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Selective Reduction of Aromatic Ketones in Aqueous Medium Mediated by Ti(III)/Mn: A Revised Mechanism

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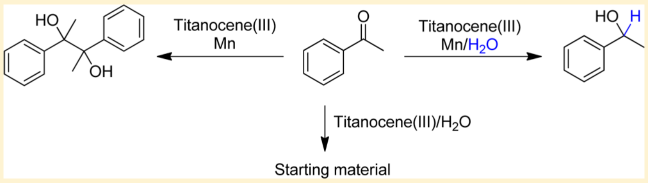
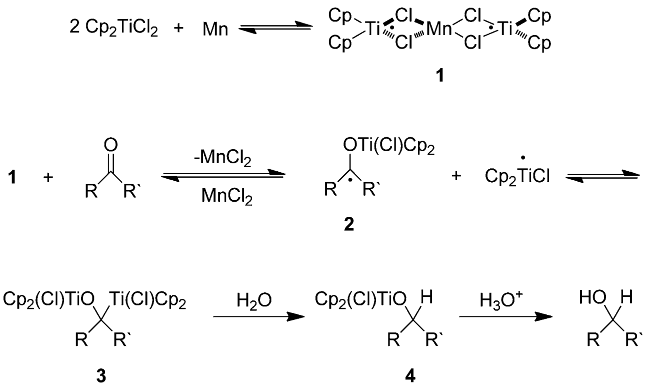
ABSTRACT: An experimental study on the role played by each of the reagents involved in the selective reduction of aromatic ketones in aqueous medium is reported. In this reaction, the reduction of aromatic ketones is mediated by Cp_2TiCl. Moreover, the presence of Mn in the reaction medium is mandatory. To account for these findings, a substantially revised mechanism is proposed.



Titanium is the seventh most abundant metal on earth, and many titanium compounds are nontoxic and environmentally friendly.[1] Among titanium catalysts, Cp_2TiCl (Nugent's reagent) has emerged as a powerful tool in organic synthesis.[2] In fact, this single-electron-transfer (SET) reagent has been shown to be capable of promoting and/or catalyzing transformations as useful as the radical opening of epoxides,[3] radical cascade cyclizations,[4] Barbier-type allylations and propargylations,[5] Michael-type additions of aldehydes to conjugated enals,[6] Reformatsky-type reactions,[7] pinacol couplings,[8] reduction of radicals by hydrogen-atom transfer from water to alkenes,[9] alkynes,[9] ketones,[10] and free radicals,[11] THF-ring formation reactions,[12] regiodivergent epoxide opening (REO) processes,[13] homolytic opening of ozonides,[14] and the synthesis of exocyclic allenes.[15] A detailed knowledge of mechanisms involved in these reactions is desirable to provide a platform for the design of novel and more efficient processes and catalysts. In this paper, we report on the reagents and experimental conditions necessarily required for the titanocene(III)-promoted reduction of ketones in aqueous medium.[10] Our results suggest that the previously proposed reduction mechanisms are not accurate and must be revised.

The observation that tertiary radicals can be efficiently reduced in the presence of titanocene(III) and water[11a] suggested to us that toxic and relatively expensive hydrogen-atom donors such as 1,4-cyclohexadiene are not required for the reduction of radicals under these conditions. Based on this finding, we devised a novel procedure for the selective reduction of aromatic ketones in aqueous medium.[10a] The originally proposed reaction mechanism was based on the assumption that, even in the presence of water, the reduction of ketones by SET from a trinuclear species of titanocene(III) such as **1** should provide titanoxy radicals such as **2** (Scheme 1). The considerable steric demand of these tertiary radicals would delay potential pinacol coupling processes, and thus, **2** could evolve to give the alkyl−Ti^{IV} complex **3** by radical coupling with a second equivalent of Cp_2TiCl. Subsequently, the organometallic derivative **3** in aqueous medium would be hydrolyzed in an irreversible step to **4**, which eventually results in the formation of the corresponding secondary alcohol after acidic quenching (Scheme 1).

