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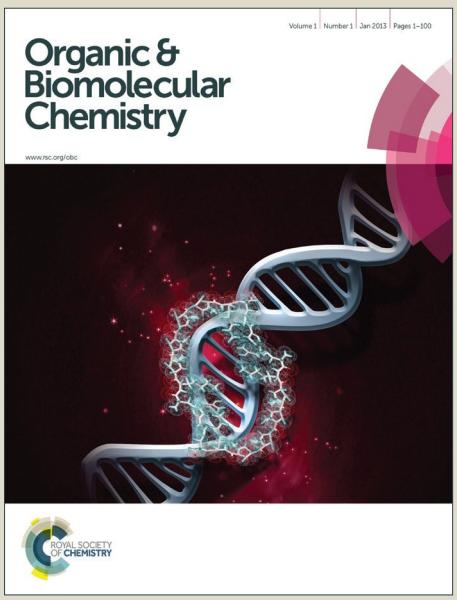

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ARTICLE

Iridium(III)-Catalyzed Regioselective Direct Arylation of sp^2 C-H Bonds with Diaryliodonium Salts

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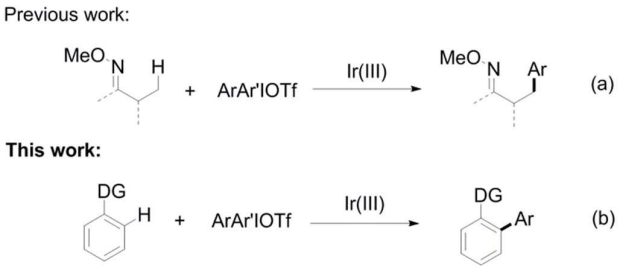
A regioselective direct arylation of arenes and olefins at the *ortho* position is reported. The key to the high selectivity is appropriate choice of diaryliodonium salts as the arylating reagent in the presence of a cationic iridium(III) catalyst. The coordination of the metal with oxygen or nitrogen atom and subsequent C-H activation allows for direct arylation with coupling partners. This reaction proceeds under mild reaction conditions and with a high tolerance of various functional groups including many halide functional groups.

Introduction

The biaryl compounds constitute an important structural motif commonly found in natural products, pharmaceuticals and other functional compounds.[1] The classical method involves the reaction of organometallic nucleophiles with a wide range of organo(pseudo)halides in presence of transition-metal catalysis.[2] Synthesis of such compounds without the aid of organometallics have drawn tremendous attention to the chemist.[3] Substitution of the preactivated species with a simple arene as a nucleophile has become the most widely used mode of attack. Typically, this strategy is limited by two fundamental challenges involving the inert nature of most C-H bonds and the requirement of controlling site selectivity in molecules that contain diverse C-H bonds. While several methods have been employed to address these issues, the most common strategies involve the use of substrates that contain directing groups.[4] The *N*-arylpyrrolidinone is a prominent structural motif which can convert to many bioactive natural products and pharmaceutically important compounds. However, only a few examples on direct arylation of N-arylpyrrolidinone substrates have been documented in the literature, which relied on Pd-catalyzed C–H activation process.[5] Nevertheless, the development of a practical and efficient method to achieve direct arylation of this type compounds systematically is still highly desirable.

Half-sandwich Cp*Ir(III) complexes have received recent research interest in C-H activation because of their catalytic activity toward various chemical transformations.[6] The cross-coupling reactions involving C-H amidation[7] and olefination[8] have been well developed. In 2014, Li and co-workers developed Cp*Ir(III)-catalyzed C–H alkynylation of (hetero)-arenes using hypervalent iodine–alkyne reagents.[9] In 2015, Wang and Li reported Cp*Ir(III)-catalyzed redox-neutral C–H arylation with quinone diazides to construct a series of arylated phenols.[10]Later, Chang et al. uncovered Cp*Ir(III)-catalyzed mild and broad C-H arylation of arenes with aryldiazonium salts.[11] Diaryliodonium salts are received tremndous attention in C-H activation field,[12] however, employing them as arylating reagents in Cp*Ir(III)-catalyzed reaction is still rare. Until recently, our group reported the first Cp*Ir(III)-catalyzed direct arylation of sp^3 C-H bonds in *O*-methyl ketoximes with diaryliodonium salts (Scheme 1a).[13] As part of our continuous effort on developing direct arylation procedure,[14] herein, we report iridium-catalyzed complementary C–H arylation of *N*-arylpyrrolidinones and the analogues with diaryliodonium salts (Scheme 1b).



