DOI: 10.1002/adsc.200900875

Copper(I)-Catalyzed Synthesis of Novel 4-(Trifluoromethyl)-[1,2,3]triazolo[1,5-*a*]quinoxalines *via* Cascade Reactions of *N*-(*o*-Haloaryl)alkynylimine with Sodium Azide

Zixian Chen,[a,b] Jiangtao Zhu,[b] Haibo Xie,[b] Shan Li,[b] Yongming Wu,[b,*] and Yuefa Gong[a,*]

[a] School of Chemistry and Chemical Engineering, Huazhong University of Science and Technology, Wuhan, Hubei 430074, People's Republic of China
E-mail: gongyf@mail.hust.edu.cn
[b] Key laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, People's Republic of China
Fax: (+86)-21-5492-5192; e-mail: ymwu@mail.sioc.ac.cn

Received: December 17, 2009; Published online: May 5, 2010

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200900875.

Abstract: Novel tricyclic 4-(trifluoromethyl)-[1,2,3]triazolo[1,5-*a*]quinoxalines were readily prepared from *N*-(*o*-haloaryl)alkynylimines and sodium azide *via* copper(I)-catalyzed tandem reactions. This synthetic strategy provides an efficient way to access a library of novel heterocyclic compounds that are of interest in drug discovery.

Keywords: cascade reactions; C–N cross-coupling; copper; quinoxalines; trifluoromethyl substituents

Due to the need for generating new chemical entities with a useful biological activity profile, methodologies for the rapid generation of structural complexity and diversity are much sought after. Recently, 1,2,3-triazolo polycyclic compounds have been widely studied because of their interesting pharmacological activities.[1] It is well known that introduction of fluorine atoms into biologically active substances may lead to improvements in pharmacological properties. In particular, the trifluoromethyl group, which is highly hydrophobic, electron-rich, and sterically demanding, occupies a prominent position in medicinal chemistry as a substituent with peculiar properties. Moreover, it can provide high *in vivo* stability and features good mimicry of several naturally occurring residues such as methyl, isopropyl, isobutyl, phenyl, and so on.[2]

Biologically active 1,2,3-triazolo polycyclic compounds have previously been reported. For instance, **A** has a good affinity towards the benzodiazepine receptors,[1d] **B** possesses remarkable affinity and selectivity for GPR109A[1a] and **C** was designed as a novel antitumor agent (Figure 1).[1b] In this context, we became interested in the preparation of potentially biologically active tricyclic fluorine-containing 1,2,3-triazolo[1,5-*a*]quinoxaline derivatives. Traditionally, the synthesis of such skeletons, rationalized by Kundu et al.,[3] was realized using alkynes, *o*-nitroaryl halides, azide, and aryl aldehydes *via* several steps. Herein we report a highly efficient and convenient approach to construct these molecules *via* a Cu(I)-catalyzed cascade cyclization/C–N bond formation process.

The formation of aryl C–N bonds *via* copper-catalyzed Ullmann coupling between aryl halides and N-centered nucleophiles has received considerable attention in the past few years.[4] The high stability and low cost of the copper catalysts enable these transformations to be a useful complement to the more exten-

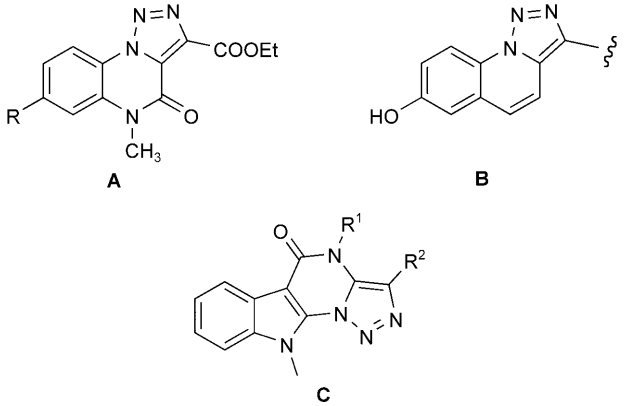
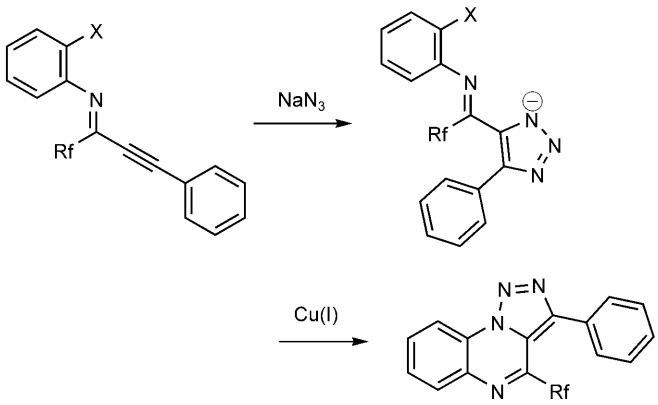


