

CrossMark  
click for updatesCite this: *Chem. Sci.*, 2015, 6, 5595Received 12th May 2015  
Accepted 24th June 2015

DOI: 10.1039/c5sc01737h

www.rsc.org/chemicalscience

# Pd(II)-catalyzed remote regiodivergent *ortho*- and *meta*-C–H functionalizations of phenylethylamines†

Shangda Li,‡<sup>a</sup> Huafang Ji,‡<sup>a</sup> Lei Cai<sup>a</sup> and Gang Li\*<sup>ab</sup>

Site selectivity control is of vital importance in the direct functionalization of inert C–H bonds. Reported here is a novel example of remote regiodivergent *ortho*- and *meta*-C–H bond functionalizations of phenylethylamine derivatives by using a novel 2-cyanobenzoyl group as the original directing functionality, where the regioselectivity was adjusted by a methylation. The potential of the method was exemplified by sequential functionalizations of both *ortho*- and *meta*-C–H bonds of a phenylethylamine derivative in a streamlined manner.

## Introduction

Controlling site selectivity is an outstanding challenge in the direct functionalization of inert C–H bonds that are ubiquitous in organic molecules.<sup>1</sup> The increasing applications of these type of transformations in organic synthesis also demand accessibility to diverse site selectivities.<sup>2</sup> While numerous directing groups have been introduced to assist the cleavage of proximal *ortho*-C–H bonds in most cases with transition metals,<sup>1,3–10</sup> directing group assisted *meta*-selective C–H functionalization of arenes has proved especially challenging and is still very rare.<sup>5,6,8,9</sup> In 2009, a remarkable breakthrough was reported by Gaunt *et al.*, who developed a carbonyl group directed unprecedented *meta*-selective C–H arylation of anilides by using a Cu(II) catalyst and diaryliodonium salts.<sup>5a</sup> This method was later extended to  $\alpha$ -aryl carbonyl compounds by the same group.<sup>5b</sup> Another impressive breakthrough came from the Frost group, who introduced an ingenious method of *meta*-selective C–H sulfonation of 2-phenylpyridines *via* cyclometalated ruthenium intermediates.<sup>6a,b</sup> A similar strategy was then employed by Ackermann to realize a *meta*-selective C–H alkylation with secondary alkyl halides.<sup>6c</sup> Recently, a small number of ground-breaking examples of Pd(II) catalyzed directed *meta*-selective C–H functionalizations of arenes that were attached with elegantly devised nitrile-based templates were disclosed, pioneered by Yu and then further

studied by Tan and Maiti.<sup>8</sup> By using the above directing group assisted *meta*-selective C–H functionalization of arenes, elegant regiodivergent functionalizations of *ortho*- and *meta*-C–H bonds have been reported by Gaunt,<sup>4b,5b</sup> Frost<sup>6b</sup> and Yu,<sup>8b</sup> and examples of reactions reported by Gaunt<sup>4b,5b</sup> and Frost<sup>6b</sup> could even be performed sequentially.<sup>8i,11,12</sup> However, the use of analogous directing groups to achieve *remote-selective* regiodivergent activation of *ortho*- and *meta*-C–H bonds has not been examined and remains a significant challenge.<sup>13,14</sup> We envision that such methodology is highly desirable for drug discovery and material sciences, since it only requires a single operation to achieve a different remote regioselectivity.<sup>2f</sup> Herein, we report a novel strategy for regiodivergent *ortho*- and *meta*-C–H functionalizations of phenylethylamine derivatives.

To test our hypothesis of a regiodivergent C–H functionalization strategy by using analogous directing groups, we selected phenylethylamines as the testing compounds, since they are a class of aromatic compounds that are important core structures of numerous drug molecules (Fig. 1). Moreover, although *ortho*-C–H functionalizations have been reported for phenylethylamine derivatives, their *meta*-selective C–H functionalization remains elusive.<sup>15</sup> Inspired by recent studies on directed *meta*-selective C–H functionalizations of arenes,<sup>8</sup> we proposed that a 2-cyanobenzoyl group could act as the key directing functionality for both *ortho*- and *meta*-C–H functionalizations of phenylethylamines with a Pd(II) catalyst by taking advantage of the  $\sigma$  and  $\pi$  coordination ability of the nitrile group (Scheme 1).<sup>16</sup> However, during our study we found that our proposed mode of *ortho*-selective C–H bond cleavage was not feasible and a novel remote-selective *ortho*-C–H bond cleavage was observed instead (*vide infra*).<sup>13,14</sup>

## Results and discussion

To examine our original hypothesis (Scheme 2), we chose olefination as the model reaction.<sup>16,17</sup> After extensive condition

<sup>a</sup>Key Laboratory of Coal to Ethylene Glycol and Its Related Technology, Fujian Institute of Research on the Structure of Matter, Chinese Academy of Sciences, 155 West Yang-Qiao Road, Fuzhou, Fujian, 350002, P. R. China. E-mail: gangli@fjirsm.ac.cn

<sup>b</sup>State Key Laboratory of Structural Chemistry, Chinese Academy of Sciences, Fuzhou, Fujian, 350002, P. R. China

† Electronic supplementary information (ESI) available: Experimental procedures and data for new compounds. CCDC 1056709 and 1406595. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5sc01737h

‡ These authors contributed equally.



