ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2018, **54**, 3899

Received 17th March 2018,
Accepted 25th March 2018

DOI: 10.1039/c8cc02158a

rsc.li/chemcomm

Copper-mediated regioselective C–H etherification of naphthylamides with arylboronic acids using water as an oxygen source†

Subhasish Roy, Sourav Pradhan and Tharmalingam Punniyamurthy *

The copper-mediated regioselective C–H activation and C–O bond formation of naphthylamides with arylboronic acids has been developed using water as an oxygen source. The kinetic isotope study suggests that C–H bond activation is the rate-determining step. The H_2O^{18} labelling experiment reveals the incorporation of oxygen from water. The substrate scope, functional group diversity and post synthetic utilities are the important practical features.

The facile unification of molecular fragments *via* C–O bond construction exemplifies a vital and challenging objective in modern synthetic chemistry. Owing to the prevalence of biaryl ether moieties in pharmaceuticals, natural products and functional materials (Fig. 1),[1] the area of C–O bond formation has been dominated by the traditional Cu-based Ullmann[2] or Chan–Evans–Lam[3] and Pd-based[4] coupling reactions. However, the routine use of the prefunctionalized substrate precursors and often harsh reaction conditions limits their potential application. Thus, there has been a resurgence of directing group assisted C–H activation[5] in the development of analogous methods to achieve comparable C–H etherification efficiencies. Following the landmark reports on the alkoxylation of unactivated C–H bonds by the Sanford[6a,b] and Yu[6c] groups, direct alkoxylation[6] has been considerably investigated, using alcoholic nucleophiles. Despite these advances, few studies have been focused on the direct aroyloxylation of arenes using phenols.[7,8] The development of new synthetic routes to synthesize biaryl ethers through direct aroyloxylation is thus in demand. Recently, the directing group assisted C–C coupling of arenes with arylboron reagents has attracted considerable attention in the presence of Pd,[9c,g] Ru,[9h] Cu[9i,f] and Co[9j,k] based systems (Scheme 1a). Herein, we wish to report an unprecedented Cu-mediated regioselective C–H etherification of naphthylamides with arylboronic acids using picolinamide[10] as the directing group and water as the oxygen source (Scheme 1b). The reaction can tolerate a variety of functional groups and is complementary to the previous methods for the synthesis of aryl naphthyl ethers.

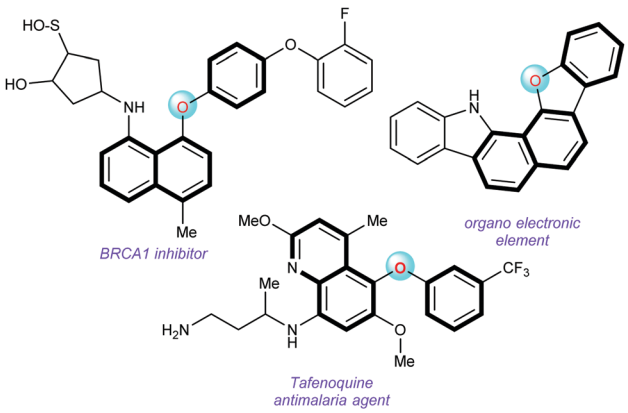
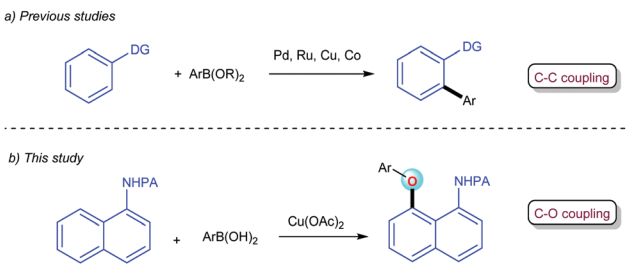


Fig. 1 Examples of some biologically important naphthyl aryl ethers.



