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Recent advances in light-driven synthesis of complex trifluoromethylated aliphatic amines and derivatives

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Trifluoromethylated aliphatic amines, particularly those with structurally complex architectures, have emerged as valuable motifs in drug discovery due to their unique capacity to enhance metabolic stability, membrane permeability, and affinity for biological targets. However, the selective and efficient synthesis of these compounds remains a significant challenge, limiting their broader incorporation into pharmaceutical agents. Recent advances in light-driven organic synthesis, employing mild and sustainable visible-light-mediated conditions, have enabled modular and practical strategies for constructing these privileged structures from simple, readily available starting materials. A variety of photoinduced reactions, photocatalytic methods, and metallaphotoredox-catalyzed transformations have been developed, facilitating the direct installation of trifluoromethyl (CF₃) groups and CF₃-containing synthons onto diverse aliphatic frameworks and amine precursors. This review presents a comprehensive overview of recent progress in the photoinduced synthesis of trifluoromethylated aliphatic amines and their derivatives, emphasizing key methodological innovations, representative pharmaceutical targets, and mechanistic insights, with the goal of guiding future efforts in the design and synthesis of fluorine-rich bioactive molecules.

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1. Introduction

In drug discovery, the strategic incorporation of heteroatoms profoundly alters the electronic, steric, and structural properties of molecules, enhancing their biological efficacy and

potential for therapeutic application.¹ Among various heteroatoms, fluorine and fluoroalkyl groups have gained prominence due to their capacity to improve pharmacokinetic properties such as metabolic stability, membrane permeability, and target-binding affinity, significantly influencing ADMET (absorption, distribution, metabolism, excretion, and toxicity) profiles.² Particularly, the introduction of trifluoromethyl (CF₃) groups into bioactive small molecules has proven to be a robust strategy for constructing hit compounds, clinical candidates,

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Highlight

and marketed pharmaceuticals.^{2,3} Indeed, CF₃-substituted arenes and heterocycles are common structural motifs in many commercially important drugs (Scheme 1A(i)), as exemplified by sitagliptin (antidiabetic), apalutamide (anticancer), and celecoxib (neurology). Remarkably, within the top 200 best-selling pharmaceuticals in 2024, fourteen drugs contain C(sp²)-CF₃ bonds.⁴

In contrast, CF₃ groups directly attached to aliphatic carbons (C(sp³)-CF₃) are far less common in pharmaceutical compounds, with only a few examples such as the 2,2,2-trifluoroethyl fragment (three instances, Scheme 1A(ii)) and α -CF₃-substituted quaternary centers (three instances, Scheme 1A(iii)), despite their steadily increasing prevalence in recent years.⁴⁻⁶ More structurally intricate trifluoromethylated aliphatic (trifluoroalkyl) motifs—particularly those featuring remote CF₃ groups embedded within saturated, three-dimensional aliphatic frameworks—remain significantly underdeveloped (Scheme 1A(iv)). This scarcity arises predominantly from synthetic challenges associated with selectively constructing these complex trifluoroalkyl frameworks, which typically require multiple synthetic steps, sensitive reagents, and harsh reaction conditions.⁷ However, molecules bearing such sophisticated trifluoroalkyl scaffolds present substantial opportunities for modulating physicochemical properties through multiple mechanisms, including the distinct contributions of the CF₃ group,^{2,3} and those arising from enhanced fraction of sp³-hybridized carbons,⁸ methyl effects,⁹ and quaternary centers¹⁰ introduced by complex aliphatic architectures. Collectively, these features may significantly accelerate the discovery and optimization of bioactive compounds.

On the other hand, amines and their derivatives constitute indispensable structural components in drug design, as nearly all best-selling pharmaceuticals contain at least one amine group (C(sp²)-N and C(sp³)-N).⁴⁻⁶ Structurally complex trifluoroalkyl amines, specifically, appear in several notable drugs such as efavirenz, alpelisib, mapracorat, masilukast, and enpatoran, underscoring their potential value in medicinal chemistry¹¹

(Scheme 1B). The electron-withdrawing nature of fluoroalkyl groups lowers both the basicity and reducing power of amines, thereby enhancing the site selectivity and oxidative stability of the resulting drug molecules.^{7,12} Nevertheless, the medicinal application of trifluoroalkyl-substituted amines significantly lags behind that of their CF₃-substituted aromatic or heteroaromatic counterparts. The primary factor hindering their broader adoption is the difficulty associated with synthesizing complex trifluoroalkyl precursors, which often entails lengthy, inefficient synthetic routes with limited structural diversity, thereby impeding the streamlined construction of structurally intricate trifluoroalkyl amines and derivatives **1A**⁷ (Scheme 1C).

Addressing these synthetic bottlenecks, light-driven synthesis has emerged in recent years as a versatile and powerful approach for assembling complex molecules from simple substrates under mild, environmentally benign conditions.^{13,14} Photocatalytic methods harness visible-light energy to enable single-electron transfer (SET)¹³ and energy-transfer (EnT)¹⁴ processes, generating reactive radical intermediates capable of forging otherwise challenging chemical bonds. Photoinduced strategies (operating without photocatalysts or metal catalysts), photocatalysis (employing a single photoexcited metal complex or photocatalyst), and metallaphotoredox catalysis (combining transition metal catalysis with photocatalysis) have opened new avenues for the direct installation of CF₃ and other trifluoroalkyl groups onto aliphatic frameworks (Scheme 1D). These methods typically employ readily accessible starting materials, including trifluoromethylating reagents, simple amines, alkyl precursors, nitroarenes, and unsaturated substrates, enabling direct construction of C(sp³)-CF₃, C(sp³)-N, and C(sp³)-C(sp³) bonds. Consequently, these modular photocatalytic strategies¹⁵ have greatly expanded synthetic accessibility to structurally complex trifluoromethylated amines and their derivatives, including cyclic amines, CF₃-substituted imines, amino acids, and medically relevant heterocycles.

In this review, we highlight recent advances in light-driven strategies for the synthesis of trifluoromethylated aliphatic amines and their derivatives, organized according to key mechanistic pathways, including alkene difunctionalization, metallaphotoredox radical cascades, inert bond functionalization, as well as photocatalyst-free and stereo-selective approaches. We highlight key methodological innovations, structural motifs of pharmaceutical relevance, and mechanistic insights. Our goal is to provide a clear and concise foundation for understanding current advances and to inspire future directions in the design of trifluoroalkyl amines and the development of fluorine-rich amine-containing pharmaceuticals.

2. Photocatalytic alkene difunctionalization

The simultaneous incorporation of trifluoromethyl and nitrogen-based functionalities across alkenes represents a powerful strategy for constructing complex trifluoromethylated

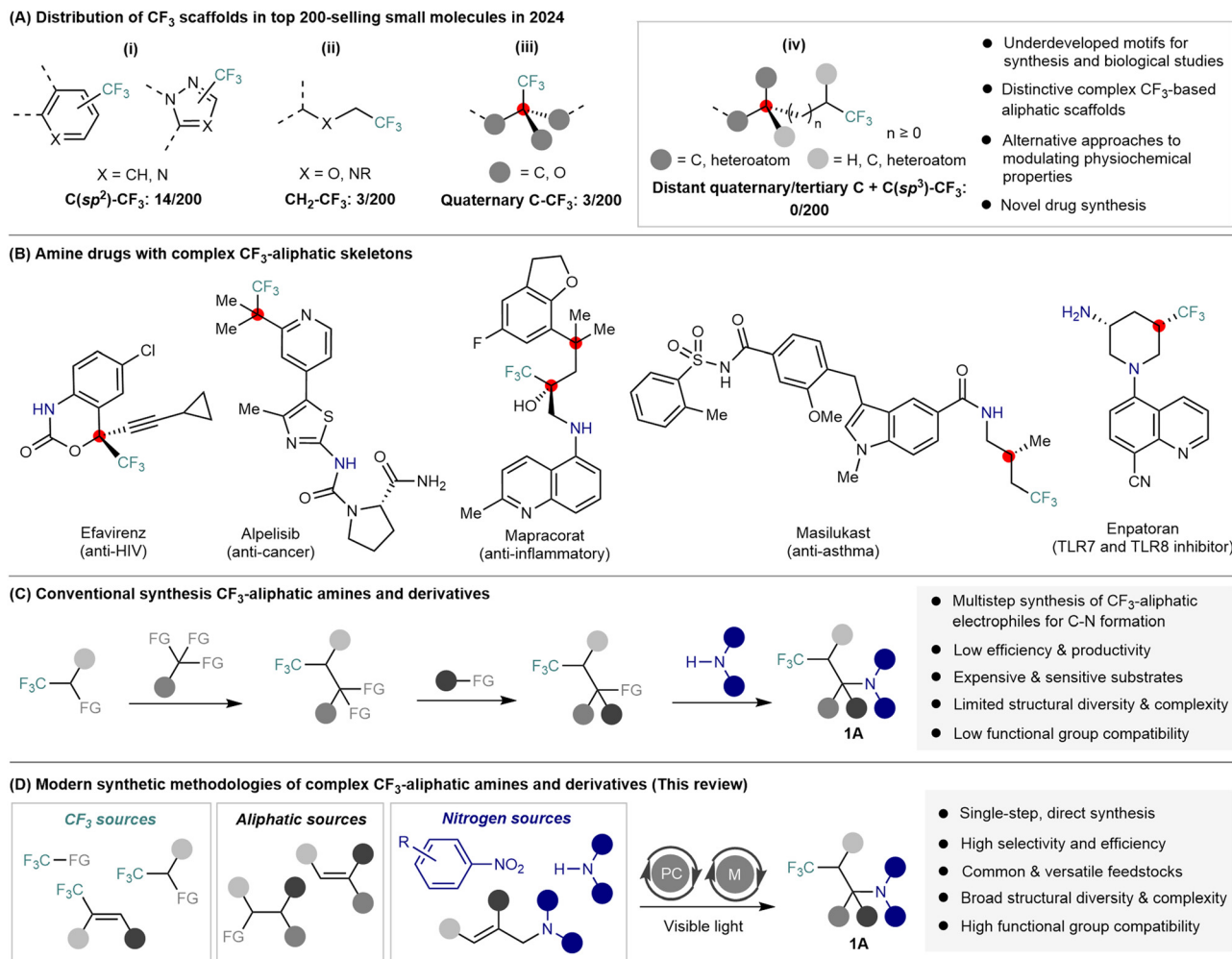


Fuk Yee Kwong

Young Academy of Science in 2020, his research focuses on phosphine ligand design for cross-coupling, C-H functionalization, and enantioselective transformations.

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Scheme 1 The significance, synthetic challenges, and recent developments in trifluoroalkyl amines and their derivatives. (A) Distribution of C(sp²)-CF₃ and C(sp³)-CF₃ scaffolds in pharmaceuticals. (B) Representative amine-based drugs bearing complex CF₃-substituted aliphatic skeletons. (C) Conventional synthetic approaches to CF₃-substituted aliphatic amines and their derivatives. (D) Modern synthetic methodologies for complex CF₃-substituted aliphatic amines and derivatives (this review).

amines from simple olefins. Photoinduced difunctionalization offers modular and regioselective access to these valuable motifs under mild conditions, typically through radical-polar crossover or radical-radical coupling pathways. This section highlights recent advances in photocatalytic simultaneous construction of C-CF₃, C-N, C-C, and C-heteroatom bonds within the unsaturated compounds to offer complex trifluoroalkyl amines and derivatives.

2.1 Simultaneous C-CF₃ and C-N bond formation

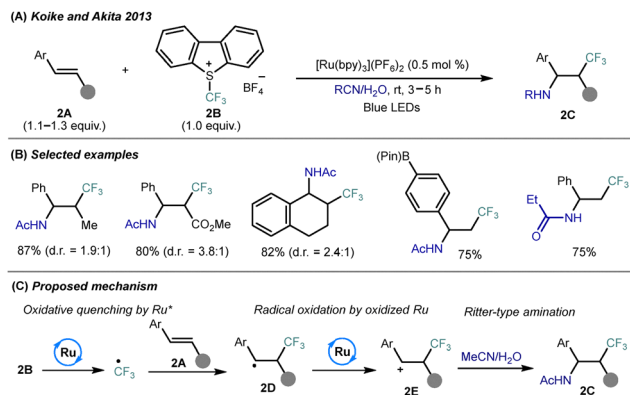
2.1.1 Photocatalytic amino-trifluoromethylation of alkenes using nitriles as nitrogen sources.

The 1,2-addition of both CF₃¹⁶ and amino groups¹⁷ to alkenes is probably the straightforward and most effective strategy to access complex β-trifluoromethylated alkylamines. The electrophilic trifluoromethylating reagents and nucleophilic nitrogen-based compounds can serve as reactive substrates to enable selective functionalization of alkenes to access these compounds. Koike, Akita, and co-workers reported a photoredox-catalyzed intermolecular amino-trifluoromethylation of alkenes **2A** using

the commercially available Umemoto reagent **2B** and nitriles (RCN) as nitrogen sources¹⁸ (Scheme 2A). Upon irradiation of styrenes and the Umemoto reagent in a nitrile/water mixture—serving as both solvent and reactants—in the presence of [Ru(bpy)₃](PF₆)₂ as the photocatalyst, efficient β-trifluoromethylation and concurrent Ritter-type amination were achieved. Acyclic terminal and internal alkenes, cyclic styrenes, as well as acetonitrile and higher homologous nitriles such as propionitrile, are well tolerated, affording a broad range of structurally complex 2-aryl-3,3,3-trifluoroacetamide derivatives **2C** with high selectivity (Scheme 2B). The scope of this transformation is restricted to styrene-based substrates for the efficient synthesis of trifluoromethylated amines. Mechanistic investigations suggest that the photoexcited Ru catalyst reduces the Umemoto reagent to generate a CF₃ radical, which adds to the alkene to form a trifluoroalkyl radical **2D** (Scheme 2C). Subsequent oxidation by the photocatalyst produces a carbocation intermediate **2E**, which undergoes a Ritter-type reaction with nitrile and water to furnish the aryl trifluoroacetamide products.



