C–C Cross-Coupling

International Edition: DOI: 10.1002/anie.201604580
German Edition: DOI: 10.1002/ange.201604580

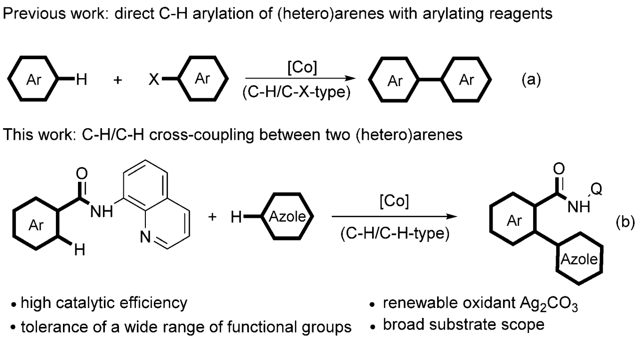
Cobalt-Catalyzed Oxidative C–H/C–H Cross-Coupling between Two Heteroarenes

*Guangying Tan, Shuang He, Xiaolei Huang, Xingrong Liao, Yangyang Cheng, and Jingsong You**

Abstract: *The first example of cobalt-catalyzed oxidative C–H/C–H cross-coupling between two heteroarenes is reported, which exhibits a broad substrate scope and a high tolerance level for sensitive functional groups. When the amount of $Co(OAc)_2 \cdot 4H_2O$ is reduced from 6.0 to 0.5 mol%, an excellent yield is still obtained at an elevated temperature with a prolonged reaction time. The method can be extended to the reaction between an arene and a heteroarene. It is worth noting that the Ag_2CO_3 oxidant is renewable. Preliminary mechanistic studies by radical trapping experiments, hydrogen/deuterium exchange experiments, kinetic isotope effect, electron paramagnetic resonance (EPR), and high resolution mass spectrometry (HRMS) suggest that a single electron transfer (SET) pathway is operative, which is distinctly different from the dual C–H bond activation pathway that the well-described oxidative C–H/C–H cross-coupling reactions between two heteroarenes typically undergo.*

Bi(hetero)aryls are highly important structural motifs distributed in natural products, pharmaceuticals, biologically active molecules, and functional materials.[1] From the viewpoint of step and atom economy, transition-metal-catalyzed oxidative C–H/C–H cross-coupling reactions between two (hetero)arenes offer the most straightforward approach to bi(hetero)aryls, which do not require pre-activated substrates such as (hetero)aryl halides/surrogates and (hetero)aryl organometallic reagents.[2] Despite tremendous efforts over the last decade, such reactions are often performed with expensive and rare second row transition-metal catalysts such as palladium, rhodium, and ruthenium complexes.[3] First row transition metals (iron, cobalt, nickel, and copper) are typically inexpensive and earth-abundant; the replacement of second row transition metals as catalysts with first row transition metals would be revolutionary. Pioneering work in this field has demonstrated that copper enables the oxidative C–H/C–H cross-coupling reaction between two (hetero)arenes.[4]

Cobalt-mediated C–H functionalization dates back to 1955, in which a cobalt-carbonyl-catalyzed *ortho*-carbonylation of azobenzene gave an isoindolinone derivative.[5] Despite this seminal discovery by Murahashi, cobalt-catalyzed C–H functionalization only started to attract attention around 2010.[6,7] Among these transformations, the cobalt-catalyzed C–H arylation of (hetero)arenes, with (hetero)arylation reagents such as (hetero)aryl halides/pseudohalides or organometallic reagents (C–H/C–X-type), has become an area of intense research (Scheme 1a).[8] For example, cobalt catalysts enable the C–H arylation of simple arenes with aryl halides by radical pathways.[8a–c] The C–H arylation of (hetero)arenes with aryl Grignard reagents, aryl chlorides, sulfamates, carbamates, and carboxylates have been established through the cobalt-catalyzed chelation-assisted strategy.[8d–f] However, the cobalt-catalyzed oxidative C–H/C–H cross-coupling between two (hetero)arenes (C–H/C–H-type) is challenging and remains unsolved so far, which is exemplified by recent reports on the cobalt-promoted dimerization of aminoquinoline benzamides and aminoquinoline thiophenecarboxylic acid amides.[9] Herein, we wish to address a solution for this significant challenge (Scheme 1b).



