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Remote *para*-C–H Functionalization of Arenes by a D-Shaped Biphenyl Template-Based Assembly

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Supporting Information

ABSTRACT: Site-selective C–H functionalization has emerged as an efficient tool in simplifying the synthesis of complex molecules. Most often, directing group (DG)-assisted metallacycle formation serves as an efficient strategy to ensure promising regioselectivity. A wide variety of *ortho*- and *meta*-C–H functionalizations stand as examples in this regard. Yet despite this significant progress, DG-assisted selective *para*-C–H functionalization in arenes has remained unexplored, mainly because it involves the formation of a geometrically constrained metallacyclic transition state. Here we report an easily recyclable, novel Si-containing biphenyl-based template that directs efficient functionalization of the distal *p*-C–H bond of toluene by forming a D-shaped assembly. This DG allows the required flexibility to support the formation of an oversized pre-transition state. By overcoming electronic and steric bias, *para*-olefination and acetoxylation were successfully performed while undermining *o*- and *m*-C–H activation. The applicability of this D-shaped biphenyl template-based strategy is demonstrated by synthesizing various complex molecules.

Innovations and subsequent improvisations play the major role in the fascinating chemistry of C–H activation. The past three decades have witnessed an unprecedented upsurge in controlling positional selectivity of inert C–H bonds by adopting strategies that deliver easier choices for retrosynthetic disconnections.[1−5] Directing group (DG)-assisted transition-metal-catalyzed reactions have been formulated to become a celebrated class in this regard. This approach provided the required impetus for *ortho*-C–H functionalization reactions in arenes, relieving them of the strict governance of electronic and steric bias (Figure 1A).[6] Template-directed *meta*-C–H activation also adds to the success story, where it solicits a metallacycle larger than a seven-membered ring (Figure 1A).[7] Intuitively, a template-based approach for targeting exclusive *para*-selectivity would entail a significantly larger metallacycle, with a consequent rise in strain energy. In our attempts to investigate the intriguing possibility of DG-facilitated remote *para*-C–H functionalization (Figure 1A), we encountered some conceptual as well as synthetic challenges: (1) forming a large yet less strained macrocylic transition state; (2) fine-tuning the chain length of the template that governs selective *para*-functionalization; and (3) regulating the proximity of the donor heteroatom in the DG towards the target C–H bond. The

