

Regioselective Cu(I)-Catalyzed Tandem A^3 -Coupling/Decarboxylative Coupling to 3-Amino-1,4-Enynes

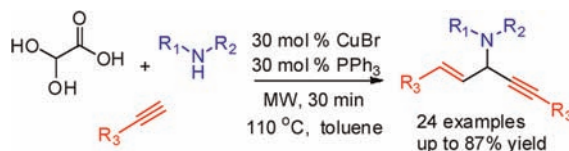
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ABSTRACT



An efficient and novel copper-mediated protocol for the synthesis of 3-amino-1,4-enynes from glyoxylic acid, an amine, and an alkyne was developed. This new reaction involving two sequential C–C bond formations is air and moisture tolerant and proceeds via a tandem A^3 -coupling and a selective decarboxylative coupling.

Transition-metal-catalyzed C–C bond formation is an important tool in modern organic chemistry.¹ Over the past decades, the most popular approaches for C–C bond formation employed transition metals such as Pd,² Cu,³

Fe,⁴ Ni,⁵ Ag,⁶ Ru,⁷ Rh,⁸ and Au.⁹ Currently the transition-metal-catalyzed decarboxylative couplings have gained particular interest due to the inherent advantage that simple carboxylic acids represent a powerful alternative for C–C bond formation under relatively neutral conditions compared to preformed organometallic reagents.¹⁰

In particular, Cu-catalyzed decarboxylative couplings have widely been used as a valuable synthetic strategy for the formation of C–C bonds.¹¹ In this regard, our group recently discovered that a Cu-catalyzed decarboxylative

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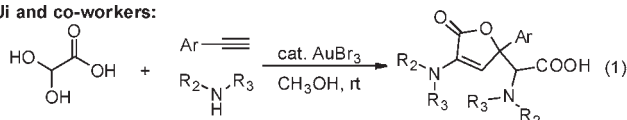
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coupling could be applied to efficiently obtain propargylamines and oxazolidinones.¹²

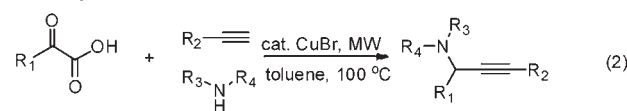
During recent years, the three-component coupling of an aldehyde, an alkyne, and an amine (A³-coupling) has received much attention,¹³ especially employing a tandem A³-coupling reaction.¹⁴ Recently, Ji and co-workers reported a gold-catalyzed direct alkyne-amine-glyoxylic acid coupling, intramolecular cyclization for the formation of polysubstituted butenolides in a tandem manner (Scheme 1, eq 1).¹⁵ Based on this report and our previous work on decarboxylative three-component couplings (eq 2), we envisaged the possibility of a decarboxylative coupling of glyoxylic acid, an amine, and an alkyne to synthesize 3-amino-1,4-enynes (eq 3), which are valuable intermediates for the preparation of useful and unusual carbocyclic products via cycloisomerization.¹⁶

Scheme 1

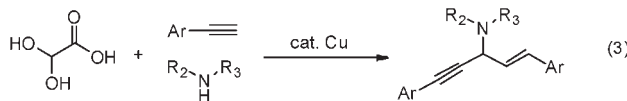
Ji and co-workers:



Van der Eycken and co-workers:



this work:



In our initial investigations, employing glyoxylic acid **1**, *N*-methylbenzylamine **2a**, and phenylacetylene **3a** as model substrates, we evaluated the efficiency of various solvents and copper catalysts under microwave irradiation

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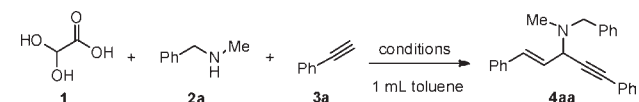
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Table 1. Optimization of the Conditions^a