Scheme 1. Evolution of cobalt-catalyzed C–H (hetero)arylation of (hetero)arene. X = Cl, Br, I, MgBr, OR (R = alkyl substituent); Q = 8-quinolinyl.

Over the last decade, *N*,*N*-bidentate directing groups have shown a powerful efficacy in palladium, ruthenium, nickel, copper, and iron-catalyzed C(sp^2)–H and C(sp^3)–H bond functionalization reactions.[4d,10] Very recently, cobalt catalysis assisted by bidentate directing groups was applied in C–H bond activation.[11] Thus, we envisaged that the *N*,*N*-bidentate-assisted strategy could enable cobalt-catalyzed oxidative C–H/C–H cross-coupling between two (hetero)arenes. Our investigation commenced with the reaction between *N*-(quinolin-8-yl)thiophene-2-carboxamide **1a** and benzoxazole **2a** (for optimization details see the Supporting Information, Tables S1–S6). As shown in Table S1

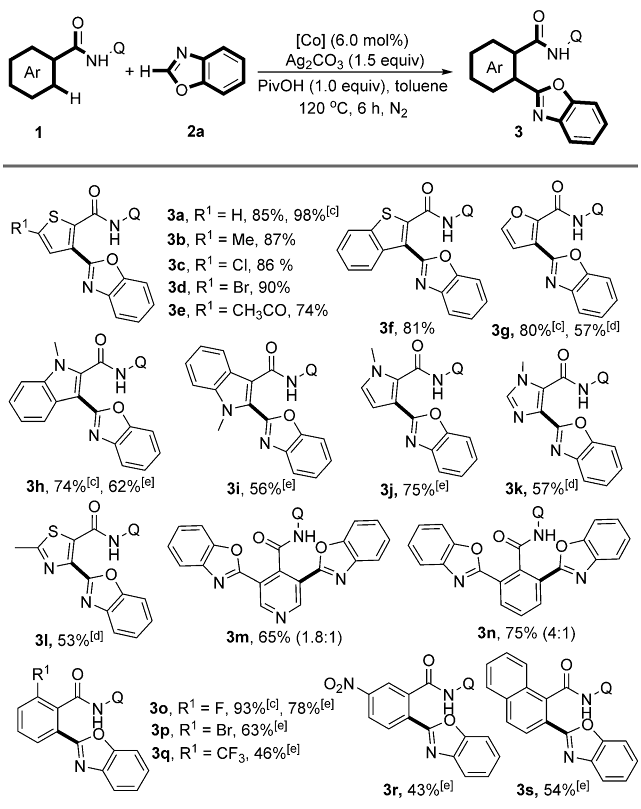
---

[*] G. Tan, S. He, X. Huang, X. Liao, Y. Cheng, Prof. Dr. J. You
Key Laboratory of Green Chemistry and Technology of Ministry of Education, College of Chemistry, Sichuan University
29 Wangjiang Road, Chengdu 610064 (P.R. China)
E-mail: jsyou@scu.edu.cn

Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.201604580.

(Supporting Information), oxidants play a crucial role in the chemoselectivity of cross-coupling over homocoupling. Silver salts are beneficial to the cross-coupling reaction. Using Ag_2CO_3 as the oxidant, the cross-coupled product **3a** was obtained in a 64% yield along with 11% of **3aa** resulting from the homocoupling of **1a**.[12] Replacing silver salts with other oxidants (for example, $Mn(OAc)_3{\cdot}2H_2O$, $K_2S_2O_8$, $PhI(OAc)_2$, $NaClO_3$, Oxone, DTBP, O_2) only gave the homocoupled product **3aa**. Solvents also significantly affect the chemoselectivity (Supporting Information, Table S2). For example, dioxane gave **3aa** in a 46% yield and **3a** was obtained in only a 7% yield. Other cobalt salts, such as $Co(acac)_2$, $CoCl_2$, and $Cp^*Co(CO)I_2$, are less effective than $Co(OAc)_2{\cdot}4H_2O$ (Supporting Information, Table S3). The addition of 1.0 equiv of pivalic acid (PivOH), which acts as both a proton donor and a ligand in the catalytic process, improved the yield to 74% (Supporting Information, Table S4). Finally, the cross-coupled product **3a** was obtained in an 85% yield with only a 4% yield of homocoupled **3aa** under the optimal catalytic system ($Co(OAc)_2{\cdot}4H_2O$ (6 mol%), Ag_2CO_3 (1.5 equiv) and PivOH (1.0 equiv) in toluene at 120°C for 6 h), and no homocoupling of benzoxazole **2a** was observed (Supporting Information, Table S5, entry 3). When the amount of $Co(OAc)_2{\cdot}4H_2O$ was reduced to 0.5 mol%, an excellent yield of 90% was obtained at 140°C for 24 h (Supporting Information, Table S5, entry 11). Interestingly, in the absence of benzoxazole **1a** underwent dimerization to give homocoupled **3aa** in an 84% yield (Supporting Information, Table S6, entry 1), which suggests that the rate of the cross-coupling path is much faster than that of homocoupling of **1a** under our optimized reaction conditions. Moreover, the other directing groups investigated did not lead to any of the desired products (see unreactive substrates **5**–**9**, Part III in the Supporting Information), revealing the significant role of the 8-aminoquinoline-containing secondary amide group.

