# Pd/Cu-Catalyzed Synthesis of Internal and Sila-Ynones by Direct Selective Acyl Sonogashira Cross-Coupling of Carboxylic Acids with Terminal Alkynes

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**Keywords:** Pd/Cu Cooperative Catalysis; Sonogashira Coupling; Carboxylic Acids; Internal Ynones; Sila-Ynones

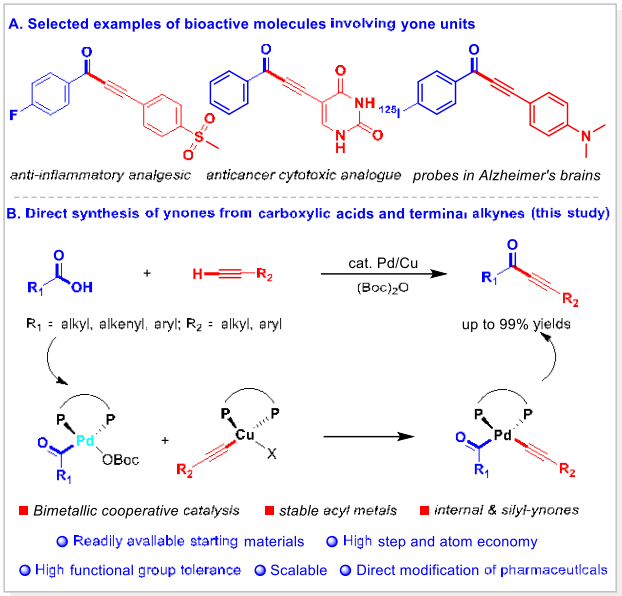
**ABSTRACT:** The direct acyl Sonogashira cross-coupling of carboxylic acids with terminal alkynes has been achieved through Pd/Cu cooperative catalysis. In this reaction, the readily available carboxylic acids act as the acyl source for the coupling with various terminal alkynes to produce highly valuable ynones in good to high yields. The reaction features high chemoselectivity and functional group tolerance. The reaction offers access to versatile silyl-ynones. The late-stage modification of bioactive molecules and gram-scale experiments highlight the synthetic value of this reaction in organic synthesis. The method enables preparation of ynones directly from carboxylic acids in the absence of C(acyl)–C(sp) decarbonylation.

## INTRODUCTION

Ynones are key structural motifs commonly occurring in various bioactive[1] and material molecules[2] (Scheme 1A). Furthermore, ynones are critical building blocks in organic synthesis for constructing complex molecules, in particular, oxygen- and nitrogen-heterocycles.[3] Therefore, the development of convenient, waste-minimized, direct and efficient methods for the preparation of ynones constitutes a major goal in organic synthesis.[4] The acylation of terminal alkynes is an important method for the synthesis of ynones. In these reactions, the combination of aryl reagents such as aryl halides,[5] aryl triflates[6] or aryl hydrazines[7] with CO gas can act as the acyl source. However, these aryl reagents must be pre-synthesized. The use of toxic CO gas leads to difficulty in operation and safety issues. Acyl halides have been used as the acyl source to produce ynones, despite the harsh reaction conditions using hard organometallics and severely limited substrate scope owing to low stability of the C(acyl)–X bond to acylative cross-coupling conditions.[8,9] In recent years, other activated precursors have also been used in reactions with terminal alkynes to produce ynones in moderate to good yields.[8–10]

