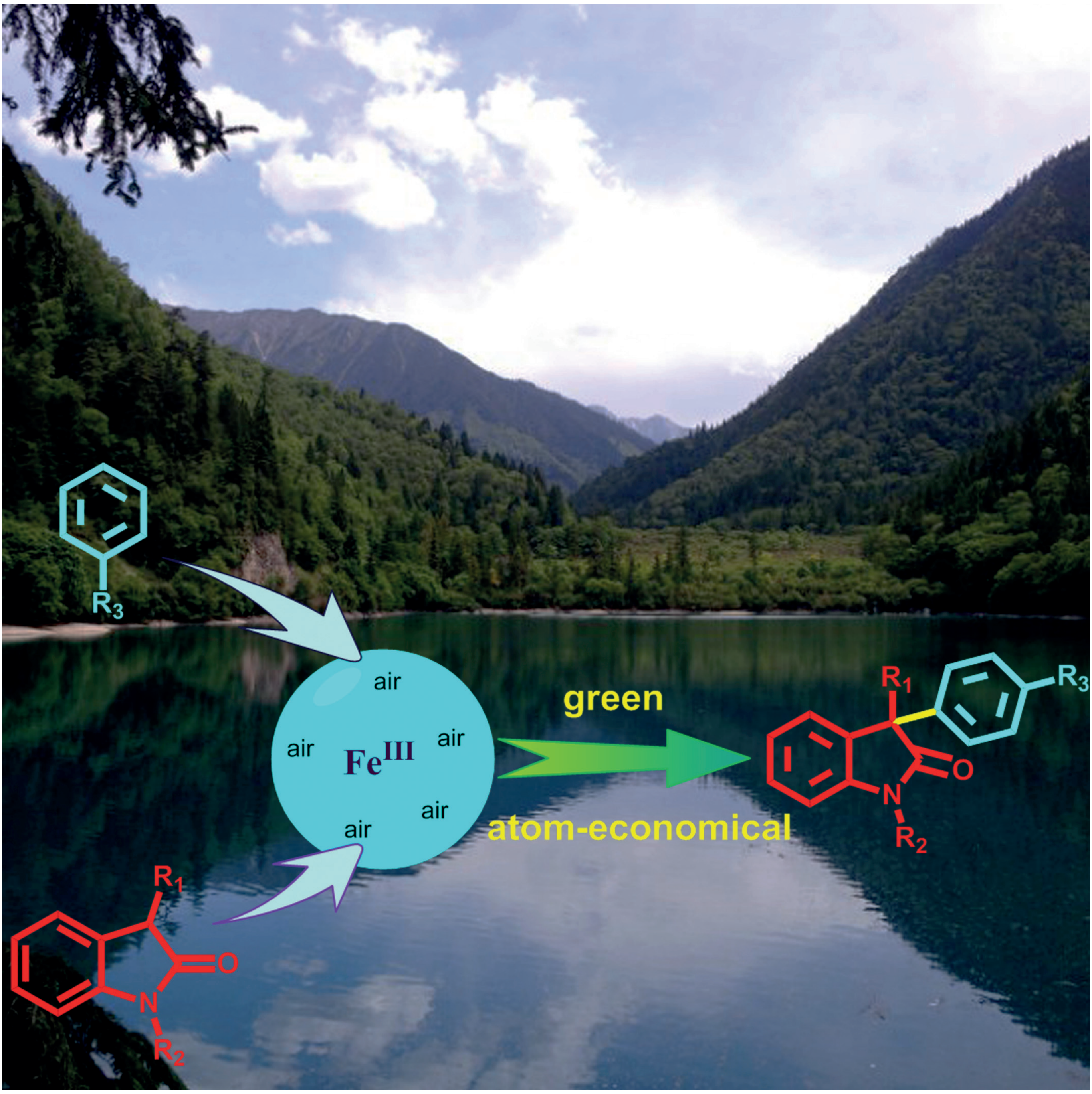
ChemPubSoc Europe
DOI: 10.1002/chem.201502519
CHEMISTRY
A European Journal
Communication

