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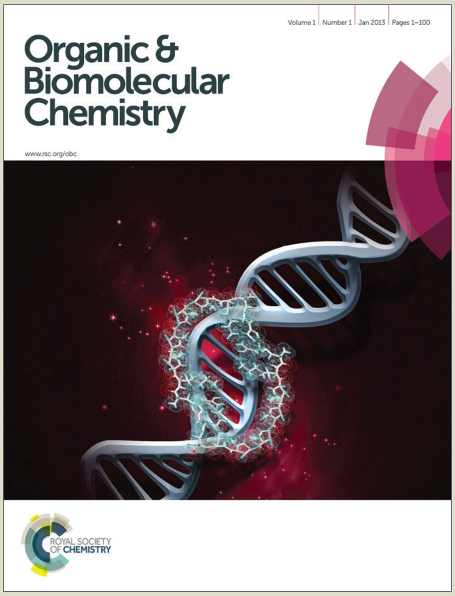

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# Pd(II)-Catalyzed C-H Arylation of Aryl and Benzyl Weinreb Amides

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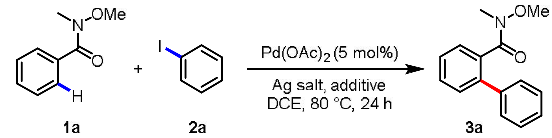
**The first example of palladium-catalyzed *ortho*-C–H arylation of aryl and benzyl Weinreb amides was developed, in which HOTf was used as a key promoter. This method exhibits good functional groups tolerance, broad substrate scope of both Weinreb amides and aryl iodides, high mono-selectivity and mild reaction conditions.**

To synthesize complex molecules in economic and rapid manners remains a major challenge in organic synthesis. Transition metal-catalyzed direct C–H functionalization provides access to fundamental building blocks from readily available compounds in an atom- and step-economical fashion, thus offering a new disconnection path for retrosynthetic analysis of natural products and drug molecules.[1] In the past two decades, directing group strategy has been widely employed to address the inertness of C–H bonds and the site selectivity control in target molecules, in which the binding of directing group to metal center directs the catalyst to the desired C–H bond for functionalization.[2] While the installation and removal of such ligands may reduce the atom- and step-economy during the transformation, the utility of functional group apt to conversion as directing group would be a good solution. Though a number of directing groups have been successfully employed to activate the inert C–H bonds with different transition metals,[2] the utility of synthetically useful group as a directing group is a good solution.

*N*-Methoxy-*N*-methylamides, also called Weinreb amides, have attracted increasing attention due to their synthetic utility, such as ease of preparation, fewer side reactions during conversion, and selective conversion to aldehydes and ketones.[3] Although such a motif was widely used in organic synthesis, the successful examples using Weinreb amides as the directing group for C–H activation were still few, including the Ru(II)-catalyzed C(sp2)-H oxygenation reported by the Ackermann group,[4] and the Rh(III)-catalyzed C–H alkenylation by us[5] and the Rovis group.[6] However, to the best of our knowledge, there was no successful report on palladium-catalyzed C–H activation directed by Weinreb amides so far, probably due to the weak coordinatation ability of carbonyl oxygen with palladium, leading to lower reactivity compared with nitrogen-, sulfur-, or phosphorus-containing directing groups.[7] In view of the directing group applicability and our continuous interests in developing practical methods for synthetic chemistry,[5,8] herein, we report the first example of palladium-catalyzed C–H arylation of arenes using aryl and benzyl Weinreb amides as directing groups under mild conditions.[9]

