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Intermolecular 1,2-difunctionalization of alkenes

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Alkenes are an important class of organic compounds with a carbon–carbon double bond and a wide range of industrial and natural sources. The presence of π bonds provides the possibility for many forms of transformations. The direct difunctionalization of olefins can continuously introduce two identical or different groups into the olefin molecule at one time, while achieving a rapid increase in molecular complexity, and it also gives the organic compound potential or specific application value. In general, olefin difunctionalization can be achieved *via* three different reaction modes. Firstly, metal species can add double bonds by employing transition metals; further coupling can then be followed to complete the difunctionalization. Another intriguing approach is that radicals add to the olefins and then are quenched in diverse ways. The ability to continuously introduce diverse functional groups is the most significant feature of this platform. The third mode is that the olefin is transformed into a cationic radical or anionic radical intermediate through single-electron transfer. This strategy is less developed and more novel, but has certain limitations. Driven by the innovation of synthetic chemistry strategies, the difunctionalization of olefins, which was previously difficult to achieve, has also been gradually achieved. This review updates the latest progress in the 1,2-difunctionalization of olefins in the past five years. We aim to classify reaction mechanisms and functional group types. It should be stated that reactions with olefin double bonds to form rings are not included here.

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1. Introduction

Alkenes are a class of hydrocarbons containing a carbon–carbon double bond.[1] They have some unique physical and chemical properties. Taking an alkene containing one double bond as an example, the carbon of the double bond is sp^2 hybridized, and the three sp^2 hybrid orbitals are in the same plane. The p-orbital that does not participate in the hybridization is perpendicular to the plane. The two carbon atoms of the

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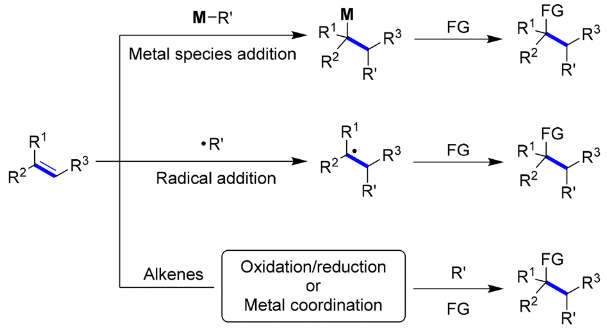

Scheme 1 Strategies to achieve 1,2-difunctionalization of olefins.

double bond each uses an sp^2 hybrid orbital to form a σ bond through axial overlap and a p-orbital to form a π bond through lateral overlap. The carbon–carbon double bond is composed of a σ bond and a π bond. The average bond energy of the C=C bond is 610.9 kJ mol^{-1}, and that of the C–C σ bond is 347.3 kJ mol^{-1}, so the bond energy of the π bond is about 263.6 kJ mol^{-1}. Therefore, the π bond is easier to open than the σ bond; the π electrons are diffused outside and are easily attacked by electrophilic reagents, so olefins are prone to electrophilic addition and radical addition reactions.[2] Owing to their ready availability and ease of continuous introduction of functional groups, olefins have become excellent precursors for constructing diverse frameworks and increasing molecular complexity. In particular, the orderly construction of two different chemical bonds with double bonds of olefins is a very efficient synthetic strategy that has long attracted attention from the chemical community (Scheme 1).[3]

When it comes to the difunctionalization of olefins, two key aspects are of particular concern. First, which types of functional groups are feasible to be introduced? Second, in a specific context, how to choose the desired functional groups in a particular sequence so that they can be installed from the double bond.[4] Considering the importance of the reaction mechanism, the contents of this review are mainly categorized into three different classes: (i) difunctionalization initiated by the addition of metal species to the double bond of alkenes; (ii) difunctionalization initiated by the addition of radical species to the double bond of alkenes; and (iii) the oxidation or reduction of alkenes, and the addition after metal coordination. Among these three types, the active intermediates involved in opening the π bond have their own characteristics. Obviously, these three methods have their own advantages and disadvantages in practical comparison. They can complement each other well and provide an overall broad scope for the difunctionalization of target olefins.[5]

The addition of the organometallic species to alkenes has also been one of the interesting research fields recently.[6] Its main reactions mainly consist of three processes: (i) the formation of organometallic species typically occurs *via* transmetalation or two-electron oxidation; (ii) the organometallic species can undergo migratory insertion across the double bond of alkenes. Additionally, the selectivity of the addition of alkenes can be controlled by ligands or other factors; and

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Xiao-Feng Wu

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(iii) the quenching of newly formed metal species is a crucial step that encompasses multiple pathways. These include electrophilic quenching, a sequence of oxidative addition through a SET process followed by reductive elimination with electrophilic reagents, and transmetalation, among other possible reactions.[7] These reactions mainly consist of boryl difunctionalization and aryl difunctionalization of alkenes.

Radical-mediated olefin difunctionalization shows diverse reactivity and efficiently builds two chemical bonds in one step, which has become an important means of alkene conversion.[7] However, since radical reactions involve the stability and polarity effects of radical species, and olefin functionalization usually involves multiple radical intermediates, this increases the complexity of the reaction system.[8] Therefore, exploring new reaction modes and achieving controllable, green, and efficient radical difunctionalization of alkenes have become the most popular research hotspot in recent years. In different systems, the addition of radicals to alkenes produces new alkyl radicals, which can then be difunctionalized through intramolecular group migration, radical coupling, redox quenching, transition metal-mediated cross-coupling, atom transfer functionalization, *etc.*[9]

One-electron oxidation or reduction of the carbon–carbon double bond can generate alkene radical cations and alkene radical anions, respectively.[10] They are the potent species for the vicinal difunctionalization of alkenes through an ionic/radical cross-over strategy. This is the third mode to achieve difunctionalization of alkenes. The key step in such reactions is the single-electron transfer (SET) of the double bond, which generates an alkene radical ion. This ion then reacts with a nucleophile or an electrophile to form a β-functionalized alkyl radical. Subsequent bond formation by the newly generated radical completes the incorporation of the difunctional group. Although the examples of single-electron transfer reactions of olefins are relatively limited compared to the two strategies mentioned above, it is necessary and valuable to pay attention to this emerging field given its rapid development and potential advantages.

This review article will focus on the research progress of intermolecular difunctionalization of olefins in the past five years, from 2020 to 2024, excluding cyclization reactions involving olefins. Emphasis will be placed on reaction mechanisms, classification of functional groups, and applicability.

2. Metal species addition

2.1 Metal–boron species addition

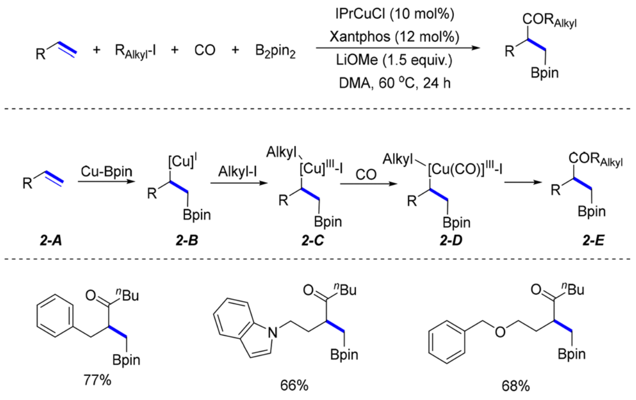
2.1.1 Cu–Bpin species. Boronic acid esters and borates are privileged functional groups in synthetic chemistry because of their stability in air and moisture.[11] Additionally, organoboron compounds are valuable synthetic intermediates in organic chemistry because of their robust abilities for further transformations to diverse functionalized compounds, such as vinylation, reduction, halogenation, oxidation, and Suzuki–Miyaura cross-coupling reaction *via* palladium catalysis.[12]

In 2020, the borofunctionalization of alkene and borocarbonylative coupling reactions of alkynes have been well established,[13] but the transformation of unactivated alkenes with alkyl halides remained a challenge. In the context of this background, Wu's group developed a Cu-catalyzed borocarbonylative coupling of unactivated alkenes with alkyl halides for the preparation of β-boryl ketones. As described in Scheme 3, the Cu–Bpin species inserts into the C=C bond to give **2-B**, which then reacts with alkyl halide to generate copper(III) complexes **2-C**. Subsequently, CO coordinates with a copper catalyst and inserts into the C–Cu bond to yield **2-D**, finally, **2-E** will be formed after reductive elimination. This reaction represents the first example of borocarbonylative coupling with alkene and provides a pioneering direction for subsequent development (Scheme 2).[14]

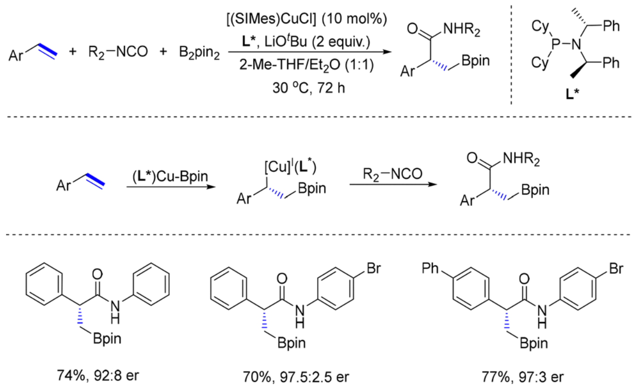
In 2020, in the context of nickel-catalyzed or rhodium-catalyzed cross-coupling between isocyanates and alkene, Mazet and co-workers elucidated a copper-catalyzed borylative carboxamidation reaction. An enantioselective variant of this transformation was developed by using a chiral phosphanamine ligand, providing a series of α-chiral amides with high enantioselectivity. The further synthetic utility of this method was demonstrated through different representative stereoretentive postcatalytic derivatizations (Scheme 3).[15]

In 2020, Wu and co-workers developed a general four-component carbonylative procedure for the synthesis of β-boryl ketones and β-boryl vinyl esters. Borocarbonylative reactions between vinylarenes, aryl halides/triflates, B_2Pin_2, and CO proceed successfully by palladium and copper co-catalysis. In the mechanism aspect, complexes **4-A** undergo transmetalation with **4-E** to obtain the β-boryl ketones. It is worth noting that **4-A** can also capture CO to give acylcopper intermediate **4-B**, which could isomerize to carbene intermediate **4-C**. Subsequently, the intermediate **4-C** undergoes α C–H bond insertion to yield the vinyl alkoxide copper species **4-D**. Transmetalation between **4-D** and acyl palladium **4-E** is followed by reductive elimination to afford the final β-boryl vinyl ester (Scheme 4). This work presents a novel example of converting carbon monoxide into carbene species (Scheme 4).[16]

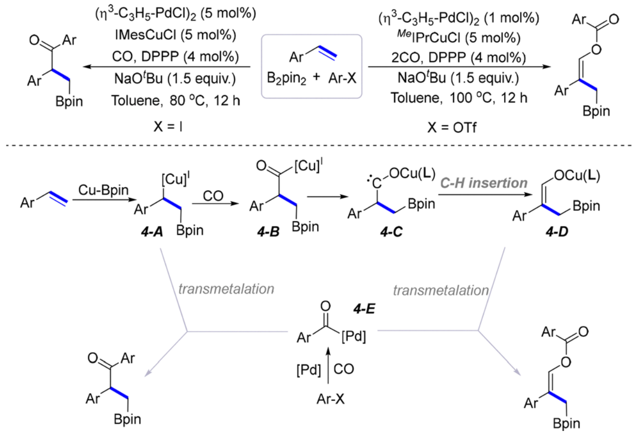
In 2022, Wu's group delineated a representative powerful approach for achieving two molecules of CO toward the



Scheme 2 Copper-catalyzed borocarbonylative coupling of unactivated alkenes with alkyl halides.



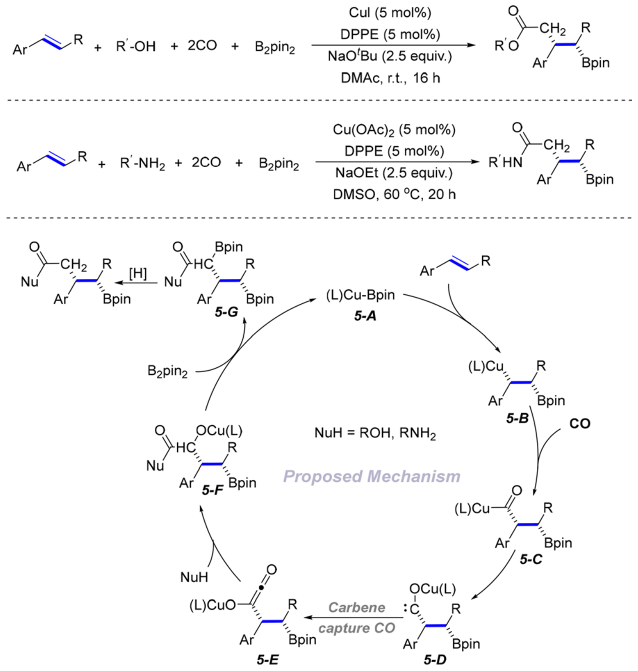
Scheme 3 Copper-catalyzed borylative carboxamidation of vinylarenes with isocyanates.



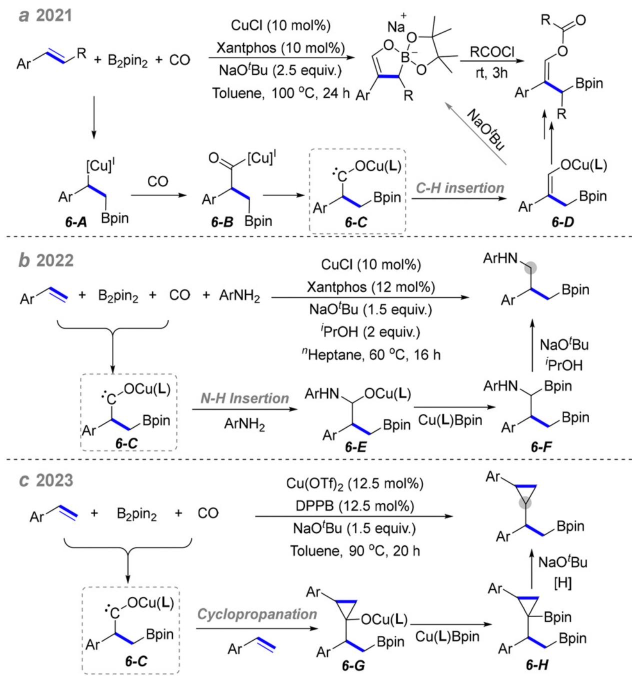
Scheme 4 Four-component borocarbonylation of aromatic alkenes enabled by Cu/Pd co-catalysis.

–CH$_2$CO– structure source. The author proposed a reasonable mechanism as depicted in Scheme 5, carbon monoxide inserted into the C–Cu bond of intermediate **5-B** to yield intermediate **5-C**, which would isomerize to carbene intermediate **5-D**. The key to this transformation is that CO was captured by carbene species to form ketene intermediate **5-D**, which is attacked by nucleophiles like amines or alcohols, borylation and protonation to obtain the corresponding products (Scheme 5).[17]

Subsequently, Wu and co-workers have developed versatile methods in which the carbene intermediates were quenched, giving several novel examples of 1,2-difunctionalization of alkenes. In 2021, the author found sodium cyclic borate intermediates from styrenes, B$_2$pin$_2$, carbon monoxide, and NaO^{t}Bu by copper catalysis, which were analyzed *via* ^{11}B NMR spectroscopy and post-treatment. The reaction not only serves as an attractive route towards various cyclic borates, but also verifies the reaction mechanism in which the carbene intermediate **6-C** inserts into the C–H bond to give intermediate **6-D** (Scheme 6a).[18] Then, a copper-catalyzed boroaminomethylation of aromatic alkenes using CO as the –CH$_2$– structural unit was developed in 2022. The author designed several strict and reasonable control experiments to prove the reaction mechanism in which the carbene intermediate **6-C** inserts into the N–H bond to achieve this process, such as ^{13}C-labelling experiments, deuterium experiments, and intermediate verification. On the other hand, various γ-boryl amines were prepared in moderate to good yields with good functional groups. The author transformed them into value-added compounds



Scheme 5 Copper-catalyzed carbonylative catenation of olefins (carbene species capture CO).



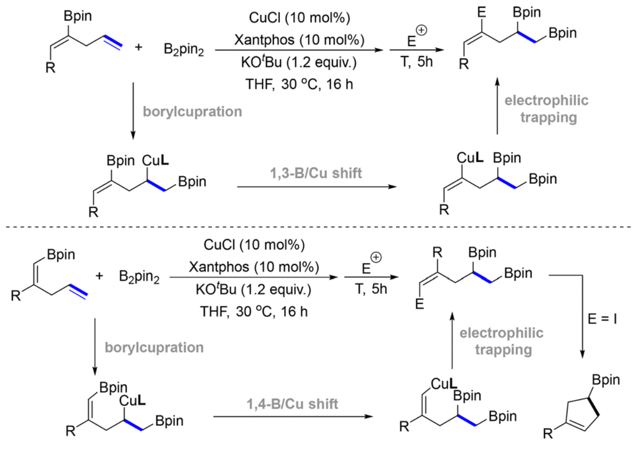
Scheme 6 Copper-catalyzed carbonylative catenation of aryl alkenes.

like quinolones and ^{13}C-labeled compounds (Scheme 6b).[19] Subsequently, Wu's group also described a copper-catalyzed boryl difunctionalization of aromatic alkenes towards cyclopropane derivatives. This reaction outlined a carbene intermediate **6-C** captured aryl olefin, which was tested by ^{13}C-labelling experiments. It provides an interesting route for the synthesis of various cyclopropane derivatives (Scheme 6c).[20]

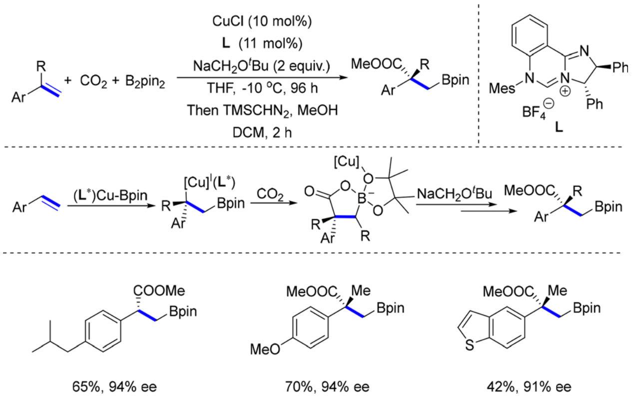
In 2023, Fernández and coworkers developed two interesting transformations of diborylation of designed olefins by 1,3-B/Cu shift and 1,4-B/Cu shift.[21] These two migration reactions occur around the alkenes with stereospecificity, contributing to the subsequent stereoselective electrophilic quenching by *in situ* addition of H^+, I_2, NBS, *etc.* The authors described that the 1,3-B/Cu shift and 1,4-B/Cu shift both occur *via* nucleophilic attack of the copper-alkyl moiety on the boron atom bonded, leading to 4-membered boracycle and 5-membered boracycle structures by DFT calculation analysis. These two reactions provide a novel boryl-functionalization of alkenes for the synthesis of diverse 1,2-bis (boryl) compounds by a migration strategy (Scheme 7).

In 2024, the enantioselective boracarboxylation of aromatic olefins with diboron and 1 atm of carbon dioxide was reported for the first time by Tang and co-workers. Despite the fact that boracarboxylation of alkenes and alkynes has been well-established in the past few decades, it remained a formidable challenge to achieve the asymmetric transformation. This work showcases a copper-catalyzed boracarboxylation with excellent enantioselectivity utilizing chiral NHC ligand **L** at low temperature. It was noteworthy that enantioenriched carboxylic acids with α-chiral all-carbon quaternary centers were prepared in good yields. The construction of three drugs verified the practicality of this boracarboxylation of alkenes (Scheme 8).[22]

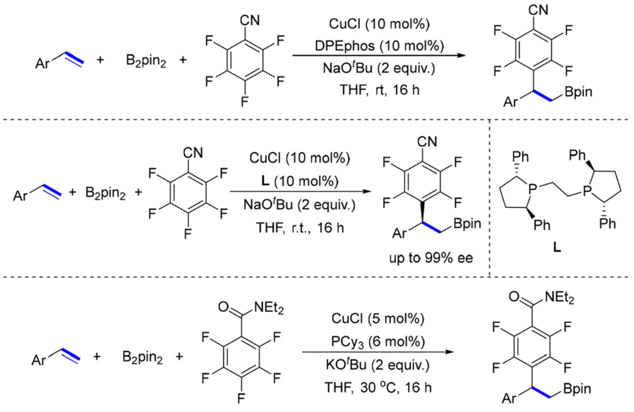
In 2023, a copper-catalyzed defluorinative arylboration was described by Wu and co-workers. The transformation provides a direct approach for the synthesis of β-polyfluoroaryl boronates with good functional group tolerance. Notably, by using **L** as the ligand, a defluorinative arylboration was also achieved with good enantioselectivity.[23a] In the same year, Zhang's group reported a similar example, which provides a range of valuable Bpin-containing polyfluoroarenes (Scheme 9).[23b]



Scheme 7 Copper-catalyzed diborylation of alkenes by B/Cu 1,3-rearrangement or 1,4-rearrangement.



Scheme 8 Copper-catalyzed regio- and enantioselective boracarboxylation of aryl alkenes.

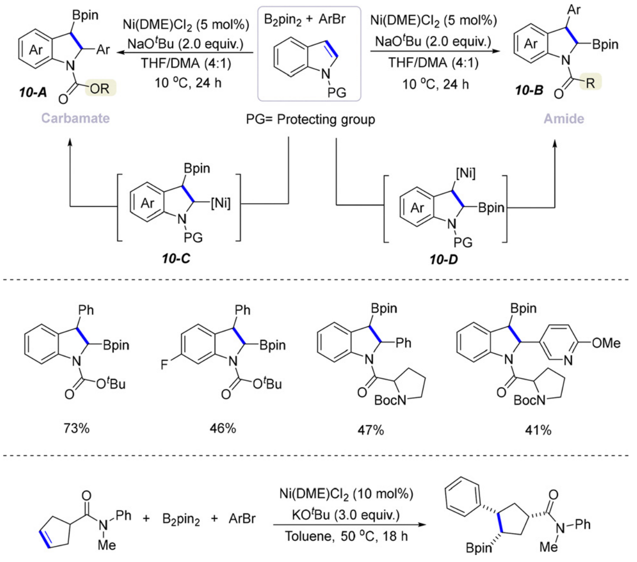


Scheme 9 Copper-catalyzed defluorinative arylboration of aryl alkenes with polyfluoroarenes.

