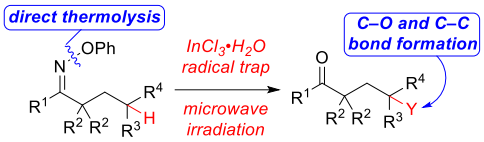
Formal γ-C(sp^3)–H Activation of Ketones via Microwave-Promoted and Iminyl-Radical-Mediated 1,5-Hydrogen Atom Transfer

Jatinder Singh, Spencer A. Jones, Tanner J. Nelson, Jesus A. Botello, and Steven L. Castle*

Department of Chemistry and Biochemistry, Brigham Young University, Provo, UT, 84602, United States

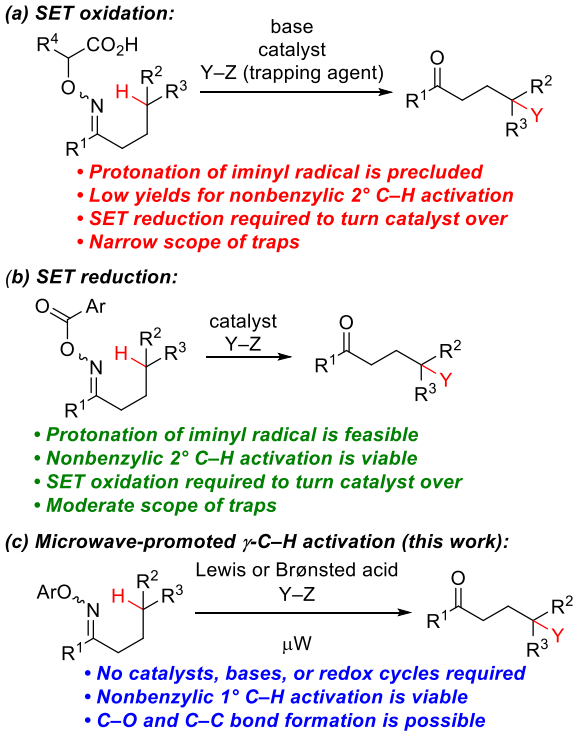


ABSTRACT: Microwave irradiation of *O*-phenyloximes triggers N–O homolysis and 1,5-hydrogen atom transfer (HAT), resulting in formal γ-C–H functionalization of ketones after trapping of the radical intermediate and in situ imine hydrolysis. The Lewis acid $InCl_3{\cdot}H_2O$ facilitated the HAT step, enabling functionalization of nonbenzylic 1° carbon atoms. Both C–O and C–C bond formation could be accomplished by this method.

The chemistry of the carbonyl group occupies a central position in the field of organic synthesis. Nucleophilic additions to carbonyl carbons, reactions of electrophiles at enolate α-carbons, and conjugate additions of nucleophiles to the β-carbon atoms of enones and enoates are among the most ubiquitous and fundamental transformations. However, processes that functionalize the γ-carbon of a carbonyl compound are considerably less common.[1] Mohr's polarity-matched additions of electrophilic radicals to electron-rich dienol ethers constitute a notable advance in this area.[2]

In 2018, Leonori[3] and Studer[4] accomplished the formal γ-functionalization of ketones via iminyl-radical-mediated 1,5-hydrogen atom transfer (HAT). The iminyl radicals were generated from α-imino-oxy acids by deprotonation, single-electron transfer (SET) oxidation of the resulting carboxylate, and decarboxylative fragmentation. After a thermodynamically favored 1,5-HAT, functionalization of the resulting carbon-centered radical and hydrolysis of the NH imine delivered the ketone products (Scheme 1a). While this work represents a significant achievement in ketone γ-C–H functionalization chemistry, the need for base precludes the use of acid to protonate the iminyl radical intermediate. Protonated iminyl radicals have significantly higher BDE values than neutral iminyl radicals, leading to more favorable HAT processes.[3,5] The inability to utilize protonated iminyl radicals limits the scope of these SET-oxidation-dependent reactions to the functionalization of 3° and benzylic 2° carbons.[3,4] Additionally, the requirement to reduce either the carbon-centered radical intermediate or the functionalized adduct to regenerate the catalyst restricts the types of trapping agents that can be used.

