Value Added Products from Feedstock Chemicals: Cobalt Catalyzed Asymmetric Hydroboration of 2-Alkyl-1,3-Dienes

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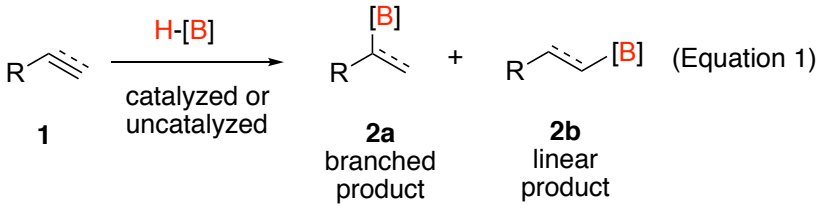
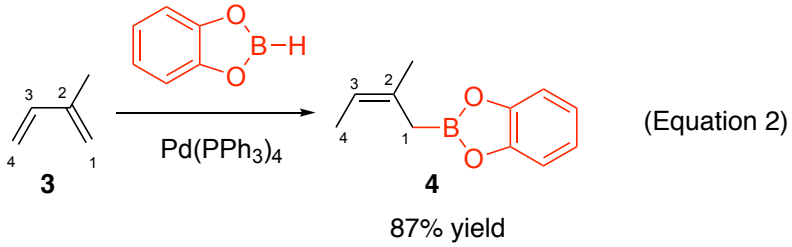
Economic methods to stitch feedstocks onto molecules using chemical synthesis can greatly impact the design and manufacture of molecules, from medicine to materials. For example, olefins, one of the most abundantly obtained class of feedstocks from the petroleum refining industry, are starting carbon units for many of the processes used to produce value-added chemicals in the pharmaceutical, agrochemical and polymer industry. However, many of these processes are often limited with harsh reaction conditions, poor yields and low selectivities. Organic chemists have long been trying to address the unmet challenges in this field; to simultaneously activate and functionalize olefins under mild reaction conditions, with the desired level of precision and selectivity in order to access high value-added molecules from cheap and abundant lower alkenes. The current work details a highly efficient catalytic protocol using the earth abundant metal, cobalt, linked to suitable ligands, to achieve the hydroboration of unactivated olefins to obtain organo-borane products with desired level of yield and selectivity. Although these are highly versatile compounds having wide synthetic utility as pharmaceutical intermediates, there is a paucity of methods to make organo-boranes directly from feedstocks.

The hydroboration of olefins is one of the most well known hydrofunctionalization reactions; it is the insertion of hydrogen boron bonds into an olefin moiety and is an atom economical method for the synthesis of carbon-boron bonds (equation 1).

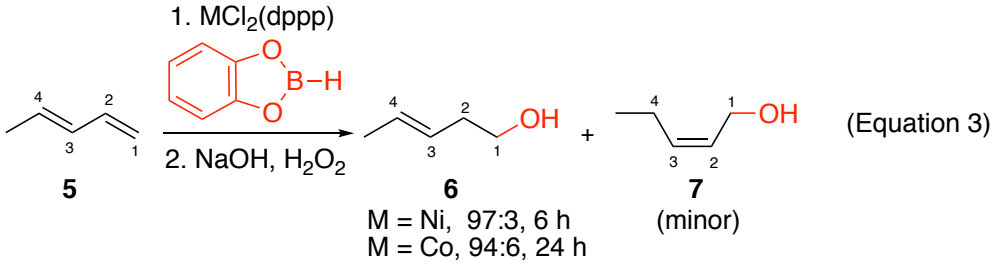
[1] Kendra R Dewese and Professor T. V. RajanBabu are the co-authors of this work and they are thanked for their contribution.



