Recent advances in visible light-induced C(sp^3)–N bond formation

Mónica Rivas[1,2,3], *Vitalii Palchykov*[1,3], *Xiangqing Jia*[1,3] *and Vladimir Gevorgyan*[1,2]✉

Abstract | Synthetic chemists have long focused on selective C(sp^3)–N bond-forming approaches in response to the high value of this motif in natural products, pharmaceutical agents and functional materials. In recent years, visible light-induced protocols have become an important synthetic platform to promote this transformation under mild reaction conditions. These photo-driven methods rely on converting visible light into chemical energy to generate reactive but controllable radical species. This Review highlights recent advances in this area, mostly after 2014, with an emphasis placed on C(sp^3)–H bond activations, including amination of olefins and carbonyl compounds, and cross-coupling reactions.

The high demand for carbocyclic and heterocyclic amines in various fields of industry, including synthesis, materials, catalysis, pharmaceuticals and agrochemicals, has resulted in a hub of knowledge about their construction. Reactions to build C(sp^2)–N bonds are now taught in college-level courses and have become a part of the synthetic chemist's usual toolbox. Some examples include the copper-catalysed Ullmann–Goldberg[1–3] and Chan–Evans–Lam couplings[4], and the palladium-catalysed Buchwald–Hartwig amination[5–7]. In comparison, formation of the more challenging C(sp^3)–N bonds en route to amines and amides is much less developed. Because the strategy to overcome this obstacle is by accessing highly reactive species such as heteroatom-centred radicals, photochemical methods have become hugely relevant as they provide mild and synthetically useful conditions to achieve this goal. In the last 10 years, the area of visible light-induced carbon–heteroatom bond formation has expanded significantly due to the discovery of many new photochemical methods. Recent reviews, which partially summarize the progress achieved in C–N bond formation, have focused mainly on traditional transition metal (TM)-catalysed reactions to construct complex aliphatic amines, with little emphasis on those mediated by visible light[8,9]. Limited summaries of selected visible light-mediated methods for reductive amination[10,11], benzylic C(sp^3)–H/N–H couplings and those not requiring exogenous photosensitizers[12,13] have been published. In this Review, we focus on reports after 2014, as earlier works were appropriately covered[14,15]. Visible light-induced methods for C(sp^2)–N bond formation are outside the scope of this Review, as they are extensively summarized elsewhere[9,14,16–19]. While this manuscript was in preparation, a review by the Roizen group was published, summarizing the generation of nitrogen-centred radicals (NCRs)[20].

General approaches for visible light-induced C(sp^3)–N bond formation are outlined in FIG. 1. Intramolecular amination of C(sp^3)–H bonds via 1,5-hydrogen atom transfer (HAT) takes its precedence from the Hofmann–Löffler–Freytag (HLF) reaction, to generate a highly electrophilic NCR, capable of HAT (FIG. 1a). The same moiety is then utilized as the intramolecular amination reagent, which is one of the most common and well-developed methodologies to synthesize five-membered azaheterocycles. An alternative mode of generating an electrophilic radical species towards C(sp^3)–H amination involves a visible light-induced ligand-to-metal charge transfer (LMCT) to generate an oxygen-centred radical, which is the hydrogen abstracting species. An exogenous amination reagent is then used to furnish the C(sp^3)–N bond. These methodologies are usually biased towards weak C(sp^3)–H bonds such as benzylic, tertiary or α-heteroatom. Another approach involves the difunctionalization of alkenes and, although scarcely, strained systems. TM and visible light catalytic systems are exploited in this scenario towards the generation of amino radical cations to be trapped generally by an alkene, and subsequently quenched by a compatible functional group (FIG. 1b). Intramolecularly, alkene functionalization can furnish a range of five-membered and six-membered azaheterocycles (FIG. 1c). This strategy has been further developed to obviate the use of TMs in favour of organo-photocatalysts. Readily available carbonyl compounds and their derivatives have proven to be versatile handles for C(sp^3)–H amination (FIG. 1d). These protocols employ the elusive α-amino radical to access hard to reach amines through reductive or alkylative methods. Alternatively, the use of NCRs for radical addition into enolates can furnish these privileged motifs. Lastly, decarboxylative, dehydrohalogenative and dehydrogenative couplings are used for the direct

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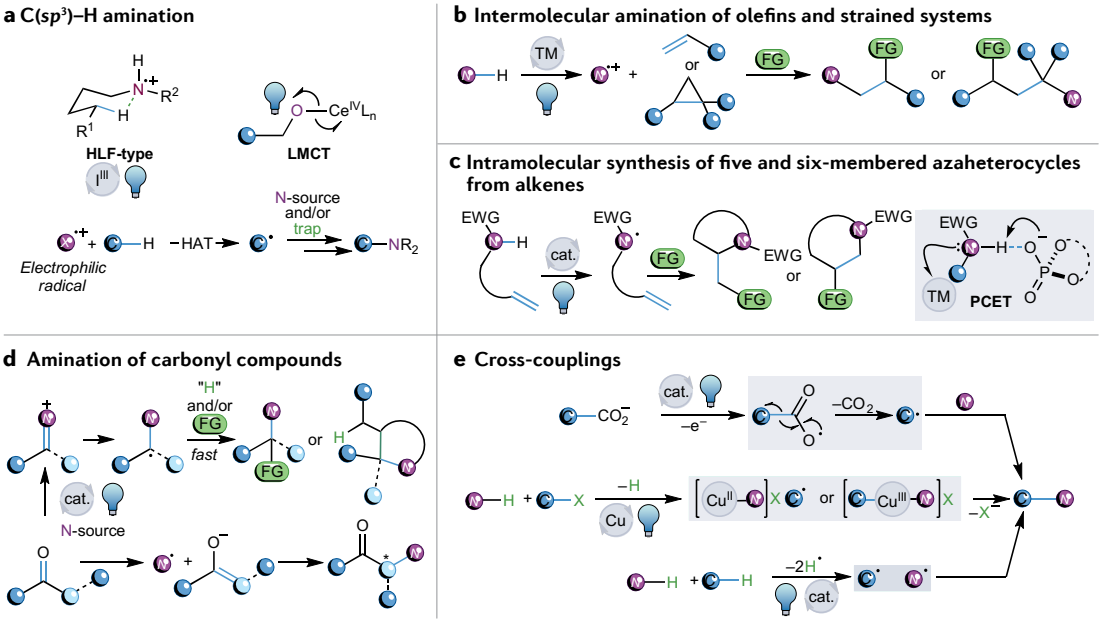

Fig. 1 | **Generalized approaches for the visible light-induced formation of C(sp^3)–N bonds. a** | Amination of C(sp^3)–H bonds by Hofmann–Löffler–Freytag (HLF)-type or ligand-to-metal charge transfer (LMCT) approaches. **b** | Transition metal (TM)-catalysed intermolecular amino-functionalization of olefins and strained systems. **c** | Intramolecular amination of alkenes towards five-membered and six-membered azaheterocycles. **d** | Amination of carbonyl compounds by reductive amination, carbonyl alkylative amination or direct α-amination. **e** | Decarboxylative, dehydrohalogenative and dehydrogenative cross-couplings. Atoms with italicized labels are fully substituted with R groups but have been retracted for clarity. PCET, proton-coupled electron transfer; EWG, electron withdrawing group; FG, functional group; HAT, hydrogen atom transfer.

transformation of alkyl halides, amines, acids and cyclic ethers into valuable nitrogen-containing compounds (FIG. 1e).

Amination of C(sp^3)–H bonds

In modern organic synthesis, selective C–H functionalizations offer new highly atom-economical approaches for synthesis[9]. So far, radical-mediated C(sp^3)–H functionalization[21] has played a less significant role within this field[22–24]. General pathways for selective visible light-induced amination of C(sp^3)–H bonds involve homolysis via HAT[25], direct photoinduced activation of weak bonds under visible light followed by radical–radical coupling[26] or nucleophilic attack. This section highlights visible light-induced TM-free directed amination[27] and TM-catalysed amination of C(sp^3)–H bonds.

Transition metal-free amination of C(sp^3)–H bonds. In the early 1880s, the first selective C(sp^3)–H amination was reported by Hofmann[28]. In 1909, Löffler and Freytag elaborated this transformation into a general method for preparation of pyrrolidines (HLF reaction)[29] (FIG. 2a). *N*-Haloamine salt **1** is subjected to heat, light or radical initiators, to produce NCR **2** via homolysis of the N–X bond. The latter undergoes intramolecular 1,5-HAT (**2** → **3**) with consequent *δ*-carbon radical trapping by a halogen atom to generate *δ*-halide **4**, which is cyclized to pyrrolidine **5** under basic conditions. It should be noted that although this method is quite powerful, it requires preparation of compounds possessing N–X bonds, which are much easier to activate than N–H bonds but require extra synthetic steps and use of non-commercially available reagents. Furthermore, the reagents or the haloamine or heteroamine salts themselves can be hazardous.

