1,2,3-Triazoles

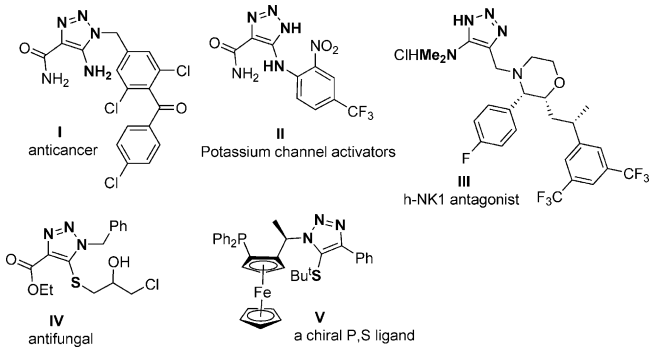
Deutsche Ausgabe: DOI: 10.1002/ange.201509124
Internationale Ausgabe: DOI: 10.1002/anie.201509124

Copper(I)-Catalyzed Interrupted Click Reaction: Synthesis of Diverse 5-Hetero-Functionalized Triazoles

*Weiguo Wang, Xianglong Peng, Fang Wei, Chen-Ho Tung, and Zhenghu Xu**

Abstract: *The 5-heterofunctionalized triazoles are important scaffolds in bioactive compounds, but current click reactions (CuAAC) cannot produce these core structures. A copper(I)-catalyzed interrupted click reaction to access diverse 5-functionalized triazoles is reported. Various 5-amino-, thio-, and selenotriazoles were readily assembled in one step in high yields. The reaction proceeds under mild conditions with complete regioselectivity. It also features a broad substrate scope and good functional group compatibility.*

The copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC)[1] forming 1,2,3-triazoles has become a prime example of click chemistry because of its reliability, specificity, and biocompatability. Click chemistry has been widely used in different areas of science, such as drug discovery, bioconjugation, polymer and supermolecular chemistry.[2] The triazole products of this reaction are more than simply connecting linkers: they are very important pharmacophores, widely used in medicinal chemistry.[3] Among them, the multisubstituted 5-heterofunctionalized 1,2,3-triazoles are a type of privileged triazoles, present in many synthetic molecules with a variety of biological activitites (Scheme 1).

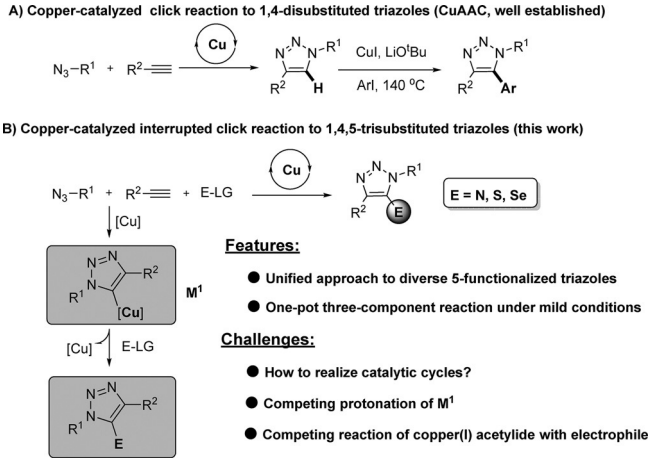


Scheme 1. Important 5-functionalized triazoles.

For instance, carboxylamidotriazole **I** (CAI) exhibits anticancer activity,[4a] the triazole **II** is an active potassium channel activator,[4b] the triazole **III** is a potent h-NK1 antagonist,[3b] the sulfur-containing triazole **IV** is a potential herbicide with antifungal activity,[4c] and the triazole **V** is an excellent chiral ligand used in asymmetric catalysis.[4d] However, the CuAAC reaction is limited to terminal alkynes and cannot produce these functionalized structures. Consequently, the development of an efficent strategy to access diverse hetero-functionailized triazoles is of great importance.