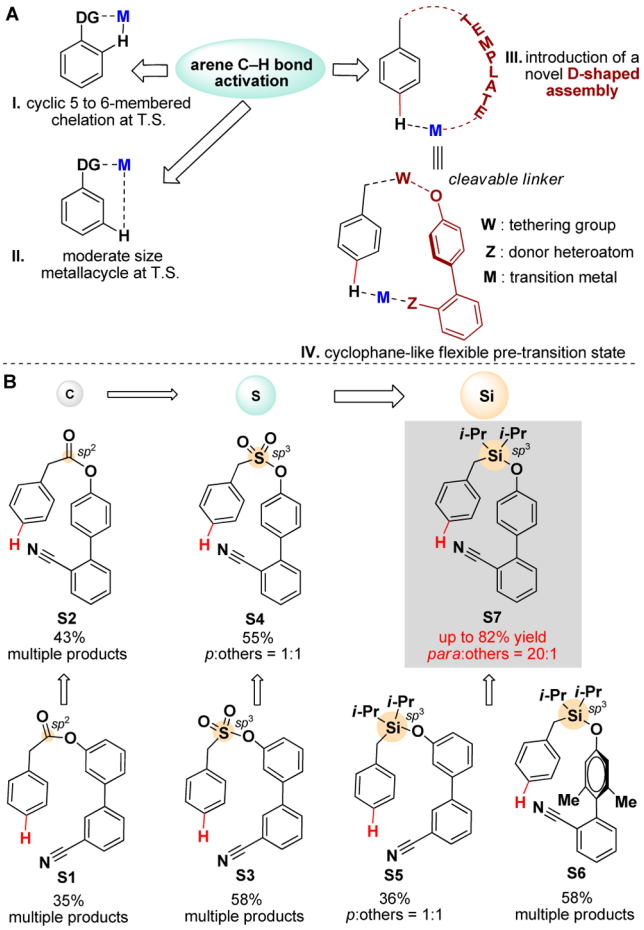

Figure 1. Template-directed *p*-C–H activation. (A) Gradual evolution of template-directed functionalization: (I) directed *o*-C–H activation; (II) directed *m*-C–H activation; (III and IV) distal *p*-C–H activation using a D-shaped assembly; DG = directing group and T. S. = transition state. (B) Screening of directing scaffolds for model olefination reaction. The red bond in each structure highlights the target C–H bond of interest. Ratios of *para*:others were determined on the basis of ^{1}H NMR of the crude reaction mixture.

design of the template was primarily aimed at facilitating delivery of a metal through a conformationally flexible assembly. The increased electrophilicity of a donor-heteroa-

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Scheme 1. Essential Features in Template Morphology

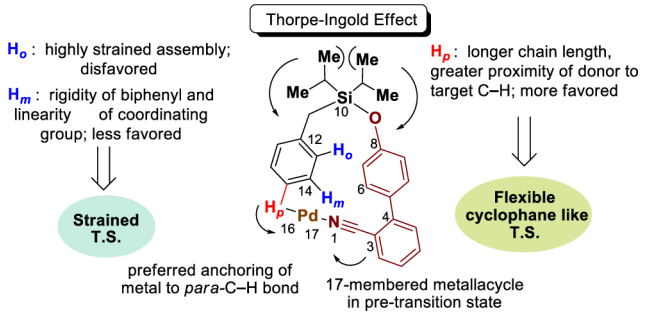
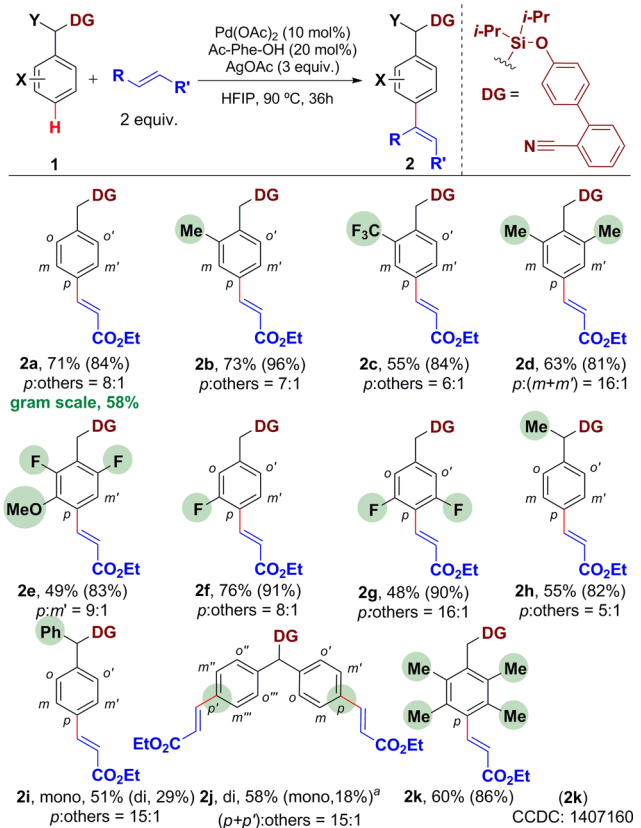
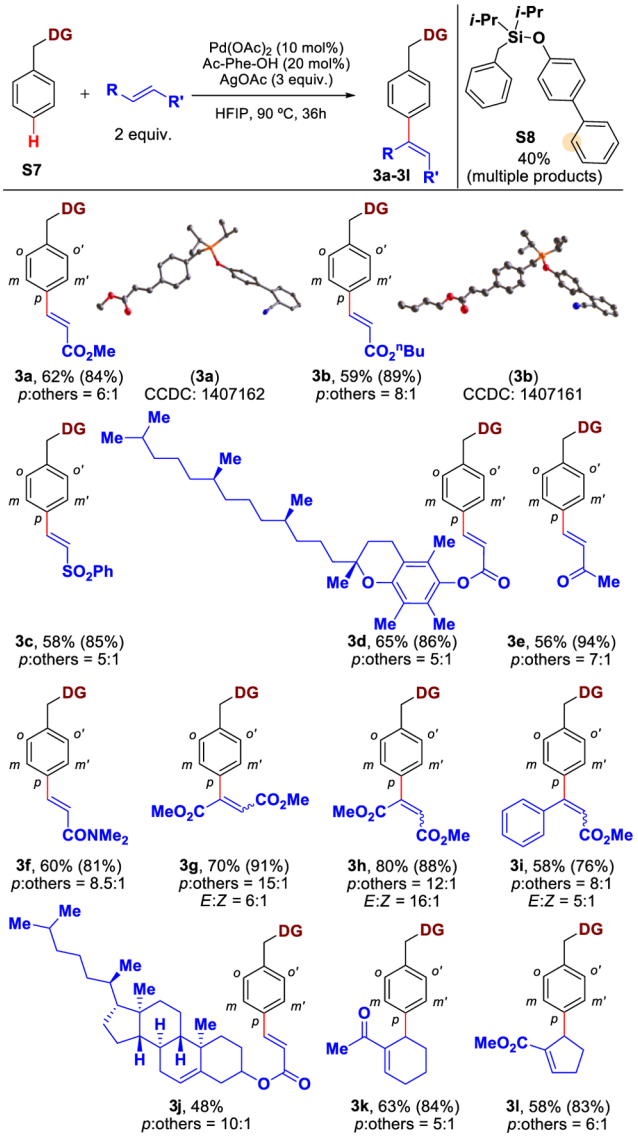


