Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron Letters 45 (2004) 8123–8126

Tetrahedron Letters

Titanocene(III) mediated reduction of organic halides under photoirradiation conditions

Grégory Hersant, Mounira Bent Sadok Ferjani and Sharon M. Bennett*

Département de chimie et de biochimie, Université du Québec à Montréal, Case postale 8888,
succursale Centre-Ville, Montréal, Québec, Canada, H3C 3P8

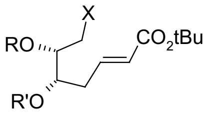
Received 2 July 2004; revised 19 August 2004; accepted 19 August 2004
Available online 17 September 2004

Abstract—Photoirradiation of reaction mixtures, with a xenon lamp in the UV–vis domain, facilitates the titanocene(III) mediated reduction of some organic halides. The substrates studied include ω-halo-α,β-unsaturated esters and a 6-iodohexose derivative.

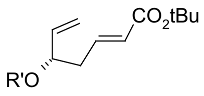
Bis(cyclopentadienyl)titanium(III) chloride is a well known titanocene(III) reagent, that is, useful in promoting radical carbon–carbon bond formation. Many of the reported reactions involve either carbonyl compounds or epoxides as radical precursors;[1] alkyl halides have attracted less attention. Alkyl and aromatic halides are reduced with the more reactive reagents Cp_2TiBH_4[2] and $[Cp_2Ti^nBu_2]^-MgCl^+$.[3] Olefins are formed by the Cp_2TiCl reduction of 1,2-dibromides[4] and the reduction of *glycosyl* halides with Cp_2TiBH_4 or Cp_2TiCl gives either anhydroalditols,[5] glycals[6] or C-glycosidic compounds.[7,8] Allyl and benzyl halides, as well as α-halocarbonyl compounds, are reduced by Cp_2TiCl at room temperature but *unactivated* alkyl halides were found to be inert under these conditions.[9,10] The growing interest in using Cp_2TiCl as a selective titanocene(III) reducing agent in organic synthesis has been attributed, in part, to its apparent requirement for alkyl halide activation as well as to the broad range of functional groups tolerated by this reagent.[11] This report summarizes results from our laboratory on the feasibility of using Cp_2TiCl to mediate intramolecular carbon–carbon bond formation, under photoirradiation conditions, using functionalized alkyl halides as radical precursors. Although photoirradiation of some organometallic compounds is known to facilitate electron transfer to organic substrates,[12,13] the use of UV–vis light as a promoter for Cp_2TiCl mediated cyclizations of unsaturated halides has not, to the best of our knowledge, previously been described in the literature.[14]

We began our study with alkyl halides **1** and **2**. Both compounds contain a neighboring acetoxy group and a pendant Michael acceptor and reaction with excess Cp_2TiCl could conceivably give rise to either the reductive cyclization products **4a** and **4b**, the acyclic β-elimination product **5**, or the simple acyclic reduction compound **6**. The reaction of **3** with Cp_2TiCl was also investigated to determine if reduction of the conjugate ester might be competitive with carbon–halogen bond reduction.

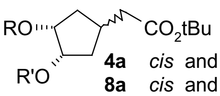
In this letter, for the sake of simplicity, we have used Cp_2TiCl to represent the mixture of Ti(III) species present in THF solutions of titanocene(III) reagents prepared by either the reduction of Cp_2TiCl_2, with Al or



1 (X = I); R,R' = Ac
2 (X = Br); R,R' = Ac
3 (X = OAc); R,R' = Ac
6 (X = H); R,R' = Ac
7 (X = I); R,R' = CMe_2
9 (X = I); R,R' = H



5 R' = Ac; **10** R' = H.

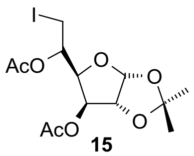


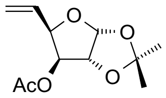
4a *cis* and **4b** *trans;* R,R' = Ac
8a *cis* and **8b** *trans;* R,R' = CMe_2
11a *cis* and **11b** *trans;* R,R' = H

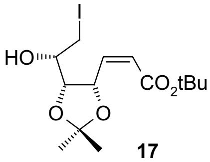
Keywords: Alkenyl halides; Cyclization; Titanium and compounds.

