Organic LETTERS
Cite This: Org. Lett. XXXX, XXX, XXX−XXX
Letter
pubs.acs.org/OrgLett

Ru/Ni Dual Catalytic Desulfinative Photoredox C_{sp^2}−C_{sp^3} Cross-Coupling of Alkyl Sulfinate Salts and Aryl Halides

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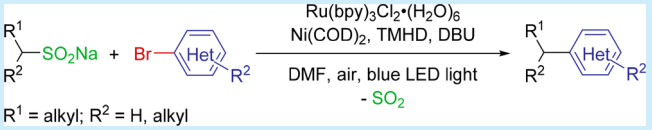
Supporting Information

ABSTRACT: A mild Ru/Ni dual catalytic desulfinative photoredox C_{sp^2}−C_{sp^3} cross-coupling reaction of alkyl sulfinate salts with aryl halides has been developed. The optimized catalyst system, consisting of $Ru(bpy)_3Cl_2$, $Ni(COD)_2$, and DBU, smoothly mediates the coupling of a diverse set of secondary and primary nonactivated alkyl sulfinate salts with a broad range of electron-deficient aryl bromides, electron-rich aryl iodides, and heteroaryl bromides under irradiation with blue light. The procedure is ideal for late-stage introduction of alkyl groups on pharmaceutical intermediates, and the C_{sp^2}−C_{sp^3} cross-coupling reaction allowed the rapid synthesis of caseine kinase 1δ inhibitor analogues via a parallel medicinal chemistry effort.



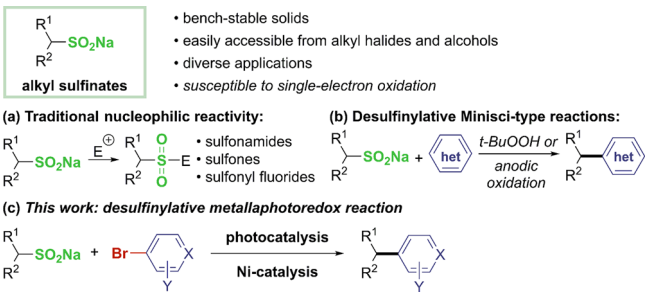
An increased fraction of C_{sp^3} centers (F_{sp^3}) has been correlated with the probability of human pharmaceutical agents advancing through clinical development.[1] Consequently, there is a high interest in drug discovery in the development of broadly applicable, robust, and concise procedures that allow the selective formation of C_{sp^2}−C_{sp^3} bonds from readily available, stable starting materials. Also, the procedures should be amendable to applications in parallel medicinal chemistry (PMC) for the rapid preparation of chemical libraries which are a vital tool to explore structure−activity relationships efficiently.

Remarkable progress has been achieved in recent decades in Ni-catalyzed C_{sp^2}−C_{sp^3} cross-coupling reactions.[2] In particular, merging Ni-catalyzed cross-coupling methods with photoredox chemistry (metallaphotoredox)[3] has introduced a powerful tool for the selective construction of aryl−alkyl bonds, and diverse sets of broadly available starting materials have been introduced as alkyl radical precursors.[4] The MacMillan and Doyle groups spearheaded the development of Ir/Ni dual catalytic decarboxylative metallaphotoredox reactions that utilize α-amino acids, α-alkoxy carboxylic acids, and monoalkyl oxalates as radical sources[5] while the Molander group enabled photoredox C_{sp^2}−C_{sp^3} cross-coupling reactions with potassium alkyl trifluoroborates as radical precursors.[6] The C_{sp^3}−H bonds in the α-position of tertiary amines and alkyl ethers have been selectively oxidized under metallaphotoredox conditions, and the resulting radical intermediates were subsequently cross-coupled with aryl halides.[7] The formation of transient silyl radical intermediates allowed the development of a visible light-mediated cross-electrophile coupling of alkyl bromides and aryl bromides.[8] Particularly mild Ru/Ni-catalyzed photoredox C_{sp^2}−C_{sp^3} coupling reactions have been achieved by the Molander and Fensterbank groups by using ammonium catechol alkyl silicates[9] which possess very low redox potentials as sources of alkyl radicals.[10] In addition, photoredox C_{sp^3}−C_{sp^3} coupling reactions,[11] etherifications,[12] thioetherificiations,[13] and amination reactions[14] have been developed.

