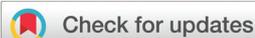


REVIEW

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Recent advances in cascade radical cyclization of radical acceptors for the synthesis of carbo- and heterocycles

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Cascade radical cyclization is an attractive synthetic method due to its high atom- and step-economy to construct carbo- and heterocycles, which have wide applications in chemical and life science industries. Radical acceptors with unsaturated bonds play a key role in realizing highly rapid, concise, and efficient cascade radical cyclization. This Review is devoted to highlighting the latest achievements in the development of cascade radical cyclization methodologies for the synthesis of carbo- and heterocycles in this rapidly growing research field. Based on the hybridization of starting materials, this Review includes C(sp)–C(sp) bond, C(sp)–C(sp²) bond, C(sp²)–C(sp²) bond, C(sp²)–C(sp³), and carbon–heteroatom bond coupling cyclization. Representative examples mainly published in last three years will be discussed for each highlighted reaction design and mechanism, providing readers with common tools for future research in cascade radical cyclization.

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1. Introduction

Carbo- and heterocycles are extremely important skeletons in organic synthesis; they are widely found in natural products

and bioactive compounds.¹ As a result, a variety of synthetic methods have been performed in the development of carbo- and heterocyclic molecules, among which cascade radical cyclization arguably constitutes the most valuable tool to date.² Because of the sustainability of synthetic processes, cascade reactions are highly recognized as powerful strategies for the construction of high-value and often complex cyclic compounds. The processes are performed in a single preparation step with a high synthetic economy to build up the for-

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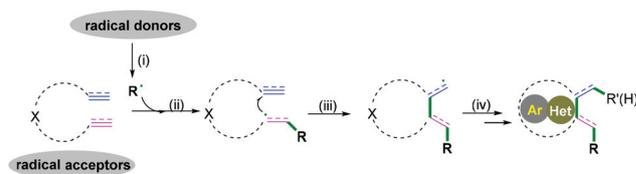
Dr Jianhua Liao was born in Jiangxi Province, People's Republic of China. In 2017, she received her PhD degree from South China University of Technology (SCUT) under the supervision of Prof. Huanfeng Jiang. During 2019 and 2020, she studied as a visiting scholar with Prof. Weiping Tang at University of Wisconsin-Madison (USA). She worked in the school of Pharmaceutical Sciences at Gannan Medical University,

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mation of more than two bonds.³ In past decades, excellent results have been achieved in this research area, and efficient protocols for the construction of carbo- and heterocycles have been disclosed. As pioneering work in radical cascade reactions, Porter and coauthors developed a systematic study of unsaturated peroxy radical cyclizations to synthesize prostaglandin analogs.^{3a,b} In the 1980s, Stork^{3c} and Curran groups^{3d} elegantly reported fascinating research in the field of radical chemistry. Transient radical species were generated from halides with *tri-n*-butyltin hydride, followed by hex-5-enyl-like radical cyclizations and finally a hydrogen atom abstraction to deliver the final products. Later, an excellent research of the cascade radical cyclization of electron-deficient alkenes with carbon species generated from the irradiation of the *N*-hydroxy-2-thiopyridone esters of suitable γ,δ -unsaturated carboxylic acids to construct complex carbocycles was developed by Zard and co-workers.^{3e} Despite these very impressive and significant advances, the synthetic potential of available chemical feedstocks as radical acceptors to construct carbo- and heterocycles with high chemo- and regioselectivity is still an imposing challenge for chemists. Therefore, many attempts have been made to create new and efficient strategies that are capable of accessing complex molecular frameworks. Different radical acceptors, such as 1,*n*-diynes, 1,*n*-enynes, alkynyl (hetero) arenes, *o*-alkenylarylisonitriles, 1,*n*-dienes, alkenyl (hetero) arenes, alkyne-tethered ketoximes, alkene-tethered ketoximes, 2-substituted phenyl isocyanides, and 2-isocyanoyl thioethers have been elegantly applied in combination with radical species in the formation of carbo- and heterocycles. Recent cascade radical cyclization generally involves four key stages: (i) a radical formation-radical species is generated from a radical donor by a single-electron transfer (SET) process; (ii) radical addition-subsequent radical addition to an unsaturated bond leads to the formation of a carbon radical intermediate; (iii) a radical cyclization-carbon-carbon/heteroatom bond is formed; (iv) the radical quenching-carbon



Scheme 1 General pathway of the cascade radical cyclization reaction.

radical intermediate is quenched by hydrogen abstraction or another radical donor coupling to construct a carbo- and heterocyclic molecule (Scheme 1).

Recently, a variety of radical cascade cyclization reactions have been developed. Although radical C–H activation/radical cross-coupling,^{2a} catalytic cascade reactions by radical relay,^{2d} cascade cyclization of 1,*n*-enynes and diynes,^{2b} and radical cascade reaction in the synthesis of 1-indenones^{2e} have been the subject of excellent reviews, we herein aim to examine a disparate region of radical chemistry in a more general review of radical cascade cyclization by highlighting the properties and reactivities of radical acceptors with different types of hybridization of the carbon-carbon/heteroatoms. According to the hybridization of the starting materials, this Review will embrace the classification of the carbon-carbon bond (e.g., C(sp)–C(sp), C(sp)–C(sp²), C(sp²)–C(sp²), and C(sp²)–C(sp³) bonds, section 2) and carbon-heteroatom bond coupling cyclization (e.g., C–O, C–N, and C–S bonds, section 3), with an emphasis on the properties and reactivities of the radical acceptor. This is important to enable the reader to directly compare and contrast reactivity patterns in the additions of diverse radicals to unsaturated substrates. Additionally, representative examples of radical cascade cyclization are selected for further discussion. Moreover, we highlight the reaction design and reaction mechanisms, providing readers with common strategies for new work on radical cascade cyclization in the future.



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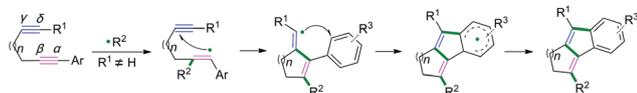
2. Carbon–carbon bond coupling cyclization

Radical cascade cyclization is widely applied to carbo- and heterocycle synthesis in the applications of medicines, agrochemicals, and other functional materials; this cyclization proceeds through a single electron transfer pathway to construct new carbon–carbon (C–C) bonds.

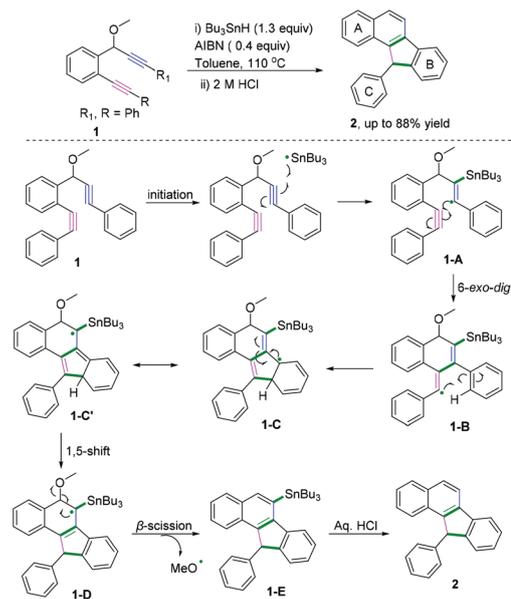
2.1 C(sp)–C(sp) bond coupling cyclization

C(sp)–C(sp) bond coupling cyclizations are usually performed with the starting radical acceptors of 1,*n*-diynes. The general reaction process for the C(sp)–C(sp) bond coupling cyclization of 1,*n*-diynes is shown in Scheme 2. A single-electron transfer proceeds, resulting in the formation of a radical species under the proper conditions. The regio- and chemoselectivity for the subsequent radical attack at an unsaturated group depends on the type of substituent group of the 1,*n*-diynes. If R¹ is not equal to H, the free radical addition attack occurs at the β position of the 1,*n*-diyne. Further radical cyclization to the γ position of another triple bond of the 1,*n*-diyne leads to a new alkenyl carbon radical intermediate, followed by further intramolecular radical cyclization with aromatics linked at the α position. Finally, deprotonation of the aryl radical intermediate with base or oxidants delivers the desired product.

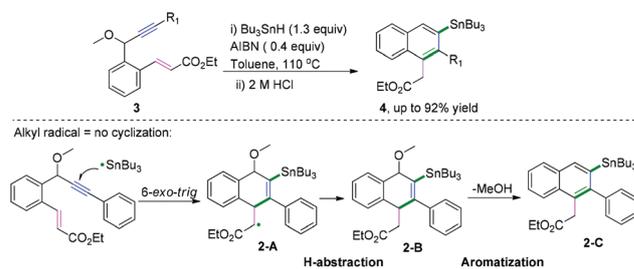
Polycyclic aromatic hydrocarbons (PAHs) are fascinating compounds that have wide utility in material sciences.⁴ In this regard, Alabugin and co-workers developed pioneering tin-mediated radical cascade processes that employed a tethered initiator or a traceless directing group to perform the initial radical attack on the polyalkyne substrates.⁵ As demonstrated in Scheme 3,^{5e} the first example of a traceless directing group in the radical cascade transformation of enynes to efficiently construct polycyclic ribbons of tunable dimensions was reported. In this transformation, high chemo- and regioselectivity of the initial attack in skipped oligoalkynes was realized by the propargyl OR moiety. It was proposed that the reaction involved an initial formation of a radical intermediate **1-A**, generated *via* the attack of the Bu₃Sn radical at the central alkyne. The subsequent 6-*exo-dig* cyclization process afforded the second vinyl radical intermediate **1-B**. Further attack of the neighboring phenyl π-system delivered a delocalized radical intermediate **1-C**, leading to rearomatization *via* a 1,5-hydrogen shift. Subsequent β-scission of the OMe afforded the intermediate **1-D**. The final fragmentation of intermediate **1-E** led to the aromatization of the top ring into a naphthalene moiety. Interestingly, when analogous 1,6-enynes were engaged in this cascade radical reaction by the same group,



Scheme 2 Plausible mechanism of radical cyclization to 1,*n*-diynes.



Scheme 3 Traceless directing groups in radical cascade transformations of oligoalkynes.

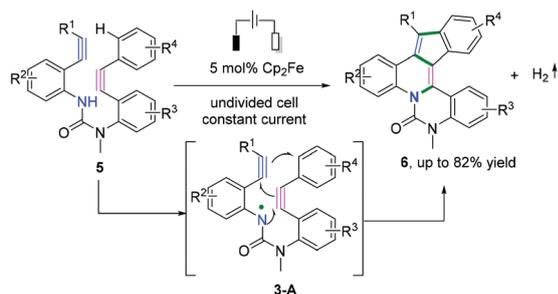


Scheme 4 Traceless directing groups in radical cascade transformations of 1,6-enynes.

