Allylation of Carbon Pronucleophiles with Alkynes in the Presence of Palladium/Acetic Acid Catalyst

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Dedicated to Joe P. Richmond on the occasion of his 60th birthday.

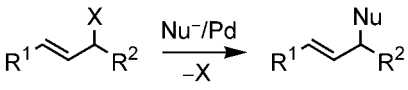
Supporting Information for this article is available on the WWW under http://asc.wiley-vch.de/.

Abstract: We have developed an efficient and eco-chemical process for the allylation of carbon pronucleophiles with alkynes. The reaction of alkynes with various active methynes and methylenes in the presence of $Pd(PPh_3)_4$/acetic acid gave the corresponding allylated products in high yields and high regioselectivities. In the present catalytic system, the key is the use of carboxylic acid which dramatically enhances the rate of the reactions. One of the important features of this process is that neither a leaving group is liberated nor is a stoichiometric amount of base needed to generate the nucleophiles.

Keywords: alkynes; allylation; carbon nucleophiles, C–C bond formation; homogeneous catalysis; palladium

Introduction

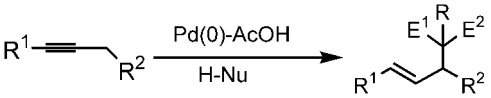
The palladium-catalyzed allylation of carbon nucleophiles is well recognized as one of the most powerful synthetic tools for the construction of carbon-carbon bonds, Eq. (1).[1] In general, the method involves the use of allylic acetates, carbonates, halides, phosphates, NR_2 etc.[2]



(1)

X = OH, OAc, OCO_2R, OTs, OTf, Br/Cl/I, $OP(O)Ph_2$, NR_2

Recently, the direct use of allylic alcohols is also gaining much interest. Some efforts have been made in this direction by the use of activators, which coordinate with the hydroxy group of allylic alcohols thereby increasing their leaving group ability.[3] However, these transformations are not necessarily the best procedure for the allylation of carbon nucleophiles from an *eco-chemical* point of view, since the use of a stoichiometric amount of base is needed to generate nucleophiles (Nu^-) from pronucleophiles (H-Nu) and a stoichiometric amount of a leaving group (X) is liberated.[4] Research in this field seeking a new and more efficient method which can overcome these problems is still needed. In this context our group reported, in 1998, an entirely new method for the allylation of carbon pronucleophiles with alkynes, which may serve as an alternative to the existing methods.[5a] In that communication, we reported the allylation of active methynes with alkynes using the $Pd(PPh_3)_4$/carboxylic acid combined catalytic system, Eq. (2). It was our earlier observation that the allylation proceeded smoothly with active methynes having two cyano group, two SO_2Ph groups, or one CN and one COOEt group, giving the quaternary allylated products in very high yields, Eq. (2).



(2)

H-Nu = $HCR(CN)_2$, HCR(CN)(COOEt), $HCR(SO_2Ph)_2$

Encouraged by these results and motivated by the importance of a regioselective carbon-carbon bond forming process, we attempted the allylation of active methylenes as they would have more synthetic potential. Accordingly, we attempted the allylation of malononitrile[6] under the established procedure; however, the product

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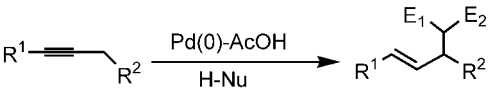
obtained was a mixture of mono- and diallylated products. At this juncture, all attempts to control the monoallylation over diallylation failed. Accidental addition of diethyl malonate to the reaction mixture led to a breakthrough; the desired monoallylation took place in high yield. Herein, we report a full account on the allylation of active methylenes with alkynes together with the previous findings, Eqs. (2) and (3).



(3)

