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Recent advances in enantioselective construction of C–N bonds involving radical intermediates

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This review offers a comprehensive overview of recent advancements in the asymmetric construction of C–N bonds involving radical intermediates. Enantioselective radical amination strategies have proven to be highly effective for synthesizing chiral amines and nitrogen-containing heterocycles. Significant progress has been made in the enantioselective installation of N-containing groups into halogenated alkanes, olefins, and dienes with the asymmetric formation of C–N bonds as the key step *via* diverse pathways including reductive elimination, radical-polar crossover, amino group substitution, radical–radical cross-coupling, *etc*. This review highlights these recent developments and the mechanistic insights that drive these transformations.

1. Introduction

The construction of C–N bonds[1–20] is a fundamental and significant transformation in organic synthesis, as C–N bond-containing compounds are crucial in pharmaceuticals, agrochemicals, and biologically active molecules. The growing demand for efficient methods to synthesize chiral amines has driven significant research into innovative synthetic strategies[13–18] that provide precise stereocontrol. Compared to polar reactions, radical chemistry[21,22] is characterized by its unique reactivity, selectivity, and tolerance for various functional groups, offering appealing alternatives for C–N bond formation. Furthermore, radical-mediated asymmetric strategies[23,24] have demonstrated the capacity to rapidly construct chiral quaternary carbon centers and carry out enantio-convergent transformations, which can be complementary to traditional asymmetric polar reactions.

Significant progress has been made in enantioselective radical amination (Scheme 1). Mechanistically, the first *in situ* generated sp^2-hybridized alkyl radicals serve as critical intermediates. These alkyl radicals can be formed through

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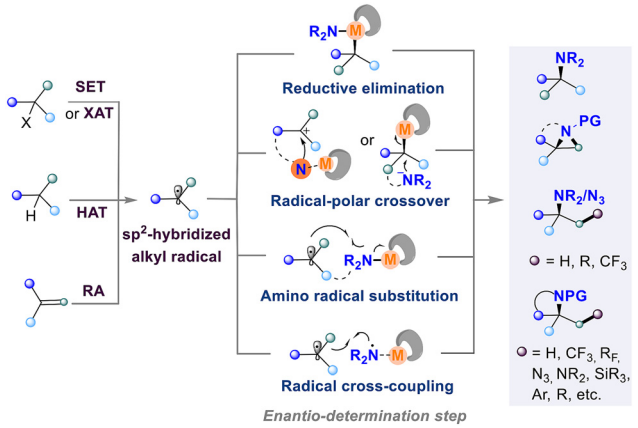

Scheme 1 Representative strategies for enantioselective construction of C–N bonds involving radical intermediates.

various methods, such as single electron transfer (SET) or halogen atom transfer (XAT) of alkyl halides, hydrogen atom transfer (HAT) from alkanes, radical addition to olefins and so on. Depending on the enantio-determining step, the subsequent C–N formation strategies can be categorized into four main classes: (1) reductive elimination of chiral alkyl-metal complexes formed by the interaction between alkyl radicals and transition metals with chiral ligands; (2) radical-polar crossover: a chiral catalyst-bound nitrogen source coupled with a carbocation or hypervalent chiral alkyl-metal species undergoing S_N2-like nucleophilic amination; (3) radical substitution of alkyl radicals with chiral N-metal species; and (4) radical–radical cross-coupling of N-centered radicals and alkyl radicals. Additionally, sporadic enantioselective addition of N-centered radicals to olefins has also been reported. As a result, a wide range of substrates, including halogenated hydrocarbons, alkanes and alkenes, could be transformed into value-added chiral amines or N-containing heterocycles *via* these enantioselective radical amination strategies.

This review offers an overview of the latest advancements in the asymmetric formation of C–N bonds that involve radical intermediates. Enzyme-facilitated strategies for C–N bond formation are not covered.[19,20] By highlighting the fundamental principles, strategies, and key intermediates involved in these transformations, this review aims to inspire further research and innovation in the field of asymmetric radical amination chemistry.

2. Enantioselective amination of alkyl halides or peresters involving radical intermediates

2.1 Cu-catalyzed enantioselective amination of alkyl halides

In 2021, Fu and co-workers[25] developed a photoinduced Cu-catalyzed asymmetric amination of unactivated racemic alkyl bromides and primary amides cooperatively employing three ligands: bisphosphine, phenoxide, and diamine. This method allowed for a diverse array of amides, including aromatic amides, aliphatic amides, and complex amides derived from natural products and chiral drugs, to function as suitable nucleophiles in asymmetric C–N coupling. For racemic unactivated secondary alkyl electrophiles, in addition to phosphoryl-substituted bromides, other directing groups such as amides, esters, ketones, sulfones, sulfonamides, and phosphine oxides were found to be compatible. A wide variety of secondary amides were synthesized with good yields and excellent enantioselectivities *via* enantioselective radical amination. After a careful investigation of the mechanism, including density functional theory (DFT) calculations, the authors proposed a catalytic cycle. This cycle involves photo-redox-catalyzed C–Br activation and enantioselective C–N bond formation. The key to the success of this reaction was the employment of three ligands to assemble the pivotal catalysts *in situ*: a bidentate phosphine and a phenoxide coordinated to Cu^{I} to form a photocatalyst (PC) **I**, which has an adequate excited-

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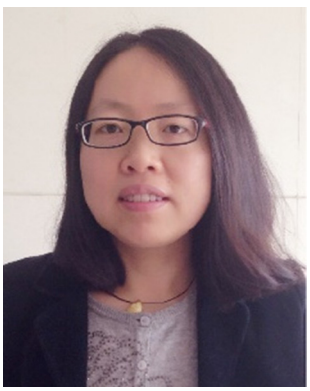

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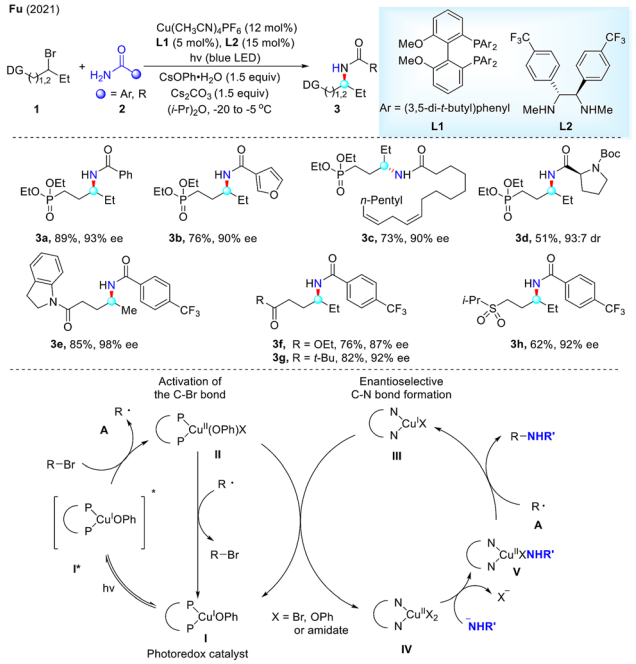
Yan Li received her Ph.D. degree from Northeast Normal University (NENU) under the guidance of Prof. Qiu Liu in 2007. She then worked in Northeast Normal University, progressing through the ranks as assistant, lecturer and associate professor. Her research interests focus on the development of novel reactions and new strategies for organic synthesis.



Scheme 2 Photoinduced Cu-catalyzed asymmetric amination *via* ligand cooperativity.

state lifetime and reduction potential to activate the C–Br bond of the electrophile, generating alkyl radical species **A**; meanwhile, a bidentate chiral diamine coordinated to Cu^{II}, generating **III**, which served as an efficient catalyst for enantioselective C–N bond formation (Scheme 2).

In 2022, the same group[26] provided detailed mechanistic insights into the key enantioselective C–N bond formation step of their previous report, a visible light-induced Cu-catalyzed enantioconvergent amination of carbazole and tertiary alkyl halides with an amide carbonyl group at the α-position.[27] They synthesized and characterized a Cu^{II} model complex, (NP)Cu^{II}cab′ **I**, which could couple with trityl radicals in toluene at −40 °C to produce *N*-alkylated carbazole in an excellent yield (91%). EPR studies and the corresponding DFT calculations supported the idea that the Cu^{II}–N complex functioned as a Cu^{II}–N metalloradical during the catalyzed coupling process. The authors proposed a possible mechanism as follows: L*Cu^{I}Cl reacts with nitrogen nucleophiles to generate the L*Cu^{I}carb complex **II**, which then undergoes irradiation to produce an excited state, [L*CuIcarb]* **III**. **III** subsequently participates in a SET with alkyl halides, resulting in the formation of an alkyl radical and the [L*Cu^{II}carb]Cl complex **IV**, which reacts with another nitrogen nucleophile to form **V**. The formation of C–N bonds through **VI** yields the desired products with good enantioselectivities (Scheme 3).

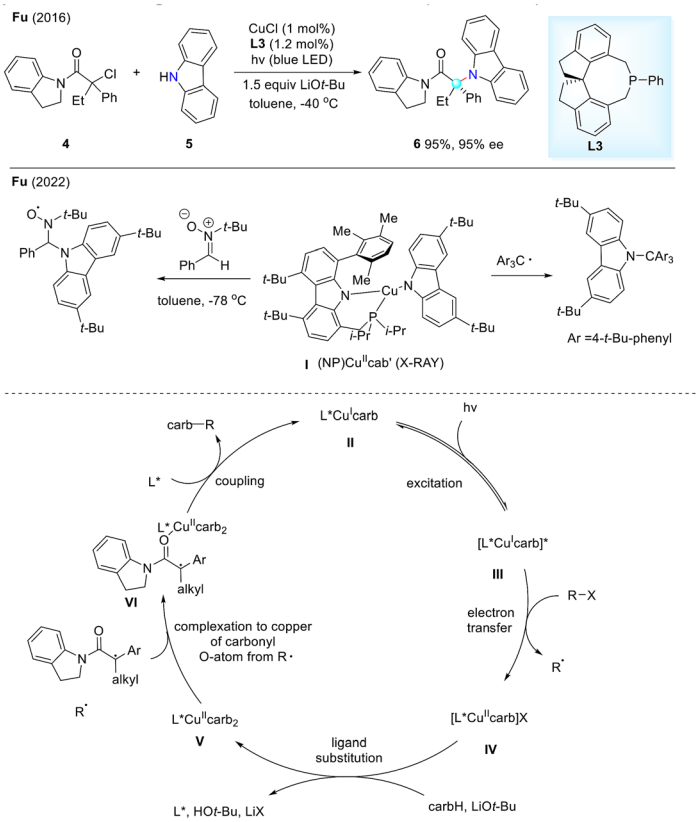
In the same year, Fu and colleagues[28] developed a photoinduced, copper-catalyzed enantioconvergent C–N coupling reaction of racemic alkyl halides with aniline derivatives. This method efficiently synthesizes chiral amines featuring a fully substituted stereocenter. A variety of racemic tertiary α-substituted α-chloro-/bromo-nitriles were identified as suitable electrophiles for producing enantioconvergent *N*-alkylation products with good enantioselectivities. However, the yield of the reaction was influenced by the size of the substituent at the α-position. Aniline derivatives with a substituent at the *para*-position yielded products in moderate to good yields and demonstrated good enantioselectivities. In contrast, when aniline was used as the nucleophile, a substantial amount of electrophilic addition occurred at the *para* position. Mechanistically, irradiation of P*$_2$$Cu^{I}$Cl **I** under blue LEDs generated the excited-state intermediate **II**. This intermediate underwent SET with alkyl halides to form Cu^{II}-species **III** and an alkyl radical. The coordination of aniline with **III** produced the intermediate **IV**, which then combined with the alkyl radical to yield the desired product with good enantioselectivity, simultaneously regenerating **I** (Scheme 4).

In 2021, the Liu group[29] developed a copper-catalyzed enantioconvergent radical C–N coupling method using diverse racemic secondary alkyl halides, employing sulfoximines as effective ammonia surrogates. This reaction efficiently produces highly enantioenriched *N*-alkyl sulfoximines featuring secondary benzyl, propargyl, α-carbonyl alkyl, and α-cyano alkyl stereocenters. The employment of electron-rich multidentate anionic *N*,*N*,*P*-ligands significantly enhances the reducing capability of Cu^{I} catalysts, allowing for the efficient generation of alkyl radicals from alkyl halides under mild thermal conditions, facilitating the enantioconvergent radical C–N coupling of racemic secondary alkyl chlorides and bromides. Mechanistically, the Cu^{I}-sulfoximine complex **I** undergoes SET with the racemic alkyl halides, generating a secondary alkyl radical **II** and a Cu^{II}-complex **III**. Subsequent enantio-determining C–N bond formation might occur, yielding highly enantioenriched N-alkyl sulfoximine derivatives (Scheme 5).

In 2023, the Liu group[30] designed and synthesized a new anionic *N*,*N*,*N*-ligand with a long spreading side arm. By means of this ligand, they extended the copper-catalyzed enan-

Qian Zhang

Prof. Qian Zhang received her BS and MS degrees from Northeast Normal University (in 1993 and 1996, respectively). She obtained her PhD degree (2003) from the Changchun Institute of Applied Chemistry, Chinese Academy of Sciences, under the supervision of Professor Lixiang Wang in the research field of organic light emitting materials, especially for designing hole transporting materials. She has worked in Northeast Normal University since 1996, progressing through the ranks as assistant, lecturer, associate professor, and professor. Her research interests focus on the development of novel reactions, new reagents and strategies for organic synthesis.



Scheme 3 Investigation of the C–N bond-forming step in a photoinduced, Cu-catalyzed enantioconvergent *N*-alkylation.

