



Copper-catalyzed decarboxylative cross-coupling of propiolic acids and terminal alkynes

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ABSTRACT

A copper-catalyzed decarboxylative cross-coupling reaction of propiolic acids with terminal alkynes is developed leading to unsymmetric 1,3-conjugated diynes under mild conditions. This method provides a novel decarboxylative cross-coupling for sp-sp bond formation. Compared to organic halides, only carbon dioxide is produced as by-products in this approach.

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Diyne are important structural motifs in a great number of natural products as well as building blocks in organic synthesis.¹ The compounds containing 1,3-conjugated diynes fragment show an interesting array of biological activities.² For example, Norcapillene is isolated from Yin Chen Hao (*Artemisia capillaris*) (Fig. 1), which is well-known in traditional Chinese medicine.³ Thiarubrine A, isolated from *Aspilia Africana* (Fig. 1), has been shown to exhibit a wide spectrum of potent antiviral, antifungal, and antibacterial activities.⁴ 19-(2-Furyl)nonadeca-5,7-diyneic acid (Fig. 1), isolated from *Polyalthia*, shows antiplasmodial activity.⁵ And falcariindiol (Fig. 1), isolated from *Panax ginseng*, is antistaphylococcal acetylene.⁶ Therefore, efficient construction of conjugated diynes, especially unsymmetrical diynes, has attracted great attention.^{1,7}

Oxidative homocoupling reaction of terminal alkynes was first reported by Glaser⁸ in 1869 (a, Scheme 1). To date this coupling reaction and related modified methods⁹ are still widely applied in the construction of symmetric diynes.⁷ Cadiot–Chodkiewicz coupling, which is Cu-catalyzed coupling between a haloalkyne and a terminal alkyne, has been reported to be a useful route to diynes for over five decades,¹⁰ and is currently the major method for constructing unsymmetric conjugated diynes.¹¹ (b, Scheme 1) A variety of organometallic acetylides, such as alkynylcoppers,¹² alkynylsilanes,^{11f} alkynylmagnesiums,¹³ and alkynylzincs¹⁴ represent interesting alternatives to the terminal alkynes utilized in Cadiot–Chodkiewicz coupling. Co^{13a} and Pd¹⁵ are also used to catalyze this cross-coupling reaction. Several new processes have been introduced to the construction of unsymmetrical conjugated diynes. Lei et al. reported a method directly coupling two different terminal alkynes with high loading of one alkyne partner.¹⁶ Negishi

et al. developed an efficient tandem protocol, utilizing terminal alkynes and ICH=CHCl as the substrates^{7b,17} (c, Scheme 1). However, halogenated substrates or alkynyl metal reagents were required and halid by-products were produced in these methods. There is still space for improvement in the synthesis of unsymmetric conjugated diynes.

Carboxylic acids have shown great potential in catalytic transformations. The protodecarboxylation of carboxylic acids is long established in organic synthesis.^{18,19} They can also be considered to be valid candidates for the replacement of organometallic compounds, or direct C–H bond activation in numerous cross-coupling reactions^{18b,20} and Heck reactions.^{19v} We hypothesized that propiolic acids could be used as the alkyne candidates, instead of alkynyl metal reagents in the construction of unsymmetric conjugated diynes (Scheme 1). Carboxylic acids are among the most common functionalities in organic molecules. They are largely available, stable, and easy to handle and store. The decarboxylative cross-coupling reaction of aryl-carboxylates and α -oxocarboxylates has been used in biaryls and aryl ketones synthesis.^{19,21} Propiolic acids were also employed for the palladium-catalyzed decarboxylative