Highlight



Scheme 2 Photocatalytic amino-trifluoromethylation of alkenes using nitriles as nitrogen sources. (A) General reaction conditions. (B) Representative substrate scope. (C) Proposed mechanism.

2.1.2 Photocatalytic azido- and amino-trifluoromethylation of alkenes using nitrogen nucleophiles. The use of transformable nitrogen-based nucleophiles and structurally diverse alkenes in 1,2-difunctionalization reactions offers an effective strategy for increasing the complexity and molecular diversity of β -trifluoromethylated alkylamine derivatives. Magnier, Masson, and co-workers developed a photoredox-catalyzed, three-component azido- and amino-trifluoromethylation of alkenes **3A**, utilizing Umemoto reagent **3B** as the CF_3 source, electron-deficient nitrogen-based substrates as nucleophiles, and catalytic $\text{Ru}(\text{bpy})_3(\text{PF}_6)_2$ under blue LED irradiation, affording the trifluoroalkyl amines and derivatives **3C**¹⁹ (Scheme 3A). This reaction protocol accommodates a broad range of nucleophiles, including azidotrimethylsilane (TMSN_3), sulfonamides, hydrazines, carbamates, and amides, and is applicable to both styrenes and 1,1- or 1,2-disubstituted alkenes (Scheme 3B). In contrast, the reaction shows limited efficiency with unactivated monosubstituted alkenes, giving low yields, and fails when alkylamines or electron-rich anilines are employed as nitrogen nucleophiles, likely due to competing side reactions or substrate decomposition.

Mechanistic studies support a radical/cationic sequence: photoexcited $\text{Ru}(\text{bpy})_3^{2+*}$ initiates SET reduction of Umemoto reagent to generate a CF_3^\bullet radical, which adds regioselectively to the alkene to form a trifluoroalkyl radical **3D** (Scheme 3C). Subsequent oxidation by $\text{Ru}(\text{bpy})_3^{3+}$ affords a β - CF_3 carbocation **3E**, which undergoes nucleophilic trapping by TMSN_3 or RNH_2 , completing the difunctionalization and regenerating the $\text{Ru}(\text{II})$ photocatalyst. This protocol represents a rare example of successful amino-trifluoromethylation involving direct use of diverse amine classes, thus providing access to structurally complex CF_3 -substituted building blocks under operationally simple and scalable conditions.

2.1.3 Photocatalytic azo-trifluoromethylation of alkenes with aryldiazonium salts. Chen, Xiao, and co-workers disclosed a visible-light-driven, photocatalytic azo-trifluoromethylation of alkenes **4A** employing sodium triflate (Langlois reagent, **4C**) and aryldiazonium salts **4B** as the CF_3 and nitrogen sources, respectively (Scheme 4A). Using $\text{Ru}(\text{bpy})_3\text{Cl}_2 \cdot 6\text{H}_2\text{O}$ as the photoredox catalyst and blue LED irradiation, a broad array of mono-

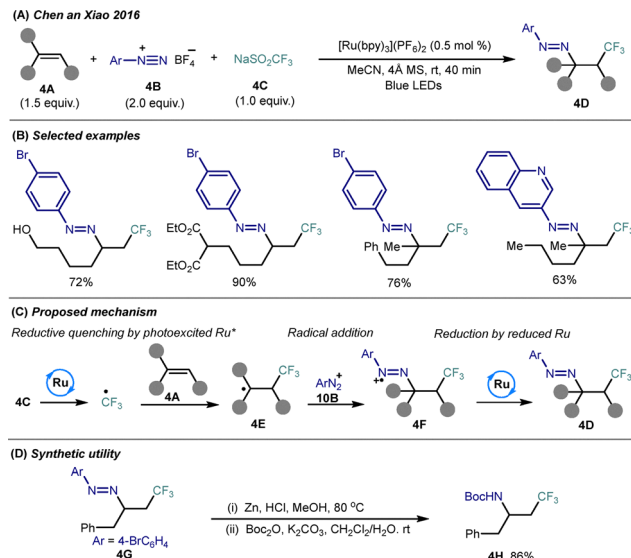


Scheme 3 Photocatalytic azido- and amino-trifluoromethylation of alkenes using nitrogen nucleophiles. (A) General reaction conditions. (B) Representative substrate scope. (C) Proposed mechanism.

and disubstituted alkenes underwent efficient difunctionalization to afford structurally diverse trifluoromethylated azo compounds **4D**²⁰ (Scheme 4B). Notably, prolonged reaction time resulted in reduced yields due to partial decomposition and (*E*)-to-(*Z*) isomerization of the products. Mechanistic studies suggest a photocatalytic cycle wherein the photoexcited $\text{Ru}(\text{II})$ complex oxidizes the Langlois reagent to a CF_3^\bullet radical, which is intercepted by alkene to give a trifluoroalkyl radical **4E** (Scheme 4C). Further interaction with the diazonium ion furnishes an azo radical cation intermediate **4F**. This species is subsequently reduced by the reduced form of Ru photocatalyst to deliver the CF_3 -based azo product **4D**. Notably, the resulting product **4G** serve as versatile intermediate for the synthesis *N*-Boc-protected trifluoroalkyl amine derivatives **4H** *via* reduction, highlighting the synthetic utility of this mild and practical transformation (Scheme 4D).

2.1.4 Photocatalytic amino-trifluoromethylation of styrenes with phenylhydrazines. Although C–N bond formation with CF_3 incorporation remains synthetically valuable, the development of efficient intermolecular amino-trifluoromethylation using new nitrogen sources remains challenging. Zheng, Gao, and co-workers reported a visible-light-photoredox-catalyzed three-component amino-trifluoromethylation reaction using phenylhydrazines **5B** as nitrogen nucleophiles and Togni reagent **5C** as the electrophilic CF_3 radical source²¹ (Scheme 5A). This reaction enables efficient access to β -trifluoromethylated amines **5D** *via* simultaneous C– CF_3 and C–N bond formation of styrenes **5A** under mild conditions. Using rose Bengal (**RB**) as the photocatalyst and K_2HPO_4 as the base, a broad range of substituted styrenes and aryl hydrazines were smoothly transformed into amino-trifluoromethylated products, demonstrating good tolerance toward both electron-donating and electron-withdrawing substituents (Scheme 5B, top). The use of fluoroalkyl iodides in



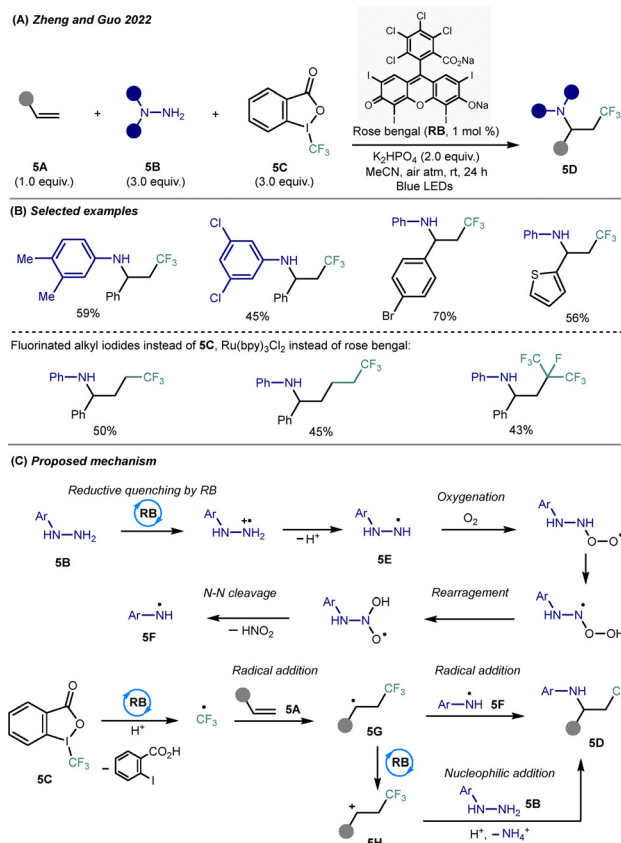


Scheme 4 Photocatalytic azo-trifluoromethylation of alkenes with aryldiazonium salts. (A) General reaction conditions. (B) Representative substrate scope. (C) Proposed mechanism. (D) Synthetic utility and applications.

conjunction with a Ru photocatalyst enables the amino-fluoroalkylation reaction, yielding homologous fluoroalkylamine products (Scheme 5B, bottom). In contrast, while the reaction with alkyl-substituted alkenes gave only trace amounts of product, the use of anilines instead of phenylhydrazines failed to afford the desired compounds altogether.

Mechanistic studies support a radical pathway involving the photocatalytic single-electron oxidation of phenylhydrazines **5B** to aryl hydrazinyl radical **5E**, followed by aerobic oxygenation, rearrangement, and N–N bond cleavage to generate nitrogen-centered *N*-aryl aminyl radical **5F** (Scheme 5C). Concurrently, the Togni reagent **5C** undergoes photoredox activation to form a CF_3 radical, which adds to the styrene to yield a benzylic radical intermediate **5G**. The resulting radical–radical coupling between the aminyl **5F** and benzylic radical **5G** furnishes the trifluoroalkylamine product **5D**. Alternatively, a stepwise pathway involving oxidation of the benzylic radical to a carbocation **5H**, followed by nucleophilic attack by the hydrazine and subsequent N–N bond cleavage, may also operate to afford **5D**. This transformation represents a rare example of intermolecular amino-trifluoromethylation utilizing aryl hydrazines as nitrogen sources.

2.1.5 Photocatalytic trifluoromethyl-imation of alkenes with bifunctional sulfonamide reagent. Energy transfer (EnT)-mediated N–heteroatom bond cleavage has emerged as an efficient photoinduced strategy for amino-functionalization of alkenes, facilitating the construction of complex amino compounds.¹⁴ Xiang, Yang, and co-workers developed a light-promoted protocol employing a rationally designed bifunctional sulfonamide reagent, *N*-(diphenylmethylene)-1,1,1-trifluoromethanesulfonamide **6D**²² (Scheme 6A). This reagent serves as a photolabile precursor capable of delivering both CF_3 and iminyl radicals upon EnT-induced N–S bond cleavage, enabling conventional 1,2-addition, or



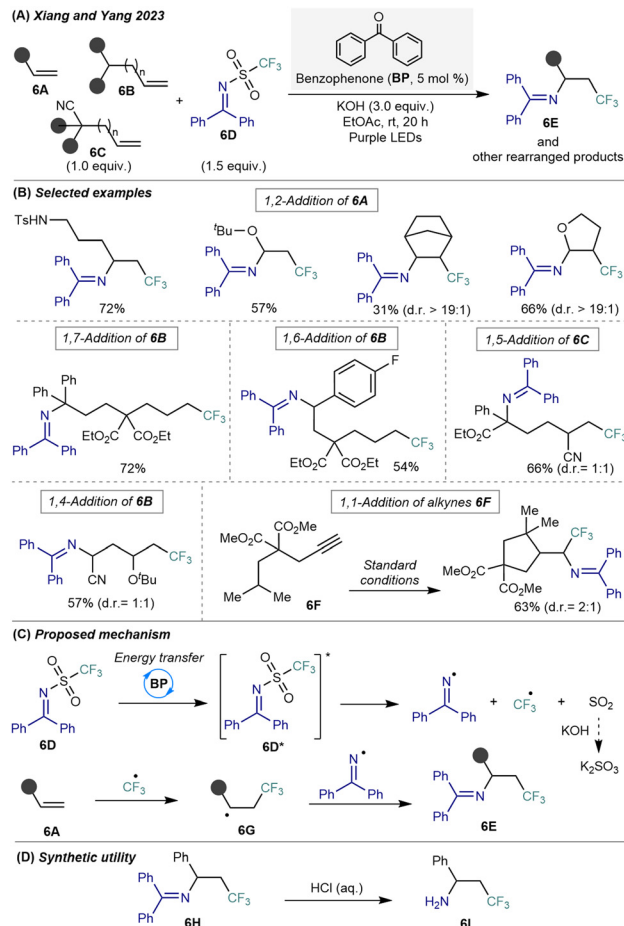
Scheme 5 Photocatalytic amino-trifluoromethylation of styrenes with phenylhydrazines. (A) General reaction conditions. (B) Representative substrate scope. (C) Proposed mechanism.

1,*n*-trifluoromethyl-imation ($n = 4\text{--}7$) of structurally diverse alkenes (**6A–6C**) through hydrogen atom transfer (HAT) or CN-migration pathways, to afford 1,2-addition products **6E** and the corresponding rearranged products (Scheme 6B). Under blue light irradiation with benzophenone (**BP**) as the photosensitizer, a broad range of non-activated acyclic and cyclic alkenes undergo efficient trifluoromethyl-imation, affording $\beta\text{-CF}_3$ imines in moderate to good yields with excellent regioselectivity. Although such remote CF_3 -imation reaction enables diverse 1,*n*-radical translocation transformations, efficient migration appears to require carefully preorganized substrates bearing bulky substituents such as esters and aryl groups along the aliphatic chain. This structural prerequisite may limit the generality of the remote functionalization strategy to substrates with appropriate conformational bias or radical-stabilizing groups.

The transformation proceeds *via* EnT from the excited-state photosensitizer to the sulfonamide **6D** to form the photoexcited species **6D***, inducing homolytic N–S bond cleavage and subsequent SO_2 extrusion to generate a CF_3 radical and a persistent diphenyliminyl radical (Scheme 6C). The CF_3 radical adds to the terminal carbon of the alkene **6A**, forming a trifluoroalkyl radical intermediate **6G**. This intermediate is intercepted by the diphenyliminyl radical to yield the $\beta\text{-CF}_3$ imine product **6E**. The addition of KOH facilitates the conversion of SO_2 into sulfite ions (SO_3^{2-}), thereby suppressing its coupling with alkyl



Highlight



Scheme 6 Photocatalytic trifluoromethyl-imation of alkenes with bifunctional sulfonamide reagent. (A) General reaction conditions. (B) Representative substrate scope. (C) Proposed mechanism.

radicals and minimizing the formation of undesired side products.