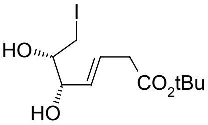
* Corresponding author. Tel.: +1 514 987 3000 4320; fax: +1 514 987 4054; e-mail: bennett.sharon_m@uqam.ca

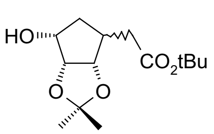
0040-4039/$ - see front matter
doi:10.1016/j.tetlet.2004.08.119


15


16


17


18


19a *cis* and **19b** *trans*

Zn,[15] or by ligand exchange from CpTl and $TiCl_3$.[16,17] Work from other groups has demonstrated that $\mathit{Cp_2TiCl}$ prepared in situ is synthetically useful and that isolation of this air sensitive reagent, prior to reaction with organic substrates, is not required.[18] The in situ reagent prepared from Cp_2TiCl_2/Zn is particularly interesting in that it is inexpensive and nontoxic. The $\mathit{Cp_2TiCl}$ solutions were all filtered before use. This step is important for the Cp_2TiCl_2/Zn preparations as activated zinc alone reacts with **1** to give a mixture of compound **5** and compounds **4a** and **4b**.[19] The reaction of **1** with the various $\mathit{Cp_2TiCl}$ solutions is chemoselective, giving only the cyclized products, but is incomplete after 6.5 h under ambient temperature and lighting conditions—even when a large excess of reagent is used (Table 1, entries a and b). We saw no evidence of competition between reduction of the carbon–iodine bond and of the conjugated ester.[20] Although reductions of **1** with *excess* $\mathit{Cp_2TiCl}$ prepared from either Cp_2TiCl_2/Al or Cp_2TiCl_2/Zn were incomplete under ambient conditions, benzyl chloride was efficiently reduced with our in situ generated reagents (vide infra). At the time the reactions of **1** were stopped, the mixture was still the characteristic green color associated with $\mathit{Cp_2TiCl}$ in THF.[21] Increasing either the quantity of Zn used to reduce Cp_2TiCl_2 or the time of contact between Zn and Cp_2TiCl_2 prior to filtration did not dramatically improve our results. The reduction of $PhCH_2Cl$ to bibenzyl (86% yield) with isolated $\mathit{Cp_2TiCl}$ (prepared from Cp_2TiCl_2 and Al) was reported a number of year ago;[10] this reaction was a useful test of the quality of our in situ prepared reagents. Both the Zn and the Al methods were satisfactory.[22] The Cp_2TiCl_2/Al reactions gave slightly better results but were not easy to run due to difficulties with consistent Al activation. The UV–vis spectra of our $\mathit{Cp_2TiCl}$ solutions are included with the Supplementary information of this letter.

We found that photoirradiation of reactions mixtures of **1** and titanocene(III), prepared from *either* Cp_2TiCl_2/Zn (entries d–f) or CpTl/$TiCl_3$ (entries g and h), was beneficial.[23] We isolated the cyclized products **4a** and **4b** in 82% and 78% yields as a 2.6:1 mixtures of isomers. A 150 W xenon lamp was used as the light source. Broad-band UV–vis light (250–950 nm) was more effective than visible light alone. The diastereoselectivity for the Ti(III) mediated reductive cyclization of **1** is similar to that previously observed for cyclizations mediated by either SmI_2/visible light at rt (2.3/1.0) or Bu_3SnH (1.9/1.0) but is significantly lower than that of the corresponding SmI_2/HMPA mediated cyclization (16/1.0).[24,25] The reactions of halides **2**, **7**, **12**, **15**, and **17** with $\mathit{Cp_2TiCl}$ solutions prepared from Cp_2TiCl_2/Zn, both in the dark and under the photoirradiation conditions that had been successfully used for compound **1**, were also examined to better understand the limitations and the issues of chemoselectivity and stereoselectivity associated with these reactions. As expected, the bromide substrate **2** is less reactive than **1** and, while photoirradiation did increase the ratio of cyclized products:unreacted starting material, we did not see the same level of rate enhancement as for iodide **1** (entries i–k). Changing the hydroxyl protecting groups of **1** from acetyl to a cyclic acetal (**7**) gave a slower reacting substrate (entry n). In an unsuccessful attempt to improve the reaction efficiency we increased the concentration of substrate **7** (entry o). However, under these conditions β-elimination becomes competitive with reductive cyclization. Reaction products were isolated as their deprotected derivatives **9**, **10, 11a**, and **11b**.[24]