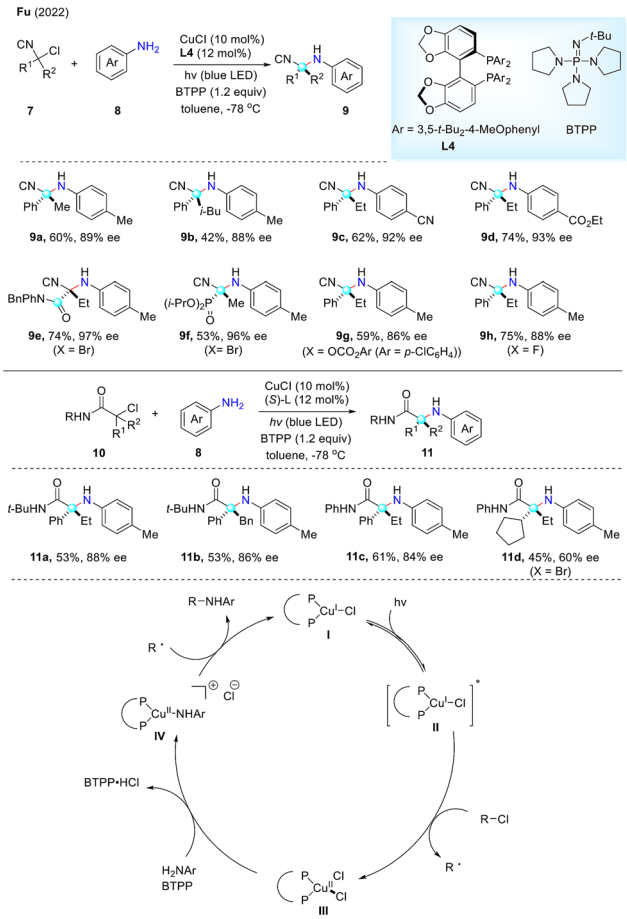
tioconvergent radical C(sp^3)–N coupling from secondary alkyl halide electrophiles to spatially crowded tertiary alkyl halides. Upon using sulfoximines as the nitrogen sources, a series of α-aminocarbonyl tertiary alkyl chlorides smoothly converted into α,α-disubstituted amino acids in good yields with high enantioselectivities (Scheme 6).

In 2023, Liu and co-workers[31] reported the utilization of chiral tridentate anionic ligands to facilitate the Cu-catalyzed enantioconvergent *N*-alkylation of aliphatic amines and α-carbonyl alkyl chlorides. This method could directly convert bulk feedstock chemicals, such as ammonia, methylamine, dimethylamine and pharmaceutically relevant amines, into chiral α-amino amides. This reaction displayed excellent enantioselectivity and functional group compatibility. Furthermore, the robust method was successfully applied in the late-stage functionalization and expedited synthesis of various amine drug molecules. The key to the achievement could be attributed to the chiral tridentate anionic *N*,*N*,*N*-ligands, which exhibit strong binding affinities to metal catalysts, not only overcoming catalyst poisoning by aliphatic amines or ammonia but also inducing high enantioselectivities. The authors proposed a possible mechanism for this reaction. It begins with the formation of Cu^I species **I**, which undergoes intramolecular oxidative addition to produce species **II** and **III**, which are in equilibrium. The subsequent outer-sphere attack of **III** by an amine leads to the enantioselective formation of intermediate **IV**. Finally, a ligand exchange with an alkyl chloride releases the chiral aliphatic amines and regenerates intermediate **I**, closing the catalytic cycle (Scheme 7). In 2024,[32] the same group expanded the range of nucleophiles to include bulky secondary and primary ones. They developed an outer-sphere nucleophilic attack mechanism to circumvent the difficulties of transmetalation that arise with sterically congested nucleophiles. This approach offers new opportunities for the construction of chiral carbon centers, particularly challenging sterically congested ones.

At the same time, Fu and colleagues[33] independently developed a copper/chiral isoxazoline-catalyzed enantioconvergent substitution of racemic α-chloro/bromo-*N*-phenylbutanamide using amines, leading to direct access to chiral α-amino amide derivatives in good to excellent yields with excellent enantioselectivities. Both aromatic and alkyl amines were compatible with this radical amination process (Scheme 8).

2.2. Fe-catalyzed asymmetric amination of peresters

In 2021, the Bao group[34] disclosed an Fe^{II}-catalyzed radical enantioselective decarboxylative azidation of benzylic peresters with $TMSN_3$. The enantioselectivity relied on the substitution pattern of the alkyl groups in the benzylic peresters. Benzylic peresters with sterically hindered alkyl groups, such as cyclopentyl, 1-adamantyl, tertiary butyl, and substituted benzyl, pro-



Scheme 4 Photoinduced, Cu-catalyzed enantioconvergent alkylations of anilines by racemic tertiary electrophiles.

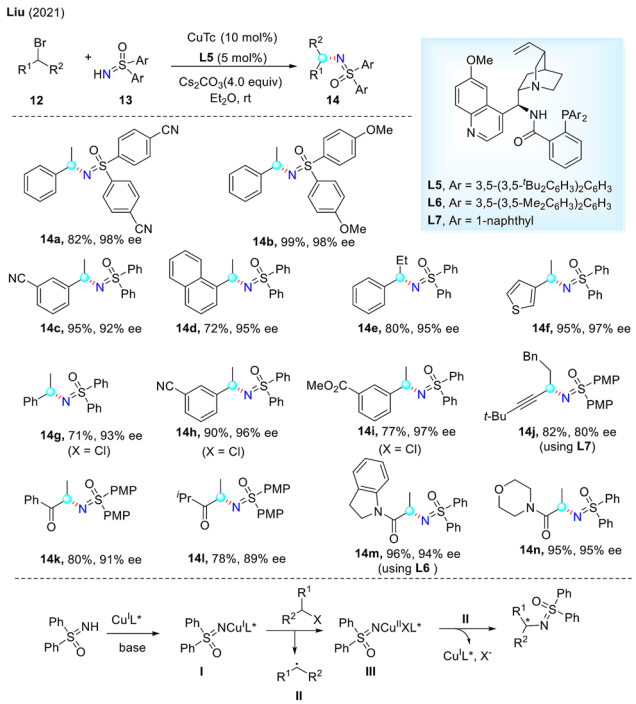
duced the corresponding products with higher enantiomeric ratios. In contrast, when a less sterically hindered group, like methyl, was used, inadequate chiral induction was observed. The authors proposed an outer-sphere azido group transfer mechanism for this transformation. Initially, ligand exchange of Fe^{II} species **I** with $TMSN_3$ forms an N_3–Fe^{II} species **II**. Then, SET of **II** by perester **24** generates a high-valent Fe^{III} species **III** and a benzyl radical **IV**, along with the release of CO_2. Finally, the enantio-determining outer-sphere azido group transfer between the N_3–Fe^{III} species **III** and the radical **IV** produced the final product **25** and regenerated the catalyst **I** (Scheme 9).

3. Enantioselective C(sp^3)–H amination involving radical intermediates

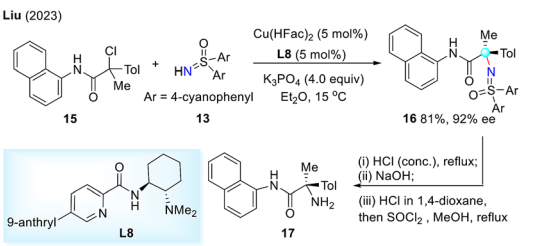
3.1. Co^{II}-based MRC-catalyzed asymmetric C(sp^3)–H amination

Metalloradical catalysis (MRC)[35,36] represents a novel approach for activating organic molecules by generating metal-coordinated radical species, which has recently gained significant attention for C–H functionalization. In this context, Zhang and colleagues developed D_2-symmetric chiral Co^{II} complexes of porphyrins that serve as stable 15-electron metalloradicals (Scheme 10). This Co^{II}-based MRC can efficiently activate organic azides, resulting in the formation of α-Co^{III}-aminyl radicals. These radicals can then undergo 1,5-, 1,6-, or intermolecular HAT processes and subsequent amino radical substitution, leading to the formation of asymmetric C–N bonds. This method opens new opportunities for effective and stereoselective C–H amination, aiding in the synthesis of chiral amine derivatives and broadening the scope of radical-mediated asymmetric transformations.

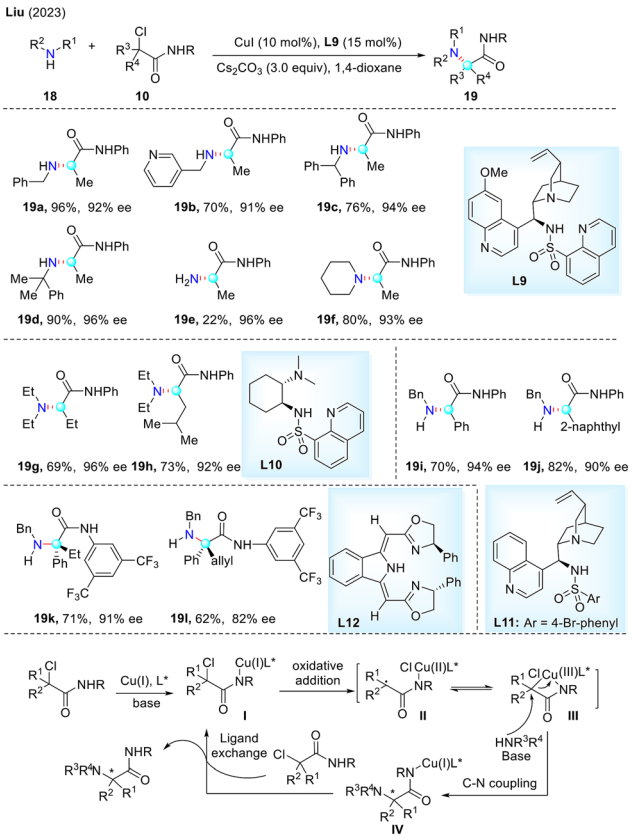
In 2018, Zhang[37] and coworkers developed a groundbreaking Co^{II}-catalyzed enantioselective amination of C(sp^3)–H bonds employing Co^{II}-based MRC. This method involved the activation of sulfamoyl azides by the Co-MRC system, which generated α-Co^{III}-aminyl radicals **I**. These radicals facilitated a 1,6-HAT followed by enantioselective C–N bond formation, producing six-membered chiral heterocyclic sulfamides **27** with



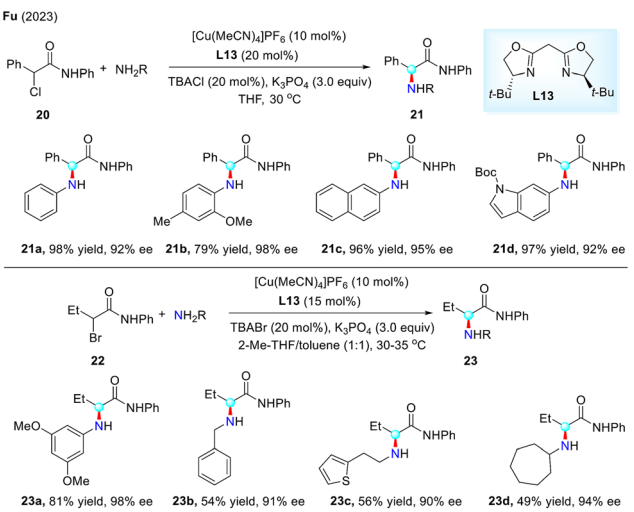
Scheme 5 Enantioconvergent Cu-catalyzed radical C–N coupling of racemic secondary alkyl halides.



Scheme 6 Cu-catalyzed enantioconvergent radical C(sp^3)–N cross-coupling for access to α,α-disubstituted amino acids.

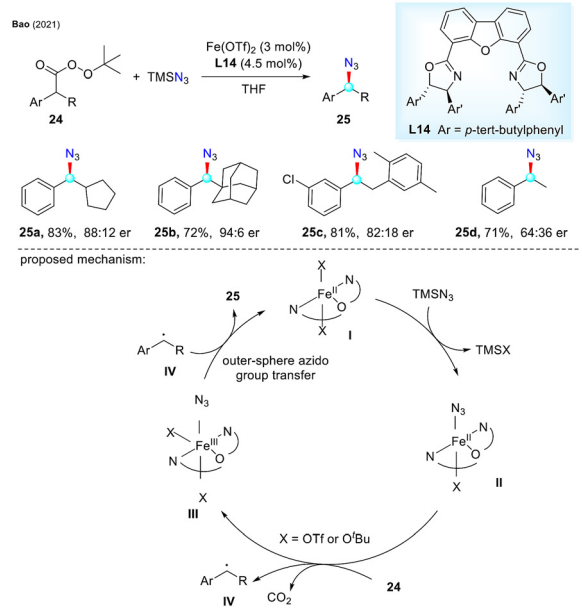


Scheme 7 Enantioconvergent Cu-catalyzed *N*-alkylation of aliphatic amines.

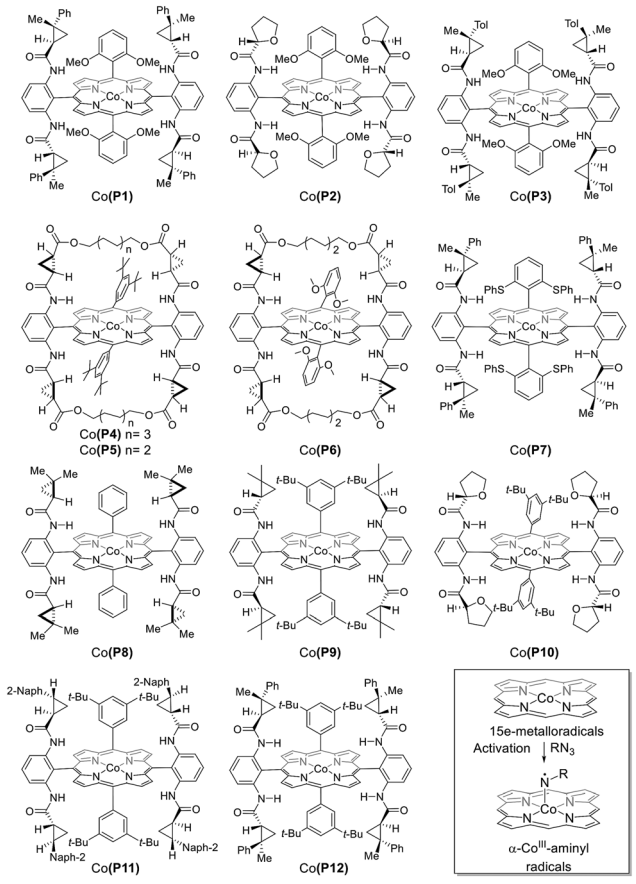


Scheme 8 Copper-catalyzed enantioconvergent alkylations of nitrogen nucleophiles.

high yields and excellent enantioselectivities. The process displayed broad substrate compatibility, including benzylic, allylic, and propargylic C(sp^3)–H bonds. Moreover, chiral cyclic sulfamides could be readily converted into valuable 1,3-diamines without loss of enantiopurity (Scheme 11, top).

