ORGANIC LETTERS

2011
Vol. 13, No. 19
5224–5227

Ligand-Free Copper-Catalyzed Regioselective C-2 Arylation of Imidazo[2,1-*b*]thiazoles

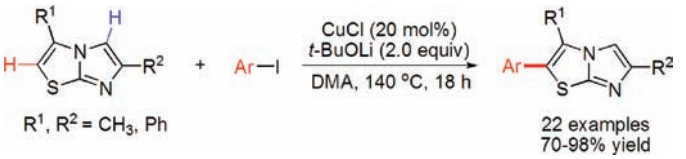
Guoli Huang,[†] Hongsheng Sun,[†] Xiaojie Qiu,[†,‡] Can Jin,[†] Chen Lin,[†] Yingzhong Shen,[‡] Juli Jiang,[*,†] and Leyong Wang[*,†]

Key Laboratory of Mesoscopic Chemistry of MOE, Institute of Chemical Biology and Drug Innovation, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing 210093, China, and College of Material Science and Technology, Nanjing University of Aeronautics and Astronautics, Nanjing 210016, China

jjl@nju.edu.cn; lywang@nju.edu.cn.

Received August 3, 2011

ABSTRACT



An effective, regioselective C-2 arylation of imidazo[2,1-*b*]thiazoles catalyzed by Cu(I) has been developed. This arylation proceeded smoothly without promotion of the ligands, and various functional (22 samples) groups were well tolerated. Preliminary mechanistic studies of this arylation are also reported.

Many natural products and biologically active compounds containing imidazo[2,1-*b*]thiazole moieties have been discovered and synthesized so far.[1] As some typical examples, anthelmintics tetramisole (**i**),[2] thieno[3,2-*d*]pyrimidinone (**ii**),[3] 5,6-diarylimidazo[2,1-*b*][1,3]thiazoles (**iii**),[4] C-2 aryl-substituted pilicides (**iv**),[5] and ^{11}C-labeled imidazo[2,1-*b*]benzothiazoles (**v**)[6] all showed effective biological and medicinal activity (Figure 1). Milne et al.[7] described the identification and characterization of a molecule (**vi**) bearing imidazo[2,1-*b*]thiazole as an activator of SIRT1, which was structurally unrelated to, and 1000-fold more potent, than resveratrol. And it can bind to the SIRT1 enzyme−peptide substrate complex at an allosteric site amino terminal to the catalytic domain and lower the Michaelis constant for acetylated substrates.

Imidazo[2,1-*b*]thiazoles designed with the desired substituents in appropriate positions were often specific (Figure 1). Current strategies for preparing imidazo[2,1-*b*]thiazole derivatives are focused on the construction of the fused ring with the desired aryl substituents or hopeful heterocycles at oriented position in advance.[8] To the best of our knowledge, there has been no reported example of direct arylation of the imidazo[2,1-*b*]-thiazole core.

[†] Nanjing University.
[‡] Nanjing University of Aeronautics and Astronautics.

(1) (a) Budriesi, R.; Ioan, P.; Leoni, A.; Pedemonte, N.; Locatelli, A.; Micucci, M.; Chiarini, A.; Galietta, L. J. V. *J. Med. Chem.* **2011**, *54*, 3885. (b) Guzeldemirci, N. U.; Kucukbasmaci, O. *Eur. J. Med. Chem.* **2010**, *45*, 63. (c) Metaye, T.; Millet, C.; Kraimps, J. L.; Saunier, B.; Barbier, J.; Begon, F. *Biochem. Pharmacol.* **1992**, *43*, 1507.

(2) Raeymaekers, A. H. M.; Allewijn, F. T. N.; J., V.; Demoen, P. J. A.; VanOffenwert, T. T. T.; Janssen, P. A. J. *J. Med. Chem.* **1966**, *9*, 545.

(3) Carpenter, A. J.; Cooper, J. P.; Handlon, A. L.; Hertzog, D. L.; Hyman, C. E.; Guo, Y. C.; Speake, J. D.; Witty, D. R. WO03033476, 2003.

