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Formation of a Quaternary Carbon Center through the Pd(0)/PhCOOH-Catalyzed Allylation of Cyclic β-Keto Esters and 1,3-Diketones with Alkynes

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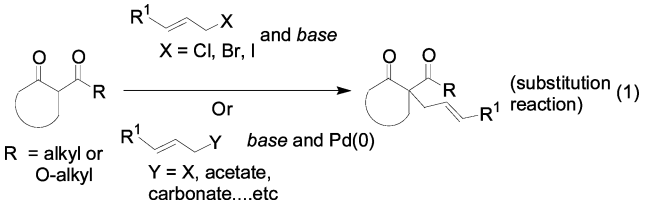
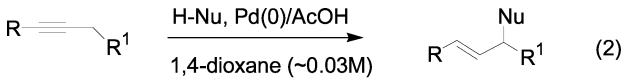
Abstract: Formation of a quaternary carbon center through the allylation of β-keto esters and 1,3-diketones with alkynes is accomplished by the use of Pd(0)/benzoic acid catalyst. Reactions of various cyclic β-keto esters and 1,3-diketones with alkynes in the presence of Pd_2dba_3·$CHCl_3$ (5 mol %), PPh_3 (40 mol %), and PhCOOH (10 mol %) proceeded at 100 °C in toluene (5 M) to give the corresponding allylation products in high yields in a regio- and stereoselective manner. The possibility of asymmetric allylation is also discussed.

The generation of a quaternary carbon center is one of the important reactions in organic chemistry.[1] It is especially quite challenging to develop efficient catalytic asymmetric protocols for the allylation of cyclic β-keto esters and 1,3-diketones that enable carbon−carbon bond formation.[2] Several methods are known in the literature and are categorized under the following two types: (1) treatment of the substrates with allyl halides in the presence of a base[3] and (2) treatment of the substrates with allylic acetates/halides/carbonates in the presence of Pd(0) and a stoichiometric amount of a base (Tsuji−Trost allylation) (eq 1).[4] Both procedures described above produce a stoichiometric amount of waste elements (X^- or Y^-), since the C−C bond formation proceeds through a substitution reaction. Furthermore, the catalysis in the presence of strong bases may also be problematic when a base-labile functional group exists in the substrate.



Recently, we reported an entirely new method for the allylation of *C*-nucleophiles with alkynes using a Pd(0)/carboxylic acid combined catalytic system (eq 2).[5a] In this process, the product is obtained via formal addition of *C*-pronucleophiles to a double bond of allenes isomerized from the alkynes. The synthetic scope of this newly developed process was rather narrow and this method was applicable for *C*-pronucleophiles having a strongly acidic hydrogen and least sterically hindered electron withdrawing group such as CN group.[6] If we can extend the Pd(0)/RCOOH-catalyzed allylation to sterically constrained β-keto esters and 1,3-diketones, the allylation methodology will become more useful and more widely applicable since those dicarbonyl substrates are more often utilized and more popular starting materials than the cyano-containing compounds for the quaternary carbon formation. After a number of attempts, we found that β-keto esters and 1,3-diketones **1** undergo the allylation with alkynes **2** in the presence of Pd(0)/PhCOOH catalysts in toluene (5 M) at 100 °C to give the desired allylation products **3** in good to high yields (eq 3). The key for this success is to use a higher concentration (5 M or even neat conditions) of the substrates than the previous conditions (0.03 M) (see eq 2).



H-Nu = $HCR_2(CN)_2$, $HCR_2(CN)(COOEt)$, $HCR_2(SO_2Ph)_2$

First, the allylation of ethyl 2-oxocyclopentanecarboxylate **1a** was examined with 1-phenyl-1-propyne **2a** with various palladium sources and phosphine ligands in toluene (5 M).[7] The reaction was carried out in the

(1) For a review see: (a) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105−10146. (b) Trost, B. M. *Chem. Pharm. Bull.* **2002**, *50*, 1−14. (c) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4545−4554. (d) Trost, B. M. *Acc. Chem. Res.* **1996**, *29*, 355−364. (e) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395−422. (f) Heumann, A.; Reglier, M. *Tetrahedron* **1995**, *51*, 975−1015. (g) Hayashi, T. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers Inc.: New York, 1993. (h) Sawamura, M.; Ito, Y. *Chem. Rev.* **1992**, *92*, 857−871. (i) Fiaud, J. C. In *Metal-Promoted Selectivity in Organic Synthesis*; Graziani, M., Hubert, A. J., Noels, A. F., Eds.; Kluwer Academic Publishers: Dordrecht, The Netherlands, 1991. (j) Consiglio, G.; Waymouth, R. M. *Chem. Rev.* **1989**, *89*, 257−276.