C−H Functionalization

Fe^{III}-Catalyzed Cross-Dehydrogenative Arylation (CDA) between Oxindoles and Arenes under an Air Atmosphere

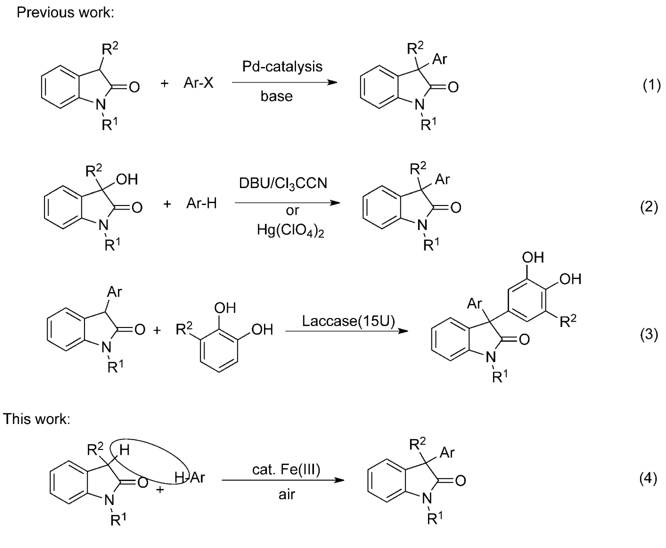
Hong-Ru Wu,[a, b] Hong-Yan Huang,[a, b] Chuan-Li Ren,[a, b] Li Liu,*[a] Dong Wang,[a] and Chao-Jun Li*[c]



Abstract: An efficient Fe^{III}-catalyzed cross-dehydrogenative arylation (CDA) of 3-substituted oxindoles with activated arenes under an air atmosphere was developed to provide 3,3′-disubstituted oxindoles in good yields.

Direct C–H functionalization to construct C–C bonds plays an important role in synthetic organic chemistry.[1] Among the methods employed, cross-dehydrogenative coupling (CDC) through direct C–H functionalization enhances synthetic efficiency—an inherent endeavor of Green Chemistry.[2] Although, the cross-coupling reaction often requires appropriate oxidants and efficient transition-metal catalysts such as palladium, ruthenium, and copper reagents.[2,3] Iron, being one of the most abundant metals, is particularly attractive for such reactions because of its low price, nontoxicity, and environmentally benign character. Indeed a considerable effort has been directed towards iron-catalyzed cross-coupling reactions through C–H bond functionalization.[4] On the other hand, the use of sacrificial oxidants such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), Oxone, $PhI(OAc)_2$, *tert*-tutyl hydroperoxide (TBHP) generates unwanted waste.[2,3] Nevertheless, dioxygen is a more economical and green oxidant because it produces water as the only byproduct, and therefore has attracted much attention in CDC reactions recently.[5]

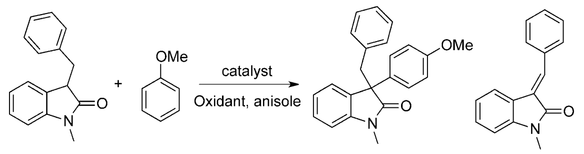
3,3′-Disubstituted oxindoles exist in a large number of natural products and biological compounds with pharmacological activities.[6] The coupling of oxindole derivatives with various aromatic compounds has become an important method to prepare 3-aryloxindoles (Scheme 1). These include: 1) a palladium-[7] or phase-transfer-agent[8]-catalyzed cross-coupling of 3-aryl-2-oxindole with aryl halides [Eq. (1)]; 2) the Friedel–Crafts reaction of 3-hydroxyl-oxindoles with activated arene mediated by a strong base (1,8-diazabicyclo[5.4.0]undec-7-ene; DBU) or catalyzed by $Hg(ClO_4)_2{\cdot}3H_2O$ to afford 3-aryloxindoles[9] [Eq. (2)]; 3) a laccase-catalyzed 3-arylation of 3-substituted oxindoles recently reported by Pietruszka and Wang,[10] in which the arene employed was limited to catechols [Eq. (3)]. Herein, we report an Fe^{III}-catalyzed cross-dehydrogenative arylation (CDA) between 3-substituted oxindoles and activated arenes under an air atmosphere for the rapid synthesis of 3,3′-disubstituted oxindoles [Eq. (4)].



