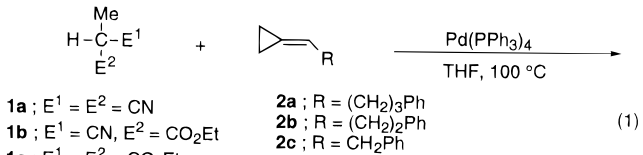
Ring Opening in the Palladium-Catalyzed Hydrocarbonation of Methylenecyclopropanes with Pronucleophiles

Naofumi Tsukada, Akinori Shibuya, Itaru Nakamura, and Yoshinori Yamamoto*

Department of Chemistry, Graduate School of Science Tohoku University, Sendai 980-77, Japan

Received January 24, 1997

The addition of a carbon nucleophile to an olefinic double bond is one of the most important methods for C−C bond formation. The Michael addition is a classical and well-known reaction among these methods, wherein anionic organometallics react with an activated alkene bearing an electron-withdrawing group.[1] Transition metal catalysts have opened the door to a new field, enabling the addition of organometallics to an unactivated alkene[2] and the addition of an active methyne and methylene to an activated alkene (Michael acceptor) under neutral conditions.[3] More recently, "hydrocarbonation" of an unactivated C═C double bond with certain pronucleophiles has been reported,[4−9] which presumably proceeds through the transition-metal-catalyzed activation of a C−H bond of pronucleophiles such as an active methyne and methylene,[4−6] a terminal alkyne,[7] an aldehyde,[8] and an aromatic ring.[9] 1,3-Dienes,[4] 1,3-enynes,[5] and allenes[6] can be used as the unactivated alkene for the addition of an active methyne and methylene. However, the addition of an active methyne and methylene to nonconjugated alkenes has not been known until now. We report that the palladium-catalyzed reaction of certain pronucleophiles (**1**) with methylenecyclopropanes (**2**) affords hydrocarbonation products (**3**) in good to high yields and gives **4** in certain cases either exclusively or as byproducts in a mixture with **3** (eq 1).



1a ; $E^1 = E^2 = CN$
1b ; $E^1 = CN$, $E^2 = CO_2Et$
1c ; $E^1 = E^2 = CO_2Et$

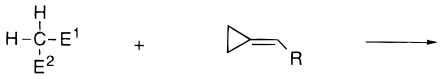
2a ; $R = (CH_2)_3Ph$
2b ; $R = (CH_2)_2Ph$
2c ; $R = CH_2Ph$
2d ; $R = Ph$ (1)

3a ; $E^1 = E^2 = CN$, $R = (CH_2)_3Ph$
3b ; $E^1 = CN$, $E^2 = CO_2Et$, $R = (CH_2)_3Ph$
3c ; $E^1 = CN$, $E^2 = CO_2Et$, $R = (CH_2)_2Ph$
3d ; $E^1 = E^2 = CO_2Et$, $R = (CH_2)_2Ph$
3e ; $E^1 = E^2 = CN$, $R = (CH_2)_2Ph$
3f ; $E^1 = E^2 = CN$, $R = CH_2Ph$
3g; $E^1 = E^2 = CO_2Et$, $R = Ph$

4a ; $E^1 = E^2 = CN$, $R = (CH_2)_2Ph$
4b ; $E^1 = E^2 = CN$, $R = CH_2Ph$
4c ; $E^1 = E^2 = CN$, $R = Ph$
4d; $E^1 = CN$, $E^2 = CO_2Et$, $R = Ph$

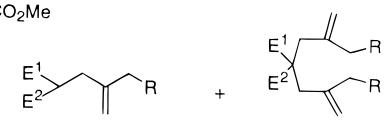
The results are summarized in Table 1. The addition of methylmalononitrile (**1a**) to 4-phenyl-1-butenylidenecyclopropane (**2a**) proceeded smoothly in the presence of catalytic amounts of $Pd(PPh_3)_4$ in THF at 100 °C to give **3a** in 82% yield (entry 1). Other palladium catalysts, such as $PdCl_2(PPh_3)_2$ and $Pd_2(dba)_3{\cdot}CHCl_3{\cdot}PPh_3$ (dba = dibenzylideneacetone), gave the addition product in lower yields. The reaction of ethyl 2-cyanopropionate (**1b**) with **2a** gave **3b** in 95% yield (entry 2). Similarly, the ring opening of 3-phenyl-1-propylidenecyclopropane (**2b**) with **1b** or **1c** afforded **3c** or **3d**, respectively, in good yields (entries 3 and 4). The reaction of **1a** with **2b** gave **3e** in 75% yield along with small amounts (10%) of **4a** (entry 5). With 2-phenylethylidenecyclopropane (**2c**), the reaction of **1a** afforded **3f** in 57% yield together with 31% yield of **4b** (entry 6). The reaction of benzylidenecyclopropane (**2d**) with **1a** or **1b** produced only **4c** or **4d** in 88 or 83% yield, respectively (entries 7 and 8). On the other hand, the reaction of **2d** with ethyl methylmalonate (**1c**) gave **3g** in 55% yield (entry 9). Accordingly, the mode of ring opening of methylenecyclopropanes depends upon both the structure of the pronucleophile and the substituent at the exomethylene carbon.

