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BISMUTH TRIFLATE–CHIRAL BIPYRIDINE COMPLEX CATALYZED ASYMMETRIC RING OPENING REACTIONS OF *MESO*-EPOXIDE IN WATER[#]

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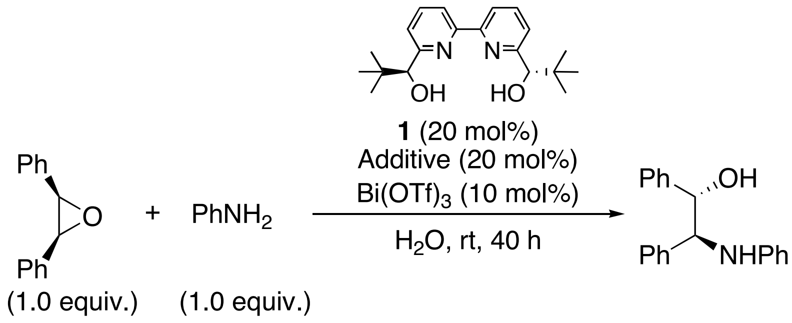
[#] Dedicated to late Professor Kenji Koga

Abstract – Catalytic asymmetric ring-opening reactions of *meso*-epoxides with aromatic amines have been explored. The reactions proceeded in the presence of a catalytic amount of bismuth triflate ($Bi(OTf)_3$), chiral bipyridine ligand (1) and sodium dodecylbenzene sulfonate (SDBS) in pure water to give the corresponding β-amino alcohols in good yields with high enantioselectivities.

The exploration of enantioselective reactions using chiral Lewis acids in water is one of the most fascinating topics in current organic chemistry. Not only do such reactions provide novel routes to compounds of great synthetic import, but are also very attractive from an environmental standpoint due to their environmentally benign nature.[1] For such reactions to proceed efficiently it is critical that the Lewis acids employed be compatible with water. Conventional Lewis acids such as titanium chloride, aluminium chloride, etc. which are known to be highly moisture sensitive, undergoing rapid decomposition on contact with water are therefore, in general, unsuited to this purpose. Bismuth triflate ($Bi(OTf)_3$), however, is reported to exist in water as an equilibrium mixture of $Bi(OTf)_3$ with bismuth hydroxide and triflic acid.[2] Up to today, only a few examples of enantioselective reactions using a chiral bismuth catalyst have been reported.[3] Quite recently, we have achieved asymmetric hydroxymethylation of silyl enol ethers using aqueous formaldehyde with a chiral bismuth catalyst prepared from $Bi(OTf)_3$ and a chiral bipyridine. To further expand the scope of organic reactions in aqueous systems, we have applied our methodology to a range of asymmetric catalytic reaction in water. Herein, we describe a new asymmetric ring-opening of *meso*-epoxides in pure water using chiral bismuth complex.[4]

Chiral β-amino alcohols are important building blocks for the preparation of chiral auxiliaries, ligands and natural products.[5] Catalytic enantioselective synthesis of these chiral building blocks mainly relies on asymmetric ring opening of *meso*-epoxides. Indeed, several examples using chiral catalysts (typically chiral Lewis acids) have been reported in the literature.[6] In the case of bismuth catalysts, however, all previous examples described non-enantioselective epoxide ring opening.[7] We therefore decided to address this problem using novel asymmetric bismuth-derived catalysts and our findings are described below (Table 1).

Table 1. Optimization of the reaction conditions



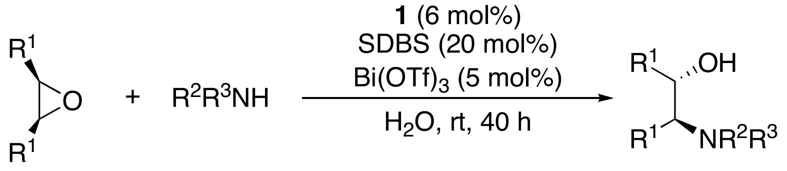
entry	solvent	additive	yield[a] (%)	ee[b] (%)
1	H_2O	–	NR	–
2	H_2O	CTAB	NR	–
3	H_2O	Triton X-100	NR	–
4	H_2O	SDS	28	83
5	H_2O	AOT[d]	65	87
6	H_2O	SDBS	70	89
7[c]	H_2O	SDBS	80	88
8	DME	–	3	50
9	CH_2Cl_2	–	15	83
10	THF	–	18	63
11	CH_3CN	–	10	60
12	Dioxane	–	17	64

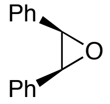
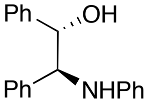
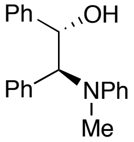
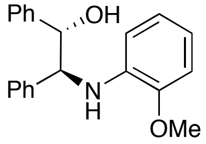
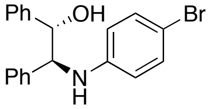
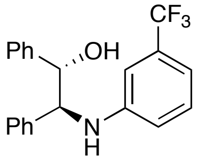
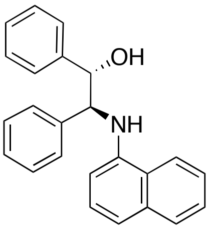
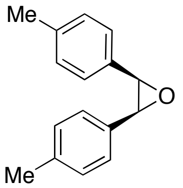
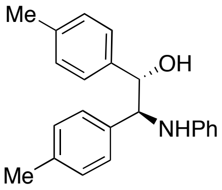
[a] Isolated yield after silica gel column chromatography. [b] Ee was determined by chiral HPLC analysis. [c] 5 mol% of $Bi(OTf)_3$ and 6 mol% of **1** were used. Reaction time: 30 h. [d] Aerosol OT, sodium dioctyl sulfosuccinate.