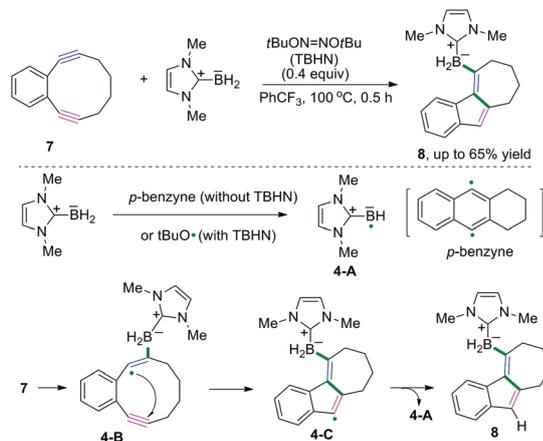
the process did not form the last five-membered ring.^{5d} As shown in Scheme 4, the final product consisted only of six-membered rings. The DFT calculations suggested that the difference between the radical cascades of oligoalkynes and enynes was the greater reactivity of vinyl radicals and the more stabilizing group of the vinyl moiety in the product in comparison with the alkyl radicals.

In 2017, Xu and coauthors also demonstrated a remarkable electrochemical synthesis of nitrogen-doped PAHs through intramolecular cascade radical cyclization of diynes in a one-step process with a high step-economy (Scheme 5).⁶ The reaction proceeded in the presence of ferrocene, a mild and selective redox catalyst, to access varieties of electron-rich PAHs without overoxidation. The process involved formation of an unprecedented amidyl radical, **3-A**, to deliver a cascade cyclization process with three rings in a single operation.

Excellent research of borylative radical cascade cyclization of 1,5-diyne to generate borylated carbocycles has been developed by Curran, Taniguchi, and coauthors (Scheme 6).⁷ The proposed mechanism suggested that boryl radical species **4-A**



Scheme 5 Electrochemical cascade radical cyclization of diynes.

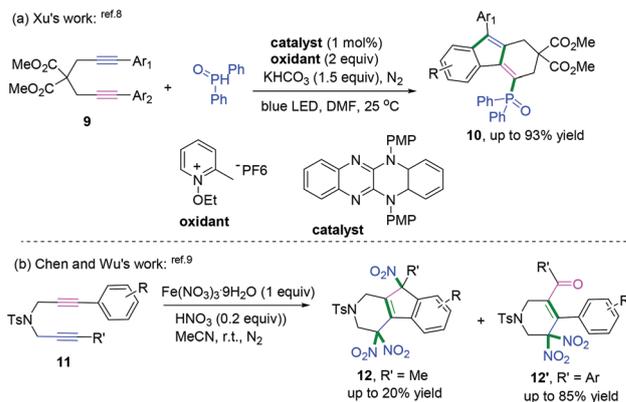


Scheme 6 Borylative radical cascade cyclization of diynes and N-heterocyclic carbene-boranes.

from N-heterocyclic carbene-boranes (NHC-boranes) were formed firstly, initiated by *di-tert*-butyl hyponitrite (TBHN), followed by intermolecular addition of NHC-boryl radicals **4-A** to the alkyne of the diyne. Subsequent *5-endo-dig* cyclization of 1,2-diethynylbenzenes generated the alkenyl radical intermediates **4-C**, whereas intermediates **4-C** could abstract a hydrogen atom from NHC-borane to deliver the final borylated products. As demonstrated in Scheme 6, stabilization of the alkenyl radical intermediates **4-B** by the aromatic ring and the strain of the alkynes may benefit the addition of the NHC-boryl radical species **4-A** to the alkynes in this transformation.

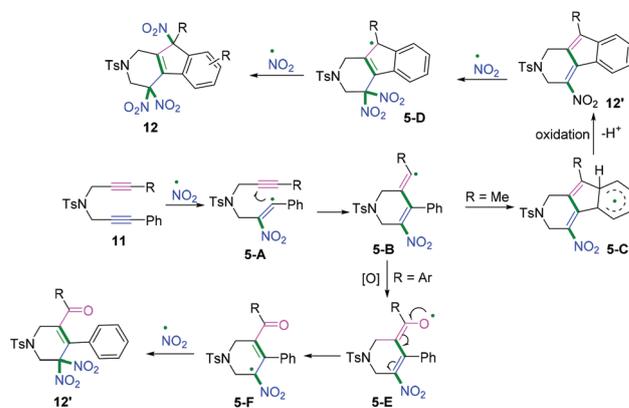
The interception of 1,6-diynes captured with radical donors, such as phosphoryl radical⁸ and nitroso radical (NO_2),⁹ delivered fluorenes bearing different functional groups. In 2018, a series of reducing organic visible-light photocatalysts with strong absorption was designed and synthesized by Xu and co-workers and further used for the radical cascade cyclization of 1,6-diynes with phosphoryl radicals (Scheme 7a).⁸ The experimental observations have been corroborated through time-dependent density functional theory calculations.

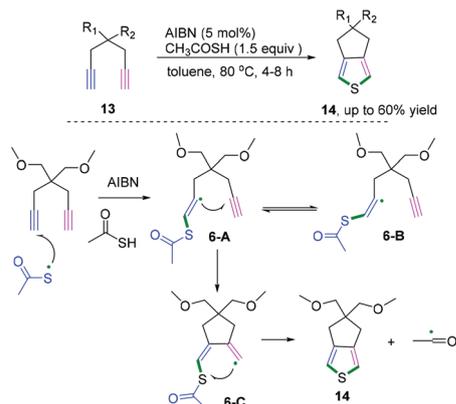
Another radical attacking addition at the β position of 1,*n*-diynes was demonstrated by Chen, Wu, and co-workers to synthesize cyclic *gem*-dinitro skeletons *via* cascade radical



Scheme 7 Radical cascade cyclization of 1,6-diynes.

nitration of 1,6-diynes (Scheme 7b).⁹ The transformation proceeded with $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ as an inexpensive nitrating agent, providing a mild nitrating source for the preparation of cyclic *gem*-dinitro compounds. The transformation was proposed to involve the initial generation of $\cdot\text{NO}_2$ radicals, followed by a sequence of cascade radical addition/cyclization/oxidation/deprotonation/further nitration processes. As demonstrated in Scheme 8, $\cdot\text{NO}_2$ was firstly generated *via* decomposition of $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$, followed by radical addition to the triple bond. Subsequently, addition of alkenyl radical **5-A** to the second triple bond afforded the cyclomethylene radical intermediates **5-B**. For the alkyl-substituted 1,6-diyne substrates, the alkenyl radical intermediates **5-B** would undergo an intramolecular radical addition process to afford the aromatic intermediates **5-C**. A further oxidation/deprotonation/nitration sequence yielded the *tri*-nitro products. Meanwhile, for the aromatic 1,6-diynes, the cyclomethylene radical intermediates **5-B** tended to be oxidized by iron oxo species ($\text{Fe}(\text{O})$), leading to the formation of oxygen radicals **5-E**, followed by rapid tautomerization to form intermediates **5-F**. Finally, the radical cross-coupling of intermediates **5-F** with $\cdot\text{NO}_2$ delivered the *gem*-*di*-nitro cyclization products. It was proposed that the two different

Scheme 8 Proposed mechanisms for the formation of **12** and **12'**.



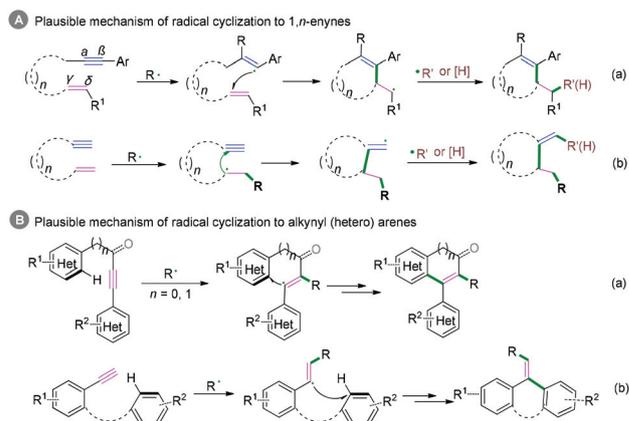
Scheme 9 Radical cascade cyclization of terminal alkynes.

reaction processes may be affected by the stabilities and activities of the alkenyl radical intermediates.

When the 1,6-diynes contain terminal alkynes, the radical addition generally occurs at a terminal position. Representative research on radical cascade cyclization of terminal alkynes for the synthesis of 3,4-fused-ring-substituted thiophenes was reported by Zade and co-workers (Scheme 9).¹⁰ The transformation proceeded in the presence of a catalytic amount of azobis(isobutyronitrile) as a radical initiator. According to the proposed mechanism, the radical cascade initiated thiophene ring 6-C was formed by the radical cyclization of thiyl radical at the terminal position of the diyne. The subsequent cyclization underwent intramolecular homolytic substitution at the sulfur to liberate the acyl radical to furnish the desired products. Notably, it was found that only the *E*-vinyl radical intermediates 6-A can generate the formation of the desired fused-ring-substituted thiophenes.

2.2 C(sp)–C(sp²) bond coupling cyclization

Generally, C(sp)–C(sp²) bond coupling cyclization is generated from 1,*n*-enynes or alkynyl (hetero) arenes, which are commonly used radical acceptors. For the radical acceptors of 1,*n*-enynes, there are two functionalities that participate in the cascade reactions, which have four possible directions for radical attack. According to previous studies, the order of priority of attacking unsaturated bonds usually depends on the structure of the radical acceptors and the reaction conditions (Scheme 10A). For the radical acceptors with non-terminal double bonds, although alkyne π -bonds are stronger and less reactive than the π -bonds of alkenes, selective radical attacking at the α position of the alkyne can be achieved, which may be due to the self-sorted kinetic process *via* the subsequent favored 5-*exo-trig* radical cyclization (Scheme 10A, a).¹¹ Meanwhile, for the terminal alkenes, regioselective addition of radical species across the double bond in the 1,*n*-enye occurs firstly. The regioselectivity is proposed by the fact that the π -bond of the alkyne is stronger than alkene, leading to the lower kinetic barrier of radical addition to the double bond.¹² Subsequently, the same intramolecular 5-*exo*-cyclization with



Scheme 10 Plausible mechanism of radical cyclization to 1,*n*-enynes or alkynyl (hetero) arenes.

