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Radicals from Epoxides. Intramolecular Addition to Aldehyde and Ketone Carbonyls[†]

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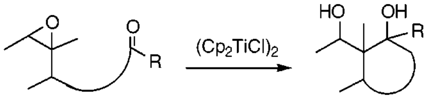
ABSTRACT



Titanocene chloride reacts with epoxides by C–O homolysis with clean regioselectivity. The resultant radicals undergo intramolecular addition to aldehyde and ketone carbonyls to afford cycloalkanols in good yields. The behavior of epoxy alcohols with titanocene chloride to afford saturated diols and epoxy esters that give unsaturated hydroxy esters deserve special mention.

Selective one-electron reduction of an epoxide to a radical intermediate promoted by titanocene chloride and the subsequent radical trapping reaction represents a valuable synthetic tool that has been used in deoxygenations, reductions, and intra- and intermolecular carbon−carbon bond-forming reactions.[1] No references to the addition of these radicals to the carbonyl group are known. Although the intramolecular radical addition to a carbonyl group is a potentially useful process for the synthesis of cycloalkanols, it was not until recently that this reaction attracted the attention of organic chemists. Recent rate studies by Beckwith and Hay[2] have shown that ring closure of radicals A and B is slower than the ring openings of the alkoxy radical counterparts A′ and B′ (Figure 1).[1b] Since alkoxyl radicals A′ and B′ are much less stable than the starting carbon radical A and B in reactions 1−2, it is necessary to prevent the β-fragmentation from trapping the former alkoxy radical if cyclization is the desired pathway. This has been partially achieved in different ways, always generating the initial carbon radical by tributyltin hydride.[3] There are no kinetic

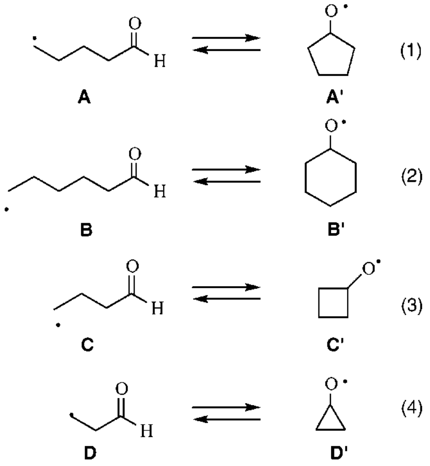


Figure 1. Intramolecular addition to carbonyl group of carbon radical and ring opening of alkoxy radicals.

[†] In respectful memory of the late Professor D. H. R. Barton.

(1) (a) Nugent, W. A.; RajanBabu, T. V. *J. Am. Chem. Soc.* **1994**, *116*, 986. (b) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon: Oxford, 1991; Vol. 4, p 815. (c) Gansaüer, A.; Pierobon, M.; Bluhm, H. *Angew. Chem., Int. Ed.* **1998**, *37*, 101. (d) Gansaüer, A. *Synlett* **1998**, 801.

(2) Beckwith, A. L. J.; Hay, B. P. *J. Am. Chem. Soc.* **1989**, *111*, 230, 2674.

(3) (a) Tsang, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1986**, *108*, 8102. (b) Chang, S. Y.; Jiaang, W. T.; Cherng, C. D.; Tang, K. H.; Huang, C. H.; Tsai, Y. M. *J. Org. Chem.* **1997**, *62*, 9089. (c) Curran, D. P.; Diederichsen; U.; Palovich, M. *J. Am. Chem. Soc.* **1997**, *119*, 4797. (d) Kim, S.; Jon, S. Y. *J. Chem. Soc., Chem. Commun.* **1996**, 1335.

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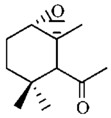
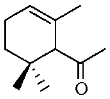
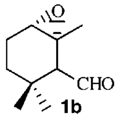
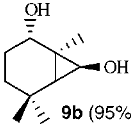
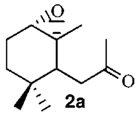
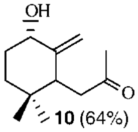
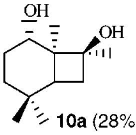
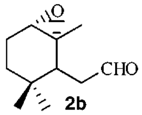
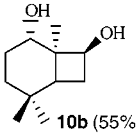
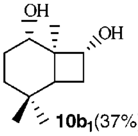
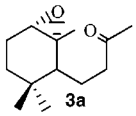
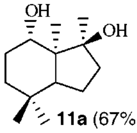
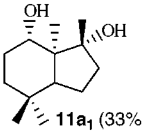
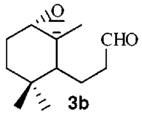
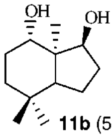
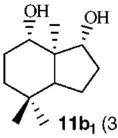
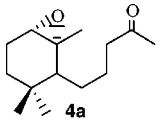
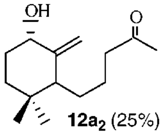
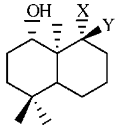
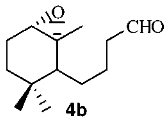
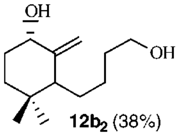
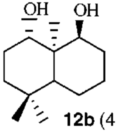
Table 1. Cycloalkanols from Oxo Epoxide