In the reaction of active methylenes, both monoalkylation and dialkylation products were obtained (eq 2). The addition of malononitrile (**1d**) to **2a** gave ca. 1:1 mixture of the monoalkylation **3h** (42%) and the dialkylation product **5a** (46%), while the ketoester **1e** gave the corresponding monoalkylation product **3i** predominantly.



2a ; $R = (CH_2)_3Ph$

1d ; $E^1 = E^2 = CN$
1e ; $E^1 = COMe$, $E^2 = CO_2Me$ (2)



3h ; $E^1 = E^2 = CN$ 42%
3i ; $E^1 = COMe$, $E^2 = CO_2Me$ 61%

5a 46%
5b 14%

Our interest was then directed to the ring opening of methylenecyclopropanes **2e**−**g** which are monosubstituted at the cyclopropane ring or gem-disubstituted at both the exocyclic vinylic carbon and the cyclopropane ring. The cyclopropane ring of **2e** opened at the distal position in the reaction with **1a** to yield **3j**[10] in 71% yield along with small amounts of other

(1) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1992. Jung, M. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, Chapter 1.1, pp 1−67.

(2) (a) Hegedus, L. S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, U.K., 1990; Vol. 4, p 571. (b) For carbometallation, see: Knochel, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, U.K., 1990; Vol. 4, p 865.

(3) (a) Murahashi, S.-I.; Naota, T.; Taki, H.; Mizuno, M.; Takaya, H.; Komiya, S.; Mizuho, Y.; Oyasato, N.; Hiraoka, M.; Hirano, M.; Fukuoka, A. *J. Am. Chem. Soc.* **1995**, *117*, 12436 and references cited therein. (b) Gómez-Bengoa, E.; Cuerva, J. M.; Mateo, C.; Echavarren, A. M. *J. Am. Chem. Soc.* **1996**, *118*, 8553.

(4) For 1,3-dienes, see: (a) Takahashi, K.; Miyake, A.; Hata, G. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 1183. (b) Andell, O. S.; Bäckvall, J.-E.; Moberg, C. *Acta. Chem. Scand. Ser. B* **1986**, *40*, 184. (c) Baker, R.; Popplestone, R. J. *Tetrahedron Lett.* **1978**, *38*, 3575. (d) Jolly, P. W.; Kokel, N. *Synthesis* **1990**, 771. (e) Trost, B. M.; Zhi, L. *Tetrahedron Lett.* **1992**, *33*, 1831.

(5) For 1,3-enynes, see: Salter, M. M.; Gevorgen, V.; Saito, S.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1996**, 17.

(6) For allenes, see: (a) Yamamoto, Y.; Al-Masum, M.; Asao, N. *J. Am. Chem. Soc.* **1994**, *116*, 6019. (b) Besson, L.; Goré, J.; Cazes, B. *Tetrahedron Lett.* **1995**, *36*, 3853. (c) Trost, B. M.; Gerusz, V. J. *J. Am. Chem. Soc.* **1995**, *117*, 5156. (d) Yamamoto, Y.; Al-Masum, M.; Fujiwara, N.; Asao, N. *Tetrahedron Lett.* **1995**, *36*, 2811. (e) Yamamoto, Y.; Al-Masum, M. *Synlett* **1995**, 969. (f) Yamamoto, Y.; Al-Masum, M.; Fujiwara, N. *J. Chem. Soc., Chem. Commun.* **1996**, 381. (g) Yamamoto, Y.; Al-Masum, M.; Takeda, A. *J. Chem. Soc., Chem. Commun.* **1996**, 831.

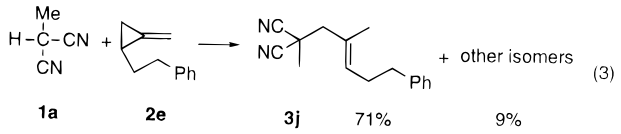
(7) For alkynes, see: (a) Trost, B. M.; Chan, C.; Rühter, G. *J. Am. Chem. Soc.* **1987**, *109*, 3486. (b) Trost, B. M.; Matsubara, S.; Caringi, J. J. *J. Am. Chem. Soc.* **1989**, *111*, 8745. For allenes, see: (c) Trost, B. M.; Kottirsch, G. *J. Am. Chem. Soc.* **1990**, *112*, 2816. (d) Yamaguchi, M.; Omata, K.; Hirama, M. *Tetrahedron Lett.* **1994**, *35*, 5689. (e) Yamaguchi, M.; Kido, Y.; Omata, K.; Hirama, M. *Synlett* **1995**, 1181.