2.1.2 Ni–Bpin species.

In 2021, Brown's group reported an interesting nickel-catalyzed regioselective dearomative arylboration of indoles toward two types of indolines, which were controlled by two protecting groups. Compounds **10-A** were obtained when using the alkoxylcarbonyl group as a protecting group, while compounds **10-B** were prepared when employing the acyl group as a protecting group. Synthetically useful C2- and C3-borylated indolines were obtained with good functional group compatibility through a simple change in the *N*-protecting group from readily available starting materials. The author explored factors like electronics of the C2–C3 π-bond and sterics *via* DFT calculation. Furthermore, this arylboration of indoles enabled the first enantioselective construction of (−)-azamedicarpin, which is a bioactive compound that has shown good activity against leukemia cell lines and inhibition of bacterial growth (Scheme 10).[24a] In the same year, this group also designed an amide-directed diastereoselective arylboration of cyclopentenes by nickel catalysis.[24b]

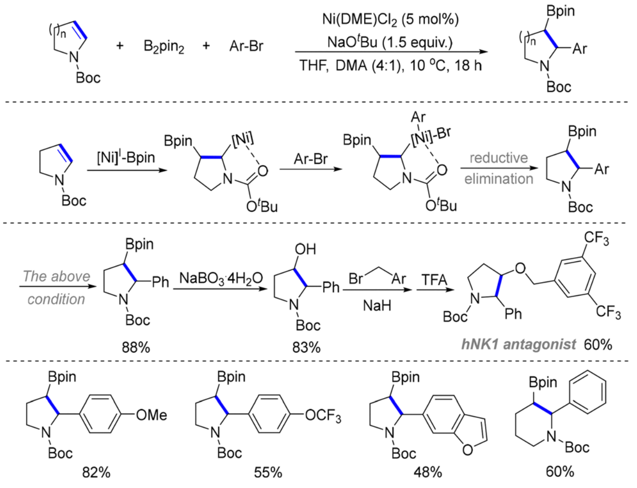
In 2022, the same group developed an efficient arylboration of endocyclic enecarbamates of ring sizes 5–7 for the rapid synthesis of diverse borylated saturated N-heterocycles. This reaction was



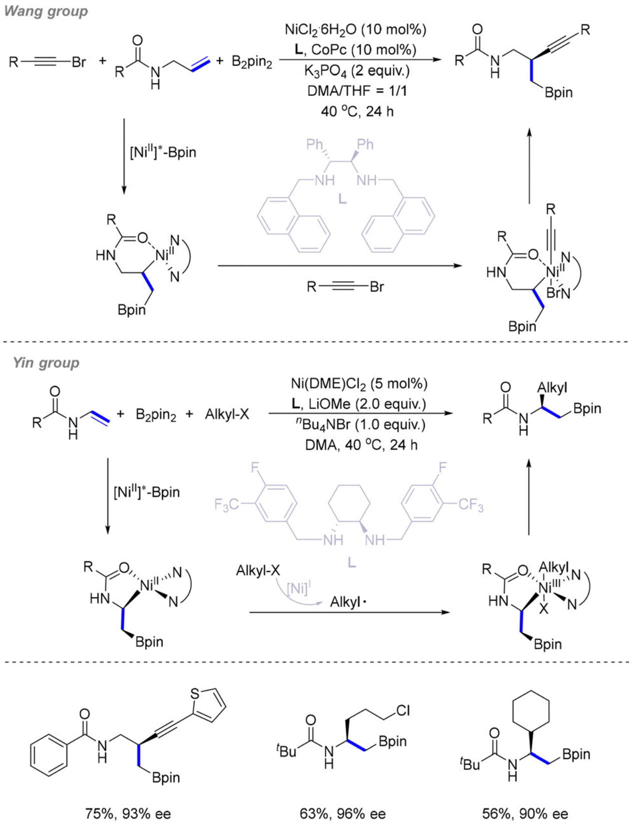
Scheme 10 Nickel-catalyzed regioselective arylboration of indoles.

amenable to scale-up under mild reaction conditions. Additionally, the synthetic versatility of the arylboration products was also demonstrated, as they can be converted to high-value-added drug molecules in short steps. This arylboration of endocyclic enecarbamates provides a rapid and efficient way for the preparation of drugs, which verifies the importance of borylfunctionalization of alkenes (Scheme 11).[25]

In 2024, Wang's group and Yin's group introduced two unprecedented nickel-catalyzed asymmetric boryl functionalization transformations of alkenes, using chiral diamines as ligands, inexpensive B$_2$pin$_2$ and organic halides as coupling partners. By using diverse carbonyl directing groups, including amides, sulfinamides, ketones, and esters, Wang's group achieved nickel-catalyzed 1,2-borylalkynylation of unactivated alkenes to enable the incorporation of a C(sp)-fragment and a boron unit across the double bond. The key to this transformation with high regioselectivity and enantioselectivity is the utilization of bulky diamine ligand **L**.[26] In the same year, Yin's group established an efficient platform towards a range of valuable chiral β-aminoboronates from simple enamides, alkyl bromides, and B$_2$pin$_2$. DFT calculations explained that the benzyl group on the ligand is crucial to the high enantioselectivity.[27] Overall, these two boryl functionalization transformations enrich the toolbox of asymmetric catalysis and provide versatile chiral boron compounds, which would be beneficial for drug discovery (Scheme 12).



Scheme 11 Nickel-catalyzed borocarbonylative coupling of endocyclic enecarbamates.

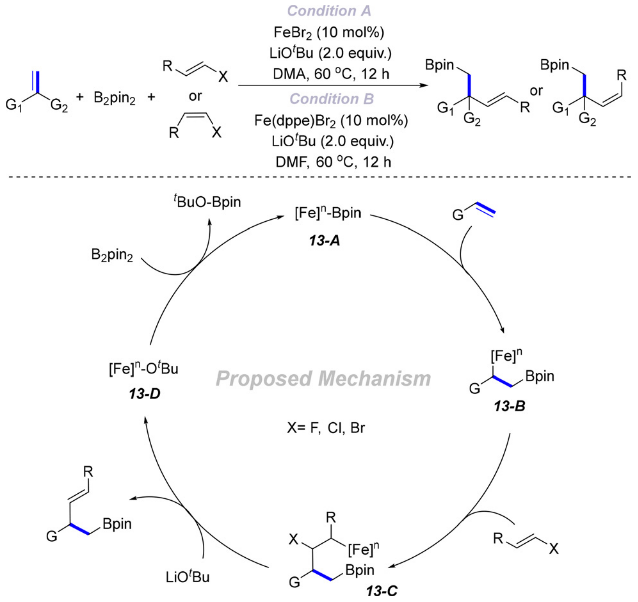


Scheme 12 Nickel-catalyzed asymmetric boryl functionalization of alkenes.

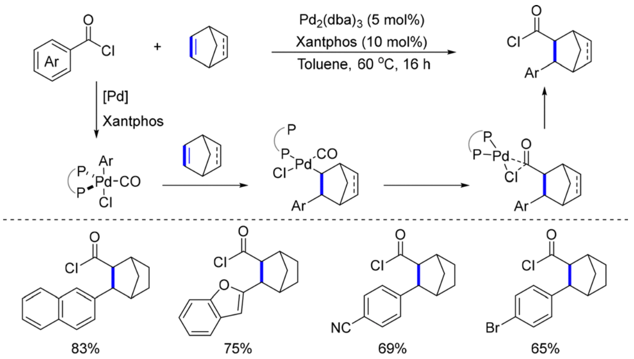
2.1.3 Fe–Bpin species. In 2021, an iron-catalyzed three-component synthesis of homoallylic boronates from simple B$_2$pin$_2$, an alkenyl halide (bromide, chloride, or fluoride), and olefins was developed for the first time. From the mechanism aspect, as shown in Scheme 13, iron–boryl species **13-A** adds to alkenes to afford intermediate **13-B**, and then association of the haloalkene π-bond with the iron center triggers a *syn*-selective carbometallation process to form intermediate **13-C**, which is susceptible to base-promoted *anti*-selective 1,2-elimination to give the alkenylboration product and generate intermediate **13-D**. Then, iron-alkoxide **13-D** was regenerated by B$_2$pin$_2$. This regioselective alkenylboration of unactivated alkenes provides us a novel reaction cycle by employing an inexpensive iron catalyst (Scheme 13).[28]

2.2 Metal–carbon species addition

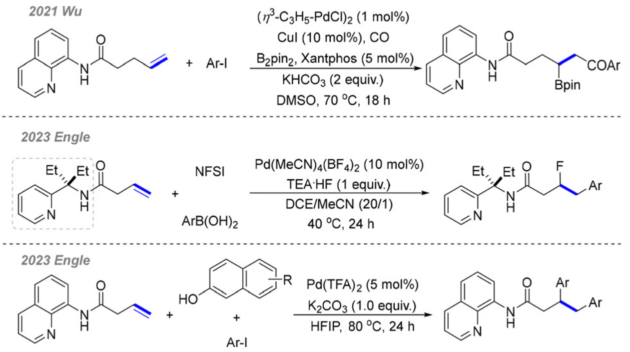
2.2.1 Palladium–carbon species. In 2021, Morandi and co-workers developed a novel difunctionalization strategy for



Scheme 13 Iron-catalyzed regioselective alkenylboration of unactivated alkenes.



Scheme 14 Palladium-catalyzed carbochlorocarbonylation of strained alkenes.



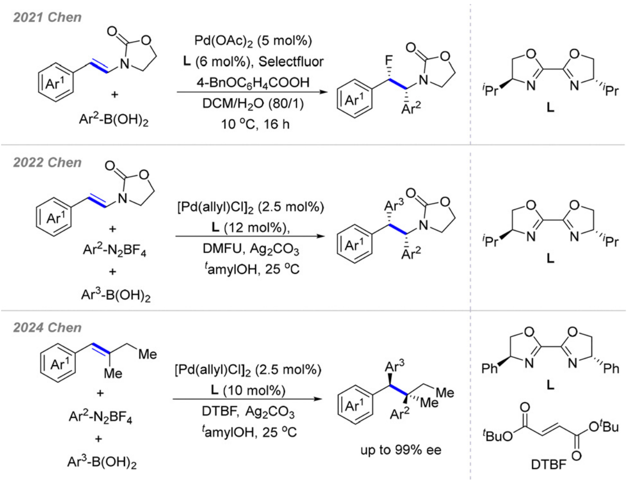
Scheme 15 Palladium-catalyzed difunctionalization of alkenes with different directing groups.

distinct olefins utilizing various acid chlorides. Remarkably, the C–COCl bond is broken and reacted across strained alkenes with high atom economy, leading to the formation of new acid chlorides. Mechanistic studies support a plausible reaction mechanism and offers insights into the reactivity and selectivity of the intermolecular transformation with norbornadiene (NBD) and norbornene (NBE), in line with experimental findings. This transformation represents a unique reaction paradigm, as the two functional groups introduced across the alkene originate from a single reagent (Scheme 14).[29]

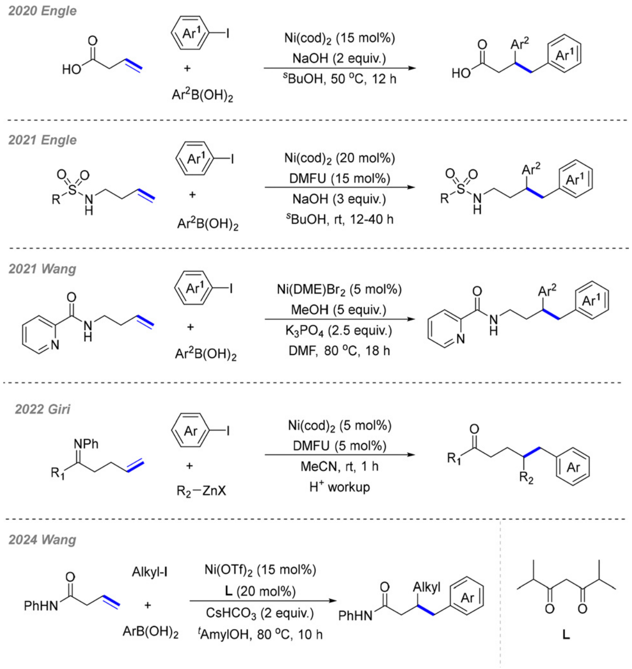
In 2021, in the context of Cu–Bpin addition to the alkenes to give terminal boron compounds, Wu and co-workers reported selectivity-reversed borocarbonylation of alkenes by Pd/Cu co-catalysis, which is assisted by 8-aminoquinoline (AQ) as a directing group.[30] In 2023, a 1,2-carbofluorination reaction of alkenes was developed by Engle's group.[31] The reaction data indicated that tuning of the steric environment on the bidentate directing auxiliary is important to this transformation. In the same year, Engle's group reported a dicarbofunctionalization of alkenes with 2-naphthol as a terminal reductant by utilizing AQ as a directing group (Scheme 15).[32]

In 2021, Chen and co-workers reported a highly enantioselective 1,2-arylfluorination of aromatic olefins, enabling the synthesis of β-fluorinated benzylamine derivatives. The high enantioselectivity was attributed to the use of a cleavable oxazolidinone auxiliary, which facilitated the migratory insertion step and stabilized the corresponding palladium intermediate.[33] Subsequently, the same group developed an asymmetric diarylation reaction of alkenes by using the same ligand **L**.[34] In 2024, Chen's group reported a palladium-catalyzed enantioselective diarylation of trisubstituted alkene to access the all-carbon quaternary containing vicinal stereocenters with high regio-, diastereo-, and enantioselectivity. Based on density functional theory (DFT) calculations, the ligand-swap strategy, employing a chiral bisoxazoline and an achiral fumarate, was found to accelerate the enantioselective migratory insertion and reductive elimination steps, respectively, in the cross-coupling process.[35] These asymmetric difunctionalizations of alkenes are interesting and elegant examples that generate a series of valuable enantioselective products (Scheme 16).[36]

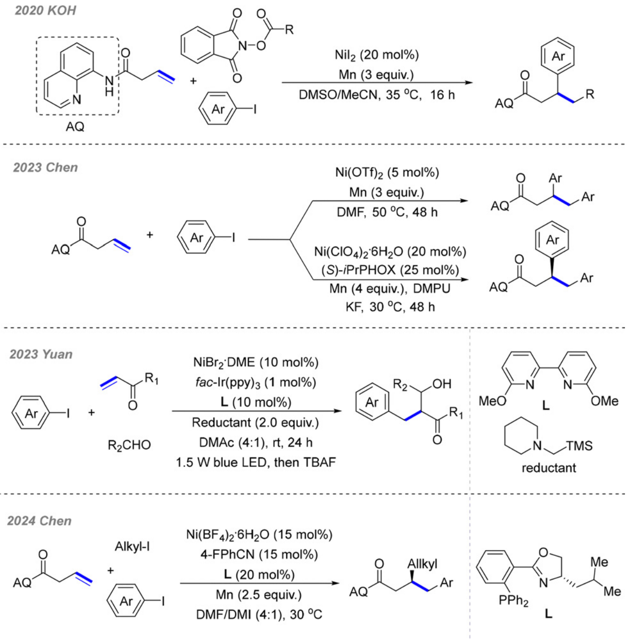
2.2.2 Nickel–carbon species. In 2020, the Engle group demonstrated that a carboxylate group can serve as a directing group to enable nickel-catalyzed 1,2-diarylation of alkenes using aryl iodides and aryl boronates in the absence of an external ligand. Furthermore, this article provides three alternative routes for the generation of bioactive molecules.[37] Then, the same group found that a 1,2-diarylation of diverse alkenyl amines was established when employing sulphonamide or ketone as directing groups in 2021.[38,39] In the same year, Wang and co-workers utilized picolinamide as a directing group to achieve 1,2-diarylation of olefins by nickel catalysis.[40] In 2022, Giri's group updated the nickel-catalyzed difunctionalization of alkenes by using primary and secondary alkylzinc reagents.[41] These reactions enriched the toolbox of diarylation and alkylarylation reactions of alkenes by a cheap nickel catalyst. In 2024, Wang's group developed an aryl-alkylation of unactivated alkenes by using a native functional group as the directing group. The key to this transformation is utilizing the bulky β-diketone ligand L_{13}, which can stabilize



Scheme 16 Palladium-catalyzed asymmetric difunctionalization of alkenes.



Scheme 17 Nickel-catalyzed difunctionalization of alkenes with aryl iodides and nucleophiles.



Scheme 18 Nickel-catalyzed difunctionalization of alkenes with two electrophiles under reductive conditions.

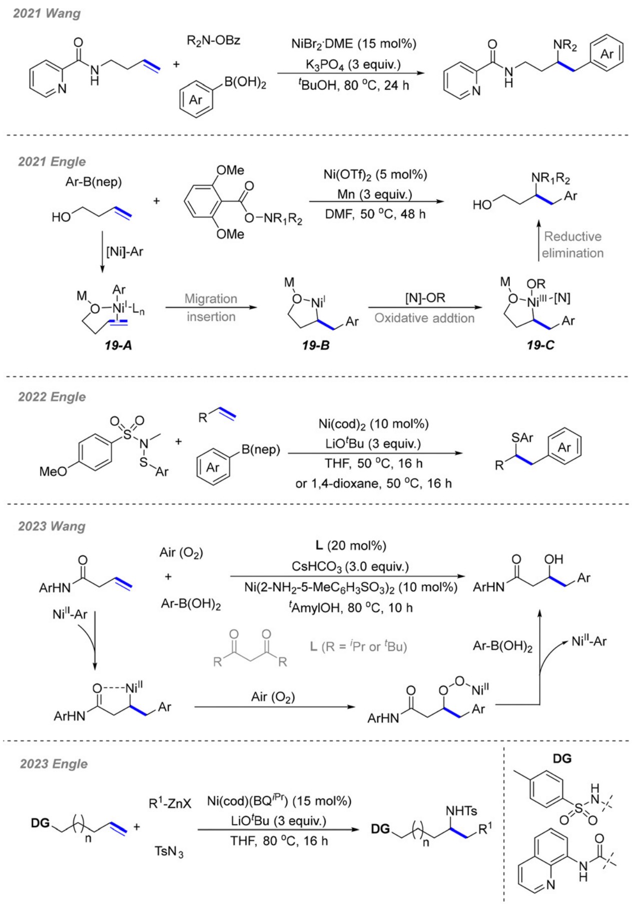
in situ formed alkyl-Ni(II) species and prevent homolytic cleavage (Scheme 17).[42]

Recently, transition-metal-catalyzed reductive difunctionalization of alkenes with two electrophiles is a popular and efficient method to construct two C–C bonds in a one-pot process. In 2020, Koh's group developed a directed nickel-catalyzed dialkylation of alkenes by using haloalkanes and aliphatic redox-active esters as reaction partners under reductive conditions. Interestingly, DFT studies delineate that the reaction selectivity originates from the orthogonal reactivity and chemoselectivity of *in situ* generated organonickel intermediates; the aliphatic redox-active esters have a better reactivity than alkyl halides in this transformation.[43a] Additionally, Wang's research group also reported similar examples.[43b] In 2023, a directed asymmetric reductive diarylation of alkenes by nickel catalysis was developed by Chen's group. The reaction features mild reductive conditions, wide substrate scope, and excellent diastereoselectivities.[44] In 2023, Yuan's group disclosed photo-induced nickel-catalyzed reductive cross-coupling of aromatic halides, aldehydes, and electron-deficient alkenes. The key to this reductive transformation is the utilization of the organic reductant α-silylamine.[45] In 2024, a highly regio- and enantioselective arylalkylation of olefins was uncovered by utilizing a radical relay strategy. This method features mild reductive reaction conditions, facile scale-up, downstream transformations of aimed products, and rapid and modular preparation of bioactive molecules.[46] These reductive cross couplings of alkenes with two electrophiles enrich the toolbox of construction of C–C bonds, providing a novel strategy for the synthesis of complicated and value-added compounds (Scheme 18).

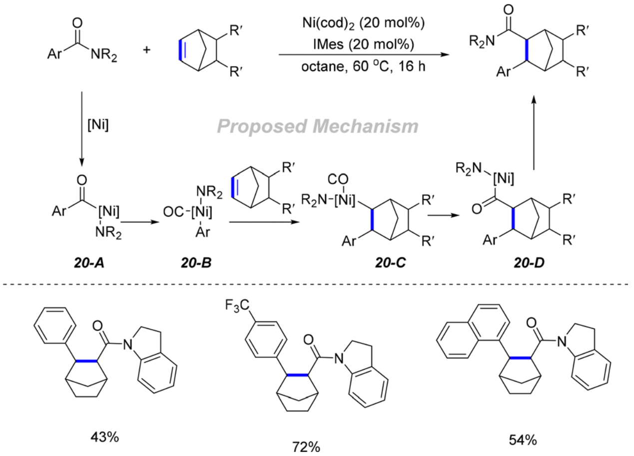
In 2021, Wang's group disclosed an intermolecular arylamination of alkenes with good functional group tolerance, which employed piperidino benzoate as a readily available amine-containing reagent.[47] In fact, the Engle group has long been dedicated to achieving the difunctionalization of alkenes through directed strategies.[48] In the same year, Engle and co-workers demonstrated an alcohol-directed 1,2-carboamination of alkenes by nickel catalysis.[48g] The author gives a rational mechanism according to the control experiments. First, 3-buten-1-ol and PhB(nep) undergo transmetalation and coordination with a nickel catalyst to yield **19-A**. Subsequently, alcohol-directed *syn*-1,2-migratory insertion was performed to deliver an alcohol-coordinated nickelacycle intermediate **19-B**. Then, **19-B** underwent oxidation with an electrophilic aminating reagent, setting up the carbon–nitrogen reductive elimination step. Finally, various aimed products were prepared. Additionally, this procedure gives two alternative routes towards SKP2 inhibitor and TRPA1 agonists with efficient and shorter steps.

Next, the same group reported an interesting carbosulfenylation of alkenes enabled by nickel catalysis. The key to this conversion is the rational design of sulfur reagents with *N*-alkylsulfonamide leaving groups.[49] In 2023, a hydroxylarylation of alkenes employing green molecular oxygen as the sole oxygen unit was developed by Wang's group.[50] The key to achieving the hydroxylarylation is the identification of bulky β-diketone ligands. In 2023, Engle's group reported the first carboamidation of alkenes, which involves alkyl unit migratory insertion and innersphere nickel-nitrenoid transfer.[51] Mechanistic studies show that electronic modulation of the important π-alkene–nickel intermediates plays a crucial role by promoting alkyl migratory insertion into the unactivated C=C double bond, thereby enhancing reactivity. These findings not only guide the development of heteroatom-based electrophiles for utilization in multi-component catalytic transformations but also enrich the toolbox of difunctionalization of alkenes (Scheme 19).

In 2022, Tobisu and co-workers developed a 1,2-carboaminocarbonylation of norbornene derivatives with an atom economy of 100% by nickel catalysis.[52] A rational mechanism for this transformation is depicted in Scheme 19. First, the reaction is initiated by the oxidative addition of the amide C(acyl)–N bond to generate intermediate **20-A.** This is followed by CO deinsertion to afford intermediate **20-B.** Subsequently, norbornene inserts into the Ar–Ni bond of intermediate **20-B**, forming intermediate **20-C**. Finally, the target product is formed through CO insertion and reductive elimination that forges the C(acyl)–N bond. It should be mentioned that this transformation is also an interesting example of catalytic addition reactions that involve cleavage of special alkenes compared with earlier work by Morandi (Scheme 20).[29a]

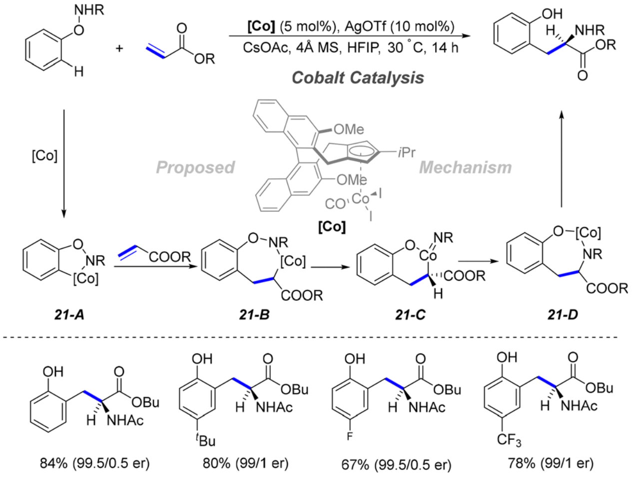


Scheme 19 Nickel-catalyzed carbosulfenylation, carboamidation, and hydroxylarylation of alkenes.

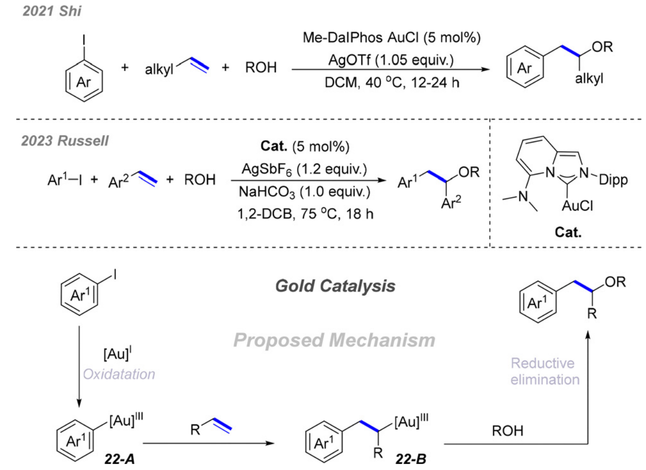


Scheme 20 Nickel-catalyzed 1,2-carboaminocarbonylation of strained alkenes.

2.2.3 Cobalt–carbon species. In 2021, Cramer and co-workers developed a highly enantioselective intermolecular carboamination of alkenes by cobalt catalysis through C–H activation.[53] The author points out a possible mechanism as depicted in Scheme 21. First, the C–H activation step proceeds through the concerted metalation–deprotonation pathway and yields a five-membered cobaltacycle **21-A**, followed by addition to alkenes to afford intermediate **21-B.** The following oxidative



Scheme 21 Cobalt-catalyzed enantioselective intermolecular carboamination of alkenes through C–H activation.



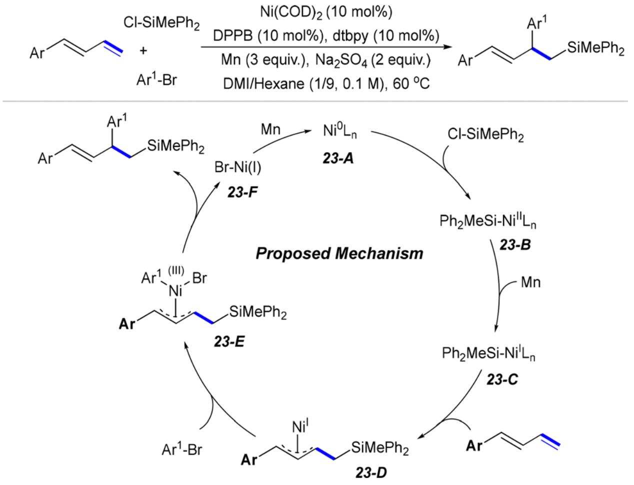
Scheme 22 Gold-catalyzed 1,2-oxyarylation of alkenes.

addition of cobalt into the O–N bond gives intermediate **21-C**. Reductive elimination then forges the new C–N bond to yield intermediate **21-D**. Protonation of the oxygen and nitrogen atoms in **21-D** releases the target products. This reaction provides a new enantioselective intermolecular carboamination by a cobalt-catalysed C–H activation strategy (Scheme 21).

