

A facile and chemoselective conjugate reduction using polymethylhydrosiloxane (PMHS) and catalytic $B(C_6F_5)_3$ †

Srivari Chandrasekhar,* Gudise Chandrashekar, Marepally Srinivasa Reddy and Pabbaraja Srihari

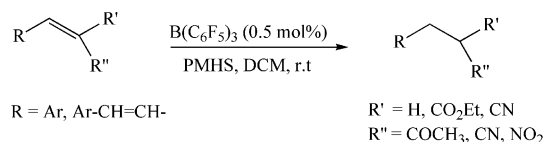
Received 2nd February 2006, Accepted 10th March 2006

First published as an Advance Article on the web 29th March 2006

DOI: 10.1039/b603610b

A highly chemoselective conjugate reduction of electron-deficient Michael acceptors, including α,β -unsaturated ketones, carboxylic esters, nitriles and nitro compounds with PMHS in the presence of catalytic $B(C_6F_5)_3$ is described.

The regioselective reduction of the carbon–carbon double bond in conjugated systems is one of the most desirable transformations in organic synthesis. Despite the fact that a plethora of reducing reagents¹ are available for this operation, new reagents, especially the catalytic versions, are still highly desirable. Most of the procedures reported for the selective reduction of activated (conjugated) olefins involve a pyrophoric hydride source or an expensive catalyst. The metals and metallic hydrides include metals such as iron,² tin,³ zinc,⁴ nickel,⁵ copper,⁶ sodium, boron and aluminium.⁷ The expensive catalytic systems include rhodium,⁸ molybdenum,⁹ cobalt,¹⁰ palladium¹¹ and platinum.¹² However, the highly hydridic nature of most of these metals (primarily sodium, boron and aluminium and their metal hydrides, but also the platinum or palladium catalysts used for hydrogenation) limits their usefulness when high chemoselectivity is required. Undoubtedly, an eco-friendly, safe and economically viable protocol would be a welcome addition to the repertoire of existing methodologies. We have now made the serendipitous observation that the system based on polymethylhydrosiloxane^{13,14} and $B(C_6F_5)_3$,^{15,16} which we have thoroughly utilized for the reduction of carbonyl groups to the methylene functionality,¹⁷ is a versatile reagent–catalyst combination for the chemo- and regioselective reduction of various conjugated olefins in excellent yields (Scheme 1). The results pertaining to this very interesting observation are documented herein.



Scheme 1

Initially, compound **1a** was treated with 2 eq. of PMHS and 0.5 mol% of $B(C_6F_5)_3$ and stirred for half an hour, providing the reduced product in 81% yield (Table 1). Encouraged by this result, several other electron-deficient Michael acceptors and

Table 1 Chemoselective reduction with $B(C_6F_5)_3$ using PMHS

Entry no.	Reactant a	Product ^a b	Time/h	Yield (%) ^b
1			0.5	81
2			3.0	75
3			4.0	82
4			4.0	85
5			10.0	76
6			1.5	89
7			1.0	83
8			12.0	80
9			2.0	85
10			0.5	78
11			0.5	71
12			0.5	74

^a All new compounds were characterized by ¹H and ¹³C NMR spectroscopy and mass spectrometry. ^b Isolated yields after column chromatography.

Organic Division-1, Indian Institute of Chemical Technology, Hyderabad, 500007, India. E-mail: srivari@iict.res.in; Fax: +91 (40)27160512; Tel: +91 (40)27193128

† Electronic supplementary information (ESI) available: ¹H and ¹³C NMR, IR, MS and HRMS spectral data for all new compounds. See DOI: 10.1039/b603610b

Table 2 Chemoselective reduction of compounds **1a** and **7a** with different Lewis acids using PMHS. A dash (—) indicates no reaction

Lewis acid	Entry 1		Entry 7	
	Time/h	Yield (%)	Time/h	Yield (%)
B(C ₆ F ₅) ₃	0.5	81	1.0	83
AlCl ₃	10	—	10	—
Ti(O ⁱ Pr) ₄	10	—	10	—
TMSOTf	10	10	10	20
BF ₃ ·Et ₂ O	10	—	10	—
ZnCl ₂ /Pd(0)	10	15	10	0
ZrCl ₄	10	—	10	—
CeCl ₃ ·7H ₂ O	10	—	10	—