Table 1: The scope of (hetero)aromatic acid derivatives.[a,b]



[a] **1** (0.2 mmol), **2a** (0.3 mmol, 1.5 equiv) and $Co(OAc)_2{\cdot}4H_2O$ (6.0 mol%) in toluene (0.5 mL) at 120°C for 6 h. [b] Isolated yields. [c] $Co(OAc)_2{\cdot}4H_2O$ (0.5 mol%) and **2a** (3.0 equiv) at 150°C for 24 h. [d] 140°C for 12 h. [e] $Cp^*Co(CO)I_2$ instead of $Co(OAc)_2{\cdot}4H_2O$.

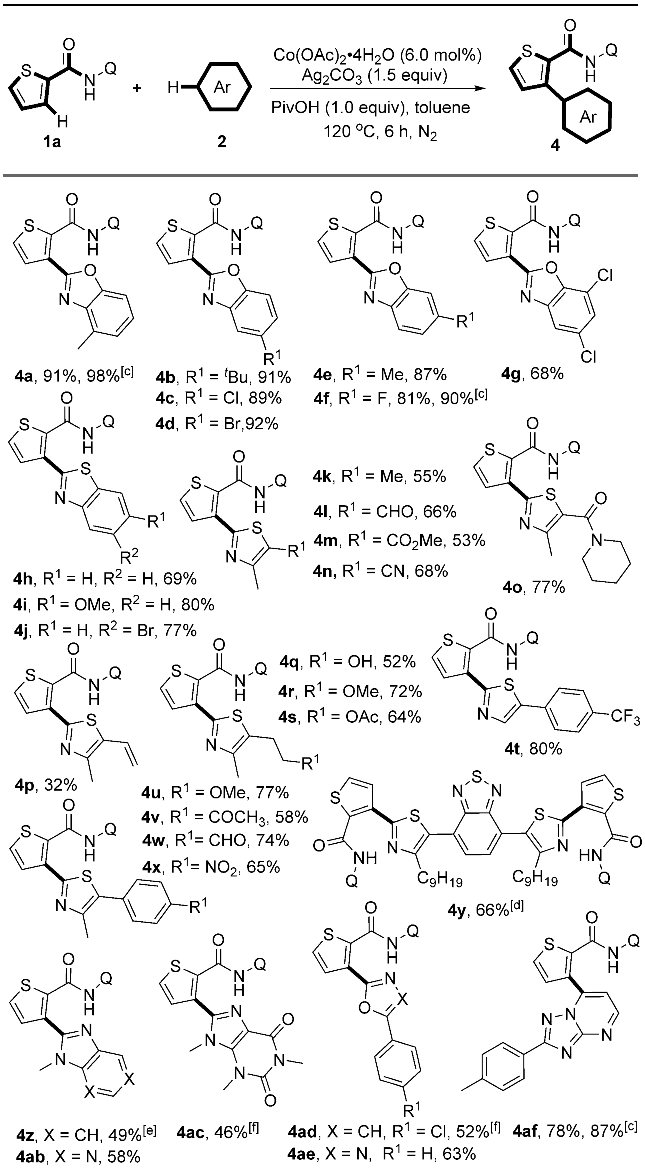
With the optimized conditions in hand, we explored the scope of heteroaromatic acids. As summarized in Table 1, a range of representative heteroarenes, such as thiophene, furan, indole, pyrrole, imidazole, thiazole, and pyridine, underwent smooth coupling with benzoxazole (**2a**), delivering the corresponding biheteroaryls (**3a**–**3m**). The substrates with two potentially reactive sites gave rise to the biheteroarylated products (**3m** and **3n**). The method could be extended to benzoic acids, affording the aryl–heteroaryl skeletons (**3n**–**3s**). For the substrate **1**, the degree of homocoupling is dependent on the reactivity of the substrate itself. In the lower yielding examples, only trace amounts of homocoupled products were observed.

