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Nitriles as radical acceptors in radical cascade reactions†

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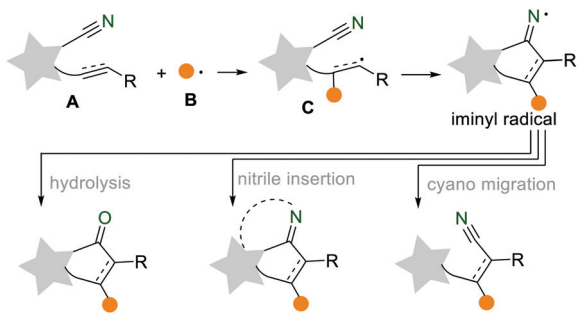
The cyano group is a valuable and readily available functional group for the preparation of various functional groups, such as amines, carboxylic acids, and ketones. In recent decades, the radical cascade reaction has emerged as a versatile tool to prepare a large variety of functional molecules. The application of the cyano group as a radical acceptor in cascade reactions provides diverse opportunities for the convenient construction of various important heterocycles and carbocycles. Such synthetic strategies will open new ways for the rapid buildup of molecular complexity. The focus of this review is the summary of the dynamic field of radical cascade processes using the cyano group as a radical acceptor, which has not been well documented so far.

1. Introduction

The development of simple, rapid, and efficient synthetic protocols for the preparation of complex organic molecules is always a goal, attracting the widespread interest of organic chemists. In the past few decades, the radical cascade reaction has been developed into a versatile synthetic platform to synthesize structurally diverse compounds with great atom-economy and step-economy.[1] The rapid development of the radical cascade reaction largely depends on the continuous discovery of novel radical acceptors, such as alkenes, alkynes, cyano and isocyano groups.[2] Among them, the cyano group is a valuable and readily available functional group for the preparation of various functional groups, such as amines, carboxylic acids, and ketones. Recently, the application of the cyano group as a radical acceptor in cascade reactions provides diverse opportunities for the convenient construction of various important heterocycles and carbocycles. As shown in Scheme 1, when the *in situ* generated radical **B** was added to the unsaturated CN-containing substrate **A**, an alkenyl radical **C** was formed. This was followed by an intramolecular cyclization to produce the key intermediate iminyl radical. Then, the iminyl radical underwent prior restoration and hydrolysis (either electron transfer or hydrogen abstraction), nitrile insertion, or cyano migration to form the corresponding ketone, N-heterocycle, and nitrile.[3] We herein would like to summarize the recent progress of the radical cascade reactions using the cyano group as a radical acceptor. This review is organized into three sections based on the different transformations of iminyl radicals: (i) hydrolysis into cyclic ketones, (ii) nitrile insertion for N-heterocycles, and (iii) remote cyano migration. We hope this review provides a scientific auxiliary tool for researchers in radical chemistry, inspiring more strategic synthetic applications in this dynamic and exciting field.

2. Hydrolysis into cyclic ketones

The application of the cyano group as a radical acceptor has attracted the increasing research interest of organic chemists for nearly half a century. The generated iminyl radicals are reduced before hydrolysis (either electron transfer or hydrogen



Scheme 1 The cyano group as a radical acceptor in the radical cascade reactions.

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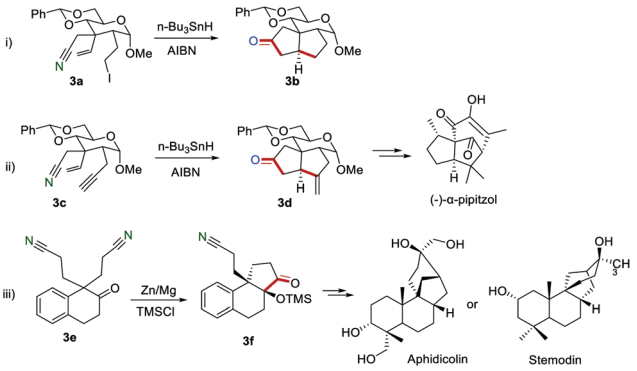
† Dedicated to the 100th anniversary of Chemistry at Nankai University.

abstraction) into cyclic ketones.[4] For example, Ogibin's group described the preparation of cyclopentanone **2c** in high yield *via* cyclization of 5-bromocyanopentane **2a** in the presence of $(n\text{-}Bu_3Sn)_2$ as early as 1975 (Scheme 2i). Iminyl radical **2b** was generated in this transformation, and the rate constant was estimated to be 4×10^4 s^{-1} at 80 °C reported by Grille and co-workers.[5] In 1983, Corey and Pyne realized the synthesis of bicyclic ketone **2e** *via* cyclization of the keto-nitrile **2d** in the presence of zinc/trimethylchlorosiIane.[6] A similar reaction could proceed in the presence of SmI_2 (Scheme 2ii).[7] In 1984, Clive and co-workers developed the construction of the fused ring systems **2g** by employing triphenyltin hydride (Ph_3SnH) and azobisisobutyronitrile (AIBN) to promote the generation of an iminyl radical *via* deoxygenation of alcohols and intramolecular cyclization (Scheme 2iii).[8] In 1992, Snider and Buckman reported the cyclization of **2h** for the generation of the bicyclic ketone **2j** in the presence of $Mn(OAc)_3$ (Scheme 2iv).[9] In this study, the five-membered cyclic ketone (n = 1) could be obtained in 40% yield, while the six-membered cyclic ketone (n = 2) was only obtained in 8% yield. In 1999, Sulsky and co-workers realized the preparation of spiro[2*H*-indol]-3(1*H*)-ones **2n** by cyclization of **2k** in the presence of Bu_3SnH *via* iminyl radical intermediate **2l** (Scheme 2v).[10]

The employment of this effective strategy to synthesize the bio-related substances has also been reported. For example, Fraser-Reid and co-workers described the preparation of five-membered cyclic ketones **3b** by the reaction of the carbohydrate framework **3a** in the presence of n-Bu_3SnH in 1986 (Scheme 3i).[11] Later, the same group achieved the transformation of the carbohydrate framework **3c** to **3d**, which was a key intermediate for the tricyclic cedrenoid sesquiterpene (−)-α-pipitzol (Scheme 3ii).[12] In 1995, Mann and Hegarty developed a new approach to access the key intermediate **3f**, which could be further converted into the biologically natural products, aphidicolin or stemodin.[13]



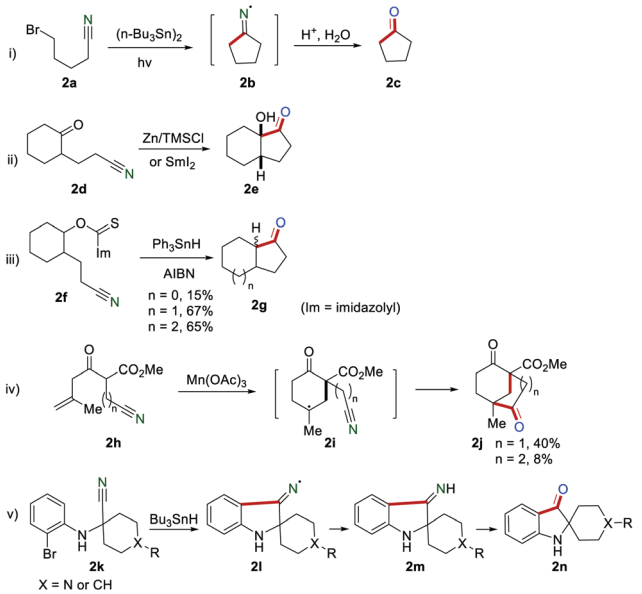
Scheme 3 The application of the cyano group as a radical acceptor to synthesize the bio-related substances.

The quite slow rate of the 6-*exo* cyclization onto the cyano group led to the challenge preparation of the six-membered cyclic ketones.[14] The reaction could proceed smoothly to produce six-membered cyclic ketones only when the reactive centers were part of a more rigid system, where the unfavorable conformations were minimized. For example, Fraser-Reid and co-workers realized the synthesis of the six-membered cyclic ketones **4b** by employing the constrained geometry of a 1,6-anhydrocarbohydrate **4a** as the starting material in 1993 (Scheme 4i).[15] In 1990, an electroreduction of the γ- and δ-cyanoketones **4c** was developed by Shono and Kise to access α-hydroxyketones **4d** and dehydroxylated ketones **4e** (Scheme 4ii).[16]

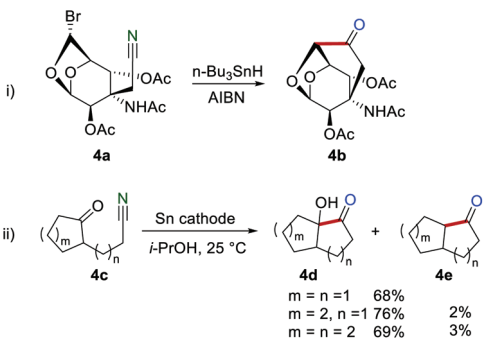
Although great achievements have been made, it is only in the last two decades that this knowledge has been widely applied in the preparation of cyclic ketones and explosive growth has been witnessed. In the following part, we will summarize the recent progress using the cyano group as a radical acceptor for the preparation of a vast array of cyclic ketones.

2.1 Synthesis of quinoline-2,4-dione derivatives

Quinoline-2,4-dione frameworks are frequently found in a large number of natural products, pharmaceuticals, and agrochemicals. In 2015, Li and co-workers reported the construc-



Scheme 2 Early studies on the iminyl radical for the construction of five-membered cyclic ketones.



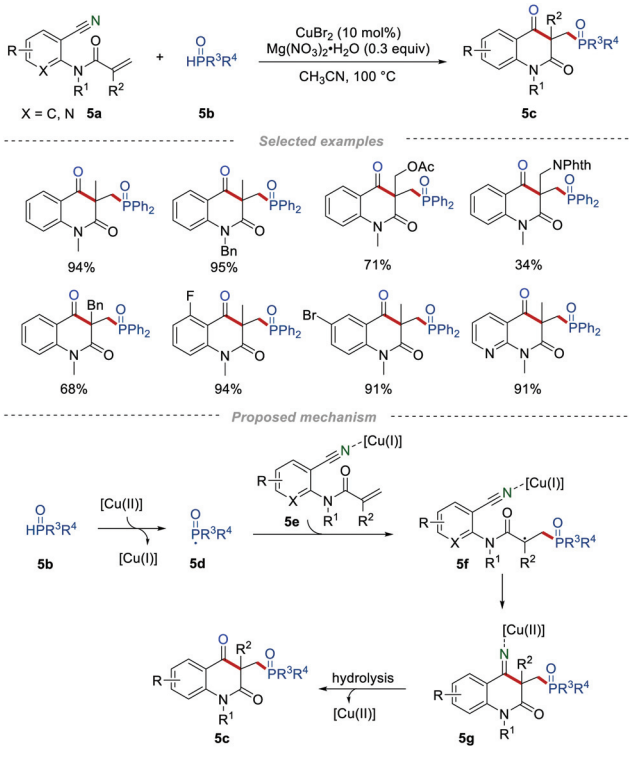
Scheme 4 Early studies on the iminyl radical for the construction of the six-membered cyclic ketones.

tion of quinoline-2,4(1*H*,3*H*)-diones *via* radical cascade reaction by reacting the readily accessible 2-cyanoarylacrylamides **5a** with the *H*-phosphonates **5b** (Scheme 5).[17] A series of 2-cyanoarylacrylamides **5a** bearing different functional groups and different kinds of *H*-phosphonates **5b** were all examined, leading to the formation of the phosphorylated quinoline-2,4(1*H*,3*H*)-diones **5c** in good yields. This efficient protocol enables the simultaneous formation of the C–C, C–O, and C–P bonds in one step, and is convenient to carry out gram-scale synthesis with similar efficiency. The radical-trapping experiments provided important support for the generation of the phosphoryl radicals in the reaction process.

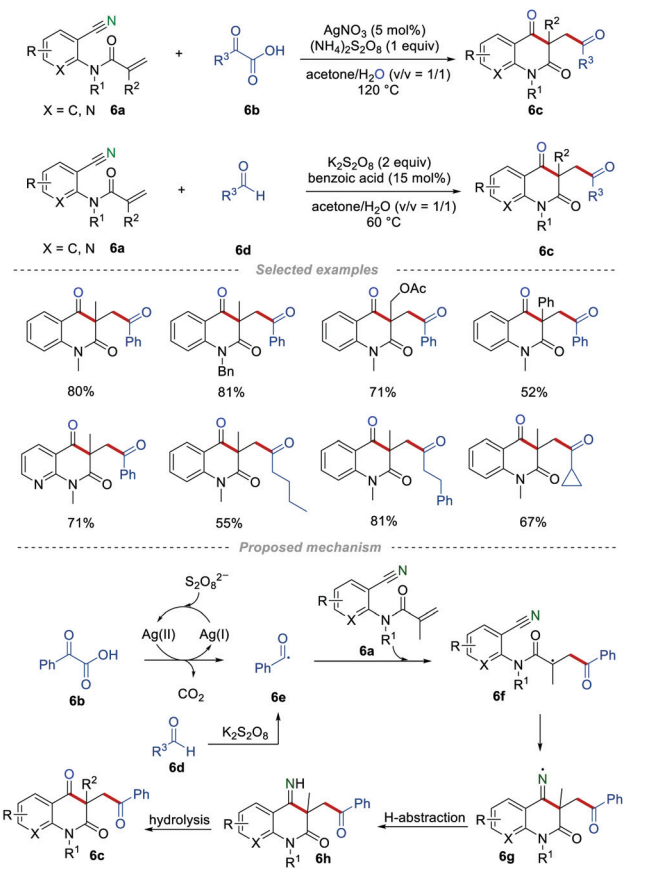
On the basis of a series of control experiments, a reasonable radical cyclization mechanism for this transformation was suggested. Initially, the phosphoryl radical **5d** was generated from *H*-phosphonate **5b** under the oxidation of Cu(II). Then, the selective addition of **5d** to the C=C bond of intermediate **5e** would give an electrophilic carbon-centered radical **5f**. **5f** would further undergo an intramolecular addition to produce the intermediate **5g**. Subsequently, the hydrolysis of **5g** provided the desired product **5c** with the release of the copper species.

Since this pioneering study, the reactions of 2-cyanoarylacrylamides with various types of radical precursors have been studied in detail. In the past few decades, aldehydes and α-keto acids have been widely used as the acyl radical precursors in the presence of transition metals and oxidants.[18] In 2016, Li and co-workers realized the construction of carbonyl-containing quinoline-2,4(1*H*,3*H*)-diones **6c** *via* the radical addition/cyclization of *o*-cyanoarylacrylamides **6a** with α-keto acids **6b** or aldehydes **6d** (Scheme 6).[19] Both aromatic and aliphatic aldehydes or α-keto acids were compatible in this transformation, and the cyclopropyl group could be tolerated during the reaction process without the ring-opening reaction. This strategy provides a simple and efficient protocol to access various carbonyl-containing quinoline-2,4(1*H*,3*H*)-diones **6c** in good yields. The radical trapping experiments demonstrated that the reaction proceeds through a radical pathway. As it can be seen, acyl radical **6e** was produced from α-keto acid **6b** or aldehyde **6d**. After undergoing a similar radical addition/cyclization process, the iminyl radical **6g** was formed, which subsequently abstracted a hydrogen atom from the surrounding to give the imine **6h**. Imine **6h** was converted to the final product **6c** through hydrolysis.

