A Two-Component Catalyst System for Asymmetric Allylic Alkylations with Alcohol Pronucleophiles

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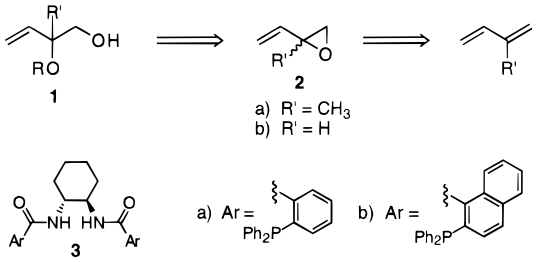
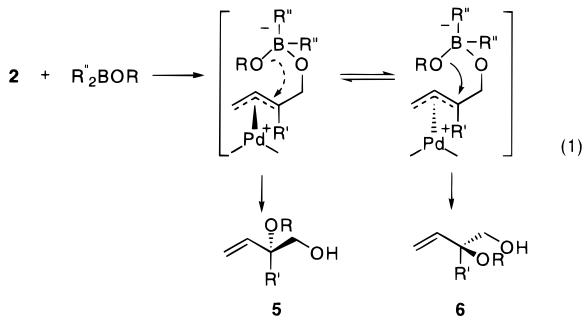
The importance of chiral nonracemic building blocks for the synthesis of biologically important target molecules continues to grow, especially as a result of the explosion of molecular targets in the pharmaceutical and agrichemical arenas. Tartaric acid exemplifies the value of chiral nonracemic oxygen-bearing synthetic intermediates[1] but also some of the problems, differentiating and manipulating the functionality. An alternative family, wherein such functional group manipulations are simpler, is the vinylglycidols **1**, but their access in chiral, nonracemic form is frequently not straightforward.[2−5] The ready access to racemic vinyl epoxides via epoxidation of 1,3-dienes[6] makes their deracemization, in contrast to a kinetic resolution, to form chiral nonracemic vinylglycidols very attractive, especially if the two hydroxyl groups are differentiated intrinsic to the deracemization reaction. Palladium-catalyzed asymmetric additions of alcohols could be a solution if (i) the normal poor reactivity of alcohols as nucleophiles[7] could be overcome, (ii) the alcohols would react regioselectively to give the vicinal hydroxyether, (iii) the product primary alcohol would not compete effectively with the reactant alcohol (a most subtle type of chemoselectivity), and (iv) diastereomeric interconversion of the π-allylpalladium intermediates could occur faster than nucleophilic attack. Whereas the palladium catalyst may control the last issue,[8] resolution of the first three prerequisites required the discovery of a catalyst for the alcohol nucleophile to provide the chemo- and regioselectivity. In our search for achieving this goal, we have uncovered a remarkable catalytic role for trialkylboranes in promoting the nucleophilic addition of alcohols chemo-, regio-, and enantioselectively to vinyl epoxides.

As suspected, the reaction of vinyl epoxide **2a** with methanol or benzyl alcohol in the presence of Pd(0) and the chiral ligand **3a** led to no reaction or almost no reaction (<6%), respectively, over 18 h.



As envisioned in eq 1, treatment of isoprene or where mono-



epoxide with 1 equiv of trimethyl borate in the presence of $(dba)_3Pd_2{\cdot}CHCl_3$ (**4**) and ligand **3a** gave the desired glycol monoether **1a** in 80% yield but only 2% ee. Independent experiments show that trialkylborates do not react with the epoxide in the absence of a palladium catalyst. Since equilibration of the π-allylpalladium intermediates (as depicted in eq 1) must be fast compared to alkoxide transfer to obtain good ee, we decreased the concentration of the transfer agent, trimethylborate, to 1% but added a stoichiometric amount of methanol. Indeed, the ee increased to 49%. Decreasing the effectiveness of the boron to form an "ate" complex by switching to diethylmethoxyborane[9,10] increased the ee in both the stoichiometric and catalytic reactions to 58% and 90%, respectively. Generating diethylmethoxyborane in situ from triethylborane and methanol led to the most convenient and best results, giving an 88% isolated yield and 94% ee of **5a** (R = R′ = CH_3).