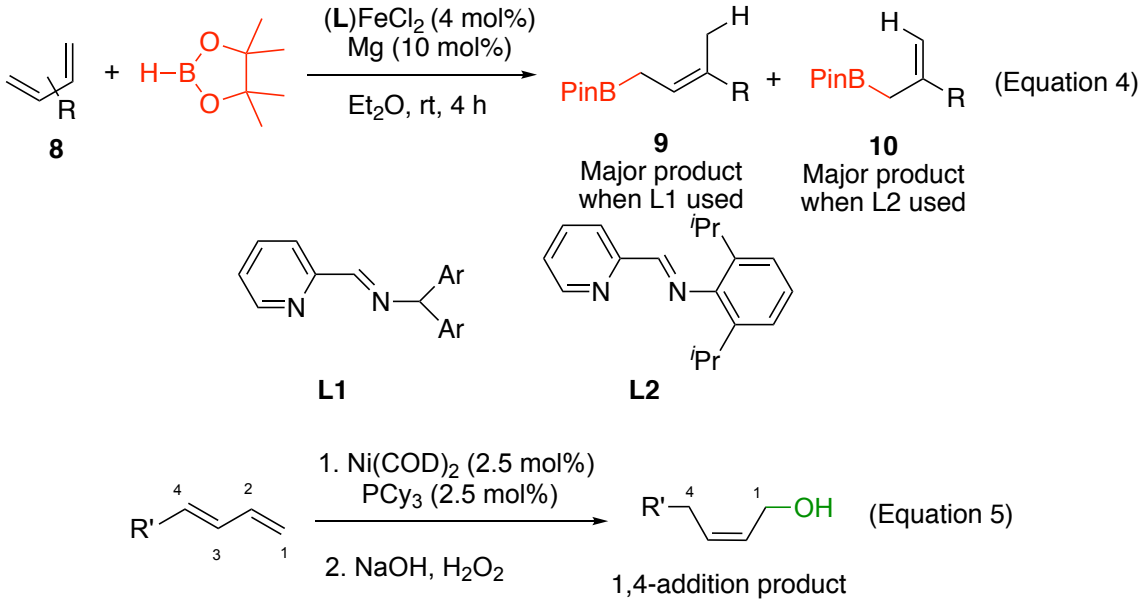
Transition metal catalyzed hydroboration has gained momentum over the past decade, with many reports of catalytic hydroboration of styrene derivatives, alkynes and terminal alkenes, using precious metal catalysts such as rhodium and iridium.[2-3] More recently, factors of high cost, low abundance and environmental impact have shifted the focus towards the earth abundant metals.[4] Although catalytic hydroboration has enjoyed much success in the realm of vinylarenes, simple alkenes and alkynes, there have been only a very few reports utilizing 1,3-dienes. The first report came from Suzuki and coworkers who showed that *tetrakis*-(triphenylphosphine)-palladium was an effective catalyst for the hydroboration of acyclic 2-substituted and 3-disubstituted 1,3-dienes to achieve a selective 1,4-addition giving Z-alkenylboranes.[5]



Zaidlewicz and Meller[6] explored a variety of transition metal catalysts for the selective hydroboration of 1,3-dienes and concluded that nickel and cobalt were the best catalysts for this transformation (equation 3).



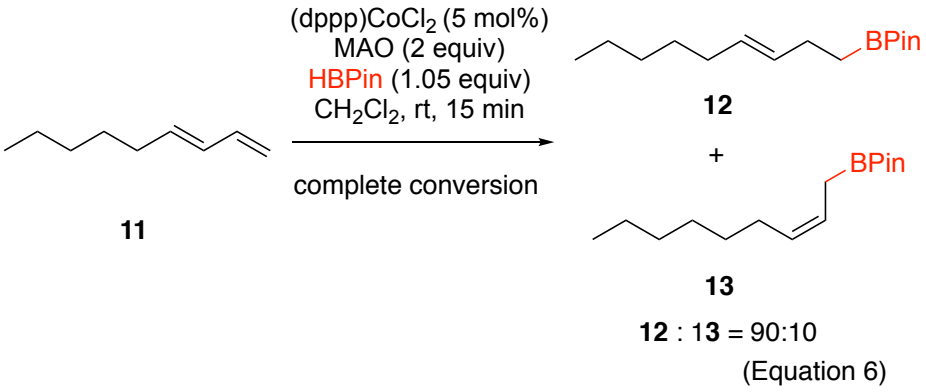
Ritter and coworkers[7] have shown that iron catalysts can be used for the catalytic hydroboration of 2-alkyl-1,3-dienes. Adjusting the steric parameters of the ligand L1 and L2 they could achieve either linear or branched 1,4-addition products (equation 4). Morken and Ely[8] reported that nickel catalyst in the presence of triphenylphosphine ligand could catalyze the hydroboration of 1,3-dienes with 1,4-regioselectivity to obtain a wide range of allylic alcohols (equation 5).



