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Asymmetric reduction of prochiral ketones using in situ generated oxazaborolidine derived from (1*S*,2*S*,3*R*,4*R*)-3-amino-7,7-dimethoxynorbornan-2-ol. An efficient synthesis of enantiopure (*R*)-tomoxetine

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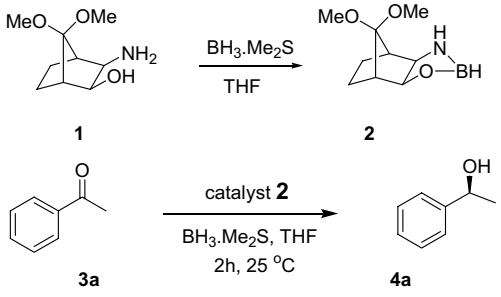
Abstract—Catalytic asymmetric reduction of prochiral ketones was examined in the presence of chiral oxazaborolidine catalyst **2** prepared in situ from (1*S*,2*S*,3*R*,4*R*)-3-amino-7,7-dimethoxynorbornan-2-ol (**1**). The optically active secondary alcohols were generally obtained in moderate to high enantiomeric excesses (ee 43–95%) and good yields (75–94%), except for ketones bearing electron-withdrawing groups. The methodology was applied to the synthesis of enantiopure (*R*)-tomoxetine, a potent anti-depressant drug.

Asymmetric reduction of prochiral ketones to obtain the corresponding optically active alcohols is among the most fundamental subjects in modern organic chemistry.[1] The discovery of oxazaborolidines as catalytic reagents for the enantioselective reduction of prochiral ketones has been an important milestone in organic chemistry. This methodology was pioneered by Itsuno et al.[2] and developed further by Corey et al.[3] who have introduced the CBS oxazaborolidines obtained from α,α-diphenylprolinol and boranes or boronic acids. Particularly, the *B*–Me oxazaborolidines prepared from methylboronic acid rank among the most general and efficient catalytic system for the enantioselective reduction of prochiral aryl and alkyl ketones.[4] Occasionally, difficulties have been reported for the preparation of the *B*–H oxazaborolidines[5] and from the several different experimental protocols reported for the preparation of the catalyst, the most convenient one appears to be stirring the chiral aminoalcohol with excess of $BH_3{\cdot}Me_2S$ at room temperature.[6] Additionally, a great number of studies have been reported over the last decade aiming to develop stable, efficient and wide scope CBS catalysts derived from aminoalcohols prepared from naturally and non-naturally occurring compounds.[7]

In a previous work, we reported the enantioselective synthesis of a new chiral norbornane-derived aminoalcohol **1** in both enantiomeric forms.[8] Herein, we report the use of chiral *exo*-aminoalcohol (1*S*,2*S*,3*R*,4*R*)-**1** for the in situ generation of the corresponding oxazaborolidine **2** (Scheme 1), evaluation of its catalytic ability in



Scheme 1.

Keywords: Oxazaborolidine; 3-Amino-7,7-dimethoxynorbornan-2-ol; Asymmetric reduction; Tomoxetine.
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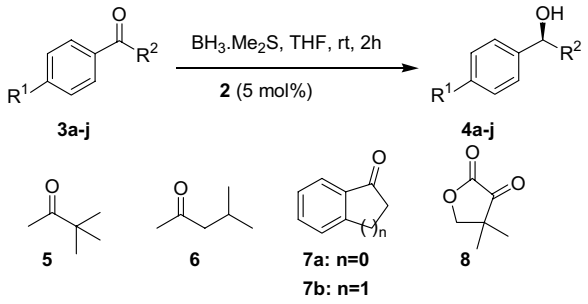
the enantioselective reduction of aromatic and aliphatic ketones and application in the asymmetric synthesis of the anti-depressant (*R*)-tomoxetine (also known as atomoxetine, brand name Strattera®), which is twice more potent than its racemate and nine times more potent than its (*S*)-enantiomer[9,10] and has been recently approved as a non-stimulant drug for the treatment of attention deficit hyperactivity disorder (ADHD) in both children and adults.[11]

