

Review

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Review

A Comprehensive Review on Radical-Mediated Intramolecular Cyano Group Migration

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Abstract: Radical-mediated intramolecular translocation of cyano groups has been recognized as a useful tool for the site-selective functionalization of organic molecules. The process is believed to proceed through the addition of an in-situ generated carbon-centered radical to the nitrile triple bond, followed by β -scission of the resulting cyclic iminyl radical intermediate to relocate the cyano group and produce a more stable carbon radical for further elaboration. Beginning in the early 1960's and continuing for the next forty years, the research in this particular area has seen a surge of growth during the past two decades with advances in radical chemistry and application of photocatalysis. The present article attempts to conduct a comprehensive review of existing studies on this topic by covering the literature from 1961 to 2025. The procedures developed for the purpose are grouped and discussed in four sections according to the strategies used to generate the initial carbon radicals, which include i) hydrogen atom transfer (HAT); ii) radical addition to π system, iii) halogen atom transfer (XAT); and iv) homolytic fission of C-C single bond. In each section, a specific emphasis will be placed on reaction conditions, substrate scopes and mechanisms.

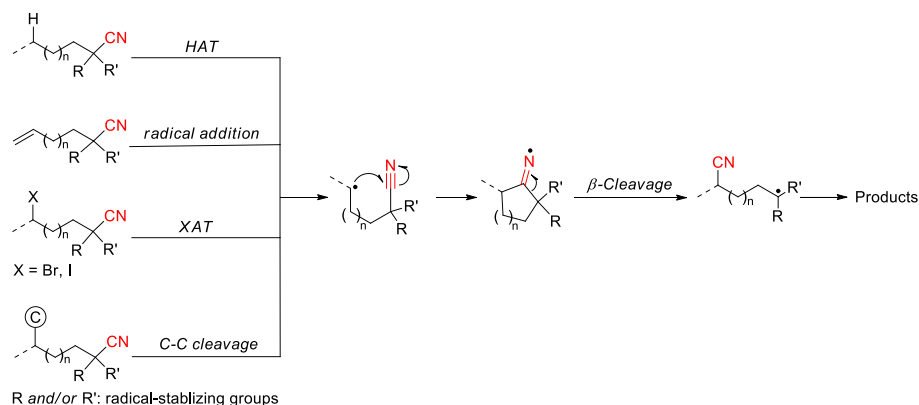
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1. Introduction

The cyano group is one of the most versatile functional groups in organic chemistry [1]. The unique reactivity imparted by the nucleophilic nitrogen atom, the electropositive carbon center and π -coordinating ability of the triple bond allows it to be easily converted into carbonyl [2–5], amino [5–7] or heterocyclic [5,8–11] functionalities under suitable conditions. It can also serve as a directing, stabilizing, activating or leaving group in many transformations, such as C-H functionalization [12], α -functionalization [13], Diels-Alder cycloaddition [14,15], cyclopropanation [16], and transition-metal-catalyzed hydrodecyanation [17]. Additionally, the cyano group has been recognized as an important pharmacophore in drug discovery field, and often required to be incorporated into the structures of lead compounds for improving pharmacological properties or combating drug resistance [18,19]. The broad utility has promoted the development of numerous methods for the preparation of cyano compounds, which can be classified into several categories according to the way of introducing the cyano group. One type of commonly used methods is based on the conversion of a pre-installed functionality, e.g. an amide [20] or aldoxime [21], into the cyano group [22]. Another category of methods involves the cyanation of various substrates with external cyano-containing reagents, such as trimethylsilyl cyanide (MeSiCN) [23], *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTs) [24], butyronitrile [25], CuCN [26] or $K_4[Fe(CN)_6]$ [27], that typically act as nucleophiles [23], electrophiles [24] or donors of CN ligand [25–27]. In some cases, NaN_3 or $TMSN_3$ was instead used as the nitrogen source for preparing aryl, alkenyl or oxo-nitriles through the C-H or C-C bond cleavage of the corresponding hydrocarbons [28]. However, even with the proven effectiveness, these traditional methods are generally not applicable for the selective installation of the cyano group at an unactivated or a sterically congested carbon site with concomitant introduction other functional group(s) of interest into a molecule. To this end, one may resort to another approach known as

intramolecular cyano group migration (or translocation), which is usually implemented with readily available cyano-containing substrates and has proven to be useful for accessing nitrile derivatives that are non-trivial to obtain by conventional methods.

The radical-mediated translocation of cyano groups has emerged as a powerful tool for the site-selective functionalization of organic molecules. The process is believed to proceed through the addition of an in-situ generated carbon radical to the nitrile triple bond, followed by β -cleavage of the resulting cyclic iminyl radical to relocate the site of the cyano group (Scheme 1). The β -cleavage step is usually driven by the formation of a more stable carbon-centered radical, which then undergoes various transformations to yield different types of products. There are four general strategies that can be used to generate the initial carbon radical, including i) hydrogen atom transfer (HAT) from C(sp³)-H scaffolds; ii) radical addition to unsaturated π system; iii) halogen atom transfer (XAT); and iv) homolytic fission of C-C single bond. The research in this particular area has begun since the early 1960s [29,30], and benefited tremendously from advances in the fields of radical chemistry and photocatalysis over the past twenty years. This article intends to provide a comprehensive review of existing studies on this topic by covering the literature from 1961 to 2025. The procedures developed for the purpose will be discussed in four sections according to the strategies for producing the initiating carbon radical, with specific emphasis on mechanism and substrate scope. Some research works discussed herein were also mentioned in several published accounts, but only as a small part of reviewing the migrations of a large array of functional groups [31–36]. Moreover, the non-radical methods reported for CN migration, mostly involving the release and recombination of cyanide anion or the formation of cyanide complex, are not included in this article.



Scheme 1. General Schemes for radical-mediated cyano group migration.

2. Radical-Mediated Translocation of Cyano Groups

2.1. Site Selectivity in CN Migration

Before we discuss the detailed synthetic strategies, it is instructive to clarify the origin of the site selectivity regarding the migratory distance of a cyano group from one carbon center to another. After the generation of the initial carbon radical, the site selectivity will be directed by the type of subsequent cyclization onto the nitrile group. It has been realized that the 1,4- or 1,5-cyano migration caused by a 5- or 6-exo-dig cyclization is generally preferred over other migration processes, e.g., 1,3-, or 1,2-migration [34,35], which is consistent with the results from a recently reported density-functional theory (DFT) study on azido radical-addition-induced cyano migration of several homologous alkenyl cyanohydrins [37]. After the addition of the azido radical to C-C double bonds, the relative free energies calculated for the cyclization step are outlined in Figure 1. The calculations suggest that 3- or 4-exo-dig cyclization ($n = 0$ or 1) accounting for the 1,2- or 1,3-migration is either impossible or formidable due to the high energy associated with the three- or four-membered cyclic

radical intermediate (or transition state), whereas 5- or 6-exo-dig cyclization ($n = 2$ or 3) is energetically favored to produce the corresponding cyclic iminyl radical intermediate. The energy profile of the 7-exo-dig cyclization ($n = 4$) appears to be more appealing when compared with that of the 3- or 4-exo-dig cyclization. However, the 1,6-cyano migration resulting from the very process is rare in the literature possibly due to an unfavorable distance between the reaction centers for intramolecular cyclization. It is also noteworthy that although 4-exo-dig cyclization is generally disfavored, the 1,3-cyano migration has been achieved in several studies by using specific substrates and/or reaction conditions as encountered in the following sections.

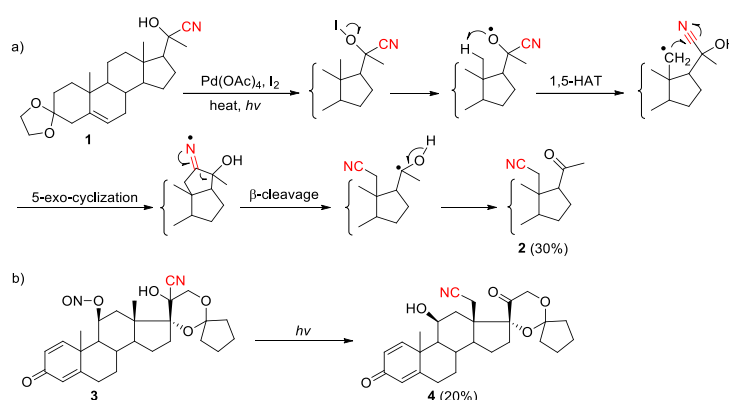
Type of cyclization	3-exo-dig ($n = 0$)*	4-exo-dig ($n = 1$)	5-exo-dig ($n = 2$)	6-exo-dig ($n = 3$)	7-exo-dig ($n = 4$)
Reaction free energy (kcal/mol)	–	9.3	-9.5	-8.9	-3.9
Activation energy (kcal/mol)	–	18.1	8.5	10	17.3
Energy of iminyl radical (kcal/mol)	–	6.6	-12.5	-13.0	-8.8
Site selectivity	1,2-migration	1,3-migration	1,4-migration	1,5-migration	1,6-migration

* No occurrence for 3-exo-dig cyclization is predicted due to high energies associated with the cyclic iminyl radical and transition state.

Figure 1. DFT energy calculation for radical cyclization onto nitrile group (Eşsiz, 2023).

2.2. CN Group Translocation via HAT

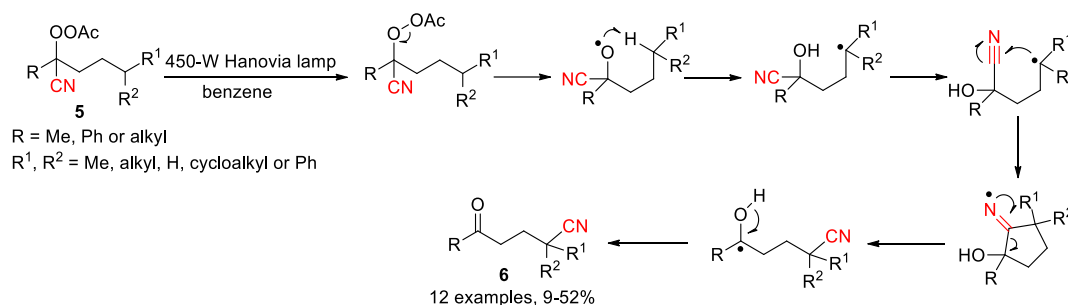
In 1961, Kalvoda reported the cyanohydrin-ketonitrile rearrangement of steroid **1** as the first known example to demonstrate the migratory aptitude of cyano group (Scheme 2, a) [29]. Mechanistically, the generation of an alkoxy radical under the Barton hypiodite reaction conditions triggered a 1,5-HAT process, allowing the creation of a carbon radical from unactivated C(sp³)-H bond in the C-18 angular methyl group. Subsequent 5-exo cyclization onto the nitrile followed by β -scission of the resulting iminyl radical provided a carbon-centered radical stabilized by the adjacent OH group. Further loss of a hydrogen atom from this intermediate gave the rearrangement product **2**. In the following report, Kalvoda also described that the 1,4-cyano migration could also be initiated by the N-O cleavage of the 11 β -nitrite group in **3**, giving the formation of the product **4** upon irradiation (Scheme 2, b) [38].



Scheme 2. 1,4-Cyano migrations of steroidal cyanohydrins via HAT (Kalvoda, 1961 and 1970).

A similar cyano-migration was reported by Watt in 1976, after performing photolysis experiments on α -peracetoxynitriles **5** (Scheme 3) [39]. The reaction was initiated by the generation of alkoxy radical through the homolytic cleavage of the O-O bond and afforded the δ -ketonitrile

products **6** in low to moderate yields. Under the employed conditions, the competitive decarboxylation of **5** and/or Norrish type II fragmentation of **6** mainly accounted for the low yields encountered in most cases. In a separate report, Watt described that this photolytic protocol was comparable to Kalvoda's method, like delivering **2** in 21% yield from the corresponding 20-peracetoxy-20-cyanosteroid [40]. The Kalvoda and Watt procedures have not found much application since they were reported [41], possibly due to the inconvenience of preparing substrates and lower yields associated with harsh reaction conditions. Despite this, these pioneering studies had provided valuable mechanistic insight into the migration process, thus creating a foundation for the future development.



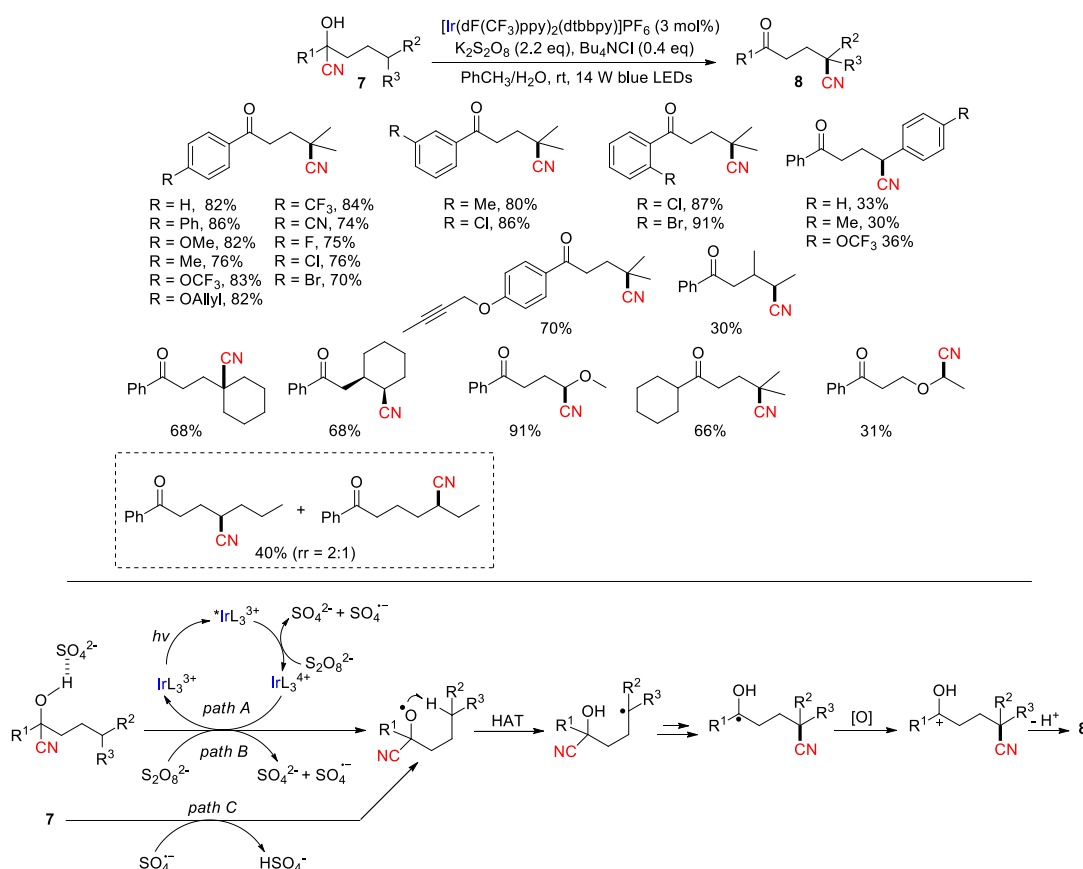
Scheme 3. Conversion of α -peracetonitriles into δ -ketonitriles via HAT-mediated 1,4-CN migration (Watt, 1976).

Organic photocatalysis, including photoredox catalysis, has aroused great attention over the past two decades as a platform for the development of new synthetic strategies [42]. The photocatalysts, such as the commonly employed polypyridyl ruthenium or iridium complexes, can pass to excited states after absorbing light in the visible region of the electromagnetic spectrum. The excited species then interacts with organic molecules through energy transfer or single-electron-transfer (SET), generating reactive intermediates, such as radical, radical anion or diradical, to perform organic transformations. The excited catalysts will fall back to the ground state via unimolecular or bimolecular chemical processes, to complete a photocatalytic cycle.

Photocatalysis has also been widely used for functional group translocations [32,36], with some studies being directed to HAT-mediated CN migration. In 2019, Zhu and co-workers reported a photoredox catalytic protocol for the direct conversion of cyanohydrins **7** into the corresponding δ -ketonitriles **8** without any pretreatment (Scheme 4) [43]. During the model study, the iridium photocatalyst Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ [dF(CF₃)ppy = 2-(2,4-difluorophenyl)-5-trifluoromethylpyridine] combined with K₂S₂O₈ oxidant and Bu₄NCl were found to be optimal among the tested variants, giving the best yield of the desired product (82%) upon visible-light irradiation (82%). The reaction was applicable to a range of cyanohydrins containing various functional groups, leading to the desired products in moderate to good yields. Besides, the selective generation of the δ -ketonitrile over its ϵ -regioisomer was observed in the presence of multiple reactive methylene sites (rr: 2:1), ascribing to kinetically more favorable six-membered cyclic transition state of 1,5-HAT.

As in all photocatalytic reactions, the process is initiated by photoexcitation of the IrL₃³⁺ catalyst to the *IrL₃³⁺ that can be further oxidized by persulfate, giving IrL₃⁴⁺ along with sulfate ion (SO₄²⁻) and sulfate radical anion (SO₄^{•-}) [44]. The IrL₃⁴⁺ species then converts the hydroxyl group into an oxy radical via a proton-coupled electron transfer (PCET) process, which is probably facilitated by the interaction with a conjugate base, e.g., sulfate ion, to reduce the oxidation barrier of the O-H bond. This event also reduces the photocatalyst back to IrL₃³⁺ to complete the catalytic cycle (pathway A). Moreover, the formation of the desired product, albeit in lower yield, was still observed when the reaction was irradiated in the absence of photocatalyst, suggesting that a persulfate-mediated chain reaction may concurrently engage in the PCET process to produce the alkoxy radical (path B). In addition, the possibility of abstracting the alcoholic hydrogen atom by SO₄^{•-} released from path A

and/or B cannot be ruled out (path C). Subsequent 1,5-HAT generates a carbon radical to trigger the cyano group migration, leading to a ketyl radical intermediate. Finally, oxidation of this intermediate followed by deprotonation of the resulting carbocation may account for the formation of the product.



Scheme 4. Conversion of cyanohydrins into δ -ketonitriles under photoredox catalytic conditions (Zhu, 2019).

The alcoholic function in the aforementioned reaction did not take part directly in the CN transfer step, but instead serving as an auxiliary group to form the first carbon radical via HAT and to stabilize the second one. The overall process results in the migration of a cyano group accompanied by the conversion of the hydroxyl group into a carbonyl and the loss of two hydrogen atoms. In a conceptually distinct contribution, Xu et al. recently reported an elegant photocatalytic, reversible C-H sampling strategy that enables the direct positional exchange between a CN group and an unactivated C-H bond without introducing any accompanying variations to a molecule (100% atom economy) [45,46]. The transformation is conducted by merging hydrogen-atom donation (HAD) catalysis with hydrogen-atom abstraction (HAA) catalysis in one reaction system, and begins with non-specific cleavage of C-H bonds by HAA to generate a series of carbon radicals (Figure 2). The resulting radicals are then sorted based on the delicately established kinetic reversibility and the rate differences for the consequence step, permitting the C-4 radical to undergo the cyclization with the nitrile to form the five-membered iminium radical whereas restoring other unfunctionalized radicals to the C-H bonds through HAD.

