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Palladium-Catalyzed Preparation of Silyl Enolates from α,β-Unsaturated Ketones or Cyclopropyl Ketones with Hydrosilanes

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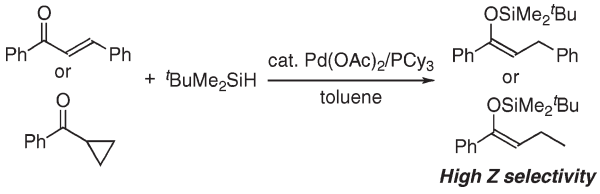
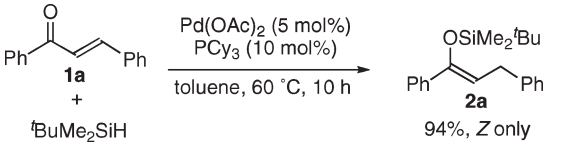


α,β-Unsaturated ketones and cyclopropyl ketones undergo palladium-catalyzed hydrosilylation with hydrosilanes to yield (*Z*)-silyl enolates.

Silyl enolates are extremely useful and valuable reagents for carbon−carbon bond formation in organic synthesis.[1] Nowadays, transition-metal-catalyzed 1,4-hydrosilylation of α,β-unsaturated carbonyl compounds is one of the most powerful methods to synthesize silyl enolates. Although some examples of 1,4-hydrosilylation of α,β-unsaturated carbonyl compounds catalyzed by Rh,[2] Pt,[3] Cu,[4] and B($(C_6F_5)_3$[5] are known, the stereoselectivities are not satisfactory in the cases of acyclic enones[2,3] and 1,2-hydrosilylation competes in some cases.[2,3] Hence, the highly selective synthesis of (*Z*)-silyl enolates remains a challenge.

Herein, we report that a combination of palladium acetate and tricyclohexylphosphine (PCy_3) is effective for 1,4-hydrosilylation of α,β-unsaturated ketones with hydrosilanes yielding silyl enolates with high *Z* selectivity. Treatment of chalcone (**1a**) with $^tBuMe_2SiH$ in the presence of a palladium/tricyclohexylphosphine catalyst in toluene at 60 °C afforded (*Z*)-silyl enolate **2a** in 94% yield (Scheme 1).[6]

SCHEME 1. Palladium-Catalyzed Reaction of Chalcone with Hydrosilane



A variety of α,β-unsaturated ketones were subjected to the reaction, and the results are summarized in Table 1. The electronic nature of the aryl group at the β-position had little effect on the yields of **2** (entries 1 and 2). The substituents R and R′ are not limited to aryl groups (entries 3−5), and aliphatic ketone **1f** could undergo efficient 1,4-hydrosilylation. Heteroaromatic rings were compatible with the reaction conditions (entries 6 and 7).

We then examined the scope of hydrosilanes. Upon treatment of chalcone with $PhMe_2SiH$, an excellent yield of the corresponding product **2i** was obtained (entry 8). While the reaction with Et_3SiH gave **2j**[2a] smoothly (entry 9), no reaction took place with $^iPr_3SiH$ (entry 10).

In contrast to the reactions of acyclic ketones, the reaction of 2-cyclohexenone with $^tBuMe_2SiH$ gave silyl enolate ***2l*** in very low yield, even when the reaction temperature was raised to 80 °C (Scheme 2). Moreover, we obtained trace amounts of the desired products when β,β-disubstituted or α-substituted enones were employed.

On the basis of the fact that the reactivities of acyclic ketones and cyclohexenone are different, a plausible mechanism is proposed in Scheme 3. Formation of oxapalladacycle intermediate **A** would occur by oxidative cyclization of the α,β-unsaturated ketone with palladium(0).[7] Competitive oxidative addition of the hydrosilane to palladium(0)[6] should be relatively slow, otherwise cyclohexenone would react as smoothly as acyclic enones by the conventional 1,4-hydrosilylation process. Transmetalation between **A** and the hydrosilane would then take place to give alkylpalladium intermediate **B**, which bears a silyl enolate moiety. Reductive elimination produces the silyl enolate with regeneration of the initial palladium(0) complex.

We could not eliminate the pathway that involves oxidative addition of the hydrosilane to palladium(0), 1,4-hydropalladation, reductive elimination because in the case of cyclic **1i** (Scheme 2), which would be able to form an oxapalladacycle, a low yield of ***2l*** was obtained. Consequently, both mechanisms could be in competition in the case of acyclic α,β-unsaturated ketones.

