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ARTICLE TYPE

Synthesis of Diarylalkynes *via* Tandem Sonogashira/Decarboxylative Reaction of Aryl Chlorides with Propiolic Acid

Xiang Li, Fan Yang* and Yangjie Wu*

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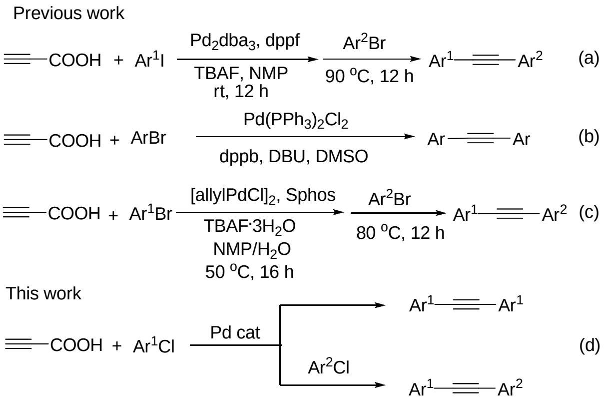
A facile and efficient protocol for one-pot synthesis of diarylalkynes *via* tandem Sonogashira/decarboxylative coupling has been developed. The remarkable features of this reaction include using commercially available aryl chlorides as starting materials and taking the propiolic acid instead of expensive terminal alkynes as an acetylene source.

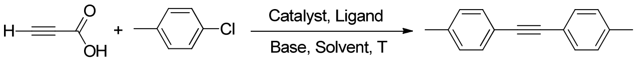
Palladium-catalyzed Sonogashira reaction has become one of the most powerful and facile methods for the synthesis of internal alkynes,[1] which has been widely applied in the fields of organic synthesis,[2] pharmaceuticals,[3] and material science.[4] Sonogashira reaction typically utilizes terminal alkynes as the coupling partner. However, terminal alkynes bearing functional groups are not commercially available and usually expensive, which hampered its large scale industrial applications.

In recent years, transition metal-catalyzed decarboxylative Sonogashira reaction of arylpropiolic acids with aryl halides has emerged an alternative route to Sonogashira reaction for the synthesis of internal alkynes.[5] Nevertheless, arylpropiolic acids still suffered from the high-cost and multistep synthetic route. To address these limitations, propiolic acid, which is usually commercial available and stable as well as easy to store, could act as the an acetylene source to fulfill the synthesis of various diarylalkynes.[6] In 2008, Lee and co-workers reported the first example for the synthesis of diarylalkynes using the propiolic acid and aryl iodides or bromides as the starting materials (Scheme 1a and b).[6a,b] Recently, Gooßen's group realized the efficient synthesis of unsymmetrical diarylalkynes from two different aryl bromides and propiolic acid (Scheme 1c).[6c] However, the substrate scope is mainly limited to aryl iodides and bromides. The reaction of the more commercially available aryl chlorides is still challenging but highly desirable, and the relative reports remain rare.[7,8] Moreover, the reported reaction procedure usually includes two isolated steps and must add the two aryl halides in sequential process, which may make the operation more complicated. Therefore, we envisioned to develop a simple, economically convenient catalytic system using aryl chlorides and propiolic acid as the starting materials. Especially in the preparation of unsymmetrical diarylalkynes, two different aryl chlorides along with the propiolic acid would be added to the reaction system in one-step (Scheme 1d).



