$Zr(DS)_4$ as an Efficient Catalyst for the Aminolysis of Epoxides in Water

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Abstract: Zirconium dodecyl sulfate [$Zr(DS)_4$] is an efficient catalyst for the aminolysis of epoxides in water at pH 5.0. Epoxides and anilines were used and the corresponding β-amino alcohols were isolated in generally high regioselectivity and excellent yields.

Key words: aqueous medium, aminolysis, epoxides, $Zr(DS)_4$, LASC, surfactants

Aminolysis of epoxides is a useful tool for the preparation of β-amino alcohols,[1] an important class of molecules used as intermediates for the synthesis of biologically active compounds[2] and nonproteinogenic amino acids.[3] They also play an important role as chiral auxiliaries in asymmetric organic synthesis.[1b,4]

Several protocols have been developed for this transformation and a large variety of catalysts have been used to increase the efficiency of the oxirane ring opening by amines in organic media, in ionic liquids, and under solvent-free conditions.[5]

Water has proven to be an excellent reaction medium for many organic transformations,[6] allowing high chemical efficiency to be obtained.[7] Among others, one example is given by the nucleophilic ring opening of epoxides.[7,8]

Only recently, the aminolysis of epoxides in water has been reported[9,10] and we have proved that the aqueous medium strongly promotes this transformation.[9a]

The use of metal-catalyzed processes opens the route to the enantioselective ring opening of oxiranes.

According to Kobayashi's results,[10,11] we also believe that Lewis acid surfactants combined catalysts (LASCs) are the best catalysts for achieving the highest efficiency in the aminolysis of epoxides in water, because they can furnish both the Lewis acidity needed for activating the oxirane ring and the hydrophobic environment for a noncharged soft nucleophile such as an amine.

In this context, excellent results have been accomplished by Kobayashi et al. by using scandium dodecyl sulfate [$Sc(DS)_3$] as LASC and enantiomerically pure bipyridine **5** in water.[10] This paper confirmed that the use of LASCs as catalysts in water is very intriguing and although several examples of their efficiency have been reported,[11] the more efficient results have been accomplished by Kobayashi who has been developing the chemistry of $Sc(DS)_3$ on various transformations,[6a,10,11] and by Engberts, who showed the efficiency of $Cu(DS)_2$, and $Zn(DS)_2$ on Diels–Alder cycloadditions of 3-aryl-1-(2-pyridyl)-2-propen-1-ones in water.[12]

We have been investigating the use of water as a reaction medium for many years.[6a,8,9a,13] More recently, we have been interested in the Lewis acid catalyzed ring opening of epoxides in water,[6a,8,9a] and we have shown that in the case of charged nucleophiles (such as N_3^-, Br^-, I^-) the best results are obtained by using Cu(II), Al(III), and In(III) salts, independent of their counter ions.

To contribute to the development of the chemistry of LASCs in aqueous media, we intend to study the use of those LASCs prepared from transition-metal salts that have been little explored and never tested in the aminolysis of epoxides.

In this paper, we have compared the catalytic efficiency of Co(II), Ni(II), Cu(II), Zn(II), and Zr(IV) salts to that of Sc(III), in the ring opening of cyclohexene oxide (**1a**) by aniline (**2a**) in water in the presence of SDS. Generally, the experiments were performed by using 2 mL of water per 1.0 mmol of **1** and **2**.

When substoichiometric amounts of SDS and a Lewis acidic metal salt were used at pH 5 and 30 °C (Table 1),[14] *trans*-2-phenylaminocyclohexanol (**3a**) was formed in high conversion after two hours (75–99%, Table 1, entries 4, 5, and 7–11). The best result was obtained by using a combination of $ZrCl_4$ (5 mol%) and SDS (20 mol%) that allowed to reach a complete conversion into the β-amino alcohol **3a** after two hours (Table 1, entry 5).

On the contrary, when $ZrCl_4$ was used in the absence of surfactant, very low conversion was observed as was the case when the reaction was performed in water in the absence of any catalyst (Table 1, entries 3 and 1, respectively). The SDS plays a crucial role in creating a hydrophobic environment in which the reaction can proceed effectively (Table 1, entry 2). Zirconium tetrachloride was still highly effective when the amount of SDS was reduced from 20 mol% to 10 mol%, in fact the conversion into **3a** was only slightly reduced from 99% to 96%, while the isolated yield of **3a** was almost identical (Table 1, entry 5 vs. 4).

