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Synthesis of Functionalized Pyrrolines via Microwave-Promoted Iminyl Radical Cyclizations

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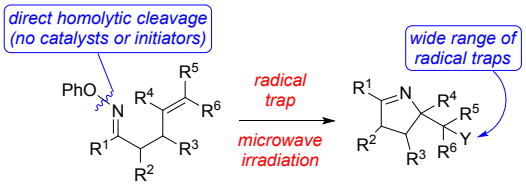
Supporting Information Placeholder

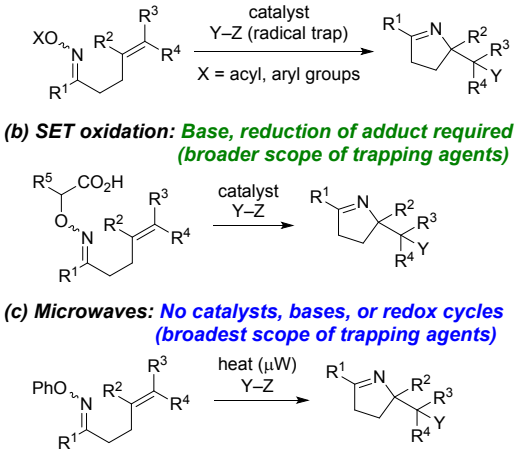


ABSTRACT: *O*-Phenyloximes tethered to alkenes undergo 5-*exo*-*trig* iminyl radical cyclizations upon microwave irradiation. Trapping of the resulting cyclic radicals results in C–C, C–N, C–O, C–S, or C–X bond formation. Allylic sulfides undergo a tandem cyclization–thiyl radical β-elimination, affording terminal alkenes. The cyclizations exhibit a broad scope, and in some cases they are highly diastereoselective. The pyrroline adducts are versatile intermediates that can be transformed into a range of different species.

The chemistry of nitrogen-centered radicals[1] is experiencing a renaissance that has largely been fueled by the development of new transformations mediated by photoredox catalysts[2] and other types of transition metal catalysts. Iminyl radical cyclizations, which were pioneered by Zard,[3] are an important subset of nitrogen-centered radical reactions.[4] Several recent reports describe the synthesis of functionalized pyrrolines via 5-*exo*-*trig* cyclizations of iminyl radicals that are generated via single-electron transfer (SET) reduction of *O*-acyloximes or *O*-aryloximes. These processes require oxidation of the cyclic adduct to facilitate catalyst turnover, which limits the scope of reagents that can be used to trap and functionalize the cyclic radical or cationic intermediate[5] (Scheme 1a). Inspired by Forrester's seminal work,[6] Studer[7] and Leonori[8] demonstrated that α-imino-oxy acids are useful substrates for cyclizations featuring iminyl radical generation via SET oxidation[9] (Scheme 1b). The cyclic adducts produced in these reactions are reduced to regenerate the catalyst, allowing a complementary set of trapping agents to be employed when compared to the reactions described above. Nonetheless, the number of viable radical traps is still constrained by reliance on a redox cycle. Additionally, base is required to deprotonate the α-imino-oxy acids prior to iminyl radical generation via SET oxidation.[7–9] Accordingly, a method of forming iminyl radicals that does not rely on SET[10] would complement these protocols by permitting the use of a wide range of radical traps, thereby enabling construction of numerous functionalized pyrrolines.

