JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

pubs.acs.org/JACS

Direct Aldehyde C–H Arylation and Alkylation via the Combination of Nickel, Hydrogen Atom Transfer, and Photoredox Catalysis

Xiaheng Zhang and David W. C. MacMillan*

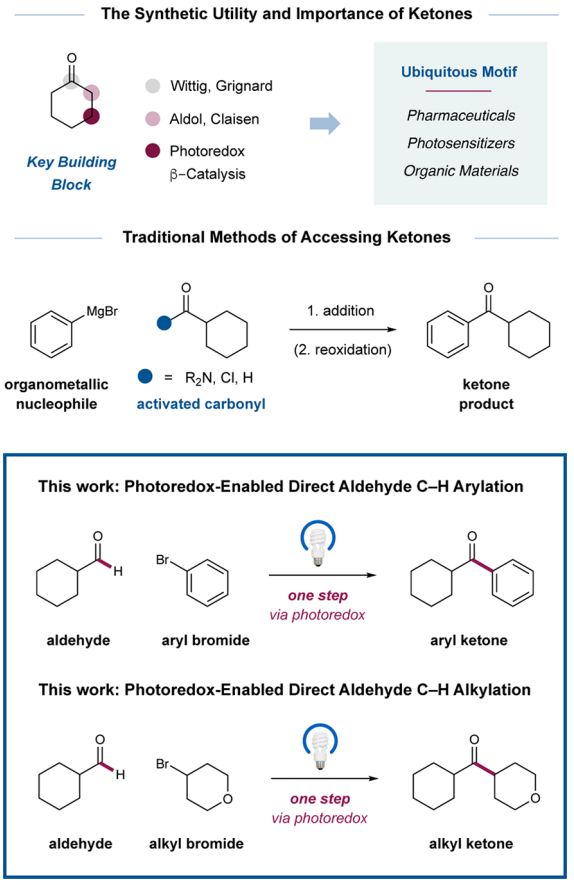
Merck Center for Catalysis at Princeton University, Princeton, New Jersey 08544, United States

Supporting Information

ABSTRACT: A mechanism that enables direct aldehyde C–H functionalization has been achieved via the synergistic merger of photoredox, nickel, and hydrogen atom transfer catalysis. This mild, operationally simple protocol transforms a wide variety of commercially available aldehydes, along with aryl or alkyl bromides, into the corresponding ketones in excellent yield. This C–H abstraction coupling technology has been successfully applied to the expedient synthesis of the medicinal agent haloperidol.

Ketones are important and ubiquitous structural motifs found in natural products, pharmaceuticals, photosensitizers, flavors, fragrances, and organic materials.[1] Moreover, within the field of synthetic organic chemistry, they represent a versatile building block that can be utilized in a diverse array of powerful bond-forming reactions. Conventional methods for the synthesis of ketones include (i) the addition of organometallic species to carbonyl moieties that include amides, anhydrides, and acid chlorides, (ii) aromatic substitution protocols such as Friedel–Crafts acylations,[2] and (iii) transition metal-catalyzed couplings of acid chlorides with aryl and alkyl stannanes and boronic esters.[3,4] Recently, an alternative yet equally attractive approach to ketone formation has emerged that involves metal-catalyzed formyl C–H functionalization, wherein aryl iodides and aldehydes were successfully combined as coupling partners.[5] While these transformations require the use of stoichiometric oxidants, reductants, or directing groups, it is important to recognize that these seminal studies were the first to employ widely available aldehydes (enolizable and non-enolizable) in a C–H arylation cross-coupling mechanism. Recently, we questioned if this overall strategy might be accomplished in a general sense using widely available aryl bromides (and for the first time alkyl halides) via the combination of three interconnected catalytic cycles, namely photoredox, nickel, and hydrogen atom transfer (HAT) catalysis. Given the intrinsic utility of ketones along with the widespread availability of both coupling partners, we envisioned that this new C–H abstraction–arylation/alkylation redox mechanism would be of conceptual and practical interest to chemists in both academic and industrial settings.

