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Radical/Polar Annulation Reactions (RPARs) Enable the Modular Construction of Cyclopropanes

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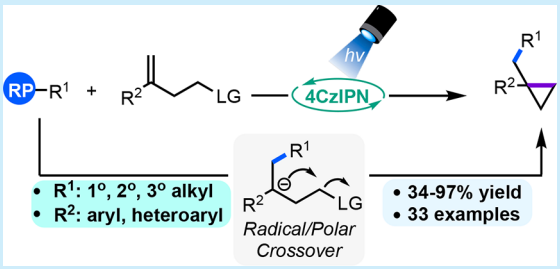
Supporting Information

ABSTRACT: An annulation process for the construction of 1,1-disubstituted cyclopropanes via a radical/polar crossover process is described. The cyclopropanation proceeds by the addition of a photocatalytically generated radical to a homoallylic tosylate. Reduction of the intermediate radical alkylation adduct (via single electron transfer) furnishes an anion that undergoes an intramolecular substitution. The process displays excellent functional group tolerance, characteristic of proceeding through odd-electron intermediates, and occurs under mild conditions with visible light irradiation.



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Annulation reactions are prized for their ability to increase molecular complexity rapidly.[1] The synthetic importance of cyclization reactions is additionally driven by the broad applicability of carbocyclic rings in fields such as medicinal chemistry, where structural rigidity (particularly in three- and four-membered rings) can impart unique binding and metabolic properties (Figure 1).[2] The crux of annulation from a synthetic standpoint, specifically for carbocyclic rings, is forging C−C bonds. Although this is typically accomplished through pericyclic processes[3] or anionic cyclizations,[4] numerous ring-closing radical cyclizations have been developed, most of which are mediated by stoichiometric Bu_3SnH or similar halogen abstractors.[5]

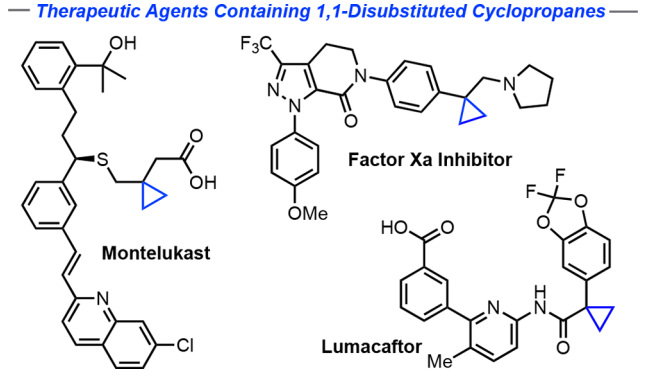

Figure 1. Examples of therapeutic agents containing a 1,1-disubstituted cyclopropane unit.

The revival of visible-light photoredox catalysis has resulted in the discovery of novel single-electron processes that, in contrast to traditional stoichiometric radical generation methods, are facilitated by selective and sequential photocatalytic oxidization/reduction events.[6] This paradigm enables reactive odd-electron species to be catalytically generated under mild conditions, providing access to previously challenging modes of single electron reactivity with broad functional group tolerance. Indeed, an array of novel "single-electron" paradigms for cross-coupling,[7] cycloaddition,[8] and radical/polar crossover processes have been developed in recent years.[9] With such a rapid influx of new synthetic strategies, it comes as no surprise that photoredox catalysis is quickly being adopted in both the academic and industrial sectors to overcome the challenges associated with two-electron processes in complex molecule synthesis.[10]

To facilitate implementation of the rapidly expanding toolbox of photoredox reactivity, we and others have developed various radical feedstocks [e.g., organotrifluoroborates, carboxylic acids, bis(catecholato)silicates, 4-alkyl dihydropyridines] that provide a palette of potential C−C bond connections through alkyl cross-coupling.[7,11] The innate functional group tolerance of odd electron carbon nucleophiles enables these precursors to be used in the presence of functional groups typically not tolerated by two-electron pathways. However, realizing that the chemistry of many of

