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Mixed disproportionation versus radical trapping in titanocene(III)-promoted epoxide openings

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ABSTRACT

The formation of either deoxygenation products or allylic alcohols from epoxides is observed when these substrates are treated with Cp₂TiCl under anhydrous conditions. It seems that processes via trisubstituted radicals give allylic alcohols whereas processes via disubstituted radicals may give deoxygenation products or allylic alcohols depending on the structure of the original epoxide. This method allows a controlled access to these functional groups, providing a useful tool in organic synthesis. A mechanistic discussion for these transformations is reported.

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1. Introduction

In recent years Cp₂TiCl.¹ a mild single-electron-transfer reagent has become an indispensable tool in organic synthesis.² It has been used in many interesting transformations, such as the homolytic ring opening of epoxides,³ the radical cascade cyclization of epoxypolyenes,⁴ Michael-type coupling between aldehydes and conjugated alkenals,⁵ pinacol coupling reactions,⁶ H-atom transfer from water to free radicals,⁷ alkenes and alkynes,⁸ divergent C–C bondforming reactions with modulation by Ni or Pd,⁹ metal-catalyzed Barbier-type cyclizations and α -prenylation of carbonyl derivatives,¹⁰ and the Reformastky-type addition of α -haloketones to carbonyl compounds.¹¹ Interestingly, during the last few years new developments in titanocene-regenerating agents have led to many transformations being carried out using only 5-20 mol % of titanium catalyst.¹² Within this context, by using a combination of 2,4,6-collidine and trimethylsilyl chloride, developed in our laboratory, we have been able to regenerate Cp₂TiCl₂ from different species such as titanium alkoxides, carboxylates and hydrides.¹³

Between 1988 and 1994 RajanBabu and Nugent developed their seminal work on the homolytic opening of epoxides promoted by Cp₂TiCl, which, among other transformations, facilitates epoxide deoxygenation under mild conditions.³ The mechanism proposed by RajanBabu and Nugent for this transformation is summarized in Scheme 1, path A. The reaction begins with the homolytic opening of the oxirane ring mediated by Cp₂TiCl,³ which leads to the most stable β -titanoxy radical. This radical can be subsequently trapped by a second Cp₂TiCl species to yield a bimetallic intermediate that

eventually evolves to an alkene, the corresponding deoxygenation product from the original epoxide.³ Nevertheless, the behaviour of trisubstituted titanoxy radicals such as **I** seems to be more complex than previously thought. In fact, we have observed that from some epoxides the main products are allylic alcohols (Scheme 2) instead



Scheme 1. Mechanistic hypothesis for Cp₂TiCl opening of epoxides.





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of the expected deoxygenation products.⁷ Thus, an alternative mechanism may be involved. On the basis of kinetic experiments we recently concluded that allylic alcohols cannot derive from a β -hydride elimination processes in bimetallic species such as II.⁷ Therefore we considered the possibility of a mixed radical disproportionation process,¹⁴ which would fit our experimental results much more coherently (Scheme 1, path B).⁷



Scheme 2. Allylic alcohols obtained from Cp₂TiCl-mediated epoxide opening.

Allylic alcohols are interesting building blocks in organic synthesis. Additionally, the enantioselective synthesis of these compounds might be easily accomplished via this procedure, remembering the fact that enantioenriched oxirane rings can be successfully prepared via well established asymmetric epoxidation reactions developed by Sharpless, Katsuki, Jacobsen, Shi and others.¹⁵ In fact, a preliminary experiment supporting this hypothesis has been recently described by us.⁷ Nevertheless, the examples reported in the literature are too scarce to infer when either the deoxygenation reaction or the formation of allylic alcohols would be favoured. In any case, both reactions have synthetic interest and a clarification of the requirements of these transformations would be highly desirable. In fact, previously described procedures for the deoxygenation of epoxides normally require stoichiometric amounts of expensive metals, such as Nb, In or Sm in their elemental state, and the reactions proceed in heterogeneous phase.¹⁶ Other metal-based electron-transfer reagents, such as Cr(II), Nb(III) and reactive SmI₂ have been used in homogeneous conditions but are not often compatible with sensitive functional groups.¹⁶ In addition, only a few versions using substoichiometric amounts of homogeneous metal complexes for epoxide deoxygenation have been described.^{16a,17}

