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Synthesis of Nitrogen-Containing Heterocycles via Imidoyl or Iminyl Radical Intermediates

Jian Lei, Dengke Li, and Qiang Zhu

Abstract Synthesis of nitrogen-containing heterocycles with isocyanides, isothiocyanates, nitriles, imines, oxime derivatives, and other related compounds has been deeply investigated in organic synthesis. This chapter mainly focuses on summarizing radical cyclization reactions of these C-N unsaturated precursors to afford *N*-heterocycles in the past decade as well as some earlier feature examples. In most cases, imidoyl or iminyl radicals are involved in cyclizing onto unsaturated systems or heteroatoms to generate *N*-heterocycles, such as phenanthridines, (iso) quinolines, pyridines, indoles, and pyrroles. A few examples via other types of radical intermediates starting from isothiocyanates, isocyanates, and analogous structures are also included.

Keywords Cyclization reactions · Homolytic substitution · Imidoyl radicals · Iminyl radicals · Nitrogen heterocycles · Radical reactions

Contents

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1 Introduction

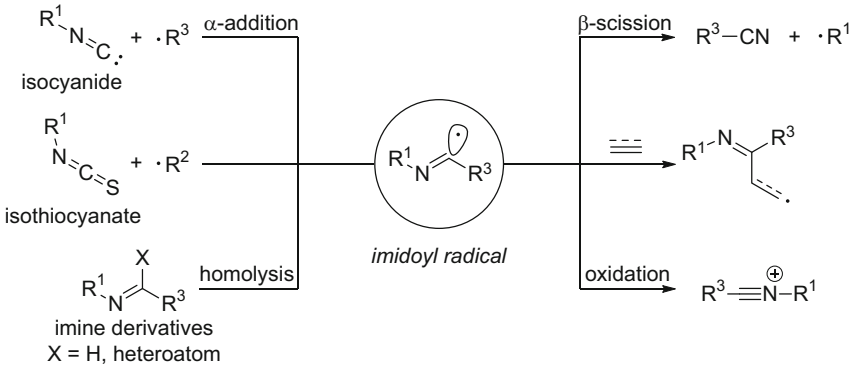
Structures containing carbon-nitrogen unsaturated bonds, including double and triple bonds, are widely distributed, showing diverse reactivity in organic synthesis.

Substrates containing C-N unsaturated bonds are also extensively applied in radical reactions. In this chapter, radical cyclization reactions involving isocyanides, isothiocyanates, nitriles, imines, oxime derivatives, and other related compounds to afford *N*-heterocycles are summarized. In most of the processes, imidoyl and iminyl radical intermediates are formed, generated from the corresponding C- and N-centered radicals. The review is organized around functional groups that generate these two types of radicals.

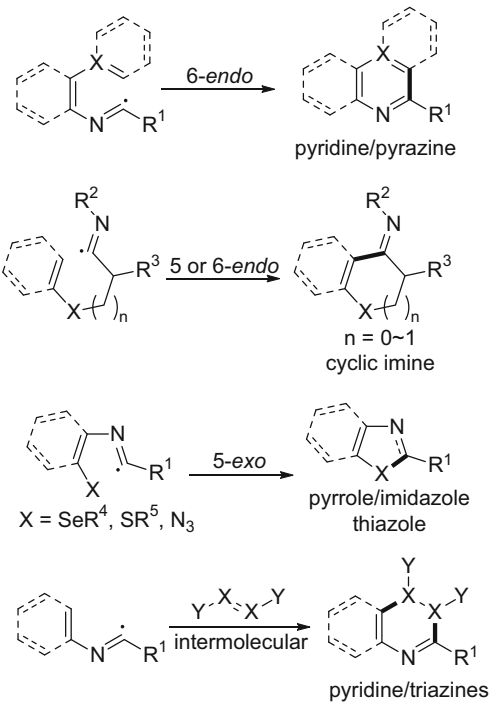
Imidoyl radical was first described over 50 years ago, and a comprehensive review covering its history, generation, structure, and reactivity was presented by Nanni in 2007 [1]. General structure of imidoyl radical can be described as a carbon radical with a single electron occupying the σ-orbital of the imidoyl group [2]. The most common way to give an imidoyl radical is α-addition of carbon-, tin-, sulfur-, phosphine-, oxygen-, and tellurium-centered radicals onto isocyanide. Radical addition to isothiocyanates also generates the corresponding sulfur-containing imidoyl radical, although limited examples were available in the literature. Homolysis of imines and their derivatives is also an efficient way to give related imidoyl radicals. The unique structure of imidoyl radical leads to three special reactivities, such as α-scission to go back to isocyanide [3] or β-scission to generate nitrile and another radical [4], which is used in cyanation or deamination [5]; oxidation of imidoyl radicals to nitriliums followed by nucleophilic attack to provide amide derivatives is also reported (Scheme 1) [6, 7].

Most importantly, like other radicals, imidoyl radicals can be trapped by alkenes, alkynes, or arenes, to generate a variety of *N*-heterocycles when processes take place intramolecularly. This process is probably the most useful transformation of imidoyl radicals, and thus it has been deeply investigated during the past decade. The products are normally 5-membered or 6-membered heterocycles including pyridines, pyrroles, pyrazine, and imidazoles (Scheme 2).

The study of iminyl radicals through EPR spectroscopy traces back to 50 years ago, [8] figuring that the single electron occupies a 2p orbital that lies orthogonal to the π-orbitals of the C-N double bond [9, 10]. The practical generation pathways of iminyl radicals include addition of carbon or nitrogen radicals to nitriles; thermal or photo-homolysis of N-X bonds in oxime derivatives, in which X may refer to O, S, N, Cl, and H; and decomposition of organic azides to release nitrogen and iminyl

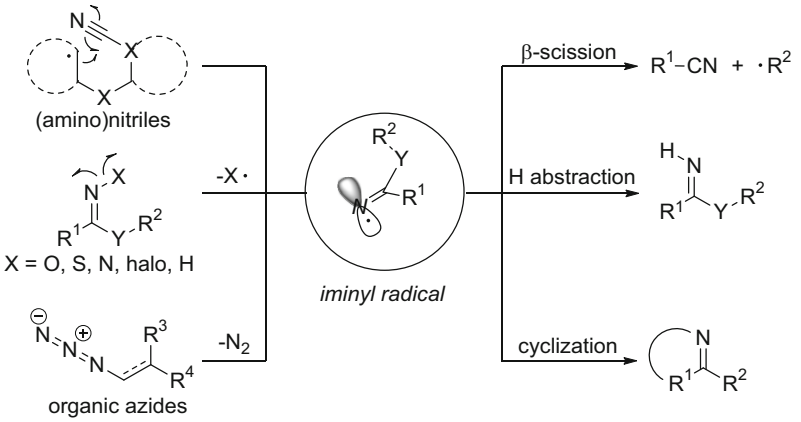


Scheme 1 Generation and conversion of imidoyl radicals

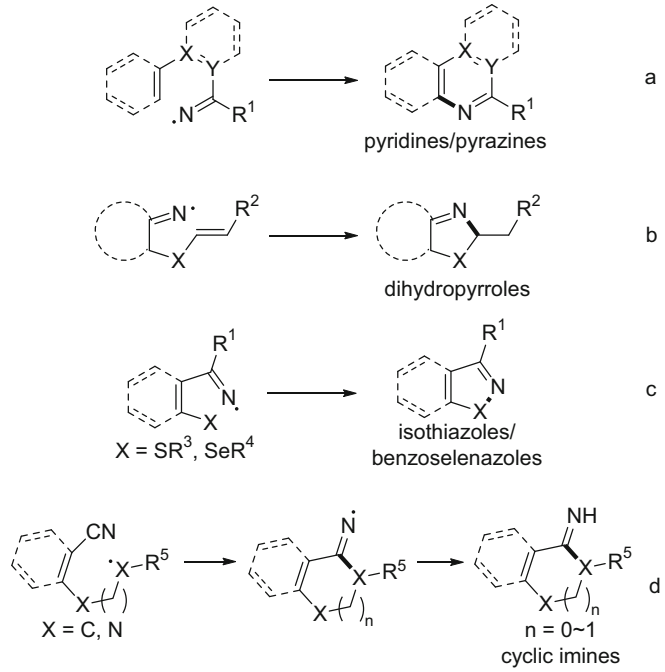


Scheme 2 Scaffolds of cyclization products of imidoyl radicals

radicals (Scheme 3). However, organic azides are not covered in this chapter for their special structure and reactivity [11, 12]. Like imidoyl radicals, the major fate of iminyl radicals is trapping by intramolecular functional groups to give nitrogen heterocycles including pyridines/pyrazines, dihydropyrroles, isothiazoles, etc. (Scheme 4). Other pathways to iminyl radical include β-scission into nitriles and alkyl radicals [13] and hydrogen abstraction to form imines and subsequent



Scheme 3 Generation and transformation of iminyl radicals



Scheme 4 Basic scaffolds of annulation products of iminyl radicals

hydrolysis into ketones. Recently, Walton and Castle reported several reviews on synthesis utilizing iminyl radicals [14–16].

Cyclization of imidoyl/iminyl radicals can result into the following two types of products: one in which both C and N atoms in the C=N bond are present into the ring (route a, b, c, Scheme 4) and the other in which only the carbon in C=N participates to the ring construction, the N atom in the heterocycle coming from

other functionalities (route d, Scheme 4). In the following parts, radical cyclization has been organized around the nature of the substrate functional groups.

2 Cyclization via Imidoyl Radicals

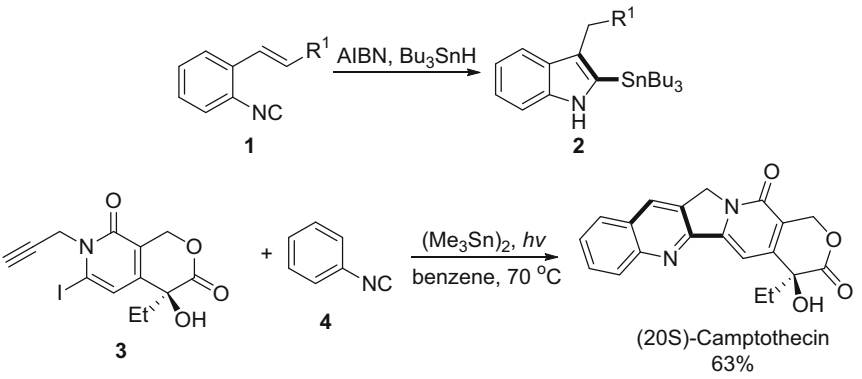
2.1 Starting from Isocyanides

Isocyanide which is isoelectronic to carbon monoxide is well-known for its versatility in bond formation. The resonance structures of isocyanide can be described as in Eq. (1). The two resonance forms are responsible for its amphiphilic reactivity [17–20], its reactivity in radical-mediated [21], and in transition metal-catalyzed insertion [22–24].

(1)

The terminal divalent carbon of isocyanide can form an imidoyl radical by accepting a radical species, forming simultaneously a σ-bond and a radical on the geminal carbon. Subsequent intramolecular addition of the resulting imidoyl radical onto unsaturated bonds or heteroatoms forms nitrogen heterocycles after radical termination. Thus, the whole cyclization process consists in the formation of two chemical bonds from the isocyanide carbon.

Cyclization of imidoyl radical to synthesize nitrogen heterocycles has been reported for decades. A seminal application of this strategy was developed by Curran for the synthesis of camptothecin and its derivatives [25–27]. Another early example was demonstrated in indole alkaloids synthesis, also known as Fukuyama indole synthesis [28–31]. These reactions could be performed under mild conditions with high bond forming efficiency, thus providing efficient alternatives for *N*-heterocycle construction. However, toxic tin reagents were inevitably used in these processes (Scheme 5).



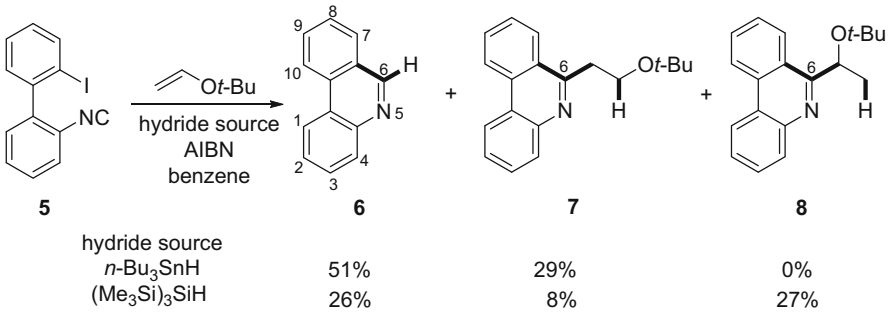
Scheme 5 Fukuyama's indole synthesis and Curran's approach to camptothecin

In recent years, significant development has been made in this area owing to the application of new free radical generation protocol and diversified functionalized isocyanides. Reviews on the synthesis of nitrogen heterocycles via imidoyl radical intermediates generated from isocyanides were reported by Studer, Xu, and Zhu group [32–34].