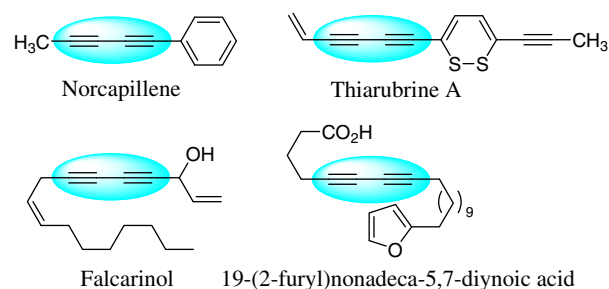
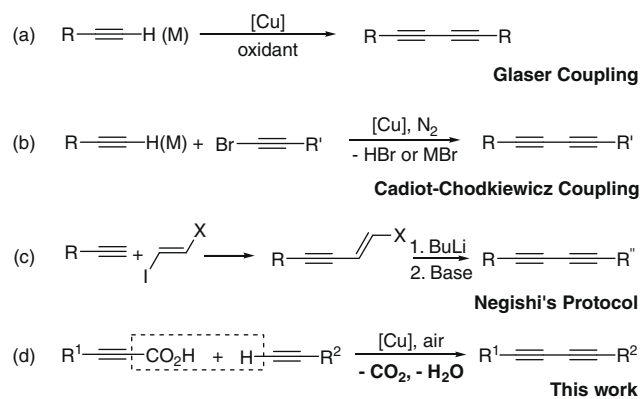


Figure 1. Examples of conjugated diynes in natural products.

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Scheme 1. Methods for synthesis of conjugated diynes.

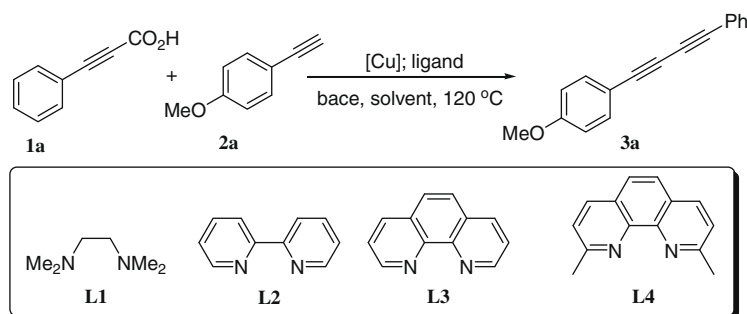
coupling reaction with aryl halides by Lee et al.^{19h,o} To the best of our knowledge, decarboxylative cross-coupling has so far only been reported for sp^3-sp^3 , sp^2-sp^2 , sp^2-sp^3 , $sp-sp^2$, and $sp-sp^3$ bond formation.²² Herein, we report a Cu-catalyzed decarboxylative $sp-sp$ cross-coupling of propiolic acids with terminal alkynes under air leading to unsymmetric conjugated diynes.

Initially, we investigated the copper-catalyzed reaction of phenyl-propionic acid **1a** and 4-methoxy phenylacetylene **2a** (Table 1). When the reaction was catalyzed by CuBr (10 mol %) in the presence of TMEDA (10 mol %) under air, only a trace amount of expected product **3a** was obtained (Table 1, entry 1). Interestingly, **3a** was produced in 10% yield when 2,2'-bipyridine was used as li-

gand instead of TMEDA (Table 1, entry 2). Then we examined the efficiency of various ligands (entries 1–4). 1,10-Phenanthroline proved most efficient for this coupling reaction (Table 1, entry 3). The organic base Et₃N showed the best activity compared to other inorganic base such as KOAc and K₃PO₄ (Table 1, entries 5–7). On the contrary, the reaction gave low yield in the absence of base (10%, Table 1, entry 8). Further investigations showed that the most effective catalyst is CuI (Table 1, entry 11). DMF proved to be a particularly suitable solvent for this transformation (Table 1, cf. entries 3 with 12 and 13). It is noteworthy that only a trace of **3a** was obtained when the reaction was carried out under N₂ (Table 1, entry 14). After a great deal of screening on different parameters, we concluded that the reaction proceeded most efficiently under these conditions: CuI (10 mol %), 1,10-phenanthroline (10 mol %), Et₃N (2.0 equiv), reacted at 120 °C in DMF under air (Table 1, entry 11).