Inspired by the groundbreaking contributions, we engaged in enabling photoredox technologies for applications in PMC. We became particularly interested in metallaphotoredox reactions that utilize alkyl radical precursors with low redox potentials ($E_{1/2}^{ox}$ < 1.00 V vs Ag/AgCl) and straightforward syntheses from substrates that are already extensively used in drug discovery.

Alkyl sulfinate salts are diversely used in drug discovery, and traditionally their nucleophilic reactivity is most frequently exploited for the synthesis of pharmaceutically privileged structural motifs such as sulfonamides, sulfones, and sulfonyl fluorides (Scheme 1, top).[15] In addition, Baran's pioneering work on desulfinative Minisci-type reactions demonstrated that alkyl radical intermediates are efficiently generated by oxidizing alkyl sulfinate salts with organic peroxides or electrochemically (Scheme 1, middle) under reaction conditions that are

Scheme 1. Applications of Alkyl Sulfinate Salts in Medicinal Chemistry



Received: October 20, 2017

DOI: 10.1021/acs.orglett.7b03280
Org. Lett. XXXX, XXX, XXX−XXX

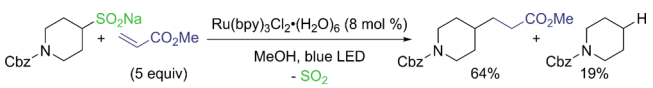
significantly milder than required for the conversion of the corresponding aliphatic carboxylic acids.[16] Furthermore, sulfinate salts have been used in transition-metal-catalyzed trifluoromethylation reactions[17] and in desulfinative biaryl syntheses.[18] In addition to their chemical properties, alkyl sulfinate salts are bench-stable, nonvolatile solids which make them easy to handle. Consequently, a broad range of operationally simple protocols have been introduced to prepare alkyl sulfinate salts from readily available precursors,[19] and a diverse set is meanwhile commercially available.

Herein we report the development of the first Ru/Ni dual catalytic desulfinative metallaphotoredox C_{sp^2}–C_{sp^3} coupling reaction of alkyl sulfinate salts and aryl halides and the application of the procedure in PMC (Scheme 1, bottom). Initially, we hypothesized that alkyl sulfinate salts could serve as radical precursors in metallaphotoredox reactions. We envisaged a catalytic cycle that relies on the generation of an alkyl radical intermediate by single-electron oxidation of the sulfinate salt by the excited triplet-state photocatalyst $[PC^n]^*$ followed by extrusion of SO_2. The subsequently generated alkyl radical species can intercept a Ni-catalyzed cycle following the mechanism proposed by the groups of Molander and Kozlowski.[20]

We started our investigation with inspiration by studies of the Nicewicz group,[21] and we decided to measure the half-potentials $E_{1/2}^{ox}$ of a set of alkyl sodium sulfinate salts by cyclic voltammetry to select photocatalysts with matching redox potentials. The cyclic voltammograms [c = 0.05 M, Et_4NBF_4 (0.10 M), scan rate: 90 mV/s] were acquired in aqueous solution at a glassy carbon working electrode and Pt wire auxiliary electrode. The potentials are reported relative to the Ag/AgCl reference electrode. The selected sulfinates were surprisingly easy to oxidize, and the measured oxidative half-potentials were $E_{1/2}^{ox}$ (tBuCH$_2$SO$_2$Na) = 0.58 V, $E_{1/2}^{ox}$ (sodium 4-tetrahydropyran sulfinate) = 0.64 V, and $E_{1/2}^{ox}$ (tBuSO$_2$Na) = 0.63 V, which are slightly lower than the half-potentials of ammonium catechol silicates [$E_{1/2}^{ox}$ = 0.83 V vs Ag/AgCl for tetramethylammonium allyl bis(catecholo) silicate in the presence of an equimolar amount of piperidine][22] and significantly lower than the oxidative potentials of alkyl carboxylic acids [$E_{1/2}^{ox}$ (Cesium N-boc-prolinate) = 0.99 V vs Ag/AgCl][23] and alkyl potassium trifluoroborates [$E_{1/2}^{ox}$ (potassium cyclohexyltrifluoroborate) = 1.53 V vs Ag/AgCl].[24] The half-potentials of the tested sulfinate salts align perfectly with the redox potential of Ru(bpy)$_3$Cl$_2$ [$E_{1/2red}$ (Ru^{II}*/Ru^{I}) = 0.82 V vs Ag/AgCl electrode] which we used in the subsequent studies.