Using these conditions, a variety of alcohols were added to isoprene monoepoxide as summarized in Table 1. The examples show good chemoselectivity wherein nitriles, esters, and ketones all are tolerated. With 2-cyanoethanol (Table 1, entry 4), the ee was 81% under our standard conditions. Assessing that the source of the somewhat diminished ee might still arise from too rapid trapping of the π-allylpalladium intermediate, we switched to a more hindered borane, tri-*sec*-butylborane, as the cocatalyst.

(1) For applications towards vinylglycidol, see: Rao, A. V.; Reddy, E. R.; Joshi, B. V.; Yadav, J. S. *Tetrahedron Lett.* **1987**, *28*, 6497; Howes, D. A.; Brookes, M. H.; Coates, D.; Golding, B. T.; Hudson, A. T. *J. Chem. Res. (M)* **1983**, 217. For an overview, see: Seebach, D.; Hungerbühler, E. In *Modern Synthetic Methods 1980*; Scheffold, R.; Ed.; Otto Salle Verlag: Frankfurt am Main, 1980; Vol. 2, pp 91−171.

(2) A kinetic resolution of butadiene monoepoxide to form vinylglycidol has been reported, see: Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936.

(3) For enzymatic resolution of derivatives of vinylglycidol, see: Boaz, N. W.; Zimmerman, R. L. *Tetrahedron: Asymmetry* **1994**, *5*, 153; Suzuki, T.; Kasai, N.; Minamiura, N. *Tetrahedron: Asymmetry* **1994**, *5*, 239. For solvolysis of the corresponding enantiomerically pure vinyl epoxide to form the monoethers of vinylglycidol in addition to varying amounts of 1,4-adduct, see: Boaz, N. W. *Tetrahedron: Asymmetry* **1995**, *6*, 15. For kinetic resolution of the monotosylate by asymmetric epoxidation, see: Neagu, C.; Hase, T. *Tetrahedron Lett.* **1993**, *34*, 1629.

(4) For other asymmetric syntheses of vinylglycidol and the 2-methyl derivative, see: Saibata, R.; Sarma, M. S. P.; Abushnab, E. *Synth. Commun.* **1989**, *19*, 3077; Jurczak, J.; Pikul, S.; Bauer, T. *Tetrahedron* **1986**, *42*, 447; Ohwa, M.; Kogure, T.; Eliel, E. L. *J. Org. Chem.* **1986**, *51*, 2599.

(5) Asymmetric dihydroxylation of butadiene or isoprene has not been reported to our knowledge. *trans*-Piperylene is reported to give moderate yields and moderate chemoselectivity with ee's of 90% and 72% for the two diols. See Becker, H.; Soler, M. A.; Sharpless, K. B. *Tetrahedron* **1995**, *51*, 1345; For a review, see Kolb, H. C.; Van Nieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

(6) Both butadiene and isoprene monoepoxides are commercially available. Such epoxides are available by the direct epoxidation of the corresponding dienes. For butadiene monoepoxide from diene and oxygen, see: Monnier, J. R. In *3rd World Congress on Oxidation Catalysis, 1997*; Grasselli, R. K., Oyama, S. T., Gaffney, A. M., Lyons, J. E., Eds.; Elsevier: New York, 1997; pp 135−149. For isoprene monoepoxide, see: Eletti-Bianchi, G.; Centini, F.; Re, L. *J. Org. Chem.* **1976**, *41*, 1648; Fransen, M. R.; Palings, I.; Lugtenberg, J. *Recl. Trav. Chim. Pays-Bas* **1980**, *99*, 384.

(7) Cf. Trost, B. M.; Tenaglia, A. *Tetrahedron Lett.* **1988**, *29*, 2931; Sinou, D.; Frappa, I.; Lhoste, P.; Powanski, S.; Kryczka, B. *Tetrahedron Lett.* **1995**, *36*, 1251; For some recent intramolecular processes, see: Fournier-Nguefack, C.; Lhoste, P.; Sinou, P. *Tetrahedron* **1997**, *53*, 4353; Thorey, C.; Wilken, J.; Hénin, F.; Martens, J.; Mehler, T.; Muzart, J. *Tetrahedron Lett.* **1995**, *36*, 5527. For a review, see: Godleski, S. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, pp 585−662.

