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Synthetic Applicability and *in Situ* Recycling of a *B*-Methoxy Oxazaborolidine Catalyst Derived from *cis*-1-Amino-indan-2-ol

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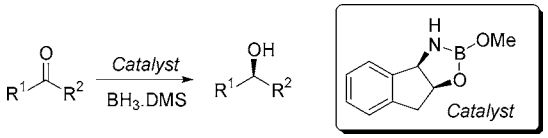
ABSTRACT



A procedure is described that greatly simplifies the use of an oxazaborolidine catalyst derived from (1*R*,2*S*) *cis*-1-amino-indan-2-ol. This *B*-OMe catalyst has been employed in the asymmetric reduction of a number of structurally diverse prochiral ketones, in particular the reduction of α-amino acetophenone and its derivatives. A method for reducing the effective catalyst loading by "*in situ* recycling" is also presented.

Asymmetric reduction of prochiral ketones using oxazaborolidines has become one of the standard tools for the synthetic chemist, allowing access to enantiomerically enriched secondary alcohols with levels of enantiomeric excess often exceeding 90%.[1] Since the introduction of this catalyst by Itsuno[2] and subsequent development by Corey,[3] this work has fueled considerable effort in areas as varied as mechanistic investigations, substrate applicability, and catalyst optimization. *cis*-1-Amino-indan-2-ol is just one of an enormous variety of catalysts that have been disclosed in the literature. This amino alcohol was first reported in 1991 for the reduction of acetophenone and oximes[4] and was subsequently used more widely in asymmetric synthesis.[5] We became interested in the use of this catalyst in asymmetric reduction because of the availability of both enantiomeric forms in large quantities. Subsequent work from this group has examined the applicability of this catalyst in the reduction of prochiral ketones[6] and *meso*-imides,[7] in addition to exploring mechanistic aspects of this chemistry.[8]

In performing asymmetric reductions with *cis*-1-amino-indan-2-ol we found it essential to prepare and use the *B*-Me complex prior to the reaction. This complex has a shelf life of only a day or so even under an atmosphere of nitrogen. Furthermore we were concerned with the cost associated with the large-scale production of this catalyst, since preparation involves a series of azeotropic distillations in the presence

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(1) (a) Wallbaum, S.; Martens, J. *Tetrahedron: Asymmetry* **1992**, *3*, 1475−1504. (b) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986−2012.

(2) (a) Hirao, A.; Itsuno, S.; Nakahama, S.; Yamazaki, N. *J. Chem. Soc., Chem. Commun.* **1981**, 315−317. (b) Hirao, A.; Itsuno, S.; Nakahama, S. Ito, K. *J. Chem. Soc., Chem. Commun.* **1983**, 469−470.

(3) Corey, E. J.; Bakshi, R. K.; Shibata, T. *J. Am. Chem. Soc.* **1987**, *109*, 5551−5553.

(4) Didier, E.; Loubinoux, B.; Ramos Tombo, G. M., Rihs, G. *Tetrahedron* **1991**, *47*, 4941−4958.

(5) (a) Hong, Y.; Gao, Y.; Nie, X.; Zepp, C. M. *Tetrahedron Lett.* **1994**, *35*, 6631−6634. (b) Simone, B. D.; Savoia, D.; Tagliavini, E.; Umani-Ronchi, A. *Tetrahedron: Asymmetry* **1995**, *6*, 301−306. (c) Hett, R.; Fang, Q. K.; Gao, Y.; Hong, Y.; Butler, H. T.; Nie, X.; Wald, S. A. *Tetrahedron Lett.* **1997**, *38*, 1125−1128. (d) Hett, R.; Senanayake, C. H.; Wald, S. A. *Tetrahedron Lett.* **1998**, *39*, 1705−1708. (e) Hett, R.; Fang, Q. K.; Gao, Y.; Wald, S. A.; Senanayake, C. H. *Org. Process Res. Dev.* **1998**, *2*, 96−99. (f) Wilkinson, H. S.; Tanoury, G. J.; Wald, S. A.; Senanayake, C. H. *Org. Process Res. Dev.* **2002**, *6*, 146−148.

(6) Jones, S.; Atherton, J. C. C. *Tetrahedron: Asymmetry* **2000**, *11*, 4543−4548.

(7) Dixon, R. A.; Jones, S. *Tetrahedron: Asymmetry* **2002**, *13*, 1115−1119.

(8) Gilmore, N. J.; Jones, S. *Tetrahedron: Asymmetry* **2003**, *14*, 2115−2118.

