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Selectivity Controlled Palladium-Catalyzed Carbonylative Synthesis of Propiolates and Chromenones from Phenols and Alkynes

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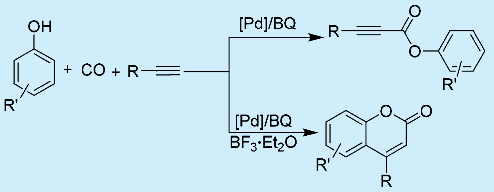
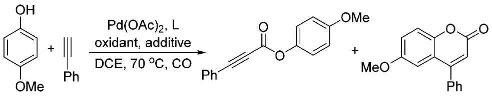
Supporting Information

ABSTRACT: An interesting selectivity-controlled palladium-catalyzed oxidative carbonylation procedure for the synthesis of propiolates and chromenones has been developed. Starting from phenols and alkynes, under slightly different conditions, various propiolates and chromenones can be isolated in moderate to good yields. Additionally, this also presents the first example of direct carbonylative annulation of nonpreactivated phenols and terminal alkynes to produce chromenones.



One of the key goals in organic chemistry is the development of new and selective catalytic processes for the synthetic toolkit. It is even more interesting that different types of products can be selectively produced from the same substrates under slightly different reaction conditions. Such types of methodologies can increase the diversity of the products obtained and also enrich the knowledge in reactivity tuning and new catalysts design.[1]

Table 1. Optimization of the Reaction Conditions[a]



1a **2a** **3aa** **4aa**

entry	ligand	oxidant	additive	3aa yield(%)	4aa yield(%)
1	PPh_3	$Cu(OAc)_2$	-	-	-
2	PPh_3	AgOAc	-	-	-
3	PPh_3	$K_2S_2O_8$	-	-	-
4	PPh_3	BQ	-	45	-
5	PPh_3	DDQ	-	-	-
6	PPh_3	DMBQ	-	-	-
7	Xantphos	BQ	-	31	-
8	DPEphos	BQ	-	42	-
9	Phen	BQ	-	-	-
10	Xphos	BQ	-	40	-
11	DPPF	BQ	-	56	-
12[b]	$Pd(dppf)Cl_2$	BQ	-	68	-
13[b]	$Pd(dppf)Cl_2$	BQ	TFA	<10	-
14[b]	$Pd(dppf)Cl_2$	BQ	HOAc	<10	-
15[b]	$Pd(dppf)Cl_2$	BQ	HOTf	-	-
16[b]	$Pd(dppf)Cl_2$	BQ	$SnCl_2$	15	-
17[b]	$Pd(dppf)Cl_2$	BQ	$(C_6F_5)_3B$	-	-
18[b]	$Pd(dppf)Cl_2$	BQ	$HBF_4{\cdot}Et_2O$	<10	<5
19[b]	$Pd(dppf)Cl_2$	BQ	$BF_3{\cdot}Et_2O$	<10	10
20[c]	DPPF	BQ	$BF_3{\cdot}Et_2O$	-	61
21[c]	DPPF	BQ	-	50	-
22[d]	DPPF	BQ	$BF_3{\cdot}Et_2O$	-	-

[a] Phenol (0.2 mmol), alkyne (0.4 mmol), $Pd(OAc)_2$ (5 mol %), additive (50 mol %), PPh_3 (10 mol %) other ligand (5 mol %), oxidant (0.3 mmol), DCE (2 mL), CO (20 bar), 70 °C, 24 h, GC yield. [b] $Pd(dppf)Cl_2$ (5 mol %) instead of $Pd(OAc)_2$ (5 mol %) and DPPF (5 mol %). [c] $Pd(TFA)_2$ (5 mol %). [d] $Pd(CH_3CN)_4(CF_3SO_3)_2$ (5 mol %).

Among all the organic transformation methods, palladium-catalyzed carbonylative reactions have now emerged as a powerful platform in organic chemistry.[2] Various carbonyl-containing compounds can be easily prepared by choosing the proper substrates. In the case of using terminal alkynes as the starting materials, valuable propiolic products can be prepared.[3] Concerning the coupling partners with terminal alkynes, arylboronic acids,[4] amines,[5] and aliphatic alcohols[6] have been achieved in recent years. However, the use of phenols as the coupling partner has not been achieved yet. The main reason is the low nucleophilicity of phenols as well as the potential to be easily oxidized. To date, the corresponding propiolates are mainly prepared by the reaction of arylpropyolic acids with phenols in the presence of an excess amount of activating reagents.

