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Asymmetric Borane Reduction of Prochiral Ketones Catalyzed by α,α-Disubstituted Aziridinemethanols

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Abstract A series of novel α,α-disubstituted aziridinemethanols have been developed for the enantioselective reduction of ketones in refluxing tetrahydrofuran. The optically active secondary alcohol products were obtained in good enantiomeric excess (~96.8%) and excellent yields. The results showed that the substituent groups on the hydroxyl-bearing carbon of aziridinemethanols obviously affected the enantioselectivity.

Keywords Asymmetric reduction · Prochiral ketones · Aziridinemethanol · Secondary alcohol

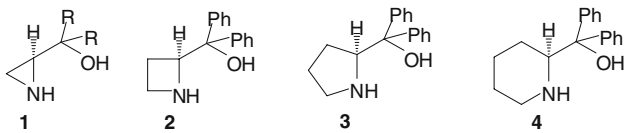
1 Introduction

Enantiomerically pure chiral secondary alcohols play a significant role in the synthesis of drugs, large, complicated target molecules and ligands for catalysis. Asymmetric reduction of prochiral ketones often provides the most efficient route to obtain optically active secondary alcohols. Extensive investigations have been carried out to develop practically useful methodologies for the asymmetric reduction [1]. One of the most popular methods involves the use of chiral 1,3,2-oxazaborolidines prepared from chiral 1,2-amino alcohols and borane for this transformation (CBS reduction), which was first reported by Itsuno [2–6] and further developed by Corey [7–12]. CBS oxazaborolidines were derived from α,α-diphenyl-2-pyrrolidinemethanol **3** (Scheme 1). Numerous examples have been reported for the application of this kind of catalyst. Modifications of these ligands have improved the enantioselectivities so that very high levels can be achieved [13–17].

The well-defined structures of the catalyst and the straightforward reaction pathway have allowed not only the rapid expansion of the scope of the CBS reduction, but also the rational modification of catalyst structure to achieve optimal enantioselectivity for a particular type of substrate. Several other chiral 1,3,2-oxazaborolidines have been reported. Aziridine [18], azetidine [19, 20], and piperidine [21] derived carbinols **1**, **2**, **4**, have been studied as basis for 1,3,2-oxazaborolidine catalysts. However, little study has been focused on aziridine-2-alcohols **1**.

Progress in the asymmetric synthesis of catalytic ligands has intensified the search for new, more specific and suitable chiral auxiliaries. Thus, in this study, our interest is to introduce the aziridine-2-alcohols **1** as precatalyst systems. Herein, we report the synthesis of chiral α,α-disubstituted aziridinemethanols and their application in the enantioselective reduction of prochiral ketones to the corresponding optically active secondary alcohols.

This paper presents the experimental results on achieving optimal enantioselectivity for a particular type of substrate and revealing the correlation between the



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

a R=p-$CH_3C_6H_4$; **b** R=Ph; **c** R=p-FC_6H_4; **d** R=p-$CF_3C_6H_4$

Scheme 1 Several cyclic chiral 1,2-amino alcohols

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aziridinemethanols with different groups and better enantioselectivity (Scheme 2).

