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4-HO-TEMPO-Catalyzed Redox Annulation of Cyclopropanols with Oxime Acetates toward Pyridine Derivatives

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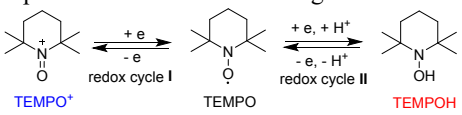
ABSTRACT: A 4-HO-TEMPO-catalyzed redox strategy for the synthesis of pyridines through the annulation of cyclopropanols and oxime acetates has been developed. This protocol features good functional group tolerance, high chemoselectivity, and also promises to be efficient for the late-stage functionalization of skeletons of drugs and natural products. Mechanism studies indicate that the reaction involves the *in-situ* generated *α,β*-unsaturated ketones and imines as the key intermediates, which derived from cyclopropanols and oxime acetates via a TEMPO/TEMPOH redox cycle, respectively. The pyridine products are formed as a result of annulation of enones with imines followed by TEMPO-catalyzed oxidative aromatization by excess oxime acetates. This method not only realizes the TEMPO-catalyzed redox reaction, but also broadens the frontiers for TEMPO in catalysis.

KEYWORDS: *nitroxyl radical catalysis • pyridines • redox reaction • iminyl radical • enones • annulation*

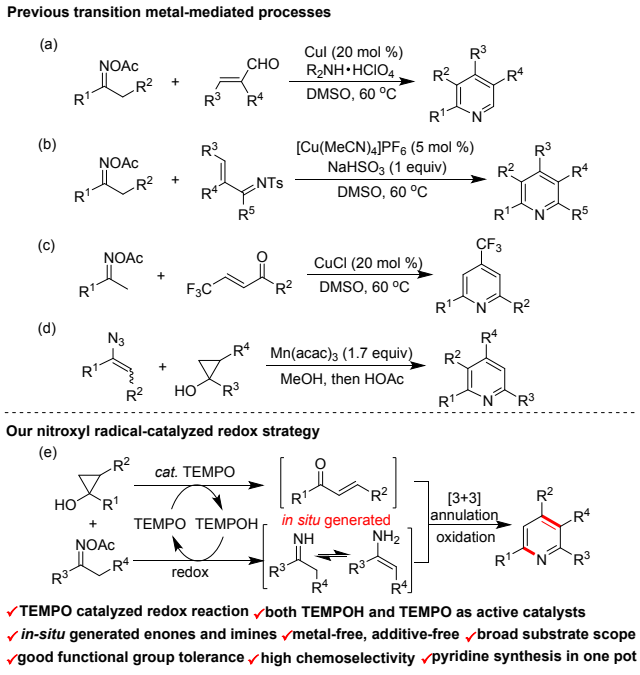
INTRODUCTION

TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl),[1] a well-known persistent nitroxyl radical, has found extensive applications in organic synthesis,[2] polymer chemistry,[3] biochemistry,[4] and material science[5] in past decades. Due to its intermediate valence, TEMPO shows redox properties which could be further oxidized to the corresponding oxoammonium species $TEMPO^+$ (cycle I) as well as undergoes a $1e^-/1H^+$ reduction to hydroxylamine TEMPOH (cycle II) (Scheme 1). Consequently, TEMPO and $TEMPO^+$ salts have been widely used as oxidants in organic reactions. Recently, more and more attention has been paid to the strategy of employing TEMPO as a catalyst in the oxidation reaction by using extra oxidants[2k-u] or electrooxidation[2v-z] to recycle TEMPO. However, most of those catalytic reactions rely on the oxidative property of TEMPO, the reduction of substrates by hydroxylamine TEMPOH has remained largely unappreciated. TEMPO-mediated redox reactions, where both TEMPOH and TEMPO are active catalysts to react with the substrates, have not been reported so far to our knowledge.



Scheme 1. Redox Cycles of TEMPO.

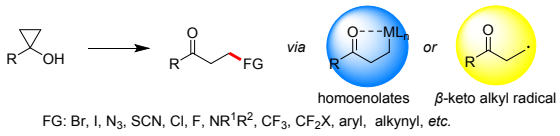
Pyridine scaffolds have attracted widespread attention because they are not only common moieties in natural products and drug molecules, but also play important roles in functional materials, coordination chemistry and organic catalysis.[6] So far, various synthetic approaches have been developed to access pyridine scaffolds.[7] Very recently, the [3+3]-type condensation reaction has been proved to be a practical strategy for constructing pyridine derivatives.[7b,7e-g,8,10a,10b] Among them, oxime esters as the C2N1 synthons as well as the internal oxi-dants have been utilized for the synthesis of structurally di-verse pyridines skeletons. For example, in 2013 and 2017, Yoshikai reported two elegant works for the synthesis of polysubstituted pyridines from oxime esters and *α,β*-unsaturated aldehydes/ketimines under copper catalysis (Scheme 2a and 2b).[8a,b] In 2018, Li and co-workers further investigated the Cu-catalyzed synthesis of fluoroalkylated pyridines from oxime acetates and *β*-CF_3-substituted *α,β*-unsaturated ketones (Scheme 2c).[8c]



Scheme 2. Strategies for Pyridines Synthesis via [3+3] Annulation.

Cyclopropanols, due to their intrinsic strain energy and ready availability, serves as valuable C3 synthons in organic synthesis.[9] During the last decades, many efforts have been made to synthesize *β*-functionalized carbonyl compounds from cyclopropanols[10] via transition-metal mediated oxidative ring-opening (Scheme 3). For instance, Chiba reported an impressive $Mn(OAc)_3$-mediated [3+3] annulation for the

synthesis of pyridines using cyclopropanols and vinyl azides as the substrates (Scheme 2d).[10a,10b] The proposed reaction mechanism involves the formation of *β*-keto alkyl radical intermediates derived from $Mn(OAc)_3$-mediated oxidative radical ring-opening of cyclopropanols, followed by radical addition to vinyl azides and annulation. Despite these achievements, however, transformations of cyclopropanols through new routes, such as the oxidative dehydrogenation to *α,β*-unsaturated ketones, has been rarely reported.[11] During the course of our research on radical-promoted heterocycle synthesis,[12] we found that TEMPO can promote the oxidative ring-opening of cyclopropanols to give *α,β*-unsaturated ketones, with TEMPO being reduced to TEMPOH. When an oxime ester was present in the reaction system, it can be reduced by the *in situ* generated TEMPOH to the corresponding imine. The thus formed imines then underwent [3+3] annulation with the *α,β*-unsaturated ketones generated in the previous step to afford dihydropyridines which were further oxidized to yield pyridine products (Scheme 2e). The whole process takes the form of oxidative annulation between cyclopropanols and oxime esters. As both TEMPO and its reduced form TEMPOH were involved in the process, only a catalytic amount of TEMPO is required to guarantee a complete conversion. To the best of our knowledge, this work represents the first example of the TEMPO-catalyzed redox reaction, where both TEMPOH and TEMPO are active catalysts. Moreover, although transition metal-mediated ring-opening of cyclopropanols[9a,10] and N-O bond cleavage of oxime esters[13] have been well studied, realization of these reactions under metal-free conditions have been rarely reported.[14] This reaction also represents the first example of TEMPO-promoted radical ring-opening of cyclopropanols as well as the first case of TEMPOH-induced N-O bond cleavage of oxime esters. As TEMPO is a nontoxic oxidant and readily available, this method is expected to find applications in the synthesis of pharmaceutically important pyridine compounds. Notably, the present method is suitable for the synthesis of 2,6-disubstituted or 2,3,6-trisubstituted pyridines. These types of pyridines are not easily accessible via annulation of terminal enones and ketoxime esters.[8a-d] Herein we report these results.

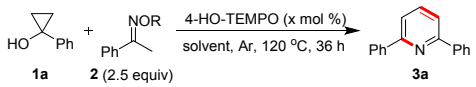


Scheme 3. Transition Metal Mediated Ring-Opening Transformations of Cyclopropanol Derivatives.

RESULTS AND DISCUSSION

We initiated our investigation by stirring 1-phenylcyclopropanol (**1a**, 0.3 mmol) and acetophenone oxime acetate (**2a**, 2.5 equiv) in the presence of 4-HO-TEMPO (20 mol %) in toluene under Ar at 120 °C. To our delight, the desired product 2,6-diphenylpyridine **3a** was produced in 29% yield (Table 1, entry 1). To enhance the reaction efficiency, other solvents such as 1,2-dichloroethane (DCE), 1,4-dioxane, *N*,*N*-dimethylformide (DMF), *N*,*N*-dimethylacetamide (DMA) and dimethylsulfoxide (DMSO) were investigated (Table 1, entries 2-6). Among them, DMSO proved to be superior to other solvents, and the yield of **3a** in DMSO was raised to 78% (Table 1, entry 6). To further improve the yield of **3a**, oxime esters with different electronic properties including pivaloyl (Piv), isobutyryl, benzoyl (Bz), 3,5-dinitro-benzoyl (3,5-dinitro-Bz) were examined (Table 1, entries 7-10). However, no better result was obtained. In addition, the loading amount of catalyst was also explored. When the amount of 4-HO-TEMPO was increased to 30 mol %, there is no significant improvement on the yield of **3a**. When the amount of 4-HO-TEMPO was decreased to 10 mol %, on the other hand, a slight decreasing in yield was observed (Table 1, entries 11 and 12). No reaction took place in the absence of 4-HO-TEMPO (Table 1, entry 13). When the protocol was performed under air, the reaction was obviously suppressed (Table 1, entry 14). TEMPO could also catalyze this reaction to give the desired **3a** in comparable yield (Table 1, entry 15). However, 4-HO-TEMPO was a better option considering its low volatility and easy separability.