Initial results were not encouraging. In the first of the experiments *cis*-stilbene oxide allowed to react with aniline in the presence of 10 mol% of Bi(OTf)$_3$ and 20 mol% of chiral ligand (**1**) in pure water (Table 1, entry 1). Under these conditions, however, no reaction took place and the starting materials were recovered. We thought that the lack of reactivity might be due to poor solubility of the reactants, and so we decided to use a surfactant to overcome this problem. While cetytrimethylammonium bromide (CTAB) and Triton X-100 did not lead to any improvement (entries 2 and 3), use of sodium dodecyl sulfate (SDS) afforded the desired product with good enantioselectivity albeit in low yield (entry 4). It was postulated that an anionic surfactant could interact with a bismuth cation to generate a Lewis acid-surfactant combined catalyst *in situ*.[8] Alternatively, it could stabilize a cationic species which might be generated on an epoxide ring by the interaction of an epoxide oxygen with Bi(OTf)$_3$. Among other anionic surfactants tested, sodium dodecylbenzene sulfonate (SDBS) was the most efficient in terms of yield and enantioselectivity (entries 5 and 6). Reducing the catalyst loading to 5 mol% and the ratio of the metal to the ligand from 2 to 1.2 did not affect the enantioselectivity, although longer reaction times were needed to obtain complete conversion (entry 7).[9] It is noted that no diol formation was observed in all cases. Interestingly, when the reaction was conducted in organic solvents, low yields and moderate enantioselectivities were observed (entries 8 to 12). It has been reported that epoxides rearranged rapidly to form aldehydes or ketones in the presence of Bi(OTf)$_3$ in organic solvents, however no rearranged products were formed under the present conditions in water.[10] Thus, the asymmetric ring opening reaction of *cis*-stilbene oxide with aniline was carried out with 5 mol% of Bi(OTf)$_3$, 6 mol% of **1** and 20 mol% of SDBS in water as the sole solvent affording the desired β-amino alcohol in 80% yield with 88% ee.

Under the optimized conditions, we next examined other substrates (Table 2).[11] Sterically hindered anilines such as *N*-methylaniline maintained high yields and led to a further increase in enantioselectivity to 91% ee (Table 2, entry 2). The ring opening with an electron-rich amine such as *o*-anisidine also proceeded smoothly with slightly lower enantioselectivity. The product (**3c**) may be easily converted into the corresponding free 1,2-amino alcohol (entry 3).[12] Besides, electron-deficient amines such as *p*-bromoaniline (entry 4) and *m*-trifluoromethylaniline (entry 5) gave the desired compounds in good yields with high enantioselectivities. The reactions between 1-naphthylamine and **2a** (entry 6), and aniline and *cis*-di-*p*-tolyloxirane (**4**) (entry 7) also proceeded efficiently.

Table 2. Asymmetric Ring Opening of *meso*-Epoxides



entry	epoxide	amine	product	yield[a] (%)	ee[b] (%)
1	 **2a**	$PhNH_2$	 **3a**	80	88
2	**2a**	PhNHMe	 **3b**	85	91
3	**2a**	*o*-$MeOC_6H_4NH_2$	 **3c**	83	84
4	**2a**	*p*-$BrC_6H_4NH_2$	 **3d**	61 (78)[c]	92 (91)
5	**2a**	*m*-$CF_3C_6H_4NH_2$	 **3e**	71 (90)[c]	94 (93)
6	**2a**	1-Naphthylamine	 **3f**	73	83
7	 **4**	$PhNH_2$	 **3g**	68	89

[a] Isolated yield after silica gel column chromatography. [b] Ee was determined by chiral HPLC analysis. [c] 10 mol% of **1** was used.

In conclusion, we have demonstrated a novel catalytic asymmetric ring-opening reaction using a bismuth-chiral bipyridine complex with SDBS in pure water. Current research efforts are directed toward further improvement of the scope of this process by ligand optimization and the use of other nucleophiles.

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9. In the case of hydroxymethylation using aqueous formaldehyde, 3.0 equivalents of **1** to $Bi(OTf)_3$ were required to obtain the best result. Here, we assumed that 1:1 complex was formed. See 3(b).
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11. General Procedure for Catalytic Asymmetric Ring-Opening of *meso*-Epoxides: To a stirred solution

of $Bi(OTf)_3$ (0.05 equiv.) and SDBS (0.20 equiv.) in water (1 M concentration with respect of the substrates) was added chiral bipyridine ligand (**1**) (0.06 equiv.). The reaction mixture was stirred for 1 h at rt upon which the amine (1.0 equiv.) and the epoxide (1.0 equiv.) were added. Vigorous stirring was continued for 40 h at rt. The reaction was quenched with saturated aqueous 1N HCl. The resultant mixture was extracted with ethyl acetate (three times), and the combined organic layers were dried over anhydrous Na_2SO_4. The solvents were evaporated, and the residue was purified by PTLC silica gel using a mixture of ether-hexane as eluent to give the pure amino alcohol. The absolute configuration of the products was assigned by comparison with the reported optical rotation values and for the unknown compounds by analogy.

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