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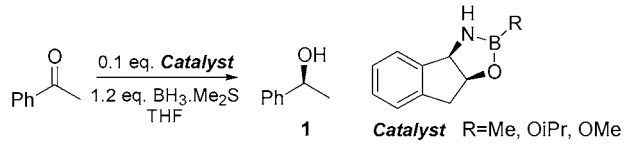
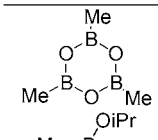
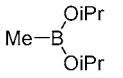
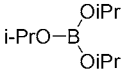
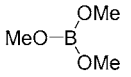
Table 1. Comparison of Use of Different Borate Esters and Methods of Use in the Asymmetric Reduction of Acetophenone



borate ester	two step process		'one–pot' process	
	yield (%)[a]	ee (%)[b]	yield (%)[a]	ee (%)[b]
	>95	85	>95	83
	>95	85	>95	83
	>95	85	>95	85
	>95	84	>95	82

[a] Refers to isolated yield. [b] Determined by chiral phase HPLC using a Chiralcel OD column (heptane/2-propanol, 90/10).

of relatively expensive trimethyl boroxine. Instead we wondered whether it would be possible to bypass preparation of the *B*-Me complex and instead generate this species *in situ*. Furthermore it should be possible to employ inexpensive borate esters, thus generating a *B*-OR complex. *In situ* preparation of 2-alkoxy oxazaborolidines is not new but has not been demonstrated with *cis*-1-amino-indan-2-ol. Masui and Shiori first reported use of these catalysts in 1997 in

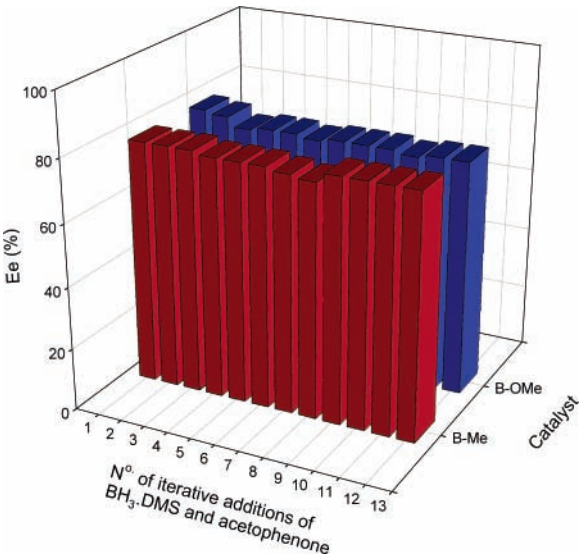
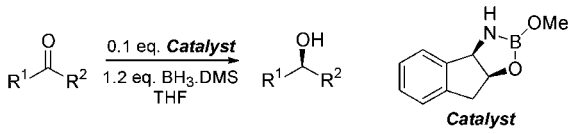
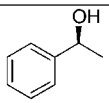
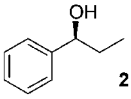
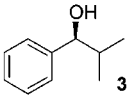
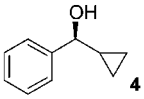
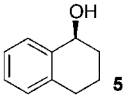
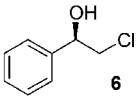
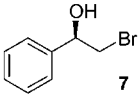
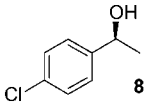
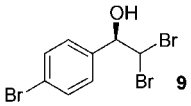
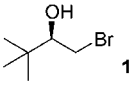


Figure 1. Comparison of catalyst endurance of *B*-Me and *B*-OMe complexes.

Table 2. Evaluation of One-Pot Asymmetric Reduction Procedure Using *B*-OMe Catalyst



