

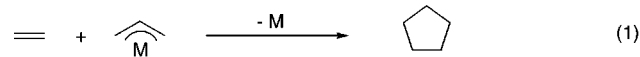
Novel Palladium Catalyzed Formal [3 + 2] Cycloaddition via Hydrocarboxation Reactions of Allenes

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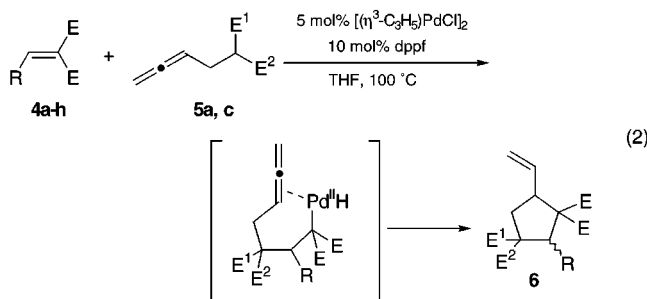
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Construction of cyclopentanoids, whose structures are frequently seen in various natural products, has been of keen interest in organic synthesis.¹ Among many useful methods, the transition metal catalyzed/mediated [3 + 2] cycloaddition reaction is one of the most powerful tools (eq 1).² Most approaches are based on the zwitterionic intermediates (Figure 1, type I), such as TMM complex 1,^{3,4} or the metallacycle intermediates **2** and **3** (type II).⁵



Herein we report an entirely new and efficient formal [3 + 2] cycloaddition based on hydrocarboxation reactions of allenenes (type III); the palladium-catalyzed reaction of activated olefins **4** with allenenes **5**, bearing an activated methine at the carbon chain terminus, gives cyclopentanes **6** with good to excellent yields (eq 2).



The reaction of the activated olefins **4** with 1.5 equiv of allene derivatives **5** was carried out in the presence of 5 mol % $[(\eta^3\text{-C}_3\text{H}_5)\text{PdCl}_2]$ and 10 mol % dppf (1,1'-bis(diphenylphosphino)ferrocene) in THF using Wheaton microreactors heated at 100 °C. The results are summarized in Table 1. The alkylidene malononitriles **4a** and **4b** reacted with allenyl malononitrile **5a** smoothly to give the corresponding vinylcyclopentanes **6a** and **6c**, respectively, in good to acceptable yields (entries 1 and 3). However, the reaction of **4a** with allenyl dimethylmalonate **5b** did not give the desired

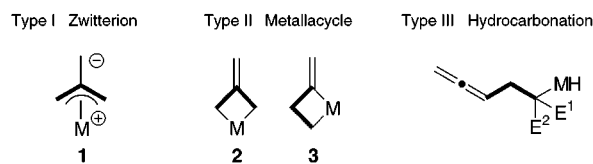


Figure 1. Three-carbon components (shown in boldface) for the transition metal catalyzed [3 + 2] cycloaddition.

Table 1. Palladium Catalyzed Formal [3 + 2] Cycloaddition^a

Entry	Activated olefin 4	Allene 5	Reaction time, h	Product	Yield, ^b %
1	4a R = Ph	5a (E ¹ = E ² = CN)	10	6a	71 (50 : 50) ^c
2	4a R = Ph	5b (E ¹ = E ² = CO ₂ Me)	24	6b	0 ^d
3	4b R = 2-furyl	5a	20	6c	48 (50 : 50) ^c
4	4c R = Ph	5a	10	6d	71 (87 : 13) ^c
5	4d R = <i>p</i> -MeOC ₆ H ₄	5a	10	6e	91 (92 : 8) ^c
6	4e R = <i>p</i> -Me ₂ NC ₆ H ₄	5a	12	6f	56 (91 : 9) ^c
7	4f R = <i>c</i> -Hex	5a	12	6g	41 (60 : 40) ^c
8	4g	5a	24	6h	65 (60 : 40) ^c
9	4h	5a	24	6i	73
10	4h	5c (E ¹ = CN, E ² = CO ₂ Me)	24	6j	70 (60 : 40) ^c

