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Review

Recent advances for the photoinduced C—C bond cleavage of cycloketone oximes

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ABSTRACT

Nitriles are widely existed in many bioactive compounds, and they can be easily transformed into other functional groups. Therefore, the synthesis of nitriles under cyanide-free conditions is of significant importance. Recent advances for the synthesis of nitriles through photoinduced C—C bond cleavage of cycloketone oximes classified by the type of C—X bond forming are summarized. Various compounds possessing nitriles can be efficiently accessed via this method.

1. Introduction

Nitrile is an important class of organic skeletons existed in many pharmaceuticals and natural products [1,2]. Additionally, the nitrile group serves as versatile synthetic building motif in organic chemistry as it can be easily transformed into other important functional groups *via* routine manipulation [3]. Therefore, chemists have long-term interest in the development of practical methods for the synthesis of nitriles. Typical strategies include dehydration of aldoximes [4–8] or amides [9], dehydrogenation of amines [10–12], and cyanation of alkyl halides [13]. Recently, the iminyl radical-triggered C—C bond cleavage of cycloketone oximes has been successfully applied in the synthesis of diverse nitriles under cyanide-free conditions. The first example for the synthesis of nitriles from cycloketone oximes traced back to the year of 1991, Zard *et al*. developed the use of carboxymethyl oximes and cyclobutanone sulfenylimines as iminyl radical precursors to prepare nitriles [14]. Later, many organic chemists reported the similar ring-opening reaction of cycloketone oximes [15–17]. Among this, photocatalysis is a convenient tool and widely used in organic synthesis due to its mild reaction conditions, availability and high efficiency [18–20]. Regarding the importance of nitriles and the efficiency of photocatalysis, recent development for the synthesis of nitriles *via* photoinduced C—C bond cleavage of cycloketone oximes is summarized in this paper, including photocatalysis and the combination of photocatalysis and metal catalysis.

According to the literature, the cycloketone oximes **1** can form iminyl radical **2** through single electron transfer (SET) under photocatalysis, which would undergo C—C cleavage to generate relatively active cyanoalkyl radical intermediate **3**. The cyanoalkyl radical **3** can be trapped by radical acceptors to form various bonds. Herein, we summarize the recent advances for the synthesis of nitriles through photoinduced C—C bond cleavage of cycloketone oximes classified by the type of C—X bond formation. Various compounds possessing nitriles can be efficiently accessed *via* this method (Scheme 1).

2. C—C bond formation

2.1. Alkene as the radical acceptor through reductive initiation

In 2017, Zhou's group reported a three-component cyanopropylation/etherification of unactivated alkenes through a photoredox approach [21]. As for the substrate scope, *O*-acyl oximes with various styrenes in MeOH furnished the corresponding products in good yields. Additionally, oximes with different functional groups all worked well, affording the desired products in good to excellent yields. Moreover, proparyl alcohol underwent reactions smoothly, though with moderate reactivity. A plausible mechanism was proposed, as shown in Scheme 2. The reactions started with the

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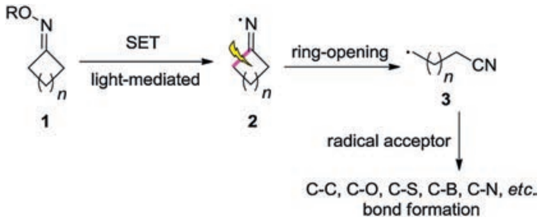
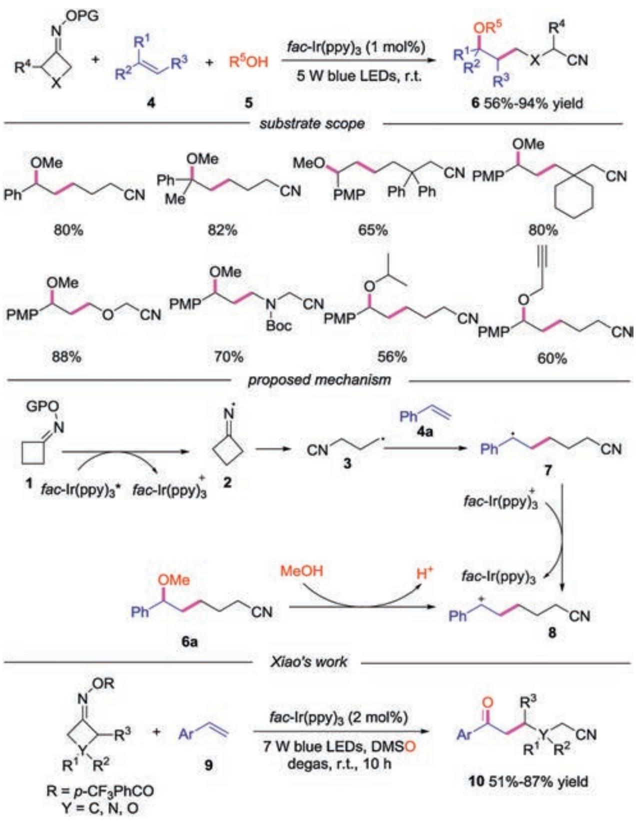


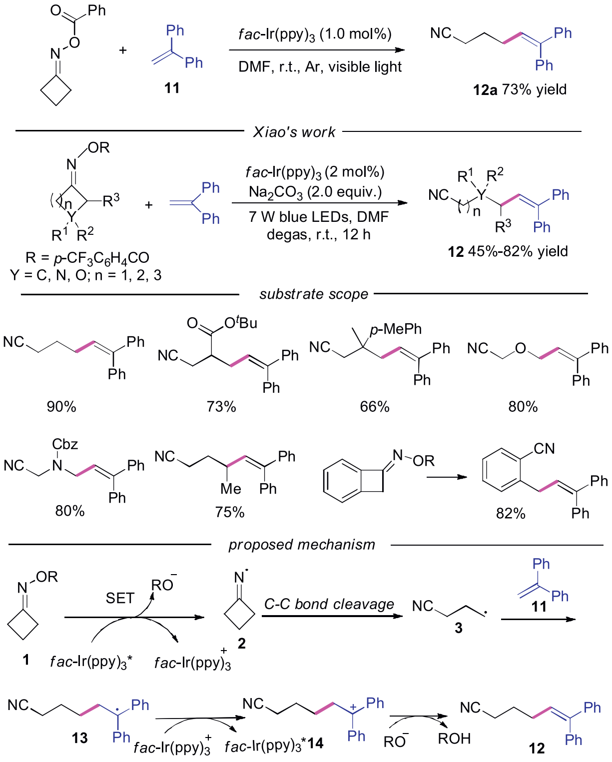
Scheme 1. Synthesis of nitriles from cycloketone oximes according to the type of bond formation.



Scheme 2. Three-component reaction for the synthesis of alkylnitriles and ketonitriles.

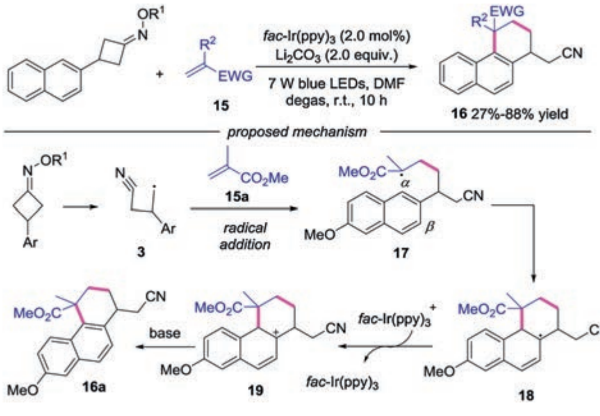
visible-light-driven SET reduction of *O*-acyl oxime **1** by the photoexcited catalyst *fac*-Ir(ppy)$_3$* to generate the iminyl radical **2** along with the oxidized photocatalyst. The iminyl radical **2** then underwent a ring-opening by C—C cleavage to form cyanoalkyl radical **3**. Addition of radical **3** to alkene **4a** produced carbon radical **7**, which was oxidized to carbocation intermediate **8** by *fac*-Ir(ppy)$_3^+$ with the regeneration of photocatalyst. Finally, the carboncation **8** went through nucleophilic reaction with MeOH to generate the final product **6a**. Except the final nucleophilic attack by MeOH, the carbocation **8** could also be oxidized by DMSO to form the ketonitriles, which was developed by Xiao and co-workers in 2018 [22].

Excepted reacting with nucleophiles, the carbocation could also went through an elimination process to provide alkene products. In 2017, Shi's group reported the copper catalyzed coupling reaction of cycloketone oximes with unsaturated compounds **11**. In this work, they also discovered that the coupling reaction could proceed successfully under photocatalysis conditions, providing the cyano-containing product **12a** in good yield [23]. In 2018, Xiao's group developed the similar visible-light-driven iminyl radical-mediated C—C bond cleavage/radical addition cascade reaction of oxime esters **1** with unsaturated compounds **11** in the presence of base [24]. Various C(sp^3)-C(sp^2) bonds could be constructed through this redox-neutral process. Symmetric monosubstituted *O*-acyl oximes bearing functional groups at 3-position and disubstituted substrates proceeded smoothly to give the desired products. Furthermore, both oxetan-3-one and 1-Cbz-3-azetidinone derived *O*-acyl oximes participated in the reaction well. Functional groups at the 2-position of *O*-acyl oximes also demonstrated good reaction efficiency. Once again, benzocyclobutenone-derived substrate proved to be suitable for the reaction. The authors proposed a mechanism shown in Scheme 3. The carbocation intermediate **14** was generated through the known process, which went through base-mediated deprotonation to afford the alkene product **12**.