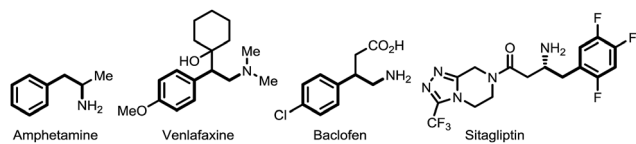
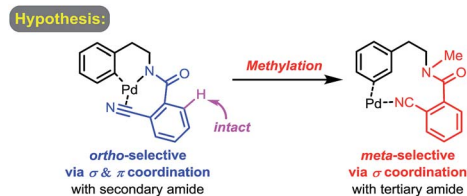


Fig. 1 Representative drugs containing a phenylethylamine core.

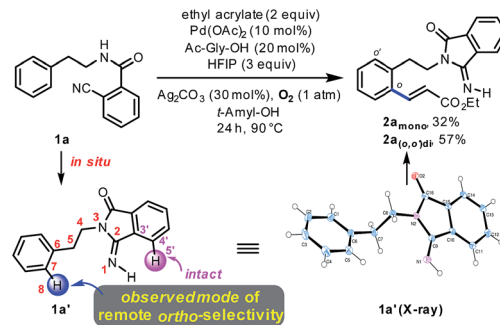


Scheme 1 Hypothesis of regioselectivity changed by a methylation.

screening with  $\text{Pd}(\text{OAc})_2$  as the catalyst (see ESI<sup>†</sup>), we were able to produce a high combined yield of *ortho*-olefinated products by treating **1a** with ethyl acrylate under oxygen with hexafluoroisopropanol (HFIP) as an additive and *N*-acetyl-glycine (Ac-Gly-OH) ligand.<sup>8a,18</sup> Interestingly, the 2-cyanobenzoyl motif cyclized to an imidamide derivative in the products. To ascertain the mechanism of this olefination, **1a** was subjected to the above reaction conditions without adding ethyl acrylate, affording **1a'** that was believed to be the reactive substrate for the olefination. Indeed, after **1a'** was treated with the same olefination conditions, the desired products were generated in similar yields (see ESI<sup>†</sup>). Although this reaction pathway is not desired from our original hypothesis, the site selectivity of this reaction is surprisingly uncommon since the imino group of **1a'**, the most likely directing group on **1a'**, directed the cleavage of a remote *ortho*-C–H bond rather than a proximal *ortho*-C–H bond on the arene attached to the imidamide, which is in marked contrast to the *ortho*-C–H functionalizations of arylimine derivatives.<sup>19</sup> The exact origin of the selectivity is unclear at present, and the study of the mechanism is under way.<sup>14</sup>

Several representative substrates were then surveyed briefly (Table 1). It was found that electron-withdrawing groups like chloride and fluoride were tolerated (**2b–c**), giving good yields of desired products. Good to excellent yields of products were also generated with substrates containing electron-donating groups such as methyl at the *meta*-position (**2d**) and methoxy at the *ortho*- (**2e**) and *para*-position (**2f**).

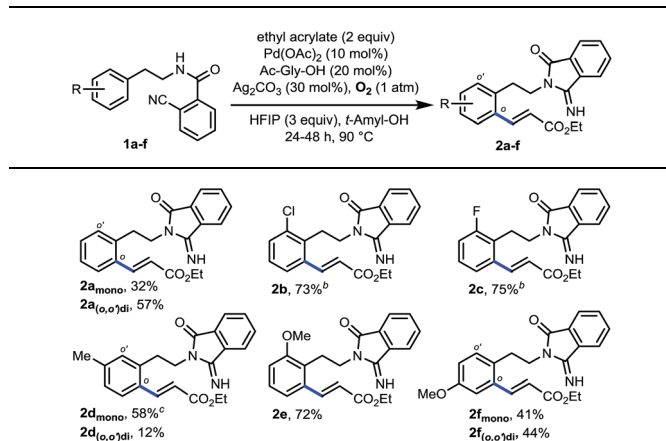
Having established the remote-selective *ortho*-C–H olefination of the secondary phenylethylamide, we were eager to test whether the selectivity could be switched to a remote-selective *meta*-C–H olefination after the secondary amide is methylated into a tertiary one (see the ESI<sup>†</sup> for methylation with MeI). Starting with the above *ortho*-olefination reaction conditions, we were very delighted to find that *N*-methyl amide **3a** could lead to a 10% yield of the desired product with a trace of other regioisomers (Table 2, entry 1). Inspired by the previous discovery that HFIP was a compatible solvent with nitrile-based templates,<sup>8</sup> we switched the solvent to HFIP and found that the combined yield of desired products was increased dramatically



Scheme 2 A novel remote-selective *ortho*-C–H olefination.

to 58% with silver acetate as the sole oxidant (entry 2). Since when using weakly acidic HFIP as the sole solvent some substrate might decompose, DCE was added as the co-solvent, resulting in an increased yield of 73% (entry 3). To optimize the solvent system, we decreased the volume of HFIP to 15% and found that the combined yield was only slightly improved (entry 4). However, a further decreased volume of HFIP led to a much diminished yield (entry 5). Other solvents were also screened, but the combination of DCE and HFIP proved to be the best. The addition of a weak base, such as  $\text{KHCO}_3$ , to tune the acidity of the reaction system was not effective either (entry 6). Since a higher catalytic turnover of the Pd catalyst was observed with 50% volume of HFIP, we repeated the reaction with this solvent system at 80 °C and found that the combined yield was improved to 90% in 32 hours under nitrogen (entry 7), representing the highest catalytic turnover of the Pd catalyst. Finally, by adding 5 equivalents of DMF we were able to get more mono-olefinated product in 28 hours while maintaining the overall efficiency (entry 8, see the ESI<sup>†</sup> for more condition screenings). However, further screening of reaction conditions could not result in better mono- vs. di-olefination selectivity at present,

Table 1 Representative substrates of remote *ortho*-C–H olefination<sup>a</sup>



<sup>a</sup> Reaction conditions: **1** (0.2 mmol), ethyl acrylate (0.4 mmol),  $\text{Pd}(\text{OAc})_2$  (10 mol%), Ac-Gly-OH (20 mol%), HFIP (0.6 mmol),  $\text{Ag}_2\text{CO}_3$  (0.06 mmol),  $\text{O}_2$  (1 atm), *t*-amyl-OH (2 mL), 24–48 h, 90 °C. Isolated yields are reported, see the ESI for details. <sup>b</sup> 80 °C. <sup>c</sup> 70 °C.