**Table 1** Optimization of Reaction Conditions [a,b]



**1a** **2a** **3a**

| entry | Pd (mol %) | [Ag] (equiv) | additive | yield (%) |
|---|---|---|---|---|
| 1 | $Pd(OAc)_2$ (5) | $Ag_2O$ (1 ) | - | N. R. |
| 2 | $Pd(OAc)_2$ (5) | $Ag_2CO_3$ (1) | - | N. R. |
| 3 | $Pd(OAc)_2$ (5) | AgTFA (2) | - | N. R. |
| 4 | $Pd(OAc)_2$ (5) | AgOAc (2) | - | N. R. |
| 5 | $Pd(OAc)_2$ (5) | AgOTf (2) | - | 69 (4) |
| **6** | **$Pd(OAc)_2$ (5)** | **AgOTf (2)** | **HOTf** | **89 (5), 91[c]** |
| 7 | $Pd(OAc)_2$ (5) | AgOTf (2) | HOAc | 66 (19) |
| 8 | $Pd(OAc)_2$ (5) | AgOTf (2) | TFA | 75 (21) |
| 9 | $Pd(OAc)_2$ (5) | AgOTf (2) | PivOH | 70 (20) |
| 10 | $Pd(OAc)_2$ (5) | AgOTf (2) | TsOH | 74 (17) |
| 11 | $Pd(OAc)_2$ (5) | AgOTf (2) | $HBF_4$ | 62 (18) |
| 12 | $Pd(OAc)_2$ (5) | AgOTf (1.5) | HOTf | 79 (5) |
| 13 | $Pd(OAc)_2$ (5) | AgOTf (1) | HOTf | 77 (3) |
| 14[d] | $Pd(OAc)_2$ (5) | AgOTf (2) | HOTf | 80 (6) |
| 15[e] | $Pd(OAc)_2$ (5) | AgOTf (2) | HOTf | 76 (3) |
| 16 | $Pd(Ph_3P)_4$ (5) | AgOTf (2) | HOTf | 90 (6) |
| 17 | $Pd_2(dba)_3$ (2.5) | AgOTf (2) | HOTf | 56 (1) |
| 18 | - | AgOTf (2) | HOTf | N. R. |
| 19 | $Pd(OAc)_2$ (1) | AgOTf (2) | HOTf | 81 (4) |

[a] Conditions: **1a** (0.2 mmol, 1.0 equiv), **2a** (2.0 equiv), $Pd(OAc)_2$ (5 mol%), silver salt (2.0 equiv), additive (0.5 equiv), DCE, 80 °C, 24 h. [b] GC yield using dodecane as internal standard, yield of diarylation product was given in the parentheses. [c] Isolated yield of monoarylation product. [d] PhI (1.1 equiv) was used. [e] 60 °C.

At the outset of our study, we examined the reaction of Weinreb amide (**1a**) and iodide benzene (**2a**) in the presence of catalytic amount of $Pd(OAc)_2$ (5 mol%) in DCE at 80 °C for 24 h under air atmosphere. Firstly, various silver salts, commonly used as halide scavenger, were carefully investigated. While none of the desired product was observed with $Ag_2O$, $Ag_2CO_3$, AgTFA or AgOAc (entries1-4, Table 1), to our delight, the addition of AgOTf afforded the corresponding biaryl amides in 69% yield along with 4% diarylation product (entry 5). The examinations of solvents were next performed, which indicated DCE was still the optimal one (see Table S2, supporting information). Considering the critical role of AgOTf played in this system, which was assumed that a highly active cationic species $Pd(OTf)_2$ generated in situ facilitated the C–H activation by easily coordinating to Weinreb amide for its enhanced Lewis acidity, we tried to add HOTf (0.5 equiv) to help generate $Pd(OTf)_2$. As a result, an improved isolated yield of 91% was obtained (entry 6), while the other acid additives examined in this catalytic system showed inferior results (entries 7-11). In addition, the investigation of the reactant equivalent indicated that the reduction of AgOTf (entries 12-13), PhI (entry 14) or $Pd(OAc)_2$ (entry 19) afforded reduced yields, as is lower reaction temperature (entry 15). Notably, the control experiment showed the C–H arylation didn't occur in the absence of $Pd(OAc)_2$ (entry 18). Interestingly, both $Pd(PPh_3)_4$ and $Pd_2(dba)_3$ were also reactive catalysts, giving the desired biaryl amide in 90% and 56% yield, respectively (entry 16-17).