In 2010, Fokin and co-workers reported a sequential halide exchange and subsequent S_NAr reaction to produce various 5-functionalized triazoles.[5] This strategy requires multiple reaction steps and a halide exchange step that involves high temperatures. The recently reported RuAAC[6a] and IrAAC[6b] reactions have partially addressed this challenge, and could afford trisubstituted triazoles with high regioselectivity. However, these approaches need to use noble metal catalysts and prepare the functionalized internal alkynes in advance. To date, no widely applicable direct synthesis of various heteroatom-functionalized triazoles from easily available terminal alkynes has been reported.[7]

The CuAAC reaction shown in Scheme 2 A is an effective approach to triazoles. The Ackermann group reported a copper-catalyzed one-pot reaction to introduce an aryl group onto the triazole ring at elevated temperature.[8] Herein, we proposed another interrupted click reaction using a heteroatom electrophile to intercept the cuprate–triazole intermediate $\mathbf{M^1}$ forming 5-hetero-functionalized triazoles (Scheme 2 B). Previously reported successful inter-



Scheme 2. Copper(I)-catalyzed interrupted click reaction by electrophiles to diverse 5-functionalized triazoles.

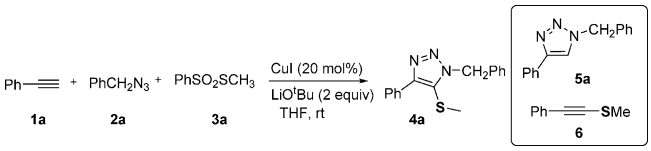
[*] W. Wang, X. Peng, F. Wei, Prof. C.-H. Tung, Prof. Z. Xu
Key Lab for Colloid and Interface Chemistry of Education Ministry
Department of Chemistry, Shandong University
No. 27 South Shanda Road, Jinan, 250100 (China)
E-mail: xuzh@sdu.edu.cn
Homepage: http://opcl.sdu.edu.cn/Teacher.aspx?tid=4
Prof. Z. Xu
State Key Laboratory of Organometallic Chemistry
Shanghai Institute of Organic Chemistry
Chinese Academy of Sciences
Shanghai 200032 (P.R. China)

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201509124.

ception of this intermediate with ICl or allyl iodide demonstrated the feasibility of this method.[9–11] However, most reactions require stoichiometric amounts of a copper(I) catalyst. Realizing a catalytic reaction is highly desirable, but completion of this catalytic cycle is challenging because of two competing reactions: (1) protonation of the cuprate–triazole intermediate **M**[1] producing the undesired 1,4-disubstituted triazole; and (2) reaction of copper(I) acetylide with the heteroatom electrophile generating a heteroatom-substituted internal alkyne, which is unreactive under click reaction conditions. Therefore, choosing an appropriate heteroatom electrophile with enough reactivity toward the vinyl copper intermediate, rather than the copper acetylide, is critically important.

Previously, S-methyl benzenesulfonothioate **3a** was used successfully by Dai and Tang to introduce a sulfenyl group into D-camphor, building a chiral sulfide.[12] Compound **3a** might be an excellent electrophilic sulfenylating reagent, because the cleaved benzenesulphinate is a good leaving group, with the pK_a of phenylsulfinic acid being 2.76. To validate this concept, the phenylacetylene **1a** and the benzylazide **2a** were selected as model substrates with which to optimize the reaction conditions (Table 1; see the

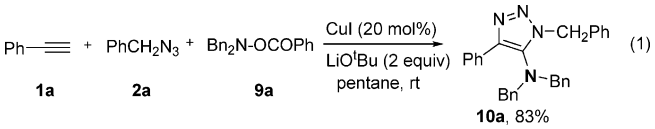
Table 1: Optimization of reaction conditions.[a]



Entry	Base	Temp [°C]	Electrophile	Yield [%][b] 4a	5a
1	LiO^{t}Bu	25	**3a**	74	8
2	LiO^{t}Bu	25	 **7**	0[c]	66
3	LiO^{t}Bu	25	 **8**	0	96
4	KO^{t}Bu	25	**3a**	< 5	64
5	NaOMe	25	**3a**	30	52
6	NaH	25	**3a**	25	56
7	K_2CO_3	25	**3a**	< 5	92
8	Et_3N	25	**3a**	< 5	94
9	LiO^{t}Bu	40	**3a**	81	5
10[d]	**LiO^{t}Bu**	**40**	**3a**	**95 (90)**	**trace**

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), **3a** (0.3 mmol), CuI (20 mol%), base (0.4 mmol), 4 Å molecular sieves (MS, 150 mg), THF (1 mL) was stirred at room temperature under N_2 atmosphere for 12 h. [b] Determined by ^{1}H NMR using trimethoxybenzene as the internal standard. The isolated yield is in parentheses. [c] 5-phenylthiotriazole product was not detected. [d] **3a** (0.4 mmol).