(2) (a) Kuwano, R.; Uchida, K.; Ito, Y. *Org. Lett.* **2003**, *5*, 2177−2179 and references therein. (b) Trost, B. M.; Radinov, R.; Grenzer, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 7879−7880 and references therein.

(3) (a) Bhar, S.; Chaudhuri, S. K.; Sahu, S. G.; Panja, C. *Tetrahedron* **2001**, *57*, 9011−9016. (b) Ueno, M.; Hisamoto, H.; Kitamori, T.; Kobayashi, S. *Chem. Commun.* **2003**, 936−937. (c) Aburel, P. S.; Romming, C.; Ma, K.; Undheim, K. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1458−1472.

(4) (a) Buono, F.; Tenaglia, A. *Synlett* **1998**, 1153−1155. (b) Hayashi, T.; Kanehira, K.; Hagihara, T.; Kumada M. *J. Org. Chem.* **1988**, *53*, 113−120. (c) Tsuji, J. *Transition Metal Reagents and Catalysts*; Wiley: New York, 2000; Chapter 4.

(5) (a) Kadota, I.; Shibuya, A.; Gyoung, Y. S.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 10262−10263. For the chemistry on alkynes as a π-allylpalladium complex, see: (b) Kadota, I.; Shibuya, A.; Lutete, M. L.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 4570−4571. (c) Lutete, M. L.; Kadota, I.; Shibuya, A.; Yamamoto, Y. *Heterocycles* **2002**, *58*, 347−357. (d) Kadota, I.; Lutete, M. L.; Shibuya, A.; Yamamoto, Y. *Tetrahedron Lett.* **2001**, *42*, 6207−6210. (e) Zhang, W.; Haight, A. R.; Hsu, M. C. *Tetrahedron Lett.* **2002**, *43*, 6575−6578. (f) Lutete, M. L.; Kadota, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 1622−1623.

(6) (a) The reaction of dimethyl methylmalonate with alkynes gave only a trace amount of the adducts even after a prolonged reaction time, although the reaction of methyl malononitrile gave the desired allylation product in high yields.[5a] (b) In the ^{1}H NMR spectra, the methyne proton of methyl malononitrile appears at δ 3.77. On the other hand, the methyne proton of dimethyl methylmalonate and **1a** (vide infra) appears at δ 3.44 and 2.30, respectively. This indicates that the methyne proton of methyl malononitrile is more acidic than dimethyl methylmalonate and **1a**.

(7) We ran the reaction at higher concentration because we observed that at lower concentrations the reaction became slower.

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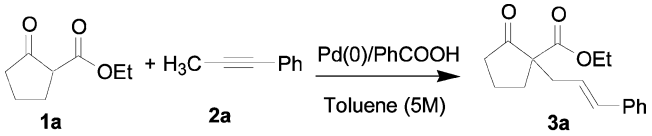
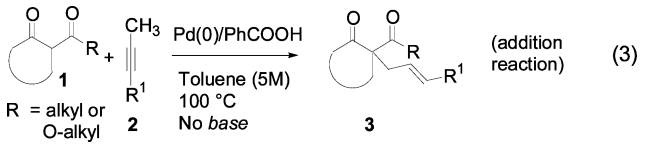
TABLE 1. Allylation of 1a with 1-Phenyl-1-propyne 2a[a]



entry	Pd catalyst (5%)	PhCOOH (mol %)	NMR yield (%)[b]
1	$Pd(PPh_3)_4$		0[c]
2	$Pd(PPh_3)_4$	10	92
3	$Pd_2dba_3{\cdot}CHCl_3$	10	0[c]
4	$Pd_2dba_3{\cdot}CHCl_3/PPh_3$	10	99 (95)[d]
5	$Pd_2dba_3{\cdot}CHCl_3/PPh_3$	10	95[e]
6	$Pd_2dba_3{\cdot}CHCl_3$/dppb	10	9
7	$Pd_2dba_3{\cdot}CHCl_3$/dppf	10	0
8	$Pd_2dba_3{\cdot}CHCl_3$/dppp	10	0

