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A CuAAC/Ullmann C−C Coupling Tandem Reaction: Copper-Catalyzed Reactions of Organic Azides with *N*-(2-Iodoaryl)-propiolamides or 2-Iodo-*N*-(prop-2-ynyl)-benzenamines

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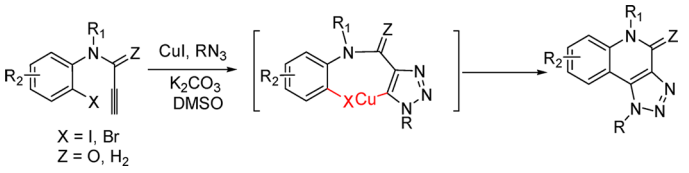
ABSTRACT



A novel copper-catalyzed tandem reaction was developed by utilizing two famous copper-catalyzed reactions, CuAAC and Ullmann coupling. The trapping of the C−Cu intermediate produced in CuAAC led to further formation of an aryl C−C bond through intramolecular Ullmann C−C coupling.

Copper-catalyzed azide−alkyne cycloaddition (CuAAC)[1] has been the subject of intensive research and has played an outstanding role in various fields of organic synthesis, medicinal chemistry, molecular biology, and materials science since its initial discovery by Fokin/Sharpless[2] and Meldal[3] groups independently. Another famous copper-catalyzed reaction is the Ullmann-type coupling, which is one of the most efficient methods for constructing carbon−heteroatom bonds, and has been extensively studied in academia and widely applied in industry.[4,5] To our surprise, although both the Ullmann-type coupling and CuAAC were catalyzed by copper salts, research about the combination of the two kinds of reactions is relatively rare. One example was the one-pot reaction of aryl halides,

(1) For some selected important reviews about CuAAC reactions and its applications, see: (a) Agalave, S. G.; Maujan, S. R.; Pore, V. S. *Chem. Asian J.* **2011**, *6*, 2696. (b) Aragão-Leoneti, V.; Campo, V. L.; Gomes, A. S.; Field, R. A.; Carvalho, I. *Tetrahedron* **2010**, *66*, 9475. (c) Franc, G.; Kakkar, A. K. *Chem. Soc. Rev.* **2010**, *39*, 1539. (d) Iha, R. K.; Wooley, K. L.; Nyström, A. M.; Burke, D. J.; Kade, M. J.; Hawker, C. J. *Chem. Rev.* **2009**, *109*, 5620. (e) Amblard, F.; Cho, J. H.; Schinazi, R. F. *Chem. Rev.* **2009**, *109*, 4207. (f) Meldal, M.; Tornøe, C. W. *Chem. Rev.* **2008**, *108*, 2951. (g) Wu, P.; Fokin, V. V. *Aldrichimica Acta* **2007**, *40*, 7. (h) Moses, J. F.; Moorhouse, A. D. *Chem. Soc. Rev.* **2007**, *36*, 1249. (i) Lutz, J. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1018. (j) Bock, V. D.; Hiemstra, H.; van Maarseveen, J. H. *Eur. J. Org. Chem.* **2006**, 51. (k) Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 5188.

(2) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596.

(3) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057.

(4) For some recent reviews about copper-catalyzed Ullmann-type coupling reactions, see: (a) Ley, S. V.; Thomas, A. W. *Angew. Chem, Int. Ed.* **2003**, *42*, 5400. (b) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337. (c) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054. (d) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6954. (e) Ma, D.; Cai, Q. *Acc. Chem. Soc.* **2008**, *41*, 1450. (f) Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2010**, *1*, 13.

