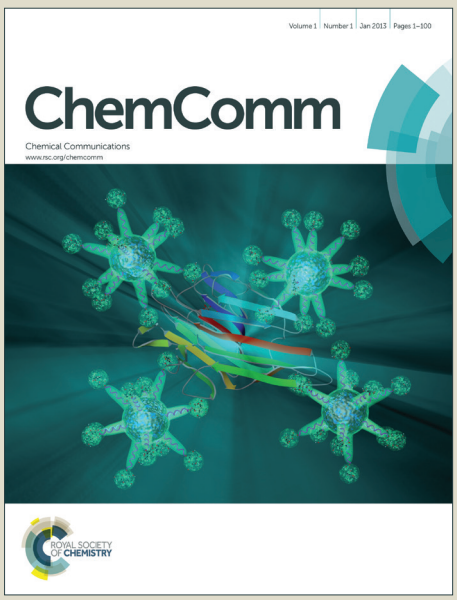
ChemComm

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

Journal Name

RSCPublishing

COMMUNICATION

A highly efficient Pd-catalyzed decarboxylative *ortho*-arylation of amides with aryl acylperoxides

Dengke Li,[a] Ning Xu,[a] Yicheng Zhang,[a] and Lei Wang*[a,b]

Cite this: DOI: 10.1039/x0xx00000x

Received ooth xxxx 2014,
Accepted ooth xxxx 2014

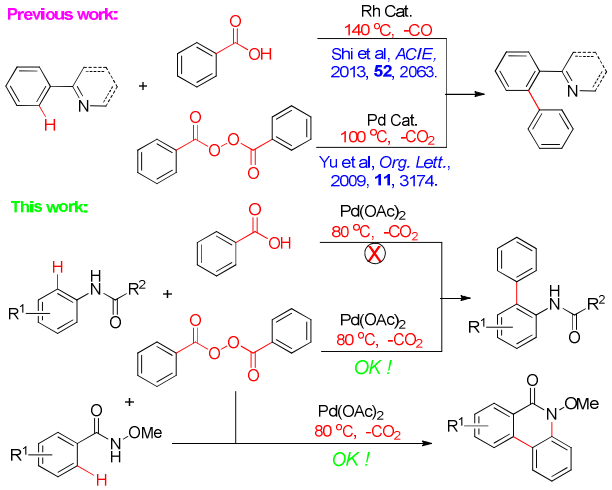
DOI: 10.1039/x0xx00000x

www.rsc.org/

An efficient Pd-catalyzed decarboxylative *ortho*-arylation of amides with aryl acylperoxides was developed. A variety of anilides reacted with aryl acylperoxides to afford the corresponding *ortho*-arylation products, and *N*-methoxyarylamides generated phenanthridinones.

During the past decades, the transition-metal-catalyzed functionalization of C–H bonds has emerged as a powerful tool in organic synthesis. Many versatile and flexible methodologies have been made to activate C–H bonds, in particular aromatic ones for the synthesis of complicated natural products, drugs and advanced materials from simple and commercially available chemicals.[1] With the assistance of an *ortho*-position directing group in C–H activation, a highly efficient and regio-selective functionalization could be achieved.[2] A wide variety of functional groups,[3–9] such as anilides,[3] amides,[4] pyridines/quinolones,[5] oximes,[6] carboxylic acids,[7] ketones,[8] *N*-methoxy amides,[9] have been developed as directing groups. Among them, directed *ortho*-arylation to construct biaryl skeleton has gained significant attention because the biaryl linkages constitute a valuable class of important structural units.[10] It showed that Ru, Rh, Pd, Cu or other transition metal complexes are efficient catalysts for the direct arylation of aromatic C–H bonds using arenes which are functionalized with boron, halides or other organometals.[11] However, their relatively high price and complicated preparation would reduce their potential applications in organic synthesis.

Most recently, the utilization of non-toxic and low cost carboxylic acids for decarboxylative arylations is an attractive development in this area.[12] It accesses reactive organometallic intermediates through the removal of CO_2 without using prefunctionalized substrates comparing to traditional cross-coupling methods. The representative examples of decarboxylative arylation cross-couplings are developed by



Scheme 1. Directing-group assisted decarboxylative C–H arylations

Goossen,[13] Forgione,[14] Myers,[15] Liu and Fu,[16] Su,[17] et *al*.[18] However, high reaction temperature and long reaction time could not be avoided in most cases.

