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Cu-Catalyzed Oxidative Amidation of Propiolic Acids Under Air via Decarboxylative Coupling

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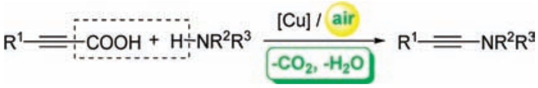
ABSTRACT



A Cu-catalyzed aerobic oxidative amidation of propiolic acids via decarboxylation under air has been developed. Only carbon dioxide is produced as byproduct in this approach. The use of air as oxidant makes this method more useful and easy to handle.

Transition metal-catalyzed C−N bond formation presents one of the most useful processes in syntheses of natural products, pharmaceuticals, and materials.[1] In particular, efficient and novel catalysis for the C(sp)−N bond has attracted much attention in the synthesis of ynamides due to their great importance in chemistry and biology.[2] Moreover, they are also versatile substrates for organic transformations.[3] Over the past decades, the use of hypervalent alkynyliodonium salts as alkynylating agent[4] and the transition metal-catalyzed coupling of amides with alkynyl halides (eq 1)[5] or 1,1-dihalo-1-alkenes (eq 2)[6] as two general strategies have mainly been developed. However, halogenated substrates were required and halide byproducts were produced in these methods. Recent advances have been achieved by Stahl and co-workers[7] through the direct amidation of terminal alkynes using O_2 (1 atm) as oxidant (eq 3). In this approach, the catalyst loading was a little high, and dropwise addition of alkyne partners (over 4 h) and a large excess of amides were required to prevent the dimerization of alkynes (eq 3).[8]

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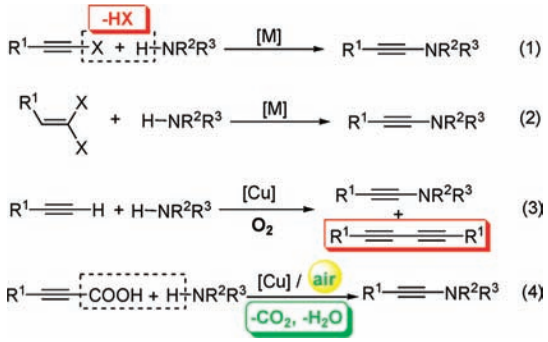
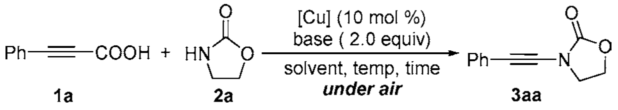
Hence, the development of environmentally benign and efficient methods for C(sp)−N bond formation is still important for continued advancements in this area.



The importance of transition metal-catalyzed decarboxylative cross-coupling chemistry has grown rapidly in recent years.[9,10] We envisioned that decarboxylative cross-coupling perhaps can provide a novel and attractive approach for ynamides from amides and propiolic acids because (1) the carboxylic acids are readily available, easy to store, and simple to handle, (2) as opposed to organic halides, only carbon dioxide is produced as byproduct, and (3) the Glaser−Hay oxidative dimerization product diynes[8] (eq 3) could be efficiently inhibited, and the amides loading could be reduced. Herein, we demonstrate a novel copper-catalyzed oxidative decarboxylative amidation of propiolic acids leading to ynamides under air (eq 4).

We initially paid attention to the decarboxylative cross-coupling of phenyl propiolic acid **1a** with 2-oxazolidinone **2a** catalyzed by inexpensive $CuCl_2$·$2H_2O$ in toluene under air (Table 1). Interestingly, the expected oxidative decarboxylative amidation product **3aa** was obtained in 5% yield in the presence of K_2CO_3 (Table 1, entry 1). When pyridine or Cs_2CO_3 was used in this reaction, the expected product **3aa** was not produced (Table 1, entries 3 and 4). Gratifyingly, 83% of **3aa** was achieved when Na_2CO_3 was employed as base (Table 1, entry 5). It is noteworthy that air participated as an ideal oxidant[11] to complete the catalytic cycle, which makes this approach more economical, readily handled, and practical. On the contrary, only a trace of **3aa** was produced when the reaction was carried out under N_2 (Table 1, entry 8). Attempts of using other copper catalysts such as $CuBr_2$,

Table 1. Cu-Catalyzed Oxidative Coupling of **1a** with **2a** via Decarboxylative Amidation[a]