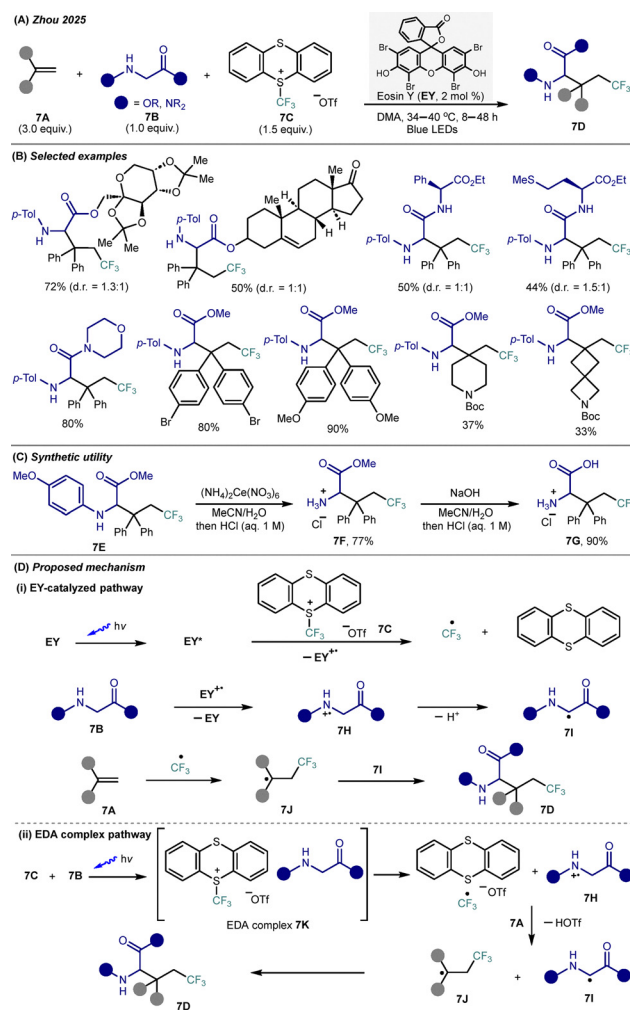
Notably, the methodology also accommodates 1,1-trifluoromethyl-imation of alkyne **6F**, offering access to CF_3 -decorated cyclopentyl imines (Scheme 6B, bottom right). Furthermore, the hydrolysis of trifluoroalkyl imine product **6H** offers trifluoroalkyl amine **6I** (Scheme 6D). This strategy provides a modular approach for vicinal and remote C–C and C–N bond construction using a single bifunctional reagent, expanding the toolkit for photochemical olefin difunctionalization and enabling access to trifluorinated imine architectures under mild, sustainable conditions.

2.2 Simultaneous C– CF_3 and C–C bond formation

2.2.1 Photocatalytic carbo-trifluoromethylation of alkenes with glycine derivatives. Fluorinated amino acids have attracted considerable interest in drug discovery; however, their efficient and streamlined synthesis remains a significant challenge. Zhou and co-workers reported a photocatalytic three-component radical cascade alkyl–trifluoromethylation reaction of glycine derivatives **7B**, trifluoromethyl thianthrenium salts **7C**, and alkenes **7A** under redox-neutral conditions²³

(Scheme 7A). This method enables the direct construction of trifluoromethylated, noncanonical α -amino acid derivatives **7D** via concurrent $\text{C}(\text{sp}^3)\text{--CF}_3$ and $\text{C}(\text{sp}^3)\text{--C}$ bond formation under mild conditions. Using Eosin Y (**EY**) as the organic photocatalyst and blue LED irradiation, a diverse range of glycine esters and amides, including those derived from natural products, pharmaceuticals, and short peptides, are successfully transformed into CF_3 -based glycine derivatives with broad substrate scope and excellent functional group tolerance (Scheme 7B). While 1,1-diaryl alkenes undergo efficient carbo-trifluoromethylation under the reported conditions, alkyl-substituted alkenes generally afford lower product yields. Trifluoroalkyl-substituted glycine product **7E** undergoes sequential *N*-dearylation to afford glycine ester **7F** followed by hydrolysis to give unprotected glycine derivative **7G**, highlighting the synthetic utility of the fluorinated non-canonical amino acids (Scheme 7C).

Mechanistically, Eosin Y is photoexcited under visible-light irradiation to its singlet excited state EY^* , which promotes single-electron reduction of the trifluoromethyl thianthrenium



Scheme 7 Photocatalytic carbo-trifluoromethylation of alkenes with glycine derivatives. (A) General reaction conditions. (B) Representative substrate scope. (C) Synthetic utility and applications. (D) Proposed mechanism.



salt **7C** to generate the electrophilic CF_3 radical (Scheme 7D). Concurrently, the glycine derivative **7B** undergoes single-electron oxidation by the resulting $\text{EY}^{+\bullet}$ species to afford an α -amino radical cation **7H**, which upon deprotonation forms the corresponding glycine-derived carbon-centered radical **7I**. The CF_3 radical adds to the diaryl alkene **7A**, yielding a stabilized tertiary trifluoroalkyl radical intermediate **7J**, which subsequently undergoes cross-coupling with the glycine-derived radical to furnish the trifluoromethylated glycine product **7D**. Notably, control experiments reveal that moderate product formation can still occur in the absence of photocatalyst, likely proceeding through a photoactive electron donor–acceptor (EDA) complex **7K** formed between the glycine derivative and the CF_3 -thianthrenium salt. Upon direct photoexcitation, this EDA complex facilitates simultaneous generation of both CF_3 and glycine-based radicals, which then engage the alkene substrate to deliver the desired product **7D**. This transformation represents a rare example of a photoredox-neutral alkyl–trifluoromethylation strategy, broadening the scope of late-stage peptide diversification and offering a streamlined approach to fluorinated α -amino acid derivatives.

2.2.2 Photocatalytic carbo-trifluoromethylation for the construction of trifluoromethylated amino-based heterocycles.

Fluorinated azaheterocycles are privileged structural motifs in the synthesis of bioactive molecules and hold significant relevance in drug discovery. In this context, trifluoromethylated tetrahydropyridazines represent valuable amine-based scaffolds in medicinal chemistry; however, their direct and regioselective synthesis remains a formidable challenge. Hu and co-workers reported a visible-light-promoted radical cascade trifluoromethylation/cyclization of *N*-isopentenyl aldehyde hydrazones **8A** using industrially available CF_3Br (**8B**) as the trifluoromethyl radical source under mild, redox-neutral conditions²⁴ (Scheme 8A). This strategy enables regioselective 6-*endo-trig* cyclization, affording a diverse range of CF_3 -functionalized, cyclic amine-based tetrahydropyridazine derivatives **8C**. The reaction proceeds under blue light irradiation, catalyzed by *fac*- $\text{Ir}(\text{ppy})_3$, and facilitated by 2,6-lutidine as base, exhibiting excellent tolerance toward *N*-carbo- and sulfonyl substituted hydrazones as well as those bearing aryl, difluoromethyl, or trifluoromethyl groups along the backbone (Scheme 8B, top). In contrast, reactions involving heteroaryl-substituted aldehyde hydrazone substrates (e.g., 1-pyridyl, furanyl) resulted in low yields or divergent reactivity. The methodology also accommodates *N*-homoallyl and *N*-allyl aldehyde hydrazones, affording 2,2,2-trifluoroethylated tetrahydropyridazine **8D** and dihydropyrazole **8E**, respectively (Scheme 8B, bottom).

Mechanistically, photoexcitation of $\text{Ir}(\text{ppy})_3$ under blue light generates the excited-state $\text{Ir}(\text{ppy})_3^*$, which engages in SET to reduce CF_3Br , generating a CF_3 radical. This electrophilic species adds to the terminal alkene of the *N*-isopentenyl aldehyde hydrazone **8A**, forming a trifluoroalkylated, stabilized tertiary carbon-centered radical **8F** intermediate, which subsequently undergoes an intramolecular 6-*endo-trig* cyclization to afford a nitrogen-centered radical azaheterocycle **8G**. Subsequent oxidation by the resulting $\text{Ir}(\text{IV})$ species generates the cationic intermediate **8H**, which undergoes deprotonation by



Scheme 8 Photocatalytic carbo-trifluoromethylation for the construction of trifluoromethylated amino-based azaheterocycles. (A) General reaction conditions. (B) Representative substrate scope. (C) Proposed mechanism.

2,6-lutidine to yield the trifluoromethylated tetrahydropyridazine product **8C**. DFT calculations support the kinetic preference for this 6-*endo-trig* pathway over competing 5-*endo-trig* or C=N-targeted cyclizations. This transformation offers a streamlined strategy for the direct incorporation of trifluoromethyl groups into N-heterocyclic frameworks *via* visible-light photocatalysis, expanding synthetic access to medicinally relevant tetrahydropyridazine architectures under operationally simple conditions.

2.3 Simultaneous C– CF_3 and C-heteroatom bond formation

The groups of Magnier and Masson reported an alternative three-component strategy for the synthesis of complex and functionalized β -trifluoromethylated amine derivatives **9C**, employing *N*-alkenyl carbamates **9A**, Togni reagent **9B**, and a variety of nucleophiles²⁵ (Scheme 9A). In the presence of methanol, α -oxy- β -trifluoromethylated aminals are formed, while the use of cyanide or azide delivers α -cyano- β - CF_3 and α -azido- β - CF_3 carbamates, respectively (Scheme 9B). In the oxytrifluoromethylation reaction, a side reaction leading to an iodo-trifluoromethylated byproduct (<10%) is observed, likely due to *in situ* iodine generation from Togni reagent.

The reaction proceeds *via* a likely radical/cationic pathway (Scheme 9C). Photoexcitation of the Ru photocatalyst facilitates single-electron reduction of the Togni reagent to generate a CF_3



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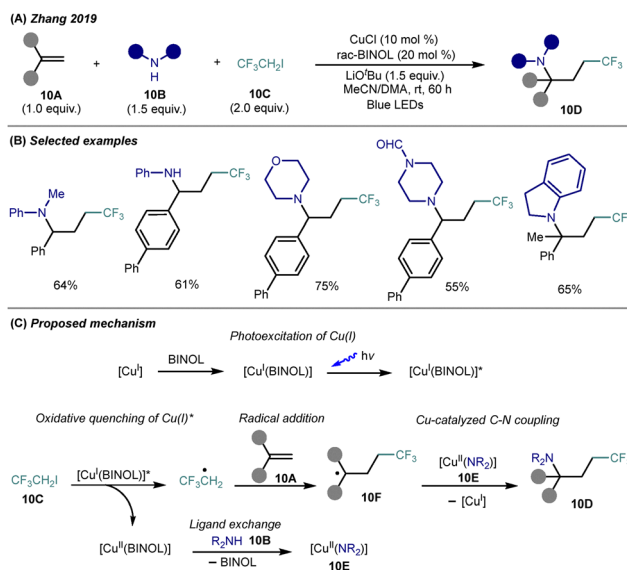
Scheme 9 Photocatalytic oxo-, cyano-, and azido-trifluoromethylation of *N*-alkenyl carbamates. (A) General reaction conditions. (B) Representative substrate scope. (C) Proposed mechanism.

radical, which adds regioselectively to the *N*-alkenyl carbamate to form an α -amidoalkyl radical **9D**. Subsequent oxidation by Ru(III) affords an *N*-acyliminium ion **9E**, which is then intercepted by O-, C-, or N-based nucleophiles to furnish the corresponding difunctionalized products **9C**. This protocol thus offers a versatile and operationally simple platform for the synthesis of β -trifluoromethylated amine derivatives with broad functional diversity. This protocol represents one of the earliest examples of intermolecular carbotrifluoromethylation of *N*-alkenyl carbamates and offers modular access to structurally diverse CF₃-functionalized amines under mild conditions.

2.4 Simultaneous C–N and C–C bond formation

Aiming to develop an operationally simple and economical route to trifluorinated amines, Zhang and co-workers reported a visible-light-induced, copper-catalyzed three-component carbamination of alkenes **10A** with amines **10B** and 1,1,1-trifluoro-2-iodoethane (**10C**)²⁶ (Scheme 10A). This method utilizes inexpensive CuCl as both photocatalyst and cross-coupling catalyst, as well as racemic BINOL as ligand, enabling the regioselective introduction of trifluoroethyl and amino groups across styrenes under mild, base-promoted conditions to create trifluoroalkyl amines **10D**. Broad amine compatibility was demonstrated, including primary and secondary anilines, cyclic amines, and indolines, with high functional group tolerance (Scheme 10B). While the amino-trifluoroethylation reaction proceeds efficiently with styrenes, the use of unactivated aliphatic alkenes results in significantly reduced reactivity and low product yields.

Mechanistic investigations suggest that *in situ* formed Cu^I(BINOL) serve as the photoactive species, which upon visible light excitation reduce 1,1,1-trifluoro-2-iodoethane (**10C**) to generate trifluoroethyl radical (Scheme 10C). This radical adds to the alkene, and the resulting carbon-centered radical **10F** is intercepted by a Cu(II)-bound amine species **10E**—formed *via* ligand exchange between the resulting Cu^{II}(BINOL) complex and the amine—to forge the C–N bond through either reductive elimination or radical recombination, affording the trifluoroalkyl amine **10D**. This transformation represents a rare example



Scheme 10 Photoinduced Cu-catalyzed amino-trifluoroethylation of alkenes. (A) General reaction conditions. (B) Representative substrate scope. (C) Proposed mechanism.

of copper-catalyzed, photoinduced intermolecular amino-fluoroalkylation, enabling the efficient construction of structurally complex γ -trifluoromethylated alkylamines.

