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Chiral Scandium-Catalysed Enantioselective Ring-Opening of *meso*-Epoxides with N-Heterocycle, Alcohol and Thiol Derivatives in Water

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Abstract: In the presence of catalytic amounts of $Sc(OSO_3C_{12}H_{25})_3$ and a chiral bipyridine ligand, asymmetric ring-opening of *meso*-epoxides with aromatic N-heterocycles, an alcohol and thiols proceeded smoothly to afford the corresponding products in moderate to good yields (34–85%) with high to excellent enantioselectivities (74–96% *ee*). Water was used as the sole and essential solvent in these important enantioselective transformations.

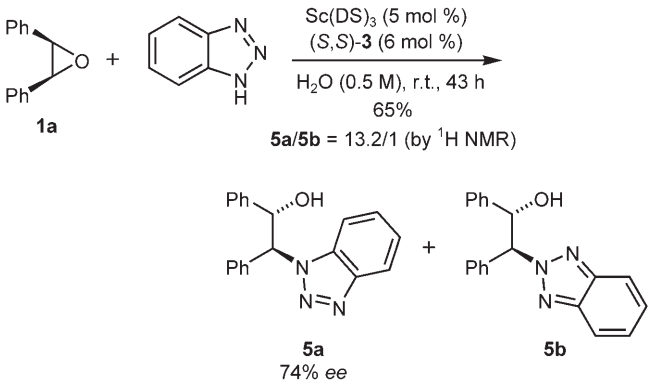
Keywords: epoxides; Lewis acids; scandium; surfactant; water chemistry

Water has emerged as a versatile solvent for organic chemistry in recent years.[1] In addition to its low cost, water is environmentally benign and frequently promotes unique reactivity and selectivity in chemical transformations. Indeed, the hydrophobic effect and solvation are expected to control reaction courses in water.

Catalytic, enantioselective ring opening of *meso*-epoxides is an efficient method to convert readily available bulk chemicals into chiral 1,2-difunctionalised fine chemicals in enantiomerically enriched form.[2] Recently, we have developed catalytic asymmetric ring-opening reactions of *meso*-epoxides with aromatic amines using a chiral scandium complex in water.[3] This is a successful example of chiral Lewis acid catalysis based on Lewis acid-surfactant combined catalysts (LASCs)[4] using water as the sole solvent. We have further investigated this unique and important catalysis and, in this paper, we describe catalytic asymmetric desymmetrisation of *meso*-epoxides with aromatic N-heterocycles, an alcohol and thiols using a chiral scandium catalyst in water.

Nitrogen-containing heterocycles and their derivatives have found broad applications in synthetic and biological chemistry.[5] Moreover, the indole framework is widely represented in natural substances and medicinal compounds.[6] Therefore, generation of chiral N-heteroaromatic derivatives in optically active form, in particular those incorporating indolic architectures, is a challenging and important facet of this research area.[7] To date, several catalytic, regioselective ring-opening of racemic epoxides[8] or chiral aromatic epoxides[9] with indole derivatives have been described. However, the catalytic enantioselective desymmetrisation of epoxides has received much less attention in the literature, and only one protocol for highly selective addition of indole derivatives to *meso*-stilbene oxide in *tert*-butyl methyl ether has been reported.[10] Furthermore, to the best of our knowledge, only one report of racemic ring-opening of epoxides with nucleophiles in pure water has appeared[11] before our recent report.[3]

Our preliminary experiment was performed using *cis*-stilbene oxide **1a** and indole as model reagents (Scheme 1). We were pleased to see that, after only



Scheme 1. Desymmetrisation of *cis*-stilbene oxide with benzotriazole.

five hours, the reaction had proceeded smoothly to give the desired alcohol in 50% yield with excellent enantioselectivity in the presence of catalytic amounts of $Sc(OSO_3C_{12}H_{25})_3$ [$Sc(DS)_3$] and bypiridine ligand (*S*,*S*)-**3**[12] (Table 1, entry 1). Running the reaction at a higher concentration increased the yield dramatically while maintaining a high level of selectivity (entry 2). It should be noted that the same reaction using $Sc(OTf)_3$ instead of $Sc(DS)_3$ in dichloromethane proceeded sluggishly under the conditions. On the other hand, neither increasing the amount of nucleophile (entry 3) nor lengthening the reaction time (entry 4) resulted in further improvement of the yield or selectivity. Thus, the desymmetrisation of *cis*-stilbene oxide **1a** with indole was carried out with 5 mol% of $Sc(DS)_3$ and 6 mol% of **3** in water as the sole solvent, affording the desired alcohol **4a** in 85% yield with 93% *ee*.

