An Easy and Convenient Synthesis of Optically Active β-Amino Alcohols and 1,2-Diamines. Applications in Enantioselective Deprotonation of Cyclohexene Oxide

Sung Hye Shin, Sang Kyu Kang, and Byung Tae Cho*

Department of Chemistry, Hallym University, Chunchon, Kangwon-Do 200-702, Korea
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Optically active β-dialkylamino alcohols[1] and 1,2-diamines[2] are not only a common structural component in a vast group of naturally occurring and synthetic molecules, but also can be widely used as versatile chiral building blocks and chiral catalysts or ligands in a variety of asymmetric synthesis, such as enantioselective dialkylzinc addition to aldehydes,[3] enantioselective conjugated addition[4] and enantioselective deprotonation of *meso* ketones and epoxides.[5] Accordingly, many synthetic methods including aminolysis of chiral epoxides,[3a,4b,5] optical resolution of their racemic mixtures[6] and reduction of non-racemic *O*-acetyl mandelamides[7], reduction of chiral α-amino carboxamides,[4a,8] asymmetric reduction of α-amino ketones[9] and aminolysis of aziridinium salts[1,5,7,8] for those compounds have been reported. However, aminolysis of chiral epoxides is commonly accompanied by the formation of undesired regioisomers. The resolution method of racemic mixture suffers from providing intrinsic limitation where the maximum yield of one enantiomer from the starting material is only 50%.[6] In the case of reduction of α-amino carboxamides, unnatural α-amino acids are not economical viable to use them as starting materials since they are expensive, but also racemization can occur in the reaction of some *N*-protected amino acids with dialkylamines to give α-amino carboxamides. For example, O'Brien *et al.* reported significant levels of racemization when *N*-protected phenylglycine was reacted with pyrrolidine in the presence of coupling reagent to form the corresponding α-amino carboxamide.[8a,10] Recently, we reported the synthesis of nearly enantiopure β-adrenergic agonists[11] and β-hydroxy nitriles[12] from optically active 1,2-diol monotosylates **1** obtained from CBS-oxazaborolidine-catalyzed borane reduction of α-sulfonyloxyketones.[13] We wish to report here an easy and simple method for the synthesis of nearly enantiopure β-dialkylamino alcohols **2** and 1,2-diamines **4-10** starting from **1** and their applications in enantioselective deprotonation of cyclohexene oxide using chiral lithium amides.

The monotosylates **1**[13] were directly reacted with 3 equiv. of *N,N'*-dialkylamines under solvent-free conditions at 40-50 °C for 2-96 h to give **2** in 80-93% yield (Scheme 1). The optical purities and absolute configurations of **2** were determined by HPLC analysis using chiral columns and/or by comparing optical rotation values of the known compounds. As shown in Table 1, all the products **2** obtained have very high optical purities approaching 100% ee. To obtain chiral diamines **4-10**, the reaction was carried out by treatment of 2.0 equiv. of methanesulfonyl chloride with each of the selected amino alcohols, such as **2c**, **2h**, **2j**, and

R =	R_1R_2N =
a: Ph	Me_2N
b: Ph	MeBnN
c: Ph	n-Bu_2N
d: Ph	pyrrolidino
e: Ph	piperidino
f: Ph	morpholino
g: p-ClC_6H_4	piperidino
h: p-PhC_6H_4	piperidino
i: 2-Np	pyrrolidino
j: 2-Np	piperidino
k: t-Bu	piperidino
l: c-C_6H_{11}	piperidino

R =	R_3	R_1R_2N =
4: Ph	Me	piperidino
5: Ph	c-C_6H_{11}	piperidino
6: Ph	Ph	piperidino
7: p-PhC_6H_4	Me	piperidino
8: 2-Np	Me	piperidino
9: c-C_6H_{11}	Me	piperidino

Np = naphthyl

Scheme 1. Reagents and conditions: i. R_1R_2NH (3.0 eq), 40-50 °C, 2-96 h (80-93%). ii. MsCl (1.0 eq), Et_3N (1.5 eq), 0 °C, 0.5 h. iii. Et_3N (1.0 eq), R_3NH_2 (3.0 eq), water (10 eq), rt, 24-72 h (76-93%).

