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Intermolecular radical carboamination of alkenes

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Vicinal alkene carboamination is a highly efficient and practical synthetic strategy for the straightforward preparation of diverse and valuable amine derivatives starting from simple compounds. During the last decade that approach has found continuous research interests and various practical methods have been developed using transition-metal catalysis. Driven by the renaissance of synthetic radical chemistry, intermolecular radical alkene carboamination comprising a C–C bond and a C–N bond forming step has been intensively investigated recently culminating in novel strategies and improved protocols which complement existing methodologies. Radical alkene carboamination can be achieved *via* three different reaction modes. Such cascades can proceed through N-radical addition to an alkene with subsequent C–C bond formation leading to 2,1-carboamination products. Alternatively, the C–C bond can be installed prior to the C–N bond *via* initial C-radical addition to the alkene with subsequent β-amination resulting in 1,2-carboamination. The third mode comprises initial single electron oxidation of the alkene to the corresponding alkene radical cation that gets trapped by an N-nucleophile and the cascade is terminated by radical C–C bond formation. In this review, the three different conceptual approaches will be discussed and examples from the recent literature will be presented. Further, the reader will get insights into the mechanism of the different transformations.

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1. Introduction

Alkenes are important and versatile synthons that engage in diverse organic transformations. Difunctionalization of alkenes by constructing two different vicinal chemical bonds is a valuable synthetic strategy that has gained great interests

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during the last few decades.[1–12] Among the various vicinal difunctionalizations known, alkene carboamination comprising a C–N bond and a C–C bond formation to provide structurally diverse amine derivatives in a straightforward manner is of particular interest. Initial studies on vicinal alkene carboamination focused on aza-Diels–Alder reactions of electron-rich alkenes with conjugated imines.[13,14] The resulting cycloadducts can be easily transformed into multi-substituted pyridines, an approach that was successfully applied to the synthesis of natural products such as (−)-mappicine[15] and (+)-camptothecin.[16] In addition, Pd or Cu catalyzed alkene carboamination with tethered nitrogen nucleophiles has been achieved through aza-Wacker cyclization followed by transition metal mediated or radical C–C coupling to provide substituted pyrrolidines with high stereoselectivity.[17–20] It is worth noting that transition metal catalyzed three component alkene carboamination has also been reported.[21–25] For instance, Rovis and co-workers disclosed a Rh-catalyzed intermolecular carboamination of alkenes by using a bifunctional reagent[21] and Engle *et al.* used a directing group to conduct Pd-catalyzed three component alkene carboamination.[22]

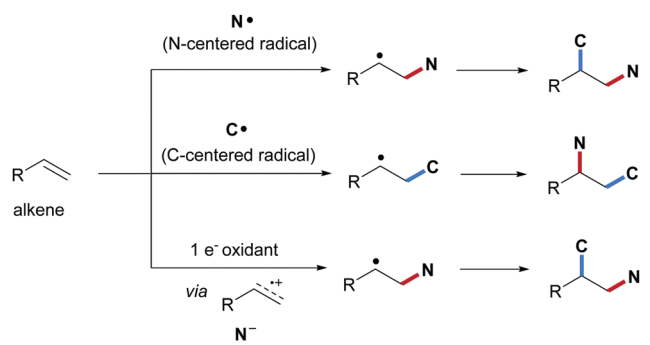
Along with these pericyclic and metal-catalyzed carboaminations, radical alkene carboamination has also been achieved. For example, carboamination comprising an N-radical cyclization followed by an intermolecular C–C bond formation to provide pyrrolidine or pyrrolidin-2-one scaffolds has been intensively explored using redox catalysis.[26–33] As compared to these cyclizing carboaminations, intermolecular vicinal radical alkene carboamination is more challenging and accordingly less well explored. Based on the nature of the initially attacking species, intermolecular alkene radical carboamination can be categorized into three different classes: (1) initial formation of the C–N bond through intermolecular addition of an N-centered radical to an alkene followed by C-radical trapping; (2) initial formation of the C–C bond through addition of a C-radical to an alkene followed by C-amination; (3) single-electron-transfer (SET) oxidation of the alkene to generate a radical cation that gets trapped with an N-nucleophile resulting in a C-radical that eventually engages in a C–C bond forming step (Scheme 1).

Considering the first class and an alkene as a C-radical acceptor, the reactivity of two different alkenes has to be controlled and the alkene carboamination selectivity is governed by polar effects.[34] Since N-radicals are electrophilic species,[35–41] initial C–N bond formation occurs highly chemoselective with an electron-rich alkene such as an aliphatic alkene, a vinyl ether or an enamide to give the corresponding nucleophilic C-radical adduct that gets trapped either *via* reaction with a π-acceptor or *via* oxidation and subsequent nucleophilic trapping. Transition metal mediated C–C bond formation is also possible. Looking at the second class, mostly aryl alkenes are used as acceptors for the C-radical and the benzylic adduct radicals generated are readily oxidized to benzylic cations.[42] C–N bond formation is finally achieved *via* nucleophilic trapping of the cation. Alternatively, the C-radical adducts can directly be trapped by a radical amination reagent or C–N bond formation is mediated with a transition metal catalyst. In the third class, an alkene substrate undergoes single-electron oxidation by a photo-excited redox catalyst, producing an alkene radical cation intermediate that can be captured intermolecularly by a nucleophilic amide to give the corresponding C-radical.[43] C–C bond formation then proceeds *via* a radical cyclization reaction to a π-acceptor.

It is obvious that these three different reaction classes nicely complement each other providing an overall broad scope concerning the targeted carboamination products. Nevertheless, pros and cons of the three approaches can clearly be identified. Considering the first reaction class, amines or amides cannot be directly used as the N-radical precursors. In general, N-heteroatom compounds that in most cases are not commercial and have to be prepared ahead are used in such transformations as N-radical precursors. This leads to an increase of the overall costs of the process. Moreover, in many cases, sulfonamidyl radicals have been applied to the carboamidation reaction. The sulfonyl group offers high reactivity to the N-radical but as a disadvantage, it is well known that the sulfonyl group is not an ideal N-protecting group in organic synthesis.

Considering the second reaction class, C–N bond formation is generally achieved with cheap and commercially available "N-donors" such as sulfonyl azides, Me_3SiN_3, NaN_3, nitriles, amines and amides among others. Moreover, also the C-radical precursors are readily available and in many cases at low cost. However, since the two first reaction classes lead to different product regioisomers, the replacement of one strategy by the other to reduce costs is not an option.

The third approach proceeding *via* alkene radical cation formation is the least general strategy in terms of substrate scope. Only alkenes that are readily oxidized to the corresponding radical cations can be applied. Accordingly, only a few examples can be provided along these lines. With respect to the regiochemistry, the third class provides the same regiosomer as the first reaction class (see Scheme 1).



Scheme 1 Three different reaction modes to conduct intermolecular radical alkene carboamination.

2. Carboamination *via* N-radical addition

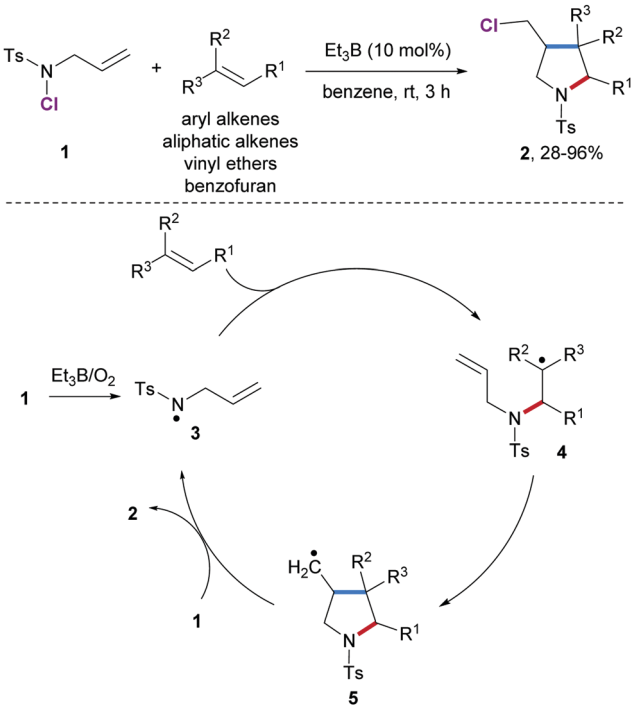
Both amidyl and azidyl radicals are electrophilic species which undergo efficient radical addition to electron rich alkenes to generate the corresponding C-radical adducts *via* C–N bond

formation. Subsequent C-radical trapping leads to the targeted 2,1-carboamination products. Generation of the N-radicals has to proceed under mild conditions that are compatible with the subsequent C–C bond formation. Along these lines, various N–X reagents and oxime derivatives have been exploited for amidyl radical generation[35–39] and the azidyl radical can be mildly accessed through SET oxidation of commercial $TMSN_3$.[44,45]

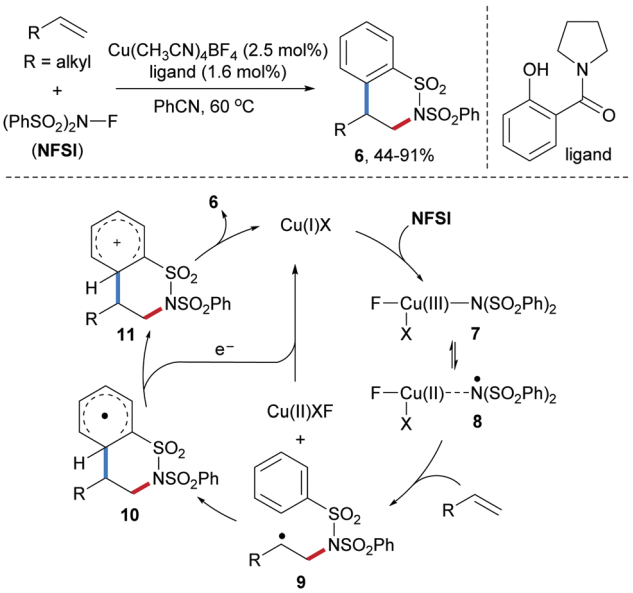
2.1 Radical 2,1-carboamidation of alkenes

In 2001, Oshima and co-workers reported an elegant radical [3+2] annulation of alkenes with *N*-allyl-*N*-chlorotosylamide (**1**) as N-radical precursor for the preparation of pyrrolidine derivatives **2** (Scheme 2).[46] This cascade proceeds through a radical chain process and features a broad scope with respect to the alkene component. Hence, aliphatic alkenes, styrenes, vinyl acetates and even benzofuran are eligible acceptors yielding the corresponding multi-substituted pyrrolidines in high yields albeit with low diastereoselectivity. Chain initiation is achieved with Et_3B/O_2 to give the amidyl radical **3** which undergoes intermolecular radical addition to the alkene acceptor to provide the C-radical **4**. Subsequent 5-exo radical cyclization leads to the primary alkyl radical **5** which undergoes chlorine atom abstraction from **1** to yield the desired pyrrolidine **2** along with the chain carrying amidyl radical **3**.

In 2013, Kanai and co-workers described a Cu-catalyzed intermolecular carboamination of aliphatic alkenes by using *N*-fluorobenzenesulfonimide[47] (NFSI) as the amidyl radical precursor (Scheme 3).[48] A variety of terminal and internal alkenes were shown react with NFSI smoothly in the presence of a Cu(I)-catalyst in combination with an amide ligand to provide six-membered ring sultams **6** in moderate to satisfactory yields.



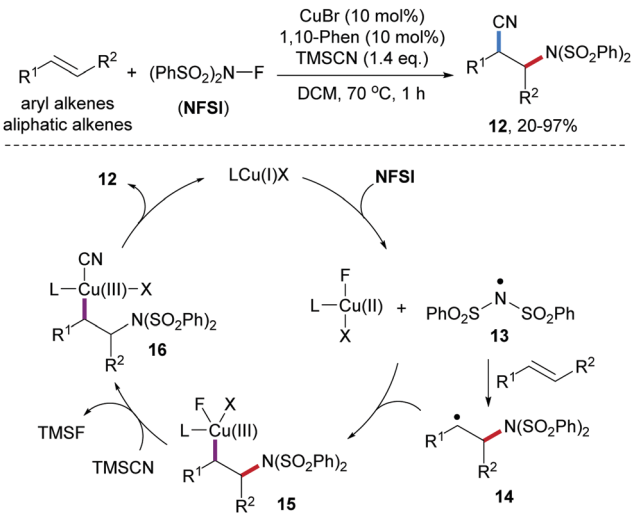
Scheme 2 Radical annulation of *N*-allyl-*N*-chlorotosylamide with alkenes.



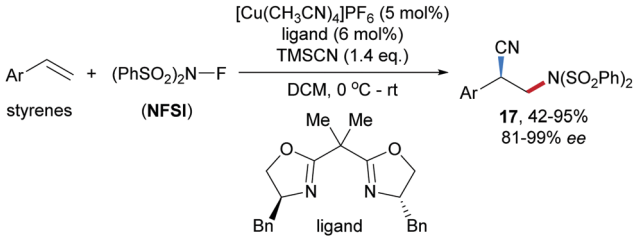
Scheme 3 Cu-Catalyzed intermolecular carboamination of alkenes with NFSI.

In the proposed catalytic cycle, the Cu(III)-species **7** existing in equilibrium with Cu(II)-stabilized N-centered radical species **8** is firstly generated through oxidative addition of NFSI to Cu(I). Subsequent N-radical addition to an alkene produces the radical adduct **9** along with a Cu(II)-species. Cyclization onto the arene leads to the cyclohexadienyl radical **10** that gets oxidized by the Cu(II)-species to the stabilized cation **11**, thereby regenerating the Cu(I)-catalyst. Deprotonation eventually leads to the sultam **6**.

The Zhang group reported Cu-catalyzed three-component radical aminocyanation of styrenes with NFSI and trimethylsilyl cyanide (TMSCN).[49] Styrenes as the amidyl radical acceptors provide the desired β-amino cyanides **12** in high yields, however, other alkenes such as vinyl ethers and aliphatic alkenes afforded the product cyanides in low yields only (Scheme 4). Mechanistically, the disulfonamidyl radical **13** generated by reduction of NFSI with



Scheme 4 Copper-catalyzed intermolecular aminocyanation of alkenes.



