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Enantioselective borane reduction of prochiral ketones catalyzed by a chloro-containing chiral β-amino alcohol

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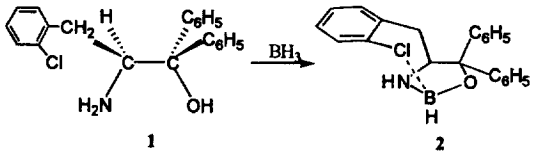
Abstract: A chloro-containing chiral β-amino alcohol (S)-2-amino-3-(2-chlorophenyl)-1,1-diphenyl-1-propanol (**1**) was prepared from the related amino acid, which was synthesized via malonic ester method. As a catalyst for the enantioselective borane reduction of prochiral ketones, **1** is better than those that have a similar structure but have no halogen atom in the molecule. © 1997 Elsevier Science Ltd

In recent years, many optically active β-amino alcohols, mostly derived from naturally occurring L-amino acids, have been incorporated into the asymmetric synthesis as chiral auxiliaries or ligands.[1] The most effective asymmetric catalysts, the oxazaborolidine–borane reagents, which were originally pioneered by Itsuno and Corey,[2] were generally prepared from chiral β-amino alcohols by the reaction with boric acid or formed *in situ* in the presence of borane. These reagents provide excellent enantioselectivity for the asymmetric reduction of most aromatic prochiral ketones.[3] However, to our knowledge, no halogen-containing β-amino alcohol reported had been applied to the asymmetric reduction of prochiral ketones.

In this communication we describe a halogen-containing chiral β-amino alcohol, (S)-2-amino-3-(2-chlorophenyl)-1,1-diphenyl-1-propanol **1** and its use as a catalyst in the enantioselective borane reduction of prochiral ketones.

The design of this amino alcohol was based on the following consideration: On treatment with borane, the amino alcohol **1** would form oxazaborolidine **2**. In the molecule of **2**, the electron-deficient boron atom may complex with the basic chloro atom attached to the benzene ring. This would keep the oxazaborolidine molecule bicyclic as shown in Scheme 1, and hence the catalyst direct the ketone molecule better in the transition state so as to achieve an efficient enantioselective hydrogen transfer to the carbonyl group.



1 **2**

Scheme 1. The formation and the possible bicyclic structure of **2**.

The synthesis of **1** is shown in Scheme 2. Diethyl acetamidomalonate was alkylated with *o*-chlorobenzyl bromide in the presence of sodium ethoxide to give N-acetyl-3-(2-chlorophenyl)-2-ethoxycarbonylalanine ethyl ester **3**, which was then hydrolyzed with sodium hydroxide and decarboxylated by reflux in dioxane, yielding (±)-N-acetyl-3-(2-chlorophenyl)alanine **4**. The enzymic resolution of **4** using subtilisin Carlsberg followed by acid hydrolysis gave (S)-(2-chlorophenyl)alanine **5**,[4] which,after converted into the methyl ester hydrochloride **6** by treatment with methanol/thionyl

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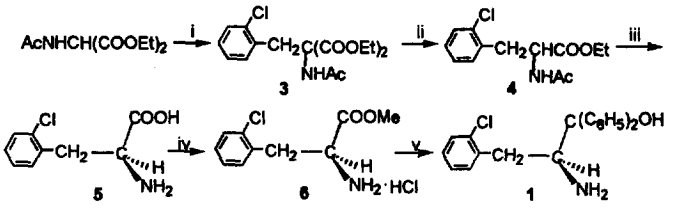
chloride, stirred with phenyl magnesium bromide (6 eq) in tetrahydrofuran at 0°C for 12 h to give the title amino alcohol **1**.[5]



i. EtONa/EtOH, *o*-chlorobenzyl bromide; ii. 1, NaOH/EtOH; 2, HCl; 3, Dioxane, reflux; iii. 1,Subtilisin carlsberg; pH7.6; 2, HCl, reflux; iv. MeOH/$SOCl_2$; v. PhMgBr/THF

Scheme 2. The synthesis of chiral β-amino alcohol **1**.

A series of prochiral ketones were reduced with excess borane and 5 mol% of **1** in THF at 30°C following the procedure described before.[6] The results are summarized in Table 1.

As shown by the data in Table 1, **1** is a good catalyst for the asymmetric synthesis of optically active secondary alcohols by borane reduction of carbonyl group (e.g. entries 2, 4, 6, and 8). As predicted, **1** is a better catalyst compared to 2-amino-1,1,3-triphenyl-1-propanol, which differs from **1** just by one chloro atom (acetophenone was reduced to chiral alcohol of 82% ee with the use of 10 mol% of this catalyst[7]).

Table 1. Catalytic enantioselective reduction of various prochiral ketones with borane and catalytic amount of **1**

Entry	mol% of 1	Ketone	Yield[a] (%)	$[\alpha]_D$	E.e.(%)[b]	Cofig.[b]
1	5	$C_6H_5COCH_3$	83.6	+35.3	83.1	R
2	10	$C_6H_5COCH_3$	85.0	+40.2	94.6	R
3	5	$C_6H_5COCH_2CH_3$	83.8	+38.4	81.6	R
4	5	$C_6H_5COC_4H_9$-*n*	92.7	+30.0	96.1	R
				(+31.0)[c]	(99.2)[c]	R
5	5	$CH_3COC_6H_4CH_3$-*p*	84.1	+40.0	72.9	R
6	5	$CH_3COC_6H_4Cl$-*p*	85.9	+49.3	98.7	R
7	5	$CH_3COC_6H_4OCH_3$-*p*	85.5	+41.5	79.8	R
8	5	$BrCH_2COC_6H_5$	91.6	+39.0	100	S
9	5	2-heptanone	81.9	-6.46	57.2	R

a.Isolated yield. b. Absolute configuration was assigned by comparison of the sign of the optical rotation with that reported and the enantiomeric excess values were calculated from specific rotations. c. Recrystallized from petroleum ether.

Acknowledgements

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4. (S)-N-Acetyl-3-(2-chlorophenyl)alanine **5** was prepared in 24.7% yield from diethyl acetamidomalonate, m.p. 168–9°C, $[\alpha]_D^{22}$ −16.4 (c=1 in EtOH, 98% ee). Elemental anal. calcd for $C_{11}H_{12}ClNO_3$: C, 54.67; H, 5.00; N, 5.80. Found: C, 54.40; H, 4.77; N, 5.76. ^{1}H NMR (δ ppm, DMSO): 1.8 (s, 3H), 2.94–3.30 (m, 2H), 4.59–4.63 (m, 1H), 7.42–7.60 (m, 4H), 8.44 (d, 1H), 12.58–12.68 (b, 1H).
5. (S)-2-Amino-3-(2-chlorophenyl)-1,1-diphenyl-1-propanol **1**, 62.4% based on **5**, m.p. 103–5°C, $[\alpha]_D^{25}$ −112 (c=3 in chloroform, 97% ee). Elemental anal. calcd. for $C_{21}H_{20}ClNO$: C,74.66; H, 5.97; N, 4.15. Found: C, 74.70; H, 5.99; N, 4.08. ^{1}H NMR (δ ppm, CDCl3): 1.20–1.23 (b, 2H), 2.54–2.76 (m, 2H), 4.26–4.29 (m, 1H), 4.50–4.60 (b, 1H), 7.01–7.18 (m, 10H), 7.46–7.50 (m, 4H).
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