Epoxide	Products Yield (%)		Cycloalkanol isomer ratio
 **1a**	 **9a** (100%)		
 **1b**	 **9b** (95%)		9b (all)
 **2a**	 **10** (64%)	 **10a** (28%)	10a (all)
 **2b**	 **10b** (55%)	 **10b$_1$**(37%)	10b/10b1 3:2
 **3a**	 **11a** (67%)	 **11a$_1$** (33%)	11a/11a$_1$ 2:1
 **3b**	 **11b** (58%)	 **11b$_1$** (38%)	11b/11b$_1$ 3:2
 **4a**	 **12a$_2$** (25%)	 **12a** X= Me Y= OH (48%) **12a$_1$** X=OH Y= Me (11%)	12a/12a$_1$ 4:1
 **4b**	 **12b$_2$** (38%)	 **12b** (46%)	12b (all)

data for reactions 3 and 4, although it is assumed that the ring openings C′ → C and D′ → D will be much faster than the ring closures C → C′and D → D′, in the same manner as described for reactions 1 and 2. There are known examples of the D → D′ cyclization depicted in the reaction 4.[4] However, the cyclopropyloxy radical D′ has not been trapped to afford a cyclopropanol derivative but rather has given through β-fragmentation other kind of products.[4] We have not found any reaction corresponding to C → C′ cyclization in the literature.

Our interest in the chemistry of titanocene chloride was triggered by our attempts at the deoxygenation of epoxides in the presence of other functional groups. However, our initial interest declined after we found that the radicals obtained by the reductive opening of some oxo epoxides were cyclized to diols.

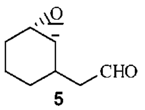
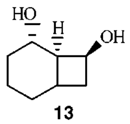
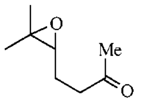
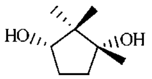
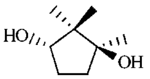
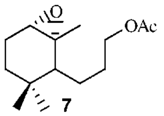
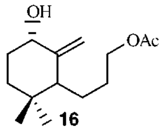
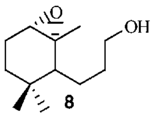
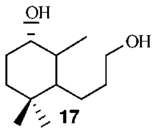
The reactions of a series of difunctional epoxides were carried out by the addition of a THF solution of the epoxide to a solution of Cp_2TiCl in THF, generated in situ from Cp_2TiCl_2 and zinc at room temperature.[1a] Test substrates **1**−**4**, **7**, and **8** were obtained from α-cyclocitral[5] by procedures to be described elsewhere. Epoxides **5** and **6** were obtained by epoxidation of comercial unsaturated aldehyde or ketone.

Treatment of epoxy ketone **1a** generated the expected unsaturated ketone **9a** in 100% yield. Surprisingly, the epoxy aldehyde **1b** afforded only the diol **9b** in 95% yield.[6]

Compounds **2a**,**b** were used to explore the possibility of cyclobutanol formation. Epoxy ketone **2a** afforded a mixture of two compounds in 92% yield, the major compound being the unsaturated hydroxy ketone **10** and the minor one the diol **10a**. By contrast, the epoxy aldehyde **2b** gave a mixture of the epimeric bicyclic diols **10b** and **10b$_1$** at a ratio of 3:2 in 92% yield (Table 1).

In the series of compounds **3a**,**b**, the formation of cyclopentanols was the only reaction observed. From **3a**, a 2:1 mixture of epimeric bicyclic diols **11a/11a$_1$** was obtained in 100% yield. A similar result was found with **3b**, a 3:2 mixture of diols **11b/11b$_1$** in 96% yield.

Table 2. Cycloalkanols from Oxo Epoxide

Epoxide	Products		Yield (%)
 **5**	 **13**		75%
 **6**	 **15a**	 **15b**	86%
 **7**	 **16**		100%
 **8**	 **17**		100%

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[4] Dowd, P.; Zhang, W. *Chem. Rev.* **1993**, *93*, 2091.

[5] Gedye, R. N.; Aura, P. C.; Deck, K. *Can. J. Chem.* **1971**, *49*, 1764.

[6] All compounds synthesized are racemic, although only one enantiomer is depicted. The relative configuration of the newly created stereocenters has been tentatively assigned.

Finally, in this series, the epoxy ketone **4a** afforded a three-product mixture in 84% yield. The major component was an epimeric mixture of the bicyclic diols **12a**/**12a$_1$** in a ratio of 4:1. The minor component was identified as the unsaturated hydroxy ketone **12a$_2$**. The epoxy aldehyde **4b** gave two products in 84% yield. The major product was the bicyclic diol **12b**, and the minor one the monocyclic unsaturated diol **12b$_2$**.