Table 1. Arene Scope for Olefination Reaction[10]



[a]For di-olefination reaction, all reagents were doubled except the arene substrate.

Table 2. Template-Assisted *p*-C–H Olefination of Toluene with Different Alkenes[10]



tom-coordinated metal followed by prompt formation of a C–X bond (e.g., X = C, O, etc.) was presumed to alleviate the cost of an entropically demanding pre-transition state. This would also lower the enthalpic cost of cleaving a thermodynamically quite stable C–H bond. The donor moiety in the DG was imagined to anchor to the metal, thereby activating the *p*-C–H bond through an agostic interaction.[8] Most importantly, the dominance of *para*-functionalization over possible formation of *ortho*- and *meta*-products must be well ensured.

As a foremost step to satisfy all these requirements, a biphenyl group was included as part of the template so that it would contain an easily coordinating heteroatom. Incorporation of biphenyl was thought to be crucial in regulating the chain length of the macrocylic assembly. Moreover, *o*- and/or *m*-C–H activation would then mean a highly strained, kinetically disfavored cyclophane assembly owing to the rigidity of the biphenyl moiety. More than proximity to the target bond, appropriate positioning of the donor moiety coupled with an adequate choice of tethering group seemed essential for achieving the desired selectivity. Of all the possibilities (Figure 1B), a carbonyl tether, **S1**, where the projection of the donor group with respect to the biphenyl axis is 120°, was first employed. However, this provided poor selectivity. Changing the projection angle to 60° led to **S2**, which increased the yield but still failed to improve selectivity. Increasing the bulk and changing the hybridization at the adhering center was presupposed to affect the approach of the donor center near the *p*-C–H bond. Replacing an sp^2 carbonyl by a larger sp^3 sulfonyl