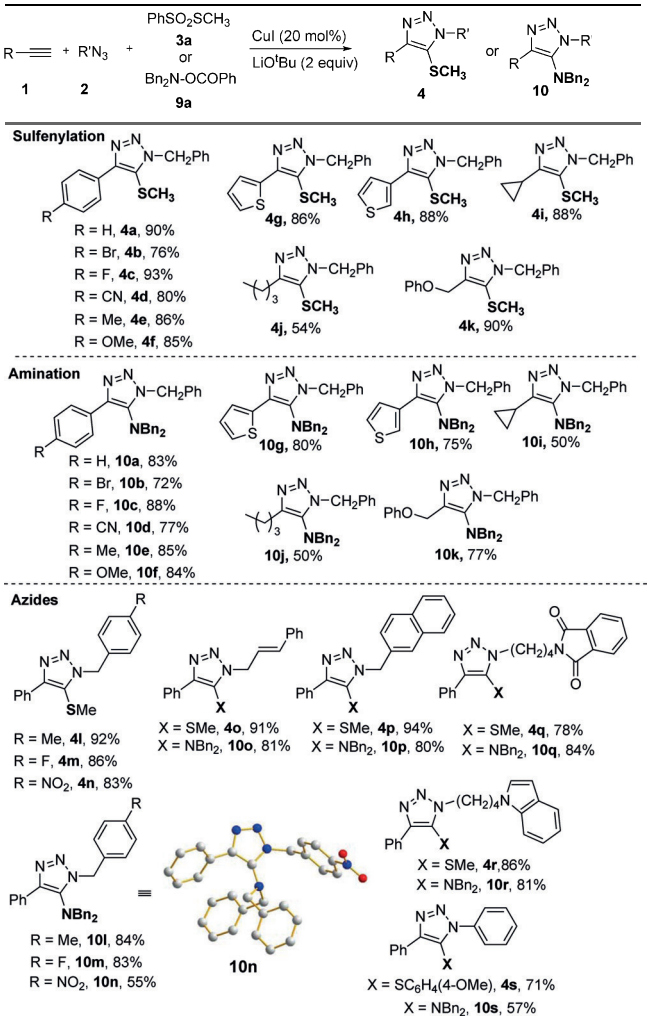
Supplementary Information for details). It was found that benzenethiosulfonate (**3a**) serves as an efficient electrophile, affording the desired 5-thiotriazole (**4a**) in 74% yield, together with 8% of the 5-H-triazole (**5a**) in the presence of 20 mol% CuI (Table 1, Entry 1). Almost no thioalkyne (**6**) was observed in the reaction. Other electrophilic sulfenylating reagents (**7, 8**)[13,14] were also tested. The expected thiotriazole was not observed, but only the click product (**5a**; Entries 2 and 3). Further screening of different bases indicated that LiO^{t}Bu was crucial for the success of this reaction (Entries 4–8). The highest isolated yield (90%; Entry 10) was obtained by raising the temperature to 40°C and increasing the amount of **3a** to two equivalents. Using an electrophilic amination reagent (**9a**),[15] 5-amino triazole (**10a**) could be obtained in 83% yield by a similar CuI-catalyzed three-component reaction [Eq. (1)].



