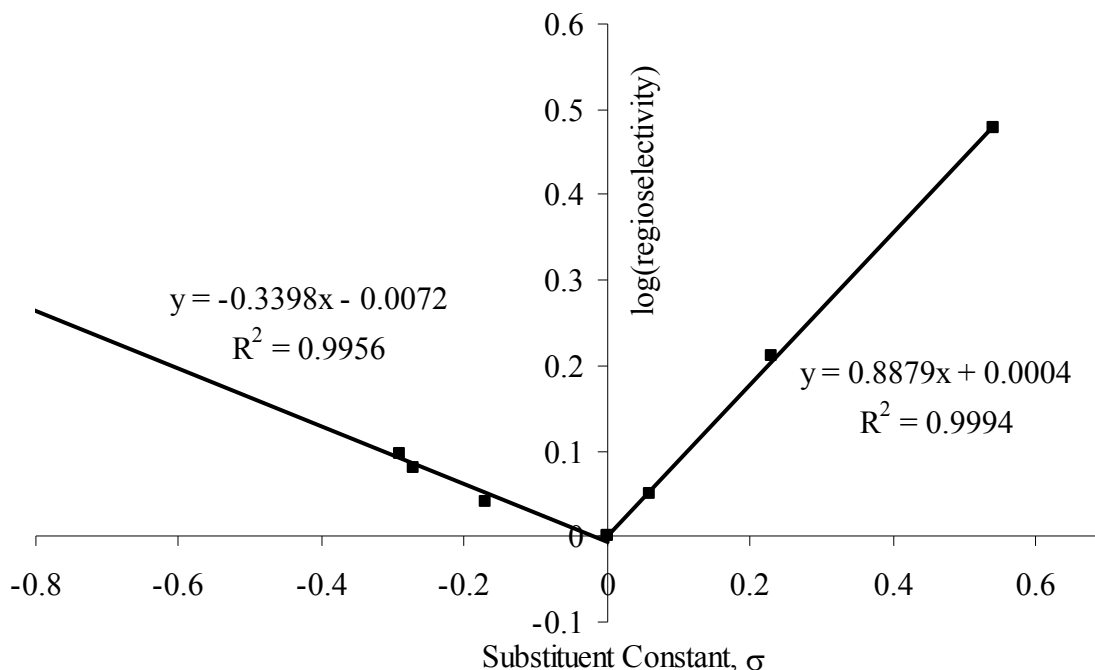
the logarithm of the isomer ratio obtained against σ , as shown in Figure 2-1, reveals a V-shaped Hammett plot, indicating the presence of two competing mechanisms.^{10,11,12} Where the same product is observed in all substrates, one mechanism appears to be favoured for electron poor substrates, whereas another mechanism dominates in electron rich olefins.

Table 2-1: Hydroboration of Unsymmetrical *cis*-stilbenes⁴



Substrate, R	σ	Ratio 2-5:2-6
2-4a , CF ₃	0.54	3.00:1
2-4b , Cl	0.23	1.63:1
2-4c , F	0.06	1.12:1
2-4d , Me	-0.17	1.10:1
2-4e , OMe	-0.27	1.20:1
2-4f , OiPr	-0.29	1.25:1
2-4g , NMe ₂	-0.83	1.89:1

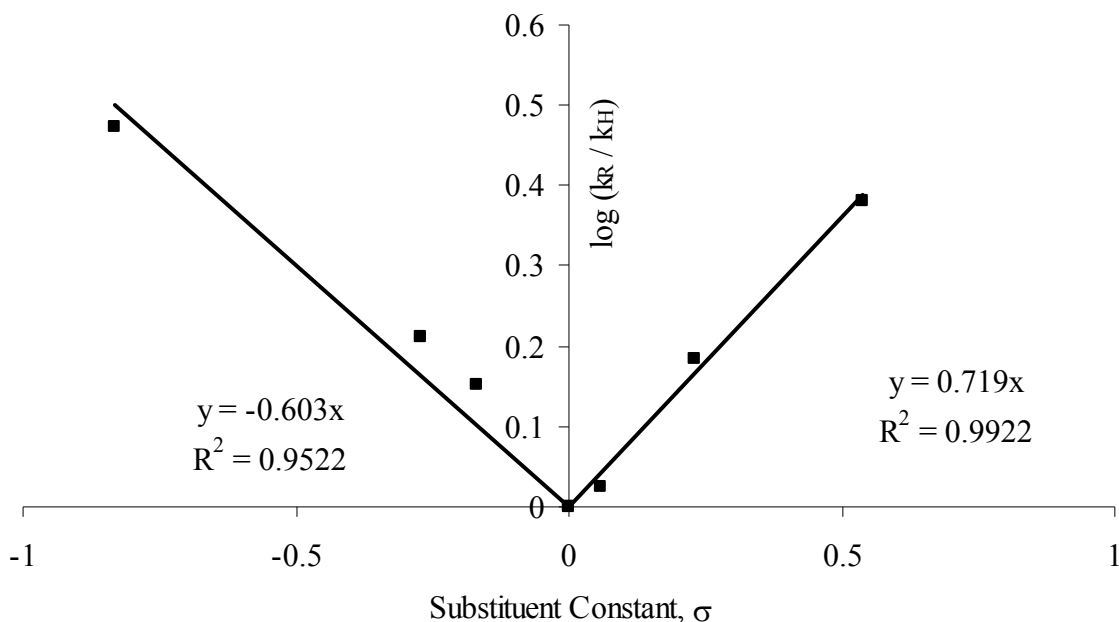
Figure 2-1: Hammett Plot for Unsymmetrically Substituted *cis*-Stilbenes⁴



Although a linear free energy relationship is observed with stilbenes, Hammett plots of internal regioselectivity are typically conducted by an intermolecular competition, not intra as is done with unsymmetrical stilbenes. However, the same reaction conditions applied in an intermolecular competition study conducted with similarly *para*-substituted vinyl arenes and styrene yield similar results, equation 2-7.⁴ Here, reaction of an equimolar solution of vinyl arene and styrene with a limiting quantity of HBPin produce a similar Hammett profile (Figure 2-2). Again, two competing mechanisms appear to be at play. The nature of the correlation observed is related to the first irreversible step of the reaction and all steps preceding it.¹⁰ This prompted further exploration of the mechanism of the catalytic cycle through labeling experiments in an attempt to discover the nature the reaction mechanism. The reaction is conducted using an excess of the two olefins relative to HBPin,

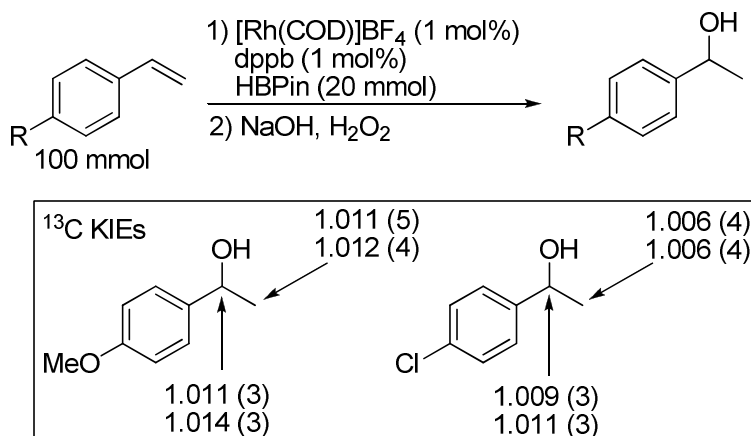
such that any starting material that incorporates a proton label via reversible hydride insertion and olefin association can be assumed to be non-participating in any further catalyzed reactions. Thus, label that is incorporated in the product originates from a productive catalytic cycle. As depicted in equation 2-1, label is incorporated into both the olefin of styrene and product alcohol in both benzylic and terminal positions indicating the hydride insertion and olefin association steps are not irreversible. If these steps were fully reversible, all label would be incorporated to unreacted styrene. Thus, since we are dealing with a situation in between fully reversible and fully irreversible, these equilibria are likely to be relevant in the overall rate of reaction and contributing to the linear free energy relationship observed (Figure 2-2). Further complicating the analysis of the data is the possibility of multiple catalytic cycles at play in the reaction as well as separate non-productive pathways, which may contribute the relative incorporations of label observed in equation 2-1.⁴ This is especially a problem for deuterium labeling studies in which stray metal hydrides can significantly complicate mechanistic analyses.

Figure 2-2: Hammett Plot for Competitions of Styrene Derivatives^{4,13}



Natural abundance ^{13}C kinetic isotope experiments conducted according to the Singleton method¹⁴ with both electron rich and electron poor vinyl arenes unfortunately yielded kinetic isotope effects of small magnitude (Figure 2-3), precluding any conclusive statement on the mechanism of these reactions. However, with a potential hydride insertion eliminated as a possible irreversible step, several mechanistic scenarios can be hypothesized. Mechanisms involving reductive elimination of the Rh-B bond at the benzylic position after a regular metal hydride insertion, or initial boryl insertion followed by reduction elimination from a Rh-H complex at the terminal position are both possible. The data also leave the possibility open for sigma bond metathesis, as is postulated in the mechanism of lanthanum catalyzed hydroboration by Harrison and Marks.¹⁵ A reversible hydride insertion step in sigma bond metathesis is postulated in hydroborations involving samarium catalysts.¹⁶

Figure 2-3: Natural abundance ^{13}C Kinetic Isotope Effects⁴

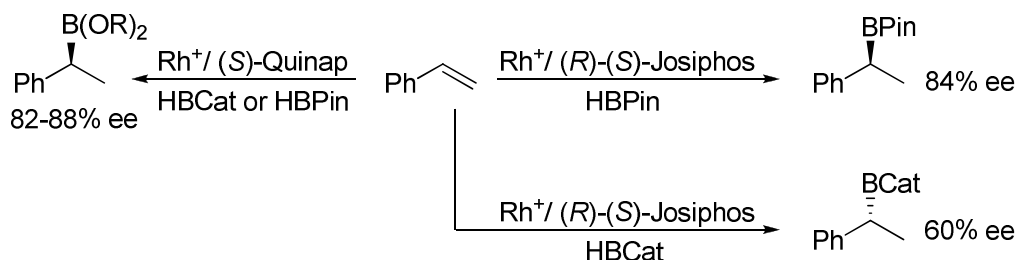


The similarities between the Hammett plots for both unsymmetrical stilbenes and vinyl arenes in their hydroboration with HBPIn and the obvious differences in the electronic effects between dppb and Quinap-ligated catalysts in the hydroboration of stilbenes with HBCat exemplify the sensitivity of the mechanism in Rh catalyzed hydroborations to both reagent and ligand employed. Questions remain, however, on how this electronic effect varies in systems utilizing HBPIn in asymmetric catalysis and how they differ from reactions with HBCat.

Although these results are interesting in their own right, they are all performed with the achiral ligand DPPB. Since different mechanisms may be operative in the case of chiral ligands, it is of interest to examine these reactions as well. In fact, remarkable differences in enantioselectivity have been reported in the hydroboration of styrene using Rh catalysts modified by chiral ligands.^{8,17} In reactions employing one antipode of Josiphos, opposite enantioselectivities were observed when the reaction was conducted with HBPIn or HBCat

(Scheme 2-2). When Quinap was employed, however, the same enantioselectivity is observed regardless of which reagent was employed.

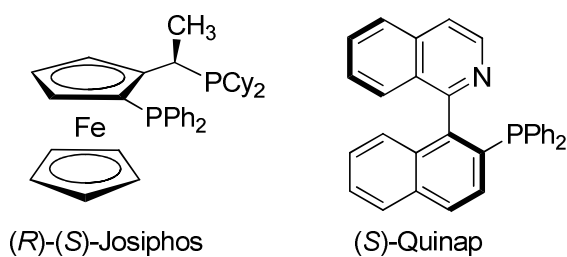
Scheme 2-2: Comparison of enantioselectivity obtained in the hydroboration of styrene with Quinap and Josiphos ligated Rh catalysts⁸



2.2 Competition Studies on Vinyl Arenes in Asymmetric Rh-Catalyzed Hydroboration

Having clearly shown that two different mechanisms are at play in the hydroboration of styrenes and stilbenes with HBPin and a Rh•dppb catalyst, we turned our attention to chiral versions of this reaction. Although there are an abundance of chiral ligands to choose from for use in asymmetric hydroboration, only two common bidentate species were selected for study. These ligands, Josiphos and Quinap (Figure 2-4), are commonly employed in Rh catalyzed asymmetric hydroborations involving HBPin as a reagent, and represent two different and highly applied classes of chiral ligand, where Quinap is a P,N-type bidentate ligand and Josiphos is P,P-type ligand.

Figure 2-4: Chiral Ligands Employed along with Rh Catalysts for Hammett Studies



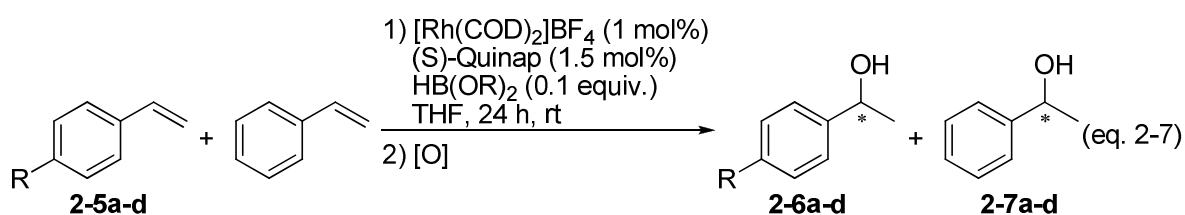
As noted above, catalysts ligated with Josiphos or Quinap display marked differences in the enantioselectivity of reactions performed with HBCat and HBPIn (Scheme 2-2).⁸ For a given antipode Quinap, both reagents yield the same enantiomer product in Rh catalyzed hydroboration of styrene. In contrast, catalysts ligated by Josiphos yield products with opposite enantioselectivity when the reaction is carried out with HBPIn or HBCat.

Thus, a series of intermolecular competition experiments^{18,19} were conducted in which 1 mmol each of styrene and a *para*-substituted vinyl arene were added to a 5 mL THF solution of chiral catalyst. The catalyst precursor was formed in situ from [Rh(COD)₂]₂BF₄ and either (R)-(S)-Josiphos or (S)-Quinap at a 1 mol% loading. Reactions were then conducted with a limiting quantity of either HBPIn or HBCat. After 24 hours, the resultant product alcohols were obtained through basic hydrogen peroxide oxidation, and analyzed via gas chromatography against an internal standard.

Equation 2-7 and Table 2-2 show the results of the hydroboration of several *para*-substituted vinyl arenes with HBPIn or HBCat in competition with styrene catalyzed by Quinap-ligated Rh. From the relative yields of the product benzylic alcohols obtained, relative rate constants were calculated, and the log of these values plotted against the Hammett substituent constant σ^{20} to yield a Hammett plot. Notably, minor amounts of linear

alcohol were also observed, and, although calibration curves were generated for these products, the low quantity of these regio-isomers precluded reliable analysis or quantification. Thus, only the branched isomer alcohols were analyzed in the competition studies.

Table 2-2: Competition Studies with Quinap Ligated Rhodium Catalysts



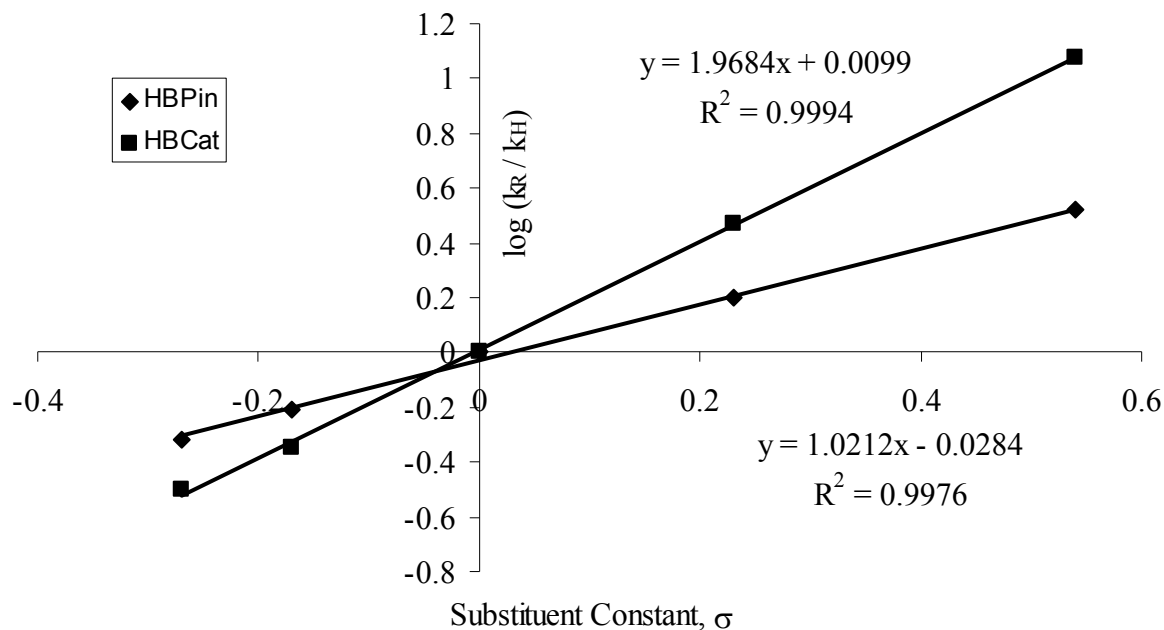
Substrate, R	HB(OR) ₂	σ	Ratio 2-6:2-7	Yield (%)	Log k_{rel}
2-5a, CF ₃	HBPIn	0.54	3.30:1	37.4	0.52
	HBCat		11.84:1	71.5	1.07
2-5b, Cl	HBPIn	0.23	1.58:1	16.7	0.20
	HBCat		2.96:1	78.3	0.47
2-5c, Me	HBPIn	-0.17	0.62:1	15.4	-0.21
	HBCat		0.32:1	44.6	-0.34
2-5d, OMe	HBPIn	-0.27	0.48:1	19.1	-0.32
	HBCat		0.45:1	69.0	-0.50

In both the hydroboration with HBPIn and HBCat, a linear free energy relationship correlating to the Hammett parameter σ is observed in which a strong positive ρ -value is observed, Figure 2-5. This indicates that regardless of the borane, the reaction is accelerated by electron withdrawing groups. Interestingly, the preference for the hydroboration of

electron-withdrawn vinyl arenes matches the electronic effect observed by Brown's group in stilbene substrates under similar Quinap-ligated rhodium catalyzed reactions.⁹ Additionally, the Hammett plot is unbroken, indicating that, perhaps not surprisingly, changing the ligand from dppb to Quinap has a significant effect on the mechanism.

Although both HBPIn and HBCat are both characterized by a positive rho value, it appears that the reaction with catecholborane is much more sensitive to the electronics of the substrate olefin, as indicated by the markedly larger ρ -value of 1.97, compared with a ρ -value of 1.02 for hydroborations with HBPIn.

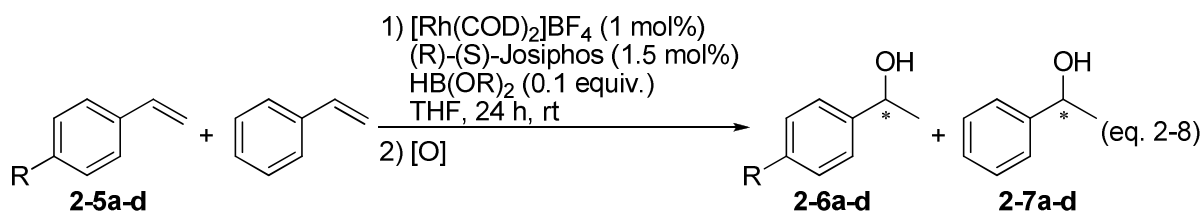
Figure 2-5: Hammett Plot for Quinap Ligated Cationic Rhodium Systems



Having obtained such a significant correlation in Quinap-ligated systems, Josiphos was next utilized under the same conditions, equation 2-8. Again, both HBCat and HBPIn

were used in the hydroboration of vinyl arenes **2-5a-d** in competition with styrene to obtain relative rate constants, Table 2-3.

Table 2-3: Competition Studies with Josiphos Ligated Rhodium Catalysts

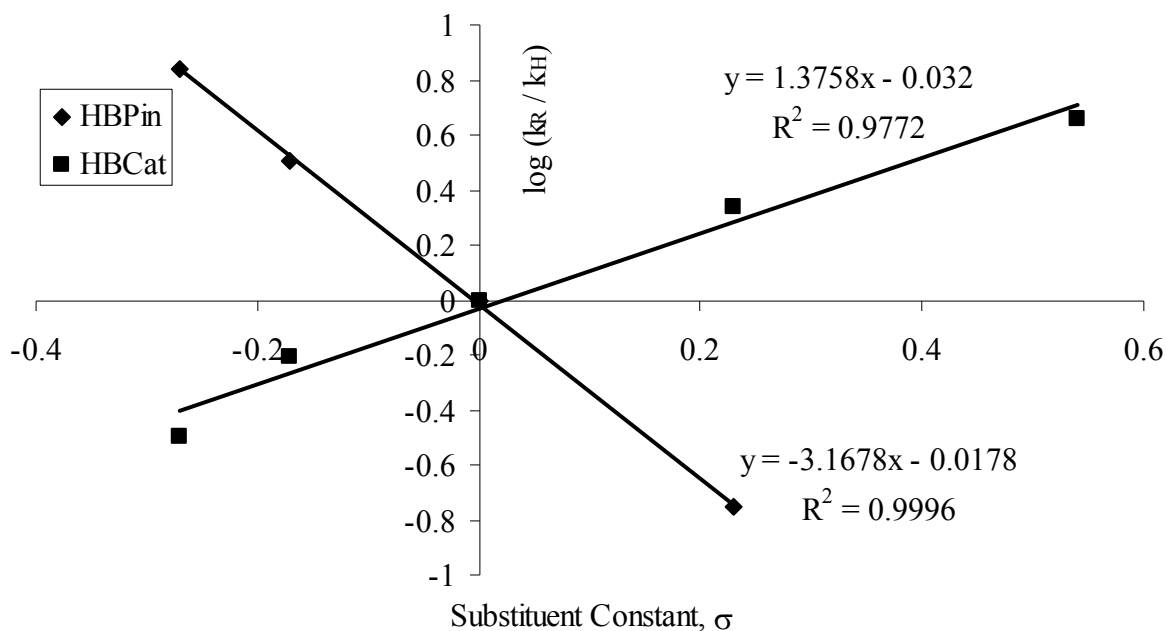


Substrate, R	$\text{HB}(\text{OR})_2$	σ	Ratio 2-6:2-7	Yield (%)	Log k_{rel}
2-5a, CF_3	HBPIn	0.54	NA	NA	NA
	HBCat		4.55:1	76.2	0.66
2-5b, Cl	HBPIn	0.23	0.19:1	24.2	-0.75
	HBCat		2.20:1	87.0	0.34
2-5c, Me	HBPIn	-0.17	3.22:1	84.0	0.51
	HBCat		0.62:1	75.0	-0.21
2-5d, OMe	HBPIn	-0.27	6.92:1	90.4	0.84
	HBCat		0.32:1	75.6	-0.50

Unlike the results obtained with Quinap, hydroborations catalyzed by Josiphos-ligated rhodium complexes differ drastically depending on the borane used. As previously noted, with HBPIn the reaction is enantioselective for the *S*-isomer product whereas hydroboration with HBCat produces the *R*-enantiomer as the major product when using (*R*)-(*S*)-Josiphos (Scheme 2-2). With HBCat, a similar trend is observed as in Quinap, although a

comparatively smaller ρ -value of 1.38 is obtained as shown in Figure 2-6. However, when HBPin is used as the hydroborating reagent, the opposite electronic trend is observed. A ρ -value of -3.17 indicates that the reaction is strongly stabilized by electron donating groups, which suggests a buildup of significant positive charge in the reaction. The stark difference in charge buildup in these two sets of competition studies is a strong indication that a different mechanism is at play in the hydroborations catalyzed by Josiphos-Rh⁺ depending on the choice of borane. Again, whereas two competing mechanisms are at play in the dppb-ligated system,⁴ both chirally-ligated Rh catalysts appear to operate via a single mechanism **for a given borane** within the range of inductively withdrawing and donating substituents tested.