(1) (a) Mukaiyama, T. *Angew. Chem., Int. Ed.* **1977**, *16*, 817–826. (b) Kobayashi, S.; Manabe, K.; Ishitani, H.; Matsuo, J. *Science of Synthesis*; Fleming, I., Ed.; Thieme: Stuttgart, Germany, 1999; Vol. 4, Chapter 4.16. (c) Miura, K.; Hosomi, A. *Main Group Metals in Organis Synthesis*; Yamamoto, H., Oshima, K., Eds.; Wiley-VCH: Weinheim, Germany, 2004; Vol. 2, Chapter 10.2.

(2) (a) Ojima, I.; Kogure, T. *Organometallics* **1982**, *1*, 1390–1399. (b) Zheng, G. Z.; Chan, T. H. *Organometallics* **1995**, *14*, 70–79. (c) Mori, A.; Kato, T. *Synlett* **2002**, 1167–1169. (d) Anada, M.; Tanaka, M.; Suzuki, K.; Nambu, H.; Hashimoto, S. *Chem. Pharm. Bull.* **2006**, *54*, 1622–1623. (e) Anada, M.; Tanaka, M.; Washio, T.; Yamawaki, M.; Abe, T.; Hashimoto, S. *Org. Lett.* **2007**, *9*, 4559–4562.

(3) (a) Bnrlow, A. P.; Boag, N. M.; Stone, F. G. A. *J. Organomet. Chem.* **1980**, *191*, 39–47. (b) Johnson, C. R.; Raheja, R. K. *J. Org. Chem.* **1994**, *59*, 2287–2288.

(4) Lipshutz, B. H.; Chrisman, W.; Noson, K.; Papa, P.; Sclafani, J. A.; Vivian, R. W.; Keith, J. M. *Tetrahedron* **2002**, *56*, 2779–2788.

(5) Blackwell, J. M.; Morrison, D. J.; Piers, W. E. *Tetrahedron* **2002**, *58*, 8247–8254.

(6) For palladium-catalyzed conjugate reduction of α,β-unsaturated carbonyl compounds with hydrosilanes, see: Keinan, E.; Greenspoon, N. *J. Am. Chem. Soc.* **1986**, *108*, 7314–7325.

(7) Canovese, L.; Santo, C.; Visentin, F. *Organometallics* **2008**, *27*, 3577–3581.

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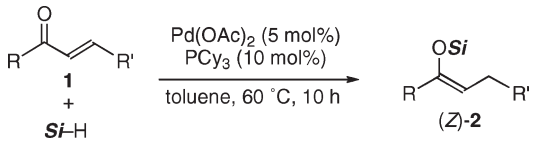
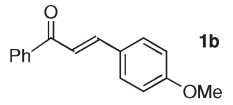
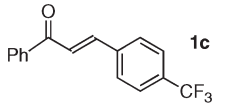
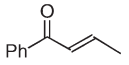
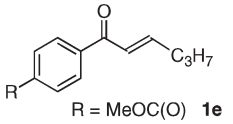
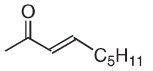
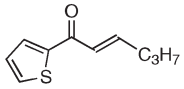
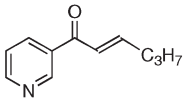
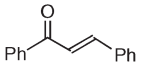
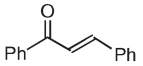
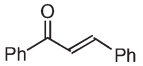
TABLE 1. Scope of α,β-Unsaturated Ketones

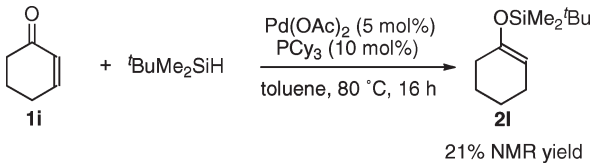


entry	substrate	*Si*	2	yield(%)[a]
1	 **1b**	^{t}BuMe$_2$Si	**2b**	77
2	 **1c**	^{t}BuMe$_2$Si	**2c**	71
3	 **1d**	^{t}BuMe$_2$Si	**2d**	65
4	 R = MeOC(O) **1e**	^{t}BuMe$_2$Si	**2e**	95[b]
5	 **1f**	^{t}BuMe$_2$Si	**2f**	92
6	 **1g**	^{t}BuMe$_2$Si	**2g**	99
7	 **1h**	^{t}BuMe$_2$Si	**2h**	50[c]
8	 **1a**	PhMe$_2$Si	**2i**	99
9	 **1a**	Et$_3$Si	**2j**	68[d]
10	 **1a**	^{i}Pr$_3$Si	**2k**	N.R.