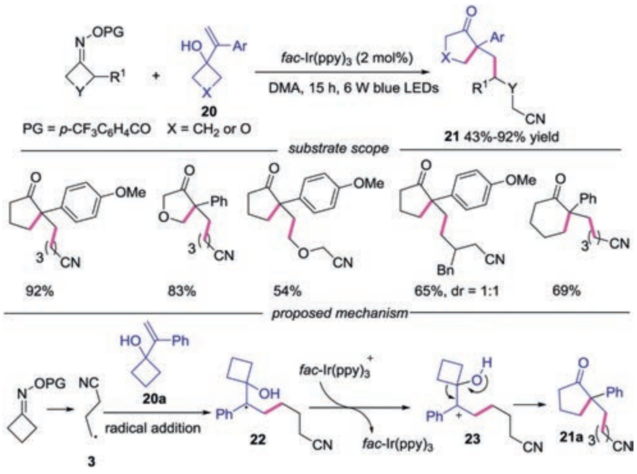


Scheme 3. Visible-light driven cascade reaction of cycloketone oxime esters and alkenes.

When cyanoalkyl radical **3** added to the electron-deficient alkene, the generated radical could attack the aromatic ring to produce the cycloadduct. In 2018, Xiao's group developed a



Scheme 4. Synthesis of tetrahydrophenanthrenes through photoinduced C—C bond cleavage of cycloketone oximes.



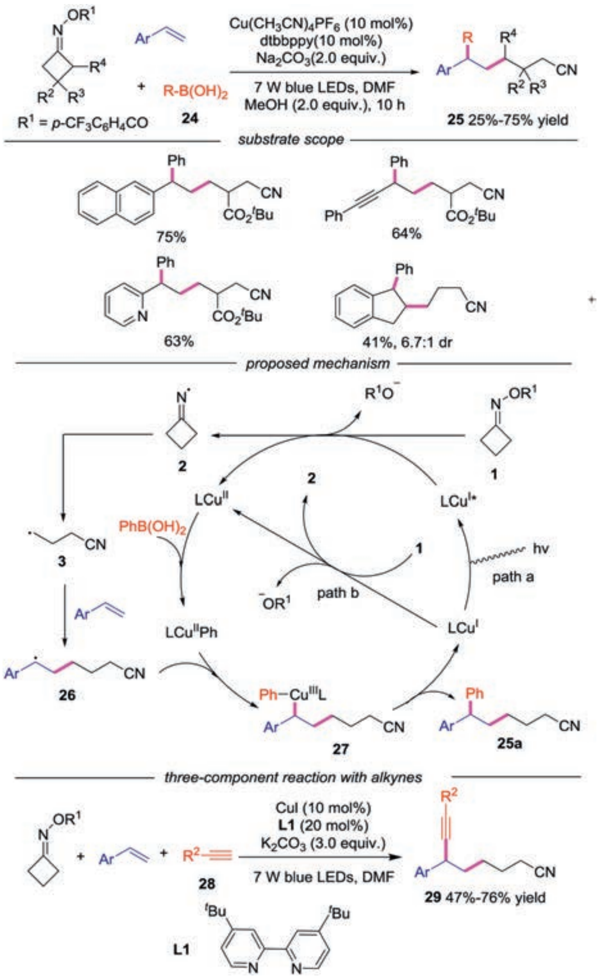
Scheme 5. Visible-light induced synthesis of cyclic ketones from cycloketone oximes with cyclopentanol.

photoredox-catalyzed radical addition/cyclization cascade to generate cyanoalkylated 1,2,3,4-tetrahydrophenanthrenes with good yields and excellent regioselectivity [25]. The authors proposed a mechanism (Scheme 4), showing that the radical addition would occur between cyanoalkyl radical **3** and electron-deficient alkene **15** leading to radical intermediate 1**7**. Then the radical **18** was afforded by the intramolecular radical addition to the α-site of naphthalene. Subsequently, the radical **18** was oxidized by *fac*-Ir(ppy)$_3$$^+$ to give rise to carbocation 1**9**, which was deprotonated under base conditions to produce the final product **16**.

In the same year, Xiao's group also employed this methodology in the reaction with alkenylcyclobutanols to prepare cyclic ketones [26]. A variety of substrates were found to be compatible under the conditions. The 3-(1-phenylvinyl)oxetan-3-ol, symmetric mono-substituted *O*-acyl oximes and unsymmetrical cyclobutanone-derived *O*-acyl oximes were suitable in this transformation. Furthermore, 1-(1-phenylvinyl)-cyclopentanol was also tolerated, affording the desired product in good yields. The plausible mechanism was shown in Scheme 5. Cyanoalkyl radical **3** reacted with 1-(1-phenylvinyl)cyclobutanol **20a** leading to radical **22**, which was oxidized to carbocation **23** by *fac*-Ir(ppy)$_3$$^+$. Finally, the carbocation **23** underwent alkyl migration and deprotonation to provide the product **21a**.

A copper-catalyzed, visible-light-driven three-component radical cross-coupling of oxime esters, boronic acids and styrenes was developed as well [27]. A wide range of boronic acids, alkenes and oxime esters were compatible in this reaction. A Cu^{I}/Cu^{II}/Cu^{III}-based catalytic cycle was proposed during the transformation. The reaction started with SET reduction of oxime esters **1** by either photoexcited LCu^{I*} or the ground-state LCu^{I} giving rise to iminyl radical **2**, which underwent C—C bond scission to provide cyanoalkyl radical **3**. Then, the radical **3** was captured by alkene to form radical **26**. Meanwhile, the LCu^{II} complex underwent transmetallation with boronic acid **24** to provide LCu^{II}Ph species. Subsequently, LCu^{II}Ph was oxidized by radical **3** to generate the high-valence Cu^{III} complex and the final product **25** was afforded through reductive elimination. In 2019, Chen and co-workers reported a three-component cross-coupling reaction of cycloketone oxime esters, alkene and terminal alkynes, providing cyanoalkyl-containing propargylic compounds in general good yields [28]. The reactions proceeded with similar mechanism shown in Scheme 6.

In 2018, Yu's group reported the photocatalyzed remote C—C vinylation of cycloketone oximes with vinyl boronic acids [29].

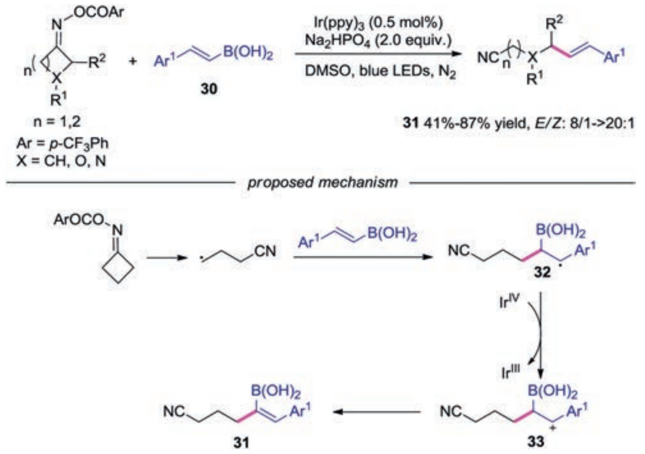


Scheme 6. Visible-light induced three-component reaction with cycloketone oxime esters, alkenes and boronic acids/alkynes.

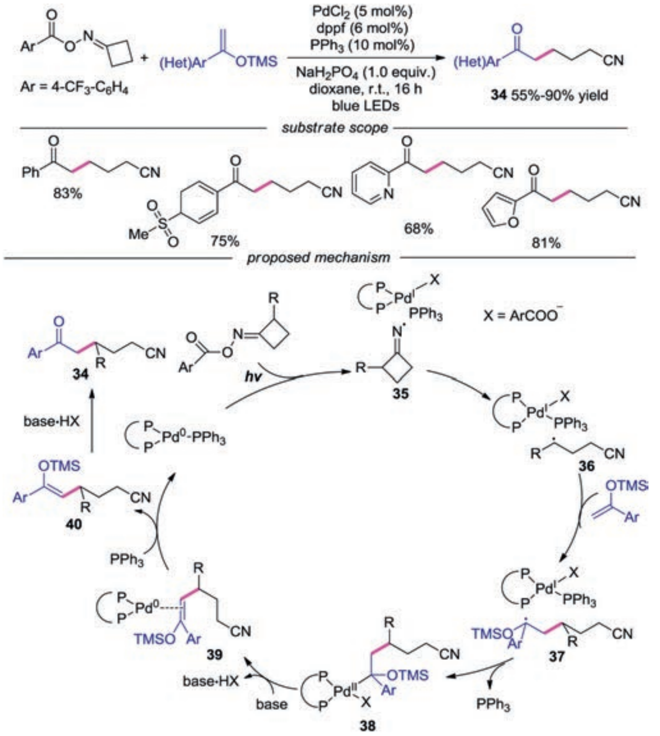
Various γ-vinyl nitriles were efficiently synthesized through this method. The authors proposed mechanism in Scheme 7. The cyanoalkyl radical **3** added to vinyl boronic acids **30** to provide the radical intermediate **32**. Subsequently, the radical **32** was oxidized by Ir^{IV} to produce carboncation **33**. Finally, deprotonation afforded the desired γ-vinyl nitriles **31**.