3. Radical cross-couplings *via* metallaphotoredox catalysis

Metallaphotoredox catalysis has enabled a new class of convergent multicomponent reactions that merge electrophilic and nucleophilic radical species to construct C(sp³)-CF₃ and C(sp³)-N bonds in a programmable fashion. These transformations combine the unique reactivity of photocatalytically generated radicals with the selectivity of transition metal catalysis, allowing for precise construction of trifluoroalkyl amines from simple, feedstock-compatible precursors. This section highlights recent advances in multicomponent synthetic methodologies that leverage dual photoredox and transition metal catalysis to access structurally complex fluoroalkyl amine derivatives.

3.1 Dual copper/photoredox-catalyzed deoxytrifluoromethylation of amino-alcohols

Alcohols are abundant and structurally diverse feedstocks that serve as versatile building blocks in complex organic synthesis, particularly in radical C–C coupling reactions.²⁷ MacMillan and co-workers developed a copper/photoredox-catalyzed deoxytrifluoromethylation protocol that converts amino alcohols into trifluoromethylated alkylamines²⁸ (Scheme 11A). In this metallaphotocatalytic strategy in the presence of an iridium photocatalyst and a copper(II) terpyridine complex [Cu(terpy)Cl₂], amino alcohols **11A** function as nucleophilic alkyl radical precursors, while dimesityl(trifluoromethyl)sulfonium trifluoromethanesulfonate (dMesSCF₃(OTf), **11B**) serves as the electrophilic CF₃ radical source. This platform accommodates a wide



variety of acyclic, cyclic, spirocyclic, and heterocyclic amino alcohols, enabling the streamlined construction of three-dimensional, densely functionalized, and heterocycle-decorated trifluoromethylated alkylamine scaffolds **11C** (Scheme 11B). Electron-rich heterocycles, such as furan and *N*-alkyl indole, when present in primary alcohols, are prone to oxidative degradation, leading to low to moderate yields under standard conditions. Sterically hindered tertiary alcohols also perform poorly, likely due to the high kinetic barriers associated with radical capture and the subsequent C–CF₃ reductive elimination. These limitations pose significant challenges to the efficient diversification of fluoroalkyl amines.

Mechanistically, the transformation proceeds *via in situ* activation of amino alcohols with benzoxazolium salts (NHC), forming NHC–alcohol adducts **11D** (Scheme 11C). Photoexcitation of the iridium catalyst initiates single-electron oxidation of **11D**, followed by deprotonation to **11E** and exothermic β-scission to generate an aminoalkyl radical **11F**. Concurrently, single-electron reduction of **11B** by the photocatalyst generates an electrophilic CF₃ radical. Reduction of Cu(terpy)Cl₂ by the photocatalyst furnishes a Cu(I) species, which reacts with the CF₃ radical to form a Cu(II)–CF₃ intermediate **11G**. Subsequent interception of **11F**

yields a high-valent Cu(III) species **11H** that undergoes reductive elimination to forge the C(sp³)–CF₃ bond, affording the trifluoroalkyl amine **11C**. Importantly, the addition of tetrabutylammonium chloride (TBACl) was found to modulate the coordination sphere of the Cu(I) complex and suppress off-cycle reduction of CF₃ radical to fluoroform (CHF₃), thereby improving reaction efficiency. This protocol offers a general, modular, and operationally simple approach to access structurally complex trifluoromethylated alkylamines from native alcohols, providing versatile building blocks for applications in organic synthesis and drug discovery.

3.2 Dual nickel/photoredox-catalyzed methyl-trifluoromethylation of amino-substituted alkenes

To address the persistent challenge of constructing C(sp³)–C(sp³) bonds *via* intermolecular alkene difunctionalization,²⁹ MacMillan and co-workers introduced a triple-radical sorting strategy that enables trimolecular 1,2-dialkylation of unactivated alkenes through bimolecular homolytic substitution (S_H2) catalysis³⁰ (Scheme 12A). This methodology achieves the regioselective union of electrophilic and nucleophilic alkyl radicals across unactivated olefins by leveraging steric and electronic differentiation to facilitate selective radical coupling. The reaction operates under dual catalysis, employing an iridium photocatalyst and an *in situ*-formed nickel catalyst based on Ni(acac)₂ in combination with sterically hindered potassium tris(pyrazolyl)borohydride (KTP*). Under visible-light metallaphotoredox conditions, methanol **12B** serves as a nucleophilic methyl radical precursor, while dimesityl(trifluoromethyl)sulfonium trifluoromethanesulfonate [dMesSCF₃(OTf)] (**12C**) acts as the electrophilic CF₃ radical source. This platform tolerates a wide range of structurally complex amino-substituted alkenes **12A**, enabling access to three-dimensional and densely functionalized trifluoromethyl-substituted alkylamine scaffolds **12D** (Scheme 12B), including drug derivatives (Scheme 12C).

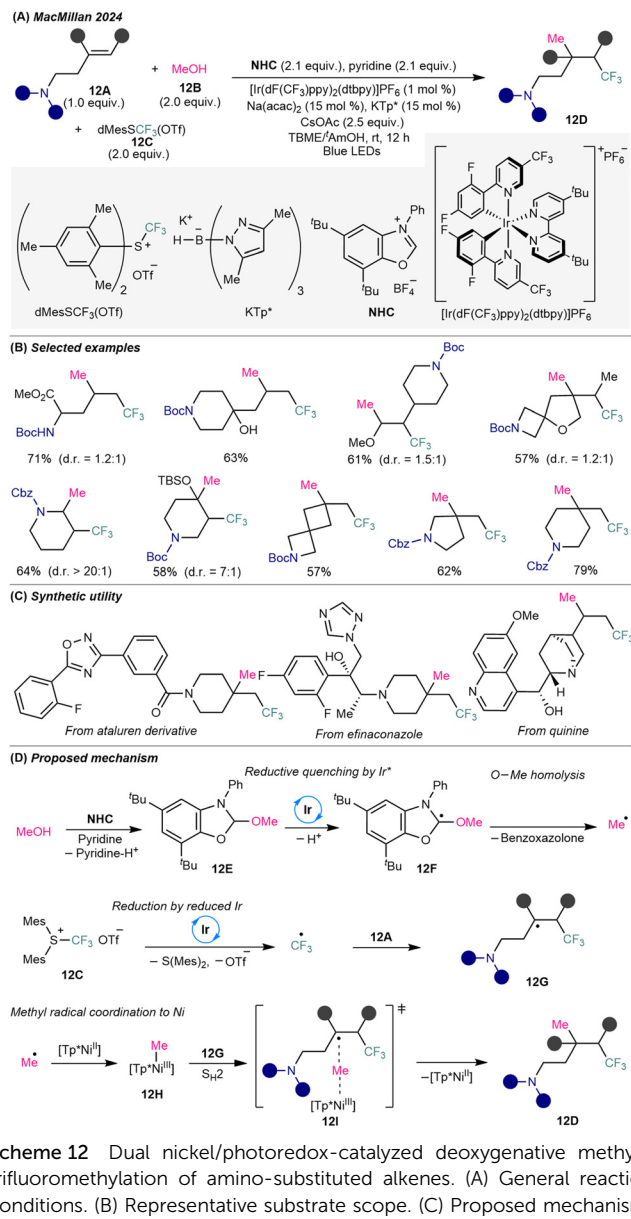
Mechanistically, methanol condenses with benzoxazolium salt (NHC) to form NHC-alcohol adduct **12E**, triggering SET transfer *via* reductive quenching by Ir(III) photocatalyst, deprotonation to species **12F**, and β-scission to release a methyl radical (Scheme 12D). In parallel, SET reduction of MesSCF₃(OTf) **12C** by the resulting Ir(II) photocatalyst forms an electrophilic CF₃ radical that adds to the electron-rich amino-alkene **12A**, generating a sterically and electronically distinct secondary or tertiary trifluoroalkyl radical **12G**. The small-sized methyl radical is intercepted by a Ni^{II}(KTP*) to form a Ni(III)–methyl intermediate **12H**, which undergoes outer-sphere S_H2 coupling with bulky radical **12G** *via* the transition state **12I**, forging the methyl–alkyl bond and offer the complex trifluoroalkyl amine **12D**. Only unactivated alkenes are employed in the methyl–trifluoromethylation reaction, presumably due to the enhanced reactivity of the resulting secondary or tertiary trifluoromethylated alkyl radicals, which facilitates their coupling with the Ni-bound methyl radical *via* S_H2 substitution. This deoxygenative strategy showcases the potential of radical sorting to overcome the selectivity and reactivity challenges in



Scheme 11 Dual copper/photoredox-catalyzed deoxytrifluoromethylation of amino-alcohols. (A) General reaction conditions. (B) Representative substrate scope. (C) Proposed mechanism.



Highlight



Scheme 12 Dual nickel/photoredox-catalyzed deoxygenative methyl-trifluoromethylation of amino-substituted alkenes. (A) General reaction conditions. (B) Representative substrate scope. (C) Proposed mechanism.

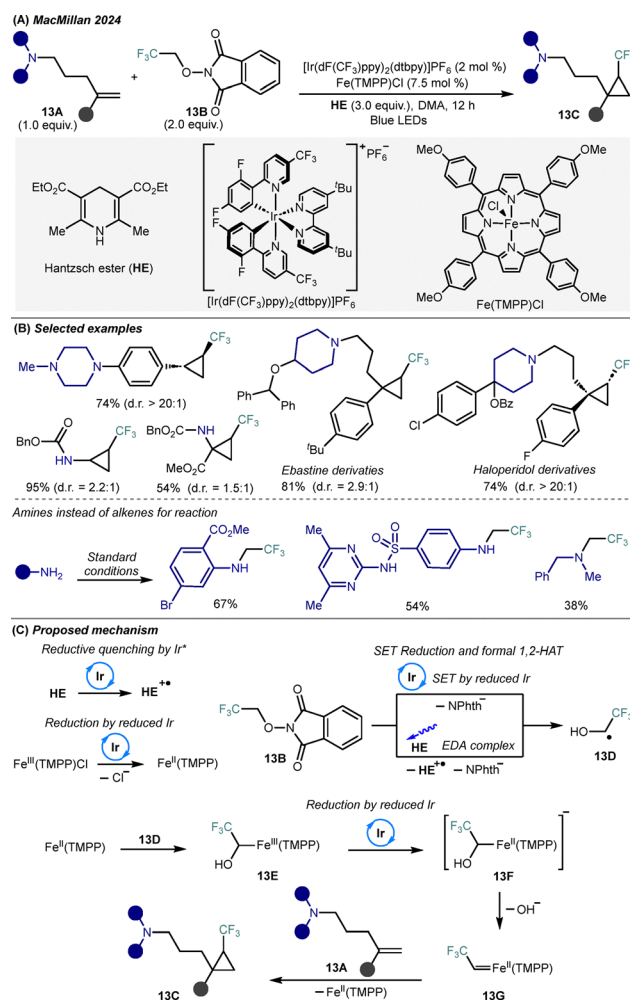
three-component alkene difunctionalization and opens a general path toward C(sp³)-rich trifluoroalkylamine architectures.

3.3 Photocatalytic generation of trifluoromethylated iron carbenes for synthesis of trifluoroalkyl amines

Trifluoromethylated carbenes are highly reactive intermediates that offer significant potential for constructing compact, fluorine-rich scaffolds with enhanced physicochemical and pharmacokinetic properties.³¹ However, traditional diazo-based methods for accessing these species often suffer from limited substrate scope and safety issues. To overcome these limitations, MacMillan and co-workers developed a general metallaphotoredox platform that generates trifluoromethylated iron carbenes from bench-stable redox-active esters (RAE) **13B** derived from 2,2,2-trifluoroethanol, enabling the [2+1] cycloaddition of amino-substituted alkenes **13A** to access CF₃-

cyclopropyl-embedded alkylamines **13C**³² (Scheme 13A). Using [Ir(dF(CF₃)ppy)₂(dtbbpy)]PF₆ as an iridium photocatalyst, iron(II) porphyrin Fe(TMPP)Cl as a catalyst, and Hantzsch ester (**HE**) as a reductant, a wide array of amino-substituted styrenes and alkenes, acrylic esters, and drug-like alkenes were efficiently converted into trifluoromethylated cyclopropylamines in good to excellent yields (Scheme 13B, top). Diastereoselectivity varies significantly across reaction substrates, with particularly low stereocontrol observed in reactions involving certain amino-substituted alkenes, potentially limiting the utility of this method in stereoselective synthesis. In addition, the same iron-carbene species enabled σ -bond insertion into N-H bonds, providing access to diverse N-2,2,2-trifluoroethylated amines (Scheme 13B, bottom).

Mechanistically, photoexcitation of the Ir(III) catalyst followed by reductive quenching by Hantzsch ester generates a strongly reducing Ir(II) species, which reduces Fe(III) porphyrin to Fe(II) species (Ir^{II}(TMPP), Scheme 13C). Simultaneously, the RAE **13B** is reduced either by Ir(II) or through the formation of a



Scheme 13 Photocatalytic generation of trifluoromethylated iron carbenes for cyclopropanation and N-H insertion reactions. (A) General reaction conditions. (B) Representative substrate scope. (C) Proposed mechanism.



photoactive EDA complex with Hantzsch ester, leading to decarboxylation and generation of a 2-hydroxytrifluoroethyl radical **13D**. This radical is intercepted by Fe(II) species to form an Fe(II)–(1-hydroxy-2,2,2-trifluoroethyl) intermediate **13E**, which undergoes a second photocatalytic single-electron reduction to give a nucleophilic alkyl-Fe(II) porphyrin species **13F**. α -Elimination from this species ejects a hydroxide ion and furnishes the reactive α -CF₃-carbene-substituted Fe(II) porphyrin **13G**. This carbene intermediate engages in cyclopropanation of alkene **13A** to deliver structurally complex CF₃-substituted alkylamines **13C**. Overall, this platform provides a mild, modular, and diazo-free approach for generating fluorinated carbene species, expanding the synthetic toolbox for late-stage functionalization of complex molecules under visible light.

