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Conformational Toolbox of Oxazaborolidine Catalysts in the Enantioselective Reduction of α-Bromo-Ketone for the Synthesis of (*R,R*)-Formoterol

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Abstract: Several conformationally constrained oxazaborolidine catalysts have been evaluated in the reduction of ketone 1. Readily accessible (1R, 2S)1-amino-2 -tetralol (B-H) derived oxazaborolidine catalyst (6b) proves to be the most effective and practical catalyst in the reduction of bromo-ketone 1 (96% ee).
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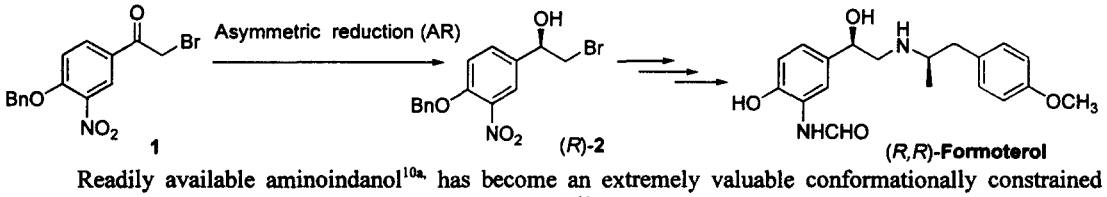
Formoterol is a long acting and extremely potent β_2-adrenergic receptor agonist, with a fast onset of action. It is used as a bronchodilator in the therapy of asthma and chronic bronchitis.[1] The (*R,R*)-enantiomer of formoterol has been shown, *in vitro*, to be 1000 times more potent than the (*S,S*)-enantiomer.[2] During our development of an asymmetric synthesis of (*R,R*)-formoterol, a reproducible and practical reducing agent, amenable for large scale preparation of chiral bromohydrin **2** from bromo-ketone **1** was required. Oxazaborolidines are an extremely important class of asymmetric reducing agents, which have been studied extensively since the extraordinary discoveries by Itsuno[3] and Corey.[4] To date, an enormous amount of chiral amino alcohols have served as backbones of oxazaborolidines. [5] While there are a great number of chiral reducing agents described in the literature, we chose to further explore conformationally constrained aminoindanol and structurally related aminoalcohols as new catalytically active oxazaborolidines. They are readily accessible from practical technologies, such as, asymmetric dihydroxylation (AD),[6] asymmetric aminohydroxylation (AA),[7] asymmetric epoxidation (AE),[8] asymmetric ring opening (ARO)[9] and simple Ritter chemistry.[10] Herein, we report on the evaluation of constrained aminoindanol and structurally related aminoalcohols as oxazaborolidines in the reduction process of bromo-ketone **1**.



Readily available aminoindanol[10a] has become an extremely valuable conformationally constrained chiral ligand in many asymmetric synthetic processes.[11] The Sepracor group has been engaged in the development of aminoindanol derived oxazaborolidine catalysts in the reduction of several different types of ketones, for example bromoketones[11a, 12] and ketoimines,[11b] in the preparation of potent anti-asthmatic drugs. Recently, we reported that catalyst **3** is an excellent asymmetric reducing agent in the reduction of bromoketone **1**. In our initial reduction process, 20 mol % *B*-methyloxazaborolidine **3a** was used as the catalyst and BH_3•THF (0.7 eq) as the reducing agent. [12] This particular catalyst has been prepared by reacting (1*R*, 2*S*)-1-amino-2-indanol with trimethylboroxine, followed by an azeotropic distillation with toluene. The high cost of these reagents and the additional handling prompted us to study the reduction with *in situ* generated B-H-oxazaborolidine **3b** as a catalyst. Selected results of this study are summarized in Table 1.

While the highest selectivities are achieved by using catalyst **3a** at -10 °C, selectivities were lower (i.e. 93% *vs* 96%) when using *in situ* prepared **3b**. As illustrated in Table 1, the boron source did not have a profound effect on the enantioselectivity of catalyst **3a** (entry 1,2). On the other hand, the B-H catalyst (**3b**) gave higher selectivities with BH_3•THF than with BH_3•Me_2S (entry 7,9). The optimum temperature for B-Me catalyst **3a** was -10 °C in the presence of either boron source. However, the optimal temperature for B-H catalyst **3b** was dependent on the boron source. The optimal temperature for BH_3•Me_2S and BH_3•THF was 25 °C and 0 °C respectively. The rate of the ketone addition to the B-H catalyst system did not have a severe effect on the outcome of the enantioselectivity (entry 12).