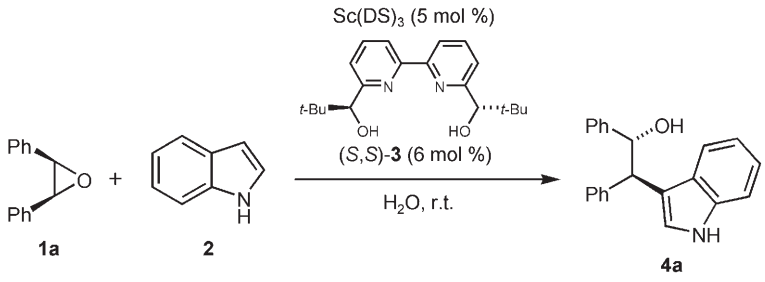
It is noteworthy that this reaction could be performed under air without epimerisation of the alcohol **4a** or loss of reactivity (Table 2, entry 1). As the next step, other indole derivatives were examined under the optimised conditions. The electron-rich 5-methoxyindole allowed the maintenance of the very high enantioselectivity and yield (entry 2) although a slight decrease in the yield and the enantioselectivity was observed for the 5-methylindole derivative **4c** (entry 3). The sterically hindered 2-methylindole gave, as expected, lower yield, although the enantioselectivity of **4d** was satisfactory (entry 4). Use of the more electron-deficient 5-bromoindole gave the corresponding alcohol **4e** in moderate yield but with high enantioselectivity (entry 5). The *meso*-epoxide *cis*-4,4′-dimethylstilbene oxide **1b** and *cis*-4,4′-dibromostilbene oxide **1c** reacted with indole and **4c** to afford the desired products **4f**, **4g** and **4h**, respectively, in moderate to good yields with high enantioselectivities (entries 6–8).

Benzotriazole bears a relatively acidic N–H proton ($pK_a = 8.2$) and exists in solution in two tautomeric forms (1*H*- and 2*H*-forms).[13] Extending our methodology to this heterocycle was highly interesting as such a moiety is present in numerous biologically active substances. For instance, the non-natural nucleoside DRBT was recognised as possessing a potent inhibitory effect on the hepatitis C virus,[14] whereas a benzotriazole-containing phosphate was described as an inhibitor of PTP1B and therefore could be a potent treatment for type 2 diabetes and obesity.[15] Potential applications might include preparation of novel non-natural nucleosides (NNNs), a class of compounds with a broad range of important biological applications.[16] This fused aromatic heterocyclic substrate was found to undergo a smooth reaction with indole, although a longer reaction time was required, generating **5a** in excellent regioselectivity (**5a**/**5b** = 13.2/1, total yield of 65%) with 74% *ee*.

The present catalytic asymmetric desymmetrisation of *meso*-epoxides was also applied to optically active diol and sulfide derivatives. In the presence of $Sc(DS)_3$ (10 mol%) and chiral bipyridine ligand (*S*,*S*)-**3** (12 mol%), *cis*-stilbene oxide **1a** reacted with *para*-bromobenzyl alcohol in water to afford the corresponding protected diol **6** in good enantioselectivity and moderate yield (Scheme 2). To the best of our knowledge, no enantioselective addition of alcohols in pure water was previously described.[17]

In addition, thiophenol and its derivatives were successfully used as nucleophiles in this asymmetric desymmetrisation (Table 3), and the corresponding sulfides **7a–e** were obtained in moderate to good yields with high enantioselectivities. While thiol derivatives

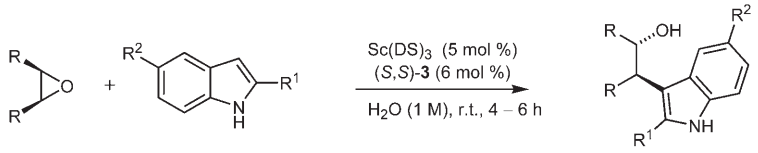
Table 1. Optimisation of the reaction conditions.

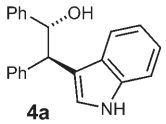
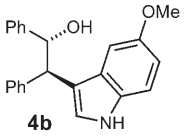
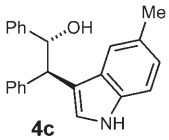
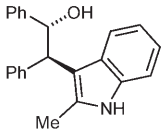
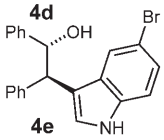
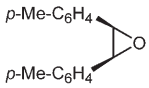
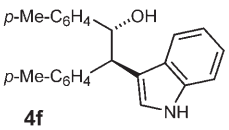
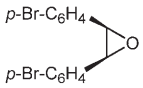
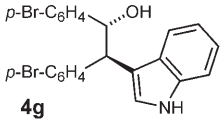
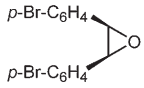
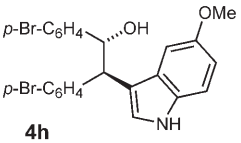