(4) Scribner, A.; Meitz, S.; Fisher, M.; Wyvratt, M.; Leavitt, P.; Liberator, P.; Gurnett, A.; Brown, C.; Mathew, J.; Thompson, D.; Schmatz, D.; Biftu, T. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5263.

(5) Chorell, E.; Pinkner, J. S.; Phan, G.; Edvinsson, S.; Buelens, F.; Remaut, H.; Waksman, G.; Hultgren, S. J.; Almqvist, F. *J. Med. Chem.* **2010**, *53*, 5690.

(6) Yousefi, B. H.; Manook, A.; Drzezga, A.; Reutern, B. V.; Schwaiger, M.; Wester, H. J.; Henriksen, G. *J. Med. Chem.* **2011**, *54*, 949.

(7) Milne, J. C.; Lambert, P. D.; Schenk, S.; Carney, D. P.; Smith, J. J.; Gagne, D. J.; Jin, L.; Boss, O.; Perni, R. B.; Vu, C. B.; Bemis, J. E.; Xie, R.; Disch, J. S.; Ng, P. Y.; Nunes, J. J.; Lynch, A. V.; Yang, H. Y.; Galonek, H.; Israelian, K.; Choy, W.; Iffland, A.; Lavu, S.; Medvedik, O.; Sinclair, D. A.; Olefsky, J. M.; Jirousek, M. R.; Elliott, P. J.; Westphal, C. H. *Nature* **2007**, *450*, 712.

10.1021/ol2021109
Published on Web 09/13/2011

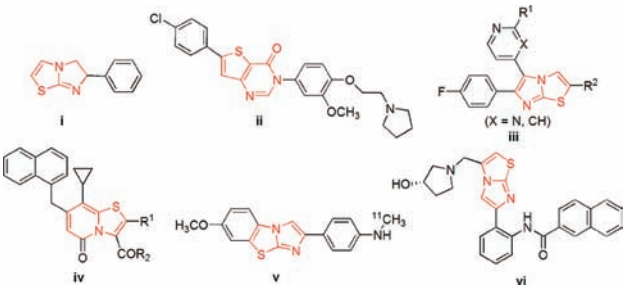
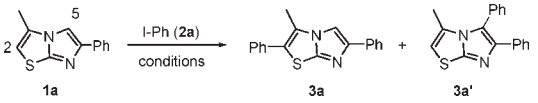


Figure 1. Imidazo[2,1-*b*]thiazoles with biological and medicinal activity.

The concept of direct arylation via C−H bond cleavage has received substantial attention over the past few years.[9] Expensive metal-catalyzed sp^2 C−H bond arylations such as palladium,[10] rhodium,[11] or ruthenium[12] have undergone explosive growth in the past few years. Less-expensive copper,[13] iron,[14] and nickel[15] compounds have also shown to be highly active in catalytic direct arylations in recent years and have great potential for future development.[9c,d] Although metal-catalyzed arylations on various heterocyclic systems such as indolizines,[16] imidazo[1,5-*a*]pyrazines,[17] xanthines,[18] and thiazoles[19] exist, no direct, regioselective arylation of the imidazo[2,1-*b*]thiazole core have been developed so far.

3-Methyl-6-phenylimidazo[2,1-*b*]thiazole (**1a**) was selected as a substrate to investigate the possibility of arylation. In this substrate (**1a**), the activity of the C_2−H bond was clearly different from that of the C_5−H bond, deduced from their different chemical shifts (6.39 ppm for C_2−H and 7.61 ppm for C_5−H).[20] We initially tested direct arylation of **1a** using typical Pd-catalyzed conditions optimized in the literature.[10i,16,21] As shown in Table 1, these approaches were largely unsuccessful. Both **3a**, C-2 arylated product, and **3a′**, C-5 arylated product, were obtained in poor yields,[22] and byproduct biphenyl was also found in the reaction (< 5% yield).