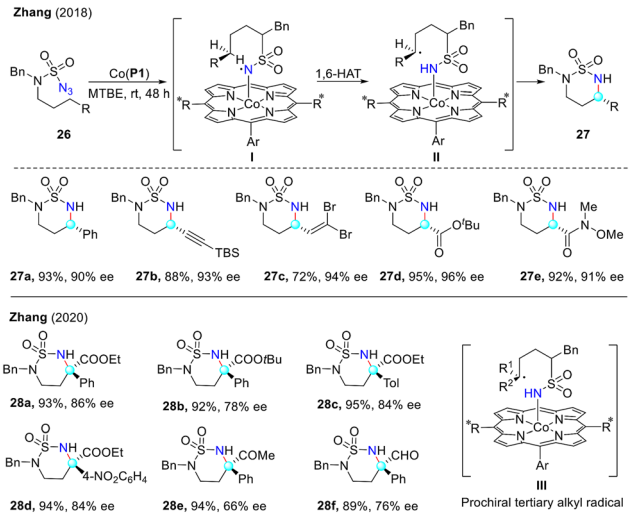


Scheme 9 Fe-catalyzed asymmetric decarboxylative azidation.

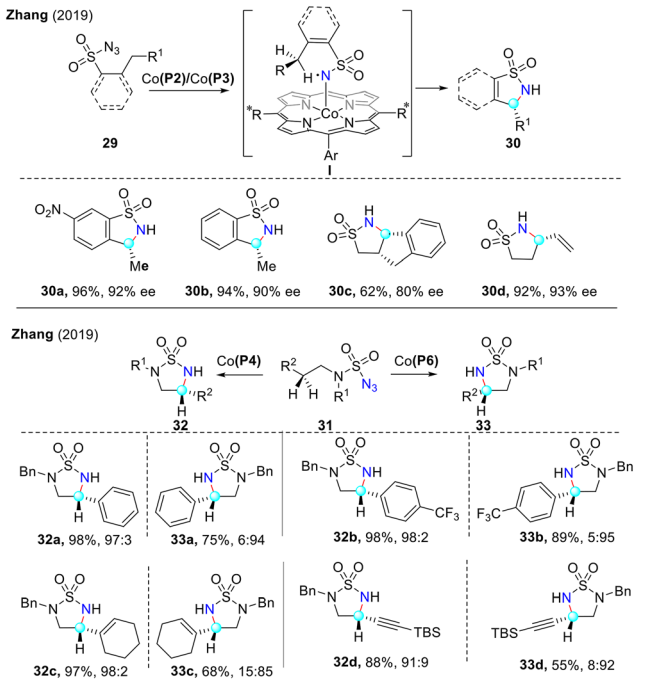


Scheme 10 Co^{II}-based D_2-symmetric chiral metalloradical catalysis.

Furthermore, the Co^{II}-based MRC-catalyzed 1,6-C(sp^3)–H amination system was further extended to the racemic tertiary C(sp^3)–H bonds.[38] As shown in Scheme 11 (bottom), this



Scheme 11 Co^{II}-based MRC-catalyzed asymmetric radical 1,6-C(sp^3)–H amination.



Scheme 12 Co^{II}-based MRC-catalyzed asymmetric radical 1,5-C(sp^3)–H amination.

approach displayed a broad substrate scope, accommodating various ester and aryl functionalities, and enabled the efficient synthesis of chiral six-membered cyclic sulfamides bearing quaternary stereocenters **28**. Detailed mechanistic studies, including KIE analysis and EPR detection of intermediates, provided valuable insights into the enantioselective control of the radical process. *In situ* generated α-Co^{III}-aminyl radicals underwent 1,6-HAT of tertiary C–H bonds, resulting in the prochiral tertiary alkyl radical center **III**, which then underwent enantio-determining radical substitution, leading to the construction of quaternary stereogenic centers. The stepwise radical mechanism, featuring HAT and radical substitution, was key in achieving enantio-convergent amination of tertiary C–H bonds.

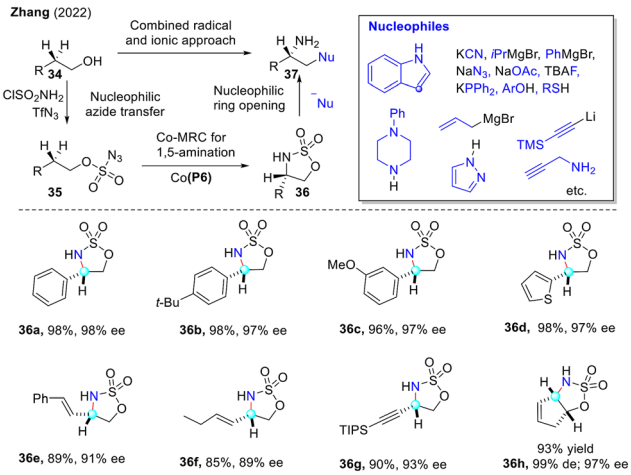
In 2019,[39] the same group developed an enantioselective Co^{II}-catalyzed radical 1,5-C–H amination of sulfonyl azides **29**. Using **Co-2** (for arylsulfonyl azides) or **Co-3** (for alkylsulfonyl azides), both types of azides underwent efficient C–H amination, producing chiral cyclic sulfonamides **30** with high yields and excellent enantioselectivities (Scheme 12, top). The reaction effectively accommodated a wide variety of functional groups, including benzylic, allylic, and non-activated C(sp^3)–H bonds. Mechanistically, the activation of organic azides by Co^{II}-MRC leads to the formation of α-Co^{III}-aminyl radicals **I**. These radicals undergo a 1,5-HAT, followed by an enantio-determining amino-radical substitution, which enables the enantioselective formation of five-membered cyclic sulfonamides. The involvement of α-Co^{III}-aminyl radical **I** was confirmed through isotropic EPR spectroscopy.

Later, they developed a novel cobalt(II)-catalyzed enantio-divergent radical 1,5-C(sp^3)–H amination of sulfamoyl azides, employing D_2-symmetric chiral porphyrins as ligands.[40] By modulating the cavity environment of the ligands (**Co-4** or **Co-6**), they allowed the enantio-divergent formation of the product. Detailed deuterium-labelling studies and DFT calculations revealed a unique mechanism of asymmetric induction, combining enantio-differentiative HAT with stereo-retentive radical substitution (Scheme 12, bottom).

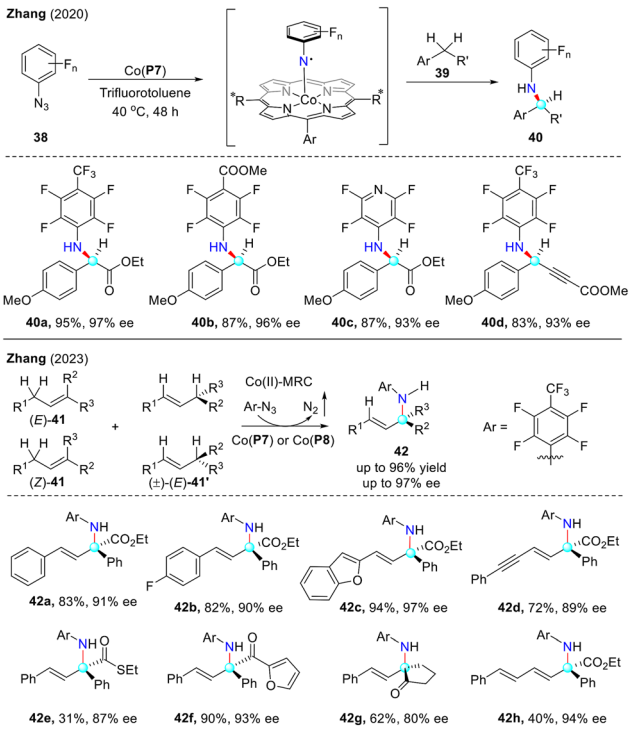
In 2022, the Zhang[41] group further extended the Co^{II}-based MRC system by combining radical and ionic approaches for the enantioselective synthesis of β-functionalized chiral amines from alcohols (Scheme 13). This innovative strategy merges an enantioselective radical process, 1,5-C–H amination of alkoxysulfonyl azides, with an enantiospecific ionic process for the ring-opening of the resulting five-membered cyclic sulfamidates. This method provides an efficient and practical route to synthesize highly enantioenriched β-functionalized amines with a broad substrate scope, high yields, and excellent stereoselectivities. Mechanistically, the Co^{II}-MRC activates alkoxysulfonyl azides to generate α-Co^{III}-aminyl radicals, which undergo 1,5-HAT and radical substitution to form chiral cyclic sulfamidates **36**. These intermediates can then undergo nucleophilic ring-opening, allowing access to a wide range of chiral amines **37**. This approach is compatible with various C–H bonds and nucleophiles, significantly expanding the synthetic toolbox for chiral amine construction.

The Co-MRC system could be extended to the enantioselective amination of simple benzylic and allylic C–H bonds through the intermolecular HAT process, providing new opportunities for the efficient and precise construction of chiral nitrogen-containing compounds.

In 2020, the Zhang[42] group reported an enantioselective intermolecular radical C–H amination of benzylic C–H bonds bearing carboxylic acid esters by employing fluoroaryl azides as the nitrogen sources, which facilitated the construction of



Scheme 13 Co^{II}-based MRC catalysis combining radical and ionic approaches for the enantioselective synthesis of β-functionalized chiral amines.



Scheme 14 Co^{II}-based MRC-catalyzed intermolecular radical C–H amination.

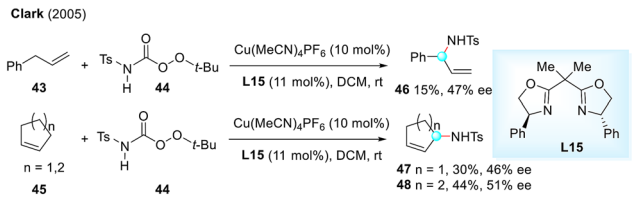
valuable chiral α-amino acid derivatives (Scheme 14, top). The key to their success was the development of D_2-symmetric chiral amidoporphyrin ligands, which enhanced noncovalent interactions and controlled both reactivity and enantioselectivity. The intermolecular C–H amination was conducted under mild conditions and demonstrated a broad substrate scope, yielding chiral amines with high chemo-selectivity and excellent enantioselectivity (**40**). Mechanistic studies uncovered a stepwise radical pathway that involved metalloradical activation of organic azides, HAT from C–H substrates, and enantio-determining radical substitution, leading to C–N bond formation.

The convergent transformation of various isomeric mixtures of alkenes poses a significant challenge in organic synthesis chemistry, requiring innovative solutions. In 2023, Zhang[43] and colleagues introduced a novel approach for the intermolecular asymmetric radical allylic C–H amination of these isomeric mixtures (Scheme 14, bottom). By utilizing Co^{II}-based MRC and modularly designed D_2-symmetric chiral amidoporphyrin ligands, this research presents a highly selective approach for synthesizing chiral α-tertiary amines **42** from organic azides and isomeric mixtures of alkenes. The versatility of this method is highlighted by its compatibility with a wide range of fluoroaryl azides and alkenes, enabling the efficient formation of allylic amines with excellent stereocontrol. Mechanistic studies, including DFT calculations and KIE analysis, reveal a stepwise radical mechanism and provide insights into the factors influencing regioselectivity and enantioselectivity. The key to achieving the chemical and stereochemical convergent transformation of isomeric mixtures of alkenes is the stepwise radical reaction mechanism and the essential property of allyl radical delocalization.

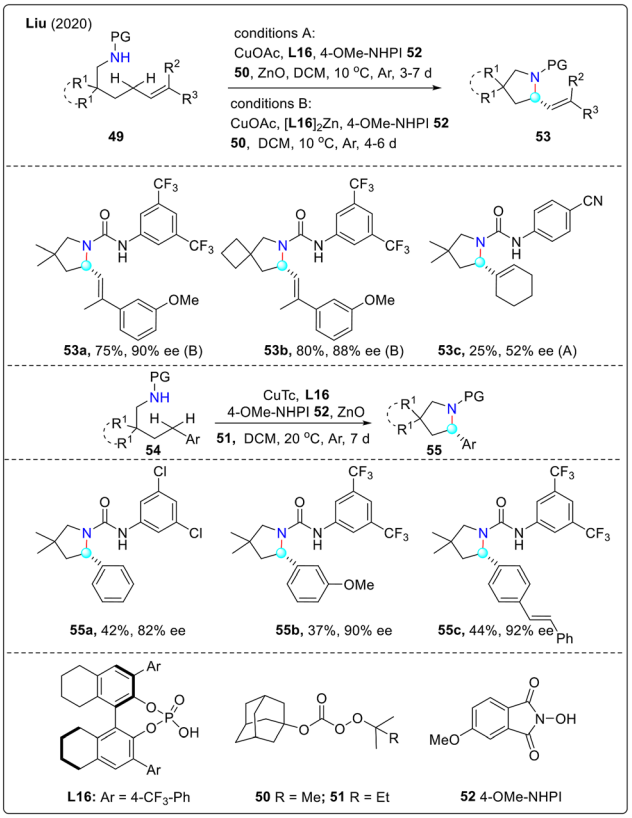
3.2. Cu-catalyzed asymmetric radical C(sp^3)–H amination

The Cu-catalyzed Kharasch–Sosnovsky reaction using a Cu/chiral bis(oxazoline) catalyst marked a pioneering step in enantioselective oxidative C–H bond functionalization, specifically within cyclic allylic substrates. In 2005, Clark[44] developed asymmetric oxidative C–H amination of benzylic and cyclic allylic C–H bonds, using peroxycarbamate as an oxidant and nitrogen source with a Cu/chiral BOX catalyst (**L15**). This approach allowed direct access to chiral allylic and benzylic amides **46–48** with moderate ee (Scheme 15).

