

Microwave-promoted transformations of iminyl radicals

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Dedicated to Prof. Samir Z. Zard for his pioneering contributions to the field of radical chemistry

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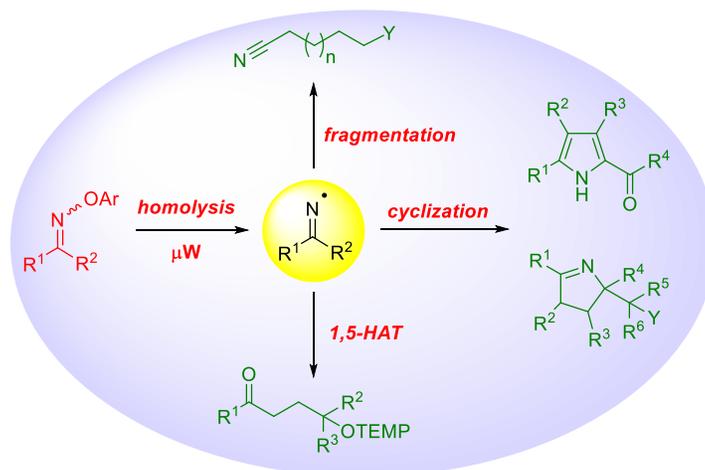
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Abstract

Microwave irradiation of *O*-aryloximes is a convenient method of generating iminyl radicals via direct N–O homolysis. These nitrogen-centered radicals can participate in cyclizations (furnishing 2-acylpyrroles and pyrrolines), ring-opening fragmentations (affording acyclic nitriles), and 1,5-hydrogen atom transfer (HAT) events (delivering γ -functionalized ketones). A wide range of radical trapping agents can be employed, facilitating C–C, C–O, C–N, C–S, or C–X bond formation. The reactions are rapid, simple to execute, and do not require catalysts.



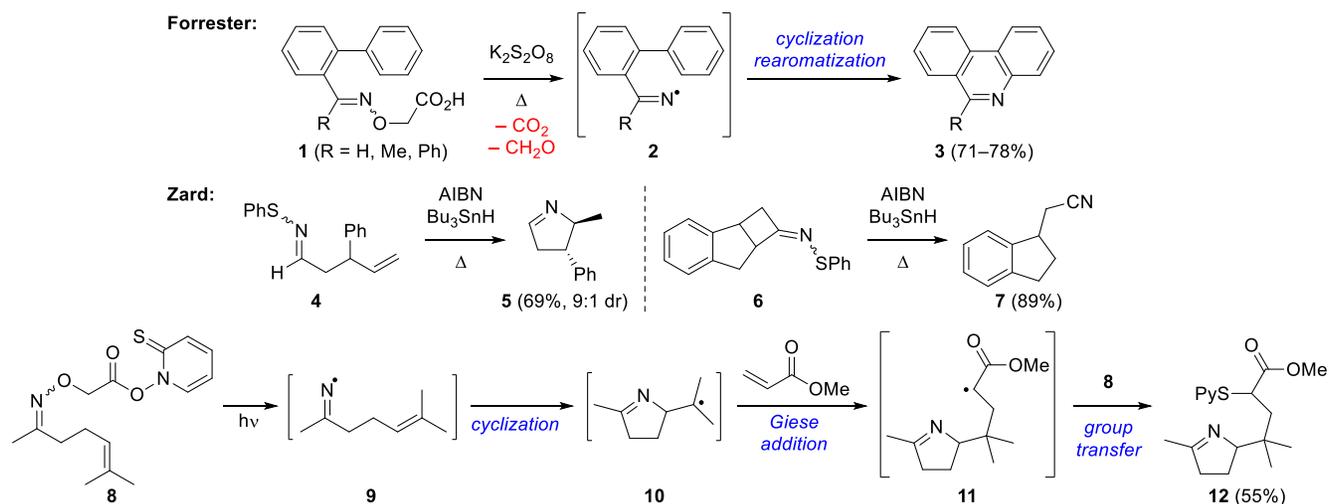
Keywords: Iminyl radicals, microwave irradiation, cyclization, fragmentation, 1,5-hydrogen atom transfer

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1. Introduction

Iminyl radicals are planar nitrogen-centered radicals that possess an unpaired electron in an sp^2 orbital.^{1,2} Accordingly, this electron is orthogonal to the C=N π electrons. The first synthetic application of iminyl radicals was disclosed in 1975 by Forrester, who found that persulfate oxidation of oximinoacetic acid derivatives **1** affords phenanthridines **3**, presumably via the intermediacy of iminyl radicals **2** as shown in Scheme 1.³ Zard subsequently advanced iminyl radical chemistry in the 1990's by developing cyclizations⁴ and ring-opening fragmentations⁵ of iminyl radicals derived from homolysis of sulfenylimines (**4**→**5** and **6**→**7**, Scheme 1). This pioneering investigator of synthetic radical chemistry also devised a cyclization–Giese addition cascade that exploits Barton decarboxylation in the iminyl radical formation step⁶ (**8**→**12**, Scheme 1). Another noteworthy discovery in the 1990's came from Weinreb, who introduced low temperature iminyl radical generation via the Hudson reaction.⁷

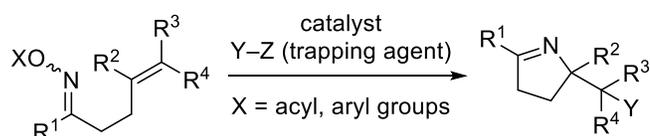


Scheme 1. The pioneering iminyl radical reactions of Forrester and Zard.

Iminyl radical chemistry made a leap forward in the late 2000's when photoredox catalysts^{8–12} and non-photoactive transition metal catalysts^{13,14} were applied to radical reactions. This advance ended the reliance on explosive radical initiators and toxic organotin reagents that was characteristic of conventional synthetic methods involving open-shell intermediates. As a result, an abundance of useful iminyl radical transformations have been introduced in recent years.^{2,15–22} Nevertheless, these modern reactions have limitations that are primarily derived from their dependence on single-electron-transfer (SET) chemistry. These drawbacks are illustrated in Scheme 2 in the context of iminyl radical cyclizations. Beginning with Leonori's seminal report in

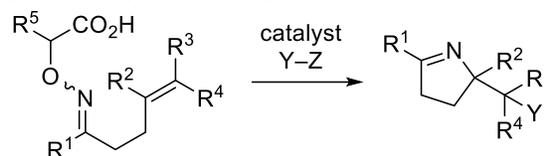
2015,²³ which was presumably inspired by Zhang and Yu's work,²⁴ several 5-*exo-trig* iminyl radical cyclizations have been devised that rely on photoredox chemistry or transition metal catalysis to furnish functionalized pyrrolines after trapping of a cyclic intermediate (i.e., radical, cation, or anion) by a suitable reagent. Most of these processes employ SET reduction of *O*-acyloximes, *O*-aryloximes, or *O*-alkyloximes to generate the requisite iminyl radicals.^{25–33} Consequently, the cyclic radical intermediates must undergo oxidation to regenerate the active catalyst either before or after the trapping event. The necessity of forming a cationic intermediate during the reaction limits the scope of viable traps. Inspired by the work of Forrester,³ in 2017 Studer³⁴ and Leonori³⁵ independently discovered catalytic methods of producing and cyclizing iminyl radicals that are triggered by SET oxidation of oximinoacetic acids (Scheme 2). These protocols achieve turnover via reduction of the cyclic radical intermediate, thereby permitting the use of some trapping agents that are incompatible with cations. However, the requisite anionic intermediate still limits the scope of traps. Additionally, the necessary deprotonation of the carboxylic acid in advance of SET oxidation precludes the use of base-sensitive traps. Clearly, the development of iminyl radical reactions that do not require SET would positively impact the organic synthesis field by overcoming these shortcomings.

