Palladium-Catalyzed Addition of Activated Methylene and Methyne Compounds to Allenes

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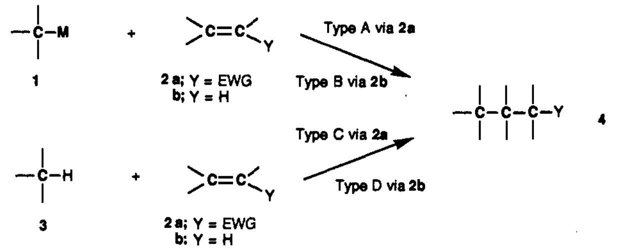
The addition of carbanionic organometallic compounds **1** to activated alkenes **2a**, such as Michael acceptors, is a classical and standard procedure for C–C bond formation (type A). In modern organic synthesis, the use of transition metal catalysts enables the addition of **1** to unactivated alkenes **2b** (type B).[1] The addition reactions of activated methylenes and methynes **3** to activated alkenes **2a** in the presence of base are commonly known as Michael reactions, which afford the C–C bond forming product **4** (type C). More recently, the transition metal catalyzed version of type C has been discovered.[2] We wish to report, for the first time, the transition metal catalyzed addition of activated methynes and methylenes **3** to allenes,[3–5] which are thought to fall under the category of unactivated alkenes (type D).



The addition of **5** to **6** proceeded smoothly in the presence of catalytic amounts of $Pd_2(dba)_3{\cdot}CHCl_3$ in THF under reflux to give the internal alkenes (**7** and/or **8**) (eq 1). The results are summarized in Table 1.

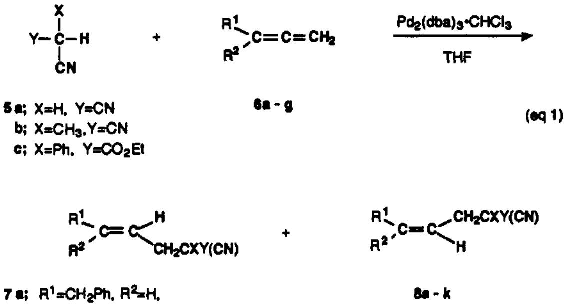
The addition of malononitrile (**5a**) and methylmalononitrile (**5b**) to 4-phenyl-1,2-butadiene (**6a**) proceeded smoothly to give exclusively the *trans*-alkenes **7a** and **7b**, respectively (entries 1, 2). It should be noted that double addition took place in the case of **5a**, because the monoadduct $R^1R^2C{=}CHCH_2CH(CN)_2$ had a more reactive tertiary C–H bond. With sterically bulkier allenes 3-cyclohexyl-1,2-propadiene (**6b**) and 3-phenyl-1,2-propadiene (**6c**), the addition reaction became sluggish (entries 3, 4) although the trans stereoselectivity was maintained. The addition of **5b** to **6c** proceeded smoothly, but a mixture of the *trans*- and *cis*-alkenes was obtained (entry 5). Compared to the monosubstituted allenes **6a–c**, the disubstituted allenes **6d–g** gave higher chemical yields and better material balance. The addition of **5b** to **6d** and **6e** afforded exclusively the *trans*-alkenes **7f** and **7g**, respectively (entries 6, 7). However, a mixture of the *trans*- and *cis*-alkenes was obtained in the addition reactions to **6f,g** (entries 8–11). The effectiveness of other transition metal catalysts toward C–C bond formation was examined; the addition of **5b** and **5c** to **6f** did not take place with other catalysts such as $RhH(CO)(Ph_3P)_3$, $Pd(Ph_3P)_4$, and $La(OiPr)_3$.

The addition of **5b** to **6d** (entry 6) is representative. A two-neck round-bottom flask fitted with a refluxing condenser and an argon balloon was charged with **6d** (65.0 mg, 0.5 mmol), methyl malononitrile (44.0 mg, 0.55 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (26.0 mg, 5 mol %), 1,4-bis(diphenylphosphino)butane, dppb (56.0 mg, 26.0 mol %), and THF (3.0 mL), and the mixture was refluxed for 48 h. When the complete conversion of the allene was observed, the reaction mixture was filtered through a small alumina column using THF as an eluent. The solvent was removed by rotary

