Organic LETTERS

Letter

pubs.acs.org/OrgLett

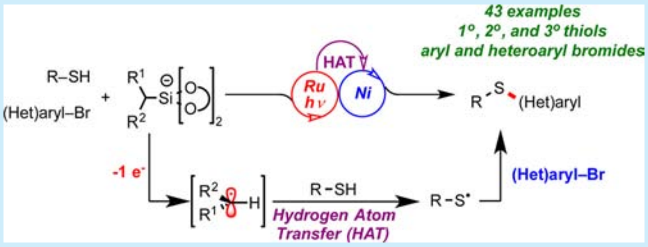
Thioetherification via Photoredox/Nickel Dual Catalysis

Matthieu Jouffroy,[†] Christopher B. Kelly,[†] and Gary A. Molander*

Roy and Diana Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, 231 South 34th Street, Philadelphia, Pennsylvania 19104-6323, United States

Supporting Information

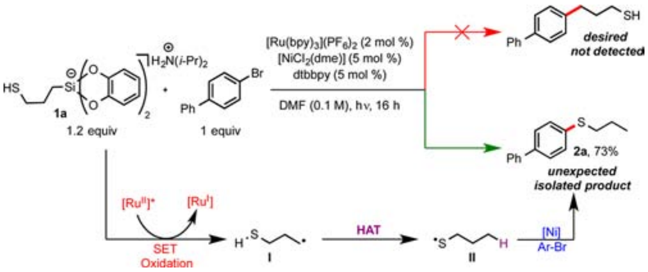
ABSTRACT: Hypervalent alkylsilicates represent new and readily accessible precursors for the generation of alkyl radicals under photoredox conditions. Alkyl radicals generated from such silicates serve as effective hydrogen atom abstractors from thiols, furnishing thiyl radicals. The reactive sulfur species generated in this manner can be funneled into a nickel-mediated cross-coupling cycle employing aromatic bromides to furnish thioethers. The serendipitous discovery of this reaction and its utilization for the thioetherification of various aryl and heteroaryl bromides with a diverse array of thiols is described. The S−H selective H atom abstraction event enables a wide range of functional groups, including those bearing protic moieties, to be tolerated.



Visible-light mediated photoredox catalysis has attracted significant attention, likely because of the unprecedented capability to control reactive radicals through discrete, single electron transfer (SET) events.[1] Because radical generation can be controlled, photoredox catalysts facilitate transformations that would be challenging using stoichiometric reagents, where unproductive redox quenching and undesired side reactions are unavoidable. Although already a powerful synthetic paradigm, recent reports by several groups, including our own, centering on integrating photoredox catalysis with transition metal cross-coupling has offered a unique solution to the challenge of transmetalation.[1d,2] By engaging C_{sp^3}-hybridized radicals generated by photoredox-mediated SET events with transition metal catalysts, facile single-electron transmetalation allows C_{sp^3}−C_{sp^2} bonds to be formed under remarkably mild conditions.[2,3] Utilization of this powerful reaction manifold has enabled the cross-coupling of benzylic,[2a,4a,b] secondary alkyl,[3a,4a,b] α-alkoxy,[2d,3a,f] and α-amino[2b,3c,d,f] C_{sp^3}-hybridized radicals with aryl and/or alkenyl electrophiles.