Table 1. Optimization of the Reaction Conditions[a]

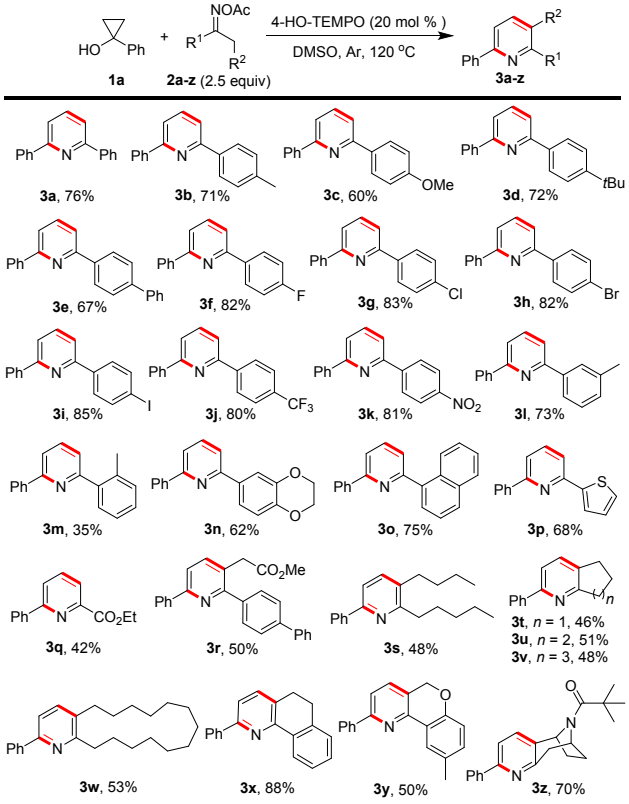


entry	R	4-HO-TEMPO (x mol %)	solvent	yield (%)[b]
1	Ac	20	toluene	29
2	Ac	20	DCE	42
3	Ac	20	1,4-dioxane	53
4	Ac	20	DMF	73
5	Ac	20	DMA	43
6	**Ac**	**20**	**DMSO**	**78**
7	Piv	20	DMSO	74
8	isobutyryl	20	DMSO	75
9	Bz	20	DMSO	50
10	3,5-dinitro-Bz	20	DMSO	43
11	Ac	30	DMSO	79
12	Ac	10	DMSO	70
13	Ac	0	DMSO	0
14[c]	Ac	20	DMSO	<10
15[d]	Ac	20	DMSO	78

[a]All reactions were carried out by stirring **1a** (0.3 mmol), **2a** (2.5 equiv) and 4-HO-TEMPO (x mol %) in solvent (1.5 mL) for 36 h under Ar unless noted otherwise. [b]Yield of isolated product. [c]Reaction was carried out under air. [d]TEMPO (20 mol %) was used instead of 4-HO-TEMPO.

With the optimal conditions established, the synthetic scope of this reaction was investigated next. Variation on oxime acetates was first tested, and the results were summarized in Scheme 4. It can be seen that para-substituted acetophenone oxime acetates with a wide variety of electronic properties reacted very well with **1a** under the indicated conditions to give the desired pyridines **3a-k** in good to excellent yields, exhibiting good tolerance of functional groups such as fluoro, chloro, bromo, iodo, trifluoromethyl, nitro, and ether. When *m*-Me and *o*-Me substituted counterparts were used, the annulation products **3l** and **3m** were obtained in 73% and 35% yields, respectively, indicating an obvious steric effect. 3,4-Disubstituted aceto-phenone oxime acetate was also converted to the expected product **3n** in 62% yield. In addition, 1-naphthyl and 2-thienyl incorporated oxime acetates participated well in the reaction and gave the desired pyridines **3o** and **3p** in good yields. Notably, oxime acetates involving *α*- or *γ*-keto ester were also compatible in the present protocol, affording the corresponding ester substituted pyridines **3q** and **3r** in moderate yields. Moreover, oxime acetates derived from

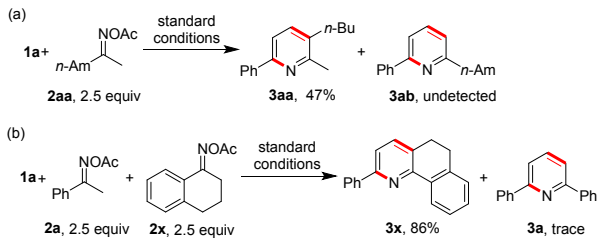
both chain-like and cyclic ketones, such as undecan-6-one, cyclopentanone, cyclohexanone, cycloheptanone, and cyclopentadecanone, were all transformed smoothly in the reaction, delivering 2,3,6-trisubstituted pyridines **3s-w** in medium yields. 3,4-Dihydronaphthalen-1(2H)-one and 6-methyl-chroman-4-one oxime acetates were also good candidates for this tactic, providing the fused pyridines **3x** and **3y** in 88% and 50% yields, respectively. Significantly, the annulation of nitrogen-containing endocyclic oxime acetate was also successful, as demonstrated by the formation of **3z** in 70 % yield.



Scheme 4. Scope of oxime acetates[a,b]

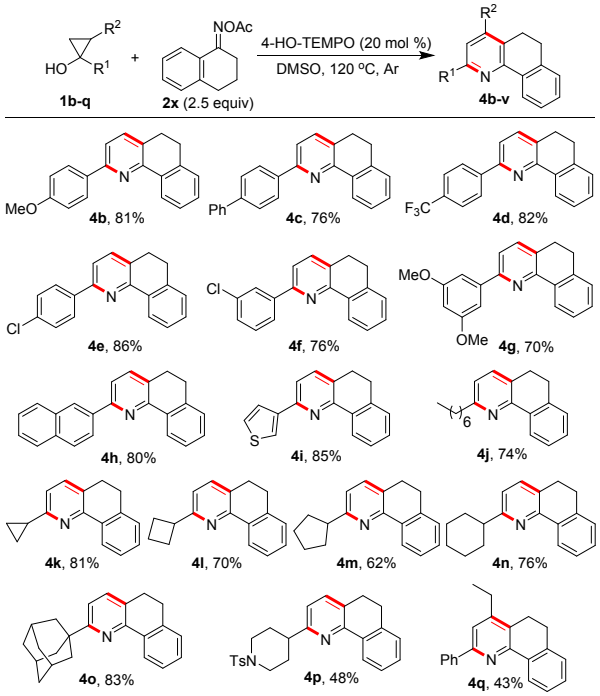
[a]All reactions were carried out by stirring **1a** (0.5 mmol), **2** (2.5 equiv) and 4-HO-TEMPO (20 mol %) in DMSO (2.5 mL) for 24-36 h under Ar unless noted otherwise. [b]Isolated yield.

To further clarify the reactivity of oxime acetate, we employed asymmetric 2-heptanone oxime acetate which possesses two distinct enolizable α-positions to react with **1a**. As shown in Scheme 5a, the reaction resulted in pyridine **3aa** in 47% yield with another possible regioisomer **3ab** undetected, reflecting the internal selectivity of enolizable α-position rather than the distal selectivity. In addition, the intermolecular competitive reaction was also conducted as shown in Scheme 5b. When the mixture of same amount of **2a** and **2x** was allowed to react with **1a**, the competitive reaction gave com pound **3x** in 86% yield along with a trace amount of **3a**, indicating that cyclic oxime acetate **2x** is more reactive than its acyclic counterparts.



Scheme 5. Regioselective and Competitive Reactions of Oxime Acetates

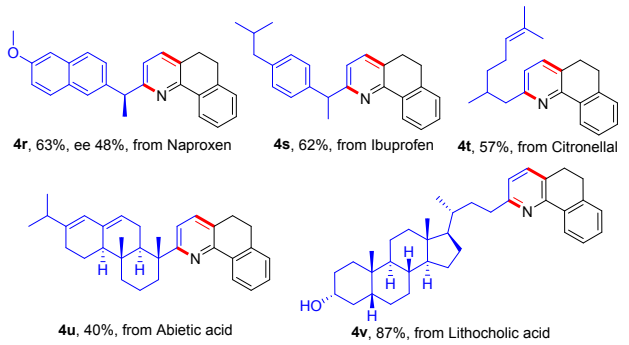
Next, a series of cyclopropanol derivates were tested, and the result is shown in Scheme 6. Phenylcyclopropanols with different substituents on the phenyl ring, such as *p*-MeO, *p*-Ph, *p*-CF_3, *p*-Cl, *m*-Cl, and 3,5-dimethoxyl, were transformed very well under the standard conditions, and the desired pyridines **4b-g** were obtained in good to excellent yields. Naphthalene-2-cyclopropanol and thiophene-3-cyclopropanol also well participated in the reaction, giving rise to the corresponding pyridines **4h** and **4i** in 80% and 85% yield, respectively. Alkyl, cycloalkyl, and adamantyl substituted cyclopropanol derivatives were all good redox partners and generated the desired products **4j-o** in 62-83% yields. In addition, piperidyl substituted cyclopropanol was compatible with this catalytic system as well and converted into the expected pyridines **4p** in 48% yield. Gratifyingly, when 2-ethyl-1-phenylcyclopropanol was involved in the reaction, 2,3,4,6-tetrasubstituted pyridine **4q** was produced in 43% yield.



