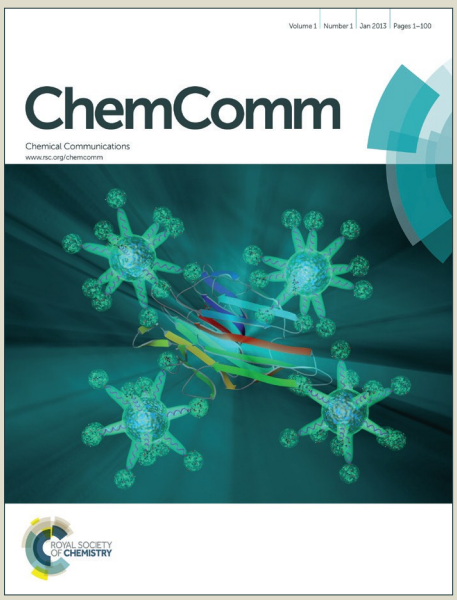
ChemComm

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: D. Sun, B. Li, J. Lan, Q. Huang and J. You, *Chem. Commun.*, 2016, DOI: 10.1039/C6CC00103C.



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

View Article Online
DOI: 10.1039/C6CC00103C

Journal Name

COMMUNICATION

Chelation-assisted Pd-catalysed *ortho*-selective oxidative C–H/C–H cross-coupling of aromatic carboxylic acids with arenes and intramolecular Friedel-Crafts acylation: one-pot formation of fluorenones

rReceived 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

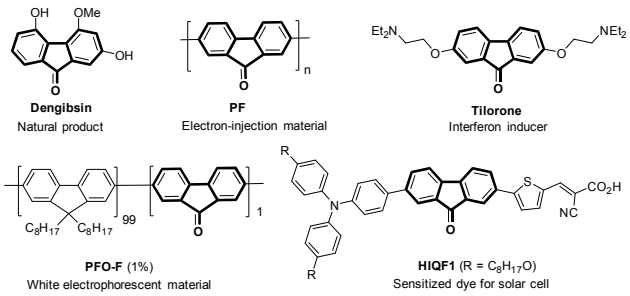
www.rsc.org/

Denan Sun, Bijin Li, Jingbo Lan,* Quan Huang and Jingsong You*

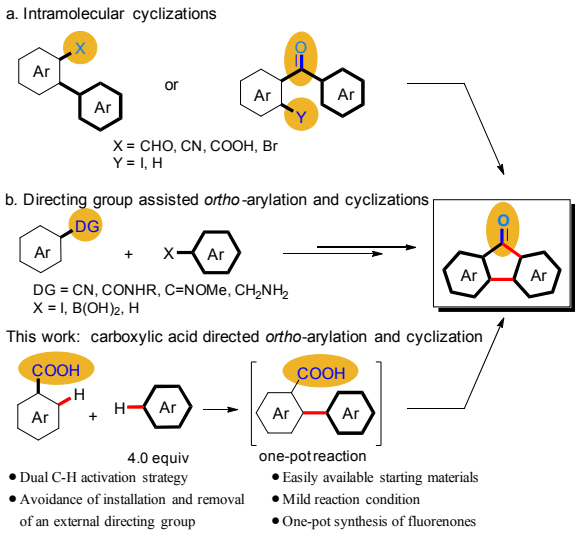
Pd-catalysed *ortho*-selective oxidative C–H/C–H cross-coupling of aromatic carboxylic acids with arenes and subsequent intramolecular Friedel-Crafts acylation has been accomplished for the first time through chelation-assisted C–H activation strategy. Starting from readily available substrates, a variety of fluorenone derivatives are obtained in one pot. The direct use of naturally occurring carboxylic acid functionalities as directing groups avoids unnecessary steps for installation and removal of an extra directing group.