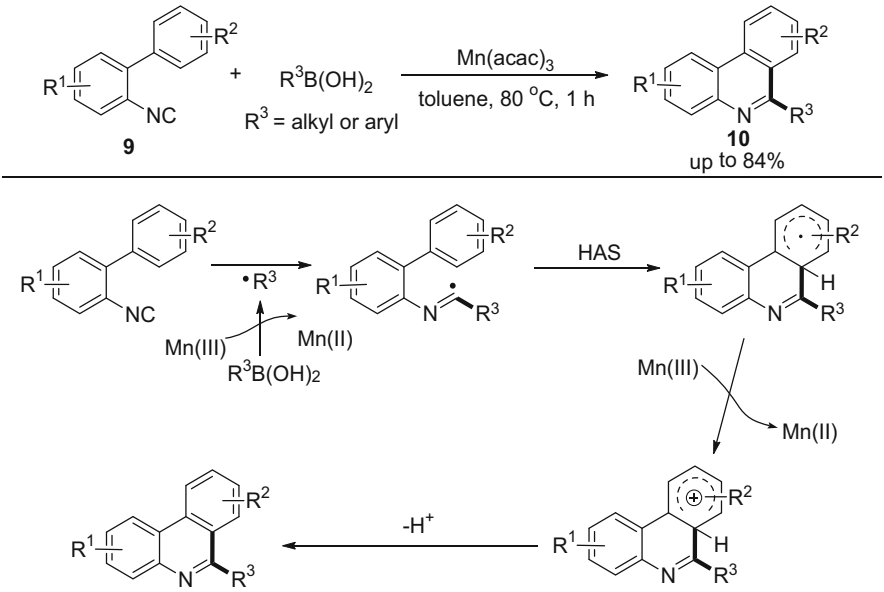
The phenanthridine core is widely distributed in natural and synthetic compounds exhibiting various biological activities [35, 36]. In 1995, Nanni reported the synthesis of 6-cyanopropyl-substituted phenanthridines with 2-isocyanobiphenyl with the aid of AIBN via an imidoyl radical intermediate [37]. Beyond cyanopropyl radical generated from AIBN, phenyl and tristrimethylsilylsilyl radicals may also be incorporated at C6 in phenanthridines. In 2000, Smith described another high-yield approach to 6-alkyl phenanthridines, starting from 2′-iodo-2-isocyanobiphenyls in the presence of *n*-Bu_3SnH/AIBN (Scheme 6) [38]. Interestingly, in the presence of excess vinyl *t*-butyl ether, addition of phenanthridine C6 radical to vinyl *t*-butyl ether affords C6-alkylated products.

In 2012, Chatani reported a novel imidoyl radical cyclization reaction starting from 2-isocyanobiphenyls and boronic acids promoted by $Mn(acac)_3$ to afford the C6-aryl- or alkyl-substituted phenanthridines in good yields (Scheme 7) [39]. Mechanistic studies revealed that over two equivalents of manganese were necessary, since $Mn(acac)_3$ acted as a single-electron oxidant for both radical generation from boronic acids and oxidation of the cyclohexadienyl radical into the corresponding cation. Moreover, the reaction was shut off by addition of TEMPO, suggesting that radical intermediates were involved in the reaction. The mechanism they proposed was well accepted, and similar mechanisms were reported in most of the following studies using other radical species.

Zhu reported an alternative method for the synthesis of 6-arylphenanthridines using aryl radicals generated in situ from inexpensive and readily available anilines and *t*-BuONO [40]. Both radical clock and radical inhibition experiments revealed that aryl radical intermediates were involved. It is known that imidoyl radicals are prone to oxidation into nitriliums. Therefore, a competitive reaction pathway was proposed, including an intramolecular homolytic aromatic substitution (HAS) or a SET oxidation to nitrilium followed by an electrophilic aromatic substitution.



Scheme 6 Phenanthridine synthesis with 2′-iodo-2-isocyanobiphenyls



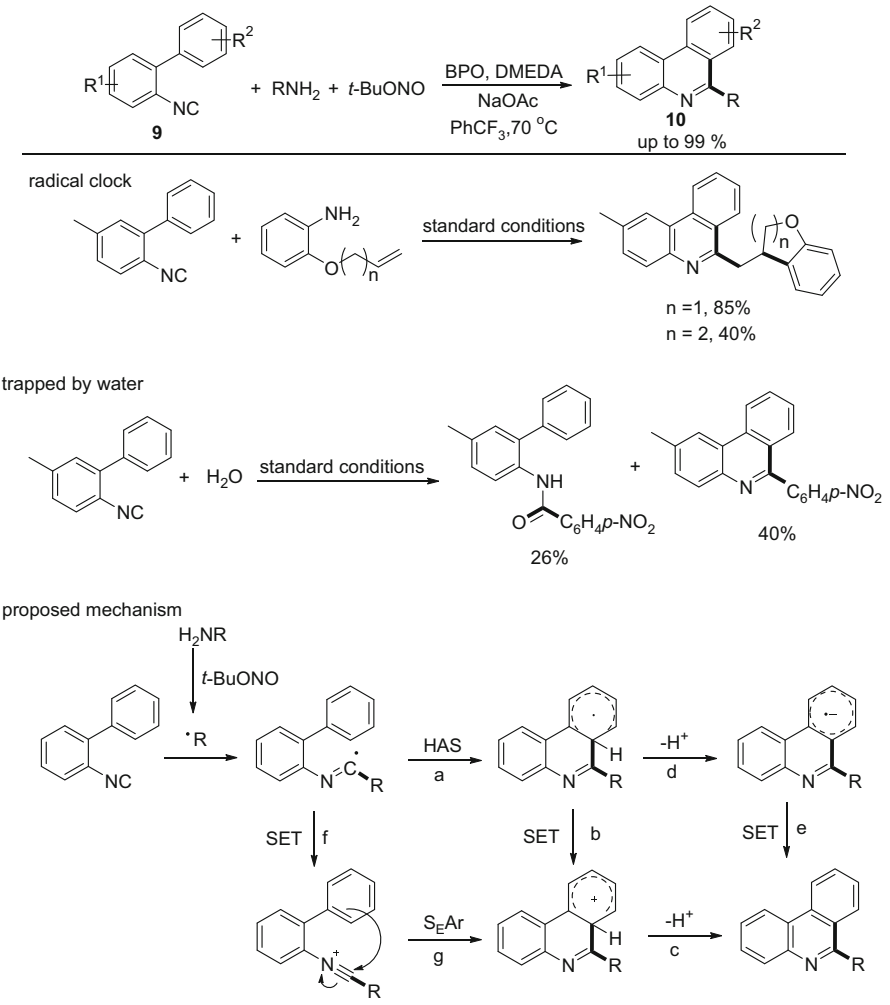
Scheme 7 Synthesis of 6-aryl/alkylphenanthridines from organoborons and $Mn(acac)_3$

When water was added into the reaction medium, the related amide product derived from addition of water to the nitrilium intermediate was isolated in low yield (vide infra). The Hammett curve with unsymmetrical 2,6-diaryl phenylisocyanides suggested that both pathways involving S_EAr of nitrilium cation and HAS of imidoyl radical were likely involved in the annulation step (f vs. a, Scheme 8). The importance of phenanthridine scaffold has prompted the incorporation of various radicals including CF_3, aryl, alkyl, $C_xH_yF_z$, acyl, phosphine, and silyl radicals to synthesize various C6-substituted phenanthridines [32–34].

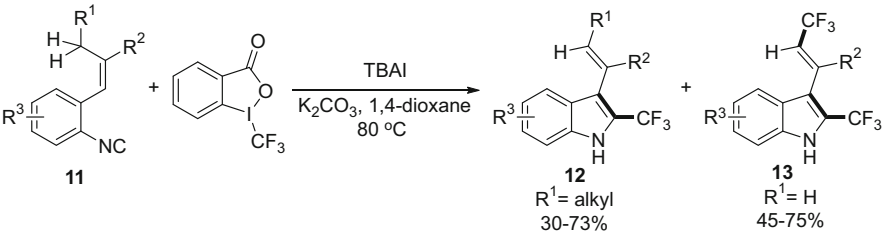
Beyond phenanthridines, other heterocycles can also be synthesized with this method by modifying isocyanide structure. For example, Studer reported radical trifluoromethylation/cyclization of 2-vinyl-substituted arylisocyanide **11** with hypervalent iodine-CF_3 reagent (Togni's reagent) and TBAI as an initiator to afford 2-trifluoromethylated indoles **12** via 5-*exo-trig* cyclization (Scheme 9) [41, 42]. When R^1 is a hydrogen, the 3-alkenyl product was trifluoromethylated further with excess Togni's reagent to provide **13**.

When 2-alkynyl arylisocyanide was used as radical acceptor, 2-substituted quinolines were synthesized. Ogawa described the synthesis of 2,4-bis-chalcogenated quinolines via visible-light-induced chalcogenation of isocyanides in modest to good yield (Scheme 10) [43]. Besides the mechanism involving an imidoyl radical-mediated cyclization, an alternative approach through addition of a phenyltellurium radical to alkyne, followed by capture of the resulting vinyl radical with isocyanide, was proposed. The 2-quinolinyl radical was then quenched by dichalcogenides to give the final product **15**.

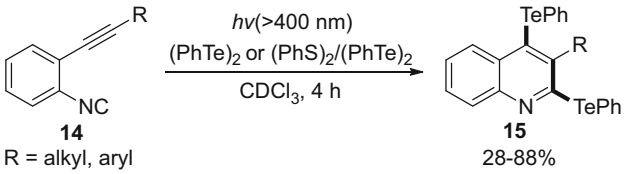
When vinyl isocyanide was used as substrate, isoquinoline or pyridine derivatives could be obtained. In 2014, Yu reported visible-light-promoted cyclization of



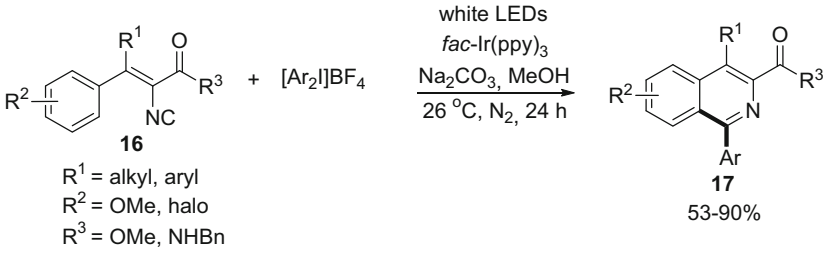
Scheme 8 Synthesis of 6-arylphenanthridines from anilines and *t*-BuONO



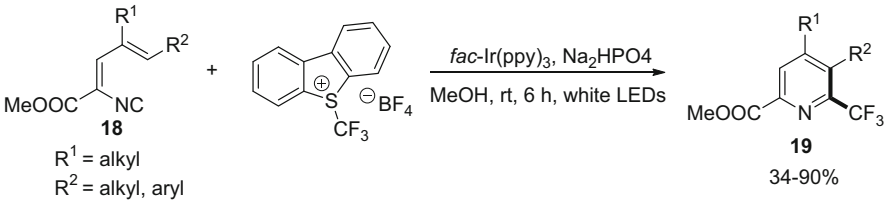
Scheme 9 Synthesis of 2-trifluoromethylated indoles with 2-vinyl arylisocyanides



Scheme 10 Reaction of O-ethynylarylisocyanides with dichalcogenides



Scheme 11 Synthesis of isoquinolines using isocyanide and diaryliodonium salt

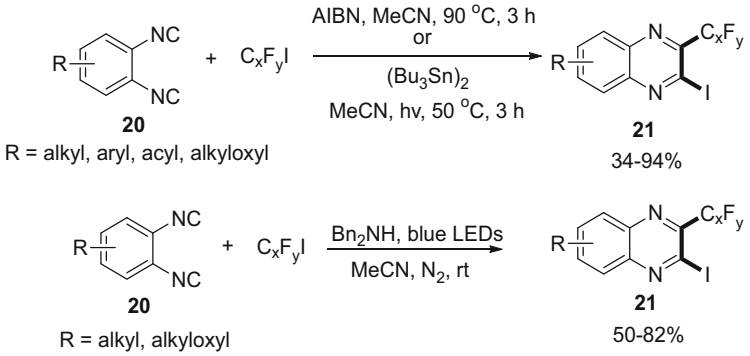


Scheme 12 Reaction of vinyl isocyanides and Umemoto's reagent to synthesize polysubstituted pyridines

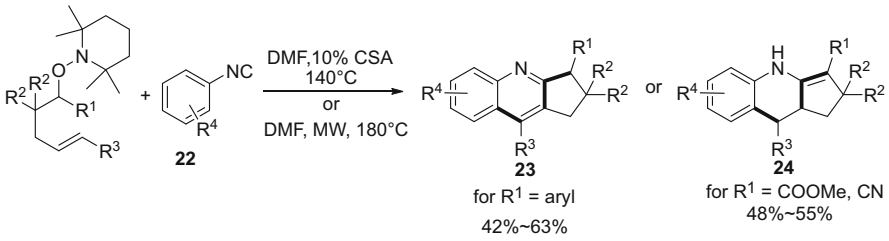
vinyl isocyanides with diaryliodonium salts to afford isoquinolines **17** (Scheme 11) [44]. Later on, they used 1,3-dienyl isocyanides to synthesize 2-(fluoro)alkylated pyridine derivatives **19** in the presence of Umemoto's reagent under visible-light conditions (Scheme 12) [45].