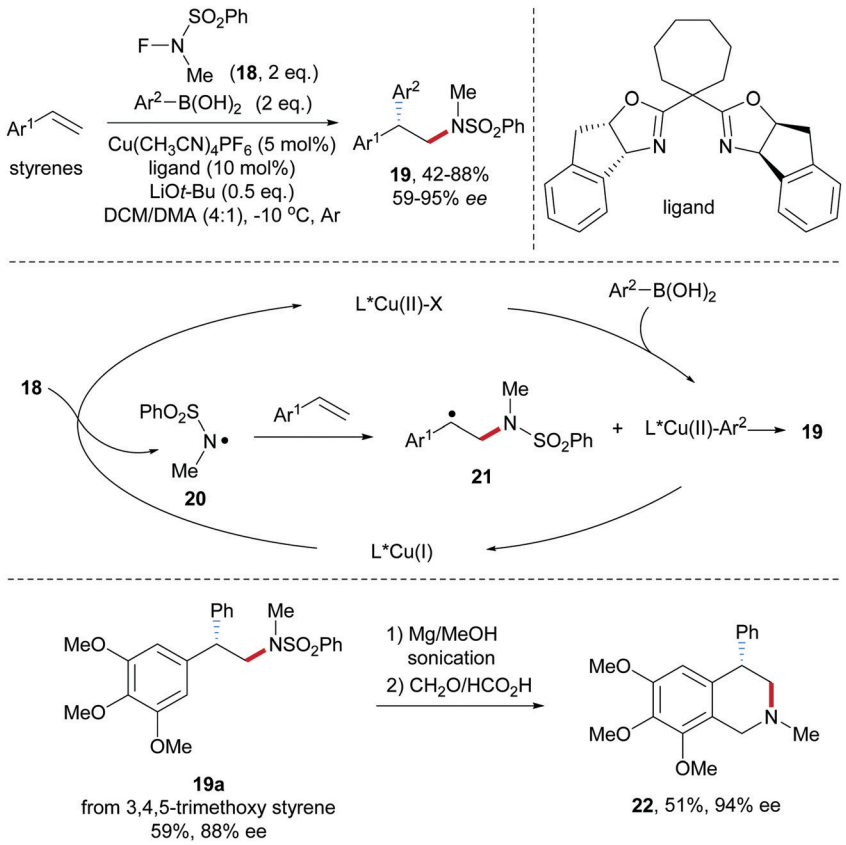
Scheme 5 Enantioselective Cu-catalyzed intermolecular aminocyanation of styrenes.

the Cu(I)-catalyst is captured by an alkene to give the benzylic radical **14**. Trapping of **14** by the intermediately generated Cu(II)-species provides the Cu(III)-intermediate **15**, which undergoes transmetalation with TMSCN to form the Cu(III)-CN complex **16**. Reductive elimination finally provides the desired aminocyanation product **12** along with the Cu(I)-catalyst. Radical clock experiments support the radical nature of this process.

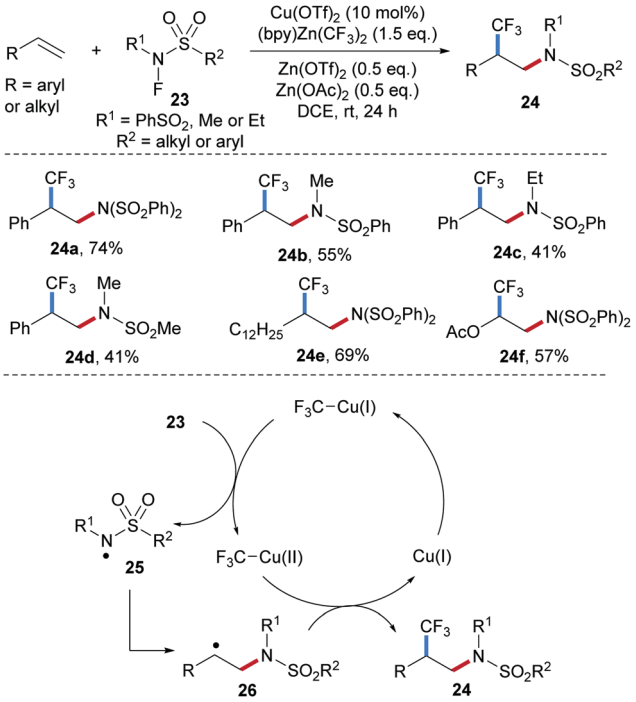
A Cu-catalyzed enantioselective radical aminocyanation of styrenes was achieved by Liu and co-workers in 2017 (Scheme 5).[50] The benzylic radical formed through radical addition of the amidyl radical derived from NFSI to a styrene derivative is captured by a chiral Box/Cu(II) cyanide complex, providing the corresponding chiral Cu(III)-complex which undergoes reductive elimination to afford the nitrile **17** in moderate to high yields and good to excellent enantioselectivity.

Fluoroamide reagents were also tested as amidyl radical precursors in a Cu-catalyzed aminoarylation of styrenes.[51] Systematic variation of the substituents in the N–F reagent revealed that *N*-fluoro-*N*-methylbenzenesulfonamide **18**, an easily prepared compound, to be the optimal amidyl radical precursor for this transformation (Scheme 6). Alkene aminoarylation was achieved by using a Box/Cu(I)-catalyst to provide the desired sulfonamides **19** in moderate to good yields and satisfactory enantioselectivity. Electronic effects at the arene moiety of the boronic acid and the styrene component are weak and both electron-rich and electron-deficient systems worked well. Mechanistically, single electronic reduction of **18** by Cu(I) generates the amidyl radical **20** along with the formation of Cu(II)–X species which in the presence of an arylboronic acid further reacts to a Cu(II)–Ar-complex. Radical addition of the amidyl radical **20** to a styrene provides the benzylic radical **21**, which is trapped by the Cu(II)–Ar species to yield the desired optically enriched 2,2-diarylethylamine **19** thereby regenerating the starting Box/Cu(I)-catalyst. Arylation likely proceeds *via* the Cu(III)Ar intermediate upon stereoselective reductive elimination. As an application to document the potential of the method, the β-diaryl amine derivative **19a** was transformed to the tetraisoquinoline **22**.

An unprecedented Cu-catalyzed radical 1,2-aminotrifluoromethylation of alkenes by using N–F reagents of type **23** as amidyl radical precursors and (bpy)-Zn$(CF_3)_2$ (bpy = 2,2′-bipyridineis) as the CF_3 donor was recently achieved by Li and co-workers (Scheme 7).[52]



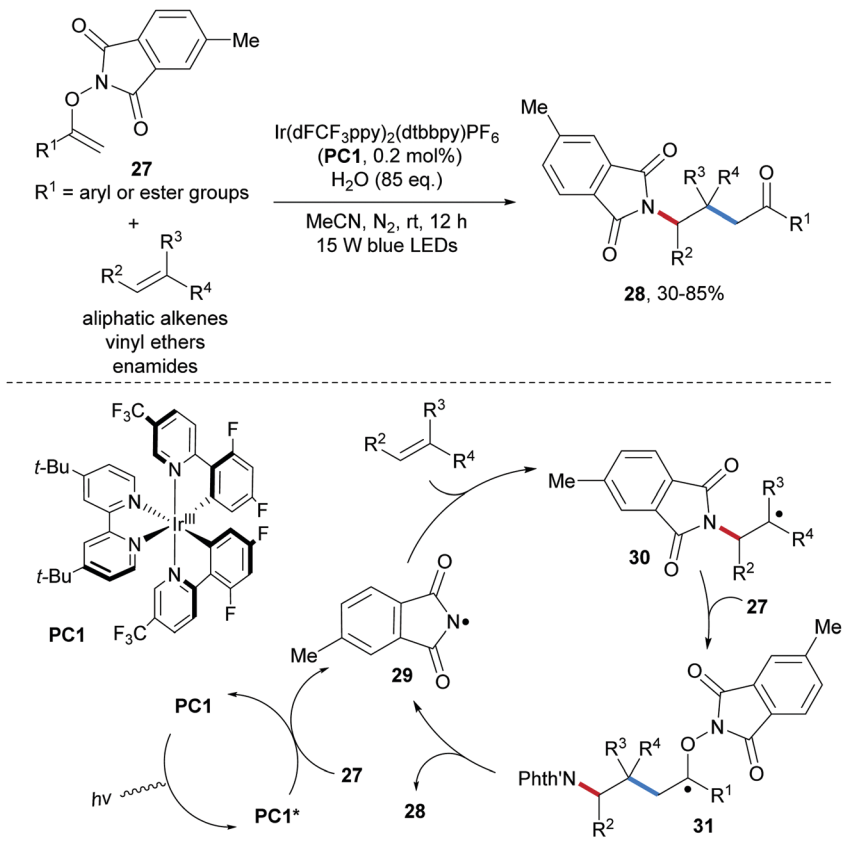
Scheme 6 Asymmetric Cu-catalyzed intermolecular aminoarylation of styrenes.



Scheme 7 Cu-Catalyzed radical aminotrifluoromethylation of alkenes.

Interestingly, the reaction efficiency is significantly improved upon simultaneous addition of $Zn(OTf)_2$ and $Zn(OAc)_2$ to the reaction system. Electrophilic amidyl radicals, generated through single-electron reduction of the easily prepared N–F sulfonamides by Cu(I), were found to react with diverse unsaturated systems including styrenes (**24a–d**), aliphatic alkenes (**24e**) and vinyl acetates (**24f**). The proposed catalytic cycle starts by transmetalation of the CF_3-anion from zinc to copper, by which the Cu(I)–CF_3 intermediate is generated. This Cu(I)-species reduces the N–F reagent **23** to generate the sulfamidyl radical **25** and a Cu(II)–CF_3 intermediate. The C-radical **26** generated through initial radical addition of the electrophilic radical **25** to an alkene is trapped by the Cu(II)–CF_3 complex either *via* direct CF_3-group transfer or formation of a Cu(III)-intermediate followed by reductive elimination to eventually provide the 1,2-aminotrifluoromethylation product and a Cu(I)-catalyst.

An inevitable drawback of using RSO_2N–F reagents as the amidyl radical precursors (especially NFSI) is the harsh conditions that have to be applied for deprotection of the product sulfonamides to access the corresponding free amines, which are generally the final targets. Therefore, the development of novel reagents that allow generating amidyl radicals bearing common N-protecting groups such as Boc, Cbz and Phth is of great importance. Along these lines, several novel and practical amidyl radical precursors have been developed in recent years. In 2018, Feng and co-workers reported the group transfer radical addition of *O*-vinylhydroxylamine derivatives **27** onto unactivated alkenes to give the carboamination products **28** (Scheme 8).[53] This valuable radical alkene carboamination

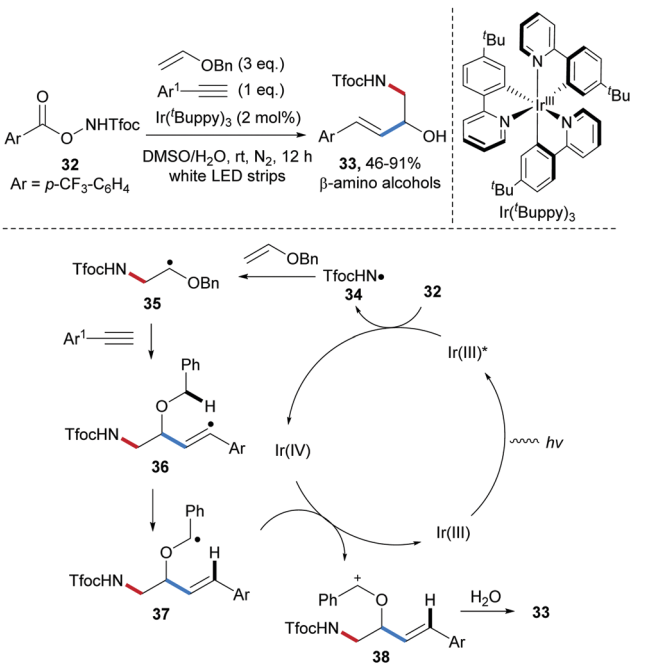


Scheme 8 Intermolecular carboamination of unactivated alkenes.

reaction is applicable to electron-rich alkenes as well as to unactivated aliphatic alkenes and works with low initiator loading (0.2 mol%), providing the desired phthaloyl-protected amines **28** in moderate to good yields.

As initiation step, energy transfer from the photo-excited Ir(III)-complex to the *O*-vinylhydroxylamine derivative **27** leads to homolytic cleavage of the weak N–O bond to give the amidyl radical **29**.[54] The electrophilic amidyl radical **29** then adds to the alkene generating the alkyl radical **30** which is chemoselectively captured by **27** to generate the tertiary C-radical **31**. Fragmentation of **31** through homolytic cleavage of the N–O bond provides the desired alkene carboamination product **28** along with the chain carrying amidyl radical **29**. This radical cascade convinces with excellent atom economy and features high chemoselectivity, thus offering a practical approach for the preparation of diverse primary amines.

Radical carboamination of vinyl ethers by photoredox catalysis[55–57] was achieved by Yu and co-workers in 2018 (Scheme 9).[58] Diverse β-amino alcohol derivatives **33** were obtained in high yields from the *O*-acyl hydroxylamine derivative **32**, benzyl vinyl ether and phenylacetylenes under mild conditions. Upon visible light irradiation, the easily prepared *O*-acyl hydroxylamine **32** is reduced by a photoexcited Ir(III)-complex to provide the electrophilic amidyl radical **34**, which undergoes chemoselective radical addition to the electron-rich benzyl vinyl ether to give the α-oxy-alkyl radical **35**. This C-radical in turn reacts with an arylacetylene to the vinyl radical intermediate **36** that further reacts *via* 1,5-hydrogen atom transfer to give the stabilized C-radical **37**, which can be oxidized by Ir(IV) to close the catalytic cycle generating the carbenium ion **38**. Trapping with water and half acetal cleavage finally provide **33**.