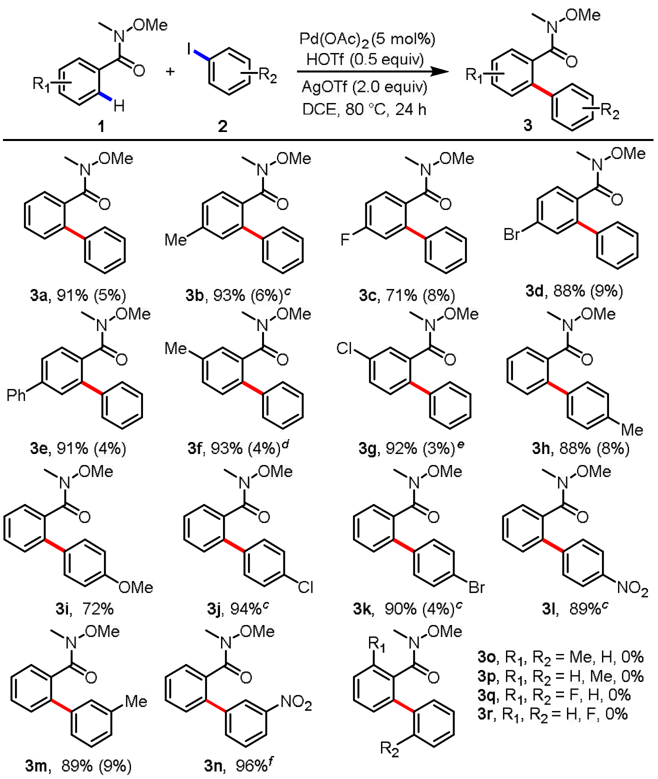


**Fig. 1** Substrate scope of aryl Weinreb amides and aryl iodides. [a] Conditions: **1** (0.2 mmol, 1.0 equiv), **2** (2.0 equiv), $Pd(OAc)_2$ (5 mol%), AgOTf (2.0 equiv), HOTf (0.5 equiv), DCE, 80 °C, 24 h. [b] Isolated yield, yield of diarylation product was determined by GC or ${}^1H$ NMR and given in the parentheses. [c] 12 h. [d] 14 h. [e] 30 h. [f] 8 h.

With the optimal reaction conditions in hand, a variety of substituted Weinreb amides and aryl iodides were examined to demonstrate the applicability and limitation of our method, as shown in Figure 1. It should be noted that not only *meta*- (**3f-g**) but also *para*-substituted (**3b-e**) Weinreb amides afforded the arylated products with generally excellent yields and high mono-selectivities, along with trace amount of diarylation products. With *meta*-substituted Weinreb amides (**3f-g**), the arylation almost exclusively occurred at less hindered C6-position with little C2,C6-diarylation products. Both electron-withdrawing groups, such as F, Cl, Br, $NO_2$, and electron-donating groups such as Me and MeO, can be well tolerated. The presence of halogen atoms (F, Cl, Br) in the aromatic ring readily offered opportunity for further manipulation. It is noteworthy that our protocol was ineffective to both substrates encountered with substituents at the *ortho*-position of Weinreb amides (**3o**, **3p**) or aryl iodides (**3p**, **3q**), presumably due to the steric hindrance to prevent the *ortho* C–H bond activation or the oxidation of ArI to palladiumcycle species.