Scheme 1. 3-Arylation of oxindoles.

To begin our study, we chose the reaction of *N*-methyl-3-benzyl-2-oxindole (**1a**) with anisole (**2a**) in anisole as a model reaction. The results are listed in Table 1. In the absence of any oxidant under a nitrogen atmosphere, the cross-coupling product **3a** was obtained in 90% yield, but required 200 mol% of the $FeCl_3$ catalyst (Table 1, entry 1). When the catalyst loading was decreased to 20 mol%, the yield of **3a** also decreased to 20% (Table 1, entry 2). The addition of DDQ into the reaction

Table 1. The dehydrogenative arylation of **1a** with **2a**.[a]



1a **2a** **3a** **4**

Entry	Catalyst (mol%)	Oxidant	T [°C]	t [h]	Yield [%][b]
1	$FeCl_3$ (200)	–[c]	120	5	90
2	$FeCl_3$ (20)	–[c]	120	3	20
3	$FeCl_3$(20)	DDQ[d]	120	1.5	72[e]
4	$FeCl_3$ (20)	O_2	120	8	56
5	$FeCl_3$ (20)	air	120	8	78
6	$FeBr_3$(20)	O_2	120	8	80
7	$FeBr_3$(20)	air	120	3	89
8	$Fe_2(SO_4)_3$ (20)	air	120	24	29
9	$FeCl_2$ (20)	air	120	24	59
10	$Ce(SO_4)_2$ (20)	air	120	24	0
11	$Cu(OTf)_2$ (20)	air	120	6	53
12	$CuBr_2$(20)	air	120	24	51
13	$FeBr_3$ (10)	air	120	4.5	88
14	$FeBr_3$ (5)	air	120	8	80
15	$FeBr_3$(20)	air	100	18	87
16	$FeBr_3$(20)	air	80	40	80

[a] The reaction of **1** (0.2 mmol) in the presence of a catalyst in anisole (3 mL) at given temperature. [b] Yield was determined by ^1H NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard. [c] Under an N_2 atmosphere. [d] 200 mol%. [e] The β-hydrogen elimination product **4** was detected (28%).

---

[a] *H.-R. Wu, H.-Y. Huang, Dr. C.-L. Ren, Prof. Dr. L. Liu, Prof. D. Wang*
Beijing National Laboratory for Molecular Sciences (BNLMS)
CAS Key Laboratory of Molecular Recognition and Function
Institute of Chemistry, Chinese Academy of Sciences
Beijing 100190 (P. R. China)
E-mail: lliu@iccas.ac.cn

[b] *H.-R. Wu, H.-Y. Huang, Dr. C.-L. Ren*
University of Chinese Academy of Sciences, Beijing 100049 (P. R. China)

[c] *Prof. Dr. C.-J. Li*
Department of Chemistry, McGill University
801 Sherbrooke Street West, Montreal, PQ, H3A 0B8 (Canada)
E-mail: cj.li@mcgill.ca

