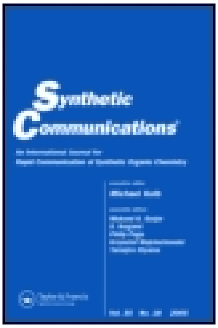

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Highly Efficient Aminolysis of Epoxides Catalyzed by Reusable Zirconyl Triflate, $ZrO(OTf)_2$

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Highly Efficient Aminolysis of Epoxides Catalyzed by Reusable Zirconyl Triflate, $ZrO(OTf)_2$

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Abstract: Efficient ring opening of epoxides with aromatic amines catalyzed by $ZrO(OTf)_2$ is reported, and the corresponding β amino (beta-amino acid) alcohols were obtained in high yields in CH_3CN as solvent. The reactions were carried out at room temperature and in the presence of only 1.25 mol% of $ZrO(OTf)_2$. This catalyst can be reused several times without loss of its activity.

Keywords: Aminolysis, epoxide, ring-opening, zirconyl triflate

INTRODUCTION

β-Amino alcohols are useful synthetic intermediates for the preparation of β-amino acids, natural products, and chiral auxiliaries. Therefore, synthesis of these compounds from epoxides and amines is an important reaction in medicinal and organic chemistry.[1,2] The classical and widely employed strategy for the synthesis of β-amino alcohols is the direct aminolysis of epoxides with an excess of amine at elevated temperature temperatures.[3] However, under these conditions less reactive epoxides or sluggish amines reacts slowly, and sensitive functional groups undergo undesirable side

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reactions. To overcome these problems, a variety of catalysts have been reported for the ring opening of epoxides with amines. These include $Sn(OTf)_2$,[4] $Cu(OTf)_2$,[4] $Bi(OTf)_3$,[5,6] $Al(OTf)_3$,[7] $TaCl_5$,[8] $InCl_3$,[9] $BiCl_3$,[10] VCl_3,[11] $ZrCl_4$,[12] $InBr_3$,[13] $CoCl_2$,[14] SmI_2,[15] $Sc(OTf)_3$,[16] montmorillonite K-10 and KSF,[17] LiOTf,[18] $Yb(OTf)_3$,[19] $Ln(OTf)_3$,[20] cyclodextrine,21 $Al(DS)_3 \cdot 3H_2O$,[22] $Cu(BF_4)_2$,23 $Zn(ClO_4)_2$,[24] heteropoly acids,[25–27] ionic liquids,[28] mesoporous aluminosilicate,[29] silica nanoparticles,[30] $MgBr_2 \cdot Oet_2$,[31] $SbCl_3$,[32] sulfated zirconia,[33] zirconium sulfophenylphosphonate,[34] and $Er(OTf)_3$.[35]

Some of these methods suffer from disadvantages such as the use of expensive or air-sensitive reagents, extended reaction times, the tedious workup procedures, or limited range of amines. Therefore, the introduction of new and efficient methods is still in demand.

Zirconium(IV) salts have recently attracted much attention because of their low cost, high catalytic activity, easy availability, and low toxicity. A variety of Zr(IV) salts have been used for several organic transformations.[36]

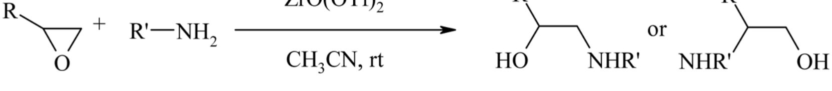
Here, we introduce an efficient room-temperature procedure for regioselective ring opening of various epoxides with aromatic amines catalyzed by reusable $ZrO(OTf)_2$ catalyst (Scheme 1).

