Aromatic Carbonyl Compound Reduction and Pinacol Coupling Processes Mediated by Titanocene(III)/Zn in Water

Juan L. Oller-López, Araceli G. Campaña, Juan M. Cuerva,* J. Enrique Oltra*

Department of Organic Chemistry, Faculty of Sciences, University of Granada, Campus Fuentenueva s/n, 18071 Granada, Spain Fax +34(958)248437; E-mail: joltra@ugr.es; E-mail: jmcuerva@ugr.es Received 7 July 2005

Abstract: A novel procedure for the reduction and pinacol coupling of aromatic aldehydes and ketones mediated by titanocene(III)/Zn in water is described. The titanocene-catalyzed version in sea water proved to be especially convenient for the reduction of aryl ketones. Mechanistically, the reaction presumably proceeds via free-radical chemistry.

Key words: green-chemistry, radical reactions, titanium, water, zinc

Water has many potential advantages in order to replace more familiar organic solvents. It is for example a no-cost, safe and environmental friendly substance and has unique chemical properties as solvent.¹ Water, however, has considerable reactivity against both carbanion and carbocation intermediates and, for this and other reasons, it has been scarcely used as solvent in organic synthesis. On the other hand, water is stable against free-radical intermediates because of its strong O–H bonds.² Therefore, in the cases where the solubility and stability of reagents and products could allow it, water might become an ideal solvent for free-radical chemistry.

With this idea in mind, we decided to study the behavior in water of radical reactions promoted by bis(cyclopentadienyl)titanium(III) chloride,³ an organometallic singleelectron transfer reagent which, in our laboratory, proved to be compatible with this solvent.⁴ This titanocene(III) complex is usually generated in situ by stirring commercial Cp₂Ti^{IV}Cl₂ with Mn or Zn in anhydrous THF, where it exists as a green mixture of the dimeric (Cp₂Ti^{III}Cl)₂ and the monomeric Cp2Ti^{III}Cl forms⁵ and is capable of catalyzing the pinacol coupling of aromatic aldehydes⁶ and other C-C bond forming reactions via radical chemistry.⁷ In 1996 Barden and Schwartz⁸observed that in THF-H₂O (4:1) green titanocene(III) hydrolyzed to a blue species, formulated as $[Cp_2Ti^{III}(H_2O)]^+$ by the authors, which in our hands proved to be capable of catalyzing the selective reduction of aromatic ketones using water as proton source.⁹ Now we have found that blue titanocene(III) can be directly generated in H₂O (including distilled, tap and sea water), by stirring Cp₂TiCl₂ with Zn in the absence of oxygen, giving stable solutions which are capable of pro-

SYNTHESIS 2005, No. 15, pp 2619–2622 Advanced online publication: 12.08.2005 DOI: 10.1055/s-2005-872163; Art ID: C04305SS © Georg Thieme Verlag Stuttgart · New York moting not only the reduction of aromatic carbonyl compounds but also their pinacol coupling.

Thus, when we treated acetophenone (1) during 24 hours with a blue mixture prepared by stirring Cp_2TiCl_2 (2 equiv) and Zn dust (8 equiv) in deoxygenated water, we obtained alcohol **2** and the pinacol coupling product **3** in similar proportions and a 74% overall yield (Scheme 1). The ¹H NMR spectrum of **3** indicated a mixture of the *dl* and *meso* stereoisomers in a 7:3 ratio respectively.¹⁰ The experiment was subsequently repeated without Cp_2TiCl_2 but then we only recovered unchanged acetophenone, showing the crucial role played by the titanocene species. Moreover, when the blue mixture of titanocene(III) and zinc in water was filtered to remove the remaining Zn dust in suspension, the filtrate turned green and was inactive against acetophenone, thus indicating that an excess of zinc was also necessary for the reaction.



Scheme 1 Titanocene(III)/Zn-promoted transformation of 1 in water

The result depicted in Scheme 1 suggests that blue titanocene in water might afford synthetic applications complementary to those of (Cp₂TiCl)₂, which shows low reactivity toward pinacol coupling of aromatic ketones.⁸ Moreover, the above observations can be rationalized if the mechanism proposed in Scheme 2 is accepted.