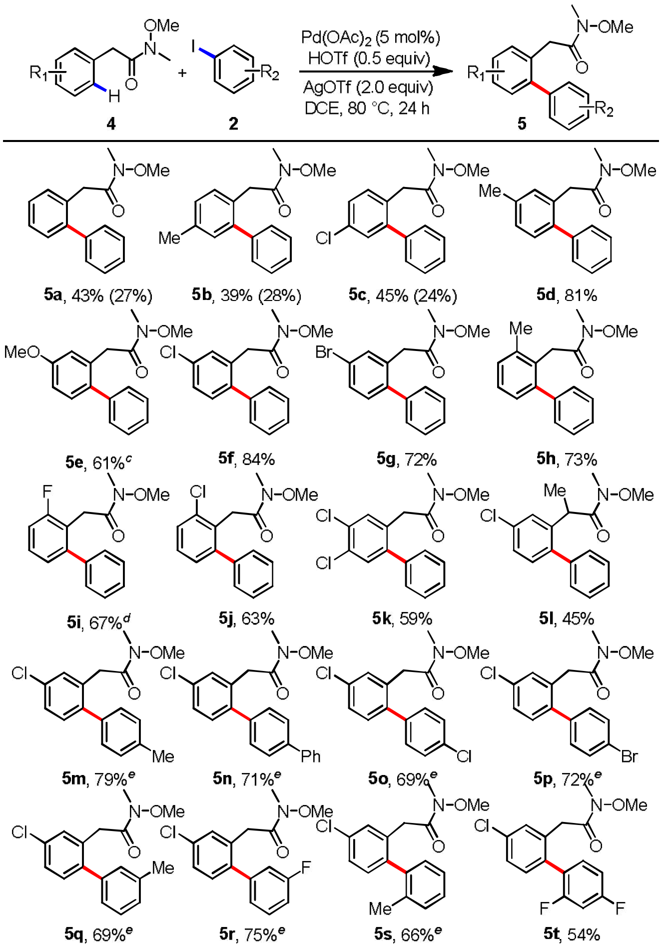
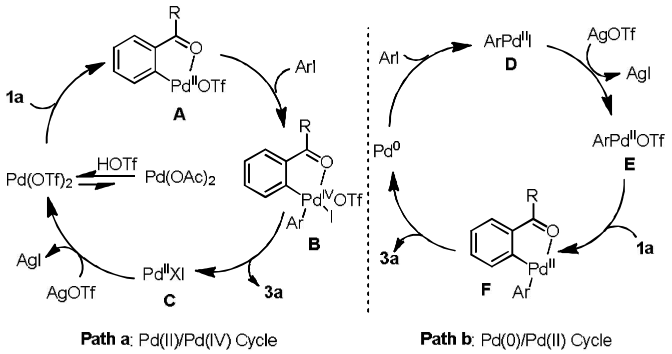


**Fig. 2** Substrate scope of benzyl Weinreb amides and aryl iodides. [a] Conditions: **1** (0.2 mmol, 1.0 equiv), **2** (2.0 equiv), $Pd(OAc)_2$ (5 mol%), AgOTf (2.0 equiv), HOTf (0.5 equiv), DCE, 80 °C, 24 h. [b] Isolated yield, yield of diarylation product was given in the parentheses. [c] 60 °C, 16 h. [d] 100 °C, 48 h. [e] 5 h

Encouraged by the efficiency of this protocol, we next surveyed an array of benzyl Weinreb amides. To the best of our knowledge, this is the first time that such kind of Weinreb amides were used as the *ortho*-directing groups.[10] To our delight, a range of benzyl Weinreb amides and aryl iodides were also compatible under the standard reaction conditions, afforded the arylation products with higher regio-selectivity and broader substrates scope, albeit with relative lower yields compared with aryl Weinreb amides (Figure 1). Notably, the benzyl Weinreb amides **4** with *ortho*-substituents, including Me, F, Cl (**5h-j**), were arylated smoothly to afford the biaryl products with moderate yields, which further corroborated that the steric hindrance of *ortho* groups in aryl Weinreb amides prevented the C–H activation. Interestingly, an amide with methyl substituent at the α-position of carbonyl group was compatible with this catalytic system, providing the corresponding product in moderate yield (**5l**). Furthermore, both electron-withdrawing and electron-donating substituents at phenyl ring were well tolerated, affording the desired arylation products with satisfactory yields. It must be pointed out that Weinreb amides bearing *para*-substituents give both mono- and di-arylation products (**5b-c**), while *meta*-substituted substrates afforded only mono- arylation product at the less steric hindered position (**5d-g**). Various aryl iodides were also investigated and the corresponding arylation products were obtained with acceptable yields. Gratifyingly, the *ortho*- substituted aryl iodides (**5s-t**) can also be used as the suitable coupling partners, which were rarely reported before.[9k,11]

To gain some insight into the reaction mechanism, the deuterated labeled experiments were next performed. The intermolecular competition experiment and parallel independent reactions determined $k_H/k_D$ to be 1.2 and 1.1 (see supporting information for detailed experiments), respectively, which revealed the aromatic C–H cleavage was not involved in the rate-determining step.