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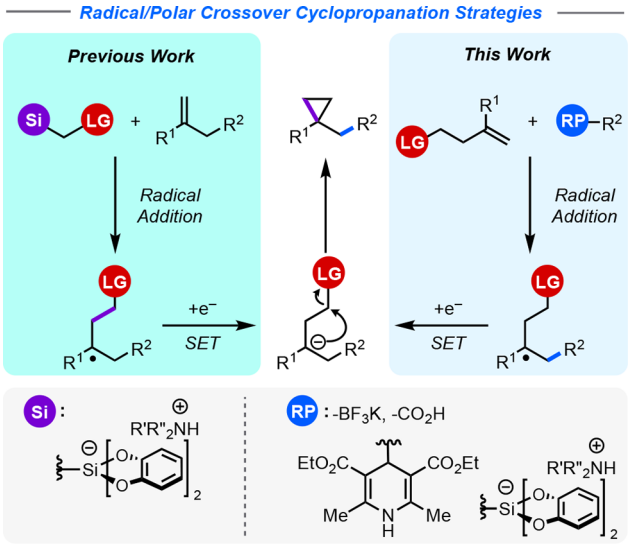
these feedstocks was poorly explored within other radical-based manifolds, we initiated a program to apply them in radical/polar crossover processes that lead to carbocyclic ring structures. Recent investigations along these lines have yielded a mechanistically distinct cyclopropanation method that proceeds via a photocatalytically generated halomethyl radical (Scheme 1, *Previous Work*).[12] Computational analysis and

Scheme 1. Comparison of Cyclopropanation Strategies and Implications of the Envisioned Approach



experimental evidence revealed that Giese-type addition of this halomethyl radical to an olefin is followed by single electron transfer (SET) from the photocatalyst, which converts the resulting radical adduct to an anion that undergoes anionic 3-*exo-tet* ring closure.

In considering the mechanism of this process, we realized that a more general strategy for cyclopropanation may exist. That is, if the electrophilic component was built into the olefin-containing species, *any* photocatalytically generated radical may be able to induce cyclization upon radical addition and single-electron reduction (Scheme 1). This approach would be conceptually related to Michael addition-mediated anionic cyclization,[13] but with distinctly greater tolerance of structural diversity in the nucleophilic partner and without the need for a strongly polarized olefin such as an enone or acrylate. Although canonical cyclopropanation strategies such as the Simmons–Smith reaction[14] have been used to access similar cyclopropane structures, the photocatalytic method envisioned would allow a modular assembly of diverse 1,1-disubstituted cyclopropane derivatives without the need to prepare an array of alkene or carbene precursors. Additionally, the size and substitution patterns of the carbocyclic ring can potentially be modulated by modifying the substrate prior to annulation. Collectively, these advantages poise radical/polar annulation reactions (RPARs) to be a powerful approach to carbocyclic ring construction via carbodifunctionalization of olefins.[15]

Exploration of this process began with an examination of tosylate **1** as a model system for RPAR-type reactivity. Substrates of this class can be readily prepared in two steps from commercially available materials [see Supporting Information (SI)]. Although the iodide analog of **1** also showed effective annulation reactivity, the tosylate leaving group was preferred because (1) the tosylate is more reactive in substitution processes than the iodide;[16] (2) the unlikelihood of tosylates to engage in S_H2-type processes would ensure that cyclization would occur by an anionic pathway;[17] (3) aryl sulfonate esters have tunable reactivity; and (4) sulfonate esters are generally less light-sensitive than alkyl halides.

The conditions previously established for our aforementioned cyclopropanation process[12a] were adapted with styrene **1** and diisopropylammonium bis(catecholato)(3-acetoxypropyl)silicate to develop this new cyclopropanation reaction. High-throughput screening experiments revealed that polar, aprotic solvents are optimal, with DMSO being the best of the solvents investigated (Table 1, entries 1, 6–9).

