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Photocatalytic, Phosphoranyl Radical-Mediated N−O Cleavage of Strained Cycloketone Oximes

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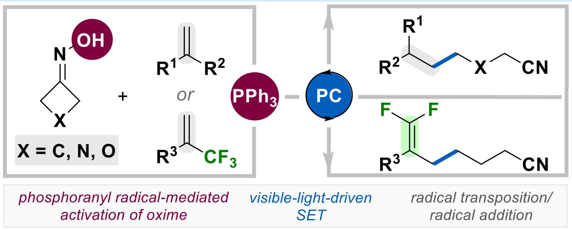
S *Supporting Information*

ABSTRACT: A photoinduced, phosphoranyl radical-mediated protocol for the direct N−O cleavage of strained cycloketone oximes via a polar/SET crossover process was developed for the first time. This visible-light-driven direct N−O activation mode for oxime offers beneficial features such as streamlined synthetic process and versatile photochemical reactivities. Consequently, the alkenes and α-trifluoromethyl alkenes with varied electronic and structural features acted as competent radical receptors in this protocol, enabling facile accesses to a range of elongated cyano and/or *gem*-difluoroalkene-bearing compounds.

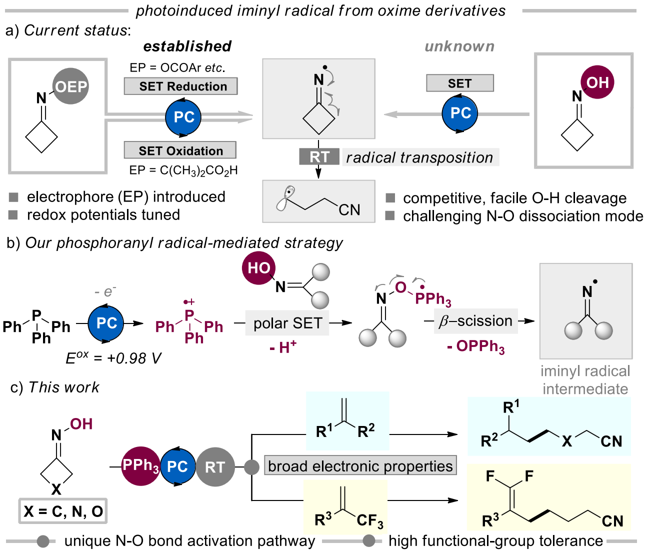


Free radical chemistry plays a vital role in producing molecules with structural complexity and diversity, which always takes a backseat to the classical two-electron-involved methodologies.[1] Development of efficient methods for generating free radicals in a convenient manner is of continuous interest. Over the past decade, visible-light photoredox catalysis, serving as a powerful tool, has witnessed rapid advancements in generating an array of carbon-centered radicals (CCRs)[2] and nitrogen-centered radicals (NCRs).[3] The visible-light photoredox catalysis with overwhelming priorities stimulates the extensive exploitation and breaks through the limit of competent radical precursors in numerous important transformations. Further, it enables facile carbon−carbon bond (C−C) and carbon−heteroatom (C−X) bond-forming.

In recent years, hydroxylamine derivatives have been actively utilized in the generation of NCRs, especially in the domain of visible-light photoredox catalysis.[3c] Specific interests have been attracted to cyclobutanone oximes and their derivatives because they are valuable and versatile intermediates in organic synthesis.[4] Noticeably, cyclobutanone oxime derivatives are capable of generating iminyl radicals through a photocatalytic single-electron transfer, which are prone to undergoing a β-fragmentation radical transposition process. This process, resembling the classical Norrish type-1 reactivity, can deliver highly reactive open-shell carbon radicals (γ-cyanoalkyl radicals).[5] Indeed, cyanoalkyl scaffolds are a class of valuable building blocks owing to their versatility in the conversion into other functional groups, which are frequently encountered in many pharmaceuticals.[6] Following this line, an array of valuable transformations based on the photocatalytic ring-opening of cyclic oxime derivatives has been established.[7,8]

Essentially, there are general two distinct mechanistic pathways depending on the redox potentials of substrates (Scheme 1a). A few elegant reductive approaches by employing redox-active cyclic oxime esters have been well-established by Xiao,[7a−c] Chen,[7a−bc] and Zhou.[7d] An impressive range of π-acceptors encompassing styrenes, alkynes, silyl enol ethers, and

Scheme 1. Photocatalytic Iminyl Radical Formation and Radical Transposition for Strained Cycloketone Oximes



