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Titanocene-catalysed, selective reduction of ketones in aqueous media. A safe, mild, inexpensive procedure for the synthesis of secondary alcohols via radical chemistry

Alejandro F. Barrero,[a] Antonio Rosales,[a] Juan M. Cuerva,[a] Andreas Gansäuer[b] and J. Enrique Oltra[a,*]

[a]*Universidad de Granada, Departamento de Química Orgánica, Facultad de Ciencias, E-18071 Granada, Spain*
[b]*Rheinische Friedrich-Wilhelms-Universität, Kekulé-Institut für Organische Chemie und Biochemie, Gerhard-Domagk-Str. 1, D-53121 Bonn, Germany*

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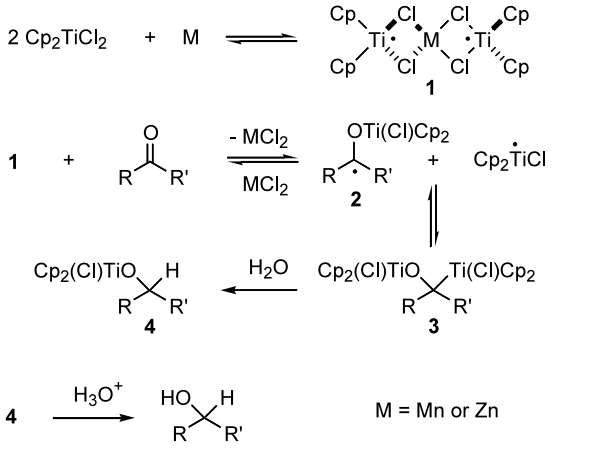
Abstract—We report here a novel procedure for the reduction of ketones to secondary alcohols using catalytic quantities of commercially available Cp_2TiCl_2, inexpensive Zn dust and water as proton source. Mechanistically the reaction presumably proceeds via titanoxy radicals. In practice this reduction process has significant advantages: it shows an interesting selectivity pattern, takes place under mild conditions using safe, cheap reagents and does not require anhydrous solvents. The proton-donor activity of water under these conditions avoids the use of the frequently poisonous hydrogen-atom donors generally required to reduce free radicals. This procedure is also highly convenient for synthesising deuterium-labelled alcohols employing relatively inexpensive D_2O as deuterium source.

The reduction of ketones to secondary alcohols is a reaction of general interest in organic chemistry. Apart from some chemo-biological methods,[1] this reduction is usually achieved by catalytic hydrogenation, by dissolving metals, or employing metal hydrides.[2] Another method, based upon hydrogen transfer from alcohols catalysed by either aluminum alkoxides (the Meerwein–Ponndorf–Verley reduction),[3] or complexes containing Ru^{II} and other metals has proved to be very fruitful, especially for asymmetric synthesis.[4–7] On the other hand, a catalytic procedure for the chemical reduction of ketones taking advantage of virtually free and environmentally sound water as proton source has not until now been developed. Although it is known that ketones can be reduced by low-valent species of transition metals such as samarium,[8–10] chromium,[11,12] and titanium in aqueous media,[13] the procedures reported to date have not proved to have wide synthetic utility, possibly because they require stoichiometric amounts of the low-valent metals.

In 1994, RajanBabu and Nugent reported the selective generation of free radicals from epoxides using titanocene(III),[14] and subsequently Gansäuer et al. developed the catalytic version of this reaction employing 1,4-cyclohexadiene as hydrogen source.[15] While applying this method to the synthesis of natural terpenoids we recently found that tertiary radicals were efficiently reduced in the presence of titanocene(III) and



Scheme 1. Hypothetic mechanism of the titanocene(III)-promoted reduction of ketones in aqueous media.

Keywords: electron transfer; free radicals; homogeneous catalysis; ketones; titanium.