Table 1. Pd-Catalyzed Arylation of Imidazo[2,1-*b*]thiazole[a]



entry	conditions	solvent	yields of **3a**/**3a′**[b] (%)
1	$Pd(OAc)_2/K_3PO_4/t$-$BuCO_2H$[d]	DMF	5/6
2	$Pd(PPh_3)_2Cl_2/KOAc/H_2O$[e]	NMP	22/13 (15)[c]
3	$Pd(OAc)_2/PPh_3/K_2CO_3$[f]	dioxane	19/3

[a] Reaction was performed with **1a** (0.5 mmol) and **2a** (1.5 mmol) in 1 mL of solvent. [b] Unless specified, the yield was estimated by ^{1}H NMR. [c] Isolated yield of **3a**. [d] See ref 10i. [e] See ref 16. [f] See ref 21.

(8) (a) Al-Tel, T. H.; Al-Qawasmeh, R. A.; Voelter, W. *Eur. J. Org. Chem.* **2010**, 5586. (b) Fidanze, S. D.; Erickson, S. A.; Wang, G. T.; Mantei, R.; Clark, R. F.; Sorensen, B. K.; Bamaung, N. Y.; Kovar, P.; Johnson, E. F.; Swinger, K. K.; Stewart, K. D.; Zhang, Q.; Tucker, L. A.; Pappano, W. N.; Wilsbacher, J. L.; Wang, J. Y.; Sheppard, G. S.; Bell, R. L.; Davidsen, S. K.; Hubbard, R. D. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2452. (c) Xu, H.; Zhang, Y.; Huang, J. Q.; Chen, W. Z. *Org. Lett.* **2010**, *12*, 3704. (d) Guchhait, S. K.; Madaan, C.; Thakkar, B. S. *Synthesis* **2009**, 3293.

(9) (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (b) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (c) Daugulis, O.; Do, H. Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074. (d) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792. (e) Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 3850.

(10) (a) Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 4972. (b) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172. (c) Yu, J. Q.; Giri, R.; Maugel, N.; Li, J. J.; Wang, D. H.; Breazzano, S. P.; Saunders, L. B. *J. Am. Chem. Soc.* **2007**, *129*, 3510. (d) Stuart, D. R.; Villemure, E.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 12072. (e) Li, B. H.; Tian, S. L.; Fang, Z.; Shi, Z. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 1115. (f) Lebrasseur, N.; Larrosa, I. *J. Am. Chem. Soc.* **2008**, *130*, 2926. (g) Yu, J. Q.; Wang, D. H.; Mei, T. S. *J. Am. Chem. Soc.* **2008**, *130*, 17676. (h) Yanagisawa, S.; Ueda, K.; Sekizawa, H.; Itami, K. *J. Am. Chem. Soc.* **2009**, *131*, 14622. (i) Zhao, D. B.; Wang, W. D.; Lian, S.; Yang, F.; Lan, J. B.; You, J. S. *Chem.—Eur. J.* **2009**, *15*, 1337. (j) Roy, D.; Mom, S.; Beauperin, M.; Doucet, H.; Hierso, J. C. *Angew. Chem., Int. Ed.* **2010**, *49*, 6650. (k) Shibahara, F.; Yamaguchi, E.; Murai, T. *Chem. Commun.* **2010**, *46*, 2471. (l) Ohnmacht, S. A.; Culshaw, A. J.; Greaney, M. F. *Org. Lett.* **2010**, *12*, 224. (m) Tamba, S.; Okubo, Y.; Tanaka, S.; Monguchi, D.; Mori, A. *J. Org. Chem.* **2010**, *75*, 6998. (n) Kirchberg, S.; Tani, S.; Ueda, K.; Yamaguchi, J.; Studer, A.; Itami, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 2387. (o) Ioannidou, H. A.; Koutentis, P. A. *Org. Lett.* **2011**, *13*, 1510.