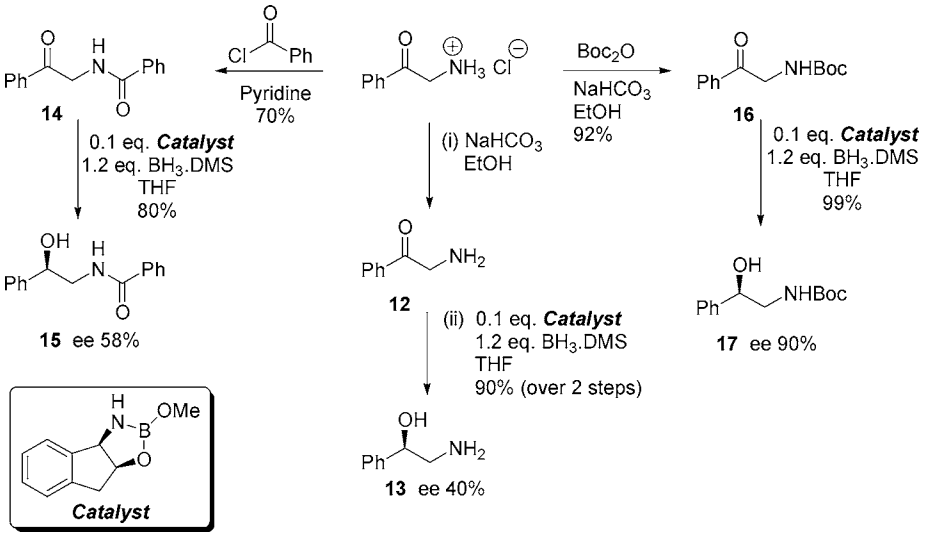
entry	product	yield (%)[a]	ee (%)[b]
1	 **1**	>99	84
2	 **2**	>99	65
3	 **3**	90	22
4	 **4**	81	30
5	 **5**	87	85
6	 **6**	>99	85
7	 **7**	>99	79
8	 **8**	70	84
9	 **9**	>99	73
10	 **10**	>99	61
11	 **11**	>99	67

[a] Refers to isolated yield. [b] Determined either by chiral HPLC (Chiralcel OD) or chiral GC (β-cyclodextrin).

the reduction of acetophenone and nitrogen-containing aromatic ketones.[9] Subsequent work has extended the range of substrates that can be reduced[10] and demonstrated its applicability on an industrial scale.[11]

(9) Masui; M.; Takayuki, S. *Synlett* **1997**, 273−274.
(10) (a) Ponzo, V. L.; Kaufman, T. S. *Molecules* **2000**, *5*, 495−496. (b) Lagasse, F.; Tsukamoto, M.; Welch, C. J.; Kagan, H. B. *J. Am. Chem. Soc.* **2003**, *125*, 7490−7491. (c) Xu, J.; Su, X.; Zhang, Q. *Tetrahedron: Asymmetry* **2003**, *14*, 1781−1786.
(11) Duquette, J.; Zhang, M.; Lei, Z.; Reeves, R. S. *Org. Process Res. Dev.* **2003**, *7*, 285−288.

Scheme 1. Asymmetric Reduction of α-Amino Acetophenone and Its Derivatives



The "one-pot" reactions were performed by stirring the amino indanol in a THF solution together with a stoichiometric quantity of borate ester. After 0.5 h, 1.0 equiv of BH_3·DMS was added, followed by 1.0 equiv of acetophenone. For comparison purposes, each reaction was also carried out by isolation of the catalyst using the conventional two-step procedure involving azeotropic distillation with toluene. Analysis of alcohol **1** was performed using a combination of HPLC and ^{1}H NMR spectroscopy (Table 1).

The results show that all of the borate esters used in the one-pot procedure perform as effectively as using the isolated catalyst. Furthermore, inexpensive trimethyl borate could be used instead of trimethyl boroxine with comparable ee.

Throughout much of the work that we have carried out with this catalyst, catalyst loadings of 10 mol % have always provided the optimum level of enantioselectivity. This is presumably because at this loading the rate of the catalyzed reaction is sufficiently faster than the background reaction with BH_3·DMS. At lower loadings the rate of the BH_3·DMS reduction becomes more significant, thus leading to a lowering of the selectivity. Rate studies using the traditional CBS catalyst have recently confirmed this.[12] To reduce the effective loading, an iterative procedure was employed whereby additional equivalents of BH_3·DMS and acetophenone were added to the reaction vessel after a 0.5 h period. The aim was to determine whether the catalyst was still active after the reaction was complete and also establish the catalyst endurance under repeated reaction conditions. The results illustrate essentially no loss of activity nor selectivity even after 12 iterative additions of acetophenone and borane, giving in this case an effective catalyst loading of 0.8 mol %.[13] Thus although there is an optimum catalyst loading that should be employed for efficient reduction with good enantioselectivity, *in situ* recycling of the catalyst is viable. (Figure 1).

