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Palladium-catalyzed hydrophenoxycarbonylation of internal alkynes by phenol and CO: the use of Zn for the formation of active catalyst

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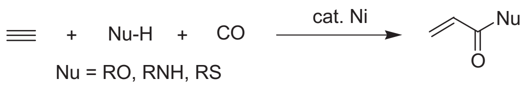
ABSTRACT

The palladium-catalyzed hydrophenoxycarbonylation of internal alkynes by phenol and carbon monoxide was successfully realized by $Pd(OAc)_2$/dppp catalyst system in the co-presence of Zn dust.

The transition metal-catalyzed addition reactions of nucleophiles and carbon monoxide to alkynes, widely known as Reppe carbonylation (Scheme 1), have been well-studied for a long period.[1–3]

For the syntheses of α,β-unsaturated esters according to this protocol, alcohols have been employed in most cases. However, the reactions with phenols, which can serve as very powerful strategy for the syntheses of α,b-unsaturated arylesters have been hardly developed. For instance, Miura and co-workers have reported Pd-catalyzed addition of phenols and CO to terminal alkynes, which is the only example of Reppe carbonylation using phenols.[4] Furthermore, to the best of our knowledge, no example of Reppe carbonylation of internal alkynes by phenol is documented. Herein we wish to report the first example of carbonylative addition of phenol and carbon monoxide to internal alkynes.



Scheme 1. Reppe carbonylation.

First, the effects of ligand (0.05 mmol) under the reaction of 4-octyne (**1a**, 1.0 mmol) with PhOH (**2**, 0.5 mmol) and CO (1 atm) in the presence of $Pd(dba)_2$ (0.05 mmol) were examined in toluene (0.5 mL) at 100 °C for 24 h (Table 1). No reaction took place when monodentate ligands such as PPh_3, PCy_3, and $P(t\text{-}Bu)_3$ were employed (entries 1–3). Treatment with bidentate phosphine exhibited catalytic activity to afford the desired α,β-unsaturated phenyl ester **3a**, albeit quite in low yields (entries 4–9). Among examined, the use of dppp resulted in the best yield (5% of **3a**, entry 6). In the case of Reppe carbonylation with alcohols, it was reported that the addition of acid is quite effective to promote the reaction. Thus, the effect of acids such as AcOH (10 mol %)[3d] and TsOH[3d,3e] (5 mol %) was next tested; however, the yields of **3a** were not improved in the reactions with **2** (entries 10 and 11). To anticipate the increase of yield of **3a**, some reactions were next tested with Pd(II)/dppp as catalysts. As a result, $Pd(OAc)_2$/dppp showed higher activity to form **3a** in 18% yield (entry 16), while no reaction took place with $PdCl_2$, $PdCl_2(MeCN)_2$, $[PdCl(C_3H_5)_2]_2$, and $Pd(acac)_2$ (entries 12–15). It was found that the production of **3a** was significantly promoted by the addition of Zn as a reducing reagent: **3a** was produced in 44% yield in the co-presence of 10 mol % of Zn (entry 17). The increase of the amount of Zn improved the yield of **3a** (entries 18–21). Gratifyingly, **3a** was produced quantitatively with 1.5 equiv of Zn (entry 21), while decreasing the amount of dppe resulted in the low yield of **3a**. Two equivalent of **1a** was required due to the formation of undetermined by-products. Although the additions of Mg and Mn were somewhat effective for the formation of **3a**, $SnCl_2$[3a,3b] and Fe rather suppressed the reaction (entries 22–25). Only 11% of **3a** was produced when DBA (10 mol %) was added to $Pd(OAc)_2$/dppp/Zn reaction system, demonstrating that the coordination of DBA to palladium complex significantly suppressed the reaction (compare entry 26 with entry 21).

