




Perspective

Cp₂TiCl/H₂O as a Sustainable System for the Reduction of Organic Functional Groups: Potential Application of Cp₂TiCl/D₂O to the Analysis of Bioactive Phenols in Olive Oil

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Abstract: Significant efforts have been made toward developing sustainable reduction reactions of organic and bioorganic compounds. In these studies, the selection of reagents and solvents has played a very important role in the development of environment-friendly methodologies. In this context, the reducing agent Cp₂TiCl/H₂O has been introduced as a safe, efficient, selective, and low-cost reagent, and thus as a sustainable alternative for the reduction of organic compounds. To facilitate understanding of the reductions mediated by this system, in this study we focus on describing the intermediates, mechanisms, and representative examples. Finally, a reflection is made on the future perspectives of this reducing agent, including its analog Cp₂TiCl/D₂O as a powerful tool for the preparation of deuterated phenols, which can be successfully used as an internal standard for analyzing bioactive phenols in olive oil.

Keywords: Cp₂TiCl/H₂O; deuterated phenols; olive oil; reduction reactions



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1. Introduction

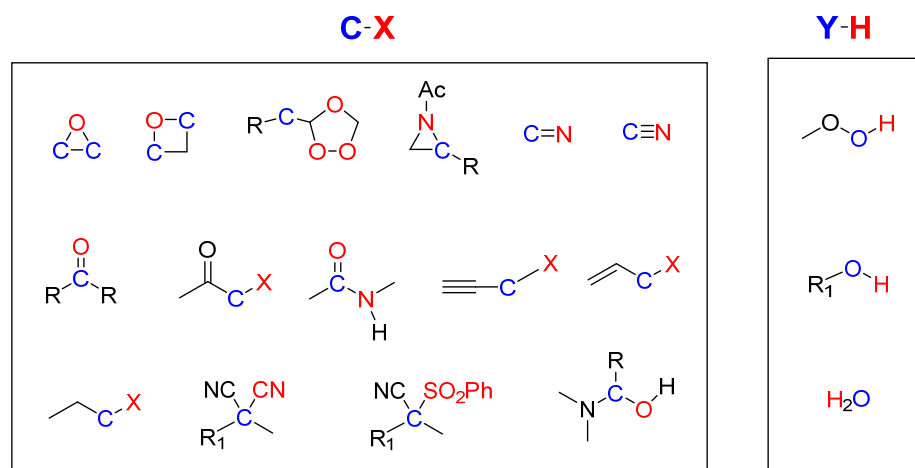
The reduction of functional groups in organic compounds is of central importance in biochemistry and organic chemistry. This reaction can be achieved through several methods, including hydride transfer reactions, catalytic hydrogenations, dissolving metal reductions, and organometallic complexes [1]. Although the reduction reaction has been known about for a long time, this reaction is a central focus of modern organic synthesis, with significant efforts directed at developing more sustainable reductions [2,3] in accordance with the principles of green chemistry [4]. In this context, this manuscript summarizes the use of Cp₂TiCl/water as a green system for the reduction of organic functional groups and its analog Cp₂TiCl/D₂O as an efficient system for the synthesis of deuterated compounds, although it is not intended to be a comprehensive review. This system is constituted by Cp₂TiCl, a single-electron transfer (SET) reagent, which has been proposed as a new green reagent that can carry out an important variety of chemical reactions such as C–C and C–O bond-forming reactions, as well as reduction, isomerization, deoxygenation, and polymerization reactions, under mild reaction conditions and with high diastereo- and regioselectivities [5–11]. This SET reagent fulfills some of the twelve principles of green chemistry, such as catalysis, safer solvents, waste minimization, atom economy, toxicity, and energy efficiency [5,6]. The other reagent is water or heavy water, an environmentally benign solvent because it is nonflammable, abundant, and nontoxic. Furthermore, the chemical nature of water leads to remarkable new reactions that cannot be achieved otherwise [12]. The most relevant mechanisms of the reduction reactions mediated by the Cp₂TiCl/H₂O system will be discussed. Of note is that the analog of this system, the one using heavy water as a deuterium atom source, is an ideal reagent

for the efficient synthesis of deuterated compounds, which present chemical and physical properties virtually identical to those of their non-deuterated analogs. These deuterated compounds have many potential applications [13], especially in the food and pharmaceutical industries. For example, in the food industry, deuterated compounds can be used as an internal standard [14,15] in the analysis of bioactive compounds. In this context, compared to other deuteration methodologies [16,17], the $\text{Cp}_2\text{TiCl}/\text{D}_2\text{O}$ system [18] is a sustainable and inexpensive reagent, very useful for the preparation of deuterated phenols that can be used as an internal standard in the analysis of some of the bioactive phenolic compounds present in olive oil [15]. In fact, the antioxidant properties of olive oil have been attributed to some of these bioactive phenols, such as tyrosol, and hydroxytyrosol and its derivatives (e.g., oleuropein) [19]. For this reason, the development of analytical methods using deuterated systems as internal standards which allow the quantification of bioactive phenols is an important goal in food and analytical chemistry. Finally, the future perspectives of this system are discussed.