Fluorenone derivatives have attracted widespread interest because of their important applications in the fields of biomedical and photoelectric materials (Scheme 1).[1] Traditional methods towards the synthesis of fluorenones include Friedel-Crafts cyclization of biaryl carboxylic acids,[2] Pschorr cyclization of 2-amino diaryl ketones,[3] and oxidation of fluorenol.[4] However, these methods suffer from some limitations such as multistep procedures, inaccessible synthetic precursors and/or tedious prefunctionalization. During recent decades, transition metal-catalysed C–H bond functionalization has emerged as a powerful method to construct C–C bonds,[5] many of which have thus been developed to access fluorenone frameworks.[6-7] For instance, the transition metal-catalysed intramolecular cyclizations of 2-aryl-benzaldehydes, 2-aryl-benzonitrile, biaryl-2-carboxylic acids, *o*-halobiaryls and CO, as well as various diaryl ketone derivatives are efficient methodologies for the synthesis of fluorenones (Scheme 2a).[6] In addition, the directing group assisted *ortho*-arylations of aryl nitriles, benzamides, aryl aldoxime ethers, or benzylamines with iodo arenes, aryl boronic acids, or simple arenes (as solvent), and subsequent intramolecular cyclizations have also been extensively studied to provide fluorenones (Scheme 2b).[6b,7]

The carboxylic acid group is one of the most common organic functionalities.[8] Aromatic carboxylic acids are widespread in natural and synthetic products.[9] From the perspective of synthetic simplicity and availability of starting materials, the direct use of naturally occurring carboxylic acid functionalities as directing groups to activate *ortho*-C–H bonds of aromatic carboxylic acids is doubtless one of the most ideal strategies to achieve the *ortho*-selective arylation of arenes, which avoid unnecessary steps for installation and removal of an extra directing group.



Scheme 1. Natural products, pharmaceutical drugs and photoelectric materials containing the fluorenone framework.



Scheme 2. Synthesis of fluorenone derivatives.

[a] *Key Laboratory of Green Chemistry and Technology of Ministry of Education, College of Chemistry, and State Key Laboratory of Biotherapy, West China Medical School, Sichuan University, 29 Wangjiang Road, Chengdu 610064, P. R. China. E-mails: jingbolan@scu.edu.cn and jsyou@scu.edu.cn*

† Supplementary Information (ESI) available: Experimental procedures, analytical data for products, NMR spectra of products. See DOI: 10.1039/x0xx00000x

View Article Online
DOI: 10.1039/C6CC00103C

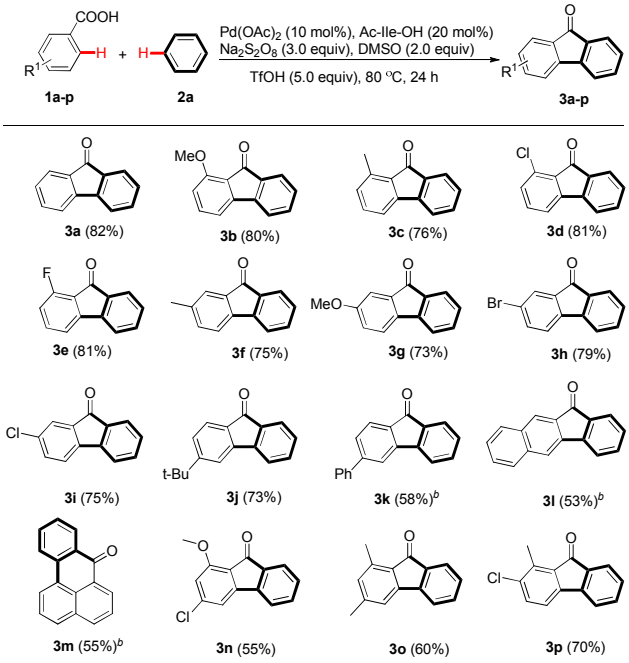
Recently, the Rh(III)-catalysed carboxylic acid directed *ortho*-C–H heteroarylation of aromatic carboxylic acids have been implemented through the oxidative C–H/C–H cross-coupling with thiophenes, furans, indoles, azoles, etc. by Su and our group, respectively.[10,11] However, the carboxylic acid directed oxidative C–H/C–H cross-coupling of aromatic carboxylic acids with simple arenes still remains unsettled. One of the greatest challenges in this transformation is that aromatic carboxylic acids are peculiarly prone to undergo decarboxylation in the presence of transition metals.[12] In addition, due to the generally low reactivity of C–H bonds, arenes are usually used as solvent or cosolvent, which impose a limitation on synthetic applications.[13] As part of our program for the C–H bond activation of (hetero)arenes,[11,14] we present the solution to these problems and disclose the direct oxidative *ortho*-C–H arylation of aromatic carboxylic acids through dual C–H activation and subsequent intramolecular Friedel-Crafts acylation to construct diverse substituted fluorenone derivatives (Scheme 2).