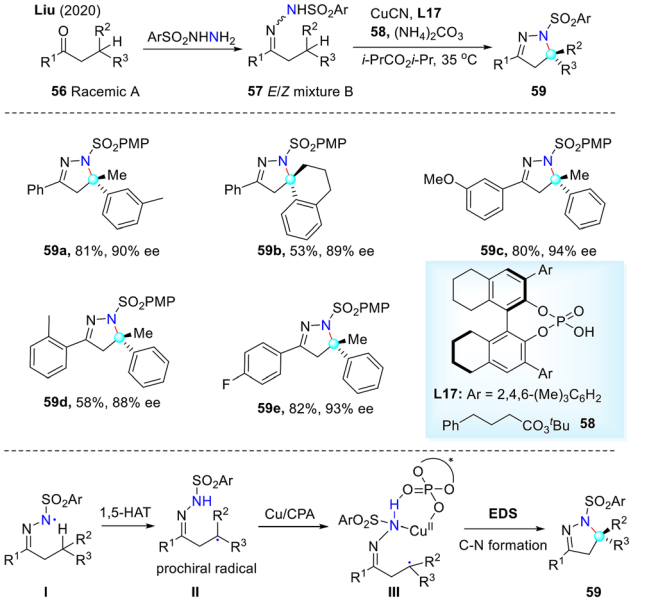
In 2020, Liu[45] and colleagues developed a Cu/chiral phosphoric acid (CPA)-catalyzed asymmetric radical intramolecular 1,5-C–H amination of allylic and benzylic substrates. This method successfully produced enantioenriched α-alkenyl and α-arylpyrrolidines (Scheme 16). The process uses *N*-hydroxyphthalimide (NHPI) to mediate intermolecular HAT, generating alkyl radicals that facilitate enantioselective C–N bond formation. This approach demonstrates high efficiency and a broad substrate range, accommodating both electron-rich and electron-deficient substituents on the allylic and benzylic C–H bonds.



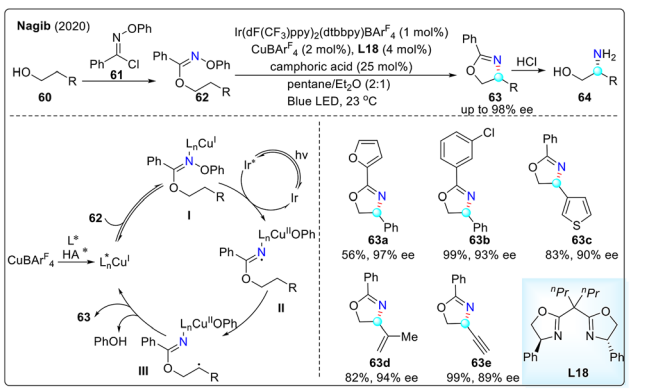
Scheme 15 Cu/chiral BOX-catalyzed asymmetric Aza-Kharasch–Sosnovsky reactions.



Scheme 16 Cu/CPA-catalyzed intramolecular asymmetric 1,5-C–H amination of allylic and benzylic substrates.



Scheme 17 Cu/CPA-catalyzed intramolecular asymmetric 1,5-C–H amination of allylic and benzylic substrates.



Scheme 18 Cu/PC dual-catalyzed intramolecular 1,5-C–H amination.

Later, the same research group[46] reported an intramolecular, radical enantioconvergent amination of tertiary β-C(sp^3)–H bonds of racemic ketones **56** catalyzed by Cu(I)/CPA (Scheme 17). The reaction demonstrates high efficiency and broad substrate compatibility, including aryl and heteroaryl ketones, with good to excellent enantioselectivity (up to 96% ee). Moreover, functional groups such as alkynes, phosphonates, and borates are well tolerated. Mechanistically, this method employs a Cu^I/CPA (**L17**) catalytic system that facilitates the generation of N-centred radicals **I**, which undergo intramolecular 1,5-HAT to form prochiral tertiary alkyl radicals **II**. **II** coordinated by Cu^I/CPA generates **III**. The subsequent intramolecular enantio-determining amino radical substitution of **III** delivers the desired products **59**. In 2023, they further extended the scope of this system to *N*-chlorosulfonamide-type substrates for synthesizing pyrrolidine structural motifs featuring an α-quaternary stereocenter with high levels of enantiopurity.[47]

Independently, Nagib[48] and coworkers developed a Cu/PC dual catalyzed intramolecular 1,5-C–H amination method for synthesizing chiral β-amino alcohols (Scheme 18). Mechanistically, addition of alcohol **60** to an imidoyl chloride **61** chaperone results in the formation of an oxime imidate **62**, which selectively binds to a chiral Cu catalyst, generating complex **I**. Energy transfer between PC* and **I** leads to the generation of a Cu-bonded N-centred radical **II**. Regio- and enantioselective HAT followed by stereoselective C–N bond formation leads to the formation of chiral oxazoline **63**. Subsequent hydrolysis yields the enantioenriched β-amino alcohol **64**. Unlike Liu's research, this approach allows for chiral induction over two steps (both HAT and alkyl radical trapping), and the intermolecular C–N formation strategy is rapid enough to retain (and enhance) chiral memory. The method successfully delivers chiral β-amino alcohols from various alcohol substrates, including those containing alkyl, allyl, and benzyl groups, offering a versatile platform for synthesizing valuable chiral β-amino alcohols under mild conditions. In 2024,[49] the same group further extended the enantioselective intramolecular C–H amination system to the synthesis of unprotected pyrrolines from oximes. The chiral pyrrolines can undergo reductions or nucleophilic additions with excellent stereocontrol, offering a modular platform for synthesizing enantioenriched chiral pyrrolidines.

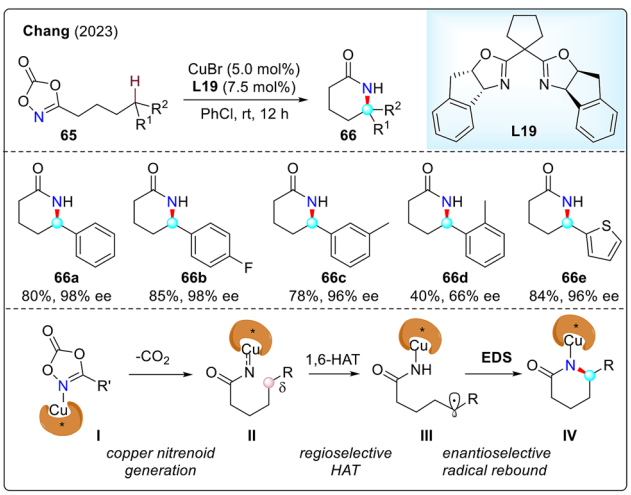
In 2023, Chang[50] and coworkers developed Cu/chiral BOX-catalyzed regio- and enantioselective δ-C(sp^3)–H amidation of dioxazolones **65**, enabling the construction of six-membered chiral lactams **66** with excellent regioselectivity and high enantioselectivities (>99 : 1 er). Mechanistic studies reveal that the open-shell Cu-nitrenoid species play a critical role, mediating regioselective 1,6-HAT, followed by enantioselective radical rebound to form the C–N bond (Scheme 19).

In 2023, Zhou and colleagues[51] developed a copper/chiral bisoxazoline (BOX)-catalyzed intermolecular enantioselective benzylic C(sp^3)–H amination. This process uses a peroxide as both the oxidant and HAT reagent, with benzamide as the nitrogen source. Mechanistically, a *tert*-butoxy radical is generated *in situ* and initiates a rate-limiting HAT with the benzylic C(sp^3)–H bond, forming a benzylic radical **IV**. This radical is then reversibly trapped by a Cu^{II}-amide complex **III**, leading to a Cu(III) intermediate **V**, which undergoes enantioselective reductive elimination to yield the chiral amide **68**. This reaction accommodates a broad functional group range and has demonstrated its utility in synthesizing bioactive chiral amines, including (*R*)-Tecalcet **68a**, Dapoxetine **68c**, and Rivastigmine **68b**, underscoring its potential for pharmaceutical applications (Scheme 20, top).

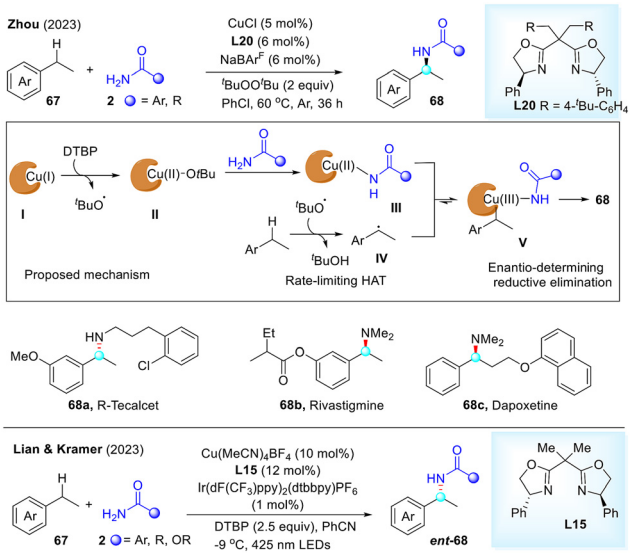
Independently, the Lian and Kramer group[52] introduced a novel copper/PC dual-catalysis strategy for enantioselective benzylic C–H amination and amidation, using benzylic C–H substrates as the limiting reagent (Scheme 20, bottom). This method efficiently produces chiral benzylic amides and carbamate-protected benzylamines through direct C–H functionalization. It is scalable, compatible with various nitrogen sources, including cost-effective ^{15}N-labeled reagents, and adaptable to drug synthesis.

3.3 Rh-catalyzed asymmetric C–H amination

In 2021, Dauban and colleagues[53] reported a sequence of reactions for C(sp^3)–H amination employing chiral sulfamates.



Scheme 19 Cu/chiral BOX-catalyzed regio- and enantioselective δ-C(sp^3)–H amidation of dioxazolones.



Scheme 20 Cu/chiral BOX-catalyzed intermolecular enantioselective benzylic C(sp^3)–H amination.

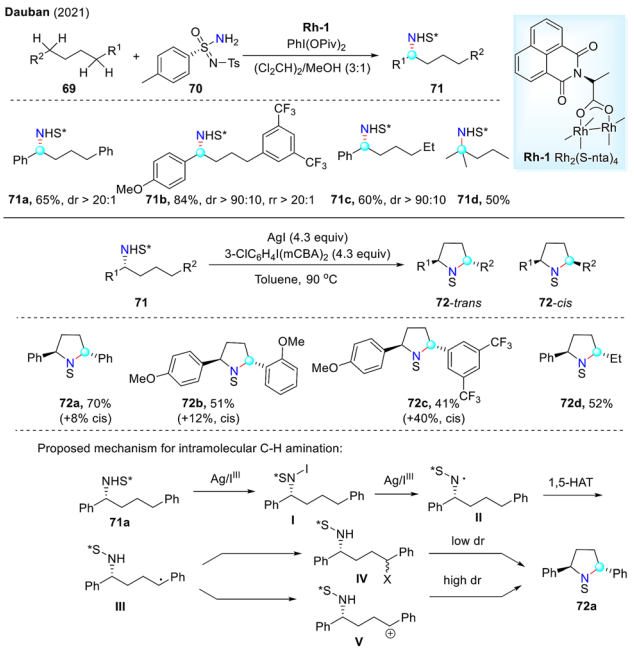
The first step involves a reaction between hydrocarbon **69** and the nitrene precursor chiral sulfamate **70**, facilitated by a rhodium catalyst, resulting in the formation of chiral amines **71** through a stereoselective nitrene insertion. Amine **71** undergoes an Ag-mediated, diastereoselective HLF-type cyclization to yield disubstituted pyrrolidines **72**. For the HLF-type cyclization, the authors proposed a radical-based mechanism. Initially, an N-centered radical **II** is generated from the iodoamine **I**, which then undergoes a HAT. The resulting carbon radical **III** can be captured to produce the corresponding iodide **IV**. Subsequently, a stereospecific S_N2-type cyclization delivers pyrrolidine **72a** with a low diastereomeric ratio. Alternatively, the radical **III** may be oxidized to form a carbocation **V**, which then undergoes an S_N1-type cyclization, leading to high diastereocontrol (Scheme 21).

3.4 Ru-catalyzed asymmetric C–H amination

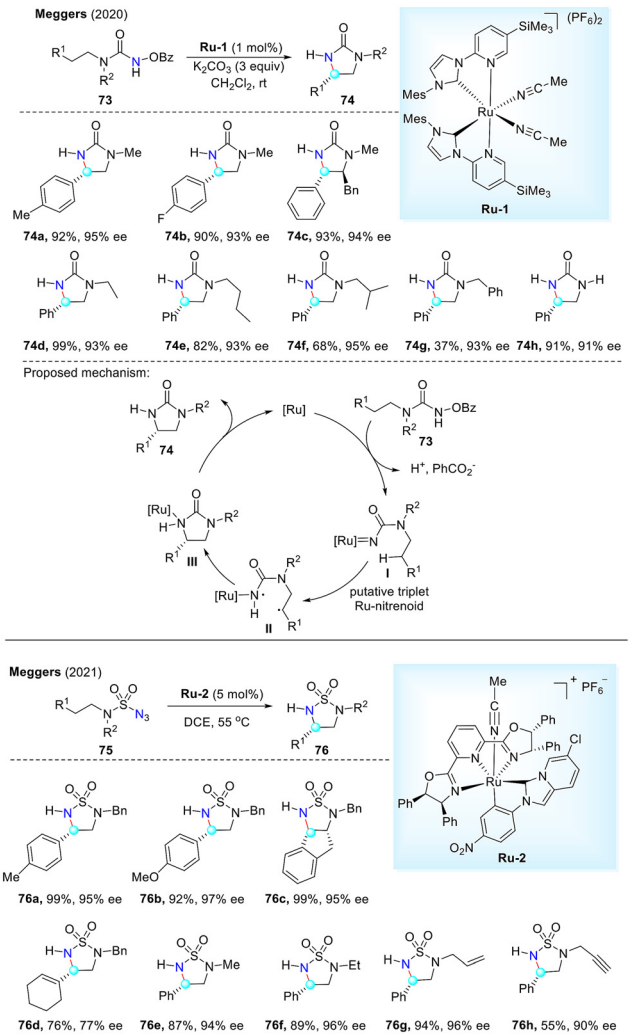
In 2020, the Meggers group[54] reported a method for chiral-at-metal ruthenium-catalyzed enantioselective intramolecular C(sp^3)–H amination using *N*-benzoyloxyurea, leading to chiral 2-imidazolidinones with up to 99% yield and 99% ee. They proposed a stepwise mechanism where a ruthenium nitrenoid triplet state initiates a 1,5-HAT, followed by a radical–radical rebound that leads to the enantioselective formation of the C–N bond (Scheme 22, top). Building on a similar strategy, the same group[55] later employed sulfamoyl azides as carbene precursors to achieve ruthenium-catalyzed asymmetric synthesis of 1,2,5-thiadiazolidine-1,1-dioxides *via* enantioselective ring-closing 1,5-C–H amination (Scheme 22, bottom).

