Organic Letters

Letter

pubs.acs.org/OrgLett

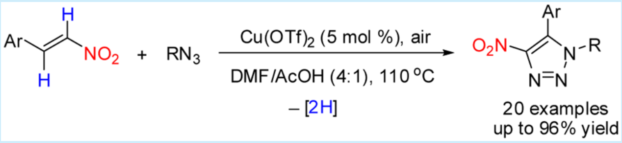
Copper-Catalyzed [3 + 2] Cycloaddition/Oxidation Reactions between Nitro-olefins and Organic Azides: Highly Regioselective Synthesis of NO_2-Substituted 1,2,3-Triazoles

Yunfeng Chen,* Gang Nie, Qi Zhang, Shan Ma, Huan Li, and Qinquan Hu

School of Chemistry and Environmental Engineering, Wuhan Institute of Technology, Wuhan 430073, China

Supporting Information

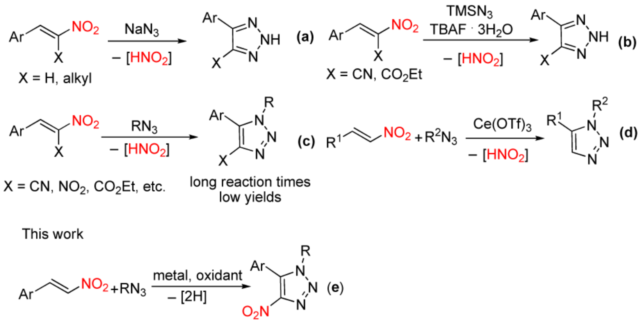
ABSTRACT: A new copper-catalyzed [3 + 2] cycloaddition/oxidation reaction of nitro-olefins with organic azides has been developed to afford 1,4(-NO_2),5-trisubstituted 1,2,3-triazoles. This reaction sequence has a broad substrate scope and affords NO_2-substituted 1,2,3-triazoles with high regioselectivities and in good to excellent yields. The involved oxidative process overcomes the elimination of HNO_2 for general cycloaddition of nitro-olefins with organic azides, which shows a high atom economy and potential applications.



1,2,3-Triazoles are an important class of heterocyclic compounds with wide applications in medicinal,[1] material,[2] and synthetic organic chemistry.[3] For example, some 1,2,3-triazoles show a broad spectrum of biological activities such as antifungal, antiviral, antiallergic, anti-HIV, and antimicrobial activities.[4] Because of their reliability, the diverse syntheses of 1,2,3-triazoles have gained much attention. The most popular methods for these kinds of compounds are based on copper(I)-[5] and ruthenium(II)-mediated[6] regioselective azide−alkyne cycloaddition reactions, which give 1,4- or 1,5-disubstituted 1,2,3-triazoles, respectively. Recently, some fully substituted 1,2,3-triazoles were also synthesized by different approaches, such as 1,4,5-trisubstituted 1,2,3-triazoles, which were obtained by metal-catalyzed cycloaddition reactions of organic azides with internal alkynes[7] and by organocatalytic cycloaddition reactions or multicomponent reactions of organic azides with activated enones, keto esters, nitriles, or aldehydes.[8] At the same time, other 1,2,3-triazoles were also synthesized by post-functionalization of *NH*-1,2,3-triazoles or 1,4-disubstituted 1,2,3-triazoles.[9]