(11) (a) Lewis, J. C.; Wiedemann, S. H.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2004**, *6*, 35. (b) Wang, X.; Lane, B. S.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 4996. (c) Yanagisawa, S.; Sudo, T.; Noyori, R.; Itami, K. *J. Am. Chem. Soc.* **2006**, *128*, 11748. (d) Ackermann, L.; Born, R.; Álvarez-Bercedo, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 6364. (e) Lewis, J. C.; Berman, A. M.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 2493. (f) Berman, A. M.; Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 14926.

(12) (a) Ackermann, L.; Vicente, R.; Althammer, A. *Org. Lett.* **2008**, *10*, 2299. (b) Arockiam, P.; Poirier, V.; Fischmeister, C.; Bruneau, C.; Dixneuf, P. H. *Green Chem.* **2009**, *11*, 1871. (c) Ackermann, L.; Vicente, R.; Potukuchi, H. K.; Pirovano, V. *Org. Lett.* **2010**, *12*, 5032. (d) Ackermann, L.; Vicente, R. *Top. Curr. Chem.* **2010**, *292*, 211. (e) Štefane, B.; Fabris, J.; Požgan, F. *Eur. J. Org. Chem.* **2011**, 3474.

(13) (a) Do, H. Q.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 12404. (b) Do, H. Q.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 1128. (c) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172. (d) Ackermann, L.; Potukuchi, H. K.; Landsberg, D.; Vicente, R. *Org. Lett.* **2008**, *10*, 3081. (e) Liebeskind, L. S.; Liu, S. *J. Am. Chem. Soc.* **2008**, *130*, 6918.

(14) (a) Wen, J.; Zhang, J.; Chen, S. Y.; Li, J.; Yu, X. Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 8897. (b) Yoshikai, N.; Matsumoto, A.; Norinder, J.; Nakamura, E. *Angew. Chem., Int. Ed.* **2009**, *48*, 2925. (c) Vallee, F.; Mousseau, J. J.; Charette, A. B. *J. Am. Chem. Soc.* **2010**, *132*, 1514. (d) Wen, J.; Qin, S.; Ma, L. F.; Dong, L. A.; Zhang, J.; Liu, S. S.; Duan, Y. S.; Chen, S. Y.; Hu, C. W.; Yu, X. Q. *Org. Lett.* **2010**, *12*, 2694.

(15) (a) Canivet, J.; Yamaguchi, J.; Ban, I.; Itami, K. *Org. Lett.* **2009**, *11*, 1733. (b) Hachiya, H.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2009**, *11*, 1737. (c) Hachiya, H.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 2202.

(16) Park, C. H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyan, V. *Org. Lett.* **2004**, *6*, 1159.

(17) Wang, J. X.; McCubbin, J. A.; Jin, M. Z.; Laufer, R. S.; Mao, Y. Y.; Crew, A. P.; Mulvihill, M. J.; Snieckus, V. *Org. Lett.* **2008**, *10*, 2923.

(18) Malakar, C. C.; Schmidt, D.; Conrad, J.; Beifuss, U. *Org. Lett.* **2011**, *13*, 1378.

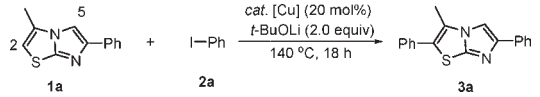
(19) (a) Masui, K.; Mori, A.; Okano, K.; Takamura, K.; Kinoshita, M.; Ikeda, T. *Org. Lett.* **2004**, *6*, 2011. (b) Turner, G. L.; Morris, J. A.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 7996.

(20) See the Supporting Information for details.

(21) Koubachi, J.; El Kazzouli, S.; Berteina-Raboin, S.; Mouaddib, A.; Guillaumet, G. *Synlett* **2006**, 3237.

(22) The arylation product (**3a** for C-2 position and **3a′** for C-5 position) was established by ^{1}H NMR; see the Supporting Information for details.