Modifications of the HLF reaction include the in situ generation of the corresponding N–I amide using iodine and a hypervalent iodine oxidant $PhI(OAc)_2$, as developed by Suárez and co-workers[30]. These reactions are usually biased towards electron-deficient substrates with protected nitrogen groups, which undergo functionalization at weak C(sp^3)–H bonds only (benzylic, tertiary, or α-heteroatom)[31–35].

In 2015, Herrera and co-workers further expanded the HLF reaction to achieve amination at primary C(sp^3)–H bonds[36]. Pyrrolidine **7** or 2-pyrrolidinone was produced by slow addition of $PhI(OAc)_2$ oxidant or iodine, respectively. Almost at the same time, a catalytic HLF reaction under visible light conditions was reported by Martínez and Muñiz, using catalytic iodine and stoichiometric hypervalent iodine oxidant PhI(*m*CBA)$_2$ (REF.[37]) (FIG. 2b, (i)). This method proved most efficient for weak benzylic (**6**), tertiary or *α*-to-oxy C(sp^3)–H bonds. A similar strategy was used by the Kanyiva and Shibata group for synthesis of 4-imidazolidinones[38]. A dual catalytic system involving molecular iodine (I_2) and photocatalyst (PC) was employed for intramolecular benzylic C(sp^3)–H amination in 2017 (FIG. 2b, (ii)). Here, the PC used was 2,4,6-triphenylpyrylium tetrafluoroborate (TPT), which preferentially effects the reoxidation of iodine co-catalyst, thus circumventing the use of stoichiometric hypervalent iodine oxidant[39]. The mechanism consists of two individual light-induced catalytic reactions. The disproportionation of I_2 in

wet medium produces the active hypoiodite catalyst, which initiates the formation of intermediate species **8** by *N*-iodination of substrate **6**. Under irradiation with visible light, the *N*-iodinated species **8** homolytically fragments into the amidyl radical species. Subsequent 1,5-HAT followed by radical chain iodine abstraction generates alkyl iodide **9**. Intramolecular substitution by sulfonamide yields desired pyrrolidine product **7** and hydroiodic acid. The latter is effectively reoxidized to molecular iodine by TPT in a single electron transfer (SET) process with molecular oxygen. The Stahl group also bypassed the use of undesirable stoichiometric oxidants, by merging photochemical and electrochemical methods for HLF-type amination of weak C(sp^3)–H bonds through the electrochemical oxidation of I^- to I_2 (REF.[40]). An iodine-catalysed Ritter-type amination of non-activated C(sp^3)–H bonds was recently reported, enabling the formation of 1,3-α-tertiary diamine **11** from **10**. The amination step is a Ritter reaction on a tertiary iodide, which is produced in a 1,6-HAT event from a sulfamidyl radical[41] (FIG. 2c).

Triiodide (I_3^-)-mediated δ-amination of unactivated secondary C(sp^3)–H bonds **12** to form pyrrolidines **13** was introduced by Nagib and co-workers[42] (FIG. 2d). Molecular iodine was generated in situ by combination of NaI and oxidant, which, in turn, forms I_3^- in the presence of excess I^-. Triiodide formation decreases the concentration of I_2 in solution, thus limiting the by-products derived from I_2 oxidation. This approach allows for selective amination of unactivated secondary C(sp^3)–H bonds in the δ-position, even when in competition with weaker tertiary bonds nearby. This phenomenon was attributed to the kinetic preference for a six-membered transition state. However, when a secondary and tertiary C–H bond were both at the δ-position, preference for the secondary bond homolysis was still observed, which was unanticipated. Interestingly, the use of NaBr or NaCl, in place of NaI, enabled formation

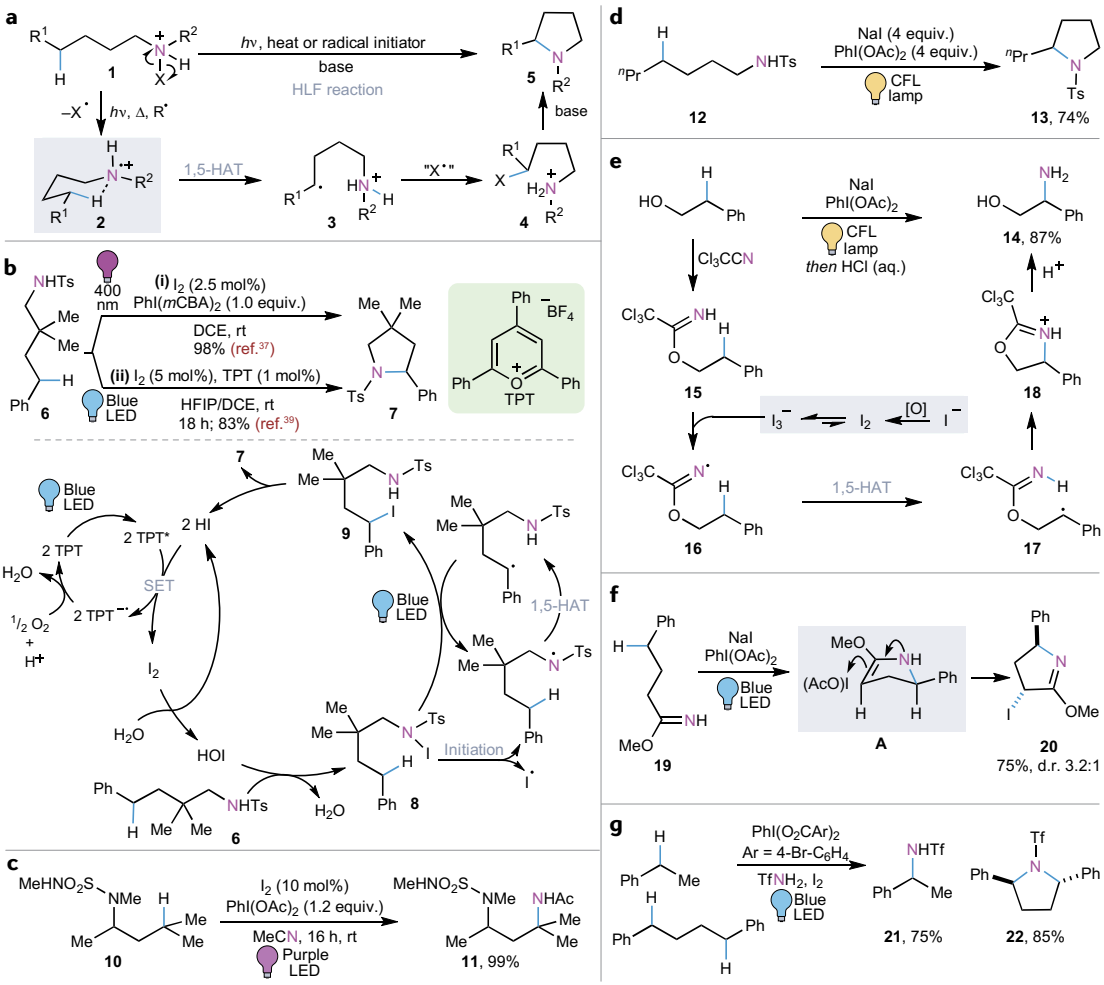

Fig. 2 | **Transition metal-free C(sp^3)–H amination. a** | Classic Hofmann–Löffler–Freytag (HLF) reaction. **b** | Iodine-catalysed HLF reaction and dual light-induced iodine and photoredox-catalysed intramolecular δ-amination of C(sp^3)–H and corresponding mechanism. **c** | Ritter-type amination of unactivated C(sp^3)–H bonds to form 1,3-α-tertiary diamines. **d** | Triiodide-mediated δ-amination of C(sp^3)–H bonds. **e** | Directed β-C(sp^3)–H amination of alcohols via radical relay chaperones. **f** | Synthesis of 4-iodo-3,4-dihydropyrrole derivatives via hydrogen atom transfer (HAT) strategy. **g** | Iodine-catalysed intermolecular amination of C(sp^3)–H and tandem iodine-catalysed twofold C(sp^3)–H amination to pyrrolidine. DCE, 1,2-dichloroethane; HFIP, 1,1,1,3,3,3-hexafluoroisopropanol; *m*CBA, 3-chlorobenzoate; SET, single electron transfer; Tf, trifluoromethanesulfonyl; $TfNH_2$, trifluoromethanesulfonamide; TPT, 2,4,6-triphenylpyrylium tetrafluoroborate; Ts, *p*-toluenesulfonyl.

of δ-carbon bromide and chloroamine intermediates, respectively.