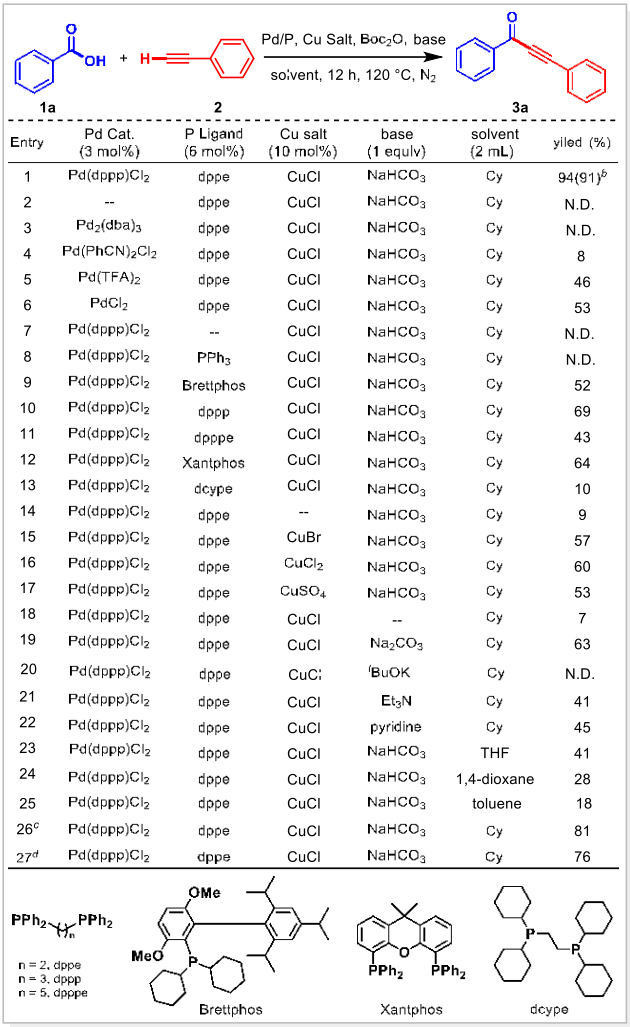
Our goal was to develop a direct and convenient method for preparing ynones from readily available carboxylic acids. Herein, we report the first direct acyl Sonogashira cross-coupling of carboxylic acids with a variety of termi-

**Scheme 1. Selected Examples of Bioactive Molecules Involving Ynone Unit and Synthesis of Ynones from Carboxylic Acids and Terminal Alkynes.**



nal alkynes to produce ynones through Pd/Cu cooperative catalysis (Scheme 1B). The reaction capitalizes on the high stability of carboxylic acids, which are tuned for acylative cross-coupling by in situ activation to form mixed anhydride. The method enables preparation of ynones directly from carboxylic acids in the absence of C(acyl)–C(sp) decarbonylation. Carboxylic acids are abundant and readily available in both nature and synthetic world. Their direct use as the acyl source avoids pre-synthesis of starting materials, thus minimizing waste, shortening the synthetic sequence and providing high efficiency of atom utilization. The synthesis of ynones through direct Sonogashira cross-coupling of carboxylic acids has never been realized.[11-13]