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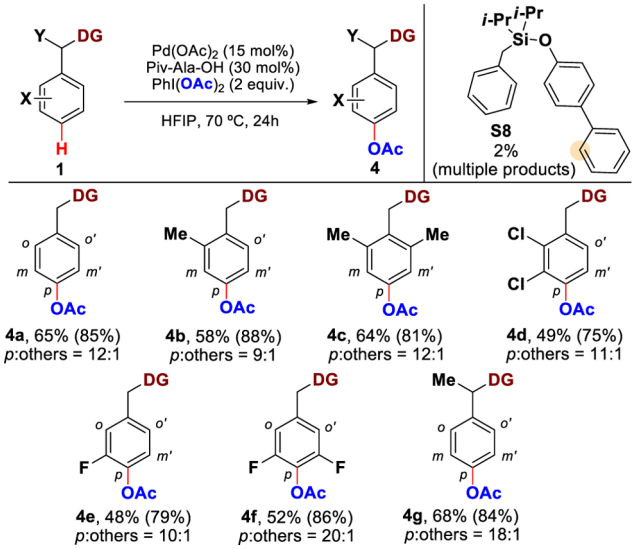
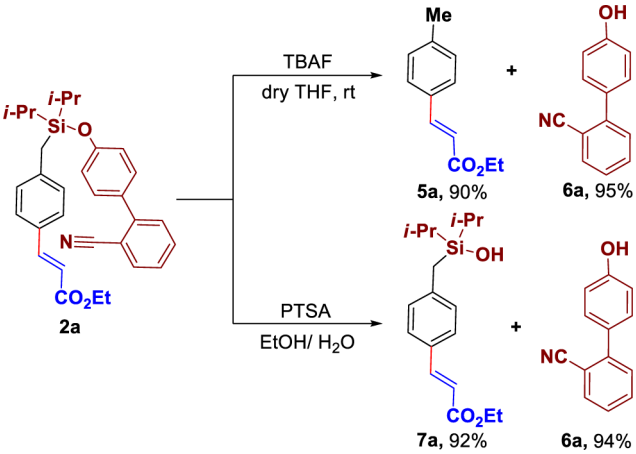
Table 3. *Para*-Acetoxylation of Substituted Toluene Derivatives[10]



Scheme 2. Removal of Directing Group[10]



group (**S4**) yielded a 1:1 ratio for *para*-product relative to other possibilities. A dialkyl-substituted Si atom was then envisaged as a ligating bridge[9] between the substrate and biphenyl (**S5** and **S6**). Because a larger Si atom results in elongated Si−C and Si−O bonds, the distance between the anchoring atom and target C−H bond is bound to be more. Increasing the rotational barrier between the two rings in biphenyl was anticipated to establish intimacy between the donor-atom-containing benzene ring and the appended substrate. Incorporating methyl groups at the 3,5-positions of biphenyl (**S6**) led to diminished selectivity, as the donor-heteroatom-coordinated Pd center would then face increased steric hindrance from *ortho*-methyl groups while coordinating to the chelating ligand. This reinforced the importance of proper placement of the donor moiety in the DG with respect to the Si tether, bringing us to **S7** (Figure 1B) as the final choice.

Installing two sterically incumbent isopropyl moieties at the Si center in **S7** effectively favored the Thorpe−Ingold effect, which might allow closer approach of the coordinating group to the *p*-C−H bond by a domino-like "steric push" (Scheme 1). The desired D-shaped assembly **S7** was thus successfully conceived, achieving improved yield and *para*-selectivity. Other factors that effectively underscore the significance of the template **S7** are its simplicity, ease of preparation, and ability to overcome innate strain in forming the inevitable macrocyclic transition state. With the D-shaped silyl-biphenyl-based assembly **S7**, we performed a Pd-catalyzed olefination reaction using an electronically unbiased substrate such as toluene. The combination of $Pd(OAc)_2$ as catalyst and AgOAc as oxidant in conjunction with *N*-acetyl-L-phenylalanine ligand provided 75% NMR yield (isolated, 71%; *p*:others = 8:1), with a significant *para*-selectivity (gram scale, 58%). The alkanoyl-protected amino acid likely played two major roles. First, dianionic ligands could chelate with the metal to generate an active pre-catalyst. Second, alkanoyl protection facilitated the C−H activation step by acting as an internal base. Additionally, coordinative interaction of the fluorinated alcohols with Pd catalyst was presumed to stabilize the macrocyclic transition state. Control experiments performed with **S8** (see Table 2) revealed a complete loss of selectivity. This aided in justifying the primal role of template morphology and coordination of heteroatom to Pd as essential prerequisites for this chemical transformation (Scheme 1).

