Synthesis of α,β-Alkynyl Esters and Unsymmetrical Maleate Esters Catalyzed by Pd/C; An Efficient Phosphine-Free Catalytic System for Oxidative Alkoxycarbonylation of Terminal Alkynes

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Abstract: Pd/C-catalyzed oxidative alkoxycarbonylation of terminal alkynes using alcohols in the presence of tetrabutylammonium iodide under CO/O_2 (5:1 atm) has been investigated. The desired α,β-alkynyl esters and unsymmetrical maleate esters are formed in good to excellent yields under different reaction conditions. The present protocol eliminates the use of phosphine ligands and has straightforward catalyst recovery. The catalyst was recycled up to six times without significant loss of catalytic activity.

Key words: alkynes, carbonylation, heterogeneous catalysis, palladium, alcohols

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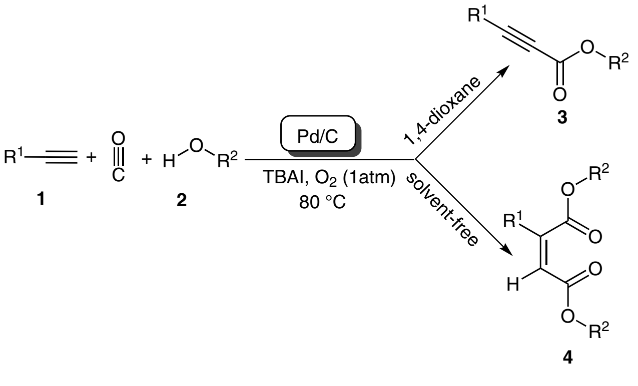
α,β-Alkynyl esters and unsymmetrical maleate esters are important compounds due their application as versatile intermediates in the synthesis of various heterocycles and natural products.[1] A general method for the synthesis of α,β-alkynyl esters involves lithiation of alk-1-ynes and subsequent quenching with chloroformate,[1h] but the use of strong base limits its application with base-sensitive compounds. Another route for the synthesis of α,β-alkynyl esters from alk-1-ynes involves carboxylative coupling of terminal alkynes, allylic halides and carbon dioxide.[2] Tsuji et al. first reported the synthesis of α,β-alkynyl esters by oxidative carbonylation of terminal alkynes using $PdCl_2/CuCl_2$ and NaOAc.[3a] Later, Ishii and co-workers reported a triple catalytic system consisting of $Pd(OAc)_2$, hydroquinone and molybdovanado-phosphate under carbon monoxide and oxygen (CO/O_2, 10:0.5 atm).[3b] In 2004, Yamamoto et al. developed a method to produce α,β-alkynyl esters from alk-1-ynes using a $Pd(OAc)_2/Ph_3P$ catalytic system.[3c]

For the synthesis of unsymmetrical maleate esters, several catalytic systems and oxidizing agents have been designed including $PdCl_2/HgCl_2$,[4a] $PdCl_2/CuCl_2/HCl$,[4b] $PdCl_2$-$CuCl_2$/NaOAc,[4c] PdI_2-KI/NaOAc,[4d] PdI_2-KI/O_2[4e] and $PdBr_2/CuBr$.[4f] However, limiting aspects of these reported methods are the use of air- or moisture-sensitive phosphine ligands, base and acids, high pressure of CO/O_2, use of copper and hydroquinone as oxidant and stoichiometric amounts of various salts such as $CuBr_2$, $CuCl_2$ and $HgCl_2$, difficulties in separation of catalyst from the reaction mixture and its consequent reuse, and low selectivity or low yield of products.

In view of the importance of palladium-catalyzed carbonylation reactions of terminal alkynes,[5] there remains a need for efficient, inexpensive, recyclable, versatile, and environmentally benign catalytic systems for oxidative alkoxycarbonylation of terminal alkynes to produce α,β-alkynyl esters and unsymmetrical maleate esters. Palladium-on-carbon (Pd/C) can be considered as a potential candidate because it can be easily recovered and reused for consecutive reactions and also provides an efficient and economic way to perform coupling reactions.[6] It is not sensitive to air or moisture and would eliminate the need for phosphine ligands. Recently, we reported a mild and recyclable protocol for the oxidative aminocarbonylation of terminal alkynes to synthesize alk-2-ynamides using Pd/C as a heterogeneous, phosphine-free catalytic system.[7]

In a continuation of our research interest in carbonylation reactions,[8] we report herein our findings on the use of Pd/C for the oxidative alkoxycarbonylation of terminal alkynes in the absence of copper and phosphine ligand giving α,β-alkynyl esters **3** and unsymmetrical maleate esters **4** in good to excellent yields (Scheme 1). To the best of our knowledge, no heterogeneous catalyst has previously been reported for the oxidative alkoxycarbonylation of terminal alkynes.