2.2.4 Gold–carbon species. In 2020, in the context of aryl halide cross-coupling with electron-rich arenes or indoles by gold catalysis, Shi's group reported an intermolecular oxyarylation of unactivated alkenes for the first time.[54a] Later, Russell and co-workers achieved oxyarylation of aromatic alkenes catalysed by an NHC–gold complex.[54b] These two works both employed the oxidative addition of aryl iodides for the formation of intermediate **22-A**. The insertion of alkenes into the Ar–Au bond gave intermediate **22-B**, which was followed by reductive elimination and nucleophilic attack of alcohols to yield target products. These transformations provide a new perspective for gold-catalyzed difunctionalization of alkenes (Scheme 22).

2.3 Metal–silicon species addition

Organosilicon compounds play an important role in synthetic chemistry, medicinal chemistry, and the material field.[55] The silylative difunctionalization of alkenes can increase the diversity of the parent molecule due to the ability to transform the silyl group. Very recently, Shu and co-workers developed a nickel-catalyzed 1,2-silyl-arylation of 1,3-dienes by employing chlorosilanes and aryl bromide.[55c] As described in Scheme 23, the author presented a possible mechanism. First, the chlorosilane reacted with Ni^0 **23-A** to yield nickel–silicon species **23-B**. Then **23-B** was reduced by Mn to give intermediate **23-C**. Next, the migratory insertion of **23-C** into 1,3-diene afforded the π-allylnickel intermediate **23-D**, which underwent oxidative addition with aromatic bromide and reductive elimination to yield the corresponding product and intermediate **23-F**. Finally, **23-F** can be reduced by Mn to reproduce the Ni^0, thus restarting the next cycle. This example represents an interesting transformation of nickel–silicon species addition to alkenes. We anticipate that other metal–silicon species addition to alkenes will be realized in the future.

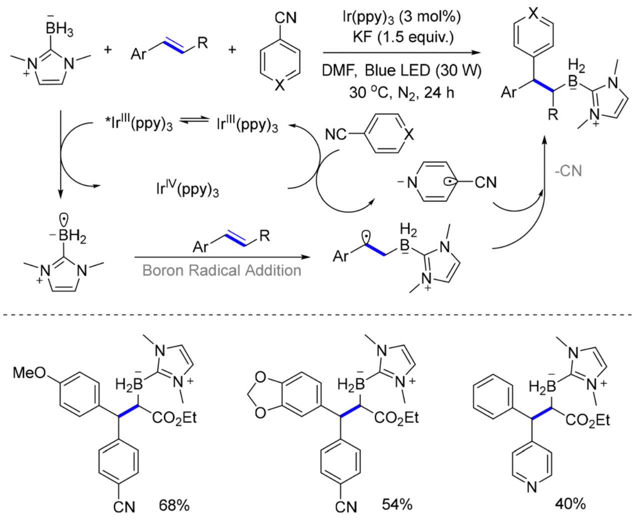


Scheme 23 Nickel-catalyzed 1,2-silyl-arylation of 1,3-dienes.

3. Difunctionalization initiated by the addition of radical species to C═C bonds

3.1 Boron radicals

NHC–BH_3-based radical borylation serves as a key method for creating organoboron compounds, with N-heterocyclic carbene (NHC)–BH_3 complexes acting as sources of boryl radicals in this significant synthetic approach for organoboron assembly.[56] In 2020, the Wang research group disclosed a new radical borylation pathway that enabled the arylboration reaction of alkenes through photoredox catalysis (Scheme 24). N-heterocyclic carbene–borane (NHC–BH_3) complexes, serving as boryl radical precursors, undergo single-electron oxidation under photoredox catalytic conditions to generate NHC–boryl radicals.



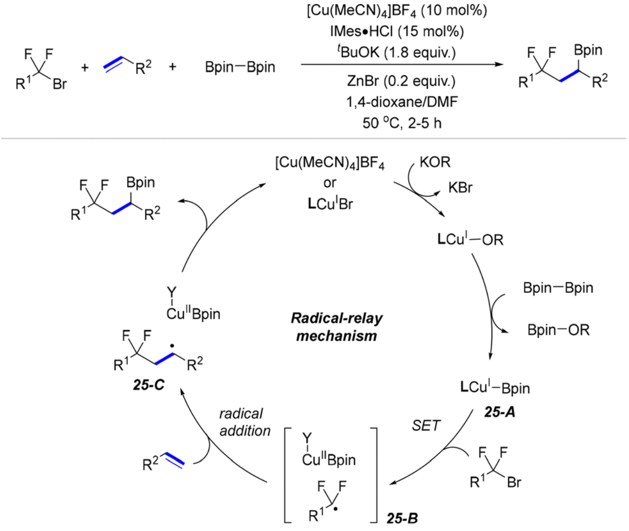
Scheme 24 1,2-Arylborylation of olefins *via* NHC–boryl radicals.

These radicals then engage in cross-coupling reactions with *in situ*-generated radical anions, enabling the synthesis of various organoboron compounds. This approach offers a novel and efficient strategy for the construction of C–B bonds, expanding the scope and diversity of organoboron synthesis.

3.2 Carbon radicals

3.2.1 Fluoroalkyl radicals. The unique properties of fluorine atoms enable fluorinated compounds to be widely used in medicine, agrochemicals, and functional materials science. The number of natural products containing fluorine is extremely limited. In order to meet the wide range of needs, many reaction strategies have been gradually established to construct fluorine-containing structures. In addition to directly introducing fluorine atoms into substrate fragments, a more practical method is to use highly active fluorine-containing species, such as fluoroalkyl radicals, to modify the substrate, thereby easily obtaining a variety of fluorine-containing structures. In recent years, the difunctionalization reaction induced by the addition of fluoroalkyl radicals to olefins has shown a spurt of growth. With the help of the constantly creative strategies, various functional groups have been introduced into the α position of olefins.

In 2021, Ito's group developed the first example of a copper-catalyzed intermolecular fluoroalkyl radical tandem borylation reaction (Scheme 25). Enable the highly selective introduction of *gem*-difluoro, monofluoro alkyl groups, and boron groups into olefins.[57] The Cu(I) salt reacts with bis(pinacolato)diboron to produce the key boryl copper(I) intermediate **25-A**, which then undergoes a single electron transfer reaction with the bromofluoroalkane to deliver an electrophilic fluoroalkyl radical **25-B**. Due to electronic effects and/or steric repulsion, fluoroalkyl radicals preferentially add to olefins rather than undergoing boryl substitution reactions with boryl copper(II) intermediates **25-C**. Finally, the recombination between the carbon radical and the boryl copper(II) intermediate builds the carbon–boron bond to release the product. Later, Chu's group reported a defluorinative 1,2-fluoroalkylborylation of alkenes with trifluoromethyl and bis(pinacolato)diboron, achieving straightforward access to γ-*gem*-difluoroalkyl boronates under synergistic photoredox/copper catalysis.[58]

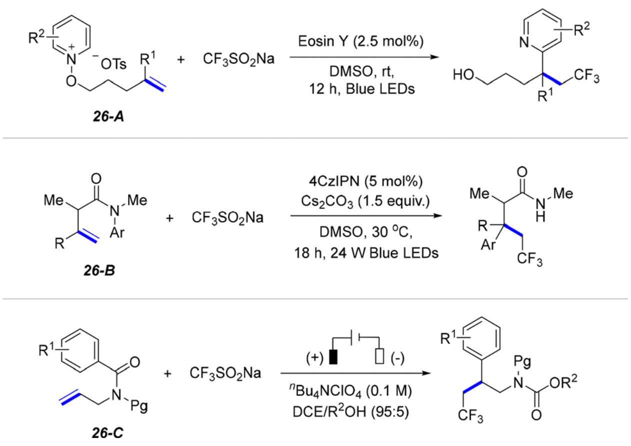


Scheme 25 1,2-Fluoroalkylborylation of unactivated olefins.

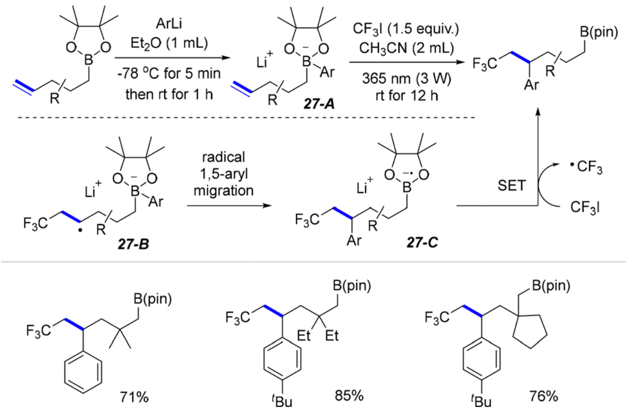
1,2-Dicarbonization is also a focus of attention for the difunctionalization of olefins. Carbon functional groups include aryl, alkynyl, cyano, carbonyl, alkyl, *etc.* The key point of the 1,2 dicarbonization of olefins induced by the addition of fluoroalkyl radicals to olefins lies in the construction of the second C–C bond. Photocatalysis, electrocatalysis, and the integration with transition metal catalysis have developed many novel coupling strategies.

The migration strategy is one of the construction options for achieving olefin arylation. In general, the mechanism involves 5-membered spirocyclization of the intermediate, followed by restoration of aromatization to promote forward transformation. Fluoroalkyl arylation of olefins can be achieved *via* radical tandem remote or proximal aromatic migration.[59] In 2020, Hong *et al.* reported visible light-induced distal heteroaryl *ipso*-migration for trifluoromethylpyridinylation of unactivated alkenes (Scheme 26).[60] Using the Langlois reagent as a trifluoromethyl radical source, the pyridine on the *N*-alkoxypyridinium salt **26-A** is transferred from the oxygen atom to the carbon of the olefin. Almost at the same time, Clayden reported a trifluoromethylarylation of vinyl ureas **26-B** *via* migration from N to O. Unlike before, the migration is triggered by carbanions generated by a reductive radical-polar crossover sequence. Recently, Claraz reported the electrochemically driven radical fluoromethylation of *N*-allylbenzamides **26-C** *via* 1,4-aryl migration. In this case, the addition of the trifluoromethyl radical to the olefin generates a β-amino radical that transfers the aromatic group carbon center to the carbon center.

In 2021, Studer's group filled the gap in the long-range migration of aromatic groups from boron to carbon atoms (Scheme 27).[61] The alkenylboronic acid esters react with an aryl lithium reagent to generate a boronate complex **27-A** *in situ*, which is attacked by a fluoroalkyl radical to give a free radical **27-B**. A rare 1,5-migration of the aromatic group from the boron



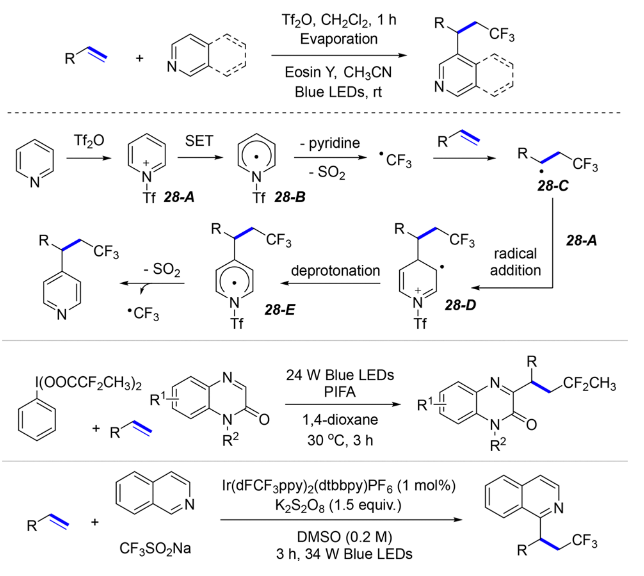
Scheme 26 1,2-Fluoroalkylarylation of alkenes *via* migration.



Scheme 27 1,2-Fluoroalkylarylation of alkenes *via* migration.

to the carbon atom then occurred. The single electron transfer between **27-C** and trifluoroiodomethane quenches the chain reaction process and regenerates the trifluoromethyl radical. This method provides a novel and practical method for the fluoroalkyl arylation of boron-containing alkenes.

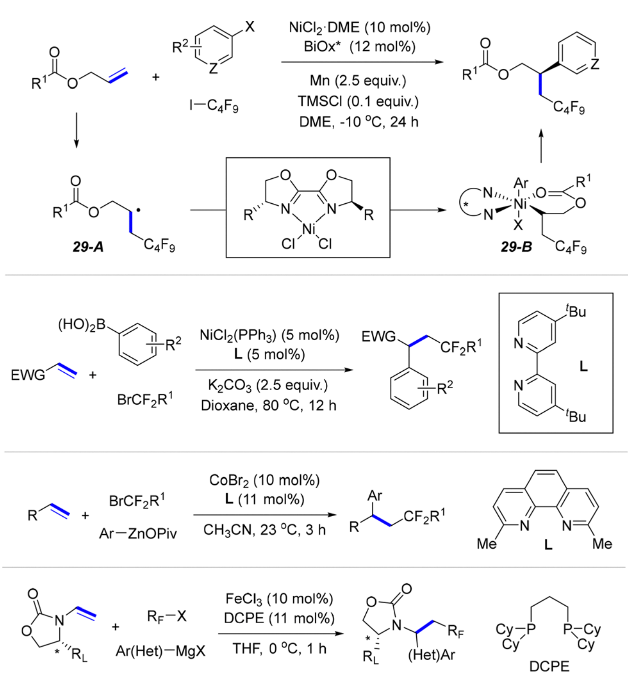
Minisci-type reaction is another classic way to build C(sp^2)–C bonds, which usually refers to the free radical addition of nucleophilic carbon radicals to protonated electron-deficient aromatic heterocycles.[62] In 2020, Hong reported a general photocatalytic trifluoromethylpyridylation of olefins (Scheme 28).[63] Triflic anhydride is both a trifluoromethyl source and an activating agent for pyridine. The *N*-trifluoromethylpyridinium salt **28-A** generated *in situ* from pyridine and Tf_2O is an effective modular bifunctional reagent that can not only provide trifluoromethyl radicals and pyridine functional groups, but also exhibit excellent C4 position selectivity in radical addition to the pyridine. The single electron reduction of **28-A** produces trifluoromethyl radicals after SO_2 is released. The radical intermediate **28-C** generated by the tandem olefin engages in radical addition to the C4 position of the pyridinium salt to **28-D**. The radical cation **28-D** undergoes deprotonation to give a cationic intermediate **28-E**, which can be oxidized by the photosensitizer to give the product and regenerate the CF_3 radical.



Scheme 28 1,2-Fluoroalkylheteroarylation of alkenes *via* Minisci-type reaction.

Other heterocyclic rings introduced into olefins through Minisci-type reactions have also been reported. For example, in 2022, Lu reported the photoinduced difluoroalkylation of quinoxalinones with alkenes under transition metal-free conditions using phenyl-λ^3-iodanediyl bis(2,2-difluoropropanoate) as a fluoroalkyl radical precursor. After that, Sharma published the polarity reversal radical cascade strategy under photooxidation conditions, in which a series of olefins were installed with trifluoromethyl and isoquinoline.[64]

The integration of transition metal-catalyzed coupling strategies and radical cascade reactions has paved the way for the utilization of electrophilic aryl/heteroaryl halides and aryl nucleophiles.[65] In 2020, Chu and co-workers described a nickel-catalyzed enantioselective intermolecular fluoroalkylation of unactivated olefins (Scheme 29). Radical intermediate **29-A** trapping with nickel, chiral BiOx ligands provides good control of stereoselectivity. Chiral β-fluoroalkyl arylalkanes are efficiently obtained after reductive elimination of aryl Ni(III) **29-B** species. The surface-activated Mn powder as a reducing agent is crucial for this reaction. In addition, Ni-catalyzed fluoroalkylarylation of olefins was also reported by Zhang's group, using the carbon nucleophile arylboronic acid to couple with carbon radicals to construct C–C (sp^2) bonds. The continuous tandem construction of C–C bonds using other transition metals and aromatic carbon nucleophiles creates a diverse platform for the realization of fluoroalkyl arylation of olefins, for example,

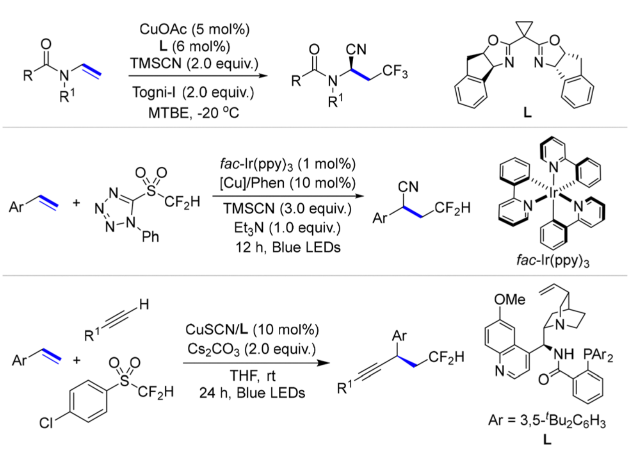


Scheme 29 1,2-Fluoroalkylheteroarylation of alkenes *via* transition metal-catalyzed coupling reaction.

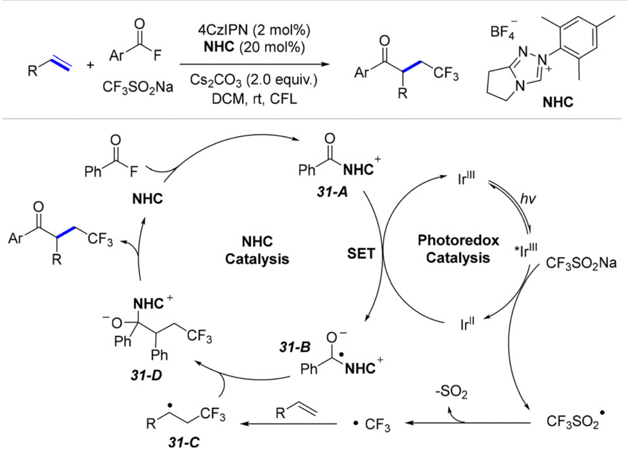
Co-catalyzed dicarbofunctionalization with α-bromodifluorocarbonyl compounds and Fe-catalyzed coupling with Grignard reagents.

Cyano groups are widely present in active drug molecules and can be further transformed into diverse functional groups. Directly introducing cyano groups into olefins is important and valuable. TMSCN is often used as a cyanide source to make nitrile compounds.[66] In 2020, Liu disclosed the first asymmetric trifluoromethylcyanation reactions of enamides. In the chiral copper(II) catalytic system, the carbon-centered radical was enantioselectively trapped by copper(II) species (Scheme 30). A series of chiral α-cyano amides and α-cyano esters were obtained with excellent enantioselectivity. In 2024, Yu and co-workers synthesized ((difluoromethyl)sulfonyl)-1-methyl-1*H*-tetrazole (DFSMT) as a novel radical CF_2H precursor and reported the cyano-difluoromethylation of aryl olefins under photocatalytic conditions. A similar copper-catalyzed strategy for constructing C–C (sp) bonds has also been implemented in the coupling reaction of alkynes. Hu developed the first example of enantioselective fluoroalkylation–alkynylation of olefins.[67] Fluoroalkyl sulfones with low reduction potentials provide fluoroalkyl radicals under photoirradiation conditions, and ligands are key to controlling chiral alkynylation.

It is also very important to introduce acyl and fluoroalkyl groups into olefins at the same time, because this is a practical and effective means to construct fluorinated and carbonyl-containing compounds.[68] In 2020, Studer reported a cooperative photoredox/NHC catalysis strategy solving the trifluoromethylacylation of alkenes (Scheme 31).[69] This reaction proceeds through the cooperative catalysis of photoredox and NHC (N-heterocyclic carbene). In this reaction, acylazolium ion intermediates **31-A**, which could easily be generated from benzoyl fluoride, are reduced *via* single electron transfer (SET) to yield ketyl-type radicals **31-B**. Then, driven by the persistent radical effect, a cross-coupling reaction between the persistent ketyl radical **31-B** and the transient C-radical **31-C** occurs, resulting in the formation of the NHC-bound intermediate **31-D**. Ultimately, the fragmentation of the NHC leads to the isolation of the product ketone, thus concluding the NHC catalytic cycle.

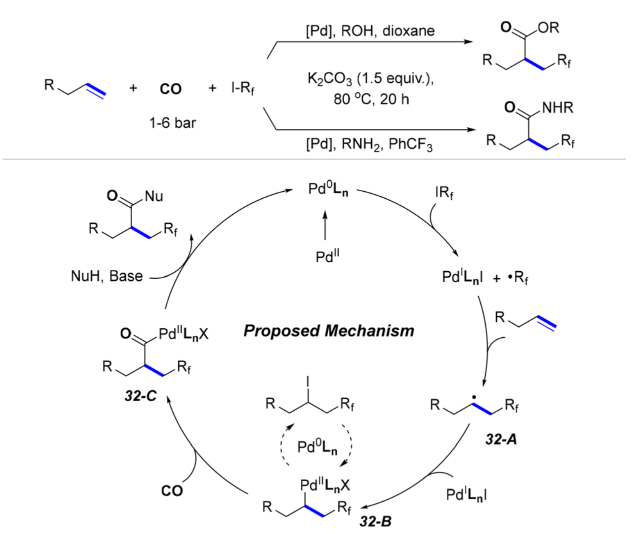


Scheme 30 1,2-Fluoroalkylcyanation and 1,2-fluoroalkylalkynylation of olefins.



Scheme 31 The cooperative strategy of photoredox and NHC catalysis enables the trifluoromethylacylation of alkenes.

Carbonylation reactions with carbon monoxide (CO) as a feedstock serve as a potent and prevalent means for the construction of diverse carbonyl compounds from easily accessible chemicals.[70] In 2020, Wu developed a palladium-catalyzed perfluoroalkylative carbonylation of unactivated alkenes. In this reaction, inexpensive and readily available carbon monoxide is used as the C1 source, and a wide variety of phenols and alcohols act as the coupling partners (Scheme 32). They can be converted into the corresponding β-perfluoroalkyl esters in high yields with good functional group tolerance. The palladium species combines with the carbon radical **32-A** to form the key intermediate **32-B**. Then, carbon monoxide (CO) inserts into intermediate **32-B** to generate intermediate **32-C**. Finally, intermediate **32-C** undergoes nucleophilic substitution and reductive elimination reactions to yield the desired final product. Chen and co-workers also reported a double aminocarbonylation

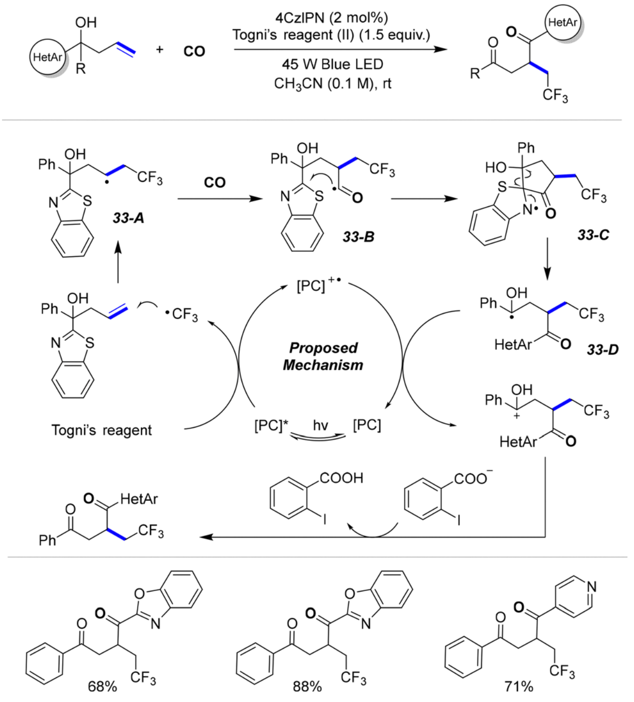


Scheme 32 Palladium-catalyzed perfluoroalkylative carbonylation of unactivated alkenes.

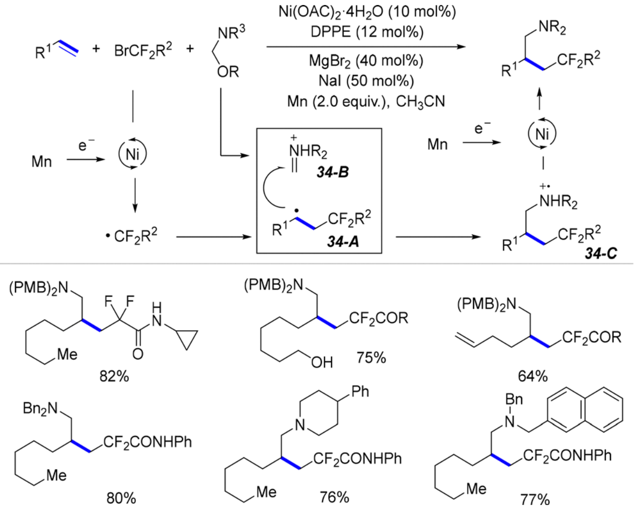
reaction of unactivated alkenes with CO in 2023. This visible-light-driven radical relay approach under metal-free conditions offers a direct way to access γ-trifluoromethyl α-ketoamides with high chemoselectivity.

