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Cu(I)-Catalyzed Carboxylative Coupling of Terminal Alkynes, Allylic Chlorides, and CO_2

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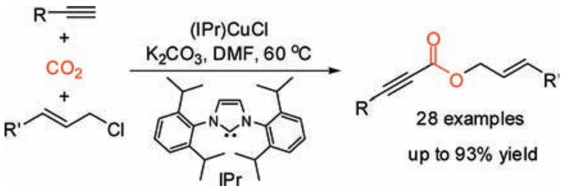
ABSTRACT



A highly selective synthesis of a variety of functionalized allylic 2-alkynoates was realized via the carboxylative coupling of terminal alkynes, allylic chlorides, and CO_2 catalyzed by the N-heterocyclic carbene copper(I) complex (IPr)CuCl. The catalyst can be easily recovered without any loss in activity and product selectivity.

Catalytic transformations of carbon dioxide (CO_2) have gained considerable attention due to its potential use as an attractive, abundant, and inexpensive C1 source and its main contribution to global warming.[1] Significant efforts have been devoted toward developing convenient approaches to convert CO_2 into carboxylic acid and derivatives.[2−6] CO_2 usually serves as a cycloaddition partner of unsaturated compounds[1c,7] and more importantly as an electrophile in the carboxylation of nucleophilic organometallic reagents.[8] Although the direct carboxylation of highly reactive organolithium and Grignard reagents with CO_2 can be easily carried out, transition-metal-catalyzed carboxylation of less reactive carbon nucleophiles such as organoboron and organozinc reagents represents a more practical method to access carboxylic acids bearing various functional groups.[3,4]

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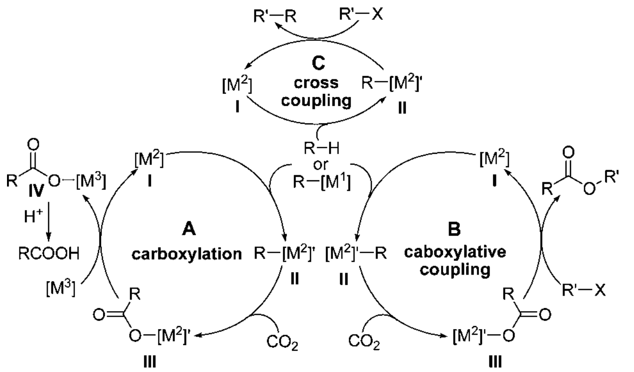
With respect to the mechanism of transition-metal-catalyzed carboxylation, active species **II** bearing a new metal−carbon bond is generally thought to be first formed through metalation of a relatively active C−H bond[9] or transmetalation of a less reactive carbon nucleophile with transition-metal catalyst **I**. The insertion of CO_2 to the metal−carbon bond affords transition-metal carboxylate **III**. Next, transmetalation of **III** with alkali metal compounds regenerates catalyst **I** and simultaneously forms carboxylate **IV** (Scheme 1, **A**). The acidification of the resulting carboxylate **IV** releases carboxylic acid. Given that an alkyl halide was introduced to the above reaction system, it is possible to produce carboxylic acid ester from the coupling between the transition-metal carboxylate **III** and alkyl halide (Scheme 1, **B**).[10] As a result, it would provide a convenient route for synthesizing carboxylic acid ester directly from the carboxylative coupling of the carbon nucleophile, alkyl halide, and CO_2. However, the easily formed byproduct from the cross-coupling between the active species **II** and alkyl halide (Scheme 1, **C**) results in poor selectivity for the carboxylative coupling product. Therefore, highly selective synthesis of carboxylic acid ester by the carboxylative coupling shown in Scheme 1 (**B**) is a promising challenge.

