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COMMUNICATION

A copper-based catalytic system for carboxylation of terminal alkynes: synthesis of alkyl 2-alkynoates†

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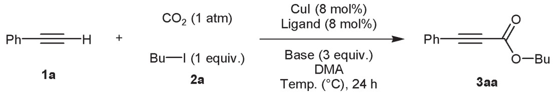
An efficient coupling of terminal alkynes and CO_2 in the presence of alkyl halides can be achieved under ambient conditions using a copper/phosphine catalyst system, providing facile access to a variety of functionalised alkyl 2-alkynoates.

Transformation involving the fixation of carbon dioxide (CO_2) into certain molecules, generally resulting in the formation of carboxylic acids and their derivatives, constitutes a highly attractive synthetic method since CO_2 is inexpensive, easily-available, non-toxic and thus can be considered as an ideal C1 unit in organic synthesis. A number of procedures, therefore, have so far been developed for the process, including recently reported transition metal-catalysed approaches.[1]

Alkynyl carboxylic acids and their derivatives are an important class of compounds due to their existence in a number of biologically active molecules[2a] as well as their utility as versatile intermediates in organic synthesis.[2b–f] The most widely reported approaches for synthesizing alkynyl carboxylic acids involve the lithiation or magnesiation of terminal alkynes followed by reacting with solid or gaseous CO_2.[3] A major drawback of the process, however, involves the poor functional group compatibility, limiting their efficiency and applicability. The palladium-catalysed oxidative carbonylation of terminal alkynes in alcoholic solvents under an atmosphere of CO, giving rise to alkynyl carboxylic acids, was first reported by Tsuji *et al.*[4a] and later studied in detail by others.[5] Although the reactions proceed under relatively mild conditions, the use of toxic CO gas seems less preferable. The copper catalyst has been reported to participate in the coupling of alkynes with gaseous CO_2, providing more efficient, applicable routes to alkynyl carboxylic acids. Inoue *et al.* previously showed that the copper-catalysed carboxylative coupling of terminal alkynes with CO_2 in the presence of alkyl bromides afforded alkyl 2-alkynoates at an elevated temperature (100 °C) in a polar, aprotic solvent.[6] Recently, synthesis of allylic 2-alkynoates *via* the coupling of terminal alkynes and allylic chlorides under an atmosphere of 1.5 MPa (*ca.* 15 atm) CO_2 has been developed making use of the copper/N-heterocyclic carbene (NHC) catalyst system.[7] During the course of this work, two other copper-based catalytic systems, one is copper/diamine[8] and another is copper/NHC,[9] have been introduced, which successfully effect the carboxylative coupling of terminal alkynes with CO_2 to give alkynyl carboxylic acids under mild conditions (rt–50 °C, 1–5 atm CO_2). Herein, we present our independent finding that the copper/phosphine system is also an active catalyst for the reaction of terminal alkynes and CO_2 in the presence of alkyl halides, producing alkyl 2-alkynoates generally in good to high yields under ambient conditions.[10,11]

Our investigation began by examination of the coupling reaction of phenylacetylene (**1a**) with CO_2 (1 atm) in the presence of butyl iodide (**2a**) in DMA to obtain the optimal reaction conditions (Table 1). The effect of base on the process was initially evaluated using 8 mol% of CuI as a catalyst. Although DBU and ^{t}BuONa turned out to be ineffective (entries 1 and 2), the use of carbonate bases such as K_2CO_3 and Cs_2CO_3 provided the desired 2-alkynoate **3aa** in good yields (entries 3–6).

Table 1 Effect of reaction parameters[a]



Entry	Base	Ligand	Temp. (°C)	Yield (%)[b]
1	DBU	none	80	trace
2	^{t}BuONa	none	80	trace
3	K_2CO_3	none	80	70
4	K_2CO_3	none	rt	trace
5	Cs_2CO_3	none	80	77
6	Cs_2CO_3	none	rt	65
7	Cs_2CO_3	IMes·HCl	rt	24[c]
8	Cs_2CO_3	IPr·HCl	rt	20[c]
9	Cs_2CO_3	2,2′-bipyridine	rt	61[c]
10	Cs_2CO_3	dppb	rt	0
11	Cs_2CO_3	PPh_3	rt	74[c]
12	Cs_2CO_3	P^tBu_3	rt	72[c]
13	Cs_2CO_3	PEt_3	rt	90
14[d]	Cs_2CO_3	none	rt	0

[a] Reactions were carried out on a 0.50 mmol scale. [b] Isolated yield. [c] Determined by ^{1}H-NMR using 1,1,2-trichloroethane as an internal standard. [d] Run in the absence of CuI.