3.5 Ni-catalyzed asymmetric C–H amination

In 2021, Betley and co-workers[56] developed Ni-catalyzed enantioselective C–H bond amination of 4-aryl-2,2-di-methyl-2-azidopentanes, leading to pyrrolidine derivatives in moderate



Scheme 21 Asymmetric synthesis of enantiopure pyrrolidines by C(sp^3)–H amination of hydrocarbons.



Scheme 22 Ruthenium-catalyzed enantioselective intramolecular C–H amination of urea derivatives or sulfamoyl azides.

to good yields with moderate ee. According to the experimental and DFT investigations, they proposed a plausible mechanism for the reaction. Initially, the chiral **Ni-1** complex underwent ligand exchange with the azide and subsequently activated the azide group, leading to the formation of a nickel iminyl species **II**. This species facilitated an intramolecular HAT, resulting in the generation of a carbo-radical intermediate **III**. Finally, a radical recombination between the nickel–amine complex and the carbo-radical species produced the chiral pyrrolidine product (Scheme 23).

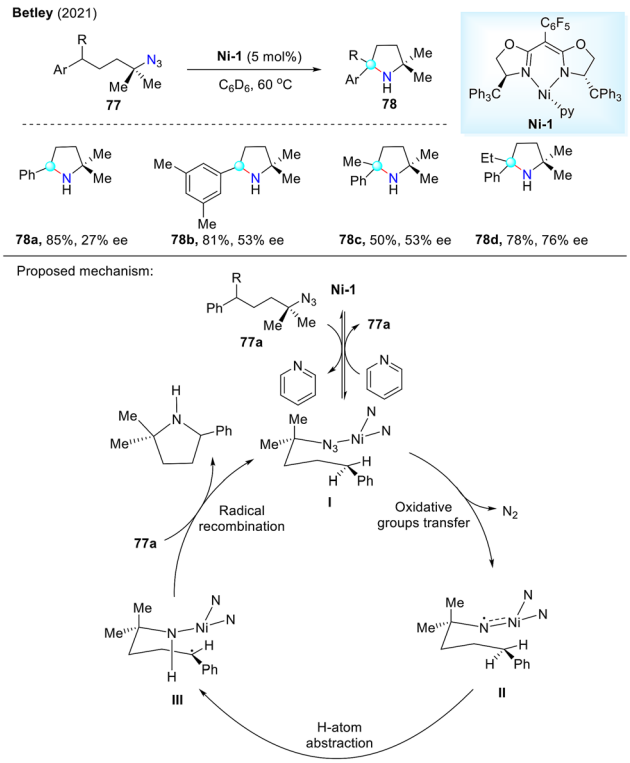
3.6 Fe-catalyzed asymmetric C–H amination

In 2023, the Che group[57] developed a chiral iron porphyrin-catalyzed asymmetric C–H amination upon visible light irradiation under redox-neutral conditions. By employing (*S*, *R*)-cmcporFeCl (**Fe-1**) and (*S*)-D_4 porFeCl (**Fe-2**) as the catalyst, they realize enantioselective C(sp^3)–H amination of aryl and arylsulfonyl azides to afford optically pure indolines and benzofused cyclic sulfonamides, respectively, with good yields and ee values. Impressively, the amination of unactivated C(sp^3)–H bonds without proximal aromatic groups was also achieved by using the iron complex as a catalyst, affording indolines in moderate yields but with low ee values. DFT investigations, for the reactions of arylsulfonyl azides, showed that the asymmetric amination reaction proceeded through a stepwise HAT/rebound mechanism with crucial cooperative noncovalent interactions including hydrogen bonding and steric hindrance provided by the ligand environment of chiral porphyrin (Scheme 24).

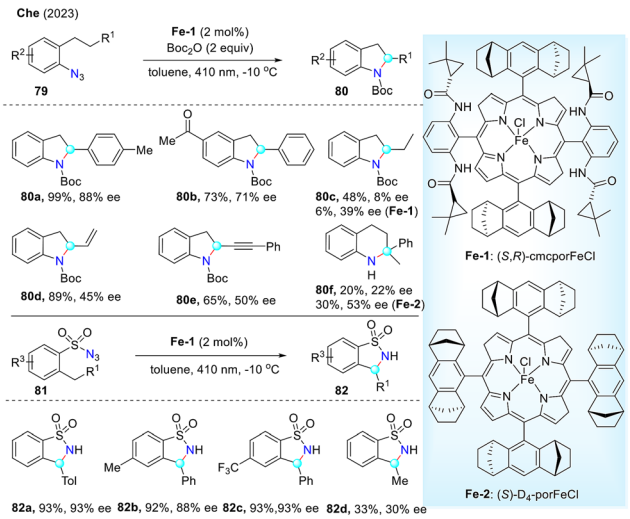
The enantioselective amination of readily available and abundant C–H bonds in alkanes represents a highly effective and straightforward strategy for synthesizing chiral amines. Radical methods can activate inert C–H bonds through the HAT process, generating highly reactive alkyl radicals that interact with transition metals to facilitate enantioselective C–N bond formation. This enantioselective radical C–H amination system offers compelling alternatives for the synthesis of chiral amines, amides, and azaheterocycles, which are vital in pharmaceuticals and organic synthesis.

4. Radical aminative functionalization of alkenes for enantioselective formation of C–N bonds

Alkenes are abundant and vital chemical feedstocks, and functionalization of alkenes represents one of the most crucial transformations in organic chemistry, serving as a key method for constructing carbon–carbon and carbon–heteroatom



Scheme 23 Enantioselective C–H amination catalyzed by nickel iminyl complexes supported by anionic bisoxazoline ligands.



Scheme 24 Chiral iron porphyrin-catalyzed enantioselective intramolecular C(sp^3)–H bond amination upon visible-light irradiation.

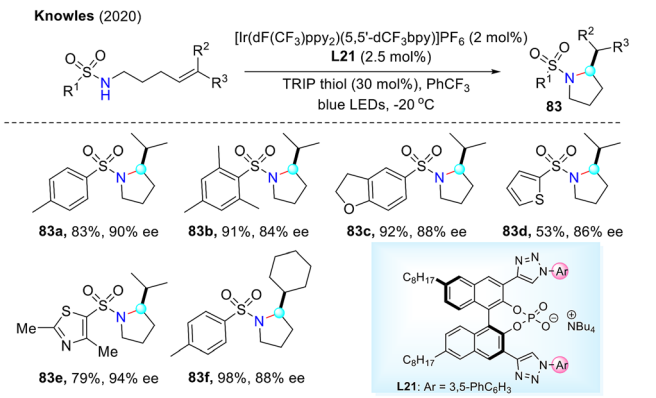
bonds. The double bond in alkenes is particularly susceptible to radical attack, making them ideal candidates for radical-initiated reactions. Radical-mediated asymmetric hydroamination and aminative difunctionalization of alkenes allow for the incorporation of electrophilic, nucleophilic, and nitrene-type nitrogen sources into double bonds, providing an efficient and versatile route to access high-value chiral amines.

4.1. Asymmetric hydroamination of alkenes involving radical intermediates

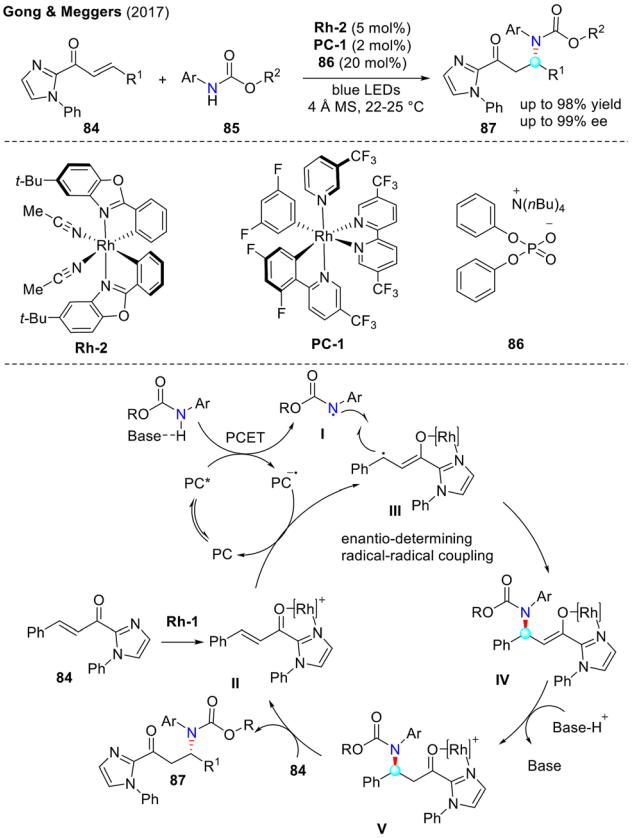
4.1.1 Chiral phosphoric acid-catalyzed asymmetric hydroamination of alkenes. In 2020, Knowles[58] and coworkers developed a CPA and PC dual-catalyzed enantioselective hydroamination of olefins with sulfonamides **83**. Mechanistic investigations revealed that N-centered radicals are generated through proton-coupled electron transfer (PCET) activation of sulfonamide N–H bonds, which undergo enantioselective 5-*exo*-trig cyclization and subsequent HAT from thiol, delivering a tetrahydropyrrole derivative. The enantioselectivity is achieved through noncovalent interactions between the neutral sulfonamidyl radical and the CPA, inducing the enantio-determining N-centered radical addition (Scheme 25).

4.1.2 Rh-catalyzed asymmetric hydroamination of alkenes. The utilization of α,β-unsaturated carbonyl compounds in conjugate amination presents a highly appealing strategy for generating value-added β-amino carbonyl building blocks. In 2017, the Gong and Meggers group[59] successfully developed a Rh/PC dual-catalyzed formal aza-Michael addition of α,β-unsaturated 2-acyl imidazole with *N*-phenyl carbamate (Scheme 26). Mechanistically, a nitrogen-centered radical is generated *via* visible light-induced phosphate base-promoted PCET of the carbamate, which produces a reduced photocatalyst radical ($PC^{\bullet-}$). The subsequent SET between $PC^{\bullet-}$ and the rhodium-bound substrate **II** forms a persistent Rh-enolate radical intermediate **III**. **III** is selectively captured by the transient nitrogen-centered radical **I**, delivering rhodium enolate **IV** with high enantioselectivity. The final product is released through BH-mediated protonation, followed by ligand exchange, regenerating the rhodium complex and completing the catalytic cycle. The *N*-phenyl imidazole group plays a critical role in ensuring excellent chiral induction throughout the process.

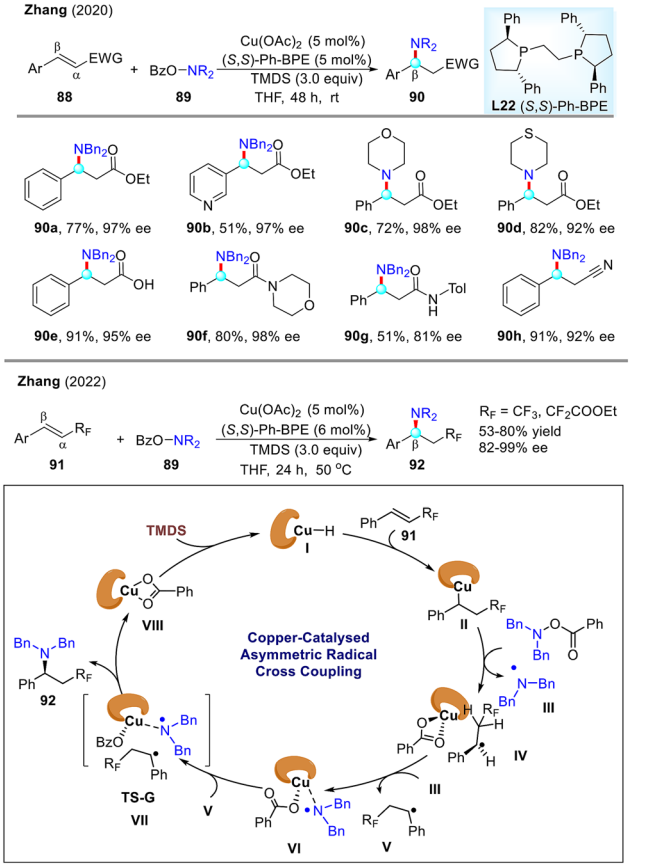
4.1.3 Cu-catalyzed asymmetric hydroamination of alkenes. The catalytic asymmetric aza-Michael reaction is widely recognized as an efficient and practical method for the synthesis of chiral β-amino acids, which are important building blocks in



Scheme 25 CPA/PC dual-catalyzed enantioselective hydroamination of alkenes with sulfonamides.



Scheme 26 Rh/PC dual-catalyzed enantioselective radical aza-Michael addition.

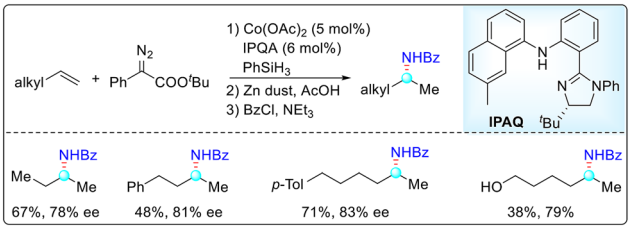


Scheme 27 Cu-catalyzed asymmetric hydroamination of Michael olefins.

the preparation of biologically active compounds. In 2020,[60] Zhang and colleagues developed a highly efficient Cu-catalyzed asymmetric reversal hydroamination reaction of Michael alkenes using hydroxylamine derivatives as electrophilic aminating reagents (Scheme 27, top). It is remarkable that a wide range of α,β-unsaturated carboxylic acids, esters, and amides, as well as simple α,β-unsaturated nitriles, could participate in this transformation, smoothly producing the corresponding β-amino acids, esters, amides, and nitriles in a highly regio- and enantioselective manner. This reaction overcomes the limitation of requiring pre-installation of stoichiometric quantities of auxiliary agents in intrinsically low reactivity Michael acceptors and provides a unified strategy for synthesizing chiral β-amino acids and their derivatives. Preliminary mechanistic studies suggest that the formation of chiral C–N bonds involves a novel asymmetric radical–radical coupling process between carbon and nitrogen radicals.

