DOI: 10.1002/ejoc.201500338

Synthesis of 5-Fluorotriazoles by Silver-Mediated Fluorination of 5-Iodotriazoles

Damin Wang,[a] Wenjing Sun,[a] and Taiwei Chu*[a]

Keywords: Heterocycles / Fluorine / Halogenation / Silver

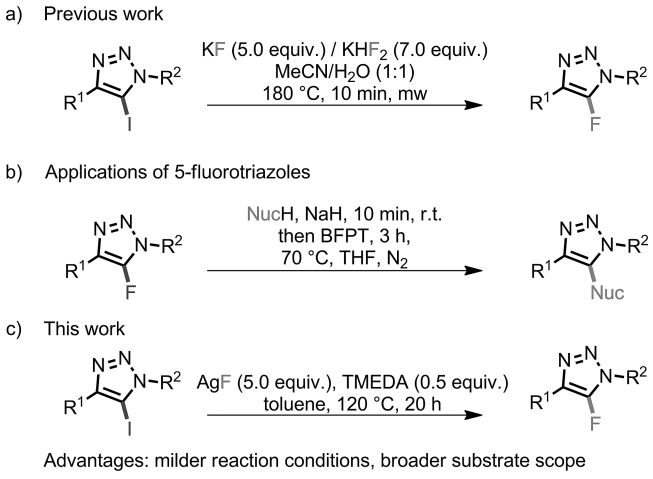
A simple method was developed for the direct fluorination of 5-iodotriazoles with AgF as fluoride source and N^1,N^1,N^2,N^2-tetramethylethane-1,2-diamine (TMEDA) as ligand. This method is compatible with various functional groups. 5-Iodotriazoles without aromatic groups at the 4-position or aliphatic substituents at the N1 position can also be smoothly converted to the corresponding 5-fluorotriazoles. Preliminary mechanism studies were also performed.

Introduction

Fluorine-containing heterocycles are one of the most prevalent structural motifs in pharmaceuticals,[1] materials,[2] and agrochemicals.[3] The introduction of fluorine-containing substituents affects the reactivity, solubility, stability, and biological properties of these compounds.

The copper(I)-catalyzed azide–alkyne cycloaddition reaction (CuAAC) is a robust, regioselective, quantitative, and rapid reaction for the synthesis of triazoles.[4] To the best of our knowledge, lots of 1,4,5-trisubstituted 1,2,3-triazoles have been successfully synthesized through different methods. The syntheses of 5-halo-1,4-disubstituted 1,2,3-triazoles have been widely studied to date, and many excellent methods have been developed on the basis of the CuAAC reaction.[5] In addition, methods for the synthesis of 5-trifluoromethyl-1,4-disubstituted 1,2,3-triazoles,[6] 1,4-disubstituted 1,2,3-triazole boronic esters,[7] 1,4-disubstituted 5-alumino-1,2,3-triazoles,[8] and other 1,4,5-trisubstituted 1,2,3-triazoles[9] have also been developed. However, reports on the preparation of 5-fluorotriazoles are rare.[10]

The first example of the synthesis of 5-fluorotriazoles was reported by Fokin and co-workers in 2012 (Scheme 1a).[11] In this work, the applications of 5-fluorotriazoles were also demonstrated (Scheme 1b). However, the conditions for these transformations are relatively harsh. Besides, both an aromatic group at the 4-position and an aliphatic substituent at the N1 position of the 5-iodotriazoles are required for an effective transformation to 5-fluorotriazoles. On this basis, methods to prepare 5-fluorotriazoles under mild and environmentally benign conditions are still needed.



Scheme 1. Synthesis and applications of 5-fluorotriazoles.