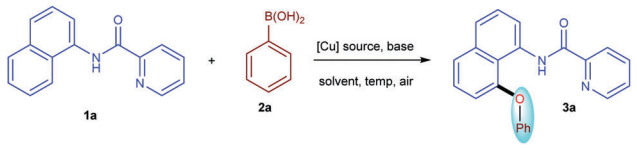
Scheme 1 Directed C–H functionalization of arenes with arylboron reagents.

We commenced the optimization studies with *N*-(naphthalen-1-yl)picolinamide **1a** and phenylboronic acid **2a** as the model substrates using various copper salts, bases and solvents (Table 1). Pleasingly, C–H etherification occurred to furnish **3a** in 46% yield when the substrates **1a** and **2a** were stirred with 1.5 equiv. of $Cu(OAc)_2 \cdot H_2O$ and 2 equiv. of Na_2CO_3 at 130 °C in DMF in air

Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati 781039, India. E-mail: tpunni@iitg.ernet.in

† Electronic supplementary information (ESI) available: Experimental procedure, characterization data and NMR spectra (^1H and ^{13}C) of **3a–z**, **4**, and **5** are given. CCDC 1528745. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8cc02158a

Table 1 Optimization of the reaction conditions[a]

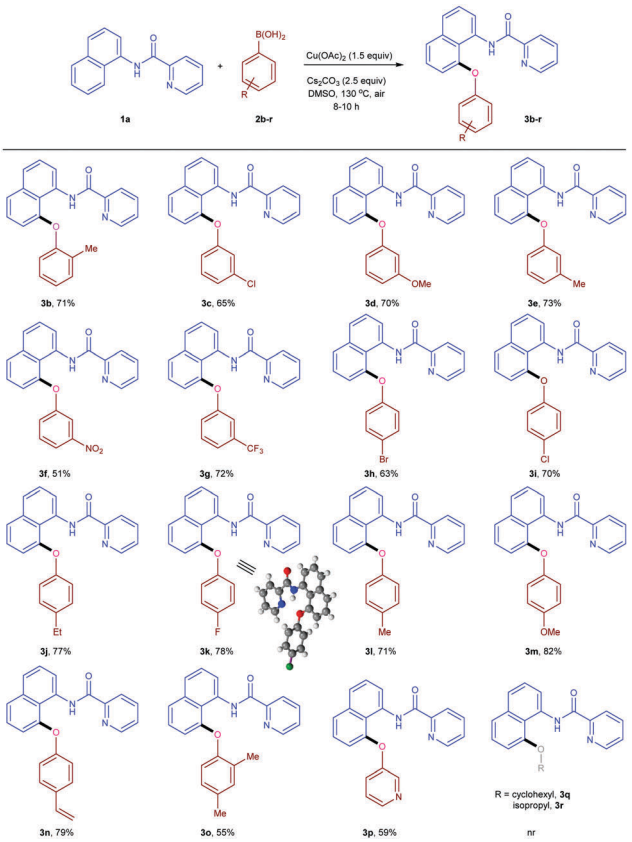


Entry	[Cu]	Base	Solvent	Yield[b] [%]
1	$Cu(OAc)_2·H_2O$	Na_2CO_3	DMF	46
2	$Cu(OAc)_2$	Na_2CO_3	DMF	57
3	CuO	Na_2CO_3	DMF	nr
4	CuI	Na_2CO_3	DMF	nr
5	$CuCl_2$	Na_2CO_3	DMF	nr
6	$CuSO_4$	Na_2CO_3	DMF	nr
7	$Cu(OAc)_2$	K_2CO_3	DMF	68
8	$Cu(OAc)_2$	K_3PO_4	DMF	64
9	$Cu(OAc)_2$	Cs_2CO_3	DMF	78
10	$Cu(OAc)_2$	Cs_2CO_3	DMSO	82
11	$Cu(OAc)_2$	Cs_2CO_3	Toluene	nr
12	$Cu(OAc)_2$	Cs_2CO_3	1,4-Dioxane	nr
13	$Cu(OAc)_2$	Cs_2CO_3	$(CH_2Cl)_2$	nr
14	$Cu(OAc)_2$	Cs_2CO_3	DMSO	50[c]
15	$Cu(OAc)_2$	Cs_2CO_3	DMSO	16[d]
16	—	Cs_2CO_3	DMSO	0

