

CrossMark  
click for updatesCite this: *Chem. Sci.*, 2017, 8, 1469Received 30th July 2016  
Accepted 21st September 2016

DOI: 10.1039/c6sc03383k

www.rsc.org/chemicalscience

Identification of monodentate oxazoline as a ligand for copper-promoted *ortho*-C–H hydroxylation and amination†Ming Shang,<sup>a</sup> Qian Shao,<sup>a</sup> Shang-Zheng Sun,<sup>c</sup> Yan-Qiao Chen,<sup>b</sup> Hui Xu,<sup>a</sup> Hui-Xiong Dai<sup>\*a</sup> and Jin-Quan Yu<sup>\*ab</sup>The use of a weakly coordinating monodentate directing group for copper mediated *ortho*-hydroxylation and amination reactions allows for the identification of an external oxazoline ligand as a promoter.

## Introduction

Over the past decade, directed C–H activation has emerged as a useful tool for organic synthesis.<sup>1</sup> Diverse carbon–carbon bond and carbon–heteroatom bond forming reactions have been developed with various transition metals. In this regard, precious metals such as Pd, Rh and Ir have shown superior catalytic reactivity. Notably, Pd catalysts have demonstrated versatility in both C(sp<sup>2</sup>)-H activation and C(sp<sup>3</sup>)-H activation *via* different manifolds including Pd(0)/Pd(II), Pd(II)/Pd(0), Pd(II)/Pd(IV) and Pd(II)/Pd(II) catalysis.<sup>2</sup> However, replacing these precious metals with first-row transition metals such as Fe and Cu is more desirable due to their high abundance and low toxicity.<sup>3,4</sup> In particular, copper-mediated C–H functionalization has made rapid progress in recent years, with various C–H transformations developed *via* different redox manifolds corresponding to the oxidants employed. However, owing to their low reactivity, nearly all of the inexpensive metals, especially in copper mediated C–H activation reactions, rely on strongly coordinating directing groups, for example, pyridine or bidentate pyridine-based auxiliaries (Fig. 1).<sup>4,5</sup> The advantage of weakly coordinating directing groups to form the less thermodynamically stable metallacycle, thereby kinetically facilitating the subsequent functionalization step, has been demonstrated with only precious metal catalysts.<sup>6</sup> The use of a weakly coordinating monodentate directing group in combination with ligand acceleration remains to be demonstrated with Cu catalysts.

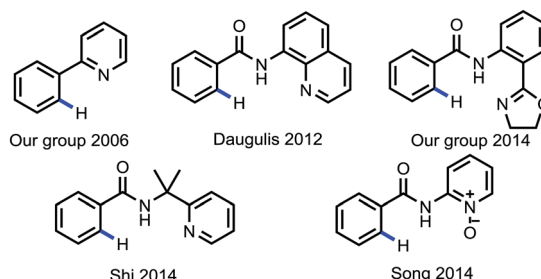
Phenols are a class of important structural motifs prevalent both in natural products and pharmaceuticals.<sup>7</sup> Direct C–H hydroxylation is an appealing method for the synthesis of functionalized phenols. Pd-mediated hydroxylation of excess benzene at 180 °C was found to give phenol in less than 5% yield in an early study.<sup>8a</sup> Recently, directed *ortho*-C–H hydroxylation of simple substrates has reached synthetically useful yields with Pd and Ru catalysts.<sup>8,9</sup> However, inexpensive metal-catalyzed or -mediated C–H hydroxylation reactions remain rare. In 2006, our group reported a pyridine-directed hydroxylation of inert C–H bonds using Cu(OAc)<sub>2</sub> as a promoter, which involved the formation of acetoxyated products and subsequent hydrolysis.<sup>10</sup> Recently, copper-mediated C–H hydroxylation of benzoic acid derivatives with the assistance of bidentate auxiliaries has also been disclosed.<sup>11</sup> Guided by the development of Pd-catalyzed C–H activation reactions enabled by ligands, we set out to explore the combination of weakly coordinating monodentate directing groups and ligands for

<sup>a</sup>State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Shanghai 20032, China. E-mail: hxdai@sioac.ac.cn; yu200@scripps.edu<sup>b</sup>Department of Chemistry, The Scripps Research Institute, 10550 N. Torrey Pines Road, La Jolla, California 92037, USA<sup>c</sup>Department of Chemistry, Innovative Drug Research Center, Shanghai University, 99 Shangda Road, 200444, China

† Electronic supplementary information (ESI) available: Data for new compounds and experimental procedures. CCDC 1496588, 1496590. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6sc03383k