Scheme 6. Substrate Scope of Cyclopropanols[a,b]

[a]All reactions were carried out by stirring **1** (0.5 mmol), **2x** (2.5 equiv) and 4-HO-TEMPO (20 mol %) in DMSO (2.5 mL) for 24-36 h under Ar unless noted otherwise. [b]Isolated yield.

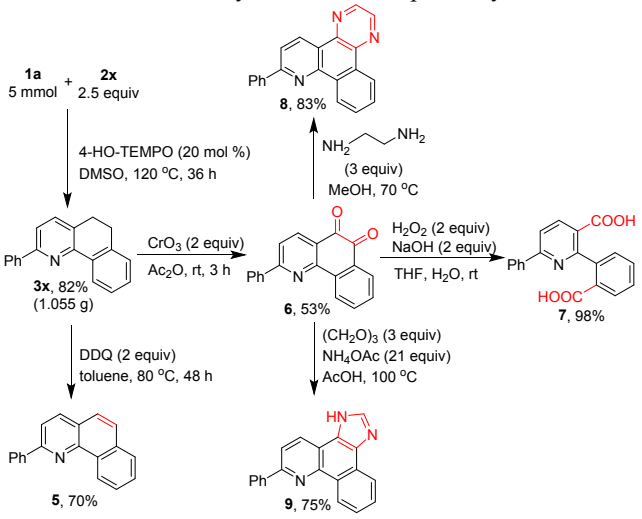
The present protocol is well suitable for late-stage functionalization of complex molecules derived from drugs and natural products (Scheme 7). For instance, cyclopropanols, which were derived from analgesic and anti-inflammatory drugs Naproxen and Ibuprofen participated smoothly in this transformation, yielding the desired products **4r** and **4s** in good yields. Product **4r** was obtained with partial racemization when chiral cyclopropanol **1r** was used. The racemization may be due to the fact that **1r** was oxidized by 4-HO-TEMPO to form a chiral enone intermediate, which is easy to racemize at the α-carbonyl position via enolization, leading to the final annulation product **4r** in partial racemization. Moreover, alkene-containing cyclopropanols derived from terpenes such as citronellal and abietic acid were also suitable for this strategy, affording the desired pyridines **4t** and **4u** in moderate yields. When steroid lithocholic acid derivative was allowed to react under the standard conditions, the corresponding cyclization product **4v** was formed in 87% yield.



Scheme 7. Applications of Natural Products and Drug Molecules[a,b]

[a]All reactions were carried out by stirring **1** (0.5 mmol), **2x** (2.5 equiv), and 4-HO-TEMPO (20 mol %) in DMSO (2.5 mL) for 24-36 h under Ar unless noted otherwise. [b]Isolated yield.

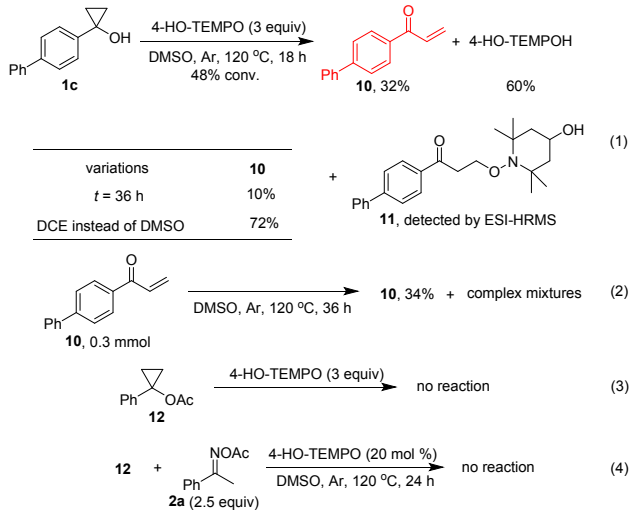
To further explore the practicability of the strategy, gram-scale synthesis of **3x** and its follow-up derivatizations were conducted. As shown in Scheme 8, the reaction of **1a** and **2x** on a gram scale gave **3x** in a yield of 82% (1.055 g). Pyridine **3x** could be converted to benzo[*h*]quinoline **5** via oxidative dehydrogenation. In addition, oxygenation of **3x** gave 2-phenylbenzo[*h*]quinoline-5,6-dione **6**, which could be further oxidized to dicarboxylic acid **7**. Condensation of compound **6** with 1,2-diaminoethane and triformol/NH_4OAc yielded the bioactive fused heterocycles **8** and **9**, respectively.[15]



Scheme 8. Gram-scale Synthesis of 3x and Its Derivatizations.

MECHANISTIC STUDIES

To gain insights into the reaction mechanism, a series of control experiments have been conducted as shown in equations 1-7. First, the oxidation of cyclopropanols by 4-HO-TEMPO as the redox half reaction in the [3+3] annulation was investigated. When cyclopropanol **1c** was treated with stoichiometric 4-HO-TEMPO under the standard conditions in 18 h, the reaction gave enone **10** in 32% yield, accompanied by the generation of 4-HO-TEMPOH in 60% yield under 48% conversion. Besides, the 4-HO-TEMPO trapping product **11** was also detected by ESI-HRMS (details, see SI). When the reaction was prolonged to 36 h till cyclopropanol **1c** was completely consumed, the yield of enone **10** was reduced to 10% due to its instability and polymerization in DMSO (eqs. 1 and 2). However, when DCE was used instead of DMSO as the solvent, the enone **10** was obtained in 72% yield. These results demonstrate that 4-HO-TEMPO could oxidize cyclopropanol to produce enone, with itself being reduced to 4-HO-TEMPOH (eq. 1). Notably, although the *in-situ* generated enones are unstable in DMSO, they could be further transformed to pyridines in the presence of ketoximes esters. In addition, cyclopropanol acetate **12** could neither be oxidized to produce enone by the treatment with 4-HO-TEMPO, nor reacted with oxime acetate **2a** to produce pyridine derivative, demonstrating that free hydroxyl group of cyclopropanol is essential for the reaction (eqs. 3 and 4). These results also indicate that a hydrogen atom transfer (HAT) process is involved in the oxidation of cyclopropanols by 4-HO-TEMPO.



To further elucidate the conversion of cyclopropanols to the corresponding enones by the oxidation of 4-HO-TEMPO under the current circumstances, DFT study (details, see SI) was conducted and the result is shown in Figure 1. The calculated O-H bond BDE of cyclopropanols **1a** is 89.5 kcal mol^{-1} which is close to the reported O-H BDE of 4-HO-TEMPOH (72.2 kcal mol^{-1})[16], indicating that a HAT process between cyclopropanol **1a** and 4-HO-TEMPOH is reasonable (ΔE, about 17.3 kcal mol^{-1}). Indeed, according to the calculations, **1a** first binds rapidly with 4-HO-TEMPO through hydrogen bonding to give intermediate **INT1,** which then undergoes rate-determining hydrogen atom transfer (HAT) to form **INT2** via **TS1**. The energy barrier (27.7 kcal mol^{-1}) for this step is not difficult to overcome at the present reaction temperature. After **INT2** is formed, it would effortlessly be transformed in to *β*-keto alkyl radicals **INT3** (energy barrier: 1.1 kcal mol^{-1}) via radical ring-opening.

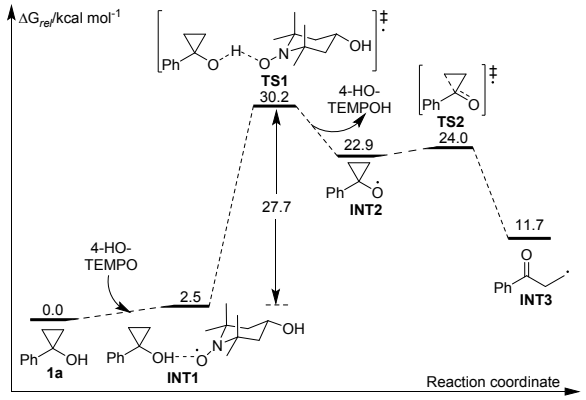


Figure 1. DFT-Computed energy profiles for 4-HO-TEMPO mediated the generation of *β*-keto alkyl radical.

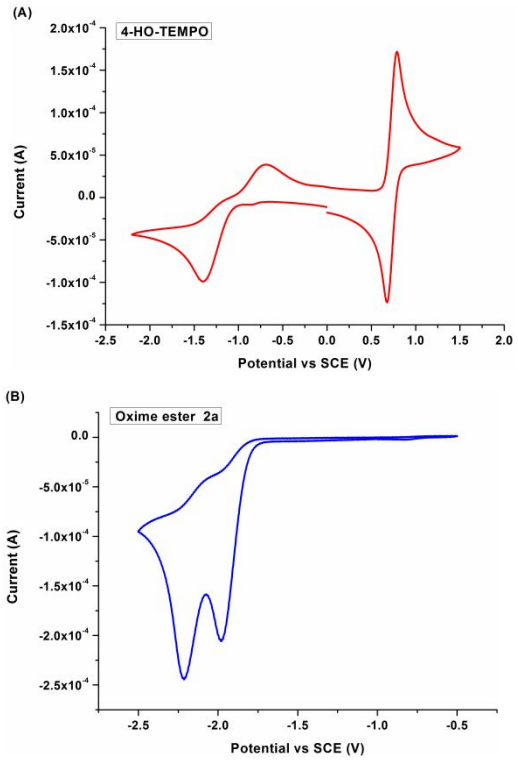
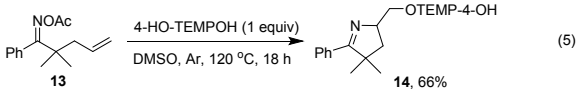


Figure 2. Cyclic voltammograms recorded on a glassy carbon electrode (the diameter: 3 mm) in 0.1 M solution of *n*-Bu_4NBF_4 in CH_3CN. (A) 5 mM 4-HO-TEMPO; (B) 5 mM acetophenone oxime acetate **2a**.