First, zinc would catalyze the hydrolysis of Cp_2TiCl_2 to the ionic green Ti^{IV} species 4.¹¹ The chloride ion of 4 should be strongly solvated by water and, therefore, the first step would be practically irreversible. Subsequently, Zn would react with 4 in an equilibrium leading to the active blue Ti^{III} species 5 (if Zn is removed from the medium the equilibrium reverses to the inactive green species 4). The trimetallic nature of 5 is reminiscent of that observed for the crystalline form of related titanocene(III) complexes.¹² In addition, 5 has a ionic character that warrants its solubility in water. Single-electron transfer from 5 to 1 would give the alkoxy- Ti^{IV} complex 6, which would spontaneously evolve towards the free radical 7 by protonation of the Ti–O bond. Finally 7 could undergo radical coupling toward 3 or Zn-mediated reduction to 2. An alterna-



Scheme 2 Hypothetical formation of 5 in H₂O and reaction with 1

tive pathway towards the pinacol coupling product via a carbanion-type intermediate seems quite unlikely in water.

The moderate stereoselectivity observed in the pinacol coupling reaction probably derives from both steric and electronic factors. Thus, in the radical-radical approach leading to the *dl* stereoisomer, the steric repulsion between the methyl groups can be minimized in an arrangement where the proximity between two phenyl and two hydroxyl groups provides stabilizing π/π interaction¹³ and *gauche* effect¹⁴ respectively. On the other hand, stabilizing effects must be lost to avoid steric hindrance in the radical approach leading to the *meso* isomer (see Figure 1).

preferred approach



Figure 1 Stereoselective radical-radical approach towards 3

Very recently, Enemærke et al. have invoked stabilizing π/π interaction and *gauche* effect to justify the high stereoselectivity observed in the synthesis of hydrobenzoin (*dl:meso* = 97:3) from benzaldehyde mediated by Cp₂TiCl₂/Zn in THF.¹⁵ Nevertheless, when we treated benzaldehyde (**8**) with a blue mixture prepared by stirring Cp₂TiCl₂ and Zn in water, besides an 11% of benzyl alcohol (**9**), we obtained a 41% yield of hydrobenzoin (**10**) as a 1:1 mixture of stereoisomers (Table 1). These results show once more the special behaviour of titanocene(III) complexes in water and confirm the role played by the methyl group in the stereoselectivity observed for the pinacol coupling of acetophenone reported here.

To check the scope and limitations of the method, we assayed the reaction with other aromatic and aliphatic aldehydes and ketones **11,13** and **16** (Figure 2) under the same conditions employed for acetophenone (see above). The results are summarized in Table 1.



Figure 2 Chemical structure of compounds 8–17

Table 1Reduction and Pinacol Coupling Products from Substrates1,8,11,13and 16^a

Substrate	R.P. ^b (yield, %)	P.C.P. ^c (yield, %)
1	2 (38)	3 (36) <i>dl:meso</i> = 7:3
8	9 (11)	10 (41) <i>dl:meso</i> = 1:1
11	12 (61)	n.d. ^d
13	14 (21)	15 (14)
16	17 (26) <i>cis:trans</i> = 1:2	n.d. ^d

^a Reactions were carried out with Cp₂TiCl₂/Zn in distilled water.

^b R.P. = reduction product.

^c P.C.P. = pinacol coupling product.

 d n.d. = not detected.

The results in Table 1 suggest that the process is faster for aromatic aldehydes and ketones than for aliphatic ones, a phenomenon which could be rationalized by the stabilizing delocalization of benzyl radicals such as **7**. This property might be exploited for selective reductions of aryl ketones and pinacol couplings of aromatic aldehydes in the presence of aliphatic carbonyl groups.