Scheme 1 Oxidative alkoxycarbonylation of terminal alkynes

Initially, we examined the model reaction of phenylacetylene (**1a**) with ethanol (**2a**) under a CO/O_2 atmosphere in the presence of tetrabutylammonium iodide (TBAI) in 1,4-dioxane using 10% Pd/C as catalyst (Table 1). Various heterogeneous catalytic systems including 10% Pd/C, and polymer-supported palladium N-heterocyclic carbene

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catalyst (PS-Pd-NHC) were screened but we found that 10% Pd/C delivered the best catalytic performance.[9] Choice of solvent has been shown to have a significant influence on oxidative carbonylations[6f] and so we surveyed the use of various solvents (Table 1, entries 1–4). The catalytic activity was poor in nonpolar solvents such toluene, but activity was significantly higher in polar solvents such as THF and 1,4-dioxane, and the best result was obtained by using 1,4-dioxane (Table 1, entry 4). Additives containing iodide along with molecular oxygen play an important role in Pd/C catalyzed oxidative carbonylation reactions,[6c,6f,7,10] therefore, we screened various iodide additives such as KI, TBAI, and the latter was found to provide the maximum yield of the desired product (Table 1, entries 4 and 5). We also screened bromide-containing additives such as tetrabutylammonium bromide (TBAB), and KBr, but these provided lower yields of product (Table 1, entries 6 and 7). This might be due to the 'softer' binding nature of iodide compared with the other halides.[10c] It was observed that, in the absence of additive, there was no product formation (Table 1, entry 8). At 60–70 °C the product yield was negligible (Table 1, entries 9 and 10), whereas at 80 °C the yield increased to 95% (Table 1, entry 4). Further increase in temperature had no profound effect on the yield (Table 1, entry 11). It was observed that a ratio of 5:1 atm seemed to be the optimum pressures for CO/O_2. Next, we examined the effect of reaction time (Table 1, entries 12 and 13) and it was observed that maximum yield of the desired product was obtained after 8 hours (Table 1, entry 4).

The optimized conditions were subsequently applied to the carbonylation of terminal alkynes with various primary aliphatic, allylic, benzyl, secondary, aromatic and sterically hindered alcohols (Table 2). It was observed that oxidative carbonylative of phenyl acetylene with various primary aliphatic alcohols afforded good to very good yields (Table 2, entries 1–4); benzyl alcohols coupled smoothly to give the corresponding α,β-alkynyl esters derivatives in excellent yield (Table 2, entry 5), while allylic alcohols, secondary alcohols and phenol were found to be unreactive. The scope of protocol was also investigated with various aliphatic alicyclic, aromatic, and heteroaromatic substituted terminal alkynes. Ethynylcyclohexane and oct-1-yne coupled with ethanol, furnishing moderate yield of products (Table 2, entries 6 and 7). Aromatic alkynes with electron-donating and electron-accepting substituents such as 4-ethynylanisole, 4-ethynyltoluene, 4-ethynyl-α,α,α-trifluorotoluene, 4-ethynyl-*N*,*N*-dimethylaniline and 1-ethynylpyrene all reacted with ethanol to provide the corresponding α,β-alkynyl esters in excellent yield (Table 2, entries 8–12). The heteroaromatic alkyne

Table 1 Optimization of the Pd/C-Catalyzed Oxidative Alkoxycarbonylation of Phenylacetylene (**1a**) with Ethanol (**2a**)

Entry	Solvent	Additive	Temp (°C)	Time (h)	Yield (%)[b]
Effect of Solvent					
1	DMSO	TBAI	80	8	0
2	toluene	TBAI	80	8	55
3	THF	TBAI	80	8	85
4	1,4-dioxane	TBAI	80	8	95
Effect of Additive					
5	1,4-dioxane	KI	80	8	92
6	1,4-dioxane	TBAB	80	8	87
7	1,4-dioxane	KBr	80	8	90
8	1,4-dioxane	–	80	8	–
Effect of Temperature					
9	1,4-dioxane	TBAI	60	8	53
10	1,4-dioxane	TBAI	70	8	82
11	1,4-dioxane	TBAI	90	8	96
Effect of Time					
12	1,4-dioxane	TBAI	80	10	95
13	1,4-dioxane	TBAI	80	6	75

[a] Reaction conditions: phenylacetylene (1 mmol), EtOH (0.5 mL), 10% Pd/C (10 mol%), CO/O_2 (5:1 atm), TBAI (0.6 mmol), 1,4-dioxane (10 mL), 80 °C, 8 h.
[b] GC yield.