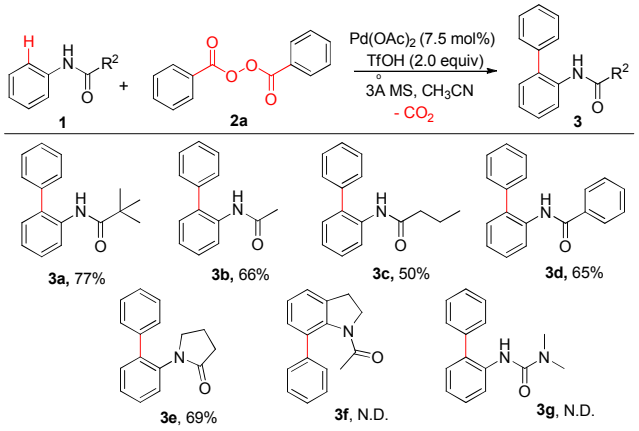
In 2009, Yu demonstrated a direct decarboxylative *ortho*-arylation of 2-phenylpyridines with benzoyl peroxides in the presence of a Pd-complex with good reactivity and selectivity for the synthesis of arylated derivatives.[19] It is the first utilization of directing groups in decarboxylative cross-coupling using a peroxide as substrate (Scheme 1).[20,21] In our continuing efforts on the sp^2 C−H activation using directing groups to construct C−C bonds,[22] herein, we will report that Pd-catalyzed direct arylation of anilides using aryl acylperoxides afforded the corresponding *ortho*-arylation products, and the reaction of *N*-methoxyarylamides with aryl acylperoxides generated the phenanthridinones (Scheme 1).

In our initial study, we focused on *N*-phenylpivalamide (**1a**), shown relatively high reactivity,[3b] and benzoyl peroxide (**2a**) as the model substrates to screen the optimal reaction conditions. Treatment of **1a** with **2a** in the presence of $Pd(OAc)_2$ (7.5 mol%) and TfOH (2.0 equiv) in CH_3CN (2.0 mL) at 80 °C for 32 h, providing the desired product **3a** in 53% yield (Table S1, ESI†). It is noteworthy that the yield of **3a** could be improved to 77% significantly, when activated 3Å molecular sieves was added to the reaction, but 4Å molecular sieves was inferior.[7c] To optimize the reaction conditions, various additives, temperature and solvents were examined. Our investigation indicated that no desired product was obtained when the model reaction was performed in the absence of TfOH or in the presence of a base, such as K_2CO_3 or NEt_3 (Table S1, ESI†), and TfOH is crucial for the reaction.[23,3a,8c] Other acids including TFA, HOAc, and pivalic acid were also surveyed, but they were all ineffective. When *p*-TsOH and CH_3SO_3H were used in the model reaction, **3a** was obtained in 31% and 35% yields, respectively. It was also found that the optimized amount of TfOH is 2.0 equiv. The reaction temperature and time were also examined and the reaction generated the desired product in highest yield at 80 °C for 32 h. The control experiments also showed that the reaction did not proceed in the absence of Pd and the Pd amount was found to be 7.5 mol%. Use of other Pd-catalysts, such as $Pd(TFA)_2$, $PdCl_2$, $Pd(PPh_3)_2Cl_2$, $Pd(PPh_3)_4$ led to the lower yields of **3a** compared with $Pd(OAc)_2$. In addition, the effect of solvent was explored. Toluene, DCE, 1,4-dioxane, DMF, DMSO, DME or HOAc/CH_3CN were employed instead of CH_3CN, poor yields of **3a** were observed (Table S1, ESI†). Therefore, the optimized reaction conditions were $Pd(OAc)_2$ (7.5 mol%), TfOH (2.0 equiv) and 3Å molecular sieves in CH_3CN at 80 °C for 32 h.