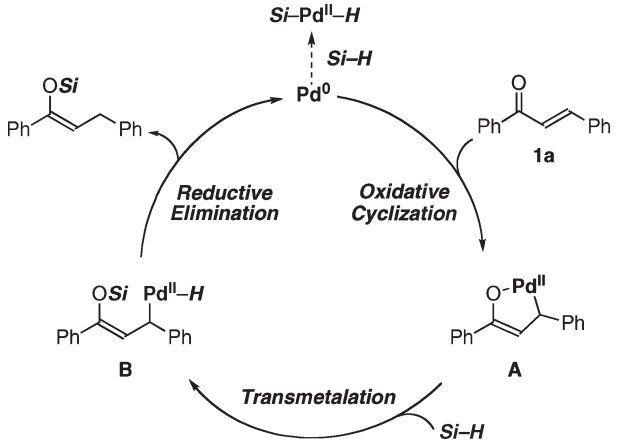
[a]Isolated yields. [b]Z/E = 96:4. [c]Z/E = 94:6. [d]Z/E = 99:1.

The implication of the formation of the oxapalladacycle intermediate led us to investigate the reaction of cyclopropyl ketones as well. Very recently, we reported a nickel-catalyzed borylative ring-opening reaction of aryl cyclopropyl ketones with bis(pinacolato)diboron yielding synthetically useful 4-oxoalkylboronates (Scheme 4, eq 1).[8] This reaction includes the formation of an oxanickelacycle as a key intermediate by oxidative cyclization of cyclopropyl ketone with nickel.[9] In the course of this study, we found that palladium was also effective for the oxidative cyclization of cyclopropyl ketones, and we decided to investigate a

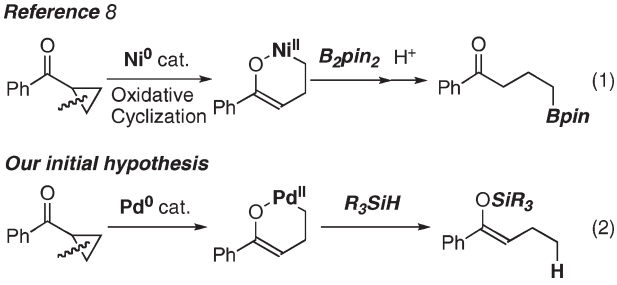
SCHEME 2. Reaction of Cyclic α,β-Unsaturated Ketones



SCHEME 3. Plausible Mechanism for Acyclic α,β-Unsaturated Ketones



SCHEME 4. Ring-Opening Reaction of Cyclopropyl Ketones



palladium-catalyzed hydrosilylative ring-opening reaction (Scheme 4, eq 2).

Indeed, treatment of cyclopropyl phenyl ketone (**3a**) with ^{t}BuMe$_2$SiH in the presence of palladium/tricyclohexylphosphine and a small amount of MeOH as an additive in toluene at 60 °C afforded the corresponding silyl enolate **2d** in 93% yield with high *Z* selectivity (Table 2, entry 1). This result encouraged us to examine the scope of various cyclopropyl ketones in the reaction, which is summarized in Table 2.

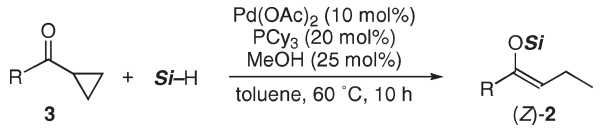
The reactions of **3b** and **3c** with Et$_3$SiH gave **2m** and **2n** in 81% and 72% yields, respectively (Table 2, entries 2 and 3). The use of **3d** having an ester group afforded silyl enolate **2o** in 87% yield (entry 4). Treatment of **3a** with Et$_3$SiH instead of ^{t}BuMe$_2$SiH yielded **2p**[2a,e] with a slightly inferior result (entry 5). To our delight, alkyl cyclopropyl ketones participated in the hydrosilylation, even though they were unreactive in the nickel-catalyzed borylation (entries 6−9).[8] In the

(8) Sumida, Y.; Yorimitsu, H.; Oshima, K. *J. Org. Chem.* **2009**, *74*, 3196–3198.

(9) Oxidative cyclization of cyclopropyl ketones with nickel complex: (a) Ogoshi, S.; Nagata, M.; Kurosawa, H. *J. Am. Chem. Soc.* **2006**, *128*, 5350–5351. (b) Liu, L.; Montgomery, J. *J. Am. Chem. Soc.* **2006**, *128*, 5348–5349.