Nitro-olefins also serve as an important partner with azides to form the 1,2,3-triazoles (Scheme 1).[10] Cyclization reactions of nitro-olefins with NaN_3 can give the *NH*-1,2,3-triazoles (Scheme 1a).[10a−c] $TMSN_3$ as a nitrogen source with tetra-*n*-butylammonium fluoride is an alternative method for the formation of *NH*-1,2,3-triazoles (Scheme 1b).[9d] In general, organic azides react with nitro-olefins to give the N-substituted 1,2,3-triazoles with low efficiency (Scheme 1c).[10e] Interestingly, Wang et al. reported that nitro-olefins could also react with organic azides in the presence of $Ce(OTf)_3$ to give 1,5-disubstituted 1,2,3-triazoles (Scheme 1d).[10f] For these four cases, the formation of 1,2,3-triazoles involved an elimination of HNO_2 process. Nitrogen-group-substituted 1,2,3-triazoles are very important for their applications; most of them were synthesized by the click reaction of electron-deficient ynamides with organic azides;[11] even so, the diverse nitrogen-group-substituted 1,2,3-triazoles are still scarce. The NO_2 group is a good nitrogen source, which is widely used for synthesis of N-containing compounds.[12] We propose that, if the dehydrogenation process is involved instead of the elimination of HNO_2 between the cyclization of nitro-olefins with organic azides, it can give the NO_2-substituted 1,2,3-triazoles. The challenge for this design is to inhibit the elimination of HNO_2 effectively. Herein we present a copper-catalyzed highly selective synthesis of NO_2-substituted 1,2,3-triazoles from nitro-olefins and organic azides, which involved the loss of two hydrogens instead of HNO_2 for nitro-olefins (Scheme 1e).

Scheme 1. Syntheses of 1,2,3-Triazoles from Nitro-olefins

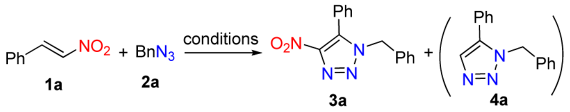


The reaction conditions were tested by using a model reaction between nitrostyrene (**1a**) and benzyl azide (**2a**), including different metal salts, solvents, and additives, and the results are shown in Table 1. The Cu(I) catalysts were first tested including CuI and CuCl because the organic azides can coordinate with copper complexes, especially the Cu(I) complex. Conversions were up to 60% using dimethylformamide (DMF) as solvent under air atmosphere; however, the yields for the proposed oxidative cycloaddition product **3a** were less than 10%, and the

Received: December 22, 2014

DOI: 10.1021/ol503687w

Table 1. Optimization of the Reaction Conditions[a]



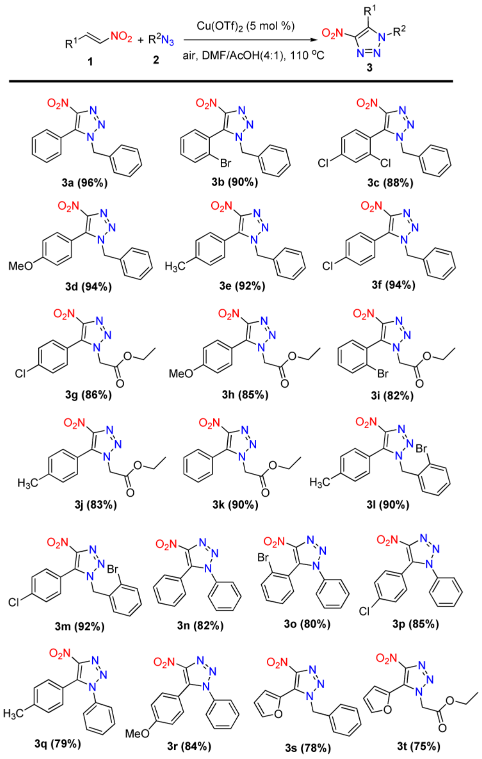
entry	catalyst	solvent	concn (%)	yield of **3a**/**4a** (%)[b]
1	CuI	DMF	67	7/23
2	CuCl	DMF	64	5/22
3	CuO	DMF	66	35/19
4	$CuCl_2$	DMF	78	23/41
5	$CuBr_2$	DMF	80	28/43
6	$Cu(OAc)_2$	DMF	73	27/36
7	$Cu(NO_3)_2$	DMF	81	56/17
8	$CuSO_4$	DMF	86	77/4
9	$Cu(OTf)_2$	DMF	90	83/trace
10	$Cu(OTf)_2$	toluene	23	trace/20
11	$Cu(OTf)_2$	MeOH	67	16/34
12	$Cu(OTf)_2$	DMSO	76	68/trace
13[c]	$Cu(OTf)_2$	DMF	95	85/<5
14	$Cu(OTf)_2$	DMF/AcOH (10%)	95	90/trace
15	$Cu(OTf)_2$	DMF/AcOH (25%)	100	96/0
16	$FeCl_3$	DMF	<5	–/–
17	$PdCl_2$	DMF	38	trace/22
18	$Pd(OAc)_2$	DMF	37	trace/30
19	$PdCl_2(PPh_3)_2$	DMF	68	trace/27