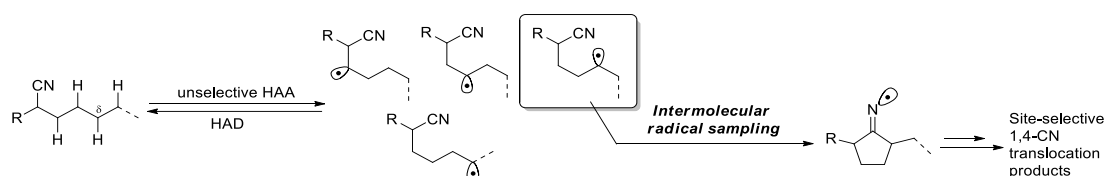
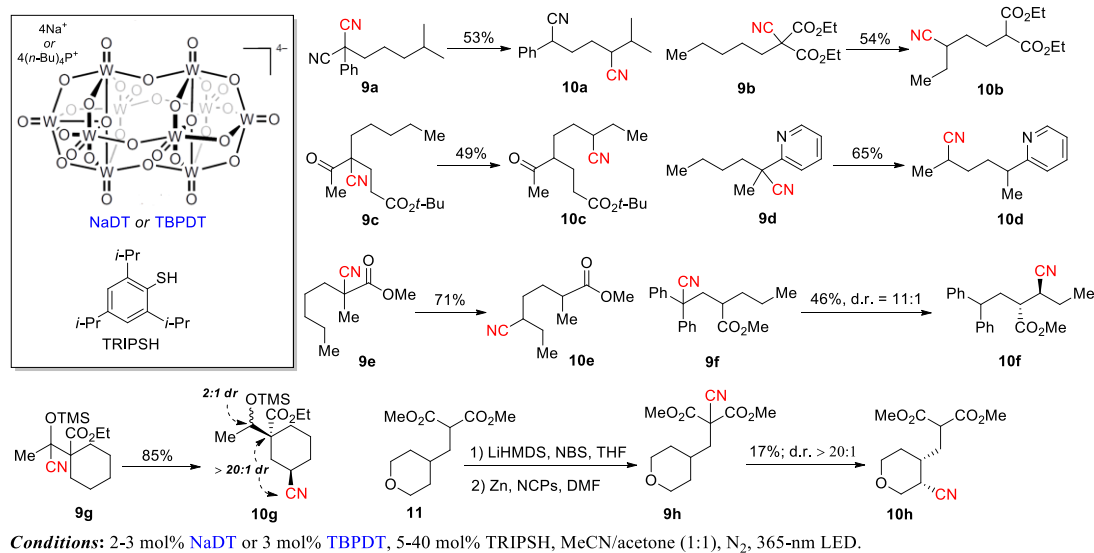


Figure 2. Concept of using radical sampling strategy to achieve 1,4-cyano translocation.

This strategy presents an unconventional paradigm to achieve site-selective C-H transformations without necessitating a site-selective C-H cleavage step. As described, a large array of malononitriles and mono-nitriles was smoothly converted to the desired 1,4-CN translocation products by using sodium or *tetra-n*-butylphosphonium decatungstate (NaDT or TBPDT) as the photo-HAA catalyst [47] and 2,4,6-triisopropylbenzenethiol (TRIPSH) as the HAD catalyst under 365-nm irradiation. Notably, the presence of a radical-stabilizing substituent at the α position of the migrating cyano group (e.g., CN, Ar, CO₂R, COR or OTMS) is essential for the transformation, which is consistent with the mechanism shown in Scheme 1. The selected examples in Scheme 5 demonstrate remarkably high functional group tolerance and site selectivity between the 1,4- and 1,5-translocation (> 20:1 r.r.) (**9a-g**→**10a-g**). Also outlined is a strategic sequence for the diastereoselective synthesis of compound **10h**, involving the initial introduction a cyano group to the readily accessible C-H site in **11** followed by relocating the CN group to a hard-to-target site in **9h** to give **10h**. The readers are encouraged to refer to the original paper for more interesting results and detailed discussions. More advances are expected with applying this 'radical sampling' strategy to the functionalization of other types of C-H bonds



Scheme 5. Selected examples for 1,4-CN migration of nitriles via radical sampling strategy (Xu, 2023).

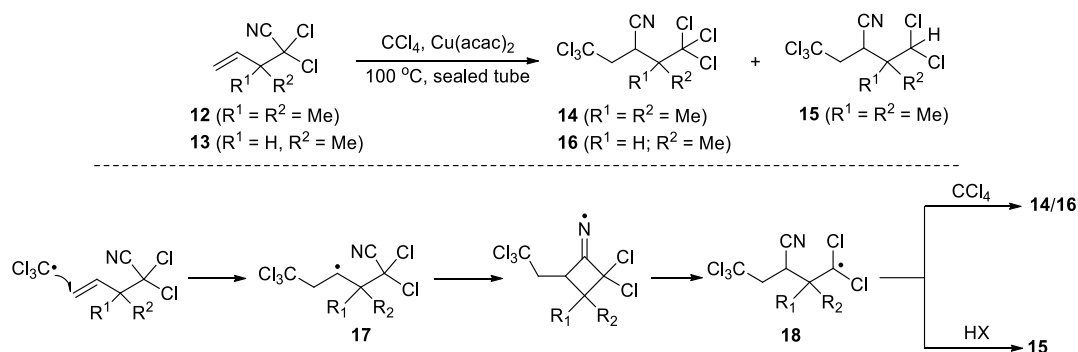
2.3. Cyano Group Migration via Radical Addition to Unsaturated CC Bonds

2.3.1. Early Reported Works

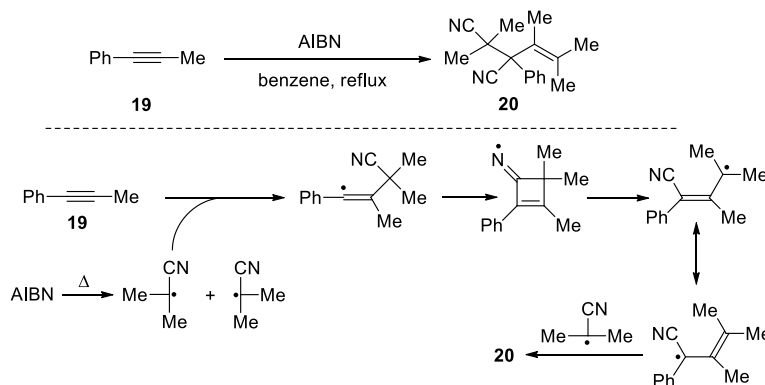
The addition of a radical species to a CC double or triple bond can serve as another approach to trigger the cyano group migration. The reactions in this category are abundant in the literature, and those reported from the late 1970s to the early 2010s are discussed in this section.

The radical used for the addition step can be directly generated from a reagent. For instance, Johnson et al. described that a trichloromethyl radical generated from CCl₄ could add to the C=C double bonds of pent-4-enenitriles **12** and **13** to trigger a 1,3-cyano migration and lead to the formation of the polychlorinated products **14-16** (Scheme 6) [48]. The driving force for the migration is the higher stability of the dichloroalkyl radical **18** than that of the secondary alkyl radical **17**. Moreover, the methyl substituents in the 3-position were found to be critical for the reaction, suggesting the favorable Thorpe-Ingold effect in the cyclization step. In 1997, Montevecchi et al. reported the formation of the product **20** via the reaction of phenylpropyne **19** with AIBN in reflux benzene. The proposed mechanism involves the addition of 2-cyano-isopropyl radical (CIR) generated by the thermal decomposition of AIBN to the C≡C triple bond. The resulting vinyl radical then cyclizes onto the C≡N bond to form a cyclobutenyl iminium species. Subsequent ring opening with β -scission of the C-CMe₂ bond affords a resonance-stabilized radical and thence **20** after trapping

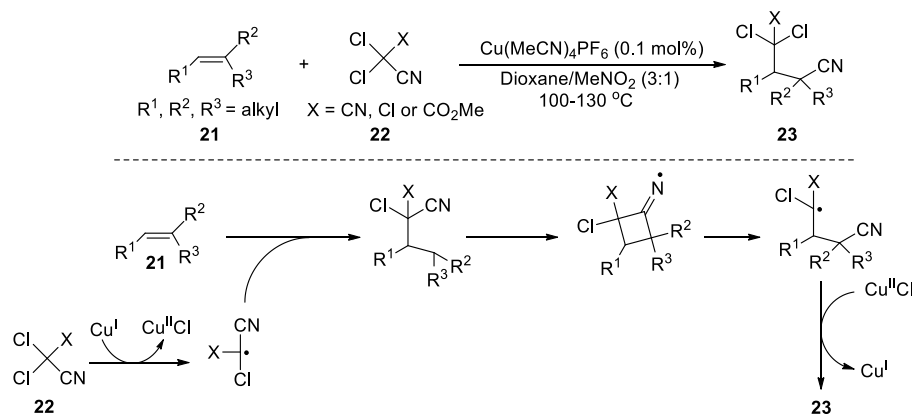
by another CIR (Scheme 7) [49]. The authors also postulated that the cyclization of the vinyl radical was facilitated by the β -methyl group, as similar treatment on phenylacetylene did not give any CN migration product. More recently, a Cu(I)-catalyzed carbocyanation reaction of trisubstituted olefins **21** with chlorinated cyanides **22** was reported by Inoue's group, giving the formation a range of adducts **23** in 24 to 78% yield (11 examples) (Scheme 8) [50]. The process begins with Cu(I)-promoted reductive C-Cl bond cleavage to give an electron-deficient carbon radical along with Cu(II)Cl. Addition of the radical to the C=C double bond in **21** from the less hindered side yields a tertiary carbon radical. Subsequent cyclization followed by β -cleavage lead to a Cl-stablized radical through the 1,3-cyano migration. Finally, abstraction of the chloride from Cu(II)Cl furnishes the products with regeneration of the Cu(I) catalyst. Notably, these reactions all involved 1,3-cyano migration and consequently required elevated temperatures to overcome the high energy barrier associated with four-membered iminyl radicals and transition states.



Scheme 6. Trichloromethyl radical-triggered 1,3-cyano migration (Johnson, 1982).

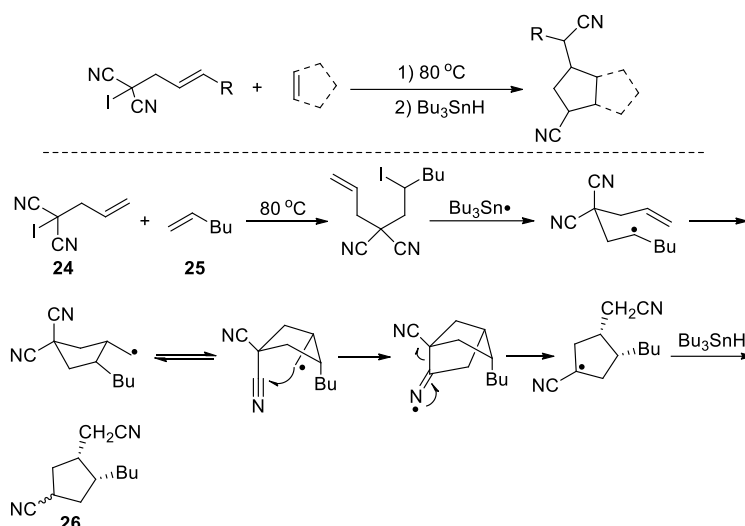


Scheme 7. 2-Cyano-isopropyl radical-triggered 1,3-CN migration (Montevecchi, 1997).

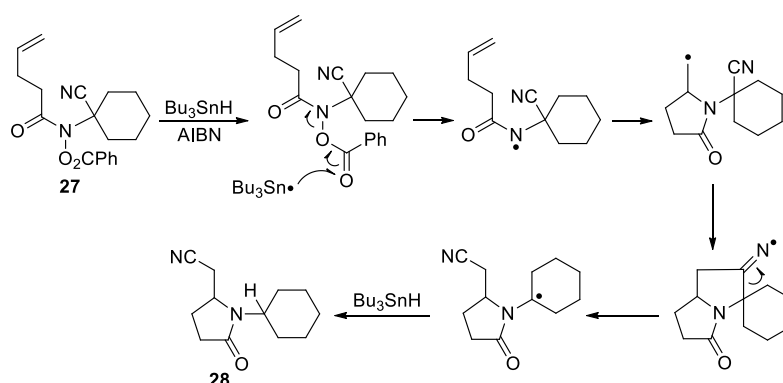


Scheme 8. Radical-mediated carbocyanation of olefins (Inoue, 2012).

The CN migration strategy is amenable to the development of cascade cyclization reactions, in which a reactive intermediate or a substrate itself acts as the radical precursor. Curran et al. reported an annulation reaction by heating iodomalnonitriles with alkenes, e.g., **24** with **25**, in the presence of tributyltin hydride (Scheme 9) [51]. The thermal coupling between **24** and **25** first produces an iodane intermediate, which serves as a radical precursor and undergoes the dehalogenation upon the action of $\text{Bu}_3\text{Sn}\cdot$ to yield a secondary alkyl radical. The addition of the radical to the terminal alkene triggered the 1,4-nitrile migration, leading to a tertiary carbon radical after 5-exo-dig-cyclization and β -cleavage. Hydrogen atom abstraction, likely from Bu_3SnH , then furnishes the cyclized product **26**. In this case, the β -cleavage is aided by relieving the ring-strain of the bicyclic iminyl radical in addition to the radical stabilising nitrile group. Zard et al. developed another cyclization process terminating on a nitrile, in which the employed cyanide substrate **27** serves as a radical precursor via a tributyltin radical-promoted N-O bond cleavage. The addition of the resulting amidyl radical to the olefin is followed by the cyclization and β -scission, yielding a tertiary carbon radical stabilized by the adjacent nitrogen atom and thence the product **28** (Scheme 10) [52].



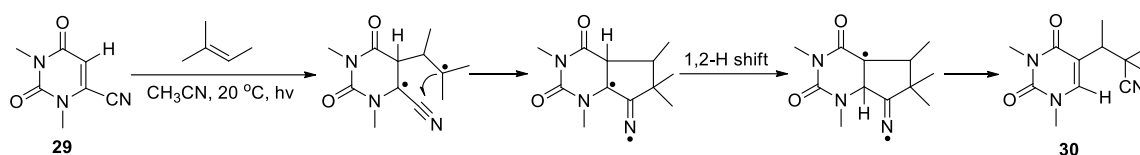
Scheme 9. Annulation involving radical-addition-triggered 1,4-CN migration (Curran, 1992).



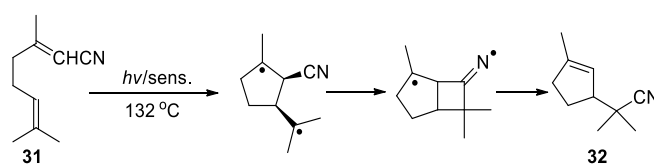
Scheme 10. Amidyl radical-induced cyclization involving 1,4-CN migration (Zard, 1994).

In two particular cases, the CN migration was proposed to proceed through biradical intermediate. Saito and Matsuura reported the formation of 5-substituted uracil **30** upon irradiating 6-cyano-1,3-dimethyluracil **29** with 2-methyl-2-butene in acetonitrile (Scheme 11) [53]. The result was rationalized by assuming that a biradical intermediate resulting from the photoaddition of **29** with the alkene could engage in a 5-exo cyclization to afford a bicyclic iminium species. Subsequent 1,2-hydrogen shift followed by β -cleavage could furnish the rearranged adduct **30**. Furthermore, Wolff and Agosta

described the photolytic conversion of geranonitrile **31** to the cyclopentene product **32** through 1,3-shift of the cyano group from a biradical intermediate (Scheme 12) [54]. This is an overall 1,6-nitrile migration reaction, and was not observed at lower temperatures.



Scheme 11. Formation of 5-substituted 1,3-dimethyluracil via photoaddition of alkene to 6-cyanouracil (Saito, 1980).

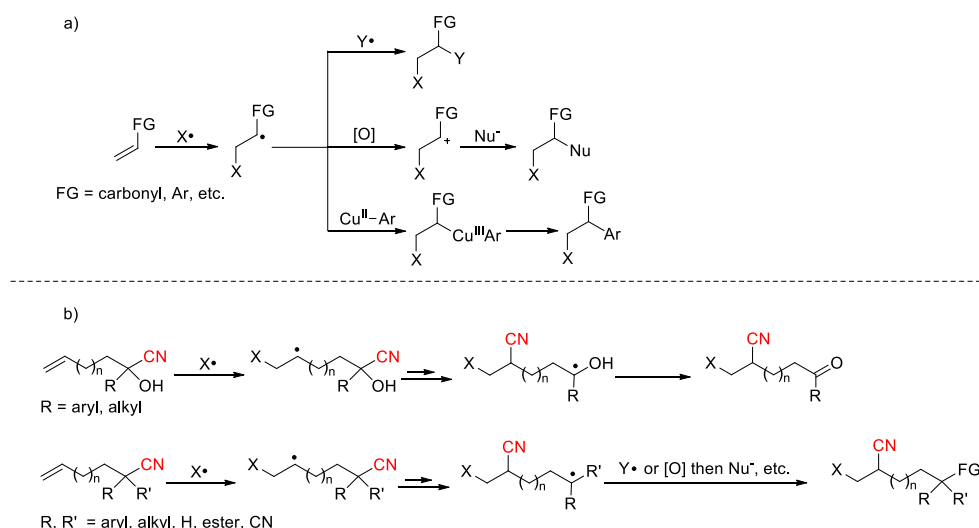


Scheme 12. 1,3-Migration of cyano group via photolysis of geranonitrile (Wolff, 1978).

The above examples have demonstrated the diversity of substrates that are eligible for radical-addition-induced cyano migration. In recent years, such an approach has been mainly used to achieve the multi-site functionalization of the unsaturated cyanohydrin or nitrile compounds. These studies, together with two recently reported cyano migration processes involving diradical or radical cation intermediates, will be discussed in the following sections (2.3.2-2.24).

2.3.2. CN Migration with Unsaturated Cyanohydrins

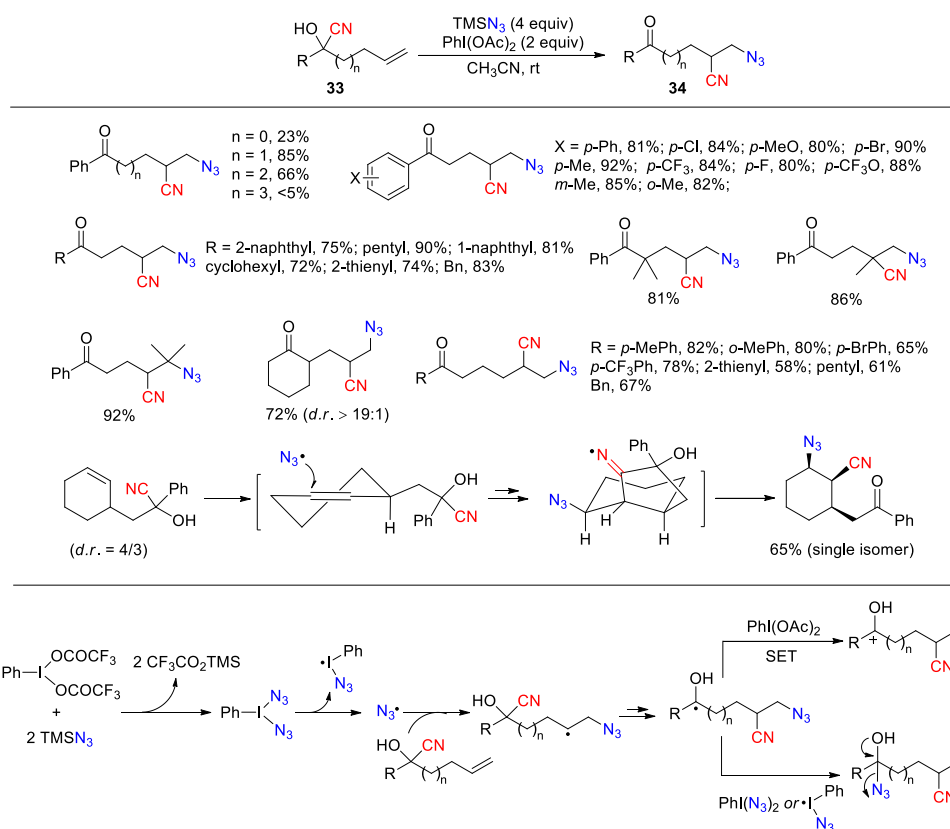
Radical-mediated olefin difunctionalization has provided a powerful tool for enhancing the molecular complexity of simple olefins. In a common paradigm, the addition of a radical ($\text{X}\cdot$) to the C-C double bond generates an alkyl radical, which can be trapped by another radical species ($\text{Y}\cdot$) [55] or oxidized into a carbocation to facilitate the incorporation of second functional group via nucleophilic attack (Nu^-) (Scheme 13, a) [55,56]. In some cases, the carbon-centered radical can be sequestered by organometallic species [57,58] (e.g., $\text{Cu}^{\text{II}}\text{-Ar}$), and functionalized through reductive elimination of the resulting complex. However, the scope of alkenes in these transformations has been largely restricted to activated alkenes, including those containing aryl [55], carbonyl [59] or heteroatom [60] substituents to confer suitable electronic properties to the double bond for efficient reaction with the incoming radical and stabilize the nascent carbon-centered radical through p- π conjugation. In comparison, the difunctionalization of unactivated alkenes (e.g., $\text{FG} = \text{alkyl}$) in a one-step fashion is more challenging and less explored [61,62]. Among several approaches to be considered, the radical-mediated distal functional group migration (FGM) has emerged as an attractive option, allowing the incorporation of diverse functionalities, such as aryl, heteroaryl, carbonyl, alkynyl, alkenyl, imino or cyano group, onto an alkene in addition to the initiating radical species [35,63,64]. Due to the pivotal roles of cyano group in organic chemistry and related fields [1–19], direct cyanofunctionalization of olefin via FGM strategy is unarguably an important subset of the alkene difunctionalization platform, which has been mostly performed with olefinic cyanohydrins or nitriles. During the processes, the ketyl radicals generated from cyanohydrins are readily oxidized to the corresponding ketones, while the radical intermediates derived from alkenyl nitriles undergo various transformations, such as radical coupling or oxidation combined with nucleophilic addition, affording different kinds of products (Scheme 13, b). Despite known for decades (Schemes 6), extensive studies on such transformations have only been carried out in recent fifteen years with flourishing developments in radical chemistry and photocatalysis that enable efficient reagent systems to become increasingly available [63].