Although several classes of radical precursors are now known, alkylbis(catecholato)silicates have recently been found to be well-suited for this type of dual catalysis because of their low oxidation potentials ($E^0 \approx +0.75$ V vs SCE for primary silicates) and the innocuous byproducts generated upon oxidation.[4] During the course of investigating the amenability of various alkylsilicates toward dual catalysis,[4a] we subjected alkylthiolsilicate **1a** to the previously reported conditions for dual catalytic cross-coupling. Rather than obtaining the expected C_{sp^3}−C_{sp^2} bond formation, a thioetherification process was serendipitously discovered (Scheme 1). We posited that formation of **2a** results from thiyl radical **II**, which formed by way of a hydrogen-atom transfer (HAT) from alkyl radical **I** [1 °C−H BDE (ethane) = 101.1 kcal mol^{-1} versus S−H BDE (methanethiol) = 87−88 kcal mol^{-1}].[5] Methods to construct C_{sp^2}−Y linkages via the dual catalytic paradigm are known for C−N,[6a] C−O,[6b] and C−P[6c,d] bonds, but no similar process for C−S bonds yet exists. Although classic Ni- and Pd-catalyzed couplings of thiols with aryl halides are known, these processes still require either high temperatures, high catalyst loadings, and/or highly alkaline conditions.[7] This may relate to the notorious sensitivity of transition metal catalysts toward thiols.[8c] Methods to effect thioetherification of aryl halides using thiols via cross-coupling are often curtailed by thiol-ligand interchange that, at best, retard reductive elimination or, worse, lead to catalyst deactivation.[8c] Efficient cross-coupling of thiols thereby requires powerful, expensive, bidentate phosphine ligands to deter undesired displacement processes while simultaneously enhancing rates of oxidative addition and reductive elimination.[8] These drawbacks thus limit the utility of this reaction to prepare a diverse array of thioethers, much less those containing a variety of functional groups. Given these facts, the ease of formation of **2a** *under such mild conditions* (base-free, room temperature) is very unusual. We therefore elected to

Scheme 1. Unexpected Thioetherification Observed When Using Alkylsilicate 1a and a Plausible Mechanistic Rationalization



Received: January 22, 2016
Published: February 8, 2016

© 2016 American Chemical Society

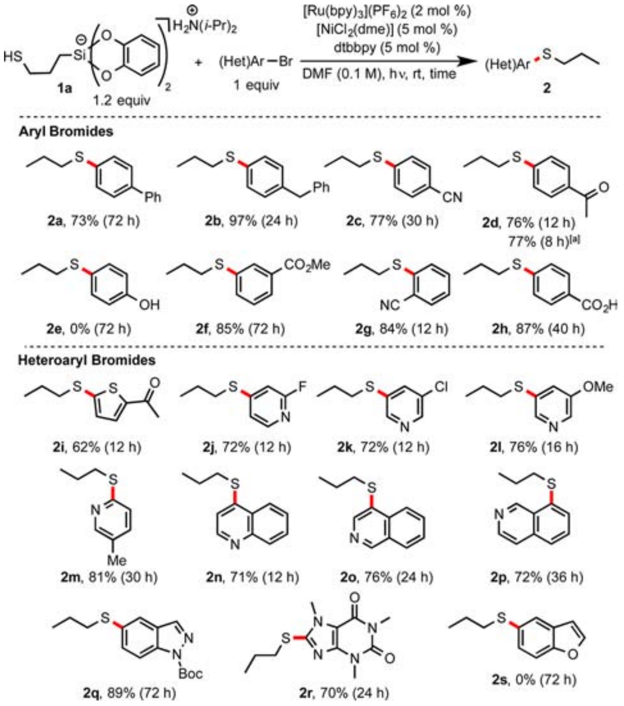
DOI: 10.1021/acs.orglett.6b00208

pursue the viability of this unusual outcome as a general method for the direct thioetherification of aryl bromides.

To understand the observed thioetherification reaction and to verify that the outcome was derived from a dual catalytic process, several control studies were performed. These studies confirmed that light, Ru photocatalyst, and Ni catalyst are required to accomplish thioetherification; without any of these three components, only trace cross-coupled product was observed (see Supporting Information). When conducting the reaction in the absence of the ligand [4,4′-di-*tert*-butyl-2,2′-dipyridyl (dtbbpy)], thioetherification was still observed. However, the reaction was slow and did not progress further than ~60% conversion after 72 h.[9]