**Table 1. Optimization of Reaction Conditions**[a]




| Entry | Pd Cat. (3 mol%) | P Ligand (6 mol%) | Cu salt (10 mol%) | base (1 equiv) | solvent (2 mL) | yiled (%) |
|---|---|---|---|---|---|---|
| 1 | $Pd(dppp)Cl_2$ | dppe | CuCl | $NaHCO_3$ | Cy | 94(91)[b] |
| 2 | -- | dppe | CuCl | $NaHCO_3$ | Cy | N.D. |
| 3 | $Pd_2(dba)_3$ | dppe | CuCl | $NaHCO_3$ | Cy | N.D. |
| 4 | $Pd(PhCN)_2Cl_2$ | dppe | CuCl | $NaHCO_3$ | Cy | 8 |
| 5 | $Pd(TFA)_2$ | dppe | CuCl | $NaHCO_3$ | Cy | 46 |
| 6 | $PdCl_2$ | dppe | CuCl | $NaHCO_3$ | Cy | 53 |
| 7 | $Pd(dppp)Cl_2$ | -- | CuCl | $NaHCO_3$ | Cy | N.D. |
| 8 | $Pd(dppp)Cl_2$ | $PPh_3$ | CuCl | $NaHCO_3$ | Cy | N.D. |
| 9 | $Pd(dppp)Cl_2$ | Brettphos | CuCl | $NaHCO_3$ | Cy | 52 |
| 10 | $Pd(dppp)Cl_2$ | dppp | CuCl | $NaHCO_3$ | Cy | 69 |
| 11 | $Pd(dppp)Cl_2$ | dpppe | CuCl | $NaHCO_3$ | Cy | 43 |
| 12 | $Pd(dppp)Cl_2$ | Xantphos | CuCl | $NaHCO_3$ | Cy | 64 |
| 13 | $Pd(dppp)Cl_2$ | dcype | CuCl | $NaHCO_3$ | Cy | 10 |
| 14 | $Pd(dppp)Cl_2$ | dppe | -- | $NaHCO_3$ | Cy | 9 |
| 15 | $Pd(dppp)Cl_2$ | dppe | CuBr | $NaHCO_3$ | Cy | 57 |
| 16 | $Pd(dppp)Cl_2$ | dppe | $CuCl_2$ | $NaHCO_3$ | Cy | 60 |
| 17 | $Pd(dppp)Cl_2$ | dppe | $CuSO_4$ | $NaHCO_3$ | Cy | 53 |
| 18 | $Pd(dppp)Cl_2$ | dppe | CuCl | -- | Cy | 7 |
| 19 | $Pd(dppp)Cl_2$ | dppe | CuCl | $Na_2CO_3$ | Cy | 63 |
| 20 | $Pd(dppp)Cl_2$ | dppe | CuCl | $^t$BuOK | Cy | N.D. |
| 21 | $Pd(dppp)Cl_2$ | dppe | CuCl | $Et_3N$ | Cy | 41 |
| 22 | $Pd(dppp)Cl_2$ | dppe | CuCl | pyridine | Cy | 45 |
| 23 | $Pd(dppp)Cl_2$ | dppe | CuCl | $NaHCO_3$ | THF | 41 |
| 24 | $Pd(dppp)Cl_2$ | dppe | CuCl | $NaHCO_3$ | 1,4-dioxane | 28 |
| 25 | $Pd(dppp)Cl_2$ | dppe | CuCl | $NaHCO_3$ | toluene | 18 |
| 26[c] | $Pd(dppp)Cl_2$ | dppe | CuCl | $NaHCO_3$ | Cy | 81 |
| 27[d] | $Pd(dppp)Cl_2$ | dppe | CuCl | $NaHCO_3$ | Cy | 76 |



