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REVIEW

Recent advances in the synthesis of nitrogen heterocycles *via* radical cascade reactions using isonitriles as radical acceptors

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Nitrogen heterocycles belong to a highly important class of compounds which are found in various natural products, biologically active structures, and medicinally relevant compounds. Therefore, there is continuing interest in the development of novel synthetic methods for the construction of nitrogen containing heterocycles. Recently, radical insertion reactions into isonitriles has emerged as an efficient and powerful strategy for the construction of nitrogen heterocycles, such as phenanthridines, indoles, quinolines, quinoxalines, and isoquinolines. This review highlights recent advances in this fast growing research area and also includes important pioneering studies in the area.

1. Introduction

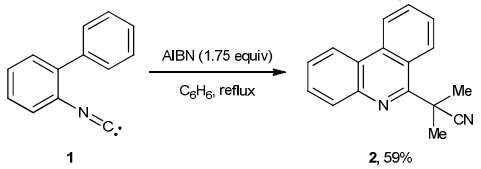
Nitrogen heterocycles are among the most important structural classes of chemical substances, which are particularly well represented among natural products, biologically active structures and medicinally relevant compounds.[1] Among them, phenanthridines, indoles, quinolines, and isoquinolines have gained considerable attention in organic synthesis, medicinal chemistry and materials science. In light of the importance of these compound classes, their preparation has always been a hot topic in organic synthesis.

Over the past decades, great efforts have been made on the development of novel and efficient methods for the construction of nitrogen containing heterocycles.[2-3] Along these lines, isonitrile insertion has emerged as a powerful strategy for their preparation.[4] In this field, significant progress has been achieved on transition metal (TM) mediated or TM-catalyzed isonitrile insertion reactions.[4] In contrast, radical isonitrile insertion has been less intensively investigated.[5] As a pioneering work in this field, in 1991, Curran and co-workers first reported the synthesis of nitrogen heterocycles *via* radical cascade reactions using isonitriles as radical acceptors.[5c] Surprisingly, this interesting area has grown relatively slow in the following two decades. However, this has very recently changed and isonitriles have gained renewed attention as highly efficient radical acceptors in cascade reactions for the construction of nitrogen heterocycles. Various radicals easily add to the isonitrile carbon atom to form the corresponding imidoyl radical intermediate, which is able to undergo subsequent cyclization to eventually afford nitrogen heterocycles. This approach has been successfully applied to the construction of important nitrogen heterocycles, such as phenanthridines, indoles, quinolines, isoquinolines and other N-containing heterocycles.

In this review, we will focus on recent advances in the synthesis of nitrogen heterocycles *via* radical cascade reactions occurring with isonitriles as radical acceptors. However, important earlier work will also be covered and in many cases we will include discussion on the mechanism of the cascades.

2. Synthesis of phenanthridine derivatives *via* radical isonitrile insertion reactions

The phenanthridine core is an important substructure occurring in many natural products which show various biological activities.[6] In 1995, Nanni and co-workers first reported preparation of a 6-substituted phenanthridine **2** *via* radical isonitrile insertion by reacting readily accessible 2-isocyanobiphenyl **1** with the AIBN-derived 2-cyanopropyl radical (Scheme 1).[7] Moreover, phenyl and tristrimethylsilyl silyl radicals were added to **1** in this initial study.



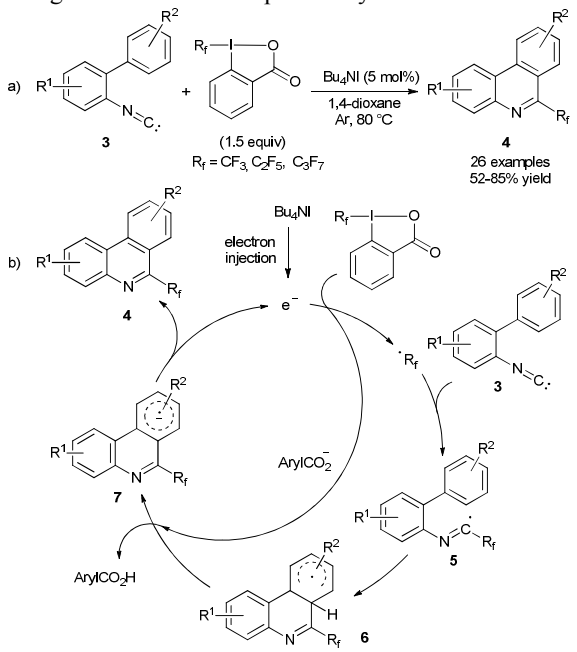
1 **2**, 59%

Scheme 1 Preparation of the 6-alkylated phenanthridine **2** *via* radical isonitrile insertion reaction.

Since this pioneering study, reactivity of 2-isocyanobiphenyls toward various types of radicals has been intensively investigated. By using different radical precursors, various important functional groups can be incorporated into the 6-position of the phenanthridine core. In the following, we will summarize successful syntheses of 6-substituted phenanthridines proceeding *via* radical isonitrile insertion reactions.

2.1 Radical isonitrile insertion reactions of 2-isocyanobiphenyls with fluoroalkyl radicals

In medicinal chemistry, the introduction of fluorine-containing functional groups into heterocycles is an important strategy for improvement of their biological activity because of enhanced bioavailability, lipophilicity, and metabolic stability of the fluorinated compounds as compared to their non-fluorinated parent derivatives.[8] Therefore, radical cascade reactions of 2-isocyanobiphenyls with fluoroalkyl radicals have attracted increasing attention over that past two years.



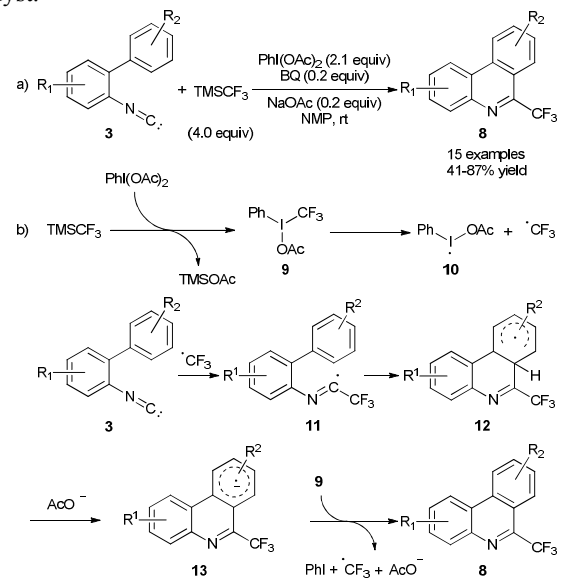
Scheme 2 6-Fluoroalkylated phenanthridines *via* radical fluoroalkylation of 2-isocyanobiphenyls using Bu_4NI as an initiator.

We reported a novel approach for the synthesis of 6-fluoroalkylated phenanthridines **4** starting with readily prepared 2-isocyanobiphenyls **3** (a, Scheme 2).[9] Togni's reagent or derivatives thereof were used as a fluoroalkyl radical precursors and the corresponding 6-fluoroalkylated phenanthridines **4** were obtained in good to excellent yields. Bu_4NI turned out to be the best initiator for this transformation.

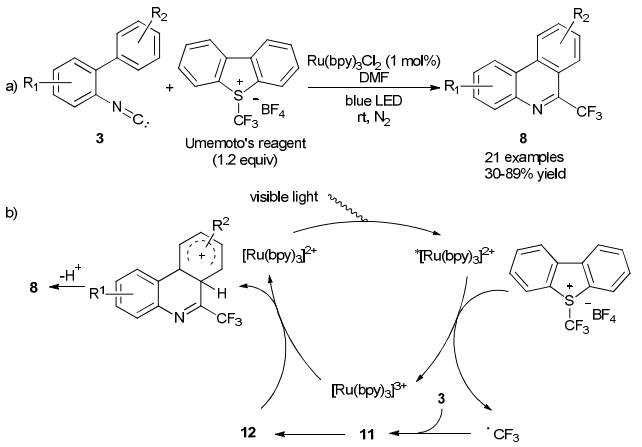
On the basis of mechanistic experiments, density functional theory (DFT) calculations, and our recent conceptual article on the "Electron as a catalyst",[10a] a possible mechanism is proposed in Scheme 2b. The catalytic cycle is started by electron injection from the iodide anion to the Togni reagent affording a CF_3 radical and *ortho*-iodobenzoic acid anion with Bu_4N^+ as the counter cation. Addition of the CF_3 radical to the isonitrile functionality in **3** provides an imidoyl radical **5**, which undergoes base-promoted homolytic aromatic substitution (BHAS)[10b] *via* cyclohexadienyl radical **6** and radical anion **7** to give the final product along with the electron, which enters the next catalytic cycle. In this process, the anion of *ortho*-iodobenzoic acid acts as base for the BHAS reaction, which is supported by high-level DFT calculations.

Almost simultaneously, Zhou and co-workers described a mild and efficient method for the synthesis of 6-trifluoromethyl phenanthridines **8** *via* radical isonitrile insertion reaction between 2-isocyanobiphenyls **3** and CF_3SiMe_3 using $PhI(OAc)_2$ as an oxidant (a, Scheme 3).[11] It is noteworthy that the reaction occurs at room temperature in good to excellent chemical yields. In Scheme 3b, a reasonable mechanism for this transformation is suggested. $PhI(OAc)_2$ reacts with CF_3SiMe_3 to give **9** along with TMSOAc, which undergoes homolysis to generate the CF_3 radical and radical **10** in the initiation step. Addition of the CF_3 radical to isonitrile functionality in **3** generates **11**. BHAS via **12** and **13** eventually provides the 6-trifluoromethylated phenanthridines **8**.