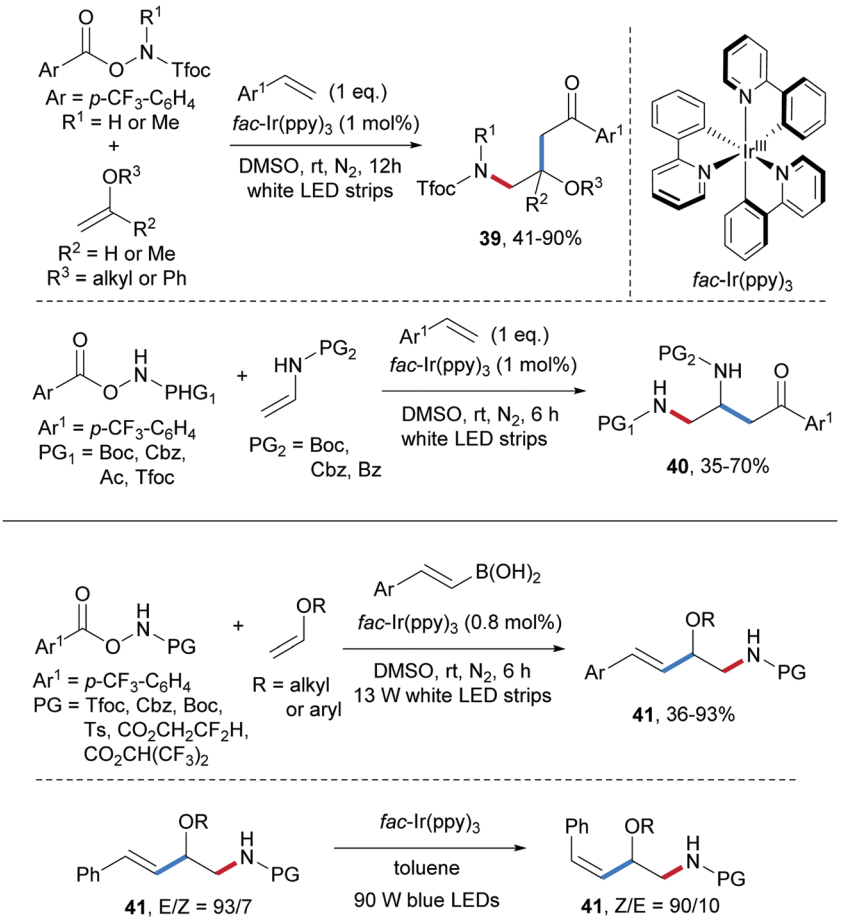
Scheme 9 Three-component radical carboamination of enols.

Three-component radical carboamination of electron-rich alkenes with *O*-acyl hydroxylamines and styrenes was accomplished by the same group (Scheme 10).[59] Electrophilic amidyl radicals, reductively generated through single electron reduction of *O*-acyl hydroxylamines by a photo-excited Ir(III)-complex, chemoselectively react with electron-rich enolethers to give the adduct C-radicals that are then trapped by styrenes with high chemoselectivity. The benzylic radicals thus formed are eventually oxidized to the corresponding cations and trapping with DMSO in a Kornblum oxidation finally provides the targeted alkene carboamination products with exclusive chemoselectivity. Diverse β-amino alcohol derivatives **39** were obtained in moderate to high yields by using vinyl ethers as amidyl radical acceptors. Moreover, by using enamides bearing commonly used N-protecting groups in place of the enol ethers, the protected 1,2-diamines **40** were formed in moderate to good yields.

Recently, the photoredox catalyzed three-component radical carboamination of enols with *O*-acyl hydroxylamines and styryl boronic acids was reported by the Yu group (see Scheme 10).[60] Various N-protecting groups in the *O*-acyl hydroxylamine component including Tfoc, Cbz, Boc, Ts are tolerated and the amidyl radicals, reductively generated by a photo-excited Ir(III), undergo efficient radical addition to vinyl ethers to give the corresponding adduct C-radicals which further react with alkenyl boronic acids to provide fully protected β-amino alcohol derivatives **41** in 36–93% yields with high *E*-selectivity. Notably, isomerization to the thermodynamically less stable *Z*-isomer can be achieved upon blue light irradiation in the presence of *fac*-Ir(ppy)$_3$ as an energy transfer catalyst.

Intermolecular radical carboamination of unactivated alkenes is of great importance but still not well established. In 2018, our group developed a transition-metal free process for aminoalkynylation of various unactivated alkenes (Scheme 11).[61] In this transformation, the α-amido-oxy acids **42** were used as amidyl radical precursors that can be oxidized by an excited photocatalyst.[62,63] By using ethynylbenziodoxolone (EBX) reagents as the alkyl radical acceptors, various β-amino alkynes could be obtained from the corresponding alkenes. The scope with respect to the amidyl radical acceptor was amazingly broad and alkenes bearing different functional groups and substitution patterns including mono-, 1,1-di-, and 1,2,2-tri-substituted alkenes, cyclic alkenes, vinyl ethers and enamides engaged in this valuable transformation (**43a–g**). Moreover, upon varying the I(III)-reagent, 1,2-amidocyanation (**44**) and 1,2-amido-alkenylation (**45**) were accomplished by using the corresponding EBX reagents, albeit with lower yields.

The proposed catalytic cycle of the radical alkene 1,2-aminoalkynylation commences with photo-excitation of 4CzlPN upon visible-light irradiation to generate the excited 4CzlPN*, which oxidizes carboxylate **46**, formed by deprotonation of α-amido-oxy acid, to generate the carboxyl radical **47** along with the radical anion of the photoredox catalyst (4CzlP$^{-\bullet}$) (Scheme 12). Sequential fragmentation of **47** with the extrusion of CO_2 and acetone generates the amidyl radical **48**, which then adds to the carbon–carbon double bond of the alkene to provide the adduct radical **49**. EBX reagent traps the C-radical **49** to give alkene



Scheme 10 Three-component radical carboamination of electron-rich alkenes with styrenes or alkenyl boronic acids.

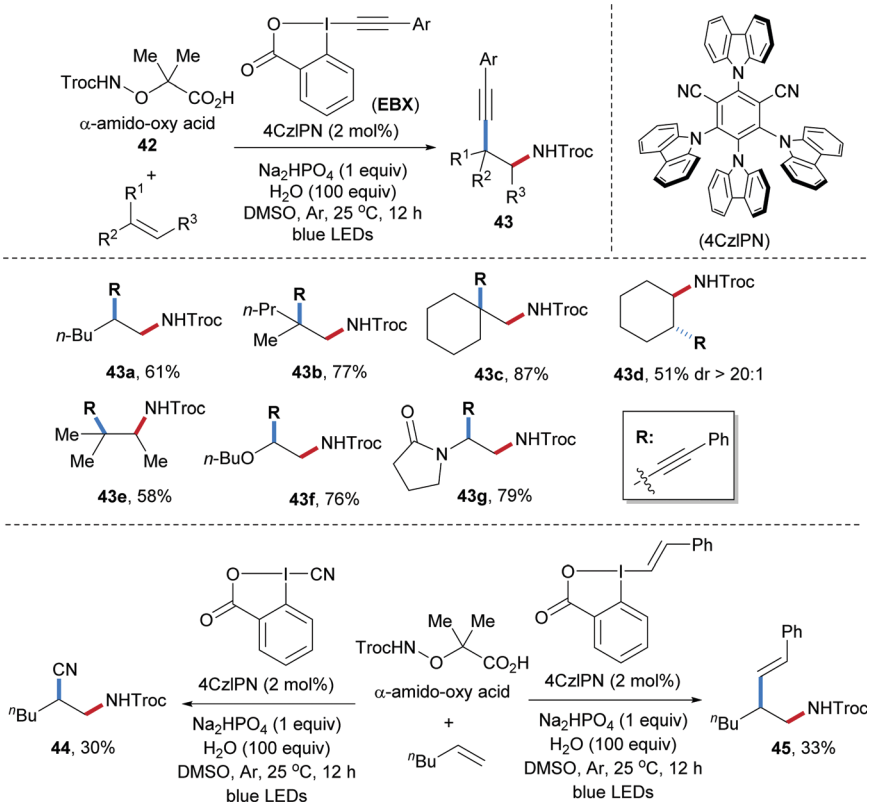
amidoalkynylation product **43** with concomitant formation of iodanyl radical **50**. Transient radical **50** is then reduced by 4CzlP$^{-\bullet}$ to give *ortho*-iodobenzoate and 4CzlPN, thereby closing the catalytic cycle.

Three-component radical carboamination including amidyl radicals, unactivated alkenes and Michael acceptors was established very recently by us (Scheme 13).[64] Commonly used N-protecting groups installed at the starting α-amido-oxy acids were tolerated and the corresponding carboamination products were obtained in satisfactory yields (**51a–h**). *N*-Methyl α-amido-oxy acids bearing electron deficient protecting groups (Troc or Tfoc) also worked well as N-radical precursors in this transformation (**51i, 51j**). This radical cascade features broad scope with respect to the alkene and Michael acceptors. For example, mono-, di-, tri- and tetra-substituted aliphatic alkenes and electron rich alkenes including vinyl ethers, vinylsilanes and enamides engaged in the cascade to provide the corresponding carboamination products in good to satisfactory yields (**51k–r**). The valuable amino-C-glycoside **51s** could be obtained with high diastereoselectivity (9 : 1) by using a glycal as the amidyl radical acceptor. Diverse Michael acceptors including acrylates, vinyl ketones, acrylamides, vinyl phosphates, methacrolein, acrylonitrile and even electron deficient styrenes were found to be eligible coupling partners for this three-component radical cascade (**51t–51ad**).

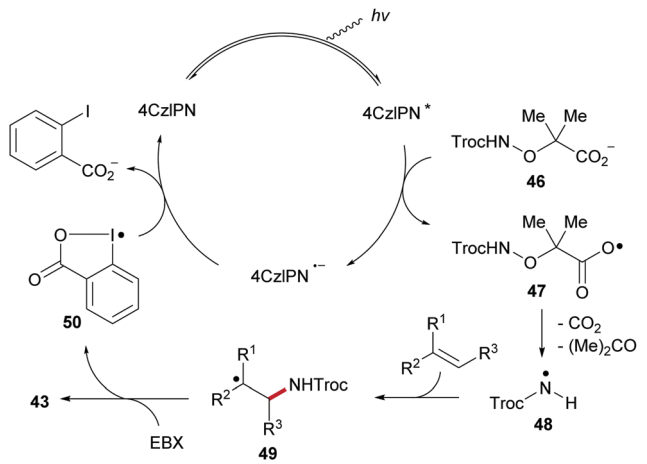
The catalytic cycle starts by photo-excitation of Ir(III) to generate the excited Ir(III)*-complex which oxidizes carboxylate **52** to the carboxyl radical **53** (Scheme 14). Sequential fragmentation with the extrusion of CO_2 and acetone generates the electrophilic amidyl radical **54**. Governed by polar effects, the amidyl radical chemoselectively adds to the CC double bond of the electron-richer alkene to provide the adduct radical **55**. Michael acceptor then traps the thus generated nucleophilic C-radical **55** to give **56**, which is reduced by the Ir(II)-complex to afford the enolate **57**, thereby closing the catalytic cycle. Protonation eventually gives the carboamination product **51**.

N-Aminopyridinium salts **58**, that were previously used as amidyl radical precursors for radical arene C–H amidation, were successfully applied as bifunctional reagents to the 1,2-aminopyridylation of electron-rich alkenes (Scheme 15).[65] This radical alkene carboamination protocol features high atom economy and proceeds under mild conditions with the use of an organic dye as a photo-sensitizer to initiate the process. Various electron-rich alkenes including vinyl ethers and enamides were found to be eligible acceptors for this carboamination and diverse functional groups at the pyridine ring are tolerated. The resulting sulfonyl protected secondary amines **59** were obtained in good to satisfactory yields (**59a–h**).

The authors proposed a radical chain reaction. Initiation proceeds *via* single-electron reduction of the *N*-aminopyridinium



Scheme 11 Three-component radical aminoalkynylation of unactivated alkenes.



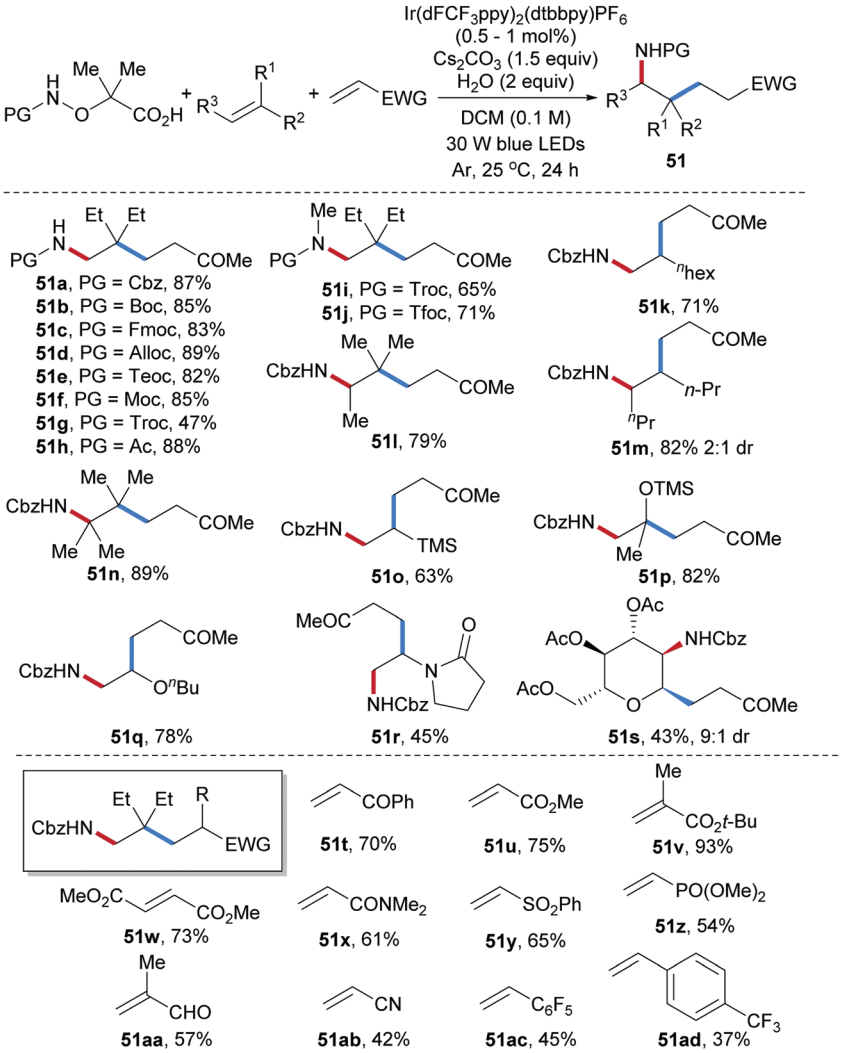
Scheme 12 Proposed mechanism for alkene aminoalkynylation.

salt **58** by a photo-excited organic dye to provide an electrophilic sulfonamidyl radical **60**, which is captured by an electron-rich alkene to generate the alkyl radical intermediate **61**. Addition of the C-radical **61** to the *N*-aminopyridinium salt **58** occurs with complete *para*-selectivity to deliver the arene radical cation **62**. Deprotonation and N–N-bond cleavage finally afford the alkene aminopyridylation product **59** along with the chain carrying sulfonamidyl radical **60**.