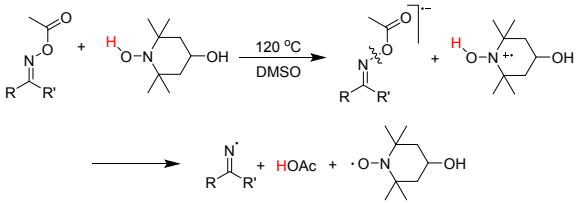
Next, the reduction of oxime acetates by 4-HO-TEMPOH as another redox half reaction in the [3+3] annulation was investigated. By cyclic voltammetry experiments (Figure 2), the half peak reduction potentials of 4-HO-TEMPO and acetophenone oxime acetate **2a** in CH_3CN are -1.2 V vs. SCE (Figure 2A) and -1.9 V vs. SCE (Figure 2B), respectively, indicating that the direct single electron transfer (SET) between ketoxime acetate and 4-HO-TEMPOH might be endoergic. However, it has been well documented that in case that a SET process is followed or accompanied by a proton transfer, it can take place as long as the energy gap does not exceed 1.0 V.[17]

Subsequent control experiments also confirmed the above process. When *γ*,*δ*-unsaturated oxime acetate **13** was treated with stoichiometric 4-HO-TEMPOH, the 4-HO-TEMPO-trapped dihydropyrrole **14** was favorably acquired in 66% yield (eq. 5). Compound **14** can only be formed via cyclization of an iminyl intermediate.



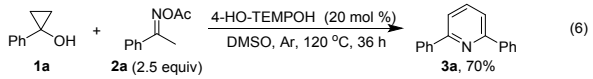
(5)

Thus, it can be concluded that the N-O bond cleavage of the oxime acetate in the reaction was effected via SET reduction by 4-HO-TEMPOH (Scheme 9).



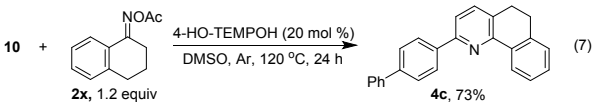
Scheme 9. SET Process between Ketoxime Acetates and 4-HO-TEMPOH.

Significantly, the reaction of **1a** with **2a** could also take place under the catalysis of 4-HO-TEMPOH and gave the same product **3a** in 70% yield, revealing that the reaction could also be initiated by the reduction of oxime acetate as well (eq. 6).



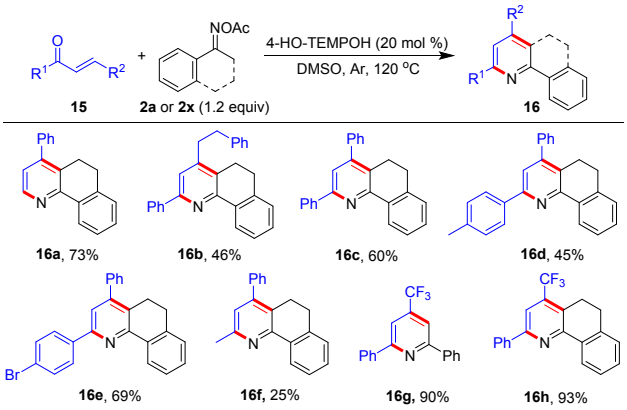
(6)

Moreover, to confirm that enone was the reaction intermediate, enone **10** was allowed to react with **2x** under the catalysis of 4-HO-TEMPOH. As expected, the reaction did take place, giving the corresponding product **4c** in 73% yield (eq. 7). In contrast, the reaction could not take place under the catalysis of 4-HO-TEMPO.



(7)

This result not only indicates that enones could also be used as an alternative of cyclopropanols to react with ketoxime acetate for the synthesis of pyridines, but also provides a novel 4-HO-TEMPOH catalyzed redox-neutral reaction. This modified protocol can be applied to variously substituted enones, with the pyridine products being generated in moderate to good yields (Scheme 10). As enones can be accessed from different precursors from those of cyclopropanols, this 4-HO-TEMPOH mediated protocol serves as the complement to that described above. However, as the terminal enones are liable to polymerize, using cyclopropanols as substrates is more suitable for the preparation of 4-unsubstituted pyridines which would otherwise involve the annulation of terminal enones with oxime acetates.[18]

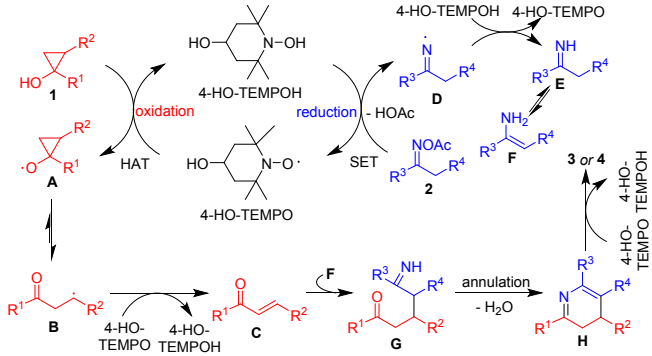


Scheme 10. 4-HO-TEMPOH Catalyzed [3+3] Annulation[a,b]

[a]All reactions were carried out by stirring **15** (0.3 mmol), **2** (1.2 equiv) and 4-HO-TEMPOH (20 mol %) in DMSO (1.5 mL) for 24 h under Ar unless noted otherwise. [b]Isolated yield.

Based on the experimental results and DFT calculation, a plausible mechanism for the TEMPO-catalyzed redox annulation is proposed in Scheme 11. Initially, a hydrogen atom transfer (HAT) process occurs between cyclopropanols **1** and 4-HO-TEMPO to produce the alkoxyl radical **A** and 4-HO-TEMPOH.[12a,12c] The former species subsequently experiences radical ring-opening to form the carbon radical **B**, which is further dehydrogenated by 4-HO-TEMPO to yield *α*,*β*-unsaturated ketone **C**.[2d,2j,12e] Meanwhile, the N-O bond reductive cleavage of oxime acetates **2** occurs by the action of 4-HO-TEMPOH through a SET process[19] to give iminyl radical **D**, HOAc and 4-HO-TEMPO. **D** further abstracts H-

atom from 4-HO-TEMPOH to yield imine **E** and 4-HO-TEMPO. The former quickly tautomerizes to enamine **F** which then nucleophilically adds to enone **C** to yield the intermediate **G**. Annulation of **G** produces dihydropyridine **H**, which is finally oxidative aromatized by 4-HO-TEMPO to pyridine **3** or **4**. Excess oxime acetate serves as a terminal oxidant to maintain the TEMPO-TEMPOH catalytic cycle.



Scheme 11. Proposed Mechanism.

CONCLUSIONS

In summary, a novel and efficient 4-HO-TEMPO-catalyzed redox approach has been developed for the synthesis of pyridine derivatives through the [3+3] annulation of cyclopropanols and oxime acetates under metal-free conditions. The reaction utilizes the redox cycle of 4-HO-TEMPO/4-HO-TEMPOH to realize the electron and proton transfer between cyclopropanols and oxime acetates. In this way, cyclopropanols and oxime acetates were converted to enones and imines, respectively, which then undergo cascade annulation and oxidative aromatization to yield pyridine derivatives. This tactic not only represents the first example for TEMPO-catalyzed redox reaction, where both TEMPOH and TEMPO are active catalysts, but also has the merits of excellent functional group tolerance, high chemoselectivity, broad substrate scope and good compatibility for the frameworks of natural products and pharmaceutical molecules. By using 4-HO-TEMPOH as the catalyst, the annulation between enones and oxime esters can take place as well to give pyridine products. Further studies on TEMPO-catalyzed redox reaction for the synthetic purpose are ongoing in our laboratory.

ASSOCIATED CONTENT

Supporting Information.

Detailed experimental procedures and spectral data for all products are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

Experimental details and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) For selected reviews including applications of TEMPO in organic synthesis, see: (a) Sheldon, R. A.; Arends, I. W. C. E.; ten Brink, G.-J.; Dijksman, A. Green, Catalytic Oxidations of Alcohols. *Acc. Chem. Res.* **2002**, *35*, 774–781. (b) Sheldon, R. A.; Arends, I. W. C. E. Organocatalytic Oxidations Mediated by Nitroxyl Radicals. *Adv. Synth. Catal.* **2004**, *346*, 1051–1071. (c) Studer, A. Tin-Free Radical Chemistry Using the Persistent Radical Effect: Alkoxyamine Isomerization, Addition Reactions and Polymerizations. *Chem. Soc. Rev.* **2004**, *33*, 267–273. (d) Galli, C.; Gentili, P.; Lanzalunga, O. Hydrogen Abstraction and Electron Transfer with Aminoxyl Radicals: Synthetic and Mechanistic Issues. *Angew. Chem., Int. Ed.* **2008**, *47*, 4790–4796. (e) Tebben, L.; Studer, A. Nitroxides: Applications in Synthesis and in Polymer Chemistry. *Angew. Chem., Int. Ed.* **2011**, *50*, 5034–5068. (f) Sonobe, T.; Oisaki, K.; Kanai, M. Catalytic Aerobic Production of Imines en Route to Mild, Green, and Concise Derivatizations of Amines. *Chem. Sci.* **2012**, *3*, 3249–3255. (g) Mancheño, O. G.; Stopka, T. TEMPO Derivatives as Alternative Mild Oxidants in Carbon-Carbon Coupling Reactions. *Synthesis* **2013**, *45*, 1602–1611. (h) Wertz, S.; Studer, A. Nitroxide-Catalyzed Transition-Metal-Free Aerobic Oxidation Processes. *Green Chem.* **2013**, *15*, 3116–3134. (i) Cao, Q.; Dornan, L. M.; Rogan, L.; Hughes, N. L.; Muldoon, M. J. Aerobic Oxidation Catalysis with Stable Radicals. *Chem. Commun.* **2014**, 50, 4524–4543. (j) Ryland, B. L.; Stahl, S. S. Practical Aerobic Oxidations of Alcohols and Amines with Homogeneous Copper/TEMPO and Related Catalyst Systems. *Angew. Chem., Int. Ed.* **2014**, *53*, 8824–8838. (k) Nutting, J. E.; Rafiee, M.; Stahl, S. S. Tetramethylpiperidine N-Oxyl (TEMPO), Phthalimide N-Oxyl (PINO), and Related N-Oxyl Species: Electrochemical Properties and Their Use in Electrocatalytic Reactions. *Chem. Rev.* **2018**, *118*, 4834–4885.