Table 2. Cu-Catalyzed C-2 Arylation of Imidazo[2,1-*b*]thiazole[a]



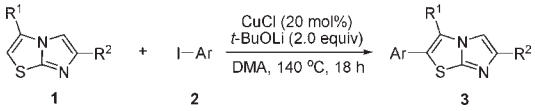
entry	[Cu]	solvent[b]	yield of **3a**[c] (%)
1	CuI	DMF/xylene (1:1)	87
2	CuCl	DMF/xylene (1:1)	89
3	CuBr	DMF/xylene (1:1)	87
4	CuCN	DMF/xylene (1:1)	80
5	$CuCl_2$	DMF/xylene (1:1)	76
6	$CuCl_2 \cdot 2H_2O$	DMF/xylene (1:1)	51
7	$Cu(OAc)_2 \cdot 2H_2O$	DMF/xylene (1:1)	68[d]
8	$Cu(OTf)_2$	DMF/xylene (1:1)	54[d]
9	$Cu(acac)_2$	DMF/xylene (1:1)	62[d]
10	CuCl	DMF	81
11	CuCl	DMA	94 (89)[d]
12	CuCl	DMA/xylene (1:1)	82

[a] The reaction was performed with **1a** (0.5 mmol) and **2a** (1.5 mmol) in 1 mL of solvent at 140 °C for 18 h. [b] Substrate concentration = 0.5 M. [c] Unless specified, the yield was estimated by ^{1}H NMR. [d] Isolated yield.

Copper, as the first transition metal used to promote C−H bond functionalization, appeared to be underutilized as a catalyst for C−H bond arylation.[23] The successful Cu-catalyzed arylation by Daugulis[13a,b] inspired us to attempt the possible direct arylation of imidazo[2,1-*b*]thiazole by Cu catalyst. The initial reaction was performed with **1a** and iodobenzene **2a** as reactants, *t*-BuOLi as a base, and DMF−xylene mixture as a solvent (Table 2). To our surprise, four Cu(I) salts showed good yields uniformly (entries 1−4). More promisingly, only regioselectively C-2-arylated imidazo[2,1-*b*]-thiazole product was obtained, and no side product biphenyl was found. Unambiguous confirmation of the structure of a representative C-2-arylated product was obtained in the form of the X-ray structure of compound **3a**[20].

As shown in Table 2, Cu(II) salts, $CuCl_2$, $CuCl_2 \cdot 2H_2O$, $Cu(OAc)_2 \cdot 2H_2O$, $Cu(OTf)_2$, and $Cu(acac)_2$, were also tested in our studies and found to be effective but a little less active than Cu(I) (entries 5−9). Subsequently, we explored the effects of the solvent, base, and Cu-catalyst loading in the arylation. Equally good results were obtained in DMF or DMA−xylene mixtures, and DMA afforded the highest yields (94%, entry 11). Reducing the catalyst loading from 20 to 10 and 5 mol % lowered the yields of product from 94% to 86% and 73%, respectively. In the absence of the Cu catalyst, no arylated product was found. With these partially optimized arylation conditions, the bases were investigated, and a variety of weak inorganic bases (K_3PO_4, Cs_2CO_3, and K_2CO_3) were all unsuccessful. We then tested other alkoxide bases, *t*-BuOK and *t*-BuONa, and yields of 24% and 59% were obtained, respectively. No arylated product was found without bases. Furthermore, PhBr or PhCl, instead of PhI, only gave traces of product under optimized conditions. Optimization experiments indicated that the best result for C-2 arylation of imidazo[2,1-*b*]thiazoles was obtained in the presence of CuCl (20 mol %), aryl iodides (3.0 equiv), and *t*-BuOLi (2.0 equiv) in DMA at 140 °C.