In 2024, the Wu research group developed a novel carbonylative radical rearrangement strategy (Scheme 33).[71] Under visible light induction, they successfully synthesized a series of 1,4-dicarbonyl compounds containing fluoroalkyl groups and heterocycles from unactivated alkenes. In this system, the CO insertion step serves as a crucial factor for functional group migration. The selective insertion of CO onto the carbon radical creates a bridge for the migration of (hetero)aryl groups. The photocatalyst in the excited state reacts with Togni's reagent to generate a trifluoromethyl radical, which adds to the alkene to produce secondary carbon radical **33-A**. Under a CO atmosphere at relatively high pressure, the γ-OH carbon radical **33-A** captures CO to form the acyl radical intermediate **33-B**. The intramolecular cyclization of the acyl radical yields a five-membered cyclic intermediate **33-C**. Subsequently, the restoration of aromaticity promotes the homolytic cleavage of the C–C bond, causing the position of the aromatic heterocycle to shift from the carbon adjacent to the hydroxyl group to the acyl group, resulting in the more stable α-OH carbon centered radical **33-D**. Finally, the photocatalyst oxidizes **33-D** by single electron transfer, and deprotonation occurs to afford the product.

Alkyl–alkyl carbon–carbon bonds are the most fundamental and indispensable parts in organic molecular scaffolds.[72] However, the methods for constructing such carbon–carbon bonds are relatively scarce. In 2023, Huang reported a nickel electron-shuttle catalysed dicarbofunctionalization of olefins (Scheme 34).[73]



Scheme 33 Fluoroalkylative carbonylation of unactivated alkenes using a carbonylative migration strategy.

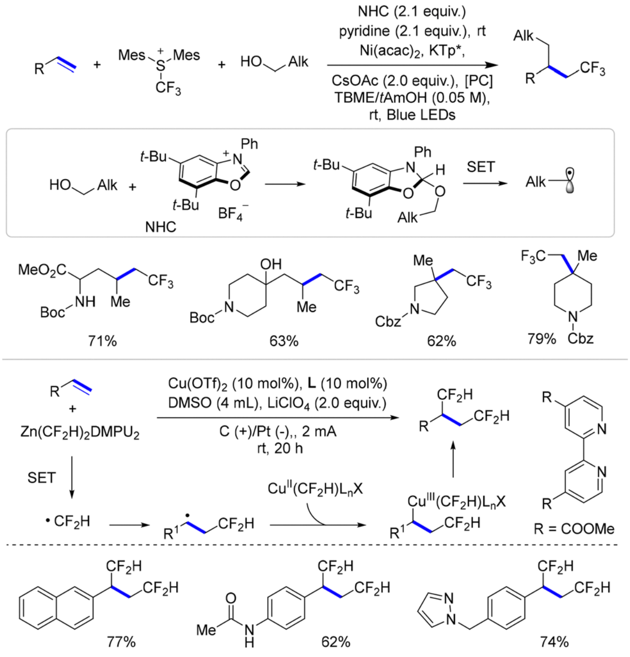


Scheme 34 Nickel electron-shuttle catalyzed alkylative aminomethylation of olefins with nickel electron-shuttle catalysis.

A fluoroalkyl radical was generated through single-electron reduction between fluoroalkyl bromide and a nickel catalyst. Subsequently, it can add to the alkene to form alkyl radical **34-A**. The iminium ion **34-B**, which is generated *via* elimination from the hemiaminal, is an ideal radical scavenger. It can combine with **34-A** to form amine radical cation **34-C** with the second alkyl–alkyl bond. Intermediate **34-C** is finally reduced by nickel to afford the desired target product. This mode bypasses the formation of traditional carbon–metal intermediates and reduces the inherent complexity in the transition-metal-catalyzed alkyl–alkyl bond-forming methods.

The Macmillan group also reported a Ni-catalyzed regioselective dialkylation of unactivated olefins (Scheme 35), in which dimesityl(trifluoromethyl)sulfonium trifluoromethanesulfonate (dMesSCF$_3$(OTf)) was used to produce electrophilic trifluoromethyl radicals, and alkyl alcohols were used as alkyl radical precursors.[74] The adduct formed by alcohol and the benzoxazolium salt (N-heterocyclic carbene (NHC)) exhibits good reactivity, which is the key to the deoxygenative activation of alcohols. The precise recognition of three types of radicals, which effectively avoids the undesired chaotic cross-coupling, is attributed to the bimolecular homolytic substitution (SH2) catalysis radical sorting mechanism.

In 2024, Kim first reported Cu-electrocatalysis vicinal bis(difluoromethylation) of alkenes (Scheme 35).[75] Traditionally, Zn(CF$_2$H)$_2$(DMPU)$_2$ mainly serves as an anionic source of the CF$_2$H group through transmetalation. In this electrochemically driven copper-catalyzed system, Zn(CF$_2$H)$_2$(DMPU)$_2$ has dual functions and can act as a CF$_2$H radical precursor under electrochemical oxidation. The addition of the CF$_2$H radical to the alkene introduces the first CF$_2$H group in the terminal position. At this point, the copper catalyst can capture the resulting carbon radical from the addition to form a Cu(III) intermediate. Subsequently, reductive elimination occurs,

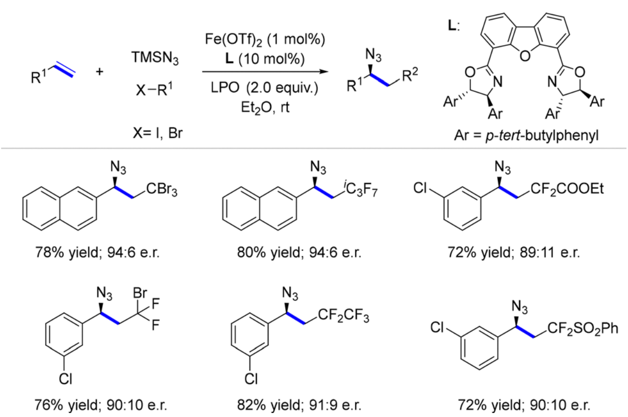


Scheme 35 Nickel catalysed dicarbofunctionalization of olefins.

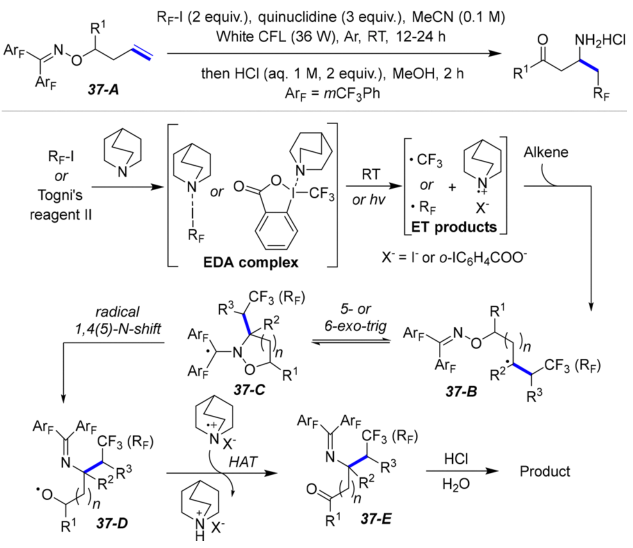
enabling the successful installation of the second CF_2H group at the internal position. The practicality of this method for successively embedding two CF_2H groups into alkenes has been highlighted through the late-stage modification of drugs.

In addition to the construction of C–C bonds described above, carbon radicals generated by the addition of fluoroalkyl groups to olefins have also been widely studied to construct carbon–heteroatom bonds.[76] An iron-catalyzed asymmetric fluoroalkylazidation reaction of alkenes has been reported by Bao's group in 2021 (Scheme 36).[77] This method can convert inexpensive chemical raw materials $TMSN_3$ into valuable chiral organic azides. This reaction mechanism demonstrates a unique way of generating fluoroalkyl radicals. Alkyl diacyl peroxide LPO (lauroyl peroxide) undergoes single electron transfer (SET) with the Fe catalyst to yield an alkyl radical. The alkyl radical abstracts an iodine atom from the fluoroalkyl iodide, thereby forming the fluoroalkyl radical. The group transfer between the carbon radical and the Fe(III) azide species is the critical step in constructing the C–N bond. In the same year, the Liu research group also published a copper-catalyzed asymmetric radical azidation of acrylamides for the synthesis of chiral alkylazides. Notably, in this protocol, the highly enantioselective control is mainly attributed to the bisoxazoline ligands. Other types of olefin substrates and catalytic systems have also been employed to achieve similar asymmetric fluoroalkyl amination reactions such as fluoroalkylazidation of α,β-unsaturated carbonyl compounds. Even the trifluoromethyl radicals can be generated from hypervalent iodine(III) reagents induced by the nonheme iron enzyme-catalyzed system.

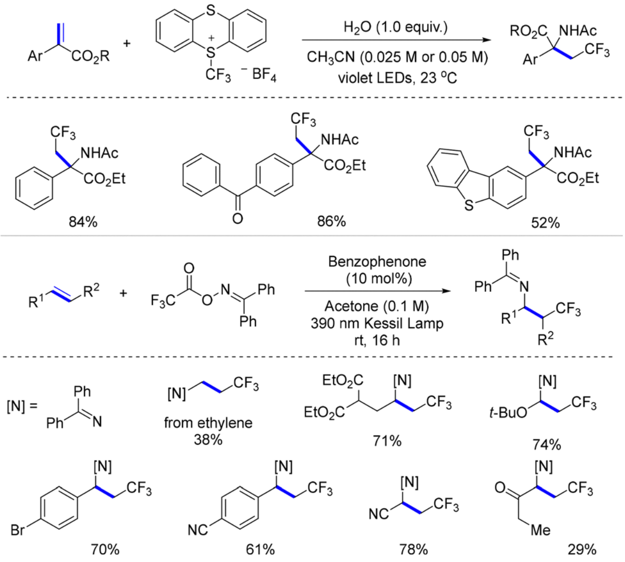
Most of the above platforms are not applicable to the functionalization of unactivated alkenes. In 2021, the group of Han developed a new 1,4/5 amino migration strategy to solve the α-position primary amination of unactivated olefins (Scheme 37).[78] Mechanistic studies have shown that the fluoroalkyl radical is generated from the electron donor–acceptor (EDA) complex formed by Togni's reagent II or fluoroalkyl iodides and quinuclidine. The designed and synthesized alkene tethered ketoxime ether **37-A** undergoes addition of the fluoroalkyl radical to yield the carbon-centered radical **37-B**. After that, this radical **37-B** goes through a 5(6)-*exo–trig* cyclization that is favorable in terms of kinetics, resulting in the formation of intermediate **37-C**. Intermediate **37-C** is promptly transformed into the corresponding O-radical **37-D** through a carbon radical β-scission, which is thermodynamically favorable and is promoted by the cleavage of the N–O bond. O-radical **37-D** was oxidized by the quinuclidine radical cation, *via* the process of hydrogen atom transfer (HAT), thus forming fluoroalkyl-substituted β(γ)-iminoketones **37-E**. These iminoketones finally experience hydrolysis to yield primary amination products. Later, this group used *N*-homoallyl-Mts-hydrazone as the substrate, integrated the Hofmann–Löffler–Freytag (HLF) reaction, cleaved the hydrazonyl N–N bond, and achieved the difluoroalkylamination of unactivated alkenes.



Scheme 36 Iron-catalyzed asymmetric fluoroalkylazidation of alkenes.



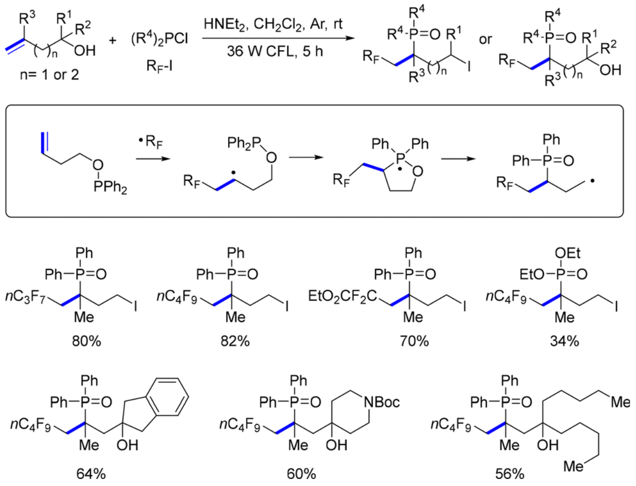
Scheme 37 Amino shift enables fluoroalkylazidation of unactivated alkenes.



Scheme 38 Transition metal-free fluoroalkylamination of alkenes.

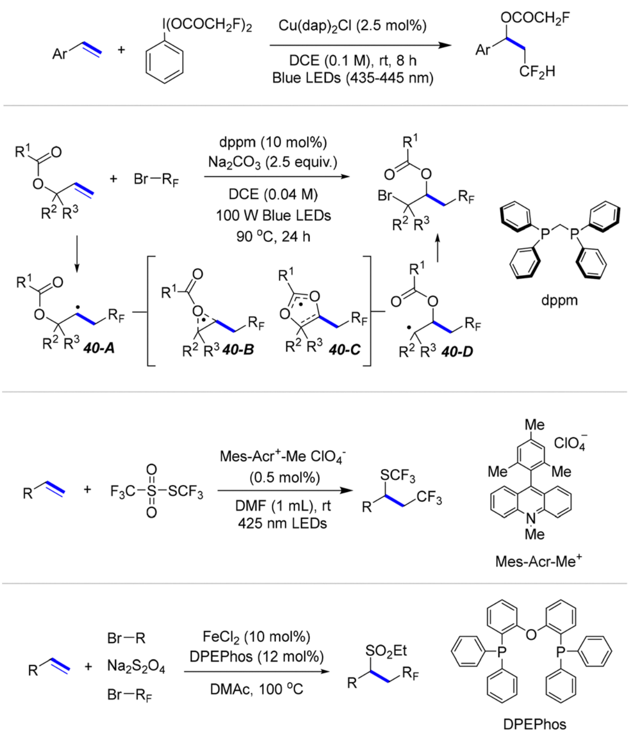
There are also some other transition-metal-free intermolecular fluoroalkylamination platforms that enrich the channels for amino groups to enter the C═C double bonds of alkenes.[79] The Ritter research group demonstrated that trifluoromethylthianthrenium salts TT-$CF_3^+BF_4^-$ and TT-$CF_3^+OTf^-$ can be obtained in a one-step process from thianthrene and triflic anhydride (Scheme 38). Under blue light conditions, the S-CF_3 single bond in TT-CF_3^+ can undergo homolytic cleavage to form a trifluoromethyl radical and a thianthrenium radical cation. The trifluoromethylamination of acrylates mediated by α-thianthrenium carbonyl species has been achieved. This reactivity enables the synthesis of C-tetrasubstituted α- and β-amino acid analogues. In 2022, the Molander research group developed a novel bifunctional reagent, the benzophenone derivative of trifluoroacetyl oxime. This new reagent contains two important functional groups, the CF_3 group and the imino group, and can serve as a direct source for both of them. They successfully applied it to the iminoalkylation reaction of diverse alkenes under transition-metal-free conditions. A notable feature of this type of oxime is that the N–O bond can undergo homolytic cleavage under light irradiation. In terms of the generality for alkenes, this transformation has a striking feature. The electrophilic trifluoromethyl radical can effectively add to both electron-deficient and electron-rich alkenes.

As is well known, organic phosphorus groups are widely present in the structures of bioactive drug molecules and functional materials. Therefore, introducing the phosphoryl group into molecules to construct C–P bonds has always been a research focus in coupling reactions. However, the regioselective phosphorylation of alkenes has always been a difficult problem to solve. Compared with the terminal positions of alkenes, it is quite challenging to assemble a phosphonyl group within the internal part of alkenes. In 2022, Han reported a one-pot two-step strategy for achieving the regioselective fluoroalkylphosphorylation of unactivated alkenes (Scheme 39).[80] The radical alkoxyphosphine rearrangement is the key to precisely introducing the phosphoryl group into the inner position of the alkene.



Scheme 39 Transition metal-free fluoroalkylphosphorylation of alkenes.

In recent years, driven by the remarkable advancements in the field of visible-light-induced photochemistry, the oxy-fluoroalkylation and fluoroalkylative sulfidation of alkenes have witnessed significant development.[81] In 2022, the Veliks research group described a simple process (Scheme 40).[82] The strategy that combines copper(I) catalysis under light irradiation conditions with hypervalent iodine(III) chemistry provides a platform for the oxy-monofluoromethylation of alkenes. In this strategy, the formation of the C–O bond proceeds *via*



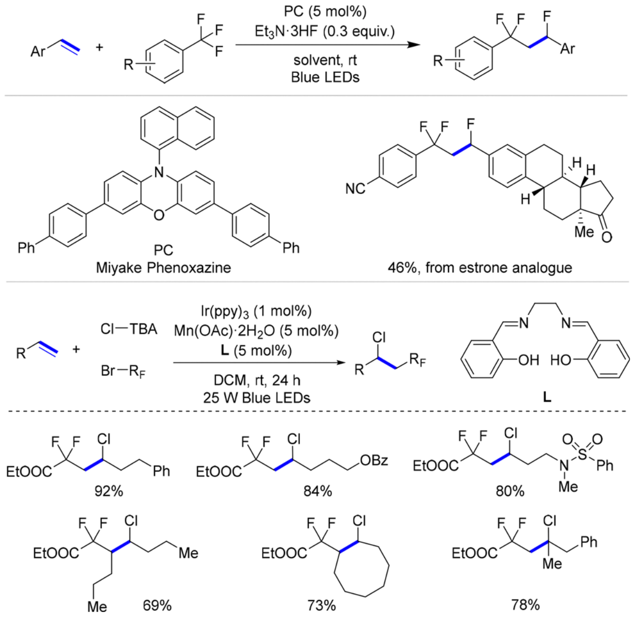
Scheme 40 Oxy-fluoroalkylation and fluoroalkylative sulfidation of alkenes.

the oxidation of the benzyl carbon radical to a benzyl carbocation, followed by its capture by the fluoroacetate anion. As a result, the applicable alkenes are limited to aryl alkenes.

In 2023, Ngai reported a visible-light-induced phosphine-catalyzed oxy-fluoroalkylation of allyl carboxylates. The phosphorus catalyst forms a donor–acceptor complex with the fluoroalkyl iodide. Under light irradiation, fluoroalkyl radicals are generated. The radicals attack the C=C double bond of allyl benzoate to form a new alkyl radical **40-A**. Subsequently, a concerted 1,2-radical migration of allyl carboxylates took place. This crucial migration step may involve a [1,2]-transfer *via* a three-membered ring **40-B** or a [2,3]-benzoyloxy transfer *via* a five-membered ring **40-C**. The greater stability of the tertiary radical intermediate **40-D** serves as the driving force for the migration. Finally, a Br atom transfer yields the desired product, and dppm is regenerated to complete the catalytic cycle.

Sulfur-containing functional groups represented by trifluoromethylthio and sulfone groups are active groups in many drug molecules.[83] In 2023, the Hammond group synthesized the air- and thermally stable trifluoromethylthiolation reagent $CF_3SO_2SCF_3$ using inexpensive CF_3SO_2Na and Tf_2O as raw materials.[84] Through reaction tests, it was found to have good reactivity and was successfully applied to the fluoroalkyl trifluoromethylthiolation of alkenes. The low synthesis cost and simple operation make this reagent a very promising trifluoromethylthiolation reagent. In addition, Huang also developed an iron-catalyzed fluoroalkylative alkylsulfonylation of alkenes, in which sodium dithionite ($Na_2S_2O_4$) serves both as the source of the sulfone and as the terminal reducing agent. The capture or release of sulfur dioxide (SO_2) by the carbon-centered alkyl radical is in an equilibrium state, and the electron shuttle catalytic effect of the iron catalyst accelerates the conversion of the sulfur-centered alkyl sulfone radical into the alkyl sulfone anion. This synthetic method of multi-component relay starting from simple alkenes demonstrates a wide range of applicability in the construction of various dialkyl sulfones.

The presence of halogen in the molecular structure indicates that a variety of couplings can be carried out, especially with the aid of transition metal catalysis.[85] The halogenation reaction at the α-position of the C=C double bond mediated by the addition of fluoroalkyl radicals to alkenes usually requires a halogen atom transfer or a carbocation intermediate (Scheme 41). In 2023, Zhang reported an effective operation for installing the α,α-difluorophenyl structure and monofluoro group onto alkenes.[86] Under the conditions of blue light irradiation, this protocol established a system catalyzed by an organic photosensitizer. Firstly, the C–F bond of benzotrifluoride was activated. Subsequently, through the intermediate of the benzyl carbocation, the C–F bond was reconstructed by using triethylamine·trifluoride ($Et_3N·3HF$) as the external fluorine source. An innovative system integrating transition metal catalysis and photocatalysis has been used to achieve the fluoroalkyl chlorination of unactivated alkenes. Atom transfer is the key step for introducing halogen into the alkenes.

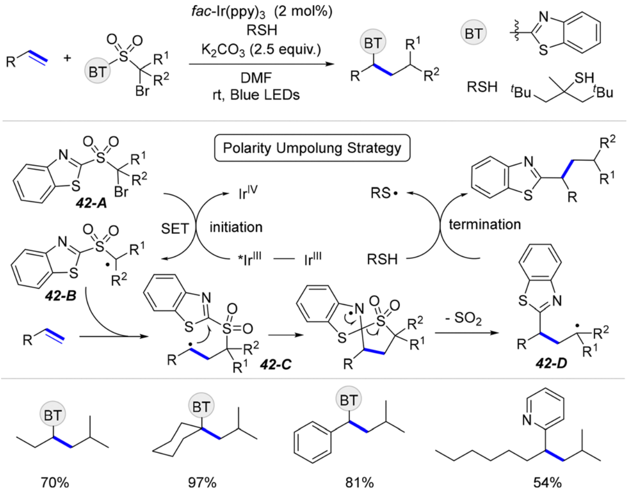


Scheme 41 Fluoroalkylative haloalkylation of alkenes.

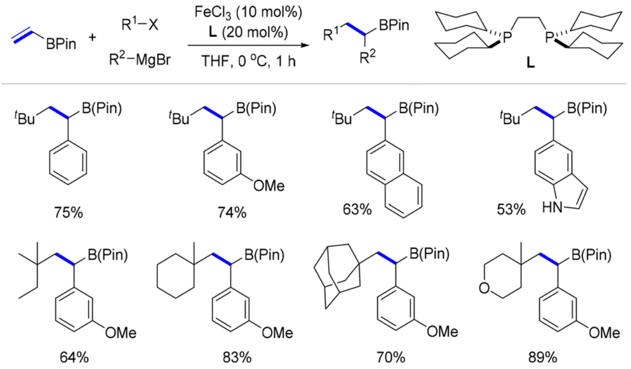
3.2.2 **Alkyl radicals.** Alkylation of alkenes mediated by alkyl carbon radicals holds great potential for constructing complex-structured aliphatic scaffolds. However, typically, the addition of carbon radicals to alkenes can be successfully achieved only when there is a match in radical polarities. As a result, both the type of carbon radicals and the electronic effects exerted by the substituents on alkenes play decisive roles in determining the feasibility of radical addition. With the continuous expansion of radical-initiation strategies, the variety of alkyl carbon radicals has been steadily increasing.[87] In line with specific synthetic demands, the functional groups incorporated into alkenes during the process of carbon-radical-promoted alkene addition have also been gradually optimized in recent years.

Notably, due to the mismatch in radical polarities, introducing electron-rich alkyl functional groups into unactivated alkenes is a challenging problem. In order to solve this problem that has been difficult to achieve, the Zhu research group designed and implemented a new polarity umpolung strategy (Scheme 42).[88] This method based on docking migration provides a reliable and practical solution for the alkylation of unactivated alkenes. They designed and synthesized a new sulfone-based alkylating bifunctional reagent **42-A**. At the beginning of the reaction, **42-A** undergoes single-electron reduction to generate an electrophilic sulfone-bearing alkyl radical **42-B**, which then adds to the alkene to **42-C**. Subsequently, intramolecular heteroaryl migration takes place and SO_2 is released. A thiol acts as a hydrogen source to quench the radical intermediate **42-D** and complete the reaction. At the same time, the polarity of the alkyl carbon radical is reversed. The key point for the success of this docking and transfer process lies in the ingenious utilization of electrophilic sulfone-containing alkyl radicals to substitute for typical nucleophilic alkyl radicals.