Scheme 1. Transition-Metal-Catalyzed Carboxylation and Carboxylative Coupling Reaction



Compared with much-studied carboxylation reactions to prepare carboxylic acid, the carboxylative coupling for directly affording carboxylic acid ester has been rarely reported. In 2000, Franks and Nicholas reported palladium-catalyzed carboxylative coupling of allylstannanes, allyl halides, and CO_2 at 5.0 MPa CO_2 pressure to produce allyl ester, but the substrate scope is very limited.[2b] Inoue and co-workers disclosed the copper-catalyzed carboxylative coupling of terminal alkynes and alkyl bromides to synthesize alkyl 2-alkynoates at 100 °C.[11] However, when allylic or benzyl 2-alkynoates, which are versatile synthetic intermediates,[12] were targeted, this methodology suffered from major formation of direct coupling or dialkyl carbonate byproduct.[13]

On the basis of the possible mechanistic aspects of carboxylative coupling shown in Scheme 1, we envisioned that, using less reactive allylic chlorides together with wise choice of catalyst, the allylic 2-alkynoates, which were generally prepared by condensation of alkynecarboxylic acid and allylic alcohol, could be directly synthesized using CO_2 as a carboxylative agent. Herein we report a convenient route for highly selective synthesis of allylic 2-alkynoates from the carboxylative coupling of terminal alkynes, allylic chlorides, and CO_2 catalyzed by the N-heterocyclic carbene (NHC) copper(I) complex.[14] Furthermore, the copper(I) catalyst can be readily recovered, without any loss in activity and product selectivity.[15]

Initially, the carboxylative coupling reaction of phenylacetylene (**1a**), cinnamyl chloride (**2a**), and CO_2 was chosen as a model reaction to identify an effective catalytic system and optimize the reaction conditions (Table 1). The reaction did not occur in the absence of any catalyst (entry 1). When copper(I) salt alone or in combination with N ligands such as 2,2′-bipyridine (bpy) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) was used as catalyst, a modest yield of carboxylative coupling product **4a** accompanied with a considerable amount of direct coupling product **3a** was obtained (entries 2−6).[16]

In this carboxylative coupling reaction, the active species **II** in Scheme 1 should be copper(I) acetylide generated by the reaction of terminal alkyne, K_2CO_3, and copper(I) catalyst, which is also proposed commonly as an intermediate in a copper-cocatalyzed Sonogashira reaction.[17] Hou and coworkers reported that N-heterocyclic carbene copper(I) complexes are excellent catalysts for carboxylation of organoboronic esters, wherein CO_2 can easily insert into an sp^2-hybridized carbon−copper(NHC) bond.[3c] Inspired by this insight, we envisioned that CO_2 could also insert into the sp-hybridized carbon−copper(NHC) bond when an N-

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(10) For copper-catalyzed C−O(carboxylate) coupling of carboxylic acids and organic halides, see: (a) Yamamoto, T. *Synth. Commun.* **1979**, *9*, 219. (b) Yamamoto, T.; Kurata, Y. *Can. J. Chem.* **1983**, *61*, 86. (c) Thasana, N.; Worayuthakarn, R.; Kradanrat, P.; Hohn, E.; Young, L.; Ruchirawat, S. *J. Org. Chem.* **2007**, *72*, 9379. (d) Sun, C.; Fang, Y.; Li, S.; Zhang, Y.; Zhao, Q.; Zhu, S.; Li, C. *Org. Lett.* **2009**, *11*, 4084.

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(13) Reaction of phenylacetylene, cinnamyl bromide, and CO_2 under the conditions of reference 11a gave 89% yield of direct coupling product and 6% yield of dicinnamyl carbonate, but no carboxylative coupling product was detected.

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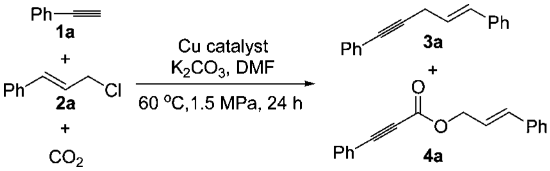
Table 1. Copper-Catalyzed Carboxylative Coupling of Phenylacetylene, Cinnamyl Chloride, and CO_2[a]

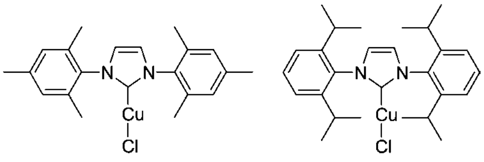


entry	catalyst	yield (%)[b]	
		3a	**4a**
1[c]	-	-	-
2	CuCl	10	46
3	CuBr	35	47
4	CuI	28	24
5	CuCl + bpy	23	52
6	CuCl + TMEDA	12	68
7	(IMes)CuCl	3	51
8[d]	(IPr)CuCl	<1	91
9[e]	(IPr)CuCl	<1	74
10[f]	(IPr)CuCl	17	-
11[g]	(IPr)CuCl	8	26