H-Nu = $CH_2(COOEt)_2$, $CH_2(COPh)(COOEt)$, $CH_2(COPh)_2$, $CH_2(SO_2Ph)(COPh)$

Results and Discussion

Initially, we carried out the reaction of 1-phenyl-1-propyne (**13**) with 1 equivalent of methylmalononitrile (**1**) in the presence of 5 mol % $Pd(PPh_3)_4$ as a catalyst in 1,4-dioxane at 100 °C. The reaction hardly proceeded, and the desired product **14** was obtained in only a trace amount. To our surprise, however, use of acetic acid (50 mol %) as an additive greatly improved the yield; **14** was obtained in 99% (Table 1, entry 1). This rate enhancement can be attributed to the cooperative effect of both the palladium catalyst and acetic acid, because either of the individual reagents alone did not give the product.[7] A variety of proton sources was then examined; among the tested acetic acid, trifluoroacetic acid, benzenesulfonic acid, and HCl, acetic acid gave the best result. Next, we examined different palladium catalysts and phosphine ligands. Among the palladium catalyst examined, $Pd(PPh_3)_4$ and the$Pd_2(dba)_3 \cdot CHCl_3$/PPh_3 combination gave the best results, however, in the latter case the reaction was slightly slower. The combination of $Pd(OAc)_2$ (5 mol %) with PPh_3 (10 mol %) could also be used, however, the reaction was slower and it took a longer time to reach completion (30 h). The use of bidentate ligands, such as dppb and dppf, with $Pd(PPh_3)_4$ or $Pd_2(dba)_3 \cdot CHCl_3$ inhibited the reaction completely. Besides these investigations, this hydrocarbonation reaction was examined in the presence of water (20 mol %) as an additive. Thus, the reaction of **13** with **1** in the presence of $Pd(PPh_3)_4$ (5 mol %)/CH_3COOH (10 mol %)/water (20 mol %) afforded **14** in 99% yield, indicating that the reaction was not sensitive to moisture.

After studying various palladium sources, phosphine ligands and additives, we then employed the $Pd(PPh_3)_4$ (5 mol %)/CH_3COOH (50 mol %) catalytic system for the hydrocarbonation of alkynes with several active methynes. The allylation proceeded smoothly with active methynes **1**–**5** (Scheme 1) giving the quaternary allylated products in very high yields. The results are summarized in Table 1.

1 R = Me, $E^1 = E^2 = CN$ **2** R = Me, E^1 = CN, $E^2 = CO_2Et$

3 R = Ph, E^1 = CN, $E^2 = CO_2Et$ **4** R = Me, $E^1 = E^2 = SO_2Ph$

5 R = OMOM, $E^1 = E^2$ = CN **6** R = Me, $E^1 = E^2 = CO_2Et$

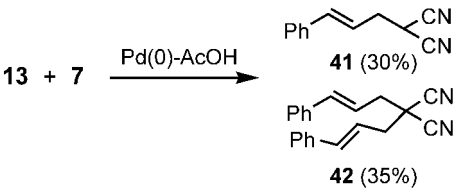
7 R = H, $E^1 = E^2$ = CN **8** R = H, $E^1 = E^2 = CO_2Et$

9 R = H, E^1 = COPh, $E^2 = CO_2Et$ **10** R = H, $E^1 = E^2$ = COPh

11 R = H, E^1 = COPh, $E^2 = SO_2Ph$ **12** R = H, $E^1 = COCH_3$, $E^2 = P(O)(OMe)_2$

Scheme 1. Various active methynes and methylenes.

We anticipated that this new palladium-catalyzed transformation could be applied widely to the synthesis of natural products if we could extend this methodology to the allylation of active methylenes. We selected malononitrile as a model substrate,[6] since the allylation of active methynes proceeded very well with methylmalononitrile and related substrates (**1**–**5**). The reaction of malononitrile (**7**; 1.2 equivs.) with 1-phenyl-1-propyne (**13**; 1 equiv.) under the standard conditions, $Pd(PPh_3)_4$ (5 mol %)/CH_3COOH (10 mol %)[8] in 1,4-dioxane at 100 °C, was carried out, Eq. (4): the diallylated product **42** was produced in 35% yield together with the monoallylated product **41** in 35% yield (Table 2, entry 1). This observation suggested that the allylation proceeded with malononitrile and the monoallylated malononitrile was more reactive than the original substrate, malononitrile. At this stage, we believed that the selective and synthetically useful allylation reaction with alkynes was restricted to active methynes bearing a CN or SO_2Ph group only. However, the accidental addition of diethyl malonate to the reaction mixture changed the mode of reaction giving the monoallylated product selectively. Our dream, although after a long gap, was fulfilled. Various active methylenes turned out to be applicable for the selective monoallylation. Perhaps the lower acidity of methylene protons of diethyl malonate hampers the formation of the diallylated product. The results are summarized in Table 2.