Iminyl radical generation by SET reduction of substrate:



- Cyclic adduct must be oxidized to turn catalyst over
- Narrow scope of traps

Iminyl radical generation by SET oxidation of substrate:



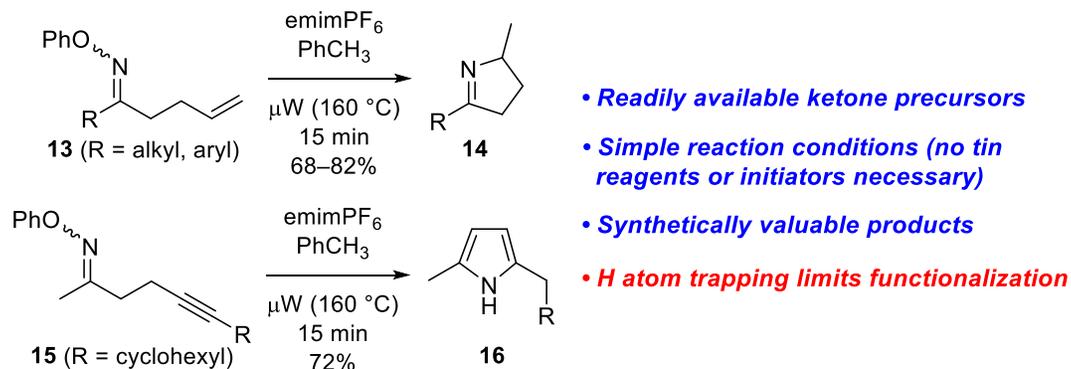
- Base required to deprotonate acid prior to SET
- Cyclic adduct must be reduced to turn catalyst over
- Broader scope of traps than SET reductions, but still limited

Scheme 2. Catalyzed iminyl radical cyclizations based on SET reduction or oxidation.

In recent years, we have investigated the microwave-promoted generation of iminyl radicals via direct N–O homolysis of *O*-aryloximes. This operationally simple process does not involve SET chemistry and is applicable to several different transformations. In this Account, we summarize the studies that we have performed to date in this area. We believe that microwave-promoted iminyl radical chemistry offers a promising and complementary alternative to contemporary methods that are based on SET processes.

2. Inspiration for Our Work

Approximately ten years ago, we encountered some intriguing publications from the Walton group in the course of writing a chapter on radical cyclizations for the second edition of *Comprehensive Organic Synthesis*.³⁶ Walton and co-workers had first discovered that the weak N–O bond of *O*-phenyloximes (BDE = ca. 35 kcal/mol) could be cleaved directly by thermolysis.³⁷ They subsequently found that microwave irradiation enabled clean and rapid iminyl radical reactions. For example, irradiation of *O*-phenyloximes **13** at 160 °C for just 15 minutes furnished pyrrolines **14** in good yield as the products of 5-*exo-trig* cyclization (Scheme 3).³⁸ Exposure of *O*-phenyloxime **15** to identical conditions induced 5-*exo-dig* cyclization followed by aromatization, delivering pyrrole **16**.³⁹

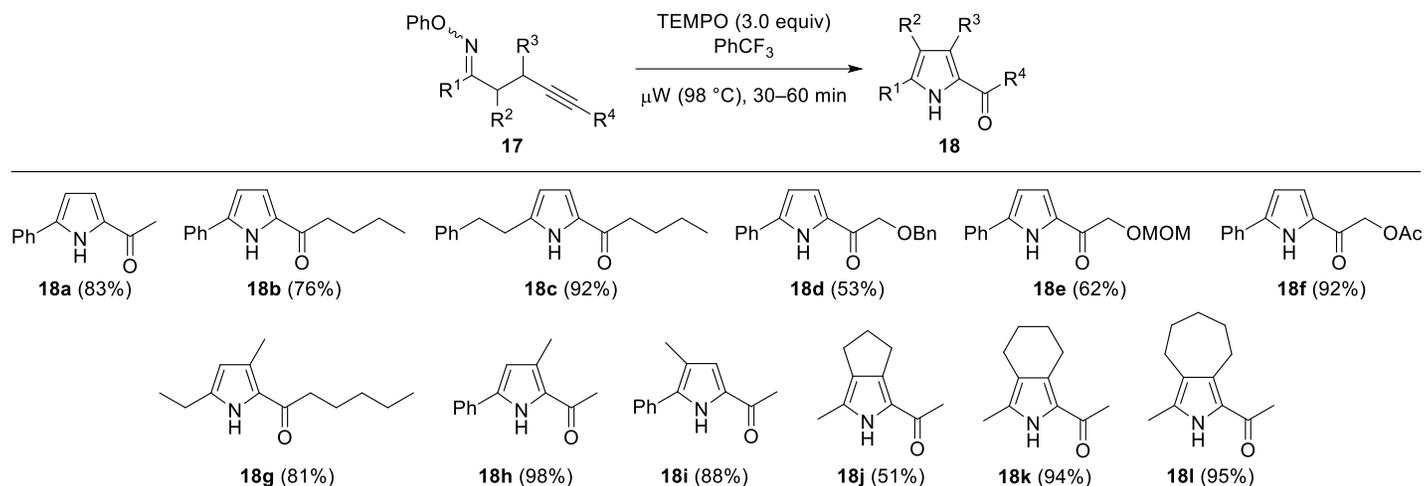


Scheme 3. Walton's microwave-promoted iminyl radical cyclizations.

We were attracted by the simplicity and utility of Walton's microwave-promoted iminyl radical cyclizations. No initiators, propagating agents, or catalysts are required, and the substrates are accessed in a single step from readily available ketones. The fact that five-membered nitrogen heterocycles occur frequently in FDA-approved pharmaceuticals⁴⁰ lends additional significance to this work. However, the main limitation of these reactions is derived from their termination via hydrogen atom abstraction from the toluene solvent, thereby preventing functionalization of the cyclic radical intermediate. We reasoned that replacing toluene with solvents that are poor hydrogen atom donors would broaden the scope of these reactions by permitting trapping of the radical intermediates by reagents capable of introducing a host of different functional groups. This hypothesis launched our investigations of microwave-promoted iminyl radical reactions.