Table 1. Palladium-Catalyzed Addition of **5** to **6**[a]

entry	6			5	product, yield (%)	stereo-selectivity 7:8	recovery of 6 (%)
		R¹	R²				
1	**6a**	$PhCH_2$	H	**5b**	**7b**, 60	~100:–	25
2	**6a**	$PhCH_2$	H	**5a**	**7a**, 30	~100:–	25
3	**6b**	$c\text{-}C_6H_{11}$	H	**5b**	**7c**, 10	~100:–	35
4	**6c**	Ph	H	**5a**	**7d**, 15	~100:–	18
5	**6c**	Ph	H	**5b**	**7e** 58 **8e**	57:43	33
6	**6d**	Ph	Me	**5b**	**7f**, 68	~100:–	
7	**6e**	Ph	Et	**5b**	**7g**, 25	~100:–	60
8	**6f**	$PhCH_2$	Me	**5b**	**7h** 62 **8h**	33:67	21
9	**6d**	Ph	Me	**5c**	**7i** 70 **8i**	24:76	16
10	**6f**	$PhCH_2$	Me	**5c**	**7j** 75 **8j**	50:50	18
11	**6g**	Ph	$PhCH_2$	**5c**	**7k** 60 **8k**	67:33	26

[a] All reactions were carried out in THF under an Ar atmosphere; **6** (0.5 mmol), **5** (0.55 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mol %)/dppb (26 mol %). The mixture was refluxed for 48 h in the cases of **5a** and **5b**, and for 20 h in the case of **5c**. All yields are of pure product isolated by column chromatography.



(eq 1)

5a; X=H, Y=CN
b; $X{=}CH_3$, Y=CN
c; X=Ph, $Y{=}CO_2Et$

6a - g

7a; $R^1{=}CH_2Ph$, $R^2{=}H$, $X{=}CH_2CH{=}CHCH_2Ph$, Y=CN
b; $R^1{=}CH_2Ph$, $R^2{=}H$, X=Me, Y=CN
c; $R^1{=}c\text{-}C_6H_{11}$, $R^2{=}H$, X=Me, Y=CN
d; $R^1{=}Ph$, $R^2{=}H$, $X{=}CH_2CH{=}CHPh$, Y=CN
e; $R^1{=}Ph$, $R^2{=}H$, X=Me, Y=CN
f; $R^1{=}Ph$, $R^2{=}Me$, X=Me, Y=CN
g; $R^1{=}Ph$, $R^2{=}Et$, X=Me, Y=CN
h; $R^1{=}PhCH_2$, $R^2{=}Me$, X=Me, Y=CN
i; $R^1{=}Ph$, $R^2{=}Me$, X=Ph, $Y{=}CO_2Et$
j; $R^1{=}PhCH_2$, $R^2{=}Me$, X=Ph, $Y{=}CO_2Et$
k; $R^1{=}Ph$, $R^2{=}PhCH_2$, X=Ph, $Y{=}CO_2Et$

8a - k

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(1) (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: Knochel, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, U.K., 1990; Vol. 4, p 865. (c) Negishi, E. *Pure Appl. Chem.* **1981**, *53*, 2333.

(2) Michael and aldol reactions. (a) Naota, T.; Taki, H.; Mizuno, M.; Murahashi, S.-I. *J. Am. Chem. Soc.* **1989**, *111*, 5954. Michael reactions. (b) Paganelli, S.; Schionata, A.; Batteghi, C. *Tetrahedron Lett.* **1991**, *32*, 2807. (c) Sawamura, M.; Hamashima, H.; Ito, Y. *J. Am. Chem. Soc.* **1992**, *114*, 8295. Imine addition. (d) Yamamoto, Y.; Kubota, N.; Honda, Y.; Fukui, H.; Asao, N.; Nemoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 3161.

(3) For the synthesis via allenes: (a) Landor, S. R. In *The Chemistry of the Allenes*; Landor, S. R., Ed.; Academic Press: London, 1982; Vol. 2, p 361. (b) Caserio, M. C. In *Selective Organic Transformations*; Thyagarajan, B. S., Ed.; Wiley-Interscience: New York, 1970; Vol. 1, p 239. (c) Brady, W. T. In *The Chemistry of Ketenes, Allenes, and Related Compounds*; Patai, S., Ed.; Wiley: New York, 1980; Vol. 1, p 279. (d) Schuster, H. F.; Coppola, G. M. In *Allenes Organic Synthesis*; Wiley-Interscience: New York, 1984.