To test the feasibility of the dual C–H activation strategy, we explored the oxidative C–H/C–H cross-coupling of benzoic acid (**1a**) and benzene (**2a**). Surprisingly, the coupling reaction of **1a** with **2a** directly provided the fluorenone **3a** in 45% yield with concomitant intramolecular Friedel-Crafts acylation in the presence of $Pd(OAc)_2$ and trifluoromethanesulfonic acid (TfOH) by using $Na_2S_2O_8$ as the oxidant (Table S1, entry 5). Considering the importance of the Fluorenone derivatives, the reaction conditions were further optimized. Several key parameters including different acids, oxidants, reaction temperature, ligands and the amount of benzene were screened, and rewardingly, this protocol produced a high yield of fluorenone in model systems at a relatively low temperature (Table S1-S6). Finally, the optimal reaction condition was obtained when **1a** (0.40 mmol), **2a** (1.60 mmol), $Pd(OAc)_2$ (10 mol%) and $Na_2S_2O_8$ (3.0 equiv) in TfOH (5.0 equiv), DMSO (2.0 equiv), and Ac-Ile-OH (20 mol%) at 80 °C for 24 h under an air atmosphere (Table S6, entry 5). We supposed that DMSO might play important roles in activating catalyst and preventing the formation of palladium black.[15] It is worthwhile to note that this coupling reaction could deliver fluorenone in 82% yield with only 4.0 equiv of arene coupling partner.[16]

Using the optimal conditions, the scope of aromatic carboxylic acids was examined with benzene (**2a**) as an arylating reagent. Aromatic carboxylic acids with *ortho*-, *meta*-, and *para*-substituents reacted with benzene in good yields (**3b**-**3k**). 2-Naphthoic acid could undergo the cross-coupling at C3-position to afford 11*H*-benzo[*b*]fluoren-11-one in acceptable yield (**3l**). 1-Naphthoic acid reacts at C8-position to produce 7*H*-benzo[*de*]anthracen-7-one in 55% yields (**3m**). The cross-coupling of both 2,4- and 2,3-disubstituted benzoic acids with benzene gave the disfunctionalized fluorenone derivatives in synthetically useful yields (**3n**-**3p**). Notably, this oxidative cross-coupling reaction could tolerate reactive chloride and bromide, which would provide a benefit for the further synthetic transformations. Unfortunately, benzoic acids with strong electron-withdrawing substituents, such as nitro and cyano could not react with benzene to afford corresponding fluorenones.

Furthermore, the scope of arenes was next examined using 2-methoxy benzoic acid (**1b**) as the coupling partner. It was found that this reaction could tolerate a wide range of arene substrates with both electron-donating groups, such as *m*-xylene, *p*-xylene and toluene, and electron-withdrawing groups, such as *o*-difluorobenzene and *p*-difluorobenzene, to deliver fluorenones in satisfactory yields (Table 2). The cross-coupling of **1b** with *o*-difluorobenzene occurred highly regioselectively at the 4-position and then intramolecular Friedel-Crafts acylation at the 5-position of benzene ring (**4c**). The coupling of **1b** with *m*-xylene also occurred at the 4-position and then acylation at 5-position (**4d**). However, the coupling reaction of **1b** with 2-chloro-*m*-xylene occurred regioselectively at the 5-position and then acylation at 4-position (**4e**). The reaction of toluene with **1b** gave fluorenone **4f** in a lower yield due to the generation of a small amount of regioisomer. The structures of **4c**, **4d**, **4e** and **4f** were verified by single-crystal X-ray analysis (Table 2), HMBC (see ESI†) or NOESY (see ESI†).