For the next step, we chose a photoredox conjugate addition reaction[25] to test our hypothesized radical generation via photoredox catalysis. N-Cbz protected sodium 4-piperidinyl sulfinate was selected as a radical precursor, and a solution in methanol was irradiated with blue light in the presence of 8 mol % of Ru(bpy)$_3$Cl$_2$·(H$_2$O)$_6$ (Scheme 2). An excess of methyl acrylate was used to trap radical intermediates efficiently. The sulfinate salt was fully consumed, and the desired product was isolated in 64% yield along with 19% of the proto-desulfinylated N-Cbz-piperidine. Control experiments confirmed that the reaction can be catalyzed by the more oxidizing Ir[dF(CF$_3$)ppy]$_2$(bpy)PF$_6$ or Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ in comparable efficiency. As

Scheme 2. Photoredox Desulfinative Conjugate Addition

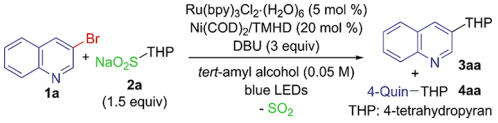


expected, only traces (<5%) of the product were detected with photocatalysts having less oxidizing excited states, e.g., Ir(ppy)$_3$ [$E_{1/2}^{red}$ (Ir^{III}*/Ir^{II}) = 0.36 V vs Ag/AgCl].

Encouraged, we set out to develop a catalyst system for a Ru/Ni dual catalytic desulfinative metallaphotoredox reaction. We chose sodium 4-tetrahydropyran sulfinate (**2a**) as a radical source and 3-bromo quinoline (**1a**) as a pharmaceutically relevant N-containing heterocycle. We sought to identify reaction conditions by high-throughput experimentation (HTE). A set of 96 test reactions were prepared in a N-filled glovebox, and each reaction was run on 2 μmol scale and 0.02 M concentration using 20 mol % of Ni(COD)$_2$ and 5 mol % of Ru(bpy)$_3$Cl$_2$ (H$_2$O)$_6$. We chose *tert*-amyl alcohol as solvent to solubilize **2a** sufficiently, and we expected the steric bulk of the alcohol to minimize the formation of undesired 3-(*tert*-pentyloxy)quinoline.[12] A set of 58 ligands (25 mol %) and 38 bases (3.0 equiv) were investigated. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) was used as a base in the ligand screen, and 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbbpy) was used as ligand in the base screen. The reaction vials were placed in a 96-well plate, irradiated from the bottom with blue LED light for 18 h at 25 °C, and the conversions were determined by UPLC. The best result was obtained with a combination of 1,1,6,6-tetramethylheptane-2,5-dione (TMHD) as ligand and DBU base.

