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Synthesis of *N*-Azolylindoles by Copper-Catalyzed C–H/N–H Coupling–Annulation Sequence of *o*-Alkynylanilines

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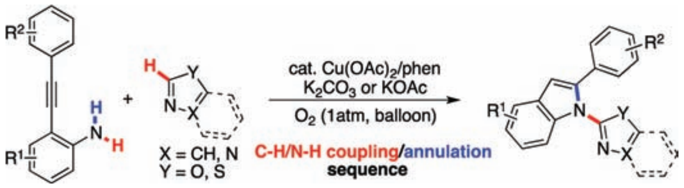
ABSTRACT



A wide range of *o*-alkynylanilines undergo a copper-catalyzed direct C–H/N–H coupling with azoles followed by benzannulation to form the corresponding *N*-azolylindoles in good yields. The domino reaction proceeds effectively with molecular oxygen as the sole oxidant and provides a new dehydrogenative access to the titled compounds of interest in pharmaceutical and material sciences.

In this letter, we report a copper-catalyzed C–H/N–H coupling–annulation sequence of *o*-alkynylanilines for the synthesis of *N*-azolylindoles.

The indole nucleus is found in many pharmaceuticals and functional materials. In particular, *N*-heteroaryl derivatives have received much attention due to their unique biological and physical properties.[1] The most common approach to the target motifs is the palladium-[2] and copper-catalyzed[3] C–N bond forming reaction of N–H indoles with heteroaryl halides.

Meanwhile, recent developments in the metal-promoted direct C–H functionalization chemistry enabled an oxidative direct C–H/N–H coupling of some heteroarenes with alkylamines, anilines, and amides.[4] Our group also succeeded in the copper-mediated direct amination of azoles.[5] In the course of this study, we attempted the direct coupling of azoles with N–H indoles leading to the *N*-azolylindoles (Scheme 1, route a). However, our preliminary experiments with 2-phenyl-1,3,4-oxadiazole (**1a**) and some N–H indoles by using copper catalysts completely failed: the reported successful systems containing Cu(OAc)$_2$/PPh$_3$/NaOAc[4l] and Cu(OAc)$_2$/pyridine/Na$_2$CO$_3$[4m] or our original conditions, Cu(OAc)$_2$/1,10-phenanthroline (phen)/K$_2$CO$_3$, resulted in no formation of the desired products. Thus, we envisioned a new working scenario with *o*-alkynylanilines, in which the first copper-catalyzed intermolecular direct C–N formation would furnish the corresponding *N*-azolylaniline intermediates, and the subsequent benzannulation under the same copper catalysis[6] could produce the *N*-azolylindoles in one synthetic operation (route b).

On the basis of the above hypothesis, treatment of 2-(phenylethynyl)aniline (**2a**) with **1a** in the presence of an excess of Cu(OAc)$_2$ and K$_2$CO$_3$ under O$_2$ (1 atm, balloon) in refluxing toluene furnished the desired *N*-azolylindole **3aa** in 71% yield (Table 1, entry 1). While

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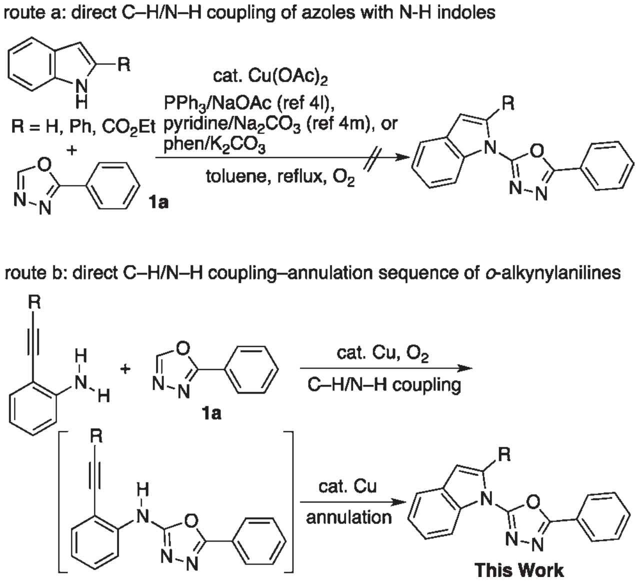
(1) Reviews: (a) Hegedus, L. S. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1113. (b) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045. (c) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873. (d) Hamphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2857. Selected examples: (e) Hall, A.; Billinton, A.; Brown, S. H.; Chowdhury, A.; Giblin, G. M. P.; Goldsmith, P.; Hurst, D. N.; Naylor, A.; Patel, S.; Scoccitti, T.; Theobald, P. J. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2684. (f) Lahser, F. C.; Gu, Z. *PCT Int. Appl.* 2010, WO 2010117939, A120101014. (g) Kim, C. S.; Cho, Y. J.; Kwon, H. J.; Kim, B. O.; Kim, S. M.; Yoon, S. S. *Int. Appl.* 2010, WO 2010107244, A2 20100923.

