Organic LETTERS

Letter

pubs.acs.org/OrgLett

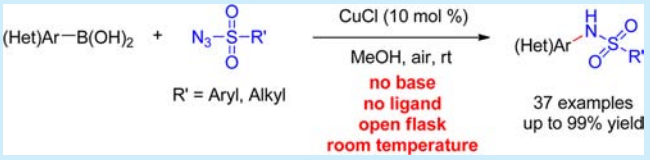
Copper-Catalyzed Chan–Lam Coupling between Sulfonyl Azides and Boronic Acids at Room Temperature

Soo-Yeon Moon, Jungsoo Nam, Kris Rathwell, and Won-Suk Kim*

Department of Chemistry and Nano Science, Ewha Womans University, Global Top 5 Program, Seoul 120-750, Korea

Supporting Information

ABSTRACT: A mild and efficient method for the synthesis of *N*-arylsulfonamides in the presence of 10 mol % of CuCl is demonstrated. The reaction proceeds readily at room temperature in an open flask using a variety of sulfonyl azides and boronic acids without any base, ligand, or additive.



N-Arylsulfonamides are a common moiety present in a large number of pharmaceutically interesting compounds (Figure 1).[1] These arylsulfonamide derivatives have become popular in SAR studies in medicinal chemistry research ever since the early discovery of their anticancer, antibacterial, anticonvulsant, and HIV protease inhibitory activities.[2] Thus, various methods have been developed to synthesize *N*-arylsulfonamides. Traditionally, these molecules have been prepared by the reaction of an aromatic amine and a sulfonyl chloride in the presence of a base (Scheme 1, eq 1). Although this approach is generally effective, alternative syntheses of *N*-arylsulfonamides employing the metal-catalyzed cross-coupling of sulfonamides with either aryl halides or arylboronic acids have been investigated in order to avoid the use of mutagenic sulfonyl chlorides and genotoxic aromatic amines (Scheme 1, eq 2).[3]

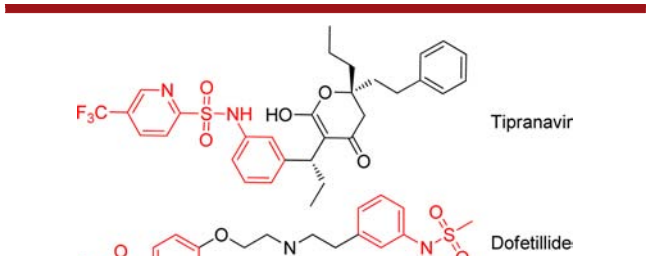


Figure 1. *N*-Arylsulfonamide-containing drugs.

Scheme 1. Synthesis of *N*-Arylsulfonamides

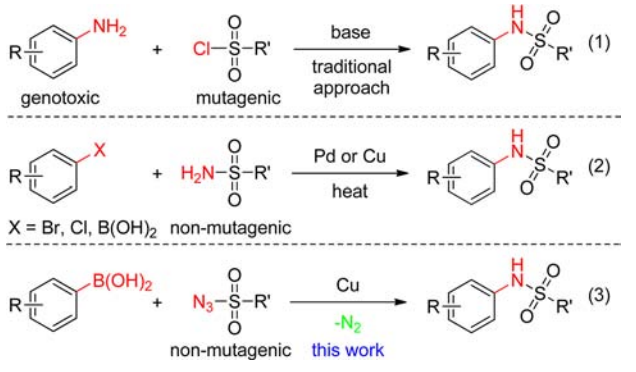
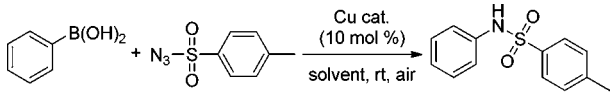


Table 1. Optimization of the *N*-Arylation Reaction of Phenylboronic Acid 1a with Tosyl Azide 2[a]



entry	Cu cat.	solvent	time (h)	yield[b] (%)
1	$Cu(OAc)_2$	MeOH	3	84
2	CuO	MeOH	24	<5
3	$CuCl_2$	MeOH	24	95
4	CuI	MeOH	24	<5
5	CuBr	MeOH	3	94
6	Cu_2O	MeOH	24	<5
7	CuBr S(CH_3)$_2$	MeOH	2	91
8	CuCl	MeOH	1	97
9	CuCl[c]	MeOH	1	91
10	CuCl[d]	MeOH	1	95
11	none	MeOH	24	0
12	CuCl	THF	24	40
13	CuCl	CH_2Cl_2	24	<5