The reaction conditions identified in the HTE screen worked well outside of a glovebox on preparative scale (250 μmol and c = 0.5 M), and we isolated the desired product **3aa** in 60% yield (Table 1, entry 1) along with a Minisci-type side product **4** and

Table 1. Optimization of the Photoredox Ru/Ni Dual Catalytic Desulfinative Cross-Coupling



entry[a]	deviation from HTE conditions	3aa [%]	4 [%]
1[b]	**HTE conditions**	**60**	**<5**
2	no Ni(COD)$_2$	0	<5
3	no Ru(bpy)$_3$Cl$_2$·(H$_2$O)$_6$	0	0
4	no light or DBU	0	0
5	no TMHD	41	10
6	dtbbpy as ligand	13	10
7	NiCl$_2$·glyme as precatalyst	39	12
8[c]	(tmeda)Ni(*o*-tolyl)Cl instead of Ni(COD)$_2$	50	0
9[d]	DMF as solvent	43	0
10[d]	**2a** (3 equiv), DMF as solvent	71	0
11[d]	**2a (3 equiv), DMF as solvent, air**	**84**	**0**

[a]Reactions were performed on 0.25 mmol scale using anhydrous conditions. Isolated yields are reported. [b]Traces of 3-(*tert*-pentyloxy)-quinoline detected. [c]20 mol %; tmeda: *N,N,N′,N′*-tetramethyl ethylenediamine. [d]1 mol % Ru(bpy)$_3$Cl$_2$·(H$_2$O)$_6$.

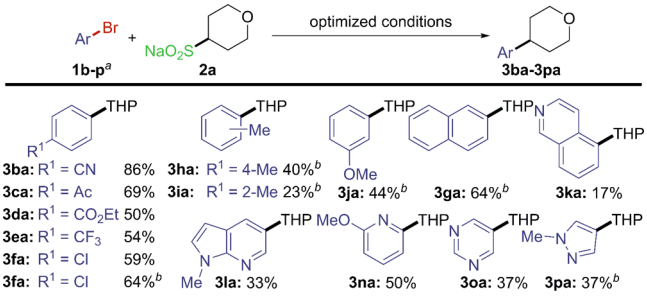
<5% of 3-(*tert*-pentyloxy)quinoline. A series of control experiments demonstrated that irradiation with blue LED light, the Ru-photocatalyst, the Ni-catalyst, and DBU are essential for the desulfinative coupling (Table 1, entries 2–4). We rationalize the observation with DBU acting as an auxiliary ligand, which prevents the formation of catalytically inactive sulfinate-Ni-complexes (Table 1, entry 4).[26] The presence of the weakly coordinating ligand TMHD proved to be beneficial, and the yields of **3aa** diminished to 41% in absence of the ligand (Table 1, entry 5). The use of 20 mol % of Ni(COD)$_2$ proved to be optimal, and lower catalyst loadings (5 mol %) resulted in a diminished

DOI: 10.1021/acs.orglett.7b03280
Org. Lett. XXXX, XXX, XXX–XXX

yield of 44%. Using $NiCl_2$·glyme as a precatalyst led to a drop in yield to 39% (Table 1, entry 7). The addition of 1,5-cyclooctadiene as a stabilizing ligand for potential Ni^0-intermediates had no influence on the reaction outcome, and **3aa** was obtained in 38% yield.[27] Air-sensitive $Ni(COD)_2$ can be replaced with air-stable (tmeda)Ni(*o*-tolyl)Cl precatalyst, and the desired product **3aa** was obtained in 50% yield (Table 1 entry 8). The formation of **3aa** was not observed when $Ru(bpy)_3Cl_2$ was replaced with substoichiometric (10 mol %)[27] or excess amounts (5.0 equiv) of *tert*-butyl hydrogen peroxide as a chemical oxidant, and the starting materials were recovered along with traces of 3,3′-biquinoline. The control experiments support our mechanistic hypothesis and render a Ni-catalyzed desulfinative radical chain reaction unlikely. The formation of the side products **4** and 3-(*tert*-pentyloxy)quinoline was efficiently suppressed by lowering the Ru-photocatalyst loading to 1 mol % and using DMF as solvent (Table 1, entry 9). An improvement in yield was obtained with 3 equiv of the sodium sulfinate **2a**, and the product **3aa** was isolated in 71% yield (Table 1, entry 10). Using a larger excess of **2a** did not improve the yield further. The presence of air in the headspace of the reaction vial resulted in another yield enhancement, which is in accordance to the mechanistic studies of Oderinde et al.[28] and allowed us to add $Ni(COD)_2$ to the reaction vessels under air. As a result of these optimization efforts, **3aa** was isolated in 84% yield (Table 1, entry 11).

