ORGANIC
LETTERS

2008
Vol. 10, No. 11
2199−2201

Palladium-Catalyzed Formal Cycloaddition of Silacyclobutanes with Enones: Synthesis of Eight-Membered Cyclic Silyl Enolates

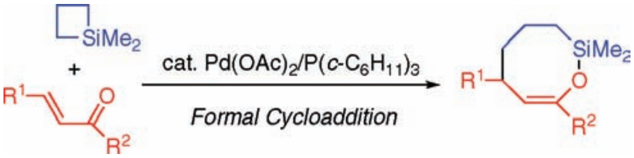
Koji Hirano, Hideki Yorimitsu,* and Koichiro Oshima*

Department of Material Chemistry, Graduate School of Engineering, Kyoto University, Kyoto-daigaku Katsura, Nishikyo-ku, Kyoto 615-8510, Japan

oshima@orgrxn.mbox.media.kyoto-u.ac.jp; yori@orgrxn.mbox.media.kyoto-u.ac.jp

Received March 15, 2008

ABSTRACT



Treatment of silacyclobutanes with enones under palladium catalysis resulted in formal cycloaddition to yield the corresponding eight-membered ring. The reaction provides a facile and convergent access to synthetically useful eight-membered cyclic silyl enolates.

Metal-mediated cycloaddition reactions provide powerful and convergent approaches to cyclic skeletons from relatively simple organic molecules.[1] Among them, the cycloaddition of two four-atom fragments ranks as the most attractive route to eight-membered ring systems.[2] Wender has developed nickel-catalyzed intramolecular cycloaddition of bis(1,3-diene)s and realized efficient construction of eight-membered carbocycles.[3] On the other hand, the intermolecular variants have still been challenging. Although highly selective dimerization reactions of 1,3-dienes have been well established,[4] only a few examples of intermolecular cross cycloaddition of two different four-atom components have been reported to date[5] except for the photochemical processes.[2] During our studies on metal-catalyzed reactions of silacyclobutanes, we have found palladium- and nickel-catalyzed formal intermolecular cycloaddition of silacyclobutanes with alkynes and aldehydes providing the corresponding six-membered rings.[6,7] In this communication, we report fully intermolecular palladium-catalyzed formal cycloaddition of silacyclobutanes with enones leading to eight-membered rings,[8] synthetically useful silyl enolates.[9]

Treatment of 1,1-dimethylsilacyclobutane (**1a**) with 1-phenyl-2-hexen-1-one (**2a**) in the presence of 7.5 mol % of Pd(OAc)$_2$ and 15 mol % of P(c-C$_6$H$_{11}$)$_3$ in refluxing THF

---

(1) (a) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49–92. (b) Frühauf, H.-W. *Chem. Rev.* **1997**, *97*, 523–596. (c) Kotha, S.; Brahmachary, E.; Lahiri, K. *Eur. J. Org. Chem.* **2005**, 4741−4767.

(2) Sieburth, S. M.; Cunard, N. T. *Tetrahedron* **1996**, *52*, 6251–6282.

(3) (a) Wender, P. A.; Ihle, N. C. *J. Am. Chem. Soc.* **1986**, *108*, 4678–4679. (b) Wender, P. A.; Ihle, N. C.; Correia, C. R. D. *J. Am. Chem. Soc.* **1988**, *110*, 5904–5906. (c) Wender, P. A.; Croatt, M. P.; Witulski, B. *Tetrahedron* **2006**, *62*, 7505–7511.

(4) (a) Keim, W.; Behr, A.; Röper, M. *In Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Ed.; Pergamon: New York, 1982; Vol. 8; pp 371−462. (b) Tenaglia, A.; Brum, P.; Waegell, B. *J. Organomet. Chem.* **1985**, *285*, 343–357. (c) Murakami, M.; Itami, K.; Ito, Y. *Synlett* **1999**, 951−953.

(5) (a) Carbonaro, A.; Cambisi, F.; Dall'Asta, G. *J. Org. Chem.* **1971**, *36*, 1443–1445. (b) Baldenius, K.-U.; tom Dieck, H.; König, W. A.; Icheln, D.; Runge, T. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 305–307. (c) Lautens, M.; Tam, W.; Lautens, J. C.; Edwards, L. G.; Crudden, C. M.; Smith, A. C. *J. Am. Chem. Soc.* **1995**, *117*, 6863–6879.

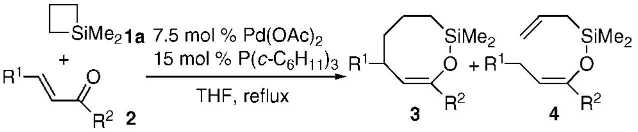
(6) (a) Takeyama, Y.; Nozaki, K.; Matsumoto, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1461–1466. (b) Hirano, K.; Yorimitsu, H.; Oshima, K *Org. Lett.* **2006**, *8*, 483–485. Also see: (c) Hirano, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2007**, *129*, 6094–6095.