Recently, Studer and Yu independently explored reactions of *ortho*-diisocyanoarenes as radical acceptors with (perfluoro)alkyl iodides to provide (perfluoro)alkyl-substituted iodoquinoxalines **21** [46, 47]. The former used traditional AIBN or Bu_3SnH/*hv* to initiate the reaction; the latter applied amines as halo-bond acceptor to promote the generation of fluoro-bearing radicals under visible-light irradiation. Following double addition of perfluoroalkyl radicals to isocyanide, an atom transfer radical addition (ATRA) took place to furnish 2-iodo-3-(perfluoro)alkyl quinoxalines in modest to excellent yields (Scheme 13).

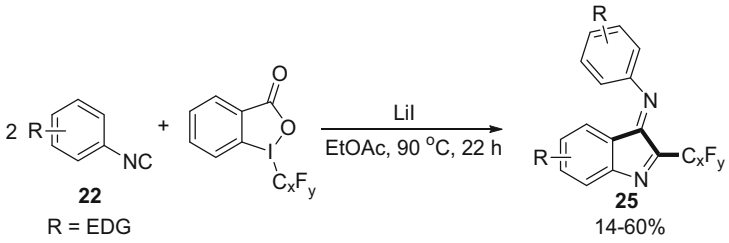
The unsaturated functionality to trap the imidoyl radical intermediate may also be introduced in situ. Pioneering work in this context was reported by Curran and coworkers during their studies on the synthesis of camptothecin and analogous alkaloids [25–27]. Later development on this protocol was developed by Studer



Scheme 13 Synthesis of iodinated (perfluoro)alkyl quinoxalines using *ortho*-diisocyanoarenes



Scheme 14 Quinoline synthesis with arylisocyanide and alkoxyamines



Scheme 15 Synthesis of indole-3-imines via a three-component reaction involving isocyanides

[48, 49]. In their approach, thermal homolysis of vinyl-substituted alkoxyamines generated alkyl radicals, which added intermolecularly to isocyanides. Sequential 5-*exo-trig* cyclization of imidoyl radical, HAS process of the alkyl radical intermediate, and rearomatization led to quinolines **23** or dihydroquinolines **24**, depending on the nature of R^1 substituent (Scheme 14).

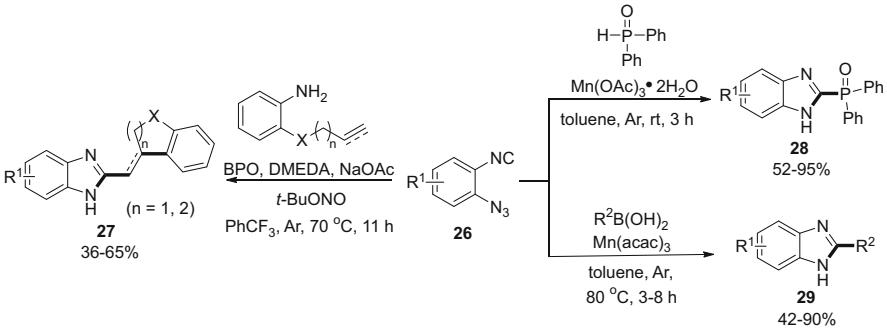
Studer and coworkers developed a multicomponent reaction in which they observed a double addition of (perfluoro)alkyl radical to arylisocyanide, yielding 2-substituted indole-3-imines **25** in low to modest yields (Scheme 15) [50].

In most cases, intramolecular imidoyl radical cyclization forms a C-C σ-bond. However, heteroatoms, like sulfur (see Sects. 2.2 and 2.3) and nitrogen, can also trap imidoyl radicals. Very recently, Zhu's group reported the first intramolecular

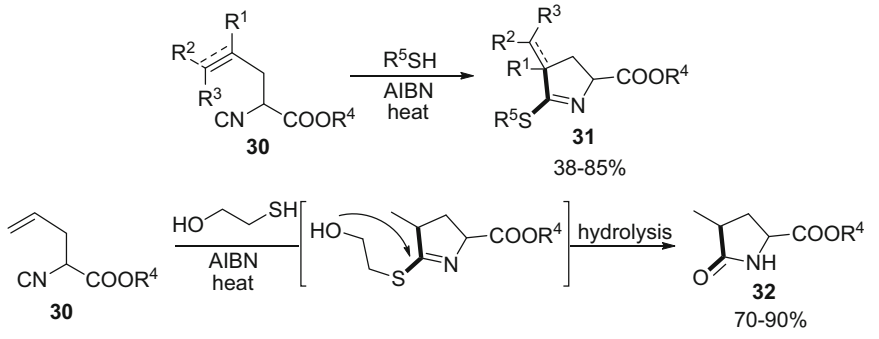
nitrogen trap for imidoyl radicals to synthesize 2-substituted benzoimidazoles starting from 1-azido-2-isocyanoarenes **26** (Scheme 16) [51, 52]. Phosphinoyl, aryl, and alkyl radicals were added to the isocyanide carbon, which was followed by a denitrogenative imidoyl radical cyclization affording the desired products. Tandem reactions to achieve synthesis of complex heterocycle-linked benzoimidazole derivatives were also realized.

Preparation of aliphatic heterocycles from isocyanide is less common in literature. Bachi reported the synthesis of pyrrolines from amino acid-derived isocyanides with suitable alkenyl or alkynyl substitution [53]. Sulfur-centered radical initiated the cyclization, delivering 2-thiopyrrolines or pyroglutamates when using 2-mercaptoethanol (Scheme 17).

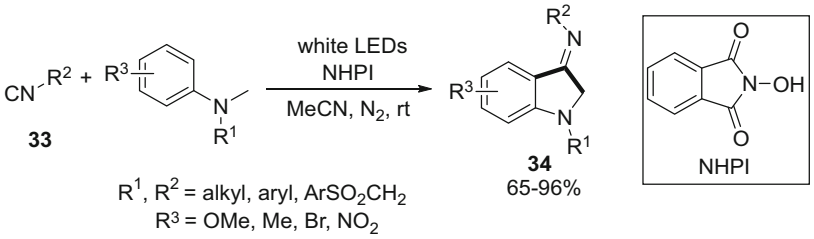
Very recently, Yadav reported radical cyclization reaction of *N*-methylanilines with isocyanides to synthesize 3-iminodihydroindoles **34** with the help of *N*-hydroxyphthalimide (NHPI) under visible-light conditions [54]. *N*-methylanilines reacted with *N*-hydroxyphthalimide radical by SET to form a radical cation. Then, *N*-methyl radical was formed after proton transfer, followed by addition to isocyanide, imidoyl radical cyclization, and aromatization to give the final 3-iminodihydroindoles (Scheme 18).



Scheme 16 Synthesis of benzoimidazoles from 1-azido-2-isocynoarenes



Scheme 17 Cyclization of amino acid-derived isocyanides to access 2-thiopyrrolines



Scheme 18 Cyclization of *N*-methylanilines with isocyanides to genesis of 3-iminodihydroindoles

2.2 Starting from Isothiocyanates

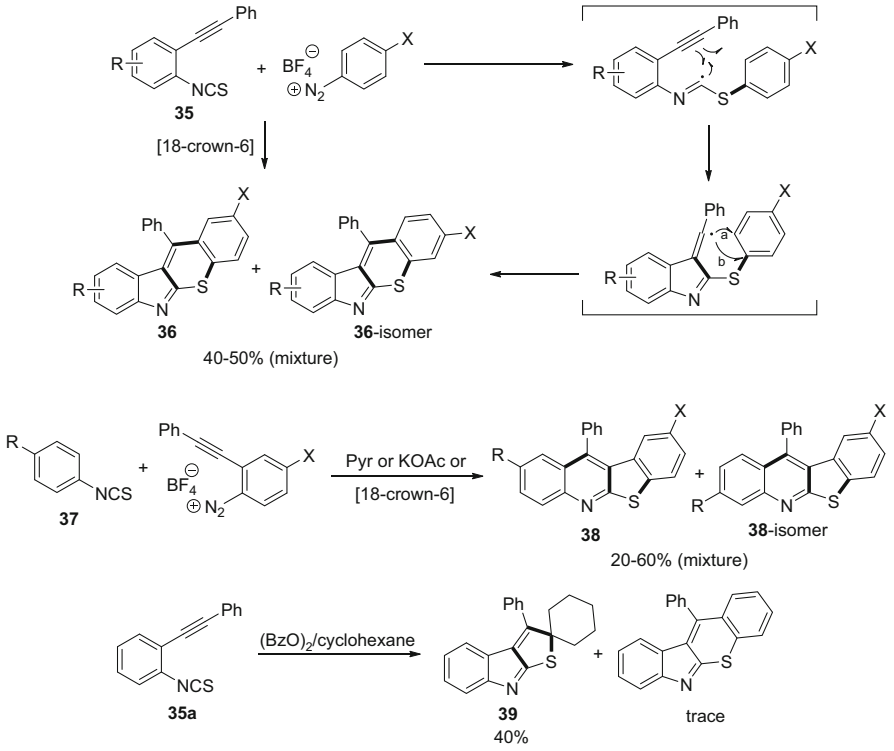
Isothiocyanates are heterocumulenes which are widely used in cycloaddition and nucleophilic addition reactions [55]. They can react with radicals as well. However, both sulfur and carbon atoms in isothiocyanates are ready to accept radicals, leading to the corresponding thioimidoyl and sulfur radicals, respectively (see part 4, Miscellaneous). This section focuses on reactions involving thioimidoyl radical intermediates. Thioimidoyl radical can also be obtained by reaction of an isocyanide with a thiyl radical (RS) [53, 56]. Cascade cyclizations of thioimidoyl radical provide an efficient way to construct complex heterocycles, although competing β-scission to produce thiocyanates may also take place [1].

In 2003, Nanni and Zanardi reported a cascade radical addition/cyclization of 2-alkynylisothiocyanates **35** with aryl diazonium salts as radical precursors (Scheme 19) [56]. A mixture of tetracyclic nitrogen heterocycles, arising from nonselective 6-*endo*- and 5-*exo*-cyclization of the vinyl radical intermediate, was obtained. Reaction of alkynyl aryl diazonium with arylisothiocyanates **37** gave similar results [57]. Cyclohexyl radical generated from cyclohexane/dibenzoyl peroxide was also used in the reaction with **35a**, delivering a unique spiro skeleton **39** via a 1,5-*H* migration. The formation of the thioimidoyl radical was confirmed by reacting isocyanide with an alkylthiol under standard radical conditions (Scheme 19) [58].

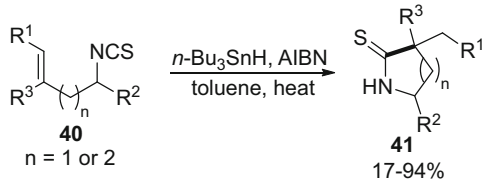
Bachi used alk-3-enyl- and alk-4-enylisothiocyanates **40** with tri-*n*-butyltin hydride and AIBN to produce tinthioimidoyl radicals, which were trapped intramolecularly by alkenes to give γ- and δ-thiolactams **41** (Scheme 20) [59]. Thomas and coworkers exploited an intramolecular addition of thioimidoyl radicals onto sulfur with cleavage of the C-S bond to provide thiazolines using methyl 6*β*-isothiocyanatopenicillanate **42** in the presence of *n*-Bu_3SnH and AIBN. Subsequent cleavage of the tin-sulfur bond was realized by treatment with TBAF (Scheme 21) [60].

2.3 Starting from Imine Derivatives

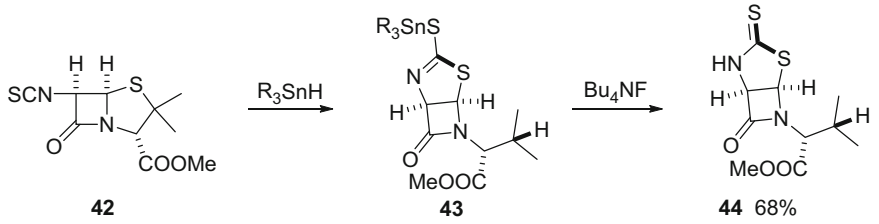
Imidoyl radicals generated by homolysis of imines or their derivatives could also be applied to heterocycle synthesis, which was reviewed by Nanni in 2007 [1].