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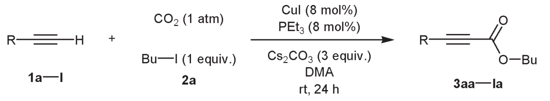
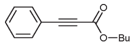
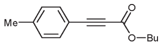
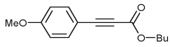
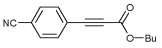
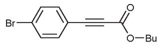
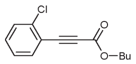
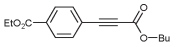
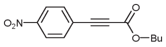
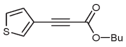
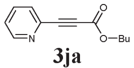
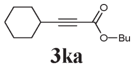
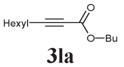
† Electronic supplementary information (ESI) available: Experimental procedures and spectral/analytical data. See DOI: 10.1039/c2ob06884b

Table 2 Substrate scope of the process (alkynes)[a,b]



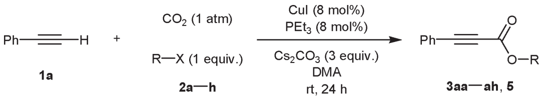
 **3aa** 90%	 **3ba** 86%	 **3ca** 83%[c]
 **3da** 0% (86%)[d,e]	 **3ea** 62% (89%)[d,e]	 **3fa** 50% (86%)[d,e]
 **3ga** 20% (36%)[d,e]	 **3ha** 0% (8%)[d,e]	 **3ia**, >99%
 **3ja** trace (trace)[d,e]	 **3ka** 51% (78%)[d,e]	 **3la** 42% (83%)[d,e]

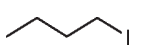
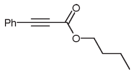
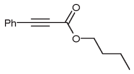
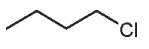
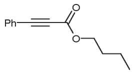
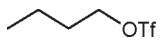
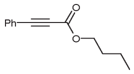
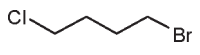
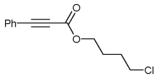
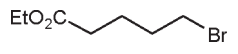
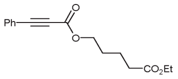
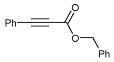
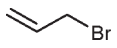
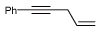
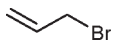
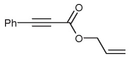
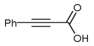
[a] Reactions were carried out on a 0.50 mmol scale. [b] Isolated yield. [d] 48 h. [d] 2,2′-Bipyridine was used instead of PEt$_3$. [e] 50 °C.

Interestingly, the reaction proceeded even at room temperature when Cs$_2$CO$_3$ was employed (entry 4 *vs.* 6). Subsequent screening of a number of ligands, including N-heterocyclic carbenes (entries 7 and 8), diamine (entry 9) and phosphines (entries 10–13), revealed that Et$_3$P was the best; in this case, **3aa** was obtained in excellent yield (entry 13). It is particularly noteworthy that the process can be performed under ambient conditions (room temperature, 1 atm CO$_2$). On the other hand, no product was obtained from the reaction in the absence of a copper catalyst (entry 14).

The catalytic activity of the system was next evaluated in the coupling reaction of an array of alkyne compounds **1b–l** (Table 2). Reactions of phenylacetylenes possessing an electron-donating group on the benzene ring (**1b** and **1c**) smoothly proceeded, producing the corresponding coupling products (**3ba** and **3ca**) in high yields. For some substrates that have an electron-withdrawing group on the benzene ring, it was found that the use of 2,2′-bipyridine as a ligand provided results superior to PEt$_3$.[12] For example, the coupling reactions of phenylacetylenes substituted with 4-cyano, 4-bromo or 2-chloro (**1d–f**) underwent smooth coupling at 50 °C in the presence of the CuI/2,2′-bipyridine catalyst system, resulting in the efficient formation of the corresponding 2-alkynoates (**3da–fa**). On the other hand, 4-ethoxycarbonylphenylacetylene (**1g**) and 4-nitrophenylacetylene (**1h**) have turned out less reactive and the coupling products (**3ga** and **3ha**) were obtained only in lower yields. Substrates bearing a heteroaromatic ring system were also employed for the process. While 3-ethynylthiophene (**1i**) efficiently participated in the coupling process to give **3ia** in quantitative yield, the reaction of 2-pyridylacetylene (**1j**) was rather sluggish and only a trace amount of **3ja** was detected from the reaction mixture. In addition, (cyclo)alkylacetylenes (**1k** and **1l**) proved suitable for the coupling and high yields were obtained, especially when a copper/2,2′-bipyridine system was employed.

