$Bi(OTf)_3$-catalyzed Regioselective Ring Opening of Epoxides with Phenols: Facile Synthesis of 1,3-Diaryloxy-2-propanols

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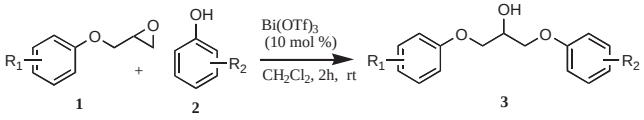
Substituted aryl oxiranes undergo the facile ring opening with phenols in the presence of catalytic amount of bismuth(III) triflate to afford 1,3-diaryloxy-2-propanols in excellent yields under mild conditions. Bismuth(III) triflate is relatively non-toxic, easy to handle and inexpensive, which makes this procedure particularly attractive for large scale synthesis.

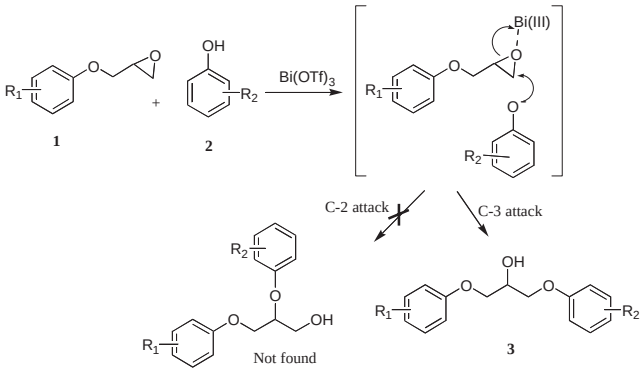
The regioselective ring opening of oxiranes with various nucleophiles is an important transformation and has wide applications in organic synthesis.[1] The chemo- and regioselectivity in the nucleophilic ring opening of oxirane depends on intrinsic and environmental factors.[2] The ring opening of terminal epoxides with phenols is the direct method for the synthesis of β-aryloxy alcohols, which are key intermediates in a variety of pharmaceutically important compounds.[3] However, it is believed that reaction of epoxides with oxygen nucleophile are rather difficult and therefore the epoxide ring opening with phenol is quite challenging. Although the reaction of oxiranes with aliphatic alcohols appears well documented in the literature, but oxirane ring opening with phenols has not been extensively studied.[4] Some of the known methods employ chiral metal complexes such as (Salen)–Co(III) complex,[5a,5b] (Salen)–Ti(IV) complex,[5c] and gallium heterobimetalic complexes[5d] but these methods have certain disadvantages viz. longer reaction time and employ expensive reagents. Epoxides have also been regioselectively opened with phenoxide ion under biomimetic conditions employing β-cyclodextrin in aqueous media[5e] and by using $Ce(OTf)_4$[5f] in micellar media. The ring opening of chiral glycidols with phenol was also reported using 5 mol % triethylamine in refluxing ethanol without serious racemization.[5g]

In recent years, bismuth(III) triflate attracted researchers for its wide range of applications for different type of transformations in organic synthesis.[6,7] Recently, bismuth(III) triflate was employed for the preparation of β-amino alcohols by epoxide ring opening with anilines.[6g] Bismuth(III) triflate is not available commercially but easily prepared in large quantity at a relatively lower cost.[7] In continuation to our ongoing research on the epoxide ring opening by different nucleophiles particularly through biocatalytic and biomimetic methods,[8] herein we wish to report the use of $Bi(OTf)_3$ as an efficient Lewis acid catalyst for the regioselective oxirane opening with different substituted phenols to obtain the corresponding 1,3-diaryloxy-2-propanols under mild reaction conditions (Scheme 1). Treatment of epoxide **1a** with phenol in the presence of catalytic amount of $Bi(OTf)_3$ in dichloromethane afforded the corresponding 1,3-diphenoxy-2-propanol **3a** in 96% yield. In a similar fashion, various aryl substituted oxiranes reacted smoothly with substituted phenols and gave corresponding 1,3-diaryloxy-2-propanols in excellent yields (Table 1). The aliphatic epoxide **1f** also gave the corresponding aryl ether **3m** in good yield (75%).



Scheme 1.

The high regioselectivity in the epoxide ring opening with bismuth(III) triflate can be explained by the in situ formation of complex between epoxide and bismuth(III) triflate, which undergoes S_N2 attack of phenols at less hindered C-3 carbon to give secondary alcohol exclusively (Scheme 2). In the present investigation among the various solvents examined for the epoxide ring opening with phenols, dichloromethane gave good results under these conditions. However, in the absence of bismuth(III) triflate the reaction did not proceed even under reflux conditions and prolonged reaction time (1 to 2 d).

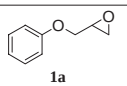
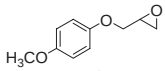
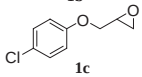
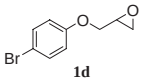
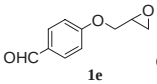
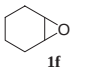


Scheme 2.