The synthesis of β-aroyl hexanenitriles and (*E*)-4-arylbut-3-enenitriles through a photoexcited Pd complex activation of cyclobutanone oxime esters was reported by Fu and co-workers [30]. For the ring-opening addition reaction, functional groups such as sulfone on trimethyl((1-phenylvinyl)oxy)silane were compatible. Additionally, α-heteroparyl silyl enol ethers including pyridyl and furanyl participated in the addition reaction well. The mechanism proposed for this palladium-catalyzed ring-opening addition of cyclobutanone oxime esters was presented in Scheme 8. The palladium complex would activate oxime ester through photoinduced SET to generate a hybrid iminyl radical Pd^{I} intermediate **35**, which underwent C—C cleavage to produce cyanoalkyl Pd^{I} species **36**. Radical **36** would then interact with silyl enol ether leading to a hybrid benzyl radical Pd^{I} **37**, which underwent benzyl association to provide benzyl-Pd^{II} **38**. After β-H elimination of **38**, intermediate **39** would be formed, which would produce alkylated silyl enol ether with the assistance of PPh$_3$. After hydrolysis, ketone product **34** would be afforded.

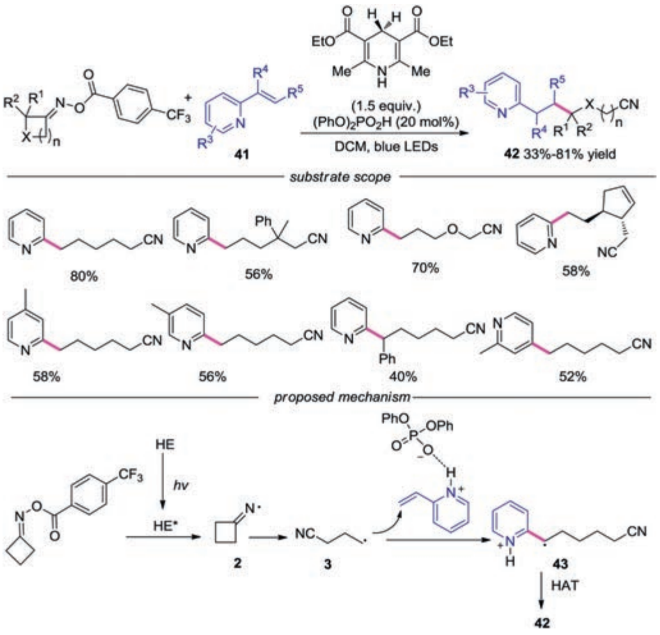
In 2020, Liu's group developed a visible-light-initiated iminyl radical-mediated C—C bond cleavage and functionalization of



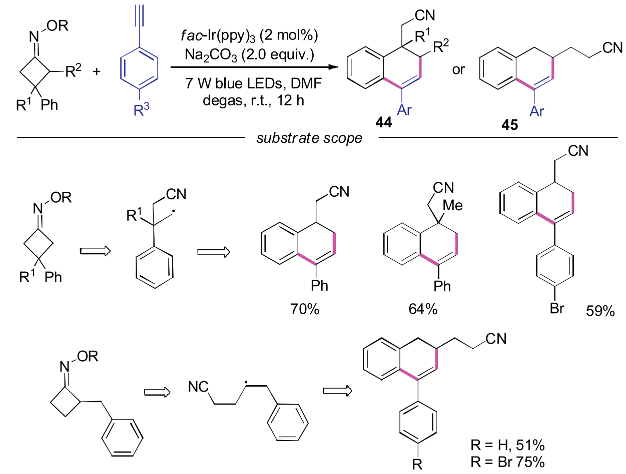
Scheme 7. Visible-light induced synthesis of γ-vinyl nitriles from cycloketone oximes with vinyl boronic acids.



Scheme 8. Photoexcited Pd^0 complex induced addition reaction of cycloketone oximes.



Scheme 9. Visible-light induced reaction of cycloketone oximes with HE as the reductant.



Scheme 10. Visible-light induced cycloaddtion reaction of cycloketone oximes and alkynes.

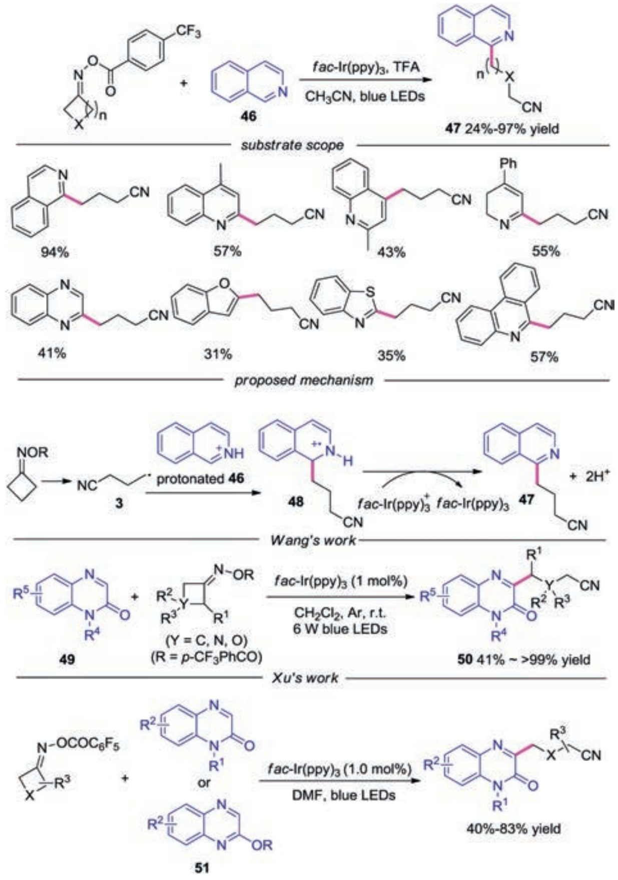
cycloketone oximes (Scheme 9) [31]. Regarding the substrates, various functional groups on the four-membered ring participated in the reaction well. 2-Alkenylpyridine and 4-vinylpyridine promoted the reaction smoothly. According to the mechanism studies, the reaction was initiated by HE* rather than an EDA complex. After a single electron transfer, cyanoalkyl radical **3** was generated through C—C bond cleavage, which was trapped by charged 2-vinylpyridine to produce alkyl radical **43**. The final product was generated through abstraction of a hydrogen atom from $HE^{\bullet +}$ or HE.

2.2. Alkane as the radical acceptor through reductive initiation

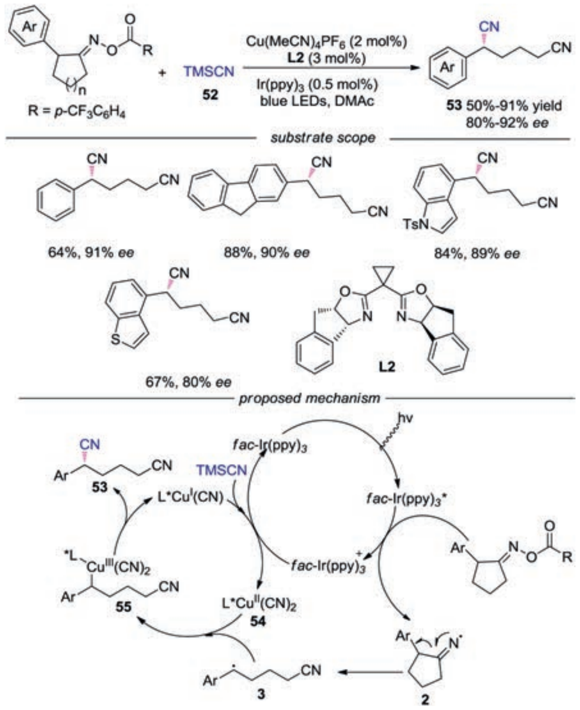
In 2018, Xiao's group described the reaction of cycloketone oximes with alkenes to generate cyano-containing alkenes (Scheme 3). Additionally, the cyclic products were produced when alkynes were employed (Scheme 10) [24]. A variety of 1,2-dihydronaphthalenes **44** and **45** were efficiently obtained through this method. The reactions were proceeded through radical cascade processes.

2.3. Aromatic ring as the radical acceptor through reductive initiation

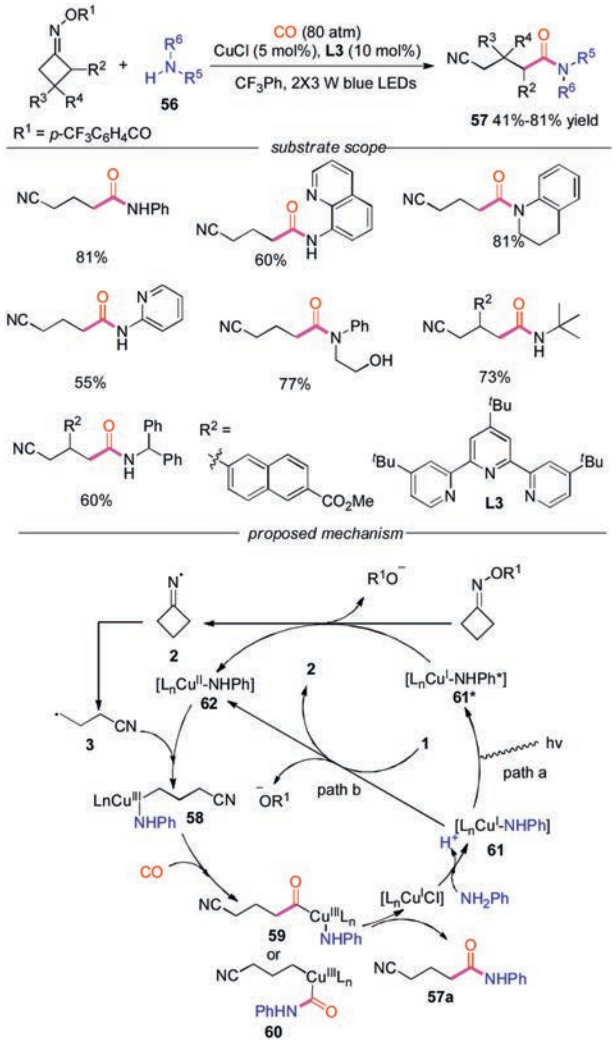
In 2019, the visible-light-driven Minisci-type C—H cyanoalkylation of heteroarene with cycloketone oximes was reported [32]. Various heterocyclic compounds were well tolerated in this reaction, such as isoquinolines, quinolones, quinoxalines, benzofurans, benzothiazoles and phenanthridins. A possible mechanism was proposed, as shown in Scheme 11. Radical **3** was captured by protonated isoquinoline to produce radical cation **48**, which was oxidized by *fac*-$Ir(ppy)_3^+$ to afford the final product. In the same year, Wang's group [33], Xu and co-workers [34] reported a similar transformation with quinoxalinones as the radical acceptor.