Entry	**2** (equivs.)	Concentration[a]	Time	Yield[b] [%]	*ee*[c] [%]
1	1.1	0.5 M	5 h	50	96
2	1.1	1 M	6 h	85	93
3	1.5	1 M	6 h	81	88
4	1.1	1 M	24 h	82	92

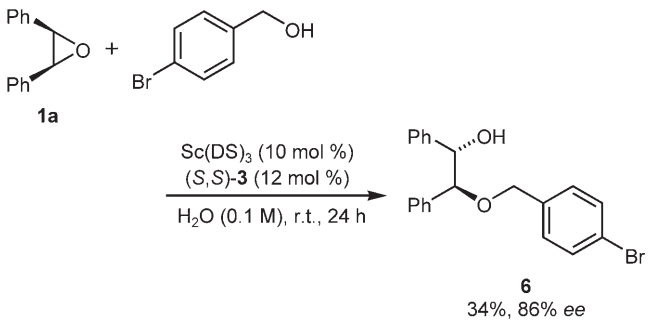
[a] With respect to the epoxide.
[b] Isolated yield after chromatographic purification.
[c] Determined by HPLC analysis on chiral stationary phase.

Table 2. Asymmetric ring opening of *meso*-epoxides with indole derivatives.



Entry	Substrate	Nucleophile	Product	Yield[a] [%]	*ee*[b] [%]
1	 **1a**	indole	 **4a**	85 85[c]	93 93[c]
2	**1a**	5-methoxyindole	 **4b**	75	92
3	**1a**	5-methylindole	 **4c**	71	85
4	**1a**	2-methylindole	 **4d**	63	85
5	**1a**	5-bromoindole	 **4e**	59	90
6	 **1b**	indole	 **4f**	62	86
7	 **1c**	indole	 **4g**	59	93
8	 **1c**	5-methoxyindole	 **4h**	56	92

[a] Isolated yield after chromatographic purification.
[b] Determined by HPLC analysis on chiral stationary phase.
[c] The reaction was conducted under air.



Scheme 2. Desymmetrisation of *cis*-stilbene oxide with 4-bromobenzyl alcohol.

have been employed in the catalytic ring-opening of *meso*-epoxides in organic solvents,[18] the present enantioselective addition is the first example in water, and it is noteworthy that high levels of enantioselectivities have been attained in pure water.

In summary, we have developed a chiral scandium-catalysed highly selective asymmetric ring-opening of *meso*-epoxides in the presence of different substituted indoles. The corresponding indolyl derivatives were isolated in moderate to good yields with high to excellent enantioselectivities. In addition, the first enantioselective addition of alcohol and thiol derivatives to *meso*-epoxide in water has been realised.

Experimental Section

General Procedure for the Catalytic Asymmetric Ring-Opening of *meso*-Epoxides with Indole Derivatives

To $Sc(DS)_3$ (12.6 mg, 0.15 mmol) and ligand (*S*,*S*)-**3** (5.9 mg, 0.18 mmol) under argon was added deionised water (300 mL, 1 M concentration with respect to the epoxide). The reaction mixture was stirred for 1 hour at room temperature (r.t.), and then an epoxide **1a**, **1b** (0.30 mmol) and an indole derivative (0.33 mmol) were successively added. Vigorous stirring was continued for 4 to 6 h at room temperature, and the reaction mixture was diluted with CH_2Cl_2 or AcOEt (20 mL). After phase separation, the aqueous layer was extracted with CH_2Cl_2 or AcOEt (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude mixture was purified by chromatography on silica gel.

Further details of the experimental procedures are described in the Supporting Information, which also contains characterisation data for the compounds made.

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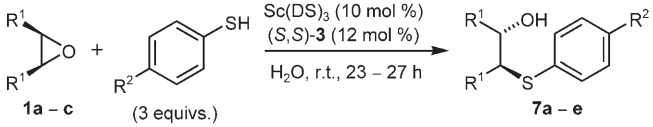
Table 3. Desymmetrisation of *meso*-oxide with thiophenol derivatives.



Entry	R^1	R^2	Concentration[a]	Product	Yield[b] [%]	*ee*[c] [%]
1	Ph	H	0.1 M	**7a**	73	89
2	4-Br-C_6H_4	H	1 M	**7b**	44	92
3	4-Br-C_6H_4	H	0.1 M	**7b**	76	85
4	4-Br-C_6H_4	*t*-Bu	0.1 M	**7c**	69	92
5	Ph	OMe	0.1 M	**7d**	66	87
6	4-Br-C_6H_4	OMe	0.1 M	**7e**	70	93

[a] With respect to the epoxide.
[b] Isolated yield after chromatographic purification.
[c] Determined by HPLC analysis on chiral stationary phase.

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