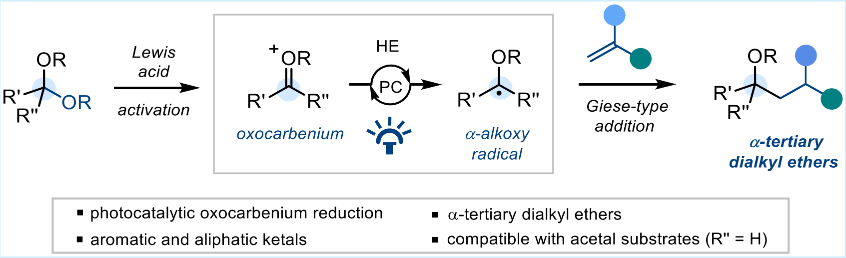
OL Organic Letters
Letter
Cite This: *Org. Lett.* XXXX, XXX, XXX−XXX
pubs.acs.org/OrgLett

Photocatalytic Reductive Formation of α-Tertiary Ethers from Ketals

Thomas Rossolini,[†] Branislav Ferko,[†,‡] and Darren J. Dixon*[,†]

[†]Department of Chemistry, University of Oxford, Chemistry Research Laboratory, 12 Mansfield Road, Oxford OX1 3TA, U.K.
[‡]Department of Organic Chemistry, Slovak University of Technology, Radlinského 9, 81237 Bratislava, Slovakia

Supporting Information



- photocatalytic oxocarbenium reduction
- aromatic and aliphatic ketals
- α-tertiary dialkyl ethers
- compatible with acetal substrates (R'' = H)

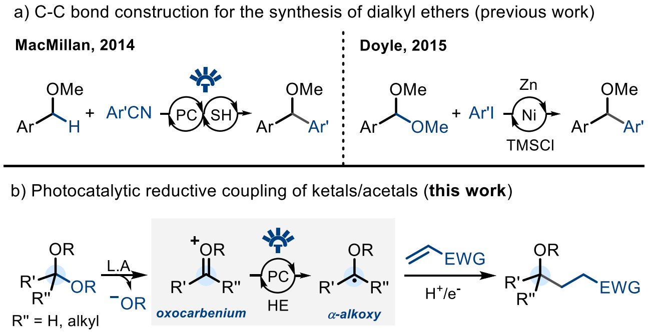
ABSTRACT: A general photocatalytic reductive strategy for the construction of unsymmetrical α-tertiary dialkyl ethers is reported. By merging Lewis acid-mediated ketal activation and visible-light photocatalytic reduction, in situ-generated α-alkoxy radicals were found to engage in addition reactions with a variety of olefinic partners. Good reaction efficiency is demonstrated with a range of ketals of aromatic and aliphatic ketones. Extension to acetal substrates is also described, demonstrating the overall synthetic utility of this methodology for complex ether synthesis.

Despite the widespread relevance of dialkyl ethers in pharmaceuticals and bioactive compounds,[1] several challenges in accessing this structural unit remain. Approaches based upon the formation of the corresponding $C(sp^3)$−O bond, such as classical Williamson ether synthesis, are widely employed to access simple ethers but are far from general for more complex systems.[2] To this end, a number of key advances exploiting bespoke reagents[3] and the intrinsic reactivity of various coupling partners[4] have been made in recent times, leading to new valuable C−C bond disconnections for ether construction.

Significant efforts in photoredox catalysis have offered mild and unique approaches for new reaction discovery via in situ generation of free radical species that can partake in radical coupling or transition metal-catalyzed cross-coupling processes.[5] In the context of ether synthesis, MacMillan and coworkers have reported an elegant synthetic procedure for the generation of benzhydryl ethers exploiting a dual photoredox/organocatalytic strategy via C−H atom abstraction, utilizing cyanoarenes as coupling partners (Scheme 1a).[6]

More recently, the Doyle group has reported a powerful method for forming similar products via a nickel-catalyzed reductive cross-coupling from acetals of aromatic aldehydes (Scheme 1a).[7] Although the chemistries described above have advanced carbon−carbon bond-forming ether syntheses,[8] new and general synthetic approaches for accessing α-tertiary alkyl ethers remain desirable. To this end, and in an effort to expand the synthetic range of photocatalytic umpolung chemistry,[9] we sought to explore alternative and common functional groups to engage in radical coupling reactions.[10] We envisaged that ketal activation with a Lewis acid[7,11] followed by visible-light-mediated single-electron transfer (SET) to the resulting oxocarbenium ion could deliver a putative nucleophilic α-alkoxy radical intermediate, which could participate in radical addition chemistry (Scheme 1b). If successful, this mild generation and controlled coupling of the α-alkoxy radical could provide direct access to α-tertiary ethers in one step from readily available starting materials.