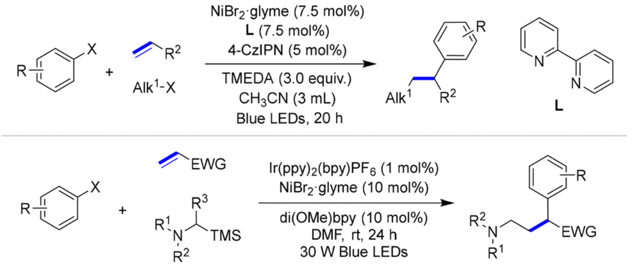
In addition to the intramolecular migration strategy to introduce alkyl and aromatic groups into olefins, transition



Scheme 42 Radical alkylation of unactivated alkenes.



Scheme 43 Iron-catalyzed alkylarylation of alkenes.

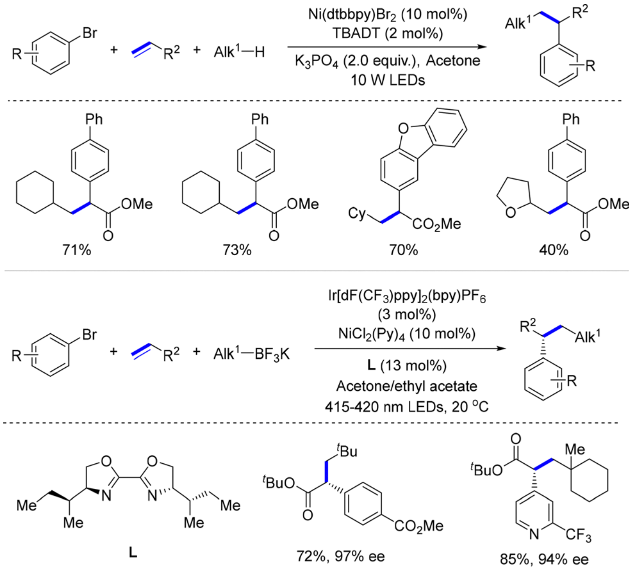


Scheme 44 Nickel-catalyzed alkylarylation of alkenes.

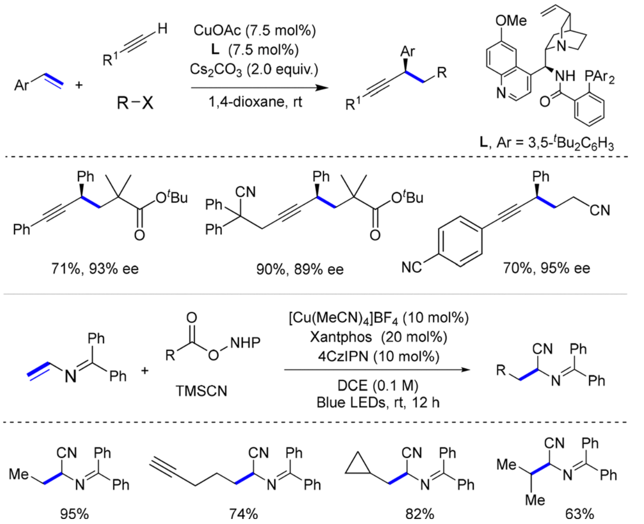
metal-catalyzed multicomponent coupling reactions are also very practical methods. In 2021, Gutierrez and his co-workers reported an iron-catalyzed cascade-cross coupling reaction that was mediated by alkyl carbon radicals (Scheme 43).[89] In this catalytic cycle, the Fe(II) species first activates the alkyl halide through a halogen abstraction reaction, generating Fe(III) species and a tertiary carbon radical simultaneously. The tertiary carbon radical can rapidly and irreversibly add to the vinyl boronate, thus forming an α-boryl radical. This radical intermediate is then captured by the Fe(II) species and transformed into an Fe(III)-alkyl intermediate. Reductive elimination promotes the formation of the target product and the Fe(I) species. The regenerated Fe(I) species can then initiate a new round of the catalytic cycle. This method provides a feasible solution for the alkylation functionalization of various electron-deficient alkenes and the late-stage functionalization of bioactive molecules.

In 2020, Martin reported a dual-catalytic system that combines photocatalysis and nickel catalysis to achieve the selective cross-coupling of two electrophiles (Scheme 44).[90] In this system, alkyl bromides are used as alkyl radical precursors,[90h] and aryl bromides serve as aryl coupling reagents, avoiding the use of stoichiometric organometallic reagents. TMEDA acts as a sacrificial electron donor and serves as the terminal reducing agent. Yuan also reported a three-component cross-coupling system of metallaphotoredox catalysis. Using 1-((trimethylsilyl)-methyl)piperidine as the alkyl radical precursor, the aryl electrophiles can be compatible with both aryl iodides and aryl bromides, providing an efficient and practical route for the synthesis of α-aryl substituted γ-amino acid derivatives.

Alkanes can also serve as precursors of alkyl radicals through the activation of aliphatic C–H bonds. The Kong group has developed a protocol for activating alkanes using a decatungstate photo-HAT (hydrogen atom transfer) catalyst under light irradiation (Scheme 45). This method replaces highly reactive alkyl halides as precursors of alkyl radicals.[91] When combined with nickel-catalyzed reductive cross-coupling, it can directly and selectively introduce alkyl and aryl groups into alkenes. The enantioselective alkylarylation reaction of alkenes has also been achieved under the dual photoredox/nickel catalysis system. The chiral bioxazoline (BiOx) ligand ((*S*,*S*)-*sec*-Bu-BiOx) is the key to controlling stereoselectivity. The capture of carbon radicals by the tetrahedral Ni(II) species is the stereodetermining step. Based on this platform, they also modularly and enantioselectively synthesized flurbiprofen analogues and the piragliatin lead compound, demonstrating the practicality of this protocol.



Scheme 45 Nickel-catalyzed alkylarylation of alkenes.

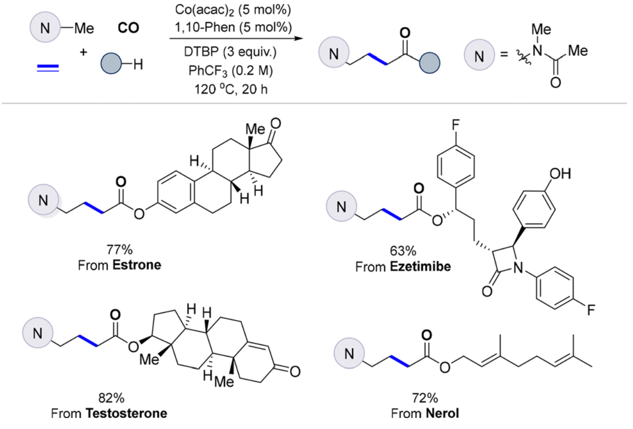


Scheme 46 Radical 1,2-carboalkynylation and 1,2-carbocyanation of alkenes.

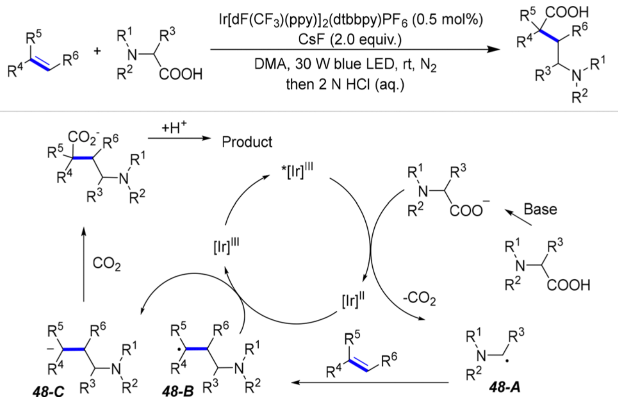
In 2020, Liu disclosed a copper-catalyzed asymmetric radical 1,2-carboalkynylation of alkenes with alkyl halides and terminal alkynes (Scheme 46).[92] The cinchona alkaloid-derived multidentate *N*,*N*,*P*-ligand is the key to controlling stereoselectivity and obtaining diverse chiral alkynes. In this reaction process, the Cu^I–alkyne intermediate reduces *tert*-butyl α-bromoisobutyrate to generate an alkyl carbon radical and a Cu^{II}–alkyne complex. Further tandem coupling and reductive elimination result in the formation of the chiral $C(sp^3)$–C(sp) bond. A remarkable feature of this method is that it can be readily adapted to activated terminal alkenes and alkynes bearing various substituents ((hetero)aryl, alkyl, and silyl groups).

Carbon-radical-mediated carbocyanation of alkenes has been developed for the synthesis of α-amino nitriles.[93] The Yang research group used redox-active esters as carbon radical precursors and TMS-CN as the cyanide source. Under the dual catalysis of copper and a photocatalyst, they chemoselectively and precisely installed an alkyl group and a cyano group at both ends of the C=C double bond of 2-azadienes. It is worth mentioning that this unique method for constructing α-amino nitrile derivatives not only exhibits excellent regioselectivity but also enables the synthesis of medicinally relevant α-amino acids.

The coupling of an alkyl radical with an acylation reagent can conveniently construct ketones and their derivatives.[94] The combination of α-aminoalkyl radicals with alkenes and carbonyl groups can be used to construct γ-amino acid derivatives. In 2023, Wu disclosed a Co-catalyzed oxidative carbonylation system that combines readily available amides, alkenes, and carbon monoxide to construct structurally complex γ-amino acid derivatives and peptides (Scheme 47).[95] The selective oxidation of electron-withdrawing alkylamines by peroxides generates an α-aminoalkyl radical intermediate, which adds to the alkene. Then, the insertion of carbon monoxide mediated by metallic cobalt, followed by reductive elimination, leads to the formation of the expected product.



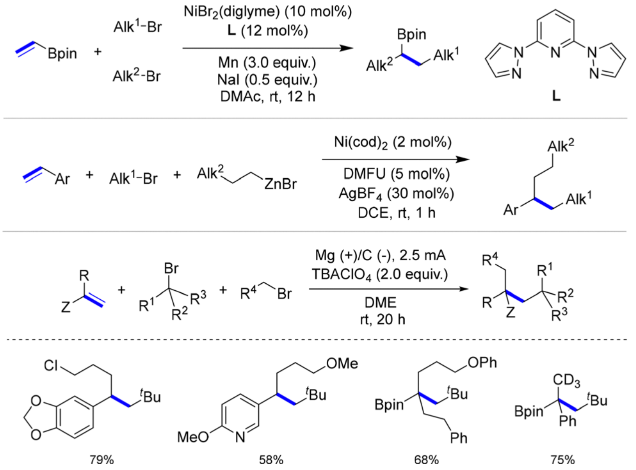
Scheme 47 Aminoalkylative carbonylation of alkenes.



Scheme 48 Carbocarboxylation of activated alkenes.

Yu also reported a unique strategy mediated by α-aminoalkyl radicals that can transform α-amino acids into γ-aminobutyric acid derivatives (Scheme 48).[96] For the first time, they achieved the use of α-amino acids as bifunctional reagents. Under the action of a photocatalyst, α-amino acids are first oxidized to undergo CO_2 elimination, generating an α-aminoalkyl radical **48-A**. This radical rapidly adds to an activated alkene to produce a benzyl radical **48-B**. The benzyl radical can be easily reduced to a carbanion **48-C** by the photocatalyst in its reduced state. The liberated CO_2 is captured through nucleophilic attack by the carbanion for reuse. This strategy of dissociating and then recycling the carboxyl group of amino acids represents an efficient and sustainable concept for organic synthesis.

In contrast to other functional groups, the coupling strategies for incorporating two alkyl ($C(sp^3)$) moieties across an alkene are rather limited.[97] When comparing the metal-mediated reductive elimination processes, the reductive elimination of $C(sp^3)$–[M]–$C(sp^3)$ is much slower than that of $C(sp^2)$–[M]–$C(sp^3)$. This shows that the dialkylation of alkenes is challenging. In 2020, Fu reported a nickel-catalyzed reductive dicarbofunctionalization of vinyl boronates (Scheme 49).[98] The combination of $NiBr_2$(diglyme) and the tridentate dipyrazolpyridine ligand (**L**) can afford excellent coupling efficiency and functional group compatibility. Mn(0) is employed as the terminal reductant, and a variety of alkyl

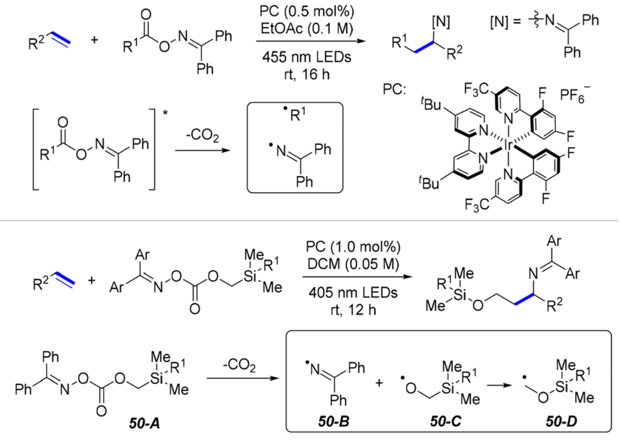


Scheme 49 Dialkylation of alkenes.

bromides can be adapted to this reaction system as alkyl coupling reagents. The reaction proceeds through the generation of a nucleophilic alkyl carbon radical from Ni(0) *via* single-electron transfer, followed by addition of this radical to the alkene. Subsequently, it involves recombination with nickel(I) and reductive elimination.

The Giri research group also disclosed a Ni-catalyzed dialkylation reaction of alkenylarenes, using α-halocarbonyls as alkyl radical precursors and alkylzinc reagents as alkyl carbon nucleophiles.[99] It is worth mentioning that this method is also applicable to cyclic internal alkenes, and in these cases, the dialkylation reaction occurs with the trans-addition of the two alkyl groups. In 2024, Lin developed a strategy of electrochemically promoted cross-electrophile coupling that enables the regioselective dialkylation of alkenes. Radical–polar crossover is the key to the successful formation of C(sp^3)–C(sp^3) bonds in this transition-metal-free system.

Introducing an alkyl group and an amino group onto the double bond of an alkene can directly construct structurally diverse amine derivatives.[100] In 2024, the Glorius research group developed a novel oxime-carbonate bifunctional reagent **50-A** (Scheme 50).[101] Energy transfer promotes the homolysis of the N–O bond in this reagent, generating an imine radical **50-B** and a carbonate oxygen radical. The elimination of CO$_2$ gives rise to a short-lived O-centered radical **50-C**, followed by a radical Brook rearrangement that causes the silyl group to transfer from carbon to oxygen, yielding a stabilized α-oxy-carbon-centered radical **50-D**. The radical intermediates **50-B** and **50-D** can effectively complete the radical addition coupling reaction with the alkene, leading to the formation of the expected target product.

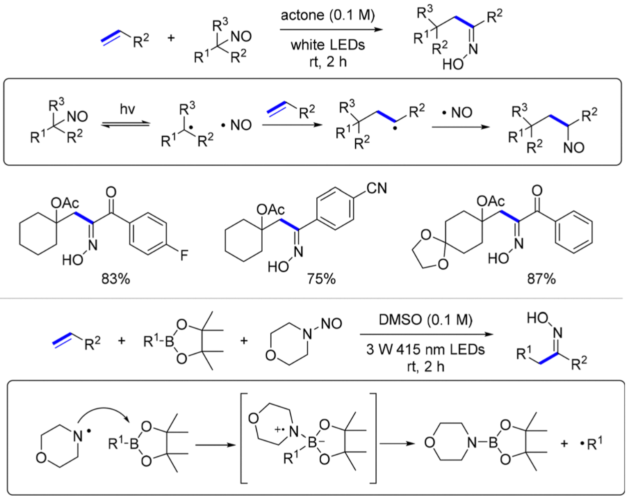


Scheme 50 Aminoalkylative amination of alkenes.

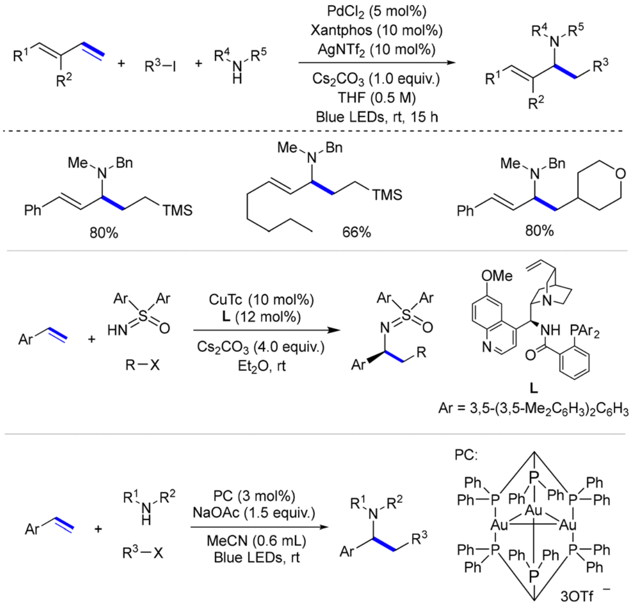
In 2021, Studer put forward a distinctive carboamination reaction of alkenes mediated by nitroso compounds (Scheme 51).[102] Inspired by the Barton nitrite ester reaction, they conceived the idea of extending the homolytic cleavage of O–NO σ-bonds to the C–NO σ-bonds. Therefore, they synthesized acyloxy nitroso compounds from oximes. Subsequently, they conducted attempts under visible-light-induced reaction conditions. The results supported the initial hypothesis. During the homolytic cleavage of the C–NO σ-bond, an alkyl carbon radical and an NO radical are generated. The nucleophilic alkyl carbon radical will add to the electron-deficient alkene, and the newly formed radical will be rapidly captured by NO to form the corresponding nitroso compound. Finally, tautomerization leads to the formation of the oxime.

In 2023, the Studer research group once again achieved the 1,2-alkyl-oximation reaction of electron-deficient olefins under photochemical conditions. In this protocol, the alkyl radicals are derived from readily accessible alkylboronic pinacol esters (APEs). The homolytic cleavage of the N–N bond in *N*-nitrosamines induced by light generates aminyl radicals. This radical species can transform alkylboronic pinacol esters into alkyl radicals through nucleohomolytic substitution. Primary, secondary, and tertiary APEs are capable of serving as alkyl radical precursors and engaging in the anticipated transformation.

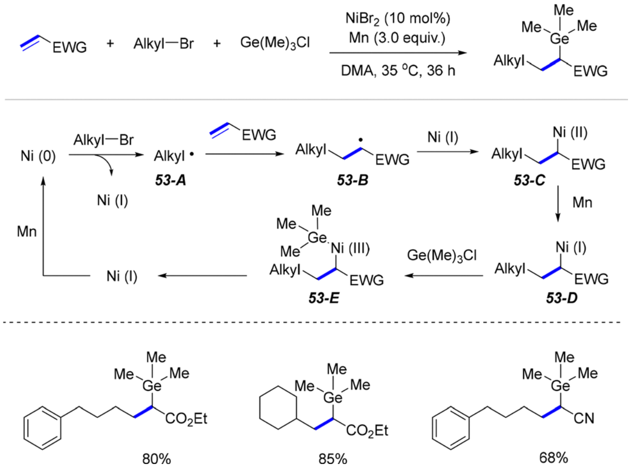
Alkylamination of olefins using amine nucleophiles as amine sources generally requires the mediation of transition metals.[103] In 2020, Gevorgyan and co-workers reported the



Scheme 51 1,2-Alkyl-oximation of alkenes.



Scheme 52 1,2-Aminoalkylation of alkenes.



Scheme 53 Germylative alkylation of alkenes.

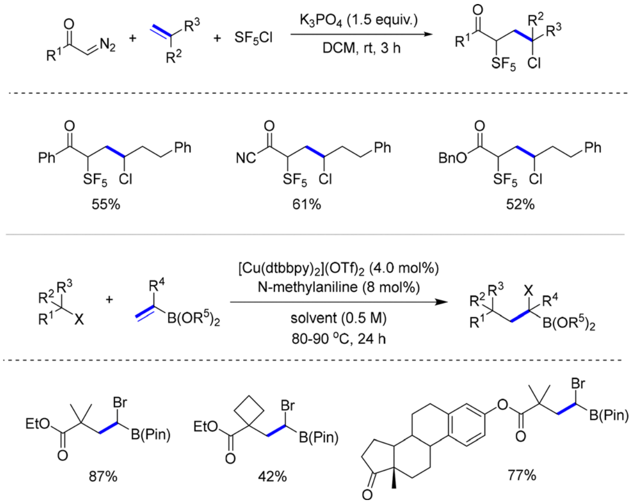
1,2-aminoalkylation of conjugated dienes (Scheme 52). In this radical-polar crossover pathway, photoexcited LnPd^0 reduces alkyl iodides to alkyl radicals *via* single-electron transfer. Subsequent radical tandem addition followed by coupling with an amine nucleophile leads to the formation of the expected product. This method has proven to be practical in the late-stage derivatization of complex molecules and drugs. In 2022, Liu presented a protocol for the chemo- and enantioselective radical 1,2-carboamination of alkenes. This copper-catalyzed system requires the collaborative regulation between the counterion and the highly sterically demanding ligand. It is worth mentioning that this system can not only accommodate sulfoximines as amine nucleophiles but also be compatible with various alkyl radical precursors. They also further developed the enantioselective radical 1,2-carbophosphonylation of styrenes. Dixon's *N*,*N*,*P*-ligand was used to control the stereoselectivity.

In 2023, Xie disclosed a unique 1,2-aminoalkylation of alkenes catalyzed by the trinuclear gold catalyst [Au$_3$(tppm)$_2$](OTf)$_3$. Mechanistic studies revealed that under light irradiation, the inner-sphere single-electron transfer pathway enables the cleavage of the unactivated C–Br bond to generate alkyl radicals. More than 100 examples demonstrate the excellent functional group compatibility of this reaction system. In addition, the carbophosphonylation of styrenes has also been reported. Liu used organophosphorus reagents as nucleophiles to stereoselectively synthesize α-chiral alkyl phosphorus compounds in a copper-catalyzed system.[104] There are also only a few examples of the carbohydroxylation of alkenes, and the substrate scope is highly limited.[105]

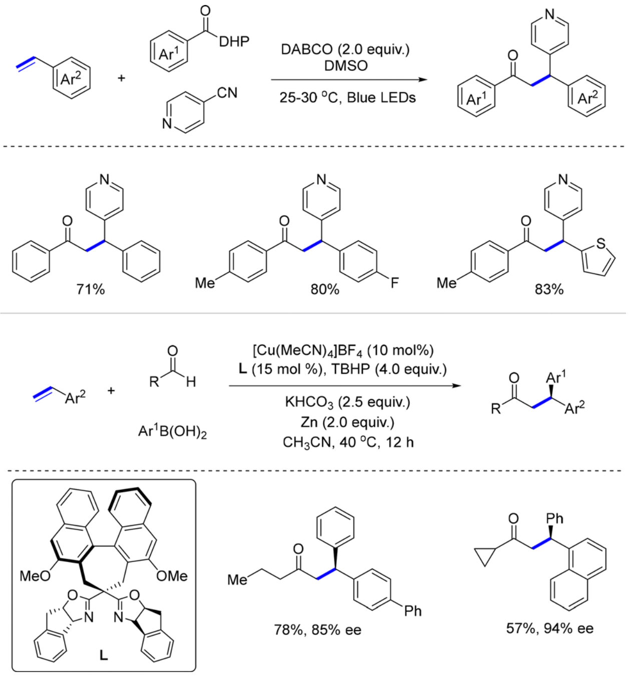
Due to its hydrophobicity and low toxicity, germanium is considered a bioisostere of carbon in medical chemistry. Organogermanium compounds are often used in biological and pharmacological research. It is challenging to modularly synthesize organogermanium compounds through the construction of C–Ge bonds.[106] In 2023, the Zhang research group disclosed a method for the germylative alkylation of activated olefins (Scheme 53). In this system, alkyl bromide serves as the alkyl radical precursor. Under the catalysis of nickel, an alkyl radical **53-A** is generated. This radical is captured by the activated olefin, giving rise to a new electrophilic carbon radical **53-B**. Ni(I) combines with **53-B** to obtain alkyl-Ni(II) **53-C**. Subsequently, manganese reduces intermediate **53-C** to the alkyl-Ni(I) intermediate **53-D**. **53-D** undergoes oxidative addition to chlorogermane to yield **53-E**, and the expected product is delivered after reductive elimination. This platform provides a powerful tool for the construction of highly structurally diverse organogermanium compounds. It is worth mentioning that the synthetic value of this protocol has been further verified. Biological experimental studies have found that the germanium-modified ospemifene compound exhibits better pharmacological effects on breast cancer cells.

The strategy of halogen atom transfer (XAT) is an effective approach for constructing carbon–halogen bonds *via* alkyl carbon radicals.[107] In 2022, Qing reported a novel three-component radical addition reaction for the selective synthesis of α-alkyl-α-SF$_5$ carbonyl compounds (Scheme 54).[108] This three-component addition reaction involves SF$_5$Cl, olefins, and diazo compounds. First, the SF$_5$ radical reacts with the diazo compound. Then, the *in situ* generated carbon radical adds to the olefin. Finally, the carbon radical abstracts a Cl atom from SF$_5$Cl to afford the final product. In 2023, the Hull research group developed a Cu-catalyzed radical addition and halogen atom transfer reaction system for the synthesis of α-haloboronic esters. Alkyl bromides were developed as carbon–halogen bifunctionalization reagents, and the halogen atom transfer of the α-boryl radical intermediate is the key to constructing the carbon–halogen bond.