EXPERIMENTAL

Chemicals were purchased from Fluka and Merck chemical companies. ^1H NMR spectra were recorded in $CDCl_3$ solvent on a Bruker AM 80-MHz or a Bruker AC 500-MHz spectrometer using TMS as an internal standard. Infrared spectra were run on a Philips PU9716 or Shimadzu IR-435 spectrophotometer. All analyses were performed on a Shimadzu GC-16A instrument with a flame ionization detector using silicon DC-200 or Carbowax 20M columns. $ZrO(OTf)_2$ was prepared according to the reported procedure.[37]

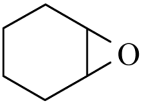
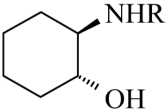
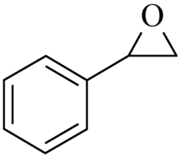
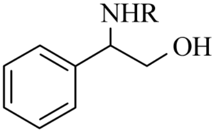
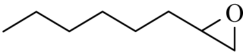
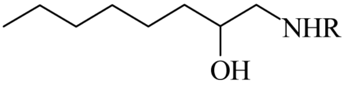
General Procedure for Aminolysis of Epoxides

$ZrO(OTf)_2$ (5 mg, 1.25 mol%) was added to a mixture of epoxide (1 mmol) and amine (2 mmol) in CH_3CN (2 mL) at room temperature,



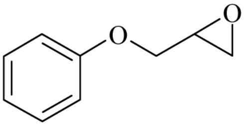
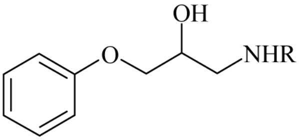
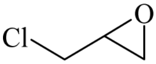
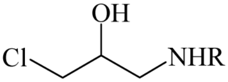
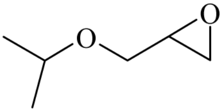
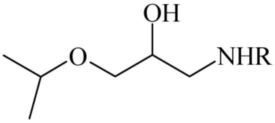
Scheme 1. Aminolysis of epoxides with amines catalyzed by $ZrO(OTf)_2$.

Table 1. Aminolysis of various epoxides catalyzed by $ZrO(OTf)_2$[a]

Entry	Epoxide	R-NH$_2$	Product/conversion (%)[b,c]
			
1		R = C_6H_5	92
2		R = 2-Cl C_6H_4	93
3		R = 2-$NO_2C_6H_4$	91
4		R = 4-$NO_2C_6H_4$	90
5		R = 4-MeC_6H_4	72
6		R = 2-MeC_6H_4	85
7		R = 3-$MeOC_6H_4$	84
8		R = 4-$MeOC_6H_4$	82
9		R = 2-$MeOC_6H_4$	82
			
10		R = C_6H_5	81
11		R = 2-ClC_6H_4	83
12		R = 2-$NO_2C_6H_4$	95
13		R = 4-$NO_2C_6H_4$	92
14		R = 4-MeC_6H_4	91
15		R = 2-MeC_6H_4	86
16		R = 3-$MeOC_6H_4$	91
17		R = 4-$MeOC_6H_4$	78
18		R = 2-$MeOC_6H_4$	82
			
19		R = C_6H_5	81
20		R = 2-ClC_6H_4	90
21		R = 2-$NO_2C_6H_4$	73
22		R = 4-$NO_2C_6H_4$	96
23		R = 4-MeC_6H_4	87
24		R = 2-MeC_6H_4	84
25		R = 3-$MeOC_6H_4$	81
26		R = 4-$MeOC_6H_4$	76
27		R = 2-$MeOC_6H_4$	96

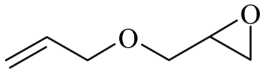
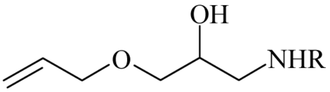
(*Continued*)

Table 1. Continued

Entry	Epoxide	R-NH_2	Product/conversion (%)^{b,c}
			
28		R = C_6H_5	90
29		R = 2-ClC_6H_4	92
30		R = 2-$NO_2C_6H_4$	92
31		R = 4-$NO_2C_6H_4$	87
32		R = 4-MeC_6H_4	98
33		R = 2-MeC_6H_4	85
34		R = 3-$MeOC_6H_4$	97
35		R = 4-$MeOC_6H_4$	97
36		R = 2-$MeOC_6H_4$	89
			
37		R = C6H5	91
38		R = 2-ClC_6H_4	90
39		R = 2-$NO_2C_6H_4$	88
40		R = 4-$NO_2C_6H_4$	92
41		R = 4-MeC_6H_4	93
42		R = 2-MeC_6H_4	88
43		R = 3-$MeOC_6H_4$	91
44		R = 4-$MeOC_6H_4$	93
45		R = 2-$MeOC_6H_4$	84
			