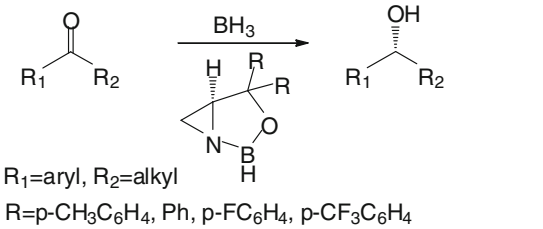
2 Experimental

2.1 General

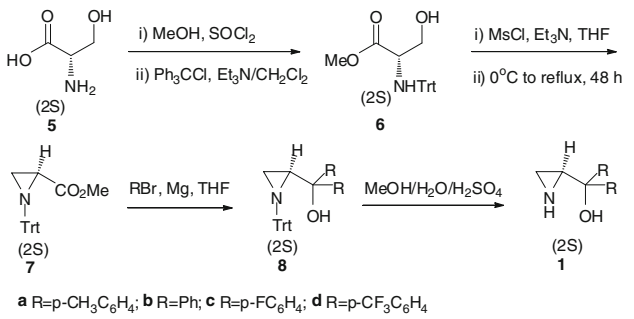
All the reactions employing dry solvents were carried out under a positive pressure of argon. THF was dried over sodium and freshly distilled before use. Ketones were further purified and were dried before use. Borane-dimethyl sulfide was obtained from J&K Chemical Ltd. The purity of all reagents was checked by NMR spectroscopy. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury 300 MHz spectrometer. IR spectra were obtained at a Perkin-Elmer 983 spectrometer. MS spectra were recorded on a Finnigan-LC Qadvantage spectrometer (ESI), and optical rotations were measured at 20 °C using the Sodium D-line by means of a Perkin-Elmer 343 plus polarimeter. Melting points were determined on a XT-4 apparatus (uncorrected). Elemental analysis was carried out on a VarioEL III (German) instrument. Silica gel was used for analytical and flash chromatography.

2.2 General Procedure for the Preparation of 1

Aziridine **7** was prepared from L-serine **5** by modification of reported procedures as outlined in Scheme 3 [22], and then allowed to react with a Grignard reagent in THF at ambient temperature. The trityl group was removed with



Scheme 2 Asymmetric reduction of prochiral ketones



Scheme 3 Synthesis of α,α-disubstituted aziridinemethanols

H_2SO_4 in mixed MeOH/H_2O solution [23, 24] to provide aziridinemethanols **1a–d** in reasonable yields. The ees of the protected aziridine alcohols **8** were determined by HPLC analysis using a chiral column (Chiralcel OD-H) and were greater than 99%.

To a stirred suspension of magnesium turnings (2.88 g, 120 mmol, 4.0 equiv) in THF (80 mL) was gradually added bromide (120 mmol, 4.0 equiv). After heating the Grignard reagent for 1 h, aziridinecarboxylate **7** (30 mmol) in THF (40 mL) was added dropwise over a period of 20 min. The reaction was monitored by TLC (hexane-EtOAc, 10:1). After 3 h the reaction was quenched with saturated aqueous NH_4Cl (60 mL). The crude reaction mixture was extracted with ethyl acetate (3 × 100 ml) and the combined organic layers were dried over Na_2SO_4 and concentrated. The crude product was dissolved in a mixture of MeOH, water and concentrated H_2SO_4 (60:8:3) (150 mL) by sonication for 5 min. After stirring for 24 h and subsequent addition of water (100 mL) as ice, the solution was made alkaline with 30% NaOH to pH 10. After the mixture was extracted with ethyl acetate (3 × 100 mL), the organic phase was washed with saturated $NaHCO_3$ (3 × 50 mL), saturated NaCl (3 × 50 mL), dried over Na_2SO_4 and concentrated in vacuo. The products were purified by flash column chromatography to yield compound **1**.

*2.2.1 (2S)-Aziridin-2-yl(bis(4-methylphenyl))methanol **1a***

Prepared as described in the general procedure to afford **1a** (5.93 g, 78%). Purified by flash column chromatography (hexane-EtOAc, 2:1). White solid. mp 145–146 °C; $[\alpha]_D^{20} = -26.7$ (*c* 1.0 $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.75 (d, $J = 3.9$, 1H, C(3)H), 1.82 (m, 1H, C(3)H), 2.34 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 2.85 (m, 1H, C(2)H), 7.13–7.36 (m, 10H, Ar); ^{13}C NMR (150 MHz $CDCl_3$): δ 21.3 (C-3), 22.2 (CH_3), 37.5 (C-2), 74.5 (CHOH), 126.5 (2X, =CH), 126.8 (2X, =CH), 129.0 (2X, =CH), 129.1 (2X, =CH), 136.9 (1X,=Cquat), 137.0 (1X, =Cquat), 142.7 (1X, =Cquat), 144.4 (1X, =Cquat); IR (KBr): 3269 3041 2948 2921 2848 1612 1541 1508 1459 1374 1233 1184 1072 992 861 cm^{-1}; MS-ESI: 255 m/z (M + 1); Anal calcd for $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.53. Found: C, 80.72; H, 7.59N, 5.55%.