After reviewing the current literature on hydroboration, we found that highly regio- and enantioselective hydroboration of linear 1,3-dienes still remains elusive to organic chemists. Finding a stream-lined, robust methodology for chemo-, regio- and enantioselective hydroboration of 1,3-dienes would be a significant advance to this area.

Using a protocol with the bisphosphine ligand 1,3-bis(diphenylphosphino)propane cobalt chloride [(dppp)$CoCl_2$] as the catalyst, with methylaluminoxane (MAO) as an activator, initial scouting experiments revealed the successful hydroboration of 1,3-nonadiene (**11**), giving predominantly a 1,2 addition to make homoallylic boronate (**12**), along with minor amount of 1,4-

addition to yield allylic boronate (**13**) in a ratio of 90:10 (equation 6). Pleasingly, the product regio-selectivity complements Morken's *Z*-allylboronates.[8]

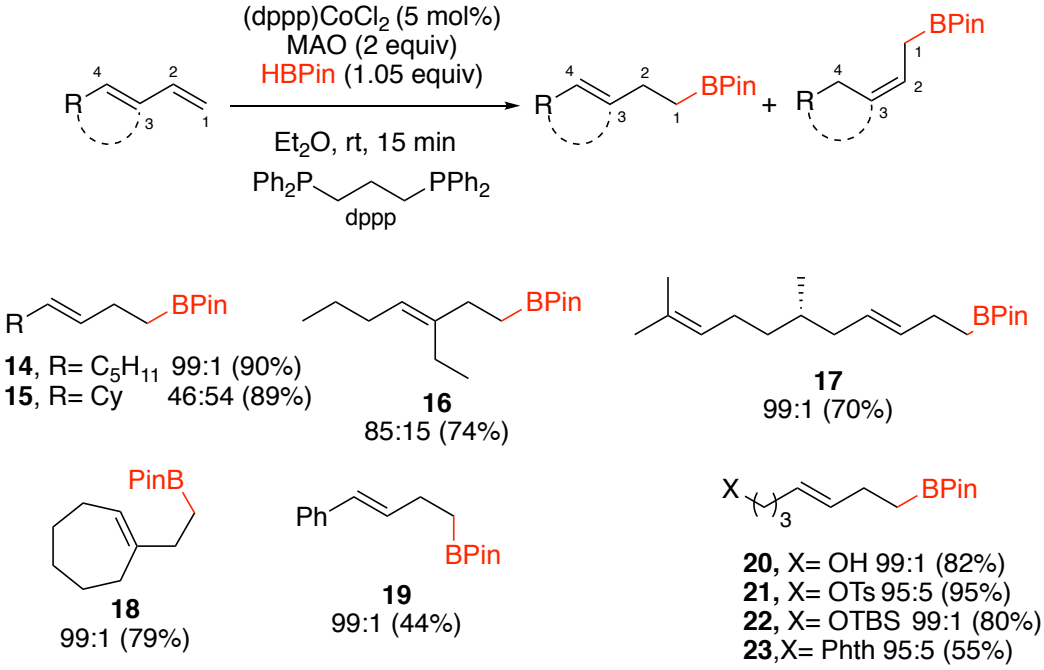


12 : **13** = 90:10

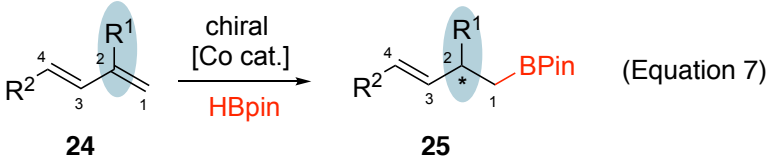
(Equation 6)