Figure 1. Examples of biologically active 1,2,3-triazolo polycyclic compounds.



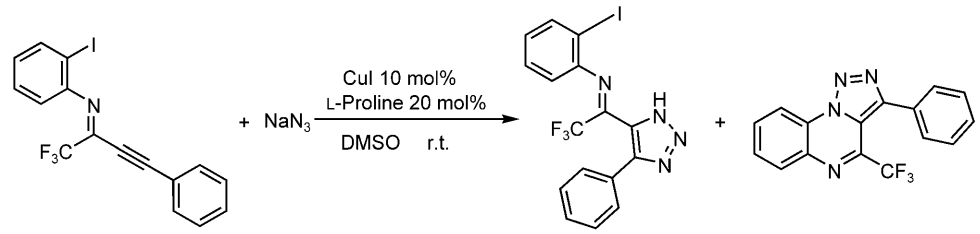
Scheme 1. Conceptual cascade approach to tricyclic rings.

sively investigated Pd(0)-catalyzed processes. By the appropriate choice of copper source, ligand, base, and reaction temperature, these coupling reactions have been developed to include a wide range of substrates under mild conditions.

Using cascade reactions to construct complex molecular skeletons starting from simple, inexpensive starting materials with high efficiency is an appealing strategy in organic synthesis. In recent years, various types of cascade reactions which involve a copper-catalyzed C–N formation process have been developed and employed in the synthesis of heterocyclic compounds.[5] We envisaged that treatment of sodium azide and *N*-(*o*-haloaryl)alkynylimine (Scheme 1) which is activated by a fluorinated imino group,[6] with a copper(I) catalyst would initiate a cascade cyclization/C–N coupling process to give the target molecule.

We began our investigations into the feasibility of this cascade process using *N*-(*o*-haloaryl)alkynylimine **1a** (Table 1) with sodium azide in DMSO at 60 °C as a model reaction, it was found that a single product **3a** was obtained in quantitative yields after purification (Table 1, entry 1). Then various catalysts and ligands were attempted. Using 10 mol% of CuI and 20 mol% tetramethylethylenediamine (TMEDA) as the ligand, **2a** was obtained in 70% yield (Table 1, entry 2),

Table 1. Optimization of the reaction conditions.[a]



1a **3a** **2a**

Entry	Catalyst/Ligand[b]	Solvent	Temp.[°C]	Time [h]	Yield [%][c]	
					3a	**2a**
1	–	DMSO	60	1 min	>98 (91)	–
2	CuI/**L1**	DMSO	60	8 h	10	70 (66)
3	CuI	DMSO	60	8 h	>98	–
4	CuI/**L2**	DMSO	60	5 min	–	98 (90)
5	CuI/**L3**	DMSO	60	5 min	–	98
6	CuI/**L3**	H_2O	60	2 h	–	–
7	CuI/**L3**	CH_3CN	60	2 h	30	–
8	CuI/**L3**	toluene	60	2 h	–	–
9	CuI/**L3**	DMF	60	1 h	7	73
10	$Cu(OAc)_2$/**L3**	DMSO	60	2 h	>98	–
11	CuI/**L3**	DMSO	r.t.	5 min	–	98
12	CuBr/**L3**	DMSO	r.t.	15 min	–	87
13	CuCl/**L3**	DMSO	r.t.	15 min	–	91
14	CuI/**L3**	DMSO	r.t.	2 h	–	98[d]
15	CuI/**L3**	DMSO	r.t.	2 h	88	7[e]

