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Enantioselective Ring Opening Reaction of *meso*-Epoxides with Aromatic and Aliphatic Amines Catalyzed by Magnesium Complexes of BINOL Derivatives

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Catalyzed by the Mg complexes of BINOL derivatives, the enantioselective ring opening reaction of various *meso*-epoxides proceeded smoothly with either aromatic or aliphatic amines as the nucleophiles to afford the corresponding chiral β-amino alcohols in moderate-to-high yields with good to excellent enantioselectivities.

Introduction

Optically active β-amino alcohols are compounds of great interest in organic chemistry as building blocks for biologically active compounds and as chiral auxiliaries or ligands for applications in asymmetric synthesis.[1] The asymmetric ring opening reaction of *meso*- or racemic epoxides with amines affords a simple route to optically enriched β-amino alcohols.[2] Over the last decade or so, a variety of chiral catalysts have been developed for this reaction, mostly including Lewis acid complexes based on various metal ions.[3] Despite this fact, however, in each case a wide generality with respect to the amine nucleophiles has not yet been achieved. Especially, the catalytic asymmetric ring opening of epoxides with aliphatic amines is a challenging goal, and so far, very few of the reported systems afford respectable *ee* values in this type of reaction. In this respect, Inaba et al. have shown that Ti^{IV} complexes of enantiopure 1,1′-bi-2-naphthol (BINOL) are efficient and highly enantioselective catalysts in the ring opening of 3,5,8-trioxabicyclo[5.1.0]octane with alkylamines to afford 2-amino-1,3,4-butanetriols in high optical purity.[4] We have investigated the mechanism of this reaction and provided spectroscopic evidence of the active species.[5] However, the protocol was found to be effective only for this chelating epoxide substrate, whereas the common *meso*-epoxides tested did not undergo reaction. It is widely recognized that, in the asymmetric ring opening reaction of epoxides, strongly Lewis base aliphatic amines as the nucleophiles can have an inherent problem of catalyst deactivation, caused by the stable complex formation of the Lewis acid catalyst with the amine nucleophile and/or the generated β-amino alcohol product.[2,6] Nevertheless, some simple metal salts have been used as efficient achiral catalysts in the non-asymmetric ring opening aminolysis of epoxides even with aliphatic amines.[7] Thus, it occurred to us that a suitable combination of a Lewis acid metal and a chiral chelating ligand might provide an adequate control of the competitive coordination to the metal center, i.e. to favor the preferential coordination and activation of the epoxide without saturation of the active site, and hence may allow for good turnovers and respectable *ee* values in the reaction by using either aromatic or aliphatic amines. Chiral complexes of strongly oxophilic magnesium(II) species seems a promising option in this respect, which have found increasing use in asymmetric catalysis of a variety of synthetic reactions.[8] Herein we report the development of efficient BINOLate/Mg catalysts for the asymmetric ring opening reaction of *meso* epoxides with both aromatic and aliphatic amines as the nucleophiles. The reactions proceed smoothly under mild conditions to afford the corresponding chiral β-amino alcohols in moderate to excellent yields with high enantioselectivities.

Results and Discussion

We initiated the study by investigating the ring opening reaction of cyclohexene epoxide **1** with aniline, using a chiral magnesium complex generated in situ by combination of a substoichiometric amount of (*R*)-BINOL and Bu_2Mg as the catalyst. As shown in Table 1, the reactions generally proceeded smoothly with moderate enantiocontrol, but both the activity and enantioselectivity are strongly influenced by the variation in the reaction conditions, including the molar ratios of BINOL and Bu_2Mg (Entries 1–7), solvents (Entries 5, 8–13), as well as the temperature (Entries

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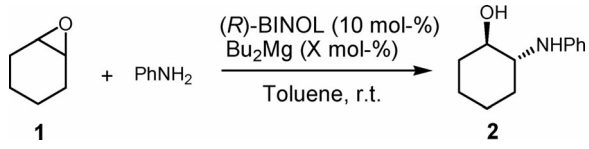
5, 14–18). For the reactions performed at room temperature in toluene, increasing the molar ratios of Bu_2Mg/BINOL from 0.5 to 1.5 led to considerable improvement in the yield of **2** (58–99%, Entries 1–7). However, the best *ee* value (53%) was attained with a Bu_2Mg/BINOL ratio of 1.3 (Entry 5), which was thus kept unchanged in the studies thereafter. A survey of the solvent indicated that toluene is the optimal choice in terms of reactivity and *ee* values (Entries 5 vs. 8–13), while the coordinating solvents THF and acetonitrile led to rather poor results (Entries 9 and 13). Under otherwise identical conditions (the use of toluene and a Bu_2Mg/BINOL ratio of 1.3), the reaction proceeded somewhat sluggishly at lower temperature (0 °C) with a slightly reduced *ee* value for **2** (Entries 5 vs. 14), while excellent yields and moderate *ee*s were attained at elevated temperatures (Entries 15–17). Finally, the reaction in toluene at 35 °C proceeded smoothly under a reduced catalyst loading (1 mol-%), wherein product **2** was isolated in excellent yield with a moderate level of enantioselectivity (Entry 18).