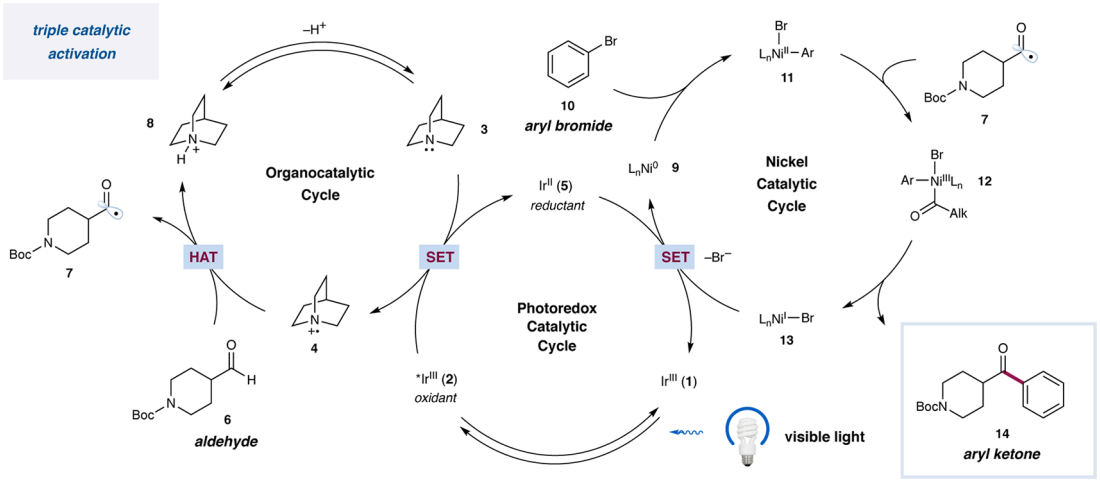
The merger of photoredox and transition metal catalysis (now termed metallaphotoredox) has enabled the invention of a large and varied range of cross-coupling reactions,[6] many of which are now being adopted by the pharmaceutical industry.[7] In this context, our laboratory has previously demonstrated a direct sp^3 C–H bond functionalization method wherein the synergistic combination of photoredox, nickel, and hydrogen atom transfer catalysis in a triple catalytic activation mechanism allows amines and ethers to undergo direct α-C–H arylation and alkylation.[8] As a critical design element, the exploitation of a polarity-matched hydrogen abstraction step using an electrophilic quinuclidinium radical cation enables a high degree of kinetic selectivity, in that bond dissociation enthalpy (BDE) considerations are less important than C–H bond polarity.[9] As a result, electron-rich sp^3 C–H bonds undergo selective and efficient H-abstraction/nickel-catalyzed arylation in the presence of weak, acidic or weak, neutral C–H systems found in methyls, methylenes, and methines. With this selectivity paradigm in mind, we recently questioned whether aldehydic sp^2 H–C(O) bonds might be



Received: July 7, 2017
Published: August 6, 2017

DOI: 10.1021/jacs.7b07078
J. Am. Chem. Soc. XXXX, XXX, XXX–XXX

Scheme 1. Proposed Mechanism for Aldehyde C−H Arylation via a Triple Catalysis Mechanism

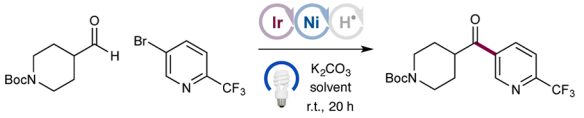


activated toward arylation and alkylation using this strategy, thereby providing a new and generic pathway to ketone construction. Herein, we describe the successful implementation of these ideals and present a broadly applicable protocol for metallaphotoredox-mediated aldehyde C−H arylation, vinylation, or alkylation.

The mechanistic details of our proposed transformation are outlined in Scheme 1. Photoexcitation with visible light of photocatalyst Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (**1**) is known to produce the strongly oxidizing complex *Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)$^+$ (**2**) ($E_{1/2}^{red}$ [*Ir^{III}/Ir^{II}] = +1.21 V vs the saturated calomel electrode (SCE) in CH$_3$CN).[10] The *Ir(III) excited state **2** can effect the oxidation of quinuclidine (**3**) ($E_{1/2}^{ox}$ = +1.1 V vs SCE in CH$_3$CN)[11] to form cationic radical **4** and the reduced Ir(II) complex **5**. At this stage, we proposed that the quinuclidinium radical cation (**4**) should engage in a HAT event with any given aldehyde (*N*-Boc-4-piperidinecarboxaldehyde (**6**) is shown) to generate the corresponding acyl radical **7**.[12] With respect to regiocontrol, we hypothesized that the hydrogen abstraction event should be selective for the formyl C−H bond given that it is both hydridic and relatively weak in comparison to most other C−H moieties. For example, the difference in the bond dissociation enthalpies of aldehyde C−H bonds vs α-amino C−H bonds (both of which exhibit hydridic bond polarization) might be sufficient to ensure exclusive formation of the acyl radical species **7**. At this stage, concurrent oxidative addition of aryl bromide **10** to L$_n$Ni^0 species **9** should deliver the aryl−Ni^{II} species **11**, which we hoped would be rapidly intercepted by the radical **7** to form the acyl−Ni^{III} complex **12**.[13] Thereafter, reductive elimination would afford the desired ketone product **14** and Ni^I species **13**. As a critical step, both the nickel and photoredox catalytic cycles would simultaneously turn over via single electron transfer from the reduced Ir^{II} species **5** ($E_{1/2}^{red}$ [Ir^{III}/Ir^{II}] = −1.37 V vs SCE in CH$_3$CN)[10] to the Ni^I complex **13** ($E_{1/2}^{red}$[Ni^{II}/Ni^0] = −1.2 V vs SCE in DMF).[14] Finally, the quinuclidine catalyst would be regenerated via deprotonation of the quinuclidinium ion **8** with inorganic base.