[a] Reactions conditions: nitrostyrene (**1a**) (1 mmol), benzyl azide (**2a**) (1.2 mmol), and catalyst (0.05 mmol), air (1 atm), solvents (5 mL for each, 0.2 M), 110 °C, 14 h. [b] Yields of products purified by column chromatography on silica gel. [c] O_2 (1 atm) was used.

major product was **4a**, which formed via elimination of HNO_2. We then tested the Cu(II) catalyst; it is gratifying that the expected **3a** was obtained with 35% separated yield by using CuO as catalyst (entry 3), and in this case, **4a** was the minor product with 19% yields. Other Cu(II) salts were tested for improving the conversion and selectivity, including $CuCl_2$, $CuBr_2$, $Cu(NO_3)_2$, $Cu(OAc)_2$, $CuSO_4$, and $Cu(OTf)_2$ (entries 4–9). By using $CuCl_2$, $CuBr_2$, and $Cu(OAc)_2$, the conversions were increased to a certain extent; however, the yields of **3a** were not modified, while the yields of **4a** were increased. When $Cu(NO_3)_2$ and $CuSO_4$ were used, the yields of **3a** were increased obviously, and the formation of **4a** was inhibited greatly when $CuSO_4$ was used. When more acidic $Cu(OTf)_2$ was chosen as catalyst, the conversion increased to 90% and the yields of **3a** increased to 83%. Other solvents were also tested for the optimization conditions, but they were not better than DMF. Because there is an oxidative process for the formation of **3a**, the reaction was tested at the oxygen atmosphere (entry 13); however, no improvement was observed in the conversion and yield. By contrast with different Cu(II) salts, we proposed that the acidities of the catalysts may be crucial for this transformation, so AcOH was introduced for this reaction system. The yield reached up to 90% if 10% AcOH was introduced, and when 25% AcOH was added, it gave 100% conversion and the yield was up to 96% (entry 15). Other metal salts were also tested for this reaction, including $FeCl_3$ and Pd(II) salts, and they did not give satisfying results.

With the optimized reaction conditions in hand, we studied the scope and limitations of this transformation with a wide range of nitro-olefins and organic azides (Scheme 2). Both electron-donating functional groups, such as methoxy (**3d**, **3h**, and **3r**), methyl substituents (**3e**, **3j**, **3l**, and **3q**), and electron-withdrawing groups, such as halogens moieties (**3b**, **3c**, **3f**, **3g**, **3i**, **3m**, **3o**, and **3p**), on the aromatic rings of the nitro-olefins were compatible with this transformation. The structure of **3b** was identified by X-ray single-crystal analysis. Furthermore, acid-sensitive furanyl-substituted nitro-olefins were also suitable substrates to react with azides (**3s** and **3t**), and yields (78 and 75%) were somewhat lower than those of other nitro-olefins; we ascribe this to the decomposition of the furanyl groups. In addition, different organic azides, including aliphatic and aromatic azides, were also suitable substrates, and the corresponding products were obtained in good to excellent yields. The structure of **3p** was also identified by X-ray single-crystal analysis (see Supporting Information). However, the reaction for nitro-olefins with the aromatic azides provided the corresponding products in slightly diminished yields in comparison with benzyl azides; furthermore, excess azides (1.5 equiv) were needed for full conversions of nitro-olefins (see Supporting Information).