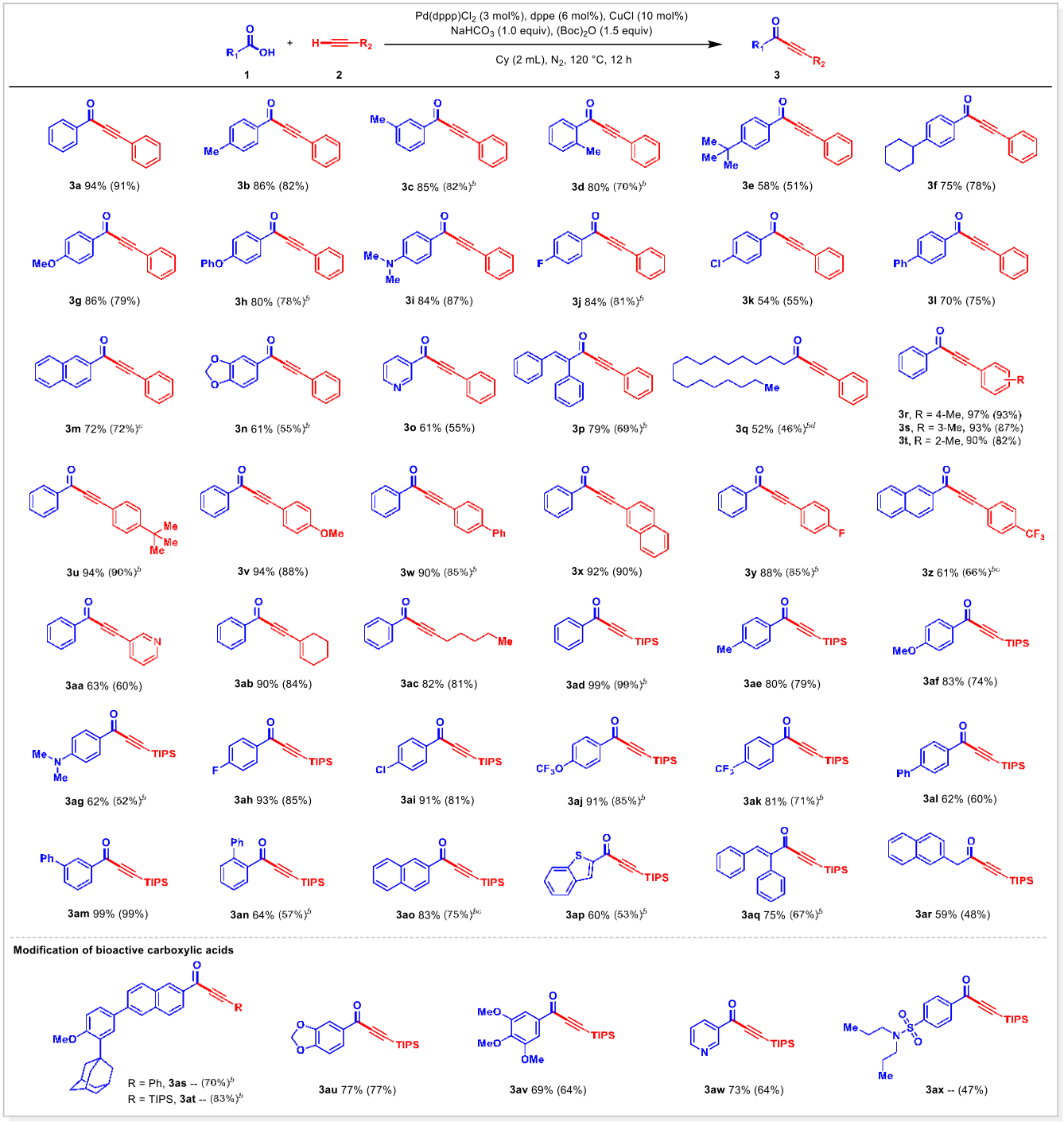

[a]Reaction conditions: **1a** (0.2 mmol, 1.0 equiv), **2a** (1.2 equiv.), Pd Cat. (3 mol%), P Ligand (6 mol%), [Cu] (10 mol%), base (1.0 equiv.), $Boc_2O$ (1.5 equiv.), solvent (2 mL), 120 °C, 12 h, $N_2$ atmosphere. Tridecane is an internal standard. [b]Isolated yield. [c]100 °C, [d]140 °C.

## RESULTS and DISSCUSSION

After a mixture of benzoic acid (**1a**) and phenyl acetylene (**2a**) in cyclohexane (2 mL) was heated at 120 °C for 12 h in the presence of $Pd(dppp)Cl_2$ (3 mol%), dppe (6 mol%), CuCl (10 mol%), $NaHCO_3$ (1.0 equiv.), $(Boc)_2O$ (1.5 equiv.), the corresponding ynone (**3a**) was produced in 94% yield with ca 33 TONs (Table 1, entry 1). The palladium catalyst was essential to this reaction as no reaction was observed in its absence (Table 1, entry 2). $Pd_2(dba)_3$ showed no catalytic efficiency under the reaction conditions (Table 1, entry 3). Other selected Pd(II) catalysts such as $Pd(PhCN)_2Cl_2$, $Pd(TFA)_2$ and $PdCl_2$ could also mediate the reaction, but the yield decreased greatly (Table 1, entries 4-6). The phosphine ligand was important in this reaction. When no external phosphine ligand or $Ph_3P$ was used, no desired product was detected (Table 1, entries 7 and 8). The yields also decreased with other phosphine ligands such as BrettPhos, dppp, dpppe, Xantphos or dcype were used (Table 1, entries 9-13). Copper catalyst is another determining factor. In its absence, only 9% yield of **3a** was detected (Table 1, entry 14). CuBr, $CuCl_2$ and $CuSO_4$ could promote this reaction, however the yield decreased to major extent (Table 1, entries 15-17). The base also played a pivotal role. Without base, **3a** was only produced in 7% yield (Table 1, entry 18). When $Na_2CO_3$ was used, 63% yield of **3a** was obtained, while no **3a** was detected with strong base $^t$BuOK (Table 1, entries 19 and 20). Organic base $Et_3N$ and pyridine also worked under the reaction conditions (Table 1, entries 21 and 22). Solvent was also screened with cyclohexane (Cy) being the best choice (Table 1, entries 1, 23-25). Lowering the reaction temperature to 100 °C led to slight decrease in yield. The yield also decreased when the reaction was conducted at 140 °C (Table 1, entries 26 and 27). Importantly, the reaction showed full selectivity for the acyl coupling vs. C(acyl)–C(sp) decarbonylation as a result of faster transmetallation than decarbonylation after carboxylate exchange.