Using alkylsilicate **1a**, the competency of various aryl and heteroaryl bromides toward photoredox thioetherifcation was assessed (Scheme 2). A range of electronically and sterically disparate aryl and heteroaryl bromides underwent thioetherification in good to excellent yield. Electron-poor (**2c–d**, **2f–h**) and electron-neutral (**2a–b**) aryl bromides were equally tolerated under our reaction conditions, although the rate of thioetherification varied significantly. Of note is substrate **2h**, whose acidic functional group was untouched during thioetherification. However, thioetherifcation of electron-rich 4-bromophenol to give **2e** was not observed, likely because of difficulties in oxidative addition. Several classes of heteroaryl bromides were also amenable toward thioetherification. Pyridyl bromides (**2j–2m**) with varying electronic and steric environments all underwent thioetherification in good yield. Additionally, isoquinolines (**2o–p**), a quinoline (**2n**), and a thiophene (**2i**) were also well-tolerated. Thioethers derived from more elaborate heteroaryl bromides such as those from 8-bromocaffeine and *N*-Boc-protected indazole (**2r** and **2q**, respectively) could be accessed with ease and in good yield. Such facile cross-coupling of heteroaryl bromides to furnish heteroaryl thioethers is rare where the more common routes are via S_N2 displacement or S_NAr reactions.[10] Scale-up of the thioetherifcation process proved facile. Neither yield nor reaction time was compromised when synthesizing thioether **2d** on a 5 mmol scale (a 10-fold increase in scale), indicating the robustness of the established method. Despite being a competent electrophile toward C_{sp^3}–C_{sp^2} Ni-photoredox cross-coupling using alkylsilicates,[4a] 5-bromobenzofuran (**2s**) failed to undergo photoredox thioetherification.

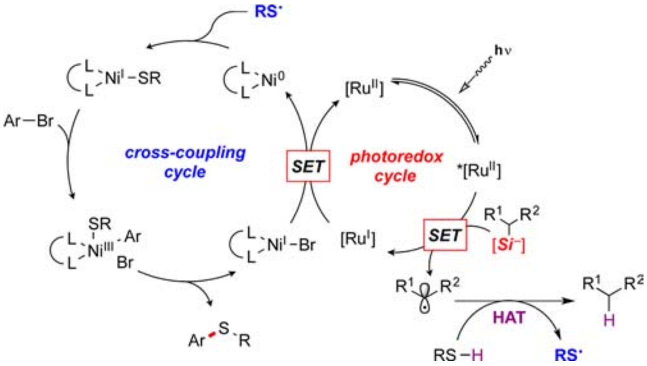
Scheme 2. Photoredox Thioetherification Using Thiolsilicate 1a



[a]Reaction run on 5 mmol using blue LEDs; all other reactions run on a 0.5 mmol scale of aryl/heteroaryl bromide.

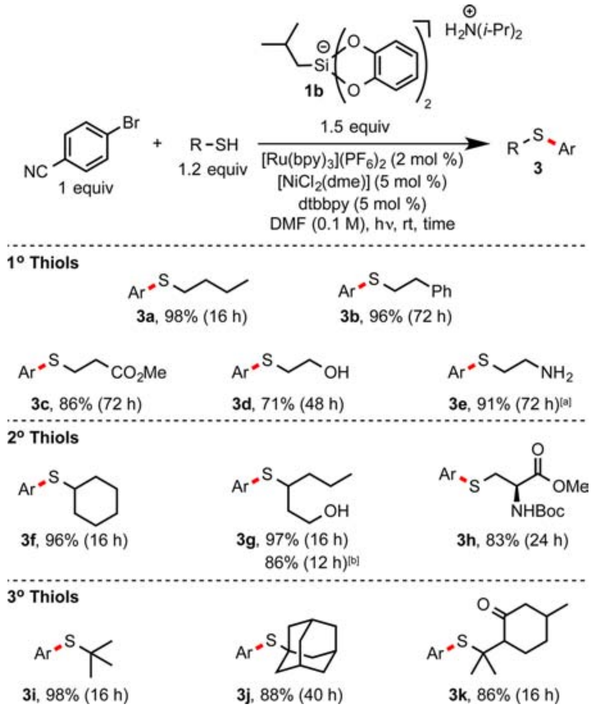
Although highly promising, the generality of the described thioetherification was hampered by the limited availability of thiol-substituted trimethoxysilanes, the requisite material needed for the synthesis of **1a** analogues. The preparation of a library of such silicates is impractical when pitted against the commercial availability of various thiols themselves. Using the mechanism for photoredox cross-coupling as a guide,[11] we envisioned that a resolution to this issue would be to perform an *intermolecular* HAT from a thiol using an alkylbis(catecholato)silicate as an H atom abstractor (Scheme 3). The generated thiyl radical could then enter the dual catalytic cycle in place of an alkyl radical. Subsequent oxidative addition and reductive elimination would afford a Ni^I–Br species that could then be reduced by the photocatalyst, closing both interlaced catalytic cycles.[11]