(7) Other groups have also focused on the synthesis of six-membered rings through metal-mediated formal cycloaddition of silacyclobutanes. (a) Sakurai, H.; Imai, T. *Chem. Lett.* **1975**, 891−894. (b) Agenet, N.; Mirebeau, J.-H.; Petit, M.; Thouvenot, R.; Gandon, V.; Malacria, M.; Aubert, C. *Organometallics* **2007**, *26*, 819–830.

10.1021/ol800603z CCC: $40.75

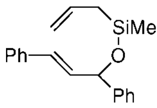
afforded cycloadduct **3a** in 80% yield with a trace amount (less than 3%) of the ring opening product **4a** (Table 1, entry 1).[10] The reaction is a straightforward way to synthesize eight-membered cyclic silyl enolates. Electron-neutral and electron-withdrawing groups on the benzene ring were tolerant toward the reaction (entries 2, 3, 5, and 6) while electron-donating group suppressed the formation of the desired product (entry 4). The reaction with **2g** also provided the cycloadduct **3g**, leaving the ester functionality untouched, although the yield was moderate due to the formation of the ring-opening product **4g** (entry 7). Naphthyl-, furyl-, thienyl-, and pyridyl-substituted enones also participated in the reaction to give the corresponding cyclic silyl enolates in moderate to good yields (entries 8−11). The cycloaddition with enones bearing substituents other than the *n*-propyl group at the *β*-position was also conducted. Enones having a smaller methyl and larger phenylethyl group **2l** and **2m** smoothly reacted with **1a** to furnish the eight-membered rings **3l** and **3m** in 75% and 79% yields, respectively (entries 12 and 13). Unfortunately, much more sterically demanding **2n** was converted to **3n** in low yield (entry 14). It is noteworthy that the benzyl ether and terminal olefin moieties were compatible under the reaction conditions (entries 15 and 16). However, the reaction with chalcone (**2q**) resulted in no formation of the cycloadduct **3q**, and two different kinds of the ring-opening products **4q** and **4q′** were obtained (entry 17).

Table 1. Formal Cycloaddition of Silacyclobutane **1a** with Enones[a]



entry	**2**	**3**, yield (%)[b]
1	**2a** ($R^1 = n$-Pr, R^2 = Ph)	**3a**, 80
2^c	**2b** ($R^1 = n$-Pr, R^2 = 4-MeC_6H_4)	**3b**, 67
3^c	**2c** ($R^1 = n$-Pr, R^2 = 4-PhC_6H_4)	**3c**, 89
4	**2d** ($R^1 = n$-Pr, R^2 = 4-$MeOC_6H_4$)	**3d**, trace
5	**2e** ($R^1 = n$-Pr, R^2 = 4-FC_6H_4)	**3e**, 82
6^d	**2f** ($R^1 = n$-Pr, R^2 = 4-$CF_3C_6H_4$)	**3f**, 90
7	**2g** ($R^1 = n$-Pr, R^2 = 4-$MeOCOC_6H_4$)	**3g**, 53 $(68)^e$
8	**2h** ($R^1 = n$-Pr, R^2 = 2-Naphthyl)	**3h**, 78
9	**2i** ($R^1 = n$-Pr, R^2 = 2-Furyl)	**3i**, 76
10	**2j** ($R^1 = n$-Pr, R^2 = 2-Thienyl)	**3j**, 62
11	**2k** ($R^1 = n$-Pr, R^2 = 3-Pyridyl)	**3k**, 44^f
12^d	**2l** (R^1 = Me, R^2 = Ph)	**3l**, 75
13	**2m** ($R^1 = Ph(CH_2)_2$, R^2 = Ph)	**3m**, $(79)^g$
14	**2n** ($R^1 = i$-Pr, R^2 = Ph)	**3n**, (32)
15	**2o** ($R^1 = CH_2{=}CH(CH_2)_8$, R^2 = Ph)	**3o**, 64
16	**2p** ($R^1 = PhCH_2O(CH_2)_9$, R^2 = Ph)	**3p**, 76
17	**2q** (R^1 = Ph, R^2 = Ph)	**3q**, 0^h

