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Catalytic Asymmetric Ring Opening of *meso*-Epoxides with Aromatic Amines in Water

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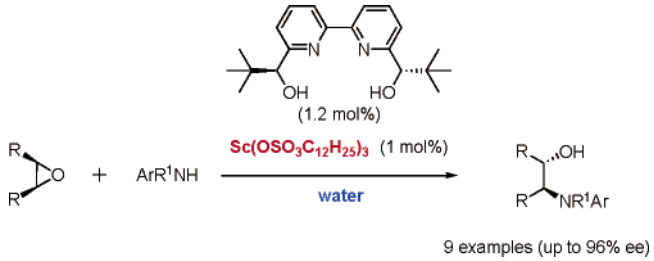
ABSTRACT



An operationally simple and environmentally benign protocol for the catalytic asymmetric ring opening of *meso*-epoxides with aromatic amines has been developed. The reactions proceeded smoothly in the presence of 1 mol % of $Sc(OSO_3C_{12}H_{25})_3$ and 1.2 mol % of a chiral bipyridine ligand in water to afford β-amino alcohols in high yields with excellent enantioselectivities.

Organic reactions in water are now of great interest. Water is a cheap, safe, and clean solvent.[1] Indeed, industry prefers to use water as a solvent rather than toxic organic solvents.[2] In general, however, water-soluble materials are preferred, whereas most organic compounds are not soluble in water. To achieve truly environmentally benign chemical syntheses, it is an important task to treat water-insoluble organic materials in water as well as to treat water-unstable materials in water. In this report, we focused on epoxides, which are important intermediates and building blocks in organic synthesis,[3] while they are readily decomposed under acidic conditions in water. We now report that optically active amino alcohols can be readily synthesized using Sc-catalyzed asymmetric ring-opening reactions of *meso*-epoxides with amines in water.

Chiral β-amino alcohol units are found in many biologically active compounds and chiral auxiliaries/ligands used in asymmetric reactions.[4] Catalytic enantioselective synthesis of these chiral building blocks mainly relies on asymmetric ring opening of *meso*-epoxides. Indeed, several examples using a chiral catalyst (typically a chiral Lewis acid) are reported in the literature;[5] however, all of these reactions proceeded in organic solvents. As a part of our ongoing program to develop new asymmetric reactions in aqueous media, we recently reported that a combination of scandium triflate ($Sc(OTf)_3$) and chiral bipyridine **1**[6] was effective to provide high enantioselectivities in catalytic asymmetric

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(3) For examples, see: (a) Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421. (b) Lauret, C. *Tetrahedron: Asymmetry* **2001**, *12*, 2359. (c) Lauret, C.; Roberts, S. M. *Aldrichimica Acta* **2002**, *35*, 47.

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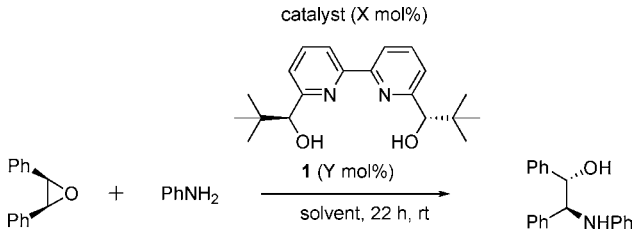
hydroxymethylation of silicon enolates.[7] To extend the use of this novel chiral scandium complex to other reactions in water, we decided to investigate the asymmetric ring opening of *cis*-stilbene oxide with aniline in water. Quite recently, Schneider et al. reported the same ring-opening reaction using $Sc(OTf)_3$ and **1** in dichloromethane.[5d] Independently, we were pleased to find that the reaction proceeded smoothly in high yield with high enantioselectivity using 10 mol % of scandium tris(dodecyl sulfate) ($Sc(DS)_3$) as a Lewis acid−surfactant combined catalyst, a concept previously introduced by our group,[8] and 20 mol % of **1** in water (Table 1, entry