Later, the same group developed β-C(sp^3)–H amination of alcohols via radical relay chaperones, mediated by NaI and a hypervalent iodine oxidant[43] (FIG. 2e). Phenylethanol addition to trichloroacetonitrile produced tethered acetimidate **15**, which afforded transient sp^2 NCR species **16** upon reaction with triiodide. The NCR undergoes 1,5-HAT (**17**) and subsequent radical trapping to form the oxazoline **18**, which can then be hydrolysed to β-amino-alcohol **14** under acidic conditions. With a benzimidate chaperone, the reaction occurred not only at weaker benzylic C(sp^3)–H bonds but also at unactivated secondary C(sp^3)–H bonds. Recently, the Shi group achieved similar transformations by phthaloyl peroxides (PPO) or malonoyl peroxides (MPO) and CsI under sunlight for β-selective and γ-selective aminations of imidates, and β-amination of amidines[44]. The mechanistic investigations confirmed a tether-tunable distonic radical anion-mediated approach. The authors excluded the triiodide, N–I bond cleavage and direct benzylic oxidation pathways. Later, Kumar et al. explored Nagib's strategy for intramolecular γ-amination of alkylimidates **19**, with unexpected diastereoselective iodination at the α-carbon[45] (FIG. 2f). Their proposed mechanism presumes that the pyrrolidine intermediate gives rise to the final product **20** via tautomerization of pyrrolidine to enamine species, followed by nucleophilic attack of enamine (**A**) on iodine monoacetate. The same group also developed the regioselective and diastereoselective approach for synthesis of bicyclic sugars via HLF-type amination, employing NaI/PhI(OAc)$_2$ or *N*-iodosuccinimide (NIS)/Cs_2CO_3 systems[46]. The iodine-catalysed β-amination of alcohols under thermal conditions was also disclosed by Nagib and co-workers[47], which exhibits faster and more efficient reactivity than their first-generation triiodide-mediated method[42]. Recently, they achieved a double functionalization of vicinal C(sp^3)–H bond in alcohols, induced by iodine and hypervalent iodine oxidant, wherein a β-amine and γ-iodide are incorporated into alcohols in a single operation[48]. The double functionalization is achieved by 1,5-HAT to produce a β-C(sp^3)–I bond. Then, molecular iodine complexation enables the formation of an allyl imidate, which can consequently undergo vicinal aminoiodination. The latter step is an example of haloamination of olefins, which is discussed later in this Review.

Muñiz and co-workers reported NIS as an efficient oxidant to promote intramolecular HLF amination, which is a valuable addition to the existing protocols relying on sodium iodide or hypervalent iodine[49]. Furthermore, *N*-bromosuccinimide (NBS) or dibrominated hydantoin could be used as the halogen promoter, but the desired pyrrolidines were obtained with unexpected dibrominated imine by-products. Moreover, homogeneous tetrabutylammonium bromide could catalyse intramolecular amination of weaker C(sp^3)–H bonds with stoichiometric *meta*-chloroperbenzoic acid (*m*-CPBA) under daylight[50]. The Muñiz group reported[51] that upon use of catalytic I_2 and stoichiometric NBS under visible light, 2-aryl-substituted piperidines were formed through catalytic intramolecular benzylic C(sp^3)–H amination instead of the expected pyrrolidines[25]. This process contains two catalytic cycles comprising a radical C–H abstraction at the benzylic position and iodine-catalysed C–N bond formation.

The HLF-type amination is not limited to intramolecular amination to form pyrrolidine derivatives, as it has also been explored intermolecularly. For example, selective intermolecular amination of ethylbenzene with trifluoromethanesulfonamide ($TfNH_2$) at weaker C–H bonds under a catalytic amount of iodine generates benzyl triflimide **21** (REF.[52]) (FIG. 2g). Furthermore, in the presence of two weak C–H bonds, two sequential C(sp^3)–H functionalizations (intermolecular and intramolecular) lead to pyrrolidine **22**. This represents a new approach towards *N*-heterocycles featuring multiple C–H aminations. Li and co-workers reported a rare hydrogen bonding charge transfer complex formed by NIS and sulfonamide to induce intermolecular C(sp^3)–H amination, while enabling an HAT relay strategy to access pyrrolidines directly from alkanes and sulfonamides[53]. Nicewicz and Alexanian succeeded in activating C–H bonds using radical traps to furnish aliphatic azides in the presence of organic acridinium PCs[54].

Transition metal-catalysed C(sp^3)–H amination. In the above-mentioned HLF-type C(sp^3)–H amination, the involved NCR was generated by iodine or triiodide. Homolysis of the N–X bond has also been achieved via an SET process by iridium photocatalysis. Thus, Qin and Yu demonstrated an HLF-type C(sp^3)–H amination of *N*-chlorosulfonamides **23** to pyrrolidines **24** in a weak basic solution with catalytic Ir-1 PC[55] (FIG. 3a). A solution of **23** was irradiated by white LED strips in the presence of PC and Na_2HPO_4. After addition of solid NaOH, the desired pyrrolidine **24** was obtained. Interestingly, C(sp^3)–H chlorination products were isolated without adding NaOH, indicating that the base promotes the intramolecular cyclization of chlorinated products, which is consistent with the early modified HLF reaction[29]. In 2019, Lu and co-workers developed a dual catalyst-controlled intramolecular amination of unactivated C(sp^3)–H bonds of carbamates **25** employing PC Ir-2 and Lewis acid catalyst[56] (FIG. 3b). The mechanism features an amidyl radical-enabled HLF-type 1,5-HAT to generate a carbon-centred radical, which is swiftly oxidized into a carbocation that is intramolecularly trapped by nitrogen nucleophiles to afford cyclization product. When $NiCl_2$ was used as the Lewis acid, intramolecular C–H amination product **26** was obtained. When $Zn(OTf)_2$ was used, however, the oxygenation product was produced. These results could be explained by the different coordination situations between metal ions and carbamates. The Ni^{2+} cation (ionic radius 69 pm) prefers to coordinate with the slightly 'harder' oxygen, thus decreasing its activity to give rise to amination product. In contrast, the Zn^{2+} cation (ionic radius 74 pm) favours coordination with the slightly 'softer' nitrogen, leading to the oxygenation product. Recently, an enantioselective β-amination of alcohols catalysed by a dual iridium triplet sensitizer and chiral copper catalyst under visible light was demonstrated by the Nagib group[57]. Feedstock aliphatic alcohols are transiently converted

