Catalytic Asymmetric Hydroboration: Recent Advances and Applications in Carbon−Carbon Bond-Forming Reactions

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The metal-catalyzed hydroboration reaction provides access to functionalized organoboron derivatives that cannot be easily prepared using traditional reagents. New developments in this reaction including neoteric reaction media and novel ligands are described in this review. A key aspect of the hydroboration reaction is the ability to further derivatize the product. Thus the conversion of boronate esters into amines, esters, alcohols, carboxylic acids and amino acids is described.

1. Introduction

The use of transition-metal catalysts in organic synthesis offers innumerable advantages to the synthetic chemist. Since the mechanisms of catalyzed and uncatalyzed reactions are often widely different, discrepancies in chemoselectivity, regiochemistry, and diastereoselectivity can be expected. The opportunity to introduce asymmetry by the use of chiral ligands on the metal catalyst is also of paramount importance. The metal-catalyzed hydroboration of olefins is a reaction that has all of these features, but the selectivity observed is dependent on the substrate (Figure 1).

Considering that the introduction of main-group organometallics such as boron into organic compounds is rarely the ultimate goal of a hydroboration reaction,[1] methods for transformation of the newly introduced carbon−boron bond with retention of stereochemistry are

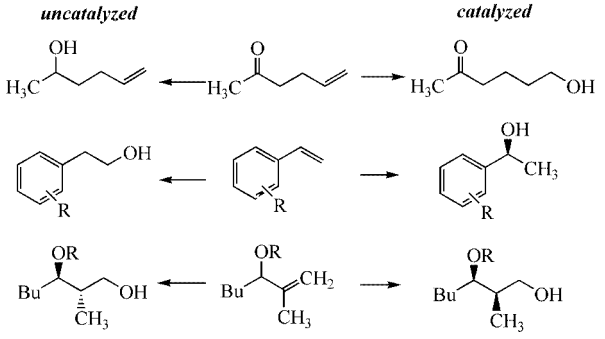

Figure 1. Chemo-, regio-, and stereoselectivity in catalyzed and uncatalyzed hydroboration/oxidation of olefins

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MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

crucial. In this review, we will describe the mechanism and selectivity of metal-catalyzed hydroborations of olefins (primarily), and recent advances in ways to functionalize the carbon−boron bond (Figure 2).[2]

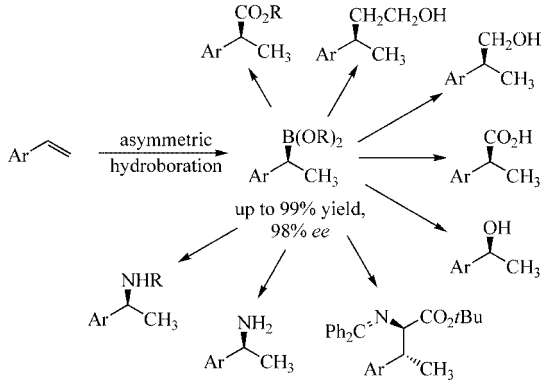
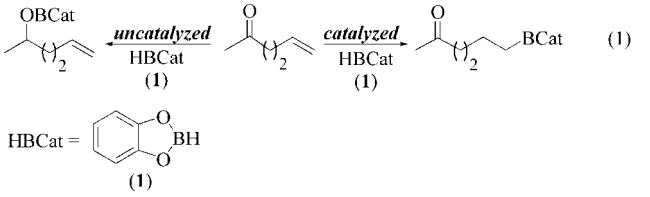


Figure 2. Transformations of the carbon−boron bond

2. Metal-Catalyzed Hydroborations

The ability of late transition metals to catalyze the hydroboration of carbon−carbon multiple bonds was first discovered by Wilczynski and Sneddon over twenty years ago.[3] Männig and Nöth's seminal paper on the use of catecholborane (**1**)[4] for catalyzed hydroborations appeared shortly thereafter, establishing the synthetic utility of the hydroboration of olefins from a synthetic organic perspective.[5] Importantly, they demonstrated that the chemoselectivity of the reaction was different in the catalyzed and uncatalyzed variants of the reaction [Equation (1)].



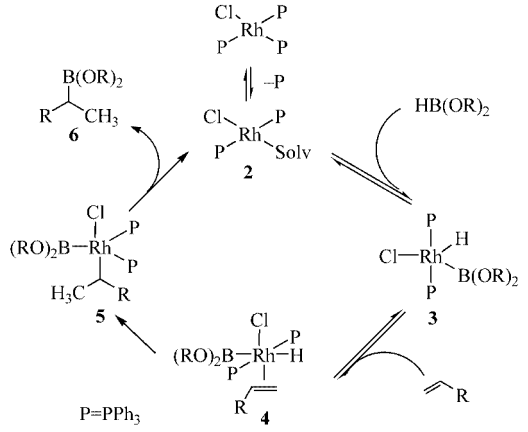
The use of catecholborane in this reaction was critical, since unlike BH_3 and alkylboranes such as 9-BBN, it reacts only sluggishly with olefins in the absence of the catalyst. Mesomeric overlap of the oxygen lone pairs with the empty orbital on boron dramatically decreases the Lewis acidity of boron, and therefore its ability to complex olefins. Similar B−H containing species have also been employed in metal-catalyzed hydroborations, and will be discussed subsequently.

The large majority of metal-catalyzed hydroborations of olefins employed rhodium complexes, but there have been scattered reports of the use of other metals. Marks,[6] Molander,[7] and Evans[8] have reported lanthanide-catalyzed hydroboration reactions, which will be reviewed in Section 2.2.2. Pd,[9] Ru,[10] Zr,[11,12] and Ti[13] have also been employed with varying degrees of success.

2.1 Hydroboration with Rhodium Catalysts

2.1.1 Mechanistic Studies

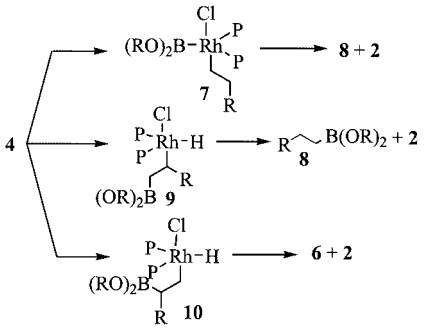
During their study of the hydroboration of styrene with catecholborane, Männig and Nöth[5] determined that Wilkinson's catalyst was the most active of the many complexes examined. Extensive mechanistic investigations have led to a detailed understanding of some of the controlling elements of the hydroboration of several types of olefins. The basic mechanism is shown in Scheme 1.



Scheme 1. Hydroboration of olefins with Wilkinson's catalyst

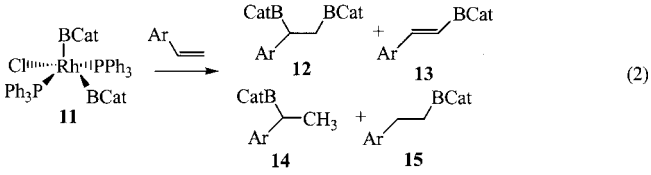
The reaction begins by dissociation of one phosphane molecule from Wilkinson's catalyst followed by oxidative addition of catecholborane. The product **3** of this reaction was isolated by Kono et al. [$HB(OR)_2$ = catecholborane and 4,4,6-trimethyl-1,3,2-dioxaborinane].[14] Westcott et al. isolated the corresponding complex, where P = P(*i*Pr)$_3$, and determined its structure by X-ray crystallography.[15] Complexation of the olefin then generates six-coordinate intermediate **4**. According to calculations by Ziegler et al., the hydride and boryl ligands are *trans* in the reactive form of this complex.[16] Insertion of the olefin into the metal−hydride bond gives **5**, and reductive elimination generates the product and regenerates the catalyst. Precedent for this last step comes from the stoichiometric studies of osmium boryl complexes by Roper and Wright.[17]

Intermediate **4** is the key species in this cycle, as it is from here that the path of the reaction may diverge (Scheme 2). Insertion of the alkene into the Rh−H bond with reverse regioselectivity yields **7**, which undergoes reductive elimination to generate the linear isomer of the product, **8**. Since the hydride and boryl ligands are proposed to be *trans* to each other,[16] they are necessarily *cis* to the coordinated alkene. Thus from **4**, insertion of the alkene into the Rh−B bond would yield **9** or **10**. Reductive elimination of the alkyl and hydride ligands then generates **6** or **8**.



Scheme 2. Mechanistic divergence from complex **4**

The feasibility of the insertion of alkenes into the rhodium boryl bond takes its precedent from the observation of a similar pathway in hydrosilylation reactions,[18] the many examples of diboration reactions that have been reported in the literature,[19,20] and the isolation of catalytically competent metal diboryl complexes by Baker et al.[21] In a key paper, Baker and coworkers demonstrated that the diborylrhodium complex **11** is able to affect the diboration, dehydrogenative borylation, and hydroboration of vinyl arenes.

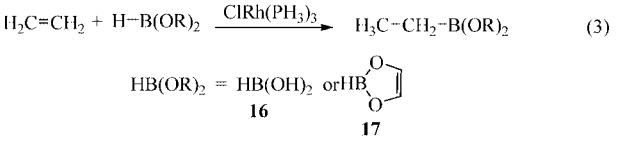


(2)

Compound **13** is also observed under regular hydroboration conditions and is believed to be linked to initial insertion of the olefin into the Rh−B bond to yield **9**, which then undergoes reductive elimination [Equation (2)]. Depending on the exact nature of the catalyst and conditions, the vinyl boronate can be the major or sole product.[22,23] Dehydrogenative borylation is frequently accompanied by alkane ($ArCH_2CH_3$) formation, resulting from hydrogenation by the liberated hydrogen gas. The presence of hydrogen in the reaction mixture can also lead to hydrogenation of the vinyl boronate itself.[24] It is therefore possible to produce alkylboronate **8** by three mechanistically distinct routes, illustrating the complexity of this reaction.

