**Free-Radical Chemistry**

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# Water: The Ideal Hydrogen-Atom Source in Free-Radical Chemistry Mediated by Ti$^{III}$ and Other Single-Electron-Transfer Metals?**

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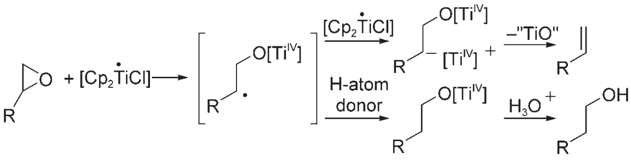
The reactivity of water with both carbanion and carbocation intermediates is well known, but until now it has generally been believed that water is inert towards free radicals.[1] This hypothetical passivity has been attributed to the strong H–OH bond, which, with a bond-dissociation energy of 117.59 ± 0.07 kcal mol$^{-1}$,[2] would impede any potential hydrogen-atom transfer from water. Some years ago, however, we chanced to observe that tertiary radicals were reduced effectively in the presence of bis(cyclopentadienyl)titanium(III) chloride[3] ([Cp$_2$TiCl]) and water.[4] This observation further facilitated the control of the final step in titanocene-catalyzed radical cyclizations, which are useful for the straightforward synthesis of complex polycyclic terpenoids.[5] However, as, at the time, the idea of water acting as a hydrogen-atom source seemed to be counterintuitive, this phenomenon was rationalized by invoking either the formation and subsequent hydrolysis of alkyl–Ti$^{IV}$ complexes or a virtually intramolecular hydrogen transfer via a quite sophisticated cyclic transition state.[4,5] We now have solid evidence to show that water really can act as a complete hydrogen-atom source rather than as a simple proton donor for radical reductions mediated by Ti$^{III}$ and, presumably, other metals that react by single-electron transfer.

Many highly selective free-radical reactions have been developed and have proved to be very useful in the total synthesis of complex organic compounds owing to the mild conditions required and their compatibility with many functional groups.[6] Within this context, RajanBabu and Nugent introduced a novel concept: homolytic oxirane opening induced by [Cp$_2$TiCl].[7] This reaction generates the most substituted (i.e., most stable) β-titanoxy radical, which, among other transformations, could be either trapped by a second [Cp$_2$TiCl] species to provide an alkene (epoxide deoxygenation) by "TiO" elimination or, in the presence of a hydrogen-atom donor such as cyclohexa-1,4-diene (1,4-CHD), reduced to an alcohol with the opposite regiochemistry to that expected from the reduction with metal hydrides (Scheme 1).[7]

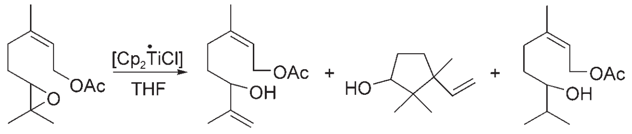


*Scheme 1.* [Cp$_2$TiCl]-induced deoxygenation and reductive opening of epoxides by radical chemistry.[7]

Since the development of the first titanocene-catalyzed reaction,[8] [Cp$_2$TiCl]-mediated processes have become formidable tools in organic synthesis.[9] However, conventional hydrogen-atom donors used in radical chemistry, such as 1,4-CHD, Bu$_3$SnH, and 2-methylpropan-2-thiol, are toxic, expensive, and/or foul smelling, thus seriously limiting the application of the reaction described by RajanBabu and Nugent and other radical reactions for large-scale preparations.[6] Therefore, the discovery of novel and more convenient hydrogen-atom sources seemed desirable.[10] In this context, we decided to explore the possibility of employing safe and inexpensive water as an ideal hydrogen source in Ti$^{III}$-mediated radical chemistry; titanocene(III)-promoted homolytic epoxide opening was used as a model process for this study.

We first examined the reaction between 6,7-epoxyneryl acetate (**1**) and an excess of [Cp$_2$TiCl] (2.5 equiv) in strictly dry THF, that is, under the conditions described by RajanBabu and Nugent for epoxide deoxygenation.[7] In this manner we obtained the allylic alcohol **2** (35 % yield of isolated **2**) together with **3** (29 %), the product of 5-*exo* cyclization, and minor amounts of the reduction product **4** (6 %); neryl acetate (**7**), the expected deoxygenation product, was not detected (Scheme 2).[11]

The formation of the major product **2** suggested that a mixed disproportionation had occurred that was slightly



**1** **2** (35%) **3** (29%) **4** (6%)

*Scheme 2.* [Cp$_2$TiCl]-promoted transformation of **1** in strictly dry THF.