3.2.3 Acyl radicals. Acyl radicals are highly reactive nucleophilic intermediate species. The groups connected to the carbonyl group can be alkyl groups, aryl groups, or other organic groups. In recent years, the acyl radical has often been



Scheme 54 Alkylhalogenation of olefins.



Scheme 55 Acylative pyridylation and acylarylation of styrenes.

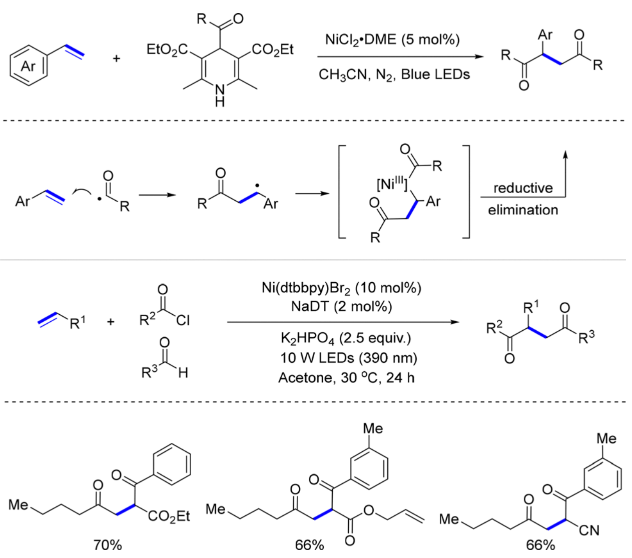
used in tandem functionalization reactions of alkenes. The precursors for generating acyl radicals can be classified into two categories: the first one is the homolytic cleavage of the C–X bond in the carbonyl-containing compound RC(O)–X to produce an acyl radical. The other is the carbonylation reaction between a carbon-centered radical and CO.

4-Cyanopyridines have been demonstrated to be an excellent reagent applicable to the intermolecular pyridylation.[109] β-Pyridinyl ketones serve as crucial structural elements in diverse bioactive substances and antibacterial agents. A visible-light-promoted acylative pyridylation of styrenes using 4-acyl-1,4-dihydropyridines (DHPs) and 4-cyanopyridines without the need for an additional photocatalyst has been reported by Chen (Scheme 55).[110] In this reaction, 4-acyl-1,4-DHPs could reduce cyanopyridines to radical anions and generate acyl radicals under visible light irradiation. Mechanistic studies show that the coupling of the cyanopyridine radical anion intermediate with the carbon radical is the core step for the successful introduction of the pyridine group. A copper-catalyzed three-component reaction has been developed. In this reaction, vinylarenes, aldehydes, and aryl boronic acids are involved, and it proceeds through a radical process to achieve asymmetric acylarylation.

A three-component acylative difunctionalization reaction of alkenes that directly utilizes readily available aldehydes as the source of acyl radicals has also been reported by Xing (Scheme 55).[111] This method initially generates acyl radicals from aldehydes *via* hydrogen atom transfer. The acyl radicals add to the alkenes, forming new benzylic radicals. Subsequently, benzylic radicals undergo copper-catalyzed enantioselective arylation to construct C–C(SP^2) bonds. It provides an effective way to synthesize useful chiral β, β-diaryl ketones. A chiral binaphthyl-tethered bisoxazoline ligand is of great significance for achieving excellent stereocontrol.

1,4-Dicarbonyl compounds, which possess two carbonyl groups in one molecule, are interesting motifs and versatile precursors for many natural compounds and bioactive pharmaceutical molecules. Directly attaching two carbonyl groups to the two ends of the C–C double bond in alkenes is a concise synthetic strategy. In recent years, the dicarbonylation of alkenes initiated by the addition of acyl radicals to unsaturated bonds has been well-developed.[112]

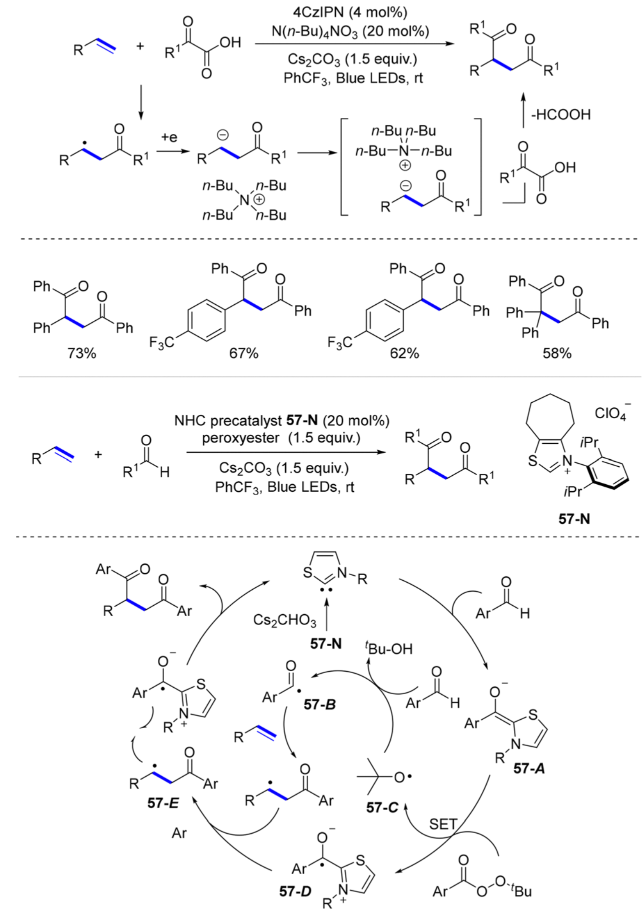
In 2020, Xia reported a Ni-catalyzed diacylation reaction of styrenes. 4-Acyl-1,4-dihydropyridines were used as acyl radical precursors. The acyl radicals added to the alkenes, and then a Ni(III) complex was formed. A reductive elimination of the Ni(III) complex occurred to construct the C–C(CO) bond and afford the desired diacylation product (Scheme 56). In 2022, Ackermann's



Scheme 56 Nickel catalyzed diacylation of alkenes.

group successfully devised a nickelaphotoredox catalysis system. By employing aldehydes as acyl radical precursors and acyl chlorides as acyl coupling reagents. This platform enables the precise and orderly installation of two different acyl groups at the two ends of the alkene. When exposed to visible light, sodium decatungstate (NaDT) gets excited to produce a photo-excited decatungstate salt. This salt can abstract a hydrogen atom from an unactivated C–H bond in aldehydes, leading to an acyl radical intermediate. When acyl radical adds to alkenes, an alkyl radical is formed. This alkyl radical can be trapped by Ni(0) to form an alkyl-Ni(I) intermediate. Subsequently, acyl chloride undergoes oxidative addition to the alkyl-Ni(I) intermediate, creating a nickel(III) species. The nickel(III) species then undergoes reductive elimination, yielding the corresponding carbonyl compounds and a nickel(I) species.

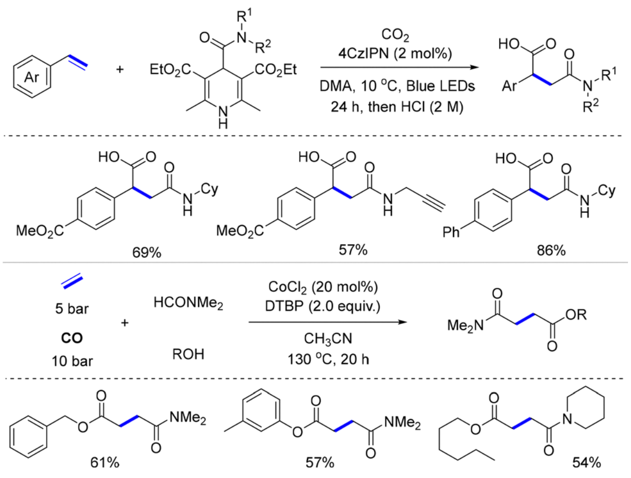
In addition, Wu reported a metal-free, redox-neutral, and regioselective 1,2-dicarbonylation reaction of alkenes through photocatalysis (Scheme 57).[113] Studies have shown that α-keto acid is an acyl precursor with tunable reducibility and electrophilicity. It can be used to generate acyl radicals and participate in electrophilic addition processes. The key to the success of this reaction is that the tetra-*n*-butylammonium ion $N(n\text{-}Bu)_4^+$ can not only combine with anions to prevent their rapid protonation but also activate α-keto acids to undergo electrophilic addition reactions. This dicarbonylation method under mild conditions shows great potential in the derivatization of biomolecules and drug molecules.



Scheme 57 Oxidative NHC-catalyzed diacylation of alkenes.

N-heterocyclic carbene (NHC) organocatalysis is a classic system that uses aldehydes as acylation coupling reagents.[114] In 2022, Li developed a novel oxidative radical NHC catalysis system (Scheme 57). By employing peroxides as external single-electron oxidants diacylation of diverse alkenes was achieved. Detailed mechanistic verification elucidated the NHC organocatalytic radical reaction mechanism. During this process, under the action of a base, the aldehyde reacts with the carbene catalyst to generate Breslow intermediate **57-A**. The single electron transfer (SET) of intermediate **57-A** to the peroxide produces acyl radical **57-B** and *t*-butyloxyl radical species **57-C**. This highly reactive oxygen-centered radical is capable of abstracting a hydrogen atom from the aldehyde substrate, thus forming the corresponding acyl radical species. This acyl radical species easily undergoes a radical addition reaction with the alkene substrate, giving rise to a stabilized benzyl radical **57-E**. Subsequently, the benzyl radical combines with the persistent ketyl radical **57-D** to create a C–C bond. This process then liberates the carbene organocatalyst and results in the generation of ketone products.

The carbamoyl radical has properties similar to those of the alkyl acyl radical and the aryl acyl radical. The research group of Paixão has presented a redox-neutral multicomponent reaction that can successfully synthesize β-amidated carboxylic acids with favorable yields (Scheme 58).[115] This reaction procedure utilizes 1,4-carbamoyldihydropyridine as the radical source material. The reduction of carbon radicals generates carbanions, which then undergo nucleophilic attack on carbon dioxide to achieve carboxylation. Especially when using $^{13}CO_2$, this approach enables the production of 1,2-dicarboxylic compounds with isotope labels. Direct and simultaneous installation of amide and ester groups on the double bond of enones is also a powerful tool for the synthesis of β-amidated carboxylic acid derivatives. The aminoacyl radical is derived from

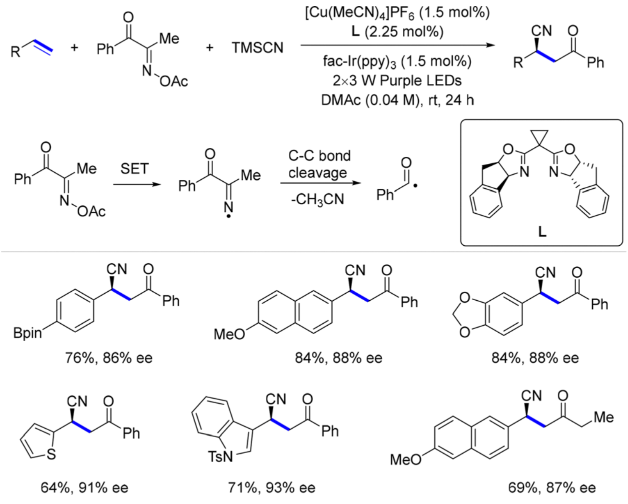


Scheme 58 Diacylation of alkenes from carbon dioxide and carbon monoxide.

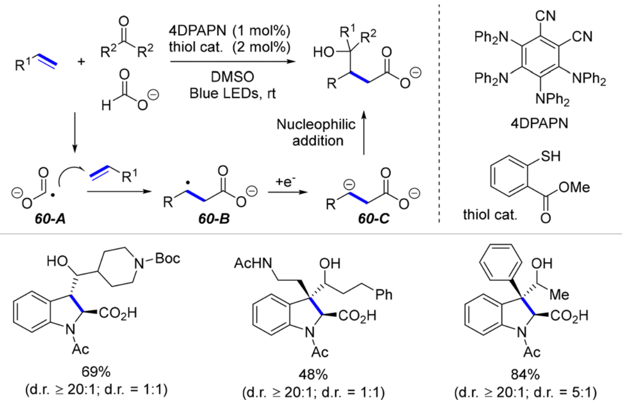
formamide. The highly reactive alkoxy radical is capable of abstracting a hydrogen atom from the acyl group in the formamide structure. Cobalt(III) metal serves as the medium for the capture of the carbon radical and the insertion of CO. The most remarkable feature of this transformation is that by using an inexpensive cobalt catalyst, two small molecular building blocks, carbon monoxide and ethylene, can be constructed into valuable motifs.

α-Carbonyl oxime esters have been designed and synthesized as precursors for acyl radicals, and these precursors exhibit excellent performance in the asymmetric dicarbofunctionalization of alkenes.[116] In 2022, the Chen group developed a dual catalytic system combining copper and photoredox catalysis, which can stereoselectively introduce two valuable functional groups, namely an acyl group and a cyano group, simultaneously to the carbon–carbon double bond of alkenes (Scheme 59). Under photocatalytic conditions, the photosensitizer transfers an iminyl radical to α-carbonyl oxime esters through single-electron transfer. The cleavage of the C–C bond triggered by the nitrogen-centered iminyl radical is the key to generating the acyl radical. The transformation of the imine bond to a cyano group is the driving force for the departure of acetonitrile. The LCu(II)(CN)$_2$ complex derived from TMSCN results in the formation of valuable optically active β-cyano ketones.

Alkene carboxy-alkylation has long been regarded as challenging. The radical polar crossover process, based on a unique mechanism, the transformation of electrophilic radicals into nucleophilic carbanions, provides important opportunities to address regioselective olefin carboxy-alkylation.[117] In 2024, Wickens employed the addition of nucleophilic $CO_2^{\bullet-}$ to alkenes to achieve carboxylation (Scheme 60), which improves upon the traditional dependence on electrophilic CO_2. In this new photocatalytic platform, sulfur radical-mediated hydrogen atom transfer can generate the nucleophilic $CO_2^{\bullet-}$ radical **60-A** from formate. Subsequently, **60-A** rapidly adds to the alkene. The further-obtained carbon radical **60-B** gains an electron through the reduction of the catalyst, leading to a radical-polar crossover. Then the key carbanion **60-C** attacks the carbonyl electrophile to obtain the designed product.



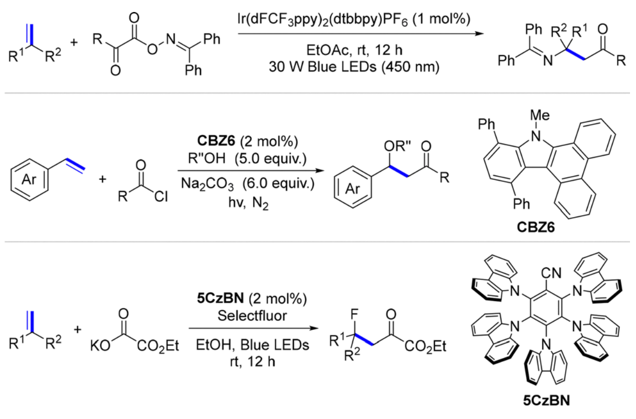
Scheme 59 Acylcyanation of alkenes.



Scheme 60 Carboxy-alkylation of alkenes.

Constructing β-aminoketone and β-amino acid ester derivatives through the carbonylative amination of alkenes has been proven to be a feasible method.[118] In 2022, the Yang research group developed a bifunctional reagent based on the structure of oxime ester capable of simultaneously generating iminyl and alkoxycarbonyl/benzoyl radicals (Scheme 61). They also established a photocatalytic synthesis protocol for the activation of oxime oxalate and oxime phenylglyoxylate. Under light irradiation, the photosensitizer acts on the bifunctional reagent through energy transfer, promoting the homolysis of the N–O bond and the decarboxylation to generate iminyl and alkoxycarbonyl/benzoyl radicals. In this reaction, the carbonyl radical is captured by the alkene to form a stable carbon-centered radical. The carbon-centered radical will form a C–N bond through cross-coupling with the long-lived nitrogen-centered iminyl radical.

In 2023, Kang revealed a photocatalytic redox-neutral alkoxyacylation reaction of alkenes for the construction of β-alkoxyketones (Scheme 61). It is worth mentioning that the organic photocatalyst CBZ6 used in this strategy has an oxidation

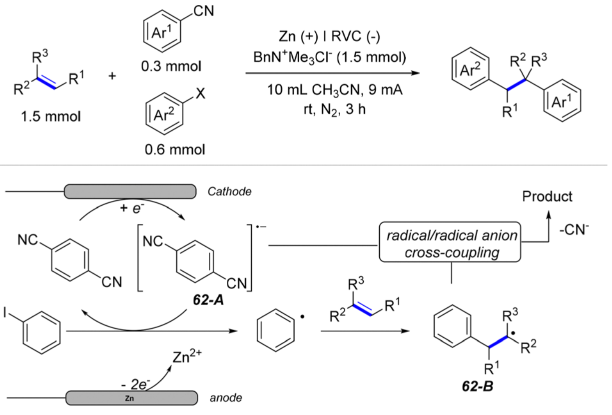


Scheme 61 Carbonylimidation/alkoxyacylation/fluorocarbonylation of alkenes.

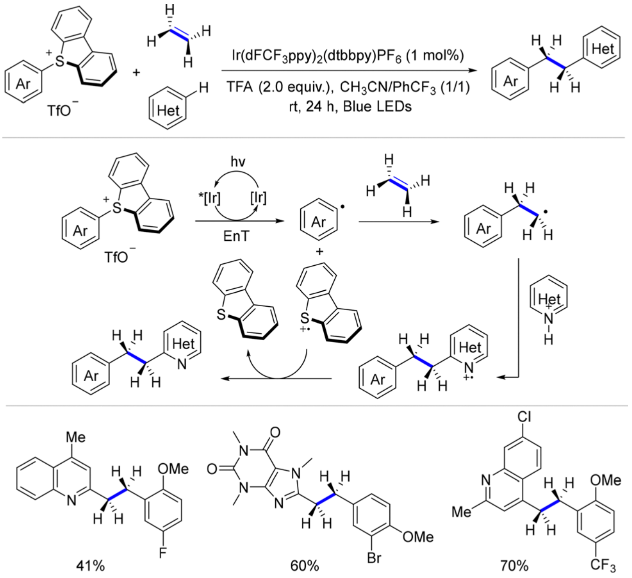
potential reaching −2.16 V (*versus* the saturated calomel electrode), which indicates that it has sufficient ability to oxidize the benzyl radical intermediate into a benzyl cation. This protocol provides a concise approach for the synthesis of β-functionalized ketones. To directly obtain β-fluorinated carboxylic acid esters from simple alkenes, Wu developed a method for the rapid simultaneous introduction of a fluorine atom and an ester group into the C=C bond.[119] In this method, potassium 2-ethoxy-2-oxoacetate serves as the radical precursor, and single-electron oxidation can lead to the decarboxylation to generate the alkoxycarbonyl radical. Selectfluor acts as both the source of the fluorine atom and the terminal oxidant.

3.2.4 Aryl radicals. Radical arylation, represented by Meerwein arylations, provides a useful method for the formation of C–C bonds. However, the use of aryl diazonium salts not only poses the risks of thermal instability and even explosiveness, but also may lead to various side reactions, often resulting in a low yield of the target transformation. In recent years, with the successive development and application of new types of aryl radical precursors, substantial achievements have been made in the field of radical arylation. Based on this, the tandem arylation of alkenes mediated by aryl radicals has also been fully developed.

The challenge in introducing two similar aryl groups into alkenes lies in effectively regulating the intricate regioselectivity.[120] In 2023, Lei's research shows that aryl nitriles can not only serve as aryl radical precursors but also act as redox mediators during the electrolysis process (Scheme 62).[121] Therefore, under the conditions of electrocatalysis, an intermolecular regioselective 1,2-diarylation of alkenes using bis-electrophilic reagents has been developed. Mechanistic studies suggest that the reaction starts at the cathode. Dicyanobenzene is reduced by a single electron at the cathode to generate cyanoarene radical anions **62-A**. Then, an electron transfer occurs between **62-A** and aryl halides to generate aryl radicals. The aryl radicals add to alkenes to construct the first C–C bond, generating a benzyl radical intermediate **62-B**. Subsequently, cyanoarene radical anions **62-A** combine with **62-B** through cross-coupling. At this point, the second C–C bond has been formed, and the cyanoanion leaves to yield the final product.



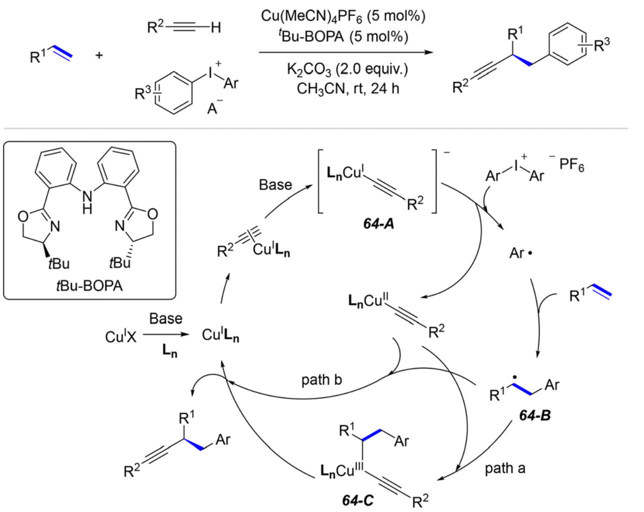
Scheme 62 Electroreduction alkene 1,2-diarylation *via* aryl radicals.



Scheme 63 Photocatalyzed alkene 1,2-diheteroarylation *via* aryl radicals.

In 2024, Wu developed an efficient visible-light photocatalysis method to assemble arenes, ethylene and heteroarenes into 1,2-arylheteroaryl ethanes (Scheme 63).[122] Aryl sulfonium salts can be readily obtained directly from arenes, which makes them an excellent choice as aryl radical precursors. Notably, although the activation of aryl sulfonium salts through single-electron transfer to generate highly reactive sp^2-hybridized aryl radicals has been extensively studied, in this protocol, the homolytic cleavage of the C–S bond in aryl sulfonium salts is initiated by triplet energy transfer (EnT). This way of activating aryl sulfonium salts under light irradiation conditions is different from other redox activation methods and is also the key step for the success of this protocol. The aryl radical will preferentially undergo a radical addition reaction with electron-rich ethylene, followed by a radical addition reaction between the nucleophilic alkyl carbon radical and the electron-deficient heteroarene. The orderly progress of this multi-component radical cascade reaction benefits from the polarity matching effect. This approach demonstrated remarkable tolerance towards functional groups. It simplifies the synthesis process of bioactive molecules along with their related derivatives. In addition, the Chen research group also reported the visible light-induced radical domino processes for achieving the 1,2-diheteroarylation of unactivated alkenes.[123] Halogenated heteroarenes, serving as radical precursors, are photocatalytically activated to generate heteroaryl radicals.

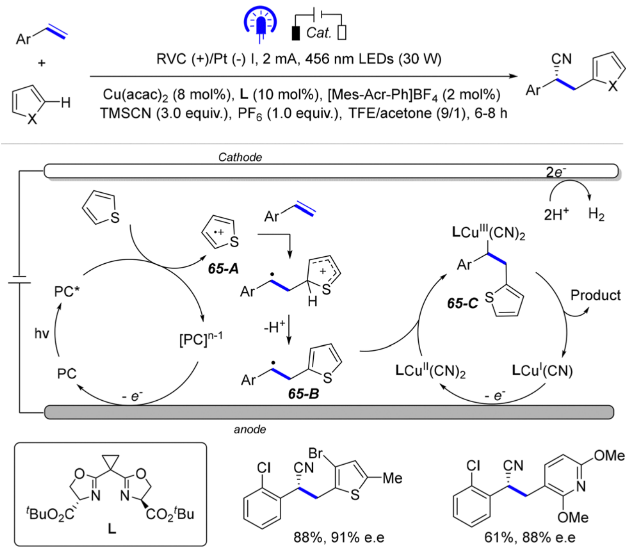
Zhang developed an enantioselective arylalkynylation reaction of alkenes, yielding synthetically valuable 1,2-diaryl-3-butynes (Scheme 64).[124] The key to the success of this copper-catalyzed three-component coupling reaction of alkenes, diaryliodonium salts, and monosubstituted alkynes is the use of the chiral bisoxazoline-phenylaniline (BOPA) ligand. In the presence of base, Cu(I)X undergoes ligand exchange to form the complex Cu(I)Ln. Subsequently, in the presence of base, it interacts with the alkyne to generate a copper(I) alkyne complex intermediate



Scheme 64 Copper-catalyzed enantioselective arylalkynylation of alkenes *via* aryl radicals.