(5) For some selected examples of Ullmann-type coupling reactions under mild conditions, see: (a) Marcoux, J. −F.; Doye, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 10539. (b) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727. (c) Shafir, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 8742. (d) Shafir, A.; Lichtor, P. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3490. (e) Ma, D.; Zhang, Y.; Yao, J.; Wu, S.; Tao, F. *J. Am. Chem. Soc.* **1998**, *120*, 12459. (f) Ma, D.; Cai, Q.; Zhang, H. *Org. Lett.* **2003**, *5*, 2453. (g) Cai, Q.; Zou, B.; Ma, D. *Angew. Chem., Int. Ed.* **2006**, *45*, 1276. (h) Cristau, H.-J.; Cellier, P. P.; Spindler, J.-F.; Taillefer, M. *Chem.—Eur. J.* **2004**, *10*, 5607. (i) Kaddouri, H.; Vicente, V.; Ouali, A.; Ouazzani, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 333. (j) Xia, N.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 337. (k) Gujahur, R. K.; Bates, C. G.; Venkataraman, D. *Org. Lett.* **2001**, *3*, 4315. (l) Kelkar, A. A.; Patil, N. M.; Chaudhari, R. V. *Tetrahedron Lett.* **2002**, *43*, 7143. (m) Okano, K.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* **2003**, 4987. (n) Jiang, D.; Fu, H.; Jiang, Y.; Zhao, Y. *J. Org. Chem.* **2007**, *72*, 672.

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sodium azide, and alkyne reported by Fokin et al.[6] in which the aryl azide was generated in situ through an Ullmann C−N coupling reaction and immediately consumed in the CuAAC reaction to form 1,4-substituted 1,2,3-triazoles.[7] Ackermann et al. further developed this one-pot reaction[8] through a sequential C−H functionalization by reacting the 1,4-disubstituted 1,2,3-triazoles and aryl iodides at 140 °C with *t*-BuOLi as the base to afford fully decorated 1,2,3-triaoles. Similar strategies were also successfully applied in the Pd-catalyzed direct arylation of 1,2,3-triazoles.[9,10]

The mechanism of CuAAC has been clearly documented as a [3 + 2] process with the formation of a highly reactive C−Cu intermediate that undergoes rapid protonation to form the stable 1,4-disubstituted 1,2,3-triazoles.[2] It has been reported that the organocopper intermediates could also be trapped by electrophiles such as ICl, alkyl halides, or acyl halides to produce 1,4,5-trisubstituted 1,2,3-triazole rather than protonation.[11] However, such reactions always needed stiochiomeric amounts of copper salts for efficient producing of the organocopper intermediate and excessive electrophiles for the trapping. During our continuing work in developing novel catalyzed tandem reactions by trapping organocopper intermediates,[12] we envisioned that the C−Cu species produced in CuAAC may be a reactive intermediate for further Ullmann C−C coupling reaction and would lead to the formation of 1,4,5-trisubstituted 1,2,3-triazoles directly. Recently, we reported a copper-catalyzed tandem reaction of *N*-(2-haloaryl)propiolamides with sodium azide for the synthesis of [1,2,3]triazolo[1,5-*a*]quinoxalin-4(5*H*)-ones.[12d] The tandem reaction was proposed to proceed through a [3 + 2] cycloaddition/copper-catalyzed intramolecular Ullmann C−N coupling process.[13] However, to the best of our knowledge, no combination of CuAAC and Ullmann C−C coupling has been reported for developing novel tandem reactions. In this paper, we want to disclose our research in the trapping of the C−Cu intermediate produced in the CuAAC reaction through an intramolecular Ullmann C−C coupling reaction, leading to the formation of *1H*-[1,2,3]triazolo[4,5-*c*]quinolin-4(5*H*)-ones (Scheme 1).[14]

