Ketone Reduction by Titanocene Borohydride

Michael C. Barden and Jeffrey Schwartz*

Department of Chemistry, Princeton University, Princeton, New Jersey, 08544–1009

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Introduction

Classically, reduction of ketones by sodium borohydride is done in protic solvents; ketone reduction in aprotic media usually requires activation, often by a metal complex, including those of Al,[1] Ca,[2] Co,[3] Fe,[3a] Li,[1,4] Mg,[2a,c] Ni,[3d] U,[5] Zn,[6] Zr,[7] and several lanthanides.[2b,3b,8] Most metal-activated procedures involving simple ligation are no more stereoselective than is reduction using $NaBH_4$ alone: reduction of the archetypal substrate 4-*tert*-butylcyclohexanone occurs with low stereoselectivity for most; notable exceptions use $CeCl_3$ (*trans:cis* = 94:6)[8c,e] or UCl_4 (*trans:cis* = 93:7)[5] for borohydride activation.[9] Sodium borohydride has long been known to react with Cp_2TiCl_2 to give Cp_2TiBH_4 (Scheme 1),[10] a species we have shown to be a powerful reagent for reduction of organic halides.[11] We now report that Cp_2TiBH_4, easily prepared either independently or *in situ*, effects reduction of ketones to the corresponding alcohols in DME rapidly, in excellent yield, and with high stereoselectivity, which makes it a reagent of practical value for use in aprotic media.

Results and Discussion

Reductions were conducted by slowly adding ketone to titanocene borohydride, Cp_2TiBH_4 (**1**), in dry DME at room temperature. Alternatively, **1** can be prepared *in situ* by simply mixing titanocene dichloride and sodium borohydride in dry DME and used without further isolation (Table 1). When THF is used instead of DME, the *in situ* production of **1** was severely retarded, and after 2 days, only Cp_2TiCl could be isolated.[12] However when recrystallized **1** was dissolved in THF, ketone reduction took place as before to give, for example, 2-decanol from 2-decanone in 98% yield.

Scheme 1. Preparation of Cp_2TiBH_4

$$Cp_2TiCl_2 + NaBH_4 \xrightarrow[-\,NaCl]{} \underset{\mathbf{1}}{Cp_2TiBH_4} + H_2 + BH_3$$

The stereoselectivity of reduction of 4-*tert*-butylcyclohexanone to 4-*tert*-butylcyclohexanol by **1** can be compared with BH_4^- activation by other metal salts (Table 2); reduction using **1** is fast, high yielding (97%), and stereoselective (*trans:cis* = 97:3). Borane is produced in the *in situ* synthesis of **1**, and it is likely that BH_3 is also produced when **1** reacts with 1 equiv of ketone. However, if 1,4-diazabicyclo[2.2.2]octane (DABCO; 1 equiv), which strongly coordinates BH_3,[13] is added to the DME solution of **1** prior to addition of 4-*tert*-butylcyclohexanone, no change in the reaction profile is observed. Indeed, Et_3N, another strongly BH_3-coordinating agent,[13] can be used even as solvent with no noticeable change in reduction yield or stereoselectivity.[14] Since BH_3 is a relatively stereochemically unselective reducing agent (Table 2), competitive ketone reduction by BH_3 is apparently negligible.

We propose that **1** reacts with a ketone to form Cp_2Ti-H(ketone), **2**, which transfers hydride to the carbonyl carbon to give titanocene(III) alkoxide **3**.[15] Hydrolytic or silylative workup of **3** yields the product alcohol or silyl ether (Scheme 2). In support of this proposal, we note that EPR analysis of **1** dissolved in acetophenone shows a doublet attributed to **2**, which is centered at $g = 1.980$ ($a = 4.0$ G). This signal slowly decays and is replaced by a broad singlet identical to that of independently prepared $Cp_2TiOC(H)(CH_3)C_6H_5$[16] ($g = 1.976$), which is typical for Ti(III). We had previously observed[11] by ^{11}B

