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Benzaldehyde- and Nickel-Catalyzed Photoredox C(sp^3)−H Alkylation/Arylation with Amides and Thioethers

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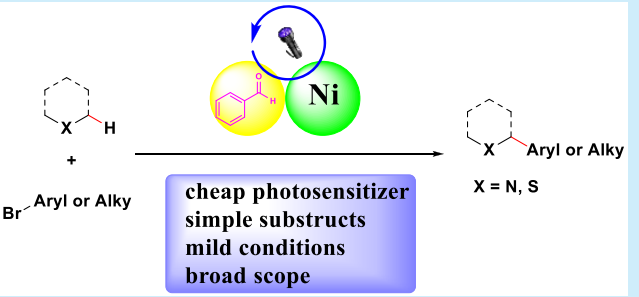
Supporting Information

ABSTRACT: Herein a synergistic combination of a nickel catalyst and benzaldehyde for the utilization of amides and thioethers in C(sp^3)−H alkylation and arylation reactions employing simple aryl or alkyl halides is reported. This method provides a simple and cheap strategy for the direct functionalization of amides and thioethers. Readily available starting materials, mild reaction conditions, a good functional-group tolerance, and a broad substrate scope make this methodology attractive and practical for pharmaceutical and synthetic chemistry.



The direct functionalization of C−H bonds is known as a reliable access to complex structures. This is based on the distinct advantages of high step- and atom-economy as well as the use of readily available substrates. Although the selective functionalization of C−H bonds has been extensively investigated during the past decades, in most of the cases, preactivation of substrates, directing groups, stoichiometric additives, or oxidants is needed.[1] The direct C(sp^3)−H arylation/alkylation is still a challenging field.

Fully or partially saturated nitrogen heterocycles are key motifs of numerous pharmaceutical structures and natural products, and the five-membered pyrrolidine ring is one of the most ubiquitous and important representatives.[2] Additionally, cyclic amines such as proline are widely applied in asymmetric synthesis.[3] There is no doubt that efficient methods for the functionalization of these systems are of importance. As is shown in Figure 1, there are different approaches to obtain α-functionalized nitrogen heterocycle derivatives. Based on previous research, the most frequently reported method for this kind of transformation involves the formation of a dipole-stabilized carbanion, followed by an electrophilic substitution or transmetalation.[4] Different electrophiles such as organotin compounds, silyl reagents, phenyl isocyanate, aldehydes, CO_2,[5] and others have been used. α-Lithiation can be followed by transmetalation with $ZnCl_2$ and, finally, by palladium-catalyzed Negishi coupling with an aryl halide to yield *N*-protected α-aryl pyrrolidine derivatives.[6] This strategy usually requires multistep sequences, and an excess of *s*-BuLi is needed for a successful conversion. Other new methods convert given amines into an electrophilic species that can be coupled with a nucleophilic partner such as an alkyne, indole, or ketone.[7] The key intermediate for this method is an iminium ion. The most frequently studied processes involved the use of copper catalysts in combination with an external chemical oxidant to form the imimium ion. Much less prevalent, recent research is based only on chemical oxidants;[8] others apply electrochemistry[9] or photochemistry[10] to generate iminium ions. Figure 1c shows a new method for direct functionalization of C(sp^3)−H bonds adjacent to nitrogen in heterocycles. An α-amino radical intermediate was generated through standard radical-forming conditions[11] or a photochemical radical-generating procedure.[12] Radical-based methods are powerful tools for the direct C(sp^3)−H activation, but still not often applied in the functionalization of nitrogen heterocycles.

Recently, organic free-radical chemistry and visible light-mediated photoredox-catalyzed reactions are regarded as valuable tools in organic synthesis, especially for late-stage

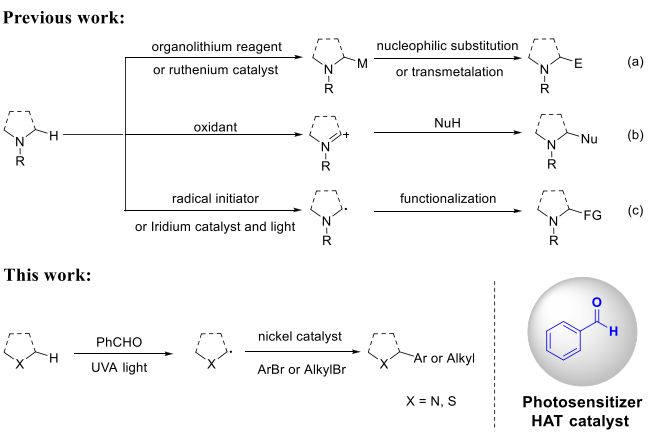


Figure 1. Methods for amine α-C−H bond functionalization and our new concept.