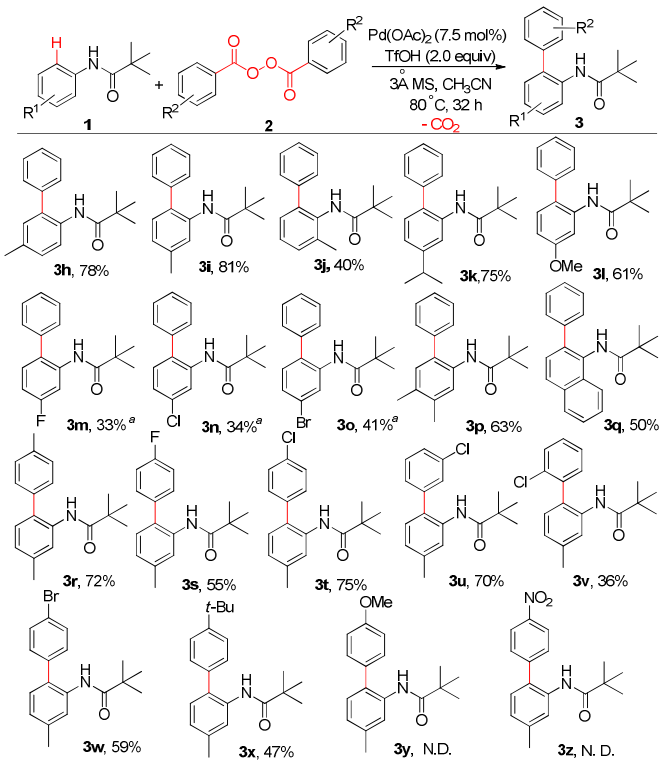
With the optimized reaction conditions in hand, the effect of *N*-substituents on the anilides including acetanilide (**1b**), *N*-phenylbutyramide (**1c**), *N*-phenylbenzamide (**1d**), 1-phenylpyrrolidin-2-one (**1e**), *N*-acetyl-2,3-dihydroindole (**1f**) and 1,1-dimethyl-3-phenylurea (**1g**) was studied and the results are shown in Scheme 2. Gratifyingly, most of them reacted with **2a** to generate the corresponding products (**3b**–**3e**) in 50–69% yields. However, **1f** and **1g** failed to react with **2a**. It showed that pivalanilide was the best one for the arylation.

Under the optimized reaction conditions, the substrate scope of *N*-arylpivalamides (**1**) and aryl acylperoxides (**2**) was investigated to illustrate the efficiency of this strategy (Scheme 3). *N*-Arylpivalamides with various substituents (Me, *i*-Pr, OMe, F, Cl, Br) on the benzene rings were explored. Pivalamides bearing electron-donating groups at *meta*- and/or *para*-positions of the phenyl rings (**1h**, **1i**, **1k**, **1l** and **1p**) underwent the decarboxylative *ortho*-arylation smoothly to generate the corresponding products (**3h**, **3i**, **3k**, **3l** and **3p**, Scheme 3) in 61–81% yields. An obvious *ortho*-substituent effect was observed in the reaction of 2-methyl substituted pivalamide **1j** with **2a**.[3a,9b] However, the substrates bearing electron-withdrawing groups (3-F, 3-Cl, 3-Br) reacted with **2a** under the standard reaction conditions, but failed. When the reactions were performed with addition of $K_2S_2O_8$ (2.0 equiv) at 130 °C, the desired *ortho*-arylation products (**3m**, **3n**, and **3o**) were obtained in 33–41% yields. Whereas the phenyl ring in **1** was instead of 1-napthyl (**1q**), it provided **3q** in 50% yield.

To further expand the substrate scope, we performed the present arylation of *N*-(*m*-tolyl)pivalamide (**1i**) with a variety of aryl acylperoxides (**2b**–**2j**), and the results are also shown in Scheme 3. Substituted groups, such as 4-methyl-, 4-fluoro-, 3-chloro-, 4-chloro-, 4-bromo-, and 4-*tert*-butylphenyl



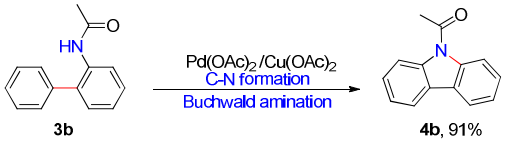
Scheme 2. Palladium-catalyzed decarboxylative *ortho*-arylation of *N*-substituted anilides with benzoyl peroxide [*Reaction conditions*: **1** (0.25 mmol), **2a** (0.40 mmol), $Pd(OAc)_2$ (7.5 mol%), TfOH (2.0 equiv), activated 3Å MS (70 mg), CH_3CN (2.0 mL), air, 80 °C, 32 h]