In all reactions in water presented above, Cp_2TiCl_2 was the most costly reagent.¹⁶ Therefore, the development of a new version catalytic in titanocene seemed desirable, especially for large-scale preparations. On the basis of the presumable formation of $Cp_2Ti(OH)Cl$ during the process (see Scheme 2), we deemed that the quantity of Cp_2TiCl_2 required might be substantially reduced by adding 2,4,6collidine hydrochloride (col·HCl), the titanocene-regenerating agent developed by Gansäuer et al.^{6b,17} This reagent should be capable of regenerating Cp_2TiCl_2 from $Cp_2Ti(OH)Cl$ releasing 2,4,6-collidine (Scheme 3), which might be recovered after work-up by simple acid-base extraction.^{6b,17}



Scheme 3 Cp_2TiCl_2 regeneration from $Cp_2Ti(OH)Cl$ by col·HCl

To check our hypothesis, we treated acetophenone (1) with a mixture of a substoichiometric quantity of Cp₂TiCl₂, Zn and 2,4,6-collidine hydrochloride in distilled water. Thus we obtained 1-phenylethanol (2) (51%) and 2,3-diphenylbutane-2,3-diol (3, dl:meso = 7:3) (9%). When the experiment was carried out starting from benzaldehyde, we obtained benzyl alcohol (30%) and hydrobenzoin (46%, *dl:meso* = 1:1), confirming that aldehydes are more prone to undergo pinacol coupling than ketones under our conditions. Moreover, we observed that addition of some salts (NaCl, KCl, NaOAc) improved the yield of reduction products. Therefore, we assayed the titanocene(III)-catalyzed reduction of acetophenone in Mediterranean Sea water (Scheme 4), which might become an interesting solvent at industrial level in Mediterranean countries. The results obtained (77% yield of 2 and 13% of 3) confirmed the viability of the catalytic version and the increase of selectivity towards reduction products under these conditions, thus reinforcing the potential interest of the method for the large-scale reduction of aromatic ketones.



Scheme 4 Titanocene(III)-catalyzed reduction of 1 in sea water

Some years ago, Tanaka et al. reported no substrate transformation when they treated acetophenone with $Zn-ZnCl_2$ in 50% aqueous THF.¹⁸ Therefore, the results depicted in Scheme 4 have to be attributed to blue titanocene(III) despite its relatively low concentration under catalytic conditions. It is also noteworthy that we did not need either an organic co-solvent or any surfactant to achieve almost complete substrate transformations. This suggests that the titanocene complex might also act aiding to solve the organic substrate in water.

In summary, the results presented here demonstrate that the titanocene(III)/Zn system is capable of promoting reductions and pinacol couplings of aromatic aldehydes and ketones using water as the exclusive solvent. This procedure admits the use of only substoichiometric proportion of the titanocene complex and, when carried out in sea water, becomes especially convenient for the reduction of aryl ketones. Mechanistically the reaction presumably proceeds via radical intermediates. In the practice the process has significant advantages as it takes place at room temperature under mild conditions using inexpensive, safe and environmental friendly reagents and solvents. These characteristics fit several principles of 'green chemistry'.¹⁹ Presently we are studying the possibility of developing an enantioselective version of our method.

Titanocene(III)-Catalyzed Reduction of Acetophenone (1) in Sea Water; Typical Procedure

Strictly deoxygenated Mediterranean Sea water²⁰ (25 mL) was added to a mixture of Cp₂TiCl₂ (41 mg, 0.17 mmol), Zn (433 mg, 6.68 mmol), and 2,4,6-collidine hydrochloride (388 mg, 2.5 mmol), and the mixture was stirred until the color turned blue (about 5 min). Then, acetophenone (1; 100 mg, 0.84 mmol) was added and the mixture was stirred at r.t. for 24 h, diluted with EtOAc, washed with brine, dried (Na₂SO₄) and the solvent removed. The residue was subjected to flash chromatography (hexane–EtOAc, 9:1) to give 92 mg of a mixture of products **2** and **3** in a 85:15 ratio (¹H NMR).

Acknowledgment

To the 'Junta de Andalucía' for the financial support to our group (FQM339). J.L.O-L. thanks the Spanish Ministry of Science and Technology for his grant.