Scheme 3. Plausible Catalytic Cycle for Thioetherification via Photoredox/Ni Dual Catalysis Using Silicates for H-Atom Abstraction



Initial studies probing the amenability of thiols to this type of cross-coupling proved very fruitful. Using a slight excess of cyclohexanethiol (1.2 equiv) and isobutylsilicate **1b** (1.5 equiv), complete conversion of 4-bromobenzonitrile to its corresponding thioether **3f** was observed (Scheme 4). Other silicates were evaluated as H atom abstractors: 1° and 2° alkylsilicates [2 °C–H BDE (cyclohexane) = 95–100 kcal mol^{-1}][5a] facilitated facile thioetherification, whereas a benzyl silicate resulted exclusively in the C_{sp^3}–C_{sp^2} bond formation described previously (see Supporting Information).[4a,b] The stabilized nature of the benzyl radical (benzyl C_{sp^3}–H BDE = 89.8 kcal mol^{-1})[5b] likely renders the HAT pathway untenable (or at the very least reversible), obviating thioetherification. Although some thioetherification was observed, phenyl and methyl silicates were poor H atom abstractors because they produce highly promiscuous radicals that undergo unproductive radical quenching with themselves or the photocatalyst.[4a,b] Using a 1-hexadecylsilicate, the fate of the alkyl component was verified, as hexadecane was observed as a major reaction product. Control studies using cyclohexanethiol and 4-bromobenzonitrile further support the postulated

Scheme 4. Photoredox Thioetherification of 4-Bromobenzonitrile Using Various Thiols and Silicate 1b as a H-Atom Abstractor



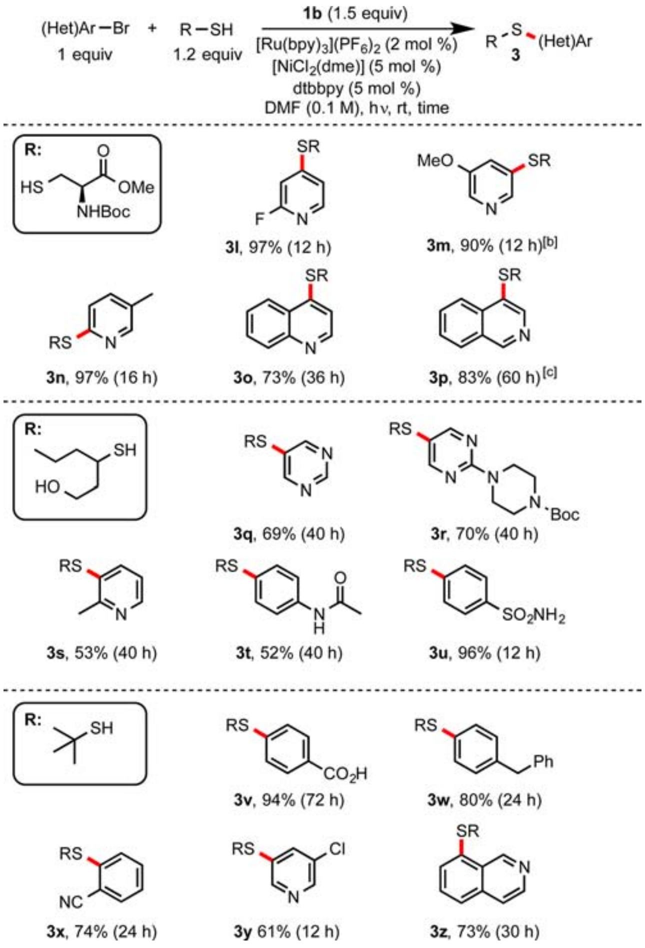
[a] Compound **3e** was prepared starting from cysteamine hydrochloride. [b] Reaction run on 5 mmol using blue LEDs; all other reactions run on a 0.5 mmol scale of 4-bromobenzonitrile.

