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Catalytic Enantioselective 1,2-Diboration of 1,3-Dienes: Versatile Reagents for Stereoselective Allylation

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Polyketides are an important class of natural products that often possess potent biological activity and intriguing chemical structures. Among the methods for constructing these ensembles, the stereoselective addition of allylmetal reagents[1] - particularly allyl boron reagents[2] - to prochiral carbonyls holds particular prominence. With Type I allylation reagents[3], this reaction not only delivers functionality that is strategically positioned for establishing appropriate oxygenation patterns, but its stereochemical predictability allows ready access to acetate, propionate, and isobutyrate synthetic equivalents. A limitation of many allylation reactions, however, is that they deliver products bearing a terminal alkene; if one desires additional substitution or functionality on the olefin, additional synthetic manipulations are often required.[4] In this regard, the vinylogous aldol reaction has proven particularly important as it delivers enoate-derived homoallylic alcohols. Unfortunately, even with the tremendous emphasis placed on the development of catalytic enantioselective vinylogous aldol reactions, an efficienct *syn*-selective asymmetric propionate version is still unavailable, as is a version that delivers quaternary centers.[5] In this report, we document the first examples of the enantioselective catalytic 1,2-diboration of 1,3-dienes (eq. 1, Scheme 1). As depicted in Scheme 1, the 1,2-diboration of 1,3-dienes delivers allylboron reagents (**1**) that are perfectly configured to participate in highly selective allylation reactions.[6,7,8] Importantly, with appropriate oxidative work-up, these reactions deliver vinylogous aldol equivalents that directly address the above-described synthesis limitations. Also of significant consequence, is that the allyl boron in the allylation product **2** may be subject to other useful bond forming reactions[9] that allow for chain-extending polyketide synthesis.

To develop the catalytic synthesis strategy in Scheme 1, efforts were first extended toward the development of an enantioselective 1,2-diboration of terminal dienes.[10] A recent study in our laboratory found that enantioselective 1,4-diboration of *trans*-1,3-dienes could be accomplished with $Pt(dba)_3$ and a chiral phosphonite ligand.[11,12] While evaluation of alternate phosphorous donors revealed ligands that furnished the desired 1,2 diboration, selectivity was suboptimal. A more reliable strategy for obtaining the 1,2-diboration product was to replace the *trans* diene substrate with *cis* 1,3-dienes. This approach furnished 1,2-diboration products (3:1 to >20:1 1,2:1,4 selectivity) across a range of substrates and generally occured with excellent enantioselection. After optimization, the ligand structures and reaction conditions depicted in Table 1 were found to be optimal. With respect to polypropionate synthesis, the diboration of *cis*-pentadiene is paramount and this was found to occur in excellent enantioselectivity (95:5 er) and good yield with ligand **L2** (**1**, Table 1).[13] Aside from the phenyl substituted diene, all other *cis* dienes examined reacted with outstanding enantiocontrol when employing ligand **L1**. The diboration of 1,1-disubstituted dienes employing ligand **L3** occured with uniformly high levels of stereocontrol

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(compounds **9**–**14**). Notably, allylic silyl ethers do not engage in allylic borylation under the reaction conditions and tethered alkenes do not appear to perturb the reaction in a detrimental way.