In 2014, Yu *et al.* disclosed a visible-light-mediated radical isonitrile insertion reaction using photoredox catalysis for preparation of 6-trifluoromethyl phenanthridines **8** (a, Scheme 4).[12] The Umemoto reagent was used as a CF_3 radical precursor and $Ru(bpy)_3Cl_2$ as a photoredox catalyst. Reactions were carried out at room temperature without any external oxidant. A possible mechanism as proposed by the authors is disclosed in Scheme 4b. $[Ru(bpy)_3]^{2+}$ is first excited by visible light irradiation to $*[Ru(bpy)_3]^{2+}$, which is oxidized by the Umemoto reagent to give $[Ru(bpy)_3]^{3+}$ along with the CF_3 radical. Subsequently, the CF_3 radical adds to the isonitrile functionality in **3** to provide the imidoyl radical **11**, which cyclizes to the arene to generate the cyclohexdienyl radical **12**. Ultimately, the radical **12** is oxidized by $[Ru(bpy)_3]^{3+}$ to provide $[Ru(bpy)_3]^{2+}$ and the corresponding radical cation, which upon deprotonation leads to the trifluoromethylatd phenanthridines **8** (b, Scheme 4). In addition, the same group reported another method for the synthesis of phenanthridines **8** from 2-isocyanobiphenyls **3** and Umemoto's reagent and suggested an ionic isonitrile insertion reaction. That process was promoted by Na_2HPO_4 as an inorganic base without any external oxidant and metal catalyst.[13]

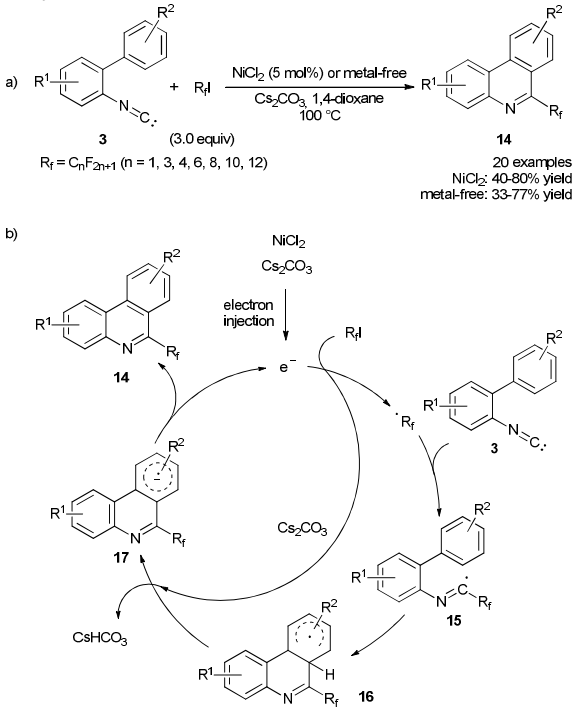


Scheme 3 $PhI(OAc)_2$-mediated synthesis of 6-trifluoromethylated phenanthridines by radical trifluoromethylation of isonitriles.



Scheme 4 6-Trifluoromethylated phenanthridines *via* visible-light-promoted radical trifluoromethylation of isonitriles.

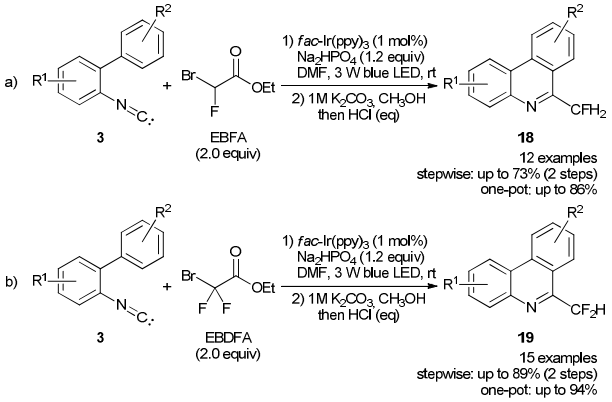
Although these methods turned out to be highly efficient for preparation of 6-trifluoromethylated phenanthridines, their application for the construction of 6-perfluoroalkylated phenanthridines is restricted, since perfluoroalkyl analogues of the applied trifluoromethylation reagents (Togni's reagent, Umemoto's reagent, or Ruppert-Prakash reagent) are expensive and/or not commercially available. Thus, development of a general method for the construction of 6-perfluoroalkylated phenanthridines using readily available perfluoroalkyl radical sources is highly desirable. Along these lines, we developed in 2014 a preparative simple and general approach to 6-perfluoroalkylated phenanthridines starting with 2-isocyanobiphenyls **3** and commercially available and cheap perfluoroalkyl iodides as perfluoroalkyl radical precursors (a, Scheme 5).[14] Reactions which can be carried out with or without using a Ni-salt as an initiator show good functional group tolerance. Under optimized conditions various 6-perfluoroalkylated phenanthridines were prepared in moderate to good yields.



Scheme 5 6-Perfluoroalkylated phenanthridines by using perfluoroalkyl iodides as perfluoroalkyl radical precursors.

On the basis of a series of control experiments, the following mechanism is proposed (b, Scheme 5). The process belongs to an electron-catalyzed reaction.[10a] For the Ni-free protocol, the electron is likely provided by traces of a transition metal. Alternatively, C-I homolysis can also initiate the chain reaction. Addition of the perfluoroalkyl radical to the isonitrile functionality in **3** forms the imidoyl radical **15**, which undergoes cyclization to give the cyclohexadienyl radical **16**. After deprotonation of **16** by Cs_2CO_3, radical anion **17** is generated which upon formal liberation of an electron provides the final product **14**. SET reduction of the perfluoroalkyl iodide provides the C-radical thereby sustaining the radical chain.

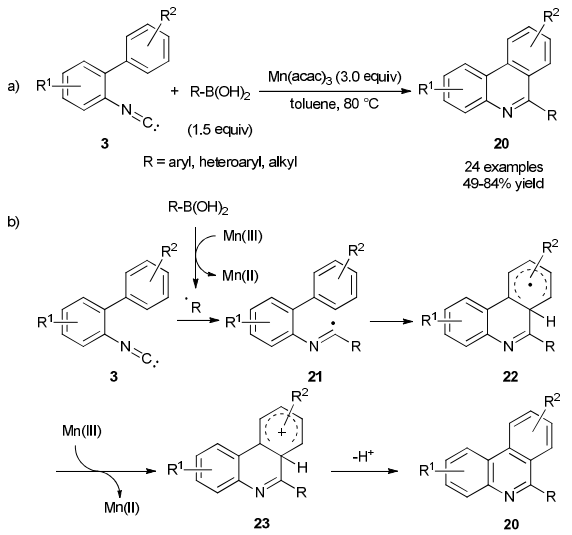
For the synthesis of 6-mono- and difluoromethylated phenanthridines, Yu *et al.* recently reported an efficient strategy comprising a visible-light-promoted radical fluoroalkylation of isonitriles and subsequent decarboxylation sequence by reacting 2-isocyanobiphenyls **3** with ethyl bromofluoroacetate (EBFA) or ethyl bromodifluoroacetate (EBDFA) (Scheme 6).[15] These reactions proceed under mild conditions. The ester functionality as a masked proton is removed after the radical cascade *via* saponification and subsequent acid-mediated decarboxylation.



Scheme 6 6-Mono- and difluoromethylated phenanthridines *via* visible-light-induced radical fluoroalkylation of isonitriles and subsequent decarboxylation.

2.2 Radical isonitrile insertion reactions of 2-isocyanobiphenyls with aryl radicals

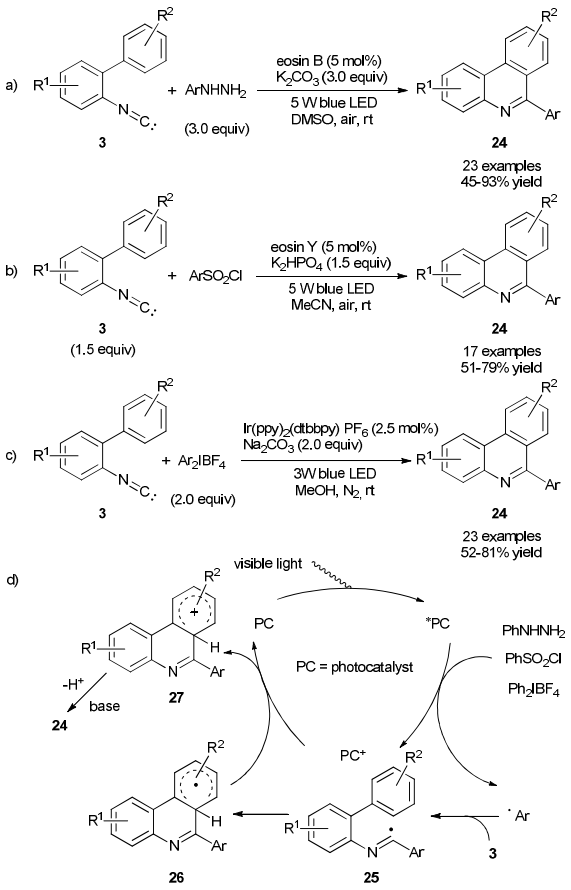
Aryl radicals can be generated from arylboronic acids upon oxidation. In 2012, Chatani and co-workers disclosed a radical isonitrile insertion reaction of 2-isocyanobiphenyls **3** with aryl or heteroaryl boronic acids with $Mn(acac)_3$ as an oxidant affording the corresponding 6-arylated or 6-heteroarylated phenanthridines in good yields (a, Scheme 7).[16] Remarkably, the methodology could also be extended to the construction of 6-alkylated phenanthridines by using alkyl boronic acids as alkyl radical sources. Based on mechanistic studies, authors suggested that reactions occur via aryl or alkyl radicals as intermediates (b Scheme 7). The oxidatively generated radical adds to the isonitrile functionality to give imidoyl radical **21** which cyclises to the arene to provide **22**. Oxidation of the cyclohexadienyl radical **22** to the corresponding cation **23** and deprotonation eventually provide product **20**.



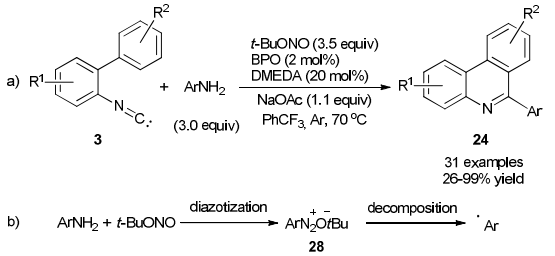
Scheme 7 6-Arylated, 6-heteroarylated, and 6-alkylated phenanthridines by using organoboron reagents as a radical precursors.

Recently, visible light photoredox catalysis has been used for aryl radical generation from arylhydrazines, arylsulfonyl chlorides, and diaryliodonium salts. In this context, Zhou's group,[17] Gu's group,[18] and Yu's group[12] independently reported the synthesis of 6-arylated phenanthridines **24** *via* visible-light-induced radical arylation of 2-isocyanobiphenyls. In the method introduced by Zhou, the organic dye eosin B has been used as a photocatalyst and arylhydrazines as aryl radical precursors (a, Scheme 8). The Gu group has employed the eosin Y as a photocatalyst in combination with arylsulfonyl chlorides as aryl radical sources (b, Scheme 8) and Yu and co-workers have applied iridium complexes as photoredox catalysts with diaryliodonium salts as aryl radical precursors (c, Scheme 8). In all these transformations, aryl radical intermediates are generated by SET processes from the excited state photocatalysts *PC either by reduction (arylhydrazines) or by oxidation (arylsulfonyl chlorides, diaryliodonium salts) of the excited photoredox catalyst (d, Scheme 8). The aryl radicals react via **25** to the cyclohexadienyl radicals **26** which are oxidized by the catalyst to cyclohexadienyl cations **27**. Deprotonation affords the final products **24**.

In addition, Zhu and co-workers demonstrated a metal-free method for the construction of 6-arylated phenanthridines **24** by radical arylation of 2-isocyanobiphenyls **3** with diazonium salts **28**, which were generated *in situ* from arylamines and *tert*-butyl nitrite (*t*-BuONO) (Scheme 9).[19] Various functional groups are tolerated and the 6-arylated phenanthridines **24** were obtained in good to excellent yields. Mechanistic studies revealed that aryl radicals are intermediates in these cascades.