**Path a**: Pd(II)/Pd(IV) Cycle

**Path b**: Pd(0)/Pd(II) Cycle

**Scheme 1** Proposed Reaction Mechanism (R=N(OMe)Me)

Based on the above results and the known reports on palladium-catalyzed C–H arylation,[9] a possible mechanism involving a Pd(II)/Pd(IV) catalytic cycle was proposed, as shown in path a, Scheme 1. Cationic $Pd(OTf)_2$, formed *in situ* by anion exchange of $Pd(OAc)_2$ and HOTf, afforded the ArPd(II) species **A** after the coordination of electrophilic Pd(II) and carbonyl oxygen followed by subsequent *ortho*-C–H activation. The oxidative addition of ArI to Pd(II) species **A** gave the corresponding Pd(IV) intermediate **B**, which underwent reductive elimination to furnish the arylation product and palladium **C**. The Pd(II) species **C** then regenerates the active $Pd(OTf)_2$ catalyst by anion exchange with AgOTf. However, since Pd(0) also showed catalytic activity for the reaction (entries16-17, Table 1), a Pd(0)/Pd(II) mechanism (path b, Scheme 1) can not be excluded at this stage (see supporting information for detailed experiments).[12]

In conclusion, we have developed a palladium-catalyzed C–H arylation of arenes using Weinreb amide, a commonly used functional group in organic synthesis, as directing group under mild conditions. This protocol exhibits good functional group tolerance and broad substrate scope. Further study toward synthetic utility and mechanism study are now underway in our laboratory.

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## Notes and references

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

1 For selected reviews of C–H activation on total synthesis, see: (a) D. F. Taber and S. E. Stiriba, *Chem.-Eur. J.*, 1998, **4**, 990; (b) K. Godula and D. Sames, *Science*, 2006, **312**, 67; (c) H. M. L Davies and J. R. Manning, *Nature*, 2008, **451**, 417; (d) T. Brückl, R. D. Baxter, Y. Ishihara and P. S. Baran, *Acc. Chem. Res.*, 2012, **45**, 826; (e) L. McMurray, F. O'Hara and M. J. Gaunt, *Chem. Soc. Rev.*, 2011, **40**, 1885; (f) W. R. Gutekunst and P. S. Baran, *Chem. Soc. Rev.*, 2011, **40**, 1976; (g) J. Yamaguchi, A. D. Yamaguchi and K. Itami, *Angew. Chem., Int. Ed.*, 2012, **51**, 8960; (h) D. Y.-K. Chen and S. W. Youn, *Chem.-Eur. J.*, 2012, 18, 9452.

2 For selected reviews, see: (a) O. Daugulis, H.-Q. Do and D. Shabashov, *Acc. Chem. Res.*, 2009, **42**, 1074; (b) X. Chen, K. M. Engle, D.-H. Wang and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2009, **48**, 5094; (c) L.-M. Xu, B.-J. Li, Z. Yang and Z.-J. Shi, *Chem. Soc. Rev.*, 2010, **39**, 712; (d) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147; (e) C. S. Yeung and V. M. Dong, *Chem. Rev.*, 2011, **111**, 1215; (f) J. Wencel-Delord, T. Dröge, F. Liu and F. Glorius, *Chem. Soc. Rev.*, 2011, **40**, 4740; (g) T.-S. Mei, L. Kou, S. Ma, K. M. Engle and J.-Q. Yu, *Synthesis*, 2012, **44**, 1778; (h) L. Ackermann, *Acc. Chem. Res.*, 2014, **47**, 281.

3 (a) S. Nahm and S. M. Weinreb, *Tetrahedron Lett.*, 1981, **22**, 3815; (b) D. A. Evans, S. W. Kaldor, T. K. Jones, J. Clardy, T. J. Stout, *J. Am. Chem. Soc.*, 1990, **112**, 7001; (c) V. K. Khlestkin and D. G. Mazhukin, *Curr. Org. Chem.*, 2003, **7**, 967; (d) Y. Ichikawa, K. Hirata, M. Ohbayashi and M. Isobe, *Chem.-Eur. J.*, 2004, **10**, 3241; (e) M. Barbazanges, C. Meyer and J. Cossy, *Org. Lett.*, 2008, **10**, 4489; (f) S. Balasubramaniam and I. S. Aidhen, *Synthesis*, 2008, **23**, 3707.