[a] Reactions conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), [Cu] (0.3 mmol), base (0.5 mmol), solvent (1.0 mL) at 130 °C for 10 h, air. [b] Isolated yield. [c] At 110 °C. [d] Using 30 mol% $Cu(OAc)_2$. nr = no reaction.

for 10 h (entry 1). The yield increased to 57% when $Cu(OAc)_2$ was employed (entry 2). In contrast, CuO, CuI, $CuCl_2$ and $CuSO_4$ showed no effect (entries 3–6). Subsequent screening of the base led to an enhancement in the yield to 82% when Cs_2CO_3 was used, whereas K_2CO_3 and K_3PO_4 gave 68 and 64% yields, respectively (entries 7–9). DMSO was found to be the solvent of choice. In contrast, toluene, 1,4-dioxane and $(CH_2Cl)_2$ failed to produce the desired product (entries 10–13). A decrease in the reaction temperature or $Cu(OAc)_2$ loading (30 mol%) led to a drop in the yield significantly (entries 14 and 15). A control experiment in the absence of copper salt revealed no product formation, and the starting material was recovered intact (entry 16). In addition, the reaction with some N/O-directing groups (**A–E**) indictaed that an *N*,*N*-bidentate coordination and the relatively acidic NH of **1a** are believed to play a crucial role in the etherification (see the ESI†).[10g]

Having optimized the reaction conditions, the scope of the *peri*-selective etherification was explored for electronically varied arylboronic acids **2b–r** with **1a** as a standard substrate (Scheme 2). The reaction of **2b** bearing a 2-methyl group gave **3b** in 71% yield. The substrates with substitutions at the 3-position with chloro **2c**, methoxy **2d**, methyl **2e**, nitro **2f** and trifluoromethyl **2g** groups underwent the reaction to afford the target ethers **3c–g** in 51–73% yields. Notably, the tolerance of strong electron-demanding groups, such as nitro and trifluoromethyl highlights the potential of this etherification. Similarly, the substrates bearing halo groups at the 4-position, **2h**, **2i** and **2k**, readily reacted to give the oxygenated products **3h**, **3i** and **3k** in 63, 70 and 78% yields, respectively. The structure of **3k** was confirmed using single crystal X-ray analysis. The electron-releasing functional groups at the 4-position of the boronic acids **2j** and **2l–m** were also amicable and provided **3j** and **3l–m** in 77, 71 and 82% yields, respectively. We were pleased to

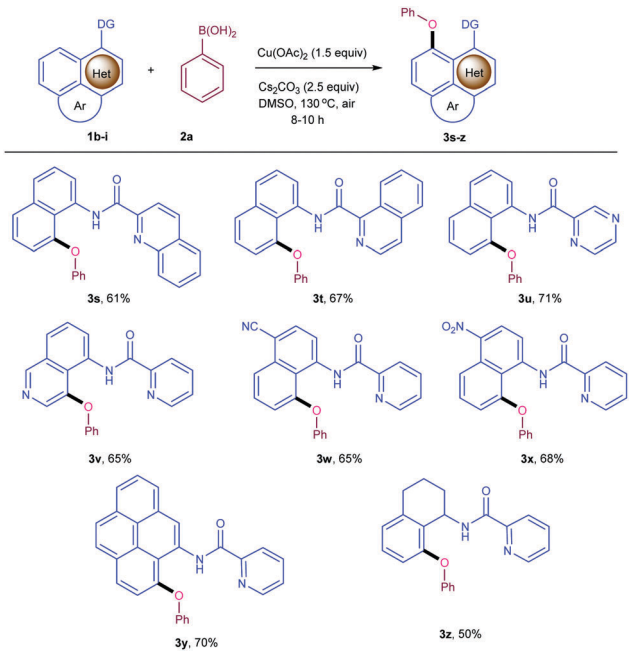


Scheme 2 Substrate scope of arylboronic acids with **1a**. Reaction conditions: **1a** (0.2 mmol), **2b–r** (0.4 mmol), $Cu(OAc)_2$ (0.3 mmol), Cs_2CO_3 (0.5 mmol), DMSO (1.0 mL), 130 °C, 8–10 h, air. Isolated yield. nr = no reaction.

