

# Copper-catalyzed decarboxylative cross-coupling of alkynyl carboxylic acids with aryl halides†

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**The copper-catalyzed decarboxylative reactions of alkynyl carboxylic acids with aryl halides were performed under relatively mild reaction conditions. Benzofurans could be further prepared smoothly by a one-pot domino protocol on the basis of decarboxylative cross-coupling of 2-iodophenol.**

The alkyne moiety is prevalent in molecular materials, pharmaceuticals, and natural products.<sup>1</sup> During the past decades, the Sonogashira coupling has become one of the most versatile and powerful methods for the preparation of arylalkynes and conjugated enynes.<sup>2,3</sup> Recently, the scope of the reaction has been extended from organic halides to various pseudohalides.<sup>4</sup> Despite remarkable advances in this type of transformation, from an academic standpoint, further development of reliable alternatives for the straightforward synthesis of internal arylalkynes, especially starting from other readily available sources rather than terminal alkynes, is still a subject of importance in this area.

Carboxylic acids are conveniently available, easy to store, and simple to handle, and carboxylate groups may function as the leaving group in cross-coupling, in which only carbon dioxide is produced as byproduct. Recently, Pd-catalyzed decarboxylative coupling reactions have provided attractive protocols for regioselective C–C or C–heteroatom bond formation.<sup>5</sup> Alkynyl carboxylic acid represents a promising alternative to terminal alkyne owing to higher reactivity, simplicity and ready availability from inexpensive aldehyde.<sup>6</sup> In particular, the use of alkynyl carboxylic acid as the coupling partner may efficiently suppress the formation of dimerization product diynes that frequently occurs in the Sonogashira reactions.<sup>7</sup> Recently, pioneering work has established that the Pd-catalyzed decarboxylative couplings of alkynyl carboxylic acids with aryl halides,<sup>8a–c</sup> arylboronic acids<sup>8d</sup> or benzyl halides<sup>8e</sup> afford internal alkynes. This strategy provides a potential alternative to achieve internal alkyne from aldehyde.<sup>6</sup> It would be useful for total synthesis of natural products containing internal alkyne frameworks. However, these palladium-mediated methods still suffer from some limitations. Firstly, tetrabutylammonium fluoride (TBAF) (2–6 equiv.), stoichiometric silver salt, and/or lithium iodide (2–3 equiv.) as additives are required to improve yields. Secondly, highly expensive, air- and/or moisture-sensitive bulky phosphines are frequently encountered in the reactions.

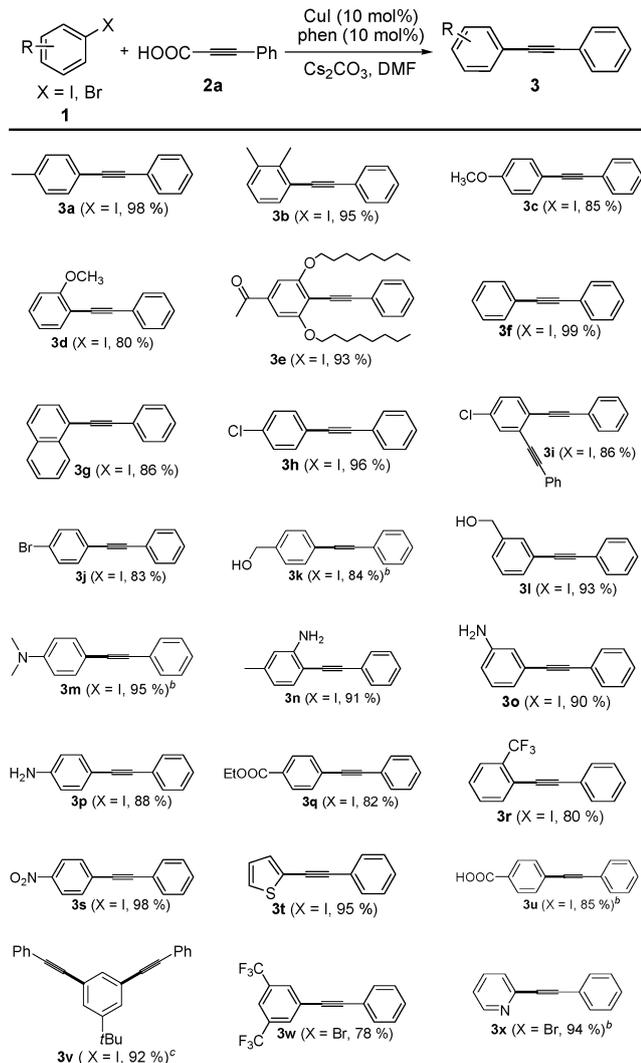
At the turn of this century, the economic attractiveness and good functional tolerance of copper-catalytic systems led to remarkable progress in the development of copper-catalyzed coupling reactions.<sup>9</sup> However, in contrast to well-established palladium-catalyzed decarboxylative coupling reactions, the copper-only-mediated systems are less developed.<sup>10</sup> To the best of our knowledge, there is no example describing the copper-catalyzed decarboxylative coupling to form C(sp)(aryl)C(sp<sup>2</sup>) bonds so far. As part of our ongoing research into the development of highly efficient, versatile copper-catalyzed cross-coupling reactions,<sup>11</sup> we herein disclose the first copper-catalyzed decarboxylative cross-coupling of alkynyl carboxylic acids with aryl halides in the presence of inexpensive and commercially available CuI and 1,10-phenanthroline (phen).