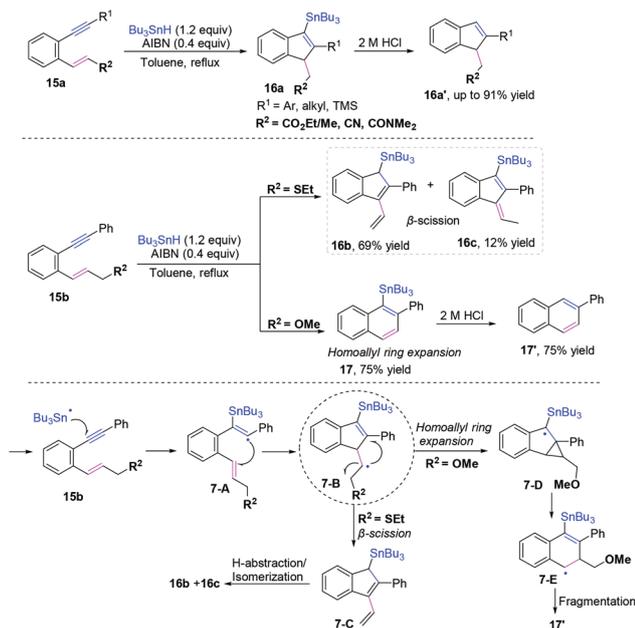
better orbital overlap for the stereoelectronic effects finishes the cyclization. Finally, the hydrogen abstraction or further radical cross-coupling takes place to generate the observed products (Scheme 10A, b).

Alkynyl (hetero) arenes are also efficient radical acceptors and are widely used in the chemical and pharmaceutical science industries. As demonstrated in Scheme 10B, there are generally two pathway strategies to realize intramolecular radical cyclization of alkynyl (hetero) arenes. One is *via* radical cyclization of the *ortho* pi-bonds of (hetero) arenes (Scheme 10B, a) while another strategy is to cyclize *via* the pi-bonds of other (hetero) arenes (Scheme 10B, b). The key success of this strategy lies in the formation of (hetero) aryl vinyl radical intermediates. The final rearomatization process affords the desired product.

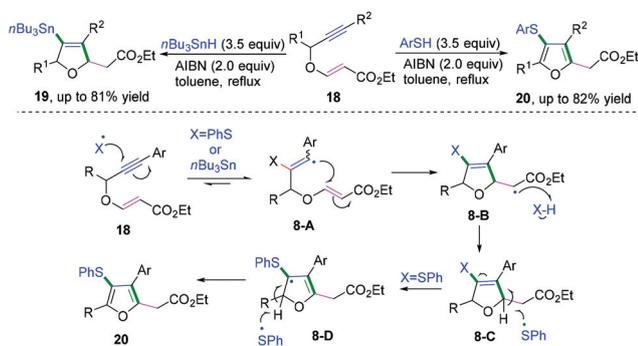
2.2.1 C(sp)–alkenyl C(sp²) bond cyclization

Cascade radical cyclization of 1,5-enynes. In pioneering research published by Alabugin and co-workers, they developed a series of reversible Bu₃Sn-mediated radical additions to alkynes and alkenes, yielding the formation of Sn-substituted indenenes and naphthalenes from 1,5-enynes (Scheme 11).^{11a-c} The radical pool mixtures are kinetically self-sorted *via* the fastest cyclization of attacking of the more reactive radical (vinyl > alkyl) at the more reactive π -bond (alkene > alkyne). The reactions were found to be highly R²-dependent, providing different products in the cascade radical cyclization of 1,5-enynes. Additionally, alkenes could be used as equivalents of alkynes in this cascade radical reaction when the cascade reaction includes a radical-ring expansion. Along the same lines, the same group developed a formal 6-*endo-dig* cyclization for the synthesis of quinolines from isonitriles using alkenes as synthetic equivalents of alkynes *via* coupling homoallylic ring expansion. The proposed mechanism revealed that a path sequence of 5-*exo*/3-*exo*/retro-3-*exo* afforded the formal 6-*endo* products.^{11c-e}

In 2019, Shelke and co-workers reported a cascade radical cyclization of 1,5-enynes to provide an efficient method for the synthesis of a variety of tetrasubstituted furans and dihydrofur-



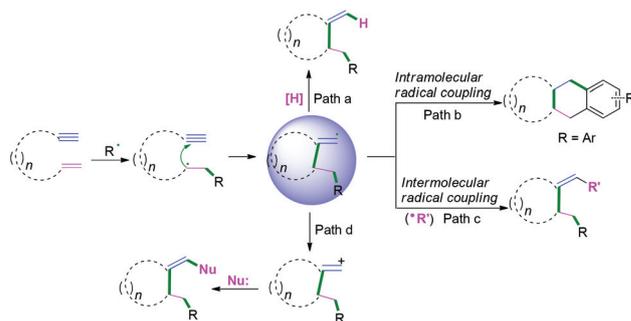
Scheme 11 Cascade radical cyclization of 1,5-enynes.



Scheme 12 Cascade radical cyclization of 1,5-enynes.

ans (Scheme 12).^{11f} The proposed mechanism showed that the first selective radical addition of an initial thiyl or stannyl radical to the triple bond generated the aryl vinyl radical intermediate **8-A**, followed by favored 5-*exo-trig* radical cyclization to afford alkyl carbon radical intermediate **8-B**. Subsequently, hydrogen abstraction of intermediate **8-B** from *n*-Bu₃SnH or PhSH formed the dihydrofuran derivative **8-C**. A further radical process was initiated in the presence of excess PhSH and AIBN, leading to the formation of resonance-stabilized allylic radical **8-D**. Finally, hydrogen abstraction of dihydrofuran intermediates **8-D** afforded the highly substituted furan products. It was supposed that because the bond energy of PhS-H is greater than that of *n*-Bu₃Sn-H, further oxidation of dihydrofurans to the corresponding furans could be performed by thiyl radical.^{11g}

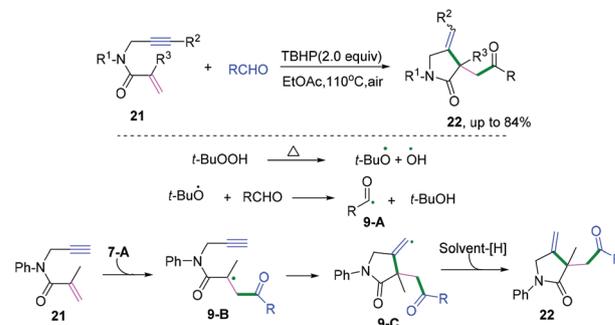
Cascade radical cyclization of 1,*n*-enynes. Compared with the radical cyclization of enynes with non-terminal double bonds, enynes with terminal alkenes have wider diversities for further

Scheme 13 Plausible mechanism of radical cyclization to 1,*n*-enynes.

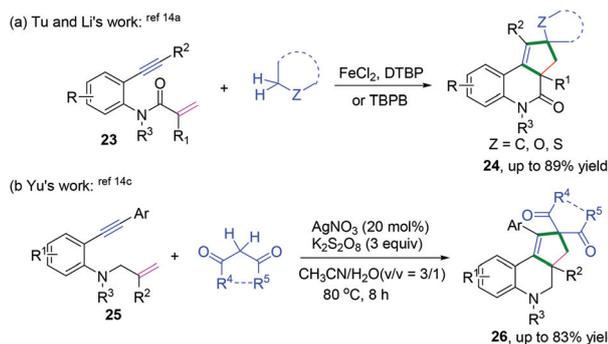
transformation. As demonstrated in Scheme 13, vinyl radical intermediates generated from regioselective radical cyclization can generally proceed in four different types of reactions to terminate the reactions, such as hydrogen abstraction (Scheme 13, path a), intramolecular radical coupling (Scheme 13, path b), intermolecular radical cross-coupling (Scheme 13, path c), or further oxidation followed by nucleophilic attack (Scheme 13, path d).

Terminated with hydrogen abstraction. In 2019, Wei and co-workers developed a *tert*-butyl hydroperoxide (TBHP)-mediated radical cyclization of 1,6-enynes with aldehydes under metal- and additive-free conditions (Scheme 14).¹³ It was proposed that the reaction involved the initial generation of acyl radicals in the presence of TBHP under heating conditions, followed by radical addition to the double bond to afford carbon radical intermediates **9-B**. Subsequently, intramolecular 5-*exo*-cyclization with the triple bond afforded the vinyl radical intermediates **9-C**. Then, final hydrogen abstraction took place to furnish the obtained products.

Terminated with intramolecular radical coupling. Vinyl radical intermediates generated from regioselective radical cyclization of enynes could be terminated by an intramolecular radical coupling process. Along these lines, Li, Tu, and Yu's groups have demonstrated remarkable intramolecular radical domino spirocyclizations of 1,7-enynes with C(sp³)-H radical donors. The reactions terminated the vinyl radical intermediates *via* 1,5-hydrogen atom shifts to generate a series of spirocycles



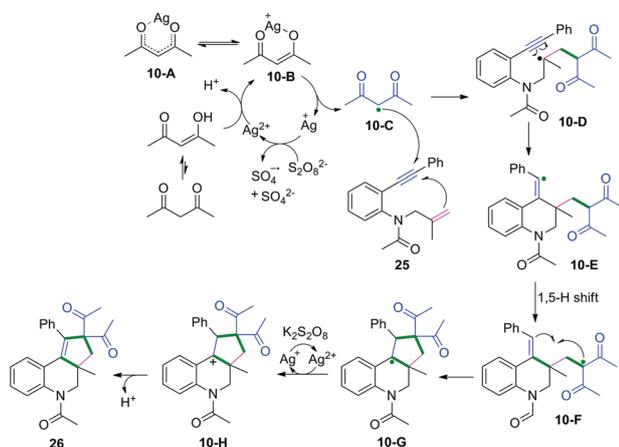
Scheme 14 Cascade radical cyclization of 1,6-enynes terminated with hydrogen abstraction.