Scheme 1. (a) Reported Methods for the Synthesis of Aialkyl Ethers and (b) Visible-Light-Mediated Direct Strategy toward the Formation of α-Tertiary Dialkyl Ethers from Ketals

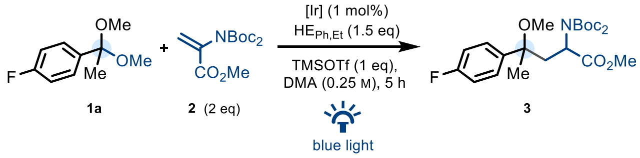


Preliminary evaluation of the proposed photocatalytic reductive coupling process was carried out with 4′-fluoroacetophenone dimethyl ketal (**1a**), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$, and dehydroalanine (DHA) derivative **2** as a coupling partner[10d,12] (Scheme 2). Initial feasibility studies

Received: July 2, 2019

DOI: 10.1021/acs.orglett.9b02273

Scheme 2. Reaction Optimization



Entry	Deviations from above	3 (%)[a]
1	none	78 (66)[b]
2	0.2 M in DMA	65
3	0.2 M in DMSO	56
4	4-CzIPN instead of [Ir]	71
5	$[Ir(dFppy)_2(dtbbpy)]PF_6$ instead of [Ir]	75
6[c]	TMSCl instead of TMSOTf	trace
7[c]	$BF_3{\bullet}OEt_2$ instead of TMSOTf	trace

a: ^{1}H NMR yield based on 1,3,5-trimethoxybenzene as internal standard. b: Isolated yield. c: 0.2 M in DMSO. [Ir] = $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$, $HE_{Ph,Et}$ = diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate, DMA = *N*,*N*-dimethylacetamide.

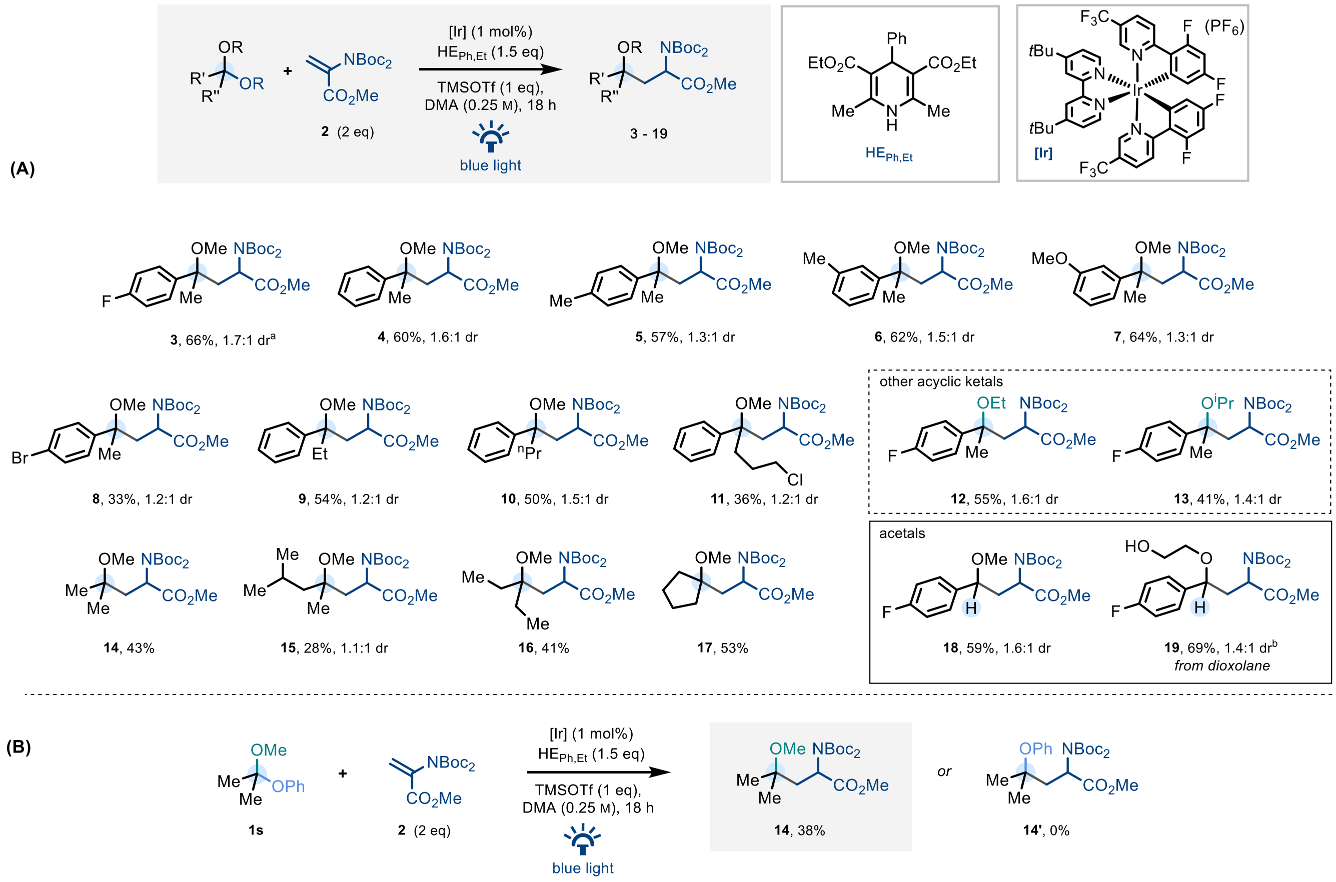
followed by reaction optimization elucidated that irradiation under blue light-emitting diode light in DMA, with trimethylsilyl trifluoromethanesulfonate (TMSOTf) as the Lewis acid and 4-phenyl Hantzsch ester ($HE_{Ph,Et}$) as the stoichiometric reductant, provided the desired tertiary methyl ether **3** in an optimal 78% NMR yield (entry 1).