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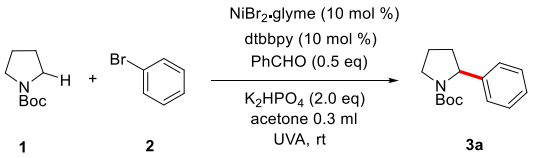
functionalization of pharmaceutical compounds.[13] Numerous outstanding strategies for functionalizing C(sp^3)−H bonds have been reported.[14] However, the direct alkylation of C(sp^3)−H bonds by normal alkyl halides is rare. In 2017, Macmillan's group first reported the C(sp^3)−H alkylation using the strategy of polarity-matching with the iridium complex Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6, a nickel catalyst, and a hydrogen atom transfer catalyst through single-electron transfer (SET) and hydrogen atom transfer (HAT) processes.[12d] There was no further study on sp^3−sp^3 coupling, until recently, when our group[15] reported a new strategy by merging cheap benzaldehyde as a photosensitizer with nickel catalysis for photoredox C(sp^3)−H arylation/alkylation mediated by UVA light. At the same time Martin's group[16] and Rueping's group[17] also reported photoredox C(sp^3)−H arylation/alkylation and C(sp^3)−H arylation of toluene and derivatives by combining benzophenone and nickel catalysis induced by CFL light.

Though recent progress allows easier access to α-functionalization of amines, several conditions must be satisfied at the same time for a successful transformation. A multistep synthesis, stoichiometric oxidants, and directing groups are usually not desired; photoredox transformation seems to be better, but the iridium complex is much too expensive. Meanwhile, the conditions usually change strongly from case to case, which makes this method much more difficult to use widely. Inspired by previous research and as continuing work on benzaldehyde-mediated C(sp^3)−H direct functionalization, the hypothesis is that this new strategy can be used for α-C−H functionalization of amides and thioethers.

The coupling of *N*-Boc pyrrolidine and bromobenzene was chosen as a model reaction for our investigation. For the initial experiments, we utilized $NiBr_2$·glyme and 4,4′-di-*tert*-butyl-2,2′-bipyridyl (dtbbpy) as the nickel catalyst, benzaldehyde as the photosensitizer, and K_2HPO_4 as the base in acetone under irradiation with UVA light for 24 h (Table 1), and the desired product **3a** was formed in 50% yield (Table 1, entry 1). Further experiments showed that the yield of **3a** was strongly influenced by the initial concentration (Table 1, entries 1−4). The optimum concentration included the use 0.3 mL of solvent; at higher concentration, the nickel catalyst did not dissolve completely (Table 1, entry 2). Previous reports indicate that an excess of pyrrolidine is needed for this type of transformation, and thus we also varied the amount of pyrrolidine (Table 1, entries 1, 5, and 6). The yield gradually increased when increasing the amount of **1**. For reasons of economy and convenient isolation, we used 5 equiv of pyrrolidine, and then the yield could be increased to 88% by prolonging the irradiation time to 60 h (Table 1, entry 14). Next, we turned our attention to different nickel salts (Table 1, entries 7−9). Other Ni(II) salts did not work well for this reaction; as expected, Ni(COD)$_2$ only gave a low yield. The control experiments shown in entries 10−13 prove that all of the parameters were significant for the success of this transformation.

We then explored the scope of this reaction. As shown in Scheme 1, a wide variety of aryl bromides tolerating either electron-donating or electron-withdrawing substituents underwent the desired C(sp^3)−H arylation products. 4-Bromoanisole worked well (**3b**, 78% yield), and an *ortho*-methyl substituent showed similar reactivity (**3c**, 74% yield). Diverse electron-withdrawing groups in the para position, such as trifluoromethyl (**3d**), nitriles (**3e**), esters (**3f**), fluoride (**3g**),

Table 1. Reaction Optimization[a]



entry	deviation from standard conditions	Yield **3a** [%][b]
1	None	50
2	0.2 mL of acetone	36
3	0.5 mL of acetone	12
4	1.0 mL of acetone	11
5	2 equiv of **1**	30
6	8 equiv of **1**	54
7	Ni(acac)$_2$ instead of $NiBr_2$·glyme	trace
8	$NiCl_2$·glyme instead of $NiBr_2$·glyme	trace
9	Ni(COD)$_2$ instead of $NiBr_2$·glyme	17
10	Without UVA	n.d.
11	Without PhCHO	n.d.
12	Without K_2HPO_4	n.d.
13	Without dtbbpy	n.d.
14	Irradiated for 60 h	88(80)[c]

