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Highly effective copper-catalyzed decarboxylative coupling of aryl halides with alkynyl carboxylic acids†

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We have developed a highly effective copper-catalyzed decarboxylative coupling of alkynylcarboxylic acids with various aryl and alkyl halides at 2 mol% loading of copper. This method is simple, economical and practical for the synthesis of disubstituted alkyne compounds.

Transition metal-mediated C(sp)–C(sp^2) bond forming reactions are of great interest in organic synthesis since molecules containing aryl alkyne units are prevalent in biological and pharmaceutical sciences.[1] Generally, the Sonogashira reactions are used to make such compounds, and are most frequently carried out by palladium catalysts together with a copper co-catalyst using an amine as solvent.[2] Since its inception, many new developments related to the Sonogashira reaction have been reported in the area of catalyst types.[3] For example, copper salts in combination with appropriate ligands have been developed as alternative catalysts.[4] In addition, numerous metal complexes or nanoparticles, such as those of iron,[5] gold,[6] indium,[7] nickel,[8] cobalt,[9] ruthenium[10] have also been reported as catalysts for the Sonogashira couplings. Recently, we have disclosed a highly effective samarium powder-catalyzed Sonogashira coupling in the absence of ligands.[11] However, few investigations have been focused on the substrates. In the past several years, decarboxylative couplings of carboxylic acids or their salts have gained interest since they are readily available and inexpensive.[12] In contrast, decarboxylative couplings of alkynyl carboxylic acids have received less attention.[13] It is noteworthy that decarboxylative couplings between alkynyl carboxylic acids and aryl halides *via* a CO_2-released process could be considered as a sub-category of Sonogashira coupling reactions. Compared with terminal alkynes as the traditional substrates, alkynyl carboxylic acids are usually easy to store and simple to handle. In 2008, S. Lee and co-workers developed the first example of such a decarboxylative coupling in the presence of $Pd_2(dba)_3$ and phosphine ligands, including dppf and dppb.[13a,13b] In addition, Kim and Lee also found that $Pd_2(dba)_3$ together with PPh_3 or Xantphos could catalyze the coupling in high yield.[13c] Very recently, Li found that the combination of $Pd(OAc)_2$ and Xphos could catalyze decarboxylative coupling reactions of alkynyl carboxylic acids with a wide range of aryl halides.[13d] Song and Lee have prepared both symmetrical and unsymmetrical diarylalkynes from propiolic acid by decarboxylative coupling using a $Pd(PPh_3)_2Cl_2$/dppb catalytic system.[13e] Thus, Pd-catalyzed decarboxylative couplings have progressed in the past five years. However, much less attention has been paid to copper-catalyzed decarboxylative cross-couplings.[13g,15] In 2010, You and Xue found that CuI/1,10-phenanthroline showed a good catalytic effect in this reaction. However, the catalyst loading is high (10 mol%) and the reaction conditions are harsh (130 °C).[16] With our ongoing interest in various cross-coupling reactions,[11,14] we describe our efforts on the development of a low-cost and stable copper catalyst system for decarboxylative coupling under more practical and milder conditions.

We began our investigation using phenylpropiolic acid and 4-iodoanisole as the model substrates. Firstly, various readily available ligands (**A–J**) were screened as shown in Fig. 1, including monodentate *P*-ligands, bidentate *P*-ligands, *N*,*N*-ligands,[16] *O*,*O*-ligands and *N*,*O*-ligands. It can be seen that PPh_3 (**A**) afforded the best catalytic effect (75% yield).