Scheme 11. Visible-light induced cyanoalkylation of heteroarene with cycloketone oxime esters.



Scheme 12. Visible-light induced 1,6-dinitriles reaction of cycloketone oximes.



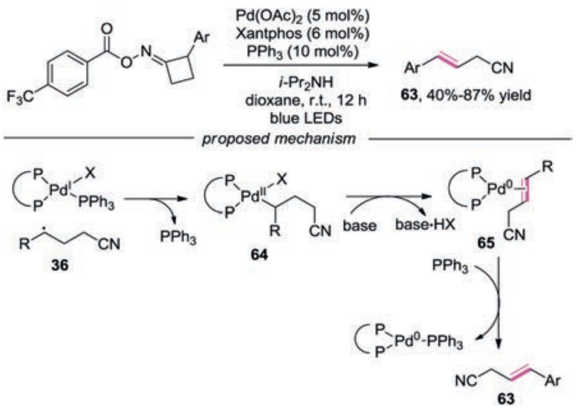
Scheme 13. Visible-light induced aminocarbonylation of cycloketone oximes.

2.4. Metal species as the radical acceptor through reductive initiation

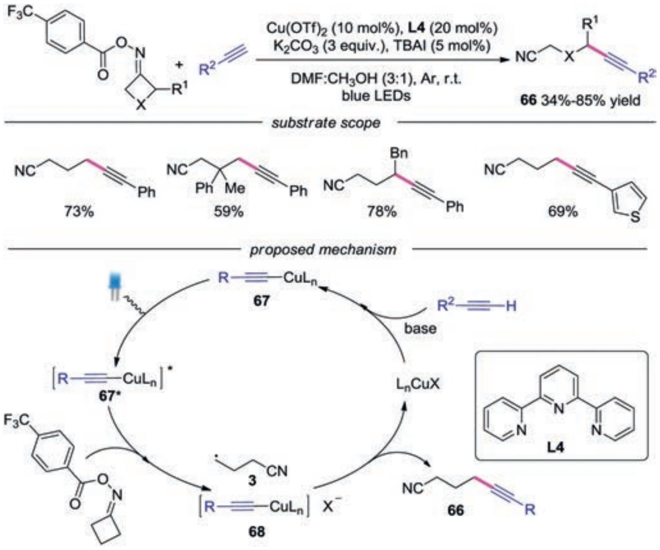
An enantioselective ring-opening cyanation reaction of cycloketone oxime esters to access chiral 1,5- and 1,6-dinitriles was described [35]. The reaction of cyclopentanone oxime esters required the dual catalyst of photo- and copper-catalysis while the reaction with cyclobutanone could be accessed by copper catalysis only. A broad substrate scope was demonstrated, and a series of cyclopentanone oxime esters with various substituted aromatic rings were well tolerated. A dual photoredox/copper catalysis mechanism for reaction of cyclopentanone oxime esters was proposed (Scheme 12). Initially, oxime ester was reduced by photoexcited *fac*-Ir$(ppy)_3^*$ to generate iminyl radical **2**. Meanwhile, the L*Cu^ICN was oxidized by *fac*-Ir$(ppy)_3^+$ species with participation of TMSCN to afford Cu^{II} species **54**. The benzylic radical **3**, produced by the C—C bond cleavage of iminyl radical **2**, was captured by L*$Cu^{II}(CN)_2$ to form Cu^{III} species **55**. Subsequently, reductive elimination of **55** would occur leading to the desired product.

A visible light-induced, copper-catalyzed radical aminocarbonaylation of oxime esters with amines and CO gas without exogenous photosensitizer was developed by Xiao and co-workers [36]. This method exhibited broad substrate scope and highly functional group tolerance with both cycloketone oxime esters and alkyl/aryl amines. Aryl amines with fused aromatic group, cyclic or acylic secondary amines and amine-substituted pyridines participated in this reaction well. Moreover, sterically demanding primary amines were compatible under the conditions. A visible-light-driven $Cu^I/Cu^{II}/Cu^{III}$-based catalytic cycle was proposed for this radical amino-carbonylation reaction (Scheme 13). The reaction would be initiated with the SET reduction of **1** by either the $LnCu^I$-NHPh* or the ground state $LnCu^I$-NHPh, affording an iminyl radical **2**. Then radical **2** underwent C—C bond cleavage to produce cyanoalkyl radical **3**, which was intercepted by Cu^{II} complex to generate high-valence Cu^{III} complex **58**. Cu^{III} complex **58** would then undergo coordination and insertion of CO to afford acylcopper intermediate **59** or **60**, which provided the final product after reductive elimination.

In 2019, Fu's group reported the photoexcited Pd^0 species induced addition reaction of cycloketone oxime esters with silyl enol ethers (Scheme 8) [30]. Additionally, β-elimination reaction occurred with cycloketone oxime esters in the absence of silyl enol ethers, affording the corresponding alkene products in good yields. The proposed mechanism was shown in Scheme 14. The Pd^I complex, generated by cycloketone and Pd^0 complex (Scheme 8), associated with cyanoalkyl radical to generate Pd^{II} complex **64** along with the release of PPh_3. Next, β-elimination occurred under base conditions, and the final product was obtained after the diassociation with palladium.



Scheme 14. Photoexcited Pd^0 complex induced β-elimination reaction of cycloketone oximes.



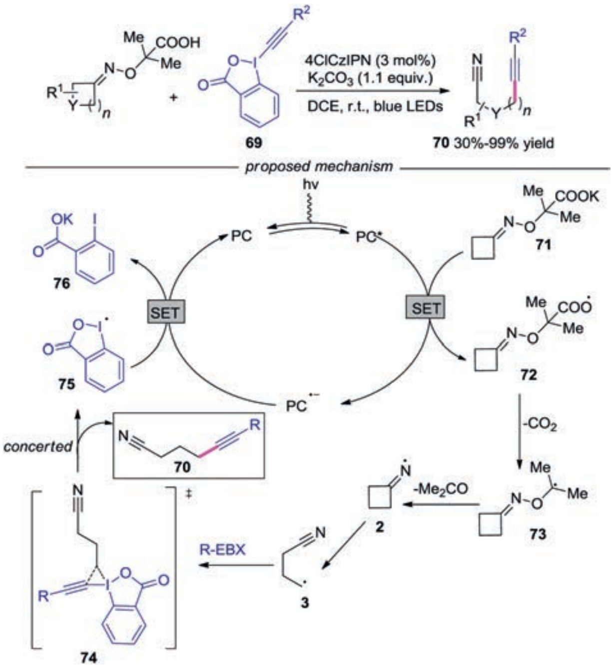
Scheme 15. Visible-light induced copper-catalyzed $C(sp^3)$-C(sp) bond formation from cycloketone oximes.

Recently, Shi and co-workers developed a novel transformation for the $C(sp^3)$-C(sp) bond formation *via* photo-induced copper-catalyzed C—C bond cleavage of cycloketone oximes (Scheme 15) [37]. Various functionalized alkynyl nitriles were easily obtained with cycloketone oximes and terminal alkynes. The proposed mechanism showed that the copper acetylide complex **67,** generated by alkyne and copper catalyst, was irradiated by visible light to afford photoexcited complex **67***. Subsequently, the cycloketone oxime esters were reducted by photoexcited complex **67*** to produce **68** and cyanoalkyl radical **3**. Finally, the cyanoalkyl radical **3** would be trapped by complex **68**, providing the alkynyl nitrile along with the copper salt.