Significant features of the 1,2-bis(boronate) resulting from the diboration of *cis*-1,3-dienes are an embedded α-chiral allylboronate and a *cis* alkene. According to the seminal studies of Hoffmann, it was anticipated that these features would render allylation reactions highly selective.[14] In an initial experiment, commercially available *cis*-piperylene was subjected to catalytic diboration with $Pt(dba)_3$ and ligand **L2** in THF. The solvent was then removed *in vacuo*, CH_2Cl_2 added, and benzaldehyde introduced to the reaction mixture. Upon oxidative work-up, the allylation product was obtained in moderate isolated yield (48%), however, the stereoisomeric purity was excellent (>20:1 *syn:anti*, 94:6 er). Examination of the unpurified reaction mixture revealed significant amounts of bis(allylation) product presumably arising from addition of the initial adduct (**15**, Table 2) to a second equivalent of aldehyde. To minimize the amount of bis(allylation), the diboration was executed on a scale that delivered a two-fold excess of 1,2-bis(boronate) relative to aldehyde. This strategy provided good yields of the monoallylation product for a range of aldehyde substrates (Table 2). As might be expected, the allylation products were found to possess *syn* relative stereochemistry (>20:1 in all cases) and the product alkene was found to be in the *trans* configuration. With respect to synthetic utility, it is significant that aromatic, aliphatic, and α,β-unsaturated aldehydes all participate and the level of chirality transfer from the allylboronate is excellent. Other notable features are that α-branched aldehydes react (entry 6) as do those that bear α-oxygenation (entries 7–9). Importantly, the regioisomeric 1,4-diboration product is not only less reactive in allylation reactions, but any derived allylation product is easily removed by silica gel chromatography. A stereochemical model that correlates reactant configuration with product configuration is depicted in ***ts-1*** (graphic, Table 2). Most likely to avoid an A(1,3) interaction with the *cis* substituent, the $CH_2B(pin)$ occupies an equatorial position in the chair-like transition structure. Bond reorganization then delivers the observed enantiomer of product with *syn* stereoselection and with a *trans* alkene.

As exemplified by the production of compounds **9**–**14** (Table 1), 1,2-diboration of 1,1-disubstituted dienes occurs with excellent selectivity. Similar to the case of *cis* dienes, it was anticipated that the intermediate bis(boronate) esters would participate in highly selective carbonyl allylation reactions. However, with 1,1-disubstitued dienes, the overall reaction sequence would furnish products bearing all-carbon quaternary centers.[15,16] Notably, the added steric encumbrance of these allylation products appeared to diminish the rate of secondary allylation such that high yields were obtained even when equimolar amounts of diene, $B_2(pin)_2$, and aldehyde were employed (Table 3). Also worth mention is that both the diboration and the allylation reactions proceeded cleanly in toluene solvent and this allowed the entire sequence to be accomplished in a single flask without solvent swapping operations. *Of particular note, either diastereomer of product could be obtained in excellent yield and enantioselectivity simply by employing the appropriate diastereomer of diene substrates.* For example, whereas diboration/allylation employing neral-derived diene **38** furnished product **26** in excellent selectivity, diboration/allylation employing geranial-derived diene **37** delivered diastereomer **27** with excellent levels of stereocontrol. Similar observations were made with propionaldehyde-derived products **28** and **29**.

An attractive feature of the synthesis strategy described above is that the allylation product can be subjected to bond-forming reactions other than oxidation. As depicted in Scheme 2 (eq. 1), when diene **37** was subjected to diboration and then employed in allylation, oxidative work-up furnished allylic alcohol **27**. Alternatively, subsequent to the allylation reaction, the intermediate allylboronate was subjected to homologation according to the Matteson protocol (eq. 2).[17] This delivered homoallylic alcohol **39**, also in excellent yield

and stereoselection. Lastly, it was found that the allylboronation product, when subjected to protodeboronation conditions similar to those described by Aggarwal[9d], was converted to the simple alkene product **40** (eq. 3). In this case, the protonation event occurred predominantly by an S_E2' pathway and delivered bishomoallylic alcohol **40** as the major product. Considering the range of transformations that are available to organoboronates, and the fact that the diboration/allylation sequence occurs cleanly in aprotic solvent, allylation intermediates may be directly transformed to a number of other useful building blocks.

In conclusion, we have described the catalytic enantioselective 1,2-diboration of 1,3-dienes and have found that the 1,2-bis(boronate) products can be employed in versatile stereoselective allylation reactions and deliver a range of functionalized chiral building blocks. Further studies on the use of these reactions in complex molecule synthesis are in progress and will be reported in due course.