The generality of the scope of the reaction was explored through installing various substituents on the diene (Scheme 1). These experiments revealed that reaction is very facile and proceeds within 60 minutes at room temperature for most substrates with 5 mol% catalyst loading and 2 equivalents of activator at 0.1M solvent concentration. Diverse functional groups were well tolerated due to the mild conditions of the reaction. Alkyl substituents at the 4-position of the diene were varied and it was found that the reaction is well tolerant towards bulky substituents such as cyclohexyl (**15**) as well as branched dienes (**16**). It was observed that in the presence of an isolated alkene functional group such as the (-) citronellal derivative (**17**), hydroboration occurred exclusively at the diene functionality to furnish the desired 1,2-addition product. Vinyl cycloalkene (**18**) was a suitable substrate for this reaction. Diene conjugated with phenyl ring (**19**) also worked well to give only 1,2-addition product. The method is very tolerant of heteroatom functional groups found commonly in organic molecules: alcohols (**20**), tosylates (**21**), silyl ethers (**22**) and phthalimides (**23**).

Scheme 1. Substrate Scope for Cobalt Catalyzed 1,2-Hydroboration of 1,3-Dienes



Having established a general method for the synthesis of homoallylic boronates via selective 1,2-hydroboration, we directed our attention to the asymmetric hydroboration of these 1,3-dienes. We envisioned that installing an alkyl group at the 2 position of the 1,3-diene would make the system prochiral, which upon 1,2-hydroboration would introduce a chiral center at the C-2 position (equation 7). Utilizing suitable chiral ligands on the cobalt complexes would furnish the corresponding enantiopure homoallylic boronates, which could serve as useful synthons. As alluded to earlier, these boronates are valuable precursors to many carbon-carbon and carbon heteroatom bond formations. Having access to enantiopure boronates is highly desirable to build a rapid library of molecules starting from readily available diene precursors