Table 1. Synthesis of Nearly Enantiopure β-dialkylamino alcohols **2** from 1,2-Diol Monotosylates **1**[a]

No	Cpd	Time (h)	Yield (%)[b]	Mp (°C)	Optical rotation (*c*, solvent)		% ee[c]	Config.[c]
					This study	Values reported		
1	**2a**	2	85	oil	$[\alpha]_D^{rt}$ 49.6 (1.10, MeOH)	$[\alpha]_D^{20}$ -47.76 (1.61, MeOH), 95%ee, *R*[6b]		
2	**2b**	24	91	oil	$[\alpha]_D^{rt}$ 56.4 (1.30, EtOH)	$[\alpha]_D^{20}$ -49.2 (2.3, EtOH), 86% ee, *R*[6b]	99	S
3	**2c**	96	93	oil	$[\alpha]_D^{20}$ 76.3 (1.44, $CHCl_3$)	d	99[e]	*S*[f]
4	**2d**	3	82	69-70 (lit.[6b] 69.5-70.5)	$[\alpha]_D^{20}$ 44.6 (0.57, EtOH)	$[\alpha]_D^{20}$ -40.3 (1.88, EtOH), 95% ee, R[6b]	99	S
5	**2e**	3	90	77-79 (lit.[6b] 69-71)	$[\alpha]_D^{20}$ 54.7 (0.53, EtOH)	$[\alpha]_D^{20}$ -51.2 (1.12, EtOH), 97%ee, *R*[6b]	99	S
6	**2f**	12	83	95-96 (lit.[7] 96-98)	$[\alpha]_D^{20}$ 55.4 (1.07, EtOH)	$[\alpha]_D^{23}$ -43.6 (1.2, EtOH), 99%ee, *R*[4c]	99[g]	S
7	**2g**	3	80	97-99	$[\alpha]_D^{20}$ 51.9 (1.04, $CHCl_3$)	d	99[e]	*S*[f]
8	**2h**	3	92	116-118 (lit.[4b] 107-108)	$[\alpha]_D^{20}$ 58.4 (0.62, $CHCl_3$)	$[\alpha]_D$ -57.8 (0.53, $CHCl_3$), 99%ee, *R*[4b]	99	S
9	**2i**	3	80	117-119	$[\alpha]_D^{20}$ 47.8(1.10, $CHCl_3$)	d	99[e]	*S*[f]
10	**2j**	3	89	111-113 (lit.[4b] 110-112)	$[\alpha]_D^{20}$ 66.2 (1.00, $CHCl_3$)	$[\alpha]_D$ -66.4 (1.00, $CHCl_3$), 99%ee, *R*[4b]	99	S
11	**2k**	3	91	oil	$[\alpha]_D^{20}$ 64.9 (1.28, $CHCl_3$)	$[\alpha]_D^{rt}$ -72.4 (18, $CHCl_3$), 99%ee, *R*[3a]	98	S
12	**2l**	2	80	oil	$[\alpha]_D^{20}$ 41.9 (1.17, $CHCl_3$)	d	99[e]	*S*[f]

[a]**1** was treated with 3.0 equiv. of *N,N'*-dialkylamines at 40-50 °C under solvent-free conditions. [b]Isolated yield. [c]Compared by optical rotation values and absolute configurations reported, unless otherwise indicated. [d]Not reported. [e]Compared by % ee of the corresponding **1** and/or optical rotation values and absolute configuration of diamines reported. [f]Not reproted, but probably *S* by analogy based on the (+)-sign of optical rotation values. [g]Determined by HPLC analysis using Chiralcel OD-H (eluent : hexane/*i*-PrOH = 9/1).