In the last decades, transition-metal-catalyzed/mediated sp^2 C–F bond formation has emerged as a powerful method for the construction of compounds containing aryl fluoride moieties.[12] Recently, several groups have reported various sp^2 C–F bond constructions mediated by transition metals including Fe,[13] Ni,[14] Cu,[15] Pd,[16] and Ag,[17] with electrophilic or nucleophilic fluorinating reagents as the source of fluorine. For example, Hartwig reported a copper-mediated fluorination of aryl iodides with AgF as fluoride source.[15e] In addition, transition-metal-catalyzed/mediated synthesis of 1,4,5-trisubstituted 1,2,3-triazoles have also been achieved. For example, Cao reported a copper-mediated trifluoromethylation of 5-iodotrizoles.[6] Born reported palladium-catalyzed direct arylations of 1,2,3-triazoles with aryl chlorides.[18] Given the importance of 5-fluorotriazoles and easy availability of 5-iodotriazoles, we conceived the preparation of 5-fluorotriazoles by transition-metal-medi-

[a] Beijing National Laboratory for Molecular Sciences,
Radiochemistry and Radiation Chemistry Key Laboratory of Fundamental Science,
College of Chemistry and Molecular Engineering,
Peking University Beijing,
100871 China
E-mail: twchu@pku.edu.cn

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201500338.

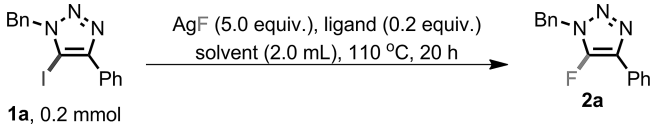
ated fluorination of 5-iodotriazoles. Herein, we report a silver-mediated fluorination of 5-iodotriazoles with AgF as both fluoride source and silver source (Scheme 1c).

Results and Discussion

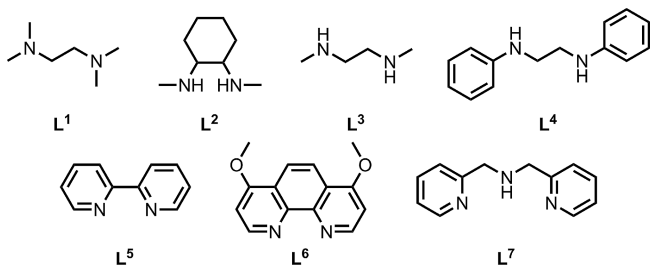
The fluorination of 1-benzyl-5-iodo-4-phenyl-1,2,3-triazole (**1a**) mediated by AgF was selected as the model reaction to initiate our studies. As we expected, the desired 1-benzyl-5-fluoro-4-phenyl-1,2,3-triazole (**2a**) could be furnished through AgF-mediated fluorination of **1a** without any additives, albeit in a low yield (45% NMR yield) (Table 1, entry 1). In view of the poor solubility of AgF in toluene, we conceived that a higher yield would be achieved by increasing the solubility of AgF. According to former reports, a set of nitrogen ligands was selected to try with this system. We found that the NMR yield was promoted to 63% when 0.2 equiv. of L^4 was used. Other ligands were also able to increase the yield of **2a** slightly (Table 1, entries 2–8). To our surprise, addition of L^6 decreased the NMR yield to 33%, possibly as a result of its electron-rich structure. On the basis of these results, L^1 (TMEDA) was selected as standard ligand, as it presents a yield (60% NMR yield) similar to that of L^4 but has a lower price.

Further investigation focused on the optimization of the solvents. After several solvents were screened (Table 1, entries 2, 9–13), we found that nonpolar solvents such as toluene and 1,4-dioxane could effectively promote the conversion of **1a** to **2a**, while polar solvents, such as DMSO, DMF, and MeCN failed to lead to satisfactory yields. Interestingly, **2a** was obtained in only 3% NMR yield in DMSO, while the main byproduct, 1-benzyl-4-phenyl-1,2,3-triazole (**3a**), was obtained in 60% NMR yield (Table 1, entry 9). Similar results were also observed in DMF and MeCN (Table 1, entries 10 and 13). We speculated that the poor conversion in the presence of polar solvents might arise from the strong coordination effect that decreases the reactivity of the catalyst.