64-A, which can reduce the diaryliodonium salt to obtain an aryl radical and a copper(II) alkyne intermediate. The carbon radical **64-B** generated by the addition of the aryl radical to the alkene is captured by the copper(II) alkyne intermediate and generates **64-C**. Finally, reductive elimination occurs to construct the C(sp^3)–C(sp) bond and produce the expected product.

Heteroarenes often serve as acceptors for nucleophilic carbon radicals in Minisci reactions. However, the C–H bonds of unfunctionalized heteroarenes are often difficult to be directly activated to obtain the corresponding highly reactive sp^2-carbon radicals. In 2024, the Xu research group utilized unfunctionalized heteroarenes as functional group donors and achieved the enantioselective heteroarylation-cyanation of aryl olefins by means of photoelectrochemical asymmetric catalysis (Scheme 65).[125] Upon photoexcitation, the excited state [Mes-Acr-Ph]$^+$* exhibits strong oxidizing property. It can abstract an electron from the heterocyclic substrate, converting it into a heteroarene radical cation. This open-shell species **65-A** is capable of adding to the aryl olefin and then losing a proton to yield a relatively stable benzyl carbon radical **65-B.** Subsequently, under the action of the Cu(II) complex (L)CuII(CN)$_2$, it goes through the Cu(III) complex **65-C** to afford the product.

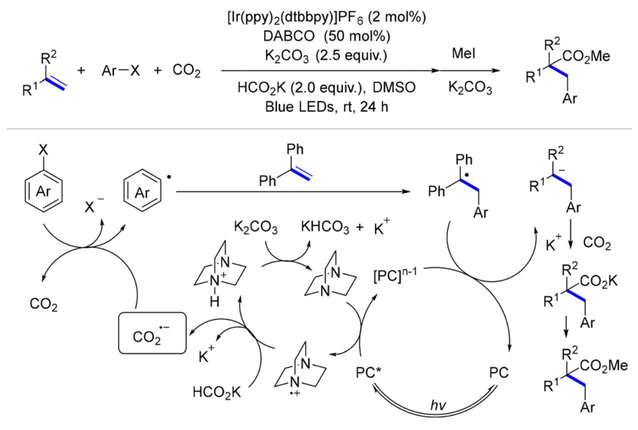


Scheme 65 Photoelectrochemical catalyzed heteroarylcyanation of alkenes *via* heteroaryl radicals.

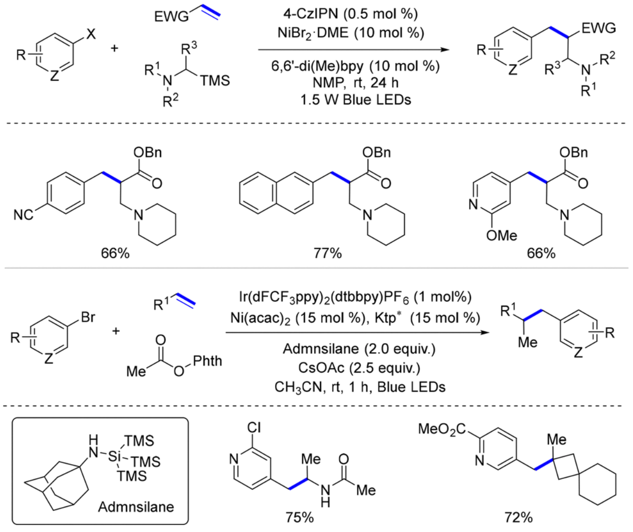
Aryl halides are arylation reagents widely used in electrophilic coupling reactions. However, their relatively high reduction potential often requires activation through an oxidative addition pathway relying on transition metals. In 2020, the Li research group disclosed a novel and highly reductive reaction protocol that can reduce aryl halides to aryl radicals (Scheme 66).[126] By combining alkenes with carbon dioxide, they successfully achieved the carboarylation of alkenes. Under visible light irradiation, this platform uses the low-cost potassium formate (HCO$_2$K) as the terminal reductant and DABCO as the proton and electron transfer medium to efficiently generate aryl radicals. Through the tandem addition to alkenes and consecutive single-electron reduction, carbon dioxide is captured by the benzyl carbanion.

Regarding the generation of aryl radicals by the activation of aryl halides, apart from the single-electron reduction mechanism, the halogen-atom transfer (XAT) is a novel way to activate C–X bonds. In 2024, the Yuan research group reported a Ni(0)-mediated halogen-atom transfer (XAT) strategy for C–I bond activation of iodobenzene (Scheme 67).[127] The role played by the transition metal Ni(0) is different from that in the traditional oxidative addition mechanism. An open-shell singlet XAT transition state has a lower activation energy barrier, and the *para*-Me-substituted bipyridyl (bpy) ligand plays a key regulatory role. This strategy has been successfully applied to the 1,2-alkylarylation of alkenes. The cross-coupling among aryl radicals, α-silylamines, and electron-deficient alkenes can concisely construct a series of β-amino acid derivatives with rich structures.

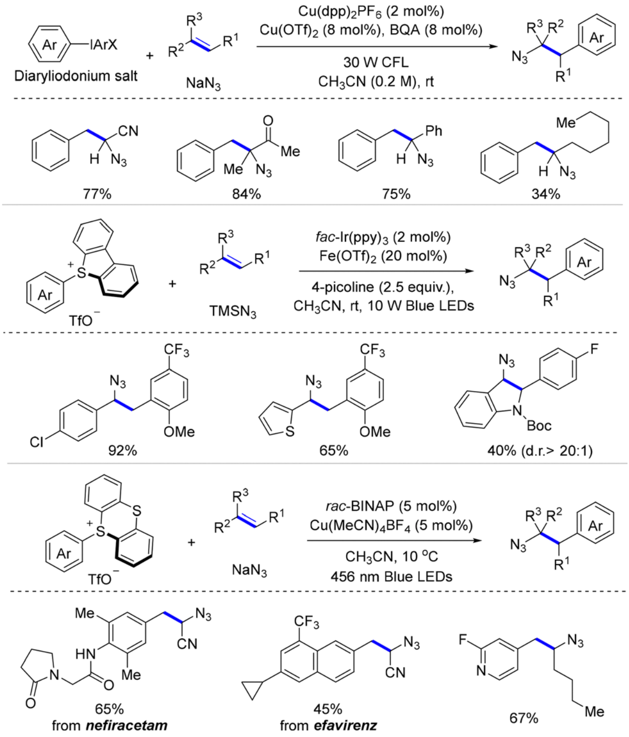
Macmillan's group also disclosed an arylalkylation strategy for alkenes in 2024 (Scheme 67).[128] This protocol ingeniously combines the XAT with the triple radical sorting mechanism, efficiently and precisely introducing two types of electrophilic



Scheme 66 Photocatalyzed alkene carboarylation *via* aryl radicals.



Scheme 67 Aryl-alkylation of alkenes *via* aryl radicals.

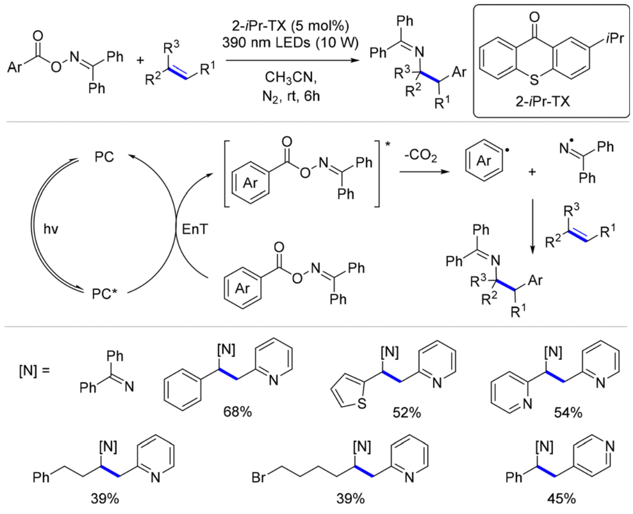


Scheme 68 Azidoarylation of alkenes *via* aryl radicals.

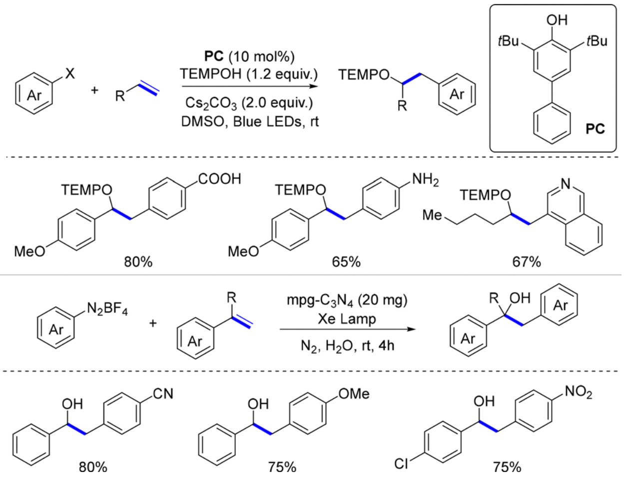
reagents, aryl and alkyl groups, into the alkenes respectively. In this process, the aryl radicals are generated through a halogen atom transfer (XAT) reaction between a silyl radical species and an aryl bromide. The silyl radicals are formed when the excited-state photocatalyst oxidizes adamantylaminosupersilane (Admn silane), followed by a rapid aza-Brook rearrangement of the adamantylaminosupersilane. Subsequently, the aryl radicals add to the unactivated alkene to form the first alkyl radical species. The redox-active ester also undergoes decarboxylation under the action of the photosensitizer to produce a primary alkyl radical. At this point, the SH_2 radical sorting catalyst plays a crucial recognition role. Influenced by the steric effect under the action of the metal complex, the two types of alkyl radicals undergo an SH2 reaction to yield the desired product. A wide range of alkenes and aryl radical precursors are applicable to this platform, which can be used to obtain complex scaffolds.

The aminoarylation of alkenes offers a direct way to obtain the β-arylethylamine core, which can act as a pharmacophore. The amino cross-coupling difunctionalization guided by the addition of aryl radicals to alkenes has expanded a new path for the construction of the β-arylethylamine skeleton. In 2021, the Gaunt research group developed a visible-light-mediated dual copper catalysis system (Scheme 68).[129] Using diaryliodonium salts as aryl radical sources and sodium azide (NaN_3) as the amine source, they successfully achieved the vicinal azidoarylation of alkenes and synthesized β-aryl azidoalkanes. Wu also developed an iron/photoredox dual catalysis system. Under mild conditions, this system allows for the modular and direct 1,2-aryl(alkenyl) amine functionalization of readily available alkenes. In this protocol, aryl DBT salts are used as aryl radical precursors and $TMSN_3$ serves as the N_3 source. The possible Fe(II)–N_3 or Fe(III)–N_3 complexes are the key to constructing the C–N bond. Subsequently, the Ritter research group utilized a single copper catalytic system composed of commercially available *rac*-BINAP and $Cu(MeCN)_4BF_4$. Without the addition of a photosensitizer, they effectively achieved the azidoarylation of alkenes *via* arylthianthrenium salts. A mechanistic study indicated that *rac*-BINAP-Cu^I-azide serves as the photoactive catalytic species.

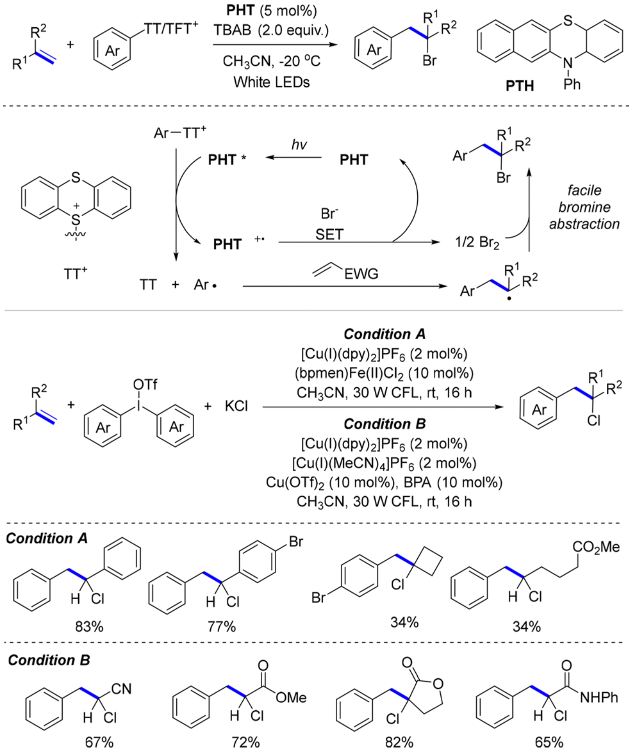
In addition, Xia reported an efficient and regioselective approach for the one-step installation of (hetero)aryl and imino groups on alkenes (Scheme 69).[130] This reaction is a photoinduced intermolecular amino(hetero)arylation reaction that does not require a metal catalyst. Under the action of an energy-transfer photocatalyst, the oxime ester compound (a stable



Scheme 69 Amino(hetero)arylation of alkenes *via* aryl or heteroaryl radicals.



Scheme 70 Oxyarylation of olefins *via* aryl radicals.



Scheme 71 Halogen-arylation of olefins *via* aryl radicals.

bifunctional reagent) undergoes homolytic cleavage to generate aryl and imino radicals. The addition of the aryl radical to the alkene, followed by the coupling with the imino radical, completes the assembly of the two functional groups.

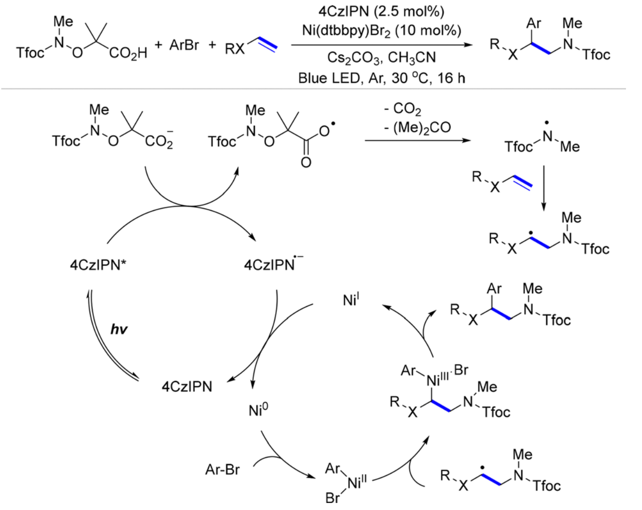
The oxidative arylation promoted by the addition of aryl radicals to alkenes provides a basis for the synthesis of arenes containing β-oxygen atoms using simple alkenes as starting materials.[131] In 2020, the Zhen research group developed a visible-light-promoted oxidative arylation reaction of alkenes catalyzed by phenolate anions (Scheme 70). They creatively discovered that phenolate anions are novel photocatalysts with a strong reduction potential. This type of photocatalyst can undergo single-electron transfer with (hetero)aryl halides to reduce them to (hetero)aryl radicals. TEMPOH can not only act as a reducing agent to participate in the photocatalyst cycle, and the released TEMPO can also couple with carbon radicals, serving as an oxygen-functional group coupling reagent. Niu also disclosed a photo-induced homogeneous hydroxyarylation reaction of alkenes. In this system, mesoporous graphitic carbon nitride (mpg-C_3N_4) is used as a recyclable photocatalyst, the diazonium salt serves as the aryl radical precursor, and water acts as both the solvent and the hydroxyl source. The excited mpg-C_3N_4 can reduce the diazonium salt to aryl radicals, which then add to the alkenes. This clean reaction system without any additives can even operate smoothly under sunlight irradiation. Its excellent substrate applicability and the ability for large-scale preparation demonstrate its advantages.

Arylthianthrenium salts and diaryliodonium salts, which are precursors that can conveniently generate aryl radicals, have also been used to introduce halogens into alkenes through the addition of aryl radicals to alkenes (Scheme 71).[132] In 2022, the Ritter research group developed a photocatalyzed Meerwein-type bromoarylation of alkenes using tetrabutylammonium bromide (TBAB) as the bromine source. Under visible-light irradiation, the organic photocatalyst PTH reaches a high-energy excited state. Arylthianthrenium salts are reduced to generate aryl radicals and $PTH^{\bullet+}$. At this time, the oxidized photocatalyst can easily oxidize bromide anions. The carbon radicals produced by the addition of aryl radicals to alkenes can readily abstract bromine.

In 2024, Gaunt reported a dual-catalytic strategy for the modular synthesis of arylchloroalkanes. This system requires visible-light induction and the combined action of a photocatalyst and a chlorine-atom-transfer catalyst to achieve the chemoselective cross-coupling of diaryliodonium salts, alkenes, and potassium chloride. Interestingly, in order to deal with different alkene substrates, they designed a series of bidentate N(sp^2)-hybridized ligands and tested them. It was found that the BPA-ligated Cu(II)-catalyst can promote the transfer of chlorine atoms to electrophilic carbon radicals, while the [(bpmen)Fe(II)Cl_2]-catalyst is more conducive to promoting the transfer of chlorine atoms to nucleophilic carbon radicals.

3.3 Nitrogen radicals

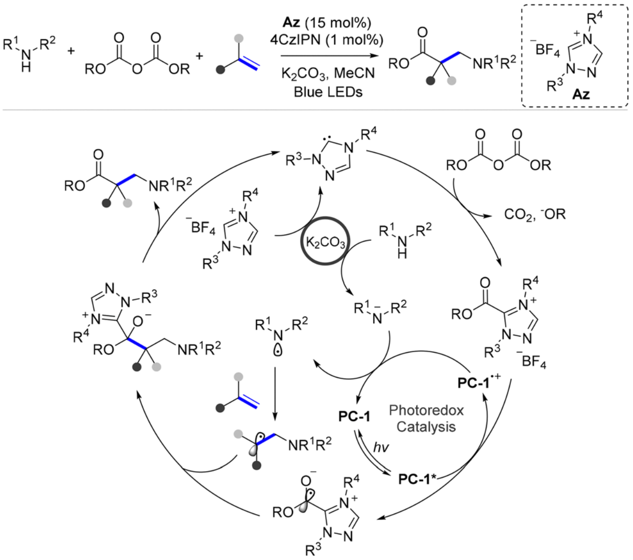
C–N bond formation is widely utilized in the synthesis of various valuable amine derivatives. Nitrogen radical-involved alkene difunctionalization has emerged as an efficient strategy for C–N bond formation. In 2021, the Studer group reported a photoredox/Ni-catalyzed 1,2-aminoacylation of vinyl ethers using acyl succinimides as electrophiles for free radical coupling (Scheme 72).[133] The catalytic cycle begins with the photoexcitation of the 4CzIPN by visible light, the excited redox photocatalyst oxidizes the acyl succinimide to generate a carboxyl radical, which fragments to produce carbon dioxide, acetone, and an electrophilic nitrogen radical. The nitrogen radical adds to the olefin to obtain a radical intermediate, which is trapped by the Ni(II)–Ar species, and undergoes reductive



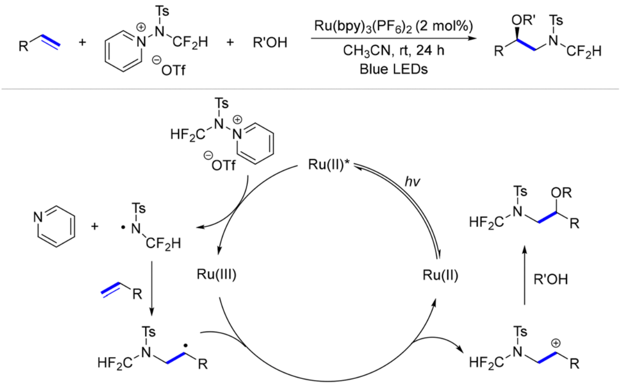
Scheme 72 Photocatalyzed aminoarylation of olefins *via* amidyl radicals.

elimination to afford the product. Using 2,2,2-trifluoroethoxycarbonyl-protected α-aminooxy acids as N-radical precursors, this method achieves the difunctionalization of electron-rich olefins under mild conditions, offering a practical route to α-aryl-β-amino alcohols and α-aryl-β-aminoalkyl amines.

β-Amino acids are valuable motifs in bioactive molecules and natural products, serving as key precursors for γ-amino-alcohols, β-lactams, and other important structures in synthesis, catalysis, and medicine. In 2023, the Scheidt group reported that dual NHC/photocatalysis with ester incorporation and a novel N-radical generation protocol would enable a new strategy for β-2,2-amino ester synthesis (Scheme 73).[134] Mechanistic investigations indicate the formation of a short-lived imidyl radical that is swiftly trapped by styrenes, along with a stabilized alkoxycarbonyl radical originating from an ester azolium generated *in situ*.



Scheme 73 Photocatalyzed aminocarboxylation of olefins *via* imidyl radicals.



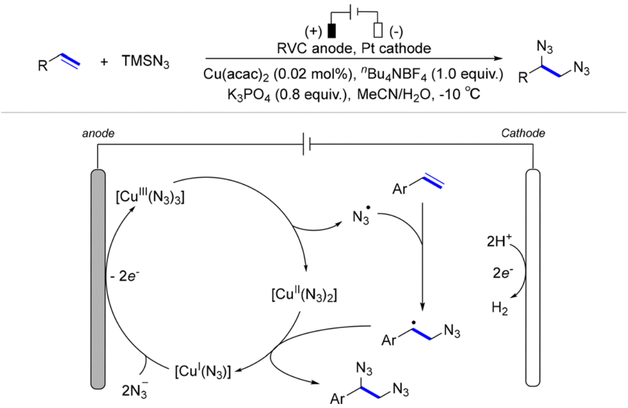
Scheme 74 Photocatalyzed *N*-(difluoromethyl)sulfonamidation of olefins.

Difluoromethyl (CF_2H) compounds have emerged as valuable hydroxyl and thiol bioisosteres, attracting significant interest for the development of agrochemicals and pharmaceuticals, with efficient incorporation methods developed. In 2023, the Prakash group successfully developed a pyridinium trifluoromethanesulfonate reagent that enables mild, visible-light-driven photoredox generation of $^{\bullet}N(Ts)CF_2H$, facilitating direct *N*-(difluoromethyl)sulfonamidation of alkenes with high efficiency (Scheme 74).[135] The excited-state ruthenium catalyst reduces the pyridinium trifluoromethanesulfonate reagent to generate the $^{\bullet}N(Ts)CF_2H$. The addition of an N-centered radical to the alkene affords an aryl radical intermediate, which undergoes oxidation to form a carbocation intermediate. Subsequently, the carbocation intermediate captured by various *O*-nucleophiles exhibits excellent functional group tolerance and outstanding regioselectivity.

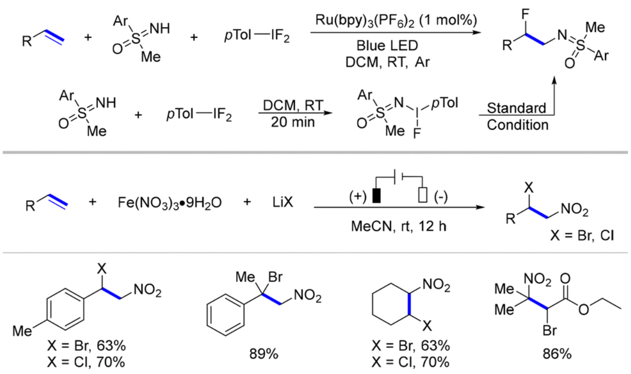
Recently, Chen's group reported a photoinduced, copper-catalyzed asymmetric three-component radical 1,2-azidooxidation reaction.[135i] This protocol, operating under mild and redox-neutral conditions, enables the efficient coupling of 1,3-dienes, azidobenziodoxolone (Ts-ABZ), and carboxylic acids, delivering valuable azidated chiral allylic esters with broad functional group tolerance, good yields, and excellent enantioselectivity.

In 2022, the Xu group reported a ligand-free copper-electrocatalytic method that enables scalable diazidation of diverse alkenes (Scheme 75).[136] The azidyl radicals generated from $Cu^{III}(N_3)_3$ at the anode react with the alkene to form an alkyl radical intermediate which attacks the copper center and undergo reductive elimination to yield the final product. The metal-catalyzed diazidation of alkenes has been successfully achieved in the past,[136t] featuring low catalyst loading, broad functional group tolerance, and scalability. This electrocatalytic method offers an attractive approach for the diazidation of α,β-unsaturated carbonyl compounds as well as mono-, di-, tri-, and tetrasubstituted unactivated alkenes, enabling efficient access to vicinal diamines.

Aminohalogenation of alkenes offers a complementary strategy for synthesizing valuable amines, providing versatile intermediates for the rapid construction of diverse derivatives. In 2020, the Bolm group developed a novel *in situ* generated hypervalent iodine(III) reagent that enables the photocatalytic



Scheme 75 Cu-electrocatalytic 1,2-diazidation of olefins *via* azide radicals.