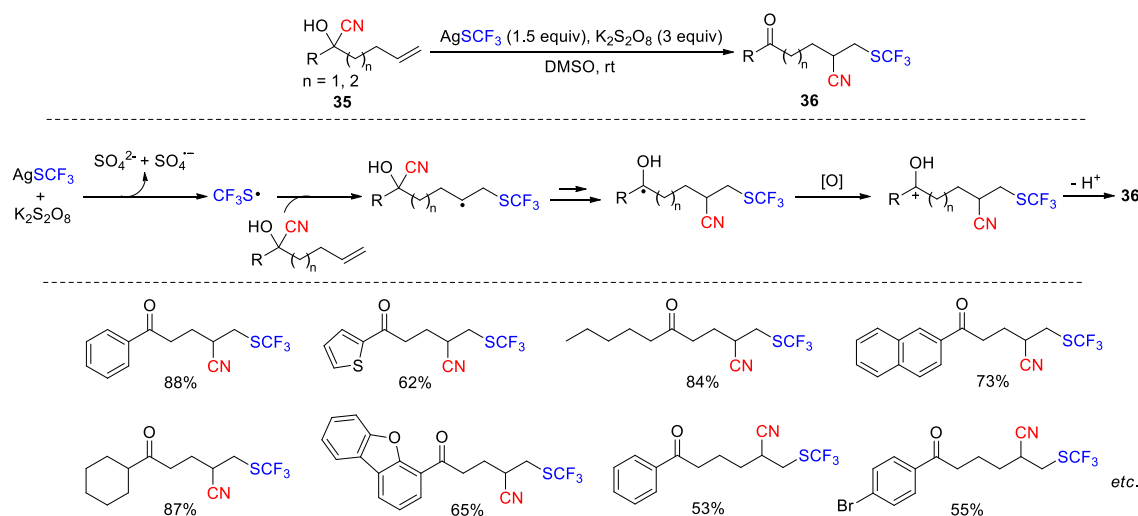
Scheme 13. Strategies for radical-mediated alkene difunctionalization.

The studies performed with unsaturated cyanohydrins are first discussed. In an early contribution, Zhu et al. reported a method for the azidocyanation of unactivated alkenes by using TMSN_3 and $\text{PhI}(\text{OAc})_2$ (PIDA) as the reagents (Scheme 14) [65]. During the initial assessment with homologues cyanohydrins, the 1,4- and 1,5-nitrile transfer reactions ($n = 1, 2$) were found to occur more efficiently than the corresponding 1,3- and 1,6-nitrile transfer reactions ($n = 0, 3$) as reflected by the yields of the obtained products. These results are also consistent with the DFT calculation results shown in Figure 1. In this context, a variety of bis- and trihomallylic cyanohydrins **33** were further evaluated, leading to the corresponding 1,2-azidonitriles **34** in good to high yields with complete regioselectivity. Particularly interesting is the generation of a single cyclohexane isomer with all-cis 1,2,3-substituents from a 4:3 diastereomeric mixture. It would seem that this could be attributed to the facial selectivity in the radical addition step directed by the conformation of the cyclohexene ring and an equatorial orientation of the side chain. Mechanistically, the interaction of TMSN_3 with $\text{PhI}(\text{OAc})_2$ produces $\text{PhI}(\text{N}_3)_2$, which then decomposes giving azido radical. The radical addition to the olefin followed by 1,4(5)-cyano migration produce an α -hydroxy alkyl radical intermediate. As proposed, the conversion of this intermediate to the product may occur in two separate events: i) PIDA-mediated single-electron oxidation to a carbonium ion followed by deprotonation, or ii) capture by the azido radical releasing from $\text{PhI}(\text{N}_3)_2$ or $\text{Ph}(\text{N}_3)\text{I}$ [66] followed by the collapse of the resulting azidohydrin.

Subsequent to their initial report, Zhu and co-workers further disclosed several methods for the functionalization of unsaturated cyanohydrins using similar strategies (Schemes 15-18). In 2017, they reported the conversion of cyanohydrins **35** to CF_3S -substituted ketonitriles **36** through the treatment with AgSCF_3 and $\text{K}_2\text{S}_2\text{O}_8$ (Scheme 15) [67]. In the process, trifluoromethyl sulfide is oxidized by persulfate to generate a trifluoromethylthio radical, which then adds to the alkene to trigger the cyano migration and produce a ketyl radical intermediate. The single-electron oxidation of this intermediate by persulfate, followed by the deprotonation of the resulting carbocation affords the final product. The reaction is applicable to a variety of substrates containing alkyl, naphthyl, thiophenyl, dibenzofuryl or phenyl groups with diverse substitution patterns, and provides the desired products in moderate to good (26 examples, 35-88%).



Scheme 14. Radical-mediated azidocyanation of alkenes via 1,4(5)-CN migration (Zhu, 2016).

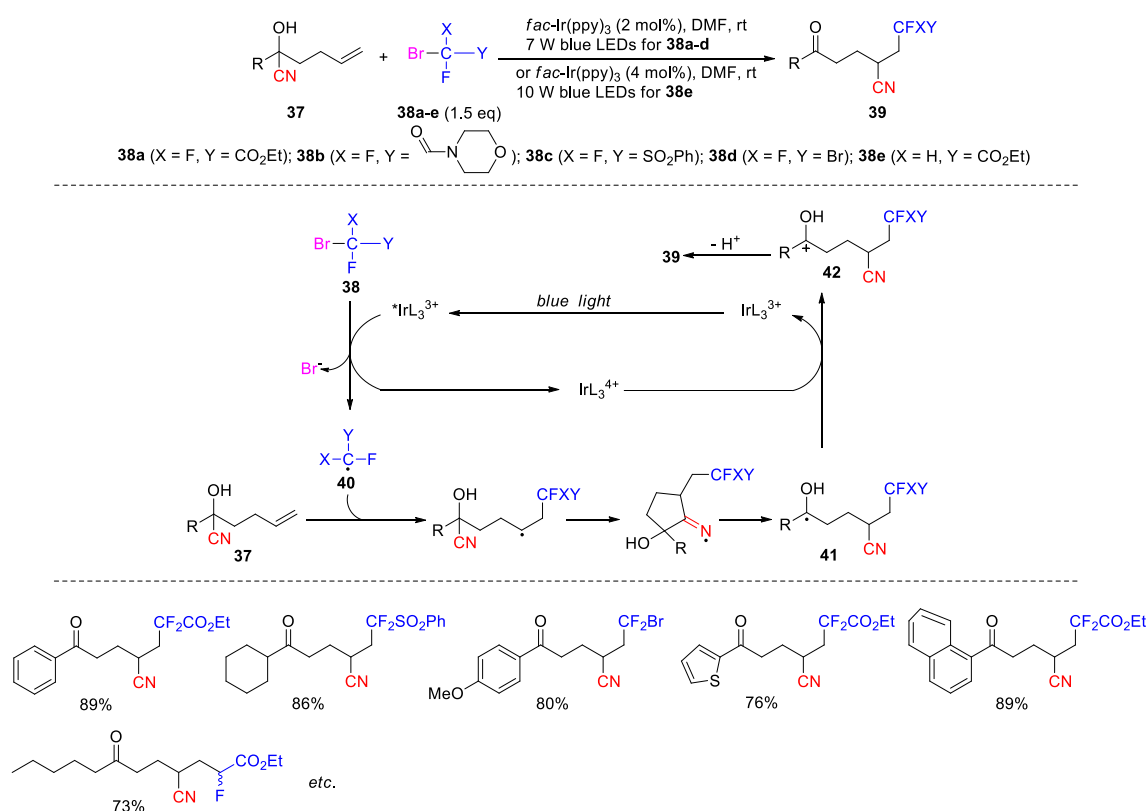


Scheme 15. Radical-mediated cyanotrifluoromethylthiolation of alkenes via 1,4(5)-CN migration (Zhu, 2017).

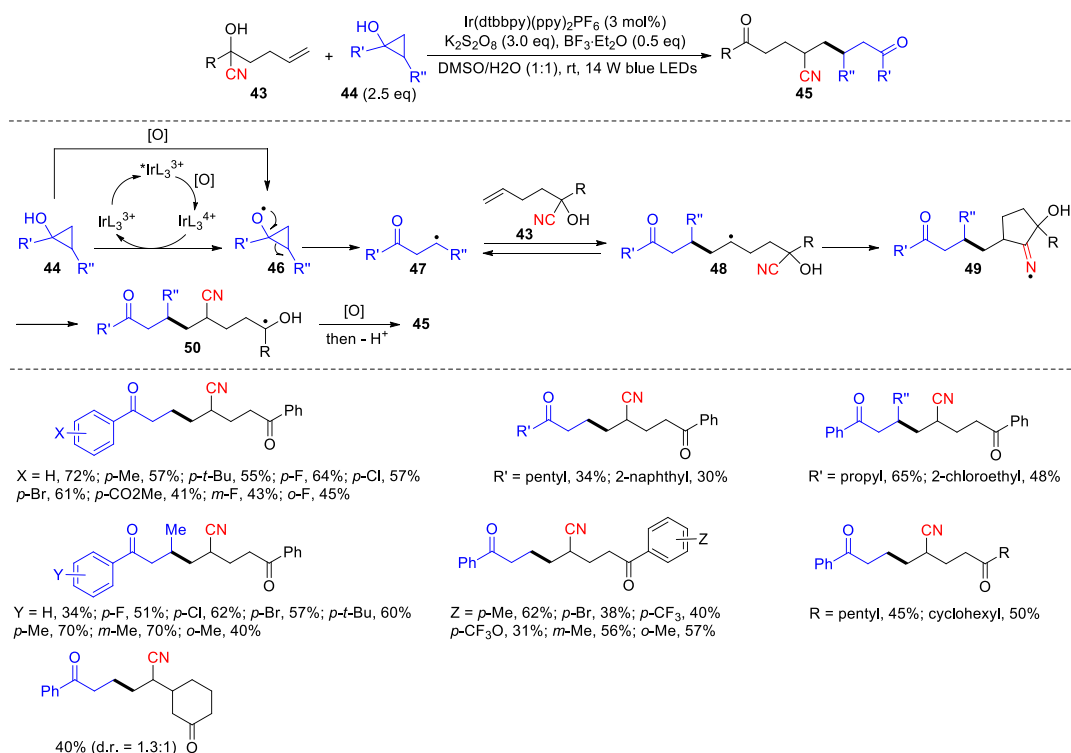
Photoredox catalysis has been utilized by Zhu's group to achieve the polyfunctionalization of alkenyl cyanohydrins. In 2017, they reported a reaction of compounds **37** with fluoro-substituted bromide reagents **38a-e**, including bromodifluoroacetate, 2-bromo-2,2-difluoro-1-morpholinoethanone, bromodifluoromethanesulfonylbenzene, dibromodifluoromethane and bromofluoroacetate, for the synthesis di- or mono-fluorinated ketonitriles **39** (Scheme 16) [68]. Mechanistically, the employed iridium catalyst $\text{fac-Ir}(\text{ppy})_3$ ($\text{ppy} = 2\text{-phenylpyridine}$) (simplified as IrL_3^{3+}) engages in single-electron transfer with **38** from its photoexcited state $^*\text{IrL}_3^{3+}$, thereby giving a IrL_3^{4+} complex. Upon the reduction, **38** may undergo mesolysis, the fragmentation of a radical anion to afford a bromide anion and a carbon radical **40** [69]. Addition of **40** to **37** followed by 5-exo-dig cyclization and β -cleavage lead to ketyl radical intermediate **41**. Oxidation of **41** by the IrL_3^{4+} species provides intermediate **42**, returning the catalyst to its $\text{Ir}(\text{III})$ oxidation state. Finally, deprotonation of

42 furnished the products **39**. Various substrates bearing naphthyl, thiophenyl, benzyl, alkyl, or phenyl group with diverse substitution patterns were allowed to react with **38a-e**, yielding over 40 products in good to high yields (50-91%). Besides, increased catalyst loading and more intense radiation were required for the reactions of **38e** to improve the yields of mono-fluorinated products.

In another work, Zhu and co-workers described the preparation of 1,8-diketone derivatives **45** via the photoredox coupling between cyanohydrins **43** and cyclopropanols **44** (30 examples, Scheme 17) [70]. A reagent system comprising Ir(dtbbpy)(ppy)₂PF₆ catalyst, K₂S₂O₈ and BF₃Et₂O was found to be optimal for the reaction, while the function of BF₃Et₂O had remained unknown to the authors. In the process, the photoexcited catalyst ^{*}IrL₃³⁺ is oxidized by K₂S₂O₈ to yield the IrL₃⁴⁺ complex, which then converts **44** to the cyclopropyloxy radical **46** with the regeneration of the IrL₃³⁺ catalyst. The formation of the desired product was still observed (in a lower yield) when the reaction was conducted in the absence of photocatalyst, suggesting that the oxidation of **44** by persulfate may concurrently contribute to the formation of **46**. The ring-opening of **46** provides a β-carbonyl radical **47**, which then adds to the olefin to produce another alkyl radical **48**. The addition step may be reversible due to similar thermodynamic stability of intermediates **47** and **48**. Nevertheless, the rapid interception of the carbon radical in **48** by the cyano group can drive the process forward to yield the iminium radical **49**, and thence the more stable ketyl radical **50** after the β-cleavage. Single-electron oxidation of **50** followed by deprotonation furnished the product.

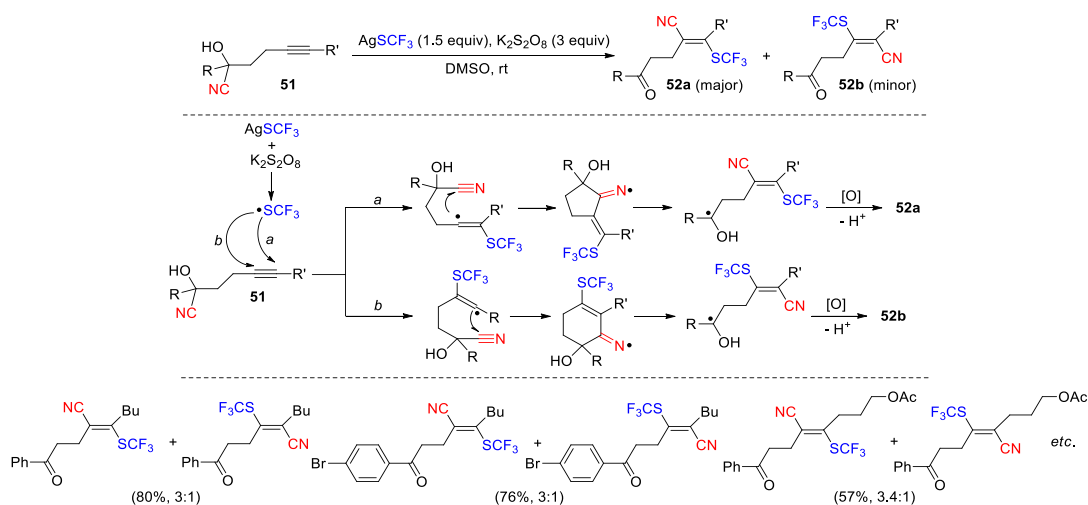


Scheme 16. Synthesis fluorinated ketonitriles via photoredox-promoted 1,4-cyano migration (Zhu, 2017).



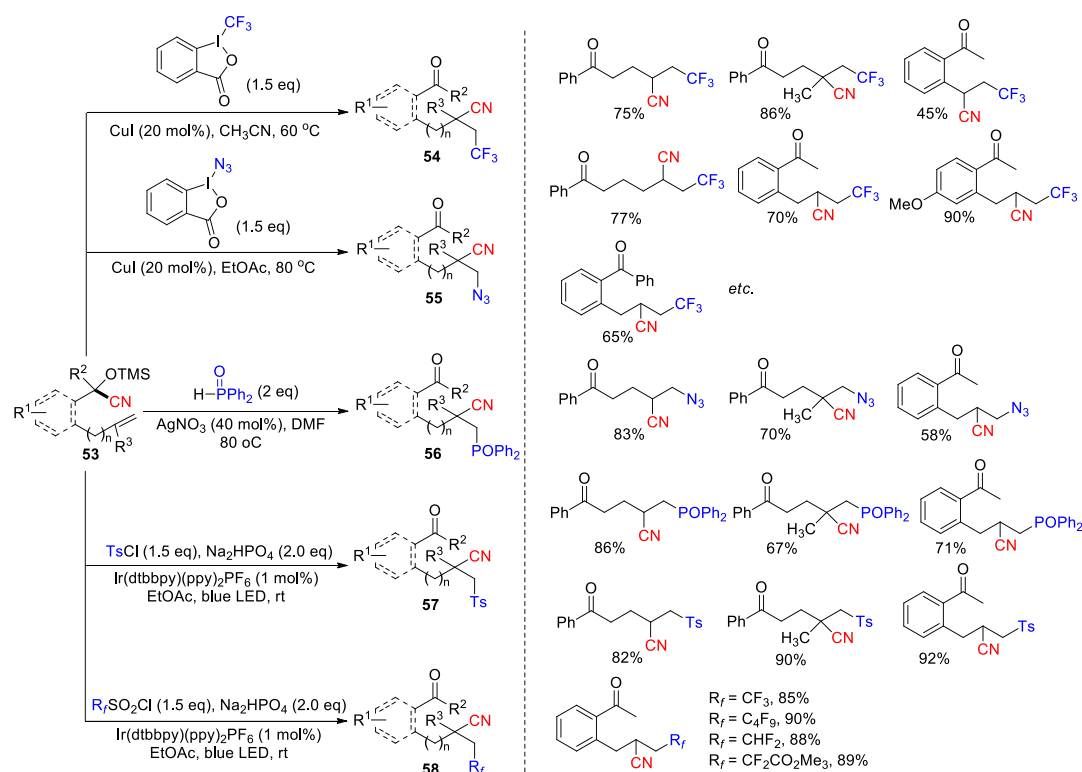
Scheme 17. Synthesis of 1,8-diketones via photoredox-promoted coupling and 1,4-cyano migration (Zhu, 2019).

Moreover, the 1,2-difunctionalization of internal alkynes was realized in a study by Zhu et al. It was found that cyanohydrins **51**, upon the treatment with AgSCF_3 (1.5 equiv) and $\text{K}_2\text{S}_2\text{O}_8$ (3 equiv), could be converted to the acrylonitrile products **52a** and **52b** as the mixtures of *E*-regioisomers (25 examples, **52a/52b** = 2:1 to 8:1, 40-83%) (Scheme 18) [71]. In the event, addition of the in-situ generated CF_3S radical occurs at both end of the alkyne. The resulting alkenyl radicals then engage in the 1,4- or 1,5-cyano migration to yield the ketyl radicals via cyclic iminium species. Oxidation of these intermediates followed by deprotonation lead to the isomeric products. The ratios between **52a** and **52b** indicated that the 1,4-cyano migration resulting from the outer-carbon addition (a) should occur more readily than the 1,5-migration triggered by the addition on the inner carbon atom (b).



Scheme 18. Cyanotrifluoromethylthiolation of alkynes via radical-mediated CN migration (Zhu, 2018).