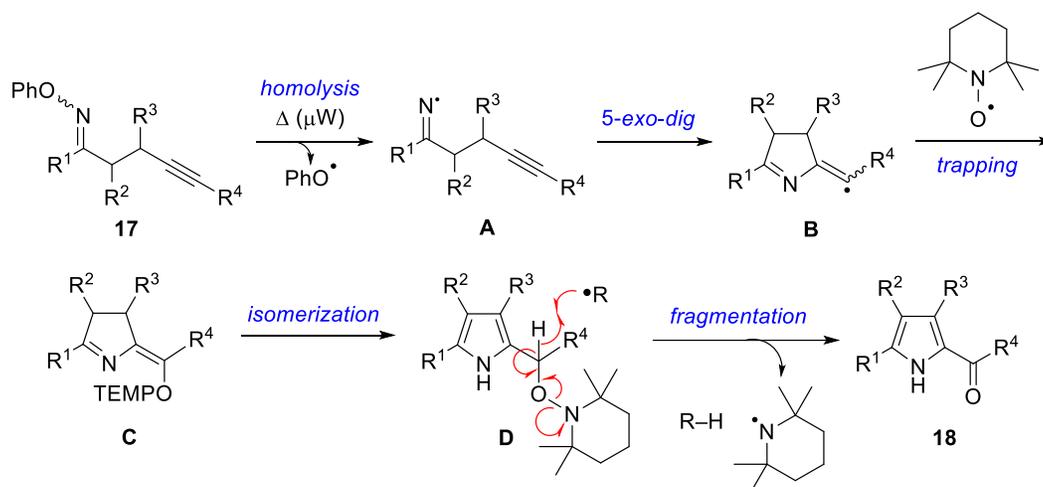
3. Iminyl Radical Cyclizations

We began by studying 5-*exo-dig* cyclizations of *O*-phenyloximes **17** that contain alkyne radical acceptors (Scheme 4). We discovered that trifluorotoluene was an excellent solvent, facilitating cyclizations of **17** at lower temperatures than were used in Walton's protocol. Moreover, the ionic liquid 1-ethyl-3-methyl-1*H*-imidazol-3-ium hexafluorophosphate (emimPF₆), which was required by Walton to enable microwave heating in nonpolar toluene, was unnecessary since the polar solvent could be directly heated by absorption of microwaves. The elimination of toluene from the reaction mixture allowed us to explore TEMPO trapping of the cyclic radical intermediates. To our surprise, 2-acylpyrroles **18** were obtained from the reactions in good to excellent yields. A wide range of products were produced under the mild reaction conditions, including those containing acid-sensitive (**18e**) or base-sensitive (**18f**) functional groups. The short reaction times (≤ 1 h) can be attributed to the rapid and uniform heating of the solution that is accomplished by microwave irradiation.⁴¹



Scheme 4. Synthesis of 2-acylpyrroles via microwave-promoted 5-*exo-dig* iminyl radical cyclizations.

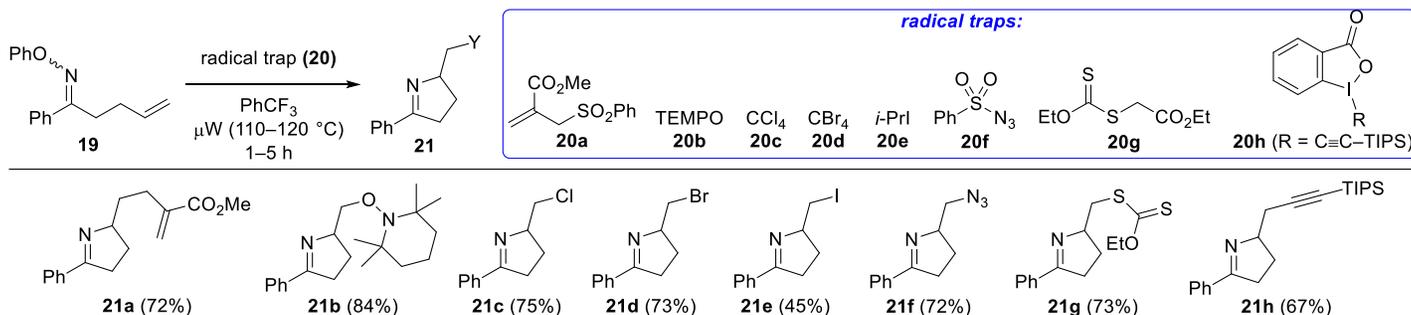
The 2-acylpyrroles were not the expected products of these iminyl radical cyclizations. Accordingly, we performed experiments designed to elucidate the reaction pathway. A mechanism that is consistent with these experiments is shown in Scheme 5. Microwave irradiation of *O*-phenyloxime **17** first triggers N–O homolysis, furnishing iminyl radical **A**. 5-*exo-dig* cyclization of this species affords vinyl radical **B**, which is trapped by TEMPO to deliver enol ether **C**. Thermally-promoted isomerization of **C** then produces pyrrole **D**, which we originally predicted would be the final product of the reaction. We did not anticipate that formation of the aromatic pyrrole ring would weaken the adjacent C–H bond sufficiently to enable a radical fragmentation.⁴² This elimination can presumably be triggered by any of the endogenous radicals (i.e., PhO[•], TEMPO, or tetramethylpiperidinyl radical).



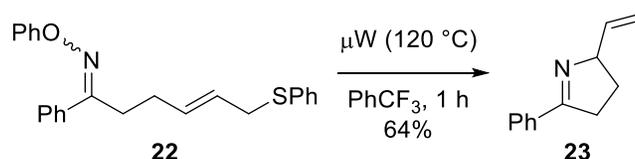
Scheme 5. Proposed mechanism of 2-acylpyrrole synthesis.

We next studied 5-*exo-trig* iminyl radical cyclizations of alkene-containing *O*-phenyloxime **19** (Scheme 6).⁴³ Although these reactions required higher temperatures and longer reaction times than the 5-*exo-dig* cyclizations, they are still more rapid (typically 1–2 h, with one example needing 5 h for completion) than the analogous transformations involving catalysts and SET chemistry (12–24 h reaction times).^{23,25–32,34,35} Importantly, the absence of SET cycles permits a broad range of trapping agents **20a–h** to be employed. Thus,

C–C, C–O, C–Cl, C–Br, C–I, C–N, and C–S bonds can all be forged, producing functionalized pyrrolines **21a–h** in good yields. Additionally, microwave irradiation of allylic sulfide **22** triggered 5-*exo-trig* cyclization followed by β -elimination of a thiyl radical^{44,45} from the cyclic alkyl radical intermediate (Scheme 7).⁴³ This tandem process delivered pyrroline **23**, which contains a terminal alkene that can be converted into various other functional groups.