Our investigation into this new HAT-metallaphotoredox-mediated aldehyde C−H arylation began with exposure of *N*-Boc-4-piperidinecarboxaldehyde and 5-bromo-2-(trifluoromethyl)pyridine to visible light in the presence of Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (**1**), NiBr$_2$·dtbbpy, quinuclidine, and K$_2$CO$_3$. Given the requirement of high dielectric solvents in our previous C−H abstraction/arylation studies, we anticipated that the desired transformation would be possible using DMSO or CH$_3$CN; however, the efficiency of ketone product formation was poor (Table 1, entries 1−2, 2−8% yield). To our surprise, we

Table 1. Optimization of the Aldehyde C−H Arylation[a]



entry	conditions	solvent	yield[b]
1	as shown	DMSO	2%
2	as shown	CH$_3$CN	8%
3	as shown	dioxane	92% (87%)
4	2 mol % Ni catalyst	dioxane	80%
5	no photocatalyst	dioxane	0%
6	no Ni catalyst	dioxane	0%
7	no light	dioxane	0%

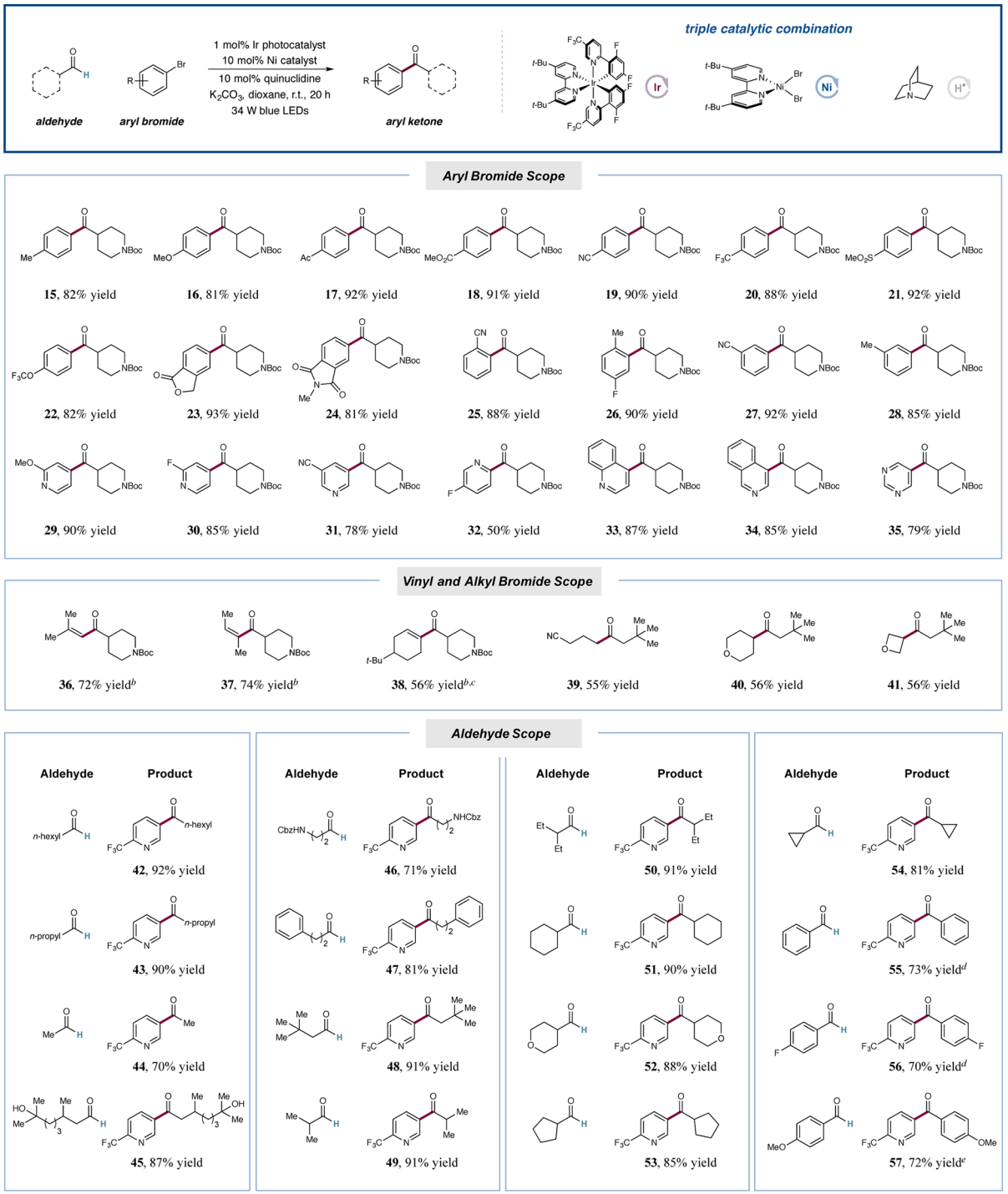
[a]Photocat **1** (1 mol %), NiBr$_2$·dtbbpy (10 mol %), quinuclidine (10 mol %), aryl halide (1.0 equiv), aldehyde (2.0 equiv), and K$_2$CO$_3$ (1.5 equiv). [b]Yield by ^{1}H NMR analysis. Isolated yields in parentheses.