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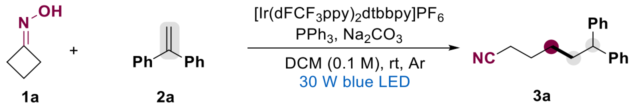
isonitriles is competent to trap the resulting γ-nitrile radicals. In contrast, only rare success on the SET oxidation generating γ-nitrile radicals was documented. Leonori and coauthors[8] strategically introduced α-imino-oxy acids as efficient and easily accessible iminyl radical precursors, which were oxidized by a photoexcited organic sensitizer to the corresponding nitrile radicals. Despite all of these advancements, the implementation of the parent oximes has been considerably overlooked as the introduction of electrophores onto the oxygen atom of cyclic oximes was necessitated to manipulate the redox potentials in all the previous cases. Up to now, to our knowledge, only one exclusive example has been reported by Weinreb and coauthors to employ an oxime for the generation of iminyl radical, in which ultralow temperature was requisite.[9] However, the photoredox generation of iminyl radicals from strained cycloketone oximes under mild conditions has never been harnessed because of the unwanted, competitive O−H bond dissociation in oxime moiety.[10]

The synthetic potentials of phosphoranyl radicals in C−O bond cleavage via β-scission were initially recognized in the early 1970s when Bentrude and coauthors detected these radicals as intermediates by ESR spectroscopy.[11] However, synthetic applications of this strategy for direct deoxygenation remain a great challenge owing to forcing conditions and limited functional group tolerance. Encouragingly, this situation changed dramatically very recently as pioneering independent works from Xie,[12] Zhu,[12b] Doyle,[13] and Rovis[13] realized the direct C−O bond activation via photoredox catalysis with phosphoranyl radicals. More recently, the radical deoxygenation of *N*-hydroxyphthalimide promoted by a phosphite to access phthalimidyl radicals has also been achieved by Schmidt and coauthors.[14] Inspired by these previous elegant works, we questioned if the photocatalytic direct N−O cleavage of oxime could be accomplished via the polar/SET crossover process between phosphoranyl radical and oxime, which might provide a unique solution for this everlasting challenge (Scheme 1b). In this work, we successfully achieved the first photoredox-catalyzed direct N−O bond activation of strained cycloketone oximes via the PPh_3 radical-mediated strategy, enabling a facile access to a series of the elongated 1,1-diarylmethanenitriles and alkyl nitriles (Scheme 1c). More importantly, this innovative pathway for directly activating N−O bond of oxime offers new avenues for synthetic methodology development. Mechanistically, the reductive quenching pathway rendered this developed protocol amenable to broader substrate scope with varied electronic features.

We initiated our investigations by monitoring the reaction of cyclobutanone oxime (**1a**) with 1,1-diphenylethylene (**2a**) in the presence of photocatalyst and phosphine (Table 1). Unless otherwise noted, all the experiments were conducted at room temperature in CH_2Cl_2 under irradiation of 30 W blue LED. Gratifyingly, upon optimization of the reaction conditions (see Table S1 in Supporting Information), 1,1-diarylmethanenitrile **3a** was furnished in a nearly quantitative yield (entry 1). Inert atmosphere and base were beneficial for this photoredox-catalyzed transformation (entries 2 and 3). Among the screened catalysts, $[Ir(dFCF_3ppy)_2dtbbpy]PF_6$ was proven to be the best choice, whereas $MesAcr^+ClO_4^-$ and $Ru(bpy)_3PF_6$ were ineffective in the reaction (entries 4 and 5). Use of $n\text{-}Bu_3P$ in place of PPh_3 resulted in a less efficient reaction (entry 6). Screening of solvents revealed that CH_2Cl_2 was the optimal solvent, and only trace amount of the desired product **3a** was obtained in MeCN (entry 7). Further exploration showed that H_2O has a negligible effect on the reaction (entry 8). As predicted, light, photocatalyst, and phosphine were indispensable for this transformation (entries 9−11).

Table 1. Optimization of the Reaction Conditions[a]