mechanistic model; light, the Ru photocatalyst, and the Ni catalyst are all essential to accomplish thioetherification. However, in the absence of a ligand, no thioetherification was observed, unlike when employing alkythiolsilicate **1a**. Rather, formation of cyclohexyl disulfide was the observed outcome of the reaction. Taken together, these studies suggest that the pathway for thioetherification is mechanistically distinct from the one posited by Macmillan for Ni/photoredox etherification of aryl bromides.[6b]

The generality of this new thioetherification was next explored in the context of thiols with various steric and electronic environments (Scheme 4). Because of the inexpensive nature of the starting trimethoxysilane ($0.06/g for isobutyltrimethoxysilane) and volatility of isobutane, we selected silicate **1b** as the H atom abstractor for our studies. A range of thiols were compatible with the developed conditions for thioetherification. Both 1°, 2°, and even 3° alkyl thiols gave excellent yields of their corresponding thioethers, often in less than 24 h. Of note are thioethers **3d**, **3e**, **3g**, and **3h** that not only demonstrate the reaction's exceptional protic group tolerance but also the *selectivity* for thioetherification rather than etherification or amination. Also of note are the thioethers **3i**–**k** obtained from sterically congested thiols. Preparation of these sterically hindered thioethers is particularly challenging, and there is currently *no* mild method for their synthesis.[8,10] Although not the focus of this study, as we were interested in *alkyl* thiol functionalization, aryl thiols were not tolerated in this reaction manifold. Unlike their alkyl congeners, the observed reaction outcome for these systems was disulfide formation, as previously noted.[12] Finally, to gauge the amenability of thioetherification to scale-up, we prepared **3g** on a 5 mmol scale. Just as when using alkylthiolsilicate **1a**, conducting the reaction on a larger scale was not problematic and gave a good yield of the desired thioether **3g**.

The substrate-diversity of the reaction was further assessed via the coupling of three distinct thiols with various aryl and heteroaryl bromides (Scheme 5). The reaction proved to be quite general. Despite bearing protic moieties, both the methyl ester of (*R*)-Boc-cysteine and 3-mercaptohexan-1-ol reacted well with aryl and heteroaryl bromides (**3l**–**u**). The observed selectivity when using the latter hydroxyl-containing thiol is especially significant given that etherification might compete with thioetherification when using traditional Pd-based approaches.[7,8,13] The tolerance of a cysteine residue *and* the mild, selective nature of the described thioetherification reaction may be of interest to the medicinal and biochemical communities (e.g., for bioconjugation/protein modification or unnatural peptide synthesis).[14] Moreover, these systems demonstrate the advantage of using the mild conditions outlined here; attempts to use the aforementioned Pd-based approaches would likely lead to undesired side reactions (e.g., deprotection, etc.) and/or decomposition. The sterically encumbered 2-methyl-2-propanethiol reacted well with electron-poor (**3v** and **3x**) and electron-neutral (**3w**) arenes alike, as well as heteroarenes (**3y**–**z**). Acidic

Scheme 5. Photoredox Thioetherification Using Various Thiols and Aryl/Heteroaryl Bromides and Silicate 1b as a H-Atom Abstractor[a]