Scheme 1. Original Mechanism Proposed for the Titanocene (III)-Promoted Reduction of Aromatic Ketones in Aqueous Media[10a]



Closely related to the above reaction, Oltra et al. reported the titanocene(III)-catalyzed reduction of free radicals, generated from epoxides in aqueous medium, by hydrogen-atom transfer (HAT) from water.[11] To rationalize this unusual reaction, the authors proposed the formation of a titanocene(III) aqua-complex, $Cp_2Ti(OH_2)Cl$, in which the H−OH bond

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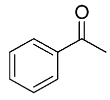
Table 1. Relative Ratio of Compounds Obtained after 60 h of Stirring of **5** with Cp_2TiCl_2, Mn, and/or Water at 25 °C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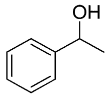
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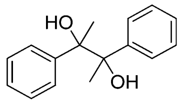
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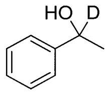
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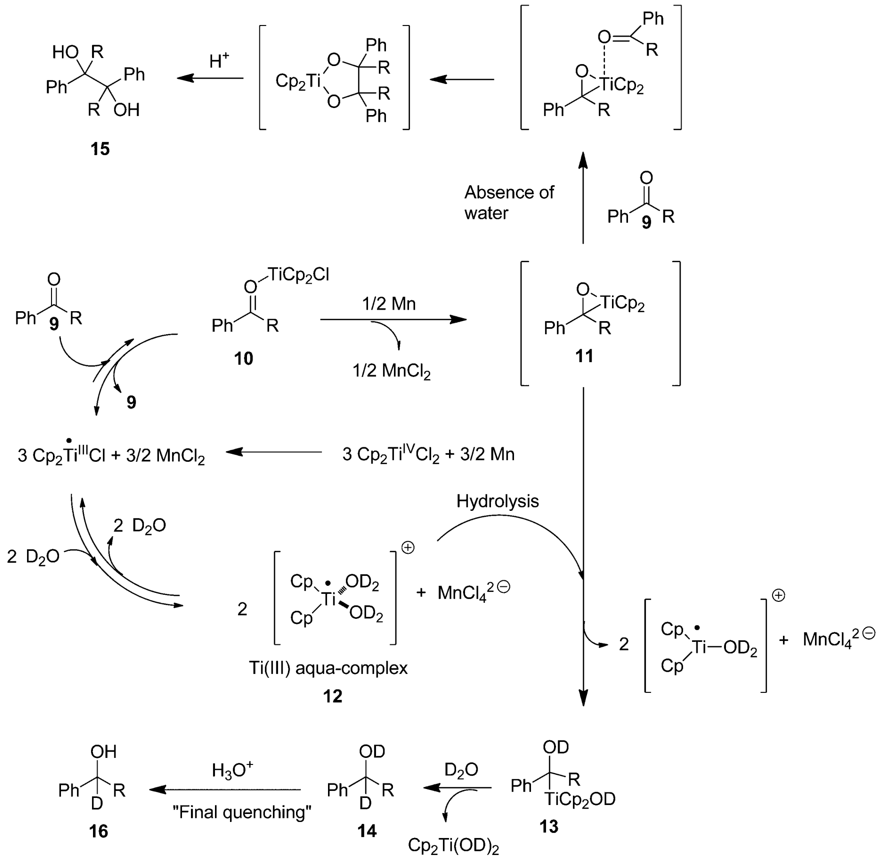
	Cp_2TiCl_2 (equiv)	Mn (equiv)	$MnCl_2$ (equiv)	H_2O (equiv)	**5** (%)	**6** (%)	**7** (%)	**8** (%)
1		8		100	100^a			
2		8	2	100	100^a			
3	1	8		100	60^a	40^a		
4	2	8		100	24^a	76^a		
5	3	8		100	4^b	94^b		
6	Cp_2TiCl 3 eq.^{c}			100	100^a			
7	3	1		100	100^a			
8	3	2		100	100^a			
9	3	4		100	15^a	85^a		
10	3	8					98^b	
11	3	8		50	31^a	52^a	17^a	
12	3	8		D_2O 100	12^a			88^a

[a] Relative ratio determined on the basis of the ^1H NMR spectrum of the reaction crude. [b] Yields of pure products isolated by flash chromatography. [c] Once titanocene(III) was formed (green solution) by reaction between Cp_2TiCl_2 and Mn dust, the solution was filtered under an inert atmosphere to remove residual Mn before addition to **5**.