In order to optimize the catalytic system, we varied the reaction temperature and the amount of catalyst in the reduction of acetophenone (**3a**). In our hands, oxazaborolidine **2** was conveniently prepared in situ after stirring *exo*-aminoalcohol **1** at 45 °C with excess of $BH_3{\cdot}Me_2S$ (Scheme 1).[12] The catalyst (10 mol%) was immediately employed at the same temperature in the reduction of ketone **3a**, which was added over 20 min to the solution of the catalyst via syringe pump. (*S*)-*sec*-Phenethyl alcohol (**4a**) was obtained in good yield but moderate enantiomeric excess (63%, Table 1, entry 1). Reduction of the amount of catalyst to 5 mol% led to a moderate increase in the enantiomeric excess (Table 1, entry 2). Based on some previously reported results, which pointed out the beneficial effect of lowering the reaction temperature in the enantiomeric excess,[13] the oxazaborolidine catalyst **2** was prepared at 25 °C and the reduction of acetophenone (**3a**) was carried out at the same temperature with 10 mol% of catalyst load to provide (*S*)-*sec*-phenethyl alcohol (**4a**) in 88% ee (Table 1, entry 3). As observed before, lowering the catalyst amount to 5 mol% increased the enantiomeric excess to 92% (Table 1, entry 4). Further decrease in the reaction temperature to 0 °C led to a significant reduction of the enantiomeric excess (61%). Therefore, the best experimental conditions found for the asymmetric reduction of acetophenone (**3a**) required the use of 5 mol% of catalyst **2**, prepared by stirring *exo*-aminoalcohol **1** with $BH_3{\cdot}Me_2S$ in THF at 25 °C, followed by dropwise addition (20 min) of the substrate via syringe pump at the same temperature.

After establishing the best reaction conditions for the reduction of acetophenone (**3a**) with our catalytic system,[14] we evaluated its scope in the reduction of aliphatic and aromatic ketones (Scheme 2). The results are summarized in Table 2. Good enantiomeric excess were observed for *para* substituted acetophenones, except for **3d** bearing the electron-withdrawing cyano substituent (Table 2, entries 1–5), which may be rationalized by the increase in the reaction rate of the uncatalyzed reduction reaction. While 2-bromoacetophenone (**3f**) provided the corresponding alcohol with good enantiomeric excess (95%) (Table 2, entry 6), the enantioselective reduction of propiophenone proceeded with lower enantioselectivity (Table 2, entry 7).

Halogen substitution on the alkyl side chain (Table 2, entry 8) or in the aromatic ring (Table 2, entries 9 and 10) of propiophenone provided moderate enantiomeric excesses. Steric bulkiness around the prochiral carbonyl group plays an important role in the enantiomeric discrimination as revealed by the low enantiomeric excess observed in the reduction of 4-methyl-2-pentanone (**6**) (Table 2, entry 12) when compared to pinacolone (**5**) (Table 2, entry 11). The catalytic asymmetric reduction of 2-indanone (**7a**) and α-tetralone (**7b**) (Table 2, entries 13 and 14) provided low enantiomeric excesses. The reduction of 3-keto-4,4-dimethylfuranone (**8**) provided (*S*)-pantolactone in low enantiomeric excess (Table 2, entry 15), which may be the result of competitive reduction via a uncatalyzed pathway, which leads to the race-



Scheme 2.

Table 1. Enantioselective reduction of acetophenone (**3a**) with catalyst **2**

Entry	Catalyst (mol%)	*T* (°C)	Yield (%)[a]	Ee (%)[b]
1	10	45	84	63
2	5	45	87	73
3	10	25	86	88
4	5	25	89	92

[a] Chemical yields (two runs) of isolated products after column chromatography.
[b] Enantiomeric excesses were determined by capillary chiral GC with Chirasil-DEX CB (25 m × 0.32 mm × 0.25 μm).

Table 2. Enantioselective reduction of prochiral aromatic and aliphatic ketones **3a–j** and **5–8** with catalyst **2**

Entry	Ketone	R^1	R^2	Ee (%)[a]	Conf.[b]	Yield[d] (%)
1	**3a**	H	CH_3	92	*S*[c]	89
2	**3b**	Br	CH_3	93	*S*[c]	94
3	**3c**	CH_3	CH_3	91	*S*	88
4	**3d**	CN	CH_3	7	*S*	93
5	**3e**	OCH_3	CH_3	78	*S*	80[e]
6	**3f**	H	CH_2Br	95	*R*	94
7	**3g**	H	CH_2CH_3	60	*S*	91
8	**3h**	H	CH_2CH_2Cl	82	*S*	89
9	**3i**	Cl	CH_2CH_3	76	*S*	85
10	**3j**	F	CH_2CH_3	76	*S*	85
11	**5**	—	—	77	*S*	75
12	**6**	—	—	49	*S*	68
13	**7a**	—	—	43	*S*	84
14	**7b**	—	—	57	*S*	87
15	**8**	—	—	4	*S*	90

[a] Enantiomeric excesses were determined by capillary chiral GC.
[b] Absolute configurations determined by comparison of optical rotation with those described in the literature.
[c] Absolute configurations determined by comparison retention time by chiral GC analyses (Chirasil-DEX CB 25 m × 0.32 mm × 0.25 μm).
[d] Chemical yields of isolated products.
[e] 8% of starting material recovered.