2. Discussion

The use of Cp_2TiCl in reduction reactions of organic compounds using water as a hydrogen atom donor has been known for more than a decade [15,16]. Cp_2TiCl is a single electron transfer reagent obtained by reducing Cp_2TiCl_2 with a nonhazardous metal in dust form, such as Zn or Mn [20]. Alternatively, photoredox catalysis [21], electrochemical reduction [22], and organosilicon reducing agents [23] can be used to obtain Cp_2TiCl from Cp_2TiCl_2 . In tetrahydrofuran (THF) or toluene, the Cp_2TiCl solution is lime green. However, it turns dark blue when water is added to the solution [24,25].

The presence of a vacant site and an unpaired *d*-electron in the inner sphere of this complex allows its coordination to functional groups with heteroatoms with free valence electrons, obtaining different intermediates if the process is energetically favorable. From these intermediates, important chemical synthesis reactions take place, such as C–C and C–O bond-forming reactions, as well as reduction, isomerization, deoxygenation, protection, epoxidation, and decyanation reactions (Scheme 1) [5–11].



C–X: X being a heteroatom with free valence electrons (O, Cl, Br, OAc, OCO_2Et).

Y–H: Y being a heteroatom with free valence electrons (O).

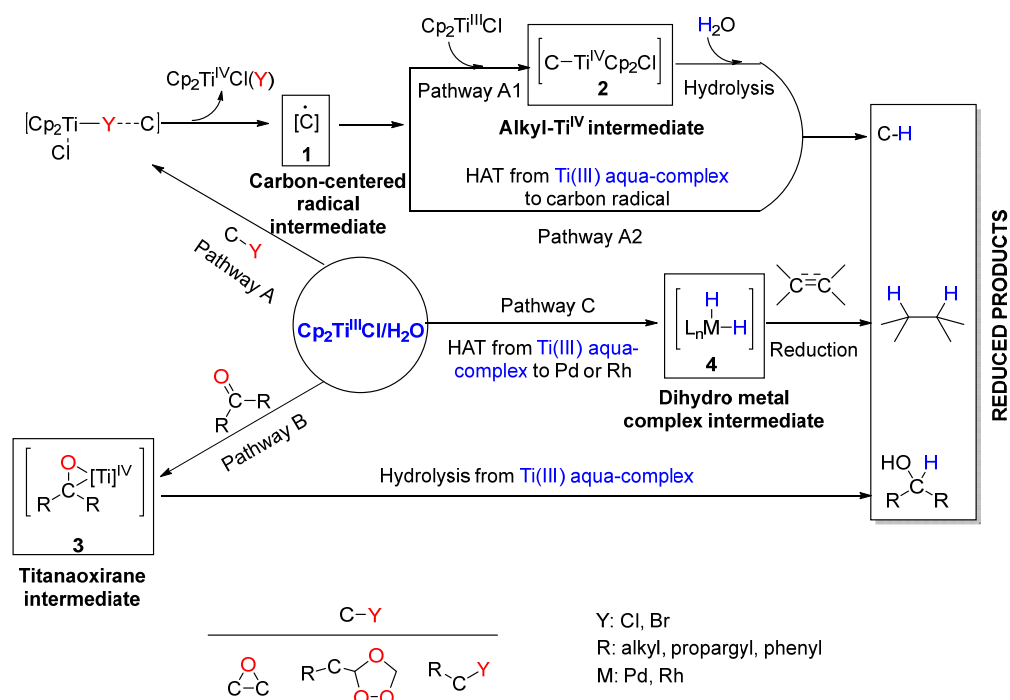
R: H, alkyl, phenyl...

R_1 : alkyl, allyl, benzyl...

Scheme 1. Target functional groups of titanocene(III).

Considering the study of reduction reactions mediated by the $\text{Cp}_2\text{TiCl}/\text{H}_2\text{O}$ system, three types of primary intermediates are formed from epoxides, ozonides, carbonyl com-

pounds, activated halides, and transition metals. Initially, the formation of carbon-centered radicals **1** was observed when C–Y is coordinated to Cp₂TiCl after a single-electron transfer (pathway A, Scheme 2). If a carbon radical **1** is trapped by a second molecule of titanocene(III), an alkyl-Ti^{IV} intermediate **2** is formed (pathway A1, Scheme 2). However, if the carbon radical **1** is hindered, it can be reduced by hydrogen atom transfer from the aqueous complex of titanocene(III) (pathway A2, Scheme 2). The titanaoxirane intermediates **3** are generated from carbonyl groups and Cp₂TiCl/Mn (pathway B, Scheme 2). Hydrolysis of these intermediates **3** generates the reduced compounds. Finally, a dihydro metal complex **4** is obtained when the Cp₂TiCl/water system reacts with a transition metal such as Pd or Rh, allowing the reduction of alkenes or alkynes (pathway C, Scheme 2). All these reaction species are susceptible to producing reductive products through the mechanisms described below.



