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Radical C–H functionalization to construct heterocyclic compounds

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Heterocyclic compounds are widely present in natural products, pharmaceuticals and bioactive molecules. Thus, organic and pharmaceutical chemists have been making extensive efforts to construct those heterocyclic frameworks through developing versatile and efficient synthetic strategies. The direct C–H functionalization *via* the radical pathway has emerged as a promising and dramatic approach towards heterocycles with high atom- and step-economy. Heterocyclic compounds such as coumarins, furans, benzofurans, xanthones, benzothiazoles, indoles, indolines, oxindoles, quinolines, isoquinolines, quinoxaline, and phenanthridines have been successfully synthesized by C–H functionalization through the radical pathway. In this review, recent advances on radical C–H functionalization to construct heterocyclic compounds are highlighted with discussions.

1. Introduction

Heterocyclic compounds are widely spread in natural products and synthetic molecules and of immense important biologically as well as industrially. Their extreme importance is reflected in many aspects, while chief among them are their biological activities. The majority of pharmaceuticals and biologically active agrochemicals are heterocyclic compounds (take the 2015 Nobel molecules *Artemisinin* and *Abamectin*, for examples). Besides, countless additives and modifiers used in industries as varied as cosmetics, reprography, information storage and plastics are heterocyclic molecules. Therefore, organic chemists have been making extensive efforts to prepare these heterocyclic compounds by developing new and efficient synthetic transformations. For quite a long history, transition-metal catalyzed synthesis occupied a particular part in the generation of heterocyclic compounds.[1] Modern radical reactions, which emerged in the 1980s, have flourished recently. In light of the relatively mild reaction conditions and high atom economy, radical synthesis has become popular nowadays, and the radical cyclization provides a new avenue in the synthesis of a great number of heterocyclic compounds, such as coumarins, furans, benzofurans, xanthones, benzothiazoles, indoles, indolines, oxindoles, quinolines, isoquinolines, quinoxaline, and phenanthridines. In recent years, direct C–H bond functionalization, which successfully avoids the time and cost consuming prefunctionalizations, has been recognized as a reliable method to construct complex molecules due to high step- and atom-economy as well as the readily

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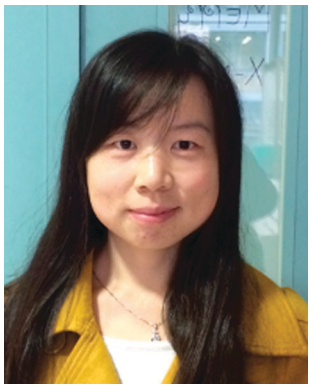

Jin-Tao Yu

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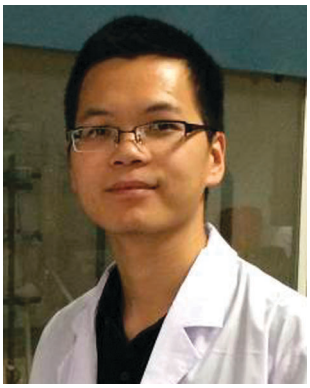

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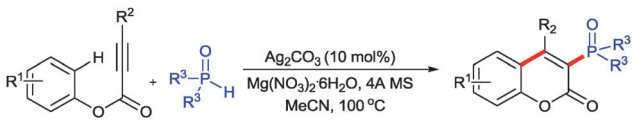
available starting materials.[2] A great number of extinguishing studies have been accomplished by talented chemists all over the world. This review focuses on the recent advances in the construction of heterocyclic compounds by radical C–H functionalization with or without metal catalysts. The scope and limitations of these cyclization reactions are discussed, as well as their mechanisms.

2. Radical cyclization towards coumarins

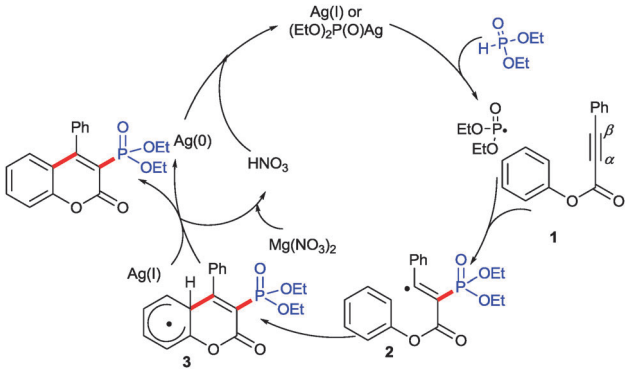
The coumarin skeleton is a core structure that widely occurs in natural products, biological molecules and dyes.[3] Traditional synthetic methods include the Pechmann reaction, Wittig reaction, and the Knoevenagel condensation. However, these protocols suffered from several drawbacks, such as inaccessible substrates and catalysts, tedious performance, hazardous reagents, low atom economy and limited substrate scopes. Recently, direct difunctionalization of readily synthesized alkynoates has been utilized as an efficient route to access coumarins.

Since aromatic organophosphorus compounds could be widely found in natural products, pharmaceuticals and materials,[4] the development of convenient C–P bond construction is crucial. P-centered radicals, which can be facilely generated from common radical initiators such as peroxides,[5] azo compounds,[6] and $Ag/K_2S_2O_8$,[7] are reliable intermediates in the construction of organophosphorus compounds. Regarding this, Wu developed the Ag_2CO_3-catalyzed sequential radical C–P/C–C coupling process for the synthesis of 3-phosphorated coumarins utilizing dialkyl *H*-phosphonates as P-radical precursors (Scheme 1).[8] Diverse dialkyl *H*-phosphonates as well as diphenylphosphine oxides are all suitable P-radical precursors to generate the desired products in moderate to good yields. The transformation is sensitive to steric hindrance. No product was detected using the substrate with a methyl group on the *ortho*-position of the phenoxy ring. The regioselectivity study using aryl alkynoates bearing a *meta*-substituted phenoxy ring showed that the cyclization preferably occurred at the position distal to the *meta*-substituent. It is worth noting that phenyl 2-octynoate is also a suitable reaction partner albeit in lower yield.

The reaction could be completely suppressed by the addition of the radical scavenger TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy), which indicates the presence of a radical intermediate. Mechanism studies showed that the P-radicals are generated from dialkyl *H*-phosphonates oxidized by Ag_2CO_3 or from the *in situ* generated $[R_2P(O)Ag]$. Accordingly, the radical cyclization mechanism is outlined in Scheme 2. Firstly, selectivity addition of the generated P-radical to the α-position of the C═O bond in alkynoates **1** gives



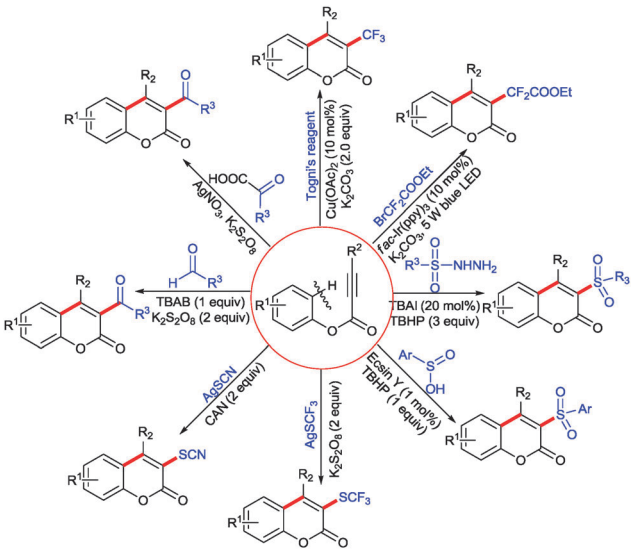
Scheme 1



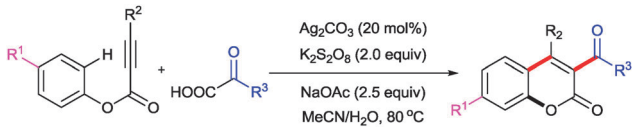
Scheme 2

vinyl radical **2**. Then **2** undergoes cyclization to generate intermediate **3**. Subsequently, a single-electron transfer (SET) from **3** to silver(I) releases the product along with HNO_3 and silver(0). Silver(0) could be oxidized to silver(I) by HNO_3 to complete the catalytic cycle.

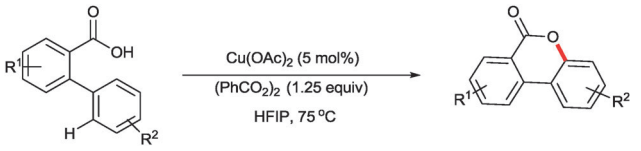
Afterwards, Wu and other groups reported a series of radical difunctionalization reactions of alkynoates, including radical trifluoromethylation/cyclization with Togni's reagent,[9] aryldifluoroacetylation/cyclization with ethyl bromodifluoroacetate,[10] arylsulfonylation/cyclization with arylsulfinic acids or sulfonyl hydrazides,[11] trifluoromethylthiolation and thiocyanation/cyclization with $AgSCF_3$ and AgSCN,[12] acylation/cyclization with aldehydes[13] and decarboxylation/cyclization with α-keto acids[14] to synthesize various coumarin derivatives (Scheme 3). The reaction pathway is similar to the phosphorylation/cyclization of alkynoates,[8] including (1) generation of carbon- or heteroatom-centered radicals *via* oxidation of external oxidants or photocatalysts; (2) selectivity addition of certain radicals to the α-position of the C═O bond in alkynoates to form the vinyl radical intermediate; (3) intramolecular radical cyclization to form another radical intermediate with a six-membered ring; (4) deprotonation and rearomatization to deliver the corresponding functionalized coumarin derivatives.



Scheme 3



Scheme 4



Scheme 6

Very interestingly, Qiu revealed that the oxidative radical cyclization of alkynoates with α-keto acids resulted in the isomeric structures rather than the above results when a catalytic amount of Ag_2CO_3 was used together with 2.5 equivalents of NaOAc as an additive (Scheme 4).[15] Thus, Qiu deduced that the transformation undergoes an unusual 5-*exo* annulation by the ester migration pathway. As illustrated in Scheme 5, silver-catalyzed decarboxylation of 2-phenyl-2-oxoacetic acid gives acyl radical **4**, which reacts with alkynoate **1** to generate intermediate **5**. The following 5-*exo* cyclization affords a spirocyclic species **6**, which is readily converted into intermediate 7 in the presence of an oxidant. Sequential ester migration and deprotonation yields the desired 3-acylcoumarin. The authors speculated that the discrepancy with Wu and other's results[8–14] is probably due to the relatively slow rate of acyl radical formation through the catalytic amount of silver-catalyzed decarboxylation which makes the concentration of intermediate **5** remain very low, such that the reaction proceeds through 5-*exo* cyclization to form intermediate **6** specifically. Alternatively, radical rearrangement of **6** to the radical form of **8** followed by oxidation and deprotonation to generate the coumarins is also possible.

As a special and important kind of coumarin, benzo-3,4-coumarin derivatives are widely found in natural bioactive compounds and frequently used in organic synthesis.[16] Thus, various methods have been discovered to synthesize those compounds. Among them, the C–H functionalization/C–O bond formation of 2-arylbenzoic acids through radical dehydrogenative lactonization proved to be efficient with high atom economy.