[a] Reactions were carried out on a 0.2 mmol scale in DMSO (2 mL) under nitrogen with sodium azide (1.1 equiv.), catalyst (10 mol%) and ligand (20 mol%) unless otherwise stated.
[b] **L1**: tetramethylethylenediamine. **L2**: *N*,*N*′-dimethylethylenediamine. **L3**: L-proline.
[c] Reported yields were based on **1a** as determined by ^{19}F NMR. Values in parentheses are the isolated yields.
[d] 5 mol% of CuI were used.
[e] 2 mol% of CuI were used.

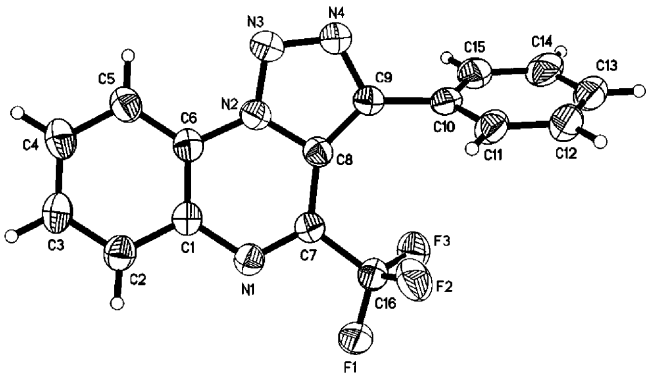
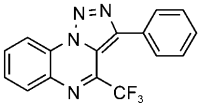
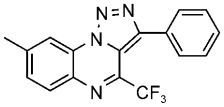
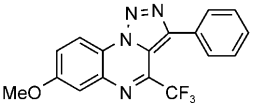
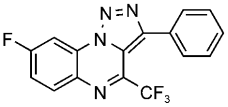
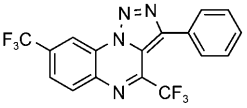
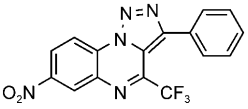
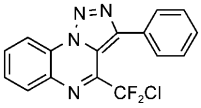


Figure 2. X-ray structure of **2a**.

which was confirmed by X-ray crystal diffraction studies (Figure 2).[7] Product **2a** was not formed in the absence of the ligand (Table 1, entry 3), indicating that the ligand effect is essential for this coupling reaction. Encouraged by this result, we next examined different ligands, such as *N*,*N*′-dimethylethylenediamine (DMEDA) and L-proline, which were used in classical copper-catalyzed Ullmann reactions. Surprisingly, both gave excellent yields (Table 1, entries 4 and 5). Then the solvent effect was investigated using L-proline as the ligand. The product was also obtained when DMF was used, although the yield (73%) was decreased (Table 1, entry 9). Other solvents such as water, acetonitrile, toluene, which were not suitable for the first step transformation,[6] could not provide the target compound (Table 1, entries 6–8). Employment of $Cu(OAc)_2$ as the catalyst also failed to form the C–N bond (Table 1, entry 10). Other Cu(I) salts, such as CuBr and CuCl, were also tested, all of them worked well even at room temperature (Table 1, entries 12 and 13), and CuI proved to be the best copper source with the highest efficiency (Table 1, entry 11). The attempt to reduce the catalyst loading led to longer reaction time and lower yields (Table 1, entries 14 and 15). After optimization, the best reaction conditions were ascertained as 10 mol% CuI, 20 mol% of L-proline, and 1.1 equivalents of sodium azide in DMSO at room temperature.