Scheme 1 Sonogashira/decarboxylative coupling of propiolic acid with aryl halides

Table 1 Reaction of propiolic acid with 4-chlorotoluene[a]



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

Entry	Catalyst	Ligand	Yield (%)[b]
1	$PdCl_2$	PCy_3	11
2	$PdCl_2$	PPh_3	<10
3	$PdCl_2$	Ruphos	28
4	$PdCl_2$	Davephos	15
5	$PdCl_2$	Johnphos	18
6	$PdCl_2$	CyJohnphos	23
7	**$PdCl_2$**	**Xphos**	**61**
8[c]	$PdCl_2$	Xphos	53
9[d]	$PdCl_2$	Xphos	56
10[e]	$PdCl_2$	Xphos	-
11	-	Xphos	-
12	$Pd(OAc)_2$	Xphos	18
13[f]	Pd_2dba_3	Xphos	33
14	$PdCl_2(PPh_3)_2$	Xphos	15

[a] Reaction conditions: propiolic acid **1a** (0.4 mmol), 4-chlorotoluene **2a** (1.0 mmol), palladium catalyst (2 mol%), ligand (4 mol%), DBU (4 equiv), DMSO (2 mL) at 120 °C for 24 h under a nitrogen atmosphere. [b] Isolated yield. [c] At 100 °C. [d] At 140 °C. [e] Under air. [f] 1 mol% of Pd_2dba_3 was used.

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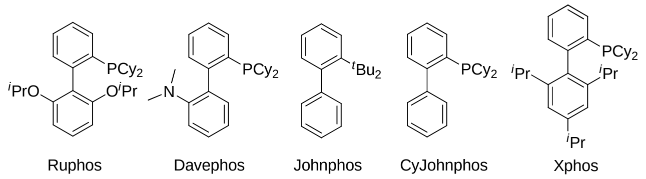
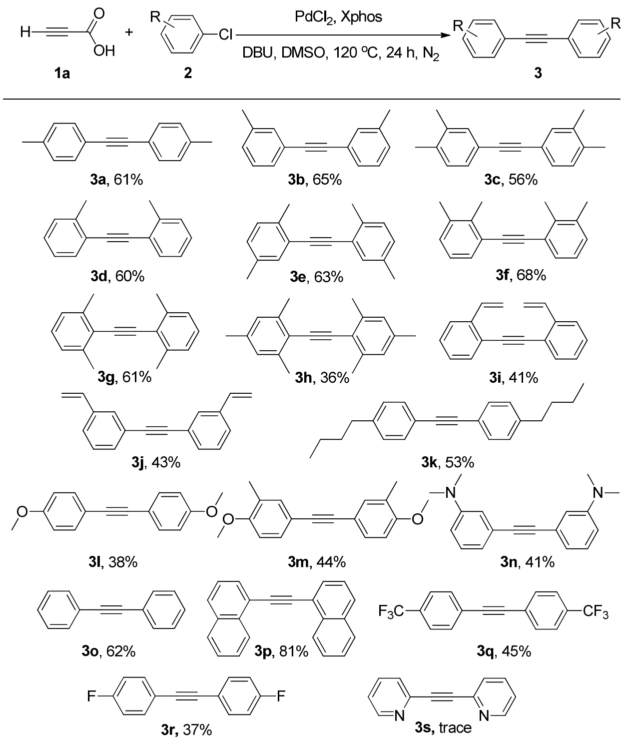


Figure 1. Phosphine ligands

Our initial investigation was performed on the screening the effect of bases, additives and solvents (See SI), and we found that the reaction of 4-chlorotoluene with propiolic acid in the presence of DBU in DMSO under catalysis of $PdCl_2/PCy_3$ could afford desired product **3a** in a low yield of 11% (Table 1, entry 1). Then, a series of commercially available ligands (e.g., PPh_3, PCy_3, Ruphos, Davephos, Johnphos, CyJohnphos and Xphos) were checked (Figure 1), and the product could be obtained in a moderate but acceptable yield of 61% by using Xphos as the ligand (Table 1, entries 2–7). However, lower yields of 53% and 56% were obtained when the temperature decreased to 100 °C or increased to 140 °C, respectively (Table 1, entries 8 and 9). Finally, some controlling experiments were also carried out. For example, the reaction did not occur at all under air or palladium-free conditions, and other palladium sources such as $Pd(OAc)_2$, Pd_2dba_3, or $PdCl_2(PPh_3)_2$ did not exhibit higher catalytic activity (Table 1, entries 10–14).