Table 1. Optimization of the Reaction Conditions



entry	catalyst	X	Y	solvent	yield[a] (%)	ee[b] (%)
1	$Sc(DS)_3$	10	20	H_2O	91	94
2	$Sc(DS)_3$	5	10	H_2O	79	94
3	$Sc(DS)_3$	3	6	H_2O	76	94
4[c]	$Sc(DS)_3$	1	2	H_2O	90	94
5[c]	$Sc(DS)_3$	1	1.2	H_2O	89	91
6	$Sc(DS)_3$	0.25	0.3	H_2O	32	91
7	$Sc(DS)_3$	1	0	H_2O	14	
8	$Sc(OTf)_3$	1	1.2	H_2O	15	85
9	$Sc(OTf)_3$	1	1.2	THF/H_2O[d]	<5	71
10	$Sc(OTf)_3$	1	1.2	CH_2Cl_2	85	74

[a] Isolated yield after silica gel chromatography. [b] Enantioselectivity was determined by chiral HPLC analysis. [c] Reaction time was 30 h. [d] THF/H_2O = 9/1.

1). It is noted that the ring-opening reaction proceeded smoothly in water, and that no diol formation was observed. Reducing the catalyst loading (entries 2−4) led to a decrease in conversion, which could be overcome by a longer reaction time (entry 4). The enantioselectivity was not affected neither by reducing the ratio of the ligand to the metal from 2 to 1.2 (entry 5) nor by the catalyst loading; indeed, the enantioselectivity was maintained even with only 0.25 mol % of the catalyst (entry 6). Hydrophobic interactions upon increasing the concentration of organic reactants may play a crucial role in these results.[9] Interestingly, the reaction proceeded sluggishly without ligand **1** (entry 7). Moreover, the use of $Sc(OTf)_3$ instead of $Sc(DS)_3$ in water (entry 8) or water/THF (entry 9) gave the desired ring-opening product in only poor yield. Finally, it has been demonstrated that

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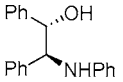
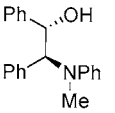
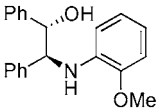
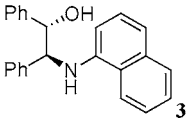
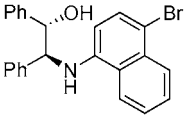
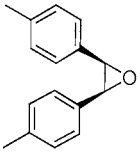
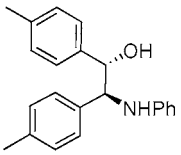
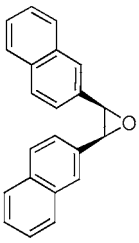
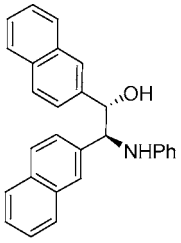
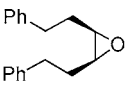
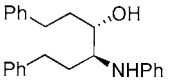
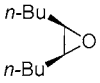
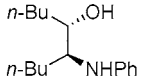
Table 2. Asymmetric Ring Opening of *meso*-Epoxides[a]

entry	substrate	amine	product	yield[b] (%)	ee[c] (%)
1	 **2a**	$PhNH_2$	 **3a**	89	91
2	**2a**	PhNHMe	 **3b**	88	96
3	**2a**	*o*-anisidine	 **3c**	81	93
4	**2a**	α-naphthylamine	 **3d**	83	91
5	**2a**	1-amino-4-bromonaphthalene	 **3e**	85	86
6	 **2b**	$PhNH_2$	 **3f**	81	90
7	 **2c**	$PhNH_2$	 **3g**	75	91
8	 **2d**	$PhNH_2$	 **3h**	61	60
9	 **2e**	$PhNH_2$	 **3i**	89	71

[a] The reaction conditions of entry 5 (Table 1), except time, were employed. [b] Isolated yield after silica gel chromatography. [c] Enantioselectivity was determined by chiral HPLC analysis.