There was no reaction between 6-iodo-1-phenylhex-1-yne (**12**) and $\mathit{Cp_2TiCl}$ after 6 h at rt in the dark; a portion of the iodoalcyne was reduced, however, under the photoirradiation conditions (UV–vis, 6 h). GC–MS analysis of the crude reaction mixture after workup indicated the presence of benzylidenecyclopentane (**14**), 1-phenylhex-1-yne (**13**) and starting material **12** in a 39:3:58 ratio. The ratio of radical cyclization product: simple reduction product (**14**:**13**) is similar to that observed for the reaction of **12** with SmI_2/DMPU.[26]

Compound **15** shares some of the characteristics of substrate **1** but it lacks a Michael acceptor. In the absence of a radical trap, reductive elimination, to give the vinyl compound **16**, is the predominant reaction pathway. We detected a higher percentage of **16** in reaction mixtures that have been photoirradiated; the CpTl/$TiCl_3$ reagent gave slightly better results than the reagent prepared from Cp_2TiCl_2/Zn (entries p–s). Finally, the reduction of **17** with $\mathit{Cp_2TiCl}$ was examined. The reaction of **17** with both SmI_2 and Bu_3SnH has previously been studied in our laboratory.[27] Under some SmI_2 conditions[28] reduction of the γ-oxygenated conjugated ester (to give **18**) competes with reduction of the carbon–halogen bond, however we found no evidence of **18** in our Ti(III) reaction mixtures. Although there was almost no reaction between **17** and $\mathit{Cp_2TiCl}$ in the dark, the reaction run under the photoirradiation conditions gave a 62:3:34 mixture of **19b**:**19a**:**17** (entries t and u).

In general, the $\mathit{Cp_2TiCl}$ mediated reductive cyclizations described in this paper are not more efficient nor more stereoselective than the corresponding reactions with SmI_2 or Bu_3SnH. The reagent prepared from Cp_2TiCl_2/Zn is however less expensive and is nontoxic. Our preliminary results demonstrate that photoirradiation of $\mathit{Cp_2TiCl}$ reaction mixtures enhances the reactivity of this mild single electron-transfer reagent; this relatively simple modification may prove useful for

Table 1. Influence of UV–vis light on *Cp_2TiCl* reductions of various organic halides

Entry	Method and substrate		Conditions[a]	Ratio of s.mat:products in crude extract[b]	Isolated products (% yield)[c]
a	Cp_2TiCl_2/Zn[a]	**1**	Ambient, 6.5 h	**1**:**4a** + **4b** (72:28)	—
b	Cp_2TiCl_2/Zn	**1**	Ambient, 6.5 h	**1**:**4a** + **4b** (54:46)	—
c	Cp_2TiCl_2/Al	**1**	Ambient, 6.5 h	**1**:**4a** + **4b** (48:52)	—
d	Cp_2TiCl_2/Zn	**1**	Dark, 2.5 h	**1**:**4a** + **4b** (80:20)	—
e	Cp_2TiCl_2/Zn	**1**	Visible light, 2.5 h	**1**:**4a** + **4b** (71:29)	—
f	Cp_2TiCl_2/Zn	**1**	UV–vis light, 2.5 h	**1**:**4a** + **4b** (4:95)	**4a** (59), **4b** (23)
g	CpTl/$TiCl_3$	**1**	Dark, 6 h	**1**:**4a** + **4b** (65:35)	—
h	CpTl/$TiCl_3$	**1**	UV–vis light, 6 h	**1**:**4a** + **4b** (1:99)	**4a** (56), **4b** (22)
i	Cp_2TiCl_2/Zn	**2**	Dark, 2.5 h	**2**:**4a** + **4b** (95:5)	—
j	Cp_2TiCl_2/Zn	**2**	UV–vis light, 2.5 h	**2**:**4a** + **4b** (82:18)	—
k	Cp_2TiCl_2/Zn	**2**	UV–vis light, 6 h	**2**:**4a** + **4b** (71:29)	**2** (56), **4a** (12), **4b** (5)
l	Cp_2TiCl_2/Zn	**7**	Dark, 2.5 h	**7**:**8a** + **8b** (77:23)	—
m	Cp_2TiCl_2/Zn	**7**	UV–vis light, 2.5 h	**7**:**8a** + **8b** (62:38)	—
n	Cp_2TiCl_2/Zn	**7**	UV–vis light, 6 h	**7**:**8a** + **8b** (44:56)	**7** (37), **8a** (16.5), **8b** (26.5)
o	Cp_2TiCl_2/Zn[d]	**7**	UV–vis light, 6 h	—[e]	**9** (9), **10** (10), **11a** (16.5), **11b** (16.5)
p	Cp_2TiCl_2/Zn	**15**	Dark, 6.5 h	**15**:**16** (94:6)	—
q	Cp_2TiCl_2/Zn	**15**	UV–vis light, 6.5 h	**15**:**16** (74:26)	**15** (51), **16** (19)
r	CpTl/$TiCl_3$	**15**	Dark, 6 h	**15**:**16** (97:3)	—
s	CpTl/$TiCl_3$	**15**	UV–vis light, 6 h	**15**:**16** (45:55)	**15** (42), **16** (48)
t	Cp_2TiCl_2/Zn	**17**	Dark, 6.5 h	**17**:**19a**:**19b** (99:0:1)	—
u	Cp_2TiCl_2/Zn	**17**	UV–vis light, 6.5 h	**17**:**19a**:**19b** (34:3:62)	**17** (25), **19b** (49)

