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Palladium-catalyzed reduction of ketones with $^n\mathrm{Bu}_2\mathrm{SnH}_2$

Ikuyo Kamiya and Akiya Ogawa*

Department of Chemistry, Faculty of Science, Nara Women's University, Kitauoyanishi-machi, Nara 630-8506, Japan

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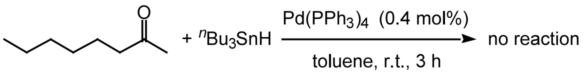
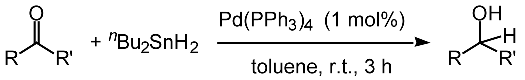
Abstract—Whereas the $\mathrm{Pd(PPh_3)_4}$-catalyzed reduction of ketones with $^n\mathrm{Bu_3SnH}$ does not proceed at all, the use of $^n\mathrm{Bu_2SnH_2}$, instead of $^n\mathrm{Bu_3SnH}$, leads to the efficient reduction of a variety of ketones in the presence of a catalytic amount of $\mathrm{Pd(PPh_3)_4}$ under mild conditions, providing the corresponding alcohols in good yields. The stereoselectivity in the reduction of cyclic ketones is also investigated by using this $\mathrm{Pd(PPh_3)_4}/^n\mathrm{Bu_2SnH_2}$ reduction system. © 2002 Elsevier Science Ltd. All rights reserved.

Organotin hydrides are extensively utilized in organic synthesis as useful reducing reagents for alkyl halides and carbonyl compounds under radical or ionic conditions.[1–3] In addition to these reactions, the tin hydride reduction of acid chlorides,[4] thioesters,[5a] and selenoesters[5b] to the corresponding aldehydes is found to take place very smoothly by using transition metal catalysts such as palladium(0) catalysts. However, little is known about the examples of transition-metal-catalyzed reduction of ketones with $^n\mathrm{Bu_3SnH}$.[6] In fact, the attempted reduction of ketones such as 2-octanone with tri(*n*-butyl)tin hydride (1.2 equiv.) in the presence of $\mathrm{Pd(PPh_3)_4}$ catalyst did not proceed at all (Eq. (1)).



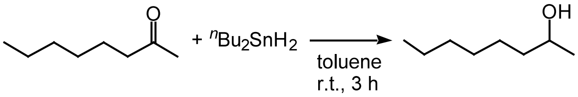
(1)

Herein we report a novel finding that, when $^n\mathrm{Bu_2SnH_2}$, instead of $^n\mathrm{Bu_3SnH}$, is employed for the $\mathrm{Pd(PPh_3)_4}$-catalyzed reduction system, a variety of ketones can be successfully reduced to the corresponding alcohols under mild conditions (Eq. (2)).



(2)

As can be seen from Eq. (3), 2-octanone is efficiently reduced with $^n\mathrm{Bu_2SnH_2}$[7] in the presence of a catalytic amount of $\mathrm{Pd(PPh_3)_4}$, while, in the absence of $\mathrm{Pd(PPh_3)_4}$, the reduction does not proceed at all in the dark. Even in the absence of $\mathrm{Pd(PPh_3)_4}$, however, the reduction of 2-octanone with $^n\mathrm{Bu_2SnH_2}$ takes place if the reaction vessel is not shielded from room light, most probably by a radical mechanism induced by room light. Therefore, the palladium(0)-catalyzed reductions of ketones were carried out in the dark.[8]



(3)

Entry	Catalyst	Mol%	Condition	Yield (%)
1	$\mathrm{Pd(PPh_3)_4}$	1	Dark	>95
2		0	Dark	0
3		0	Room light	84

Table 1 represents the results of the $\mathrm{Pd(PPh_3)_4}$-catalyzed reduction of ketones with $^n\mathrm{Bu_2SnH_2}$.[9,10] A variety of ketones undergo the palladium-catalyzed reduction with $^n\mathrm{Bu_2SnH_2}$ conveniently, providing the corresponding alcohols in good yields. Functionalities such as olefinic (both unconjugate and conjugate[11]), ester, alkoxyl, and fluoro groups, are tolerant to the reduction (entries 1, 4, 3, 6, and 7). On the other hand, the palladium-catalyzed reduction of di(*sec*-alkyl) ketones such as dicyclohexyl ketone led to the formation of the corresponding alcohol in low yields (56%), probably due to the sterical hindrance. Although aromatic ketones, e.g. benzophenone, generally provide the low

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Keywords: transition metal catalyst; tin hydrides; mild conditions; high efficiency.