Observations made during reaction optimization revealed the importance of concentration and solvent selection on reaction outcome (see the Supporting Information for more details). Significant enhancement was achieved employing a higher substrate concentration, with DMA proving to be the most suitable medium (entries 1–3). Notably, and in contrast to previous reports,[7,11] we recognized that trimethylsilyl chloride (TMSCl) was not an appropriate Lewis acid for promoting ketal functionalization, as product **3** was afforded in negligible yield (entry 6). Additionally, Lewis acidic boron complexes, such as $BF_3{}^{\bullet}OEt_2$, were also found to be ineffective (entry 7).[13]

With optimized conditions established, we sought to explore the scope of this photocatalytic carbon–carbon bond-forming reductive coupling reaction with respect to the ketal moiety (Scheme 3A).[14] Initially, substitution around the aromatic ring was investigated (**3**–**8**). Efficient reaction outcomes were observed with electron-releasing functional groups (**5** and **6**), supporting a nucleophilic character of the putative α-alkoxy radical intermediate.[12] Conversely, suppressed reactivity was observed with electron-withdrawing groups; for example, a bromine atom in the *para* position afforded product **8** in 33% yield.

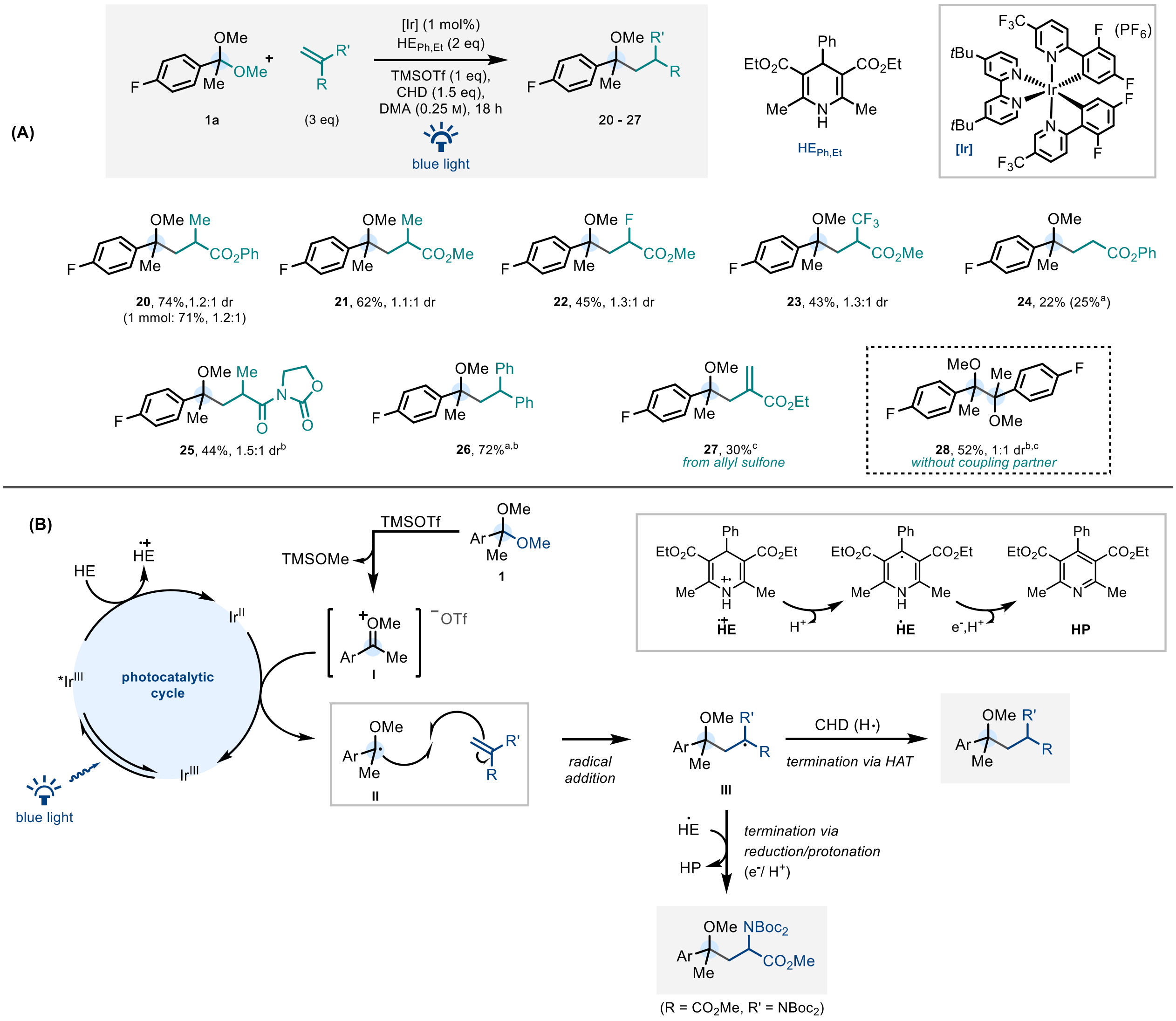
Ketals bearing larger alkyl substituents underwent the reaction with good yields (**9** and **10**). The small decrease in reactivity was consistent with the increasing steric hindrance compared to that of methyl-substituted **4**.[15] A chlorine-containing side chain was also tolerated, and coupled product **11** was delivered in 36% yield. Importantly, the substrate scope of this transformation was successfully expanded to diethyl and diisopropyl ketals in moderate to good yields (**12** and **13**), and this reactivity represents a significant improvement considering