Scheme 19 Cascade radical cyclization of alkynyl-substituted aryl isothiocyanates

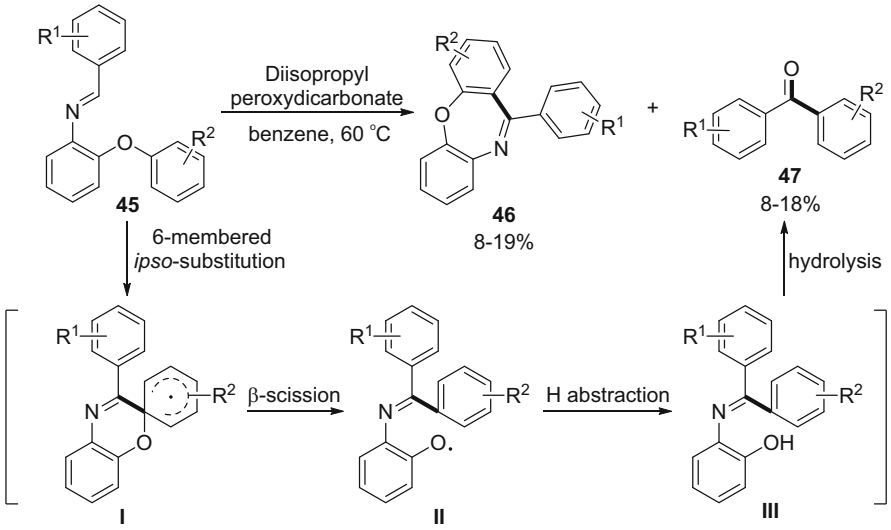


Scheme 20 Synthesis of thiolactams with isothiocyanates

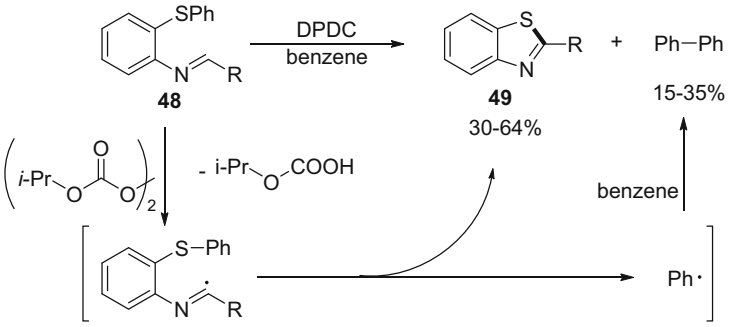


Scheme 21 Tinthioimidoyl radical-induced sulfur-carbon cleavage

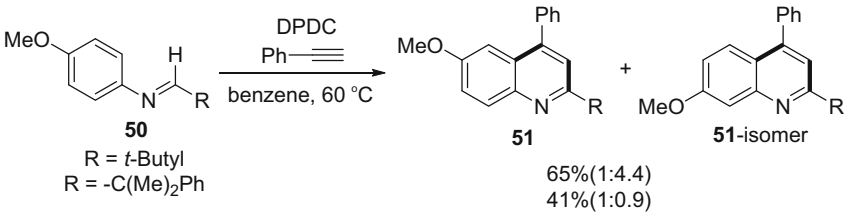
Interestingly, no larger than 6-membered ring construction was realized from isocyanide-derived imidoyl radicals. However, a work by Nanni demonstrated that imidoyl radical generated by hydrogen abstraction in *N*-arylidene-2-phenoxyanilines **45** allowed the formation of 7-membered oxazepine **46**, albeit in very low yield (Scheme 22) [61, 62]. Benzophenones were isolated as by-products, resulting from intermediate **I** and consequent hydrolysis. Leardini reported a novel synthesis of benzothiazoles by reaction of 2-phenylthioarylimines **48** with diisopropyl peroxydicarbonate (DPDC), which resulted in the capture of imidoyl radicals by sulfur with phenyl radical as a leaving group (Scheme 23) [63]. In another example reported by Nanni, arylimine reacted with phenylacetylene to afford polysubstituted quinoline **51** in modest yield. However, along with the desired quinoline product, a regioisomer was also isolated, resulting from a



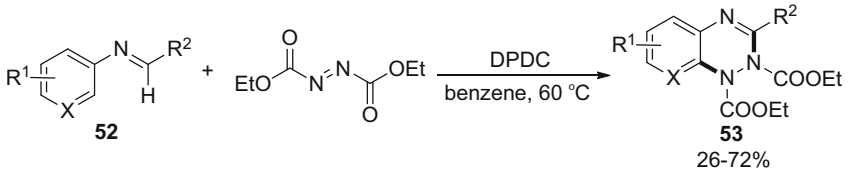
Scheme 22 Synthesis of 7-membered ring starting from imines



Scheme 23 Synthesis of benzothiazoles from imines via a radical pathway



Scheme 24 Intermolecular trapping of imidoyl radical with alkynes to approach polysubstituted quinoline



Scheme 25 Intermolecular capture of imidoyl radical with DEAD to provide 1,2,4-triazines

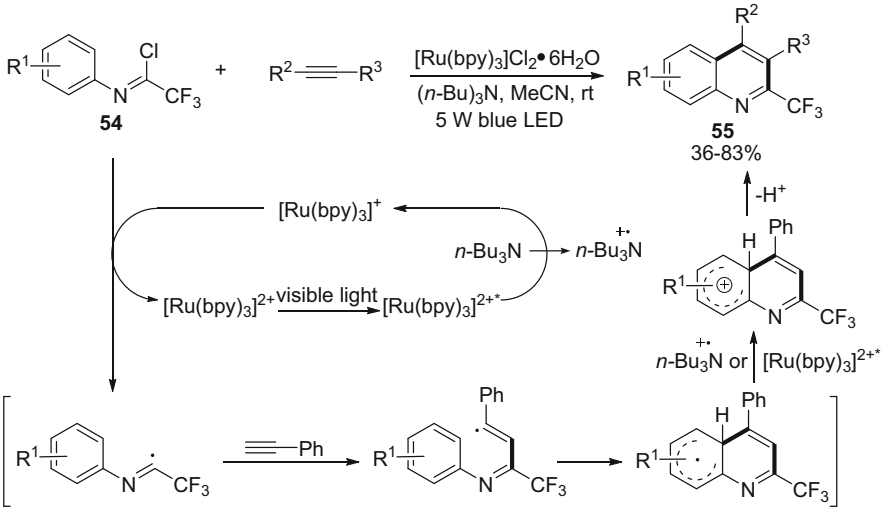
5-membered *ipso*-cyclization of a vinyl radical intermediate (Scheme 24) [3]. Besides carbon unsaturated system, diethyl azodicarboxylate (DEAD) could act as an intermolecular imidoyl radical trap to give 1,2,4-triazine derivatives **53** (Scheme 25) [64].

However, little progress has been made on this topic in the past 10 years. In 2013, Zhou reported a photoinduced intermolecular alkyne addition and cyclization of trifluoroacetimidoyl chlorides to form 2-trifluoromethylquinolines such as **55** at ambient temperature (Scheme 26) [65]. The reaction was initiated by photoactivation of $[Ru(bpy)_3]^{2+}$ to $[Ru(bpy)_3]^{2+}*$, followed by SET from $(n\text{-}Bu)_3N$ to $[Ru(bpy)_3]^{2+}*$. The resulting $[Ru(bpy)_3]^{+}$ was oxidized by the imidoyl chloride affording the imidoyl radical. The latter then underwent sequential intermolecular addition to alkynes, followed by an intramolecular homolytic aromatic substitution (HAS) to provide a cyclohexadienyl radical intermediate. Then, another SET led to the cyclohexadienyl cation intermediate. Finally, elimination of a proton and aromatization provided the quinoline products. Later, Zhou and Fu independently reported light-induced intramolecular versions to synthesize trifluoromethyl-substituted 3-acylindoles **57** and phenanthridines **59** (Scheme 27) [66, 67].

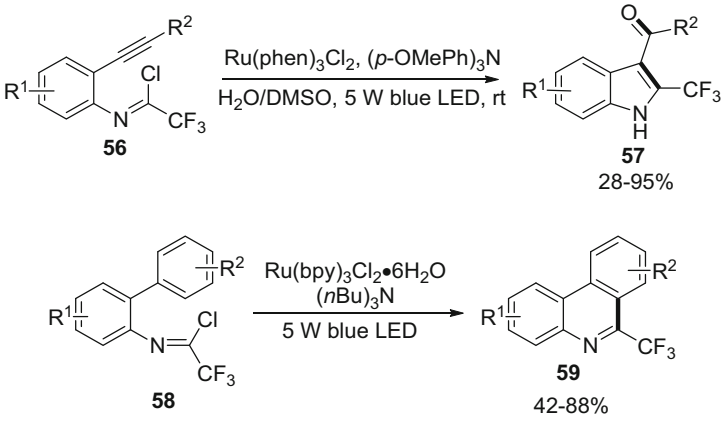
3 Cyclization via Iminyl Radicals

3.1 Starting from Nitriles

Nitriles can also act as free radical acceptors, generating iminyl radicals after addition of a radical species on the carbon center. Two modes of cyclization have



Scheme 26 Visible-light-promoted imidoyl radical addition and cyclization to provide quinolines



Scheme 27 Synthesis of 2-trifluoromethyl indoles and 6-trifluoromethyl phenanthridines with imidoyl chloride

been documented to construct heterocycles via iminyl radical intermediates. One is the intramolecular addition of heteroatom-centered radicals onto the nitrile followed by H-abstraction; the other is a cyclization of the iminyl radical onto an unsaturated system. In some cases, side reaction such as β-scission may occur depending on the nature of the substituents [68].

To illustrate the first type of cyclization, Spagnolo and Leardini reported a reaction of azidoalkyl malononitrile in the presence of *n*-Bu_3SnH and AIBN. Stannylaminyl radical was initially formed from tin radical and azide, followed

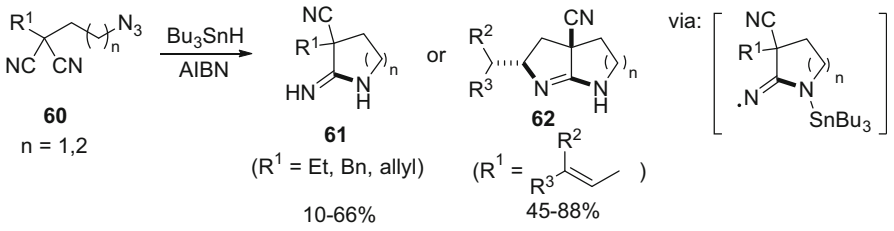
by 5- or 6-*exo*-cyclization onto one of the cyano groups to give aminoiminyl radicals. H-abstraction gave the cyclic amidines **61** [69]. The iminyl radicals could also be trapped by an internal alkene functionality, delivering bicyclic amidines **62** (Scheme 28).

For the second type of cyclization, Curran reported that vinyl radical could undergo tandem radical cyclization to give quinolines in good yields. The reaction was initiated by a tin radical, which was formed from hexamethylditin through photo-irradiation (Scheme 29) [70].

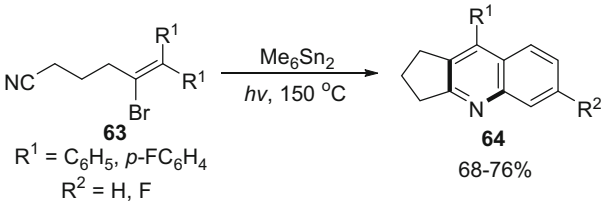
By elegant design, cascade iminyl and imidoyl radical formation have been utilized in the construction of complex heterocyclic systems. Nanni pioneered the area in 1998 with the reaction of cyano-substituted alkyl iodide **65** and arylisocyanide in the presence of hexamethylditin and sunlamp irradiation, which afforded cyclopentaquinoxalines **66** (Scheme 30) [71]. In this study, cyano-substituted thiols and disulfides were also examined as substrates to give thienoquinoxalines **68** and **70** in modest yields under thermal or photochemical conditions.

In 2014, Yu reported visible-light-promoted cascade reaction of arylisocyanides and bromo-substituted alkylnitriles to prepare quinoxalines **72** under mild conditions in 43–88% yields (Scheme 31) [72]. Homolysis of the C-Br bond generated alkyl radicals with the help of a photocatalyst and light, which then added onto the isocyanide.