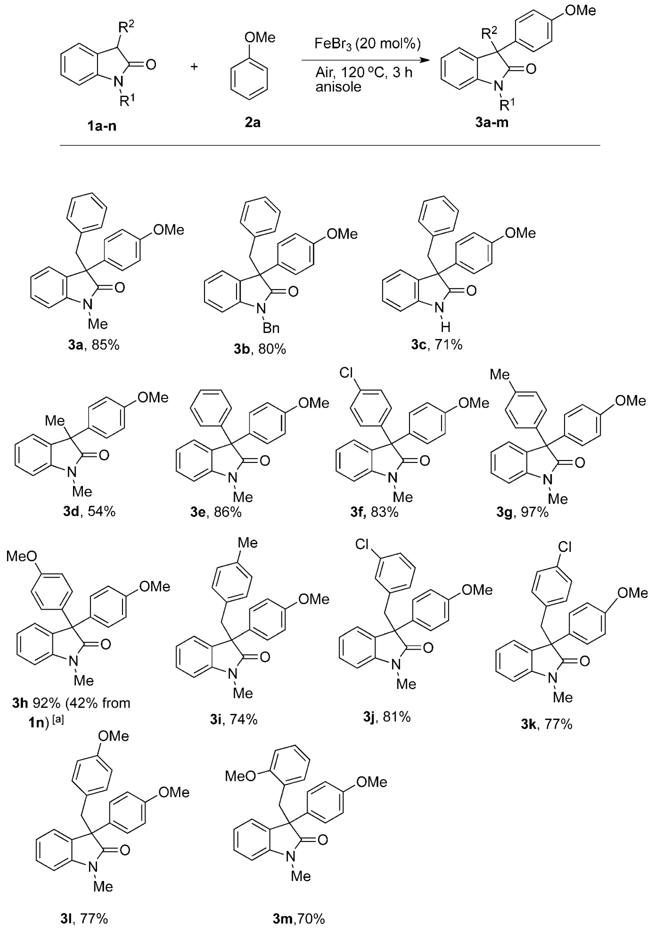
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201502519.

afforded **3a** in 72% yield together with the compound **4** in 28% (Table 1, entry 3).

Treatment of **1a** in the presence of 20 mol% of $FeCl_3$ in anisole (3 mL) at 120 °C for 8 h under an oxygen atmosphere led to the desired product **3a** in 56% yield (Table 1, entry 4). Gratifyingly, the yield of **3a** increased significantly to 78% when the reaction was performed under air (Table 1, entry 5). Replacing the $FeCl_3$ catalyst by $FeBr_3$ gave better results; the yield of **3a** rose to 80% and 89%, under an oxygen atmosphere and under air, respectively (Table 1, entries 6 and 7). Interestingly, although there are two possible reaction sites, namely the *para*- and *ortho*-positions of the phenyl group of anisole, the product **3a** shows an exclusive *para*-regioselectivity (see the Supporting Information for X-ray crystal structure analysis).

After examining a series of iron and copper salts it was found that $FeBr_3$ was the most effective (Table 1, entries 8–12). Further studies revealed that varying the amount of $FeBr_3$ used had little effect on the product yields of **3a** and the optimum results were obtained when the reaction was conducted at 120 °C (Table 1, entry 7 versus 13–16).

Under the optimal conditions, several 2-oxindoles with different *N*-substituents were allowed to react with **2a** to give the corresponding products **3a**–**c** (Scheme 2). It was noted that the *N*-substituents had little effect on the product yields. For example, both the *N*-methyl- and *N*-benzyl-substituted oxindoles gave the corresponding products, **3a** and **3b**, in a range of 80–85% yield. Unsubstituted 2-oxindole also worked to give **3c** in a good yield.



Scheme 2. Scope of oxindoles; yields reported are of isolated products; [a] yield reported in parentheses was obtained from the reaction of *N*-methyl-2-oxindole (R^2 = H; **1n**) with anisole.