Figure 2-6: Hammett Plot for Josiphos Ligated Cationic Rhodium Systems



The data obtained from the Hammett studies suggest that the nature of the substituent on the vinyl arene has a significant effect on the outcome of the reaction. However, the

catalytic system also appears to be extremely sensitive to the ligand environment as well as the borane reagent added. In order to determine whether or not any of the reaction mechanisms involve the generation of a cation, both of the Hammett plots above were recalculated using the σ^+ substituent parameter, which is known to give a stronger correlation for reactions involving cations. These results are given in Figures 2-7 and 2-8.

Figure 2-7: σ^+ Hammett Plot for Quinap Ligated Cationic Rhodium System

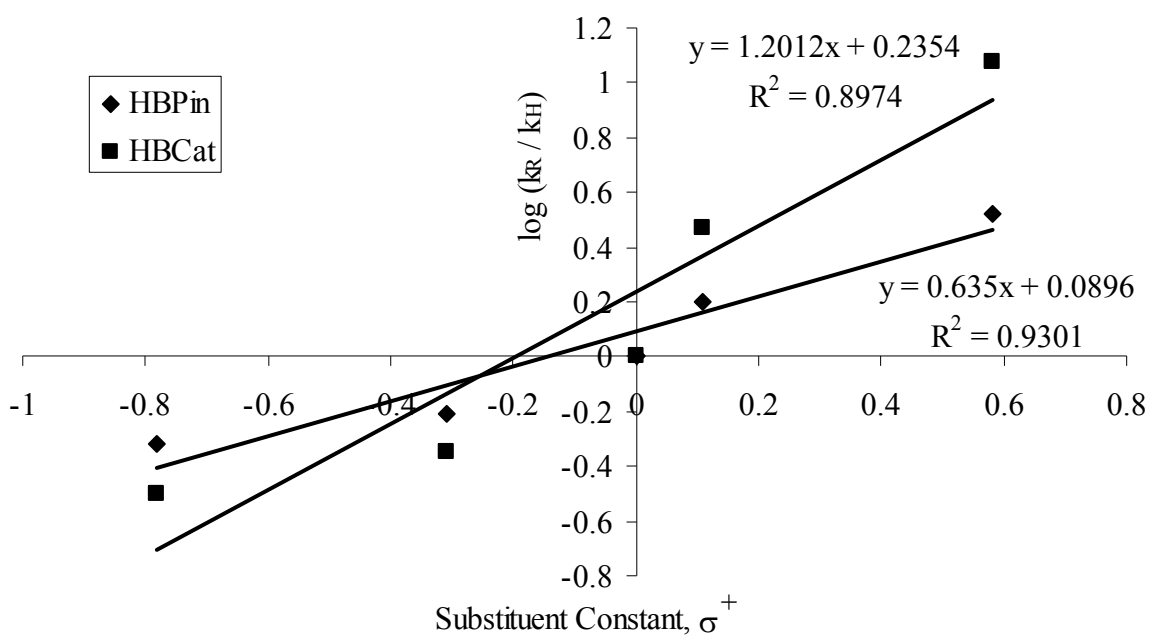
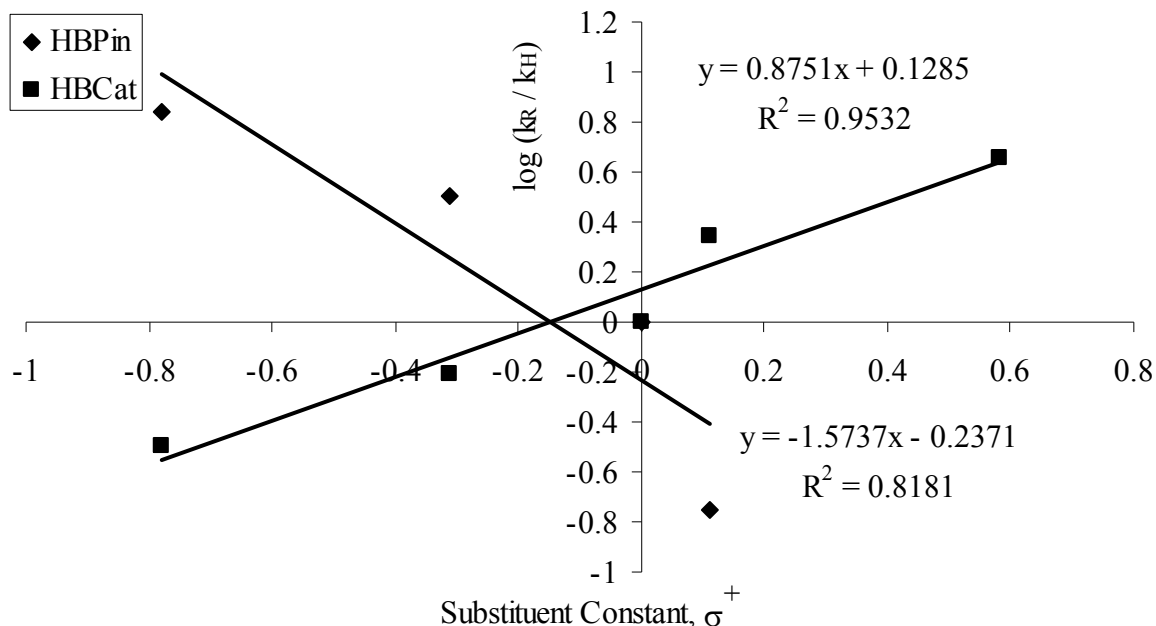


Figure 2-8: σ^+ Hammett Plot for Josiphos Ligated Cationic Rhodium System



As shown in Figures 2-7 and 2-8, a poorer correlation was obtained with the σ^+ substituent parameter, implying that the inductive effect of the substituent groups tested is more important than resonance electronic effects, which would correlate more strongly with the σ^+ substituent parameter.

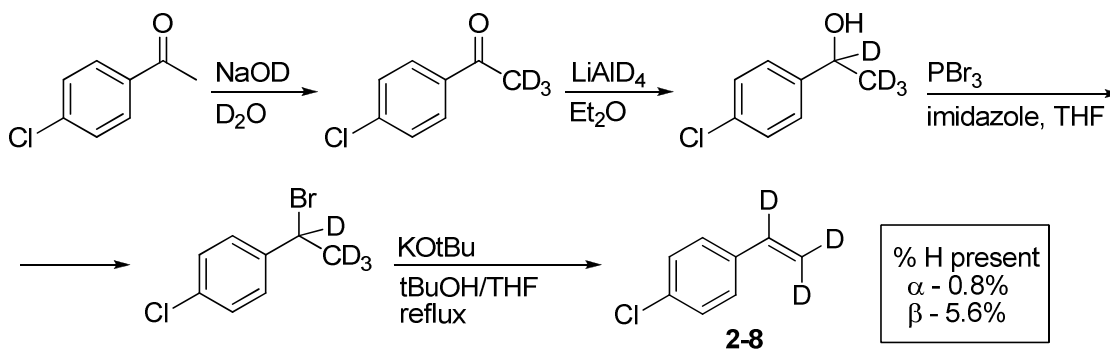
Although Hammett correlations are widely employed in the study of “traditional” organic reaction mechanisms, they are less widely employed in reactions involving transition metal catalysts. Exceptions to this statement include the pioneering study of the hydrogenation of styrenes by Halpern,²¹ recent reports of Rh-catalyzed decarbonylation²² hydroacylation reactions,²³ asymmetric Rh-catalyzed hydroformylation,²⁴ as well as Pd catalyzed enantioselective allylic substitution reactions.²⁵

2.3 Synthesis and Hydroboration of Deuterated Vinyl Arenes

The notable difference in the electronic effects observed for Josiphos-ligated Rh hydroboration with the different boranes correlates with stark differences in the enantioselectivity of this reaction when conducted with HBPIn and HBCat.

Thus, labeling experiments were devised in order to probe the mechanism of the reaction in the four reaction scenarios. Although these experiments are typically conducted with deuterated boranes in the literature,^{3,27} difficulties were encountered in our group in obtaining good deuterium balances in reactions employing DBPin, which may have been due to trace metal impurities present in the reagent.²⁶ Therefore, labeling experiments were conducted with α,β,β -deuterated 4-chlorostyrene **2-8**, synthesized as shown in Scheme 2-3. This synthesis was developed in the Crudden lab, and was utilized due to availability of the reagents in our lab. Although a greater number of steps were involved than in an existing literature procedure,²⁷ this route avoids the use of expensive deuterium gas in reduction of the corresponding alkyne of **2-8**.²⁷

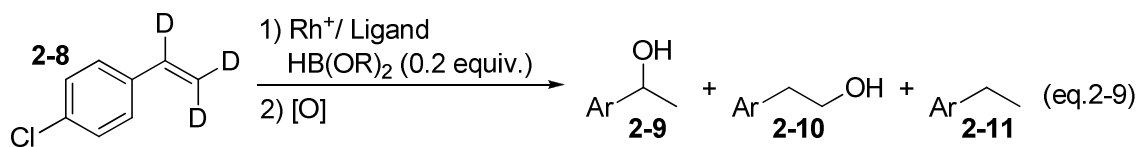
Scheme 2-3: Synthesis of d_3 -4-chlorostyrene



The hydroboration of **2-8** with a limiting amount of borane using Quinap or Josiphos-ligated Rh catalyst as described by Evans during his deuterium labeling studies³ furnished the corresponding linear and branched alcohols after oxidation. Subsequently, quantitative ¹H-NMR analysis of the proton label incorporation to the alcohol products and recovered starting material was conducted after separation by column chromatography. The purification and separation of these components was necessary, as the crude mixture after oxidation did not give a clean NMR spectrum. Proton rather than deuterium label was monitored by quantitative ¹H-NMR with a D1 relaxation time of 10 seconds. Relative proton label incorporation was calculated based on the integration of product and starting material peaks relative to the integration of their corresponding aromatic signals. Due to the necessary purification required, full recovery of unreacted styrene was not possible. Mass balance of the substrate was recorded, but proton label incorporation was extrapolated based on assumed full recovery. Reduced product **2-11**, which co-eluted with recovered starting material on purification, was treated in the same manner, where the quantity of label incorporation and yield were assumed relative to the styrene substrate by NMR (see section 2.5 for details).

As shown in Table 2-4, the level of incorporation of proton label varied according to both borane and ligand employed in the reaction. Unfortunately, a significant amount of reduced product was observed in these experiments, and significant amounts of label were incorporated in this species, which makes conclusive statements regarding the mechanism of the reaction difficult.

Table 2-4: Proton Label Incorporation in Catalyzed Hydroboration ^a



Ligand, Borane	Recovered	Branched	Linear	Reduced	Proton
	2-8	2-9	2-10	2-11	Balance (%)
Josiphos, HBCat	α <1	α 0	α 13	α 12	91
	β 5	β 35	β 3	β 19	
Josiphos, HBPIn	α 3	α 2	α 10	α 17	117
	β 31	β 33	β 5	β 16	
Quinap, HBCat	α 3	α 0	α 10	α 6	81
	β 32	β 17	β 1	β 11	
Quinap, HBPIn	α 9	α ND	α ND	α 14	65
	β 8	β ND	β ND	β 33	

^[a] Label incorporation was corrected for the initial proton present in each position of the starting material.
 ND: not determined

Table 2-5: Yields Determined for Labeled Products

Ligand, Borane	Recovered	Branched	Linear	Reduced
	2-8^a	2-9	2-10	2-11^b
Josiphos, HBCat	39.1%	32.3%	14.8%	19.9%
Josiphos, HBPin	46.3%	48.9%	21.6%	24.1%
Quinap, HBCat	28.0%	17.3%	12.5%	8.5%
Quinap, HBPin	58.7%	ND	ND	22.2%

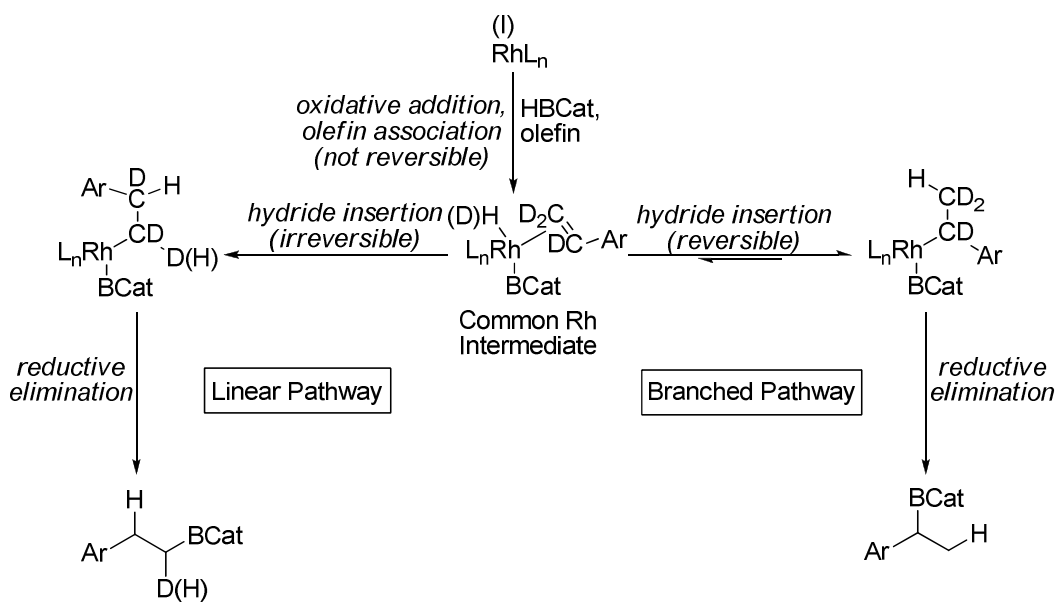
^[a] Isolated % yields calculated based on assumed full conversion of borane ^[b] Yield for reduced product was calculated based on relative NMR integration to starting material of assumed full recovery

In addition to the presence of reduced product, it must also be noted that the error in NMR integration appears to be significant. As deuterated **2-8** was extremely precious, reactions were conducted on 1 mmol scale, and as such product yields were subject to some level of irreproducibility. The volatility and general sensitivity of styrenes to aqueous workup and purification precluded the recovery of 100% of the unreacted substrate. As such, relative integrations for proton incorporation in the recovered olefin were extrapolated assuming full recovery.²⁸

Despite the aforementioned caveats, there do appear to be tangible differences in the proton incorporation that would suggest differences in mechanism. In the Josiphos system, almost no label is incorporated into the recovered olefin when HBCat is used. There also appears to be no proton label incorporated into the α -position of the branched product **2-9**, strongly suggesting that the reaction pathway to this product is fully selective for hydride insertion or final reductive elimination of the hydride to the β -position of the olefin. For

product **2-9** where there is no label in the α -position, this may suggest irreversible hydride insertion. However, it is impossible to be conclusive on this point, due to the presence of linear product. The linear product has a small amount of label present at the β -position which implies that hydride insertion is partially reversible for this terminal position and irreversible for the benzylic position en route to **2-10**. Given these data, it is unknown if branched and linear products originate from separate catalytic cycles or if their production is linked. If the linear product originates from a common catalyst intermediate that can also produce branched product, then the data could be rationalized as in Scheme 2-4. This possible mechanism relies on the association step of vinyl arene **2-8** to the catalyst being largely irreversible, which is consistent with the observation of only a small level of label incorporation in the starting olefin. In addition, it should be noted that the small proton label content observed in recovered styrene **2-8** may originate from a catalytic cycle en route to product **2-11**.

Scheme 2-4: Possible Reaction Pathway in HBCat Hydroboration with Rh/Josiphos Catalyst

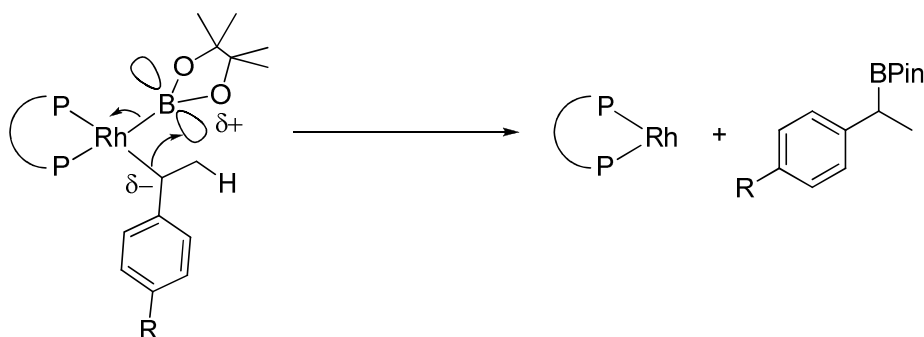


In Josiphos-Rh⁺ reactions with HBPIn and **2-8**, a notably different pattern of label incorporation is observed. Significantly, 31% of the proton label is accumulated in the β -position and 2% in the α -position of recovered **2-8**, indicating reversible association, oxidative addition, and hydride insertion steps in the production of chiral product **2-9**. In product **2-9** itself, the majority of label is present at the β -position, 33%, although a small amount (2%) is incorporated at the benzylic position. Interestingly, these numbers match closely with those observed for recovered starting material, which may indicate an inherent preference in the regioselectivity of hydride insertion in this case. The linear product **2-10** accumulates proton mostly at the α -position, but also contains 5% of the label at the linear position, which is a relatively large amount considering the total incorporation of 15%. This may indicate that a reversible hydride insertion followed by irreversible reductive elimination from a Rh-boryl intermediate. However, another possibility that cannot be ruled out is that the hydride insertion occurs rapidly and reproducibly, but does not lead to product, which is instead generated by irreversible boryl insertion and reductive elimination via the resulting Rh-hydride intermediate.

The increased reversibility of hydride insertion relative to the reaction with HBCat implies a slower reductive elimination step in the catalytic cycle and is similar to results obtained in the case of dppb-ligated Rh catalyzed hydroboration of deuterated styrene (equation 2-1).⁴ Furthermore, the Hammett study of this system shows that reactions catalyzed by Josiphos-ligated Rh are accelerated by electron donating substituted vinyl arenes. Thus, reductive elimination from a Rh-boryl intermediate may be facilitated by more electron rich vinyl arenes. This may be due to an increased ability of the resulting electron rich alkyl species on Rh to act as a nucleophile in a postulated mechanism of reductive

elimination shown in Scheme 2-5, which indicates a nucleophilic attack of the Rh-alkyl species on the vacant p-orbital on boron.

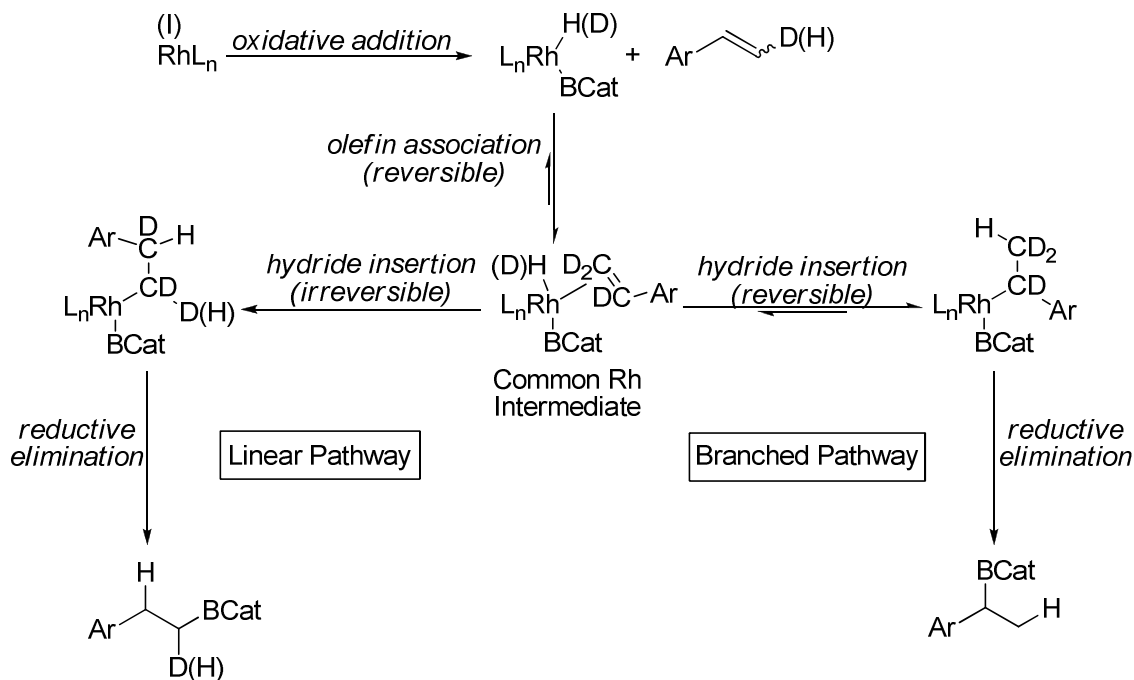
Scheme 2-5: Possible Final Step in Josiphos/Rh⁺ Hydroborations with HBPIn



In Quinap systems, in which the reaction is accelerated by electron withdrawing substrates, similarities can be observed in the labeling results with HBCat to that of the Josiphos system employing the same borane. Again, no label is incorporated into the benzylic position of the branched product **2-9**. Likewise, the majority of label in **2-10** is present at the α -position, with a small amount of proton in the β -position as well. However, a notable difference to the Quinap system from that of Josiphos-ligated Rh catalysis is a significant washing of 35% of available proton into **2-8** primarily at the terminal position of the olefin, indicating a much greater reversibility of hydride insertion, and olefin association in the branched product pathway. These data suggest that reductive elimination from a Rh-boryl intermediate generated by hydride insertion to the olefin is the slow step of the reaction. Again, however, the preceding steps do not appear to be fully reversible, indicating a more complex mechanism (Scheme 2-6). Another possibility is that a non-productive

reversible hydride insertion pathway en route to product **2-9** is operating, and irreversible boryl insertion followed by Rh-hydride reductive elimination.

Scheme 2-6: Possible Reaction Pathway in HBCat Hydroboration with Rh/Quinap Catalyst



Unfortunately, the labeling study with HBPIn in Quinap/Rh⁺ systems was unsuccessful, and product alcohols could not be obtained. This was not completely unexpected, as previous attempts using these reaction conditions with styrene and HBPIn in equal stoichiometry met with a low reported yield of 30% for the boronate ester products.⁸ With the conditions employed for labeling involving sub-stoichiometric amount of borane (0.2 mmol), and subsequent oxidation and purification, no observable product was obtained. Although this reaction was unsuccessful, it should be noted that successful reactions have been reported by Fernandez for Quinap-ligated Rh hydroboration with HBPIn.¹⁷ Herein,

Fernandez reports a 99% yield for the hydroboration of styrene catalyzed under the same conditions utilized in our group.⁸ This discrepancy may originate from a difference in catalyst preparation, where Fernandez uses pre-formed $[\text{Rh}(\text{COD})(\text{Quinap})]\text{BF}_4$ directly in the reaction. In experiments conducted in this study this catalyst was generated *in situ* from separately added Quinap and $[\text{Rh}(\text{COD})_2]\text{BF}_4$.