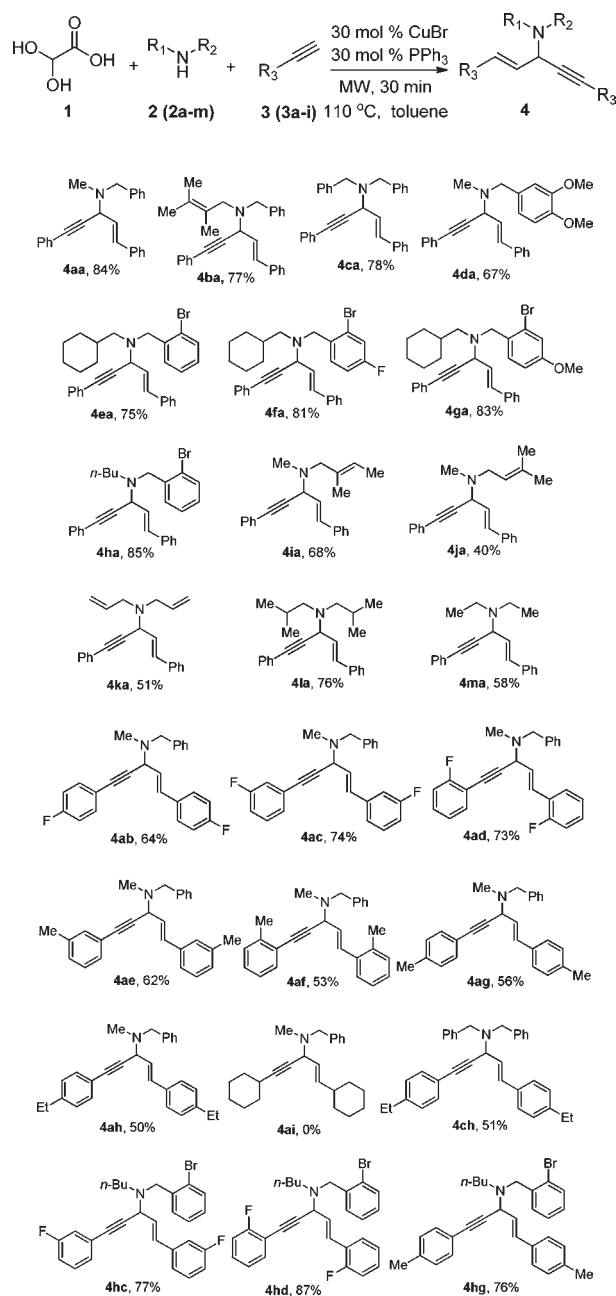


entry	CuX (mol %)/ ligand (mol %)	2a/3a (mmol)	time (min)	yield ^b (%)
1	CuBr(30)/none	1:3	30	50
2	CuBr(30)/none	1:5	30	65
3	CuBr(30)/none	1:6	30	68
4	CuBr(30)/PPh ₃ (30)	1:6	30	84
5	CuBr(30)/TOTP(30)	1:6	30	71
6	CuBr(30)/TFP(30)	1:6	30	55
7	CuBr(30)/ DPEPhos(30)	1:6	30	39
8	CuBr(30)/DPPF(30)	1:6	30	72
9	CuBr(30)/DPPB(30)	1:6	30	60
10	CuBr (30)/DPPP(30)	1:6	30	65
11	CuBr (30)/ 10-Phenanthroline (30)	1:6	30	53
12	CuBr(15)/PPh ₃ (30)	1:6	30	72
13	CuBr (30)/PPh ₃ (60)	1:6	30	77
14	CuBr(40)/PPh ₃ (40)	1:6	30	73
15 ^c	CuBr(30)/PPh ₃ (30)	1:6	30	79
16 ^d	CuBr(30)/PPh ₃ (30)	1:6	30	74
17	CuBr(30)/PPh ₃ (30)	1:6	20	80
18	CuBr(30)/PPh ₃ (30)	1:6	45	73
19 ^e	CuBr(30)/PPh ₃ (30)	1:6	24 h	67

^a Reactions were performed using **1** (0.55 mmol), **2a** (0.5 mmol), **3a**, and toluene (1 mL) under microwave irradiation at 110 °C and 80 W maximum power. ^b Isolated yields based on **2a**. ^c Reaction carried out at 130 °C. ^d Reaction carried out at 95 °C. ^e Conventional heating. TOTP = Tri-*ortho*-tolylphosphine. TFP = Tri-(2-furyl)-phosphine. DPPF = Bis(diphenylphosphino)ferrocene. DPPB = 1,4-Bis(diphenylphosphino)-butane. DPEPhos = Bis(2-diphenyl-phosphinophenyl)ether. DPPP = 1,3-Bis(diphenylphosphino) propane.

without ligands. From the results, we found that toluene is the solvent of choice, and CuBr seemed to be the most effective for the formation of the 3-amino-1,4-enynes **4a**.¹⁷ Further inspection of the reaction parameters revealed that the ratio of substrates **2a/3a** significantly affects the yield. A 1:6 ratio provided the best result (Table 1, entries 1–3). Encouraged by these findings, we subsequently evaluated the influence of the application of ligands. To our delight, when a combination of CuBr and PPh₃ was used, 3-amino-1,4-enyne **4a** was obtained in 84% yield (Table 1, entry 4). Thus, a variety of ligands were examined, but all of them failed to further improve the yields (Table 1, entries 5–11). Regarding the ratio of CuBr to the PPh₃ ligand, we found that when using 30% of both additives the highest yield was obtained (Table 1, entries 4 and 12–14). Further screening of the reaction temperature and reaction time showed that increasing either the temperature or the reaction time resulted in a decreased yield (Table 1, entries 15 and 18), while the reaction at a lower temperature or in a shorter reaction period afforded **4a** in 74% and 80% yield