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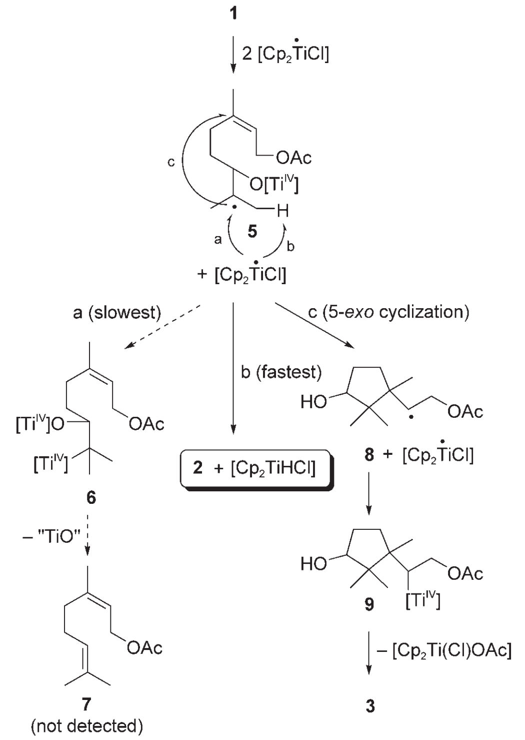
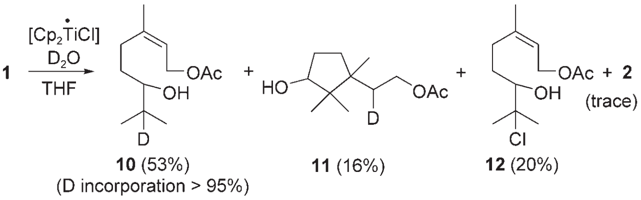
faster than the cyclization process to give **3** and much faster than the potential trapping (or two-electron reduction) of the tertiary radical **5** by a second [$Cp_2TiCl$] species (Scheme 3). Such kinetics would explain why the deoxygenation product **7** was not formed. This behavior, reminiscent of that of bulky bases in the presence of tertiary alkyl halides and sulfonates, might simply be due to steric factors.



*Scheme 3.* Mixed disproportionation (b) versus 5-*exo* cyclization (c) and radical trapping of **5** (a).

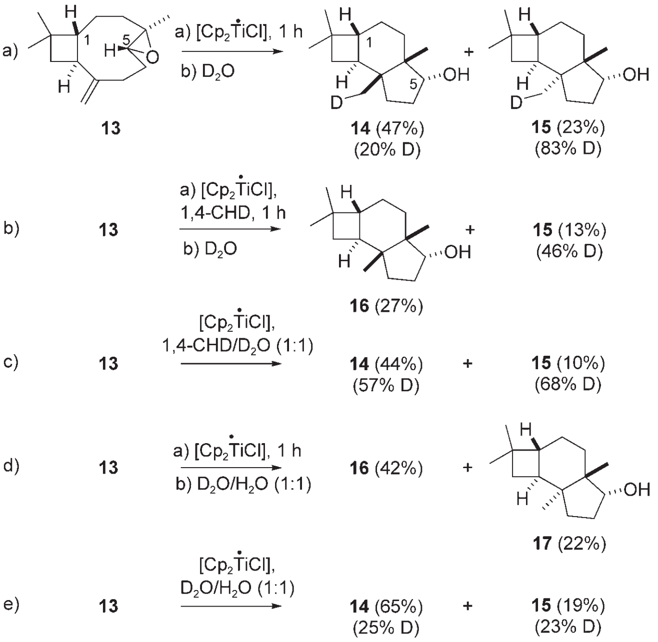
In the light of the above observations, the following experiments clarified the situation considerably. First, when we treated **1** with [$Cp_2TiCl$] (2.5 equiv) in the presence of $D_2O$ (10 equiv), the reduced derivative **10** became the main product at the expense of the allylic alcohol **2** (Scheme 4). These results indicated that the water-mediated reduction of radical **5** was faster than the mixed-disproportionation process, which in turn had been shown to be much faster than the potential radical trapping by a second [$Cp_2TiCl$] species. Additionally, when we treated **1** with [$Cp_2TiCl$] (2.5 equiv) in the presence of an equimolar mixture of $D_2O$ and 1,4-CHD (10 equiv) we obtained **10** with 70% deuterium incorporation. Thus, the transfer of deuterium from $D_2O$ was even faster than that of a hydrogen atom from 1,4-CHD. As these observations on the kinetics of the process ruled out the possibility of **10** being formed by the hydrolysis of an alkyl–$Ti^{IV}$ complex, we considered for the first time the hypothesis that the coordination of water with [$Ti^{III}$] might diminish the bond-dissociation energy of water to values that allow the transfer of a whole hydrogen atom (or deuterium atom) to the tertiary radical **5**.