Acknowledgments

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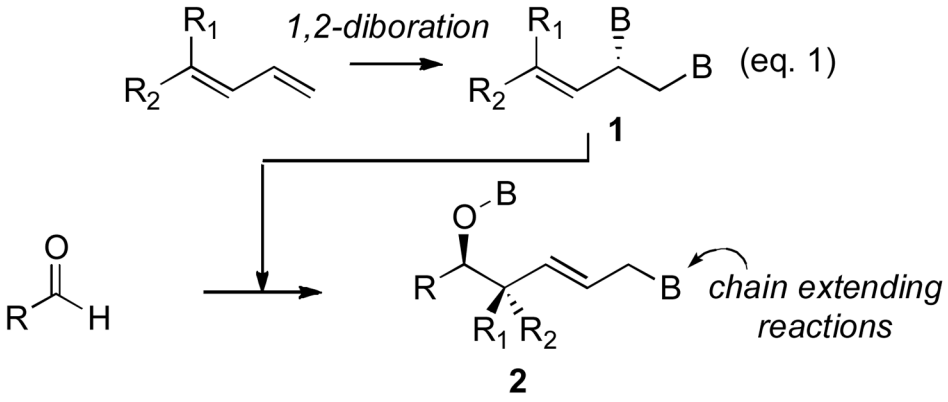
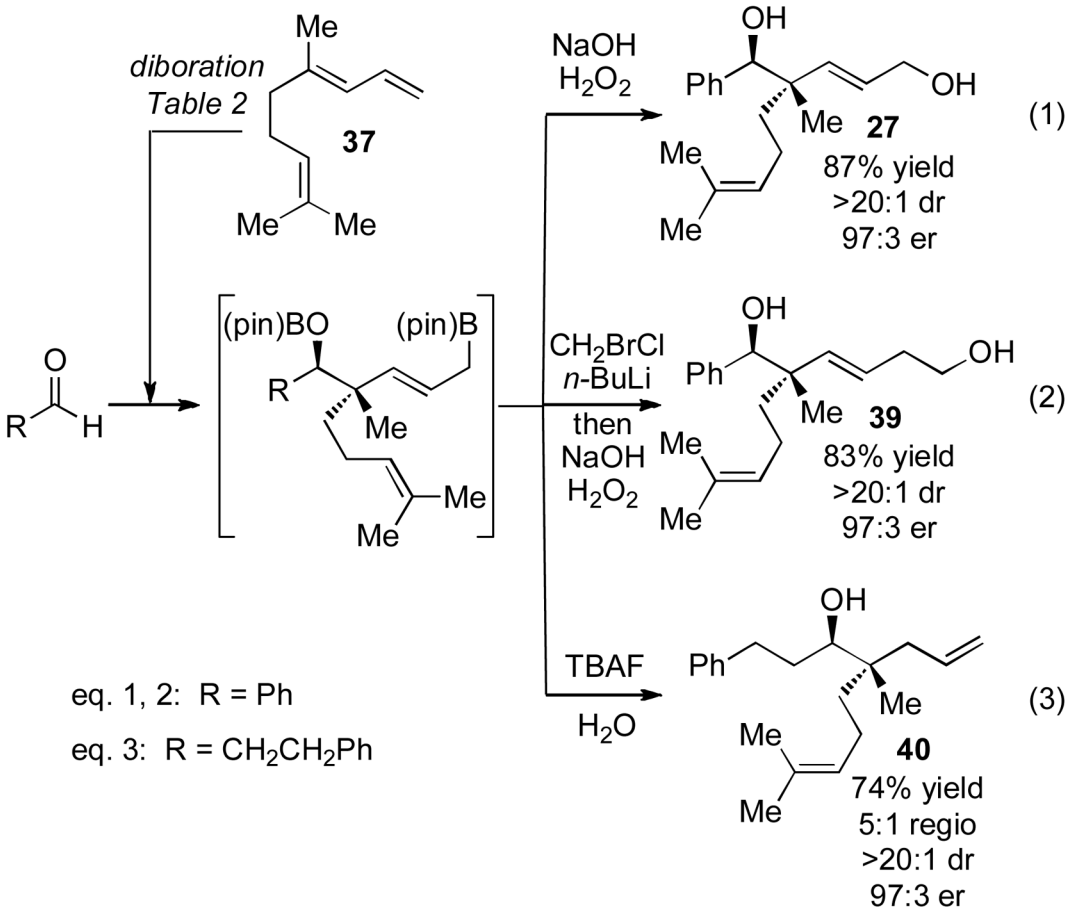