Table 2. Synthesis of Nearly Enantiopure 1,2-diamines **4-9** from **2**[a]

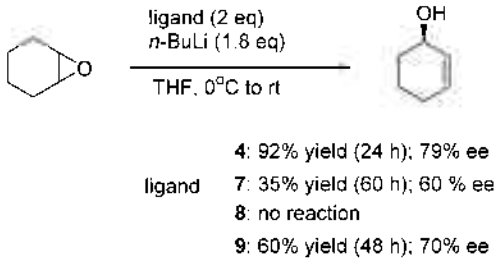
No	Cpd	Time (h)	Yield (%)[b]	Mp (°C)	Optical rotation (*c*, solvent)		% ee[c]	Config.[c]
					This study	Values reported		
1	**4**	24	88	oil	$[\alpha]_D^{20}$ 111.5 (1.15, $CHCl_3$)	$[\alpha]_D^{25}$ 109.1 (1.8, $CHCl_3$), 98% ee, *S*[4a]	99	S
2	**5**	72	83	oil (lit.[7] 58-60)	$[\alpha]_D^{20}$ 94.1 (1.00, $CHCl_3$)	$[\alpha]_D^{25}$ 93.0 (7.0, $CHCl_3$), *S*[7]	99	S
3	**6**	72	81	oil (lit.[7] 63-64)	$[\alpha]_D^{20}$ 7.6 (1.44, $CHCl_3$)	$[\alpha]_D^{25}$ 7.2 (6.5, $CHCl_3$), *S*[7]	99	S
4	7	48	93	88-89 (lit.[4b] 92-93)	$[\alpha]_D^{rt}$ 88.6 (1.01, $CHCl_3$)	$[\alpha]_D^{20}$ -88.3 (1.20, $CHCl_3$), *R*[4b]	99	S
5	**8**	48	84	54-56 (lit.[4b] 119-120)	$[\alpha]_D^{rt}$ 93.7 (0.51, $CHCl_3$)	$[\alpha]_D^{20}$ -64.4 (1.31, $CHCl_3$), *R*[4b]	99	S
6	**9**	48	88	oil	$[\alpha]_D^{20}$ 15.9 (1.22, $CHCl_3$)	d	99[e]	S

[a]The reaction was carried out with treatment of 2.0 equiv. of methanesulfonyl chloride with amino alcohols **2** in the presence of 3.0 equiv. of Et_3N in ether, followed by direct treatment of 3.0 equiv of $MeNH_2$, *c*-C_6H_{11} or $PhNH_2$ with the resulting aziridium salts **3** in the presence of water at room temperature. [b-e]See the corresponding footnotes in Table 1.

2l, in the presence of 3.0 equiv. of Et_3N in ether, followed by aminolysis of the resulting aziridium salts **3** with 3.0 equiv of $MeNH_2$, *c*-C_6H_{11} or $PhNH_2$ in the presence of water at room temperature.[4b,10] The reaction produced nearly enantiopure diamines in 76-93% yields with no racemisation (Scheme 1 and Table 2).

In order to study the effect of substituents attached on the asymmetric center of chiral amines used as precursors of chiral lithium amides in the enantioselective deprotonation of *meso*-epoxide, we selected structurally different chiral diamines **4**, **7**, **8** and **9** bearing phenyl, *p*-phenylphenyl, 2-naphtyl and cyclohexyl groups at the steregenic center, respectively. We examined the enantioselective deprotonation of cyclohexene oxide using chiral lithium amides obtained from treatment of *n*-butyl lithium with these diamines by the known procedure.[8a] Of the chiral bases examined, **4-Li** afforded the best result to give (*R*)-2-cyclohexen-1-ol with 79% ee. **7-Li** and **9-Li** provided 60% ee and 70% ee, respectively. However the deprotonation using **8-Li** which is a bulkier lithium amide did not occur. The results are summarized in Scheme 2.

In summary, we have established an easy and convenient method for the synthesis of the optically active β-dialkylamino alcohols **2** and 1,2-diamines **4-9** with near 100% ee that avoids the formation of undesired regioisomers. Enantioselective deprotonation of cyclohexene oxide using chiral lithium amides prepared from **4** and **9** provided (R)-2-cyclohexen-1-ol with 79% ee and 70% ee, respectively.