Next we investigated the scope of the 3-substituted *N*-methyl oxindoles (Scheme 2). *N*-Methyl-3-methyl-oxindole gave the desired product **3d** in 54% yield. However, when 3-methyl was replaced with a phenyl group the reactivity increased and **3e** was obtained in 86% yield. Electron-donating substituents at the *para*-position of the 3-phenyl ring (R^2 = 4-CH_3Ph (**3g**; 97%) and CH_3OPh (**3h**; 92%)) gave higher yields compared with an electron-withdrawing substituent (R^2 = 4-ClPh (**3f**; 83%). For the cases where R^2 is a benzyl group with different substituents at the *ortho*-, *meta*-, and *para*-positions of the phenyl ring, the products **3i**–**3m** were obtained in good yields (70–81%). *N*-Methyl-2-oxindole (R^2 = H) (**1n**) was also compatible under the reaction conditions, albeit giving the disubstituted product **3h** in lower yield (42%). When the cyclic ketone, 8-benzylbicyclo[4.2.0]octa-1,3,5-trien-7-one, was used instead of oxindole, no reaction occurred. The X-ray crystal structure of **3j** is shown in Figure 1.[13]

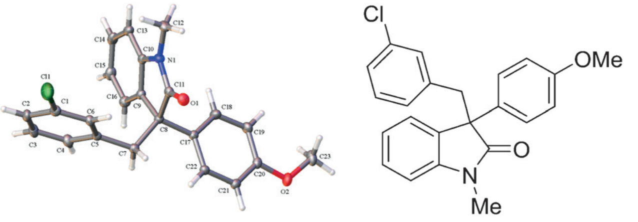
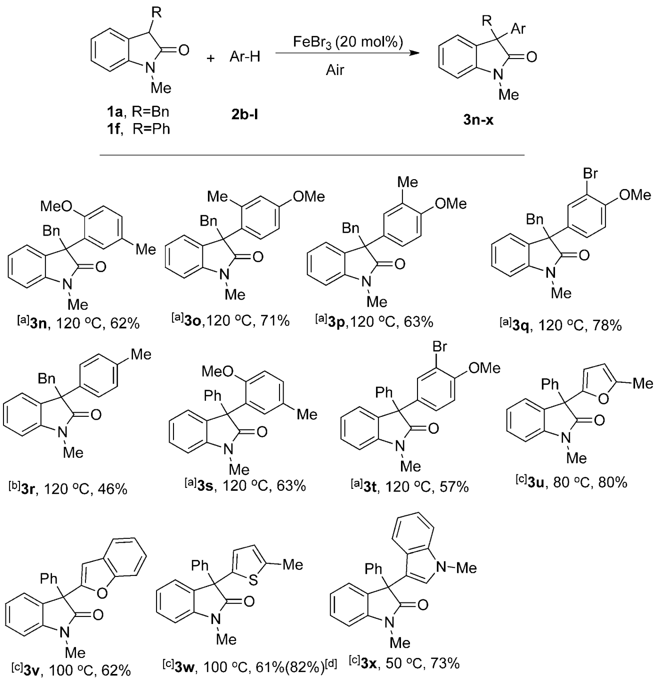


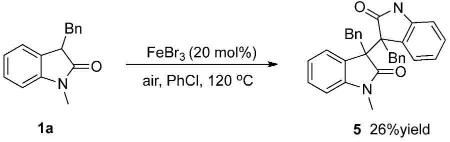
Figure 1. X-ray crystal structure of compound **3j**.

Next, various aromatic compounds were tested in the reaction with **1a** or **1f**, and the resulting CDA products are shown in Scheme 3. Surprisingly, when toluene was used as an arene substrate the desired product **3r** was obtained in only 46% isolated yield, albeit using 200 mol% of $FeCl_3$. With the *para*-position of the phenyl ring blocked by a methyl group, an excellent *ortho*-regioselectivity was observed in the case of the products **3n** and **3s**. More electron-rich heteroaromatic compounds also gave the CDA products **3u**–**3x** in good yields with PhCl as the solvent. Moreover, the reaction temperature could be lowered to 50 °C in a few cases. When dichlorobenzene was used as a solvent, the amount of aromatic compound required could be reduced. The reaction of **1a** (0.2 mmol) with 2-methylthiophene (**2k**) (0.4 mmol) in 1,2-dichlorobenzene (3 mL) provided the coupling product **3w** in 82% yield. When benzene or chlorobenzene was used as the arene substrate, the coupling product was not obtained. It is clear that increasing the electron density on the aromatic ring is beneficial for the reaction, which showed Friedel–Crafts type features. To gain a better understanding of the reaction mechanism, some control experiments were performed. When **1a** was treated in chlorobenzene at 120 °C in the presence of $FeBr_3$ (20 mol%), the dimeric product **5** was isolated in 26%