Scheme 3. (A) Scope with Respect to the Ketal Substrate and (B) Performance Evaluation of Mixed Ketal Substrate 1s[c]



[a] Reaction time of 5 h. [b] Reaction time of 48 h. [c] Combined isolated yields on a 0.2 mmol scale.

Scheme 4. (A) Scope with Respect to the Alkene Coupling Partner and (B) Plausible Reaction Mechanism[d]



[a]Ten equivalents of coupling partner. [b]Reaction performed on a 0.1 mmol scale. [c]Reaction performed without CHD. [d]Combined isolated yields on a 0.2 mmol scale. CHD = 1,4-cyclohexadiene.

previously reported limitations on acyclic acetals.[7] Moreover, ketals of aliphatic ketones were found to be competent substrates for radical generation, delivering the corresponding products in synthetically useful yields after conjugate addition (**14**–**16**), with dimethoxy cyclopentane affording compound **17** in 53% yield. To demonstrate the generality of this transformation, we looked to expand the scope to include acetal substrates. Pleasingly, good reaction efficiency was achieved with both acyclic and cyclic acetals (**18** and **19**, respectively), illustrating complementarity with previous works.[7,11b] Finally, the role of the alkoxide functionality was examined with mixed ketal **1s** (Scheme 3B). Interestingly, phenyl ether **14′** was not formed under the reaction conditions; however, methyl ether **14** was isolated in 38% yield [comparable to that with dimethoxy propane ketal as the starting material (Scheme 3A), **14**]. This observation could be attributed to the leaving group ability of the phenoxy group being better than that of the methoxy group.

We next examined the scope of this reaction with respect to the acceptor component, using ketal **1a** as a model substrate (Scheme 4A). It should be noted that to further improve reactivity with acrylate-type acceptors, we investigated alternative reagents to favor radical termination after Giese-type addition. In contrast to a radical reduction/protonation mechanism for DHA, a different termination via hydrogen atom transfer (HAT) has been proposed previously for acrylate substrates.[16] Catalytic methods involving thiols were not found to be viable for this purpose.[16,17] However, H-atom abstraction from stoichiometric 1,4-cyclohexadiene (CHD) proved to be beneficial for improving reaction yields (see the Supporting Information for details).[18] Using these modified conditions, photocatalytic reductive coupling was achieved between **1a**, phenyl methacrylate, and methyl methacrylate to give the corresponding tertiary methyl ethers in 74% and 62% yields (**20** and **21**, respectively). Variations to the *α*-position of the acrylate component were found to play a pivotal role in reactivity. Pleasingly, fluorine incorporation was tolerated; monofluorinated **22** and trifluoromethylated **23** were both afforded in synthetically useful yields. No *gem*-difluoroalkene adducts were formed under these reaction conditions.[11b,19] Unsubstituted phenyl acrylate resulted in suppressed efficiency even when a large excess of coupling partner was used (**24**).

Furthermore, coupling with methacryloyloxazolidinone furnished **25** in moderate yield. These results indicate a key stabilizing captodative effect arising from the α-substituent, a conclusion further supported by successful coupling with electron neutral alkenes. In fact, significant efficiency was observed with diphenylethylene as the acceptor olefin (**26**).