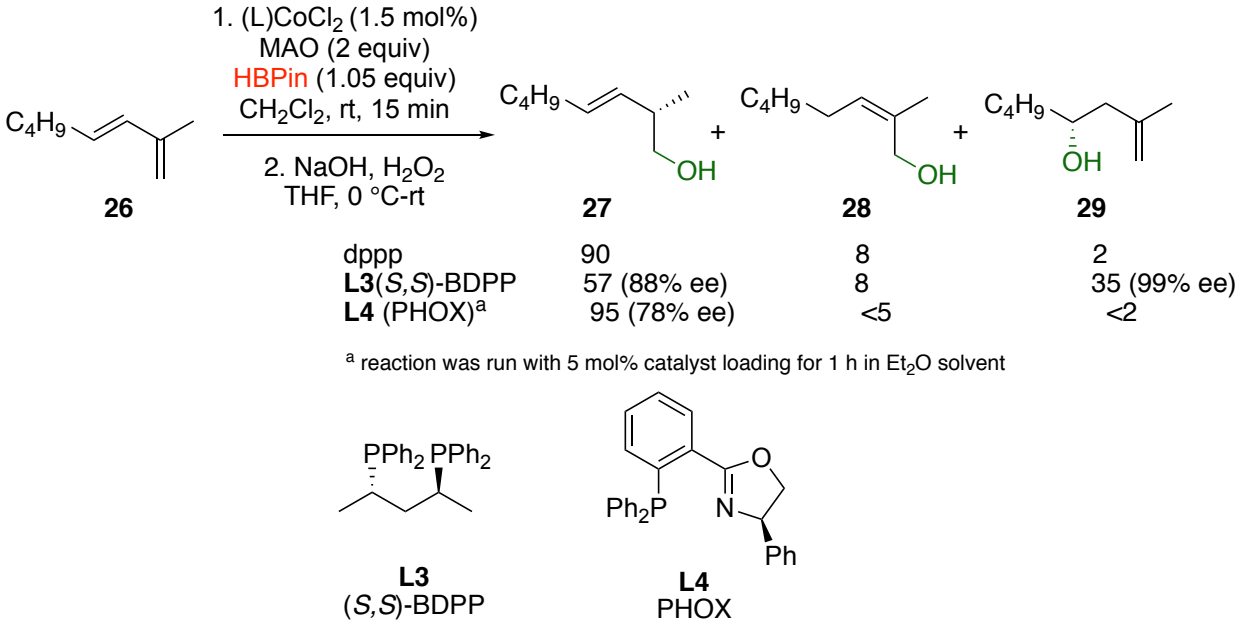


(Equation 7)

We set out to study the conditions for this transformation. Using methyl group as the alkyl substituent, the prochiral diene (*E*)-2-methyl-octa-1,3-diene (**26**) was initially subjected to the

standard hydroboration conditions (Scheme 2). Using standard achiral ligand dppp the expected regioselectivity giving the 1,2 adduct homoallylic boronate (**27**) in 90:10 selectivity was observed. The commercially available chiral ligand structurally analogous to dppp, 2,3-bis(diphenylphosphino)pentane (BDPP), was initially chosen for the enantioselective reaction. In addition to the expected predominant regioselectivity for the terminal 1,2-addition product (**27**), an achiral 1,4-adduct (**28**, ~8%) we also observed a new product in upto 35% yield. This new product (**29**) was identified as a 1,2-addition product across the internal alkene (Scheme 2).

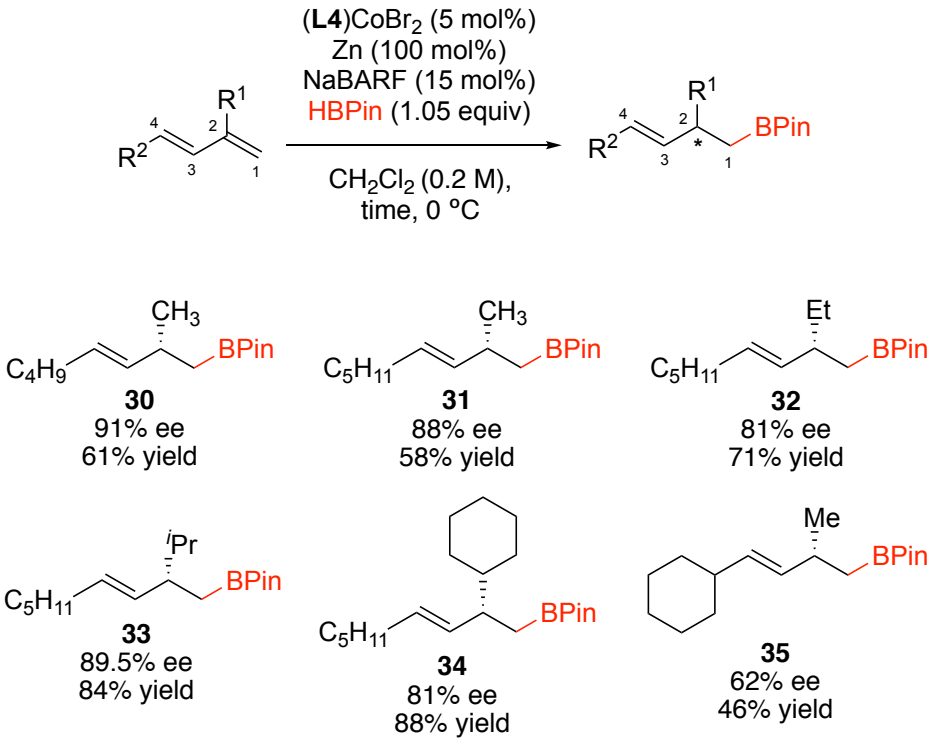
Scheme 2. Asymmetric Hydroboration of Prochiral 1,3-Dienes Using Chiral Ligands