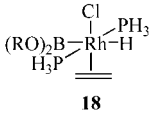
2.1.2 Theoretical Studies

Widauer, Grutzmacher and Ziegler have performed extensive theoretical calculations on the rhodium-catalyzed hydroboration reaction shown in Equation (3).[16]

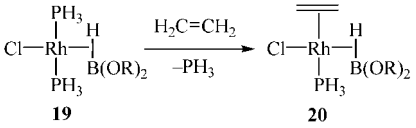


(3)

The key step in the reaction is the migratory insertion of the olefin into the Rh−H or Rh−B bonds from compound **18**. Somewhat surprisingly, the two pathways are kinetically and thermodynamically very similar. Both are exothermic (15−22 kcal/mol) and proceed with small barriers (<3.5 kcal/mol). Reductive elimination is again similar, occurring in both cases with a barrier of about 9 kcal/mol. Thus for these particular reactants, either boryl or hydride migrations are feasible pathways.



Ziegler et al. also examined the "dissociative" pathway, initially proposed by Männig and Nöth,[5] in which complexation of the olefin to complex **19** brings about displacement of one of the phosphanes yielding **20** [Equation (4)].



(4)

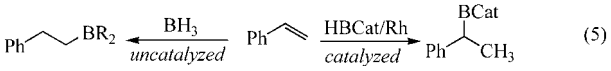
Examining the hydride and boryl insertions from compound **20**, Ziegler found a dramatic kinetic difference between the two routes. Insertion into the Rh−H bond occurs readily and with *virtually no barrier*, but is followed by a difficult reductive elimination step with a high barrier of almost 15 kcal/mol. On the other hand, initial boryl migration has a high barrier (19.5 kcal/mol) but is followed by a facile C−H reductive elimination step. These results led Ziegler to conclude that the *boryl migration may be preferred because on the hydride path, the initial rapid preequilibrium followed by a high activation barrier "hinders product formation on this path".* Interestingly, this provides a potential rationale for the dramatic differences observed for the selectivity of the hydroboration depending on the number of phosphane ligands.

2.1.3 Phosphane Oxidation and Side Reactions

Loss of phosphane ligands generally results from accidental oxidation of the catalyst, which is known to occur in solution and even in the solid state. The products of oxidation are Rh^{III} peroxo species and triphenylphosphane oxide and can make up a significant percentage of the catalyst. Although peroxo Rh complexes are not themselves catalysts for hydroboration or hydrogenation, catalytically active Rh^{I} complexes can be generated under the reaction conditions by reduction of the dioxo species. The end result is the production of a catalyst that contains fewer phosphane units than the starting complex. Ironically, this can actually improve the catalytic activity of Wilkinson's catalyst, as was noted in hydrogenation studies.[25]

The adventitious removal of phosphanes by oxidation has a significant effect on the regioselectivity of the hydro-

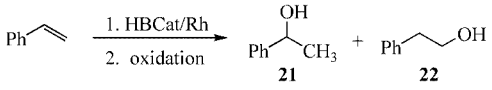
boration reaction.[26−28] The effect varies from substrate to substrate, and has been most thoroughly studied for vinyl arenes. Under carefully controlled (oxygen-free) catalytic conditions, the branched isomer is the major product while the linear isomer predominates in the noncatalyzed hydroboration [Equation (5)].[29]



(5)

It was originally thought that the specific combination of tertiary phosphanes and a cationic rhodium source, $[Rh(COD)_2]^+BF_4^-$, was responsible for the unprecedented Markovnikov addition yielding **21**.[29] It was later shown, however, that neutral rhodium complexes such as Wilkinson's catalyst and $[Rh(COD)Cl]_2/4PPh_3$ [30] also react with high selectivity for the branched isomer. This fact took some time to be clarified because oxidation of the catalyst leads to increased production of the linear isomer **22**.[31] Using a neutral catalyst without any phosphanes ($[Rh(COD)Cl]_2$), almost 80% of the alcohol observed is the linear isomer.[30] Interestingly, the high selectivity for the branched isomer exhibited by a fresh batch of Wilkinson's catalyst can be completely regained by the addition of phosphane to the oxidized catalyst (Table 1).[32]

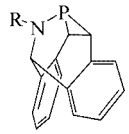
Table 1. Effect of catalyst purity on regioselectivity



Catalyst	Purity	21	22
$ClRh(PPh_3)_3$	Fresh	> 99	< 1[a]
$ClRh(PPh_3)_3$	Oxygen treated	60	40[a]
$[Rh(COD)Cl]_2$	Fresh	27	73[b]
$ClRh(PPh_3)_3$	O_2 treated, then add 2 PPh_3	> 99	< 1[a]

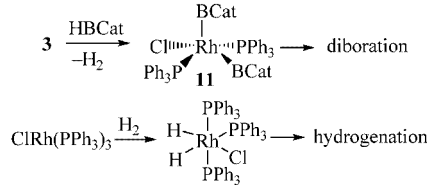
[a] Taken from ref.[26] [b] Taken from ref.[30]

Grüzmacher has reported the synthesis and application of a new phosphane ligand (Barbarphos, **23**) which is resistant to oxidation both in its isolated form and as a complex with Rh. This complex was employed in the hydroboration of styrene and gave an 80:20 mixture of **21**/**22**.[33]



23
BARBAR-Phos

Secondary reactions of catecholborane can be detrimental depending on the substrate. The reaction between catecholborane and $[ClRh(PPh_3)_3]$ generates several complexes including $[HRhCl(BCat)(PPh_3)_2]$ (**3**), $[H_2RhCl(PPh_3)_3]$, $[HRh(PPh_3)_4]$, and $[RhCl(BCat)_2(PPh_3)_2]$ (Scheme 3). If the olefin is unreactive, complex **3** is exposed to a huge excess of catecholborane, with which it reacts a second time, generating complex **11** and H_2. Complex **11** is a functional diboration/dehydrogenative borylation catalyst [Equation (2)].[21] The reaction between Wilkinson's catalyst and hydrogen generates $[H_2RhCl(PPh_3)_3]$, which can lead to hydrogenation of the substrate. Thus in order to carry out the hydroboration of hindered olefins, more robust hydroborating reagents need to be developed.



Scheme 3. Side reactions observed with Wilkinson's catalyst and catecholborane (HBCat)

The decomposition of catecholborane also occurs upon treatment with nucleophiles such as phosphanes. This obviously poses a problem as phosphanes are generated in the first step of the reaction by dissociation from Wilkinson's catalyst. The decomposition of catecholborane promoted by PPh_3 takes place with a half life of 4.5 h and yields a phosphane−borane adduct.[34] This same reaction is observed when PCy_3 or $PiPr_3$ are employed.

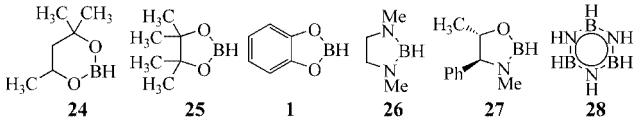
Considering the number of possible side reactions, it is perhaps surprising that the rhodium-catalyzed hydroboration reaction is a valuable synthetic tool. This is because under properly controlled conditions, and most importantly with the proper substrate, the reaction proceeds cleanly and with high selectivity. Difficulties arise with unreactive substrates, and thus the major limitation of the catalytic hydroboration is the substrate scope. The most commonly employed substrates are vinyl arenes, 1,1-disubstituted olefins and cyclohexene derivatives (Figure 1). Highly substituted olefins are essentially unreactive, and reaction of some functional groups with HBCat is also a complication. A wide variety of olefins can be hydroborated under these conditions, but the advantages over non-metal-catalyzed hydroborations are not always obvious. Alkenes with fluorine substituents in the allylic position are an interesting new class of olefins that have been subjected to catalytic hydroboration.[35] For a comprehensive review of the scope of the Rh-catalyzed hydroborations, see the review by Pelter and Beletskaya.[2]

2.1.4 Alternative Reagents for Hydroboration with Rhodium Catalysts

Given the instability of catecholborane under the reaction conditions, it is somewhat surprising that it remains the most frequently used reagent for the hydroboration of olefins. Other borane reagents have been successfully employed in the catalytic hydroboration reaction.[36] Like catecholborane, they all contain heteroatoms directly attached

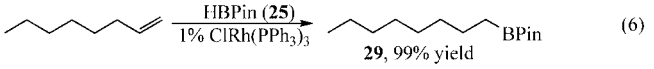
to boron in order to limit the background (uncatalyzed) reaction.[37]

In Männig and Nöth's original report, borane **24** (Scheme 4) was also reported to react with olefins in the presence of Wilkinson's catalyst. Despite this fact, it has remained largely unexplored. The closely related pinacolborane (**25,** HBPin) has received some attention, mostly by the groups of Srebnik[12] and Westcott.[38] Molander has employed the less reactive borane **26** in reactions catalyzed by lanthanides.[7] J. M. Brown's group pioneered the use of chiral oxazaborolidine reagents such as **27** in the metal-catalyzed hydroboration of styrene.[39] More exotic reagents such as borazine **28**[40] and polyhedral boranes have also been employed, but the cost of these reagents makes them unlikely to be used in organic synthesis.