* Corresponding author. Tel.: +81-742-20-3979; fax: +81-742-20-3979; e-mail: a.ogawa@cc.nara-wu.ac.jp

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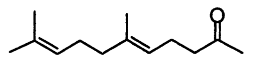
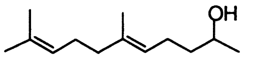
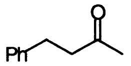
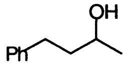
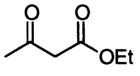
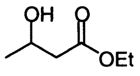
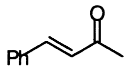
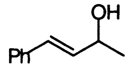
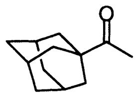
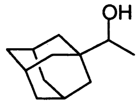
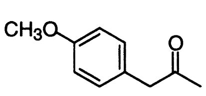
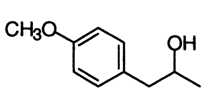
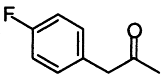
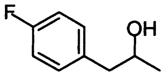
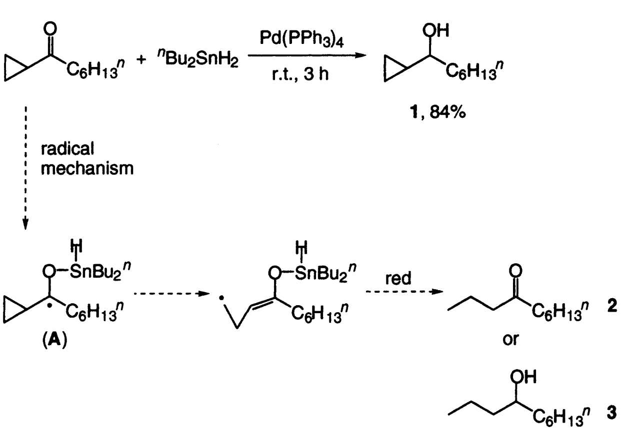
Table 1. Palladium(0)-catalyzed reduction with $^{n}Bu_2SnH_2$^{a}

entry	substrate	product	yield, %^{b}
1			83
2			>95
3			82
4			54
5			85
6			>95
7 8 9			>95 >95^{c} 18^{d}

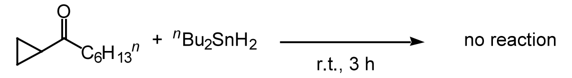
^{a}Reaction conditions: substrate (1 mmol), $^{n}Bu_2SnH_2$ (2 mmol, added dropwise over 2 h), $Pd(PPh_3)_4$ (1 mol%), toluene (1 mL), 25 °C, 3 h. ^{b}Determined by ^{1}H NMR. $^{c}Pd(PPh_3)_4$ (1 mol%), Galvinoxyl (30 mol%), 0 °C, 3 h. ^{d}Without catalyst, Galvinoxyl (30 mol%), 0 °C, 3 h.

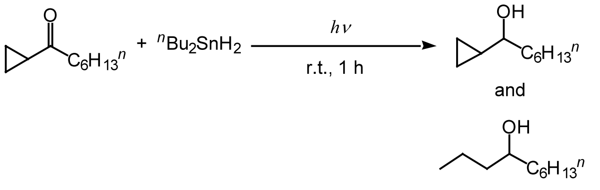
yield (32%) of the corresponding alcohols under the standard reduction conditions, prolonged reaction time (4 h) leads to the increase of the yield (91%).

To get insight into the reaction pathway, a cyclopropyl n-hexyl ketone was used as a substrate for the palladium-catalyzed reduction. If radical species such as $^{n}Bu_2SnH^{\bullet}$ participates in this reduction, cyclopropylcarbinyl radical intermediate (**A**) might be generated in situ. Since the ring-opening rate for cyclopropylcarbinyl radicals is known to be as fast as 10^{8} s^{-1},[12] a ring-opened reduction products (**2** or **3**) might be formed. However, such products were not observed at all and only 1-cyclopropyl-1-heptanol (**1**) was obtained in the palladium-catalyzed reduction (Scheme 1). In addition, cyclopropyl n-hexyl ketone was not reduced with $^{n}Bu_2SnH_2$ in the absence of $Pd(PPh_3)_4$, as can be seen from Eq. (4). On the other hand, the reduction of cyclopropyl n-hexyl ketone, upon irradiation with a tungsten lamp through Pyrex ($h\nu$ >300 nm), proceeded and gave the alcohol (**1**) and the ring-opened alcohol (**3**) in the ratio of 8:2 (Eq. (5)). These results suggest that the present palladium-catalyzed reduction does not involve the radical mechanism.



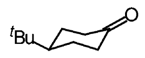
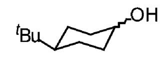
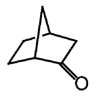
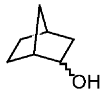
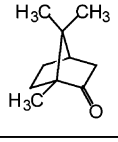
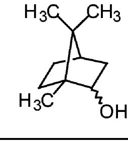
Scheme 1. Reduction of a cyclopropyl ketone.