Table 1. Scope of benzoic acids[a]



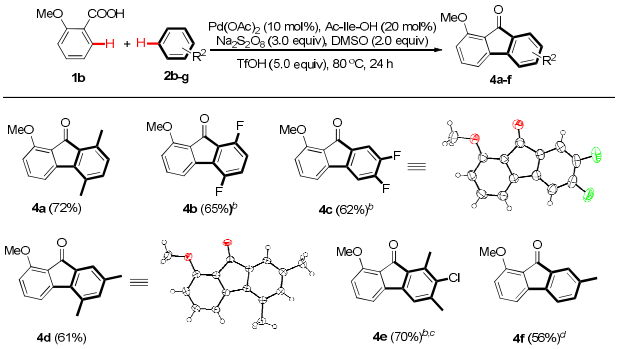
[a]Reaction conditions: aromatic carboxylic acid (0.4 mmol), arene (4.0 equiv), $Pd(OAc)_2$ (10 mol%), $Na_2S_2O_8$ (3.0 equiv), TfOH (5.0 equiv), DMSO (2.0 equiv), Ac-Ile-OH (20 mol%) at 80 °C under an air atmosphere for 24 h. [b]**2a** (10.0 equiv) DMSO = dimethyl sulfoxide. Ac-Ile-OH = 2-acetamido-3-methylpentanoic acid.

To gather further insight into the oxidative C–H/C–H cross-coupling of aromatic carboxylic acids with arenes and intramolecular Friedel-Crafts acylation, the kinetic H/D isotope effect (KIE) studies were performed for both benzoic acid and benzene. The intermolecular competition reaction between benzoic acid and benzoic-d_5 acid gave a small KIE value (k_H/k_D = 1.0) [see Eq. (S1)], indicating that the C–H bond cleavage of benzoic acid would not be the rate-determining step. However, a significant KIE (k_H/k_D = 2.0) was observed in the competition experiment of benzene and benzene-d_6 [see Eq. (S2)], suggesting that the C–H bond breaking of benzene might be the rate-limiting step. Based on these findings, a plausible catalytic cycle could involve: the coordination of **1a** to Pd(II) and subsequent *ortho*-C–H activation form the five membered palladacycle **IM-1**;[17] The oxidation of **IM-1** generates the

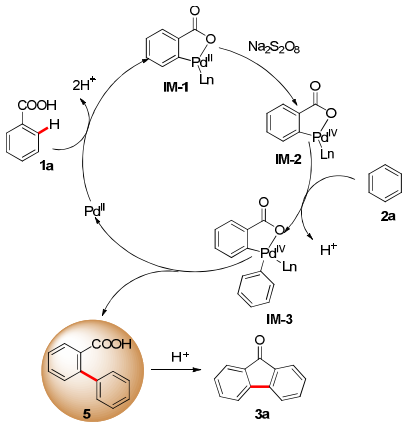
View Article Online
DOI: 10.1039/C6CC00103C

Pd(IV) intermediate **IM-2**, which reacted with the substrate **2a** to afford the critical aryl–palladacycle intermediate **IM-3**; Reductive elimination leads to the *ortho*-arylated product **5** and Pd(II) for the next catalytic cycle; The Friedel-Crafts acylation of **5** gives fluorenone **3a** (Scheme 3).