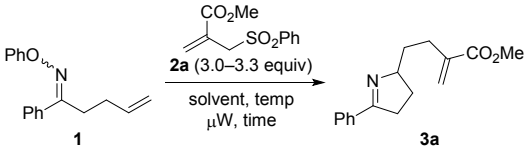
In 2007, Walton showed that microwave-promoted homolytic cleavage of the weak N–O bond of *O*-phenyloximes (BDE = ca. 35 kcal/mol)[11] could trigger initiator- and catalyst-free iminyl radical cyclizations that employ toluene as both solvent and radical trap.[12] By using solvents that do not readily undergo hydrogen atom abstraction (e.g., $PhCF_3$, CH_3CN), we modified this protocol and synthesized 2-acylpyrroles via 5-*exo*-*dig* cyclizations and functionalized nitriles via fragmentations of iminyl radicals.[13,14] A large number of radical traps are compatible with the fragmentations, allowing formation of C–C, C–O, C–N, or C–X bonds.[14] Based on these results, we reasoned that application of our protocol to Walton's original microwave-promoted pyrroline synthesis would enable trapping of the cyclic radical intermediate with a host of agents, greatly expanding the scope of this transformation (Scheme 1c). Herein we report the results of our study, which establish microwave-promoted 5-*exo*-*trig* iminyl radical cyclizations as convenient and user-friendly reactions that forge pyrrolines endowed with diverse functionality. The broad scope of this process can be attributed to the catalyst- and base-free conditions as well as the absence of redox cycles. The reactions are also fast, easy to perform, and in some cases stereoselective.

Scheme 1. Pyrrolines via Iminyl Radical Cyclizations



We began by probing the microwave-promoted cyclization of *O*-phenyloxime **1** in the presence of allylsulfone **2a**[15] (Table 1). This radical trap permitted convenient measurement of reaction yields via ^{1}H NMR spectroscopy. Performing the cyclization at 100 °C in $PhCF_3$ as solvent afforded a low yield of pyrroline **3a** (entry 1). Elevating the temperature to 120 °C delivered better results (entry 2), but a further increase was not beneficial (entry 3). Switching to a more polar solvent did not significantly improve the yield (entries 4 and 5). Finally, we were pleased to discover that extending the reaction time to 2 h furnished **3a** in a satisfactory 72% isolated yield (entry 6).

Table 1. Optimization of Cyclization Conditions



entry	solvent	temp (°C)	time (min)	yield of **3a** (%)
1	$PhCF_3$	100	60	20[a]
2	$PhCF_3$	120	45	35[a]
3	$PhCF_3$	130	45	30[a]
4	CH_3OH	110	45	30[a]
5	CH_3CN	120	120	41[b]
6	$PhCF_3$	120	120	72[b]

[a]Calculated from ^{1}H NMR spectra of reaction mixtures. [b]Isolated yield.

We then evaluated several other radical traps in the microwave-promoted cyclization of **1** (Figure 1). A host of different reagents were viable, affording pyrrolines **3** in generally good yields. For example, C–O bond formation could be accomplished by trapping the cyclic radical intermediate with TEMPO (entry 1). C–X bonds were forged by employing CCl_4,[16a] CBr_4,[17] or 2-iodopropane.[18] (entries 2–4). C–N and C–S bonds were constructed by using sulfonyl azide **2f**[19] and xanthate **2g**,[20] respectively (entries 5 and 6). Finally, C–C bond formation was achieved by trapping with benziodoxolone-based hypervalent iodine reagent **2i**[21] (entry 8). The ability to install a diverse range of functional groups is clearly a hallmark of this radical process that does not require SET.

Unfortunately, use of Selectfluor[16] (**2h**) as a radical trap yielded only trace amounts of the desired fluorinated adduct **3h** (entry 7). The major product (ca. 10–15%) was an adduct of the cyclic radical intermediate with $PhCF_3$. Apparently, the rate of radical trapping by Selectfluor was slower than the rate of trapping by the solvent. The poor solubility of Selectfluor in $PhCF_3$ was likely responsible for this problem. However, other solvents such as CH_3CN or CH_3OH did not afford detectable amounts of the desired product. Microwave irradiation of a solution of **1** in $PhCF_3$ in the absence of radical traps resulted in slow formation of the $PhCF_3$ adduct. Thus, practical radical traps in these iminyl radical cyclizations must be able to outcompete the solvent for the cyclic radical intermediate.