* Corresponding author. Tel.: 34 958 24 80 91; fax: 34 958 24 84 37; e-mail: joltra@ugr.es

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water,[16] suggesting that hydrogen-atom donors such as 1,4-cyclohexadiene are not necessarily required for the reduction of free radicals under these conditions. These observations prompted us to attempt a novel procedure for the reduction of ketones via ketyl radicals using catalytic quantities of titanocene in aqueous media. We considered that such a method would be inexpensive, mild and safe, avoiding the use of strong bases (alkaline metals, metal hydrides and alkoxides), dangerous molecular hydrogen and carcinogenic 1,4-cyclohexadiene. Additionally, the organometallic nature of the catalyst might facilitate the subsequent development of an asymmetric version using chiral organic ligands.

Our initial hypothesis (Scheme 1) was based upon the assumption that even in the presence of water the reaction between ketones and a trinuclear complex of titanocene(III) such as **1**,[†] by single electron transfer (SET), should provide titanoxy radicals such as **2**, closely related to those proposed for the pinacol coupling of aromatic and α,β-unsaturated aldehydes.[20]

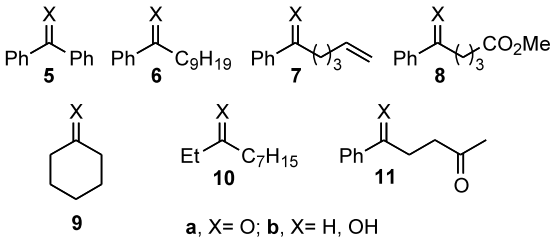
With ketones, however, the higher steric hindrance inherent in these compounds should delay pinacol coupling, and thus **2** could evolve to give the alkyl–Ti^{IV} complex **3** by radical coupling with a second unit of Cp_2TiCl released from **1** in the vicinity of the ketyl radical. Subsequently the organometallic derivative **3** would be hydrolysed in an irreversible step leading to **4**, which should give the corresponding secondary alcohol after acidic quenching.

To check our hypothesis we chose acetophenone. When this ketone was treated with titanocene(III) generated in situ,[†] in dry THF we obtained the pinacol coupling product 2,3-diphenyl-2,3-butanediol.[‡] In contrast, when water was added to the reaction medium, acetophenone was reduced to 1-phenylethanol as we expected. At least 2 equiv. of Cp_2TiCl_2 were required to complete this reduction, supporting the stoichiometric relationships suggested in Scheme 1.

To confirm the role played by water, the experiment was repeated using D_2O instead of H_2O. Thus we obtained 1-deuterio-1-phenylethanol at a yield of 79% (isolated product). GC–MS analysis indicated 87% deuterium incorporation. These results confirmed the proton-donor role of water and showed the potential value of this procedure for the synthesis of deuterium-labelled alcohols (D_2O is the cheapest deuterated reagent known).

Once we were confident about the role of water we decided to explore the scope and limitations of the method. Therefore, we assayed the reduction of ketones **5a**–**11a** bearing various additional functional groups.

Table 1. Relative proportions[a] (%) of compounds obtained by titanocene(III)-promoted reduction of **5a**–**11a** in aqueous media



Substrate	Metal (equiv.)	Time (h)	Products (%)
5a	Mn (8)	24	**5a** (<5), **5b** (>95)
6a	Mn (8)	48	**6a** (83), **6b** (17)
6a	Zn (8)	24	**6a** (<5), **6b** (>95)
7a	Zn (8)	24	**7a** (<5), **7b** (>95)
8a	Zn (8)	24	**8a** (<5), **8b** (>95)
9a	Zn (8)	60	**9a** (20), **9b** (80)
10a	Zn (8)	60	**10a** (100)
11a	Zn (8)	60	**11a** (18), **11b** (82)
9a+**10a**[b]	Zn (8)	60	**9a** (10), **9b** (40), **10a** (50)

er > **10a** (50)

[a] Reductions were performed by treatment with Cp_2TiCl_2 (3 equiv. per ketone) and Mn or Zn, in THF/H_2O (4/1) at rt. Relative proportions were determined on the basis of the ^1H NMR spectra of the mixtures formed in every experiment.

[b] Equimolar mixture.