Scheme 4. Boranes for catalyzed hydroborations

Pereira and Srebnik have shown that pinacolborane is able to hydroborate a wide variety of alkenes[12] in the presence of rhodium and zirconium catalysts [Equation (6)]. The major product in all cases is the linear isomer **29**, even when an internal alkene is employed [Equation (7)]. This is in contrast to the results obtained by Suzuki, Miyaura et al. for the hydroboration of internal olefins with catecholborane,[41] a result Srebnik attributes to the greater steric demands of the pinacol group. Srebnik has also demonstrated the utility of pinacolborane in the hydroboration of alkynes with $[Cp_2ZrHCl]$.[11] In this case, the use of pinacolborane gave greater selectivity and ease of isolation of the products.



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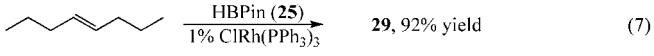
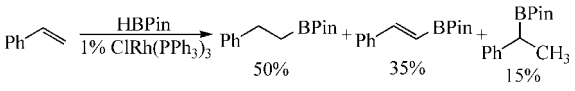


(7)

In hydroborations of styrene with pinacolborane, a mixture of hydroboration and dehydrogenative borylation products are observed, in which the branched isomer is the smallest component of the product mixture [Equation (8)].[12] Masuda has reported that $[Rh(COD)Cl]_2$ also catalyzes the reaction of pinacolborane and styrene, but with this phosphane-free catalyst, dehydrogenative borylation (and attendant alkene hydrogenation) is the observed pathway [Equation (9)].[42] Considering the utility of vinylboronates in coupling reactions, this is a useful reaction for their preparation, the only drawback being that a full equivalent of the alkene is consumed by hydrogenation.



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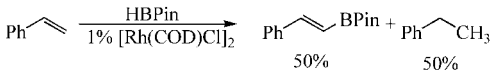
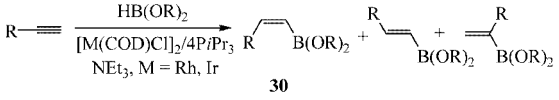


(9)

An alternative way to access vinyl boronates is by hydroboration of alkynes. Srebnik has used this reaction in concert with a Suzuki coupling, as a hydroarylation reaction.[43] In this case, a simple thermal hydroboration was employed, but Miyaura has reported that Rh and Ir complexes can catalyze this reaction [Equation (10)].[44] When Rh is used as the catalyst, the *cis*-boronate ester **30** is the major product (selectivities greater than 99%) and there is little difference between the reaction with pinacolborane or catecholborane. In the case of iridium, the selectivities are eroded, and the reaction with pinacolborane gives a higher yield (73% vs. 43%).

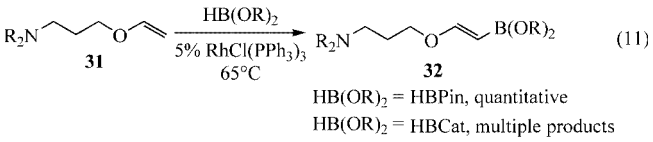


(10)

Alkynes and alkenes can also be hydroborated with pinacol (or catechol) borane in the absence of a catalyst.[45] Unlike hydroborations of alkenes with alkylboranes such as 9-BBN or BH_3, uncatalyzed reactions with dialkoxyboranes must be heated in order to take place. Knochel has described the thermal addition of pinacolborane to a variety of alkenes and alkynes. In the case of olefins, the reaction must be heated for several days in order to go to completion, but the hydroboration of alkynes is surprisingly facile in the absence of a catalyst (88% yield after 2 h at 25 °C for a terminal alkyne). The same reaction can be performed with catecholborane, but with a decreased selectivity for the *trans*-boronate ester.

Maddaluno et al. also examined the hydroboration of various olefins with catecholborane and pinacolborane using Wilkinson's catalyst and found significant differences in reactivity and regioselectivity between these two reagents.[46] They also examined the effect of pressure on the reaction and found that in some cases yields were improved by the application of high pressures (13 kbar). Finally, in an elegant demonstration of the effect of Lewis acidity on the hydroboration of functionalized alkenes, Westcott, Vogels et al. demonstrated that the reaction of the aminopropyl vinyl ether **31** is significantly improved when pinacolborane is used in place of catecholborane [Equation (11)].[38,47] The reaction with pinacolborane is reported to be significantly cleaner than with catecholborane, a fact attributed to the decreased Lewis acidity of HBPin. Westcott's group has demonstrated that the basic nitrogen reacts rapidly with

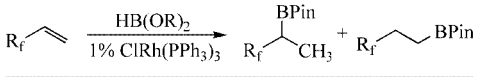
HBCat, complicating the desired reaction (in this case dehydrogenative borylation).



(11)

An additional substrate class that benefits from hydroboration with pinacolborane is fluorinated olefins. Ramachandran and Brown have shown that under otherwise identical conditions, the use of pinacolborane instead of catecholborane leads to improved selectivity for the linear isomer, even in the case of vinyl arenes, which almost always provide the branched isomer as the major product.[35] The results are shown in Table 2.

Table 2. Effect of hydroborating reagent on regioselectivity



R_f	$HB(OR)_2$	Branched	Linear
CF_3	HBCat	47	53
CF_3	HBPin	8	92
C_6F_5	HBCat	79	21
C_6F_5	HBPin	25	60[a]

[a] 15% vinylboronate detected as well.

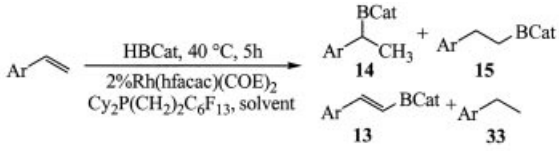
These studies illustrate that the hydroboration reaction can be extremely sensitive to the size and electronic properties of the reagent. An added advantage of using pinacolborane is the ease of handling of the boronate ester products, which are stable even to chromatography.

Aside from pinacol and catecholborane, few other boranes have been seriously investigated for this reaction.[48] Most notably, Sneddon has employed borazine to prepare precursors to boron carbide and boron nitride materials.[40] In the initial phases of work on the hydroboration of olefins, polyhedral boranes were used, as described previously. Finally, the only other significant borane species employed in catalyzed hydroborations are oxazaborolidines, which were used by Lloyd-Jones and J. M. Brown in their studies of the asymmetric hydroboration of styrene.[24] This chemistry will be discussed in Section 3.2 (enantioselective hydroborations).

2.1.5 Hydroboration with Catalysts on Inorganic Supports or in Neoteric Media

The hydroboration of various vinyl arenes in supercritical CO_2 was recently investigated by Tumas, Baker et al.

Table 3. Effect of solvent and phosphane on selectivity of hydroboration of vinyl arenes (Ar = 4-$MeOC_6H_4$)



Solvent	14	15	13	33
THF	32	34	17	17
$CF_3C_6F_{11}$	25	41	17	17
$scCO_2$ (2800 psig)	100	–	–	–

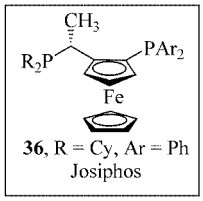
(Table 3).[49] Relative to other solvents such as THF and $CF_3C_6F_{11}$, $scCO_2$ was found to give higher selectivities for the hydroboration of 4-vinylanisole using a range of fluorinated phosphane ligands. For example, using $Cy_2PCH_2CH_2C_6F_{13}$ as the ligand and [(hfacac)Rh(COE)$_2$] as the catalyst, the reaction showed low selectivity in THF, but 100% selectivity was observed in $scCO_2$.

Horvath, Gladysz and coworkers have described hydroboration reactions in fluorous solvents as a means to effect catalyst recovery.[50] Rh complexes substituted with highly fluorinated phosphanes such as $P(CH_2CH_2C_6F_{13})_3$ have increased solubility in fluorinated solvents by virtue of their fluorous "pony tails". The reactions are run in $CF_3C_6F_{11}$ and the boronate esters extracted into THF upon completion. The catalyst then remains in the fluorinated solvent where it can be reused up to 5 times without discernible loss of activity, and with very little leaching of Rh (less than 5 ppm Rh per mole of substrate). The activity of the fluorinated catalyst relative to Wilkinson's catalyst was examined by running both reactions in $CF_3C_6F_{11}$. The reactivity and regioselectivity of the $P(CH_2CH_2C_6F_{13})_3$-substituted catalyst is significantly less than for Wilkinson's catalyst. It appears that this is actually a function of the aliphatic nature of the phosphane substituents rather than the fluorine substitution. Research into the preparation of aromatic ligands containing fluorous pony tails is thus underway. Importantly, this was the first report of a recyclable catalyst for the hydroboration reaction.

Subsequent to this work, Fernandez, Claver et al. reported that various rhodium complexes with chiral ligands could be immobilized on dehydrated Montmorillinite by simple ion exchange.[51] Although the immobilized catalysts initially gave lower enantioselectivities, regioselectivities and yields than the homogeneous catalysts, upon reuse, results matching the homogeneous catalysts were obtained. Most remarkably, the catalysts could be reused even after filtering in air, without loss of activity or selectivity.

Köllner and Togni have described a dendrimeric version of their Josiphos ligand (**36**, see Scheme 5).[52] This ligand was shown to react with similar levels of enantioselectivity in the asymmetric hydroboration of styrene. Like all dendrimeric ligands, the potential to recover the ligand by mic-

rofiltration exists, although it was not demonstrated in this case.