entry	Cu	base	solvent	temp (°C)	time (h)	yield of **3aa** (%)[b]
1	$CuCl_2$·$2H_2O$	K_2CO_3	toluene	100	16	5
2	$CuCl_2$·$2H_2O$	$NaHCO_3$	toluene	100	2.5	28
3	$CuCl_2$·$2H_2O$	pyridine	toluene	100	9	0
4	$CuCl_2$·$2H_2O$	Cs_2CO_3	toluene	100	19	0
5	$CuCl_2$·$2H_2O$	Na_2CO_3	toluene	100	12	83
6[c]	$CuCl_2$·$2H_2O$	Na_2CO_3	toluene	100	12	47
7[d]	$CuCl_2$·$2H_2O$	Na_2CO_3	toluene	100	16.5	69
8[e]	$CuCl_2$·$2H_2O$	Na_2CO_3	toluene	100	13	trace
9	$CuBr_2$	Na_2CO_3	toluene	100	12	70
10	$Cu(OAc)_2$·H_2O	Na_2CO_3	toluene	100	12	68
11	$CuSO_4$·$5H_2O$	Na_2CO_3	toluene	100	12	66
12	Cu_2O	Na_2CO_3	toluene	100	12	56
13	$CuCl_2$·$2H_2O$	Na_2CO_3	xylene	90	12	trace
14	$CuCl_2$·$2H_2O$	Na_2CO_3	CH_3CN	reflux	12	38
15	$CuCl_2$·$2H_2O$	Na_2CO_3	benzene	reflux	12	87
16	$CuCl_2$·$2H_2O$	Na_2CO_3	toluene	reflux	12	48

[a] General conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), Cu (10 mol %), base (2.0 equiv), solvent (2 mL), under air. [b] Isolated yield. Homocoupled dimer product was observed in some reactions. [c] 5 mol % of $CuCl_2$·$2H_2O$ was employed. [d] The reaction was carried out in the presence of pyridine (20 mol %) as additive. [e] The reaction was carried out under N_2.

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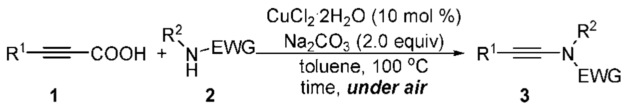
$Cu(OAc)_2{\cdot}H_2O$, $CuSO_4{\cdot}5H_2O$, or Cu_2O gave lower yields (Table 1, entries 9−12). After a great deal of screening on different parameters (see the Supporting Information), we found that the oxidative decarboxylative amidation catalyzed by $CuCl_2{\cdot}2H_2O$ (10 mol %) with Na_2CO_3 as base refluxed in benzene led to the highest efficiency (87% yield, Table 1, entry 15). As we expected, 2.0 equiv of amide **2a** loading efficiently completed this transformation, and the homocoupled dimer product was obviously inhibited (9%) (Table 1, entry 15). However, when the reaction was refluxed in toluene instead of benzene, **3aa** was obtained in only 48% yield, which is lower than that at 100 °C in toluene or refluxed in benzene (cf. entries 5, 15, and 16).

The scope of the transformation was further expanded to a variety of propiolic acids (Table 2). It is observed that aryl- and alkyl-substituted propiolic acids are good precoupling partners for this transformation (22−86% yield). Aryl propiolic acids with electron-donating substituents proceeded efficiently in good yields (Table 2, entries 1−4 and 9−12). Markedly, alkenyl-substituted propiolic acids such as (*E*)-5-phenylpent-4-en-2-ynoic acid **1f** underwent this transformation with **2a** and **2b** leading to **3fa** and **3fb**, respectively (Table 2, entries 5 and 13).

Table 2. Cu-Catalyzed Oxidative Decarboxylative Amidation of **1** with **2**[a]

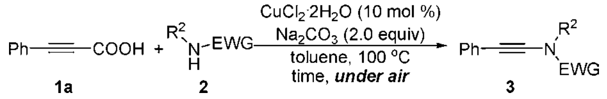


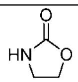
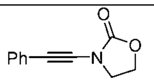
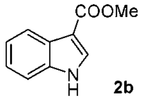
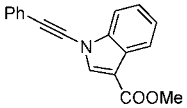
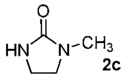
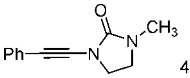
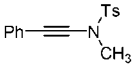
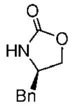
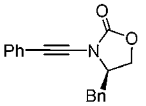
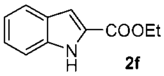
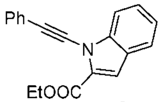
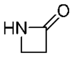
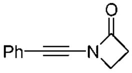
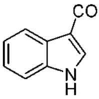
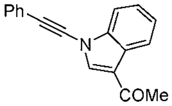
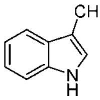
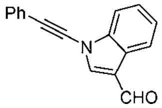
entry	R^1 (**1**)	**2**	time (h)	yield of **3** (%)[b]
1	4-MeO-C_6H_4− (**1b**)	**2a**	28	84 (**3ba**)
2	4-Me-C_6H_4− (**1c**)		28	76 (**3ca**)
3	3-Me-C_6H_4− (**1d**)		26	75 (**3da**)
4[c]	3,4-$(MeO)_2$-C_6H_3− (**1e**)		46	86 (**3ea**)
5[c]	(*E*)-PhCH= CH (**1f**)		24	42 (**3fa**)
6	*n*-Hep (**1g**)		12	65 (**3ga**)
7	*c*-Hex (**1h**)		20	65 (**3ha**)
8[c]	2-furyl− (**1i**)		26	22 (**3ia**)
9[d]	4-MeO-C_6H_4− (**1b**)	**2b**	48	70 (**3bb**)
10[d]	4-Me-C_6H_4− (**1c**)		31	61 (**3cb**)
11[d]	3-Me-C_6H_4− (**1d**)		26	66 (**3db**)
12[c,d]	3,4-$(MeO)_2$-C_6H_3− (**1e**)		48	65 (**3eb**)
13[c,d]	(*E*)-PhCH-CH− (**1f**)		60	34 (**3fb**)
14[d]	*n*-Hep (**1g**)		26	75 (**3gb**)
15[c,d]	*c*-Hex (**1h**)		27	79 (**3hb**)
16[c,d]	2-furyl− (**1i**)		48	22 (**3ib**)
17[d]	*i*-Pr (**1j**)		36	44 (**3jb**)