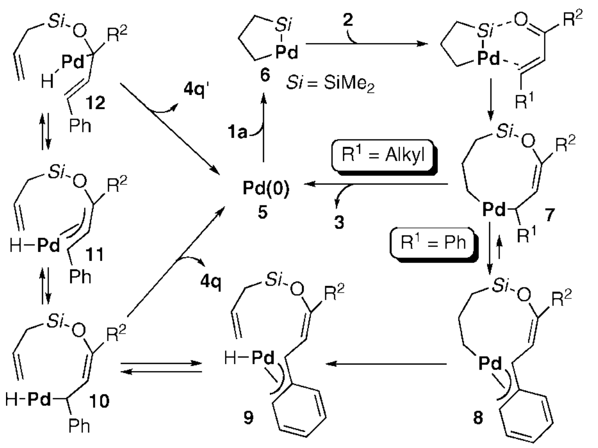
[a] A mixture of $Pd(OAc)_2$ (0.038 mmol), $P(c\text{-}C_6H_{11})_3$ (0.075 mmol), **1a** (1.5 mmol), and **2** (0.50 mmol) was boiled in THF (5.0 mL) for 20−24 h. [b] Isolated yields. ^1H NMR yields are in parentheses. Unless otherwise noted, **4** was detected in <3% yield in the crude mixture. [c] Reaction time was 40 h. [d] In the presence of 5 mol % of $Pd(OAc)_2$ and 10 mol % of $P(c\text{-}C_6H_{11})_3$. [e] Ring-opening product **4g** was detected in 26% yield. [f] Ring-opening product **4k** was detected in 15% yield. [g] Contaminated with 7% of **4m**. [h] Two ring-opening products **4q** and **4q′** were detected in 60% and 13% yields, respectively.



4q'

Based on the results of Table 1, we are tempted to assume the reaction mechanism for the formal cycloaddition of the silacyclobutane **1a** with enones **2** as follows (Scheme 1).

Scheme 1



Initial oxidative addition of silacyclobutane **1a** to zerovalent palladium species **5** provides palladasilacyclopentane **6**.[11] Subsequent coordination of enones **2** to **6**, in which the olefin and carbonyl moieties of enones are coordinated to the palladium and silicon centers, respectively,[12] followed by insertion to the Si−Pd bond of **6** gives nine-membered palladacycle **7**. Strong *π* back-donation from the palladium center of **6** to the olefin moiety would increase the electron

---

(8) Transition-metal-catalyzed formal cycloaddition of 1,2-disilacyclobutenes with 1,3-dienes under thermal- or photochemical conditions was known to give 1,4-disila-2,6-cyclooctadienes. (a) Sakurai, H.; Kobayashi, T.; Nakadaira, Y. *J. Organomet. Chem.* **1978**, *162*, C43–C47. (b) Jzang, T. T.; Lee, C. Y.; Liu, C. S. *Organometallics* **1988**, *7*, 1265–1270. (c) Jzang, T. T.; Liu, C. S. *Organometallics* **1988**, *7*, 1271–1277. (d) Huang, C. Y.; Liu, C. S. *J. Organomet. Chem.* **1989**, *373*, 353–364. (e) Chiang, H.-J.; Liu, C. S. *J. Organomet. Chem.* **1992**, *438*, C9–C12.

(9) Synthesis of five-membered cyclic silyl enolates via silylene transfer from silacyclopropane and hydrodisilane to enones was reported. (a) Calad, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 2046−2047. (b) Okamoto, K.; Hayashi, T. *Chem. Lett.* **2008**, 108−109. Unexpected reactions of enones with the silylene source affording six-membered cyclic silyl enolates. (c) Okamoto, K.; Hayashi, T. *Org. Lett.* **2007**, *9*, 5067–5069. Tanaka reported palladium-catalyzed coupling reaction of silacyclobutanes with acid halides in the presence of a suitable base yielding six-membered cyclic silyl enolates. (d) Tanaka, Y.; Yamashita, H.; Tanaka, M. *Organometallics* **1996**, *15*, 1524–1526. (e) Chauhan, B. P. S.; Tanaka, Y.; Yamashita, H.; Tanaka, M. *Chem. Commun.* **1996**, 1207−1208. (f) Tanaka, Y.; Yamashita, M. *Appl. Organomet. Chem.* **2002**, *16*, 51–54.

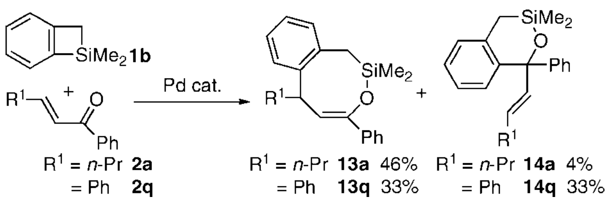
(10) Other ligands such as $P(t\text{-}Bu)_3$, $P(n\text{-}Bu)_3$, and PPh_3 were ineffective. A $Ni(cod)_2/2P(c\text{-}C_6H_{11})_3$ catalyst system did not catalyze the reaction.

