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Palladium-catalyzed benzannulation of conjugated enynes. Enhanced reactivity of alkoxycarbonyl- and cyanoenynes

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Abstract

We report the high reactivity of alkoxycarbonyl- and cyanoenynes in the homo-benzannulation of conjugated enynes. The introduction of these electron-withdrawing groups enabled us to carry out the benzannulation of 1-substituted enynes as well as 1,2- and 2,4-disubstituted enynes, which have much lower reactivity compared to 2- or 4-monosubstituted enynes. Polysubstituted benzenes were prepared in a highly regioselective manner in good to excellent yields. © 1999 Elsevier Science Ltd. All rights reserved.

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Though polysubstituted benzenes are important synthetic intermediates in organic synthesis, the regioselective preparation of these compounds by traditional synthetic methods such as the Friedel–Crafts reaction is not easy. Recently, we discovered a novel palladium-catalyzed benzannulation reaction (cyclodimerization) of 2-substituted enynes which is useful for the synthesis of 1,4-disubstituted benzenes (Eq. 1).[1] It was also found that 4-substituted enynes were good substrates for the homo-benzannulation reaction which produced 2,6-disubstituted styrenes (Eq. 1).[2,3] These reactions have been applied to the synthesis of many substituted benzenes such as paracyclophanes and phenols.[4] Unfortunately, 1,2-di- and 2,4-disubstituted enynes did not undergo homo-benzannulation in the presence of a Pd catalyst (Eq. 2). While we were studying the substituent effects on the reactivity of the conjugated enynes, we noticed that the reactivity of some conjugated enynes which were substituted with an electron withdrawing group was much higher compared to alkyl enynes.[5] In this paper we report the high reactivity of alkoxycarbonyl- and cyanoenynes in the homo-benzannulation of conjugated enynes (Eq. 3).

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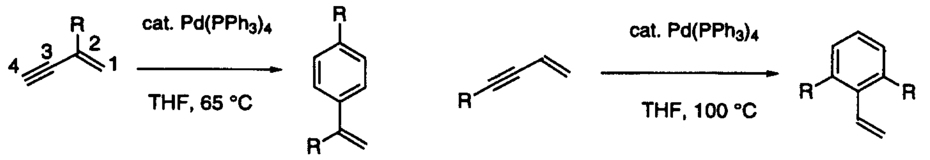
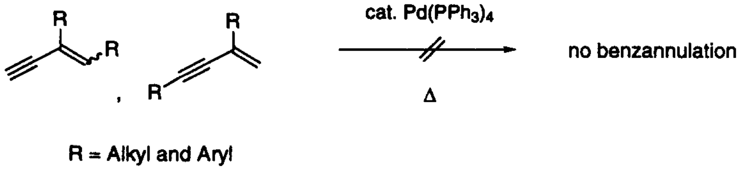


(1)



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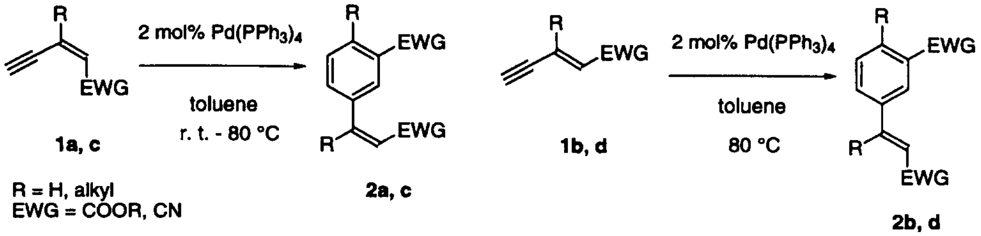


(3)

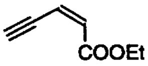
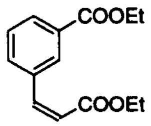
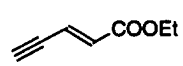
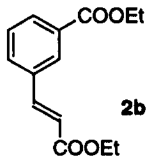
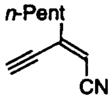
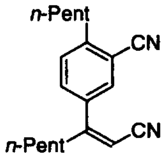
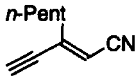
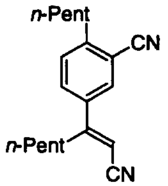
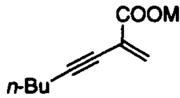
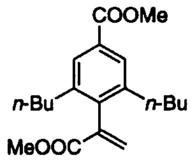
(*Z*)-1-Ethoxycarbonyl-1-buten-3-yne (**1a**) cyclodimerized in the presence of a catalytic amount of $Pd(PPh_3)_4$ to give a 1,3-disubstituted benzene (**2a**) in good yield (Table 1, entry 1). It is noteworthy that the reactivity of this enyne was significantly higher compared to other alkyl enynes,^{1,2} and the reaction proceeded smoothly even at room temperature^{6} in a highly regioselective manner; no isomeric product was isolated. While it has been shown that the reactivity of (*E*)-enynes was much lower compared to that of (*Z*)-enynes in the cross-benzannulation reaction,^{3b} we found that the homo-benzannulation of the (*E*)-ethoxycarbonylenyne **1b** proceeded (entry 2). However, compared to the reaction of the (*Z*)-counterpart **1a**, the yield of the product was lower and the higher reaction temperature was required. The stereochemistry of the olefinic moiety was unaffected during the reaction, and the (*Z*)-styrene **2a** was obtained from the (*Z*)-enyne **1a**, and the (*E*)-styrene **2b** was obtained from the (*E*)-enyne **1b**.