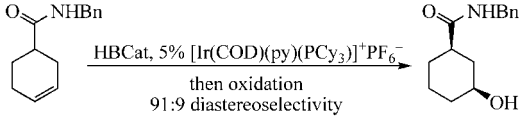


Scheme 5. Josiphos ligand class

2.2 Hydroboration Catalyzed by Metals Other than Rhodium

2.2.1 Iridium

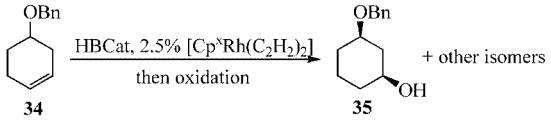
Second to rhodium, iridium is the most widely used hydroboration catalyst.[2,53,54] Evans and Fu reported that Crabtree's catalyst, $[Ir(COD)PCy_3(py)]^+PF_6^-$, was highly effective for the directed hydroboration of allylic- and homoallylic amides [Equation (12)].[55] This report was a significant improvement on their original efforts to direct hydroboration reactions using diphenyl phosphinites in which stoichiometric quantities of Rh were required.[56]



(12)

Following this study, Fu reported independently that the use of indenyl-ligated Rh complexes showed improved selectivity for directed hydroborations.[57] This was the first use of the indenyl ligand as a method for obtaining the necessary coordinative unsaturation on the metal required to bind the olefin, the directing group and the reagent, HBCat. Remarkably, Fu showed that the diastereoselectivity of the hydroboration could be directly correlated to the ability of the indenyl or cyclopentenyl ligand to "slip" to a lower coordination form (η^3 from η^5, Table 4). This was also the first report of an ether-directed hydroboration.

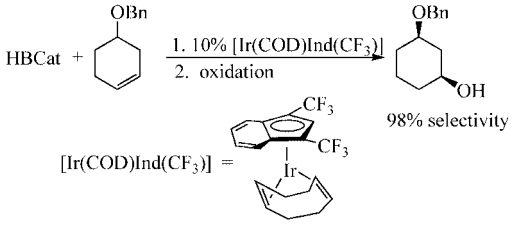
Table 4. Indenyl and cyclopentadienyl ligands in hydroboration



Cp^x	cis-1,3	cis-1,4	trans isomers
Ind	75	7	19
Me_3Ind	65	10	25
Cp	30	28	42
Cp*	26	29	45

Ind > Me_3Ind > Cp > Cp* *increasing propensity for ring slippage*

Subsequent to this work, Sowa Jr. demonstrated that changing the metal to Ir and employing highly electron-deficient indenyl ligands gave significantly improved selectivity.[58] Under optimized conditions, up to 98% selectivity for the 1,3-*cis* isomer could be achieved [Equation (13)].

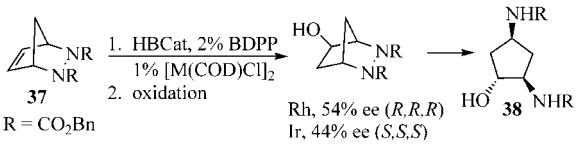


(13)

The significant effect that the indenyl ligand has on the reaction implies that it remains attached to the catalyst during the hydroboration. This is remarkable since it has been reported that related η^3-ligands are destroyed during the hydroboration of vinyl-arene-type substrates.[59] In stoichiometric studies, [(η^5-indenyl)Ir(COD)] is converted quantitatively into [(η^6-arene)Ir($BCat)_3$] upon treatment with 5 equivalents of catecholborane.[60] However, it should be kept in mind that the reactivity of metal complexes in the presence or absence of alkenes (substrates) can be significantly different.

To date, there have been only two reports of enantioselective hydroborations employing Ir complexes. As part of his comprehensive studies of the Josiphos class of ligands (**36**, Scheme 5), Togni reported that replacing rhodium with iridium led to a decrease in regioselectivity.[61] The enantioselectivity of the hydroboration of styrene dropped from 91% *ee* to 77% *ee*.[62] Westcott, Baker et al. have shown that a variety of Ir/monodentate phosphane complexes catalyze the hydroboration of vinyl arenes with high levels of selectivity for the *linear* isomer (70−98% linear).[63]

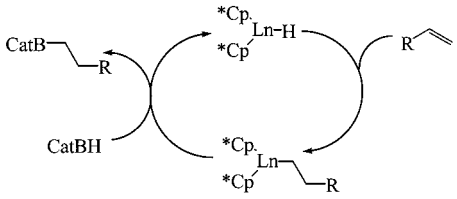
Bonin, Micouin and coworkers have disclosed that in the presence of catecholborane, $[Ir(COD)Cl]_2$ and a chiral ligand, olefin **37** undergoes an enantioselective hydroboration [Equation (14)].[64] This particular substrate is valuable since it can be converted into a highly functionalized diamine **38**. Although the enantiomeric excesses obtained were not remarkable, the researchers found that the sense of induction changed when Rh was employed instead of Ir. The highest enantioselectivity obtained using Ir was obtained when Josiphos was employed (64% *ee* at 0 °C). The authors have interpreted these data as being the result of a change in mechanism. They propose that the hydroboration with Rh takes place via insertion of the alkene into a metal−hydride bond, while the Ir-catalyzed process involves insertion into the metal−boron bond.



(14)

2.2.2. Samarium

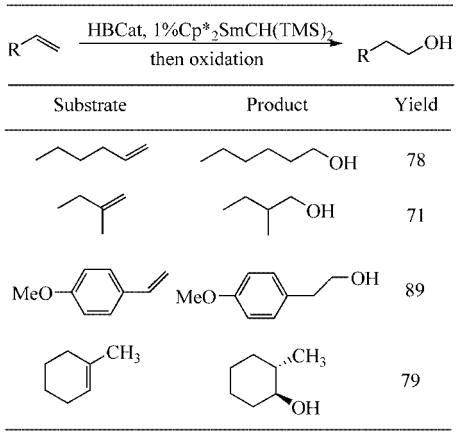
Shortly after the key mechanistic papers on the Rh-catalyzed hydroboration appeared, Marks reported a hydroboration reaction catalyzed by lanthanide complexes that proceeds by a completely different mechanism.[6,65] As in other reactions catalyzed by lanthanides, it is proposed that the entire catalytic cycle takes place without any changes in oxidation state of the central metal. The proposed mechanism is shown in Scheme 6. The true catalyst (Cp^*_2LnH) is generated by reaction of the precatalyst with catecholborane.



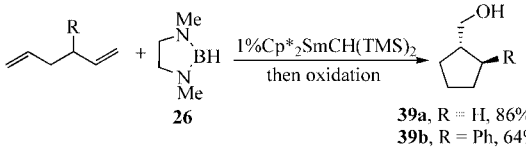
Scheme 6. Proposed mechanism for hydroboration with lanthanides

Since the mechanism is significantly different, it is not surprising that the regioselectivity and scope are also distinct. Several notable examples are given in Table 5. Unlike the reaction catalyzed by Rh complexes, vinyl arenes react to give predominantly the linear isomer. Most remarkably, trisubstituted olefins can be hydroborated in high yield.

Table 5. Hydroboration of olefins with $Cp^*_2SmCH(TMS)_2$



Molander[7] showed that under similar reaction conditions dienes yield cyclopentanols such as **39** [Equation (15)]. In order to accomplish this transformation in a reasonable yield, the reagent employed had to be changed from catecholborane, which afforded none of the desired product, to borane **26**, which gave an 86% yield. The significant effect of the hydroborating reagent was believed to stem from the competition between σ-bond metathesis and cyclization to yield **39**. Interestingly, substitution of one of the allylic hydrogen atoms slowed the reaction so dramatically that it had to be heated to 80 °C in order to obtain a reasonable yield.



(15)

The development of an enantioselective hydroboration catalyzed by an asymmetric version of $[Cp^*_2SmCH(TMS)_2]$ would be a significant achievement considering the high reactivity of this catalyst towards trisubstituted olefins.

2.2.3. Other Metals

Lewis acidic early transition-metal species have also been investigated and shown to catalyze the hydroboration of olefins.[13] In many cases, however, the role of the transition metal has merely been to catalyze the decomposition of HBCat to BH_3, which then hydroborates the alkenes. Hartwig has reported an example of a "true" hydroboration catalyzed by $[TiCp_2L_2]$.[13] Srebnik has shown that $[ZrCp_2HCl]$ is a very effective catalyst for the hydroboration of alkynes with pinacolborane.[11]

Late transition metals in the nickel/palladium/platinum series have been shown to catalyze the hydroboration of alkynes with varying degrees of effectiveness.[9]

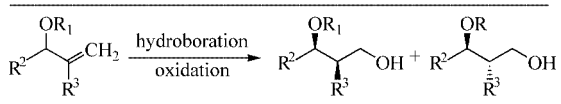
3. Stereocontrol in Catalyzed Hydroborations

3.1 Diastereoselective Hydroborations

The use of inherent substrate chirality to control the direction of hydrogenation reactions has been studied in great detail by Brown,[66] Evans[67] and Crabtree.[68] Similar levels of control can be obtained in the hydroboration reaction, although this has been investigated to a significantly lesser extent. Steric constraints (specifically $A^{1,3}$-strain)[69] and directing functional groups have both been used successfully in diastereoselective hydroborations. The most successful directed hydroborations were described by Sowa Jr. et al. for the hydroboration of cyclohexenols catalyzed by iridium indenyl complexes [Equation (13), Section 2.2.1).[58]

In the case of 1,1-disubstituted olefins with a stereocentre in the allylic position, high levels of stereocontrol can be obtained in both the catalyzed and uncatalyzed systems.[70] As shown in Table 6, the hydroboration of alkenes **40a**−**d** gives the *syn* isomer selectively under catalytic conditions while the anti isomer predominates with 9-BBN.