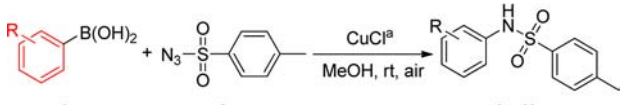
[a]Reaction conditions: 1.0 mmol of tosyl azide, 1.2 mmol of phenylboronic acid, solvent (0.5 M), air, rt. [b]Isolated yield. [c]5 mol % of CuCl. [d]1.0 mmol of phenylboronic acid, 1.2 mmol of tosyl azide.

Significant progress has been achieved in the palladium- or copper-catalyzed couplings of sulfonamides with aryl halides pioneered by Buchwald[4] and Wu,[5] but these reactions are generally carried out at elevated temperatures due to the low nucleophilicity of sulfonamides.[6] In 2001, Lam and co-workers reported the synthesis of *N*-arylsulfonamides employing sulfonamides and arylboronic acids.[7] Since then, many extensions and modifications for the Chan–Lam coupling reaction of sulfonamides with arylboronic acids have been

Received: October 11, 2013
Published: January 9, 2014

   dx.doi.org/10.1021/ol403717f | *Org. Lett.* 2014, 16, 338–341

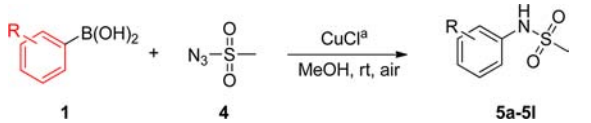
Table 2. Cu-Catalyzed *N*-Arylation of Arylboronic Acids 1 with Tosyl Azide 2



entry	product yield (%)[b], time	entry	product yield (%)[b], time
1	**3a**, 97, 1 h	7	**3g**, 95, 0.5 h
2	**3b**, 96, 0.5 h	8	**3h**, 93, 1 h[c]
3	**3c**, 96, 2 h	9	**3i**, 92, 3 h[c]
4	**3d**, 99, 0.5 h	10	**3j**, 72, 1 h
5	**3e**, 92, 0.5 h	11	**3k**, 91, 2 h
6	**3f**, 93, 0.5 h	12	**3l**, 90, 2 h

[a]Reaction conditions: 1.0 mmol of tosyl azide, 1.2 mmol of arylboronic acid, 10 mol % of CuCl, MeOH (0.5 M), air, rt. [b]Isolated yield. [c]2.0 mmol of arylboronic acid.

Table 3. Cu-Catalyzed *N*-Arylation of Arylboronic Acids 1 with Mesyl Azide 4



entry	product yield (%)[b], time	entry	product yield (%)[b], time
1	**5a**, 98, 1 h	7	**5g**, 99, 0.5 h
2	**5b**, 93, 1 h	8	**5h**, 90, 1 h[c]
3	**5c**, 99, 1 h	9	**5i**, 86, 3 h[c]
4	**5d**, 97, 1 h	10	**5j**, 87, 2 h
5	**5e**, 93, 2 h	11	**5k**, 90, 0.5 h
6	**5f**, 95, 1 h	12	**5l**, 88, 1 h

[a]Reaction conditions: 1.0 mmol of mesyl azide, 1.2 mmol of arylboronic acid, 10 mol % of CuCl, MeOH (0.5 M), air, rt. [b]Isolated yield. [c]2.0 mmol of arylboronic acid.

demonstrated.[8] However, in general, these reactions are slow, requiring more than 12 h to proceed to completion. Therefore, it is still necessary to develop a general, mild, and expedient method for the synthesis of *N*-arylsulfonamides.

Recently, Chan–Lam coupling reactions employing azides as substrates were demonstrated by Guo[9] and Reddy.[10] While the former reacted sodium azide with arylboronic acids giving rise to aryl azides, the latter coupled aryl azides with arylboronic acids using indium metal and catalytic $Cu(OAc)_2$ to produce diaryl amines. Together they demonstrated that azides can be used for C–N bond formation in the absence of ligands or bases. Furthermore, to the best of our knowledge, the copper-catalyzed Chan–Lam coupling reaction with boronic acids and sulfonyl azides at room temperature has not yet been reported. And, while organic azides require special precautions, they are stable enough to have found a wide range of uses in general organic synthesis.[11]

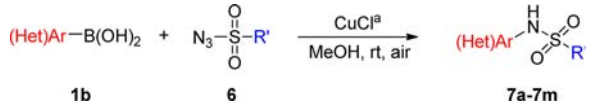
With these considerations in mind, we herein report a simple and efficient method for the synthesis of *N*-arylsulfonamides using boronic acids and sulfonyl azides.