(10) (a) Stork, G.; Hudrlik, P. F. *J. Am. Chem. Soc.* **1968**, *90*, 4462–4464. (b) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324–2336. For kinetic control, see: Henderson, K. W.; Kerr, W. J.; Moir, J. H. *Tetrahedron* **2002**, *58*, 4573–4587. For thermodynamic control, see: Yamamoto, Y.; Matui, C. *Organometallics* **1997**, *16*, 2204–2206.

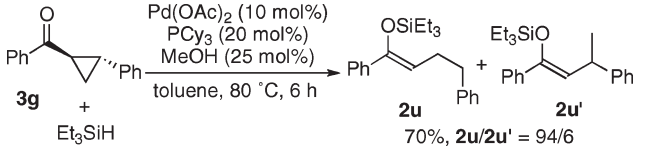
TABLE 2. Scope of Cyclopropyl Ketones



entry	R	*Si*	2	yield (%)[a]
1	Ph (**3a**)	^{t}BuMe$_2$Si	**2d**	93[b]
2	4-MeC$_6$H$_4$ (**3b**)	Et$_3$Si	**2m**	81[b]
3	4-MeOC$_6$H$_4$ (**3c**)	Et$_3$Si	**2n**	72[b]
4	4-EtOC(O)C$_6$H$_4$ (**3d**)	Et$_3$Si	**2o**	87
5	Ph (**3a**)	Et$_3$Si	**2p**	81[b]
6	Me (**3e**)	Et$_3$Si	**2q**	(45)[c,d]
7	Me (**3e**)	^{t}BuMe$_2$Si	**2r**	79[d]
8	PhCH$_2$ (**3f**)	Et$_3$Si	**2s**	(52)[c,d]
9	PhCH$_2$ (**3f**)	^{t}BuMe$_2$Si	**2t**	85[d]

[a]Isolated yields. [b]Z/E = 99:1. [c]NMR yields. [d]At 80 °C.

SCHEME 5. Reaction of Disubstituted Cyclopropane



reactions of alkyl cyclopropyl ketones **3e** and **3f**, ^{t}BuMe$_2$SiH was more reactive than Et$_3$SiH. Benzyl cyclopropyl ketone (**3f**) was transformed to the corresponding enolate **2t**, which is difficult to synthesize by using known methods.[10] In all cases, we could prepare silyl enolates with high Z selectivity.

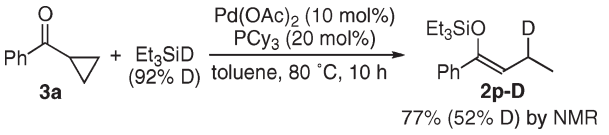
When cyclopropyl ketone **3g** having an additional substituent on the cyclopropane ring was used, the hydrosilylative ring-opening reaction of **3g** predominantly gave **2u** through selective cleavage of the most substituted C−C bond (Scheme 5).

To study the reaction mechanism in detail, the reaction of cyclopropyl phenyl ketone with deuterated silane, Et$_3$SiD,[11] was examined. Contrary to our expectations (Scheme 4, eq 2), deuterium was introduced into the β-position (Scheme 6).

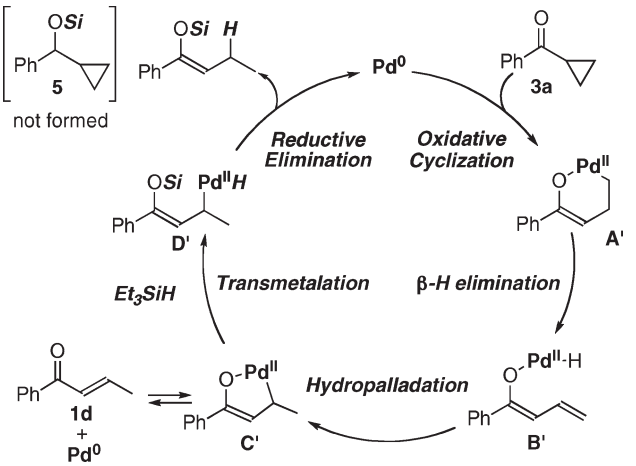
Accordingly, we propose the reaction mechanism as follows (Scheme 7). Oxidative cyclization of the cyclopropyl ketone to palladium(0) gives six-membered oxapalladacycle intermediate **A′**. The subsequent β-hydride elimination generates palladium hydride species **B′**. Intramolecular hydropalladation would occur rapidly to afford five-membered oxapalladacycle intermediate **C′** analogous in the case of α,β-unsaturated ketones. Although the release of **1d** and palladium(0) might be possible, they could be converted smoothly to the five-membered oxapalladacycle intermediate **C′** reversibly.[12] The remaining steps are similar to those of the proposed mechanism outlined in Scheme 3.