Scheme 1 Ir(III)-catalyzed direct arylation of sp^3 and sp^2 C-H bonds.

Results and discussion

Initial studies involved the evaluation of the selective direct arylation of *N*-phenylpyrrolidinone (**1a**) and Ph_2IOTf (**2a**) (equation 1). We started our investigation based on the former developed reaction conditions and controlling experiments

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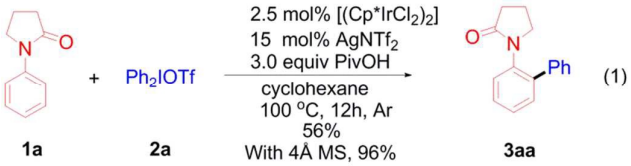
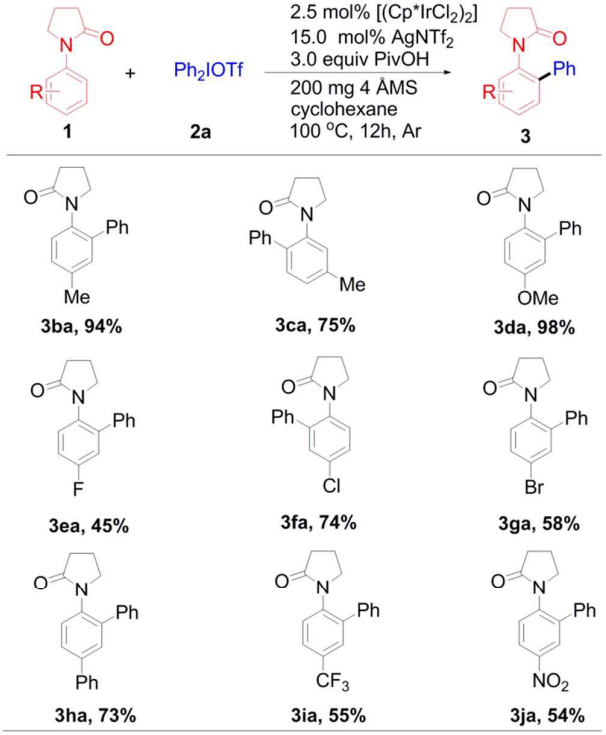


show that each component was essential in this reaction. By employing 2.5 mol % $[(Cp^*IrCl_2)_2]$ and 20mol % of $AgNTf_2$ as the catalyst, 3.0 equiv of PivOH as the additive in cyclohexane at 100°C, we indeed observed ortho-arylated product 3aa in 56% yield. Remarkably, the addition of 4 Å MS improved the efficiency of the reaction dramatically affording the corresponding product 3aa in 96% yield.