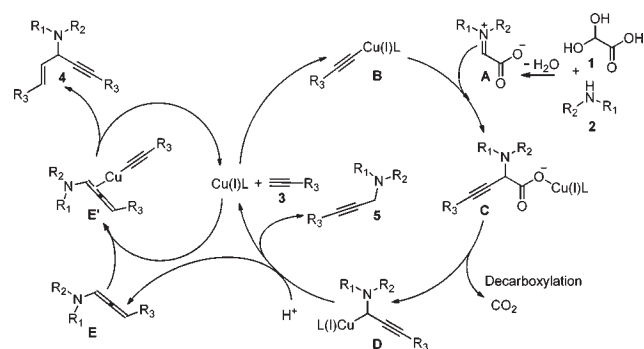
(17) See the Supporting Information for details.

Table 2. Scope and Limitations of the Protocol

respectively (Table 1, entries 16 and 17). In comparison, when the reaction was conducted under conventional heating using the same conditions, the desired product **4a** was obtained in a yield of 67% after an extended reaction time of 24 h (Table 1, entry 19).

Having optimized the reaction conditions (Table 1, entry 4), we next evaluated the scope and limitations of the process. A variety of secondary amines were reacted with glyoxylic acid and phenylacetylenes to afford the corresponding 3-amino-1,4-enynes **4aa–ma** in good and high yields (Table 2, entries 1–13). Amines **2a–h** bearing both an aliphatic R_1 -substituent and a benzylic R_2 -substituent provided good yields of the desired products ranging from

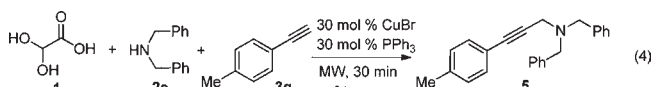
67% to 85%. The reaction was not significantly affected when an amine **2i–m** bearing two aliphatic substituents was used, although slightly lower yields were obtained. To expand the scope of the protocol, the application of a series of alkynes was also investigated. Both electron-poor and -rich aryl-substituted alkynes **3b–d**, **3e–h** were effective, yielding the desired compounds **4ab–ah** in 50–74% yield (Table 2, entries 14–20). However, similar to A^3 -coupling, the aliphatic alkynes usually provided the desired compounds only in low yield. In this protocol, no product **4ai** was observed when the cyclohexylalkyne (**3i**) was used (Table 2, entry 21). Finally, we evaluated the reaction of different amines and alkynes. The desired 3-amino-1,4-enynes **4hc–ch** were obtained in moderate to good yields (Table 2, entries 22–25).

Scheme 2. Proposed Mechanism

Based on these findings, a plausible mechanism for this tandem A^3 -coupling/decarboxylative coupling is presented in Scheme 2. Iminium salt **A**, *in situ* formed from glyoxylic acid **1** and amine **2**, undergoes a Cu(I)-catalyzed A^3 -coupling of copper acetylide **B** resulting in the formation of intermediate **C**. Then a Cu(I)-catalyzed decarboxylation of **C** affords the copper-propargylamine species **D**.^{11b,18} Further conversion results in the formation of the allene **E** in conjunction with the regeneration of the Cu(I) catalyst. It is worth mentioning that if the protonation occurs at the carbon atom attached to copper, the propargylamine would be obtained.¹⁹ Finally, electrophilic addition of this allene **E** to copper acetylide **B** would form 3-amino-1,4-enynes **4** via a plausible transition state **E'**.²⁰ The coupling constants ($J^{1,3} = 15.8–16.1$ Hz) in the ^1H NMR spectrum support the E-configuration of the vinyl motif.

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(19) By application of our previously optimized conditions, the propargylamine **5** was formed in 60% yield when amine **2c** and acetylene **3g** were used.



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In summary, we have successfully developed a novel microwave-assisted three-component cascade approach for the selective preparation of diversely functionalized 3-amino-1,4-enynes starting from glyoxylic acid, an alkyne, and an amine. This tandem reaction involves a Cu(I)-catalyzed A^3 -coupling followed by a decarboxylative coupling. Interestingly, the Cu(I)-catalyzed decarboxylative coupling of glyoxylic acid can serve as a C_1 source, and this approach may open up potentially relevant copper-catalyzed chemical processes.

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Supporting Information Available. Experimental procedures and copies of 1H NMR and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.