Subsequently, the scope of azoles was examined (Table 2). Benzoxazoles with both electron-withdrawing and electron-donating groups engaged in this reaction with excellent yields (**4a**–**4g**). Benzothiazoles and thiazoles were also compatible with this method (**4h**–**4y**). Especially sensitive functional groups, such as chloro, bromo, formyl, ester, cyano, vinyl, acetyl, nitro, acetoxyl, and even hydroxyl, were well-tolerated under the optimized conditions. Using 4,7-bis(4-nonylthiazol-5-yl)benzo[*c*][1,2,5]thiadiazole **2z** as the coupling partner, the bis-heteroarylated product was obtained in a 66% yield (**4y**). Other azoles, such as imidazoles, purines, caffeine, oxazoles, and 1,3,4-oxadiazoles, reacted with **1a** to give the desired products in moderate yields (**4z**-**4ae**). Furthermore, 2-(*p*-tolyl)-[1,2,4]triazolo[1,5-*a*]pyrimidine underwent arylation at the C7 position to provide **4af** in a 78% yield.[12] Notably, for the acidic C−H azole partner **2**, no homocoupling was observed.

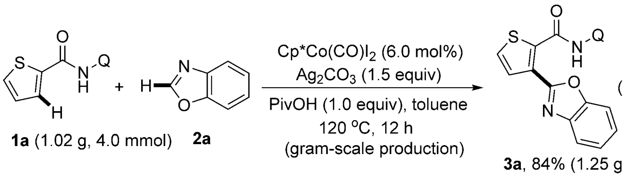
Consultation of Table 2 reveals that the cross-coupling reactions occur at the relatively acidic C−H position of azoles.[13] Benzoxazole ($pKa = 24.8$) exhibits an excellent reactivity. Thiazoles ($pKa \approx 28$) are also compatible with this method. The less acidic *N*-methylbenzimidazole ($pK_a = 32.5$) requires an elevated temperature to deliver the desired product. The acidic C−H bonds of the aforementioned azoles possess pK_a values ranging from approximately 24 to 32. However, pK_a value does not exclusively determine reactivity and does not enable prediction of coupling for other (hetero)arenes. For example, polyfluoroarenes failed to give any desired product.

Considering the synthetic usefulness of the coupling method, we further illustrated the scalability of the reaction. Under the standard conditions, the reaction of **1a** (1.02 g) with **2a** was performed and the desired **3a** was obtained in an 84% yield, which represents a gram-scale preparation [Eq. (1)].

Table 2: The scope of azoles.[a,b]

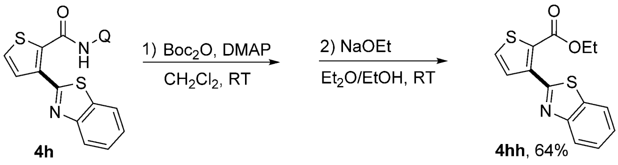


[a] **1a** (0.2 mmol) and **2** (0.3 mmol, 1.5 equiv) in toluene (0.5 mL) at 120 °C for 6 h. [b] Isolated yields. [c] $Co(OAc)_2·4H_2O$ (0.5 mol %) and **2a** (3.0 equiv) at 150 °C for 24 h. [d] **1a** (0.3 mmol) and **2z** (0.1 mmol). [e] 140 °C. [f] 150 °C.



