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Copper(II) Tetrafluoroborate Catalyzed Ring-Opening Reaction of Epoxides with Alcohols at Room Temperature

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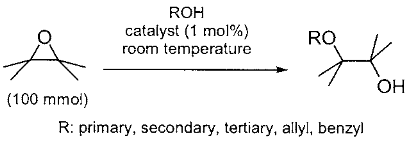
ABSTRACT



Efficient ring opening of different epoxides by reaction with representative alcohols is presented. These processes were carried out at room temperature and rely on the usefulness of commercial copper tetrafluoroborate as catalyst.

Alcohols behave as poor nucleophilic reagents in substitution processes. Nevertheless, under strongly acidic or basic conditions[1] their use for ring-opening reactions of epoxides[2] is well established and provides a powerful entry to β-alkoxyalcohols.[3] The harsh conditions associated with those procedures have spurred a search for new and mild methodologies. Major attempts have focused on testing different heterogeneous conditions. Significant advances have been accomplished; however, the reported scope of this approach is constrained at room temperature to only primary alcohols.[4] Thus, there is ongoing activity aimed to establish a more general, simple, and efficient catalytic protocol to accomplish this transformation.[5] Herein, we report on the use of commercial hydrated copper(II) tetrafluoroborate as a more suitable and convenient catalyst to induce ring-opening reactions of epoxides by incorporation of a set of representative alcohols, in all cases at room temperature.

Our initial studies showed that $Cu(BF_4)_2{\cdot}nH_2O$ (**1**) is an adequate catalyst for the ring opening of cyclohexene oxide **2** by methanol **3**. A single adduct, *trans*-2-methoxycyclohexanol **4**[6] (71% isolated yield) was obtained upon reaction for 1 h at room temperature of **2** (5 mmol) with **3** (20 mL), in the presence of 10 mol % of the catalyst. Interestingly, further experiments showed that the amount of both alcohol and catalyst can be lowered without affecting the performance of the process at room temperature. Overall, these facts establish a sharp difference with respect to the already reported features of alternative methodologies. The process can be efficiently conducted on a 100 mmol basis of **2**, using 1 mmol of catalyst (0.01 equiv with respect to **2**). The

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[2] For a review, see: Smith, J. G. *Synthesis* **1984**, 629−656.

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[6] All the reported ring-opened epoxide derivatives gave analytical and spectroscopic data in agreement with the proposed structures.

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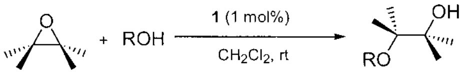
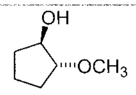
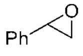
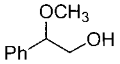
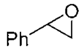
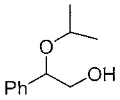
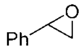
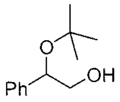
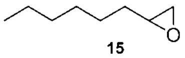
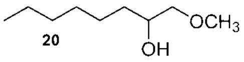
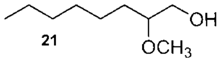
Table 1. Room-Temperature Alcoholysis of Epoxides Catalyzed by $Cu(BF_4)_2 \cdot nH_2O$ (**1**)

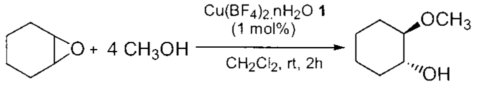


Entry	Epoxide[a]	Alcohol[b]	Time (h)	Product	Yield (%)[c]
1	 **13**	CH_3OH **3**	2	 **16**	94
2	 **14**	CH_3OH **3**	2	 **17**	95
3	 **14**	$(CH_3)_2CHOH$ **7**	3.5	 **18**	69[d]
4	 **14**	$(CH_3)_3COH$ **8**	12	 **19**	87[e]
5	 **15**	CH_3OH **3**	33	 **20**  **21**	60[f] (65)[g]

[a] 25 mmol of epoxide was used. [b] 4 equiv of alcohol was used per equiv of epoxide [c] Based on isolated compounds and referred to epoxide. [d] 20% of unreacted **14** was recovered. [e] **19** was obtained in near 70% yield upon reaction for 6 h. [f] Combined yield from isolated amounts of pure **20** (34%) and **21** (26%), after separation by column chromatography on silica gel (hexane/ethyl acetate 10/1, as eluent). [g] Based on GC analysis of the crude reaction mixture, for 1.3:1 molar ratio **20**:**21**, respectively.

reaction has been optimized using a 1:4 molar ratio of **2**:**3**,[7] to yield **4** in nearly quantitative isolated yield (Scheme 1) after reacting for 2 h at room temperature in CH_2Cl_2 (60 mL).

Scheme 1. Optimized Conditions for the $Cu(BF_4)_2 \cdot nH_2O$-Catalyzed Ring-Opening Methanolysis of Cyclohexeneoxide



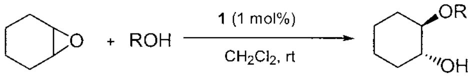
2 (100 mmol) **3** **4** (99%)

The influence of the substitution pattern on the alcohol was tested, and the results are summarized in Scheme 2. Along this series,[8] 25 mmol of epoxide **2** was subjected to reaction under the conditions above outlined for methanol.