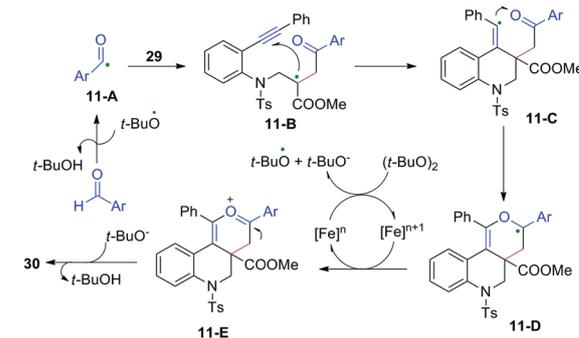
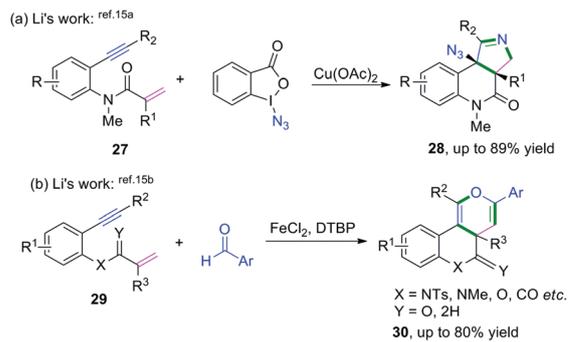
Scheme 15 Cascade radical cyclization of 1,7-enynes terminated with intramolecular C(sp³)-H coupling.

(Scheme 15).¹⁴ Based on the mechanistic studies, Yu and co-workers proposed a detailed mechanistic pathway, as depicted in Scheme 16.^{14c} Ag(II) cations were initially generated from the reaction of Ag(I) with persulfate anions that further reacted with acetylacetone to afford silver ion complexes **10-B** or **10-A**, which were converted to dicarbonyl radicals **10-C** along with regeneration of Ag(I) for a new catalytic cycle. Subsequently, regioselective radical addition to the double bonds of 1,7-enynes afforded alkyl carbon radical intermediates **10-D**, followed by intramolecular cyclization to yield vinyl radical intermediates **10-E**. Afterward, the obtained vinyl radical intermediates **10-E** underwent a 1,5-H shift process to form alkyl radical intermediates **10-F**, followed by intramolecular domino spirocyclization to afford the intermediates **10-G**. Finally, oxidation of intermediates **10-G** with AgNO₃/K₂S₂O₈ and subsequent deprotonation of radical intermediates **10-H** afforded the final desired products.

Metal-catalyzed cascade radical cyclization of 1,*n*-enynes (*n* = 6, 7) with azides or aldehydes are important methods for the synthesis of a variety of fascinating fused compounds.¹⁵ Copper-catalyzed radical [2 + 2 + 1] annulation of benzene-linked 1,*n*-enynes (*n* = 6, 7) with azides was developed by Song, Li, and co-workers (Scheme 17a).^{15a} This protocol was successfully applied for the construction of a series of fused pyrroline



Scheme 16 Proposed mechanisms for the formation of **26**.

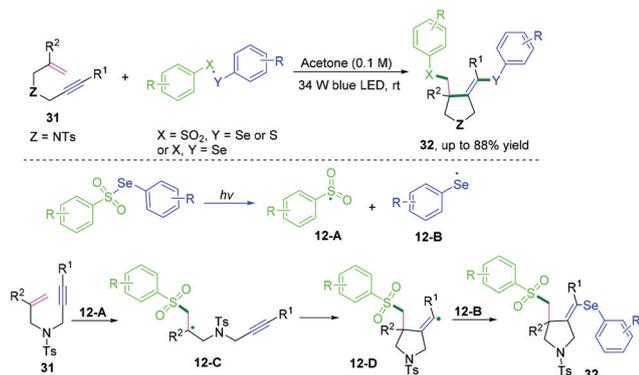


Scheme 17 Cascade radical cyclization of 1,7-enynes terminated with intramolecular radical coupling.

compounds, which proceeded *via* a cascade radical addition/cyclization/annulation/azidation sequence. Later, Li and co-authors reported an iron-catalyzed cascade radical [2 + 2 + 2] annulation of benzene-linked 1,7-enynes with aldehydes to access a variety of fused pyran compounds (Scheme 17b).^{15b} Vinyl radical intermediates **11-C** generated from aldehydic radical cyclization were terminated with carbonyl compounds, reacting in a dual role to realize the domino cyclization.

Terminated with intermolecular radical cross-coupling. Vinyl radical intermediates terminated by intermolecular radical cross-coupling provide a novel strategy to construct functionalized heterocycles.¹⁶ In 2020, cascade radical cyclization of unactivated 1,6-enynes with chalcogens to access chalcogen-substituted pyrrolidines was also achieved by Wang and co-workers (Scheme 18).¹⁶ The reaction realized three new bonds in one step with the formation of C-SO₂, C-C, and C-Se bonds under visible-light-induced conditions. The detailed mechanistic study suggested that tosyl **12-A** and phenylselenenyl **12-B** free radicals were first generated from photo-irradiation of Se-phenyl 4-methylbenzenesulfonoseleate, followed by regio- and chemoselective tosyl radical addition to the double bonds of 1,6-enynes to afford alkyl radical intermediates **12-C**. Subsequent 5-*exo-dig* cyclization afforded the vinyl radical intermediates **12-D**, which were terminated by phenylselenenyl **12-B** radicals to furnish the final products.

Terminated with nucleophiles. A further electron transfer process for vinyl radical intermediates can take place to afford vinyl carbocations terminated by nucleophiles. The Li,^{17a} Jiang,^{17b} and Kumar^{17c} groups have demonstrated cascade radical cyclization of 1,6-enynes with nucleophiles to syn-

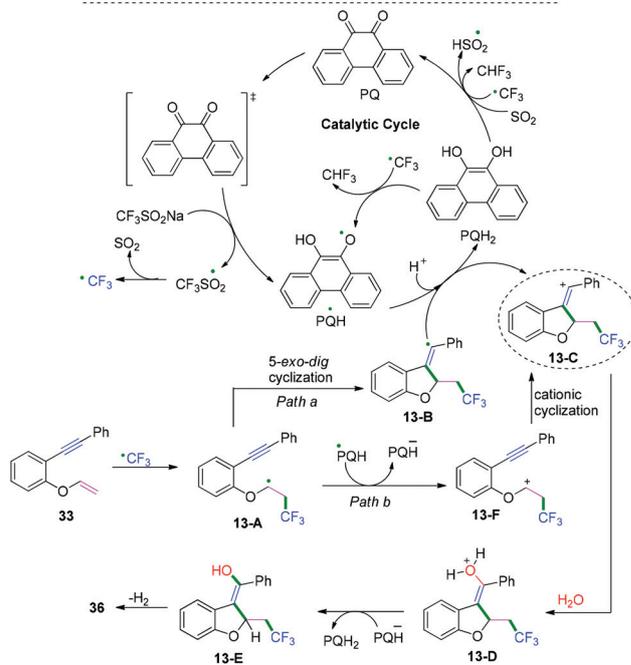
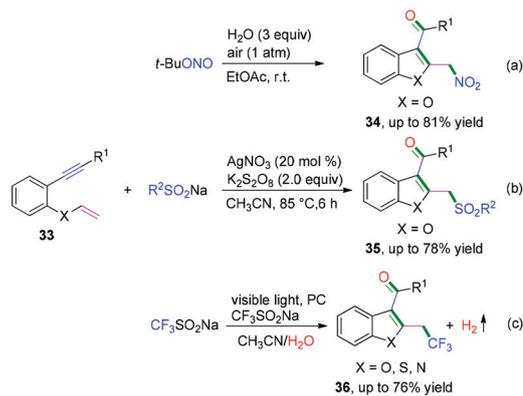


Scheme 18 Cascade radical cyclization of 1,6-enynes terminated with intermolecular radical cross-coupling.

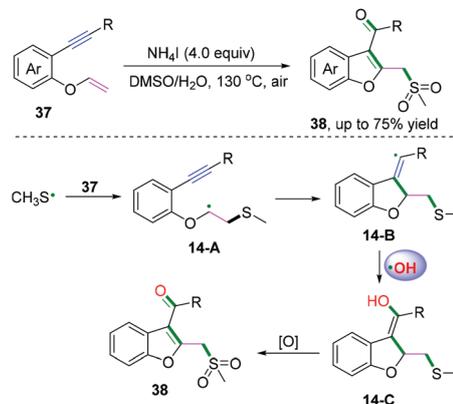
synthesize a series of functional-substituted C₃-aryloyl/acetylated benzofuran, benzothiophene, and indole compounds (Scheme 19).¹⁷ As demonstrated in Scheme 19c, Kumar and co-workers have realized visible-light-induced dehydrogenative cascade radical cyclization of 1,6-enynes with CF₃SO₂Na as the trifluoromethyl reagent and water as the oxygen source to synthesize a series of CF₃-substituted C₃-aryloyl/acetylated benzofuran, benzothiophene, and indole compounds (Scheme 19c).^{17c} The proposed mechanism showed that a single electron transfer process of CF₃SO₂Na was activated firstly to afford CF₃ radicals by photo-catalysis followed by regioselective radical addition to the double bond of 1,6-enynes, leading to the formation of alkyl carbon radical intermediates **13-A**. Subsequent 5-*exo-dig* cyclization of intermediates **13-A** afforded vinyl radical intermediates **13-B**, which underwent further electron transfer by photocatalysis to afford vinyl carbocation intermediates **13-C** and PQH₂. The existence of vinyl carbocation **13-C** with a high energy state and the photo-catalyst would facilitate the formation by the second electron-accepting process. Afterward, nucleophilic attack of the vinyl carbocation by H₂O and final oxidation of intermediates **13-E** achieved the desired products. An alternative pathway for the formation of vinyl carbocation **13-F** by an intramolecular cationic cyclization cannot be completely ruled out.

DMSO is one of the simplest starting materials used in organic chemistry. Liu, Sun, and co-workers extended the scope of cascade radical cyclization of oxygen-linked 1,6-enynes with DMSO to synthesize methylsulfonylated and carbonylated benzofurans (Scheme 20).^{17d} In this reaction, vinyl radical intermediates **14-B** were terminated by a hydroxyl radical coupling process to afford intermediates **14-C**, followed by further keto-enol tautomerism and thioether oxidation to furnish the final products. However, oxidation of **14-A** or **14-B** into the corresponding carbocations and trapping of the vinyl cation with a water molecule to afford **14-C** could not be ruled out.^{17b,c}

2.2.2 C(sp)-(hetero) aryl C(sp²) bond cyclization. *N*-Propargylindoles can act as efficient radical acceptors to



Scheme 19 Cascade radical cyclization of 1,6-enynes terminated with nucleophiles.