1a (1.02 g, 4.0 mmol) **2a** **3a**, 84% (1.25 g) (1)

Notably, using only 0.5 mol % of $Co(OAc)_2·4H_2O$, the desired **3a** product could also be obtained in a 61 % yield [Eq. (S3)]. Furthermore, the directing group could be removed from the coupled product **4h** [Eq. (2)].[4d]

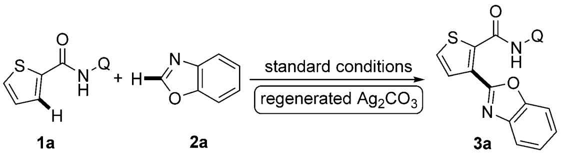


4h **4hh**, 64% (2)

For the sake of reducing cost and waste, we sought to recycle oxidant Ag_2CO_3. To our delight, silver residue could be recycled by simple treatment with HNO_3 and Na_2CO_3 in sequence [Eq. (3)].

$$\boxed{\text{silver residue}} \xrightarrow{HNO_3} AgNO_3 \xrightarrow{Na_2CO_3} \boxed{\text{Regenerated } Ag_2CO_3} \qquad (3)$$

The regenerated Ag_2CO_3 promoted the coupling reaction, affording **3a** in an 81 % yield [Eq. (4)]. It is worth noting that Ag_2CO_3 barely lost activity after a fifth recovery round (Supporting Information, Table S7).



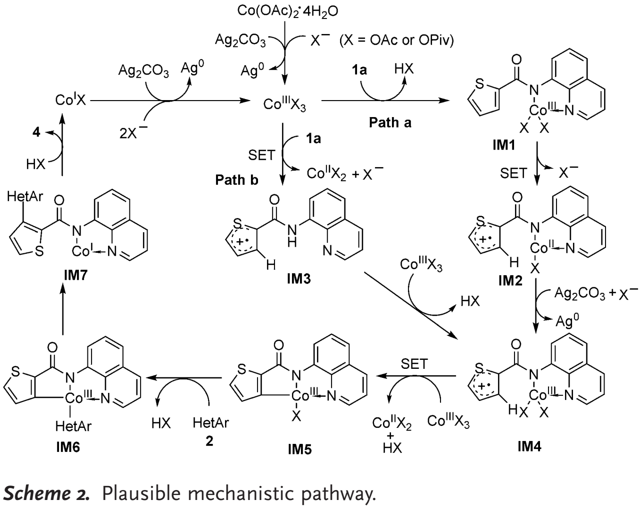
1a **2a** **3a** (4)

the first round recovery: 81% yield of **3a**
the fifth round recovery: 80% yield of **3a**

To gain some insight into the reaction mechanism, hydrogen/deuterium exchange experiments were performed (Supporting Information, Equations (S7)–(S11)). When *N*-(quinolin-8-yl)benzamide **1n** reacted with D_2O (20 equiv) in both the presence and absence of benzoxazole **2a** under the standard conditions for 2 h, deuterated $[D_n]$-**1n** was not obtained (Supporting Information, Equations (S7) and (S11)), suggesting that the cleavage of the C–H bond of *N*-(quinolin-8-yl)benzamide is an irreversible process. While **2a** reacted with D_2O only in the presence of Ag_2CO_3 and PivOH (Supporting Information, Equation (S10)), the H/D exchange ratio of **2a** was 63 %. Under the same conditions, $Co(OAc)_2·4H_2O$ gave only 9 % of deuterated [D]-**2a** (Supporting Information, Equation (S9)). In the presence of cobalt and silver, the H/D exchange ratio of **2a** was 92 % (Supporting Information, Equation (S8)). These results imply that silver salt may serve a key role in the cleavage of the C–H bond of azole[14] and explain the significance of a silver oxidant with respect to product selectivity. However, at the present stage we require clearer evidence to certify the formation of an azole–silver species. Subsequently, kinetic isotope effects (KIE) for both coupling partners were investigated. Two parallel competition reactions between **2a** or [D]-**2a** with **1n** did not give a significant kinetic isotope effect (KIE) value ($k_H/k_D = 1.0$; Supporting Information, Equation (S12)). A primary KIE of 1.0 was observed for **1n** and [D$_5$]-**1n** with **2a** (Supporting Information, Eq. (S13)). The low KIE value implies that the C–H bond cleavage of arenes is not involved in the rate-determining step.[8a,b,11f] The above observations suggest that the reaction mechanism is distinct from those of the well-described C–H/C–H cross-coupling reactions between two (hetero)arenes, in which significant isotope effects are generally observed.[3e,f,4b,d,f]