Table 1. Optimization of the asymmetric ring opening reaction of epoxide **1** and aniline catalyzed by the (*R*)-BINOL/Bu_2Mg complex.[a]



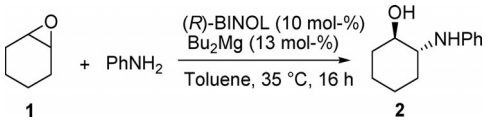
1 **2**

Entry	X/10	Solvent	*T* [°C]	Time [h]	Yield [%][b]	*ee* [%][c]
1	0.5	toluene	25	16	58	25
2	1.0	toluene	25	16	74	38
3	1.1	toluene	25	16	93	45
4	1.2	toluene	25	16	92	44
5	1.3	toluene	25	16	94	53
6	1.4	toluene	25	16	96	50
7	1.5	toluene	25	16	99	46
8	1.3	CH_2Cl_2	25	24	87	42
9	1.3	THF	25	24	37	18
10	1.3	pentane	25	24	97	34
11	1.3	$CHCl_3$	25	24	90	37
12	1.3	Et_2O	25	24	78	29
13	1.3	CH_3CN	25	24	34	21
14	1.3	toluene	0	36	89	46
15	1.3	toluene	35	6	99	54
16	1.3	toluene	50	2	98	55
17	1.3	toluene	70	2	98	48
18[d]	1.3	toluene	35	16	94	53

[a] Unless otherwise noted, all the reactions were performed with 1.0 mmol of aniline and 1.5 mmol of **1** in the presence of 10 mol-% BINOL and a specified amount of Bu_2Mg. [b] The yield of isolated product based on aniline. [c] Determined by HPLC on a chiral AD column. In each case, the absolute configuration was found to be (1*R*,2*R*) by comparison of the $[\alpha]_D$ value with that of the literature (see ref.[3h]). [d] The loading of (*R*)-BINOL is 1 mol-%.

Encouraged by these results, we attempted to further improve the enantioselectivity of the catalysis by introduction of various additives into the reaction system. A variety of additives were examined, including Lewis bases (Ph_3P, Ph_3PO, Et_3N, DMAP), carboxylic acids (benzoic acid, 4-nitrobenzoic acid, adipic acid, and cinnamic acid), *p*-toluene sulfonic acid, and 4-Å molecular sieves, and the results were summarized in Table 2. A marginal enhancement of the *ee* value of **2** from 54 to 61% was obtained with a proper amount of Ph_3PO or benzoic acid (ca 5 mol-%) as the additive (Entries 4 and 6).[9] Notably, the addition of 1 mol-% MeLi to the reaction system at 35 °C under a catalyst loading of 1 mol-% resulted in a drastic improvement of the *ee* value of **2** to 73%, albeit accompanied with a slight drop in yield (Entries 14 vs. 13).[10] A control experiment showed that BINOL/MeLi alone is not effective for the ring opening reaction of **1** under otherwise identical conditions, thus confirming the synergistic effect of the Li-containing species in the BINOLate/Mg-mediated catalysis.[11] Several other alkaline metal species were also tested as the additives in the reaction (Entries 15–17). Even though they also exhibited some beneficial effect on the enantioselectivity, in each case the *ee* value was inferior to that with the MeLi additive.