(4)

At first, the treatment of 1-phenyl-1-propyne (**13**) with one equivalent of diethyl malonate (**8**) under the standard conditions gave the monoallylated product **43** in

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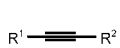
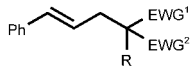
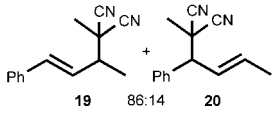
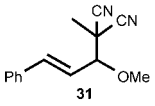
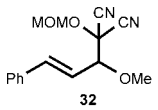
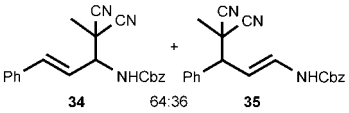
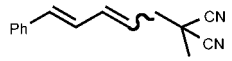
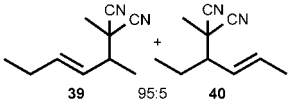
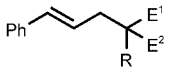
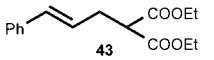
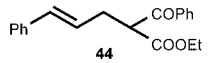
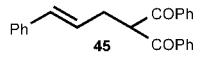
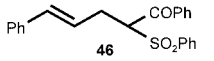
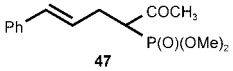
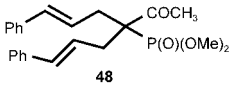
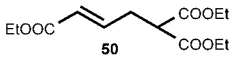
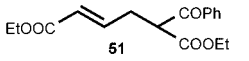
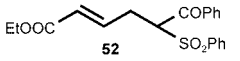
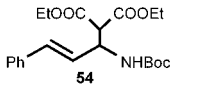
Table 1. Pd(0)/AcOH-catalyzed allylation of active methynes with alkynes.[a]

Entry	Alkyne	H-Nu	Product	Yield [%][b]
				
1	**13** R^1 = Ph, R^2 = CH_3	**1**	**14** R = Me, E^1 = E^2 = CN	99
2	**13** R^1 = Ph, R^2 = CH_3	**2**	**15** R = Me, E^1 = CN, E^2 = COOEt	89
3	**13** R^1 = Ph, R^2 = CH_3	**3**	**16** R = Ph, E^1 = CN, E^2 = COOEt	96
4	**13** R^1 = Ph, R^2 = CH_3	**4**	**17** R = Me, E^1 = E^2 = SO_2Ph	92
5	**18** R^1 = Ph, R^2 = Et	**1**	 **19** 86:14 **20**	81[c]
6	**30** R^1 = Ph, R^2 = CH_2OMe	**1**	 **31**	98
7	**30** R^1 = Ph, R^2 = CH_2OMe	**5**	 **32**	86
8	**33** R^1 = Ph, R^2 = CH_2NHCbz	**1**	 **34** 64:36 **35**	64
9	**36** R^1 = Ph, R^2 = cyclopropyl	**1**	 **37a**(*E*):**37b**(*Z*) = 81:19	83
10	**38** R^1 = R^2 = Et	**1**	 **39** 95:5 **40**	89[c]

[a] 50 mol% acetic acid was used in all the cases.
[b] Yield of isolated product.
[c] Inseparable mixture of regioisomers. Ratios were determined by ^{1}H NMR analysis.

Table 2. $Pd(PPh_3)_4$/AcOH-catalyzed allylation of active methylenes with various alkynes.[a]

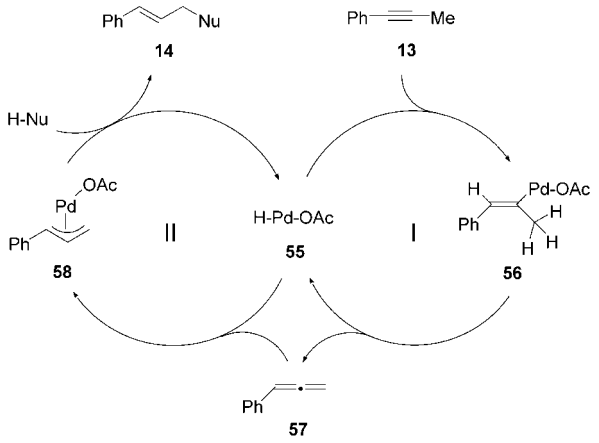
Entry	Alkynes	H-Nu[b]	Product	Yield [%][c]
				
1	**13** R^1 = Ph, R^2 = CH_3	**8**	 **43**	92
2	**13** R^1 = Ph, R^2 = CH_3	**9**	 **44**	90
3	**13** R^1 = Ph, R^2 = CH_3	**10**	 **45**	71
4	**13** R^1 = Ph, R^2 = CH_3	**11**	 **46**	95
5	**13** R^1 = Ph, R^2 = CH_3	**12**	 **47**	31
			 **48**	20
6	**49** R^1 = CO_2Et, R^2 = CH_3	**8**	 **50**	85
7	**49** R^1 = CO_2Et, R^2 = CH_3	**9**	 **51**	83
8	**49** R^1 = CO_2Et, R^2 = CH_3	**10**	 **52**	81
9	**53** R^1 = Ph, R^2 = CH_2NHBoc	**8**	 **54**	68

[a] All reactions were carried out with 5 mol % of $Pd(PPh_3)_4$ and 10 mol % acetic acid in 1,4-dioxane at 100 °C for 12 h.
[b] 1.2 equivs. of pronucleophiles were used.
[c] Yields of isolated products based on alkynes.