In lieu of the complicated numbers attained for the proton labeling study, it is difficult to assign the reaction mechanism with any certainty. As such, further study mechanistic study is still required in order to firmly grasp the nature of the mechanism in each ligand and borane combination studied. The observation of multiple products, which may be due to the deuterated nature of the olefin, precludes a straightforward analysis, as it is impossible to conclude, based on the data, if the products originate from a common catalyst intermediate or if they are produced from separate and competing active catalyst species. Thus, further studies are required in order to better describe the mechanism of these catalyzed hydroborations, would likely require kinetic analysis of the reactions.

2.4 Conclusions

The Rh catalyzed hydroboration is a complex system in which changes in the substrate vinyl arene, the borane reagent employed, as well as the ligand utilized on the metal complex can have remarkable effects on the mechanism of reaction. In the previously studied dppb-ligated systems, two different mechanisms were apparent by the observed local minimum in the Hammett study, where one mechanism dominated for electron donating substituents and the other for withdrawing groups. By contrast, when either Josiphos or

Quinap are used on the Rh catalyst, no change in the mechanism is observed within a set of substrates. However, differences in mechanism are observed when either ligand or borane is changed. These mechanistic differences appear to correlate with a reversal in enantioselectivity in the case of Josiphos.

In catalysts modified by Quinap, hydroboration with either HBPIn or HBCat yields a linear free energy correlation with the substituent parameter, σ . While both boranes yield a positive correlation, implying that the reaction is accelerated by electron withdrawing substituents, hydroborations with HBCat are more sensitive to electronic effects, with an observed rho-value of +1.97 relative to the rho-value of 1.02 obtained with HBPIn. As the reactivity of both boranes differs, a difference in sensitivity to vinyl arene electronics can be expected. Furthermore, as both HBPIn and HBCat yield the same major enantiomer for a given antipode of Quinap, this would seem to suggest largely similar mechanisms. However, this does not fully preclude the possibility of two differing mechanisms in which the enantio-defining step is different in each case.

In the case of Josiphos, a marked difference in the mechanism was apparent. Again, in each set of conditions, one mechanism was observed within a set of vinyl arenes tested. Correlations to the substituent constant, σ , were again observed. With HBCat as a reagent, the irreversible step showed a buildup of negative charge, with a rho-value of +1.38. However, with HBPIn a rho-value of -3.17 was observed, indicating that the reaction is accelerated by electron rich substituents. The labeling data suggest that the irreversible step in the case of reactions with HBCat may be hydride insertion. With HBPIn, label incorporation to the starting material suggests partially reversible olefin association,

oxidative addition, and hydride insertion steps, indicating reductive elimination as the slow step of the reaction. However, the complex mixture of products from the reaction precludes conclusive mechanistic statements.

No labeling experiment indicated full reversibility of the hydride insertion and olefin complexation, as would be indicated by full incorporation of the label in the starting material. This suggests that the mechanism of the catalyzed hydroboration is a complex multi-step reaction in which kinetically relevant equilibria exist. Thus, further study of these systems is required in order to understand its mechanism.

2.5 Experimental Section

General Experimental Consideration: All competition experiments were performed in disposable oven-dried glassware under oxygen and moisture free glovebox conditions. Reactions were carried out without the use of stirbars, except for the subsequent oxidation reactions, which were stirred under air. THF solvent was retrieved from an alumina-dried solvent purification system (Innovative Technologies SPS) and further subjected to distillation from sodium/benzophenone and then degassed via three freeze-pump-thaw cycles. Vinyl arene substrates were purchased from Aldrich at the highest level of purity and were further purified via bulb-to-bulb distillation, then degassed prior to use. These compounds were also stored at -20°C in the darkness under inert atmosphere. Neat pinacolborane and catecholborane were also purchased from Aldrich and vacuum distilled and deoxygenated before storage in the glovebox. HBCat was stored at -20°C whereas HBPin was left at ambient glovebox temperature (30°C). (*R*)-(*S*)-Josiphos and (*S*)-Quinap were purchased from Strem and stored and used in the glovebox. Product alcohols of

competition runs were also analyzed by GC using an Agilent 6850 series Gas Chromatograph employing an HP-5 column as a verification of accuracy. All product alcohols were obtained as authentic samples from Aldrich at the highest purity for the purposes of calibration curves.

Representative competitive hydroboration with cationic rhodium using chiral ligand: In an N₂-filled glovebox (H₂O less than 1 ppm; O₂ 4-8 ppm), a disposable glass vial, previously oven-dried and brought into the antechamber while hot, was charged with [Rh(COD)₂]BF₄ (1 mol%, 4.7 mg, 0.01 mmol, stored cold in box) and (*S*)-QUINAP (1.5 mol%, 6.6 mg, 0.015 mmol, stored at r.t.). The solid was then dissolved in 1 mL of THF and let sit for 10 minutes, forming a red homogenous solution. Styrene (1 mmol, 104.15 mg) and 4-chlorostyrene (1 mmol, 138.59 mg) substrates were added into a small tared vial together, then transferred to the catalyst solution via pipette; the vial was washed with 1 mL of THF and transferred. After 10 minutes, HBPIn (0.1 mmol, 12.80 mg) was added in the same manner as the styrenes, and the reaction vial was sealed and left in the glovebox for 24 hours. When removed from air-free atmosphere for oxidation, the solution colour had markedly darkened.

Representative oxidation and workup of competition reaction: The glass vial containing the reaction solution was placed in an ice bath and allowed to cool, at which time the vial was opened. To the vial, 1 mL of 2M aqueous sodium hydroxide solution was then added followed by 1 mL of 30% aqueous hydrogen peroxide. The solution was typically observed to froth and change colour to greenish yellow. After 1 hour at 0°C in the ice bath, the vial was removed and allowed to come to r.t. A stirbar was added to the vial and the reaction was stirred for another hour. The solution was then washed into a separatory funnel and worked

up in 3x25 mL anhydrous diethyl ether, which was subsequently dried under MgSO_4 , filtered, and concentrated under vacuum to yield yellow oil. Hexanes were added to precipitate any rhodium metal, and the mixture was filtered through a plug of Celite filter agent to give a colourless hexanes solution. This solution was then diluted further with Hexanes to 10 mL. A sample of known volume of this solution was then mixed with a known volume a prepared stock solution of external standard for chromatographic analysis. Biphenyl was utilized as internal standard for GC analysis.

Synthesis of bis-(cyclooctadiene)rhodium(I) tetrafluoroborate: In an N_2 -filled glovebox, a dry flask with stirbar was charged with AgBF_4 (242 mg, 1.2 mmol, stored under N_2) and roughly 10 mL of THF (stored under N_2). The flask was sealed and removed from the glovebox and, via cannula, was transferred into a Schlenk tube (dry, under N_2) containing a stirring THF solution of $[\text{Rh}(\text{COD})\text{Cl}]_2$ (300 mg, 0.61 mmol). Stirring for 1.5 hours, a yellow precipitate was observed to form. An oven-dried Schlenk filter with added Celite was used to remove precipitate and transfer filtrate to a second oven-dried Schlenk with stirbar under standard Schlenk conditions. While stirring, 1.5 mL of previously distilled and de-oxygenated COD was added via syringe, causing dark reddish precipitate to crash out of solution. The mixture was stirred for a further 2.5 hours before removing THF solvent under vacuum overnight. The remaining reddish precipitate was quickly scraped into a dry vial and brought into the glovebox.

Synthesis of d_3 - α,β -4-chlorostyrene 2-8:

d_3 -4-chloroacetophenone. A flame-dried flask equipped with a reflux condenser under dry nitrogen flow was charged with sodium metal (20 mmol, 450 mg). The metal was dissolved through the slow addition of 5 mL D_2O , followed by dilution with D_2O to 45 mL. Freshly distilled 4-chloroacetophenone (60 mmol, 9.3 g) was added to the basic D_2O solution. The flask was then placed in an oil bath and heated under stirring at reflux for 24 hours. An aqueous workup with Et_2O , followed by drying of the organic solution with $MgSO_4$ furnished the deuterium exchange product in 92% yield and greater than 96% deuterium incorporation. 1H -NMR ($CDCl_3$, 400 MHz): δ 2.53, (br, 0.04H, trace H of CD_3), 7.42 (d, 2H, J 8.8 Hz), 7.86 (d, 2H, J 8.8 Hz).

d_4 -1-(4-chlorophenyl)ethanol. A dry flask under dry nitrogen flow was charged with 100 mL of dry distilled Et_2O . To the solvent, $LiAlD_4$ was carefully added (83 mmol, 3.5 g). The flask was then placed in an ice bath under stirring while d_3 -4-chloroacetophenone (55 mmol, 8.6 g) was slowly added to the reducing solution. A dry reflux condenser was then attached to the flask, which was subsequently refluxed for 16 hours. The product was obtained in 96% yield after aqueous NH_4Cl quench and extraction. The product, a colourless oil, was submitted directly to next step in synthesis. 1H -NMR (CD_2Cl_2 , 400 MHz): δ 1.49 (s, br, 0.03H, trace H on CD_3), 4.85 (br, 0.008H, trace H on benzylic C), 7.23 (s, 4H)

d_4 -1-(4-chlorophenyl)bromoethane. A sample of d_4 -1-(4-chlorophenyl)ethanol from the previous step (39 mmol, 6.2 g) was mixed with pyridine (1 mmol, 0.8 mL) in 160 mL of CH_2Cl_2 in a dry flask under dry nitrogen flow. The solution was stirred in a methanol-ice bath at $-10^\circ C$. A dropper funnel charged with phosphorous tribromide (60 mmol, 5 mL) in 80 mL of CH_2Cl_2 was attached to the flask, and was added slowly over a period of 20

minutes. The reaction was left to stir 16 hours to room temperature, and then quenched with a saturated NaHCO₃ solution. Workup in CH₂Cl₂ and drying of the collected organic layer with MgSO₄, followed by removal of the solvent in vacuo furnishes the product as a light yellow oil (94% yield).

*d*₃-4-chlorostyrene **2-8**. To a two-neck flask containing *tert*-butanol (50 mL) and THF (85 mL), potassium *tert*-butoxide (67 mmol, 7.5 g) was added. A dropper funnel containing *d*₄-1(4-chlorophenyl)bromoethane (37 mmol, 8.3 g) in 40 mL THF was attached to one neck of the flask and a reflux condenser was fastened to the other. Under a nitrogen atmosphere, the flask was brought to reflux at 75 °C and the reactant was added over a period of 30 minutes. The reaction was refluxed for 16 hours, then cooled. Workup in brine furnishes a red-orange oil after concentration of organic layer. The crude oil was further purified by silica column chromatography, and eluted with petroleum ether. Collected fractions were concentrated to yield pure product, a colourless oil that was bulb-to-bulb distilled and stored in the glovebox fridge at -20 °C (1.33 g, 25% yield). ¹H-NMR (CD₂Cl₂, 400 MHz): δ 5.28 (br, 0.028H, trace H on olefinic C; β-transoid), 5.82 (br, 0.028H trace H on olefinic C; β-cisoid), 6.75, (br, 0.008H, trace H on olefinic α-C), 7.34 (d, 2H, *J* 8.5 Hz), 7.54 (d, 2H, *J* 8.5 Hz).

Kinetic treatment: As relatively little is known regarding the mechanism and kinetics of the catalyzed hydroboration reaction and how they vary with change in substrate, catalyst ligand, and/or hydroborating reagent, the rate formulas were hypothesized (equations 2-10 and 2-11). Note that 4-chlorostyrene is used as an example substituted styrene in these equations:

$$\frac{dP_R}{dt} = k_R [\text{borane}] [4\text{-chlorostyrene}] [\text{catalyst}] \quad (\text{eq. 2-10})$$

$$\frac{dP_H}{dt} = k_H [\text{borane}] [\text{styrene}] [\text{catalyst}] \quad (\text{eq. 2-11})$$

Thus, when the theoretical rate expression for the substituted styrene is divided by that of the un-substituted styrene in equation 2-12, all common terms in the competition reaction cancel:

$$\frac{dP_R}{dP_H} = \frac{k_R}{k_H} \cdot \frac{[4\text{-chlorostyrene}]}{[\text{styrene}]} \quad (\text{eq. 2-12})$$

Because both substrates are present in the same amount of solvent THF, the concentration ratio simplifies to the molar ratio between the added styrene and substituted styrene. The dP terms simplify to the amount of each observed product alcohol, which allow the k_{rel} term to be derived in equation 2-13:

$$k_{rel} = \frac{k_R}{k_H} = \frac{rel.yieldP_R}{rel.yieldP_H} \cdot \frac{n_{(styrene)}}{n_{(4\text{-chlorostyrene})}} \quad (\text{eq. 2-13})$$

Yields were calculated based on signal area ratios between the branched alcohol peaks and that of the external standard, which were then input to the specific standard curves for the alcohols obtained to yield concentration ratios. These values were at first transformed to mass yields by multiplying the ratio by the existing concentration of external standard in

the sample. Then, the ratio of the mass yield (p-X/p-H) was taken and multiplied by the inverse ratio of their molecular weights (p-H/p-X). However, it proved simpler and mathematically equivalent to take the ratio of the calculated concentration ratios for a given competition reaction, as both branched product peaks were relative the same external standard peak. Thus, the concept of analysis remained the same but allowed simpler calculation of k_{rel} .

Labeling Studies

General considerations. All reactions were conducted under inert N₂ atmosphere in a dry glovebox. Quantitative ¹H-NMR analysis of purified products and recovered starting material were conducted on a 400MHz Bruker Avance spectrometer in which D1 relaxation time was set to 10 seconds and number of scans was set to 32.

Representative treatment of labeling experiments. A vial was charged with [Rh(COD)₂]₂BF₄ (1 mol%, 4.7 mg, 0.01 mmol, stored cold in glovebox) and (*S*)-QUINAP (1.5 mol%, 6.6 mg, 0.015 mmol, stored at r.t.). The solid was then dissolved in 1 mL of THF and let sit for 10 minutes, forming a red homogenous solution. *d*₃-4-chlorostyrene (1 mmol, 138.59 mg) substrate was weighed in a separate small vial then transferred to the catalyst solution via pipette; the vial was washed with 1 mL of THF and transferred. After 10 minutes, HBPin (0.1 mmol, 12.80 mg) was added in the same manner as the styrenes for a total solution volume of 4 mL. The reaction vial was sealed and left in the glovebox for 24 hours, at which time the reaction was removed for oxidation, workup, and purification.

Representative oxidation and purification of labeling experiments. The reaction vial was placed in an ice bath and 1 mL of 2M NaOH and 1 mL of 30% H₂O₂ was added. The

solution was stirred as the bath warmed to r.t. for 3 hours. 5 mL of saturated aqueous NaCl solution was added. The reaction was worked up in 3x15 mL of petroleum ether, where the organic layer was collected and concentrated in vacuo. The resultant crude oil, which contained recovered styrene, reduced product, and alcohol products, was further purified by column chromatography. Non-polar starting material **2-8** and reduced product **2-11** were co-eluted in petroleum ether, resulting in a colourless oil after concentration in vacuo. Alcohol products **2-9** and **2-10** were co-eluted in 7:1 hexanes:ethyl acetate and concentrated in vacuo. Isolated yields of alcohols products were calculated based on the isolated mass of the product pair corrected based on molar ratio of the product mix by quantitative ¹H-NMR.

Label incorporation. Proton integrations were corrected for trace proton in the starting material before reaction. For product alcohols, label incorporation was quantified based on isolated yield. Proton label was integrated as a ratio at α and β positions against an aromatic proton peak for the corresponding alcohol. Percent label incorporation at each position was calculated based on the amount of proton label added to the reaction. As full recovery of volatile styrene and reduced product was not possible, the relative proton label incorporation at each position for these two compounds was quantified based on assumed full recovery of styrene.

2.6 References

¹ Hayashi, T.; Matsumoto, Y.; Ito, Y. *J. Am. Chem. Soc.* **1989**, 111, 3426-3428.

² Doucet, H.; Fernandez, E.; Layzell, T.P.; Brown, J.M. *Chem. Eur. J.* **1999**, 5, 1320-1330.

³ Evans, D.A.; Fu, G.C.; Anderson, B.A. *J. Am. Chem. Soc.* **1992**, 114, 6679-6685.

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- ⁴ Edwards, D.R.; Hleba, Y.B.; Lata, C.J.; Calhoun, L.A.; Crudden, C.M. *Angew. Chemie. Int. Ed.* **2007**, 46, 7799-7802.
- ⁵ Hayashi, T.; Matsumoto, Y.; Ito, Y. *Tetrahedron: Asymm.* **1991**, 2, 601-612
- ⁶ Fryzuk, M.D.; McConville, D.H.; Rettig, S.J. *J. Organomet. Chem.* **1993**, 445, 245-256.
- ⁷ Bleuel, E.; Schwab, P.; Laubender, M.; Werner, H. *J. Chem. Soc., Dalton Trans.* **2001**, 266-273.
- ⁸ Crudden, C.M.; Hleba, Y.B.; Chen, A.C. *J. Am. Chem. Soc.* **2004**, 126, 9200-9201.
- ⁹ Black, A.; Brown, J.M.; Pichon, C. *Chem. Commun.* **2005**, 5284-5286.
- ¹⁰ Isaacs, N. *Physical Organic Chemistry*, Longman Group, London **1998**. Chapter 4, pages 163-164.
- ¹¹ Apeloig, Y.; Nakash, M. *J. Am. Chem. Soc.* **1996**, 118, 9798-9799.
- ¹² Denmark, S.E.; Bui, T.; *J. Org. Chem.* **2005**, 70, 10393-10399.
- ¹³ Note: raw data for Hammett plot for styrene derivative competitions were extracted from the Ph.D. thesis of Dr. David R. Edwards published at Queen's University, August 2007.
- ¹⁴ Singleton, D.A.; Thomas, A.A. *J. Am. Chem. Soc.* **1995**, 117, 9357-9358.
- ¹⁵ Harrison, K.N. and Marks, T.J. *J. Am. Chem. Soc.* **1992**, 114, 9220-9221.
- ¹⁶ Evans, D.A.; Muci, A.R.; Stürmer, R. *J. Org. Chem.* **1993**, 58, 5307-5309.
- ¹⁷ Segarra, A.M.; Daura-Oller, E.; Claver, C.; Poblet, J.M.; Bo, C.; Fernández, E. *Chem. Eur. J.* **2004**, 10, 6456-6467.
- ¹⁸ Fristrup, P.; Jensen, G.H.; Anderesen, M.L.N.; Tanner, D.; Norrby, P.-O. *J. Organomet. Chem.* **2006**, 691, 2182-2198.

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- ¹⁹ Yamataka, H.; Nagareda, K.; Takai, Y.; Sawada, M.; Hanafusa, T. *J. Org. Chem.* **1988**, *53*, 3877-3879.
- ²⁰ Hansch, C.; Leo, A.; Taft, R.W. *Chem. Rev.* **1991**, *91*, 165-195.
- ²¹ Halpern, J.; Okamoto, T. *Inorg. Chim. Acta.* **1984**, *89*, L53-L54.
- ²² Fristrup, P.; Kreis, M.; Palmelund, A.; Norrby, P.-O.; Madsen, R. *J. Am. Chem. Soc.* **2008**, *130*, 5206-5215.
- ²³ Shen, Z.; Dorman, P.K.; Khan, H.A.; Woo, T.K.; Dong, V.M. *J. Am. Chem. Soc.* **2009**, *131*, 1077-1091.
- ²⁴ Watkins, A.L.; Hashiguchi, B.G.; Landis, C.R. *Org. Lett.* **2008**, *10*, 4553-4556.
- ²⁵ Constantine, R.N.; Kim, N.; Bunt, R.C. *Org. Lett.* **2003**, *5*, 2279-2282.
- ²⁶ Hleba, Y.B.; Crudden, C.M. Unpublished results
- ²⁷ Brown, J.M.; Lloyd-Jones, G.C. *J. Am. Chem. Soc.* **1994**, *116*, 866-878.
- ²⁸ Full recovery of deuterated styrene after labeling reactions was not possible. As such, the relative proton incorporation to the partially recovered starting material was quantified by assuming full mass recovery and complete conversion of the borane.

Chapter 3 – Lewis Acid Mediated Rhodium Catalyzed Hydroboration

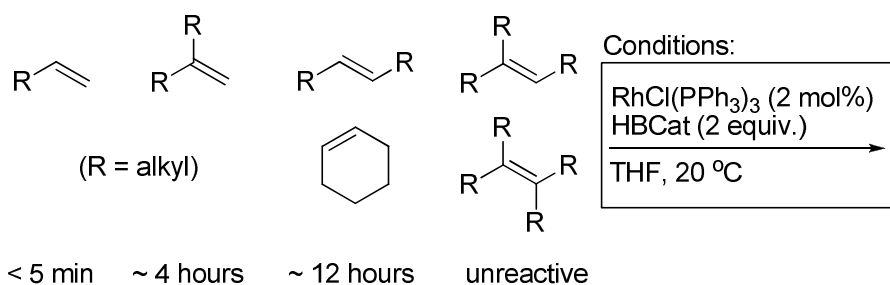
3.1 Introduction

The rhodium catalyzed hydroboration reaction presents an extremely powerful means with which to create organoboron compounds, which find can be used to generate molecules of greater complexity in a wide array of secondary transformations.^{1,2} These reactions often yield chemo, regio, and stereoselectivity that is complimentary to the uncatalyzed hydroboration, expanding the scope of the hydroboration reaction as a whole.^{3,4}

Although the Rh catalyzed reaction⁵ is itself highly tunable with respect to selectivity through careful choice of the ligand and reagent,⁶ there are still limitations to the scope of substrates that may be utilized. Thus, many challenges in this regard remain to be overcome. For example, olefins that are polysubstituted as in Figure 3-1 are markedly less reactive than terminal olefins, as indicated by the increased reaction times required to affect full conversion.⁷ The low reactivity these substrates display with reagents such as HBCat is exacerbated with the less reactive hydroborating reagent HBPIn. As already discussed in Section 1.4, when HBPIn is employed, internal olefins are isomerized by reversible hydride insertions and β -hydride eliminations,^{8,9,10} likely because reductive elimination of the alkyl-BPin moiety is kinetically much slower than beta hydride elimination in the case of a secondary alkyl unit. Thus, a linear boronate ester is typically obtained through reductive elimination from the less hindered primary

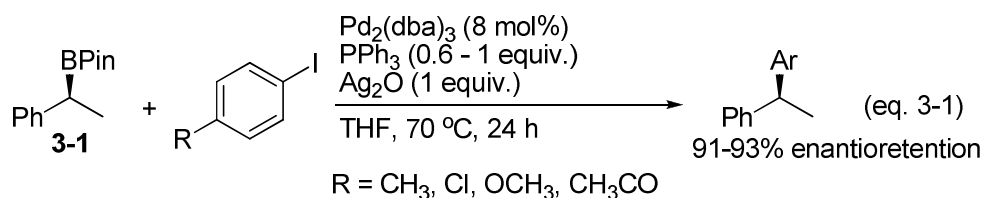
carbon at the terminus of an alkyl chain, representing a loss of the original regioselectivity of the starting olefin.¹¹

Figure 3-1: Relative Rates of Wilkinson's Catalyzed Hydroboration⁷

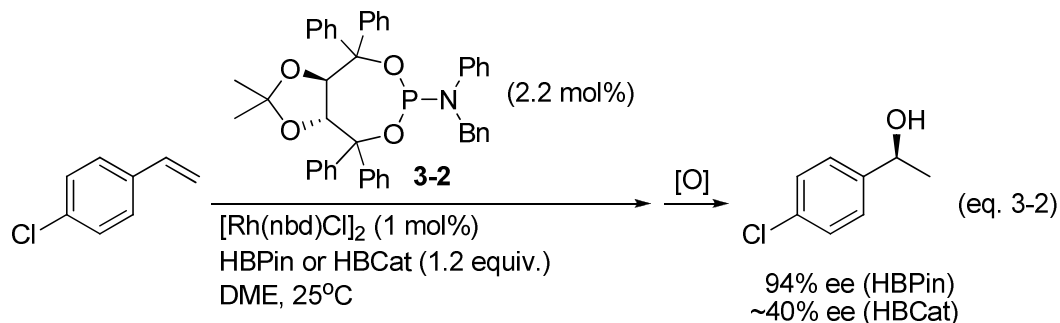


Although this change in selectivity observed in Rh catalyzed reactions with HBPIn versus HBCat has found utility in the conversion of olefin mixtures to pure linear products,¹⁰ the development of a method for the hydroboration of internal olefins with retention of regiochemistry with HBPIn is desirable. This is due to the low yields observed with HBCat in the case of internal olefins, and the fact that HBPIn is significantly easier to handle than HBCat. For example, HBCat is degraded both thermally and by the presence of free phosphine,^{6,12} generating the undesirable and highly reactive BH₃. The production of BH₃ is a serious complication, since it can hydroborate olefinic substrates in a non-catalyzed fashion, which can affect regio and enantioselectivity. Furthermore, the pinacol boronate ester products obtained from catalyzed HBPIn hydroboration are much more stable than the analogous catechol boronate esters, being both air and water stable, as well as amenable to purification by column chromatography. Because of this, HBPIn has been utilized extensively by our group^{6,10} and by the groups of Westcott,¹³ Miyaoura,^{14,15} and Gevorgyan.¹⁶

Although pinacol boronates may be obtained from catechol derivatives through a pinacol quench,¹⁷ HBPIn generates these products directly in a more efficient and atom economical manner. Recently, secondary pinacol boronates such as **3-1** have been utilized in sp^2 - sp^3 Suzuki-Miyaura cross coupling with high enantio-retention of the substrate, equation 3-1.¹⁸ The successful reaction of secondary sp^3 carbon centers, which has previously posed a challenge in cross coupling reactions, adds significant value to pinacol boronates as substrates in fine chemical synthesis.