The reaction worked also at pH 3.0, although an 8% conversion of cyclohexane-1,2-diol (coming from the hydrolysis of **1a**) was also formed (Table 1, entry 13). At pH 7 the reaction was slower, giving 45% in two hours (Table 1, entry 12) proving that the concentration of

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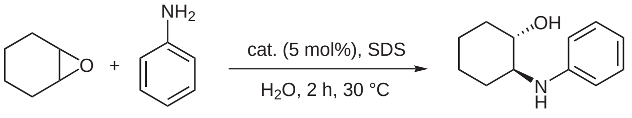
hydroxide ions also plays a role in the efficiency of the LASC catalyst.[14]

It is interesting to note that **1a** and **2a** (1.0 mmol each) in water (2 mL) formed two separate layers, as they are insoluble in water over the pH range 3.0–7.0. When Cu(II), Co(II), Ni(II), or Zn(II) salts and/or SDS were added (entries 2, 8–11), the aqueous solution was still homogeneous and separated from the organic layer of the two reactants. On the contrary, when $Sc(OTf)_3$ or $ZrCl_4$ were used, the reaction mixtures were completely heterogeneous with the formation of a white solid [$Sc(DS)_3$[11c] and $Zr(DS)_4$, respectively].

We have isolated both solids formed when 0.05 mmol of $ZrCl_4$ were mixed with 0.1 or 0.2 mmol of SDS in 2 mL of water, and elemental analyses proved that in both cases there were no traces of chlorine atoms and only $Zr(DS)_4$ was formed. As a further proof, when $Zr(DS)_4$ was prepared, isolated and used as catalyst, it gave the same results as when it was prepared in situ.

It is worth noting that by using more water, to ensure complete dissolution of $Zr(DS)_4$, the aminolysis was much slower, confirming that the highest efficiency for this LASC was achieved under heterogeneous conditions (Table 1, entry 4 vs. 6).

Table 1 Aminolysis of Cyclohexene Oxide (**1a**) with Aniline (**2a**)



1a **2a** **3a**

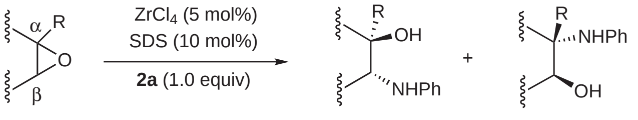
Entry	pH	Cat. (5 mol%)	SDS (mol%)	Conversion (%)[a]
1	5.0	–	–	15
2	5.0	–	10	65
3	5.0	$ZrCl_4$	–	16
4	5.0	$ZrCl_4$	10	96[b]
5	5.0	$ZrCl_4$	20	99[b]
6	5.0	$ZrCl_4$	10	30[c]
7	5.0	$Sc(OTf)_3$	15	90
8	5.0	$Cu(OTf)_2$	10	91
9	5.0	$CoCl_2$	10	85
10	5.0	$NiCl_2$	10	76
11	5.0	$Zn(OTf)_2$	10	75
12	7.0	$ZrCl_4$	20	45
13	3.0	$ZrCl_4$	20	99[d]

[a] Conditions: 1.0 mmol of **1a** and **2a**, 2 mL of H_2O, conversion measured by GLC analyses, the remaining material was the unreacted **1a**.
[b] Compound **3a** was isolated in 90% yield.
[c] Conditions: 12 mL of H_2O for 1.0 mmol of reagents were used.
[d] Conversion: 8% of *trans*-1,2-cyclohexandiol was formed.

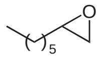
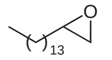
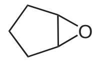
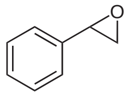
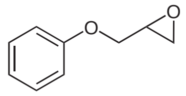
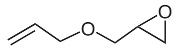
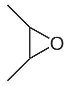
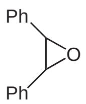
The most convenient reaction conditions (0.05 mmol of $ZrCl_4$, 0.10 mmol of SDS at pH 5 in 2 mL of water for 1.0 mmol of epoxides) were then extended to the aminolysis of epoxides **1b**–**i** to obtain the β-amino alcohols **3b**–**d**, **3f**–**h**, and **4e** in short times (1–6 h) and with good yields (80–88%, Table 2). The only exception was given by *cis*-stilbene oxide (**1i**), a less reactive epoxide, which took 3 days to complete the transformation at 30 °C. When the temperature was raised to 60 °C, the desired product was isolated after 35 hours in 85% yield (Table 2, entry 9).