Table 2 Screening of reaction conditions for *meta*-C–H olefination<sup>a</sup>

Entry	Solvents [v/v]	T (°C)	Yield (%) [ <b>4a</b> <sub>mono</sub> , <b>4a</b> <sub>(m,m')di</sub> ]	<b>3a</b> (%)
1 <sup>b</sup>	<i>t</i> -Amyl-OH	90	10 [10, 0]	90
2	HFIP	90	58 [13, 45]	Trace
3	DCE/HFIP [50/50]	90	71 [32, 39]	Trace
4	DCE/HFIP [85/15]	90	73 [48, 25]	10
5	DCE/HFIP [95/5]	90	39 [32, 7]	44
6 <sup>c</sup>	DCE/HFIP [85/15]	90	26 [26, 0]	55
7 <sup>d,e</sup>	<b>DCE/HFIP [50/50]</b>	<b>80</b>	<b>90 [46, 44]</b>	<b>Trace</b>
8 <sup>d,f</sup>	DCE/HFIP [50/50]	80	90 [58, 32]	Trace

<sup>a</sup> Reaction conditions: **3a** (0.2 mmol), ethyl acrylate (0.4 mmol), Pd(OAc)<sub>2</sub> (10 mol%), Ac-Gly-OH (20 mol%), AgOAc (0.6 mmol), solvent (2 mL), 24 h, 80–90 °C. Yield was determined by <sup>1</sup>H NMR analysis using CH<sub>2</sub>Br<sub>2</sub> as the internal standard. <sup>b</sup> Using the same conditions as in Scheme 2. <sup>c</sup> KHCO<sub>3</sub> (2 equiv.) was added. <sup>d</sup> Under N<sub>2</sub>. <sup>e</sup> 32 h. Isolated yields were 45% of **4a**<sub>mono</sub> and 37% of **4a**<sub>(m,m')di</sub>. <sup>f</sup> 28 h, DMF (5 equiv.) was added.

and a study on this issue is actively being carried out in our laboratory. The *meta*-selectivity was unambiguously verified by X-ray crystallographic analysis of a derivative obtained by hydrolyzing the ester group of **4a**<sub>mono</sub> (see the ESI†).

With the optimized conditions at hand, we examined the scope of this remote *meta*-selective olefination protocol (Table 3). *Ortho*-substituted substrates with both electron-donating methyl and methoxy and electron-withdrawing bromo and chloro groups proved to be suitable substrates, producing good combined yields of *meta*-olefinated products (**4b–4e**). It is worth noting that arenes bearing bromo or chloro substituents (**4d** and **4e**) were compatible substrates, enabling further elaboration at the halogenated positions. Moreover, although we could not circumvent di-olefination (**4b**, **4d–e**), the fact that both *meta*-positions of 2-substituted substrates could be functionalized provides a great opportunity for synthesis of diversely substituted arenes, which is particularly beneficial for the drug discovery industry. The remaining *meta*-position of *meta*-substituted substrates was also selectively olefinated in high yields (**4f–4i**). *Para*-substituted compounds carrying methoxy or halide groups were also viable substrates for obtaining high yields of the desired products (**4j–4l**). Notably, despite the steric hindrance, the olefin partner could also be installed selectively at the *meta*-position with poly-substituted substrates (**4m–4n**), displaying an uncommon procedure for constructing new penta-substituted phenylethylamines. It is interesting to note that the reaction was not sensitive to the difference of steric hindrance and both *meta*-positions of **3n** could be olefinated. Finally, substituents at the benzylic position were also tolerated (**4o** and **4p**), presenting the potential utility of this protocol with a drug molecule (**4p**). The *meta*-selectivity of various substrates

was generally excellent with only minor amounts of other isomers whose amounts were hard to determine due to the presence of rotamers in the <sup>1</sup>H NMR spectra of the crude olefinated products. The exceptional substrate is **3g**, which also generated around 10% of other isomeric products owing to the electron-donating methoxy substituent. However, it is notable that the intrinsic electronic biases of the molecules were overall successfully overridden (**4d–4f**, **4k–4n**). Moreover, removal of the directing group was smoothly realized by hydrolysis with HCl to afford high yields of new *meta*-substituted phenylethylamines (see the ESI†).