The development of analogous processes that rely on SET reduction instead of oxidation to generate iminyl radicals[6] has permitted the use of Lewis or Brønsted acids to promote 1,5-HAT. As a result, nonbenzylic 2° carbons can be activated in some cases (Scheme 1b).[6c,6d] However, catalyst turnover requires SET oxidation of the adduct. Thus, only traps that afford readily oxidizable adducts can be employed. Clearly, the generation of iminyl radicals by methods that do not rely on SET would increase the scope of HAT-mediated γ-C–H activation.[7]



Scheme 1. Comparison of HAT Methods Using Iminyl Radicals.

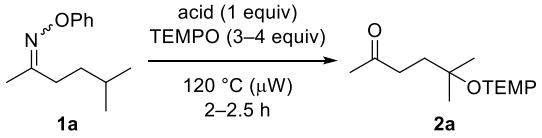
In 2007, Walton reported that the weak N–O bond of *O*-phenyloximes (BDE = ca. 35 kcal/mol)[8] could be cleaved by microwave irradiation, producing iminyl radicals that subsequently undergo 5-*exo-trig* and 5-*exo-dig* cyclizations.[9] Inspired by this seminal work that does not rely on SET, we initiated a program to explore the utility of thermally generated iminyl radicals. Our first contribution to this area involved the synthesis of 2-acylpyrroles via microwave-promoted 5-

exo-dig iminyl radical cyclization followed by TEMPO trapping.[10] We subsequently reported the construction of functionalized nitriles by means of microwave-promoted fragmentations of 4- and 5-membered cyclic iminyl radicals.[11] Recently, we generated a variety of functionalized pyrrolines via 5-*exo-trig* iminyl radical cyclizations. These reactions could be triggered by either microwave irradiation or conventional heating.[12] The lack of SET events and redox cycles has enabled a broad range of radical traps to be employed in both the fragmentations and the cyclizations.

We recognized that application of microwave-promoted iminyl radical chemistry to the γ-C–H functionalization of ketones could potentially expand the scope of radical traps and/or substrates compared to the previously discussed processes that rely on SET oxidation and reduction. Herein, we report our investigations in this area, which have revealed that the ability to employ a Lewis acid in these base- and catalyst-free reactions enables the unprecedented functionalization of nonbenzylic 1° γ-carbon atoms (Scheme 1c).

We commenced our efforts to develop thermally-promoted γ-C–H functionalizations by selecting *O*-phenyloxime **1a** as the test substrate and TEMPO as the radical trap (Table 1). We elected to trigger iminyl radical formation via microwave irradiation rather than conventional heating due to the rapid rates inherent to this technique.[9–12] Reactions performed without additives were low-yielding and afforded complex mixtures, so we evaluated the use of Brønsted or Lewis acids. Various carboxylic acids promoted the desired C–H activation (entries 1–5), with chloroacetic acid delivering the best yield of ketone **2a** (entry 3). However, we shifted our attention to $InCl_3{\cdot}H_2O$[6h] when this Lewis acid furnished **2a** in an improved yield (entry 6). A survey of various solvents (entries 7–12) revealed the combination of $InCl_3{\cdot}H_2O$ and $PhCF_3$–*i*PrOH–H_2O 23:1:1 to be optimal (entry 12). We studied this solvent system based on reports that it forms a single phase at elevated temperatures.[13]