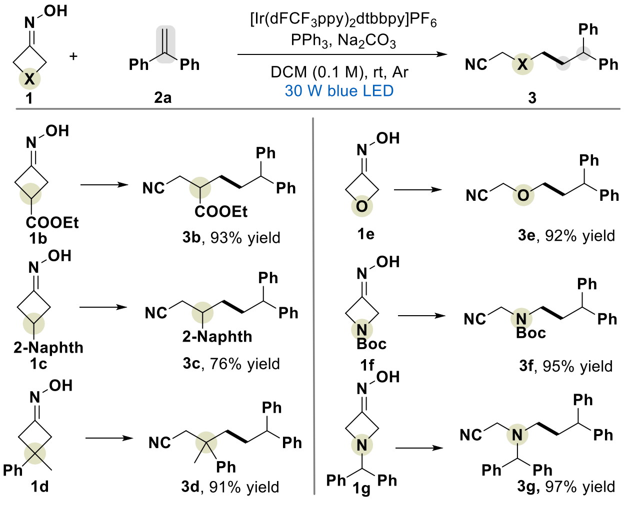


entry	variation from the "standard conditions"	yield (%)[b]
1	none	98
2	under air atmosphere	43
3	without Na_2CO_3	67
4	$MesAcr^+ClO_4^-$ instead of $[Ir(dFCF_3ppy)_2dtbbpy]PF_6$	0
5	$Ru(bpy)_3PF_6$ instead of $[Ir(dFCF_3ppy)_2dtbbpy]PF_6$	trace
6	$n\text{-}Bu_3P$ instead of PPh_3	45
7	MeCN instead of CH_2Cl_2 as the solvent	trace
8	10 equiv of H_2O in 2 mL of CH_2Cl_2	92
9	no PPh_3	0
10	no light	0
11	no photocatalyst	0

[a]Standard conditions: oxime **1a** (0.6 mmol, 3 equiv), 1,1-diphenylethylene **2a** (0.2 mmol, 1 equiv), PPh_3 (0.72 mmol, 3.6 equiv), Na_2CO_3 (0.3 mmol, 1.5 equiv), $[Ir(dFCF_3ppy)_2dtbbpy]PF_6$ (2 mmol %), CH_2Cl_2 (2 mL), 30 W blue LED, argon atmosphere, rt, 5 days. [b]Yield of isolated product.

Having established the optimal conditions for this photoredox-catalyzed transformation, the substrate scope and limitations were subsequently explored. As summarized in Scheme 2, the substitution patterns on the cyclobutanone oximes were first varied and investigated, which were generally tolerated well in the reaction. Substituted oximes **1b**−**1d** bearing various functional groups such as carboxylate and naphthyl are amenable substrates, affording the desired products **3b**−**3d** in good to excellent yields. Notably, this reaction system was also suitable for oxetan-3-one oxime and *N*-substituted azetidinone

Scheme 2. Scope With Respect to Oximes[a]

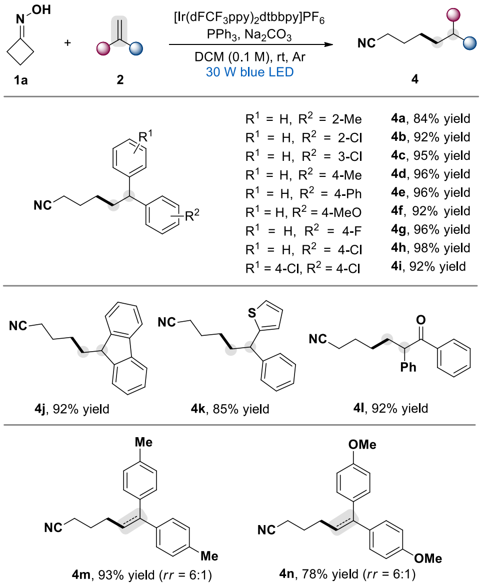


[a]Standard conditions: oximes **1** (0.6 mmol, 3 equiv), alkene **2a** (0.2 mmol, 1 equiv), PPh_3 (0.72 mmol, 3.6 equiv), Na_2CO_3 (0.3 mmol, 1.5 equiv), $[Ir(dFCF_3ppy)_2dtbbpy]PF_6$ (2 mmol %), CH_2Cl_2 (2 mL), 30 W blue LED, argon atmosphere, rt, 5 days. Yield of isolated product.

oximes, delivering the corresponding ether **3e** and amines **3f** and **3g** in excellent yields.

Author: Encouraged by the above results, we continued to investigate the substrate generality with a range of 1,1-disubstituted alkenes under the standard conditions. As shown in Scheme 3, the substitution patterns and electronic characteristics of 1,1-diphenylenes have slight effects on their reaction efficiency, with the desired products **4a**−**4i** being obtained in excellent yields. The fluorene analogue **2j** also proceeded smoothly to give the corresponding product **4j** in 92% yield. Moreover, this strategy was applicable as well to the olefin containing heterocycle **2k**. In the case of olefin with electron-withdrawing group attached **2l**, an excellent yield was also secured, further expanding the practical range of substrates. Interestingly, when electron-rich olefins **2m** and **2n** were employed, a Heck-type pathway occurred, and C−C double bond remained predominant with a reactivity ratio (rr) of 6:1, leading to alkenyl nitriles **4m** and **4n** in good to excellent yields. Presumably, the difference in the product structures stemmed from the relatively higher reductive potential of the intermediates for these electron-rich olefins, slowing down the single electron reduction step and facilitating the ultimate elimination process.