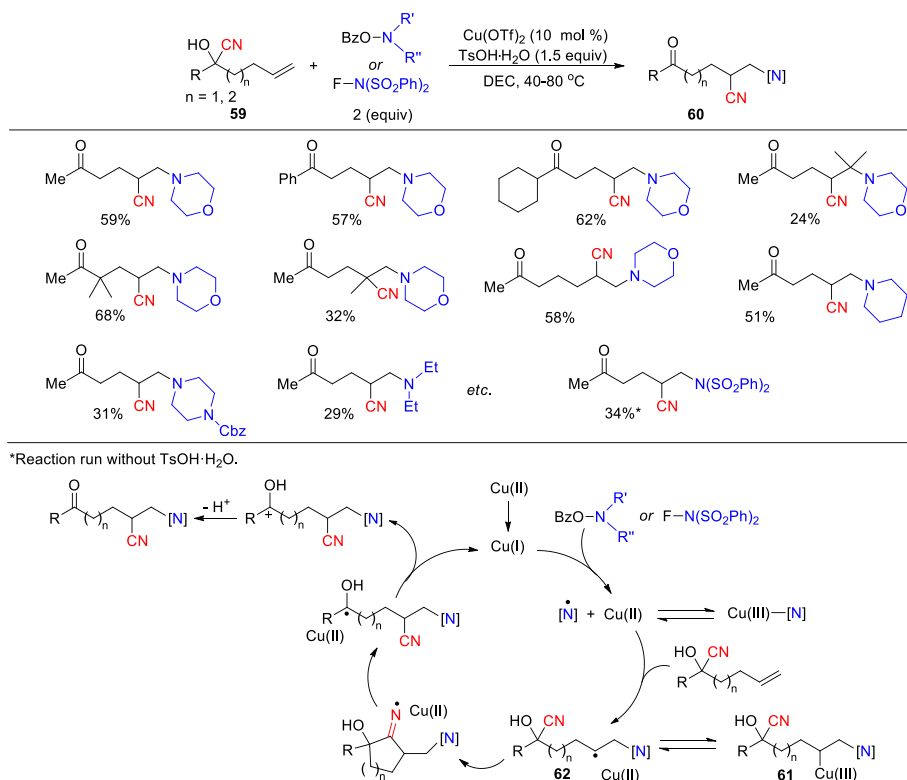
Given the efficient generation of carbon- or heteroatom-centered radicals, the aforementioned studies by Zhu et al. has demonstrated the feasibility of achieving the cyanofunctionalization of unsaturated CC bonds in cyanohydrins. In addition, the contributions from several other groups have also been noticed in the literature. In 2016, Liu et al. collectively reported a series of reactions of acyclic or aryl-tethered trimethylsilyl-protected cyanohydrins **53**, enabling the generation of the corresponding β -functionalized nitriles **54–58** via the trifluoromethyl, azido, phosphonyl, sulfonyl or perfluoroalkyl radical-triggered 1,4(5)-cyano migration followed by oxidation and TMS-deprotection (Scheme 19) [72]. The trifluoromethylation and azidation reactions were conducted with Togni's and Zhdankin reagents in the presence of CuI catalyst, while diphenyl phosphine oxide and AgNO₃ were employed to effect the phosphonylation. The sulfonylation and perfluoroalkylation were both performed under photoredox catalysis by using *p*-toluenesulfonyl chloride or fluorinated sulfonyl chlorides as radical sources. Although not providing in the report, the detailed mechanism for the generation of initiating radical species as well as the rational for catalysis can be found in or deduced from other literature [73–78]. In a more recent report (2024), Li et al. similarly employed CF₃SO₂Cl as radical precursor to achieve the trifluoromethylation of cyanohydrins as in the production of **58** (R_f = CF₃) but without using metal catalyst (455 nm Blue LED/diethyl ether/rt). The photo-induced C-Cl cleavage followed by desulfonylation was proposed to account for the generation of CF₃ radical [79].



Scheme 19. Diverse difunctionalization of alkenes via radical-mediated 1,4(5)-CN migration (Liu, 2016).

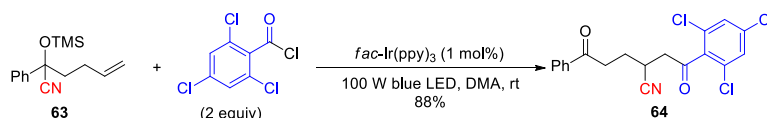
Wang and co-worker have developed another copper-catalyzed method for the 1,2-aminocyanation by using *O*-benzoylhydroxylamines and *N*-fluorobenzenesulfonimide (NFSI) as nitrogen precursors. Treatment of cyanohydrins **59** with these reagents in the presence of 10 mol% of Cu(OTf)₂ and 1.5 equiv of TsOH afforded β -amino and β -sulfonimido nitriles **60** in varying yields (29 examples, 24-68%) (Scheme 20) [80]. The positive effect of *p*-TsOH on the formation of the desired product was observed but had not been fully understood by the authors. In the proposed mechanisms, the employed Cu(OTf)₂ is first activated into the Cu(I) catalyst presumably through the action of a nitrogen-containing ligand (*O*-benzoylhydroxylamine or NFSI) [81]. The resulting Cu(I) catalyst further engages in the oxidative addition with *O*-benzoylhydroxylamine or NFSI to generate an amino-Cu(III) complex. Addition of this complex to the alkene affords the complex **61**, which then

undergoes reversible single-electron transfer to yield copper(II) and the secondary carbon radical **62**. Alternatively, intermediate **62** can be produced through the addition of a N-centered radical released from the amino-Cu(III) complex to the olefin. Subsequent cyano migration through the cyclic iminium radical intermediate provides a more stable ketyl radical. Finally, the SET oxidation by Cu(II) can transfer this radical to a carbocation, affording the product after deprotonation and regenerating the copper(I) catalyst.

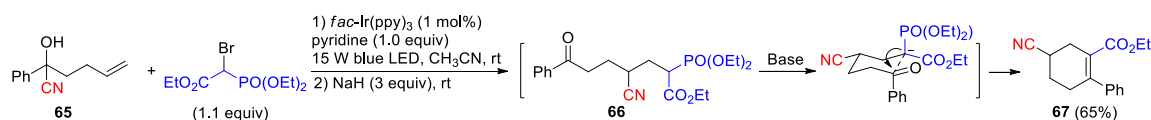


Scheme 20. Copper-catalyzed 1,2-aminocyanation of alkenes via 1,4-CN migration (Wang, 2020).

Two isolated photoredox reactions have also been reported by using *fac*-Ir(ppy)₃ as catalyst. As a part of investigating the distal migration of a variety of functional groups, Ngai et al. demonstrated that an aroyl radical, generated upon the reduction of 2,4,6-trichlorobenzoyl by the excited photoredox catalyst, could add to the alkene in the TMS-protected cyanohydrin **63** to trigger the 1,4-cyano migration and give the formation of the β -cyanated-1,6-diketone **64** after a further oxidation-deprotection sequence (Scheme 21) [82]. Feng et al. described the construction of cyclohexene **67** by merging the catalytic reaction between the cyanohydrin **65** and 2-bromo-2-phosphorylacetate with the one-pot HWE olefination of the resulting product **66** (Scheme 22) [83]. The proposed pathway leading to **66** is similar to that shown in Scheme 16 for the generation of **39**.

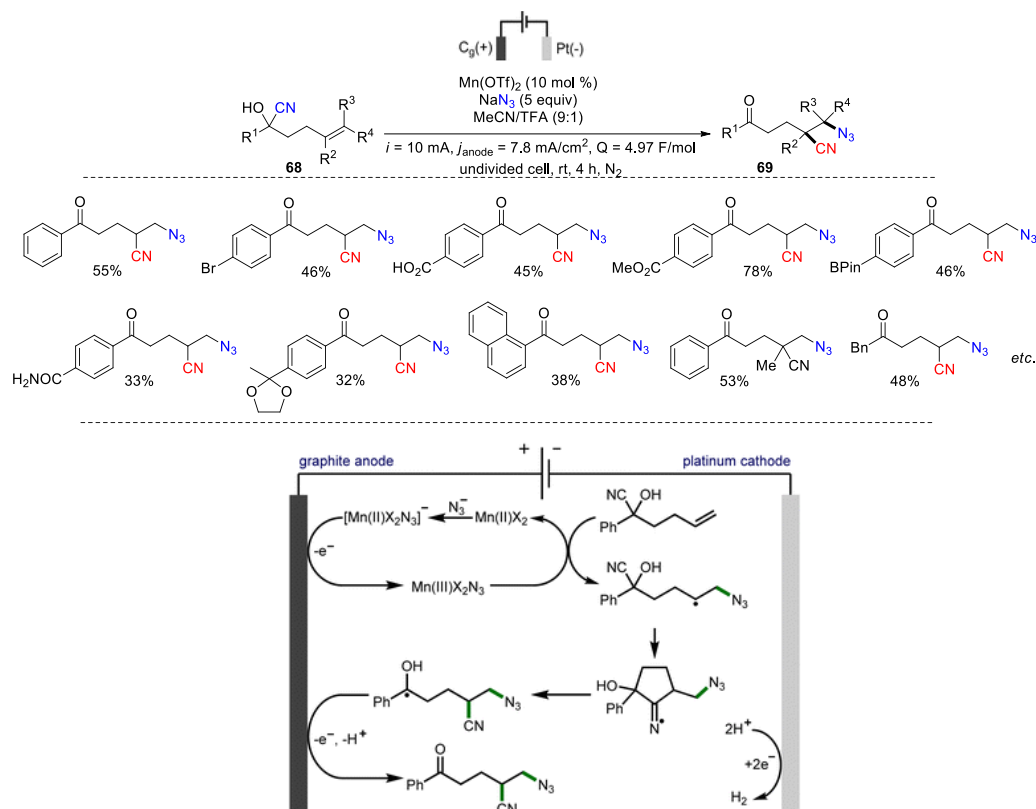


Scheme 21. Benzoylcyanation of alkene via Photoredox-promoted 1,4-CN migration (Ngai, 2019).



Scheme 22. Construction of cyclohexene via radical-mediated cyanofunctionalization of alkene and HWE olefination (Feng, 2021).

The azidocyanation reaction shown in Scheme 14 utilizes PIDA as a high molecular weight oxidant, generating stoichiometric organic waste that requires separation from the desired products. In a conceptually distinct contribution, Morrill and co-workers have developed an alternative oxidant-free protocol to achieve the azidocyanation of alkenes under electrochemical conditions. It was found that a system composed of $\text{Mn}(\text{OTf})_2$ and NaN_3 as both azide source and electrolyte in MeCN/TFA was capable of converting aromatic ($\text{R}^1 = \text{aryl}$) and aliphatic ($\text{R}^1 = \text{alkyl}$) cyanohydrins **68** into the 1,2-azidonitriles **69** upon galvanostatic cycling (28 examples, 33-55%) (Scheme 23). [84]. Besides, an array of useful functional groups, such as halogen, carboxylic acid, ester, borane, amide, and ketal in the 4-position of phenyl ring were tolerated, giving the potential for further derivatization. Based on the results obtained from the radical clock and cyclic voltammetry studies, the authors proposed that the process is initiated by the formation of $[\text{Mn}(\text{II})\text{X}_2\text{N}_3]$ from $\text{Mn}(\text{II})\text{X}_2$ and NaN_3 , which is oxidized at the anode to form $\text{Mn}(\text{III})\text{X}_2\text{N}_3$. This intermediate may deliver an azide radical to the cyanohydrin, giving a secondary alkyl radical. After the 1,4-nitrile migration, a second oxidation of the resulting ketyl radical at the anode, followed by proton loss provides the final product. Meanwhile, hydrogen gas is evolved via proton reduction at the cathode.



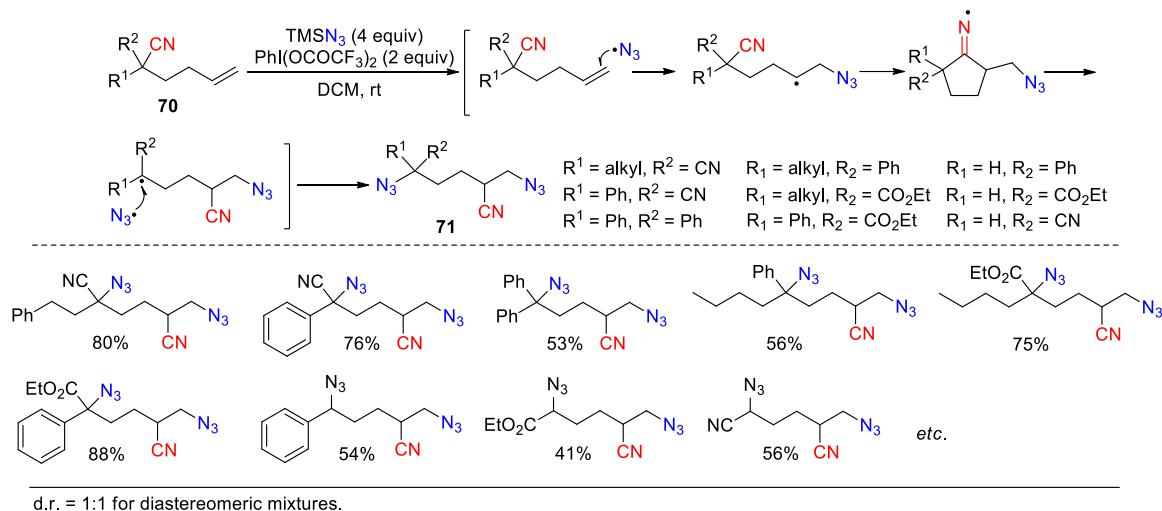
Scheme 23. Electrochemical alkene azidocyanation via 1,4-nitrile migration (Morrill, 2022).

2.3.3. CN Migration with Alkenyl Nitriles

Radical-addition-triggered CN migration has also been widely used for the multi-site functionalization of alkenyl nitriles, mostly as 5-enenitriles. The resulting carbon radicals generated in this fashion were shown undergo a variety of subsequent transformations (Scheme 13, b), which are discussed below in four aspects: i) radical coupling, ii) oxidation to carbocations followed by nucleophilic attack, iii) formation of CC double bonds via oxidation/deprotonation, coupling/elimination or HAT sequence, and iv) reduction to a carboanions followed by protonation or nucleophilic substitution.

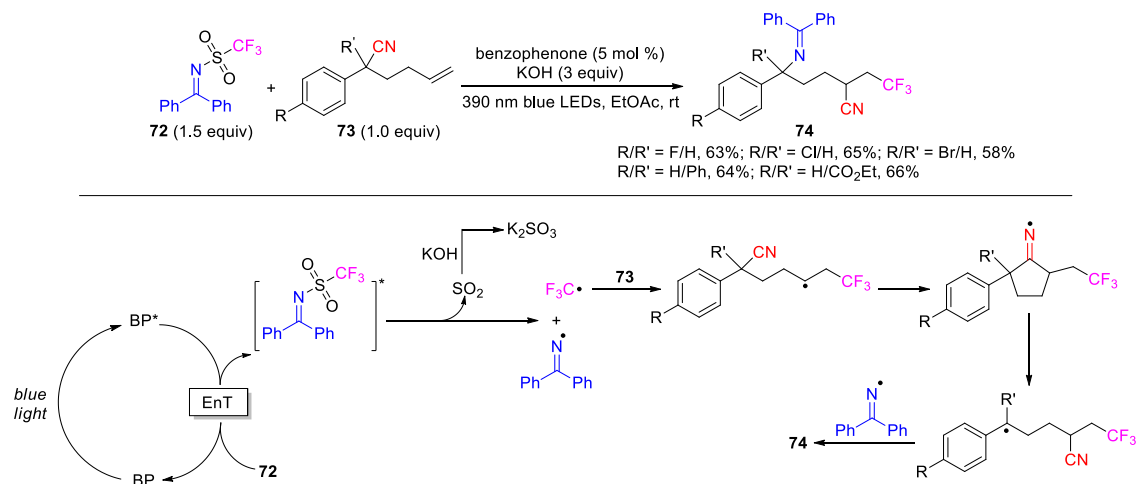
First, they can be captured by external radical species, either identical to or different from those used for the addition step (Schemes 24-27). Zhu et al. in 2022 reported the conversion of a variety of hexenenitriles **70** into the diazidation products **71** by using TMSN_3 as the radical source and PIFA as

a stoichiometric agent (30 examples, 41-90%) (Scheme 24) [85]. In the process, azido radicals should be generated in similar way as shown in Scheme 14. After this, one azido radical triggers the 1,4-cyano migration through the addition to **70**, while the other one intercepts the resulting carbon radical to give the product. Once again, the presence of at least one radical stabilizing substituent (R^1 and/or $R^2 = \text{CN}$, Ph, CO_2Et) is required to facilitate the β -C-C bond cleavage in the cyclic iminyl radical intermediate.



Scheme 24. Trifunctionalization of hexenenitriles via azido radical-mediated cyano migration (Zhu, 2022).

Yang et al. have developed a photolytic protocol for the trifluoromethyliminium of alkenes by using (diphenylmethylene)-1,1,1-trifluoromethanesulfonamide **72** as a bifunctional reagent. In the event, a benzophenone (BP)-mediated photosensitized energy transfer (EnT) promotes the successive N-S-C bond cleavage in **72** to generate a diphenyl iminyl and trifluoromethyl radical pair after the extrusion of SO_2 . Consecutive delivery of these radicals to an alkene provides the β - CF_3 imine product. Moreover, KOH was used as an external base to remove the released SO_2 . When the reactions were performed with the alkenes **73** tethered to a cyano group, the 1,4-CN migration occurred prior to the radical coupling to give the trifunctionalization products **74** as shown in Scheme 25 [86].

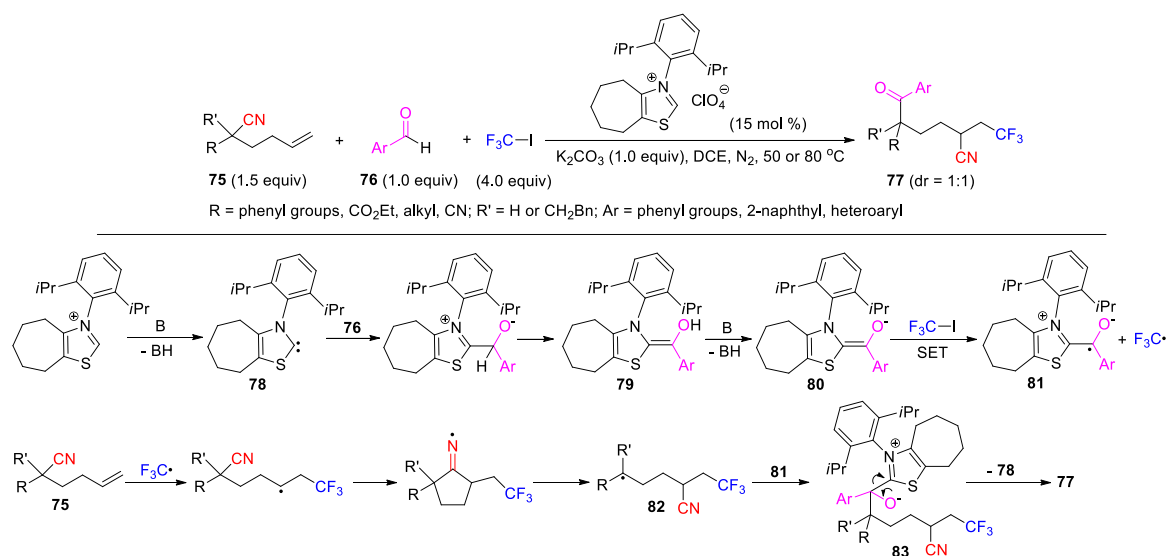


Scheme 25. Photochemical alkene trifluoromethyliminium involving 1,4-CN migration (Yang, 2023).

