Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 1747–1752

TETRAHEDRON: *ASYMMETRY*

Desymmetric ring-opening of *meso*-epoxides with anilines: a simple way to chiral β-amino alcohols

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Received 23 March 1998; accepted 17 April 1998

Abstract

Chiral β-amino alcohols were afforded by desymmetric ring-opening of *meso*-epoxides with anilines catalyzed by chiral Yb triflate complex in up to 80.1% ee.

1. Introduction

β-Amino alcohols are compounds of undoubted interest in synthetic organic chemistry being found as subunits in many important biologically active natural and synthetic products.[1–3] They have also been used as chiral auxiliaries and ligands in asymmetric synthesis.[4] One of the most straightforward routes to β-amino alcohols would be the asymmetric ring-opening of *meso*-epoxides by using nitrogen-containing nucleophiles as reagents, but few reports employing this strategy have appeared in the literature.[5,6] Yamashita and Wu reported the ring-opening of cyclohexene oxide with aniline and a moderate ee was obtained.[6a,b,g] Jacobsen achieved an excellent result by using $TMSN_3$ in the presence of a chiral Cr complex, but the products had to be reduced in order to obtain amines.[5] Recently, Yamamoto and Crotti reported the ring-opening of epoxides with amines using $Yb(OTf)_3$ as the catalyst.[7,8] On the other hand, Kobayashi and coworkers have demonstrated that (*R*)-BINOL modified $Sc(OTf)_3$ or $Yb(OTf)_3$ and tertiary amines are efficient catalysts for asymmetric Diels–Alder reactions.[9] As a program aimed at the synthesis of epoxides and aziridines and their applications in organic synthesis,[10] we studied the ring-opening reactions of epoxides and aziridines and found that asymmetric ring-opening of *meso*-epoxides with anilines was accomplished in the presence of chiral BINOL–Yb triflate complexes and amines. Herein we would like to disclose our results.

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0957-4166/98/$19.00
PII: S0957-4166(98)00153-0

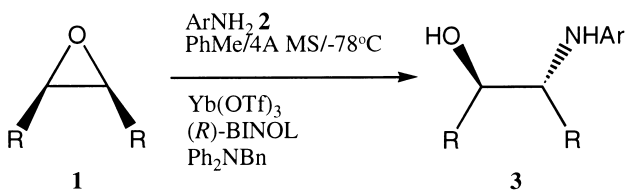
Table 1
Asymmetric ring-opening of *meso*-epoxides **1** with anilines **2**

Entry	Epoxide	Ar	Yield (%)[a]	e.e. (%)[b]	Config.[e]
1	**1a**	Ph	90	80.1(98.0)[c]	*1R, 2R*
2	**1a**	*o*-EtC_6H_4	74	39.0	(*1R, 2R*)
3	**1a**	*p*-ClC_6H_4	98	75.5(93.0)[c]	(*1R, 2R*)
4	**1a**	*p*-BrC_6H_4	78	73.6	(*1R, 2R*)
5	**1a**	*p*-$MeOC_6H_4$	64	37.4	(*1R, 2R*)
6	**1b**	Ph	98	11.6	(*1R, 2R*)
7	**1c**	Ph	/	/	/
8	**1d**	Ph	92	17.4[d]	(*1R, 2R*)
9	**1e**	Ph	99	42.7	(*1R, 2R*)
10	**1f**	Ph	71	12.6[d]	(*1R, 2R*)

[a] Isolated yield based on epoxide. [b] Determined by chiral HPLC.(OD, AD column). [c] E.e. values in parenthesis refer to that after single recrystallization. [d] The reaction proceeded at room temperature. [e] Compared with the authentic specfic rotation in ref. 6a,b. The Configuration in the parenthesis is estimated by analogy with (1R,2R)-2-phenylamino-1-cyclohexanol.

2. Results and discussion

Reaction of *meso*-epoxides **1** and anilines **2** catalyzed by $Yb(OTf)_3$ and (*R*)-BINOL in the presence of amine gave rise to β-amino alcohols **3** (Eq. 1); the results are shown in Table 1.