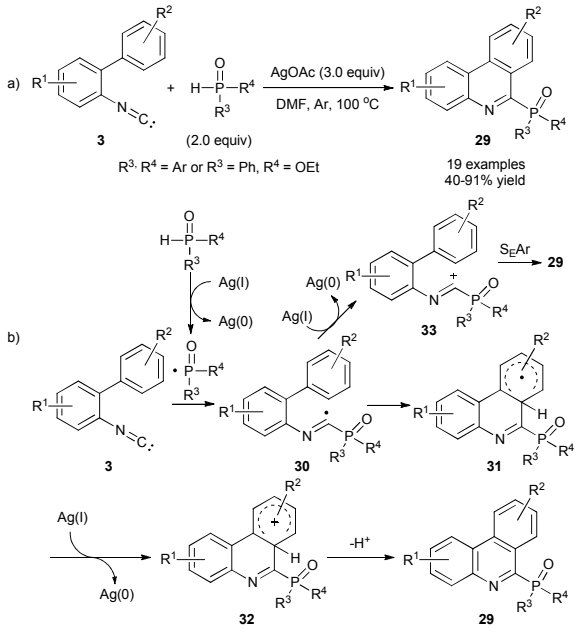
Scheme 8 6-Arylated phenanthridines *via* visible-light-induced radical arylation of isonitriles.



Scheme 9 6-Arylated phenanthridines from 2-isocyanobiphenyls by using anilines as aryl radical precursors.

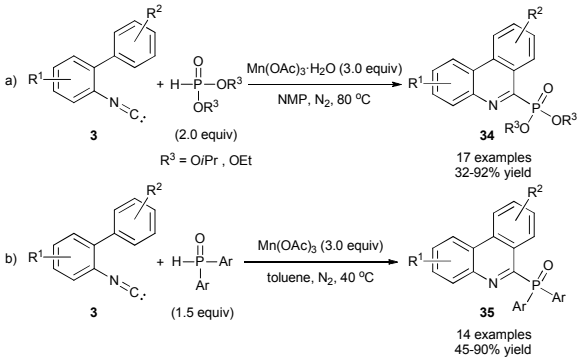
2.3 Radical isonitrile insertion reactions of 2-isocyanobiphenyls with P-centered radicals

Aromatic organophosphorus compounds are an important class of compounds, which are widely applied in organic synthesis, medicinal chemistry, and materials science.[20,21] Therefore, the development of novel synthetic methods for C-P bond formation is very important. In this context, we reported the first examples on the preparation of 6-phosphorylated phenanthridines by radical phosphorylation of isonitriles by using AgOAc as an oxidant and the commercially available diphenylphosphine oxide as a P-radical precursor (a, Scheme 10).[22] Under the optimized conditions, a wide range of 6-phosphorylated phenanthridines **29** bearing various electron-donating and electron-withdrawing substituents were obtained in moderate to good yields. Along with diphenylphosphine oxide, ethyl phenylphosphinate turned also out to be a suitable P-radical precursor for this cascade.



Scheme 10 6-Phosphorylated phenanthridines *via* radical phosphorylation of isonitriles by using AgOAc as an oxidant.

Based on experimental findings, a plausible reaction mechanism is depicted in Scheme 10b. Diarylphosphine oxide is first oxidized by AgOAc to the corresponding P-centered radical and Ag(0), which was identified as silver mirror at the reaction flask. Addition of the P-centered radical to the isonitrile functionality in **3** provides the imidoyl radical **30**, which undergoes cyclization to cyclohexadienyl radical **31** which is subsequently oxidized by AgOAc to cyclohexadienyl cation **32** by a SET process. Finally, **32** gets deprotonated to afford the isolated product **29**. As an alternative mechanistic option, the imidoyl radical **30** might be directly oxidized by the silver(I) salt to the cation **33**, which can then further react to **29** via electrophilic aromatic substitution (S_EAr).



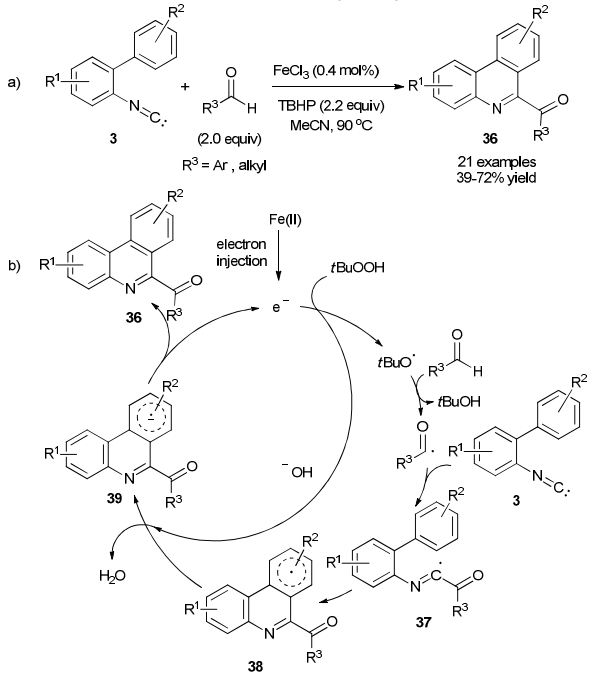
Scheme 11 6-Phosphorylated phenanthridines *via* radical phosphorylation of isonitriles by using $Mn(OAc)_3$ as an oxidant.

Shortly after this report, a similar route to 6-phosphorylated phenanthridines was reported by the Wu[23] (a, Scheme 11) and the Zhao group[24] (b, Scheme 11). In contrast to our procedure, these two groups used manganese(III)acetate as an oxidant. Mechanistic studies on these reactions revealed that P-centered radicals are involved in these transformations and the mechanism is similar to the one suggested in Scheme 10b.[22-24]

2.4 Radical isonitrile insertion reactions of 2-isocyanobiphenyls with acyl radicals

To further broaden the scope of radical phenanthridine synthesis toward library formation, acyl radicals were also applied to radical isonitrile insertion reactions leading to 6-acylated phenanthridines. In 2013, we disclosed a novel approach for the construction of 6-aroylated phenanthridines by radical aroylation of 2-isocyanobiphenyls **3** with aromatic aldehydes as acyl radical precursors (a, Scheme 12).[25] $FeCl_3$ was used as a radical initiator and TBHP (*t*BuOOH) as a stoichiometric oxidant. The method showed broad substrate scope and the targeted 6-aroylated phenanthridines **36** were isolated in moderate to good yields. Notably, also aliphatic aldehydes can be used in this cascade reaction.

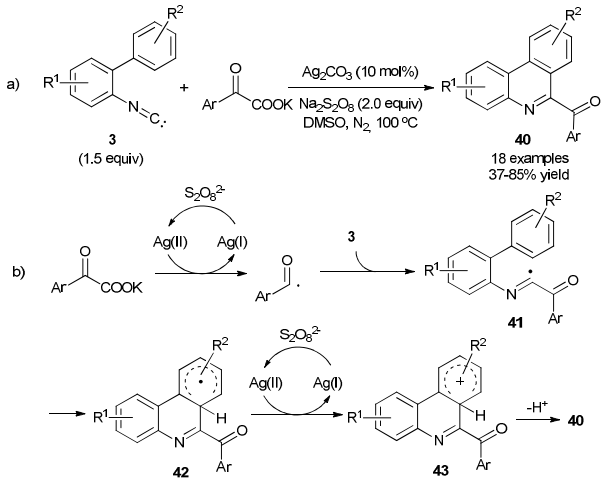
A plausible mechanism considering the electron as a catalyst[10a] is proposed in Scheme 12b. $FeCl_2$ is formed *in situ* from $FeCl_3$ and TBHP *via* ligand exchange and subsequent Fe-O homolysis.[26] Reduction of TBHP by the Fe(II)-salt generates a *tert*-butoxyl radical, Fe(III), and OH^-. The *tert*-butoxyl radical then abstracts the H-atom from the aldehyde to form an acyl radical, which adds to the isonitrile **3** to generate the imidoyl radical **37**. BHAS through radical intermediate **38** and radical anion **39** eventually provides the final product **36** along with an electron, which enters the next catalytic cycle.



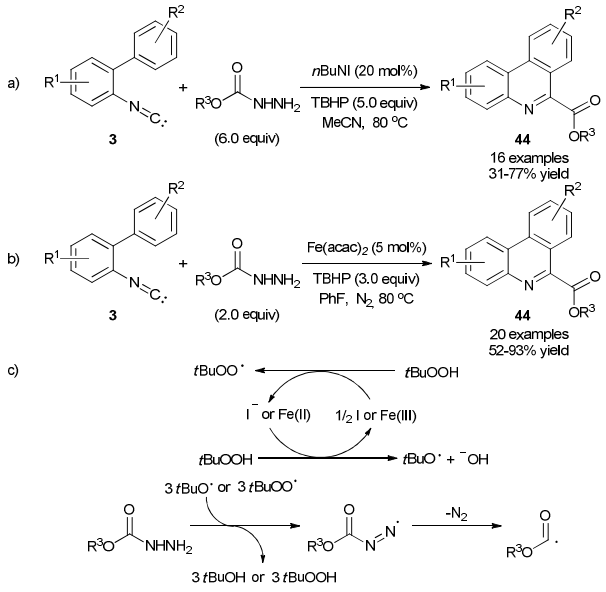
Scheme 12 6-Aroylated phenanthridines *via* radical aroylation of isonitriles by using aldehydes as acyl radical precursors.

In 2014, Lei and co-workers described a silver catalysed process for the synthesis of 6-aroylated phenanthridines by using readily available *α*-oxocarboxylates as acyl radical precursors in combination with $Na_2S_2O_8$ as an oxidant (a, Scheme 13).[27] This method tolerates a variety of functional groups, such as methyl, methoxyl, acetyl, fluoro, chloro, and trifluoromethyl substituents. Oxidative radical decarboxylation involves an Ag(I)-Ag(II) catalytic cycle *via* initial SET, as supported by electron paramagnetic resonance (EPR) experiments. Based on the EPR-studies, the authors proposed a plausible reaction mechanism (b, Scheme 13). The benzoyl radical, generated from an *α*-oxocarboxylate in the presence of Ag_2CO_3 and $Na_2S_2O_8$ *via* oxidative radical decarboxylation, adds to the

isonitrile functionality of **3** to give the imidoyl radical **41**. The imidoyl radical **41** then cyclizes to the arene to provide cyclohexadienyl radical **42**, which is oxidized by Ag(II) to the cation **43**. Deprotonation eventually gives the final product **40**.