[a]Standard reaction conditions: bromobenzene (0.2 mmol, 1.0 equiv), *N*-Boc pyrrolidine (1.0 mmol, 5.0 equiv), benzaldehyde (0.1 mmol, 0.5 equiv), $NiBr_2$·glyme (0.02 mmol, 10 mol %), dtbbpy (0.02 mmol, 10 mol %), K_2HPO_4 (0.4 mmol, 2.0 equiv), acetone (0.3 mL), 24 h. [b]Yield determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as the internal standard. [c]Isolated yield.

and ketones (**3h**), were perfectly tolerated and gave a good yield (50−85%). A pyridine ring (**3i**) and a thiophene ring (**3j**) also worked. Next, we checked *N*-substituted pyrrolidines (**3k−o**), *tert*-butoxycarbonyl (Boc), benzyloxycarbonyl (Cbz), acetyl (Ac), pivalate (Piv), and phenylacetyl groups; all were tolerated, but for acetyl and pivalate substituted pyrrolidine the yields dropped to 26% (**3m**) and 23% (**3n**). Ureas, dimethylaniline, amide, and lactams (**3p−r**) could be converted, too. *N*-Methylpyrrolidinone (**3s**) underwent α-arylation in good yield and regioselectivity for the endocyclic secondary position.

C(sp^3)−C(sp^3) coupling is an important but difficult area. On one hand, this can be an atom-economic transformation with high importance for the late-stage modification of pharmaceuticals and natural products. On the other hand, controlling the stereochemistry is a big challenge for sp^3-hybridized carbon atoms, and the natural tendency of transient alkyl metal species for parasitic homodimerization or β-hydride elimination[16] is to restrict the development of this kind of reaction. With the results of Scheme 1 in hand, we wondered whether our photochemical strategy could be extended to C(sp^3)−H alkylation of pyrrolidine. As shown in Scheme 2, with respect to aliphatic bromides which contain various functional groups all were compatible with moderate to good yields. We initially used the same optimized conditions of the arylation reaction, but the yield of **4a** was only 15%. Another round of condition screening revealed that changing the solvent to acetonitrile could greatly improve the yield of **4a** to 62%. To our delight, our protocol could be applied to the challenging acyclic (**4b**) and cyclic (**4c**) secondary alkyl bromides. Other alkyl fragments carrying commonly used functional groups (**4d−f**) such as cyclohexylmethyl, esters, and trifluoromethyl were all used in good yields (40%−76%).