## Previous work

Strongly coordinating auxiliaries for copper mediated C–H activation



## This work

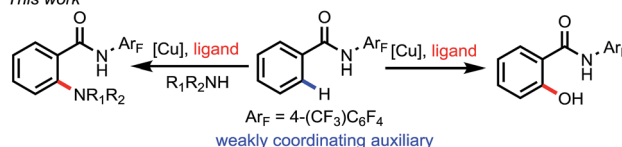
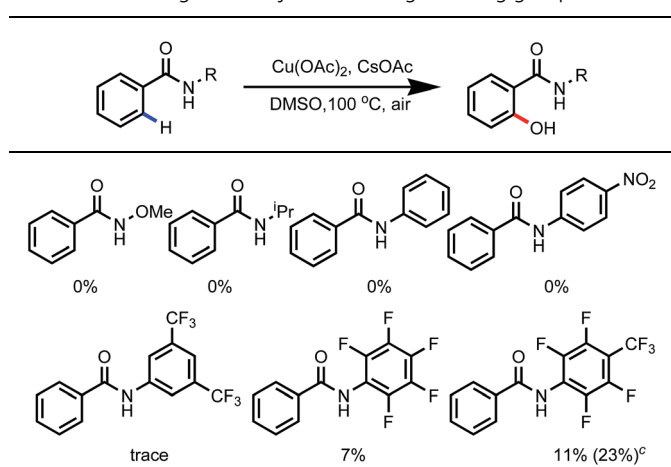
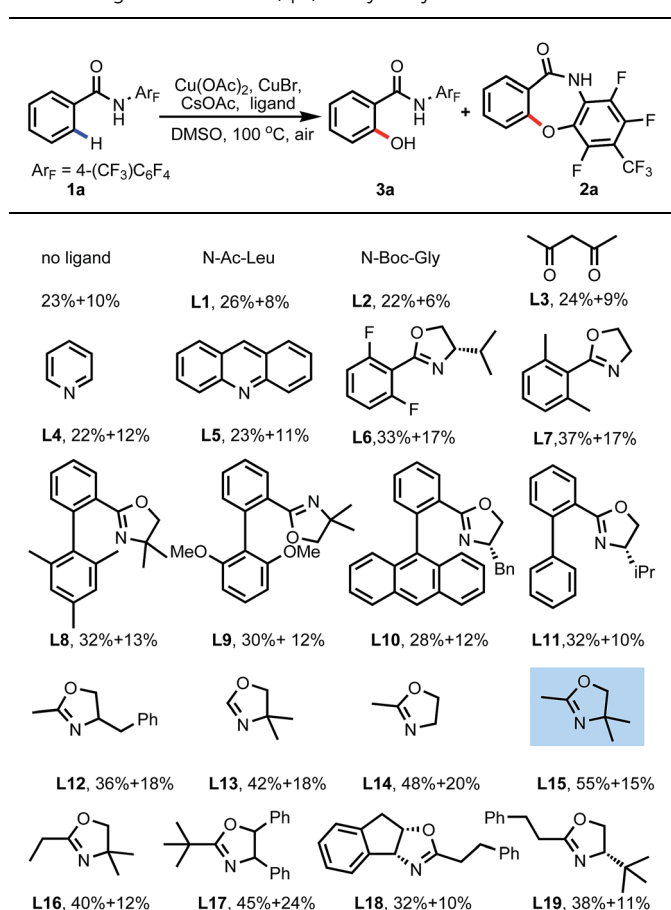


Fig. 1 Auxiliaries used for copper-mediated C–H activation.



Table 1 Screening of weakly coordinating directing groups<sup>a,b</sup>

<sup>a</sup> Reaction conditions: **1a** (0.1 mmol), Cu(OAc)<sub>2</sub> (0.2 mmol), CsOAc (0.2 mmol), DMSO (1.0 mL), 100 °C, air, 6 h. <sup>b</sup> Yield determined by <sup>1</sup>H NMR analysis of crude reaction mixture using CH<sub>2</sub>Br<sub>2</sub> as an internal standard. <sup>c</sup> CuBr (0.8 eq.) as an additive.

Table 2 Ligand effect on C(sp<sup>2</sup>)-H hydroxylation<sup>a,b</sup>

<sup>a</sup> Reaction conditions: **1a** (0.1 mmol), Cu(OAc)<sub>2</sub> (0.2 mmol), CuBr (0.08 mmol), CsOAc (0.2 mmol), ligand (0.1 mmol), DMSO (1.0 mL), 100 °C, air, 6 h. <sup>b</sup> Yield determined by <sup>1</sup>H NMR analysis of crude reaction mixture using CH<sub>2</sub>Br<sub>2</sub> as an internal standard.