71% yield with the formation of the diallylated product in 10% yield. The formation of the diallylated product was totally suppressed by the use of 1.2 equivalents of diethyl malonate giving **43** in 92% isolated yield (entry 1). Similarly, the reaction of **13** with 1.2 equivs. of **9**, **10** and **11** gave the monoallylated products **44**, **45** and **46**, respectively, in good to high yields (entries 2–4), and the corresponding diallylated products were not isolated. However, in the case of **12**, a mixture of mono- and diallylated products **47** and **48** was obtained (entry 5).

Tetrolic acid ethyl ester (**49**) also reacted smoothly with the nucleophiles **8**, **9** and **10** to give the monoallylated products **50**, **51**, and **52**, respectively, in high yields (entries 6–8). The reaction of the *N*-Boc protected propargylamine derivative **53** gave only one regioisomer **54** in 68% yield while another regioisomer could not be detected at all (entry 9).

A proposed mechanism for the allylation of *C*-nucleophiles with alkynes under Pd(0)/acetic acid is shown in Scheme 2. The initial step would be hydropalladation of **13** with the hydridopalladium species **55** generated from Pd^0 and acetic acid (catalytic cycle **I**).[7a] The resulting vinylpalladium species **56** would produce phenylallene **57** and the active catalyst **55** *via* β-elimination.[9] Hydropalladation of **57** with **55** would give the π-allyl-



Scheme 2. Proposed mechanism for the allylation of *C*-nucleophiles with alkynes.

palladium species **58** which reacts with a pronucleophile to give the product **14** along with the hydridopalladium **55** (cycle **II**).

Conclusions

In summary, we have developed an efficient method for the allylation of carbon pronucleophiles with simple alkynes using the palladium/acetic acid combined catalytic system. Thus, we are now in a position to allylate a variety of active methylenes and methynes by using this newly developed procedure. The reaction possesses several synthetically attractive features: (1) simple procedure allowing large-scale preparation, (2) high regioselectivity, (3) the ease of the preparation of the substrates, especially in the case of the intramolecular reactions,[5a] (4) no base is needed to generate the nucleophile, (5) no need for dry solvent, (6) possibility of asymmetric version. 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 one to carry out an eco-chemical process without liberating leaving groups. Further attempts to make this reaction enantioselective, are now underway in our laboratory.

Experimental Section

Reaction of Methylmalonontrile with 1-Phenyl-1-Propyne; Typical Procedure

To a mixture of 1-phenyl-1-propyne **13** (0.20 g, 1.72 mmol), diethyl malonate **8** (0.33 g, 2.07 mmol), $Pd(PPh_3)_4$ (0.099 g, 0.086 mmol) in dry 1,4-dioxane (5 mL) was added acetic acid (0.010 g, 0.17 mmol), and the mixture was stirred for 12 h 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 a silica gel column chromatography (hexane/AcOEt, 4:1) to give **43**; yield: 0.44 g (92%).

Supporting Information

Experimental details, characterization data of all compounds, ^{1}H NMR spectral data of compounds **43–48** and **50–54** (15 pages).

Acknowledgements

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[3] The following inorganic acid anhydrides have been used as an activator: a) As_2O_3: X. Lu, L. Lu, S. Junhui, *J. Mol. Cat.* **1987**, *41*, 245; b) B_2O_3: X. Lu, X. Jiang, X. Tao, *J. Organomet. Chem.* **1988**, *344*, 109; c) CO_2: M. Sakamoto, I. Shimizu, A. Yamamoto, *Bull. Chem. Soc. Jpn.* **1996**, *69*, 1065; d) F. Ozawa, H. Okamoto, S. Kawagishi, S. Yamamoto, T. Minami, M. Yoshifuji, *J. Am. Chem. Soc.* **2002**, *124*, 10968–10969 and references cited therein.

