ORGANIC LETTERS

2012
Vol. 14, No. 7
1688–1691

Direct Arylation of Imidazo[1,2-*a*]pyridine at C-3 with Aryl Iodides, Bromides, and Triflates via Copper(I)-Catalyzed C−H Bond Functionalization

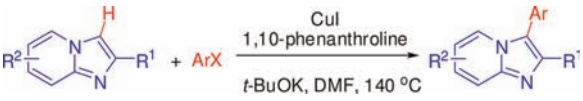
Hua Cao,*,† Haiying Zhan,† Yuanguang Lin,† Xiulian Lin,† Zuodong Du,† and Huanfeng Jiang*,‡

School of Chemistry and Chemical Engineering, Guangdong Pharmaceutical University, Guangzhou 510006, P. R. China, and School of Chemistry and Chemical Engineering, South China University of Technology, Guangzhou 510640, P. R. China

hua.cao@mail.scut.edu.cn; jianghf@scut.edu.cn

Received January 29, 2012

ABSTRACT



A convenient method for the copper(I)-catalyzed arylation of substituted imidazo[1,2-*a*]pyridine has been developed. This method is applicable to a variety of aryl electrophiles, including bromides, iodides, and triflates. It represents the first general process for C-3 arylation of substituted imidazo[1,2-*a*]pyridine by Cu(I) catalysis to construct various functionalized imidazo[1,2-*a*]pyridine core π-systems.

Transition-metal-catalyzed direct C−H functionalization represents a powerful tool for the formation of heteroaromatic molecules via coupling of two different fragments in organic synthesis[1] and has attracted considerable interest[2] among chemists. These heteroaromatic molecules play an important role in predominant structural motifs of many natural products and bioactive molecules.[3] In recent decades, a variety of direct arylation reactions to synthesize these compounds have been developed by C−H bond functionalization due to its high efficiency. In particular, Pd-,[4] Rh-,[5]and Ru-[6]catalyzed direct C−H arylations of heteroaromatic compounds have been extensively studied. Compared with those expensive catalysts, inexpensive Cu,[7] Fe,[8] and Ni[9] salts proved to be highly effective for direct arylation but showed more potential in future development. Although a variety of heterocyclic compounds, such as imidazo[2,1-*b*]thiazole, indolizines, imidazo [1,5-*a*]pyrazines, xanthines, and thiazoles, have been developed to construct heteroaromatic molecules via several metal-catalyzed direct arylations, there is still an intrinsic need to develop and construct new heteroaromatic molecules by Cu-catalyzed direct C−H functionalization under much milder conditions and simpler catalytic system.[10]

† Guangdong Pharmaceutical University.
‡ South China University of Technology.

(1) (a) Ackermann, L.; Vicente, R. *Top. Curr. Chem.* **2010**, *292*, 211–229. (b) Daugulis, O.; Do, H. Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074–1086. (c) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 211–241. (d) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238.

(2) (a) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173–1193. (b) Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 3850–3850. (c) Wang, X.; Leow, D.; Yu, J. Q. *J. Am. Chem. Soc.* **2011**, *133*, 13864–13867.

(3) (a) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359–1469. (b) Corbet, J. P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651–2710.

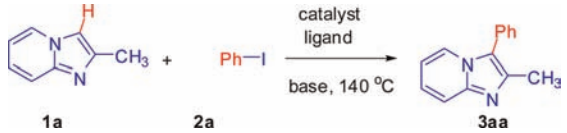
(4) (a) Kirchberg, S.; Tani, S.; Ueda, K.; Yamaguchi, J.; Studer, A.; Itami, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 2387–2391. (b) Ioannidou, H. A.; Koutentis, P. A. *Org. Lett.* **2011**, *13*, 1510–1513. (c) Tamba, S.; Okubo, Y.; Tanaka, S.; Monguchi, D.; Mori, A. *J. Org. Chem.* **2010**, *75*, 6998–7001. (d) Caron, L.; Campeau, L.-C.; Fagnou, K. *Org. Lett.* **2008**, *10*, 4533–4536. (e) McClure, M. S.; Glover, B.; McSorley, E.; Millar, A.; Osterhout, M. H.; Roschangar, F. *Org. Lett.* **2001**, *3*, 1677–1680. (f) Kobayashi, K.; Sugie, A.; Takahashi, M.; Masui, K.; Mori, A. *Org. Lett.* **2005**, *7*, 5083–5085. (g) Daugulis, O.; Zaitsev, V. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4046–4048. (h) Campeau, L. C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020–18021. (i) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050–8057. (j) Leclerc, J. P.; Fagnou, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 7781–7786. (k) Nadres, E. T.; Lazareva, A.; Daugulis, O. *J. Org. Chem.* **2011**, *76*, 471–483.