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Next our attention was aimed at exploring the effect of small quantities of water on the selectivity of the reaction. Consistent with other literature reports, [5c,d] very small quantities of water (5 mol % = 2.5 mg H_2O/ g **1**) lowered the selectivities (entry 14). Water sensitivity required thorough drying of the equipment, the starting materials and the solvents. In the case of THF, drying was achieved by using activated molecular sieves 5 Å, which was determined by KF titration (< 0.005 %). On the other hand, solvents used for crystallization of the starting material, such as 2-propanol and acetonitrile showed only little effect on the enantioselectivities of the reaction (entries 16 and 17).

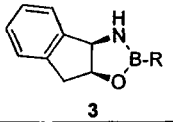
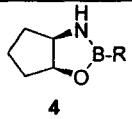
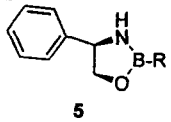
After understanding the critical parameters of the reduction process, catalyst **3b** was chosen for our process, because it was easier to handle, the preparation is less time consuming and no expensive reagents were involved. More importantly, bromohydrin **2** was isolated by crystallization and thus enriched in its enantiopurity. In addition, in the B-H catalyst system, the catalytic loading could be reduced to 1 mol% with only little effect on yield or optical purity. These conditions presented the most cost and time efficient preparation of **2** for the overall process.

Table 1: Enantioselectivities of the Asymmetric Reduction of Bromo-ketone 1

Entry	Catalyst	Mol %	Boron source	Additive (mol %)	Temperature (°C)	ee % (R)
1	**3a**	10	BH_3•THF		-10	95
2	**3a**	**10**	**BMS**		**-10**	**96**
3	**3a**	10	BMS		0	90
4	**3a**	10	BMS		25	90
5	**3b**	10	BMS		-10	32
6	**3b**	10	BMS		0	82
7	**3b**	10	BMS		25	90
8	**3b**	10	BH_3•THF		-10	87
9	**3b**	10	BH_3•THF		0	93
10	**3b**	10	BH_3•THF		25	89
11	**3b**	**5**	**BH_3•THF**		**0**	**93**
12	**3b**	5	BH_3•THF*		0	93
13	**3b**	1	BH_3•THF		0	88
14	**3b**	10	BH_3•THF	H_2O (5)	0	85
15	**3b**	10	BH_3•THF	H_2O (20)	0	50
16	**3b**	10	BH_3•THF	CH_3CN (20)	0	92
17	**3b**	10	BH_3•THF	2-propanol (20)	0	91

Reactions were run at a concentration of 0.3 M in THF. The ketone was added to the mixture of the catalyst and borane over a 2 h period. *Addition time was 30 min.

Table 2: Optimal Reduction Conditions for Catalysts 3, 4 and 5

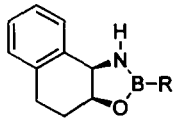
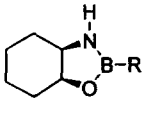
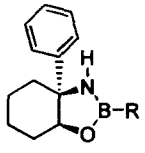
	 **3**	 **4**	 **5**
catalyst **a**, R = Me (10 mol %)	(*R*), 96% ee, 0 °C, BH_3•THF	(*R*), 20% ee, 0 °C, BH_3•THF	(*R*), 75% ee, 0 °C, BH_3•THF
catalyst **b**, R = H (10 mol %)	(*R*), 93% ee, 0 °C, BH_3•THF	(*R*), 87% ee, 0 °C, BH_3•THF	(*R*), 91% ee* 25 °C, BMS

* Using catalyst **5b**, BH_3•THF at 0 °C the ee was 65%, at 25 °C the ee was 82%.

After finding the optimal condition for catalyst **3** in the reduction process, our focus was then aimed at understanding the conformational role of the phenyl moiety and the cyclopentane ring system of catalyst **3**. To verify the conformational issues, catalyst **4** and catalyst **5** were evaluated in the reduction of ketone **1**. As shown in Table 2, the results indicate that removal of the phenyl group from the aminoindanol platform decreased enantioselectivity.[9] Detaching of the methylene link in catalyst **3** displayed some interesting results: the B-H system **5a** provided slightly lower selectivity compared to catalyst **3** however, the B-Me system **5a** displayed a dramatic decrease in enantioselectivity (Table 2). Direct comparison studies of catalyst **3**, **4** and **5** on the enantioselectivity of the reduction of ketone **2** indicated that the constrained indane platform displayed a higher degree of selectivity.