Scheme 2. Substrate Scope for the Cycloaddition Reaction of Nitro-olefins 1 and Azides 2[a]

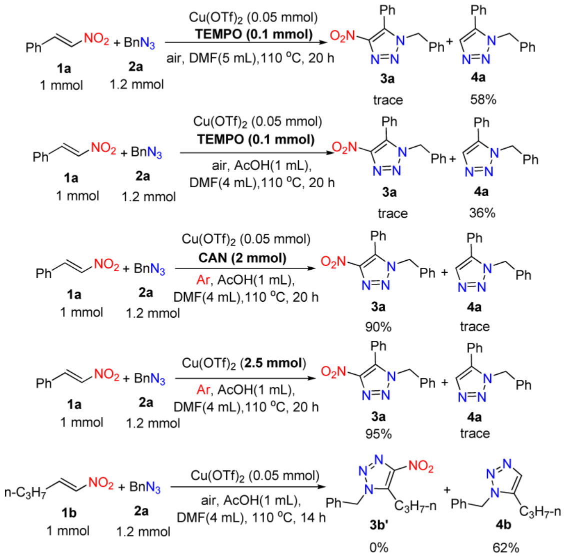


[a] Reactions conditions: **1** (1 equiv), **2** (1.2–1.5 equiv), and $Cu(OTf)_2$ (5 mol %), air (1 atm), DMF/AcOH (4:1, v/v, 0.2 M), 14–20 h. Yields of isolated products are given.

This strategy is a direct method for synthesis of NO_2-substituted 1,2,3-triazoles via introduction of an oxidative dehydrogenative process instead of the elimination of HNO_2, which shows higher atom economy. More importantly, the corresponding NO_2-substituted 1,2,3-triazoles are difficult to obtain by nitration of C4(5)–H 1,2,3-triazoles.[13]

To get insight into the mechanism of the reaction, some control experiments were done (Scheme 3). The Cu/TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl) system was widely used for aerobic oxidation reactions,[14] and TEMPO was first

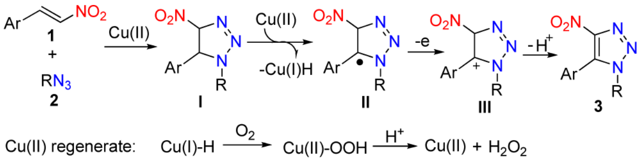
Scheme 3. Control Experiments for the Cyclization of Nitro-olefins with BnN_3



introduced for this reaction; however, it was found that formation of **3a** was totally inhibited. In this case, **4a** via elimination of HNO_2 also formed with 58% yield. When AcOH was used, **3a** still cannot be detected, but the elimination of HNO_2 may be inhibited to a certain extent (only 36% yield for **4a**). We proposed that the formation of **3a** should involve a radical process: TEMPO served as a radical inhibitor,[15] while formation of **4a** was not related to the oxidation process. Furthermore, the reaction was run under Ar atmosphere using 2 equiv of CAN (ceric ammonium nitrate) as oxidant or a stoichiometric amount (2.5 equiv) of $Cu(OTf)_2$, and **3a** was normally formed with 90 and 95% separated yields, respectively. So the air just served as an oxidant to promote the regeneration of the Cu(II) catalyst. We also checked the alkyl-substituted nitro-olefin **1b** under standard conditions. The reaction gave 100% conversion; however, the corresponding product was 1,5-disubstituted 1,2,3-triazole **4b**.