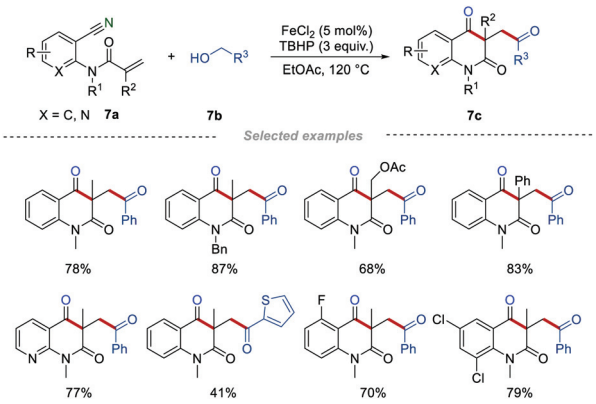
It is well known that alcohol could be oxidized into the corresponding aldehyde in the presence of suitable oxidants.[20] In 2016, Li's group employed benzylic alcohols **7b** instead of α-keto acids or aldehydes as acyl radical precursors to access carbonyl-containing quinoline-2,4-diones **7c** (Scheme 7).[21] This method provides an alternative to synthesizing the carbonyl-containing quinoline-2,4-diones **7c**, showing good functional group compatibility. In this work, the oxidant of the



Scheme 5 The preparation of the phosphorylated quinoline-2,4-diones.



Scheme 6 The construction of the carbonyl-containing quinoline-2,4-diones.



Scheme 7 The construction of carbonyl-containing quinoline-2,4-diones from alcohols.

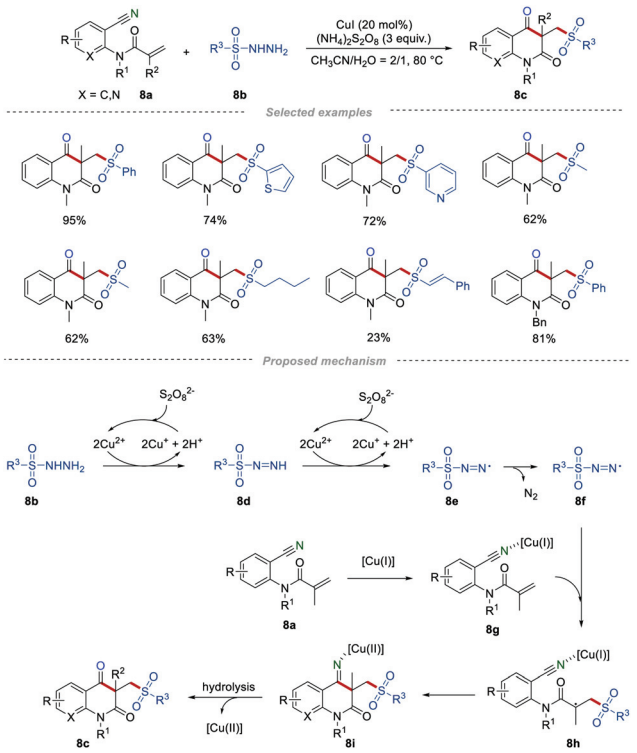
benzylic alcohols **7b** to the corresponding aldehydes in the presence of $FeCl_2$/TBHP was critical. Mechanistic studies indicated that acyl radicals are important intermediates, which were produced from the *in situ* generated aldehydes.

Sulfone-containing molecules are widely found in a large variety of biologically active compounds, drug molecules, and versatile synthetic intermediates.[22] The addition of sulfonyl radicals to the unsaturated C–C bond has been an effective method for the synthesis of organic sulfones.[23] In this context, Wang's group reported the synthesis of sulfonated quinoline-2,4-diones **8c** by employing easily available sulfonyl hydrazides **8b** as sulfonyl radical precursors (Scheme 8).[24] There was a wide range of *o*-cyanoarylacrylamides **8a** possessing diverse steric and electronic properties that were applicable in this transformation. Moreover, the aryl and alkyl sulfonyl hydrazides **8b**, and even those sulfonyl hydrazides containing C=C bonds were suitable in this reaction, producing sulfonated quinoline-2,4-diones **8c** in moderate to good yields. Presumably, the sulfonyl radicals were generated from sulfonyl hydrazides *via* single electron transfer and the deprotonation process in the presence of CuI and $(NH_4)_2S_2O_8$. After the addition of the sulfonyl radical to the C=C bond, intramolecular cyclization, and hydrolysis, the final product **8c** was produced.

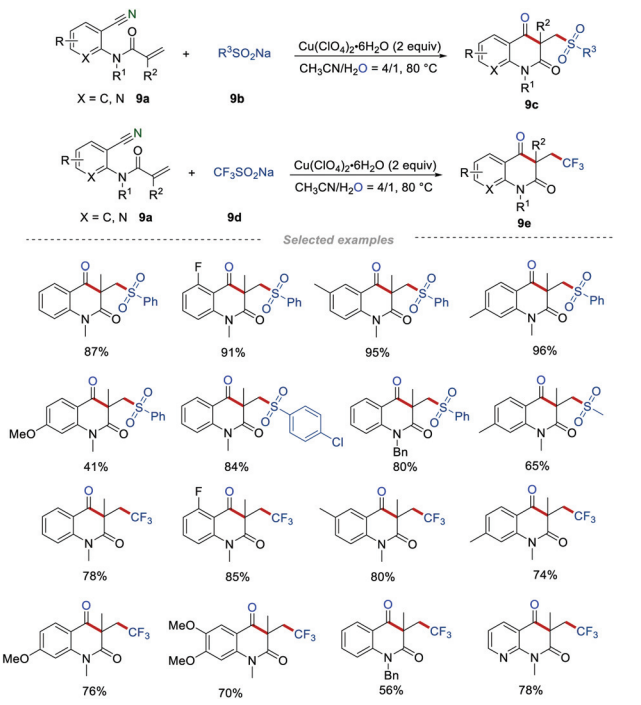
In contrast to Wang's procedure, Li's group[25] employed sodium sulfinates **9b** as sulfonyl radical precursors and $Cu(ClO_4)_2$ as a catalyst to access the sulfonated quinoline-2,4-diones **9c** (Scheme 9). Besides the aromatic sulfonyl radical precursors, the aliphatic sulfonyl radical precursors also showed good reactivities in the preparation of the sulfonated quinoline-2,4-diones **9b**, giving the corresponding heterocycles in reasonable yields. In addition, the synthesis of trifluoromethylated quinoline-2,4-diones **9c** *via* the radical cascade reaction was disclosed when sodium trifluoromethanesulfonate **9d** (Langlois' reagent) was applied as a reactant. Under the optimized conditions, various trifluoromethylated quinoline-2,4-diones **9e** were obtained in moderate to good yields.

2.2 Synthesis of indenones

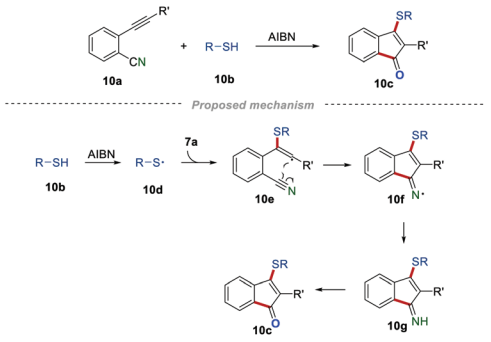
As important skeletons, indenones are extensively found in natural products and many synthetic compounds with various biological activities. Developing powerful and reliable methods



Scheme 8 The construction of sulfonated quinoline-2,4-diones.



Scheme 9 The construction of sulfonated and trifluoromethylated quinoline-2,4-diones.



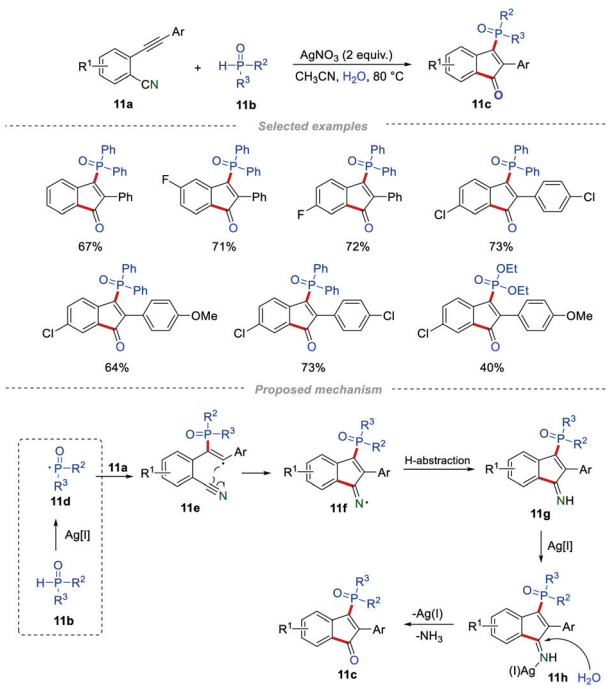
Scheme 10 The construction of sulfanylated indenones.

for the construction of indenone frameworks has attracted a lot of attention in the past few decades. In 1998, Montevecchi and co-workers synthesized sulfanylated indenones **10c** by reactions of 2-alkynylbenzonitriles **10a** and thiols **10b** (Scheme 10).[26] When R′ was an alkyl substituent, the desired product **10c** could be only obtained in low yield, which might be caused by the unstable intermediate. The regioselective addition of sulfanyl radicals **10d** to the C–C triple bond generated vinyl radical **10e**. The intramolecular cyclization of radical **10e** led to the formation of the C–N bond to access the iminyl radical **10f**, which further underwent hydrogen abstraction and hydrolysis to produce the desired products **10c**.

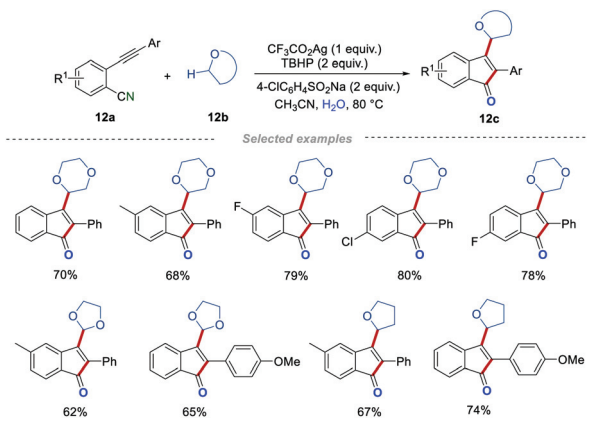
In 2016, the group of Tu and Jiang disclosed a novel and straightforward approach for the preparation of phosphinylated 1-indenones from 2-alkynylbenzonitriles and disubstituted phosphine oxides in the presence of $AgNO_3$ (Scheme 11).[27] After optimization of the reaction conditions, it was found that the highest yield was obtained in the presence of 2 equiv. of $AgNO_3$ in CH_3CN at 80 °C. The main merits of this method are that the reaction could be carried out under mild reaction conditions with a broad substrate scope and high functional group tolerance. Based on the control experiments, a reasonable mechanism was proposed, as illustrated in Scheme 11. In the presence of Ag(I), **11b** could form a phosphorus-centered radical **11d**, which further underwent regioselective addition to yield the alkenyl radical **11e**. After an intramolecular cyclization, the radical intermediate **11f** was produced. This subsequently abstracted a hydrogen atom, leading to the formation of imine **11g**. Finally, the silver(I)-catalyzed hydrolysis of **11g** produced the final product **11c** in the presence of H_2O.

After that, the same group developed an interesting and easy-to-handle protocol, by which a large variety of 3-alkylated 1-indenones **12c** were prepared from 2-alkynylbenzonitriles **12a** and cyclic ethers.[28] This procedure was amenable to 2-alkynylbenzonitriles with diverse functionalities, such as fluoro, chloro, bromo, methyl, ethyl, *t*-butyl, and methoxy groups. Moreover, 1,4-dioxane, tetrahydrofuran (THF) as well as 1,3-dioxolane were all suitable for this transformation. The control experiments showed that a radical pathway was involved in this transformation, and the oxygen atom of the carbonyl in products **12c** indeed comes from water. It is particularly worth mentioning that the cyclic ether acts as both a C-centered radical precursor and a reaction medium in this reaction process. Interestingly, two different radical precursors (cyclic ethers and 4-$ClC_6H_4SO_2Na$) can be well tolerated simultaneously in this transformation without disturbing the reaction process (Scheme 12).

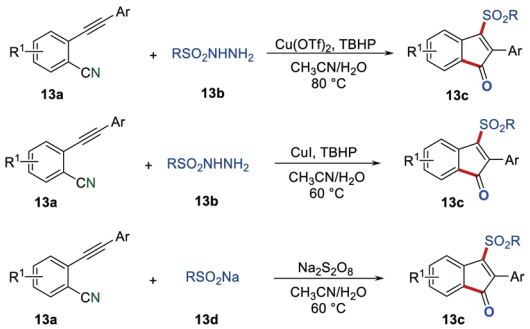
Due to the importance of sulfonyl-containing compounds, various methods were developed for the introduction of the sulfonyl group to indenones.[29] For example, Jiang's group, Yu's group, and Liang's group independently reported the preparation of 3-sulfonated indenones **13c** *via* the sulfonyl radical-initiated cascade cyclization (Scheme 13).[30] By using different sulfonyl radical precursors, there was a wide range of 3-sulfonated indenones **13c** that were synthesized in satisfac-



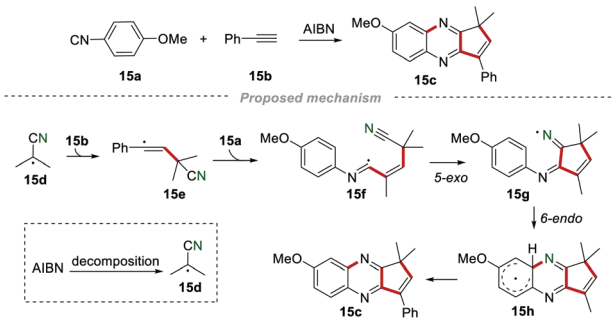
Scheme 11 The synthesis of phosphinylated indenones.



Scheme 12 The construction of 3-alkylated indenones.



Scheme 13 The preparation of 3-sulfonated indenones.



Scheme 15 The construction of cyclopenta-fused quinoxaline.

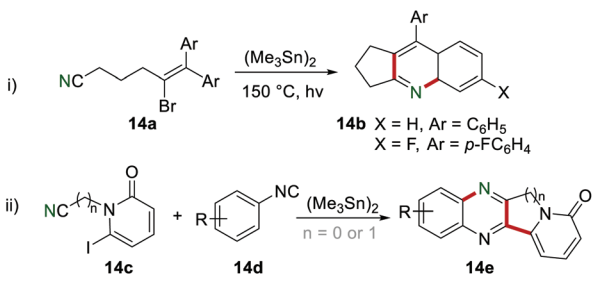
tory yields. Moreover, in the report of Yu's group, the synthesized compounds were proven to own typical aggregation-induced emission (AIE) properties, which showed promising application in live-cell imaging. Additionally, in Liang's report, the trifluoromethylated indenone could be obtained in 35% isolated yield by employing CF_3SO_2Na as a radical precursor.

3. Nitrile insertion for N-heterocycles

Nitrogen-containing heterocycles are highly privileged frameworks with unique biological activity and are widespread in various natural products, playing significant roles in biologically active molecules and pharmaceuticals. In the past decades, great efforts have been devoted to developing novel and efficient synthetic methodologies for the preparation of N-heterocycles.[31] Importantly, the radical cascade reactions using the cyano group as a radical acceptor have emerged as a powerful strategy for the construction of N-heterocycles through a nitrile insertion process.

3.1 Synthesis of fused quinoline and quinoxaline derivatives

In 1991, Curran and Liu utilized the cyano group as a radical acceptor to provide a simple procedure to synthesize the cyclopenta-fused quinolines **14b** by cyclization of **14a** in the presence of $(Me_3Sn)_2$ (Scheme 14i).[32] In 1996, the synthesis of the fused quinoxaline **14e** was also achieved by the same group, leading to the formation of two C–C bonds and one C–N bond in one step (Scheme 14ii).[33]

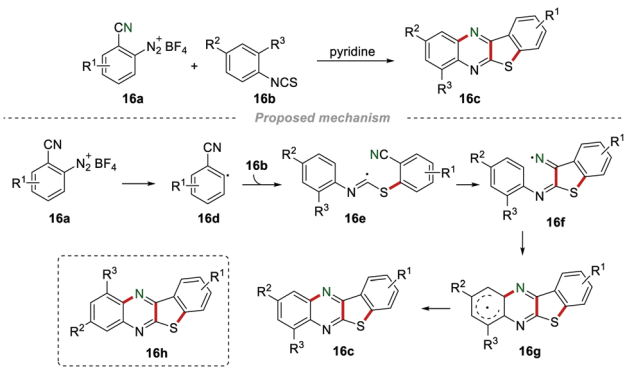


Scheme 14 The construction of fused quinoline and quinoxaline derivatives.