(2) For selected examples on TEMPO in organic synthesis, see: (a) Liu, Y.-C.; Jiang. Z. Studies on Nitroxides -I- the Synthesis and Reactions of Piperidine Nitroxides. *Chem. J. Chinese U.* **1980**, *1*, 71–80. (b) Maji, M. S.; Pfeifer, T.; Studer, A. Oxidative Homocoupling of Aryl, Alkenyl, and Alkynyl Grignard Reagents with TEMPO and Dioxygen. *Angew. Chem., Int. Ed.* **2008**, *47*, 9547–9550. (c) Nagasawa, S.; Sasano, Y.; Iwabuchi, Y. Synthesis of 1,3-Cycloalkadienes from Cycloalkenes: Unprecedented Reactivity of Oxoammonium Salts. *Angew. Chem., Int. Ed.* **2016**, *55*, 13189–13194. (d) Hu, X.-Q.; Qi, X.; Chen, J.-R.; Zhao, Q.-Q.; Wei, Q.; Lan, Y.; Xiao, W.-J. Catalytic N-radical Cascade Reaction of Hydrazones by Oxidative Deprotonation Electron Transfer and TEMPO Mediation. *Nat. Commun.* **2016**, *7*, 11188–11200. (e) Hu, X.-Q.; Chen, J.; Chen, J.-R.; Yan, D.-M.; Xiao, W.-J. Organophotocatalytic Generation of N- and O-Centred Radicals Enables Aerobic Oxyamination and Dioxygenation of Alkenes. *Chem. Eur. J.* **2016**, *22*, 14141–14146. (f) Türkyilmaz, F.; Kehr, G.; Li, J.; Daniliuc, C. G.; Tesch, M.; Studer, A.; Erker, G. Selective N,O-Addition of the TEMPO Radical to Conjugated Boryldienes. *Angew. Chem., Int. Ed.* **2016**, *55*, 1470–1473. (g) Hamada, S.; Furuta, T.; Wada, Y.; Kawabata, T. Chemoselective Oxidation by Electronically Tuned Nitroxyl Radical Catalysts. *Angew. Chem., Int. Ed.* **2013**, *52*, 8093–8097. (h) Li, X.; Lin, F.; Huang, K.; Wei, J.; Li, X.; Wang, X.; Geng, X.; Jiao, N. Selective α-Oxyamination and Hydroxylation of Aliphatic Amides. *Angew. Chem., Int. Ed.* **2017**, *56*, 12307–12311. (i) Scepaniak, J. J.; Wright, A. M.; Lewis, R. A.; Wu, G.; Hayton, T. W. Tuning the Reactivity of TEMPO by Coordination to a Lewis Acid: Isolation and Reactivity of $MCl_3(\eta^1$-TEMPO) (M = Fe, Al). *J. Am. Chem. Soc.* **2012**, *134*, 19350–19353. (j) Jie, X.; Shang, Y.; Zhang, X.; Su, W. Cu-Catalyzed Sequential Dehydrogenation–Conjugate Addition for β-Functionalization of Saturated Ketones: Scope and Mechanism. *J. Am. Chem. Soc.* **2016**, *138*, 5623–5633. (k) Wang, T.; Jiao, N. TEMPO-catalyzed Aerobic Oxygenation and Nitrogenation of Olefins via C=C

Double-Bond Cleavage. *J. Am. Chem. Soc.* **2013**, *135*, 11692–11695. (l) Moriyama, K.; Kuramochi, M.; Fujii, K.; Morita, T.; Togo, H. Nitroxyl-Radical-Catalyzed Oxidative Coupling of Amides with Silylated Nucleophiles through N-Halogenation. *Angew. Chem., Int. Ed.* **2016**, *55*, 14546–14551. (m) Jiang, X.; Zhang, J.; Ma, S. Iron Catalysis for Room-Temperature Aerobic Oxidation of Alcohols to Carboxylic Acids. *J. Am. Chem. Soc.* **2016**, *138*, 8344–8347. (n) Shibuya, M.; Tomizawa, M.; Suzuki, I.; Iwabuchi, Y. 2-Azaadamantane N-Oxyl (AZADO) and 1-Me-AZADO: Highly Efficient Organocatalysts for Oxidation of Alcohols. *J. Am. Chem. Soc.* **2006**, *128*, 8412–8413. (o) Hoover, J. M.; Stahl, S. S. Highly Practical Copper(I)/TEMPO Catalyst System for Chemoselective Aerobic Oxidation of Primary Alcohols. *J. Am. Chem. Soc.* **2011**, *133*, 16901–16910. (p) Steves, J. E.; Stahl, S. S. Copper(I)/ABNO-Catalyzed Aerobic Alcohol Oxidation: Alleviating Steric and Electronic Constraints of Cu/TEMPO Catalyst Systems. *J. Am. Chem. Soc.* **2013**, *135*, 15742–15745. (q) Maity, S.; Manna, S.; Rana, S.; Naveen, T.; Mallick, A.; Maiti, D. Efficient and Stereoselective Nitration of Mono- and Disubstituted Olefins with $AgNO_2$ and TEMPO. *J. Am. Chem. Soc*. **2013**, *135*, 3355–3358. (r) Zultanski, S. L.; Zhao, J.; Stahl, S. S. Practical Synthesis of Amides via Copper/ABNO-Catalyzed Aerobic Oxidative Coupling of Alcohols and Amines. *J. Am. Chem. Soc.* **2016**, *138*, 6416–6419. (s) Zhang, M.; Chen, C.; Ma, W.; Zhao, J. Visible-Light-Induced Aerobic Oxidation of Alcohols in a Coupled Photocatalytic System of Dye-Sensitized TiO_2 and TEMPO. *Angew. Chem., Int. Ed.* **2008**, *47*, 9730–9733. (t) Lang, X.; Zhao, J.; Chen, X. Visible-Light-Induced Photoredox Catalysis of Dye-Sensitized Titanium Dioxide: Selective Aerobic Oxidation of Organic Sulfides. *Angew. Chem., Int. Ed.* **2016**, *55*, 4697–4700. (u) Romero, N. A.; Margrey, K. A.; Tay, N. E.; Nicewicz, D. A. Site-Selective Arene C-H Amination via Photoredox Catalysis. *Science* **2015**, *349*, 1326–1330. (v) Rafiee, M.; Miles, K. C.; Stahl, S. S. Electrocatalytic Alcohol Oxidation with TEMPO and Bicyclic Nitroxyl Derivatives: Driving Force Trumps Steric Effects. *J. Am. Chem. Soc.* **2015**, *137*, 14751–14757. (w) Badalyan, A.; Stahl, S. S. Cooperative Electrocatalytic Alcohol Oxidation with Electron-Proton-Transfer Mediators. *Nature* **2018**, *535*, 406–410. (x) Qian, X.-Y.; Li, S.-Q.; Song, J.; Xu, H.-C. TEMPO-Catalyzed Electrochemical C–H Thiolation: Synthesis of Benzothiazoles and Thiazolopyridines from Thioamides. *ACS Catal.* **2017**, *7*, 2730–2734. (y) Wu, Y.; Yi, H.; Lei, A. Electrochemical Acceptorless Dehydrogenation of N-Heterocycles Utilizing TEMPO as Organo-Electrocatalyst. *ACS Catal.* **2018**, *8*, 1192–1196. (z) Zhao, H.-B.; Xu, P.; Song, J.; Xu, H.-C. Cathode Material Determines Product Selectivity for Electrochemical C-H Functionalization of Biaryl Ketoximes. *Angew. Chem., Int. Ed.* **2018**, *57*, 15153–15156.

(3) (a) Maehata, H.; Buragina, C.; Cunningham, M. Compartmentalization in TEMPO-Mediated Styrene Miniemulsion Polymerization. *Macromolecules* **2007**, *40*, 7126–7131. (b) Joo, Y.; Agarkar, V.; Sung, S. H.; Savoie, B. M.; Boudouris, B. W. A Nonconjugated Radical Polymer Glass with High Electrical Conductivity. *Science* **2018**, *359*, 1391–1395. (c) Li, F.; Gore, D.; Wang, S.; Lutkenhaus, J. Unusual Internal Electron Transfer in Conjugated Radical Polymers. *Angew. Chem., Int. Ed.* **2017**, *56*, 9856–9859. (d) Tesch, M.; Hepperle, J. A. M.; Klaasen, H.; Letzel, M.; Studer, A. Alternating Copolymerization by Nitroxide-Mediated Polymerization and Subsequent Orthogonal Functionalization. *Angew. Chem., Int. Ed.* **2015**, *54*, 5054–5059.