Disappointed at the lack of regioselectivity with the chiral bisphosphine (*S,S*)-BDPP, we then evaluated the nonsymmetrical ligand with two different coordinating atoms, the phenyl phosphine oxazoline ligand (PHOX, **L4**) as a ligand in the Co-catalyzed hydroboration reactions of prochiral 1,3-dienes. Very gratifyingly, it was found that this ligand gave an excellent regio-selectivity for the terminal 1,2-hydroboration (Scheme 2). More excitingly, the desired 1,2 adduct (**27**) showed a highly promising enantiomeric excess of 78%. Optimizing the activators for this reaction, we found that a protocol using zinc as a reductant along with sodium *tetrakis*[(3,5-

trifluoromethyl)phenyl]borate (NaBARF) was very effective for this reaction. With these conditions, we set out to study the substrate scope of the asymmetric hydroboration reaction. We started our studies by varying the alkyl substituent at the 2-position of the 2-alkyl-1,3-diene (Scheme 3). It was found that the reaction conditions tolerate both sterically less demanding methyl substituents (**30, 31, 35**) as well as the sterically demanding groups, e.g. ethyl (**32**), isopropyl (**33**) and cyclohexyl (**34**) substituents. It was found that for all the substrates, 1,2-hydroboration was obtained with very high regioselectivity (>95:5). The enantioselectivities were determined by oxidizing the homoallylic boronates to their corresponding alcohols.

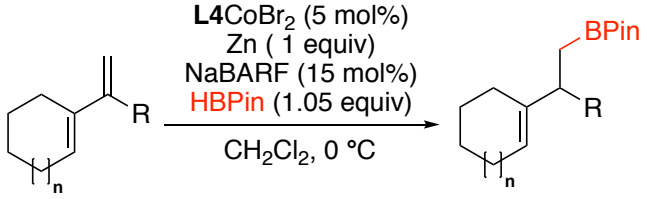
Scheme 3. Substrate Scope for Asymmetric Hydroboration of 2-Alkyl-1,3-diene Backbone

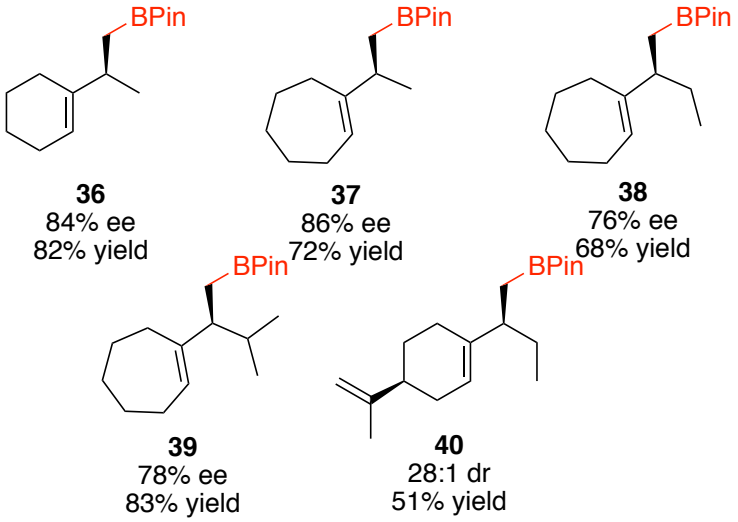


This reaction is also highly suitable for installing a stereogenic center next to carbocyclic rings, which is a long standing challenge in organic synthesis.[9-10] Utilizing vinyl cyloalkenes with prochiral substituents, we were delighted to find that this reaction occurs with high 1,2-

regioselectivity and synthetically useful enantioselectivity (Scheme 4). This reaction worked for both six membered as well as seven membered rings. It was found that the steric effects of the alkyl substituent effect the enantioselectivity of the product. Keeping the ring size constant, increasing the steric demand from methyl (**37**) to ethyl (**38**) and isopropyl group (**39**) lowered the enantioselectivity from 86% to 78%. Additionally, the reaction showed high chemo-selectivity towards dienes as it was found that the (-) perillaldehyde derivative reacted only at the diene moiety with complete chemo-selectivity to give the product in very high diastereoselectivity (dr 28:1) to give **40**. These enantiopure homoallylic boronates with desired alkyl stereogenic centers next to the carbocyclic ring provides an unprecedented opportunity in the synthesis of many terpenoid and steroid fragments.