3-ethynyl pyridine gave the desired product in 79% yield (Table 2, entry 13).

Further investigations using similar reaction conditions were performed in ethanol and methanol instead of 1,4-dioxane, wherein we observed the formation of maleate esters by double carbonylation. The major product was the *Z*-isomer with a trace of *E*-isomer being observed. The ratios of *Z*- and *E*-isomers were determined by GC analysis and the stereochemistries were assigned on the basis of the chemical shift of the olefinic proton.[1j,11] Phenylacetylene gave diethyl 2-phenylmaleate and dimethyl 2-phenylmaleate in ethanol and methanol, respectively, in excellent yields (Table 2, entries 14 and 15). Aliphatic alkyne **1b** showed similar reactivity, affording moderate to good yields (Table 2, entry 16).

Table 2 Oxidative Alkoxycarbonylation of Alk-1-ynes with Alcohols[a]

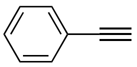
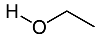
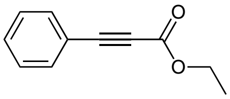
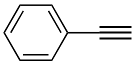
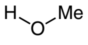
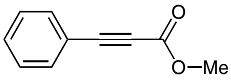
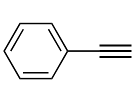
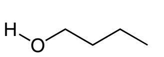
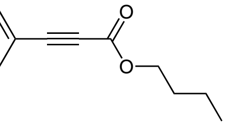
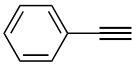
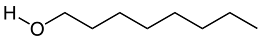
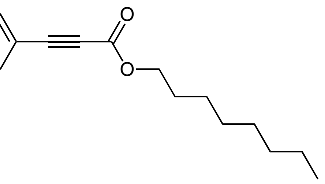
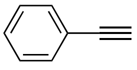
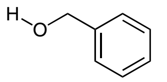
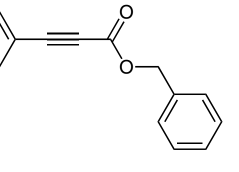
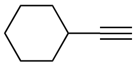
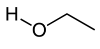
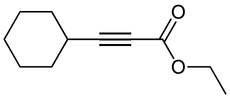
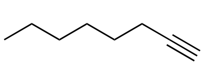
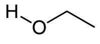
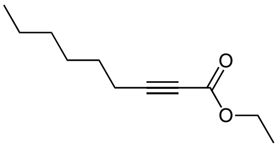
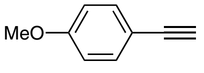
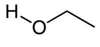
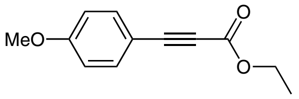
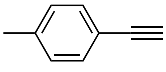
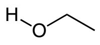
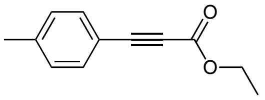
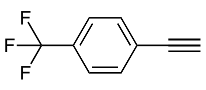
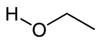
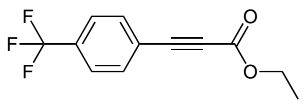
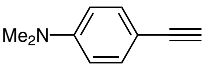
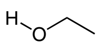
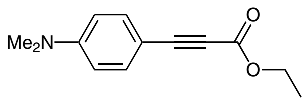
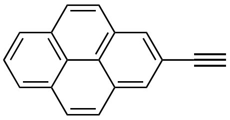
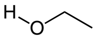
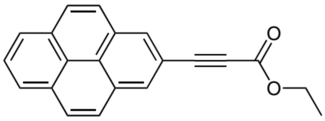
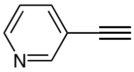
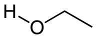
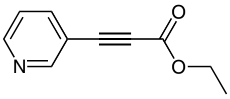
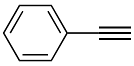
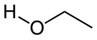
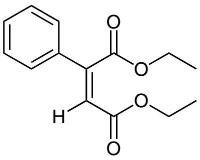
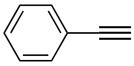
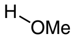
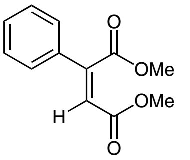
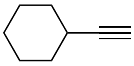
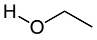
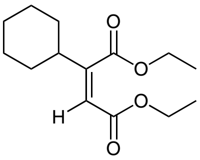
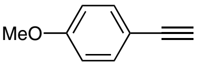
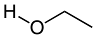
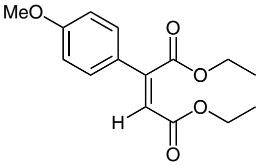
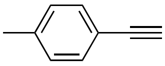
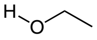
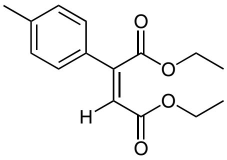
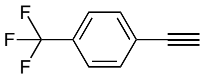
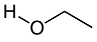
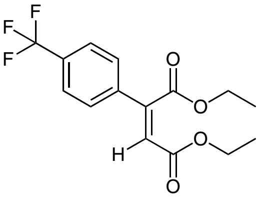
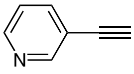
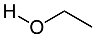
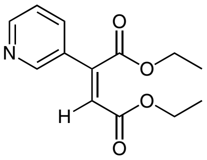
Entry	Alk-1-yne		Alcohol		Product		Yield (%)[b]
1	**1a**		**2a**		**3a**		94
2	**1a**		**2b**		**3b**		90
3	**1a**		**2c**		**3c**		82
4	**1a**		**2d**		**3d**		76
5	**1a**		**2e**		**3e**		78
6	**1b**		**2a**		**3f**		60
7	**1c**		**2a**		**3g**		63
8	**1d**		**2a**		**3h**		86
9	**1e**		**2a**		**3i**		88
10	**1f**		**2a**		**3j**		83
11	**1g**		**2a**		**3k**		90