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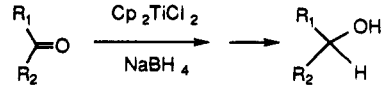
(2) (a) Kollonitsch, J.; Fuchs, O.; Gabor, V. *Nature* **1954**, *173*, 125. (b) Fujii, H.; Oshima, K.; Utimoto, K. *Chem. Lett.* **1991**, 1847. (c) Matsubara, S.; Takahashi, H.; Utimoto, K. *Chem. Lett.* **1992**, 2173.
(3) (a) Kashima, C.; Yamamoto, Y. *Chem. Lett.* **1978**, 1285. (b) Adams, C. *Synth. Commun.* **1984**, *14*, 1349. (c) Okamoto, T.; Oka, S. *J. Mol. Cat.* **1984**, *23*, 107. (d) Back, T. G.; Baron, D. L.; Yang, K. *J. Org. Chem.* **1993**, *58*, 2407.
(4) (a) Ritchie, C. D. *Tetrahedron Lett.* **1963**, *30*, 2145. (b) Handel, H.; Pierre, J.-L. *Tetrahedron Lett.* **1976**, *24*, 2029. (c) Risbood, P. A.; Ruthven, D. M. *J. Org. Chem.* **1979**, *44*, 3969. (d) Soai, K.; Yamanoi, T.; Hitoshi, H. *J. Organomet. Chem.* **1985**, *290*, C23.
(5) Adam, R.; Villiers, C.; Ephritikhine, M.; Lance, M.; Nierlich, M.; Vigner, J. *New J. Chem.* **1993**, *17*, 455.
(6) For example see: (a) Nakata, T.; Tanaka, T.; Oishi, T. *Tetrahedron Lett.* **1983**, *24*, 2653. (b) DiPardo, R. M.; Brock, M. G. *Tetrahedron Lett.* **1983**, *24*, 4805. (c) Ito, Y.; Yamaguchi, M. *Tetrahedron Lett.* **1983**, *24*, 5385. (d) Oishi, T.; Nakata, T. *Acc. Chem. Res.* **1984**, *17*, 338. (e) Evans, D. A.; Ennis, M. D.; Le, T. *J. Am. Chem. Soc.* **1984**, *106*, 1154. (f) Takahashi, T.; Miyazawa, M.; Tsuji, J. *Tetrahedron Lett.* **1985**, *26*, 5139. (g) Guanti, G.; Banfi, L. R.; Zannetti, M. T. *Tetrahedron Lett.* **1993**, *34*, 5483. (h) Zhang, H.-C.; Costanzo, M. J.; Maryanoff, B. E. *Tetrahedron Lett.* **1994**, *35*, 4891.
(7) (a) Sorrell, T. N. *Tetrahedron Lett.* **1978**, *50*, 4985. (b) Itsuno, S.; Sakurai, Y.; Ito, K. *Synthesis* **1988**, 995. (c) Tamami, B.; Gourdarzian, N. *J. Chem. Soc., Chem. Commun.* **1994**, 1079.
(8) (a) Luche, J.-L. *J. Am Chem. Soc.* **1978**, *100*, 2226. (b) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1979**, *101*, 5848. (c) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454. (d) Komiya, S.; Tsutsumi, O. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3423. (e) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29.
(9) In fact, two different alcohols from the reduction of 2 equiv of 4-*tert*-butylcyclohexanone by $U(BH_4)_4$ can be isolated; the ROH from $U(BH_4)_3(OR)$ (*trans:cis* = 95:5) and ROH from BH_2OR (86:14).
(10) (a) Nöth, H.; Hartwimmer, R. *Chem. Ber.* **1960**, *93*, 2338. (b) Lucas, C. R. *Inorg. Synth.* **1977**, *17*, 91.
(11) (a) Liu, Y.; Schwartz, J. *J. Org. Chem.* **1994**, *59*, 940. (b) Liu, Y.; Schwartz, J. *Tetrahedron* **1995**, *51*, 4471.
(12) Coutts, R. S. P.; Wailes, P. C.; Martin, R. L. *J. Organomet. Chem.* **1973**, *47*, 375.
(13) (a) Lance, C. F. *Aldrichchim. Acta* **1971**, *6*, 21. (b) Brown, H. C.; Murray, L. T. *Inorg. Chem.* **1984**, *23*, 2746.
(14) Representative data for reduction of 4-*tert*-butylcyclohexanone in the presence of increasing equivalent amounts of triethylamine are listed below:

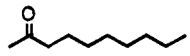
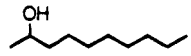
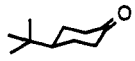
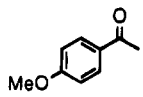
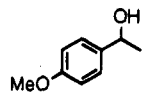
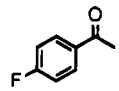
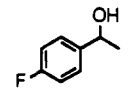
Equiv. Et_3N	% Yield	*trans: cis*
0	99	96:4
0.5	100	94:6
1.0	90	96:4
2.0	94	96:4
5.0	97	97:3
10.0	93	97:3
100.0	99	97:3

(15) It is interesting that Cp_2ZrHCl is no more stereoselective a reagent for reduction of 4-*tert*-butylcyclohexanone (*trans:cis* = 85:15) than is $NaBH_4$. Perhaps the higher coordination number of the Zr reagent relative to the Ti one results in weaker coordination of the ketone to Zr than to Ti in the transition state for carbonyl group reduction.
(16) Lappert, M. F.; Sanger, A. R. *J. Chem. Soc. (A)* **1971**, 1314.

0022-3263/95/1960-5963$09.00/0

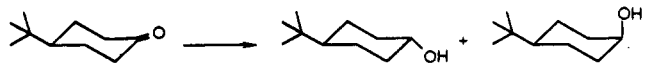
Table 1. Reduction of ketones to alcohols by $Cp_2TiCl_2/NaBH_4$



Ketone	Product	Time	Yield (%)[a]	
		5 min	98	
		5 min	90	
		5 min	97	*trans:cis* = 97:3
		5 min	82	*exo:endo* = 5:95
		5 min	85	*exo:endo* = 94:6
		6 hr	91	
		18 hr	86	
		6 hr	96	

[a]Yields were determined by GC analysis of silylated product alcohol derivatives.

Table 2. Reduction of 4-*tert*-Butylcyclohexanone (25 °C)



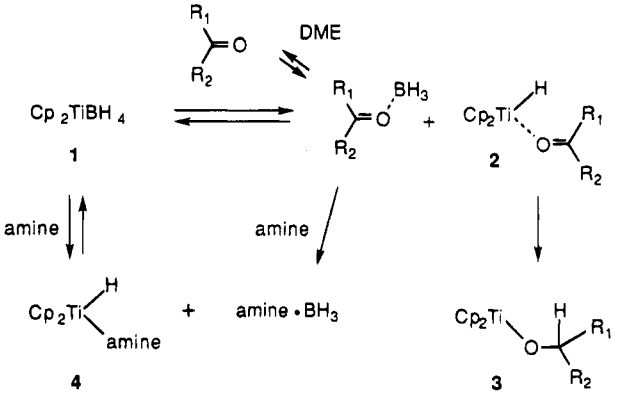
reagent	solvent	time	yield (%)	*trans:cis*	ref
BH_3[a]	diglyme	1 h	90	84:16	19a
BH_3[b]	THF	1 h	90	90:10	19
Me_3N-BH_3[a]	diglyme	3 d	55	83:17	19a
$(n\text{-}Bu)_4NBH_4$	THF	48 h	17	53:47	this work
$NaBH_4$	THF	72 h	90	86:14	4b, this work
$NaBH_4$	DME	48 h	88	85:15	4b, this work
$LiBH_4$	THF	12 h	99	86:14	4b, this work
$LiBH_4$	DME	0.5 h	80	85:15	4b, this work
$CeCl_3/NaBH_4$	MeOH/THF	5 min	100	94:6	10c,e
$UCl_4/NaBH_4$	THF	2 d	77	93:7	7
$Cp_2Zr(Cl)BH_4$	benzene	15 min	90	66:33	9a
$Cp_2Zr(Cl)H$	DME	8 h	90	85:15	this work
Cp_2TiBH_4	THF	5 min	97	97:3	this work
$Cp_2TiCl_2/NaBH_4$	DME	5 min	96	96:4	this work
Cp_2TiBH_4/DABCO	DME	5 min	96	97:3	this work

[a] Steam bath. [b] Ice bath.