(4) Carbopalladation of allenic compounds ($RCH{=}C{=}CH_2$) by vinylic and arylic palladium species ($R'PdX$) affords 2-substituted π-allylpalladium complexes ($RCH\cdots CR'\cdots CH_2)PdLn$, which react with stabilized carbanions (^-Nu) to give 1,2-disubstituted alkenes ($RCH{=}CR'{-}CH_2Nu$). Cazes, B. *Pure Appl. Chem.* **1990**, *62*, 1867. See also references cited therein.

(5) The addition of silylcuprates to allenes is known. Fleming, I.; Pulido, F. J. *J. Chem. Soc., Chem. Commun.* **1986**, 1010.

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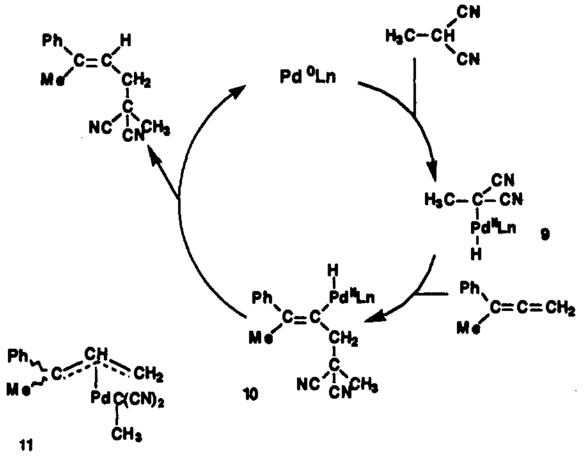
Scheme 1



evaporator under vacuo. The crude product was filtered through a silica gel column with hexane/ethyl acetate (12/1) as eluent, affording 2-cyano-2-methyl-5-phenyl-4(*E*)-hexenenitrile (**7f**) in 68% yield.

A mechanistic rationale which accounts for the unprecedented addition[6] of certain activated nucleophiles to allenes is shown in Scheme 1. The oxidative insertion of Pd(0) into the C–H bond of the activated nucleophile[7] would produce the Pd(II) species **9** (or alternatively a tautomeric structure $H_3C(CN)$-C=C=NPdHLn may be more suitable). The carbopalladation of the allene with **9** would afford the alkenylpalladium(II) complex **10**, which would undergo reductive coupling to give the addition product and Pd(0) species. As an alternative mechanism, it may be considered that the hydropalladation of the allene with **9** gives the π-allylpalladium complex **11**, which undergoes reductive coupling to afford the adduct and palladium (0) species. Although it is not easy to conclude definitely which mechanism is operating for the C–C bond formation, we prefer the former mechanism for the following reasons.

If the hydropalladation mechanism is involved, reduced products of the allene (*cis*- and *trans*-2-phenyl-2-butenes, 3-phenyl-1-butene, and 2-phenylbutane) might be formed as minor products. However, such products were not detected. Reaction of methylmalononitrile with phenylacetylene in the presence of the Pd catalyst did not proceed at all; if the hydropalladium complex **9** is involved, the reduction of phenylacetylene may take place. However, the starting materials were recovered completely. Further, if the π-allylpalladium mechanism is operating, a regioisomeric adduct may be formed as a minor product in the case of monosubstituted allenes such as **6a–c**. Such a regioisomeric adduct was not detected.

The palladium-catalyzed addition of activated nucleophiles **5** to allenes **6** proceeds under essentially neutral conditions to give regioselectively and (in some cases) stereoselectively the internal alkenes. This finding opens a door to a new area in allene chemistry as well as in transition metal catalyzed chemistry.

Supplementary Material Available: Full spectroscopic and analytical characterization of the products (14 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(6) The palladium-catalyzed addition of terminal acetylenes to activated allenes (2,3-alkadienoates) is known: Trost, B. M.; Kottirsch, G. *J. Am. Chem. Soc.* **1990**, *112*, 2816. The rhodium catalyzed addition of terminal acetylenes to allenes produces *endo*-(*E*)-enynes in high yields: Hirama, M.; Yamaguchi, M.; Omata, K., unpublished results.

(7) Several rhenium complexes of activated nucleophiles have been isolated. Hirano, M.; Ito, Y.; Hirai, M.; Fukuoka, A.; Komiya, S. *Chem. Lett.* **1993**, 2057. We confirmed a rapid C–H insertion of Pd(0) into methylmalononitrile by using its deuterated derivative. No deuterium exchange took place when $MeCD(CN)_2$ was treated with dppb (26 mol %) in THF. When $Pd_2(dba)_3 \cdot CHCl_3$ (5 mol %) was added to this mixture, rapid deuterium exchange occurred to give $MeCH(CN)_2$.