*2.2.2 (2S)-Aziridin2-yl(diphenyl)methanol **1b***

Prepared as described in the general procedure to afford **1b** (5.94 g, 88%). Purified by flash column chromatography (hexane-EtOAc, 5:1). White solid. mp 155–157 °C; $[\alpha]_D^{20} = -22.6$ (*c* 1.0 $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.73(d, $J = 3.3$, 1H, C(3)H), 1.82 (d, $J = 3.6$, 1H, C(3)H), 2.87 (m, 1H, C(2)H), 7.22–7.45 (m, 10H, Ar); ^{13}C

NMR (75 MHz, $CDCl_3$): δ 22.3 (C-3), 37.3 (C-2), 74.6 (CHOH), 126.6 (2X, =CH), 126.8 (2X, =CH), 127.4 (2X, =CH), 128.3 (2X, =CH), 128.4 (2X, =CH), 145.4 (1X, =Cquat), 147.5 (1X, =Cquat); IR (KBr): 3309 3000 1599 1488 1425 1363 1312 1271 1242 1217 1199 1179 1106 1082 cm^{-1}; MS-ESI: 226 m/z (M + 1).

2.2.3 (2S)-Aziridin-2-yl(bis(4-fluorophenyl))methanol *1c*

Prepared as described in the general procedure to afford **1c** (6.42 g, 82%). Purified by flash column chromatography (hexane-EtOAc, 2:1). White solid. mp 47–48 °C; $[\alpha]_D^{20} = -14.1$ (*c* 1.0 $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.73 (d, J = 3.6, 1H, C(3)H), 1.89 (d, J = 5.4, 1H, C(3)H), 2.86 (m, 1H, C(2)H), 6.98–7.61 (m, 8H, Ar); ^{13}C NMR (150 MHz, $CDCl_3$): δ 22.2 (C-3), 37.4 (C-2), 74.0 (CHOH), 115.2 (d, J = 21.2, 2X, =CH), 115.2 (d, J = 21.3, 2X, =CH), 128.2 (d, J = 7.4, 2X, =CH), 128.6 (2X, =CH), 141.2 (1X, =Cquat), 143.1 (1X, =Cquat), 142.9 (1X, =Cquat), 145.1 (1X, =Cquat), 162.14 (d, J = 244.1, 2X, =CF); IR (KBr): 3271 3178 3075 3003 1602 1509 1407 1378 1234 1158 1073 981 867 835 cm^{-1}; MS-ESI: 276 m/z (M + 1); Anal calcd for $C_{15}H_{13}F_6NO$: C, 68.96; H, 5.02; F, 14.54; N, 5.36. Found: C, 68.99; H, 5.00; F, 14.52; N, 5.35%.