Additionally, chromenone is an important class of heterocycles with broad applications in pharmaceutical and agrochemical industries.[7] Without surprise, carbonylative procedures have successfully been explored in the synthesis of chromenones.[8] These methodologies require the use of 2-iodophenols, 2-alkynylphenols, 2-alkenylphenols, or *o*-hydroxyacetophenones as the starting materials. More recently, we reported an iridium-catalyzed carbonylative cyclization of simple phenols with internal alkynes to produce chromenones.[9] The selectivity can be tuned by choosing the proper phosphine ligand. However, only disubstituted products can be obtained and we failed with terminal alkynes.

Based on our continuous interest in carbonylative reactions, we became interested in studying the challenges discussed above. With the success of carbonylation of phenols and terminal alkynes, propiolates and chromenones can be produced.

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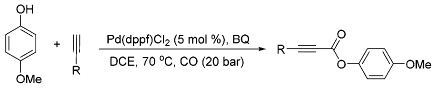
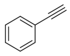
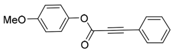
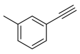
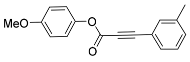
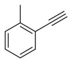
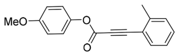
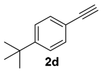
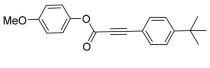
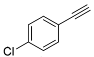
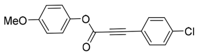
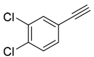
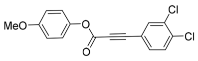
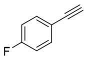
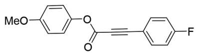
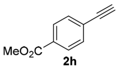
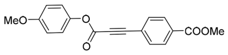
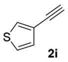
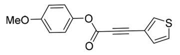
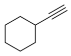
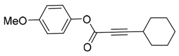
Table 2. Pd-Catalyzed Carbonylative Propiolate Synthesis: Substrate Scope of Alkynes[a]

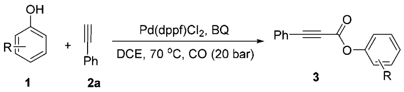


1a **2** **3**

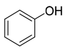
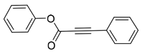
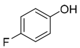
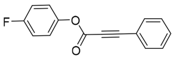
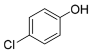
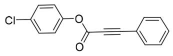
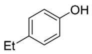
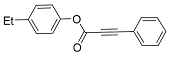
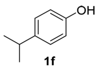
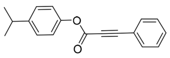
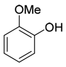
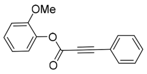
entry	alkynes	products	yield (%)
1	 **2a**	 **3aa**	68
2	 **2b**	 **3ab**	65
3	 **2c**	 **3ac**	67
4	 **2d**	 **3ad**	71
5	 **2e**	 **3ae**	61
6	 **2f**	 **3af**	63
7	 **2g**	 **3ag**	62
8	 **2h**	 **3ah**	69
9	 **2i**	 **3ai**	59
10	 **2j**	 **3aj**	65

[a]Phenol (0.2 mmol), alkynes (0.4 mmol), Pd(dppf)Cl$_2$ (5 mol %), BQ (0.3 mmol), DCE (2 mL), CO (20 bar), 70 °C, 24 h, isolated yield.

Table 3. Pd-Catalyzed Carbonylative Propiolate Synthesis: Substrate Scope of Phenols[a]



1 **2a** **3**

entry	phenols	products	yield (%)
1	 **1b**	 **3ba**	51
2	 **1c**	 **3ca**	52
3	 **1d**	 **3da**	53
4	 **1e**	 **3ea**	53
5	 **1f**	 **3fa**	51
6	 **1g**	 **3ga**	55

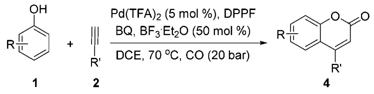
[a]Phenol (0.2 mmol), alkynes (0.4 mmol), Pd(dppf)Cl$_2$ (5 mol %), BQ (0.3 mmol), DCE (2 mL), CO (20 bar), 70 °C, 24 h, isolated yield.