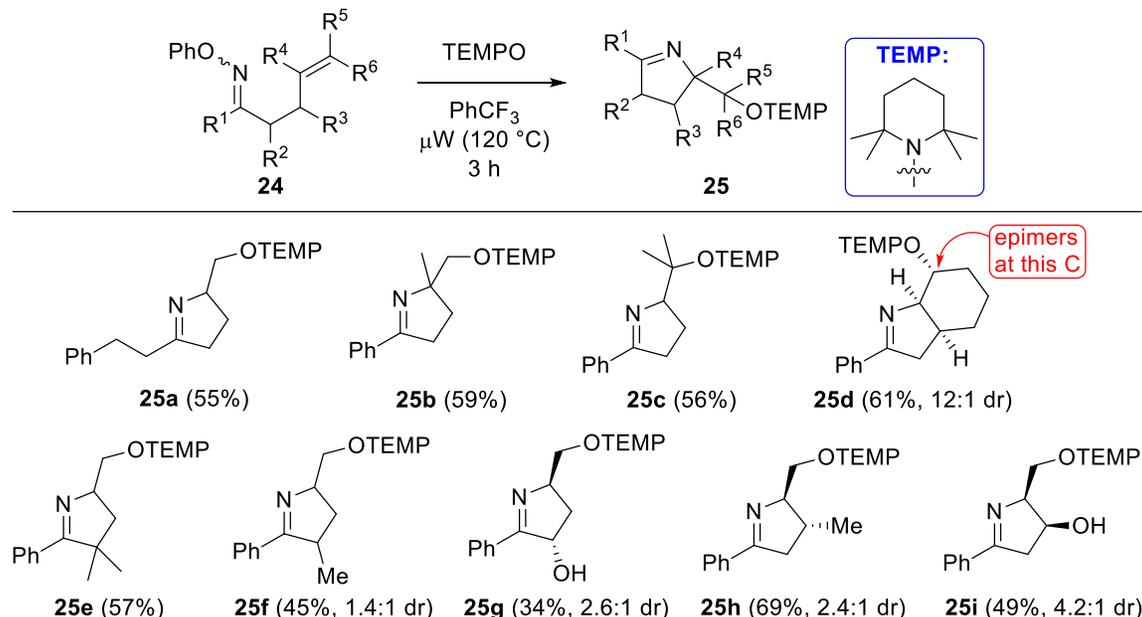


Scheme 6. Scope of radical traps in microwave-promoted 5-*exo-trig* iminyl radical cyclizations.



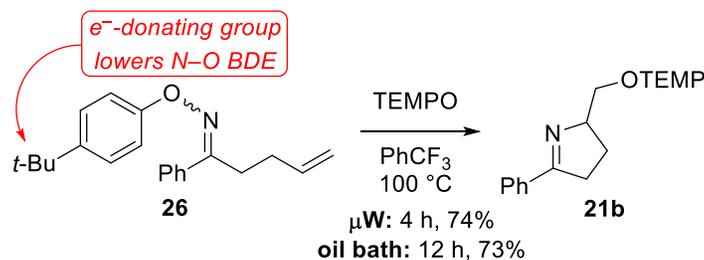
Scheme 7. Tandem 5-*exo-trig* cyclization–thiyl radical β -elimination.

The cyclizations exhibited a wide scope with respect to the *O*-phenyloxime substrates **24** (Scheme 8).⁴³ Previously investigated substrates **19** and **22** contained a phenyl group conjugated to the oxime ether moiety. This conjugation was not required, as evidenced by the production of alkyl-substituted pyrroline **25a**. Alkyl groups were tolerated on the alkene acceptor (e.g., **25b–d**), and substitution of the sp^3 carbons connecting the oxime ether and the alkene was also permitted (e.g., **25e–i**), albeit with modest diastereoselectivity. α,α -Dimethyl-substituted pyrroline **25e** was obtained in good yield, indicating that the iminyl radical intermediate undergoes 5-*exo-trig* cyclization in preference to fragmentation that would generate a nitrile and a tertiary alkyl radical. Although a few of the yields are low, we believe that the large number of viable substrates renders this method useful to the organic synthesis community.



Scheme 8. Scope of *O*-phenyloxime substrates in 5-*exo-trig* iminyl radical cyclizations.

We reasoned that attaching an electron-donating group to the aryl moiety of the oxime would lower the N–O BDE, thereby permitting cyclizations to be conducted at lower temperatures. Accordingly, we prepared substrate **26** bearing a *p*-*tert*-butylphenoxy group. We were pleased to find that **26** underwent facile cyclization and TEMPO trapping when heated to 100 °C in a microwave reactor, delivering pyrroline **21b** in 74% yield (Scheme 9).⁴⁶ Importantly, the reaction proceeded equally well under conventional heating in an oil bath, albeit with a longer reaction time (12 h versus 4 h). Executing iminyl radical cyclizations at lower temperatures can be beneficial for heat-sensitive substrates. Moreover, the ability to perform the reactions in an oil bath simplifies scale-up and benefits researchers who do not have access to a microwave reactor.

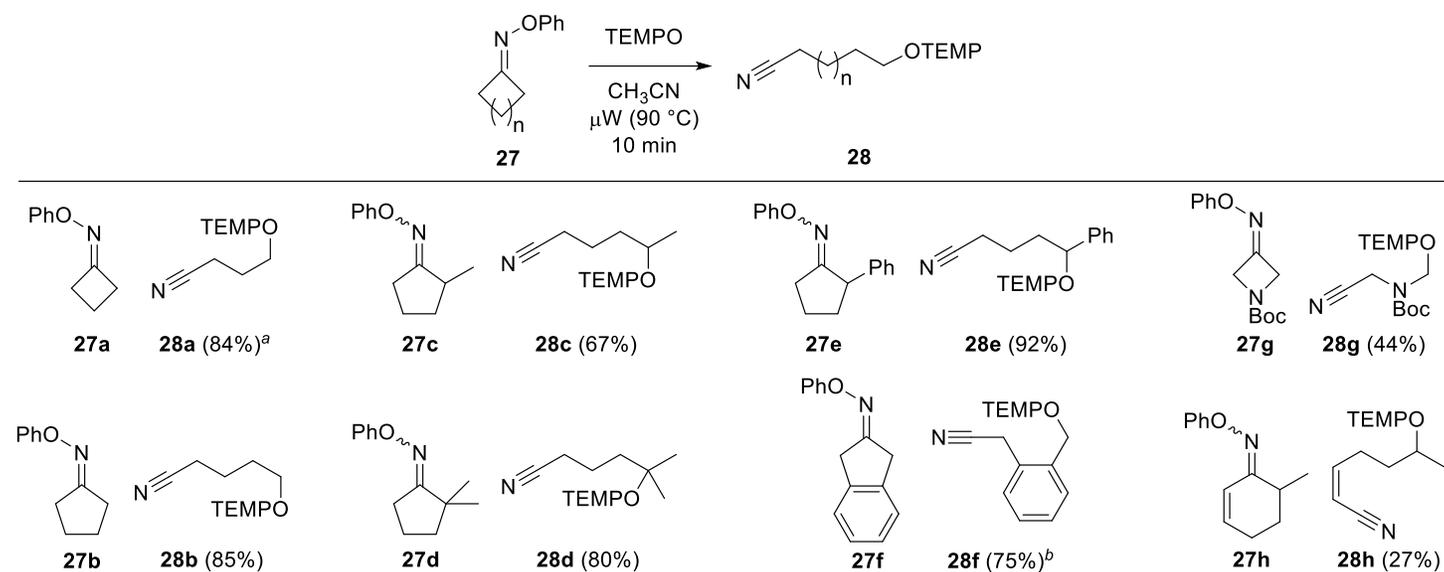


Scheme 9. Second-generation iminyl radical precursor.

