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.\cite{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\(^{-1}\),\cite{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\cite{3} ([Cp\(_2\)TiCl]) and water.\cite{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.\cite{5} However, as, at the time, the idea of water acting as a hydrogen-source seemed to be counterintuitive, this phenomenon was rationalized by invoking either the formation and subsequent hydrolysis of alkyl–Ti\textsuperscript{IV} complexes or a virtually intramolecular hydrogen transfer.\cite{6} Since the development of the first titanocene-catalyzed reaction,\cite{7} [Cp\(_2\)TiCl]-mediated processes have become formidable tools in organic synthesis.\cite{8} 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.\cite{9} Therefore, the discovery of novel and more convenient hydrogen-atom sources seemed desirable.\cite{10} In this context, we decided to explore the possibility of employing safe and inexpensive water as an ideal hydrogen-source in Ti\textsuperscript{III}-mediated radical chemistry; titanocene(III)-promoted homolytic epoxide opening was used as a model process for this study.

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.\cite{11} Within this context, RajanBabu and Nugent introduced a novel concept: homolytic oxirane opening induced by [Cp\(_2\)TiCl].\cite{7} This reaction generates the most substituted (i.e., most stable) 5-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).\cite{7}

Since the development of the first titanocene-catalyzed reaction,\cite{7} [Cp\(_2\)TiCl]-mediated processes have become formidable tools in organic synthesis.\cite{8} 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.\cite{9} Therefore, the discovery of novel and more convenient hydrogen-atom sources seemed desirable.\cite{10} In this context, we decided to explore the possibility of employing safe and inexpensive water as an ideal hydrogen-source in Ti\textsuperscript{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.\cite{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).\cite{11}

The formation of the major product 2 suggested that a mixed disproportionation had occurred that was slightly
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 [Cp2TiCl] 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.

In the light of the above observations, the following experiments clarified the situation considerably. First, when we treated 1 with [Cp2TiCl] (2.5 equiv) in the presence of D2O (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 [Cp2TiCl] species. Additionally, when we treated 1 with [Cp2TiCl] (2.5 equiv) in the presence of an equimolar mixture of D2O and 1,4-CHD (10 equiv) we obtained 10 with 70% deuterium incorporation. Thus, the transfer of deuterium from D2O 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-TiIV complex, we considered for the first time the hypothesis that the coordination of water with [TiIV] 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.

The acetate 11 might derive from either the hydrolysis of the alkyl–TiIV complex 9, or, more plausibly, deuterium-atom transfer to the secondary radical 8 (Scheme 5). In the latter case the formation of 9 and the subsequent elimination of [Cp2TiCl]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 [Cp2TiCl] to give alkyl–TiIV complexes. Thus, hydrogen-atom transfer from water might be masked as the apparent simple hydrolysis of a TiIV complex. In an attempt to avoid this misleading possibility we chose to investigate the [Cp2TiCl]-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–TiIV complexes.

Thus, we treated the epoxide 13 with [Cp2TiCl] in strictly dry THF and added D2O 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).
The relatively low proportion of deuterium incorporated into 14 suggested that the coupling of radical 18 with \([\text{Cp}_2\text{TiCl}]\) to give the alkyl–\(\text{Ti}^{IV}\) 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 \([\text{Cp}_2\text{TiCl}]\). Finally, we treated 13 with \([\text{Cp}_2\text{TiCl}]\) 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–\(\text{Ti}^{IV}\) complex 19. In other words, the \([\text{Cp}_2\text{TiCl}]\)/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 \(\beta\)-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–\(\text{Ti}^{IV}\) complex (the C8 epimer of 19) was formed upon the treatment of 13 with \([\text{Cp}_2\text{TiCl}]\) 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 \([\text{Cp}_2\text{TiCl}]\) 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 \(\text{Ti}^{IV}\) complex. In contrast, when we treated 13 with \([\text{Cp}_2\text{TiCl}]\) 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 \(K_{\text{D}}/K_0\) 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 \([\text{Cp}_2\text{TiCl}]\) does not derive from the hydrolysis of alkyl–\(\text{Ti}^{IV}\) 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 \(\text{tBuSH}\) to the primary 1-nonyl radical (\(K_{\text{D}}/K_0 = 3.40\)).\[13\]

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 \([\text{Ti}^{III}]\) complex, such as 21. Finally, 21 might evolve to HCl and stable \([\text{Cp}_2\text{Ti}^{IV}]\), 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.\[14\]