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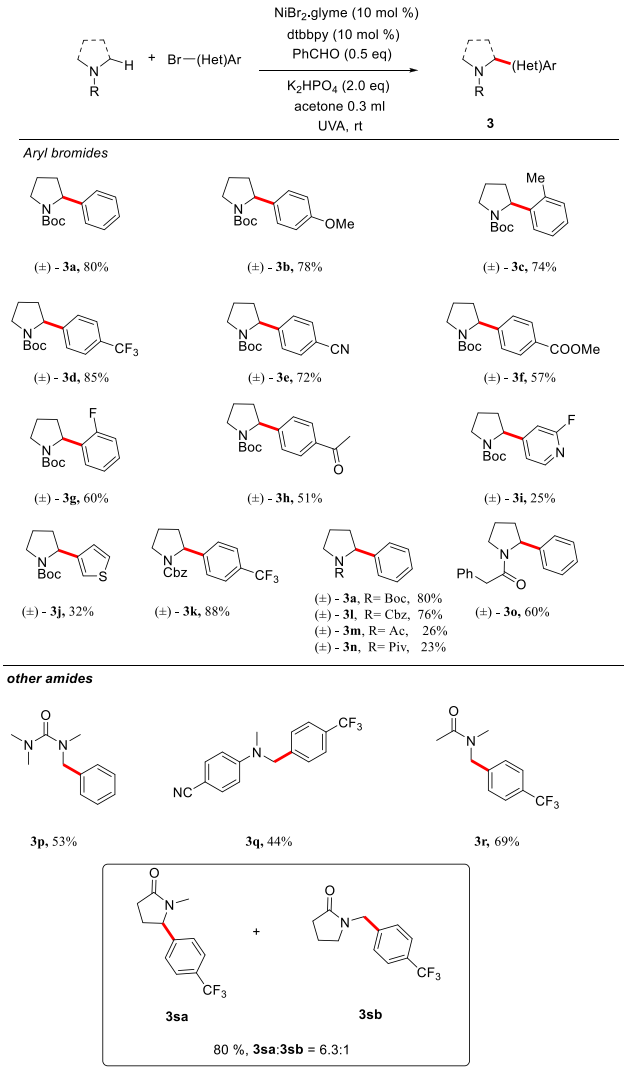
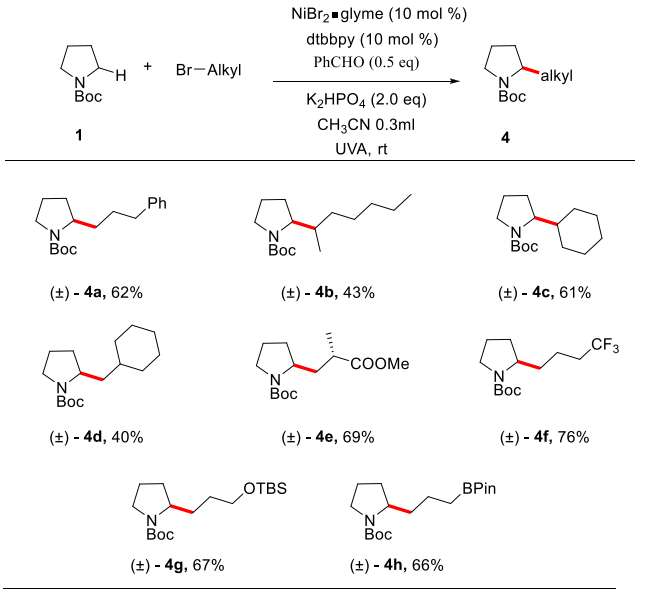
Scheme 1. Scope of the sp^3-C−H Arylation of Amides[a]



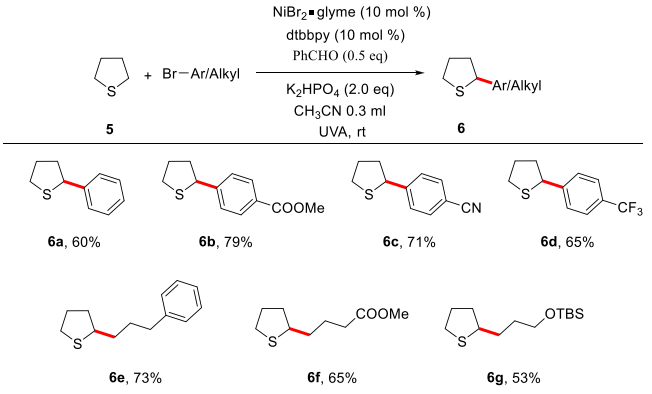
[a]Reactions were performed on 0.2 mmol scale by following the general procedure. Yields are isolated yields.

Scheme 2. Scope of the sp^3-C−H Alkylation of Amides[a]



[a]Reactions were performed with 0.2 mmol scale by following the general procedure. Yields are isolated yields.

Scheme 3. Attempts for sp^3-C−H Arylation/Alkylation of Thio-Containing Substrate[a]



[a]Reaction were performed with 0.2 mmol scale by following the general procedure. Yields were isolated yields.

Beyond that, organosilyl (**4g**) and boronate (**4h**) groups were tolerated.

Based on previous research, our system could be used for C(sp^3)−H bond functionalization in ethers, too. We postulated that other heteroatoms that can imbue a hydridic nature to their neighboring α-C−H bonds might be susceptible to this approach. Tetrahydrothiophene was tested, and surprisingly, the corresponding arylation and alkylation product were purified in high yields as shown in Scheme 3. For an arylation product, esters (**6b**), nitriles (**6c**), and trifluoromethyl (**6d**) were tolerated and gave good yields (65−79%). Our methodology could also be used for sp^3-C−H alkylation of tetrahydrothiophene. Compounds **6e−g** were synthesized with moderate to good yield (53−73%).

In conclusion, we have developed a facile and efficient photoredox C(sp^3)−H alkylation and arylation methodology catalyzed by the merging of a benzaldehyde and nickel catalyst and showed the successful application of it on ethers and amides. The combination of inexpensive and common organic-photosensitizer with a cheap transition metal would be a promising strategy in the near future, as it offers access to challenging C(sp^3)−C(sp^2) and C(sp^3)−C(sp^3) bond formation in organic synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02226.