Scheme 2. Revised Mechanism for the Titanocene(III)/Mn-Promoted Reduction of Ketones in Aqueous Medium



dissociation energy (BDE) would be considerably lower than the BDE of water.[11b] The effect of a Lewis acid on the BDE of water was first described by Wood et al.[16] and Renaud et al.[17] This observation suggested us a partially revised mechanism for ketone reduction in aqueous medium by HAT from $Cp_2Ti(OH_2)Cl$.[10b] Subsequently, Gansäuer et al. revised the structure of the titanocene(III) aqua-complex on the basis of the results obtained from EPR techniques, cyclic voltammetry, and calculations.[18]

Here, we report new results which cannot be explained with the mechanisms previously proposed for the titanocene(III)-catalyzed reduction of ketones in aqueous medium. To avoid the mechanistic complexity arising from the Cp_2TiCl regenerating reagents required in the catalytic version, we decided to study the stoichiometric Cp_2TiCl-mediated reduction of acetophenone **5** in aqueous media. These findings would provide a solid basis for the understanding of the related catalytic systems. Our results are summarized in Table 1.

After 60 h stirring of **5** with Mn dust and water in the absence of titanocene, **5** was recovered unchanged (entry 1), strongly supporting the original assumption that Cp_2TiCl is a key reagent in the reduction process.[10a] Under the usual conditions, $Cp_2Ti^{III}Cl$ is generated in situ by reduction of commercial $Cp_2Ti^{IV}Cl_2$ by Mn (or Zn) dust. This results in the formation of 0.5 equiv of $MnCl_2$ per Cp_2TiCl in the reaction mixture.[19] Therefore, we performed a second control experiment, in the absence of titanocene, by adding Mn dust, water, and $MnCl_2$ to **5** (entry 2). Under these conditions, **5** was recovered quantitatively, too. This definitively confirms that Cp_2TiCl is essential for the reduction process. We determined the exact amount of Cp_2TiCl needed to complete the reduction process by means of three experiments with increasing amounts of Cp_2TiCl_2 (entries 3−5). It turned out that at least 3 equiv of titanocene is needed to complete the process and to obtain an excellent 94% yield of alcohol **6** (entry 5).

We subsequently investigated the role played by manganese in a series of five experiments with increasing amounts of this metal (entries 6−9). We decided to start with a control experiment in the absence of Mn. To this end, we prepared a green suspension of Cp_2TiCl by stirring Cp_2TiCl_2 with Mn dust, filtered of the excess of Mn and added the filtrate, the typical and transparent green solution of Cp_2TiCl devoid of Mn, to **5** under an inert atmosphere. After 60 h of stirring, **5** was recovered unchanged (entry 6), showing that Mn is required not only for the reduction of Cp_2TiCl_2 to Cp_2TiCl but also for the step in which the reduction of ketone **5** to **6** takes place. The results summarized in entries 7 and 8 suggest that with less than 2 equiv of Mn the metal is completely consumed in the reduction of Cp_2TiCl_2 to Cp_2TiCl, and therefore, reduction of **5** to **6** cannot take place. Nevertheless, with 4 equiv of Mn in aqueous THF a significant quantity of reduction **6** (85%) was obtained (entry 9). The optimum yield (94%) of **6**, however, was obtained with 8 equiv of Mn (entry 5). It should be noted that the excess of Mn can be easily recovered at the end of the experiment by simple filtration. Nevertheless, the most important observation is that in the absence of Mn neither reduction nor pinacol-coupling products were detected (entry 6), suggesting that Mn is needed to efficiently generate a key species involved in the reduction processes.

Finally, we corroborated the role played by water. As above, we started with a control experiment in the absence of water (dry THF, entry 10). Under these conditions, only **7** was detected. In contrast, when we added 50 equiv of water, **6** (52%) was the main product (entry 11). The optium yield of **6** (94%), however, was obtained with 100 equiv of water (entry 5). Finally, we treated **5** with Cp_2TiCl_2, Mn, and D_2O (entry 12). In this manner, we obtained deuterium labeled **8** with a 90% deuterium incorporation (DI).

The observations mentioned above cannot be explained by the originally proposed mechanism (see Scheme 1).[10a] Moreover, the partially revised mechanism reported by Paradas et al.[10b] does not account for the direct participation of Mn as mandatory reagent. On the other hand, the revised mechanism depicted in Scheme 2 suitably accommodates all experimental observations reported to date.