3.4 Dual nickel/photoredox-catalyzed methyl-trifluoroethylation of amino-substituted alkyl alkenes

To expand the scope of C(sp³)–C(sp³) bond formation *via* alkene difunctionalization, Koh and co-workers developed a photoredox/nickel dual-catalyzed platform that enables trimolecular 1,2-dialkylation of unactivated alkenes through a S_H2 mechanism^{3,3} (Scheme 14A). This strategy allows for the

simultaneous installation of electrophilic and nucleophilic alkyl radicals across unactivated amino-substituted alkenes without the need for directing auxiliaries. Under optimized conditions, the reaction combines 1,1,1-trifluoro-2-iodoethane (**14B**), a hypervalent iodine(III) reagent (PhI(OAc)₂, **14C**), and a variety of mono- and 1,1-disubstituted amino-substituted alkenes **14A** in the presence of Ni(acac)₂ catalyst, KTp* ligand, and the organic photocatalyst 4CzIPN, affording complex trifluoroalkyl amine derivatives **14D** bearing tertiary or quaternary carbon centers in good to excellent yields with high chemo- and regioselectivity. Similar to the MacMillan metallophotocatalytic system (Scheme 12), alkyl-substituted alkenes are required to enhance reactivity and productivity for accessing trifluoroalkylamine products.

Mechanistic studies suggest that a nucleophilic methyl radical is generated *via* O–I bond homolysis of photoexcited PhI(OAc)₂* (**14C***), triggered by triplet–triplet energy transfer from the photoexcited 4CzIPN. The nucleophilic methyl radical selectively initiates halogen atom transfer (XAT) with electron-deficient 1,1,1-trifluoro-2-iodoethane to produce an electrophilic trifluoroethyl radical **14E**, which subsequently undergoes a polarity-matched addition to the electron-rich amino-alkene substrate (**14A**), forming the amino-trifluoroalkyl radical **14F**. The methyl group also binds with Ni^{II}(KTp*), forming the Me-Ni^{III}(KTp*) species **14G**. The resulting bulky secondary trifluoroalkyl radical **14F** is subsequently intercepted through an outer-sphere S_H2 coupling event with the Ni(KTp)-bound methyl radical *via* the transition state **14H**, forging the second C(sp³)–C(sp³) bond to deliver the trifluoroalkyl amine **14D**. This transformation represents a significant advance in site-selective dialkylation of unactivated alkenes, offering a modular strategy for constructing structurally complex, three-dimensional, carbon-rich trifluoroalkylamine scaffolds.

3.5 Dual nickel/photoredox-catalyzed synthesis of masked arylaminomethyl trifluoromethyl ketones

Structurally elaborate trifluoromethyl ketones (TFMKs) bearing aminomethyl groups are attractive intermediates in pharmaceutical and agrochemical synthesis, yet their direct construction remains challenging due to the inherent reactivity mismatch between nucleophilic amines and electrophilic trifluoroacetyl moieties.³⁴ To address this, Cheung, Ma, and co-workers reported a modular metallophotoredox-catalyzed three-component coupling of nitroarenes **15A**, tertiary alkylamines **15B**, and 2-(trifluoromethyl)-1,3-dioxolane-2-carboxylic acid (**15C**)—serving as a masked trifluoroacetyl radical precursor³⁴ (Scheme 15A). Employing an iridium photocatalyst in combination with a phenanthroline–nickel complex as the catalytic system, this strategy enables direct access to structurally diverse *N*-(CF₃-dioxolanyl)methyl anilines **15D** as protected surrogates of aminomethyl TFMKs, offering enhanced chemo-selectivity and functional group tolerance (Scheme 15B). The resulting acetal-masked products can be unmasked to access otherwise unstable aminomethyl TFMKs or derivatized into valuable fluorinated azaheterocycles.



Scheme 14 Dual nickel/photocatalytic methyl-trifluoroethylation of amino-substituted alkyl alkenes. (A) General reaction conditions. (B) Representative substrate scope. (C) Proposed mechanism.



Highlight



Scheme 15 Dual nickel/photoredox-catalyzed synthesis of masked arylaminomethyl trifluoromethyl ketones from nitroarenes, tertiary alkylamines, and CF_3 -dioxolanyl precursors. (A) General reaction conditions. (B) Representative substrate scope. (C) Proposed mechanism. (D) Synthetic utility and applications.

Mechanistically, photoexcitation of $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ initiates an oxidative quenching process with the tertiary alkylamine **15B**, generating an α -aminoalkyl radical **15E** (Scheme 15C). Concurrently, CF_3 -dioxolanyl-carboxylic acid **15C** is deprotonated by excess tertiary alkylamine to its anionic form, which undergoes photocatalytic SET oxidation to afford radical species **15F**, followed by facile decarboxylation to yield the CF_3 -dioxolanyl radical **15G**. The resulting Ir(II) species reduces a nitroarene, furnishing nitrogen-centered intermediates (e.g., nitrosoarenes or diarylhydrazines), which ultimately form the *N*-aryl aminyl radical **15H** through sequential reduction pathways. In parallel, the Ni(II) catalyst is photochemically reduced to low-valent Ni(I) and Ni(0) species. The nucleophilic α -aminoalkyl radical **15E** couples with the electrophilic *N*-aryl aminyl radical

15H to form amination intermediate **15I**, which undergoes Ni-mediated dealkylation to generate the *N*-arylaminomethyl-Ni(II) species **15J**. Crucially, the final $C(sp^3)-C(sp^3)$ bond formation proceeds either *via* an inner-sphere Ni-mediated reductive elimination through a Ni(III) complex **15K**, or *via* an outer-sphere S_H2 mechanism through transition state **15L** between the Ni(II)-alkyl intermediate **15J** and the sterically bulky CF_3 -dioxolanyl radical **15E**, ultimately affording the masked TFMK product **15D** with high selectivity.

The synthetic utility of this method is underscored by its late-stage diversification potential and compatibility with downstream transformations (Scheme 15D). For instance, product **15M** undergoes BBr_3 -promoted deprotection to yield the annulated product, CF_3 -substituted dihydrooxazine **15P**. The corresponding trifluoromethyl ketone (TFMK) **15N** and its hydrated form **15O**—detectable only by high-resolution mass spectrometry—were found to be unstable, thereby significantly limiting the general applicability of this method for the synthesis and further study of arylamino TFMK compounds. Nevertheless, **15P** serves as a valuable synthetic intermediate, undergoing condensation with hydroxylamine to furnish CF_3 -substituted piperazine **15Q** and reduction to generate *N*-(2-hydroxy-3,3,3-trifluoropropyl)anilines **15R**. Collectively, this work expands the synthetic toolbox for the construction of complex, functionalized trifluorinated amines and their derivatives, offering novel compounds with potential applications in organic synthesis, drug discovery, and agrochemical development.

3.6 Dual Ni/photoredox-catalyzed synthesis of complex *N*-trifluoroalkyl anilines

Structurally complex CF_3 -incorporated *N*-alkyl anilines represent a valuable class of fluorinated scaffolds with promising applications in drug discovery. However, conventional approaches typically require multistep prefunctionalization to prepare reactive trifluoroalkyl electrophiles for coupling with anilines, thus limiting molecular diversity and synthetic efficiency. To overcome these challenges, Ma, Cheung, and co-workers developed a metallaphotoredox-catalyzed three-component amination strategy that achieves formal C–N transposition and $C(sp^3)-H$ alkylation of tertiary alkylamines **16B** with nitroarenes **16A** and RAEs (**16C**) derived from CF_3 -containing carboxylic acids³⁵ (Scheme 16A). The reaction employs $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ as the photocatalyst, a bathophenanthroline-ligated Ni(II) complex as the transition metal co-catalyst, and Hantzsch ester (**HE**) as the reductant, operating under mild, redox-neutral conditions. Two examples of trifluoroalkyl aniline products **16D** are demonstrated (Scheme 16B). In contrast, the use of electron-deficient nitroarenes and branched tertiary alkylamines typically resulted in diminished yields, likely due to reduced reactivity and increased steric hindrance.

Mechanistically, visible-light excitation of the Ir(III) photocatalyst triggers SET with triethylamine **16B'** to form an α -aminoalkyl radical **16E** *via* reductive quenching and deprotonation (Scheme 16C). Simultaneously, Ir(III) undergoes SET with Hantzsch ester to generate a highly reducing Ir(II) species, which sequentially reduces both the nitroarene **16A** (in the presence of triflic acid (HOTf)) to form an *N*-aryl aminyl radical





Scheme 16 Photocatalytic synthesis of *N*-trifluoroalkyl anilines from nitroarenes, alkylamines, and CF₃-substituted redox-active esters. (A) General reaction conditions. (B) Representative substrate scope. (C) Proposed mechanism.

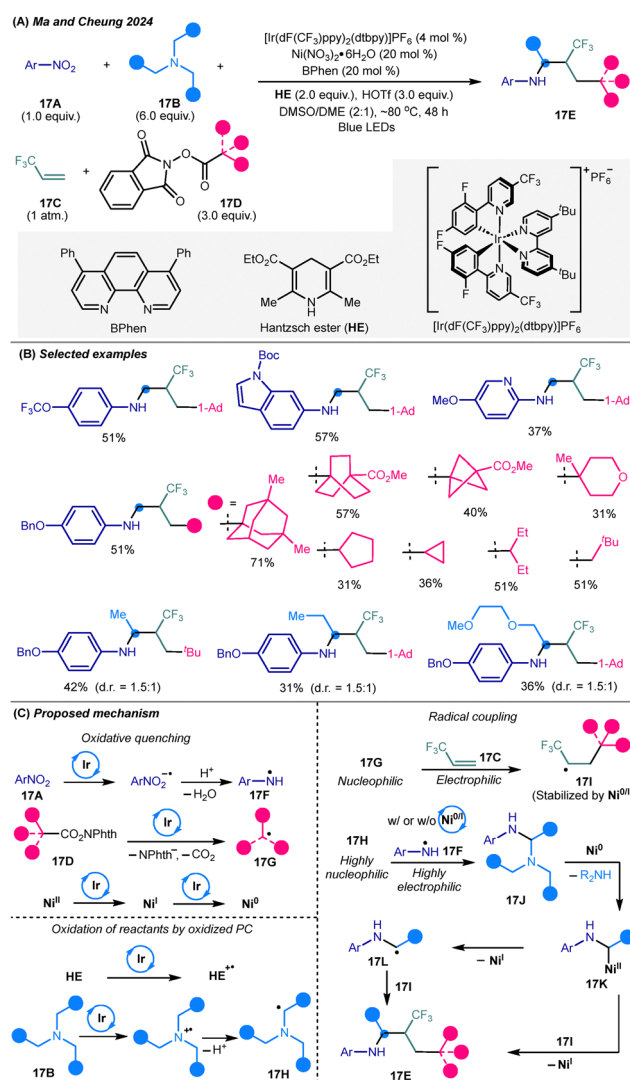
16F and the CF₃-alkyl RAE **16C** to produce a trifluoroalkyl radical **16G**. Ni(II) salt is also photocatalytically reduced to low-valent Ni(I) or Ni(0) species. The nucleophilic α -aminoalkyl radical **16E** couples with the electrophilic *N*-aryl aminyl radical **16F**—either directly or *via* Ni-mediated C–N bond formation—to furnish an amination intermediate **16H**. This intermediate undergoes Lewis acidic Ni(II)-promoted deamination to generate an *N*-aryl imine **16I**, which is then trapped by the trifluoroalkyl radical **16G** (potentially stabilized by Ni(I) or Ni(0)) to form a trifluoroalkylated aminyl radical **16J**. Finally, this radical undergoes photoreduction or HAT by the Hantzsch ester radical cation, furnishing the *N*-trifluoroalkyl aniline product **16D**. Although demonstrated in a limited number of examples, this strategy provides a modular and efficient route to access structurally intricate trifluoroalkylated *N*-alkyl anilines that are otherwise difficult to synthesize using classical two-component methods.

3.7 Dual nickel/photoredox-catalyzed four-component synthesis of complex trifluoroalkyl anilines

Structurally elaborate *N*-trifluoroalkyl anilines are valuable motifs in pharmaceutical research due to their improved metabolic stability, lipophilicity, and biological activity. However, conventional strategies for accessing such scaffolds often

suffer from limited efficiency and structural diversity. Four-component reactions offer a powerful synthetic platform for the rapid construction of complex trifluoroalkylated amines from simple precursors. By integrating multiple radical coupling events and bond-forming processes in a single operation, these approaches enable direct access to densely substituted, functionally rich trifluoroalkyl amines, highlighting the potential of photocatalytic radical chemistry in medicinal compound development.

In this context, Ma, Cheung, and co-workers developed a modular metallaphotoredox-catalyzed four-component amination strategy that merges nitroarenes **17A**, tertiary alkylamines **17B**, 3,3,3-trifluoropropene **17C**, and RAEs **17D** derived from aliphatic carboxylic acids⁷ (Scheme 17A). This platform enables streamlined access to *N*-trifluoroalkyl anilines **17E**, bearing both CF₃ units and distal tertiary or quaternary carbon centers along



Scheme 17 Nickel/photoredox-catalyzed synthesis of *N*-trifluoroalkyl anilines from nitroarenes, tertiary amines, redox-active esters, and 3,3,3-trifluoropropene. (A) General reaction conditions. (B) Representative substrate scope. (C) Proposed mechanism.



Highlight

the alkyl chain. The reaction employs $[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{dtbbpy})]\text{PF}_6$ as the photocatalyst, a bathophenanthroline-ligated $\text{Ni}(\text{II})$ complex as the transition metal co-catalyst, Hantzsch ester (**HE**) as a sacrificial reductant, and HOTf as an additive, operating under blue light irradiation at approximately 80 °C. A broad range of functionalized nitroarenes, tertiary alkylamines, and structurally diverse RAEs—including primary, secondary, and tertiary alkyl derivatives—are well tolerated, enabling the synthesis of a diverse array of *N*-trifluoroalkyl aniline products (Scheme 17B). In contrast, the use of electron-deficient nitroarenes and RAEs derived from primary and secondary carboxylic acids resulted in lower product yields, likely due to the instability of the corresponding nitrogen- and carbon-centered radicals, which tend to undergo competing two- or three-component side reactions, thereby impeding efficient four-component bond formation.