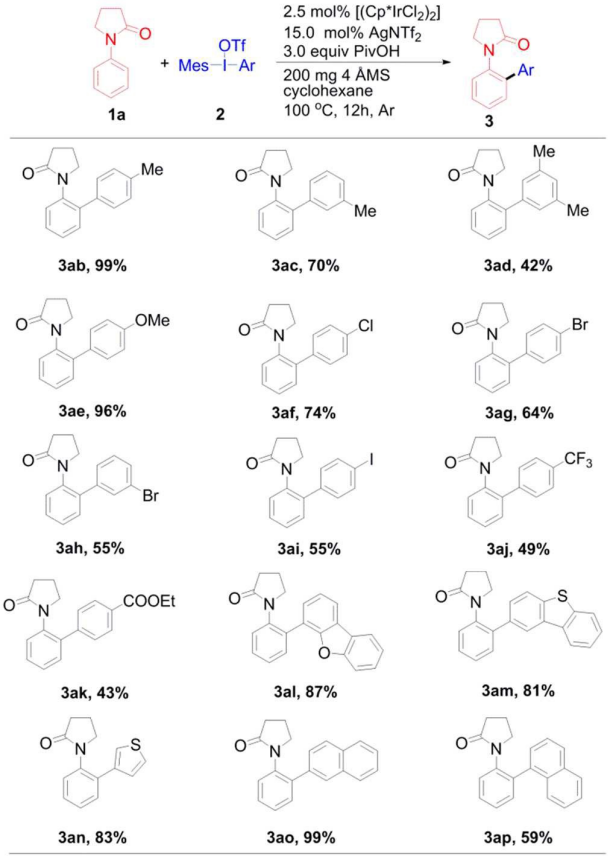
Table 1 Substrate scope of *N*-aryllpyrrolidinone derivatives.[a]



[a]Reaction conditions: **1** (0.24 mmol), **2a** (0.20 mmol), 2.5 mol% $[(Cp^*IrCl_2)_2]$, 15.0mmol% $AgNTf_2$, 3.0 equiv PivOH and 200 mg 4 ÅMS in cyclohexane (1.0 mL) at 100 °C, 12 h, under Ar; isolated yields.

With the best conditions in hand, we have examined the scope of this direct arylation process (Table 1). Cross-coupling reactions of Ph_2IOTf (**2a**) with a broad range of *N*-arylpyrrolidinones were first examined. *N*-arylpyrrolidinones bearing electron-neutral and donating substituents including methyl (**3ba**-**3ca**) and methoxy (**3da**) groups underwent facile arylation affording the corresponding products in excellent yields. In particular, the halogen-containing motifs (F, Cl, and Br) work very well in the *ortho* selective arylation (**3ea**-**3ga**), highlighting the potential of this process in combination with further conventional cross-coupling transformations. An indole substrate bearing a phenyl group at C3-position was converted in good efficiency (**3ha**), but the substrates (**3ia**-**3ja**) with electron-deficient trifluoromethyl and nitro substituents were obviously lower.

Table 2 Substrate scope with respect to diaryliodonium salts.[a]



[a]Reaction conditions: **1a** (0.24 mmol), **2** (0.20 mmol), 2.5 mol% $[(Cp^*IrCl_2)_2]$, 15.0 mmol% $AgNTf_2$, 3.0 equiv PivOH and 200 mg 4 ÅMS in cyclohexane (1.0 mL) at 100 °C, 12 h, under Ar; isolated yields.

Next, we examined the scope of diaryliodonium salt coupling partners with *N*-phenylpyrrolidinone (**1a**) (Table 2). Gratifyingly, a wide range of diaryliodonium salts that incorporate electron- neutral, electron-donating and electron-withdrawing substituents were readily tolerated (**3ab**-**3ak**). Remarkably, chloride, bromide, and iodide substituents were all well tolerated under the reaction condition (**3af**-**3ai**). They serve as valuable synthetic handles for further manipulation of the products. An electron-withdrawing substitution group, such as ethyl ester and trifluoromethyl groups could be tolerated in this protocol, although reduced yield was observed (**3aj**-**3ak**). We were pleased that the coupling of polycyclic and heterocyclic aromatic motifs was possible and proceeded in moderate to excellent yields (**3al**-**3ap**), thus further enhancing the scope of our reaction.

Our iridium-catalyzed system is not limited to the use of N-pyrrolidinone as the sole directing group (Table 3). Under the optimal conditions, reaction with N-phenylpyrrolidinone derivative **1k** and **2a** provided the desired product **3ka** in 65% yield. Interestingly, Spiral ring substrate **1l** is also compatible. In addition, ε-lactams such as **1m** can also be *ortho*-arylated in our catalytic system affording product **3ma** in 93% yield.

