# *Communications*

## Convenient Preparation of Chiral Primary Alcohols *via* Catalytic Asymmetric Reduction of Aldehydes Using $Bu_3SnD$

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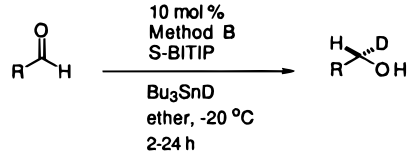
Chiral primary alcohols have been used extensively in the study of enzymatic mechanisms and as precursors for other labeled compounds such as [$^1$H,$^2$H,$^3$H]acetic acid.[1] Convenient methods for the incorporation of isotopic labels can also assist investigations of complex metabolic pathways, such as *in vitro* metabolism of drug candidates. We describe herein a particularly convenient method for the enantioselective introduction of deuterium *via* catalytic asymmetric reduction of aldehydes,[2] yielding chiral primary carbinols RCHDOH. With minor modifications, the method should be applicable to chiral tritiated alcohols as well.

In a recent series of papers, we have documented the utility of "BITIP" catalysts (acronymn denotes catalyst preparation from BINOL and titanium tetraisopropoxide) in catalytic asymmetric C−C bond-forming reactions such as allylstannane additions[3] and Mukaiyama aldol condensations,[4] using aldehydes as substrates. Since stannanes such as $Bu_3SnH$ are known to reduce aldehyde or ketone carbonyl groups by either "one-electron" or "two-electron" mechanisms,[5] it was of interest to see if these catalytic asymmetric reactions utilizing aldehydes as substrates could be extended to encompass catalytic asymmetric reductions.

Initial experiments using benzaldehyde as substrate indicated that such reactions could in fact be accomplished catalytically. Of the procedures previously reported, "method B" gave the best results in this instance. Thus, reduction of benzaldehyde with $Bu_3SnD$ using 10 mol % (titanium relative to substrate PhCHO) of catalyst prepared according to "method B" previously reported by us afforded product of 94% ee (analysis *via* the corresponding Mosher ester). Methods A and D afforded 84% and 70% ee, respectively. In these reductions, little difference was noted between reactions conducted in ether *vs* those run using dichloromethane. The same trends in enantiomeric excess obtained using methods A, B, and D were also observed when 3-phenylpropionaldehyde was used as substrate, indicating that method B was probably the optimum procedure for these reductions.

**Table 1. Yields and Ee's for Chiral Primary Alcohols**




| entry | aldehyde | reaction time (h) | yield[a] (%) | ee[b] (%) |
|---|---|---|---|---|
| 1 | benzaldehyde | 2 | 92 | 94 |
| 2 | furaldehyde | 2 | 80 | 97 |
| 3 | $PhCH_2CH_2CHO$ | 20 | 90 | 95 |
| 4 | (*E*)-PhCH=CHCHO | 20 | 83 | 93 |
| 5 | geranial | 24 | 81 | 95 |
| 6 | $BnOCH_2CHO$ | 24 | 75 | 90 |

[a] All yields are isolated yields. [b] ee was determined by $^1$H NMR analysis of the corresponding MTPA ester.

Application of the method B protocol to several aldehydic substrates afforded the results summarized in Table 1. In all cases, good yields of products with ≥90% ee were obtained. Since analysis in all cases was *via* NMR spectroscopy of the derived Mosher esters, it proved difficult to assay ee's in this range precisely, particularly for ee's ≥95%. Thus, both the precision and accuracy of these measurements are not as high as those achievable using chromatographic methods, but it is nonetheless clear that the enantioselectivity of this process is excellent and competitive with other known methods.

Perhaps the most commonly used method, developed by Midland,[6] for preparing such D-labeled alcohols utilizes the reduction of RCDO with 3-pinanyl-9-BBN (prepared from pinene and 9-BBN) or reduction of RCHO with the deuterated borane prepared from pinene and 9-BBN-*9-d*. These methods require either optically pure (+)- and (−)-pinene or "correction" of the product ee for the % ee of the pinene employed. The reductions of benzaldehyde, cinnamaldehyde, and geranial reported by Midland with 9-BBN-*9-d*, after correction for the deuterium content of the reagent and the % ee of pinene, proceed with 98, 84, and 81% ee, respectively. Clearly, the simple catalytic protocol described herein compares quite favorably (for these cases) with the stoichiometric borane-based methodology, and no such corrections are necessary.

Although the results described in Table 1 apply to $Bu_3SnD$ reduction of RCHO, it seems clear that $Bu_3SnH$ reduction of RCDO could be accomplished equally well. It also seems clear that chiral tritiated carbinols could be prepared by this approach, using $RC^3HO$ with $Bu_3SnD$ or RCDO with $Bu_3Sn^3H$. In this context, it should be noted that $Bu_3SnD$ is commercially available or can be conveniently prepared from $Bu_3SnH$ by reaction with LDA[7] followed by quenching with $D_2O$.[8] A similar

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(2) We are aware of only one previous report on the catalytic asymmetric reduction of aldehydes: Corey, E. J.; Link, J. O. *Tetrahedron Lett.* **1989**, *30*, 6275.