The coordination between **9** and Cp_2TiCl would provide the intermediate **10** in an equilibrium reaction shifted toward Cp_2TiCl and **9**. We propose this equilibrium because in the absence of Mn **5** is recovered unchanged (entry 6). Then, Mn present in the reaction medium would reduce Cp_2TiCl coordinated to **9** in an irreversible process leading to the titanaoxirane **11**. This type of metallaoxiranes is well-known. In fact, both zirconaoxiranes and titanaoxiranes closely related to **11** have been reported previously.[20] In the absence of Mn, the key intermediate **11** is not formed, and consequently, neither pinacol-coupling nor reduction products are observed (entry 6). In the presence of Mn, but absence of water, formation of **11** and subsequent coordination to a second molecule of **9** would lead to pinacol-coupling products such as **15** (**7** when R = Me, entry 10) via five-membered titanadioxolanes as previously reported.[20c] In aqueous medium, however, a Ti(III) aqua-complex such as **12** is formed.[11b,18] It is known that this aqua-complex can act as an efficient H atom donor for the reduction of carbon-centered free radicals.[11] Nevertheless, in the absence of radicals, aqua-complex **12**, which would probably be more acidic than uncomplexed water, could promote the hydrolysis of **11** to alkyl-TI(IV) products such as **13**, precursors of reduction products like **6** or **8** (when D_2O is used instead of H_2O). Formation of **12** from Cp_2TiCl would be an equilibrium reaction, and thus, when the proportion of water increases, a higher amount of the reduction product **9** is obtained (compare entries 5 and 11).

In conclusion, a detailed experimental study of the role played by each of the reagents involved in the selective reduction of aromatic ketones in aqueous medium, promoted by Cp_2TiCl_2/Mn, is reported. Thus, we have observed that Mn is required not only to reduce $Cp_2Ti^{IV}Cl_2$ to $Cp_2Ti^{III}Cl$ but also for the irreversible generation of a key intermediate, the titanaoxirane **11**. In the presence of water, this intermediate undergoes hydrolysis toward alcohols, such as **6** or **8**. Nevertheless, under anhydrous conditions the intermediate is transformed into pinacol-coupling products such as **15**. Thus, the free-radical character conventionally assumed for these chemical processes should be reconsidered.

■ EXPERIMENTAL SECTION

General Methods. General details have been described elsewhere.[11c] Silica gel was used as solid support for flash chromatography. Compounds **6** and **7** are commercial.

Treatment of Acetophenone (5) with Mn and H_2O (Entry 1). Deoxygenated THF (18 mL) was added to Mn (438 mg, 8 mmol) under an argon atmosphere. The suspension was stirred, and then a solution of acetophenone (**5**) (120 mg, 1 mmol) and water (1.8 mL, 100 mmol) in THF (12 mL) was added. The solution was stirred for 60 h at 25 °C. The reaction was then quenched with 2 N HCl and extracted with Et_2O. The organic layer was washed with brine and dried (anhyd Na_2SO_4), and the solvent was removed to afford starting material **5**. The relative ratio (see entry 1 in Table 1) was determined on the basis of their ^1H NMR spectra.

Treatment of Acetophenone (5) with Mn, $MnCl_2$, and H_2O (Entry 2). Deoxygenated THF (18 mL) was added to a mixture of $MnCl_2$ (251 mg, 2 mmol) and Mn (438 mg, 8 mmol) under an argon atmosphere. The suspension was stirred, and then a solution of acetophenone (**5**) (120 mg, 1 mmol) and water (1.8 mL, 100 mmol) in THF (12 mL) was added. The solution was stirred for 60 h at 25 °C. The reaction was then quenched with 2 N HCl and extracted with Et_2O. The organic layer was washed with brine and dried (anhyd Na_2SO_4) and the solvent removed to afford starting material **5**. The relative ratio (see entry 2 in Table 1) was determined on the basis of their ^1H NMR spectra.

General Procedure for Ti(III)/Mn-Mediated Reduction of Acetophenone (5) in Aqueous Media (Entries 3−5). Deoxygenated THF (18 mL) was added to a mixture of Cp_2TiCl_2 (247 mg, 1 mmol (entry 3); 494 mg, 2 mmol (entry 4) or 741 mg, 3 mmol (entry 5 and 11)) and Mn (438 mg, 8 mmol) under an argon atmosphere, and the suspension was stirred at 25 °C until it turned lime green (after about 15 min). Then a solution of acetophenone (**5**) (120 mg, 1 mmol) and water (1.8 mL, 100 mmol (entries 3−5) or 0.9 mL, 50 mmol (entry 11)) in THF (12 mL) was added, and the solution (it turned blue when water was used) was stirred for 60 h at 25 °C. The reaction was then quenched with 2 N HCl and extracted with Et_2O. The organic layer was washed with brine and dried (anhyd Na_2SO_4) and the solvent removed. The residue of the entry 5 was submitted to flash chromatography (hexane/AcOEt 9:1) affording the products indicated in Table 1. NMR data of **6** are identical that reported from commercial sample. For the other entries (3, 4, and 11 in Table 1), the relative ratio of products was determined on the basis of their ^1H NMR spectra.