α,β -unsaturated ketones were reduced with good yields (Table 1).¹⁸ Surprisingly, the reagent system was found to be highly chemoselective. For instance, the reagent system reduced selectively the α,β -carbon–carbon double bonds in the $\alpha,\beta,\gamma,\delta$ -diunsaturated compounds **4a** and **9a**. Easily reducible aromatic halides (entries **2** and **8**), nitro compounds (entries **5** and **8**), nitriles (entry **6**) and terminal alkenes (entries **3** and **10**) were also tolerated by this unique reagent, which therefore provides an attractive alternative system for chemoselective reductions.

When attempts were made to improve the yields by increasing the amount of the catalyst B(C₆F₅)₃ to 1 mol%, the result was a complex mixture of saturated and unsaturated compounds, with partial reduction of the ketone moiety to the methylene functionality. For comparison, entries **1** and entry **7** were studied with several other Lewis acids [*viz.*, AlCl₃, Ti(OⁱPr)₄, TMSOTf, BF₃·Et₂O, ZnCl₂ (in the presence of 2.0 mol% Pd(PPh₃)₄ and 1 eq. ZnCl₂), ZrCl₄ and CeCl₃·7H₂O] with PMHS, following a similar protocol (Table 2). The reaction with zinc chloride and TMSOTf looked promising but suffered from lower yields and longer reaction times than the PMHS–B(C₆F₅)₃ system. Even when the amount of the catalysts AlCl₃, Ti(OⁱPr)₄, BF₃·Et₂O, ZrCl₄ and CeCl₃·7H₂O were increased from 0.5 mol% to 20 mol%, the reactions did not proceed. Thus the PMHS–B(C₆F₅)₃ system was found to be superior than other PMHS–Lewis acid combinations.

In conclusion, PMHS along with a catalytic amount of B(C₆F₅)₃ was found to be a unique reagent system for the conjugate reduction of Michael acceptors. Currently, development of a chiral version¹⁹ of this novel reagent and further studies on the scope of this reagent system are in progress.

References

- 1 *Comprehensive Organic Transformations*, ed. R. C. Larock, VCH, New York, 1989, pp. 8–17.
- 2 J. P. Collman, R. G. Finke, P. L. Matlock, R. Wahren, R. G. Komoto and J. I. Brauman, *J. Am. Chem. Soc.*, 1978, **100**, 1119.
- 3 (a) P. Four and F. Guibe, *Tetrahedron Lett.*, 1982, **23**, 1825; (b) E. Keinan and P. A. Gleize, *Tetrahedron Lett.*, 1982, **23**, 477; (c) E. Keinan and N. Greenspoon, *Tetrahedron Lett.*, 1982, **23**, 241; (d) I. Terstiege and E. R. Maleczka, Jr., *J. Org. Chem.*, 1999, **64**, 342.
- 4 C. Petrier and J. L. Luche, *Tetrahedron Lett.*, 1987, **28**, 2347.
- 5 (a) A. F. Barrero, E. J. Alvarez-Manzaneda, R. Chahboun and R. Meneses, *Synlett*, 1999, **10**, 1663; (b) P. Boudjouk, S. B. Choi, B. J. Jauck and A. B. Rajkumar, *Tetrahedron Lett.*, 1998, **39**, 3951.