Subsequently, we found that radical scavengers, such as 2,2,6,6-tetramethylpiperidine (TEMPO), 2,6-di-*tert*-butyl-4-methylphenol (BHT), and ascorbic acid, significantly inhibited the reaction, suggesting the possibility of a radical pathway (Supporting Information, Table S8). To further clarify this hypothesis, a series of EPR experiments were carried out with the addition of free-radical spin-trapping agent DMPO (5,5-dimethyl-1-pyrroline *N*-oxide). To our delight, EPR signals were observed when DMPO was added to the reaction system (Supporting Information, Figure S3). HRMS analysis revealed formation of an adduct of **1a** with DMPO (*m*/*z* 366.1276), suggesting that the generated radical was trapped by DMPO to form a relatively stable radical species (Supporting Information, Figure S6). A mixture of Co^{III} [Cp*Co(CO)I$_2$] and **1a** in toluene showed an EPR signal (Supporting Information, Figure S4), whereas Co^{II} did not give rise to any significant information, indicating that the radical might be triggered by Co^{III}. The Co^{III} species involved in the catalytic cycle is generated by oxidation of Co^{II} with Ag$_2$CO$_3$. Indeed, the product (**3a**) was obtained in a 90% yield using Cp*Co(CO)I$_2$ instead of Co(OAc)$_2$·4H$_2$O. Moreover, a mixture of Cp*Co(CO)I$_2$ and **2a** in toluene did not lead to any significant EPR signal (Supporting Information, Figure S5).

Based on the above observations and known cobalt-catalyzed C–H bond functionalizations, two plausible mechanistic pathways are proposed (Scheme 2).[8a,b,11,15] In Path a, the coordination of amide **1a** to a Co^{III} species (generated from the oxidation of Co(OAc)$_2$·4H$_2$O) forms the intermediate **IM1**,[11a] followed by an intramolecular SET process from the thiophene ring to the coordinated Co^{III}, to form the cation–radical intermediate **IM2**.[15c] The resulting coordinated Co^{II} species was oxidized into the Co^{III} intermediate **IM4** in the presence of Ag$_2$CO$_3$.[11a,f] In Path b, Co^{III} species reacts with **1a** to generate **IM3** via an intermolecular SET process.[11f] The coordination of **IM3** to Co^{III} species generates **IM4**. However, in the absence of Ag$_2$CO$_3$ neither catalytic nor stoichiometric amounts of Cp*Co(CO)I$_2$ afforded any cross- and homocoupled products, except for the recovery of **1a** and **2a** (Supporting Information, Equations (S14)–(S16)), implying that Path b is less favorable than Path a. Subsequently, an irreversible intermolecular SET process between **IM4** and Co^{III} afforded **IM5** with the loss of a proton.[11f,15a] **IM5** reacts with a heteroarene to form the key heterocoupling intermediate **IM6** with the aid of Ag$_2$CO$_3$,[14] followed by reductive elimination to release the coupled product. The generated Co^{I} species is re-oxidized into the Co^{III} species by Ag$^+$ to complete the catalytic cycle.



Scheme 2. Plausible mechanistic pathway.

In summary, we have developed a unique cobalt-catalyzed oxidative C–H/C–H cross-coupling reaction between two (hetero)aromatics, which delivers a wide array of bi(hetero)aryls. A broad range of functional groups, especially for sensitive functional groups such as chloro, bromo, formyl, ester, cyano, vinyl, acetyl, nitro, acetoxyl, and even hydroxyl, are tolerated well. A preliminary mechanistic study suggests a SET pathway. Further investigation to extend the application of this method is in progress.

Acknowledgements

This work was supported by grants from the National NSF of China (Nos. 21432005, 21272160 and 21321061).

Keywords: bi(hetero)aryls · cobalt catalysis · oxidative C–H/C–H cross-coupling · SET pathway

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 10414–10418
Angew. Chem. **2016**, *128*, 10570–10574

---

[1] a) A. R. Murphy, J. M. J. Fréchet, *Chem. Rev.* **2007**, *107*, 1066; b) I. S. Young, P. D. Thornton, A. Thompson, *Nat. Prod. Rep.* **2010**, *27*, 1801; c) C. Wang, H. Dong, W. Hu, Y. Liu, D. Zhu, *Chem. Rev.* **2012**, *112*, 2208.

[2] a) C. Liu, H. Zhang, W. Shi, A. Lei, *Chem. Rev.* **2011**, *111*, 1780; b) S. H. Cho, J. Y. Kim, J. Kwak, S. Chang, *Chem. Soc. Rev.* **2011**, *40*, 5068; c) D. Zhao, J. You, C. Hu, *Chem. Eur. J.* **2011**, *17*, 5466.