References

- (a) Engberts, J. B. F. N.; Blandamer, M. J. Chem. Commun.
 2001, 1701. (b) Ribe, S.; Wipf, P. Chem. Commun. 2001,
 299. (c) Lindström, U. M. Chem. Rev. 2002, 102, 2751.
- (2) For excellent overviews on contemporary free-radical chemistry, see: (a) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, **1996**. (b) *Radicals in Organic Synthesis*, Vol. 1,2; Renaud, P.; Sibi, M. P., Eds.; Wiley-VCH: Weinheim, **2001**.
- (3) RajanBabu, T. V.; Nugent, W. A. J. Am. Chem. Soc. 1994, 116, 986.
- (4) Barrero, A. F.; Oltra, J. E.; Cuerva, J. M.; Rosales, A. J. Org. Chem. 2002, 67, 2566.
- (5) Enemærke, R. J.; Larsen, J.; Skrydstrup, T.; Daasbjerg, K. J. Am. Chem. Soc. 2004, 126, 7853.
- (6) (a) Gansäuer, A. Chem. Commun. 1997, 457. (b) Gansäuer,
 A.; Bauer, D. J. Org. Chem. 1998, 63, 2070.
- (7) For exhaustive reviews on the chemistry of bis(cyclopentadienyl)titanium(III) chloride in organic solvents, see: (a) Gansäuer, A.; Bluhm, H. *Chem. Rev.* 2000, *100*, 2771. (b) Gansäuer, A.; Pierobon, M. In *Radicals in Organic Synthesis*, Vol. 2; Renaud, P.; Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001, 207–220. (c) Gansäuer, A.; Rinker, B. *Tetrahedron* 2002, *58*, 7017. (d) Gansäuer, A.; Narayan, S. *Adv. Synth. Catal.* 2002, *344*, 465.
 (e) Gansäuer, A.; Rinker, B. In *Titanium and Zirconium in Organic Synthesis*; Marek, I., Ed.; Wiley-VCH: Weinheim, 2002, 435–450. (f) Gansäuer, A.; Lauterbach, T.; Narayan, S. *Angew. Chem. Int. Ed.* 2003, *42*, 5556.
- (8) Barden, M. C.; Schwartz, J. J. Am. Chem. Soc. 1996, 118, 5484.
- (9) Barrero, A. F.; Rosales, A.; Cuerva, J. M.; Gansäuer, A.; Oltra, J. E. *Tetrahedron Lett.* **2003**, *44*, 1079.
- (10) Fürstner, A.; Csuk, R.; Rohrer, C.; Weidmann, H. J. Chem. Soc., Perkin Trans. 1 1988, 1729.

Synthesis 2005, No. 15, 2619-2622 © Thieme Stuttgart · New York

- (11) In the absence of Zn, the red-brown color of a Cp_2TiCl_2 solution in deoxygenated water became only yellow after ten hours stirring. When we added Zn, however, the color of the solution immediately changed to green and, after a couple of minutes, to blue.
- (12) (a) Sekutowski, D. G.; Stucky, G. D. *Inorg. Chem.* 1975, *14*, 2192. (b) Sekutowski, D.; Jungst, R.; Stucky, G. D. *Inorg. Chem.* 1978, *17*, 1848. (c) Stephan, D. W. *Organometallics* 1992, *11*, 996.
- (13) Tsuzuki, S.; Honda, K.; Uchimaru, T.; Mikami, M.; Tanabe, K. J. Am. Chem. Soc. 2002, 124, 104.
- (14) Ganguly, B.; Fuchs, B. J. Org. Chem. 2000, 65, 558.

- (15) Enemærke, R. J.; Larsen, J.; Hjøllund, G. H.; Skrydstrup, T.; Daasbjerg, K. Organometallics 2005, 24, 1252.
- (16) Cp_2TiCl_2 is not too expensive (10 g = 28.50, Aldrich catalogue), but Zn dust is considerably cheaper (1 Kg = 21.70).
- (17) Gansäuer, A.; Bluhm, H.; Pierobon, M. J. Am. Chem. Soc. 1998, 120, 12849.
- (18) Tanaka, K.; Kishigami, S.; Toda, F. J. Org. Chem. **1990**, 55, 2981.
- (19) McDonough, W.; Braungart, M.; Anastas, P. T.; Zimmerman, J. B. *Environ. Sci. Technol.* 2003, 435A.
- (20) Mediterranean Sea water was taken from 'Las Acacias' beach, Málaga (Spain), in August 2004.