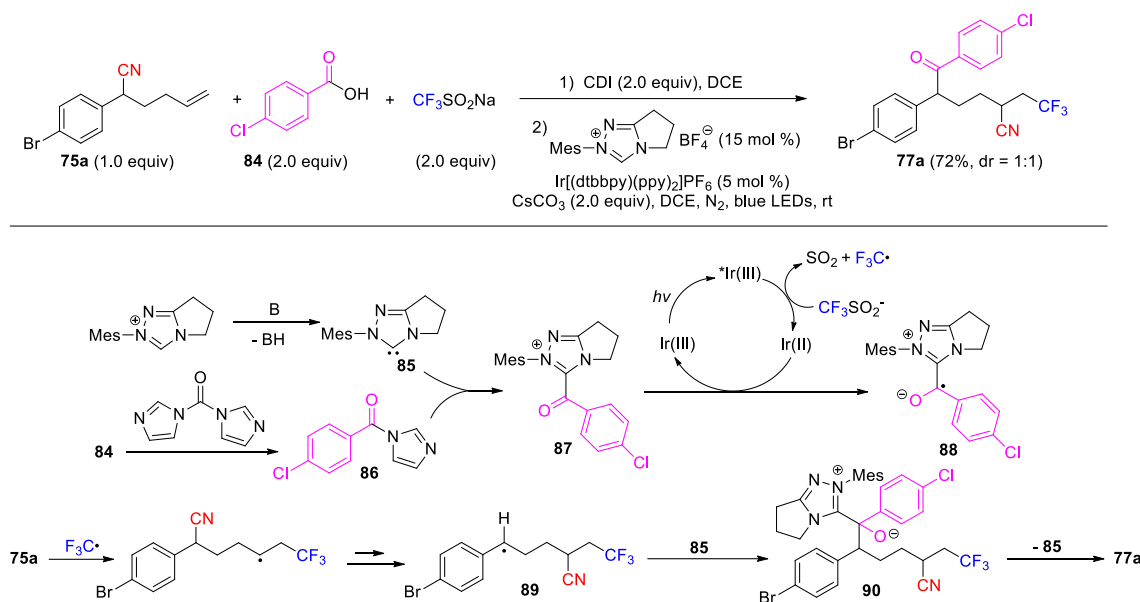
The radical-mediated trifunctionalization of alkenyl nitriles has also been realized via *N*-heterocyclic carbene (NHC) organocatalysis. In 2023, Du et al. reported an NHC-catalyzed three-

component reaction of hexenenitriles **75** with aromatic aldehydes **76** and trifluoromethyl iodide, which provided the products **77** (33 examples, 55-87%) by using a thiazolium salt as precatalyst and K_2CO_3 as base (Scheme 26) [87]. In the proposed pathway, the carbene **78** derived from the precatalyst reacts with **76** to form enaminol **79** (so called Breslow intermediate) and further enolate **80** after proton abstraction. A single electron transfer (SET) from **80** [88] to CF_3-I would produce NHC-bound ketyl anion radicals **81** along with a trifluoromethyl radical. Subsequent addition of the CF_3 radical to **75** followed by the 1,4-CN migration provides carbon radical **82**, which then undergo the coupling with **81** to give intermediates **83**. Finally, collapse of **83** leads to the product **77** and regeneration of carbene **78** for the next cycle. In addition to CF_3I , this radical-relay protocol was also applicable to several other fluorinated reagents including $BrCF_2CO_2Et$, CF_2Br_2 and $C_6F_{13}I$ as well as ICH_2Ts . However, it was not compatible with the tested aliphatic aldehyde as a replacement for **76**.

More recently, the same research group has described an alternative method for the trifluoromethylation-acylation of hexenenitriles by instead using aromatic acids and CF_3SO_2Na as the reactants. A dual NHC/photoredox catalysis system comprising a triazolium salt, $Ir(dtbbpy)(ppy)_2PF_6$ catalyst and Cs_2CO_3 was capable of effecting the transformation upon visible-light irradiation [89]. Besides, this method also requires the pre-activation of the acids into the corresponding benzoylimidazoles through the in-situ treatment with 1,1'-carbonyldiimidazole. As a typical example, the reaction of hexenenitrile **75a** with CF_3SO_2Na and acid **84** under the developed conditions affords the product **77a** in good yield (Scheme 27). A likely mechanism involves the addition of NHC **85** to the carbonyl group of benzoylimidazole **86**, giving acyl azolium **87**. Meanwhile, the single-electron oxidation of CF_3SO_2Na by the excited catalyst produces a CF_3 radical along with the Ir(II) species that is sufficiently reducing to donate an electron to **87**, thereby generating NHC-bounded radical anion **88**. Addition of the CF_3 radical to **75a** followed by cyano migration provides benzylic radical **89**, which can couple with **88** to yield a highly congested intermediate **90**. Finally, decomposition of **90** furnishes the product **77a** with regeneration of **85** to complete the cycle.



Scheme 26. NHC-catalyzed radical relay trifluoromethylation-acylation of hexenenitriles via cyano migration (Du, 2023).



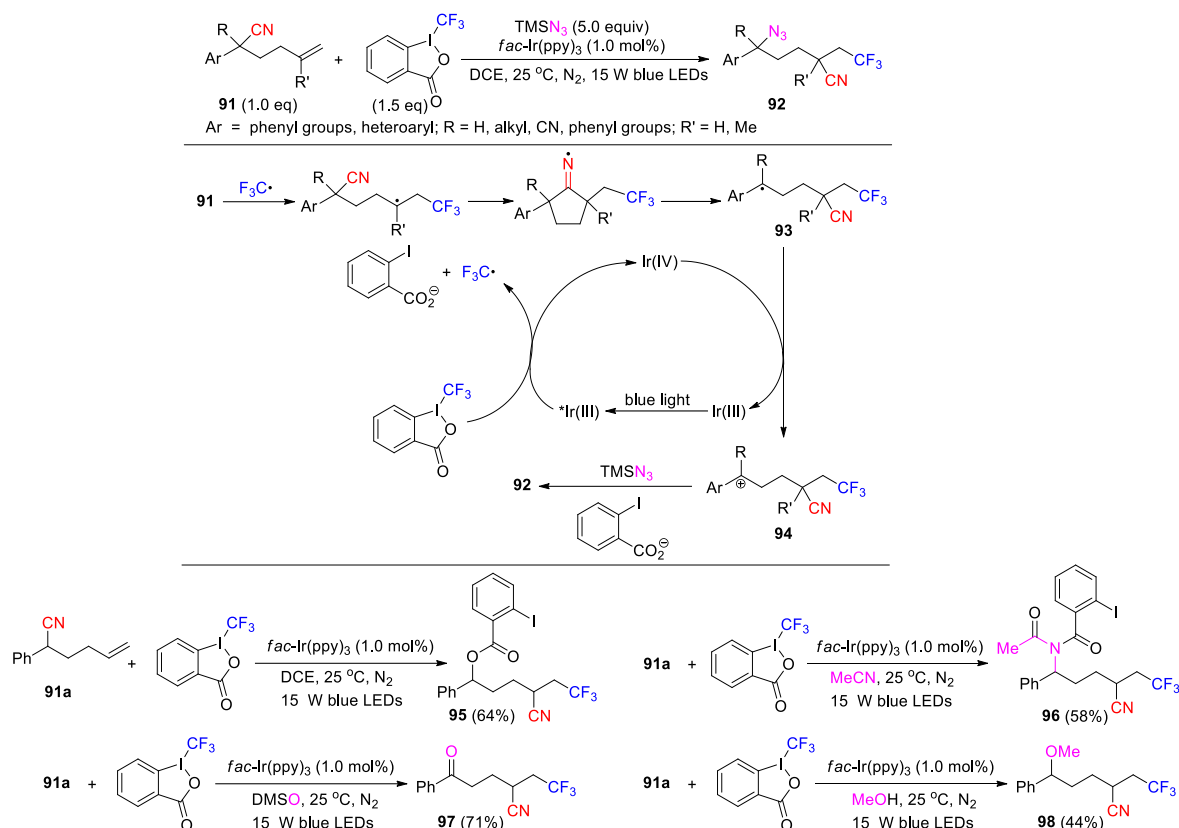
Scheme 27. Dual NHC/photoredox catalytic trifluoromethylation-acylation of hexenenitriles via cyano migration (Du, 2024).

The carbon radical resulting from the CN migration can be oxidized into a carbocation, thus offering an opportunity for the incorporation of second functional group via nucleophilic attack (Schemes 28-30). Chen and Zhu's group in 2022 reported the photoredox trifunctionalization of 5-hexenenitriles **91** using Togni's reagent II as radical source and TMSN₃ as nucleophile precursor. The reaction was conducted with *fac*-Ir(ppy)₃ catalyst to give the polyfunctionalized products **92** upon visible light irradiation in DCE (31 examples, 32-86%) (Scheme 28) [90]. In the process, reduction of Togni's reagent by the excited Ir(III) catalyst gives a trifluoromethyl radical and 2-iodobenzoate. The addition of the CF₃ radical to **91** triggers the 1,4-CN migration to provide a benzyl radical **93** after the cyclization and β-cleavage of the iminyl radical intermediate. Then, single-electron oxidation of **93** by Ir(IV) species proceeds to afford the corresponding carbocation **94** with the regeneration of ground state Ir(III) catalyst. Finally, nucleophilic attack of the azide anion on **94** furnishes the product. It was additionally found that the reaction could be carried out in concert with other external nucleophiles. In the absence of TMSN₃, Togni's reagent served as both the radical source and the nucleophile precursor to give the ester product **95**. When MeCN was employed as the solvent, a Ritter-type addition dominated to yield the amidation product **96** via subsequent nucleophilic attack by 2-iodobenzoate and Mumm rearrangement. DMSO and MeOH were also attempted as the nucleophiles, leading to the formation of the products **97** and **98**, respectively.

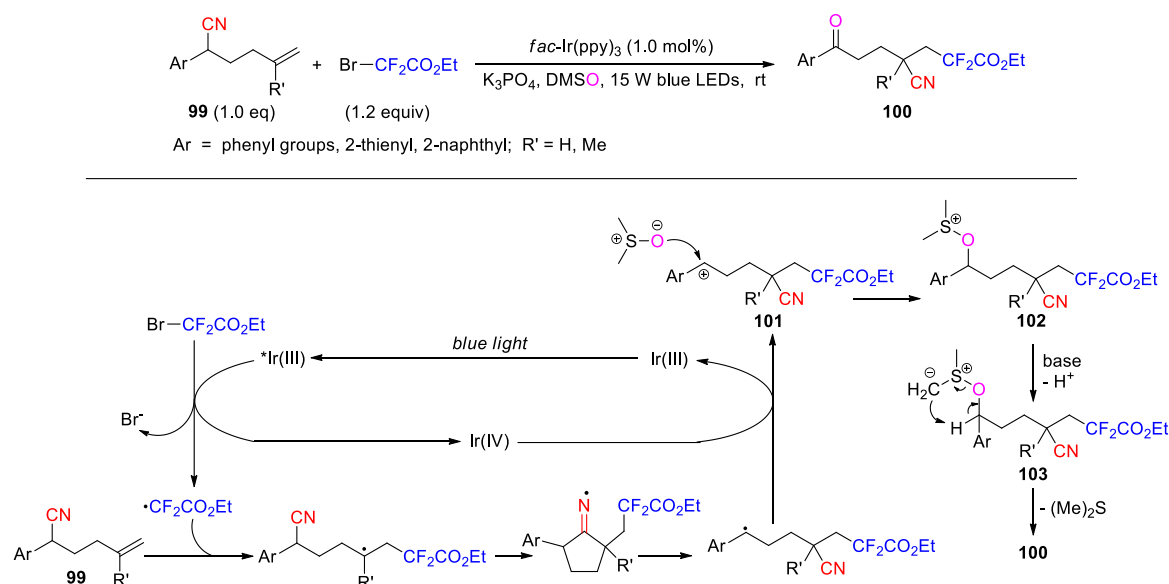
Guo later described the photoredox conversion of 5-hexenenitriles **99** to difluoroalkylated ketonitriles **100** through the reaction with BrCF₂CO₂Et in DMSO using *fac*-Ir(ppy)₃ as catalyst and K₃PO₄ as a base (Scheme 29) [91], in which DMSO acts as both solvent and nucleophile as in the formation of **97**. Once the carbocation intermediate **101** is formed via the oxidation of the benzylic radical, it will be captured by DMSO to give an alkoxysulfonium ion **102**. Further deprotonation affords an alkoxysulfonium ylide **103**, which then converts to the product through a [2,3]-sigmatropic shift.

More recently, *O*-acyl hydroxylamines, such as **105**, have been employed as bifunctional reagents to achieve the diamidation of 5-hexenenitriles **104** under photoredox catalysis. The reaction was conducted with 1 mol % of *fac*-Ir(ppy)₃ in acetonitrile (as in the reaction to give **96**) to afford the distal-imido β-amino nitriles **106** in varying yields (22 example, 21-81%) (Scheme 30) [92]. Mechanistically, the *O*-acyl hydroxylamine undergoes the cleavage upon the single-electron reduction by the excited Ir(III) catalyst, affording a N-centered radical and a carboxylate anion. The 1,4-CN migration induced by the radical addition provides a benzylic radical that can be further oxidized into a carbocation by Ir(IV). The carbocation is then intercepted by acetonitrile to give a

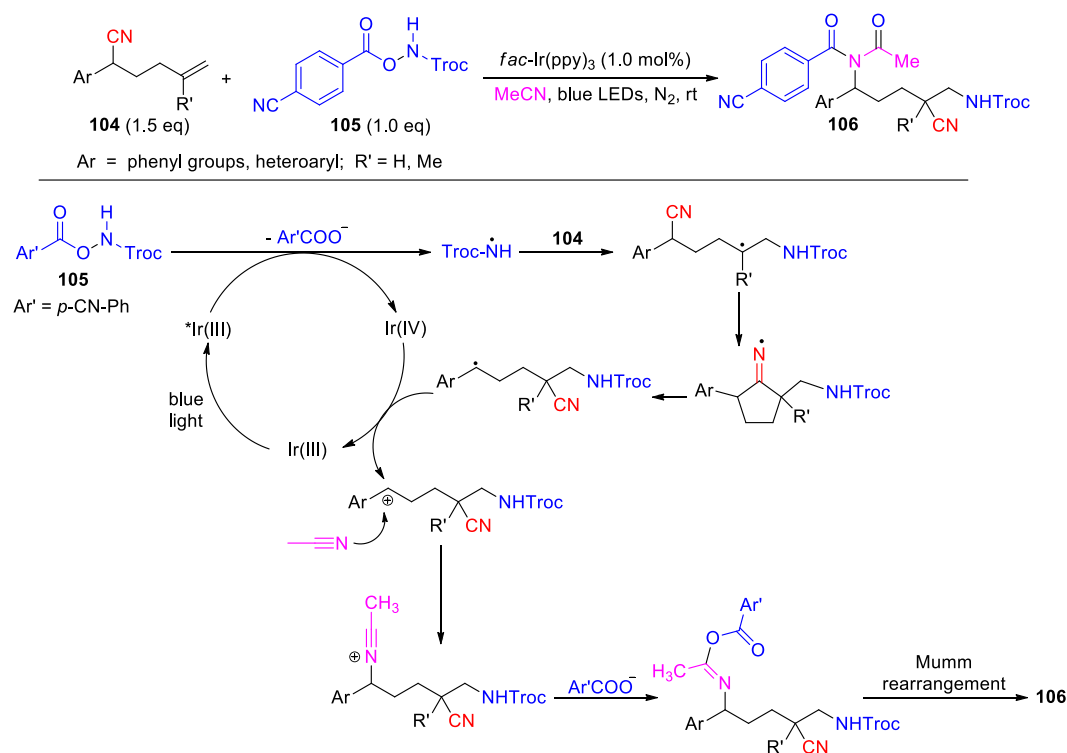
nitrilium ion. Attack of the nitrilium ion by the carboxylate anion combined with Mumm rearrangement furnish the desired product.



Scheme 28. Photoredox functionalization of hexenenitriles with Togni II reagent and external nucleophiles (Chen, 2022).



Scheme 29. Photoredox functionalization of hexenenitriles with $Br\text{CF}_2\text{CO}_2\text{Et}$ in MeCN (Guo, 2023).

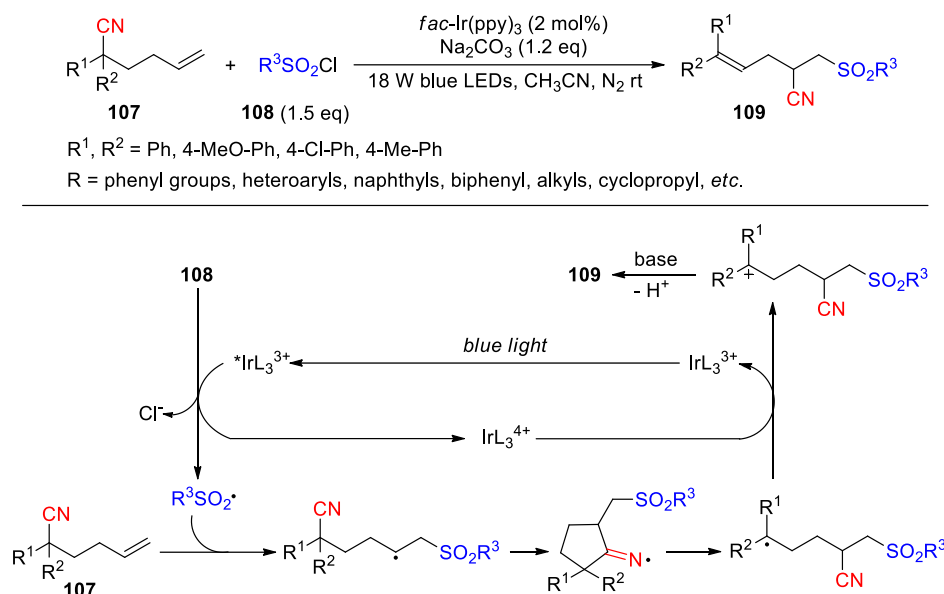


Scheme 30. Photoredox diamidation of hexenenitriles using O-acyl hydroxylamine in MeCN (Akondi, 2025).

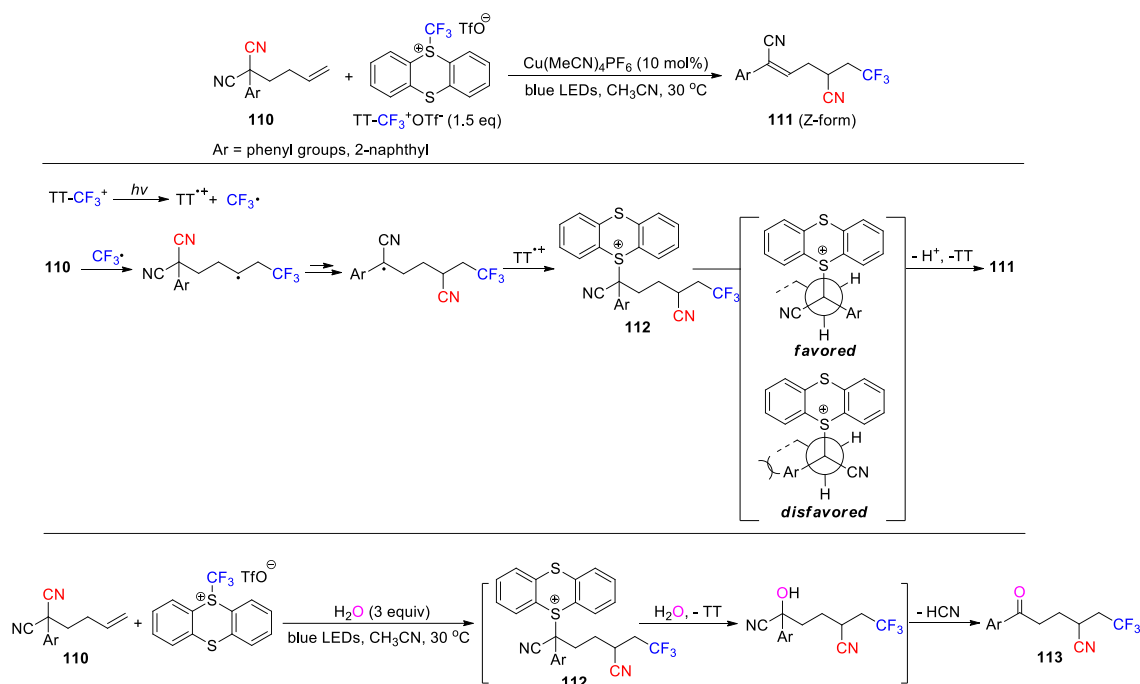
In some reported cases, the employed reaction conditions enabled the in-situ creation a carbon-carbon double bond after distal cyano group migration (Scheme 31-33). Zhu and co-workers have developed a method allowing for the cyanosulfonylation of terminal alkenes with concurrent incorporation of a new C=C bond into the structure [93]. By using *fac*-Ir(ppy)₃ as catalyst and Na₂CO₃ as base, the photo-reaction of diphenyl hexenenitriles **107** with sulfonyl chlorides **108** afforded olefinic β-cyanosulfones **109** via consecutive sulfonylation, cyano migration, single-electron oxidation of the benzyl radical followed by deprotonation (26 examples, 35-88%) (Scheme 31). The reaction accommodates both aryl and aliphatic sulfonyl chlorides containing a broad range of substituents, but is not compatible to the alkyl-phenyl- or dialkyl-substituted hexenenitrile due to the weakened stability of radical or cation intermediate. Moreover, the desired products were obtained as the mixtures of *Z/E* isomers from unsymmetrically-substituted substrates (R¹ ≠ R²).