find that a vinyl functionality, di-substitution and heteroarylboronic acid congeners **2n**, **2o** and **2p** efficiently oxygenated to furnish the biaryl ethers **3n**, **3o** and **3p** in 79, 55 and 59% yields, respectively, which were proven to be challenging substrates. In contrast, alkylboronic acids, such as **2q–r** failed to yield the desired products.

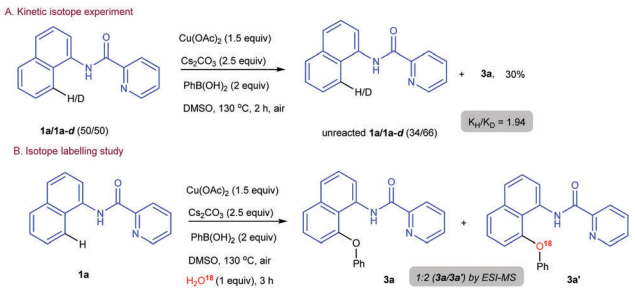
The scope of the procedure was extended for the reaction of diversely decorated naphthylamides **1b–i** with boronic acid **2a** as a standard substrate (Scheme 3). The reactions of the structurally similar picolinic acid derived naphthylamides **1b–d** were envisaged. Gratifyingly, the outcome was comparable to those with the parent picolinamide derivative **1a** and offered the ethers **3s**, **3t** and **3u** in 61, 67 and 71% yields, respectively. Notably, the aminoisoquinoline **1e** effectively oxygenated to give the ether **3v** in 65% yield, demonstrating the overriding potential of this reaction in heteroatom poisoning for [Cu] deactivation. In addition, the substrates **1f** and **1g** bearing the electron-withdrawing 4-cyano and 4-nitro groups were amenable for producing the desired products **3w** and **3x** in 65 and 68% yields, respectively. Intriguingly, an extended π-cycle, such as pyrenyl derivative **1h** was also proficiently oxygenated to give the ether **3y** in 70% yield. Furthermore, the directing group having an –NH group attached to the aliphatic ring **1i** efficiently responded to the methodology to furnish the ether **3z** in 50% yield.

To gain insight into the mechanism,[11] an intermolecular kinetic isotope experiment was performed using **1a** and **1a–d** as

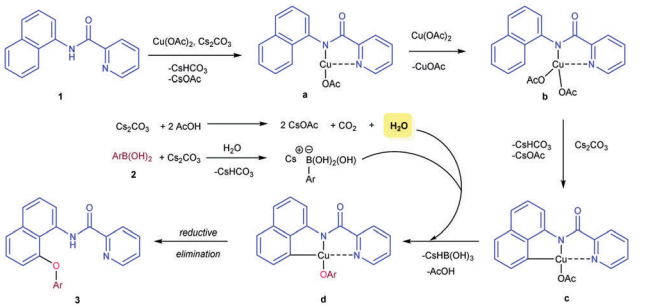


Scheme 3 Substrate scope of naphthylamides with **2a**. Reaction conditions: **1b–i** (0.2 mmol), **2a** (0.4 mmol), $Cu(OAc)_2$ (0.3 mmol); Cs_2CO_3 (0.5 mmol), DMSO (1.0 mL), 130 °C, 8–10 h, air. Isolated yield.