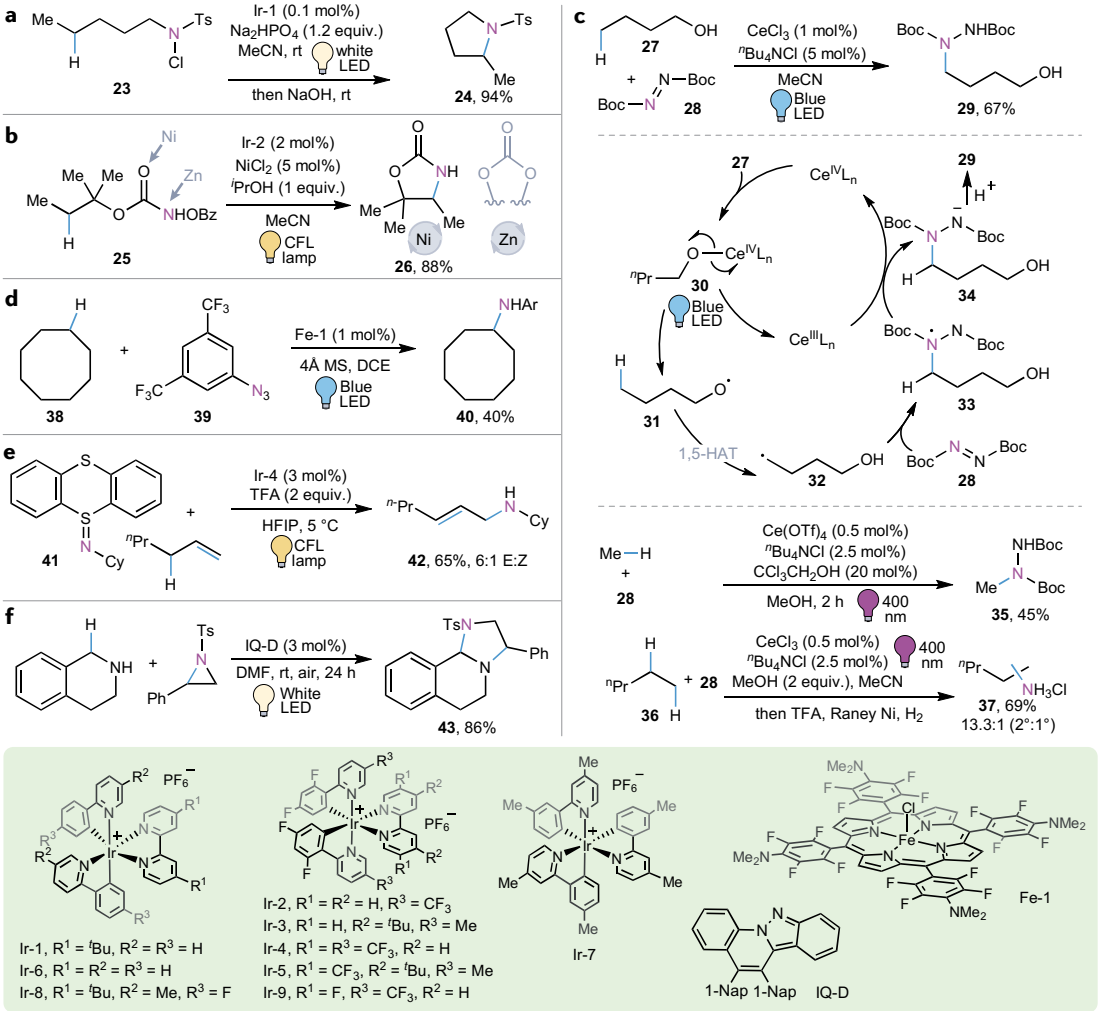

Fig. 3 | **Transition metal-catalysed amination of C(sp^3)–H. a** | Visible light-induced remote amination of *N*-chlorosulfonamides. **b** | Dual catalyst-controlled amination of carbamates. **c** | δ-Selective amination of primary alcohols enabled by visible light-induced ligand-to-metal charge transfer (LCMT) and proposed mechanism. Selective amination of alkanes by photoinduced LMCT-enabled hydrogen atom transfer (HAT) catalysis. **d** | Iron porphyrin-catalysed light-driven C(sp^3)–H amination. **e** | Allylic C(sp^3)–H amination enabled by thianthrenylideneamides. **f** | Assembly of fused imidazolidines via tandem ring opening/oxidative amination of aziridines. Boc, *tert*-butoxycarbonyl; Bz, benzoyl; DCE, 1,2-dichloroethane; DMF, *N*,*N*-dimethylformamide; HFIP, 1,1,1,3,3,3-hexafluoroisopropanol; MS, molecular sieve; 1-Nap, 1-naphthyl; TFA, trifluoroacetic acid; Ts, *p*-toluenesulfonyl.

into the corresponding imidate radical, which is coordinated with chiral copper complex, followed by regioselective and enantioselective HAT to furnish a new carbon-centred radical. After the stereoselective amination, enantioenriched oxazoline is afforded, which undergoes acidic hydrolysis to deliver β-amino-alcohol. This multi-catalytic, asymmetric, radical C–H amination showcases the remarkable utility of radical relay chaperone strategy.

An alternative strategy for C(sp^3)–H amination, using a LMCT approach, was explored by Zuo and co-workers[58]. They developed δ-amination of cyclic[59] and primary alcohols enabled by visible light-induced LMCT using an inexpensive cerium PC[60] (FIG. 3c). Under the reaction conditions, cerium(III) salt ($E_{1/2}(Ce^{III}/Ce^{IV})$ = 0.41 V versus SCE in CH_3CN) can be in situ activated by a photoinduced single electron oxidation with di-*tert*-butylazodicarboxylate **28** (E^* = 1.66 V versus SCE in CH_3CN). Primary alcohol **27** ligated to the cerium centre forges coordination complex **30**, which could undergo homolysis via excitation with visible light to generate transient alkoxy radical **31**. The latter engages in 1,5-HAT to produce nucleophilic alkyl radical **32**, which would readily couple with **28** to afford NCR **33**. Reduction of NCR **33** by cerium(III) regenerates the active catalyst and delivers the nitrogen anion **34**. Finally, δ-amination product **29** is formed upon protonation of **34**. Later, the Zuo group demonstrated the catalytic and selective amination of light alkanes (methane, ethane, propane and butane) under visible light irradiation at room temperature by LMCT-enabled HAT catalysis[61]. Simple alcohols, such as methanol or 2,2,2-trichloroethanol, act as the HAT catalysts, whereas cerium salts act as PCs to activate light alkanes. The turnover numbers of amination of methane and ethane are up to 2,900 and 9,700, respectively. This method

was then extended to higher and more complex liquid hydrocarbons to forge amination product **35** (REF.[62]). Non-cyclic alkanes such as **36** gave good degrees of stereocontrol for weaker secondary versus primary C–H bonds, to yield amination products **37** (FIG. 3c). More recently, Walsh, Schelter and co-workers confirmed the presence of the chlorine radical (Cl•), which forms [Cl•][alcohol] adducts when alcohols are present, exhibiting an alternative pathway for alkane amination catalysed by cerium[63].

Later, visible light-driven iron(III) porphyrin-catalysed selective C(sp^3)–H amination of aliphatic (**38**), allylic and benzylic C–H bonds with organic azides **39** was reported by the Che group[64] (FIG. 3d). Mechanistic studies revealed that iron porphyrin Fe-1 was both the light-absorbing species and the catalyst of the transformation via an iron-nitrene intermediate for subsequent C–N bond formation to yield **40**. The iron porphyrin can also catalyse the intramolecular C(sp^3)–H amination of alkyl azides and α-azidoketones or the aziridination of olefins with organic azides. The reactivity trend of C(sp^3)–H bonds was consistent with their bond dissociation energies (benzylic ≈ allylic > 3° > 2° > 1°). Bao and co-workers demonstrated similar iron-catalysed nitrene transformation for intermolecular C(sp^3)–H amination[65]. Contrastingly, this method avoids the use of organic azides by employing readily available and bench-top stable dioxazolones as nitrene precursors. However, the C(sp^3)–H substrates are limited to 1,3-dicarbonyl and diphenyl methane compounds. König and co-workers developed the photoinduced alkylation of amides and nitrogen nucleophiles with unactivated alkanes using a copper(II) peroxide catalytic system[66]. Upon light irradiation (385-390 nm), di-*tert*-butyl peroxide serves as an HAT reagent to activate alkanes for the reaction with various nitrogen nucleophiles.

Allylic C–H amination was previously accomplished only with (sulfon)amides or carbamates, as known synthetic methodologies were unsuccessful for alkylamines due to their incompatibility with the TMs used. Ritter and co-workers demonstrated the first allylic C–H amination reaction that can directly furnish alkyl allylamines, enabled by thianthrenylideneamines **41** (REF.[67]) (FIG. 3e). The mechanistic studies validated that the reaction occurred through NCR addition to the olefin, followed by radical recombination and deprotonation to deliver the allylic amination product **42**.

The use of aziridines as nitrogen sources was accomplished recently to synthesize imidazolidines **43** (FIG. 3f). Indazoquinoline PC was employed in a sequential stereospecific ring opening of strained systems, to activate C(sp^3)–H in secondary cyclic amines[68]. Notably, the open chain product was isolated in the absence of catalyst and light.

Amination of alkenes and strained systems

Olefin amination is a powerful approach to C(sp^3)–N bond construction, including intramolecular and intermolecular hydroamination, aziridination, haloamination, carboamination, aminohydroxylation[69,70], azotrifluoromethylation[71], diamination[72,73] and sulfoximidoyl amination[74]. Additionally, intramolecular alkene difunctionalization is a prevalent and highly useful strategy to access five-membered and six-membered azaheterocycles.

Intermolecular hydroamination. In 2013, the Nicewicz group published an organo-photocatalytic method to promote the oxidation of alkenes to a carbon-centred radical cation, which could be trapped intermolecularly by a pendant amine. The resulting transposed alkyl radical would then undergo HAT with a thiophenol hydrogen donor[75]. Later, this group succeeded to employ acridinium catalysts to achieve the intermolecular version of this reaction[76–78]. The same year, the Knowles group reported the aniline-derived aminium radical cation generated via single electron oxidation of arylamine by excited-state PCs, which efficiently underwent intramolecular addition to olefin acceptors[79,80]. In 2017, they developed this transformation for unactivated olefins with cyclic secondary alkylamines in an intermolecular setting[81] (FIG. 4a). The excited-state iridium PC (Ir-3) first oxidizes secondary amine to the corresponding aminium radical cation **45**, which then undergoes intermolecular addition to an olefin acceptor to forge a new C–N bond vicinal to carbon-centred radical **46**. This alkyl radical undergoes HAT with a thiol catalyst, to form intermediate **47** and a transient thiyl radical, which is quickly reduced by the PC to produce thiolate. The catalytic cycle is closed when the latter deprotonates the aminium ion to deliver the targeted tertiary amine product **44**. Knowles and co-workers also demonstrated the intermolecular anti-Markovnikov amination of unactivated olefins with primary alkylamines to produce secondary alkylamines via aminium radical cation intermediates[82]. Despite the presence of excess olefin, only secondary amines were observed, instead of the undesired tertiary amines, due to the superior reactivity of the primary aminium radical cation over that of the secondary. Additionally, as depicted in FIG. 4b, they developed a version of this reaction to form compound **48** with primary and secondary sulfonamides, enabled by proton-coupled electron transfer (PCET)[83,84]. Based on the mechanistic studies and previous work[85], they proposed that the NCR was generated via concerted PCET activation of the sulfonamide N–H bond[86]. This work nicely illustrates the potential of PCET processes for activation of strong heteroatom–hydrogen bonds to generate radicals that undergo intermolecular and intramolecular transformations. In the next section, we further discuss the intramolecular aminocyclization of olefins via PCET. More recently, Doyle and co-workers disclosed intermolecular anti-Markovnikov amination of unactivated olefins, using a dual phosphine and photoredox catalytic system, generating NCR via α-scission of the P–N bond of a phosphoranyl radical intermediate, formed by sulfonamide and a phosphine radical cation[87].