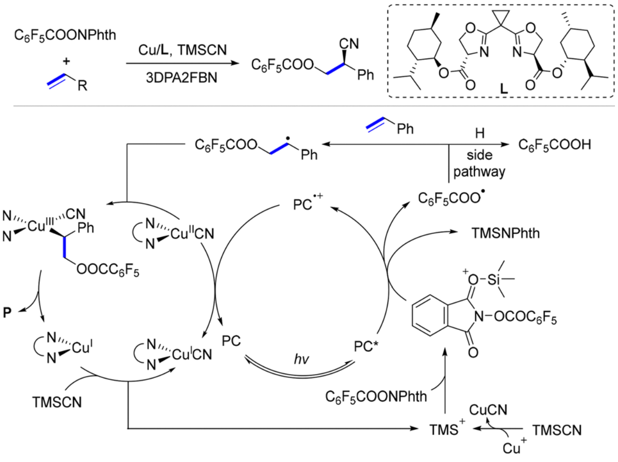


Scheme 76 Halonitration of olefins *via* N-centered radicals.

fluoro sulfoximination of alkenes in a single operational step (Scheme 76).[137] The mechanism study shows that the hypervalent iodine(III) reagent is the key intermediate that radically adds two of its iodine-bound substituents to alkenes. Recently, Katayev published an electrocatalytic nitrohalogenation of olefins *via* nitro radical intermediates.[137g] This strategy enables redox-mediated activation of $Fe(NO_3)_3$ at ambient temperature, providing a versatile platform for modular synthesis of structurally diversified nitroarenes under mild conditions.

3.4 Oxygen-centered radicals

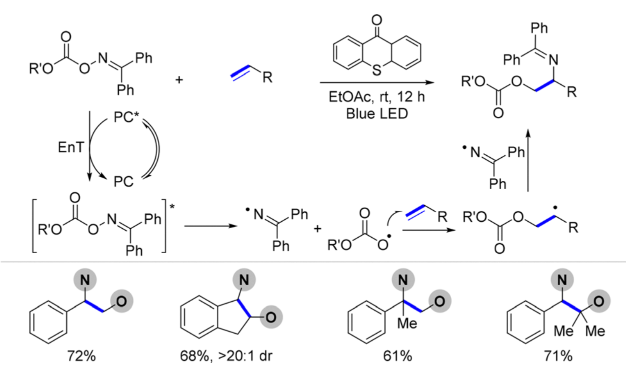
Compounds bearing oxygen atoms are ubiquitous in bioactive molecules and functional materials, driving intense research efforts toward innovative strategies for constructing C–O bonds through novel synthetic methodologies. In 2021, the Lu group reported the enantioselective oxocyanation and aminocyanation of alkenes *via* a dual photoredox/copper catalytic system, where *N*-(aroyloxy)phthalimide serves as a common precursor to selectively generate either oxygen-centered aroyloxy radicals or nitrogen-centered phthalimidyl radicals (Scheme 77).[138] The excited photocatalyst oxidate the *N*-(aroyloxy)phthalimide to generate a phthalimidyl radical, which adds to styrene to form an alkyl radical intermediate. The addition of radicals to Cu(II) produces Cu(III), leading to the desired aminocyanation product by reductive elimination with excellent functional group tolerance and outstanding regioselectivity.



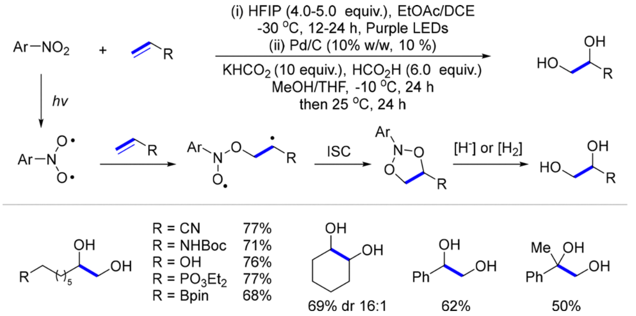
Scheme 77 Photocatalyzed halonitration of olefins *via* N-centered radicals.

In 2023, the Glorius group explored an oxime carbonate for the regioselective oxyimination of unactivated alkenes, enabling one-step construction of biologically critical 1,2-aminoalcohol scaffolds, with the EnT event between the excited photocatalyst and oxime carbonate (Scheme 78).[139] The alkoxycarbonyloxyl and iminyl radicals were generated through the homolytic cleavage of the N–O bond, and the alkoxycarbonyloxyl radical is captured by the alkene to generate a stabilized C-centred radical, which finally couples with long-lived N-centred iminyl radical to generate the desired 1,2-oxyimination product. The divergent reactivities of radicals enable oxyimination of alkenes under mild and modular conditions, demonstrating broad compatibility with diverse functional groups.

Vicinal diols are widely present in both natural and synthetic molecules, playing a crucial role as valuable intermediates in organic synthesis, particularly in the development of bioactive compounds and high-value pharmaceuticals. Recently, the Leonori group reported a one-pot reductive protocol for the general dihydroxylation of olefins, utilizing nitroarenes as photoactive oxidants to achieve selective N–O bond cleavage under visible-light irradiation (Scheme 79).[140] Purple LED irradiation could activate the nitroarenes; following the intersystem crossing



Scheme 78 Photocatalyzed halonitration of olefins *via* N-centered radicals.

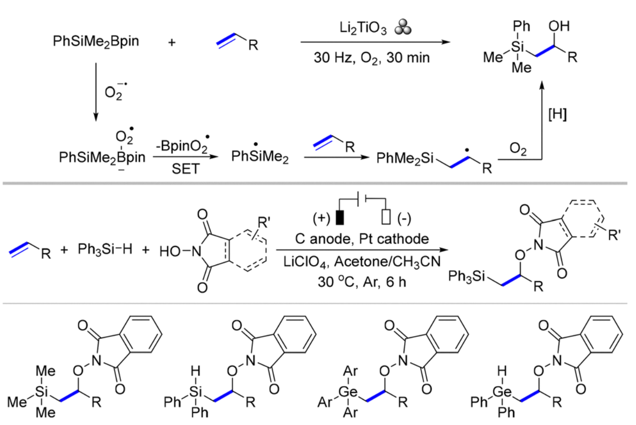


Scheme 79 Dihydroxylation of olefins using nitroarenes as photoresponsive oxidants.

(ISC), a long-lived triplet state nitroarene ensures addition to olefins to produce an intermediate triplet biradical. With the involvement of intersystem crossing (ISC), the intermediate undergoes cyclization to form the 1,3,2-dioxazolidine species, which is then subsequently reduced by H2 to yield the final product.

3.5 Silicon-centered radicals

Organosilicon compounds, owing to their unique properties have attracted significant interest in the development of efficient synthetic methods across diverse fields. In 2021, the He group developed an electrochemical radical silyl-oxygenation of electron-deficient alkenes, enabling the efficient and selective synthesis of diverse silicon-containing molecules under mild, metal-free conditions (Scheme 80).[141] Electrochemical activation of Si–H bonds to generate silyl radicals offers a promising strategy for the sustainable and green synthesis of valuable organosilicon compounds, which is also compatible with Ge–H bond activation. Recently, the Lian group reported a novel mechanochemical 1,2-hydroxysilylation of alkenes *via* a single-electron transfer pathway, using piezoelectric Li_2TiO_3 as a redox catalyst under mild, operationally simple conditions with broad substrate scope.[142] The mechanism shows that superoxide radicals were reduced *via* ball-milling. This mild method features excellent functional group compatibility, operates under simple and solvent-free conditions, and enables rapid reaction times. Mechanistic studies suggest that under ball-milling conditions, silylboronates are converted into silicon radicals by highly polarized Li_2TiO_3 particles in the presence of oxygen.

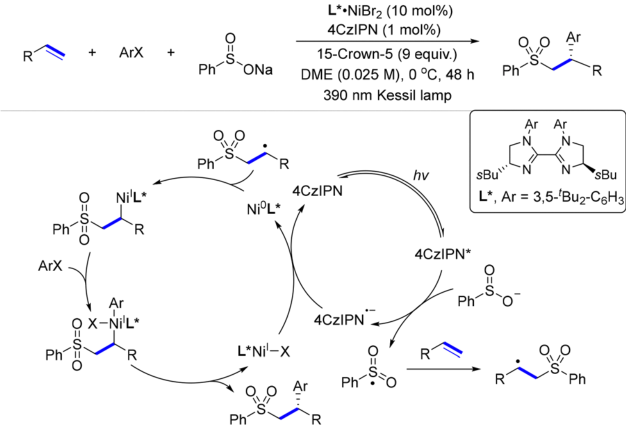


Scheme 80 Silyl-oxygenation of olefins *via* silyl radicals.

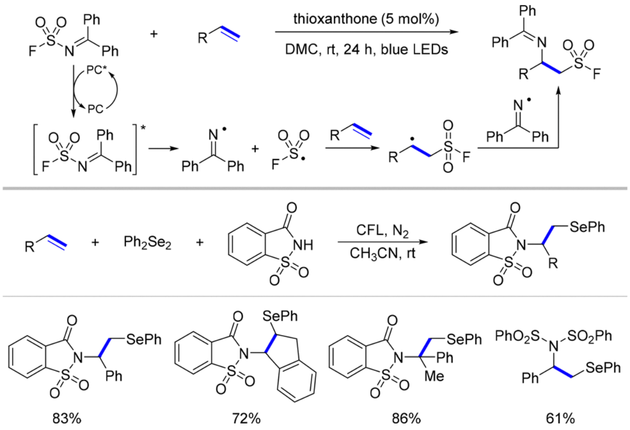
3.6 Sulfur-centered radicals

Sulfones are valuable structural units with broad applications, and visible-light-mediated sulfonylation using readily available sulfonyl chlorides or benzenesulfinate offers an efficient strategy for their introduction in organic synthesis.[143] In 2023, the Nevado group reported a dual nickel/photoredox catalytic system, enabling the arylsulfonylation of olefins with excellent regioselectivity and absolute stereocontrol (Scheme 81).[144] The photoredox cycle starts by photoexcitation of 4-CzIPN, which oxidizes sodium benzenesulfinate to generate the sulfonyl radical. The sulfonyl radical adds to the alkene to form a secondary alkyl radical, which is promptly trapped by Ni(0) to generate an (alkyl)Ni(I) intermediate, followed by oxidative addition of the aryl iodide and reductive elimination to deliver the carbosulfonylation product. This visible light-induced synergistic strategy enables the efficient and enantioselective synthesis of a broad range of β-aryl and β-alkenyl sulfones from readily available substrates under mild conditions, featuring high yields, excellent enantioselectivity, and broad functional group tolerance.

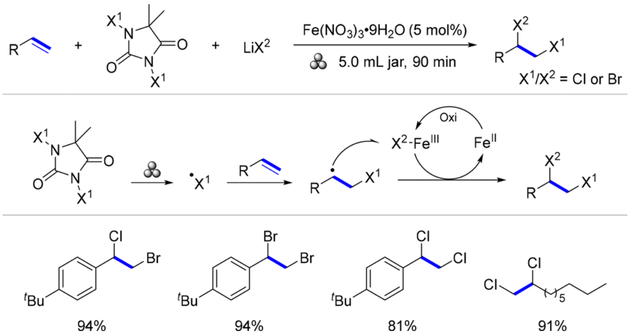
In 2023, the Glorius group developed a visible-light-driven, three-component intermolecular aminoselenation of alkenes, enabling the reaction with sulfonimides and diselenides under mild, additive- and photocatalyst-free conditions (Scheme 82).[145] Notably, this method utilizes natural sunlight and allows for the modification of styrene-functionalized biomolecules. Mechanistic experiments indicate an energy transfer (EnT) mediated process, leading to homolysis of the weak N–S σ-bond, enabling the iminofluorosulfonylation of alkene. Selenium-containing compounds are widely used in organic synthesis, driving the development of efficient methods for their simultaneous incorporation into molecules. In 2021, the Ling group reported a visible-light-driven, three-component intermolecular aminoselenation of alkenes, using sulfonimides and diselenides under mild conditions.[146] The phenylseleno radical is generated upon irradiation with visible light which operates without additives or photocatalysts.



Scheme 81 Nickel/photoredox-catalyzed carbosulfonylation of olefins *via* sulfonyl radicals.



Scheme 82 Photoredox-catalyzed imino-fluorosulfonylation of olefins *via* sulfonyl fluoride radicals.



Scheme 83 Mechanochemical dihalogenation for both activated and unactivated alkenes.

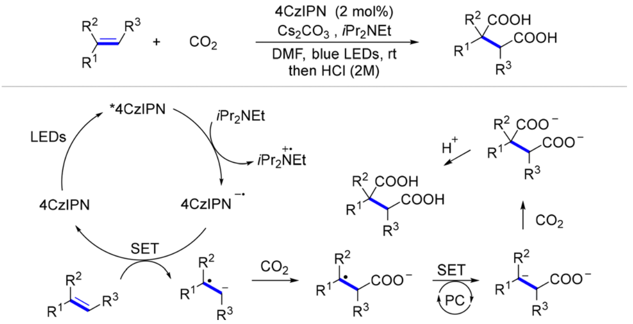
3.7 Halogen-centered radicals

Vicinal dihalides serve as key structural motifs that enable modulation of physicochemical and biological properties, leading to improved pharmacokinetic and pharmacodynamic profiles. In 2024, the Katayev group published a solvent-free, mechanochemical dihalogenation strategy using iron-mediated radical ligand transfer (RLT) catalysis, enabling tunable and efficient synthesis of diverse vicinal dihalides from alkenes (Scheme 83).[147] By using the imide-type reagents, the corresponding halogen radicals could be liberated under solvent-free, mechanochemical conditions. The halogen radicals will add to the alkenes forming the corresponding alkyl radical intermediates, which are captured by an Fe–Nu species to yield vicinal dihalides. Binding to the RLT catalyst in mechanochemistry enables the targeted transformation of a wide variety of alkenes into their corresponding vicinal dibromo, dichloro, or bromochloro products.

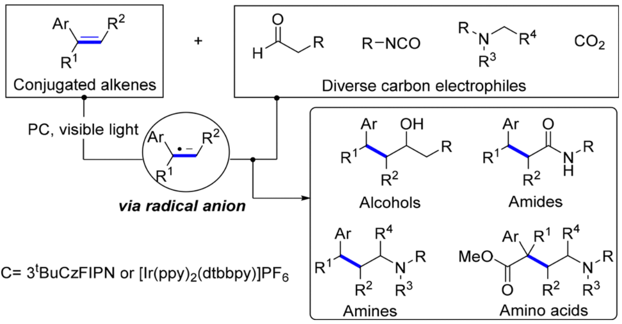
4. Oxidation or reduction of the alkenes and metal coordination with alkenes

4.1 Single-electron reduction of alkenes

In 2021, Yu's group realized the insertion of double CO$_2$ molecules into olefins through the visible light photoredox pathway (Scheme 84). This reaction contains no transition



Scheme 84 Dicarboxylation of alkenes with two CO$_2$ molecules *via* a photoredox pathway.



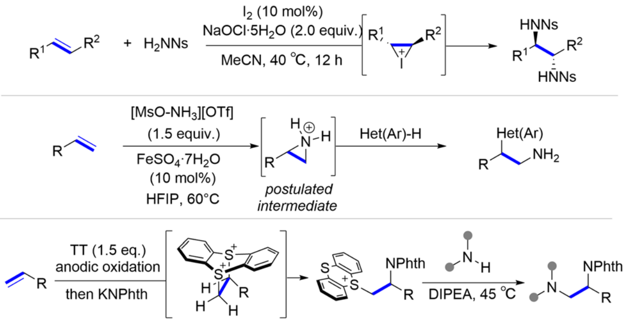
Scheme 85 Aryl alkenes are photocatalyzed to generate alkyl carbanions.

metals, has mild reaction conditions, high chemical selectivity and diasteroselectivity, and a wide range of substrates. It has broad application prospects in organic synthesis, medicinal chemistry, and materials science. The mechanism study indicates that the key intermediate is the olefin radical anion obtained by reducing the photocatalyst. Based on the above, the research group further achieved the aminocarboxylation of alkenes under light/copper co-catalysis conditions using bis-naphthol derivatives as photocatalysts. A series of valuable β-amino acid derivatives can be obtained through this reaction.[148]

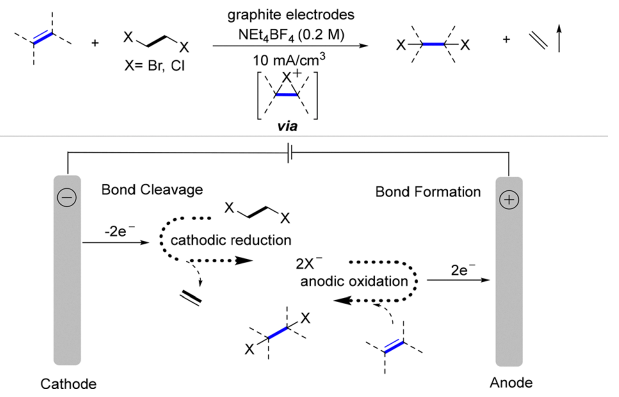
In 2024, Polyzos' research group achieved C–C bond formation reactions with various carbon electrophiles by using aryl alkenes as the source of alkyl anions through a multi-photon photoredox pathway (Scheme 85). This reaction can easily and quickly afford a series of alcohols, amides, alkylamines, and amino acid derivatives with potential application value.[149]

4.2 Oxidation of alkenes

Oxidative bifunctionalization of alkenes is usually achieved through intermediates such as iodonium, selenium, and aziridine.[150,151] For example, in 2021, Okumura's group achieved 1,2-diamination of unactivated alkenes through an iodonium intermediate.[150a] It is worth mentioning that the substrate (nitrogen source) controlled the reaction's stereoselectivity. Next, the Leboeuf group achieved 1,2-aminoarylation of alkenes through the aziridine intermediate with HFIP as the key solvent, catalyzed by iron salts.[150b] This reaction can afford a range of unprotected β-arylamines. In 2023, the Wickens group further developed the



Scheme 86 Oxidative difunctionalization of olefins *via* cyclic intermediates.



Scheme 87 Electrocatalytic dihalogenation of olefins.

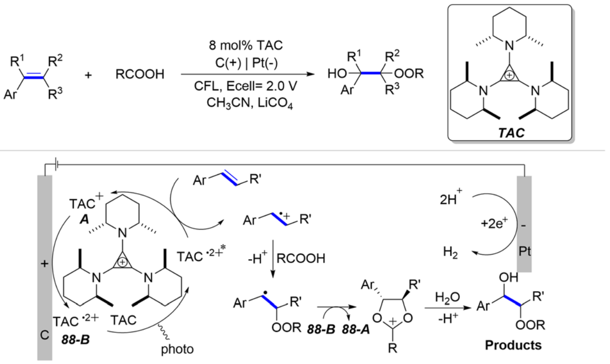
1,2-diamination of unactivated alkenes with the thianthrenium salt as a key intermediate (Scheme 86).[150c]

In addition, with the rise of electrochemistry and photochemistry in recent years, the oxidative difunctionalization of alkenes has been further developed.[152,153] For instance, in 2021, Morandi's group achieved the double halogenation of alkenes by electrocatalysis using halogenated ethane as the halogen source.[152a] This reaction is characterized by green environmental protection and high atom utilization (Scheme 87).

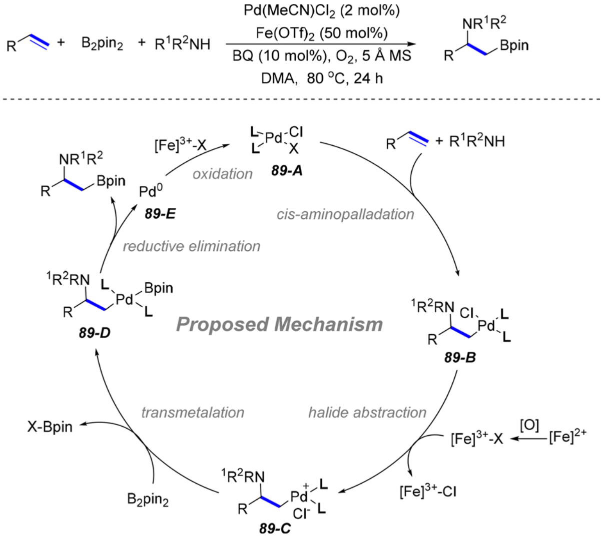
The same year, the Lambert research group used a tri-aminocyclopropene (TAC) ion catalyst to achieve selective acetoxy hydroxylation of alkenes under photoelectric synergy, with high chemical and enantiomeric selectivity.[152b] This method can be carried out in batch or flow and can achieve multiple syntheses of monoester products (Scheme 88).

4.3 Metal coordination with alkenes

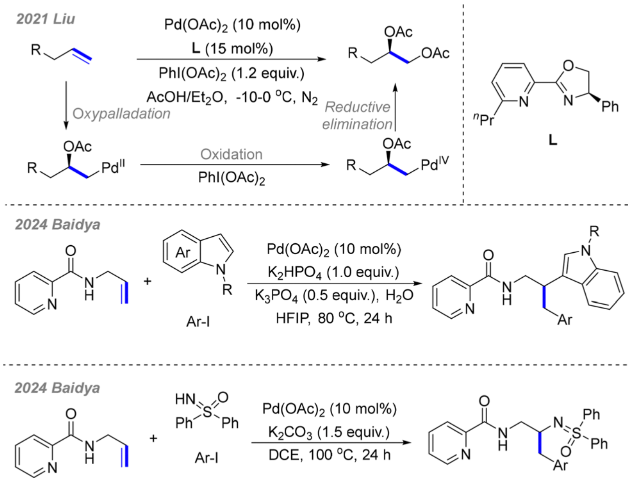
Oxypalladation and aminopalladation are the typical metal coordination and addition processes in which an oxygen atom or a nitrogen atom and a palladium atom are added across a double bond. It is well known that Wacker oxidation refers generally to the reaction of alkenes with ketones through the action of a palladium(II) catalyst, water, and oxygen. The key process to achieve this transformation is the oxypalladation of alkenes. In 2023, the Hull group developed a palladium and iron cocatalyzed alkene aminoboration *via* an aminopalladation process. The possible mechanism is depicted in Scheme 89: (i) ligand exchange with Pd(II) catalyst **89-A**, (ii) then *cis*-aminopalladation of



Scheme 88 Photoelectro-synergistic catalysis of acetyloxy hydroxylation of alkenes.



Scheme 89 Palladium iron cocatalyzed difunctionalization of olefins *via* metal coordination.



Scheme 90 Palladium-catalyzed difunctionalization of olefins *via* metal coordination.

the alkene gives **89-B**, (iii) [Fe^{3+}] abstracts the halide to form **89-C**, (iv) **89-C** transmetalates with B_2pin_2 to generate **89-D**, and finally, **89-D** takes reductive elimination to yield the aminoboration product and **89-E**. Pd(0) is either directly oxidized to **89-A** or aggregate to **89-D**, which is oxidatively leached by Fe and Cl^- to regenerate **89-A**.

Liu and co-workers found that introducing a sterically bulky group at the C-6 position of a chiral Pyox ligand markedly increased $Pd(OAc)_2$'s electrophilicity, facilitating alkene activation in intramolecular reactions.[154] By employing a chiral ligand, an asymmetric diacetoxylation of terminal alkenes with good enantioselectivity was developed *via* palladium catalysis. It contains coordination, oxypalladation, oxidation, and reductive elimination processes. In 2024, Baidya and co-workers reported two examples of difunctionalization of alkenes with a picolinamide directing group. One of the examples is arylation-indolylation of alkenes,[155] the other one is intermolecular carboamination reaction of allylamines.[156] These two reactions proceed under mild conditions with good functional group tolerance (Scheme 90).

5. Conclusions

In the past five years, the intermolecular difunctionalization reactions of unsaturated π bonds have witnessed exciting and vigorous development. An increasing number of new catalytic systems and activation strategies have been developed and applied to the difunctionalization of alkenes. The addition of active metal species represented by Cu–Bpin to alkenes not only effectively introduces functional groups but also exhibits the advantage of adjustable chemoselectivity and regioselectivity. The addition of radical species to alkenes has greatly enriched the types of functional groups that can be introduced into the C=C double bond. The emergence of many new reagents has provided convenient pathways for the functionalization that was originally difficult to achieve. The development of the visible light reaction system has also provided innovative ideas for the diverse functionalization of alkenes under mild conditions. The single electron transfer strategy of alkenes, a newly emerging and unique activation mode of alkenes, has demonstrated irreplaceable superior performance in the construction reactions of functional groups such as amino groups and hydroxyl groups.

The extensive sources and good reactivity of alkenes indicate that the difunctionalization transformation of alkenes has great potential in drug research and development as well as organic synthesis, which has long inspired the innovation of organic synthesis methodologies. There are still many limitations that have not been overcome, such as the dependence on expensive transition metals and ligands with complex structures, harsh reaction conditions, and difficulties in precisely controlling the chemoselectivity, regioselectivity, and stereoselectivity. However, we believe that with the development of catalytic systems and the change of activation methods, once these problems are solved, the application scope of the difunctionalization reaction of alkenes will be significantly expanded.

Conflicts of interest

There are no conflicts to declare.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

Acknowledgements

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