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Rh-Catalyzed Enantioselective Hydrogenation of Vinyl Boronates for the Construction of Secondary Boronic Esters

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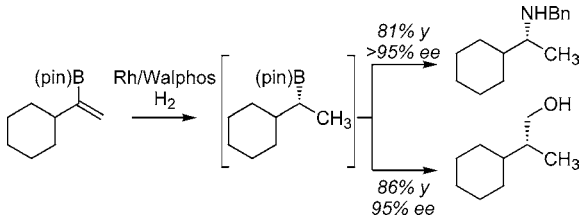
ABSTRACT



Rh-catalyzed hydrogenation of prochiral vinyl boronates occurs in an enantioselective fashion in the presence of the chiral ligand Walphos 1. This transformation provides access to chiral secondary organoboronates that are not available from alkene hydroboration reactions. The chiral reaction products should be useful in organic synthesis, and preliminary experiments suggest that they may participate in one-pot amination and homologation reactions.

Controlled construction of secondary organoboron derivatives is a difficult problem in organic synthesis, and yet, because the boron atom may be replaced with a variety of functional groups, solutions to this problem have important ramifications for the preparation of chiral compounds.[1] Alkene hydroboration is the most common route to alkylboron derivatives. However, aside from styrenes, hydroboration of 1-alkenes does not deliver secondary organoboron compounds.[2] Hydroboration of 1,2-disubstituted alkenes is similarly ineffective because this substrate class generally suffers from low position selectivity. In fact, the α-haloboronic ester strategy developed by Matteson is the only general route to such compounds in a nonracemic fashion.[3]

In this report we describe a catalytic enantioselective route to versatile secondary boronic esters that are not available from other catalytic reactions. Attractive features of this process are that the reaction proceeds under mild conditions and operates on readily available substrates that are prepared in an efficient, inexpensive fashion.[4]

As part of a program aimed at the development of catalytic asymmetric processes for the generation of chiral reactive intermediates, we recently described the hydrogenation of vinylbis(boronic esters).[5] This transformation provides an alternative to enantioselective alkene diboration as a route to the production of chiral alkyl-1,2-bis(boronic esters). In a similar fashion, it was imagined that hydrogenation of vinylboronic esters might provide an alternative to alkene hydroboration for the synthesis of chiral secondary organo-

(1) (a) Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Syntheses via Boranes*; Wiley-Interscience: New York, 1975. (b) Brown, H. C.; Singaram, B. *Acc. Chem. Res.* **1988**, *21*, 287.

(2) For recent reviews of catalytic hydroboration, see: (a) Crudden, C. M.; Edwards, D. *Eur. J. Org. Chem.* **2004**, 4695. (b) Beletskaya, I.; Pelter, A. *Tetrahedron* **1997**, *53*, 4957.

(3) Review: Matteson, D. S. *Tetrahedron* **1998**, *54*, 10555.

(4) (a) Takagi, J.; Takashi, K.; Ishiyama, T.; Miyaura, N. *J. Am. Chem. Soc.* **2002**, *124*, 8001. (b) Morrill, C.; Funk, T. W.; Grubbs, R. H. *Tetrahedron Lett.* **2004**, *45*, 7733.

(5) Morgan, J. B.; Morken, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 15338.

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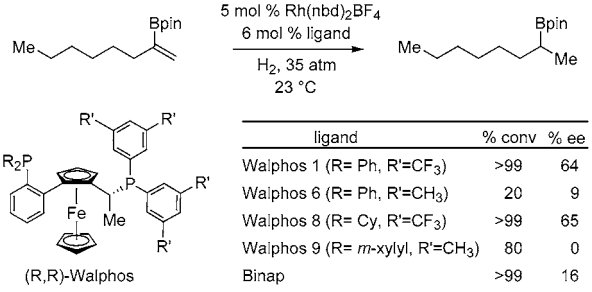
boron compounds.[6] Importantly, in this approach the position selectivity of the chiral organoboron product is controlled during construction of the hydrogenation substrate and should ultimately allow access to a broad array of secondary organoboronates in a regiodefined fashion.

Many catalytic reactions proceed by transmetalation of vinyl groups from boron to Rh(I), and this elementary step has been observed in the Rh-catalyzed addition of arylboronates to enones.[7] For this reason, it was initially considered that Rh-catalyzed hydrogenation of vinyl boronic esters might suffer from significant competitive side reactions. Likely because the hydrogenation reactions were carried out in the absence of exogenous base, transmetalation appears not to be a problem and very high yields of saturated organoboron derivatives may be obtained from this route. A sample of the many ligands examined is depicted in Table 1 where it can be seen that the Walphos 1[8] and Walphos 8

Table 1. Effect of Chiral Ligand on the Rh-Catalyzed Hydrogenation of Vinylboronic Esters



ligand	% conv	% ee
Walphos 1 (R= Ph, R'=CF_3)	>99	64
Walphos 6 (R= Ph, R'=CH_3)	20	9
Walphos 8 (R= Cy, R'=CF_3)	>99	65
Walphos 9 (R= *m*-xylyl, R'=CH_3)	80	0
Binap	>99	16