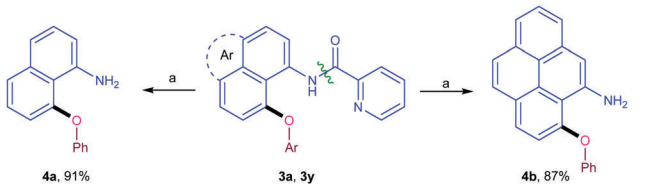
the representative examples to give k_H/k_D = 1.94 (Scheme 4A), which suggests that the C–H bond cleavage might be the rate-determining step.[11c] Next, the reaction was performed under an argon atmosphere. The reaction occurred to produce the ether **3a** in 70% yield, which suggests that air may not be involved as the oxygen source. Then, the reaction was investigated using labelled water (H_2O^{18}) (Scheme 4B). Mass analysis revealed the incorporation of O^{18} in **3a** ($O^{18}:O^{16} \approx 2:1$), which suggests that H_2O is the oxygen source. Thus, the reaction of $Cu(OAc)_2$ with substrate **1** using a base can give Cu(II) species ***a*** that can be oxidized by $Cu(OAc)_2$ to furnish the tetracoordinated Cu(III) complex ***b*** (Scheme 5). The intramolecular activation of the C–H bond *via* a cyclometalation can lead to the formation of copper(III) species ***c*** that can react with a boronate complex[9a,b,d,e] and water to produce copper(III) intermediate ***d***. The latter can lead to the reductive elimination to furnish the ether scaffold **3** and Cu(I) species. The described reaction pathway explains the requirement of an excess of $Cu(OAc)_2$ and base to obtain the ethers in good yields.



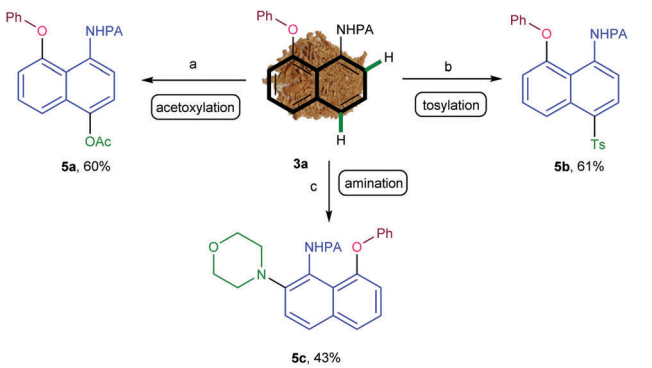
Scheme 4 Preliminary mechanistic investigation.



Scheme 5 Proposed mechanism.



Scheme 6 Removal of the directing group. Reaction conditions: [a] **3a**/**3y** (0.1 mmol), NaOH (0.7 mmol), EtOH (2 mL), reflux, 3 h.



Scheme 7 Synthetic applications. Reaction conditions: [a] **3a** (0.1 mmol), $Cu(OAc)_2{\cdot}H_2O$ (20 mol%), $PhI(OAc)_2$ (0.2 mmol), AcOH (1 mL), 80 °C, air, 6 h; [b] **3a** (0.1 mmol), $Cu(OAc)_2{\cdot}H_2O$ (20 mol%), K_2CO_3 (0.2 mmol), TsCl (0.3 mmol), $(CH_2Cl)_2$ (1 mL), 80 °C, air, 16 h; [c] **3a** (0.1 mmol), morpholine (0.2 mmol), $Cu(OAc)_2{\cdot}H_2O$ (10 mol%), $MgCl_2$ (20 mol%), 1,4-dioxane (2 mL), 25 °C, 8 h, argon. PA = picolinamide.

Finally, the synthetic utility of the protocol was investigated. The facile exclusion of the directing group was accomplished using NaOH/EtOH to afford **4a** and **4b** in 91 and 87% yields, respectively, as the representative examples (Scheme 6). Next, bidentate chelation induced SET pathway[12] guided regioselective transformation of the ether **3a** was carried out (Scheme 7). Appreciably, we were able to install the acetyl (**5a**, 60% yield) and tosyl (**5b**, 61% yield) groups at the remote C-4 position and conduct *ortho*-amination (**5c**, 43% yield) using morpholine. These post-synthetic elaborations reflect the remarkable potential of our approach to build functional scaffolds through sequential C–H activation.

In conclusion, we have developed a Cu-mediated selective etherification of naphthylamides with arylboronic acids using water as an oxygen source *via* a picolinamide directed C(γ)–H activation.