- 6 (a) T. Tsuda, T. Fuhii, K. Kawasaki and T. Saegusa, *J. Chem. Soc., Chem. Commun.*, 1980, 1013; (b) E. C. Ashby, J. J. Lin and A. B. Goel, *J. Org. Chem.*, 1978, **43**, 183; (c) M. F. Semmelhack and R. D. Stauffer, *J. Org. Chem.*, 1975, **40**, 3619; (d) R. K. Baekman, Jr. and R. Michalak, *J. Am. Chem. Soc.*, 1974, **96**, 1623; (e) W. S. Mahoney, D. M. Brestensky and J. M. Strucker, *J. Am. Chem. Soc.*, 1988, **110**, 291; (f) B. H. Lipshutz, W. Chrisman, K. Noson, P. P. Papa, J. A. Sclafani, R. W. Vivian and J. K. Keith, *Tetrahedron*, 2000, **56**, 2779; (g) N. Ravasio, M. Antenori, M. Gargano and P. Mastroilli, *Tetrahedron Lett.*, 1996, **37**, 3529; (h) B. H. Lipshutz, J. Keith, P. P. Papa and R. Vivian, *Tetrahedron Lett.*, 1998, **39**, 4627; (i) A. Mori, A. Fujita, H. Kajiro, Y. Nishihara and T. Hiyama, *Tetrahedron*, 1999, **55**, 4573; (j) A. Mori, A. Fujita, H. Kajiro, Y. Nishihara and T. Hiyama, *Chem. Commun.*, 1997, 2159.
- 7 (a) R. W. Goetz and M. Orchin, *J. Am. Chem. Soc.*, 1963, **85**, 2782; (b) S. B. Kadin, *J. Org. Chem.*, 1966, **31**, 620; (c) L. Mordenti, J. J. Brunet and P. Caubere, *J. Org. Chem.*, 1981, **46**, 192; (d) T. Tsuda, T. Hayashi, H. Satomi, T. Kawamoto and T. Saegusa, *J. Org. Chem.*, 1986, **51**, 537; (e) K. E. Kim, S. B. Park and N. M. Yoon, *Synth. Commun.*, 1988, **18**, 89; (f) C. Bianchini, E. Farnetti, M. Graziani, M. Peruzzini and A. Polo, *Organometallics*, 1993, **12**, 3753; (g) B. C. Ranu and S. Samanta, *J. Org. Chem.*, 2003, **68**, 7130.
- 8 (a) I. Ojima and T. Kogure, *Organometallics*, 1982, **1**, 1390; (b) R. E. Harmon, J. L. Parsons, D. W. Cooke, S. K. Gupta and J. Schoolenberg, *J. Org. Chem.*, 1969, **34**, 3684; (c) D. A. Evans and G. C. Fu, *J. Org. Chem.*, 1990, **55**, 5678; (d) H. J. Liu and B. Ramani, *Synth. Commun.*, 1985, **15**, 965.
- 9 E. Keinan and D. Perez, *J. Org. Chem.*, 1987, **52**, 2576.
- 10 (a) P. L. Maux, V. Massonneau and G. Simonneaux, *J. Organomet. Chem.*, 1985, **284**, 101; (b) T. Keno, T. Kimura, Y. Ohtsuka and T. Yamada, *Synlett*, 1999, 96.
- 11 (a) E. Keinan and N. Greenspoon, *J. Org. Chem.*, 1983, **48**, 3545; (b) E. Keinan and N. Greenspoon, *J. Am. Chem. Soc.*, 1986, **108**, 7314; (c) E. Keinan and N. Greenspoon, *Isr. J. Chem.*, 1984, **24**, 82; (d) N. A. Cortese and R. F. Rheck, *J. Org. Chem.*, 1978, **43**, 3985; (e) E. Keinan and N. Greenspoon, *Tetrahedron Lett.*, 1985, **26**, 1353; (f) P. A. Aristoff, P. D. Johnson and A. W. Harrison, *J. Am. Chem. Soc.*, 1985, **107**, 7967.
- 12 E. Yoshii, H. Ikeshima and K. Ozaki, *Chem. Pharm. Bull.*, 1972, **20**, 1827.
- 13 (a) J. Lipowitz and S. A. Bowman, *Aldrichimica Acta*, 1973, **6**, 1; (b) R. Q. Savers, W. J. Scheiber and S. O. Brewer, *J. Am. Chem. Soc.*, 1946, **68**, 962; (c) A. L. Klyashchitskaya, G. N. Krasovskii and S. A. Fridlyand, *Gig. Sanit.*, 1970, **35**, 28; A. L. Klyashchitskaya, G. N. Krasovskii and S. A. Fridlyand, *Chem. Abstr.*, 1970, **72**, 124864.