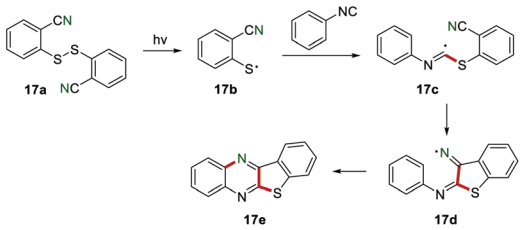
In 1995, Nanni and co-workers achieved the construction of the cyclopenta-fused quinoxaline **15c** by reacting 4-methoxyphenylisonitrile **15a** and phenylacetylene **15b** in a refluxing benzene solution in the presence of AIBN (Scheme 15).[34] The decomposition of AIBN produced the 2-cyanoprop-2-yl radical **15d**, which was added to the C–C triple bond of phenylacetylene **15b** to access the vinyl radical **15e**. The vinyl radical **15e** subsequently attacked the carbon atom of isonitrile **15a** to generate imidoyl **15f**. Imidoyl **15f** further underwent cascade 5-*exo* and 6-*endo* cyclization to give the radical **15h**, which transformed into the desired product **15c** *via* aromatization.

In 1997, Zanardi *et al.* accomplished the synthesis of benzothienoquinoxalines **16c** by annulation of aryl diazonium tetrafluoroborates **16a** with isothiocyanates **16b** (Scheme 16).[35] The aryl radical **16d** attacked the sulfur atom of the isothiocyanate **16b** to produce the imidoyl radical **16e**, which subsequently was added to the cyano group to give iminyl **16f**. Iminyl **16f** further underwent an intramolecular cyclization and aromatization to access the desired product **16c**. Importantly, no product **16h** was observed, indicating that the intramolecular cyclization of **16f** *via* 5-membered *ipso*-cyclization followed by rearrangement was impossible.

After that, Nanni and co-workers reported the photocatalytic synthesis of benzothienoquinoxalines **17e** in 1998 (Scheme 17).[36] The cleavage of an S–S bond generated the sulfanyl radical **17b**, which was added to the isocyano group to produce an imidoyl radical **17c**. Subsequently, the imidoyl



Scheme 16 The construction of benzothienoquinoxalines.

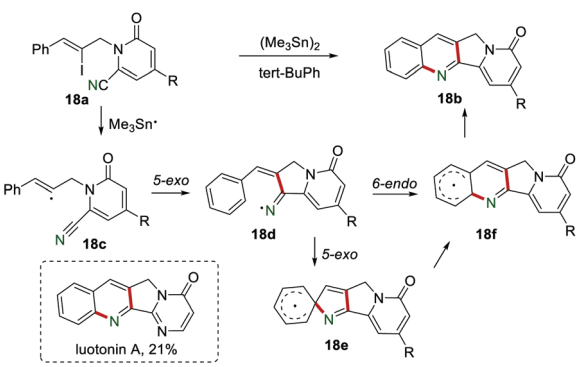


Scheme 17 Photocatalytic synthesis of benzothienoquinoxalines.

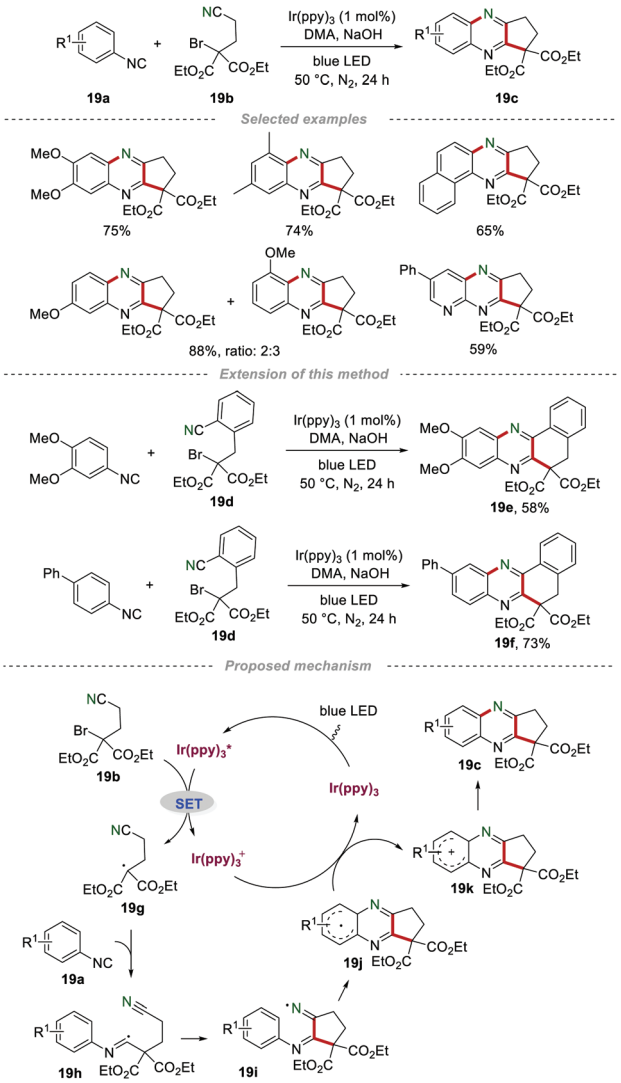
radical **17c** underwent an intramolecular cyclization reaction to give an iminyl radical **17d**, which further suffered from cyclization to complete this transformation.

In 2005, Bowman *et al.* reported the synthesis of tetracycline **18b** containing the 2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinoline ring system in the presence of $(Me_3Sn)_2$ and *tert*-BuPh (Scheme 18).[37] By using this novel protocol, the biologically active luotonin A could be obtained in 21% yield. The mechanism showed that the reaction of vinyl iodide **18a** and $Me_3Sn^{\bullet}$ produced vinyl radical **18c**, which subsequently was added to the cyano group to afford the iminyl radical **18d**. The rate of iodine abstraction by $Bu_3Sn^{\bullet}$ from the vinyl iodide **18a** is theoretically faster than bromine abstraction (10^6–10^7 M^{-1} s^{-1}),[38] which might not be the rate-determining step. The iminyl radical **18d** underwent 6-*endo* intramolecular cyclization (or 5-*exo* intramolecular cyclization followed by rearrangement) to generate the radical intermediate **18f**, which lost a $H^{\bullet}$ in a H-abstraction step to yield the desired product **18b**. Both the intramolecular cyclization, including 5-*exo* cyclization onto the cyano group and iminyl radical onto the phenyl ring, were slow. A control experiment without $(Me_3Sn)_2$ led to the formation of the trace product **18b**, suggesting that iodine homolysis or the Diels–Alder cyclization might be the possible minor mechanisms.

In 2014, Yu's group developed a practical and eco-friendly strategy for the construction of two C–C bonds and one C–N bond in one step to access the fused quinoxaline derivatives **19c** under the irradiation of visible light (Scheme 19).[39] A variety of 5-membered ring-fused quinoxalines **19c** were prepared in moderate to good yields. Moreover, 6-membered ring-



Scheme 18 The synthesis of tetracycline.

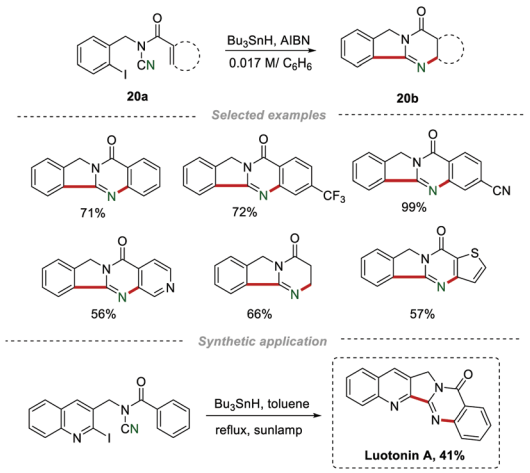


Scheme 19 The synthesis of fused quinoxaline derivatives.

fused quinoxalines could be obtained by using nitrile **19d** with a benzene ring as a linker. The proposed mechanism showed that the photocatalyst *fac*-Ir(ppy)$_3$ was irradiated to the excited state *fac*-Ir(ppy)$_3^*$ under the irradiation of visible light, which was oxidized by bromide **19b** to *fac*-Ir(ppy)$_3^+$, along with the formation of radical **19g**. Subsequently, the addition of **19g** to isocyanide **19a** generated the imidoyl radical **19h**, which subsequently underwent intramolecular cyclization to access the iminyl radical **19i**. Radical **19i** underwent homolytic aromatic substitution to produce the radical **19j**, which was oxidized by *fac*-Ir(ppy)$_3^+$ to yield the radical cation **19k**, along with the regeneration of *fac*-Ir(ppy)$_3$ for the next cycle. Finally, the aromatization of radical cation **19k** led to the formation of the desired products **19c** by deprotonation.

3.2 Synthesis of quinazolinones

In 2007, Malacria *et al.* reported a radical cascade cyclization of *N*-acyl-*N*-(2-iodobenzyl)cyanamides **20a** for the construction

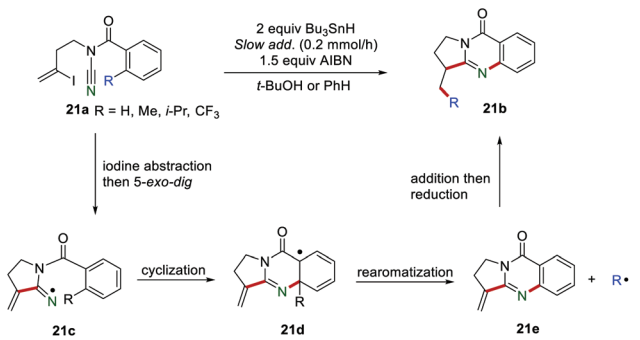


Scheme 20 Radical migration for the construction of quinazolinones.

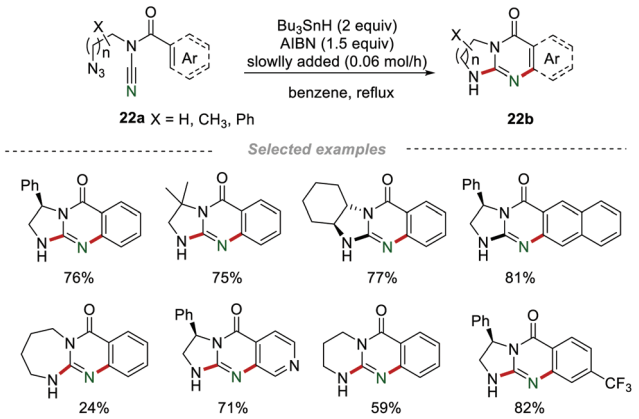
of quinazolinones **20b** (Scheme 20).[40] Under the optimized conditions, a large number of quinazolinones **20b** with good regioselectivity were obtained in satisfactory yields. More importantly, the total synthesis of the natural product, luotonin A, with DNA topoisomerase I poison could be achieved by this method.

Afterward, the same group introduced a C=C bond in the substrate and the reaction can proceed smoothly to access quinazolinones **21b** (Scheme 21).[41] The mechanism investigations indicated that the iminyl radical **21c** was formed by iodine abstraction and regioselective 5-*exo-dig* cyclization, which immediately underwent an intramolecular cyclization onto the aromatic ring, rendering the radical intermediate **21d**. Subsequently, the intermediate **21e** was formed *via* rearomatization, releasing the radical R$^{\bullet}$. Finally, the addition of R$^{\bullet}$ to the C=C bond of **21e** gave the product **21b**.

In 2010, Malacria *et al.* developed an efficient strategy for the preparation of bi- and tricyclic guanidines **22b** *via* a radical domino process involving cyanamides as relay partners (Scheme 22).[42] Various functional groups, including the electron-withdrawing groups and electron-donating groups, were all well tolerated, and the corresponding guanidines **22b** were obtained in moderate to good yields. Moreover, when the final



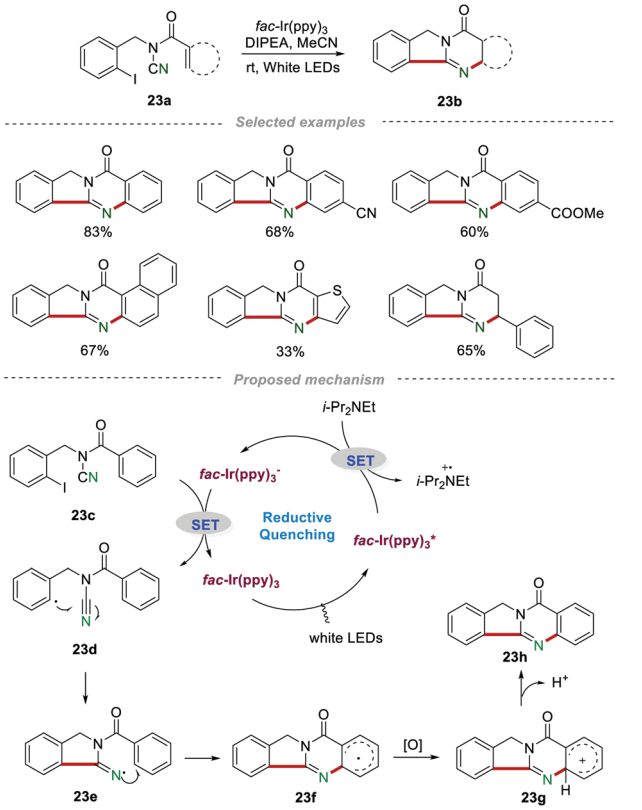
Scheme 21 Radical migration for the construction of quinazolinones.



Scheme 22 The construction of guanidines.

acceptor aryl group was replaced by an olefin, the reaction also reacted smoothly under the standard reaction conditions.

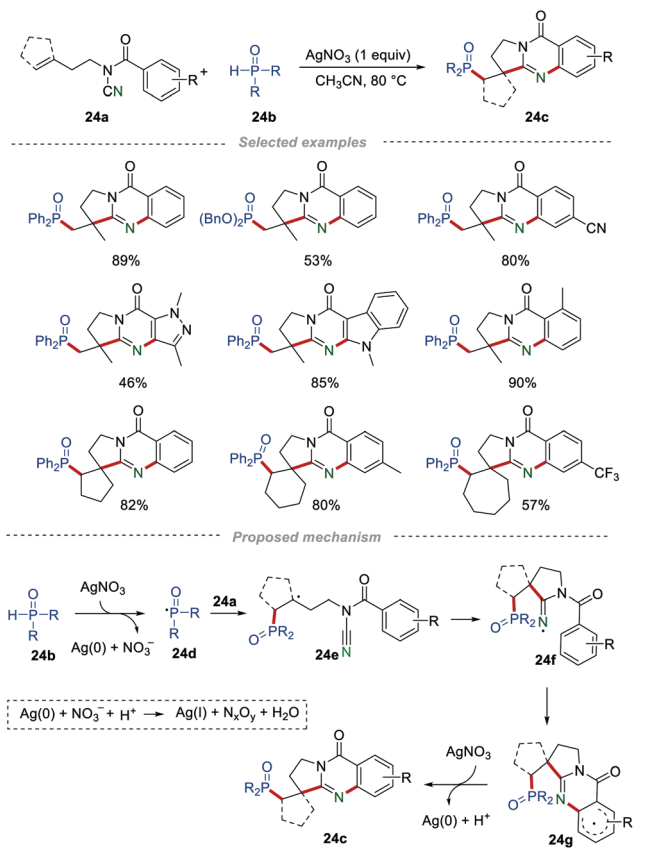
The above-mentioned methods are normally performed in the presence of toxic reagents (*e.g.*, Bu_3SnH) or proceed at high reaction temperature, which might limit the application of these methods. In order to overcome these drawbacks, Yu and co-workers developed a visible-light-promoted intramolecular radical cyclization procedure for the preparation of quinazolinones **23b** (Scheme 23).[43] This protocol would avoid the use of



Scheme 23 The construction of quinazolinones *via* visible-light-promoted radical cyclization.

toxic Bu_3SnH and high reaction temperature, rendering the reaction more practical from the viewpoint of the environment and safety. In order to gain further insight into the mechanism, a series of emission quenching experiments were carried out. The result showed that the excited state *fac*-Ir(ppy)$_3^*$ was indeed quenched by DIPEA (i-Pr_2NEt), indicating that a reductive quenching was involved between DIPEA and *fac*-Ir(ppy)$_3^*$ *via* single electron transfer. The proposed mechanism showed that *fac*-Ir(ppy)$_3^*$ was formed under the irradiation of visible light, which further reacted with i-Pr_2NEt to give *fac*-Ir(ppy)$_3^-$, along with the *N*-centered radical cation species. Subsequently, a single-electron transfer between *fac*-Ir(ppy)$_3^-$ and reactant **23c** led to the generation of the radical intermediate **23d**. After a similar intramolecular radical cyclization, single-electron oxidation, and deprotonation process, the final product **23h** was produced.