Recently, our group achieved an asymmetric radical aminoarylation of vinyl acetamides by merging chiral Brønsted acid catalysis and photoredox catalysis (Scheme 16).[66] Four protected 1,2-diamine derivatives **64** could be obtained in high yields and enantioselectivities through a three-component Minisci reaction using the *O*-acyl hydroxylamine **63**, vinyl acetamide and quinolines as components. In the proposed mechanism, photo excitation of Ir(III) provides Ir(III)* which can be oxidatively quenched to Ir(IV) by the *O*-acyl hydroxylamine **63** to generate the corresponding amidyl radical by reductive N–O bond cleavage. Amidyl radical addition to vinyl acetamide leads to the adduct radical **65** which undergoes an acid promoted Minisci type reaction to give the aminoarylation product **64**. It is assumed that hydrogen bonding as suggested in structure **66** helps orienting the reaction partners to give the addition intermediate **67** in a reversible reaction. The stereodetermining step is likely deprotonation of **67** to give **68** and oxidation with Ir(IV) finally provides the isolated quinoline **64**.

2.2 2,1-Carboazidation of alkenes

Wang and co-workers developed a Cu-catalyzed azidocyanation of aryl alkenes with TMSCN and $TMSN_3$ in the presence of an I(III)-reagent as an oxidant (Scheme 17).[67] Firstly, the reaction of $TMSN_3$ with $PhI(OAc)_2$ produces $PhI(N_3)_2$ which through single-electron reduction by Cu(I) delivers an azidyl radical. Addition of the electrophilic azidyl radical to the aryl alkene provides the C-radical **70**, which is oxidized by Cu(II) to give the benzylic cation **71**, thereby regenerating the starting Cu(I)-complex. Nucleophilic trapping of the cation **71** with TMSCN finally affords the azidocyanation product **69** in moderate to good yield.

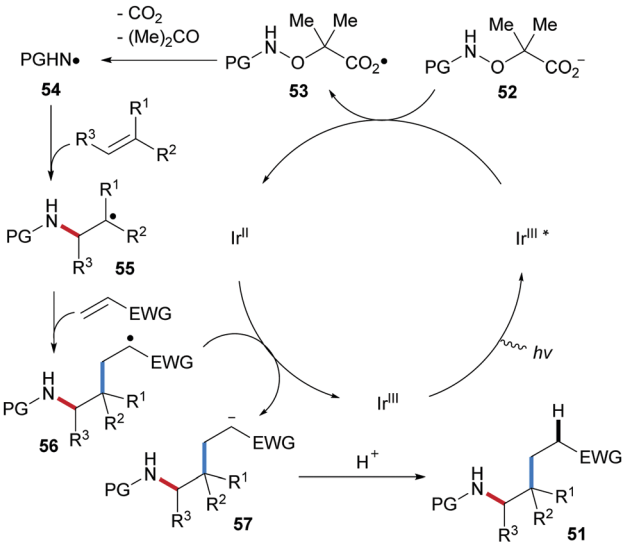


Scheme 13 Three-component radical Giese reaction for alkene carboamination.

The asymmetric azidocyanation of aryl alkenes through a Cu-catalyzed radical cascade was achieved by the Liu group in 2017 (Scheme 18).[50] A chiral box-type ligand was used in combination with $CuCl_2$ and various enantiomerically enriched β-azido alkylnitriles **72** were obtained with good to excellent enantioselectivity. These products are highly valuable as documented by follow-up chemistry on azide **72a** to the thiazole derivative **73**, bocylated β-amino alkylnitrile **74** and triazole **75**.

Amidoheteroarylation of aliphatic alkenes through a radical cascade process using TMSCN, aliphatic alkenes and heteroarenes as reaction components was reported by Liu and co-workers (Scheme 19).[68] $PhI(N_3)_2$ **77** is generated *in situ* from $PhI(OAc)_2$ and $TMSN_3$. Upon heating, homolytic cleavage of the $I–N_3$ bond in **77** occurs generating an azidyl radical which adds to the alkene to give the C-radical **78**. Minisci type C–H alkylation proceeds through radical addition of the alkyl radical **78** to a TFA activated heteroarene to give the radical cation intermediate **79**, which undergoes single-electron oxidation by $PhI(OAc)_2$ to eventually afford the desired azidoarylation product **76**. Various heteroarenes including quinolines (**76a** and **76b**), isoquinolines (**76c**), pyridines (**76d**), phenanthridines (**76e**), pyrazines (**76f**), quinoxalines (**76g**), quinazolines (**76h**), pyrimidines (**76i**), pyrido[3,4-*b*]pyrazines (**76j**), pyrido[2,3-*b*]pyrazines (**76k**) and phthalazines (**76l**) engaged in this transformation to afford the corresponding alkene azidoheteroarylation products in good yields.

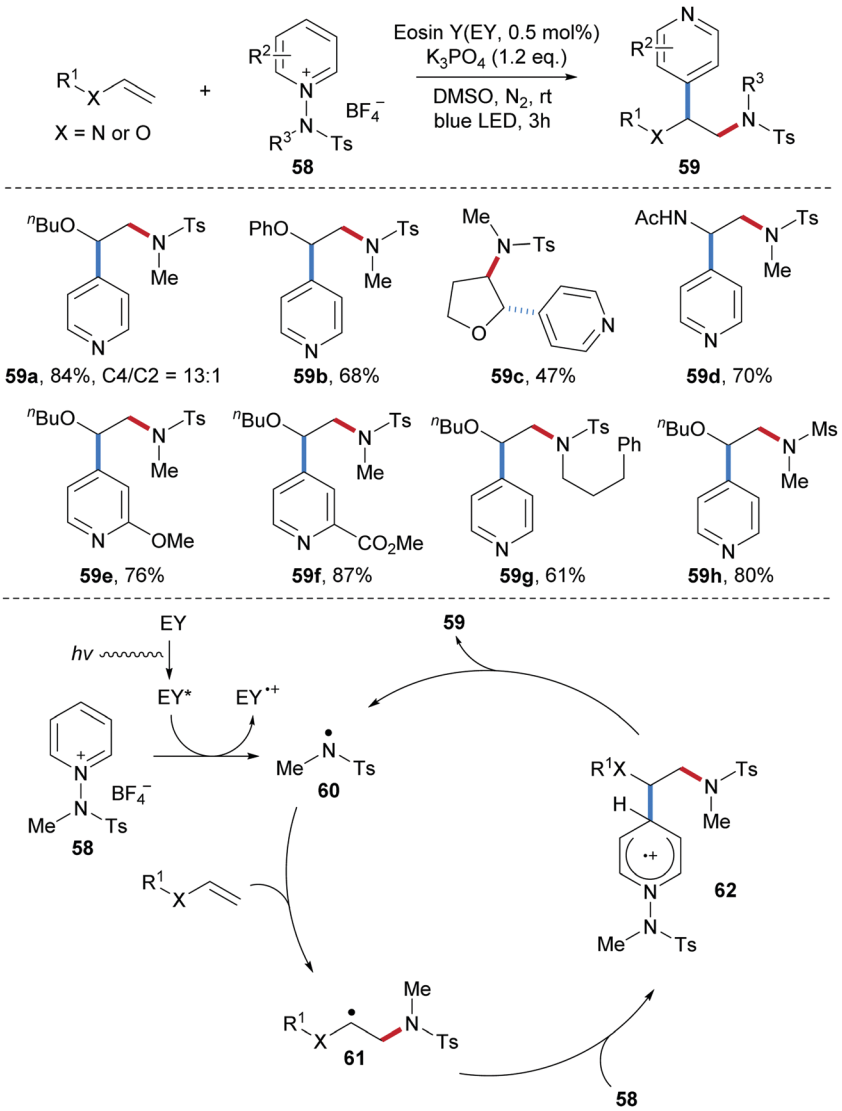
Lu and co-workers reported a photoredox catalyzed three-component carboazidation of alkenes with $TMSN_3$ and acrylonitrile (Scheme 20).[69] Diverse δ-azido nitriles **80** could be efficiently accessed from styrenes and aliphatic alkenes. It was suggested that single-electron oxidation of $TMSN_3$ by the photo-excited Ir(III) complex leads to the electrophilic azidyl radical which adds to the alkene to give the corresponding adduct C-radical **81**. Steered by polar effects, **81** reacts chemoselectively with acrylonitrile to **82**. Single electron reduction of **82** by Ir(II) closes the catalytic cycle thereby generating the anion **83** that gets finally protonated to afford the isolated carboazidation product **80**.



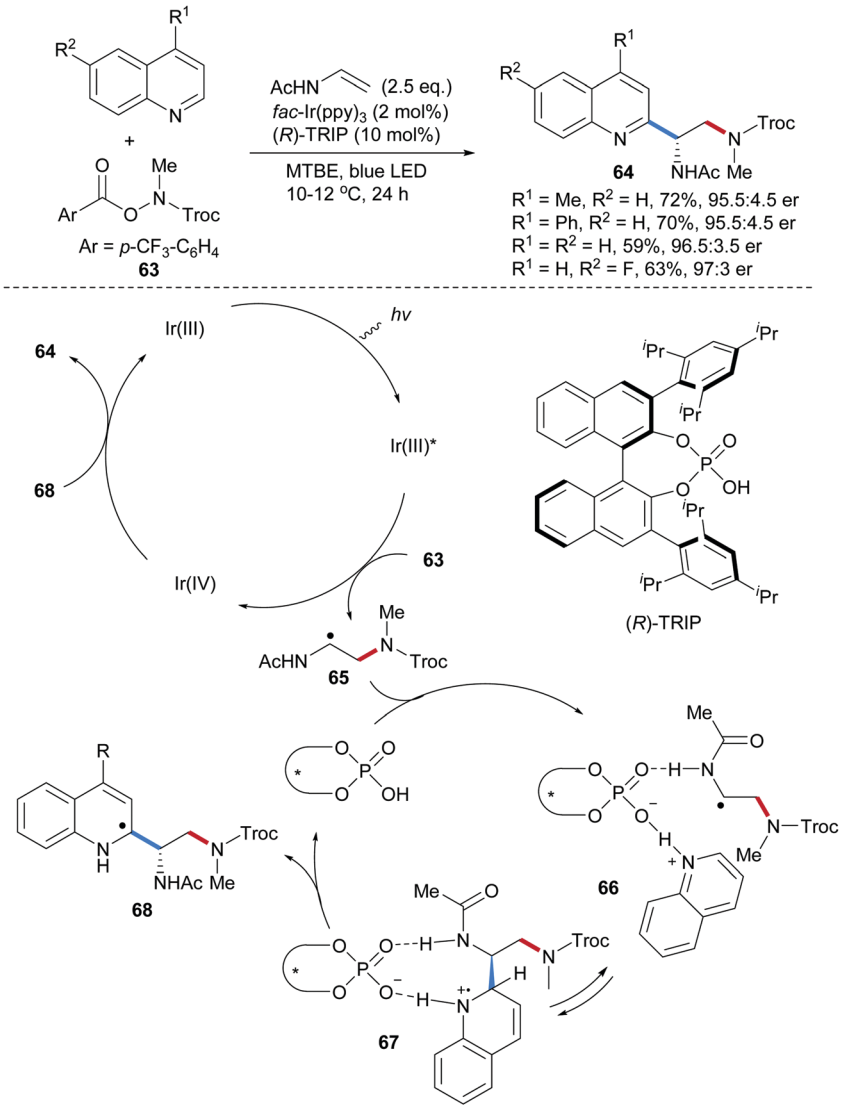
Scheme 14 Proposed mechanism for three-component Giese reaction.

3. Carboamination *via* C-radical addition

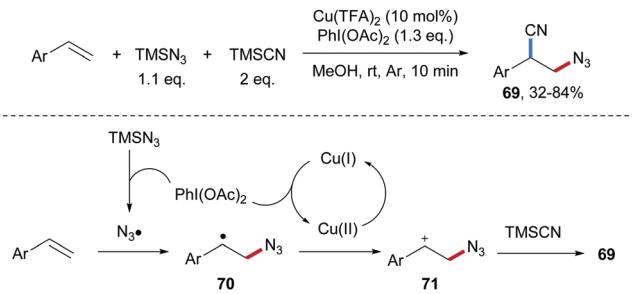
An early study on an intermolecular formal carboamination proceeding *via* alkyl radical addition to an alkene followed by C–N bond formation was reported by the Renaud group in 2002.[70] α-Bromo acetic acid ethyl ester was used as a C-radical precursor, di-*tert*-butylhypodinitrite as an initiator, $(Bu_3Sn)_2$ as a chain carrier and phenylsulfonyl azide as a radical azidation reagent. Governed by the polar effect, the electrophilic α-ester radical **85** adds to an unactivated alkene to form a nucleophilic alkyl radical **86.** Azidyl group transfer from phenylsulfonyl azide to the alkyl radical **86** provides the carboazidation product **84** along with the phenylsulfonyl radical (Scheme 21). Reaction of the latter radical with $(Bu_3Sn)_2$ leads to the tributyl tin radical which abstracts the bromine atom from the α-bromo-ester to give the corresponding α-ester radical **85,** sustaining the chain. Along with the bromo ester, the corresponding iodide (see **87**),



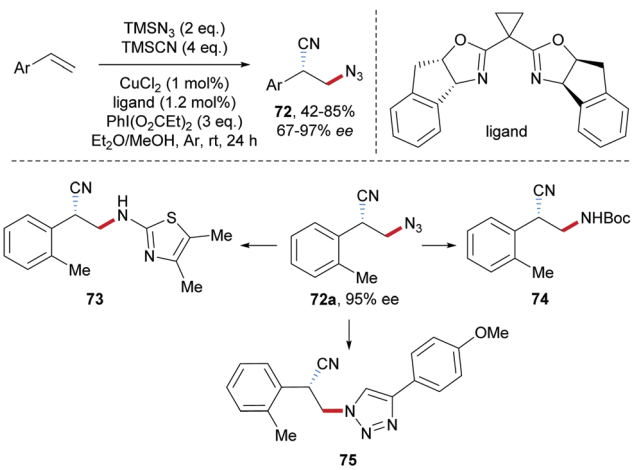
Scheme 15 Radical alkene aminopyridylation using *N*-aminopyridium salts as bifunctional reagents.