Various substituents in the phenyl ring did not effect the epoxide ring opening as both the electron donating and electron withdrawing substituents provided the secondary alcohols in good yields. In all the cases, the reaction proceeds spontaneously at room temperature giving only one regioisomers whereas the earlier reported methods afforded both the regioisomers employing $Ce(OTf)_4$ in micellar media.[5e] Interestingly, no rearranged products were formed under these conditions as reported in the earlier methods.[6c] Various substituted aryl oxiranes (**1a**–**1f**) were prepared quantitatively by treating corresponding phenols with epichlorohydrin in sodium hydroxide with the reported method.[8d]

In conjunction with our earlier studies[10] on the enzymatic resolution of various biologically important compounds including secondary alcohols employing different lipases, it was considered worthwhile, to attempt the resolution of 1,3-diaryloxy-

Table 1. $Bi(OTF)_3$ catalyzed synthesis of 1,3-diaryloxy-2-propanols[9]

Epoxide (**1**)	Phenol (**2**)	Product[a] (**3**)	Yield[b]/%
 **1a**	C_6H_5OH	**3a** Ar = C_6H_5	96
	p-Cl-C_6H_4OH	**3b** Ar = *p*-Cl-C_6H_4	88
	p-NO_2-C_6H_4OH	**3c** Ar = *p*-NO_2-C_6H_4	84
 **1b**	C_6H_5OH	**3d** Ar = C_6H_5	94
	p-Cl-C_6H_4OH	**3e** Ar = *p*-Cl-C_6H_4	86
 **1c**	C_6H_5OH	**3f**	84
 **1d**	C_6H_5OH	**3g** Ar = C_6H_5	86
	p-OMe-C_6H_4OH	**3h** Ar = *p*-OMe-C_6H_4	88
	α-$C_{10}H_7OH$	**3i** Ar = α-$C_{10}H_7$	92
 **1e**	C_6H_5OH	**3j** Ar = C_6H_5	91
	p-Cl-C_6H_4OH	**3k** Ar = *p*-Cl-C_6H_4	87
	p-NO_2-C_6H_4OH	**3l** Ar = *p*-NO_2-C_6H_4	85
 **1f**	C_6H_5OH	**3m**	75

[a]All products were characterized by ^1H NMR, IR, and mass spectroscopy. [b]Yields refers to pure product after column chromatography.

2-propanols by employing lipases. It was observed that lipase-mediated transesterifications employing various lipases and solvents under different conditions offered the corresponding alcohols and acetates in low enantioselectivities (<40%ee). The insignificant enantioselectivity for these substrates is probably due to the steric factor at the asymmetric centre. However, 1,3-diaryloxypropanols **3** have been synthesized in high enantiopurity by employing bismuth(III) triflate and the corresponding chiral epoxide precursors **1**. The chiral epoxides for this purpose were obtained by lipase (PS-C) mediated resolution of the corresponding chlorohydrins with 80–95%ee.[11]

In summary, we have described a facile and practical method for the epoxide ring opening with substituted phenols using catalytic amount of $Bi(OTf)_3$ under mild reaction conditions. High regioselectivity, spontaneity, experimental simplicity, and quantitative yields make this procedure an attractive alternative over the conventional methods for the synthesis of biologically important 1,3-diaryloxy-2-propanols.

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9 General Procedure for the Synthesis of 1,3-diaryloxy-2-propanols: A mixture of 1-aryloxy-2,3-epoxypropane **1** (1 mmol), $Bi(OTf)_3$ (0.1 mmol) and phenol **2** (1.2 mmol) in dichloromethane (10 mL) was stirred at room temperature for 2 h. After completion of the reaction as indicated by TLC, the reaction mixture was diluted with dichloromethane and washed with saturated $NaHCO_3$ (10 mL) followed by brine solution. The organic layer was separated, dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel using ethyl acetate:hexane (1:9) to afford the pure 1,3-diaryloxy-2-propanols. The spectroscopic data of all the products were identical with data reported in literature.[5e] Spectral data for selected products, **3a**: IR (KBr) 3490 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.8 (1H, brs), 4.0–4.2 (4H, m), 4.2–4.5 (1H, m), 6.9–7.1 (6H, m), 7.2–7.4 (4H, m); EI Mass (*m*/*z*): 244 (M^+); Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60%. Found: C, 73.35; H, 6.39%. **3k**: IR (KBr) 3450 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.6 (1H, brs), 4.0–4.3 (4H, m), 4.4–4.5 (1H, m), 6.84 (2H, d, J = 8.92 Hz), 7.0 (2H, d, J = 8.92 Hz), 7.24 (2H, d, J = 8.92 Hz), 7.83 (2H, d, J = 8.92 Hz), 9.9 (1H, brs); EI Mass (*m*/*z*): 306 (M^+); Anal. Calcd for $C_{16}H_{15}ClO_4$: C, 62.65; H, 4.93%. Found: C, 62.53; H, 4.76%.

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11 Spectral data for epoxide **1b**: mp 43 °C; 96%ee (*S*)-**1b**, 80%ee (*R*)-**1b**; (HPLC analysis DAICEL CHIRALCEL OD column (0.46 × 25 cm); eluent: hexane/isopropanol = 90/10; flow rate: 0.7 mL/min.; detector: 254 nm.); $[\alpha]_D^{25}$ (*S*)-**1b** +11.66 (*c* 0.6, MeOH) [lit.[12] +11.04 (*c* 1.08, MeOH) 96%ee], $[\alpha]_D^{25}$ (*R*)-**1b** −10.72 (*c* 1, MeOH) [lit.[12] −11.72 (*c* 1.06, MeOH) 100%ee] IR (Neat) 3425, 2100 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.6–2.7 (1H, m), 2.8–2.9 (1H, m), 3.2–3.3 (1H, m), 3.7 (3H, s), 3.9 (1H, dd, J = 10.98, 5.12 Hz), 4.1 (1H, dd, J = 10.98, 3.66 Hz), 6.7–6.9 (4H, m); EI Mass (*m*/*z*): 178 (M^+); Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71%. Found: C, 66.53; H, 6.64%.

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