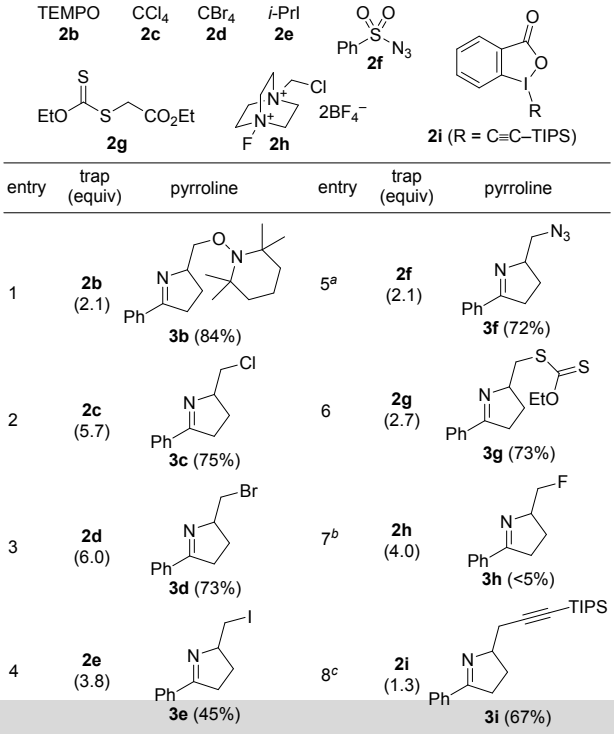
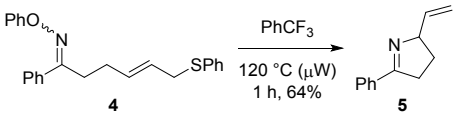


Figure 1. Scope of radical traps in cyclizations of **1**. Conditions were $PhCF_3$, 120 °C (μW), and 1–2 h unless otherwise specified. [a]Irradiated at 110 °C for 5 h. [b]Irradiated at 120 °C for 3 h. The major detected product was an adduct where the cyclic radical was trapped with $PhCF_3$. [c]Irradiated at 110 °C for 2 h.

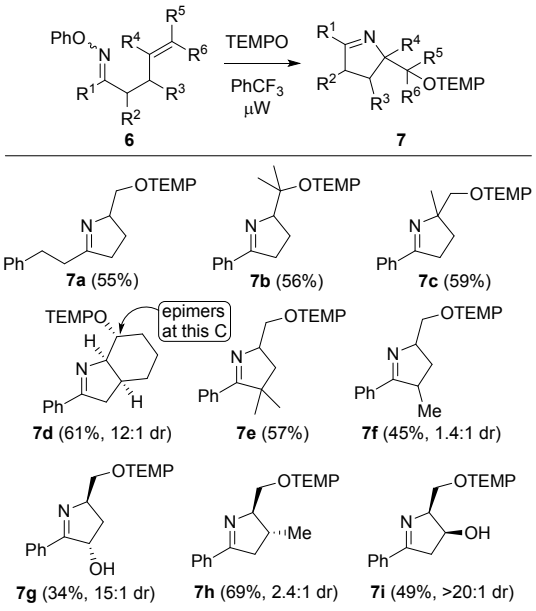
Substrates that can undergo β-elimination of a thiyl radical after cyclization[22] provide an attractive alternative to using radical traps, as the resulting alkene can be elaborated to introduce numerous functional groups. Accordingly, we performed the cyclization of allylic sulfide **4** (Scheme 2). Gratifyingly, this substrate reacted smoothly under microwave irradiation to produce alkene-containing pyrroline **5** in good yield.