With optimized reaction conditions in hand, we set out to explore the scope of the desulfinative metallaphotoredox reaction with regard to aryl halides (**1a−p**) (Scheme 3). Electron-deficient

Scheme 3. Scope of the Aryl and Heteroaryl Halides in Ru/Ni-Catalyzed Desulfinative Cross-Coupling



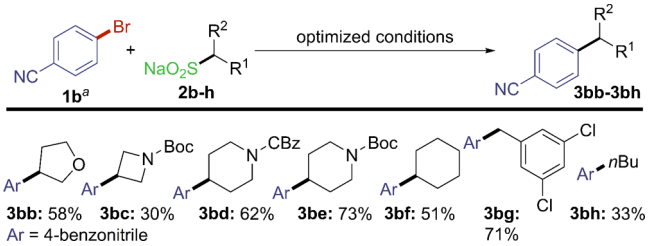
[a]Reactions were performed on 0.25 mmol scale using aryl or heteroaryl cross-coupling partners (X = Br) and anhydrous conditions unless otherwise reported. Isolated yields are reported. [b]Aryl iodide (X = I) was used in place of aryl bromide.

aryl bromides (**1b−f**) and electron-neutral aryl iodides (**1g−j**) were successfully coupled with **2a**. Many pharmaceutically important N-containing heterocycles, including pyridines (**1m** and **1n**), isoquinoline (**1k**), indole (**1l**), pyrimidine (**1o**), and pyrazole (**1p**), were successfully converted, which are often challenging in cross-coupling reactions because of coordination of the basic N-atoms to the Ni-catalyst.[29]

Next, we attempted scaling up the reaction to 1 mmol, but compound **3ba** was isolated in 1% yield. The development of elegant flow processes allowed the scaleup of photoredox chemistry,[30] but the development of such a protocol is beyond the scope of this letter.

Our attention then turned toward the scope of the sodium alkyl sulfinates, and we selected a diverse set of commercially available sulfinate salts (**2b−h**) as test substrates. The selected sulfinate

Scheme 4. Scope of the Desulfinative Cross-Coupling with Regard to Sodium Alkyl Sulfinates



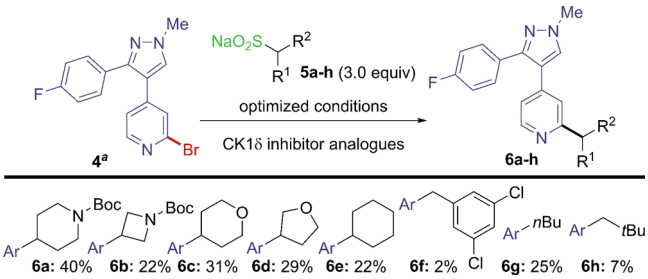
[a]Reactions were performed on 0.25 mmol scale using anhydrous conditions unless otherwise reported. Isolated yields are reported.

salts **2b−h** were successfully cross-coupled with 4-bromo benzonitrile (**1b**) (Scheme 4).

Secondary sulfinates (**2b−2f**), the benzylic sulfinate **2g** (71%), and even primary sodium *n*-butane-1-sulfinate (**2h**) were smoothly converted. Steric bulk proved to be detrimental, and consequently traces of the desired product were detected with sodium neopentyl sulfinate (<5%); no product was detected with sodium *tert*-butane sulfinate (0%). Noteworthy, the azetidine sulfinate **2c** was well converted, but the separation of the desired product **3bc** from a small amount of nonconverted **1b** was surprisingly challenging, and **3bc** was obtained in 30% yield.