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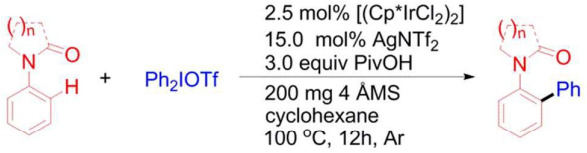
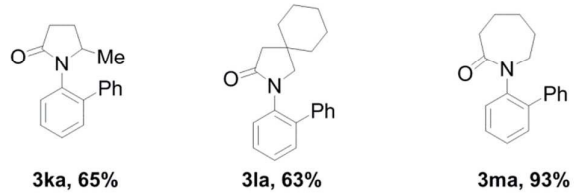
Table 3 Direct arylation of *N*-arylpyrrolidinone analogues.[a]

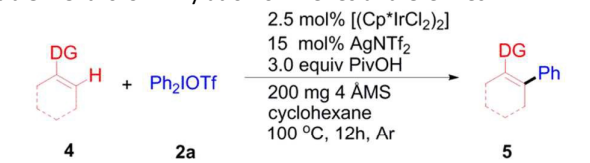


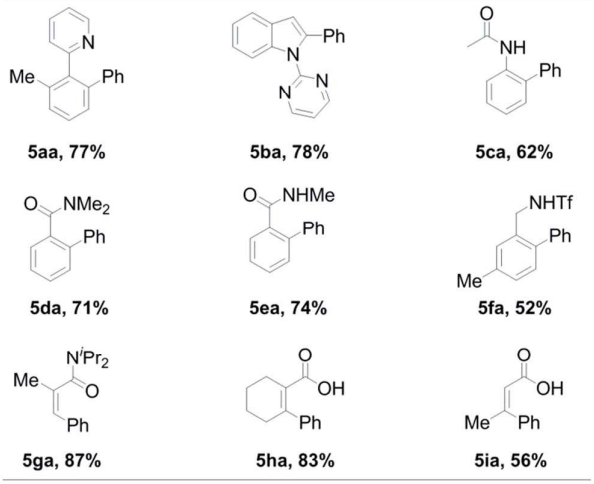


[a]Reaction conditions: **1** (0.24 mmol), **2a** (0.20 mmol), 2.5 mol% $[(Cp^*IrCl_2)_2]$, 15.0 mmol% $AgNTf_2$, 3.0 equiv PivOH and 200 mg 4 ÅMS in cyclohexane (1.0 mL) at 100 °C, 12 h, under Ar; isolated yields.

In order to examine the efficacy of the catalytic system, we also extended the scope of the substrates to other arenes (table 4). Phenylpyridine **4a** and indole **4b** underwent smooth coupling affording the desired products **5aa** and **5ba** in good yields. This catalytic system also worked well with arenes including *N*-phenyl amide **4c**, benzamides **4d**-**4e** and sulphonamide **4i**. Interstingly, in case of the enamide **4g** with both vinylic and allylic C-H bonds, the sp^2 C-H arylation product **5ga** can be selectively obtained in excellent yield, indicating the functionalization of a vinylic C-H bond is also much more favourable. In addition, the vinyl carboxylic acids **4h**-**4i** can yield the desired products **5kb**-**5ib** in 56-83% yields as well.

Table 4 *Ortho* C-H Arylation of Arenes and Olefines.[a]





[a]Reaction conditions: **4** (0.24 mmol), **2b** (0.20 mmol), 2.5 mol% $[(Cp^*IrCl_2)_2]$, 15.0mmol% $AgNTf_2$, 3.0 equiv PivOH and 200 mg 4 ÅMS in cyclohexane (1.0 mL) at 100 °C, 12 h, under Ar; isolated yields.

Conclusions

In summary, we have developed the examples of Cp*Ir(III)-catalyzed C-H arylation of various arenes and olefins with diaryliodonium salts under mild conditions. The method provides access to biaryl compounds and shows high functional group compatibility. Further studies on the mechanism and applications of this novel method are going to be researched in our group.