[a] The reactions of **1a** (1 mmol) with alkyne **2a** (1 mmol) in the presence of $Pd_2dba_3{\cdot}CHCl_3$ (0.05 mmol), phosphine ligands (0.40 mmol for monophosphines and 0.20 mmol for bisphosphine), and benzoic acid (0.1 mmol) were carried out at 100 °C in toluene (5 M) for 6 h. [b] Yields were determined by ^{1}H NMR spectroscopy with dibromomethane as an internal standard. [c] The starting material was recovered. [d] Isolated yields are shown in parentheses. [e] Reaction performed without solvent.



presence of $Pd_2dba_3{\cdot}CHCl_3$ (5 mol %), benzoic acid (10 mol %), and phosphine ligands (20 mol % for bisphosphines or 40 mol % for monophosphines) at 100 °C under argon atmosphere. The results are summarized in Table 1. As anticipated, the reaction of **1a** with **2a** in the presence of $Pd(PPh_3)_4$, without addition of benzoic acid, did not give the desired product at all, the starting material being recovered (entry 1). As shown in entry 2, the addition of 10 mol % of benzoic acid gave the product **3a** as the *E*-isomer in 92% yield. When $Pd_2dba_3{\cdot}CHCl_3$ was employed alone as a palladium source, the reaction did not proceed (entry 3). The combination of $Pd_2dba_3{\cdot}CHCl_3$ and 40 mol % of PPh_3 worked well and the desired compound was isolated in 95% yield (entry 4). When the same experiment was carried out under neat conditions, the starting material was consumed within 4 h and the product was obtained in 95% yield (entry 5). In the case of the bidentate ligands such as dppb, dppf, and dppm, however, inferior results were obtained (entries 6−8). Although the yields of the reactions shown in entries 4 and 5 were comparable, we preferred the former condition (in 5 M toluene) because of the cleanness of the process judging from the ^{1}H NMR spectrum of the crude reaction mixture.

Once suitable conditions for the allylation reaction were established, we next investigated the allylation of various β-keto esters and 1,3-diketones. The results are summarized in Table 2. Treatment of β-keto ester **1a** with **2b** under the standard conditions gave the desired product **3b** in 98% yield (entry 1). The reaction of alkynes **2c** and **2d** with **1a** also proceeded smoothly to produce the products **3c** and **3d** in 92% and 91% yields, respectively (entries 2 and 3). The six-membered cyclic β-keto ester **1b**, however, was found to be a poor substrate for

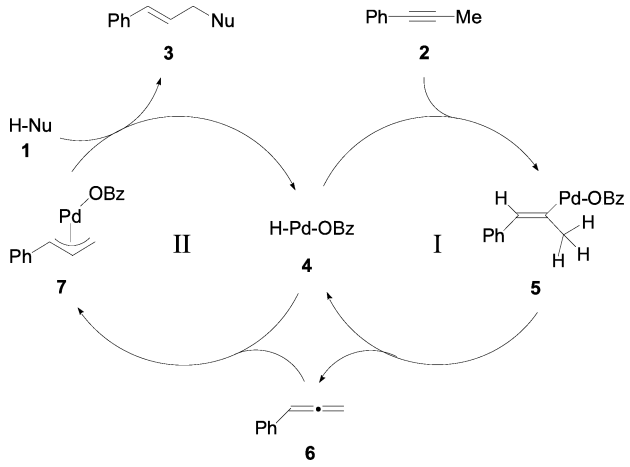


FIGURE 1. Proposed mechanism for the allylation of β-keto esters and 1,3-diketones with alkynes.