Scheme 16 Asymmetric radical aminoarylation of enamides.



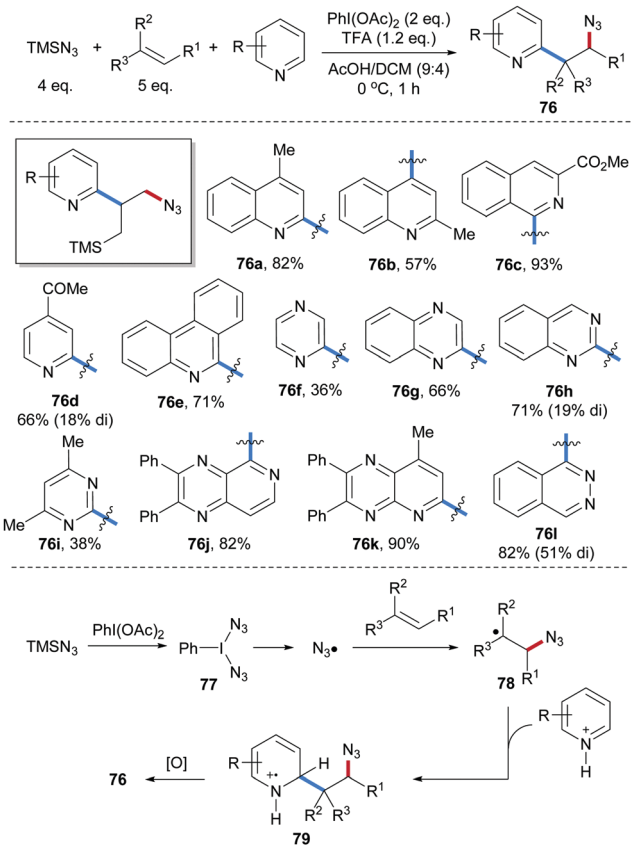
Scheme 17 Cu-Catalyzed three-component radical azidocyanation of alkenes.



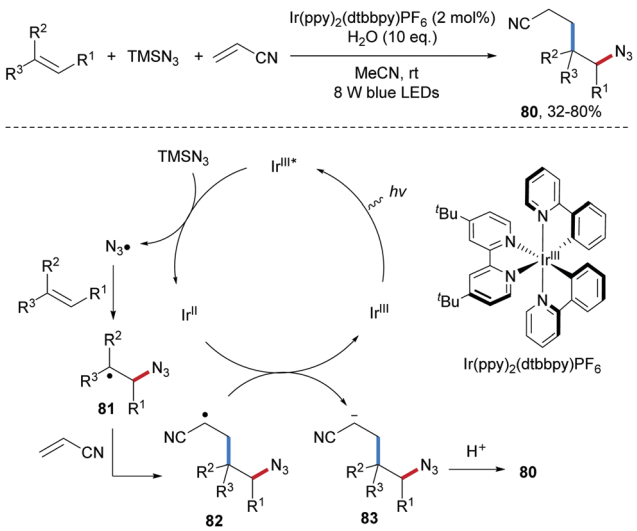
Scheme 18 Enantioselective azidocyanation of alkenes.

xanthogenate and phenylselenide were successfully used as C-radical precursors in this sequence. Notably, chain initiation can also be achieved with Et_3B/O_2 in place of di-*tert*-butylhypodinitrite.[71]

Several alkaloids including (±)-cylindricine C,[72] hyacinthacine A1,[73] (−)-indolizidine 167B[74] and (±)-lepadiformine[75] were



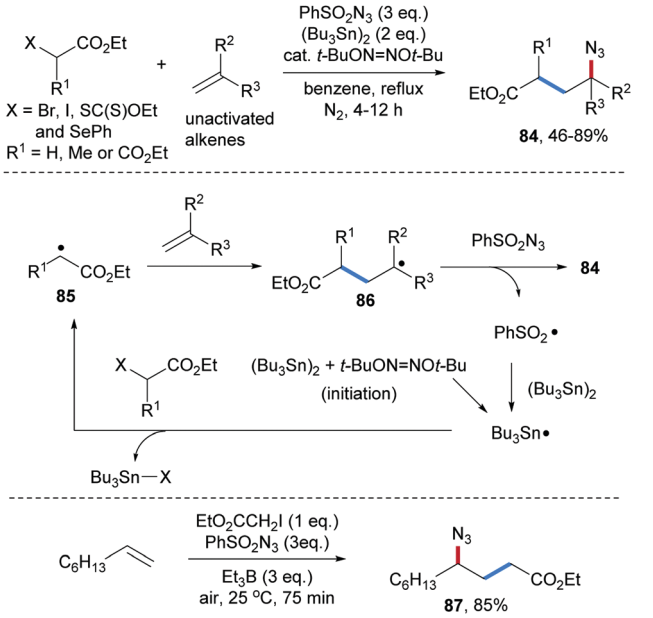
Scheme 19 Three-component radical azidoheteroarylation of alkenes.



Scheme 20 Three-component carboazidation of unactivated alkenes with $TMSN_3$ and acrylonitrile.

synthesized by using this three-component radical carboazidation as the key step (Scheme 22).

An atom economic alkene carboazidation reaction was reported by the same group in 2010 (Scheme 23).[76] The sulfonyl azide **88** was used as a bifunctional reagent allowing to transfer both an alkyl and an azidyl group to an unactivated alkene.

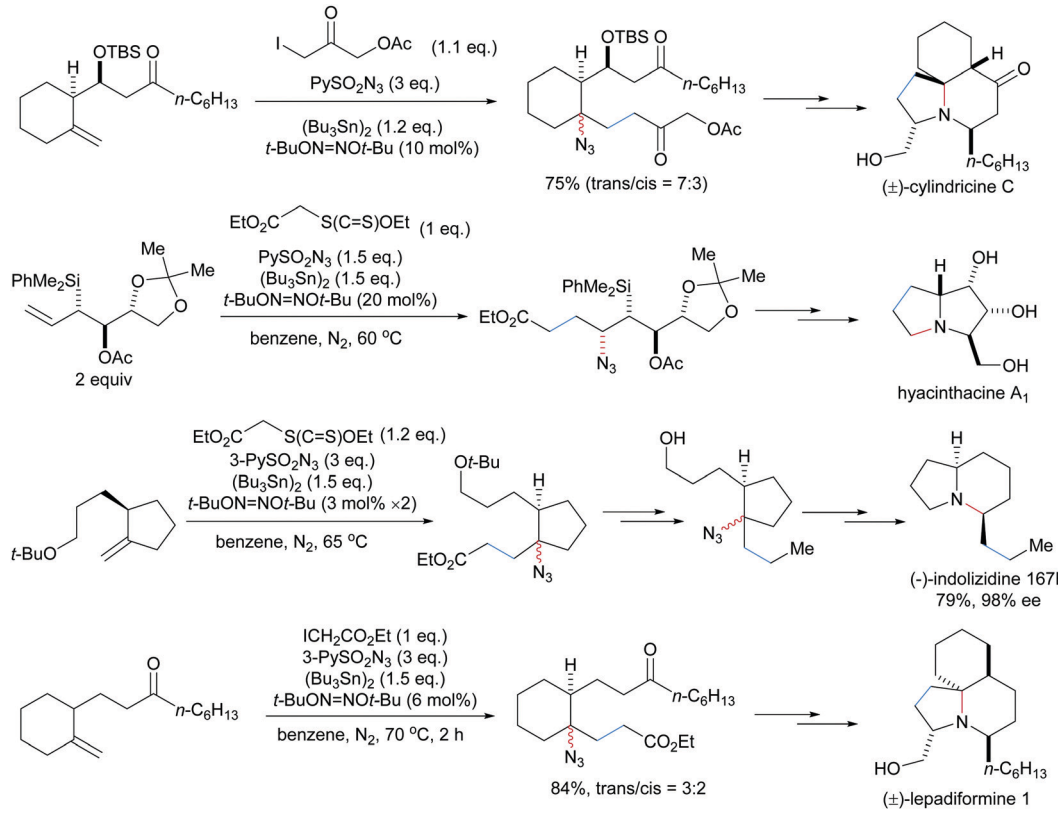


Scheme 21 Three-component radical carboazidation of alkenes through a chain process.

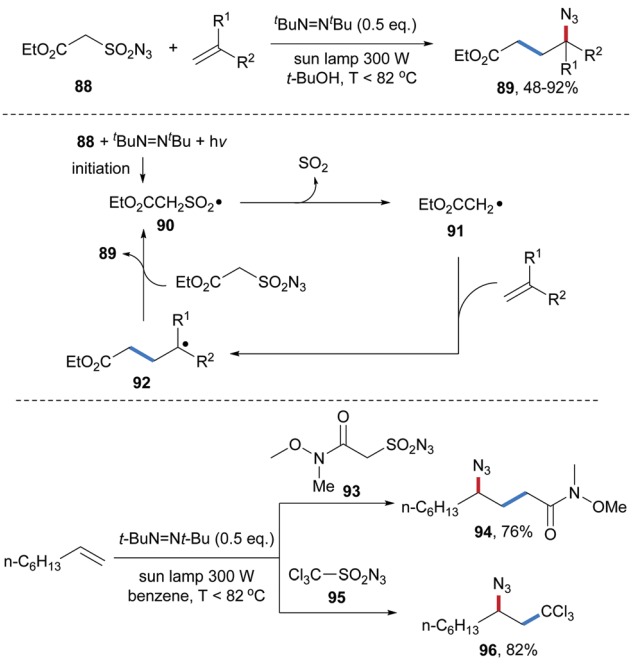
Initiation was achieved with di-*tert*-butyldiazene upon light irradiation leading to the generation of the alkylsulfonyl radical **90**. Fragmentation of SO_2 generates the electrophilic C-radical **91**, which can be trapped by an aliphatic alkene to form the adduct radical **92**. Azidyl group transfer from the sulfonyl azide **88** to the alkyl radical **92** furnishes the desired carboazidation product **89** along with the sulfonyl radical **90** that propagates the chain. By using the Weinreb amide **93** or trichloromethylsulfonyl azide **95** as bifunctional reagents, the corresponding carboazidaton products **94** and **96** were obtained in good yields applying the same conditions.

The incorporation of CF_3 or F-containing functional groups into bioactive compounds heavily impacts their physical and chemical properties.[77] Due to the ubiquity of amino groups in bio-active compounds and drug candidates, the development of alkene carboamination reactions with concomitant introduction of fluorinated alkyl groups is of great importance. Photoredox catalysis has been successfully used to conduct radical fluoroalkylamination reactions. An early protocol along these lines was reported by Akita and co-workers in 2013 (Scheme 24).[78] A CF_3-radical generated through SET reduction of the Umemoto reagent by a photo-excited Ru-complex is trapped by a styrene derivative to form the benzylic radical **98**. The Ru(III)-complex generated through oxidative quenching oxidizes **98** to the benzylic cation **99** thereby regenerating the starting Ru(II)-species. Ritter type amination of **99** with CH_3CN finally leads to the desired aminotrifluoromethylation product **97** that could be isolated in good to excellent yields.

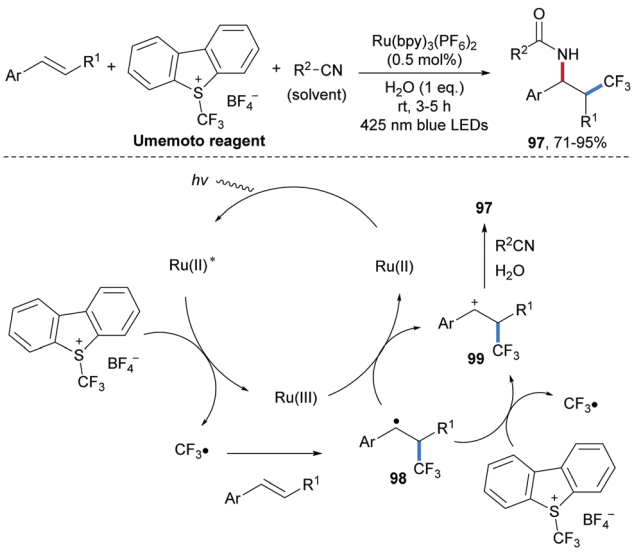
Shortly after, a photoredox catalyzed alkene aminotrifluoromethylation was also disclosed by the Masson group, in which again the Umemoto reagent was used as the CF_3-radical precursor in combination with anilines or $TMSN_3$ as nucleophiles to trap the



Scheme 22 Natural product synthesis through three-component radical alkene carboazidation.



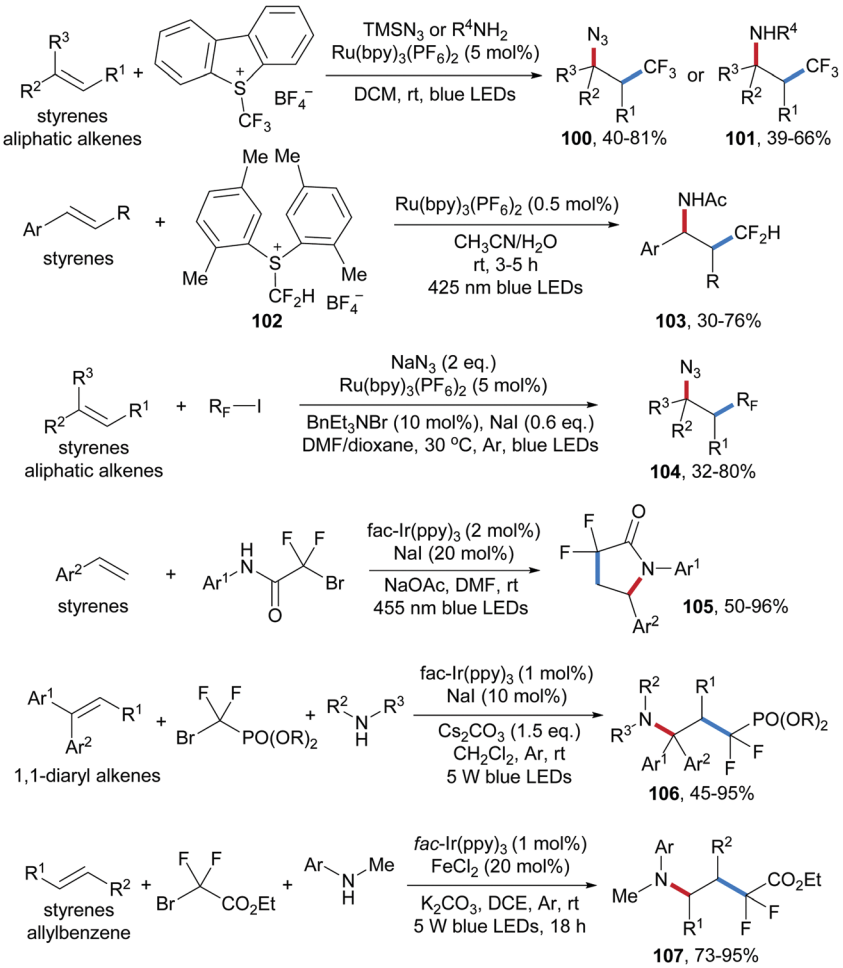
Scheme 23 Carboazidation of alkenes using a radical desulfonylative azide transfer process.