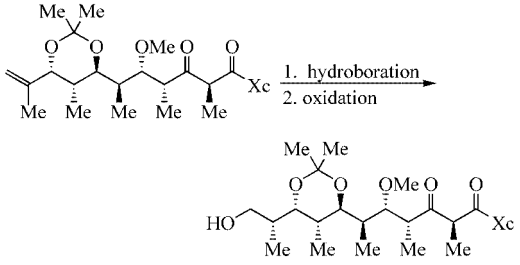
Table 6. Diastereoselective hydroborations of 1,1-disubstituted olefins



Substrate	R^1	R^2	R^3	Conditions	*syn*-41	*anti*-41
40a[a]	H	Me	*n*Pr	9-BBN	8	92
				Rh/HBcat	75	25
40b[a]	Si*t*BuMe$_2$	Me	*n*Pr	9-BBN	11	89
				Rh/HBcat	96	4
40c[b]	COCF$_3$	*n*Bu	Me	9-BBN	7	93
				Rh/HBcat	88	12
40d[b]	CO*t*Bu	*n*Bu	Me	9-BBN	4	96
				Rh/HBcat	87	13

[a] Taken from ref.[72] [b] Taken from ref.[73]

Although several rationales for the observed change in selectivity have been advanced,[71] the reaction has synthetic importance for the preparation of highly substituted propionate units as demonstrated by Evans and Sheppard in the synthesis of lonomycin [Equation (16)].[72]

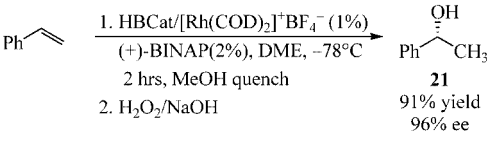


(16)

3.2 Enantioselective Hydroborations

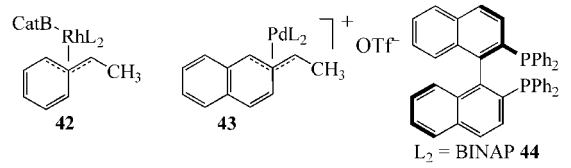
3.2.1. Chiral Bisphosphane Ligands

Following Männig and Nöth's 1985 report of the Rh-catalyzed hydroboration with catecholborane,[5] attention quickly turned to performing the reaction enantioselectively. Promising results were initially reported by Burgess[73] and Suzuki,[41] but it was Hayashi's work with vinyl arenes that provided definitive proof that high levels of enantioselection were attainable[30,31] [Equation (17)]. Perhaps the most intriguing feature of the Hayashi report was the complete reversal in regiochemistry observed in the catalytic hydroboration relative to the uncatalyzed reaction.



(17)

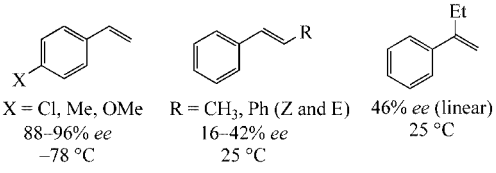
The rationale for the preferential production of the branched isomer was provided by Hayashi, who suggested the potential intervention of a π-benzyl complex such as **42**.[30] Addition of the Rh−H in the opposite sense, which leads ultimately to the linear isomer, does not benefit from the potentially stabilizing interaction between the catalyst and the arene. Related π-benzyl complexes have been isolated in several cases, most recently by Nettekoven and Hartwig (Scheme 7).[74]



Scheme 7. π-Benzyl intermediates

Further evidence for this effect is found in J. M. Brown's study of the hydroboration of *ortho*-substituted styrenes using QUINAP (Section 3.2.2).[75] Although 2,4-dimethylstyrene is hydroborated with good enantioselectivity and (more importantly) 95−97% regioselectivity in favour of the secondary product, introduction of a second *ortho*-methyl group (2,4,6-trimethylstyrene) results in a precipitous decrease in regioselectivity to 63%. Brown attributes this to the fact that the second *ortho*-substituent prevents the arene from achieving coplanarity with the alkene, negating the establishment of the stabilizing η^3-benzylrhodium interaction.[75]

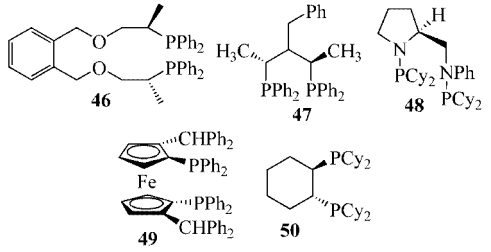
The Hayashi study employed atropisomeric BINAP (**44**) as the chiral ligand, which is still one of the best ligands for the Rh-catalyzed hydroboration of styrenes in terms of asymmetric induction and activity.[76] A variety of substituted styrenes were studied, with electron-rich olefins giving higher enantioselectivities than electron-poor substrates. Styrene derivatives that are more sterically hindered, including *ortho*-substituted styrenes, react with lower yields and lower levels of asymmetric induction. β-methyl styrene derivatives are hydroborated with modest enantioselectivities, mainly because of the decreased reactivity of these substrates, which necessitates performing the reaction at 25 °C (Scheme 8).[30]



Scheme 8. Enantioselective hydroborations with [Rh(COD)$_2$]BF$_4$ and BINAP

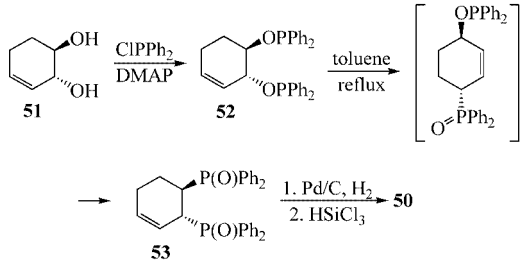
Other diphosphanes that have been examined include compounds **46**−**50** (Scheme 9). Hemilabile ligand **46** was prepared by Flor and coworkers.[77] The two ether linkages are postulated to function as coordinated solvent groups. Unfortunately, enantioselectivities, even in the optimized case, were too low to be of any synthetic utility. Bianchini prepared the C_1-symmetric ligand BDPBzP (**47**), which

gave 26% enantioselectivity in the hydroboration of styrene (at 0 °C).[78] Better results were obtained with Buono's bis(aminophosphane) ligand, **48**.[79] Using this ligand, norbornene was hydroborated at −78 °C with 77% *ee*. The hydroboration of styrene was less enantioselective (42% *ee*). Bisphosphane **49** was prepared by Kang et al. and resulted in an 85% *ee* for the hydroboration of styrene at low temperature.[80]



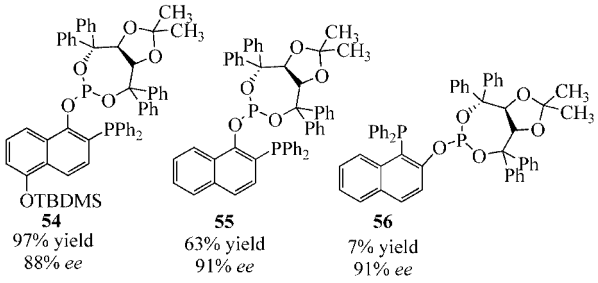
Scheme 9. Chiral bisphosphanes for asymmetric hydroborations

Finally, Knochel has reported the preparation and catalytic activity of trialkylbis(phosphane) **50**, which has demonstrated excellent chemo-, regio-, and enantioselectivity in the Rh-catalyzed hydroboration of styrene derivatives.[81] **50** is prepared by an innovative route shown in Scheme 10. Chiral diol **51** is reacted with $ClPPh_2$ yielding **52**. The P−O bonds are then converted into P−C bonds by a tandem [2,3]-rearrangement in refluxing toluene. Reduction of both the phenyl substituents and the olefin with Pd/C and hydrogen is followed by $HSiCl_3$ reduction of the phosphane oxide. A number of *para*- and *meta*-substituted styrenes were hydroborated with enantioselectivities in the range of 76−93%, excluding the anomalous result obtained with the purely electron-withdrawing *p*-CF_3 substituent (58% *ee*). Even *ortho*-substituted styrenes react with relatively high enantioselectivity (77−82% *ee*).



Scheme 10. Preparation of phosphane **50**

Several phosphane−phosphite ligands have been identified by screening a ligand library.[82] Of the ligands screened, **54** was the best in terms of yield and selectivity (Scheme 11). Removing the OTBDMS substituent led to a decrease in yield, although the enantioselectivity was approximately the same. Exchanging the positions of the phosphane and phosphite on the naphthalene core had a dramatic effect on the reactivity of the resulting Rh complex, illustrating the sensitivity of this reaction to ostensibly minor changes in the ligand structure.

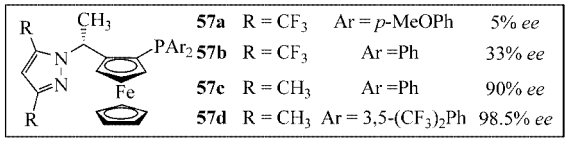


Scheme 11. Taddol-based phosphane-phosphite ligands

3.2.2. Chiral P,N Ligands

The largest class of ligands that have been effectively employed in the hydroboration reaction are P,N ligands. Togni developed a particularly successful P,N ligand based on studies of the bisphosphane Josiphos (**36**, Scheme 5), also developed by his group.[83] High yields and enantioselectivities are obtained when styrene is reacted with catecholborane in the presence of Josiphos and 2 mol % $[Rh(NBD)_2]BF_4$ at −78 °C. Both regio- and enantioselectivities are on par with the Rh/BINAP system (99% and 91.5%, respectively). Like BINAP, Josiphos-ligated Rh complexes are not sufficiently active in the hydroboration of substituted styrene derivatives to permit their application at low temperature. For example, indene reacted at room temperature giving (after oxidation) indanol of 42% optical purity.