Table 2. Scope of arenes[a]



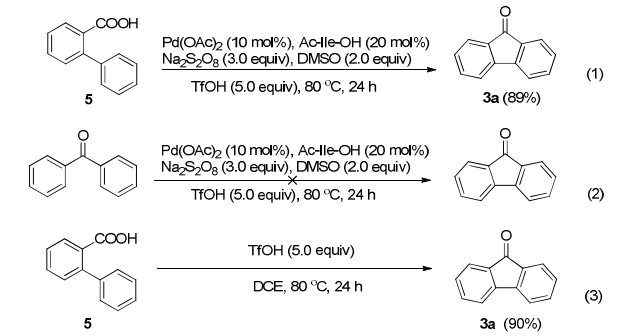
[a]Reaction conditions: aromatic carboxylic acid (0.4 mmol), arene (4.0 equiv), $Pd(OAc)_2$ (10 mol%), $Na_2S_2O_8$ (3.0 equiv), TfOH (5.0 equiv), DMSO (2.0 equiv), Ac-Ile-OH (20 mol%) at 80 °C under an air atmosphere for 24 h. [b]MeCN (2.0 equiv). [c]Structure was verified by NOESY. [d]Structure was verified by HMBC.

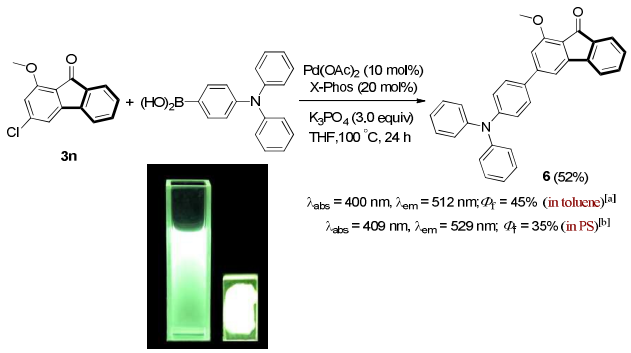


Scheme 3. Proposed mechanism for the catalytic reaction of benzoic acid (**1a**) with benzene (**2a**)

To support this catalytic cycle, the biphenyl-2-carboxylic acid (**5**) was prepared and its reactivity was examined. Under optimal conditions, the intramolecular Friedel-Crafts reaction of **5** occurred readily to afford the cyclization product 9-fluorenone in 89% yield [Eq. (1)]. However, when benzophenone was treated in the same condition, the cyclization product was not obtained [Eq. (2)]. Moreover, when the same reaction was carried out in the absence of $Pd(OAc)_2$ and $Na_2S_2O_8$, **3a** was obtained in 90% yield [Eq. (3)]. The observations indicate that fluorenone could be formed by the intramolecular Friedel-Crafts reaction of biphenyl-2-carboxylic acid in the presence of TfOH.

The triphenylamine (TPA) group is widespread in various photoelectric materials due to their good electron-donating property, hole-transporting capability and nonplanar characteristic.[18] To illuminate the synthetic utility of our methodology and highlight the importance of fluorenone skeletons in the construction of organic luminescent materials, 3-(4-(diphenylamino)phenyl)-1-methoxy-9*H*-fluoren-9-one (**6**) was synthesized *via* the Suzuki coupling of **3n** and (4-(diphenylamino)phenyl)boronic acid (Scheme 4).[14a] Gratifyingly, **6** exhibits strong yellow-green emissions and high fluorescence quantum yields in both toluene solution (45%) and PS film (35%) (Scheme 4, and see Figure S2).





Scheme 4 Synthesis of 3-(4-(diphenylamino)phenyl)-1-methoxy-9*H*-fluoren-9-one (**6**). Absolute quantum yields, absorption and emission maxima were measured [a] in toluene (5.0×10^{-5} M) and [b] in PS films (5.0 wt%), respectively. Insert: fluorescence images of **6** in toluene (5.0×10^{-5} M), and in PS films (5.0 wt%) under UV light (365 nm).

