SHORT COMMUNICATION

Stereoselective Reduction of α-Substituted β-Keto Esters by Hydrostannane/Organotin Triflate

Tsuneo Sato and Junzo Otera
Department of Applied Chemistry, Okayama University of Science, Ridai-cho, Okayama 700, Japan

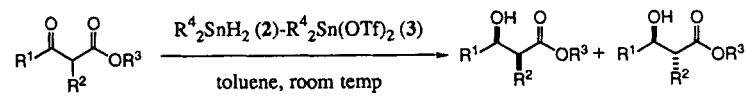
Stereoselective reduction of α-substituted β-keto esters is achieved by the combined use of hydrostannane/organotin triflate. *syn*-Aldols are obtained with more than 90% selectivities.

Keywords: α substituted β-keto esters, reduction, stereoselectivity, organotin triflate

Stereoselective reduction of α-substituted β-keto acid derivatives is of great synthetic value because the aldol reaction between a ketone and an ester enolate is not always satisfactory.[1,2] In this context, hydrogenation[3–5] as well as metal hydride reduction with various borohydrides [$Zn(BH_4)_2$,[6–12] KEt_3BH,[13] $Ca(BH_4)_2$,[14] and $NaBH_4$[15,16]] and $LiAlH_4$[17] was invoked. Moreover, Group 14 metal hydrides are also promising. Hiyama and coworkers have reported stereoselective reduction of α-substituted β-keto amides by means of hydrosilane/F^- and hydrosilane/H^+ reagents.[18–21] A hydrostannane, Bu_3SnH, was employed for reduction of α-methylacetoacetate ester under polar or radical reaction conditions by Quintard and Pereyre.[22] Unfortunately, however, low selectivities were attained under both conditions. In the course of our study on organotin triflates as synthetically useful Lewis acids,[23–27] we have found that the stereoselectivity of hydrostannane-based reduction of α-substituted β-keto esters is dramatically improved by combination with an organotin triflate.

As shown in Table 1, treatment of β-keto ester **1** (1 equiv.) with $(c\text{-}C_6H_{11})_2SnH_2$ (**2a**) (2 equiv.) gives rise to little stereoselectivity (experiment 1). Yet, upon addition of $(c\text{-}C_6H_{11})_2Sn(OTf)_2$ (**3a**),[27] the *syn*-selectivity is improved and the use of 2 equiv. of **3a** results in 99:1 selectivity (experiments 2–4); the stereochemistry was assigned by NMR according to Heathcock[28,29]. Combination of the butyltin compounds **2b** and **3b** is also effective but the selectivity is somewhat lower than that with the cyclohexyl analogues (experi-

Table 1 Reduction of β-keto esters by organotin hydride/organotin triflate



Experiment	R^1	R^2	R^3	2 (equiv.)		3 (equiv.)		Reaction time (h)	Yield (%)[a]	**4a**:**4b**[b]
1	4-ClC_6H_4	Me	Me	$(c\text{-}C_6H_{11})_2SnH_2$ (**2a**)	(2)[c]	$(c\text{-}C_6H_{11})_2Sn(OTf)_2$ (**3a**)	(0)	18	82	54:46
2	4-ClC_6H_4	Me	Me	**2a**	(2)	**3a**	(0.6)	18	87	76:24
3	4-ClC_6H_4	Me	Me	**2a**	(2)	**3a**	(1.2)	18	56	77:23
4	4-ClC_6H_4	Me	Me	**2a**	(2)	**3a**	(2)	18	66	99:1
5	4-ClC_6H_4	Me	Me	Bu_2SnH_2 (**2b**)	(2)	$Bu_2Sn(OTf)_2$ (**3b**)	(2)	32	65	95:5
6	C_6H_5	Me	Me	**2a**	(2)	**3a**	(2)	16	63	98:2
7	C_6H_5	Me	Et	**2a**	(2)	**3a**	(2)	18	63	98:2
8	C_6H_5	Et	Me	**2a**	(2)	**3a**	(2)	21	65	92:8

[a] Isolated yields. [b] Determined by HPLC. [c] No. of equivalents in parentheses.

CCC 0268–2605/94/040431–02

Received 23 February 1994
Accepted 22 March 1994

ment 5). High selectivity holds with other substrates (experiments 6–8).

It should be noted that use of equimolar amounts of **2** and **3** is crucial for high selectivity. When these two components are stirred in toluene, compound **3**, innately insoluble in this solvent, begins to dissolve and a clear solution soon develops. Apparently, the two components react to each other. We have not succeeded in identifying what has been formed. However, it is conceivable that a disproportionation product $R_2SnH(OTf)$ works as an active species for the stereoselective reduction. Formation of dialkyltin halide hydrides (R_2SnHX) from the corresponding dihalides and dihydrides has been reported.[30–33]

A typical procedure is as follows. A mixture of **2a** (144 mg, 0.5 mmol) and **3a** (292 mg, 0.5 mmol) in toluene (1 ml) was stirred at room temperature for 30 min. A clear solution was obtained. To this solution was added methyl 3-(4-chlorophenyl)-2-methyl-3-oxopropanoate (57 mg, 0.25 mmol) in toluene (0.5 ml). After the mixture had been stirred at room temperature for 18 h, acetaldehyde (0.11 ml) was added. The resulting mixture was stirred for 30 min and then worked up to give an oil. HPLC analysis of this material indicated that *syn*- and *anti*-methyl 3-(4-chlorophenyl)-3-hydroxy-2-methylpropanoates were produced in a 99:1 ratio. Column chromatography on silica gel (9:1 hexane–ethyl acetate) afforded the desired product (38 mg, 66%).