- 14 For our contributions on PMHS, see: (a) S. Chandrasekhar, Y. R. Reddy and C. Ramarao, *Synth. Commun.*, 1997, **27**, 2251; (b) S. Chandrasekhar, Y. R. Reddy and Ch. R. Reddy, *Chem. Lett.*, 1998, **29**, 1273; (c) S. Chandrasekhar, M. V. Reddy and L. Chandraiah, *Synth. Commun.*, 1999, 3981; (d) S. Chandrasekhar and Md. Ahmed, *Tetrahedron Lett.*, 1999, **40**, 9325; (e) S. Chandrasekhar, L. Chandraiah, Ch. R. Reddy and M. V. Reddy, *Chem. Lett.*, 2000, 780; (f) S. Chandrasekhar, Ch. R. Reddy and Md. Ahmed, *Synlett*, 2000, 1655; (g) S. Chandrasekhar, L. Chandraiah and M. V. Reddy, *Synlett*, 2000, 1351; (h) S. Chandrasekhar, Ch. R. Reddy and R. J. Rao, *Tetrahedron*, 2001, **57**, 3435; (i) S. Chandrasekhar, Ch. R. Reddy and R. J. Rao, *Synlett*, 2001, 1561; (j) S. Chandrasekhar, Ch. R. Reddy and B. N. Babu, *Tetrahedron Lett.*, 2003, **44**, 2057; (k) S. Chandrasekhar, B. N. Babu, Md. Ahmed, M. V. Reddy, P. Srihari, B. Jagadeesh and A. Prabhakar, *Synlett*, 2004, 1303.
- 15 (a) D. J. Parks and W. E. Piers, *J. Am. Chem. Soc.*, 1996, **118**, 9440; (b) J. M. Blackwell, K. L. Foster, V. H. Beck and W. E. Piers, *J. Org. Chem.*, 1999, **64**, 4887; (c) J. M. Blackwell, D. J. Morrison and W. E. Piers, *Tetrahedron*, 2002, **58**, 8247; (d) G. Erker, *Dalton Trans.*, 2005, 1883 and references therein.
- 16 (a) S. Chandrasekhar, G. Chandrasekar, B. N. Babu, K. Vijeender and K. V. Reddy, *Tetrahedron Lett.*, 2004, **45**, 5497; (b) S. Chandrasekhar, Ch. R. Reddy, B. N. Babu and G. Chandrasekar, *Tetrahedron Lett.*, 2002, **43**, 3801; (c) S. Chandrasekhar, Y. S. Rao and N. R. Reddy, *Synlett*, 2005, 1471; (d) S. Chandrasekhar, Ch. R. Reddy and G. Chandrasekar, *Tetrahedron Lett.*, 2004, **45**, 6481; (e) For a review on tris(pentafluorophenyl)borane, see our contribution to the 'Electronic Encyclopedia of Organic Reagents for Organic Synthesis', S. Chandrasekar, B. N. Babu and G. Chandrasekar, *eEROS*, 2005, and references therein.

- 17 S. Chandrasekhar, C. R. Reddy and B. N. Babu, *J. Org. Chem.*, 2002, **67**, 9080.
- 18 General experimental procedure: To a solution of the α,β -unsaturated ketone (2 mmol) in anhydrous methylene chloride (5 mL) was added $\text{B}(\text{C}_6\text{F}_5)_3$ (5 mg, 0.01 mmol) and PMHS (4 mmol), and the solution was stirred at room temperature for the appropriate time (monitored by TLC). Water was added to the reaction mixture, which was then extracted with methylene chloride (3×5 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, concentrated *in vacuo*, and the crude product purified by flash chromatography.
- 19 For a few earlier chiral asymmetric conjugate reductions, see: (a) B. H. Lipshutz, J. M. Servesko, T. B. Petersen, P. P. Papa and A. A. Lover, *Org. Lett.*, 2004, **6**, 1273 and references therein; (b) C. Czekelius and E. M. Carreira, *Org. Lett.*, 2004, **6**, 4575 and references therein; (c) M. P. Rainka, Y. Aye and S. L. Buchwald, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5821 and references therein.