Cu-catalyzed C-H activation reactions. Herein, we report the first example of copper-mediated C-H hydroxylation and amination using a weakly coordinating directing group under the assistance of a monodentate ligand.

## Results and discussion

### Initial studies and reaction optimization

We commenced our studies with screening of a series of weakly coordinating amides (Table 1). Although displaying good reactivity in Pd-catalyzed C-H activation reactions, the N-OMe substituted amide gave no product. Other simple amides, such as N-isopropyl, N-phenyl and N-(4-NO<sub>2</sub>)-phenyl substituted amides, were also unreactive, with starting material fully recovered. Encouragingly, when N-(3,5-di-trifluoromethyl)-phenyl amide was employed as the substrate, trace product was observed. Further decreasing the electron density of the N-aryl group by using a 2,3,5,6-tetrafluoro-4-(trifluoromethyl) substituent increased the yield to 11%.<sup>12</sup> When using 0.8 equiv. CuBr as an additive, the yield was improved to 23%. However, a side product (**2a**) arising from nucleophilic attack of the hydroxyl group to the C-F bond on the directing group was observed in 10% yield.

During the past several years, we have developed two kinds of ligand, the N-protected amino acid ligand and pyridine- or quinoline-based ligand, for accelerating or promoting Pd catalyzed C(sp<sup>2</sup>)-H and C(sp<sup>3</sup>)-H bond activation.<sup>13</sup> Based on these results, we next tested the ligand effect on this reaction (Table 2). N-protected amino acids, such as N-Ac-Leu (**L1**) and N-Boc-Gly (**L2**), and pyridine- (**L4**) or quinoline-based (**L5**) ligands are found to have negligible effect on the yield.

Table 3 Further optimization of C(sp<sup>2</sup>)-H hydroxylation<sup>a,b</sup>

Entry	Copper salts	Base	Acid	Yield	
				<b>3a</b>	<b>2a</b>
1	Cu(OAc) <sub>2</sub> + CuBr	Cs <sub>2</sub> CO <sub>3</sub>	PivOH	59	12
2	Cu(OAc) <sub>2</sub> + CuBr	Cs <sub>2</sub> CO <sub>3</sub>	1-Ad-COOH	61	13
3 <sup>c</sup>	Cu(OAc) <sub>2</sub> + CuBr	Cs <sub>2</sub> CO <sub>3</sub>	1-Ad-COOH	63	12
4 <sup>c,d</sup>	Cu(OAc) <sub>2</sub> + CuBr	Cs <sub>2</sub> CO <sub>3</sub>	1-Ad-COOH	63	11
5 <sup>c,d,e</sup>	Cu(OAc) <sub>2</sub> + CuBr	Cs <sub>2</sub> CO <sub>3</sub>	1-Ad-COOH	66	8
6 <sup>c,d,e,f</sup>	Cu(OAc) <sub>2</sub> + CuBr	Cs <sub>2</sub> CO <sub>3</sub>	1-Ad-COOH	67	8
7 <sup>c,d,e,f</sup>	<b>Cu(OPiv)<sub>2</sub> + CuBr</b>	Cs <sub>2</sub> CO <sub>3</sub>	<b>1-Ad-COOH</b>	<b>75(80)<sup>g</sup></b>	<b>0</b>
8 <sup>c,d,e,f</sup>	Cu(OCO <sup>t</sup> Pr) <sub>2</sub> + CuBr	Cs <sub>2</sub> CO <sub>3</sub>	1-Ad-COOH	68	0
9 <sup>c,d,e,f</sup>	Cu(OCO) <sub>2</sub> + CuBr	Cs <sub>2</sub> CO <sub>3</sub>	1-Ad-COOH	45	0

<sup>a</sup> Reaction conditions: **1** (0.1 mmol), Cu(OAc)<sub>2</sub> (0.2 mmol), CuBr (0.08 mmol), base (0.15 mmol), acid (0.15 mmol), ligand (0.1 mmol), DMSO (1.0 mL), 100 °C, air, 6 h. <sup>b</sup> Yield determined by <sup>1</sup>H NMR analysis of crude reaction mixture using CH<sub>2</sub>Br<sub>2</sub> as an internal standard. <sup>c</sup> Acid (0.18 mmol). <sup>d</sup> CuX<sub>2</sub> (0.15 mmol). <sup>e</sup> DMSO (0.5 mL). <sup>f</sup> Ligand (0.04 mmol). <sup>g</sup> 105 °C.



