Palladium/Acetic Acid Catalyzed Allylation of Some Pronucleophiles with Simple Alkynes

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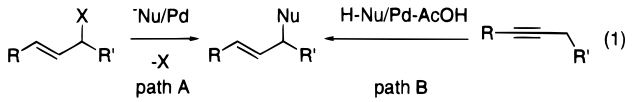
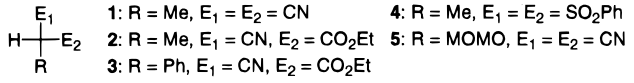
Received April 17, 1998

The palladium-catalyzed allylation of carbon nucleophiles is well-recognized as one of the most powerful synthetic tools for the construction of carbon−carbon bonds (eq 1, path A).[1]



However, this transformation is not necessarily the best procedure for the allylation from an *eco-chemical* point of view since the use of a stoichiometric amount of bases is needed to generate nucleophiles ($^-$Nu) and a stoichiometric amount of a leaving group (X) is liberated.[2] Herein we report a method for the allylation of carbon pronucleophiles in which nothing is liberated from starting materials;[3] the reaction of certain acetylenes with pronucleophiles in the presence of 5 mol % $Pd(PPh_3)_4$ and 50 mol % acetic acid gave the corresponding allylation products in good to high yields (eq 1, path B).

In initial experiments, methylmalononitrile **1** was treated with 1 equiv of 1-phenyl-1-propyne (**6**), $Pd(PPh_3)_4$ (5 mol %), and acetic acid (50 mol %) in dioxane at 100 °C to give the adduct **7**[4a] as a sole product in 99% yield (Table 1, entry 1). Similarly, the reactions of **6** with pronucleophiles **2**−**4** gave the adducts



1: R = Me, $E_1 = E_2$ = CN **4**: R = Me, $E_1 = E_2 = SO_2Ph$
2: R = Me, E_1 = CN, $E_2 = CO_2Et$ **5**: R = MOMO, $E_1 = E_2$ = CN
3: R = Ph, E_1 = CN, $E_2 = CO_2Et$

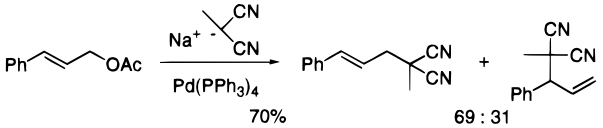
8−**10**, respectively, in high yields (entries 2−4). The perfect regioselectivities observed are in marked contrast with those of the usual allylation of nucleophiles via allylic substrates.[5] The reaction of diethyl and dimethyl methylmalonate with various alkynes gave only a trace amount of the adducts even after a prolonged reaction time. As shown in entry 4, a CN group is not necessarily essential as an E group of pronucleophiles. The reaction in the absence of acetic acid gave a trace amount of the product. The use of bidentate ligands such as dppb and dppf with $Pd_2(dba)_3{\cdot}CHCl_3$ inhibited the reaction completely. Other examples with various alkynes are summarized in Table 1. When 1-phenyl-1-butyne, **11**, was employed as a substrate, the regioselectivity was decreased to 86:14 (entry 5). However, the reaction of propargyl ether derivative **14** with **1** or protected hydroxymalononitrile **5** gave **15** or **16**, respectively, as a single regioisomer in high yields (entries 6 and 7). As we reported in our previous papers, the adduct **16** can be readily converted to an activated ester which reacts with certain nucleophiles to give

Table 1. Pd/AcOH Catalyzed Allylation of Pronucleophiles with Various Alkynes

entry	alkyne	pronucleophile	product	yield (%)[a]
1	Ph−≡−Me (**6**)	**1**	Ph, CN, CN (**7**)	99
2	**6**	**2**	Ph, CN, CO_2Et (**8**)	89
3	**6**	**3**	Ph, CN, CO_2Et, Ph (**9**)	96
4	**6**	**4**	Ph, SO_2Ph, SO_2Ph (**10**)	92
5	Ph−≡− (**11**)	**1**	**12** : **13** = 86 : 14	81[b]
6	Ph−≡−OMe (**14**)	**1**	Ph, CN, CN, OMe (**15**)	98
7	**14**	**5**	MOMO, CN, CN, Ph, OMe (**16**)	86
8	Ph−≡−NCbz, H (**17**)	**1**	**18** : **19** = 64 : 36	64
9	Ph−≡− (**20**)	**1**	**21** (*E*) : **22** (*Z*) = 81 : 19	83
10	(**23**)	**1**	**24** : **25** = >95 : 5	89[b]

[a] Isolated yield. [b] Inseparable mixture of the regioisomers. Ratios were determined by ^{1}H NMR analysis.

(5) For example, the palladium catalyzed reaction of cinnamyl acetate with the sodium salt of methylmalononitrile gave a mixture of regioisomers.



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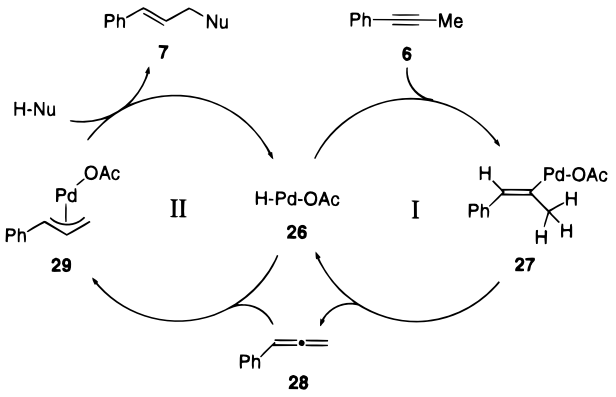
(2) Although allylic carbonates and epoxides react with pronucleophiles in the absence of external bases, a stoichiometric amount of alkoxides generated from the substrates acts as a base in these reactions.