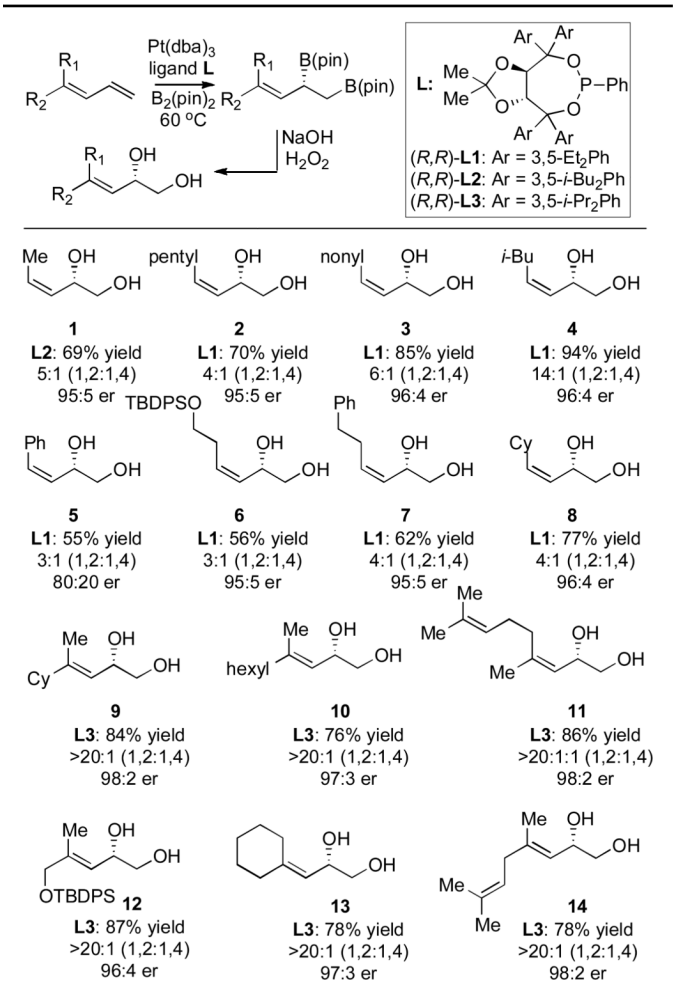
Scheme 1.
Strategy for chain-extending polyketide synthesis using 1,2-diboration of 1,3-dienes.



Scheme 2.
Diboration-Allylation-Functionalization Sequence.

Table 1

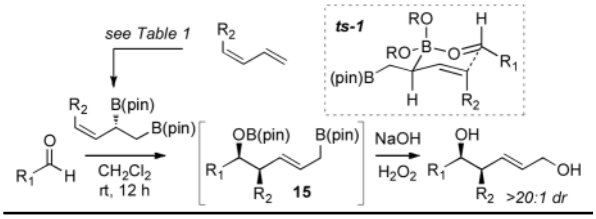
Catalytic Enantioselective 1,2-Diboration of 1,3-Dienes[a]

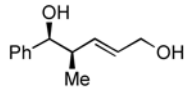
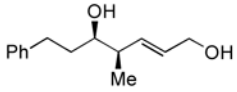
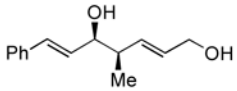
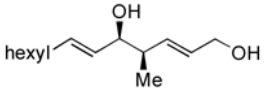
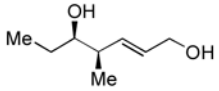
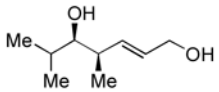
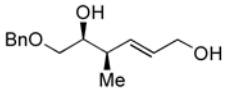
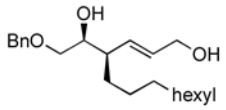
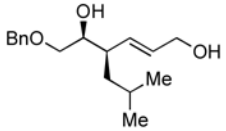


[a]Reaction carried out at 60 °C for 12 h, followed by oxidation with 30% H_2O_2 and 3 M NaOH for 4 h. For products **1** to **8**, 3 mol % $Pt(dba)_3$, 6 mol % ligand, and THF solvent employed; for products **9** to **14** 3 mol % $Pt(dba)_3$, 3.6 mol % ligand employed. Percent yield of purified 1,2-diol, average of two experiments. Enantiomeric purity determined by GC analysis of a derivative employing a chiral stationary phase (see SI for details).