Scheme 24 Three-component radical aminotrifluoromethylation of alkenes using photoredox catalysis.

intermediate benzylic cation, providing aminotrifluoromethylation product **100** and azidotrifluoromethylation product **101** respectively (Scheme 25).[79]

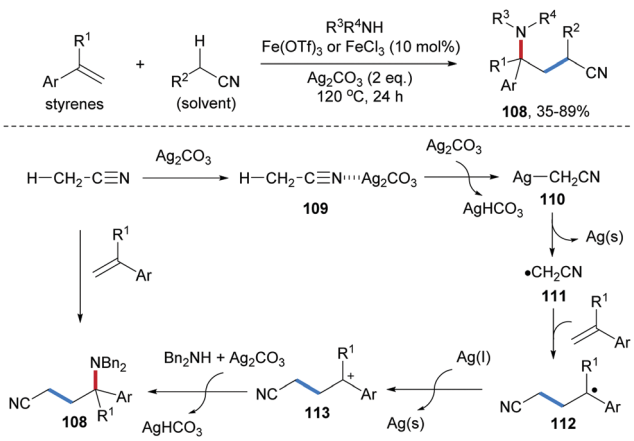
Several approaches on three-component radical azidofluoroalkylation reactions by using photoredox catalysis have been reported recently (Scheme 25). As above, all these reactions proceed *via* radical/ionic cross over and various electrophilic fluoroalkylation reagents were used to generate the corresponding fluoroalkyl radicals. Radical addition is followed by oxidation to the corresponding cations and C–N bond



Scheme 25 Radical aminoperfluoroalkylation of alkenes.

formation occurs through nucleophilic trapping by amines or azides. For instance, The *S*-(difluoromethyl)sulfonium reagent **102**, a difluoromethyl radical precursor that can be readily prepared in three steps from 2,5-dimethyl thiophenol, was used for aminodifluoromethylation of aryl alkenes (see **103**).[80] The Jiao group reported three-component radical azidoperfluoroalkylation of alkenes (**104**), in which the perfluoroalkyl radicals are generated from the corresponding iodides which can be reduced by a Ru(I)-complex.[81] Several examples on three-component aminodifluoroalkylation of alkenes were presented by using α-bromo-α,α′-difluoro-amides,[82] -esters[83] and -phosphonates[84] as difluoroalkyl radical precursors, yielding the corresponding alkene aminodifluoroalkylation products **105–107** under mild conditions in good to excellent yields.

Li and co-workers reported a silver mediated radical carboamination of alkenes with alkyl nitriles and amines to prepare diverse γ-amino alkyl nitriles **108** (Scheme 26).[85] The use of Ag_2CO_3 as an SET oxidant was shown to be necessary. The yield of this cascade could significantly be increased upon using a catalytic amount of $Fe(OTf)_3$ as a Lewis acid. The scope of this transformation with respect to the alkene is restricted to aryl alkenes and the alkyl nitriles that serve as alkyl radical precursors are used as solvents. Various nucleophiles including



Scheme 26 Oxidative radical carboamination of alkenes with alkyl nitriles and amines.

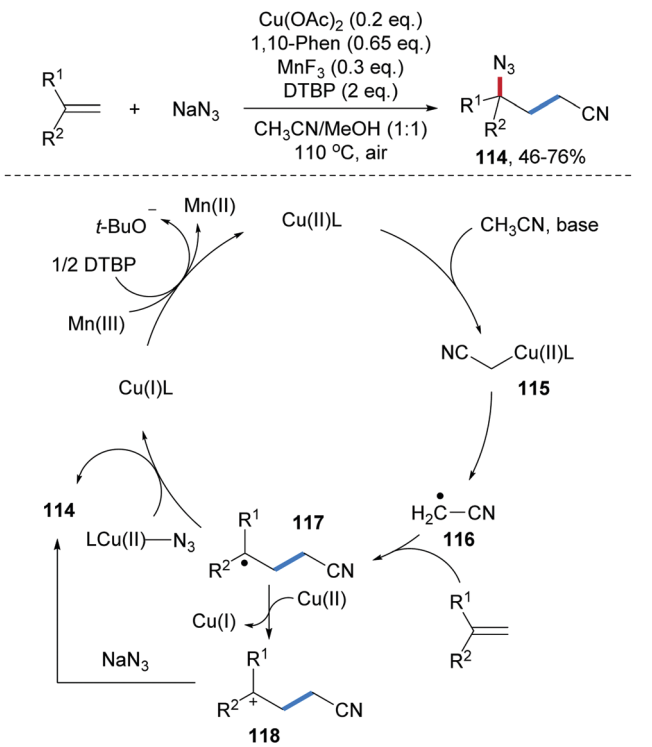
primary and secondary amines and sulfonamides are competent for the formation of the C–N bond through nucleophilic trapping. In the proposed mechanism, the cyano group in CH_3CN is firstly coordinated with Ag_2CO_3 to form the complex **109**, in which the acidity of the adjacent C–H bond is increased significantly. Deprotonation of **109** provides $AgCH_2CN$ **110**,

which undergoes SET oxidation by Ag(I) to give the radical **111** along with Ag(0). Subsequently, the α-cyano carbon radical **111** adds to the styrene derivative to generate the benzylic radical **112** which is then oxidized by Ag(I) to the corresponding benzylic cation **113**. Nucleophilic trapping with an amine finally provides the γ-amino alkyl nitrile **106** in moderate to high yield.

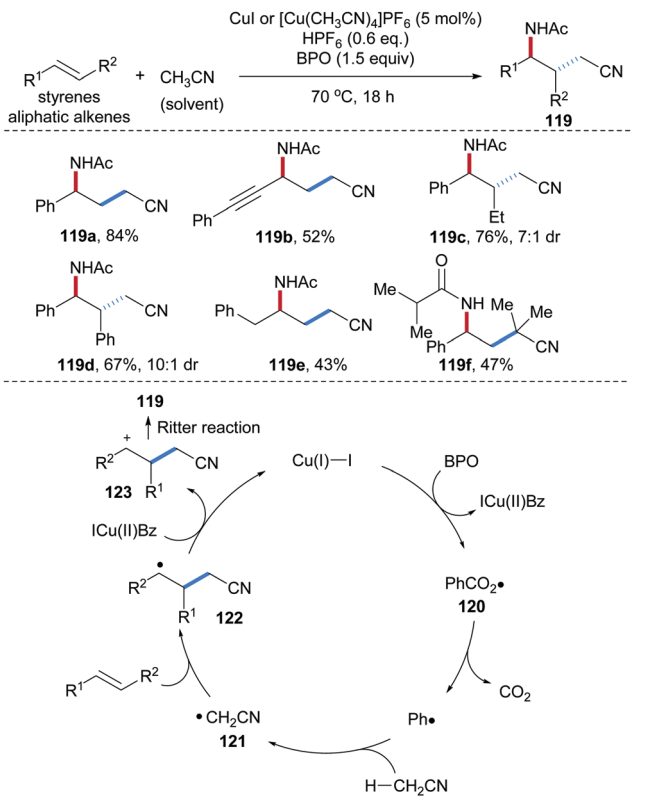
Cu-Catalyzed three-component radical carboazidation of aryl alkenes was reported by the Zhu group (Scheme 27).[86] Mono- and 1,1-disubstituted aryl alkenes serve as radical acceptors and the reaction features good functional group tolerance, providing diverse γ-azido alkyl nitriles **114** in moderate to good yields. Mechanistically, coordination of CH_3CN to Cu(II) mediates deprotonation of CH_3CN to give an alkyl-Cu(II)-complex **115**, which undergoes Cu-alkyl bond homolysis to give an electrophilic radical **116**. Addition of **116** to an alkene provides the adduct radical **117**. N_3-group transfer proceeds *via* capture of **117** by $CuLN_3$ to give a Cu(III)-complex which upon reductive elimination eventually provides the targeted carboazidation product **114** with the concurrent formation of the starting Cu(I)-complex. Direct azidyl group transfer from $CuLN_3$ to **117** is also feasible. Finally, SET-oxidation of Cu(I) by a Mn(III)/DTBP-couple regenerates the Cu(II)-species. An alternative pathway proceeding *via* single electron oxidation of the C-radical **117** to give cation **118** that gets trapped by NaN_3 to **114** is less likely since competing trapping with MeOH, which is used as a co-solvent, should occur.

Bao and co-workers also used acetonitrile as an alkyl radical precursor and amination reagent for radical alkene carboamination reactions where a Cu(I)-complex acted as a redox catalyst (Scheme 28).[87] Their efficient alkene carboamination protocol features broad substrate scope, and diverse alkenes including aryl alkenes, enynes and nonconjugated alkenes provided the desired carboamination products in good yields with high diastereoselectivity (**119a–e**). Other commercial alkyl nitriles were found to be competent reaction partners in this radical cascade. For example, isobutyronitrile used as a solvent delivered in the reaction with styrene the γ-amino alkyl nitrile **119f** in 47% yield. The proposed catalytic cycle starts by single electron oxidation of Cu(I) by BPO to give a Cu(II)-species along with the phenyl carboxyl radical **120**. Decarboxylation of **120** generates the phenyl radical which subsequently abstracts an H-atom from CH_3CN to give the C-radical **121**. Radical addition of **121** to styrene provides the benzylic radical **122**. Single-electron oxidation of **122** by Cu(II) to **123** and subsequent Ritter reaction provide the γ-amino alkyl nitrile **119** thereby regenerating the Cu(I)-catalyst.

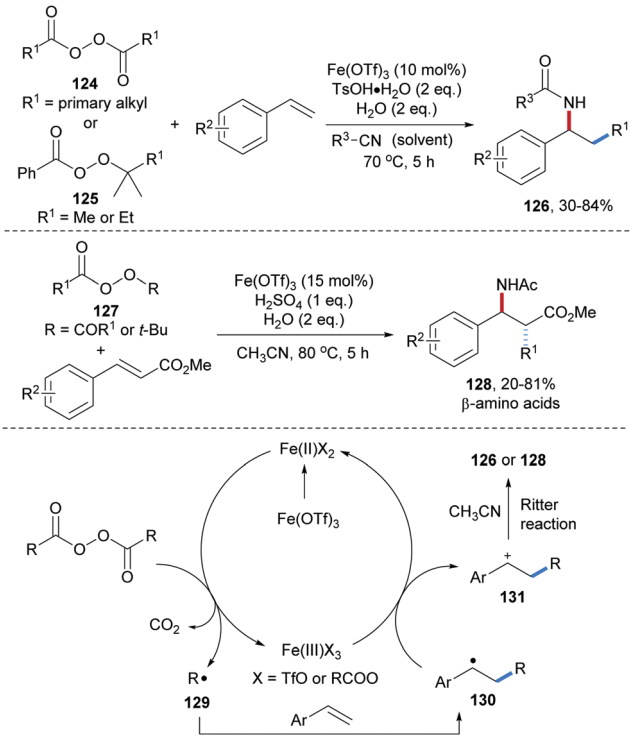
Fe-Catalyzed three-component radical carboamination of alkenes with peroxides and alkyl nitriles was reported by Bao and co-workers (Scheme 29).[88] Readily prepared aliphatic peracids were used as precursors to generate alkyl radicals **129** through single-electron reduction by an Fe(II)-complex. Radical addition of **129** to an alkene generates the C-radical **130**, which further undergoes single electron oxidation by Fe(III) to generate the carbon cation **131**. Ritter amidation of **131** with acetonitrile yields the targeted carboamidation product **126**. Considering the aminomethylation and aminoethylation, the peresters **125** were used as methyl respectively ethyl radical precursors.



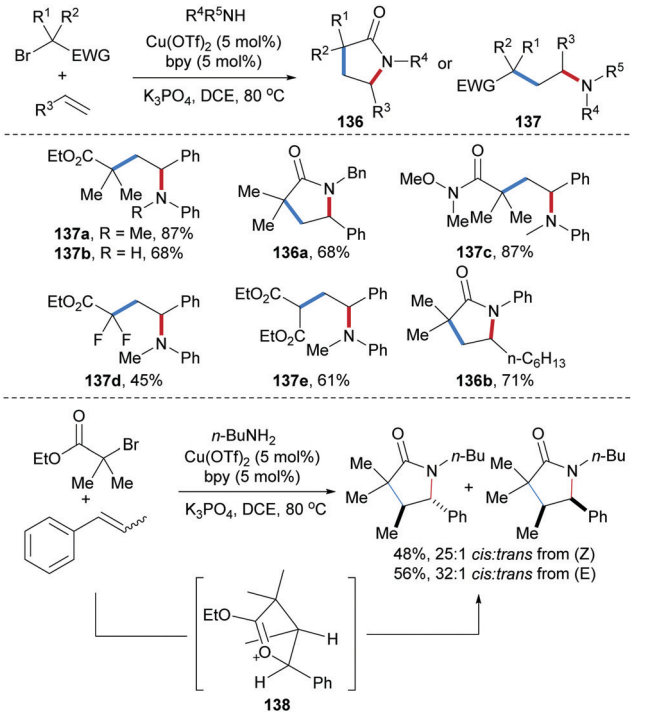
Scheme 27 Cu-catalyzed three-component carboazidation of alkenes with acetonitrile and sodium azide.



Scheme 28 Cu-Catalyzed carboamination of alkenes with acetonitrile.