Scheme 3. The scope of Pd-catalyzed decarboxylative *ortho*-arylation of anilides with aryl acylperoxides [*Reaction conditions:* **1** (0.25 mmol), **2** (0.40 mmol), $Pd(OAc)_2$ (7.5 mol%), TfOH (2.0 equiv), activated 3Å MS (70 mg), CH_3CN (2.0 mL), air, 80 °C, 32 h; [a] With $K_2S_2O_8$ (2.0 equiv) at 130 °C for 32 h]

acylperoxides underwent the coupling with **1i** smoothly, giving the coupling products **3r**–**3u**, **3w** and **3x** in 55–75%, 59% and 47% yields, respectively. An *ortho*-substituent effect was also found during the formation of **3v** in 36% yield. However, neither the strong electron-withdrawing (*p*-NO_2) nor the strong electron-donating group (*p*-CH_3O) could be functionalized to generate the desired product in the reaction with starting materials unchanged and recovered (**3y** and **3z**).

With the obtained **3b** in hand, its transformation through an intramolecular cyclization under Buchwald amination conditions was examined, providing carbazole **4b** in 91% yield (Scheme 4).[24]

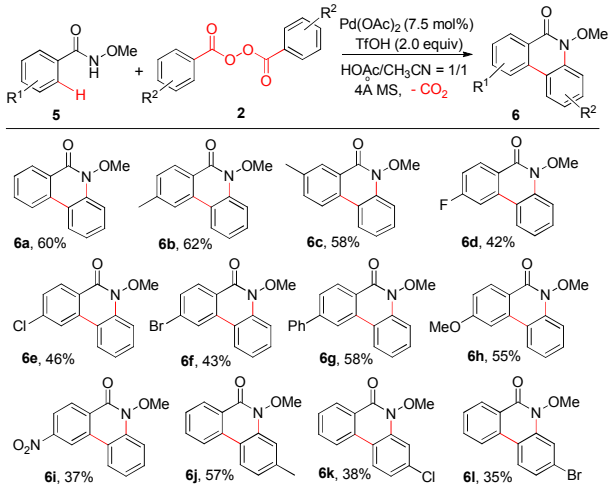


3b 4b, 91%

Scheme 4. Synthesis of carbazole via Buchwald amination

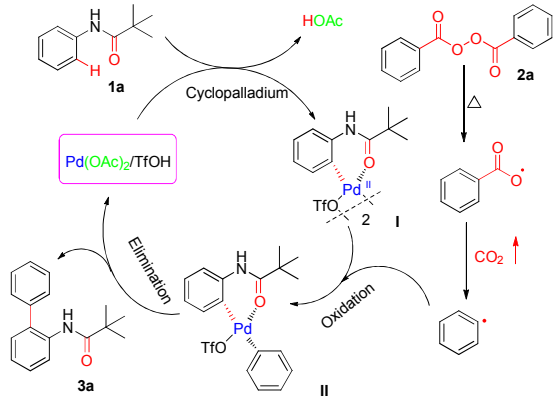
Subsequently, other amide substrates were carried out for the purpose of broadening the application of current methodology. A series of amides, such as benzamide, *N*-*iso*-propylbenzamide, *N*-tosylbenzamide were used for the reaction with benzoyl peroxide, but failed. Much to our pleasure, *N*-methoxybenzamide (**5a**) was found to be a promising coupling partner in the reaction, providing an arylation-cyclization product phenanthridinone (**6a**), as an important structural motif in numerous biologically molecules, in one-pot with 21% yield (Table S2, ESI†). Further optimization revealed that a best of reaction conditions is consisted of $Pd(OAc)_2$ (7.5 mol%), TfOH (2.0 equiv) and 4Å molecular sieves in $HOAc/CH_3CN$ (V/V = 1/1) at 80 °C for 24 h.

Using this strategy, a number of phenanthridinone derivatives could be prepared in moderate to good yields and the results are summarized in Scheme 5. A variety of *N*-methoxyarylamides with either electron-donating or electron-withdrawing groups, even the strong electron-withdrawing group (*p*-NO_2), on the benzene rings could be tolerated under the employed reaction conditions, and afforded the desired products in moderate to good yields. It should be noted that *N*-methoxyarylamides with electron-donating groups on the benzene rings gave a higher yield than that with electron-withdrawing groups on the benzene rings (55–62% yields for **6b**, **6c**, **6g** and **6h** *vs* 37–46% yields for **6d**, **6e**, **6f** and **6i**). *N*-Methoxyarylamides with an electron-donating group such as methyl (Me), phenyl (Ph), and methoxy (MeO) at the *para*- or *meta*-position of the phenyl rings gave the comparable product yields to non-substituted one (*N*-methoxybenzamide, **5a**). To further expand the substrate scope, some aryl acylperoxides, including 4-methylphenyl acylperoxide, 4-chlorophenyl acylperoxide, and 4-bromophenyl acylperoxide, were used to react with **5a**, providing the corresponding products (**6j**–**6l**) in 35–57% yields.