With the optimized reaction conditions in hand, the substrate scope was subsequently investigated. As shown in Table 2, a wide range of carboxylic acids coupled readily with various terminal alkynes to produce the corresponding ynones in good to high yields. Thus, in addition to benzoic acid, high yields were also obtained from the carboxylic acids bearing 4-Me, 3-Me, 2-Me, 4-$^t$Bu, 4-Cy, 4-MeO, 4-PhO and 4-$Me_2N$ groups at the aryl ring (**3a**-**3i**). Halogens, F and Cl, were well compatible under the reaction conditions, enabling further functionalization of the products (**3j** and **3k**). π-Extensive and heterocyclic substrates also worked well and were converted into the desired yones in good yields (**3l**-**3o**). However, when benzoic acids bearing electron-withdrawing group like $CF_3$ and $CF_3O$ group were reacted with phenylacetylene, low yields (< 20% yield) were observed due to the formation of *tert*-butyl esters through esterification of the corresponding mixed anhydrie with *t*-BuOH generated in situ from thermal decomposition of the Boc fragment. It is worth noting is that alkenyl carboxylic acids as exemplified by α-phenyl cinnamic acid also coupled smoothly with phenylacetylene by slightly tuning the reaction conditions, generating yone **3p** in 79% yield. In particular, the aliphatic stearic acid was also transformed into the expected coupling product **3q**.

**Table 2. Acyl Sonogashira Alkynylation of Carboxylic Acids with Terminal Alkynes**[a]

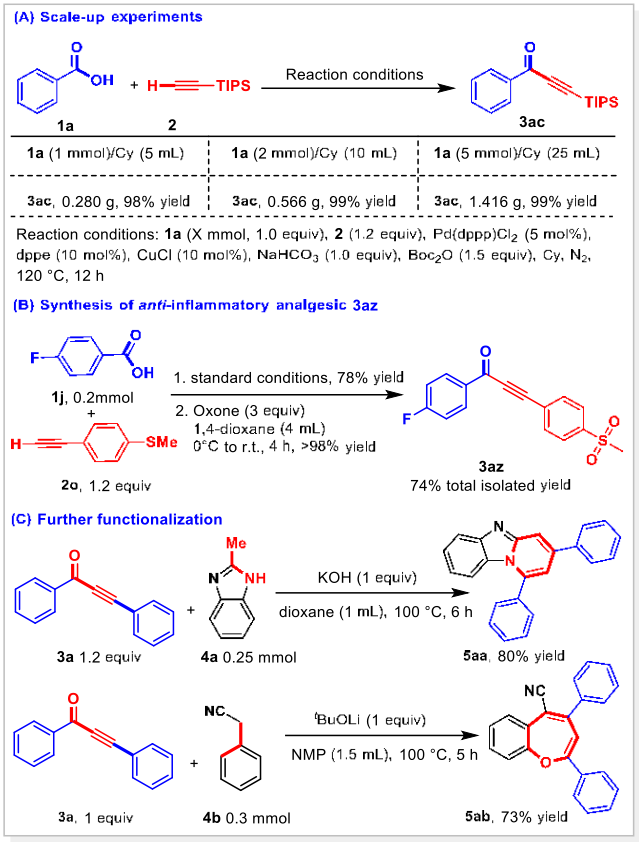



[a]Reaction conditions: **1** (0.2 mmol, 1.0 equiv), **2** (1.2 equiv.), Pd(dppp)Cl2 (3 mol%), dppe (6 mol%), CuCl (10 mol%), $NaHCO_3$ (1.0 equiv.), $(Boc)_2O$ (1.5 equiv.), Cy (2 mL), 120 °C, 12 h, $N_2$ atmosphere. GC yields using tridecane as an internal standard (the data in bracket are isolated yields). [b]Pd(dppp)Cl2 (5 mol%), dppe (10 mol%). [c]100 °C. [d]CuCl (40 mol%), 6 h.