The Studer group reported anti-Markovnikov hydroamidation and deuteroamidation of unactivated alkenes by cooperative photoredox and thiol catalysis[88]. Carbobenzyloxyl (Cbz)-protected α-amido-oxy acids were oxidized by a PC to produce carboxyl radical. Upon fragmentation, the resulting NCR was added to

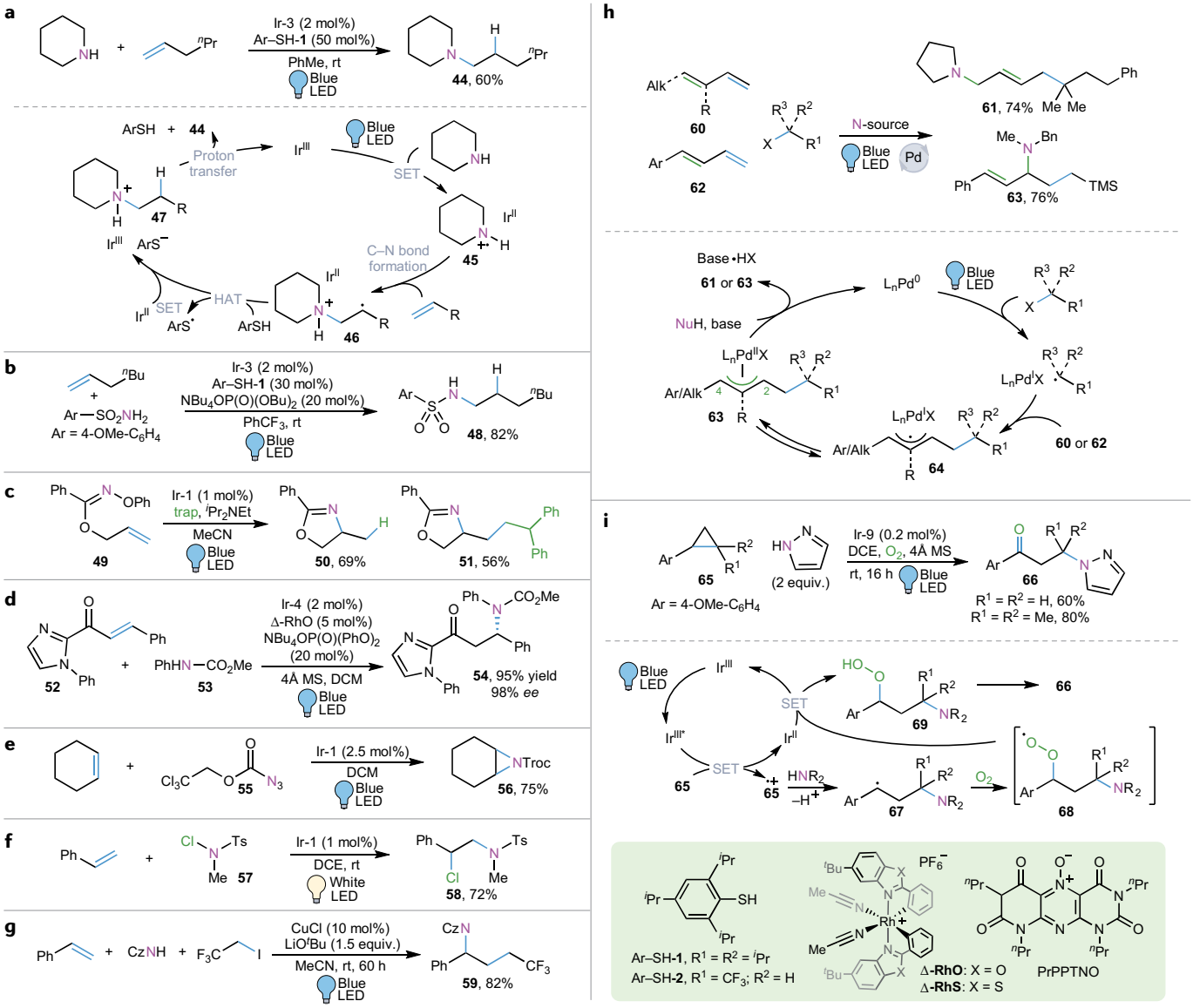

Fig. 4 | **Photoinduced intermolecular amination of olefins and strained systems. a** | Intermolecular anti-Markovnikov hydroamination of unactivated olefins with secondary amines via aminium radical cation. **b** | Intermolecular anti-Markovnikov hydroamination of unactivated olefins with sulfonamide via nitrogen-centred radical (NCR). **c** | Hydroamination and alkylamination of allylic alcohols via radical relay. **d** | Enantioselective hydroamination of α,β-unsaturated carbonyl compounds. **e** | Photocatalytic aziridination of olefins with in situ generated triplet nitrenes from azidoformates. **f** | Haloamination of styrene with *N*-chlorosulfonamides as both nitrogen and chlorine sources under photoredox catalysis. **g** | Copper-catalysed three-component intermolecular carboamination of alkenes induced by visible light. **h** | Photoinduced three-component 1,2-alkylamination of 1,3-dienes catalysed by palladium under visible light. **i** | Photocatalyzed oxo-amination of aryl cyclopropanes. Bz, benzoyl; Cz, carbazoyl; DCE, 1,2-dichloroethane; DCM, dichloromethane; HAT, hydrogen atom transfer; MS, molecular sieve; PrPPTN, pyrimidopteridine; SET, single electron transfer; TMS, trimethylsilyl.

olefins to give the corresponding alkyl radical adduct, followed by reduction with thiol to afford the hydroamination product. In addition, the anti-Markovnikov hydroazidation of styrene derivatives catalysed by an organic acridinium salt under irradiation from blue LEDs was demonstrated by Nicewicz and co-workers[89]. Recently, photoredox-catalysed phosphite promoted anti-Markovnikov olefin hydroamination with *N*-hydroxyphthalimide (NHPI) was reported. Direct cleavage of NHPI was initiated by PCET via PhthNO–phosphine adduct in the presence of phosphines[90]. Moreover, the additive-free hydroamination of stilbenes with primary amines catalysed by pyrimidopteridine (PrPPTN) (FIG. 4) was disclosed, in which the catalyst serves as a dual photoredox and HAT catalyst[91].

The Zhang[92] and Zeng[93] groups demonstrated visible light-induced Markovnikov hydroamination of styrenes by copper and TPT catalyst, respectively. Zhang and co-workers used 9*H*-carbozole as a nitrogen source, which formed a complex with copper salt and styrene to generate PC in situ. Mechanistic studies suggested that HAT from acetonitrile solvent may be involved in the hydroamination pathway, giving rise to a stable benzylic radical, which subsequently couples with nucleophilic amine to afford a Markovnikov hydroamination product. Zeng and co-workers proposed that photoexcited alkene

under green light could trap a proton to produce alkyl carbocation in the presence of Brønsted acid, which subsequently reacted with amine to give the Markovnikov hydroamination product. Noting that the transformation still afforded 49–57% yield of hydroamination product without PC and photoirradiation, they suggested that the Brønsted acid promoted the intermolecular hydroamination to a certain degree. Excited-state 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) abstracted a hydrogen atom by homolytic cleavage of N–H bond in *N*-alkoxyamides to furnish the amidyl radical and DDQH[94,95]. The amidyl radical then added to enol ethers to produce the hydroamination product. This reaction constitutes a metal and peroxide-free catalytic hydroamination reaction[94]. Recently, Markovnikov hydroamination of styrenes with nitrogen-based heterocycles employing visible light-mediated cobalt/ruthenium dual catalysis was developed by the Zhu group[96]. The key step involves photochemical oxidation of cobalt(III) species derived from HAT. In this protocol, a hypervalent iodine reagent or *N*-fluoropyridinium salt works as an oxidant to complete the catalytic cycle.

