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Catalytic Asymmetric Carbohydroxylation of Alkenes by a Tandem Diboration/Suzuki Cross-Coupling/Oxidation Reaction

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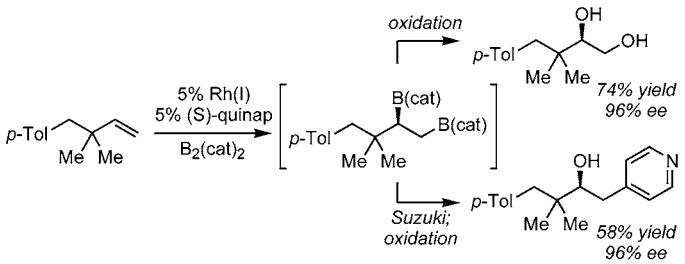
ABSTRACT



Chiral nonsymmetric 1,2-diboron adducts are generated by catalytic enantioselective diboration. Oxidation of these adducts provides 1,2-diols in good yield. Alternatively, 1,2-diboron compounds may be reacted, in situ, with aryl halides wherein the less hindered C–B bond participates in cross-coupling. The remaining C–B bond is then oxidized in the reaction workup thereby allowing for net asymmetric carbohydroxylation of alkenes in a tandem one-pot diboration/Suzuki coupling/oxidation sequence.

Catalytic asymmetric complexity-generating reactions are valuable tools for enantioselective synthesis of natural products and basic organic building blocks. In an effort to expand the number of complexity-generating reactions which are available to simple alkenes, we recently began developing the asymmetric diboration reaction as a platform for introducing new asymmetric alkene transformations.[1,2] The asymmetric diboration of olefins provides versatile reactive 1,2-diboron intermediates in a catalytic enantioselective fashion from commercially available reagents and catalyst. While these intermediates are readily converted to the corresponding diols by oxidative workup, it appeared tenable that intermediate diboron adducts might also engage in cross-coupling reactions. This transformation would allow catalytic conversion of alkenes to optically active compounds which are not readily accessible by other means. These efforts are described in this letter where the net catalytic enantioselective carbohydroxylation of alkenes by a tandem single-pot diboration/Suzuki cross-coupling/oxidation process is described.[3]

The rhodium-catalyzed asymmetric diboration reaction provides aliphatic boronic esters which are not as well-studied in cross-coupling reactions as their aryl and vinyl counterparts.[4] Available evidence indicates that primary

(1) Morgan, J. B.; Miller, S. P.; Morken, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 8702.

(2) For nonenantioselective alkene diboration with Rh, see: (a) Baker, R. T.; Nguyen, P.; Marder, T. B.; Westcott, S. A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1336. (b) Dai, C.; Robins, E. G.; Scott, A. J.; Clegg, W.; Yufit, D. S.; Howard, J. A. K.; Marder, T. B. *Chem. Commun.* **1998**, 1983. (c) Nguyen, P.; Coapes, R. B.; Woodward, A. D.; Taylor, N. J.; Burke, J. M.; Howard, J. A. K.; Marder, T. B. *J. Organomet. Chem.* **2002**, *652*, 77. With Pt, see: (d) Iverson, C. N.; Smith, M. R., III *Organometallics* **1997**, *16*, 2757. (e) Ishiyama, T.; Yamamoto, M.; Miyaura, N. *Chem. Commun.* **1997**, 689. (f) Marder, T. B.; Norman, N. C.; Rice, C. R. *Tetrahedron Lett.* **1998**, *39*, 155. (g) Ishiyama, T.; Momota, S.; Miyaura, N. *Synlett* **1999**, 1790.

(3) Asymmetric carbometalation/oxidation also accomplishes net carbohydroxylation albeit usually providing the primary alcohol. For a review see: Marek, I. *J. Chem. Soc., Perkin Trans. 1* **1999**, 545.

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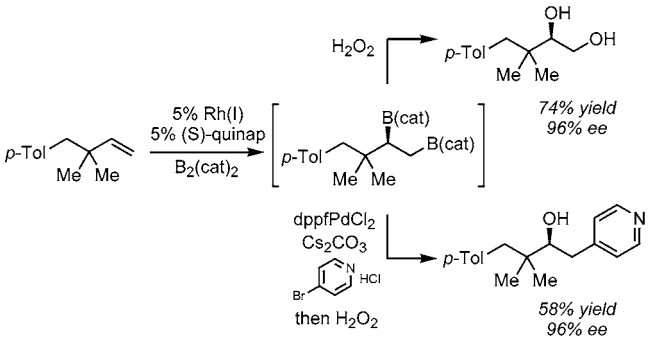
alkylboronic esters and their derivatives can participate in Pd-catalyzed Suzuki coupling reactions, but that secondary boronates are reluctant to react.[5] This fact suggests that unsymmetrical 1,2-bis(boronates), such as those derived from terminal alkenes, might engage in selective cross-coupling reactions. In this process, the more accessible C−B bond would react faster leaving the secondary C−B bond available for further transformation. Since there are no reports of Suzuki couplings involving aliphatic 1,2-diboron adducts, the stereochemical integrity of the nonreacting C−B bond was uncertain. A recent report by Hartwig suggests the potential for isomerization during Suzuki couplings of alkylboronic acids, presumably by β-hydride elimination/hydrometalation.[6] In the context of 1,2-diboron reagents, this complication might racemize the remaining C−B bond and was cause for concern.