Table 1. Screening of Conditions for the Cyclopropanation Process

entry[a]	deviation from standard conditions	yield (%)[b,c]
1	none	87 (74)
2	under air	44
3	$[Ir\{dF(CF_3)ppy\}_2(bpy)]PF_6$ (5 mol %)	94
4	$[Ru(bpy)_3](PF_6)_2$ (5 mol %)	88
5	$MesAcr^+$ (5 mol %)	0
6	DMF (0.05 M)	50
7	dioxane (0.05 M)	4
8	MeCN (0.05 M)	3
9	$PhCF_3$ (0.05 M)	0
10	DMSO (0.10 M)	83
11	DMSO (0.025 M)	81
11	no photocatalyst	0
12	no light	0
13	MsO instead of TsO	(66)

[a]Unless otherwise noted, reactions were run using alkene **1** (0.025 mmol, 1 equiv), diisopropylammonium bis(catecholato)(3-acetoxypropyl)silicate (0.038 mmol, 1.5 equiv), 4CzIPN (0.0013 mmol, 5 mol %), and DMSO (0.5 mL, 0.05 M). [b]Yield determined by UPLC using 4,4′-dimethylbiphenyl as a standard. [c]Isolated yield in parentheses.

Photocatalyst variation revealed that either 4CzIPN or Ir- or Ru-based photocatalysts were effective (entries 1, 3, 4). Importantly, the former organic dye can be prepared at a significantly lower cost and therefore was favored. Reaction concentration proved to be critical. Decreasing the concentration to 0.05 M improved the isolated yield, likely by reducing the rate of competitive polymerization of the styryl radical intermediate (compare entries 1, 10, and 11). A "zero-precautions" reaction demonstrated that the described process is rather robust; conducting the reaction with an air atmosphere and nonrigorously dried DMSO still afforded the product, albeit in reduced yield (entry 2). Control studies confirmed that this was indeed a photocatalytic process; both light and the photocatalyst were necessary for reactivity (entries 11–12). The mesylate analog of **1** also underwent cyclization in comparable (66%) isolated yield and can presumably be used interchangeably with the tosylate derivative (entry 13).