Difunctionalization of allylic alcohols by photocatalytic reduction of their oxime imidates was demonstrated by Nagib and co-workers[97,98] (FIG. 4c). Oxime imidate **49**, prepared from 2-propen-1-ol in one step, generated the imidate radical catalysed by Ir-1. Intramolecular amination followed by trapping with hydrogen atom donor 1,4-cyclohexadiene (CHD), olefin acceptor or cyanoarene then furnishes the respective hydroamination **50**, aminoalkylation **51** or aminoarylation products. Yu, Zhou and co-workers later reported the use of Rose Bengal (RB) as the organic PC in this type of transformation[99].

As summarized above, olefin hydroamination has been extensively reported, but there are very few examples of its enantioselective equivalent. Gong, Meggers and co-workers demonstrated the enantioselective hydroamination of α,β-unsaturated 2-acyl imidazoles **52** with *N*-aryl carbamic acid esters **53** using iridium photoredox catalyst (Ir-4) in combination with chiral at rhodium Lewis acid catalyst Δ-RhO and a weak phosphate base, leading to β-amination product **54** with excellent yield and enantioselectivity[100] (FIG. 4d). The reaction occurred via a photoinduced PCET process, followed by highly stereoselective radical cross-recombination controlled by a chiral rhodium-enolate radical intermediate. In this transformation, the imidazole substituent in the substrates is necessary for coordination with the rhodium centre in the stereoselectivity determining step, which limits the application of this method to some extent. Recently, Hyster et al. reported a dual photocatalytic and biocatalytic method to achieve highly enantioselective hydroamination products using complementary (*R*)-selective and (*S*)-selective enzymes[101].

Aziridination. Aziridines are versatile intermediates in the synthesis of nitrogen-containing compounds. Photocatalytic olefin aziridination via visible light triplet sensitization of azidoformate **55** was developed by Yoon and co-workers[102]. Aliphatic and aromatic alkenes, as limiting reagents, can be aziridinated under facile batch conditions to form products **56** (FIG. 4e). Unlike acyl azides, nitrenes derived from azidoformates have little access to Curtius-type rearrangements. Besides, azidoformates are less easily reduced than acyl azides, which should disfavour azide decomposition by photo reductive pathways. Moreover, azidoformate with electron-withdrawing substituent increased the rate of aziridination. Later, Lu and co-workers, inspired by Yoon's work, demonstrated visible light-induced intramolecular aziridination reactions of *o*-allylphenyl azidoformates to afford [5.1.0]-bicyclic aziridines[103]. The aziridines were obtained via visible light-induced functionalization of styrene derivatives with nitrogen-protected aminopyridinium salts as NCRs, as reported by the Xu group[104]. The mechanistic studies revealed that the NCR species is generated via reduction by the iridium excited state. According to the proposed mechanism, the electrophilic radical adds to olefins to give rise to a carbon-centred radical, which is oxidized to form the stabilized carbocationic intermediate that is intramolecularly trapped by the nitrogen nucleophile to deliver the aziridine product.

Haloamination. Vicinal haloamine derivatives can be used for functional materials and for synthesis of biologically active compounds[105]. Yu and co-workers disclosed chloramination of olefins with *N*-chlorosulfonamides **57** as both the nitrogen and chlorine sources under photoredox catalysis, which is an atom-economical approach for synthesis of vicinal haloamines[106] (FIG. 4f). NCR generated from reduction of **57** by Ir-1 PC adds to aryl or aliphatic olefins to afford a carbon-centred radical. The latter can undergo chlorine atom abstraction from **57**, or oxidation to carbocation and trapping by chloride, to arrive at vicinal chloramines **58**. The Luo group used *N*-bromosaccharin or *N*-chlorosaccharin with olefins under ambient light to generate haloamines and haloethers together, which could be separated by column chromatography[107]. In addition, with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the base, a clean imidation product was obtained via a one-pot radical addition–elimination protocol. Hu, Xu and co-workers developed a three-component haloamination of olefins under photoredox catalysis[108]. *N*-*p*-toluenesulfonyl (Ts)-protected 1-aminopyridine salt was used as the nitrogen radical precursor, and the commercially available hydrogen fluoride-pyridine or hydrogen chloride-pyridine was used as the nucleophilic halide source. New hypervalent iodine(III) reagents in situ generated from difluoroiodotoluene and *NH*-sulfoximines could also be used as nitrogen and fluorine sources to give the fluoro-sulfoximidation product of styrenes[109]. Recently, Ruffoni, Leonori and co-workers demonstrated the vicinal chloroamination of olefins with N-chlorosuccinimide (NCS) and cycloamine under photo redox catalysis. The resulting β-chloroamines are powerful building blocks for further transformations to the corresponding aziridinium ions. The latter intermediates can then undergo in situ ring-opening reaction with primary, secondary and aromatic amine nucleophiles to produce regioselective vicinal diamine products[110]. This strategy streamlined the preparation

of vicinal diamines in a single chemical operation. Intermolecular azido-hydrazination of unactivated alkenes through a selective radical addition sequence can also be used to construct vicinal diamines under visible light[111]. For this purpose, fluorenone has been discovered as a powerful catalyst to generate azide radical from $TMSN_3$ under visible light. An azide radical would add to olefins to furnish the alkyl radical intermediate, which is captured by azodicarboxylate and, subsequently, quenched by methanol to give rise to the final product.

Carboamination. Carboamination of olefins is a powerful method for production of commodity chemicals. Zhang and co-workers reported three-component carboamination of olefins catalysed by copper under visible light, leading to valuable fluoroalkyl-containing amines **59** (REF.[112]) (FIG. 4g). When the reaction involved styrene derivatives, 9*H*-carbozole and 1,1,1-trifluoro-2-iodoethane, inexpensive CuCl was used as the sole PC and coupling catalyst. When employing a further reduced π-system such as simple indoline as a nucleophile, the capability of the resulting Cu–Nu complex in photoexcitation or coupling was decreased, which was remedied by adding *rac*-BINOL.

1,3-Dienes are readily available versatile building blocks, which have tremendous applications in synthesis, medical chemistry and materials. The difunctionalization of 1,3-dienes provided rapid access to complex molecules in one step, which also could be induced by visible light. Glorius and co-workers reported 1,4-aminoalkylation of 1,3-dienes with NHPI esters as a nitrogen and alkyl source under visible light via π-allylpalladium intermediates[113]. Later, the same group developed a palladium-catalysed three-component 1,4-aminoalkylation of 1,3-dienes **60** involving unactivated tertiary alkyl halides and amine nucleophiles under visible light to afford compounds **61** (REF.[114]) (FIG. 4h). Nucleophiles based on oxygen, sulfur and carbon could all be tolerated in this transformation. Simultaneously, the Gevorgyan group demonstrated the 1,2-aminoalkylation variant of this transformation using 1,3-dienes **62** under visible light with alkyl iodides and nitrogen, carbon or oxygen nucleophiles[115]. Photoexcited palladium(0) undergoes SET with alkyl halide to produce alkyl palladium radical species, which adds to the terminal position of 1,3-dienes to produce allylic radical species **64**, in equilibrium with π-allylpalladium complex **65**. Subsequent nucleophilic attack at the 4 or 2-position yields products **61** or **63**, respectively. Gaunt and co-workers reported a multicomponent dual catalytic strategy to achieve arylazidation of alkenes, employing a copper-based PC for initial radical arylation, and a group transfer catalyst for anionic azide group transfer[116].

Strained systems. An emerging tool for C(sp^3)–N bond formation lies in exploiting strained systems for dual functionalization, as they are thermodynamically inclined to release their ring strain. Nonetheless, the challenge in controlling selectivity and regiochemistry of activation has limited this approach to one recent example to produce compounds **66** from electronically biased **65** (REF.[117]) (FIG. 4i). Aryl cyclopropanes **65** can be oxidized by SET from Ir-9 PC to produce radical cation intermediate $\mathbf{65}^{\bullet+}$, which is posed for a concerted ring opening and nucleophilic attack by pyrazole, leading to transposed benzylic radical **67**. Radical combination with oxygen gas results in alkylperoxide radical intermediate **68**, which will oxidize and regenerate catalyst to form entity **69**. Further oxidation affords β-amino ketones **66** in good yields.