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(9) For alkenylborane coupling, see: Miyaura, N.; Tanabe, Y.; Suginome, H.; Suzuki, A. *J. Organomet. Chem.* **1982**, *233*, C13.

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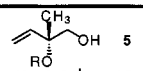
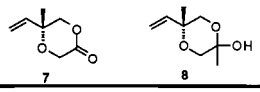
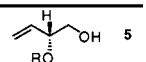
Table 1. Boron Co-Catalyzed Asymmetric Addition of Alcohols to Isoprene Monoepoxide[a]

Entry	R of ROH	R"$_3$B	Time (h)	 5 % yield[b] (ee)[c]
1	CH_3	$(C_2H_5)_3B$	3	**5a**, 88% (94%)
2	CH_2=$CHCH_2$	$(C_2H_5)_3B$	3	**5b**, 83% (95%)
3	p-$CH_3OC_6H_4CH_2$	$(C_2H_5)_3B$	3	**5c**, 91% (94%)[d]
4	$NCCH_2CH_2$	$(C_2H_5)_3B$	18	**5d**, 82% (81%)
	$NCCH_2CH_2$	(s-$C_4H_9)_3B$[e]	4	**5d**, 81% (90%)
5	$CH_3CH(OH)(CH_2)_2$	$(C_2H_5)_3B$[e]	3	**5e**, 63% (85%)[f]
	$CH_3CH(OH)(CH_2)_2$	(s-$C_4H_9)_3B$[e]	18	**5e**, 43% (98%)[f]
6	$CH_3O_2CCH_2$	$(C_2H_5)_3B$	4	**7**, 79% (77%)
	$CH_3O_2CCH_2$	(s-$C_4H_9)_3B$[e]	4	**7**, 75% (94%)
7	CH_3COCH_2	$(C_2H_5)_3B$[g]	18	**8**, 77% (98%)[h]



[a] All reactions performed using a 1:1 ratio of alcohol to **2a** with 1 mol % **4**, 3 mol % ligand **3a**, 1 mol % R_3B in methylene chloride at room temperature unless stated otherwise. [b] Yields are for isolated pure product. [c] Determined by chiral GC with J&W Cyclosil B column or HPLC with Chiralcel OD or Chiralpak AS columns. [d] Analysis performed on corresponding benzoate. [e] Reaction performed at 40 °C. [f] Corresponds to enantioselectivity at tertiary center, secondary alcohol is a 1:1 epimeric mixture. [g] Also required 5 mol % DMAP. [h] Determined after dehydration to 1,4-dioxene.

Table 2. Boron Co-Catalyzed Asymmetric Addition of Alcohols to Butadiene Monoepoxide[a]

Entry	R of ROH	R"$_3$B	Time (h)	 5 % yield[b] (ee)
1	CH_3	$(C_2H_5)_3B$	18	**5f**, [70%] (84%)
	CH_3	(s-$C_4H_9)_3B$	3	**5f**, 82% (89%)
2	CH_2=$CHCH_2$	$(C_2H_5)_3B$	18	**5g**, [80%] (87%)
	CH_2=$CHCH_2$	(s-$C_4H_9)_3B$	18	**5g**, 81% (92%)
3	CH≡CCH_2	$(C_2H_5)_3B$	5	**5h**, 78% (88%)
4	$(CH_3)_3Si(CH_2)_2$	$(C_2H_5)_3B$[c]	3	**5i**, 85% (94%)
	$(CH_3)_3Si(CH_2)_2$	(s-$C_4H_9)_3B$[d]	18	**5i**, 41% (94%)
5	p-$CH_3OC_6H_4CH_2$	$(C_2H_5)_3B$[e]	3	**5j**, 82% (91%)[f]
	p-$CH_3OC_6H_4CH_2$	(s-$C_4H_9)_3B$	18	**5j**, 76% (84%)