According to these control experiments, a plausible mechanism for this Cu(II)-catalyzed oxidative [3 + 2] cycloaddition reaction is outlined in Scheme 4. The first step of the reaction is the regioselective 1,3-dipolar cycloaddition of nitro-olefin **1** with azide **2** to form the triazoline intermediate **I** (attempts to synthesize intermediate **I** were unsuccessful); this process can be promoted by transition metal complexes.[10d−f] Then a radical **II** is formed with the help of the Cu(II) catalyst; this radical can be stabilized by an Ar group, which facilitates the loss of another electron to give the cation intermediate **III**, which loses a proton to form NO_2-substituted 1,2,3-triazole **3**. Formation of the same kind of radical **II** for the alkyl-substituted nitro-olefin is not as favorable in energy as that of Ar-substituted nitro-olefins, so it tends to form 1,5-disubstituted 1,2,3-triazoles via elimination of HNO_2 under the same conditions. The Cu(II) can be regenerated from Cu(I) species with oxygen under acidic condition. The Cu(I) species react with oxygen to generate [Cu(II)−O−O•] or [Cu(II)−O−OH][16] then dissociates to form H_2O_2 and regenerates the Cu(II) catalyst.

Scheme 4. Plausible Mechanim for Cu(II)-Catalyzed [3 + 2] Cycloaddition/Oxidation Reaction



$$\text{Cu(I)-H} \xrightarrow{O_2} \text{Cu(II)-OOH} \xrightarrow{H^+} \text{Cu(II)} + H_2O_2$$

In conclusion, we report a copper-catalyzed [3 + 2] cycloaddition/oxidation reaction of organic azides with nitro-olefins. The reactions give 1,4(-NO_2),5-trisubstituted 1,2,3-triazoles with high selectivity in good to excellent yields, and it proceeds from simple building blocks and tolerates a broad range of functional groups as well as readily available reagents. The potential viability and generality of this reaction for the construction of various 4-amino 1,2,3-triazoles may be anticipated (reduction of the NO_2 group); derivatives such as 4-amino 1,2,3-triazoles have already been found to increase potency as antibacterial agents.[17] The detailed reaction mechanism and synthetic applications of this reaction to synthesize other diverse 1,2,3-triazoles and other NO_2-substituted heterocycles together with biological activities are under investigation.

■ ASSOCIATED CONTENT

Supporting Information

General experimental procedure, characterization data of the compounds, and CIF data for **3b** and **3p**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: chyfch@hotmail.com.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the National Natural Science Foundation of China (21002076), the Scientific Research Foundation for the Returned Overseas Chinese Scholars, and Wuhan Youth Chenguang Program of Science and Technology (201271031374) for financial support.

■ REFERENCES

(1) For selected reviews, see: (a) Bohacek, R. S.; McMartin, C.; Guida, W. C. *Med. Res. Rev.* **1996**, *16*, 3. (b) Moses, J. E.; Moorhouse, A. D. *Chem. Soc. Rev.* **2007**, *36*, 1249. (c) Tron, G. C.; Pirali, T.; Billington, R. A.; Canonico, P. L.; Sorba, G.; Genazzani, A. A. *Med. Res. Rev.* **2008**, *28*, 278. (d) Sheng, C.; Zhang, W. *Curr. Med. Chem.* **2011**, *18*, 733. (e) Agalave, S. G.; Maujan, S. R.; Pore, V. S. *Chem. Asian J.* **2011**, *6*, 2696. (f) Thirumurugan, P.; Matosiuk, D.; Jozwiak, K. *Chem. Rev.* **2013**, *113*, 4905.

(2) For selected reviews, see: (a) Chu, C.; Liu, R. *Chem. Soc. Rev.* **2011**, *40*, 2177. (b) Lau, Y. H.; Rutledge, P. J.; Watkinson, M.; Todd, M. H. *Chem. Soc. Rev.* **2011**, *40*, 2848. (c) Astruc, D.; Liang, L.; Rapakousiou, A.; Ruiz, J. *Acc. Chem. Res.* **2012**, *45*, 630. (d) Muller, T.; Bräse, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 11844.