To further expand the scope of this reaction, we examined various olefin coupling partners and found olefination of **3f** with  $\alpha,\beta$ -unsaturated ketone, amide and phosphonate afforded desired products in good yields (Table 4, **6a–6c**). We were also pleased to find *trans*-2-butenone reacted stereoselectively with **3f** to give **6d** in moderate yield. It is noteworthy that this reaction was also compatible with cyclic tri-substituted olefin to give high yield of allylated product (**6e**). Finally, electron deficient

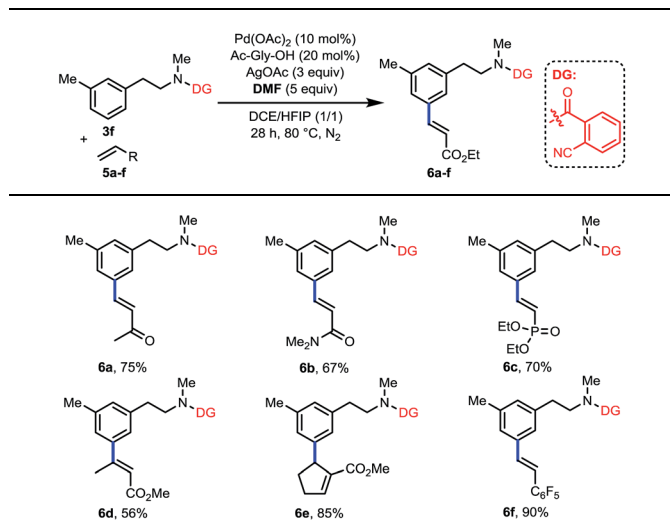
Table 3 *meta*-Olefination of phenylethylamine derivatives<sup>a</sup>

Product	Yield (%)
<b>4a</b> <sub>mono</sub>	45%
<b>4a</b> <sub>(m,m')di</sub>	37%
<b>4b</b> <sub>mono</sub>	59% <sup>b,c</sup>
<b>4b</b> <sub>(m,m')di</sub>	15%
<b>4c</b>	61% <sup>c</sup>
<b>4d</b> <sub>mono (m)</sub>	11% <sup>b,d</sup>
<b>4d</b> <sub>mono (m')</sub>	39%
<b>4d</b> <sub>(m,m')di</sub>	29%
<b>4e</b> <sub>mono (m)</sub>	13% <sup>b,d</sup>
<b>4e</b> <sub>mono (m')</sub>	28%
<b>4e</b> <sub>(m,m')di</sub>	41%
<b>4f</b>	76% <sup>c</sup>
<b>4g</b>	63% <sup>c,e</sup>
<b>4h</b>	78% <sup>c</sup>
<b>4i</b>	78% <sup>b,d</sup>
<b>4j</b>	74% <sup>c</sup>
<b>4k</b> <sub>mono</sub>	61% <sup>b</sup>
<b>4k</b> <sub>(m,m')di</sub>	19%
<b>4l</b> <sub>mono</sub>	59% <sup>b</sup>
<b>4l</b> <sub>(m,m')di</sub>	27%
<b>4m</b> <sub>mono</sub>	50% <sup>b,d</sup>
<b>4m</b> <sub>(m,m')di</sub>	24%
<b>4n</b> <sub>mono (m)</sub>	24% <sup>b,d</sup>
<b>4n</b> <sub>mono (m')</sub>	20%
<b>4n</b> <sub>(m,m')di</sub>	29%
<b>4o</b> <sub>mono</sub>	59% <sup>c</sup>
<b>4o</b> <sub>(m,m')di</sub>	19%
<b>4p</b> <sub>mono</sub>	37% <sup>b</sup>
<b>4p</b> <sub>(m,m')di</sub>	35%

**Baclofen Derivatives**

<sup>a</sup> Reaction conditions: **3** (0.2 mmol), ethyl acrylate (0.4 mmol), Pd(OAc)<sub>2</sub> (10 mol%), Ac-Gly-OH (20 mol%), AgOAc (0.6 mmol), DCE (1 mL), HFIP (1 mL), 24–48 h, 80 °C, N<sub>2</sub>. Isolated yields are reported, see the ESI† for details. <sup>b</sup> 90 °C. <sup>c</sup> DMF (1 mmol) was added. <sup>d</sup> DCE (0 mL)/HFIP (2 mL). <sup>e</sup> Around 10% of other isomers detected by <sup>1</sup>H NMR.

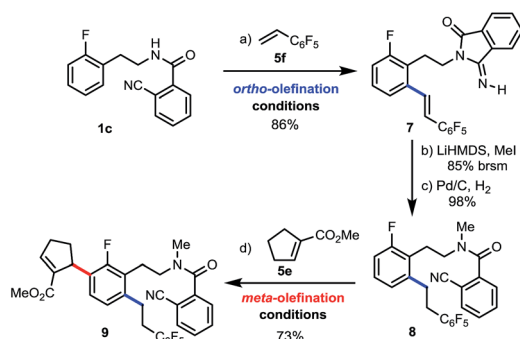


Table 4 Scope of olefin coupling partners<sup>a</sup>

<sup>a</sup> Reaction conditions: **3f** (0.1 mmol), **5** (0.2 mmol), Pd(OAc)<sub>2</sub> (10 mol%), Ac-Gly-OH (20 mol%), AgOAc (0.3 mmol), DMF (0.5 mmol), DCE (0.5 mL), HFIP (0.5 mL), 28 h, 80 °C, N<sub>2</sub>. Isolated yields are reported.

styrene such as pentafluorostyrene **5f** was also effective with this method to produce excellent yield of product (**6f**), albeit electron-rich styrenes were not applicable coupling partners.

Finally, to demonstrate the potential of our method for streamlined synthesis of highly substituted arenes, we first subjected **1c** to our standard *ortho*-olefination conditions with **5f** and obtained *ortho*-olefinated **7** in 86% yield (Scheme 3). Then, much to our delight, we were able to convert **7** to the desired amide **8** with the required nitrile group which was reconstructed simultaneously with methylation by using LiHMDS, followed by hydrogenation of the double bond.<sup>20</sup> Lastly, the *meta*-selective allylation proceeded efficiently with tri-substituted olefin **5e** to afford tetrasubstituted arene **9** in good yield, enabling the building of complexity in a concise manner.