$Sc(DS)_3$ and **1** in water gave higher yield and enantioselectivity than $Sc(OTf)_3$ and **1** in dichloromethane (entry 10). Conducting the reaction at lower temperature (5 °C) had no effect on the enantioselectivity, while the conversion was significantly slowed. On the other hand, higher temperature (40 °C) increased the reaction rate but had a detrimental effect on the enantioselectivity (not shown in the table).

Thus, the asymmetric ring-opening reaction of *cis*-stilbene oxide with aniline was carried out with only 1 mol % of $Sc(DS)_3$ and 1.2 mol % of **1** in water as the sole solvent, affording the desired β-amino alcohol in 89% yield and 91% ee. In general, even a trace amount of water exerts a detrimental effect on yield and enantioselectivity, and only few examples of enantioselective Lewis acid-catalyzed reactions in pure water have been reported.[10] To the best of our knowledge, this is, to date, the first example of an asymmetric epoxide ring opening in pure water.[11]

Under the optimized conditions, we next examined other substrates (Table 2). Sterically hindered anilines, such as *N*-methylaniline, maintained high yields and led to a further increase in enantioselectivity to 96% ee (Table 2, entry 2). The ring opening with an electron-rich amine, such as *o*-anisidine, proceeded with slightly improved enantioselectivity and yielded product **3c**, which may be easily converted into the free 1,2-amino alcohol (entry 3). α-Naphthylamine also reacted smoothly to provide the amino alcohol **3d** in high yield with high enantioselectivity. Similarly, α-naphthylamine bearing a functional group, such as 1-amino-4-bromo naphthalene, gave the desired product **3e**, which could be further transformed to introduce other functional groups (entry 5). On the other hand, benzylamine and other aliphatic amines did not yield the desired products. Aromatic *cis*-epoxides, *cis*-4,4′-dimethylstilbene oxide **2b** and *cis*-1,2-dinaphthylethylene oxide **2c**, reacted with aniline in good yields with high enantioselectivity to furnish 1,2-amino alcohol **3f** and **3g**, respectively (entries 6 and 7). Aliphatic epoxides, *cis*-1,6-diphenyl-3-hexene oxide (**2c**) and *cis*-5-decene oxide (**2d**), reacted with aniline under otherwise identical reaction conditions to afford the desired products **3g** and **3h**, respectively, in good to high yields with good enantioselectivity (entries 8 and 9).

In conclusion, we have established the first catalytic, enantioselective addition of amines to *meso*-epoxides employing a scandium−bipyridine complex in pure water. Chiral β-amino alcohols were prepared in mostly high yields with excellent enantioselectivities. It is noted that the use of water as a solvent gave a higher yield and enantioselectivity than that of dichloromethane. Current research efforts are directed toward further improvement of the scope of this process by ligand optimization and studying others nucleophiles.

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Supporting Information Available: Experimental procedures, analytical data, and ^1H and ^{13}C NMR spectra of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) (a) Otto, S.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1999**, *121*, 6798. (b) Manabe, K.; Kobayashi, S. *Chem.—Eur. J.* **2002**, *8*, 4094. (c) Sinou, D.; Rabeyrin, C.; Nguefack, C. *Adv. Synth. Catal.* **2003**, *345*, 357. (d) Hamada, T.; Manabe, K.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 7768.

(11) For examples of nonenantioselective ring opening of *meso*-epoxides in water, see: (a) Iranpoor, N.; Firouzabadi, H.; Shekarize, M. *Org. Biomol. Chem.* **2003**, *1*, 724. (b) Fan, R. H.; Hou, X. L. *J. Org. Chem.* **2003**, *68*, 726. (c) Ollevier, T.; Lavie-Compain, G. *Tetrahedron Lett.* **2004**, *45*, 49.