Considering that oxazoline ligands have been demonstrated to be effective in various copper-mediated reactions, we subsequently focused on investigating these ligands. To our delight, with ligand **L6** as an additive, the yield of **3a** could be increased to 33%, though it also promoted the nucleophilic attack process, correspondingly affording **2a** in 17% yield. Modifying the phenyl moiety on the oxazoline ligand with a biaryl framework (**L8–L11**) provided no improvement. Interestingly, when employing readily available oxazoline **L15** as a ligand, the yield was improved to 55%. Further optimization by changing the steric bulk and electron-donating ability of the ligands proved ineffective (**L16–L19**, and see ESI†).

Having identified the optimal ligand, we next performed further optimization of the reaction conditions to suppress the undesired product **2a** (Table 3). By using  $\text{Cs}_2\text{CO}_3$  and PivOH as a combined additive to generate  $\text{CsOPiv}$  *in situ*, the yield of **3a** could be increased to 59% while decreasing the yield of **2a** to

12% (Table 3, entry 1). 1-Ad-COOH proved to be a better acid, which gave the product **3a** in 61% yield (Table 3, entry 2). The yield could be slightly improved to 63% when increasing the amount of 1-Ad-COOH to 1.8 equiv. (Table 3, entry 3). The reaction proceeded in the presence of 1.5 equiv.  $\text{Cu}(\text{OAc})_2$ , 0.4 equiv. ligand and 0.5 mL DMSO to provide the product in 67% yield (Table 3, entry 4–6). After a brief survey of  $\text{Cu}(\text{II})$  salts, we found that using  $\text{Cu}(\text{OPiv})_2$  could inhibit the undesired product completely and increase the product yield to 75% (Table 3, entry 7–9). Finally, slightly increasing the temperature to 105 °C improved the yield to 80%.

### Substrate scope

With the optimal conditions in hand, we next investigated the substrate scope (Table 4).<sup>†</sup> Arenes containing *o*-methyl and *p*-methyl substitutions gave yields of 41% and 65% respectively (**3b** and **3d**), whereas an *m*-methyl-substituted arene afforded two regioisomers in a total of 60% yield (**3c**). Other electron-donating groups such as *tert*-butyl, methoxyl and phenyl were also well tolerated to give the corresponding products in 56–84% yields (**3e–3g**). An arene with *m*-fluoro substitution afforded a mixture of hydroxylation products at the C-2 and C-6 positions, with the sterically less hindered C-6 position as the major product (**3h**), while the reaction with *p*-fluoroarene

Table 4 Scope of C–H hydroxylation<sup>a,b</sup>



<sup>a</sup> Reaction conditions: **1a–1r** (0.1 mmol),  $\text{Cu}(\text{OPiv})_2$  (0.15 mmol),  $\text{CuBr}$  (0.08 mmol),  $\text{Cs}_2\text{CO}_3$  (0.15 mmol), 1-Ad-COOH (0.18 mmol), ligand (0.04 mmol), DMSO (0.5 mL), 105 °C, air, 6 h. <sup>b</sup> Isolated yield.

Table 5 Scope of C–H amination<sup>a,b</sup>



<sup>a</sup> Reaction conditions: **1** (0.1 mmol), **4a–4e** (0.3 mmol),  $\text{Cu}(\text{OAc})_2$  (0.2 mmol),  $\text{CuBr}$  (0.1 mmol),  $\text{CsOAc}$  (0.2 mmol),  $\text{LiOAc}$  (0.1 mmol), ligand (0.05 mmol), DMSO (1.0 mL), 100 °C, air, 6 h. <sup>b</sup> Isolated yield.



proceeded smoothly to give the product in 84% yield (**3i**). Importantly, this reaction was also compatible with Cl-, Br-, and I-substituted arenes, which left synthetic handles for further functionalization (**3j–3m**). Arenes bearing strong electron-withdrawing functional groups underwent C–H activation efficiently, thus providing the hydroxylated products in good to excellent yields (**3n–3q**). Notably, this hydroxylation protocol was also compatible with a vinyl-substituted arene, which is rare in noble metal-catalyzed C–H activation reactions.

With the success of achieving C–H hydroxylation of weakly coordinating amides, we wondered whether this newly developed external ligand-promoted C–H activation protocol could be compatible with C–H amination reactions using a free alkyl amine donor, which is still an unsolved problem with weakly coordinating auxiliaries.<sup>14</sup> To our delight, using unprotected morpholine as the amine coupling partner, the C–H amination reaction proceeded smoothly providing the desired products in moderate yields (Table 5). A variety of substituted arenes containing electron donating and electron withdrawing groups gave acceptable yields (**5b–5g**). Different cyclic alkyl amines also showed good compatibility with this reaction (**5h–5k**).