Experimental

General information

All new compounds were fully characterized. NMR-spectra were recorded on Bruker ARX-400 MHz. Mass spectra were conducted at Micromass Q-Tof instrument (ESI) and Agilent Technologies 5973N (EI). All reactions were carried out in flame-dried reaction vessels with Teflon screw caps under argon. Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. $[Cp^*IrCl_2]_2$ was purchased from TCI. $AgSbF_6$ was purchased from Sigma-Aldrich. PivOH and Cyclohexane were purchased from Acros. The preparation of diaryliodonium salts was described according to the literatures.[15]

General procedures

To a 25 mL Schlenk tube was added 200 mg 4Å MS (actived in situ by heating to 600 °C for 5 minutes under vaccum) and purged with argon for three times. Then the tube was added arenes **1** or **4** (1.2 equiv, 0.24 mmol), diaryliodonium salt **2** (1.0 equiv, 0.2 mmol), $[Cp^*IrCl_2]_2$ (4.0 mg, 2.5 mol %), $AgNTf_2$ (11.6 mg, 15 mol %), PivOH (61.2 mg, 3.0 equiv) and cyclohexane (1.0 mL). The formed mixture was stirred at 100 °C under Ar for 12 hours as monitored by TLC. The solution was then cooled to room temperature, and the solvent was removed under vaccum directly. The crude product was purified by column chromatography on silica gel to afford the arylation products.

Acknowledgements

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Notes and references

1 (*a*) J. Hassan, M. Sévignon, C. Gozzi, E.Schulz, M. Lemaire, *Chem. Rev.*, 2002, **102**, 1359; (*b*) D. A. Horton, G. T. Bourne, M. L. Smythe, *Chem. Rev.*,2003, **103**, 893; (*c*) E. R. Kay, D. A. Leigh, F. Zerbetto, *Angew. Chem. Int. Ed.*, 2007, **46**, 72; (*d*) Y. Liu, S. Zhang, P. J. M. Abreu, *Nat. Prod. Rep.*, 2006, **23**, 630; (*e*) R. A. Hughes, C. J. Moody, *Angew. Chem. Int. Ed.*, 2007, **46**, 7930.

2 (*a*) K. Tamao, K. Sumitani, M. Kumada, *J. Am. Chem. Soc.*, **1972**, 94, 4374; (*b*) M. Yamamura, I. Moritani, S. Murahashi,

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DOI: 10.1039/C6OB01145D

J. Organomet. *Chem*., 1975, **91**, 39; (*c*) D. Milstein, L. K. Stille, *J. Am*. *Chem*. *Soc*., 1978, **100**, 3636; (*d*) J. K. Stille, *Angew*. *Chem*. *Int*. *Ed*.,1986, **25**, 508; (*e*) D. Milstein, L. K. Stille, *J. Am*. *Chem*. *Soc*., 1979, *101*, 4992; (*f*) N. Miyaura, T. Yanagi, A. Suzuki, *Synth*. *Commun*., 1981, **11**, 513; (*g*) N. Miyaura, A. Suzuki, *Chem*. *Rev*., 1995, **95**, 2457; (*h*) S. Baba, E. I. Negishi, *J. Am*. *Chem*. *Soc*., 1976, **98**, 6729.