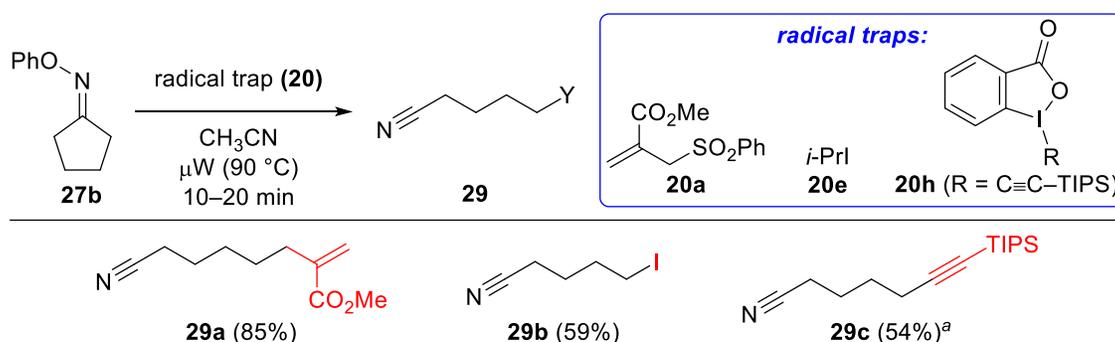
4. Ring-Opening Fragmentations of Iminyl Radicals

Inspired by Zard's work,⁵ we examined microwave-promoted ring-opening fragmentations of cyclic *O*-phenyloximes **27** (Scheme 10).⁴⁷ Microwave irradiation of these substrates in the presence of TEMPO rapidly furnished acyclic nitriles **28**. Four- and five-membered cyclic *O*-phenyloximes underwent facile ring-opening fragmentations, and unsymmetrical substrates (i.e., **27c–e**) produced the less-substituted nitriles exclusively as

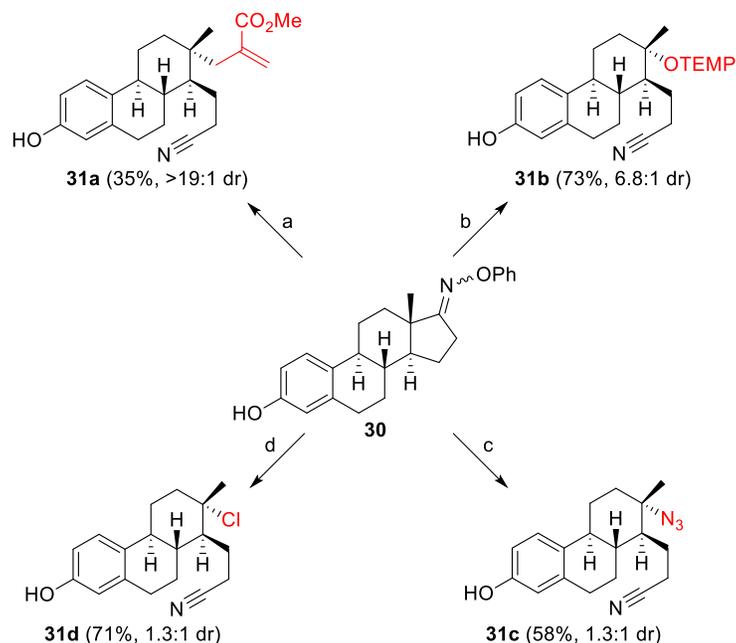
a consequence of generating the more-substituted radical intermediates. Although fragmentation of a cyclohexanone-derived substrate was unsuccessful, presumably due to the lack of ring strain, cyclohexenone-derived *O*-phenyloxime **27h** afforded nitrile **28h** in modest yield. A brief survey of radical traps other than TEMPO with five-membered substrate **27b** revealed that C–C and C–I bonds could be forged in good yields (Scheme 11). The mild reaction conditions and simple protocol rendered this process useful for generating structural diversity via ring-distortion of natural products.⁴⁸ For example, estrone-derived substrate **30** was smoothly transformed into tricyclic adducts **31a–d** (Scheme 12). In the context of this investigation, we expanded the scope of radical trapping to include C–N (i.e., **31c**) and C–Cl (i.e., **31d**) bond formation.⁴⁷



Scheme 10. Fragmentations of cyclic *O*-phenyloximes with TEMPO trapping. ^aPhCF₃ was used as solvent. ^bCH₃CN–CH₂Cl₂ 4:1 was used as solvent.



Scheme 11. Additional radical traps in ring-opening iminyl radical fragmentations. ^aCF₃CH₂OH was used as solvent.

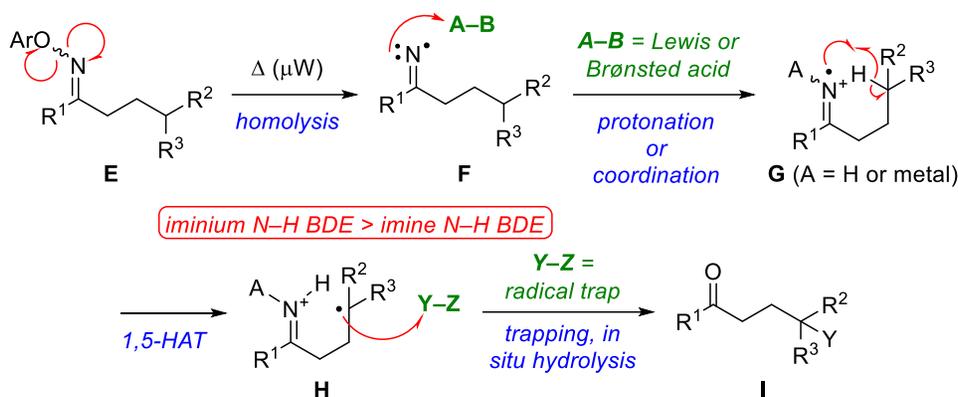


Scheme 12. Fragmentations of estrone-derived *O*-phenyloxime **30**. Reagents and conditions: ^a**20a**, CH₃CN–PhCF₃ 9:1, μ W (90 °C), 20 min; ^b**20b**, CH₃CN–PhCF₃ 9:1, μ W (90 °C), 20 min; ^c**3-PySO₂N₃**, CH₃CN–PhCF₃ 9:1, μ W (90 °C), 20 min; ^d**20c**, CH₃CN–PhCF₃ 9:1, μ W (90 °C), 20 min.

Our paper describing microwave-promoted iminyl radical fragmentations was published in early 2018, and several examples of similar reactions involving transition-metal or organophotoredox catalysts were disclosed concurrently or shortly thereafter.^{25,49–59} Our work is distinguished from these other reports by its simplicity, as iminyl radical formation via direct N–O homolysis enables a rapid and catalyst-free protocol. Moreover, the scope of our method is broad with respect to both substrates (i.e., 4- and 5-membered rings) and radical traps (i.e., C–O, C–C, C–N, C–Cl, and C–I bond formation). Accordingly, we believe that this process will be valuable to the organic synthesis community.