Scheme 1. Design of CuAAC−Intramolecular Ullmann C−C Coupling Tandem Reactions

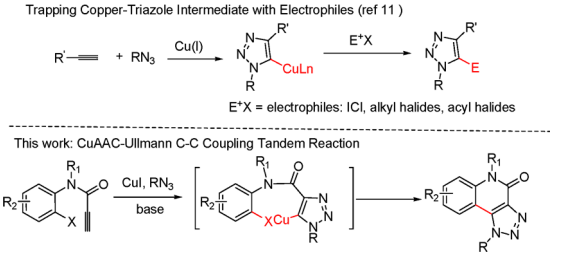
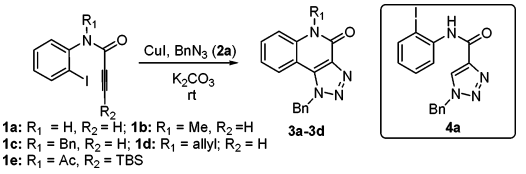


Table 1. Condition Screening[a]



entry	substrate	solvent	product	yield[b] (%)
1	**1a**	DMSO	**3a**	[c]
2	**1b**	DMSO	**3b**	97[d]
3	**1c**	DMSO	**3c**	99
4	**1d**	DMSO	**3d**	97
5	**1e**	DMSO	**3a**	32
6	**1b**	DMF	**3b**	87
7	**1b**	MeCN	**3b**	85
8	**1b**	1,4-dioxane	**3b**	72
9	**1b**	H_2O	**3b**	21

[a] Reagents and conditions: 1 (0.5 mmol), **2a** (0.5 mmol), CuI (0.05 mmol), K_2CO_3 (1.0 mmol), solvent 1 mL, rt, 1 h. [b] Isolated yields. [c] No **3a** was detected. [d] 23% of **3b** was isolated without the base.

To test the idea of intramolecular trapping of the organocopper intermediate produced in the CuAAC reaction, we initially explored the copper-catalyzed reaction of

(6) Feldman, A. K.; Colasson, B.; Fokin, V. V. *Org. Lett.* **2004**, *6*, 3897.

(7) For other selected examples involving in situ generated organic azides followed by click chemistry in one pot, see: (a) Alonso, F.; Moglie, Y.; Radivoy, G.; Yus, M. *J. Org. Chem.* **2011**, *76*, 8394. (b) Li, W.-T.; Wu, W.-H.; Tang, C.-H.; Tai, R.; Chen, S.-T. *ACS Comb. Sci.* **2011**, *13*, 72. (c) Attanasi, O. A.; Favi, G.; Filippone, P.; Mantellini, F.; Moscatelli, G. Perrulli, F. R. *Org. Lett.* **2010**, *12*, 468. (d) Reddy, P. S.; Sreedhar, B. *Synthesis* **2009**, *24*, 4203. (e) Kumar, D.; Reddy, V. B.; Varma, R. S. *Tetrahedron Lett.* **2009**, *50*, 2065. (f) Chttaboina, S.; Xie, F.; Wang, Q. *Tetrahedron Lett.* **2005**, *46*, 2331. (g) Kacprzak, K. *Synlett* **2005**, 943. (h) Appukkuttan, P.; Dehaen, W.; Fokin, V. V.; Van der Eycken, E. *Org. Lett.* **2004**, *6*, 4223.

(8) Ackermann, L.; Potukuchi, H. K.; Landsberg, D.; Vicente, R. *Org. Lett.* **2008**, *10*, 3081.

(9) For a review about the CuAAC/C−H bond functionalization, see: Ackermann, L.; Potukuchi, H. K. *Org. Biomol. Chem.* **2010**, *8*, 4503.

(10) For selected examples of Pd-catalyzed arylation of 1,2,3-triazoles, see: (a) Ackermann, L.; Jeyachandran, R.; Potukuchi, H. K.; Novák, P.; Bütter, L. *Org. Lett.* **2010**, *12*, 2056. (b) Panteleev, J.; Geyer, K.; Aguilar-Aguilar, A.; Wang, L.; Lautens, M. *Org. Lett.* **2010**, *12*, 5092. (c) Ackermann, L.; Vicente, R. *Org. Lett.* **2009**, *11*, 4922. (d) Ackermann, L.; Vicente, R.; Born, R. *Adv. Synth. Catal.* **2008**, *350*, 741. (e) Basolo, L.; Beccalli, E. M.; Borsini, E.; Broggini, G.; Pellegrino, S. *Tetrahedron* **2008**, *64*, 8182. (f) Iwasaki, M.; Yorimitsu, H.; Oshima, K. *Chem. Asian J.* **2007**, *2*, 1430. (g) Chuprakov, S.; Chenyak, N.; Dudnik, A. S.; Gevorgyan, V. *Org. Lett.* **2007**, *9*, 2333.