The epoxy aldehyde **5** served as a test to probe the regioselectivity cleavage of a disubstituted epoxide (Table 2). The reaction with Cp$_2$TiCl afforded exclusively the bicyclic system [4.2.0] represented by the diol **13** in 75% yield.

The regioselectivity cleavage of the trisubstituted epoxide **6**, with a different skeleton with respect to the examples seen before, remains invariable. The reaction of **6** with Cp$_2$TiCl provided a 1:1 mixture of epimeric diols **15a** and **15b** in 86% yield. It is interesting to note that the hydroxy group arising from the epoxide lies within the newly formed ring.

Although a more indepth study of the reaction mechanism is required, most of the above experiments provide evidence that a radical addition to carbonyl is involved (Figure 2).

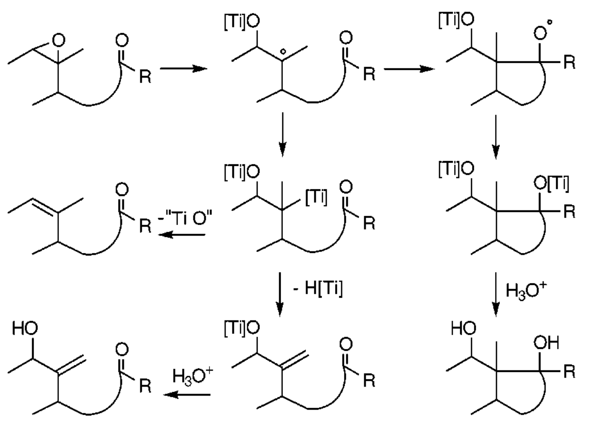
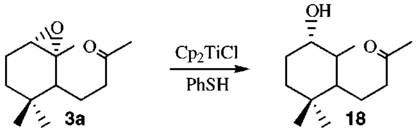


Figure 2. Reaction mechanism of Ti(III) with epoxy ketone.

The alternative ionic mechanism would be less probable. If the initial radical generated by the homolytic cleavage of the epoxide were reduced to the anion, a β-elimination of a titanium-oxo moiety to the corresponding olefin would occur.[1a] A similar elimination has been described by Molander for similar compounds reacting with samariun diiodide.[7] This ionic mechanism seems to operate only in the epoxy ketone **1a** because of the impossibility of achieving radical addition to the carbonyl, due to steric hindrance; for the compounds **2a**, **4a**, and **4b**, in addition to the radical cyclization a competitive reduction of the tertiary radical to the alkyl titanium species followed by β hydrogen elimination is the main side reaction. A similar elimination has been described by Molander for a tertiary alkyl iodide with samariun diiodide.[8]

Two other compounds, **7** and **8**, were subjected to the titanocene chloride treatment to explore the scope of the reaction. The epoxy acetate **7** afforded exclusively the unsaturated hydroxy acetate **16** in 100% yield. The inability of the radical arising from **7** to be cyclized only affords after reduction the β hydrogen elimination. The same result is obtained in the presence of methanol. Surprisingly, the epoxy alcohol **8** gave only the saturated diol **17** in quantitative yield. Here, some kind of interaction with the hydroxyl group must operate to afford the reduction product; however this reaction deserve further study.



In addition, several side chain observations are noteworthy. First, the presence of a large excess of methanol or phenol in the **3a** → **11** and **6** → **15** reactions did not modify the result obtained in their absence. Second, the presence of thiophenol in the reaction of titanocene chloride with **3a** afforded the hydroxy ketone **18** in quantitative yield. The two probes seem to indicate a radical mechanism. With the first, the ionic addition mechanism would be improbable in the presence of a proton source such as phenol.[1d]

The second probe corroborates the radical mechanism, invoking the "radical clock",[9] which indicates that the rate constant of the radical reduction with thiophenol is much larger than that of the addition to a carbonyl group.[2]

The synthesis of cyclopropanols and cyclobutanols by radical addition to the carbonyl group has not been reported previously in the literature. The addition of a radical to a ketone carbonyl to afford cyclopentanols and cyclohexanols is also very unusual.

Acknowledgment. Financial support for this work from the Ministerio de Educación y Ciencia of Spain (PB 95-0943) and the Junta de Castilla y León (SA 45/97) is gratefully acknowledged. We also thank the Junta de Castilla y León for the fellowship to A.R.S. and the Ministerio de Educación y Ciencia for the fellowship to E.M.N.

Supporting Information Available: Full characterization and NMR spectral data listings for compounds **1**−**8** and **9**−**18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Molander, G. A.; Etter, J. B. *Synth. Commun.* **1987**, 17, 901. Curran, D. P.; Gu, X.; Zhang, W.; Dowd, P. *Tetrahedron* **1997**, 53, 9023.

(8) Molander, G. A.; Harris, C. R. *J. Org. Chem.* **1997**, *62*, 7418.

(9) Newcomb, M. *Tetrahedron* **1993**, *49*, 1151.