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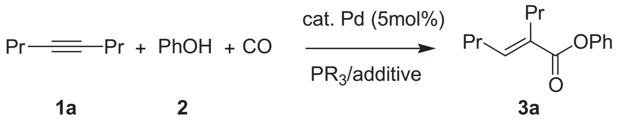
Table 1
Palladium-catalyzed hydrophenoxycarbonylation of 4-ocyne (**1a**)[a]



Entry	Pd	PR$_3$[b]	Additive[b]	**3a**(%)[c]
1	Pd(dba)$_2$	PPh$_3$ (10)	–	0
2	Pd(dba)$_2$	PCy$_3$ (10)	–	0
3	Pd(dba)$_2$	P(*t*-Bu)$_3$ (10)	–	0
4	Pd(dba)$_2$	dppm (5)	–	1
5	Pd(dba)$_2$	dppe (5)	–	3
6	Pd(dba)$_2$	dppp (5)	–	5
7	Pd(dba)$_2$	dppb (5)	–	2
8	Pd(dba)$_2$	dppf (5)	–	4
9	Pd(dba)$_2$	Xantphos (5)	–	1
10	Pd(dba)$_2$	dppp (5)	AcOH (10)	3
11	Pd(dba)$_2$	dppp (5)	TsOH (5)	5
12	PdCl$_2$	dppp (5)	–	0
13	PdCl$_2$(MeCN)$_2$	dppp (5)	–	0
14	[PdCl(C$_3$H$_5$)$_2$]$_2$	dppp (5)	–	0
15	Pd(acac)$_2$	dppp (5)	–	0
16	Pd(OAc)$_2$	dppp (5)	–	18
17	Pd(OAc)$_2$	dppp (5)	Zn (10)	44
18	Pd(OAc)$_2$	dppp (5)	Zn (20)	82
19	Pd(OAc)$_2$	dppp (5)	Zn (50)	92
20	Pd(OAc)$_2$	dppp (5)	Zn (100)	92
21	Pd(OAc)$_2$	dppp (5)	Zn (150)	99 (94)[d]
22	Pd(OAc)$_2$	dppp (5)	Mg (150)	65
23	Pd(OAc)$_2$	dppp (5)	Mn (100)	29
24	Pd(OAc)$_2$	dppp (5)	SnCl$_2$	0
25	Pd(OAc)$_2$	dppp (5)	Fe (150)	0
26[e]	Pd(OAc)$_2$	dppp (5)	Zn (150)	11

[a] Unless otherwise noted, **1a** (1.0 mmol), **2** (0.5 mmol), and CO (1 atm) was treated in toluene (0.5 mL) at 100 °C for 24 h.
[b] mol % is shown in parentheses.
[c] GLC yield.
[d] Isolated yield.
[e] DBA (10 mol %) was added.

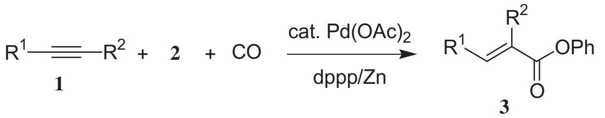
The results of reactions of some alkynes **1** with **2** and CO under the optimized conditions are summarized in Table 2. Unlike the case of reaction by Pd(PPh$_3$)$_4$-catalyzed carbonylation of terminal alkyne by phenols,[4] the reaction using aliphatic terminal alkyne **1b** produced only 22% of **3b** and 4% of **3b**′ along with complicated by-products (entry 1). On the other hand, the treatment with diphenyl acetylene (**1c**) produced the corresponding adduct **3c** in 91% yield (entry 2). The X-ray crystallographic analyses of **3c** and **3d** demonstrated that the PhOC(O) group and H attached in a *cis*-fashion and, in the case of **3d**, PhOC(O) group was bound at the α-carbon of Ph group, showing that Pd-catalyzed regio- and stereoselective hydrophenoxycarbonylation took place successfully (Figs. 1 and 2).[5–7]

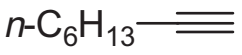
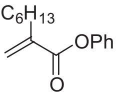
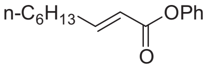
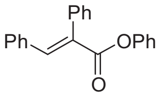
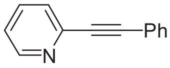
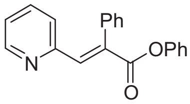
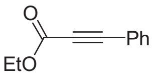
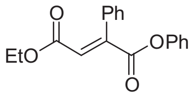
The additions to **1e** and **1f** also were accomplished regio- and stereoselectively to furnish the corresponding adducts **3e** and **3f** in 84% and 59% yields, respectively (entries 4 and 5). The reactions with trimethylsilyl substituted internal alkyne **1g** and **1h** afforded **3g** and **3h** with PhOC(O) group substituted at β-carbon of TMS group (entries 6 and 7). The reaction with 1-phenyl-1-propyne (**1i**) produced a mixture of regioisomer **3i** (63%) and **3i**′ (35%) (entry 8). In stark contrast to these internal alkynes, no reactions occurred with TMSCCC(O)OEt (**1j**), TMSCCTMS (**1k**), and PhCCCH$_2$OMe (**1l**) (not shown).