Table 2

Asymmetric Allylboration of Carbonyls[a]



Entry	Product	% Yield[b]	er[c]	es[d]
1	 **16**	71	94:6	98
2	 **17**	66	94:6	98
3	 **18**	64	95:5	>99
4	 **19**	66	96:4	>99
5	 **20**	72	94:6	98
6	 **21**	62	93:7	96
7	 **22**	72	94:6	98
8	 **23**	90	97:3	>99
9	 **24**	68	96:4	>99

[a] Diboration reaction carried out at 60 C for 12 h with ligand **L2** for entries 1–7 and ligand **L1** for entries 8–9; allylation at room temperature for 12 h with 2:1 ratio of diboron to aldehyde; oxidation with 30% H_2O_2 and 3 M NaOH for 12 h.

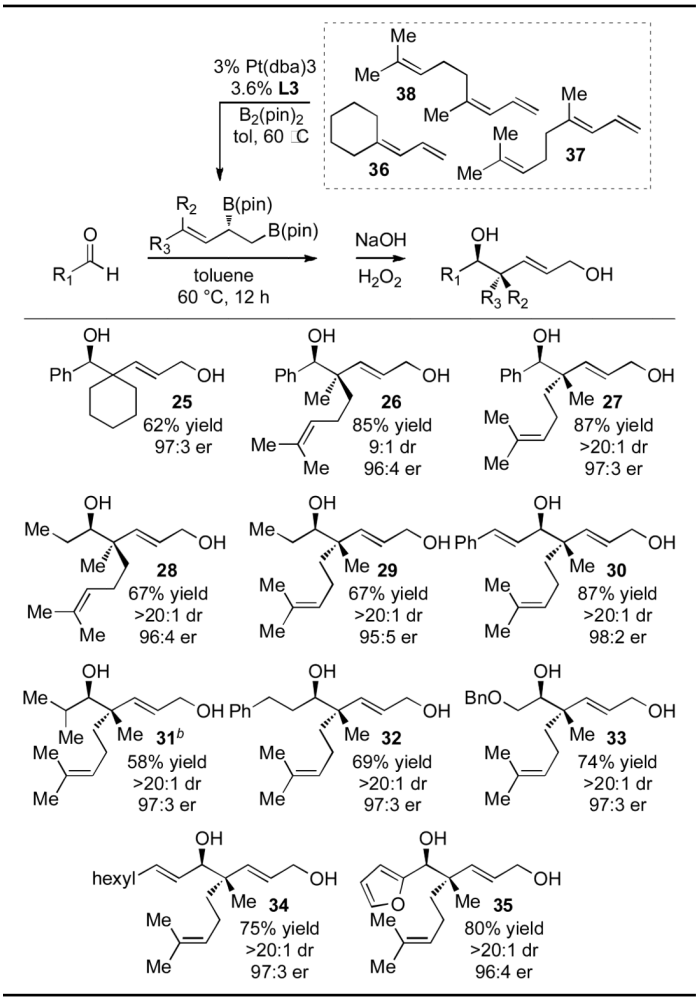
[b] Percent yield of purified material, average of two experiments.

[c] Enantiopurity determined by GC or SFC analysis employing a chiral stationary phase.

[d] Enantiospecificity (es) calculated as follows: (%ee allylation product / %ee diboration product)*100; value ≥ 100% for entries 3,4 and 9, likely a result of error in the measurement of er.

Table 3

Asymmetric Allylboration of Carbonyls with γ,γ-Disubstituted Allylboronates.[a]



[a]Diboration reaction carried out at 60 °C for 12 h with ligand **L3** and with [substrate] = 1.0 M in toluene. Allylations were conducted at 60 °C for 24 h with 1 equiv. of aldehyde relative to diene and $B_2(pin)_2$. Oxidation conducted with 30% H_2O_2 and 3 M NaOH for 4 h. Percentyield is of purified material and an average of two experiments. Enantiomer ratio determined by HPLC or SFC analysis employing a chiral stationary phase.

[b]Experiment employed 3 equiv. *i*-PrCHO.