The reaction generally proceeded through attack of the aniline (**2a**) to the less substituted C-β carbon as expected from an S_N2 attack. Similarly, in the case of styrene oxide (**1e**) the outcome is consistent with a borderline S_N2 pro-

Table 2 Aminolysis of Epoxides **1b**–**i** by Aniline (**2a**)[a]



1 **3** **4**

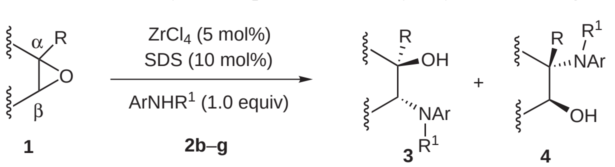
Entry	Epoxide	Time (h)	Ratio **3**/**4**[b]	Yield (%)[c]
1	 **1b**	3	91:9	82
2	 **1c**	6	87:13	80
3	 **1d**	4	–	81
4	 **1e**	1	5:95	85
5	 **1f**	4	99:1	64
6		4	99:1	84[d]
7	 **1g**	4	98:2	88
8	 **1h**	3	–	83
9	 **1i**	35[e]	–	85

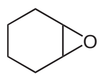
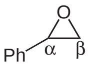
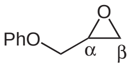
[a] Conditions: aniline (**2a**, 1.0 equiv) in H_2O, pH 5, 30 °C.
[b] Ratios evaluated by GLC analyses.
[c] Yield of the isolated β-amino alcohol products.
[d] By using 2 mol/equiv of **2a**.
[e] Reaction carried out at 60 °C.

cess. With epoxides **1b** and **1c**, we observed the formation of a small amount (5%) of the bis-adducts, which are those products deriving from the attack of the β-amino alcohol **3b** and **3c** on another molecule of the corresponding epoxide **1b** or **1c**. In the case of epoxides **1f**, 2 equivalents of aniline (**2a**) were used to reduce the bis-adduct from 17% to 6% (Table 2, entry 5 vs. 6).

In order to extend the scope of this study on the efficiency of Zr(DS)$_4$, we have also considered the reaction of typical epoxides **1a**,**e**,**f** with arylamines **2b**–**g**. The procedure worked well either with electron-rich or electron-poor anilines as well as with secondary amine such as *N*-methylaniline (**2g**) or highly hydrophobic naphthylamine (**2d**, Table 3). The regioselectivity observed confirmed the results reported in Table 2 and in the case of styrene oxide (**1e**) almost only α-products were obtained, while in the case of phenyl glycidol (**1f**) the β-products were exclusively formed.

Table 3 Aminolysis of Epoxides **1a**,**e**,**f** by Arylamines **2b**–**g**[a]

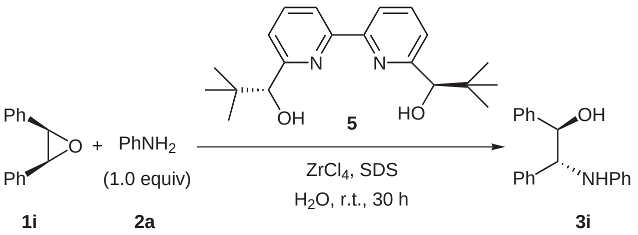


Entry	Epoxide	ArNHR^1	Time (h)	Ratio **3**/**4**[b]	Yield (%)[c]
1		**2b** 4-methoxyaniline	2	–	88
2		**2c** 4-methylaniline	4	–	91
3	**1a**	**2d** 2-aminonaphthalene	6	–	78
4		**2e** 2-fluoroaniline	4	–	83
5		**2f** 4-bromoaniline	3	–	81
6		**2g** *N*-methylaniline	6	–	85
7		**2b**	1	3:97	83
8	**1e**	**2c**	2	4:96	86
9		**2d**	6	6:94	80
10		**2e**	2	2:98	86
11		**2f**	2	5:95	85
12		**2g**	1	2:98	82
13		**2b**	4	>99:<1	79
14		**2c**	4	>99:<1	72
15	**1f**	**2d**	6	>99:<1	76
16		**2e**	7	>99:<1	91
17		**2f**	6	>99:<1	85
18		**2g**	8	>99:<1	84

[a] Conditions: arylamines **2b**–**g** (1.0 equiv) in H_2O, pH 5, 30 °C.
[b] Ratios evaluated by GLC analyses.
[c] Yield of the isolated β-amino alcohol products.