Thus we obtained alcohols **5b**–**9b** and **11b** in relative proportions ranging from 80% to >95% (Table 1).

Throughout these experiments we made the following observations: (i) the method seemed to be generally valid for the reduction of aromatic ketones and cyclohexanone, but failed with the acyclic ketone **10a**, which was recovered unchanged; (ii) the reaction rates increased when Zn was used instead of Mn; (iii) the reduction process was able to discriminate not only between ketones and alkenes, ketones and esters, and aromatic and aliphatic ketones, but also between cyclic and acyclic aliphatic ketones. This noticeable selectivity pattern is difficult to achieve by conventional reduction methods, especially working at room temperature as we did in all the experiments described here.

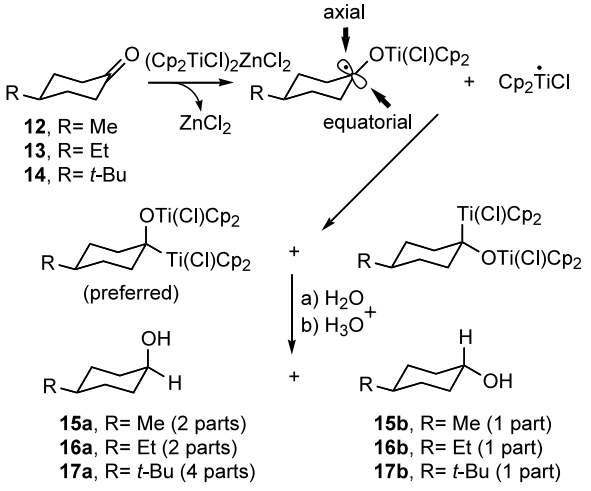
We subsequently attempted the reduction of the substituted cyclohexanones **12**–**14** to gain more information about the stereochemical outcome of the reaction. In all cases the axial alcohol obtained (*cis* isomers **15a**–**17a**) predominated over the equatorial one (*trans* isomers **15b**–**17b**). These results might derive from the preferred equatorial attack by the bulky titanocene(III) upon the cyclic titanoxy radical (Scheme 2).

[†] Titanocene(III) can be generated in situ by stirring commercially available Cp_2TiCl_2 and either Mn or Zn. Under these conditions, trinuclear species such as **1** are obtained.[17–19]

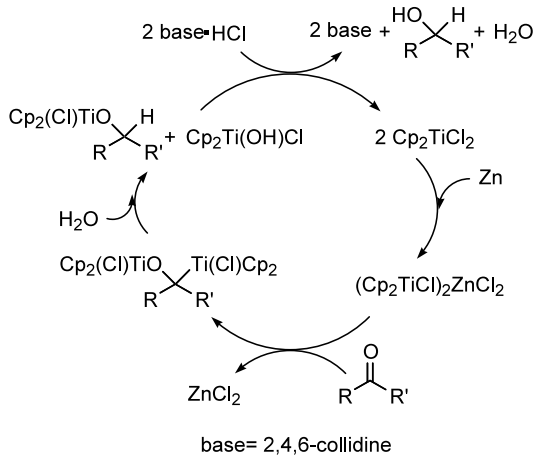
[‡] All products obtained were isolated and characterised by spectroscopic techniques.

This stereochemical behaviour is similar to that reported for bulky hydride reducing agents,[21] (contrary to that shown by titanocene borohydride),[22] thus providing an alternative method for the synthesis of axial alcohols under non-alkaline conditions.

Catalysis plays a crucial role in chemical synthesis.[6,23] Therefore, once we knew the main features of the stoichiometric reduction we could focus our attention on the development of the catalytic version, which was the main aim of the present work. Gansäuer et al. successfully used 2,4,6-collidine hydrochloride to regenerate Cp_2TiCl_2 from the alkoxy-titanium species formed during the titanocene-catalysed opening of epoxides.[15] With this idea in mind, we chose this hydrochloride to regenerate Cp_2TiCl_2 from the titanium derivatives presumably formed in our process. Subsequently Cp_2TiCl_2 could be reduced once more to titanocene(III) by the surplus of Zn in the medium. Thus, the catalytic cycle depicted in Scheme 3 should be completed.