46		R = C_6H_5	90
47		R = 2-ClC_6H_4	92
48		R = 2-$NO_2C_6H_4$	84
49		R = 4-$NO_2C_6H_4$	83
50		R = 4-MeC_6H_4	92
51		R = 2-MeC_6H_4	91
52		R = 3-$MeOC_6H_4$	87

(*Continued*)

Table 1. Continued

Entry	Epoxide	R-NH_2	Product/conversion $(\%)^{b,c}$
53		R = 4-$MeOC_6H_4$	84
54		R = 2-$MeOC_6H_4$	91
			
55		R = C_6H_5	93
56		R = 2-ClC_6H_4	97
57		R = 2-$NO_2C_6H_4$	98
58		R = 4-$NO_2C_6H_4$	87
59		R = 4-MeC_6H_4	92
60		R = 2-MeC_6H_4	88
61		R = 3-$MeOC_6H_4$	86
62		R = 4-$MeOC_6H_4$	95
63		R = 2-$MeOC_6H_4$	80

[a] Reaction conditions: epoxide, 1 mmol; amine, 2 mL; catalyst, 5 mg, 1.25 mol%; and reaction time, 1 h.

[b] All products were identified by comparison of their physical and spectral data with those of authentic samples.[1–20]

[c] Yields refer to isolated products.

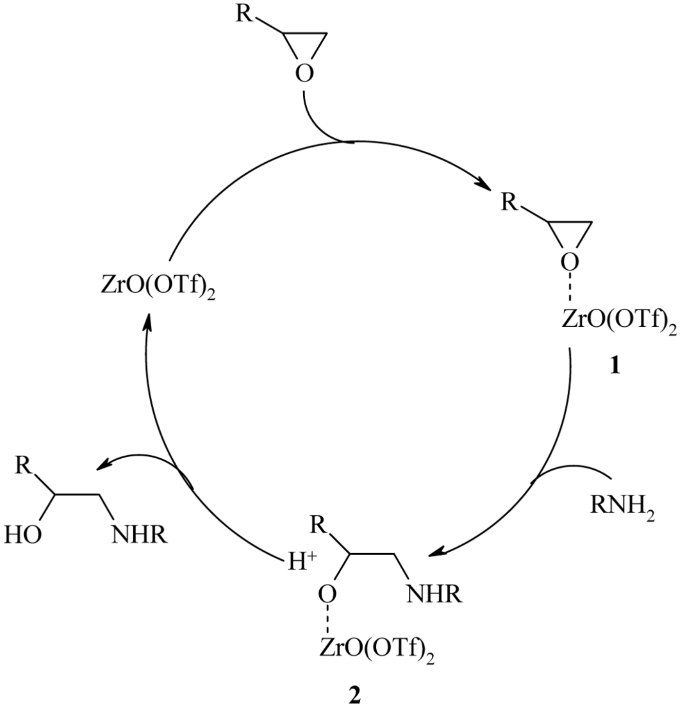
and the reaction mixture were stirred for 1 h. The reaction progress was monitored by thin-layer chromatography (TLC) or gas chromatography (GC). After the reaction was completed, the solvent was evaporated, Et_2O (20 mL) was added, and the catalyst was filtered. After that, the organic solution was dried ($MgSO_4$), concentrated, and chromatographed on a silica-gel column to furnish the pure β-amino alcohol.

RESULTS AND DISCUSSION

First, the ability of $ZrO(OTf)_2$ was investigated in the ring opening of cyclohexene oxide with aniline. The results showed that in the presence of catalytic amounts of $ZrO(OTf)_2$ (1.25 mol%) and at room temperature, 90% of amino alcohol (with *trans*-configuration, indicated by ^1H NMR) was obtained after 1 h in CH_3CN as solvent. The reaction was generalized to various aromatic amines. As shown in Table 1, the reaction was also efficient with other epoxides such as styrene oxide, 1,2-epoxyoctane, phenylglycidyl ether, and epichlorohydrine. In all cases, only one product was observed in the reaction mixture. Because of the predominant attack of amine on the less substituted carbon of epoxide, all terminal epoxides furnished highly regioselective β-amino alcohol in quantitative yields. In the aminolysis of styrene oxide, as a result of the formation of the stabilized benzylic cation, α-amino alcohol was produced. In the case of epichlorohydrine, in which an electron-deficient substituent is present in the epoxide structure, the aminolysis was performed efficiently, and the corresponding β-amino alcohol was obtained in excellent yield.