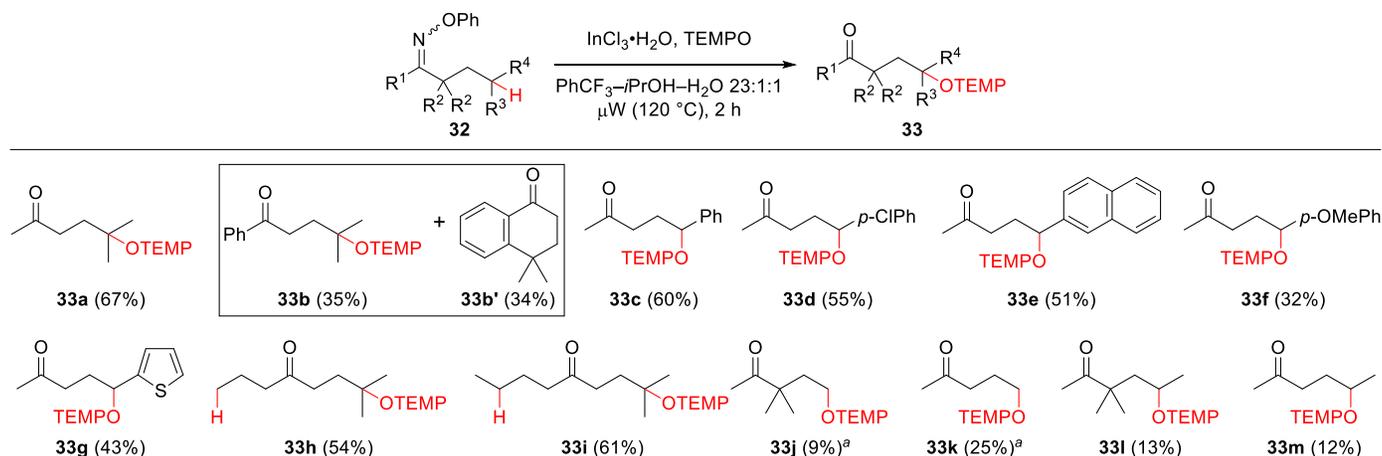
5. 1,5-Hydrogen Atom Transfer Mediated by Iminyl Radicals

The fact that nitrogen-centered radicals are typically of higher energy than alkyl radicals provides a driving force for 1,5-hydrogen atom transfers (HAT) mediated by iminyl radicals.⁶⁰ Indeed, SET-dependent reactions of this type have recently been reported.^{61–70} However, our first attempts at achieving microwave-promoted C–H activation via 1,5-HAT were low-yielding. We reasoned that protonation of the iminyl radical intermediate or coordination of it to a Lewis acid would enhance the prospects for 1,5-HAT due to the substantially higher N–H BDE values of iminium ions relative to those of neutral imines.^{60,61} Thus, protonation or coordination of iminyl radical **F** (generated via homolysis of *O*-aryloxime **E**) would furnish **G**, with the latter possessing a greater propensity to undergo 1,5-HAT than the former (Scheme 13). Then, alkyl radical **H** would be engaged by a radical trap, and in situ hydrolysis of the iminium ion would furnish ketone **I**. The entire process would constitute a formal γ -C(sp³)–H activation of a ketone, since a ketone is the immediate precursor to substrate **E**.



Scheme 13. Proposed mechanism of 1,5-hydrogen atom transfer with acid activation.

We found that $\text{InCl}_3 \cdot \text{H}_2\text{O}$ could facilitate the desired transformation with TEMPO as the radical trap, but its poor solubility in organic solvents was problematic. Fortunately, the PhCF_3 - $i\text{PrOH}$ - H_2O solvent system, which forms a single phase at elevated temperatures,⁷¹ afforded good yields of γ -OTEMP ketone **33a** (Scheme 14).⁷² The scope of the C-H activation is good when tertiary or benzylic secondary radicals are formed, although cyclization of a tertiary radical onto an aromatic ring can compete with TEMPO trapping (i.e., **33b** and **33b'**). The exclusive formation of ketones **33h** and **33i** indicates that tertiary radicals are produced by the 1,5-HAT in



Scheme 14. Scope of formal ketone $\gamma\text{-C}(\text{sp}^3)\text{-H}$ activation. ${}^a\text{ClCH}_2\text{CO}_2\text{H}$ was used instead of $\text{InCl}_3 \cdot \text{H}_2\text{O}$, with CH_3CN as solvent.

preference to primary or secondary radicals. Nonbenzylic secondary and primary radicals could also be created by this method, albeit in low yields (i.e., **33j**-**m**). Although more work is necessary for this method to become synthetically useful, it is important to note that related protocols involving catalysts and SET chemistry have yet to achieve C-H activation of a nonstabilized primary carbon.⁶³⁻⁶⁵

6. Conclusions

Inspired by the work of Walton,^{37–39} we have investigated the microwave-promoted homolysis of *O*-aryloximes and subsequent transformations of the iminyl radicals generated by this process. Employing solvents that are poor hydrogen atom donors unlocks the ability to introduce a wide range of functional groups by using radical trapping agents. When the iminyl radicals are tethered to alkynes or alkenes, 5-*exo* cyclizations proceed to furnish 2-acylpyrroles⁴¹ or functionalized pyrrolines,^{43,46} respectively. Formation of 4-, 5-, or in some cases 6-membered cyclic iminyl radicals triggers ring-opening fragmentation, delivering acyclic nitriles.⁴⁷ Finally, activation of iminyl radicals by coordination to a Lewis acid facilitates 1,5-HAT, affording γ -functionalized ketones.⁷² When compared to contemporary iminyl radical transformations that involve SET cycles and require catalysts, our catalyst-free microwave-promoted reactions are distinguished by their simplicity, rapid reaction times, and broad scope. Accordingly, we believe that this methodology will be widely used by the organic synthesis community.

Acknowledgements

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References

1. Walton, J. C. *Acc. Chem. Res.* **2014**, *47*, 1406–1416.
<https://doi.org/10.1021/ar500017f>
2. Pratley, C.; Fenner, S.; Murphy, J. A. *Chem. Rev.* **2022**, *122*, 8181–8260.
<https://doi.org/10.1021/acs.chemrev.1c00831>
3. Forrester, A. R.; Gill, M.; Sadd, J. S.; Thomson, R. H. *J. Chem. Soc., Chem. Commun.* **1975**, 291–292.
<https://doi.org/10.1039/C39750000291>
4. Boivin, J.; Fouquet, E.; Zard, S. Z. *Tetrahedron* **1994**, *50*, 1745–1756.
[https://doi.org/10.1016/S0040-4020\(01\)80849-8](https://doi.org/10.1016/S0040-4020(01)80849-8)
5. Boivin, J.; Fouquet, E.; Zard, S. Z. *Tetrahedron* **1994**, *50*, 1757–1768.
[https://doi.org/10.1016/S0040-4020\(01\)80850-4](https://doi.org/10.1016/S0040-4020(01)80850-4)
6. Boivin, J.; Fouquet, E.; Schiano, A.-M.; Zard, S. Z. *Tetrahedron* **1994**, *50*, 1769–1776.
[https://doi.org/10.1016/S0040-4020\(01\)80851-6](https://doi.org/10.1016/S0040-4020(01)80851-6)
7. Lin, X.; Stien, D.; Weinreb, S. M. *Org. Lett.* **1999**, *1*, 637–639.
<https://doi.org/10.1021/ol990720e>
8. Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322–5363.
<https://doi.org/10.1021/cr300503r>
9. Romero, N. A.; Nicewicz, D. A. *Chem. Rev.* **2016**, *116*, 10075–10166.
<https://doi.org/10.1021/acs.chemrev.6b00057>
10. Chan, A. Y.; Perry, I. B.; Bissonnette, N. B.; Buksh, B. F.; Edwards, G. A.; Frye, L. I.; Garry, O. L.; Lavagnino, M. N.; Li, B. X.; Liang, Y.; Mao, E.; Millet, A.; Oakley, J. V.; Reed, N. L.; Sakai, H. A.; Seath, C. P.; MacMillan, D. W. C. *Chem. Rev.* **2022**, *122*, 1485–1542.
<https://doi.org/10.1021/acs.chemrev.1c00383>