To investigate the scope of the proposed synthetic strategy, a number of fluorine-containing *N*-(*o*-haloYaryl)alkynylimines were tested, which could be prepared from the CuI-catalyzed coupling of terminal alkynes with fluoroalkylimidoyl chlorides in high yields.[8] As Table 2 shows, *N*-(*o*-bromoaryl)alkynylimine could also give a good yield at 60 °C (Table 2, entry 1). Even the *N*-phenyl group with a chlorine atom provided the product in moderate yield, although with a higher temperature (130 °C) and a longer reaction time (Table 2, entry 2).[9] The *o*-iodophenyl rings substituted by electron-donating substituents such as Me and OMe afforded the desired products in good yields within several hours (87–90%,

Table 2. Studies on the *N*-*o*-haloaryl moiety.[a]

Entry		Product	Time [h]	Temp. [°C]	Yield [%][b]
1	**2a**		10	60	95[c,d,e]
2			10	130	65[c,d,f]
3	**2b**		1.5	r.t.	90
4	**2c**		4	60	87
5	**2d**		10	60	80
6	**2e**		24	60	75
7	**2f**		10	80	70
8	**2g**		10	60	70

[a] Reactions were carried out on a 0.3 mmol (X = I) scale in DMSO (2 mL) under nitrogen with sodium azide (1.1 equiv.) ,catalyst (10 mol%) and ligand (20 mol%) unless otherwise stated.
[b] Isolated yield.
[c] Yield determined by ^{19}F NMR.
[d] CuI (20 mol%) and ligand (40 mol%) were used.
[e] X = Br.
[f] X = Cl.

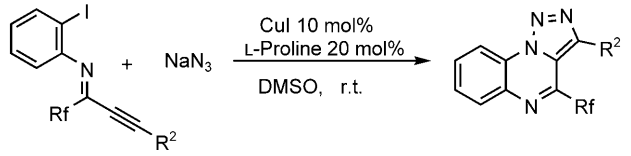
Table 2, entries 3 and 4). In contrast, electron-withdrawing groups such as fluorine, trifluoromethyl or nitro led to decreased yields with longer reaction times (Table 2, entries 5–7). Other fluoroalkyl groups were attempted, the CF_2Cl was also a suitable substituent (Table 2, entry 8) for this process compared with the CF_2Br group, which led to decompose of the starting material.

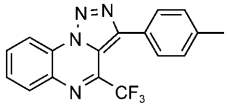
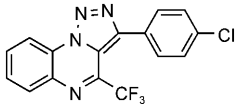
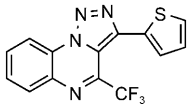
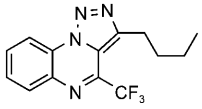
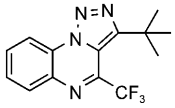
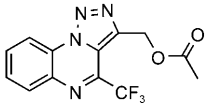
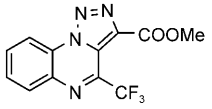
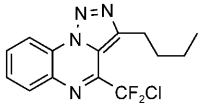
Good functional group tolerance of this methodology also allows for the modification of the alkyne

moiety. Yields for all substrates were moderate to good (56–97%, Table 3). The electron-rich alkynes gave good yields under mild conditions (Table 3, entries 1, 3–6), while electron-deficient alkynes needed raised temperature with lower yields (Table 3, entries 2 and 7). The alkyne with a *tert*-butyl group also formed the product in 91% yield, which indicated that steric bulk did not significantly affect the reactivity (Table 3, entry 5). A substrate containing a CF_2Cl group still gave a favourable yield (Table 3, entry 8).

In conclusion, we have designed a new cascade cyclization/C–N coupling reaction to provide novel fluorine-containing 1,2,3-triazolo tricyclic compounds. This tandem process involves copper-catalyzed formation of a C–N bond by intramolecular cyclization under base free conditions, which is also suitable for aryl bromides and aryl chlorides. A variety of functional groups can be employed, rendering this method particularly attractive for the efficient preparation of biologically and medicinally interesting molecules.

Table 3. Studies on the alkyne moiety.[a]



Entry		Product	Time [h]	Temp. [°C]	Yield [%][b]
1	**2h**		30 min	r.t.	94
2	**2i**		10 h	80	87
3	**2j**		10 h	60	92
4	**2k**		30 min	r.t.	97
5	**2l**		1 h	r.t.	91
6	**2m**		10 h	r.t.	65
7	**2n**		10 h	60	56
8	**2o**		2 h	60	70

[a] Reactions were carried out on a 0.3 mmol scale in DMSO (2 mL) under nitrogen with sodium azide (1.1 equiv.) , catalyst (10 mol%) and ligand (20 mol%) unless otherwise stated.