Mechanistically, photoexcitation of the $\text{Ir}(\text{III})$ photocatalyst initiates single-electron reduction of the nitroarene **17A** to generate an *N*-aryl aminyl radical **17F**, while concurrently reducing the RAE **17D** to furnish an alkyl radical **17G** and the ligated $\text{Ni}(\text{II})$ salt to low-valent $\text{Ni}(\text{I})$ and $\text{Ni}(\text{0})$ species (Scheme 17C). Concurrently, both Hantzsch ester and tertiary alkylamine **17B** undergo oxidative quenching with the resulting $\text{Ir}(\text{IV})$ species to generate Hantzsch ester radical cation and α -aminoalkyl radical **17H**, respectively. The nucleophilic alkyl radical **17G** adds to the electron-deficient 3,3,3-trifluoropropene **17C** to generate a trifluoroalkyl radical **17I**. Meanwhile, the highly nucleophilic α -aminoalkyl radical **17H** couples with the highly electrophilic *N*-aryl aminyl radical **17F** to form an amination intermediate **17J**, which likely undergoes $\text{Ni}(\text{0})$ -mediated dealkylation to furnish an *N*-arylaminoethyl- $\text{Ni}(\text{II})$ complex **17K**. This complex subsequently releases an *N*-arylaminoethyl radical **17L**, which is intercepted by the trifluoroalkyl radical **17I** to deliver

the final *N*-trifluoroalkyl aniline product **17E**. Low-valent nickel species ($\text{Ni}^{\text{0}}/\text{Ni}^{\text{I}}$) are proposed to play key roles in stabilizing the trifluoroalkyl radical **17I** and facilitating both C–C and C–N bond-forming events, thereby enhancing overall reaction efficiency. This work represents a significant advance in multicomponent trifluoromethylation chemistry, offering an efficient and programmable route to highly architecturally complex *N*-trifluoroalkyl aniline scaffolds that are otherwise difficult to access using conventional approaches.

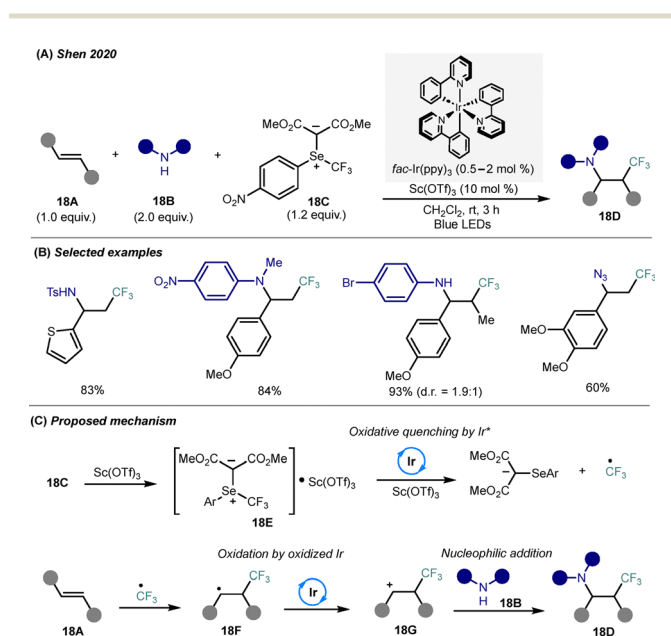
3.8 Scandium/photoredox-catalyzed amido-, amino-, and azido-trifluoromethylation of alkenes

In an effort to develop highly efficient trifluoromethylative difunctionalization of alkenes, Shen and co-workers reported a synergistic Lewis acid and photoredox-catalyzed method employing a selenium ylide-based trifluoromethylating reagent **18C**³⁶ (Scheme 18A). Using *fac*- $\text{Ir}(\text{ppy})_3$ as photocatalyst and $\text{Sc}(\text{OTf})_3$ as a Lewis acid co-catalyst, a broad range of aromatic and heterocyclic alkenes **18A** underwent smooth amino-trifluoromethylation reaction with various nitrogen-based nucleophiles **18B**, such as sulfonamides, anilines and azide, under blue light irradiation (Scheme 18B). A variety of β -trifluoromethylated alkylamines and azo compounds **18D** decorated with diverse functional groups are formed. In contrast, electron-deficient styrenes, alkyl-substituted alkenes, and Cbz-protected amines failed to afford the desired difunctionalized products under the optimized conditions.

Mechanistic investigations reveal that $\text{Sc}(\text{OTf})_3$ forms a Lewis acid–base complex **18E** with the electrophilic ylide reagent **18C** (Scheme 18C). **18E** significantly enhances the SET reactivity with the photoexcited $\text{Ir}(\text{ppy})_3$ by lowering the LUMO energy and raising the reduction potential. Cyclic voltammetry and DFT studies suggest that **18E** is more readily reduced than the free ylide **18C**, facilitating SET event and CF_3 radical generation. The CF_3 radical adds to the alkene to generate trifluoroalkyl radical **18F**, which undergoes photocatalytic oxidation to form cationic intermediate **18G**. Subsequent nucleophilic trapping by a nitrogen nucleophile completes the 1,2-difunctionalization, affording the trifluoroalkylamine product **18D**. This study highlights the power of Lewis acid modulation in tuning radical generation from electrophilic reagents and establishes a general platform for constructing CF_3 -bearing molecules with high efficiency and functional diversity.

4. Inert bond functionalization for direct $\text{C}(\text{sp}^3)\text{--CF}_3$ bond formation

Direct $\text{C}(\text{sp}^3)\text{--H}$ and $\text{C}(\text{sp}^3)\text{--N}$ functionalization strategies obviate the need for prefunctionalized substrates, providing streamlined access to trifluoromethylated aliphatic amines from native feedstocks. Visible-light-mediated approaches, leveraging either HAT or deaminative radical generation, enable regioselective and late-stage incorporation of CF_3 groups. This section highlights representative photoinduced methodologies



Scheme 18 Synergistic scandium/photoredox-catalyzed amido-, amino-, and azido-trifluoromethylation of alkenes. (A) General reaction conditions. (B) Representative substrate scope. (C) Proposed mechanism.



that achieve site-selective trifluoromethylation of unactivated aliphatic amines *via* C–H or C–N activation.

4.1 Copper/ decatungstate-catalyzed C–H trifluoromethylation

C(sp³)–H trifluoromethylation provides a direct strategy for the synthesis of fluorinated molecules; however, achieving regioselective C–H activation in the absence of directing groups remains a longstanding challenge.³⁷ To address this challenge, MacMillan and co-workers developed a dual catalytic platform combining decatungstate photocatalysis with copper catalysis, enabling the direct trifluoromethylation of both strong, unactivated aliphatic C–H bonds and weaker benzylic C–H bonds in simple alkylamine feedstocks **19A**³⁸ (Scheme 19A). This strategy

employs bench-stable, commercially available Togni reagent (**19B**) as the CF₃ source, sodium decatungstate (NaDT) as a potent HAT photocatalyst, Cu(II) salt as co-catalyst, and sulfuric acid (H₂SO₄) along with sodium chloride (NaCl) as key additives. The method exhibits broad substrate scope, accommodating linear, cyclic, and aromatic alkylamines (Scheme 19B), as well as amine-containing bioactive compounds, natural products, and pharmaceuticals (Scheme 19C), without the need for prefunctionalization or directing groups, delivering trifluoromethylated alkylamines **19C** in modest to good yields. However, for aliphatic amines bearing multiple types of C(sp³)–H bonds with similar bond strengths, the regioselective C–H trifluoromethylation is typically modest to moderate, underscoring the challenge of achieving high site selectivity in such systems.

Notably, the regioselectivity of C–H trifluoromethylation is governed by both steric and electronic factors (Scheme 19D). Upon protonation of the amine nitrogen—such as in pyrrolidine (**19D**)—by H₂SO₄, the corresponding ammonium salt (**19E**) is formed, which converts the typically hydridic α-C–H bond into an acidic one. Under near-UV irradiation, the photoexcited decatungstate ion ([W₁₀O₃₂]^{4–*}), bearing an electrophilic W–O• radical, selectively abstracts a hydrogen atom from the electron-neutral and sterically accessible C(sp³)–H bond to generate an alkyl radical (*e.g.*, β-C–H abstraction of protonated pyrrolidine to form a pyrrolidinyl radical **19F**). Deprotonation of the resulting H[W₁₀O₃₂]^{5–} species to form [W₁₀O₃₂]^{5–} significantly enhances its reducing power, enabling SET to the Togni reagent **19B** and subsequent generation of a CF₃ radical. Simultaneously, CuCl₂ is reduced by [W₁₀O₃₂]^{5–} to Cu(I), which interacts with the CF₃ radical to form a Cu(II)–CF₃ species **19G**. Capture of the alkyl radical **19F** and subsequent reductive elimination from (Alkyl)(CF₃)Cu(III) species **19H** furnishes the trifluoromethylated alkylamine product **19I**. The NaCl additive likely suppresses oxidative degradation pathways in sensitive alkylamines and may serve as an additional source of chloride radicals under photooxidative conditions, further facilitating selective HAT from protonated amines. This work represents a significant advance in non-directed C(sp³)–H trifluoromethylation and underscores the potential of metallaphotoredox catalysis for site-selective, late-stage molecular editing to access trifluoroalkylamine architectures.

4.2 Deaminative trifluoromethylation of primary alkylamines

Alkylamines are not only versatile feedstocks in synthesis and industrial processing, but also transformable groups to allow structural modifications.³⁹ To address the underdeveloped yet challenging area of deaminative functionalizations, Li, Wang, and co-workers developed a site-specific, radical-mediated trifluoromethylation of aliphatic primary amines under visible light using *N*-anomeric amide (Levin reagent, **20C**) and copper(III) tris(trifluoromethyl) complex (Grushin reagent, Cu^{III}(bipy)(CF₃)₃, **20B**)⁴⁰ (Scheme 20A). This transformation enables direct conversion of diamine scaffolds **20A** (*e.g.*, amino-substituted carbamates, amides, and cyclic amines) into trifluoroalkyl amine derivatives **20D** (Scheme 20B), including



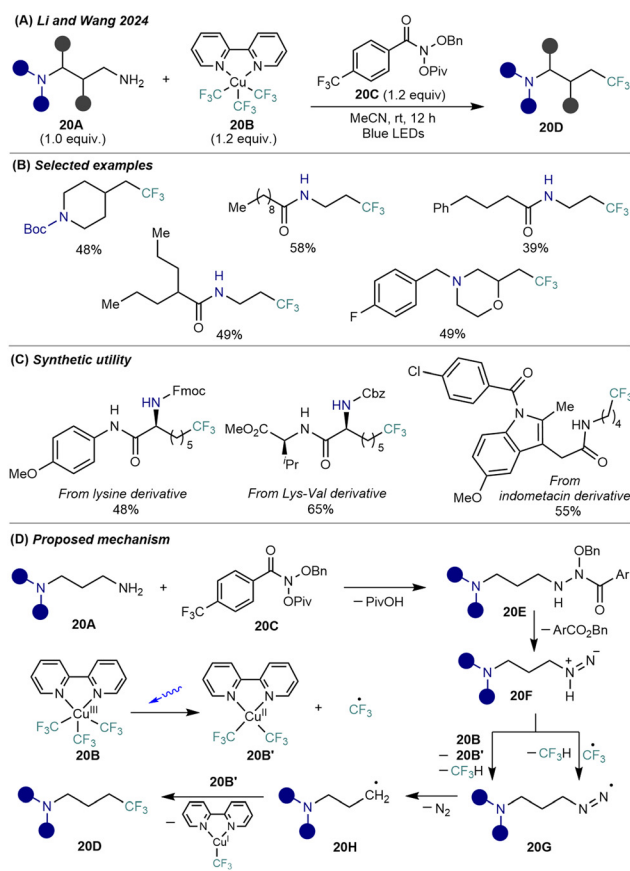
Scheme 19 Copper/decatungstate photocatalytic trifluoromethylation of aliphatic C(sp³)–H bonds in alkylamines. (A) General reaction conditions. (B) Representative substrate scope. (C) Synthetic utility and applications. (D) Proposed mechanism.



Highlight

amino acids, dipeptides, and drug derivatives (Scheme 20C), without requiring preactivation of native amino groups or harsh conditions. More sterically bulky α -branched substrates, such as α -secondary carbon-based primary amines, also underwent the reaction; however, only low yields of the trifluoromethylated products were obtained, likely due to increased steric hindrance that hampers the formation of key reactive intermediates.

The protocol proceeds *via in situ* generation of an intermediate **20E** from the diamine **20A** and Levin reagent **20C**, followed by facile decomposition to isodiazene **20F** (Scheme 20D). Upon blue-light irradiation, the photolysis of the Grushin reagent **20B** takes place to form both CF_3 radical and $\text{Cu}^{\text{II}}(\text{bipy})(\text{CF}_3)_2$ species **20B'**. The CF_3 radical engages in HAT event from **20F** to generate the diazenyl radical **20G**. Alternatively, **20F** reacts directly with the CF_3 groups in the Grushin reagent to form **20G**. **20G** then undergoes N_2 elimination to yield an aminoalkyl radical **20H**, which interacts with $\text{Cu}^{\text{II}}(\text{bipy})(\text{CF}_3)_2$ to furnish a high-valent $\text{Cu}(\text{III})$ species that undergoes reductive elimination to construct the $\text{C}(\text{sp}^3)\text{-CF}_3$ bond, creating the complex trifluoroalkyl amine product **20D**. This strategy significantly expands the toolbox for direct amine-to- CF_3 conversion and offers a general approach for site-specific alkyl trifluoromethylation in complex molecular settings.



Scheme 20 Photoinduced deaminative trifluoromethylation of alkylamines. (A) General reaction conditions. (B) Representative substrate scope. (C) Synthetic utility and applications. (D) Proposed mechanism.