Table 1. Optimization of Reaction Conditions

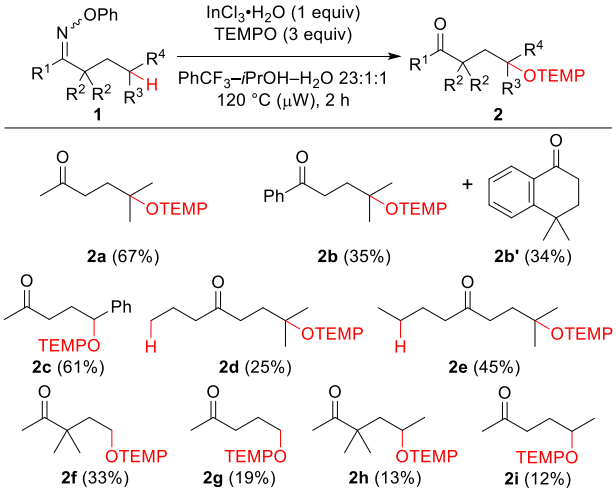


entry	acid	solvent	% yield[a]
1	CH_3CO_2H	CH_3CN	23
2	CH_3CO_2H[b]	CH_3CN	28
3	$ClCH_2CO_2H$[b]	CH_3CN	45
4	Cl_2CHCO_2H[b]	CH_3CN	38
5	Cl_3CCO_2H[b]	CH_3CN	19
6	$InCl_3{\cdot}H_2O$	CH_3CN–THF 2:1	49
7	$InCl_3{\cdot}H_2O$	CH_3OH	30
8	$InCl_3{\cdot}H_2O$	CH_3CN–CH_3OH 25:1	40
9	$InCl_3{\cdot}H_2O$	$PhCF_3$–THF–CH_3CN 4:2:1	38
10	$ClCH_2CO_2H$	$PhCF_3$–CH_3CN 25:1	40
11	$InCl_3{\cdot}H_2O$	$PhCF_3$–*i*PrOH–H_2O 8:1:1	58
12	$InCl_3{\cdot}H_2O$	$PhCF_3$–*i*PrOH–H_2O 23:1:1	67

[a]Isolated yield. [b]2 equiv of acid was used.

The scope of the ketone γ-C–H functionalization was explored by subjecting a variety of *O*-phenyloximes **1** to the optimal reaction conditions (Scheme 2). The substrates were constructed in a single step by pyridine-mediated condensation of ketone precursors with $PhONH_2{\cdot}HCl$.[14] Benzoyl-containing substrate **1b** furnished a 1:1 mixture of adduct **2b** and tetralone **2b'**, indicating that cyclization of the intermediate radical onto the neighboring aromatic ring[5,15] is competitive with TEMPO trapping. Phenyl-substituted oxime ether **1c** delivered γ-functionalized ketone **2c** in good yield, demonstrating the viability of 2° benzylic radicals as intermediates in this reaction. Ketones **2d** and **2e** were obtained in modest yields compared to ketone **2a**, presumably due to the existence of two different types of γ-hydrogens in the substrates **1d** and **1e**. Although no products derived from TEMPO trapping at the primary (**1d**) or secondary (**1e**) γ-carbon were isolated, ^{1}H NMR spectra of the crude reaction mixtures indicated the presence of several minor components. Thus, it appears that substrates containing multiple sets of γ-hydrogens afford reduced yields due to the possibility of multiple reaction pathways.

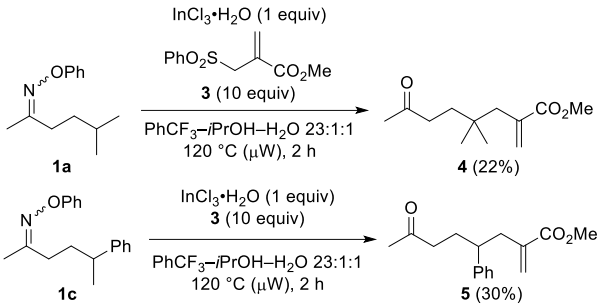
Scheme 2. Scope of *O*-Phenyloxime Substrates



Substrates possessing nonbenzylic 1° or 2° γ-carbons underwent the γ-C–H functionalization, albeit with modest yields (**2f–2i**). *gem*-Dimethylation was beneficial for substrates with a 1° γ-carbon (see **2f** and **2g**), but it had no impact on reactions involving a 2° γ-carbon (see **2h** and **2i**). We are uncertain why this is the case, but it is clear that further advances are required for γ-C–H functionalization at nonbenzylic 1° and 2° carbons to become a synthetically useful process. Our results are nonetheless noteworthy, as comparable protocols that are reliant on SET chemistry are known to fail completely with substrates bearing a nonbenzylic 1° γ-carbon.[6b,6c,16]

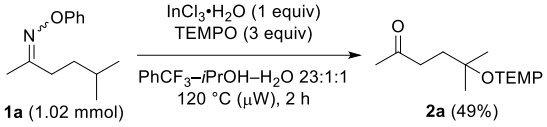
To determine if C–C bonds could be forged by this method, we examined the microwave-promoted γ-C–H functionalization of *O*-phenyloximes **1a** and **1c** with allylsulfone **3**[17] as the radical trap (Scheme 3). The reactions did not proceed with 3 equivalents of **3**, but increasing the amount of the radical trap to 10 equivalents afforded the desired adducts **4** and **5**. Although the yields are modest, this result demonstrates the possibility of merging microwave-promoted and iminyl-radical-mediated 1,5-HAT with C–C bond formation.

Scheme 3. γ-C–C Bond Formation Using Allylsulfone 3



The γ-C–H functionalization could be performed on a preparative scale. Subjection of ca. 1 mmol of **1a** to the standard reaction conditions furnished ketone **2a** in 49% yield (Scheme 4). It is unclear why the yield of this reaction is lower than the analogous smaller-scale reaction reported in Scheme 2.