In summary, it has turned out that hydrostannanes are employable for stereoselective reduction of α-substituted β-keto esters when coupled with organotin triflate. Due to its mildness the present method will find practical use in preparing stereo-defined aldols.

REFERENCES

1. T. Oishi and T. Nakata, *J. Synth. Chem. Jpn.* **39**, 633 (1981).
2. T. Oishi and T. Nakata, *Acc. Chem. Res.* **17**, 338 (1984).
3. A. Tai, H. Watanabe and T. Harada, *Bull. Chem. Soc. Jpn.* **52**, 1468 (1979).
4. R. Noyori, T. Ikeda, T. Ohkuma, M. Widhalm, M. Kitamura, H. Takaya, S. Akutagawa, S. Sayo, T. Saito, T. Taketomi and H. Kumobayashi, *J. Am. Chem. Soc.* **111**, 9134 (1989).
5. M. Kitamura, T. Ohkuma, M. Tokunaga and R. Noyori, *Tetrahedron: Asymmetry* **1**, 1 (1990).
6. T. Nakata and T. Oishi, *Tetrahedron Lett.* **21**, 1641 (1980).
7. T. Nakata, T. Kuwabara, Y. Tani and T. Oishi, *Tetrahedron Lett.* **23**, 1015 (1982).
8. T. Nakata, M. Fukui and T. Oishi, *Tetrahedron Lett.* **24**, 2657 (1983).
9. R. M. DiPardo and M. Bock, *Tetrahedron Lett.* **24**, 4805 (1983).
10. Y. Ito and M. Yamaguchi, *Tetrahedron Lett.* **24**, 5385 (1983).
11. D. A. Evans, M. D. Ennis, T. Le, N. Mandel and G. Mandel, *J. Am. Chem. Soc.* **106**, 1154 (1984).
12. G. R. Brown and A. J. Foubister, *J. Chem. Soc., Chem. Commun.* 455 (1985).
13. Y. Ito, T. Katsuki and M. Yamaguchi, *Tetrahedron Lett.* **26**, 4643 (1985).
14. M. Shimagaki, M. Shiokawa, K. Sugai, T. Teranaka, T. Nakata and T. Oishi, *Tetrahedron Lett.* **29**, 659 (1988).
15. H. Fujii, K. Oshima and K. Utimoto, *Tetrahedron Lett.* **32**, 6174 (1991).
16. M. Taniguchi, H. Fujii, K. Oshima and K. Utimoto, *Tetrahedron* **49**, 11169 (1993).
17. J. Cancill and J. Jacques, *Bull. Soc. Chim. Fr.*, 2180 (1970).
18. M. Fujita and T. Hiyama, *J. Am. Chem. Soc.* **107**, 8294 (1985).
19. M. Fujita and T. Hiyama, *J. Org. Chem.* **53**, 5405 (1988).
20. M. Fujita and T. Hiyama, *J. Org. Chem.* **53**, 5415 (1988).
21. M. Fujita and T. Hiyama, *Org. Synth.*, Coll. Vol. **8**, 326 (1993).
22. J.-P. Quintard and M. Pereyre, *J. Organomet. Chem.* **82**, 103 (1974).
23. T. Sato, J. Otera and H. Nozaki, *J. Am. Chem. Soc.* **112**, 901 (1990).
24. T. Sato, Y. Wakahara, J. Otera and H. Nozaki, *Tetrahedron Lett.* **31**, 1581 (1990).
25. T. Sato, Y. Wakahara, J. Otera, H. Nozaki and S. Fukuzumi, *J. Am. Chem. Soc.* **113**, 4028 (1991).
26. T. Sato, Y. Wakahara, J. Otera and H. Nozaki, *Tetrahedron* **47**, 9773 (1991).
27. T. Sato, J. Otera and H. Nozaki, *J. Org. Chem.* **58**, 4971 (1993).
28. C. H. Heathcock, *Asymmetric Synthesis*, Morrison, J. D., Ed.; Academic Press: New York (1984) Vol. 3. p111.
29. C. H. Heathcock, *Comprehensive Carbanion Chemistry*, Part B, edited by E. Bucel and T. Durst, p. 177. Elsevier, Amsterdam (1984).
30. A. K. Sawyer and H. G. Kuivila, *Chem. Ind. (London)*, 260 (1960).
31. A. K. Sawyer, J. E. Brown and E. L. Hanson, *J. Organomet. Chem.* **3**, 464 (1965).
32. W. P. Neumann and J. Pedain, *Tetrahedron Lett.*, 2461 (1964).
33. K. Kawakami, T. Saito and R. Okawara, *J. Organomet. Chem.* **8**, 377 (1967).