(1)

With the optimized conditions defined, we investigated the scope of various alkyne structures (Table 2). Both

Table 2: Substrate scope of alkynes and azides.[a]



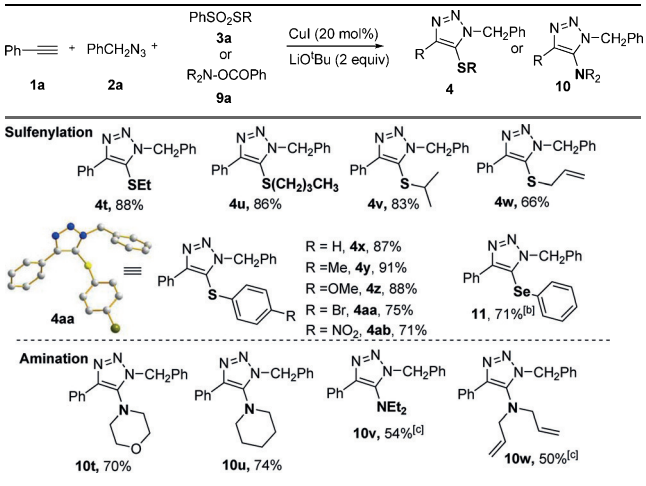
[a] Reaction conditions: Sulfenylation: (Condition A) **1** (0.2 mmol), **2** (0.3 mmol), **3a** (0.4 mmol), CuI (20 mol%), base (0.4 mmol), 4 Å MS (150 mg), THF (1 mL) was stirred at 40°C under N_2 atmosphere for 12 h; Amination: (Condition B) **1** (0.2 mmol), **2** (0.3 mmol), **9a** (0.3 mmol), CuI (20 mol%), base (0.4 mmol), 4 Å MS (150 mg), pentane (1 mL) was stirred at room temperature under N_2 atmosphere for 12 h. Isolated yields were reported.

aromatic and aliphatic alkynes can participate in this three-component reaction to give the 5-thio- or 5-amino-triazoles in good to excellent yields. Electron-donating groups, such as methyl (**4e** and **10e**) and methoxyl (**4f** and **10f**), and electron-withdrawing groups, such as halogen (**4b**,**c** and **10b**,**c**) and cyano (**4d** and **10d**) moieties, are compatible with the reaction. Alkynes substituted by thienyl (**4g**,**h** and **10g**,**h**), cyclopropyl (**4i** and **10i**), and phenoxyl (**4k** and **10k**) are also suitable for this transformation, giving good yields of the corresponding triazoles.

The reaction is also efficient with various alkyl and aromatic azides (Table 2). All of the aliphatic azides tested were effective substrates, giving the corresponding triazoles in good to excellent yields under standard conditions. Cinnamyl groups (**4o** and **10o**), phthalimide-protected amines (**4q** and **10q**), and indole skeletons (**4r** and **10r**) are all tolerated under these mild conditions. Furthermore, the reaction is also efficient for aromatic azides, generating the 5-thio- and aminotriazoles in good yields (**4s** and **10s**).

We next examined the scope of this transformation with respect to different heteroatom electrophiles (Table 3). For

Table 3: Substrate scope of hetero-atoms.[a]

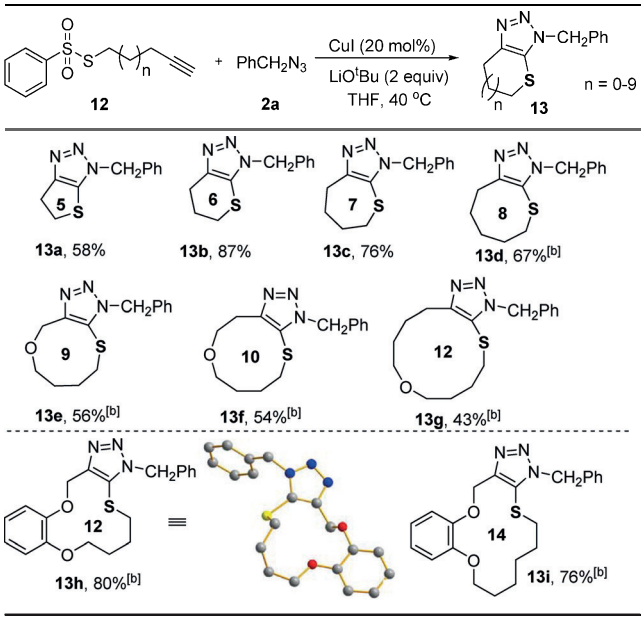


[a] Isolated yields. Condition A for sulfenylation, condition B for amination. [b] $PhSO_2SePh$ was slowly injected in 6 h by syringe pump. [c] at 40 °C.