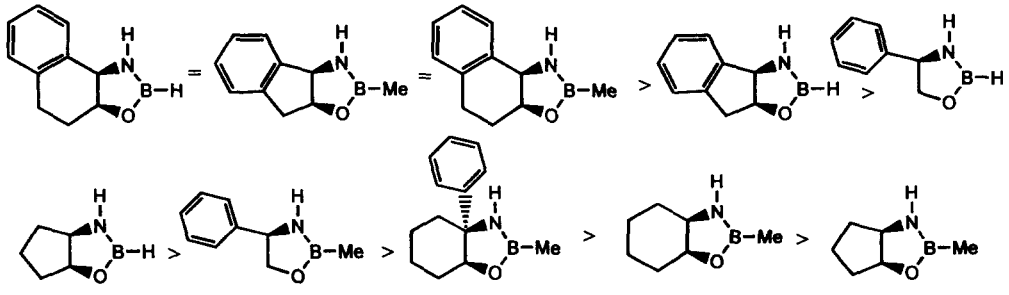
In an effort to understand the rigid indane platform, which behaves as a conformationally restricted phenyl glycinol equivalent, the homologous six-membered[10b] catalyst **6** in the AR process was examined. Surprisingly, less rigid B-H catalyst **6b** displayed a higher degree of enantioselection than the corresponding indane catalyst **3b** (Table 3), while B-Me catalyst **6a** displayed similar selectivity as did B-Me catalyst **3a**. The increased selectivity of catalyst **6b** may be due to the closer proximity of the C_{ortho}-H with N-BH_3 moiety in catalyst **6b**.[14]

Table 3: Reduction Conditions for Catalysts 6, 7 and 8

	 **6**	 **7**	 **8**
Catalyst a R = Me	(*R*), 95% ee -10 °C, BMS	(*R*), 12% ee, -10 °C, BMS*	(*R*), 12% ee, -10 °C, BH_3•THF*
Catalyst b R = H	(*R*), 96% ee, 0°C, BH_3•THF	(*R*), 62% ee, 25 °C, BH_3•THF *	(*R*), 26% ee, 25 °C, BMS*

*Unoptimized

Figure 1: Order of the Selectivity in the Reduction of Ketone 1



Since the reduction process of bromo-ketone **1** with catalyst **6b** displayed a higher selectivity compared to other structurally related systems, our attention was then focused on verifying the importance of the phenyl and cyclohexane influence on the enantioselectivity. As depicted in Table 3, quite surprising results have been observed. Removal of the phenyl moiety from the tetralin platform (catalyst **7**)[9] provided lower to moderate selectivity. On the other hand, moving the phenyl ring on the C-1 position of the cyclohexane (catalyst **8**)[10c] displayed extremely low induction.

This study has clearly shown that B-H and B-Me catalysts have different optimal conditions for each catalyst system in the reduction of prochiral ketones. The observed order of selectivity of catalysts **3-8** is shown in Figure **1**. The highest selectivities are observed with catalyst **6b** (tetralin platform) and catalyst **3a**, and the lowest with catalysts **7a** and **8a**. From a practical point of view, B-H catalyst systems are much more preferred than B-alkyl systems. Therefore, the development of highly effective B-H oxazaborolidine catalysts from readily accessible tetralin platform is our current effort.

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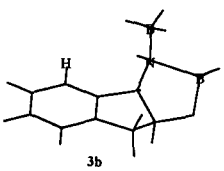
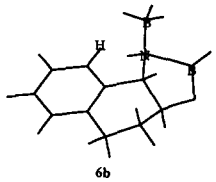
References