Having established the optimum one-pot procedure,[14] the *B*-OMe catalyst was applied to a number of prochiral ketones (Table 2). In all cases except entry 3, the selectivities were comparable or better than those obtained previously with the *B*-Me amino-indanol catalyst prepared before use. The low selectivity obtained with isopropyl and cyclopropyl analogues (entries 3 and 4) is consistent with those previously reported and illustrates the limitations of this system.[6] α-Halogenated substrates, which are versatile intermediates for further synthetic manipulations, were reduced with good enantioselectivity (entries 7 and 8), as was the α,α-dibromo analogue (entry 9). This latter entry is important, since it is a masked α-hydroxy aldehyde. Only two aliphatic ketones were used in this study (entries 10 and 11), both giving moderate ee's. This is unusual since these are good substrates for the CBS catalyst, yet in comparison only gave ee's of 50% and 42%, respectively, with the *B*-Me catalyst from *cis*-aminoindanol.

α-Amino aromatic ketones are important substrates for asymmetric reductions because the product amino-alcohols are found in a wide variety of biologically active substances. Natural products containing this motif have been isolated from the plants *Oxytropis myriophylla*[15] and *Isodon excisus*[16]

(12) Xu, J.; Wei, T.; Zhang, Q. *J. Org. Chem.* **2003**, *68*, 10146−10151.

(13) Note that in both cases the selectivities are lower than noted in Table 1 or as reported previously. This is simply a consequence of the rate of addition of ketone and borane, which could not be controlled in this experiment because of the apparatus employed (Radleys Carousel).

(14) **Typical Procedure.** Trimethyl borate (0.02 cm^3, 0.17 mmol) was added to a solution of (1*R*,2*S*) *cis*-1-amino-indan-2-ol (0.25 mg, 0.17 mmol) in dry THF (1 cm^3), and the mixture was stirred at room temperature under a nitrogen atmosphere for 30 min. BH_3·DMS (0.11 cm^3, 1.83 mmol) was added, the reaction left to stir for 30 min, and then acetophenone (0.2 cm^3, 1.67 mmol) in dry THF (2 cm^3) was added via cannula. The reaction was stirred for 30 min, and then MeOH (5 cm^3) added. Water (5 cm^3) was added, the solvent evaporated, and the remaining aqueous layers extracted with CH_2Cl_2 (3 × 10 cm^3). The combined organic layers were washed with 1 M HCl (3 × 10 cm^3) and water (3 × 10 cm^3) and dried over $MgSO_4$. Filtration and removal of solvent gave crude material. Isolation by column chromatography on silica gel gave the pure material.

(15) Kojima, K.; Purevsuren, S.; Narantuya, S.; Tsetsegmaa, S.; Jamyansan, Y.; Kimio, I.; Yukio, O. *Sci. Pharm.* **2001**, *69*, 383−388.

(16) Lee, C.; Kim, J.; Lee, H.; Lee, S.; Kho, Y. *J. Nat. Prod.* **2001**, *64*, 659−660.

and from turmeric (*Curcuma longa*).[17] Recently, a library of related compounds have been prepared as selective apoptosis-inducing agents that may be of use as chemotherapeutic agents,[18] and Formoterol is well-established as a long-acting β_2-agonist used in the treatment of asthma and chronic bronchitis.[5e,f]

Unfortunately, direct reduction of α-amino acetophenone **12** proceeded with poor enantioselectivity with both *B*-Me and *B*-OMe catalysts but in good yield (Scheme 1). It is possible in these cases that the product amino alcohol **13** is itself acting as nondiscriminative oxazaborolidine catalyst. Protection of the nitrogen atom of the amino ketone with benzoyl chloride facilitated reduction of the amide **14** in an acceptable yield (80%), although with low enantioselectivity (ee 58%).[19] However, protection as *tert*-butyl carbamate **16** gave the desired protected amino alcohol **17** in excellent yield (99%) and enantioselectivity (ee 90%). The reasons for the differences observed with these two different protecting groups is not yet apparent, since both are in essence of the same steric bulk.

In summary, we have further demonstrated the use of *cis*-1-aminoindanol for the asymmetric reduction of a variety of prochiral ketones using a *B*-OMe catalyst generated *in situ*. This and the traditional *B*-Me catalyst have significant endurance during iterative reaction sequences, allowing for *in situ* recycling.

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Supporting Information Available: ^{1}H NMR spectra and data of all products and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

OL048916O

(17) Park, S. Y.; Kim, D. S. H. L. *J. Nat. Prod.* **2002**, *65*, 1227−1231.
(18) Nesterenko, V.; Putt, K. S.; Hergenrother, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 14672−14673.
(19) Compound **15** has recently been isolated from *Oxytropis myriophylla*. See ref 15.