In 2016, Cui *et al.* developed a silver(I)-mediated radical cascade phosphorylation/cyclization of *N*-cyanamide alkenes **24a** for the preparation of phosphorylated quinazolinone derivatives **24c** (Scheme 24).[44] Different kinds of *N*-cyanamide alkenes were investigated in this transformation, producing the desired phosphorylated quinazolinone derivatives **24c** in good yields. The radical trapping experiments were conducted to gain a deeper understanding of the mechanism. For instance, by adding radical scavengers (TEMPO or BHT), the reaction was severely inhibited. Based on the results of the control experiments, a reasonable mechanism involving a radical pathway was suggested. In the beginning, the *H*-phosphonates **24b** was oxidized by $AgNO_3$ to give the phosphorus-centered radical **24d**. Then, the addition of the phosphoryl radical **24d** to the C=C bond of **24a** formed the radical intermediate **24e**, which subsequently underwent an intramolecular cyclization to afford the iminyl radical intermediate **24f**. Afterward, an intramolecular cyclization of **24f** led to the formation of the aryl radical **24g**. **24g** was then oxidized by Ag(I) to produce the phosphorylated quinazolinones **24c**, along with the release of Ag(0). Partial Ag(0) could be reoxidized to Ag(I); therefore, 1 equiv. of $AgNO_3$ was enough for this transformation.



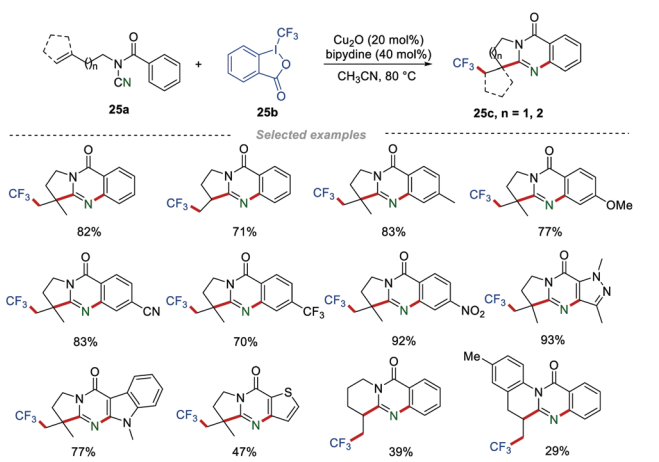
Scheme 24 The preparation of phosphorus quinazolinones.

Encouraged by the importance of the trifluoromethyl group in medicinal chemistry, Cui and co-workers successfully achieved the synthesis of trifluoromethylated quinazolinones **25c** in 2016 (Scheme 25).[45] In this transformation, the CF_3 radical was generated from the Togni's reagent **25b** with the assistance of the Cu(I) catalyst. A broad range of substrates bearing electron-withdrawing groups and electron-donating groups were performed smoothly, delivering the desired products in moderate to good yields. In addition, heterocyclic moieties (such as indole, pyrazole, and thiophene) were all suitable for this radical cyclization reaction.

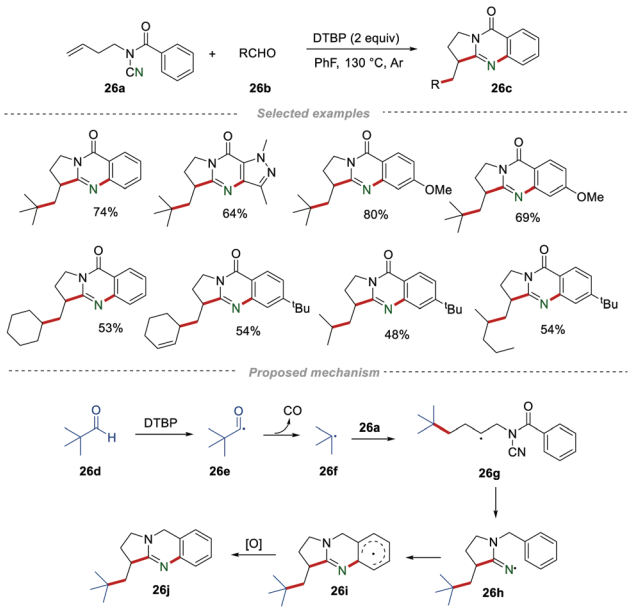
Afterward, Wang *et al.* reported a metal-free cascade annulation of *N*-cyanamide alkenes **26a** by using the readily available aldehydes **26b** as alkyl radical precursors for the construction of the alkyl-substituted quinazolinones **26c** (Scheme 26).[46] In this reaction, the alkyl radical was generated from aliphatic aldehydes *via* a decarbonylation process in the presence of DTBP.[47] After going through a similar radical addition and cyclization process, a wide range of alkyl-substituted quinazolinones **26c** could be obtained in satisfactory yields. In this transformation, a large variety of alkyl aldehydes, including secondary and tertiary alkyl aldehydes, could be successfully applied.

3.3 Synthesis of phenanthridines

As early in 1998, Zanardi *et al.* reported the synthesis of cyclopentaphenanthridines **27c** by reacting the aryldiazonium salt



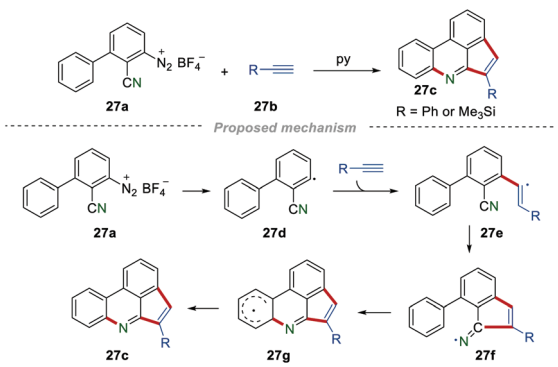
Scheme 25 The preparation of trifluoromethylated quinazolinones.



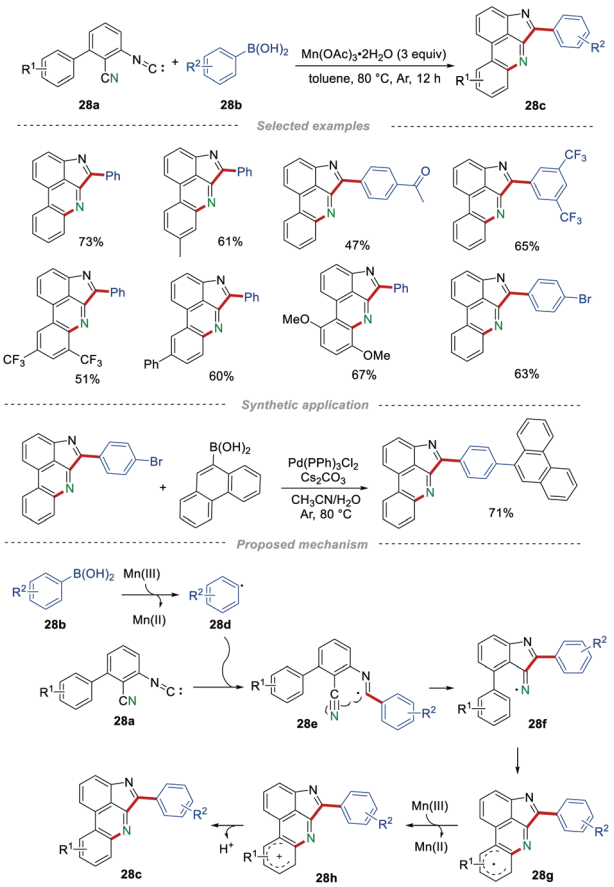
Scheme 26 The preparation of alkyl-substituted quinazolinones.

27a with phenylacetylene or trimethylsilylacetylene 27b (Scheme 27).[48] Initially, the aryl radical 27d added to the C–C triple bond to give the vinyl radical 27e, which further underwent intramolecular cyclization onto the cyano group to afford the iminyl radical 27f. Subsequently, 27f underwent intramolecular cyclization and H-abstraction to access the desired product 27c.

In 2019, Ji and Wang's group demonstrated an efficient and regioselective construction of pyrroloporidine compounds 28c by the reaction of multifunctionalized 3-isocyano-[1,1′-biphenyl]-2-carbonitriles 28a and arylboronic acids 28b in the presence of $Mn(OAc)_3$ (Scheme 28).[49] The efficiency of this simple protocol was obviously affected by the steric hindrance effect of the substituents on arylboronic acids, and *o*-tolylboronic acid failed to furnish the corresponding product. Arylboronic acids bearing different substituents, including electron-withdrawing and electron-donating groups on other positions of the phenyl ring, reacted smoothly to access the desired products 28c in moderate to good yields. In addition, halo substituents were compatible in this transformation, providing the possibility for further cross-coupling reactions to afford structurally diverse pyrroloporidine compounds. On the basis of the radical trapping experiments, a possible mechanism involving a radical pathway was presented. The aryl radical 28d, generated from arylboronic acids under the assistance of Mn(III), attacked the isocyano group in 28a to produce the imdoyl radical 28e. Then, radical 28e underwent an intramolecular cyclization with the cyano group to afford the iminyl radical 28f, which underwent another intramolecular cyclization with the phenyl ring to give radical 28g. After single-electron oxidation by Mn(III) and deprotonation, the desired product 28c was generated.

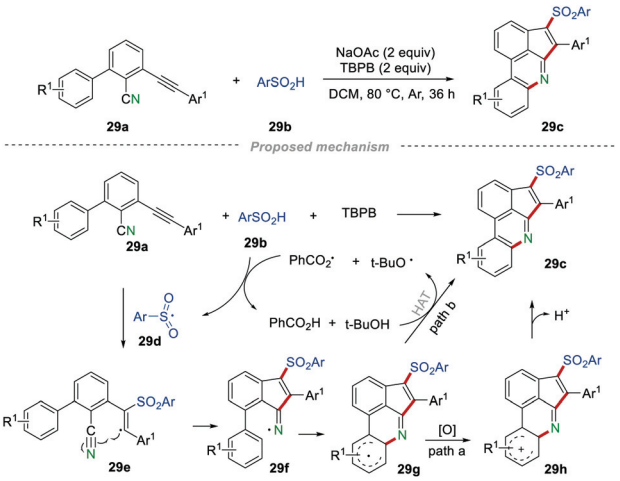


Scheme 27 The construction of cyclopentaphenanthridines.

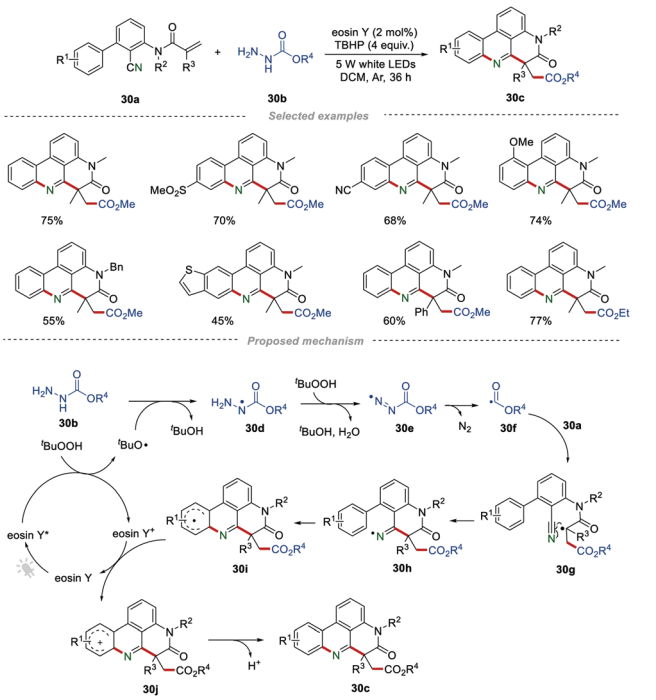


Scheme 28 The construction of pyrroloporidine compounds.

Almost at the same time, Zhou's group replaced the isocyano group with an unsaturated C–C triple bond to develop a novel and mild protocol for the synthesis of 3-sulfonated cyclopenta[*gh*]phenanthridines 29c (Scheme 29).[50] The reaction worked well for both electron-donating and electron-withdrawing group-substituted substrates, providing the desired products 29c in moderate to good yields. Unfortunately, no desired products could be obtained when the Ar^1 was replaced with the halogen or alkyl group (n-C_4H_9), which might be caused by the unstable alkenyl radical intermediate. A detailed



Scheme 29 The construction of 3-sulfonated cyclopenta[*gh*] phenanthridines.



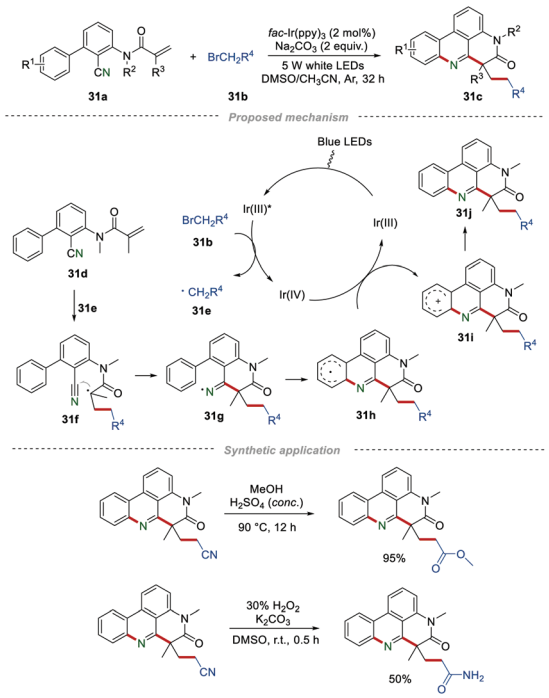
Scheme 30 The construction of ester-functionalized phenanthridines.

assessment of the control experiments suggested that a radical process might be involved. Ultimately, the arylsulfonyl radical **29d** was formed from the reaction between the sulfinic acids **29b** and $PhCO_2^{\bullet}$ or *t*-BuO$^{\bullet}$, which was generated from the thermal decomposition of TBPB. Then, the addition of radical **29d** to the C–C triple bond of **29a** resulted in the alkenyl radical **29e**, which then underwent intramolecular cyclization with the cyano group to produce the radical intermediate **29g**. The radical intermediate **29g** was further oxidized to radical cation **29h**, which subsequently regenerated the aromatic ring by deprotonation (path a). On the other hand, radical intermediate **29g** could also convert into the desired product **29g** *via* hydrogen atom transfer (path b).