NMR[17] that reaction between **1** and *N,N*-dimethyloctylamine gives *N,N*-dimethyloctylamine·BH_3 and, likely, Cp_2Ti-H(amine), **4**. EPR analysis of the reaction between **1** and *N,N*-dimethyloctylamine shows a doublet for **4** ($g = 1.976$; $a = 5.0$ G). Since a typical "organic" radical has $g \approx 2.00$, the higher g value found for **2** *vs* **4** is consistent with 20% delocalization of unpaired spin density from Ti to the carbonyl carbon of **2**; the 20% reduction in

(17) Nöth, H.; Wrackmeyer, B. Nuclear Resonance Spectroscopy of Boron Compounds. In *NMR Basic Principles and Progress*; Diehl, P., Fluck, E., Kosfled, R., Eds.; Springer-Verlag: New York, 1978; Ch. 7, p 88; Table LXV, p 311.

Scheme 2. Reduction of Ketones by Cp_2TiBH_4



coupling constant is also as expected for such delocalization.[18]

Clearly, efficient and stereoselective reduction of ketones to alcohols can now be easily achieved using easy to handle Cp_2TiCl_2 and $NaBH_4$, and this procedure represents a convenient alternative to currently employed methodologies. Work is now in progress to enable catalytic utilization of Ti in this process.

(18) Titanocene(III) hydrides are among the intermediates proposed in the catalytic hydrosilylation of esters and ketones ((a) Berk, S. C.; Kreuzer, K. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1991**, *113*, 5093. (b) Berk, S. C.; Buchwald, S. L. *J. Org. Chem.* **1992**, *57*, 3751. (c) Barr, K. J. ; Berk, S. C.; Buchwald, S. L. *J. Org. Chem.* **1994**, *59*, 4323. (d) Halterman, R. L.; Ramsey, T. M.; Chen, Z. *J. Org. Chem.* **1994**, *59*, 2642. (e) Carter, M. B.; Schiøtt, B.; Gutierrez, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 11667). There may be significant structural differences between the active reducing agent in the catalyst system and the reduction reagent discussed herein: In our hands, the catalyst system (Cp_2TiCl_2, BuLi, $(EtO)_3SiH$, THF, two days) reduced 4-*tert*-butylcyclohexanone to 4-*tert*-butylcyclohexanol (74%), but with only poor stereoselectivity (*trans*:*cis* = 78:22).

(19) (a) Jones, W. M. *J. Am. Chem. Soc.* **1960**, *82*, 2528. (b) Buono, G.; Triantaphylides, C.; Peiffer, G. *Synthesis* **1982**, 1030.

Experimental Section

Materials. All manipulations were performed either on a vacuum line using standard Schlenk techniques or in a glove box with a purified nitrogen atmosphere. Dimethoxyethane (DME) and tetrahydrofuran (THF) were distilled from sodium/benzophenone ketyl. Titanocene dichloride, ketones, alcohols (Aldrich), sodium borohydride (Johnson Matthey), and silylating reagents (Supelco) were commercially available and used as received.

General Procedure for Reductions. Ketone (2 mmol) in 5 mL of DME is added dropwise to a 5 mL DME solution of Cp_2TiBH_4 (2.10 mmol). After 5 min, GC analysis of a hydrolyzed aliquot shows complete disappearance of the ketone. The reaction mixture is worked up by exposure to air and then by acetaldehyde addition (2 mL; to quench any residual borane or borohydride), stirred for 1 h, poured into 1 N NaOH, and extracted with Et_2O to give the alcohol. The crude residue can be treated with a silylating agent (Sylon BZT) and analyzed for quantitative determinations by GLC. It can then be purified by column chromatography and identified by the usual spectroscopic methods and compared with authentic samples. Alternatively, Cp_2TiBH_4 can be prepared *in situ* by adding 0.160 g (4.23 mmol) of $NaBH_4$ in 5 mL of DME to 0.5 g (2.01 mmol) of Cp_2TiCl_2, under dry nitrogen, and used without isolation.

EPR Spectra. A 2×10^{-3} M solution of Cp_2TiBH_4 in acetophenone is transferred in a dry-box to an EPR tube (containing a sealed capillary of 2,2-bis(4-*tert*-octylphenyl)-1-picrylhydrazyl (DOPH) as internal standard) and is sealed with a rubber septum. Spectra were obtained on a Bruker ESP 300 spectrometer. The spectrometer was routinely operated at microwave powers of 0.2–0.5 mW; no saturation was observed. Field modulations were kept below 0.2 G in order to enhance spectral resolution.

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