Prior to exploring the tandem diboration/Suzuki sequence, access to an enantioselective diboration of sterically nonsymmetric alkenes was required. Preliminary studies indicated that diboration of both styrene (33% ee) and α-methylstyrene (46% ee) is nonselective.[1] Noting that regioselection during alkene insertion into rhodium hydrides is dependent on alkene electronics,[7] it was reasoned that aliphatic 1-alkenes might exhibit different enantioselectivity patterns compared to aromatic olefins and these substrates were therefore examined. As shown in Scheme 1, aliphatic alkenes

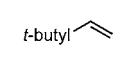
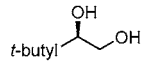
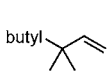
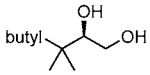
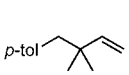
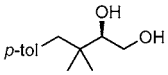
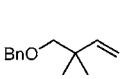
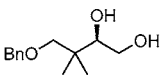
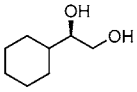
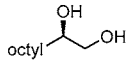
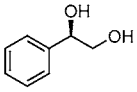
Scheme 1



can undergo efficient diboration in a highly selective fashion and provide, after oxidative workup, the derived 1,2-diol in high enantiopurity. To explore the Suzuki cross-coupling reaction, the same 1,2-diboron intermediate was subjected to in situ cross-coupling. In this experiment, the diboration reaction mixture was diluted with THF/H_2O and then 10 mol % of (dppf)$PdCl_2$, 4 equiv of Cs_2CO_3, and 2 equiv of 4-bromopyridine hydrochloride were added.[8] The reaction was stirred at 80 °C for 18 h, cooled to room temperature, and treated with alkaline H_2O_2. Upon purification, the carbohydroxylation adduct was isolated in 58% yield and in an identical level of selectivity as the simple oxidation adduct. That is, the configuration of secondary C−B was unaltered during the cross-coupling process.

To explore the potential generality of the tandem diboration/Suzuki coupling reaction, diboration of other 1-alkene substrates was examined. As shown in Table 1, encumbered

Table 1. Enantioselective Diboration/Oxidation of 1-Alkenes[a]

entry	substrate	product	% yield[b]	% ee
1			47	94
2			82	95
3			74	96
4			71	93[c]
5			81	59
6			82	62
7			68	33

[a] Conditions: 5 mol % of (*S*)-Quinap, 5 mol % of (nbd)Rh(acac), 1.5 equiv of $B_2(cat)_2$, THF, rt, 6 h. Oxidative workup with $NaOH/H_2O_2$. [b] Isolated yield of purified material. [c] This number was determined based on the enantiopurity of the corresponding diboration/cross-coupling adduct.

α-olefins generally provide excellent levels of enantioselection although the level of induction tends to decrease with diminished steric bulk adjacent to the reacting site. It also appears that while both aromatic and aliphatic alkenes react to form diols of the same configuration, aliphatic alkenes react with higher selectivity than similarly sized aromatic olefins (cf. entries 5 and 7).

Having established the level of enantioselection in the diboration of 1-alkenes and therefore the level of selectivity one can expect in carbohydroxylation adducts, the scope of the single-pot cross-coupling process was examined. As shown in Table 2, both aryl halides and aryl triflates can provide acceptable yields of tandem reaction product.

(4) For recent reviews of the Suzuki coupling reaction, see: (a) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147. (b) Kohta, S.; Lahirir, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633.

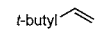
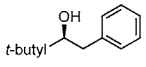
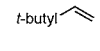
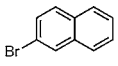
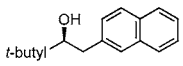
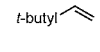
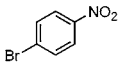
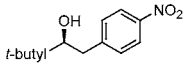
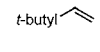
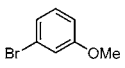
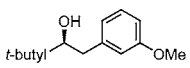
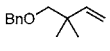
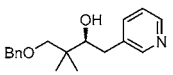
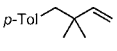
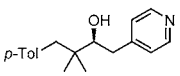
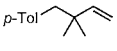
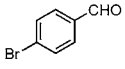
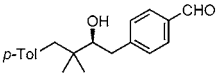
(5) (a) Kirchhoff, J. H.; Dai, C.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 1945. (b) Netherton, N. R.; Dai, C.; Neuschütz, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 10099. (c) Zou, G.; Falck, J. R. *Tetrahedron Lett.* **2001**, *42*, 5817.

(6) Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553.

(7) (a) Hayashi, T.; Matsumoto, Y.; Ito, Y. *J. Am. Chem. Soc.* **1989**, *111*, 3426. (b) Evans, D. A.; Fu, G. C.; Anderson, B. A. *J. Am. Chem. Soc.* **1992**, *114*, 6679.