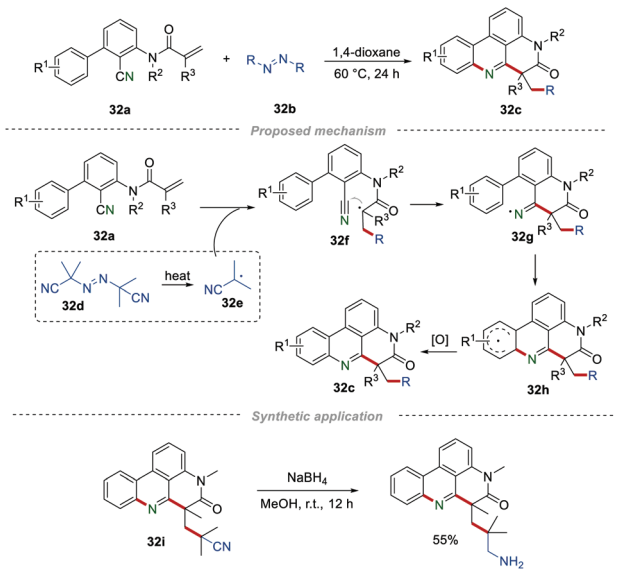
In recent years, the radical addition/cyclization of 2-cyano-3-arylaniline-derived acrylamides has been developed for the efficient preparation of phenanthridines. In 2017, Sun *et al.* described a novel visible-light-induced radical cascade reaction for the construction of ester-functionalized phenanthridines (Scheme 30).[51] This protocol employed alkyl carbazates **30b** as the alkoxycarbonyl radical precursor, providing a convenient access to 1,4-dicarbonyl compounds **30c** in moderate to excellent yields. The structure of the products was interesting not only because of the generation of one C–N bond and two C–C bonds, but also the challenging all-carbon quaternary centers generated through a single step. It was proposed that the key step for the reaction was the generation of the *tert*-butoxyl radical *via* single electron transfer between eosin Y* and TBHP, which would thus lead to the formation of the nitrogen radical intermediate **30d**. Then, the sequential dehydrogenation of the intermediate **30d** by TBHP generated the alkoxycarbonyl diazo radical **30e**, which then released a molecule of nitrogen to form the important alkoxycarbonyl radical **30f**. The addition of the radical **30f** to the C=C bond of **30a** afforded the radical intermediate **30g**, which further underwent an intramolecular cyclization with a cyano group to produce the radical intermediate **30i**. Subsequently, **30i** was oxidized by eosin Y$^+$ to obtain the intermediate **30j**, along with the regeneration of eosin Y. Finally, **30j** underwent a rearomatization process, producing the target products **30c** *via* deprotonation.

As their follow-up work, various alkylated phenanthridines **31c** were synthesized by using 2-bromoacetonitrile, ethyl 2-bromoacetate, or 2-bromo-*N*,*N*-dimethylacetamide **31b** as the active methylene radical precursors (Scheme 31).[52] This eco-friendly procedure was conducted under visible-light, affording the desired products **31c** in moderate to good yields, showing a wide substrate scope. The control experiments demonstrated that the reaction process involved a radical pathway. The reactant **31b** could react with [*fac*-Ir^{III}(ppy)$_3$]* to produce active primary radicals **31e**. After a similar process including radical addition and cyclization, single-electron oxidation, and deprotonation, the final product **31j** was generated. Furthermore, the cyano group in the products could be further transformed into other functional groups, such as an ester group or amide group.

Azo compounds, such as azobisisobutyronitrile (AIBN), can generate free radicals under mild conditions. The exploration of azo compounds as radical sources to prepare different functionalized molecules is always arguably of high interest. In 2018, Sun *et al.* used azo compounds **32b** as radical precursors to complete a radical cascade reaction for the construction of phenanthridine derivatives **32c** (Scheme 32).[53] Notably, most of the azo compounds attached with alkyl groups were suitable for this transformation, and a broad range of the desired products were obtained under the catalyst- and oxidant-free conditions. Under the heating reaction conditions, the thermal decomposition of AIBN (**32d**) led to the radical **32e**, along with



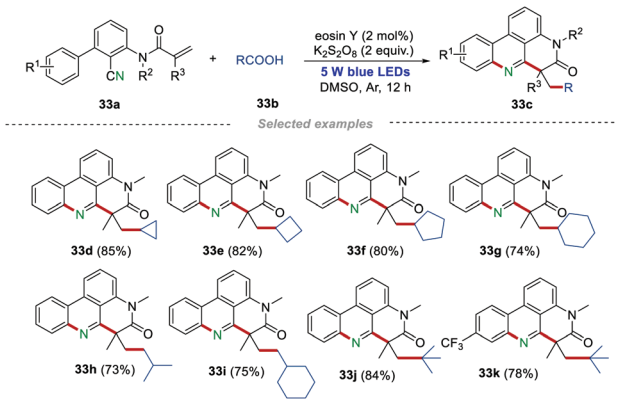
Scheme 31 The construction of alkylated phenanthridines.



Scheme 32 Azo compounds as radical sources to prepare alkylated phenanthridines.

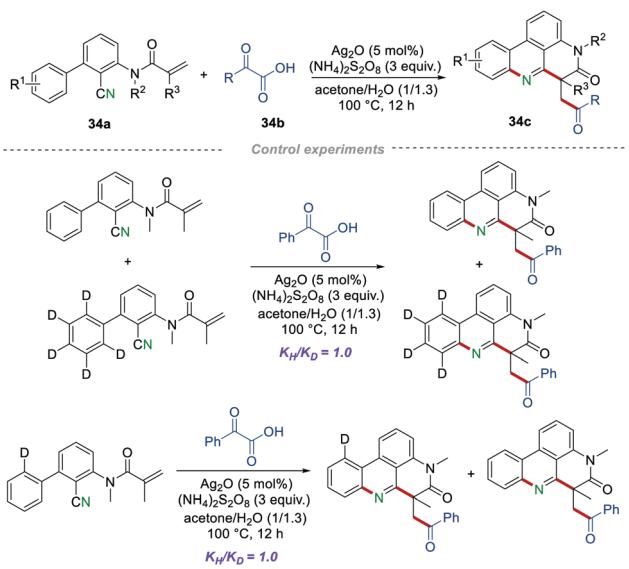
the release of N_2. Due to their high thermal stability, diethyl azodicarboxylate and azobenzene cannot be applied to this conversion. Additionally, the cyano group in product **32i** could be easily reduced by $NaBH_4$ to generate the aminomethyl group in moderated yield.

Using inexpensive carboxylic acids as the radical sources, Sun and co-workers reported an efficient protocol to construct alkylated phenanthridines (Scheme 33).[54] The environmentally-friendly $(NH_4)_2S_2O_8$/eosin Y system was employed for the decarboxylation of aliphatic carboxylic acids under photoredox catalysis. It is worth noting that the primary carboxylic acids (isovaleric acid, 2-cyclohexylacetic acid) and cyclic secondary carboxylic acids, as well as the tertiary carboxylic acid, were all suitable in this transformation, leading to the formation of products **33c** in good to excellent yields under mild reaction conditions. Notably, the trifluoromethyl group, which was widely found in drugs, was also compatible, affording the product **33k** with good isolated yield.



Scheme 33 Carboxylic acids as radical sources to prepare alkylated phenanthridines.

Moreover, α-keto acids **34b** as acyl radical precursors[55] were applied as substrates to react with the 2-cyano-3-arylaniline derived acrylamides **34a**, proving a simple and efficient synthetic strategy to access the carbonyl-containing phenanthridines **34c** (Scheme 34).[56] A large variety of carbonyl-containing phenanthridines **34c** were obtained in moderate to good yields



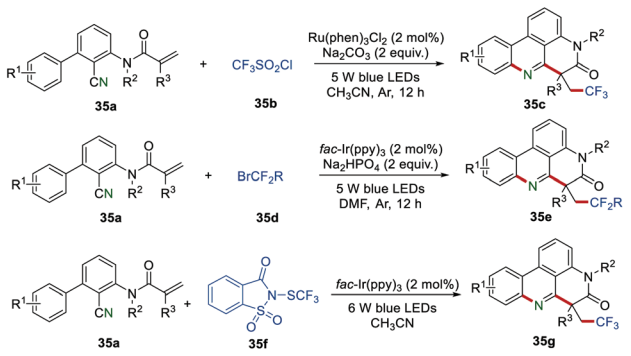
Scheme 34 α-Keto acids as radical sources to prepare the carbonyl-containing phenanthridines.

under the optimized conditions without obvious electronic and steric hindrance effects. However, when the substitution of R^2 was an acetyl, tosyl, or H, the reaction could not react smoothly to give the desired products. The radical trapping reaction showed that the reaction was almost completely suppressed by adding the radical inhibitor TEMPO or BHT to the standard reaction system, implying that a radical pathway should be involved in this transformation. Moreover, the results of the kinetic isotope effects (KIE) suggested that the cleavage of the C(sp^2)–H bond that occurred after the formation of the C(sp^2)–N bond might not be the rate-determining step.

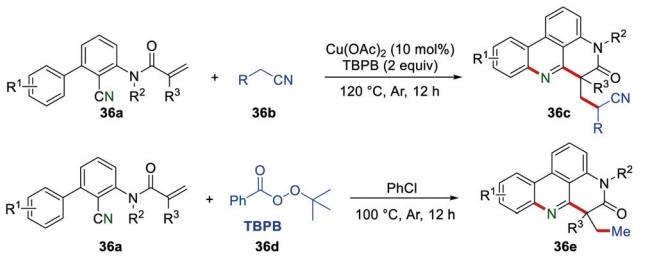
The importance of fluorine-containing compounds has prompted chemists to continuously develop new synthetic methods for the synthesis of fluorine-contained phenanthridine derivatives. In 2018, Sun *et al.* reported another visible-light-induced radical reaction of 2-cyano-3-arylaniline derived acrylamides **35a**.[57] By changing different fluorine-containing radical sources, trifluoroalkyl phenanthridine **35c** or difluoroalkyl phenanthridine derivatives **35e** could be obtained in moderate to good yields. This method provides a green and efficient transformation for the preparation of trifluoroalkyl or difluoroalkyl phenanthridine derivatives. Recently, the Fu group successfully employed *N*-trifluoromethylthiosaccharin **35f** as an effective precursor of SCF_3 radical to access the SCF_3-containing phenanthridine derivatives **35g**.[58] A large variety of trifluoromethylthiolated phenanthridine derivatives with electron-donating and electron-withdrawing groups could be obtained in moderate to good yields (Scheme 35).

In 2018, Li *et al.* reported a copper-catalyzed radical cascade reaction of 2-cyano-3-arylaniline-derived acrylamides **36a** and acetonitriles **36b** (Scheme 36). This work provided a powerful and easy-handle approach to access cyano-substituted phenanthridines **36c** using the $Cu(OAc)_2$/TBPB system. In addition, various methyl-substituted phenanthridines **36e** were obtained when acetonitriles were replaced by PhCl under metal-free conditions.[59]

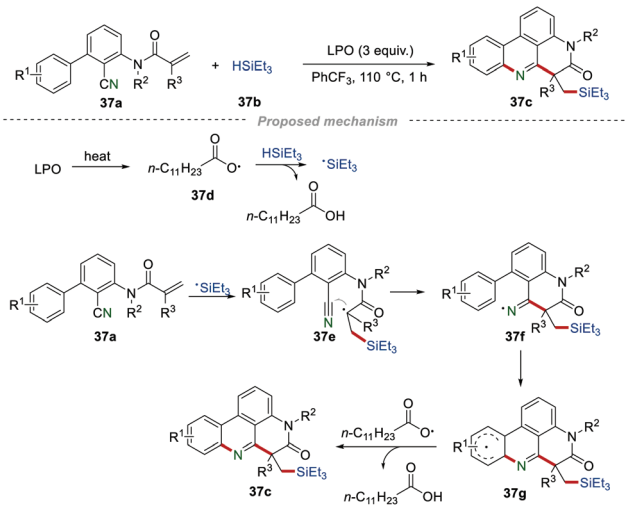
Moreover, the Sun group successfully developed a silyl radical-initiated cyclization reaction for the synthesis of silyl-substituted phenanthridines **37c** (Scheme 37).[60] This protocol



Scheme 35 The construction of trifluoroalkyl, difluoroalkyl, or trifluoromethylthiolated phenanthridine derivatives.



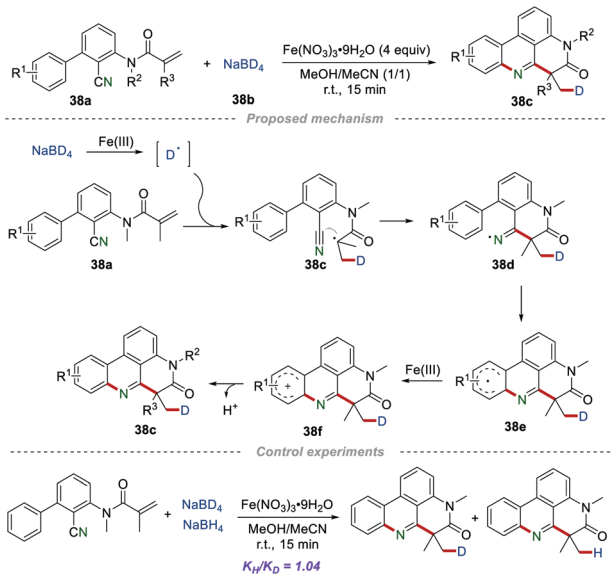
Scheme 36 The construction of cyano substituted phenanthridines and methyl-substituted phenanthridines.



Scheme 37 The construction of silyl substituted phenanthridines.

displayed the advantages of the wide substrate scope and good functional group tolerance, affording the silyl-substituted phenanthridines **37c** in good yields. According to the proposed mechanism, the silyl radical could be generated under the oxidant of lauroyl peroxide (LPO), which then underwent a similar radical addition and intramolecular cyclization to form the radical **37g** with the formation of the C–Si, C–C, and C–N bonds. Finally, radical **37g** was further converted into the corresponding product **37c** through hydrogen atom abstraction by the radical **37d**.

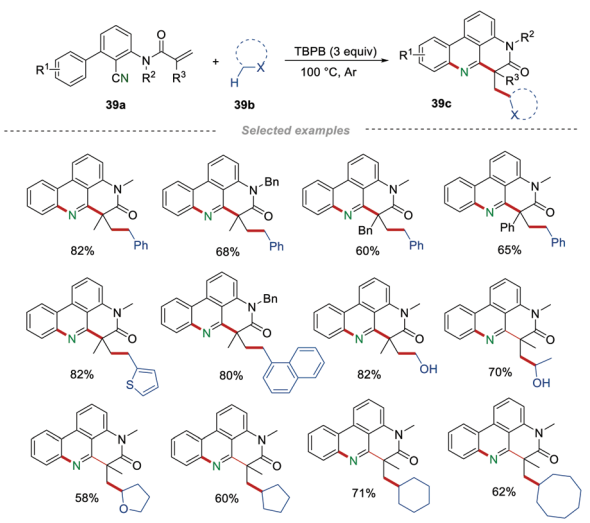
The introduction of deuterium into drug molecules has attracted huge attention due to the improved pharmacokinetic properties, such as enhanced absorption, distribution, as well as metabolic stability. In 2020, the Sun group described a powerful strategy for the construction of deuterium-labeled phenanthridines **38c** *via* the deuterium addition cascade cyano insertion/cyclization of the 2-cyano-3-arylaniline-derived acrylamides **38a** with $NaBD_4$ (Scheme 38).[61] In the presence of inexpensive $Fe(NO_3)_3{\cdot}9H_2O$, numerous desired products could be obtained in satisfactory yield. Moreover, the gram-scale reaction with no obvious decrease in efficiency showed the practicality of this method. The control experiments demonstrated that a radical pathway might be involved in the reaction



Scheme 38 The construction of deuterium-labelled phenanthridines.

process, and the rate-determining step was not the generation or introduction of a deuterium atom in this cyano insertion/cyclization reaction. The proposed mechanism showed that the key intermediate deuterium radical was generated *via* the oxidation of $NaBD_4$ in the presence of $Fe(NO_3)_3{\cdot}9H_2O$. Then, the addition of the deuterium radical to the C=C bond of **38a** formed radical **38c**, which further attacked the cyano group to yield the iminyl radical **38d**. After cyclization and single-electron oxidation by Fe(III), the radical cation **38f** was formed, which subsequently lost a proton to afford the product **38c**.