Treatment of Acetophenone (5) with Cp_2TiCl and H_2O (Entry 6). Deoxygenated THF (18 mL) was added to a mixture of Cp_2TiCl_2 (741 mg, 3 mmol) and Mn (438 mg, 8 mmol) under an argon atmosphere, and the suspension was stirred at 25 °C until it turned lime green (after about 15 min). Once titanocene(III) was formed (green solution), the solution was filtered under an inert atmosphere, to remove residual Mn. Then, a solution of acetophenone (**5**) (120 mg, 1 mmol) and water (1.8 mL, 100 mmol) in THF (12 mL) was added, and the solution was stirred for 60 h at 25 °C. The reaction was then quenched with 2 N HCl and extracted with Et_2O. The organic layer was washed with brine and dried (anhyd Na_2SO_4) and the solvent removed to afford starting material **5**. The relative ratio (see entry 6 in Table 1) was determined on the basis on the basis of the ^1H NMR spectra.

Treatment of Acetophenone (5) with Cp_2TiCl, Mn, and H_2O (Entries 7−9). Deoxygenated THF (18 mL) was added to a mixture of Cp_2TiCl_2 (741 mg, 3 mmol) and Mn (54.7 mg, 1 mmol (entry 7); 109.4 mg, 2 mmol (entry 8) or 219 mg, 4 mmol (entry 9)) under an argon atmosphere, and the suspension was stirred at 25 °C for 15 min. Then, a solution of acetophenone (**5**) (120 mg, 1 mmol) and water (1.8 mL, 100 mmol) in THF (12 mL) was added, and the solution (it turned blue when water was used) was stirred for 60 h at 25 °C. The reaction was then quenched with 2 N HCl and extracted with Et_2O. The organic layer was washed with brine and dried (anhyd Na_2SO_4) and the solvent removed to afford the products indicated in entries 7−9 in Table 1. The relative ratio (see entries 7−9 in Table 1) was determined on the basis of their ^1H NMR spectra.

Pinacolization of Acetophenone (5) with Cp_2TiCl and Mn (Entry 10). Deoxygenated THF (18 mL) was added to a mixture of Cp_2TiCl_2 (741 mg, 3 mmol) and Mn (438 mg, 8 mmol) under an argon atmosphere, and the suspension was stirred at 25 °C until it turned lime green (after about 15 min). Then, a solution of acetophenone (**5**) (120 mg, 1 mmol) in THF (12 mL) was added, and the solution was stirred for 60 h at 25 °C. The reaction was then quenched with 2 N HCl and extracted with Et_2O. The organic layer was washed with brine and dried (anhyd Na_2SO_4) and the solvent removed. The crude of reaction was submitted to flash chromatography (hexane/AcOEt 9:1) affording **7** in a yield of 98%. NMR data of **7** are identical to those reported for a commercial sample.

Experimental Procedure for Ti(III)/Mn-Mediated Synthesis of 1-Deutero-1-phenylethanol (8) in D_2O (Entry 12). Deoxygenated THF (18 mL) was added to a mixture of Cp_2TiCl_2 (741 mg, 3 mmol) and Mn (438 mg, 8 mmol) under an argon atmosphere, and the suspension was stirred at 25 °C until it turned lime green (after about 15 min.). Then, a solution of acetophenone (**5**) (120 mg, 1 mmol) and D_2O (1.9 mL, 100 mmol) in THF (12 mL) was added, and the solution (it turned blue when water was used) was stirred for 60 h at 25 °C. The reaction was then quenched with 2 N HCl and extracted with Et_2O. The organic layer was washed with brine and dried (anhyd Na_2SO_4) and the solvent removed to afford the products indicated in entry 12 in Table 1. Deuterium-labeled alcohol **8** was obtained with a 90% deuterium incorporation. ^1H NMR data of **8** are identical to those reported for a commercial sample.

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Notes

The authors declare no competing financial interest.

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