[a] Reactions performed on a 0.5 mmol scale of aryl/heteroaryl bromide unless otherwise noted. [b] Performed on 0.41 mmol scale. [c] Performed on 0.37 mmol scale.

moieties (e.g., the carboxyl group of **3v**) are, again, unaffected by thioetherification. Overall, the diversity of the thioetherifications using thiols matched the observed trends with alkylthiolsilicate **1a**.[15]

In summary, a mild, *S*-selective method for the thioetherification of aryl bromides using photoredox/Ni-dual catalysis is presented. Although alkylthiolsilicates can be used directly, the reaction scope was extended to include simple thiols by way of an intermolecular HAT pathway using alkylsilicates as H-atom abstractors. This base-free, room-temperature reaction tolerates a variety of aryl and heteroaryl bromides. Additionally, protic (even those containing acidic moieties) and sterically congested thiols were all competent toward thioetherification. The broad tolerance and mild nature of the described reaction could potentially be employed to prepare sulfides with biological relevance or for bioconjugation. Moreover, it provides unprecedented access to new chemical space for thioethers, unlocking their potential for examination by drug discovery groups or agroscience.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00208.

Experimental details and spectral characterization (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: gmolandr@sas.upenn.edu.

Author Contributions

†These authors contributed equally to this work.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Kingson Lin (University of Pennsylvania) for the preparation of alkylsilicates and Geraint H. M. Davies (University of Pennsylvania) for helpful discussions/technical assistance. We thank NIGMS (RO1 GM113878) for financial support of this research.

■ REFERENCES

(1) (a) Douglas, J. J.; Nguyen, J. D.; Cole, K. P.; Stephenson, C. R. J. *Aldrichimica Acta* **2014**, *47*, 15. (b) Tucker, J. W.; Stephenson, C. R. J. *J. Org. Chem.* **2012**, *77*, 1617. (c) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322. (d) Hopkinson, M. N.; Sahoo, B.; Li, J.-L.; Glorius, F. *Chem. - Eur. J.* **2014**, *20*, 3874.

(2) Seminal reports: (a) Tellis, J. C.; Primer, D. N.; Molander, G. A. *Science* **2014**, *345*, 433. (b) Zuo, Z. W.; Ahneman, D. T.; Chu, L. L.; Terrett, J. A.; Doyle, A. G.; MacMillan, D. W. C. *Science* **2014**, *345*, 437. (c) Kalyani, D.; McMurtrey, K. B.; Neufeldt, S. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 18566. (d) Ye, Y.; Sanford, M. S. *J. Am. Chem. Soc.* **2012**, *134*, 9034. (e) Sahoo, B.; Hopkinson, M. N.; Glorius, F. *J. Am. Chem. Soc.* **2013**, *135*, 5505.

(3) Recent work in photoredox dual catalysis: (a) Primer, D. N.; Karakaya, I.; Tellis, J. C.; Molander, G. A. *J. Am. Chem. Soc.* **2015**, *137*, 2195. (b) Karakaya, I.; Primer, D. N.; Molander, G. A. *Org. Lett.* **2015**, *17*, 3294. (c) El Khatib, M.; Serafim, R. A. M.; Molander, G. A. *Angew. Chem., Int. Ed.* **2016**, *55*, 254. (d) Rueping, M.; Koenigs, R. M.; Poscharny, K.; Fabry, D. C.; Leonori, D.; Vila, C. *Chem. - Eur. J.* **2012**, *18*, 5170. (e) Shu, X. Z.; Zhang, M.; He, Y.; Frei, H.; Toste, F. D. *J. Am. Chem. Soc.* **2014**, *136*, 5844. (f) Noble, A.; McCarver, S. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2015**, *137*, 624. (g) Chu, L.; Lipshultz, J. M.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2015**, *54*, 7929. (h) Le, C. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2015**, *137*, 11938.