[a] Reaction conditions: **1a** (2 mmol), **2a** (3 mmol), K_2CO_3 (4 mmol), Cu catalyst (10 mol %), 20 mL of DMF. [b] Isolated yield. [c] In the absence of catalyst. [d] 92% catalyst was recovered after reaction. [e] 5 mol % catalyst. [f] In the absence of CO_2. [g] 0.2 MPa CO_2.

heterocyclic carbene copper(I) complex was used as catalyst in this carboxylative coupling reaction. We delightedly found that the copper(I) complex (IPr)CuCl (Scheme 2) could function as a highly active catalyst for this reaction to selectively afford the carboxylative coupling product **4a** (entry 8). Notably, the catalyst (IPr)CuCl was easily recovered in 92% yield by column chromatography after the reaction. It is noteworthy that no carboxylative coupling product **4a** was obtained in the absence of CO_2 (entry 10). Also, a carboxylative coupling reaction using ^{13}C-labeled CO_2 gave product $^{13}C_{carbonyl}$-labeled (*E*)-cinnamyl phenylpropiolate (**4a′**) in high yield (see Supporting Information). These results suggest that the CO_2 unit in **4a** orginates from free CO_2 rather than K_2CO_3. The presence of CO_2 resulting in the enhanced conversion of reactants suggests that the coupling reaction of cinnamyl chloride with copper(I) acetylide species is slower than that with the copper(I) carboxylate intermediate, indicating the fast insertion of CO_2 to the sp-hybridized carbon−copper(NHC) bond.

Scheme 2. N-Heterocyclic Carbene Copper(I) Complexes

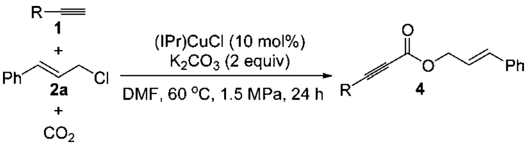


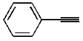
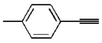
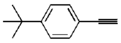
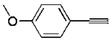
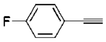
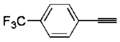
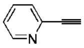
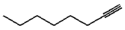
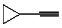
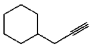
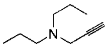
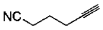
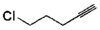
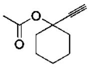
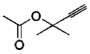
(IMes)CuCl (IPr)CuCl

The CO_2 pressure has a promising effect on reaction rate and product selectivity (entry 11). Relatively high CO_2 pressure (1.5 MPa) is beneficial to suppressing the formation of direct coupling byproduct **3a** and signficantly improving the reaction rate. Further screening of reaction parameters (see Supporting Information) established the optimum conditions: CO_2 (1.5 MPa), (IPr)CuCl (10 mol %), K_2CO_3 (2 equiv), DMF, 60 °C, 24 h.

Under the optimized reaction conditions, the scope of carboxylative coupling of terminal alkynes, allylic chlorides, and CO_2 was investigated. Carboxylative coupling reaction of a variety of aryl- and alkyl-substituted terminal alkynes with cinnamyl chloride proceeded smoothly to afford the corresponding cinnamyl 2-alkynoates in good yield and excellent selectivity (Table 2). As expected, the catalyst (IPr)CuCl could be recovered without any loss in activity and product selectivity. This catalytic system exhibited good tolerance toward a wide range of functional groups including ether, cyclopropane, cyano, and ester (entries 4, 9, 12, 14, and 15). It should be emphasized that no self-coupling product was detected in the system of **1m**, indicating that the chloride group in **1m** showed no reactivity at the reaction conditions (entry 13). However, the reaction concerning

Table 2. (IPr)CuCl-Catalyzed Carboxylative Coupling of Terminal Alkynes, Cinnamyl Chloride, and CO_2[a]