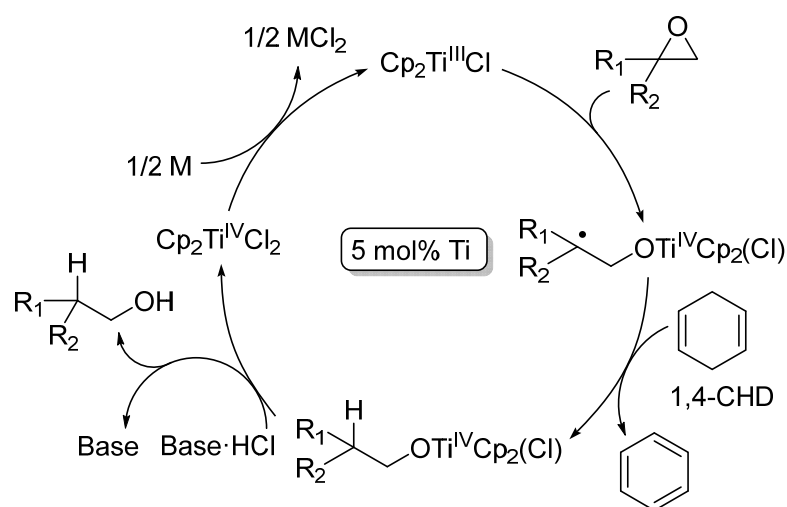
Scheme 2. Intermediates generated in the reduction of functional groups with the Cp₂TiCl/H₂O system.

A breakthrough in the use of the Cp₂TiCl/H₂O system as a new reducing reagent was the development of a catalytic cycle under reductive conditions reported by Gansäuer et al. [26]. In this catalytic cycle, hydrochloride-substituted pyridines (collidine hydrochloride) were employed as versatile acids to protonate the Ti–C or the Ti–O bonds to generate Cp₂TiCl₂ (Scheme 3) [26]. This catalytic cycle has been used successfully for different target functional groups and uses water as a hydrogen source.

The mechanism involved in the reduction of these intermediates and some examples are discussed below.

2.1. Carbon-Centered Radical Intermediates

Homolysis of one epoxide C–O bond, one ozonide O–O bond, or C–halogen bond occurs by inner-sphere electron transfer and results in the generation of a carbon-centered radical intermediate (pathway A, Scheme 2). Under aqueous conditions, the carbon-centered radical intermediate **1** can be reduced through hydrogen atom transfer (HAT) (pathway A, Scheme 4) from an aqua complex of titanocene(III) or by hydrolysis of an organometallic alkyl-Ti^{IV} intermediate **2** generated when the radical is trapped by a second species of titanocene(III) (pathway B, Scheme 4).



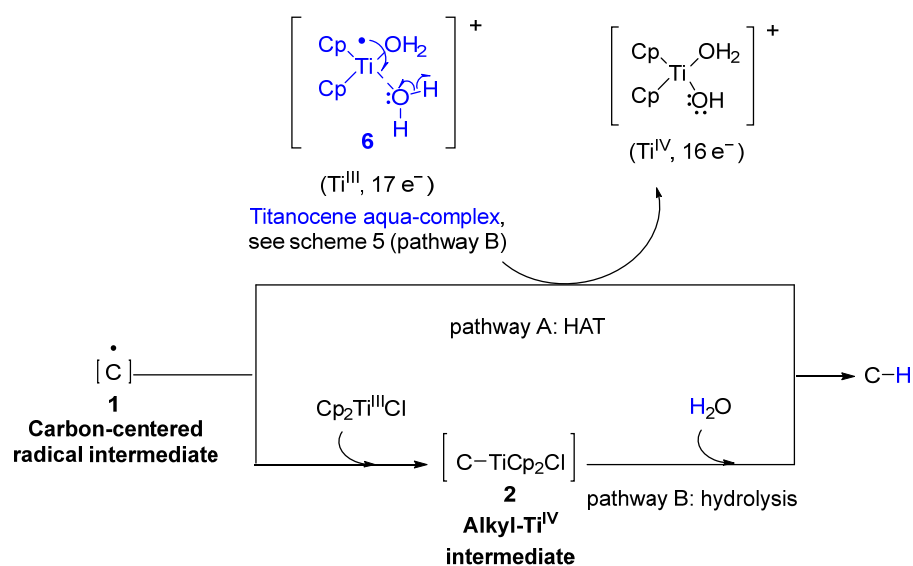
M = Mn, Zn

R₁ = CH₃, R₂ = CH₂CH₂Ph

Base = 2,4,6-collidine

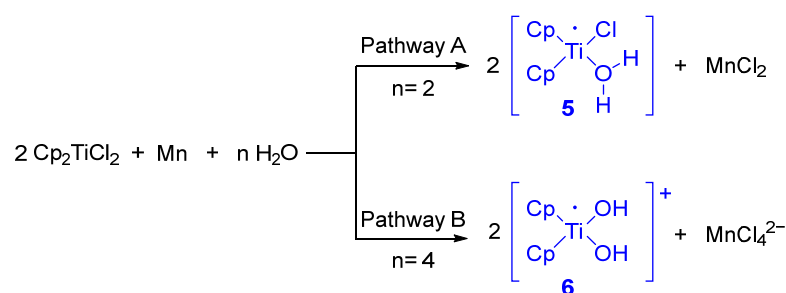
Yield = 88%

Scheme 3. Catalytic Cp₂TiCl epoxide opening using 2,4,6-collidine as a regenerator and 1,4-cyclohexadiene (1,4-CHD) as a hydrogen source.