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

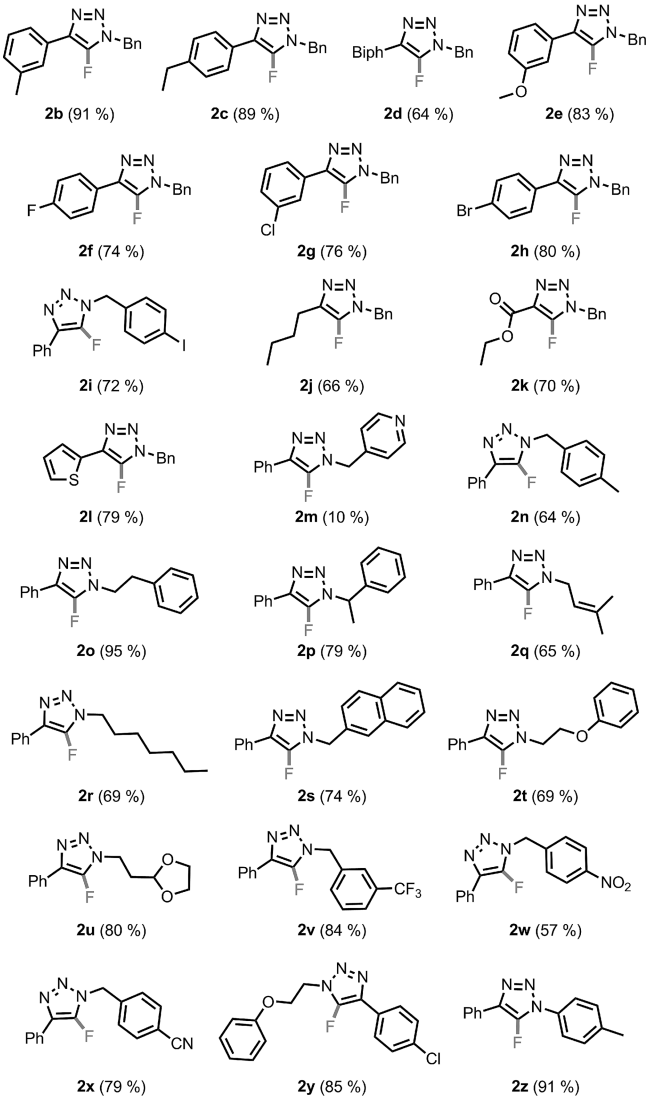


Entry	**1a** [equiv.]	Ligand	Solvent	Yield[b]
1	1.0	–	toluene	43%
2	1.0	TMEDA	toluene	60%
3	1.0	L^2	toluene	55%
4	1.0	L^3	toluene	50%
5	1.0	L^4	toluene	63%
6	1.0	L^5	toluene	48%
7	1.0	L^6	toluene	33%
8	1.0	L^7	toluene	45%
9	1.0	TMEDA	DMSO	3% + 60%[c]
10	1.0	TMEDA	DMF	39% + 40%[c]
11	1.0	TMEDA	1,4-dioxane	59%
12	1.0	TMEDA	THF	53%
13	1.0	TMEDA	MeCN	10% + 45%[c]
14[d]	1.0	TMEDA	toluene	82%
15[d,e]	1.0	TMEDA	toluene	89%, 79%[f]



[a] All reactions were carried out at 110 °C on a 0.2 mmol scale. [b] Yield determined by ^{1}H NMR spectroscopy by using dibromomethane as internal standard. [c] Yield of **2a** + **3a** determined by ^{1}H NMR spectroscopy by using dibromomethane as internal standard. [d] The reaction was carried out with 0.5 equiv. of TMEDA. [e] The reaction was carried out at 120 °C. [f] Isolated yield.

Table 2. Scope of 5-fluorotriazoles.[a,b]



[a] All reactions were carried out on a 0.2 mmol scale under the standard conditions. [b] Isolated yield.