(1) Nelson, H. S. *N. Engl. J. Med.* **1995**, *333*, 499.
(2) Trofast, J.; Österberg, K.; Källström, B.-L.; Waldeck, B. *Chirality* **1991**, *3*, 443.
(3) (a) Hirao, A; Itsuno, S; Nakahama, S.; Yamazaki, N. *J. Chem. Soc. Chem. Comm.* **1981**, 315; (b) Itsuno, S.; Sakurai, Y.; Ito, A.; Hirao, A; Nakahama, S. Bull. Chem. Soc. Jpn. **1987**, *60*, 395.
(4) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1988**, *110*, 1968.
(5) (a) Wallbaum, S.; Martens, J. *Tetrahedron: Asymmetry* **1992**, *3*, 1475; (b) Deloux, L.; Srebnlk, M. *Chem. Rev.* **1993**, *93*, 763. (C) Jones, T. K.; Mohan, J.J.; Xavier, L.; Blacklock, T. J.; Mathre, D. J.; Sohar, P.; Tunner Jones, E.T.; Reamer, R. A.; Grabowski, E. J. *J. Org. Chem.* **1991**, 56, 763; (d) Salunkhe, A. M.; Burkhardt, E. R. *Tetrahedron Lett.* **1997**, *38*, 1523.
(6) (a) Sharpless, B. K.; King, S. B. *Tetrahedron Lett.* **1994**, *35*, 5611; (b) Sharpless, B. K.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. S.; Kwong, H. L.; Morikawa, K.; Wang, Z. M.; Xu, D.; Zhang, X. L. *J. Org. Chem.* **1992**, 57, 2768.
(7) Li, G.; Chang, H. T.; Sharpless, K. B. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 451.
(8) (a) Jacobsen, E. N.; Larrow, F. J. *J. Am. Chem. Soc.* **1994**, *116*, 12129; (b) Practical application of Jacobsen's epoxidation in the preparation of *cis*-1-amino-2-indanol see: Senanayake, C. H.; Smith, G. B.; Fredenburgh, L. E.; Liu, J.; Ryan, K. M.; Roberts, F. E.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1996**, *37*, 3271.
(9) Martinez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 7420.
(10) (a) Senanayake, C. H.; Roberts, F. E.; DiMichele, L. M.; Ryan, K. M.; Liu, J.; Fredenburgh, L. E.; Foster, B. S.; Douglas, A. W.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1995**, *36*, 3993; (b) Senanayake, C. H.; DiMichele, L. M.; Liu, J.; Fredenburgh, L. E.; Ryan, K. M.; Roberts, F. E.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1995**, *36*, 7615
(11) (a) Hong, Y.; Gao, Y.; Nie, X.; Zepp, C. M. *Tetrahedron Lett.* **1994**, *35*, 6631; (b) Hong, Y.; Gao, Y.; Nie, X.; Zepp, C. M. *Tetrahedron Lett.* **1994**, *35*, 5551; (c) Davis, I. W.; Senanayake, C. H.; Castonguay, L.; Larsen, R. D. Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1995**, *36*, 7619; (d) Davis, I. W.; Senanayake, C. H.; Castonguay, L.; Larsen, R. D. Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1996**, *37*, 1725; (e) Davis, I. W.; Gerena, L.; Castonguay, L.; Senanayake, C. H.; Larsen, R. D. Verhoeven, T. R.; Reider, P. J *J. Chem. Comm.* **1996**, 1753. (f) Ghosh, K. A.; Mathivanan, P.; Cappiello, J. *Tetrahedron Lett.* **1996**, *37*, 3815; (g) Ghosh, K. A.; Chen, Y. *Tetrahedron Lett.* **1995**, *36*, 6811; (h) Ghosh, K. A.; Mathivanan, P.; Cappiello, J. *Tetrahedron Lett.* **1997**, *38*, 2427 and references cited therein; (I) McWilliams, J. C.; Armstrong, J. D.; Zheng, N.; Bhupathy, M.; Volante, R. P.; Reider, P. J. *J. Am. Chem. Soc.* **1997**, *119*, 11970; (J) Palmer, M.; Walsgrove, T.; Wills, M. *J. Org. Chem.* **1997**, 62, 5226
(12) Hett, R.; Fang, K. Q.; Gao, Y.; Hong, Y.; Butler, H. T.; Nie, X.; Wald, A. S *Tetrahedron Lett.* **1997**, *38*, 1125.
(13) Dongwei, C.; Tschaen, D.; Shi, Y.J.; Verhoeven, T.R.; Reamer, R. A.; Douglas. A. W. *Tetrahedron Lett.* **1993**, *34*, 3243.
(14) Inspection of molecular model of oxazaborolidine **3b** and **6b** indicated that the distance of hydrogen (C_{ortho}-H) to boron (N-BH_3) of **6b** is closer than **3b**.



3b



6b

(15) **Typical experimental procedure**: A dry three-necked flask equipped with a stir bar, septum and thermometer was charged with the appropriate aminoalcohol (1 mmol) and dry THF (2 mL). A solution of BH_3•THF was added at ambient temperature over 5 minutes. After 15 min the flask was immersed in a cooling bath with the desired temperature (see tables for temperatures). The bromoketone (3.5 g, 10 mmol) in dry THF (35 mL) was added using a syringe pump over a period of 2 h. The reaction was quenched with methanol (5 mL) and concentrated *in vacuo*. The residue was dissolved in toluene (50 mL), washed with 0.2 M H_2SO_4 (2 x 20 mL) and with brine (20 mL). The organic layer was concentrated to a volume of 10 mL and cooled to 0 °C. Heptane (20 mL) was added at 0°C and the mixture aged for 2 h. The precipitate was filtered to give 3.1 g (90%) of crystalline (*R*)-2-Bromo(4-benzyloxy-3-formamidophenyl)ethanol. The ee increases by 2-3 % during the isolation process (ee before isolation are listed in Tables 1, 2 and 3). Enantiomeric excesses were determined by HPLC (Chiracel OJ column with 30 % EtOH in hexane at 1 ml/min, UV detection @ 230 nm, (*R*) = 21 min, (*S*) = 23 min).