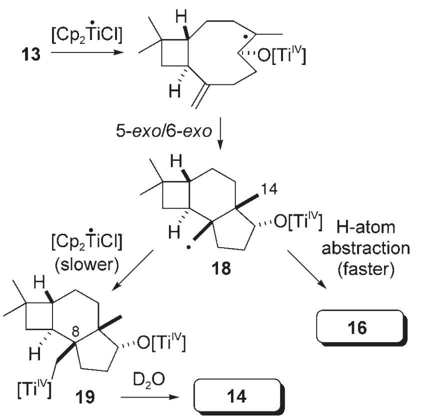
*Scheme 4.* [$Cp_2TiCl$]-promoted reductive opening of the epoxide **1** with $D_2O$ as the hydrogen-atom source.

The acetate **11** might derive from either the hydrolysis of the alkyl–$Ti^{IV}$ complex **9**, or, more plausibly, deuterium-atom transfer to the secondary radical **8** (see Scheme 3). In the latter case the formation of **9** and the subsequent elimination of [$Cp_2Ti(Cl)OAc$] to give the alkene **3** are avoided. We decided to confirm the possibility of hydrogen-atom transfer from water not only to tertiary but also to primary and secondary radicals. Primary and secondary radicals are generally less hindered sterically than tertiary radicals and therefore can be readily trapped by [$Cp_2TiCl$] to give alkyl–$Ti^{IV}$ complexes.[7] Thus, hydrogen-atom transfer from water might be masked as the apparent simple hydrolysis of a $Ti^{IV}$ complex. In an attempt to avoid this misleading possibility we chose to investigate the [$Cp_2TiCl$]-promoted transannular cyclization of caryophyllene oxide (**13**, Scheme 5) because the β-trisubstituted primary radicals formed in the expected 5-*exo*/6-*exo* cyclization (see **18** in Scheme 6) might be sufficiently sterically protected to impede the formation of alkyl–$Ti^{IV}$ complexes.

Thus, we treated the epoxide **13** with [$Cp_2TiCl$] in strictly dry THF and added $D_2O$ after 1 h, when the starting material had been consumed completely (thin-layer chromatography (TLC) analysis). In this way we obtained the tricyclic alcohol **14** (only 20% incorporation of D) together with its epimer **15** as a minor product (Scheme 5a).[12]



*Scheme 5.* a)–e) [$Cp_2TiCl$]-induced transannular cyclization of **13** under different conditions.

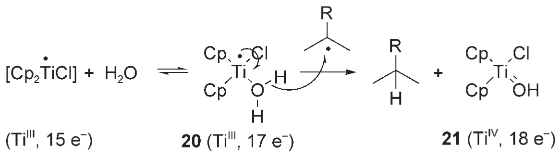


*Scheme 6.* Competing reactions of the primary radical **18** with [Cp$_2$TiCl] and hydrogen-atom donors.