observed that a competing α-amino C−H arylation mechanism was operating in both media. Remarkably, by switching to 1,4-dioxane, we observed exclusive formation of the desired ketone product (entry 3, 87% isolated yield) without any observable α-amino C−H arylation. We surmised that solvent dielectric constant might play an important role in stabilizing the ionic nature of the quinuclidinium radical cation species and likely impacts the relative roles of BDEs vs degree of bond polarization. It is worth noting that, under the optimized conditions, the nickel catalyst loading could be reduced without an impact on the efficiency of this reaction (entry 4, 80% yield). Control experiments (entries 5−7) revealed that the photocatalyst, nickel catalyst, quinuclidine, base, and visible light were all essential for the success of this new aldehyde C−H arylation.

With the optimized conditions in hand, we next sought to determine the generality of the aryl halide component in this new ketone-forming reaction. As shown in Table 2, electron-rich arenes containing alkyl and methoxy groups performed well (**15** and **16**, 82% and 81% yield, respectively). Moreover, a diverse array of electron-deficient bromoarenes that incorporate a variety of substituents (ketone, ester, nitrile, trifluoromethyl, sulfone,

DOI: 10.1021/jacs.7b07078
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Table 2. From Aldehydes to Ketone Adducts: Scope of Triple Catalytic Cross-Coupling with Aryl, Alkyl Bromides and Aldehydes[a]



[a]Isolated yields. Performed with photocat **1** (1 mol %), $NiBr_2$·dtbbpy (10 mol %), quinuclidine (10 mol %), aryl/alkyl bromide, aldehyde, and K_2CO_3. See Supporting Information. [b]K_2CO_3 (2.0 equiv). [c]Aldehyde (3.0 equiv). [d]Aldehyde (10.0 equiv). [e]Aldehyde (6.0 equiv).

and trifluoromethoxy groups) were found to be competent substrates (**17**–**22**, 82–92% yield).[15] Bicyclic aromatics such as phthalides and phthalimides were also coupled with high levels of efficiency (**23** and **24**, 93% and 81% yield, respectively). Notably, the efficiency of the reaction was not impeded by ortho substituents on the aromatic ring (**25**–**26**, 88–90% yield). With respect to heteroaromatic coupling partners, we have found that a range of substituted pyridyl bromides are also effective electrophiles (**29**–**32**, 50–90% yield). Perhaps most importantly, this transformation is not limited to electron-deficient pyridines. For example, quinoline, isoquinoline, and pyrimidine can be readily employed in this HAT-metallaphotoredox-mediated aldehyde C–H arylation (**33**–**35**, 79–87% yield).