(3) This process is similar to that reported by Trost et al. for the allylation of acetic acid with alkynes to give allyl acetates: Trost. B. M.; Brieden, W.; Baringhaus, K. H. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1335−1336.

(4) (a) Yamamoto, Y.; Al-Masum, M.; Asao, N. *J. Am. Chem. Soc.* **1994**, *116*, 6019−6020. (b) Trost. B. M.; Gerusz, V. *J. Am. Chem. Soc.* **1995**, *117*, 5156−5157. (c) Besson, L.; Goré, J.; Cazes, B. *Tetrahedron Lett.* **1995**, *36*, 3853−3856. (d) Meguro, M.; Kamijo, S.; Yamamoto, Y. *Tetrahedron Lett.* **1996**, *37*, 7453−7456 and references therein. (e) Trost, B. M.; Michellys, P.-Y.; Gerusz, V. J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1750−1753.

S0002-7863(98)01299-2 CCC: $15.00
Published on Web 09/17/1998

Scheme 1

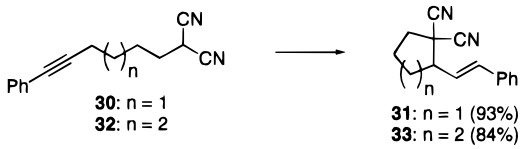


a variety of carbonyl compounds.[6] In contrast, the reaction of the nitrogen counterpart **17** gave a 64:36 mixture of **18** and **19** in 64% yield (entry 8). Interestingly, the reaction of cyclopropyl phenyl acetylene, **20**,[7] produced the linear adducts **21** and **22** in the ratio of 81:19 in 83% yield (entry 9). The reaction of a symmetric alkyne, 3-hexyne **23**, gave the adducts **24** and **25** with very high regioselectivity (>95:5) in 89% yield (entry 10).[8]

The reaction of methylmalononitrile with 1-phenyl-1-propyne, **6**, is representative. To a mixture of methylmalononitrile (27 mg, 0.34 mmol), **6** (43 μL, 0.34 mmol), and $Pd(PPh_3)_4$ (20 mg, 0.017 mmol) in dry dioxane (2 mL) was added acetic acid (10 μL, 0.17 mmol), and the mixture was stirred overnight at 100 °C. The reaction mixture was then filtered through a short silica gel column using ether as an eluent, and the filtrate was concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc, 4:1) to give **7** (66 mg, 99%).

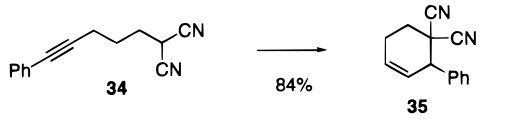
A plausible mechanism for this allylation is illustrated in Scheme 1. The initial step would be hydropalladation of **6** with the hydridopalladium species **26** generated from Pd^0 and acetic acid (catalytic cycle I).[9] The resulting vinyl palladium species **27** would produce phenyl allene **28** and the active catalyst **26** via β-elimination.[3,10] Hydropalladation of **28** with **26** would give the π-allylpalladium species **29** which reacts with a pronucleophile to give the product **7** along with the hydridopalladium **26** (cycle II). Although the key intermediate **28** could not be detected in the reaction, the hypothesis is strongly supported by the following observations: (1) The palladium-catalyzed addition of pronucleophiles to allenes is known,[4] which corresponds to the transformation of **28** to **7** in the catalytic cycle II. (2) The reactions of the alkoxy-substituted alkyne **14** gave **15** and **16**, respectively, as a single regioisomer. These results suggest that the reaction would proceed via the π-allylpalladium intermediate **29** because the regioselectivity in the reaction of **14** is completely identical with that of the palladium-catalyzed allylic substitution of 3-alkoxy-2-propenyl acetates with carbon nucleophiles.[11] (3) The palladium-catalyzed reaction of **6** with a stoichiometric amount of acetic acid in the absence of pronucleophiles gave cinnamyl acetate in 70% yield, which would be produced from **29** via reductive elimination.[3,12]

The usefulness of this methodology is demonstrated further by the intramolecular version (eq 2). Treatment of the internal



(2)

alkynes **30** and **32**, having a dicyanomethine at the terminus of the carbon chain, with palladium/acetic acid catalyst gave the medium-sized carbocycles **31** and **33**, respectively, in high yields. Interestingly, the cyclization of **34**[13] proceeded with endo manner to give the cyclohexene derivative **35** as a sole product in 84%



(3)

yield. The regioselectivity of the intramolecular cyclization strongly depends on the ring size of the products.

In conclusion, we have developed an efficient method for the allylation of pronucleophiles with simple alkynes using palladium/acetic acid catalyst. The advantage of this methodology is not only the high yield and high regioselectivity but also the ease of the preparation of the substrates, especially in the case of the intramolecular reactions (see Supporting Information). Furthermore, to the best of our knowledge, the present reaction is the first example for the formal allylic substitution reaction with simple alkynes, which enables an eco-chemical process to be carried out without liberating leaving groups.

Acknowledgment. This work was financially supported by the Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture of Japan.

Supporting Information Available: Experimental procedures and characterization data for **7**−**10**, **12**, **13**, **15**−**19**, **21**, **22**, **24**, **30**−**33**, and **35** (5 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

JA981299C

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