10.1021/ol300232a
Published on Web 03/14/2012

In contrast, imidazo[1,2-*a*]pyridine derivatives as important fine chemicals have been found to be key structural units in many natural products and drugs and exhibited a wide range of biological activities,[11] such as zolpidem, zolimidine, and alpidem. Thus, the development of an efficient transformation to form novel imidazo[1,2-*a*]pyridine derivatives is a long-standing and challenging goal of organic chemists. To the best of our knowledge, there has been no report of a Cu(I)-catalyzed example of direct arylation of the imidazo[1,2-*a*]pyridine.

2-Methylimidazo[1,2-*a*]pyridine **1a** and iodobenzene **2a** were chosen as model substrates to optimize the reaction conditions. Without any ligand, treatment of **1a** with **2a** using Cs_2CO_3 as the base and CuCl as the copper source in DMF afforded very poor conversion, yielding only 5% of **3aa** (Table 1, entry 1). In the absence of base, reaction fails completely (entry 2). The desired product **3aa** was obtained in 25% yield, when the reaction was carried out in the presence of CuCl as the catalyst, PPh_3 as the ligand, and Cs_2CO_3 as the base at 140 °C for 24 h (entry 3). Other Cu(I) catalysts, such as CuBr, CuI, CuCN, were examined at 140 °C for 24 h (entries 4−6). Excitingly, CuI proved to be an ideal choice among the catalysts investigated. Subsequently, our study focused on the arylation of **1a** by testing various ligands, such as PBu_3, Phen, pyridine, Bpy, DMEDA, TMEDA, and DABCO (entries 7−13).The use of Phen as a ligand significantly improved the catalytic efficiency. Bases such as Cs_2CO_3, K_2CO_3, *t*-BuOLi, *t*-BuOK, and K_3PO_4 were found to facilitate this coupling reaction, and among them *t*-BuOK was the best (entries 14−17). After a variety of solvents were examined, such as DMF, NMP, DMA, and toluene, DMF was clearly the best solvent system (entries 18−20). These preliminary results revealed that Phen acts as a good ligand with optimum conditions which include the presence of *t*-BuOK and CuI as the copper source in DMF solvent at 140 °C for 24 h. The results proved that the conditions previously reported by Daugulis are optimal for direct arylation.

Table 1. Optimization of Reaction Conditions [a]



1a 2a 3aa

entry	cat.	ligand[b]	base	solvent	yield (%)[c]
1	CuCl	–	Cs_2CO_3	DMF	5
2	CuCl	PPh_3	–	DMF	–
3	CuCl	PPh_3	Cs_2CO_3	DMF	25
4	CuBr	PPh_3	Cs_2CO_3	DMF	22
5	CuI	PPh_3	Cs_2CO_3	DMF	39
6	CuCN	PPh_3	Cs_2CO_3	DMF	35
7	CuI	PBu_3	Cs_2CO_3	DMF	36
8	CuI	Phen	Cs_2CO_3	DMF	70
9	CuI	pyridine	Cs_2CO_3	DMF	43
10	CuI	Bpy	Cs_2CO_3	DMF	58
11	CuI	DMEDA	Cs_2CO_3	DMF	56
12	CuI	TMEDA	Cs_2CO_3	DMF	21
13	CuI	DABCO	Cs_2CO_3	DMF	17
14	CuI	Phen	K_2CO_3	DMF	73
15	CuI	Phen	*t*-BuOLi	DMF	86
16	CuI	Phen	*t*-BuOK	DMF	92(87)[d]
17	CuI	Phen	K_3PO_4	DMF	41
18	CuI	Phen	*t*-BuOK	DMA	86
19	CuI	Phen	*t*-BuOK	NMP	85
20	CuI	Phen	*t*-BuOK	toluene	74

[a] Reaction conditions: **1a** (1 mmol), **2a** (1.5 mmol), CuI (5 mol %), ligand (10 mol %), and base (2.5 mmol) in 2 mL of solvent at 140 °C for 24 h. [b] Phen = 1,10-phenanthroline; Bpy = 2,2′-bipyridine; DMEDA = *N*,*N*′-dimethylethylene diamine; TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylene diamine; DABCO = 1,4-diazabicyclo[2.2.2]octane. [c] GC yield. [d] Isolated yield.