Experimental procedures and compound characterization (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731−1770. (b) Chen, X.; Engle, K. E.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094−5115. (c) Daugulis, O.; Do, J.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074−1086. (d) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890−931. (e) Ackermann, L. *Chem. Commun.* **2010**, *46*, 4866−4877. (f) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147−1169. (g) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068−5083. (h) Colby, D. A.; Tsai, A. S.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2012**, *45*, 814−825.

(2) (a) Mitchell, E. A.; Peschiulli, A.; Lefevre, N.; Meerpoel, L.; Maes, B. U. *Chem. - Eur. J.* **2012**, *18*, 10092−10142. (b) Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 10257−10274. (c) Campos, K. R. *Chem. Soc. Rev.* **2007**, *36*, 1069−1084. (d) Baudoin, O. *Chem. Soc. Rev.* **2011**, *40*, 4902−4911. (e) Qin, Y.; Lv, J.; Luo, S. *Tetrahedron Lett.* **2014**, *55*, 551−558.

(3) (a) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471−5569. (b) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827−833. (c) List, B.; Pojarliev, P.; Martin, H. J. Efficient. *Org. Lett.* **2001**, *3*, 2423−2425. (d) List, B.; Pojarliev, P.; Castello, C. *Org. Lett.* **2001**, *3*, 573−575. (e) List, B.; Notz, W. *J. Am. Chem. Soc.* **2000**, *122*, 7386−7387.

(4) (a) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552−560. (b) Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2282−2316. (c) Pastine, S. J.; Gribkov, D. V.; Sames, D. *J. Am. Chem. Soc.* **2006**, *128*, 14220−14221.

(5) (a) Ashweek, N. J.; Brandt, P.; Coldham, I.; Dufour, S.; Gawley, R. E.; Hæffner, F.; Klein, R.; Sanchez-Jimenez, G. *J. Am. Chem. Soc.* **2005**, *127*, 449−457. (b) Barker, G.; O'Brien, P. O.; Campos, K. R. *Org. Lett.* **2010**, *12*, 4176−4179. (c) Stead, D.; Carbone, G.; O'Brien, P. O.; Campos, K. R.; Coldham, I.; Sanderson, A. *J. Am. Chem. Soc.* **2010**, *132*, 7260−7261. (d) Mita, T.; Sato, Y. *Chem. - Asian J.* **2019**, *14*, 2038.

(6) (a) Campos, K. R.; Klapars, A.; Waldman, J. H.; Dormer, P. G.; Chen, C. Y. *J. Am. Chem. Soc.* **2006**, *128*, 3538−3539. (b) Barker, G.; McGrath, J. L.; Klapars, A.; Stead, D.; Zhou, G.; Campos, K. R.; O'Brien, P. *J. Org. Chem.* **2011**, *76*, 5936−5953.

(7) (a) Li, C.; Li, C.-J. *Org. Lett.* **2004**, *6*, 4997−4999. (b) Li, Z.; Bohle, D. S.; Li, C. J. *Proc. Natl. Acad. Sci. U. S. A.* **2006**, *103*, 8928−8933. (c) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2004**, *126*, 11810−11811. (d) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 3672−3673. (e) Li, Z.; Li, C.-J. *Eur. J. Org. Chem.* **2005**, *2005*, 3173−3176.

(8) (a) Allen, J. M.; Lambert, T. H. *J. Am. Chem. Soc.* **2011**, *133*, 1260−1262. (b) Shu, X. Z.; Xia, X. F.; Yang, Y. F.; Ji, K. G.; Liu, X. Y.; Liang, Y. M. *J. Org. Chem.* **2009**, *74*, 7464−7469.

(9) (a) Maruyama, T.; Mizuno, Y.; Shimizu, I.; Suga, S.; Yoshida, J. I. *J. Am. Chem. Soc.* **2007**, *129*, 1902−1903. (b) Yoshida, J. I.; Kataoka, K.; Horcajada, R.; Nagaki, A. *Chem. Rev.* **2008**, *108*, 2265−2299. (c) Yoshida, J. I.; Suga, S. *Chem. - Eur. J.* **2002**, *8*, 2650−2658.