## Conclusions

In conclusion, we have developed a Cu-promoted C–H hydroxylation and amination of weakly coordinating amides with the assistance of an external oxazoline ligand. This finding provides guidance for further ligand development in promoting copper-catalyzed C–H activation reactions in the future.

## Acknowledgements

We gratefully acknowledge the Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, the CAS/SAFEA International Partnership Program for Creative Research Teams, NSFC-21121062, NSFC-21472211, NSFC-21421091, Youth Innovation Promotion Association CAS (No.2014229), and The Recruitment Program of Global Experts for financial support. We gratefully acknowledge The Scripps Research Institute for financial support. This work was supported by NSF under the CCI Center for Selective C–H Functionalization, CHE-1205646, and Novartis for an unrestricted grant.

## Notes and references

‡ General procedure for copper-promoted *ortho*-C–H hydroxylation: to a 15 mL sealed tube was added substrate **1** (0.1 mmol, 1.0 equiv.), Cu(OPiv)<sub>2</sub> (0.15 mmol), CuBr (0.08 mmol), Cs<sub>2</sub>CO<sub>3</sub> (0.15 mmol), 1-Ad-COOH (0.18 mmol), ligand **L15** (0.04 mmol) and DMSO (0.5 mL). The reaction tube was then placed into a pre-heated oil bath and stirred at 105 °C for 6 h under air. Upon completion, EtOAc was added to dilute the mixture, which was then washed with NH<sub>3</sub>·H<sub>2</sub>O and saturated NaCl(aq). The organic fraction was dried over Na<sub>2</sub>SO<sub>4</sub>, evaporated and purified by preparative TLC (EtOAc/hexane) to provide the corresponding products as white solids.

1 For selected reviews on C–H functionalization using transition metals, see: (a) F. Kakiuchi, S. Sekine, Y. Tanaka, A. Kamatani, M. Sonoda, N. Chatani and S. Murai, *Bull.*

*Chem. Soc. Jpn.*, 1995, **68**, 62–83; (b) X. Chen, K. M. Engle, D.-H. Wang and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2009, **48**, 5094–5115; (c) R. Giri, B.-F. Shi, K. M. Engle, N. Maugel and J.-Q. Yu, *Chem. Soc. Rev.*, 2009, **38**, 3242–3272; (d) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147–1169; (e) D. A. Colby, R. G. Bergman and J. A. Ellman, *Chem. Rev.*, 2010, **110**, 624–655; (f) J. Wencel-Delord, T. Dröge, F. Liu and F. Glorius, *Chem. Soc. Rev.*, 2011, **40**, 4740–4761; (g) P. B. Arockiam, C. Bruneau and P. H. Dixneuf, *Chem. Rev.*, 2012, **112**, 5879–5918; (h) L. Ackermann, *Acc. Chem. Res.*, 2014, **47**, 281–295.

2 For Pd-catalyzed C–H functionalizations *via* various redox manifolds, see: (a) O. Baudoin, A. Herrbach and F. Guéritte, *Angew. Chem., Int. Ed.*, 2003, **42**, 5736–5740; (b) L. S. Campeau, S. Rousseaux and K. Fagnou, *J. Am. Chem. Soc.*, 2005, **127**, 18020–18021; (c) M. Wasa, K. M. Engle and J.-Q. Yu, *J. Am. Chem. Soc.*, 2009, **131**, 9886–9887; (d) C. Jia, D. Piao, J. Oyamada, W. Lu, T. Kitamura and Y. Fujiwara, *Science*, 2000, **287**, 1992–1995; (e) X. Chen, C. E. Goodhue and J.-Q. Yu, *J. Am. Chem. Soc.*, 2006, **128**, 12634–12635; (f) N. D. Ball, J. W. Kampf and M. S. Sanford, *J. Am. Chem. Soc.*, 2010, **132**, 2878–2879; (g) S. Ma, G. Villa, P. S. Thuy-Boun, A. Homs and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2014, **53**, 734–737.