Scheme 2. Stereoselective reduction of cyclohexanones promoted by titanocene(III) in aqueous media.



Scheme 3. Titanocene-catalysed reduction of ketones in aqueous media.

We were pleased to find that treatment of keto ester **8a** with a substoichiometric quantity (10 mol%) of commercially available Cp_2TiCl_2,§ 2,4,6-collidine hydrochloride, Zn dust and water gave secondary alcohol **8b** in 66% yield.¶

Additionally, titanocene-catalysed reduction of **14** gave a mixture of **17a** (25% yield) and **17b** (8%), indicating that the stereoselectivity showed by the stoichiometric reaction was roughly retained under catalytic conditions. The results obtained in the catalytic reduction of acetophenone,§ and the keto ester **8a**¶ support the concept outlined in Scheme 3 and reinforce the synthetic value of the method.

Deuterium-labelled compounds are powerful tools for mechanistic studies of both chemical and biochemical reactions. Nevertheless, the synthesis of deuterium-labelled alcohols by the conventional treatment of ketones with $NaBD_4$ may be limited in some cases by the relatively high cost of this reagent. In this context we thought that a titanium-catalysed reduction, employing the less expensive D_2O (roughly 80-fold cheaper than $NaBD_4$) as deuterium source, might offer a convenient alternative for the synthesis of labelled alcohols. As we expected, the titanocene-catalysed reduction of acetophenone and keto ester **8a**, using D_2O instead of H_2O,¶ gave 1-deuterio-1-phenylethanol (35% yield) and the deuterated isotopomer of **8b** (64% yield), respectively. Collidine and any surplus Zn can be easily recovered at the end of these experiments and thus the main cost of the process derives from the relatively inexpensive catalytic quantity of Cp_2TiCl_2 and the D_2O consumed. These results confirm the potential of our catalytic process for the synthesis of some labelled alcohols in economical terms.

§ The role played by the titanium catalyst is essential and thus, when acetophenone was treated under similar conditions but excluding titanium, the starting ketone was recovered unchanged. When a catalytic amount of Cp_2TiCl_2 was added, on the other hand, 1-phenylethanol was obtained (71% yield of isolated product).

¶ **Titanocene-catalysed reduction of keto ester 8a (a model experimental procedure)**: Strictly deoxygenated THF (10 mL) was added to a mixture of commercially available Cp_2TiCl_2 (6.5 mg, 0.026 mmol) and Zn dust (135 mg) under an Ar atmosphere, and the suspension was stirred at rt until it turned lime green (after about 15 min). Subsequently, keto ester **8a** (50 mg, 0.26 mmol) in THF (5 mL), H_2O (28 μL, 1.56 mmol), and 2,4,6-collidine hydrochloride (163 mg, 1.03 mmol) were added to the green suspension, giving a deep-blue mixture which was stirred at rt for 48 h. The suspension was then filtered (to recover the excess of Zn) and the solvent was removed from the filtrate, *t*-BuOMe (30 mL) was added to the residue and the ethereal solution was washed with 2N HCl and brine. The organic layer was dried over anhyd. Na_2SO_4 and the ether was removed. Flash chromatography (hexane/*t*-BuOMe, 1/1) of the residue afforded hydroxy ester **8b** (33 mg, 66% yield), and starting ketone **8a** (13 mg, 26%). The recovered ketone was reduced once more under similar conditions, rising the overall yield of **8b** until 83%. Collidine can be also recovered at the end of the experiment (by simple acid–base extraction),[15] treated with HCl, and used again.

Deuterium-labelled alcohols were obtained under the same experimental conditions but using D_2O instead of H_2O. In these experiments collidine hydrochloride was treated with D_2O prior to use.