(8) (a) Gray, M.; Andrews, I. P.; Hook, D. F.; Kitteringham, J.; Voyle, M. *Tetrahedron Lett.* **2000**, *41*, 6237. (b) Molander, G. A.; Ito, T. *Org. Lett.* **2001**, *3*, 393. (c) Molander, G. A.; Yun, C. S. *Tetrahedron* **2002**, *58*, 1465. For other Suzuki reactions with alkylboronic acids, see: Ag(I) acceleration: (d) Occhiato, E. G.; Trabocchi, A.; Guarna, A. *J. Org. Chem.* **2001**, *66*, 2459. (e) Zou, G.; Reddy, Y. K.; Falck, J. R. *Tetrahedron Lett.* **2001**, *42*, 7213. Fluoride acceleration: (f) Wright, S. W.; Hageman, D. L.; McClure, L. D. *J. Org. Chem.* **1994**, *59*, 6095. Palladacycle catalysts: (g) Botella, L.; Nájera, C. *J. Organomet. Chem.* **2003**, *663*, 46.

Table 2. Single-Pot Asymmetric Diboration/Suzuki Coupling[a]

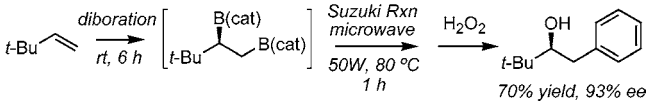
entry	alkene	coupling partner	product	% yield	% ee
1				76[b]	94
2				69	92
3				62	94
4				77	95
5				58	93
6				58	96
7				48	96

[a] Conditions: 5 mol % of (*S*)-Quinap, 5 mol % of (nbd)Rh(acac), 1.5 equiv of $B_2(cat)_2$, THF, rt, 6 h; then 3 equiv of Cs_2CO_3, 2 equiv of aryl halide, 10 mol % of (dppf)$PdCl_2$, THF/H_2O, 80 °C, 18 h. Oxidative workup with H_2O_2/NaOH, 6 h. [b] Suzuki coupling at 50 °C for 24 h.

Heterocycles are accommodated in the reaction and, notably, pyridines and aldehydes are unaltered during the oxidation.

Many organic transformations are accelerated by microwave reaction conditions[9] and the Suzuki coupling of arylboronic acids is no exception.[10] To determine whether the diboration/cross-coupling/oxidation reaction sequence could be accelerated by microwave irradiation during the *alkyl* Suzuki coupling step, this transformation was examined in further detail (Scheme 2). After diboration for 6 h, the

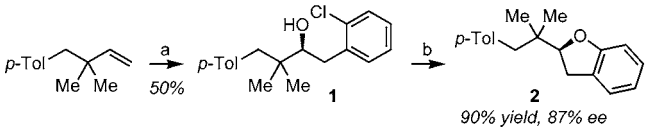
Scheme 2



abovementioned cross-coupling reagents were added and the reaction subject to microwave irradiation at 50 W and 80 °C for 1 h. Oxidation provided the carbohydroxylation adduct in 70% yield and 93% ee demonstrating that microwave irradiation accelerates the alkyl boronic acid Suzuki coupling without racemization of the adjacent C−B bond.

The example in Scheme 3 demonstrates that the tandem diboration/cross-coupling/oxidation sequence can be used to

Scheme 3 [a]



[a] Reagents and conditions: (a) 5 mol % of (*S*)-Quinap, 5 mol % of (nbd)Rh(acac), 1.5 equiv of $B_2(cat)_2$, THF, rt, 6 h; then 3 equiv of Cs_2CO_3, 2 equiv of bromochlorobenzene, 10 mol % of (dppf)-$PdCl_2$, THF/H_2O, 80 °C, 18 h; oxidative workup with H_2O_2/NaOH, 6 h. (b) 10 mol % of $Pd(OAc)_2$, 12 mol % of (*t*-Bu)$_2$P(2-biphenyl), 1.5 equiv of Cs_2CO_3, 80 °C, 28 h.

prepare versatile intermediates in a concise fashion. Engaging bromochlorobenzene in the tandem reaction sequence provides intermediate **1** in 50% isolated yield. Catalytic intramolecular etherification[11] using the Buchwald ligand preserves substrate configuration[11c] provides benzofuran **2** in 87% ee and 90% yield. This sequence makes the optically active heterocycle available from the simple alkene in a concise two-pot reaction sequence.

In summary, we have described an operationally simple, single-pot carbohydroxylation of olefin substrates. Current research efforts are directed toward expanding the range of synthetic transformations of chiral 1,2-diboron reagents.

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Supporting Information Available: Characterization data and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) For a review on the utility of microwave heating see: Lïndstrom, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225.

(10) (a) Larhed, M.; Hallberg, A. *J. Org. Chem.* **1996**, *61*, 9582. (b) Leadbeater, N. E.; Marco, M. *Org. Lett.* **2002**, *17*, 2973. (c) Leadbeater, N. E.; Marco, M. *J. Org. Chem.* **2003**, *68*, 888.

(11) (a) Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 10333. (b) Mann, G.; Harwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 13109. (c) Kuwabe, S.; Torraca, K. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 12202.