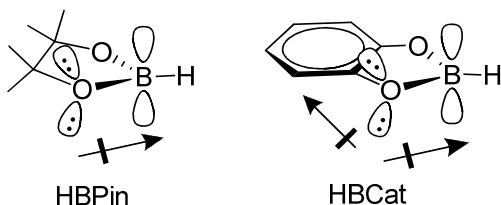
Even in asymmetric Rh catalyzed hydroboration, the use of HBPIn generates higher enantioselectivities in some case than the corresponding conditions applied with HBCat.^{6,19} For example, the Takacs group has applied phosphoramidite ligand **3-2** in the hydroboration of 4-chlorostyrene, achieving an enantiomeric excess of 94% using HBPIn in equation 3-2.¹⁹ However, the same conditions applied with HBCat result in a drastic decrease in enantioselectivity to roughly 40%.



The promising advances made in both Rh-catalyzed hydroboration with HBPIn and the applications of its products make expanding the breadth of reactivity with this reagent highly desirable. Perhaps the most limiting factor precluding more widespread use of pinacolborane is its inability to affect the hydroboration of internal olefins with retention of the original substrate regiochemistry. Thus, the development of catalytic methodologies that would allow direct hydroboration without olefin isomerization is highly valuable.

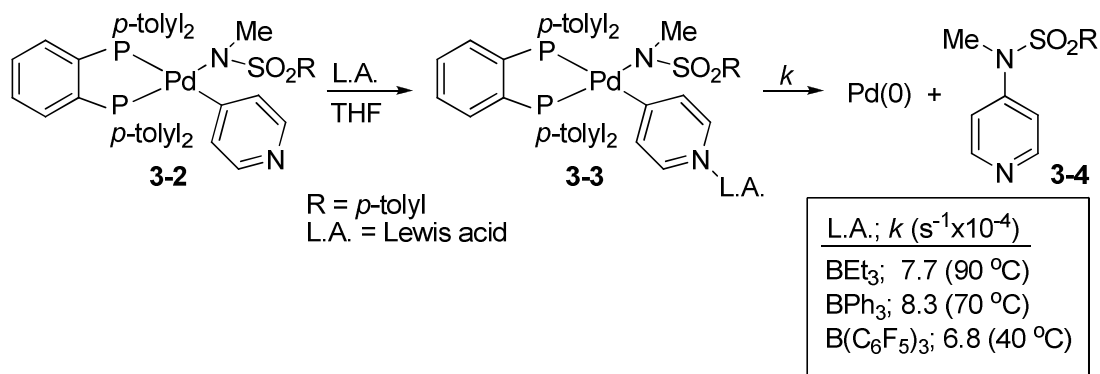
Several factors were considered with this goal in mind. With internal alkyl olefins, catalysis using HBPIn involves reductive elimination as the most likely rate determining step, which is indicated by the observed isomerization to linear product as well as by deuterium labeling studies.^{10,20} Thus, in order to increase the regioselectivity of the reaction, it would seem reasonable to target a means by which either reductive elimination could be accelerated or β -hydride elimination could be inhibited. HBCat proceeds to hydroborate internal disubstituted olefins directly without isomerization under Wilkinson's catalyzed conditions,⁷ indicative of a faster reductive elimination such that β -hydride elimination does not occur. The reasons for this can be considered to be two-fold. First, the planar catechol backbone of HBCat is significantly less sterically hindered, which may facilitate reductive elimination at a secondary carbon compared to the much more bulky HBPIn. Secondly, HBCat is significantly more reactive than HBPIn.¹¹ This is due in part to the hindered nature of HBPIn, but also due to the fact that the lone pairs of electrons on oxygen are donating both into the π system of the aromatic ring and also the p-orbital of boron in the case of catechol borane, as indicated in Figure 3-2.

Figure 3-2: Electronic Differences in HBPIn and HBCat



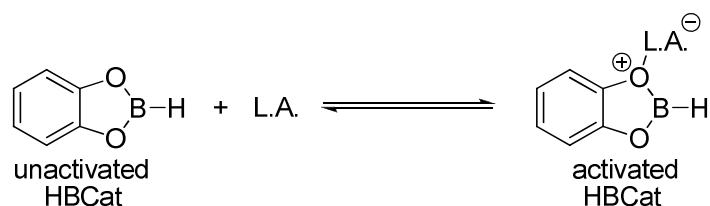
Thus, it was the initial aim of the project to attenuate the Lewis acidity of the boron atom of HBPIn in an attempt to increase the reactivity, and subsequently, the regioselectivity of reactions with this reagent. The use of Lewis acidic reagents has precedent in the literature in the acceleration of reductive elimination.^{21,22} For example, Hartwig reported the acceleration of Pd-catalyzed amination of pyridyl compounds via the addition of boron-based Lewis acids.²² Using stoichiometric amounts of the precursor to reductive elimination **3-2**, kinetic studies were carried out which showed that the rate of reductive elimination was accelerated by the addition of the Lewis acid. As the Lewis acid is made more electrophilic by the use of stronger electron withdrawing groups on the boron, the rate of reductive elimination to the amination product **3-4** is accelerated. The added Lewis acid was found to bind the lone pair electrons of the pyridyl nitrogen in complex **3-3**.

Figure 3-3: Lewis Acid Enhanced Reductive Elimination²²



Evans and co-workers have shown that lanthanides such as SmI_3 can catalyze the hydroboration reaction in the absence of transition metals.²³ They propose the activation of the borane through a reversible complexation of the lanthanide as a Lewis acid adduct, shown in Scheme 3-1, as one possibility for the mechanism of action of the Lewis acid.

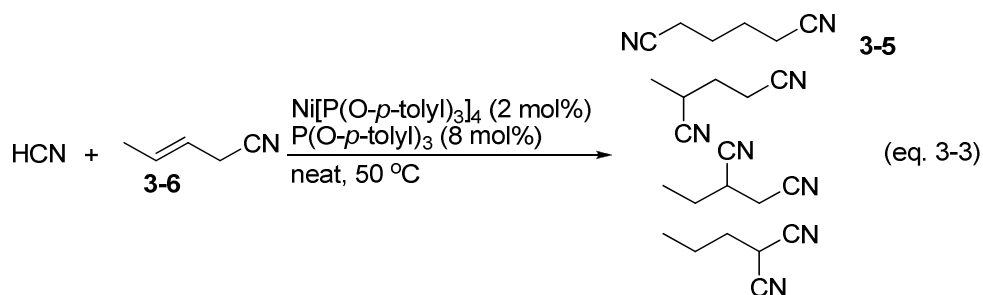
Scheme 3-1: Proposed Activation of Catecholborane²³



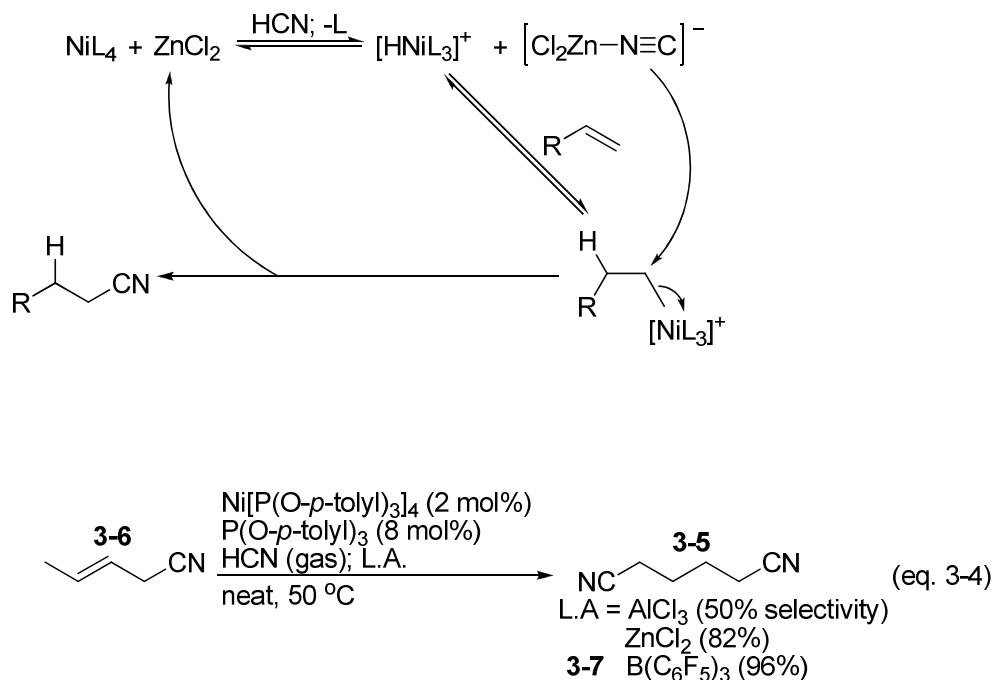
3.2 Lewis Acids in Catalysis

The notion that the use of a Lewis acid could be beneficially modified for a more regioselective reaction in catalyzed hydroboration prompted an investigation into other instances in the literature involving similar strategies. Lewis acids have been

successfully utilized as additives or catalysts in various reactions in order to improve their properties.²⁴ Perhaps one of the most well known examples is the hydrocyanation of olefins, a process that can be catalyzed by nickel complexes primarily for the generation of adiponitrile **3-5** for downstream use in the manufacture of nylon.²⁵ The process involves the hydrocyanation of 3-pentenitrile **3-6** with a nickel catalyst ligated by triphenylphosphite, which normally yields a mixture of isomeric dinitrile products through isomerization of the olefin, equation 3-3.²⁶ However, it was discovered that the addition of a Lewis acid both accelerated the reaction as well as increased the selectivity for the desired product **3-5**.²⁷ The proposed mechanism involves Lewis acid association to hydrogen cyanide via the nitrogen atom, weakening the C-H bond and allowing protonation of the nickel catalyst. The cyanide anion is stabilized by the Lewis acid and is hypothesized to attack the substrate following protonation by formally cationic nickel, as shown in Scheme 3-2 with ZnCl₂ as the Lewis acid. It was later confirmed that the selectivity enhancement observed through Lewis acid addition originates from its steric bulk, since nucleophilic attack of the cyanide anion at secondary carbon centers is hindered.²⁶ As shown in equation 3-4, the use of progressively bulkier Lewis acids yields corresponding increases in the desired hydrocyanation to produce **3-5**, where the best selectivity was obtained with tris(pentafluorophenyl)boron **3-7**.



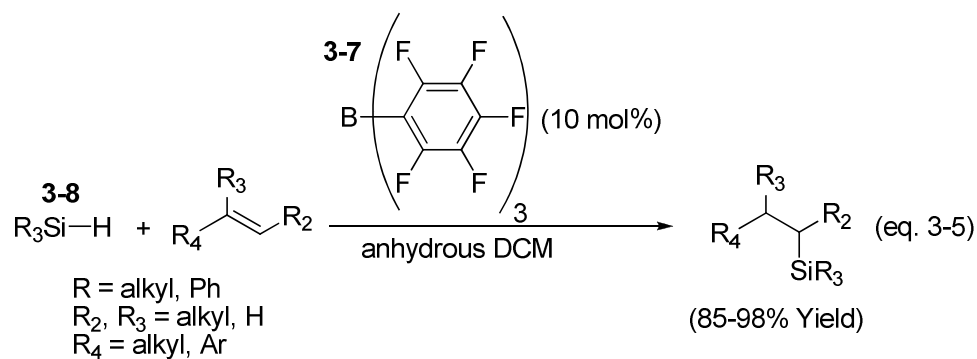
Scheme 3-2: Mechanism of Lewis Acid Mediated Hydrocyanation



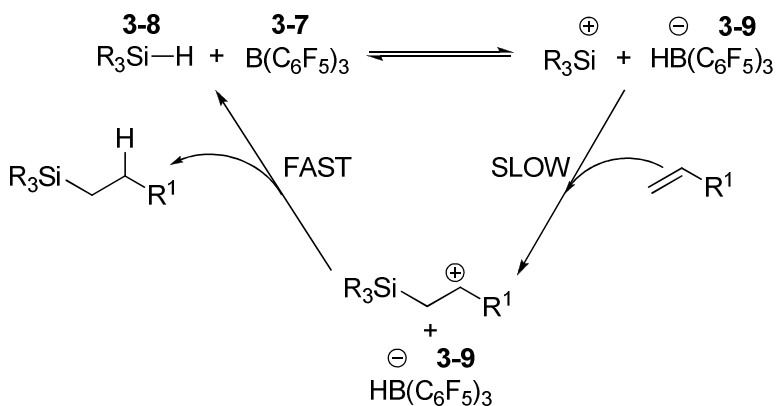
Although it is steric bulk that changes the selectivity, it is interesting that this modification causes the heterolytic dissociation of the C-H bond in hydrogen cyanide, resulting in the reduction of the olefin substrate in two steps involving the Ni^+ species and the Lewis acid adduct of the cyanide anion.

Heterolytic cleavage of an H-E bond, where E is a main group organometallic, by Lewis acids has also been reported by Piers²⁸ and Gevorgyan.²⁹ This reactivity results in the hydrosilylation of carbonyl and olefin moieties with silanes, respectively. Again, Lewis acid **3-7**, which has come to be known as FAB, was the optimal catalyst. However, in this method of hydrosilylation, **3-7** is the only catalyst required to affect conversion to silylated product, as shown in equation 3-5. The mechanism of catalysis, which was elucidated by insightful deuterium labeling experiments, involves the

heterolytic cleavage of the Si-H bond of the silane reagent **3-8**, forming the corresponding borohydride **3-9** of FAB and a silylium cation (Scheme 3-3).²⁹



Scheme 3-3: Mechanism of FAB Catalyzed Hydrosilylation of Olefins

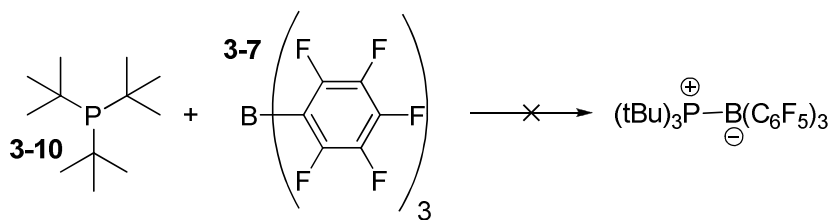


Aside from FAB catalyzed hydrosilylation, this Lewis acid and related analogues have also found utility in the field of frustrated Lewis acid-base chemistry. This emerging area of chemistry has primarily been developed by the research group of Stephan,³⁰ and involves the use of sterically bulky, or frustrated Lewis acid-base pairs, FLPs. The original theory behind this chemistry, which has been recently amended to include equilibrium processes (Scheme 3-4),³¹ is that if both moieties are sufficiently

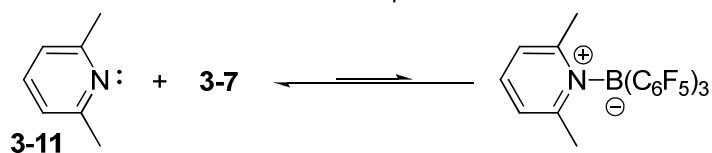
bulky, then the normal and expected adduct formation cannot occur, allowing free Lewis acid and Lewis base to exist in the same solution.

Scheme 3-4: Sterically Bulky Lewis Acid-Base Pairs

Steric bulk precludes adduct formation:

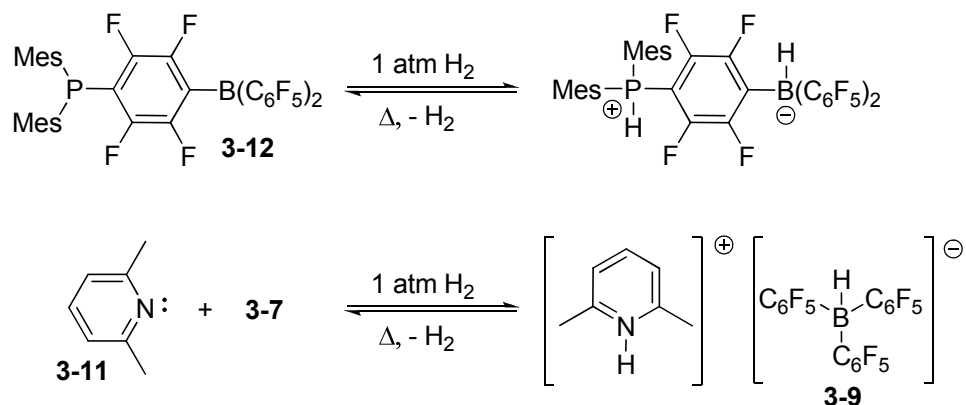


Steric bulk creates adduct-disfavoured equilibrium:

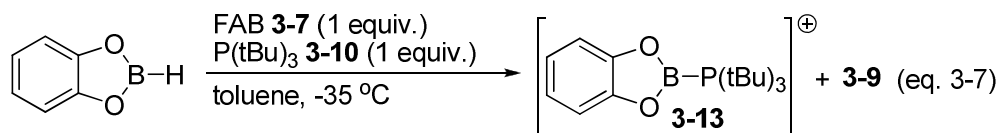
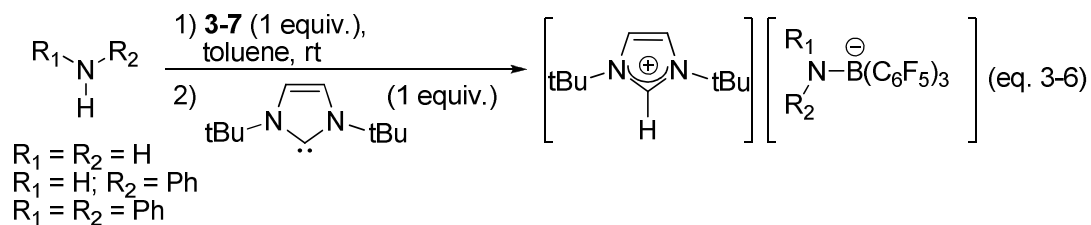


As shown in Scheme 3-4, the reaction of bulky phosphine **3-10** with FAB does not yield an adduct. Similarly, analogue **3-12**, which contains both Lewis acidic and basic moieties on the same molecule do not interact to form adducts.³² Interestingly, these FLPs show unique reactivity in the reversible heterolytic activation of dihydrogen, Scheme 3-5.^{31,32} This metal free cleavage of hydrogen can be coupled to the hydrogenation of unsaturated compounds such as imines, nitriles, and azridines.³³ Furthermore, in some cases, hydrogenation of imines requires only FAB in catalytic quantities, as the imine substrate itself acts as the bulky Lewis base.³⁴

Scheme 3-5: Reversible Hydrogen Activation by FLPs



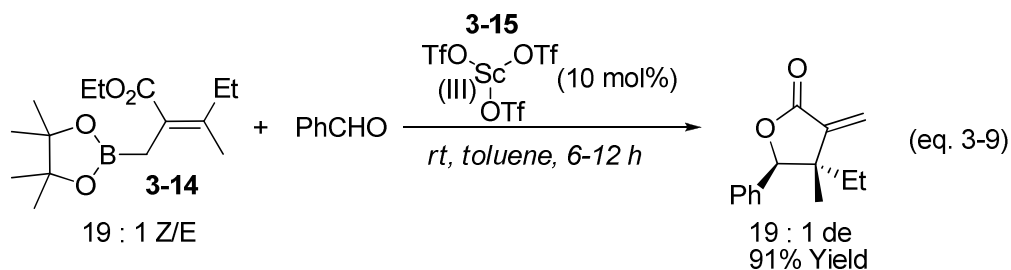
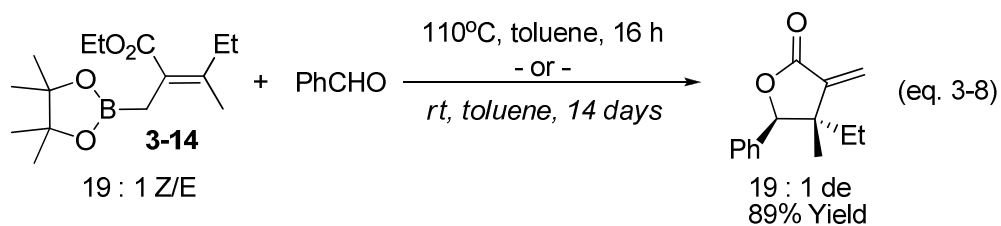
In addition to the FLPs discussed above, both bulky amines³⁵ and N-heterocyclic carbenes³⁶ may be used as Lewis base partners with FAB in the activation of dihydrogen. However, the substrate scope of this bond cleaving methodology is not limited to the H-H bond. Bulky carbenes and FAB can also directly cleave the N-H bond of various amines, equation 3-6.³⁶ Furthermore, and perhaps of most utility to hydroboration, the heterolytic cleavage of the B-H bond of HBCat has been described using FLP methodology. Specifically, tri-*tert*-butylphospine **3-10** and FAB (**3-7**) facilitate the heterolysis of HBCat in equation 3-7 to the corresponding borohydride **3-9** and a phosphine stabilized borenium cation **3-13** as shown in equation 3-7.³⁷ Presently, the N-H and B-H bond activations are not catalytic in reactions that generate a new organic product whilst re-generating the FLP. However, these unsymmetrical bond cleavages indicate the potential of this methodology to activate B-H bonds.