5. Photoinduced catalyst-free synthesis of trifluoroalkyl amines

The elimination of catalysts in trifluoromethylation chemistry aligns with the growing demand for sustainable and pharmaceutically compatible synthetic methodologies. Catalyst-free, light-driven transformations offer notable advantages, including operational simplicity, lower cost, and the avoidance of residual metal contaminants. This section highlights a recent catalyst-free protocol for the construction of trifluoroalkyl amines *via* a radical pathway, employing readily available substrates under ambient conditions.

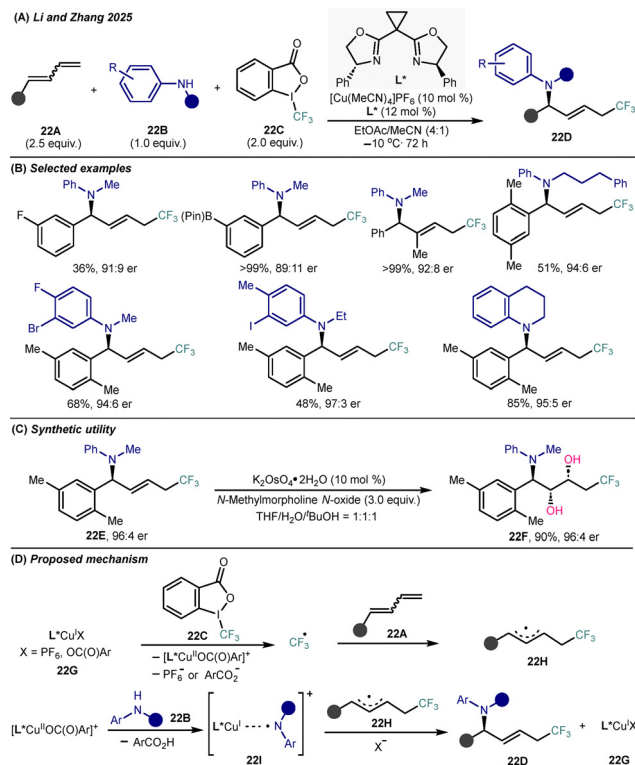
Gaunt and co-workers developed a visible-light-mediated, multi-component carbonyl trifluoromethylative amination protocol that directly couples aldehydes **21A**, secondary amines **21B**, and the Ritter trifluoroiodomethane–DMSO reagent (CF_3I -DMSO, **21C**) to afford β -trifluoromethylated tertiary alkylamines **21D**⁴¹ (Scheme 21A). Notably, this transformation proceeds under mild conditions without the need for a photocatalyst or transition metal, relying solely on visible light. The method exhibits broad substrate scope, accommodating a wide range of functionalized aliphatic aldehydes and secondary alkylamines, including medicinally relevant scaffolds, thus highlighting its potential for late-stage modification and lead optimization in drug discovery (Scheme 21B). In contrast, α -substituted aldehydes fail to deliver the corresponding trifluoromethylated amines, likely due to steric hindrance that impedes the radical addition step.

Mechanistically, the reaction initiates *via* condensation of the aldehyde and amine to generate an iminium ion **21E**, which undergoes tautomerization to the corresponding enamine **21F**. Upon visible-light promoted conditions, CF_3I is converted to CF_3



Scheme 21 Photoinduced carbonyl trifluoromethylative amination of aldehydes. (A) General reaction conditions. (B) Representative substrate scope. (C) Proposed mechanism.





Scheme 22 Cu-catalyzed enantioselective radical 1,4-trifluoroalkylation of 1,3-dienes. (A) General reaction conditions. (B) Representative substrate scope. (C) Synthetic utility and applications. (D) Proposed mechanism.

radical, which undergoes regioselective addition to the electron-rich enamine to form a transient α -amino radical **21G**. This intermediate is proposed to undergo either single-electron oxidation by CF_3I , or XAT with CF_3I to iodo-trifluoroalkyl amine intermediate **21H** followed by iodide elimination, to generate a β -trifluoromethylated iminium species **21I**. Subsequent reductive workup with sodium triacetoxyborohydride furnishes the desired β -trifluoromethylated tertiary alkylamine **21D**. This methodology provides a simple and efficient strategy for constructing structurally intricate trifluoroalkylamines that are otherwise challenging to access using conventional synthetic approaches.

6. Stereoselective and asymmetric approaches

Achieving stereocontrol in trifluoromethylative difunctionalization reactions remains a formidable challenge due to the high reactivity of CF_3 radicals and aminyl intermediates. Recent progress in asymmetric photocatalysis has demonstrated that regio- and enantioselective amino-trifluoromethylation of dienes is feasible through judicious design of chiral catalysts and radical coupling pathways. This section highlights an emerging strategy for the enantioselective synthesis of chiral trifluoroalkyl amines *via* radical-based difunctionalization, illustrating the potential of stereochemically defined fluorinated scaffolds in medicinal chemistry.

Despite the synthetic appeal of enantioselective aminative difunctionalization of 1,3-dienes, previous efforts have been largely limited to two-component systems or 1,2-selective processes, with limited success in achieving 1,4-regioselectivity—particularly when employing anilines, which are weak nucleophiles and prone to catalyst deactivation *via* coordination. The development of a regio- and enantioselective three-component protocol that directly couples simple anilines, 1,3-dienes, and CF_3 radicals thus poses both a significant synthetic challenge and a conceptual advance in radical C–N bond-forming methodologies. A recent study by Li, Zhang, and co-workers has addressed this challenge by developing a copper-catalyzed, enantioselective three-component 1,4-trifluoroalkylation of 1,3-dienes **22A**, employing anilines **22B** as the nitrogen source and a Togni reagent **22C** as the CF_3 source under mild conditions⁴² (Scheme 22A). This transformation enables highly regio- and stereoselective access to a structurally diverse library of chiral trifluoromethylated allylic anilines **22D**. A wide range of aryl-substituted 1,3-dienes and drug-like frameworks were converted to the desired products in high yields and good enantioselectivities (Scheme 22B). Both electron-rich and electron-deficient primary and secondary anilines prove compatible under the optimized conditions. Conversely, trifluoromethylation with aliphatic 1,3-dienes (*e.g.*, 1-benzyl-1,3-diene) and aliphatic amines (*e.g.*, dibenzylamine, benzylamine, morpholine, and *N*-methyl benzylamine) proved unproductive under the standard conditions. Selective oxidation of product **22E** afforded the highly stereoselective dihydroxylated trifluoroalkyl aniline **22F**, thereby increasing the molecular complexity (Scheme 22C).

Mechanistically, the reaction proceeds *via* copper-mediated SET from the chiral ligand-coordinated Cu(I) complex **22G** to the Togni reagent, generating a CF_3 radical and a Cu(II) benzoate species (Scheme 22D). The CF_3 radical undergoes regioselective addition to the terminal position of the 1,3-diene, forming a trifluoromethylated allylic radical **22H**. Simultaneously, ligand exchange between the Cu(II) benzoate and aniline yields a Cu(II)-aminyl species, existing as an aminyl radical-associated Cu(I) complex **22I**. The enantioselective C–N bond formation arises from radical–radical cross-coupling between the allylic radical **22H** and the chiral Cu(I)-bound aminyl radical, affording the trifluoromethylated allyl aniline **22D** in an enantiomerically enriched form. The high enantioselectivity arises from noncovalent interactions between the chiral bisoxazoline ligand's aromatic rings, the C–F bond of the CF_3 radical **22H**, and the methyl C–H bond of the aminyl radical derived from secondary anilines in species **22I**. This work showcases a rare yet powerful platform for stereocontrolled radical difunctionalization of dienes, opening new avenues for the synthesis of fluorinated allylic amines with high regio- and stereoselectivity. It represents a significant advancement in asymmetric radical chemistry and enriches the toolkit for constructing fluorine-containing molecules of pharmaceutical relevance.

7. Conclusion

In this review, we summarize recent advances in the light-driven synthesis of trifluoromethylated aliphatic amines,



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organized by reaction strategy and disconnection logic. Key developments include direct formation of C(sp³)-CF₃ bonds from inert precursors, alkene difunctionalization *via* radical-polar crossover or radical trapping, and metallaphotoredox-catalyzed cascades that forge C-CF₃, C-N, and C-C bonds in a convergent fashion. Additionally, emerging examples of photocatalyst-free and asymmetric strategies have begun to expand the synthetic toolbox. Collectively, these approaches underscore the power of photocatalysis to construct structurally complex, fluorine-rich amines from simple building blocks under mild and modular conditions.

Despite these advances, several challenges and opportunities remain. Most reported transformations proceed in a racemic manner; therefore, the development of enantioselective variants represents a critical yet underexplored frontier. The design of highly efficient chiral Brønsted acids, Lewis acids, and transition-metal catalysts, along with the strategic use of chiral auxiliaries on substrates, will be pivotal for enabling asymmetric bond formation and accessing chiral analogues. Emerging photoenzymatic radical-based coupling reactions may also pave the way toward highly stereoselective synthesis. In addition, many current protocols rely on photocatalysts or transition-metal complexes, which can limit their pharmaceutical applicability due to concerns over cost, regulatory hurdles, and residual metal contamination. In this context, the growing use of electron donor-acceptor (EDA) complexes provides a promising metal-free alternative for initiating radical processes, particularly when targeting drug-like or sensitive substrates. Furthermore, while photoredox catalysis has demonstrated impressive reactivity on the laboratory scale, scalability remains a major bottleneck for industrial translation. The development of more efficient, scalable, and continuous-flow-compatible photochemical systems will be essential to unlock the full potential of these methodologies for large-scale synthesis. Looking ahead, future innovations that integrate asymmetric catalysis, metal-free or photocatalyst-free radical generation, and process intensification are expected to significantly expand the practical utility of light-driven synthesis across both academic and industrial settings.

In conclusion, the light-driven synthesis of trifluoromethylated aliphatic amines constitutes a rapidly evolving and highly promising field, offering powerful strategies to access molecular architectures of significant pharmaceutical relevance. Continued innovation in photocatalysis is poised to enable increasingly sophisticated synthetic methodologies, thereby expanding chemical space for drug discovery and facilitating the streamlined synthesis of novel, fluorine-rich bioactive compounds.

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 analyzed as part of this review.

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Notes and references

- (a) R. D. Taylor, M. MacCoss and A. D. G. Lawson, Rings in drugs, *J. Med. Chem.*, 2014, **57**, 5845–5859; (b) M. A. M. Subbaiah and N. A. Meanwell, Bioisosteres of the phenyl ring: recent strategic applications in lead optimization and drug design, *J. Med. Chem.*, 2021, **64**, 14046–14128; (c) J. Shearer, J. L. Castro, A. D. G. Lawson, M. MacCoss and R. D. Taylor, Rings in clinical trials and drugs: present and future, *J. Med. Chem.*, 2022, **65**, 8699–8712; (d) N. A. Meanwell, Applications of bioisosteres in the design of biologically active compounds, *J. Agric. Food Chem.*, 2023, **71**, 18087–18122.
- (a) N. A. Meanwell, Fluorine and fluorinated motifs in the design and application of bioisosteres for drug design, *J. Med. Chem.*, 2018, **61**, 5822–5880; (b) M. Inoue, Y. Sumii and N. Shibata, Contribution of organofluorine compounds to pharmaceuticals, *ACS Omega*, 2020, **5**, 10633–10640; (c) C. Zhang, Fluorine in medicinal chemistry: in perspective to COVID-19, *ACS Omega*, 2022, **7**, 18206–18212.
- (a) W. Zhu, J. Wang, S. Wang, Z. Gu, J. L. Acena, K. Izawa, H. Liu and V. A. Soloshonok, Recent advances in the trifluoromethylation methodology and new CF₃-containing drugs, *J. Fluorine Chem.*, 2014, **167**, 37–54; (b) A. S. Nair, A. K. Singh, A. Kumar, S. Kumar, S. Sukumaran, V. P. Koyiparambath, L. K. Pappachen, T. M. Rangarajan, H. Kim and B. Mathew, FDA-approved trifluoromethyl group-containing drugs: a review of 20 years, *Processes*, 2022, **10**, 2054.
- H. M. Leatherwood and J. T. Njardarson, *Top 200 Small Molecule Drugs by Retail Sales in 2024*, The Njardarson Group, University of Arizona, 2024, <https://sites.arizona.edu/njardarson-lab/top200-posters/> (accessed June 1, 2025).
- R. E. Williams, H. M. Leatherwood and J. T. Njardarson, *Top 200 Small Molecule Drugs by Retail Sales in 2023*, The Njardarson Group, University of Arizona, 2023, <https://sites.arizona.edu/njardarson-lab/top200-posters/> (accessed June 1, 2025).
- R. E. Williams and J. T. Njardarson, *Top 200 Small Molecule Drugs by Retail Sales in 2022*, The Njardarson Group, University of Arizona, 2022, <https://sites.arizona.edu/njardarson-lab/top200-posters/> (accessed June 1, 2025).
- Z. Zhou, Z.-W. Zhang, J. Nie, F. Y. Kwong, J.-A. Ma and C. W. Cheung, Metallaphotocatalytic triple couplings for modular synthesis of elaborate N-trifluoroalkyl anilines, *Nat. Commun.*, 2024, **15**, 9926.
- F. Lovering, J. Bikker and C. Humblet, Escape from flatland: increasing saturation as an approach to improving clinical success, *J. Med. Chem.*, 2009, **52**, 6752–6756.
- (a) H. Scoherr and T. Cernak, Profound methyl effects in drug discovery and a call for new C-H methylation reactions, *Angew. Chem., Int. Ed.*, 2013, **52**, 12256–12267; (b) E. J. Barreiro, A. E. Kümmerle and C. A. M. Fraga, The methylation effect in medicinal chemistry, *Chem. Rev.*, 2011, **111**, 5215–5246; (c) C. S. Leung, S. S. F. Leung, J. Tirado-Rives and W. L. Jorgensen, Methyl effects on protein-ligand binding, *J. Med. Chem.*, 2012, **55**, 4489–4500; (d) S. Sun and J. Fu, Methyl-containing pharmaceuticals: methylation in drug design, *Bioorg. Med. Chem. Lett.*, 2018, **28**, 3283–3289.
- (a) T. T. Talele, Opportunities for tapping into three-dimensional chemical space through a quaternary carbon, *J. Med. Chem.*, 2020, **63**, 13291–13315; (b) I. P. Silvestri and P. J. J. Colbon, The growing importance of chirality in 3D chemical space exploration and modern drug discovery approaches for hit-ID, *ACS Med. Chem. Lett.*, 2021, **12**, 1220–1229; (c) J. Tsien, C. Hu, R. R. Merchant and T. Qin, Three-dimensional saturated C(sp³)-rich bioisosteres for benzene, *Nat. Rev. Chem.*, 2024, **8**, 605–627.
- DrugBank*, <https://go.drugbank.com> (accessed June 1, 2025).