These results nicely prove that derivatives of labile primary alcohols, such as benzylic and allylic systems, are easily prepared following this approach. Similarly, compounds incorporating more hindered hydroxyl functionalies are conveniently synthesized through this mild and simple approach. In each case, products were obtained as single diastereoisomer having *trans* stereochemistry.

The influence of the epoxide over the outcome of the reaction was also tested (see Table 1). Linear epoxides **14** and **15** give information about the regiochemistry of the opening reaction. The epoxide **14** led always to the formation of one regiosomer, incorporating the alcohol at the phenyl-

Scheme 2. Alcohol Compatibility



2 (**5**-**8**) (**9**-**12**)

ROH		time (h)	adduct
R: CH_2=$CHCH_2$	**5**	2	**9** (90%)
R: $C_6H_5CH_2$	**6**	2	**10** (95%)
R: $(CH_3)_2CH$	**7**	3	**11** (91%)
R: $(CH_3)_3C$	**8**	4	**12** (94%)

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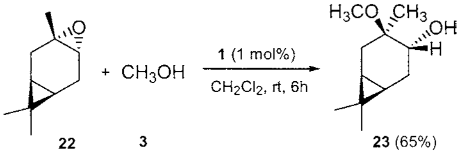
(7) The use of lower values of alcohol-to-epoxide ratio gave rise to competitive formation of several epoxide oligomers. Thus, when the reaction was run adding 2 equiv of **3** per equiv of **2**, adduct **4** was isolated in 40% yield; in addition, a compound of formula HO-C_6H_{10}-O-C_6H_{10}-OCH_3 was isolated in 10% yield, along a mixture of several other oligomers.

(8) One mole percent of **1** and 20 mL of CH_2Cl_2 were routinely employed.

substituted carbon, irrespectively of the nature of the alcohol, as expected for a charge-controlled ring-opening process.[9] However, for the alkyl-substituted system **15**, two adducts were obtained upon reaction with methanol in the presence of **1**.[10] Products **20** and **21**were formed at room temperature in a 1.3:1 molar ratio, respectively. They reflect the expected competition of opening pathways for this type of epoxide.[11] The reaction temperature was tested in an attempt to modulate the regiochemistry of the process. At −40 °C a more sluggish reaction takes place, requiring longer reaction time to be completed, but without major impact over the selectivity.

Furthermore, the reaction of an enantiopure epoxide derived from the chiral pool was tested (Scheme 3). Epoxide **22** was prepared from commercial (+)-3-carene in one step[12] and subjected to reaction with methanol under the general conditions already established. It is also a challenging substrate that proves the opening of a more substituted epoxide. Upon reaction for 6 h at room temperature, the formation of **23** as sole reaction product in 65% isolated yield was noticed (on a 4 mmol basis of **22**, using 1:4 molar ratio of **22**:**3**).

Scheme 3. Derivatives from (+)-3-Carene



The assigned structure for **23** is based on its analytical and spectroscopic data. 2D-HMQC, 2D-HMBC, and NOESY experiments were determinant to establish the regiochemistry and to elucidate the stereochemistry. The observed stereochemistry bodes well with that previously reported for ring-opening reactions of **22** by water, and more recently by morpholine.[13]

In summary, an efficient method at room temperature for the ring-opening reaction of epoxides by a wide set of representative alcohols is reported. The procedure takes place under very mild conditions and relies simply on the addition of catalytic amounts of a cheap and commercial copper salt. The process is easily able to transform 0.1 mol of epoxide, features a nice and predictable selectivity, and eventually might have additional interest to broach new approaches to the as yet elusive enantioselective desymmetryzation[14] reaction of achiral epoxides with alcohols.[15] Work is in progress to explore this possibility.

Acknowledgment. We thank Spanish DGES (PB97-1271) for financial support.

Supporting Information Available: General experimental procedure, characterization data (copies of ^{1}H and ^{13}C NMR spectra of β-alkoxyalcohols reported), and full characterization data for compound **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) The fact that **15** reacts under these conditions establishes a marked contrast with the previously noticed unreactivity of alkyl-substituted terminal epoxides in copper(II)-catalyzed opening reaction in the presence of acetone at 60 °C; see: Hanzlik, R. P.; Leinwetter, M. *J. Org. Chem.* **1978**, *43*, 438−440.

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(12) For the preparation of **22** and studies on its ring opening by water, see: Brown, H. C.; Suzuki, A. *J. Am. Chem. Soc.* **1967**, *89*, 1933−1941.

(13) For the $MgBr_2$-promoted reaction, the amino alcohol derivative obtained also holds a *trans* relationship for these two functional groups; however, the opposite regioisomer was formed. See: Kauffman, G. S.; Harris, G. D.; Dorow, R. L.; Stone, B. R. P.; Parsons Jr., R. L.; Pesti, J. A.; Magnus, N. A.; Fortunak, J. M.; Confalone, P. N.; Nugent, W. A. *Org. Lett.* **2000**, *2*, 3119−3121.

(14) For reviews, see: (a) Hodgson, D. M.; Gibbs, A. R.; Lee, G. P. *Tetrahedron* **1996**, *52*, 14361−14384. (b) Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421−431.

(15) For the first examples of intermolecular kinetic resolution of epoxides with alcohols catalyzed by metal complexes, see: Ready, J. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 2687−2688. For related recent work, see: Ready, J. M.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2002**, *41*, 1374−1377.