Under these reaction conditions, reductive allylation of ketal **1a** with a sulfone derivative afforded compound **27** in 30% yield, despite the different reaction mechanism involved with these coupling partners.[9d,e]

Finally, **1a** was subjected to reaction conditions without an acceptor partner, which afforded dimerized aryl methyl ether **28** in 52% yield as a 1:1 mixture of diastereomers. Rueping and co-workers have reported the reductive dimerization of aldehydes and ketones via ketyl radical generation under visible-light irradiation.[20] Accordingly, this result supports a radical pinacol-type dimerization and provides direct access to ether pinacol adducts from easily accessible starting materials.

Control experiments established the essential role of the Lewis acid; no conversion of starting material was observed without TMSOTf (see the Supporting Information for details). Moreover, none of the desired reactivity was achieved in the absence of light, photocatalyst, or Hantzsch ester. On the basis of these results, we propose the following reaction mechanism (Scheme 4B).[13] Initially, ketal **1** is activated by TMSOTf to form oxocarbenium ion intermediate **I** as disclosed in previous reports.[7,11] A highly reducing $\mathrm{Ir^{II}}$ species ($E_{1/2\mathrm{red}} = -1.37$ V vs SCE in MeCN),[5b] generated by electron transfer from the Hantzsch ester following photoexcitation of $\mathrm{Ir^{III}}$, is capable of reducing **I** to generate α-alkoxy radical **II.**[21] The key nucleophilic intermediate (**I**) can engage in radical addition with an appropriate acceptor olefin moiety. After this Giese-type addition, the resulting free radical intermediate (**III**) undergoes a reduction/protonation sequence mediated by the Hantzsch ester ($\mathrm{HE}^{\bullet}$), or HAT termination favored by the presence of CHD, depending on the nature of the coupling partner.[16]

In summary, the photocatalytic reductive coupling of readily accessible ketals and acceptor olefins has been developed. This methodology provides a new approach for generating challenging α-tertiary dialkyl ethers in a single step and is also amenable to acetal components. Extension to pinacol coupling adducts via an α-alkoxy radical dimerization process has been demonstrated, thus providing insight into the mechanism. We believe that this methodology provides a complementary new synthetic approach to complex α-tertiary ether architectures and that the photocatalytic SET reduction of oxocarbenium ions will provide new opportunities for future reaction development.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02273.

Synthetic procedures and full characterization data of compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: darren.dixon@chem.ox.ac.uk.

ORCID

Thomas Rossolini: 0000-0002-4083-5091
Darren J. Dixon: 0000-0003-2456-5236

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

D.J.D. and T.R. thank Astex Pharmaceuticals, Ltd., for generous financial support and Dr. Steven Howard (Astex Pharmaceuticals, Ltd.) and Dr. Rachel Grainger (Astex Pharmaceuticals, Ltd.) for helpful discussion. B.F. thanks the Slovak Academic Information Agency (SAIA) for his research mobility grant. The authors thank Tatiana Rogova (University of Oxford) for providing computational data and Prof. Fernanda Duarte (University of Oxford) for advice and supervision.

■ REFERENCES

(1) (a) De Martino, G.; La Regina, G.; Di Pasquali, A.; Ragno, R.; Bergamini, A.; Ciaprini, C.; Sinistro, A.; Maga, G.; Crespan, E.; Artico, M.; Silvestri, R. Novel 1-[2-(Diarylmethoxy)ethyl]-2-methyl-5-nitroimidazoles as HIV-1 Non-Nucleoside Reverse Transcriptase Inhibitors. A Structure–Activity Relationship Investigation. *J. Med. Chem.* **2005**, *48*, 4378–4388. (b) Schmidt, F.; Stemmler, R. T.; Rudolph, J.; Bolm, C. Catalytic asymmetric approaches towards enantiomerically enriched diarylmethanols and diarylamines. *Chem. Soc. Rev.* **2006**, *35*, 454–470. (c) Eildal, J. N. N.; Andersen, J.; Kristensen, A. S.; Jørgensen, A. M.; Bang-Andersen, B.; Jørgensen, M.; Strømgaard, K. From the Selective Serotonin Transporter Inhibitor Citalopram to the Selective Norepinephrine Transporter Inhibitor Talopram: Synthesis and Structure–Activity Relationship Studies. *J. Med. Chem.* **2008**, *51*, 3045–3048. (d) Roughley, S. D.; Jordan, A. M. The Medicinal Chemist's Toolbox: An Analysis of Reactions Used in the Pursuit of Drug Candidates. *J. Med. Chem.* **2011**, *54*, 3451–3479. (e) Ameen, D.; Snape, T. J. Chiral 1,1-diaryl compounds as important pharmacophores. *MedChemComm* **2013**, *4*, 893–907.