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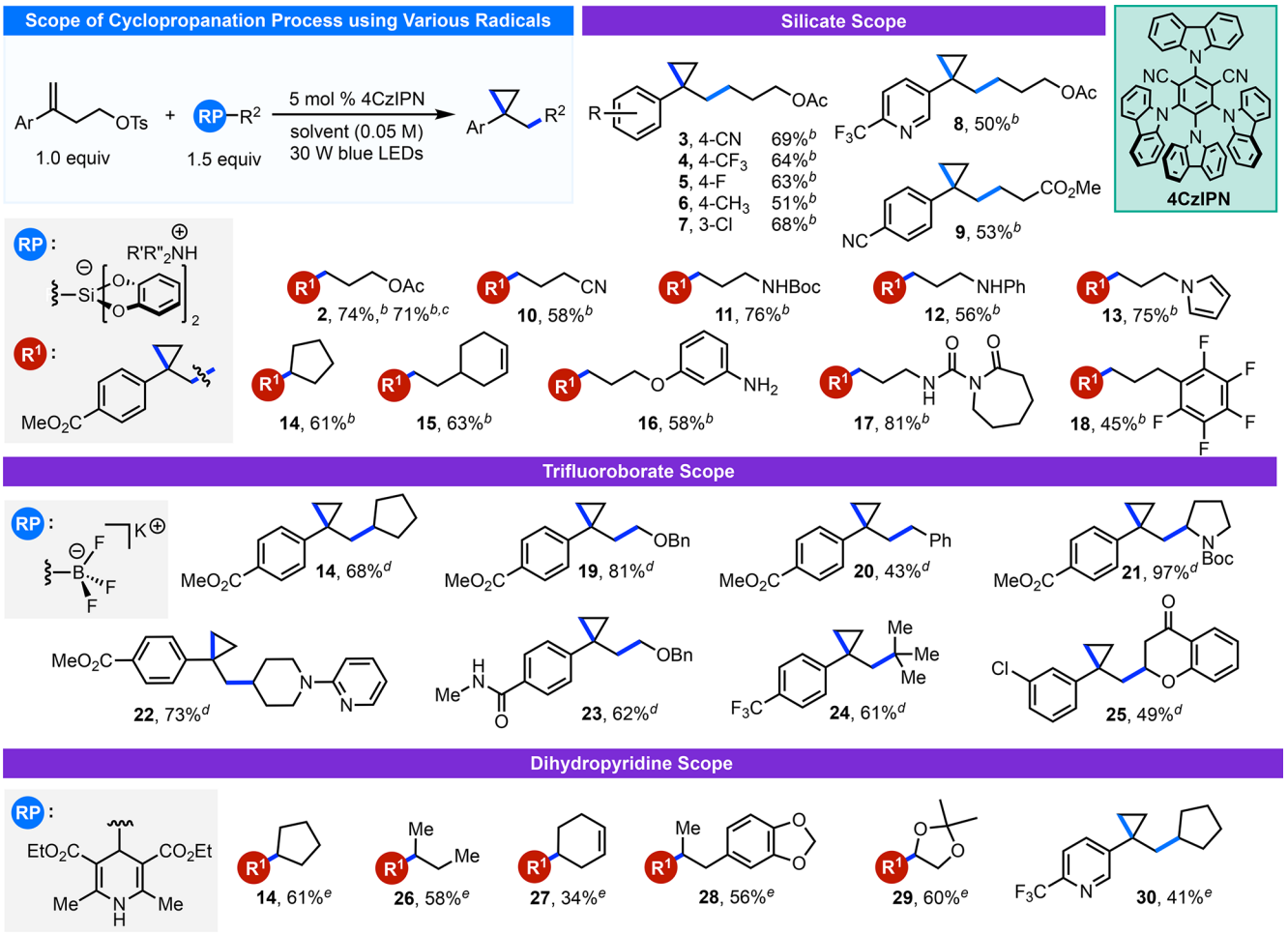
Scheme 2. Scope of the Annulative Process via Radical/Polar Crossover[a]



[a]Unless otherwise noted, the reactions were carried out on a 0.3 mmol scale at 35 °C; isolated yields after purification. [b]Reaction carried out in DMSO for 2 h. [c]Reaction conducted on 1 mmol scale. [d]Reaction carried out in DMSO for 16 h. [e]Reaction carried out in DMA for 4 h.

The generality of the cyclopropantion process was assessed on a series of 1,1-disubstituted alkenes. Overall, radical alkylation/cyclization proceeded smoothly across an array of different styryl systems, faring best with electron-deficient arenes. In contrast, 1,1-dialkyl olefins did not react with the radical species, an observation that is consistent with our previous studies.[12a] The reaction nonetheless permits the installation of an array of functionalized alkyl fragments onto the styrene precursor. Alkylsilicates are ideal for generating primary, nonstabilized alkyl radical partners for this cyclopropanation because of their low, relatively uniform redox potentials.[11a]

The breadth of silicate reagents employed demonstrates that RPAR cyclopropanation tolerates traditionally electrophilic subunits both on the arene and on the radical itself. These moieties can be readily diversified through classical two-electron processes (e.g., hydrolysis of **2** or acylation of **16**). In addition, this cyclization strategy is insensitive to the presence of protic groups (**11**, **16**, **17**) and demonstrates olefin selectivity (**15**) (Scheme 2). The rather general nature of this process can likely be attributed to the mild conditions under which RPAR occurs (room temperature, near-neutral pH, and absence of any additives) in addition to the general benefits associated with odd-electron intermediates.[7]

A UPLC-based robustness screen[18] confirmed that the representative RPAR cyclopropanation of tosylate **1** to afford cyclopropane **2** can be carried out in the presence of a variety of additives containing functional groups such as unprotected phenols and alcohols. Lewis basic heterocycles and free amines, which are incompatible with the electrophilic carbenoid species used in the Simmons–Smith cyclopropanation,[14] are also tolerated (see the SI for details on this screen).