Finally, on the basis of the results obtained by Kobayashi et al.[10] in the asymmetric ring opening of *meso*-epoxides in water, we used Zr(DS)$_4$ in the presence of the same chiral ligand (*S*,*S*)-6,6′-bis(1-hydroxy-2,2-dimethylpropyl)-2,2′-bipyridine (**5**) which gave good results in the case of Sc(DS)$_3$. Unfortunately, the results obtained with Zr(DS)$_4$ were unsatisfactory. In fact, β-amino alcohol **3i** coming from the ring opening of *cis*-stilbene oxide (**1i**) by aniline (**2a**) was obtained with low conversion and low enantiomeric excess (Table 4). These results revealed the superiority of Sc(III) over Zr(IV) in the desymmetrization of *meso*-epoxides by using bipyridine **5**, although the ZrCl$_4$ is a more efficient catalyst for the racemic process (Table 1).

Table 4 Aminolysis of *cis*-Stylbene Oxide (**1i**) by Aniline (**2a**)[a]



Entry	ZrCl$_4$ (mol%)	SDS (mol%)	Ligand (mol%)	Conversion (%)[b]	ee (%)[c]
1	1.0	1.0	1.2	21	5
2	1.0	2.0	1.2	37	22
3	1.0	4.0	1.2	32	6
4	1.0	4.0	2.0	30	6
5	5.0	20.0	10.0	55	22

[a] Conditions: aniline (**2a**) in H_2O, r.t., 30 h.
[b] Conversion measured by GLC analyses, the remaining material was the unreacted **1i**.
[c] Enantioselectivity was determined by chiral HPLC analysis.

Further studies will be oriented towards different types of chiral ligands, which, due to the high oxophilicity of ZrCl$_4$, should probably contain more oxygen atoms than **5**.

In conclusion, we have found an efficient and environmentally friendly catalytic system for the aminolysis of epoxides that affords β-amino alcohols in good yields and short times.

β-Amino alcohols **3** and **4** are known compounds except **3fe** which is a new compound and its spectroscopic data are reported below.

Zr(DS)$_4$-Catalyzed Aminolysis of Epoxides – Typical Procedure for the Aminolysis of 1f with 2e

In a screw-capped vial equipped with a magnetic stirrer, ZrCl$_4$ (0.05 mmol) and SDS (0.10 mmol) were stirred in H_2O (2 mL) for 5 min at 30 °C and then 2-fluoroaniline (**2e**, 1.0 mmol) was added. After adjusting the pH to 5.0 with a few drops of aq 5 M NaOH, 2,3-epoxypropyl phenyl ether (**1f**, 1.0 mmol) was added. The reaction mixture was stirred for 7 h, then basified with aq 5 M NaOH to pH

10 and extracted with EtOAc (3 × 2 mL). The combined organic layers were dried over anhyd Na_2SO_4, the solvent was evaporated, and the crude product was charged on a Et_3N pretreated silica gel column chromatography [Et_2O–PE (1:1); silica/sample = 30:1]. Pure 1-phenoxy-3-(2′-fluorophenylamino)propan-2-ol (**3fe**) was isolated as a colorless oil (91% yield).

Physical Data for 3fe

^{1}H NMR ($CDCl_3$): δ = 2.80–3.70 (br s, 2 H), 3.34 (dd, 1 H, J = 6.9, 12.9 Hz), 3.47 (dd, 1 H, J = 3.9, 13.0 Hz), 4.00–4.15 (m, 2 H), 4.20–4.35 (m, 1 H), 6.60–6.70 (m, 1 H), 6.77 (t, 1 H, J = 8.2 Hz), 6.90–7.05 (m 5 H), 7.20–7.35 (m 2 H). ^{13}C NMR ($CDCl_3$): δ = 158.3, 151.9, 136.3, 129.6, 124.6, 121.4, 117.5, 114.7, 114.5, 112.6, 69.9, 68.7, 46.4. ^{19}F NMR ($CDCl_3$): δ = –136.3 (m). Anal. Calcd for $C_{15}H_{16}FNO_2$: C, 68.95; H, 6.17; F, 7.27; N, 5.36. Found: C, 68.81; H, 5.92; F, 7.02; N, 5.44. GC-MS (EI): m/z (%) = 261 (13) [M^+], 124 (100), 77 (30).

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(14) The pH value reported is that measured in the clear aqueous layer completely separated from the organic one. A pH meter equipped with a combined refillable pH electrode and with an autocompensating temperature control (ATC) probe was used.