With the optimized CuI/**A** catalytic system in hand, we then screened various catalytic conditions. The results are listed in Table 1. K_2CO_3 instead of K_3PO_4 as the base resulted in an almost quantitative yield of the desired product (Table 1, entry 2). Under the same conditions, control experiments showed that CuI alone afforded only 29% of the corresponding product (Table 1, entry 3), whereas ligand **A** alone also did not catalyze the reaction (Table 1, entry 4). Subsequently, various inorganic and organic bases, including Cs_2CO_3, KOH, ^{t}BuOK, KF and TEA (triethylamine), were incorporated in the reaction (Table 1, entries 5–9). Among them, ^{t}BuOK showed the best conversion efficiency (Table 1, entry 7). But considering the cost of the base as well, K_2CO_3 was selected as the best base to use. Reduced loading of CuI/**A** also gave the satisfactory yields until the loading was decreased to 1 mol% (Table 1, entries 10–12). Thus, the optimized catalytic loading is 2 mol% of CuI and 4 mol% **A** (Table 1, entry 11). Then, different commonly-used solvents were screened and DMF afforded good yields, which is inferior only to DMSO (Table 1, entries 13–16). Different copper salts were then evaluated (Table 1, entries 18–21). It was a welcome discovery that CuI showed higher activity than Cu powder, CuBr, Cu_2O and $Cu(OAc)_2$. To control the experiment against potential metal contamination, we carried out experiments in new flasks with new stirring bars and new caps, using CuI of the highest purity from Aldrich (99.999%), which was found to

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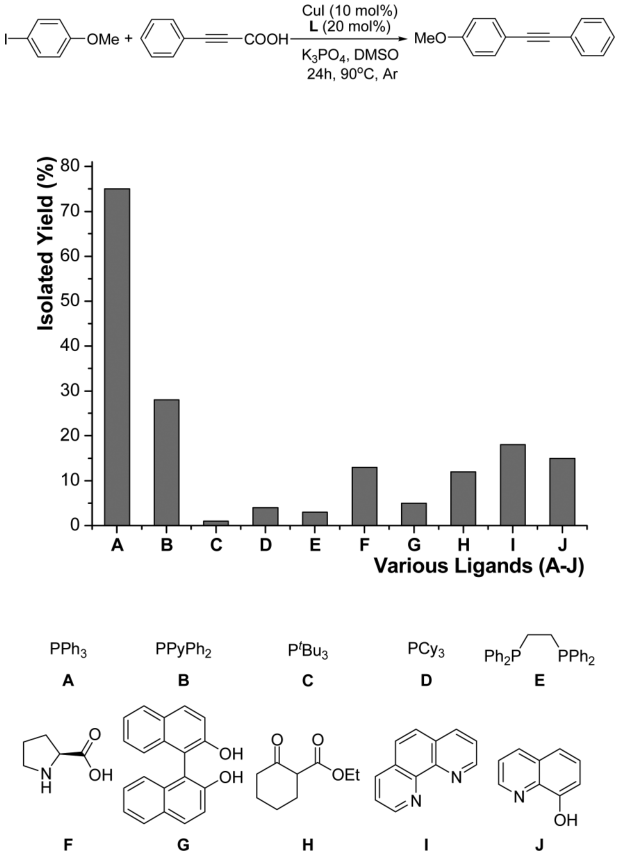
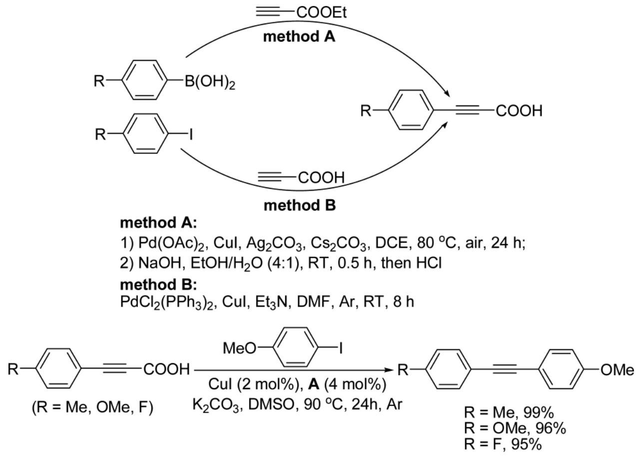


Fig. 1 Screening various ligands for the coupling reaction. Conditions: CuI (10 mol%), ligand (20 mol%), 4-iodoanisole (0.5 mmol), phenylpropiolic acid (0.6 mmol), K$_3$PO$_4$ (1.0 mmol), DMSO (2 mL), 90 °C, 24 h, under Ar.