(2) Selected publications: (a) Mann, G.; Hartwig, J. F.; Driver, M. S.; Fernández-Rivas, C. J. *J. Am. Chem. Soc.* **1998**, *120*, 827. (b) Old, D. W.; Harris, M. C.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1403. (c) Watanabe, M.; Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **2000**, *41*, 481. (d) Grasa, G. A.; Viciu, M. S.; Huang, J.; Nolan, S. P. *J. Org. Chem.* **2001**, *66*, 7729.

(3) (a) Antilla, J. C.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 11684. Relevant Chan–Lam coupling: (b) Mederski, W. W. K. R.; Lefort, M.; Germann, M.; Kux, D. *Tetrahedron* **1999**, *55*, 12757. (c) Yu, S.; Saenz, J.; Srirangam Jayaram, K. *J. Org. Chem.* **2002**, *67*, 1699. (d) Bekolo, H. *Can. J. Chem.* **2007**, *85*, 42.

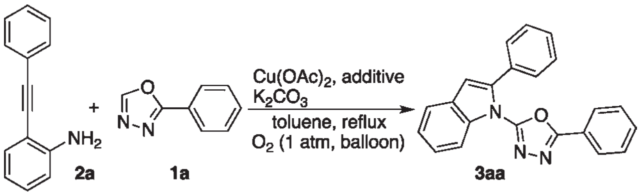
10.1021/ol203392r

Scheme 1. Dehydrogenative Approaches to *N*-Azolylindoles



stoichiometric in copper, our postulated process would be operative. We then turned our attention to the catalytic variant. Not surprisingly, a decrease in the amount of $Cu(OAc)_2$ to 20 mol % resulted in a lower yield of **3aa**

Table 1. Optimization Studies for Copper-Catalyzed C–H/N–H Coupling–Annulation Sequence of 2-(Phenylethynyl)aniline (**2a**) with 2-Phenyl-1,3,4-oxadiazole (**1a**) for the Synthesis of **3aa**[a]



entry	$Cu(OAc)_2$ (mol %)	additive (mol %)	**3aa**, % yield[b]
1	200	none	(71)
2	20	none	46
3	20	pyridine (100)	65
4	20	bpy[c] (20)	53
5	20	phen[d] (20)	85 (79)
6	20	bathophen[e] (20)	75
7[f]	200	none	19
8[f]	20	phen (20)	2

[a] Reaction conditions: $Cu(OAc)_2$, additive, K_2CO_3 (0.60 mmol), **1a** (0.60 mmol), **2a** (0.30 mmol), toluene (2.0 mL), reflux, 3–10 h, O_2 (1 atm, balloon). [b] The yields are determined by ^1H NMR. Yield of isolated product is in parentheses. [c] 2,2′-Bipyridine. [d] 1,10-Phenanthroline. [e] 4,7-Diphenyl-1,10-phenanthroline. [f] Under N_2.

(entry 2). Thus, we subsequently tested the addition of some additives to support the copper center. Nitrogen-based ligands generally improved the reaction efficiency (entries 3–6), with phen proving to be optimal (entry 5). Other reaction systems using $CuCl_2$, $Cu(OTf)_2$, Na_2CO_3, Cs_2CO_3, DMF, or DMSO gave no positive effect on yield (data not shown). In the absence of molecular oxygen, the yield largely dropped under either stoichiometric or catalytic conditions (entries 7 and 8).

With catalytic conditions employed for entry 5 in Table 1, we performed the domino reaction of **2a** with a range of 1,3,4-oxadiazoles **1**. The representative *N*-azolylindole products are illustrated in Table 2. Oxadiazoles **1** containing electron-donating methoxy as well as electron-withdrawing chloro and trifluoromethyl groups underwent the reaction very smoothly to afford the corresponding indoles **3ba**–**da** in good yields. A bulky naphthalene motif could be employed without any difficulties (**3ea**). While the alkyl-substituted oxadiazole showed somewhat lower reactivity, the satisfactory yield was obtained under stoichiometric conditions (**3fa**). The generality of *o*-alkynylanilines was also good. At the alkyne terminus, electronically and sterically diverse functions such as methyl, methoxy, chloro, trifluoromethyl, and 1-naphthyl groups were equally tolerated (**3ab**–**af** and **3cb**–**cd**). The thienyl-substituted aniline was transformed to the indole–thiophene conjugation **3ag** in a comparable yield. Moreover, the copper catalysis could accommodate primary, secondary, and tertiary alkyl substituents (**3ah**–**aj**). The C5-substituted indoles **3ak** and **3al** were also readily accessible under standard conditions.