(3) (a) Fan, W. Q.; Katritzky, A. R. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Elsevier Science: Oxford, U.K., 1996; Vol. 4, p 1. (b) Chattopadhyay, B.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 862. (c) Urankar, D.; Pinter, B.; Pevec, A.; De Proft, F.; Turel, I.; Košmrlj, J. *Inorg. Chem.* **2010**, *49*, 4820. (d) Struthers, H.; Mindt, T. L.; Schibli, R. *Dalton. Trans.* **2010**, *39*, 675. (e) Johnson, T. C.; Totty, W. G.; Wills, M. *Org. Lett.* **2012**, *14*,

5230. (f) Saleem, F.; Rao, G. K.; Kumar, A.; Mukherjee, G.; Singh, A. K. *Organometallics.* **2013**, *32*, 3595.

(4) (a) Alvarez, R.; Velazquez, S.; San-Felix, A.; Aquaro, S.; De Clercq, E.; Perno, C.-F.; Karlsson, A.; Balzarini, J.; Camarasa, M. J. *J. Med. Chem.* **1994**, *37*, 4185. (b) Tam, A.; Arnold, U.; Soellner, M. B.; Raines, R. T. *J. Am. Chem. Soc.* **2007**, *129*, 12670. (c) Carta, A.; Palomba, M.; Paglietti, G.; Molicotti, P.; Paglietti, B.; Cannas, S.; Zanetti, S. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4791. (d) Mohapatra, D. K.; Maity, P. K.; Shabab, M.; Khan, M. I. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5241. (e) Anderson, M. O.; Zhang, J.; Liu, Y.; Yao, C.; Phuan, P.-W.; Verkman, A. S. *J. Med. Chem.* **2012**, *55*, 5942. (f) Galibert, M.; Dumy, P.; Boturyn, D. *Angew. Chem., Int. Ed.* **2009**, *48*, 2576.

(5) For selected examples, see: (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596. (b) Tornoe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057. (c) Appukkuttan, P.; Dehaen, W.; Fokin, V. V.; Van der Eycken, E. *Org. Lett.* **2004**, *6*, 4223. (d) Meldal, M.; Tornoe, C. W. *Chem. Rev.* **2008**, *108*, 2952.

(6) (a) Zhang, L.; Chen, X.; Xue, P.; Sun, H. H.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V.; Jia, G. *J. Am. Chem. Soc.* **2005**, *127*, 15998. (b) Rasmussen, L. K.; Boren, B. C.; Fokin, V. V. *Org. Lett.* **2007**, *9*, 5337.

(7) (a) Krasinski, A.; Fokin, V. V.; Sharpless, K. B. *Org. Lett.* **2004**, *6*, 1237. (b) Wu, W.-M.; Deng, J.; Li, Y.; Chen, Q.-Y. *Synthesis* **2005**, *8*, 1314. (c) Majireck, M. M.; Weinreb, S. M. J. *J. Org. Chem.* **2006**, *71*, 8680. (d) Majireck, M. M.; Weinreb, S. M. J. *J. Org. Chem.* **2006**, *71*, 8680. (e) Boren, B. C.; Narayan, S.; Rasmussen, L. K.; Zhang, L.; Zhao, H.; Lin, Z.; Jia, G.; Fokin, V. V. *J. Am. Chem. Soc.* **2008**, *130*, 8923. (f) Drez-Gonzalez, S.; Stevens, D. D.; Nolan, S. P. *Chem. Commun.* **2008**, 4747. (g) Boren, B. C.; Narayan, S.; Rasmussen, L. K.; Zhang, L.; Zhao, H.; Lin, Z.; Jia, G.; Fokin, V. V. *J. Am. Chem. Soc.* **2008**, *130*, 8923. (h) Drez-Gonzalez, S.; Stevens, D. D.; Nolan, S. P. *Chem. Commun.* **2008**, 4747. (i) Zhang, H.; Tanimoto, H.; Morimoto, T.; Nishiyama, Y.; Kakiuchi, K. *Org. Lett.* **2013**, *15*, 5222.