(2) (a) Williamson, A. W. On Etherification. *Q. J. Chem. Soc.* **1852**, *4*, 229–239. (b) Barluenga, J.; Tomás-Gamasa, M.; Aznar, F.; Valdés, C. Straightforward Synthesis of Ethers: Metal-Free Reductive Coupling of Tosylhydrazones with Alcohols or Phenols. *Angew. Chem., Int. Ed.* **2010**, *49*, 4993–4996. Blackmond and Baran have recently reported a new C-O bond forming approach based on electrogenerated carbocations: (c) Xiang, J.; Shang, M.; Kawamata, Y.; Lundberg, H.; Reisberg, S. H.; Chen, M.; Mykhailiuk, P.; Beutner, G.; Collins, M. R.; Davies, A.; Del Bel, M.; Gallego, G. M.; Spangler, J. E.; Starr, J.; Yang, S.; Blackmond, D. G.; Baran, P. S. Hindered Dialkyl Ether Synthesis via Electrongenerated Carbocations. *ChemRxiv* **2019**, DOI: 10.26434/chemrxiv.8144294.v1.

(3) (a) Molander, G. A.; Wisniewski, S. R. Stereospecific Cross-Coupling of Secondary Organotrifluoroborates: Potassium 1-(Benzyloxy)alkyltrifluoroborates. *J. Am. Chem. Soc.* **2012**, *134*, 16856–16868. (b) Vo, C.-V. T.; Mitchell, T. A.; Bode, J. W. Expanded Substrate Scope and Improved Reactivity of Ether-Forming Cross-Coupling Reactions of Organotrifluoroborates and Acetals. *J. Am. Chem. Soc.* **2011**, *133*, 14082–14089.

(4) Moquist, P. N.; Kodama, T.; Schaus, S. E. Enantioselective Addition of Boronates to Chromene Acetals Catalyzed by a Chiral Brønsted Acid/Lewis Acid System. *Angew. Chem., Int. Ed.* **2010**, *49*, 7096–7100.

(5) For selected reviews, see: (a) Narayanam, J. M. R.; Stephenson, C. R. J. Visible light photoredox catalysis: applications in organic synthesis. *Chem. Soc. Rev.* **2011**, *40*, 102–113. (b) 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*, 5322–5363. (c) Skubi, K. L.; Blum, T. R.; Yoon, T. P. Dual Catalysis Strategies in Photochemical

Synthesis. *Chem. Rev.* **2016**, *116*, 10035−10074. (d) Twilton, J.; Le, C.; Zhang, P.; Shaw, M. H.; Evans, R. W.; MacMillan, D. W. C. The merger of transition metal and photocatalysis. *Nat. Rev. Chem.* **2017**, *1*, 0052. (e) Silvi, M.; Melchiorre, P. Enhanching the potential of enantioselective organocatalysis with light. *Nature* **2018**, *554*, 41−49.

(6) (a) Qvortrup, K.; Rankic, D. A.; MacMillan, D. W. C. A General Strategy for Organocatalytic Activation of C−H Bonds via Photoredox Catalysis: Direct Arylation of Benzylic Ethers. *J. Am. Chem. Soc.* **2014**, *136*, 626−629. For β-amino ether synthesis, see: (b) Hager, D.; MacMillan, D. W. C. Activation of C−H Bonds via the Merger of Photoredox and Organocatalysis: A Coupling of Benzylic Ethers with Schiff Bases. *J. Am. Chem. Soc.* **2014**, *136*, 16986−16989. For another designed example of ether synthesis via C−H atom abstraction, see: (c) Zhang, J.; Li, Y.; Zhang, F.; Hu, C.; Chen, Y. Generation of Alkoxyl Radicals by Photoredox Catalysis Enables Selective C(sp^3)-H Functionalization under Mild Reaction Conditions. *Angew. Chem., Int. Ed.* **2016**, *55*, 1872−1875.

(7) Arendt, K. M.; Doyle, A. G. Dialkyl Ether Formation by Nickel-Catalyzed Cross-Coupling of Acetals and Aryl Iodides. *Angew. Chem., Int. Ed.* **2015**, *54*, 9876−9880.

(8) MacMillan and co-workers have reported access to allylic ethers via decarboxylative coupling of α-oxy carboxylic acids with vinyl halides: (a) Noble, A.; McCarver, S. J.; MacMillan, D. W. C. Merging Photoredox and Nickel Catalysis: Decarboxylative Cross-Coupling of Carboxylic Acids with Vinyl Halides. *J. Am. Chem. Soc.* **2015**, *137*, 624−627. For other methods involving α-oxy radical generation, see: (b) Ramirez, N. P.; Gonzalez-Gomez, J. C. Decarboxylative Giese-Type Reaction of Carboxylic Acids Promoted by Visible Light: A sustainable and Photoredox-Neutral Protocol. *Eur. J. Org. Chem.* **2017**, *2017*, 2154−2163. (c) Barton, D. H. R.; Gateau-Olesker, A.; Géro, S. D.; Lacher, B.; Tachdjian, C.; Zard, S. Z. Radical Decarboxylative Alkylation of Tartaric Acid. *Tetrahedron* **1993**, *49*, 4589−4602. (d) Matsuda, F.; Kawatsura, M.; Hosaka, K.; Shirahama, H. Hydroxyl-Directed Intramolecular Ketone-Olefin Couplings Promoted by SmI$_2$. *Chem. - Eur. J.* **1999**, *5*, 3252−3259.