Table 2 Oxidative Alkoxycarbonylation of Alk-1-ynes with Alcohols[a] (continued)

Entry	Alk-1-yne		Alcohol		Product		Yield (%)[b]
12	**1h**		**2a**		**3l**		85
13	**1i**		**2a**		**3m**		79
14[c]	**1a**		**2a**		**4a**		91
15[d]	**1a**		**2b**		**4b**		83
16[c]	**1b**		**2a**		**4c**		70
17[c]	**1d**		**2a**		**4d**		85
18[c]	**1e**		**2a**		**4e**		90
19[c]	**1f**		**2a**		**4f**		93
20[c]	**1i**		**2a**		**4g**		89

[a] Reaction conditions: alk-1-yne (1 mmol), alcohol (0.5 mL), 10% Pd/C (10 mol%), CO/O_2 (5:1 atm), TBAI (0.6 mmol), 1,4-dioxane (10 mL), 80 °C, 8 h.

[b] Isolated yield.

[c] EtOH used as solvent, 4 h reaction time.

[d] MeOH used as solvent, 4 h reaction time.

It can be seen that electron-donating (OMe and Me) and electron-withdrawing (CF_3) substituted aromatic or heterocyclic aromatic substrates show excellent selectivity towards *Z*-isomer formation, giving very good yields of the desired product (Table 2, entries 17–20).

The catalyst showed remarkable recyclability, being used in up to six consecutive cycles without loss of activity or selectivity (Figure 1). We also performed the reaction on larger scale (5 mmol of **1a**) and carried out ICP-AES analysis of the bulk reaction, finding palladium leaching to be below detectable levels.

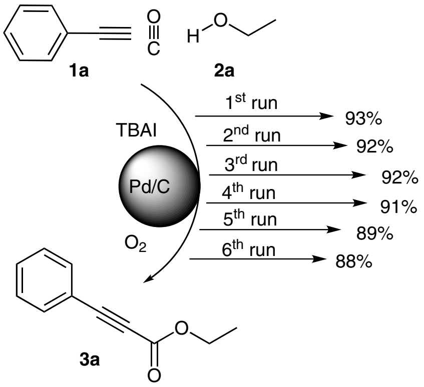


Figure 1 Recycle study of oxidative alkoxycarbonylation of terminal alkyne

In summary, we have developed a heterogeneous, recyclable protocol for the preparation of α,β-alkynyl esters and unsymmetrical maleate esters by oxidative alkoxycarbonylation of terminal alkynes.[12] The reaction proceeds under mild conditions using simple starting materials. The catalytic system has competitive advantages in that it eliminates the use of phosphine ligands, bases, and acids, and enables easy catalyst recovery allowing several cycles of reuse without significant loss in catalytic activity or selectivity.