[a] Ar atmosphere, rt; [substrate] in THF = 0.008 M (Cp_2TiCl_2 prep) or 0.01 M (CpTl/$TiCl_3$ prep and entries a–c). An excess of Ti(III) reagent was used (8 equiv based on the s.mat) except for entry a (2 equiv). A xenon lamp was used for photoirradiation exps.

[b] Determined by GC–MS after workup and before chromatography; neither diastereoisomers **4a** and **4b** nor **8a** and **8b** were separable using our method.

[c] Isolated yields after chromatography on silica gel. Compounds **4a** and **4b**, as well as isomers **8a** and **8b** and isomers **11a** and **11b**, were isolated as diastereomeric mixtures; the yields reported for each isomer were calculated using NMR ratios.

[d] Reaction was run at [**7**] = 0.024 M.

[e] Compounds **7**, **8a**, and **8b** were not detected in crude after workup.

other types of *Cp_2TiCl* mediated reductions. For the examples discussed in this letter, the increased reactivity occurred without concomitant loss of chemoselectivity.

Acknowledgements

We thank the Natural Sciences and Engineering Research Council of Canada (NSERC) and the Université du Québec à Montréal for financial support. We thank Duc Phuong Ngo and Jean-François Brazeau (undergraduate NSERC summer students) for their assistance with preliminary work on this project.

Supplementary data

Experimental procedures, characterization data for compounds and UV–vis spectra for *Cp_2TiCl* solutions. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.08.119.

References and notes

1. For recent reviews see: Gansäuer, A.; Bluhm, H. *Chem. Rev.* **2000**, *100*, 2771–2788; Gansäuer, A.; Rinker, B. In *Titanium and Zirconium in Organic Synthesis*; Marek, I., Ed.; Wiley–VCH: Weinheim, Germany, 2002, pp 435–456.
2. Liu, Y.; Schwartz, J. *J. Org. Chem.* **1994**, *59*, 940–942.
3. (a) Nii, S.; Terao, J.; Kambe, N. *J. Org. Chem.* **2000**, *65*, 5291–5297; (b) Nii, S.; Terao, J.; Kambe, N. *J. Org. Chem.* **2004**, *69*, 573–576.
4. (a) Davies, S. G.; Thomas, S. E. *Synthesis* **1984**, 1027–1029; (b) Qian, Y.; Li, G.; Zheng, X.; Huang, Y.-Z. *Synlett* **1991**, 489–490.
5. Cavallaro, C. L.; Schwartz, J. *J. Org. Chem.* **1996**, *61*, 3863–3864.
6. (a) Cavallaro, C. L.; Schwartz, J. *J. Org. Chem.* **1995**, *60*, 7055–7057; (b) Schwartz, J.; Spencer, R. P. *Tetrahedron Lett.* **1996**, *37*, 4357–4360; (c) Hansen, T.; Daasbjerg, K.; Skrydstrup, T. *Tetrahedron Lett.* **2000**, *41*, 8645–8649.
7. Spencer, R. P.; Schwartz, J. *J. Org. Chem.* **1997**, *62*, 4204–4205.
8. These reductions involve formation of a glycosyl radical that may (i) abstract a hydrogen atom to give an anhydroalditol, or (ii) add intermolecularly to a Michael acceptor giving a C-glycoside, or (iii) be reduced by a second equivalent of Ti(III) to give a glycosyltitanium(IV) complex, which then eliminates a neighboring 2-*O*-acetyl group to form a glycal. See Ref. 2.
9. (a) Parrish, J. D.; Shelton, D. R.; Little, R. D. *Org. Lett.* **2003**, *5*, 3615–3617; (b) Chen, L.; Zhao, G.; Ding, Y. *Tetrahedron Lett.* **2003**, *44*, 2611–2614.
10. Yanlong, Q.; Guisheng, L.; Huang, Y. Z. *J. Organomet. Chem.* **1990**, *381*, 29–34.
11. Spencer, R. P.; Schwartz, J. *Tetrahedron* **2000**, *56*, 2103–2112.
12. Hubig, S. M.; Kochi, J. M. In *Electron Transfer in Chemistry;* Balzani, V., Ed.; Wiley–VCH: Weinheim, Germany, 2001; Vol. 2, Part II, Chapter 9.
13. (a) This principle has been successfully used to promote the reduction of organic halides by lanthanide reagents as well. See: Ogawa, A.; Ohya, S.; Sumino, Y.; Sonoda, N.; Hirao, T. *Tetrahedron Lett.* **1997**, 38, 9017–9018;