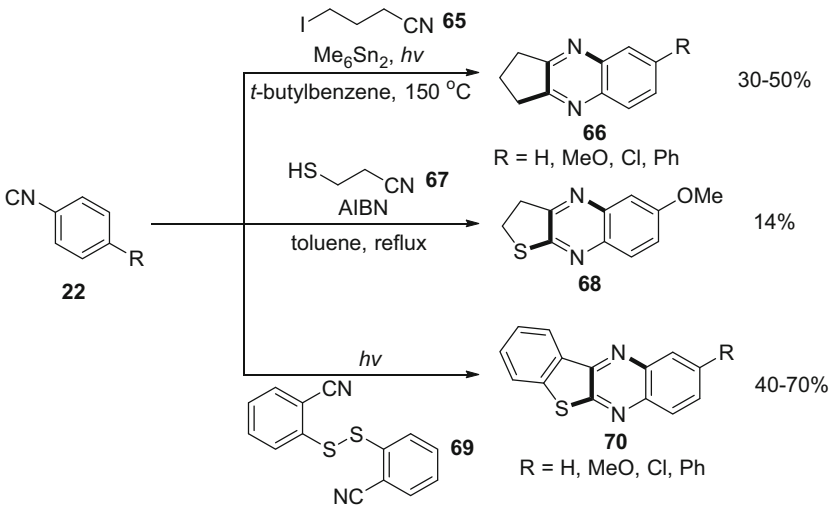
Nanni and coworkers reported another example of imidoyl and iminyl radical cyclization cascades starting from 2-cyanoaryl diazonium salts **73** and arylisothiocyanates **37**. The reaction proceeded through an intermolecular thioimidoyl radical formation, then a 5-*exo*-dig cyclization on the cyano group, followed by an *ortho*- or *ipso*-aryl cyclization of the resulting iminyl radical intermediate.



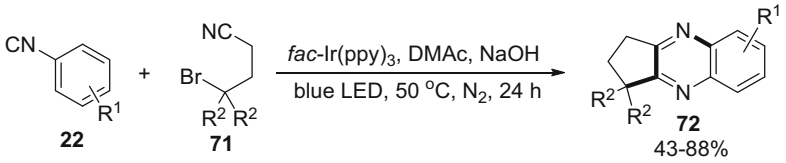
Scheme 28 Reductive cyclization of azide onto substituted nitriles mediated by tin hydride



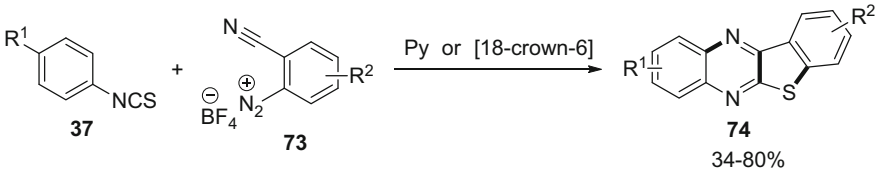
Scheme 29 Synthesis of quinolines from alkenylnitriles bearing a vinyl bromide moiety



Scheme 30 Cascade radical process of arylisocyanides and functionalized nitriles



Scheme 31 Visible-light-mediated cascade reactions of arylisocyanides and bromo-substituted alkylnitriles



Scheme 32 Radical cascades starting from arylisothiocyanates and 2-cyanoaryl diazonium salts

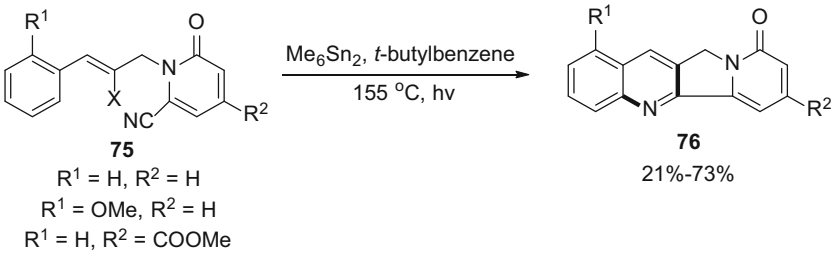
After rearrangement (in case of the *ipso*-aryl cyclization), SET oxidation, and deprotonation-aromatization, a tetracyclic fused scaffold **74** was formed in one step (Scheme 32) [73].

3.2 *Starting from Cyano-Amides*

Cyano-amides in this review refer to structures in which the cyano group is located one or more carbons away from nitrogen or the cyano group is directly attached to the nitrogen amide. Guanidines and quinazolinone-type alkaloids were approached efficiently with the latter strategy, which was pioneered by Lacôte, Malacria, Fensterbank, and coworkers [74, 75].

Bowman reported an alternative approach to Curran's synthesis of camptothecin. 2-Cyanopyridinone derivatives **75** were exposed to hexamethylditin and *t*-butylbenzene under UV irradiation at 150°C to give tetracyclic alkaloids **76** in low to good yields (Scheme 33) [76, 77].

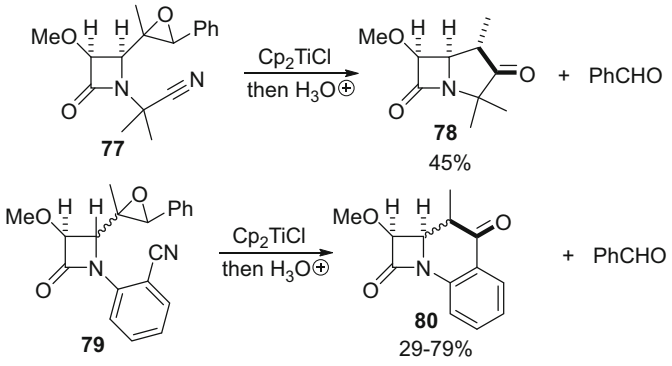
A Ti(III)-assisted reductive cyclization of β-lactams containing epoxide and nitrile functionalities as in **77** and **79** was reported by Grande and coworkers [78]. The reaction was regio- and diastereoselective via 5-*exo* or 6-*exo* processes, affording carbapenem and benzocarbacephem scaffolds. Reductive ring opening of the epoxide with Cp_2TiCl generated alkyl radicals, which cyclized onto the cyano group. Reduction of the iminyl radical intermediate and hydrolysis gave the corresponding cyclic ketones **78** and **80** (Scheme 34). Later, these authors extended the protocol to 1,5- and 1,6-epoxynitriles [79].



75
R^1 = H, R^2 = H
R^1 = OMe, R^2 = H
R^1 = H, R^2 = COOMe

76
21%-73%

Scheme 33 Synthesis of tetracyclic and pentacyclic alkaloids via iminyl radicals



77

78
45%

79

80
29-79%

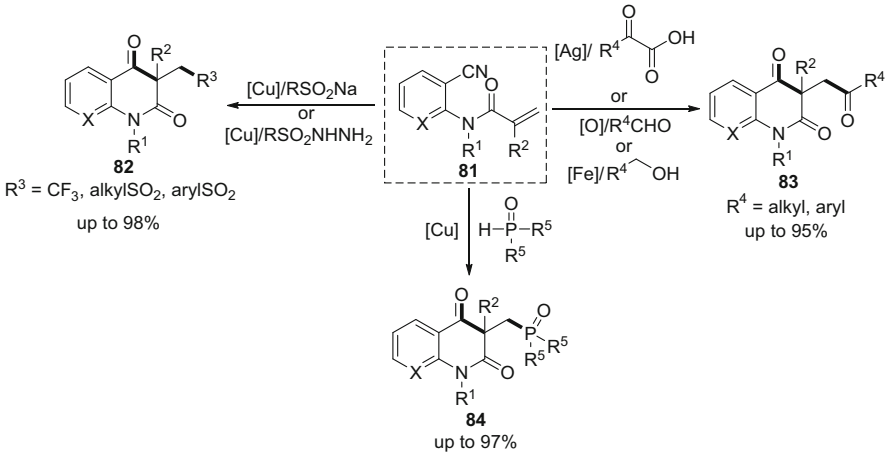
Scheme 34 Reductive cyclization of epoxynitriles with Ti(III) species

Cascade radical addition to alkenes and cyclization onto nitriles were applied to the construction of quinoline-2,4(1*H*,3*H*)-diones [80–84]. With this protocol, aldehydes [80], phenylglyoxylic acids [80], sodium trifluoromethanesulfonate [81], sulfinic acid salts [81], diphenylphosphine oxide [82], sulfonylhydrazides [83], and alcohols [84] acted as radical precursors under oxidative conditions (Scheme 35).

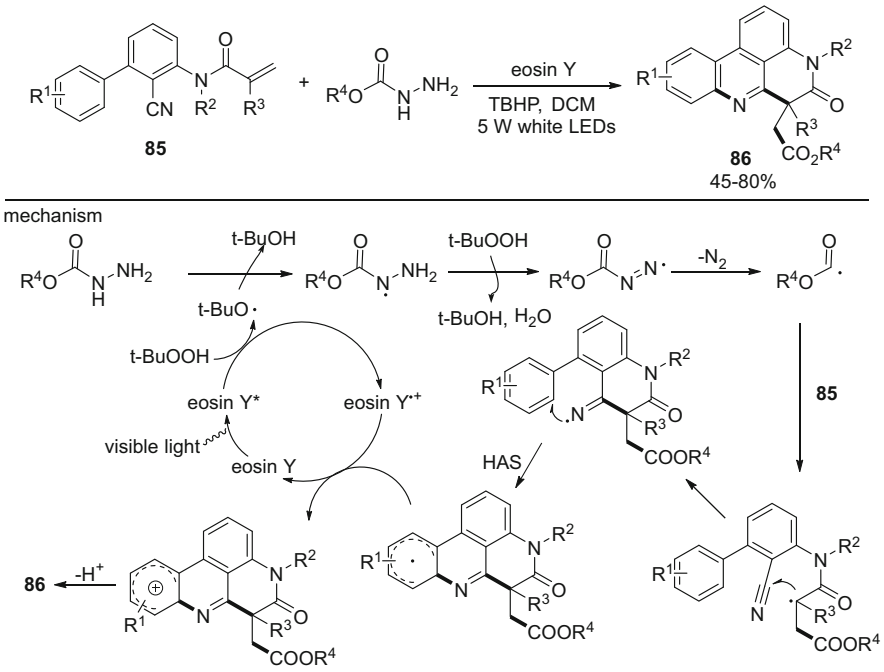
In this context, Sun developed a novel and efficient visible-light-induced cascade reaction for the preparation of ester-functionalized pyrido[4,3,2-*gh*] phenanthridine derivatives **86** under metal-free conditions (Scheme 36) [85]. The reaction was initiated by an intermolecular radical addition to *N*-arylacrylamide derivatives using alkylcarbazates as the ester source, followed by the cyclization of the resulting iminyl radical onto the cyano group. The desired products were obtained in moderate to good yields with broad substrate scope.

Fensterbank et al. designed a series of *N*-acylcyanamide for the synthesis of natural and biologically active quinazolinone derivatives [86, 87]. They tested alkyl phenylselenates as alkyl radical precursors to prepare quinazolinones **88** under slow addition of Bu_3SnH and AIBN in refluxing benzene [88]. Iodoaryl-substituted *N*-acylcyanamides **89** were designed to approach alkaloids of the luotonin A family in modest yield [89, 90]. Interestingly, during their study using vinyl iodide **91** in cascade annulation reactions, the same authors found an unprecedented substituent migration from the *ortho*-position of aryl groups to the alkenyl moiety [91]. The migration could be finely controlled with a selection of solvent. Finally, azide-substituted *N*-acylcyanamide was also used in cascade reactions to generate guanidines **94** in modest to good yields (Scheme 37) [92].

Hu reported a SmI_2-promoted cascade cyclization with imine-substituted cyanamides or cyanamines **95** to provide polycyclic nitrogen heterocycles **96** (Scheme 38) [93]. Aryl radical generated by single-electron reduction of SmI_2 initiated the radical addition, which was followed by the cyclization through the resulting aminoiminyl radical intermediate.