The cleavage of the B-H bond is particularly astonishing in that boryl cations are typically very unstable.^{38,39} However, sufficient stabilization by an appropriate Lewis base allows FAB to fully extract a hydride from HBCat. An earlier example of borenium ion formation from BCl₃ with 4-methylpyridine as a Lewis acid and aluminum trichloride as a Lewis acid was reported, where chloride rather than hydride abstraction from boron was observed to take place.⁴⁰

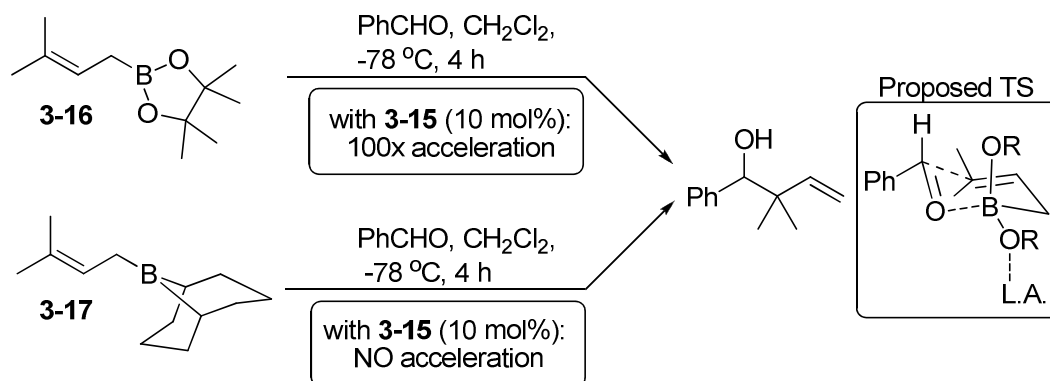
Although FLP chemistry with boron Lewis acids is a growing field, other Lewis acids continue to find new application in the improvement of existing reactions. Of particular note to reactions involving boron is allylboration. Typically, allylic pinacol boronates such as **3-14** containing highly substituted olefins require extended reaction times up to 14 days for full conversion, equation 3-8.^{41,42} However, if a catalytic amount of scandium triflate **3-15** is added to the reaction, complete conversion is observed in mere hours while maintaining the selectivity of the uncatalyzed reaction, equation 3-9.^{41,43} Many metal triflates, as well as classical Lewis acids such as aluminum trichloride were screened in this reaction by Hall⁴¹ but found to be inferior to **3-15**. Similar results

were reported by Miyaura,⁴⁴ although chiral ligated scandium Lewis acids were found to be inactive.



$\text{Sc}(\text{OTf})_3$ is very oxophilic,⁴⁵ however the mode of activation is proposed to involve binding of the Lewis acid to an oxygen atom of the allylic pinacolboronate ester and not the carbonyl oxygen of aldehyde in these reactions, as is shown in Scheme 3-6. Whereas the reaction of boronate ester **3-16** with benzaldehyde is accelerated by **3-15**, $\text{Sc}(\text{OTf})_3$ has no effect on the allylborane analogue **3-17**, which does not have an oxygen substituent.^{41,46}

Scheme 3-6: Observed Acceleration of Allylboration with Scandium Triflate⁴⁷



Clearly, Lewis acids have diverse utility in catalysis, and may play many roles as either co-catalytic additives or as catalyst in their own right. From our point of view, the ability of Lewis acids to affect B-H bond activation of HBCat, a common reagent in hydroboration, and the acceleration of the allylboration reaction by association of Sc(OTf)₃ to oxygen in the pinacol backbone of the substrate are both key facts. For this reason, we explored the use Lewis acid additives in Rh catalyzed hydroborations with HBPIn.

3.3 Lewis Acid Mediated Rhodium Catalyzed Hydroboration

3.3.1 Initial Results and Optimization

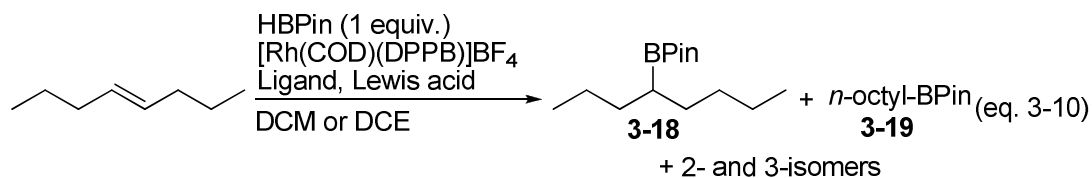
The notable and inspiring effects of Lewis acids reported by Hall⁴¹ and Miyaura⁴⁴ in allylboration with boronic esters, as well as the effect of SmI₃ reported by Evans²³ in hydroboration prompted the exploration of Lewis acids in the Rh catalyzed hydroboration reaction. Scandium triflate **3-15** was examined first in the hydroboration of *trans*-4-

octene as shown in equation 3-10. The reactions were originally attempted in THF, however, the combination of $\text{Sc}(\text{OTf})_3$ with the cationic Rh catalysts employed in the study led to solvent polymerization. Therefore, the reactions were carried out in dichloromethane (DCM) or dichloroethane (DCE). Interestingly, in these solvents, the Rh complexes employed ($[\text{Rh}(\text{COD})_2]\text{BF}_4/\text{DPPB}$ and $[\text{Rh}(\text{COD})(\text{DPPB})]\text{BF}_4$) do not catalyze hydroboration, Table 3-1, entry 1. However, to our delight, the addition of 2 mol% of $\text{Sc}(\text{OTf})_3$ generated an active catalyst that furnished the linear boronate ester product **3-19** as the major product, with minor amounts of 2-, 3-, and 4-isomers (entry 2). As the amount of $\text{Sc}(\text{OTf})_3$ was increased a greater proportion of the desired branched isomer **3-18** was observed. At an 8 mol% loading of Lewis acid, roughly equal amounts of the direct hydroboration product and linear **3-19** were present (entry 4). Unfortunately, due to the poor solubility of $\text{Sc}(\text{OTf})_3$, the loading could not be reliably increased above this level. However, this result prompted a screen of other ligands in order to optimize the reaction for regioselectivity. Several bidentate phosphine ligands were screened, and it was found that DPPB gave the best selectivity for **3-18** at a Lewis acid loading of 2 mol% (entry 5).

Rather than forming the precatalyst *in situ*, a pre-ligated Rh catalyst, $[\text{Rh}(\text{COD})(\text{DPPB})]\text{BF}_4 \cdot \text{THF}$ **3-20**, was synthesized and found to give identical selectivity (entry 6). This simplified the procedure and ensured a 1:1 stoichiometry between the Rh and DPPB. Finally, reactions conducted with catalytic amounts of either $\text{Sc}(\text{OTf})_3$ (entry 9) and FAB (entry 10) in the absence of Rh catalyst did not promote the hydroboration reaction. These important controls rule out a mechanism such as that reported for FAB-

catalyzed hydrosilylation of olefins and carbonyl substrates,^{28,29} as discussed in Section 3.2.⁴⁸

Table 3-1: Effect of Lewis Acids on the Regioselectivity of Rh Catalyzed Hydroboration^a



Entry	Ligand	Lewis acid, Mol%	Branched : Linear (3-18 : 3-19)	Yield (%) ^b
1	PPh ₃ or DPPB	0	—	0
2	PPh ₃	Sc(OTf) ₃ , 2 %	17 : 83	65
3	PPh ₃	Sc(OTf) ₃ , 4%	34 : 66	55
4	PPh ₃	Sc(OTf) ₃ , 8%	53 : 47	71
5	DPPB	Sc(OTf) ₃ , 2%	88 : 12	81
6	DPPB ^c	Sc(OTf) ₃ , 2%	87 : 13	92
7	DPPB ^c	FAB, 2%	92 : 8	99
8	DPPB ^c	FAB, 2%	98 : 2	94 ^d
9	— ^e	Sc(OTf) ₃ , 2%	—	0
10	— ^e	FAB, 2%	—	0

^[a] Reaction conditions: 1 mol% Rh catalyst, 1.5 mol% ligand, 0.1 M, 30 °C, 24 h, nitrogen atmosphere.

^[b] GC Yields vs. internal standards. Approx. 15% 2- and 3-isomers detected except in entry 8 where only 7% of the 3-isomer was observed. ^[c] Preformed [Rh(COD)(DPPB)]BF₄•THF employed.

^[d] Temp = - 20 °C, 9 h. ^[e] No Rh catalyst.

With an optimal catalyst, other Lewis acids were screened for both selectivity as well as activity (Table 3-2). Most Lewis acids tested gave **3-18** as the major product, although yields varied. Interestingly, the most active and selective co-catalyst was found to be FAB **3-7** (Table 3-1, entries 7, 8), in which the reaction was observed to go to completion in roughly 30 minutes (Table 3-2, entry 2). Furthermore, a **3-18** to **3-19** ratio of 62:1 was observed when the reaction was cooled to -20 °C (entry 3). Unlike Sc(OTf)₃, the solubility of **3-7** was not a problem. Most importantly, however, was the observation that neither Sc(OTf)₃ nor FAB was able to catalyze the hydroboration in the absence of the Rh catalyst (Table 3-1, entries 9, 10). This was a crucial control to run, given the FAB-catalyzed hydrosilylation of both carbonyl and olefinic compounds discussed in Section 3.2.^{28, 29}

Table 3-2: Lewis Acid Screen in Hydroborations with [Rh(COD)(DPPB)]BF₄•THF^a

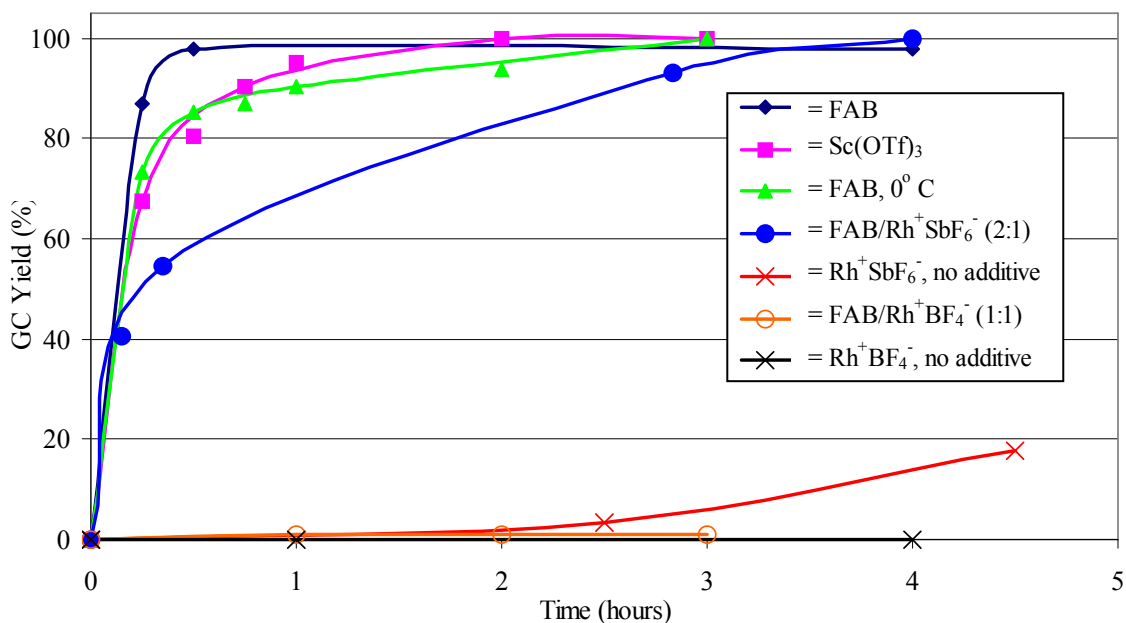
Entry	Lewis Acid	Reaction Time (hours)	Yield (%) ^b	Product Distribution (%)			
				3-18	3-isomer	2-isomer	3-19
1	Sc(OTf) ₃	5	92	77	14	3	10
2	FAB	0.5	99	91	14	2	7
3	FAB ^c	9	94	71	6	1	2
4	La(OTf) ₃	20	99	64	14	3	12
5	Y(OTf) ₃	17	<5	78	7	7	22
6	Zn(OTf) ₂	90	15	24	11	3	8
7	AlCl ₃	50	2	24	1	11	64

^[a] Same conditions as in Table 3-1; 2 mol% Lewis acid. ^[b] GC Yield vs. internal std. ^[c] Temp = -20 °C.

Unfortunately, the lack of activity in the hydroboration of *trans*-4-octene in DCE in the absence of a Lewis acid precludes direct comparison of catalyst activity with **3-20**. However, it was confirmed that rate acceleration due to the presence of a Lewis acid co-catalyst was occurring through the use of an analogous precatalyst bearing an SbF_6^- counterion rather than BF_4^- . Hydroboration does proceed slowly in DCE with $[\text{Rh}(\text{COD})(\text{DPPB})]\text{SbF}_6$ (Figure 3-4), although strikingly the major product in this case is still the branched boronate ester **3-18**, suggesting that the product regioselectivity of the Rh catalyzed hydroboration of *trans*-4-octene is due to a solvent effect (See Section 3.3.3). Nonetheless, when FAB is present, conversion to product occurs more rapidly in this system.

The plot of reaction yield versus time for various catalysts and conditions is shown in Figure 3-4. Interestingly, when the amount of FAB added to the reaction was equimolar to **3-20**, no reaction was observed, in other words, the Lewis acid had no effect. This indicated that this Lewis acid must be in excess of the Rh^+BF_4^- catalyst to affect turnover to product.

Figure 3-4: Yield Versus Time in Catalyzed Hydroboration Variants



3.3.2 Substrate Screen

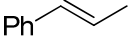
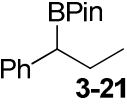

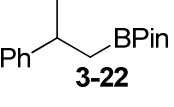
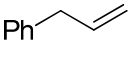
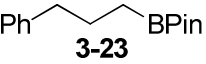
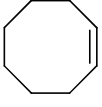
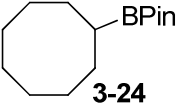
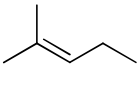
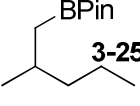
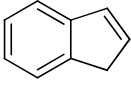
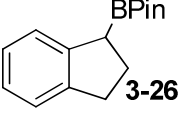
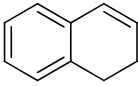
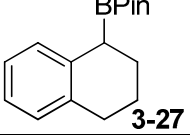
Having developed optimized conditions for the hydroboration of *trans*-4-octene, we examined hydroboration of other alkenes in order to determine the generality of the Lewis acid effect (Table 3-3). Similar trends were observed, where activity and selectivity increased dramatically upon the addition of the Lewis acid co-catalyst. Notably, arene-containing olefins are different from purely aliphatic olefins in that they do undergo hydroboration in DCE in the absence of a Lewis acid (entries 1 to 3, Table 3-3). However, turnover to product is slow, and markedly improved yields and selectivities are observed upon the addition of FAB. As shown in entries 4 and 5, other aliphatic olefins behave in the same manner as *trans*-4-octene in that they do not undergo conversion to product at all in the absence of a Lewis acid in DCE (Table 3-3).⁴⁹

In the case of β -methylstyrene (entry 1), the selectivity for the benzylic boronate

ester **3-21** is greatly enhanced from 2.5:1 to 75:1, the linear terminal boronate **3-22** being the minor isomer. In the case of 1-alkenes such as allylbenzene, the selectivity for the linear product also increases from 9:1 to 32:1, with a significant increase in yield at comparative reaction times (entry 3). This is a particularly interesting reaction, in which the only two products observed are the branched boronate ester where boron is placed proximal to the phenyl ring, and the linear boronate ester from direct reaction. Finally, tri-substituted olefins, which are completely unreactive in the absence of the Lewis acid, give high yields in the presence of a Lewis acid co-catalyst, (entry 5). Although the product of the reaction is isomerized, yielding boronate **3-25**, the reaction is completely selective and very rapid, reaching an isolated yield of 84% in 3 hours. This is a remarkable result, as normally tri-substituted olefins are difficult substrates to hydroborate even with the more reactive HBCat, which usually require extended reaction times and/or elevated temperatures.⁷

Other aryl olefins (entries 6 and 7) further demonstrate the ability of FAB to promote the catalyzed hydroboration. Better yields of **3-26** are obtained in the hydroboration of indene in the presence of Lewis acid compared to the normal reaction (entry 6). The reaction of 3,4-dihydronaphthalene in the presence of FAB also resulted in a better yield of **3-27** (entry 7), though in this case the increase is marginal.

Table 3-3: Effects of FAB on Yield and Selectivity in Catalyzed Hydroboration^a

Entry	Substrate	Major Product	No Lewis Acid	FAB (2 mol%)
1			15% Yield 2.5 : 1	84% Yield 75 : 1
2			12% Yield	87% Yield > 99 : 1
3			19% Yield 9 : 1	70% Yield 32 : 1
4			No reaction	90% Yield
5			No reaction	84% Yield > 99 : 1
6			26% Yield	81% Yield
7			62% Yield	87% Yield

^[a] Reaction conditions as in Table 3-1 using catalyst **3-20** (1 mol%) in DCE. Entries 1, 2, and 6: 9 h., 70 °C; Entry 7: 21 h, 70 °C; Entries 4 and 5: 6 h., 30 °C; and Entry 3: 24 h., 30 °C. Reaction times and temperatures are identical for reactions with and without added FAB.

3.3.3 Solvent Effect Studies

In order to probe the reason for the effect of the Lewis acid catalyst, the reaction was run in different solvents, and with various catalyst counterions and additives, as

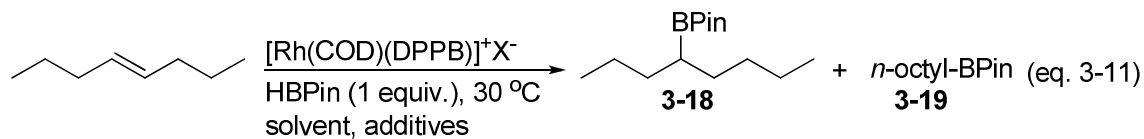
shown in Table 3-4. As noted previously, the catalyst **3-20**, which contains a BF_4^- counterion, is not reactive for the hydroboration of *trans*-4-octene in DCE and gives the linear isomer **3-19** in THF (Table 3-4, entries 1 and 2). Other coordinating solvents such as C_6H_6 and 2-MeTHF were also found to give the linear isomer (entries 3 and 4). Unfortunately, since there was no reaction in DCE in the absence of Lewis acids with catalyst **3-20**, it was difficult to determine whether the Lewis acid is changing the selectivity in this case, or whether it is merely activating the catalyst. However, the fact that the SbF_6^- analogue of catalyst **3-20** does catalyze the reaction in DCE yielding the branched isomer without the addition of any Lewis acid (entry 5), albeit slowly, suggests that the change in selectivity is solvent related. That is, in polar, non-coordinating solvents, the branched product predominates, while in polar coordinating solvents such as THF, the linear isomer is observed. To confirm that selectivity change was not due to polarity, reactions were conducted in solvent mixtures of DCE and THF (entries 7 and 8). As expected, the polar coordinating solvent dominates the reaction regardless of its ratio with DCE, and the linear isomer **3-19** is the major product in both cases. However, catalyst activity is hindered when the solvent of majority is made non-coordinating, resulting in only a 16% yield in 50 hours (entry 8).

We hypothesized that the reason for low activity could be due to tight binding of the COD ligand onto the Rh catalyst in non-coordinating solvents. Subsequently, Rh complex was pre-treated with hydrogen gas in order hydrogenate COD, removing it as a ligand. This resulted in catalyst activity in DCE for the hydroboration of *trans*-4-octene, producing branched product **3-18** (entry 12). Although quantitative yield could not be

attained, the activation of the reaction suggests that added Lewis acid may result in removal of COD as a ligand in some fashion.

Although the selectivity of the reaction appears to be due to a solvent effect, a Lewis acid is still required to permit the reaction to occur in a reasonable time frame, as shown in entries 9 and 10, respectively. However, for this effect to be observed, the amount of FAB is critical (entries 10 and 11). At 2 mol% loading, which is a 2:1 molar ratio with the catalyst, high activity and selectivity are observed with catalyst **3-20**. However at a 1:1 ratio, the added Lewis acid had no apparent effect, and no product was observed. This suggests that FAB is participating in a stoichiometric 1:1 interaction with some part of the Rh catalyst that does not result in the activation of catalysis in the hydroboration of alkyl olefins.

Table 3-4: Solvent Effects in Selectivity and Activity in the Hydroboration of 4-octene.^a



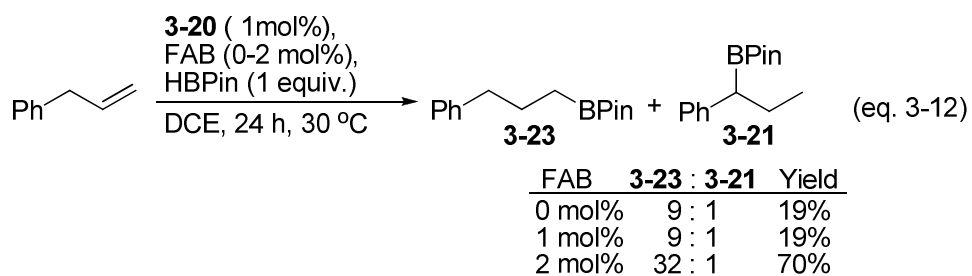
Entry	Anion, X	Additive	Solvent	Yield (Time)	Selectivity (3-18 : 3-19)
1	BF ₄ ⁻	None	DCE	0	—
2	BF ₄ ⁻	None	THF	80% (24 h)	1:99
3	BF ₄ ⁻	None	C ₆ H ₆	19% (22 h)	5:95
4	BF ₄ ⁻	None	2-MeTHF	75% (10 h)	3:97
5	SbF ₆ ⁻	None	DCE	4% (3 h) 99% (24 h)	90:10
6	SbF ₆ ⁻	None	THF	93% (24 h)	7:93
7	SbF ₆ ⁻	None	DCE/THF (1:3)	60% (24 h)	9:91
8	SbF ₆ ⁻	None	DCE/THF (3:1)	16% (50 h)	10:90
9	SbF ₆ ⁻	FAB, 2 mol%	DCE	93% (3 h)	95:5
10	BF ₄ ⁻	FAB, 2 mol%	DCE	>99% (0.5 h)	92:8
11	BF ₄ ⁻	FAB, 1 mol%	DCE	0	—
12	BF ₄ ⁻	H ₂ pre-treatment ^b	DCE	87% (0.5 h)	92:8

^[a] Reaction conditions: 1 mol% Rh catalyst, 0.1 M, 30 °C, nitrogen atmosphere (glove box).

^[b] Catalyst in DCE treated by bubbling H₂ gas for 1 hour before addition of HBPIn and olefin

Whereas the regioselectivity observed in hydroborations of *trans*-4-octene is attributed to an effect of the solvent, both β -methylstyrene and allylbenzene, aromatic olefins, reacted with increased selectivity in the presence of FAB relative to its absence (Table 3-3, entries 1 and 3). It was postulated that, in these cases, the selectivity

enhancement relative to the hydroboration in the absence of Lewis acid was due to the interaction of the first equivalent of Lewis acid to the Rh catalyst **3-20**. However, no increase in selectivity was observed in the hydroboration of allylbenzene in the presence of Rh catalyst and FAB in a 1:1 ratio, as shown in equation 3-12. This suggests that the increase in selectivity for the linear isomer **3-23** is concomitant with reaction acceleration, and may involve a change in the mechanism in the presence of free Lewis acid.