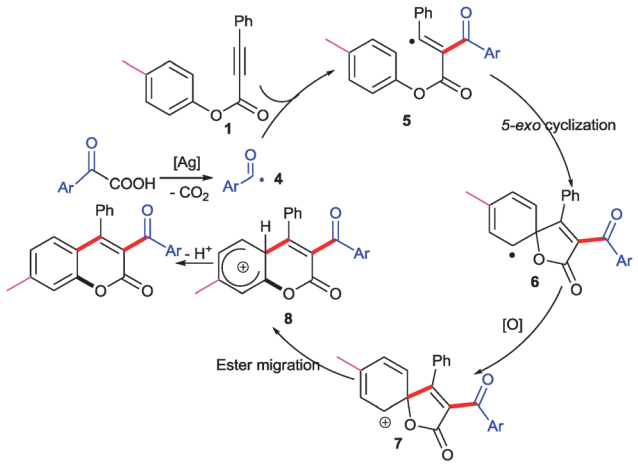
In the year 2013, Martin and Gevorgyan developed the $Cu(OAc)_2$-catalyzed remote C–H bond functionalization/lactonization of 2-arylbenzoic acids under the oxidation of $(PhCO_2)_2$ or $PhCO_2OtBu$, respectively (Schemes 6 and 7).[17,18] The reaction has broad substrate scopes and a host of benzoic acids could be transferred into their corresponding benzo-3,4-coumarins in good yields. In particular, this procedure is mild enough to tolerate benzyl alcohols.

The reaction pathway is listed in Scheme 8. An active Cu^{III} intermediate **9** is involved in the catalytic procedure, which abstracts the adjacent H atom to form aryl radical **10** (Path A). Upon oxidative ring closure **10′** is produced, followed by a reductive elimination to form coumarin products. Alternatively, a single-electron transfer (SET) process in **9** would give radical–cation species **11** (Path B), which would be transformed into coumarin by a subsequent C–O bond formation.

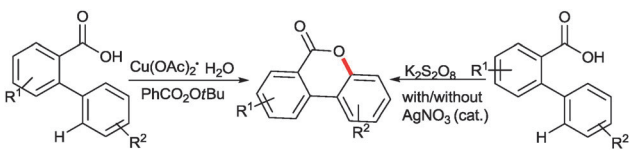
Gevorgyan also described his metal-free $K_2S_2O_8$-mediated lactionization procedure.[18] Where, benzoic acid is firstly oxidized to *O*-centered carboxylic radical **12**, which undergoes radical addition to the arene ring to form aryl radical intermediate **13** (Scheme 9, Path A). **13** then converts into the benzocoumarin product upon loss of a H atom. The alternative mechanism involving abstraction of a hydrogen radical from the aromatic ring of **12** to form the aryl radical **14** cannot be ruled out at this stage (Scheme 9, Path B). The mechanism is supported by experiments on cyclization of substrates containing 2-haloaryl substituents, where dehalocoupling is involved without the detection of possible halo-containing C–H coupling products.

One year later, Martin developed another more practical procedure to accomplish the $C(sp^2)$–H functionalization/C–O formation of 2-arylbenzoic acids using *in situ* generated I^{III} as a catalyst with AcOOH as the oxidant (Scheme 10).[19] This procedure is more user-friendly that occurred under mild organo-catalyzed metal-free conditions, and can be carried out in air. Compared with the copper-catalyzed protocol,[17,18] this reaction has wide substrate scope with high site-selectivity. Interestingly, for 3′-methoxybiphenyl-2-carboxylic acid analogues, the site-selectivity could be switched by the selection of appropriate catalysts as well as the amount of AcOOH used. Thus, an incipient positive charge is generated on the electron-rich aromatic ring, thus triggering a [1,2]-aryl shift.

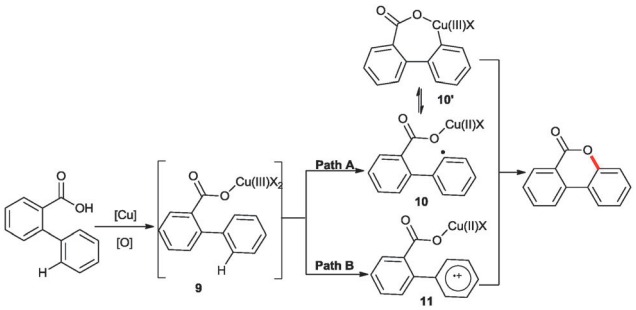
When phenyl or electron-poor aromatic frameworks are employed, the *in situ* generated hypervalent iodine(III) reagent triggers the formation of an acyloxy radical that subsequently promotes the cyclization event. However, the hypervalent iodine(III) reagent might initiate the formation of a radical cation with an



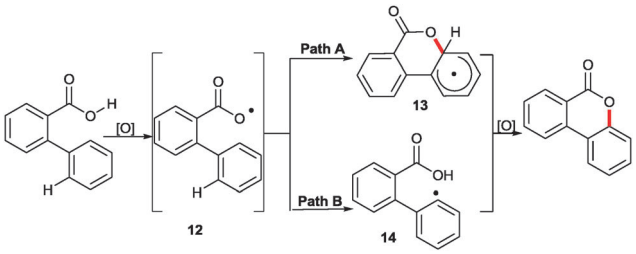
Scheme 5



Scheme 7



Scheme 8



Scheme 9

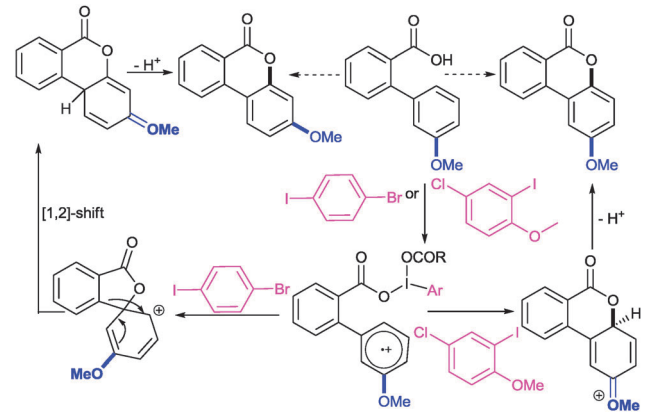
electron-rich aromatic motif that facilitates the addition of the incoming carboxylic acid motif. Thus after the [1,2]-aryl shift, the site-selective isomer is formed (Scheme 11).

Using inexpensive $AgNO_3$ as the catalyst and environmentally friendly $(NH_4)_2S_2O_8$ as the oxidant, Xu's group gave an alternatively efficient protocol to realize such transformation (Scheme 12).[20] The reaction conducted at room temperature in an open flask and is scalable without the loss of efficiency. Various lactones were obtained in good to excellent yields with high chemoselectivity. It is worth noting that 2-arylbenzoic acids bearing an unprotected OH group as well as terminal alkene are all well tolerated. The kinetic isotope effect (KIE) study showed that the cleavage of the aryl C–H bond is not the rate determining step and the carboxyl radical would be the intermediate. After sequential radical cyclization, one-electron oxidation together with deprotonation, the final product is obtained (Scheme 12).

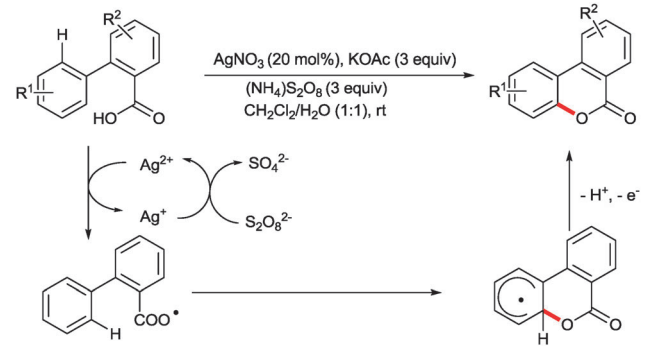
Very recently, Gonzalez-Gomez and coworkers developed the first visible-light-induced photoredox catalyzed synthesis of benzo-3,4-coumarins.[21] In this transformation 9-mesityl-10-methylacridinium perchlorate ([Acr-Mes]ClO_4) was selected as the appropriate photocatalyst for its strong oxidability in the excited state ($E_{1/2\,red}$ = +2.08 V *vs.* SCE).

The mechanism study showed that, in the absence of light or photocatalyst, as well as in the presence of TEMPO (1 equiv.),

Scheme 10



Scheme 11

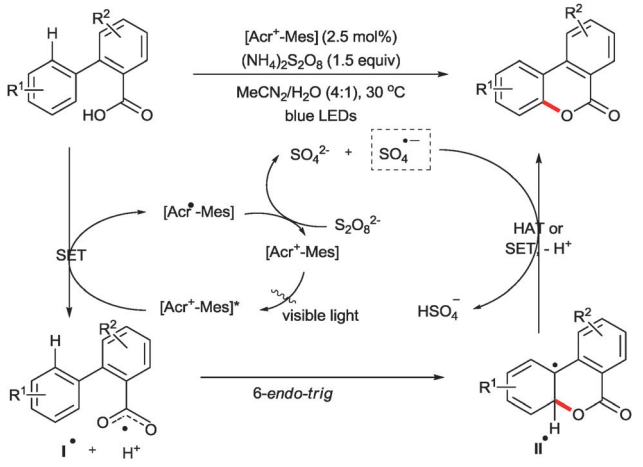


Scheme 12

the reaction was completely inhibited. Thus, a radical pathway is most likely involved. Firstly, the activated photocatalyst generates benzoyloxy radical **I•** *via* single electron transfer (SET). Afterwards, 6-*endo-trig* cyclization of **I•** gives intermediate **II•**, which is finally oxidized to afford the product *via* hydrogen atom abstraction (HAT) or SET/deprotonation processes (Scheme 13).

3 Radical cyclization towards furans and benzofurans

Furans and related 5-membered cyclic ethers are common structural motifs in many natural products and pharmaceuticals.[22] Among the various synthetic strategies, radical insertion in alkenes has attracted particular attention in the construction of those compounds. Utilizing readily available phenols as bis-nucleophiles and the olefins as linkers, the synthesis of dihydrobenzofurans was achieved through the $FeCl_3$-catalyzed oxidative radical cross-coupling/cyclization process by Lei and coworkers (Scheme 14).[23] This reaction has wide substrate scope, as phenols with various substituents, alkyl or aryl olefins are all well tolerated providing the corresponding dihydrobenzofurans in good yields. Mechanism studies showed that the transformation could not occur without 2,3-dichloro-5,6-dicyano-1,4-benzoqinone (DDQ) or in the presence of TEMPO.



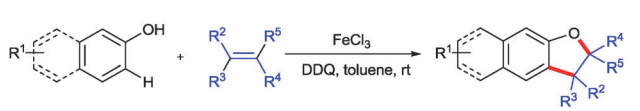
Scheme 13

Electron paramagnetic resonance (EPR) and operando IR experiments showed that DDQ is the vital oxidant in the initiating step and $FeCl_3$ works as a Lewis acid in the transformation.