Optimization of the Cu-catalyzed Chan–Lam C–N cross-coupling was initially conducted at room temperature employing phenylboronic acid **1a** and tosyl azide **2** (Table 1). Various copper catalysts were investigated in an open flask using MeOH as a solvent to furnish the desired product **3a** (Table 1, entries 1–9). The best results were observed when 10 mol % of CuCl was employed giving **3a** in 97% yield (Table 1, entry 8). In addition, when the reaction was carried out in MeOH with a lower catalyst loading, 5 mol % instead of 10 mol %, the coupled product **3a** was isolated in a slightly lower 91% yield (Table 1, entry 9). Also, when an excess of tosyl azide **2** was utilized, product **3a** was isolated in a slightly lower 95% yield (Table 1, entry 10). Without the aid of a copper catalyst, no conversion was observed (Table 1, entry 11). Furthermore, when different solvents (cf., THF, CH_2Cl_2) were employed in the presence of 10 mol % CuCl, the coupled product **3a** was obtained in low yields (Table 1, entries 12 and 13).

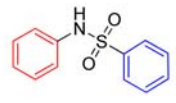
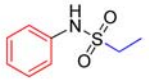
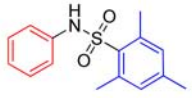
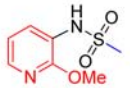
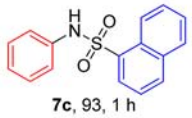
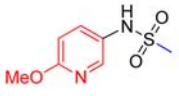
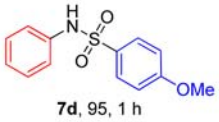
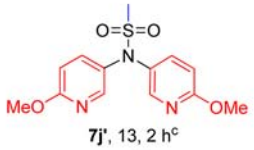
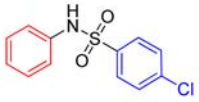
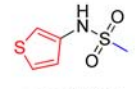
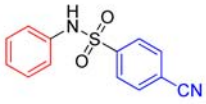
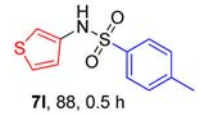
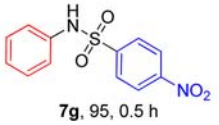
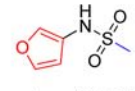
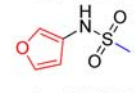
With the optimized conditions in hand, we first investigated the scope of the Cu-catalyzed Chan–Lam coupling utilizing various arylboronic acids. As shown in Table 2, most of the arylboronic acids employed under the optimized conditions furnished good-to-excellent yields within 2 h at room temperature. When arylboronic acids with electron-donating alkyl, alkoxy, and alkenyl groups were used as a coupling partner, the desired products **3a–h** were obtained in yields ranging from 92% to 99% (Table 2, entries 1–8). Interestingly,

dx.doi.org/10.1021/ol403717f | *Org. Lett.* 2014, 16, 338–341

Table 4. Cu-Catalyzed *N*-Arylation of Aryl and Heteroaryl Boronic Acids 1b with Various Sulfonyl Azides 6



1b 6 7a-7m

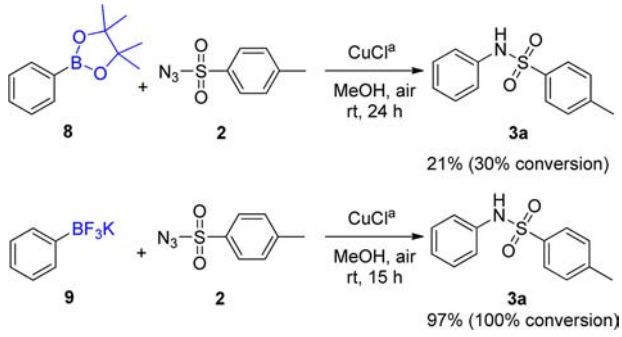
entry	product yield (%)[b], time	entry	product yield (%)[b], time
1	 **7a**, 94, 0.5 h	8	 **7h**, 95, 1 h
2	 **7b**, 98, 2 h	9	 **7i**, 50, 1 h[c]
3	 **7c**, 93, 1 h	10	 **7j**, 28, 2 h[c]
4	 **7d**, 95, 1 h		 **7j'**, 13, 2 h[c]
5	 **7e**, 95, 0.5 h	11	 **7k**, 94, 0.5 h
6	 **7f**, 92, 1 h	12	 **7l**, 88, 0.5 h
7	 **7g**, 95, 0.5 h	13	 **7m**, 48, 1 h[c]
		14	 **7m**, 74, 0.5 h[c,d]