Given that the success of RPAR cyclopropanation should be independent of the radical source, the transformation was conducted with other classes of radical precursors. In doing so, radicals with a range of stereoelectronic environments and whose corresponding silicates would be challenging to prepare were incorporated. Potassium alkyltrifluoroborates, for example, served as competent precursors in the cyclopropanation. Secondary, tertiary, benzylic, and α-heteroatom C-centered radicals were generated from their corresponding trifluoroborate reagents and engaged in the cyclopropanation. The radical structure appeared to have minimal effect on the reaction success and allowed an array of motifs to be incorporated. For example, chromanone **25** demonstrates the potential of RPAR to construct cyclopropanes containing medicinally relevant fragments. 4-Alkyldihydropyridines (DHPs), a class of radical precursors that are readily prepared from the corresponding aldehydes,[11b] showed similar trends in reactivity.

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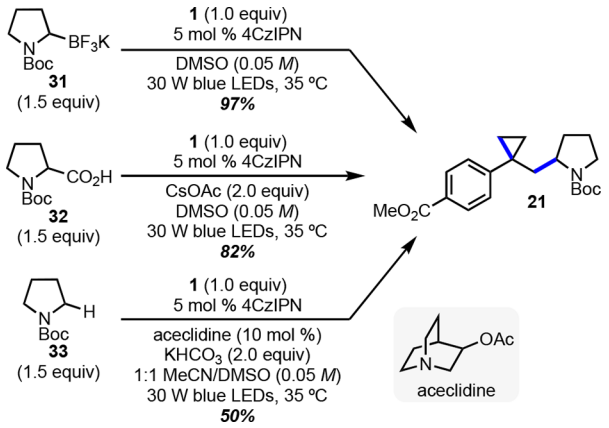
The cyclopropanation process is consistent across the various radical precursors. Cyclopentylmethyl cyclopropane **14**, for example, was obtained from cyclopentylsilicate, -trifluoroborate, and -dihydropyridine radical precursors in very similar yields (61%, 68%, and 61%, respectively). Pyrrolidine **21** was also prepared from either the corresponding trifluoroborate or by decarboxylative fragmentation of Boc-proline[7b] in high yield (Scheme 3). In addition, pyrrolidine **33**

Scheme 3. Synthesis of Pyrrolidine 21 from Various Radical Precursors



was activated using H-atom transfer (HAT) chemistry to form a stabilized α-amino radical,[19] which successfully underwent cyclopropanation. Aside from demonstrating the fidelity of RPAR cyclization toward *C*-centered radicals, the versatility of this process suggests that it may be amenable toward merger with catalytic processes beyond those examined here.

Regardless of the origin of the radical, we suggest the following sequence of mechanistic events for the cyclopropanation process: (1) visible light-mediated photoexcitation of 4CzIPN **I** to its excited state **II**; (2) reductive quenching of **II** by any of the radical precursors **IV** whose oxidation potentials fall below that of 4CzIPN ($E_{1/2}$ [PC*/PC]: 1.35 V vs SCE[20]); (3) after homolytic fragmentation of the precursor, Giese-type addition by an alkyl radical **V** into the olefin to generate **VI**; (4) SET reduction of **VI** by the reduced state of 4CzIPN **III**; (5) anionic cyclization resulting in assembly of the carbocyclic ring by displacement of the sulfonate ester (Figure 2). To aid in a clearer mechanistic understanding, the role of arene electronics was probed