Scheme 35 Radical cascades of O-cyanoarylacrylamides

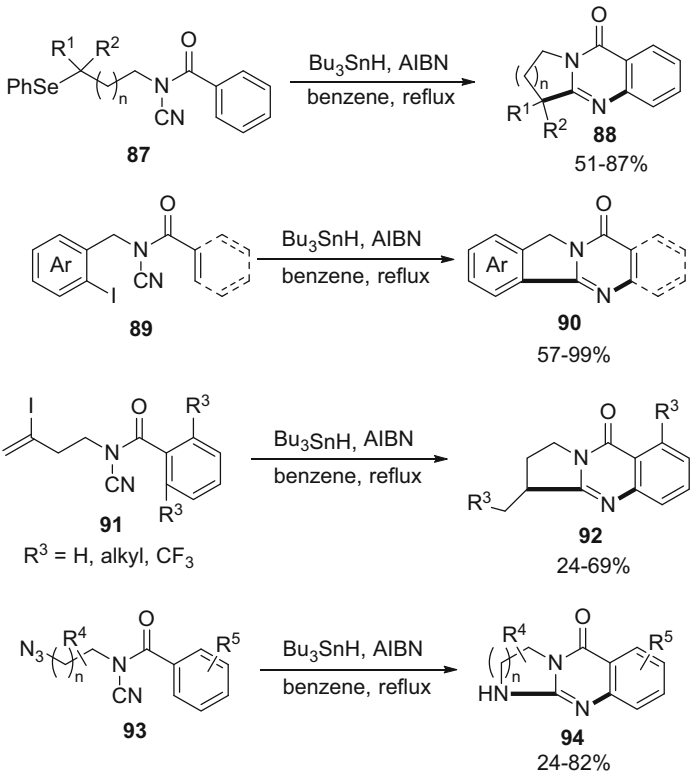


Scheme 36 Visible-light-induced cascade reaction of *N*-(2-cyano-[1,1-biphenyl]-3-yl)-*N*-arylacrylamides

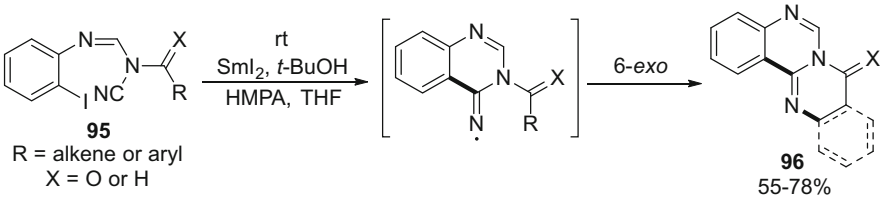
Recently, Cui reported a phosphorylation/cyclization cascade of *N*-acylcyanamide **97** bearing an alkenyl moiety to access dihydroisoquinolinones **98** or quinazolinones **99** [94]. Reaction of diphenylphosphine oxide with $AgNO_3$ provided the phosphoryl radical. Subsequent radical addition of the latter to the alkene fragments generated alkyl radicals, which were trapped by the aryl group or the cyano group, depending on the proximity between alkyl radical and the cyano group (Scheme 39).

3.3 Starting from Oxime and Derivatives

Oxime and its derivatives, like hydrazones and sulfenimines, contain relative weak N-X (X refers to O, S, N, halo, etc.) bonds which can be cleaved homolytically into iminyl radicals and X-centered radicals under thermal conditions, transition metal catalysis, UV irradiation, or photoredox catalysis. Many oxime derivatives are easily available, nontoxic, and bench stable, making them versatile precursors of iminyl radicals for heterocycle synthesis [95]. Recently, Walton and Castle independently reviewed this chemistry [14–16].

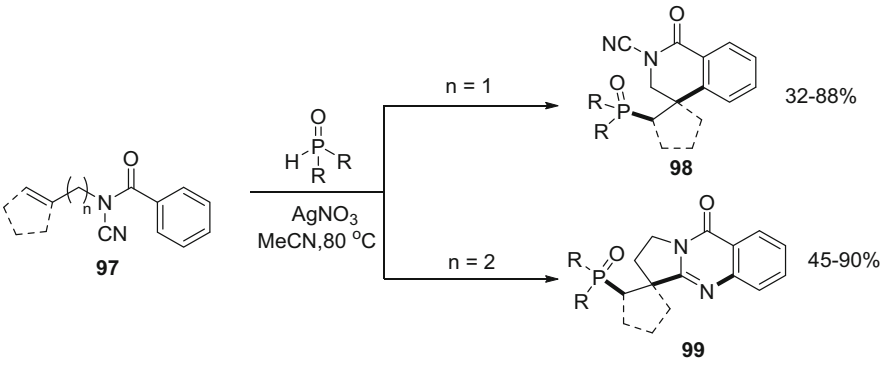


Scheme 37 Radical cyclization of *N*-acylcyanamide to access quinazolinones

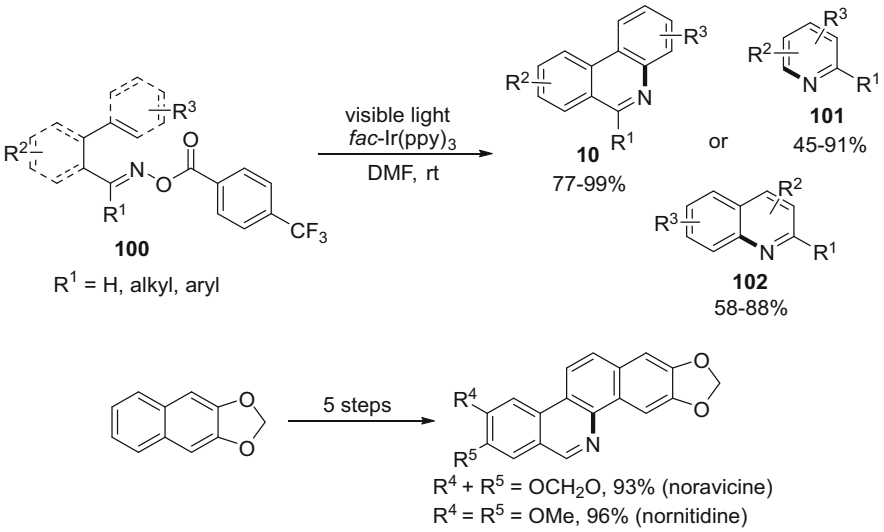


Scheme 38 Radical cascades of imine-substituted cyanamide to generate heterocycles

Yu and Zhang reported visible-light-promoted cyclization of acyl oximes to access 6-membered azaheterocycles [96]. They carefully screened acyl substituents in acyl oximes to find that *p*-trifluoromethylbenzoate oxime substrate is highly active with *fac*-Ir(ppy)$_3$ (ppy = 2-phenylpyridine) as photocatalyst at room temperature. The active photocatalyst reduced acyl oxime into iminyl radicals, which were then engaged into cyclization processes. With this methodology, phenanthridines **10**, pyridines **101**, and quinolines **102** were prepared in good to excellent yields. Moreover, this protocol was used as a key step in a five-step total synthesis of biologically active alkaloids noravicine and nornitidine (Scheme 40).



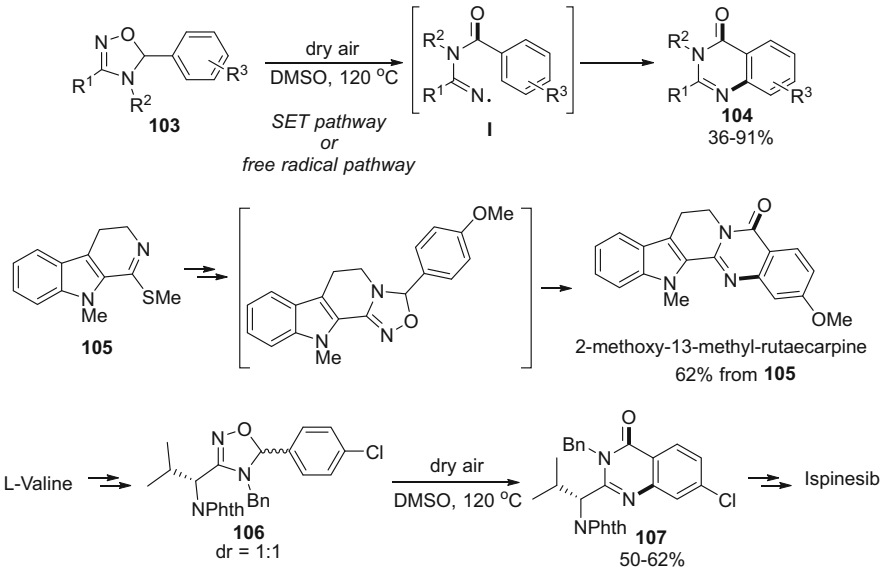
Scheme 39 Phosphorylation/cyclization cascade of *N*-cyanamide alkenes to provide heterocycles



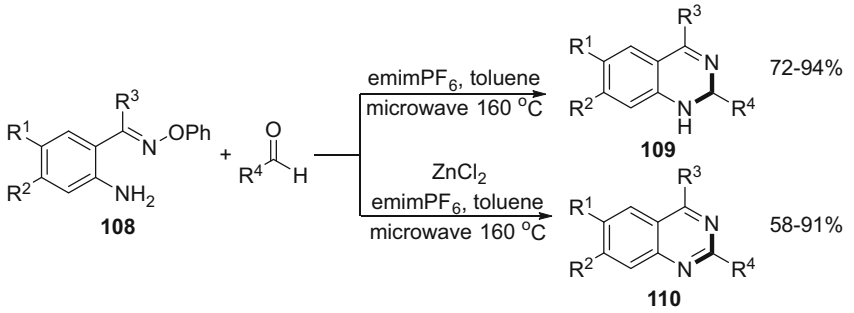
Scheme 40 Visible-light-promoted iminyl radical formation from acyl oximes for the elaboration of pyridines, quinolines, and phenanthridines

Chiba and coworkers designed an oxidative skeletal rearrangement of 5-aryl-4,5-di- hydro-1,2,4-oxadiazoles **103** into quinazolinones **104** in DMSO at 120°C [97]. The proposed mechanism involved thermolysis of dihydro-1,2,4-oxadiazoles to generate iminyl radicals **I**, which gave heterocyclic products after HAS and SET process. To demonstrate the utility of this protocol, they synthesized an indoloquinazoline alkaloid and a key precursor of ispinesib, a potent, specific, and reversible inhibitor of kinesin spindle protein (Scheme 41).

Walton discovered that 2-(aminoaryl)alkanone O-phenyl oximes **108** and carbonyl compounds could provide dihydroquinazolines **109** under microwave conditions in ionic liquid emimPF_6 [98, 99]. Possible mechanism involved the imine



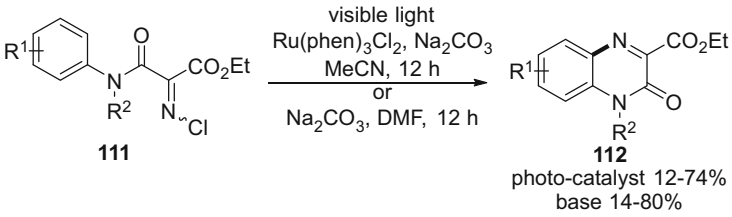
Scheme 41 Synthesis of quinazolinones via oxidative radical rearrangement



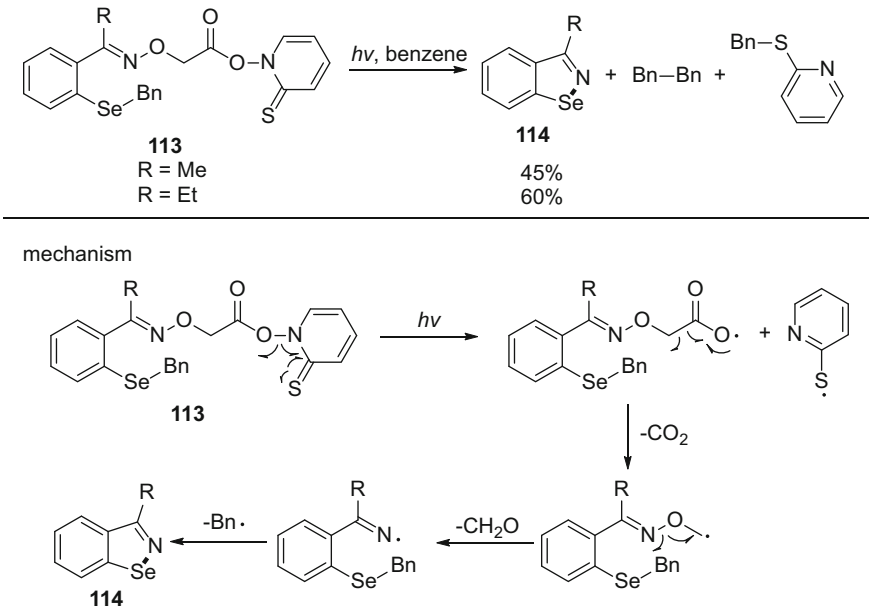
Scheme 42 Synthesis of dihydroquinazolines or quinazolines with O-phenyl imines

formation and thermolysis of the N-O bond of the oxime into an iminyl radical. Toluene acted as a hydrogen donor to trap the aminyl radical. In the presence of $ZnCl_2$, aromatic quinazolines **110** were formed instead of dihydroquinazolines (Scheme 42).

In 2015, Yu and coworkers developed two efficient photochemical protocols for the generation of iminyl radicals from easily available 2-(*N*-arylcarbamoyl)-2-chloroiminoacetates **111** via N-Cl cleavage (Scheme 43) [100]. $Ru(phen)_3Cl_2$ acted as a photoredox catalyst under visible-light irradiation to induce N-Cl bond cleavage by a single-electron transfer pathway. Interestingly, when the reaction was performed in DMF in the presence of Na_2CO_3, only visible light was required to initiate the reaction without a photocatalyst. The methodology provided a practical approach to quinoxalin-2(1*H*)-ones **112** via iminyl radical intermediates.