Scheme 4. Substrate Scope for Asymmetric Hydroboration of 1,1'-Disubstituted Vinylcycloalkene Substrates





36
84% ee
82% yield

37
86% ee
72% yield

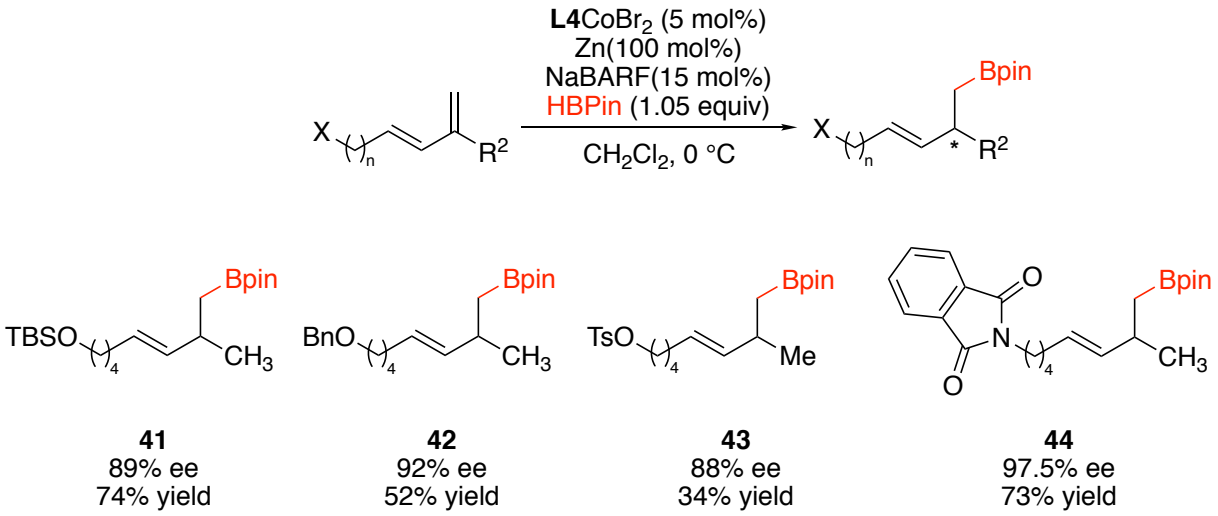
38
76% ee
68% yield

39
78% ee
83% yield

40
28:1 dr
51% yield

It was found that the 1,2-selective asymmetric hydroboration reaction also worked well in the presence of functional groups, giving a high enantioselectivity (Scheme 5). Thus compounds containing protected alcohol functional groups including silyl ethers (**41**), benzyl ethers (**42**) tosylates(**43**) and phthalimides (**44**) were obtained in very good enantioselectivities and good yields.

Scheme 5. Substrate Scope for Asymmetric Hydroboration of Functionalized 1,3-Dienes