The relatively low proportion of deuterium incorporated into **14** suggested that the coupling of radical **18** with [Cp$_2$TiCl] to give the alkyl–Ti$^{\text{IV}}$ complex **19** was slower than a competing process of hydrogen-atom abstraction from the solvent (THF; formation of **16**; Scheme 6). This result prompted us to repeat the experiment in the presence of 1,4-CHD (Scheme 5b), a more efficient hydrogen-atom donor than THF. In this way we obtained alcohol **16** together with **15**, but the deuterated derivative **14** was not detected: a clear indication that hydrogen-atom transfer from 1,4-CHD was faster than radical coupling to [Cp$_2$TiCl]. Finally, we treated **13** with [Cp$_2$TiCl] in the presence of an equimolar mixture of D$_2$O and 1,4-CHD, and thus once more obtained the deuterated derivatives **14** and **15** (Scheme 5c). In this case the incorporation of deuterium into **14** was 57 %. Thus, deuterium transfer from D$_2$O was slightly faster than hydrogen-atom transfer from 1,4-CHD, which in turn had been shown to be much faster than the formation of the alkyl–Ti$^{\text{IV}}$ complex **19**. In other words, the [Cp$_2$TiCl]/water-promoted reduction of the primary radical **18** was faster than the formation of the complex **19**, and consequently 57 % of deuterium incorporation into **14** could not be attributed to the hydrolysis of **19**. Moreover, because the radical **18** has no hydrogen atom at the β position, a six-membered cyclic transition state, such as that proposed by some of us in 2002 (see ref. [4]), could not be involved in the process either.

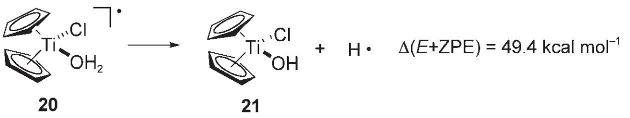
The relatively high deuterium incorporation (83 %) into the minor product **15** in the experiment summarized in Scheme 5a shows that a high proportion of an alkyl–Ti$^{\text{IV}}$ complex (the C8 epimer of **19**) was formed upon the treatment of **13** with [Cp$_2$TiCl] in dry THF for 1 h (see ref. [7]). Therefore, we had the opportunity to measure and compare isotope effects. To this end, we treated **13** with [Cp$_2$TiCl] in dry THF once again and after 1 h added a 1:1 mixture of D$_2$O and H$_2$O (Scheme 5d). In this way we obtained the tricyclic isomers **16** and **17**. The deuterated derivative **15** was not detected, which suggests that a large isotope effect exists for the hydrolysis of the Ti$^{\text{IV}}$ complex. In contrast, when we treated **13** with [Cp$_2$TiCl] in the presence of a 1:1 mixture of D$_2$O and H$_2$O (Scheme 5e), we obtained, along with **14**, the deuterated derivative **15** with 23 % deuterium incorporation. This result corresponds to a $K_H/K_D$ ratio of only 3.35 for the radical-reduction process. Different isotope effects are indicative of different reaction mechanisms; therefore, these results support the conclusion obtained from the kinetics-based evidence that radical reduction in the presence of water and [Cp$_2$TiCl] does not derive from the hydrolysis of alkyl–Ti$^{\text{IV}}$ complexes. Moreover, the magnitude of the isotope effect observed for this reduction of a primary radical (3.35) is virtually the same as that reported for hydrogen-atom transfer from *t*BuSH to the primary 1-nonyl radical ($K_H/K_D = 3.40$).[13]

Under these circumstances, the most plausible assumption seemed to be that an aqua complex, such as **20** (Scheme 7), might act as an efficient hydrogen-atom donor by means of an inner-sphere, single-electron transfer to the oxygen atom, with concomitant oxidation to a [Ti$^{\text{IV}}$] complex, such as **21**. Finally, **21** might evolve to HCl and stable [Cp$_2$Ti=O], which would also explain why the formation of the chlorohydrin **12** (see Scheme 4), presumably by HCl-induced epoxide opening, was only observed in the presence of water.[14]



*Scheme 7.* Mechanism, Ti oxidation states, and electrons in the metal bonding shell for the hydrogen-atom transfer from water to a free radical via the aqua complex **20**.