Building on this research, the same group[61] further expanded the utilization of this transformation by employing CuH to catalyze the asymmetric radical hydroamination of β-polyfluoroalkyl alkenes **91**, a weak Michael receptor, thus facilitating the production of enantioenriched β-polyfluoroalkyl-substituted α-chiral tertiary alkylamines. The authors conducted density functional theory (DFT) calculations to shed light on the regio- and stereoselectivity of the reaction. As demonstrated in Scheme 27, bottom, the *in situ*-generated Cu–H species **I** undergoes migratory insertion into olefins to form a benzyl-Cu^{I} complex **II**. Subsequent SET between complex **II** and the electrophilic aminating reagent generates an alkylamine radical **III**, which is stabilized by chiral Cu^{II} species through coordination. The enantio-determining radical–radical coupling occurs between the alkyl radical **V** and the Cu^{I}-bounded dialkyl amine radical species **VI**, delivering the desired β-fluoroalkyl-substituted chiral amines and regenerating the Cu catalyst. Such an elegant asymmetric radical cross-coupling of *in situ*-generated nitrogen radicals with a carbon-based radical species to create an asymmetric C–N bond provides a promising new strategy for enantioselective C–N bond formation, making it a valuable tool in organic synthesis.

4.1.4 Co-catalyzed asymmetric hydroamination of alkenes. In 2020, Lu[62] and colleagues developed a Co-catalyzed Markovnikov-type hydroamination of alkenes, utilizing diazo compounds as the nitrogen source and silanes as the hydrogen donor. By employing chiral *N*-imidazolinylphenyl 8-aminoquinoline ligands (**IPAQ**), they achieved enantioselective hydroamination of unactivated aliphatic terminal alkenes, resulting in chiral amine derivatives with good enantioselectivities (Scheme 28). The substrate scope was quite broad, demonstrat-

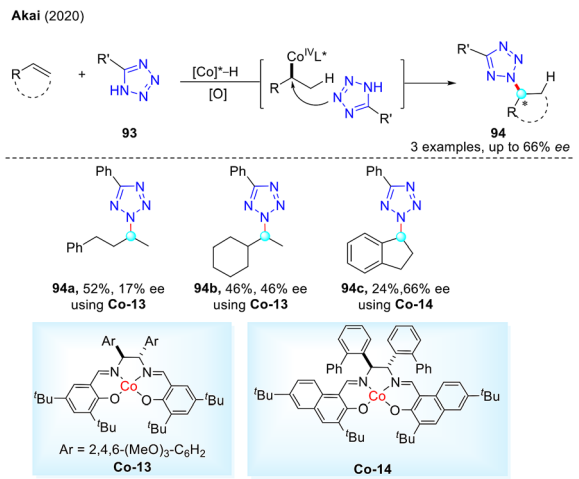


Scheme 28 Co-catalyzed Markovnikov-type hydroamination of alkenes.

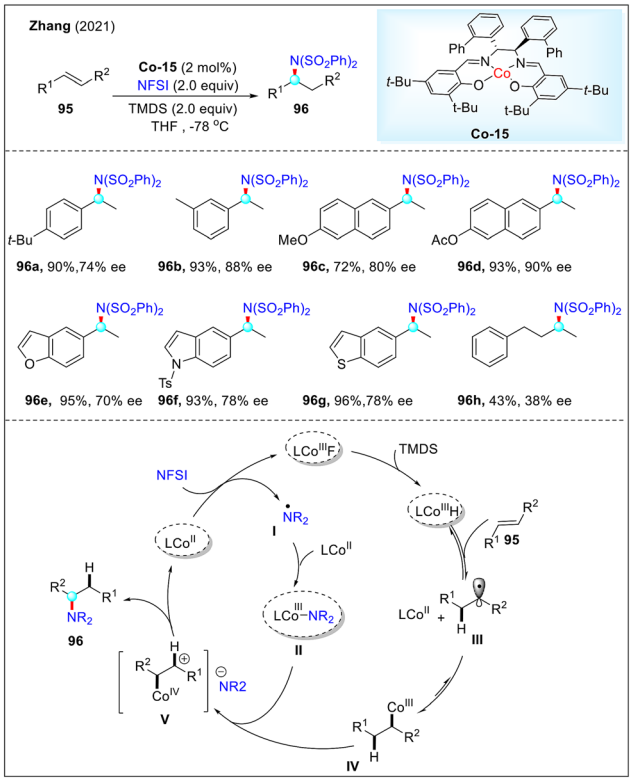
ing tolerance for various functional groups, including halides, ethers, and indoles.

In 2020, Akai[63] and coworkers reported an asymmetric hydroamination of nonactivated alkenes with benzotriazoles using an optically active Co(salen) complex, an *N*-fluoropyridinium salt, and a phenylsilane reagent. However, the enantioselective excess achieved was only up to 16%. When 5-phenyl tetrazole was utilized as the nitrogen source,[64] the asymmetric hydroamination of 4-phenyl-1-butene did not exceed 20% ee with any of the tested chiral cobalt catalysts. The most favourable outcome was observed in the asymmetric hydroamination of indene with tetrazole, resulting in a 66% enantiomeric excess and 24% yield of chiral amine **94** (Scheme 29).

In 2021, the Zhang group[65] successfully developed the first highly enantioselective hydroamination of alkenes utilizing *N*-fluorobenzenesulfonimides (NFSI) as both a nitrogen source and an oxidant under chiral cobalt catalysis (Scheme 30). This reaction features mild conditions, excellent regioselectivity, and wide functional group tolerance, and demonstrates a broad substrate scope. A variety of alkenes including styrenes, aliphatic alkenes and α,β-unsaturated carbonyl compounds can be engaged in this transformation to deliver the desired chiral amides with good to excellent yields. Mechanistic



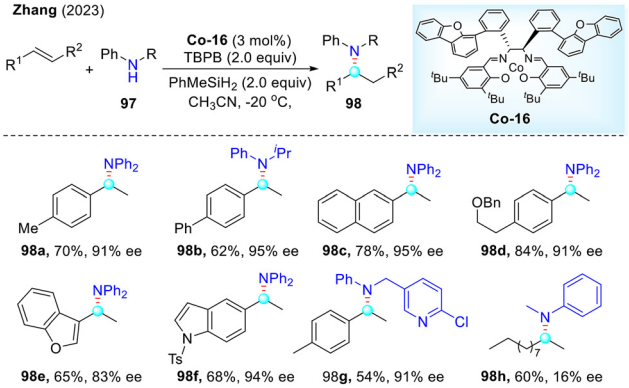
Scheme 29 Co-catalyzed asymmetric radical hydroamination of alkenes using 5-substituted tetrazoles.



Scheme 30 Co-catalyzed asymmetric hydroamination of olefins employing NFSI as the oxidant and amination source.

studies suggest that this reaction involves a cobalt(III)-hydride-mediated HAT to generate alkyl radicals **III**, which can be trapped by Co^{II} species to generate the Co^{III}-alkyl intermediates **IV**. Notably, the Co^{III}-alkyl intermediates **IV** can be further oxidized to high-valent Co^{IV}-alkyl intermediates, which act as electrophiles and are intercepted by a nitrogen source through an elegant S_N2-substitution. Due to the involvement of radical intermediates, the enantiocontrol of the hydroamination of aliphatic alkenes is relatively lower than that of styrene. This reaction offers a novel and general method for enantioselective hydroamination.

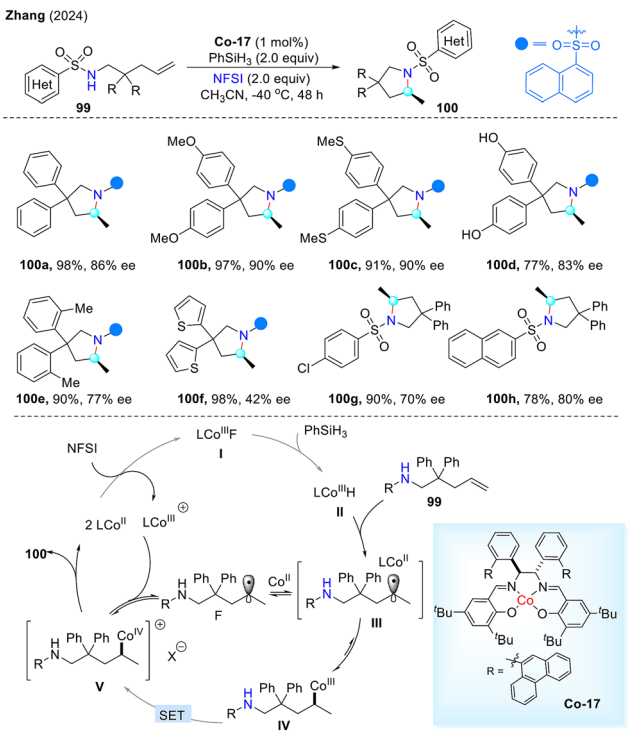
The catalytic asymmetric hydroamination of alkenes using Lewis basic amines has long been a challenging task in synthetic chemistry, due to the inherent strong coordination of Lewis basic amines that can potentially deactivate the chiral metal catalyst. Later in 2023, Zhang and colleagues developed a highly enantioselective hydroamination of aryl alkenes with secondary amines by leveraging cobalt hydride-mediated HAT, followed by a radical-polar crossover process involving high-valent cobalt(IV) species, significantly broadening the application of the approach (Scheme 31).[66] Diarylamines, cyclic acyclic secondary anilines with various *N*-alkyl substituents, and dialkylamines are all valid nitrogen sources, producing the desired α-chiral tertiary amines with good to excellent yields and enantioselectivities. Some secondary amines bearing a –CN or pyridyl group, which easily coordinate with chiral metal centres, are also well accommodated. The reaction



Scheme 31 Co-catalyzed asymmetric hydroamination of olefins with free amine.

can be utilized in the derivatization of natural products and drug derivatives, showcasing a high level of tolerance towards functional groups. The authors propose that both the generation of cobalt(III)-alkyl and the S_N2-substitution of alkylcobalt(IV) with nucleophiles play a significant role in the formation of enantioselective C–N bonds.

Prompted by these findings, the same group further reported a cobalt-catalyzed intramolecularly enantioselective hydroamination of unactivated amino alkenes (Scheme 32).[67] They used a phenanthrene-containing cobalt(salen) complex **Co-17** as the catalyst, NFSI as the oxidant and phenylsilane as the hydride source to perform the reaction, delivering a series



Scheme 32 Co-catalyzed intermolecular asymmetric hydroamination of inactivated olefins.

of chiral pyrrolidines **98**, which are key structures in pharmaceuticals and biologically active molecules. This reaction is remarkable in its ability to outcompete two different nucleophilic nitrogen sources within the same system, achieving high chemical selectivity in the conversion of intramolecular sulfonamides. Similar to the previous report, preliminary mechanistic studies demonstrated the involvement of a carbon radical intermediate and suggested that an S_N2-type displacement of the Co^{IV}–alkyl intermediate may be operative in the enantioselective transformation.

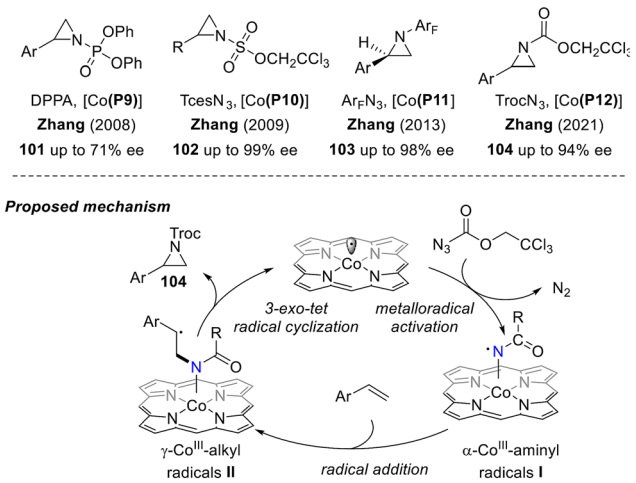
This catalytic platform has been further expanded very recently to the enantioselective C–O and C–C bond formation by trapping the *in situ* generated carbon radical intermediates with oxygen and carbon nucleophiles, respectively. It is undeniable that the use of this cobalt catalytic system greatly expands the potential applications of cobalt chemistry and asymmetric radical reactions. It introduces a new method for achieving highly enantioselective coupling of radical intermediates with nucleophiles by trapping the radical intermediate to produce an unusual, electrophilic cationic alkylcobalt(IV) species. This innovative reaction pathway, based on Co^{IV} intermediates and their enantioselective control, represents significant advancements in catalytic synthetic methodology and will find wide application in the future.

4.2. Asymmetric aziridination of alkenes involving radical intermediates

Chiral aziridines play a crucial role in drug design, asymmetric synthesis, and the development of bioactive molecules. Asymmetric catalytic aziridination of olefins is one of the most straightforward approaches for the synthesis of chiral aziridines[68,69] and received increasing attention.

In 2008, Zhang and coworkers[70] introduced the first use of cobalt(II) complexes with D_2-symmetric chiral porphyrins for the asymmetric aziridination of olefins, utilizing diphenylphosphoryl azide (DPPA) as the nitrene source. This catalytic system enabled the formation of *N*-phosphorylated aziridines in good yields with moderate enantioselectivities. This study marks a noteworthy milestone, as it showcases the first cobalt (II)-catalyzed asymmetric olefin aziridination using DPPA, thus laying a foundation for further advancements in chiral cobalt catalysts aimed at achieving more efficient and enantioselective synthesis of aziridines.

The Co^{II}-based metalloradical system enables the homolytic activation of a wide variety of organic azides with different electronic characteristics, facilitating the stereoselective synthesis of three-membered heterocycles. The researchers expanded the substrate scope to include trichloroethoxysulfonyl azides ($TcesN_3$),[71] *N*-fluoroaryl azides (Ar_FN_3),[72] and *N*-carbonyl azides ($TrocN_3$),[73] achieving high yields and excellent enantioselectivities (**102–104**). Mechanistically, this system generates an α-Co^{III}-aminyl radical intermediate **I** from organic azides, which then undergoes regioselective addition to olefins, forming a γ-Co^{III}-alkyl radical intermediate **II**. This intermediate undergoes an enantioselective *3-exo-tet* radical cyclization, resulting in the formation of chiral aziridines **104** (Scheme 33).