[a]Reaction conditions: 1.0 mmol of sulfonyl azide, 1.2 mmol of boronic acid, 10 mol % of CuCl, MeOH (0.5 M), air, rt. [b]Isolated yield. [c]2.0 mmol of boronic acid. [d]20 mol % of CuCl.

when either sterically hindered *ortho* or trifluoromethyl-substituted arylboronic acids were used, the reaction did not go to completion due to competitive homocoupling of the arylboronic acid. However, the use of 2.0 equiv of arylboronic acid provided a full conversion and gave the desired products **3h** and **3i** in 93% and 92% yield, respectively (Table 2, entries 8 and 9). When a methoxycarbonyl-substituted arylboronic acid was employed, it showed less reactivity and provided a lower yield, 72% (Table 2, entry 10). Halo-substituted arylboronic acids proved effective coupling partners, furnishing the desired products **3k** and **3l** in 90% and 91% yield, respectively (Table 2, entries 11 and 12).

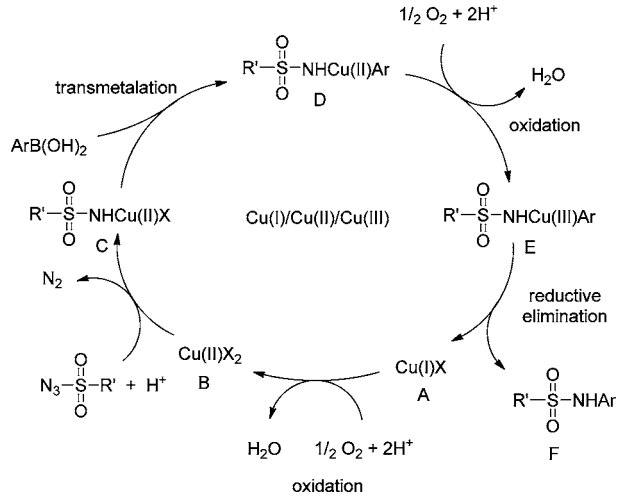
Next, we turned our attention to the preparation of the *N*-arylmethanesulfonamide unit present in multiple commercially available drugs (cf., dofetillide, delavirdine). Pleasingly, a variety of arylboronic acids containing electron-neutral, -donating, and

Scheme 2. Cu-Catalyzed *N*-Arylation of Boronic Acid Derivatives with Tosyl Azide 2[a]



[a]Reaction conditions: 1.0 mmol of sulfonyl azide, 1.2 mmol of boronic acid derivative, 10 mol % of CuCl, MeOH (0.5 M), air, rt.

Scheme 3. Plausible Mechanism



-withdrawing groups were transformed into *N*-arylmethanesulfonamides **5a–l** in 86% to 99% yield when mesyl azide **4** was employed as an electrophile under conditions (cf., CuCl, MeOH, air) that proved effective with tosyl azide **2** (Table 3).

Encouraged by the viability of the Cu-catalyzed Chan–Lam C–N cross-coupling reactions employing sulfonyl azide **2** or **4** with arylboronic acids at room temperature, we focused on utilizing various sulfonyl azides **6**[12] and various heteroarylboronic acids. As illustrated in Table 4, the coupling of various aryl or alkylsulfonyl azides with phenylboronic acid furnished the corresponding products (**7a–h**) in good-to-excellent yields ranging from 92% to 98% when using an open flask at room temperature (Table 4, entries 1–8). When aryl and alkylsulfonyl azides were reacted with heteroarylboronic acids, the coupled sulfonamides (**7i–m**) were obtained in moderate to good yield (Table 4, entries 9–14).