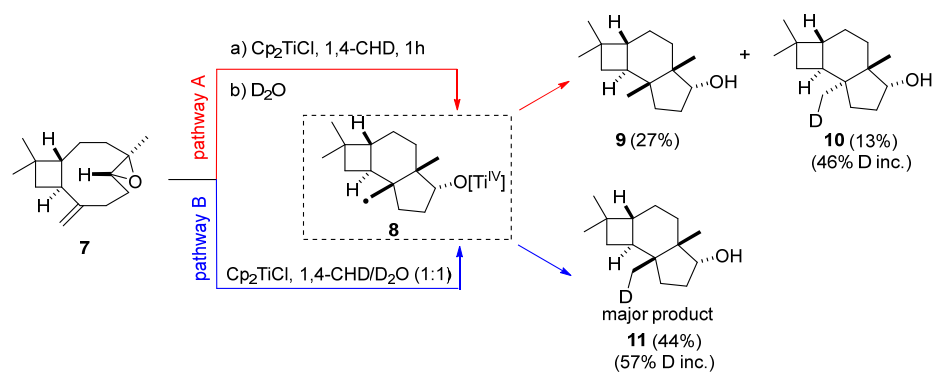
Scheme 4. Reduction of carbon-centered radical intermediates. Pathway A: HAT from water to free radicals mediated by an aqua complex of titanocene(III). Pathway B: Hydrolysis of an alkyl-Ti^{IV} intermediate.

The HAT pathway is only possible because the activation of water by Cp₂TiCl takes place. This activation of water for HAT was initially reported by us in the radical cyclization of epoxygermacrolides [27]. In that paper, we published the following comment: “Contrary to general belief, water can act as a reactive hydrogen atom donor in radical chemistry mediated by Ti(III) species”. The propensity of water to act as a HAT reagent could be explained by a lowering of the dissociation energy of the O–H bond of almost 60 kcal/mol in the presence of Cp₂TiCl. Initially, aqua complex 5 was proposed as a HAT reagent (pathway A, Scheme 5) [17]. However, after extending and refining the theoretical calculations, studies of cyclic voltammetry, mass spectrometric analysis, and electro-paramagnetic resonance techniques suggested that aqua complex 6 is the active HAT reagent (pathway B, Scheme 5) [25,28].



Scheme 5. Proposed Cp_2TiCl aqua complexes.

Water as a HAT reagent was rigorously demonstrated in the transannular cyclization of caryophyllene oxide **7** (Scheme 6) [24]. The radical opening of epoxide **7** mediated by Cp_2TiCl generates a hindered primary radical **8**. Several experiments were carried out to determine the reduction mechanism of the radical generated. In this way, treating **7** with titanocene(III) in the presence of 1,4-CHD (a hydrogen atom donor) and subsequent addition of D_2O (after consumption of **7** (1 h)) gave a mixture of **9** and **10** (pathway A, Scheme 6). The lack of deuterium labeling in **9** was a result that allowed us to indicate that the reduction of the hindered radical as **8** took place by the transfer of hydrogen atoms from 1,4-CHD and not by the hydrolysis of the organometallic intermediate which may be generated when the radical is trapped by a second molecule of Cp_2TiCl . In another experiment, epoxide **7** was treated with Cp_2TiCl in the presence of D_2O and 1,4-CHD. Under these conditions, the main isolated product was **11** (pathway B, Scheme 6). The presence of deuterium labeling in **11** indicated that deuterium atom transfer from D_2O was faster than hydrogen atom transfer from 1,4-CHD, which in the previous experiment (pathway A, Scheme 6) was observed to be much faster than the formation of an organometallic alkyl- Ti^{IV} intermediate.



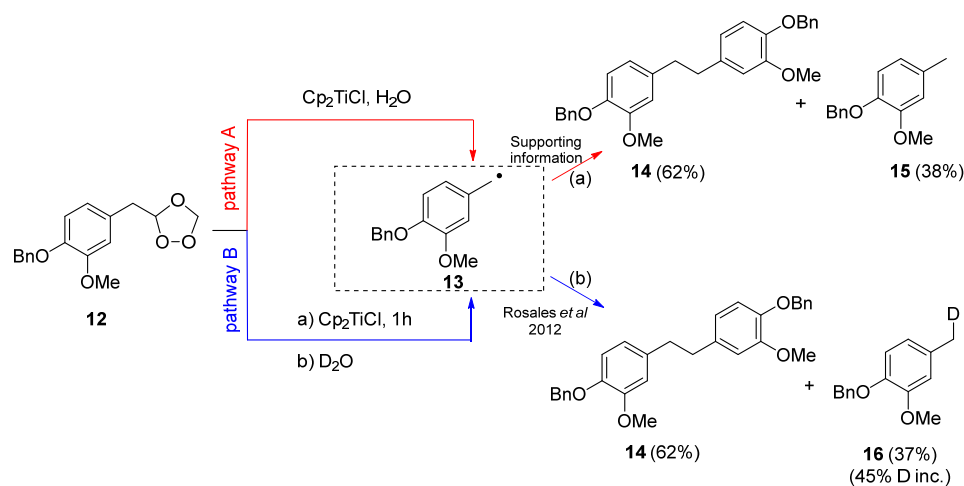
Scheme 6. Deuteration experiments in the cyclization of **7**. (a) Addition of D_2O after 1 h of reaction; (b) addition of D_2O from the beginning.