2.2.4 (2S)-Aziridin-2-yl(bis(4-trifluoromethylphenyl)) methanol *1d*

Prepared as described in the general procedure to afford **1d** (7.58 g, 70%). The product was purified by flash column chromatography (hexane-EtOAc, 2:1) and was obtained as a white solid. mp 126–128 °C; $[\alpha]_D^{20} = -30.1$ (*c* 1.0 $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.72 (d, J = 3.6, 1H, $C(3)H_2$), 1.96 (d, J = 5.1, 1H, $C(3)H_2$), 2.99 (m, 1H, C(2)H), 7.54–7.62 (m, 8H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.1 (C-3), 36.6 (C-2), 74.1 (CHOH), 124.3 (d, J = 270.3, 2X, CF_3), 125.5 (4X, =CH), 126.8 (2X, =CH), 127.1 (2X, =CH), 129.9 (d, J = 32.0, 2X, $=C(CF_3)$), 148.6 (1X, =Cquat), 150.8 (1X, =Cquat); IR (KBr): 3352 3278 3179 3009 1618 1411 1327 1253 1178 1116 1069 1016 871 822 cm^{-1}; MS-ESI: 398 m/z (M + Na); Anal calcd for $C_{17}H_{13}F_6NO$: C, 56.52; H, 3.63; F, 31.55; N, 3.88. Found: C, 56.55; H, 3.61; F, 31.52; N, 3.86%.

2.3 General Procedure for Asymmetric Reduction of Ketones

Under an argon atmosphere, $BH_3{\cdot}SMe_2$ (0.6 mmol) was added to a solution of aziridinemethanol catalyst **1** (0.2 mmol) in THF (8 mL). The solution was stirred and refluxed for 1 h. After the addition of $BH_3{\cdot}SMe_2$ (1.2 mmol), a THF (2 mL) solution of ketone (2.0 mmol) was added immediately. After the addition was completed, the reaction was quenched with methanol (1 mL) and 5% H_2SO_4 (10 mL) was added with stirring. The mixture was extracted with diethyl ether (3 × 5.0 mL). The organic layer was treated with saturated $NaHCO_3$ solution and brine, then dried over anhydrous Mg_2SO_4. After removal of solvent, the residue was purified by flash column chromatography on silica gel to give the alcohol products.

3 Results

3.1 Establishment of Catalysis Conditions

The stereoselectivity of asymmetic catalysis reduction is affected greatly by solvent, temperature and the amount of catalyst. To find the optimum reaction conditions, we examined the reduction of acetophenone with **1b** under various experimental conditions. The detailed results are outlined in Table 1. First, solvent effects were examined. At room temperature, the reductions were completed within 5 h in toluene and 3 h in THF with low ee values (entries 1 and 2). Level of enantiomeric excess is sensitive to the reaction temperature, when the reaction temperature was raised from room temperature to reflux in THF, the ee value increased from 41.9% to 91.2% and the reduction was completed in 5 min (entries 1 and 4). Possibly, the reaction was hard to process at room temperature in THF, which led to relatively low convention rate and stereoselectivity. Apart from the reaction temperature and solvent, the ratio of the catalyst has an impact on the reduction. When the amount of catalyst was increased from 5 to 10 mol%, the enantiomeric excess increased from 65.6% to 91.2% (entries 5 and 6). However, by further increasing the amount of catalyst to 15 mol%, the ee had not increased simultaneously (entry 6). As mentioned above, it can be deduced that THF at reflux provides the best result [15, 25].

Table 1 Effect of temperature, solvent, the amount of catalyst[a]

Entry	Solvent	Catalyst (mol%)	Temperature	Yield[b]	ee (%)[c]
1	THF	10	rt	65	41.9
2	Toluene	10	rt	71	30.2
3	Toluene	10	Reflux	81	23.3
4	THF	10	Reflux	97	91.2
5	THF	5	Reflux	90	65.6
6	THF	15	Reflux	96	90.4

[a] Experiments were performed on a 2.0 mmol scale. Molar ratio, $PhCOCH_3/BH_3{\cdot}SMe_2$ 1.0:0.9