Having demonstrated the capacity of aryl bromides to participate in this new ketone-forming reaction, we were delighted to find that vinyl electrophiles can also be incorporated (**36**–**38**, 56–74% yield). Perhaps more important was the finding that alkyl halides can also be employed to generate

DOI: 10.1021/jacs.7b07078
J. Am. Chem. Soc. XXXX, XXX, XXX–XXX

nonconjugated ketones. Indeed, we have found that this transformation can accommodate cyclic and acyclic aliphatic bromides with useful levels of efficiency (**39**–**41**, ≥55% yield). To our knowledge, this is the first time that aldehydes have been merged with aliphatic bromides to generate saturated ketones in one chemical step.

We next turned our attention to the scope of the formyl component. As shown in Table 2, an assortment of readily available aldehydes are viable. For example, primary aldehydes are effective coupling partners, including substrates that incorporate carbamate, phenyl, unprotected alcohol, and *tert*-butyl groups (**42**–**48**, 70–92% yield). Notably, acetaldehyde, which is extremely volatile, can be readily employed (**44**, 70% yield). Moreover, α-branched alkanals were found to readily undergo this C–H arylation (**49** and **50**, both 91% yield). Ring-bearing formyl systems were also successful, including cyclohexyl, cyclopentyl, cyclopropyl, and tetrahydropyranyl carboxaldehyde (**51**–**54**, 81–90% yield). Lastly, aromatic aldehydes were found to couple with aryl halides proficiently despite the diminished hydridic nature of these formyl C–H bonds (**55**–**57**, 70–73% yield).

To highlight the synthetic utility of this triple catalytic mechanism and its potential application to drug-like molecules, we have accomplished a two-step synthesis of haloperidol, a well-established antipsychotic medication.[16] As shown in Figure 1, 4-

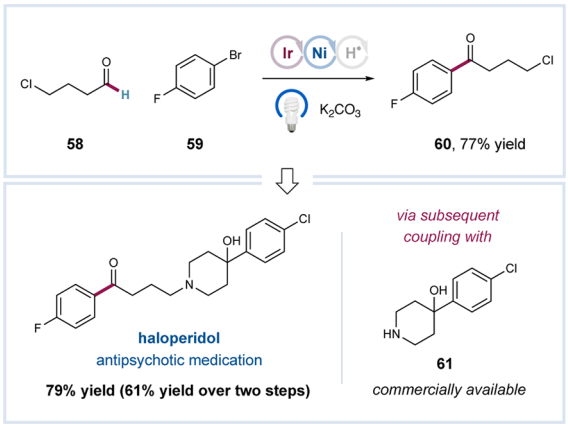


Figure 1. Two-step synthesis of haloperidol.

chlorobutanal **58** and 1-bromo-4-fluorobenzene **59** were successfully combined using our aldehyde coupling protocol to forge ketone **60** in good yield (77%). Exposure of this γ-chloroarylketone to the piperidine nucleophile **61** subsequently delivered haloperidol in relatively short order.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b07078.

Experimental procedures and compound characterization data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*dmacmill@princeton.edu

ORCID

David W. C. MacMillan: 0000-0001-6447-0587

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support provided by the NIHGMS (R01 GM103558-05) and kind gifts from Merck, BMS, Janssen, and Eli Lilly. X.Z. is grateful for a postdoctoral fellowship from the Shanghai Institute of Organic Chemistry.

■ REFERENCES

(1) (a) McDaniel, R.; Thamchaipenet, A.; Gustafsson, C.; Fu, H.; Betlach, M.; Betlach, M.; Ashley, G. *Proc. Natl. Acad. Sci. U. S. A.* **1999**, *96*, 1846. (b) Cuquerella, M. C.; Lhiaubet-Vallet, V.; Cadet, J.; Miranda, M. A. *Acc. Chem. Res.* **2012**, *45*, 1558. (c) Kamat, P. V. *Chem. Rev.* **1993**, *93*, 267.

(2) (a) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815. (b) Sartori, G.; Maggi, R. *Chem. Rev.* **2006**, *106*, 1077. (c) Bechara, W. S.; Pelletier, G.; Charette, A. B. *Nat. Chem.* **2012**, *4*, 228.