Scheme 4. Preparative Scale Reaction



In conclusion, we have demonstrated that *O*-phenyloximes can undergo microwave-promoted N–O homolysis followed by 1,5-HAT, delivering the products of a formal γ-C(sp^3)–H ketone activation. The use of $InCl_3 \cdot H_2O$ was beneficial, presumably due to its ability to coordinate iminyl radicals and increase their reactivity to hydrogen atom abstraction. It is presumably this enhanced reactivity that enables generation of unstabilized primary radicals by this process, a feat that has not been achieved using SET-dependent iminyl radical chemistry that in many cases precludes the use of acidic promoters. Both C–O and C–C bond formation could be accomplished by using TEMPO and an allylsulfone as radical traps. The reactions are rapid and involve simple experimental protocols. Although more work is necessary for the yields to reach synthetically useful levels, we believe that the potential of this method justifies further investigation.

AUTHOR INFORMATION

Corresponding Author

*scastle@chem.byu.edu

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We thank the National Science Foundation (CHE-1856530), and Brigham Young University (Undergraduate Research Awards to S.A.J and T.J.N.) for financial support. Funding for J.A.B. was provided by the National Science Foundation Chemistry and Biochemistry REU Site to Prepare Students for Graduate School and an Industrial Career under award CHE-1757627.

REFERENCES

(1) Selected examples: (a) Bryson, T. A.; Gammill, R. B. Enamine Chemistry I. Carbanion Alkylations. *Tetrahedron Lett.* **1974**, *96*, 3963–3966. (b) Fleming, I.; Goldhill, J.; Paterson, I. γ-Alkylation of Unsaturated Ketones and Esters: Zinc Bromide-Catalysed Alkylation of *O*-Silylated Dienolates. *Tetrahedron Lett.* **1979**, *20*, 3209–3212. (c) Majewski, M.; Mpango, G. B.; Thomas, M. T.; Wu, A.; Snieckus, V. Metalated Unsaturated Amides. Regio- and Stereoselective γ-Alkylation. *J. Org. Chem.* **1981**, *46*, 2029–2045. (d) Saito, S.; Shiozawa, M.; Ito, M.; Yamamoto, H. Conceptually New Directed Aldol Condensation Using Aluminum Tris(2,6-diphenylphenoxide). *J. Am. Chem. Soc.* **1998**, *120*, 813–814. (e) Kim, S.; Lim, C. J. Radical-Mediated γ-Functionalizations of α,β-Unsaturated Carboxylic Amides. *Angew. Chem., Int. Ed.* **2004**, *43*, 5378–5380. (f) Smith, S. W.; Fu, G. C. Asymmetric Carbon–Carbon Bond Formation γ to a Carbonyl Group: Phosphine-Catalyzed Addition of Nitromethane to Allenes. *J. Am. Chem. Soc.* **2009**, *131*, 14231–14233. (g) Li, S.; Zhu, R.-Y.; Xiao, K.-J.; Yu, J.-Q. Ligand-Enabled Arylation of γ-C–H Bonds. *Angew. Chem., Int. Ed.* **2016**, *55*, 4317–4321. (h) Liu, W.-B.; Okamoto, N.; Alexy, E. J.; Hong, A. Y.; Tran, K.; Stoltz, B. M. Enantioselective γ-Alkylation of α,β-Unsaturated Malonates and Ketoesters by a Sequential Ir-Catalyzed Asymmetric Allylic Alkylation/Cope Rearrangement. *J. Am. Chem. Soc.* **2016**, *138*, 5234–5237. (i) Fu, L.; Guptill, D. M.; Davies, H. M. L. Rhodium(II)-Catalyzed C–H Functionalization of Electron-Deficient Methyl Groups. *J. Am. Chem. Soc.* **2016**, *138*, 5761–5764.

(2) (a) Liu, X.; Chen. X.; Mohr, J. T. Cu-Catalyzed γ-Sulfonylation of α,β-Unsaturated Carbonyl Compounds by Means of Silyl Dienol Ethers. *Org. Lett.* **2015**, *17*, 3572–3575. (b) Chen, X.; Liu, X.; Mohr, J. T. Cu-Catalyzed Stereoselective γ-Alkylation of Enones. *J. Am. Chem. Soc.* **2016**, *138*, 6364–6367. (c) Liu, X.; Chen. X.; Mohr, J. T. Regiocontrolled Oxidative C–C Coupling of Dienol Ethers and 1,3-Dicarbonyl Compounds. *Org. Lett.* **2016**, *18*, 3182–3185.