(b) Ogawa, A.; Sumino, Y.; Nanke, T.; Ohya, S.; Sonoda, N.; Hirao, T. *J. Am. Chem. Soc.* **1997**, *119*, 2745–2746; (c) Ogawa, A.; Ohya, S.; Doi, M.; Sumino, Y.; Sonoda, N.; Hirao, T. *Tetrahedron Lett.* **1998**, *39*, 6341–6342.

14. The photochemistry of Cp_2TiCl_2 was studied a number of years ago; see: Tsai, Z. T.; Brubaker, C. H., Jr. *J. Organomet. Chem.* **1979**, *166*, 199–210, and references cited therein.
15. Coutts, R. S. P.; Wailes, P. C.; Martin, R. L. *J. Organomet. Chem.* **1973**, *47*, 375–382.
16. Manzer, L. E. *Inorg. Synth.* **1982**, *21*, 84–86.
17. For a discussion see: Enemaerke; Larsen, J.; Skrydstrup, T.; Daasbjerg, K. *J. Am. Chem. Soc.* **2004**, *126*, 7853–7864, and references cited therein.
18. (a) Nugent, W. A.; Rajanbabu, T. V. *J. Am. Chem. Soc.* **1988**, *110*, 8561–8562; (b) Rajanbabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1994**, *116*, 986–997.
19. GC–MS analysis of crude products of the reaction of **1** with 8 equiv of activated zinc alone showed a 70:30 mixture of **4a** + **4b**:**5**. There was no reaction for the corresponding experiment with Al.
20. Crude and purified products were analyzed by GC–MS and NMR. As an additional test, **3** was exposed to an excess of *Cp₂TiCl* for 6 h but was found to be inert.
21. This was true for all of the reactions described in this manuscript except for the $PhCH_2Cl$ reactions with 1.0 equiv of titanocene reagent. Note that prolonged photoirradiation (>6.5 h) of reaction mixtures resulted in a color change from green to green-blue.
22. See Supplementary data for more details.
23. Exposure of **1** to UV–vis light alone had no effect. Parallel control experiments were run, in the presence of Cp_2TiCl, in the dark. Literature reports suggest that Cp_2TiCl_2 is not inert under photoirradiation conditions (see Ref. 14) but we made no attempt to isolate titanocene photolysis products.
24. Salari, B. S. F.; Biboutou, R. K.; Bennett, S. M. *Tetrahedron* **2000**, *56*, 6385–6400.
25. For a comparison of Cp_2TiCl with SmI_2 and other agents see: Gansäuer, A.; Rinker, B. *Tetrahedron* **2002**, *58*, 7017–7026.
26. Zhou, Z.; Larouche, D.; Bennett, S. M. *Tetrahedron* **1995**, *51*, 11623–11644.
27. Bennett, S. M.; Biboutou, R. K.; Zhou, Z.; Pion, R. *Tetrahedron* **1998**, *54*, 4761–4786.
28. At rt, in the absence of HMPA, SmI_2 and **17** give **18** as the major product; with SmI_2/HMPA **19b** is formed almost exclusively.[27]