[b] Yields of isolated products after purification by column chromatography

[c] Determined by using chiral HPLC before isolation-chromatography

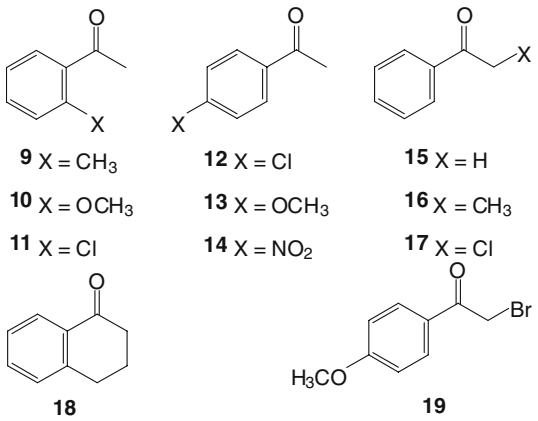


Chart 1

3.2 Asymmetric Reduction of Ketones Using Aziridinemethanols

The application of various α,α-disubstituted aziridinemethanols to the reduction of ketones (Chart 1) was investigated using a catalytic amount (10 mol%) of aziridinemethanols in refluxing THF, which has been established for the best reaction conditions. The results are summarized in Table 2. All reductions were completed in 5 min. In most cases, the products were obtained in excellent yields (>95%) and in high ee. Excellent enantiomeric excesses were obtained for ketones **10**, **14**, **15**, **17**, and **18**. Enantiomeric excesses were determined by Chiralcel OD-H column according to the methods described in the Supplemental File [26–29].

4 Discussion

Comparison of the results obtained from *p*-methoxyacetophenone and *p*-nitroacetophenone indicated that electron-withdrawing groups were relatively beneficial for enantioselectivity. We also found the reduction of α-haloacetophenone obtained much higher enantiomeric excesses under the same conditions. α-Tetralone was proved to be an excellent substrate and gave the product with excellent ee, which may be due to the rigidity of the

Table 2 Asymmetric reduction of ketones[a] with aziridinemethanols **1a–d**

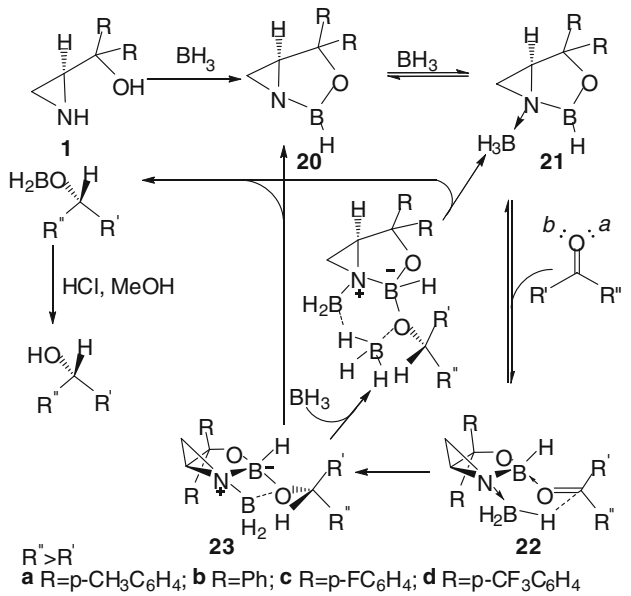
Entry	Ketone	Precatalyst	Yield[b]	Config.[c] of product (% ee[d])	Entry	Ketone	Precatalyst	Yield[b]	Config.[c] of product (% ee[d])
1	9	1a	96	R (43.2)	23	14	1c	97	R (86.8)
2	9	1b	94	R (56.6)	24	14	1d	98	R (90.4)
3	9	1c	97	R (59.4)	25	15	1a	94	R (73.6)
4	9	1d	95	R (56.4)	26	15	1b	95	R (91.2)
5	10	1a	95	R (41.8)	27	15	1c	97	R (94.6)
6	10	1b	93	R (69.8)	28	15	1d	96	R (96.8)
7	10	1c	94	R (85.2)	29	16	1a	95	R (27.6)
8	10	1d	92	R (88.0)	30	16	1b	95	R (51.6)
9	11	1a	94	R (60.6)	31	16	1c	98	R (62.2)
10	11	1b	95	R (63.0)	32	16	1d	99	R (65.6)
11	11	1c	95	R (65.0)	33	17	1a	97	S (78.6)
12	11	1d	96	R (69.2)	34	17	1b	96	S (91.8)
13	12	1a	94	R (61.6)	35	17	1c	98	S (93.0)
14	12	1b	95	R (65.0)	36	17	1d	98	S (94.6)
15	12	1c	93	R (72.4)	37	18	1a	96	R (66.2)
16	12	1d	95	R (81.0)	38	18	1b	96	R (86.6)
17	13	1a	94	R (33.2)	39	18	1c	97	R (92.0)
18	13	1b	94	R (50.2)	40	18	1d	98	R (95.2)
19	13	1c	93	R (65.4)	41	19	1a	94	S (80.8)
20	13	1d	95	R (62.4)	42	19	1b	95	S (81.0)
21	14	1a	94	R (73.4)	43	19	1c	95	S (85.8)
22	14	1b	95	R (86.2)	44	19	1d	97	S (87.8)