This mechanism of reduction through HAT was also observed with propargyl radicals [29]. Based on deuteration studies, propargyl radicals were reported to be effectively reduced by HAT from H_2O in a process mediated by Cp_2TiCl .

As can be observed, due to their mild experimental conditions and high chemoselectivity, HAT reactions using the $\text{Cp}_2\text{TiCl}/\text{H}_2\text{O}$ system represent an excellent methodology for reducing carbon-centered radicals of diverse nature. A deep theoretical and experimental study [30] indicated that the success of this reaction is based on two key features: (a) an excellent binding capacity of H_2O to Cp_2TiCl and (b) a low activation energy for the HAT step. If the activation energy for the HAT step is high, the dimerization of the radicals usually prevails over their reduction.

Alternatively, the carbon-centered radical intermediate **1** can be reduced by a more conventional mechanism that involves the formation of an organometallic alkyl- Ti^{IV} in-

intermediate **2** and subsequent hydrolysis by water (pathway B, Scheme 4). This other mechanism was demonstrated based on the experimental and theoretical observations we obtained in the radical opening of ozonides [31]. When ozonide **12** is treated with Cp_2TiCl , an unhindered primary radical **13** is formed. Several reactions were carried out to determine the mechanism of reduction of this benzylic radical **13**. When ozonide **12** was treated with titanocene(III) and water, a mixture of homocoupling product **14** (62%) and reductive product **15** (38%) was obtained (pathway A, Scheme 7) [32]. This result is reported in Supplementary Materials. In another experiment, ozonide **12** was treated with Cp_2TiCl and, after consumption of **12** (1 h), D_2O was added, observing a mixture of **14** and deuterium-labeled product **16** (pathway B, Scheme 7) [31]. The 45% deuterium incorporation in **16** together with the same relative ratio of homocoupling and reductive products in both experiments indicated that the reduction of the unhindered primary radical could be due to the hydrolysis of an organometallic alkyl- Ti^{IV} intermediate formed by trapping the radical with a second molecule of titanocene(III).



Scheme 7. Experiments in the radical opening of ozonide **12**. (a) Reaction in the absence of deuterium source [32]; (b) Reaction quenched with D_2O [31].

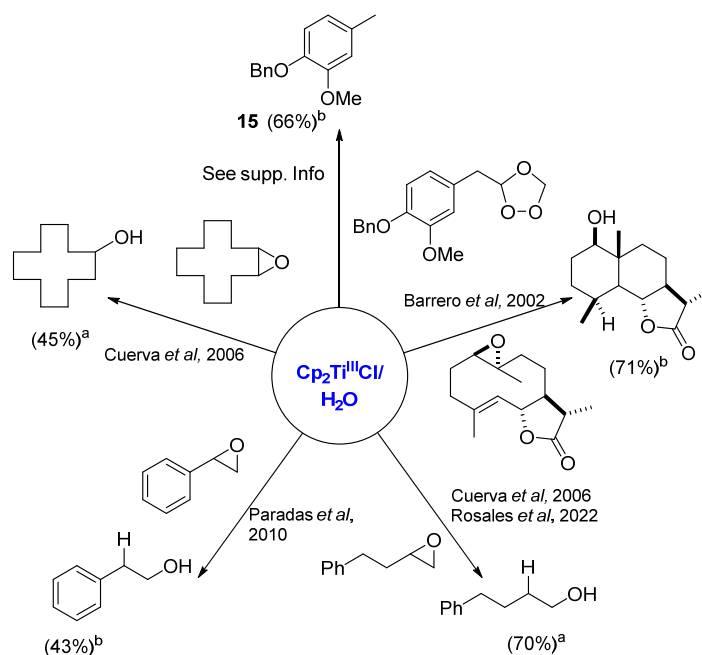
To decrease the dimerization of radical **13**, Cp_2TiCl was added dropwise to ozonide **12** in dry THF, and finally hydrolysis with HCl (2N) resulted in **15** as the main product [32] (see the example in Scheme 8).