Scheme 33 Co^{II}-based MRC-catalyzed intermolecular asymmetric aziridination of olefins.

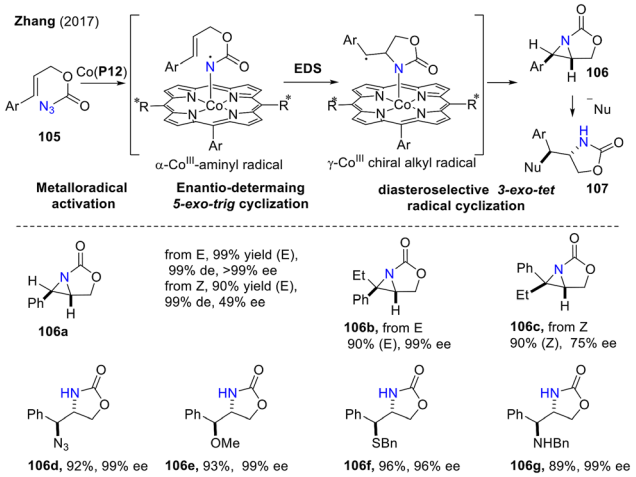
In 2017, the Zhang[74] group developed an innovative application of cobalt(II)-based MRC for the enantioselective radical bicyclization of allyl azidoformates (Scheme 34). This approach aimed to create a highly efficient and stereoselective catalytic system for constructing aziridine/oxazolidinone-fused bicyclic structures, which are crucial intermediates in the synthesis of biologically relevant compounds like chiral oxazolidinones and vicinal amino alcohols. This method demonstrated broad substrate compatibility, allowing a variety of allyl azidoformates with different substituents (aryl, vinyl, acyl) to undergo radical bicyclization, yielding products in high yields and with excellent stereocontrol. Mechanistic studies, including EPR spectroscopy and the use of both (*E*)- and (*Z*)-isomers of allyl azidoformates, indicated a stepwise radical bicyclization pathway that involves α-Co^{III}-aminyl and γ-Co^{III}-alkyl radicals. The enantioselective 5-*exo*-trig cyclization of the α-Co^{III}-aminyl radical is followed by a diastereoselective 3-*exo*-*tet* cyclization of the γ-Co^{III}-alkyl radical. Notably, the reaction proceeds *via* diastereoconvergent bicyclization with 1,2-substituted olefins, while diastereospecific bicyclization occurs for 1,1,2-trisubstituted olefins.

In 2024, the same group[75] developed enantioselective radical N-heterobicyclization using a cobalt(II)-based MRC system. Unlike previous reports, the Co^{III}-aminyl radical undergoes 6-*endo*-*trig* addition to a terminal olefin, forming a γ-Co^{III}-alkyl radical intermediate, which then cyclizes stereospecifically *via* 3-*exo*-*tet* radical cyclization (Scheme 35). Detailed experimental and computational studies revealed that enantioface-selective radical addition, followed by stereospecific radical substitution, are the key steps in achieving high enantioselectivities.

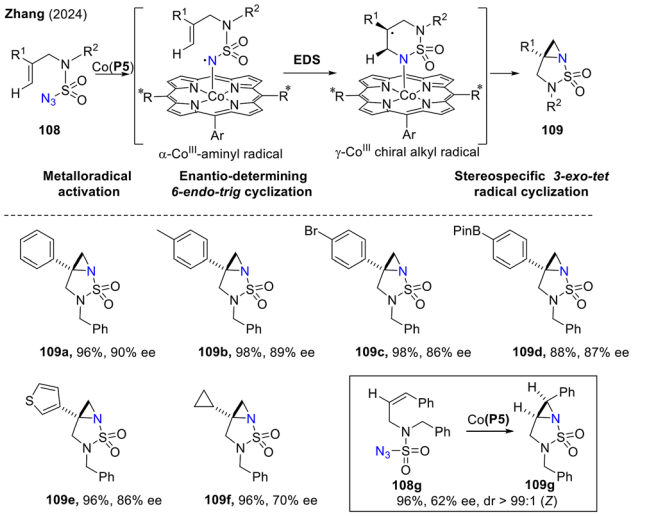
4.3. Asymmetric radical amination-difunctionalization of alkenes

The asymmetric radical amination-difunctionalization of alkenes allows for the simultaneous introduction of an amino group and other distinct functional groups across a carbon–carbon double bond *via* radical addition and subsequent enantio-determining C–N bond formation. This method provides an efficient and versatile pathway for synthesizing structurally complex chiral amines and N-heterocycles with high step economy.

4.3.1 Cu-catalyzed asymmetric amination-difunctionalization of alkenes. In 2016, Liu and coworkers[76] developed copper(I) and CPA dual-catalyzed enantioselective aminotrifluoromethylation of alkenes. This approach enables the efficient construction of CF_3-containing azaheterocycles **112** with α-tertiary stereocenters, achieving up to 88% yield and 98% ee. Mechanistically, the combination of a copper(I) catalyst and CPA facilitates the generation of CF_3 radicals from Togni's reagent **111**, which adds to the alkenes to form an alkyl radical intermediate **I**. This intermediate undergoes



Scheme 34 Co^{II}-based MRC-catalyzed enantioselective radical bicyclization initiated by 5-*exo*-*trig* cyclization.



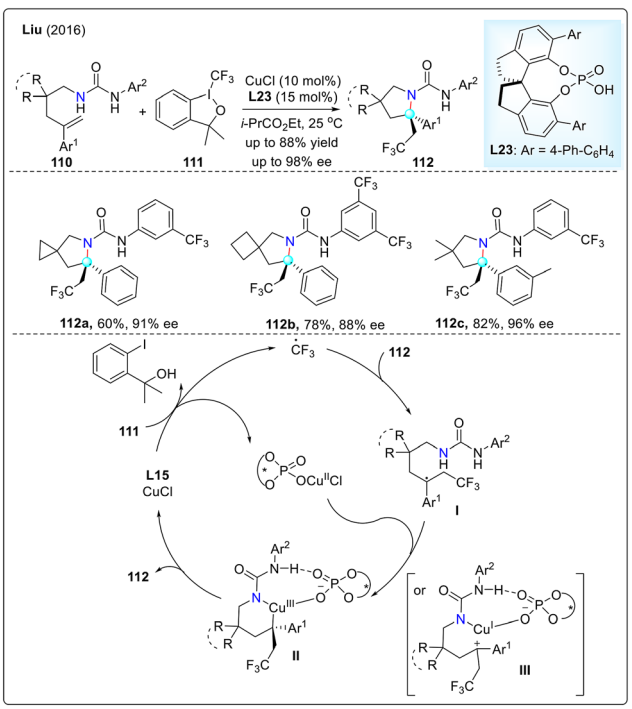
Scheme 35 Co^{II}-based MRC-catalyzed enantioselective radical bicyclization initiated by 6-*endo*-*trig* cyclization.

enantio-determining cyclization, leading to aminotrifluoromethylated products **112** with high enantioselectivities. The study proposes two potential pathways: one involving a chiral ion-pair complex **III** and another featuring a chiral alkylcopper (III) intermediate **II**, both contributing to stereocontrol. This method exhibits broad substrate compatibility, efficiently transforming a range of alkenyl ureas and alkenes into the desired products with good yields and excellent ee (Scheme 36).

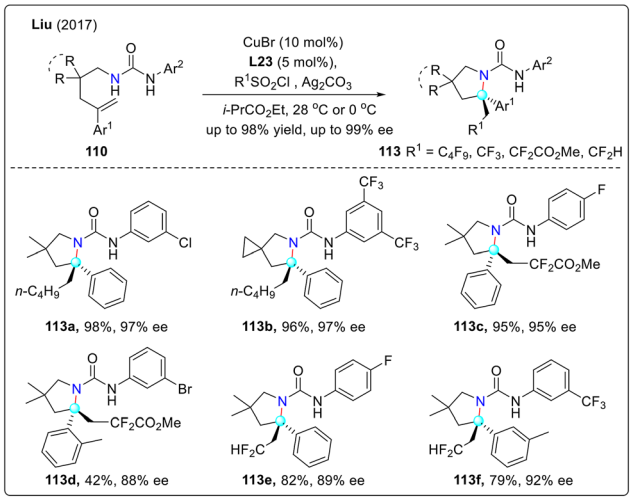
In 2017, the same group[77] developed an asymmetric aminofluoroalkylation of arylated alkenes involving radical intermediates. Using sulfonyl chloride as the fluoroalkyl radical source and Cu^{I}/CPA (**L23**) as the SET catalyst, they successfully introduced perfluorobutanyl, trifluoromethyl, difluoroacetyl and difluoromethyl groups into urea-substituted olefins. This method provided a direct route to a variety of chiral β-fluoroalkyl amines **113** (Scheme 37).

The Liu group further expanded the scope of this strategy to other transformations, including di-amination and azido amination,[78] aminosilylation,[79] and arylamination[80] reactions. Mechanistic investigations indicated that the chiral C–N bond formation likely occurs through a carbocation intermediate rather than *via* a Cu^{III} elimination pathway. This radical-based asymmetric amination strategy provides direct access to a wide range of valuable substituted chiral pyrroles **116–119** (Scheme 38).

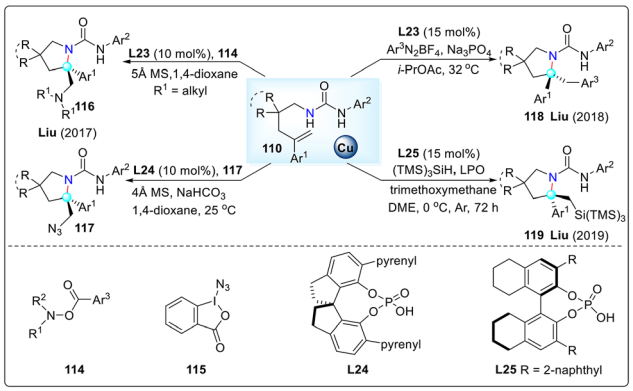
This Cu(I)/CPA cooperative system can also be extended to the enantioselective three-component trifluoromethylative amination of alkenes,[81] incorporating a convertible hydroxy group as a directing group, using hydrazines and Togni's



Scheme 36 Cu/CPA-catalyzed asymmetric aminotrifluoromethylation.



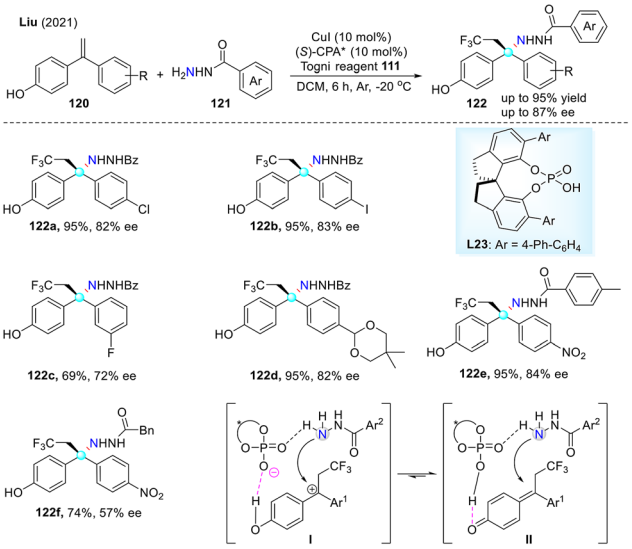
Scheme 37 Cu/CPA-catalyzed asymmetric aminofluoroalkylation.



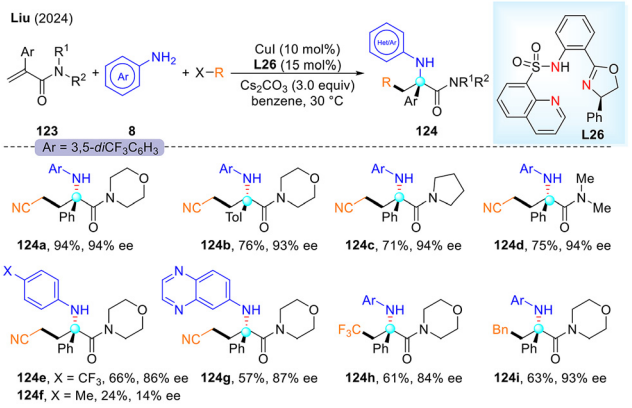
Scheme 38 Cu/CPA-catalyzed asymmetric aminative difunctionalization of olefins.

reagent. The reaction proceeds through a radical-carbocation crossover mechanism. The high levels of stereocontrol in the formation of the asymmetric C–N bond are attributed to hydrogen-bonding and ion-pair interactions between the carbocation intermediate and the CPA. This methodology exhibits broad functional group tolerance, effectively accommodating both electron-rich and electron-deficient substituents on the aromatic ring. Moreover, it successfully incorporates various hydrazines, leading to the formation of enantioenriched diarylmethylamines **122** with an α-tertiary stereocentre (Scheme 39).

Very recently, Liu and coworkers[82] developed a Cu/anionic chiral *N*,*N*,*N*-ligand (**L26**)-catalyzed asymmetric radical carboamination of 1,1-disubstituted alkenes, using readily available alkyl halides and arylamines (Scheme 40). This method provides direct access to value-added chiral α-tertiary *N*-arylamines **124**. The protocol demonstrated broad substrate tolerance, accommodating a wide range of α-aryl-substituted acrylamides, electron-deficient aryl and heteroaryl amines, as



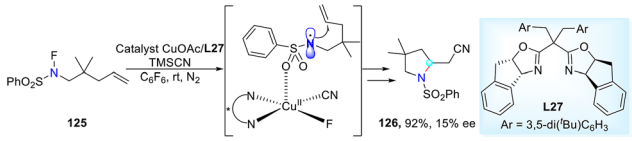
Scheme 39 Cu/CPA-catalyzed three-component trifluoromethylative amination of alkenes.



Scheme 40 Cu-catalyzed asymmetric carboamination of electron-deficient alkenes.

well as alkyl halides and sulfonyl chlorides, all with good to excellent enantioselectivities. However, for aromatic amines with electron-neutral or -donating groups, dramatically decreased enantioselectivities were observed. This approach offers a versatile platform for the direct synthesis of chiral α-tertiary *N*-arylamine building blocks, expanding the toolbox for asymmetric amination reactions.