3 For iron catalyzed sp<sup>2</sup> and sp<sup>3</sup> C–H functionalizations, see: (a) A. Matsumoto, L. Ilies and E. Nakamura, *J. Am. Chem. Soc.*, 2011, **133**, 6557–6559; (b) S. Asako, L. Ilies and E. Nakamura, *J. Am. Chem. Soc.*, 2013, **135**, 17755–17757; (c) R. Shang, L. Ilies, A. Matsumoto and E. Nakamura, *J. Am. Chem. Soc.*, 2013, **135**, 6030–6032; (d) L. Ilies, T. Matsubara, S. Ichikawa, S. Asako and E. Nakamura, *J. Am. Chem. Soc.*, 2014, **136**, 13126–13129; (e) R. Shang, L. Ilies, S. Asako and E. Nakamura, *J. Am. Chem. Soc.*, 2014, **136**, 14349–14352; (f) R. Shang, L. Ilies and E. Nakamura, *J. Am. Chem. Soc.*, 2015, **137**, 7660–7663.

4 For recent development of Cu-catalyzed C–H functionalizations, see: (a) G. Brasche and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2008, **47**, 1932–1934; (b) S. Ueda and H. Nagasawa, *Angew. Chem., Int. Ed.*, 2008, **47**, 6411–6413; (c) L. M. Huffman and S. S. Stahl, *J. Am. Chem. Soc.*, 2008, **130**, 9196–9197; (d) I. Ban, T. Sudo, T. Taniguchi and K. Itami, *Org. Lett.*, 2008, **10**, 3607–3609; (e) W. Wang, F. Luo, S. Zhang and J. Cheng, *J. Org. Chem.*, 2010, **75**, 2415–2418; (f) A. M. Suess, M. Z. Ertem, C. J. Cramer and S. S. Stahl, *J. Am. Chem. Soc.*, 2013, **135**, 9797–9804; (g) A. T. Parsons and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2011, **50**, 9120–9123; (h) A. John and K. M. Nicholas, *J. Org. Chem.*, 2011, **76**, 4158–4162; (i) L. D. Tran, I. Popov and O. Daugulis, *J. Am. Chem. Soc.*, 2012, **134**, 18237–18240; (j) Z.-K. Ni, Q. Zhang, T. Xiong, Y.-Y. Zheng, Y. Li, H.-W. Zhang, J.-P. Zhang and Q. Liu, *Angew. Chem., Int. Ed.*, 2012, **51**, 1244–1247; (k) J. Roane and O. Daugulis, *Org. Lett.*, 2013, **15**, 5842–5845; (l) J. Gallardo-Donaire and R. Martin, *J. Am. Chem. Soc.*, 2013, **135**, 9350–9353; (m) S. Bhadra, W. I. Dzik and L. J. Gooßen, *Angew. Chem., Int. Ed.*, 2013, **52**, 2959–2962; (n) M. Nishino, K. Hirano, T. Satoh and M. Miura, *Angew. Chem., Int. Ed.*, 2013, **52**, 4457–4461; (o) T. Truong, K. Klimovica and O. Daugulis, *J.*