Very recently, Li's group achieved the functionalization of the alkyl C(sp^3)–H bond *via* oxidative cascade cyclization of 2-cyano 3-arylaniline-derived acrylamides **39a** (Scheme 39).[62] In this transformation, good functional group tolerance was observed and some sensitive functional groups, such as the hydroxyl group, could survive in this transformation. Moreover, toluenes, ethers, aliphatic alcohols, and simple alkanes could be applied as alkyl radical precursors for the synthesis of the alkyl-substituted phenanthridines **39c** *via* the formation of a C(sp^3)–C(sp^3)/C(sp^2)–C(sp^3)/C(sp^2)–N bond in one step, demonstrating the wide range of the substrate applicability and step-/atom-economy.

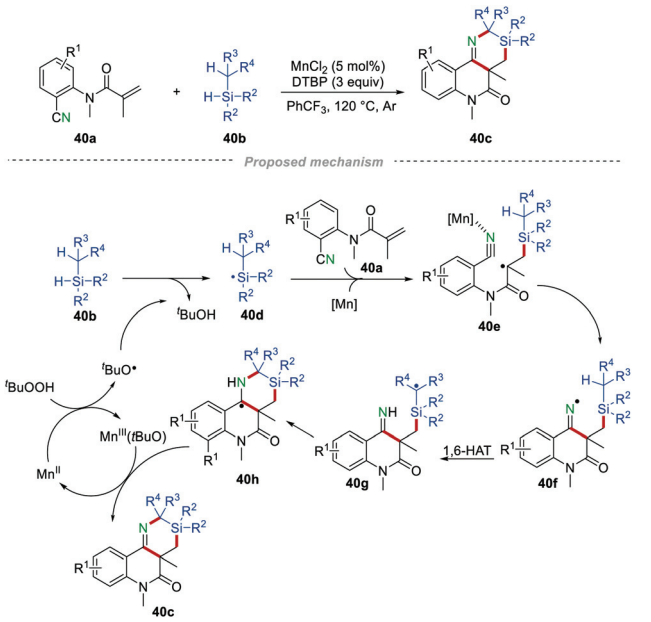


Scheme 39 The construction of alkyl-substituted phenanthridines.

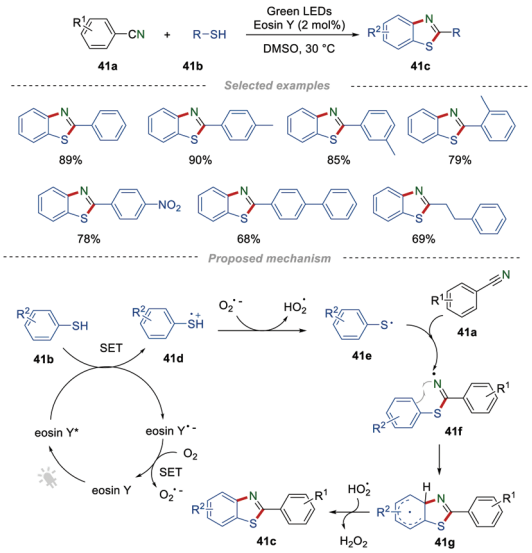
3.4 Other heterocycles

Silicon/nitrogen heterocycles have gained particular attention due to their highly valued applications in pharmaceuticals and drug lead compounds.[63] Different from the work of Sun's group in Scheme 37, He *et al.* developed an efficient Mn-promoted intermolecular oxidative heteroannulation of *N*-(2-cyanoaryl) acrylamides **40a** with tertiary silanes **40b** in 2018 (Scheme 40). This work provided a novel approach to the preparation of silicon/nitrogen heterocycles **40c** using the $MnCl_2$/DTBP system.[64] The transformation was proposed to begin with the reaction of DTBP and Mn(II), generating a *tert*-butoxyl radical and the Mn(III)(*t*BuO) species. Then, the *tert*-butoxyl radical abstracted one hydrogen atom from tertiary silane **40b** to form the silicon-centered radical **40d**, which further underwent an addition reaction to the C=C bond of **40a** to afford radical intermediate **40e**. Afterwards, the intramolecular cyclization of **40e** with the cyano group afforded the iminyl radical **40f**. Then, the 1,6-hydrogen atom transfer (1,6-HAT) of radical **40f** produced the intermediate **40g**, which would attack the C=N bond to provide **40h**. Finally, the single electron oxidation of the radical **40h** by Mn(III)(*t*BuO), followed by subsequent deprotonation eventually provided silicon/nitrogen heterocycles **40c**.

In 2018, Natarajan *et al.* reported a visible light-mediated radical reaction between nitriles **41a** and thiophenols **41b**.[65]



Scheme 40 The construction of silicon/nitrogen heterocycles.



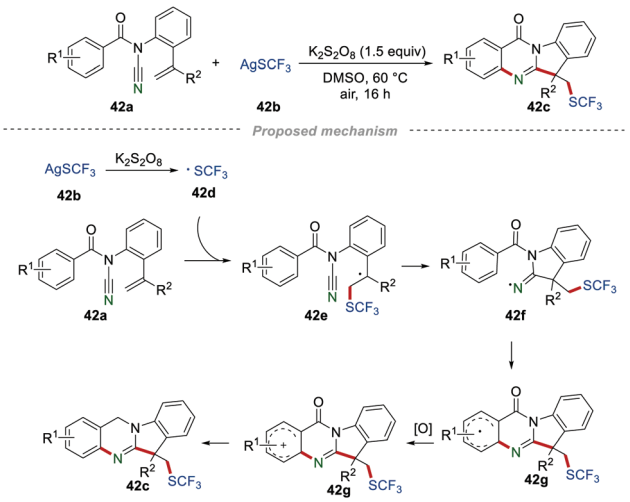
Scheme 41 The construction of benzothiazoles.

The reaction was conducted under mild reaction conditions, providing an efficient strategy for the construction of benzothiazoles **41c** in good to excellent yields. A possible mechanism, as proposed by the authors, was disclosed in Scheme 41. Upon the irradiation of visible light, eosin Y was excited to eosin Y*, which then was quenched by thiophenols **41b** *via* single-electron transfer to form the radical cation **41d** and eosin $Y^{\bullet-}$. The eosin $Y^{\bullet-}$ was further oxidized to the ground state by oxygen, releasing a superoxide radical anion ($O_2^{\bullet-}$). Then, a deprotonation reaction between the radical cation **41d** and $O_2^{\bullet-}$ generated the thiyl radical **41e**, which then attacked the cyano group in **41a** to afford the iminyl radical **41f**. Finally, the intramolecular cyclization of the iminyl radical **41f** afforded radical **41g**, which further lost a hydrogen atom to produce the desired products **41c**.

Tryptanthrin derivatives, which consist of quinazolines and indoles, were widely spread in natural products, but without simple synthetic approaches. Very recently, the synthesis of the SCF_3-substituted tryptanthrin derivatives **42c** was developed by the Wang group (Scheme 42).[66] A large variety of desired products **42c** were obtained in moderate to good yields, demonstrating the broad range of substrates. The proposed mechanism showed that $^{\bullet}SCF_3$ was generated from $AgSCF_3$ (**42b**) in the presence of $K_2S_2O_8$. After the similar progress of the radical addition/cyclization, single-electron oxidation and deprotonation, the formation of the C(sp^3)–SCF_3 bond, C(sp^2)–C bond, and C(sp^2)–N bond were achieved in one step to access the desired products **42c**.

4. Remote cyano migration

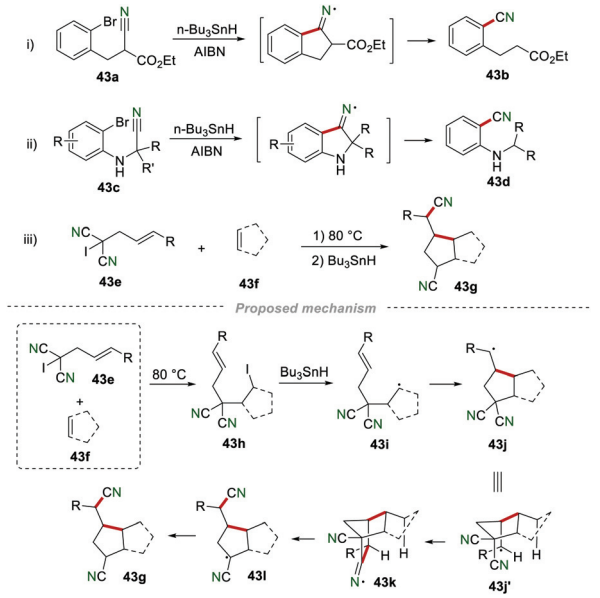
In 1987, Beckwith and co-workers reported the cyano migration to afford nitrile **43b** in 59% yield by using **43a** as the starting material in the presence of *n*-Bu_3SnH and AIBN



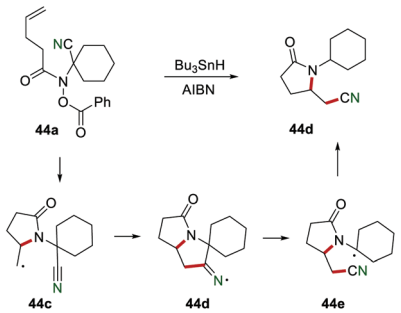
Scheme 42 Synthesis of SCF_3-substituted tryptanthrin derivatives.

(Scheme 43i).[67] Later in 1995, a similar reaction was achieved by Cossy and co-workers for the synthesis of 2-(alkylamino) benzonitriles **43d** from α-(bromoarylamino)nitriles **43c** (Scheme 43ii).[68] In 1992, Curran and co-workers reported a novel cyano migration reaction (Scheme 43iii).[69] The proposed mechanism showed that allyl iodomalononitrile **43g** synthesized from the reaction of **43e** and **43f** could yield radical **43i** in the presence of Bu_3SnH. Radical **43i** subsequently added to the C=C bond to produce radical **43j**, which further underwent intramolecular cyclization to give iminyl radical **43k**. Finally, **43k** underwent homolysis and H-abstraction to access the desired product **43g**.

Another interesting cyano migration reaction was disclosed for the preparation of nitrile **44d** in 83% yield (Scheme 44).[70]



Scheme 43 Remote cyano migration to access nitriles.



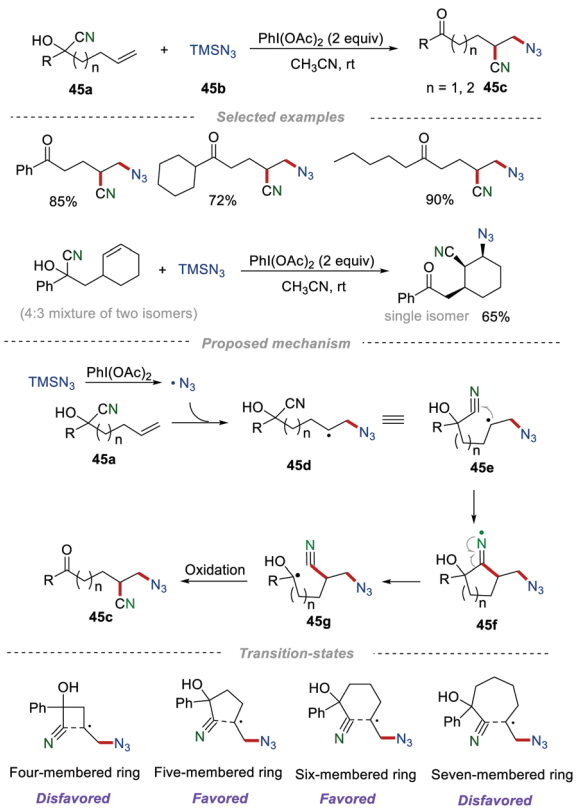
Scheme 44 Remote cyano migration to access nitrile starting from benzoate.

In the presence of Bu_3SnH and AIBN, radical **44c** was produced from benzoate **44a**. Radical **44c** was further added to the cyano group to afford the iminyl radical **44d**, which subsequently underwent homolysis and H-abstraction to yield product **44d**.

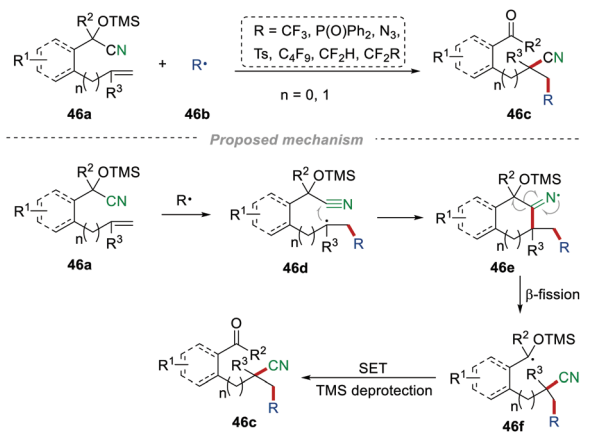
Recently, the distal migration reaction of the cyano groups has been continuously developed.[71] In 2016, Zhu *et al.* developed a metal-free remote cyano migration triggered by the azidyl radical addition to unactivated alkenes (Scheme 45).[72] In this reaction, various important azido-substituted alkyl nitriles **45c** were prepared in good yields when n = 1 or 2, due to the favored five- or six-membered cyclic transition states. In sharp contrast, no satisfactory results were obtained when n = 0 or 3, which were mainly caused by the disfavored four- or seven-membered cyclic transition states. Notably, this cyano migration reaction showed excellent stereoselectivities to access corresponding single diastereomeric products. Mechanism studies showed that the azido radical ($^{\bullet}N_3$) was initially generated from $TMSN_3$ in the presence of $PhI(OAc)_2$. Then, the selective addition of the azido radical to alkene **45a** generated the alkyl radical **45d**, which then underwent intramolecular cyclization with the cyano group to afford the cyclic iminium radical **45f**. Immediately, the unstable cyclic iminium radical **45f** underwent homolysis to produce a more stable hydroxyalkyl radical **45g** with the cyano migration. Finally, the oxidation of radical **45g** produced the azido-substituted alkyl nitriles **45c**.

Another example of long-distance cyano migration was recently reported by the Liu group. The diverse radical-mediated 1,2-cyanofunctionalization of unactivated alkenes **46a** was successfully developed (Scheme 46).[73] This simple strategy provided an efficient procedure for the synthesis of various important β-functionalized alkyl nitriles **46c** bearing carbonyl, cyano, and other various functional groups. This synthetic approach showed a broad substrate scope and excellent selectivity. The addition of a radical to the unsaturated C=C bond and the cyclization with the cyano group led to the formation of the alkyliminyl radical **46e**. Through selective β-fission, the TMS-protected radical **46f** was generated. Afterward, it underwent single-electron oxidation and TMS deprotection to access the final product **46c**. The control experiment indicated that the TMS-protection of the hydroxyl group was a necessary factor for high yields.