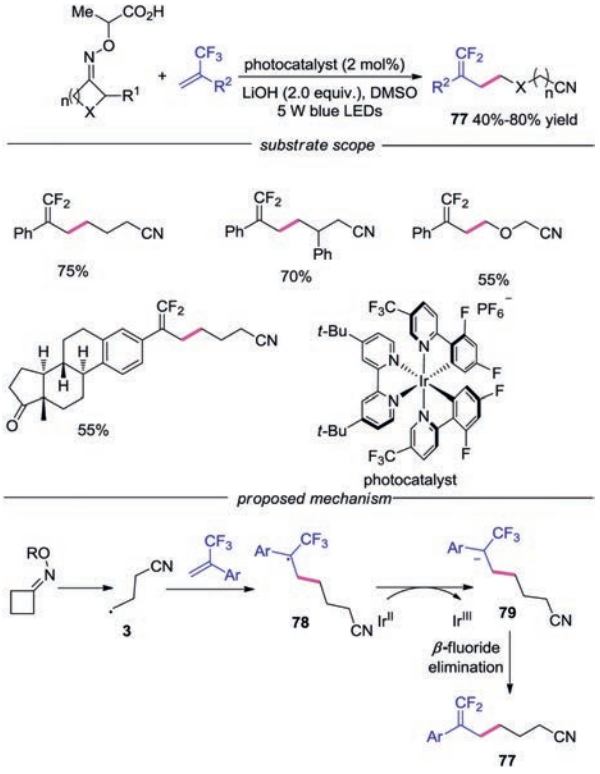
2.5. Reactions through oxidative initiation

Waser's group described the synthesis of alkynyl nitriles with cycloketone oximes by organic dyes (Scheme 16) [38]. Various functional groups were well tolerated during the transformation. Mechanistic studies showed that the reaction was initiated with the oxidation of potassium carboxylate **71** by the excited state of organic dye to generate radical **72**. Then, the fast decarboxylation gave rise to α-oxy radical **73**, which would provide the iminyl radical **2** by N–O scission with the release of acetone. Afterwards, the iminyl radical **2** fragmented into alkyl nitrile radical **3**, which reacted with EBX affording the desired alkynylnitrile **70** through **74**.

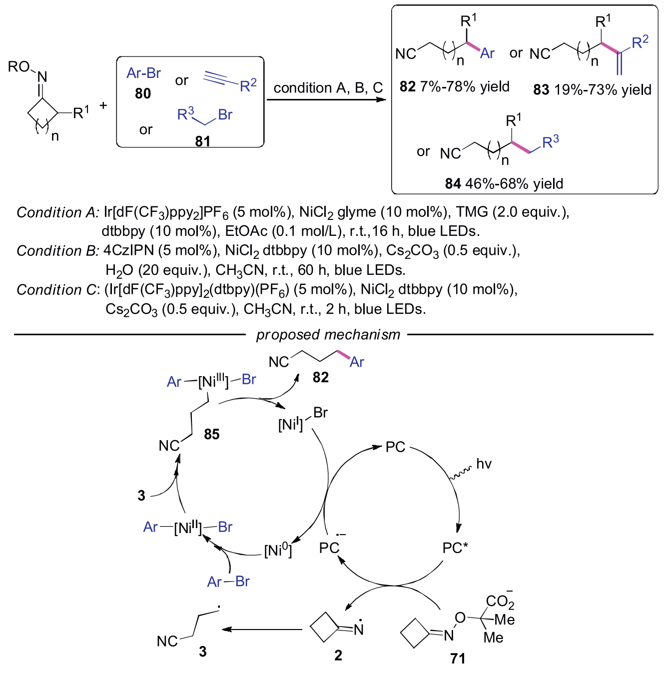
A visible-light-driven γ,γ-difluoroalkylation of cycloketone oximes esters with trifluoromethyl alkenes *via* C—C and C—F bond cleavage was developed, providing a series of cyano-substituted gem-difluoroalkenes in good yields (Scheme 17) [39]. A wide range of substrates with sensitive functional groups were well tolerated in this reaction, including alkenes derived from estrone, symmetrical cyclobutanone oxime esters, oxime ethers derived from oxetan-3-one. As for the mechanism, the cyanoalkyl radical **3** was generated through similar pathway shown in Scheme 15. Subsequently, radical **3** would attack the double bond



Scheme 16. Visible-light-induced synthesis of alkynyl nitriles from cycloketone oximes and EBX.



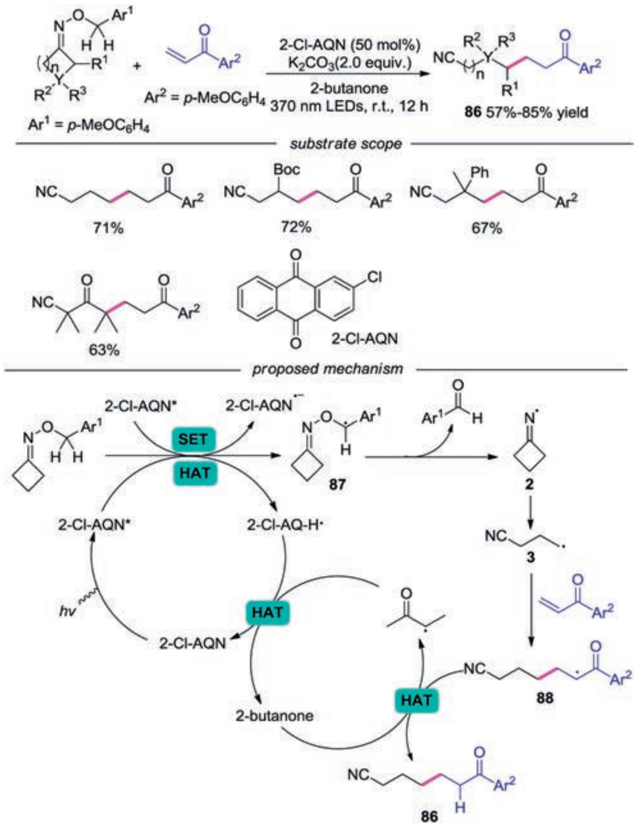
Scheme 17. Visible-light-induced γ,γ-difluoroalkylation of cycloketone oximes esters.



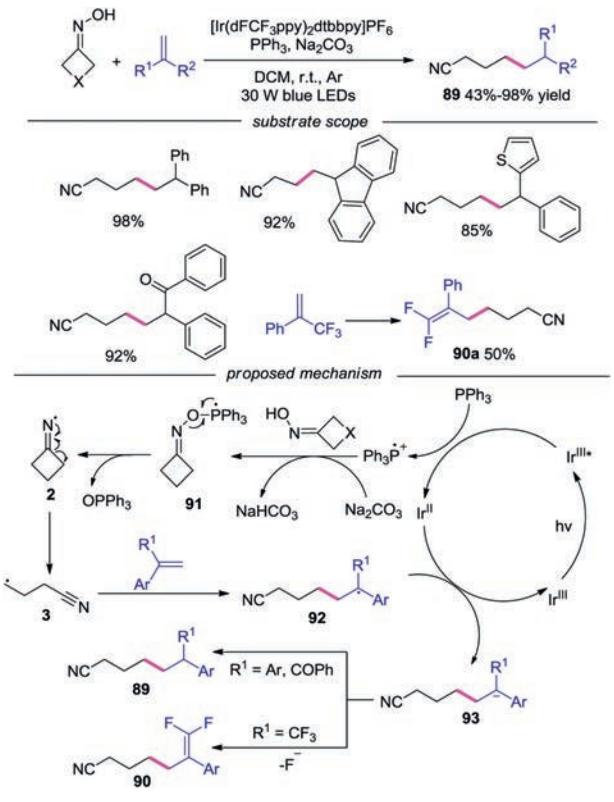
Scheme 18. Photo/nickel catalyzed remote functionalization with cycloketone oximes.

of α-CF$_3$ alkene leading to α-CF$_3$ alkyl radical **78**. Reduction of α-CF$_3$ alkyl radical **78** afforded carbanion **79**, which would went through β-fluoride elimination to deliver the final cyano-substituted gem-difluoroalkene **77**.

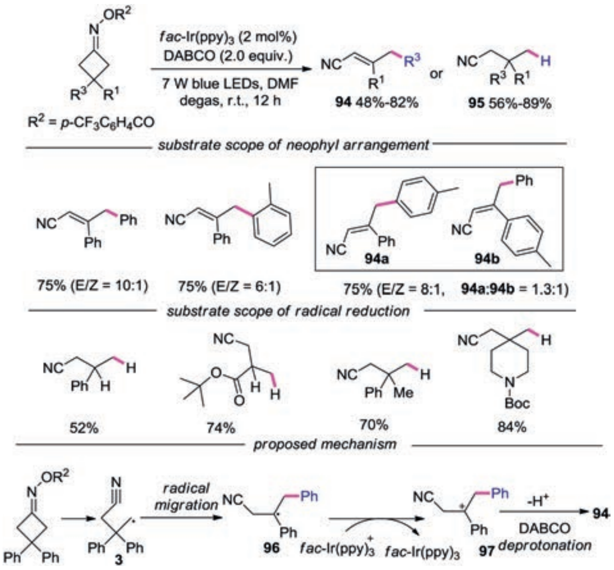
In 2019, Leonori's group described a dual photoredox/nickel strategy for remote functionalization with cycloketone oximes *via* iminyl radicals (Scheme 18) [40]. Aryl bromide, alkynes and alkyl



Scheme 19. Light-induced C—C bond forming reaction of cycloketone oxime ethers and alkenes.



Scheme 20. Photoinduced phosphoranyl radical-mediated C—C bond forming reaction of cycloketone oximes.