(10) (a) Condie, A. G.; González-Gómez, J. C.; Stephenson, C. R. *J. Am. Chem. Soc.* **2010**, *132*, 1464−1465. (b) Hari, D. P.; König, B. *Org. Lett.* **2011**, *13*, 3852−3855. (c) Liu, Q.; Li, Y. N.; Zhang, H. H.; Chen, B.; Tung, C. H.; Wu, L. Z. *Chem. - Eur. J.* **2012**, *18*, 620−627. (d) Pan, Y.; Kee, C. W.; Chen, L.; Tan, C. H. *Green Chem.* **2011**, *13*, 2682−2685. (e) Rueping, M.; Vila, C.; Koenigs, R. M.; Poscharny, K.; Fabry, D. C. *Chem. Commun.* **2011**, *47*, 2360−2362.

(11) Yoshikai, N.; Mieczkowski, A.; Matsumoto, A.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2010**, *132*, 5568−5569.

(12) (a) Kamijo, S.; Hoshikawa, T.; Inoue, M. *Org. Lett.* **2011**, *13*, 5928−5931. (b) McNally, A.; Prier, C. K.; MacMillan, D. W. *Science* **2011**, *334*, 1114−1117. (c) Shaw, M. H.; Shurtleff, V. W.; Terrett, J. A.; Cuthbertson, J. D.; MacMillan, D. W. *Science* **2016**, *352*, 1304−1308. (d) Le, C.; Liang, Y.; Evans, R. W.; Li, X.; MacMillan, D. W. *Nature* **2017**, *547*, 79−83.

(13) (a) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322−5363. (b) Shaw, M. H.; Twilton, J.; MacMillan, D. W. C. *J. Org. Chem.* **2016**, *81*, 6898−6926. (c) Kärkäs, M. D.; Porco, J. A.; Stephenson, C. R. J. *Chem. Rev.* **2016**, *116*, 9683−9747. (d) DiRocco, D. A.; Dykstra, K.; Krska, S.; Vachal, P.; Conway, D. V.; Tudge, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 4802−4806. (e) Zuo, Z. W.; Ahneman, D. T.; Chu, L. L.; Terrett, J. A.; Doyle, A. G.; MacMillan, D. W. C. *Science* **2014**, *345*, 437−440. (f) Xie, J.; Shi, S.; Zhang, T.; Mehrkens, N.; Rudolph, M.; Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2015**, *54*, 6046−6050. (g) Xie, J.; Zhang, T.; Chen, F.; Mehrkens, N.; Rominger, F.; Rudolph, M.; Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2016**, *55*, 2934−2938. (h) Xie, J.; Yu, J.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2016**, *55*, 9416−9421. (i) Xie, J.; Jin, H.; Hashmi, A. S. K. *Chem. Soc. Rev.* **2017**, *46*, 5193−5203.

(14) (a) Sun, Z.; Kumagai, N.; Shibasaki, M. *Org. Lett.* **2017**, *19*, 3727−3730. (b) Jin, J.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2015**, *54*, 1565−1569. (c) Fan, X. Z.; Rong, J. W.; Wu, H. L.; Zhou, Q.; Deng, H. P.; Tan, J. D.; Xue, C. W.; Wu, L. Z.; Tao, H. R.; Wu, J. *Angew. Chem., Int. Ed.* **2018**, *57*, 8514−8518. (d) Heitz, D. R.; Tellis, J. C.; Molander, G. A. *J. Am. Chem. Soc.* **2016**, *138*, 12715−12718. (e) Shields, B. J.; Doyle, A. G. *J. Am. Chem. Soc.* **2016**, *138*, 12719−12722. (f) Deng, H. P.; Fan, X. Z.; Chen, Z. H.; Xu, Q. H.; Wu, J. *J. Am. Chem. Soc.* **2017**, *139*, 13579−13584. (g) Nielsen, M. K.; Shields, B. J.; Liu, J.; Williams, M. J.; Zacuto, M. J.; Doyle, A. G. *Angew. Chem., Int. Ed.* **2017**, *56*, 7191−7194.

(15) Zhang, L.; Si, X.; Yang, Y.; Zimmer, M.; Witzel, S.; Sekine, K.; Rudolph, M.; Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2019**, *58*, 1823−1827.

(16) Shen, Y.; Gu, Y.; Martin, R. *J. Am. Chem. Soc.* **2018**, *140*, 12200−12209.

(17) Dewanji, A.; Krach, P. E.; Rueping, M. *Angew. Chem., Int. Ed.* **2019**, *58*, 3566−3570.

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