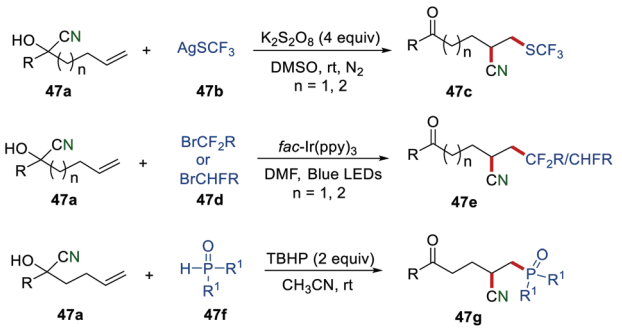
After these disclosures, Zhu and co-workers further applied this powerful and efficient strategy to achieve more structurally diverse alkyl nitriles by using a different radical source (Scheme 47). In the presence of $K_2S_2O_8$, various CF_3S-substituted alkyl nitriles **47c** were obtained in good yields by employing $AgSCF_3$ as a radical precursor.[74] Afterwards, a visible light-driven photoredox catalysis for the cyanofluoroalkylation of unactivated alkenes **47a** *via* remote cyano migration was devel-



Scheme 45 Remote cyano migration for azidocyanation of unactivated alkenes.



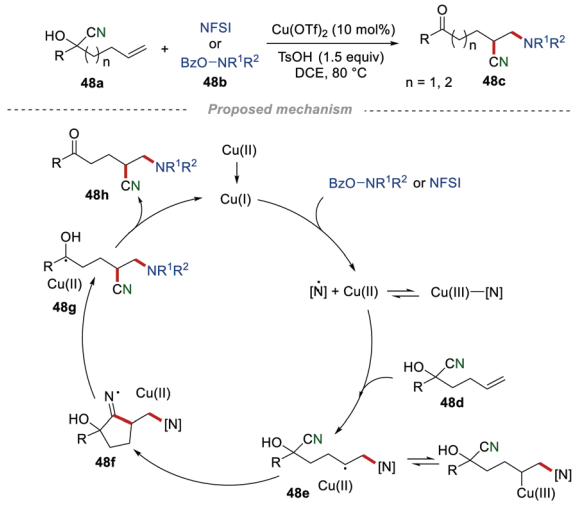
Scheme 46 Remote cyano migration of TMS-protected tertiary alcohols.



Scheme 47 Remote cyano migration for structurally diverse alkyl nitriles.

oped. Under optimized conditions, a large variety of di- and monofluorinated alkyl nitriles **47e** could be readily obtained in good yields under mild reaction conditions. Recently, a phosphinoyl radical-triggered cyanophosphinoylation of unactivated alkenes *via* the distal migration of cyano groups has been described.[75] During the optimization of the reaction conditions, it was found that the phosphinoyl radical could be generated from **47f** at room temperature under metal-free conditions.

Stimulated by the importance of nitrogen-containing molecules and their wide applications in organic synthesis, pharmaceuticals, and materials, the Wang group discovered a highly regioselective approach for the aminocyanation of unactivated alkenes *via* distal cyano migration by reacting *o*-benzoylhydroxylamines **48a** with *N*-fluorobenzenesulfonimides (NFSI) **48b** (Scheme 48).[76] In the presence of copper, the aminocyanation of alkenes *via* similar cyano migration protocol readily proceeded in moderate to good yields with a broad substrate scope. The proposed mechanism showed that *o*-benzoylhydroxylamine or NFSI **48b** was oxidized by Cu(I) to generate an amino–Cu(III) complex, which was selectively added to the C=C bond of alkene **48d**, delivering the intermediate **48e**. Subsequently, the



Scheme 48 Aminocyanation of alkenes.

intramolecular cyclization of intermediate **48e** afforded the cyclic iminium radical intermediate **48f**, followed by β-cleavage, leading to the formation of the hydroxyalkyl radical **48g**. Finally, radical **48g** was further oxidized to access the desired product **48h**, along with the regeneration of Cu(I).

5. Summary and outlook

By using cyano groups as radical acceptors, radical cascade cyclization reactions afford diverse opportunities for the convenient construction of various important heterocycles, carbocycles, and structurally diverse alkyl nitriles. In this review, the recent advances in radical cascade reactions using cyano groups as radical acceptors have been comprehensively discussed. It is shown that quinoline-2,4-diones, indenones, quinazolinones, phenanthridines, and benzothiazoles are readily accessible by using this approach. Moreover, various important functionalized alkyl nitriles can also be realized *via* this straightforward modular way. Although great progress has been achieved in this area in recent years, there are still many challenges remaining to be solved. For example, all of these reactions discussed in this review were carried out in conventional volatile organic solvents, which would make a great impact on the environment. Therefore, the development of novel catalytic systems in green solvents for these transformations is highly desired. Moreover, technologies including photocatalysis and electrocatalysis have emerged as novel tools for radical reactions. Although some photocatalytic systems have been reported in the above-mentioned reactions, the application of photo/electrochemical approaches to initiate various radicals for the radical cascade cyclization reaction should be attractive. We hope this review will stimulate the advancement of studies in this field.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

1 (*a*) H.-M. Huang, M. H. Garduño-Castro, C. Morrill and D. J. Procter, Catalytic cascade reactions by radical relay, *Chem. Soc. Rev.*, 2019, **48**, 4626; (*b*) M. P. Plesniak, H.-M. Huang and D. J. Procter, Radical cascade reactions triggered by single electron transfer, *Nat. Rev. Chem.*, 2017,

1, 0077; (*c*) A. Studer and D. P. Curran, The electron is a catalyst, *Nat. Chem.*, 2014, **6**, 765; (*d*) Y. Zhao, Y. Lv and W. Xia, Synthesis of Cyclic Compounds via Photoinduced Radical Cyclization Cascade of C=C bonds, *Chem. Rec.*, 2019, **19**, 424; (*e*) M.-H. Huang, W.-J. Hao and B. Jiang, Recent Advances in Radical-Enabled Bicyclization and Annulation/1,n-Bifunctionalization Reactions, *Chem. – Asian J.*, 2018, **13**, 2958; (*f*) M.-H. Huang, W.-J. Hao, G. Li, S.-J. Tu and B. Jiang, Recent advances in radical transformations of internal alkynes, *Chem. Commun.*, 2018, **54**, 10791; (*g*) Z. Cao, Q. Zhu, Y.-W. Lin and W.-M. He, The concept of dual roles design in clean organic preparation, *Chin. Chem. Lett.*, 2019, **30**, 2132; (*h*) P. Mao, J. Zhu, J. Yuan, L. Yang, Y. Xiao and C. Zhang, Recent Advances on the Catalytic Functionalization of Quinoxalin-2(1H)-ones via C-H Bond Activation, *Chin. J. Org. Chem.*, 2019, **39**, 1529; (*i*) X.-Y. Yuan, F.-L. Zeng, H.-L. Zhu, Y. Liu, Q.-Y. Lv, X.-L. Chen, L. Peng and B. Yu, A Metal-Free Visible-Light-Promoted Phosphorylation/Cyclization Reaction in Water towards 3-Phosphorylated Benzothiophenes, *Org. Chem. Front.*, 2020, **7**, 1884.

2 (*a*) H. Jiang and A. Studer, Chemistry With N-Centered Radicals Generated by Single-Electron Transfer-Oxidation Using Photoredox Catalysis, *CCS Chem.*, 2019, **1**, 38; (*b*) T.-Y. Shang, L.-H. Lu, Z. Cao, Y. Liu, W.-M. He and B. Yu, Recent Advances of 1,2,3,5-Tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzI.PN) in Photocatalytic Transformations, *Chem. Commun.*, 2019, **55**, 5408.

3 (*a*) X.-Y. Yu, Q.-Q. Zhao, J. Chen, W.-J. Xiao and J.-R. Chen, When Light Meets Nitrogen-Centered Radicals: From Reagents to Catalysts, *Acc. Chem. Res.*, 2020, **53**, 1066; (*b*) W. Yin and X. Wang, Recent advances in iminyl radical-mediated catalytic cyclizations and ring-opening reactions, *New J. Chem.*, 2019, **43**, 3254; (*c*) P. Xiong and H.-C. Xu, Chemistry with Electrochemically Generated N-Centered Radicals, *Acc. Chem. Res.*, 2019, **52**, 3339; (*d*) S. Z. Zard, Iminyl Radicals: A Fresh Look at a Forgotten Species (and Some of its Relatives), *Synlett*, 1996, 1148; (*e*) W. R. Bowman, C. F. Bridge and P. Brookes, Radical cyclisation onto nitriles, *Tetrahedron Lett.*, 2000, **41**, 8989.

4 J. W. Grissom, D. Klingberg, S. Meyenburg and B. L. Stallman, Enediyne- and Tributyltin Hydride-Mediated Aryl Radical Additions onto Various Radical Acceptors, *J. Org. Chem.*, 1994, **59**, 7876.

5 D. Griller, P. Schmid and K. U. Ingold, Cyclization of the 4-cyanobutyl radical, *Can. J. Chem.*, 1979, **57**, 831.

6 E. J. Corey and S. G. Pyne, Conversion of ketones having δ, ε-π-functions to cyclopentanols by zinc-trimethylchlorosilane, *Tetrahedron Lett.*, 1983, **24**, 2821.

7 G. A. Molander and C. N. Wolfe, Intramolecular Ketone–Nitrile Reductive Coupling Reactions Promoted by Samarium(II) Iodide, *J. Org. Chem.*, 1998, **63**, 9031.

8 D. L. J. Clive and P. L. Beaulieu, Synthesis of ketones by cyclization of cyano and acetylenic radicals: use of .delta.-hydroxy nitriles and .delta.- or .epsilon.-hydroxy acetylenes, *J. Org. Chem.*, 1984, **49**, 1313.

9 B. B. Snider and B. O. Buckman, Termination of manganese(III)-based oxidative free-radical cyclizations by addition to nitriles. Formation of cyclopentanones and cyclohexanones, *J. Org. Chem.*, 1992, **57**, 322.

10 R. Sulsky, J. Z. Gougoutas, J. DiMarco and S. A. Biller, Conformational Switching and the Synthesis of Spiro[2H-indol]-3(1H)-ones by Radical Cyclization, *J. Org. Chem.*, 1999, **64**, 5504.

11 R. Tsang and B. Fraser-Reid, Serial radical cyclization via a vinyl group immobilized by a pyranoside. A route to bis-annulated pyranosides, *J. Am. Chem. Soc.*, 1986, **108**, 2116.

12 H. Pak, I. I. Canalda and B. Fraser-Reid, Carbohydrates to carbocycles: a synthesis of (-)-.alpha.-pipitzol, *J. Org. Chem.*, 1990, **55**, 3009.

13 P. Hegarty and J. Mann, A new approach to the skeletons of both the aphidicolin and stemodin diterpenoids, *Tetrahedron*, 1995, **51**, 9079.

14 (*a*) P. M. Esch, H. Hiemstra and W. N. Speckamp, Synthesis of cyclic α-amino acids through ring closure of glycine derived free radicals, *Tetrahedron Lett.*, 1990, **31**, 759–762; (*b*) S. Knapp, F. S. Gibson and Y. H. Choe, Radical based annulations of iodo lactams, *Tetrahedron Lett.*, 1990, **31**, 5397; (*c*) B. Chenera, C. P. Chuang, D. J. Hart and L. Y. Hsu, Observations regarding .delta.- and .epsilon.-cyano radical cyclizations, *J. Org. Chem.*, 1985, **50**, 5409.

15 R. A. Alonso, C. S. Burgey, B. V. Rao, G. D. Vite, R. Vollerthun, M. A. Zottola and B. Fraser-Reid, Carbohydrates to carbocycles: synthesis of the densely functionalized carbocyclic core of tetrodotoxin by radical cyclization of an anhydro sugar precursor, *J. Am. Chem. Soc.*, 1993, **115**, 6666.

16 T. Shono and N. Kise, Electroreductive intramolecular coupling of γ- and δ-cyanoketones, *Tetrahedron Lett.*, 1990, **31**, 1303.

17 Y.-M. Li, S.-S. Wang, F. Yu, Y. Shen and K.-J. Chang, Copper-catalyzed cascade addition/cyclization: highly efficient access to phosphonylated quinoline-2,4(1H,3H)-diones, *Org. Biomol. Chem.*, 2015, **13**, 5376.

18 L. Xiong, H. Hu, C.-W. Wei and B. Yu, Radical reactions for the synthesis of 3-substituted chroman-4-ones, *Eur. J. Org. Chem.*, 2020, 1588.

19 S.-S. Wang, H. Fu, Y. Shen, M. Sun and Y.-M. Li, Oxidative Radical Addition/Cyclization Cascade for the Construction of Carbonyl-Containing Quinoline-2,4(1H,3H)-Diones, *J. Org. Chem.*, 2016, **81**, 2920.

20 (*a*) K.-J. Liu, S. Jiang, L.-H. Lu, L.-L. Tang, S.-S. Tang, H.-S. Tang, Z. Tang, W.-M. He and X. Xu, Bis(methoxypropyl) ether-promoted oxidation of aromatic alcohols into aromatic carboxylic acids and aromatic ketones with O2 under metal- and base-free conditions, *Green Chem.*, 2018, **20**, 3038; (*b*) P. Li, Y. Wang, X. Wang, Y. Wang, Y. Liu, K. Huang, J. Hu, L. Duan, C. Hu and J. Liu, Selective Oxidation of Benzylic C–H Bonds Catalyzed by Cu(II)/{PMo12}, *J. Org. Chem.*, 2020, **85**, 3101; (*c*) D. Zhai and S. Ma, Copper catalysis for highly selective aerobic oxidation of alcohols to aldehydes/ketones, *Org. Chem. Front.*, 2019, **6**, 3101.

21 S.-S. Wang, H. Fu, G. Wang, M. Sun and Y.-M. Li, , Iron-catalyzed addition/cyclization cascade of activated alkenes with alcohols: access to carbonyl substituted quinoline-2,4-diones, *RSC Adv.*, 2016, **6**, 52391.

22 (*a*) K. Sun, X.-L. Chen, X. Li, L.-B. Qu, W.-Z. Bi, X. Chen, H.-L. Ma, S.-T. Zhang, B.-W. Han, Y.-F. Zhao and C.-J. Li, H-phosphonate-mediated sulfonylation of heteroaromatic N-oxides: a mild and metal-free one-pot synthesis of 2-sulfonyl quinolines/pyridines, *Chem. Commun.*, 2015, **51**, 12111; (*b*) J.-N. Desrosiers and A. B. Charette, Catalytic Enantioselective Reduction of β,β-Disubstituted Vinyl Phenyl Sulfones by Using Bisphosphine Monoxide Ligands, *Angew. Chem., Int. Ed.*, 2007, **46**, 5955; (*c*) L. Tang, K. Du, B. Yu and L. He, Oxidation of aromatic sulfides with molecular oxygen: Controllable synthesis of sulfoxides or sulfones, *Chin. Chem. Lett.*, 2020, **31**(12), 2991; (*d*) S. Peng, Y.-X. Song, J.-Y. He, S.-S. Tang, J.-X. Tan, Z. Cao, Y.-W. Lin and W.-M. He, TsCl-promoted sulfonylation of quinoline N-oxides with sodium sulfinates in water, *Chin. Chem. Lett.*, 2019, **30**, 2287.

23 (*a*) F.-L. Yang and S.-K. Tian, Sulfonyl hydrazides as sulfonyl sources in organic synthesis, *Tetrahedron Lett.*, 2017, **58**, 487; (*b*) Y.-Q. Jiang, J. Li, Z.-W. Feng, G.-Q. Xu, X. Shi, Q.-J. Ding, W. Li, C.-H. Ma and B. Yu, Ethylene Glycol: A Green Solvent for Visible Light-Promoted Aerobic Transition Metal-Free Cascade Sulfonation/Cyclization Reaction, *Adv. Synth. Catal.*, 2020, **362**, 2609; (*c*) Z. Wang and W.-M. He, Radical Cyclization Strategy towards Indolo [1,2-a]quinolines, *Chin. J. Org. Chem.*, 2019, **39**, 3594.

24 S. Wang, X. Huang, Q. Wang, Z. Ge, X. Wang and R. Li, An efficient synthesis of sulfonated quinoline diones by copper catalyzed sulfonylation of activated alkenes with sulfonylhydrazides, *RSC Adv.*, 2016, **6**, 11754.

