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Modular Asymmetric Synthesis of 1,2-Diols by Single-Pot Allene Diboration/Hydroboration/Cross-Coupling

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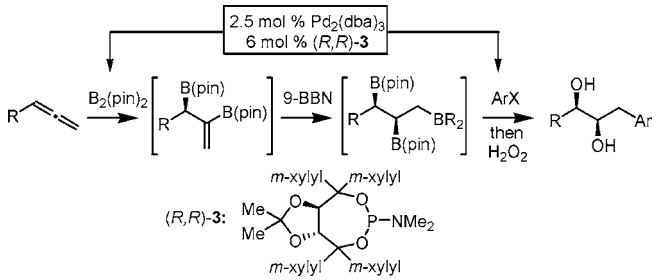
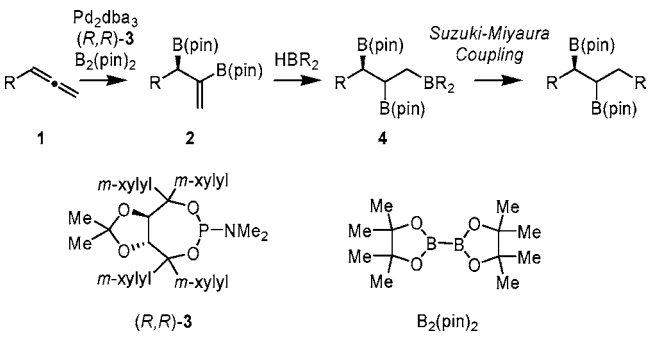
ABSTRACT



Chiral allyl vinyl boronates are generated by catalytic enantioselective diboration of prochiral allenes. They may then be reacted, in situ, with a hydroborating reagent to form a novel triboron intermediate. The least hindered and most reactive C–B bond then participates in cross-coupling wherein the coupling is brought about by the same catalyst as that which catalyzed the diboration reaction. The remaining C–B bonds are then oxidized in the reaction workup, thereby allowing for the modular synthesis of chiral diols in a concise single-pot fashion.

Single-pot reaction sequences that accomplish fragment couplings are important tools for the assembly of organic molecules. Those that give rise to new chirality centers, in a stereoselective fashion, offer an added advantage. As part of a program to engineer new reaction sequences with the abovementioned characteristics, we have developed the enantioselective diboration of simple allene substrates (**1**→**2**, Scheme 1) with the notion that the C−B linkages might be employed in an array of useful bond constructions.[1] For instance, after the diboration reaction, the intermediate organodiboron **2** may directly engage in stereoselective carbonyl or imine allylation reactions.[2] In this report, we describe an alternate single-pot C−C bond-forming sequence that arises from sequential allene diboration, hydroboration, and Suzuki−Miyaura cross-coupling reactions.[3,4] This sequence proceeds through an unusual organotriboron intermediate (**4**) and, upon oxidative workup, provides optically enriched 1,2-diols. Of note, many of the products of this

Scheme 1



(1) (a) Pelz, N. F.; Woodward, A. R.; Burks, H. E.; Sieber, J. D.; Morken, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 16328. For nonenantioselective processes, see: (b) Ishiyama, T.; Kitano, T.; Miyaura, N. *Tetrahedron Lett.* **1998**, *39*, 2357. (c) Fang, F.-Y.; Cheng, C.-H. *J. Am. Chem. Soc.* **2001**, *123*, 761. For borylsilation and borylstannation, see: (d) Suginome, M.; Ohmori, Y.; Ito, Y. *J. Organomet. Chem.* **2000**, *611*, 403. (e) Onozawa, S.; Hatanaka, Y.; Tanaka, M. *Chem. Commun.* **1999**, 1863. For an asymmetric silaboration with a chiral silylboron, see: (f) Suginome, M.; Ohmura, T.; Miyake, Y.; Mitani, S.; Ito, Y.; Murakami, M. *J. Am. Chem. Soc.* **2003**, *125*, 11174.

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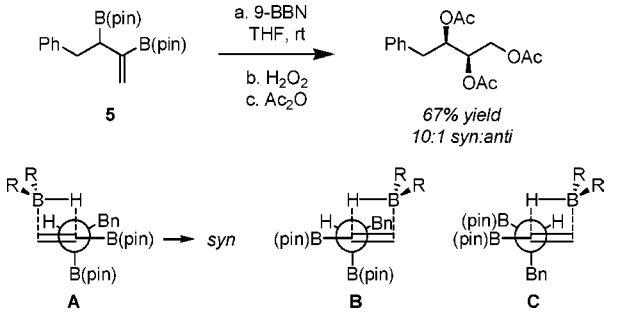
sequence are difficult to access from alternate catalytic asymmetric reactions.