With the establishment of a viable reaction system, the scope of this coupling reaction was further expanded and the results are summarized in Table 2. To explore the scope of the arylation reaction, a variety of different imidazo[1,2-*a*]pyridines (**1a**−**1d**) and diverse aryl iodides (**2a**−**2p**) were examined under optimal conditions to form the corresponding product. First, by using **1a** as a fixed substrate, we carried out the arylation of **1a** with various types of aryl iodides. From Table 2, it was found that the reaction conditions were useful for **2a**−**2o** and in most cases the corresponding products **3aa**−**3ao** were obtained in moderate to good yields (entries 1−15). The results clearly indicate that this protocol is general and applicable for

(5) (a) Berman, A. M.; Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 14926–14927. (b) Lewis, J. C.; Berman, A. M.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 2493–2500. (c) Wiedemann, S. H.; Lewis, J. C.; Ellman, J. A.; Bergman, R. G. *J. Am. Chem. Soc.* **2006**, *128*, 2452–2462. (d) Lewis, J. C.; Wu, J. Y.; Bergman, R. G.; Ellman, J. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1589–1591.

(6) (a) Stefane, B.; Fabris, J.; Požzgan, F. *Eur. J. Org. Chem.* **2011**, 3474–3481. (b) Arockiam, P.; Poirier, V.; Fischmeister, C.; Bruneau, C.; Dixneuf, P. H. *Green Chem.* **2009**, *11*, 1871–1875. (c) Özdemir, I.; Demir, S.; Cetinkaya, B.; Gourlaouen, C.; Maseras, F.; Bruneau, C.; Dixneuf, P. H. *J. Am. Chem. Soc.* **2008**, *130*, 1156–1157. (d) Ackermann, L. *Org. Lett.* **2005**, *7*, 3123–3125. (e) Ackermann, L.; Althammer, A.; Born, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 2619–2622. (f) Ackermann, L.; Mulzer, M. *Org. Lett.* **2008**, *10*, 5043–5045.

(7) (a) Alvarado, J.; Do, H. Q.; Daugulis, O.; Marsden, P. C.; Ellman, J. A. *Org. Synth.* **2011**, *87*, 184–191. (b) Do, H. Q.; Daugulis, O. *J. Am. Chem. Soc.* **2011**, *133*, 13577–13586. (c) Popov, I.; Lindeman, S.; Daugulis, O. *J. Am. Chem. Soc.* **2011**, *133*, 9286–9289. (d) Truong, T.; Daugulis, O. *J. Am. Chem. Soc.* **2011**, *133*, 4243–4245. (e) Do, H. Q.; Daugulis, O. *Org. Lett.* **2010**, *12*, 2517–2519. (f) Kawano, T.; Yoshizumi, T.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2009**, *11*, 3072–3075. (g) Huang, G.; Sun, H.; Qiu, X.; Jin, C.; Lin, C.; Shen, Y.; Jiang, J.; Wang, L. *Org. Lett.* **2011**, *13*, 5224–5227. (h) Do, H. Q.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 12404–12405.

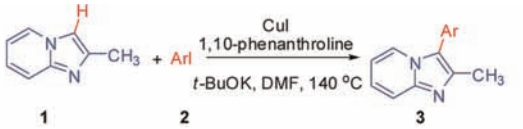
(8) (a) Vallee, F.; Mousseau, J. J.; Charette, A. B. *J. Am. Chem. Soc.* **2010**, *132*, 1514–1516. (b) Yoshikai, N.; Matsumoto, A.; Norinder, J.; Nakamura, E. *Angew. Chem., Int. Ed.* **2009**, *48*, 2925–2928. (c) Wen, J.; Zhang, J.; Chen, S. Y.; Li, J.; Yu, X. Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 8897–8900.

(9) (a) Hachiya, H.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 2202–2205. (b) Hachiya, H.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2009**, *11*, 1737–1740.

(10) Rout, L.; Regati, S.; Zhao, C. G. *Adv. Synth. Catal.* **2011**, *353*, 3340–3346.

(11) (a) Husinec, S.; Markovic, R.; Petkovic, M.; Nasufovic, V.; Savic, V. *Org. Lett.* **2011**, *13*, 2286–2289. (b) Trapani, G.; Franco, M.; Latrofa, A.; Ricciardi, L.; Carotti, A.; Serra, M.; Sanna, E.; Biggio, G.; Liso, G. *J. Med. Chem.* **1999**, *42*, 3934–3941. (c) Linton, A.; Kang, P.; Ornelas, M.; Kephart, S.; Hu, Q.; Pairish, M.; Jiang, Y.; Guo, C. *J. Med. Chem.* **2011**, *54*, 7705–7712. (d) Dai, W.; Petersen, J. L.; Wang, K. K. *J. Org. Chem.* **2005**, *70*, 6647–6650. (e) Toure, B. B.; Lane, B. S.; Sames, D. *Org. Lett.* **2006**, *8*, 1979–1982.