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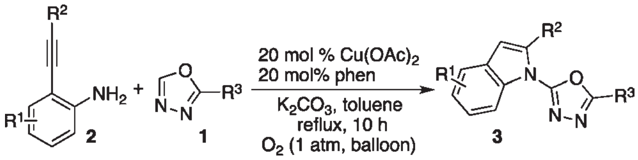
(4) With palladium, see: (a) Tsang, W. C. P.; Zheng, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560. (b) Thu, H.-Y.; Yu, W.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2006**, *128*, 9048. (c) Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14058. (d) Jordan-Hore, A. A.; Johansson, C. C. C.; Gulias, M.; Beck, E. M.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 16184. (e) Mei, T.-S.; Wang, X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 10806. (f) Xiao, B.; Gong, T.-J.; Xu, J.; Liu, Z.-J.; Liu, L. *J. Am. Chem. Soc.* **2011**, *133*, 1466. (g) Sun, K.; Li, Y.; Xiong, T.; Zhang, J.; Zhang, Q. *J. Am. Chem. Soc.* **2011**, *133*, 1694. (h) Cho, S. H.; Yoon, J.; Chang, S. *J. Am. Chem. Soc.* **2011**, *133*, 5996. (i) Youn, S. W.; Bihn, J. H.; Kim, B. S. *Org. Lett.* **2011**, *13*, 3738. With copper, see: (j) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790. (k) Uemura, T.; Imoto, S.; Chatani, N. *Chem. Lett.* **2006**, *35*, 842. (l) Monguchi, D.; Fujiwara, T.; Furukawa, H.; Mori, A. *Org. Lett.* **2009**, *11*, 1607. (m) Wang, Q.; Schreiber, S. L. *Org. Lett.* **2009**, *11*, 5178. (n) Shuai, Q.; Deng, G.; Chua, Z.; Bohle, D. S.; Li, C.-J. *Adv. Synth. Catal.* **2010**, *352*, 632. (o) Zhao, H.; Wang, M.; Su, W.; Hong, M. *Adv. Synth. Catal.* **2010**, *352*, 1301. (p) John, A.; Nicholas, K. M. *J. Org. Chem.* **2011**, *76*, 4158. With silver, see: (q) Cho, S. H.; Kim, J. Y.; Lee, S. Y.; Chang, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 9127. With cobalt and manganese, see: (r) Kim, J. Y.; Cho, S. H.; Joseph, J.; Chang, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 9899. Metal-free processes: (s) Antonchick, A. P.; Samanta, R.; Kulikov, K.; Lategahn, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 8605. (t) Froehr, T.; Sindkinger, C. P.; Kloeckner, U.; Finkbeiner, P.; Nachtsheim, B. J. *Org. Lett.* **2011**, *13*, 3754. (u) Lamani, M.; Prabhu, K. R. *J. Org. Chem.* **2011**, *76*, 7938. (v) Kim, H. J.; Kim, J.; Cho, S. H.; Chang, S. *J. Am. Chem. Soc.* **2011**, *133*, 16382. (w) Wertz, S.; Kodama, S.; Studer, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 11511. (x) Kantak, A. A.; Potavathri, S.; Barham, R. A.; Romano, K. M.; DeBoef, B. *J. Am. Chem. Soc.* **2011**, *133*, 19960. Also see: (y) Armstrong, A.; Collins, J. C. *Angew. Chem., Int. Ed.* **2010**, *49*, 2282. (z) Zhang, M. *Synthesis* **2011**, 3408.

(5) (a) Kawano, T.; Hirano, K.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2010**, *132*, 6900. (b) Miyasaka, M.; Hirano, K.; Satoh, T.; Kowalczyk, R.; Bolm, C.; Miura, M. *Org. Lett.* **2011**, *13*, 359. (c) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2011**, *13*, 2860.

(6) Reviews: (a) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395. (b) Vicente, R. *Org. Biomol. Chem.* **2011**, *9*, 6469. Copper-based systems: (c) Hiroya, K.; Itoh, S.; Sakamoto, T. *J. Org. Chem.* **2004**, *69*, 1126. (d) Swamy, N. K.; Yazici, A.; Pyne, S. G. *J. Org. Chem.* **2010**, *75*, 3412. (e) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2012**, *77*, 617.