Scheme 3. Scope of arenes; [a] arene substrate (3 mL) as a solvent; [b] toluene (3 mL) as a solvent and $FeCl_3$ (200 mol %); [c] **1 f** (0.2 mmol) in PhCl (3 mL) and arene substrate (2 mmol); [d] **1 f** (0.2 mmol) in 1,2-dichlorobenzene (3 mL) and arene substrate (0.4 mmol).

yield, but no CDA product was detected (Scheme 4). Based on these findings, a tentative mechanism is proposed (Figure 2). First, the oxindole substrate **1 a** tautomerizes to its enol form **1 a**′ in the presence of $Fe^{III}X_3$, which is easily oxidized to the corresponding radical **A** via a single-electron-transfer (SET), while at the same time Fe^{II} is formed.[4,11,12] Then radical **A** and Fe^{II} are oxidized to the cation species **B** and Fe^{III}, respectively, by air or Fe^{III} under a N_2 atmosphere. Air can be considered as a diluted oxygen, which may be better than oxygen in the reaction, thus avoiding side-reactions. The attack of intermediate **B** at anisole (**2 a**) provides cation intermediate **C**, which following the loss of H^+ affords the desired CDA product **3 a**.



Scheme 4. Control experiment.

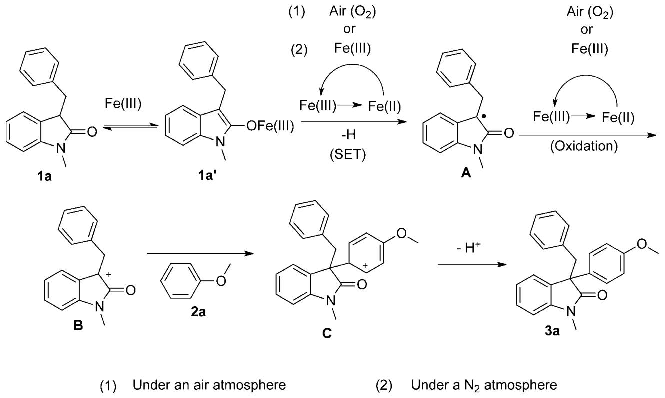


Figure 2. Proposed mechanism for the Fe^{III}-catalyzed CDA reaction of oxindole with arenes.

In summary, we have developed a new and efficient iron-catalyzed cross-dehydrogenative arylation of 3-substituted oxindoles with electron-rich aromatic and heteroaromatic compounds by using aerobic oxygen as an oxidant source. We anticipate that this cross-coupling will find more useful applications in organic synthesis.

Experimental Section

General procedure for the cross-dehydrogenative arylation of *N*-methyl-3-substituted-2-oxindole with anisole: A mixture of *N*-methyl-3-substituted-2-oxindole (0.2 mmol) and $FeBr_3$ (0.04 mmol) in anisole (3 mL) was stirred at 120 °C for 3 h. The mixture was cooled to room temperature, and the anisole was removed under reduced pressure. The residue was purified by flash column chromatography by using ethyl acetate/petroleum ether to afford the desired product.

General procedure for the cross-dehydrogenative arylation of *N*-methyl-3-substituted-2-oxindole with aromatic and heteroaromatic compounds: A mixture of *N*-methyl-3-substituted-2-oxindole **1 a** or **1 f** (0.2 mmol) and $FeBr_3$ (0.04 mmol) in arene substrates **2 b**–**2 h** (3 mL) was stirred at 120 °C for 3 h, while **2 i**–**2 l** (2 mmol) in PhCl (3 mL) were stirred at 80 °C, 100 °C, 100 °C, and 50 °C, respectively. The mixture was cooled to room temperature, and the aromatic or heteroaromatic compounds were removed under reduced pressure. The residue was purified by flash column chromatography by using ethyl acetate/petroleum ether to afford the desired product.