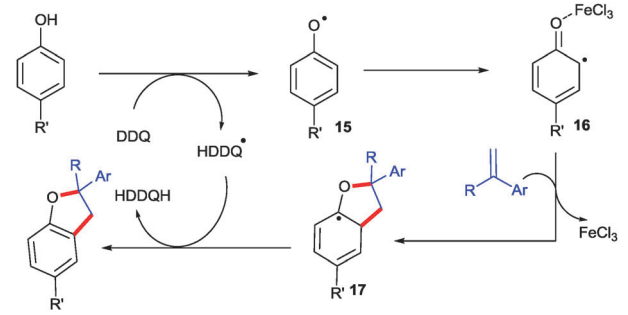
A proposed mechanism is outlined in Scheme 15. Firstly, phenol is oxidized by DDQ to produce the phenol radical **15** and the HDDQ radical. The enol form of **15** is stabilized by $FeCl_3$ and the radical transfers from an *O*-radical to a *C*-radical in **16**. Subsequently, the radical addition of **16** with alkenes produces the intermediate **17**. Finally, after releasing a hydrogen radical, dihydrobenzofuran is produced. In this transformation, the role of $FeCl_3$ is to coordinate with the *O*-atom thus stabilize the *C*-radical and increase the activity of radical **16** to react with alkenes and guarantees the high selectivity towards the oxidative cross-product.

Other alkene analogues, such as enamides, can also be utilized to generate dihydrofurans. For example, Li reported Mn(III)-mediated direct oxidative coupling of α-aryl enamides with 1,3-dicarbonyl compounds to construct dihydrofurans (Scheme 16).[24] Initially, an electron-deficient radical **18** is generated from the 1,3-dicarbonyl compound catalyzed by $Mn(OAc)_3$. **18** is then added to the electron-rich enamides to afford radical **19** which can be further oxidized by $Mn(OAc)_3$ to carbocation **20** or iminium ion **21**, which undergoes cyclization/deprotonation to give the desired dihydrofurans (Scheme 17). This procedure can tolerate a variety of α-aryl enamides and 1,3-dicarbonyl substrates and can scale up without the loss of efficiency. Owing to the easy leaving property of amides, corresponding furans and pyrroles can be generated *via* the Paal–Knorr reaction from those dihydrofuran products.

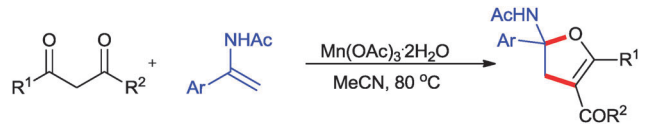
Regarding the synthesis of polysubstituted furans, one of the most powerful methodologies is the oxidative C–H/C–H functionalization of 1,3-dicarbonyl compounds with terminal alkynes catalyzed by transition-metals.[25] While, thanks to the



Scheme 14



Scheme 15

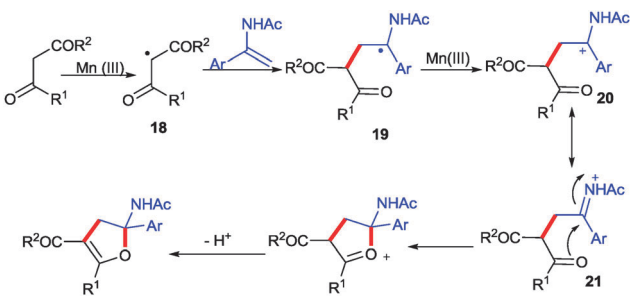


Scheme 16

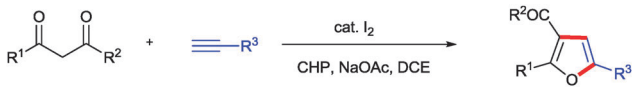
rapid development of radical chemistry, such transformations can also undergo the radical pathway. Using molecular iodine as the efficient catalyst, oxidative C(sp^3)–H/C(sp)–H bond cross-coupling between terminal alkynes and β-keto esters was achieved, providing a variety of furans in good yields (Scheme 18).[26] Different β-keto esters, aryl and alkyl alkynes are all suitable for this transformation, while 1,3-diketones are too active to generate the desired products. Mechanism studies revealed that the α-C(sp^3)–H iodination product is the key intermediate which is proved by NMR experiments. Isotope labelling and radical inhibition experiments all supported the radical addition/cyclization reaction pathway. DFT calculations showed that HI elimination is likely to be involved.

Based on those experimental results, Lei proposed the reaction mechanism (Scheme 19): firstly, oxidation of **22** by the *in situ* generated hypoiodite (I^+) forms **23**. Then, carbon radical **24** is formed under heating. Next, the radical addition of **24** to alkyne gives the olefinic carbon radical **25**. Subsequent intramolecular radical addition to a C–O double bond generates hydrofuran radical intermediate **26**. Finally, **26** is further oxidized to furnish the final product.

Despite terminal alkynes, electron-deficient disubstituted internal acetylenes can also act as efficient linkers in the construction of furan motifs. Recently, Antonchick described



Scheme 17

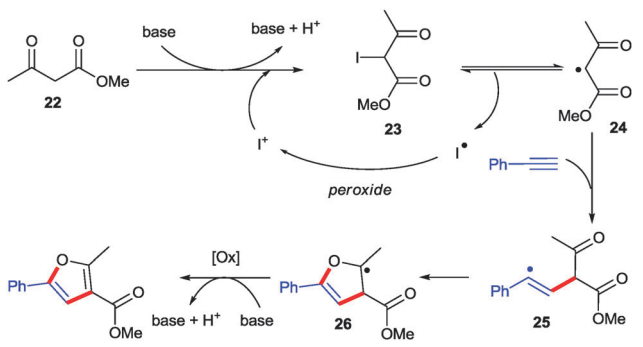


Scheme 18

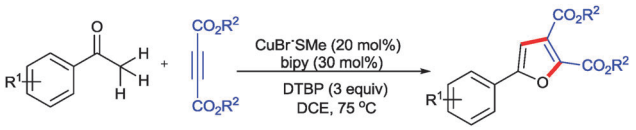
a novel procedure for the synthesis of multisubstituted furans from readily available acetophenones and electron-deficient internal alkynes *via* direct C(sp^3)–H bond functionalization under the catalysis of Cu(I) salts with di-*tert*-butyl (DTBP) peroxide as an external oxidant (Scheme 20).[27] Various aryl methyl ketones and a series of alkyl acetylenedicarboxylates worked smoothly to deliver the corresponding furans in moderate to good yields. Unfortunately, electron-rich aryl ketones were not well tolerated.

A large kinetic isotope effect ($k_H/k_D \approx 4.5$) was observed, indicating that the abstraction of at least one hydrogen from acetophenone is the rate-determining step. Mechanism studies strongly suggest that a radical pathway is involved. Thus, the reaction goes like this: firstly, copper(I) was oxidized to the reactive copper(II) species by DTBP. Then, radical **27** is generated *via* oxidation of the enol form of acetophenone by copper(II). In an alternative mechanism, Cu(I) reacts with DTBP to produce Cu(II)O*t*Bu and *t*BuO$^\bullet$, which abstracts the α-H of acetophenone to generate acyl radical **27** and *t*BuOH. A subsequent attack of radical **27** on alkyne gives intermediate **28**, which leads to intermediate **29** after the oxidative addition of copper(II). Ligand exchange of intermediate **30** (enol form of **29**) produces metallocycle **31**. Finally, the furan product is obtained after reductive elimination and copper(I) is released to complete the catalytic cycle (Scheme 21). This protocol is highly practical by utilizing easily available starting materials that used without preliminary functionalizations.

Quite recently, Cheng developed a more sustainable procedure by employing diethylene glycol as cheap and environmentally friendly ethyne equivalent to synthesise 2,3-disubstituted furans (Scheme 22).[28] Using *tert*-butyl peroxide (TBHP) as the oxidant, this copper(II)-catalyzed cyclization of 1,3-dicarbonyl compounds coupled with diethylene glycol involves a sequential *O*- and *C*-functionalization process. Delightly, the substrate scope is not limited to phenylacetoacetic acid esters, as ketone, amide, and thioester analogues all worked well under the standard procedure and generated the corresponding furans in moderate to good yields.



Scheme 19

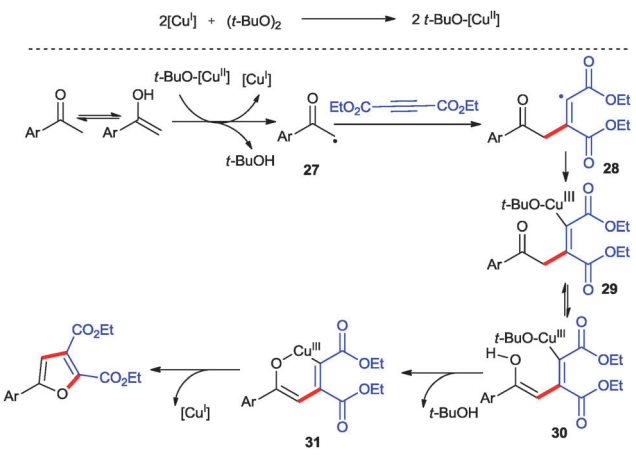


Scheme 20

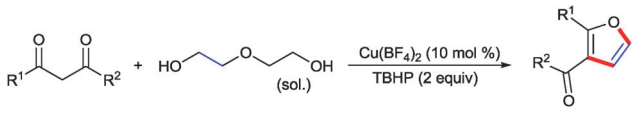
The reaction pathway is outlined in Scheme 23. Firstly, the α-functionalization of diethylene glycol takes place at the *O* atom in the β-ketoester and produces intermediate **32**, along with the loss of H_2O. A radical pathway may be involved in this step, which is confirmed by the radical scavenger experiment. After that, the *C*-functionalization occurs at the α′-position of intermediate **32** affording intermediate **33**. Finally, the elimination of 1 equiv. of glycol constructs the framework of furan. This procedure features with the application of diethylene glycol as a sustainable substrate with the release of H_2O and glycol as clean by-products and represents a sustainable pathway to access 2,3-disubstituted furans.

4. Radical cyclization towards xanthones

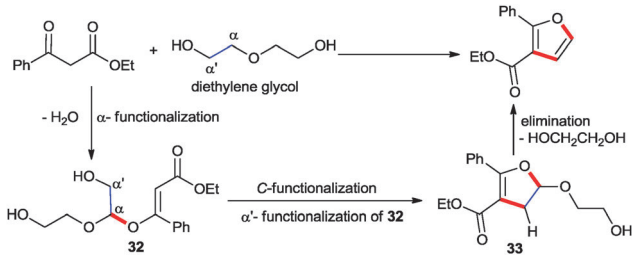
Xanthones are the core structures of many naturally occurring and pharmaceutically important compounds that have exhibited extraordinary biological activities (*e.g.*, anticancer, antioxidant, and antibacterial).[29] Thus, the construction of xanthone skeletons has attracted considerable interest. Cross-dehydrogenative coupling (CDC) where prefunctionalization of the substrates is not necessary has emerged as an atom economic approach in the area of xanthone synthesis. In the year 2013, Studer developed an efficient protocol for the construction of xanthones *via* the radical CDC process (Scheme 24).[30] In this procedure, $FeCp_2$ initiated, base-promoted homolytic aromatic substitutions of readily available *ortho*-formyl biphenylethers were involved and a series of xanthones were obtained in moderate to good yields. Electronic effects are not obvious in this transformation, substrates bearing electron-donating and -withdrawing substituents at the *para*-position of the radical



Scheme 21



Scheme 22



Scheme 23

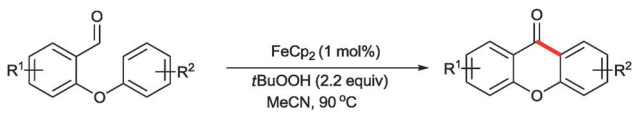
accepting arenes afforded similar yields, while the *meta*-methyl derivative gave two regioisomeric xanthones.