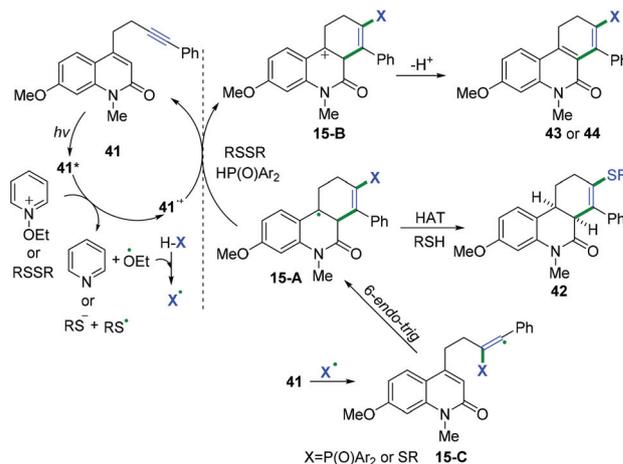


Scheme 20 Cascade radical cyclization of 1,6-enynes terminated with intermolecular radical cross-coupling.

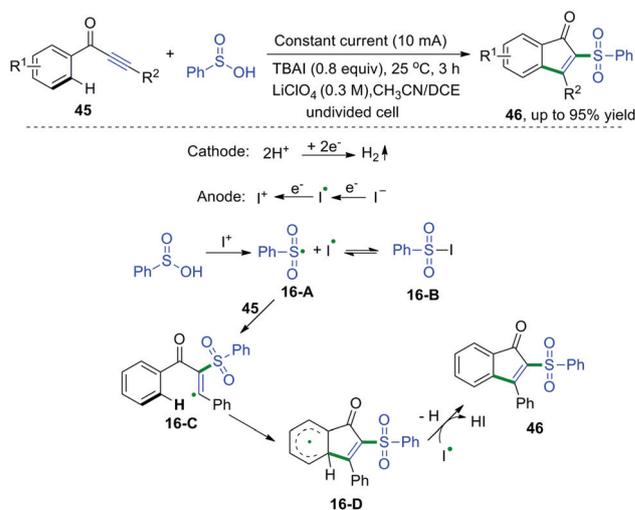
capture free radicals, such as S,¹⁸ P,¹⁹ sulfonyl,²⁰ and acyl-containing²¹ radicals, which proceed to cascade cyclization to access 2-functionalized pyrrolo[1,2-*a*]indoles (Scheme 21).

In 2019, Hong and co-workers achieved visible-light-induced radical cyclization of quinolinone-containing radical acceptors for the synthesis of a variety of dihydro- or tetrahydrophenanthridin-6(5*H*)-ones (Scheme 22).²² It was proposed that the reaction involved the initial generation of S- or P-centered radicals and a subsequent cascade radical addition/6-*endo-trig* cyclization/hydrogen atom transfer/electron transfer sequence (Scheme 23).

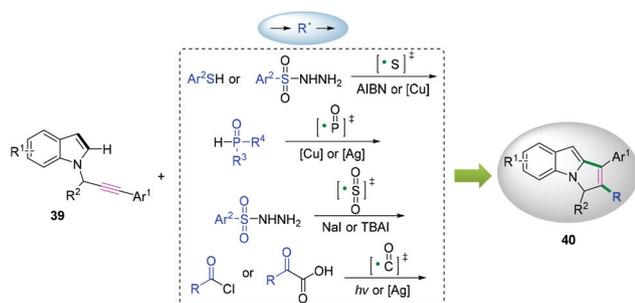
1,3-Diarylprop-2-yn-1-ones are fascinating scaffolds that have broad utility in organic chemistry. In 2017, electrooxidative cascade cyclization of 1,3-diarylprop-2-yn-1-ones with sulfonic acids was developed by Lei and co-workers (Scheme 24).²³ This synthetic method was successfully applied for the construction of a series of sulfonated indenones. The proposed mechanism showed that the I⁺ species was formed firstly *via* anodic oxidation of the iodide ion, followed by reaction with sulfonic acids to access sulfonyl radical species and iodine radicals. Subsequent radical addition of sulfonyl radicals to 1,3-diarylprop-2-yn-1-one afforded vinyl radical intermediates **16-C**. Then, intramolecular cyclization of intermediates **16-C** gen-



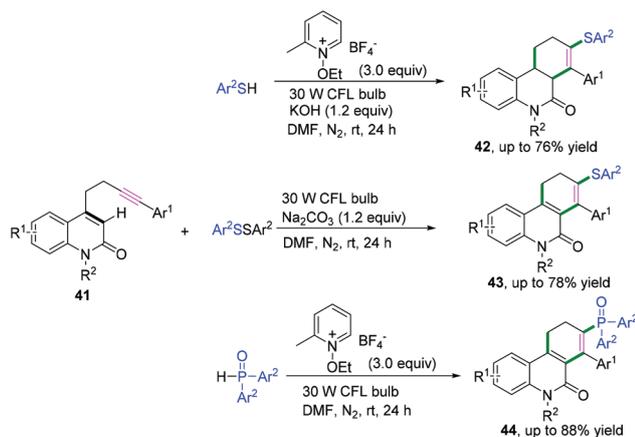
Scheme 23 Proposed mechanisms for the formation of **42–44**.



Scheme 24 Cascade radical cyclization of 1,3-diarylprop-2-yn-1-ones with sulfonic acids.



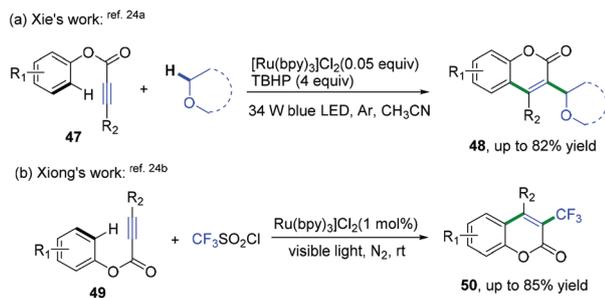
Scheme 21 Cascade radical cyclization of *N*-propargylindoles.



Scheme 22 Cascade radical cyclization of quinolinone-containing substrates.

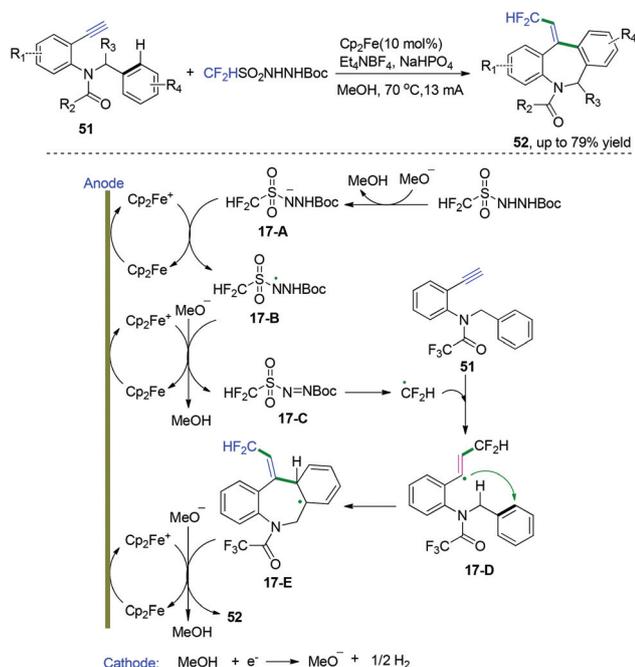
erated the radical intermediates **16-D**. The final oxidation of **16-D** finished the desired products.

Later, She, Xiong, and co-workers also realized domino radical cyclization of ester arylpropiolates to synthesize 3-substituted coumarin derivatives (Scheme 25).²⁴ As shown in Scheme 25a, a highly regioselective visible-light-promoted difunctionalization of ester arylpropiolates with an α -Csp³-H bond in ether derivatives to construct coumarins was achieved.^{24a} The key intermediate of this reaction is the formation of α -oxo radical species generated by photoredox-mediated oxidation of ethers. The cascade radical cyclization of ester 3-arylpropiolates with CF₃SO₂Cl as the trifluoromethyl radical source was also developed (Scheme 25b).^{24b} This reaction proceeded *via* a similar photo-catalytic mechanism of a cascade addition/dearomative cyclization/oxidation/aromatization process to afford a variety of 3-trifluoromethyl coumarins.



Scheme 25 Cascade radical cyclization of ester 3-arylpropiolates.

In 2018, Xu and co-workers developed an unprecedented electrochemical difluoromethylation of alkynes to construct fluorinated dibenzazepines (Scheme 26).²⁵ This protocol was performed with a new air-stable difluoromethylation reagent, $\text{CF}_2\text{HSO}_2\text{NHNHBoc}$, pre-synthesized from commercially available reagents $\text{CF}_2\text{HSO}_2\text{Cl}$ and NH_2NHBoc in one step. Based on their mechanistic research, they proposed a detailed catalytic cycle, as depicted in Scheme 26. Firstly, electrolytic anodic oxidation of Cp_2Fe would afford the Cp_2Fe^+ species, along with the reduction of MeOH to afford H_2 and MeO^- at the cathode. Subsequent oxidation of intermediates **17-A** and the conjugate base of $\text{CF}_2\text{HSO}_2\text{NHNHBoc}$ by Cp_2Fe^+ species generated diazene intermediates **17-C** *via* the intermediacy of *N*-radical intermediates **17-B**, followed by decomposition to generate CF_2H radical, which then reacted with the triple bonds in the alkynes to furnish the vinyl radical intermediates **17-D**. *C*-Radical intermediates **17-D** underwent the preferred *7-ortho* cyclization with the *N*-benzyl group to afford



Scheme 26 Electrochemical cascade radical cyclization of alkynes.

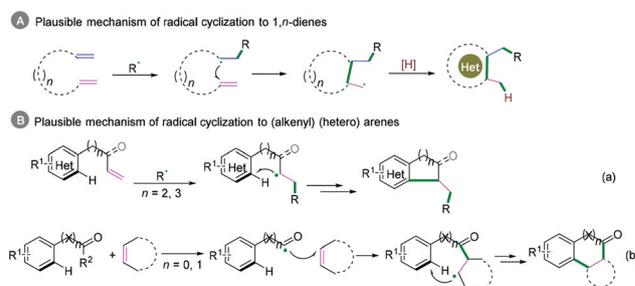
the radical intermediates **17-E** in a regio- and stereoselective manner. The *N*-benzyl group attacked the vinyl radical from the side away from the difluoromethyl substituent to avoid steric repulsion, leading to the *Z*-configuration of the trisubstituted alkenes in intermediates **17-E**. Final rearomatization of intermediates **17-E** through electron and proton elimination afforded the desired dibenzazepine products.