(8) For intramolecular reactions, see: (a) Larock, R. C.; Oertle, K.; Potter, G. F. *J. Am. Chem. Soc.* **1980**, *102*, 190. (b) Campbell, R. E.; Lochow, C. F.; Vora, K. P.; Miller, R. G. *J. Am. Chem. Soc.* **1980**, *102*, 5824. (c) Gable, K. P.; Benz, G. A. *Tetrahedron Lett.* **1991**, *32*, 3473. For intermolecular reactions, see: (d) Kondo, T.; Akazome, M.; Tsuji, Y.; Watanabe, Y. *J. Org. Chem.* **1990**, *55*, 1286. (e) Tsuda, T.; Kiyoi, T.; Saegusa, T. *J. Org. Chem.* **1990**, *55*, 2554. For asymmetric additions, see: (f) Wu, X. M.; Funakoshi, K.; Sakai, K. *Tetrahedron Lett.* **1993**, *34*, 5927. (g) Barnhart, R. W.; Wang, X.; Noheda, P.; Bergens, S. H.; Whelen, J.; Bosnich, B. *Tetrahedron* **1994**, *50*, 4335.

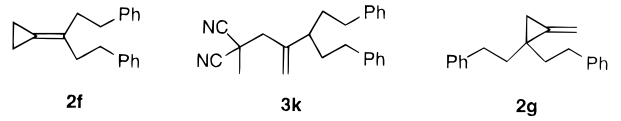
(9) Murai, S.; Kakiuchi, S.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature (London)* **1993**, *366*, 529.

S0002-7863(97)00261-8 CCC: $14.00

isomers (eq 3). In this reaction, **3e** was not obtained at all,

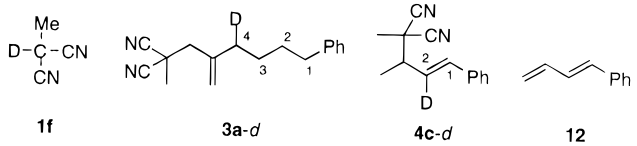


while it was produced in the reaction of **2b** having a 2-phenylethyl substituent at the exomethylene carbon. The reaction of **1a** with **2f** gave **3k** in 85% yield, but the reaction with **2g** did not give the desired hydrocarbonation product at all.



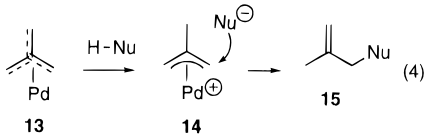
A plausible mechanism for the ring opening of **2** with pronucleophiles **1** is shown in Scheme 1. Oxidative addition of Pd(0) into the C−H bond of pronucleophiles **1** would generate the palladium hydride complex **6**. The hydropalladation of methylenecyclopropanes **2** with **6** would afford the alkylpalladium complexes **7** and/or **8**. The complex **7** would undergo rearrangement to the π-allylpalladium **9** (route **A**). The reductive elimination of Pd(0) from **9** would produce **3**. The palladium complex **8** would isomerize to the π-allylpalladium complex **11** *via* **10** (route **B**). The reductive elimination would give **4** and Pd(0). Presumably, the reaction of **2d** with **1a** took route **B**, whereas the reaction of **2a** with **1a** proceeded through route **A**.[11]

The reaction with deuterated methylmalononitrile (**1f**) substantiated the hydrocarbonation mechanism. The reaction of **1f** with **2a** under the same conditions as above gave **3a**-*d* in 82% yield in which the deuterium content at the C-4 position was 85%. On the other hand, the reaction of **1f** with **2d** afforded



4c-*d* in 86% yield in which the deuterium content at the C-2 position was 27% and the other protons were not deuterated at all. The former observation is in good agreement with the proposed route **A**. The latter result supports the proposed route **B**, but the very low deuterium content at the C-2 position could not be accounted for. We monitored the reaction of **2d** by using ^{1}H NMR and found that 1-phenyl-1,3-butadiene (**12**) was produced as an intermediate; its production reached a maximum after 25 h and decreased along with the reaction progress. No 1,3-butadiene formation was observed in the reaction of **2a**! The result clearly indicates that **12** is produced *via* the β-H−Pd elimination of **10** and the elimination−addition process occurs on the way from **10** to **11** in which loss of deuterium occurs.