the sulfenylation reaction, a large variety of alkyl and aromatic thio groups could be easily introduced onto the triazole ring, giving 5-thiotriazoles (**4t-ab**), mostly in very good yields, and functional groups such as allyl, halogen, and nitro are well tolerated. Significantly, 5-phenylselenyl triazole (**11**) could be produced in 71% yield by this approach under very mild conditions. Various amines such as morpholine, piperidine, diethyl amine, and diallyl amine can all be installed on the triazole ring and give good yields (**10t–w**). The structures of **4aa** and **10n** were unambiguously characterized by single-crystal X-ray crystallography. All of these heteroatom electrophiles can easily be prepared from readily available starting materials (Supporting Information), thus making this method a practical approach to various 5-hetero-functionalized triazoles.

The construction of medium and large rings is always a challenge in the organic synthesis,[16] and we questioned whether this copper-catalyzed reaction can be applied to an intramolecular reaction to construct various ring systems. By linking the thiosulfonyl and alkyne groups in the same molecule, we synthesized the functionalized alkyne **12** (Supporting Information). The reaction of alkyne **12** with azide **2a** afforded the fused bicyclic triazole **13** in moderate to good yields (Table 4). Many 5- and 6-membered rings, and

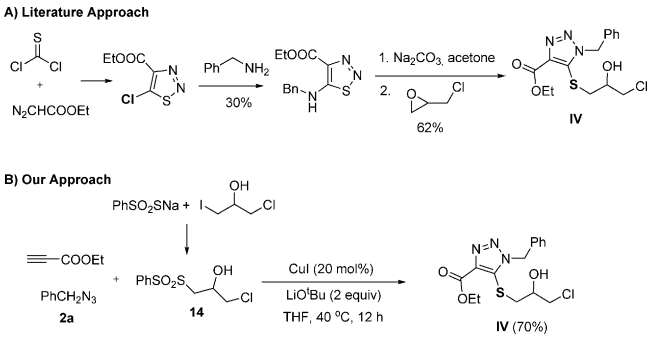
Table 4: Intramolecular reaction to construct various-sized rings.[a]



[a] Isolated yields. [b] **12** was slowly injected in 5 h by syringe pump.

also 7- to 14-membered medium and large rings, can all be synthesized in good yields. Notably, the catechol-derived 12-membered ring **13h** and 14-membered ring **13i** can be formed in 80% and 76% yield, respectively. The structure of **13h** was confirmed by single-crystal X-ray crystallography.[17] For formation of 8–14-membered ring systems, a slow injection of the alkyne substrate **12** into the reaction system was necessary.

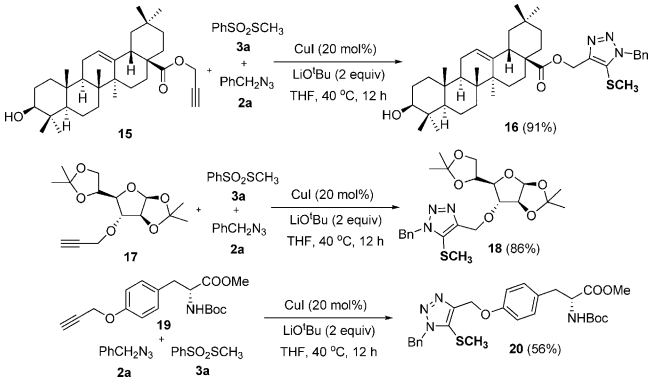
The utility of this chemistry is demonstrated by its application to a two-step synthesis of the antifungal thiotriazole **IV** (Scheme 3).[4d] This biologically active compound was



Scheme 3. Synthesis of antifungal active thiotriazole **IV**.

originally prepared from highly toxic thiophosgene and ethyl diazoacetate in multiple reaction steps with less than 15% overall yield. However, it can be synthesized in 70% yield by the standard three-component reaction of the azide **2a**, propiolic acid ethyl ester, and the sulfenylating reagent **14**, which can be easily prepared by the reaction of $PhSO_2SNa$ with corresponding iodide.