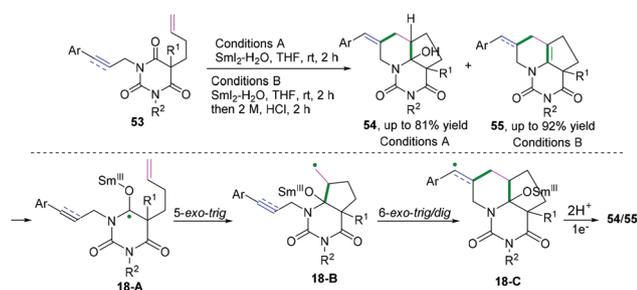
2.3 $\text{C}(\text{sp}^2)\text{-C}(\text{sp}^2)$ bond coupling cyclization

1,n-Dienes or alkenyl (hetero) arenes are also usual radical acceptors, which would benefit the construction of complex cycle structures *via* coupling cyclization reactions. In the past decades, many excellent xanthate-based cascade radical reactions to construct complex structures, as reported by Zard and coauthors, have been realized.²⁶ Due to the instability of radical intermediates, coupling cyclization of *1,n*-dienes is difficult to realize efficiently (Scheme 27A), while for the radical acceptors of alkenyl (hetero) arenes, the efficiency of the coupling cyclization reaction depends on whether the cyclization is intramolecular or intermolecular (Scheme 27B). Alkenyl (hetero) arenes usually act as radical acceptors with an activated terminal carbon-carbon double bond, which contributes to highly efficient intramolecular cyclization (Scheme 27B, a), while intermolecular cyclization is rarely realized efficiently owing to the higher energy barrier (Scheme 27B, b).

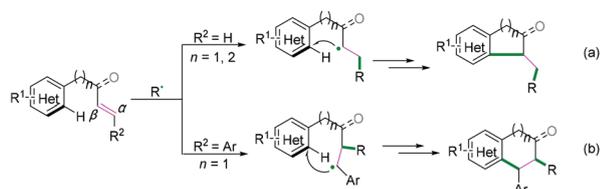
2.3.1 Alkenyl $\text{C}(\text{sp}^2)$ -alkenyl $\text{C}(\text{sp}^2)$ bond coupling cyclization. In 2016, Procter and co-workers achieved radical-radical cyclization cascades for the synthesis of hemiaminal- or enamine-containing tricyclic compounds with up to five contiguous stereo-centers (Scheme 28).²⁷ The transformation underwent an electron-transfer reduction of amide-type carbonyls by $\text{SmI}_2\text{-H}_2\text{O}$. The proposed mechanism suggested that LiBr had a beneficial effect on achieving highly efficient radical-radical cyclization cascades. According to the reaction mechanism, enyne **53** proceeded through *5-exo-trig* radical cyclization to afford radical intermediates **18-B**, followed by *6-exo-trig* cyclization to generate intermediates **18-C**. Further reduction and protonation delivered tricyclic hemiaminals **54** or the corresponding enamines **55** after a dehydration process.

2.3.2 Alkenyl $\text{C}(\text{sp}^2)$ -(hetero) aryl $\text{C}(\text{sp}^2)$ bond coupling cyclization

Scheme 27 Plausible mechanism of radical cyclization of *1,n*-dienes or (alkenyl) (hetero) arenes.



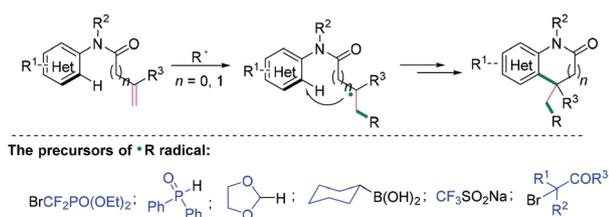
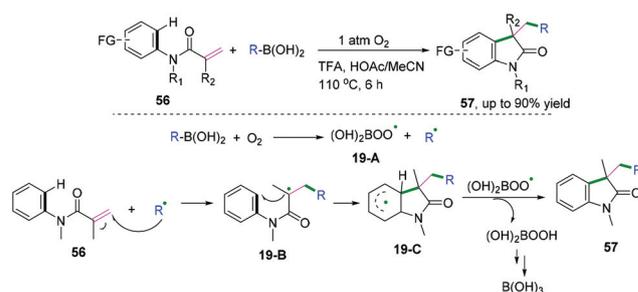
Scheme 28 Cascade radical cyclization of dienes/enynes.

Scheme 29 Intramolecular alkenyl C(sp²)-(hetero) aryl C(sp²) bond coupling cyclization.

Intramolecular cyclization. As demonstrated in Scheme 29, for radical acceptors of alkenyl (hetero) arenes, the order of priority of the attacking position of the carbon-carbon double bond depends on the type of R^2 substituent group (Scheme 29). When R^2 is H, the priority attacking position of the carbon-carbon double bond occurs at the α position (Scheme 29a), while it reacts at the β position for the aryl substitute; this may be due to the steric hindrance effect (Scheme 29b).

Functionalization of alkenyl *N*-arylamides with radical donors has become a more efficient and straightforward way to generate a variety of nitrogen heterocyclics. Radical cyclization of alkenyl *N*-arylamides with free radical precursors,^{28–34} such as $\text{BrCF}_2\text{PO}(\text{OEt})_2$,²⁸ diphenylphosphine oxide,²⁹ 1,3-dioxolane,³⁰ cyclohexylboronic acid,³¹ $\text{CF}_3\text{SO}_2\text{Na}$,³² and alkyl bromides,³³ finished the final alkenyl C(sp²)-(hetero) aryl C(sp²) bond construction (Scheme 30).

In 2018, Liu and co-workers demonstrated an efficient metal-free alkylation of *N*-arylacrylamides with organoboronic acid to access a wide range of medical and natural privileged scaffolds (Scheme 31).³¹ The control experimental results indi-

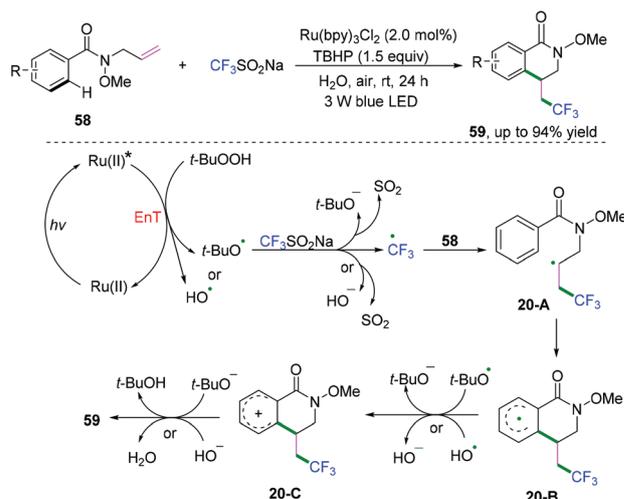
Scheme 30 Cascade radical cyclization of alkenyl *N*-arylamides with radical donors.

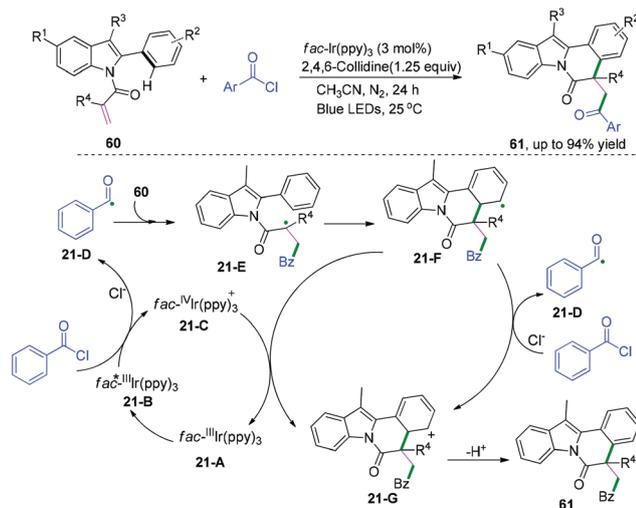
Scheme 31 Molecular oxygen-promoted radical alkylation with organoboronic acid.

cated that molecular oxygen was used as the terminal oxidant and that site-specificity was achieved. The proposed mechanism showed that radical **19-A** and alkyl radicals were generated initially from the reaction of boronic acid and molecular oxygen. Subsequent addition of the alkyl radical to the alkene followed by cyclization would afford radical intermediate **19-C**. Then, a hydrogen-atom transfer process from intermediate **19-C** to **19-A** furnished the desired product and peroxyboronic acid, leading finally to boric acid.

Later, Li, Wang, and coauthors reported a visible-light-induced method for cyclization of *N*-allylbenzamides with $\text{CF}_3\text{SO}_2\text{Na}$ to synthesize trifluoromethylated dihydroisoquinoline derivatives under mild and green reaction conditions (Scheme 32).³² Radical cyclization transformation was realized efficiently to access the desired products in high yields in water at room temperature.

Indolo[2,1-*a*]isoquinoline derivatives are fascinating scaffolds that are widely found in natural products and pharmaceuticals;³⁵ thus, they are attracting a wide range of attention in organic synthesis.^{36,37} Recently, visible-light-induced radical cascade transformation of 2-aryl indoles with acyl

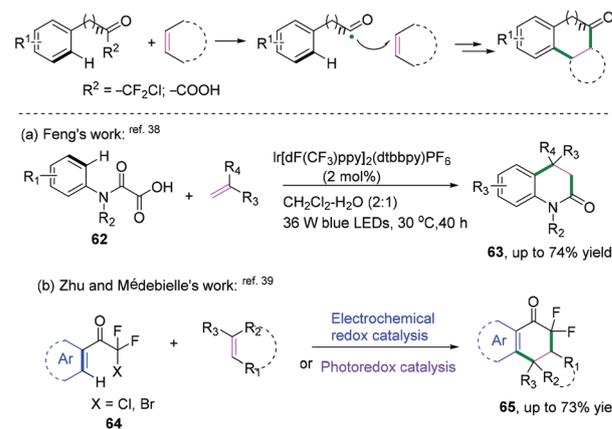
Scheme 32 Visible-light-induced radical cyclization of *N*-allylbenzamides with $\text{CF}_3\text{SO}_2\text{Na}$.