Scheme 5. The scope of one-pot Pd-catalyzed decarboxylative reaction anilides with aryl acylperoxides for the synthesis of phenanthridinones [*Reaction conditions:* **5** (0.25 mmol), **2** (0.40 mmol), $Pd(OAc)_2$ (7.5 mol%), TfOH (2.0 equiv), activated 4Å MS (70 mg), $HOAc/CH_3CN$ (V/V = 1/1, 2.0 mL), air, 80 °C, 24 h]

Based on the literatures and our observation,[19] a possible reaction pathway is proposed in Scheme 6 although the mechanism is not clear. Initially, a six-membered cyclopalladated intermediate **I** was generated through chelate-directed C–H activation of *N*-phenylpivalamide (**1a**) with the assistance of TfOH. Meanwhile, phenyl radical produced in situ by the thermal decomposition of benzoyl peroxide (**2a**) along with release of CO_2, reacted with intermediate **I** to realize the oxidation of Pd(II) to dimeric Pd(III) or Pd(IV) (intermediate **II**).[25] Finally, Pd(II) species was regenerated through the reductive elimination of **II**, with providing the desired product **3a**. When the radical scavengers, such as TEMPO (2,2,6,6-tetramethylpiperidyl-1-oxyl) and ascorbic acid were added up to 1.0 equiv in the reaction, no desired product was observed, suggesting the reaction may be undergo a radical process (Table S3, ESI†).



Scheme 6. A plausible reaction mechanism

In summary, a highly efficient palladium-catalyzed decarboxylative *ortho*-arylation of amides with aryl acylperoxides via C–H activation and functionalization was developed. This synthetic methodology provides a simple and direct route to a wide variety of diversely *ortho*-functionalized biaryl compounds from anilides, and phenanthridinones from *N*-methoxyarylamides through an arylation-cyclization process. The further investigation is currently underway.

This work was financially supported by the National Science Foundation of China (No. 21172092).

Notes and reference

[a] Department of Chemistry, Huaibei Normal University, Huaibei, Anhui 235000, P R China; E-mail: leiwang@chnu.edu.cn
Tel.: +86-561-380-2069; fax: +86-561-309-0518
[b] State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, P R China

† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

1 (*a*) *Transitions Metals for Organic Chemistry*, *2nd ed.* (Eds.: M. Beller, C. Bolm), Wiley-VCH, Weinheim, 2004; (*b*) J. A. Labinger and J. E. Bercaw, *Nature*, 2002, **417**, 507; (*c*) K. Godula and D. Sames, *Science*, 2006, **312**, 67.

2 For selected directing-group assisted C-H activation reviews, see: (*a*) D. A. Colby, A. S. Tsai, R. G. Bergman and J. A. Ellman, *Acc. Chem. Res.*, 2012, **45**, 814; (*b*) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147; (*c*) C. S. Yeung and V. M. Dong, *Chem. Rev.*, 2011, **111**, 1215; (*d*) K. M. Engle, T.-S. Mei, M. Wasa and J.-Q. Yu, *Acc. Chem. Res.*, 2012, **45**, 788.

3 (*a*) M. D. K. Boele, G. P. F. van Strijdonck, A. H. M. de Vries, P. C. J. Kamer, J. G. de Vries, and P. W. N. M. van Leeuwen, *J. Am. Chem. Soc.*, 2002, **124**, 1586; (*b*) O. Daugulis and V. G. Zaitsev, *Angew. Chem. Int. Ed.*, 2005, **44**, 4046; (*c*) S. Yang, B. Li, X. Wan and Z. Shi, *J. Am. Chem. Soc.*, 2007, **129**, 6066; (*d*) Z. Shi, B. Li, X. Wan, J. Cheng, Z. Fang, B. Cao, C. Qin and Y. Wang, *Angew. Chem. Int. Ed.*, 2007, **46**, 5554; (*e*) D. R. Stuart, M. Bertrand-Laperle, K. M. N. Burgess and K. Fagnou, *J. Am. Chem. Soc.*, 2008, **130**, 16474; (*f*) R. Giri, J. K. Lam and J.-Q. Yu, *J. Am. Chem. Soc.*, 2010, **132**, 686.