(9) For imine umpolung chemistry, see: (a) Rono, L. J.; Yayla, H. G.; Wang, D. Y.; Armstrong, M. F.; Knowles, R. R. Enantioselective Photoredox Catalysis Enabled by Proton-Coupled Electron Transfer: Development of an Asymmetric Aza-Pinacol Cyclization. *J. Am. Chem. Soc.* **2013**, *135*, 17735−17738. (b) Jeffrey, J. L.; Petronijević, F. R.; MacMillan, D. W. C. Selective Radical−Radical Cross-Couplings: Design of a Formal β-Mannich Reaction. *J. Am. Chem. Soc.* **2015**, *137*, 8404−8407. (c) Uraguchi, D.; Kinoshita, N.; Kizu, T.; Ooi, T. Synergistic Catalysis of Ionic Brønsted Acid and Photosensitizer for a Redox Neutral Asymmetric α-Coupling of N-Arylaminomethanes with Aldimines. *J. Am. Chem. Soc.* **2015**, *137*, 13768−13771. (d) Qi, L.; Chen, Y. Polarity-Reversed Allylations of Aldehydes, Ketones, and Imines Enabled by Hantzsch Ester in Photoredox Catalysis. *Angew. Chem., Int. Ed.* **2016**, *55*, 13312−13315. (e) Fuentes de Arriba, A. L.; Urbitsch, F.; Dixon, D. J. Umpolung synthesis of branched a-functionalized amines from imines via photocatalytic three component reductive coupling reactions. *Chem. Commun.* **2016**, *52*, 14434−14437. (f) Fava, E.; Millet, A.; Nakajima, M.; Loescher, S.; Rueping, M. Reductive Umpolung of Carbonyl Derivatives with Visible-Light Photoredox Catalysis: Direct Access to Vicinal Diamines and Amino Alcohols via α-Amino Radicals and Ketyl Radicals. *Angew. Chem., Int. Ed.* **2016**, *55*, 6776−6779. (g) Lee, K. N.; Lei, Z.; Ngai, M.-Y. β-Selective Reductive Coupling of Alkenylpyridines with Aldehydes and Imines via Synergistic Lewis Acid/Photoredox Catalysis. *J. Am. Chem. Soc.* **2017**, *139*, 5003−5006. (h) Leitch, J. A.; Fuentes de Arriba, A. L.; Tan, J.; Hoff, O.; Martinez, C. M.; Dixon, D. J. Photocatalytic reverse polarity Povarov reaction. *Chem. Sci.* **2018**, *9*, 6653−6658. (i) Trowbridge, A.; Reich, D.; Gaunt, M. J. Multicomponent synthesis of tertiary alkylamines by photocatalytic olefin-hydroaminoalkylation. *Nature* **2018**, *561*, 522−527. (j) Vasu, D.; Fuentes de Arriba, A. L.; Leitch, J. A.; de Gombert, A.; Dixon, D. J. Primary α-tertiary amine synthesis via α-C−H functionalization. *Chem. Sci.* **2019**, *10*, 3401−3407. For aldehyde and ketone umpolung chemistry see: (k) Ischay, M. A.; Anzovino, M. E.; Du, J.; Yoon, T. P. Efficient Visible Light Photocatalysis of [2 + 2] Enone Cycloadditions. *J. Am. Chem. Soc.* **2008**, *130*, 12886−12887. (l) Tarantino, K. T.; Liu, P.; Knowles, R. R. Catalytic Ketyl-Olefin Cyclizations Enabled by Proton-Coupled Electron Transfer. *J. Am. Chem. Soc.* **2013**, *135*, 10022−10025. (m) Wang, C.; Qin, J.; Shen, X.; Riedel, R.; Harms, K.; Meggers, E. Asymmetric Radical−Radical Cross-Coupling through Visible-Light-Activated Iridium Catalysis. *Angew. Chem., Int. Ed.* **2016**, *55*, 685−688. (n) Chen, M.; Zhao, X.; Yang, C.; Xia, W. Visible-Light-Triggered Directly Reductive Arylation of Carbonyl/Iminyl Derivatives through Photocatalytic PCET. *Org. Lett.* **2017**, *19*, 3807−3810. (o) Berger, A. L.; Donabauer, K.; König, B. Photocatalytic Barbier reaction − visible-light induced allylation and benzylation of aldehydes and ketones. *Chem. Sci.* **2018**, *9*, 7230−7235. (p) Wang, L.; Lear, J. M.; Rafferty, S. M.; Fosu, S. C.; Nagib, D. A. Ketyl radical reactivity via atom transfer catalysis. *Science* **2018**, *362*, 225−229.