(4) (a) Hickey, D. P.; McCammant, M. S.; Giroud, F.; Sigman, M. S.; Minteer, S. D. Hybrid Enzymatic and Organic Electrocatalytic Cascade for the Complete Oxidation of Glycerol. *J. Am. Chem. Soc.* **2014**, *136*, 15917–15920. (b) Jiang, J.; Ye, W.; Liu, L.; Wang, Z.; Fan, Y.; Saito, T.; Isogai, A. Cellulose Nanofibers Prepared Using the TEMPO/Laccase/O_2 System. *Biomacromolecules* **2017**, *18*, 288–294.

(5) (a) Bergner, B. J.; Schürmann, A.; Peppler, K.; Garsuch, A.; Janek, J. TEMPO: A Mobile Catalyst for Rechargeable Li-O_2 Batteries. *J. Am. Chem. Soc.* **2014**, *136*, 15054–15064. (b) Wei, X.; Xu, W.; Vijayakumar, M.; Cosimbescu, L.; Liu, T.; Sprenkle, V.; Wang, W. TEMPO-Based Catholyte for High-Energy Density Nonaqueous Redox Flow Batteries. *Adv. Mater.* **2014**, *26*, 7649–7653. (c) Luo, J.; Hu, B.; Debruler, C.; Liu, T. L. A π-Conjugation Extended Viologen as a Two-Electron Storage Anolyte for Total Organic Aqueous Redox Flow Batteries. *Angew. Chem., Int. Ed.* **2018**, *57*, 231–235. (d) Hu, L.; Shi, C.; Guo, K.; Zhai, T.; Li, H.; Wang, Y. Electrochemical Double-Layer Capacitor Energized by Adding an Ambipolar Organic Redox Radical into the Electrolyte. *Angew. Chem., Int. Ed.* **2018**, *57*, 8214–8218.

(6) (a) Horiuch, M.; Murakami, C.; Fukamiya, N.; Yu, D.; Chen, T.-H.; Bastow, K. F.; Zhang, D.-C.; Takaishi, Y.; Imakura, Y.; Lee, K.-H. Tripfordines A−C, Sesquiterpene Pyridine Alkaloids from Tripterygium wilfordii, and Structure Anti-HIV Activity Relationships of Tripterygium Alkaloids. *J. Nat. Prod.* **2006**, *69*, 1271–1274. (b) Fischer, D. F.; Sarpong, R. Total Synthesis of (+)-Complanadine A Using an Iridium-Catalyzed Pyridine C−H Functionalization. *J. Am. Chem. Soc.* **2010**, *132*, 5926–5927. (c) El-Sayed Ali, T. Synthesis of Some Novel Pyrazolo[3,4-*b*]pyridine and Pyrazolo[3,4-*d*]pyrimidine Derivatives Bearing 5,6-Diphenyl-1,2,4-triazine Moiety as Potential Antimicrobial Agents. *Eur. J. Med. Chem.* **2009**, 44, 4385–4392. (d) Zhang, W.; Chen, Y.; Chen, W.; Liu, Z.; Li, Z. Designing Tetrahydroimidazo[1,2-*a*]pyridine Derivatives via Catalyst-Free Aza-Diels−Alder Reaction (ADAR) and Their Insecticidal Evaluation. *J. Agric. Food Chem.* **2010**, *58*, 6296–6299. (e) Makiura, R.; Motoyama, S.; Umemura, Y.; Yamanaka, H.; Sakata, O.; Kitagawa, H. Surface Nano-Architecture of a Metal-Organic Framework. *Nat. Mater.* **2010**, *9*, 565–571. (f) Sasabe, H.; Kido, J. Multifunctional Materials in High-Performance OLEDs: Challenges for Solid-State Lighting. *Chem. Mater.* **2011**, *23*, 621–630. (g) Zhou, M.-D.; Jain, K. R.; Günyar, A.; Baxter, P. N. W.; Herdtweck, E.; Kühn, F. E. Bidentate Lewis Base Adducts of Methyltrioxidorhenium(VII): Ligand Influence on Catalytic Performance and Stability. *Eur. J. Inorg. Chem.* **2009**, 2907–2914. (h) Belhadj, E.; El-Ghayoury, A.; Mazari, M.; Sallé, M. The Parent Tetrathiafulvalene-Terpyridine Dyad: Synthesis and Metal Binding Properties. *Tetrahedron Lett.* **2013**, *54*, 3051–3054. (i) Fu, G. C. Asymmetric Catalysis with "Planar-Chiral" Derivatives of 4-(Dimethylamino)pyridine. *Acc. Chem. Res*. **2004**, *37*, 542–547. (j) Rycke, N. D.; Couty, F.; David, O. R. P. Increasing the Reactivity of Nitrogen Catalysts. *Chem. Eur. J.* **2011**, *17*, 12852–12871.

(7) For selected examples of pyridines synthesis, see: (a) Varela, J. A.; Saá, C. Construction of Pyridine Rings by Metal-Mediated[2 + 2 + 2] Cycloaddition. *Chem. Rev.* **2003**, *103*, 3787–3802. (b) Henry, G. D. De Novo Synthesis of Substituted Pyridines. *Tetrahedron* **2004**, *60*, 6043–6061. (c) Heller, B.; Hapke, M. The Fascinating Construction of Pyridine Ring Systems by Transition Metal-Catalysed [2 + 2 + 2] Cycloaddition Reactions. *Chem. Soc. Rev.* **2007**, *36*, 1085–1094. (d) Varela, J. A.; Saá, C. Recent Advances in the Synthesis of Pyridines by Transition-Metal-Catalyzed [2+2+2] Cycloaddition. *Synlett.* **2008**, *17*, 2571–2578. (e) Hill, M. D. Recent Strategies for the Synthesis of Pyridine Derivatives. *Chem. Eur. J.* **2010**, *16*, 12052–12062. (f) Gulevich, A. V.; Dudnik, A. S.; Chernyak, N.; Gevorgyan, V. Transition Metal-Mediated Synthesis of Monocyclic Aromatic Heterocycles. *Chem. Rev.* **2013***, 113,* 3084–3213. (g) Allais, C.; Grassot, J.-M.; Rodriguez, J.; Constantieux, T. Metal-Free Multicomponent Syntheses of Pyridines. *Chem. Rev.* **2014***, 114,* 10829–10868. (h) Jiang, H.; An, X.; Tong, K.; Zheng, T.; Zhang, Y.; Yu, S. Light-Promoted Iminyl-Radical Formation from Acyl Oximes: A Unified Approach to Pyridines, Quinolines, and Phenanthridines. *Angew. Chem., Int. Ed.* **2015**, *54*, 4055–4059. (i) Ren, Z.-H.; Zhang, Z.-Y.; Yang, B.-Q.; Wang, Y.-Y.; Guan, Z.-H. Copper-Catalyzed Coupling of Oxime Acetates with Aldehydes: A New Strategy for Synthesis of Pyridines. *Org. Lett.* **2011**, *13*, 5394–5397. (j) Zhao, M.-N.; Ren, Z.-H.; Yu, L.; Wang, Y.-Y.; Guan, Z.-H. Iron-Catalyzed Cyclization of Ketoxime Carboxylates and Tertiary Anilines for the Synthesis of Pyridines. *Org. Lett.* **2016,** *18*, 1194–1197.

(8) (a) Wei, Y.; Yoshikai, N. Modular Pyridine Synthesis from Oximes and Enals through Synergistic Copper/Iminium Catalysis. *J. Am. Chem. Soc.* **2013**, *135*, 3756–3759. (b) Tan, W. W.; Ong, Y. J.; Yoshikai, N. Synthesis of Highly Substituted Pyridines through Copper-Catalyzed Condensation of Oximes and α,β-Unsaturated Imines. *Angew. Chem., Int. Ed.* **2017**, *56*, 8240–8244. (c) Bai, D.; Wang, X.; Zheng, G.; Li, X. Redox-Divergent Synthesis of Fluoroalkylated Pyridines and 2-Pyridones through Cu-Catalyzed N-O Cleavage of Oxime Acetates. *Angew. Chem., Int. Ed.* **2018**, *57*, 6633–6637. (d) Huang, H.; Cai, J.; Tang, L.; Wang, Z.; Li, F.; Deng, G.-J. Metal-Free Assembly of Polysubstituted Pyridines from Oximes

and Acroleins. *J. Org. Chem.* **2016**, *81*, 1499–1505. (e) Huang, H.; Cai, J.; Xie, H.; Tan, J.; Li, F.; Deng, G.-J. Transition-Metal-Free N-O Reduction of Oximes: A Modular Synthesis of Fluorinated Pyridines. *Org. Lett.* **2017**, *19*, 3743–3746. (f) Gade, N. R.; Devendram, V.; Pal, M.; Iqbal, J. IBX Mediated Reaction of β-Enamino Esters with Allylic Alcohols: a One Pot Metal Free Domino Approach to Functionalized Pyridines. *Chem. Commun.* **2013**, *49*, 7926–7928. (g) Zhou, Y.; Tang, Z.; Song, Q. Lewis Acid-Mediated [3+3] Annulation for the Construction of Substituted Pyrimidine and Pyridine Derivatives. *Adv. Synth. Catal.* **2017**, *359*, 952–958. (h) Hirai, S.; Horikawa, Y.; Asahara, H.; Nishiwaki, N. Tailor-Made Synthesis of Fully Alkylated/Arylated Nicotinates by $FeCl_3$-Mediated Condensation of Enamino Esters with Enones. *Chem. Commun.* **2017**, *53*, 2390–2393. (i) Chen, G.; Wang, Z.; Zhang, X.; Fan, X. Synthesis of Functionalized Pyridines via Cu(II)-Catalyzed One-Pot Cascade Reactions of Inactivated Saturated Ketones with Electron-Deficient Enamines. *J. Org. Chem.* **2017**, *82*, 11230–11237. (j) Ling, F.; Xiao, L.; Fang, L.; Lv, Y.; Zhong, W. Copper Catalysis for Nicotinate Synthesis through β-Alkenylation/Cyclization of Saturated Ketones with β-Enamino Esters. *Adv. Synth. Catal.* **2018**, *360*, 444–448.