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 \([\text{Ti}^{III}]\) 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 \([\text{Cp}_2\text{Ti}^{III}\text{Cl}]\). 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
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.\footnote{14} 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.\footnote{17} With valuable mechanistic data in hand, we decided to explore the synthetic usefulness of the [Cp2TiCl]/H2O 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 [Cp2TiCl] (2.2 equiv) and H2O (40 equiv) in THF.\footnote{18} The results are summarized in Table 1.

\begin{table}
\centering
\begin{tabular}{c c c c c}
\hline
Substrate & Product (yield [%]) & Substrate & Product (yield [%]) \\
\hline
\hline
22 & 31 (78) & 23 & 32 (85) \\
24 & 33 (62) & 25 & 34 (60, racemic) \\
26 & 35 (60) & 27 & (racemic) \\
28 & (racemic) & 29 & (racemic) \\
30 & (racemic) & 31 & (racemic) \\
32 & (78) & 33 & (62) \\
34 & (60, racemic) & 35 & (60) \\
36 & (43, racemic) & 37 & (68, racemic) \\
38 & (67, racemic) & 39 & (67, racemic) \\
\hline
\end{tabular}
\caption{Reductive opening of epoxides 1 and 22–30 mediated by [Cp2TiCl]/H2O.}
\end{table}

\footnote{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. \footnote{b} Optically pure. \footnote{c} TBDMS = tert-butyldimethylsilyl. \footnote{d} Bz = benzoyl.

Competing deoxygenation is a serious problem when the reductive opening of terminal epoxides is performed with 1,4-CHD.\footnote{15} 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\footnote{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 [Cp2TiCl]/H2O-promoted reductive opening of optically active 1, prepared from nerol with the aid of the chiral ketone described by Wang and Shi,\footnote{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.\footnote{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.\footnote{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 [Cp2TiCl] (0.2 equiv) and H2O (8 equiv) in the presence of 2,4,6-collidine hydrochloride as the titanocene-regenerating agent\footnote{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...
ability of the MnIII aqua complex in the manganese cluster of photosystem II,\textsuperscript{[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 [Cp₂Zr(HI(Cl)OH₂] and [Cp₂H₂(HI(Cl)OH₂] 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 TiIII 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 alkyl- and enantioselective radicals. We are currently studying the hydrogen-atom-transfer ability of other aqua complexes with different transition metals.

Received: March 3, 2006
Published online: July 19, 2006

**Keywords:** epoxides · hydrogen transfer · radicals · titanium · water

---


\[3\] The single-electron-transfer reagent bis(cyclopentadienyl)titanium(III) chloride can be generated in situ by stirring commercial [Cp₂TiCl] with Mn dust in THF, where it exists as a mixture of the mononuclear [Cp₂TiCl] and the dinuclear [(Cp₂TiCl)₂] species; see: R. J. Enemærke, J. Larsen, T. Skrydstrup, K. Daasbjerg, *J. Am. Chem. Soc.* 2004, 126, 7853–7864; for the sake of clarity, we represent this complex herein as [Cp₂TiCl]²⁻.


\[10\] The quest for novel hydrogen-atom donors for titanocene-mediated reductive epoxide opening has been the focus of recent research; see: A. Ganshäuser, A. Burchuk, D. Fiebenbach, *Synthesis* 2004, 2567–2573.

\[11\] The results depicted in Scheme 2 suggest that the formation of the minor product 4 and an equimolar amount of 2 (6%) might be the result of a radical–radical disproportionation process. In this aspect, our reaction differs from the reduction of tertiary radicals by Sml₂, in which, in the absence of any proton source, radical–radical disproportionation products were the main components of the mixtures obtained; see: T. Nagashima, A. Rivkin, D. P. Curran, *Can. J. Chem.* 2000, 78, 791–799.

\[12\] The relatively low deuterium incorporation in 14 compared with what is in 15 is presumably due to the increased steric hindrance introduced in the radical 18 by the cis disposition of the C14 methyl group relative to the adjacent primary radical. This steric hindrance impedes the corresponding radical coupling with bulky [Cp₂TiCl]⁺.


\[14\] Moreover, epoxide 1 was recovered unchanged after treatment with H₂O, MnCl₂, and Mn dust in the absence of [Cp₂TiCl₂].


\[18\] We tested the reaction with different quantities of water and found that for 2.2 equivalents of [Cp₂TiCl], the yields of the major product 4 were 74–76%.


\[20\] Note that alkene epoxidation followed by [Cp₂TiCl]⁺H₂O-mediated epoxide opening might provide a useful (and complementary) alternative to the hydroboration–oxidation method.