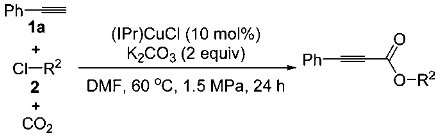
entry	alkyne		yield (%)[b]	catalyst recovery (%)
1		**1a**	91 (**4a**)	92
2		**1b**	92 (**4b**)	85
3		**1c**	80 (**4c**)	87
4		**1d**	87 (**4d**)	94
5		**1e**	91 (**4e**)	90
6		**1f**	82 (**4f**)	88
7		**1g**	56 (**4g**)	42
8		**1h**	82 (**4h**)	87
9		**1i**	87 (**4i**)	91
10		**1j**	61 (**4j**)	85
11		**1k**	72 (**4k**)	78
12		**1l**	83 (**4l**)	86
13		**1m**	76 (**4m**)	92
14		**1n**	63 (**4n**)	91
15		**1o**	71 (**4o**)	89

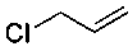
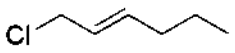
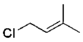
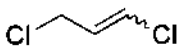
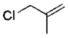
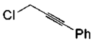
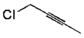
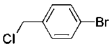
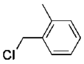
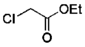
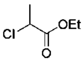
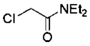
[a] Reaction conditions: **1** (2 mmol), **2a** (3 mmol), 20 mL of DMF. [b] Isolated yield, <1% yield of direct coupling byproduct was obtained.

heteroaryl-substituted alkyne **1g** gave the corresponding product **4g** in modest yield and relatively low catalyst recovery (entry 7).

Various allylic chlorides could undergo a carboxylative coupling reaction with phenylacetylene and CO_2 to selectively afford the corresponding allylic phenylpropiolates in good yield (Table 3, entries 2−5). Propargylic chlorides were also found to be suitable substrates (entries 6−8).[18] Anastas and co-workers reported that silver-catalyzed reaction of phenylacetylene, CO_2, and 3-bromo-1-phenyl-1-propyne afforded arylnaphthalene lactones.[19] On the contrary, in our reaction conditions, propargylic phenylpropiolates were predominantly obtained. This catalytic system also proved applicable for a carboxylative coupling reaction concerning benzyl chlorides and α-chloro carbonyl compounds (entries 9−13). Likewise, the catalyst (IPr)CuCl could be recovered in high yield (72−93%) through simple chromatography after the reaction (Table 3).

Table 3. (IPr)CuCl-Catalyzed Carboxylative Coupling of **1a** with Allylic Chlorides and Other Chloride Compounds[a]



entry	chloride compounds		yield (%)[b]	catalyst recovery (%)
1		**2b**	42 (**4p**)	91
2		**2c**	75 (**4q**)	89
3		**2d**	93 (**4r**)	92
4		**2e**	90 (**4s**)	93
5		**2f**	74 (**4t**)	90
6		**2g**	88 (**4u**)	87
7		**2h**	82 (**4v**)	78
8		**2i**	79 (**4w**)	81
9		**2j**	91 (**5a**)	81
10		**2k**	86 (**5b**)	72
11		**2l**	68 (**6a**)	86
12		**2m**	47 (**6b**)	85
13		**2n**	84 (**7**)	88

[a] Reaction conditions: **1a** (2 mmol), **2** (3 mmol), 20 mL of DMF. [b] Isolated yield, <1% yield of direct coupling byproduct were obtained.

In summary, we have developed an effective method for selectively synthesizing functionalized allylic 2-alkynoates by the carboxylative coupling of terminal alkynes, allylic chlorides, and CO_2. N-Heterocyclic carbene copper(I) complex (IPr)CuCl proved to be a highly selective and active catalyst for this reaction. Also, the catalyst (IPr)CuCl can be easily recovered in high yield by simple chromatography. Further exploration of highly active catalyst systems for carboxylative coupling and mechanistic study on CO_2 as a carboxylation reagent are in progress in our laboratory.

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Supporting Information Available: Experimental procedure and characterization of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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[18] When propargylic chlorides were used as substrates, no allene byproduct was detected in our reaction conditions.

[19] Eghbali, N.; Eddy, J.; Anastas, P. T. *J. Org. Chem.* **2008**, *73*, 6932.