^a The reactions were carried out in THF in the presence of 5 mol % $[(\eta^3\text{-C}_3\text{H}_5)\text{PdCl}_2]$, 10 mol % dppf. ^b Isolated yield. ^c The diastereomeric ratios were determined by ¹H NMR analyses of the crude products. ^d Complete recovery of the starting materials.

product **6b** (entry 2). As observed previously in the hydrocarboxation of allenenes,⁶ it appears that pronucleophiles must have at least one CN group (vide infra). The reactions of other activated olefins **4c–f**, derived from Meldrum's acid, with **5a** gave the corresponding cycloadducts **6d–g** in acceptable to high yields (entries 4–7). In comparison with malononitrile derivative **4a** (entry 1), higher diastereoselectivities were observed in the reaction of derivatives **4c–e** (entries 4–6). The stereochemistries of the major products **6d–f** were assigned as *cis* using ¹H NMR NOE difference spectroscopy.⁷ As shown in entry 8, the activated olefin **4g** bearing CN and CO₂Me groups worked well to afford the cycloadduct **6h** in 65% yield. It should be noted that only two of the four possible stereoisomers were obtained in the reaction of benzylidene cyanoacetate **4g** with **5a**.⁸ Disulfone-

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(2) For reviews: (a) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49–92. (b) Chan, D. M. T. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, pp 271–314. (c) Binger, P.; Fox, D. In *Methods of Organic Chemistry (Houben-Weyl)*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Georg Thieme Verlag: Stuttgart, 1995; vol. E21c, pp 2997–3059.

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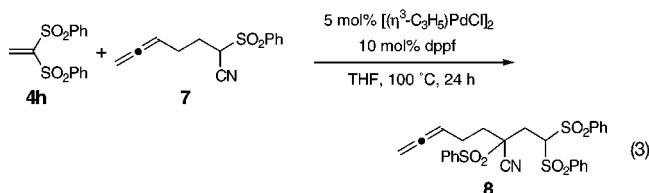
(6) (a) Yamamoto, Y.; Al-Masum, M.; Asao, N. *J. Am. Chem. Soc.* **1994**, *116*, 6019–6020. (b) Yamamoto, Y. *Pure Appl. Chem.* **1996**, *68*, 9–14. (c) Yamamoto, Y.; Al-Masum, M.; Fujiwara, N.; Asao, N. *Tetrahedron Lett.* **1995**, *36*, 2811–2814. (d) Yamamoto, Y.; Al-Masum, M. *Synlett* **1995**, 969–970. (e) Yamamoto, Y.; Al-Masum, M.; Fujiwara, N. *Chem. Commun.* **1996**, 381–382. (f) Yamamoto, Y.; Al-Masum, M.; Takeda, A. *Chem. Commun.* **1996**, 831–832.

(7) See the Supporting Information. The *cis* stereoselectivities in entries 4–6 (Table 1) were significantly high. The reason for this high *cis* selectivity is not known at present.

(8) The stereochemistries of the diastereomers were not assigned. Balme's group also observed similar phenomena in their reactions. See: Marat, X.; Monteiro, N.; Balme, G. *Synlett* **1997**, 845–847.

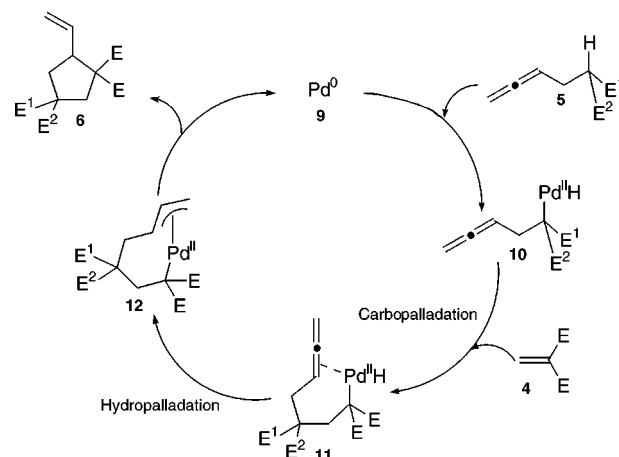
substituted activated olefin **4h** reacted with **5a** and **5c**, in which CN and CO₂Me were electron-withdrawing groups, to afford **6i** and **6j**, respectively, in good yields (entries 9 and 10). However, the reaction of **4h** with the allene **5d**, in which SO₂Ph and CO₂Me are electron-withdrawing groups did not give the desired product at all, but the starting materials were recovered.