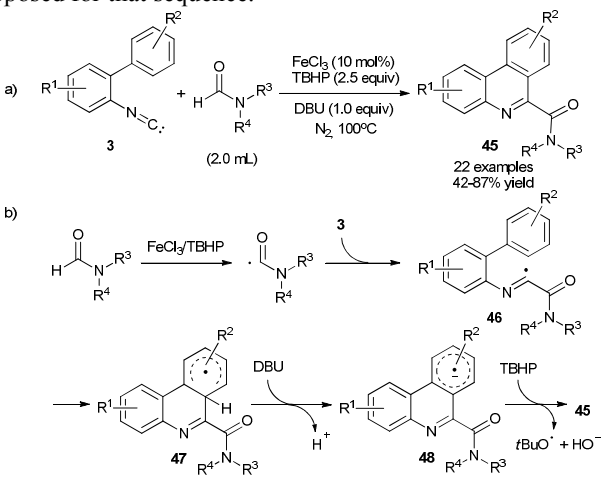
Scheme 13 6-Aroylated phenanthridines *via* radical aroylation of isonitriles by using α-oxocarboxylates as acyl radical precursors.



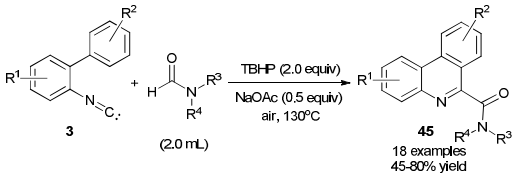
Scheme 14 6-Carboxylated phenanthridines *via* radical alkoxycarbonylation of isonitriles by using carbazates as alkoxycarbonyl radical precursors.

In addition to aroyl radicals, alkoxycarbonyl radicals have also proved to be suitable for conduction of isonitrile insertions for preparation of 6-carboxylated phenanthridines. Xu *et al.* demonstrated a metal-free variant with readily available carbazates as alkoxycarbonyl radical sources and TBHP as a stoichiometric oxidant (a, Scheme 14).[28] At the same time, Zhu and co-workers reported independently a similar strategy for preparation of 6-carboxylated phenanthridines from 2-isocyanobiphenyls **3** and carbazates by using a catalytic amount of $Fe(acac)_2$ in combination with TBHP (b, Scheme 14).[29] In these reactions, authors suggested the alkoxycarbonyl radicals to be generated from sequential oxidation of carbazates with nBu$_4$NI/TBHP or $Fe(acac)_2$/TBHP (c, Scheme 14).

Development of efficient methodologies for incorporation of the amide functional group into organic molecules is very important because amides are abundant in biologically active molecules.[30] In 2014, Zhang *et al.* reported an iron-promoted radical cascade carboxamidation of 2-isocyanobiphenyls **3** with formamides as C-radical precursors, affording the phenanthridine-6-carboxamides **45** in moderate to excellent yields (a, Scheme 15).[31] This strategy was applied to a wide range of 2-isocyanobiphenyls and formamides. On the basis of a radical capture experiment with TEMPO, the authors proposed that the reaction involves addition of aminoacyl radicals to isonitriles to give **46** followed by BHAS *via* **47** and **48** to finally provide the phenanthridine-6-carboxamides **45** (b, Scheme 15). In the same year, Yu *et al.* reported a metal-free protocol for the synthesis of phenanthridine-6-carboxamides **45** by using the same starting materials (Scheme 16).[32] Compared to Zhang's method, this cascade proceeds under air and does not need any metal-based initiator. A similar mechanism was proposed for that sequence.[32]



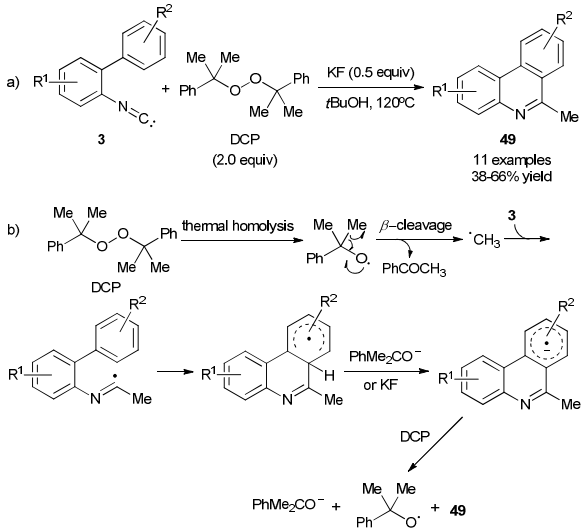
Scheme 15 Phenanthridine-6-carboxamides *via* radical amidation of isonitriles using formamides as radical precursors.



Scheme 16 Phenanthridine-6-carboxamides *via* radical amidation of isonitriles under metal-free conditions.

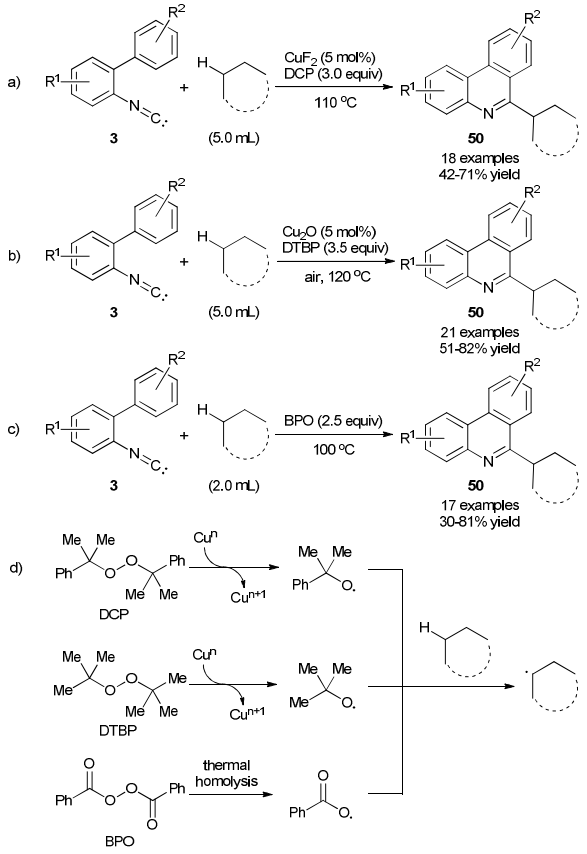
2.5 Radical isonitrile insertion reactions of 2-isocyanobiphenyls with alkyl radicals

Recently, Liu's group demonstrated a metal-free radical cascade methylation and cyclization of 2-isocyanobiphenyls **3** with dicumyl peroxide (DCP) as a methyl radical source (a, Scheme 17).[33] This method provides convenient access to a wide range of 6-methylated phenanthridines **49** with various functional groups in moderate to good yields.



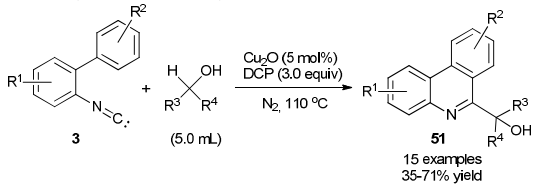
Scheme 17 6-Methylated phenanthridines *via* radical methylation of isonitriles using dicumyl peroxide as a methyl radical source.

Control experiments with TEMPO as a radical scavenger provided strong support for the radical nature of that process. In these transformations, initiation occurs by thermal decomposition of dicumyl peroxide followed by β-cleavage of the cumyloxyl radical to generate the methyl radical, which undergoes sequential radical isonitrile addition and cyclization to form the final product **49** (b, Scheme 17). Reactions proceed *via* BHAS where either the fluoride anion or the cumyloxy anion generated by SET to the peroxide act as bases.



Scheme 18 6-Alkylated phenanthridines *via* radical alkylation of isonitriles by using alkanes as alkyl radical precursors.

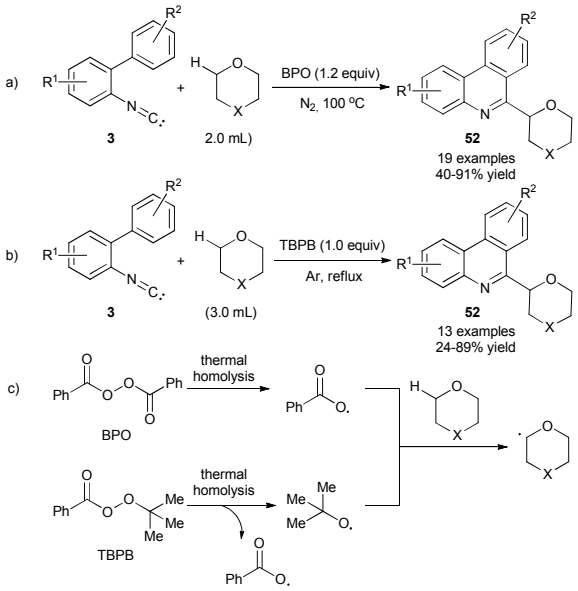
Direct and selective functionalization of unactivated sp^3 C-H bonds is difficult and highly challenging. Recently, radical functionalization of unactivated sp^3 C-H bonds has received great attention.[34] Along these lines, radical isonitrile insertion by using unactivated alkanes as alkyl radical sources has become a powerful strategy for the preparation of 6-alkylated phenanthridines. In 2014, Liu *et al.* reported a copper(II) fluoride-initiated radical cascade starting with 2-isocyanobiphenyls **3** and alkanes to provide 6-alkylated phenanthridines **50** in moderate to good yields (a, Scheme 18).[35] This method shows high functional group compatibility with respect to the isonitrile component. The Huang group also described a similar sequence for the preparation of 6-alkylated phenanthridines **50** (b, Scheme 18).[36] Di-*tert*-butyl peroxide (DTBP) proved to be the ideal oxidant for this transformation. Moreover, a metal-free protocol to access 6-alkylated phenanthridines **50** from the same starting materials was disclosed by the Cheng group (c, Scheme 18).[37] In these reactions, initiation occurs either by Cu-metal salt induced SET or by homolysis to generate reactive O-centered radicals which undergo H-abstraction from the alkane to give the C-radical which then reacts with the isonitrile functionality and subsequent BHAS in analogy to the mechanism discussed in Scheme 17b (d, Scheme 18).



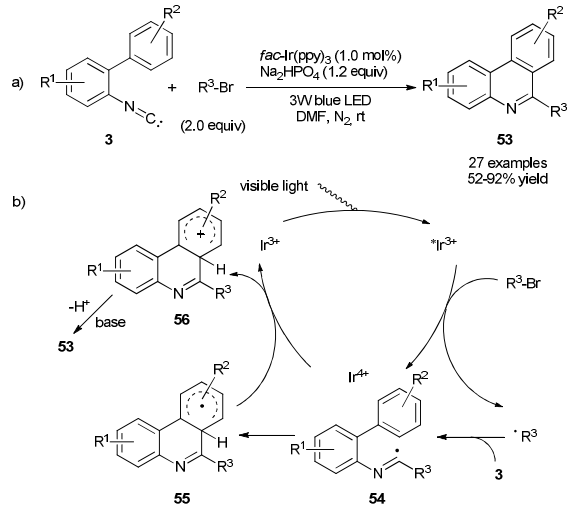
Scheme 19 6-Hydroxyalkylated phenanthridines *via* radical hydroxyalkylation of isonitriles by using alcohols as radical precursors.