Interestingly, the reaction between mesyl azide and 2.0 equiv of 2-methoxypyridine-3-boronic acid provided only the desired coupled product **7i** in 50% yield (Table 4, entry 9), while using 2.0 equiv of 2-methoxypyridine-5-boronic acid provided coupled product **7j** in 28% yield along with the side product **7j′** arising from the coupling of **7j** with another equivalent of the boronic acid (Table 4, entry 10). 3-Thienylboronic acid reacted with mesyl and tosyl azide to form the respective sulfonamides **7k** and **7l** in good yield (Table 4, entries 11 and 12). When 3-furanylboronic acid was coupled with mesyl azide

dx.doi.org/10.1021/ol403717f | *Org. Lett.* 2014, 16, 338–341

a moderate yield of 48% was obtained (Table 4, entry 13). Increasing the catalyst loading to 20 mol %, however, afforded the desired furanyl coupled product in 74% in 30 min.

To further investigate the scope of this reaction, sulfonyl azide was reacted with various phenylboronic acid derivatives. Thus, pinacol phenylboronate **8** and potassium phenyltrifluoroborate **9** were reacted with tosyl azide **2** (Scheme 2). In general, reaction times were longer than for the boronic acids, and, even after 24 h, boronate **8** only afforded the desired sulfonamide **3a** in 21% yield and 70% recovery of starting material. In contrast, after 15 h, coupling with trifluoroborate **9** proceeded in an excellent 97% yield and 100% conversion.

The proposed mechanism of the Chan–Lam coupling between sulfonyl azides and boronic acids is shown in Scheme 3.[13] Initially, air oxidation of Cu(I) to Cu(II) occurs. The sulfonyl azide can then coordinate to the Cu(II) salt B forming complex C that subsequently undergoes transmetalation with an boronic acid to afford complex D. In the presence of oxygen, air oxidation of the Cu(II) complex provides the higher oxidation-state Cu(III) complex E, which can more efficiently undergo reductive elimination to furnish the product F and Cu(I) species A.[14]

In summary, we have demonstrated a new synthetic method for the preparation of *N*-arylsulfonamides via Cu-catalyzed Chan–Lam C–N cross-coupling reactions employing various sulfonyl azides and boronic acids. In particular, most reactions proceeded to completion in 2 h using an open flask at room temperature without the aid of any base, ligand, or additive. Further investigation into the use of other organoazides as an amine source is currently ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

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

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: wonsukk@ewha.ac.kr.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) (NRF-2012R1A1A1006123) and the New & Renewable Energy of the Korea Institute of Energy Technology Evaluation and Planning (KETEP) grant (No. 20133030000210).

■ REFERENCES

(1) For a list of *N*-arylsulfonamide-containing drugs. see: (a) Scozzafava, A.; Owa, T.; Mastrolorenzo, A.; Supuran, C. T. *Curr. Med. Chem.* **2003**, *10*, 925–953. (b) Smith, D. A.; Jones, R. M. *Curr. Opin. Drug Discovery Dev.* **2008**, *11*, 72–79.

(2) (a) Scozzafava, A.; Owa, T.; Mastrolorenzo, A.; Supuran, C. T. *Curr. Med. Chem.* **2003**, *10*, 925–953. (b) Supuran, C. T.; Casini, A.; Scozzafava, A. *Med. Res. Rev.* **2003**, *5*, 535–558. (c) Reddy, N. S. M.; Mallireddigari, R.; Cosenza, K. G.; Bell, S. C.; Reddy, E. P.; Reddy, M. V. R *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4093–4097. (d) Stranix, B. R.; Lavallée, J.-F.; Sévigny, G.; Yelle, J.; Perron, V.; LeBerre, N.; Herbart, D.; Wu, J. J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3459–3462. (e) Siddiqui, N.; Pandeya, S. N.; Khan, S. A.; Stables, J.; Rana, A.; Alam, M.; Arshad, M. F.; Bhat, M. A. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 255–259. (f) Basanagouda, M.; Shivashankar, K.; Kulkarni, M. V.; Rasal, V. P.; Patel, H.; Mutha, S. S.; Mohite, A. A. *Eur. J. Med. Chem.* **2010**, *45*, 1151–1157. (g) Chohan, Z. H.; Youssoufi, M. H.; Jarrahpour, A.; Hadda, T. B. *Eur. J. Med. Chem.* **2010**, *45*, 1189–1199.

(3) (a) Pierson, D. A.; Olsen, B. A.; Robbins, D. K.; DeVries, K. M.; Varie, D. L. *Org. Process Res. Dev.* **2009**, *13*, 285–291. (b) Snodin, D. J. *Org. Process Res. Dev.* **2010**, *14*, 960–976. (c) Skipper, P. L.; Kim, M. Y.; Sun, H.-L. P.; Wogan, G. N.; Tannenbaum, S. R. *Carcinogenesis* **2010**, *31*, 50–58.