In 2019, Liu and colleagues[83] reported a copper/chiral BOX-catalyzed, site- and enantioselective allylic C–H cyanation of complex alkenes. Notably, when an N–F reagent was used with distal olefins as the starting material, the resulting aminocyanation product was obtained with a 92% yield, although it exhibited only 15% enantioselectivity (see Scheme 41). Despite this low enantioselectivity, this work represents a rare example of enantioselective C–N bond formation *via* N-centered radical addition, highlighting its potential for further advancements in asymmetric radical chemistry.

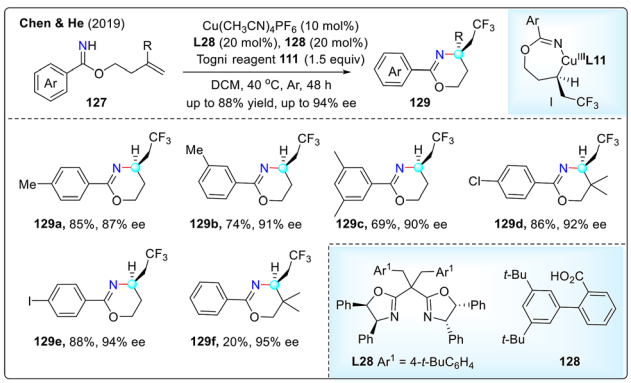


Scheme 41 Cu/chiral BOX-catalyzed asymmetric aminocyanation.

In 2019, the Chen and He group[84] developed a Cu/chiral BOX-catalyzed enantioselective trifluoromethylative amination of *O*-homoallyl benzimidates. This methodology displays broad functional group tolerance, efficiently converting substrates bearing both electron-donating and electron-withdrawing groups on the phenyl ring, and exhibiting exceptional compatibility with halogen substituents, including iodine (Scheme 42). Mechanistically, the process involves the formation of alkyl radicals from the addition of CF_3 radicals to olefins. These alkyl radicals are enantioselectively captured by a chiral Cu^{II} species, leading to the formation of a Cu^{III} intermediate, which then undergoes C–N reductive elimination to generate CF_3-containing heterocycles.

4.3.2 Fe-catalyzed asymmetric amination-difunctionalization of alkenes. The carboazidation of olefins is an effective method for transforming chemical feedstocks into nitrogen-containing molecules, which have wide applications in medicine and materials science. Although there has been significant progress in carboazidation reactions, asymmetric radical carboazidations are still relatively unexplored. In 2021, the Bao group[85] pioneered an iron-catalyzed enantioselective carboazidation of styrenes, enabling the formation of chiral halogenated organoazides **130**. These organoazides are valuable precursors for various nitrogen-containing synthetic targets. This process introduces azido groups into olefins with high stereoselectivity, converting inexpensive industrial feedstocks into valuable chiral compounds.

The proposed mechanism involves SET between LPO and Fe^{II}–N_3 to generate an Fe^{III}–N_3 species **III** and alkyl radicals **IV**. **IV** abstract the halogen atom from fluoroalkyl iodides to form fluoroalkyl radicals, which subsequently add to the double



Scheme 42 Cu/chiral BOX-catalyzed asymmetric trifluoromethylative amination of alkenes.

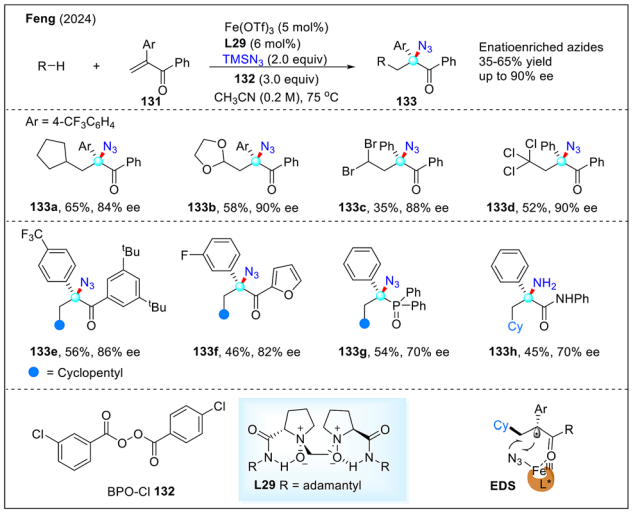
bond, generating benzylic radicals **V**. The benzylic radicals then undergo an enantioselective azido group transfer, resulting in chiral organoazides **130**. Mechanistic studies, supported by mass spectrometry and computational analysis, indicate that stereoselectivity is achieved through weak non-covalent interactions and steric effects within the chiral environment. This work marks a significant advancement in enantioselective radical azidation and underscores the potential of iron catalysis for further developments in asymmetric radical chemistry (Scheme 43).

Very recently, Feng and coworkers[86] developed an iron-catalyzed, asymmetric three-component radical carboazidation of electron-deficient alkenes, including α,β-unsaturated ketones, amides, and phosphine oxides, using C(sp^3)–H-containing partners as alkyl radical precursors (Scheme 44). The chiral *N*,*N*′-dioxide ligand (**L29**), designed by their group, efficiently facilitates this radical carboazidation, yielding enantioenriched chiral azide compounds **133** bearing a quaternary stereocenter with good yields and high enantioselectivities. The carbonyl group on the olefins acts as a directing group, enhancing asymmetric azide transfer. This protocol is notable for directly utilizing abundant and cost-effective hydrocarbons as alkylating sources, providing rapid access to valuable chiral alkylazides.

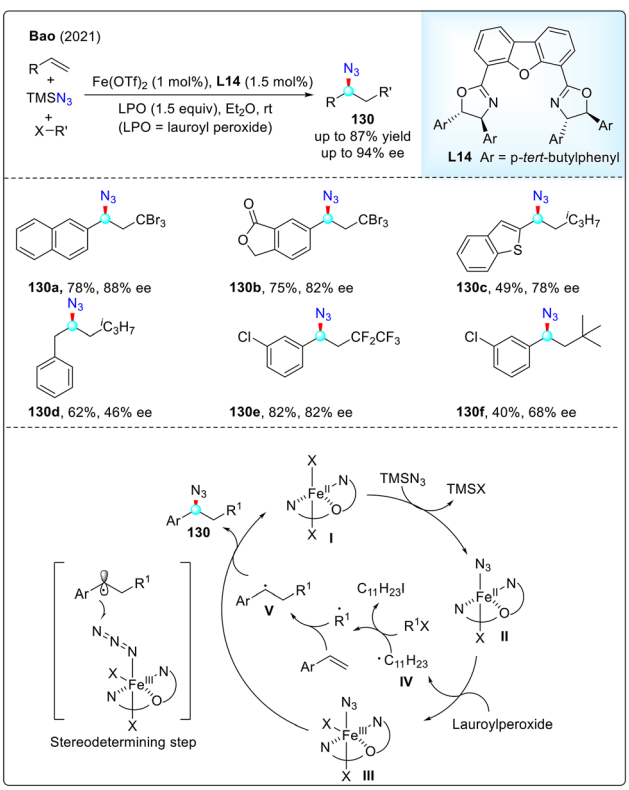
4.3.3 Asymmetric amination-difunctionalization of conjugated dienes. In 2008, Shi and coworkers[87] developed a Cu^I-catalyzed asymmetric diamination of conjugated dienes, employing (*R*)-DTBM-SEGPHOS **L13** as the chiral ligand and di-*tert*-butyldiaziridinone **135** as the nitrogen source. The authors proposed a radical mechanism for the Cu^I-catalyzed diamination, which presents challenges in achieving precise asymmetric control, with enantioselectivities reaching up to 74% ee (Scheme 45). Furthermore, the Cu/CPA system[88] could also promote this two-component asymmetric diamination, albeit with moderate enantioselectivities.

In 2024, Gong and coworkers[89] developed a photoinduced Pd-catalyzed three-component enantioselective carboamination of dienes (Scheme 46). A broad range of abundant C(sp^3)–H-containing partners, such as toluene-type substrates, ethers, amines, esters, and ketones, served as alkyl radical sources, while free amines, including aliphatic, aromatic, primary, and secondary amines, were used as nitrogen sources. This method enabled the synthesis of chiral allylamines with moderate to excellent enantioselectivities under mild conditions. The efficient construction of chiral allyl amines from cost-effective and readily available chemical raw materials is undoubtedly highly appealing.

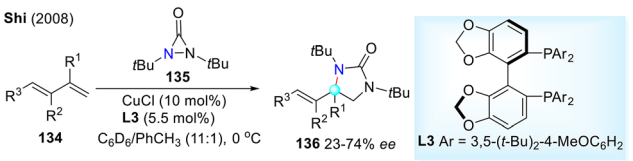
Mechanistically, Pd^0 was irradiated by blue LEDs to generate excited Pd^0L^*, which underwent SET with ArBr, producing an aryl radical and Pd^IL. The aryl radical then engaged in SET with the C(sp^3)–H-containing partners to generate alkyl radicals **II**. These radicals underwent addition to dienes, forming an allyl radical intermediate **III**. Radical recombination with



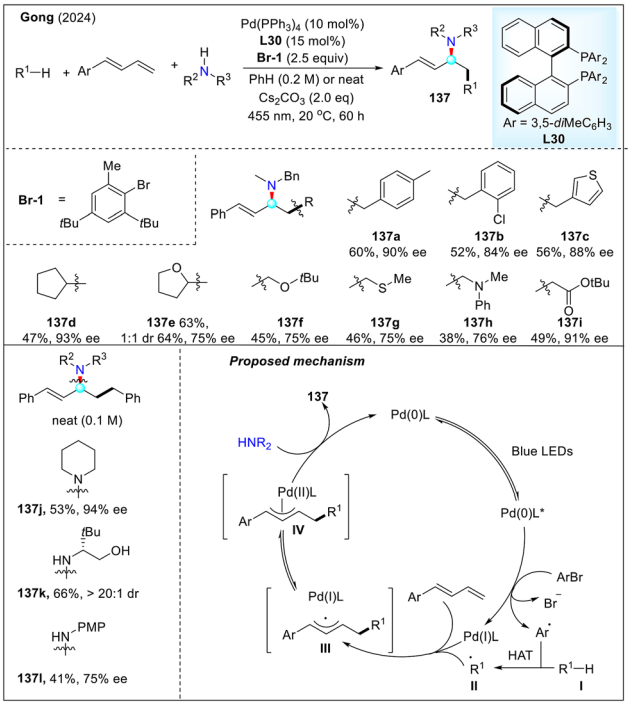
Scheme 44 Fe-catalyzed asymmetric carboazidation of electron-deficient alkenes.



Scheme 43 Fe-catalyzed asymmetric carboazidation of styrene.



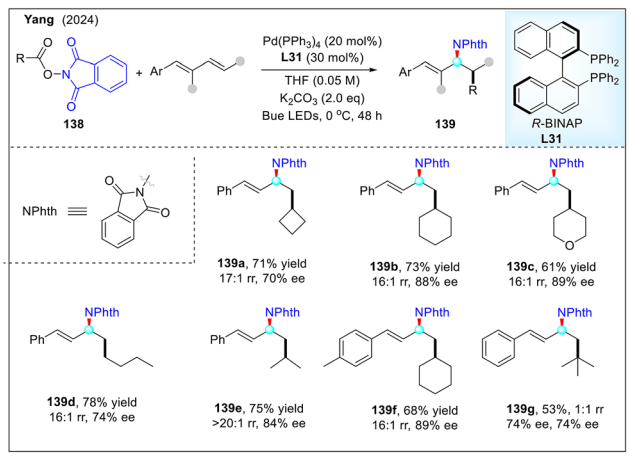
Scheme 45 Cu-catalyzed asymmetric diamination of dienes.



Scheme 46 Photoinduced Pd-catalyzed asymmetric 1,2-carboamination of 1,3-dienes *via* activation of aliphatic C–H bonds.

Pd^{I} resulted in a π-allyl Pd^{II} complex, which then underwent regio- and enantioselective nucleophilic substitution by the amine, delivering the final products. The use of bulky aryl bromides was crucial to avoid direct aryl radical addition to the 1,3-diene.

Shortly thereafter, Yang and coworkers[90] developed a photoinduced Pd-catalyzed asymmetric 1,2-carboamination of conjugated 1,3-dienes using *N*-hydroxyphthalimide (**138**) esters as bifunctional reagents (Scheme 47). This method demonstrated broad substrate compatibility, accommodating NHPI esters derived from primary, cyclic, and noncyclic secondary carboxylic acids, and delivering 1,2-carboamination products **139** with moderate to high enantioselectivities.



Scheme 47 Photoinduced Pd-catalyzed asymmetric 1,2-carboamination of 1,3-dienes.

5. Conclusions

Radical-mediated enantioselective amination has been proven to be an effective and appealing method for synthesizing chiral amines and nitrogen-containing heterocycles, as highlighted in this review. These processes involve the formation of C–N bonds enantioselectively through mechanisms such as reductive elimination, radical-polar crossover, amino group substitution, radical cross-coupling, and radical addition. Recent research has demonstrated that enantioselectivity can be well controlled by employing various metals and chiral ligands. In those transformations, alkyl-metal species, N-metal species, and chiral catalyst-bonded N-centered or alkyl radicals serve as key intermediates that play a crucial role in chiral induction. A thorough understanding of these pivotal intermediates provides valuable insights for future advancements in enantioselective radical amination.

All of these achievements showcase the promising development of the catalyzed enantioselective radical amination strategy *via* asymmetric formation of C–N bonds. However, it remains a dynamic and emerging field, with several issues needing further development: (1) alkyl radicals, such as benzyl, α-carbonyl, and allylic/propargyl radicals, have been effectively utilized for enantioselective radical amination; however, achieving enantio-differentiation between two alkyl groups connected by alkyl radicals remains a significant challenge; (2) although radical amination employing NFSI, N–O reagents, organic azides, dioxazolones, amides, and aniline derivatives as nitrogen sources has been successfully realized, direct enantioselective amination of alkylamines or ammonia remains a considerable obstacle; and (3) most reactions rely on transition metal catalysis for enantioselectivity control. For addressing these challenges, the exploration of new reaction modes as well as innovative chiral catalyst design might be necessary. A new methodology for enantioselective C–N bond formation without employing a metal catalyst is highly desirable. It is expected that this research field will attract widespread attention and make further progress in the near future.

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.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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