A substantial increase in enantioselectivity is achieved upon substitution of the pseudo-benzylic phosphane donor group with a pyrazole moiety (**57**).[84] This ligand has provided the highest enantioselectivity for the hydroboration of styrene to date (98.5%). These pyrazole-containing ferrocenes have the advantage of inducing excellent levels of enantioselection at ambient temperatures but the regioselectivity suffers, being 79% in the best of cases. The most remarkable feature of these ligands is the extent to which they translate electronic asymmetry into enantioselectivity.[85] As shown in Scheme 12, increased enantioselectivities are correlated with electron-rich pyrazoles and electron-deficient phosphanes. For example, ligand **57b**, in which the pyrazole is substituted with two CF_3 groups, gives 33% enantioselectivity for the hydroboration of styrene, while ligand **57d**, in which the CF_3 groups are now on the phosphane and the pyrazole is substituted with electron-donating methyl groups, gives the best results obtained thus far (98.5% *ee*).

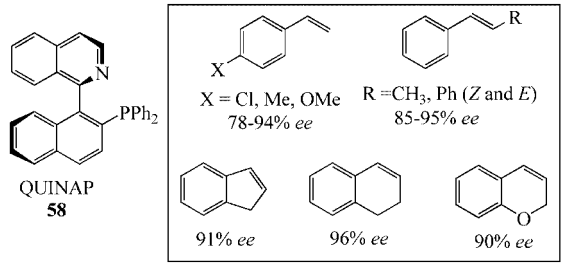


57a	R = CF_3	Ar = *p*-MeOPh	5% *ee*
57b	R = CF_3	Ar = Ph	33% *ee*
57c	R = CH_3	Ar = Ph	90% *ee*
57d	R = CH_3	Ar = 3,5-$(CF_3)_2$Ph	98.5% *ee*

Scheme 12. Asymmetric hydroboration of styrene with Josiphos derivatives **57a−d**

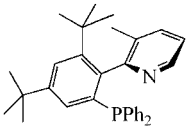
The other class of P,N ligands that are highly successful in asymmetric hydroboration is exemplified by QUINAP

(**58**).[86] Unlike BINAP, QUINAP is able to induce significant asymmetry at ambient temperatures. This provides the significant advantage that sterically demanding substrates can be hydroborated with high levels of enantioselectivity (Scheme 13).[87]



Scheme 13. Hydroboration of mono- and disubstituted olefins with QUINAP

A pronounced increase in stereoselectivity is observed when carrying out the hydroboration of electron-rich olefins, as compared to electron-deficient substrates. In a series of *para*-substituted styrenes, enantioselection increases in the order *p*-Cl < *p*-H < *p*-OMe with enantioselectivities ranging from 78 to 94%. Highly electron-deficient substrates such as *p*-CF_3Ph react with significantly reduced enantioselectivity (45% *ee*). Chan observes this same trend with another P,N ligand **59** (Pyphos), that is capable of hydroborating styrene with 90% enantioselectivity at 0 °C.[88]



59
Pyphos

Chan and Brown have proposed models to explain the observed correlation between enantioselectivity and electron density of the substrate. Both arguments take into consideration a key study by Kurosawa and Ikeda of the exchange of free and bound olefins in *trans*-[Cl_2Pt(py)(olefin)].[89] They found that electron-rich olefins bind more strongly to Pt by at least an order of magnitude. Chan proposes that in Pyphos complexes such as **60a**, the substrate always binds to the position *trans* to nitrogen, but for electron-rich olefins, such as *p*-methoxystyrene, the bond to cationic Rh is tighter and therefore the substrate is more strongly influenced by the chiral environment. Electron-deficient substrates coordinate less tightly and there is less difference between the diastereomeric complexes formed by binding to either face of the olefin (**60a** and **60b,** Figure 3).

Brown's proposal is slightly different. He suggests that the electronic nature of the olefin exerts a greater influence on the binding when the olefin is bound *trans* to the pyridine ring of QUINAP (Figure 4, a) than when it is bound *trans* to phosphorous (Figure 4, b).[75] Implicit in this argument is that in the reactive complex, the olefin prefers to bind *trans* to nitrogen than phosphorous. In **61a**, the olefin

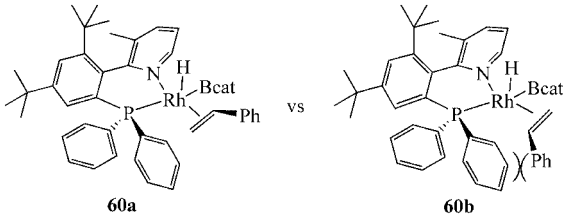


Figure 3. Proposal to explain relationship between enantioselectivity and olefin substituent for hydroborations with Pyphos complex **60**

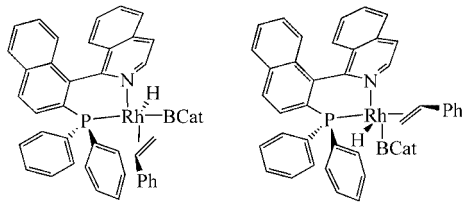
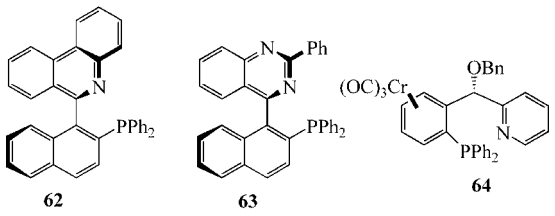


Figure 4. Model for enantioselectivity in hydroborations with QUINAP Rh complex **61**

is situated *cis* to the chiral environment of the phosphane, which helps differentiate the two enantiotopic faces, and is therefore important for the transfer of chirality. The decreased selectivity observed for electron-poor substrates can then be correlated with their decreased preference to bind *trans* to pyridine. Coordination of the olefin *cis* to the pyridine ring (**61b**) places the aromatic ring in a much less sterically demanding quadrant, which leads to reaction by a less enantioselective process.

Several other derivatives of QUINAP have been reported, including PHENAP (**62**) prepared by Brown[90] and 2-phenylquinazolinap (**63**) developed by Guiry et al.[91] Both react with similar regio- and enantioselectivities to QUINAP. A significantly different P,N-atropisomeric ligand recently reported is **64**, prepared by Chung et al. (Scheme 14).[92] All provide good enantioselectivity for the hydroboration of styrene derivatives; **63** is optimal for hydroborations of indene. Interestingly, hydroborations with **64** were not subject to the same differentiation between electron-rich and electron-poor substrates.

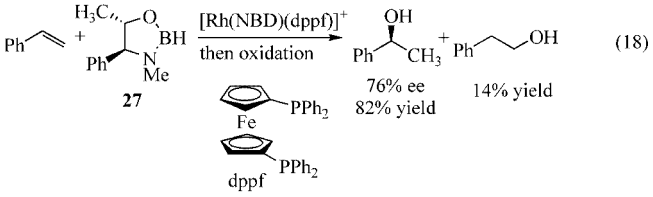


Scheme 14. P,N-Atropisomeric ligands for asymmetric hydroboration

3.2.3. Chiral Hydroborating Agents

An alternative method for effecting enantioselective hydroborations is to use a chiral reagent. The advantage of this method is the ability to employ chiral ligands concurrently, with the aim to increase enantioselectivity by the

matching/mismatching principle. Brown and Lloyd-Jones were able to obtain up to 76% enantioselectivity for the hydroboration of styrene using the pseudoephedrine borane **27**, although the use of chiral ligands did not provide a significant increase in the enantioselectivity.[24] In fact, optimum results were obtained using an achiral Rhdppf complex [Equation (18)].[39]



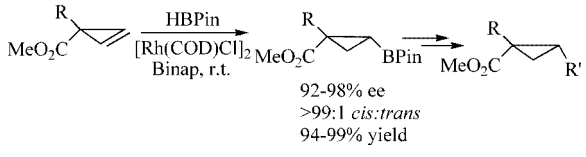
(18)

When the reaction was run using (*R*)-BINAP as the ligand, the enantioselectivity was reported to be low, but using (*S*)-BINAP, the desired isomer was obtained in 42% yield and 83% *ee*. It is interesting to note that in this case, the sense of asymmetric induction was opposite to that observed with catecholborane. The reaction is highly sensitive to steric hindrance at nitrogen; when the methyl group was replaced with an isopropyl group, the expected reaction pathway (hydroboration) was not observed. Instead, the catalyst was only active after oxidative loss of the phosphanes, and then the preferred pathway was dehydrogenative borylation.

3.2.4 Scope and Limitations

At the present time, the weakest feature of the catalytic asymmetric hydroboration reaction is the substrate scope. The only substrates that react with high regio- and enantioselectivity are vinyl arene based. J. M. Brown's discovery of QUINAP has widened the scope to include 1,2-disubstituted olefins, but they still must be conjugated with an aromatic ring for the regioselectivity to be reasonable. However, two interesting recent developments will undoubtedly spark more research.

Gevorgyan et al. have recently published an important expansion of the scope of the catalytic enantioselective hydroboration to include cyclopropenes [Equation (19)].[93] The use of pinacolborane led to improved diastereoselectivity compared to catecholborane, and the placement of an ester directing group was found to be important for high enantioselectivity. Under optimized conditions, a variety of ester-substituted cyclopropenes undergo hydroboration with enantioselectivities in the high 90s. The synthetic utility of these substrates is illustrated by their conversion into trisubstituted cyclopropanes. This report represents a significant advance in the synthetic utility of the catalytic asymmetric hydroboration reaction.



(19)

The second advance involves a modification of norbornene. Norbornene has always been a good substrate since regioselectivity is not an issue, but the product is of little or no synthetic value. Recently Bonin, Micouin and coworkers reported the hydroboration of a diazo version of norbornene (**37**, Equation (14)], which can be converted into a highly functionalized diamine **38** after hydroboration.[64] Although the enantiomeric excesses obtained were not remarkable (62% after optimization), the synthetic utility of the product is significant.