(9) (a) Nikolaev, A.; Orellana, A. Transition-Metal-Catalyzed C-C and C-X Bond-Forming Reactions Using Cyclopropanols. *Synthesis* **2016**, *48*, 1741–1768. (b) Kulinkovich, O. G. The Chemistry of Cyclopropanols. *Chem. Rev.* **2003**, *103*, 2597–2632.

(10) (a) Wang, Y.-F.; Chiba, S. Mn(III)-Mediated Reactions of Cyclopropanols with Vinyl Azides: Synthesis of Pyridine and 2-Azabicyclo[3.3.1]non-2-en-1-ol Derivatives. *J. Am. Chem. Soc.* **2009**, *131*, 12570–12572. (b) Wang, Y.-F.; Toh, K. K.; Ng, E. P. J.; Chiba, S. Mn(III)-Mediated Formal [3+3]-Annulation of Vinyl Azides and Cyclopropanols: A Divergent Synthesis of Azaheterocycles. *J. Am. Chem. Soc.* **2011**, *133*, 6411–6421. (c) Das, P. P.; Belmore, K.; Cha, J. K. SN2′ Alkylation of Cyclopropanols via Homoenolates. *Angew. Chem., Int. Ed.* **2012**, *51*, 9517–9520, (d) Nithiy, N.; Orellana, A. Palladium-Catalyzed Cross-Coupling of Benzyl Chlorides with Cyclopropanol-Derived Ketone Homoenolates. *Org. Lett.* **2014**, *16*, 5854–5857. (e) Ye, Z.; Dai, M. An Umpolung Strategy for the Synthesis of β-Aminoketones via Copper-Catalyzed Electrophilic Amination of Cyclopropanols. *Org. Lett.* **2015**, *17*, 2190–2193. (f) Ye, Z.; Gettys, K. E.; Shen, X.; Dai, M. Copper-Catalyzed Cyclopropanol Ring Opening Csp^3–Csp^3 Cross-Couplings with (Fluoro)Alkyl Halides. *Org. Lett.* **2015**, *17*, 6074–6077. (g) Ydhyam, S.; Cha, J. K. Construction of Seven-Membered Carbocycles via Cyclopropanols. *Org. Lett.* **2015**, *17*, 5820–5823. (h) Zhou, X.; Yu, S.; Kong, L.; Li, X. Rhodium(III)-Catalyzed Coupling of Arenes with Cyclopropanols via C-H Activation and Ring Opening. *ACS Catal.* **2016**, *6,* 647–651. (i) Zhang, H.; Wu, G.; Yi, H.; Sun, T.; Wang, B.; Zhang, Y.; Dong, G.; Wang, J. Copper(I)-Catalyzed Chemoselective Coupling of Cyclopropanols with Diazoesters: Ring-Opening C-C Bond Formations. *Angew. Chem., Int. Ed.* **2017**, *56*, 3945–3950. (j) Jiao, J.; Nguyen, L. X.; Patterson, D. R.; Flowers, R. A. An Efficient and General Approach to β-Functionalized Ketones. *Org. Lett.* **2007**, *9*, 1323–1326. (k) Ilangovan, A.; Saravanakumar, S.; Malayappasamy, S. γ-Carbonyl Quinones: Radical Strategy for the Synthesis of Evelynin and Its Analogues by C-H Activation of Quinones Using Cyclopropanols. *Org. Lett*. **2013**, *15,* 4968–4971. (l) Zhao, H.; Fan, X.; Yu, J.; Zhu, C. Silver-Catalyzed Ring-Opening Strategy for the Synthesis of β- and γ-Fluorinated Ketones. *J. Am. Chem. Soc.* **2015**, *137*, 3490–3493. (m) Kananovich, D. G.; Konik, Y. A.; Zubrytski, D. M.; Järvinga, I.; Lopp, M. Simple Access to β-Trifluoromethyl-Substituted Ketones via Copper-Catalyzed Ring-Opening Trifluoromethylation of Substituted Cyclopropanols. *Chem. Commun.* **2015**, *51*, 8349–8352. (n) Fan, X.; Zhao, H.; Yu, J.; Bao, X.; Zhu, C. Regiospecific Synthesis of Distally Chlorinated Ketones via C-C bond Cleavage of Cycloalkanols. *Org. Chem. Front.* **2016**, *3*, 227–232. (o) Jia, K.; Zhang, F.; Huang, H.; Chen, Y. Visible-Light-Induced Alkoxyl Radical Generation Enables Selective $C(sp^3)$-$C(sp^3)$ Bond Cleavage and Functionalizations. *J. Am. Chem. Soc.* **2016**, *138*, 1514–1517. (p) Elek, G. Z.; Borovkov, V.; Lopp, M.; Kananovich, D. G. Enantioselective One-Pot Synthesis of α,β-Epoxy Ketones via Aerobic Oxidation of Cyclopropanols. *Org. Lett.* **2017**, *19*, 3544–3547. (q) Che, C.; Qian, Z.; Wu, M.; Zhao, Y.; Zhu, G. Intermolecular Oxidative Radical Addition to Aromatic Aldehydes: Direct Access to 1,4- and 1,5-Diketones via Silver-Catalyzed Ring-Opening Acylation of Cyclopropanols and Cyclobutanols. *J. Org. Chem.* **2018**, *83*, 5665–5673.

(11) Ye, Z.; Cai, X.; Li, J.; Dai, M. Catalytic Cyclopropanol Ring Opening for Divergent Syntheses of γ-Butyrolactones and δ-Ketoesters Containing All-Carbon Quaternary Centers. *ACS Catal.* **2018**, *8*, 5907–5914.

(12) (a) Chen, Y.-X.; Qian, L.-F.; Zhang, W.; Han, B. Efficient Aerobic Oxidative Synthesis of 2-Substituted Benzoxazoles, Benzothiazoles, and Benzimidazoles Catalyzed by 4-Methoxy-TEMPO. *Angew. Chem., Int. Ed.* **2008**, *47*, 9330–9333. (b) Han, B.; Wang, C.; Han, R.-F.; Yu, W.; Duan, X.-Y.; Fang, R.; Yang X.-L. Efficient Aerobic Oxidative Synthesis of 2-Aryl Quinazolines via Benzyl C–H Bond Amination Catalyzed by 4-Hydroxy-TEMPO. *Chem*. *Commun*. **2011**, *47*, 7818–7820. (c) Han, B.; Yang, X.-L.; Fang, R.; Yu, W.; Wang, C.; Duan, X.-Y.; Liu, S. Oxime Radical Promoted Dioxygenation, Oxyamination, and Diamination of Alkenes: Synthesis of Isoxazolines and Cyclic Nitrones. *Angew. Chem., Int. Ed.* **2012**, *51*, 8816–8820. (d) Duan, X.-Y.; Zhou, N.-N.; Fang, R.; Yang, X.-L.; Yu, W.; Han, B. Transition from π Radicals to σ Radicals: Substituent-Tuned Cyclization of Hydrazonyl Radicals. *Angew. Chem., Int. Ed.* **2014**, *53*, 3158–3162. (e) Yang, X.-L.; Peng, X.-X.; Chen, F.; Han, B. TEMPO-Mediated Aza-Diels-Alder Reaction: Synthesis of Tetrahydropyridazines Using Ketohydrazones and Olefins. *Org. Lett.*, **2016**, *18*, 2070–2073. (f) Liu, R.-H.; Wei, D.; Han, B.; Yu, W. Copper-Catalyzed Oxidative Oxyamination/Diamination of Internal Alkenes of Unsaturated Oximes with Simple Amines. *ACS Catal.* **2016**, *6*, 6525–6530. (g) Peng, X.-X.; Wei, D.; Han, W.-J.; Chen, F.; Yu, W.; Han, B. Dioxygen Activation via Cu-Catalyzed Cascade Radical Reaction: An Approach to Isoxazoline/Cyclic Nitrone-Featured α-Ketols. *ACS Catal.* **2017**, *7*, 7830–7834. (h) Chen, H.-L.; Wei, D.; Zhang, J.-W.; Li, C.-L.; Yu, W.; Han, B. Synthesis of Halomethyl Isoxazoles/Cyclic Nitrones via Cascade Sequence: 1,2-Halogen Radical Shift as a Key Link. *Org. Lett.* **2018**, *20*, 2906–2910. (i) Chen, F.; Lai, S.-Q.; Zhu, F.-F.; Meng, Q.; Jiang, Y.; Yu, W.; Han, B. Cu-Catalyzed Radical Cascade Annulations of Alkyne-Tethered N-Alkoxyamides with Air: Facile Access to Isoxazolidine/1,2-Oxazinane-Fused Isoquinolin-1(2H)-ones. *ACS Catal.* **2018**, *8*, 8925–8931.