α-Hydroxyalkyl radicals are important reactive intermediates which have recently found wide application in organic synthesis.[38] In 2014, Liu *et al.* disclosed an efficient Cu_2O-initiated radical addition and cyclization sequence by using 2-isocyanobiphenyls **3** and various primary and secondary alcohols as reaction partners with DCP as an oxidant (Scheme 19).[35] The procedure features high functional group tolerance and various 6-hydroxyalkylated phenanthridines **51** were obtained in moderate to good yields by using this approach.

Alkyl radicals generated from α-H abstraction in ethers turned out to be useful reactive intermediates in the reaction with 2-isocyanobiphenyls. The Cheng group[39] and the Ji group[40] independently reported a metal-free approach to 6-α-oxyalkylated phenanthridines **52** *via* isonitrile insertion reactions of 2-isocyanobiphenyls **3** with various ethers as alkyl radical precursors in the presence of benzoyl peroxide (BPO) or *tert*-butyl peroxybenzoate (TBPB) as oxidants (a and b, Scheme 20). These protocols exhibited broad substrate scope with respect to the isonitrile component and the targeted 6-alkylated phenanthridines **52** were isolated in good to excellent yields. Initiation of the radical cascade occurs by thermal homolysis of the weak O-O bond in BPO or TBPB to generate the corresponding O-centered radicals, which then abstract a hydrogen atom from the activated α-position of the ether to generate the corresponding alkyl radicals (c, Scheme 20). The alkyl radicals then react with the isonitrile to imidoyl radicals followed by a BHAS to eventually give **52** in analogy to the mechanism discussed in Scheme 17b.

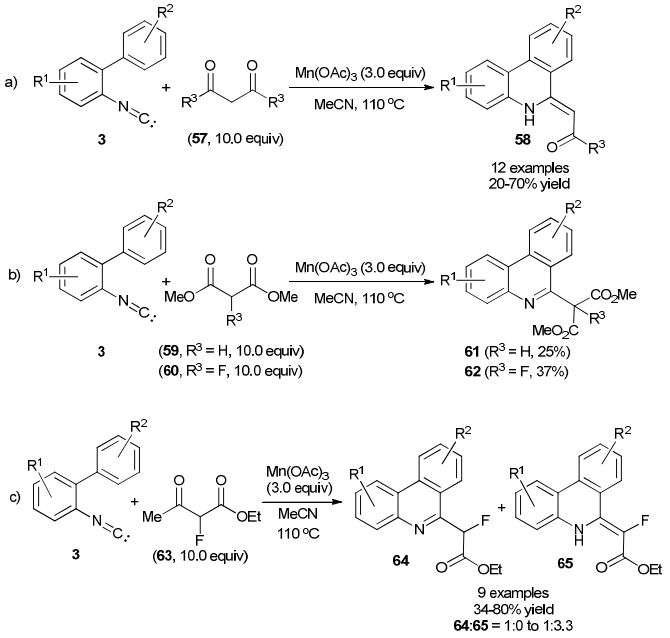


Scheme 20 6-α-Oxyalkylated phenanthridines *via* radical alkylation of isonitriles by using ethers as alkyl radical precursors.



Scheme 21 6-Alkylated phenanthridines *via* visible-light-promoted radical alkylation of isonitriles by using alkyl bromides as alkyl radical precursors.

In 2013, Yu *et al.* disclosed a visible-light-promoted radical alkylation of 2-isocyanobiphenyls **3** with readily available α-bromo esters and perfluoroalkyl bromides as radical sources.[41] This efficient synthetic approach offers simple and rapid access to 6-alkylated phenanthridines **53** which are obtained under mild conditions in good to excellent yields (a, Scheme 21). A possible reaction mechanism was postulated for this transformation based on experimental observations (b, Scheme 21). Firstly, the excited state photocatalyst $*Ir^{3+}$ generated upon irradiation is oxidatively quenched by alkyl bromides with the formation of an Ir^{4+} complex along with an alkyl radical. The alkyl radical then adds to **3** to give the imidoyl radical **54**, which cyclizes to the cyclohexadienyl radical **55**. Subsequently, **55** gets oxidized by Ir^{4+} to form the radical cation **56** thereby regenerating the Ir^{3+} catalyst. Finally, deprotonation of **56** eventually affords **53**.

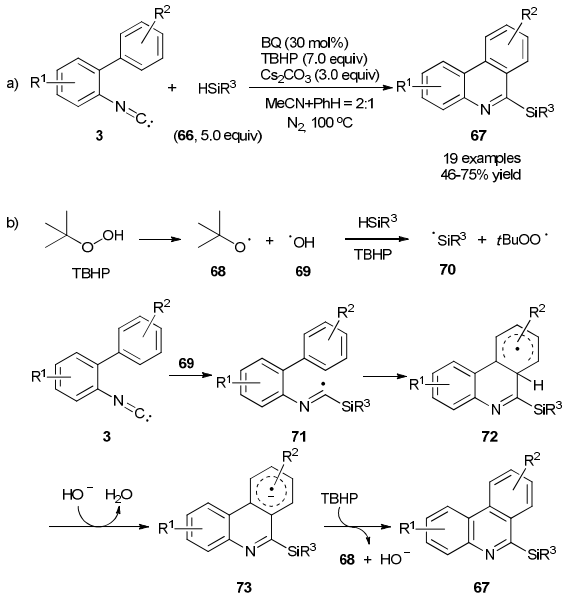


Scheme 22 6-Alkylated phenanthridines *via* radical alkylation of isonitriles using 1,3-dicarbonyl compounds as alkyl radical precursors.

Furthermore, Mn(III)-mediated radical isonitrile insertion reaction of 2-isocyanobiphenyls **3** with 1,3-dicarbonyl compounds **57**, **59**, **60**, and **63** was reported by Ji and co-workers (a-c, Scheme 22).[42] This procedure provides an efficient entry to 6-substituted phenanthridine derivatives **58**, **61**, and **62**. In addition, 6-monofluoroalkylated phenanthridines **64** were prepared by using fluorinated ester **63** as an alkyl radical source. In the formation of **58** and **64** the radical isonitrile insertion with subsequent BHAS reaction is followed by an ionic deacylation process.

2.6 Radical isonitrile insertion reactions of 2-isocyanobiphenyls with silyl radicals

Due to their interesting physical and biological properties, silyl-substituted aromatic compounds have attracted the interests of materials scientists and medicinal chemists.[43] Moreover, silylated aromatic compounds are useful synthetic intermediates for construction of complex organic molecules.[44] Thus, the development of novel and efficient methods for arene C-Si bond formation is important. In this context, Yu and co-workers developed a facile and straightforward method for the preparation of 6-silylated phenanthridines with 2-isocyanobiphenyls **3** and silanes **66** and TBHP as a stoichiometric oxidant (a, Scheme 23).[45] Various 6-silylated phenanthridines **67** bearing different functional groups were obtained in moderate to good yields. Preliminary mechanistic investigations involving kinetic isotope effect studies and radical quenching experiments with TEMPO revealed that these reactions proceed *via* a radical process. We suggest the mechanism depicted in Scheme 23b for this interesting transformation. Initiation likely occurs by O-O bond homolysis of TBHP to give the *tert*-butoxyl radical **68** and the hydroxyl radical **69**. Both species can abstract the H atom of the silane to give the silyl radical **70**. Alternatively, the reactive O-centered radicals **68** and **69** can also react with TBHP to give the *tert*-butyl peroxyl radical which itself is able to abstract an H atom from the silane. Silyl radical addition to **3** provides **71** which then undergoes *via* **72** and **73** a BHAS to finally afford phenanthridine **67**.

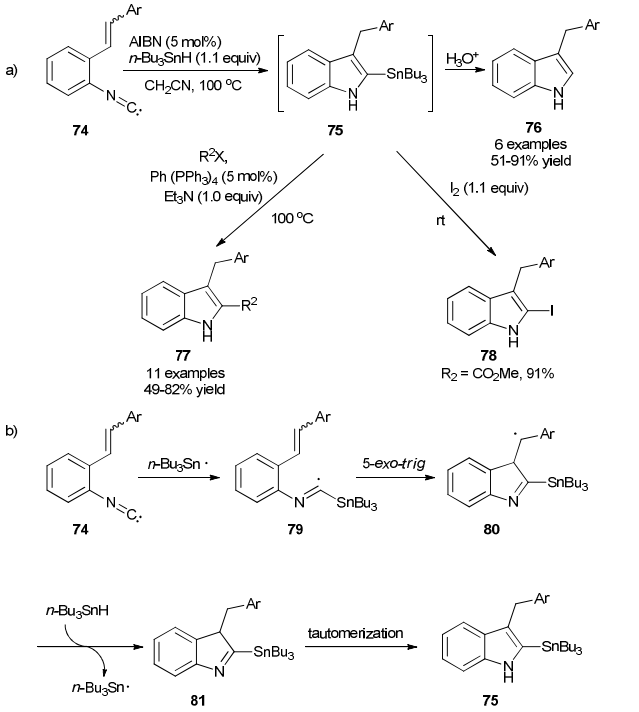


Scheme 23 6-Silylated phenanthridines *via* radical silylation of isonitriles by using trialkyl silanes as silyl radical precursors.

3. Synthesis of indole derivatives *via* radical isonitrile insertion reactions

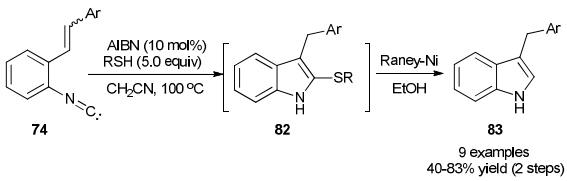
The indole scaffold is a privileged chemical entity that can be found in a wide range of natural products and drug candidates.[46] In the field of radical chemistry, some important advances have been made in the construction of the indole scaffold proceeding *via* isonitrile insertion reactions over the past 20 years.

In 1994, Fukuyama and co-workers described the formation of 2-stannylated indoles from 2-alkenylaryl isocyanides **74** and tri-*n*-butyltin hydride in the presence of AIBN as a radical initiator (a, Scheme 24).[47] It is noteworthy that the generated 2-stannylated indoles **75** could be readily converted to either 3-substituted (**76**) or 2,3-disubstituted indoles **77** by an acidic workup or palladium-mediated Stille coupling reactions in a one-pot procedure. Along with protons, 2-stannylated indoles **75** also react smoothly with other electrophiles, such as iodine, affording the 2-iodoindoles **78**, which are useful substrates for various cross-coupling reactions.[48] Thus, the developed cascade provides an efficient and convenient approach to various 3-substituted or 2,3-disubstituted indole derivatives. In the proposed mechanism, authors suggested that the initially formed tri-*n*-butyltin radical reacts with the 2-alkenylaryl isocyanide **74** to give the imidoyl radical **79**, which undergoes a 5-*exo*-*trig* cyclization to give radical **80**. Subsequently, **80** is reduced by tri-*n*-butyltin hydride to provide the intermediate **81**. Finally, tautomerization of **81** affords the targeted 2-stannylated indole **75** (b, Scheme 24).