Huang et al. in 2023 demonstrated the conversion of 2-aryl- 2-(but-3-en-1-yl)malononitriles **110** into trifluoromethylated (*Z*)-alkenyl products **111** using trifluoromethyl thianthrenium triflate (TT-CF₃⁺ OTf⁻) as reagent and Cu(MeCN)₄PF₆ as catalyst under the illumination of blue LEDs (19 examples, 49-82%) (Scheme 32) [94]. The reaction was carried out with phenyl- or 2-naphthyl-substituted substrates, which worked particularly well for the those possessing *para*-electron-donating groups at the phenyl ring. It is postulated that TT-CF₃⁺ can fragment into TT⁺ and trifluoromethyl radical upon absorption of blue light. Addition of the CF₃ radical to the terminal olefin followed by the 1,4-cyano migration leads to a tertiary radical intermediate, which is captured by TT⁺ to afford an α-thianthrenium cyano species **112** as ascertained through high-resolution mass spectrometry. Intermediate **112** then undergoes a *trans*-elimination, possibly with the assistance of the copper catalyst, to provide the product and release TT. The remarkable *Z*-selectivity observed in this reaction is rationalized by the conformation adopted for the *trans*-elimination, in which the steric interaction between the bulky aryl group and alkyl chain can be significantly minimized. Furthermore, addition of 1 mol % of Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ to the reaction mixture was shown to improve the yield of the desired product (Ar = Ph, 93% vs. 70%), but result in poorer diastereoselectivity (*Z/E* ratio = 3:1) due to an alkene isomerization enabled by the energy transfer photocatalyst. The report also revealed that the reaction pathway of intermediate **112** was altered in

the presence of water, yielding the ketone products **113** via a nucleophilic substitution process (12 examples, 48-77%).



Scheme 31. Formation of olefinic β -cyanosulfones via radical-mediated functionalization of diphenyl hexenenitrile (Zhu, 2023).

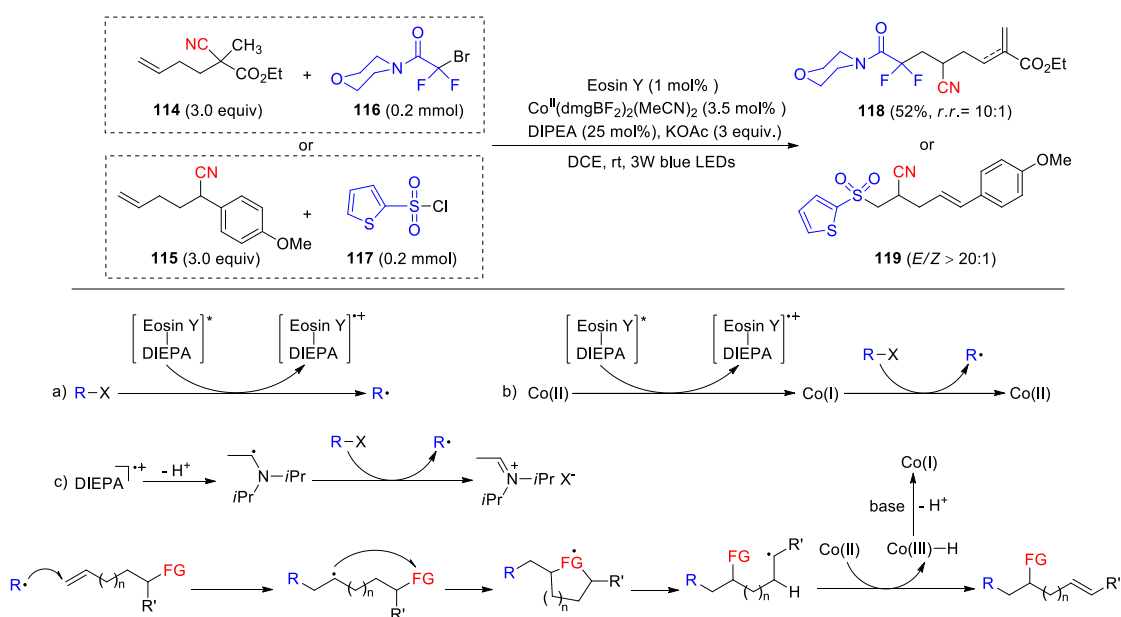


Scheme 32. Photolytic reactions of alkenyl malononitriles with trifluoromethyl thianthrenium salt (Huang, 2023).

Employing photo/cobalt dual catalysis, Lei and co-workers has recently reported an alternative method for alkene difunctionalization with simultaneous creation of a C-C double bond via radical-triggered translocation of functional groups and Co-promoted remote C(sp^3)-H desaturation [95]. It shows good compatibility with diverse fluoroalkyl and sulfonyl radical precursors, enabling the migration of benzoyloxy, acetoxy, formyl, heteroaryl and cyano groups in different types of alkenes to achieve the modular synthesis of polyfunctionalized products. In the study, ethyl 2-cyano-2-methylhex-5-enoate **114** and several phenyl-substituted 5-enenitriles (e.g., **115**) were investigated for

the 1,4- cyano migration using 2-bromo-2,2-difluoroacetamides such as **116** and sulfonyl chlorides such as **117** as radical precursors. The optimum reaction conditions involve the use of 1 mol% Eosin Y as the photocatalyst, 3.5 mol% $\text{Co}^{\text{II}}(\text{dmgBF}_2)_2(\text{MeCN})_2$ as the HAT catalyst (dmg = dimethylglyoxime), 25 mol% DIPEA and 3 equiv. of KOAc as the base in a DCE solution under blue-LED illumination. The reactions proceeded smoothly to afford a total of 20 products with a remarkable site- and stereo-selectivity ($E:Z > 20:1$) as exemplified by **118** and **119** (Scheme 33).

On the basis of detailed mechanistic studies and DFT calculations, a general pathway involving the migration of functional groups (FG) was proposed. There may be several ways to generate radicals to trigger this reaction. Ultraviolet–visible and other experiments suggest the formation of a complex between Eosin Y and DIPEA. This complex, upon photoexcitation, could be reductively quenched by radical precursors R-X to form radicals (a) [96] or reduce cobaloxime(II) to Co(I). The Co(I) species then leads to radical generation via a halogen atom transfer (XAT) (b). In these processes, DIPEA may as a reducing agent to yield an aminoalkyl radical after an oxidative deprotonation. Thus, participation of the aminoalkyl radical in XAT activation to generate radicals along with the iminium salt is also feasible (c) [97]. The addition of the resulting radicals to olefin triggers the FG migration, yielding thermodynamically more stable radicals. With the formation of these carbon-centered radicals, the adjacent $\text{C}(\text{sp}^3)\text{-H}$ bonds can be effectively weakened, allowing for a cobaloxime(II)-assisted HAT process to give the products.

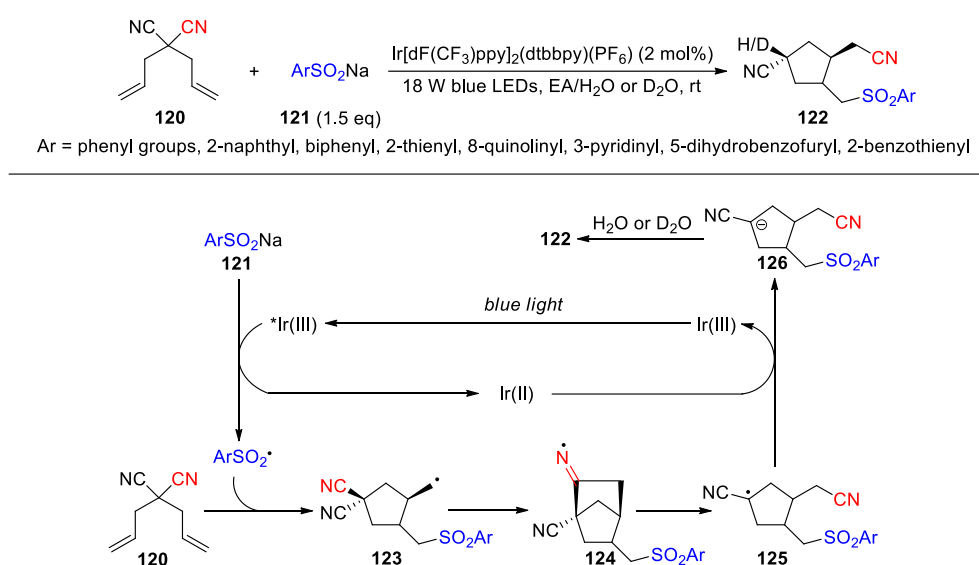


Scheme 33. Photo/cobalt-catalyzed functionalization of alkenes via FGM and Co-promoted HAT (Lei, 2024).

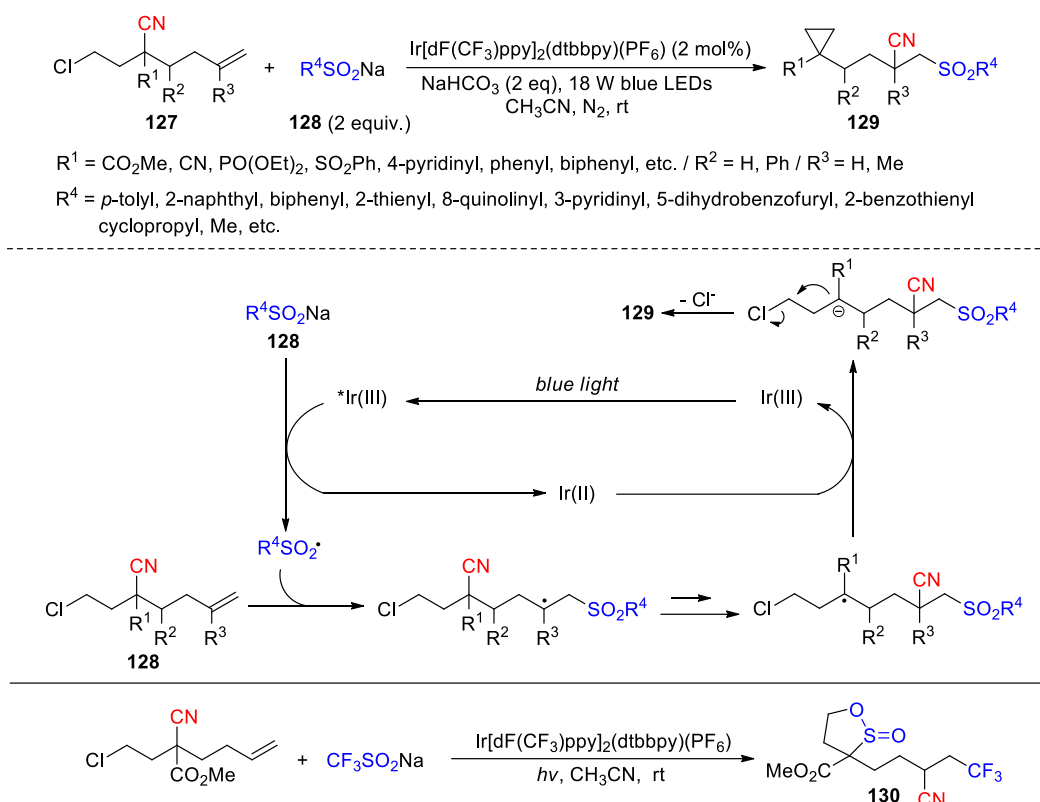
Finally, the carbon radicals resulting from 1,4-cyano migration can be in-situ reduced to carbanions that are capable of undergoing protonation or nucleophilic substitution (Schemes 34-36). Zhu and co-workers have demonstrated the construction of trisubstituted cyclopentanes **122** via the photoredox catalytic reaction of 4,4-dicyano-1,6-diene **120** with sodium (hetero)aryl sulfinates **121** in the presence of H_2O or D_2O (Scheme 34) [98]. Mechanistically, the addition of an extra sulfonyl radical triggers the intramolecular cyclization of **120** and produces cyclopentane intermediate **123** bearing a primary alkyl radical. Intramolecular addition of the alkyl radical to the suprafacial cyano group affords the bicyclic iminyl radical **124**, which subsequently undergoes a β -scission yielding intermediate **125**. The β -scission is considered to be driven by the relief of ring-strain in **124** in addition to the radical stabilising nitrile group [99]. Reduction of the alkyl radical in **125** by Ir(II) gives carbanion **126** and regenerates the ground-state Ir(III). Finally, intermediate **126** can be trapped by a proton or a deuterium ion to furnish the product. An array of sodium sulfinates containing various

aryl and heteroaryl groups was employed for the reaction, and the desired products were all obtained as diastereomeric mixtures in about 1:1 ratio (25 examples, 51-96%).

In another report, Zhu's group disclosed a radical-polar crossover (RPC) reaction of 2-(2-chloroethyl)hex-5-enitriles **127** with sodium sulfonates **128** under photocatalytic conditions, in which, the carboanions generated through the reduction of the radical intermediates were shown to displace the terminal chloride to form multisubstituted cyclopropanes **129** (40 examples, 22-98%) (Scheme 35) [100]. Both aryl and aliphatic sodium sulfonates could be used for the reaction, while the compatibility with aliphatic sulfonates is particularly noteworthy as they are susceptible to free radical desulfonylation under harsh conditions. The protocol also exhibited good tolerance to a wide range of functional groups present in **127** (R^1), thus further enriching the diversity of the cyclopropane structures. Interestingly, when the reaction was conducted with Langlois' reagent, the formation of a distinct sultine product **130** was observed through the insertion of SO_2 during the cyclopropanation process.

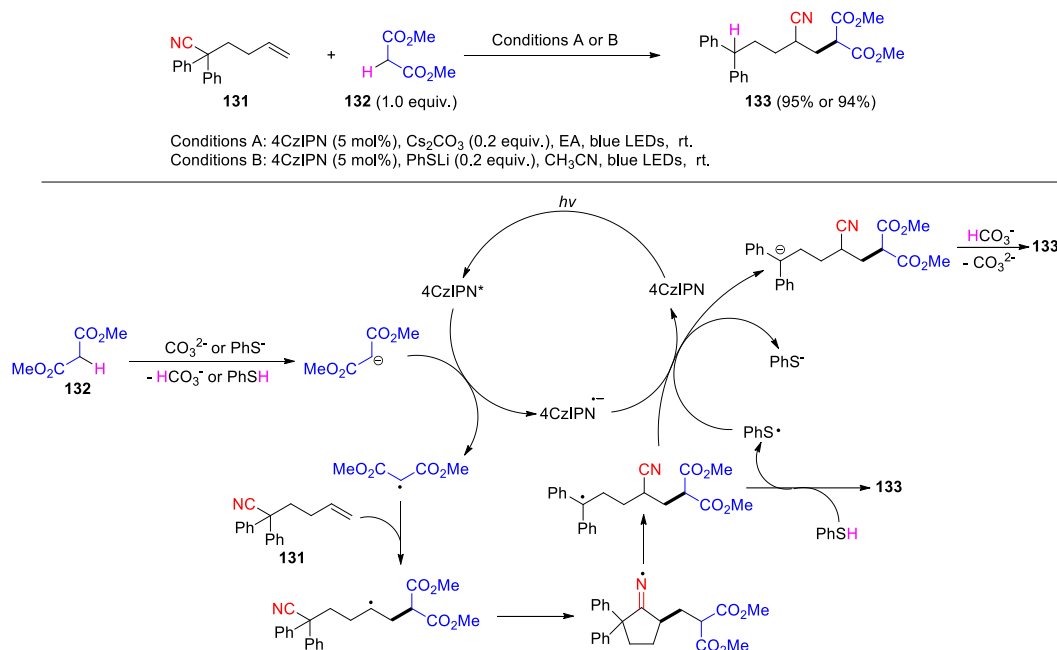


Scheme 34. Construction of substituted cyclopentanes via radical-triggered transannular cyano migration (Zhu, 2025).



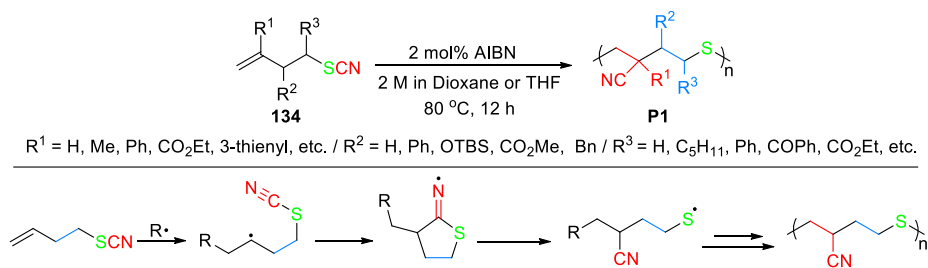
Scheme 35. Cyano migration-mediated radical-polar crossover cyclopropanation and formation of sultine product (Zhu, 2024).

Using photoredox/Brønsted–Lowry base dual catalysis, Deng et al. have developed a protocol for the alkylcyanation of unactivated alkenes with protic C(*sp*³)-H feedstocks via 1,4-cyano group migration [101]. As described in the report, several mono- or diaryl-substituted 5-enenitriles were allowed to react with dimethyl malonate, triethyl methanetricarboxylate, methyl-Meldrum's acid, methyl acetoacetate or 1,3-cycloheptanedione in the presence of 2 mol% of 4CzIPN as the photocatalyst and 20 mol% of Cs₂CO₃ (Conditions A) or PhSLi (Conditions B) as base, leading to the generation of the alkylated nitrile products in varying yields depending on the reactivity of the substrates and radical precursors (13 examples, 24–95%). The reaction of 2,2-diphenylhex-5-enenitrile **131** with dimethyl malonate **132** to yield product **133** is illustrated as an example for all cases (Scheme 36). Mechanistically the carbanion generated via the deprotonation of **132** is oxidized by the photoexcited 4CzIPN to give the malonate radical. Addition of the radical to **131** triggers the cyano migration leading to the benzylic radical intermediate that could be converted into **133** in two different ways. Under the conditions A, the benzylic radical may react with the reduced photocatalyst to deliver the benzylic anion. Further proton exchange with the conjugate acid furnishes **133** along with the neutral base. Under the conditions B, the product is achieved directly from the benzylic radical through the hydrogen atom transfer with PhSH. Reduction of the resulting phenyl sulfide radical by 4CzIPN^{•–} species completes the photocatalytic cycle with regeneration of phenyl sulfide anion.



Scheme 36. Alkylcyanation of unactivated Alkenes with protic C(sp³)-H feedstocks via cyano group migration (Deng, 2025).

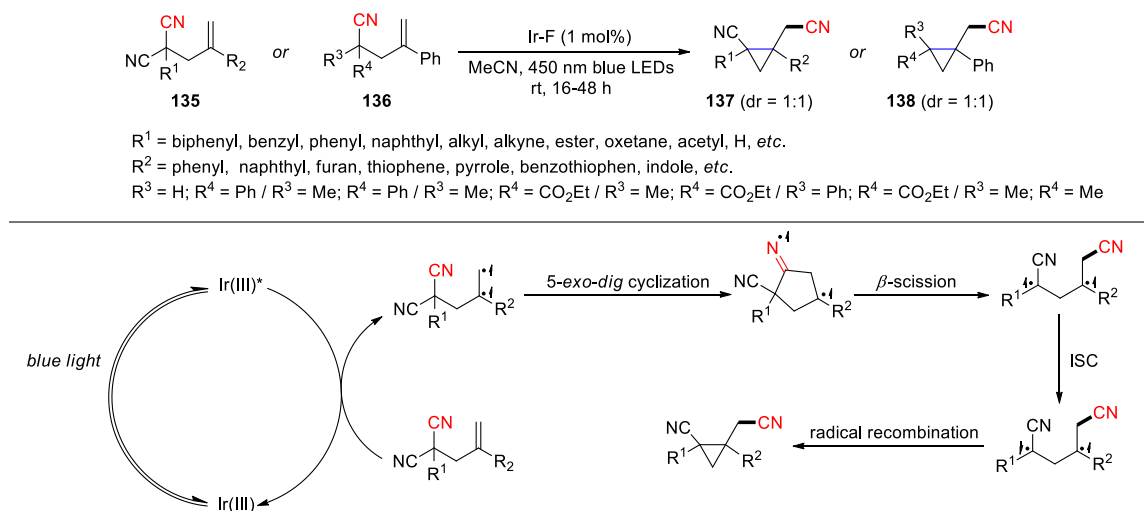
In addition to the aforementioned modifications, the radical addition-triggered cyano group migration has also been applied to polymer synthesis [102–105]. It is well-accepted that α -olefins and their functionalized derivatives are nearly impossible undergo homopolymerization under radical conditions due to the interference from chain-transfer side reactions. For instance, the highly reactive propagating secondary carbon-centered radicals tend to abstract an allylic hydrogen atom from another monomer to generate more stable allylic radicals, instead of adding to the double bond. To cope with this problem, Li et al. have recently reported a study on the homopolymerization of thiocyanate functionalized linear α -olefins enabled by radical-mediated 1,4-cyano transfer [104]. A vast array of monomers **134** with different functionalities could undergo such polymerization, allowing access to a library of ABC sequence-regulated polymers **P1** with high molecular weights and unprecedented structures (Scheme 37). By taking 4-thiocyanato-1-butene as an example, the pathway proposed for its polymerization involves a 5-exo-dig addition of the initial carbon-centered radical onto the cyano group followed by β -fragmentation of the created iminyl radical intermediate to generate a relatively stable thiyl radical. The thiyl radical then performs rapid addition with another monomer, and so on to eventually lead to the polymerized product [Conv. > 95%; M_n = 28.7 k (Dioxane), 20.3 k (THF)]. In another noteworthy report, Sun et al. revealed the preparation of several ABC sequence-defined polymers from the corresponding functionalized hept-6-enenitriles via 1,5-cyano migration under radical conditions [105].