Table 1 Screening catalytic conditions in decarboxylative coupling between 4-iodoanisole and phenylpropiolic acid[a]

Entry	Cat. (mol%)	**A** (mol%)	Base/solvent	Yield (%)[b]
1	CuI (10)	20	K$_3$PO$_4$/DMSO	75
2	CuI (10)	20	K$_2$CO$_3$/DMSO	99
3	CuI (10)	—	K$_2$CO$_3$/DMSO	29
4	—	20	K$_2$CO$_3$/DMSO	—
5	CuI (10)	20	Cs$_2$CO$_3$/DMSO	16
6	CuI (10)	20	KOH/DMSO	96
7	CuI (10)	20	^{t}BuOK/DMSO	99
8	CuI (10)	20	KF/DMSO	49
9	CuI (10)	20	TEA/DMSO	29
10	CuI (5)	10	K$_2$CO$_3$/DMSO	99
11	CuI (2)	4	K$_2$CO$_3$/DMSO	***99***
12	CuI (1)	2	K$_2$CO$_3$/DMSO	47
13	CuI (2)	4	K$_2$CO$_3$/Toluene	29
14	CuI (2)	4	K$_2$CO$_3$/Dioxane	78
15	CuI (2)	4	K$_2$CO$_3$/NMP	11
16	CuI (2)	4	K$_2$CO$_3$/DMF	97
17[c]	CuI (2)	4	K$_2$CO$_3$/DMSO	70
18	Cu powder (2)	4	K$_2$CO$_3$/DMSO	10
19	CuBr (2)	4	K$_2$CO$_3$/DMSO	69
20	Cu$_2$O (2)	4	K$_2$CO$_3$/DMSO	Trace
21	Cu(OAc)$_2$ (2)	4	K$_2$CO$_3$/DMSO	20
22[d]	CuI (2)	4	K$_2$CO$_3$/DMSO	99

[a] Reaction conditions: 4-Iodoanisole (0.5 mmol), phenylpropiolic acid (0.6 mmol), base (1.0 mmol), solvent (2 mL), 90 °C, 24 h, under Ar. [b] Isolated yield (based on 4-iodoanisole). [c] 10 h. [d] CuI (99.999%) from Aldrich was employed in the reaction.



Scheme 1 Two approaches to prepare the substituted arylpropiolic acids and their decarboxylative coupling.

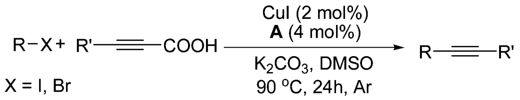
catalyze the coupling in the same yield (99%) (Table 1, entry 22) (for the certificate of analysis, see supporting information†).

Under the optimized reaction conditions, a variety of aryl halides were coupled with alkynoic acids to afford the corresponding products in good yields (Table 2). For the decarboxylative couplings of phenylpropiolic acid and aryl iodides with electron-deficient substituents or with electron-rich ones, all proceeded well (Table 2, entries 1–10). *ortho*-Substituted aryl iodides afforded good yields only at higher temperature (110 °C) (Table 2, entry 4 and entry 9). It is noteworthy that our protocol could tolerate some useful functional groups, such as ketone, ester or amine (Table 2, entries 11–13). Furthermore, it is notable that the coupling of an alkyl iodide also proceeded smoothly (Table 2, entry 14). Next, the decarboxylative couplings of 2-octynoic acid as the aliphatic alkynoic acid were performed with different aryl iodides (Table 2, entries 15–19). In addition, the coupling of 4-iodoanisole and 2-butynoic acid afforded the expected product in 86% yield (Table 2, entry 20). Finally, the decarboxylative couplings of aryl bromides were studied. In the presence of CuI (5 mol%), **A** (10 mol%) and NaI (1.0 mmol) as the additives, the corresponding products were acquired in moderate yields at 110 °C (Table 2, entries 21–23). Experimentally, the reactivity of alkynoic acids are in the following order: phenylpropiolic acid > 2-octynoic acid > 2-butynoic acid.