[a] Experiments were performed on a 2.0 mmol scale

[b] Yields of isolated products after purification by column chromatography

[c] Determined by using chiral HPLC before isolation-chromatography

[d] The absolute configurations were determined by optical rotation



Scheme 4 Proposed mechanism of the oxazaborolidine-catalyzed ketone reduction

structurally constrained cyclic ketone. Besides, it also showed that the enantioselectivity of the reduction may be dependent on steric effect.

Moreover, comparison of the results of catalyst **1a–d** indicates that electron-withdrawing groups are much more beneficial for enantioselectivity than electron-donating groups to all ketones in our study. Aziridinemethanols substituted with 4-fluorophenyl group and 4-trifluoromethylphenyl group obtained exceptional enantioselectivity for the reduction of acetophenone (up to 96.8% ee) as well as numerous other substrates. The results demonstrate that the electronic effects have a significant impact on the enantioselectivity. Based on our experiments and earlier literatures [6, 15], the proposed mechanism of reduction can be concluded (Scheme 4). It can be deduced that for amino alcohol **1** electron-withdrawing groups disubstituted on hydroxy-bearing carbon contribute to produce the chiral 1,3,2-oxazaborolidine. As Table 3 depicted, electron-withdrawing groups can increase the positive charge of the boron atom, thus can also increase the Lewis acidity of the endocyclic boron atom. The strongly Lewis acidic complex then readily binds to the ketone substrate, at the more sterically accessible electron lone pair (*b*) and *cis* to the vicinal BH_3 group, face-selective hydride transfer via a six-membered transition state takes place to form the reduction product **23**. Furthermore, adequate electron-withdrawing effects do not prevent regeneration of the oxazaborolidine catalyst. For the electron-donating groups, however, just the reverse is true.

Table 3 The calculation of the atomic charge of the boron atom of Compounds 20[a]

Compound	The atomic charge of the boron atom (e)
20a	0.122760
20b	0.123611
20c	0.126442
20d	0.132299

[a] Data were calculated via semi-empirical methods by Gaussian (R) program

5 Conclusion

In conclusion, α,α-disubstituted aziridinemethanols **1** are readily available in all enantiomeric forms starting from L-serine. Aromatic ketones can be reduced quantitatively and with a high degree of enantioselectivity using α,α-disubstituted aziridinemethanols and borane under a facile reaction condition. The reaction products can be easily separated from the catalyst by simple liquid extraction. The substituent groups on the hydroxyl-bearing carbon of aziridinemethanols obviously affect the enantioselectivity. Aziridinemethanols α,α-disubstituted with electron-withdrawing groups display much higher enantioselectivity than those with electron-releasing groups, which conduce to modifying and diversifying the chiral ligands of catalysts to achieve increased enantioselectivity.

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