(3) For selected reviews, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Willis, M. C. *Chem. Rev.* **2010**, *110*, 725. (c) Wu, X.-F.; Neumann, H.; Beller, M. *Chem. Soc. Rev.* **2011**, *40*, 4986. (d) Moragas, T.; Correa, A.; Martin, R. *Chem. - Eur. J.* **2014**, *20*, 8242.

(4) For selected examples, see: (a) Takemiya, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 14800. (b) Gooßen, L. J.; Rudolphi, F.; Oppel, C.; Rodríguez, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 3043. (c) Weires, N. A.; Baker, E. L.; Garg, N. K. *Nat. Chem.* **2016**, *8*, 75. (d) Amani, J.; Molander, G. A. *J. Org. Chem.* **2017**, *82*, 1856.

(5) (a) Huang, Y.-C.; Majumdar, K. K.; Cheng, C.-H. *J. Org. Chem.* **2002**, *67*, 1682. (b) Pucheault, M.; Darses, S.; Genet, J.-P. *J. Am. Chem. Soc.* **2004**, *126*, 15356. (c) Ko, S.; Kang, B.; Chang, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 455. (d) Ruan, J.; Saidi, O.; Iggo, J. A.; Xiao, J. *J. Am. Chem. Soc.* **2008**, *130*, 10510. (e) Suchand, B.; Satyanarayana, G. *J. Org. Chem.* **2016**, *81*, 6409.

(6) (a) Kalyani, D.; McMurtrey, K. B.; Neufeldt, S. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 18566. (b) Sahoo, B.; Hopkinson, M. N.; Glorius, F. *J. Am. Chem. Soc.* **2013**, *135*, 5505. (c) Shu, X.-z.; Zhang, M.; He, Y.; Frei, H.; Toste, F. D. *J. Am. Chem. Soc.* **2014**, *136*, 5844. (d) Zuo, Z.; Ahneman, D. T.; Chu, L.; Terrett, J. A.; Doyle, A. G.; MacMillan, D. W. C. *Science* **2014**, *345*, 437. (e) Tellis, J. C.; Primer, D. N.; Molander, G. A. *Science* **2014**, *345*, 433.

(7) (a) Corcoran, E. B.; Pirnot, M. T.; Lin, S.; Dreher, S. D.; DiRocco, D. A.; Davies, I. W.; Buchwald, S. L.; MacMillan, D. W. C. *Science* **2016**, *353*, 279. (b) Oderinde, M. S.; Frenette, M.; Robbins, D. W.; Aquila, B.; Johannes, J. W. *J. Am. Chem. Soc.* **2016**, *138*, 1760. (c) Oderinde, M. S.; Jones, N. H.; Juneau, A.; Frenette, M.; Aquila, B.; Tentarelli, S.; Robbins, D. W.; Johannes, J. W. *Angew. Chem., Int. Ed.* **2016**, *55*, 13219.

(8) (a) Shaw, M. H.; Shurtleff, V. W.; Terrett, J. A.; Cuthbertson, J. D.; MacMillan, D. W. C. *Science* **2016**, *352*, 1304. (b) Le, C.; Liang, Y.; Evans, R. W.; Li, X.; MacMillan, D. W. C. *Nature* **2017**, *547*, 79.

(9) Roberts, B. P. *Chem. Soc. Rev.* **1999**, *28*, 25.

(10) Lowry, M. S.; Goldsmith, J. I.; Slinker, J. D.; Rohl, R.; Pascal, R. A., Jr.; Malliaras, G. G.; Bernhard, S. *Chem. Mater.* **2005**, *17*, 5712.

(11) Jeffrey, J. L.; Terrett, J. A.; MacMillan, D. W. C. *Science* **2015**, *349*, 1532.

(12) (a) Fontana, F.; Minisci, F.; Barbosa, M. C. N.; Vismara, E. *J. Org. Chem.* **1991**, *56*, 2866. (b) Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, *99*, 1991.

(13) Chu, L.; Lipshultz, J. M.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2015**, *54*, 7929.

(14) Durandetti, M.; Devaud, M.; Périchon, J. *New J. Chem.* **1996**, *20*, 659.

(15) Electron-deficient aryl chlorides are also competent substrates for this arylation protocol, albeit with reduced levels of efficiency.

(16) Kook, C. S.; Reed, M. F.; Digenis, G. A. *J. Med. Chem.* **1975**, *18*, 533.

DOI: 10.1021/jacs.7b07078
J. Am. Chem. Soc. XXXX, XXX, XXX–XXX