The reaction pathway is outlined in Scheme 25. Initially, reducing *t*BuOOH with Fe(II) gives the *tert*-butoxyl radical along with an Fe(III)-complex. *t*BuO• then abstracts the H-atom from the aldehyde to generate acyl radical **34** which attacks the arene to form the cyclohexadienyl radical **35**. Deprotonation with the basic hydroxide anion leads to the biaryl radical anion **34**. **34** then reduces *t*BuOOH through SET to provide xanthones and the chain propagating *t*BuO• along with the basic hydroxide anion.

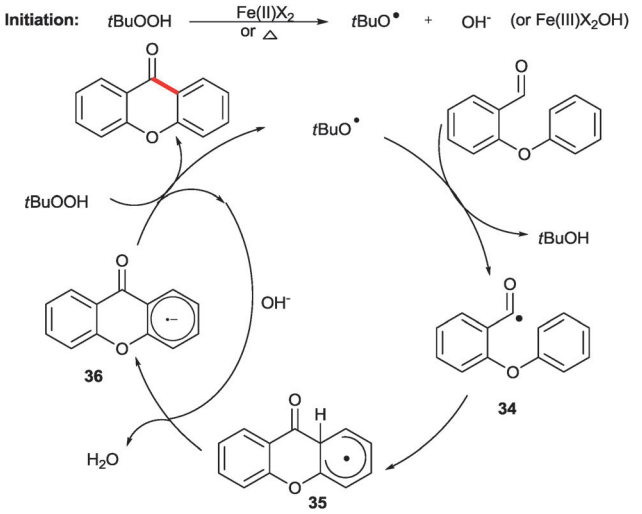
Subsequently, Rao and Li disclosed another metal-free CDC procedure to achieve the construction of xanthones *via* radical annulation of 2-aryloxybenzaldehydes using *tert*-butylammonium bromide (TBAB) as a promoter in aqueous medium (Scheme 26).[31] This strategy involves the oxidative coupling of the aldehyde C–H bond/aromatic C–H bond and displays excellent functional group tolerance. In particular, the aldehyde C–H bond selectively couples with the 2-phenoxy part of 2-(4′-phenoxyphenoxy)-benzaldehyde while leaving the 4′-phenoxy part intact, which indicates that the oxidative coupling protocol favours the intramolecular route. In addition, thioxanthones could be facially obtained using this procedure thus further expanding the substrate scopes.

5. Radical cyclization towards benzothiazoles

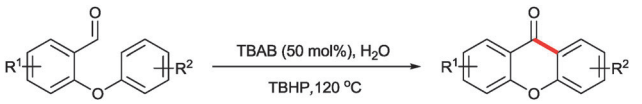
Benzothiazoles are an important class of bicyclic privileged substructures owing to their potent utility as imaging agents for β-amyloid, antitumor agents, calcium channel antagonists, antituberculotics, chemiluminescent agents, and also as photosensitizers.[32] Traditionally, arylbenzthiazoles are synthesized



Scheme 24



Scheme 25



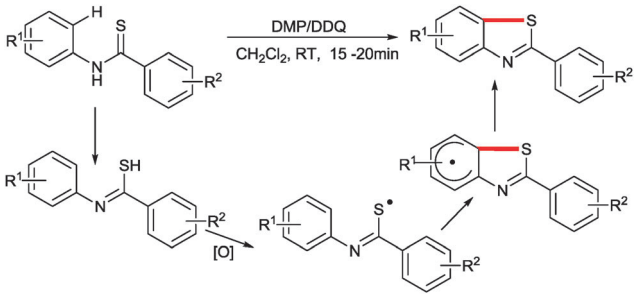
Scheme 26

via two major routes: condensation of *o*-aminothiophenols with substituted nitriles, aldehydes, carboxylic acids, acyl chlorides, esters, *etc.*[33] or through Jacobson's cyclization of thiobenzanilides.[34] In 1991, Bowman developed the radical reductive cyclization of iodothioamides using Bu_3SnH both as an initiator and a base.[35]

Later on, Zou and Bose's group developed the intramolecular C–H functionalization of thioformanilides to generate benzothiazoles catalyzed by Dess–Martin periodinane (DMP) or 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), respectively (Scheme 27).[36] The reaction was conducted in CH_2Cl_2 at room temperature for a short period of time with excellent yields. A plausible mechanism of the DMP/DDQ promoted cyclization reaction is presented in Scheme 27. The role of the catalyst is to abstract a H atom from thioiminol. Subsequent radical cyclization of the thiyl radical followed by aromatization gives 2-arylbenzothiazole.

In early 2012, Lei and co-workers developed a mild protocol of the Fe-catalyzed direct C–H oxidative cross-coupling procedure to construct benzothiazoles (Scheme 28).[37] The reaction has broad substrate scopes and a series of 2-aryl benzothiazoles were obtained using a standard procedure. The substituent on the aryl group of the thiobenzoyl part has little influence on the transformation and generates benzothiazoles in good to excellent yields except for strong electron-withdrawing groups as NO_2 only gives moderate yield. Moreover, *N*-aryl alkylthioamides and thiourea could also undergo the C–H activation/C–S bond formation to generate the corresponding products in moderate to excellent yields (71–92%). However, *N*-phenyl alkylthioamides bearing a less hindered substituted group give lower yields (R = benzyl) or no reaction at all (R = Me).

To gain insights into the mechanism, the authors carried out a lot of control experiments: isotopic effect experiments

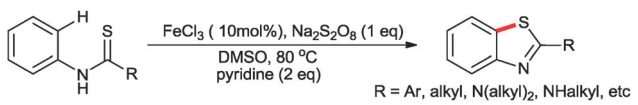


Scheme 27

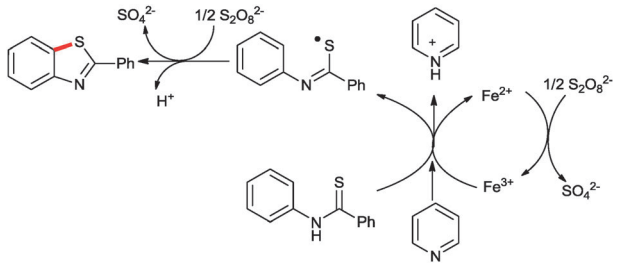
showed that the C–H bond cleavage is not the rate-determining-step and the radical scavenger (TEMPO) could obviously inhibit the reaction, which indicated the presence of the radical intermediate. Kinetic investigation showed that the reaction was first order in [thioamide], and zero order in the oxidant [$Na_2S_2O_8$]. The *in situ* IR showed that pyridine is crucial for the high selectivity of C–H activation/C–S bond formation. Based on those experimental results, the authors proposed a mechanism shown in Scheme 29. Firstly, *N*-phenyl benzothioamide is oxidized by Fe(III) to form the thiyl radical intermediate by losing an electron and a H^+ and Fe(III) is reduced to Fe(II) which is re-oxidized by $Na_2S_2O_8$ to regenerate Fe(III). Then, intramolecular cyclization of the thiyl radical intermediate followed by oxidation in the presence of $Na_2S_2O_8$ gives the desired 2-phenyl benzothiazole product.

Almost at the same time, Li reported an aerobic visible-light induced photoredox catalytic formation of 2-substituted benzothiazole through radical cyclization of thioanilides with no direct metal involvement except the sensitizer (Scheme 30).[38] $Ru(bpy)_3Cl_2{\cdot}6H_2O$ was used as the photoredox catalyst, and the reaction was conducted under a household 14 W fluorescence light with DBU as the base at rt. This mild procedure tolerates many functional groups as well as the oxidation-sensitive thioether. Besides, the *ortho*-selective arylation results strongly suggest that the reaction goes through a radical pathway. The intramolecular isotope effect (k_H/k_D = 5) suggesting that the C–H bond cleavage is the rate-determining step.

The plausible mechanism is listed in Scheme 31. Firstly, $Ru(bpy)_3^{2+}$ accepts a photon to generate the excited $^*Ru(bpy)_3^{2+}$. Subsequently, $^*Ru(bpy)_3^{2+}$ is oxidized to $Ru(bpy)_3^{3+}$ by molecular oxygen together with the formation of an $O_2^{\bullet-}$ radical anion. On the other hand, thioanilide is deprotonated to form a thioyl anion and immediately reduced to a radical through single electron transfer (SET). The thiyl radical attacks the benzene ring to form intermediate **37**. Upon giving away a hydrogen atom to $O_2^{\bullet-}$, radical **37** rearomatizes to provide benzothiazole and completes the reaction. However, a reductive quenching mechanism, in which $^*Ru(bpy)_3^{2+}$ is reduced to $Ru(bpy)_3^{+}$ by the thioyl anion to form the thiyl radical intermediate, and then molecular oxygen



Scheme 28

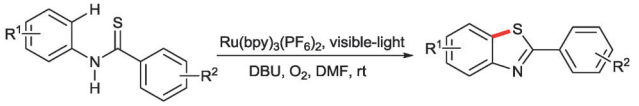


Scheme 29

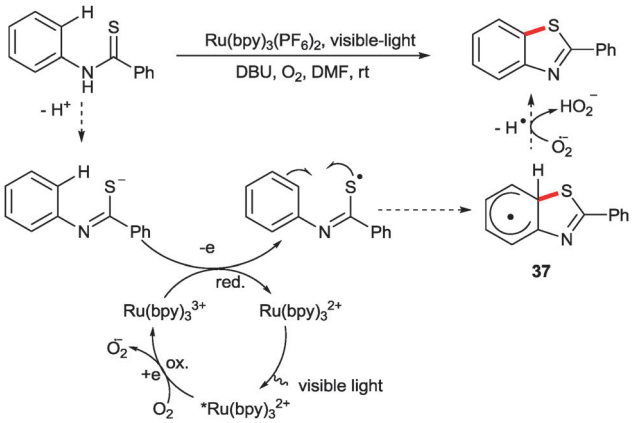
oxidizes $Ru(bpy)_3^{+}$ back to $Ru(bpy)_3^{2+}$ and generates $O_2^{\bullet-}$, could not be ruled out. In this procedure, visible-light and readily available molecular oxygen were used in the C–H functionalization/C–S bond formation instead of an excess amount of external oxidants with water as the only by-product. This method is complementary to the existing benzothiozole synthesis with the advantages of high efficiency, unique selectivity and an environmentally friendly nature.