Another limitation in the catalytic hydroboration reaction that is beginning to be overcome concerns functionalization of the boronate ester product. Despite the obvious utility and reactivity of carbon−boron bonds, catalytic hydroborations are normally concluded by oxidation to the corresponding alcohol.[94] Considering the number of successful methods for the synthesis of chiral secondary alcohols, this sequence has represented little more than a means of identifying the level of asymmetric induction achieved in the hydroboration. Transformation of the installed carbon−boron bond into carbon−nitrogen or carbon−carbon bonds has been demonstrated recently, significantly expanding the synthetic utility of the catalytic hydroboration reaction.

4. Functionalization of C−B Bonds in Boronate Ester Products

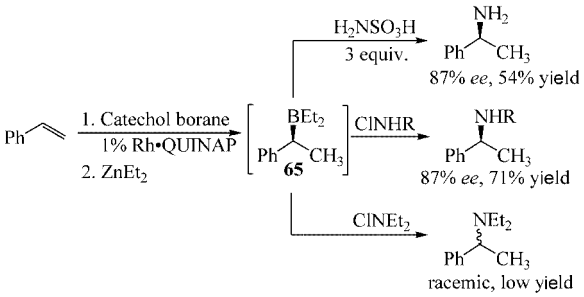
The use of dioxaborinanes or dioxaborolanes in the catalytic hydroboration reaction is critical to suppress the background reaction and permit transfer of chirality from the ligands to the substrate.[95] However, relatively few transformations have been reported for alkyl boronates, which are less electrophilic than trialkylboranes, thereby limiting the synthetic applicability of the hydroboration reaction. It is not surprising, therefore, that several groups have undertaken efforts to extend the scope of transformations available after hydroboration.

4.1 Amination

One approach to circumvent the decreased reactivity of boronate esters is to remove the alkoxy groups. This transformation can be easily affected by treating the boronate ester with RMgBr or ZnR_2.[96] Brown unambiguously demonstrates that this process proceeds with retention of configuration at the stereogenic center created by the hydroboration reaction.

After hydroboration of a vinyl arene with the Rh−QUINAP complex, the BCat moiety is converted into BEt_2 using $ZnEt_2$, and amination is effected with a threefold excess of hydroxylamine-*O*-sulfonic acid, H_2NOSO_3H (Scheme 15). It should be noted that although ethyl migration is technically possible, it is not observed, presumably due to the greater migratory aptitude of the benzylic substituent.[97] Each sequence in Scheme 15 is carried out

at 25 °C and without prior isolation of the intermediates making this one-pot reaction highly attractive.

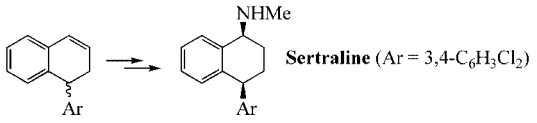


Scheme 15. Synthesis of enantiomerically enriched amines

Secondary amines can also be prepared by carrying out the amination using *N*-alkylated hydroxylamine-*O*-sulfonic acids, but better results are observed using chloroamines (ClNHR) as the aminating reagents. Reaction of the amine, borane and hypochlorite in one pot is not useful because concomitant oxidation of the borane occurs to a large extent (26−88%), but reaction of the primary amine with sodium hypochlorite prior to the addition of the borane proved successful. Several secondary benzylic amines can be synthesized with complete retention of stereochemistry and with yields between 48 and 82% (Scheme 15).

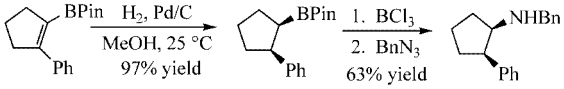
A method for the preparation of enantiomerically enriched tertiary amines has not yet been reported. Secondary chloroamines such as $ClNEt_2$ do effect the desired transformation, but the product is isolated in low yield and as a racemate. It is believed that the tertiary amine is formed by a radical pathway, which explains the loss of stereochemistry. Brown's method provides a unique alternative to the direct asymmetric hydroamination of styrene. The method is applicable to any substrates that are effectively hydroborated under catalytic conditions, providing that the substituents are compatible with the aminating reagents.

Maeda and Brown have also shown that the hydroboration/amination sequence can be used for the preparation of Sertraline, an antidepressant (Scheme 16).[98] In order to effect the transformation shown, the racemic olefin is first resolved by a catalytic asymmetric hydroboration with Rh−QUINAP. The reaction yields the resolved olefin in 38% yield and 97% *ee* (Ar = Ph). The enantiomerically enriched olefin is then used in a second hydroboration/amination reaction, but with the opposite enantiomer of Rh−QUINAP. Unfortunately, the desired *cis* isomer was obtained as the minor diastereomer (*cis*/*trans*, 29:71), but the synthetic scheme illustrates the versatility of the hydroboration reaction.



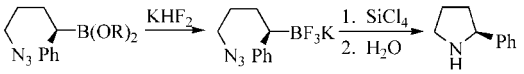
Scheme 16. Synthesis of sertraline by resolution of a vinylarene using hydroboration

Subsequent to this work, Knochel[99] demonstrated that the B−C bond of a pinacol ester could be converted into an N−C bond using a method described by Vaultier.[100] In this case, the BPin group is first converted into a BCl_2 substituent by treatment with BCl_3. Reaction of this species with benzylazide yields the corresponding benzylamine [Equation (20)].



(20)

Matteson and Kim have also employed the reaction of boronate ester derived compounds with azides to produce heterocyclic amines.[101] As shown in Equation (21), a boronate ester containing an azide is first treated with KHF_2 to generate the isolable trifluoroborate species. The difluoroborane is then generated by reaction with $SiCl_4$, leading to cyclization. Aqueous workup yields 2-phenylpyrrolidine.

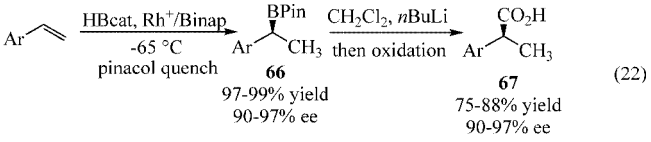


(21)

4.2 Carbon−Carbon Bond Formation

The conversion of B−C bonds in boronate esters (generated by catalytic asymmetric hydroboration) into C−C bonds has also been accomplished in the last few years.[102] As demonstrated in the previous section, the reactivity of the boron atom to nucleophiles can be increased by converting the alkoxy substituents into alkyl groups. This strategy permits the application of many homologating reagents that H. C. Brown and coworkers have developed for use with trialkylboranes, including Cl_2CHOMe, CO and CN^-.[103] Nitrogen[104] and sulfur ylides[105] have also been shown to homologate trialkylboranes. The difficulty with this methodology is that all three alkyl groups are generally homologated at the same time. Thus in order to achieve selective homologation of the desired substituent, inert substituents such as 9-BBN must be employed.

Alternatively, boronate esters can be employed directly if the reactivity of the homologating reagent is sufficient. The advantage of this approach is that there is only one alkyl group on boron capable of migration during the homologation step.[106] (The strength of the boron−oxygen bonds — approximately 30−40 kcal/mol greater than an alkyl−boron bond — precludes migration of these substituents during homologation.)[107] Our group has demonstrated this approach in the synthesis of 2-aryl propionic acids from vinyl arenes by a two step hydroboration-homologation procedure [Equation (22)].[102] The resulting acids are highly active and effective as non-steroidal anti-inflammatory agents. They include Naproxen (**67**, Ar = 6-MeONap) and Ibuprofen (**67**, Ar = 4-*i*BuPh).

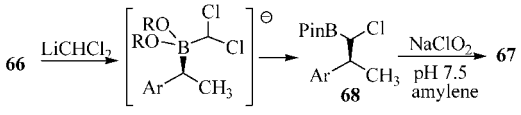


(22)

Hydroboration was carried out using the Hayashi protocol with a slight but significant modification. We initially intended to develop a one pot procedure for the hydroboration/homologation but found this unsuccessful and thus attempted to isolate the initially formed boronate ester. Catecholboronates are unstable on silica gel and have limited stability even in air, although they can be isolated by distillation under reduced pressure.[108] However, the Hayashi protocol requires a methanol quench to prevent less selective hydroborations from taking place as the reaction warms. We envisioned that quenching our hydroboration reaction with an excess of pinacol would serve the dual purpose of stopping the hydroboration at low temperature and converting the catecholate into a more stable pinacolate. This strategy proved successful and the resulting pinacolates **66** were isolated in virtually quantitative yields (97−99%) after column chromatography. The level of enantioselection achieved (90−97% *ee*) was on par with other published procedures, and depended on the electronic nature of the arene.

Several approaches for converting the boronate ester **66** to the desired 2-arylpropionic acid were considered. A number of one-carbon homologating reagents have been reported in the literature, but most have been used on trialkylboranes. Halomethyllithium reagents[109] methoxy(phenylthio)methyllithium (MPML)[110] and, more recently, $LiCH(OR)_2$ [111] have all been reported to react with boronate esters. Initial attempts were made to react **66** with MPML, but yields were low and reproducibility a problem. In addition, the requirement for a stoichiometric amount of $HgCl_2$ to promote the migration was less than attractive.

Matteson has developed an elegant procedure for the homologation of boronate esters of pinanediol, in which the chiral diol is used to control which of two diastereotopic chlorine atoms are displaced. This approach has been applied to the synthesis of a number of natural products, all with superb diastereoselectivity.[112] We chose to employ the Matteson procedure not to install a new stereocentre, but simply as an achiral reagent for the homologation of our already enantioenriched boronate esters **66**. Thus, *n*BuLi was added to precooled dichloromethane to furnish $LiCHCl_2$, which was then treated with **66** to furnish the desired α-chloroboronic esters **68** [Equation (23)].