(3) (a) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467. (b) Keck, G. E.; Geraci, L. S. *Tetrahedron Lett.* **1993**, *34*, 7827. (c) Keck, G. E.; Krishnamurthy, D.; Grier, M. C. *J. Org. Chem.* **1993**, *58*, 6543.

(4) (a) Keck, G. E.; Krishnamurthy, D. *J. Am. Chem. Soc.* **1995**, *117*, 2363. (b) Keck, G. E.; Li, X.-Y.; Krishnamurthy, D. *J. Org.Chem.* **1995**, *60*, 5998. (c) Descriptions of catalyst preparations herein are used as consistent with our previous reports.

(5) The literature on this subject is extensive. For representative and leading references, see: (a) Tanner, D. D.; Singh, H. K. *J. Org. Chem.* **1986**, *51*, 5182. (b) Shibata, I.; Yoshida, T.; Kawakami, T.; Baba, A.; Matsuda, H. *J. Org. Chem.* **1992**, *57*, 4049. (c) Zelechonok, Y.; Silverman, R. B. *J. Org. Chem.* **1992**, *57*, 5785. (d) Vedejs, E.; Duncan, S. M.; Haight, A. R. *J. Org. Chem.* **1993**, *58*, 3046. (e) Hays, D. S.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 4.

(6) (a) Midland, M. M.; Tramontano, A.; Zderic, S. A. *J. Am. Chem. Soc.* **1977**, *99*, 5211. (b) Midland, M. M.; Greer, S.; Tramontano, A.; Zderic, S. A. *J. Am. Chem. Soc.* **1979**, *101*, 2352.

(7) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481.

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protocol should serve to prepare $Bu_3Sn^3H$, perhaps by quenching with $AcO^3H$ (from $Ac_2O + {}^3H_2O$). Although we have not prepared $Bu_3Sn^3H$ or employed this reagent in reductions due to the special regulations that are involved for handling radioactive materials, we can see no reason why such reactions should not proceed with equally high enantiomeric excess as those described herein.

Several features of these reactions are worthy of note. First of all, the reducing agent employed possesses only one transferable hydrogen that can come directly ($Bu_3SnD$) or perhaps indirectly ($Bu_3Sn^3H$) from water *via* a simple depronation/quenching protocol. Thus, the reagent is easily prepared from a convenient and inexpensive source of label and can be stored indefinitely. Secondly, both enantiomers of BINOL are commercially available with essentially 100% enantiomeric excess.[9] This ensures that any (*R*)/(*S*) pairs of labeled primary alcohols prepared using this procedure will be of the same enantiomeric excess (within experimental error) and can be used without tedious corrections for the differing ee's of *R* and *S* enantiomers, a correction that is generally necessary if the pinene based borane reduction is used to prepare (R)/(S) pairs.[10]

In all of the reactions described to date, the use of BITIP catalysts derived from (*R*)-BINOL results in nucleophilic addition to the *re* face of the aldehyde substrate. The same appears true of the reduction process described herein—reduction of benzaldehyde using catalyst prepared from (*S*)-BINOL gave *S* product, as determined by $^1$H NMR experiments using $Eu(hfc)_3$, as previously reported by Midland.[6] The same sense of addition is assumed for the other substrates employed.

**Preparation of (*S*)-1-Deuteriogeraniol.** A mixture of (*S*)-(−)-BINOL (28.6 mg, 0.1 mmol), 1 M $Ti(O\text{-}i\text{-}Pr)_4$ in $CH_2Cl_2$ (50 $\mu$L, 0.05 mmol), $CF_3CO_2H$ (0.003 mL, 0.5 M in $CH_2Cl_2$), and oven-dried powdered 4 Å molecular sieves (200 mg) in ether (2.0 mL) was heated at reflux for 1 h. The red-brown mixture was cooled to rt, and geranial (76 mg, 0.5 mmol) was added. The mixture was stirred for 5 min and cooled to −78 °C, $Bu_3SnD$ (103 mg, 0.59 mmol) was added, and the contents were stirred for 10 min and then placed in a −20 °C freezer (without stirring) for 24 h. Saturated $NaHCO_3$ solution (0.5 mL) was added, and the contents were stirred for 1 h and then filtered through a plug of Celite. The organic layer was separated, and the aqueous layer was extracted with ether (3 × 2 mL). The combined organic layers were dried over $Na_2SO_4$ and concentrated. The crude material was purified by flash chromatography, eluting with 10% acetone in hexanes, to afford 66 mg (85%) of geraniol-*1-d*. The enantiomeric purity was determined to be 95% by 500 MHz $^1$H NMR analysis of corresponding MTPA ester.

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(8) The preparation of $Bu_3SnD$ from $Bu_3SnCl$ has also been described: Kühlein, K.; Neumann, W. P.; Mohring, H. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 455.

(9) Alternatively, resolution of racemic BINOL can be accomplished by a number of procedures; the procedure developed recently at Merck is particularly convenient: Cai, D.; Hughes, D. L.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1995**, *36*, 7991.

(10) However, Brown and co-workers have reported procedures to increase the optical purity of pinene to essentially 100%: (a) Brown, H. C.; Yoo, N. M. *Isr. J. Chem.* **1977**, *15*, 12. (b) Brown, H. C.; Singaram, B. *J. Org. Chem.* **1984**, *49*, 945.