Our initial investigation aimed at the coupling of readily available phenylpropionic acid with *p*-chloriodobenzene in 1,2-dimethoxyethane (DME) using copper(I) iodide as the catalyst. As Cs<sub>2</sub>CO<sub>3</sub> was used as the base, initial reaction screening led to disappointing results in the absence of ligand. We subsequently screened a variety of ligands, solvents, and bases (Table S1). The best results were obtained in DMF at 130 °C for 24 h by using Cs<sub>2</sub>CO<sub>3</sub> as base in the presence of CuI (10 mol%) and phen (10 mol%).

With optimized conditions now in hand, we explored the scope of this process with respect to a wide array of aryl halide structure as summarized in Table 1. Gratifyingly, no matter whether the aryl iodides were electron-rich, electron-poor, or sterically bulky, all of them afforded good to excellent yields (Table 1). The high yields observed in the reaction of 4-chlorophenyl iodide or 4-bromophenyl iodide implied that there was good chemoselectivity between aryl iodide and bromide or chloride (Table 1, **3h–3j**). The heteroaryl iodide was also coupled with phenylpropionic acid in a good yield (Table 1, **3t**). Moreover, high-yielding decarboxylative coupling was possible with aryl bromide bearing an electron-withdrawing group or heteroaryl bromide, although the reaction has not yet been investigated in detail (Table 1, **3w** and **3x**). It is important to stress that the reaction conditions were compatible with the presence of functional groups such as hydroxymethyl, ketone, amino, ester and nitro groups, which may then be subject to further synthetic transformations (Table 1, **3k–s**). When *t*-butyl-3,5-diiodobenzene was treated with phenylpropionic acid, a two-fold decarboxylative coupling took place to afford the conjugated alkyne in 92% yield (Table 1, **3v**), which indicated that the current copper-catalysis may have a broad potential for constructing extended  $\pi$ -electron systems. Importantly, when aryl iodide bore the carboxyl group, phenylpropionic acid preferably underwent the decarboxylation rather than arenecarboxylic acid (Table 1, **3u**).

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**Table 1** Copper-catalyzed decarboxylative coupling of phenylpropionic acid with a variety of aryl halides<sup>a</sup>

<sup>a</sup> Conditions: aryl halide (0.25 mmol), phenylpropionic acid (0.35 mmol), CuI (10 mol%), phen (10 mol%), Cs<sub>2</sub>CO<sub>3</sub> (0.375 mmol), DMF (1 mL), 24 h, 130 °C. Isolated yield given in parentheses. <sup>b</sup> CuI (20 mol%). <sup>c</sup> CuI (20 mol%), phenylpropionic acid (0.70 mmol).

To expand the scope of our methodology, we used this catalytic system in the decarboxylative couplings of other alkynyl carboxylic acids with aryl iodides (Table 2). Overall, we were pleased with the generality of our methodology. As shown in Table 2, various alkynyl carboxylic acids proceeded smoothly to afford the desired arylated alkynes in good to excellent yields. A variety of aromatic alkynyl carboxylic acids could be efficiently converted into the corresponding coupling products, which demonstrated that electronic and steric effects of substituents could be neglected nearly (Table 2, entries 1–5). Heteroaryl alkynyl carboxylic acid was reactive (Table 2, entry 6). Worthy of note was that aliphatic alkynyl carboxylic acids could be effectively coupled with aryl iodides to furnish the desired products in good to excellent yields (Table 2, entries 7–10).