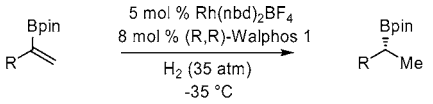
ligands are uniquely selective for this transformation. Whereas only moderate selectivity was observed under the conditions for the initial ligand survey (35 atm H_2, room temperature), executing the reaction at lower temperatures led to a significant improvement in enantioselectivity when Walphos 1 was the chiral modifiying ligand. The optimal reaction conditions are presented in Table 2 where it can be observed that very high levels of selectivity and excellent product yield may be obtained. Interestingly, both coordinating and noncoordinating functionality may be present in the substrate and the selectivity is similar. Entries 8 and 9 demonstrate that the reaction of chiral substrates is controlled by the catalyst alone and that resident chirality does not significantly alter the reaction outcome.

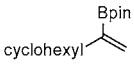
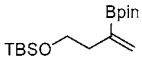
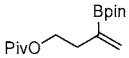
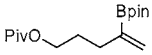
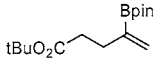
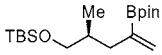
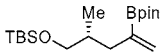
(6) (a) Matteson, D. S.; Bowie, R. A. *J. Am. Chem. Soc.* **1965**, *87*, 2587. (b) Matteson, D. S.; Bowie, R. A.; Srivastava, G. *J. Organomet. Chem.* **1969**, *16*, 33. (c) Suginome, M.; Nakamura, H.; Ito, Y. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2516. (d) Hupe, E.; Marek, I. Knochel, P. *Org. Lett.* **2002**, *4*, 2861. (e) Gamsey, S.; DeLaTorre, K.; Singaram, B. *Tetrahedron: Asymmetry* **2005**, *16*, 711. For a previous approach to catalytic asymmetric reduction of vinylboronates, see: (f) Ueda, M.; Saitoh, A.; Miyaura, N. *J. Organomet. Chem.* **2002**, *642*, 145. For vinylsilanes: (g) Lautens, M.; Zhang, C.; Crudden, C. M. *Angew. Chem., Int. Ed. Engl.* **1992**, 232. (h) Murakami, M.; Oike, H.; Sugawara, M.; Suginome, M.; Ito, Y. *Tetrahedron* **1993**, *19*, 3933.

(7) Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **2002**, *124*, 5052.

(8) Sturm, T.; Weissensteiner, W.; Spindler, F. *Adv. Synth. Catal.* **2003**, *345*, 160.

Table 2. Rh/Walphos 1-Catalyzed Hydrogenation of Vinylboronic Esters[a]

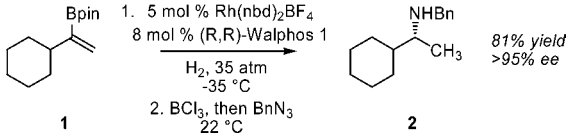


entry	substrate	solvent	% yield[b]	% ee[c]
1		toluene	>95	97
		dichloroethane	>95	95
2		toluene	>95	81
		dichloroethane	>95	84
3		toluene	>95	90
		dichloroethane	>95	85
4		toluene	>95	90
		dichloroethane	>95	86
5		toluene	>95	92
		dichloroethane	>95	89
6		toluene	>95	94
		dichloroethane	>95	59
7		toluene	>95	88
		dichloroethane	>95	79
8		toluene	>95	>20:1 dr
		dichloroethane	>95	>20:1 dr
9		toluene	>95	>20:1 dr
		dichloroethane	>95	>20:1 dr

[a] All reactions were conducted for 12 h in a stainless steel bomb immersed in a Cryocool. [b] Isolated yield after passage of the reaction mixture though a silica gel plug. In general, the reaction products are >95% pure by spectroscopic analysis. [c] Enantiomeric excess determined after conversion to the derived alcohol by treatment with NaOH/ H_2O_2.

An attractive feature of the vinylboronate hydrogenation reaction is that the immediate reaction product is pure enough for use directly in other transformations. The experiment in Scheme 1 demonstrates this feature where, after the asymmetric hydrogenation, the alkylboronic ester is treated with BCl_3 and then benzyl azide.[9] This reaction sequence directly provides chiral secondary amine **2** in good yield and excellent enantiomeric excess.

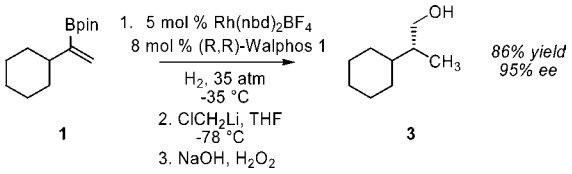
Scheme 1



(9) (a) Chlorination: (a) Jego, J. M.; Carboni, B.; Vaultier, M.; Carrié, R. *J. Chem. Soc., Chem. Commun.* **1989**, 142. (b) Brindley, P. B.; Gerrard, W.; Lappert, M. F. *J. Chem. Soc.* **1956**, 824. (c) Amination: Brown, H. C.; Midland, M. M.; Levy, A. B. *J. Am. Chem. Soc.* **1973**, *95*, 2394.