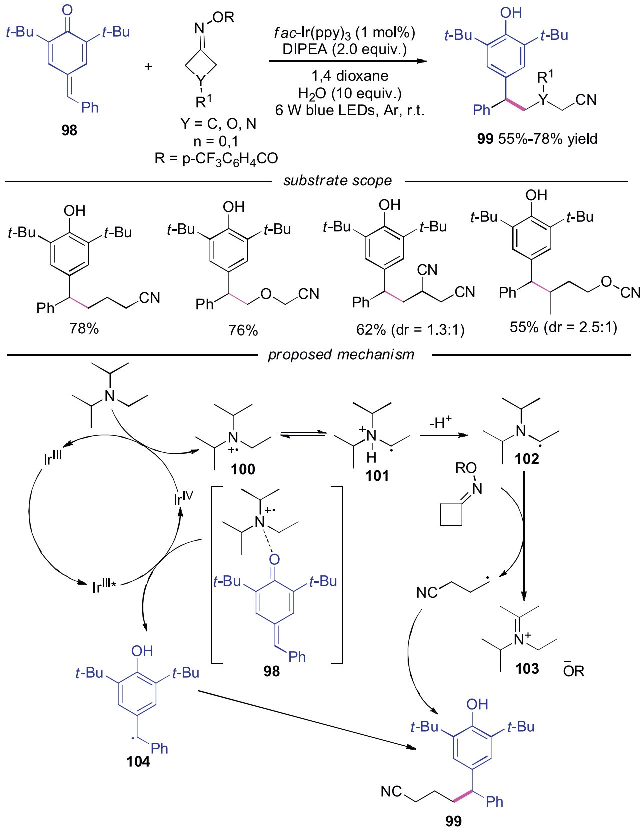


Scheme 21. Neophyl rearrangement and radical reduction reaction of cycloketone oximes.

bromide were well tolerated, enabling the development of distal arylation, vinylation and alkylation of nitrile-containing compounds. The proposed mechanism was shown in Scheme 17. The reaction started with the oxidation of oxime-carboxylate **71** by photoexcited photocatalysis to produce cyanoalkyl radical **3**. Meanwhile, the Ni^0 catalyst would undergo oxidative addition on an aryl bromide to produce Ni^{II} species [41]. Then, the radical transmetallation between radical **3** and Ni^{II} species delivered Ni^{III} species **85**, which went through reductive elimination to afford the final product **82**.

In 2019, a metal-free, light-driven and iminyl radical-mediated ring opening C—C bond cleavage/addition cascade reaction of *O*-4-methoxybenzyl oxime ethers with alkenes was described (Scheme 19) [42]. This reaction showed a broad substrate with excellent functional group tolerance, affording the corresponding oxo-nitriles in good yields. For example, monosubstituted and 3,3-disubstituted *O*-benzyl oxime ethers promoted the reaction well. Additionally, oxetan-3-one derived oxime ether was well employed in this reaction. The proposed mechanism indicated that the reaction was initiated with the abstraction of hydrogen atom at the benzylic position of cycloketone oximes by photoexcited catalyst 2-Cl-AQN* to form benzylic radical **87**, which underwent *β*-N—O bond scission to provide cyclic iminyl radical **2**. Further *β*-C-C bond cleavage of iminyl radical **2** would give rise to cyanoalkyl radical **3**, which would attack alkene subsequently to furnish radical **88**. Followed by another HAT from solvent, the final product **86** would be produced.

Yang and co-workers developed a photoinduced, phosphoranyl radical-mediated method for the direct N—O cleavage of cycloketone oximes through a polar/SET crossover process (Scheme 20) [43]. Alkenes with varied electronic and structural features participated in this reaction well. The fluorine analogue, olefins containing heterocycles and olefins with electron-withdrawing groups were well tolerated under the conditions. Moreover, *β*-flouride elimination occurred to afford *gem*-difluoroalkenes under the standard conditions when *α*-CF_3 alkenes were employed. A possible mechanism was proposed, which showed that Ph_3P was oxidized by photoexcited Ir^{III*} to generate $Ph_3P^{•+}$. Subsequently, a polar/SET crossover process took place to furnish radical **91** in the presence of Na_2CO_3. Radical **91** would undergo N—O scission to generate the key iminyl radical **2**, which would go through C—C bond cleavage giving rise to cyanoalkyl radical **3**. Cyanoalkyl radical **3** was then captured by alkene to produce radical **92**. The carbanion intermediate **93** was formed through reduction by Ir^{II}. Protonation of intermediate **93** occurred with regular alkene to form alkyl nitrile, while *β*-flouride elimination of **93** afforded the gem-difluoroalkene in the case of *α*-CF_3 alkene.



Scheme 22. Visible-light induced synthesis of cyanoalkylated diarylmethanes from cycloketone oxime ketone and *para*-quinone methides.

2.6. Miscellaneous

In 2018, Chen and co-workers reported the photocatalytic neophyl rearrangement and reduction of distal carbon radicals under visible light irradiation of *O*-acyl oximes (Scheme 21) [44]. Regarding for the substrate scope of neophyl rearrangement, symmetric disubstituted substrates with functional groups at the *para*-position worked well. When R^3 and R^1 were different substituted aryl groups, the selectivity of migration was dependent on their steric and electronic characters. Substrate with a methyl group at the *para*-position provided products **94a** and **94b** with moderate selectivity of aryl migration, while substrate with a methyl group at the *ortho*-position of one phenyl ring resulted in preferential migration. For the substrate scope of reduction of distal carbon radicals, the mono-substituted substrates at 3-position participated in the reaction well. Aryl and alkyl disubstituted substrates proceeded smoothly to furnish 3,3-disubstituted propionitriles. The proposed mechanism showed that carbon radical **3** went through neophyl rearrangement to afford more stabilized secondary carbon radical **96**. Subsequently, radical **96** was oxidized by *fac*-Ir(ppy)$_3$ to form carbocation **97**. Ultimately, DABCO promoted deprotonation of carboncation **97** would afford *α*,*β*-unsaturated nitrile **94**.

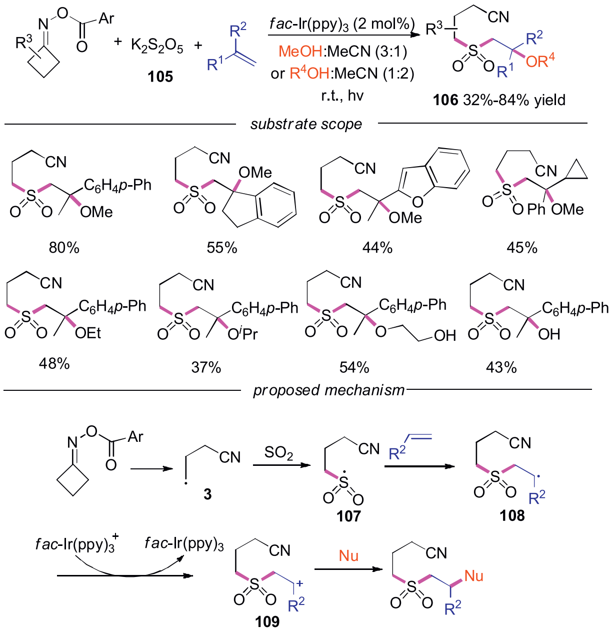
In 2019, Li and co-workers reported an efficient method to synthesize cyanoalkylated diarylmethanes, which were the key intermediates for the synthesis of GPR 40 agonists (Scheme 22)

[45]. Bromoacetonitriles and cycloketone oxime esters were employed as the cyanoalkyl radical source. For the reactions in which cycloketone oxime esters acted as cyanoalkyl radical source, various substituted cyanoalkylated diarylmethanes **99** were efficient obtained in moderate to good yields. The authors proposed the mechanism in Scheme 22. The photoexcited Ir^{III*} catalyst was oxidized by *para*-quinone methides **98** to generate Ir^{IV} catalyst and benzyl radical **104**. Subsequently, α-amino radical **101** generated by DIPEA was oxidized by cycloketone oxime esters to afford the cyanoalkyl radical along with the iminium salt **103**. Finally, the radical coupling between benzyl radical **104** and cyanoalkyl produced the desired cyanoalkylated diarylmethanes **99**.

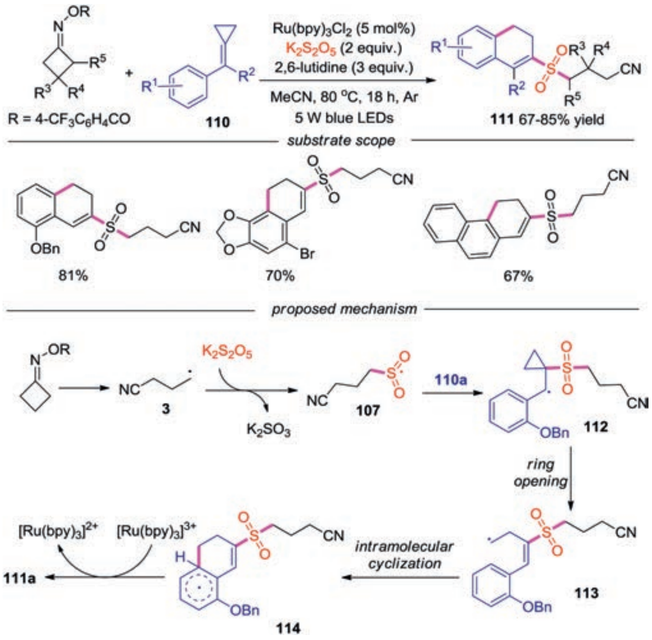
3. C—S, C—Se bond formation

Organosulfur compounds existed widely in nature products and bioactive compounds. Therefore, the formation of C—S bond has gained great interest in recent years [46]. In 2019, Wu and co-workers reported a photoinduced multicomponent sulfonylation of *O*-acyl oximes through iminyl radicals with the insertion of sulfur dioxide (Scheme 23) [47]. Variation of alkenes, oximes and alcohols were compatible in this transformation. For example, alkenes with benzofuranyl and cyclopropane substitutions were well suitable. Moreover, ethane-1,2-diol and other secondly alcohol participated the reaction smoothly. Additionally, various β-hydroxy sulfones were produced when the reactions were proceeded in water and MeCN. Mechanistic studies showed that the cyanoalkyl radical **3** was trapped by sulfur dioxide to form sulfony radical **107**, which attacked the alkene to generate another radical intermediate **108**. Subsequently, radical intermediate **108** was oxidized by photocatalyst to afford radical cation **109**, which would react with nucleophile to form the desired product **106**.