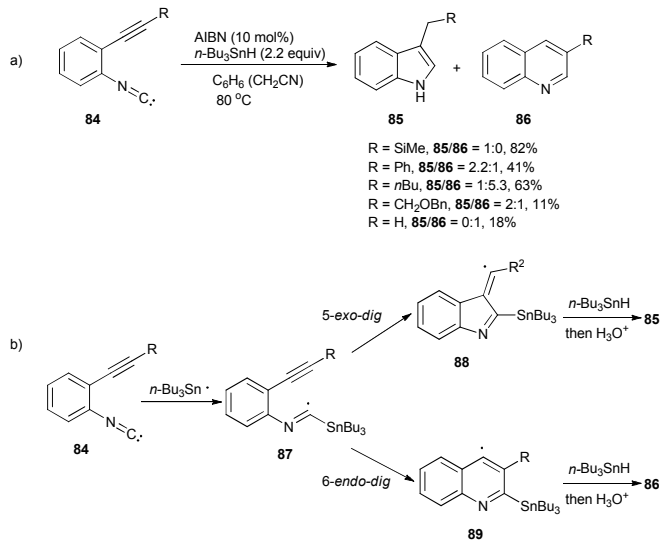
Scheme 24 Tri-*n*-butyltin radical induced synthesis of indoles using 2-alkenylphenyl isocyanides as radical acceptors.

As a continuation of these studies, Fukuyama and co-workers also accomplished selective formation of 2-alkylthiylindoles **82** by reacting isonitriles **74** with alkylthiols under radical conditions (Scheme 25).[49] The formed 2-alkylthiolated indoles **82** could be easily desulfurized after the radical cascade reaction by using Raney-Ni in EtOH to give the corresponding indoles derivatives **83**.



Scheme 25 Preparation of indoles by adding alkylthiyl radicals to 2-alkenylphenyl isocyanides.

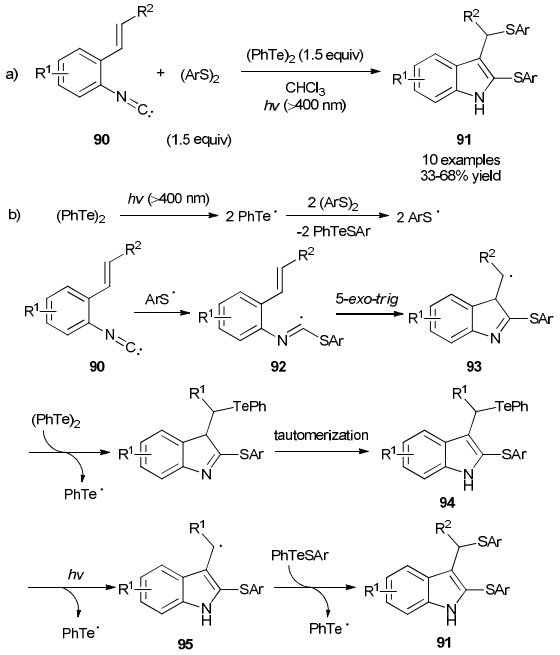
Shortly thereafter, Rainier and co-workers developed a similar strategy to construct 3-substituted indoles **85** by using tri-*n*-butyltin radical-mediated addition/cyclization sequence with 2-alkynylphenyl isocyanides **84** as substrates (a, Scheme 26).[50] In these processes, addition of the initially formed tri-*n*-butyltin radical to the isonitrile functionality in **84** generates the imidoyl radical **87**, which undergoes a 5-*exo*-*dig* cyclization to give vinyl radical **88** which subsequently abstracts a hydrogen atom from tri-*n*-butyltin hydride. The α,β-unsaturated imine thus generated is then hydrostannylated by Bu_3SnH. Finally, protodestannylation during acidic work-up eventually yields the 3-substituted indole **85**. However, the imidoyl radical **87** is in part undergoing a 6-*endo*-*dig* cyclization to give aryl radical **89** which upon tri-*n*-butyltin hydride reduction and subsequent protodestannylation provides the 3-substituted quinoline **86** (b, Scheme 26). The ratio of these two products depends on the nature of the alkynyl substituent of the starting isonitrile.



Scheme 26 Tri-*n*-butyltin radical induced synthesis of indoles by using 2-alkynylphenyl isocyanides as radical acceptors.

In 2011, Ogawa *et al.* reported a photoinduced intramolecular radical cascade cyclization of 2-alkenylphenyl isocyanides **90** with organic disulfides in the presence of diphenyl ditelluride (a, Scheme 27).[51] This reaction proceeds under mild conditions upon visible-light irradiation and provides the bisthiolated indoles **91** in moderate to good yields. In addition, the method exhibits good tolerance to various functional groups.

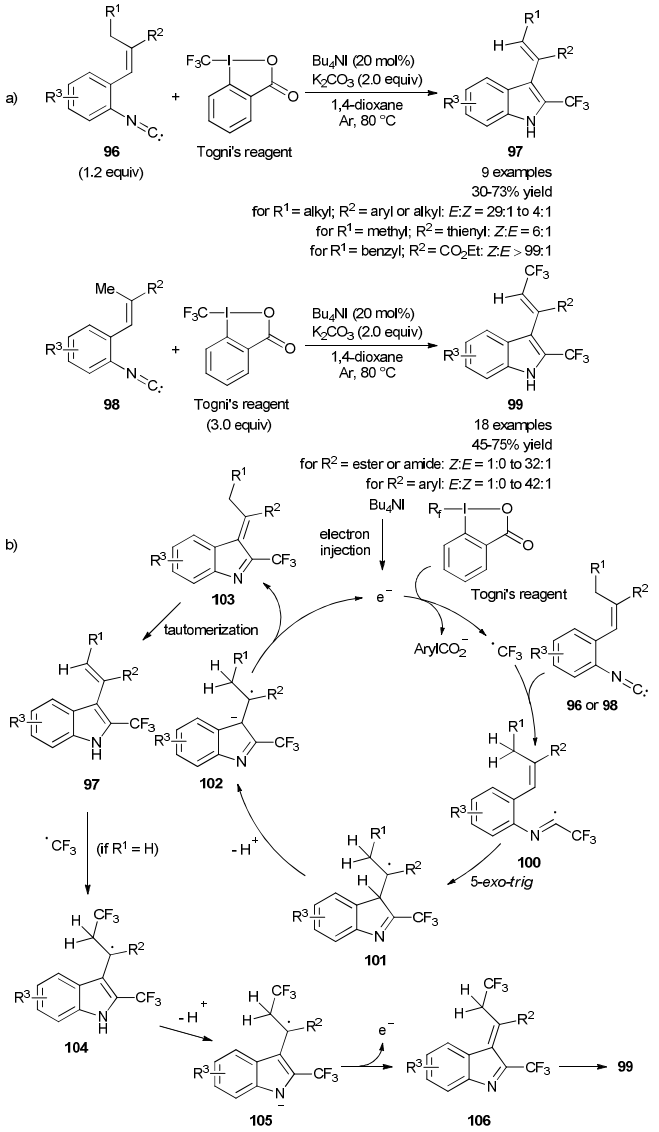
On the basis of author's previous work,[52] they proposed a possible reaction pathway for this interesting multistep transformation (b, Scheme 27). In the initiation step, the phenyltellanyl radical is generated by homolytic cleavage of diphenyl ditelluride upon photoirradiation, which reacts with the organic diaryldisulfide to form the corresponding arylthiyl radical. Addition of the ArS-radical to the isonitrile moiety in **90** gives the imidoyl radical **92**, which undergoes a 5-*exo-trig* cyclization to form the radical **93**. Subsequently, **93** is trapped by $(PhTe)_2$ followed by tautomerization to give indole derivative **94**. Homolytic cleavage of the C-Te-bond in **94** generates the radical **95** which reacts with PhTeSeAr *via* an ArS-group transfer process to provide the final indole **91** along with the PhTe-radical, thereby sustaining the radical chain.



Scheme 27 Photoinduced synthesis of indoles by using 2-alkenylphenyl isocyanides as radical acceptors.

Very recently, we described a novel approach to the synthesis of 2-trifluoromethylated indoles **97** starting with 2-alkenylphenyl isocyanides **96** and the commercially available Togni reagent as a CF_3 radical source (a, Scheme 28).[53] This reaction which is easy to conduct occurs with excellent *trans/cis*-stereocontrol. Importantly, the cascade proceeds without the help of any transition metal salt. Interestingly, in addition to the monotrifluoromethylated indoles **97**, the bistrifluoromethylated congeners **99** can be prepared by using 3.0 equiv of the Togni reagent in combination with 2-alkenylphenyl isocyanides **98** as starting materials.

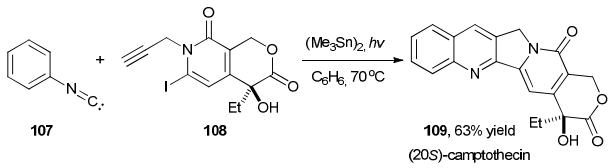
A radical capture experiment by TEMPO clearly revealed that CF_3 radicals are involved in these reactions. A possible reaction mechanism is proposed in Scheme 28b. Initiation of the radical chain occurs by SET reduction of the Togni reagent with Bu_4NI as an electron donor to generate the CF_3 radical. Addition of the CF_3 radical to the isonitrile carbon atom provides imidoyl radical **100**, which undergoes 5-*exo-trig* cyclization to give the tertiary alkyl radical **101**. Deprotonation of **101** by K_2CO_3 generates radical anion **102,** which formally liberates an electron to afford intermediate **103** thereby closing the catalytic cycle. Tautomerization of **103** finally provides the targeted monotrifluoromethylated indole **97**. If R^1 is an H-atom, addition of a second CF_3 radical to the C=C double bond in **97** is possible to afford the adduct **104**, which gets deprotonated by K_2CO_3 to radical anion **105**. The radical anion **105** formally expels an electron to give intermediate **106**. Finally, bistrifluoromethylated indole **99** is formed by tautomerization of **106**.



Scheme 28 2-Trifluoromethylated indoles by radical trifluoromethylation of isonitriles with Bu_4NI as the initiator.

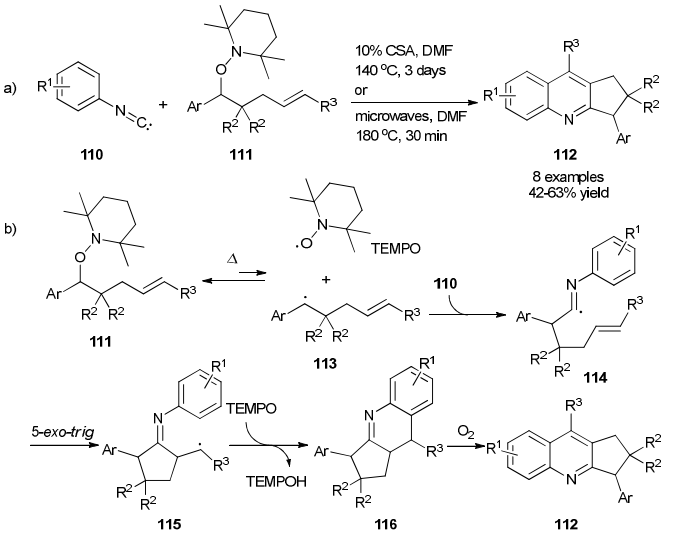
4. Synthesis of quinoline and quinoxaline derivatives *via* radical isonitrile insertion reactions

Construction of quinoline and quinoxaline skeletons *via* radical isonitrile insertion reactions has also been achieved. These heterocycles are important in various research areas, such as in natural product synthesis, in medicinal chemistry, and in materials science.[54] One of the most impressive example along these lines was reported by Curran and co-workers: radical cascade reaction of isonitrile **107** with halide **108** as a vinyl radical precursor directly provides the antitumor agent (20*S*)-camptothecin **109** in a good overall yield (Scheme 29).[55a] Later, Curran and co-workers reported the preparation of a 560-membered library of analogues of the natural product mappicine[55b] and a 115-membered library of analogues of homosilatecan[55c] *via* radical isonitrile insertion, convincingly illustrating how robust radical isonitrile chemistry is.