To our delight, the alkyne scope was general under the reaction conditions. Both aromatic and aliphatic terminal alkynes coupled readily with benzoic acids to produce the expected ynones in good to excellent yields. Thus, phenylacetylenes with 4-Me, 3-Me, 2-Me, 4-$^t$Bu, and 4-MeO at the aryl ring worked well (**3r**-**3v**). The π-extensive substrates gave the expected products in high yields (**3w** and **3x**). Halogens, such as fluoro group, were well tolerated (**3y**). The electron-deficient 4-trifluoromethyl phenylacetylene served as efficient substrates (**3z**). The *N*-heterocyclic terminal alkynes also worked well (**3aa**). It is worth noting that alkenyl and alkyl acetylenes were also converted into the corresponding ynones in high yields by this strategy (**3ab** and **3ac**). Notably, silylacetylenes could couple with benzoic acid to give **3ad** in almost quantitative yield under the reaction conditions. It is known that silyl alkynes can

easily couple with a nucleophile to produce a new internal alkyne.[14] The silyl group can also be easily removed to give a new terminal alkyne.[15] These specific properties indicate that the resulting internal silyl alkynes can be further functionalized to give further high value molecules through cross coupling and other transformations. Considering the synthetic utility of silyl-ynones, the carboxylic acid scope was re-investigated with silylacetylene. Similarly broad substrate scope was found (**3ad**-**3ar**). In particular, although the electron-deficient carboxylic acids could not react efficiently with phenylacetylene, these substrates coupled smoothly with silylacetylene to give the expected ynones in high yields in the current catalytic system (**3aj** and **3ak**). The resulting internal silyl alkynes can be conveniently exploited in C–Si functionalization, being well complementary to the method with terminal alkynes.

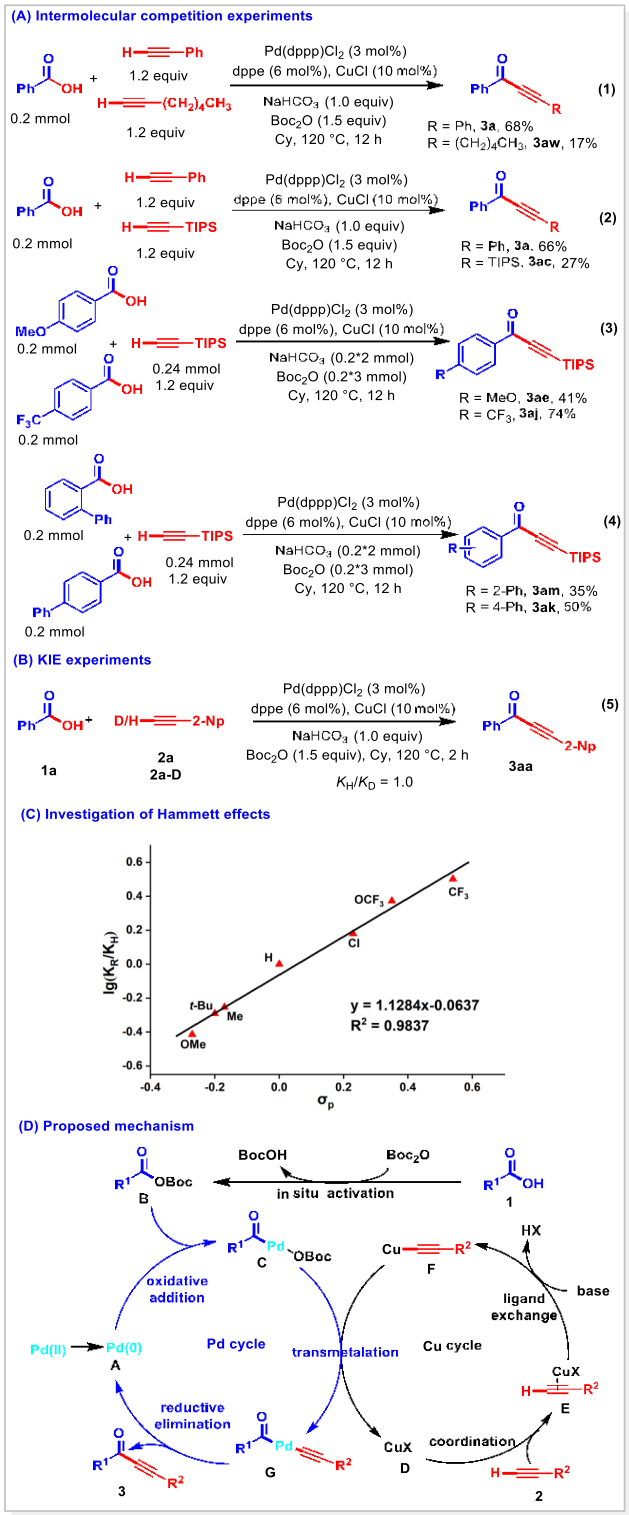
**Scheme 2. Gram-Scale Experiments, Synthesis of Drugs and Further Derivatization of Ynones**