Scheme 2. Cyclization–Thiyl Radical β-Elimination



Upon establishing the wide scope of the iminyl radical cyclization with respect to radical traps, we subsequently demonstrated the viability of various *O*-phenyloximes **6** in iminyl radical cyclizations with TEMPO trapping (Scheme 3). These substrates were readily obtained by condensation of the corresponding ketones with *O*-phenylhydroxylamine hydrochloride ($PhONH_2$•HCl). Replacement of the phenyl substituent in **1** with an alkyl group was permitted, albeit with a somewhat lower cyclization yield (**7a**; cf. Figure 1, entry 1). Alkyl substitution of the alkene acceptor at the distal (**7b**) or proximal (**7c**) positions was also tolerated. The use of a cyclic alkene substrate afforded *cis*-fused bicycle **7d** as a 12:1 mixture of C–O epimers, with TEMPO trapping favored from the convex face of the radical intermediate. A geminal dimethyl-substituted *O*-phenyloxime furnished pyrroline **7e** in good yield, demonstrating that 5-*exo*-*trig* cyclization of the iminyl radical intermediate is faster than the undesired fragmentation that would have afforded a tertiary radical in this case. Interestingly, cyclizations of α- and β-hydroxy-substituted *O*-phenyloximes afforded pyrrolines **7g** and **7i** with excellent diastereoselectivity (15:1 and >20:1 dr, respectively), whereas cyclizations of the corresponding methyl-substituted substrates yielded pyrrolines **7f** and **7h** with negligible levels of selectivity (1.4:1 and 2.4:1 dr, respectively). The reasons for this disparity are unclear and will be the subject of future investigation. The modest yields of **7g** and **7i** can at least partially be attributed to degradation during the purification process that may be a result of the labile nature of the alcohol moiety.

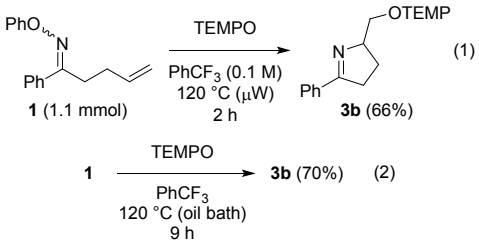
Scheme 3. Scope of *O*-Phenyloxime Substrates[a]



[a]Conditions: 120 °C (μW), 3h.

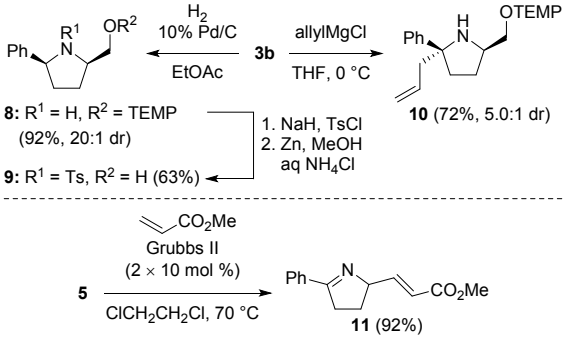
In an effort to probe the scalability of the reaction, ca. 1 mmol of *O*-phenyloxime **1** was subjected to microwave irradiation in the presence of TEMPO. We were pleased to find that pyrroline **3b** was produced in good yield (Scheme 4, eq 1). Additionally, conventional heating using an oil bath was explored as an alternative to microwave irradiation. Although a longer reaction time was required, cyclization of **1** in an oil bath with TEMPO trapping proceeded in comparable yield to the analogous microwave-mediated reaction (Scheme 4, eq 2). Our results contrast with those of Walton and co-workers, who observed lower yields when iminyl radical cyclizations were promoted via conventional heating instead of microwave irradiation.[12] While the reason for this discrepancy is yet to be determined, we are gratified that our iminyl radical cyclizations are accessible to researchers who do not possess a microwave reactor.

Scheme 4. Cyclizations on a Larger Scale and with Conventional Heating



The pyrrolines generated by the iminyl radical cyclizations are versatile and can be transformed into functionalized pyrrolidines as illustrated in Scheme 5. Pd-catalyzed hydrogenation of **3b** afforded pyrrolidine **8** in high yield and excellent selectivity for the *cis*-diastereomer. This reduction could also be mediated by $NaBH(OAc)_3$ or $NaBH_3CN$, albeit with lower yields and dr values. Subsequent tosylation and reductive N–O bond cleavage[23] furnished alcohol **9**. Grignard addition to **3b** was also diastereoselective, generating pyrrolidine **10** as the major product due to preferential attack on the less-hindered face of the pyrroline ring. Finally, subjection of terminal alkene **5** to cross metathesis with methyl acrylate and the Grubbs second-generation catalyst afforded enoate **11** in excellent yield. A second loading of the catalyst was required to drive the reaction to completion, possibly due to catalyst decomposition facilitated by the basic imine moiety.