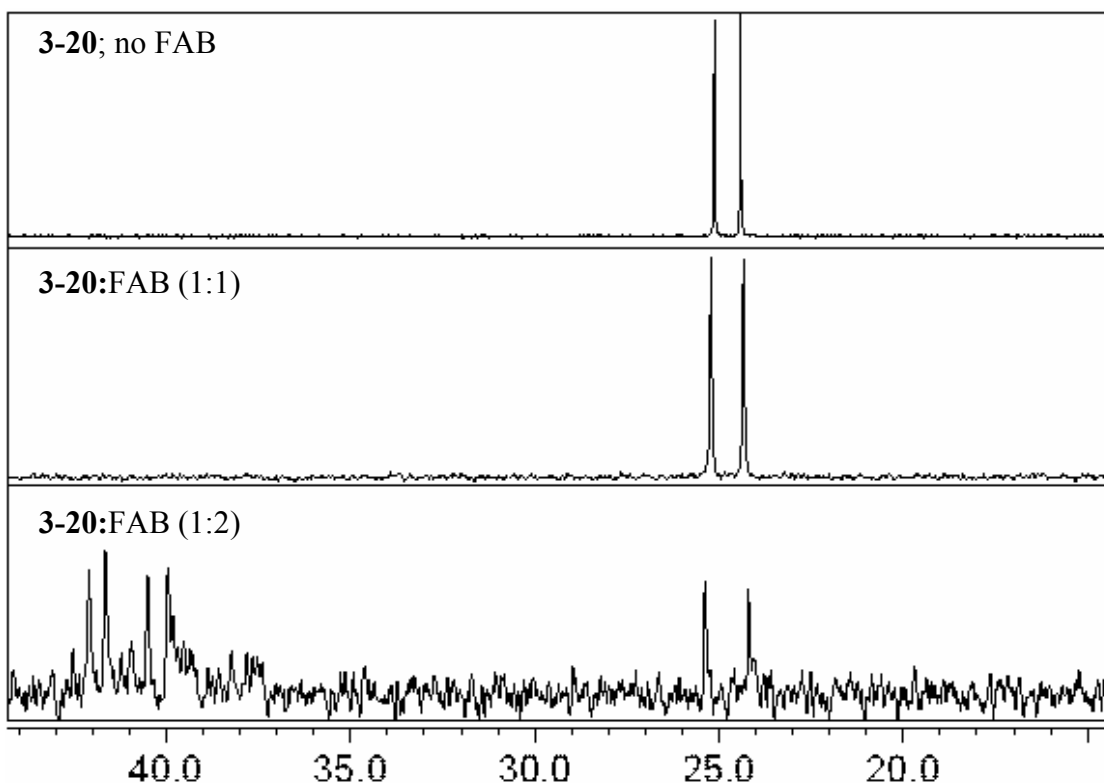


3.3.4 NMR Studies

The peculiar requirement for more than one equivalent of FAB relative to the Rh catalyst prompted the examination of various mixtures of this Lewis acid and [Rh(COD)(DPPB)]BF₄•THF **3-20** by ¹⁹F and ³¹P NMR in *d*₂-dichloromethane. As shown in Figure 3-5, no change in the Rh catalyst is observed by ³¹P NMR in the presence of HBPIn when 1 equivalent of FAB relative to Rh is present. In both cases, a doublet corresponding to DPPB coupled to Rh (*J* = 143 Hz) is observed. However, at a 2:1 ratio of FAB to **3-20**, a large decrease in the intensity of the catalyst precursor signal was observed with the appearance of new species with apparently smaller Rh-P coupling constants. Although clearly more than one species is present, the observation of new

peaks in the ^{31}P NMR implies that an active catalyst has been generated by the addition of the second equivalent of FAB.

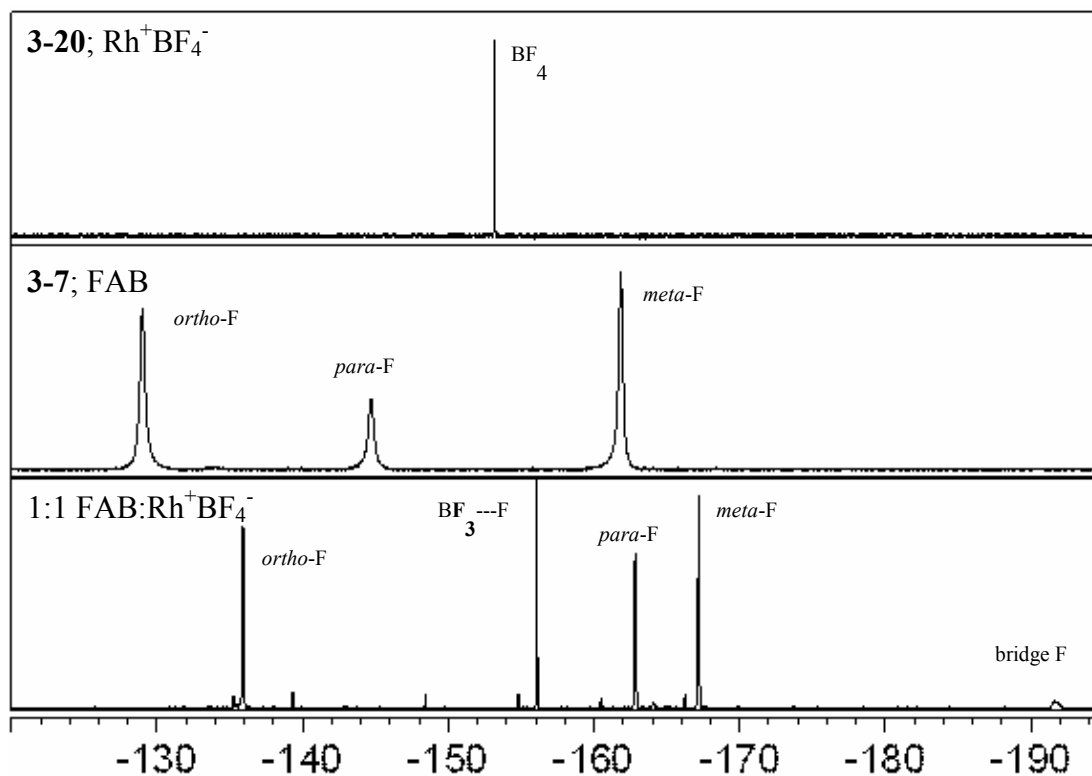
Figure 3-5: ^{31}P NMR of Various Ratios in **3-20** and FAB in the presence of HBPIn



Next, ^{19}F NMR experiments were conducted to discern the fate of FAB in a 1:1 stoichiometry with the Rh catalyst. In this scenario, no free BF_4^- or FAB is observed. Surprisingly, a strong interaction between these two moieties is observed, where both resonances assigned to FAB and BF_4^- become shifted upfield. Furthermore, a new resonance was observed at -192 ppm. Through an additional 2D ^{19}F NOESY experiment, it was determined that this peak was in exchange with the shifted counterion peak. This data strongly suggests either a 1:1 binding interaction⁵⁰ between FAB and BF_4^- through a

bridging μ -F or a reversible transfer of fluoride from BF_4^- to generate $[\text{FB}(\text{C}_6\text{F}_5)_3]^-$ and BF_3 . Reported fluorine chemical shifts of $[\text{FB}(\text{C}_6\text{F}_5)_3]^-$ are similar to the observed peak at -192 ppm, which seems to suggest the latter scenario.⁵¹ However, the possibility of a bridging fluorine interaction cannot be ruled out.⁵² Nonetheless, this data clearly shows that the first equivalent of FAB is tied up by the outer sphere anion of the Rh catalyst. Thus, FAB must be present in excess of the quantity of catalyst such that there is free Lewis acid to affect the activation of the hydroboration reaction.

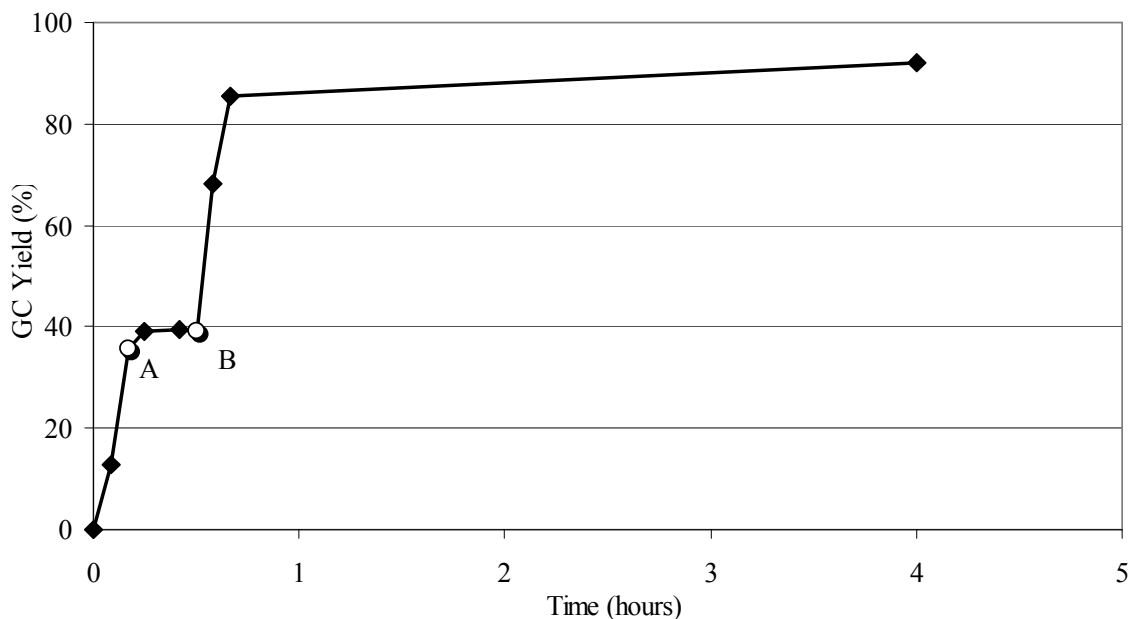
Figure 3-6: ^{19}F NMR Overlay of **3-20**, FAB, and 1:1 Mixture



3.3.5 Inhibition Study

The discovery of the ability of FAB to bind fluoride provided an opportunity to further investigate the role of this Lewis acid in the activation of hydroboration. An inhibition experiment was devised in which a soluble BF_4^- source, $\text{Bu}_4\text{N}^+\text{BF}_4^-$, was utilized in order to bind free FAB in a hydroboration system. The hydroboration of *trans*-4-octene with HBPIn in the presence of 1 mol% $[\text{Rh}(\text{COD})(\text{DPPB})]\text{BF}_4 \cdot \text{THF}$ and 2 mol% FAB was allowed to proceed to roughly 40% conversion, followed by the addition of 4 mol% $\text{Bu}_4\text{N}^+\text{BF}_4^-$ (Figure 3-7). This immediately leads to a halt in the reaction. Subsequently, the addition of another 4 mol% of FAB to the reaction, restoring free Lewis acid to the system, causes hydroboration to re-commence. This re-activation of the catalytic system clearly proves that FAB is not merely initiating the Rh catalyst to an active form, and is required throughout the reaction in order to effect conversion to product.

Figure 3-7: Inhibition of Hydroboration Through FAB Binding^a



[^a] Reaction Conditions: *trans*-4-octene (0.1M), HBPin (1 equiv.), **3-20** (1 mol%), FAB (2 mol%), DCE. A = addition of 4 mol% Bu₄N⁺BF₄⁻; B = addition of 4 mol% FAB.

3.3.6 Mechanistic Investigation

Because of the way in which it is prepared, the precatalyst **3-20** contains one equivalent of co-crystallized THF. Proton NMR of this catalyst in the presence of 2 equivalents of FAB revealed a marked downfield shift of the peaks assigned to THF, indicating binding to the Lewis acid, Figure 3-8. Initially, this suggested that THF might bind tightly to the Rh catalyst in DCE or DCM such that it cannot affect hydroboration. Subsequently, the addition of 2 mol% Lewis acid would sequester bound THF and allows the reaction to proceed. Thus, a new batch of Rh catalyst was synthesized in the absence of any THF solvent. However, it was found that THF-free [Rh(COD)(DPPB)]BF₄ was

similarly inactive in the hydroboration reaction in DCE (Table 3-5). Furthermore, the addition of FAB to the reaction with THF-free catalyst did not activate the reaction, clearly indicating that the binding of THF by the Lewis is not involved in the activation of catalysis. However, the experiments conducted with THF-free $[\text{Rh}(\text{COD})(\text{DPPB})]\text{BF}_4$ also clearly show that the stoichiometric equivalent of THF with respect to the Rh catalyst is absolutely required to affect turnover to product in the Lewis acid assisted methodology. Unlike in solvent effect studies, where higher levels of THF cause the hydroboration to proceed with linear selectivity, the catalytic amount of this molecule appears to be important in the ability of added FAB to activate catalysis.

Figure 3-8: Proton NMR of **3-20** and FAB Mixtures in d_2 -DCM

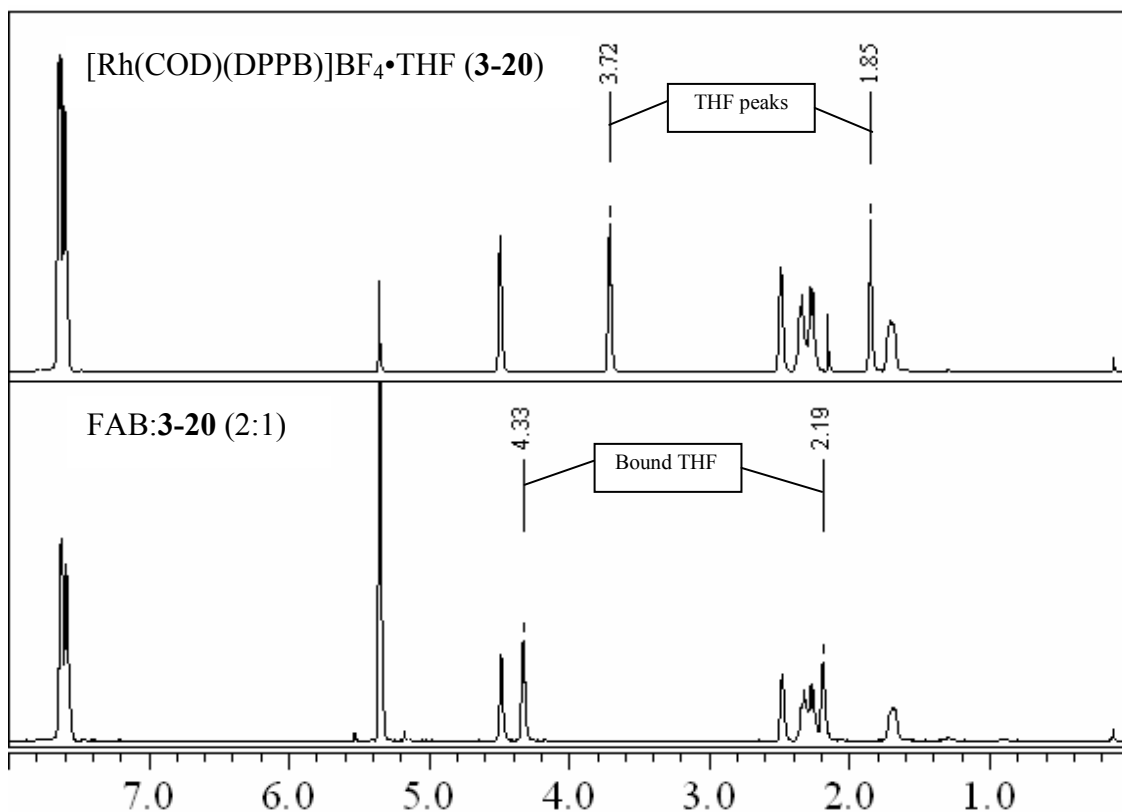
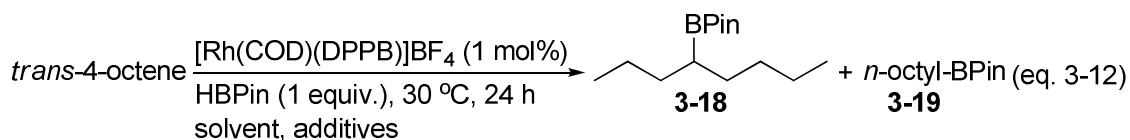


Table 3-5: THF-Free [Rh(COD)(DPPB)]BF₄ Catalyzed Hydroboration of 4-octene



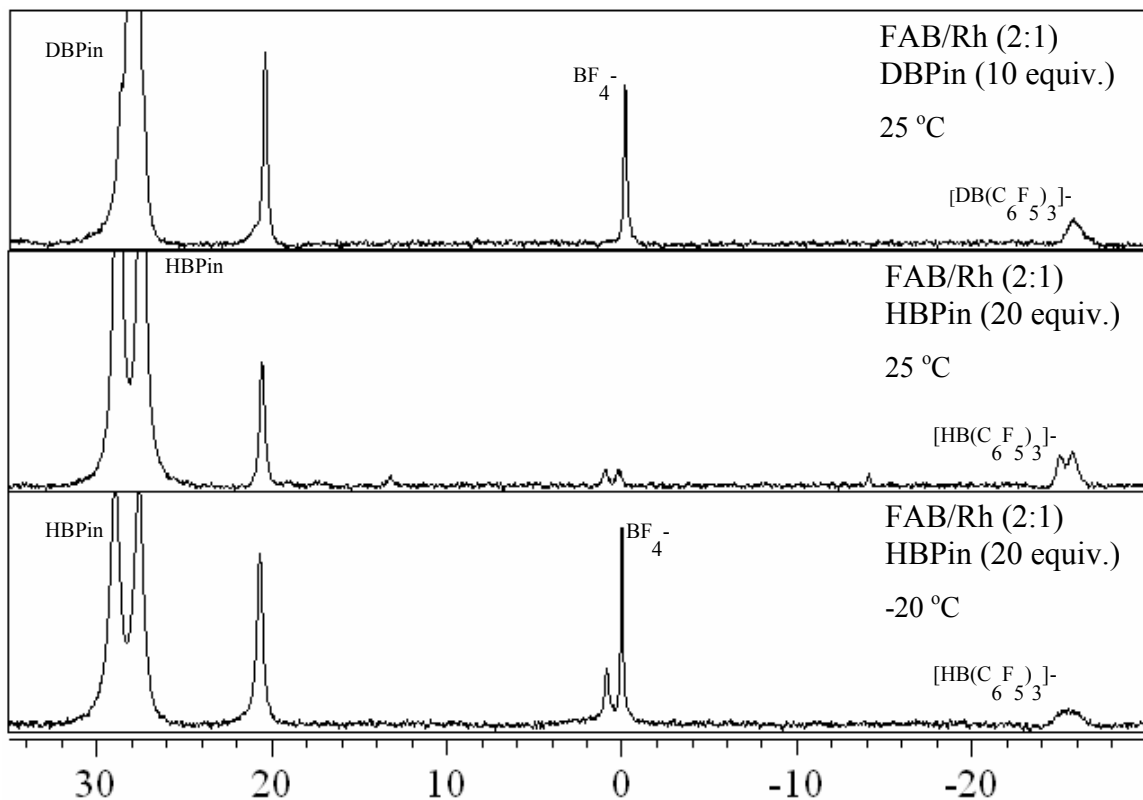
Entry	Solvent	Additive	GC Yield (%)	3-18 : 3-19
1	DCE	None	0	-
2	DCE	FAB (2 mol%)	0	-
3	THF	None	> 99	3 : 97

In order to establish the importance of THF in Lewis acid assisted hydroborations, a series of ¹¹B NMR experiments were conducted. Both **3-20** and its THF-free variant were mixed with an excess of HBPin and 2 equivalents of FAB in DCE. Surprisingly, a doublet at -25 ppm, characterized in the literature as [HB(C₆F₅)₃]⁻⁵³ is apparent in the mixture with **3-20**, but is not observed with the THF-free Rh catalyst. As shown in Figure 3-9, the hydride in [HB(C₆F₅)₃]⁻, originates from the borane, indicated by the lack of proton coupling in the borohydride peak when DBPin is applied instead of HBPin.

These results indicate that THF is required in addition to FAB to promote the formation of [HB(C₆F₅)₃]⁻, which is likely formed by an FLP-type heterolytic cleavage of the B-H bond of HBPin.⁵⁴ Borohydride accelerated thermal hydroboration has been reported.⁵⁵ However, the Rh catalyst is still required in the Lewis acid mediated methodology, since a control reaction with catalytic equimolar quantities of THF and

FAB did not catalyze the reaction of 4-octene and HBPIn. Thus, the Lewis acid-base system is not itself sufficient to promote olefin hydroboration.⁵⁶

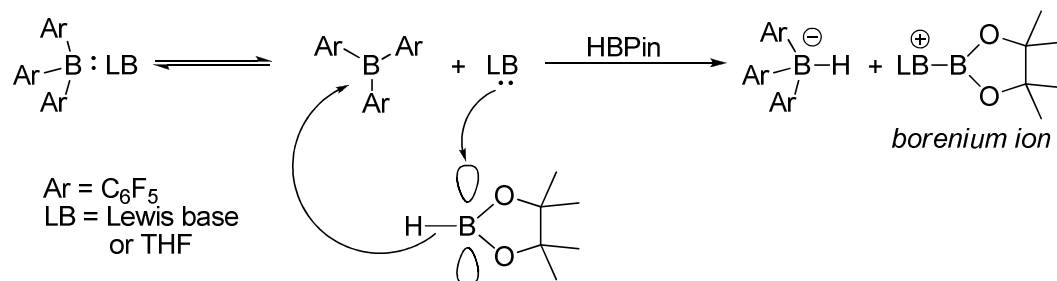
Figure 3-9: Catalyst **3-20** and FAB in the Cleavage of HBPIn



Since THF can act as a Lewis base, the cleavage of the B-H bond of HBPIn by FAB and THF resembles the frustrated Lewis acid-base chemistry popularized by Stephan and discussed in Section 3.2. Although THF can by no means be deemed sterically hindered, the results of the NMR studies clearly suggest that free and FAB-bound THF are in equilibrium such that it can act as a Lewis base in the cleavage of HBPIn as shown in Scheme 3-7. This hypothesis is supported by a recent *in silico* study,

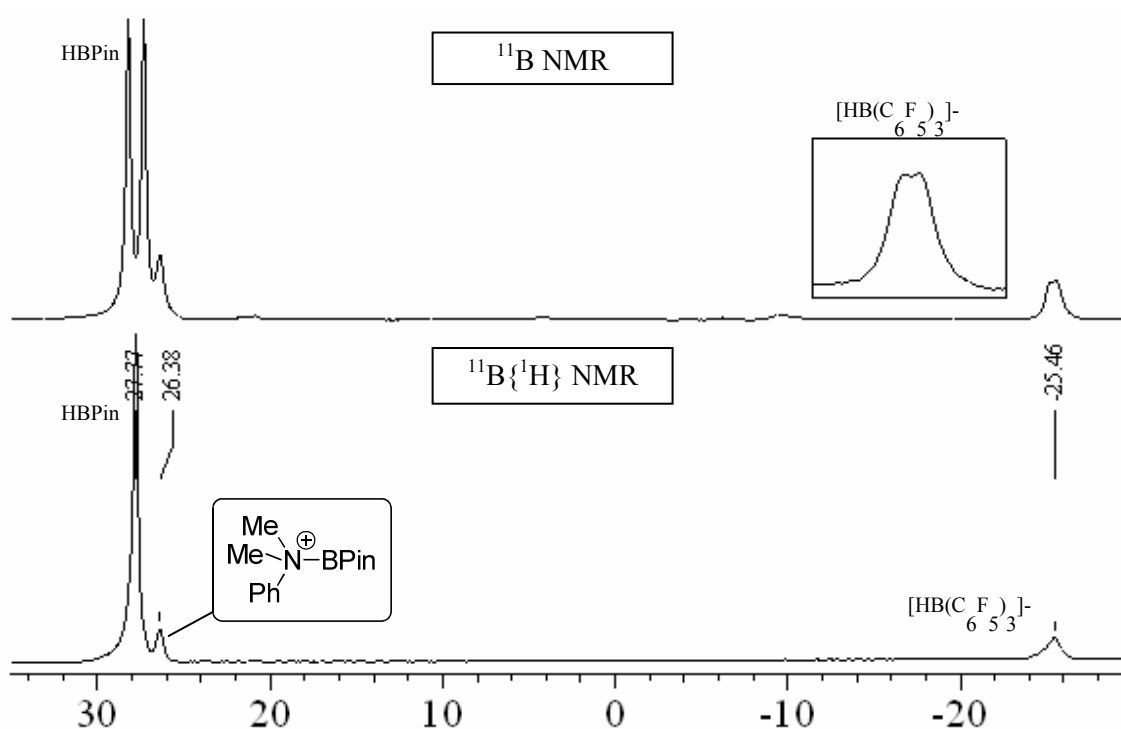
which calculates the dissociation energy of hydride and FAB to be 528 kJmol^{-1} , whereas for THF the dissociation energy is calculated at 4 kJmol^{-1} .⁵⁷

Scheme 3-7: Lewis Acid-Base Mediated B-H Bond Heterolysis

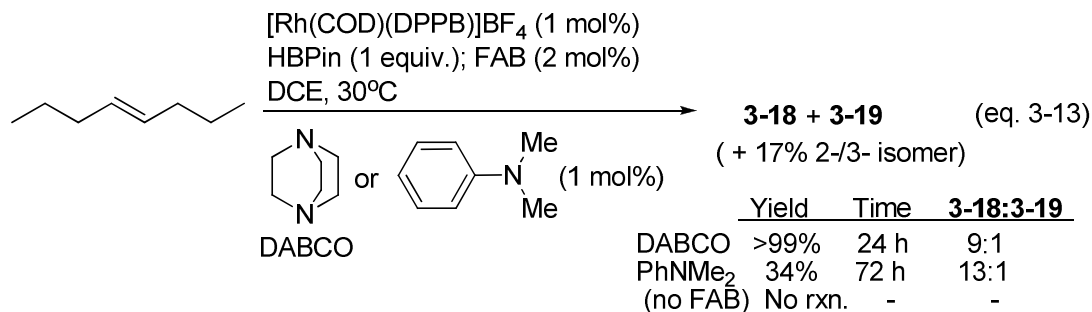


Although no peak could be observed for the borenium ion that would result from Lewis acid-base mediated B-H bond heterolysis in the case of THF containing mixtures, other Lewis bases were found to yield observable borenium ions. Both DABCO and PhNMe₂ were found to be viable Lewis base partners to FAB for the cleavage of HBPin. As shown in Figure 3-10, the cleavage with PhNMe₂ is much cleaner than in the case of THF, with no degradation of the reagent to B₂Pin₃. Most importantly, the borenium ion can be reasonably observed in the proton-decoupled ¹¹B spectrum at 26.4 ppm. Borenium ions have been reported in this region of the boron spectrum,³⁸ and resolution of this peak could only be observed on a high field 600 MHz NMR spectrometer due to its proximity to the boron signal of HBPin.