Acknowledgment

We are grateful to Dr. C.V. Rode from the National Chemical Laboratory, Pune for providing HRMS analysis of products. S.T.G. is grateful to the Council of Scientific and Industrial Research, New Delhi for providing a Research Fellowship.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(12) **Oxidative Alkoxycarbonylation of Terminal Alkynes; General Procedure:** To a 100 mL stainless steel autoclave, the alk-1-yne (1 mmol), the alcohol (0.5 mL), 10% Pd/C (10 mol%), TBAI (0.6 mmol), and 1,4-dioxane (10 mL) were added. The autoclave was closed and pressurized with oxygen (1 atm) and CO (5 atm) without flushing. The reaction mixture was stirred (550 rpm) and heated at 80 °C

for 8 h. The reactor was then cooled to r.t. and the pressure released. The reaction mixture was filtered and the filtrate was washed with saturated sodium thiosulphate (3 × 4 mL), dried over Na_2SO_4, filtered and the solvent evaporated. The crude product was purified by column chromatography.

Ethyl 3-[4(Trifluoromethyl)phenyl]propiolate (3j):[13] Yield: 83%; colorless liquid; IR (neat): 2253, 1711 cm^{-1}; GCMS (EI, 70 eV): *m*/*z* (%) = 242 (7) [M^+], 223 (3), 197 (100), 170 (67), 147 (7); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.71–7.59 (m, 4 H, ArC*H*), 4.32 (q, *J* = 6.9 Hz, 2 H, C*H*$_2$CH$_3$), 1.46 (t, *J* = 6.9 Hz, 3 H, CH$_2$C*H*$_3$).

Ethyl 3-(Pyren-2-yl)propiolate (3l): Yield: 85%; yellowish solid; IR (KBr): 2205, 1704 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.57 (d, *J* = 9.1 Hz, 1 H, ArC*H*), 8.27–8.04 (m, 8 H, ArC*H*), 4.40 (q, *J* = 7.1 Hz, 2 H, C*H*$_2$CH$_3$), 1.44 (t, *J* = 7.1 Hz, 3 H, CH$_2$C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.30, 133.26, 132.63, 130.69, 130.63, 130.48, 129.14, 129.02, 126.74, 126.23, 126.13, 125.99, 124.53, 124.11, 123.76, 123.53, 113.08, 85.94, 85.59, 62.05, 14.17; HRMS (ESI): *m*/*z* calcd. for $[C_{21}H_{14}O_2Na]^+$: 321.0886; found: 321.0879.

Diethyl 2-(Pyridin-3-yl)maleate (4g): Yield: 89%; yellowish liquid; IR (neat): 1723, 1629 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.76 (d, *J* = 1.8 Hz, 1 H, ArC*H*), 8.67–8.65 (m, 1 H, ArC*H*), 7.86–7.82 (m, 1 H, ArC*H*), 7.41–7.37 (m, 1 H, ArC*H*), 6.35 (s, 1 H, COCH=CCO), 4.43 (q, *J* = 6.9 Hz, 2 H, CH$_3$C*H*$_2$O), 4.26 (q, *J* = 6.9 Hz, 2 H, CH$_3$C*H*$_2$O), 1.38 (t, *J* = 6.9 Hz, 3 H, C*H*$_3$CH$_2$O), 1.33 (t, *J* = 6.9 Hz, 3 H, C*H*$_3$CH$_2$O); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.92, 164.44, 150.60, 147.40, 145.12, 134.60, 130.11, 123.92, 120.14, 62.32, 61.38, 14.22, 14.06; GCMS (EI, 70 eV): *m*/*z* (%) = 249 (13) [M^+], 220 (78), 204 (55), 192 (16), 176 (91), 148 (100), 132 (25), 120 (18), 104 (56), 76 (33), 50 (24); HRMS (ESI): *m*/*z* calcd. for $[C_{13}H_{15}O_4N + H]^+$: 250.1074; found: 250.1070.

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