Very recently, Lei reported another benzothiazole synthetic procedure, which involves the external oxidant-free intramolecular oxidative cross-coupling for aromatic C–H thiolation by visible-light photoredox/cobalt catalysis (Scheme 32).[39] They found that the appropriate base is the crucial factor of the transformation, which should meet three criteria: (a) the pK_b should be low enough to abstract a proton from substrates; (b) a mild conjugate acid should act as a hydrogen atom donor to achieve the protonation process of the proton reducing catalysts; and (c) redox inertia. Both electron-rich and electron-poor substituents on the *N*-aryl or 2-aryl group reacted smoothly to give the corresponding benzothiazoles in high yields. Besides, 2-alkylbenzothiazoles could be obtained through this procedure when a catalytic amount of TBAOH was used as the base. In particular, the oxidative by-product *N*-arylbenzamide was completely avoided with H_2 as the only side product. Moreover, the reaction can be scaled up to the gram-scale, and can be used in the synthesis of the potent antitumor agent. Deuterium experiments showed that the released H_2 directly originates from the substrates. Further studies revealed that the C–H bond cleavage might not be the rate-determining step and the interaction between the proton-reducing catalyst and the dissociated proton might be a slow step. The proposed mechanism is shown in Scheme 33.

Initially, $Ru(bpy)_3^{2+}$ is excited by visible light to provide $^*Ru(bpy)_3^{2+}$. Then after a single electron transfer (SET) process with the anion intermediate of thioamide, which is formed after the deprotonation of *N*-phenylbenzothioamide, $Ru(bpy)_3^{+}$ is produced. The potent reductant $Ru(bpy)^{3+}$ rapidly reacts with [Co^{III}] to give [Co^{II}] while itself being regenerated to complete the photoredox cycle ($E_{1/2\,red}$ Co^{III}/Co^{II} = − 0.83 V *vs.* SCE).[40]



Scheme 30



Scheme 31

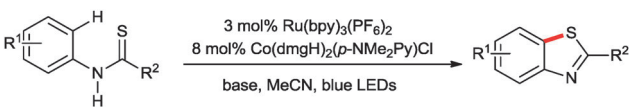
On the other hand, the addition of thiyl radical **38** to the benzene ring produces the reactive aryl radical **39**. Thereafter, radical **39** gives an electron to [Co^{II}] to generate a cation intermediate **40**, which would release a proton and rearomatize to provide benzothiazole. The [Co^{I}] species can be protonated to form [Co^{III}–H] species by the conjugate acid of base. Then this hydride could react with another proton to release H_2 and regenerate [Co^{III}].

Besides the C–H functionalization/C–S bond formation involved cyclization of thioanilides, Yoshida disclosed an alternative route to synthesise 2-aminobenzothiazoles through electrochemical intramolecular C–H amination of 2-pyrimidythiobenzenes (which could be easily formed from thiophenols treated by piperidine) (Scheme 34).[41] The procedure successfully avoids over-oxidation and generates a series of 2-aminobenzothiazoles in good yields with excellent selectivity. This work provides a new avenue to the construction of 2-aminobenzothiazoles which serves as an intriguing motif in medicinal chemistry.

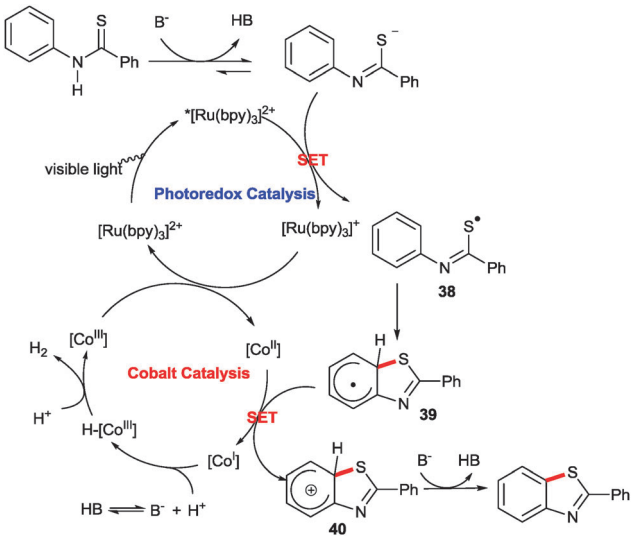
The reaction mechanism is outlined in Scheme 35. One-electron oxidation of **41** gives the corresponding radical cation. Then intramolecular attack of the nitrogen atom followed by one electron oxidation and extrusion of a proton give cyclized cationic intermediate **42**. Next, the attack of piperidine followed by ring opening and the attack of another molecule of piperidine on the resulting imine gives 2-aminobenzoxazole **43**.

6. Radical cyclization towards indoles, indolines and oxindoles

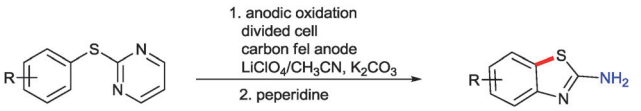
Indoles are an important class of motifs that are widely found in a range of natural products, pharmaceuticals and organic dyes and have remarkable biological and medicinal activities. In indole synthesis, the cyclization approaches which involve



Scheme 32



Scheme 33

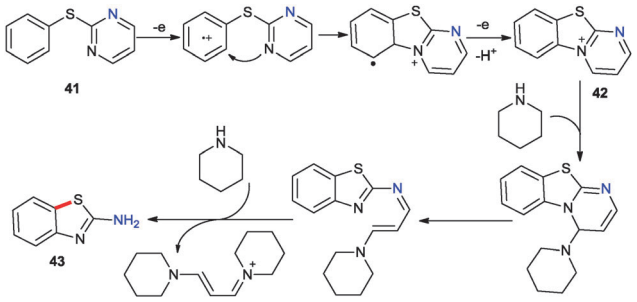


Scheme 34

the C–H oxidative functionalization process are proved to be efficient, high atom-economic and sustainable.[42] While, the majority of these approaches suffered from the requirement of noble transition metal catalysts and limited substrate scopes. Recently, Li developed a metal-free approach for the synthesis of 3-notroindoles through the nitrative cyclization of *N*-aryl imines (Scheme 36).[43] The reaction has broad substrate scopes and *N*-aryl imines with a range of substituents on phenyls are well-tolerated. Besides, a variety of aryl groups either electron-rich or electron-deficient at the 1-position of ethylamine work smoothly to generate the corresponding indoles. Unfortunately, the substrate with the aliphatic group (as Me) has no reactivity for the reaction.

Mechanism studies imply that the by-product (*E*)-2-methyl-*N*-(2-nitro-1-phenylvinyl) aniline **45** is the intermediate of the nitrative cyclization process. Additionally, two radical inhibitors, TEMPO and BHT, were added to the reaction and resulted in no detectable product, thus suggesting that a radical process may be included.

The possible mechanism is outlined in Scheme 37. Initially, *t*BuONO splits into a *t*BuO$^{\bullet}$ radical and an $^{\bullet}$NO radical under heating. Subsequently, those two radicals react with H_2O to produce HNO_2, which is rapidly decomposed into NO_2, NO and H_2O. This is supported by the ^{18}O-labeled experiment using $H_2{}^{18}O$. In the presence of NO_2, NO and air, substrate **44** is converted into intermediate **45**, followed by the hydrogen-abstraction of intermediate **45** by a *t*BuO$^{\bullet}$ radical forming radical intermediate **46**. Cyclization of intermediate **46** takes place to produce radical intermediate **47**. Finally, dehydrogenation and isomerization of intermediate **47** give the indole product.



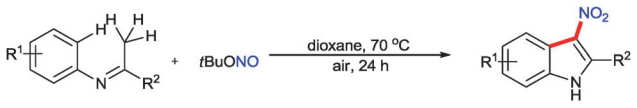
Scheme 35

This nitrative cyclization of *N*-aryl imines with *tert*-butyl nitrite involves the cascade oxidative dehydrogenation, nitration, cyclization and isomerization sequence, and provides an operationally simple and atom economical access to indoles with high functional group compatibility under metal-free conditions, and thus has potential practical applications.

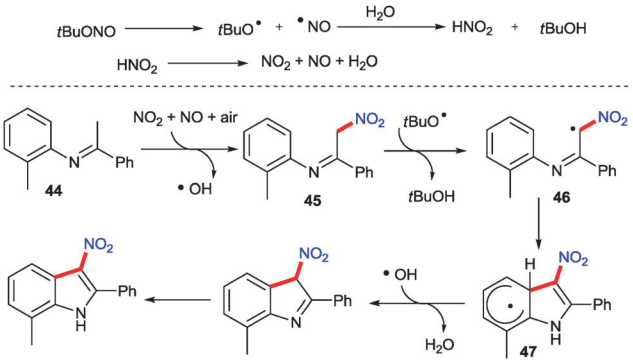
In early 2015, Alexanian reported their great achievements in palladium-catalyzed aromatic C–H alkylation to construct indoline derivatives with simple alkyl halides (Scheme 38).[44] The radical cyclization of *N*-(2-halopropyl)-*N*-arylmethanesulfonamide (halo = I or Br) delivered a series of indoline products in good to moderate yields with excellent functional group tolerance. These reactions did not require particular electronic modulation of the aromatic substrates. *N*-Protected aniline substrates containing a boronic acid pinacol ester, ketone, alcohol and alkene are all well-tolerated. This procedure can also be used to generate tetrahydroquinoline or tetrahydroisoquinoline derivatives *via* simply extending the tether unit and changing the site of *N*-substitution in the tether.

The radical trapping experiment indicates the involvement of the carbon-centered radical. Additionally, the enantioenriched substrate leads to the racemic product also consistent with a single-electron pathway rather than an S_N2-type activation of the alkyl halide. The reaction is initiated by a reversible single-electron oxidative addition of the alkyl halide substrate and generates the carbon-centered radical. The radical is then added to the arene ring to produce a cyclohexadienyl radical intermediate. Finally, rearomatization occurs *via* single-electron oxidation and the loss of one proton to give the indoline along with the regeneration of the palladium(0) catalyst.

The recently developed transition metal-catalyzed or metal-free oxidative difunctionalization of activated alkenes becomes a particularly fascinating approach to build diversely functionalized oxindoles owing to its high step- and atom-economy. By employing different radical precursors, the incorporations of many functional groups (*e.g.*, cyano, carbonyl, hydroxyl, phosphoryl, trifluoromethyl, azidyl, and nitro) into the C3-position of oxindole frameworks were successfully achieved. In those transformations, the general reaction



Scheme 36

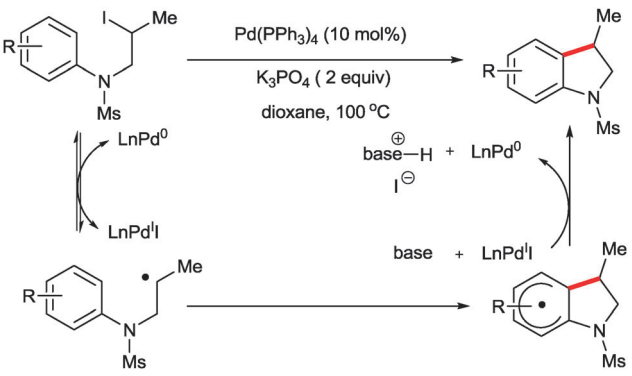


Scheme 37

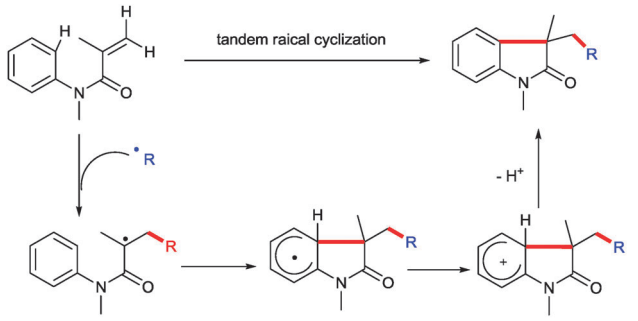
pathway includes: (1) generation of a carbon- or heteroatom-centered radical under certain conditions; (2) selective addition of the radical to the C–C multiple bond in *N*-arylacrylamide; (3) intramolecular radical cyclization; (4) hydrogen abstraction/rearomatization (Scheme 39). Most of those studies have been comprehensively summarized by Li, Xiao and Mai lately.[45] Thus, the detailed description of specific reactions will not listed in this review.