Intramolecular azaheterocycle synthesis. The recent advent of NCR chemistry under synthetically useful conditions has brought radical cascades to the forefront towards synthesis of highly valuable five-membered and six-membered heterocycles. PCET, a process involving the reductive or oxidative transfer of an electron and a proton at the same time, has become a useful tool to access these scaffolds. Although PCET has been extensively exploited in biology, inorganic chemistry and solar energy conversion, its use in the context of synthetic organic chemistry was not well developed until the Knowles group reported a series of elegant works[83,118–121] (FIG. 5a). To cleave the strong N–H bond of sulfonyl-protected *N*-aryl/alkylamide **70** and generate an NCR that can engage in radical cyclization and alkene functionalization, a dual catalytic system of iridium PC and a phosphate base is required. Thiophenol can then be used as a hydrogen source to yield hydroamination product **71** (REFS.[119,120]). Alternatively, radical traps can yield a new C–C or C–heteroatom bond (**72**)[121,122]. Asymmetric induction was later accomplished using chiral phosphoric acid (CPA-1) in a benchmark transformation[83] to produce compound **73** in excellent yield and enantioselectivity[118].

Molander, Hong and co-workers approached the regioselective and stereoselective 1,2-aminoacylation of olefins with a combined nickel/PCET catalytic system to synthesize compounds **75** from **74** (REF.[123]) (FIG. 5b). This mild protocol obviates the use of carbon monoxide reagent, which had until then represented a major limitation in the construction of these types of molecules. Commercially accessible acyl electrophiles, such as alkyl and aryl acyl chlorides, anhydrides and carboxylic acids were successfully applied. Mechanistic studies validated the PCET step between amide and iridium/phosphate and rationalized the diastereoselectivity-determining step that resulted in the kinetic product. A metal-free reaction featuring diazonium salt as an oxidant and electrophilic nitrogen source under blue light was later reported, converting phenyl carbamates **76** into diamines **77** through intramolecular amidyl radical addition to olefins[124].

The use of NCR in a cascade reaction, reported by Stephenson and co-workers, achieved diastereoselective arene dearomatization to produce fused sultams **79** (REF.[125]). Formation of an electrophilic oxygen radical by SET between Ir-4 PC and a phosphate base enables amide hydrogen abstraction to produce NCR from **78**, which is trapped by the pendant alkene. The resulting transposed primary radical then cyclizes into the arene, to produce a stabilized cyclohexadienyl radical. The catalytic cycle is closed upon single electron reduction with PC to form an anion, which is protonated by *tert*-butanol, as confirmed by deuterium labelling studies. This catalytic cycle contrasts with that proposed by

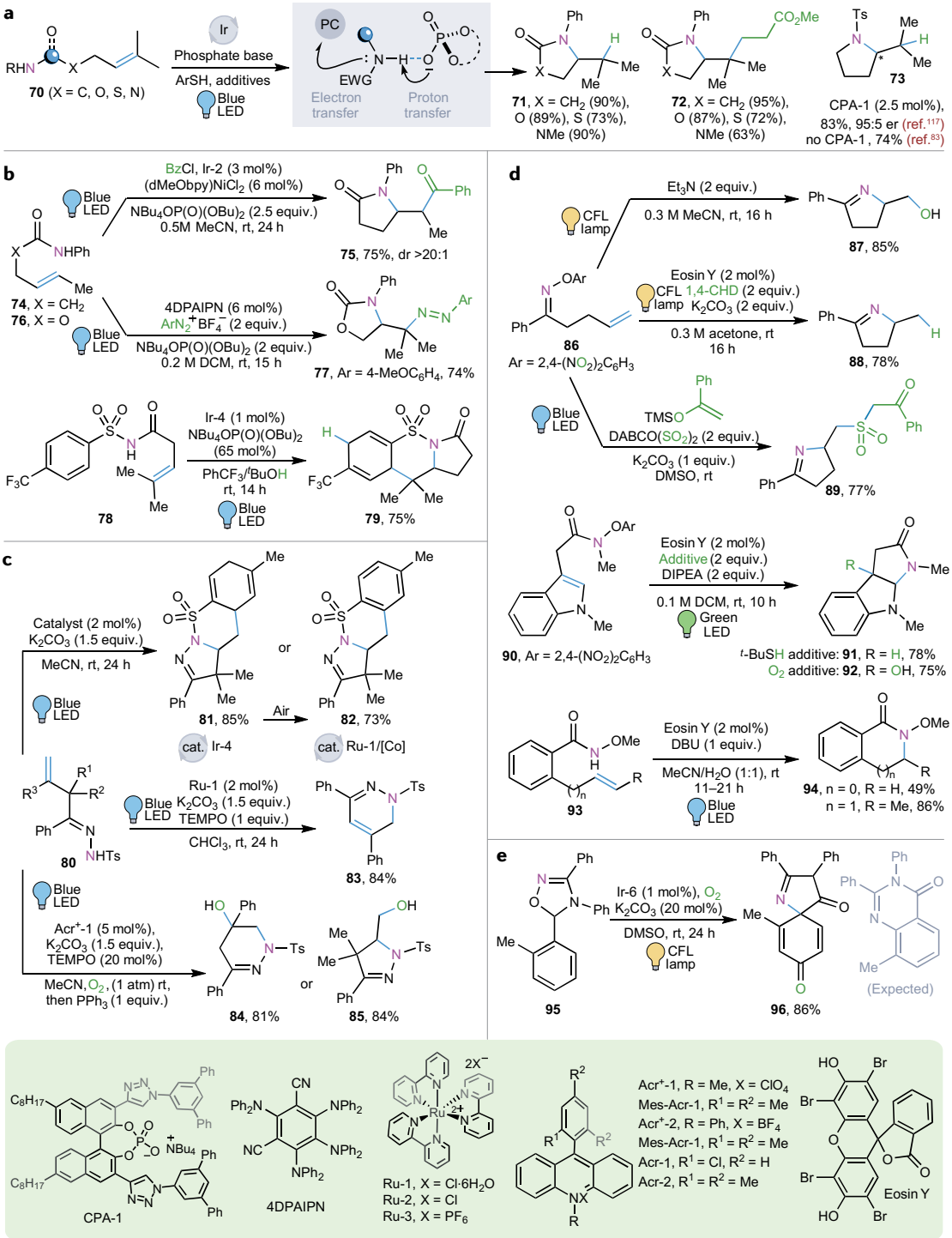

Fig. 5 | **Intramolecular synthesis of five-membered and six-membered azaheterocycles from alkenes. a** | Catalytic olefin hydroamidation and carboamidation. **b** | Selective 1,2-diamination, aminoacylation and aminoalkylation of olefins. **c** | Rhodium and iridium-catalysed synthesis of five-membered and six-membered azaheterocycles. **d** | Eosin Y-catalysed syntheses of azaheterocycles. **e** | Remote double functionalization of arenes facilitated by singlet oxygen. CHD, 1,4-cyclohexadiene; CPA-1, chiral phosphoric acid; DBU, 1,8-diazabicyclo[5.4.0]-7-undecene; DCM, dichloromethane; DIPEA, *N*,*N*-diisopropylethylamine; DMSO, dimethylsulfoxide; PC, photocatalyst; TEMPO, 2,2,6,6-tetramethyl-1-piperidinyloxy; Ts, *p*-toluenesulfonyl.

the Knowles group[83], likely due to the acidity differences between their substrates.

Tosyl hydrazones **80** were found by Chen, Xiao and co-workers to undergo base-mediated deprotonation followed by electron transfer to PC to furnish an NCR that can be further functionalized, generally in a catalyst-dependent manner[126] (FIG. 5c). This versatile approach, dubbed oxidative deprotonation electron

transfer, was explored in the context of five-membered and six-membered heterocycle synthesis, stemming from benchmark substrate type **80**. For instance, synthesis of dearomatized heterocycle **81** was achieved using Ir-4. This product could then be oxidized under aerobic conditions to produce **82** or accessed directly using a Ru-1/[Co] catalytic system[127]. Such radical cascades were also successful vehicles for synthesis of dihydropyrazoles in a redox neutral process without exogenous oxidants[128]; by radical hydroamination[129]; or via cascade allylation[130]. The latter method could also produce tetrahydropyridazines. Additionally, Ru-1 PC and stoichiometric amounts of 2,2,6,6-tetra methyl-1-piperidinyloxy (TEMPO) could be used to obtain the analogous 1,6-dihydropyridazines **83** (REF.[131]). TM-free conditions with molecular oxygen as a mild oxidant could afford 2,3,4,5-tetrahydropyridazines **84** and 4,5-dihydro-1*H*-pyrazoles **85** in a selective olefin oxyamination through two SET processes[132].