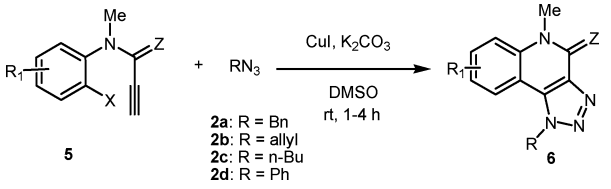
(11) (a) Wu, Y.-M.; Deng, J.; Li, Y.; Chen, Q.-Y. *Synthesis* **2005**, 1314. (b) Cassidy, M. P.; Raushel, J.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2006**, *45*, 3154.

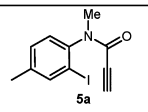
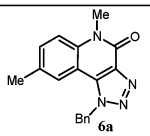
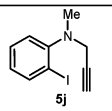
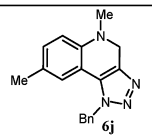
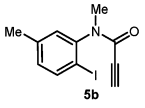
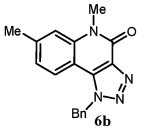
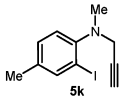
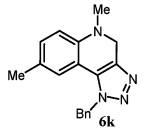
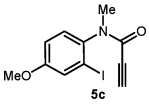
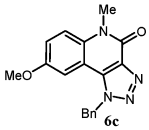
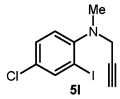
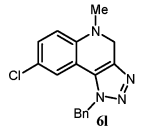
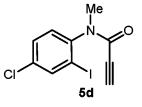
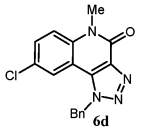
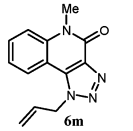
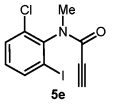
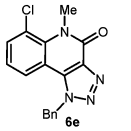
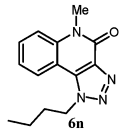
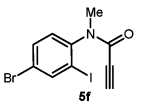
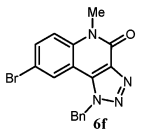
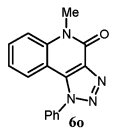
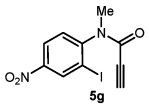
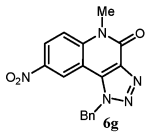
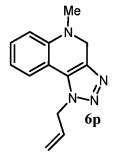
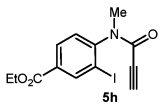
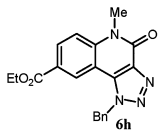
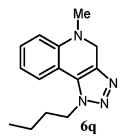
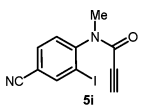
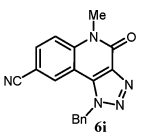
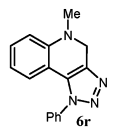
(12) (a) Zhou, F.; Liu, J.; Ding, K.; Liu, J.; Cai, Q. *J. Org. Chem.* **2011**, *76*, 5346. (b) Zhou, F.; Fu, L.; Wei, J.; Ding, K.; Cai, Q. *Synthesis* **2011**, 3037. (c) Cai, Q.; Zhou, F.; Xu, T.; Fu, L.; Ding, K. *Org. Lett.* **2011**, *13*, 340. (d) Yan, J.; Zhou, F.; Qin, D.; Cai, T.; Ding, K.; Cai, Q. *Org. Lett.* **2012**, *14*, 1262.