With the optimized conditions, we contemplated the scope of substrates that displayed the first template-facilitated *p*-C−H functionalization of electronically unbiased arenes (Table 1). Both electron-donating and -withdrawing groups (**2b−2g**) were well tolerated with distinguished levels of *para*-selectivity. Distinctive *para*-functionalization (mono- and di-) was also possible in the presence of multiple C−H bonds (**2i** and **2j**). However, in such a case, control over the amount of reagents was vital in obtaining the desired ratio for di-olefination compared to mono-olefination.

Successful *para*-olefination with **2k** paved a new way for the synthesis of hexa-substituted arenes. A closer look at the X-ray crystal structure of **2k** (Table 1) further supports our initial hypothesis for the requirement of a D-shaped assembly for the *para*-selective C−H functionalization reaction.

We then explored the scope of the reaction with various olefinic coupling partners (Table 2). Appreciable selectivity for *para*-olefinated products was obtained in the presence of *α,β*-unsaturated esters, sulfone, and amide (**3a−3l**). Tolerance toward bulky olefin partners was exemplified by *para*-olefination with acrylates of vitamin E (**3d**) and cholesterol (**3j**). *Para*-olefinated products were obtained even with five- or six-membered rings containing substituted endocyclic double bonds (**2b**$_1$, **3k**, and **3l**).

The versatility of this functionalization strategy was extended to carbon−heteroatom bond-forming processes by performing *para*-acetoxylation (Table 3) in quantifiable yields. Excellent levels of *para*-selectivity were obtained with various *ortho*- and/or *meta*-substituted toluene derivatives. As expected, the control experiment without the DG (**S8**) failed to deliver the *para*-acetoxylation product.

Cleavage of the template was performed by hydrolysis with TBAF, yielding *para*-functionalized product **5a** (yield 90%) along with recovery of the nitrile-containing biphenyl (Scheme 2). Treatment of **2a** under acid-catalyzed deprotection conditions led to **7a**, along with recovery of the directing moiety **6a** (Scheme 2).[11]

In summary, remote *p*-C−H functionalization of arene was executed using a biphenyl-silyl-tethered D-shaped assembly. The intricate template morphology helped us to sustain a large transition state that favored exquisite site selectivity in performing successful *para*-olefination and acetoxylation.

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■ ASSOCIATED CONTENT

Supporting Information

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Experimental details, characterization data, and spectra (PDF)

X-ray crystallographic data for **2k** (CIF)

X-ray crystallographic data for **3a** (CIF)

X-ray crystallographic data for **3b** (CIF)

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Notes

The authors declare the following competing financial interest(s): Two patent applications are filed based on the work described in this manuscript.

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■ REFERENCES

(1) For selected examples of undirected C−H activation, see: (a) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633. (b) Hartwig, J. F. *Chem. Soc. Rev.* **2011**, *40*, 1992. (c) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (d) Sun, C.-L.; Li, H.; Yu, D.-G.; Yu, M.; Zhou, X.; Lu, X.-Y.; Huang, K.; Zheng, S.-F.; Li, B.-J.; Shi, Z.-J. *Nat. Chem.* **2010**, *2*, 1044. (e) Zhou, L.; Lu, W. *Chem. - Eur. J.* **2014**, *20*, 634.