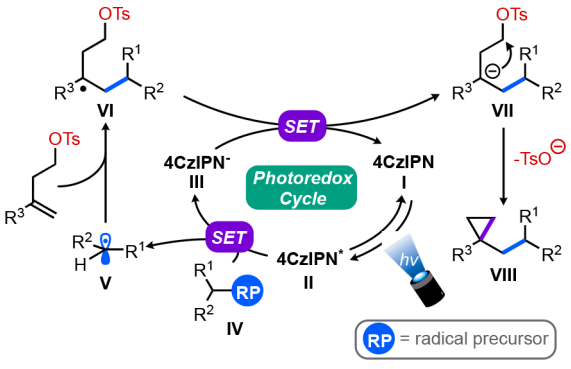


Figure 2. Proposed mechanistic pathway for the described annulation process.

through a competition study. Several analogs of tosylate **1** bearing either π- or σ-electron-withdrawing groups were subjected to the reaction conditions, and UPLC analyses were conducted during the initial period of the reaction (~10 min; see SI for data). These studies suggested that the electron-deficient arene promotes the overall transformation. This could be due to either accelerating the initial Giese-type addition or by stabilizing the transient anion intermediate **VII**. More comprehensive computational studies of these particular mechanistic aspects are ongoing.

The method described herein allows the rapid and efficient assembly of a diverse array of 1,1-disubstituted cyclopropanes from readily accessible homoallylic tosylates and various radical precursors. This modular process is compatible with an array of stereoelectronically distinct radicals and tolerates a variety of functional groups. Further applications of RPAR reactivity for the preparation of more diverse and highly substituted carbocyclic rings are underway and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02968.

Experimental procedures, details regarding mechanistic experiments and high-throughput screening, and ^{1}H, ^{13}C, and ^{19}F NMR spectra for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Ma, S. *Handbook of Cyclization Reactions*, 1st ed.; Wiley-VCH: Weinheim, 2009. (b) Molander, G. A. Diverse Methods for Medium Ring Synthesis. *Acc. Chem. Res.* **1998**, *31*, 603.

(2) (a) Talele, T. T. The "Cyclopropyl Fragment" is a Versatile Player that Frequently Appears in Preclinical/Clinical Drug Molecules. *J. Med. Chem.* **2016**, *59*, 8712. (b) Taylor, R. D.; MacCoss, M.; Lawson, A. D. G. Rings in Drugs. *J. Med. Chem.* **2014**,

DOI: 10.1021/acs.orglett.8b02968
Org. Lett. XXXX, XXX, XXX−XXX

57, 5845. (c) Chen, D. Y.-K.; Pouwer, R. H.; Richard, J.-A. Recent advances in the total synthesis of cyclopropane-containing natural products. *Chem. Soc. Rev.* **2012**, *41*, 4631. (d) Hansen, T. V.; Stenstrøm, Y. Naturally Occurring Cyclobutanes. In *Organic Synthesis: Theory and Applications*; Hudlicky, T., Ed.; Elsevier: Oxford, U.K., 2001; Vol. 5, pp 1−38.

(3) (a) Funel, J. A.; Abele, S. Industrial Applications of the Diels−Alder Reaction. *Angew. Chem., Int. Ed.* **2013**, *52*, 3822. (b) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. The Diels−Alder Reaction in Total Synthesis. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668. (c) Remy, R.; Bochet, C. G. Arene−Alkene Cycloaddition. *Chem. Rev.* **2016**, *116*, 9816. (d) Jones, A. C.; May, J. A.; Sarpong, R.; Stoltz, B. M. Toward a Symphony of Reactivity: Cascades Involving Catalysis and Sigmatropic Rearrangements. *Angew. Chem., Int. Ed.* **2014**, *53*, 2556.

(4) Mal, D. *Anionic Annulations in Organic Synthesis: A Versatile and Prolific Class of Ring-Forming Reactions*, 1st ed.; Elsevier Science: USA, 2018.

(5) (a) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. Radical reactions in natural product synthesis. *Chem. Rev.* **1991**, *91*, 1237. (b) Giese, B.; Kopping, B.; Göbel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. Radical Cyclization Reactions. *Org. React.* **1996**, *48*, 301. (c) Romero, K. J.; Galliher, M. S.; Pratt, D. A.; Stephenson, C. R. J. Radicals in natural product synthesis *Chem. Soc. Rev.*, **2018** Advance article, DOI: 10.1039/C8CS00379C.