4 F. Yang and L. Ackermann, *Org. Lett.*, 2013, **15**, 718.

5 Y. Wang, C. Li, Y. Li, F. Yin and X.-S. Wang, *Adv. Synth. Catal.*, 2013, **355**, 1724.

6 T. A. Davis, T. K. Hyster and T. Rovis, *Angew. Chem., Int. Ed.*, 2013, **52**, 14181.

7 (a) K. M. Engle, T.-S. Mei, M. Wasa and J.-Q. Yu, *Acc. Chem. Res.*, 2012, **45**, 788; (b) Y. Rao, *Synlett.*, 2013, **24**, 2472; (c) Q.-Z. Zheng and N. Jiao, *Tetrahedron Lett.*, 2014, **55**, 1121.

8 (a) X.-F. Cheng, Y. Li, Y.-M. Su, F. Yin, J.-Y. Wang, J. Sheng, H. U. Vora, X.-S. Wang and J.-Q. Yu, *J. Am. Chem. Soc.*, 2013, **135**, 1236; (b) Y. Li, Y.-J. Ding, J.-Y. Wang, Y.-M. Su and X.-S. Wang, *Org. Lett.*, 2013, **15**, 2574.

9 For selected reviews: (a) G. P. McGlacken and L. M. Bateman, *Chem. Soc. Rev.*, 2009, **38**, 2447; (b) B. Li, P. H. Dixneuf, *Chem. Soc. Rev.*, 2013, **42**, 5744; (c) see also Ref. 2a. For selected examples of Pd-catalyzed C-H arylations using ArI: (d) O. Daugulis and V. G. Zaitsev, *Angew. Chem., Int. Ed.*, 2005, **44**, 4046; (e) V. G. Zaitsev and O. Daugulis, *J. Am. Chem. Soc.*, 2005, **127**, 4156; (f) P. Gandeepan, K. Parthasarathy and C.-H. Cheng, *J. Am. Chem.Soc.*, 2010, **132**, 8569; (g) T. Nishikata, A. R. Abela and B.H. Lipshutz, *Angew. Chem., Int. Ed.*, 2010, **49**, 781; (h) G.-W. Wang, T.-T. Yuan, D.-D. Li, *Angew. Chem. Int. Ed.*, 2011, **50**, 1380; (i) W. Li, Z. Xu, P. Sun, X. Jiang and M. Fang, *Org. Lett.* 2011, **13**, 1286; (j) D.-D. Li, T.-T. Yuan and G.-W. Wang, *J. Org. Chem.*, 2012, **77**, 3341; (k) F. Peron, C. Fossey, T. Cailly and F. Fabis, *Org. Lett.*, 2012, **14**, 1827; (l) Z.-J. Liang, H. Feng, R.-K. Yin and Y.-H. Zhang, *Org. Lett.*, 2013, **15**, 4544; (m) J.-C. Wan, J.-M. Huang, Y.-H. Jhan and J.-C. Hsieh, *Org. Lett.*, 2013, **15**, 2742; (n) C. Arroniz, A. Ironmonger, G. Rassias and I. Larrosa, *Org. Lett.*, 2013, **15**, 910; (o) Z. Jiang, L. Zhang, C. Dong, X. Su, H. Li, W. Tang, L. Xu and Q. Fan, *RSC Adv.*, 2013, **3**, 1025; (p) R. Feng, J. Yao, Z. Liang, Z. Liu and Y. Zhang, *J. Org. Chem.*, 2013, **78**, 3688; (q) L. C. Misal Castro, N. Chatani, *Chem. Eur. J.*, 2014, **20**, 4548. (r) J.-F. Luo, S. Preciado and I. Larrosa, *J. Am.Chem. Soc.*, 2014, 136, 4109.

10 For an elegant work with Weinreb amides used for Cu(II)-catalyzed *meta*-selective direct arylation, see: R. J. Phipps and M. J. Gaunt, *Angew. Chem., Int. Ed.*, 2011, **50**, 463.

11 O. Rene, K. Fagnou, *Adv. Synth. Catal.*, 2010, **352**, 2116; (b) G. He and G. Chen, *Angew. Chem., Int. Ed.*, 2011, **50**, 5192.

12 (a) N. Lebrasseur and L. Larrosa, *J. Am. Chem. Soc.*, 2008, **130**, 2926; (b) L.-C. Campeau, M. Parisien, A. Jean and K. Fagnou, *J. Am. Chem. Soc.*, 2006, **128**, 581; (c) See also Ref. 9e, 9l, and 9p.