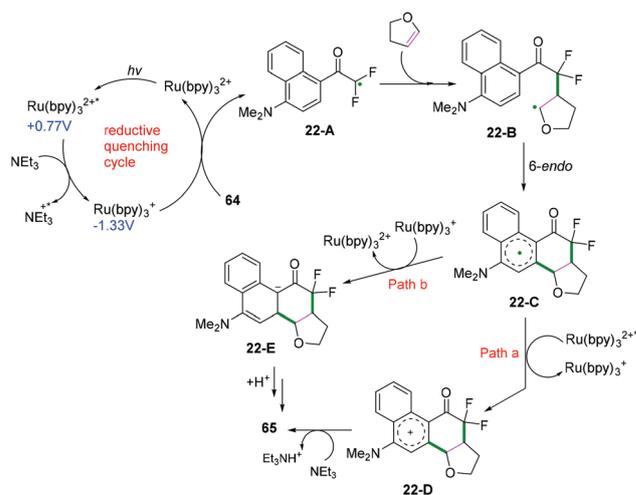
Scheme 33 Visible-light-induced radical cascade cyclization of 2-aryl indoles with acyl chlorides.

chlorides has been developed by Xu and co-workers (Scheme 33).³⁷ This redox-neutral reaction was successfully applied for the construction of a series of functionalized valuable indolo[2,1-*a*]isoquinoline derivatives. The transformation proceeded initially with the formation of acyl radical species **21-D** under the photo-catalytic cycle, followed by the addition reaction with 2-aryl indoles to afford a new α -acyl radical intermediate, **21-E**. Subsequently, the radical intermediate **21-F** was delivered *via* cyclization reaction of species **21-E**, and the further oxidation of species **21-F** afforded the cation intermediate **21-G** through a SET process with the oxidized photocatalyst $fac\text{-Ir}^{\text{IV}}(\text{ppy})_3$, regenerating the ground state photocatalyst $fac\text{-Ir}(\text{ppy})_3$ for the next new photocatalytic cycle; meanwhile, alternative oxidation of species **21-F** by benzoyl chloride to generate the cation **21-G** cannot be ruled out. The final rapid deprotonation of cation species **21-G** proceeded to regain its aromaticity and furnished the desired product.

Intermolecular cyclization. In addition to the aforementioned intermolecular cyclization, intermolecular cyclization of alkenes with aryl-substituted radical donors was an efficient synthetic strategy to construct (hetero)cycles. A highly photoredoxactive decarboxylation of oxamic acids was accomplished by Feng and co-workers (Scheme 34a).³⁸ The Zhu and Médebielle groups also realized the formation of cyclic gem-difluoroacyl scaffolds by intermolecular cyclization of alkenes with heteroaryl halogendifluoromethyl ketones (Scheme 34b).³⁹ As demonstrated in Scheme 35, the transformation was supposed to proceed firstly through a reductive quenching cycle for the formation of α,α -difluoroacyl radical intermediate **22-A**, followed by radical addition to 2,3-dihydrofuran to generate radical adduct **22-B**, which then underwent a subsequent 6-*endo* cyclization to afford a stabilized radical intermediate, **22-C**. Further oxidation and final deprotonation processes would afford the target product. An alternative pathway of further reduction and final protonation/aromatization would finish this transformation.



Scheme 34 Intermolecular cyclization of alkenes with aryl-substituted radical donors.



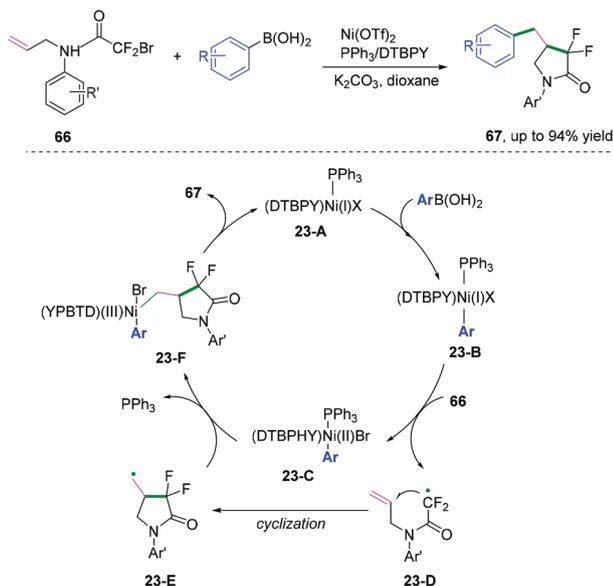
Scheme 35 Proposed mechanism for the formation of **65**.

2.4 C(sp²)-C(sp³) bond coupling cyclization

Compared with C(sp)-C(sp²) and C(sp²)-C(sp²) bond coupling cyclization, C(sp²)-C(sp³) cyclization is more challenging because the alkyl radical version to afford coupling cyclization has a higher energy barrier. In 2018, Mai, Lu, and co-workers developed a nickel-catalyzed radical cascade cyclization/arylation to access a series of 4-benzyl-3,3-difluoro- γ -lactam derivatives (Scheme 36).⁴⁰ The reaction was supposed to proceed through the formation of a primary alkyl radical generated from Ni(I) complex **23-B** initiated *via* a single electron transfer process. Further intermolecular Suzuki-type coupling cyclization afforded the desired product.

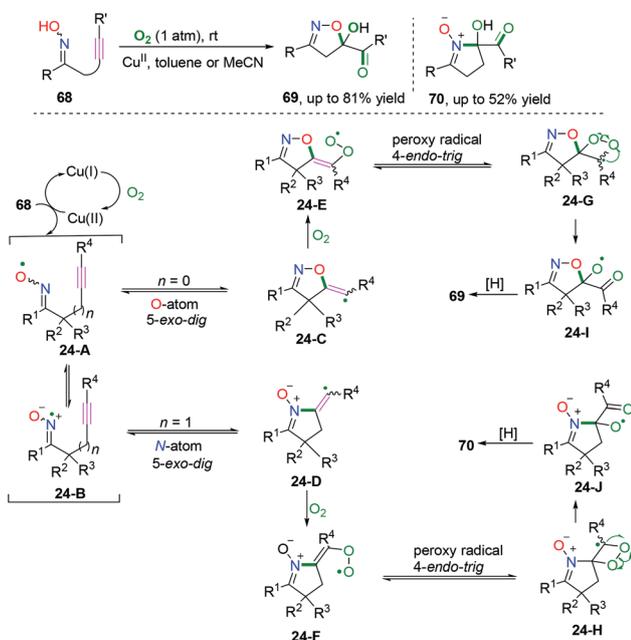
3. Carbon-heteroatom bond coupling cyclization

In addition to the aforementioned studies, carbon-heteroatom bond coupling cyclization initiated by heteroatom radicals is an efficient synthetic method to generate heterocycles.⁴¹

Scheme 36 Nickel-catalyzed C(sp²)-C(sp³) bond coupling cyclization.

3.1 C(sp)-Heteroatom bond

Alkyne-tethered ketoxime compounds can also serve as highly efficient radical acceptors to perform radical coupling cyclization, as reflected in the Cu-catalyzed dioxygen-activated cascade radical coupling reaction developed by Han and co-workers (Scheme 37).⁴² This transformation successfully accessed a range of isoxazoline/cyclic nitronone-featured α -ketols under mild conditions. A cascade iminoxyl radical dichotomous 5-*exo-dig* cyclization/oxygen activation/peroxy radical 4-



Scheme 37 Cu-catalyzed cascade radical reaction of alkyne-tethered ketoximes.

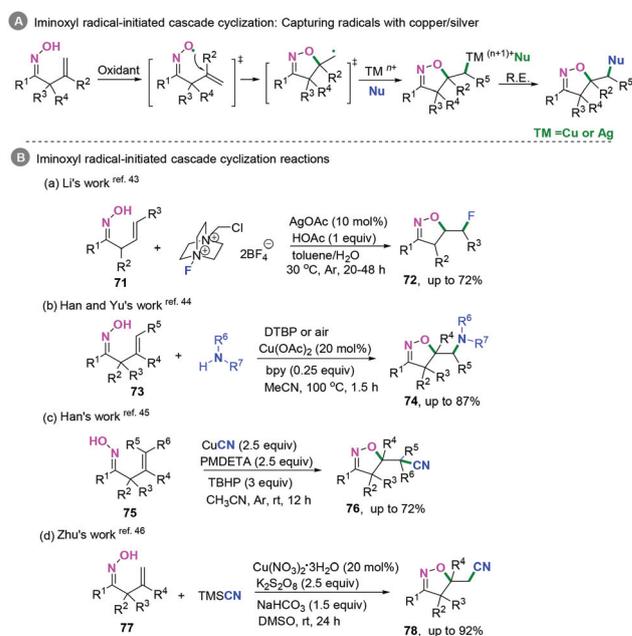
endo-trig cyclization process was proposed by ¹⁸O isotope tracing experiments and DFT calculations.

3.2 C(sp²)-Heteroatom bond

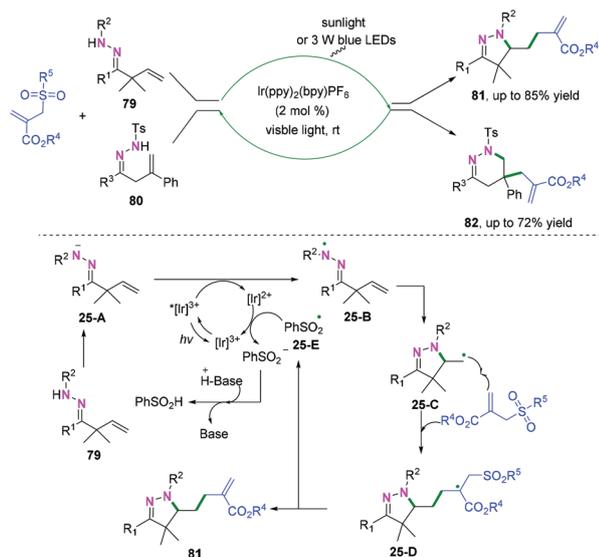
Recently, transition-metal catalyzed iminoxyl radical-initiated cyclization has been applied in realizing C(sp²)-heteroatom bond coupling cyclization.^{43–46} The general transition-metal catalyzed mechanism involves capturing the carbon-centered radical intermediates by TMⁿ⁺Nu to form high-valent transient TM⁽ⁿ⁺¹⁾⁺Nu species, followed by reductive elimination to afford the final products (Scheme 38A).

Additionally, photo-catalyzed hydrazonyl radical-mediated cyclization is an efficient strategy to realize C(sp²)-heteroatom bond coupling cyclization, as reported by Chen and coauthors (Scheme 39).⁴⁷ As demonstrated in Scheme 39, carbon-centered radical intermediates 25-C generated by hydrazonyl radical 25-B-initiated cyclization are selectively trapped by allyl sulfones to afford intermediate 25-D, followed by hemolytic fragmentation to access the final desired compounds with release of the sulfonyl radical 25-E. Finally, the sulfonyl radical intermediate 25-E undergoes further single-electron transfer reduction by the reducing [Ir(ppy)₂bpy]²⁺ species to afford the sulfonate anion and regenerate the ground state photocatalyst for the new photocatalytic cycle.