7. Radical cyclization towards isoquinolines and quinolines

The isoquinoline skeleton is recognized as a privileged structure occurring in natural compounds and pharmaceutical drugs with unique biological and pharmacological activities.[46] Traditional isoquinoline syntheses primarily rely on Friedel–Crafts type acylation, such as Bischler–Napieralski and Pomeranz–Fritsch reactions.[47] These methods are normally carried out under acidic conditions and are limited to electron-rich carbocycles. Thus, developing efficient and practical synthetic procedures under mild conditions is highly demanding. In the year 2006, Rodríguez and coworkers did pioneering work in isoquinoline synthesis by light-induced radical cyclization of acyloximes.[48] The reaction was carried out with a 400 W mercury lamp through Pyrex under Ar. Iminyl radicals, that generated from the UV irradiation of acyloximes, participate in the intramolecular



Scheme 38



Scheme 39

cyclization processes and in intermolecular addition–intramolecular cyclization sequences generate a series of isoquinolines.

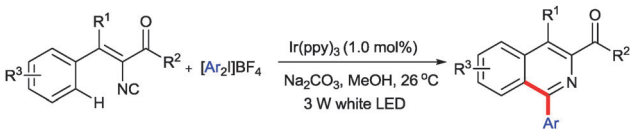
In 2014, Yu provided a brand new method of isoquinoline synthesis *via* the somophilic isocyanide insertion process using visible light-promoted vinyl isocyanide insertion with diaryliodonium salts (Scheme 40).[49] Diaryl ketone-derived vinyl isocyanides, aliphatic aryl ketone-derived vinyl isocyanides as well as the amide-based vinyl isocyanides all reacted smoothly to provide a variety of multi-substituted isoquinoline derivatives in moderate to excellent yields. Diaryliodonium salts with electron-deficient substituents give the corresponding isoquinolines in higher yields (up to 90%) compared with diaryliodonium salts with electron-rich substituents. This phenomenon was further approved by the control experiment that the electron-deficient phenyl group transferred faster than the electron-rich one. Those results suggest that the radical pathway is preferred.

The first step of the transformation is the formation of excited state *fac*-Ir(ppy)$_3$* from the irradiation of photocatalyst *fac*-Ir(ppy)$_3$. *fac*-Ir(ppy)$_3$* is then oxidatively quenched by diaryliodonium salts and produces *fac*-Ir(ppy)$_3^+$ and an aryl radical, respectively. The addition of the aryl radical to vinyl isocyanide **48** gives the imidoyl radical intermediate **49**. Intramolecular HAS of **49** leads to radical intermediate **50**, which is immediately oxidized by *fac*-Ir(ppy)$_3^+$ to form cation intermediate **51** and regenerate *fac*-Ir(ppy)$_3$. Finally, base-promoted deprotonation of **51** gives isoquinoline (Scheme 41).

Using a similar strategy, they achieved the regiospecific synthesis of 1-trifluoromethyl isoquinolines through photoredox somophilic insertion of vinyl isocyanide with Umemoto's reagent (Scheme 42).[50]

Shortly thereafter, Studer also realized the synthesis of 1-trifluoromethylated isoquinolines *via* radical trifluoromethylation of isonitriles. Togni's reagent is employed as a trifluoromethyl radical precursor in his case (Scheme 43).[51]

Using visible light as the driving force, Zhou and co-workers successfully achieved the activation of the C(sp^2)–X bond of imidoyl halides to generate trifluoroacetimidoyl radicals, which were then trapped by alkynes to give a series of 2-trifluoromethyl quinolines in moderate to good yields (Scheme 44).[52] The reaction has wide substrate scopes, as terminal and internal, and aryl and alkyl alkynes all react smoothly to generate the corresponding 2-trifluoromethyl quinolines. Notably, trifluoroacetimidoyl chlorides

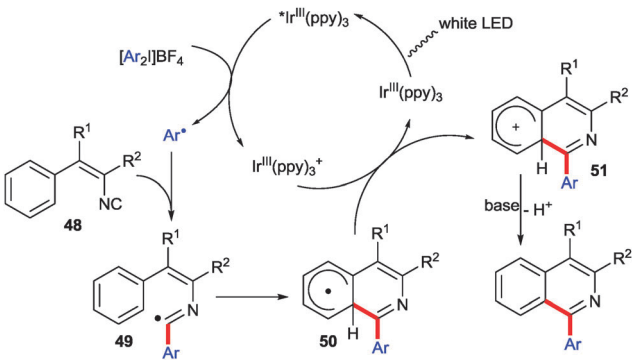


Scheme 40

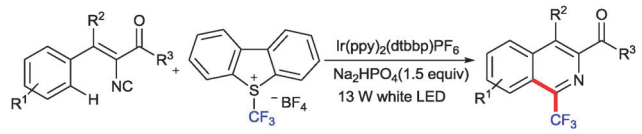
with *para* substituent on the aromatic ring result in two regioisomers, while the 2,5-disubstituted imidoyl chloride affords the sole regioisomeric product.

Mechanism studies showed that the reductive quenching of the photocatalyst by (*n*Bu)$_3$N is the key step during this single-electron transfer process. A plausible mechanism is outlined in Scheme 44. Initially, photo-excitation of [Ru(bpy)$_3$]$^{2+}$ by visible light generates excited *[Ru(bpy)$_3$]$^{2+}$ and then quenched by (*n*Bu)$_3$N to produce [Ru(bpy)$_3$]$^+$. Reduction of the C(sp^2)–Cl bond by [Ru(bpy)$_3$]$^+$ gives radical intermediate **53** along with the regeneration of [Ru(bpy)$_3$]$^{2+}$. Intermolecular addition of radical **53** with alkynes leads to vinyl radical **54**, which undergoes a homolytic aromatic substitution giving cyclohexadienyl radical intermediate **55** (path a). An electron is transferred from radical **55** to either the photoexcited *[Ru(bpy)$_3$]$^{2+}$ or the radical cation (*n*Bu)$_3$N to provide cation **56**. Finally, quinoline **52** was formed through the deprotonation of intermediate **56**. Alternatively, radical **54** may undergo *ipso* cyclization, subsequently C–N bond cleavage and aromatization lead to rearranged radical **55′** and afford the minor unexpected regioisomeric quinoline **52′** in a similar process as described in path a (Scheme 45).

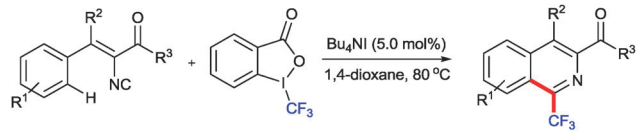
Recently, they developed another visible-light induced radical reaction of vinyl azides with α-carbonyl benzyl bromides to generate quinolines *via* a C–C and C–N bond formation sequence (Scheme 46).[53] The reaction tolerates a variety of functional groups, α-methoxycarbonyl benzyl bromides as well as α-bromo ketones all react smoothly with aryl vinyl azides to generate the corresponding quinolines in moderate to good yields. Owing to the fast decomposition of alkyl vinyl azides, no corresponding quinoline could be produced. This is the first example of using vinyl azide as a radical acceptor under visible-light irradiation conditions to access quinolines. Elaborate selection of the appropriate radical precursor to maintain the addition of the radical to vinyl azide prior to its decomposition is the key factor of the success.



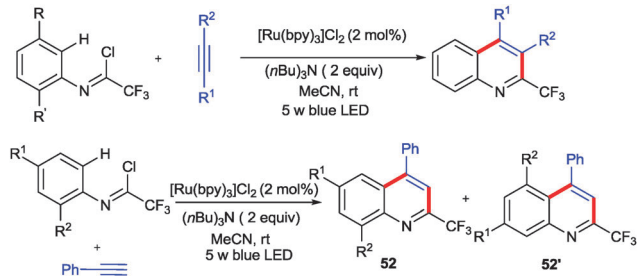
Scheme 41



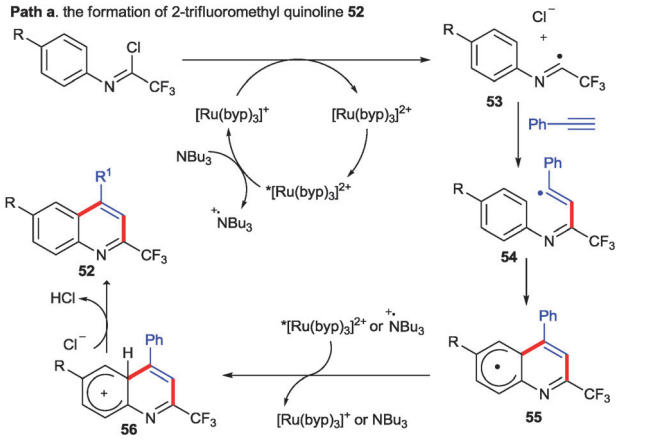
Scheme 42



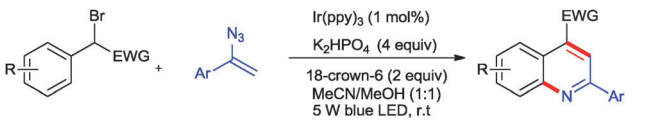
Scheme 43



Scheme 44



Scheme 45



Scheme 46

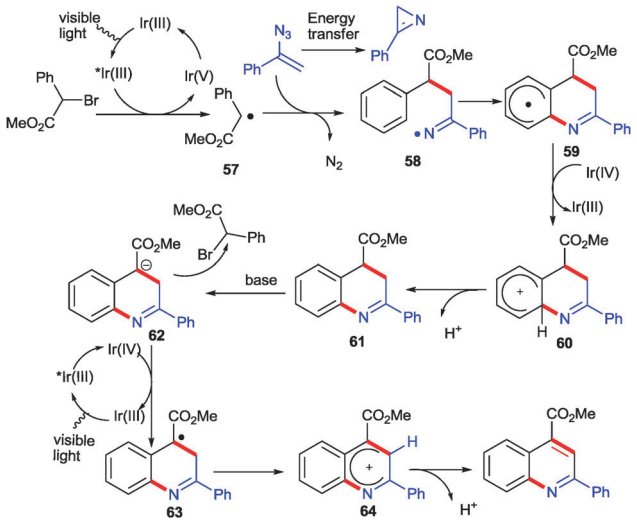
A tentative mechanism is described in Scheme 47. First, visible light-induced photo-excitation of Ir^{III} generates triplet Ir^{III}*, which is oxidatively quenched by α-carbonyl bromide to produce an Ir(IV) complex and radical **57**. The addition of radical **57** to vinyl azide affords iminyl radical **58** with the release of N_2. The following intramolecular radical cyclization of **58** gives radical intermediate **59**. Reduction of Ir(IV) by **59** regenerates the catalyst along with the formation of cation intermediate **60**, which produces 2*H*-quinoline **61** *via* deprotonation. Finally, the dehydrogenation/aromatization of **61** forms quinoline. Alternatively, benzyl bromide might act as the oxidant in the dehydrogenation of 2*H*-quinoline **61** to generate **62**, which might form a EDA (electron donor–acceptor) complex with α-carbonyl bromide to promote the reduction of α-carbonyl bromide, giving radical **63** and **57**. The oxidation of **63** by Ir(IV) leads to cation **64**, which forms quinoline after deprotonation.