The substituted arylpropiolic acids used in the coupling reactions are easily prepared from two approaches as shown in Scheme 1. With our protocol, decarboxylative coupling of these arylpropiolic acids and 4-iodoanisole resulted in excellent yields of coupled products (95–99%).

In order to extend the application of our methodology, the coupling of various diiodobenzenes and phenylpropiolic acid or 2-octynoic acid was carried out using the system as shown in Scheme 2. It was interesting to observe that at 90 °C, the decarboxylative coupling of 1,3-diiodobenzene with phenylpropiolic acid or 2-octynoic acid afforded the bis-coupled products in 95% and 72% yields, respectively. However, under the same conditions, the reactions using 1,2- or 1,4-diiodobenzene did not occur. A higher reaction temperature (110 °C) was needed to induce coupling with 1,4-diiodobenzene (96% and 95% yield, respectively). The further increase of the reaction temperature (130 °C) resulted in the effective decarboxylative coupling between

Table 2 Scope of copper-catalyzed decarboxylative coupling of various aryl halides and alkynoic acids in the presence of **A**[a]



$$R{-}X + R'{-}{\equiv}{-}COOH \xrightarrow[K_2CO_3,\ DMSO,\ 90\ ^{o}C,\ 24h,\ Ar]{CuI\ (2\ mol\%),\ \mathbf{A}\ (4\ mol\%)} R{-}{\equiv}{-}R'$$

X = I, Br

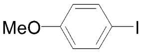
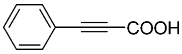
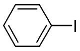
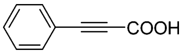
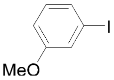
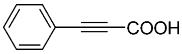
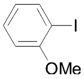
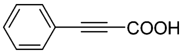
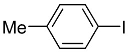
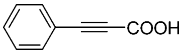
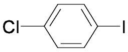
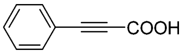
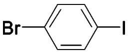
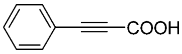
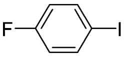
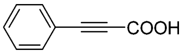
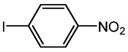
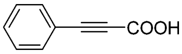
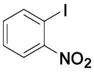
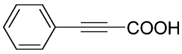
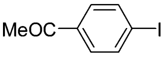
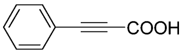
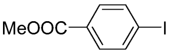
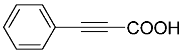
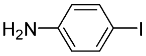
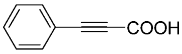
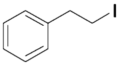
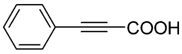
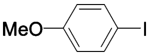
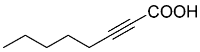
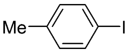
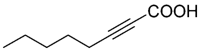
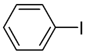
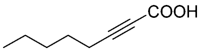
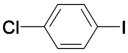
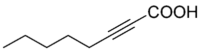
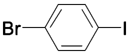
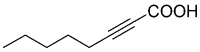
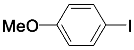
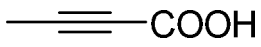
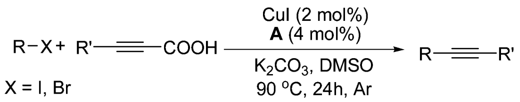
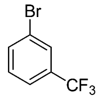
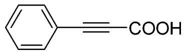
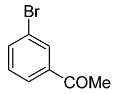
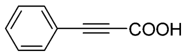
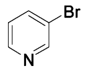
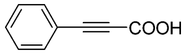
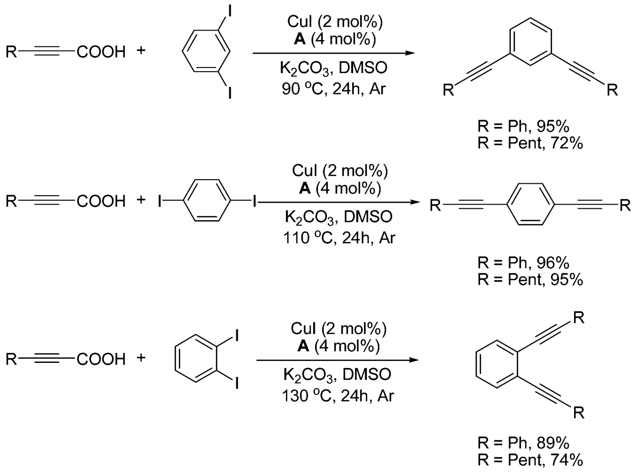
Entry	RX	R′C≡COOH	$T/°C$	Yield (%)[b]
1			90	99
2			90	97
3			90	99
4			110	96
5			90	99
6			90	99
7			90	98
8			90	97
9			90	92
10			110	96
11			90	98
12			90	99
13			90	95
14			90	85
15			90	99
16			90	95
17			90	95
18			90	88
19			90	94
20			90	86