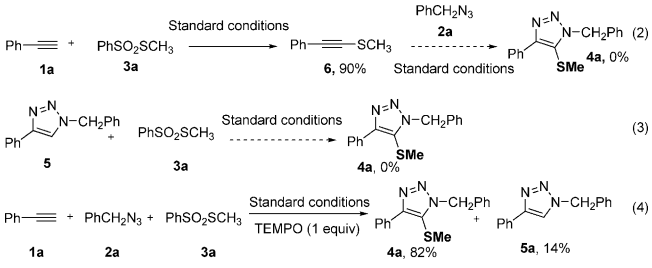
The significance of this chemistry is seen in the late-stage click/functionalization of bioactive natural compounds, saccharides, and amino acid derivatives shown in Scheme 4. Treatment of oleanane-type triterpene-derived alkyne **15**



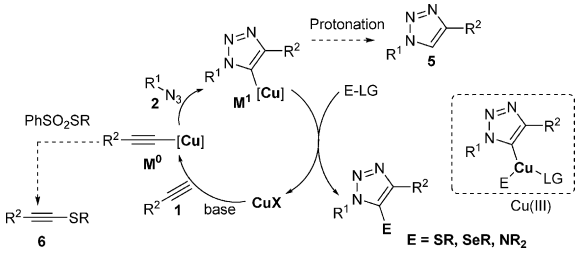
Scheme 4. Late-stage functionalization of biologically active molecules.

under standard reaction conditions afforded the corresponding thiotriazole **16** in 91% yield. This reaction has great potential for drug discovery and development. Furthermore, the glucose derivative **17** and the amino acid derivative **19** were also amenable to this transformation giving desired products **18** and **20** with good yields.

To gain an improved understanding of the reaction mechanism, controlled experiments were conducted. The reaction of phenylacetylene (**1a**) with **3a** under standard conditions afforded the thioalkyne (**6**) in 90% yield. However, the reaction of **6** with benzyl azide (**2a**) failed to afford the target product (**4a**) [Eq. (2)]. Disubstituted triazole (**5**),



the major by-product of this reaction, failed to react with **3a** to form **4a** [Eq. (3)]. Addition of one equivalent of tetramethylpiperidine-1-oxyl (TEMPO), had almost no effect on the reaction, indicating that a radical process may not be involved [Eq. (4)]. Based on these experiments, a possible reaction mechanism was proposed (Scheme 5). The cycloaddition of copper(I) acetylide $\mathbf{M^0}$ with the azide **2** generates the cuprate–



Scheme 5. Proposed reaction mechanism.

triazole $\mathbf{M^1}$. This intermediate reacts with the heteroatom electrophile E-LG to form the product **4**, possibly through an oxidative addition and reductive elimination sequence. The recovered Cu-LG reacts with the alkyne in the presence of base to form copper(I) acetylide $\mathbf{M^0}$, completing the catalytic cycle.

In summary, we have developed a copper(I)-catalyzed interrupted click reaction to access diverse 5-functionalized triazoles. The reaction proceeds under very mild conditions, with only catalytic amounts of an inexpensive copper catalyst and no required ligands. This practical method exhibits a very broad scope with respect to alkynes, azides, and also different heteroatom electrophiles. The intramolecular reaction can be used to construct bicyclic triazoles with various ring sizes. A notable feature of this reaction is the late-stage functionalization of bioactive compounds, thus providing efficient and practical synthetic routes for drug discovery and development, which the current click reaction (CuAAC) is unable to do. Further applications of this interrupted click reaction in medicinal chemistry are in progress in our laboratory.

Acknowledgements

We are grateful for the financial support from Natural Science Foundation of China and Shandong province (No. 21572118 and JQ201505), and subject construction funds of Shandong University (104.205.2.5 and 2014JC008).

Keywords: aminations · click reactions · sulfenylation · triazoles

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 649–653
Angew. Chem. **2016**, *128*, 659–663

[1] a) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2002**, *41*, 2596; *Angew. Chem.* **2002**, *114*, 2708; b) C. W. Tornøe, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, *67*, 3057.