[a] General conditions: **1** (0.2 mmol), **2** (0.4 mmol), $CuCl_2{\cdot}2H_2O$ (10 mol %), Na_2CO_3 (2.0 equiv), toluene (2 mL), 100 °C, under air. [b] Isolated yield. Homocoupled dimer product was observed in some reactions but in low yield. [c] The reaction was refluxed in benzene. [d] The reaction was carried out in the presence of pyridine (2.0 equiv) as additive.

Under the optimal reaction conditions, different amides such as nitrogen nucleophiles were investigated (Table 3). Oxazolidinones and indoles with electron-withdrawing groups at the 2- or 3-position converted to the desired ynamides efficiently in good yields (Table 3, entries 1−2 and 5−6). Imidazolidinones were tolerated in this transformation. When **2c** was used as nitrogen nucleophile, the expected **3ac** was obtained in 48% yield (Table 3, entry 3). Moreover, an acyclic nitrogen nucleophile such as *N*-methyl benzensulfonamide **2d** could successfully be transformed into **3ad**, but with lower yield (Table 3, entry 4).

Table 3. Cu-Catalyzed Oxidative Decarboxylative Amidation of **1a** with Different Amides **2**[a]



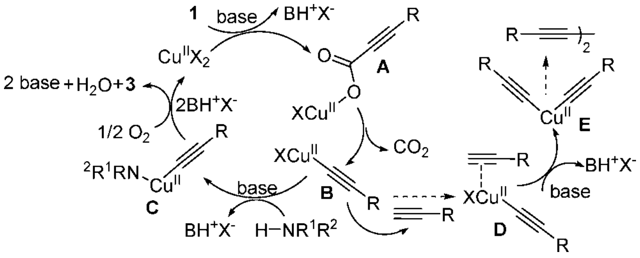
entry	R^2–NH−EWG	time (h)	yield of **3** (%)[b]
1	 **2a**	12	 83 (**3aa**)
2[c]	 **2b**	20	 68 (**3ab**)
3	 **2c**	17	 48 (**3ac**)
4	CH_3NHTs **2d**	31	 32(**3ad**)
5	 **2e**	12	 68 (**3ae**)
6[c]	 **2f**	47	 56 (**3af**)
7[d]	 **2g**	22	 33 (**3ag**)
8[c,d]	 **2h**	41	 39 (**3ah**)
9[c]	 **2i**	29	 39 (**3ai**)

[a] General conditions: **1a** (0.2 mmol), **2** (0.4 mmol), $CuCl_2{\cdot}2H_2O$ (10 mol %), Na_2CO_3 (2.0 equiv), toluene (2 mL), 100 °C, under air. [b] Isolated yield. Homocoupled dimer product was observed in some reactions but in low yield. [c] The reaction was carried out in the presence of pyridine (2.0 equiv) as additive. [d] The reaction was refluxed in benzene.

A plausible mechanism for the transformation of **1** with amide **2** is illustrated in Scheme 1. The copper(II) intermediates **A** are initially formed, which undergo decarboxylation to produce the alkynyl copper(II) intermediates **B**. Nucleophilic attack by amide **2** affords the Cu^{II}(alkynyl)(amidate) intermediates **C**, followed by C−N reductive elimination leading to the expected products **3**. Cu catalyst was then reoxidized by dioxygen to fulfill the catalytic cycle.

We hypothesize that the reason for the reduction of diynes formation is probably due to the absence of abundant alkynes in this catalytic system in which propiolic acids were

Scheme 1. A Proposed Mechanism for the Direct Transformation



employed as precoupling partners. Hence, the bis-alkynyl-Cu(II) intermediate **E**,[7] which would result in the undesired diyne byproduct, could not be efficiently formed (Scheme 1).

In summary, we have developed a novel Cu-catalyzed aerobic oxidative amidation of propiolic acids via decarboxylation under air. To the best of our knowledge, this is the first intermolecular sp-carbon−heteroatom bond formation via decarboxylation. The use of propiolic acid derivatives, which are readily available, easy to store, and simple to handle, as the coupling partner efficiently inhibits the formation of dimerization product diynes, as well as reduces the loading of the catalyst and the amide nucleophiles. Moreover, as opposed to organic halides, only carbon dioxide is produced as byproduct in this approach. The use of air as oxidant makes this method more attractive not only for academic research, but also for industrial application. Further studies on the reaction scope and synthetic applications are ongoing in our group.

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Supporting Information Available: Experimental details and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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