The kinetic isotope experiment suggests that the C–H activation is the rate-determining step. The broad substrate scope, functional group tolerance and use of water as the oxygen source are the important features.

We thank the Science and Engineering Research Board (EMR-2015-43) and the Council of Scientific and Industrial Research (02(0255)-2016-EMR-II) for the financial support. One of us (SR) thanks the Science and Engineering Research Board for a National Postdoctoral Fellowship (PDF/2016/001594). We also thank the Central Instruments Facility, Indian Institute of Technology for NMR analysis (FIST).

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 (*a*) H.-G. Elias, *An introduction to Polymer Sciences*, Wiley-VCH, Weinheim, 1997; (*b*) J. J. Li and D. S. Johnson, *Modern Drug Synthesis*, Wiley, Hoboken, 2010; (*c*) S. Enthaler and A. Company, *Chem. Soc. Rev.*, 2011, **40**, 4912; (*d*) S. D. Roughley and A. M. Jordan, *J. Med. Chem.*, 2011, **54**, 345; (*e*) R. Takise, R. Isshiki, K. Muto, K. Itami and J. Yamaguchi, *J. Am. Chem. Soc.*, 2017, **139**, 3340.

2 (*a*) F. Ullmann and P. Sponagel, *Ber. Dtsch. Chem. Ges.*, 1905, **38**, 2211; (*b*) F. Monnier and M. Taillefer, *Angew. Chem., Int. Ed.*, 2009, **48**, 6954; (*c*) H. Lin and D. Sun, *Org. Prep. Proced. Int.*, 2013, **45**, 341; (*d*) C. Sambiagio, S. P. Marsden, A. J. Blackera and P. C. McGowan, *Chem. Soc. Rev.*, 2014, **43**, 3525.

3 (*a*) D. M. T. Chan, K. L. Monaco, R.-P. Wang and M. P. Winters, *Tetrahedron Lett.*, 1998, **39**, 2933; (*b*) D. A. Evans, J. L. Katz and T. R. West, *Tetrahedron Lett.*, 1998, **39**, 2937; (*c*) P. Y. S. Lam, G. Vincent, D. Bonnie and C. G. Clark, *Tetrahedron Lett.*, 2003, **44**, 4927; (*d*) O. Bistri, A. Correa and C. Bolm, *Angew. Chem., Int. Ed.*, 2008, **47**, 586; (*e*) C. H. Burgoes, T. E. Barder, X. Huang and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2006, **45**, 4321; (*f*) J. X. Qiao and P. Y. S. Lam, *Synthesis*, 2011, 829; (*g*) Y. Zhang, G. Ni, C. Li, S. Xu, Z. Zhang and X. Xie, *Tetrahedron*, 2015, **71**, 4927; (*h*) J. S. Marcum, K. A. McGarry, C. J. Ferber and T. B. Clark, *J. Org. Chem.*, 2016, **81**, 7963; (*i*) S. Bhunia, G. G. Pawar, S. V. Kumar, Y. Jiang and D. Ma, *Angew. Chem., Int. Ed.*, 2017, **56**, 16136.

4 (*a*) J. F. Hartwig, *Angew. Chem., Int. Ed.*, 1998, **37**, 2046; (*b*) J. F. Hartwig, *Nature*, 2008, **455**, 314; (*c*) T. Hu, T. Schulz, C. Torborg, X. Chen, J. Wang, M. Beller and J. Huang, *Chem. Commun.*, 2009, 7330.

5 For recent reviews on C–H activation, see: (*a*) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147; (*b*) A. E. Wendlandt, A. M. Suess and S. S. Stahl, *Angew. Chem., Int. Ed.*, 2011, **50**, 11062; (*c*) L. Ackermann, *Chem. Rev.*, 2011, **111**, 1315; (*d*) P. B. Arockiam, C. Bruneau and P. H. Dixneuf, *Chem. Rev.*, 2012, **112**, 5879; (*e*) G. Rouquet and N. Chatani, *Angew. Chem., Int. Ed.*, 2013, **52**, 11726; (*f*) M.-L. Louillat and F. W. Patureau, *Chem. Soc. Rev.*, 2014, **43**, 901; (*g*) Z. Chen, B. Wang, J. Zhang, W. Yu, Z. Liu and Y. Zhang, *Org. Chem. Front.*, 2015, **2**, 1107; (*h*) O. Daugulis, J. Roane and L. D. Tran, *Acc. Chem. Res.*, 2015, **48**, 1053; (*i*) R.-Y. Zhu, M. E. Farmer, Y.-Q. Chen and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2016, **55**, 10578; (*j*) J. A. Leitch, Y. Bhonoah and C. G. Frost, *ACS Catal.*, 2017, **7**, 5618.