(2) For selected reviews on *o*-C−H activation, see: (a) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074. (b) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (c) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (d) Satoh, T.; Miura, M. *Synthesis* **2010**, *2010*, 3395. (e) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (f) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068. (g) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011**, *111*, 1780. (h) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2011**, *111*, 1293. (i) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (j) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879. (k) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 10236. (l) Neufeldt, S. R.; Sanford, M. S. *Acc. Chem. Res.* **2012**, *45*, 936. (m) Sigman, M. S.; Werner, E. W. *Acc. Chem. Res.* **2012**, *45*, 874. (n) Ackermann, L. *Acc. Chem. Res.* **2014**, *47*, 281. (o) De Sarkar, S.; Liu, W.; Kozhushkov, S. I.; Ackermann, L. *Adv. Synth. Catal.* **2014**, *356*, 1461. (p) Zhang, F.; Spring, D. R. *Chem. Soc. Rev.* **2014**, *43*, 6906. (q) Topczewski, J. J.; Sanford, M. S. *Chem. Sci.* **2015**, *6*, 70.

(3) For selected examples of *m*-C−H activation, see: (a) Cho, J.-Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E.; Smith, M. R. *Science* **2002**, *295*, 305. (b) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 390. (c) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172. (d) Do, H.-Q.; Khan, R. M. K.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 15185. (e) Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593. (f) Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 5072. (g) Cornella, J.; Righi, M.; Larrosa, I. *Angew. Chem., Int. Ed.* **2011**, *50*, 9429. (h) Ye, M.; Gao, G.-L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 6964. (i) Zhou, L.; Lu, W. *Organometallics* **2012**, *31*, 2124. (j) Wang, Y.-N.; Guo, X.-Q.; Zhu, X.-H.; Zhong, R.; Cai, L.-H.; Hou, X.-F. *Chem. Commun.* **2012**, *48*, 10437. (k) Hofmann, N.; Ackermann, L. *J. Am. Chem. Soc.* **2013**, *135*, 5877. (l) Dai, F.; Gui, Q.; Liu, J.; Yang, Z.; Chen, X.; Guo, R.; Tan, Z. *Chem. Commun.* **2013**, *49*, 4634. (m) Cong, X.; Tang, H.; Wu, C.; Zeng, X. *Organometallics* **2013**, *32*, 6565. (n) Luo, J.; Preciado, S.; Larrosa, I. *J. Am. Chem. Soc.* **2014**, *136*, 4109. (o) Martínez-Martínez, A. J.; Kennedy, A. R.; Mulvey, R. E.; O'Hara, C. T. *Science* **2014**, *346*, 834. (p) Schranck, J.; Tlili, A.; Beller, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 9426. (q) Cheng, C.; Hartwig, J. F. *Science* **2014**, *343*, 853. (r) Wang, X.-C.; Gong, W.; Fang, L.-Z.; Zhu, R.-Y.; Li, S.; Engle, K. M.; Yu, J.-Q. *Nature* **2015**, *519*, 334.

(4) For selected examples of C−H activation using frustrated Lewis pairs, see: (a) Ménard, G.; Stephan, D. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 4409. (b) Ménard, G.; Hatnean, J. A.; Cowley, H. J.; Lough, A. J.; Rawson, J. M.; Stephan, D. W. *J. Am. Chem. Soc.* **2013**, *135*, 6446. (c) Winkelhaus, D.; Stephan, D. W. *Angew. Chem., Int. Ed.* **2014**, *53*, 5414. (d) Holthausen, M. H.; Mahdi, T.; Schlepphorst, C.; Hounjet, L. J.; Weigand, J. J.; Stephan, D. W. *Chem. Commun.* **2014**, *50*, 10038.