[4] Although allylic carbonates and epoxides react with pronucleophiles in the absence of an external base, a stoichiometric amount of alkoxides generated from the substrates acts as a base in these reactions.

[5] For preliminary communication, see: a) I. Kadota, A. Shibuya, Y. S. Gyoung, Y. Yamamoto, *J. Am. Chem. Soc.* **199 8**, *120*, 10262–10263; during the course of these studies, we also reported the hydroamination and hydroalkoxyla-

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ton of alkynes, see: b) I. Kadota, A. Shibuya, M. L. Lutete, Y. Yamamoto, *J. Org. Chem.* **1999**, *64*, 4570–4571; c) M. L. Lutete, I. Kadota, A. Shibuya, Y. Yamamoto, *Heterocycles.* **2002**, *58*, 347–357; d) I. Kadota, M. L. Lutete, A. Shibuya, Y. Yamamoto, *Tetrahedron Lett.* **2001**, *42*, 6207–6210. While the work was in progress, another group reported the hydrocarboxylation of alkynes based on the same concept, see: e) W. Zhang, A. R Haight, M. C. Hsu, *Tetrahedron Lett.* **2002**, *43*, 6575–6578. We also reported, previously, the hydrocarbonaton of the substrates other than alkynes. For hydrocarbonation of allenes, see: f) Y. Yamamoto, M. Al-Masum, N. Asao, *J. Am. Chem. Soc.* **1994**, *116*, 6019–6020; g) Y. Yamamoto, M. Al-Masum, N. Fujiwara, *Chem. Commun.* **1996**, 381–382; h) Y. Yamamoto, M. Al-Masum, A. Takeda, *Chem. Commun.* **1996**, 831–832; i) Y. Yamamoto, M. Al-Masum, N. Fujiwara, N. Asao, *Tetrahedron Lett.* **1995**, *36*, 2811–2814; j) Y. Yamamoto, M. Al-Masum, *Synlett* **1995**, 969–970; k) M. Meguro, S. Kamijo, Y. Yamamoto, *Tetrahedron Lett.* **1996**, *37*, 7453–7456. For the hydrocarbonation of 1,3-enynes, see: l) M. M. Salter, V. Gevorgyan, S. Saito, Y. Yamamoto, *Chem. Commun.* **1996**, 17; for the hydrocarbonation of 3,3-dihexylcyclopropene, see: m) I. Nakamura, G. B. Bajracharya, Y. Yamamoto, *J. Org. Chem.* **2003**, *68*, 2297–2299. For the hydrocarbonation of methyleneaziridines, see: n) B. H. Oh, I. Nakamura, Y. Yamamoto, *Tetrahedron Lett.* **2002**, *43*, 9625–9628. For the hydrocarbonation of methylenecyclopropanes, see: o) N. Tsukada, A. Shibuya, I. Nakamura, Y. Yamamoto, *J. Am. Chem. Soc.* **1997**, *119*, 8123; p) N. Tsukada, A. Shibuya, I. Nakamura, H. Kitahara, Y. Yamamoto, *Tetrahedron* **1999**, *55*, 8833.

[6] It was also reported in ref.[5a] that the allylation of diethyl methylmalonate was very sluggish and only a trace amount of the corresponding allylated product was obtained even after prolonged reaction time. At this stage, we believed that the allylation reaction was restricted to active methynes, bearing less bulky and strong electron-withdrawing groups such as CN and SO_2Ph. Therefore, we chose malononitrile as a model substrate for active methylenes.

[7] Enhancement of reaction rate by the use of Pd(0)/carboxylic acid combined catalytic system is also observed by others, see: a) B. M. Trost, F. Rise, *J. Am. Chem. Soc.* **19 87**, *109*, 3161–3163; b) B. M. Trost, C. Jakel, B. Plietker, *J. Am. Chem. Soc.* **2003**, *125*, 4438–4439.

[8] Initially we used 50 mol % of acetic acid in the reactions as reported in the previous communication,[5a] but later found that 10 mol % of acetic acid was also enough without affecting the reaction in terms of yield, time and regioselectivity.

[9] Palladium-catalyzed isomerization of alkynes to allenes, see: a) H. Sheng, S. Lin, Y. Huang, *Tetrahedron Lett.* **19 86**, *27*, 4893–4894; b) B. M. Trost, T. Schmidt, *J. Am. Chem. Soc.* **1988**, *110*, 2301–2303; c) X. Lu, J. Ji, D. Ma, W. Shen, *J. Org. Chem.* **1991**, *56*, 5774–5778.

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