Although a number of hydroalkoxycarbonylation have been reported,[2,3] attempted reactions using primary, secondary, and tertiary alcohols instead of phenol were all ineffective under the present reaction conditions.

A proposed reaction mechanism for the Pd-catalyzed hydrophenoxycarbonylation of internal alkynes (**1**) by phenol (**2**) and CO is shown in Scheme 2. The reduction of Pd(OAc)$_2$ by Zn in the presence of DPPP would trigger the reaction to give highly active Pd(0)-complex.[8,9] The following oxidative addition of H–O bond of **2** to the Pd(0)-complex would yield phenoxy palladium **5**.[10] Then the insertion of CO into O–Pd bond of **5** would form phenoxycarbonyl complex **6**.[11] The insertion of **1** either into the resultant

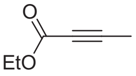
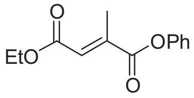
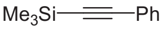
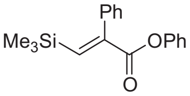
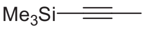
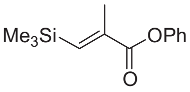
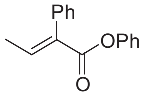
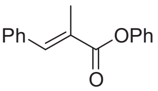
Table 2
Palladium-catalyzed hydrophenoxycarbonylation of **1** with **2a**[a]



Entry	1	Product 3	Yield[b]
1	 **1b**	 **3b**  **3b'**	26%[c] (22/4)
2	 **1c**	 **3c**	91%
3	 **1d**	 **3d**	54%
4	 **1e**	 **3e**	84%

(*continued on next page*)

Table 2 (*continued*)

Entry	**1**	Product **3**		Yield[b]
5	 **1f**	 **3f**		59%
6	 **1g**	 **3g**		53%
7	 **1h**	 **3h**		44%
8	 **1i**	 **3i**	 **3i'**	98% (64/36)

[a] Conditions: **1** (1.0 mmol), **2** (0.5 mmol), CO (1 atm), $Pd(OAc)_2$ (0.05 mmol) DPPE (0.05 mmol), Zn (0.75 mmol), and toluene (0.5 mL) at 100 °C for 24 h.

[b] Isolated yield.

[c] GLC yield. A complicated mixture was also produced.

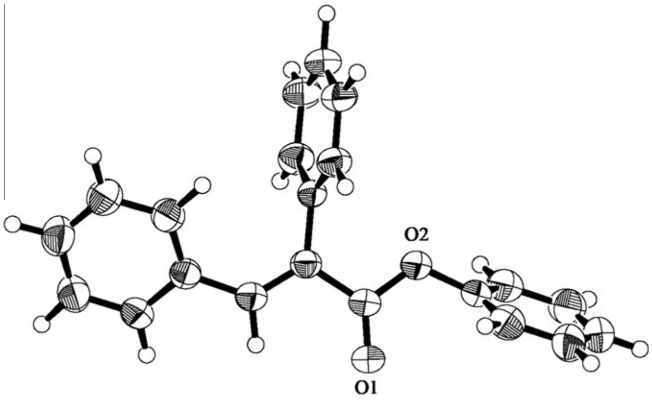


Figure 1. ORTEP diagram of **3c**.