(10) For selected publications, see: (a) Nawrat, C. C.; Jamison, C. R.; Slutskyy, Y.; MacMillan, D. W. C.; Overman, L. E. Oxalates as Activating Groups for Alcohols in Visible Light Photoredox Catalysis: Formation of Quaternary Centers by Redox-Neutral Fragment Coupling. *J. Am. Chem. Soc.* **2015**, *137*, 11270−11273. (b) Choi, G. J.; Zhu, Q.; Miller, D. C.; Gu, C. J.; Knowles, R. R. Catalytic alkylation of remote C−H bonds enabled by proton-coupled electron transfer. *Nature* **2016**, *539*, 268−271. (c) Patel, N. R.; Kelly, C. B.; Siegenfeld, A. P.; Molander, G. A. Mild, Redox-Neutral Alkylation of Imines Enabled by an Organic Photocatalyst. *ACS Catal.* **2017**, *7*, 1766−1770. (d) Aycock, R. A.; Vogt, D. B.; Jui, N. T. A practical and scalable system for heteroaryl amino acid synthesis. *Chem. Sci.* **2017**, *8*, 7998−8003. (e) Shu, C.; Mega, R. S.; Andreassen, B. J.; Noble, A.; Aggarwal, V. K. Synthesis of Functionalized Cyclopropanes from Carboxylic Acids by a Radical Addition−Polar Cyclization Cascade. *Angew. Chem., Int. Ed.* **2018**, *57*, 15430−15434.

(11) For acetal activation by Lewis acids, see: (a) Hatano, B.; Nagahashi, K.; Habaue, S. Reductive Coupling of Aromatic Dialkyl Acetals Using the Combination of Zinc and Chlorotrimethylsilane in the Presence of Potassium Carbonate. *Chem. Lett.* **2007**, *36*, 1418−1419. (b) Lin, Z.; Lan, Y.; Wang, C. Synthesis of *gem*-Difluoroalkenes via Nickel-Catalyzed Reductive C−F and C−O Bond Cleavage. *ACS Catal.* **2019**, *9*, 775−780.

(12) Rossolini, T.; Leitch, J. A.; Grainger, R.; Dixon, D. J. Photocatalytic Three-Component Umpolung Synthesis of 1,3-Diamines. *Org. Lett.* **2018**, *20*, 6794−6798.

(13) See the Supporting Information for further details.

(14) The model substrate showed full conversion after 5 h. However, to ensure consistency for all starting materials, reactions were run for 18 h.

(15) Ketals of α-branched ketones as well as heterocycle-containing derivatives were not reactive under these conditions.

(16) Seath, C. P.; Vogt, D. B.; Xu, Z.; Boyington, A. J.; Jui, N. T. Radical Hydroarylation of Functionalized Olefins and Mechanistic Investigation of Photocatalytic Pyridyl Radical Reactions. *J. Am. Chem. Soc.* **2018**, *140*, 15525−15534.

(17) (a) Musacchio, A. J.; Lainhart, B. C.; Zhang, X.; Naguib, S. G.; Sherwood, T. C.; Knowles, R. R. Catalytic intermolecular hydroaminations of unactivated olefins with secondary alkyl amines. *Science* **2017**, *355*, 727−730. (b) Zhu, Q.; Graff, D. E.; Knowles, R. R. Intermolecular Anti-Markovnikov Hydroamination of Unactivated Alkenes with Sulfonamides Enabled by Proton-Coupled Electron Transfer. *J. Am. Chem. Soc.* **2018**, *140*, 741−747. (c) Nguyen, S. T.; Zhu, Q.; Knowles, R. R. PCET-Enabled Olefin Hydroamidation Reactions with N-Alkyl Amides. *ACS Catal.* **2019**, *9*, 4502−4507.

(18) (a) Davies, J.; Svejstrup, T. D.; Fernandez Reina, D.; Sheikh, N. S.; Leonori, D. Visible-Light-Mediated Synthesis of Amidyl Radicals: Transition-Metal-Free Hydroamination and *N*-Arylation Reactions. *J. Am. Chem. Soc.* **2016**, *138*, 8092−8095. (b) Schweitzer-Chaput, B.; Horwitz, M. A.; de Pedro Beato, E.; Melchiorre, P. Photochemical generation of radicals from alkyl electrophiles using a nucleophilic organic catalyst. *Nat. Chem.* **2019**, *11*, 129−135.

(19) 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*, 15073−15077.

(20) Nakajima, M.; Fava, E.; Loescher, S.; Jiang, Z.; Rueping, M. Photoredox-Catalyzed Reductive Coupling of Aldehydes, Ketones, and Imines with Visible Light. *Angew. Chem., Int. Ed.* **2015**, *54*, 8828−8832.

(21) The TfOH would be neutralized by the Hantzsch pyridine (HP) generated in the reaction.