Acknowledgements

We thank the National Natural Science Foundation of China (Nos. 21420102003, 21372224, and 21232008), the Ministry of Science and Technology of China (973 Program 2011CB808600), Shandong Province Independent Innovation and Achievements Transformation Major Project (2014XGC06001), and the Chinese Academy of Sciences for financial support.

Keywords: air · arenes · CH activation · cross-dehydrogenative arylation · iron · oxindoles

[1] For selected examples, see: a) C. Jia, T. Kitamura, Y. Fujiwara, *Acc. Chem. Res.* **2001**, *34*, 633 – 639; b) J. A. Labinger, J. E. Bercaw, *Nature* **2002**, *417*, 507 – 514; c) V. Ritleng, C. Sirlin, M. Pfeffer, *Chem. Rev.* **2002**, *102*, 1731 – 1789; d) F. Kakiuchi, S. Murai, *Acc. Chem. Res.* **2002**, *35*, 826 – 834; e) H. M. L. Davies, R. E. J. Beckwith, *Chem. Rev.* **2003**, *103*, 2861 – 2903; f) K. Godula, D. Sames, *Science* **2006**, *312*, 67 – 72; g) R. G. Bergman, *Nature* **2007**, *446*, 391 – 393; h) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174 – 238; i) H. M. L. Davies, J. R. Manning, *Nature* **2008**, *451*, 417 – 424.

[2] For reviews on CDC reactions, see: a) C. S. Yeung, V. M. Dong, *Chem. Rev.* **2011**, *111*, 1215 – 1292; b) S. A. Girard, T. Knauber, C.-J. Li, *Angew.*

Chem. Int. Ed. **2014**, *53*, 74 – 100; *Angew. Chem.* **2014**, *126*, 76 – 103; c) C.-J. Li, *Acc. Chem. Res.* **2009**, *42*, 335 – 344; d) C. J. Scheuermann, *Chem. Asian J.* **2010**, *5*, 436 – 451.

[3] For reviews on transition-metal-catalyzed C–H activations, see: a) B.-J. Li, Z.-J. Shi, *Chem. Soc. Rev.* **2012**, *41*, 5588 – 5598; b) J. Wencel-Delord, T. Dröge, F. Liu, F. Glorius, *Chem. Soc. Rev.* **2011**, *40*, 4740 – 4761; c) C. L. Sun, B.-J. Li, Z.-J. Shi, *Chem. Commun.* **2010**, *46*, 677 – 685; d) R. Giri, B.-F. Shi, K. M. Engle, N. Maugel, J.-Q. Yu, *Chem. Soc. Rev.* **2009**, *38*, 3242 – 3272; e) M. Lersch, M. Tilset, *Chem. Rev.* **2005**, *105*, 2471 – 2526; see also references [1b,e,g].

[4] Selected examples, see: a) W.-T. Wei, M.-B. Zhou, J.-H. Fan, W. Liu, R.-J. Song, Y. Liu, M. Hu, P. Xie, J.-H. Li, *Angew. Chem. Int. Ed.* **2013**, *52*, 3638 – 3641; *Angew. Chem.* **2013**, *125*, 3726 – 3729; b) F. Jia, Z. Li, *Org. Chem. Front.* **2014**, *1*, 194 – 214 ; c) Y.-Z. Li, B.-J. Li, X.-Y. Lu, S. Lin, Z.-J. Shi, *Angew. Chem. Int. Ed.* **2009**, *48*, 3817 – 3820; *Angew. Chem.* **2009**, *121*, 3875 – 3878; d) C.-L. Sun, B.-J. Li, Z.-J. Shi, *Chem. Rev.* **2011**, *111*, 1293 – 1314.