Aside from amination and oxidation, the capacity of chiral organoboronic esters to participate in C−C bond-forming reactions is also a noteworthy trait. The direct conversion of vinyl boronate **1** to **3** can be accomplished as depicted in Scheme 2.[10] For this transformation, a solvent-swap of

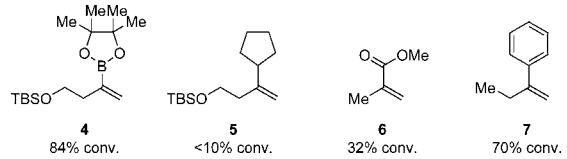
Scheme 2



toluene for THF is required, but the unpurified hydrogenation mixture may be used directly and provides the α-chiral alcohol **3** in high yield and enantiomeric excess.

Vinyl boron compounds may exhibit unique reactivity relative to that of typical alkene substrates (i.e., omniphilic reactivity in cycloadditions).[11] A priori one might anticipate that in the Rh-catalyzed hydrogenation the boronic ester oxygen atoms may coordinate to the cationic metal center and provide transition state organization.[12] Experiments in Table 2 suggest that this is not the case. Substrate functionality of varying Lewis basicity, and presumably varying ability to compete with a putatively coordinating boronate, all provide similar enantioselection. This argument is consistent with the minimal basicity[13] of boronate oxygen atoms, which arises from $n_O \rightarrow p_B$ orbital overlap. Alternatively, one might consider the electronic properties of the boronic ester as an important element in the reaction. To probe these effects, the alkenes in Scheme 3 were compared in the Rh/Walphos-catalyzed hydrogenation. The activating effect of the boronate

Scheme 3. Conversion at 10 min in Isolated Experiments[a]



[a] Reagents and conditions: 5 mol % $Rh(nbd)_2BF_4$, 8 mol % Walphos 1, 35 atm H_2, −35 °C.

relative to an alkyl substituent is clear when comparing boronate **4** (84% conversion) to similarly sized alkene **5** (<10% conversion). One might ascribe this difference to the π-acceptor properties[14] of the boron atom. However, the low reactivity observed with methyl methacrylate argues against the solitary importance of this feature. Alternatively, one might ascribe the enhanced reactivity of vinyl boronates to inductive donation from boron to carbon.[15] However, an inductively withdrawing phenyl ring (**7**) provides levels of reactivity comparable to that of the vinyl boronate (70% conversion) albeit no enantioselection (<5% ee). Clearly, the nature of the boronate's involvement in the reaction is not simple and more detailed experiments are required to understand the nature of this reaction.

In conclusion, we have documented a highly enantioselective catalytic asymmetric hydrogenation of vinyl boronates, which in many cases provides products that are unattainable from hydroboration reactions. Further examination of the scope and utility of this process is in progress.

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

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(10) (a) Ren, L.; Crudden, C. M. *Chem. Commun.* **2000**, 721. (b) Sadhu, K. M.; Matteson, D. S. *Organometallics* **1985**, *4*, 1687.
(11) Singleton, D. A.; Martinez, J. P.; Watson, J. V. *Tetrahedron Lett.* **1992**, *33*, 1017.
(12) Coordination of a Lewis acid to a pinacol boronate oxygen has been detected by NMR; see: Kennedy, J. W. J.; Hall, D. G. *J. Am. Chem. Soc.* **2002**, *124*, 11586.
(13) Pola, J.; Jakoubková, M.; Václav, C. *Collect. Czech. Chem. Commun.* **1979**, *44*, 3688.
(14) (a) Exner, O.; Bose, R. *Collect. Czech. Chem. Commun.* **1974**, *39*, 2234. (b) Kiplinger, J. P.; Crowder, C. A.; Sorensen, D. N.; Bartmess, J. E. *J. Am. Soc. Mass Spectrom.* **1994**, *5*, 169.
(15) The Pauling electronegativites for boron and carbon are 2.04 and 2.55, respectively (Allred, A. L. *J. Inorg. Nucl. Chem.* **1961**, *17*, 215). Based on chemical shift data for a boronic ester (Nöth, H.; Vahrenkamp, H. *J. Organomet. Chem.* **1968**, *12*, 23) the electronegativity of this group is 1.96 according to the modified Dailey-Shoolery equation. See: (a) Narasimhan, P. T.; Rogers, M. T. *J. Am. Chem. Soc.* **1960**, *82*, 34. (b) Ohashi, O.; Kurita, Y.; Totani, T.; Watanabe, H.; Nakagawa, T.; Kubo, M. *Bull Chem.* Soc. Jpn. **1962**, *35*, 1317.