25 H. Fu, S.-S. Wang and Y.-M. Li, Copper-Mediated Oxidative Radical Addition/Cyclization Cascade: Synthesis of Trifluoromethylated and Sulfonated Quinoline-2,4(1H,3H)-diones, *Adv. Synth. Catal.*, 2016, **358**, 3616.

26 P. C. Montevecchi, M. L. Navacchia and P. Spagnolo, Attempts at vinyl radical carbonylation through cyclization onto carbonyl and cyano groups, *Tetrahedron*, 1998, **54**, 8207.

27 X.-T. Zhu, Q. Zhao, F. Liu, A.-F. Wang, P.-J. Cai, W.-J. Hao, S.-J. Tu and B. Jiang, Silver-mediated radical 5-exo-dig cyclization of 2-alkynylbenzonitriles: synthesis of phosphinylated 1-indenones, *Chem. Commun.*, 2017, **53**, 6828.

28 Z. Xiao-Tong, Z. Tian-Shu, Z. Qi, C. Pei-Jun, H. Wen-Juan, T. Shu-Jiang and J. Bo, Sulfinate-Salt-Mediated Radical Relay Cyclization of Cyclic Ethers with 2-Alkynylbenzonitriles toward 3-Alkylated 1-Indenones, *Chem. – Asian J.*, 2018, **13**, 1157.

29 Y. Zhang, K. Sun, Q. Lv, X. Chen, L. Qu and B. Yu, Recent applications of radical cascade reaction in the synthesis of functionalized 1-indenones, *Chin. Chem. Lett.*, 2019, **30**, 1361.

30 (*a*) X.-T. Zhu, Q.-L. Lu, X. Wang, T.-S. Zhang, W.-J. Hao, S.-J. Tu and B. Jiang, Substrate-Controlled Generation of 3-Sulfonylated 1-Indenones and 3-Arylated (Z)-Indenes via Cu-Catalyzed Radical Cyclization Cascades of o-Alkynylbenzonitriles, *J. Org. Chem.*, 2018, **83**, 9890; (*b*) B. Zhou, W. Chen, Y. Yang, Y. Yang, G. Deng and Y. Liang, A radical cyclization cascade of 2-alkynylbenzonitriles with sodium arylsulfinates, *Org. Biomol. Chem.*, 2018, **16**, 7959; (*c*) K. Sun, X.-L. Chen, S.-J. Li, D.-H. Wei, X.-C. Liu, Y.-L. Zhang, Y. Liu, L.-L. Fan, L.-B. Qu, B. Yu, K. Li, Y.-Q. Sun and Y.-F. Zhao, Copper-Catalyzed Radical Cascade Cyclization To Access 3-Sulfonated Indenones with the AIE Phenomenon, *J. Org. Chem.*, 2018, **83**, 14419.

31 B. Zhang and A. Studer, Recent advances in the synthesis of nitrogen heterocycles via radical cascade reactions using isonitriles as radical acceptors, *Chem. Soc. Rev.*, 2015, **44**, 3505.

32 D. P. Curran and H. Liu, 4+1 Radical annulations with isonitriles: a simple route to cyclopenta-fused quinolines, *J. Am. Chem. Soc.*, 1991, **113**, 2127.

33 D. P. Curran, H. Liu, H. Josien and S.-B. Ko, Tandem radical reactions of isonitriles with 2-pyridonyl and other aryl radicals: Scope and limitations, and a first generation synthesis of (±)-camptothecin, *Tetrahedron*, 1996, **52**, 11385.

34 D. Nanni, P. Pareschi, C. Rizzoli, P. Sgarabotto and A. Tundo, Radical annulations and cyclisations with isonitriles: the fate of the intermediate imidoyl and cyclohexadienyl radicals, *Tetrahedron*, 1995, **51**, 9045.

35 R. Leardini, D. Nanni, P. Pareschi, A. Tundo and G. Zanardi, α-(Arylthio)imidoyl Radicals: [3 + 2] Radical Annulation of Aryl Isothiocyanates with 2-Cyano-Substituted Aryl Radicals, *J. Org. Chem.*, 1997, **62**, 8394.

36 C. M. Camaggi, R. Leardini, D. Nanni and G. Zanardi, Radical annulations with nitriles: Novel cascade reactions of cyano-substituted alkyl and sulfanyl radicals with isonitriles, *Tetrahedron*, 1998, **54**, 5587.

37 W. R. Bowman, M. O. Cloonan, A. J. Fletcher and T. Stein, Synthesis of heteroarenes using cascade radical cyclisation via iminyl radicals, *Org. Biomol. Chem.*, 2005, **3**, 1460.

38 D. P. Curran, C. P. Jasperse and M. J. Totleben, Approximate absolute rate constants for the reactions of tributyltin radicals with aryl and vinyl halides, *J. Org. Chem.*, 1991, **56**, 7169.

39 X. Sun, J. Li, Y. Ni, D. Ren, Z. Hu and S. Yu, Synthesis of Fused Quinoline and Quinoxaline Derivatives Enabled by Domino Radical Triple Bond Insertions, *Asian J. Org. Chem.*, 2014, **3**, 1317.

40 A. Servais, M. Azzouz, D. Lopes, C. Courillon and M. Malacria, Radical Cyclization of N-Acylcyanamides: Total Synthesis of Luotonin A, *Angew. Chem., Int. Ed.*, 2007, **46**, 576.

41 M.-H. Larraufie, C. Courillon, C. Ollivier, E. Lacôte, M. Malacria and L. Fensterbank, Radical Migration of Substituents of Aryl Groups on Quinazolinones Derived from N-Acyl Cyanamides, *J. Am. Chem. Soc.*, 2010, **132**, 4381.

42 M.-H. Larraufie, C. Ollivier, L. Fensterbank, M. Malacria and E. Lacôte, Radical Synthesis of Guanidines from N-Acyl Cyanamides, *Angew. Chem., Int. Ed.*, 2010, **49**, 2178.

43 Y.-Y. Han, H. Jiang, R. Wang and S. Yu, Synthesis of Tetracyclic Quinazolinones Using a Visible-Light-Promoted Radical Cascade Approach, *J. Org. Chem.*, 2016, **81**, 7276.
44 J. Zheng, Y. Zhang, D. Wang and S. Cui, Silver(I)-Mediated Phosphorylation/Cyclization Cascade of N-Cyanamide Alkenes for Divergent Access to Quinazolinones and Dihydroisoquinolinones, *Org. Lett.*, 2016, **18**, 1768.
45 J. Zheng, Z. Deng, Y. Zhang and S. Cui, Copper-Catalyzed Divergent Trifluoromethylation/Cyclization of Unactivated Alkenes, *Adv. Synth. Catal.*, 2016, **358**, 746.
46 X. Liu, P. Qian, Y. Wang and Y. Pan, Metal-free sequential decarbonylative annulation of N-cyanamides for the construction of 2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-ones, *Org. Chem. Front.*, 2017, **4**, 2370.
47 (*a*) W.-C. Yang, J.-G. Feng, L. Wu and Y.-Q. Zhang, Aliphatic Aldehydes: Novel Radical Alkylating Reagents, *Adv. Synth. Catal.*, 2019, **361**, 1700; (*b*) L. Kong, Y. Zhou, F. Luo and G. Zhu, Recent Advances on Oxidative Radical Addition to Aldehydes, *Chin. J. Org. Chem.*, 2018, **38**, 2858.
48 R. Leardini, D. Nanni, A. Tundo and G. Zanardi, Novel [3 + 2] radical annulations of cyano-substituted aryl radicals with alkynes, *Tetrahedron Lett.*, 1998, **39**, 2441.
49 P. Xu, Y.-M. Zhu, F. Wang, S.-Y. Wang and S.-J. Ji, Mn(III)-Mediated Cascade Cyclization of 3-Isocyano-[1,1′-biphenyl]-2-carbonitrile with Arylboronic Acid: Construction of Pyrrolopyridine Derivatives, *Org. Lett.*, 2019, **21**, 683.
50 N. Zhou, M. Wu, M. Zhang, X. Zhou and W. Zhou, TBPB-initiated cascade cyclization of 3-arylethynyl-[1,1′-biphenyl]-2-carbonitriles with sulfinic acids: access to sulfone-containing cyclopenta[gh]phenanthridines, *Org. Biomol. Chem.*, 2020, **18**, 1733.
51 X. Li, X. Fang, S. Zhuang, P. Liu and P. Sun, Photoredox Catalysis: Construction of Polyheterocycles via Alkoxycarbonylation/Addition/Cyclization Sequence, *Org. Lett.*, 2017, **19**, 3580.
52 Y. Yu, Z. Cai, W. Yuan, P. Liu and P. Sun, Radical Addition/Insertion/Cyclization Cascade Reaction To Assemble Phenanthridines from N-Arylacrylamide Using Cyano as a Bridge under Photoredox Catalysis, *J. Org. Chem.*, 2017, **82**, 8148.
53 C. Zhang, J. Pi, S. Chen, P. Liu and P. Sun, Construction of a 4H-pyrido[4,3,2-gh]phenanthridin-5(6H)-one skeleton via a catalyst-free radical cascade addition/cyclization using azo compounds as radical sources, *Org. Chem. Front.*, 2018, **5**, 793.
54 Y. Yu, W. Yuan, H. Huang, Z. Cai, P. Liu and P. Sun, Visible-Light-Mediated Decarboxylative Alkylation Cascade Cyano Insertion/Cyclization of N-Arylacrylamides under Transition-Metal-Free Conditions, *J. Org. Chem.*, 2018, **83**, 1654.
55 L. Ruan, C. Chen, X. Zhang and J. Sun, Recent Advances on the Photo-Induced Reactions of Acyl Radical, *Chin. J. Org. Chem.*, 2018, **38**, 3155.
56 J.-Q. Shang, X.-X. Wang, Y. Xin, Y. Li, B. Zhou and Y.-M. Li, Decarboxylative cascade cyclization of α-keto acids with 2-cyano-3-arylaniline-derived acrylamides, *Org. Biomol. Chem.*, 2019, **17**, 9447.
57 X. Liu, Z. Wu, Z. Zhang, P. Liu and P. Sun, Synthesis of trifluoroalkyl or difluoroalkyl phenanthridine derivatives via cascade reaction using an intramolecular cyano group as a radical acceptor under photoredox catalysis, *Org. Biomol. Chem.*, 2018, **16**, 414.
58 M. Zhu, W. Fu, W. Guo, Y. Tian, Z. Wang and B. Ji, Visible-light-induced radical trifluoromethylthiolation of N-(o-cyanobiaryl)acrylamides, *Org. Biomol. Chem.*, 2019, **17**, 3374.
59 J.-Q. Shang, S.-S. Wang, H. Fu, Y. Li, T. Yang and Y.-M. Li, Oxidative radical cascade cyclization involving C(sp3)–C(sp3), C(sp3)–C(sp2) and C(sp2)–N bonds formation: direct construction of cyano and methyl substituted polyheterocycles, *Org. Chem. Front.*, 2018, **5**, 1945.
60 C. Zhang, J. Pi, L. Wang, P. Liu and P. Sun, Silyl radical initiated radical cascade addition/cyclization: synthesis of silyl functionalized 4H-pyrido[4,3,2-gh]phenanthridin-5(6H)-ones, *Org. Biomol. Chem.*, 2018, **16**, 9223.
61 L. Ji, W. Gu, P. Liu and P. Sun, Iron-mediated deuterium addition cascade cyano insertion/cyclization of N-arylacrylamides to access deuterium-labelled phenanthridines, *Org. Biomol. Chem.*, 2020, **18**, 6126.
62 W.-J. Xia, Y. Xin, Z.-W. Zhao, X. Chen, X.-X. Wang, Y. Li, G. Wang and Y.-M. Li, Oxidative cascade cyclization of 2-cyano-3-arylaniline derived acrylamides with toluenes, ethers, aliphatic alcohols or simple alkanes, *Org. Chem. Front.*, 2020, **7**, 1997.
63 D. Hernández, L. Nielsen, K. B. Lindsay, M. López-García, K. Bjerglund and T. Skrydstrup, Stereocontrolled Synthesis of 2-Substituted-1,3-Azasilaheterocycles, *Org. Lett.*, 2010, **12**, 3528.
64 L.-J. Wu, Y. Yang, R.-J. Song, J.-X. Yu, J.-H. Li and D.-L. He, An access to 1,3-azasiline-fused quinolinones via oxidative heteroannulation involving silyl C(sp3)–H functionalization, *Chem. Commun.*, 2018, **54**, 1367.
65 P. Natarajan, Manjeet, Muskan, N. K. Brar and J. J. Kaur, Visible light photoredox catalysis: conversion of a mixture of thiophenols and nitriles into 2-substituted benzothiazoles via consecutive C–S and C–N bond formation reactions, *Org. Chem. Front.*, 2018, **5**, 1527.
66 J. Guo, Y. Hao, G. Li, Z. Wang, Y. Liu, Y. Li and Q. Wang, Efficient synthesis of SCF3-substituted tryptanthrins by a radical tandem cyclization, *Org. Biomol. Chem.*, 2020, **18**, 1994.
67 (*a*) A. L. J. Beckwith, D. M. O'Shea and S. W. Westwood, Rearrangement of suitably constituted aryl, alkyl, or vinyl radicals by acyl or cyano group migration, *J. Am. Chem. Soc.*, 1988, **110**, 2565; (*b*) A. L. J. Beckwith, D. M. O'Shea, S. Gerba and S. W. Westwood, Cyano or acyl group migration by consecutive homolytic addition and β-fission, *J. Chem. Soc., Chem. Commun.*, 1987, 666.
68 J. Cossy, C. Poitevin, D. G. Pardo and J. L. Peglion, Synthesis of 2-(Alkylamino)benzonitriles from α-(Bromoarylamino)nitriles, *Synthesis*, 1995, 1368.
69 D. P. Curran and C. M. Seong, Radical annulation reactions of allyl iodomalononitriles, *Tetrahedron*, 1992, **48**, 2175.
70 (*a*) A.-C. Callier, B. Quiclet-Sire and S. Z. Zard, Amidyl and carbamyl radicals by stannane mediated cleavage of

O-benzoyl hydroxamic acid derivatives, *Tetrahedron Lett.*, 1994, **35**, 6109; (*b*) J. Boivin, A.-C. Callier-Dublanchet, B. Quiclet-Sire, A.-M. Schiano and S. Z. Zard, Iminyl, amidyl, and carbamyl radicals from O-benzoyl oximes and O-benzoyl hydroxamic acid derivatives, *Tetrahedron*, 1995, **51**, 6517.

71 X. Wu and C. Zhu, Radical-Mediated Remote Functional Group Migration, *Acc. Chem. Res.*, 2020, **53**, 1620.

72 Z. Wu, R. Ren and C. Zhu, Combination of a Cyano Migration Strategy and Alkene Difunctionalization: The Elusive Selective Azidocyanation of Unactivated Olefins, *Angew. Chem., Int. Ed.*, 2016, **55**, 10821.

73 N. Wang, L. Li, Z.-L. Li, N.-Y. Yang, Z. Guo, H.-X. Zhang and X.-Y. Liu, Catalytic Diverse Radical-Mediated 1,2-Cyanofunctionalization of Unactivated Alkenes via Synergistic Remote Cyano Migration and Protected Strategies, *Org. Lett.*, 2016, **18**, 6026.

74 M. Ji, Z. Wu, J. Yu, X. Wan and C. Zhu, Cyanotrifluoromethylthiolation of Unactivated Olefins through Intramolecular Cyano Migration, *Adv. Synth. Catal.*, 2017, **359**, 1959.

75 D. Chen, Z. Wu, Y. Yao and C. Zhu, Phosphinoyl-functionalization of unactivated alkenes through phosphinoyl radical-triggered distal functional group migration, *Org. Chem. Front.*, 2018, **5**, 2370.

76 Y. Kwon and Q. Wang, Copper-Catalyzed 1,2-Aminocyanation of Unactivated Alkenes via Cyano Migration, *Org. Lett.*, 2020, **22**, 4141.