Scheme 5. Transformations of Pyrroline Adducts



In conclusion, we have developed microwave-promoted 5-*exo* iminyl radical cyclizations for the synthesis of functionalized pyrrolines. The simple protocol, short reaction times, and in some cases excellent stereoselectivity are noteworthy. The direct thermal generation of iminyl radicals from *O*-phenyloximes proceeds in the absence of catalysts and SET cycles, allowing a wide range of radical traps to be

employed.[24] The process is scalable and can be performed with conventional heating instead of microwave irradiation, albeit with longer reaction times. The pyrroline adducts can undergo a number of interesting transformations. We anticipate that this practical method will be valuable to the organic synthesis community.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, compound characterization data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Zard, S. Z. Recent Progress in the Generation and Use of Nitrogen-Centred Radicals. *Chem. Soc. Rev.* **2008**, *37*, 1603–1618. (b) Xiong, T.; Zhang, Q. New Amination Strategies Based on Nitrogen-Centered Radical Chemistry. *Chem. Soc. Rev.* **2016**, *45*, 3069–3087.

(2) (a) Chen, J.-R.; Hu, X.-Q.; Lu, L.-Q.; Xiao, W.-J. Visible Light Photoredox-Controlled Reactions of N-Radicals and Radical Ions. *Chem. Soc. Rev.* **2016**, *45*, 2044–2056. (b) Kärkäs, M. D. Photochemical Generation of Nitrogen-Centered Amidyl, Hydrazonyl, and Imidyl Radicals: Methodology Developments and Catalytic Applications. *ACS Catal.* **2017**, *7*, 4999–5022. (c) Davies, J.; Morcillo, S. P.; Douglas, J. J.; Leonori, D. Hydroxylamine Derivatives as Nitrogen-Radical Precursors in Visible-Light Photochemistry. *Chem. - Eur. J.* **2018**, *24*, 12154–12163. (d) Jiang, H.; Studer, A. Chemistry with N-Centered Radicals Generated by Single-Electron Transfer-Oxidation Using Photoredox Catalysis. *CCS Chem.* **2019**, *1*, 38–49.

(3) (a) Boivin, J.; Fouquet, E.; Zard, S. Z. Iminyl Radicals: Part I. Generation and Intramolecular Capture by an Olefin. *Tetrahedron* **1994**, *50*, 1745–1756. (b) Boivin, J.; Callier-Dublanchet, A.-C.; Quiclet-Sire, B.; Schiano, A.-M.; Zard, S. Z. Iminyl, Amidyl, and Carbamyl Radicals from O-Benzoyl Oximes and O-Benzoyl Hydroxamic Acid Derivatives. *Tetrahedron* **1995**, *51*, 6517–6528. (c) Bingham, M.; Moutrille, C.; Zard, S. Z. A Simple Route to Functionalized Δ^1-Pyrrolines. *Heterocycles* **2014**, *88*, 953–960.

(4) (a) Walton, J. C. Synthetic Strategies for 5- and 6-Membered Ring Azaheterocycles Facilitated by Iminyl Radicals. *Molecules* **2016**, *21*, 660. (b) Jackman, M. M.; Cai, Y.; Castle, S. L. Recent Advances in Iminyl Radical Cyclizations. *Synthesis* **2017**, *49*, 1785–1795. (c) Lei, J.; Li, D.; Zhu, Q. Synthesis of Nitrogen-Containing Heterocycles via Imidoyl or Iminyl Radical Intermediates. *Top. Heterocycl. Chem.* **2018**, *54*, 285–320. (d) Yin, W.; Wang, X. Recent Advances in Iminyl Radical-Mediated Catalytic Cyclizations and Ring-Opening Reactions. *New. J. Chem.* **2019**, *43*, 3254–3264.