Table 2 Tandem Sonogashira/decarboxylative reaction of propiolic acid with aryl chlorides^a

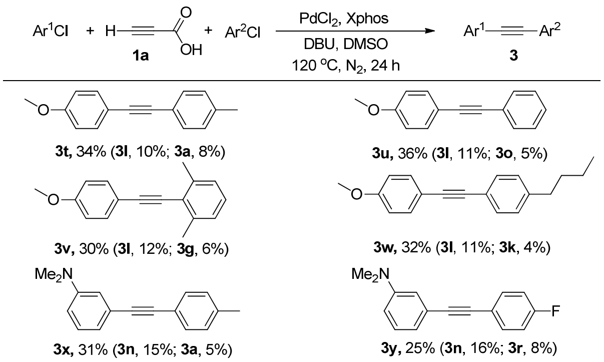


^{a} Reaction conditions: propiolic acid **1a** (0.4 mmol), aryl chlorides **2** (1.0 mmol), $PdCl_2$ (2 mol%), Xphos (4 mol%), DBU (4 equiv), DMSO (2 mL) at 120 °C for 24 h under a nitrogen atmosphere. ^{b} Isolated yield.

With the optimized conditions in hand, we next explored the substrate scope and the result was summarized in Table 2. Generally, various functional groups such as vinyl, OMe, NMe_2, CF_3 and F could be tolerated in this reaction and electron-rich, electron-neutral, or electron-poor aryl chlorides could smoothly be transferred into the corresponding products. It is noteworthy that the sterically hindered aryl chlorides could also afford the desired products in moderate yields (Table 2, **3d**–**3i**). Especially, 2-chloro-*m*-xylene could be coupled with propiolic acid in a moderate yield of 61% (Table 2, **3g**). Surprisingly, the reaction of 1-chloronaphthalene generated the product in a high yield of up to 81% (Table 2, **3p**). However, the reaction could not tolerate the heterocyclic chloride 2-chloropyridine (Table 2, **3s**).

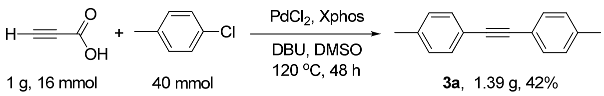
In addition, the synthesis of unsymmetrical diarylacetylenes was also performed, and Table 3 shows that the unsymmetrical diarylacetylenes (**3r**–**3u**) could be obtained in yields of 30–36%. In this process the corresponding symmetrical diarylactelyenes were also obtained in about 15–25% yields. It is necessary to point out that two different aryl chlorides along with propiolic acid were added to the catalytic system in one-step, which made the operation simpler and more facile.

Table 3 One-pot synthesis of unsymmetrical diarylacetylenes from two different aryl chlorides and propiolic acid^{a,b}



^{a} Reaction conditions: propiolic acid **1a** (0.6 mmol), Ar^{1}Cl (0.4 mmol), Ar^{2}Cl (0.4 mmol), $PdCl_2$ (2 mol%), Xphos (4 mol%), DBU (4 equiv), DMSO (2 mL) at 120 °C for 24 h under a nitrogen atmosphere. ^{b} Isolated yield.

To further highlight the synthetic utility of this protocol, a gram-scale experiment of Sonogashira/decarboxylative reaction of 4-chlorotoluene with propiolic acid was performed under standard conditions, and the desired product was obtained in a yield of 42% (Scheme 2).