- 12 (a) A. T. Brusoe and J. F. Hartwig, Palladium-catalyzed arylation of fluoroalkylamines, *J. Am. Chem. Soc.*, 2015, **137**, 8460–8468; (b) R. T. McGuire, A. A. Yadav and M. Stradiotto, Nickel-catalyzed N-arylation of fluoroalkylamines, *Angew. Chem., Int. Ed.*, 2021, **60**, 4080–4084; (c) S. Liu, J. Zhou, L. Yu, Y. Liu, Y. Huang, Y. Ouyang, G.-K. Liu, X.-H. Xu and N. Shibata, Nitrogen-based organofluorine functional molecules: synthesis and applications, *Chem. Rev.*, 2025, **125**, 4603–4764.
- 13 (a) J. Twilton, C. Le, P. Zhang, M. H. Shaw, R. W. Evans and D. W. C. MacMillan, The merger of transition metal and photocatalysis, *Nat. Rev. Chem.*, 2017, **1**, 0052; (b) C. K. Prier, D. A. Rankic and D. W. C. MacMillan, Visible light photoredox catalysis with transition metal complexes: applications in organic synthesis, *Chem. Rev.*, 2013, **113**, 5322–5363; (c) A. Y. Chan, I. B. Perry, N. B. Bissonnette, B. F. Buksh, G. A. Edwards, L. I. Frye, O. L. Garry, M. N. Lavagnino, B. X. Li, Y. Liang, E. Mao, A. Millet, J. V. Oakley, N. L. Reed, H. A. Sakai, C. P. Seath and D. W. C. MacMillan, Metallaphotoredox: the merger of photoredox and transition metal catalysis, *Chem. Rev.*, 2022, **122**, 1485–1542; (d) N. Holmberg-Douglas and D. A. Nicewicz, Photoredox-catalyzed C–H functionalization reactions, *Chem. Rev.*, 2022, **122**, 1925–2016.
- 14 (a) F. Strieth-Kalthoff, M. J. James, M. Teders, L. Pitzer and F. Glorius, Energy transfer catalysis mediated by visible light: principles, applications, directions, *Chem. Soc. Rev.*, 2018, **47**, 7190–7202; (b) F. Strieth-Kalthoff and F. Glorius, Triplet energy transfer photocatalysis: unlocking the next level, *Chem*, 2020, **6**, 1888–1903; (c) S. Dutta, J. E. Erchinger, F. Strieth-Kalthoff, R. Kleinmans and F. Glorius, Energy transfer photocatalysis: exciting modes of reactivity, *Chem. Soc. Rev.*, 2024, **53**, 1068–1089.
- 15 (a) E. Ruijter, R. Scheffelaar and R. V. A. Orru, Multicomponent reaction design in the quest for molecular complexity and diversity, *Angew. Chem., Int. Ed.*, 2011, **50**, 6234–6246; (b) M. J. Buskes, A. Coffin, D. M. Troast, R. Stein and M.-J. Blanco, Accelerating drug discovery: synthesis of complex chemotypes via multicomponent reactions, *ACS Med. Chem. Lett.*, 2023, **14**, 376–385.
- 16 (a) S. Barata-Vallejo, B. Lantano and A. Postigo, Recent advances in trifluoromethylation reactions with electrophilic trifluoromethylating reagents, *Chem. – Eur. J.*, 2014, **20**, 16806–16829; (b) R. T. Kareem, B. Azizi, M. Asnaashariisfahani, A. Ebadid and E. Vessally, Vicinal halo-trifluoromethylation of alkenes, *RSC Adv.*, 2021, **11**, 14941–14955.
- 17 (a) T. E. Muller, K. C. Hultzsich, M. Yus, F. Foubelo and M. Tada, Hydroamination: direct addition of amines to alkenes and alkynes, *Chem. Rev.*, 2008, **108**, 3795–3892; (b) P. Kalck and M. Urrutigoity, Tandem hydroaminomethylation reaction to synthesize amines from alkenes, *Chem. Rev.*, 2018, **118**, 3833–3861; (c) R. Y. Liu and S. L. Buchwald, CuH-catalyzed olefin functionalization: from hydroamination to carbonyl addition, *Acc. Chem. Res.*, 2020, **53**, 1229–1243; (d) H. Jiang and A. Studer, Intermolecular radical carboamination of alkenes, *Chem. Soc. Rev.*, 2020, **49**, 1790–1811; (e) K. Kwon, R. T. Simons, M. Nandakumar and J. L. Roizen, Strategies to generate nitrogen-centered radicals that may rely on photoredox catalysis: development in reaction methodology and applications in organic synthesis, *Chem. Rev.*, 2022, **122**, 2353–2428; (f) C. Pratley, S. Fenner and J. A. Murphy, Nitrogen-centered radicals in functionalization of sp^2 systems: generation, reactivity, and applications in synthesis, *Chem. Rev.*, 2022, **122**, 8181–8260.
- 18 Y. Yasu, T. Koike and M. Akita, Intermolecular aminotrifluoromethylation of alkenes by visible-light-driven photoredox catalysis, *Org. Lett.*, 2013, **15**, 2136–2139.
- 19 G. Dagousset, A. Carboni, E. Magnier and G. Masson, Photoredox-induced three-component azido- and aminotrifluoromethylation of alkenes, *Org. Lett.*, 2014, **16**, 4340–4343.
- 20 X.-L. Yu, J.-R. Chen, D.-Z. Chen and W.-J. Xiao, Visible-light-induced photocatalytic azotrifluoromethylation of alkenes with aryldiazonium salts and sodium triflinate, *Chem. Commun.*, 2016, **52**, 8275–8278.
- 21 L. Zheng, L. Cai, X. Zhuo, L. Deng, Y. Wu, B. Yang, Y. Wang and W. Guo, Direct intermolecular three-component aminotrifluoromethylation of styrenes by visible-light-photoredox catalysis, *Org. Chem. Front.*, 2022, **9**, 6498–6504.
- 22 Y. Zheng, Z. Liao, Z. Xie, H. Chen, K. Chen, H. Xiang and H. Yang, Photochemical alkene trifluoromethyliminium enabled by trifluoromethylsulfonylamide as a bifunctional reagent, *Org. Lett.*, 2023, **25**, 2129–2133.
- 23 C. Zhou, X. Wang, P. Kong, D. Ji, P. Zhou and C. Huo, Alkyl-Trifluoromethylation of Glycine Derivatives, *Org. Lett.*, 2025, **27**, 7126–7131.
- 24 Y. Ren, Y. Zhou, K.-H. Wang, J. Wang, D. Huang and Y. Hu, A visible light promoted regioselective cascade radical trifluoromethylation/cyclization of N-isopentenyl aldehyde hydrazones: access to trifluoromethylated tetrahydropyridazine derivatives, *Org. Lett.*, 2025, **27**, 7033–7038.
- 25 A. Carboni, G. Dagousset, E. Magnier and G. Masson, Photoredox-induced three-component oxy-, amino- and carbotrifluoromethylation of enecarbamates, *Org. Lett.*, 2014, **16**, 1240–1243.
- 26 Y. Xiong, X. Ma and G. Zhang, Copper-catalyzed intermolecular carboamination of alkenes induced by visible light, *Org. Lett.*, 2019, **21**, 1699–1703.
- 27 (a) J. A. Rossi-Ashton, A. K. Clarke, W. P. Unsworth and R. J. K. Taylor, Phosphoranyl radical fragmentation reactions driven by photoredox catalysis, *ACS Catal.*, 2020, **10**, 7250–7261; (b) T. Mandal, S. Mallick, M. Islam and S. De Sarkar, Alcohols as alkyl synthons enabled by photoredox-catalyzed deoxygenative activation, *ACS Catal.*, 2024, **14**, 13451–13496; (c) W. Luo, Z. Chen and B. Yu, Photocatalytic deoxygenative alkylation with alcohols via xanthates or thionocarbonates, *Asian J. Org. Chem.*, 2025, **14**, e202400627.
- 28 N. E. Intermaggio, A. Millet, D. L. Davis and D. W. C. MacMillan, Deoxytrifluoromethylation of alcohols, *J. Am. Chem. Soc.*, 2022, **144**, 11961–11968.
- 29 (a) C. Lei and Q. Zhou, Advances on nickel-catalyzed $C(sp^3)$ – $C(sp^3)$ bond formation, *Acta Chim. Sin.*, 2020, **78**, 1017–1029; (b) Q.-Y. Huang and M. Shi, Recent advancements in Ni/photoredox dual catalysis for $C(sp^3)$ – $C(sp^3)$ cross-coupling reactions, *Org. Chem. Front.*, 2024, **11**, 4913–4925.
- 30 J. Z. Wang, W. L. Lyon and D. W. C. MacMillan, Alkene dialkylation by triple radical sorting, *Nature*, 2024, **628**, 104–109.
- 31 (a) P. K. Mykhailiuk, 2,2,2-Trifluorodiazethane (CF_3CHN_2): a long journey since 1943, *Chem. Rev.*, 2020, **120**, 12718–12755; (b) P. K. Mykhailiuk, Fluorinated pyrazoles: from synthesis to applications, *Chem. Rev.*, 2021, **121**, 1670–1715.
- 32 B. T. Boyle, N. W. Dow, C. B. Kelly, M. C. Bryan and D. W. C. MacMillan, Unlocking carbene reactivity by metallaphotoredox α -elimination, *Nature*, 2024, **631**, 789–795.
- 33 F. Cong, G.-Q. Sun, S.-H. Ye, R. Hu, W. Rao and M. J. Koh, A bimolecular homolytic substitution-enabled platform for multicomponent cross-coupling of unactivated alkenes, *J. Am. Chem. Soc.*, 2024, **146**, 10274–10280.
- 34 Y.-W. Jiang, Z.-W. Zhang, C. W. Cheung and J.-A. Ma, Metallaphotocatalytic modular synthesis of masked arylaminomethyl trifluoromethyl ketones, *Cell Rep. Phys. Sci.*, 2025, **6**, 102564.
- 35 Z.-W. Zhang, Z. Feng, J.-A. Ma and C. W. Cheung, Metallaphotocatalytic synthesis of anilines through tandem C–N transposition and C–H alkylation of alkylamines, *Nat. Synth.*, 2023, **2**, 1171–1183.
- 36 H. Ge, B. Wu, Y. Liu, H. Wang and Q. Shen, Synergistic Lewis acid and photoredox-catalyzed trifluoromethylative difunctionalization of alkenes with selenium ylide-based trifluoromethylating reagent, *ACS Catal.*, 2020, **10**, 12414–12424.
- 37 (a) G. Choi, G. S. Lee, B. Park, D. Kim and S. H. Hong, Direct $C(sp^3)$ –H trifluoromethylation of unactivated alkanes enabled by multifunctional trifluoromethyl copper complexes, *Angew. Chem., Int. Ed.*, 2021, **60**, 5467–5474; (b) J. He, T. N. Nguyen, S. Guo and S. P. Cook, Csp^3 –H trifluoromethylation of unactivated aliphatic systems, *Org. Lett.*, 2021, **23**, 702–705.
- 38 P. J. Sarver, V. Bacauanu, D. M. Schultz, D. A. DiRocco, Y. Lam, E. C. Sherer and D. W. C. MacMillan, The merger of decatungstate and copper catalysis to enable aliphatic $C(sp^3)$ –H trifluoromethylation, *Nat. Chem.*, 2020, **12**, 459–467.
- 39 (a) Y. Pang, D. Moser and J. Cornell, Pyrylium salts: selective reagents for the activation of primary amino groups in organic synthesis, *Synthesis*, 2020, 489–503; (b) K. J. Berger and M. D. Levin, Reframing primary alkyl amines as aliphatic building blocks, *Org. Biomol. Chem.*, 2021, **19**, 11–36; (c) B. Saxena, R. I. Patel and A. Sharma, Recent advances in electron donor-acceptor (EDA) complex reactions involving quaternary pyridinium derivatives, *Adv. Synth. Catal.*, 2023, **365**, 1538–1564; (d) J. U. Kim, E. S. Lim,



- J. Y. Park, D. Jung and S. Lee, Radical approaches for C(sp³)-N bond cleavage in deaminative transformations, *Chem. Commun.*, 2025, **61**, 6997–7008; (e) S. Singh, D. Gambhir and R. P. Singh, Photoinduced stereoselective reactions using pyridinium salts as radical precursors, *Chem. Commun.*, 2025, **61**, 3436–3446.
- 40 J.-H. Xue, Y. Li, Y. Liu, Q. Li and H. Wang, Site-specific deaminative trifluoromethylation of aliphatic primary amines, *Angew. Chem., Int. Ed.*, 2024, **63**, e202319030.
- 41 K. Kolahdouzan, R. Kumar and M. J. Gaunt, Visible-light mediated carbonyl trifluoromethylative amination as a practical method for the synthesis of β -trifluoromethyl tertiary alkylamines, *Chem. Sci.*, 2020, **11**, 12089–12094.
- 42 X. Shangguan, L. Zhu, Y. Zhang, Y. Li and Q. Zhang, Copper-catalyzed enantioselective three-component radical 1,4-perfluoroalkylamination of 1,3-dienes, *Nat. Commun.*, 2025, **16**, 4939.