Scheme 2

Experimental Section

General. The reactions were monitored by TLC using silica gel plates and the products were purified by flash column chromatography on silica gel (Merck; 230-400 mesh). NMR spectra were recorded at 300 MHz for ^1H and

75 MHz for ^{13}C using Me_4Si as the internal standard in $CDCl_3$ unless otherwise noted. Optical rotations were measured with a high resolution digital polarimeter. Melting points were uncorrected. The starting materials **1** were prepared by (*S*)-CBS-oxazaborolidine-catalyzed borane reduction of a-tosyloxy ketones.[13]

Preparation of Chiral β-Dialkylamino alcohols 2 from 1.

General procedure: The monotosylates **1** (2 mmol) were treated with dialkylamines (6 mmol) at 40-50 °C for appropriate times under solvent-free conditions. When **1** was disappeared from the reaction mixture by TLC examination. excess of amines were pumped off under reduced pressure. The residue was triturated with 1 N NaOH (20 mL) and extracted with ether. The extract was dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product **2** obtained was further purified by flash chromatography on silica-gel using ethyl acetate/methanol (1/2) or EtOAc/hexane (1/2) as an eluent. The solid products were recrystallized from hexane. All the products **2** except **2c**, **2g**, **2i** and **2l** are the known compounds which have been reported in literatures.[3a,4b,6c,7] All spectroscopic data (IR, ^1H and ^{13}C NMR) of these compounds are good agreement with those data reported.

(*S*)-2-*N*,*N*-Dibutylamino-1-phenylethanol 2c: R_f 0.26 (EtOAc/hexane 1 : 2); oil; $[\alpha]_D^{19}$ 76.24 (*c* 1.44, $CHCl_3$); IR (KBr, neat, cm^{-1}) 3438, 3406, 2956, 2931, 2871, 2861, 2823, 1467, 1061, 699; ^1H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, 6H, J = 7.43 Hz), 1.26-1.52 (m, 8H), 2.39-2.67 (m, 6H), 4.33 (br s, 1H), 4.62 (dd, 1H, J = 3.58 & 10.45 Hz), 7.24-7.38 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.53, 20.98, 29.69, 53.97, 63.38, 69.50, 126.02, 127.53, 128.49, 142.73; Calcd. for $C_{16}H_{27}NO$: C, 77.06; H, 10.91; N, 5.62. Found: C, 77.00; H, 10.94; N, 5.45.

(*S*)-2-(1-Piperidino)-1-(4-chlorophenyl)ethanol 2g: R_f 0.21 (EtOAc/MeOH 1 : 2); mp 97-99 °C (hexane); $[\alpha]_D^{20}$ 51.9 (*c* 1.04, $CHCl_3$); IR (KBr, cm^{-1}) 3110, 3095, 2959, 2932, 2877, 2808, 1486, 1150, 1090, 879, 823; ^1H NMR (300 MHz, $CDCl_3$) δ 1.81-1.83 (m, 6H), 2.42-2.54 (m, 4H), 2.71-2.77 (m, 2H), 4.15 (br s, 1H), 4.67 (dd, 1H, J = 3.30 & 10.59 Hz), 7.30-7.35 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.91, 54.03, 64.17, 70.25, 127.47, 128.67, 133.21, 141.24; Calcd. for $C_{13}H_{16}ClNO$: C, 65.13; H, 7.57; N, 5.84. Found: C, 65.16; H, 7.43; N, 5.88.

(*S*)-2-(1-Pyrrolidino)-1-(2-naphthyl)ethanol 2i: R_f 0.16 (EtOAc/MeOH 1 : 2); mp 117-119 °C (hexane); $[\alpha]_D^{20}$ 47.8 (*c* 1.10, $CHCl_3$); IR (KBr, cm^{-1}) 3442, 3406, 3102, 1096, 3056, 2968, 2938, 2816, 2701, 1125, 823, 891; ^1H NMR (300 MHz, $CDCl_3$) δ 1.81-1.85 (m, 4H), 2.54-2.59 (m, 4H), 2.76-2.90 (m, 2H), 4.21 (br s, 1H), 4.88 (dd, 1H, J = 3.16 & 10.59 Hz), 7.45-7.52 (m, 3H), 7.82-7.87 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.36, 54.66, 64.69, 71.51, 124.77, 125.24, 125.41, 126.76, 128.70, 134.10, 140.57; Calcd. for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.57; H, 7.489; N, 5.82.

