Bis(cyclopentadienyl)zirconium dichloride: an efficient catalyst for highly selective formation of β-alkoxy alcohols via ring opening of 1,2-epoxides with alcohols

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Bis(cyclopentadienyl)zirconium dichloride catalyzed ring-opening reactions of epoxides derived from styrene, cyclohexene, norbornene and stilbene, in the presence of primary, secondary, tertiary, cyclohexyl, allyl and propargyl alcohols, resulted in the formation of β-alkoxy alcohols in good to excellent yields with high regio- and stereoselectivity.

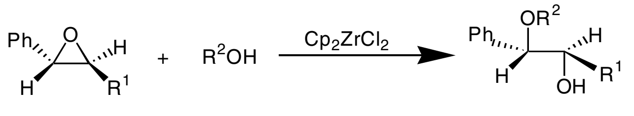
KEY WORDS: *bis*(cyclopentadienyl)zirconium dichloride; ring opening of epoxide; β-alkoxy alcohol; stereoselectivity.

1. Introduction

Transformation of epoxides to 1,2-disubstituted products is one of the important processes in organic synthesis. The strain of the three-membered ring together with the polarization of the C–O bond of epoxides make them susceptible to reaction with a large variety of nucleophilic reagents [1]. Various approaches have been made to obtain β-alkoxy alcohols, which serve as valuable intermediates for α-alkoxy ketones, α-alkoxy acids and natural products [2]. The common protocol for synthesis of β-alkoxy alcohols is the ring opening of 1,2-epoxides with appropriate alcohols under acidic or basic conditions, the alcohol itself being the reaction solvent.

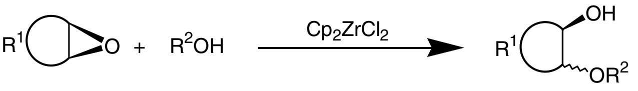
However, the yields are not always satisfactory and the reaction needs high temperatures, which consequently results in extensive polymerization and low regioselectivity [3]. Many reagents [4] have been reported as effective catalysts or promoters for the alcoholysis of epoxides under mild conditions. However, the reported procedures have limitations in terms of high reaction temperature, critical handling of catalysts, tedious workup procedures and unsatisfactory selectivity, thereby restricting their widespread applicability.

Zirconocenes have hitherto been exclusively used in polymerization reactions [5]. We report in this paper the highly efficient *bis*(cyclopentadienyl)zirconium dichloride (Cp_2ZrCl_2) catalyzed ring-opening reaction of 1,2-epoxides derived from styrene, cyclohexene, norbornene and stilbene, in the presence of primary, secondary, tertiary, cyclohexyl, allyl and propargyl alcohols, resulting in the formation of β-alkoxy alcohols in good to excellent yields with high regio- and stereoselectivity. (equations (1) and (2)).



1a-1b **2a-2i** **3a-3j**

(1)



1c-1d **2a-2b** **3k-3m**

(2)

2. Experimental

2.1. Preparation of the catalyst

The catalyst *bis*(cyclopentadienyl)zirconium dichloride was synthesized following the reported literature procedure [6]. Sodium metal (2.4 g, 0.1 mol) was dispersed in 15 mL of toluene at 115 °C to obtain particle size ca. 50 μ under a blanket of nitrogen. To this dispersion, the cyclopentadiene monomer (10 mL, 0.12 mol) was added dropwise at 0 °C over a period of 15 min and then allowed to stir at room temperature for 4 h under nitrogen atmosphere to obtain sodium cyclopentadienide. A suspension of zirconium tetrachloride (11.6 g, 0.05 mol) was prepared by using dry THF (10 mL) in a nitrogen atmosphere, and the formed sodium cyclopentadienide was added to it dropwise

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over a period of 20 min and then allowed to stir for 4 h. The reaction mixture was concentrated by rotavapor and the solid obtained was subjected to Soxhlet extraction with chloroform, saturated with HCl gas, for 6 h. The chloroform extract was concentrated to ca. 10 mL and crystallized at −30 °C (dry ice/acetone) to get *bis*(cyclopentadienyl) zirconium dichloride (9.1 g, 62% yield). m.p. 243–245 °C (lit. m.p. 242–245 °C). ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.45 (s, 10 H) [7].

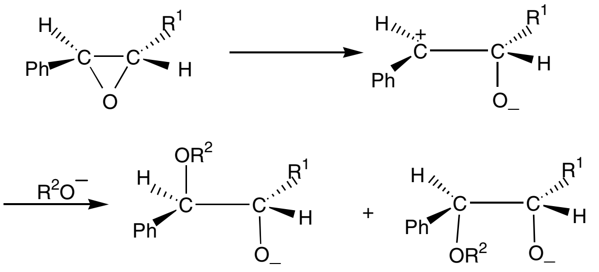
2.2. *A typical experimental procedure for ring opening of epoxides with alcohols*

In a typical run, styrene epoxide **1a** (120 mg, 1.0 mmol) was added to a stirred solution of *bis*(cyclopentadienyl)zirconium dichloride (4 mg, 1.4 mol% based on epoxide) in dry methanol **2a** (3.0 mL). The stirring was continued at the reaction temperature for the required period (monitored by TLC). The reaction mixture was concentrated using rotavapor and the residual mass was extracted with diethyl ether, concentrated and purified by column chromatography (silica gel 60–120 mesh, petroleum ether/ethyl acetate 9 : 1 as eluent) to give the product **3a** (146 mg, 96% Yield). ^{1}H NMR (200 MHz, $CDCl_3$) of **3a**, δ 7.2–7.4 (m, 5H), 4.25 (dd, 1H, J = 10.25 and 5.12 Hz), 3.5–3.6 (m, 2H), 3.2 (s, 3H), 2.4 (br, OH); EIMS e/z: 152. The isolated yields are calculated on the basis of the weight of the pure product obtained.