**Table 2** Copper-catalyzed decarboxylative coupling of alkynyl carboxylic acids with aryl iodides<sup>a</sup>

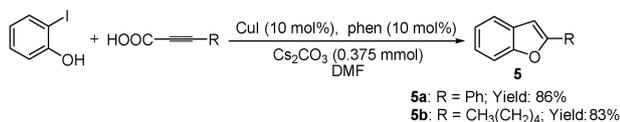
Reaction scheme for Table 2:  $\text{Ar-I} + \text{HOOC-C}\equiv\text{C-R} \xrightarrow[\text{Cs}_2\text{CO}_3, \text{DMF}]{\text{CuI (10 mol\%), phen (10 mol\%)}} \text{Ar-C}\equiv\text{C-R}$

Entry	Ar	R	Product	Yield <sup>b</sup>
1	4-MeC <sub>6</sub> H <sub>4</sub>	4-ClC <sub>6</sub> H <sub>4</sub>	4a	91%
2	4-NH <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	4-MeC <sub>6</sub> H <sub>4</sub>	4b	82%
3	4-ClC <sub>6</sub> H <sub>4</sub>	2-MeOC <sub>6</sub> H <sub>4</sub>	4c	90% <sup>c</sup>
4	4-ClC <sub>6</sub> H <sub>4</sub>	4-MeOC <sub>6</sub> H <sub>4</sub>	4d	92%
5	4-ClC <sub>6</sub> H <sub>4</sub>	1-naphthyl	4e	90%
6	4-ClC <sub>6</sub> H <sub>4</sub>	2-thienyl	4f	87%
7	4-MeC <sub>6</sub> H <sub>4</sub>	<i>n</i> -Pent	4g	85%
8	1-naphthyl	<i>n</i> -Bu	4h	88% <sup>c</sup>
9	4-ClC <sub>6</sub> H <sub>4</sub>	<i>n</i> -Pent	4i	87%
10	4-NH <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	<i>n</i> -Bu	4j	84% <sup>c</sup>

<sup>a</sup> Conditions: aryl iodide (0.25 mmol), alkynyl carboxylic acid (0.35 mmol), CuI (10 mol%), phen (10 mol%), Cs<sub>2</sub>CO<sub>3</sub> (0.375 mmol), DMF (1 mL), 24 h, 130 °C. <sup>b</sup> Yield of isolated product. <sup>c</sup> CuI (20 mol%).

Benzofuran-containing molecules are frequently found in a variety of biologically active compounds. Although these bioactive properties have motivated the development of efficient methods for creating the benzofuran framework, exploring improved routes is still a very active and prolific field of research. Herein, we utilized our protocol to prepare substituted benzofurans directly from 2-iodophenol by a sequential one-pot reaction. For example, 2-iodophenol underwent the domino reactions involving decarboxylative coupling and subsequent intramolecular hydroalkoxylation to provide the benzofuran derivatives in good yields (Scheme 1).

Although more detailed investigations of the reaction mechanism are currently underway, we have addressed the competition between decarboxylation and oxidative addition with the DFT calculations of the corresponding reaction mechanisms (Fig. S1). Computational investigation suggests that the oxidant addition should occur at first on copper(I) to generate the copper(III) intermediate, which subsequently reacts with alkynyl carboxylic acid to produce the coupling



**Scheme 1** Synthesis of benzofurans from 2-iodophenol.

product through decarboxylation and reductive elimination. Notably, the preferential oxidative addition established herein is opposite to the previously reported copper-catalyzed decarboxylative coupling of potassium polyfluorobenzoates, in which the oxidative addition occurred on copper(I) after the decarboxylation.<sup>10</sup>

In conclusion, we have developed for the first time the copper-catalyzed decarboxylative reactions that allow the cross-coupling of alkynyl carboxylic acids with aryl halides. The process is not only simple and convenient in terms of the reaction conditions and purification, but is also tolerant of a variety of functional groups, which constitutes a practical route to give unsymmetric internal arylalkynes. Although aryl bromides or iodides rather than chlorides are required in this copper-catalyzed system, the scope, experimental ease, and reliability of a system are often much more important factors in terms of practical application. In addition, benzofurans are prepared smoothly by treatment of 2-iodophenol with alkynyl carboxylic acids under relatively mild reaction conditions. We believe that these simple procedures outlined here will find wide applications in various fields of synthetic chemistry.

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## Notes and references

- 1 (a) L. Brandsma, *Synthesis of Acetylenes, Allenes and Cumulenes: Methods and Techniques*, Elsevier, Oxford, 2004; (b) F. Diederich, P. Stang and R. R. Tykwinski, *Acetylene Chemistry: Chemistry, Biology, and Material Science*, Wiley-VCH, Weinheim, 2005.