Table 2. Copper-Catalyzed C−H/N−H Coupling−Annulation Sequence for the Synthesis of Various *N*-Azolylindoles **3**[a]



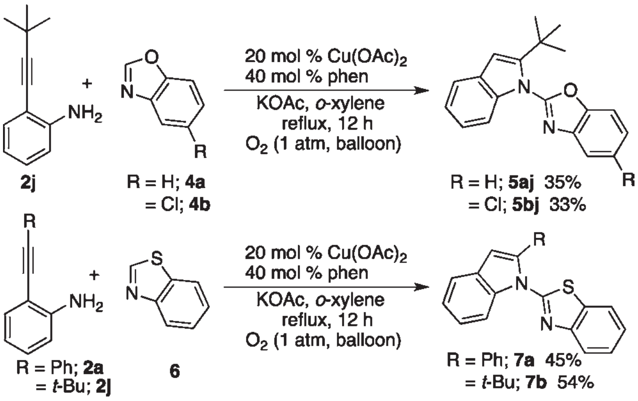
entry	R^1, R^2 **2**	R^3 **1**	**3**, % yield[b]
1	R^1 = H, R^2 = Ph (**2a**)	R^3 = 4-MeOC$_6$H$_4$ (**1b**)	**3ba**, 79
2	**2a**	R^3 = 4-ClC$_6$H$_4$ (**1c**)	**3ca**, 85
3	**2a**	R^3 = 4-CF$_3$C$_6$H$_4$ (**1d**)	**3da**, 89
4	**2a**	R^3 = 1-naphthyl (**1e**)	**3ea**, 81
5[c]	**2a**	R^3 = 2-phenethyl (**1f**)	**3fa**, 72
6	R^1 = H, R^2 = 4-MeC$_6$H$_4$ (**2b**)	R^3 = Ph (**1a**)	**3ab**, 84
7	**2b**	**1c**	**3cb**, 83
8	R^1 = H, R^2 = 4-MeOC$_6$H$_4$ (**2c**)	**1a**	**3ac**, 78
9	**2c**	**1c**	**3cc**, 87
10	R^1 = H, R^2 = 4-ClC$_6$H$_4$ (**2d**)	**1a**	**3ad**, 76
11	**2d**	**1c**	**3 cd**, 81
12	R^1 = H, R^2 = 4-CF$_3$C$_6$H$_4$ (**2e**)	**1a**	**3ae**, 69
13	R^1 = H, R^2 = 1-naphthyl (**2f**)	**1a**	**3af**, 83
14	R^1 = H, R^2 = 3-thienyl (**2g**)	**1a**	**3ag**, 83
15	R^1 = H, R^2 = Bu (**2h**)	**1a**	**3ah**, 83
16	R^1 = H, R^2 = cyclohexyl (**2i**)	**1a**	**3ai**, 84
17	R^1 = H, R^2 = *t*-Bu (**2j**)	**1a**	**3aj**, 90
18	R^1 = 4-Me, R^2 = Bu (**2k**)	**1a**	**3ak**, 90
19	R^1 = 4-Cl, R^2 = Bu (**2l**)	**1a**	**3al**, 83

[a] Reaction conditions: Cu(OAc)$_2$ (0.060 mmol), phen (0.060 mmol), K$_2$CO$_3$ (0.60 mmol), **1a** (0.60 mmol), **2a** (0.30 mmol), toluene (2.0 mL), reflux, 10 h, O$_2$ (1 atm, balloon). [b] Isolated yield of products is shown. [c] With 0.30 mmol of Cu(OAc)$_2$ and without phen.

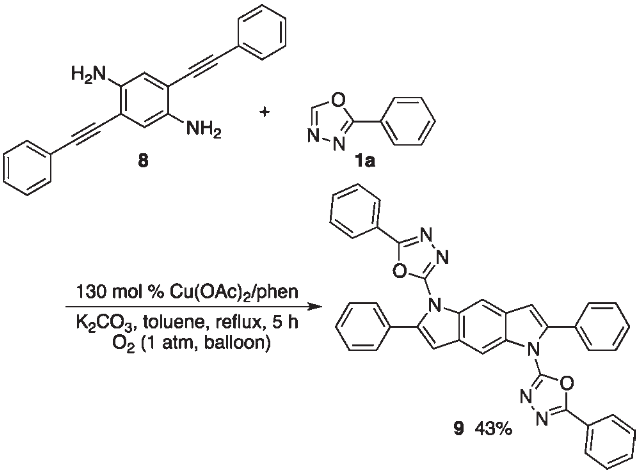
We next turned our attention to some 1,3-azoles other than 1,3,4-oxadiazoles (Scheme 2). Under modified conditions with KOAc and *o*-xylene as a base and a solvent, respectively, benzoxazoles **4** and benzothiazole (**6**) took part in the reaction to form the desired *N*-azolylindoles **5** and **7** albeit with moderate efficiencies. Attempts to apply benzimidazole and polyfluoroarenes remained unsuccessful at this stage.