This reaction is applicable to the direct modification of bioactive carboxylic acids as outlined in Table 2. For example, adapalene is a dermatological drug for clinical skin treatment of acne vulgaris with acne, papules and pustules.[16] This drug could react readily with both phenylacetylene and silylacetylene to produce the corresponding ynones **3as** and **3at** in 70% and 83% yields, respectively. The bioactive carboxylic acids such as piperonylic acid, trimethylgallic acid and nicotinic acid could be applied, furnishing the expected coupling products in high yields (**3au**-**3aw**). Probenecid is clinically used for reducing joint damage by alleviating the formation of urate nodules.[17]

Despite the electron-deficient property, it also coupled with silylacetylene under the reaction conditions to produce the desired ynone **3ax**.

**Scheme 3. Control Experiments, KIE Experiment, Hammett Analysis and Proposed Mechanism**




Moreover, this reaction is scalable. As shown in Scheme 2A, benzoic acid (1 mmol) coupled smoothly with silylacetylene (1.2 equiv) under the reaction conditions. After isolation and

purification through chromatography, 98% yield of **3ac** (0.28 g) was obtained. Similar high yields were also obtained at 2 mmol and 5 mmol scale. Importantly, this reaction was applicable to the synthesis of drugs (Scheme 2B). For example, the anti-inflammatory analgesic **3az** was easily synthesized in 74% total yield by coupling 4-F benzoic acid with (4-ethynylphenyl)(methyl)sulfane under the reaction conditions followed by simple oxidation. Practically, product ynones can be easily further functionalized (Scheme 2C). In the presence of 1 equiv KOH, ynone **3a** can react readily with 2-methyl-1*H*-benzo[*d*]imidazole **4a** to produce a six-membered fused pyridine **5aa** in 80% yield. The seven-membered benzofused oxacycle **5ab** was also readily obtained in 73% yield from the reaction of ynone **3a** and 2-phenylacetonitrile **4b** in the presence of $^{t}$BuOLi. Overall, the late-stage modification of pharmaceuticals, scalability and derivatization well demonstrate the practical value of this new reaction in organic synthesis.

Intermolecular competition experiments were conducted to probe the selectivity of this reaction. When benzoic acid **1a** was allowed to react with phenyl acetylene and 1-heptyne under the reaction conditions, **3a** was obtained in 68% yield, while **3aw** was only produced in 17% yield, indicating that aromatic terminal alkynes show higher reactivity in this reaction (Scheme 3, eq 1). Similar result was also obtained from the intermolecular competition experiment of benzoic acid **1a** with phenyl acetylene and silyl acetylene (Scheme 3, eq 2). When electron-rich 4-methoxyl benzoic acid and electron-deficient 4-trifluoromethyl benzoic acid was reacted with silyl acetylene, **3ae** was produced in 41% yield as well as **3aj** in 74% yield (Scheme 3, eq 3). The result implied that this reaction favors electron-deficient benzoic acids. Steric hindrance also seems to affect the reaction. For instance, when 2-phenyl benzoic acid and 4-phenyl benzoic acid compete to couple with silyl acetylene under the reaction conditions, **3am** was obtained in 35% yield, while **3ak** was generated in 50% yield, suggesting that carboxylic acids with smaller steric hindrance react preferentially (Scheme 3, eq 4).