Figure 3-10: $^{11}\text{B}\{^1\text{H}\}$ and ^{11}B NMR of HBPin in the presence of PhNMe₂ and FAB

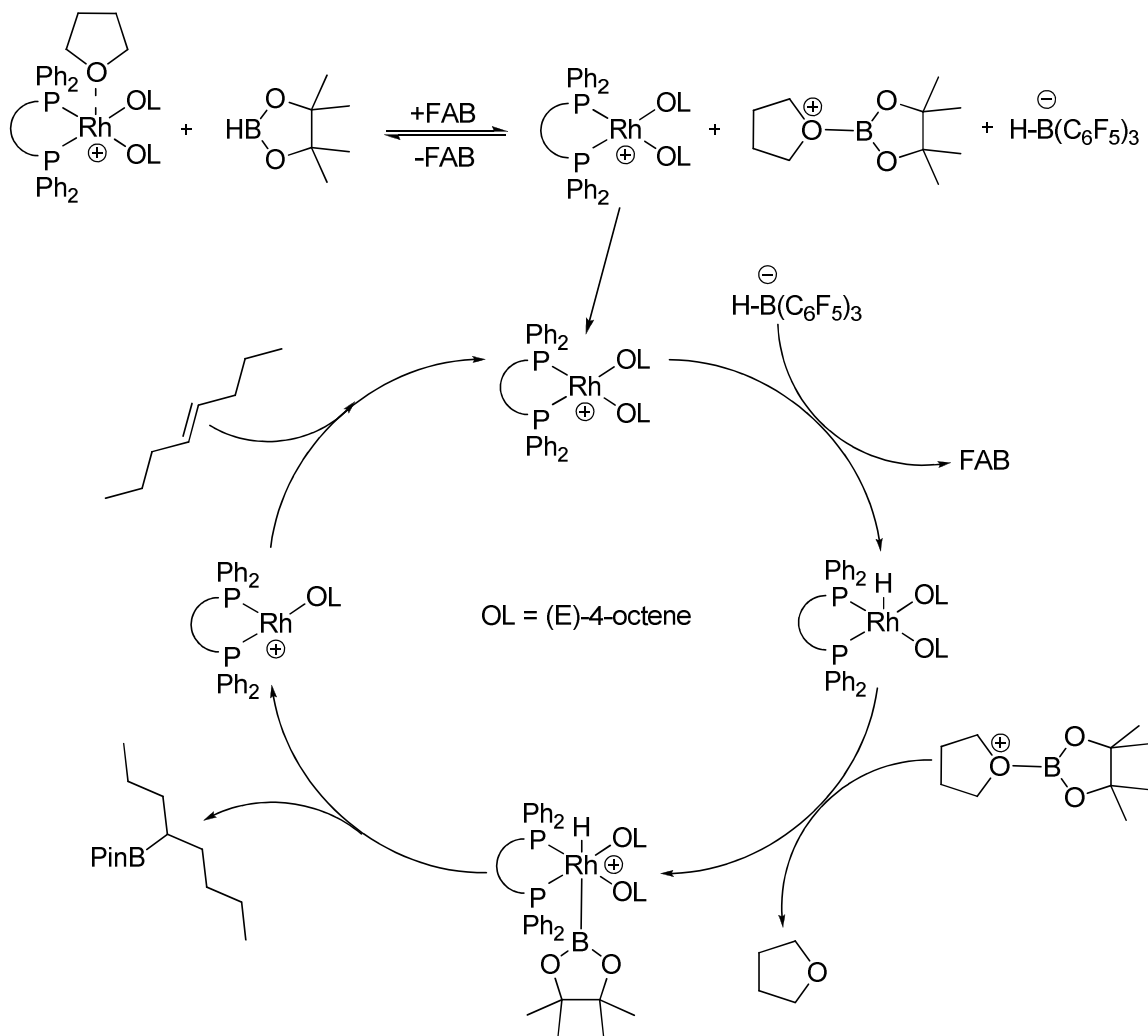


Eager to prove the generality of this reaction, we employed both DABCO and PhMe₂ in hydroborations of 4-octene with THF-free $[\text{Rh}(\text{COD})(\text{DPPB})]\text{BF}_4$ in the presence of FAB, equation 3-13. As expected, both Lewis bases led to conversion to product, although much more slowly than in the optimized case with **3-20**, which may be due to competitive binding of the Lewis base to FAB or the Rh catalyst. Importantly, a similar Lewis base, DMAP, has been reported to accelerate the hydroboration of vinyl arenes with neutral Rh catalyst.⁵⁸ However, a control reaction in the absence of FAB but with PhNMe₂ present did not catalyze the reaction, equation 3-13.



With the concomitant observation of B-H heterolysis of HBPIn and catalytic activity, a mechanism was proposed involving Lewis acid mediated transfer of hydride to the Rh catalyst, shown in Scheme 3-8. Rather than a typical oxidative addition of HBPIn to the catalyst, the borane is first cleaved heterolytically and is then transferred to Rh, which proceeds to hydroborate the olefin.

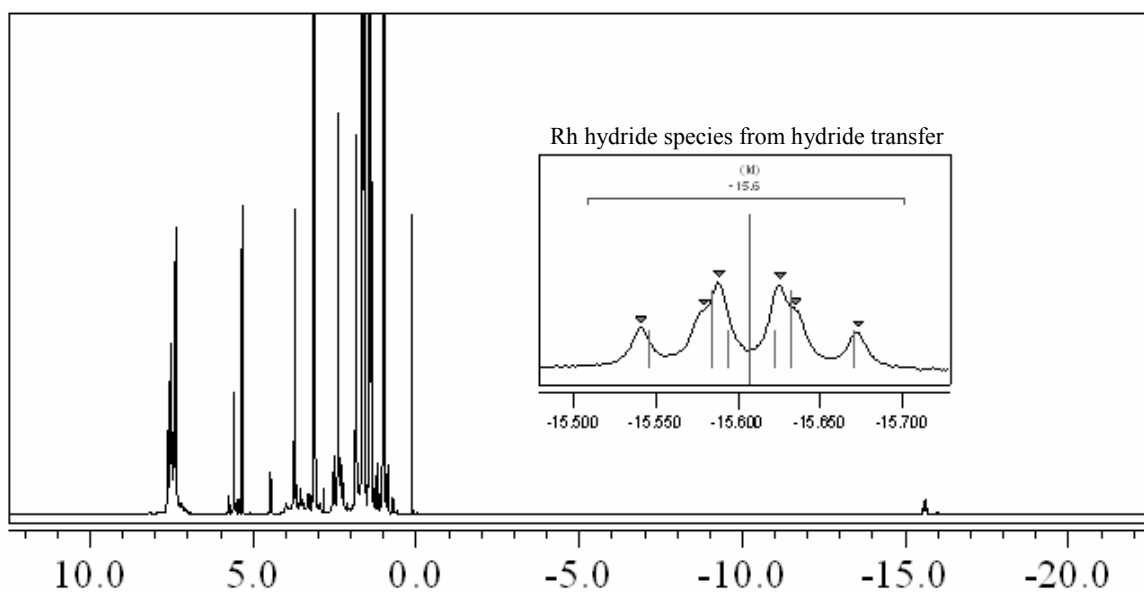
Scheme 3-8: First Proposed Mechanism of FAB Mediated Rh Catalyzed Hydroboration



The mechanism displayed in Scheme 3-8 requires that the borohydride $[\text{HB}(\text{C}_6\text{F}_5)_3]^-$ is able to transfer its hydride to the Rh catalyst. $[\text{Bu}_4\text{N}][\text{HB}(\text{C}_6\text{F}_5)_3]$, synthesized according to a literature procedure,⁵³ when reacted with $[\text{Rh}(\text{COD})(\text{DPPB})]\text{BF}_4 \cdot \text{THF}$ in a 6:1 ratio, yields rhodium hydrides according to ^1H NMR (Figure 3-11).⁵⁹ This is consistent with the work of DuBois⁶⁰, who demonstrated that rhodium hydrides and borohydrides are in equilibrium. The excess of borohydride

necessary to observe transfer to Rh is also consistent with DuBois' report, in which the equilibrium favours the hydride on boron.^{60,61} Thus, FAB mediated transfer of hydride from HBPIn to the Rh catalyst is viable, even if it is not thermodynamically favourable since the generated rhodium hydride can be quickly consumed by hydroboration of the olefin.

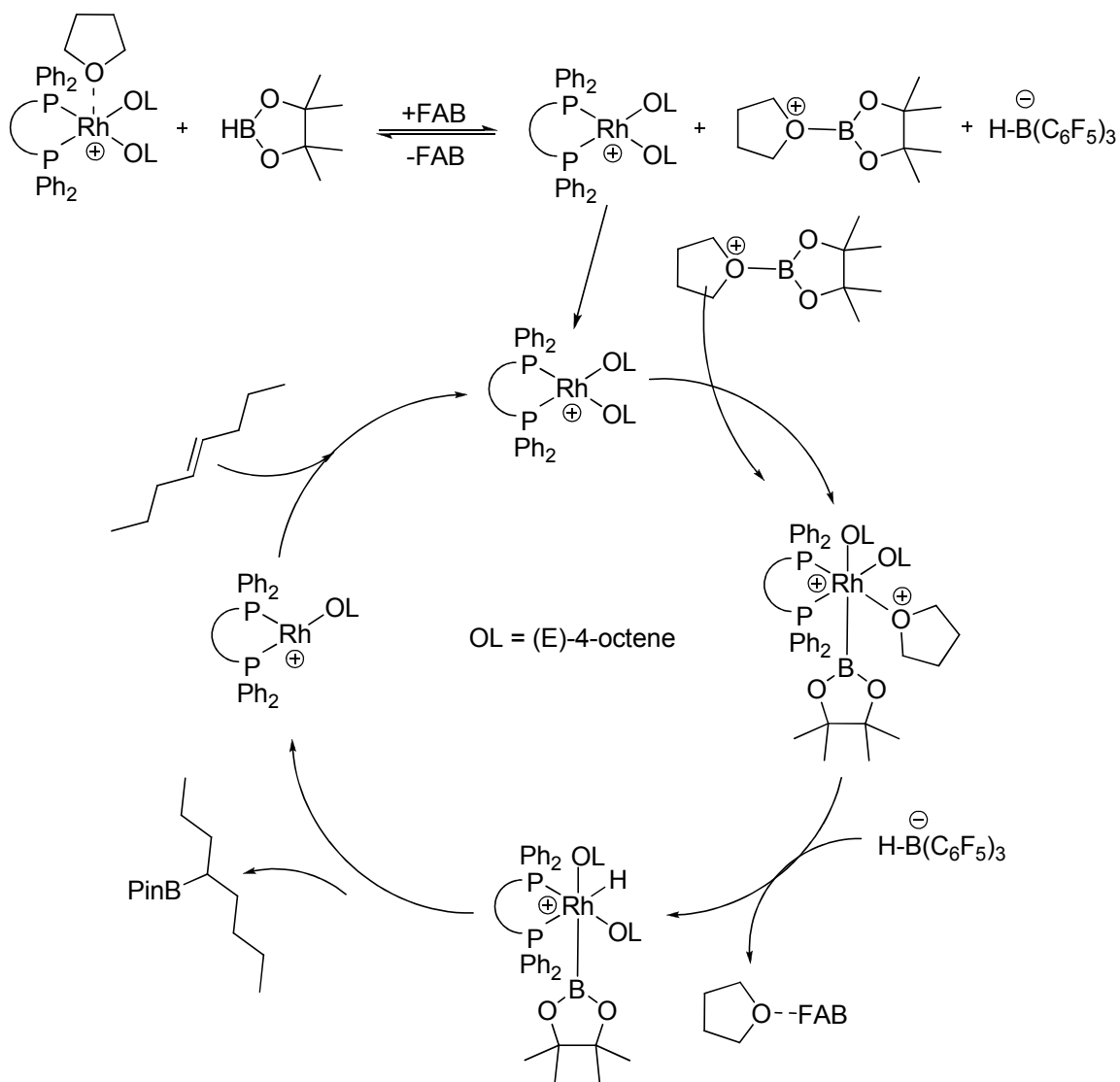
Figure 3-11: ¹H NMR of 6:1 Mixture of [HB(C₆F₅)₃]⁻ and **3-20**



Although the possibility of hydride transfer from boron to Rh catalyst was confirmed, the equilibrium favouring hydride placement on FAB suggested that perhaps hydride transfer to Rh was not the initial step in the catalytic cycle. As shown in Scheme 3-9, transfer of the stabilized boryl cation to Rh may precede hydride transfer. Although this requires a formally dicationic rhodium intermediate, the boryl cation likely more reactive than the borohydride, and may be more unstable than a dicationic rhodium

complex. Whereas $[\text{HB}(\text{C}_6\text{F}_5)_3]^-$ may be observed by NMR, the THF-stabilized boryl cation is not. Previous work with similar borenium ions revealed that these species do not accumulate under hydride abstraction conditions due to their highly reactive nature.³⁹

Scheme 3-9: Alternate Proposed Mechanism for FAB Assisted Hydroboration



3.4 Conclusions

Lewis acids such as FAB have a clear effect on the hydroboration of olefins with pinacol borane. The developed methodology represents an expansion of the scope of this Rh catalyzed reaction in regioselective transformations of olefins. The nature of the effect of Lewis acid addition varies depending on substrate class, although the end result is similar in that an increased selectivity and reactivity is observed. With internal aliphatic olefins, the change in regioselectivity appears to originate from a solvent effect, such that in coordinating solvents the hydroboration of 4-octene yields linear boronate ester product, whereas non-coordinating solvents primarily yield the branched product **3-18**. However, in non-coordinating solvents such as DCE or DCM, the addition of Lewis acid does activate or accelerate the reaction, completing the hydroboration of 4-octene in 30 minutes under optimized conditions. Comparatively, no reaction is observed with **3-20** and only slow conversion occurs with the SbF_6^- analogue in the absence of co-catalytic Lewis acid in non-coordinating solvent.

When aryl olefins such as β -methylstyrene are employed in the reaction, the addition of FAB also affects an increase in selectivity and activity. However, with this class of substrate, the increase in regioselectivity is not due to a solvent effect. This may involve a change in the mechanism, as these substrates do undergo conversion to boronate products in the absence of FAB in chlorinated solvents.

^{19}F NMR studies indicated that at a 1:1 ratio of FAB to Rh catalyst, there is no free FAB present in solution, as it is subjected to complexation and/or reaction with the

BF_4^- counterion of the catalyst. Correspondingly, in the 1:1 system, no hydroboration was observed upon the addition of HBPIn and 4-octene. However, upon addition of FAB in excess of the catalyst loading, changes were observed in the catalyst by ^{31}P NMR, concomitant with the observation of catalytic activity. Additional poisoning studies using $[\text{Bu}_4\text{N}][\text{BF}_4]$ to scavenge any free FAB in reactions that are ongoing confirmed that the FAB effect was not merely confined to initiation, and was required over the course of the reaction.

The effect of FAB was found to be closely linked with the presence of Lewis base, where the acid-base pair affects the heterolytic B-H bond cleavage of HBPIn, which is concomitant with the activation of catalysis. Specifically, in the case of the preformed catalyst **3-20**, the Lewis base was found to be co-crystallized THF. The same precatalyst synthesized in the absence of this common solvent such that it was THF-free was not active for the hydroboration of 4-octene with HBPIn in DCE and could not be activated by the addition of FAB. Furthermore, no bond heterolysis of HBPIn was observed in this case by ^{11}B NMR.

The THF-stabilized boryl cation generated from the heterolysis of HBPIn could not be observed by NMR. However, the use of other Lewis bases such as PhNMe_2 with FAB in this reaction did result in the cleavage of the B-H bond and the generation of an amine-stabilized borenium ion that is observable in the ^{11}B NMR spectrum. Additionally, both DABCO and PhNMe_2 added to reactions involving THF-free $[\text{Rh}(\text{COD})(\text{DPPB})]\text{BF}_4$ resulted in the hydroboration of 4-octene in the presence of FAB in DCE.

Unlike hydrosylations reported by Piers²⁸ and Gevorgyan²⁹, which are purely FAB catalyzed, the Lewis acid assisted hydroboration requires the Rh catalyst in order to achieve conversion. In light of the lack of precatalyst activation by ³¹P NMR in the presence of olefin and HBPIn without FAB, it appears that the Lewis acid activates hydroboration through the transfer of the borane in parts to Rh, resulting in a net oxidative addition. The hydride transfer from [HB(C₆F₅)₃]⁻ to Rh is observed by proton NMR when excess borohydride is applied, indicating an equilibrium that favours hydride placement on boron rather than Rh. Thus, hydride transfer to Rh may be driven by the eventual hydroboration of olefin. Another possibility involves transfer of the reactive boryl cation to Rh preceding hydride transfer. In either case, the Lewis acid mediates oxidative addition. For aliphatic olefins this hypothesis fits the data, as the regioselectivity of the reaction in DCE is unchanged. For aromatic alkenes, in which an improvement in selectivity is observed upon the addition of FAB, a more complex effect is at play.

In conclusion, it has been clearly shown that in metal-catalyzed hydroborations with HBPIn, the addition of catalytic amounts of Lewis acids such as FAB has a dramatic effect, accelerating the rate of reaction, and improving the regioselectivity. The coordinating ability of the solvent also plays a role in the activity and selectivity of the Rh catalyst, most notably in the hydroboration of aliphatic olefins. The observation of [HB(C₆F₅)₃]⁻ in these reactions implicates this species in the overall transformation via B-H bond cleavage of the reagent borane, although further work is required to firmly establish the role of this species, and the corresponding boryl cation, in the catalytic cycle.

3.5 Experimental Section

3.5.1 Synthetic Procedures

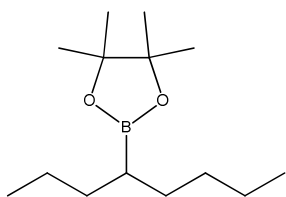
General. Unless otherwise noted, all reactions were conducted in an inert atmosphere (Nitrogen) in a glovebox using dried glassware. Reaction solvents were all dried according to literature procedures and de-oxygenated via a minimum of three freeze-pump-thaw cycles before storage under nitrogen. As a precaution, all solvents were stored over 4 angstrom molecular sieves to remove trace moisture. All reagent olefins used were purified via bulb-to-bulb distillation followed by a minimum of three freeze-pump-thaw cycles to remove oxygen before storage at -20 °C under nitrogen in the glovebox. 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (HBPin) was purchased from Aldrich, distilled and de-oxygenated as above, and also stored in the glovebox at -20 °C. Lewis acids employed were obtained from Aldrich and Strem and were brought into the glovebox sealed and used as purchased. B(C₆F₅)₃ (CAS Registry No.: 1109-15-5) is referred to as FAB **3-7**. All NMR spectra were obtained on 400 and 500 MHz Bruker Avance spectrometers. All GC spectra were obtained using an Agilent 6850 chromatograph with FID detector loaded with an HP-5 column (L= 30 metres; ID= 0.32 mm) and operating with splitless injection (He carrier gas). All samples analyzed by GC were done so with the following methodology: Initial Temp. = 80 °C (held for 6min.); Rate = 10 °C/min; Final Temp. = 220 °C.

*Synthesis of [rhodium(1,4-cyclooctadiene)(bis-diphenylphosphinobutane)] tetrafluoroborate (**3-20**) and hexafluoroantimonate (THF-bound).* [Rh(COD)Cl]₂ (300.4 mg, 0.61 mmol) was added into a flame-dried Schlenck flask under argon. The atmosphere was removed and re-filled 3 times to remove traces of oxygen. Via cannula,

5 mL of dry, distilled, deoxygenated THF was added to the flask to dissolve the solid with stirring. AgBF₄ (241.4 mg, 1.24 mmol) or AgSbF₆ (412 mg, 1.22 mmol), depending on which anion was desired, was added to a dry RBF flask in the glovebox, which was removed sealed and placed under argon. THF (5 mL) was added via cannula and the resulting solution was stirred for 10 min. The AgBF₄ solution was cannulated into the Schlenck flask, at which point a grey-white precipitate formed. The solution was stirred for 2 hours. The filtrate was transferred via cannula filter into a second flame-dried Schlenck flask containing DPPB (519.3 mg, 1.22 mmol) in 10 mL of THF, causing the solution to turn red. Red-orange crystals formed over time (789 mg, 89% yield). Solvent was reduced to roughly 2 mL under vacuum. The remaining liquid was removed by syringe. The crystals were washed once with 2 mL of THF, dried under vacuum and brought into the box to be stored in fridge. Rh⁺BF₄⁻: ³¹P{¹H}-NMR: δ 24.84 ppm(d, *J* = 143 Hz). ¹⁹F-NMR: δ -153.2(s, int = 1.00), -153.1(s, int = 0.25) ppm. ¹H-NMR (CD₂Cl₂): δ 1.70, (br, 4H, alkyl H of DPPB), 1.85 (br, 4H, THF), 2.21-2.40 (m, 8H, alkyl H of COD), 2.49 (br, 4H, alkyl H of DPPB), 3.72 (br, 4H, THF), 4.49 (br, 4H, olefinic H of COD), 7.55-7.67 (m, 20 H, PPh₂) ppm.