(3) Dauncey, E. M.; Morcillo, S. P.; Douglas, J. J.; Sheikh, N. S.; Leonori, D. Photoinduced Remote Functionalisations by Iminyl Radical Promoted C–C and C–H Bond Cleavage Cascades. *Angew. Chem., Int. Ed.* **2018**, *57*, 744–748.

(4) Jiang, H.; Studer, A. α-Aminoxy-Acid-Auxiliary-Enabled Intermolecular Radical γ-C(sp^3)–H Functionalization of Ketones. *Angew. Chem., Int. Ed.* **2018**, *57*, 1692–1696.

(5) Forrester, A. R.; Gill, M.; Napier, R. J.; Thomson, R. H. "Iminyls. Part 5. Intramolecular Hydrogen Abstraction by Alkyl(aryl)-iminyls. A New Tetralone Synthesis. *J. Chem. Soc. Perkin Trans. 1* **1979**, 632–636.

(6) (a) Shen, X.; Zhao, J.-J.; Yu, S. Photoredox-Catalyzed Intermolecular Remote C–H and C–C Vinylation via Iminyl Radicals. *Org. Lett.* **2018**, *20*, 5523–5527. (b) Ma, Z.-Y.; Guo, L.-N.; Gu, Y.-R.; Chen, L.; Duan, X.-H. Iminyl Radical-Mediated Controlled Hydroxyalkylation of Remote C(sp^3)-H Bond via Tandem 1,5-HAT and Difunctionalization of Aryl Alkenes. *Adv. Synth. Catal.* **2018**, *360*, 4341–4347. (c) Gu, Y.-R.; Duan, X.-H.; Chen, L.; Ma, Z.-Y.; Gao, P.; Guo, L.-N. Iminyl Radical-Triggered Intermolecular Distal C(sp^3)–H Heteroarylation via 1,5-Hydrogen-Atom Transfer (HAT) Cascade. *Org. Lett.* **2019**, *21*, 917–920. (d) Chen, L.; Guo, L.-N.; Ma, Z.-Y.; Gu, Y.-R.; Zhang, J.; Duan, X.-H. Iminyl Radical-Triggered 1,5-Hydrogen-Atom Transfer/Heck-Type Coupling by Visible-Light Photoredox Catalysis. *J. Org. Chem.* **2019**, *84*, 6475–6482. (e) Yin, Z.; Zhang, Z.; Zhang, Y.; Dixneuf, P. H.; Wu, X.-F. Carbonylation of Tertiary Carbon Radicals: Synthesis of Lactams. *Chem. Commun.* **2019**, *55*, 4655–4658. (f) Torres-Ochoa, R. O.; Leclair, A.; Wang, Q.; Zhu, J. Iron-Catalysed Remote C(sp^3)–H Azidation of *O*-Acyl Oximes and *N*-Acyloxy Imidates Enabled by 1,5-Hydrogen Atom Transfer of Iminyl and Imidate Radicals: Synthesis of γ-Azido Ketones and β-Azido Alcohols. *Chem. Eur. J.* **2019**, *25*, 9477–9484. (g) Li, Z.; Torres-Ochoa, R. O.; Wang, Q.; Zhu, J. Functionalization of Remote C(sp^3)-H Bonds Enabled by Copper-Catalyzed Coupling of O-Acyloximes with Terminal Alkynes. *Nat. Commun.* **2020**, *11*, 403. (h) Wu, D.; Cui, S.-S.; Bian, F.; Yu, W. Visible Light Driven and Copper-Catalyzed C(sp^3)–H Functionalization of *O*-Pentafluorobenzoyl Ketone Oximes. *Org. Lett.* **2021**, *23*, 6057–6061.

(7) Reviews: (a) Liu, L.; Duan, X.-H.; Guo, L.-N. Recent Advance in Iminyl Radical Triggered C–H and C–C Bond Functionalization of Oxime Esters via 1,5-HAT and β-Carbon Scission. *Synthesis* **2021**, *53*, 4375–4388. (b) Krylov, I. B.; Segida, O. O.; Budnikov, A. S.; Terent'ev, A. O. Oxime-Derived Iminyl Radicals in Selective Processes of Hydrogen Atom Transfer and Addition to Carbon-Carbon π-

Bonds. *Adv. Synth. Catal.* **2021**, *363*, 2502–2528. (c) Guo, W.; Wang, Q.; Zhu, J. Visible Light Photoredox-Catalysed Remote C–H Functionalisation Enabled by 1,5-Hydrogen Atom Transfer (1,5-HAT). *Chem. Soc. Rev*. **2021**, *50*, 7359–7377. (d) Goswami, N.; Maiti, D. An Update on Distal C(sp^3)–H Functionalization Involving 1,5-HAT Emerging from Nitrogen Radicals. *Isr. J. Chem.* **2020**, *60*, 303–312.