Almost at the same time, Yu established another strategy of iminyl radical formation *via* visible-light initiated reaction of acyl oximes (Scheme 48).[54] Using *fac*-[Ir(ppy)$_3$] as a photoredox catalyst, the acyl oximes were converted by 1e$^-$ reduction into iminyl radical intermediates, which then underwent intramolecular homolytic aromatic substitution (HAS) to give the *N*-containing arenes through N–O bond cleavage and C–N bond formation. The reaction can tolerate a series of substituent groups giving the corresponding quinoline derivatives in good yields. In addition, if biphenyl acyl oximes or pentadienal acyl oximes are subjected to the reaction under standard conditions, phenanthridines or polysubstituted pyridines were obtained in moderate to good yields. Moreover, this strategy was used in the five-step total syntheses of the biologically active benzo[*c*]phenanthridine alkaloids, noravicine and nornitidine, as the key step and showed high efficiency compared with the traditional 11-step procedure.

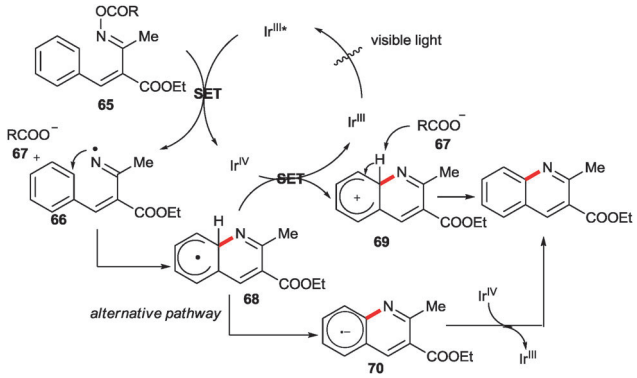
The catalytic cycle begins with the visible-light-induced photoexcitation of a photocatalyst Ir^{III} to the excited state (Ir^{III}*). Then (Ir^{III}*)-promoted reductive cleavage of acyl oxime **65** produces iminyl radical **66**, acyl anion **67** and Ir^{IV}. Radical **66** undergoes intramolecular homolytic aromatic substitution (HAS) and forms radical intermediate **68**, which is then oxidized by Ir^{IV} to form cationic intermediate **69** and regenerate the photocatalyst. Finally, deprotonation of **69** by **67** yields quinoline. Alternatively, **68** can also generate radical-anion intermediate **70** by losing a proton, **70** is then oxidized by Ir^{IV} to give a quinoline structure and regenerate the photocatalyst (Scheme 49).

8. Radical cyclization towards quinolinones

The synthesis of quinolinones and dihydroquinolin-2(1*H*)-ones has attracted considerable attention in view of their cardiovascular, anti-inflammatory and phosphodiesterase inhibitory activities.[55] Difunctionalization of alkenes through radical cyclization turned out to be an efficient and practical synthetic procedure. In 2014, Mai and coworkers developed a silver-catalyzed tandem decarboxylative radical addition/cyclization with *N*-arylcinnamamides and aliphatic carboxylic acids towards



Scheme 47



Scheme 49

3,4-disubstituted dihydroquinolin-2(1*H*)-ones in aqueous solution (Scheme 50).[56] Anilines with electron-donating or -withdrawing groups at either *ortho*-, *meta*-, or *para*-positions all worked smoothly to generate the corresponding products in moderate to good yields. Different *N*-protected groups have no influence on the overall yields. Primary, secondary, and tertiary aliphatic carboxylic acids all underwent efficient intermolecular ring closure to provide the 3-alkylated 3,4-dihydroquinolin-2(1*H*)-ones. Moreover, the CF_3 group could be introduced into the 3-position of 3,4-dihydroquinolin-2(1*H*)-one successfully when CF_3SO_2Na (Langlois reagent) was employed as the CF_3 radical provider.

The mechanism is listed in Scheme 51. Initially, Ag^+ is oxidized by $S_2O_8^{2-}$ to generate the Ag^{2+} cation and the sulfate radical anion. Then, the Ag^{2+} cation abstracts a single electron from carboxylate to produce the carboxyl radical. Subsequent decarboxylation of the carboxyl radical provides the corresponding alkyl radical **71**. Radical addition of **71** to the double bond of cinnamamide produces intermediate **72**. Intramolecular cyclization of **72** gives the intermediate **73**. Finally, **73** undergoes aromatization and hydrogen abstraction by the sulfate radical anion affords the desired product.

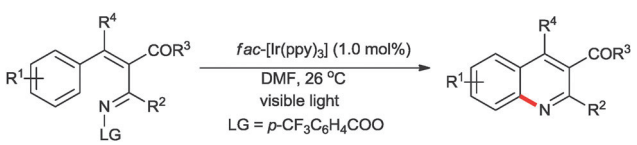
After this pioneering work of tandem oxidative cyclization of cinnamamides with alkyl radicals, a variety of studies were published on the generation of various 3-functionalized 3,4-dihydroquinolin-2(1*H*)-ones. For example, employing unactivated benzyl hydrocarbons as the alkyl radical source, 3-alkylated 3,4-dihydroquinolin-2(1*H*)-ones were obtained *via* a tandem intermolecular radical addition and an intramolecular 6-*endo*-*trig* cyclization process catalyzed by Cu_2O in the presence of TBPB as the oxidant.[57] Other types of substrates contain relatively inert C(sp^3)–H bonds, such as the readily available ethers (1,4-dioxane and tetrahydrofuran), alcohols, cyclohexane and cyclopentane also good reaction partners to construct the desired 3-functionalized dihydroquinolinones in moderate yields.

Employing ketoacids as an acyl radical source, Mai[58a] and Duan[59] achieved the synthesis of 3-acyl-4-arylquinolin-2(1*H*)-ones using $K_2S_2O_8$ as the oxidant, independently (Scheme 52). The reaction catalyzed by silver in aqueous solution includes sequential decarboxylation, cyclization and dehydrogenation processes in one step, which make the method green and atom-economic. The reaction was further developed by Mai using aldehydes as acyl radical precursors under metal-free conditions.[58b]

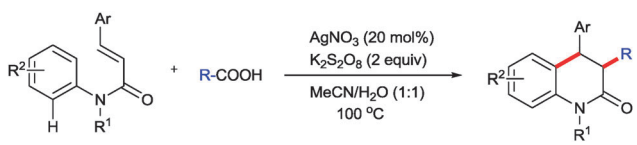
Recently, Wang[60] and Xia[61] developed the successful aryltrifluoromethylation of *N*-phenylcinnamamides using readily available Togni's reagent as the CF_3 radical precursor (Schemes 53 and 54). In Wang's procedure, CuI was used as the catalyst, and a diverse array of 3-trifluoromethylated 3,4-dihydroquinolin-2(1*H*)-ones was prepared in moderate yields with excellent regio- and diastereoselectivity. While, Xia achieved the visible-light induced trifluoromethylation of *N*-arylcinnamamides at room temperature with *fac*-Ir(ppy)$_3$ as the photocatalyst under 5 W blue LEDs. In this visible-light activated reaction, the CF_3 radical is generated through radical quenching of the excited state of the photocatalyst. After sequential radial addition and oxidative cyclization, 3-trifluoromethylated 3,4-dihydroquinolin-2(1*H*)-ones are formed.

9. Radical cyclization towards quinoxalines

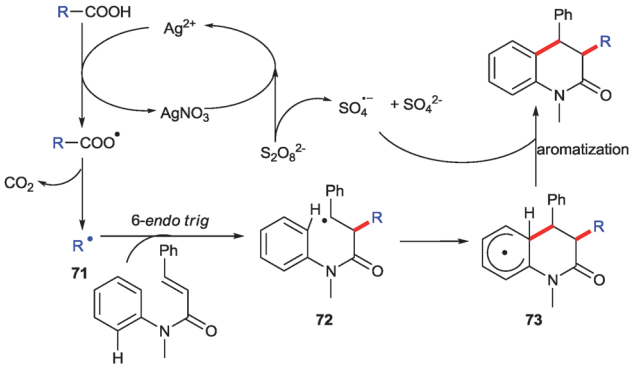
Quinoxaline derivatives are bioactive compounds and have plenty of applications as functional materials.[62] Jiao and coworkers



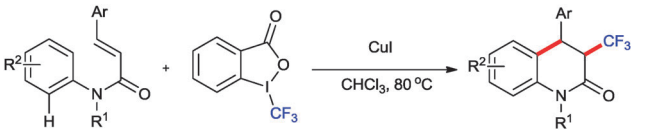
Scheme 48



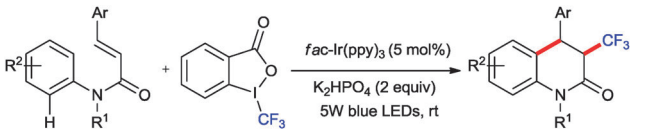
Scheme 50



Scheme 51



Scheme 53



Scheme 54

developed a metal-free dehydrogenative *N*-incorporation approach for the synthesis of quinoxaline *N*-oxides (Scheme 55).[63] The overall transformation involves the cleavage of one C(sp^2)–H and two C(sp^3)–H bonds to achieve the C–N bond formation. The procedure using readily available imines as the substrate and simple and commercial available *tert*-butyl nitrite (TBN) was employed as the NO source. Various substituted imines, which could be easily synthesized from amines with different aromatic ketones, were suitable substrates for this direct *N*-oxide synthesis. Moreover, the one-pot synthesis of quinoxaline *N*-oxides directly from amines and ketones was successfully achieved, which makes this protocol more practical.

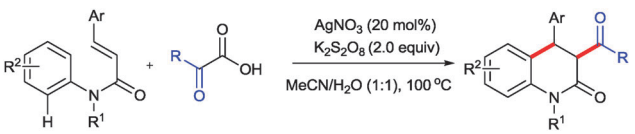
The reaction pathway is listed in Scheme 56. Initially, *tert*-butyl nitrite decomposes into an NO radical and a *tert*-butoxy radical. The methyl imine radical **74** is generated by giving a hydrogen atom to the *tert*-butoxy radical. Then, radical coupling of **74** with the NO radical forms **75**, which is then attacked by a *tert*-butoxy radical to produce **76** immediately. The cyclic intermediate **77** is formed through the electrocyclic reaction of **76**. Finally, after giving a hydrogen atom to a *tert*-butoxy radical and aromatization, quinoxaline *N*-oxide is produced (Scheme 4). The reaction pathway is supported by control experiments, FT-IR, EPR, DFT calculations as well as radical trapping experiments.