Although the role of MeOH is not clear at this stage, the reaction required MeOH to achieve a high yield. We suspect

SCHEME 6. Reaction of Cyclopropyl Ketone with Et$_3$SiD



SCHEME 7. Plausible Mechanism for Cyclopropyl Ketones



it may activate hydrosilane species as a Lewis base and promote transmetalation.[13]

In 1999, Slough et al. reported a rhodium-catalyzed hydrosilylation of cyclopropyl phenyl ketones with Et$_3$SiH.[14] Since they observed silyl ether **5** (Scheme 7), in addition to E/Z mixtures of silyl enolates, they proposed a different mechanism in which occurred oxidative addition of Et$_3$SiH to rhodium complex followed by 1,2-hydrosilylation of a cyclopropyl ketone. Although no generation of silyl ether **5** was observed in our case, the mechanism they proposed could not be excluded as a possibility.

In summary, we have developed a new hydrosilylation reaction under palladium catalysis by using α,β-unsaturated ketones or cyclopropyl ketones as substrates, which allows the highly Z selective synthesis of silyl enolates.

Experimental Section

Typical Procedure for Synthesis of Silyl Enolate. Pd(OAc)$_2$ (5.6 mg, 0.025 mmol) and PCy$_3$ (14 mg, 0.05 mmol) were placed in a 20-mL reaction flask under argon. After toluene (1.5 mL) was added at 0 °C, the resulting solution was stirred for 10 min. Chalcone (**1a**) (104 mg, 0.50 mmol) and ^{t}BuMe$_2$SiH (0.16 mL, 1.0 mmol) were then added. The mixture was allowed to warm to 60 °C and stirred for 10 h. The reaction mixture was filtered by alumina (Wako, activated), and the filtrate was concentrated in vacuo to afford an oil. The crude oil was purified on silica gel (Kanto Chemical, silica gel 60N, hexane) by using a dry ice/acetone-jacketed chromatographic column to yield **2a** (152 mg, 0.47 mmol) in 94% yield. (***Z*)-1-*tert*-Butyldimethylsiloxy-1,3-diphenyl-1-propene (2a)**: IR (neat) 2930, 2857, 1647, 1493, 1390, 1254, 1006, 939, 668 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 0.01 (s, 6H), 1.03 (s, 9H), 3.60 (d, J = 7.5 Hz, 2H), 5.32 (t, J = 7.5 Hz 1H), 7.20 (t, J = 6.5 Hz, 1H), 7.24−7.32 (m, 7H), 7.49 (d, J = 7.5 Hz, 2H);

(11) Et$_3$SiD were obtained according to the literature procedure: Caseri, W.; Pregosin, P. S. *J. Organomet. Chem.* **1988**, *356*, 259–269.

(12) In the absence of triethylsilane, Pd-catalyzed isomerization of cyclopropyl ketone to α,β-unsaturated ketone indeed took place although the resulting α,β-unsaturated ketone immediately underwent dimerization in situ as reported previously (ref 9).

(13) (a) Corriu, R. J. P.; Perz, R.; Reye, C. *Tetrahedron* **1983**, *39*, 999–1009. (b) Sakada, H.; Watanabe, S.; Kabuto, C.; Kabuto, K. *J. Am. Chem. Soc.* **2003**, *125*, 2842–2843. (c) Leigh, W. J.; Owens, T. R.; Bendikov, M.; Zade, S. S.; Apeloig, Y. *J. Am. Chem. Soc.* **2006**, *128*, 10772–10783.

(14) Sun, C.; Tu, A.; Slough, G. A. *J. Organomet. Chem.* **1999**, *582*, 235–245.

^{13}C NMR ($CDCl_3$) δ −3.9, 18.3, 25.9, 32.3, 110.3, 125.8, 126.0, 127.6, 127.9, 128.3, 128.4, 139.5, 141.6, 150.0; HRMS (EI) found 324.1911 [M^+], calcd for $C_{21}H_{28}OSi$ 324.1909

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Supporting Information Available: Characterization data for products. This material is available free of charge via the Internet at http://pubs.acs.org.