Although more computational and experimental studies are being conducted [32] to verify the proposed mechanism of reduction of carbon radicals, as a general rule it can be observed that hindered and tertiary carbon radicals are normally reduced by HAT from water in a process promoted by Cp_2TiCl , while unhindered and primary radicals are generally reduced via hydrolysis of an organometallic alkyl- Ti^{IV} intermediate. Several examples of the reduction of epoxides and ozonides by the $\text{Cp}_2\text{TiCl}/\text{H}_2\text{O}$ system are illustrated in Scheme 8. As can be observed in Scheme 8, the regioselective opening of epoxides mediated by Cp_2TiCl , where water is used as the donor of hydrogen atoms, is a highly green procedure for obtaining anti-Markovnikov alcohols [26,33].

2.2. Titanaoxirane Intermediates

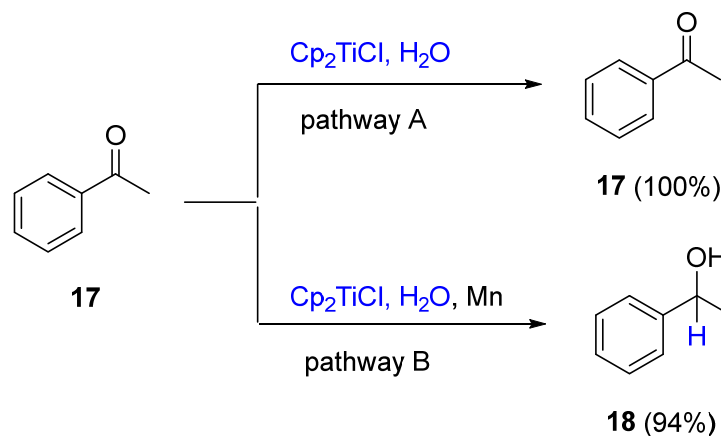
The $\text{Cp}_2\text{TiCl}/\text{H}_2\text{O}$ system can also be used to reduce titanaoxirane species **3** (pathway B, Scheme 2) obtained when carbonyl groups are treated with $\text{Cp}_2\text{TiCl}/\text{Mn}$. Rosales Martínez et al. [34] explored the reduction mechanism of the carbonyl group with titanocene(III) in an aqueous medium. After treating acetophenone **17** with Cp_2TiCl in the absence of manganese, the starting material **17** was recovered unchanged (pathway A, Scheme 9). However, the same reaction in the presence of manganese gave alcohol **18** with a yield of 94% (pathway B, Scheme 9). These results indicated that manganese is

required not only for reducing Cp_2TiCl_2 to Cp_2TiCl , but also for generating the intermediate titanoxirane **20** as the key intermediate (Scheme 10a).



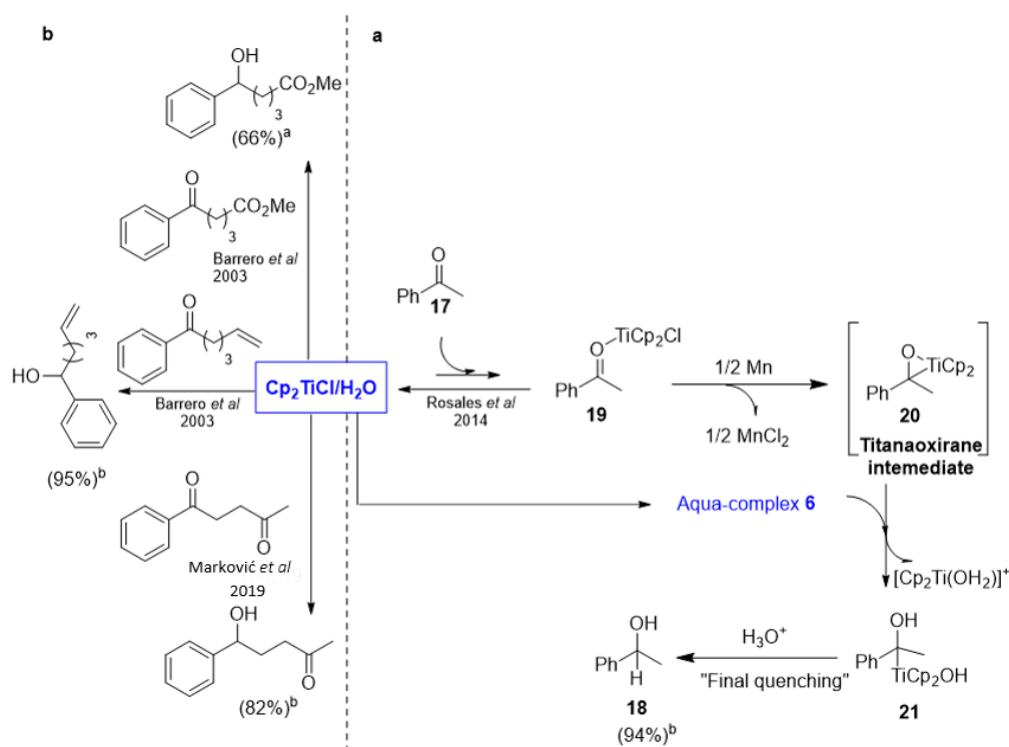
Scheme 8. Examples of reductions of epoxides and ozonides with the $\text{Cp}_2\text{TiCl}/\text{H}_2\text{O}$ system [24,27,30,32,33].