The reactivity of the substituted enynes in the benzannulation reaction dramatically decreased when the number of the substituents attached to the enynes became larger as mentioned above (Eq. 2). However, the reaction of 1,2-disubstituted enynes proceeded smoothly when an electron-withdrawing group was attached to the enyne. Thus, (*Z*)-1-cyano-2-pentyl-1-buten-3-yne **1c** cyclodimerized smoothly in the presence of $Pd(PPh_3)_4$ at 80°C to give the 1,2,4-trisubstituted benzene **2c** in good yield (entry 3). The reaction of (*E*)-1-cyano-2-pentyl-1-buten-3-yne **1d** also proceeded smoothly but the yield of the product **2d** was lower (entry 4). While some 2,4-disubstituted enynes did not undergo benzannulation (Eq. 2), we found that the reaction of a 2,4-disubstituted enyne substituted with an electron-withdrawing group proceeded rapidly under extremely mild conditions. Thus, the palladium-catalyzed cyclodimerization of the 2-methoxycarbonylenyne **1e** proceeded at 30°C to give the 1,2,3,5-tetrasubstituted benzene **2e** in good yield (entry 5).

A typical experimental procedure is as follows: To a yellow solution of $Pd(PPh_3)_4$ (11.6 mg, 0.01 mmol) in dry toluene (0.5 mL) was added **1a** (62 mg, 0.5 mmol) at room temperature and the mixture was stirred for 2 h. The mixture was passed through a short column packed with silica gel (ether) and evaporated. The residue was further purified by column chromatography (silica gel, hexane:ethyl acetate=20:1) to give **2a** as a pale yellow oil (55 mg, 88%).

The precise mechanism of this benzannulation is not clear at present, and therefore the role of the electron-withdrawing group in the reaction is very difficult to understand. Currently we assume that the

Table 1
Homo-benzannulation of alkoxycarbonyl- and cyanoenynes

		reaction conditions			isolated
entry	enyne 1	temp (°C)	time (h)	product 2	yield (%)
1	 **1a**	r. t.	2	 **2a**	88
2	 **1b**	80	2	 **2b**	43
3	 **1c**	80	1	 **2c**	78
4	 **1d**	80	1	 **2d**	49
5	 **1e**	30	5	 **2e**	68

increased reactivity of the enynes might be explained in terms of stronger interaction of the electron deficient enynes with the Pd catalyst.

In summary, we have found that some alkoxycarbonylenynes and cyanoenynes are highly reactive substrates for the palladium catalyzed homo-benzannulation. Now we are in a position to prepare some polysubstituted functionalized benzenes in a highly regioselective manner under mild conditions.

References

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3. These conjugated enynes also reacted with conjugated diynes in the presence of palladium catalysts to give benzene derivatives. See: (a) Gevorgyan, V.; Takeda, A.; Yamamoto, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11313–11314. (b) Gevorgyan, V.; Sadayori, N.; Yamamoto, Y. *Tetrahedron Lett.* **1997**, *38*, 8603–8604.
4. (a) Saito, S.; Tsuboya, N.; Yamamoto, Y. *J. Org. Chem.* **1997**, *62*, 5042–5047. (b) Weibel, D.; Gevorgyan, V.; Yamamoto, Y. *J. Org. Chem.* **1998**, *63*, 1217–1220. (c) Gevorgyan, V.; Quan, L.-G.; Yamamoto, Y. *J. Org. Chem.* **1998**, *63*, 1244–1247.
5. The enhanced reactivity of alkoxycarbonylenynes in the cross benzannulation was reported. See Ref. 3b.
6. On the other hand, higher temperature (65°C or 100°C) were required for the reaction of 2-alkylenynes or 4-alkylenynes. See Refs. 1 and 2.