(8) Blake, J. A.; Pratt, D. A.; Lin, S.; Walton, J. C.; Mulder, P.; Ingold, K. U. Thermolyses of *O*-Phenyl Oxime Ethers. A New Source of Iminyl Radicals and a New Source of Aryloxyl Radicals. *J. Org. Chem.* **2004**, *69*, 3112–3120.

(9) (a) Portella-Cubillo, F.; Scott, J. S.; Walton, J. C. Microwave-Assisted Preparations of Dihydropyrroles from Alkenone *O*-Phenyl Oximes. *Chem. Commun.* **2007**, 4041–4043. (b) Portella-Cubillo, F.; Scott, J. S.; Walton, J. C. Microwave-Assisted Syntheses of *N*-Heterocycles Using Alkenone-, Alkynone- and Aryl-Carbonyl *O*-Phenyl Oximes: Formal Synthesis of Neocryptolepine. *J. Org. Chem.* **2008**, *73*, 5558–5565.

(10) Cai, Y.; Jalan, A.; Kubosumi, A. R.; Castle, S. L. Microwave-Promoted Tin-Free Iminyl Radical Cyclization with TEMPO Trapping: A Practical Synthesis of 2-Acylpyrroles. *Org. Lett.* **2015**, *17*, 488–491.

(11) Jackman, M. M.; Im, S.; Bohman, S. R.; Lo, C. C. L.; Garrity, A. L.; Castle, S. L. Synthesis of Functionalized Nitriles via Microwave-Promoted Fragmentations of Cyclic Iminyl Radicals. *Chem. - Eur. J.* **2018**, *24*, 594–598.

(12) (a) Singh, J.; Nickel, G. A.; Cai, Y.; Jones, D. D.; Nelson, T. J.; Small, J. E.; Castle, S. L. Synthesis of Functionalized Pyrrolines via Microwave-Promoted Iminyl Radical Cyclizations. *Org. Lett.* **2021**, *23*, 3970–3974. (b) Singh, J.; Nelson, T. J.; Mansfield, S. A.; Nickel, G. A.; Cai, Y.; Jones, D. D.; Small, J. E.; Ess, D. H.; Castle, S. L. Microwave- and Thermally-Promoted Iminyl Radical Cyclizations: A Versatile Method for the Synthesis of Functionalized Pyrrolines. *J. Org. Chem.* **2022**, *submitted for publication*.

(13) Atik, Z.; Chaou, M. Solubilities and Phase Equilibria for Ternary Solutions of α,α,α-Trifluorotoluene, Water, and 2-Propanol at Three Temperatures and Pressure of 101.2kPa. *J. Chem. Eng. Data* **2007**, *52*, 932–935.

(14) Petrassi, H. M.; Sharpless, K. B.; Kelly, J. W. The Copper-Mediated Cross-Coupling of Arylboronic Acids and *N*-Hydroxyphthalimide at Room Temperature: Synthesis of Aryloxyamines. *Org. Lett.* **2001**, *3*, 139–142.

(15) (a) Shu, W.; Nevado, C. Visible-Light-Mediated Remote Aliphatic C–H Functionalizations through a 1,5-Hydrogen Transfer Cascade. *Angew. Chem., Int. Ed.* **2017**, *56*, 1881–1884. (b) Zhang, Y.; Yin, Z.; Wu, X.-F. Iron-Catalyzed Synthesis of Dihydronaphthalenones from Aromatic Oxime Esters. *Adv. Synth. Catal.* **2019**, *361*, 3223–3227.

(16) Substrates bearing a 1° γ-carbon that is benzylic or adjacent to an oxygen atom can undergo SET-promoted γ-C–H functionalization, albeit with modest yields; see ref 6a.

(17) Rouquet, G.; Robert, F.; Méreau, R.; Castet, F.; Landais, Y. Allylsilanes in “Tin-free” Oximation, Alkenylation, and Allylation of Alkyl Halides. *Chem. - Eur. J.* **2011**, *17*, 13904–13911.