Furthermore, the known methods for the synthesis of allylic alcohols from epoxides usually require very basic conditions not compatible with the presence of several functional groups.¹⁸ In contrast, Cp₂TiCl-mediated transformations take place under mild, neutral conditions, which are compatible with many functional groups.

Within the context of these precedents, we describe here an indepth study of the homolytic opening of epoxides mediated by Cp₂TiCl under anhydrous conditions. Instead of the expected alkenes, allylic alcohols are obtained from some substrates, a transformation with few precedents in Ti(III) chemistry.^{7,19} What is especially noteworthy is that these reactions can be carried out using only substoichiometric amounts of the Ti(III) catalyst.

2. Results

Epoxides 1-9 were treated with stoichiometric quantities of Cp₂TiCl in anhydrous THF, that are the conditions described by RajanBabu and Nugent for epoxide deoxygenation.³ Under these conditions, however, allylic alcohols **10–18** were obtained (Table 1), whereas deoxygenation products were not detected.

Results summarized in Table 1 confirm that, under anhydrous conditions, the Ti(III)-mediated opening of epoxides via trisubstituted radicals gives the corresponding allylic alcohols as main

Table 1	l
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Ti(III)-mediated opening of epoxides via tertiary radicals^a



^a Reactions were carried out by stirring the corresponding epoxide (1 mmol) with Cp₂TiCl₂ (2.5 mmol) and Mn dust at rt in dry THF.

19% reduction product was observed.

^c A trace of transesterification compound was observed. ^d 32% reduction product was obtained.

^e Mixture 1:1 of stereoisomers.

products, with no deoxygenation compounds. This fact cannot be put down to a titanium radical trapping process to give an organometallic alkyl-Ti(IV) intermediate, followed by β -hydride elimination, because we have previously demonstrated that tertiary radicals are not (or only very slowly) trapped by the bulky titanocene(III) species.⁷ Moreover, it is known that primary and secondary alkyl titanium(IV) intermediates do not result in β -hydride elimination processes under some conditions.²⁰ Our experimental results can be better explained on the basis of an intermolecular mixed disproportionation process, which leads to the formation of an allylic alcohol, as set out above in Scheme 1, path B. This reaction may be considered as being a milder alternative to previously reported processes for the preparation of allylic alcohols, providing greater selectivity and avoiding the mixtures of oxidation compounds obtained with previously described reagents.¹⁸

With epoxides **3** and **5**, products (**12** and **14**) derived from the homolytic opening of the four-membered ring were obtained, showing that the original β -titanoxy radical rearranged to a new trisubstituted radical before the intermolecular mixed disproportionation process took place. In these cases, minor quantities of reduction products were also found. It is worth noting that, under treatment with the Cp₂TiCl₂/In couple, epoxides **5** and **6** gave deoxygenation products whilst formation of allylic alcohols **14** and **15** was not reported.^{16e}

We also studied the behaviour of mono- and disubstituted epoxides **19–26** using the same reaction conditions as those just described (stoichiometric Cp₂TiCl, dry THF). The results obtained are summarized in Table 2.

Table 2

Ti(III)-mediated opening of epoxides via secondary radicals



^a Volatile product **32** was obtained as a roughly 1:1 mixture of cis/trans isomers.
^b Mixture 7:3 of *Z:E* isomers.