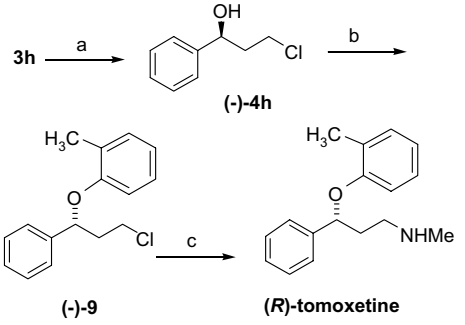
mic alcohol due to the electron-withdrawing nature of the carboalkoxy group in **8**.

Having established the scope of the catalytic system prepared from *exo*-aminoalcohol **1**, we proceeded to demonstrate its usefulness in the enantioselective synthesis of (*R*)-tomoxetine (Scheme 3).[15] As depicted in Table 2, reduction of 3-chloropropriophenone (**3h**) afforded (*S*)-3-chloro-1-phenyl-1-propanol (**4h**) in 82% ee and 89% yield. Its enantiomeric purity could be enriched to more than 99% after a single recrystallization from hexanes ($[\alpha]_D$ −23.5 (*c* 1, $CHCl_3$)), which afforded (−)-**4h** in 65% yield from 3-chloropropriophenone (**3h**). Mitsunobu inversion (Ph_3P and DEAD) with *o*-cresol provided (*R*)-1-chloro-3-phenyl-3-(2-methylphenoxy)propane (**9**), $[\alpha]_D$ −21 (*c* 3.9, $CHCl_3$), in 75% yield, which upon treatment with aqueous methylamine in ethanol furnished enantiomerically pure (*R*)-tomoxetine, $[\alpha]_D$ −42 (*c* 0.8, MeOH) (lit.[8] $[\alpha]_D$ −43 (*c* 0.8, MeOH) in 96% yield from (−)-**9** and 47% overall yield from 3-chloropropiophenone (**3h**).

The results described above for oxazaborolidine **2** derived from (1*S*,2*S*,3*R*,4*R*)-**1** compare favourably with those reported for other oxazaborolidines prepared from *exo*-1,2-aminoalcohols.[13a] Although the reason for the enantiomeric discrimination provided by oxazaborolidine **2** is not clear at this point, we speculate that it may result from a restricted conformation enforced by a hydrogen bond between one of the methoxy groups at C-7 and the hydrogen of the *B*–H bond and binding of the substrate *exo* to the methoxy group at C-7 (Fig. 1). Binding of acetophenone (**3a**) through its sterically more accessible electron lone pair (*cis* to methyl group) with a *syn*-coplanar arrangement of the carbonyl group and the *B*–H bond allows reduction to take place via a chair-like transition state through the *Re* face leading to (*S*)-**4a** preferentially (Fig. 1A).

Alternatively, binding of the substrate by the less sterically hindered lone pair but *endo* to the methoxy group at C-7, which would lead to reduction through the carbonyl *Si* face seems to be disfavoured based on electronic repulsion between the lone electron pairs of the oxygen atoms of the methoxy group and the carbonyl group (Fig. 1B).

In summary, moderate to high enantiomeric excesses and good yields were obtained in the reduction of prochiral aromatic ketones with in situ prepared *B*–H oxazaborolidine catalyst derived from norbornane-derived *exo*-aminoalcohol **1**. The catalyst is prepared in situ and the reduction reaction was carried out in THF at room temperature. (*R*)-tomoxetine was prepared in optically pure form in 47% overall yield from 3-chloropropriophenone (**3h**). This synthetic route should be amenable for the preparation of other pharmaceuticals such as fluoxetine and nisoxetine.



Scheme 3. Reagents and conditions: (a) catalyst **2** (5 mol%), THF, 25 °C, recrystallization from hexanes (two steps, 65%, 99% ee); (b) Ph_3P, DEAD, *o*-cresol, THF (75%); (c) aq $MeNH_2$ (40%), 130 °C, EtOH (96%).

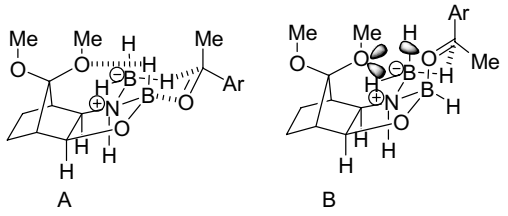


Figure 1.