(13) For selected examples of the combination of triazole formation with other reactions such as the Biginelli reaction, Ugi reaction, etc., see: (a) Khanetskyy, B.; Dallinger, D.; Kappe, C. O. *J. Comb. Chem.* **2004**, *6*, 884. (b) Akritopoulou-Zanze, I.; Gracias, V.; Djuric, S. W. *Tetrahedron Lett.* **2004**, *45*, 8439. (c) Ramachary, D. B.; Barbas, C. F., III. *Chem. Eur, J.* **2004**, *10*, 5323.

(14) For the biological activity exploration of such compounds, see: Suzuki, F.; Kuroda, T.; Nakasato, Y.; Manabe, H.; Ohmori, K.; Kitamura, S.; Ichikawa, S.; Ohno, T. *J. Med. Chem.* **1992**, *35*, 4045.

Table 2. Screening of Substrate Scope[a]



entry	substrate **1**	product **3**	yield (%) [b]	entry	substrate **1**	product **3**	yield (%) [b]
1	 **5a**	 **6a**	95 (40)[c]	**10**	 **5j**	 **6j**	53 (95)[d]
2	 **5b**	 **6b**	96	**11**	 **5k**	 **6k**	50 (88)[d]
3	 **5c**	 **6c**	94	**12**	 **5l**	 **6l**	47 (80)[d]
4	 **5d**	 **6d**	88	**13**	**1b**	 **6m**	75
5	 **5e**	 **6e**	79	**14**	**1b**	 **6n**	87
6	 **5f**	 **6f**	94	**15**	**1b**	 **6o**	36[e]
7	 **5g**	 **6g**	87	**16**	**5j**	 **6p**	75[d]
8	 **5h**	 **6h**	82	**17**	**5j**	 **6q**	85[d]
9	 **5i**	 **6i**	89	**18**	**5j**	 **6r**	51[e]

[a] Reagents and conditions: substrate **5** or **1b** (0.5 mmol), **2** (0.5 mmol), CuI (0.05 mmol), K_2CO_3 (1.0 mmol), solvent 1 mL, rt, 1−2 h. For entries 1−12, **2a** was used as the reactant; for entries 13−18, other organic azides **2b**−**d** were used. [b] Isolated yields. [c] Aryl bromide was used as the reactant at 60 °C. [d] 50 °C. [e] 90 °C.

N-(2-iodophenyl)propiolamide **1a** with BnN_3 **2a**. As shown in Table 1, no desired product **3a** was obtained either with K_2CO_3 or without the base. The only isolated product was the CuAAC product **4a**. Similar results have been observed in our previous research, and it could be explained by the rapid quench of the C−Cu intermediate by the proton attached to the amide bond.[12a] To overcome this problem, a variety of *N*-substituted substrates **1b**−**d**

were tested for the CuI-catalyzed tandem reactions[15] in DMSO at room temperature with K_2CO_3 as the necessary base. As expected, all delivered the corresponding products **3b**–**d** in good to excellent yields (Table 1, entries 2–4). The reaction of **1a** with **2a** failed to afford the tandem product **3a**; however, when *N*-acetyl-3-(*tert*-butyldimethylsilyl)-*N*-(2-iodophenyl)propiolamide **1e** was used in the reaction, the deprotected product **3a** was delivered in 32% yield (Table 1, entry 5). When **1b** was reacted with **2a**, other solvents such as DMF, 1,4-dixone, MeCN, and water were also screened, and all gave reduced outcome (Table 1, entries 6–9). It is noticeable that the reaction of **1b** with **2a** even delivered the product **3b** in 21% yield at room temperature with H_2O as the solvent, with the recovery of most starting materials (Table 1, entry 9).