We attempted to conduct the formal [4 + 2] cycloaddition between **4h** and **7**. However, the expected cycloadduct was not obtained at all, and instead, the Michael adduct **8** was produced (eq 3).⁹



A speculative mechanism that accounts for the present cycloaddition is shown in Scheme 1. The palladium(0) produced in situ would add oxidatively to acidic C–H bond of **5** to give hydridopalladium(II) intermediate **10**. This complex **10** would undergo carbopalladation reaction with **4** to lead to another hydridopalladium species **11**. Intramolecular hydropalladation of **11** would give π -allylpalladium complex **12**.¹⁰ Reductive elimination of Pd(0) from **12** would give the carbocycle **6**.¹¹

Scheme 1. Carbopalladation–Hydropalladation Mechanism



Alternatively, hydropalladation of **4** with **10** followed by the reductive coupling would produce the Michael addition product (similar to **8**) and Pd(0).¹² Oxidative addition of Pd(0) into the active methyne of the adduct would produce **11**, which would give **6** as shown in Scheme 1. Although further investigation is needed to determine its mechanism, the present cycloaddition reaction provides an entirely new procedure for constructing cyclopentanoids under neutral conditions.

The reaction of *p*-methoxybenzylidene Meldrum's acid **4d** with **5a** is representative. To a solution of **4d** (131 mg, 0.50 mmol) and 2-cyano-4,5-dienitrile **5a** (89 mg, 0.75 mmol) in THF (4.0 mL) in an argon-filled pressure vial were added consecutively [(η^3 -C₃H₅)PdCl]₂ (9 mg, 0.025 mmol) and dpfp (28 mg, 0.050 mmol). After being stirred at 100 °C for 10 h, the reaction mixture was cooled to room temperature. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography using *n*-hexanes–ethyl acetate (5:1) as an eluent. 2,2-Dicyano-8,8-dimethyl-1-(*p*-methoxyphenyl)-4-vinyl-7,9-dioxaspiro[4,5]decane-6,10-dione **6e** was obtained in 91% yield (173 mg).

Supporting Information Available: Experimental procedures for obtained compounds.

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(12) We could not isolate the Michael addition product in the case of the reactions with **5**.

(9) For recent examples of transition metal catalyzed Michael additions, see: (a) Naota, T.; Taki, H.; Mizuno, M.; Murahashi, S.-I. *J. Am. Chem. Soc.* **1989**, *111*, 5954–5955. (b) 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*, 12436–12451 and references therein. (c) Sawamura, M.; Hamashita, H.; Ito, Y. *Tetrahedron* **1994**, *50*, 4439–4454. (d) Sawamura, M.; Hamashita, H.; Ito, Y. *J. Am. Chem. Soc.* **1992**, *114*, 8295–8296. (e) Paganelli, S.; Schionato, A.; Botteghi, C. *Tetrahedron Lett.* **1991**, *32*, 2807–2810. (f) Gómez-Bengoa, E.; Cuerva, J. M.; Mateo, C.; Echavarren, A. M. *J. Am. Chem. Soc.* **1996**, *118*, 8553–8565. (g) Murahashi, S.-I.; Naota, T. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 1805–1824.

(10) Trost and Gerusz proposed a hydropalladation mechanism for the palladium catalyzed reactions of allenes with active methylene compounds. See: (a) Trost, B. M.; Gerusz, V. J. *J. Am. Chem. Soc.* **1995**, *117*, 5156–5157. We also proposed his mechanism for the intramolecular reactions. See also: (b) Meguro, M.; Kamijo, S.; Yamamoto, Y. *Tetrahedron Lett.* **1996**, *37*, 7453–7456.

(11) Without palladium catalysts, the reactions of **4** and **5** did not proceed at all.