1 **3** (1)

1a, R,R = -$(CH_2)_4$-; **1d**, R = Ph;
1b, R,R = -$CH_2)_3$-; **1e**, R = Me;
1c, R,R = -$(CH_2)_6$-; **1f**, R,R = -$(CH_2CH_2CH)_2$-.

From Table 1 it can be found that all reactions proceeded smoothly under these conditions to afford the desired amino alcohols in high yield except in the case of cyclooctene oxide (entry 7). Moderate to good enantioselectivities were observed and the highest ee was 80.1% for cyclohexene oxide (Entry 1). In the reaction of cyclohexene oxide with an aniline having an electron-withdrawing group in the *para*-position, higher ee values are obtained (entries 3 and 4) compared with a methoxy group in the *para*-position (entry 5) or an ethyl group in the *ortho*-position (entry 2). For 1,2-diphenyl epoxide **1d** and 1,5-cyclooctadiene monooxide **1f**, the results obtained at room temperature (17.4% and 12.6% ee respectively, entries 8

and 10) are better than those at −78°C (12.0% and 10.0% ee, respectively; not shown in Table 1). It is worthwhile noting that the amine plays an important role in this reaction and the choice of its structure is crucial. Better enantioselectivities were achieved when a tertiary amine was used as the additive rather than primary and secondary amines. The best results were achieved when Ph_2NBn was used in toluene. Although enantioselectivities exceeding 70% were observed only with selected substrates (entries 1, 3, 4), the crystallinity of the β-amino alcohols allows an enhancement of their enantiomeric purity via a single recrystallization. For example, 2-phenylamino-1-cyclohexanol, generated in 90% yield and 80.1% ee from the ring-opening of cyclohexene oxide, was obtained in 98.0% ee and 72% overall yield after a single recrystallization from CH_2Cl_2/heptane.

In conclusion, a facile and convenient method to synthesize the chiral β-amino alcohol compounds has been developed through the chiral $Yb(OTf)_3$-catalyzed desymmetrization of *meso*-epoxides with anilines. Ring-opening using other classes of nucleophiles and extension of this methodology to other racemic compounds are under investigation.

3. Experimental section

3.1. General method

All reactions were performed under a nitrogen atmosphere using oven-dried glassware. Toluene was treated prior to use according to the standard method. The commercially available reagents were used as received without further purification. Melting points are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AMX-300 (300 MHz) spectrometer in $CDCl_3$ at room temperature. Chemical shifts are given in parts per million downfield from tetramethylsilane. Optical rotations were measured using a Perkin–Elmer 241 MC polarimeter with a thermally jacketed 10 cm cell at 20°C (concentration c given as g/100 mL). IR spectra were recorded in KBr and measured in cm^{-1}, using a Shimadzu IR-440 infrared spectrophotometer. Mass spectra and high-resolution mass spectra were taken using HP5989A and Finnigan MAT mass spectrometers, respectively. Elemental analyses were performed on a Foss–Heraeus Vario EL instrument. Enantiomeric excesses were determined by chiral HPLC on a Chiralcel OD column or a Chiralpak AD column. $Yb(OTf)_3$ and Ph_2NBn were prepared according to the literature procedures.[9,14]

3.2. General procedure

To a stirred solution of 4A molecular sieves (125 mg) in toluene (3.0 ml) under nitrogen was added $Yb(OTf)_3$ (62 mg, 0.1 mmol) and (*R*)-BINOL (35 mg, 0.12 mmol). The resulting mixture was cooled to 0°C. Ph_2NBn (62 mg, 0.24 mmol) was added and the reaction mixture was stirred at 0°C for 30 min. It was then cooled to −78°C and epoxide (1.0 mmol) and aniline (1.2 mmol) were added. The reaction mixture was stirred at −78°C till complete comsumption of the epoxide, then it was filtered through a plug of silica gel and washed with 20 ml of CH_2Cl_2. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography to furnish the corresponding product.