Monosubstituted epoxides (**19–22**) always provided deoxygenation compounds, as might be expected.²¹ This can be explained if we bear in mind path A shown in Scheme 1, proposed by RajanBabu and Nugent.³ In this kind of epoxides, where steric hindrance is low, the β -titanoxy radical can be trapped by a second Cp₂TiCl species to give an alkyl-Ti(IV) intermediate. This organometallic intermediate would give rise to an alkene, via β titanoxy elimination. It should be noted that styrene oxide (**20**) only gave a 6% yield of the corresponding deoxygenation product (**28**). This failed reaction could be due to the formation of a very stabilized benzylic radical, which may go on to generate dimerization products,²² and thus constitutes the main limitation of this deoxygenation method.

A more complex behaviour was found with disubstituted epoxides. With cyclic 1,2-disubstituted epoxides (23 and 24) we observed that alkenes or allylic alcohols are obtained (entries 5 and 6), depending on the size of the ring, which indicates a different mechanism for each transformation. It is possible that the different ring strain of the eight-membered and 12-membered rings may be involved in this phenomenon. In the flexible 12-membered ring²³ the β -titanoxy radical formed after the epoxide opening may be trapped by a second titanocene(III) species, leading to the deoxygenation product **32**, according to the mechanism proposed by RajanBabu and Nugent.³ On the other hand, in the relatively strained eight-membered ring,²³ the β -titanoxy radical can hardly be trapped by a second Cp₂TiCl species and so it undergoes a mixed disproportionation process leading to allylic alcohol **31** (Scheme 1, path B). In the case of acyclic 1,2-disubstituted epoxides, deoxygenation products are always obtained (entries 7 and 8) following path A of Scheme 1. In the case of entry 7, we started from a 2:8 mixture of the cis/trans isomers of 25 and obtained a 7:3 mixture of the Z:E isomers of **33**. Similar isomerisation processes were observed by RajanBabu and Nugent,³ who obtained the same mixture of alkenes (7:3, Z:E) from both *cis* and *trans* epoxides.

The Ti(III)-based method, which facilitates the preparation of either allylic alcohols or alkenes from suitable substrates in a predictable way, can also be undertaken using substoichiometric

Table 3						
Ti-catalyzed	opening of	epoxides 5,	7, 19	, 21 ,	24 and	26 ^a



 ^a Reactions were carried out by stirring the corresponding epoxide (1 mmol) with Cp₂TiCl₂ (0.2 mmol) and Mn dust at rt in dry, THF.
^b 36% reduction product was obtained.

^c Volatile product **32** was obtained as a roughly 1:1 mixture of cis/trans isomers.

amounts of Cp₂TiCl, and a mixture of 2,4,6-collidine and Me₃SiCl as titanocene-regenerating agent.¹³ Ti-catalyzed opening of epoxides **5**, **7**, **19**, **21**, **24** and **26** under these conditions gave products **14**, **16**, **27**, **29**, **32** and **34**, respectively, in moderate (35% for volatile **32**) to excellent (94% for **29**) yields (Table 3).

The results obtained under catalytic conditions have the same profile as those observed when using stoichiometric proportions of Cp₂TiCl. To our knowledge this is the first metal-catalyzed procedure for the controlled deoxygenation of epoxides at room temperature, under mild conditions compatible with many functional groups.

3. Conclusion

We describe a method for the deoxygenation or formation of allylic alcohols from suitable epoxides mediated/catalyzed by titanocene(III). This method facilitates the access to these versatile functional groups in a controlled way, providing a useful tool in organic synthesis. Additionally, our results allow us to propose a plausible mechanism involving a mixed disproportionation process to explain the formation of allylic alcohols instead of deoxygenation products from tertiary radicals.