4 (*a*) K. Chen, F. Hu, S.-Q. Zhang and B.-F. Shi, *Chem. Sci.*, 2013, **4**, 3906; (*b*) C. S. Yeung, X. Zhao, N. Borduas and V. M. Dong, *Chem. Sci.*, 2010, **1**, 331; (*c*) F. Péron, C. Fossey, T. Cailly and F. Fabis, *Org. Lett.*, 2012, **14**, 1827; (*d*) J. Wencel-Delord, C. Nimphius, F. W. Patureau and F. Glorius, *Angew. Chem. Int. Ed.*, 2012, **51**, 2247.

5 (*a*) Q. Shuai, L. Yang, X. Guo, O. Baslé and C.-J. Li, *J. Am. Chem. Soc.*, 2010, **132**, 1221; (*b*) D. Kalyani, N. R. Deprez, L. V. Desai and M. S. Sanford, *J. Am. Chem. Soc.*, 2005, **127**, 7330; (*c*) X. Chen, C. E. Goodhue and J.-Q. Yu, *J. Am. Chem. Soc.*, 2006, **128**, 12634; (*d*) W.-Y. Yu, W. N. Sit, K.-M. Lai, Z. Zhou and A. S. C. Chan. *J. Am. Chem. Soc.*, 2008, **130**, 3304; (*e*) J. Kim and S. Chang, *J. Am. Chem. Soc.*, 2010, **132**, 10272.

6 (*a*) C.-L. Sun, N. Liu, B.-J. Li, D.-G. Yu, Y. Wang and Z.-J. Shi, *Org. Lett.*, 2010, **12**, 184; (*b*) C.-W. Chan, Z. Zhou, A. S. C. Chan and W.-Y. Yu, *Org. Lett.*, 2010, **12**, 3926.

7 (*a*) K. Ueura, T. Satoh and M. Miura, *Org. Lett.*, 2007, **9**, 1407; (*b*) R. Giri, N. Maugel, J.-J. Li, D.-H. Wang, S. P. Breazzano, L. B. Saunders and J.-Q. Yu, *J. Am. Chem. Soc.*, 2007, **129**, 3510; (*c*) H. A. Chiong, Q.-N. Pham and O. Daugulis, *J. Am. Chem. Soc.*, **2007**, *129*, 9879.

8 (*a*) P. Gandeepan, K. Parthasarathy and C.-H. Cheng, *J. Am. Chem. Soc.*, 2010, **132**, 8569; (*b*) F. W. Patureau, T. Besset, N. Kuhl and F. Glorius, *J. Am. Chem. Soc.*, 2011, **133**, 2154; (*c*) B. Xiao, T.-J. Gong, J. Xu, Z.-J. Liu and L. Liu, *J. Am. Chem. Soc.*, 2011, **133**, 1466.

9 (*a*) D.-H. Wang, M. Wasa, R. Giri and J.-Q. Yu, *J. Am. Chem. Soc.*, 2008, **130**, 7190; (*b*) G.-W. Wang, T.-T. Yuan and D.-D. Li, *Angew. Chem. Int. Ed.*, 2011, **50**, 1380; (*c*) J. Karthikeyan and C.-H. Cheng, *Angew. Chem. Int. Ed.*, 2011, **50**, 9880; (*d*) J. Karthikeyan, R. Haridharan and C.-H. Cheng, *Angew. Chem. Int. Ed.*, 2012, **51**, 12343.

10 (*a*) J. Hassan, M. Sévignon, C. Gozzi, E. Schulz and M. Lemaire, *Chem. Rev.*, 2002, **102**, 1359; (*b*) D. A. Horton, G. T. Bourne and M. L. Smythe, *Chem. Rev.*, 2003, **103**, 893.

11 For arylation reviews, see: (*a*) L. Ackermann, *Chem. Rev.*, 2011, **111**, 1351; (*b*) C. Liu, H. Zhang, W. Shi and A. Lei, *Chem. Rev.*, 2011, **111**, 1780; (*c*) C.-L. Sun, B.-J. Li and Z.-J. Shi, *Chem. Rev.*, 2011, **111**, 1293.