^a Substoichiometric amount of Cp_2TiCl . ^b Stoichiometric amount of Cp_2TiCl .



Scheme 9. Experiments on the reduction of acetophenone **17** with the $\text{Cp}_2\text{TiCl}/\text{H}_2\text{O}$ system.

The observations mentioned were explained by the mechanism proposed in Scheme 10a. Coordination between acetophenone **17** and titanocene(III) would provide the reaction intermediate **19** in an equilibrium reaction shifted toward titanocene(III) and acetophenone **17**. This equilibrium was proposed because, in the absence of manganese, the starting material **17** was recovered unchanged. Therefore, the manganese present in the reaction medium could reduce the Cp_2TiCl coordinated to acetophenone **17** through an irreversible process leading to the formation of the titanoxirane intermediate **20**. When water is present in the reaction medium, the aqua complex **6** is formed, which would probably be more acidic than the non-coordinated water and, therefore, could promote the hydrolysis of the intermediate **20** to an alkyl- Ti^{IV} intermediate such as **21**, a precursor of alcohol **18**. Several examples of the selective reduction of ketones by $\text{Cp}_2\text{TiCl}/\text{H}_2\text{O}$ are presented in Scheme 10b.



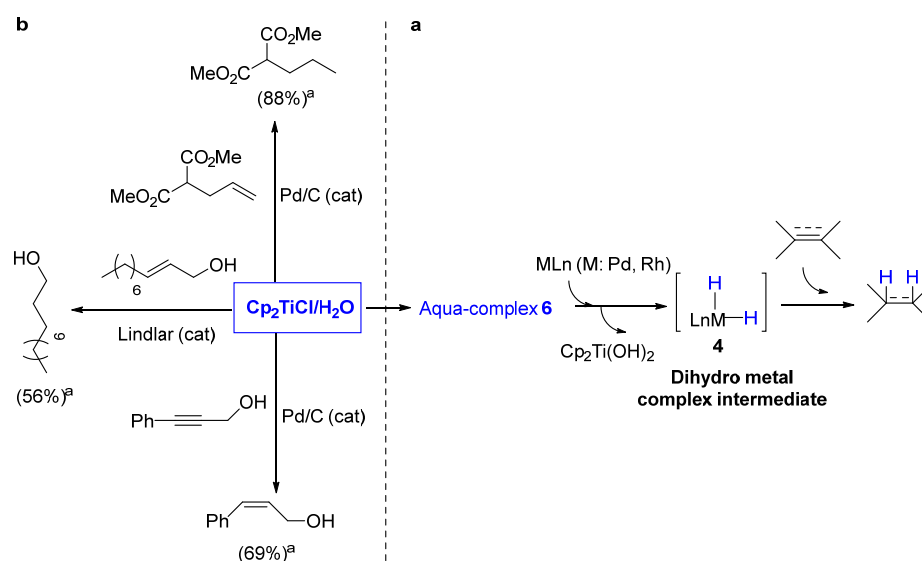
Scheme 10. (a) Proposed mechanism for the titanocene(III)/Mn-promoted reduction of acetophenone 17 in an aqueous medium [34]. (b) Examples of selective reduction of ketones by $\text{Cp}_2\text{TiCl}_2/\text{H}_2\text{O}$ [19,35]. ^a Substoichiometric amount of Cp_2TiCl_2 . ^b Stoichiometric amount of Cp_2TiCl_2 .

2.3. Dihydro Metal Complex Intermediates

In the presence of transition metals such as Rh or Pd, the $\text{Cp}_2\text{TiCl}_2/\text{H}_2\text{O}$ system was also used to reduce alkynes and alkenes [36]. The mechanism of this reduction was explained by the formation of the aqua complex 6, which is able to facilitate the transfer of hydrogen atoms from water to late transition metals (Pd or Rh) to give metal hydride intermediates 4. These intermediates could subsequently bring about alkyne (and alkene) hydrogenation as depicted in Scheme 11a. This mechanism was supported by theoretical and experimental evidence. In this way, theoretical calculations suggested an activation energy of only 17.3 kcal/mol for the hydrogen atom transfer. Several examples of the reduction of alkynes/alkenes by the $\text{Cp}_2\text{TiCl}_2/\text{H}_2\text{O}$ system are presented in Scheme 11b.