Our group also described palladium and photoredox-catalyzed oxy-/aminofluoroalkylative cascade radical cyclization of alkenes with available R₁-I reagents to generate fluoroalkylated 2,3-dihydrobenzofuran and indolin derivatives in good to excellent yields under mild conditions (Scheme 40).^{48,49} As shown in Scheme 40,⁴⁹ first, irradiation of the photocatalyst would lead to an excited-state adduct ^{*}fac-Ir(PPy)₃ 26-A, which



Scheme 38 Transition-metal catalyzed iminoxyl radical-initiated cyclization.

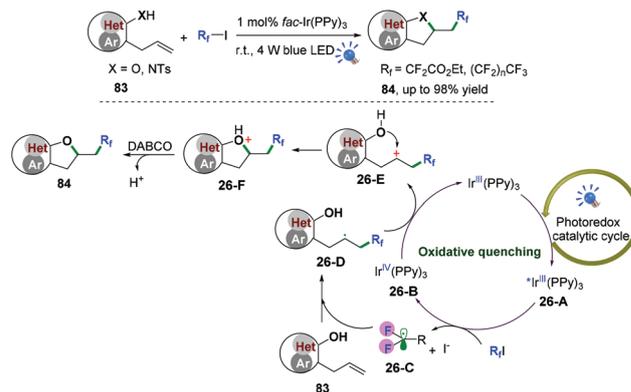


Scheme 39 Proposed mechanism for the formation of **81**.

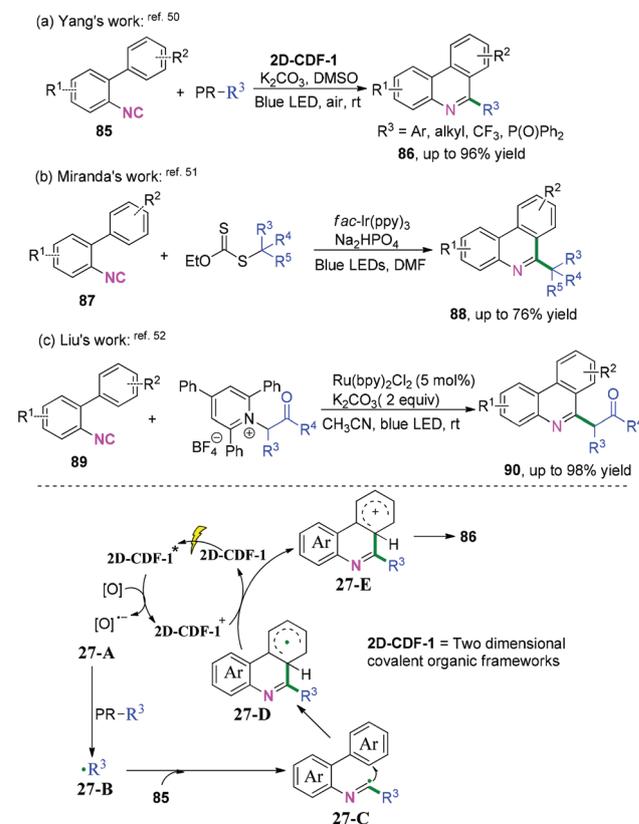
would then engage in electron transfer with fluoroalkyl iodide reagents (R_fI) to afford the fluoroalkyl radical species **26-C** and intermediates $fac\text{-Ir}^{\text{IV}}(\text{PPy})_3$ **26-B**. Subsequent radical addition of **26-C** to alkenes would generate the alkyl radicals **26-D**. Further oxidation of radical intermediates **26-D** with $fac\text{-Ir}^{\text{IV}}(\text{PPy})_3$ via a second SET process afforded the carbocation intermediates **26-E** and recycled the ground state $fac\text{-Ir}^{\text{III}}(\text{PPy})_3$ for the new catalytic cycle. A new C–O bond was then constructed via intramolecular 5-*exo-trig* cyclization to afford intermediates **26-F**. Final deprotonation with DABCO would deliver the desired cyclization products. Additionally, reaction of the intermediates **26-D** with iodofluoroalkane to form the corresponding secondary iodides followed by nucleophilic substitution cannot be ruled out for this reaction.

4. Miscellaneous examples

2-Substituted phenyl isocyanides have wide and extensive applications in nitrogen-containing synthesis.^{50–53} In a pioneering study published in 2019, Yang and co-workers developed a visible-light-induced cascade radical cyclization of 2-aryl phenyl isocyanides to construct varieties of 6-substituted phenanthridines (Scheme 41a).⁵⁰ This synthetic transformation proceeded through recyclable covalent organic frameworks (2D-COFs) reacting as photocatalysts. In light of the authors' recycling experiments, excellent recyclability of this organic framework photocatalyst was demonstrated. Later, Miranda and coauthors demonstrated a photocatalytic xanthate-based tandem radical cyclization of 2-biphenyl isocyanides for the construction of 6-alkylated phenanthridines (Scheme 41b).⁵¹ This transformation proceeded without a stoichiometric amount of oxidant in moderate yield under mild conditions. Liu and co-workers also reported an efficient visible-light-induced radical alkylation of isocyanides for the



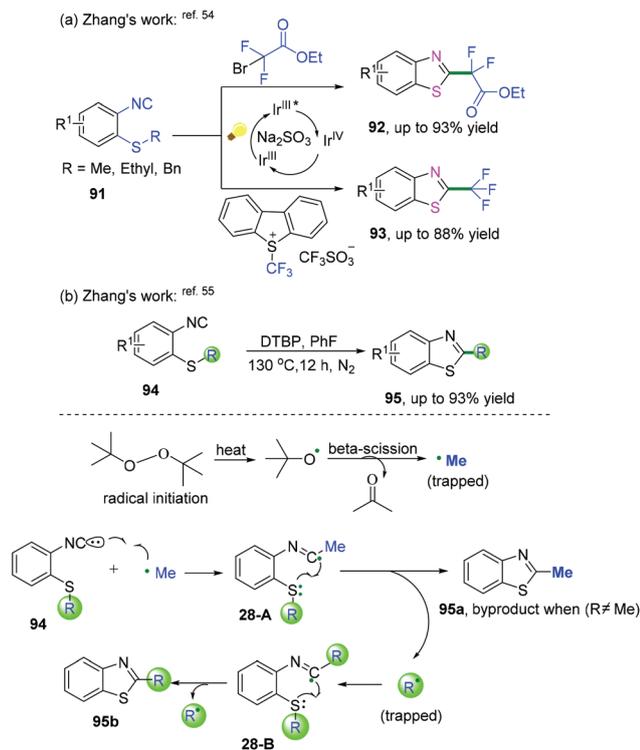
Scheme 40 Photoredox-catalyzed oxy-/aminofluoroalkylative cyclization of alkenes.



Scheme 41 Visible-light-induced cascade radical cyclization of 2-substituted phenyl isocyanides.

synthesis of 6-alkylated phenanthridines. In this transformation, available Katritzky pyridinium salts derived from amino acids/peptides were used as radical precursors (Scheme 41c).⁵²

2-Isocyanoyl thioether derivatives are highly valuable starting materials in organic chemistry. Zhang, Wu, and co-workers have further extended the radical cyclization of 2-isocyanoyl thioethers to synthesize benzothiazole derivatives (Scheme 42).^{54,55} The proposed mechanism showed that



Scheme 42 Cascade radical cyclization of 2-isocyanoaryl thioethers.

sodium sulfite participated in the photocatalytic cycle as a reductant, which benefited the transformation of Ir⁴⁺ into Ir³⁺ to perform the fluoroalkylation under mild reaction conditions (Scheme 42a).⁵⁴ Meanwhile, in the presence of *di-tert*-butyl peroxide, heat-induced homolytic dissociation of DTBP initially afforded a *tert*-butyl oxide radical, which then underwent β -scission to afford a methyl radical species. Further radical attack of the obtained methyl at the terminal carbon of the isocyano moiety delivered an imidoyl radical intermediate **28-A**, with subsequent cyclization to instantaneously afford 2-methylbenzothiazole **95a** with the release of R radical. The preferred *R*-substituted product was obtained *via* a similar pathway through intermediates **28-B** when the R group was not equal to the methyl group (Scheme 42b).⁵⁵

5. Conclusions and outlook

Cascade radical cyclization has emerged as a versatile and efficient tool for the rapid synthesis of high-value and complex carbo- and heterocycles, which has attracted considerable attention in synthetic organic chemistry. This Review highlights the latest advances in cascade radical cyclization of radical acceptors. A wide range of recent achievements in the development of cascade radical cyclization for the synthesis of carbo- and heterocycles have been investigated along with these areas. Different types of hybridization of the starting materials by coupling cyclization were categorized, including C(sp)²–C(sp), C(sp)²–C(sp²), C(sp²)–C(sp²), C(sp²)–C(sp³) bond

coupling cyclization and carbon–heteroatom bond (*e.g.*, C–O, C–N, C–S bond) coupling cyclization. For the C(sp)²–C(sp) and C(sp)²–C(sp²) bond coupling cyclization, 1,5-diyne (enynes) or 1,6-diyne (enynes) react as preferred efficient radical acceptors, which benefits the construction of five- or six-membered cycles with low energy barriers as well as the C(sp)²–(hetero) aryl C(sp²) and alkenyl C(sp²)–(hetero) aryl C(sp²) coupling cyclization. Additionally, for the reactions of C(sp)²–alkenyl C(sp²), C(sp)²–(hetero) aryl C(sp²), alkenyl C(sp²)–alkenyl C(sp²), and intramolecular alkenyl C(sp²)–(hetero) aryl C(sp²) bond cyclization, a radical acceptor with an activated terminal carbon–carbon double bond delivers high efficiency in cascade radical cyclization; this may be due to the high stability of the alkyl radical intermediate generated from radical addition to the double bond.

Despite the significant progress and extensive efforts that have been made in the past few years, several challenges remain to be addressed: (i) simple, available synthetic chemical feedstocks reacted as radical acceptors to construct carbo- and heterocycles instead of highly activated unsaturated substrates; (ii) controlled high chemo- and regioselectivity of radical species to realize excellent asymmetric synthesis; (iii) further exploitation of detailed and exact cascade radical cyclization mechanisms. We hope this Review will benefit readers who wish to exploit new protocols to construct various biological carbo- and heterocycles in the future.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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