Scheme 29 (20*S*)-Camptothecin synthesis *via* a radical isonitrile insertion reaction.

In 2006, we developed an efficient approach for the preparation of quinolines starting from readily available alkoxyamines and aryl isonitriles *via* radical cascade/cyclization reactions (a, Scheme 30).[56] Simple heating of the two starting components **110** and **111** delivers the desired quinolines **112** in moderate to good yields. Notably, these reactions can also be carried out under microwave conditions and reaction times can be significantly shortened from 3 days to 30 min. The suggested mechanism is depicted in Scheme 30b. Thermal C-O bond homolysis of alkoxyamine **111** generates TEMPO along with the radical **113**, which will either react with TEMPO to reform starting material **111** or with the aryl isonitrile **110** to give the imidoyl radical **114**. The imidoyl radical **114** then reacts in a 5-*exo*-*trig* type cyclization to afford the alkyl radical **115**, which undergoes homolytic aromatic substitution to provide imine **116**, which gets readily oxidized by dioxygen during workup to provide the isolated quinoline **112**.

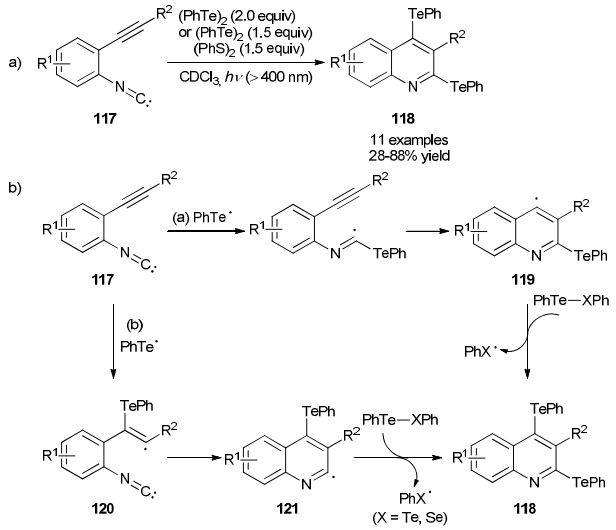


Scheme 30 Quinoline derivatives by radical isonitrile insertion reaction.

In 2009, Ogawa *et al.* reported a novel visible-light-induced radical cascade cyclization of 2-ethynylaryl isocyanides in the presence of diphenyl ditelluride, leading to bistellurated quinolines in moderate to good yields (a, Scheme 31).[57] Various functional groups are tolerated in this transformation. Noteworthy, the formed C-Te bond in the product can be readily cleaved by using an organolithium reagent.

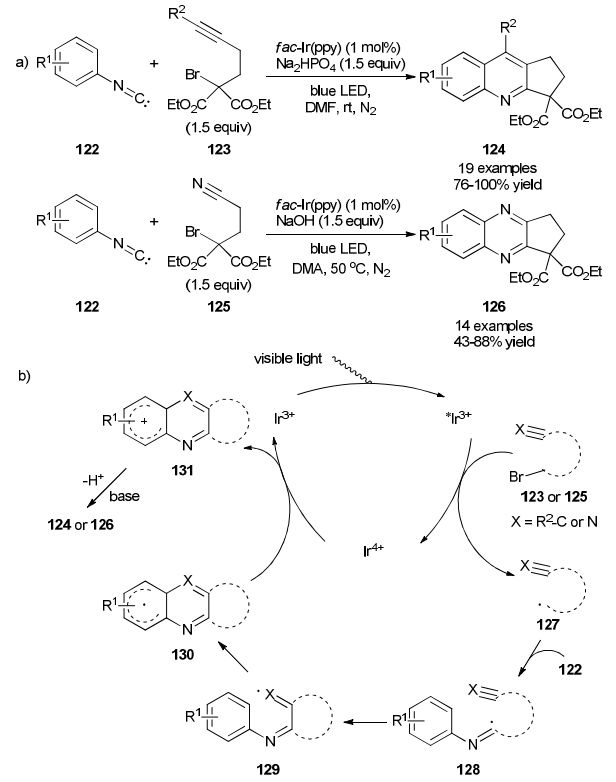
Two possible reaction mechanisms were proposed for this transformation (b, Scheme 31). In path a, addition of the generated PhTe radical to the isonitrile carbon atom affords the corresponding imidoyl radical which undergoes a 6-*endo*-*dig* cyclization to form the radical intermediate **119**. The radical intermediate **119** undergoes phenyltellanyl group abstraction to provide the quinoline **118**. In path b, addition of the phenyltellanyl radical to the ethynyl group provides a vinyl radical **120**, which undergoes 6-*endo* cyclization to give aryl

radical **121**. PhTe-group transfer eventually leads to the quinoline **118**.



Scheme 31 Photoinduced synthesis of quinolines using 2-alkenylphenyl isocyanides as radical acceptors.

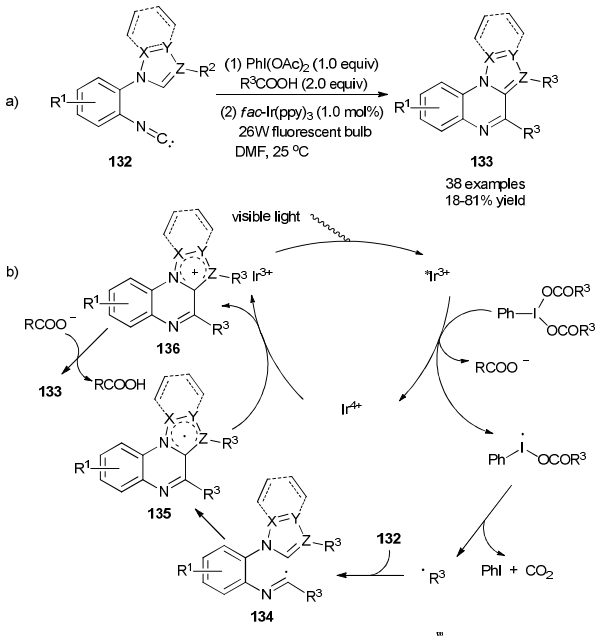
In 2014, Yu *et al.* developed a visible-light-induced radical isonitrile insertion reaction between aryl isonitriles **122** and bromides **123** or **125** to construct quinolines or quinoxalines (a, Scheme 32).[58] These reactions which show broad substrate scope can be conducted under mild conditions and products are obtained in good to excellent yields.



Scheme 32 Quinolines and quinoxalines *via* visible-light-induced radical cascade reactions.

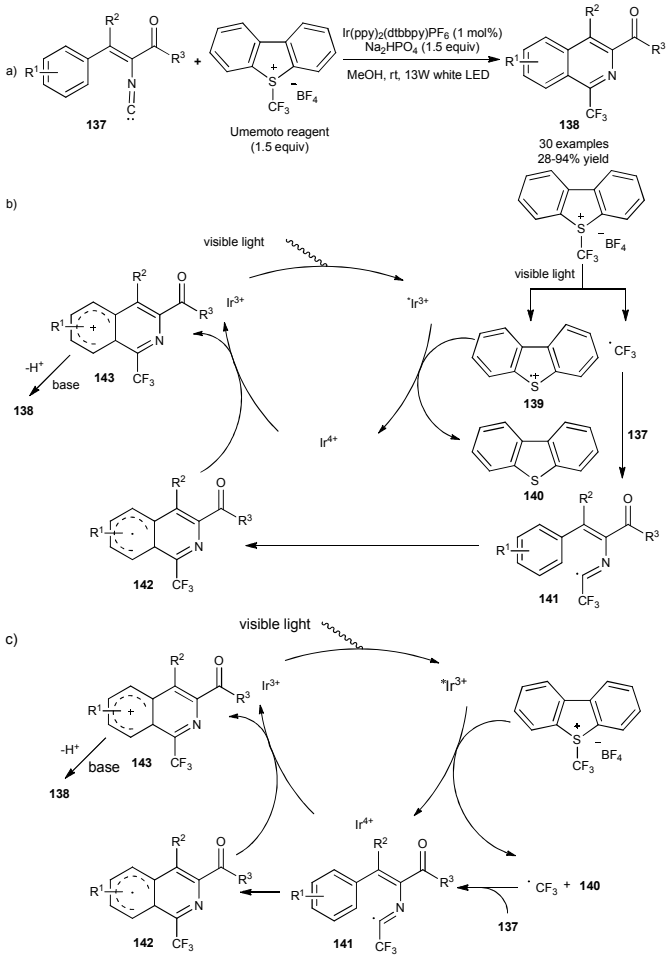
The authors proposed a possible mechanism for these transformations (b, Scheme 32). Firstly, the excited state photocatalyst $*Ir^{3+}$ is generated from Ir^{3+} under irradiation, which is oxidatively quenched by bromides **123** or **125** to produce the corresponding Ir^{4+} complex along with a malonyl radical **127**. The radical **127** subsequently adds to the isonitrile component to generate the imidoyl radical **128**, which then cyclizes to the triple bond to vinyl (X = CR^2) or iminyl (X = N) radical **129**. The radical **129** adds to the arene to afford the cyclohexadienyl radical **130**, which is oxidized by the Ir^{4+} complex to give the cationic intermediate **131** and Ir^{3+} catalyst, thereby closing the catalytic cycle. Finally, **131** gets deprotonated to yield the quinoline **124** or quinoxaline **126**.

More recently, Jamison *et al.* demonstrated a mild and efficient route to quinoxaline derivatives by a visible-light-induced decarboxylative radical cyclization of *ortho*-substituted arylisocyanides (a, Scheme 33).[59] This approach employs phenyliodine(III) dicarboxylates as a easily accessible radical precursors and exhibits excellent functional group compatibility. Interestingly, the authors achieved telescoped preparation of quinoxaline by integration of isonitrile formation and photochemical cyclization in a three-step continuous flow system.



Scheme 33 Quinoxaline synthesis *via* visible-light-induced radical isonitrile insertion reaction.