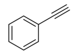
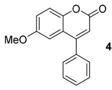
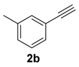
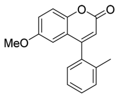
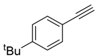
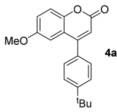
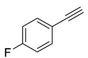
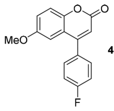
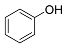
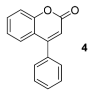
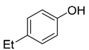
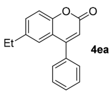
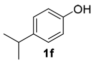
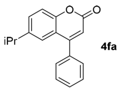
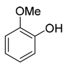
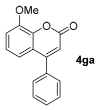
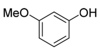
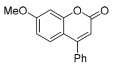
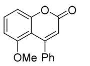
Initially, 4-methoxyphenol (**1a**) and phenylacetylene (**2a**) were chosen as the model substrates using Pd(OAc)$_2$ as the catalyst and DCE as the solvent to establish this carbonylation procedure (Table 1). The reaction was totally ineffective when different commonly applied oxidants such as Cu(OAc)$_2$, AgOAc, and K$_2$S$_2$O$_8$ were employed (Table 1, entries 1−3). To our delight, 4-methoxyphenyl 3-phenylpropiolate (**3aa**) can be detected with BQ as the oxidant and PPh$_3$ as the ligand (Table 1, entry 4). Encouraged by this exciting result, we then tested DDQ and DMBQ (DMBQ, 2,5-dimethyl-1,4-benzoquinone) as the oxidant, but could not find any of the desired product (Table 1, entries 5−6). Then variations of ligands were carried out subsequently (Table 1, entries 7−11; XantPhos, 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene; DPEPhos, bis-(2-diphenylphosphinophenyl)ether; Phen, 1,10-phenanthrolin; DPPF, 1,1′-bis(diphenylphosphino)ferrocene; XPhos, 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl). The yields can be improved by using DPPF as the ligand (Table 1, entry 11), and 68% of propiolate can be formed with Pd(dppf)Cl$_2$ as the catalyst (Table 1, entry 12). In order to obtain the chromenone product, different additives were checked (Table 1, entries 13−19), and 10% of the 6-methoxy-4-phenyl-2*H*-chromen-2-one (**4aa**) can be achieved when using BF$_3$·Et$_2$O as the additive (Table 1, entry 19). Based on these conditions, we also tested the influence of palladium catalysts (Table 1, entries 20−22) and found the yield can be increased to 61% when using Pd(TFA)$_2$ as the catalyst (Table 1, entry 20). Fine-tuning loadings of catalyst and acid could not further improve the yield of the desired produced. The choice of solvent and CO pressure is critical as well. Dramatically decreased yields of the products were observed when using DMF, DMSO, toluene, or 1,4-dioxane as the solvent or under lower or higher CO pressure. Here, it is also important to mention that hydration of the alkyne could occur in the presence of acid when the desired reaction did not proceed.

With the optimum conditions in hand, the carbonylative oxidative cross-coupling of different terminal alkynes with 4-methoxyphenol to construct the corresponding propiolates were first explored. As depicted in Table 2, different aromatic alkynes can be effectively transformed with 4-methoxyphenol and afford the corresponding products in moderate to good yields. 3-Ethynylthiophene can be applied as well and gave the corresponding propiolate derivative in good yield (Table 2, **3ai**). Ethynylcyclohexane as an example of an aliphatic alkyne can be reacted successfully as well with good results under our standard conditions (Table 2, **3aj**). Subsequently, different phenols were also tested (Table 3). Phenols with electron-donating or -withdrawing functional groups are all suitable substrates for this methodology. Good yields of the desired products can be achieved in all the tested cases.