(5) (a) Davies, J.; Booth, S. G.; Essafi, S.; Dryfe, R. A. W.; Leonori, D. Visible-Light-Mediated Generation of Nitrogen-Centered Radicals: Metal-Free Hydroimination and Iminohydroxylation Cyclization Reactions. *Angew. Chem., Int. Ed.* **2015**, *54*, 14017–14021. (b) Yang, H.-B.; Selander, N. Divergent Iron-Catalyzed Coupling of *O*-Acyloximes with Silyl Enol Ethers. *Chem. - Eur. J.* **2017**, *23*, 1779–1783. (c) Yan, H.-B.; Pathipati, S. R.; Selander, N. Nickel-Catalyzed 1,2-Aminoarylation of Oxime Ester-Tethered Alkenes with Boronic Acids. *ACS Catal.* **2017**, *7*, 8441–8445. (d) Cai, S.-H.; Xie, J.-H.; Song, S.; Ye, L.; Feng, C.; Loh, T.-P. Visible-Light Promoted Carboimination of Unactivated Alkenes for the Synthesis of Densely Functionalized Pyrroline Derivatives. *ACS Catal.* **2016**, *6*, 5571–5574. (e) Guo, K.; Zhang, H.; Cao, S.; Gu, C.; Zhou, H.; Li, J.; Zhu, Y. Copper-Catalyzed Domino Cyclization/Trifluoromethylthiolation of Unactivated Alkenes: Access to SCF_3-Containing Pyrrolines. *Org. Lett.* **2018**, *20*, 2261–2264. (f) Shimbayashi, T.; Nakamoto, D.; Okamoto, K.; Ohe, K. Facile Construction of Tetrahydropyrrolizines by Iron-Catalyzed Double Cyclization of Alkene-Tethered Oxime Esters with 1,2-Disubstituted Alkenes. *Org. Lett.* **2018**, *20*, 3044–3048. (g) Wang, Y.; Ding, J.; Zhao, J.; Sun, W.; Lian, C.; Chen, C.; Zhu, B. Iminyl Radical-Promoted Imino Sulfonylation, Imino Cyanogenation and Imino Thiocyanation of γ,δ-Unsaturated Oxime Esters: Synthesis of Versatile Functionalized Pyrrolines. *Org. Chem. Front.* **2019**, *6*, 2240–2244. (h) Chen, C.; Bao, Y.; Zhao, J.; Zhu, B. Silver-Promoted Cascade Radical Cyclization of γ,δ-Unsaturated Oxime Esters with P(O)H Compounds: Synthesis of Phosphorylated Pyrrolines. *Chem. Commun.* **2019**, *55*, 14697–14700. (i) Chen, C.; Ding, J.; Wang, Y.; Shi, X.; Jiao, D.; Zhu, B. Copper-Catalyzed Iminohalogenation of γ,δ-Unsaturated Oxime Esters with Halide Salts: Synthesis of 2-Halomethyl Pyrrolines. *Tetrahedron Lett.* **2019**, *60*, 151000. (j) Zhao, J.; Bao, Y.; Wang, Y.; Chen, C.; Zhu, B. Copper-Catalyzed Group-Transfer Radical Cyclization of γ,δ-Unsaturated Oxime Esters: Synthesis of Ester-Functionalized Pyrrolines. *Asian J. Org. Chem.* **2019**, *8*, 1317. (k) Wang, L.; Wang, C. Copper-Catalyzed Diamination of Oxime Ester-Tethered Unactivated Alkenes with Unprotected Amines. *J. Org. Chem.* **2019**, *84*, 6547–6556. (l) Zhang, Y.; Yin, Z.; Wang, H.; Wu, X.-F. Iron-Catalyzed Carbonylative Cyclization of γ,δ-Unsaturated Aromatic Oxime Esters to Functionalized Pyrrolines. *Chem. Commun.* **2020**, *56*, 7045–7048. (m) Zhang, Y.; Ai, H.-J.; Wu, X.-F. Copper-Catalyzed Carbonylative Synthesis of Pyrrolidine-Containing Amides from γ,δ-Unsaturated Aromatic Oxime Esters. *Org. Chem. Front.* **2020**, *7*, 2986–2990. (n) Zhang, Y.; Wu, X.-F. Iron-Catalyzed Carbonylative Cyclization of γ,δ-Unsaturated Aromatic Oxime Esters with Amines. *Chem. Commun.* **2020**, *56*, 14605–14608.