Effective deployment of the catalytic diboration/hydroboration/cross-coupling sequence for stereoselective organic synthesis requires that hydroboration of the allene diboration product (**2**, Scheme 1) proceeds in a stereoselective fashion and provides a primary organoboron (**4**) that is able to participate in cross-coupling reactions. Diastereoselective hydroboration of α-chiral 1,1-disubstituted olefins[5] is well studied, as is the hydroboration of chiral allylsilanes.[6] However, the hydroboration of unsaturated organoboron compounds is less studied, with only a few investigations on the reaction of vinylborons[7] and allylborons.[8] To assess the stereoselection in hydroboration of allene diboration products, experiments were conducted on purified racemic **5** (Scheme 2). As can be observed in Scheme 2, when

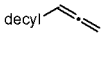
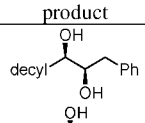
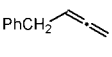
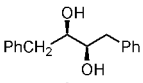
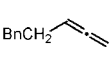
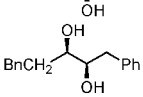
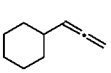
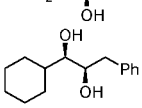
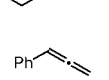
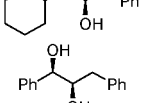
Scheme 2



compound **5** was subjected to hydroboration with 9-BBN, followed by oxidation and acylation (to ease manipulation and analysis), the resulting triacetate was obtained in good yield and diastereoselection. Similar to the stereoelectronic effect proposed by Fleming[6] to explain the stereochemical favoritism in the hydroboration of allylic silanes, the origin of diastereoselectivity in Scheme 2 can be rationalized beginning with a transition structure that involves alignment of the electron-rich allylic C−B bond with the reacting π-system. Similar to the "H-inside" preference in the Still[5a] and Houk[9] models for hydroboration of chiral allylic alcohols, the syn diastereomer in Scheme 1 may arise from Model A. Support for this hypothesis arises from the hydroboration with borane as the reductant, which proceeds with 2:1 syn/anti stereoselection (data not shown). Arguably, with the smaller borane, the benzyl group may adopt the inside position (i.e., Model B) thereby alleviating an A(1,2) interaction between the Bn and B(pin) groups that is present in Model A. Also consistent with this model is the observation that stereoselection is diminished as the size of the allene substituent is enhanced (vide infra). This outcome likely arises from an enhanced A(1,2) interaction in Model A that can be alleviated by adopting Model C.

B-Alkyl Suzuki cross-coupling reactions often employ 9-BBN-derived organoboranes and are catalyzed by palladium complexes in conjunction with phosphorus-based ligands.[4,10] Accordingly, the sequential diboration/hydroboration/cross-coupling reaction was examined. Noting that the characteristics of the catalyst for the diboration are similar to those of common cross-coupling catalysts, the reaction sequence was attempted without introduction of an additional catalyst for the cross-coupling, beyond that which is present from the diboration process. In the event, catalytic diboration of 1,2-tridecadiene was accomplished with 2.5 mol % of $Pd_2(dba)_3$ and 6 mol % of (*R*,*R*)-**3** in toluene solvent. After 12 h of reaction, 9-BBN was added directly to the reaction mixture which was stirred for 14 h. Then, simply adding iodobenzene and 2 equiv of cesium carbonate, *without an additional palladium catalyst or ligand*, was sufficient to bring about cross-coupling in good yield and diastereoselection and with excellent control of the absolute configuration. This "recycling" of the original palladium diboration catalyst for the Suzuki cross-coupling thereby reduces both reaction cost and generation of palladium waste. The described reaction sequence was examined with the allenes

Table 1. Single-Pot Diboration/Hydroboration/Suzuki Coupling/Oxidation[a]

entry	allene	product	dr	% yield	% ee
1			10:1	62	93
2			11:1	56	94
3			10:1	54	93
4			1.5:1	37	94
5			1.4:1	49	91

[a] Conditions: 2.5 mol % of $Pd_2(dba)_3$, 6 mol % of ligand, 1.2 equiv of $B_2(pin)_2$, PhMe, room temp, 14 h; then 1.2 equiv of 9-BBN, 9 h; then 2.25 equiv of Cs_2CO_3, 2.25 equiv of PhI, 80 °C, 12 h; then oxidative workup with H_2O_2/NaOH, 8 h.

(2) (a) Woodward, A. R.; Burks, H. E.; Chan, L. M.; Morken, J. P. *Org. Lett.* **2005**, *7*, 5505. (b) Sieber, J. D.; Morken, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 74.

(3) For a related sequential asymmetric alkene diboration/cross-coupling, see: Miller, S. P.; Morgan, J. B.; Nepveux, F. J.; Morken, J. P. *Org. Lett.* **2004**, *6*, 131.

(4) For many examples of fragment couplings based on B-alkyl Suzuki reactions, see: Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544.