the allylation reaction with **2a** giving **3e** in 51% yield (entry 4). The indanone-derived β-keto ester **1c**[8] on reaction with **2a** and **2d** afforded the corresponding allylated products **3f** and **3g**, respectively, in excellent yields (entries 5 and 6). The reaction of 2-acetyl tetralone **1d** proceeded without problem with alkynes **2a**−**d** to give the corresponding products **3h**−**k** in excellent yields (entries 7−10). 2-Acetyl cyclopentanone **1e** also underwent facile allylation with **2a** and **2d** to give the corresponding products **3l** and **3m** in 89% and 87% yields, respectively (entries 11 and 12). Similarly, 2-acetyl cyclohexanone **1f** underwent smooth allylation reaction with **2a** and **2d** to produce **3n** and **3o** in 78% and 69% yields, respectively (entries 13 and 14). The alkynes such as 3-hexyne and 1-phenyl-1-butyne did not react with any of the *C*-pronucleophiles mentioned above, under these reaction conditions.

The mechanism of this reaction is presumably similar to those of the hydrocarbonation reported previously and is shown in Figure 1. The initial step is the hydropalladation of **2** with the hydridopalladium species **4** generated from Pd(0) and PhCOOH (or HOAc) (catalytic cycle I).[9] The resulting vinyl palladium species **5** would produce phenyl allene **6** and the active catalyst **4** via β-elimination.[10] Hydropalladation of **6** with **4** presumably gives the π-allylpalladium species **7** which reacts with a pronucleophiles **1** to give the product **3** along with the hydridopalladium **4** (cycle II).

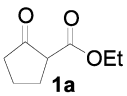
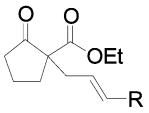
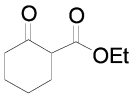
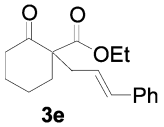
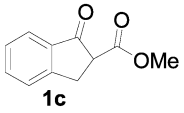
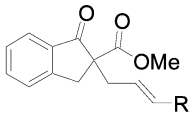
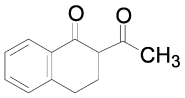
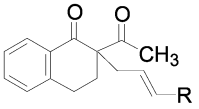
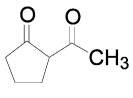
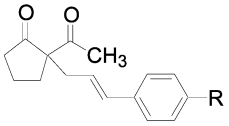
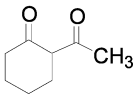
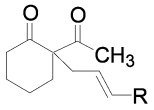
It is clear that the scope and synthetic utility of this newly born process would be enhanced dramatically if the quaternary carbon center formation proceeds in a catalytic asymmetric manner. For this, several nonracemic chiral ligands were examined (see the Supporting Information). Among them, (*S*,*S*)-CHIRAPHOS gave a better result. The reaction of **1a** with 1-phenyl-1-propyne **2a** catalyzed by $Pd_2dba_3{\cdot}CHCl_3$ and (*S*,*S*)-CHIRAPHOS occurred in 63% yield and 27% ee (eq 4). Though modest

(8) Emelem K. V.; Wit, T. D.; Hoornaert, G. J.; Compernolle, F. *Tetrahedron* **2002**, *58*, 4225−4236.

(9) Trost, B. M.; Rise, F. *J. Am. Chem. Soc.* **1987**, *109*, 3161−3163.

(10) Palladium-catalyzed isomerization of alkynes to allenes, see: (a) Sheng, H.; Lin, S.; Huang, Y. *Tetrahedron Lett.* **1986**, *27*, 4893−4894. (b) Trost, B. M.; Schmidt, T. *J. Am. Chem. Soc.* **1988**, *110*, 2301−2303. (c) Lu, X.; Ji, J.; Ma, D.; Shen, W. *J. Org. Chem.* **1991**, *56*, 5774−5778.