12 For recent reviews, see: (*a*) L. J. Gooßen, N. Rodríguez and K. Gooßen, *Angew. Chem. Int. Ed.*, 2008, **47**, 3100; (*b*) N. Rodríguez and L. J. Goossen, *Chem. Soc. Rev.*, 2011, **40**, 5030; (*c*) J. D. Weaver, A. Recio III, A. J. Grenning and J. A. Tunge, *Chem. Rev.*, 2011, **111**, 1846.

13 (*a*) L. J. Gooßen, G. Deng and L. M. Levy, *Science*, 2006, **313**, 662; (*b*) L. J. Gooßen, N. Rodríguez, P. P. Lange and C. Linder, *Angew. Chem. Int. Ed.*, 2010, **49**, 1111.

14 P. Forgione, M.-C. Brochu, M. St-Onge, K. H. Thesen, M. D. Bailey and F. Bilodeau, *J. Am. Chem. Soc.*, 2006, **128**, 11350.

15 (*a*) A. G. Myers, D. Tanaka and M. R. Mannion, *J. Am. Chem. Soc.*, 2002, **124**, 11250; (*b*) D. Tanaka, S. P. Romeril and A. G. Myers, *J. Am. Chem. Soc.*, 2005, **127**, 10323.

16 (*a*) R. Shang, Y. Fu, Y. Wang, Q. Xu, H.-Z. Yu and L. Liu, *Angew. Chem. Int. Ed.*, 2009, **48**, 9350; (*b*) S.-L. Zhang, Y. Fu, R. Shang, Q.-X. Guo and L. Liu, *J. Am. Chem. Soc.*, 2010, **132**, 638.

17 (*a*) P. Hu, M. Zhang, X. Jie and W. Su, *Angew. Chem. Int. Ed.*, 2012, **51**, 227; (*b*) P. Hu, Y. Shang and W. Su, *Angew. Chem. Int. Ed.*, 2012, **51**, 5945.

18 (*a*) K. Xie, Z. Yang, X. Zhou, X. Li, S. Wang, Z. Tan, X. An and C.-C. Guo, *Org. Lett.*, 2010, **12**, 1564; (*b*) Y. Zhang, S. Patel and N. Mainolfi, *Chem. Sci.*, 2012, **3**, 3196.

19 W.-Y. Yu, W. N. Sit, Z. Zhou and A. S.-C. Chan, *Org. Lett.*, 2009, **11**, 3174.

20 F. Pan, Z.-Q. Lei, H. Wang, H. Li, J. Sun and Z.-J. Shi, *Angew. Chem. Int. Ed.*, 2013, **52**, 2063.

21 (*a*) Y. Zhang, J. Feng and C.-J. Li, *J. Am. Chem. Soc.*, 2008, **130**, 2900; (*b*) Q. Xia, X. Liu, Y. Zhang, C. Chen and W. Chen, *Org. Lett.*, 2013, **15**, 3326; (*c*) Q. Dai, J. Yu, Y. Jiang, S. Guo, H. Yang and J. Cheng, *Chem. Commun.*, 2014, **50**, 3865.

22 (*a*) H. Li, P. Li and L. Wang, *Org. Lett.*, 2013, **15**, 620; (*b*) H. Li, P. Li, H. Tan and L. Wang, *Chem. Eur. J.*, 2013, **19**, 14432.

23 (*a*) N. Lebrasseur and I. Larrosa, *J. Am. Chem. Soc.*, 2008, **130**, 2926; (*b*) T. Nishikata, A. R. Abela, S. Huang and B. H. Lipshutz, *J. Am. Chem. Soc.*, 2010, **132**, 4978; (*c*) B. Xiao, Y. Fu, J. Xu, T.-J. Gong, J.-J. Dai, J. Yi and L. Liu, *J. Am. Chem. Soc.*, 2010, **132**, 468.

24 W. C. P. Tsang, N. Zheng and S. L. Buchwald, *J. Am. Chem. Soc.*, 2005, **127**, 14560.

25 (*a*) N. R. Deprez and M. S. Sanford, *J. Am. Chem. Soc.,* 2009, **131**, 11234; (*b*) J. M. Racowski, A. R. Dick and M. S. Sanford, *J. Am. Chem. Soc.,* 2009, **131**, 10974.