(4) (a) Jouffroy, M.; Primer, D. N.; Molander, G. A. *J. Am. Chem. Soc.* **2016**, *138*, 475. (b) Corce, V.; Chamoreau, L.-M.; Derat, E.; Goddard, J.-P.; Ollivier, C.; Fensterbank, L. *Angew. Chem., Int. Ed.* **2015**, *54*, 11414. (c) Matsuoka, D.; Nishigaichi, Y. *Chem. Lett.* **2014**, *43*, 559. (d) Matsuoka, D.; Nishigaichi, Y. *Chem. Lett.* **2015**, *44*, 163.

(5) (a) Tian, Z.; Fattahi, A.; Lis, L.; Kass, S. R. *J. Am. Chem. Soc.* **2006**, *128*, 17087. (b) Blanksby, S. J.; Ellison, G. B. *Acc. Chem. Res.* **2003**, *36*, 255. (c) Huston, P.; Espenson, J. H.; Bakac, A. *J. Am. Chem. Soc.* **1992**, *114*, 9510. (d) Review on thiyl radicals: Denes, F.; Pichowicz, M.; Povie, G.; Renaud, P. *Chem. Rev.* **2014**, *114*, 2587.

(6) (a) Tasker, S. Z.; Jamison, T. F. *J. Am. Chem. Soc.* **2015**, *137*, 9531. (b) Terrett, J. A.; Cuthbertson, J. D.; Shurtleff, V. W.; MacMillan, D. W. C. *Nature* **2015**, *524*, 330. (c) He, Y.; Wu, H.; Toste, F. D. *Chem. Sci.* **2015**, *6*, 1194. (d) Xuan, J.; Zeng, T.-T.; Chen, J.-T.; Lu, L.-Q.; Xiao, W. J. *Chem. - Eur. J.* **2015**, *21*, 4962.

(7) Beletskaya, I. P.; Ananikov, V. P. *Chem. Rev.* **2011**, *111*, 1596.

(8) (a) Fernández-Rodríguez, M. A.; Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 2180. (b) Fernández-Rodríguez, M. A.; Hartwig, J. F. *J. Org. Chem.* **2009**, *74*, 1663. (c) Hartwig, J. F. *Acc. Chem. Res.* **2008**, *41*, 1534.

(9) Formation of dinuclear Ni-complexes having bridged thiolate ligands, which would be mitigated when using dtbbpy, might explain this observation. See: Louie, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 11598.

(10) (a) Peach, M. E. In *The Chemistry of the Thiol Group*; Patai, S., Ed.; John Wiley & Sons: London, 1974; pp 721−784. (b) Yin, J.; Pidgeon, C. *Tetrahedron Lett.* **1997**, *38*, 5953. (c) Beletskaya, I. P.; Ananikov, D. P. *Chem. Rev.* **2011**, *111*, 1596. (d) Eichman, C. C.; Stambuli, J. P. *Molecules* **2011**, *16*, 590. (e) Bichler, P.; Love, J. A. *Top. Organomet. Chem.* **2010**, *31*, 39. (f) Kondo, T.; Mitsudo, T. *Chem. Rev.* **2000**, *100*, 3205.

(11) Alternatively, oxidative addition may precede thiyl radical metalation, but would still lead to a closed cycle; for a detailed mechanistic analysis of photoredox/Ni dual catalysis. See: Gutierrez, O.; Tellis, J. C.; Primer, D. N.; Molander, G. A.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2015**, *137*, 4896.

(12) Straathof, N. J. W.; Tegelbeckers, B. J. P.; Hessel, V.; Wang, X.; Noël, T. *Chem. Sci.* **2014**, *5*, 4768.

(13) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046.

(14) Vinogradova, E. V.; Zhang, C.; Spokoyny, A. M.; Pentelute, B. L.; Buchwald, S. L. *Nature* **2015**, *526*, 687.

(15) Although not explicitly shown in Scheme 5, attempts to employ electron-rich aryl bromides with these three thiols were not met with success.