Table 3. Scope of Cu-Catalyzed Arylation of Imidazo[2,1-*b*] thiazole[a]



entry	Ar	R^1	R^2	product (% yield)[b]
1	Ph	CH_3	Ph	**3a** (89) (94)[c]
2	4-$CH_3C_6H_4$	CH_3	Ph	**3b** (91) (97)[c]
3	4-$OCH_3C_6H_4$	CH_3	Ph	**3c** (91)
4	4-FC_6H_4	CH_3	Ph	**3d** (87)
5	4-$CF_3C_6H_4$	CH_3	Ph	**3e** (70)
6	3-$OCH_3C_6H_4$	CH_3	Ph	**3f** (87)
7	2-$C_2H_5C_6H_4$	CH_3	Ph	**3g** (94)
8	1-naphthyl	CH_3	Ph	**3h** (97)
9	Ph	CH_3	CH_3	**3i** (80)
10	4-$CH_3C_6H_4$	CH_3	CH_3	**3j** (84)
11	4-$OCH_3C_6H_4$	CH_3	CH_3	**3k** (87)
12	4-FC_6H_4	CH_3	CH_3	**3l** (72)
13	2-$C_2H_5C_6H_4$	CH_3	CH_3	**3m** (92)
14	3-$OCH_3C_6H_4$	CH_3	CH_3	**3n** (81)
15	1-naphthyl	CH_3	CH_3	**3o** (95)
16	Ph	Ph	Ph	**3p** (98)
17	4-$CH_3C_6H_4$	Ph	Ph	**3q** (91)
18	4-$OCH_3C_6H_4$	Ph	Ph	**3r** (92)
19	2-$C_2H_5C_6H_4$	Ph	Ph	**3s** (86)
20	4-FC_6H_4	Ph	Ph	**3t** (74)
21	4-$CF_3C_6H_4$	Ph	Ph	**3u** (84)
22	1-naphthyl	Ph	Ph	**3v** (98)

[a] The reaction was performed with **1** (0.5 mmol), **2** (1.5 mmol), *t*-BuOLi (2.0 equiv), and CuCl (20 mol %) in 1 mL of DMA at 140 °C for 18 h. [b] Isolated yield after column chromatography of the crude. [c] Determination from ^{1}H NMR.

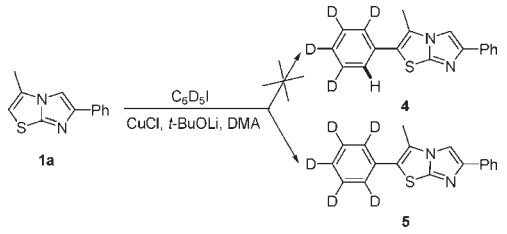
With optimized conditions in hand, the scope with respect to aryl iodides and imidazo[2,1-*b*]thiazoles was investigated (Table 3). A variety of functional groups on the substituents of the aryl iodides were well-tolerated. The electron-deficient and electron-rich aryl iodides were reactive in moderate to excellent yields (entries 1−8). Electron-rich aryl iodides gave a slightly higher yield than electron-deficient ones under the optimized conditions (entries 2, 3 vs entries 4, 5). Substantial steric hindrance was tolerated on the aryl iodides at the para-, meta-, and ortho-positions (entries 3 vs 6 vs 7) and afforded good results. Most

(23) (a) Steinkopf, W.; Leitsmann, R.; Hofmann, K. H. *Liebigs Ann. Chem.* **1941**, *546*, 180. (b) Nilsson, M. *Tetrahedron Lett.* **1966**, *7*, 679. (c) Björklund, C.; Nilsson, M. *Acta Chem. Scand.* **1968**, *22*, 2338. (d) Ljusberg, H.; Wahren, R. *Acta Chem. Scand.* **1973**, *27*, 2717.

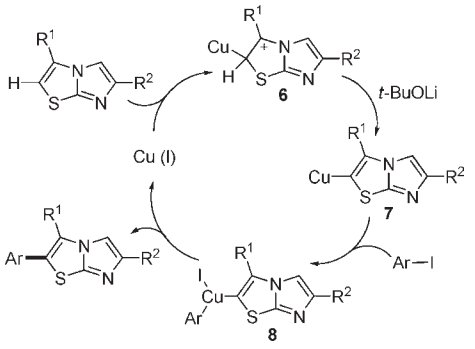
(24) Lindley, J. *Tetrahedron* **1984**, *40*, 1433.