Inspired by the good results of propiolates synthesis, we turned our attention to the substrate scope of oxidative carbonylation with phenols and alkynes to synthesize different chromenones (Table 4). Alkynes with electron-donating or

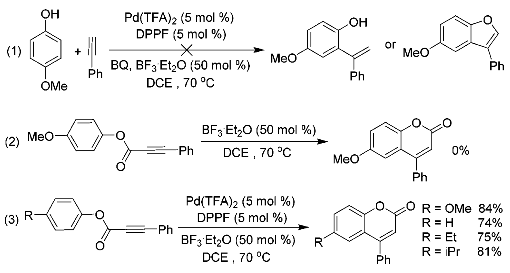
Table 4. Pd-Catalyzed Carbonylative Coumarins Synthesis[a]



entry	substrates	products	yield(%)
1	 2a	 4aa	58 49^b
2	 2b	 4ab	55
3	 2d	 4ad	57
4	 2g	 4af	59
5^b	 1b	 4ba	43
6^b	 1e	 4ea	46
7^b	 1f	 4fa	47
8^c	 1g	 4ga	45
9	 1h	 4ha  4ha'	54 (4ha:4ha' = 1:2)

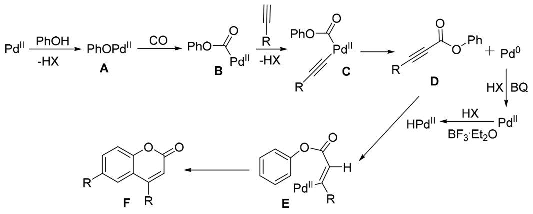
[a] Phenol (0.2 mmol), alkynes (0.4 mmol), Pd(TFA)$_2$ (5 mol %), DPPF (5 mol %), BF$_3$·Et$_2$O (50 mol %), BQ (0.3 mmol), DCE (2 mL), CO (20 bar), 70 °C, 24 h, isolated yield. [b] 1 mmol scale. [c] Phenols (0.2 mmol), alkyne (0.4 mmol), Pd(TFA)$_2$ (5 mol %), DPPF (5 mol %), BQ (0.3 mmol), DCE (2 mL), CO (20 bar), 70 °C, 24 h, then BF$_3$·Et$_2$O (50 mol %), 70 °C, 24 h, isolated yield.

Scheme 1. Control Experiments



-withdrawing functional groups are all suitable substrates for this methodology. Good yields can be achieved in all the tested cases. Different phenols were also tested, and except for the electron-withdrawing functional groups, good yields can be achieved. However, in the case of meta-substituted phenol being applied, a mixture of two isomers was obtained (Table 4, entry 9). It is also important to mention that a 1 mmol scale experiment was carried out as well and 49% of the desired product was obtained (Table 4, entry 1).

Scheme 2. Plausible Reaction Mechanistic



In order to gain insight into the reaction pathway, control experiments were performed (Scheme 1). Under identical conditions, but in the absence of carbon monoxide, no reaction of phenol with phenylacetylene could be observed (Scheme 1, eq 1). No cyclization product could be detected in the presence of only BF$_3$·Et$_2$O (Scheme 1, eq 2). To our delight, propiolates can be cyclized with the addition of a palladium catalyst and good yields of chromenones can be achieved in the absence of BQ (Scheme 1, eq 3).

Based on the above mechanistic studies and according to the existing knowledge on palladium-catalyzed oxidative carbonylation of alkynes, we propose the reaction pathway, as shown in Scheme 2. Initially, phenol with Pd^{II} generated PhOPd^{II} species **A**, and then the CO insertion into the Pd−O bond allowing the formation of complex **B**. Intermediate **B** then reacted with alkyne, to give the intermediate **C** which eliminates the terminal propiolate product **D**. The formed Pd(0) will be oxidized back to Pd(II) by BQ. While in the presence of BF$_3$·Et$_2$O, palladium hydride will be generated and added to the propiolate to give intermediate **E**, which will give the final chromenone product. However, for the cyclization step, an electrophilic addition mechanism can not be excluded.

In conclusion, an interesting selectivity controlled reaction for the direct synthesis of propiolates and chromenones from simple phenols and alkynes has been developed. With palladium as the catalyst, various desired propiolates and chromenones were prepared in moderate to good yields. Remarkably, these represent the first examples of oxidative carbonylation of phenols and terminal alkynes to propiolates and also the direct carbonylative annulation of simple phenols and terminal alkynes to produce chromenones.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01368.

Additional experimental results and procedures and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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