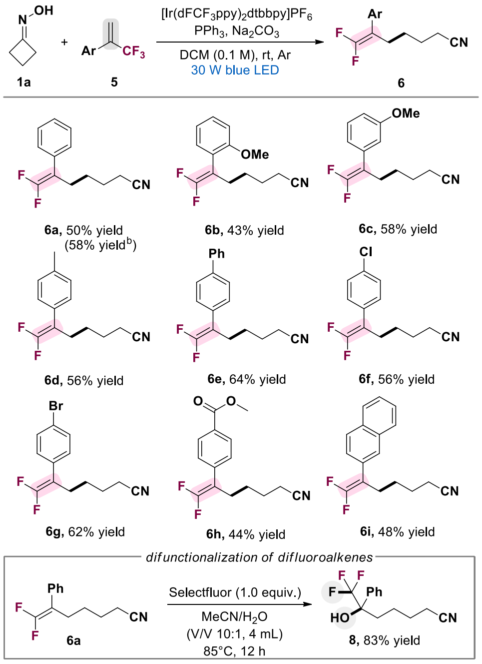
Scheme 3. Scope with Respect to Alkenes[a]



[a] Standard conditions: oxime **1a** (0.6 mmol, 3 equiv), alkenes **2** (0.2 mmol, 1 equiv), PPh_3 (0.72 mmol, 3.6 equiv), Na_2CO_3 (0.3 mmol, 1.5 equiv), $[Ir(dFCF_3ppy)_2dtbbpy]PF_6$ (2 mmol %), CH_2Cl_2 (2 mL), 30 W blue LED, argon atmosphere, rt, 5 days. Yield of isolated product.

Mechanistically, we speculated that α-trifluoromethyl alkenes[15] should be amenable to this developed platform to give functionalized 1,1-difluoroalkenes as the ultimate reductive quenching step in the reaction could be facilitated by E1cB-type fluoride elimination via a radical-polar crossover pathway. We began this part of the investigations by examining the reaction of cyclobutanone oxime **1a** with α-trifluoromethylstyrene **5a** (Scheme 4). Satisfyingly, the desired product *gem*-difluoroalkene **6a** was obtained in a moderate yield under the standard conditions. Otherwise, a range of CF_3-styrenes bearing various substitutents was also suitable as reaction partners, giving the corresponding *gem*-difluorostyrenes **6b**−**6h** in moderate yields. Additionally, CF_3-naphthalene worked well and gave difluoronaphthalene **6i**. Moreover, *gem*-difluoroalkene moiety is known to serve as a carbonyl bioisostere with less susceptibility and a versatile precursor for the synthesis of fluorine-containing molecules; these results are thus of particular significance for drug discovery. Noticing mildness of the reaction conditions, we were devoted to exploiting the practicality and scalability of this protocol. The title reaction for oxime **1a** with **5a** was performed at gram-scale under the standard reaction conditions, which proceeded smoothly to give the corresponding product **6a** in 58% yield without any loss of efficiency. As expected, the desired product **6a** bearing a *gem*-difluoroalkene moiety can be readily transformed into highly functionalized alkyl derivative **8**. Inevitably, at the current stage, there are still some limitations for some special reaction partners, as listed in the Supporting Information.

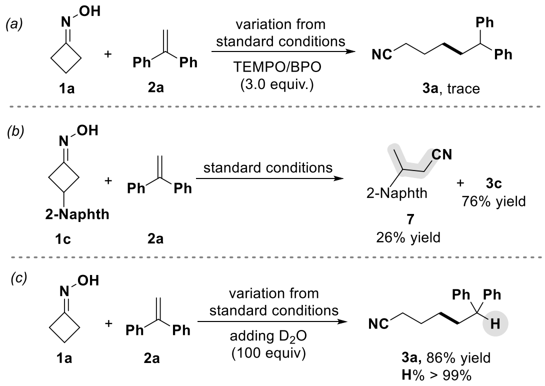
Scheme 4. Scope with Respect to α-trifluoromethyl Alkenes[a]



[a] Standard conditions: oxime **1a** (0.6 mmol, 3 equiv), alkenes **5** (0.2 mmol, 1 equiv), PPh_3 (0.72 mmol, 3.6 equiv), Na_2CO_3 (0.3 mmol, 1.5 equiv), $[Ir(dFCF_3ppy)_2dtbbpy]PF_6$ (2 mmol %), CH_2Cl_2 (2 mL), 30 W blue LED, argon atmosphere, rt, 5 days. Yield of isolated product. [b] Performed at 4 mmol scale of **5a**.