Table 2. Additive effects in the asymmetric ring opening reaction of epoxide **1** and aniline catalyzed by the (*R*)-BINOL/Bu_2Mg complex.[a]



1 **2**

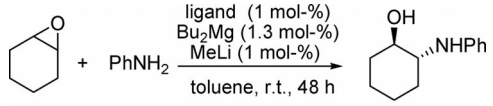
Entry	Additive (mol-%)	Yield [%][b]	*ee* [%][c]
1	none	95	55
2[d]	DMAP (6)	63	19
3[d]	Et_3N (10)	85	36
4	TPP(O) (5)	99	61
5	TPP (5)	99	51
6	PhCOOH (5)	98	61
7	4-nitrobenzoic acid (5)	99	57
8	adipic Acid (5)	99	45
9	L-leucine (5)	97	51
10	cinnamic acid (5)	97	54
11	TsOH (3)	98	53
12	4 Å MS (50 mg)	99	0
13[e]	none	99	55
14[e]	MeLi (1)	87	73
15[e]	LiCl (1)	94	57
16[e]	NaH (1)	75	60
17[e]	*n*BuLi (1)	90	67

[a] Unless otherwise noted, all the reactions were carried out in toluene at 35 °C by using 1.0 mmol of aniline and 1.5 mmol of **1** in the presence of 10 mol-% BINOL and 13 mol-% of Bu_2Mg. [b] The yield of isolated product based on aniline. [c] Determined by HPLC on a chiral AD column. In each case, the absolute configuration was found to be (1*R*,2*R*) by comparison of the $[\alpha]_D$ value with that of the literature (see ref.[3h]). [d] Room temperature, 24 h. [e] The reactions were carried out in the presence of 1.0 mol-% BINOL and 1.3 mol-% Bu_2Mg.

Subsequently, a variety of BINOL derivatives were screened as the ligands for the Bu_2Mg/MeLi catalyzed reaction. As shown in Table 3, the partially reduced BINOLs (*R*)-5,6,7,8-tetrahydro-1,1′-bi-2-naphthol (H_4-BINOL)[12] and (*R*)-5,5′,6,6′,7,7′,8,8′-1,1′-bi-2-naphthol (H_8-BINOL)[13] exhibited a comparable enantioselectivity as BINOL itself, but the reactivity was somewhat inferior (Entries 2, 3 vs. 1). The 6,6′-dihalogen substituted BINOLs showed excellent

reactivity, but with slightly decreased *ee* values (Entries 4, 5). The 3,3′-diiodine substituted BINOL gave a relatively poor result (Entry 6), however. Thus, BINOL still turns out to be optimal for this reaction in terms both reactivity and enantioselectivity.

Table 3. Ligand screening for BINOLate/Bu_2Mg/MeLi-catalyzed ring opening reaction of epoxide **1** with aniline.[a]



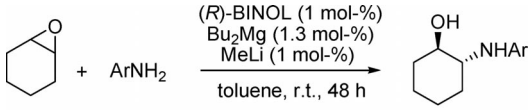
1 **2**

Entry	Ligand	Yield [%][b]	*ee* [%][c]
1	(*R*)-BINOL	87	73
2	(*R*)-H_4-BINOL	68	76
3	(*R*)-H_8-BINOL	63	71
4	(*R*)-6,6′-Br_2-BINOL	92	67
5	(*R*)-6,6′-I_2-BINOL	91	68
6	(*R*)-3,3′–I_2-BINOL	22	16

[a] All reactions were performed with 1.0 mmol of $PhNH_2$ and 1.5 mmol of **1** in toluene (1 mL) at room temperature. [b] The yield of isolated product based on aniline. [c] Determined by HPLC on a chiral AD column. In each case, the absolute configuration was found to be (1*R*,2*R*) by comparison of the $[a]_D$ value with that of the literature (see ref.[3h]).

Under the optimized reaction conditions, the enantioselective ring opening aminolysis of epoxide **1** was examined with a variety of aniline derivatives as nucleophiles. As shown in Table 4, the corresponding chiral β-amino alcohols **2**–**10** were generally obtained in moderate to high yields with good *ee* values (up to 82%, Entry 6).

Table 4. The enantioselective ring opening reactions of epoxide **1** and aromatic amines catalyzed by BINOLate/Bu_2Mg/MeLi system.[a]



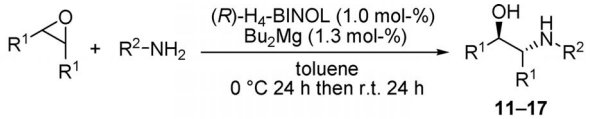
1 **2–10**

Entry	$ArNH_2$	Yield [%][b]	*ee* [%][c]
1	$PhNH_2$	87	73 (**2**)
2	3-$CH_3OC_6H_4NH_2$	55	65 (**3**)
3	2-$CH_3OC_6H_4NH_2$	92	65 (**4**)
4	4-$CH_3OC_6H_4NH_2$	90	69 (**5**)
5	3-$CH_3C_6H_4NH_2$	82	80 (**6**)
6[d]	3-$CH_3C_6H_4NH_2$	73	82 (**6**)
7	2-$CH_3C_6H_4NH_2$	75	69 (**7**)
8	4-$C_2H_5C_6H_4NH_2$	90	75 (**8**)
9	3,5-$(CH_3)_2C_6H_3NH_2$	75	72 (**9**)
10	3-$IC_6H_4NH_2$	71	72 (**10**)