Acknowledgements

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References and notes

1. (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons: New York, 1994; (b) Ojima, I. *Catalytic Asymmetric Synthesis*; VHC: Berlin, 1993.
2. Itsuno, S.; Ito, K.; Hirao, A.; Nakahama, S. *J. Chem. Soc., Chem. Commun.* **1983**, 469–470.
3. Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551–5553.
4. For reviews on oxazaborolidines, see: (a) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1987–2012; (b) Deloux, L.; Srebnik, M. *Chem. Rev.* **1993**, *93*, 763–784; (c) Martens, J.; Wallbaum, S. *Tetrahedron: Asymmetry* **1992**, *3*, 1475–1504.
5. Mathre, D. J.; Thompson, A. S.; Douglas, A. W.; Hoogsteen, K.; Carroll, J. D.; Corley, E. G.; Grabowski, E. J. J. *J. Org. Chem.* **1993**, *58*, 2880–2888.
6. Quallich, G. J.; Woodall, T. M. *Synlett* **1993**, 929–930.
7. For recent examples: (a) Jiang, B.; Feng, Y.; Hang, J. F. *Tetrahedron: Asymmetry* **2001**, *12*, 2323–2329; (b) Brunin, T.; Cabou, J.; Bastin, S.; Brocard, J.; Pelinski, L. *Tetrahedron: Asymmetry* **2002**, *13*, 1241–1243; (c) Zhou, H.; Lü, S.; Xie, R.; Chan, A. S. C.; Yang, T.-K. *Tetrahedron Lett.* **2001**, *42*, 1107–1110.
8. Lapis, A. A. M.; Kreutz, O. C.; Pohlmann, A. R.; Costa, V. E. U. *Tetrahedron: Asymmetry* **2001**, *12*, 557–561.
9. Zerbe, R. L.; Rowe, H.; Enas, G. G.; Wong, D.; Farid, N.; Lemberger, L. *J. Pharmacol. Exp. Ther.* **1985**, *232*, 139–143.

10. Kamal, A.; Khanna, G. B. R.; Ramu, R. *Tetrahedron: Asymmetry* **2002**, *13*, 2039–2051.
11. Bymaster, F. P.; Katner, J. S.; Nelson, D. L.; Hemrick-Luecke, S. K.; Threlkeld, P. G.; Heiligenstein, J. H.; Morin, S. M.; Gehlert, D. R.; Perry, K. W. *Neuropsychopharmacology* **2002**, *27*, 699–711.
12. Prasad, K. R. K.; Joshi, N. N. *Tetrahedron: Asymmetry* **1996**, *7*, 3147–3152.
13. (a) Santhi, V.; Rao, J. M. *Tetrahedron: Asymmetry* **2000**, *11*, 3553–3560; (b) Xu, J.; Wei, T.; Zhang, Q. *J. Org. Chem.* **2003**, *68*, 10146–10151.
14. General procedure for the asymmetric reduction with catalyst **2**: to a solution of aminoalcohol **1** (9.6 mg, 0.05 mmol) in THF (1.5 mL) was added $BH_3{\cdot}Me_2S$ (85 μL of 10 M soln in Me_2S, 0.85 mmol), under argon atmosphere, and the mixture was stirred at rt for 1 h. A soln of ketone (1 mmol) in THF (2 mL) was added dropwise (using a syringe pump) over a period of 20 min. When the addition was over, the reaction mixture was continued to stir at rt for 2 h. Then, MeOH was added (1 mL) and the solvent was evaporated. The pure alcohol was obtained after filtration of the crude product on silicagel (hexane/ethyl acetate as eluent).
15. Synthesis of tomoxetine: (a) Ref. 10; (b) Trost, B. M.; Fraisse, P. L.; Ball, Z. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 1059–1061; (c) Ali, I. S.; Sudalai, A. *Tetrahedron Lett.* **2002**, *43*, 5435–5436; (d) Devine, P. N.; Heid, R. M.; Tschaen, D. M. *Tetrahedron* **1997**, *53*, 6739–6746; (e) Bracher, F.; Litz, T. *Bioorg. Med. Chem.* **1996**, *4*, 877–880; (f) Gao, Y.; Sharpless, K. B. *J. Org. Chem.* **1988**, *53*, 4081–4084; (g) Srebnik, M.; Ramachandran, P. V.; Brown, H. C. *J. Org. Chem.* **1988**, *53*, 2916–2920.