[2] a) J. E. Hein, V. V. Fokin, *Chem. Soc. Rev.* **2010**, *39*, 1302; b) S. K. Mamidyala, M. G. Finn, *Chem. Soc. Rev.* **2010**, *39*, 1252; c) P. L. Golas, K. Matyjaszewski, *Chem. Soc. Rev.* **2010**, *39*, 1338; d) J. C. Jewett, C. R. Bertozzi, *Chem. Soc. Rev.* **2010**, *39*, 1272; e) M. Meldal, C. W. Tornøe, *Chem. Rev.* **2008**, *108*, 2952; f) J. E. Moses, A. D. Moorhouse, *Chem. Soc. Rev.* **2007**, *36*, 1249.

[3] For reviews, see: a) P. Thirumurugan, D. Matosiuk, K. Jozwiak, *Chem. Rev.* **2013**, *113*, 4905; b) S. G. Agalave, S. R. Maujan, V. S. Pore, *Chem. Asian J.* **2011**, *6*, 2696.

[4] a) M. J. Soltis, H. J. Yeh, K. A. Cole, N. Whittaker, R. P. Wersto, E. C. Kohn, *Drug Metab. Dispos.* **1996**, *24*, 799; b) G. Biagi, V.

Calderone, I. Giorgi, O. Livi, V. Scartoni, B. Baragatti, E. Martinotti, *Eur. J. Med. Chem.* **2000**, *35*, 715; c) Y. Morzherin, P. E. Prokhorova, D. A. Musikhin, T. V. Glukhareva, Z. Fan, *Pure Appl. Chem.* **2011**, *83*, 715; d) I. Oura, K. Shimizu, K. Ogata, S.-i. Fukuzawa, *Org. Lett.* **2010**, *12*, 1752.

[5] B. T. Worrell, J. E. Hein, V. V. Fokin, *Angew. Chem. Int. Ed.* **2012**, *51*, 11791; *Angew. Chem.* **2012**, *124*, 11961.

[6] a) B. C. Boren, S. Narayan, L. K. Rasmussen, L. Zhang, H. Zhao, Z. Lin, G. Jia, V. V. Fokin, *J. Am. Chem. Soc.* **2008**, *130*, 8923; b) S. Ding, G. Jia, J. Sun, *Angew. Chem. Int. Ed.* **2014**, *53*, 1877; *Angew. Chem.* **2014**, *126*, 1908.

[7] C. J. Smith, N. Nikbin, S. V. Ley, H. Lange, I. R. Baxendale, *Org. Biomol. Chem.* **2011**, *9*, 1938.

[8] a) L. Ackermann, H. K. Potukuchi, D. Landsberg, R. Vicente, *Org. Lett.* **2008**, *10*, 3081; b) R. Jeyachandran, H. K. Potukuchi, L. Ackermann, *Beilstein J. Org. Chem.* **2012**, *8*, 1771; c) L. Ackermann, R. Jeyachandran, H. K. Potukuchi, P. Novák, L. Büttner, *Org. Lett.* **2010**, *12*, 2056.

[9] a) C. Spiteri, J. E. Moses, *Angew. Chem. Int. Ed.* **2010**, *49*, 31; *Angew. Chem.* **2010**, *122*, 33; b) L. Ackermann, H. K. Potukuchi, *Org. Biomol. Chem.* **2010**, *8*, 4503; c) Z. Zhang, Q. Zhou, F. Ye, Y. Xia, G. Wu, M. L. Hossain, Y. Zhang, J. Wang, *Adv. Synth. Catal.* **2015**, *357*, 2277; d) F. Wei, H. Li, C. Song, Y. Ma, L. Zhou, C.-H. Tung, Z. Xu, *Org. Lett.* **2015**, *17*, 2860; e) L. Li, G. Hao, A. Zhu, X. Fan, G. Zhang, L. Zhang, *Chem. Eur. J.* **2013**, *19*, 14403; f) L. Li, G. Zhang, A. Zhu, L. Zhang, *J. Org. Chem.* **2008**, *73*, 3630; g) X. Zhang, R. P. Hsung, H. Li, *Chem. Commun.* **2007**, 2420; h) B. Gerard, J. Ryan, A. B. Beeler, J. A. Porco, Jr., *Tetrahedron* **2006**, *62*, 6405; i) Y. Wu, J. Deng, Y. Li, Q.-Y. Chen, *Synthesis* **2005**, 1314.