11. Holmberg-Douglas, N.; Nicewicz, D. A. *Chem. Rev.* **2022**, *122*, 1925–2016.
<https://doi.org/10.1021/acs.chemrev.1c00311>
12. Murray, P. R. D.; Cox, J. H.; Chiappini, N. D.; Roos, C. B.; McLoughlin, E. A.; Hejna, B. G.; Nguyen, S. T.; Ripberger, H. H.; Ganley, J. M.; Tsui, E.; Shin, N. Y.; Koronkiewicz, B.; Qiu, G.; Knowles, R. R. *Chem. Rev.* **2022**, *122*, 2017–2291.
<https://doi.org/10.1021/acs.chemrev.1c00374>
13. Yan, M.; Lo, J. C.; Edwards, J. T.; Baran, P. S. *J. Am. Chem. Soc.* **2016**, *138*, 12692–12714.
<https://doi.org/10.1021/jacs.6b08856>
14. Fu, G. C. *ACS Cent. Sci.* **2017**, *3*, 692–700.
<https://doi.org/10.1021/acscentsci.7b00212>
15. Jackman, M. M.; Cai, Y.; Castle, S. L. *Synthesis* **2017**, *49*, 1785–1795.
<https://doi.org/10.1055/s-0036-1588707>
16. Yin, W.; Wang, X. *New J. Chem.* **2019**, *43*, 3254–3264.
<https://doi.org/10.1039/C8NJ06165C>
17. Xiao, T.; Huang, H.; Anand, D.; Zhou, L. *Synthesis* **2020**, *52*, 1585–1601.
<https://doi.org/10.1055/s-0039-1690844>
18. Chen, C.; Zhao, J.; Shi, X.; Liu, L.; Zhu, Y.-P.; Sun, W.; Zhu, B. *Org. Chem. Front.* **2020**, *7*, 1948–1969.
<https://doi.org/10.1039/D0QO00397B>
19. Xiao, F.; Guo, Y.; Zeng, Y.-F. *Adv. Synth. Catal.* **2021**, *363*, 120–143.
<https://doi.org/10.1002/adsc.202001093>
20. Krylov, I. B.; Segida, O. O.; Budnikov, A. S.; Terent'ev, A. O. *Adv. Synth. Catal.* **2021**, *363*, 2502–2528.
<https://doi.org/10.1002/adsc.202100058>
21. Liu, L.; Duan, X.-H.; Guo, L.-N. *Synthesis* **2021**, *53*, 4375–4388.
<https://doi.org/10.1055/a-1545-6874>
22. Kwon, K.; Simons, R. T.; Nandakumar, M.; Roizen, J. L. *Chem. Rev.* **2022**, *122*, 2353–2428.
<https://doi.org/10.1021/acs.chemrev.1c00444>
23. Davies, J.; Booth, S. G.; Essafi, S.; Dryfe, R. A. W.; Leonori, D. *Angew. Chem., Int. Ed.* **2015**, *54*, 14017–14021.
<https://doi.org/10.1002/anie.201507641>
24. Jiang, H.; An, X.; Tong, K.; Zheng, T.; Zhang, Y.; Yu, S. *Angew. Chem., Int. Ed.* **2015**, *54*, 4055–4059.
<https://doi.org/10.1002/anie.201411342>
25. Yang, H.-B.; Selander, N. *Chem. - Eur. J.* **2017**, *23*, 1779–1783.
<https://doi.org/10.1002/chem.201605636>
26. Cai, S.-H.; Xie, J.-H.; Song, S.; Ye, L.; Feng, C.; Loh, T.-P. *ACS Catal.* **2016**, *6*, 5571–5574.
<https://doi.org/10.1021/acscatal.6b01230>
27. Guo, K.; Zhang, H.; Cao, S.; Gu, C.; Zhou, H.; Li, J.; Zhu, Y. *Org. Lett.* **2018**, *20*, 2261–2264.
<https://doi.org/10.1021/acs.orglett.8b00614>
28. Shimbayashi, T.; Nakamoto, D.; Okamoto, K.; Ohe, K. *Org. Lett.* **2018**, *20*, 3044–3048.
<https://doi.org/10.1021/acs.orglett.8b01073>
29. Chen, C.; Bao, Y.; Zhao, J.; Zhu, B. *Chem. Commun.* **2019**, *55*, 14697–14700.
<https://doi.org/10.1039/C9CC08124K>
30. Wang, L.; Wang, C. *J. Org. Chem.* **2019**, *84*, 6547–6556.
<https://doi.org/10.1021/acs.joc.9b00936>
31. Zhang, Y.; Yin, Z.; Wang, H.; Wu, X.-F. *Chem. Commun.* **2020**, *56*, 7045–7048.