Encouraged by the scope of the desulfinative photoredox coupling, we investigated the transfer of the new method into a reliable PMC protocol. We chose compound **4** as the pharmaceutically relevant test substrate, as it serves as an advanced intermediate for the synthesis of selective ATP-competitive inhibitors of casein kinase 1δ, which is associated with the regulation of the circadian rhythm.[31] A stock solution of the aryl bromide **4** and the catalyst system was prepared and added to the reaction vials containing a set of 8 diverse sodium alkyl sulfinates **5a−h** (Scheme 5). The reactions (0.1 mmol scale)

Scheme 5. Preparation of Caseine Kinase 1δ Inihibitor Analogues Using the Desulfinative Coupling in PMC



[a]Reactions were performed on 0.1 mmol scale and anhydrous conditions unless otherwise reported. Isolated yields from preparative UPLC are reported.

were irradiated in parallel with visible blue light and purified by semipreparative UPLC. The test library was highly successful, and all the desired products **6a−h** could be obtained in sufficient amounts and high purity. Even **6h** was isolated from the coupling of sodium neopentyl sulfinate **5h**.

In conclusion, alkyl sulfinate salts which are frequently used in medicinal chemistry for the generation of sulfonamide and sulfone analogue libraries have been introduced as versatile, easy-to-handle, and mild radical precursors in desulfinative Ru/Ni dual catalytic metallaphotoredox C_{sp^2}−C_{sp^3} coupling reactions. Initial

DOI: 10.1021/acs.orglett.7b03280
Org. Lett. XXXX, XXX, XXX−XXX

cyclic voltammetry studies revealed the very low oxidative half-potentials of the substrate class and led to the development of a mild catalyst system that uses inexpensive $Ru(bpy)_3Cl_2$ as a photocatalyst. The optimized reaction conditions allow the smooth coupling of a broad range of nonstabilized secondary and primary sodium sulfinate salts with electron-rich aryl iodides, electron-deficient aryl bromides, and pharmaceutically important heteroaryl halides. The desulfinative metallaphotoredox reaction marks an efficient strategy to functionalize advanced pharmaceutical intermediates in parallel as the rapid generation of casein kinase 1δ inhibitors analogues.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03280.

Experimental procedures, characterizations, ^1H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Lara Czabaniuk (Amgen Inc.) for support and Dr. Kevin Hesp (Pfizer Inc.), Dr. Hatice Yayla (Pfizer Inc.), Dr. Martins Oderinde (Pfizer Inc.), and Dr. Anabella Villalobos (Biogen Inc.) for fruitful discussions.