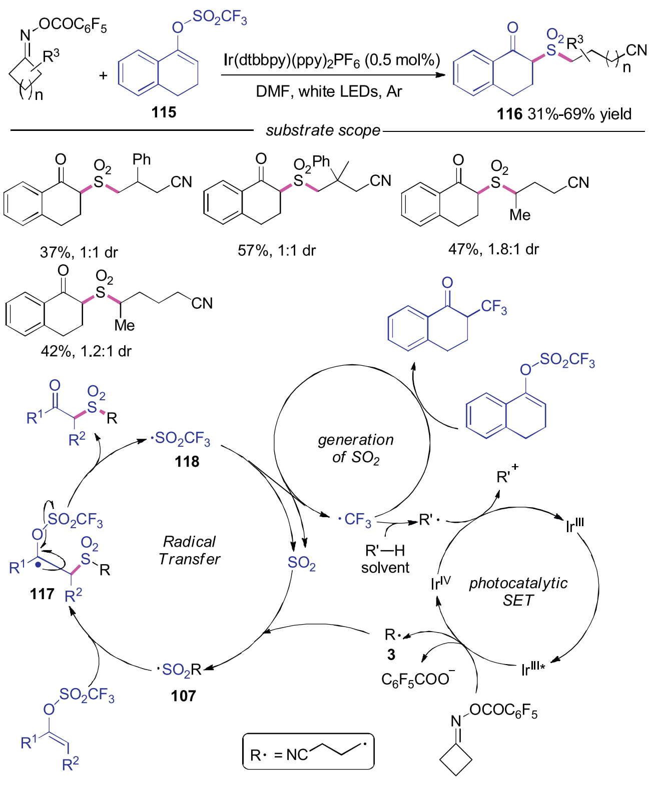
In 2020, Tang and co-workers reported a visible-light induced dual C—C bond cleavage of cycloketone oximes and methylenecyclipropanes (MCPs) for the synthesis of 2-cyanoalkylsulfonated 3,4-dihydronaphthalenes *via* the insertion of sulfur dioxide (Scheme 24) [48]. Variation of substitution on cycloketone oxime esters and methylenecyclipropanes were well compatible under the conditions. For instance, reactions of halo-substituted MCPs and naphthyl-substituted MCP proceeded smoothly. The proposed mechanism revealed that the cyanoalkyl radical **3** captured sulfur dioxide to form cyanoalkylsulfonyl radical **107**, which would attack the double bond in **110a** leading to radical **112**. Another cleavage of C—C bond would then occur to afford radical **113**, which underwent intramolecular cyclization giving rise to radical **114**. Followed by SET *via* $[Ru(bpy)_3]^{3+}$ and deprotonation by 2,6-lutidine, the target product **111a** would be afforded.



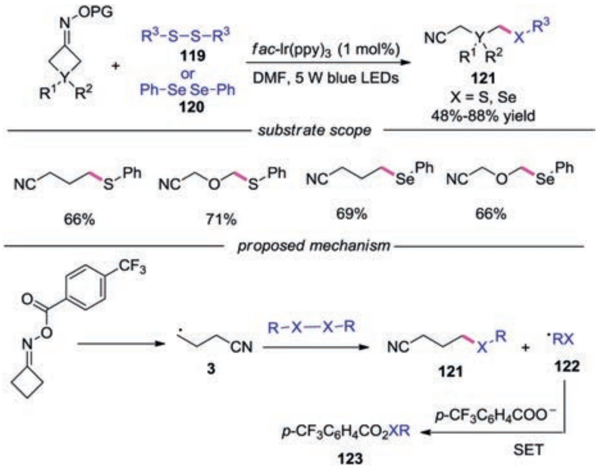
Scheme 23. Photoinduced multi-component sulfonylation reaction of cycloketone oximes.



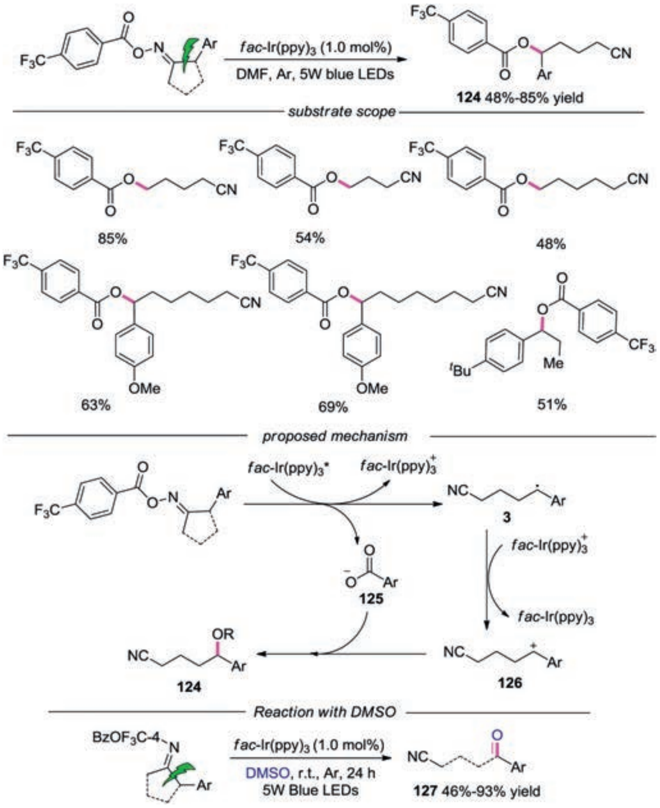
Scheme 24. Photoinduced multi-component sulfonylation reaction of cycloketone oximes.



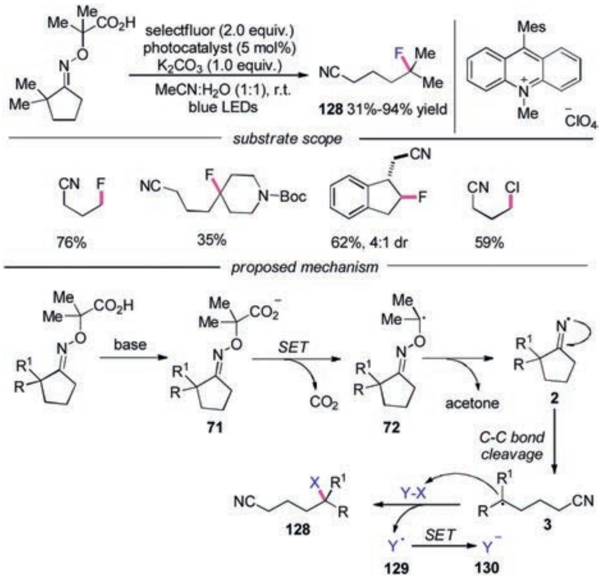
Scheme 25. Photoinduced SO_2-capture reaction of cycloketone oximes.



Scheme 26. Photoinduced C—S/Se bond formation reaction of cycloketone oximes.



Scheme 27. Photoinduced fragmentation/rearrangement and oxidation reaction of cycloketone oximes.



Scheme 28. Photoinduced C—F/Cl bond formation with cycloketone oximes.

A photoredox-catalyzed *in situ* SO_2-capture reaction was developed by Lu's group (Scheme 25) [49]. This reaction tolerated a variety of functional groups, and a range of desired products was afforded in good yields. The proposed mechanism showed that the cyanoalkyl radical **3** was generated through reduction of cycloketone oxime by photoexcited catalyst followed by C—C cleavage. Then, this cyanoalkyl radical **3** captured the *in situ* generated SO_2 to form sulfonyl radical **107**, which reacted with enol triflate **115** leading to intermediate **117**. Elimination of radical intermediate **117** provided the product **116** with the release of trifluoromethylsulfonyl radical **118**, which would regenerate SO_2 through fragmentation along with the release of trifluoromethyl radical. The trifluoromethyl radical had two functions: it could participate in the decomposition of **115** to produce α-trifluoromethylated ketone as the side product. On the other hand, hydrogen abstraction from solvent (R′-H) would afford radical $R'^{\bullet}$, which could reduce Ir^{IV} to Ir^{III} to complete the catalytic cycle.