[3] For selected oxidative C–H/C–H cross-coupling between two heteroarenes with Pd, Rh, and Ru, see: a) P. Xi, F. Yang, S. Qin, D. Zhao, J. Lan, G. Gao, C. Hu, J. You, *J. Am. Chem. Soc.* **2010**, *132*, 1822; b) C.-Y. He, S. Fan, X. Zhang, *J. Am. Chem. Soc.* **2010**, *132*, 12850; c) Z. Wang, K. Li, D. Zhao, J. Lan, J. You, *Angew. Chem. Int. Ed.* **2011**, *50*, 5365; *Angew. Chem.* **2011**, *123*, 5477; d) N. Kuhl, M. N. Hopkinson, F. Glorius, *Angew. Chem. Int. Ed.* **2012**, *51*, 8230; *Angew. Chem.* **2012**, *124*, 8354; e) X. Qin, H. Liu, D. Qin, Q. Wu, J. You, D. Zhao, Q. Guo, X. Huang, J. Lan, *Chem. Sci.* **2013**, *4*, 1964; f) C.-Y. He, Z. Wang, C.-Z. Wu, F.-L. Qing, X. Zhang, *Chem. Sci.* **2013**, *4*, 3508; g) X. Qin, X. Li, Q. Huang, H. Liu, D. Wu, Q. Guo, J. Lan, R. Wang, J. You, *Angew. Chem. Int. Ed.* **2015**, *54*, 7167; *Angew. Chem.* **2015**, *127*, 7273.

[4] a) M. Kitahara, N. Umeda, K. Hirano, T. Satoh, M. Miura, *J. Am. Chem. Soc.* **2011**, *133*, 2160; b) M. Nishino, K. Hirano, T. Satoh, M. Miura, *Angew. Chem. Int. Ed.* **2012**, *51*, 6993; *Angew. Chem.* **2012**, *124*, 7099; c) X. Qin, B. Feng, J. Dong, X. Li, Y. Xue, J. Lan,

J. You, *J. Org. Chem.* **2012**, *77*, 7677; d) M. Nishino, K. Hirano, T. Satoh, M. Miura, *Angew. Chem. Int. Ed.* **2013**, *52*, 4457; *Angew. Chem.* **2013**, *125*, 4553; e) R. Odani, K. Hirano, T. Satoh, M. Miura, *Angew. Chem. Int. Ed.* **2014**, *53*, 10784; *Angew. Chem.* **2014**, *126*, 10960; f) S. Zhao, J. Yuan, Y.-C. Li, B.-F. Shi, *Chem. Commun.* **2015**, *51*, 12823.

[5] S. Murahashi, S. Horite, *J. Am. Chem. Soc.* **1955**, *77*, 6403.

[6] a) K. Gao, N. Yoshikai, *Acc. Chem. Res.* **2014**, *47*, 1208; b) L. Ackermann, *J. Org. Chem.* **2014**, *79*, 8948; c) N. Yoshikai, *Bull. Chem. Soc. Jpn.* **2014**, *87*, 843; d) D. Tilly, G. Dayaker, P. Bachu, *Catal. Sci. Technol.* **2014**, *4*, 2756.

[7] a) K. Gao, P.-S. Lee, T. Fujita, N. Yoshikai, *J. Am. Chem. Soc.* **2010**, *132*, 12249; b) L. Ilies, Q. Chen, X. Zeng, E. Nakamura, *J. Am. Chem. Soc.* **2011**, *133*, 5221; c) T. Yoshino, H. Ikemoto, S. Matsunaga, M. Kanai, *Chem. Eur. J.* **2013**, *19*, 9142; d) T. Yoshino, H. Ikemoto, S. Matsunaga, M. Kanai, *Angew. Chem. Int. Ed.* **2013**, *52*, 2207; *Angew. Chem.* **2013**, *125*, 2263; e) B. Sun, T. Yoshino, S. Matsunaga, M. Kanai, *Adv. Synth. Catal.* **2014**, *356*, 1491; f) D.-G. Yu, T. Gensch, F. de Azambuja, S. Vásquez-Céspedes, F. Glorius, *J. Am. Chem. Soc.* **2014**, *136*, 17722; g) J. Li, L. Ackermann, *Angew. Chem. Int. Ed.* **2015**, *54*, 8551; *Angew. Chem.* **2015**, *127*, 8671; h) J. R. Hummel, J. A. Ellman, *J. Am. Chem. Soc.* **2015**, *137*, 490.