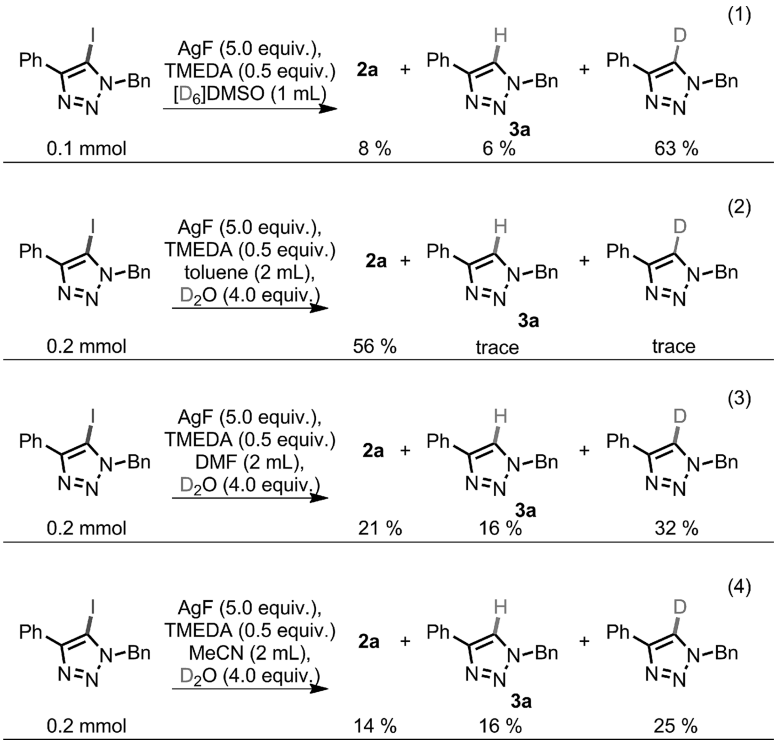
Other fluoride and silver sources were also systemically examined. In the absence of a silver source, no conversion was observed when the reactions were only conducted with KF and CsF (see Supporting Information). When a combination of different fluoride salts and catalytic amounts of Ag salts (0.5 equiv. of AgF or AgOTf) were used in the reaction, the desired product were obtained in low yields. On the other hand, an excess amount of Ag salts might lead to the cleavage of C–I in the substrates. Accordingly, various amounts of AgF and TMEDA were carefully tested, and the results revealed that 5.0 equiv. of AgF and 0.5 equiv. of TMEDA promoted the yield to 89%. Investigation of the reaction temperature (see Supporting Information) indicated that 120 °C was obligatory for full conversion of **1a**.

With the optimized conditions in hand, we proceeded to explore the substrate scope with respect to various 5-iodotriazoles (Table 2). The standard fluorination conditions were applicable to a wide range of 5-iodotriazoles bearing electron-rich and electron-poor substituent groups. For most substrates, practical yields were obtained under standard reaction conditions. Substrates containing alkyl (**2b**, **2c**, **2n**–**2p**, **2r**), alkenyl (**2q**), halogen (**2f**–**2i**), and trifluoromethyl (**2v**) groups could be converted into the corresponding fluorination products in good to excellent yields. It is worthy to note that, for substrates containing two sp^2 C–I bonds, the fluorination selectively occurred at the 5-position of the 5-iodotriazoles (**1i**). The methodology also presented good functional group tolerance: functionalities such as esters (**2k**), heterocycles (**2l**), acetals (**2u**), aromatic ethers (**2t**, **2y**), and nitro (**2w**) and nitrile (**2x**) groups survived very well under the standard conditions. It should be noted that compound **2m** was obtained in only 10% yield under the standard conditions, that is, the pyridine group coordinated to AgF strongly and led to a low catalytic reactivity.

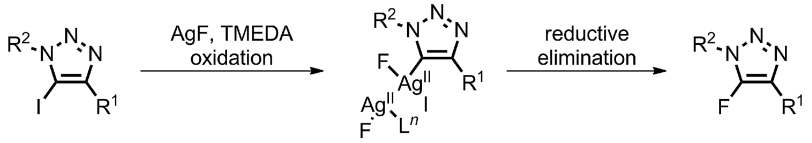
Aliphatic substituents at the 4-position, which resulted in complex mixtures under Fokin's conditions,[11] did not lead to obvious complications in our system (66% and 70% isolated yields were obtained for **2j** and **2k**, respectively). Triazoles with an aromatic substituent at the N1 position could also be transformed to the corresponding 5-fluorotriazoles in excellent yield (91% isolated yield was obtained for **2z**) under our conditions, while only 32% yield of **2z** was obtained by the microwave method.[11]

During some of these fluorination reactions of 5-iodotriazoles, a certain amount of protonation products were formed. To get insight into the formation of protonation products, preliminary mechanistic experiments were carried out. The source of proton was investigated by deuterium-labeling experiments. The reaction of **1a**, AgF, and TMEDA was performed in [D_6]DMSO [Scheme 2, equation (1)] and furnished **3a** in 70% NMR yield, including 63% deuterated **3a**. This result revealed that the acidic proton of the DMSO is one source leading to the protonated and dehalogenated triazole.