Scheme 2 The gram-scale experiment

As we know, the Sonogashira reaction could not well applied to electron-poor terminal alkynes. Therefore, we conducted a comparative experiment of 4-chlorotoluene (**2a**) with an electron-deficient acetylene source ethyl propiolate (4a) and propiolic acid (**1a**). The reaction of 4a did not occur at all and 1a gave the product (**3a**) in a high yield of 61%, which indicated that propiolic acid as an acetylene source had its unique advantages (Scheme 3). It may be attributed to the carboxylic acid anion generated by the reaction of propiolic acid with DBU in situ,

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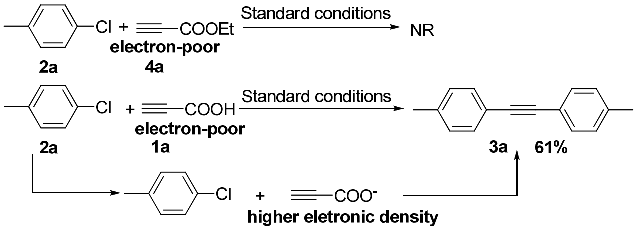
which can remarkably enhance the electronic density from the electron-poor propiolic acid to propiolic acid anion.

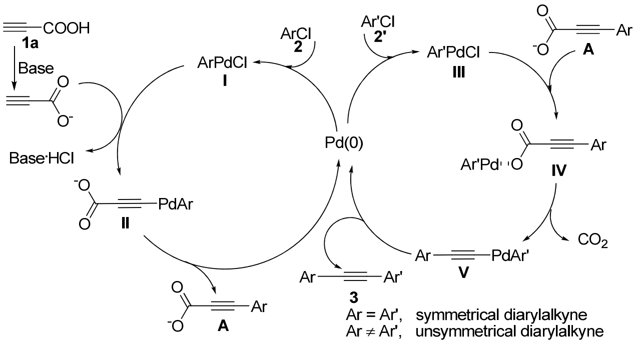


Scheme 3 The comparative experiment

To further investigate the mechanism for palladium-catalyzed tandem Sonogashira/decarboxylative coupling, the reaction of phenylpropiolic acid (**5a**) with chlorobenzene (**2o**) was performed and the desired product was obtained in 50% yield (Scheme 4). This result suggested that the phenylpropiolic onion was an intermediate in the reaction.

Scheme 4 The controlling experiment

On the basis of the above-mentioned results and reported works,[9] a tentative mechanism for palladium-catalyzed tandem Sonogashira/decarboxylative coupling was outlined in Scheme 5. The initial step would be the oxidative addition of aryl chloride (**2**) to Pd(0) species to form the Pd(II) intermediate **I**. And then, the ligand replacement between intermediate **I** and the propiolic acid anion, which was generated from propiolic acid **1a** and base, took place to form intermediate **II**. The reductive elimination of intermediate **II** afforded Sonogashira product as arylpropiolic acid anion **A** and the active Pd(0) species to fulfill the catalytic cycle. On the other hand, the reaction of aryl chloride (**2'**) with Pd(0) species could form the Pd(II) intermediate **III**. The ligand exchange between the arylpropiolic acid anion **A** and intermediate **III** occurred to give the Pd(II) intermediate **IV**. After intermediate **IV** underwent the decarboxylative reaction to release one molecular CO_2 to form intermediate **V**, the reductive elimination of intermediate **V** could afford the desired product (**3**) and regenerate the active Pd(0) species.



Scheme 5 A tentative mechanism

In conclusion, we have developed the first palladium-catalyzed tandem Sonogashira/decarboxylative cross coupling reaction of propiolic acid with the more challenging aryl chlorides as the coupling partners. Notably, the reaction could well tolerate *ortho*-sterically hindered aryl chlorides affording the desired products in moderate yields, and the substrate scope could be extended to electron-rich, electron-neutral, and even electron-poor aryl chlorides. Moreover, adding two different aryl chlorides simultaneously in one-pot makes the method more convenient and practical for the preparation of unsymmetrical diarylalkynes.

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Notes and references

The College of Chemistry and Molecular Engineering, Henan Key Laboratory of Chemical Biology and Organic Chemistry, Key Laboratory of Applied Chemistry of Henan Universities, Zhengzhou University, Zhengzhou 450052, People's Republic of China
Tel/Fax: (+86)-371-6797-9408. E-mail: yangf@zzu.edu.cn; wyj@zzu.edu.cn

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