The actual mechanism of these reactions is not clear at present. However, a plausible explanation is that epoxide is first activated by the catalyst to afford **1**. This happens via coordination of Zr^{4+} with the oxygen of epoxide. This makes the epoxide susceptible to nucleophilic attack by the amine to give **2**, which in turn converts to the final product and releases the catalyst for the next catalytic cycle (Scheme 2). This probable mechanism was also reported previously.[12]

To show the applicability and efficiency of this method further, the results of the aminolysis of cyclohexane oxide with this catalyst has been compared with some of those recently reported. As can be seen in Table 2,



Scheme 2. Proposed mechanism for aminolysis of epoxides with amines catalyzed by $ZrO(OTf)_2$.

Table 2. Comparison of the obtained results for the aminolysis of cyclohexene oxide catalyzed by $ZrO(OTf)_2$ with those obtained by the recently reported catalysts

Entry	Catalyst	Catalyst amount (mol%)	Time (h)	Conversion (%)	TOF (h^{-1})	Ref.
1	$ZrO(OTf)_2$	1.25	1	92	73.6	—
2	$Sn(OTf)_2$	5	20	94	0.94	4
3	$Cu(OTf)_2$	5	30	95	0.63	4
4	$Bi(OTf)_3$	10	7	83	1.19	5, 6
5	$TaCl_5$	10	1	85	8.5	8
6	$InCl_3$	2	12	90	3.75	9
7	$BiCl_3$	10	—	84	—	10
8	$ZrCl_4$	5	0.25	100	80	12
9	$InBr_3$	5	12	84	1.4	13
10	SmI_2	10	18	75	0.42	15
11	Montmorillonite K-10	10% w/w	3	93	—	17
12	Montmorillonite KSF	10% w/w	24	100	—	17
13	Cyclodextrine	25	24	82	0.14	21
14	$Cu(BF_4)_2$	10	1/12	97	116.4	23
15	$(NH_4)_8[CeW_{12}O_{36}]$	4	0.5	100	50	25
16	$K_5[CoW_{12}O_{40}]$	5	3	93	6.2	26
17	$H_3PW_{12}O_{40}$	2	2	93	23.25	27
18	Aluminosilicate	120 mg	6	85	—	29
19	Silica nanoparticle	40 mg	0.25	88	—	30
20	$MgBr_2 \cdot OEt_2$	10	0.25	91	36.4	31
21	$SbCl_3$	10	7	85	1.22	33

all methods give 100% of the desired amino alcohol. Our method is superior to the most of the previously reported methods in terms of turnover frequency (TOF) and reusability.

The reusability of $ZrO(OTf)_2$ was also investigated in the aminolysis of cyclohexene oxide (5 mmol) with aniline. After the reaction was completed, Et_2O was added, and the catalyst was filtered and reused in another reaction. The results showed that the catalyst can be reused several times (four consecutive times were checked) without loss of its activity. (The amount of product was 89% at the end of fourth run with 100% selectivity.) The nature of the recovered catalyst was followed by Fourier transform infrared (FT-IR) spectroscopy. The results showed that after reusing the catalyst several times, no change was observed in its IR spectrum. To check the catalyst leaching, fresh epoxide and amine were added to the filtrates. The results showed that the amount of produced amino alcohol is comparable to the blank experiments (less than 5%).

In conclusion, we have found that $ZrO(OTf)_2$ is an efficient and reusable catalyst for ring opening of epoxides with a wide range of aromatic amines at room temperature in CH_3CN as solvent, and the corresponding β-amino alcohols were obtained in high to excellent yields.

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