When 4.0 equiv. of D_2O was added under the standard conditions [Scheme 2, equation (2)], a low conversion of **1a** and a trace amount of **3a** were obtained. The poor solubility of D_2O in toluene and the fact that most of the D_2O was consumed by the excess AgF (deuterated water quickly turned black upon contact with AgF) might be the reason for this result. Similar reactions were also conducted in



Scheme 2. Mechanistic studies on the fluorination of 5-iodotriazoles.



Scheme 3. Proposed mechanism.

DMF and MeCN [Scheme 2, equations (3) and (4)]: **3a** was obtained as the major product in 48% and 41% yield, with 32% and 25% deuterated **3a**, respectively. Those data suggest that adventitious water might be another source of the protonated and dehalogenated triazole. Hence, the rigorous exclusion of water is essential for high yields.

As no desired product was obtained at all with KF or CsF in the absence of AgF, the S_NAr mechanism was ruled out as a possible pathway.[11] On the basis of the mechanistic studies mentioned above and previous reports,[11,17c] we propose the mechanism of our reaction as shown in Scheme 3. Oxidative addition of silver to the C–I bond and the formation of a bimetallic aryl silver intermediate are the first steps. The bimetallic aryl silver complex subsequently undergoes reductive elimination to afford the desired 5-fluorotriazoles.

Conclusions

In summary, we have developed a powerful method for the direct fluorination of 5-iodotriazoles with AgF under mild conditions. This method shows good functional group tolerance and provides a complementary way to give the corresponding 5-fluorotriazoles in excellent yields. 5-Iodotriazoles without aromatic groups at the 4-position or aliphatic substituents at the N1 position can be smoothly converted to the corresponding 5-fluorotriazoles. Mechanistic studies indicate that this reaction might proceed through a bimetallic Ag^{II} intermediate. Further investigations to broaden the substrate scope and elucidate the detailed mechanism are underway.

Experimental Section

General Procedures for the Synthesis of 5-Fluorotriazoles: In an argon-filled glove box, AgF (126.9 mg, 1.0 mmol, 5.0 equiv.) and 5-iodotriazoles (0.2 mmol, 1.0 equiv.) were added to a 25 mL oven-dried glassware containing a stirring bar. Then, TMEDA (15.0 μL, 0.5 equiv.) and anhydrous toluene (2.0 mL) were added. Finally, the glassware was heated at 120 °C in oil bath.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (Grant No. 21371017).

[1] a) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320–330; b) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881–1886; c) S. Swallow, *Fluorine in Pharmaceutical and Medicinal Chemistry* (Eds.: V. Gouverneur, K. Müller), World Scientific, London, **2012**, pp. 141–174; d) T. Hiyama, H. Yamamoto, *Organofluorine Compounds* (Ed.: H. Yamamoto), Springer, Berlin, **2000**, pp. 137–182; e) P. Kirsch, *Modern Fluoroorganic Chemistry*, Wiley-VCH, Weinheim, **2013**, pp. 299–350.

[2] a) R. Berger, G. Resnati, P. Metrangolo, E. Weber, J. Hulliger, *Chem. Soc. Rev.* **2011**, *40*, 3496–3508; b) C. Botta, E. Cariati, G. Cavallo, V. Dichiarante, A. Forni, P. Metrangolo, T. Pilati, G. Resnati, S. Righetto, G. Terraneo, E. Tordin, *J. Mater. Chem. C* **2014**, *2*, 5275–5279.

[3] a) W. Hong, "Agricultural Products Based on Fluorinated Heterocyclic Compounds", in *Fluorinated Heterocyclic Compounds: Synthesis Chemistry, and Applications* (Ed.: V. A. Petrov), John Wiley & Sons, Inc., Hoboken, NJ, **2009**, pp. 397–418; b) P. Jeschke, *ChemBioChem* **2004**, *5*, 570–589.