(6) For reviews on photoredox catalysis, see: (a) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. Visible Light Photoredox Catalysis with Transition Metal Complexes: Applications in Organic Synthesis. *Chem. Rev.* **2013**, *113*, 5322. (b) Romero, N. A.; Nicewicz, D. A. Organic Photoredox Catalysis. *Chem. Rev.* **2016**, *116*, 10075. (c) Matsui, J. K.; Lang, S. B.; Heitz, D. R.; Molander, G. A. Photoredox-Mediated Routes to Radicals: The Value of Catalytic Radical Generation in Synthetic Methods Development. *ACS Catal.* **2017**, *7*, 2563. (d) Shaw, M. H.; Twilton, J.; MacMillan, D. W. C. Photoredox Catalysis in Organic Chemistry. *J. Org. Chem.* **2016**, *81*, 6898.

(7) For seminal reports, see: (a) Tellis, J. C.; Primer, D. N.; Molander, G. A. Single-electron transmetalation in organoboron cross-coupling by photoredox/nickel dual catalysis. *Science* **2014**, *345*, 433. (b) Zuo, Z.; Ahneman, D. T.; Chu, L.; Terrett, J. A.; Doyle, A. G.; MacMillan, D. W. C. Merging photoredox with nickel catalysis: Coupling of α-carboxyl sp3-carbons with aryl halides. *Science* **2014**, *345*, 437. For reviews, see: (c) Tellis, J. C.; Kelly, C. B.; Primer, D. N.; Jouffroy, M.; Patel, N. R.; Molander, G. A. Single-Electron Transmetalation via Photoredox/Nickel Dual Catalysis: Unlocking a New Paradigm for sp^3−sp^2 Cross-Coupling. *Acc. Chem. Res.* **2016**, *49*, 1429. (d) Skubi, K. L.; Blum, T. R.; Yoon, T. P. Dual Catalysis Strategies in Photochemical Synthesis. *Chem. Rev.* **2016**, *116*, 10035. (e) Gui, Y.-Y.; Sun, L.; Lu, Z.-P.; Yu, D.-G. Photoredox sheds new light on nickel catalysis: from carbon−carbon to carbon−heteroatom bond formation. *Org. Chem. Front.* **2016**, *3*, 522.

(8) Yoon, T. P. Visible Light Photocatalysis: The Development of Photocatalytic Radical Ion Cycloadditions. *ACS Catal.* **2013**, *3*, 895.

(9) For examples, see: (a) Lang, S. B.; Wiles, R. J.; Kelly, C. B.; Molander, G. A. Photoredox Generation of Carbon-Centered Radicals Enables the Construction of 1,1-Difluoroalkene Carbonyl Mimics. *Angew. Chem., Int. Ed.* **2017**, *56*, 15073. (b) Kischkewitz, M.; Okamoto, K.; Muck-Lichtenfeld, C.; Studer, A. *Science* **2017**, *355*, 936−938. (c) Koike, T.; Akita, M. *Acc. Chem. Res.* **2016**, *49*, 1937−1945.

(10) (a) Zhang, R.; Li, G.; Wismer, M.; Vachal, P.; Colletti, S. L.; Shi, Z.-C. Profiling and Application of Photoredox $C(sp^3)$−$C(sp^2)$ Cross-Coupling in Medicinal Chemistry. *ACS Med. Chem. Lett.* **2018**, *9*, 773. (b) Douglas, J. J.; Sevrin, M. J.; Stephenson, C. R. J. Visible Light Photocatalysis: Applications and New Disconnections in the Synthesis of Pharmaceutical Agents. *Org. Process Res. Dev.* **2016**, *20*, 1134. (c) König, B. Photocatalysis in Organic Synthesis − Past, Present, and Future. *Eur. J. Org. Chem.* **2017**, *2017*, 1979.