Table 2. Direct Arylation of Substituted Imidazo[1,2-*a*]pyridine with Aryl Iodides[a]



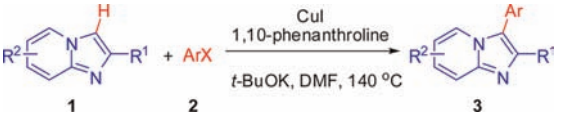
entry	1	2	3	yields[b]
1	1a	2a	3aa	87
2	1a	2b	3ab	83
3	1a	2c	3ac	86
4	1a	2d	3ad	89
5	1a	2e	3ae	84
6	1a	2f	3af	83
7	1a	2g	3ag	81
8	1a	2h	3ah	87
9	1a	2i	3ai	84
10	1a	2j	3aj	86
11	1a	2k	3ak	85
12	1a	2l	3al	88
13	1a	2m	3am	84
14	1a	2n	3an	89
15	1a	2o	3ao	72
16	1b	2a	3ba	82
17	1b	2c	3bc	84
18	1b	2e	3be	79
19	1b	2p	3bp	82
20	1b	2l	3bl	80
21	1b	2m	3bm	77
22	1c	2c	3cc	86
23	1c	2g	3cg	88
24	1c	2j	3cj	86
25	1c	2l	3cl	84
26	1d	2l	3dl	83
27	1e	2q	3dq	80
28	1f	2a	3fa	89
29	1f	2g	3fg	86
30	1f	2r	3fa	-

[a] Reaction conditions: **1** (1 mmol), **2** (1.5 mmol), CuI (5 mol %), 1,10-phenanthroline (10 mol %), and *t*-BuOK (2.5 mmol) in DMF (2 mL) at 140 °C for 24 h. [b] Isolated yield.

reactions of a wide variety of electron-rich and -deficient aryl iodides. It is noteworthy that the present strategy was tolerant of many other functional groups including *o*-F, *m*-F, *p*-F, and *p*-CN, (entries 9−11, 15). Also this arylation is less sensitive to steric factors and gives good yields which has been evident in all ortho-substituted iodoarenes (entries 2, 7, 13). Furthermore, other different substituted imidazo[1,2-*a*]pyridines, such as 2-(trifluoromethyl)imidazo[1,2-*a*]pyridine (**1b**), 6-chloro-2-methylimidazo[1,2-*a*]pyridine (**1c**), ethyl 5-methylimidazo[1,2-*a*]pyridine-2-carboxylate (**1d**), ethyl imidazo[1,2-*a*]pyridine-2-carboxylate (**1e**), and 2-phenylimidazo[1,2-*a*]pyridine (**1f**), were also tested and coupled with aryl iodides to give the corresponding products in good yields. From Table 2, it is observed that this transformation occurs smoothly. Also this process is applicable for arylation of a variety of electron-deficient groups at C-2, such as $-CF_3$ and $-CO_2Et$. However, the corresponding product **3fr** was not detected, when the arylation of **1f** with **2r** was carried out.

We also applied these direct arylation conditions to other phenyl electrophiles, such as aryl bromides, triflates. As shown in Table 3, we are pleased to find that the aryl bromides coupled with **1a**, **1b**, or **1c** smoothly to afford the expected products in good yields under the optimal conditions (entries 1−11). To our surprise, the arylation of the triflates, such as phenyl triflate and *p*-tolyl triflate, with **1a** or **1b** also reacted to give the corresponding product **3aa**, **3ad**, **3bc** in moderate to good yields (entries 1, 3, 8). All of these

Table 3. Arylation of **1** with Aryl Bromides or Triflates[a]



entry	1	ArX	product	yield (%)[b]
1	**1a**	X = Br, OTf	**3aa**	81 (76)[c]
2	**1a**	X = Br	**3ac**	79
3	**1a**	X = Br, OTf	**3ad**	84 (81)
4	**1a**	X = Br	**3af**	77
5	**1a**	X = Br	**3ag**	72
7	**1a**	X = Br	**3ah**	85
7	**1a**	X = Br	**3ak**	81
8	**1b**	X = Br, OTf	**3bc**	78 (75)[c]
9	**1b**	X = Br	**3be**	76
10	**1c**	X = Br	**3cc**	83

[a] Reaction conditions: **1** (1 mmol), **2** (1.5 mmol), CuI (5 mol %),1,10-phenanthroline (10 mol %), and *t*-BuOK (2.5 mmol) in DMF (2 mL) at 140 °C for 24 h. [b] Isolated yield. [c] Using triflates as substrates.

results in Tables 2 and 3 demonstrate clearly that this copper(I) catalytic systems are applicable to a variety of aryl electrophiles, including bromides, iodides, and triflates.