3. Results and discussion

The results obtained with some representative epoxides are summarized in table 1. Table 1 shows that in the presence of a catalyst with concentration as small as 1.4 mol%, the styrene epoxide **1a** undergoes facile reaction with various classes of alcohols, namely, aliphatic 1°, 2° and 3° alcohols **2a–2f**, cyclic alcohol **2g** and unsaturated alcohols **2h, 2i** to afford 2-alkoxy-2-phenyl ethanols **3a–3i** with excellent to good yields. Products **3a–3i** are identified as 2-alkoxy-2-phenyl ethanol by oxidation to the corresponding aldehyde, which demonstrates that the epoxide **1a** undergoes a regioselective ring opening under the influence of the catalyst (equation (1)). The benzylic cation, being far more stabilized than the primary carbocation [8], becomes the favorable site for the nucleophilic attack, thus giving rise to the formation of 2-alkoxy-2-phenyl ethanol **3a-3i** with essentially high regioselectivity. In the absence of Cp_2ZrCl_2, when the reaction is performed under identical conditions, **1a** is recovered entirely unreacted (entry 14).

Disubstituted, alicyclic as well as bicyclic epoxides **1b, 1c** and **1d** undergo facile reaction to yield the corresponding β-alkoxy alcohols (entry 10–13). In the case of *trans*-stilbene oxide **1b**, the product **3j** is obtained as a mixture of two diastereoisomers in the racemic form with a modest diastereoselectivity, as determined by ^{1}H NMR [9] (threo : erythro = 85 : 15, entry 10). The formation of two diastereoisomers is indicative of a



Scheme 1.

Table 1
Cp_2ZrCl_2-catalyzed reaction of 1,2-epoxides with alcohols to form β–alkoxy alcohols[a]

Entry	R^1	R^2	Time (h)/ temp.(°C)	Product[b]	Yield[c] (%)
1	H	Methyl	6/rt	**3a**	96
2	H	Ethyl	24/rt	**3b**	91
3	H	*n*-Propyl	24/rt	**3c**	81
4	H	*i*-Propyl	31/50	**3d**	82
5	H	*n*-Butyl	33/90	**3e**	96
6	H	*t*-Butyl	24/60	**3f**	90
7	H	Cyclohexyl	24/rt	**3g**	82
8	H	Allyl	27/rt	**3h**	71
9	H	Propargyl	24/rt	**3i**	80
10	Phenyl	Methyl	18/rt	**3j**	84
11	Cyclohexyl	Methyl	22/rt	**3k**	91
12	Cyclohexyl	Ethyl	22/rt	**3l**	90
13	Exo-norbornyl	Methyl	24/rt	**3m**	69
14	H	Methyl	24/rt	**3a**	0

[a] Reaction conditions: epoxide (1.0 mmol), alcohol (3 mL).

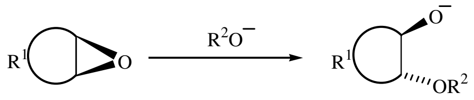
[b] Products are characterized on the basis of ^{1}H NMR and mass.

[c] Isolated yield on the basis of the weight of the pure product obtained.

dissociative mechanism (scheme1) and rules out the S_N2 mechanism.

Reactions following an S_N1 mechanism involve the formation of an intermediate carbonium ion, and since the three bonds attached to the central carbon atom of a carbonium ion are coplanar, the reagent can attack from either side to give a mixture of products (scheme 1). Similarly, the product obtained from the reaction of norbornene epoxide **1d** with MeOH resulted in a mixture of *exo*- and *endo*-methoxy isomers in the ratio 50 : 50, as determined by ^{1}HNMR. These results are an obvious consequence of the involvement of a carbocation intermediate [10,11].

On the other hand, a facile reaction of cyclohexene epoxide **1c** with alcohols **2a** and **2b** affords *trans*-hydroxy ethers **3k** and **3l** in excellent yields signifying that the reaction is highly anti-stereoselective (equation (2)). The stereochemical evidence revealed that the inversion of configuration is expected as a result of an S_N2 mechanism because of the approach of the reagent on the side remote from the displaced group (scheme 2).



Scheme 2.

Low yields with unsaturated alcohols (entry 9) are due to the formation of unidentified side product. Steric effects are responsible for lower yields in case of norbornene epoxide (entry 13).

4. Conclusions

In conclusion, a simple highly efficient method for the preparation of β-alkoxy alcohols is presented via regio- and stereoselective ring opening of 1,2-epoxides by using Cp_2ZrCl_2 as a catalyst. The procedure is applied successfully to unsaturated alcohols and is expected to be safe for substrates that contain sensitive functionalities.

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