**Scheme 3** Sequential *ortho*- and *meta*-C–H functionalizations. (a) **5f** (2 equiv.), Pd(OAc)<sub>2</sub> (10 mol%), Ac-Gly-OH (20 mol%), HFIP (3 equiv.), Ag<sub>2</sub>CO<sub>3</sub> (30 mol%), O<sub>2</sub> (1 atm), *t*-amyl-OH, 24 h, 90 °C, 86% yield; (b) LiHMDS (2.5 equiv.), MeI (3 equiv.), THF, –15 °C, 58% yield (85% yield based on recovered starting material [brsm]); (c) Pd/C (12 mol%), H<sub>2</sub> (1 atm), MeOH, 98%; (d) **5e** (2 equiv.), Pd(OAc)<sub>2</sub> (10 mol%), Ac-Gly-OH (20 mol%), AgOAc (3 equiv.), DCE (1 mL)/HFIP (1 mL), 48 h, 90 °C, N<sub>2</sub>, 73%.

## Conclusions

In summary, a novel example of remote regiodivergent *ortho*- and *meta*-C–H functionalizations has been developed with phenylethylamine derivatives by introducing a novel 2-cyanobenzoyl group as the original directing functionality. A single methylation was sufficient to switch the remote regioselectivity. This method also enabled the novel sequential functionalizations of *ortho*- and *meta*-C–H bonds of a phenylethylamine derivative. Further development of this strategy will improve C–H functionalization to become a more versatile synthetic tool.

## Acknowledgements

This work was supported by the Fujian Institute of Research on the Structure of Matter, NSFC (21402198) and “The 1000 Youth Talents Program”. We gratefully appreciate Prof. Jin-Quan Yu at The Scripps Research Institute, Prof. Weiping Su at FJIRSM and Prof. Richard P. Hsung at the University of Wisconsin-Madison for helpful comments. We also thank Prof. Daqiang Yuan at FJIRSM for crystallographic analysis.

## Notes and references

- Selected recent reviews: (a) D. Alberico, M. E. Scott and M. Lautens, *Chem. Rev.*, 2007, **107**, 174; (b) I. V. Seregin and V. Gevorgyan, *Chem. Soc. Rev.*, 2007, **36**, 1173; (c) F. Kakiuchi and T. Kochi, *Synthesis*, 2008, **2008**, 3013; (d) X. Chen, K. M. Engle, D.-H. Wang and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2009, **48**, 5094; (e) O. Daugulis, H.-Q. Do and D. Shabashov, *Acc. Chem. Res.*, 2009, **42**, 1074; (f) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147; (g) D. A. Colby, R. G. Bergman and J. A. Ellman, *Chem. Rev.*, 2010, **110**, 624; (h) C.-L. Sun, B.-J. Li and Z.-J. Shi, *Chem. Rev.*, 2010, **111**, 1293; (i) T. Satoh and M. Miura, *Synthesis*, 2010, **2010**, 3395; (j) O. Baudoin, *Chem. Soc. Rev.*, 2011, **40**, 4902; (k) J. F. Hartwig, *Chem. Soc. Rev.*, 2011, **40**, 1992; (l) S. H. Cho, J. Y. Kim, J. Kwak and S. Chang, *Chem. Soc. Rev.*, 2011, **40**, 5068; (m) M. S. Sigman and E. W. Werner, *Acc. Chem. Res.*, 2012, **45**, 874; (n) C. Liu, H. Zhang, W. Shi and A. Lei, *Chem. Rev.*, 2011, **111**, 1780; (o) C. S. Yeung and V. M. Dong, *Chem. Rev.*, 2011, **111**, 1215; (p) S. R. Neufeldt and M. S. Sanford, *Acc. Chem. Res.*, 2012, **45**, 936; (q) N. Kuhl, M. N. Hopkinson, J. Wencel-Delord and F. Glorius, *Angew. Chem., Int. Ed.*, 2012, **51**, 10236; (r) P. B. Arockiam, C. Bruneau and P. H. Dixneuf, *Chem. Rev.*, 2012, **112**, 5879; (s) M. C. White, *Science*, 2012, **335**, 807; (t) G. Rouquet and N. Chatani, *Angew. Chem., Int. Ed.*, 2013, **52**, 11726; (u) L. Ackermann, *Acc. Chem. Res.*, 2014, **47**, 281; (v) M. Zhang, Y. Zhang, X. Jie, H. Zhao, G. Li and W. Su, *Org. Chem. Front.*, 2014, **1**, 843; (w) J. J. Topczewski and M. S. Sanford, *Chem. Sci.*, 2015, **6**, 70.
- (a) H. M. L. Davies and J. R. Manning, *Nature*, 2008, **451**, 417; (b) L. McMurray, F. O'Hara and M. J. Gaunt, *Chem. Soc. Rev.*, 2011, **40**, 1885; (c) W. R. Gutekunst and P. S. Baran, *Chem.*