Using visible-light photoredox catalysis, Jamison developed a mild and facile strategy for preparing highly functionalized 4-alkylated heterocycle-fused quinoxalines (Scheme 57).[64] Those products were formed from *ortho*-heterocycle-substituted arylisocyanides by a photoredox decarboxylative radical cyclization, with phenyliodine(III) dicarboxylates as easily accessible and environmentally friendly alkyl radical precursors. This transformation has excellent functional-group compatibility as a wide range of substituted arylisocyanides and phenyliodine(III) dicarboxylates reacted smoothly to deliver the corresponding products in moderate to good yields. Moreover, telescoped preparation of pyrrolo[1,2-*a*]quinoxaline by the integration of inline isocyanide formation and photochemical cyclization was achieved in a three-step continuous-flow system.

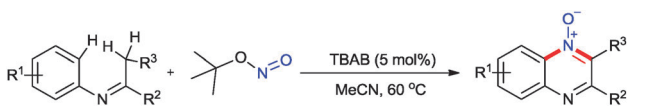
A plausible catalytic cycle for the [*fac*-Ir(ppy)$_3$]-catalyzed visible-light-mediated cyclization process is proposed (Scheme 58). The initial reaction of **78** with [*IrIII(ppy)$_3$] generates a cyclohexyl radical and the strong oxidant [Ir^{IV}(ppy)$_3$]. The resulting alkyl radical subsequently is added to **79** to produce an imidoyl radical **80**, which undergoes intramolecular homolytic aromatic substitution with the nearby pyrrole ring to give the radical intermediate **81**. Radical **81** is then oxidized by [Ir^{IV}(ppy)$_3$] to produce the cation intermediate **82** and regenerate the catalyst [*fac*-Ir(ppy)$_3$] to complete the photoredox cycle. Ultimately, after being deprotonated by the carboxylate anion, the final pyrrolo[1,2-*a*]quinoxaline product is generated.

10. Radical cyclization towards phenanthridines

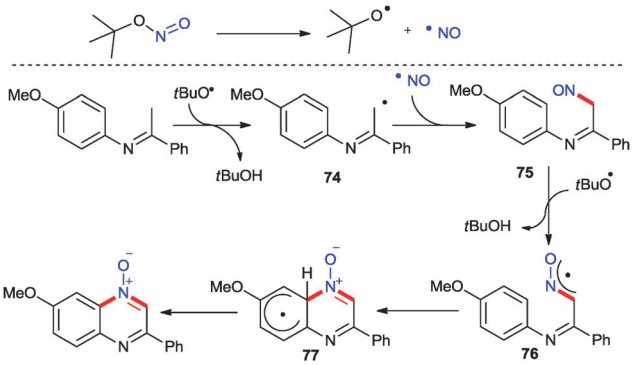
Phenanthridines were demonstrated as an important substructure in pharmaceutical and natural products.[65] In 2012, Chatani pioneered an oxidative radical cyclization of 2-isocyanobiphenyls with organoboron reagents to generate 6-aryl/alkyl phenanthridines (Scheme 59).[66] The reaction mechanism is listed in Scheme 60. Initially, the reaction of boronic acid with Mn^{III} generates aryl/alkyl radical **83**. Subsequently, intermolecular radical addition of **83** with isocyanide produces the imidoyl radical **84**. Then intramolecular cyclization of radical **84** gives radical intermediate **85**, which is quickly oxidized to cation intermediate **86**. Finally, **86** undergoes the deprotonation process to afford the corresponding phenanthridine product. From then, a great many of research groups all over the world have made outstanding achievements in such radical insertion reactions with 2-isocyanobiphenyls as the radical acceptor. Various alkyl, aryl, fluoroalkyl, acyl, P-centered and siyl radicals reacted with 2-isocyanobiphenyls



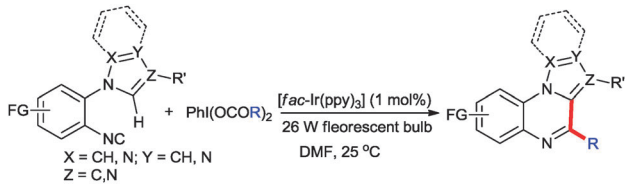
Scheme 52



Scheme 55



Scheme 56

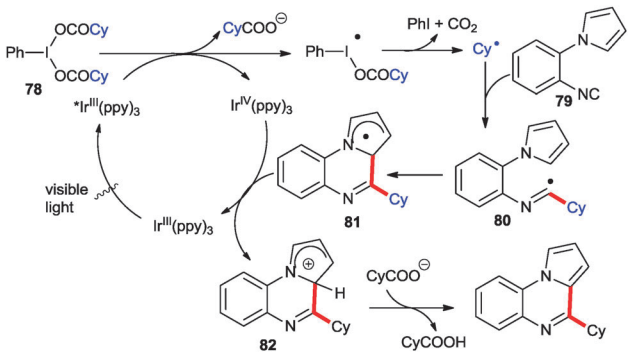


Scheme 57

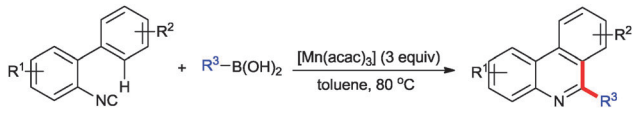
under metal-catalysis, metal-free or photoredox-catalyzed conditions, leading to a variety of 6-functionalized phenanthridines *via* a similar oxidative radical cyclization pathway as Chatani's. As Studer and Xu have reported detailed summarization of those studies very recently,[67] we will not discuss those studies in this review.

11. Radical cyclization towards benzo[*b*]phosphole oxides, silafluorenes and silaindenes

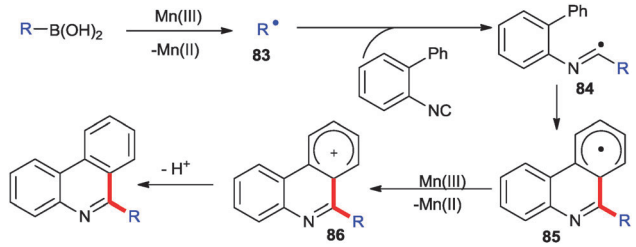
The synthesis of benzo[*b*]phospholes has recently received considerable attention due to their inherent physical and optical properties.[68] In light of this, Duan developed a Ag-mediated radical C–H/P–H functionalization of arylphosphine oxides with internal alkynes for the direct construction of benzo[*b*]-phosphole oxides (Scheme 61).[69] The unusual aryl migration/cyclization leads to a series of benzo[*b*]-phosphole oxides.



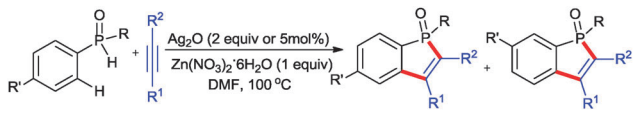
Scheme 58



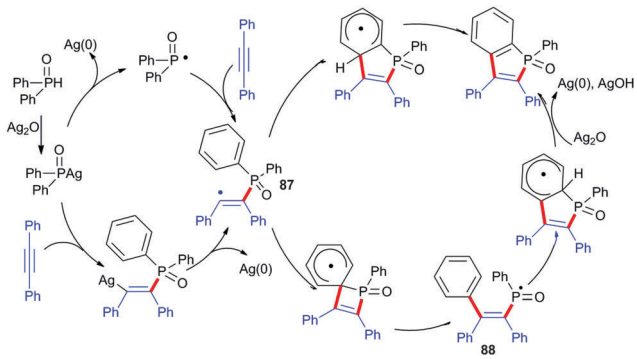
Scheme 59



Scheme 60



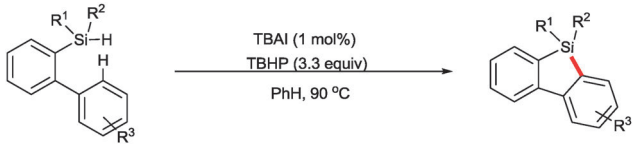
Scheme 61



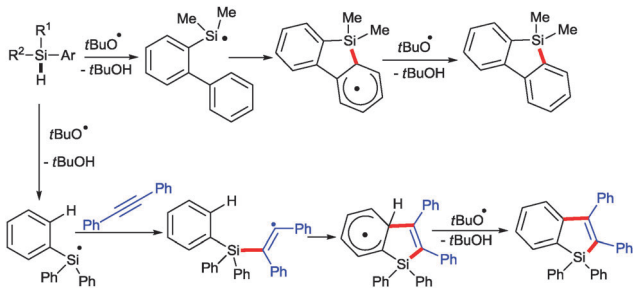
Scheme 62

The reaction pathway is listed in Scheme 62. Firstly, the phosphorus radical is generated from silver diphenylphosphine oxide and is added to alkyne to afford an alkenyl radical **87**. Alternatively, radical **87** might be generated from the addition of silver diphenylphosphine oxide to alkyne, followed by silver oxidation. Next, intramolecular addition of **87** to the *ortho* position of the P atom, followed by the oxidation with Ag_2O and releasing a proton afford the phosphorus heterocycle. On the other hand, alkenyl radical **87** attacks the aryl ring at the carbon atom directly attached to the P atom, and then undergoes C–P bond cleavage furnishing phosphorus radical **88**. Ultimately, radical phosphination of arene at the *cis*-position, followed by Ag_2O oxidation, produces the phosphorus heterocycle with selective aryl migration.

Silicon bridged biaryls, as 9-silafluorenes, have gained particular attention due to their highly valued applications in functional organic materials.[70] Studer developed the electron



Scheme 63



Scheme 64

catalyzed intramolecular homolytic aromatic radical silylation of biphenyl-2-hydrosilanes to generate silafluorenes through intramolecular cross dehydrogenative silylation (Scheme 63).[71] Later, Li also reported the intramolecular radical silylation of 2-diphenylsilylbiaryls towards silafluorenes. Besides, they further developed this strategy for the efficient synthesis of silaindenes with internal alkynes as the radical acceptors (Scheme 64).[72]

12. Conclusions and outlooks

The rapid development of radical chemistry affords diverse opportunities for the convenient construction of heterocyclic compounds. Indeed, radical reactions have become a routine consideration in actual synthetic planning. Heterocyclic molecules, as those O, S, N, Si, P, *etc.* containing ones, could be constructed *via* radical C–H functionalization procedures in high efficiency. In most cases, multiple new bonds are constructed along with the cleavage of multiple old bonds under certain conditions in one single procedure, making those strategies more atom and step economic. In addition to traditional radical generation methods, such as reduction, oxidation and thermolysis, photolysis appears as a clean and efficient alternative, and most of the photolysis reactions could be conducted at room temperature under mild conditions. Besides, technical improvements, as the EPR, even make radicals "visible" and help chemists to understand the intrinsic mechanisms and make use of the radical C–H functionalization procedures to generate more complex heterocyclic products.

Despite those great achievements over the past few years in this area, many challenges still exist. Radicals are highly reactive intermediates that react with many kinds of organic molecules, including solvents. Thus, one of the primary challenges is to react efficiently and selectively. Since radicals are mostly generated under oxidative conditions, many substrates with vulnerable functional groups are ruled out or need to be protected in advance. In view of the high complexity of natural products and pharmaceuticals, total synthesis of those compounds *via* radical C–H functionalization still has a long way to go.

Acknowledgements

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