To check the feasibility of this mechanism, we performed a computational study to determine how the bond-dissociation energy of water might be affected by coordination to [Ti$^{\text{III}}$] in the putative aqua complex **20**. Calculations were performed by using density functional theory (DFT), since high-accuracy ab initio methods are prohibitive for these complexes. The calculated dissociation energy for H$_2$O at the B3LYP/6-31G(d) level is 108.1 kcal mol$^{-1}$, which is just slightly lower than the experimental value (117.6 kcal mol$^{-1}$) and the theoretical value previously calculated at the ab initio G3 level (116 kcal mol$^{-1}$).[15] Interestingly, homolytic O–H bond dissociation is favored to an extraordinary extent by the coordination of H$_2$O to [Cp$_2$Ti$^{\text{III}}$Cl]. Thus, at the same DFT level, the calculated reaction energy for O–H dissociation from complex **20** to afford **21** is only 49.4 kcal mol$^{-1}$ (Scheme 8). This dramatic decrease strongly supports the mechanism depicted in Scheme 7. Moreover, comparison of the calculated structures shows that the Ti–O distance is much longer in **20** (2.28 Å) than in **21** (1.86 Å), and thus

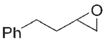
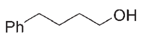
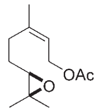
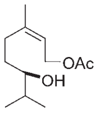
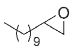
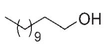
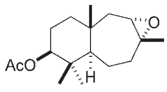
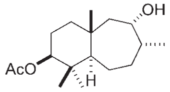
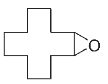
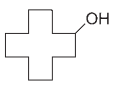
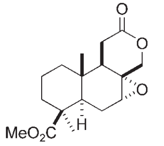
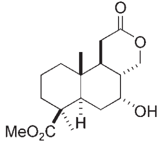
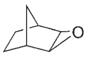
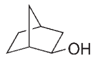
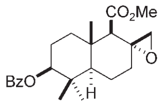
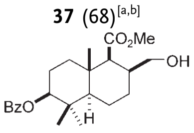
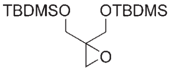
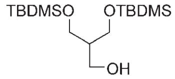
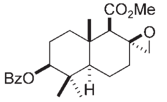


*Scheme 8.* Calculated reaction energy for the homolytic O–H bond dissociation in the aqua complex **20**.

confirms that after O—H dissociation the Ti—O bond acquires a certain double-bond character by additional pairing of the electrons of Ti and O.[16]

Epoxides are one of the most versatile functional groups in organic chemistry. Because of the success of methods for asymmetric epoxidation developed by the research groups of Sharpless, Katsuki, Jacobsen, Shi, and others, these compounds have become crucial intermediates for enantioselective synthesis.[17] With valuable mechanistic data in hand, we decided to explore the synthetic usefulness of the [$Cp_2TiCl$]/$H_2O$ combination for the reductive opening of epoxides, thus avoiding the use of harmful hydrogen-atom donors. To this end we prepared a number of epoxides (**1**, **22**–**30**) and treated them with [$Cp_2TiCl$] (2.2 equiv) and $H_2O$ (40 equiv) in THF.[18] The results are summarized in Table 1.

***Table 1:*** Reductive opening of epoxides **1** and **22**–**30** mediated by [$Cp_2TiCl$]/$H_2O$.

| Substrate | Product (yield [%]) | Substrate | Product (yield [%]) |
|---|---|---|---|
| <br>**22** | <br>**31** (78) | <br>**1** (70% *ee*) | <br>(+)-**4** (72, 73% *ee*)[a] |
| <br>**23** | <br>**32** (85) | <br>**27** (racemic) | <br>**36** (43, racemic)[a] |
| <br>**24** | <br>**33** (62)[a] | <br>**28**[b] | <br>**37** (68)[a,b] |
| <br>**25** | <br>**34** (60, racemic)[a] | <br>**29** (racemic)[d] | <br>**38** (81, racemic) |
| <br>**26**[c] | <br>**35** (60)[a] | <br>**30** (racemic) | **38** (67, racemic)[a] |

[a] Besides the main product, minor quantities of by-products, such as chlorohydrins and/or *vic* diols, which are presumably derived from HCl-induced heterolytic epoxide opening, were also detected. [b] Optically pure. [c] TBDMS = *tert*-butyldimethylsilyl. [d] Bz = benzoyl.