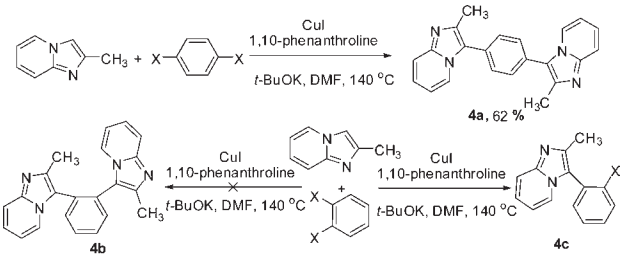
Finally, we attempted to construct more complex imidazo[1,2-*a*]pyridine derivatives by coupling **1a** with 1,4-diiodobenzene, 1,4-dibromobenzene, 1,2-diiodobenzene, and 1,2-dibromobenzene (Scheme 1). Interestingly, the desired product 1,4-bis(2-methylimidazo[1,2-*a*]pyridin-3-yl)-benzene **4a** was formed, when the reaction was carried out by using 1,4-diiodobenzene or 1,4-dibromobenzene as the substrate. However, when 1,2-diiodobenzene or 1,2-dibromobenzene was used as the substrate, the target compound **4b** was not detected and trace amounts of product **4c** was detected by GC-MS.

A proposed mechanism is described in Scheme 2. The mechanism was consistent with previous studies on the arylation of heterocycles.[12] First, deprotonation utilizing *t*-BuOK would generate intermediate **A**. And then transmetalation to copper formed the intermediate **B**, which possibly would then undergo PhI reversible oxidative addition to give the intermediate **C**. Finally intermediate **C** underwent reductive elimination to give the product **3aa** and released the Cu(I) catalyst.

In conclusion, we have developed an inexpensive copper(I) catalytic system for the efficient direct arylation of substituted imidazo[1,2-*a*]pyridines (**1a**−**1f**) with diverse aryl iodides, aryl bromides, and triflates to give rise to the corresponding π-conjugated compounds. This transformation provides a new avenue for developing C−C

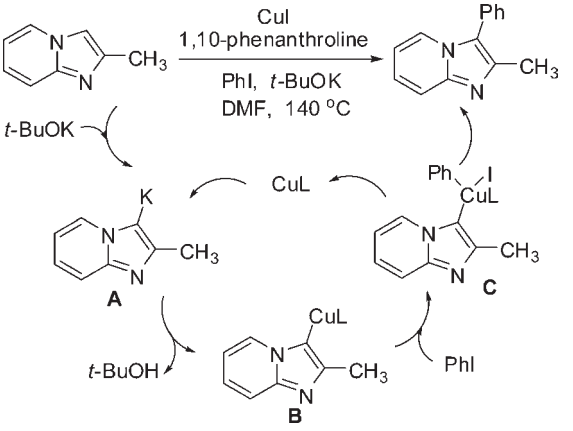
(12) Do, H. Q.; Khan, R. M. K.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 15185–15192.

Scheme 1. Arylation of **1a** with Aryl Dihalides



X=Br, I; Reaction condition: **1a** (1.5 mmol), Aryl halides (1.0 mmol); Isolated yields

Scheme 2. Proposed Mechanism for CuI-Catalyzed Arylation



bond-forming processes of multisubstituted imidazo[1,2-*a*] pyridine which is a common structural motif in natural products and pharmaceuticals. The advantage of this arylation is the usage of inexpensive copper, rather than expensive palladium, as a catalyst with better yields.

Acknowledgment. The work was financially supported by the Foundation for Distinguished Young Talentsin Higher Education of Guangdong, China (LYM11083), National Natural Science Foundation of China (20932002 and 21172076), National Basic Research Program of China (973 Program) (2011CB808600), Doctoral Fund of the Ministry of Education of China (20090172110014), and Guangdong Natural Science Foundation (10351064101000000).

Supporting Information Available. Scheme 1, experimental procedure and characterization of compounds **3aa**−**3fg**, **4a**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.