[8] a) W. Liu, H. Cao, J. Xin, L. Jin, A. Lei, *Chem. Eur. J.* **2011**, *17*, 3588; b) H. Li, C.-L. Sun, M. Yu, D.-G. Yu, B.-J. Li, Z.-J. Shi, *Chem. Eur. J.* **2011**, *17*, 3593; c) C. T. To, T. L. Chan, B. Z. Li, Y. Y. Hui, T. Y. Kwok, S. Y. Lam, K. S. Chan, *Tetrahedron Lett.* **2011**, *52*, 1023; d) B. Li, Z.-H. Wu, Y.-F. Gu, C.-L. Sun, B.-Q. Wang, Z.-J. Shi, *Angew. Chem. Int. Ed.* **2011**, *50*, 1109; *Angew. Chem.* **2011**, *123*, 1141; e) W. Song, L. Ackermann, *Angew. Chem. Int. Ed.* **2012**, *51*, 8251; *Angew. Chem.* **2012**, *124*, 8376; f) K. Gao, P.-S. Lee, C. Long, N. Yoshikai, *Org. Lett.* **2012**, *14*, 4234.

[9] a) T. Truong, J. Alvarado, L. D. Tran, O. Daugulis, *Org. Lett.* **2010**, *12*, 1200; b) L. Grigorjeva, O. Daugulis, *Org. Lett.* **2015**, *17*, 1204.

[10] a) V. G. Zaitsev, D. Shabashov, O. Daugulis, *J. Am. Chem. Soc.* **2005**, *127*, 13154; b) Y. Aihara, N. Chatani, *J. Am. Chem. Soc.* **2014**, *136*, 898; c) S. Asako, L. Ilies, E. Nakamura, *J. Am. Chem. Soc.* **2013**, *135*, 17755; d) G. Rouquet, N. Chatani, *Chem. Sci.* **2013**, *4*, 2201; e) R. Shang, L. Ilies, E. Nakamura, *J. Am. Chem. Soc.* **2015**, *137*, 7660.

[11] a) L. Grigorjeva, O. Daugulis, *Angew. Chem. Int. Ed.* **2014**, *53*, 10209; *Angew. Chem.* **2014**, *126*, 10373; b) L. Grigorjeva, O. Daugulis, *Org. Lett.* **2014**, *16*, 4684; c) L. Grigorjeva, O. Daugulis, *Org. Lett.* **2014**, *16*, 4688; d) X. Wu, K. Yang, Y. Zhao, H. Sun, G. Li, H. Ge, *Nat. Commun.* **2015**, *6*, 6462; e) L.-B. Zhang, X.-Q. Hao, Z.-J. Liu, X.-X. Zheng, S.-K. Zhang, J.-F. Gong, J.-L. Niu, M.-P. Song, *Angew. Chem. Int. Ed.* **2015**, *54*, 272; *Angew. Chem.* **2015**, *127*, 274; f) X.-K. Guo, L.-B. Zhang, D. Wei, J.-L. Niu, *Chem. Sci.* **2015**, *6*, 7059; g) J. Zhang, H. Chen, C. Lin, Z. Liu, C. Wang, Y. Zhang, *J. Am. Chem. Soc.* **2015**, *137*, 12990.

[12] CCDC 1433074 (**3a**) and 1442502 (**4af**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[13] For calculated pK_a values in DMSO, see: K. Shen, Y. Fu, J.-N. Li, L. Liu, Q.-X. Guo, *Tetrahedron* **2007**, *63*, 1568.

[14] W. Han, P. Mayer, A. R. Ofial, *Angew. Chem. Int. Ed.* **2011**, *50*, 2178; *Angew. Chem.* **2011**, *123*, 2226.

[15] a) J. K. Kochi, R. T. Tang, T. Bernath, *J. Am. Chem. Soc.* **1973**, *95*, 7114; b) J. Iqbal, B. Bhatia, N. K. Nayyar, *Chem. Rev.* **1994**, *94*, 519; c) X. Chen, X.-S. Hao, C. E. Goodhue, J.-Q. Yu, *J. Am. Chem. Soc.* **2006**, *128*, 6790.

Received: May 11, 2016