Table 3 Substrate scope of the process (alkyl halides)[a]

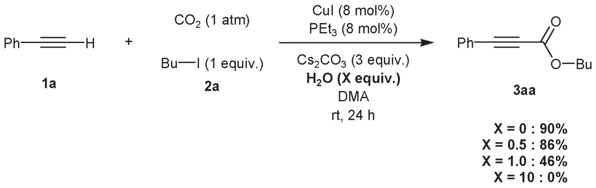


Entry	R–X	2	Product		Yield (%)[b]
1		**2a**		**3aa**	90
2		**2b**		**3aa**	80
3		**2c**		**3aa**	0
4		**2d**		**3aa**	0
5		**2e**		**3ae**	81
6		**2f**		**3af**	91
7		**2g**		**3ag**	67
8		**2h**		**4**	(94)[c]
9[d]		**2h**		**3ah**	65
10				**5**	81

[a] Reactions were carried out on a 0.50 mmol scale. [b] Isolated yield. [c] Yield of **4**. [d] Allyl bromide (**2h**) was added after 24 h and 36 h (0.25 mmol each).

The coupling process was next performed using a variety of alkyl halides (Table 3). In addition to alkyl iodide **2a** (entry 1), alkyl bromide **2b** was found to be a suitable substrate for the process (entry 2). On the other hand, alkyl chloride **2c** and triflate **2d** were completely unreactive (entries 3 and 4).[13] The reaction using 1-bromo-4-chlorobutane **2e** occurred selectively at the bromine site to give **3ae** in high yield (entry 5). Alkyl bromide **2f**, possessing an ethoxycarbonyl group, also participated in the process, providing the corresponding coupling product **3af** in high yield (entry 6). Moreover, the reaction efficiently proceeded in the presence of benzyl bromide **2g**, affording benzyl 2-alkynoate **3ag** in good yield (entry 7). We did not obtain the desired product **3ah** at all when allyl bromide **2h** was employed: in this case, byproduct **4** which resulted from the direct coupling of **1a** with **2h** was isolated in 94% yield (entry 8). On the contrary, it was found that the coupling product **3ah** can indeed be obtained if the reaction was first carried out in the absence of **2h** and then **2h** was added into the reaction mixture (entry 9). Furthermore, the reaction of **1a** with CO$_2$ without adding any alkyl halides **2** provided the carboxylic acid **5** in high yield (entry 10).

Influence of the added H$_2$O in the coupling process was also examined (Scheme 1). It was found that an increased amount of H$_2$O shuts down the reaction, suggesting that the removal of



Scheme 1 Influence of added H_2O.

H_2O from the reaction system, especially from a relatively hygroscopic inorganic base, is crucial for successful coupling.

In summary, we have described new copper-based catalyst systems that successfully achieved the coupling reactions of terminal alkynes and CO_2 in the presence of alkyl halides to afford various alkyl 2-alkynoates. The method allows the reactions to proceed under ambient conditions (room temperature to 50 °C, 1 atm of CO_2), which compares favourably with the recently reported, similar Cu-catalysed methods[6–8] in which an elevated temperature or a high pressure of CO_2 is necessary for efficient coupling. The choice of the ligand turned out to be considerably important for the efficient conversion. Further studies to broaden the substrate scope of the process are underway in our laboratory.

Acknowledgements

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Notes and references

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11 For related copper-catalysed carboxylation of (hetero)aryl compounds using CO_2, see: (*a*) L. Zhang, J. Cheng, T. Ohishi and Z. Hou, *Angew. Chem., Int. Ed.*, 2010, **49**, 8670; (*b*) I. I. F. Boogaerts, G. C. Fortman, M. R. L. Furst, C. S. J. Cazin and S. P. Nolan, *Angew. Chem., Int. Ed.*, 2010, **49**, 8674.

12 Lower reactivity of electron-withdrawing group-substituted phenylacetylenes in a similar process has previously been observed, see reference 9.

13 Reactions of 2° alkyl halides such as isopropyl iodide, cyclohexyl iodide and cyclohexyl bromide also resulted in no formation of the desired coupling products.