■ REFERENCES

(1) Lovering, F.; Bikker, J.; Humblet, C. *J. Med. Chem.* **2009**, *52*, 6752.
(2) Tasker, S. Z.; Standley, E. A.; Jamison, T. F. *Nature* **2014**, *509*, 299.
(3) (a) Reiser, O. *Acc. Chem. Res.* **2016**, *49*, 1990. (b) Nakajima, K.; Miyake, Y.; Nishibayashi, Y. *Acc. Chem. Res.* **2016**, *49*, 1946. (c) Jamison, C. R.; Overman, L. E. *Acc. Chem. Res.* **2016**, *49*, 1578. (d) Ghosh, I.; Marzo, L.; Das, A.; Shaikh, R.; König, B. *Acc. Chem. Res.* **2016**, *49*, 1566. (e) Gentry, E. C.; Knowles, R. R. *Acc. Chem. Res.* **2016**, *49*, 1546. (f) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322.
(4) (a) Goddard, J.-P.; Ollivier, C.; Fensterbank, L. *Acc. Chem. Res.* **2016**, *49*, 1924. (b) Shaw, M. H.; Twilton, J.; MacMillan, D. W. C. *J. Org. Chem.* **2016**, *81*, 6898. (c) Tellis, J. C.; Kelly, C. B.; Primer, D. N.; Jouffroy, M.; Patel, N. R.; Molander, G. A. *Acc. Chem. Res.* **2016**, *49*, 1429. (d) Vila, C. *ChemCatChem* **2015**, *7*, 1790.
(5) (a) Zuo, Z.; Ahneman, D. T.; Chu, L.; Terrett, J. A.; Doyle, A. G.; MacMillan, D. W. C. *Science* **2014**, *345*, 437. (b) Chu, L.; Lipshultz, J. M.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2015**, *54*, 7929. (c) Noble, A.; McCarver, S. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2015**, *137*, 624. (d) Zuo, Z.; Cong, H.; Li, W.; Choi, J.; Fu, G. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2016**, *138*, 1832. (e) Zhang, X.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2016**, *138*, 13862.
(6) (a) Tellis, J. C.; Primer, D. N.; Molander, G. A. *Science* **2014**, *345*, 433. (b) Primer, D. N.; Karakaya, I.; Tellis, J. C.; Molander, G. A. *J. Am. Chem. Soc.* **2015**, *137*, 2195. (c) Yamashita, Y.; Tellis, J. C.; Molander, G. A. *Proc. Natl. Acad. Sci. U. S. A.* **2015**, *112*, 12026. (d) El Khatib, M.; Serafim, R. A. M.; Molander, G. A. *Angew. Chem., Int. Ed.* **2016**, *55*, 254.
(7) (a) Ahneman, D. T.; Doyle, A. G. *Chem. Sci.* **2016**, *7*, 7002. (b) Heitz, D. R.; Tellis, J. C.; Molander, G. A. *J. Am. Chem. Soc.* **2016**, *138*, 12715. (c) Joe, C. L.; Doyle, A. G. *Angew. Chem., Int. Ed.* **2016**, *55*, 4040.
(8) (a) Zhang, P.; Le, C. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2016**, *138*, 8084. (b) Duan, Z.; Li, W.; Lei, A. *Org. Lett.* **2016**, *18*, 4012.
(9) (a) Corcé, V.; Chamoreau, L.-M.; Derat, E.; Goddard, J.-P.; Ollivier, C.; Fensterbank, L. *Angew. Chem., Int. Ed.* **2015**, *54*, 11414. (b) Jouffroy, M.; Primer, D. N.; Molander, G. A. *J. Am. Chem. Soc.* **2016**, *138*, 475.
(10) (a) Nishigaichi, Y.; Suzuki, A.; Takuwa, A. *Tetrahedron Lett.* **2007**, *48*, 211. (b) Lévêque, C.; Corcé, V.; Chenneberg, L.; Ollivier, C.; Fensterbank, L. *Eur. J. Org. Chem.* **2017**, *2017*, 2118.
(11) Johnston, C. P.; Smith, R. T.; Allmendinger, S.; MacMillan, D. W. C. *Nature* **2016**, *536*, 322.
(12) Terrett, J. A.; Cuthbertson, J. D.; Shurtleff, V. W.; MacMillan, D. W. C. *Nature* **2015**, *524*, 330.
(13) (a) Oderinde, M. S.; Frenette, M.; Robbins, D. W.; Aquila, B.; Johannes, J. W. *J. Am. Chem. Soc.* **2016**, *138*, 1760. (b) Jouffroy, M.; Kelly, C. B.; Molander, G. A. *Org. Lett.* **2016**, *18*, 876.
