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Asymmetric Reduction of α-Ketoimines with Oxazaborolidine Catalysts: A Novel, Practical Approach to Chiral Arylethanolamines

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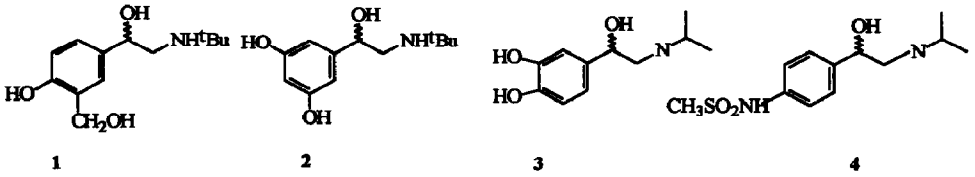
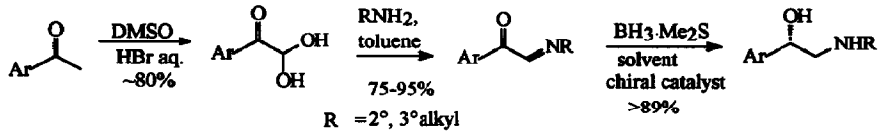
Abstract: *Asymmetric borane reduction of α-ketoimines with oxazaborolidine catalysts has been studied. The ee's of the resulting arylethanolamines are up to 93% using 20 mol% of the catalyst.*

Many β-Amino arylethanol derivatives, such as albuterol **1**, terbutaline **2**, isoproterenol **3** and sotalol **4**, are well known β-blockers or agonists and used in the treatment of asthma, glaucoma and cardiovascular disease.[1] Recent studies have demonstrated that two enantiomers of a chiral drug usually display different biological activities.[2] Preliminary investigations on the arylethanolamine-type drugs also show the same trend.[1a,3] Up to date, a few optically pure arylethanolamine drugs have been prepared.[4,5,6] The synthetic approaches to these compounds include tedious diastereomeric resolution[4] or using high-cost reagents or lengthy multistep syntheses[5] with low overall yields.[5,6] It has been reported that asymmetric hydrogenation of α-amino ketones catalyzed by BINAP-Ru complex gives β-amino alcohols with high enantioselectivity.[7] Herein we wish to report a simple and practical method for the synthesis of the optically active β-amino arylethanol compounds from readily available α-ketoimines as shown in Scheme 1.



1 **2** **3** **4**

Scheme 1

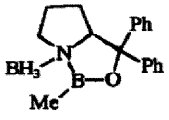


The key transformation of this approach is the asymmetric reduction of prochiral α-ketoimines with borane in the presence of oxazaborolidine catalysts. Although high enantioselectivity of simple ketones has been achieved in asymmetric borane reduction catalyzed by chiral axazaborolidines,[8] α-amino substituted ketones give disappointedly low ee's.[9] So far, no methods have been reported for the catalytic asymmetric reduction of α-ketoimines to give chiral β-amino alcohols.

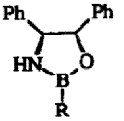
Based on a literature procedure,[10] arylglyoxals prepared from acetophenone derivatives[11] were converted to the corresponding α-ketoimines in good to excellent yields (75-95%).[12,13] Due to the demand of optically pure albuterol, α-ketoimine **5**[13] was chosen as a model compound. The asymmetric reduction was performed following a literature procedure[14] with modifications (*vide supra*) and the chemical yields are very

high in all cases studied (89-100%).[15] Enantiomeric purity was determined by HPLC analysis on a chiral column.

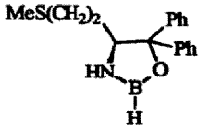
Among of the chiral catalysts (or promoters) screened (I,[14] IIa,[16] IIb,[16] and III[17]), the diphenyl proline-derived catalyst I developed by Corey[18] and the Merck group[14] gave the most promising results as shown in Table 1. Therefore, further investigations were focused on the use of catalyst I.



I



IIa R = Me
IIb R = H
(Pfizer catalysts)



III
(Martens catalyst)

Table 1. Nature of the catalysts in reduction of ketoimine (4)[a]

5 (S)-1

entry	catalyst (mol%)	ee (%)[b]	config.[c]	yield (%)[d]
1	I (20)	76	S	99
2	I (100)	97	S	97
3	IIa (20)	6	S	99
4	IIb (100)	33	S	89
5	III (20)	25	S	100

a. The reaction was performed by slow addition of ketoimine 5 to the solution of borane and the catalyst over 3 h. Then the reaction mixture was heated under reflux for 5 h to ensure a complete reduction of COOMe functionality (*vide supra*). b. ee's were determined by HPLC on a Sumichiral OA 4900 column; mobile phase: hexane/CH_2Cl_2/MeOH/CF_3CO_2H (240:140:20:1); flow rate: 1 mL/min; detector: UV 280 nm. c. Absolute configuration was assigned by comparison of the optical rotations with that of authentic compound. d. Isolated yield.

Two solvents (CH_2Cl_2 and toluene) were used in the reduction and toluene gives slightly higher ee than CH_2Cl_2 (Table 2). Since stereoseletivity greatly depends on the reaction temperature, we decided to study this effect in more details using 20 mol% catalyst I by slow addition of ketoimine 5 over 3 h. At -40 °C or below, the reduction of the keto group was slow, and the product was obtained in low ee (36%) after workup. Essentially no differences in stereoselectivity were observed at 0 °C and -20 °C (Table 2, entries 2, 3, 4, 5), whereas a significant decrease in ee was observed at 20 °C (Table 2, entry 6).