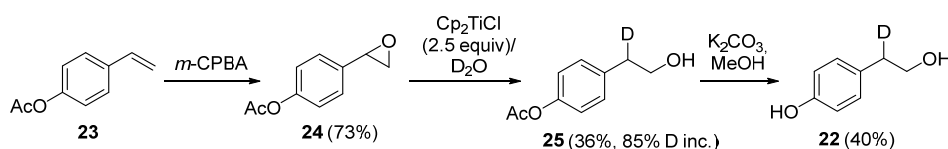
All these results show that the $\text{Cp}_2\text{TiCl}_2/\text{H}_2\text{O}$ system is an excellent sustainable reagent for reduction reactions. This system avoids the use of traditional hydrogen atom donors, such as trialkyl stannane hydrides, which are toxic and sometimes produce side products. Moreover, the moderate efficiency of HAT from this system compared with the trialkylstannanes results in chemical advantages in the involved radical chain reactions, since the radical species will not be prematurely reduced. Moreover, this system avoids the use of cyclohexadiene, silanes, and related compounds as HAT reagents, which are expensive, toxic, and/or foul-smelling. Another attractive feature of this system is that it can be used with a catalytic amount of Cp_2TiCl_2 , unlike other novel HAT reagents such as borane complex with *N*-heterocyclic carbenes since these reagents are employed in stoichiometric amounts.

Finally, the analog of this system that uses heavy water as a deuterium source is used to generate complex deuterium-labeled compounds [16], which can be applied as an internal standard in food analysis. The first synthesis of a deuterated sample of tyrosol, using the $\text{Cp}_2\text{TiCl}_2/\text{D}_2\text{O}$ system as a reducing reagent, was used as an internal standard in determining the concentration of bioactive tyrosol in an olive leaf extract [15]. The result given in mg tyrosol/g of dry weight olive leaves was 0.2 ± 0.05 mg/g.



Scheme 11. (a) Proposed mechanism for the hydrogenation of alkenes or alkynes with $\text{Cp}_2\text{TiCl}/\text{H}_2\text{O}$ in the presence of Pd or Rh catalysts [36]. (b) Examples of the reduction of alkenes and alkynes. ^a Stoichiometric amount of Cp_2TiCl .

Although the overall yield of deuterated tyrosol (**22**) was not high (10.5%), this compound was synthesized from commercially available acetoxystyrene (**23**) in only three steps: (a) epoxidation of **23** with *m*-chloroperoxybenzoic acid (*m*CPBA) to give **24**; (b) radical opening of epoxide **24** with the Ti(III)/ D_2O system to produce deuterated alcohol **25**; and (c) deacetylation of **25** to form **22** (Scheme 12). The moderate deuterium incorporation obtained in alcohol **25** may be due to the fact that part of the alkyl-Ti^{IV} intermediate generated after the opening of the epoxide **24** with titanocene(III) is not hydrolyzed with the heavy water present in the reaction medium due to a high isotope effect. Part of this intermediate could be hydrolyzed after working up the reaction with H_3O^+ .



Scheme 12. Synthesis of deuterated tyrosol (**22**).

3. Conclusions and Perspectives

In summary, we have presented an article showing that $\text{Cp}_2\text{TiCl}/\text{H}_2\text{O}$ is a novel hydrogen atom donor system. It is characterized by being a sustainable, efficient, selective, and economic system that allows the reduction of ozonides, epoxides, carbonyl compounds, alkenes, and alkynes to be carried out. These reductions occur under mild and environmentally safe reaction conditions avoiding the use of other toxic and relatively expensive hydrogen atom donors, such as 1,4-cyclohexadiene or Bu_3SnH . Moreover, its analog using heavy water has been postulated as a much cheaper and safer alternative compared to the traditional reducing reagents used to obtain deuterated alcohols such as NaBD_4 and LiAlH_4 . Despite recent advances in the use of this system as a reducing reagent in radical and organometallic chemistry, many challenges remain: (1) A wide range of other functional groups needs to be further explored with Cp_2TiCl . (2) Asymmetric reduction is another issue due to two factors: the need to use chiral titanocene(III) reagents [37] and that the key intermediate in the reduction process must be organometallic and non-radical in nature. (3) Developing and optimizing the solvent-free reduction process. (4) Extrapolating this system to industrial chemical reductions. (5) Using the $\text{Cp}_2\text{TiCl}/\text{D}_2\text{O}$ system as a deuterium source to generate more deuterated compounds of interest in the food industry,

such as deuterated isomers of hydroxytyrosol, oleacein, oleocanthal, and oleuropein, some of them of major importance in the olive oil industry. These deuterated compounds can be used as internal standards to quantify their non-deuterated analogs present in olive oil. For this purpose, high-performance liquid chromatography (HPLC) allied with mass spectrometry detection, using electrospray ionization as an interface can be used [15].

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/pr11040979/s1>, Figure S1: Experimental procedures for reference [25]; Figure S2: ^1H NMR (CDCl_3 , 300 MHz) of the reaction of the crude ozonide **12** with Cp_2TiCl_2 and Mn in THF, showing the relative ratio of products **14** and **15**; Figure S3: ^1H NMR (CDCl_3 , 300 MHz) of **14**; Figure S4: DEPT 135 and ^{13}C NMR (CDCl_3 , 75 MHz) of **14**; Figure S5: ^1H NMR (CDCl_3 , 300 MHz) of **15**; Figure S6: DEPT 135 and ^{13}C NMR (CDCl_3 , 75 MHz) of **15**.

Author Contributions: A.R.M.: design and coordination of the project, writing—original draft, and writing—review and editing. J.F.G.-M.: review. I.R.-G.: writing—review. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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