[5] a) W.-Q. Wu, H.-F. Jiang, *Acc. Chem. Res.* **2012**, *45*, 1736 – 1748. For selected papers, see: b) K. Mochida, K. Kawasumi, Y. Segawa, K. Itami, *J. Am. Chem. Soc.* **2011**, *133*, 10716; c) K.-T. Yip, R. Y. Nimje, M. V. Leskinen, P. M. Pihko, *Chem. Eur. J.* **2012**, *18*, 12590 – 12594; d) A. G. Condie, J. C. Gonzalez-Gomez, C. R. J. Stephenson, *J. Am. Chem. Soc.* **2010**, *132*, 1464 – 1465; e) C. Galli, P. Gentili, O. Lanzalunga, *Angew. Chem. Int. Ed.* **2008**, *47*, 4790 – 4796; *Angew. Chem.* **2008**, *120*, 4868 – 4874; f) J. Maes, T. R. M. Rauws, B. U. W. Maes, *Chem. Eur. J.* **2013**, *19*, 9137 – 9241; g) T. Zhang, W. Bao, *J. Org. Chem.* **2013**, *78*, 1317 – 1322.

[6] a) C. Marti, E. M. Carreira, *Eur. J. Org. Chem.* **2003**, 2209 – 2219; b) C. V. Galliford, K. A. Scheidt, *Angew. Chem. Int. Ed.* **2007**, *46*, 8748 – 8758; *Angew. Chem.* **2007**, *119*, 8902 – 8912; c) B. M. Trost, M. K. Brennan, *Synthesis* **2009**, 3003 – 3025; d) F. Zhou, Y.-L. Liu, J. Zhou, *Adv. Synth. Catal.* **2010**, *352*, 1381 – 1407; e) J. E. M. N. Klein, R. J. K. Taylor, *Eur. J. Org. Chem.* **2011**, 6821 – 6841; f) L. Hong, R. Wang, *Adv. Synth. Catal.* **2013**, *355*, 1023 – 1052.

[7] a) P.-F. Li, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2011**, *50*, 6396 – 6400; *Angew. Chem.* **2011**, *123*, 6520 – 6524; b) A. M. Taylor, R. A. Altman, S. L. Buchwald, *J. Am. Chem. Soc.* **2009**, *131*, 9900 – 9901; c) M. J. Durbin, M. C. Willis, *Org. Lett.* **2008**, *10*, 1413 – 1415; d) Z.-K. Xiao, H.-Y. Yin, L.-X. Shao, *Org. Lett.* **2013**, *15*, 1254 – 1257; e) C.-K. Mai, M. F. Sammons, T. Sammakia, *Org. Lett.* **2010**, *12*, 2306 – 2309.

[8] S. Shirakawa, K. Koga, T. Tokuda, K. Yamamoto, K. Maruoka, *Angew. Chem. Int. Ed.* **2014**, *53*, 6220 – 6223; *Angew. Chem.* **2014**, *126*, 6334 – 6337.

[9] a) C. Piemontesi, Q. Wang, J. Zhu, *Org. Biomol. Chem.* **2013**, *11*, 1533 – 1536; b) F. Zhou, Z.-Y. Cao, J. Zhang, H.-B. Yang, J. Zhou, *Chem. Asian J.* **2012**, *7*, 233 – 241.

[10] J. Pietruszka, C. Wang, *ChemCatChem* **2012**, *4*, 782 – 785.

[11] T. Niwa, S. Ishii, A. Hiramatsu, T. Osawa, *Biosci. Biotechnol. Biochem.* **2003**, *67*, 1870 – 1874.

[12] a) A. Harriman, *J. Phys. Chem.* **1987**, *91*, 6102 – 6104; b) M. Schmittel, U, Baumann, *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 541 – 543; *Angew. Chem.* **1990**, *102*, 571 – 572.

[13] CCDC 1037303 (**3j**) contains the supplementary crystallographic data. These data can be obtained free of charge by The Cambridge Crystallographic Data Centre.

Received: June 29, 2015