- Soc. Rev.*, 2011, **40**, 1976; (d) D. Y. K. Chen and S. W. Youn, *Chem.–Eur. J.*, 2012, **18**, 9452; (e) J. Yamaguchi, A. D. Yamaguchi and K. Itami, *Angew. Chem., Int. Ed.*, 2012, **51**, 8960; (f) W.-D. Joanna and G. Frank, *Nat. Chem.*, 2013, **5**, 369.
- 3 Selected examples of Pd-catalyzed regioselective C–H functionalizations: (a) N. R. Deprez, D. Kalyani, A. Krause and M. S. Sanford, *J. Am. Chem. Soc.*, 2006, **128**, 4972; (b) D. R. Stuart and K. Fagnou, *Science*, 2007, **316**, 1172; (c) C. S. Yeung, X. Zhao, N. Borduas and V. M. Dong, *Chem. Sci.*, 2010, **1**, 331; (d) K. Ueda, S. Yanagisawa, J. Yamaguchi and K. Itami, *Angew. Chem., Int. Ed.*, 2010, **49**, 8946; (e) A. J. Hickman and M. S. Sanford, *ACS Catal.*, 2011, **1**, 170; (f) J. Karthikeyan and C.-H. Cheng, *Angew. Chem., Int. Ed.*, 2011, **50**, 9880; (g) A. N. Campbell, E. B. Meyer and S. S. Stahl, *Chem. Commun.*, 2011, **47**, 10257; (h) X. Wang, D. Leow and J.-Q. Yu, *J. Am. Chem. Soc.*, 2011, **133**, 13864; (i) K. Sun, Y. Li, T. Xiong, J. Zhang and Q. Zhang, *J. Am. Chem. Soc.*, 2011, **133**, 1694; (j) L. Jiao and T. Bach, *J. Am. Chem. Soc.*, 2011, **133**, 12990; (k) Z. Wu, F. Luo, S. Chen, Z. Li, H. Xiang and X. Zhou, *Chem. Commun.*, 2013, **49**, 7653; (l) R. Shrestha, P. Mukherjee, Y. Tan, Z. C. Litman and J. F. Hartwig, *J. Am. Chem. Soc.*, 2013, **135**, 8480; (m) D.-T. D. Tang, K. D. Collins, J. B. Ernst and F. Glorius, *Angew. Chem., Int. Ed.*, 2014, **53**, 1809.
- 4 Selected examples of non-Pd-catalyzed regioselective C–H functionalizations: (a) H. Chen, S. Schlecht, T. C. Semple and J. F. Hartwig, *Science*, 2000, **287**, 1995; (b) C.-L. Ciana, R. J. Phipps, J. R. Brandt, F.-M. Meyer and M. J. Gaunt, *Angew. Chem., Int. Ed.*, 2011, **50**, 458; (c) S. Mochida, K. Hirano, T. Satoh and M. Miura, *J. Org. Chem.*, 2011, **76**, 3024; (d) J. Kwak, M. Kim and S. Chang, *J. Am. Chem. Soc.*, 2011, **133**, 3780; (e) B. Li, Z.-H. Wu, Y.-F. Gu, C.-L. Sun, B.-Q. Wang and Z.-J. Shi, *Angew. Chem., Int. Ed.*, 2011, **50**, 1109; (f) J. Wencel-Delord, C. Nimphius, F. W. Patureau and F. Glorius, *Chem.–Asian J.*, 2012, **7**, 1208; (g) T. Andou, Y. Saga, H. Komai, S. Matsunaga and M. Kanai, *Angew. Chem., Int. Ed.*, 2013, **52**, 3213; (h) K. Ueda, K. Amaike, R. M. Maceiczky, K. Itami and J. Yamaguchi, *J. Am. Chem. Soc.*, 2014, **136**, 13226.
- 5 (a) R. J. Phipps and M. J. Gaunt, *Science*, 2009, **323**, 1593; (b) H. A. Duong, R. E. Gilligan, M. L. Cooke, R. J. Phipps and M. J. Gaunt, *Angew. Chem., Int. Ed.*, 2011, **50**, 463.
- 6 (a) O. Saidi, J. Marafie, A. E. W. Ledger, P. M. Liu, M. F. Mahon, G. Kociok-Köhn, M. K. Whittlesey and C. G. Frost, *J. Am. Chem. Soc.*, 2011, **133**, 19298; (b) C. Frost, W. Reynolds, P. Liu and G. Kociok-Köhn, *Synlett*, 2013, **24**, 2687; (c) N. Hofmann and L. Ackermann, *J. Am. Chem. Soc.*, 2013, **135**, 5877.
- 7 For other examples of non-Pd-catalyzed *meta*-C–H functionalizations: (a) J.-Y. Cho, M. K. Tse, D. Holmes, R. E. Maleczka and M. R. Smith, *Science*, 2002, **295**, 305; (b) T. Ishiyama, J. Takagi, K. Ishida, N. Miyaura, N. R. Anastasi and J. F. Hartwig, *J. Am. Chem. Soc.*, 2002, **124**, 390; (c) H.-Q. Do, R. M. K. Khan and O. Daugulis, *J. Am. Chem. Soc.*, 2008, **130**, 15185; (d) B.-J. Li and Z.-J. Shi, *Chem. Sci.*, 2011, **2**, 488; (e) C. Cheng and J. F. Hartwig, *Science*, 2014, **343**, 853.