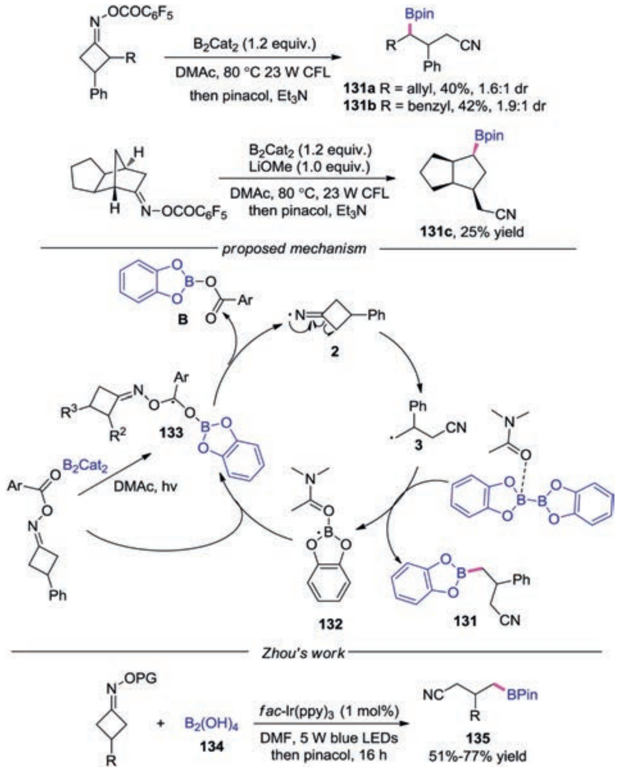
In 2019, Zhou's group reported the photocatalytic thiolation and selenylation of cycloketone oxime esters *via* iminyl radical-triggered C—C bond cleavage, providing a unified approach to alkyl sulfur and selenium compounds tethered to nitrile group (Scheme 26) [50]. Again, oxime esters with various functional groups were well tolerated under the conditions, providing the desired products in generally good yields. A plausible mechanism for this $C(sp^3)$-S, $C(sp^3)$-Se bond forming reaction was proposed. It was reasoned that the cyanoalkyl radical **3** would be captured by disulfide or diselenide leading to $C(sp^3)$-S or $C(sp^3)$-Se bond respectively along with the formation of radical **122**. The radical **122** was then oxidized by Ir^{IV} to complete the catalytic cycle.

4. C—O bond formation

In 2018, Shi's group described a photoinduced protocol for the synthesis of cyano-containing benzoates by fragmentation-rearrangement sequence of cycloketoxime esters (Scheme 27) [51]. It was found that four-membered and less-strained substrates were tolerated in this transformation. Furthermore, the noncyclic oxime esters were also suitable, providing the products without cyano group. The proposed mechanism revealed that the reaction was initiated with the reduction of cycloketone oximes ester by photoexcited catalyst leading to cyano radical **3** with the release of carboxylate **125**. Subsequently, cyanoalkyl radical **3** was oxidized by Ir^{IV} to afford cationic intermediate **126**. Followed by the nucleophilic attack between carboxylate **125** and cationic intermediate **126**, the final product **124** would be produced. Almost the same time, Shi and co-workers also reported a photoinduced strategy for the synthesis of cyano-containing ketones by C—C bond scission/oxidation sequence of cycloketone oximes [52]. In this reaction, the cation intermediate **126** was oxidized by DMSO to form the final ketone product **127**.

5. C—X (F,Cl) bond formation

In 2018, Leonori's group described the synthesis of a variety of differentially functionalized nitriles *via* a photoinduced cascade strategy (Scheme 28) [53]. These mild, visible light mediated



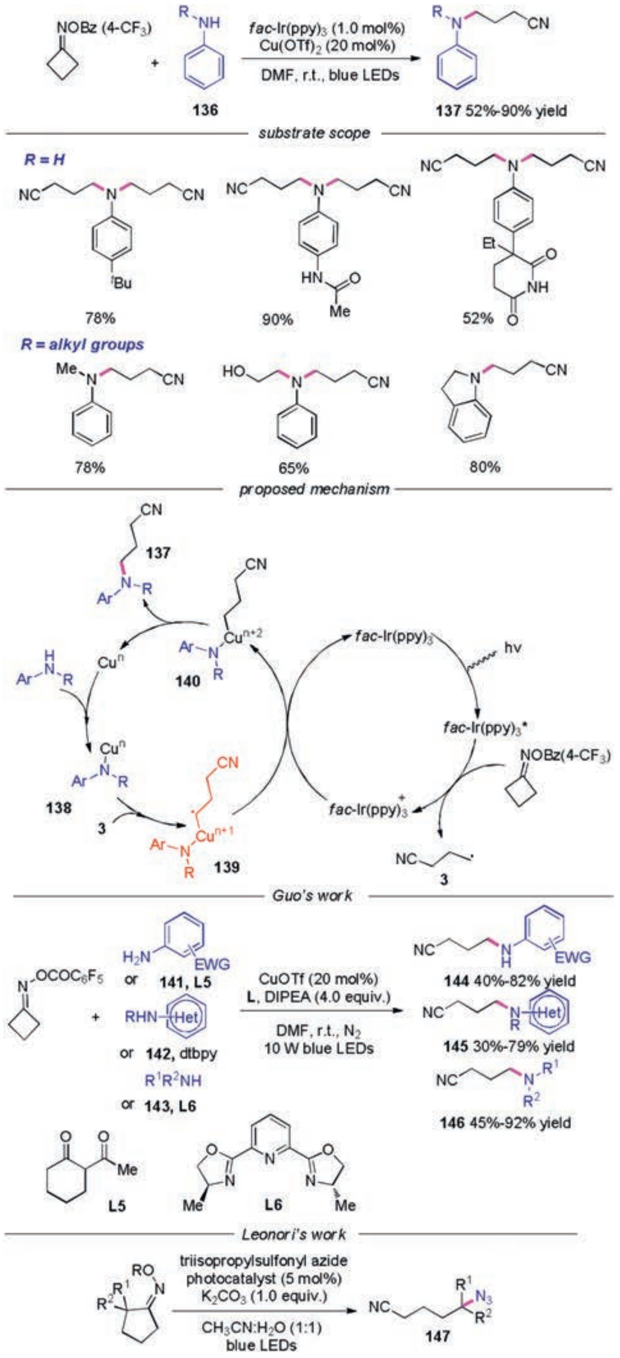
Scheme 29. Photoinduced C—B bond formation with cycloketone oximes.

protocols could be used for remote fluorination, chlorination and azidation, and the modification of structurally complex molecules and bioactive compounds. Oximes derived from cyclobutanes, cyclopentanones, cyclohexanones and even cycloheptanones were workable in this reaction, affording a broad range of fluorination and chlorination products in good yields. Mechanistic studies showed that after oxidation of oxime, radical **72** would be generated and underwent N—O bond cleavage to form iminyl radical **2**. The C—C bond cleavage of iminyl radical **2** would provide cyanoalkyl radical **3**, which reacted with SOMOphile giving rise to the desired products **128**.

6. C—B bond formation

In 2019, Guo's group reported the transition-metal free C—C bond scission/borylation of cyclobutanone oxime esters (Scheme 29) [54]. This method is amenable for the synthesis of both primary and secondary boronic esters. For the preparation of secondary boronic esters, light irradiation was essential to promote the reaction. A plausible radical chain propagation mechanism was proposed. Initially, radical intermediate **133** was formed through light-irradiation of $B_2(Cat)_2{}^{\bullet}$DMAc complex with cyclobutanone oxime ester. Then, iminyl radical **2** was generated by the cleavage of N—O bond, and the cyanoalkyl radical **3** was afforded through the C—C bond scission of iminyl radical **2**. Subsequently, the radical **3** would react with $B_2(Cat)_2{}^{\bullet}$DMAc giving rise to the desired product **131** and DMAc-stabilized boryl radical **132**. The resulting boryl radical **132** might propagate a radical chain process. The C—B bond formation with diboron was also reported by Zhou and co-workers [50].

7. C—N bond formation



Scheme 30. Photoinduced C—N bond formation with cycloketone oximes.

In 2017, Shi and co-workers developed a SET induced selective C(sp^3)-N coupling with anilines *via* C – C bond cleavage under synergetic photoredox/copper-catalytic reaction systems (Scheme 30) [55]. A broad range of free anilines was examined, affording the dialkyl-functionalization products in good yields. Meanwhile, *N*-alkyl substituted anilines were workable in this reaction. Moreover, free alcohol and indoline were also suitable substrate under the conditions. A mechanism was proposed for this dual copper/photoredox catalytic cycle, as shown in Scheme 30. The distal radical **3** was generated by the reduction of photoexcited *fac*-Ir(ppy)$_3$* followed by the C—C bond cleavage. Concurrently, the aniline coordinated with a low-valence copper catalyst to form a copper amido complex **138**. Then, radical **3** would be trapped by copper amido complex **138** leading to intermediate **139**. A high-valence copper alkyl amido complex **140** would be obtained through a single-electron oxidation of complex **139** by photocatalyst, which would undergo reductive elimination to provide the desired product

137. In the same year, Guo's group reported the similar C—N bond formation between cycloketone oximes and aromatic amines or secondly amine under visible light conditions [56]. Leonori's group also described the C—N bond formation reaction of cycloketone oximes with azide compounds [53].

8. Conclusion

In conclusion, recent advances for the synthesis of nitriles through photoinduced C—C bond cleavage of cycloketone oximes classified by the type of C—X bond forming are summarized. Various compounds possessing nitriles can be efficiently accessed *via* this method. The photoinduced conditions for the C—C bond cleavage of cycloketone oximes are mild, and the cyanoalkyl radical generated by single-electron-transfer and C—C bond cleavage is served as the key intermediate. A wide range of reactions with radical acceptors can be compatible under the conditions.

Despite the significant achievements in this field, there are still many issues to be solved. For example, the α-substituted carbon of cycloketone oximes was prochiral carbon after C—C bond cleavage, so is it possible to use this property to achieve asymmetric transformations? Furthermore, there is still room to investigate the asymmetric transformation of cyanoalkyl radical with *in situ* generated chiral compounds in catalytic way. Moreover, transformations on the alkyl chain of distal cyano group have yet been achieved, is there any useful transformation which utilize the carbon chain of distal cyano group? We wish this review would be useful for chemists who are interested in the synthetic transformation of cycloketone oximes.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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