3.3. 2-Phenylamino-1-cyclohexanol[6a]

172 mg, yield: 90%; ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 1.10 (m, 1H), 1.20–1.50 (m, 3H), 1.65–1.85 (m, 2H), 2.05–2.20 (m, 2H), 3.15 (m, 3H), 3.40 (m, 1H), 6.75 (m, 3H), 7.20 (m, 2H); EIMS (relative

intensity): 192 (MH^+, 7.22), 191 (M^+, 43.18), 174 (0.82), 148 (13.49), 132 (100.00), 118 (25.03), 106 (34.74), 93 (10.94), 77 (13.73), 65 (3.52); mp: 78–80°C (lit:[6a] 78–81°C); ee: 80.1%; $[\alpha]_D^{20}=-78.4$ (c 1.5, CH_2Cl_2). After recrystallization: 72% overall yield; ee: 98.0%; $[\alpha]_D^{20}=-98.0$ (c 0.5, CH_2Cl_2).

3.4. 2-(2-Ethylphenyl)amino-1-cyclohexanol

162 mg, yield: 74%; ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 0.90–1.20 (m, 1H), 1.20–1.40 (m, 6H), 1.60–1.75 (m, 2H), 2.00–2.10 (m, 2H), 2.40 (q, J=15.03, 7.53, 7.51 Hz, 2H), 2.55–2.80 (br, 1H), 3.10–3.20 (m, 1H), 3.30–3.40 (m, 1H), 6.65–6.80 (m, 2H), 7.00–7.10 (m, 2H); EIMS (relative intensity): 220 (MH^+, 28.79), 219 (M^+, 100.00), 202 (1.81), 176 (14.77), 160 (87.15), 132 (64.38), 118 (13.86), 106 (9.74), 91 (6.91), 77 (10.41), 65 (3.37); IR (KBr): 3429, 3213, 2935, 2857, 1605, 1586, 1510, 1451, 1350, 1259, 1059 cm^{-1}; HRMS: $C_{14}H_{21}NO$ calcd: 219.1623; found: 219.1592; mp: 41–42°C; ee: 39.0%; $[\alpha]_D^{20}=-40.4$ (c 2.1, CH_2Cl_2).

3.5. 2-(4-Chlorophenyl)amino-1-cyclohexanol

220 mg, yield: 98%; ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 1.00 (m, 1H), 1.25 (m, 3H), 1.70 (m, 2H), 2.05 (m, 2H), 2.70–3.10 (m, 3H), 3.25 (m, 1H), 6.55 (d, J=5.20 Hz, 2H), 7.05 (d, J=5.29 Hz, 2H); EIMS (relative intensity): 227 (M^+, 48.24, ^{37}Cl), 226 ($(M+1)^+$, 61.65), 225 (M^+, 100.00, ^{35}Cl), 208 (7.26), 194 (1.74), 182 (9.26), 166 (61.77), 153 (13.77), 140 (26.49), 130 (23.37), 117 (8.24), 91 (8.31); IR (KBr): 3416, 3388, 3322, 2934, 2861, 1871, 1597, 1509, 1451, 1324, 1260 cm^{-1}. Anal. calcd for $C_{12}H_{16}ClNO$: C, 63.85; H, 7.14; N, 6.21. Found: C, 63.56; H, 7.11; N, 6.00; mp: 102–104°C; ee: 75.5%; $[\alpha]_D^{20}=-52.2$ (c 0.6, CH_2Cl_2). After recrystallization: 64% overall yield; ee: 93.0%; $[\alpha]_D^{20}=-64.5$ (c 0.4, CH_2Cl_2).

3.6. 2-(4-Bromophenyl)amino-1-cyclohexanol[6g]

211 mg, yield: 78%; ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 0.95–1.15 (m, 1H), 1.20–1.50 (m, 3H), 1.65–1.90 (m, 2H), 2.05–2.20 (m, 2H), 2.40–3.30 (m, 3H), 3.40–3.50 (m, 1H), 6.60 (d, J=8.56 Hz, 2H), 7.25 (d, J=8.16 Hz, 2H); IR (KBr): 3508, 3410, 3378, 3285, 2984, 2860, 1591, 1510, 1487, 1450, 1402, 1324, 1259, 1070 cm^{-1}; mp: 122–123°C; ee: 73.6%; $[\alpha]_D^{20}=-39.9$ (c 1.0, CH_2Cl_2).