- 8 For Pd-catalyzed *meta*-C–H functionalizations using a chelating directing template: (a) D. Leow, G. Li, T.-S. Mei and J.-Q. Yu, *Nature*, 2012, **486**, 518; (b) H.-X. Dai, G. Li, X.-G. Zhang, A. F. Stepan and J.-Q. Yu, *J. Am. Chem. Soc.*, 2013, **135**, 7567; (c) L. Wan, N. Dastbaravardeh, G. Li and J.-Q. Yu, *J. Am. Chem. Soc.*, 2013, **135**, 18056; (d) R.-Y. Tang, G. Li and J.-Q. Yu, *Nature*, 2014, **507**, 215; (e) G. Yang, P. Lindovska, D. Zhu, J. Kim, P. Wang, R.-Y. Tang, M. Movassaghi and J.-Q. Yu, *J. Am. Chem. Soc.*, 2014, **136**, 10807; (f) Y. Deng and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2015, **54**, 888; (g) S. Lee, H. Lee and K. L. Tan, *J. Am. Chem. Soc.*, 2013, **135**, 18778; (h) M. Bera, A. Modak, T. Patra, A. Maji and D. Maiti, *Org. Lett.*, 2014, **16**, 5760; (i) M. Bera, A. Maji, S. K. Sahoo and D. Maiti, *Angew. Chem., Int. Ed.*, 2015, DOI: 10.1002/anie.201503112.
- 9 During the preparation of our manuscript, two impressive reports on *meta*-selective C–H functionalizations *via* Pd/norbornene catalysis appeared: (a) X.-C. Wang, W. Gong, L.-Z. Fang, R.-Y. Zhu, S. Li, K. M. Engle and J.-Q. Yu, *Nature*, 2015, **519**, 334; (b) Z. Dong, J. Wang and G. Dong, *J. Am. Chem. Soc.*, 2015, **137**, 5887.
- 10 For other Pd-catalyzed *meta*-C–H functionalizations: (a) Y.-H. Zhang, B.-F. Shi and J.-Q. Yu, *J. Am. Chem. Soc.*, 2009, **131**, 5072; (b) J. Cornella, M. Righi and I. Larrosa, *Angew. Chem., Int. Ed.*, 2011, **50**, 9429; (c) M. Ye, G.-L. Gao and J.-Q. Yu, *J. Am. Chem. Soc.*, 2011, **133**, 6964; (d) M. Ye, G.-L. Gao, A. J. F. Edmunds, P. A. Worthington, J. A. Morris and J.-Q. Yu, *J. Am. Chem. Soc.*, 2011, **133**, 19090; (e) L. Zhou and W. Lu, *Organometallics*, 2012, **31**, 2124; (f) Y.-N. Wang, X.-Q. Guo, X.-H. Zhu, R. Zhong, L.-H. Cai and X.-F. Hou, *Chem. Commun.*, 2012, **48**, 10437; (g) F. Dai, Q. Gui, J. Liu, Z. Yang, X. Chen, R. Guo and Z. Tan, *Chem. Commun.*, 2013, **49**, 4634; (h) X. Cong, H. Tang, C. Wu and X. Zeng, *Organometallics*, 2013, **32**, 6565; (i) J. Luo, S. Preciado and I. Larrosa, *J. Am. Chem. Soc.*, 2014, **136**, 4109.
- 11 For other types of metal-catalyzed regiodivergent and/or sequential C–H functionalizations: (a) N. P. Grimster, C. Gauntlett, C. R. A. Godfrey and M. J. Gaunt, *Angew. Chem., Int. Ed.*, 2005, **44**, 3125; (b) E. M. Beck, N. P. Grimster, R. Hatley and M. J. Gaunt, *J. Am. Chem. Soc.*, 2006, **128**, 2528; (c) D. R. Stuart, E. Villemure and K. Fagnou, *J. Am. Chem. Soc.*, 2007, **129**, 12072; (d) E. M. Beck, R. Hatley and M. J. Gaunt, *Angew. Chem., Int. Ed.*, 2008, **47**, 3004; (e) T. W. Lyons, K. L. Hull and M. S. Sanford, *J. Am. Chem. Soc.*, 2011, **133**, 4455; (f) D. Katayev, M. Nakanishi, T. Burgi and E. P. Kundig, *Chem. Sci.*, 2012, **3**, 1422; (g) A. M. Wagner, A. J. Hickman and M. S. Sanford, *J. Am. Chem. Soc.*, 2013, **135**, 15710; (h) J. D. Dooley, S. Reddy Chidipudi and H. W. Lam, *J. Am. Chem. Soc.*, 2013, **135**, 10829; (i) Y. Su, H. Zhou, J. Chen, J. Xu, X. Wu, A. Lin and H. Yao, *Org. Lett.*, 2014, **16**, 4884; (j) N. Schroder, F. Lied and F. Glorius, *J. Am. Chem. Soc.*, 2015, **137**, 1448.
- 12 For more selected examples of sequential C–H functionalizations: (a) S. Yanagisawa, K. Ueda, H. Sekizawa