Trost and Chan reported that the addition of pronucleophiles to the trimethylenemethane (TMM) palladium complex **13** derived from 2-(acetoxymethyl)-3-allyltrimethylsilane afforded the adduct **15** via **14** (eq 4).[12] On the other hand, it was



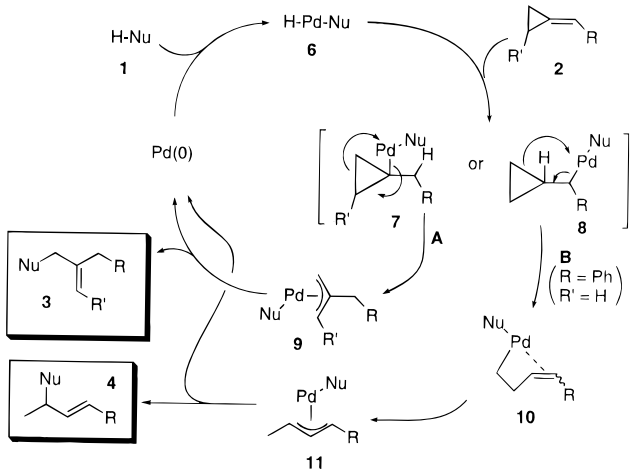
proposed that the TMM−palladium complex **13** would be involved as an intermediate in the palladium-catalyzed [3 + 2] cycloaddition of methylenecyclopropanes with olefins.[13] If the present hydrocarbonation reaction proceeds through a TMM−palladium complex (**16**), the same product (or product ratio)

Table 1. Palladium Catalyzed Addition of **1** to **2**[a]

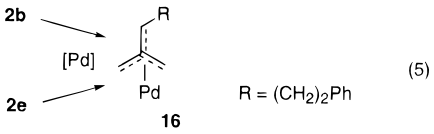
entry	1	2	yield of **3** (%)	yield of **4** (%)
1	**1a**	**2a**	**3a** (82)	
2	**1b**	**2a**	**3b** (95)	
3	**1b**	**2b**	**3c** (67)	
4	**1c**	**2b**	**3d** (70)	
5	**1a**	**2b**	**3e** (75)	**4a** (10)
6	**1a**	**2c**	**3f** (57)	**4b** (31)
7	**1a**	**2d**		**4c** (88)
8	**1b**	**2d**		**4d** (83)
9	**1c**	**2d**	**3g** (55)	

[a] The reaction of **1** (0.5 mmol) and **2** (1.0 mmol) was carried out in the presence of $Pd(PPh_3)_4$ (10 mol %) in THF at 100 °C for 2−3 days. All yields are of pure product isolated by column chromatography. The configuration of the double bond of **4** was confirmed by the coupling constant of the olefin protons (15.2−15.8 Hz).

Scheme 1



should be obtained from **2b** and **2e** (eq 5). However, the actual



reactions afforded totally different results; only **3a** was obtained from the reaction of **2b**, whereas **3j** was produced predominantly from **2e**. Accordingly, it is not likely that the TMM−palladium complex **16** is an intermediate in the addition reactions of **1a** to **2b** and **2e**.

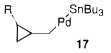
Ring opening mainly occurred at the distal position, which is different from the hydrostannation[11a] and the Heck reaction[11b,c] of methylenecyclopropanes, although in some cases the proximal bond of cyclopropanes was cleaved exclusively or as a side reaction.

Supporting Information Available: Experimental procedures and spectroscopic and analytical data for products **3** and **4** (3 pages). See any current masthead page for ordering and Internet access instructions.

JA970261H

(10) The configuration of the double bond of **3j** was confirmed by NOE experiments; see the Supporting Information.

(11) Palladium-catalyzed hydrostannation of methylenecyclopropanes proceeds through intermediate **17**: (a) Lautens, M.; Meyer, C.; Lorenz, A.



J. Am. Chem. Soc. **1996**, *118*, 10676. For the Heck reaction of ArX with methylenecyclopropane, see: (b) Fournet, G.; Balme, G.; Goré, J. *Tetrahedron* **1988**, *44*, 5809. See also: (c) Bräse, S.; de Meijere, A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2545.

(12) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1979**, *101*, 6432.

(13) For a review, see: (a) Binger, P.; Büch, H. M. *Top. Curr. Chem.* **1987**, *135*, 77. For an early report, see: (b) Noyori, R.; Odagi, T.; Takaya, H. *J. Am. Chem. Soc.* **1970**, *92*, 5780. See also: (c) Lautens, M.; Ren-Yi.; Delanghe, P. H. M. *J. Am. Chem. Soc.* **1994**, *116*, 8821. (d) Oishi, Y.; Sakamoto, E.; Fujimoto, H. *Inorg. Chem.* **1996**, *35*, 231.