[b] Isolated yield.

Experimental Section

Typical Experimental Procedure for CuI-Catalyzed Cascade Reactions of *N*-(*o*-Haloaryl)alkynylimine with Sodium Azide

Compound **1** (0.3 mmol) was added to a solution of CuI (10 mol%), L-proline (20 mol%), sodium azide (0.33 mmol, 1.1 equiv.) in DMSO (2.0 mL), The reaction mixture was then stirred under a nitrogen atmosphere until completion of the reaction as indicated by TLC. The mixture was partitioned between ethyl acetate and water, the organic layer was washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography on silica gel to provide **2**.

Acknowledgements

We gratefully acknowledge financial support from the National Science Foundation of China (Nos. 20532040 and 20772145).

References

[1] a) H. C. Shen, F. Ding, Q. Deng, L. C. Wilsie, M. L. Krsmanovic, A. K. Taggart, E. Carballo-Jane, N. Ren, T. Cai, T. Wu, K. K. Wu, K. Cheng, Q. Chen, M. S. Wolff, X. Tong, T. G. Holt, M. G. Waters, M. L. Hammond, J. R. Tata, S. L. Colletti, *J. Med. Chem.* **2009**, *52*, 2587–2602; b) A. Lauria, C. Patella, G. Dattolo, A. M. Almerico, *J. Med. Chem.* **2008**, *51*, 2037–2046; c) F. Da Settimo, G. Primofiore, S. Taliani, A. M. Marini, C. La Motta, F. Simorini, S. Salerno, V. Sergianni, T. Tuccinardi, A. Martinelli, B. Cosimelli, G. Greco, E. Novellino, O. Ciampi, M. L. Trincavelli, C. Martini, *J. Med. Chem.* **2007**, *50*, 5676–5684; d) G. Biagi, I. Giorgi, O. Livi, V. Scartoni, L. Betti, G. Giannaccini, M. L. Trincavelli, *Eur. J. Med. Chem.* **2002**, *37*, 565–571; e) A. W. Thomas, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1881–1884; f) L. Bertelli, G. Biagi, I. Giorgi, C. Manera, O. Livi, V. Scartoni, L. Betti, G. Giannaccini, L. Trincavelli, P. L. Barili, *Eur. J. Med. Chem.* **1998**, *33*, 113–122; g) L. Betti, G. Biagi, G. Giannaccini, I. Giorgi, O. Livi, A. Lucacchini, C. Manera, V. Scartoni, *J. Med. Chem.* **1998**, *41*, 668–673; h) J. L. Kelley, C. S. Koble, R. G. Davis, E. W. McLean, F. E. Soroko, B. R. Cooper, *J. Med. Chem.* **1995**, *38*, 4131–4134; i) I. R. Ager, A. C. Barnes, G. W. Danswan, P. W. Hairsine, D. P. Kay, P. D. Kennewell, S. S. Matharu,

P. Miller, P. Robson, *J. Med. Chem.* **1988**, *31*, 1098–1115; j) E. J. Trybulski, L. Benjamin, S. Vitone, A. Walser, R. I. Fryer, *J. Med. Chem.* **1983**, *26*, 367–372.

[2] I. Ojima, *Fluorine in Medicinal Chemistry and Chemical Biology*, Wiley-Blackwell, **2009**.

[3] B. Saha, S. Sharma, D. Sawant, B. Kundu, *Tetrahedron* **2008**, *64*, 8676–8684.