- <https://doi.org/10.1039/D0CC02784G>
32. Shen, X.; Huang, C.; Yuan, X.-A.; Yu, S. *Angew. Chem., Int. Ed.* **2021**, *60*, 9672–9679.
<https://doi.org/10.1002/anie.202016941>
33. Huang, F.; Zhang, S. *Org. Lett.* **2019**, *21*, 7430–7434.
<https://doi.org/10.1021/acs.orglett.9b02740>
34. Jiang, H.; Studer, A. *Angew. Chem., Int. Ed.* **2017**, *56*, 12273–12276.
<https://doi.org/10.1002/anie.201706270>
35. Davies, J.; Sheikh, N. S.; Leonori, D. *Angew. Chem., Int. Ed.* **2017**, *56*, 13361–13365.
<https://doi.org/10.1002/anie.201708497>
36. Loertscher, B. M.; Castle, S. L. In *Comprehensive Organic Synthesis*, 2nd Ed.; Molander, G. A., Knochel, P., Eds.; Elsevier: Oxford, 2014; Vol. 4, pp 742–809.
<https://doi.org/10.1016/B978-0-08-097742-3.00419-5>
37. Blake, J. A.; Pratt, D. A.; Lin, S.; Walton, J. C.; Mulder, P.; Ingold, K. U. *J. Org. Chem.* **2004**, *69*, 3112–3120.
<https://doi.org/10.1021/jo049927y>
38. Portella-Cubillo, F.; Scott, J. S.; Walton, J. C. *Chem. Commun.* **2007**, 4041–4043.
<https://doi.org/10.1039/B712582H>
39. Portella-Cubillo, F.; Scott, J. S.; Walton, J. C. *J. Org. Chem.* **2008**, *73*, 5558–5565.
<https://doi.org/10.1021/jo800847h>
40. Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 10257–10274.
<https://doi.org/10.1021/jm501100b>
41. Cai, Y.; Jalan, A.; Kubosumi, A. R.; Castle, S. L. *Org. Lett.* **2015**, *17*, 488–491.
<https://doi.org/10.1021/ol5035047>
42. Yeung, S. K.; Chan, K. S. *Organometallics* **2005**, *24*, 6426–6430.
<https://doi.org/10.1021/om050661a>
43. Singh, J.; Nickel, G. A.; Cai, Y.; Jones, D. D.; Nelson, T. J.; Small, J. E.; Castle, S. L. *Org. Lett.* **2021**, *23*, 3970–3974.
<https://doi.org/10.1021/acs.orglett.1c01148>
44. Boger, D. L.; Wysocki, R. J., Jr.; Ishizaki, T. *J. Am. Chem. Soc.* **1990**, *112*, 5230–5240.
<https://doi.org/10.1021/ja00169a034>
45. Parker, K. A.; Fokas, D. *J. Am. Chem. Soc.* **1992**, *114*, 9688–9689.
<https://doi.org/10.1021/ja00050a075>
46. 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. *J. Org. Chem.* **2022**, *87*, 16250–16262.
<https://doi.org/10.1021/acs.joc.2c01806>
47. Jackman, M. M.; Im, S.; Bohman, S. R.; Lo, C. C. L.; Garrity, A. L.; Castle, S. L. *Chem.–Eur. J.* **2018**, *24*, 594–598.
<https://doi.org/10.1002/chem.201705728>
48. Huigens, R. W., III; Morrison, K. C.; Hicklin, R. W.; Flood, T. A., Jr; Richter, M. F.; Hergenrother, P. J. *Nat. Chem.* **2013**, *5*, 195–202.
<https://doi.org/10.1038/nchem.1549>
49. Zhao, B.; Shi, Z. *Angew. Chem., Int. Ed.* **2017**, *56*, 12727–12731.
<https://doi.org/10.1002/anie.201707181>
50. Li, L.; Chen, H.; Mei, M.; Zhou, L. *Chem. Commun.* **2017**, *53*, 11544–11547.
<https://doi.org/10.1039/C7CC07347J>

51. Gu, Y.-R.; Duan, X.-H.; Yang, L.; Guo, L.-N. *Org. Lett.* **2017**, *19*, 5908–5911.
<https://doi.org/10.1021/acs.orglett.7b02902>
52. Yang, L.; Gao, P.; Duan, X.-H.; Gu, Y.-R.; Guo, L.-N. *Org. Lett.* **2018**, *20*, 1034–1037.
<https://doi.org/10.1021/acs.orglett.7b03984>
53. Zhang, J.-Y.; Duan, X.-H.; Yang, J.-C.; Guo, L.-N. *J. Org. Chem.* **2018**, *83*, 4239–4249.
<https://doi.org/10.1021/acs.joc.8b00271>
54. Zhao, J.-F.; Duan, X.-H.; Gu, Y.-R.; Gao, P.; Guo, L.-N. *Org. Lett.* **2018**, *20*, 4614–4617.
<https://doi.org/10.1021/acs.orglett.8b01901>
55. Ai, W.; Liu, Y.; Wang, Q.; Lu, Z.; Liu, Q. *Org. Lett.* **2018**, *20*, 409–412.
<https://doi.org/10.1021/acs.orglett.7b03707>
56. Yu, X.-Y.; Chen, J.-R.; Wang, P.-Z.; Yang, M.-N.; Liang, D.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2018**, *57*, 738–743.
<https://doi.org/10.1002/anie.201710618>
57. Yao, S.; Zhang, K.; Zhou, Q.-Q.; Zhao, Y.; Shi, D.-Q.; Xiao, W.-J. *Chem. Commun.* **2018**, *54*, 8096–8099.
<https://doi.org/10.1039/C8CC04503H>
58. Dauncey, E. M.; Morcillo, S. P.; Douglas, J. J.; Sheikh, N. S.; Leonori, D. *Angew. Chem., Int. Ed.* **2018**, *57*, 744–748.
<https://doi.org/10.1002/anie.201710790>
59. Le Vaillant, F.; Garreau, M.; Nicolai, S.; Gryn'ova, G.; Corminboeuf, C.; Waser, J. *Chem. Sci.* **2018**, *9*, 5883–5889.
<https://doi.org/10.1039/C8SC01818A>
60. Forrester, A. R.; Gill, M.; Napier, R. J.; Thomson, R. H. *J. Chem. Soc., Perkin Trans. 1* **1979**, 632–636.
<https://doi.org/10.1039/P19790000632>
61. Dauncey, E. M.; Morcillo, S. P.; Douglas, J. J.; Sheikh, N. S.; Leonori, D. *Angew. Chem., Int. Ed.* **2018**, *57*, 744–748.
<https://doi.org/10.1002/anie.201710790>
62. Jiang, H.; Studer, A. *Angew. Chem., Int. Ed.* **2018**, *57*, 1692–1696.
<https://doi.org/10.1002/anie.201712066>
63. Shen, X.; Zhao, J.-J.; Yu, S. *Org. Lett.* **2018**, *20*, 5523–5527.
<https://doi.org/10.1021/acs.orglett.8b02540>
64. Ma, Z.-Y.; Guo, L.-N.; Gu, Y.-R.; Chen, L.; Duan, X.-H. *Adv. Synth. Catal.* **2018**, *360*, 4341–4347.
<https://doi.org/10.1002/adsc.201801198>
65. Gu, Y.-R.; Duan, X.-H.; Chen, L.; Ma, Z.-Y.; Gao, P.; Guo, L.-N. *Org. Lett.* **2019**, *21*, 917–920.
<https://doi.org/10.1021/acs.orglett.8b03865>
66. Chen, L.; Guo, L.-N.; Ma, Z.-Y.; Gu, Y.-R.; Zhang, J.; Duan, X.-H. *J. Org. Chem.* **2019**, *84*, 6475–6482.
<https://doi.org/10.1021/acs.joc.9b00525>
67. Yin, Z.; Zhang, Z.; Zhang, Y.; Dixneuf, P. H.; Wu, X.-F. *Chem. Commun.* **2019**, *55*, 4655–4658.
<https://doi.org/10.1039/C9CC02112D>
68. Torres-Ochoa, R. O.; Leclair, A.; Wang, Q.; Zhu, J. *Chem.–Eur. J.* **2019**, *25*, 9477–9484.
<https://doi.org/10.1002/chem.201901079>
69. Li, Z.; Torres-Ochoa, R. O.; Wang, Q.; Zhu, J. *Nat. Commun.* **2020**, *11*, 403.
<https://doi.org/10.1038/s41467-020-14292-2>
70. Wu, D.; Cui, S.-S.; Bian, F.; Yu, W. *Org. Lett.* **2021**, *23*, 6057–6061.
<https://doi.org/10.1021/acs.orglett.1c02133>

71. Atik, Z.; Chaou, M. J. *Chem. Eng. Data* **2007**, *52*, 932–935.

<https://doi.org/10.1021/je600526x>

72. Singh, J.; Jones, S. A.; Nelson, T. J.; Botello, J. A.; Castle, S. L. *J. Org. Chem.* **2023**, *88*, 10287–10297.

<https://doi.org/10.1021/acs.joc.3c00915>

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