6 For some examples on C–O bond formation and alkoxylation, see: (*a*) L. V. Desai, K. L. Hull and M. S. Sanford, *J. Am. Chem. Soc.*, 2004, **126**, 9542; (*b*) L. V. Desai, H. A. Malik and M. S. Sanford, *Org. Lett.*, 2006, **8**, 1141; (*c*) X. Chen, X.-S. Hao, C. E. Goodhue and J.-Q. Yu, *J. Am. Chem. Soc.*, 2006, **128**, 6790; (*d*) S.-Y. Zhang, G. He, Y. Zhao, K. Wright, W. A. Nack and G. Chen, *J. Am. Chem. Soc.*, 2012, **134**, 7313; (*e*) G. Shan, X. Yang, Y. Zong and Y. Rao, *Angew. Chem., Int. Ed.*, 2013, **52**, 13606; (*f*) S. Bhadra, W. I. Dzik and L. J. Gooßen, *Angew. Chem., Int. Ed.*, 2013, **52**, 2959; (*g*) F.-J. Chen, S. Zhao, F. Hu, K. Chen, Q. Zhang, S.-Q. Zhang and B.-F. Shi, *Chem. Sci.*, 2013, **4**, 4187; (*h*) L.-B. Zhang, X.-Q. Hao, S.-K. Zhang, K. Liu, B. Ren, J.-F. Gong, J.-L. Niu and M.-P. Song, *J. Org. Chem.*, 2014, **79**, 10399; (*i*) X.-K. Guo, L.-B. Zhang, D. Wei and J.-L. Niu, *Chem. Sci.*, 2015, **6**, 7059; (*j*) X.-S. Yin, Y.-C. Li, J. Yuan, W.-J. Gu and B.-F. Shi, *Org. Chem. Front.*, 2015, **2**, 119; (*k*) J. Zhang, H. Chen, B. Wang, Z. Liu and Y. Zhang, *Org. Lett.*, 2015, **17**, 2768; a review; (*l*) B. Liu and B.-F. Shi, *Tetrahedron Lett.*, 2015, **56**, 15.

7 For examples of directed C–O cyclization and benzofuran synthesis, see: (*a*) X. Wang, Y. Lu, H.-X. Dai and J.-Q. Yu, *J. Am. Chem. Soc.*, 2010, **132**, 12203; (*b*) B. Xiao, T.-J. Gong, Z.-J. Liu, J.-H. Liu, D.-F. Luo, J. Xu and L. Liu, *J. Am. Chem. Soc.*, 2011, **133**, 9250; (*c*) Y. Wei and N. Yoshikai, *Org. Lett.*, 2011, **13**, 5504; (*d*) J. Zhao, Y. Wang, Y. He, L. Liu and Q. Zhu, *Org. Lett.*, 2012, **14**, 1078.

8 For directed C(sp^2)–H bond coupling with phenol, see: (*a*) J. Roane and O. Daugulis, *Org. Lett.*, 2013, **15**, 5842; (*b*) X.-Q. Hao, L.-J. Chen, B. Ren, L.-Y. Li, X.-Y. Yang, J.-F. Gong, J.-L. Niu and M.-P. Song, *Org. Lett.*, 2014, **16**, 1104.