Table 2 (*Contd.*)



Entry	RX	$R'C\equiv COOH$	$T/°C$	Yield (%)[b]
21[c]			110	60
22[c]			110	51
23[c]			110	57

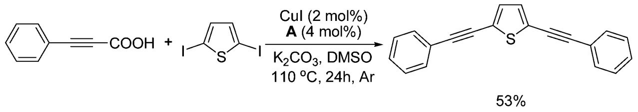
[a] Reaction conditions: Aryl halide (0.5 mmol), alkynoic acid (0.6 mmol), CuI (2 mol%), **A** (4 mol%), K_2CO_3 (1.0 mmol), DMSO (2 mL), 90–110 °C, 24 h, under Ar. [b] Isolated yield based on aryl halide (average of two runs). [c] CuI (5 mol%), **A** (10 mol%), NaI (1.0 mmol).



Scheme 2 Coupling of aryl diiodobenzene and 2-octynoic acid or phenylpropiolic acid using CuI (2 mol%) and **A** (4 mol%).

1,2-diiodobenzene and alkynoic acids, where the desired products could be obtained in 89% and 74% yields, respectively.

When phenylpropiolic acid and 2,5-diiodothiophene were employed as coupling partners (Scheme 3), a decrease in the yield was observed (53%), which may be attributed to competitive complexation with the CuI catalyst.



Scheme 3 Coupling of aryl 2,5-diiodothiophene and phenylpropiolic acid in the presence of CuI (2 mol%) and **A** (4 mol%).

To further highlight the synthetic utility of our new protocol, the decarboxylative coupling of 4-iodoanisole and phenylpropiolic acid was scaled-up to gram scale. The desired product was obtained in 96% yield (1.51 g).

These results beg an interesting mechanistic question of whether the coupling proceeded by alkynylcarboxylic acids followed by the known copper-catalyzed Sonogashira coupling reaction?[17] In order to examine this question, the coupling of 4-iodoanisole and phenylacetylene, instead of phenylpropiolic acid, was carried out at 90 °C for 24 h under an argon atmosphere. Only a trace of the desired product was obtained. Thus, it can be seen that a CO_2-release process takes place simultaneously during the coupling, although the actual active species is unknown at this time. Mechanistic investigations are underway in our group.[18]

In conclusion, we have developed a highly effective copper-catalyzed decarboxylative coupling between various aryl and alkyl halides with alkynoic acids and the corresponding target products were obtained in good to excellent yields. It is noteworthy that these substrates include aromatic and aliphatic ones. The protocol employed inexpensive and a low-loading of copper-based catalyst under mild conditions, and provides an alternative to traditional Pd-catalysts for these transformations. Thus, it is potentially useful for the synthesis of some biologically active molecules. Further investigations in this direction are in progress.

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