3 (*a*) M. Lautens and P. Thansandote, *Chem. Eur. J.,* 2009, **15**, 5874; (*b*) R. Giri, B.-F. Shi, K. M. Engle, N. Maugel and J.-Q. Yu, *Chem. Soc. Rev.,* 2009, **38**, 3242; (*c*) R. Jazzar, J. Hitce, A. Renaudat, J. Sofack-Kreutzer and O. Baudoin, *Chem. Eur. J.,* 2010, **16**, 2654; (*d*) S. H. Cho, J. Y. Kim, J. Kwak and S. Chang, *Chem. Soc. Rev.,* 2011, **40**, 5068; (*e*) C.-L. Sun, B.-J. Li and Z.-J. Shi, *Chem. Rev.,* 2011, 111, 1293; (*f*) J. Wencel-Delord, T. Dröge, F. Liu and F. Glorius, *Chem. Soc. Rev.,* 2011, **40**, 4740; (*g*) T. Newhouse and P. S. Baran, *Angew. Chem., Int. Ed.,* 2011, **50**, 3362; (*i*) L. Ackermann, *Chem. Rev.,* 2011, **111**, 1315; (*h*) L. McMurray, F. O'Hara and M. J. Gaunt, *Chem. Soc. Rev.,* 2011, **40**, 1885; (*j*) C. S. Yeung and V. M. Dong, *Chem Rev.,* 2011, **111**, 1215; (*k*) Z. Shi, C. Zhang, C. Tang and N. Jiao, *Chem. Soc. Rev.,* 2012, **41**, 3381; (*l*) B.-J. Li and Z.-J. Shi, *Chem. Soc. Rev.,* 2012, **41**, 5588; (*m*) M. C. White, *Science,* 2012, **335**, 807; (*n*) K. M. Engle, T.-S. Mei, M. Wasa and J.-Q. Yu, *Acc. Chem. Res.,* 2012, **45**, 788; (*o*) J. Yamaguchi, A. D. Yamaguchi and K. Itami, *Angew. Chem., Int. Ed.,* 2012, **51**, 8960; (*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) J. Wencel-Delord and F. Glorius, *Nat. Chem.,* 2013, **5**, 369; (*s*) X.-X. Cuo, D.-W. Gu, Z. Wu and W. Zhang, *Chem. Rev.,* 2015, **115**, 1622.

4 (*a*) T. W. Lyons and M. S. Sanford, *Chem. Rev.,* 2010, **110**, 1147; (b) b) F. Zhang, D. R. Spring, *Chem. Soc. Rev.,* 2014, **43**, 6906.

5 (*a*) D. Kalyani, N. R. Deprez, L. V. Desai and M. S. Sanford, *J. Am. Chem. Soc.,* 2005, **127**, 7330; (b) C. S. Yeung, X. Zhao, N. Borduas, V. M. Dong, *Chem. Sci*., 2010, **1**, 331; (c) S. R. Neufeldta, M. S. Sanford, *Adv. Syn. Cat*., 2012, **354**, 3517.

6 For selected reviews see: (a) T. Satoh, M. Miura, *Chem. Eur. J*., 2010, **16**, 11212; (b) G. Song, F. Wang, X. Li, *Chem. Soc. Rev*., 2012, **41**, 3651; (c) N. Kuhl, N. Schroder, F. Glorius, *Adv. Synth. Catal*., 2014, **356**, 1443; (d) G. Song, X. Li, *Acc. Chem. Res*., 2015, **48**, 1007.

7 (a) J. Ryu, J. Kwak, K. Shin, D. Lee, S. Chang, *J. Am*. *Chem*. *Soc*., 2013, **135**, 12861; (*b*) T. Kang, Y. Kim, D. Lee, Z. Wang, S. Chang, *J. Am. Chem. Soc.*, 2014, **136**, 4141; (*c*) T. Kang, H. Kim, J. G. Kim and S. Chang, *Chem. Commun.,* 2014, **50**, 12073; (d) D. Lee, S. Chang, *Chem. Eur. J*., 2015, **21**, 5364; (e) J. Kim, S. Chang, *Angew. Chem. Int. Ed.*, 2014, **53**, 2203; (f) P. Becker, R. Pirwerdjan, C. Bolm, *Angew. Chem. Int. Ed.*, 2015, **54**, 15493; (g) L. Lu, J. Ma, P. Qu, F. Li, *Org. Lett*., 2015, **17**, 2350; (h) Y. Kim, J. Park, S. Chang, *Org. Lett*., 2016, **18**, 1892; (i) Z. Song, A. P. Antonchick, *Org. Biomol. Chem*., 2016, **14**, 4804; (j) T. Zhang, X. Hu, Z. Wang, T. Yang, H. Sun, G. Li, H. Lu, *Chem. Eur. J*., 2016, **22**, 2920; (k) G. N. Hermann, P. Becker, C. Bolm, *Angew. Chem. Int. Ed.*, 2016, **55**, 3781.