In conclusion, we have developed an efficient method for the synthesis of fluorenone derivatives through chelation-assisted Pd-catalysed *ortho*-selective oxidative C–H/C–H cross-coupling of aromatic carboxylic acids with arenes and subsequent intramolecular Friedel-Crafts acylation. A variety of fluorenones are obtained in good yield with only 4.0 equiv of arene coupling partner. Furthermore, the direct use of naturally occurring carboxylic acid functionalities as directing groups avoids unnecessary steps for installation and removal of an extra directing group. As an example to illuminate the synthetic utility of our protocol, we furthermore demonstrated that the TPA-modified fluorenone derivative **6** is a potential organic luminescent material.

This work was supported by grants from the National NSF of China (Nos 21432005, 21372164, 21321061 and 21272160), and Sichuan Provincial Foundation (2012JQ0002).

Notes and references

‡ CCDC 1444004 (**4c**) and 1443932 (**4d**) contain the supplementary crystallographic data for this paper. These data

View Article Online
DOI: 10.1039/C6CC00103C

can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

1 (a) R. F. Krueger, G. D. Mayer, *Science*, 1970, **169**, 1213; (b) W. D. Jones, Jr., F. L. Ciske, *J. Org. Chem.*, 1996, **61**, 3920; (c) X. Gong, D. Moses, A. J. Heeger, *J. Phys. Chem. B*, 2004, **108**, 8601; (d) F. Uckert, Y.-H. Tak, K. Müllen, H. Bässler, *Adv. Mater.*, 2000, **12**, 905; (e) C. Qin, A. Islam, L. Han, *J. Mater. Chem.,* 2012, **22**, 19236.
2 L. G. Wade, Jr., K. J. Acker, R. A. Earl, R. A. Osteryoung, *J. Org. Chem.*, 1979*,* **44***,* 3724.
3 M. Orchin, L. Reggel, *J. Am. Chem. Soc.*, 1951, **73**, 436.
4 (a) Q. Wang, W. Du, T. Liu, H. Chai, Z. Yu, *Tetrahedron Lett.*, 2014*,* **55***,* 1585; (b) L. J. Mitchell, C. J. Moody, *J. Org. Chem.*, 2014, **79**, 11091; (c) R. A. Fernandes, V. Bethi, *RSC Advances,* 2014, **4**, 40561.
5 For selected recent reviews, see: (a) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem. Int. Ed.,* 2009, **48**, 5094; (b) T. W. Lyons, M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147; (c) C. S. Yeung, V. M. Dong, *Chem. Rev.*, 2011, **111**, 1215; (d) S. H. Cho, J. Y. Kim, J. Kwak, S. Chang, *Chem. Soc. Rev.*, 2011, **40**, 5068; (e) N. Kuhl, M. N. Hopkinson, J. Wencel-Delord, F. Glorius, *Angew. Chem. Int. Ed.,* 2012, **51**, 10236; (f) K. Hirano, M. Miura, *Chem. Commun.*, 2012, **48**, 10704; (g) Y. Wu, J. Wang, F. Mao, F. Y. Kwong, *Chem. Asian J.*, 2014, **9**, 26; (h) C. Liu, J. Yuan, M. Gao, S. Tang, W. Li, R. Shi, A. Lei, *Chem. Rev.*, 2015, **115**, 12318.