(*S*)-2-(1-Piperidino)-1-cyclohexylethanol 2l: R_f 0.19 (EtOAc/MeOH 1 : 1); oil; $[\alpha]_D^{20}$ 41.9 (*c* 1.10, $CHCl_3$); IR (KBr, neat, cm^{-1}) 3426, 2927, 2852, 2793, 1448; ^1H NMR (300 MHz, $CDCl_3$) δ 0.97-1.31 (m, 6H), 1.38-1.76 (m, 11H), 1.91-2.60 (m, 6H), 3.78 (m, 1H), 4.32 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.66, 26.45, 26.52, 26.96, 28.81, 29.44, 42.83, 62.67, 70.04; Calcd. for $C_{13}H_{25}NO$: C, 73.88; H, 11.92; N, 6.63. Found: C, 73.85; H, 11.86; N, 6.57.

Preparation of Chiral Diamines 4-9.

General procedure[4b,10]**:** To a stirred solution of amino alcohol 2 (2 mmol) in dry ether (10 mL) were added Et_3N (6 mmol). It was cooled to 0 °C and mathanesulfonyl chloride (4 mmol) was added drowise. The resulting reaction mixture became sticky. After 0.5 h, Et_3N (4 mmol) and $MeNH_2$ (2.5 mL, 40% aqueous solution; 16 mmol) was added and the reaction mixture was stirred at 0 °C to room temperature for 20 h [When *c*-$C_5H_{11}NH_2$ and $PhNH_2$ instead of $MeNH_2$ were used, the same reaction was carried out with the amine (6 mmol) in the presence of water (10 mmol)]. The organic and aqueous layers were separated and the aqueous layer was extracted with ether (15 mL × 3). The combined ether extracts were washed with saturated $NaHCO_3$ and brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude product diamines were further purified by flash chromatography on silica-gel using ethyl acetate/methanol (1/4) or hexane//-PrOH (1/1) as an eluent. All the products except **7** and **9** are the known compounds have been reported in literatures.[4a,7,8a] All spectroscopic data (IR, ^1H and ^{13}C NMR) of these compounds are good agreement with those data reported.

(*S*)-*N*-Methyl-1-cyclohexyl-2-(1-piperidino)ethanamine 9: R_f 0.11 (EtOAc/MeOH 1 : 4); oil; $[\alpha]_D^{20}$ -15.9 (*c* 1.22, $CHCl_3$); IR (KBr, neat, cm^{-1}) 3318, 2924, 2850, 2789, 1447; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87-1.31 (m, 10H), 1.43-1.58 (m, 6H), 1.59-1.71 (m, 4H), 2.43 s, 3H), 2.39-2.53 (m, 3H), 2.68 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.38, 26.83, 27.74, 30.61, 32.96, 26.78, 37.69, 50.12, 50.63, 69.51; Calcd. for $C_{14}H_{28}N_2$: C, 74.94; H, 12.58; N, 12.48. Found: C, 75.16; H, 12.28; N, 12.33.

Enantioselective Deprotonation of Cyclohexene Oxide.[8] The reaction using **9-Li** as a chiral base is representative. To a solution of **9** (2 mmol) in THF (6 mL) was added a solution of *n*-BuLi in hexane (1.6 M, 2.2 mL; 3.5 mmol) dropwise at 0 °C. After stirring for 0.5 min, a solution of cyclohexane oxide (2 mmol) in THF was added slowly and the mixture was stirred at 0 °C to room temperature for 48 h. Most of THF was removed in vacuo at 0 °C, and the reaction mixture was extracted with ether (15 mL × 3). The combined extracts were washed with water and brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was chromatographed to provide 2-cyclohexen-1-ol in 60% yield. Its optical purity determined by a capillary GC analysis using a 30 m β-Dex 120 chiral column (Supelco) showed it to be 70% ee in *R*-enantiomer (oven temp:100 °C; isothermal; t_R 32.76 min for *S*-isomer and t_R 33.70 min for *R*-isomer).

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