A plausible catalytic cycle for this valuable process was proposed by the authors (b, Scheme 33). Firstly, the phenyliodine(III) dicarboxylate, *in situ* generated from $PhI(OAc)_2$ and R_3COOH, is reduced by the excited state of $*Ir^{3+}$ to afford *via* a carboxyl radical an alkyl radical and an Ir^{4+} complex. Subsequently, the alkyl radical adds to isonitrile **132** to give an imidoyl radical **134**, which undergoes cyclization to provide the radical intermediate **135**. The radical intermediate **135** is next oxidized by the Ir^{4+} complex to form the corresponding cation **136** thereby regenerating the initial Ir^{3+} complex, which enters the next catalytic cycle. Finally, deprotonation of **136** by the carboxylate anion provides the product **133**.



Scheme 34 1-Trifluoromethylated isoquinolines *via* visible-light-induced radical isonitrile insertion reaction.

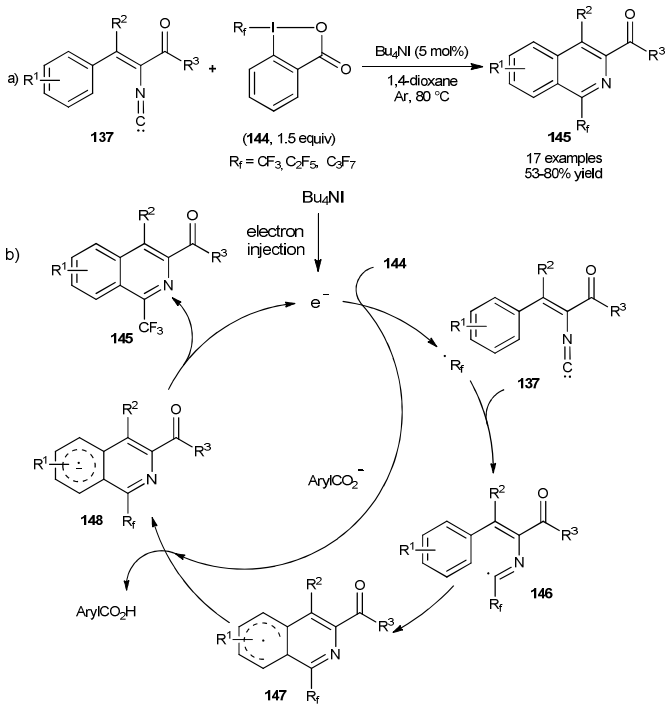
5. Synthesis of isoquinoline derivatives *via* radical isonitrile insertion reactions

5.1 Radical isonitrile insertion reaction of 2-isocyanobiphenyls with trifluoromethyl radicals

The isoquinoline scaffold is found in various natural products, drug candidates, and biologically active compounds.[60] Thus, there is continuing interest in the development of novel synthetic methods for the preparation of isoquinolines. Along these lines, Yu *et al.* described an efficient approach to construct 1-trifluoromethylated isoquinolines **138** in good to excellent yields (a, Scheme 34).[61] These cascades proceed *via* visible-light-induced radical isonitrile insertion reactions by using the Umemoto reagent as a CF_3 radical precursor under mild conditions. Isoquinolines **138** were obtained in moderate to good yields.

On the basis of experimental observations and theoretical calculations, authors proposed the mechanism depicted in Scheme 34b. Visible light-induced S-CF_3-homolysis of the Umemoto reagent forms the CF_3 radical and the sulfur-centered radical cation **139**. Radical cation **139** is reduced to sulfide **140** by the excited state $*Ir^{3+}$, which is generated from Ir^{3+} upon irradiation with a 13W white LED. Addition of the CF_3 radical to vinyl isocyanide **137** gives the imidoyl radical **141**, which undergoes cyclization to cyclohexadienyl radical **142**. Then, **142** gets oxidized by Ir^{4+} to form cyclohexadienyl cation **143** along with Ir^{3+}. Finally, deprotonation yields the 1-trifluoromethylated isoquinoline **138**. In addition, an alternative mechanism was also proposed for the same transformation based on a previous report (see c, Scheme 34).[12]

Shortly thereafter, we reported a simple and metal-free approach to 6-fluoroalkylated isoquinolines **145** starting with vinyl isocyanides **137** and the Togni reagent or readily prepared derivatives thereof (**144**) as fluoroalkyl radical precursors.[62] The radical cascade uses Bu_4NI as a radical initiator and various 6-fluoroalkylated isoquinolines **145** were obtained in good yields (a, Scheme 35). Based on previous reports,[9,10,25] a plausible mechanism considering the electron as a catalyst was proposed as depicted in Scheme 35b. SET reduction of **144** provides the corresponding fluoroalkyl radical which then adds to the isonitrile carbon atom in **137** to give the imidoyl radical **146**. Base promoted homolytic aromatic substitution *via* **147** and **148** leads to product **145** along with the electron which enters the next catalytic cycle.

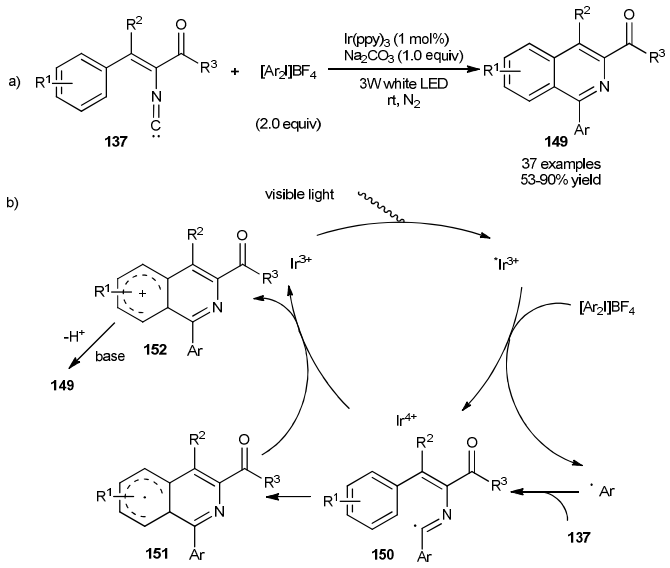


Scheme 35 1-Fluoroalkylated isoquinolines *via* radical fluoroalkylation of isonitriles by using Bu_4NI as an initiator.

5.2 Radical isonitrile insertion reaction of 2-isocyanobiphenyls with aryl radicals

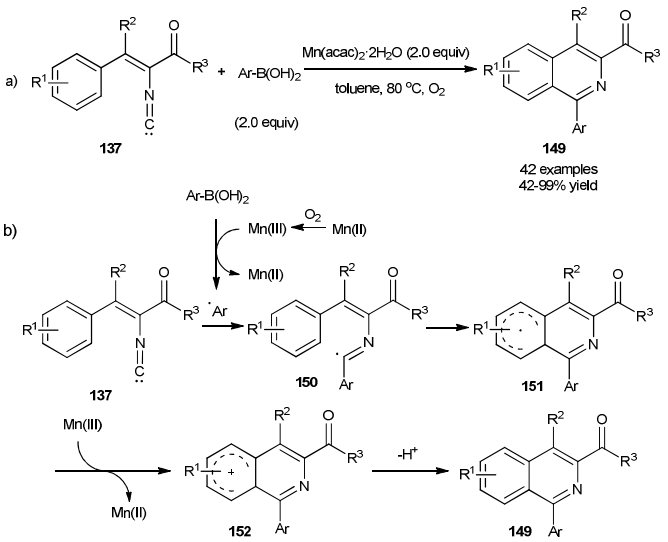
Aryl radicals were also applied as reactive intermediates in radical vinyl isonitrile insertion reactions for the preparation of 1-arylated isoquinolines. Recently, Yu *et al.* described the first examples of visible-light-induced radical arylation of vinyl isonitriles with diaryliodonium salts as aryl radical sources (a, Scheme 36).[63] This methodology offers rapid access to 1-arylated isoquinolines **149** bearing various functional groups in good to excellent yields. Importantly, reactions proceed at room temperature without the use of any external stoichiometric oxidant.

On the basis of a series of control experiments, the authors proposed a plausible catalytic cycle (b, Scheme 36). The first step is the formation of excited state $*Ir^{3+}$ from Ir^{3+} by irradiation with a 3W white LED bulb. Subsequently, $*Ir^{3+}$ is oxidatively quenched by the diaryliodonium salt to form an Ir^{4+} complex along with an aryl radical which adds to the vinyl isonitrile **137** to provide the imidoyl radical **150**. Radical **150** then cyclizes to the arene to give the radical intermediate **151**, which is oxidized by the Ir^{4+} complex to afford cyclohexadienyl cation **152**. Finally, deprotonation of **152** gives the 1-arylated isoquinoline **149**.



Scheme 36 1-Arylated isoquinolines *via* visible-light-induced radical isonitrile insertion reaction.

Alternatively, 1-(hetero)arylated isoquinolines **149** were also successfully prepared by Xu and co-workers *via* manganese(II)/O_2 promoted radical cascade reactions from vinyl isocyanides **137** and arylboronic acids as aryl precursors.[64] This method features a broad substrate scope and provides access to a series of 1-arylated isoquinolines with operational simplicity in good to excellent yields (a, Scheme 37). Preliminary mechanistic studies revealed that aryl radicals are likely involved in these transformations.



Scheme 37 1-Arylated and 1-heteroarylated isoquinolines by using organoboron reagents as radical precursors.

A reasonable mechanism as suggested by the authors is shown in Scheme 37b. Aryl radical generation occurs by oxidation of the arylboronic acid with $Mn(OAc)_3$.[65] The aryl radical then reacts with the isonitrile to **150**. Cyclization onto the arene generates the cyclohexadienyl radical **151** which gets oxidized by $Mn(OAc)_3$ to the cation **152**. Deprotonation eventually leads to product **149**.

Conclusions

Radical isonitrile insertion reactions are highly valuable for the construction of various important nitrogen containing heterocycles. In this review, recent progress and also pioneering efforts on the synthesis of nitrogen heterocycles *via* radical cascade reactions using isonitriles as radical acceptors have been discussed. It is shown that phenanthridines, indoles, quinolines, quinoxalines, and isoquinolines are readily accessible by using this approach in a straightforward modular way. The many successful examples presented convincingly document the high potential of this approach in drug discovery, organic synthesis, and materials science. Despite great achievements over the past few years in this area, many challenges and problems remain to be solved. For instance, most of the cascades discussed herein work with two different reaction partners. Multi-component radical isonitrile insertion reactions comprising three or even more components, which would further enlarge structural space of the accessible compounds, are not well explored. It is obvious from the high activities in this area that exciting results along these lines can be expected in the near future.

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Notes and references

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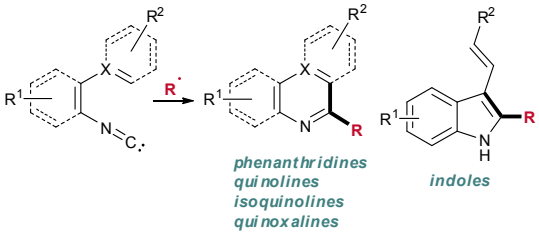
Table of contents entry:



Radical isonitrile insertion reactions are highly valuable for construction of N-containing heterocycles such as phenanthridines, quinolines, isoquinolines, quinoxalines and indoles.