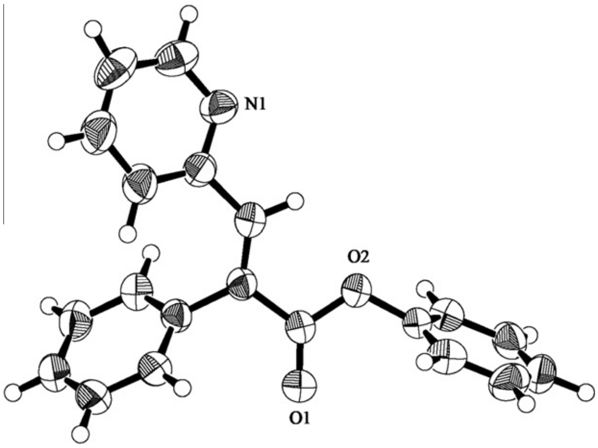
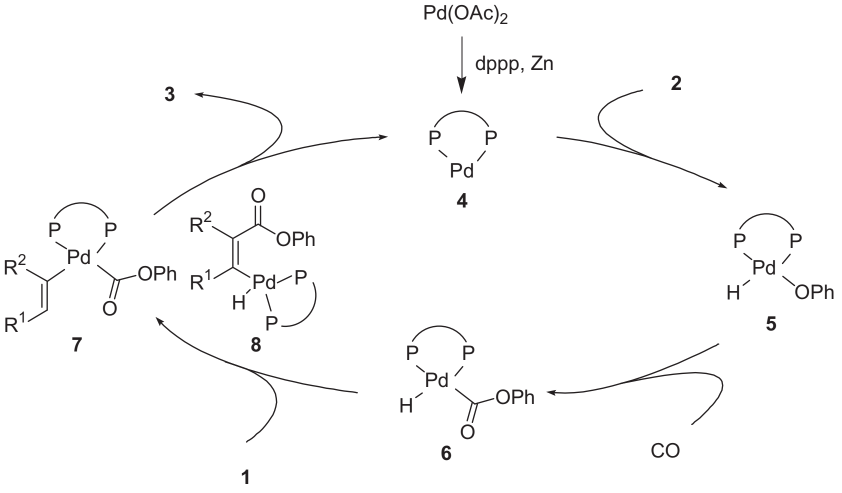


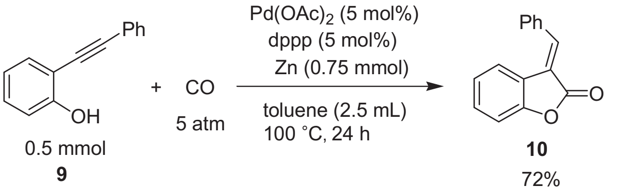
Figure 2. ORTEP diagram of **3d**.



Scheme 2. A possible reaction mechanism.

H–Pd bond of **6** or into the C–Pd bond of **6** would follow to form either **7** or **8**. Finally, C–C or C–H bond-forming reductive elimination of **3** would occur to regenerate Pd(0) complex.

The present phenoxycarbonylation prototype was also applied to the intermolecular cyclization reaction (Eq. 1). When the solution of 2-phenylethynyl-1-phenol (**9**) in the presence of $Pd(OAc)_2$/dppp/Zn was carried out under 5 atm of CO, the anticipated benzofuranone derivative **10** was produced in 72% yield (Eq. 1).[12,13]



(1)

In summary, this study substantiated that some internal alkynes exhibited high catalytic activity as substrates of Reppe carbonylation by phenol and CO to provide α,β-unsaturated arylesters, which are of great importance as synthetic intermediates. The reaction can be achieved by using $Pd(OAc)_2$/dppp and excess amount of Zn. The scope and limitations as well as mechanistic details of the present transformation are under investigation.

Acknowledgment

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4. Itoh, K.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **1992**, *33*, 5369.
5. Crystal data for **3c**: Space group $P2_1/n$ (#14) with $a = 14.6545(3)$ Å, $b = 5.8047(1)$ Å, $c = 19.1876(3)$ Å, $\beta = 97.8266(8)°$, $Z = 4$, $\rho = 1.234$ g/cm^3, $R = 0.186$, and $Rw = 0.151$.
6. Crystal data for **3d**: Space group $P2_1/n$ (#14) with $a = 12.0800(2)$ Å, $b = 5.9938(1)$ Å, $c = 22.8585(5)$ Å, $\beta = 110.5010(8)°$, $Z = 4$, $\rho = 1.291$ g/cm^3, $R = 0.155$, and $Rw = 0.149$.
7. For the determination of regio- and stereochemistry of other **3**, see the Supplementary data for more details.
8. The ^{31}P NMR spectrum of the reaction of $Pd(OAc)_2$ with DPPP in the presence of Zn in toluene-d_8 suggested the quantitative formation of $Pd(dppp)_2$ (a) Portnoy, M.; Milstein, D. *Organometallics* **1993**, *12*, 1655; (b) Mason, M. R.; Verkade, J. G. *Organometallics* **1992**, *11*, 2212.
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13. When the reaction was performed in the presence of 1 atm of CO, 5-end cyclization without incorporating CO took place as a side reaction.