(5) (a) Still, W. C.; Barrish, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 2487. (b) McGarvey, G. J.; Bajwa, J. S. *Tetrahedron Lett.* **1985**, *26*, 6297. (c) Evans, D. A.; Bartroli, A.; Godel, T. *Tetrahedron Lett.* **1982**, *23*, 4577. (d) Birtwistle, D. H.; Brown, J. M.; Foxton, M. W. *Tetrahedron Lett.* **1986**, *27*, 4367. (e) Midland, M. M.; Kwon, Y. C. *J. Am. Chem. Soc.* **1983**, *105*, 3725.

(6) (a) Fleming, I.; Lawrence, N. J. *J. Chem. Soc., Perkin Trans. 1* **1992**, 3309. (b) Fleming, I.; Lawrence, N. J. *Tetrahedron Lett.* **1988**, *29*, 2077. (c) Fleming, I.; Lawrence, N. J. *Tetrahedron Lett.* **1988**, *29*, 2073.

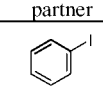
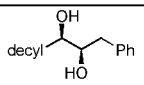
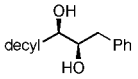
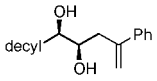
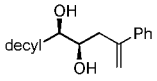
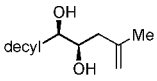
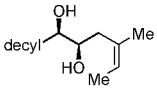
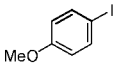
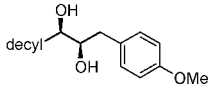
(7) (a) Pasto, D. J.; Chow, J.; Arora, S. K. *Tetrahedron Lett.* **1967**, 723. (b) Aronovich, P. M.; Bogdanov, V. S.; Mikhailov, B. M. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1969**, 362. (c) Matteson, D. S.; Bowie, R. A.; Srivasta, G *J. Organomet. Chem.* **1969**, *16*, 33. (d) Pasto, D. J.; Chow, J.; Arora, S. K. *Tetrahedron* **1969**, *25*, 1557. (e) Wiesauer, C.; Weissensteiner, W. *Tetrahedron: Asymmetry* **1996**, *7*, 5.

(8) Mikhailov, B. M.; Pozdnev, V. F.; Kiselev *Dokl. Akad. Nauk SSR* **1963**, *151*, 577.

depicted in Table 1 and generally occurred in moderate yields and with excellent enantioselection. The diastereoselection was substrate dependent and varied in a manner that was predictable based on the models in Scheme 2.

Other electrophiles were examined in the sequential diboration/hydroboration/cross-coupling sequence, and these are depicted in Table 2. In addition to iodobenzene which was employed in Table 1, it was found that phenyl triflate was also effective as a cross-coupling partner. Notably, vinyl halides are also reactive and provide homoallylic diols as the reaction product. These compounds might be difficult to access in a regioselective fashion with dihydroxylation-based approaches, and this highlights some attractive features of this approach. As anticipated, vinyl triflates also participate in the multistep sequence although, like the reaction of vinyl halides, the yield appears diminished compared to the reaction with aryl electrophiles. Surprisingly, even the sterically encumbered (*Z*)-2-bromo-2-butene underwent Suzuki cross-coupling and provided the chiral trisubstituted alkene with good levels of diastereoselection. As expected, the enantioselection was relatively constant and high, regardless of the nature of the electrophilic substrate employed in the cross-coupling.

Table 2. Synthesis of Homoallylic/Bishomoallylic Diols[a]

entry	coupling partner	product	dr	% yield	% ee
1			10:1	62	93
2			10:1	54	93
3			10:1	42	90
4			11:1	39	92
5			9:1	44	90
6			10:1	40	89
7			10:1	50	93

[a] Conditions: 2.5 mol % of $Pd_2(dba)_3$, 6 mol % of ligand, 1.2 equiv of $B_2(pin)_2$, PhMe, room temp, 14 h; then 1.2 equiv of 9-BBN, 9 h; then 2.25 of equiv Cs_2CO_3, 2.25 equiv of the coupling partner, 80 °C, 12 h; then oxidative workup with H_2O_2/NaOH, 8 h.

In summary, we have described an operationally simple, single-pot diboration/hydroboration/Suzuki cross-coupling/oxidation sequence that facilitates the synthesis of a variety of chiral aromatic and alkenyl diols in an enantioselective fashion. The protocol requires only purification of the final product and uses the same palladium source to catalyze two different steps in the sequence.

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Supporting Information Available: Complete experimental procedures, characterization data (^{1}H, ^{13}C, IR, and mass spectrometry), and enantiomeric purity data (chiral SFC; ^{1}H NMR). This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Lead references: (a) Miyaura, N.; Ishiyama, T.; Ishikawa, M.; Suzuki, A. *Tetrahedron Lett.* **1986**, *27*, 6369. (b) Ohe, T.; Miyaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201. (c) Matos, K.; Soderquist, J. A. *J. Org. Chem.* **1998**, *63*, 461. (d) Netherton, M. R.; Dai, C.; Neuschutz, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 10099. Reviews: (e) Suzuki, A. *Pure Appl. Chem.* **1991**, *63*, 419. (f) Suzuki, A. *Pure Appl. Chem.* **1994**, *66*, 213. (g) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147.