(8) (a) Ramachary, D. B.; Ramakumar, K.; Narayana, V. V. *Chem.—Eur. J.* **2008**, *14*, 9143. (b) Danence, L. J. T.; Gao, Y.; Li, M.; Huang, Y.; Wang, J. *Chem.—Eur. J.* **2011**, *17*, 3584. (c) Wang, L.; Peng, S. Y.; Danence, L. J. T.; Gao, Y.; Wang, J. *Chem.—Eur. J.* **2012**, *18*, 6088. (d) Seus, N.; Goncalves, L. C.; Deobald, A. M.; Savegnago, L.; Alves, D.; Paixao, M. W. *Tetrahedron* **2012**, *68*, 10456. (e) Li, W.; Jia, Q.; Du, Z.; Wang, J. *Chem. Commun.* **2013**, *49*, 10187. (f) Ramachary, D. B.; Shashank, A. B. *Chem.—Eur. J.* **2013**, *19*, 13175. (g) Ramachary, D. B.; Shashank, A. B.; Karthik, S. *Angew. Chem., Int. Ed.* **2014**, *53*, 10420. (h) Cheng, G.; Zeng, X.; Shen, J.; Wang, X.; Cui, X. *Angew. Chem., Int. Ed.* **2013**, *52*, 13265. (i) Tian, L.; Hu, X.- Q.; Li, Y.- F.; Xu, P.- F. *Chem. Commun.* **2013**, *49*, 7213.

(9) For selected examples, see: (a) Chen, Y.; Liu, Y.; Petersen, J. L.; Shi, X. *Chem. Commun.* **2008**, 3254. (b) Liu, Y.; Yan, W.; Chen, Y.; Petersen, J. L.; Shi, X. *Org. Lett.* **2008**, *10*, 5389. (c) Ackermann, L.; Potukuchi, H. K.; Landsberg, D.; Vicente, R. *Org. Lett.* **2008**, *10*, 3081. (d) Wang, X.; Zhang, L.; Lee, H.; Haddad, N.; Krishnamurthy, D.; Senanayake, C. H. *Org. Lett.* **2009**, *11*, 5026. (e) Wang, X.; Sidhu, K.; Zhang, L.; Campbell, S.; Haddad, N.; Reeves, D. C.; Krishnamurthy, D.; Senanayake, C. H. *Org. Lett.* **2009**, *11*, 5490. (f) Zhang, Y.; Li, X.; Li, J.; Chen, J.; Meng, X.; Zhao, M.; Chen, B. *Org. Lett.* **2012**, *14*, 26.

(10) (a) Quan, X.-J.; Ren, Z.-H.; Wang, Y.-Y.; Guan, Z.-H. *Org. Lett.* **2014**, *16*, 5728. (b) Sengupta, S.; Duan, H.; Lu, W.; Petersen, J. L.; Shi, X. *Org. Lett.* **2008**, *10*, 1493. (c) Quiclet-Sire, B.; Zard, S. Z. *Synthesis* **2005**, 3319. (d) Amantini, D.; Fringuelli, F.; Piermatti, O.; Pizzo, F.; Zunino, E.; Vaccaro, L. *J. Org. Chem.* **2005**, *70*, 6526. (e) Piet, J. C.; Le, H. G.; Cailleux, P.; Benhaoua, H.; Carrie, R. *Bull. Soc. Chim. Belg.* **1996**, *105*, 33. (f) Wang, Y.-C.; Xie, Y.-Y.; Qu, H.-E.; Wang, H.-S.; Pan, Y.-M.; Huang, F.-P. *J. Org. Chem.* **2014**, *79*, 4463.