(11) Silacyclobutanes were found to undergo oxidative addition to platinum, palladium, and cobalt complexes. (a) Yamashita, H.; Tanaka, M.; Honda, K. *J. Am. Chem. Soc.* **1995**, *117*, 8873–8874. (b) Tanaka, Y.; Yamashita, H.; Shimada, S.; Tanaka, M. *Organometallics* **1997**, *16*, 3246–3248, and ref 7b.

density of the carbonyl oxygen because a supported ligand is strongly σ-donating $P(c\text{-}C_6H_{11})_3$ and enables the type of complexation despite that the Lewis acidity of the silicon of **6** would not appear to be very high. In the case of the β-alkyl-substituted enones, rapid reductive elimination generally takes place to afford the cycloadduct **3** along with the starting zerovalent palladium complex to complete the catalytic cycle. However, in the reaction with **2q** (R^1 = Ph), palladacycle intermediate **7** is a σ-benzylpalladium so that the isomerization to the more stable π-benzylpalladium **8** preferably occurs to delay the reductive elimination. Consequently, β-hydride elimination proceeds to give palladium hydride **9** and its isomers **10** and **12**, which are in equilibrium through π-allylpalladium intermediate **11**, en route to **4q** and **4q′**.[13]

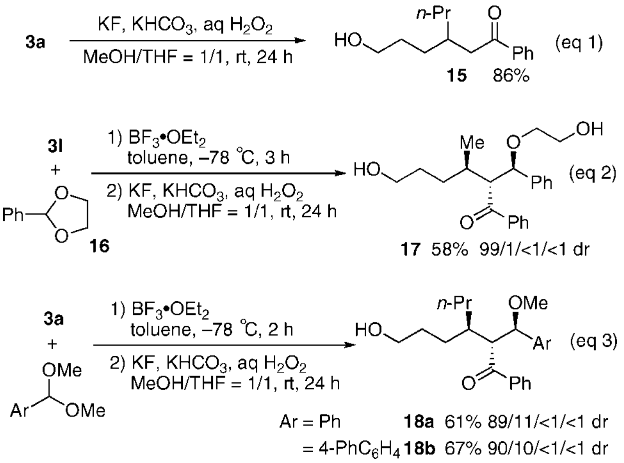
With the reaction conditions described above, formal cycloaddition of benzene-fused silacyclobutane **1b** was also carried out (Scheme 2). The reaction with **2a** led to expected benzene-fused eight-membered cyclic product **13a** in 46% yield with contamination by 4% of six-membered cyclic silyl ether **14a**. Interestingly, chalcone (**2q**), the reaction of which with 1,1-dimethylsilacyclobutane (**1a**) did not provide the cyclic product (Table 1, entry 17), also underwent the formal cycloaddition, although the product comprised a 1:1 mixture of the silyl enolate **13q** and the silyl ether **14q** (see Supporting Information for the detailed reaction mechanism).

Scheme 2



Finally, to establish the synthetic utility of the catalytic reaction, we attempted to explore the transformation of the cycloadducts (Scheme 3). Tamao-Fleming oxidation of the product **3a** led to the corresponding alcohol **15** in 86% yield (eq 1). The overall transformation is regarded as a conjugate addition of the hydroxypropyl group to enones. Moreover, the products were silyl enolates so that they took part in Mukaiyama aldol-type reaction (eqs 2 and 3). The reaction of **3l** with cyclic acetal **16** in the presence of $BF_3{\cdot}OEt_2$ followed by oxidation afforded **17** with excellent diastereoselectivity. Aldol reactions of **3a** with dimethylacetals also provided the corresponding highly functionalized ketones **18** stereoselectively (see Supporting Information for the stereochemical assignment).

Scheme 3



In conclusion, we have found palladium-catalyzed formal cycloaddition of silacyclobutanes with enones that efficiently provides eight-membered cyclic silyl enolates of synthetic value.

Acknowledgment. This work was supported by Grants-in-Aid for Scientific Research and Global COE Research from MEXT, Japan. K.H. acknowledges JSPS for financial support.

Supporting Information Available: Detailed experimental procedures and characterization data of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL800603Z

---

(12) The reaction of 1,1-diphenylsilacyclobutane resulted in the recovery of the starting materials. The fact suggests that the coordination of the carbonyl moiety of enones to the silicon atom of the palladasilacyclopentane would be crucial for the reaction. The bulky substituents on the silicon atom would block out the coordination.

(13) The ring-opening byproducts resulting from the reactions with alkyl-substituted enones would be formed through a similar reaction pathway.