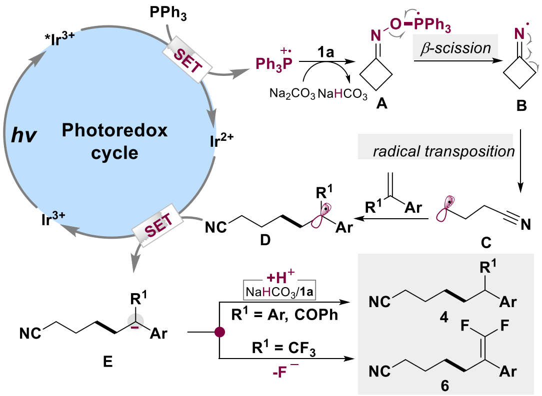
To gain mechanistic insights into the process, several control experiments were carried out (Scheme 5). The radical inhibition experiments were conducted by adding 2,2,6,6-tetramethyl-1-piperdinyloxy (TEMPO) or dibenzoyl peroxide (BPO) under the standard reaction conditions, and the reactions were significantly inhibited (Scheme 5a). These results indicated that a free-radical pathway was probably involved in this photocatalytic transformation. Moreover, the isolation of byproduct **7** suggested the radical transposition in the cascade process of N−O and C−C cleavage of oxime (Scheme 5b). Further deuterium-labeling experiment by adding D_2O was performed, but no deuterated product was detected (Scheme 5c). Thus, water seems impossible to be the proton source for this transformation. Presumably, excess free oxime served as the major proton source (see Supporting Information). The corresponding Stern−Volmer studies further reveals that

Scheme 5. Control Experiments



photoexcited Ir(dF(CF_3)ppy$)_2$(dtbbpy)]PF_6 was quenched by triphenylphosphine (see Supporting Information). Additionally, the quantum yields for the synthesis of **3a** and **6a** in this reaction system were also measured to be 0.53 and 0.25, respectively, suggesting that a long-chain progress is unlikely to be involved (see Supporting Information).

Scheme 6. Plausible Mechanistic Pathways



On the basis of the above-mentioned results and the redox potentials of the involved species, a possible photoredox cycle is proposed in Scheme 6. Initially, the excitation of the photocatalyst resulted in the excited *Ir(dF(CF_3)-ppy$)_2$(dtbbpy)]PF_6 [$E_{1/2}^{\text{red}}$ (*Ir^{III}/Ir^{II}) = +1.21 V vs SCE],[16] which was quenched by Ph_3P ($E_{1/2}^{\text{red}}$ = +0.98 V vs SCE)[17] to generate Ir^{II} and triphenylphosphine radical cation. Subsequently, in the presence of Na_2CO_3, a polar/SET crossover process followed by the β-scission occurred sequentially to undergo the proposed radical deoxygenation, generating the key iminyl radical **B**. A facile radical transposition through a strain-relieved C−C single bond cleavage delivered a cyanoalkyl radical species **C**. This highly reactive CCR immediately was rapidly captured by the alkenes to generate radical species **D**, which was then quickly reduced by Ir^{II} to form carbanion intermediate **E** with the concurrent regeneration of photocatalyst,[18] thus completing the photocatalytic cycle. As for regular alkenes, direct protonation of intermediate **D** yielded the corresponding 1,1-diarylmethanenitriles or alkyl nitriles **4**. Otherwise, in the case of CF_3-styrene carbanions, a β-fluoride elimination of intermediate **E** ultimately afforded the corresponding gem-difluoroalkenes **6**.

In summary, a unique, visible-light-driven direct N−O bond activation protocol by employing phosphines to access distinct radical species from strained cycloketone oximes has been established for the first time. This photocatalytic phosphoranyl radical-mediated approach significantly avoids the voltage-directed derivatizations of oximes and expands the functional group tolerance. By fully taking advantage of the activation mode in the iminyl radical formation, alkenes and α-trifluoromethyl alkenes with varied electronic and structural features worked as effective radical receptors, readily affording a range of elongated functionalized cyano compounds and cyano difluorostyrenes. The versatility and scalability of this transformation would greatly broaden synthetic utilizations of oximes in the domain of photochemistry. More importantly, this photoredox-catalyzed phosphoranyl radical-mediated pathway offers a new dimensionality for N−O bond activation

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00651.

Experimental procedures and spectral data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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