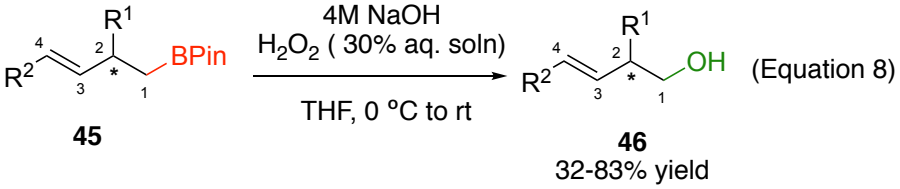
41
89% ee
74% yield

42
92% ee
52% yield

43
88% ee
34% yield

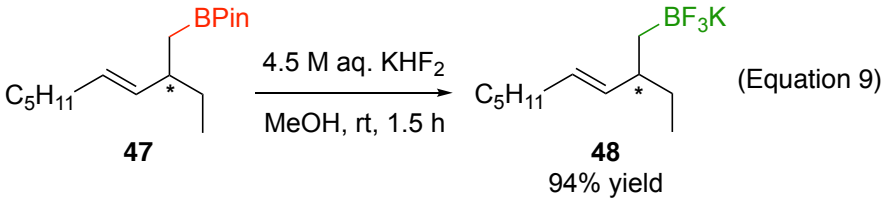
44
97.5% ee
73% yield

Organoboron reagents are an extremely versatile class of reagents in organic synthesis as they can participate in a wide variety of bond forming reactions. Some of the advantages of organoboron reagents are their stability, the tunability of their properties, the relative non-toxicity of the byproducts generated in their reactions, and their wide functional group compatibility.[11] The oxidation of organoboron compounds is one of the most widely used functionalization reactions. Utilizing basic hydrogen peroxide, the linear, cyclic and functionalized enantiopure boronates were converted to their corresponding alcohols (equation 8). This method provides a direct access to enantioenriched homoallylic alcohols starting from simple prochiral 1,3-dienes.



(Equation 8)

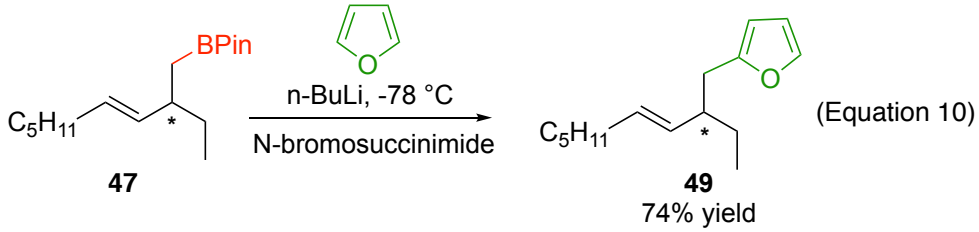
Organotrifluoroborates have gained much popularity recently as coupling partners for Suzuki Miayura cross coupling reactions, used as protected boronic acids.[12] The tetra-coordinate nature of the boron as well as the strong B-F bond makes them air and water stable, and compatible with a wide range of functional groups. The conversion of homoallylic bononate (**47**) to the corresponding potassium trifluoroborate salt (**48**) was accomplished by reaction with aqueous potassium bifluoride in methanol with high yield (94%, Equation 9).



(Equation 9)

Apart from their utility as cross coupling partners in the Suzuki-Miyaura reactions, boronate esters can also be used to couple directly with electron rich aromatics such as furans. Using established

conditions,[13] we could generate the arylated products starting from enantiopure homoallylic boronate (**47**)to give chiral aryl coupled product (**49**).



Thus, based on mechanistic insights and experimental observations, the asymmetric hydroboration method for 2-alkyl-1,3-dienes was developed to get the best regio-, chemo- and enantoselectivity of the desired value-added products from substituted dienes. The operationally simple, yet unprecedented reactions we discovered expand the realm of hydrofunctionalizations to provide direct access to a number of boranes, of interest in organic synthesis. The resulting boron compounds were further transformed into several chiral building blocks, thus expanding the scope of the primary process for advanced synthesis. We strongly believe that our hydroboration methodology will add to the toolbox of transformations available for the synthesis of biologically relevant targets. We expect that the discoveries made will shorten the considerable distance between the conceptualization of a molecule as a drug candidate and its large-scale synthesis. Our mild reaction conditions, stability of catalysts and high yields of products give opportunities to utilize this chemistry on large industrial scales. Beyond this transformation we anticipate that this reactivity will inspire further advances in olefin functionalization.

References

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