[10] a) M. Selvaraju, C.-M. Sun, *Adv. Synth. Catal.* **2014**, *356*, 1329; b) Q. Cai, J. Yan, K. Ding, *Org. Lett.* **2012**, *14*, 3332; c) B. T. Worrell, S. P. Ellery, V. V. Fokin, *Angew. Chem. Int. Ed.* **2013**, *52*, 13037; *Angew. Chem.* **2013**, *125*, 13275; d) C. D. Smith, M. F. Greaney, *Org. Lett.* **2013**, *15*, 4826; e) Y. Zhou, T. Lecourt, L. Micouin, *Angew. Chem. Int. Ed.* **2010**, *49*, 2607; *Angew. Chem.* **2010**, *122*, 2661.

[11] a) W. Li, J. Wang, *Angew. Chem. Int. Ed.* **2014**, *53*, 14186; *Angew. Chem.* **2014**, *126*, 14410; b) J. Thomas, J. John, N. Parekh, W. Dehaen, *Angew. Chem. Int. Ed.* **2014**, *53*, 10155; *Angew. Chem.* **2014**, *126*, 10319; c) D. B. Ramachary, A. B. Shashank, S. Karthik, *Angew. Chem. Int. Ed.* **2014**, *53*, 10420; *Angew. Chem.* **2014**, *126*, 10588; d) Z. Chen, Q. Yan, Z. Liu, Y. Xu, Y. Zhang, *Angew. Chem. Int. Ed.* **2013**, *52*, 13324; *Angew. Chem.* **2013**, *125*, 13566.

[12] a) S. Ye, Z. Huang, C. Xia, Y. Tang, L.-X. Dai, *J. Am. Chem. Soc.* **2002**, *124*, 2432; b) X. Deng, P. Cai, S. Ye, X. Sun, W. Liao, K. Li, Y. Tang, Y. Wu, L.-X. Dai, *J. Am. Chem. Soc.* **2006**, *128*, 9730.

[13] a) T. Hostier, V. Ferey, G. Ricci, D. G. Pardo, J. Cossy, *Org. Lett.* **2015**, *17*, 3898; b) T. Hostier, V. Ferey, G. Ricci, D. G. Pardo, J. Cossy, *Chem. Commun.* **2015**, *51*, 13898; c) H. Tian, C. Zhu, H. Yang, H. Fu, *Chem. Commun.* **2014**, *50*, 8875.

[14] a) Z. Qiao, N. Ge, X. Jiang, *Chem. Commun.* **2015**, *51*, 10295; b) Y. Li, J. Pu, X. Jiang, *Org. Lett.* **2014**, *16*, 2692; c) J. T. Reeves, K. Camara, Z. S. Han, Y. Xu, H. Lee, C. A. Busacca, C. H. Senanayake, *Org. Lett.* **2014**, *16*, 1196.

[15] a) S. Shi, S. L. Buchwald, *Nat. Chem.* **2015**, *7*, 38; b) N. Niljianskul, S. Zhu, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2015**, *54*, 1638; *Angew. Chem.* **2015**, *127*, 1658; c) R. Sakae, K. Hirano, T. Satoh, M. Miura, *Angew. Chem. Int. Ed.* **2015**, *54*, 613; *Angew. Chem.* **2015**, *127*, 623; d) Y. Miki, K. Hirano, T. Satoh, M. Miura, *Angew. Chem. Int. Ed.* **2013**, *52*, 10830; *Angew. Chem.* **2013**, *125*, 11030.

[16] a) W. Zhao, Z. Li, J. Sun, *J. Am. Chem. Soc.* **2013**, *135*, 4680; b) W. Zhao, H. Qian, Z. Li, J. Sun, *Angew. Chem. Int. Ed.* **2015**, *54*, 10005; *Angew. Chem.* **2015**, *127*, 10143.

[17] CCDC 1422828, 1422829, and 1422830 (**4aa**, **10n**, **13h**) contain 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.

Received: September 29, 2015
Revised: November 7, 2015
Published online: November 27, 2015