 (4)

 (5)

Moreover, the stereoselectivity of this reduction was investigated by using several cyclic ketones (Table 2). $LiAlH_4$ and $NaBH_4$, as general reducing agents for carbonyl compounds, are known to indicate the axial attack preferentially,[13] whereas bulky reagents such as $Li[(CH_3)_2CHCH(CH_3)]_3BH$ prefer the equatorial attack

Table 2. Stereoselectivity in the reduction of cyclic ketones

entry	substrate	product	yield, %^{b}	*cis*/*trans* or *endo*/*exo*
1			~100	6/94
2			~100	39/61
3			~100	80/20
4			31	0/100

^{a}Reaction conditions: substrate (1 mmol), $^{n}Bu_2SnH_2$ (2 mmol, added dropwise over 2 h), $Pd(PPh_3)_4$ (1 mol%), toluene (1 mL), 25 °C, 3 h. ^{b}Determined by ^{1}H NMR.

due to the steric repulsion with substrates.[14] The present reduction of cyclic ketones proceeded almost quantitatively, and their stereoselectivities indicated similar trends as the $LiAlH_4$- and $NaBH_4$-reduction.

In conclusion, we have developed the first example of palladium-catalyzed reduction with $^{n}Bu_2SnH_2$. Although the transition-metal-catalyzed reduction of ketones with $^{n}Bu_3SnH$ does not take place at all, the use of $^{n}Bu_2SnH_2$ in the palladium-catalyzed reduction system makes it possible to reduce various ketones. Further investigations to clarify the precise reaction pathway are now in progress.

Acknowledgements

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References

1. Pereyre, M.; Quintard, J.-P.; Ralhm, A. *Tin in Organic Synthesis*; Butterworths: London, 1987.
2. Harrison, P. G. *Chemistry of Tin*; Blackie & Son: New York, 1989.
3. Davies, A. G. *Organotin Chemistry*; VCH: Weinheim, 1997.
4. Four, P.; Guibe, F. *J. Org. Chem.* **1981**, *46*, 4439.
5. (a) Kuniyasu, H.; Ogawa, A.; Sonoda, N. *Tetrahedron Lett.* **1993**, *34*, 2491; (b) Kuniyasu, H.; Ogawa, A.; Higaki, K.; Sonoda, N. *Organometallics* **1992**, *11*, 3937.
6. Keinan, E.; Gleize, P. A. *Tetrahedron Lett.* **1982**, *23*, 477.
7. Ferkous, F.; Messadi, D.; De Jeso, B.; Degueil-Castaing, M.; Maillard, B. *J. Organomet. Chem.* **1991**, *420*, 315.
8. A trace amount of oxygen contaminated in the reduction system sometimes induces the radical reduction with $^{n}Bu_2SnH_2$, of some ketones bearing an electron-withdrawing group. In these cases, we examined the transition-metal-catalyzed reduction in the presence of Galvinoxyl as a radical inhibitor at lower temperature (0°C), because these conditions suppress the radical reduction effectively (see entries 7–9 in Table 1).
9. The following is a general method for the palladium-catalyzed reduction of ketones: Di-*n*-butyltin dihydride ($^{n}Bu_2SnH_2$) was prepared by the reduction of $^{n}Bu_2SnCl_2$ (82 mmol) with $LiAlH_4$ (62 mmol) in diethyl ether (100 mL) at 40°C for 4 h, and was purified by distillation under reduced pressure (bp 55°C/7 mmHg).[7] Toluene was purified by distillation from calcium hydride (CaH_2). All reactions were carried out in a flame-dried two-necked flask in the dark under an atmosphere of nitrogen with magnetic stirring. $^{n}Bu_2SnH_2$ (2 mmol) was added dropwise over 2 h via a syringe to a solution of substrate (1 mmol) and $Pd(PPh_3)_4$ (1 mol% = 0.01 mmol) in toluene (1 mL) at room temperature (or 0°C). After the reaction mixture was stirred for 1 h, toluene was removed under reduced pressure. Purification of the product was carried out by using a recycling preparative HPLC (Japan Analytical Industry Co. Ltd., model LC-908) equipped with JAIGEL-1H and -2H columns (GPC) using $CHCl_3$ as an eluent.
10. In the presence of palladium catalyst, $^{n}Bu_2SnH_2$ is easily decomposed to di-(or oligo-) stannane and molecular hydrogen. To suppress this side reaction, the palladium-catalyzed reduction of ketones requires the use of excess $^{n}Bu_2SnH_2$ (1.5–2.0 equiv.) and the slowly dropping of $^{n}Bu_2SnH_2$.
11. $Pd(PPh_3)_4$-catalyzed reduction of α,β-unsaturated ketones with $^{n}Bu_3SnH$ in more polar solvents such as THF in the presence of proton sources is reported to provide the corresponding saturated ketones (see Ref. 6).
12. (a) Bowry, V. W.; Lusztyk, J.; Ingold, K. U. *J. Am. Chem. Soc.* **1991**, *113*, 5687; (b) Bowry, V. W.; Ingold, K. U. *J. Am. Chem. Soc.* **1991**, *113*, 5699.
13. (a) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2205; (b) Cherest, M.; Felkin, H. *Tetrahedron Lett.* **1971**, 383.
14. Krishnamurthy, S.; Brown, H. C. *J. Am. Chem. Soc.* **1976**, *98*, 3383.