Competing deoxygenation is a serious problem when the reductive opening of terminal epoxides is performed with 1,4-CHD.[7] The yields of the alcohol products of the reduction of **22** and **23** (Table 1) revealed that our combination of the titanium reagent and water was not only safer and cheaper but also more efficient than the method of RajanBabu and Nugent[7] for this type of substrate. Additionally, Table 1 shows that our method also worked well with di- and trisubstituted epoxides, and even with the sterically congested substrate **26**, the reaction of which gave the alcohol **35** in an acceptable yield of 60%. Moreover, the [$Cp_2TiCl$]/$H_2O$-promoted reductive opening of optically active **1**, prepared from nerol with the aid of the chiral ketone described by Wang and Shi,[19] gave the alcohol (+)-**4** (73% *ee*), which suggests that the combination of our process with well-established methods for asymmetric epoxidation could afford a practical two-step procedure for the enantioselective synthesis of anti-Markovnikov alcohols from prochiral alkenes.[20]

Our procedure also showed considerable regio- and stereoselectivity, as was demonstrated in the reduction of the cyclic substrates **27** and **28** to the *cis*-substituted secondary alcohols **36** and **37**, with the incoming hydrogen atom in an *anti* relationship to the OH group. This stereoselectivity is opposite (and complementary) to that observed in the hydroboration–oxidation process.[20] Nevertheless, the reduction of the epimeric spiroepoxides **29** and **30** gave the same product. The formation of **38** from both epimers indicates that for this kind of compound the reaction is stereoselective but not stereospecific. These results can be rationalized readily (and predicted with confidence) by considering that the attack of the bulky aqua complex **20** takes place preferentially at the less hindered face of the intermediate radical formed in each case.

Finally, in a titanocene-catalyzed version of the process the required quantity of the titanocene was decreased by one order of magnitude, but the alcohol products were obtained in slightly lower yields. Thus, the treatment of **22**, **24**, and **25** with a substoichiometric amount of [$Cp_2TiCl$] (0.2 equiv) and $H_2O$ (8 equiv) in the presence of 2,4,6-collidine hydrochloride as the titanocene-regenerating agent[8] gave the alcohols **31**, **33**, and **34** in yields of 70, 45, and 50%, respectively.

During the course of the study described herein the research group of Wood reported that water could be used as hydrogen-atom source in trialkylborane-mediated variants of the Barton–McCombie reaction and from calculations carried out on the $Me_3Al{\cdot}OH_2$ complex deduced that the observed reaction might be unique to trialkylborane–water ($R_3B{\cdot}OH_2$) systems.[15,21] Our results demonstrate, however, that hydrogen-atom transfer from water can be mediated not only by trialkylboranes but also by $Ti^{III}$ complexes, as we had previously suspected.[4] Furthermore, a careful inspection of the mechanism and electron counts depicted in Scheme 7 suggests that this phenomenon might be more general than expected, and might be mediated by any single-electron-transfer metal with an orbital vacancy to coordinate with $H_2O$. In this sense, closely related reaction mechanisms might help to explain the hydrogen-atom-donor ability of the $Mn^{II}$ aqua complex in the manganese cluster of photosystem II,[22] or the highly exothermic generation of hydrogen by the reaction between sodium and water. In fact, our calculations of the bond-dissociation energy of the O–H bond in the aqua complexes $[Cp_2Zr^{III}(Cl)OH_2]$ and $[Cp_2Hf^{III}(Cl)OH_2]$ provided values of only 25.5 and 13.7 kcal $mol^{-1}$, respectively. These low values strongly support the hypothesis that hydrogen-atom transfer from water might be mediated by different metals capable of single-electron transfer.

In summary, we have presented theoretical and experimental evidence that indicates that water can act as an efficient hydrogen-atom source in radical reductions mediated by $Ti^{III}$ complexes and, presumably, other metals that react by single-electron transfer. Moreover, this property can be exploited advantageously for the reductive opening of epoxides to provide a mild, safe, inexpensive two-step procedure (complementary to the hydroboration–oxidation method) for the preparation from alkenes of anti-Markovnikov alcohols, even in deuterated form and/or enantioselectively. We are currently studying the hydrogen-atom-transfer ability of other aqua complexes with different transition metals.

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