(25) (a) Do, H. O.; Khan, R. M. K.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 15185. (b) Do, H. Q.; Daugulis, O. *Org. Lett.* **2009**, *11*, 421.

Scheme 1. Mechanistic Considerations



Scheme 2. Possible Mechanism for Cu-Catalyzed Arylation of Imidazo[2,1-*b*]thiazoles



remarkably, the sterically hindered 1-naphthyl iodide also gave the desired regioselective C-2 arylation product in excellent yield (> 95%, entries 8, 15, and 22). It should be noted that the substrates with aromatic groups at C-5 and C-3 gave better yields than the aliphatic groups (entries 1 vs 9 vs 16). Presumably, electronic effects rather than steric effects played a more important role in this reaction.

Naturally, we were interested in elucidating the mechanism for this arylation reaction and carried out preliminary mechanistic investigations of the coupling process. (i) Cu-assisted benzyne-type mechanisms,[24] (ii) deprotonation−metalation mechanisms, and (iii) typical F−C alkylations were considered. C_6D_5I was applied to the optimized conditions for mechanistic consideration (Scheme 1). Only compound **5**, instead of **4**, was found in the reaction, and no H−D exchange was observed. This result could not support the assumption that the reaction proceeded via a copper-assisted benzyne-type mechanism. And, according to the result that no desired arylated product was found without bases, the possibility of typical F−C alkylation was excluded because in typical F−C alkylation a Lewis acid is always necessary as catalyst.

Detailed mechanistic insight into this catalytic system led to the proposition that the addition between Cu(I) and heterocycle gave the unstable cationic intermediates **6**, then C_2−H proton was removed by *t*-BuOLi (Scheme 2) to give the organocopper species (**7**).[25] Reaction of **7** with aryl iodide gave a possilble cu(III)−aryl species (**8**), and the desired arylation product was obtained by a reductive elimination from **8**. **8** was proposed to be involved as a key intermediate. Imidazo[2,1-*b*]thiazole contains both a π-deficient ring and a π-excessive ring. **8** formed at C-2 of the π-excessive thiazole ring should be more stable than the copper(III)−aryl species formed at C-5 of the π-deficient imidazole ring. Moreover, the possibility of neighbored-S atom strong concerted coordination made **8** more stable. Futhermore, cu(III)−aryl species from electron-rich aryl iodides were more stable than electron-deficient ones, and as a result, electron-rich aryl iodides gave higher yields than electron-deficient aryl iodide as shown in Table 3. In addition, the better results provided by the aromatic substrate compared to the aliphatic substrate can also be foreseen.

While monitoring the Cu(II)-catalyzed reaction, we observed that the purple reaction solution turned into a brown solution, just as the reaction with Cu(I) salt. This color change phenomenon can be understood on the basis of the catalytic cycle in Scheme 2. Cu(II) was initially transformed to Cu(I) and entered the cycle[13c] to accumulate the reaction. It was also understood that Cu(II) showed somewhat low reactivity relative to Cu(I).

In summary, an efficient, ligandless copper-catalyzed method for the regioselective arylation of imidazo[2,1-*b*]thiazole was first developed. This protocol provided a new avenue for developing C−C bond-forming reactions of fused heteroarene. The best result was obtained with copper(I) catalyst, aryl iodide coupling partner, DMA solvent, and *t*-BuOLi base. Mechanistic investigations of the arylation process were also described. Further research will be focused on alkylation of imidazo[2,1-*b*]thiazole with aliphatic iodide in the presence of Cu(I).

Acknowledgment. We acknowledge support from the Natural Science Foundation of China (Nos. 20932004, 21072093), the National Basic Research Program of China (nos. 2007CB925103, 2011CB808600), the Doctoral Fund of Ministry of Education of China (20090091110017), and the fundamental research funds for the central universities (Nos. 1103020505, 1107020526). We also acknowledge Dr. Shouyun Yu for discussions about the mechanism.

Supporting Information Available. Crystallographic data, experimental procedures, and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.