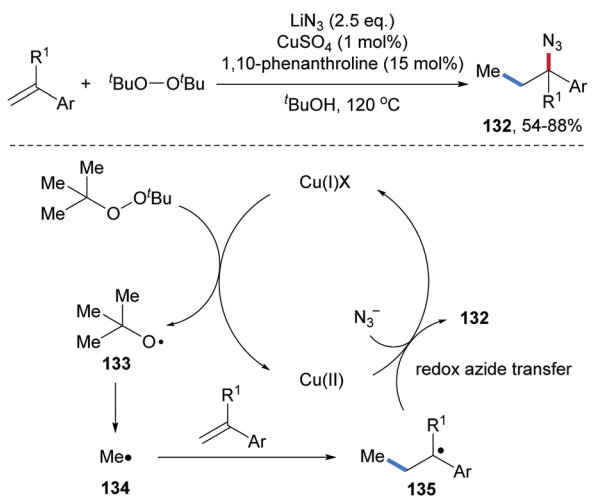
Scheme 29 Fe-Catalyzed carboamination of alkenes.



Scheme 31 Cu-Catalyzed three-component radical carboamination of alkenes for the synthesis of lactams.

By using methyl cinnamate derivatives as alkyl radical acceptors, a set of β-amino acid derivatives **128** could be obtained in moderate to good yields. Notably, the Ritter reaction occurred with high diastereoselectivity and the stereochemical outcome of the cascade could be understood based on computational studies.

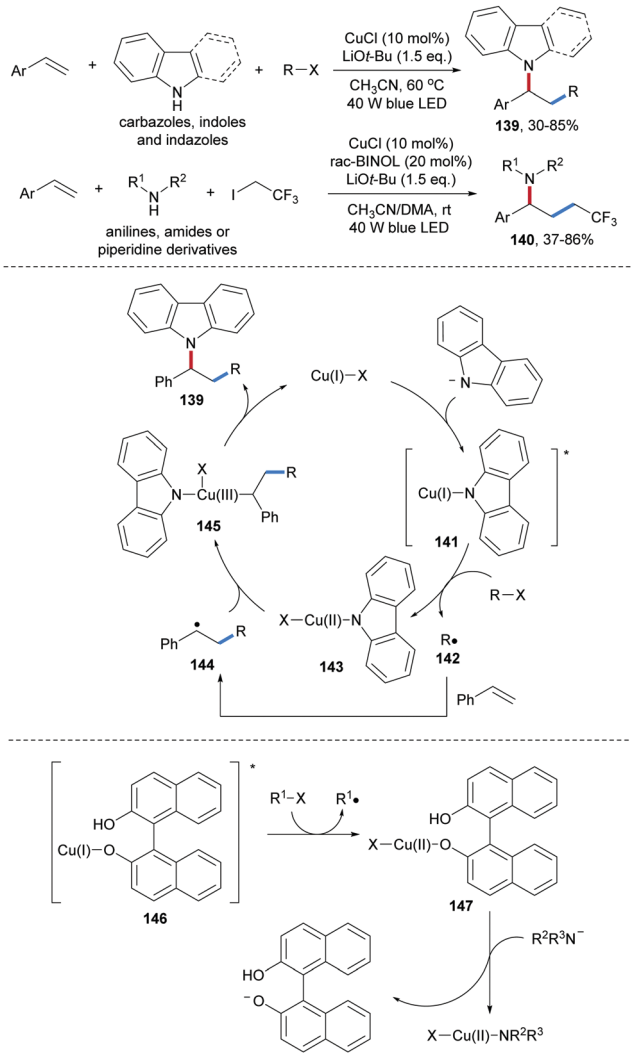
Later, Cu catalyzed three-component radical azidomethylation of aryl alkenes was reported by the Zhu group (Scheme 30).[89] Di-*tert*-butyl peroxide first gets reduced by Cu(I) *via* SET to give a *tert*-butyloxyl radical **133**, which undergoes fragmentation to generate a methyl radical **134** that adds to an alkene to give the C-radical **135**. Cu(II)-mediated azide transfer provides the desired azidomethylation product **132** along with the starting Cu(I)-complex. The targeted alkyl azides **132** were obtained with high efficiency and very broad functional group tolerance in good to very good yields.



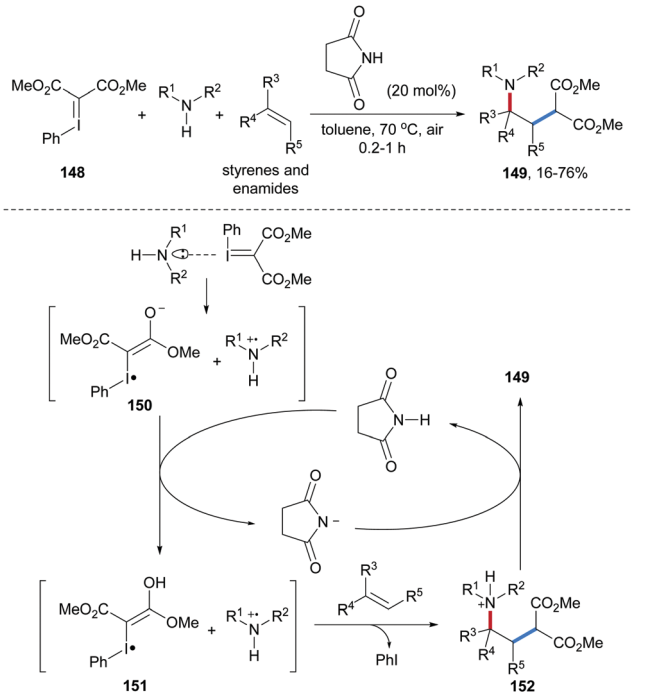
Scheme 30 Cu-Catalyzed radical azidomethylation of styrenes.

Copper-catalyzed intermolecular carboamination of alkenes with α-haloacid derivatives and amines were reported by Hull and co-workers (Scheme 31).[90] Considering the styrene derivatives as acceptors, both electron donating and withdrawing groups at the aryl group are tolerated and diverse halides including α-bromoesters (**137a,b,d** and **136a**), α-bromoamides (**137c**) and bromomalonates (**137e**) were used as C-radical precursors, providing the corresponding carboamination products in good yields. Aliphatic alkenes were found to be competent acceptors for this cascade, as documented by the preparation of the lactam **136b**. Notably, both *Z* and *E*-β-methylstyrene provided the *cis*-product as major isomer with high selectivity. This result indicates that the thermodynamically more stable *trans*-oxocarbenium intermediate **138** is generated. Stereoselective nucleophilic ring-opening of **138** with butylamine followed by lactamization yields the corresponding *cis*-product.

Zhang and co-workers reported Cu-catalyzed three-component radical carboamination of alkenes with secondary amines and alkyl halides upon blue light irradiation (Scheme 32).[91] As N-donors, carbazoles, indoles and indazoles were found to participate in this radical cascade in combination with aryl alkenes and alkyl halides, providing the carboamination products **139** in moderate to satisfactory yields. This cascade features broad scope with respect to the halide component and alkyl iodides, α-bromo esters, secondary alkyl halides and even dichloromethane were found to be eligible C-radical precursors. It is



Scheme 32 Cu-Catalyzed intermolecular carboamination of alkenes induced by visible light.



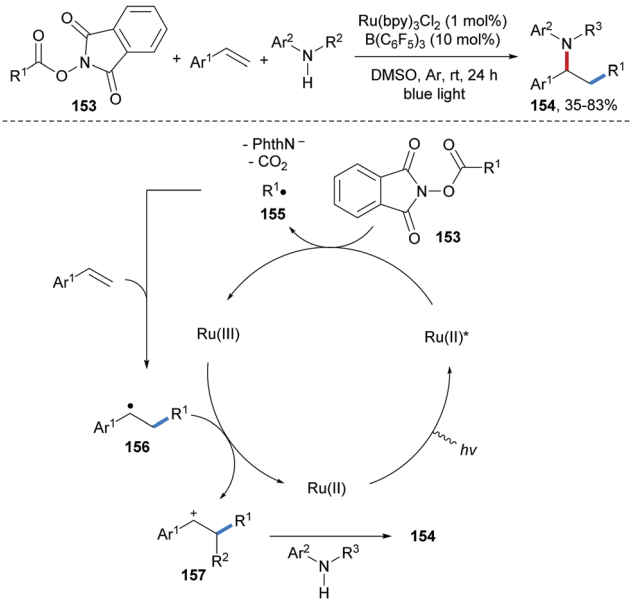
Scheme 33 Succinimide-catalyzed radical malonylamination of alkenes.

noteworthy that upon using anilines and aliphatic amines as nucleophiles, *rac*-BINOL was required as an additive (**140**). The authors proposed that the photo-excited Cu(I)-complex **141** or **146** is capable of reducing the substrate halides to the corresponding C-radicals **142**. Subsequent radical addition of **142** to an alkene followed by Cu(II) (**143** or **147**) mediated radical C–N bond formation affords the desired carboamination product thereby regenerating the Cu(I)-species. The radical nature of this cascade was supported by radical clock experiments.

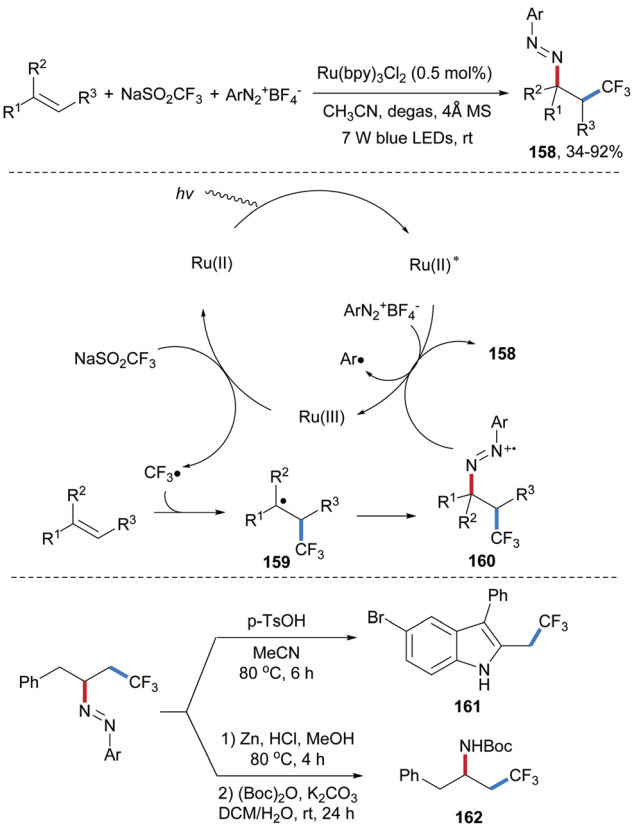
An efficient method for radical alkene malonylamination with amines and iodonium ylides **148** was recently disclosed by Wang and co-workers (Scheme 33).[92] A catalytic amount of succinimide was used as a "proton shuttle" to conduct the radical cascade and the interesting transformation proceeds in the absence of any transition-metal catalyst. Diverse unactivated alkenes and enamides qualify as radical acceptors and the malonyl radical is generated from **148** through electron-transfer. Primary and secondary anilines were used as aminating reagents to afford the γ-amino acid derivatives **149** in low to high yields. Halogen bonding between iodonium ylide **148** and the amine component leads to a complex that undergoes intramolecular SET to generate an ammonium radical cation and the iodanyl radical anion **150**. Protonation of **150** by succinimide gives the neutral iodanyl radical **151**, which undergoes fragmentation to the malonyl radical and iodobenzene. Radical addition of the malonyl radical to an alkene generates an alkyl radical which is trapped by the ammonium radical cation to give the ammonium salt **152**. Deprotonation of **152** by the succinimide anion eventually provides the desired carboamination product **149** and succinimide is regenerated.

Photoredox catalyzed carboamination of aryl alkenes with alkyl *N*-hydroxyphthalimide esters **153** and anilines was reported by Li and co-workers (Scheme 34).[93] In the presence of $B(C_6H_5)_3$ as a Lewis acid, single electron reduction of **153** by a photo-excited Ru(II)-complex provides the corresponding C-radical **155**, which gets trapped by an alkene to give the adduct radical **156**. The Ru(III)-complex generated in the initial oxidative quenching of Ru(II)* then oxidizes **156** to the benzylic cation **157**, which is trapped by an aniline to afford the final aminoalkylation product **154** in moderate to good yield.

Three-component radical aminotrifluoromethylation of unactivated alkenes with aryldiazonium salts and sodium triflinate was disclosed by the Xiao group (Scheme 35).[94] A Ru(II)-complex is irradiated to give excited Ru(II)*, which is oxidatively quenched by an aryldiazonium salt to give the corresponding Ru(III)-complex. The Ru(III)-species in turn oxidizes sodium triflinate to give after SO_2-fragmentation a trifluoromethyl radical, which adds to an alkene to provide the adduct radical **159** that gets trapped by an aryldiazonium salt to provide the azo radical cation **160**. The isolated diazene product **158** obtained in



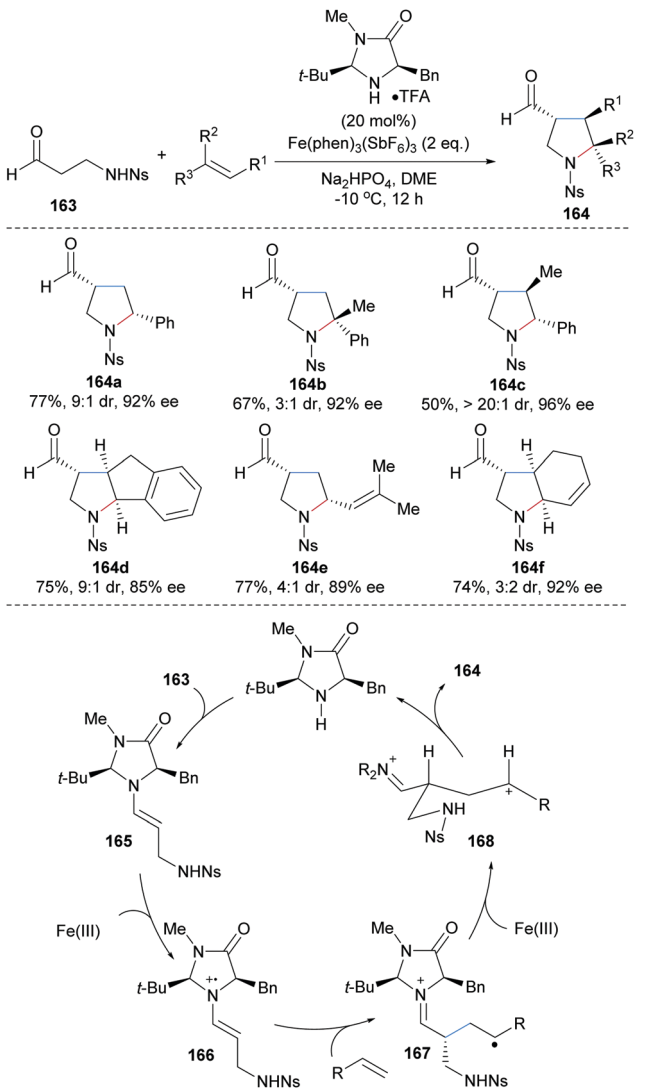
Scheme 34 Three-component alkylamination of styrenes with alkyl *N*-hydroxyphthalimide esters and amines.