Scheme 37. Homopolymerization of linear α -olefins enabled by radical-mediated 1,4-cyano group migration (2024, Li).

2.3.4. Recently Reported Cyano Migrations Involving Diradical or Radical Cation Intermediates

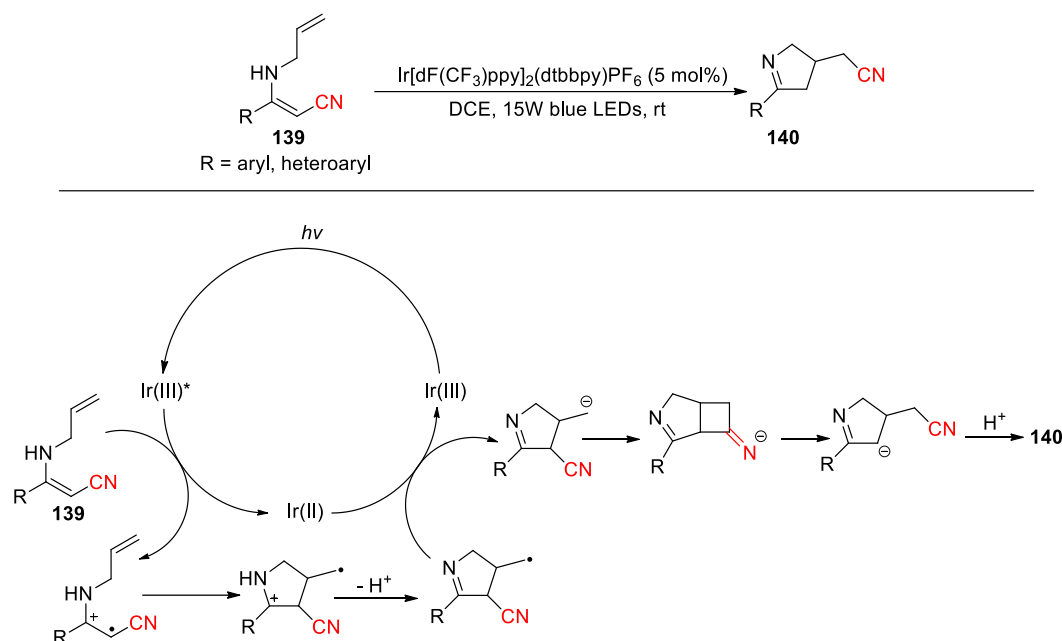
Recent advance in the study of photocatalysis has led to the development of several strategies to achieve the cyano migration of alkenyl nitrile compounds without altering their overall composition. Huang and co-workers in 2024 reported the rearrangement of 2-allylmalononitriles **135** and 4-pentenitriles **136** into the cyclopropane products **137** and **138**, respectively, using 1 mol% Ir-F as photocatalyst in CH₃CN under blue-light irradiation (Scheme 38) [106]. In the proposed mechanism, a diradical intermediate is first generated from the C-C double bond through energy-transfer catalysis. Subsequent 5-exo-dig cyclization followed by β -scission of the resulting imido radical could produce another diradical intermediate. After intersystem crossing (ISC), the newly formed diradical intermediate may undergo a radical-radical recombination to give the three-membered-ring products. This unprecedented approach was defined as a di- π -ethane rearrangement in order to differentiate from the known di- π -methane rearrangement (Zimmerman rearrangement) wherein two π systems engaging in photochemical rearrangement are separated by one sp^3 carbon atom (methane-like). Over fifty substrates **135** containing various R¹ and R² substituents, together with the indicated **136**, underwent the reaction smoothly, achieving good to excellent yields under the optimal conditions (48-98%, mostly > 90%). In a few exceptional cases, the desired products were not obtained from the 4-pentenitriles with hydrogen atom(s) or a piperidinyl ring (R³ = R⁴ = H; R³ = Me/R⁴ = H; R³ = CO₂Et/R⁴ = H or R³ = R⁴ = -CH₂CH₂N(Boc)CH₂CH₂-) as well as the malononitriles bearing tri- or tetrasubstituted alkenyl groups probably due to altered reactivity of in-situ formed radical species or steric hindrance. The author also demonstrated that this protocol was not applicable to the translocation of a cyano group through a three- or six-membered-ring transition state. Shortly after the report from Huang's group, Zhong et al. published a similar method involving the migration of cyano and aryl functional groups by using 0.01 to 1 mol% 2-chlorothioxanthone as photosensitizer [107].



Scheme 38. Di- π -ethane rearrangement of cyano groups via energy-transfer catalysis (Huang, 2024).

The earlier reported 1,3-cyano migration reactions generally required elevated temperatures to overcome the energy barrier associated with highly strained four-membered ring intermediates (Schemes 6-8, 12). Pan et al. recently reported a visible-light-induced tandem cyclization/1,3-cyano migration process, which allowed the conversion of nitrile-substituted *N*-allyl enamines **139** into the corresponding cyclic imines **140** under relatively mild conditions (26 example, 44-93%) (Scheme 39) [108]. Moreover, a 1,3-acyl migration could also be realized with replacing the cyano moiety in **139** by an ester group. Mechanistic studies and DFT calculations suggest that the reaction may proceed through SET oxidation of *N*-allyl enamine by the photoexcited Ir(III) catalyst to generate a radical cation. Subsequent 5-exo-trig cyclization followed by deprotonation allows the formation of a cyclic imine intermediate bearing a methylene radical. This intermediate could be further reduced into a

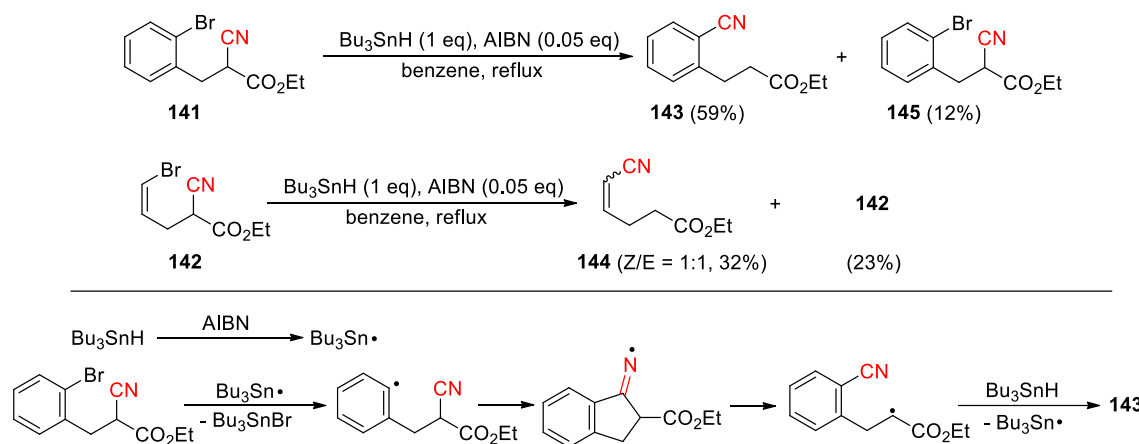
carbanion by Ir(II) species. Then, the nucleophilic addition to the cyano group is followed by the ring-opening and protonation to afford the products.



Scheme 39. Synthesis of cyclic imines via radical-triggered 1,3-cyano migration of *N*-allyl enamines (Pan, 2024).

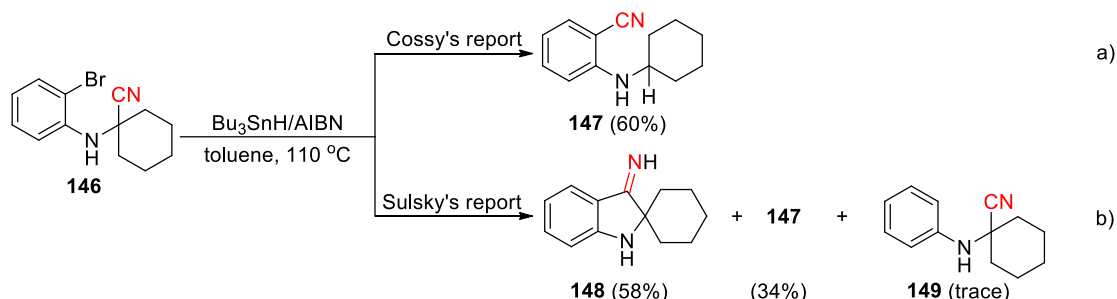
2.4. Cyano Group Migrations via Halogen Atom Transfer

The generation of carbon-centered radical via halogen atom transfer (XAT) between carbon-halogen bonds and tributyltin radical has been used for many years to promote cyano migrations. In the earlier reports (1987 and 1988), Beckwith demonstrated that heating of cyanoacetate **141** or **142** with *n*-Bu₃SnH and AIBN initiator in refluxing benzene could produce the 1,4-transfer products **143** and **144**, along with the simple dehalogenation product **145** or recovered starting material (Scheme 40) [109,110]. The most probable route for the translocation involves the cyclisation of the initially formed aryl (or vinyl) radical onto the nitrile to give a cyclic iminyl radical. This intermediate undergoes rapid β -scission to yield **143** (or **144**) after hydrogen atom abstraction. In these cases, the β -scission is aided by the presence of a radical stabilizing ester substituent.



Scheme 40. XAT-mediated CN migration of *o*-bromophenyl and bromovinyl cyanoacetates (Beckwith, 1987, 1988).

About a decade later, Cossy et al. shown that the similar nitrile transfer reaction could proceed in moderate yields with α -(bromophenylamino)nitriles such as **146** upon the treatment with $\text{Bu}_3\text{SnH/AIBN}$ in refluxing toluene, affording 2-(alkylamino)benzonitriles such as **147** as the only isolated products (Scheme 41, a) [111]. However, a subsequent report by Sulsky and co-workers described a very different outcome from those reported by Cossy [112]. For example, compound **146**, treated under apparently identical conditions, led to the spiroindoxylimine **148** as the major product (58%), together with a 24:1 mixture of **147** and the direct reduction product **149** in 35% yield (Scheme 41, b). They speculated that the highly polar **148** could not have been isolated under the chromatography conditions described by Cossy, and may well have been present in the unpurified reaction mixture. Through single-crystal X-ray analyses, it was also discovered that the relative configuration of the anilino nitrogen in precursor **150** (equatorial/trans to the *tert*-butyl group) had been inverted during the cyclization into its spiroimine derivative **151** (axial/cis to the *tert*-butyl group). This suggests that ring opening and configuration inversion, followed by ring closure must be rapid and reversible relative to the quenching of intermediates with Bu_3SnH , and that the *cis* isomer is more stable than the *trans* isomer (Figure 3).



Scheme 41. Reactions reported for α -(bromophenylamino)nitrile **146** under same conditions (Cossy, 1995; Sulsky, 1999).

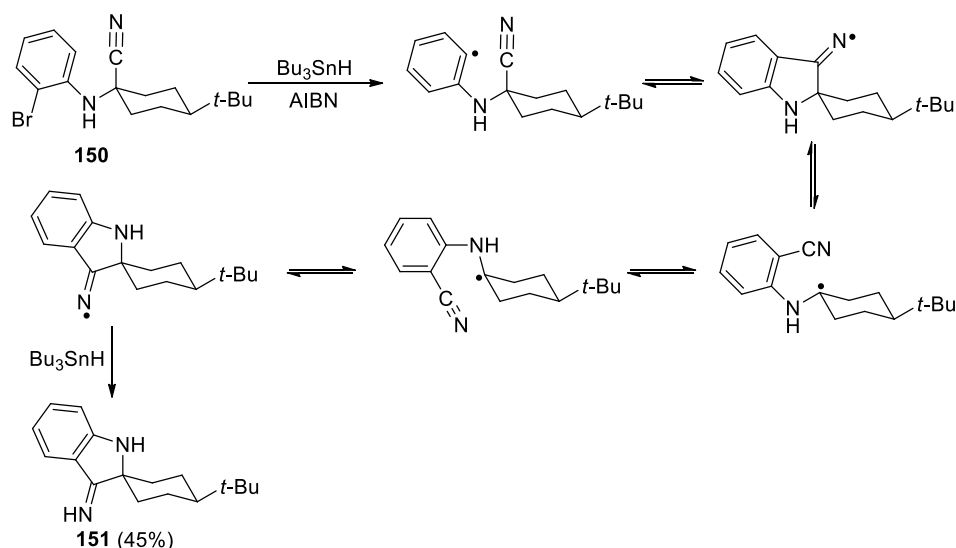
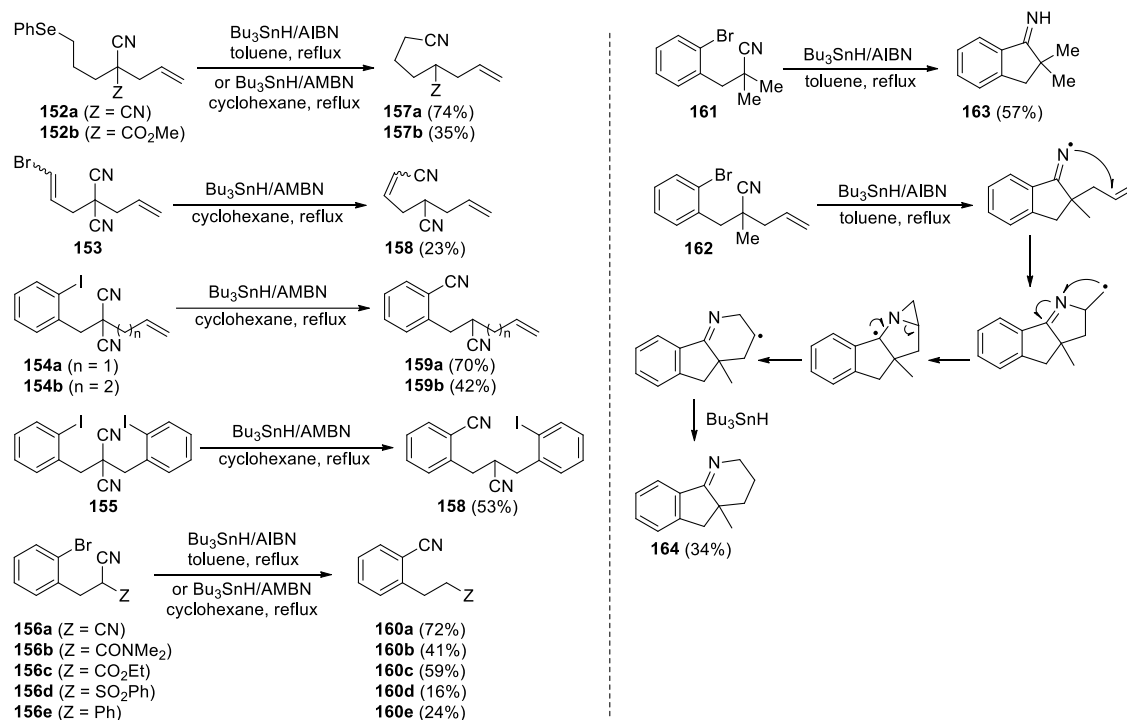


Figure 3. Configuration inversion during the cyclization of **150** into **151** (Sulsky, 1999).

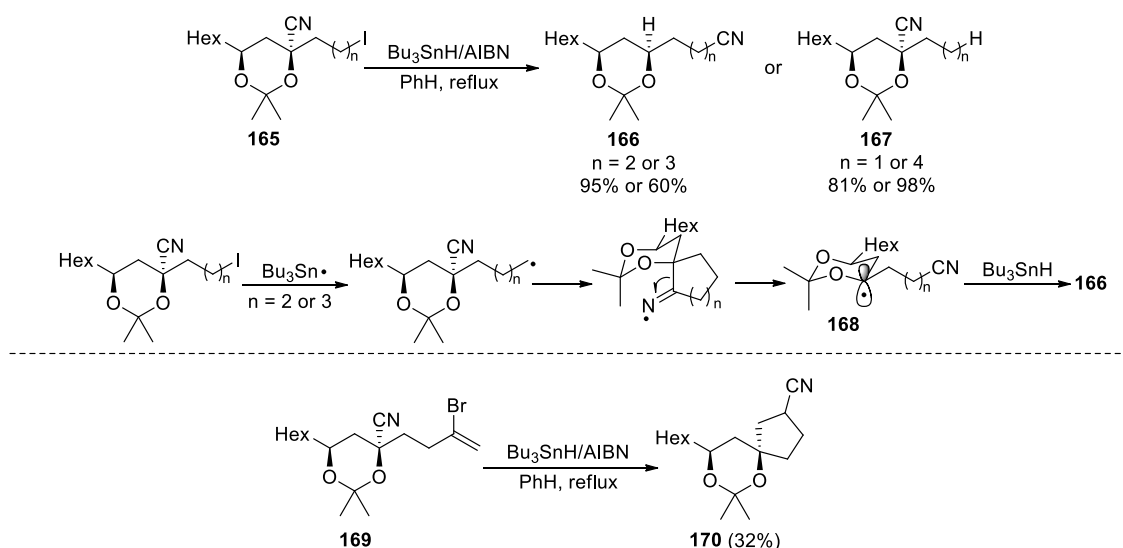
The inconsistent results illustrated above suggest that the reactivity of intermediate iminyl radicals, generated by 5-exo cyclisation of C-centred radicals onto nitriles, could be influenced by α -substituent, i.e., ester, amino or alkyl group. A study carried out by Bowman et al. has further validated this concept by using a set of phenylselenenyl, bromo and iodo radical precursors [113]. With the presence of α -CN, CO_2R , CONMe_2 , SO_2Ph or Ph substituent, the iminyl radicals derived from **152-156** tended to undergo β -scission to yield stable/irreversible ring-opened radicals and thus the nitrile translocation products **157-160** (Scheme 42). Note that an unusual C-Se bond cleavage was utilized

to generate the alkyl carbon radicals to perform the addition with the nitriles in the production of **157**. When the α -substituent was an alkyl group, the formation of nitrile transfer products was not observed but rather cyclised imines or triheterocycle derivative, as is shown with the conversion of **161** and **162** into **163** and **164**.



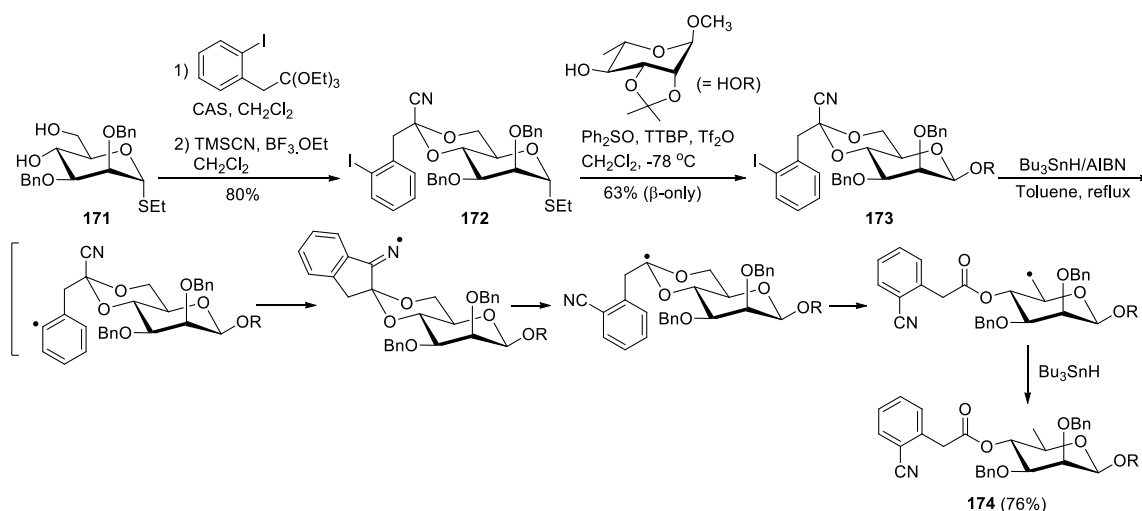
Scheme 42. Nitrile transfer or cyclization reactions influenced by α -substituents (Bowman, 2000).