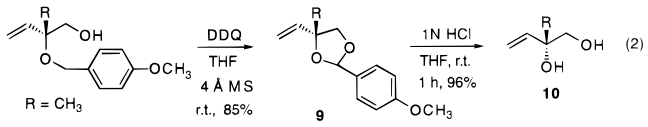
[a] See footnote a, Table 2, except that 3 mol % of ligand **3b** was employed. [b] Yields in brackets are based upon NMR and GC analyses; otherwise yields are for isolated pure product. [c] Reaction performed with a 2:1 ratio of alcohol to epoxide at 40 °C in the presence of 5% DMAP. [d] Reaction performed at 40 °C. [e] Performed with a 1.1:1 ratio of alcohol to epoxide at 40 °C in the presence of 5% DMAP.

Indeed, the ee increased to 90%. A similar effect was observed with methyl glycolate as the nucleophile (Table 1, entry 6). Secondary alcohols do not participate, a fact that is dramatically illustrated by entry 5 (Table 1). It should be noted that no regioisomeric 1,4- products were detected in any case.

Extension to butadiene monoepoxide must take cognizance of the higher susceptibility of the secondary center toward nucleophilic addition. In this regard, the fact that the carbon undergoing attack in the isoprene epoxide case is tertiary, which slows down reaction, becomes beneficial with respect to ee. Indeed, under our standard conditions with ligand **3a** and methanol as a nucleophile, a 78% yield of adduct of only 25% ee was obtained. In addition, a significant amount of oligomer, wherein the initial product served as nucleophile, was also produced. Replacing the benzo-linked ligand **3a** with the naphtho-linked ligand **3b**[8] decreased the amount of the oligomer and enhanced the ee. Table 2 summarizes the results. In most cases, the use of tri-*sec*-butylborane was advantageous over that of triethylborane.

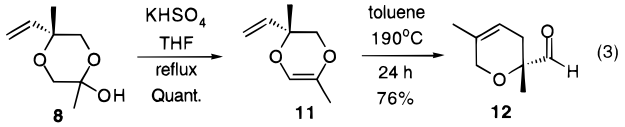
The effect of boranes on the ability of alcohols to serve as nucleophiles in their asymmetric addition to vinyl epoxides in a dynamic kinetic resolution is dramatic and decisive. Thus, this two-component catalytic system has the palladium activating the electrophile and boron, the nucleophile. Although the current observations question the role, if any, of the boron in the epoxide opening as in eq 1, a fuller discussion of the mechanism is postponed until more detailed studies are completed.

This new chemo-, regio-, and enantioselective opening of racemic vinyl epoxides in a dynamic kinetic resolution (a deracemization) is a valuable and flexible entry to these versatile building blocks. These materials constitute differentiated diols wherein the more substituted alcohol is selectively "protected," a type of differentiation not readily accessible by selective monoprotection of the diol. As an example, the PMB derivative can readily be converted to the benzylidene analogue **9**,[11] wherein both alcohols are protected, and the latter hydrolyzed to the glycidol analogue **10**[12] (eq 2). A 1,4-dioxanone **7** (Table 1, entry



(2)

6) and a 1,4-dioxene **11** (Table 1, entry 7 and eq 3) are also accessed asymmetrically. A Claisen rearrangement[13] of the latter provided a pyrane **12** asymmetrically (eq 3).



(3)

The concept of this two-component catalyst system to activate both the nucleophile and electrophile may expand the metal-catalyzed allylic alkylation to additional nucleophiles beyond alcohols, thereby considerably expanding the scope of this important transformation. Interestingly, and in stark contrast to Suzuki-type couplings, alkoxy transfer dominates over alkyl or hydride transfer with the dialkylalkoxyboranes and the electrophiles used herein.

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Supporting Information Available: General experimental procedure and characterization data for **5a**−**5j**, **7**−**9**, **11**, **12**, and benzoate ester of **5c** and Table, Effect of Boron Source in Additions of Methanol to Isoprene Monoepoxide (9 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(12) Ohwa, M.; Kogure, T.; Eliel, E. L. *J. Org. Chem.* **1986**, *51*, 2599.
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