Scheme 43 Photoinduced iminyl radical cyclization via N-Cl bond cleavage



Scheme 44 Synthesis of benzoselenazoles with O-carboxymethyl oxime derivatives

Besides carbon unsaturated systems, benzylthio- and selenoethers were also suitable traps for iminyl radicals [101]. Schiesser and coworker realized cyclization of benzylseleno-substituted thiohydroxamic esters **113** to produce l,2-benzoselenazoles **114** in modest yield [102]. Upon irradiation, oxime **113** decomposed, through release of a 2-pyridinethiyl radical, followed by decarboxylation and elimination of formaldehyde, into an iminyl radical, which reacted at selenium (homolytic substitution) affording benzoselenazoles. A benzyl radical was also formed which dimerized (Scheme 44).

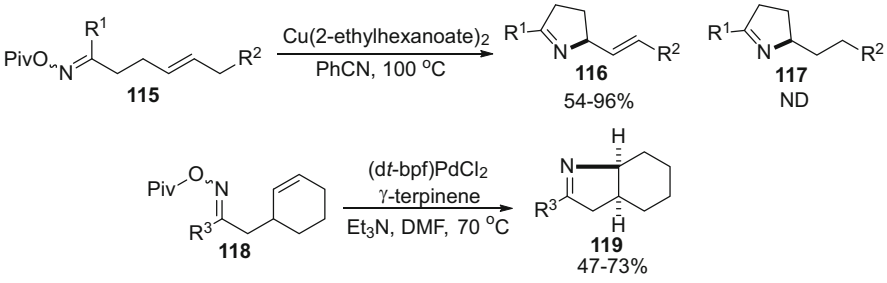
For aliphatic heterocycle synthesis, Bower reported copper-catalyzed radical cyclization of alkenyl oxime esters **115**, which provides alkene-substituted dihydropyrroles **116** in high yields [103]. No corresponding alkyl-substituted by-product **117** was found. Later, they investigated the Pd-catalyzed cyclization of alkene-substituted oxime esters **118** [104]. Interestingly, the reaction mechanism was

ligand-dependent. Electron-deficient phosphine ligands like $P[3,5\text{-}(CF_3)_2C_6H_3]_3$ led to aza-Heck products, while electron rich ligands such as 1,1′-bis(di-*tert*-butylphosphino)ferrocene (dt-bpf) resulted in **119** through iminyl radical intermediates (Scheme 45).

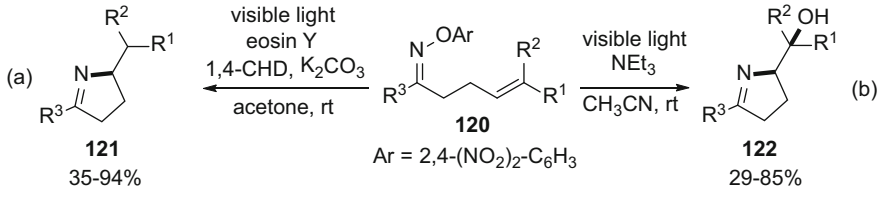
Leonori developed iminyl radical-mediated cyclizations of unactivated olefins under visible-light irradiation (Scheme 46) [105]. When organic dye eosin Y was used as a photocatalyst in the presence of 1,4-cyclohexadiene (CHD) as a hydrogen donor and K_2CO_3, dihydropyrroles **121** were obtained in good yields (route a, Scheme 46). Interestingly, when the reaction was irradiated in the absence of a photocatalyst, a complementary iminohydroxylation process occurred to deliver alcohol **122** (route b, Scheme 46). The oxygen atom in the alcohol products **122** was believed to originate from one of the nitro groups of the leaving phenoxy moiety.

Later, to extend the scope of the valuable imine motif, Leonori reported decarboxylation of oxyacid **123** with methyl acridinium perchlorate **124** under visible-light conditions, generating an iminyl radical, which cyclized in a 5-exo-mode (Scheme 47) [106]. The resulting radical then reacted intermolecularly with various radical acceptors, including *N*-chlorosuccinimide (NCS), *N*-iodosuccinimide (NIS), *N*-fluorobenzenesulfonimide (NFSI), but also TsN_3, DEAD, or ethynylbenziodoxolones and vinylbenziodoxolones, as carbon sources.

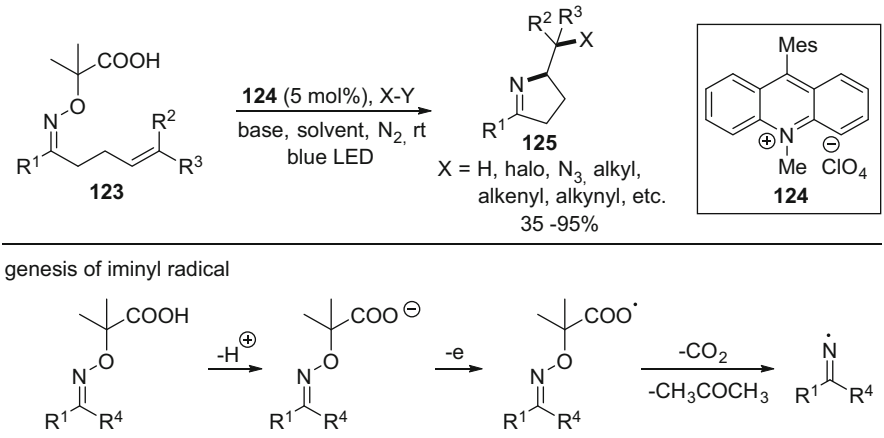
Independently, Studer developed a related decarboxylation of α-iminooxy propionic acids **126** to form iminyl radicals using photoredox catalyst **127** (Scheme 48) [107]. Through this initiation process, they achieved the carboimination of alkenes. The sequence of iminyl radical generation, 5-exo-trig



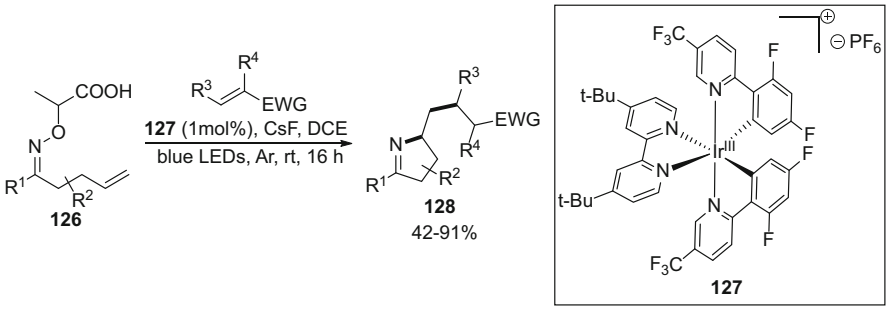
Scheme 45 Copper- or palladium-catalyzed cyclization via iminyl radicals



Scheme 46 Visible-light-mediated hydroimination and iminohydroxylation cyclizations of iminyl radicals



Scheme 47 Imino-functionalizations of alkenes under photoredox conditions

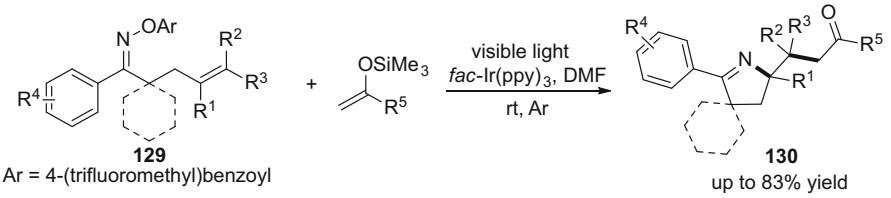


Scheme 48 Genesis of iminyl radicals by oxidation of α-imino-oxy acids

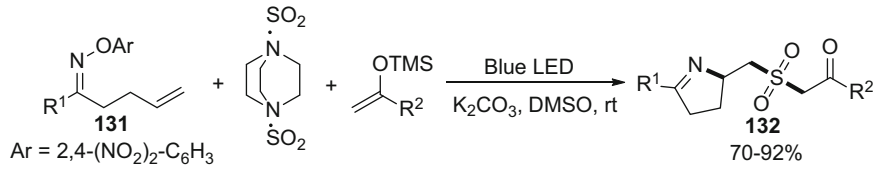
cyclization, intermolecular conjugate addition to a Michael acceptor, completed with a SET reduction process, was shown to provide various pyrrole derivatives **128**.

When iminyl radical undergoes cascade cyclization and functionalization instead of hydrogen abstraction, densely substituted pyrroline derivatives **130** are expected. Loh applied silyl enol ethers as coupling partners to trap the alkyl radical intermediate generated from iminyl radical cyclization, which eventually gave alkyl ketone-substituted pyrrolines (Scheme 49) [108].

Wu reported a novel *N*-radical-initiated cyclization, followed by sulfonylation and alkene addition under visible-light irradiation and catalyst-free conditions (Scheme 50) [109]. A range of sulfonyl compounds **132** could be easily produced through the cascade radical process involving sulfur dioxide insertion using 1,4-diazabicyclo[2.2.2]octane disulfate (DABCO·$(SO_2)_2$ or DABSO) as surrogate of gaseous sulfur dioxide.



Scheme 49 Visible-light-induced cascade cyclization and functionalization of iminyl radicals



Scheme 50 Photoinduced *N*-radical-mediated cyclization through insertion of sulfur dioxide

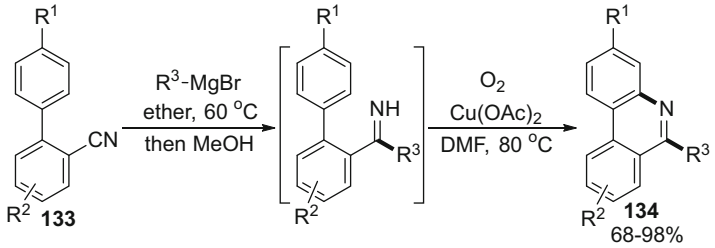
3.4 Starting from N-H Ketimines or Amidines

Single-electron oxidation of N-H ketimines or amidines could also generate iminyl radical in an environmentally benign manner. Chiba and coworkers reported a series of transformations involving iminyl radicals generated from imines under copper-catalyzed aerobic conditions [110]. They used biaryl-2-carbonitriles **133** and Grignard reagents to generate imines in situ. Cu-iminyl radical was formed after aerobic oxidation, and subsequent cyclization delivered phenanthridine derivatives **134** (Scheme 51) [111]. Based on a similar protocol, azaspirocyclohexadienone **136** synthesis was also achieved efficiently from the corresponding arylnitriles (Scheme 52) [112].

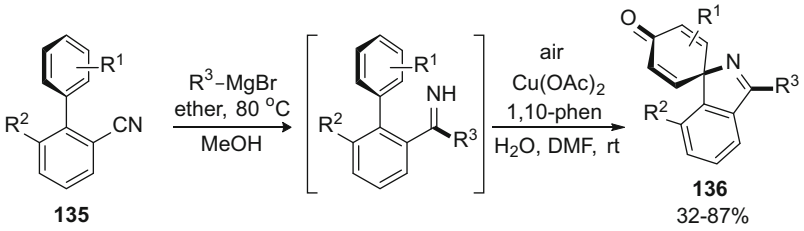
Very recently, Nagib reported an unprecedented β-C−H amination of imidates **137** using a NaI/PhI(OAc)$_2$ system to generate β-amino alcohols (Scheme 53) [113]. The process includes the oxidation of a trichloroacetimidate or a benzimidate into an imidate radical, which is followed by a 1,5-hydrogen atom transfer (HAT), generating regioselectively a carbon radical. The latter is then trapped by an iodine radical, nucleophilic substitution eventually forming oxazoline **138**. A simple hydrolysis finally leads to the related β-amino analogs.

Yu used stable α-imino-*N*-arylamides **141** as precursors of iminyl radical [114]. In this reaction, TBHP/TBAI promoted iminyl radical formation through single-electron oxidation of the imino moiety. Subsequent intramolecular 5-*exo*-mode cyclization onto the aryl group gave azaspirocyclohexadienyl radical intermediates, which were trapped by oxygen to form azaspirocyclohexadienones **142**. In the absence of oxygen, quinoxalin-2-ones were detected as by-products (Scheme 54).