6 (a) D. E. Ames, A. Opalko, *Tetrahedron,*1984, **40**, 1919; (b) M. A. Campo R. C. Larock, *Org. Lett.,* 2000, **2**, 3675; (c) P. Gandeepan, C.-H. Hung, C.-H. Cheng, *Chem. Commun.,* 2012, **48**, 9379; (d) H. Li, R.-Y Zhu, W.-J. Shi, K.-H. He, Z.-J. Shi, *Org. Lett.,* 2012, **14**, 4850; (e) Z. Shi, F. Glorius, *Chem. Sci.*, 2013, **4**, 829; (f) J.-C. Wan, J.-M. Huang, Y.-H. Jhan, J.-C. Hsieh, *Org. Lett.,* 2013, **15**, 2742; (g) T. Fukuyama, S. Maetani, K. Miyagawa, I. Ryu, *Org. Lett.,* 2014, **16**, 3216.
7 (a) V. S. Thirunavukkarasu, K. Parthasarathy, C.-H. Cheng, *Angew. Chem. Int. Ed.,* 2008, **47**, 9462; (b) C.-L. Sun, N. Liu, B.-J. Li, D.-G. Yu, Y. Wang, Z.-J. Shi, *Org. Lett.,* 2010, **12**, 184; (c) V. S. Thirunavukkarasu, C.-H. Cheng, *Chem. Eur. J.*, 2011, **17**, 14723; (d) R. K. Chinnagolla, M. Jeganmohan, *Org. Lett.,* 2012, **14**, 5246; (e) D. R. Kumar, G. Satyanarayana, *Org. Lett.,* 2015, **17**, 5894.
8 L. J. Gooßen, N. Rodríguez, K. Gooßen, *Angew. Chem. Int. Ed.,* 2008, **47**, 3100.
9 L. J. Gooßen, N. Rodríguez, *Chem. Commun.,* 2004, 724.
10 Y. Zhang, H. Zhao, M. Zhang, W. Su, *Angew. Chem. Int. Ed.,* 2015, **54**, 3817.
11 (a) 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; (b) X. Qin, D. Sun, Q. You, Y. Cheng, J. Lan, J. You, *Org. Lett.,* 2015, **17**, 1762.
12 (a) N. Rodríguez, L. J. Goossen, *Chem. Soc. Rev.*, 2011, **40**, 5030; (b) J. Kan, S. Huang, J. Lin, M. Zhang, W. Su, *Angew. Chem. Int. Ed.*, 2015, **54**, 2199; (c) S. Zhao, Y.-J. Liu, S.-Y. Yan, F.-J. Chen, Z.-Z. Zhang, B.-F. Shi, *Org. Lett.,* 2015, **17**, 3338.
13 (a) D. R. Stuart, K. Fagnou, *Science*, 2007, **316**, 1172; (b) D. R. Stuart, E. Villemure, K. Fagnou, *J. Am. Chem. Soc.*, 2007, **129**, 12072; (c) K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.,* 2007, **129**, 11904; (d) X. Zhao, C. S. Yeung, V. M. Dong, *J. Am. Chem. Soc.,* 2010, **132**, 5837; (e) S. Potavathri, K. C. Pereira, S. I. Gorelsky, A. Pike, A. P. LeBris, B. DeBoef, *J. Am. Chem. Soc.,* 2010, **132**, 14676; (f) Y. Wei, W. Su, *J. Am. Chem. Soc.,* 2010, **132**, 16377; (g) X. Wang, D. Leow, J.-Q. Yu, *J. Am. Chem. Soc.,* 2011, **133**, 13864; (h) J. Wencel-Delord, C. Nimphius, H. Wang, F. Glorius, *Angew. Chem. Int. Ed.,* 2012, **51**, 13001; (i) T. E. Storr, F. Namata, M. F. Greaney, *Chem. Commun.,* 2014, **50**, 13275.
14 (a) X. Qin, H. Liu, D. Qin, Q. Wu, J. You, D. Zhao, Q. Guo, X. Huang, J. Lan, *Chem. Sci.*, 2013, **4**, 1964; (b) B. Li, J. Lan, D. Wu, J. You, *Angew. Chem. Int. Ed.,* 2015, **54**, 14008.
15 (a) B. A. Steinhoff, S. S. Stahl, *J. Am. Chem. Soc.*, 2006, **128**, 4348; (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.
16 (a) B.-J Li, S.-L Tian, Z. Fang, Z.-J. Shi, *Angew. Chem. Int. Ed.,* 2008, **47**, 1115; (b) G. Brasche, J. García-Fortanet, S. L. Buchwald, *Org. Lett.,* 2008, **10**, 2207.
17 T.-S. Mei, R. Giri, N. Maugel, J.-Q. Yu, *Angew. Chem. Int. Ed.*, 2008, **47**, 5215
18 M. Zhu, C. Yang, *Chem. Soc. Rev.,* 2013, **42**, 4963.