To gain more information on the mechanism, the kinetic isotope experiments (KIE) were subsequently conducted. A kinetic isotope effect ($k_H/k_D$ = 1.0) was obtained from the parallel experiments by using 2-naphthyl acetylene **2a** and deuterated 2-naphthyl acetylene **2a**-D (Scheme 3, eq 5), indicating that C–H cleavage is not the rate-determining step in this reaction. Hammett analysis was also performed (Scheme 3C). A positive slope ($\rho$ = +1.13) was observed for the reaction of *para*-substitutied benzoic acids with silyl alkyne. This large positive $\rho$ value indicates that the oxidative addition would be the rate-determining step in this reaction. Those experimental results was also well consisted with intermolecular competition experiments. Finally, the mercury poisoning experiments were conducted. It was found that ynone could still be produced from the reaction of benzoic acid with silyl acetylene by adding excessive mercury, despite the fact that the yield decreased to some extent (For experimental data, see S2.7 in SI). Therefore, We think the active catalyst would be molecular Pd(0) species in this reaction.

On the basis of experimental results and previous studies,[13,18-22] a plausible mechanism is proposed. As shown in Scheme 3D, the carboxylic acid is first in situ activated by $Boc_2O$ to produce a mixed anhydride **B**, followed by oxidative addition with the active Pd(0) complex[20] generated in situ to give intermediate **C**. Meanwhile, terminal alkyne is activated by copper and base to yield intermediate **F**.[21] Transmetallation between the resulting complex **C** and acetylene copper **F** takes place to give species **G**,[22] which undergoes reductive elimination to produce the target product ynone **3** and re-generates the active Pd(0) catalyst.

## CONCLUSION

In summary, we have disclosed the first direct acyl Sonogashira cross-coupling of carboxylic acids for the synthesis of ynones through Pd/Cu bimetallic catalysis. This reaction uses abundant and readily available carboxylic acids as the acyl source, greatly improving operational simplicity, shortening the synthetic sequence and improving the overall atom utilization efficiency. The substrate scope is extensively broad, enabling electron-rich and electron-deficient aromatic carboxylic acids, even the aliphatic carboxylic acids to couple with both aromatic and aliphatic terminal alkynes. Importantly, the reaction proceeds selectively in the absence of C(acyl)–C(sp) decarbonylation. Further, the method offers access to versatile silyl-ynones. The advantages of this new reaction are well demonstrated by the late modification of bioactive carboxylic acids, scalability and functionalization of the ynone products. The method establishes access to multifaceted ynones, and greatly expands the application scope of carboxylic acids in chemical synthesis and catalysis.

## ASSOCIATED CONTENT

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### Notes

The authors declare no competing financial interests.

### Supporting Information

The Supporting Information including general information, experimental procedures, characterization data, copies of $^{1}$H, $^{13}$C and $^{19}$F NMR spectra is available free of charge on the ACS Publications website.

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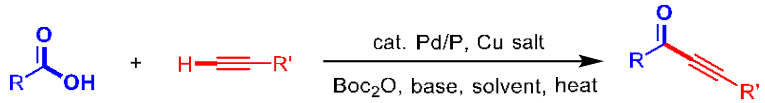
***Direct Acyl Cross-Coupling of Carboxylic Acids with Terminal Alkynes***




*R = aryl, alkenyl, alkyl; R' = aryl, alkenyl, alkyl, silyl*

- ***Ubiquitous carboxylic acid substrates***
- ***High step-economic efficiency***
- ***Wide substrate scope***
- ***High functional group tolerance***
- ***Scalable***
- ***Direct modification of pharmaceuticals***
- ***Internal & silyl-ynones***