(14) (a) Oderinde, M. S.; Jones, N. S.; Juneau, A.; Frenette, M.; Aquila, B.; Tentarelli, S.; Robbins, D. W.; Johannes, J. W. *Angew. Chem., Int. Ed.* **2016**, *55*, 13219. (b) 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.
(15) Dong, J.; Krasnova, L.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2014**, *53*, 9430.
(16) (a) Yan, M.; Lo, J. C.; Edwards, J. T.; Baran, P. S. *J. Am. Chem. Soc.* **2016**, *138*, 12692. (b) Michaudel, Q.; Ishihara, Y.; Baran, P. S. *Acc. Chem. Res.* **2015**, *48*, 712.
(17) (a) Li, Y.; Wu, L.; Neumann, H.; Beller, M. *Chem. Commun.* **2013**, *49*, 2628. (b) Li, Z.; Cui, Z.; Liu, Z.-Q. *Org. Lett.* **2013**, *15*, 406. (c) Ye, Y.; Künzi, S. A.; Sanford, M. S. *Org. Lett.* **2012**, *14*, 4979.
(18) (a) Markovic, T.; Rocke, B. N.; Blakemore, D. C.; Mascitti, V.; Willis, M. C. *Chem. Sci.* **2017**, *8*, 4437. (b) Sévigny, S.; Forgione, P. *Chem. - Eur. J.* **2013**, *19*, 2256.
(19) (a) Lenstra, D. C.; Vedovato, V.; Flegeau, E. F.; Maydom, J.; Willis, M. C. *Org. Lett.* **2016**, *18*, 2086. (b) Shavnya, A.; Coffey, S. B.; Hesp, K. D.; Ross, S. C.; Tsai, A. S. *Org. Lett.* **2016**, *18*, 5848. (c) Davies, A. T.; Curto, J. M.; Bagley, S. W.; Willis, M. C. *Chem. Sci.* **2017**, *8*, 1233. (d) Gianatassio, R.; Kawamura, S.; Eprile, C. L.; Foo, K.; Ge, J.; Burns, A. C.; Collins, M. R.; Baran, P. S. *Angew. Chem., Int. Ed.* **2014**, *53*, 9851.
(20) Gutierrez, O.; Tellis, J. C.; Primer, D. N.; Molander, G. A.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2015**, *137*, 4896.
(21) Roth, H. G.; Romero, N. A.; Nicewicz, D. A. *Synlett* **2016**, *27*, 714.
(22) Nishigaichi, Y.; Suzuki, A.; Takuwa, A. *Tetrahedron Lett.* **2007**, *48*, 211.
(23) Zuo, Z.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2014**, *136*, 5257.
(24) Yasu, Y.; Koike, T.; Akita, M. *Adv. Synth. Catal.* **2012**, *354*, 3414.
(25) (a) Schnermann, M. J.; Overman, L. E. *Angew. Chem., Int. Ed.* **2012**, *51*, 9576. (b) Nawrat, C. C.; Jamison, C. R.; Slutskyy, Y.; MacMillan, D. W. C.; Overman, L. E. *J. Am. Chem. Soc.* **2015**, *137*, 11270. (c) Chu, L.; Ohta, C.; Zuo, Z.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2014**, *136*, 10886.
(26) Farmer, P. J.; Reibenspies, J. H.; Lindahl, P. A.; Darensbourg, M. Y. *J. Am. Chem. Soc.* **1993**, *115*, 4665.
(27) See Supporting Information for further information.
(28) Oderinde, M. S.; Varela-Alvarez, A.; Aquila, B.; Robbins, D. W.; Johannes, J. W. *J. Org. Chem.* **2015**, *80*, 7642.
(29) Slagt, V. F.; de Vries, A. H. M.; de Vries, J. G.; Kellogg, R. M. *Org. Process Res. Dev.* **2010**, *14*, 30.
(30) Staveness, D.; Bosque, I.; Stephenson, C. R. J. *Acc. Chem. Res.* **2016**, *49*, 2295.
(31) Mente, S.; Arnold, E.; Butler, T.; Chakrapani, S.; Chandrasekaran, R.; Cherry, K.; DiRico, K.; Doran, A.; Fisher, K.; Galatsis, P.; Green, M.; Hayward, M.; Humphrey, J.; Knafels, J.; Li, J.; Liu, S.; Marconi, M.; McDonald, S.; Ohren, J.; Paradis, V.; Sneed, B.; Walton, K.; Wager, T. J. *J. Med. Chem.* **2013**, *56*, 6819.

DOI: 10.1021/acs.orglett.7b03280
Org. Lett. XXXX, XXX, XXX−XXX