- Am. Chem. Soc.*, 2013, **135**, 9342–9345; (p) M. Shang, H.-L. Wang, S.-Z. Sun, H.-X. Dai and J.-Q. Yu, *J. Am. Chem. Soc.*, 2014, **136**, 11590–11593; (q) M. Shang, S.-Z. Sun, H.-L. Wang, B. N. Laforteza, H.-X. Dai and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2014, **53**, 10439–10442; (r) M. Shang, S.-Z. Sun, H.-X. Dai and J.-Q. Yu, *Org. Lett.*, 2014, **16**, 5666–5669; (s) J. Dong, F. Wang and J. You, *Org. Lett.*, 2014, **16**, 2884–2887; (t) S. Wang, R. Guo, G. Wang, S.-Y. Chen and X.-Q. Yu, *Chem. Commun.*, 2014, **50**, 12718–12721; (u) F.-J. Chen, G. Liao, X. Li, J. Wu and B.-F. Shi, *Org. Lett.*, 2014, **16**, 5644–5647; (v) 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**, 1104–1107; (w) S. L. McDonald, C. E. Hendrick and Q. Wang, *Angew. Chem., Int. Ed.*, 2014, **53**, 4667–4670; (x) Z. Wang, J. Ni, Y. Ni and M. Kanai, *Angew. Chem., Int. Ed.*, 2014, **53**, 3496–3499; (y) Z. Wang, Y. Kuninobu and M. Kanai, *Org. Lett.*, 2014, **16**, 4790–4793; (z) K. Takamatsu, K. Hirano and M. Miura, *Org. Lett.*, 2015, **17**, 4066–4069.
- 5 For a few examples of Fe- and Co-catalyzed C–H functionalizations with a weakly coordinating DG, see: (a) Q. Chen, L. Ilies, N. Yoshikai and E. Nakamura, *Org. Lett.*, 2011, **13**, 3232–3234; (b) Q. Chen, L. Ilies and E. Nakamura, *J. Am. Chem. Soc.*, 2011, **133**, 5221–5223; (c) L. Ilies, E. Konno, Q. Chen and E. Nakamura, *Asian J. Org. Chem.*, 2012, **1**, 142–145.
- 6 (a) K. M. Engle, T.-S. Mei, M. Wasa and J.-Q. Yu, *Acc. Chem. Res.*, 2012, **45**, 788–802; (b) S. D. Sarkar, W. Liu, S. I. Kozhushkov and L. Ackermann, *Adv. Synth. Catal.*, 2014, **356**, 1461–1479; (c) D.-H. Wang and J.-Q. Yu, *J. Am. Chem. Soc.*, 2011, **133**, 5767–5769; (d) F. W. Patureau, T. Besset and F. Glorius, *Angew. Chem., Int. Ed.*, 2011, **50**, 1064–1067; (e) K. M. Engle, P. S. Thuy-Boun, M. Dang and J.-Q. Yu, *J. Am. Chem. Soc.*, 2011, **133**, 18183–18193; (f) D. Leow, G. Li, T.-S. Mei and J.-Q. Yu, *Nature*, 2012, **486**, 518–522; (g) C. Grohmann, H. Wang and F. Glorius, *Org. Lett.*, 2012, **14**, 656–659; (h) L. Chu, K.-J. Xiao and J.-Q. Yu, *Science*, 2014, **346**, 451–455; (i) Y.-J. Liu, H. Xu, W.-J. Kong, M. Shang, H.-X. Dai and J.-Q. Yu, *Nature*, 2014, **515**, 389–393; (j) Z.-J. Du, J. Guan, G.-J. Wu, P. Xu, L.-X. Gao and F.-S. Han, *J. Am. Chem. Soc.*, 2015, **137**, 632–635; (k) S. Warratz, C. Kornhaaß, A. Cajaraville, B. Niepötter, D. Stalke and L. Ackermann, *Angew. Chem., Int. Ed.*, 2015, **54**, 5513–5517; (l) A. Bechtoldt, C. Tirlir, K. Raghuvanshi, S. Warratz, C. Kornhaab and L. Ackermann, *Angew. Chem., Int. Ed.*, 2016, **55**, 264–267.
- 7 (a) J. H. P. Tyman, *Synthetic and Natural Phenols*, Elsevier, New York, 1996; (b) Z. Rappoport, *The Chemistry of Phenols*, Wiley-VCH, Weinheim, 2003; (c) W.-Y. Huang, Y.-Z. Cai and Y. Zhang, *Nutr. Cancer*, 2010, **62**, 1–20.
- 8 For palladium-catalyzed direct hydroxylation of arenes, see: (a) T. Jintoku, K. Nishimura, K. Takaki and Y. Fujiwara, *Chem. Lett.*, 1991, 193–194; (b) Y.-H. Zhang and J.-Q. Yu, *J. Am. Chem. Soc.*, 2009, **131**, 14654–14655; (c) G. Shan, X. Yang, L. Ma and Y. Rao, *Angew. Chem., Int. Ed.*, 2012, **51**, 13070–13074; (d) F. Mo, L. J. Trzepakowski and G. Dong, *Angew. Chem., Int. Ed.*, 2012, **51**, 13075–13079; (e) P. Y. Choy and F. Y. Kwong, *Org. Lett.*, 2013, **15**, 270–273; (f) Y. Yan, P. Feng, Q.-Z. Zheng, Y.-F. Liang, J.-F. Lu, Y. Cui and N. Jiao, *Angew. Chem., Int. Ed.*, 2013, **52**, 5827–5831; (g) H.-Y. Zhang, H.-M. Yi, G.-W. Wang, B. Yang and S.-D. Yang, *Org. Lett.*, 2013, **15**, 6186–6189.