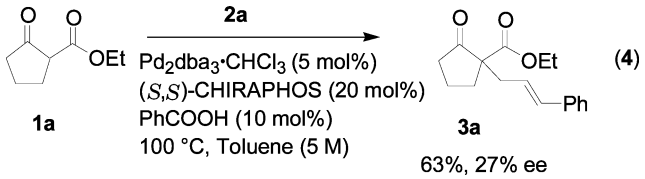
TABLE 2. Allylation of Cyclic β-Keto Esters and 1,3-Diketones with Alkynes[a]

entry	substrate	alkyne	product[b]	yield (%)[c]
	 **1a**			
1		**2b** R = C_6H_4-*p*Cl	**3b** R = C_6H_4-*p*Cl	98
2		**2c** R = C_6H_4-*p*OMe	**3c** R = C_6H_4-*p*OMe	92
3		**2d** R = COOEt	**3d** R = COOEt	91
4	 **1b**	**2a**	 **3e**	51
	 **1c**			
5		**2a**	**3f** R = Ph	92
6		**2d**	**3g** R = C_6H_4-*p*OMe	88
	 **1d**			
7		**2a**	**3h** R = Ph	81
8		**2b**	**3i** R = C_6H_4-*p*Cl	88
9		**2c**	**3j** R = C_6H_4-*p*OMe	85
10		**2d**	**3k** R = COOEt	83
	 **1e**			
11		**2a**	**3l** = R = Ph	89
12		**2d**	**3m** R = COOEt	87
	 **1f**			
13		**2a**	**3n** R = Ph	78
14		**2d**	**3o** R = COOEt	69

[a] The reactions of **1** (1 equiv) with alkynes **2** (1 equiv) in the presence Pd_2dba_3·$CHCl_3$ (0.05 equiv), PPh_3 (0.40 equiv), and benzoic acid (0.1 equiv) were carried out at 100 °C in toluene (5 M) for 8−15 h. [b] All products obtained were identified as *E*-isomers by ^{1}H NMR spectra. [c] Isolated yields.

in yield and poor in ee, these data demonstrate the feasibility of enantioselective allylation.

In summary, we have developed an improved strategy for the *E*-stereoselective allylation of cyclic β-keto esters and 1,3-diketones with alkynes. This process allows the facile and efficient construction of a quaternary carbon. It should be noted that neither leaving group is liberated



(4)

nor base is needed for the process and the product is obtained via formal addition of *C*-pronucleophiles to allenes isomerized from alkynes. This is the first report wherein the allylation of cyclic β-keto ester and 1,3-diketones is achieved via the formal addition of them to alkynes.[11] We have also shown the possibility of asymmetric induction and it became clear that the search for a suitable ligand is needed to improve the yield and ee, and that will be the quest of our future research.

Experimental Section

A representative procedure for the palladium/benzoic acid-catalyzed allylation is as follows. To a solution of **1a** (0.053 g, 0.3443 mmol) in toluene (0.07 mL) were added 1-phenyl-1-propyne **2a** (0.040 g, 0.3443 mmol), $Pd_2dba_3{\cdot}CHCl_3$ (0.018 g, 0.0172 mmol), PPh_3 (0.036 g, 0.1377 mmol), and PhCOOH (0.004 g, 0.0344 mmol). The mixture was stirred at 100 °C for 8−15 h in a screw-capped vial. The reaction progress was monitored by TLC. The solvent was removed under reduced pressure, and the residue was purified by short silica gel column with hexane:ethyl acetate (9:1) to give **3a** (0.088 g) in 95% yield.

(11) The addition of cyclic β-keto esters to Michael acceptor is known, see: (a) Ooi, T.; Miki, T.; Taniguchi, M.; Shiraishi, M.; Takeuchi, M.; Maruoka, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 3796−3798 and references therein. The direct intramolecular addition of cyclic β-keto esters to alkynes and alkenes is known; see: (b) Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4526−4527 and references therein. (c) Nakamura, M.; Endo, K.; Nakamura, E. *J. Am. Chem. Soc.* **2003**, *125*, 13002−13003 and references therein.

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Supporting Information Available: Experimental details, characterization data, and ^{1}H NMR spectrum of newly synthesized compounds **3b**, **3c**, **3f**, **3g**, **3i**, **3j**, **3k**, and **3o**. This material is available free of charge via the Internet at http://pubs.acs.org.

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