In summary, we describe here a novel procedure for the selective reduction of ketones to secondary alcohols catalysed by a titanocene complex in aqueous media. Mechanistically the reaction probably proceeds via titanoxy radicals. In practice this reduction has significant advantages over the conventional methods: it shows a noticeable selectivity pattern, takes place under mild conditions using inexpensive and safe reagents and does not require pre-dried solvents. To the best of our knowledge this is the first procedure described for the reduction of ketones catalysed by an organometallic complex and employing water as proton source. The proton-donor activity shown by water under these conditions avoids the use of the frequently poisonous hydrogen-atom donors usually required to reduce free radicals.[24] Moreover, the organometallic nature of the catalyst is a relevant feature with regard to asymmetric synthesis. As Professor Noyori has recently pointed out, the virtually unlimited structural variation in the organic ligand offers great opportunities for asymmetric catalysis.[23] Along these lines, we are currently pursuing studies towards an enantioselective version of the method reported here using well-established chiral titanocene catalysts.[25]

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References

1. Faber, K. *Biotransformations in Organic Chemistry*; 3rd ed.; Springer: Berlin, 1997.
2. Larock, R. C. *Comprehensive Organic Transformations*; 2nd ed.; Wiley: New York, 1999.
3. Ooi, T.; Ichikawa, H.; Maruoka, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 3610–3612 and references cited therein.
4. Yamakawa, M.; Ito, H.; Noyori, R. *J. Am. Chem. Soc.* **2000**, *122*, 1466–1478.
5. Yamakawa, M.; Yamada, I.; Noyori, R. *Angew. Chem.* **2001**, *113*, 2900–2903.
6. Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40–73.
7. Hartmann, R.; Chen, P. *Angew. Chem., Int. Ed.* **2001**, *40*, 3581–3585.
8. Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693–2698.
9. Hasegawa, D. P.; Curran, D. P. *J. Org. Chem.* **1993**, *58*, 5008–5010.
10. Dahlén, A.; Hilmersson, G. *Tetrahedron Lett.* **2002**, *43*, 7197–7200.
11. Patonay, T.; Hajdu, C.; Jeko, J.; Lévai, A.; Micskei, K.; Zucchi, C. *Tetrahedron Lett.* **1999**, *40*, 1373–1374.
12. Micskei, K.; Gyarmati, J.; Kovács, G.; Makleit, S.; Simon, C.; Szabó, Z.; Marton, J.; Hosztafi, S.; Reinke, H.; Drexler, H. J. *Eur. J. Org. Chem.* **1999**, 149–153.
13. For a review of low-valent titanium chemistry, see: Fürstner, A.; Bogdanovic, B. *Angew. Chem., Int. Ed.* **1996**, *35*, 2442–2469.
14. RajanBabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1994**, *116*, 986–997.
15. Gansäuer, A.; Bluhm, H.; Pierobon, M. *J. Am. Chem. Soc.* **1998**, *120*, 12849–12859.
16. Barrero, A. F.; Oltra, J. E.; Cuerva, J. M.; Rosales, A. *J. Org. Chem.* **2002**, *67*, 2566–2571.
17. Sekutowski, D. G.; Stucky, G. D. *Inorg. Chem.* **1975**, *14*, 2192–2199.
18. Sekutowski, D.; Jungst, R.; Stucky, G. D. *Inorg. Chem.* **1978**, *17*, 1848–1855.
19. Stephan, D. W. *Organometallics* **1992**, *11*, 996–999.
20. Barden, M. C.; Schwartz, J. *J. Am. Chem. Soc.* **1996**, *118*, 5484–5485.
21. Greeves, N. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 8, pp. 1–24.
22. Barden, M. C.; Schwartz, J. *J. Org. Chem.* **1995**, *60*, 5963–5965.
23. Nobel Lecture: Noyori, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2008–2022.
24. For a recent overview on free-radical chemistry, see: *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 1, Basic Principles, and Vol. 2, Applications.
25. Gansäuer, A.; Bluhm, H. *Chem. Rev.* **2000**, *100*, 2771–2788.