(5) For examples of *p*-C−H activation, see: (a) Tsai, C.-C.; Shih, W.-C.; Fang, C.-H.; Li, C.-Y.; Ong, T.-G.; Yap, G. P. A. *J. Am. Chem. Soc.* **2010**, *132*, 11887. (b) Ciana, C.-L.; Phipps, R. J.; Brandt, J. R.; Meyer, F.-M.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 458. (c) Sun, K.; Li, Y.; Xiong, T.; Zhang, J.; Zhang, Q. *J. Am. Chem. Soc.* **2011**, *133*, 1694. (d) Wang, X.; Leow, D.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 13864. (e) Imahori, T.; Tokuda, T.; Taguchi, T.; Takahata, H. *Org. Lett.* **2012**, *14*, 1172. (f) Kamata, K.; Yamaura, T.; Mizuno, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 7275. (g) Wu, Z.; Luo, F.; Chen, S.; Li, Z.; Xiang, H.; Zhou, X. *Chem. Commun.* **2013**, *49*, 7653. (h) Liu, W.; Ackermann, L. *Org. Lett.* **2013**, *15*, 3484. (i) Yu, Z.; Ma, B.; Chen, M.; Wu, H.-H.; Liu, L.; Zhang, J. *J. Am. Chem. Soc.* **2014**, *136*, 6904. (j) Pialat, A.; Berges, J.; Sabourin, A.; Vinck, R.; Liegault, B.; Taillefer, M. *Chem. - Eur. J.* **2015**, *21*, 10014. (k) Li, J.; De Sarkar, S.; Ackermann, L. *Topics in Organometallic Chemistry*; Springer: Berlin, 2015.10.1007/3418_2015_130.

(6) (a) Brasche, G.; García-Fortanet, J.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 2207. (b) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (c) Rakshit, S.; Grohmann, C.; Besset, T.; Glorius, F. *J. Am. Chem. Soc.* **2011**, *133*, 2350. (d) Deb, A.; Bag, S.; Kancherla, R.; Maiti, D. *J. Am. Chem. Soc.* **2014**, *136*, 13602.

(7) For examples of *m*-C−H activation by chelation assistance, see: (a) Leow, D.; Li, G.; Mei, T.-S.; Yu, J.-Q. *Nature* **2012**, *486*, 518. (b) Lee, S.; Lee, H.; Tan, K. L. *J. Am. Chem. Soc.* **2013**, *135*, 18778. (c) Dai, H.-X.; Li, G.; Zhang, X.-G.; Stepan, A. F.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 7567. (d) Tang, R.-Y.; Li, G.; Yu, J.-Q. *Nature* **2014**, *507*, 215. (e) Yang, Y.-F.; Cheng, G.-J.; Liu, P.; Leow, D.; Sun, T.-Y.; Chen, P.; Zhang, X.; Yu, J.-Q.; Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **2014**, *136*, 344. (f) Yang, G.; Lindovska, P.; Zhu, D.; Kim, J.; Wang, P.; Tang, R.-Y.; Movassaghi, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 10807. (g) Bera, M.; Modak, A.; Patra, T.; Maji, A.; Maiti, D. *Org. Lett.* **2014**, *16*, 5760. (h) Deng, Y.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2015**, *54*, 888. (i) Bera, M.; Maji, A.; Sahoo, S. K.; Maiti, D. *Angew. Chem., Int. Ed.* **2015**, *54*, 8515. (j) Li, S.; Ji, H.; Cai, L.; Li, G. *Chem. Sci.* **2015**, DOI: 10.1039/C5SC01737H.

(8) Brookhart, M.; Green, M. L. H.; Parkin, G. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 6908.

(9) Sarkar, D.; Melkonyan, F. S.; Gulevich, A. V.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2013**, *52*, 10800.

(10) See the Supporting Information for a detailed description.

(11) (a) Vorbruggen, H.; Krolikiewicz, K. *Tetrahedron Lett.* **1983**, *24*, 889. (b) Boebel, T. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 7534. (c) Wang, C.; Ge, H. *Chem. - Eur. J.* **2011**, *17*, 14371. (d) Huang, C.; Ghavtadze, N.; Godoi, B.; Gevorgyan, V. *Chem. - Eur. J.* **2012**, *18*, 9789. (e) Das, M.; O'Shea, D. F. *Tetrahedron* **2013**, *69*, 6448.

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