- and K. Itami, *J. Am. Chem. Soc.*, 2009, **131**, 14622; (b) K. M. Engle, D.-H. Wang and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2010, **49**, 6169; (c) W. R. Gutekunst and P. S. Baran, *J. Am. Chem. Soc.*, 2011, **133**, 19076; (d) H. Wang, G. Li, K. M. Engle, J.-Q. Yu and H. M. L. Davies, *J. Am. Chem. Soc.*, 2013, **135**, 6774; (e) H. J. Kim, M. J. Ajitha, Y. Lee, J. Ryu, J. Kim, Y. Lee, Y. Jung and S. Chang, *J. Am. Chem. Soc.*, 2014, **136**, 1132; (f) A. D. Yamaguchi, K. M. Chepiga, J. Yamaguchi, K. Itami and H. M. Davies, *J. Am. Chem. Soc.*, 2015, **137**, 644.
- 13 For remote C–H functionalizations: (a) R. Breslow, *Acc. Chem. Res.*, 1980, **13**, 170; (b) H. Schwarz, *Acc. Chem. Res.*, 1989, **22**, 282; (c) S. Das, C. D. Incarvito, R. H. Crabtree and G. W. Brudvig, *Science*, 2006, **312**, 1941; (d) J.-J. Li, R. Giri and J.-Q. Yu, *Tetrahedron*, 2008, **64**, 6979; (e) D. G. Pintori and M. F. Greaney, *J. Am. Chem. Soc.*, 2010, **133**, 1209; (f) E. E. Stache, C. A. Seizert and E. M. Ferreira, *Chem. Sci.*, 2012, **3**, 1623; (g) W. A. Nack, G. He, S.-Y. Zhang, C. Lu and G. Chen, *Org. Lett.*, 2013, **15**, 3440; (h) J. Schranck, A. Tlili and M. Beller, *Angew. Chem., Int. Ed.*, 2014, **53**, 9426.
- 14 For remote-selective *ortho*-C–H bond functionalization: (a) T. Saget and N. Cramer, *Angew. Chem., Int. Ed.*, 2013, **52**, 7865; *Angew. Chem.*, 2013, **125**, 8019; (b) W. B. Cross, E. G. Hope, Y.-H. Lin, S. A. Macgregor, K. Singh, G. A. Solan and N. Yahya, *Chem. Commun.*, 2013, **49**, 1918; (c) For a reverse selectivity, see: M. Lafrance, S. I. Gorelsky and K. Fagnou, *J. Am. Chem. Soc.*, 2007, **129**, 14570.
- 15 (a) J.-J. Li, T.-S. Mei and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2008, **47**, 6452; (b) G. He, C. Lu, Y. Zhao, W. A. Nack and G. Chen, *Org. Lett.*, 2012, **14**, 2944; (c) T.-S. Mei, D. Leow, H. Xiao, B. N. Laforteza and J.-Q. Yu, *Org. Lett.*, 2013, **15**, 3058; (d) A. Rodriguez, J. Albert, X. Ariza, J. Garcia, J. Granell, J. Farras, A. La Mela and E. Nicolas, *J. Org. Chem.*, 2014, **79**, 9578; (e) X. Ye and X. Shi, *Org. Lett.*, 2014, **16**, 4448; (f) J. Han, P. Liu, C. Wang, Q. Wang, J. Zhang, Y. Zhao, D. Shi, Z. Huang and Y. Zhao, *Org. Lett.*, 2014, **16**, 5682.
- 16 For  $\pi$ -coordination of nitrile group in C–H functionalizations: (a) P. Gandeepan and C. H. Cheng, *Chem.-Asian J.*, 2015, **10**, 824; (b) F. Kakiuchi, M. Sonoda, T. Tsujimoto, N. Chatani and S. Murai, *Chem. Lett.*, 1999, **28**, 1083; (c) W. Li, Z. Xu, P. Sun, X. Jiang and M. Fang, *Org. Lett.*, 2011, **13**, 1286; (d) J.-C. Wan, J.-M. Huang, Y.-H. Jhan and J.-C. Hsieh, *Org. Lett.*, 2013, **15**, 2742.
- 17 For reviews and selected recent examples of Pd-catalyzed C–H olefinations: (a) C. Jia, T. Kitamura and Y. Fujiwara, *Acc. Chem. Res.*, 2001, **34**, 633; (b) J. Le Bras and J. Muzart, *Chem. Rev.*, 2011, **111**, 1170; (c) L. Zhou and W. Lu, *Chem.-Eur. J.*, 2014, **20**, 634; (d) K. J. Stowers, K. C. Fortner and M. S. Sanford, *J. Am. Chem. Soc.*, 2011, **133**, 6541; (e) C. Huang, B. Chattopadhyay and V. Gevorgyan, *J. Am. Chem. Soc.*, 2011, **133**, 12406; (f) P. Gandeepan and C. H. Cheng, *J. Am. Chem. Soc.*, 2012, **134**, 5738; (g) R. Shi, L. Lu, H. Zhang, B. Chen, Y. Sha, C. Liu and A. Lei, *Angew. Chem., Int. Ed.*, 2013, **52**, 10582; (h) Y. Shang, X. Jie, J. Zhou, P. Hu, S. Huang and W. Su, *Angew. Chem., Int. Ed.*, 2013, **52**, 1299; (i) A. Deb, S. Bag, R. Kancharla and D. Maiti, *J. Am. Chem. Soc.*, 2014, **136**, 13602.
- 18 (a) K. M. Engle, D.-H. Wang and J.-Q. Yu, *J. Am. Chem. Soc.*, 2010, **132**, 14137; (b) G.-J. Cheng, Y.-F. Yang, P. Liu, P. Chen, T.-Y. Sun, G. Li, X.-H. Zhang, K. N. Houk, J.-Q. Yu and Y.-D. Wu, *J. Am. Chem. Soc.*, 2014, **136**, 894.
- 19 Selected examples: (a) A. R. Dick, K. L. Hull and M. S. Sanford, *J. Am. Chem. Soc.*, 2004, **126**, 2300; (b) H.-Y. Thu, W.-Y. Yu and C.-M. Che, *J. Am. Chem. Soc.*, 2006, **128**, 9048; (c) V. S. Thirunavukkarasu, K. Parthasarathy and C.-H. Cheng, *Angew. Chem., Int. Ed.*, 2008, **47**, 9462; (d) Y. Tan and J. F. Hartwig, *J. Am. Chem. Soc.*, 2010, **132**, 3676; (e) S.-J. Lou, D.-Q. Xu and Z.-Y. Xu, *Angew. Chem., Int. Ed.*, 2014, **53**, 10330.
- 20 The hydrogenation after the methylation was necessary to avoid the resulting substrate with a double bond acting as an olefin coupling partner in the following *meta*-selective olefination step.