3.7. 2-(4-Methoxyphenyl)amino-1-cyclohexanol[6g]

141 mg, yield: 64%; ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 0.95–1.10 (m, 1H), 1.20–1.50 (m, 3H), 1.65–1.90 (m, 2H), 2.05–2.20 (m, 2H), 2.90–3.20 (m, 3H), 3.30–3.45 (m, 1H), 3.80 (s, 3H), 6.65–6.72 (m, 2H), 6.72–6.85 (m, 2H); mp: 63–64°C; ee: 37.4%; $[\alpha]_D^{20}=-28.8$ (c 1.0, CH_2Cl_2).

3.8. 2-Phenylamino-1-cyclopentanol[11e]

173 mg, yield: 98%; ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 1.35–1.50 (m, 1H), 1.60–1.90 (m, 3H), 1.90–2.05 (m, 1H), 2.15–2.35 (m, 1H), 2.40–3.10 (br, 2H), 3.55–3.65 (m, 1H), 4.00–4.20 (m, 1H), 6.65–6.80 (m, 3H), 7.10–7.25 (m, 2H); mp: 57–58°C (lit:[11e] 57–58°C); ee: 11.6%; $[\alpha]_D^{20}=-3.6$ (c 1.0, CH_2Cl_2).

3.9. 1-Phenyl-2-phenylaminobenzeneethanol[12]

265 mg, yield: 92%; ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 3.10–3.70 (br, 2H), 4.52 (d, J=5.88 Hz, 1H), 4.85 (d, J=5.91 Hz, 1H), 6.55 (d, J=8.58 Hz, 2H), 6.50–6.80 (m, 3H), 7.00–7.40 (m, 10H); mp: 118–120°C (lit:[12] mp: 118–120°C); ee: 17.4%; $[\alpha]_D^{20}$=9.4 (c 0.9, CH_2Cl_2).

3.10. 8-Phenylamino-4-cyclocten-1-ol

154 mg, yield: 71%; ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 1.05–1.45 (m, 1H), 1.50–1.80 (m, 2H), 1.95–2.15 (m, 2H), 2.20–2.55 (m, 3H), 3.40–3.50 (m, 1H), 3.60–3.70 (m, 1H), 3.70–4.50 (br, 2H), 5.50–5.60 (m, 1H), 5.65–5.80 (m, 1H), 6.70–6.90 (m, 3H), 7.20 (m, 2H); EIMS (relative intensity): 218 (MH^+, 77.85), 217 (M^+, 100.00), 200 (3.42), 158 (5.58), 119 (45.63), 106 (4.90), 91 (6.09), 77 (7.50), 65 (3.56); IR (KBr): 3315, 3107, 3054, 3027, 2941, 1923, 1690, 1604, 1520, 1498, 1465, 1306, 1256 cm^{-1}; HRMS: $C_{14}H_{19}NO$ calcd: 217.1466; found: 217.1465; mp: 54–55°C; ee: 12.6%; $[\alpha]_D^{20}$=2.1 (c 0.9, CH_2Cl_2).

3.11. 3-Phenylamino-2-butanol[13]

163 mg, yield: 99%; ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 1.15 (d, J=6.47 Hz, 3H), 1.25 (d, J=6.18 Hz, 3H), 2.60–3.30 (br, 2H), 3.30–3.40 (m, 1H), 3.60–3.70 (m, 1H), 6.65–6.85 (m, 3H), 7.20 (t, J=8.29, 7.50 Hz, 2H); ee: 42.7%; $[\alpha]_D^{20}$=−36.2 (c 1.5, CH_2Cl_2).

Acknowledgements

This work was supported by the National Natural Science Foundation of China (Project 29790127) and the Chinese Academy of Sciences.

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