(11) (a) Jouffroy, M.; Primer, D. N.; Molander, G. A. Base-Free Photoredox/Nickel Dual Catalytic Cross-Coupling of Ammonium Alkylsilicates. *J. Am. Chem. Soc.* **2016**, *138*, 475−478. (b) Gutierrez-Bonet, A.; Tellis, J. C.; Matsui, J. K.; Vara, B. A.; Molander, G. A. 1,4-Dihydropyridines as Alkyl Radical Precursors: Introducing the Aldehyde Feedstock to Nickel/Photoredox Dual Catalysis. *ACS Catal.* **2016**, *6*, 8004−8008.

(12) (a) Phelan, J. P.; Lang, S. B.; Compton, J. S.; Kelly, C. B.; Dykstra, R.; Gutierrez, O.; Molander, G. A. Redox-Neutral Photocatalytic Cyclopropanation via Radical/Polar Crossover. *J. Am. Chem. Soc.* **2018**, *140*, 8037. (b) Guo, T.; Zhang, L.; Liu, X.; Fang, Y.; Jin, X.; Yang, Y.; Li, Y.; Chen, B.; Ouyang, M. *Adv. Synth. Catal.* **2018**, DOI: 10.1002/adsc.201800761.

(13) For examples of this type of ring closure in cyclopropane synthesis, see: (a) Lachia, M.; Iriart, S.; Baalouch, M.; De Mesmaeker, A.; Beaudegnies, R. Ethyl-2-(2-chloroethyl)acrylate: a new very versatile a-cyclopropylester cation synthon. *Tetrahedron Lett.* **2011**, *52*, 3219−3222. (b) Lebel, H.; Marcoux, J.-M.; Molinaro, C.; Charette, A. B. Stereoselective Cyclopropanation Reactions. *Chem. Rev.* **2003**, *103*, 977. (c) Little, R. D.; Dawson, J. R. MIRC (Michael Initiated Ring Closure) Reactions Formation of Three, Five, Six and Seven Membered Rings. *Tetrahedron Lett.* **1980**, *21*, 2609.

(14) Charette, A. B.; Beauchemin, A. Simmons-Smith Cyclopropanation Reaction. *Org. React.* **2001**, *58*, 1−395.

(15) During the preparation of this manuscript, a report was disclosed verifying the feasibility of this approach with carboxylic acid radical precursors. See: Shu, C.; Mega, R. S.; Andreassen, B. J.; Noble, A.; Aggarwal, V. K. Synthesis of Functionalized Cyclopropanes from Carboxylic Acids via a Radical Addition-Polar Cyclization Cascade. *Angew. Chem., Int. Ed.* **2018**, DOI: 10.1002/anie.201808598.

(16) Lepore, S. D.; Mondal, D. Recent advances in heterolytic nucleofugal leaving groups. *Tetrahedron* **2007**, *63*, 5103.

(17) C−O bonds generally are ∼85 kcal/mol whereas the C−I bonds are typically only ∼57 kcal/mol for Csp^3 centers, making them homolytically much weaker. See: Blanksby, S. J.; Ellison, G. B. Bond Dissociation Energies of Organic Molecules. *Acc. Chem. Res.* **2003**, *36*, 255.

(18) Collins, K. D.; Glorius, F. A robustness screen for the rapid assessment of chemical reactions. *Nat. Chem.* **2013**, *5*, 597.

(19) Capaldo, L.; Ravelli, D. Hydrogen Atom Transfer (HAT): A Versatile Strategy for Substrate Activation in Photocatalyzed Organic Synthesis. *Eur. J. Org. Chem.* **2017**, *2017*, 2056.

(20) Luo, J.; Zhang, J. Donor-Acceptor Fluorophores for Visible-Light-Promoted Organic Synthesis: Photoredox/Ni Dual Catalytic $C(sp^3)$-$C(sp^2)$ Cross-Coupling. *ACS Catal.* **2016**, *6*, 873−877.

DOI: 10.1021/acs.orglett.8b02968
Org. Lett. XXXX, XXX, XXX−XXX