In asymmetric catalysis it is well known that the mixing protocol of reagents and substrates have profound influences on the degree of the asymmetric induction.[19] Only 27% ee was obtained when the catalyst, reagent ($BH_3 \cdot Me_2S$) and ketoimine 5 were mixed at once. However, by slow addition of the starting material over a period of 3 h to the solution of borane and the catalyst, the enantioselectivity increased dramatically (Table 3, entry 2). Under these conditions, the effective concentration of the catalyst was

increased. Furthermore, we reason that the keto group is reduced faster than the imine group and the resulting imine-alcohol intermediate does not complex with borane as strongly as the catalyst does, and thus has a lessened effect on the desired asymmetric induction.[20] When the ketoimine and borane were added simultaneously to the catalyst solution over a period of 3 h, an even higher ee (9% increase) was obtained (Table 3, entry 3). Thus, this process provides a unique example of the sequential reduction of three functional groups in ketoimine **5** in one-pot with high enantioselectivity.

Table 2. Effects of solvent and temperature[a]

entry	solvent	temperature (°C)	ee(%)
1	CH_2Cl_2	-40	36
2	"	-20	83
3	"	0	83
4	toluene	-20	87
5	"	0	86
6	"	20	76

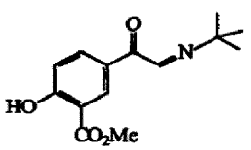
a. Slow addition of the ketoimine to the reaction mixture containing BH_3 reagent and 20 mol% of catalyst **I** over 3 h. Chemical yields >89%.

Based on these studies, further effort was directed to reduce the amounts of the catalyst. It was found that (S)-albuterol with 93-95% ee could be obtained with only 10 mol% catalyst by simultaneous addition of the ketoimine and borane to the catalyst solution in toluene at 0 °C.[21] To expand the utility of the present method, ketoimines **6** and **7** have been prepared and reduced to the corresponding β-aminoalcohols in high ee's under similar conditions[21] using 20 mol% of catalyst **I**.

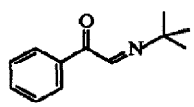
Table 3. Effects of addition manner[a]

entry	addition manner and conditions	ee(%)
1	ketoimine **5**, catalyst **I**, $BH_3{\cdot}Me_2S$ added together, 20°C 3 h, then reflux 5 h in toluene	27
2	ketoimine **5** added over 3 h at 20 °C, then reflux 5 h in toluene	76
3	ketoimine **5** and $BH_3{\cdot}Me_2S$ added over 3 h at 20 °C, then reflux 5 h in toluene	85

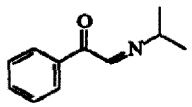
a. 20 mol% of **I** was used, chemical yields >89%.



5
93-95% ee(S)
(10 mol% cat. I)



6
85% ee (S)[22]
(20 mol% cat. I)



7
93% ee (S)[22]
(20 mol% cat. I)

In summary, a new practical method for the preparation of optically active (S)- and (R)-albuterol and other arylethanolamines has been developed. The significance of the present method is the use of readily accessible α-ketoimines as starting materials and the subsequent one-step reduction with borane to provide the

desired arylethanolamines in high chemical yield and high enantiomeric excess. The reaction is performed in catalytic fashion and the oxazaborolidine I proved to be the best catalyst so far. Free hydroxyl group does not interfere with the desired asymmetric induction as demonstrated in the case of the albuterol preparation. Further studies on new catalysts, detailed reaction pathway and double asymmetric reduction using chiral α-ketoimines are currently in progress.

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12. All α-ketoimine compounds (**5**, **6** and **7**) were characterized by ^1H NMR, ^{13}C NMR, IR and elemental analyses.
13. Attempts to isolate ketoimines from reaction of arylglyoxal with straight chain amines (RNH_2, R = 1° alkyl) was unsuccessful due to the instability of these ketoimines (polymerization and hydrolysis). Thus, we were unable to study the asymmetric reduction on these compounds. About instability of such α-ketoimines also see ref. 9.
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15. All arylethanolamine products were characterized by ^1H NMR, ^{13}C NMR, IR and elemental analyses.
16. Catalyst **IIa,b** were prepared following Pfizer's protocol, see ref. 9a and Quallich, G.; Woodall, T. M. *Synlett* **1993**, 929.
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20. When the reduction reaction was quenched after simultaneous 3 h slow addition of **5** and $BH_3{\cdot}Me_2S$ at 0 °C, IR of the product mixture showed no ketone carbonyl absorption but a strong C=N absorption at 1520 cm^{-1}.
21. **Experimental procedure for (S)-albuterol**: A 50 mL three neck flask equipped with a reflux condenser and a thermometer was charged with 4 mL of anhydrous toluene and 0.2 mmol of catalyst I (10 mol%) at room temperature under nitrogen. After cooling to 0 °C, 600 μl of $BH_3{\cdot}Me_2S$ (BMS) (10 M, 6.0 mmol, 3.0 eq) and a solution of 1 mmol of ketoimine **5** (2.0 eq) in 6 mL of toluene were added simultaneously *via* syringe over 3 h at 0 °C. After the addition, the solution was stirred for an additional hour, then was heated under reflux for 5 h. After cooling to 5 °C, the reaction mixture was quenched with 4 mL of MeOH. The resulting solution was stirred at rt for 10 min and then at reflux for 1 h. The solvent and MeOH were removed by distillation. The residual white solid was washed with 3 x 10 mL of 2:1 hexane/EtOAc at 50-60 °C. The solid was further purified by passing through a short pad of silica gel (0.5 cm) eluting with MeOH. After removal of MeOH, optically active (S)-albuterol was obtained in >89% yield and ee was analyzed by HPLC to be 93-95%.
22. Ee determination see Table 1 note b. The absolute configration was tentatively assigned by comparison with (S)-albuterol.

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