8 (a) Y. Quan, Z. Xie, *J. Am*. *Chem*. *Soc*., 2014, **136**, 15513; (b) J. Kim, S.-W. Park, M.-H. Baik, S. Chang, *J. Am*. *Chem*. *Soc*., 2015, **137**, 13448.

9 (a) F. Xie, Z. S. Qi, S. J. Yu, X.-W. Li, *J. Am*. *Chem*. *Soc*. 2014. **136**. 4780; (b) H. Wang, F. Xie, Z. Qi, X. Li, *Org. Lett*., 2015, **17**, 920.

10 S.-S. Zhang, C.-Y. Jiang, J.-Q. Wu, X.-G. Liu, Q. Li, Z.-S. Huang, D. Li, H. Wang, *Chem. Commun*., 2015, **51**, 10240.

11 K. Shin, S.-W. Park, S. Chang, *J. Am. Chem. Soc*., 2015, **137**, 8584.

12 (*a*) S. G. Modha, M. F. Greaney, *J. Am. Chem. Soc.,* 2015, **137**, 1416; *(b*) Zhang, F.; Das, S.; Walkinshaw, A. J.; Casitas, A.; Taylor, M.; Suero, M. G.; Gaunt, M. J. *J. Am. Chem. Soc.,* 2014, **136**, 8851; (*c*) Sokolovs, I.; Lubriks, D.; Suna, E. *J. Am. Chem. Soc.,* 2014, **136**, 6920; (*d*) Walkinshaw, A. J.; Xu, W.; Suero, M. G.; Gaunt, M. J. *J. Am. Chem. Soc.,* 2013, **135**, 12532; (*e*) Wang, Y.; Chen, C.; Peng, J.; Li, M. *Angew. Chem. Int. Ed.,* 2013, **52**, 5323; (*f*) Kieffer, M. E.; Chuang, K. V.; Reisman, S. E. *J. Am. Chem. Soc.,* 2013, **135**, 5557; (*g*) Zhu, S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* 2012, **134**, 10815; (*h*) Skucas, E.; MacMillan, D. W. C. *J. Am. Chem. Soc.,* 2012, **134**, 9090; (*i*) R. J. Phipps, L. McMurray, S. Ritter, H. A. Duong, M. J. Gaunt, *J. Am*. *Chem*. *Soc*., 2012, **134**, 10773; (*j*) Harvey, J. S.; Simonovich, S. P.; Jamison, C. R.; MacMillan, D. W. C. *J. Am. Chem. Soc.,* 2011, **133**, 13782; (*k*) H. A. Duong, R. E. Gilligan, M. L. Cooke, R. J. Phipps, M. J. Gaunt, *Angew*. *Chem*. *Int*. *Ed*., 2011, **50**, 463.

13 (*a*) P. Gao, W. Guo, J.-J. Xue, Y. Zhao, Y. Yuan, Y.-Z. Xia, Z.-Z. Shi. *J. Am*. *Chem*. *Soc*., 2015, **137**, 12231; (*b*) X. Yang, H. Wang, X. Zhou, X. Li, *Org. Biomol. Chem*., 2016, **14**, 5233; For Pd-catalyzed direct arylation of sp^3 C-H bonds in *O*-methyl ketoximes, see: (*c*) J. Peng, C. Xi, C. Chao, *Chem*. *Sci*., 2016. **7**. 1383; (*d*) Y. Mu, X. Tan, Y. Zhang, X. Jing, Z. Shi, *Org. Chem. Front.,* 2016, **3**, 380.

14 Y. Yang, X. Qiu, Y. Zhao, Y. Mu, Z. Shi, *J. Am. Chem. Soc.*, 2016, **138**, 495.

15 (*a*) R. J. Phipps, N. P. Grimster, M. J. Gaunt, *J. Am*. *Chem*. *Soc*., 2008, **130**, 8172; (*b*) A. Bigot, A. E. Williamson, M. J. Gaunt, *J. Am*. *Chem*. *Soc*., 2011, **133**, 13778; (*c*) N. Ichiishi, A. J. Canty, B. F. Yates, M. S. Sanford, *Org*. *Lett*., 2013, **15**, 5134.

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