[4] a) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2002**, *41*, 2596–2599; *Angew. Chem.* **2002**, *114*, 2708–2711; b) J. E. Hein, V. V. Fokin, *Chem. Soc. Rev.* **2010**, *39*, 1302–1315; c) J. E. Moses, A. D. Moorhouse, *Chem. Soc. Rev.* **2007**, *36*, 1249–1262.

[5] a) C. Spiteri, J. E. Moses, *Angew. Chem. Int. Ed.* **2010**, *49*, 31–33; *Angew. Chem.* **2010**, *122*, 33–36; b) L. Li, G. Zhang, A. Zhu, L. Zhang, *J. Org. Chem.* **2008**, *73*, 3630–3633; c) W. S. Brotherton, R. J. Clark, L. Zhu, *J. Org. Chem.* **2012**, *77*, 6443–6455; d) R. Yan, K. Sander, E. Galante, V. Rajkumar, A. Badar, M. Robson, E. El-Emir, M. F. Lythgoe, R. B. Pedley, E. Arstad, *J. Am. Chem. Soc.* **2013**, *135*, 703–709; e) D. Goyard, J. P. Praly, S. Vidal, *Carbohydr. Res.* **2012**, *362*, 79–83; f) L. J. Li, Y. Y. Li, R. Li, A. L. Zhu, G. S. Zhang, *Aust. J. Chem.* **2011**, *64*, 1383–1389; g) J. E. Hein, J. C. Tripp, L. B. Krasnova, K. B. Sharpless, V. V. Fokin, *Angew. Chem. Int. Ed.* **2009**, *48*, 8018–8021; *Angew. Chem.* **2009**, *121*, 8162–8165; h) R. Yan, E. El-Emir, V. Rajkumar, M. Robson, A. P. Jathoul, R. B. Pedley, E. Arstad, *Angew. Chem. Int. Ed.* **2011**, *50*, 6793–6795; *Angew. Chem.* **2011**, *123*, 6925–6927.

[6] F. A. Dan, Z. A. Jian, S. Cao, *J. Fluorine Chem.* **2013**, *156*, 170–176.

[7] J. Huang, S. J. F. Macdonald, J. P. A. Harrity, *Chem. Commun.* **2009**, 436–438.

[8] Y. Zhou, T. Lecourt, L. Micouin, *Angew. Chem. Int. Ed.* **2010**, *49*, 2607–2610; *Angew. Chem.* **2010**, *122*, 2661–2664.

[9] a) X. Zhang, R. P. Hsung, H. Li, *Chem. Commun.* **2007**, 2420–2422; b) L. J. Li, Y. Q. Zhang, Y. Zhang, A.-L. Zhu, G.-S. Zhang, *Chin. Chem. Lett.* **2014**, *25*, 1161–1164; c) B. Gerard, J. Ryan, A. B. Beeler, J. A. Porco, *Tetrahedron* **2006**, *62*, 6405–6411; d) D. V. Partyka, L. Gao, T. S. Teets, J. B. Updegraff, N. Deligonul, T. G. Gray, *Organometallics* **2009**, *28*, 6171–6182; e) A. Krasiński, V. V. Fokin, K. B. Sharpless, *Org. Lett.* **2004**, *6*, 1237–1240; f) S. Chuprakov, N. Chernyak, A. S. Dudnik, V. Gevorgyan, *Org. Lett.* **2007**, *9*, 2333–2336; g) H. Zhang, H. Tanimoto, T. Morimoto, Y. Nishiyama, K. Kakiuchi, *Org. Lett.* **2013**, *15*, 5222–5225; h) J. Deng, Y. M. Wu, Q. Y. Chen, *Synthesis* **2005**, 2730–2738; i) J. Thibonnet, Y. Carcenac, F. D. Quillot, M. Abarbri, A. Duchêne, *Synthesis* **2013**, *45*, 633–638.

[10] Only one report of fluorinated triazoles was found using Scifinder.

[11] B. T. Worrell, J. E. Hein, V. V. Fokin, *Angew. Chem. Int. Ed.* **2012**, *51*, 11791–11794; *Angew. Chem.* **2012**, *124*, 11961–11964.