Finally, we applied the domino C−H/N−H coupling−annulation to the reaction of 2,5-dialkynylphenylenediamine **8** for the synthesis of the benzodipyrrole skeleton[7] that bears the azole group on nitrogen (Scheme 3). Synthetic utilities of this double cyclization approach have been demonstrated by Tsuji and Nakamura,[8] and Field.[9] Pleasingly, when oxadiazole **1a** and **8** were subjected to substoichiometric conditions (130 mol % Cu(OAc)$_2$/phen to **8**), the desired benzodipyrrole core **9** was obtained in 43% yield.

Scheme 2. Copper-Catalyzed C−H/N−H Coupling−Annulation Sequence of *o*-Alkynylanilines **2** with Benzoxazoles **4** and Benzothiazole (**6**)



Scheme 3. A Double Cyclization Approach to *N*-Azolylbenzodipyrrole



Although the exact reaction mechanism still remains unclear at the present stage, a Cu(II)/O$_2$-catalyzed oxidative C−N coupling of azole **1** with aniline **2** could initially occur through a (heteroaryl)(ArNH)Cu species,[10] forming the *N*-azolylaniline intermediate.[11] Given the necessity of molecular oxygen (Table 1, entries 7 and 8), an O$_2$-promoted oxidation process of Cu(II) to Cu(III) might

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(7) For unique lower ionization potential and electron affinities of benzodipyrroles, see: Salzner, U.; Lagowski, J. B.; Pickup, P. G.; Poirier, R. A. *Synth. Met.* **1998**, *96*, 177.

(8) (a) Tsuji, H.; Yokoi, Y.; Mitsui, C.; Ilies, L.; Sato, Y.; Nakamura, E. *Chem.—Asian J.* **2009**, *4*, 655. Also see: (b) Nakamura, M.; Ilies, L.; Otsubo, S.; Nakamura, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 944. (c) Tsuji, H.; Mitsui, C.; Ilies, L.; Sato, Y.; Nakamura, E. *J. Am. Chem. Soc.* **2007**, *129*, 11902.

(9) Clentsmith, G. K. B.; Field, L. D.; Messerle, B. A.; Shasha, A.; Turner, P. *Tetrahedron Lett.* **2009**, *50*, 1469.

(10) Relevant reaction mechanism: (a) Hamada, T.; Ye, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 833. (b) Kitahara, M.; Hirano, K.; Tsurugi, H.; Satoh, T.; Miura, M. *Chem.—Eur. J.* **2010**, *16*, 1772. (c) Wei, Y.; Zhao, H.; Kan, J.; Su, W.; Hong, M. *J. Am. Chem. Soc.* **2010**, *132*, 2522 and ref 4l, m, and o.

be involved prior to the C–N bond formation.[12] Subsequent annulation of this intermediate proceeds via an electrophilic activation of the alkynyl moiety by the π-acidic nature of a Cu(II) salt to afford the product **3**.

In conclusion, we have developed a copper-catalyzed oxidative C–H/N–H coupling–annulation sequence between azoles and *o*-alkynylanilines. This domino reaction provides a new dehydrogenative approach to *N*-azolylindoles of biological and physical interest. Moreover, this protocol can be applied to the synthesis of the π-extended *N*-azolylbenzodipyrrole structure.

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

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(11) A copper-catalyzed oxidative C–H/N–H coupling of primary anilines is not trivial. The reported successful examples are limited to special anilines that bear electron-deficient groups such as NO_2; see ref 4o and 4p. Thus, we speculate that the *o*-alkynyl group can act as a directing group for the efficient intermolecular C–N coupling. For a related directing effect of alkynyl groups, see: Asao, N.; Asano, T.; Ohishi, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*, 4817.

(12) (a) Huffman, L. M.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 9196. (b) King, A. E.; Brunold, T. C.; Stahl, S. S. *J. Am. Chem. Soc.* **2009**, *131*, 5044. (c) King, A. E.; Huffman, L. M.; Casitas, A.; Costas, M.; Ribas, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2010**, *132*, 12068.