Under the optimal reaction conditions, different propiolic acids and terminal alkynes were surveyed, respectively. The results are summarized in Table 2. Substituted arylpropionic acid with substituents at the *para* or *meta* positions of the aryl group could react with terminal alkynes smoothly (Table 2, entries 2, 3, and 6–13). The reaction of 3-(2-furfuryl)-propionic acid **1d** gave a lower yield than other reactions (Table 2, entry 4). It is noteworthy that 4-styrylpropionic acid **1e** reacted successfully with **2a** giving the desired product **3e** in 47% yield (Table 2, entry 5). Notably, halogen-substituted phenylacetylenes are also tolerable to this kind of transformation (Table 2, entries 9, and 11). Moreover, heterocycle substituted alkyne **2h** reacted smoothly with arylpropionic acid **1f** producing the desired 1,3-conjugated diynes **3j** in 46% yield (Table 2, entry 12). Even alkynes with an alkenyl group or an alkyl group

Table 1
Cu-catalyzed decarboxylative coupling reaction of phenyl-propionic acid and 4-methoxyphenylacetylene.^{a,b}



Entry	[Cu]	Ligand	Base	Solvent	Yield ^c (%)
1	CuBr	L1	K ₂ CO ₃	DMF	Trace
2	CuBr	L2	K ₂ CO ₃	DMF	10
3	CuBr	L3	K ₂ CO ₃	DMF	45
4	CuBr	L4	K ₂ CO ₃	DMF	43
5	CuBr	L3	KOAc	DMF	42
6	CuBr	L3	K ₃ PO ₄	DMF	34
7	CuBr	L3	Et ₃ N	DMF	48
8	CuBr	L3	–	DMF	10
9	CuCl	L3	K ₂ CO ₃	DMF	34
10	Cu(OAc) ₂	L3	K ₂ CO ₃	DMF	35
11	CuI	L3	Et ₃ N	DMF	51
12	CuBr	L3	K ₂ CO ₃	DMSO	42
13	CuBr	L3	K ₂ CO ₃	DMA	39
14 ^d	CuBr	L3	K ₂ CO ₃	DMF	Trace
15 ^e	CuI	L3	K ₂ CO ₃	DMF	Trace

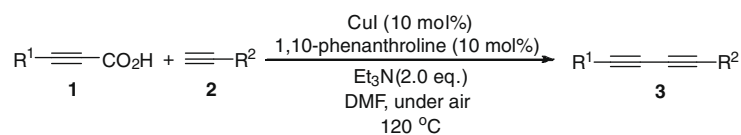
^a The reaction was carried out with **1a** (0.6 mmol), **2a** (0.5 mmol, 1.0 equiv), copper-catalyzer (0.05 mmol), ligand (0.05 mmol), base, and solvent (3 mL) heated to 120 °C under air for 20 h.

^b The product of homocoupling of **1a** and **2a** were observed in all the reactions.

^c Isolated yield.

^d The reaction was carried out under N₂.

^e 0.01 mmol of CuI and 0.01 mmol of **L3** was used.

Table 2Cu-catalyzed decarboxylative coupling reaction of propiolic acids and terminal alkynes^a

Entry	1	2	R ¹ —C≡C—R ²	3	Yield ^b (%)
1	1a	2a		3a	51
2	1b	2a		3b	53
3	1c	2a		3c	54
4	1d	2a		3d	33
5	1e	2a		3e	47
6	1f	2b		3b	51
7	1f	2c		3a	46
8	1f	2d		3f	46
9	1f	2e		3g	47
10	1f	2f		3h	49
11	1f	2g		3i	40
12	1f	2h		3j	46
13	1g	2c		3k	57
14	1f	2i		3l	36
15	1f	2j		3m	32

^a The reaction was carried out with **1** (0.3 mmol), **2** (0.25 mmol), CuI (0.025 mmol), 1,10-phenanthroline (0.025 mmol), Et₃N (0.5 mmol), and DMF (1.5 mL) heated to 120 °C under air for 20 h.

^b Isolated yield.

reacted successfully with arylpropionic acid, but the yields were lower than other reactions (Table 2, entries 14 and 15).

In conclusion, we have developed a copper-catalyzed decarboxylative cross-coupling reaction of propiolic acids with terminal alkynes under air, leading to 1,3-conjugated unsymmetric diynes. This method provides a novel decarboxylative cross-coupling for sp–sp bond formation. Compared to organic halides, only carbon dioxide is produced as by-products in this approach. The reaction is carried out at mild conditions, avoiding the use of haloalkynes and alkynyl metal reagents. Further study on the application of this method in organic synthesis is ongoing in our laboratory.

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Supplementary data

Supplementary data (experimental details and NMR spectra) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.12.138.

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