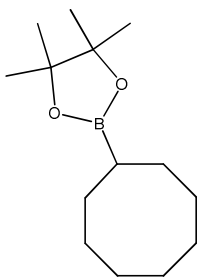
General Hydroboration Procedure. All reactions were set up in a nitrogen-filled glovebox in dry disposable glass vials fitted with Teflon seal screw caps. A 4-dram glass vial was charged with **3-20** (7.2 mg, 0.01 mmol) and FAB (10.2 mg, 0.02 mmol) and 2 mL of DCE was added. The vial was then sealed and agitated until solids had dissolved. A separate 1-dram vial was charged with dodecane as internal standard (unless isolated yields were desired, in which case the internal standard was omitted), *trans*-4-octene or

other olefin (1 mmol), and HBPin (128 mg, 1 mmol). This solution was added with excess DCE to the catalyst/Lewis acid solution for a total reaction volume of 4 mL. If GC yield was desired, an aliquot of the reaction was diluted in Hexanes in a GC vial and run accordingly. If isolated yield was required, the reaction was removed from the glovebox and diluted with petroleum ether in the reaction vial (6 mL). Distilled water was added to the vial (5 mL) in order to quench unreacted borane, and the organic layer was removed and collected in a separate flask. The remaining aqueous layer was further extracted in vial with 2x4 mL. The collected organic layer was dried with MgSO₄ and filtered through a plug of silica gel to remove rhodium metal. The filtrate was collected into a tared round-bottom flask. Solvent was removed in vacuo leaving boronate ester products, typically colourless oils.



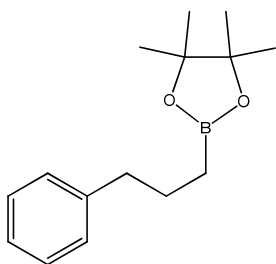
4,4,5,5-Tetramethyl-2-(1-propyl-pentyl)-[1,3,2]dioxaborolane

(3-18). Synthesized as described above: (E)-4-octene (112 mg, 1.0 mmol), HBPin (128 mg, 1.0 mmol), **3-20** (7.8 mg, 1.0 mol%), FAB (10.2 mg, 2.0 mol%), DCE (4 mL), -20 °C for 8 hours. Reaction worked up to yield a colourless oil. ¹H-NMR (CDCl₃): δ 0.80 (t, 3H, *J* = 7.2 Hz), 0.81 (t, 3H, *J* = 7.1 Hz), 1.17 (s, 12H), 1.18-1.40 (m, 11H) ppm. ¹³C-NMR (CDCl₃): δ 82.8, 33.8, 31.6, 31.1, 24.8, 23.0, 22.4, 14.5, 14.1 ppm. HRMS calcd. for C₁₄H₂₉BO₂ (M⁺): 240.2261; found: 240.2258.



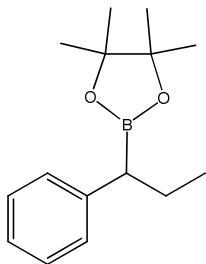
2-Cyclooctyl-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (3-24).

Synthesized as described above: cyclooctene (110 mg, 1.0 mmol), HBPin (128 mg, 1.0 mmol), **3-20** (7.6 mg, 1.0 mol%), FAB (10.0 mg, 2.0 mol%), DCE (4 mL), 30 °C for 3 hours. Colourless oil isolated in 90% yield. ¹H-NMR (CDCl₃): δ 0.75-0.84 (m, 1H), 1,16 (s, 12H), 1.35-1.52 (m, 11H), 1.53-1.71 (m, 3H) ppm. ¹³C-NMR (CDCl₃): δ 24.7, 26.7, 26.9, 27.0, 27.6, 82.8 ppm. HRMS calcd. for C₁₄H₂₇BO₂ (M⁺): 238.2104; found: 238.2115.



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

(3-23). Synthesized as described above: allylbenzene (117 mg, 1.0 mmol), HBPin (139 mg, 1.1 mmol), **3-20** (7.0 mg, 1.0 mol%), FAB (11.0 mg, 2.3 mol%), DCE (4 mL), 70 °C for 7 hours. ¹H-NMR (CDCl₃): δ 0.85 (t, 2H, *J* = 7.9 Hz), 1.27 (s, 12H), 1.76 (quintet, 2H, *J* = 7.9 Hz), 2.63 (t, 2H, *J* = 7.9 Hz) 7.20 (m, 3H), 7.28 (dd, 2H, *J* = 10.3, 4.6 Hz) ppm. ¹³C-NMR (CDCl₃): δ 24.9, 26.1, 38.6, 83.0, 125.6, 128.19, 128.22, 128.4, 128.6, 142.7 ppm. HRMS calcd. for C₁₅H₂₃BO₂ (M⁺): 246.1791; found: 246.1801.

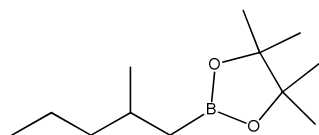


4,4,5,5-Tetramethyl-2-(1-phenyl-propyl)-[1,3,2]dioxaborolane (3-21).

Synthesized as described above: beta-methylstyrene (130 mg, 1.10 mmol), HBPin (187 mg, 1.46 mmol), **3-20** (7.5 mg, 0.9 mol%), FAB (10.5 mg, 1.8 mol%), DCE (4 mL), 70 °C for 9 hours. Colourless oil isolated in 84% yield. ¹H-NMR (CD₂Cl₂): δ 0.80 (t, 3H, *J* 7.3 Hz), 1.10 (s, 6H), 1.12 (s, 6H), 1.55 (m, 1H), 1.76 (m, 1H), 2.09 (t, 1H, *J* 7.8 Hz), 7.01-7.11 (m, 3H), 7.13-7.19 (m,

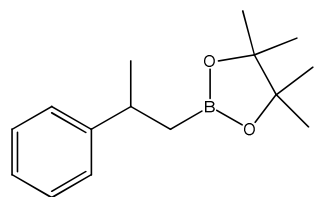
2H) ppm. ^{13}C -NMR (CD_2Cl_2): δ 14.0, 24.8, 24.9, 26.1, 83.6, 125.8, 128.6, 128.8, 144.1 ppm. HRMS calcd. for $\text{C}_{15}\text{H}_{23}\text{BO}_2$ (M^+): 246.1791; found: 246.1791.

4,4,5,5-Tetramethyl-2-(2-methyl-pentyl)-[1,3,2]dioxaborolane (3-25). Synthesized as



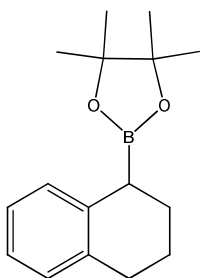
described above: 2-methyl-2-pentene (90 mg, 1.1 mmol), HBPin (131 mg, 1.02 mmol), **3-20** (7.2 mg, 1.0 mol%), FAB (10.3 mg, 2.0 mol%), DCE (4 mL), 30 °C for 3 hours. Colourless oil isolated in 84% yield. ^1H -NMR (CDCl_3): δ 0.56 (dd, 1H, $J = 15.3, 8.4$ Hz), 0.76 (dd, 1H, $J = 15.3, 5.8$ Hz), 0.80 (t, 3H, $J = 7.1$ Hz), 0.83 (d, 3H, $J = 6.6$ Hz), 1.09 (m, 2H *det. by COSY*), 1.18 (s, 12H), 1.25 (m, 2H *det. by COSY*), 1.63 (dq, 1H, $J = 6.5, 13.2$ Hz) ppm. ^{13}C -NMR (CDCl_3): δ 14.3, 20.4, 22.3, 24.8, 24.9, 29.2, 42.0, 82.8 ppm. HRMS calcd. for $\text{C}_{12}\text{H}_{25}\text{BO}_2$ (M^+): 212.1948; found: 212.1956.

4,4,5,5-Tetramethyl-2-(2-phenyl-propyl)-[1,3,2]dioxaborolane (3-22). Synthesized as



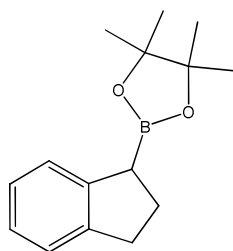
described above: α -methylstyrene (115 mg, 1 mmol), HBPin (141 mg, 1.1 mmol), **3-20** (7.3 mg, 1.0 mol%), FAB (11.2 mg, 2.2 mol%), DCE (4 mL), 70 °C for 9 hours. Colourless oil isolated in 87% yield. ^1H NMR (CD_2Cl_2): δ 1.02 (d, 2H, $J = 7.6$ Hz), 1.09 (s, 12H), 1.20 (d, 3H, $J = 6.9$ Hz), 2.96 (m, 1H), 7.02-7.08 (m, 1H), 7.10-7.22 (m, 4H) ppm. ^{13}C -NMR (CDCl_3): δ 24.7, 24.8, 24.9, 35.8, 83.0, 125.5, 125.7, 126.6, 128.2, 149.2 ppm. HRMS calcd. for $\text{C}_{15}\text{H}_{23}\text{BO}_2$ (M^+): 246.1791; found: 246.1794.

4,4,5,5-Tetramethyl-2-(1,2,3,4-tetrahydro-naphthalen-1-yl)-[1,3,2]dioxaborolane.



Synthesized as described above: 3,4-2*H*-naphthalene (68 mg, 0.5 mmol), HBPin (90 mg, 0.7 mmol), **3-20** (4.2 mg, 1.1 mol%), FAB (5.9 mg, 2.2 mol%), 70 °C for 9 hours. Colourless oil isolated in 81% yield. ¹H-NMR (CD₂Cl₂): δ 1.13 (s, 6H), 1.14 (s, 6H), 1.60-1.74 (m, 2H), 1.74-1.82 (m, 2H), 2.45 (t, 1H, *J* 5.5 Hz), 2.65 (t, 2H, *J* 6.3 Hz), 6.89-6.98 (m, 4H) ppm. ¹³C-NMR (CD₂Cl₂): δ 23.1, 24.8, 24.9, 25.5, 30.0, 83.7, 125.0, 125.6, 129.6, 129.8, 137.1, 138.5 ppm. HRMS calcd. for C₁₆H₂₃BO₂ (M⁺): 258.1791; found: 258.1786.

2-Indan-1-yl-4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane. Synthesized as described above:



Indene (136 mg, 1.2 mmol), HBPin (163 mg, 1.3 mmol), **3-20** (7.5 mg, 0.9 mol%), FAB (10.22 mg, 1.7 mol%), DCE (4 mL), 70 °C for 48 hours. Colourless oil isolated in 93% yield. ¹H-NMR (CD₂Cl₂): δ 1.45 (s, 6H), 1.54 (s, 6H), 1.96 (dq, 1H, *J* 8.4, 12.4 Hz), 2.12 (m, 1H), 2.61, (t, 1H, *J* 8.4 Hz), 2.81 (m, 2H), 6.98 (m, 2H), 7.12 (m, 2H) ppm. ¹³C-NMR (CD₂Cl₂): δ 24.9, 25.0, 28.3, 33.6, 83.7, 124.5, 124.7, 125.8, 126.3, 144.7, 145.8 ppm. HRMS calcd. for C₁₅H₂₁BO₂ (M⁺): 244.1635; found: 244.1630.

3.5.2 NMR Studies

General Considerations. All NMR experiments were conducted using sealed J. Yung tubes, and were prepared under inert N₂ atmosphere in the glovebox. Where necessary, CD₂Cl₂, which was distilled and de-oxygenated before use, was employed as

solvent. In heteronuclear experiments, DCE was commonly utilized, and the experiments were externally calibrated for the appropriate nucleus of observation. ^{11}B NMR was externally calibrated to $\text{BF}_3\cdot\text{OEt}_2$, ^{31}P NMR was calibrated to H_3PO_4 , and ^{19}F NMR was calibrated to CFCl_3 . Experiments were observed on 400 or 500 MHz Bruker Avance spectrometers unless otherwise indicated.

1:1 Lewis acid to 3-20 experiments. To a small vial, **3-20** (14.2 mg, 0.02 mmol) and either $\text{Sc}(\text{OTf})_3$ (9.8 mg, 0.02 mmol) or FAB (10.2 mg, 0.02 mmol) were added. 1 mL of solvent was added, and the solution was transferred to the NMR tube. The same ^{31}P spectrum was obtained regardless of Lewis acid. $^{31}\text{P}\{^1\text{H}\}$ -NMR (DCE): δ 24.8 (d, J 143 Hz) ppm. *With FAB:* ^{11}B -NMR (DCE): δ 0.57, -1.39 ppm. ^{19}F -NMR (DCE): δ -135.9 (s, broad, 6F), -156.0 (s, 0.6F, ^{10}B isotopic signal), -156.1 (s, 2.3F, ^{11}B isotopic signal), -162.8 (t, J 20.1 Hz, 3F), -167.2 (t, broad, J 19.1 Hz, 6F), -191.6 (s, broad, 1F) ppm. 2D- ^{19}F -COSY: -135.9(-167.2), -156.1(-167.2), -167.2(-135.9, -156.1). 2D-F-NOESY(mix=0.4): -156.1(-191.6).

2:1 FAB to 3-20 ^{11}B and ^1H experiment. To a small vial, **3-20** (7.2 mg, 0.01 mmol) and FAB (10.2 mg, 0.02 mmol) were added. 1 mL of solvent was added, and the solution was transferred to the NMR tube. ^1H -NMR (CD_2Cl_2): δ 1.70 (br, 4H, alkyl H of DPPB), 2.19 (br, 4H, FAB-bound THF), 2.21-2.40 (m, 8H, alkyl H of COD), 2.49 (br, 4H, alkyl H of DPPB), 4.43 (br, 4H, FAB-bound THF), 4.49 (br, 4H, olefinic H of COD), 7.55-7.67 (m, 20H, PPh_2) ppm. *With 10 equiv. HBPin added:* ^{11}B -NMR (DCE): δ -25.1 (d, J 93 Hz, $[\text{HB}(\text{C}_6\text{F}_5)_3]^-$), 21.4 (s, B_2Pin_3), 28.0 (d, J 174 Hz, HBPin) ppm.

1:1 FAB to PhNMe₂ with 5 equiv. of HBPIn. FAB (20.5 mg, 0.04 mmol) was added to a small vial and dissolved in 0.5 mL of CD₂Cl₂. In a separate vial, PhNMe₂ (5 mg, 0.04 mmol) was also added and diluted with 0.5 mL. The two solutions were mixed and transferred to an NMR tube. The mixture was observed by boron NMR, but the experiment had to be conducted on a 600 MHz Bruker Avance spectrometer under proton decoupled conditions in order to resolve the peak assigned to the borenium ion. ¹¹B{¹H}: (CD₂Cl₂, 192MHz): δ -25.4 (s, [HB(C₆F₅)₃]⁺), 26.4 (s, PhMe₂N-BPin), 27.8 (s, HBPIn) ppm.

3.6 References

- ¹ Crudden, C.M., Glasspoole, B.W., Lata, C.J. *Chem. Commun.* **2009**, in press
- ² Crudden, C.M.; Edwards, D. *Eur. J. Org. Chem.* **2003**, 4695-4712.
- ³ Mannig, D.; Noth, H. *Angew. Chem. Int. Ed. Engl.* **1985**, 24, 878-879.
- ⁴ Beletskaya, I.; Pelter, A. *Tetrahedron* **1997**, 53, 4957-5026.
- ⁵ a) Hayashi, T.; Matsumoto, Y.; Ito, Y. *Tetrahedron: Asymm.* **1991**, 2, 601-612.
b) Hayashi, T.; Matsumoto, Y.; Ito, Y. *J. Am. Chem. Soc.* **1989**, 111, 3426-3428
- ⁶ Crudden, C.M.; Hleba, Y.B.; Chen, A.C. *J. Am. Chem. Soc.* **2004**, 126, 9200-9201.
- ⁷ Evans, D.A.; Fu, G.C.; Hoveyda, A.H. *J. Am. Chem. Soc.* **1992**, 114, 6671-6679.
- ⁸ Evans, D. A.; Fu, G. C.; Anderson, B. A. *J. Am. Chem. Soc.* **1992**, 114, 6679-6685.
- ⁹ Hadebe, S. W.; Robinson, R. S. *Tetrahedron Lett.* **2006**, 47, 1299-1302.
- ¹⁰ Edwards, D.R.; Crudden, C.M.; Yam, K. *Adv. Synth. Catal.* **2005**, 347, 50-54.
- ¹¹ Pereira, S.; Srebnik, M. *Tetrahedron Lett.* **1996**, 37, 3283-3286.

-
- ¹² Burgess, K.; Van Der Donk, W.A.; Westcott, S.A.; Marder, T.B.; Baker, R.T.; Calabrese, J.C. *J. Am. Chem. Soc.* **1992**, 114, 9350-9359.
- ¹³ Vogels, C. M.; O'Connor, P. E.; Phillips, T. E.; Watson, K. J.; Shaver, M. P.; Hayes, P. G.; Westcott, S. A. *Can. J. Chem.* **2001**, 79, 1898-1905.
- ¹⁴ Ohmura, T.; Yamamoto, Y.; Miyaura, N. *J. Am. Chem. Soc.* **2000**, 122, 4990-4991.
- ¹⁵ Yamamoto, Y.; Fujikawa, R.; Umemoto, T.; Miyaura, N. *Tetrahedron* **2004**, 60, 10695-10700.
- ¹⁶ Rubina, M.; Rubin, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2003**, 125, 7198-7199.
- ¹⁷ Chen, A.C.; Ren, L.; Crudden, C.M. *Chem. Commun.* **1999**, 611-612.
- ¹⁸ Imao, D.; Glasspoole, B.W.; Laberge, V.S.; Crudden, C.M. *J. Am. Chem. Soc.* **2009**, 131, 5024-5025.
- ¹⁹ Moteki, S.A.; Wu, D.; Chandra, K.L.; Reddy, S.; Takacs, J.M. *Org. Lett.* **2006**, 8, 3097-3100.
- ²⁰ Edwards, D.E.; Hleba, Y.B.; Lata, C.J.; Calhoun, L.A.; Crudden, C.M. *Angew. Chem. Int. Ed.* **2007**, 46, 7799-7802.
- ²¹ Baranano, D.; Hartwig, J.F. *J. Am. Chem. Soc.* **1995**, 117, 2937-2938.
- ²² Shen, Q, and Hartwig, J.F. *J. Am. Chem. Soc.* **2007**, 129, 7734-7735.
- ²³ Evans, D.A.; Muci, A.R.; Stürmer, R. *J. Org. Chem.* **1993**, 53, 5307-5309.
- ²⁴ Yamamoto, H.; Ishihara, K. *Acid Catalysis in Modern Organic Synthesis, Volume 1*. Wiley-VCH: Weinheim, 2008.
- ²⁵ Matar, S.; Hatch, L.F. *Chemistry of Petrochemical Processes* 2nd Edition. Gulf Professional Publishing: Boston, 2001, pg. 256-257.

-
- ²⁶ McKinney, R.J.; Nugent, W.A. *Organometallics* **1989**, 8, 2871-2875.
- ²⁷ Taylor, B.W.; Swift, H.E. *J. Catal.* **1972**, 26, 254-260.
- ²⁸ Parks, D. J.; Piers, W. E. *J. Am. Chem. Soc.* **1996**, 118, 9440-9441.
- ²⁹ Rubin, M.; Schwier, T.; Gevorgyan, N. *J. Org. Chem.* **2002**, 67, 1936-1940.
- ³⁰ Stephan, D.W. *Org. Biomol. Chem.* **2008**, 6, 1535-1539.
- ³¹ Geier, S.J.; Stephan, D.W. *J. Am. Chem. Soc.* **2009**, 131, 3476-3477.
- ³² Welch, G.C.; San Juan, R.R.; Masuda, J.D.; Stephan, D.W. *Science* **2006**, 314, 1124-1126.
- ³³ Chase, P.A.; Welch, G.C.; Jurca, T.; Stephan, D.W. *Angew. Chem. Int. Ed.* **2007**, 46, 8050-8053.
- ³⁴ Chase, P.A.; Jurca, T.; Stephan, D.W. *Chem. Commun.* **2008**, 1701-1703.
- ³⁵ Sumerin, V.; Schulz, F.; Nieger, M.; Leskelä, M.; Repo, T.; Rieger, B. *Angew. Chem. Int. Ed.* **2008**, 47, 6001-6003.
- ³⁶ Chase, P.A.; Stephan, D.W. *Angew. Chem. Int. Ed.* **2008**, 47, 7433-7437.
- ³⁷ Dureen, M.A.; Lough, A.; Gilbert, T.M.; Stephan, D.W. *Chem. Commun.* **2008**, 4303-4305.
- ³⁸ Piers, W.E.; Bourke, S.C.; Conroy, K.D. *Angew. Chem. Int. Ed.* **2005**, 44, 5016-5036.
- ³⁹ De Vries, T.S.; Vedejs, E. *Organometallics* **2007**, 26, 3079-3081.
- ⁴⁰ Ryschkewitsch, G.E.; Wiggins, J.W. *J. Am. Chem. Soc.* **1970**, 92, 1790-1791.
- ⁴¹ Hall, D.G. *Synlett* **2007**, 11, 1644-1655.
- ⁴² Kennedy, J.W.J.; Hall, D.G. *J. Am. Chem. Soc.* **2002**, 124, 898-899.
- ⁴³ Kennedy, J.W.J.; Hall, D.G. *J. Am. Chem. Soc.* **2002**, 124, 11586-11587.

-
- ⁴⁴ Ishiyama, T.; Ahiko, T.; Miyaura, N. *J. Am. Chem. Soc.* **2002**, 124, 12414-12415.
- ⁴⁵ Kobayashi, S. *Eur. J. Org. Chem.* **1999**, 15-27.
- ⁴⁶ Rauniyar, V.; Hall, D.G. *J. Am. Chem. Soc.* **2004**, 126, 4518-4519.
- ⁴⁷ Acceleration values are based on the $t_{1/2}$ values extrapolated for each reaction compared to the same conditions in which **3-15** is not added.
- ⁴⁸ No interaction was observed between FAB and HBPIn by ¹¹B-NMR.
- ⁴⁹ Reactions of internal olefins with [Rh(COD)(DPPB)]BF₄ do proceed with HBPIn in THF to furnish linear pinacol boronate esters.
- ⁵⁰ The observation of cross peaks in the ¹⁹F NOESY spectrum between the signal at -192 ppm (integrating to one fluorine, and assigned to the bridging or transferred F⁻) and that at -156 ppm (integrating to three fluorines and assigned as the BF₃ remnant of the BF₄⁻ counterion) is indicative either of a bridging event or of a full transfer followed by exchange of the fluorine in question between the two boron-based Lewis acids. It should be noted that the hydroboration was not accelerated by the addition of BF₃ etherate even in large quantities.
- ⁵¹ Chen, M.-C.; Roberts, J.A.S.; Marks, T.J. *J. Am. Chem. Soc.* **2004**, 126, 4605-4625.
- ⁵² BF₃•OEt₂ added to Rh catalyzed hydroborations of *trans*-4-octene does not activate the reaction in DCE or DCM.
- ⁵³ Blackwell, J.M.; Morrison, D.J.; Piers, W.E. *Tetrahedron* **2002**, 58, 8247-8254.
- ⁵⁴ Boron NMR studies with equimolar FAB and THF confirm the requirement of THF in the B-H bond cleavage of HBPIn.

-
- ⁵⁵ Arase, A.; Nunokawa, Y.; Masuda, Y.; Hoshi, M. *J. Chem. Soc., Chem. Commun.* **1992**, 51-52.
- ⁵⁶ McCahill, J. S. J.; Welch, G. C.; Stephan, D. W. *Angew. Chem. Int. Ed.* **2007**, *46*, 4968-4971.
- ⁵⁷ Timoshkin, A. Y.; Frenking, G. *Organometallics* **2008**, *27*, 371-380.
- ⁵⁸ Endo, K.; Hirokami, M.; Takeuchi, K.; Shibata, T. *Synlett* **2008**, *20*, 3231-3233.
- ⁵⁹ The rhodium hydride peak was assigned as a doublet of triplets at δ -15.6 ppm (J 14.8, 18.6 Hz).
- ⁶⁰ DuBois, D. L.; Blake, D. M.; Miedaner, A.; Curtis, C. J.; DuBois, M. R.; Franz, J. A.; Linehan, J. C. *Organometallics* **2006**, *25*, 4414-4419.
- ⁶¹ Price, A. J.; Ciancanelli, R.; Noll, B. C.; Curtis, C. J.; DuBois, D. L.; DuBois, M. R. *Organometallics* **2002**, *21*, 4833-4839.