With the optimized conditions in hand, we then explored the substrate scope, and the results are shown in Table 2. In most cases, the tandem reactions of *N*-methyl-*N*-(2-iodoaryl)propiolamides with BnN_3 **2a** afforded the desired products in good to excellent yields in 1–2 h at room temperature. Both the electron-donating and -withdrawing groups on the aryl ring were well tolerated (Table 2, entries 1–9). To further explore the substrate scope, other substrates such as 2-iodo-*N*-methyl-*N*-(prop-2-ynyl)-benzenamine derivatives **5j**–**l** were also tested in our reactions; although only moderate yields were obtained at room temperature, much better results were obtained at elevated temperatures of 50 °C (Table 2, entries 10–12). Aryl bromides were also tested under our reaction conditions, and the corresponding products were obtained in moderate yields at 60 °C, with most of the CuAAC product being isolated (Table 2, entry 1). However, for aryl chlorides, only a small amount of the desired products was detected even at 90 °C (data not shown).

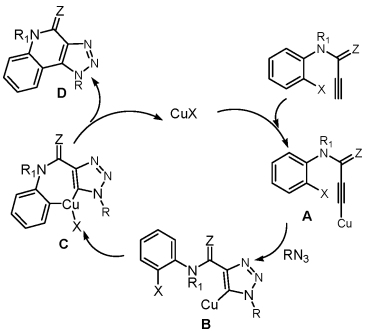
Further, different organic azides such as *n*-BuN_3 and allyl azide were also explored by reaction with **1b** and afforded the corresponding tandem products in good yields (Table 2, entries 13 and 14). However, when PhN_3 was reacted with **1b**, no desired product **6o** was detected at room temperature, and it was obtained only at low yield even when the reaction temperature was elevated to 90 °C, with most of the starting material **1b** recovered (Table 2, entry 15). Similar results were observed when 2-iodo-*N*-methyl-*N*-(prop-2-ynyl)benzenamine **5j** was reacted with different organic azides (Table 2, entries 16–18).

On the basis of the literature reports[2,11] and our experimental observations, a plausible reaction mechanism was proposed as shown in Scheme 2. First, the reactive C–Cu intermediate **B** was formed through the CuAAC reaction mechanism, which was then inserted into the aryl halide bond and led to the formation of aryl C–C bond.

However, the products may also be formed through a two-step sequential process similar to Ackermann's report.[8,9] First, a stable CuAAC product was formed, which then underwent C–H functionalization under basic conditions to produce the desired C–C coupling products.

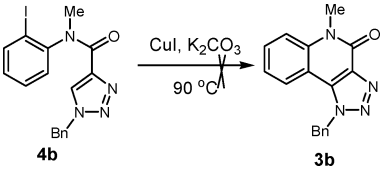
(15) Other copper sources like CuBr, CuCl, CuOTf, and CuOAc were also explored, and all worked well for the tandem reactions.

Scheme 2. Plausible Mechanism



To exclude such a mechansim, we then performed a controlling experiment by heating 1-benzyl-*N*-(2-iodophenyl)-*N*-methyl-1*H*-1,2,3-triazole-4-carboxamide **4b** in DMSO at the presence of CuI and K_2CO_3 at 90 °C (Scheme 3). However, no coupling product was detected after 24 h, which proved that the desired product was not formed through the two-step sequential process but most possibly through direct rapid trapping of the reactive organocopper intermediate **B**.

Scheme 3. Controlling Experiment



In summary, we have developed a novel tandem reaction by utilizing two famous copper-catalyzed reactions, CuAAC and Ullmann coupling. The intramolecular trapping of the C–Cu intermediate produced in CuAAC led to further formation of an aryl C–C bond through Ullmann C–C coupling. The process took place efficiently when a variety of *N*-(2-iodoaryl)-propiolamides or 2-iodo-*N*-(prop-2-ynyl)benzenamines were used, and it displayed a wide range of functional group compatibility. This chemistry should be interesting for further application in drug discovery and other fields.

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Supporting Information Available. Full experimental procedures and characterization data for all the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.