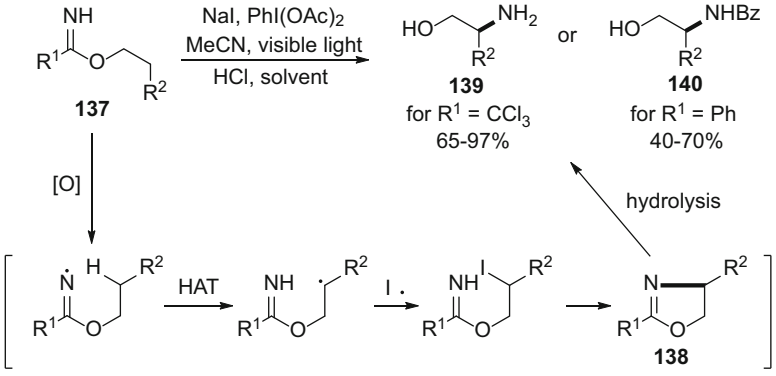
Electron-rich amidines are relatively stable and easy to handle. Oxidation of N-H bond of amidines generates amidinyl radicals, which can be used in nitrogen heterocycle synthesis as well. Very recently, Xu reported the anodic cleavage of



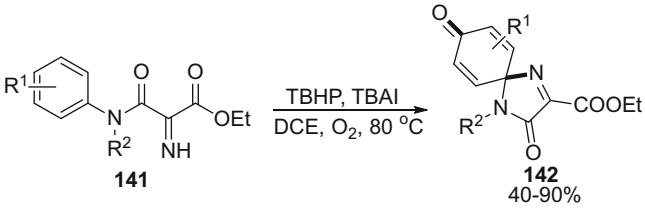
Scheme 51 Cu-iminyl radical cyclization to phenanthridine via Cu/O_2 oxidation of imines



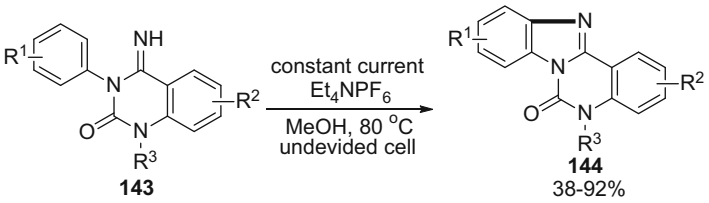
Scheme 52 Cu/O_2 oxidation of imines to provide azaspirocyclohexadienones



Scheme 53 β-C−H amination of imidates under oxidative conditions



Scheme 54 Oxidation of imine with TBHP/TBAI to approach azaspirocyclohexadienones



Scheme 55 Anodic cleavage of N-H bonds of amidines to access tetracyclic benzimidazoles

N-H bonds of amidines **143** to provide aminoiminyl radicals, which were captured by (hetero)arenes to afford tetracyclic benzimidazoles **144** (Scheme 55) [115].

4 Miscellaneous

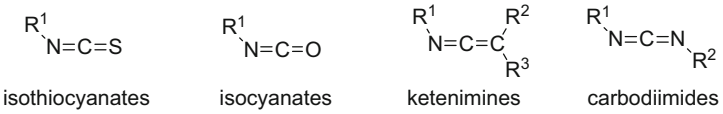
Both sulfur and carbon atoms in isothiocyanates can accept radical attack, generating the corresponding imidoyl radical and sulfur radical, respectively. Some related structures like isocyanates, ketenimines, and carbodiimides exhibit similar reactivity (Scheme 56). In this section, only scattered examples are given using these heterocumulenes in radical cyclization (Scheme 57).

Yadav reported a copper-catalyzed synthesis of 2-alkylbenzoxa(thia)azoles from arylisocyanates/isothiocyanates and simple alkanes [116]. The protocol utilized di-*tert*-butyl peroxide (DTBP) as a radical initiator to generate the alkyl radical, which adds onto the NCX moiety at the central carbon. Sequential C-C and C-X (X=O, S) bond formation was followed by aromatization to afford expected **146** (Scheme 58).

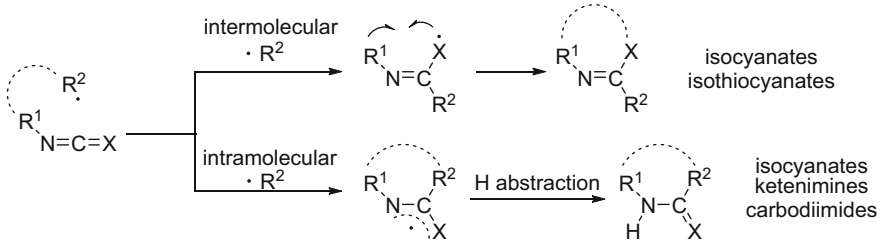
Zhu et al. described the reaction between aryl isothiocyanates and formamides under metal-free conditions, which led to the synthesis of 2-aminobenzothiazoles **147** (Scheme 59) [117]. Mechanistic studies suggest that the reaction is initiated by decarbonylative aminyl radical formation in the presence of *n*-Bu_4NI and TBHP, followed by aminyl radical addition to isothiocyanates and cyclization via sulfur-centered radical intermediates.

Lei also developed a mild method for the synthesis of 2-aminobenzothiazoles **148** from isothiocyanates and commercially available amines via an intramolecular dehydrogenative C-S bond formation. Catalyst- and external oxidant-free electrolytic conditions were demonstrated to be efficient in this cross-coupling reaction (Scheme 60) [118].

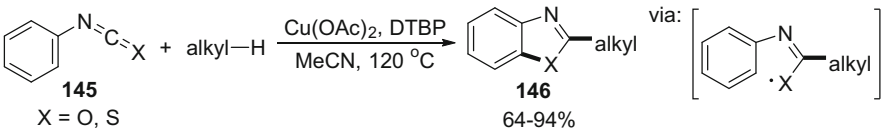
Walton reported that radical cyclization of 2-(2-isocyanatophenyl)ethyl bromide **149** led to 2,3-dihydroindole-1-carbaldehyde **150** and 3,4-dihydro-1*H*-quinolin-2-one **151**, respectively, in 16% and 44% yield [119]. In this case, the 6-*endo*-mode for the cyclization of the alkyl radical was preferable over the 5-*exo*-cyclization onto the isocyanate. DFT calculations of reaction enthalpies and rate constants were performed to rationalize the selectivity (Scheme 61).



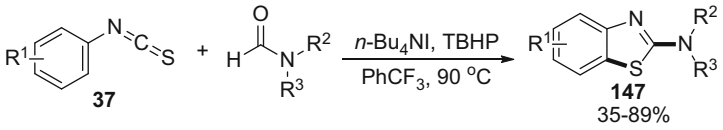
Scheme 56 Structure of isothiocyanates, isocyanates, ketenimines, and carbodiimides



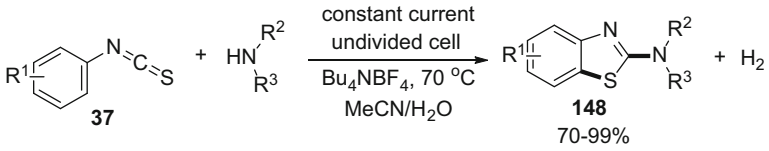
Scheme 57 Reaction mode of isothiocyanates, isocyanates, ketenimines, and carbodiimides



Scheme 58 Construction of 2-alkylbenzo-1,3-azoles from iso(thio)cyanates and alkanes

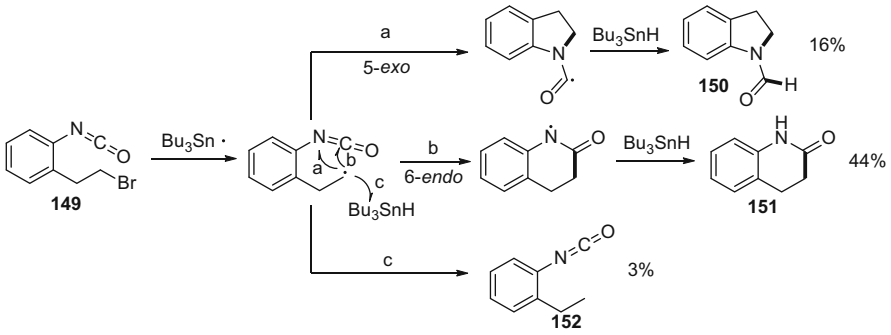


Scheme 59 Synthesis of 2-aminobenzothiazoles from isothiocyanates and formamides

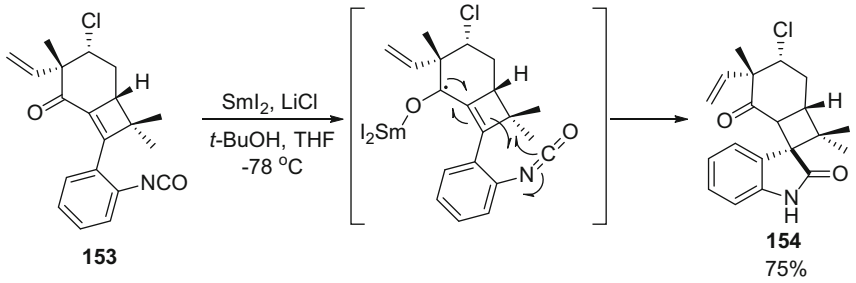


Scheme 60 Synthesis of 2-aminobenzothiazoles from isothiocyanates and amines under undivided electrolytic conditions

Another isocyanate that participated in radical cyclization reaction was reported by Wood and coworkers during their studies on the synthesis of welwitindolinone A [120–122]. The key step involved a SmI_2-mediated reductive cyclization of a precursor bearing an isocyanate, to build up the spiro-oxindole core structure **154** in good yield. The reaction was highly regio- and diastereoselective (Scheme 62).



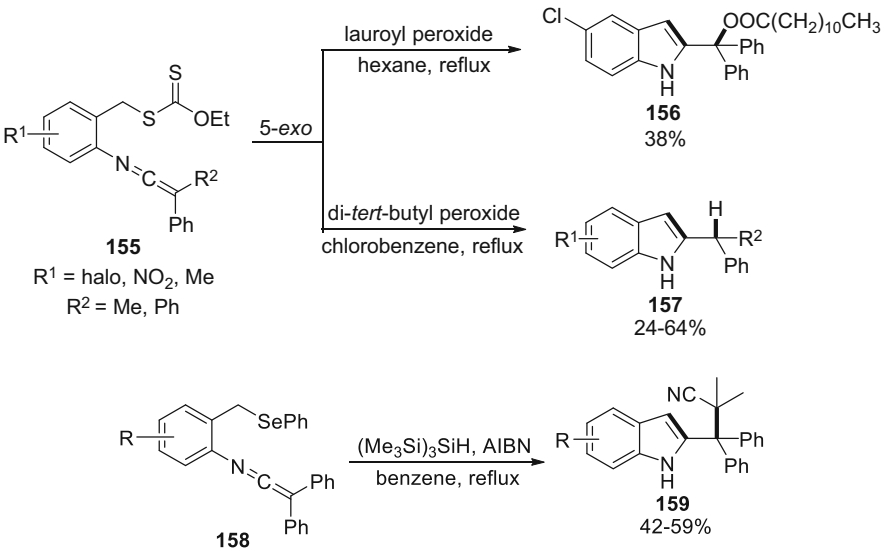
Scheme 61 Isocyanates as radical acceptors in cyclization



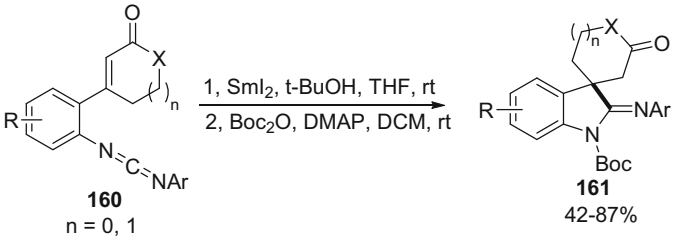
Scheme 62 SmI_2-promoted reductive cyclization of isocyanate

Ketenimines and carbodiimides were also reported to be potent radical acceptors in radical annulation reactions [123]. Vidal reported an intramolecular addition of benzylic radical to ketenimines, leading to 2-alkylindoles **156**, **157**, and **159** in low to modest yields [124, 125]. The fate of the triarylmethyl-type radical intermediate was determined by the nature of the radical initiator. A lauroyloxy fragment was thus incorporated into the product when lauroyl peroxide was used, while H-abstraction product was obtained when di-*tert*-butyl peroxide in chlorobenzene was applied. Later, they reported a similar reaction of ketenimines with a pending phenyl selenide in the presence of a silane and AIBN to afford indole derivatives with the 1-cyano-1-methylethyl group from AIBN being trapped (Scheme 63) [126].

Takemoto reported a SmI_2-mediated reductive cyclization of carbodiimides bearing an α,β-unsaturated carbonyl moiety to give spiro-2-iminoindolines **161** [127]. The proposed mechanism included a one-electron reduction of the unsaturated carbon group into a radical anion, a subsequent addition to the carbodiimide moiety, further reduction by SmI_2 to an amidinate, and finally hydrolysis by *t*-BuOH to afford the iminoindoline (Scheme 64). They also used the strategy to construct the core structure of perophoramidine [128].



Scheme 63 Construction of 2-substituted indole core with ketenimines



Scheme 64 Reductive cyclization of carbodiimides to approach spiro-2-iminoindolines

5 Conclusion

This chapter described various radical cyclizations of isocyanides, isothiocyanates, nitriles, and other C-N unsaturated bond systems. A variety of 5- and 6-membered nitrogen-containing heterocycles were prepared via imidoyl or iminyl radical intermediates. In general, multiple chemical bonds are formed in these processes, and the reaction conditions are mild, representing an environmentally benign approach for heterocycle synthesis. With the rapid growth especially in the area of photoinduced radical processes, more practical heterocycle synthesis is expected in not too distant a future, which should meet with the strong requirements for application in medicinal chemistry and material science.

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