(11) For Cu(I) catalysis, see: (a) Zhang, X.; Li, H.; You, L.; Tang, Y.; Hsung, R. P. *Adv. Synth. Catal.* **2006**, *348*, 2437. (b) Zhang, X.; Hsung, R. P.; You, L. *Org. Biomol. Chem.* **2006**, *4*, 2679. (c) IJsselstijn, M.; Cintrat, J.-C. *Tetrahedron* **2006**, *62*, 3837. (d) Beveridge, R. E.; Batey, R. A. *Org. Lett.* **2012**, *14*, 540. For Ru(II) catalysis, see: (e) Oppilliart, S.; Mousseau, G.; Zhang, L.; Jia, G.; Thuéry, P.; Rousseau, B.; Cintrat, J.-C. *Tetrahedron* **2007**, *63*, 8094. (f) Boren, B. C.; Narayan, S.; Rasmussen, L. K.; Zhang, L.; Zhao, H.; Lin, Z.; Jia, G.; Fokin, V. V. *J. Am. Chem. Soc.* **2008**, *133*, 8923.

(12) (a) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH, Weinheim, Germany, 2005. (b) Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137. (c) Gobel, M.; Klapotke, T. M. *Adv. Funct. Mater.* **2009**, *19*, 347. (d) Zhang, Q.; Zhang, J.; Parrish, D. A.; Shreeve, J. M. *Chem.—Eur. J.* **2013**, *19*, 11000. (e) Zhang, Y.; Parrish, D. A.; Shreeve. *J. Mater. Chem. A* **2013**, *1*, 585.

(13) The nitration of **4a** to synthesize **3a** was unsuccessful.

(14) (a) Semmelhack, M. F.; Schmid, C. R.; Cortes, D. A.; Chou, C. S. *J. Am. Chem. Soc.* **1984**, *106*, 3374. (b) Ragagnin, G.; Betzemeier, B.; Quici, S.; Knochel, P. *Tetrahedron* **2002**, *58*, 3985. (c) Jiang, N.; Ragauskas, A. J. *J. Org. Chem.* **2006**, *71*, 7087. (d) Mannam, S.; Alamsetti, S. K.; Sekar, G. *Adv. Synth. Catal.* **2007**, *349*, 2253. (e) Hoover, J. M.; Stahl, S. S. *J. Am. Chem. Soc.* **2011**, *133*, 16901. (f) Kim, J.; Stahl, S. S. *ACS Catal.* **2013**, *3*, 1652.

(15) (a) Vogler, T.; Studer, A. *Synthesis* **2008**, 1979. (b) Jahn, U.; Muller, M.; Aussieker, S. *J. Am. Chem. Soc.* **2000**, *122*, 5212. (c) Jahn, U.; Hartmann, P.; Dix, I.; Jones, P. G. *Eur. J. Org. Chem.* **2001**, 3333.

(16) (a) Esguerra, K. V. N.; Fall, Y.; Lumb, J.-P. *Angew. Chem., Int. Ed.* **2014**, *53*, 5877. (b) Li, M.; Xie, Y.; Ye, Y.; Zou, Y.; Jiang, H.; Zeng, W. *Org. Lett.* **2014**, *16*, 6232. (c) Zhang, C.; Feng, P.; Jiao, N. *J. Am. Chem. Soc.* **2013**, *135*, 15257. (d) Wang, H.; Wang, Y.; Liang, D.; Liu, L.; Zhang, J.; Zhu, Q. *Angew. Chem., Int. Ed.* **2011**, *50*, 5678. (e) Toh, K. K.; Wang, Y. F.; Ng, E. P. J.; Chiba, S. *J. Am. Chem. Soc.* **2011**, *133*, 13942.

(17) (a) Sueda, T.; Oshima, A.; Teno, N. *Org. Lett.* **2011**, *13*, 3996. (b) Demchuk, D. V.; Samet, A. V.; Chernysheva, N. B.; Ushkarov, V. I.; Stashina, G. A.; Konyushkin, L. D.; Raihstat, M. M.; Firgang, S. I.; Philchenkov, A. A.; Zavelevich, M. P.; Kuiava, L. M.; Chekhun, V. F.; Blokhin, D. Y.; Kiselyov, A. S.; Semenova, M. N.; Semenov, V. V. *Bioorg. Med. Chem.* **2014**, *22*, 738.