4. Experimental section

4.1. General details

For all reactions with titanocene(III) the solvents and additives were thoroughly deoxygenated prior to use. The following known compounds were isolated as pure samples and showed NMR spectra matching those of the reported compounds: **1**,²⁴ **2**,²⁵ **4**,²⁶ **7**,²⁷ **8**,⁷ **10**,²⁸ **11**,²⁹ **12**,³⁰ **15**,³¹ **16**,³² **17**,⁷ **19**,³³ **22**,³⁴ **26**,³⁵ **31**,³⁶ and **33**.³⁷

4.2. General procedure for the preparation of epoxides (1 and 2) from ketones

A solution of ketone (1 mmol), CH_2Br_2 (2 mmol) in THF (15 mL) was cooled to -78 °C and then BuLi (2.5 M in hexane, 1.1 mmol) was added dropwise for 5 min. The mixture was stirred for 5 min at -78 °C and then for 24 h at rt. AcOEt was then added and the organic layer was washed with saturated solution of NH₄Cl, dried over anhydrous Na₂SO₄ and the solvent removed. In this manner products **1–2** were obtained, subsequently purified by flash chromatography on silica gel (mixtures of hexane/EtOAc) and finally characterized by spectroscopic techniques.

4.3. General procedure for the preparation of epoxides (4, 7–9, 19, 22 and 24–26) from alkenes

A sample of MCPBA (2 mmol, 70% purity) was added to a solution of epoxide (1 mmol) in CH_2Cl_2 , and the mixture was stirred at rt until the starting material was consumed (TLC analysis). CH_2Cl_2 was then added and the solution was washed with 2 N NaOH, dried over anhydrous Na_2SO_4 and the solvent removed. In this manner products **4**, **7–9**, **19**, **22**, **24–26** were obtained, purified by flash chromatography on silica gel (mixtures of hexane/EtOAc) and characterized by spectroscopic techniques.

4.3.1. Compound **9**. Colourless oil; ¹H NMR (300 MHz, CDCl₃) δ 8.02 (d, *J*=7.5 Hz, 2H), 7.53 (t, *J*=7.5 Hz, 1H), 7.43 (t, *J*=7.5 Hz, 2H), 4.70 (dd, *J*=11.1, 4.2 Hz, 1H), 4.33 (dd, *J*=11.5, 4.5 Hz, 1H), 4.03 (dd, *J*=11.5, 4.5 Hz, 1H), 3.05 (br s, 1H), 2.08 (s, 3H), 2.05–1.60 (m, 6H), 1.35 (s, 3H), 1.08 (s, 3H), 1.07–0.93 (m, 2H), 0.93 (s, 3H), 0.89 (s, 3H); ¹³C NMR (75 MHz, CDCl₃; DEPT) δ 171.1 (C), 166.2 (C), 132.9 (CH), 130.9 (C), 129.7 (CH), 128.7 (CH), 80.8 (CH₂), 34.9 (C), 27.7 (CH₃), 23.8 (CH₂),

22.5 (CH₂), 21.9 (CH₃), 21.3 (CH₃), 16.8 (CH₃), 15.4 (CH₃); HRMS (FAB) m/z calcd for C₂₄H₃₂O₅Na [M⁺+Na] 423.2147, found 423.2144.

4.3.2. Compound **25**. Mixture 2:8 of *Z*:*E* isomers. Colourless oil; ¹H NMR (400 MHz, CDCl₃) δ 3.66 (s, 3H), 3.65 (s, 3H), 2.64–2.61 (m, 2H), 2.03 (dd, *J*=14.3, 4.8 Hz, 1H), 1.90 (dd, *J*=14.3, 6.4 Hz, 1H), 1.18 (d, *J*=4.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃; DEPT) δ 172.1 (C), 55.6 (CH), 54.2 (CH), 53.0 (CH, *Z* isomer), 52.6 (CH₃), 52.5 (CH₃), 51.9 (CH, *Z* isomer), 38.5 (CH₂), 33.8 (CH₂, *Z* isomer), 20.4 (CH₃), 20.2 (CH₃, *Z* isomer), 17.3 (CH₃), 13.1 (CH₃, *Z* isomer); HRMS (ES+) *m*/*z* calcd for C₁₀H₁₇O₅ [M+H]⁺ 217.1076, found 217.1072.