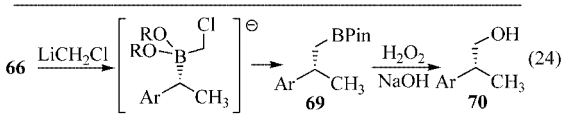


(23)

Having established a suitable procedure for preparation of α-chloropinacolates, our attention turned to converting these species into the corresponding 2-arylpropionic acids. Control of the pH during oxidation was crucial in order to retain optical purity and prevent degradation of the various intermediates. The traditional reagent for oxidation, $NaOH/H_2O_2$, was unsuccessful[113] and Kabalka's reagent, $NaBO_3$,[114] gave good yields of the corresponding aldehyde, but with significant loss of optical activity (5−30%), presumably because of racemization of the aldehyde under the basic reaction conditions (pH 9.5). Finally, another of Matteson's procedures involving buffered sodium hypochlorite proved successful and gave the desired acid directly and with no loss of enantiomeric purity.[115] Optimization revealed that adding $NaClO_2$ in two aliquots led to an improvement in the yield to approximately 80% after purification. Overall the procedure is equivalent to an asymmetric hydrocarboxylation of styrene, without the need for carbon monoxide.

Applying a slight variation to the aforementioned procedure furnishes the product of hydrohydroxymethylation, also with good yields and levels of enantioselection (Table 7). Substituting bromochloromethane for dichloromethane causes halogen/lithium exchange instead of deprotonation, generating $LiCH_2Cl$. Homologation of **66** with $LiCH_2Cl$ produces the non-halogenated boronate ester **69** after rearrangement of the borate complex [Equation (24)]. This species can then be oxidized in the usual manner with $NaOH/H_2O_2$, since the product alcohol **70** is not sensitive to racemization. Conversions are slightly lower than we observed for the hydrocarboxylation reaction but most importantly, the reaction proceeds with complete retention of stereochemistry.

Table 7. Homologation of boronate ester **66** with $BrCH_2Cl/n$BuLi



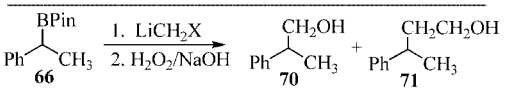
(24)

Ar	conversion (%)	isolated yield (%)	enantiomeric excess (%)
Ph (**66a**)	98	78	95 (*R*)
Ph (*ent*-**66a**)	88	68	88 (*S*)
p-MePh (**66b**)	87	69	96 (*R*)
p-ClPh (**66c**)	70	69	91 (*R*)

Interestingly, when $LiCH_2Br$ or $LiCH_2I$ were employed, multiple homologations were observed with incorporation of up to three methylene groups (Table 8).[116] This was the first observation of multiple homologations with lithium halomethane reagents. The use of $LiCH_2Cl$, even in excess, does not give any multiple homologation products. This is critical for the synthetic application of the reagent since the separation of alcohols **70** and **71** is extremely difficult.

Le Gall and Mioskowski have also reported that $TMSCHN_2$ can be used to homologate boronate esters.[117] After homologation with this reagent, the B−C bond is oxi-

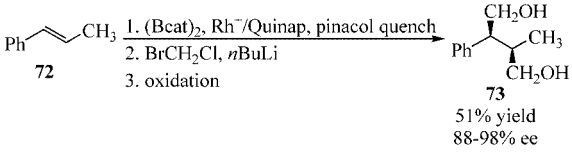
Table 8. Homologation of boronate esters with halomethane reagents



Reagent	Equiv.	70	71
$LiCH_2Cl$	1.1	88	0
$LiCH_2Br$	1.1	74	15
$LiCH_2I$	1.1	33	32
$LiCH_2Cl$	2.0	83	0

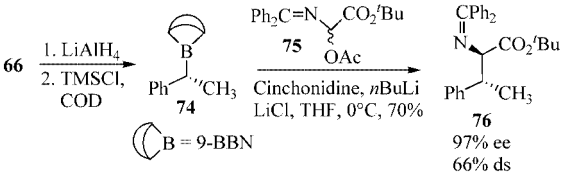
dized to give a vicinal silyl alcohol, and the Si−C bond cleaved with TBAF. This sequence provides a useful alternative to the homologation with $LiCH_2Cl$, although it does require the use of an excess of the diazo reagent.

Morken et al. have recently employed $LiCH_2Cl$ to homologate diboronate esters generated by the asymmetric diboration of a wide range of olefins [Equation (25)].[20] In order to effect the diboration reaction, Morken employs $[Rh(QUINAP)(COD)]^+BF_4^-$. Remarkably, this diboration reaction occurs with higher selectivity for substituted olefins than vinyl arenes [compare *trans*-β-methylstyrene (93% *ee*) with styrene (33% *ee*)]. Another interesting feature of this reaction is the high level of enantioselectivity obtained for the diboration of aliphatic olefins (98% *ee* for *trans*-5-decene).



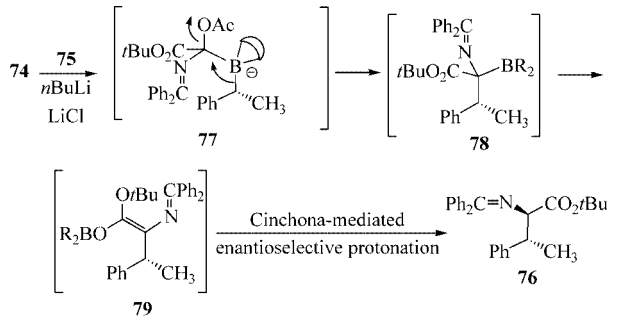
(25)

Carbon−carbon bond-forming reactions have also been carried out on boronate esters by changing the alkoxy substituents to trialkyl substitutents in a manner similar to that demonstrated by Brown. In this case, the migratory aptitudes of the various alkyl groups must be carefully controlled. O'Donnell demonstrated that the chemistry developed by his group for the synthesis of non-natural amino acids could be expanded by the use of the borane **74**, prepared from **66** as shown in Equation (26).[118] The product **76** of this reaction can be converted into a β-branched-α-amino acid. Such compounds are of interest for the study of conformationally restricted peptides.



(26)

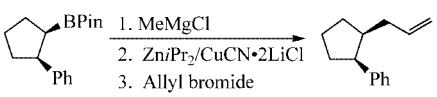
The reaction is believed to begin with formation of borate complex **77** (Scheme 17). Migration then occurs with loss of the acetate group giving **78**. This ester then rearranges to give boron enolate **79**, which is protonated under the influence of the cinchona alkaloid to yield optically enriched **76**.[119]



Scheme 17. Proposed mechanism for synthesis of **76**

In order to ensure that the desired group migrates in the transformation from **77** to **78**, it is necessary to use an alkyl group with low migratory aptitude. Thus, after enantioselective hydroboration, O'Donnell trapped the initially formed catecholate with pinacol, and then transformed the BPin substituent into a 9-BBN group using a procedure reported by H. C. Brown.[120] Reduction of the B−O bond is effected by treatment with $LiAlH_4$ (which generates $LiRBH_3$), followed by TMSCl, to afford RBH_2. The hydroboration of 1,5-COD with this reagent gives the 9-BBN derivative **71**.[121] Although the conversion of the pinacolboronate into the 9-BBN derivative is lengthy, it increases the synthetic scope of the asymmetric hydroboration significantly since the wide range of homologation and functionalization reagents developed by H. C. Brown[103] can now be applied to the product of the catalytic asymmetric hydroboration.

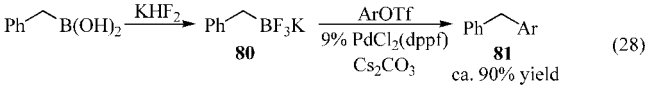
Knochel has also shown that the C−B bond of trialkylboranes can be functionalized by transmetallation and reaction with electrophiles.[99] He employs J. M. Brown's method for the conversion of the boronate ester to a trialkylborane, and then carries out a transmetallation with $ZniPr_2$ and CuCN·2LiCl. The resulting organometallic reagent reacts with allyl bromide with retention of relative stereochemistry [Equation (27)].



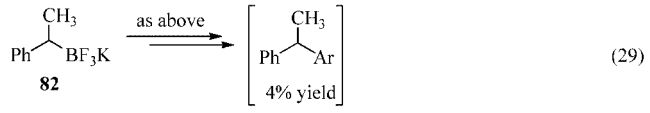
(27)

Activation of the B−C bond with transition metals and concomitant C−C bond formation can also be accomplished, but it is quite substrate specific. B−C(sp^2) bonds or B−cyclopropyl bonds can react with Pd and undergo Suzuki coupling. Aliphatic primary boranes can also react under Suzuki-type conditions but the substituent on

boron is critical; 9-BBN and BF_3K undergo facile reaction with Pd complexes, while boronic acids and esters do not [Equation (28)].[122] Unfortunately, the coupling reaction is *not* viable with secondary chiral boranes such as **82**, since β-hydride elimination regenerating the olefin is the major pathway [Equation (29)].[123]



(28)



(29)

5. Conclusions

The catalytic asymmetric hydroboration of olefins has advanced considerably since Hayashi's seminal paper in 1989.[29] The range of chiral ligands that can be used to effect enantioselective hydroborations has increased substantially, with the most notable example being QUINAP.[75] The key feature of this ligand is that it permits the highly enantioselective hydroboration of more highly substituted olefins such as indene and β-methyl styrene. The scope of the catalytic asymmetric hydroboration still needs to be expanded significantly if the reaction is to be of truly general application. In order to accommodate less reactive substrates, the development of new catalysts and reagents is likely to be necessary. Additionally, the development of new methods for transforming the carbon−boron bond into other functionalities will make a serious impact into the use of the catalytic asymmetric hydroboration in synthesis.

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