(6) (a) Forrester, A. R.; Gill, M.; Sadd, J. S.; Thomson, R. H. New Chemistry of Iminyl Radicals. *J. Chem. Soc., Chem. Commun.* **1975**, 291–292. (b) Atmaram, S.; Forrester, A. R.; Gill, M.; Thomson, R. H. Iminyls. Part 9. Intramolecular Addition of an Iminyl to an Alkene. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1721–1724. (c) For an extension of Forrester's observations, see: Boivin, J.; Fouquet, E.; Schiano, A.-M.; Zard, S. Z. Iminyl Radicals: Part III. Further Synthetically Useful Sources of Iminyl Radicals. *Tetrahedron* **1994**, *50*, 1769–1776.

(7) Jiang, H.; Studer, A. Iminyl-Radicals by Oxidation of α-Imino-Oxy Acids: Photoredox-Neutral Alkene Carboimination for the Synthesis of Pyrrolines. *Angew. Chem., Int. Ed.* **2017**, *56*, 12273–12276.

(8) Davies, J.; Sheikh, N. S.; Leonori, D. Photoredox Imino Functionalizations of Olefins. *Angew. Chem., Int. Ed.* **2017**, *56*, 13361–13365.

(9) For recent examples, see: (a) Tu, J.-L.; Liu, J.-L.; Tang, W.; Su, M.; Liu, F. Radical Aza-Cyclization of α-Imino-oxy Acids for Synthesis of Alkene-Containing *N*-Heterocycles via Dual Cobaloxime and Photoredox Catalysis. *Org. Lett.* **2020**, *22*, 1222–1226. (b) Yan, X.; Li, X.; Wang, Y.; Dai, Y.; Yan, X.; Zhao, D.; Xu, X. Iminyl-Radical-Mediated C–C Cleavage/Amination and Alkene Iminoamination Enabled by Visible-Light-Induced Cerium Catalysis. *ACS Sustainable Chem. Eng.* **2021**, *9*, 101–105.

(10) For alternative methods of generating iminyl radicals, see: (a) Gagosz, F.; Zard, S. Z. Generation and Capture of Iminyl Radicals from Ketoxime Xanthates. *Synlett* **1999**, 1978–1980. (b) Lin, X.; Artman, G. D., III; Stien, D.; Weinreb, S. M. Development of

Efficient New Methodology for Generation, Cyclization and Functional Trapping of Iminyl and Amidyl Radicals. *Tetrahedron* **2001**, *57*, 8779–8791. (c) Usami, K.; Yamaguchi, E.; Tada, N.; Itoh, A. Visible-Light-Mediated Iminyl Radical Generation from Benzyl Oxime Ether: Synthesis of Pyrroline via Hydroimination Cyclization. *Org. Lett.* **2018**, *20*, 5714–5717.

(11) (a) 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. (b) For a summary of pioneering work on the generation of iminyl radicals from *O*-aryl oxime ethers, see: Narasaka, K. Synthesis of Azaheterocycles from Oxime Derivatives. *Pure Appl. Chem.* **2003**, *75*, 19–28.

(12) (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.

(13) 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.

(14) 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.

(15) 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.