9 For C–C coupling using arylboron reagents, see: (*a*) A. A. C. Braga, N. H. Mrogan, G. Ujaque and F. Masers, *J. Am. Chem. Soc.*, 2005, **127**, 9298; (*b*) A. N. Cammidge, V. H. M. Goddard, H. Gopee, N. L. Harrison, D. L. Hughes, C. J. Schubert, B. M. Sutton, G. L. Watts and A. J. Whitehead, *Org. Lett.*, 2006, **8**, 4071; (*c*) Z. Shi, B. Li, X. Wan, J. Cheng, Z. Fing, B. Cao, C. Qin and Y. Wang, *Angew. Chem., Int. Ed.*, 2007, **46**, 5554; (*d*) J. Xu, X. Wang, C. Shao, D. Su, G. Cheng and Y. Hu, *Org. Lett.*, 2010, **12**, 1964; (*e*) K. Inamoto, K. Nozawa, M. Yonemoto and Y. Kondo, *Chem. Commun.*, 2011, **47**, 11775; (*f*) M. Shang, S.-Z. Sun, H.-X. Dai and J.-Q. Yu, *Org. Lett.*, 2014, **16**, 5666; (*g*) Y. Yang, X. Qiu, Y. Zhao, Y. Mu and Z. Shi, *J. Am. Chem. Soc.*, 2016, **138**, 495; (*h*) P. Nareddy, F. Jordan, S. E. Brenner-Moyer and M. Szostak, *ACS Catal.*, 2016, **6**, 4755; (*i*) Q. Gui, X. Chen, L. Hu, D. Wang, J. Liu and Z. Tan, *Adv. Synth. Catal.*, 2016, **358**, 509; (*j*) X. Zhu, J.-H. Su, C. Du, Z.-L. Wang, C.-J. Ren, J.-L. Niu and M.-P. Song, *Org. Lett.*, 2017, **19**, 596; (*k*) P. B. De, S. Pradhan, S. Banerjee and T. Punniyamurthy, *Chem. Commun.*, 2018, **54**, 2494.

10 For examples of picolinamide directed C–H activation, see: (*a*) E. T. Nadres, G. I. F. Santos, D. Shabashov and O. Daugulis, *J. Org. Chem.*, 2013, **78**, 9689; (*b*) R. Odani, K. Hirano, T. Satoh and M. Miura, *J. Org. Chem.*, 2013, **78**, 11045; (*c*) M. Iwasaki, W. Kaneshika, Y. Tsuchiya, K. Nakajima and Y. Nishihara, *J. Org. Chem.*, 2014, **79**, 11330; (*d*) L. Huang, X. Sun, Q. Li and C. Qi, *J. Org. Chem.*, 2014, **79**, 6720; (*e*) R. Shang, L. Ilies and E. Nakamura, *J. Am. Chem. Soc.*, 2015, **137**, 7660; (*f*) J. Lan, H. Xie, X. Lu, Y. Deng, H. Jiang and W. Zeng, *Org. Lett.*, 2017, **19**, 4279; (*g*) S. Pradhan, P. B. De and T. Punniyamurthy, *J. Org. Chem.*, 2017, **82**, 4883.

11 (*a*) A. E. King, L. M. Huffman, A. Casitas, M. Costas, X. Ribas and S. S. Stahl, *J. Am. Chem. Soc.*, 2010, **132**, 12068; (*b*) L. M. Huffman, A. Casitas, M. Font, M. Canta, M. Costas, X. Ribas and S. S. Stahl, *Chem. – Eur. J.*, 2011, **17**, 10643; (*c*) E. M. Simmons and J. F. Hartwig, *Angew. Chem., Int. Ed.*, 2012, **51**, 3066; (*d*) A. M. Suess, M. Z. Ertem, C. J. Cramer and S. S. Stahl, *J. Am. Chem. Soc.*, 2013, **135**, 9797.

12 (*a*) Q. Li, S.-Y. Zhang, G. He, Z. Ai, W. A. Nack and G. Chen, *Org. Lett.*, 2014, **16**, 1764; (*b*) J.-M. Li, Y.-H. Wang, Y. Yu, R.-B. Wu, J. Weng and G. Lu, *ACS Catal.*, 2017, **7**, 2661.