- 9 For ruthenium-catalyzed direct hydroxylation of arenes, see: (a) Y. Yang, Y. Lin and Y. Rao, *Org. Lett.*, 2012, **14**, 2874–2877; (b) V. S. Thirunavukkarasu, J. Hubrich and L. Ackermann, *Org. Lett.*, 2012, **14**, 4210–4213; (c) V. S. Thirunavukkarasu and L. Ackermann, *Org. Lett.*, 2012, **14**, 6206–6209; (d) F. Yang and L. Ackermann, *Org. Lett.*, 2013, **15**, 718–720; (e) X. Yang, G. Shan and Y. Rao, *Org. Lett.*, 2013, **15**, 2334–2337; (f) W. Liu and L. Ackermann, *Org. Lett.*, 2013, **15**, 3484–3486; (g) F. Yang, K. Rauch, K. Kettelhoit and L. Ackermann, *Angew. Chem., Int. Ed.*, 2014, **53**, 11285–11288.
- 10 (a) X. Chen, X.-S. Hao, C. E. Goodhue and J.-Q. Yu, *J. Am. Chem. Soc.*, 2006, **128**, 6790–6791; (b) For a Cu-mediated C–H amidation see: T. Uemura, S. Imoto and N. Chatani, *Chem. Lett.*, 2006, **35**, 842–843.
- 11 (a) X. Li, Y.-H. Liu, W.-J. Gu, B. Li, F.-J. Chen and B.-F. Shi, *Org. Lett.*, 2014, **16**, 3904–3907; (b) S.-Z. Sun, M. Shang, H.-L. Wang, H.-X. Lin, H.-X. Dai and J.-Q. Yu, *J. Org. Chem.*, 2015, **80**, 8843–8848; (c) B. K. Singh and R. Jana, *J. Org. Chem.*, 2016, **81**, 831–841.
- 12 (a) M. Wasa, K. M. Engle and J.-Q. Yu, *J. Am. Chem. Soc.*, 2009, **131**, 9886–9887; (b) M. Wasa, K. M. Engle and J.-Q. Yu, *J. Am. Chem. Soc.*, 2010, **132**, 3680–3681.
- 13 For ligand-enabled or -promoted C–H activation reactions using Pd catalyst, see: (a) D.-H. Wang, K. M. Engle, B.-F. Shi and J.-Q. Yu, *Science*, 2010, **327**, 315–319; (b) K. M. Engle, D.-H. Wang and J.-Q. Yu, *J. Am. Chem. Soc.*, 2010, **132**, 14137–14151; (c) M. Wasa, K. S. L. Chan, X.-G. Zhang, J. He, M. Miura and J.-Q. Yu, *J. Am. Chem. Soc.*, 2012, **134**, 18570–18572; (d) J. He, S. Li, Y. Deng, H. Fu, B. N. Laforteza, J. E. Spangler, A. Homs and J.-Q. Yu, *Science*, 2014, **343**, 1216–1220; (e) S. Li, G. Chen, C.-G. Feng, W. Gong and J.-Q. Yu, *J. Am. Chem. Soc.*, 2014, **136**, 5267–5270; (f) R.-Y. Zhu, K. Tanaka, G.-C. Li, J. He, H.-Y. Fu, S.-H. Li and J.-Q. Yu, *J. Am. Chem. Soc.*, 2015, **137**, 7067–7070; (g) J. Li, S. Warratz, D. Zell, S. D. Sarkar, E. E. Ishikawa and L. Ackermann, *J. Am. Chem. Soc.*, 2015, **137**, 13894–13901; (h) Y. Yang, X. Qiu, Y. Zhao, Y. Mu and Z. Shi, *J. Am. Chem. Soc.*, 2016, **138**, 495–498.
- 14 For selective examples of C–H amination reactions, see: (a) H.-Y. Thu, W.-Y. Yu and C.-M. Che, *J. Am. Chem. Soc.*, 2006, **128**, 9048–9049; (b) K.-H. Ng, A. S. C. Chan and W.-Y. Yu, *J. Am. Chem. Soc.*, 2010, **132**, 12862–12864; (c) B. Xiao, T.-J. Gong, J. Xu, Z.-J. Liu and L. Liu, *J. Am. Chem. Soc.*, 2011, **133**, 1466–1470; (d) K. Sun, Y. Li, T. Xiong, J. Zhang and Q. Zhang, *J. Am. Chem. Soc.*, 2011, **133**, 1694–1697; (e) E. J. Yoo, S. Ma, T.-S. Mei, K. S. L. Chan and J.-Q. Yu, *J. Am. Chem. Soc.*, 2011, **133**, 7652–7655; (f) K.-H. Ng, Z. Zhou and W.-Y. Yu, *Org. Lett.*, 2012, **14**, 272–275; (g) C. Grohmann, H. Wang and F. Glorius, *Org. Lett.*, 2012, **14**, 656–659; (h) L. D. Tran, J. Roane and O. Daugulis, *Angew. Chem., Int. Ed.*, 2013, **52**, 6043–6046; (i) M. Shang, S.-Z. Sun, H.-X. Dai and J.-Q. Yu, *J. Am. Chem. Soc.*, 2014, **136**, 3354–3357.