(16) (a) Yayla, H. G.; Wang, H.; Tarantino, K. T.; Orbe, H. S.; Knowles, R. R. Catalytic Ring-Opening of Cyclic Alcohols Enabled by PCET Activation of Strong O–H Bonds. *J. Am. Chem. Soc.* **2016**, *138*, 10794–10797. (b) For the use of *N*-fluorobenzenesulfonimide as a radical trap, see: Rueda-Becerril, M.; Chatalova Sazepin, C.; Leung, J. C. T.; Okbinoglu, T.; Kennepohl, P.; Paquin, J.-F.; Sammis, G. M. Fluorine Transfer to Alkyl Radicals. *J. Am. Chem. Soc.* **2012**, *134*, 4026–4029.

(17) Hou, T.; Lu, P.; Li, P. Visible-Light-Mediated Benzylic sp^3 C–H Bond Functionalization to C–Br or C–N Bond. *Tetrahedron Lett.* **2016**, *57*, 2273–2276.

(18) Bovino, M. T.; Chemler, S. R. Catalytic Enantioselective Alkene Aminohalogenation/Cyclization Involving Atom Transfer. *Angew. Chem., Int. Ed.* **2012**, *51*, 3923–3927.

(19) Panchaud, P.; Chabaud, L.; Landais, Y.; Ollivier, C.; Renaud, P.; Zigmantas, S. Radical Amination with Sulfonyl Azides: A Powerful Method for the Formation of C–N Bonds. *Chem. - Eur. J.* **2004**, *10*, 3606–3614.

(20) Quiclet-Sire, B.; Zard, S. Z. Fun with Radicals: Some New Perspectives for Organic Synthesis. *Pure Appl. Chem.* **2011**, *83*, 519–551.

(21) (a) Zhdankin, V. V.; Kuehl, C. J.; Krasutsky, A. P.; Bolz, J. T.; Simonsen, A. J. 1-(Organosulfonyloxy)-3(1*H*)-1,2-benziodoxoles: Preparation and Reactions with Alkynyltrimethylsilanes. *J. Org. Chem.* **1996**, *61*, 6547–6551. (b) Liu, X.; Yu, L.; Luo, M.; Zhu, J.; Wei, W. Radical-Induced Metal-Free Alkynylation of Aldehydes by Direct C–H Activation. *Chem. - Eur. J.* **2015**, *21*, 8745–8749.

(22) (a) Boger, D. L.; Wysocki, R. J., Jr.; Ishizaki, T. Synthesis of *N*-(Phenylsulfonyl)-CI, *N*-((*tert*)-Butyloxy)carbonyl)-CI, CI-$CDPI_1$, and CI-$CDPI_2$: CC-1065 Functional Analogues Incorporating the Parent 1,2,7,7a-Tetrahydrocycloprop[1,2-*c*]indol-4-one (CI) Left-Hand Subunit. *J. Am. Chem. Soc.* **1990**, *112*, 5230–5240. (b) Parker, K. A.; Fokas, D. Convergent Synthesis of (±)-Dihydroisocodeine in 11 Steps by the Tandem Radical Cyclization Strategy. A Formal Total Synthesis of (±)-Morphine. *J. Am. Chem. Soc.* **1992**, *114*, 9688–9689.

(23) Paderes, M. C.; Keister, J. B.; Chemler, S. R. Mechanistic Analysis and Optimization of the Copper-Catalyzed Enantioselective Intramolecular Alkene Aminooxygenation. *J. Org. Chem.* **2013**, *78*, 506–515.

(24) While this manuscript was in preparation, a thermally-promoted iminyl radical cyclization was reported: Xue, Y.; Xue, D.; He, Q.; Ge, Q.; Li, W.; Shao, L. Additive-Free Radical Cascade Reaction of Oxime Esters: Synthesis of Pyrroline-Functionalized Phenathridines. *J. Org. Chem.* **2020**, *85*, 12284–12293. This process requires very high temperatures (180 °C) and has only been demonstrated to be viable with isonitriles as radical traps.