[12] a) M. G. Campbell, T. Ritter, *Chem. Rev.* **2015**, *115*, 612–633; b) X. Yang, T. Wu, R. J. Phipps, F. D. Toste, *Chem. Rev.* **2015**, *115*, 826–870; c) C. Hollingworth, V. Gouverneur, *Chem. Com-*

mun. **2012**, *48*, 2929–2942; d) T. Furuya, A. S. Kamlet, T. Ritter, *Nature* **2011**, *473*, 470–477; e) V. V. Grushin, *Acc. Chem. Res.* **2010**, *43*, 160–171.

[13] S. Dubbaka, S. Gadde, V. Narreddula, *Synthesis* **2015**, *47*, 854–860.

[14] a) E. Lee, J. M. Hooker, T. Ritter, *J. Am. Chem. Soc.* **2012**, *134*, 17456–17458; b) H. Ren, H. Y. Wey, M. Strebl, R. Neelamegam, T. Ritter, J. M. Hooker, *ACS Chem. Neurosci.* **2014**, *5*, 611–615; c) S. D. Timpa, J. Zhou, N. Bhuvanesh, O. V. Ozerov, *Organometallics* **2014**, *33*, 6210–6217.

[15] a) A. Casitas, A. E. King, T. Parella, M. Costas, S. S. Stahl, X. Ribas, *Chem. Sci.* **2010**, *1*, 326–330; b) X. Mu, H. Zhang, P. H. Chen, G. S. Liu, *Chem. Sci.* **2014**, *5*, 275–280; c) R. Y. He, H. T. Zeng, J. M. Huang, *Eur. J. Org. Chem.* **2014**, 4258–4263; d) A. Casitas, M. Canta, M. Sola, M. Costas, X. Ribas, *J. Am. Chem. Soc.* **2011**, *133*, 19386–19392; e) P. S. Fier, J. F. Hartwig, *J. Am. Chem. Soc.* **2012**, *134*, 10795–10798; f) P. S. Fier, J. Luo, J. F. Hartwig, *J. Am. Chem. Soc.* **2013**, *135*, 2552–2559; g) T. Truong, K. Klimovica, O. Daugulis, *J. Am. Chem. Soc.* **2013**, *135*, 9342–9345; h) Y. Ye, M. S. Sanford, *J. Am. Chem. Soc.* **2013**, *135*, 4648–4651; i) Y. Ye, S. D. Schimler, P. S. Hanley, M. S. Sanford, *J. Am. Chem. Soc.* **2013**, *135*, 16292–16295; j) N. Ichiishi, A. J. Canty, B. F. Yates, M. S. Sanford, *Org. Lett.* **2013**, *15*, 5134–5137; k) M. A. Subramanian, L. E. Manzer, *Science* **2002**, *297*, 1665–1665.

[16] a) A. R. Mazzotti, M. G. Campbell, P. Tang, J. M. Murphy, T. Ritter, *J. Am. Chem. Soc.* **2013**, *135*, 14012–14015; b) T. J. Maimone, P. J. Milner, T. Kinzel, Y. Zhang, M. K. Takase, S. L. Buchwald, *J. Am. Chem. Soc.* **2011**, *133*, 18106–18109; c) S. J. Lou, D. Q. Xu, A. B. Xia, Y. F. Wang, Y. K. Liu, X. H. Du, Z. Y. Xu, *Chem. Commun.* **2013**, *49*, 6218–6220.

[17] a) P. Tang, T. Furuya, T. Ritter, *J. Am. Chem. Soc.* **2010**, *132*, 12150–12154; b) T. Furuya, T. Ritter, *Org. Lett.* **2009**, *11*, 2860–2863; c) T. Furuya, A. E. Strom, T. Ritter, *J. Am. Chem. Soc.* **2009**, *131*, 1662–1663; d) P. Tang, T. Ritter, *Tetrahedron* **2011**, *67*, 4449–4454; e) K. P. Wang, S. Y. Yun, P. Mamidipalli, D. Lee, *Chem. Sci.* **2013**, *4*, 3205–3211; f) S. R. Dubbaka, V. R. Narreddula, S. Gadde, T. Mathew, *Tetrahedron* **2014**, *70*, 9676–9681.

[18] L. Ackermann, R. Vicente, R. Born, *Adv. Synth. Catal.* **2008**, *350*, 741–748.

Received: March 12, 2015
Published Online: May 27, 2015