For 1,3-dioxane-4-nitriles **165**, Rylcmovsky demonstrated that the 1,4- and 1,5-nitrile transfer reactions (n = 2, 3) could take place efficiently to give the products **166**, whereas the corresponding 1,3- and 1,6-nitrile transfer reactions (n = 1, 4) were not observed and instead led to the dehalogenation products **167** (Scheme 43) [114]. During the nitrile transfer, the ring-opening of the iminyl radical should be encouraged by the formation of the stabilised α -alkoxy radical. Besides, products **166** were exclusively obtained as the *syn*-1,3-diol isomers, which is presumably a result of the stereoselective reduction of intermediate **168** with Bu₃SnH. The authors also revealed that the α -alkoxy radicals produced in nitrile transfer could participate in a cyclization with appropriate unsaturated substituents. For instance, treatment of vinyl bromide **169** with Bu₃SnH and catalytic AIBN in refluxing benzene provided the spirocyclic compound **170** via a tandem transfer-cyclization process. Although a 5-endo-trig cyclization like this one is generally disfavored according to Baldwin's rules, the complementary electronic distributions of the α -alkoxy radical and β -cyano alkene are supposed to favor the cyclization.

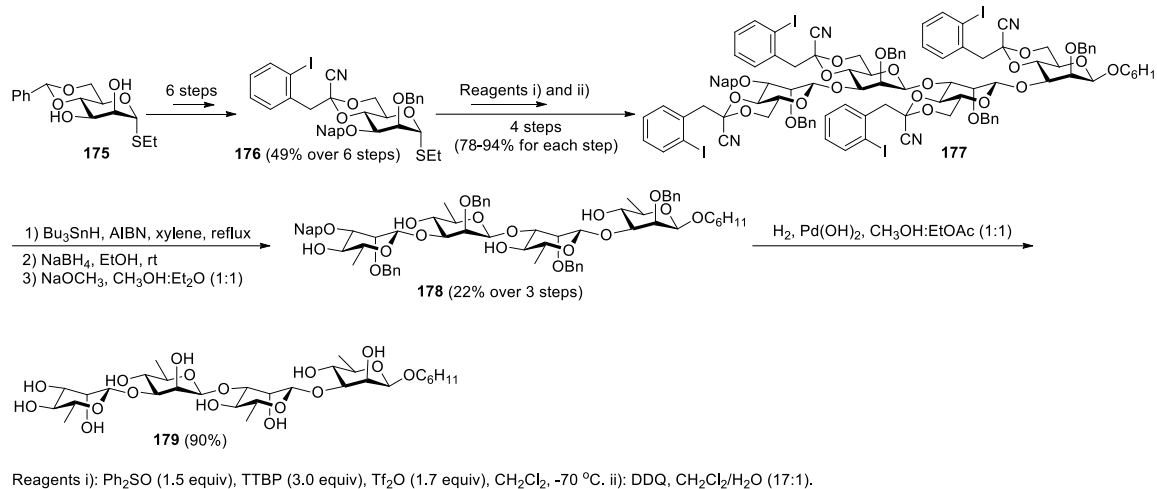


Scheme 43. XAT-mediated cyano migration of 1,3-dioxane-4-nitriles (Ryclmovsky, 1997).

The strategy described in this section has been utilized in the syntheses of complex and biologically important natural molecules. Crich and Bowers reported a method for the preparation of β -rhamnopyranosides from thioglycosides, as exemplified by the conversion of **171** into **174** (Scheme 44) [115]. In the sequence, the 4,6-*O*-[1-cyano-2-(2-iodophenyl)-ethylidene] group was first introduced to **171** as a single diastereomer via the acid-catalyzed reaction of the 4,6-diol with triethyl (2-iodophenyl)orthoacetate, followed by $\text{BF}_3 \cdot \text{OEt}_2$ -promoted cyanation. The acetal-protecting group in the resulting product **172** conveys strong β -selectivity to allow the stereocontrolled formation of β -mannoside **173** through the coupling with methyl 2,3-*O*-isopropylidene-*R*-*L*-rhamnopyranoside. As a key operation, treatment of **173** with tributyltin hydride and AIBN in toluene at reflux triggered a cyano transfer/fragmentation process to produce the product **174**. The utility of this method was further demonstrated by the concise synthesis of a naturally occurring β -(1 $\rightarrow$ 3)-*D*-rhamnotetraose via a one-pot quadruple radical fragmentation [116]. To this end, a suitably protected monomer **176** was first synthesized from 4,6-*O*-benzylidene-protected thiomannoside **175** in 6 steps (Scheme 45) [116]. After this, the sequential coupling reactions of **176** were carried out, first with cyclohexanol and then with 3-*OH*-deprotected oligomer formed in each step, to give the formation of a β -mannotetraose **177**. Subjection of **177** to conditions of radical fragmentation in refluxing xylenes, followed by NaBH_4 reduction to facilitate removal of the tin residues, and then saponification provided the precursor tetraol **178**. Finally, deprotection of **178** via hydrogenation eventually furnished the target molecule **179** in 90% yield.

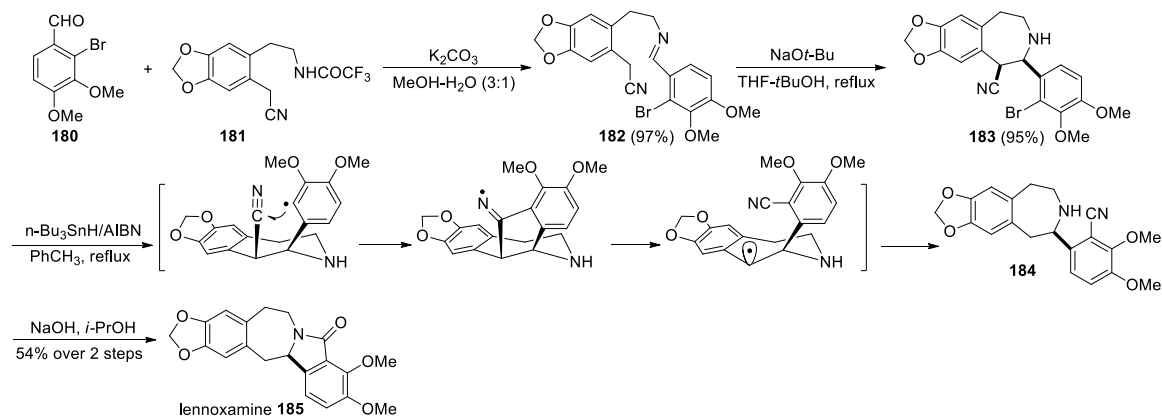


Scheme 44. Preparation of β -rhamnopyranoside from thioglycoside via nitrile transfer/fragmentation (Crich, 2006).



Scheme 45. Total synthesis of a natural tetrasaccharide via one-pot quadruple radical fragmentation (Crich, 2006).

Orito and co-workers reported the total synthesis of a natural isoindolobenzazepine alkaloid, lennoxamine, based on a radical migration of a cyano group (Scheme 46) [117]. Their route involved the condensation of bromobenzaldehyde **180** with trifluoroacetamide **181** to give imine **182**, which then underwent cyclization under basic conditions yielding benzazepine **183**. Subsequent migration of the cyano group under radical conditions, followed by basic cyclization of the resulting precursor **184** completed the synthesis of lennoxamine **185**.



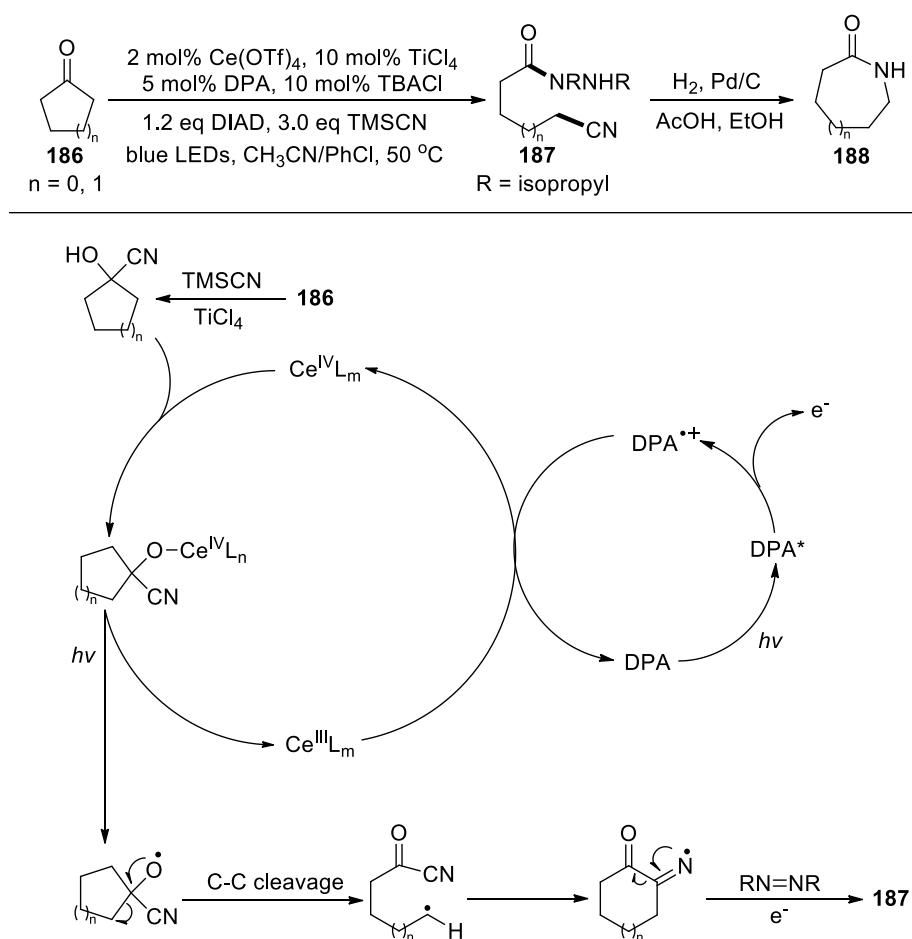
Scheme 46. Synthesis of lennoxamine through cyano migration (Orito, 2009).

2.5. Cyano Group Migrations via C-C Bond Fragmentation

Radical-mediated C-C bond fragmentation can be used as another approach for producing the carbon-centered radical to trigger nitrile migration, yet it has only been limited to a few reports including one of ours.

Zuo and colleagues exploited the selective C-C bond cleavage of ketones through a cooperative utilization of Lewis acid catalysis and ligand-to-metal charge transfer (LMCT) excitation [118]. During the study, a migration of a cyano group was observed for the reactions of clobutanones and cyclopentanones **186**, yielding the cyanated hydrazides **187** under the conditions shown in Scheme 47 (18 examples, 51-97%). The resulting products could be further elaborated into the corresponding lactam **188** by a simple hydrogenation.

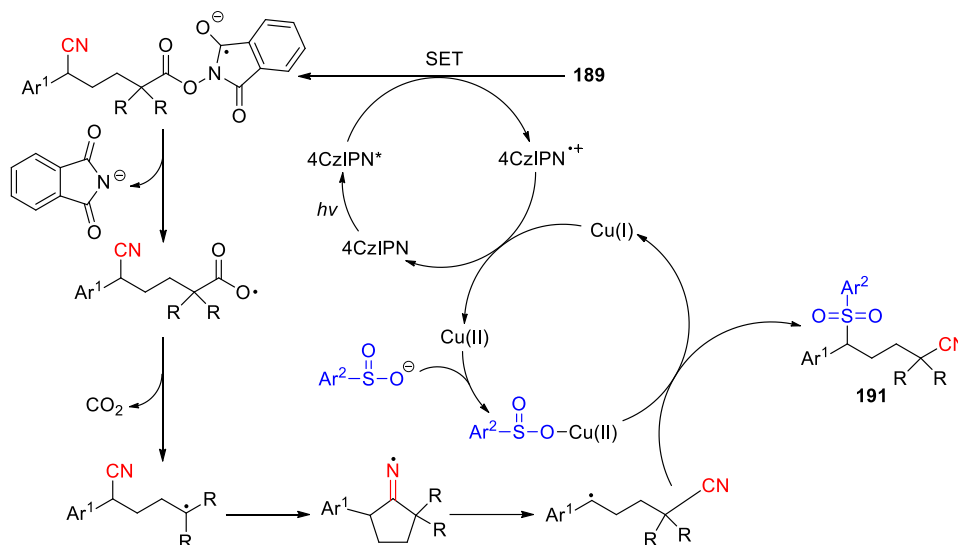
The proposed pathway to **187** involves the generation of a cyanohydrin by the nucleophilic addition with TMS-CN. In addition to cerium triflate, titanium tetrachloride catalyst is required in this step to convert inactive cyanohydrin silyl ether into the cyanohydrin. Under blue light irradiation, the cerium(IV)-cyanohydrin coordination complex can be excited to promote the homolysis of the Ce-O bond, generating an alkoxy radical. Subsequent scission of the α -C-C bond produces a carbon-centered radical, which will trigger the migration of the cyano group to give a carbonyl radical intermediate. Trapping of this intermediate by diisopropyl azodicarboxylate (DIAD), followed by a photo-induced single-electron reduction with 9,10-diphenylanthracene (DPA) provides the product **187** along with a radical cation of DPA. The radical cation then engages in single-electron transfer with cerium(III) to complete the catalytic cycle. In the cases of α -substituted cyclic ketones, the C-C bond between the most substituted α -carbon and the carbonyl group was shown to be selectively cleaved to form more stable carbon radical. Moreover, the radical intermediates derived from 6-membered and larger cyclic ketones, as well as acyclic ketones, did not undergo cyano migration after the C-C bond cleavage, but instead reacted with DIAD and introduced methanol to afford aminated carboxylic esters as the products.



Scheme 47. Functionalization of cyclic ketones via LMCT-mediated C-C bond cleavage and cyano migration (Zou, 2020).

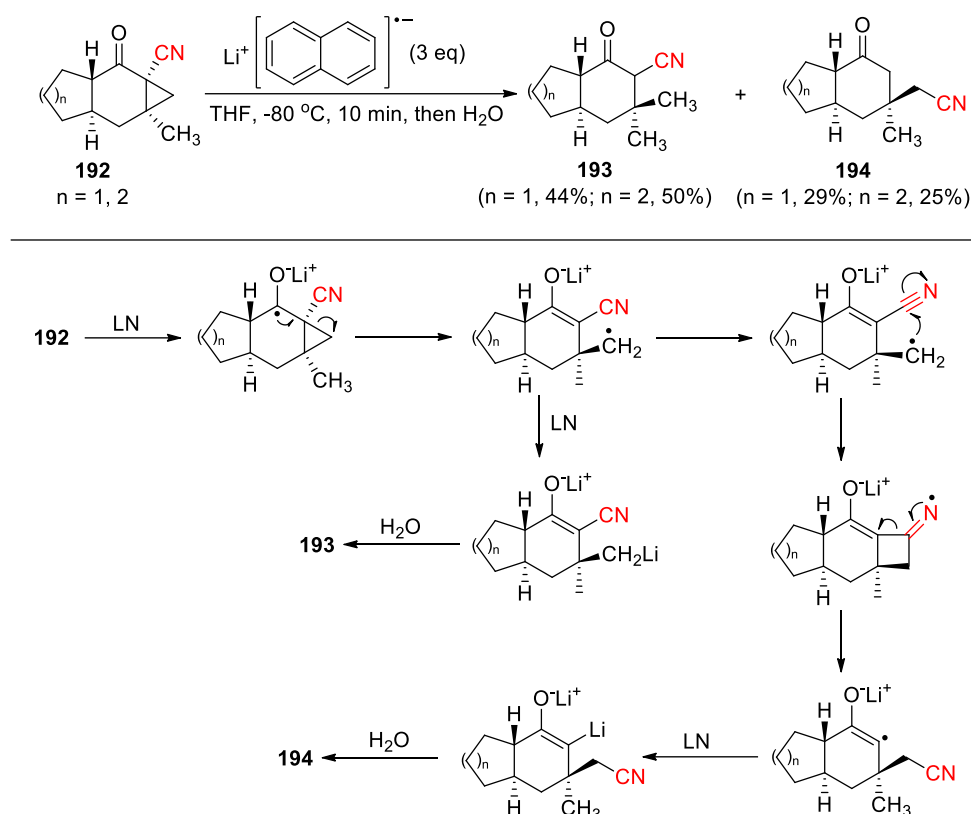
A photoredox/Cu dual catalyzed 1,4-cyanosulfonylation of NHPI esters **189** with sodium arylsulfonates **190** has been established by Chen et al., which provides a variety of δ -sulfonyl nitriles **191** via a decarboxylation-triggered remote cyano migration under the conditions shown in Scheme 48 (30 examples, 30-72%) [119]. In their proposed mechanism, the SET reduction of **189** by the excited photocatalyst 4CzIPN* takes place to produce intermediate **192** and the 4CzIPN radical cation. Elimination of the imide anion from **192** via a N-O bond cleavage gives the carboxyl radical **193**, which subsequently undergoes a decarboxylation yielding an alkyl radical to trigger the 1,4-cyano

migration. Afterwards, the resulting benzylic radical **194** could be trapped by the sulfonate radical released from the in-situ formed Cu(II)-arylsulfonate complex to furnish the product **191**. The Cu(I) generated in this step can be re-oxidized by the 4CzIPN radical cation, leading to the regeneration of both Cu(II) and 4CzIPN catalysts.



Scheme 48. Preparation of δ -sulfonyl nitriles via decarboxylation-triggered 1,4-cyano migration (Chen, 2024).

We previously synthesized the fused tricyclic α -keto cyclopropyl nitriles **192** via the rhodium-catalyzed intramolecular cyclopropanation. Treatment of **192** with lithium naphthalenide (LN) as an electron-donating agent caused the ring-opening of the cyclopropane to give α -cyano ketones **193** as the major products, along with γ -cyano ketones **194** resulting from an additional 1,3-cyano migration (Scheme 49) [120]. We proposed that the carbonyl group in **192** was first reduced to a ketyl radical anion by LN, which then triggered consecutive ring opening and cyano migration to yield a vinyl radical anion intermediate. Further reduction followed by hydrolysis gave the formation of **194**. The carbon radical derived from the ring-opening could also be reduced into a carbanion in the presence of excess of LN to provide **193**, and the reduction seemed to occur faster than the addition to the nitrile group as suggested by the yields obtained for the products. Moreover, exclusive formation of α -cyano ketone products was observed when the angular methyl groups in **192** was replaced by a hydrogen atom, implying that the methyl groups might play a role in directing reaction pathway possibly through steric effects.



Scheme 49. 1,3-Cyano migration triggered by reductive ring opening (Zhu, 2017). .

3. Conclusions

The radical-mediated distal cyano group migration has served as an important tool for the site-selective functionalization of organic molecules. The process requires the initial generation of a carbon-centered radical to trigger the CN migration and provide a more stable carbon radical for further elaboration. Decades of studies on this topic have led to the discovery of a plethora of procedures for the migration, which are systematically reviewed in four sections according to the strategies used to generate the initial carbon radicals. As we have shown, the early reported reactions were often conducted under harsh thermal conditions, resulting in relatively low yields for desired products. In recent twenty years, advances in radical chemistry together with application of photocatalysis have stimulated the development of a number of mild and efficient methods to achieve the migration with various nitrile substrates. Particularly remarkable is the diversity of photocatalytic techniques that have been used for such transformations, such as photoredox catalysis, organo-photocatalysis, dual NHC/photoredox catalysis, dual metal/photoredox catalysis, and photo-induced ligand-to-metal charge transfer (LMCT). The utility of these catalytic systems arises from their ability to effectively generate reactive intermediates, e.g., radical, radical cation, or radical anion, via single-electron transfer, thus facilitating the migration along with the incorporation of other functional group(s) into a molecule. Overall, this article provides a comprehensive assessment of all achievements in this area, which may inspire the researchers to develop more useful synthetic tools for radical-mediated functional group migration.

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