- 2 For reviews of Sonogashira reactions, see: (a) R. Chinchilla and C. Najera, *Chem. Rev.*, 2007, **107**, 874; (b) H. Doucet and J.-C. Hierso, *Angew. Chem., Int. Ed.*, 2007, **46**, 834; (c) H. Plenio, *Angew. Chem., Int. Ed.*, 2008, **47**, 6954.
- 3 For selected examples of new catalytic systems, see: (a) C. González-Arellano, A. Abad, A. Corma, H. Garca, M. Iglesias and F. Sánchez, *Angew. Chem., Int. Ed.*, 2007, **46**, 1536; (b) F. Monnier, F. Turtaut, L. Duroure and M. Taillefer, *Org. Lett.*, 2008, **10**, 3203; (c) O. Vechorkin, D. Barmaz, V. Proust and X. Hu, *J. Am. Chem. Soc.*, 2009, **131**, 12078; (d) E. Zuidema and C. Bolm, *Chem.–Eur. J.*, 2010, **16**, 4181.
- 4 For selected examples of Sonogashira reactions with pseudohalides, see: (a) S. Silva, B. Sylla, F. Suzenet, A. Tatibouët, A. P. Rauter and P. Rollin, *Org. Lett.*, 2008, **10**, 853; (b) G. Fabrizi, A. Goggiamani, A. Sferrazza and S. Cacchi, *Angew. Chem., Int. Ed.*, 2010, **49**, 4067.
- 5 For examples of the decarboxylative coupling reactions, see: (a) L. J. Gooßen, G. Deng and L. M. Levy, *Science*, 2006, **313**, 662; (b) H.-P. Bi, L. Zhao, Y.-M. Liang and C.-J. Li, *Angew. Chem., Int. Ed.*, 2009, **48**, 792; (c) C. Zhang and D. Seidel, *J. Am. Chem. Soc.*, 2010, **132**, 1798; (d) C. Wang, I. Piel and F. Glorius, *J. Am. Chem. Soc.*, 2009, **131**, 4194; (e) F. Zhang and M. F. Greaney, *Angew. Chem., Int. Ed.*, 2010, **49**, 2768; (f) W. Jia and N. Jiao, *Org. Lett.*, 2010, **12**, 2000; (g) R. R. P. Torregrosa, Y. Ariyaratna, K. Chattopadhyay and J. A. Tunge, *J. Am. Chem. Soc.*, 2010, **132**, 9280.
- 6 J. P. Das, U. K. Roy and S. Roy, *Organometallics*, 2005, **24**, 6136.
- 7 For a review, see: P. Siemsen, R. C. Livingston and F. Diederich, *Angew. Chem., Int. Ed.*, 2000, **39**, 2632.
- 8 (a) J. Moon, M. Jeong, H. Nam, J. Ju, J. H. Moon, H. M. Jung and S. Lee, *Org. Lett.*, 2008, **10**, 945; (b) H. Kim and P. H. Lee, *Adv. Synth. Catal.*, 2009, **351**, 2827; (c) J. Moon, M. Jang and S. Lee, *J. Org. Chem.*, 2009, **74**, 1403; (d) C. Feng and T.-P. Loh, *Chem. Commun.*, 2010, **46**, 4779; (e) W.-W. Zhang, X.-G. Zhang and J.-H. Li, *J. Org. Chem.*, 2010, **75**, 5259.
- 9 For reviews, see: (a) S. V. Ley and A. W. Thomas, *Angew. Chem., Int. Ed.*, 2003, **42**, 5400; (b) G. Evano, N. Blanchard and M. Toumi, *Chem. Rev.*, 2008, **108**, 3054; (c) F. Monnier and M. Taillefer, *Angew. Chem., Int. Ed.*, 2009, **48**, 6954.
- 10 Only one example for the copper-only system has been described so far, and see: R. Shang, Y. Fu, Y. Wang, Q. Xu, H.-Z. Yu and L. Liu, *Angew. Chem., Int. Ed.*, 2009, **48**, 9350.
- 11 For selected examples, see: (a) D. Zhao, W. Wang, F. Yang, J. Lan, L. Yang, G. Gao and J. You, *Angew. Chem., Int. Ed.*, 2009, **48**, 3296; (b) D. Zhao, N. Wu, S. Zhang, P. Xi, X. Su, J. Lan and J. You, *Angew. Chem., Int. Ed.*, 2009, **48**, 8729; (c) P. Xi, F. Yang, S. Qin, D. Zhao, J. Lan, G. Gao, C. Hu and J. You, *J. Am. Chem. Soc.*, 2010, **132**, 1822.