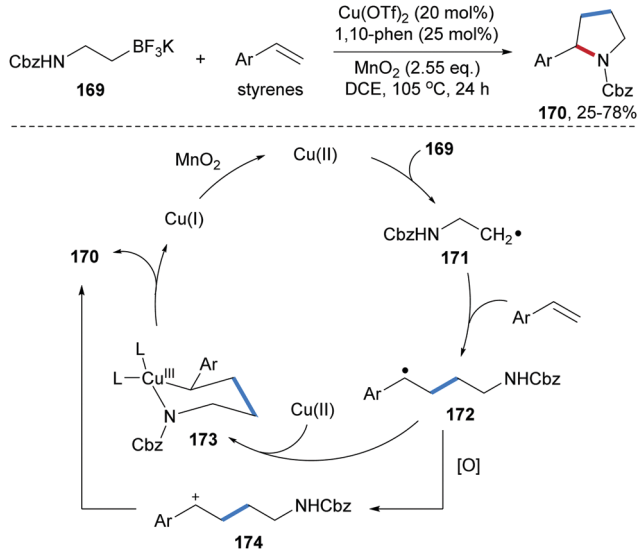
Scheme 35 Azotrifluoromethylation of alkenes with aryldiazonium salts and sodium triflinate.

moderate to very good yield results through single-electron reduction of **160** by the photo-excited Ru(II)-complex closing the redox catalysis cycle. Noteworthy, the product diazenes are readily transferred to indoles **161** and amides **162** illustrating the synthetic potential of the method. It should be pointed out that an Ag/H_2O_2-mediated radical cascade comprising alkenes, aryldiazonium salts and sodium triflinate as reaction partners to afford indoles was reported by the Antonchick group, in which diazo compounds of type **160** were also suggested as intermediates.[95]

The MacMillan group reported an enantioselective 3+2 coupling of the N-protected β-amino aldehyde **163** and various activated alkenes to access multi-substituted pyrrolidines **164** with moderate to high diastereoselectivity and high enantioselectivity (Scheme 36).[96] Styrenes (**164a–d**), conjugated linear (**164d**) and cyclic (**164e**) dienes engage in the cascade to provide the desired pyrrolidines **164** with high efficiency. Mechanistically, the enamine **165** generated through condensation of **163** and the MacMillan catalyst undergoes single electron oxidation by Fe(III) to generate a radical cation intermediate **166**. Stereoselective addition of **166** to an activated alkene leads to the distonic radical cation **167**. Single electron oxidation of **167** by



Scheme 36 Enantioselective radical alkene carboamination for the preparation of pyrrolidines.



Scheme 37 Cu-Catalyzed radical carboamination of alkenes with potassium β-aminoethyl trifluoroborates for the preparation of pyrrolidines.

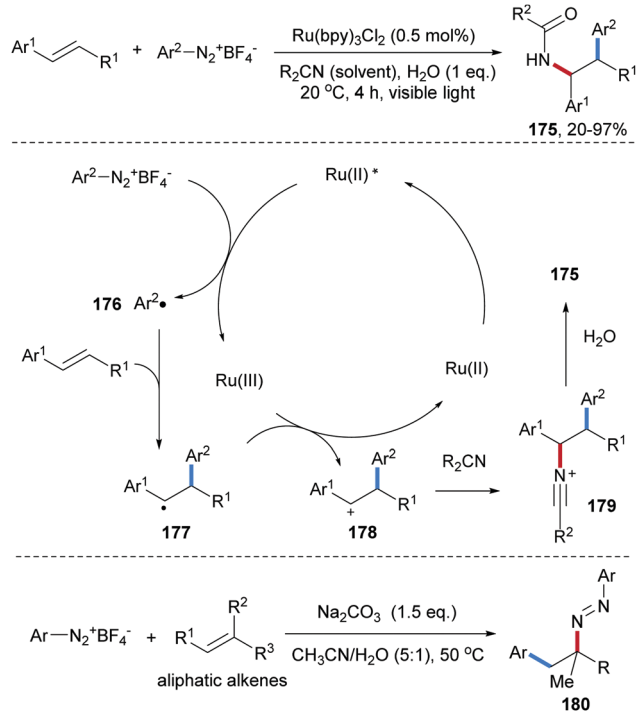
Fe(III) generates the corresponding benzylic or allylic cation **168**, which undergoes cyclization to provide after iminium ion hydrolysis the functionalized pyrrolidine **164**.

Chemler and co-workers developed an efficient method for the preparation of pyrrolidines **170** through Cu-catalyzed radical coupling of alkenes with potassium *N*-carbamoyl-β-aminoethyltrifluoroborates **169** (Scheme 37).[97] Single electron oxidation of the trifluoroborate **169** by Cu(II) produces the corresponding C-radical **171**, which reacts with an alkene to provide the adduct radical **172**. Trapping of **172** by the Cu(II)-complex and ligand exchange afford the Cu(III) species **173** which undergoes reductive elimination to give the desired pyrrolidine **170**. Alternatively, single-electron oxidation of **172** by Cu(II) leads to the cation **174** which directly cyclizes to afford **170**.

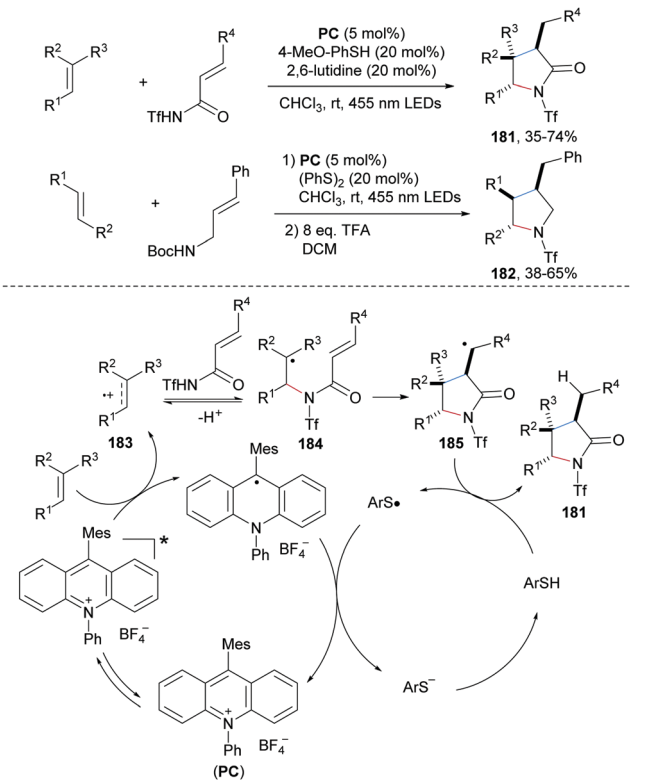
A photoredox-catalyzed Meerwein addition with styrenes as acceptors and subsequent Ritter type amidation was reported by the König group (Scheme 38).[98] An aryl diazonium salt is first reduced by the photo-excited Ru(II)-complex to generate an aryl radical **176**. Intermolecular radical addition of **176** to an alkene provides the corresponding adduct C-radical **177** which gets oxidized by the Ru(III)-complex to generate a carbon cation **178** along with the Ru(II)-catalyst. By using alkyl nitriles as the solvent, Ritter amidation *via* **179** is achieved to eventually give the amidoarylation product **175** in moderate to high yield. Later, a transition metal free protocol for Meerwein-type aminoarylation was disclosed by Heinrich and co-workers, in which the diazonium salt is used as aryl radical precursor and also as a radical amination reagent to afford a β-aryl diazene **180** as the final product.[99]

4. Carboamination by oxidation of alkenes

The Nicewicz group reported a photoredox and thiol co-catalyzed carboamination of readily oxidizable electron-rich alkenes with α,β-unsaturated amides to provide γ-lactams **181** with good steroselectivity in moderate to good yields (Scheme 39).[100]



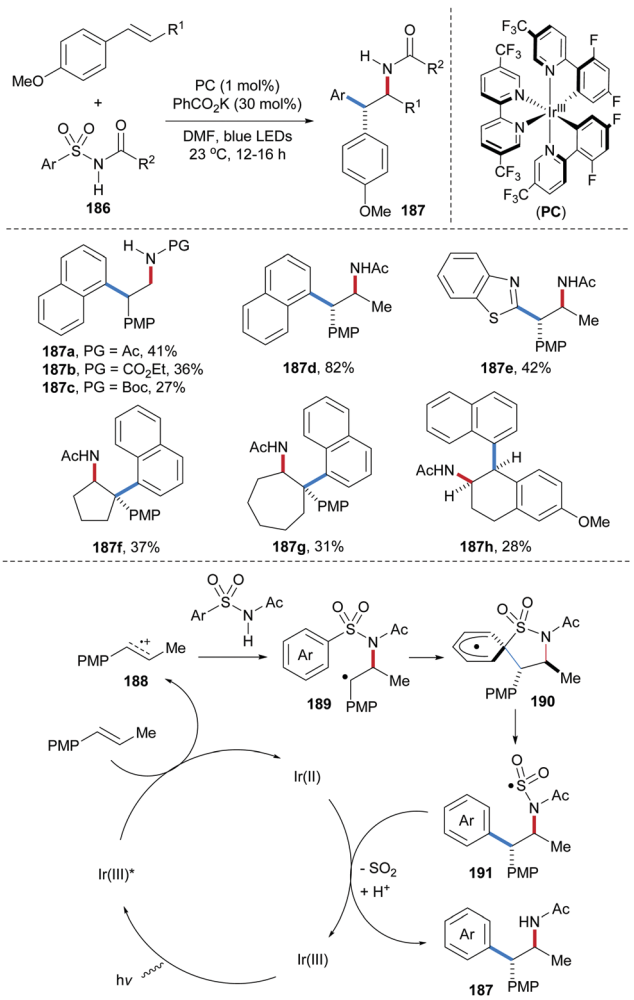
Scheme 38 Photoredox-catalyzed Meerwein addition and subsequent Ritter reaction and transition metal free alkene aminoarylation.



Scheme 39 Alkene carboamination through polar radical crossover cycloaddition.

N-Bocylated cinnamyl amine also engages in this cascade to afford multi-substituted pyrrolidines **182** with good diastereoselectivity. The proposed mechanism starts by single-electron oxidation of the electron-rich alkene by the photo-excited acridinium salt to give the alkene radical cation **183** and the reduced acridine radical. Nucleophilic addition of an unsaturated amide to **183** leads after deprotonation to the C-radical **184**, which undergoes 5-exo-cyclization to the C-radical **185**. Reduction of **185** by thiophenol affords the desired γ-lactam **181** and a thiyl radical. The redox catalysis cycle gets closed by SET reduction of the thiyl radical with the acridine radical.

An elegant photoredox catalyzed aminoarylation of electron-rich styrenes with *N*-arylsulfonyl-acetamides **186** was developed by the Stephenson group (Scheme 40).[101] In the presence of a photoredox catalyst, the arylsulfonylacetamides serve as bifunctional reagents to add across an alkene to form structurally useful β-diaryl amides of type **187**. Noteworthy, internal alkenes provide *cis* addition and targeted amides were formed with excellent diasteroselectivity (**187d–h**). Considering the mechanism, single-electron oxidation of the electron-rich alkene by a photo-excited Ir(III)-complex provides radical cation **188**, which undergoes nucleophilic trapping by the arylsulfonylacetamide **186** to give the benzylic radical **189**. 1,4-Radical aryl migration from sulfur to the benzylic radical *via* cyclohexadienyl radical **190** leads to the translocated S-radical **191**. Reduction of **191** by the Ir(II)-complex and SO_2-fragmenation eventually afford the isolated carboamidation product **187**.



Scheme 40 Alkene aminoarylation by using *N*-arylsulfonylacetamides as bifunctional reagents.

5. Summary and outlook

In this review different approaches to conduct intermolecular radical alkene carboamination have been discussed. Considering non-radical alkene carboaminations, the radical processes nicely complement these methods and accordingly have been successfully used for the preparation of various valuable amine derivatives. Such radical cascades can be conducted following three different reaction modes: (a) by an N-radical adding to an alkene, (b) by a C-radical adding to an alkene or (c) by oxidation of an alkene with subsequent nucleophilic amination. Considering the first approach, readily accessed oxime derivatives, N-halo compounds, *N*-pyridinium salts and $TMSN_3$ have been used as N-radical precursors, providing the corresponding N-radicals or the azidyl radical through a single-electron transfer pathway or *via* homolytic cleavage of a weak covalent bond. Focusing on the second reaction mode, various C-radical precursors have been implemented in alkene carboaminations in combination with various amination reagents. In many of these processes, single electron reduction and oxidation steps are involved and consequently radical carboamination is often conducted with the help of a redox catalyst. In the ideal case, the overall sequence is a redox neutral process improving economy of the cascade.

In both strategies (a and b), formation of the second σ-bond can proceed *via* a free radical addition reaction. Alternatively, the C-radical resulting from N- or C-radical addition to the alkene can be oxidized to the corresponding carbenium ion that can eventually be trapped by C- or N-type nucleophiles. Both, the radical trapping and also the ionic pathway are difficult to run enantioselectively. Considering this great challenge, C-radical trapping can also be catalyzed by a transition metal in a so-called radical/transition metal cross-over process. This has been well documented for C–C bond formation and also for C–N bond formation mainly using Cu-catalysis. As advantage of this latter cross-over strategy, enantioselective trapping is feasible and indeed has been realized in few cases. In particular, in this area we see great potential and future activities of this emerging field.

Carboamination *via* alkene radical cations according to reaction mode (c) is underdeveloped. This is mainly due to the fact that alkene single electron oxidation is currently restricted to electron-rich activated alkenes. This problem has to be solved and then this strategy will gain further importance.

By looking at radical alkene carboamination more generally, the full potential of radical chemistry has to be harnessed in future in particular considering the mild reaction conditions mostly used to run such radical cascades. This ensures high functional group tolerance and radical carboamination should

be well applicable to very complex alkenes at a late stage of the synthesis. Therefore, we expect the novel methodologies to be applied more often in complex natural product synthesis.

Conflicts of interest

There are no conflicts to declare.

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