4.4. General procedure for Ti-promoted epoxide openings

Thoroughly deoxygenated THF (20 mL) was added to a mixture of commercial Cp_2TiCl_2 (2.5 mmol) and Mn dust (8 mmol) under an Ar atmosphere and the suspension was stirred at room temperature until it turned lime green (after about 15 min). A solution of epoxide (1 mmol) in THF (1 mL) was then added and the mixture was stirred for 6–18 h, after which the reaction was quenched with a saturated solution of KHSO₄ and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na₂SO₄ and the solvent removed. Products **10–18** and **27–34** were purified by flash chromatography on silica gel (mixtures of hexane/EtOAc) and characterized by spectroscopic techniques. Yields obtained are reported in Tables 1 and 2.

4.4.1. *Compound* **13**. Colourless oil; ¹H NMR (400 MHz, CDCl₃) δ 8.05 (d, *J*=7.5 Hz, 2H), 7.56 (t, *J*=7.5 Hz, 1H), 7.46 (t, *J*=7.5 Hz, 2H), 5.15 (br s, 1H), 5.03 (br s, 1H), 4.45–4.23 (m, 3H), 1.83 (s, 3H); ¹³C NMR (100 MHz, CDCl₃; DEPT) δ 162.0 (C), 143.8 (C), 133.4 (CH), 130.1 (C), 129.9 (CH), 128.7 (CH), 113.1 (CH₂), 73.9 (CH), 67.9 (CH₂), 18.9 (CH₃); HRMS (ES+) *m*/*z* calcd for C₁₂H₁₄O₂ [M–OH]⁺ 190.0994, found 190.0974.

4.4.2. Compound **18**. Colourless oil; ¹H NMR (300 MHz, CDCl₃) δ 8.02 (d, *J*=7.5 Hz, 2H), 7.53 (t, *J*=7.5 Hz, 1H), 7.43 (t, *J*=7.5 Hz, 2H), 5.07 (br s, 1H), 4.79 (dd, *J*=11.1, 4.2 Hz, 1H), 4.66 (br s, 1H), 4.38 (m, 1H), 4.27 (dd, *J*=11.4, 4.2 Hz, 1H), 4.20 (dd, *J*=11.4, 7.8 Hz, 1H), 2.59 (t, *J*=6.9 Hz, 1H), 2.00 (s, 3H), 1.95–1.58 (m, 7H), 1.00 (s, 3H), 0.95 (s, 3H), 0.79 (s, 3H); ¹³C NMR (75 MHz, CDCl₃; DEPT) δ 171.3 (C), 166.2 (C), 147.7 (C), 132.9 (CH), 130.9 (C), 129.6 (CH), 128.4 (CH), 110.8 (CH₂), 81.1 (CH), 73.3 (CH), 61.4 (CH₂), 48.9 (CH), 46.7 (CH), 38.8 (C), 38.0 (C), 36.5 (CH₂), 30.1 (CH₂), 28.2 (CH₃), 24.2 (CH₂), 21.1 (CH₃), 16.9 (CH₃), 14.3 (CH₃); HRMS (FAB) *m/z* calcd for C₂₄H₃₂O₅Na [M⁺+Na] 423.2147, found 423.2144.

4.5. General procedure for Ti-catalyzed epoxide openings

Thoroughly deoxygenated THF (20 mL) was added to a mixture of commercial Cp₂TiCl₂ (0.2 mmol) and Mn dust (8.0 mmol) under an Ar atmosphere and the suspension was stirred at room temperature until it turned lime green (after about 15 min). A solution of epoxide (1 mmol) and 2,4,6-collidine (7 mmol) in THF (2 mL), and Me₃SiCl (4 mmol) were then added and the mixture was stirred for 12–18 h. The reaction was then quenched with a saturated solution of KHSO₄ and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na₂SO₄ and the solvent removed. Products **14**, **16**, **27**, **29**, **32** and **34** were purified by flash chromatography on silica gel (mixtures of hexane/EtOAc) and characterized by spectroscopic techniques. Yields obtained are reported in Table 3.

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