(13) For selected examples about the production of iminyl radicals from oxime esters by transition metals, see: (a) Huang, H.; Ji, X.; Wu, W.; Jiang, H. Transition Metal-Catalyzed C-H Functionalization of N-oxyenamine Internal Oxidants. *Chem. Soc. Rev.* **2015**, *44*, 1155–1171. (b) Tang, X.; Huang, L.; Xu, Y.; Yang, J.; Wu, W.; Jiang, H. Copper-Catalyzed Coupling of Oxime Acetates with Sodium Sulfinates: An Efficient Synthesis of Sulfone Derivatives. *Angew. Chem., Int. Ed.* **2014**, *53*, 4205–4208. (c) Huang, H.; Cai, J.; Ji, X.; Xiao, F.; Chen, Y.; Deng, G.-J. Internal Oxidant-Triggered Aerobic Oxygenation and Cyclization of Indoles under Copper Catalysis. *Angew. Chem., Int. Ed.* **2016**, *55*, 307–311. (d) Alonso, R.; Campos, P. J.; García, B.; Rodríguez, M. A. New Light-Induced Iminyl Radical Cyclization Reactions of Acyloximes to Isoquinolines. *Org. Lett.* **2006**, *8*, 3521–3523. (e) Yu, X.-Y.; Chen, J.-R.; Wang, P.-Z.; Yang, M.-N.; Liang, D.; Xiao, W.-J. A Visible-Light-Driven Iminyl Radical-Mediated C-C Single Bond Cleavage/Radical Addition Cascade of Oxime Esters. *Angew. Chem., Int. Ed.* **2018**, *57*, 738–743. (f) 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. (g) Zard, S. Z. Recent Progress in the Generation and Use of Nitrogen-Centred Radicals. *Chem. Soc. Rev.* **2008**, *37*, 1603–1618. (h) Boivin, J.; Schiano, A.-M.; Zard, S. Z.; Zhang, H. A New Method for the Generation and Capture of Iminyl Radicals. *Tetrahedron Lett.* **1999**, *40*, 4531–4534. (i) Gennet, D.; Zard, S. Z.; Zhang, H. Amidinyl Radicals: New and Useful Intermediates for the Synthesis of Imidazolines and Imidazoles. *Chem. Commun.* **2003**, 1870–1871. (j) Ke, J.; Tang, Y.; Yi, H.; Li, Y.; Cheng, Y.; Liu, C.; Lei, A. Copper-Catalyzed Radical/Radical C_{sp3}-H/P-H Cross-Coupling: α-Phosphorylation of Aryl Ketone O-Acetyloximes. *Angew. Chem., Int. Ed.* **2015**, *54*, 6604–6607. (k) Zhu, Z.; Tang, X.; Li, J.; Li, X.; Wu, W.; Deng, G.; Jiang, H. Synthesis of Enaminones via Copper-Catalyzed Decarboxylative Coupling Reaction under Redox-Neutral Conditions. *Chem. Commun.* **2017**, *53*, 3228–3231. (l) Zhao, B.; Liang, H.-W.; Yang, J.; Yang, Z.; Wei, Y. Copper-Catalyzed Intermolecular Cyclization between Oximes and

Alkenes: A Facile Access to Spiropyrrolines. *ACS Catal.* **2017**, *7*, 5612–5617.

(14) For metal-free ring-opening of cyclopropanols, see: (a) Wang, S.; Guo, L.-N.; Wang, H.; Duan, X.-H. Alkynylation of TertiaryCycloalkanols via Radical C-C Bond Cleavage: A Route to Distal Alkynylated Ketones. *Org. Lett.* **2015**, *17*, 4798–4801. (b) Bloom, S.; Bume, D. D.; Pitts, C. R.; Lectka, T. Site-Selective Approach to β-Fluorination: Photocatalyzed Ring Opening of Cyclopropanols. *Chem. Eur. J.* **2015**, *21*, 8060–8063. For metal-free reduction on oxime esters, see: *ref.* 8d, 8e and (c) Yin, Z.; Rabeah, J.; Brückner, A.; Wu, X.-F. Gallic Acid-Promoted SET Process for Cyclobutanone Oximes Activation and (Carbonylative-)Alkylation of Olefins. *ACS Catal.* **2018**, *8*, 10926–10930. (d) Zhang, J.-J.; Duan, X.-H.; Wu, Y.; Yang, J.-C.; Guo, L.-N. Transition-Metal Free C-C Bond Cleavage/Borylation of Cycloketone Oxime Esters. *Chem. Sci.* **2019**, *10*, 161–166.

(15) (a) Chen, Y.-M.; Liu, Y.-J.; Li, Q.; Wang, K.-Z. pH- and DNA-Induced Dual Molecular Light Switches Based on a Novel Ruthenium(II) Complex. *J. Inorg. Biochem.* **2009**, *103*, 1395–1404. (b) Sainuddin, T.; McCain, J.; Pinto, M.; Yin, H.; Gibson, J.; Hetu, M.; McFarland, S. A. Organometallic Ru(II) Photosensitizers Derived from π-Expansive Cyclometalating Ligands: Surprising Theranostic PDT Effects. *Inorg. Chem.* **2016**, *55*, 83–95. (c) Douaron, G. L.; Ferrié, L.; Sepulveda-Diaz, J. E.; Séon-Méniel, B.; Raisman-Vozari, R.; Michel, P. P.; Figadère, B. Identification of a Novel 1,4,8-Triazaphenanthrene Derivative as a Neuroprotectant for Dopamine Neurons Vulnerable in Parkinson's Disease. *ACS Chem. Neurosci.* **2017,** *8*, 1222–1231. (d) Nagababu, P.; Barui, A. K.; Thulasiram, B.; Devi, C. S.; Satyanarayana, S.; Patra, C. R.; Sreedhar, B. Antiangiogenic Activity of Mononuclear Copper(II) Polypyridyl Complexes for the Treatment of Cancers. *J. Med. Chem.* **2015**, *58*, 5226–5241. (e) Cote, B.; Ducharme, Y.; Frenette, R.; Friesen, R.; Girous, A.; Martins, E.; Hamel, P. Phenanthrene Derivatives as MPGES-1Inhibitors. U.S. Patent 20090209571, Aug 20, 2009.

(16) (a) Luo, Y.-R. *Handbook of Bond Dissociation Energies in Organic Compounds*; CRC Press: New York, 2003; pp 170–208. (b) Mahoney, L. R.; Mendenhall, G. D.; Ingold, K. U. Calorimetric and Equilibrium Studies on Some Stable Nitroxide and Iminoxy Radicals. Approximate Oxygen-Hydrogen Bond Dissociation Energies in Hydroxylamines and Oximes. *J. Am. Chem. Soc.* **1973**, *95*, 8610–8614.

(17) (a) Eberson, L. *Electron-Transfer Reactions in Organic Chemistry*; Springer-Verlag: New York, 1987. (b) Cheng, J.-P.; Lu, Y.; Zhu, X.; Mu, L. Energetics of Multistep versus One-step Hydride Transfer Reactions of Reduced Nicotinamide Adenine Dinucleotide (NADH) Models with Organic Cations and *p*-Quinones. *J. Org. Chem.* **1998**, *63*, 6108–6114. (c) Yang, C.; Liu, Y.; Yang, J.-D.; Li, Y.-H.; Li, X.; Cheng, J.-P. Amination of 3-Substituted Benzofuran-2(3H)-ones Triggered by Single-Electron Transfer. *Org. Lett.* **2016**, *18*, 1036–1039.

(18) (a) Basavaiah, D.; Gowriswarl, V. V. L.; Bharathi, T. K. DABCO Catalyzed Dimerization of α,β-Unsaturated Ketones and Nitriles. *Tetrahedron Lett.* **1987**, *28*, 4591–4592. (b) Inanga, J.; Handa, Y.; Tabuchi, T.; Ostubo, K.; Yamaguchi, M.; Honamato, T. A Facile Reductive Dimerization of Conjugated Acid Derivatives with Samarium Diiodide. *Tetrahedron Lett.* **1991**, *32*, 6557–6558. (c) Lemhadri, M.; Fall, Y.; Doucet, H.; Santelli, M. Palladium-Catalysed Heck Reactions of Alk-1-en-3-ones with Aryl Bromides: A Very Simple Access to (E)-1-Arylalk-1-en-3-ones. *Synthesis* **2009**, *6*, 1021–1035.

(19) For selected examples about TEMPONa as a stoichiometric reductant, see: (a) Li, Y.; Studer, A. Transition-Metal-Free TrifluoromethylAminoxylation of Alkenes. *Angew. Chem., Int. Ed.* **2012**, *51*, 8221–8224. (b) Hartmann, M.; Li, Y.; Studer, A. Transition-Metal-Free Oxyarylation of Alkenes with Aryl Diazonium Salts and TEMPONa. *J. Am. Chem. Soc.* **2012**, *134*, 16516–16519. (c) Zhang, B.; Studer, A. Stereoselective Radical Azidooxygenation of Alkenes. *Org. Lett.* **2013**, *15*, 4548–4551. (d) Hartmann, M.; Li, Y.; Mück-Lichtenfeld, C.; Studer, A. Generation of Aryl Radicals through Reduction of Hypervalent Iodine(III) Compounds with TEMPONa: Radical Alkene Oxyarylation. *Chem. Eur. J.* **2016**, *22*, 3485–3490. (e) Wang, X.; Studer, A. Iodine(III) Reagents in Radical Chemistry. *Acc. Chem. Res.* **2017**, *50*, 1712–1724.

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