[4] For copper-catalyzed C–N bond formation reactions, see: a) D. W. Ma, Y. D. Zhang, J. C. Yao, S. H. Wu, F. G. Tao, *J. Am. Chem. Soc.* **1998**, *120*, 12459–12467; b) A. Klapars, X. H. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 7421–7428; c) J. C. Antilla, A. Klapars, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 11684–11688; d) F. Y. Kwong, A. Klapars, S. L. Buchwald, *Org. Lett.* **2002**, *4*, 581–584; e) D. W. Ma, Q. Cai, H. Zhang, *Org. Lett.* **2003**, *5*, 2453–2455; f) H. J. Cristau, P. P. Cellier, J. F. Spindler, M. Taillefer, *Chem. Eur. J.* **2004**, *10*, 5607–5622; g) H. H. Rao, H. Fu, Y. Y. Jiang, Y. F. Zhao, *J. Org. Chem.* **2005**, *70*, 8107–8109; h) H. Zhang, Q. Cai, D. W. Ma, *J. Org. Chem.* **2005**, *70*, 5164–5173; i) Z. Lu, R. J. Twieg, *Tetrahedron Lett.* **2005**, *46*, 2997–3001; j) A. Shafir, S. L. Buchwald, *J. Am. Chem. Soc.* **2006**, *128*, 8742–8743; k) B. De Lange, M. H. Lambers-Verstappen, L. Schmieder-van de Vondervoort, N. Sereinig, R. de Rijk, A. de Vries, *Synlett* **2006**, 3105–3109; l) L. Rout, S. Jammi, T. Punniyamurthy, *Org. Lett.* **2007**, *9*, 3397–3399; m) R. A. Altman, E. D. Koval, S. L. Buchwald, *J. Org. Chem.* **2007**, *72*, 6190–6199; n) R. A. Altman, A. Shafir, A. Choi, P. A. Lichtor, S. L. Buchwald, *J. Org. Chem.* **2008**, *73*, 284–286.

[5] For cascade processes involving a copper-catalyzed C–N coupling reaction, see: a) X. Y. Yuan, X. B. Xu, X. B. Zhou, J. W. Yuan, L. G. Mai, Y. Z. Li, *J. Org. Chem.* **2007**, *72*, 1510–1513; b) C. P. Jones, K. W. Anderson, S. L. Buchwald, *J. Org. Chem.* **2007**, *72*, 7968–7973; c) B. L. Zou, O. L. Yuan, D. W. Ma, *Org. Lett.* **2007**, *9*, 4291–4294; d) B. L. Zou, Q. L. Yuan, D. W. Ma, *Angew. Chem.* **2007**, *119*, 2652–2655; *Angew. Chem. Int. Ed.* **2007**, *46*, 2598–2601; e) F. S. Melkonyan, A. V. Karchava, M. A. Yurovskaya, *J. Org. Chem.* **2008**, *73*, 4275–4278; f) D. S. Yang, H. Fu, L. M. Hu, Y. Y. Jiang, Y. F. Zhao, *J. Org. Chem.* **2008**, *73*, 7841–7844; g) K. Hasegawa, N. Kimura, S. Arai, A. Nishida, *J. Org. Chem.* **2008**, *73*, 6363–6368; h) A. Minatti, S. L. Buchwald, *Org. Lett.* **2008**, *10*, 2721–2724; i) L. Guo, B. Li, W. L. Huang, G. Pei, D. W. Ma, *Synlett* **2008**, 1833–1836; j) J. T. Zhu, H. B. Xie, Z. X. Chen, S. Li, Y. M. Wu, *Chem. Commun.* **2009**, 2338–2340.

[6] Y. Tanaka, S. R. Velen, S. I. Miller, *Tetrahedron* **1973**, *29*, 3271–3283.

[7] CCDC 755240 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[8] Fluorine-containing *N*-(*o*-haloaryl)alkynylimines were synthesized using a new method created by our group recently (in press), which is detailed in the Supporting Information.

[9] For copper-catalyzed C–N bond formation with aryl chlorides, see: a) A. Klapars, X. H. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 7421–7428; b) S. U. Son, I. K. Park, J. Park, T. Hyeon, *Chem. Commun.* **2004**, 778–779; c) H. C. Ma, X. Z. Jiang, *J. Org. Chem.* **2007**, *72*, 8943–8946; d) H. H. Xu, C. Wolf, *Chem. Commun.* **2009**, 1715–1717; e) H. H. Xu, C. Wolf, *Chem. Commun.* **2009**, 3035–3037.