(4) (a) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 6043–6048. (b) Yin, J.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1101–1104. (c) Wolfe, J. P.; Rennels, R. A.; Buchwald, S. L. *Tetrahedron* **1996**, *52*, 7525–7546.

(5) He, H.; Wu, Y.-J. *Tetrahedron Lett.* **2003**, *44*, 3385–3386.

(6) For selective examples employing Pd catalysis, see: (a) Burton, G.; Cao, P.; Li, G.; Rivero, R. *Org. Lett.* **2003**, *5*, 4373–4376. (b) Steinhuebel, D.; Palucki, M.; Askin, D.; Drolling, U. *Tetrahedron Lett.* **2004**, *45*, 3305–3307. (c) Ikawa, T.; Barder, T. E.; Biscoe, M. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 13001–13009. (d) Hicks, J. D.; Hyde, A. M.; Cuezva, A. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 16720–16734. (e) Shekhar, S.; Dunn, T. B.; Kotecki, B. J.; Montavon, D. K.; Cullen, S. C. *J. Org. Chem.* **2011**, *76*, 4552–4563. (f) Rosen, B. R.; Ruble, J. C.; Beauchamp, T. J.; Navarro, A. *Org. Lett.* **2011**, *13*, 2564–2567. For selective examples employing Cu catalysis, see: (a) Cristau, H.-J.; Cellier, P. P.; Spindler, J.-F.; Taillefer, M. *Chem.—Eur. J.* **2004**, *10*, 5607–5622. (b) Deng, W.; Liu, L.; Zhang, C.; Liu, M.; Guo, Q.-X. *Tetrahedron Lett.* **2005**, *46*, 7295–7298. (c) Baffoe, J.; Hoe, M. Y.; Touré, B. B. *Org. Lett.* **2010**, *12*, 1532–1535. (d) Han, X. *Tetrahedron Lett.* **2010**, *51*, 360–362. (e) Teo, Y.-C.; Yong, F.-F. *Synlett* **2011**, *6*, 837–843. (f) Wang, X.; Guram, A.; Ronk, M.; Milne, J. E.; Tedrow, J. S.; Faul, M. M. *Tetrahedron Lett.* **2012**, *53*, 7–10.

(7) Lam, P. Y. S.; Vincent, G.; Clark, C. G.; Deudon, S.; Jadhav, P. K. *Tetrahedron Lett.* **2001**, *42*, 3415–3418.

(8) (a) For a recent review, see: Rao, K. S.; Wu, T.-S. *Tetrahedron* **2012**, *68*, 7735–7754. (b) Lan, J.-B.; Zhang, G.-L.; Yu, X.-Q.; You, J.-S.; Chen, L.; Yan, M.; Xie, R.-G. *Synlett* **2004**, *6*, 1095–1097. (c) Kantam, M. L.; Neelima, B.; Reddy, C. V.; Neeraja, V. *J. Mol. Catal. A: Chem.* **2006**, *249*, 201–206. (d) Pan, C.; Cheng, J.; Wu, H.; Ding, J.; Liu, M. *Synth. Commun.* **2009**, *39*, 2082–2092.

(9) Tao, C.-Z.; Cui, X.; Li, J.; Liu, A.-X.; Liu, L.; Guo, Q.-X. *Tetrahedron Lett.* **2007**, *48*, 3525–3539.

(10) Reddy, B. V. S.; Reddy, N. S.; Reddy, Y. J.; Reddy, Y. V. *Tetrahedron Lett.* **2011**, *52*, 2547–2549.

(11) Bräse, S.; Gil, C.; Knepper, K.; Zimmerman, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 5188–5240.

(12) Kim, J.-G.; Jang, D.-O. *Synlett* **2008**, *13*, 2072–2074.

(13) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Averill, K. M.; Chan, D. M. T.; Combs, A. *Synlett* **2000**, *5*, 674–676.

(14) (a) King, A. E.; Brunold, T. C.; Stahl, S. S. *J. Am. Chem. Soc.* **2009**, *131*, 5044–5045. (b) King, A. E.; Huffman, L. M.; Casitas, A.; Costas, M.; Ribas, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2010**, *132*, 12068–12073.