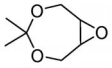
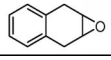
[a] All reactions were performed with 1.0 mmol of aromatic amines and 1.5 mmol of epoxide **1** in toluene (1 mL). [b] The yield of isolated product based on the amine. [c] Determined by chiral HPLC. The absolute configuration of the major enantiomer (1*R*,2*R*) was assigned by comparison of the rotation values in the literature (see ref.[3a,3h]) or by analogy.

Remarkably, the catalytic system generated in situ by mixing of BINOL analogues and Bu_2Mg were also found effective for the more challenging asymmetric ring opening reactions of *meso*-epoxides and aliphatic amines, as summarized in Table 5. A preliminary survey of the asymmetric ring opening of epoxide **1** with isopropylamine, with the BINOLate/Bu_2Mg/MeLi catalytic system optimized above, gave the corresponding amino alcohol **11** in 62% yield with 74% *ee* (Entry 1). Interestingly, the same reaction catalyzed by BINOLate/Bu_2Mg alone under otherwise identical conditions led to a significant enhancement in both the yield (82%) and *ee* value (81%) of **11** (Entry 2). Further elaboration of the procedure by using the partially reduced (*R*)-BINOL derivative, (*R*)-H_4-BINOL, instead of BINOL as the ligand led to a substantial increase in both yield (90%) and *ee* value (94%) of the product (Entry 3). Subsequently, the (*R*)-H_4-BINOL/Bu_2Mg system was extended to the catalysis of reactions between *meso*-epoxides and aliphatic amines (Entries 4–9). Good to excellent reactivity was observed in most cases. Especially, the reactions involving sterically bulky isopropyl or *tert*-butylamines gave the corresponding amino alcohols in high *ee* values (81–94%, Entries 3, 4, 7–9).

Table 5. (*R*)-H_4-BINOL/$MgBu_2$-catalyzed enantioselective ring opening of epoxides with aliphatic amines.[a]



11–17

Entry	Epoxide	Amine	Yield (%)[b]	ee (%)[c]
1[d]	**1**	*i*$PrNH_2$	62	74
2[e]	**1**	*i*$PrNH_2$	82	81
3	**1**	*i*$PrNH_2$	90	94 (**11**)
4	**1**	*t*$BuNH_2$	80	84 (**12**)
5	**1**	$BnNH_2$	92	56 (**13**)
6	**1**	piperidine	85	47 (**14**)
7		*i*$PrNH_2$	76	81 (**15**)
8		*i*$PrNH_2$	90	90 (**16**)
9		*i*$PrNH_2$	46	85 (**17**)

[a] All reactions were performed with 1.5 mmol of the amines and 1.0 mmol of the epoxide in toluene (1 mL). [b] The yield of the isolated product based on the epoxide. [c] *ee* values were determined by chiral GC (**11**, **12**, **14**–**17**) or HPLC (**13**) analysis. Absolute configurations were not assigned. [d] The reaction was carried out in toluene at room temperature for 48 h, with BINOLate/Bu_2Mg/MeLi (0.01:0.013:0.01 molar equiv. of epoxide **1**) as the catalyst. [e] Same as Entry 1, with the exception that MeLi was not used in this case.

Conclusions

In summary, the chiral BINOLate/Bu_2Mg complex was found to be efficient for enantioselective catalysis of ring opening aminolysis of *meso*-epoxides under mild condi-

tions. With minor alterations of catalyst composition (i.e. with or without MeLi as the additive), both aromatic and aliphatic amines can be used as nucleophiles to afford the corresponding β-amino alcohols in good yields with moderate-to-high *ee* values. The salient features of the present protocol include the ready and cheap availability of both the ligands and the metal sources. Last but not least, the use of aliphatic amines as effective nucleophiles in the asymmetric ring opening of epoxides is particularly noteworthy, as this should represent a rare example of achieving both good reactivity and enantioselectivity for these substrates to the best of our knowledge.

Supporting Information (see footnote on the first page of this article): Detailed experimental procedures and product characterization for the catalytic enantioselective ring opening reaction of the *meso*-epoxides, data for the water effect, and the HPLC/GC chromatograms of the amino alcohol products are presented.

Acknowledgments

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