Moving away from TM PCs to benign organophotocatalysts has been a useful strategy to produce five-membered and six-membered azaheterocycles (FIG. 5d). The development of organo-photoredox reactions of aryloxy amides and oximes for generation of NCRs and their use in intramolecular hydroamination, hydroimination, iminohydroxylation and intermolecular *N*-arylation reactions was reported for the first time by Leonori and co-workers[133,134]. Evaluation of the redox profiles of various aryl oximes with the goal of identifying the most suitable/active substrates by cyclic voltammetry revealed irreversible reduction profiles that are in accordance with the expected fragmentation process. Almost all of the oximes examined by the authors were expected to undergo SET reduction by excited iridium(III) species[134], whereas only the nitro-substituted substrates have $E_{1/2}^{red}$ potentials compatible with excited eosin Y PC. They chose the most reactive 2,4-dinitro-substituted substrate **86**. The experimental observations indicated a unique trifunctional role of the nitroaromatic unit of the *O*-aryl oximes, which sequentially serves as a sensitizer, electron acceptor and oxidant. This enabled the development of triethylamine and visible light-mediated iminohydroxylation cyclization into dyhydropyrroles **87** and **88**. An important modification of this reaction achieved synthesis of sulfonylated *N*-heterocycle **89** through an unprecedented nitrogen radical-mediated cyclization of **86** by insertion of sulfur dioxide under PC-free conditions[135]. The reaction starts from the formation of an iminyl radical under visible light and subsequent tandem addition of the iminyl radical to unactivated alkene and sulfur dioxide. The resulting sulfonyl radical is trapped by a silyl enolate, leading to sulfonylated dyhydropyrrole **89**. Thus, synthesis of pyrrolidin-2-ones, oxazolidin-2-ones and thiazolidin-2-ones was achieved, using optimized conditions from the same general methodology[133]. This protocol was applied to indolilamide **90** to produce amidyl radical that can be treated with *tert*-BuSH to form **91**, or molecular oxygen to form **92** (REF.[136]). Conformationally rigid *N*-alkoxyamides **93** prefer thermodynamically driven cyclization to *δ*-lactams **94** (REF.[137]). Unlike all of the above-mentioned iridium/ruthenium-catalysed protocols that use blue LED light, the use of eosin Y is also effective under green LED and CFL irradiation. Yuan, Yu and co-workers extended this chemistry to the iminoalkylation of oximes using iridium catalysis and alkenylboronic acids to produce (*E*) and (*Z*)-cinnamylpyrrolidines selectively. The origin for isomer selectivity was the change in mechanism, where SET occurred in dichloromethane (DCM) solvent, and energy transfer when using THF solvent[138].

In contrast to the established approaches using SET for NCR generation, Cho, You and co-workers reported the first synthesis of difunctionalized spiro-azalactams **96** by photocatalytic energy transfer from easily accessible heterocycles (**95**), as validated by mechanistic studies[139] (FIG. 5e). Reaction of the excited state of **95** with singlet oxygen results in fragmentation to produce peroxide and imidyl radicals. The latter undergoes dearomatization/spirocyclization by selective ipso attack, instead of the expected homolytic aromatic substitution reaction. This unprecedented step affords the cyclohexadienyl radical that can be intermolecularly trapped by previously generated peroxide radical species to produce the desired **96**.

Amination of carbonyl compounds

Synthesis of amines from readily available carbonyl precursors is a reliable and widely used approach. Major limitations such as reagent toxicity and lack of generalizable and robust methods have been addressed by the use of photocatalysis.

Reductive amination and related methods. Despite its great utility, reductive amination of carbonyl compounds and their derivatives has been dependent on toxic and impractical reductants such as sodium cyanoborohydride. New efforts towards a more benign strategy for reductive amination have been recently reported, pairing visible light conditions with milder reducing agents, such as molecular hydrogen, silanes, formates or Hantzsch esters (HEs)[11].

Photochemical reductive amination involves a highly unstable *α*-aminoalkyl radical as the key intermediate. Thus, it is crucial to intercept it with a fast, hopefully irreversible step, to avoid unproductive side reactions. Wenger, Guo and co-workers employed radical polarity matching for this purpose[11] (FIG. 6a). The Ru-2 photocatalytic system relied on ascorbic acid ($AscH_2$) to reduce iminium cation produced in situ from alkyl carbonyl substrate and aniline to access nucleophilic *α*-aminoalkyl radical intermediate **97**. This electrophilic radical will abstract the most hydridic hydrogen from thiol (87.4 kcal mol^{-1}) over the weaker O–H bond (72.3 kcal mol^{-1}) with a more protic hydrogen from ascorbate ($AscH^-$). Nonetheless, product **98** formation requires the fast and irreversible reduction of the formed thiyl radical, carried out by ascorbate. This way, the equilibrium of the reversible first HAT step can be pushed forward by thiol regeneration[140]. The complementary extension of this chemistry to tolerate aryl aldehydes was realized to obtain benzylamines **99** using Ir-2 PC, Lewis acid and water scavenger additive boron trioxide, even without the use of exogenous hydrogen sources in certain cases[141] (FIG. 6b).

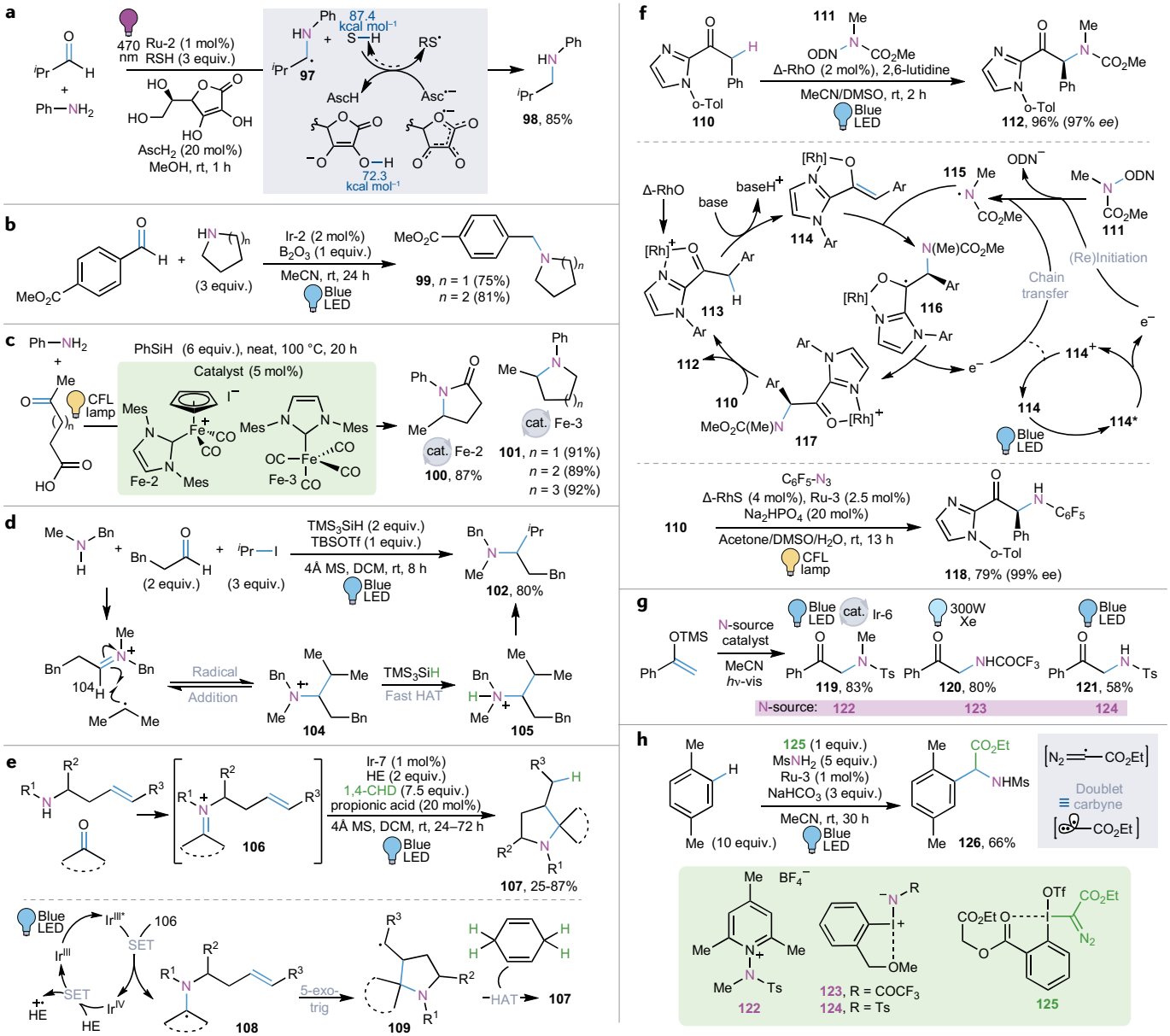

Fig. 6 | **Reductive amination of carbonyl compounds and direct α-amination of carbonyl compounds and their enol derivatives. a** | First reductive amination of aldehydes and ketones with amines by photoredox catalysis. **b** | Photocatalyzed direct reductive amination of aldehydes without external hydrogen/hydride source. **c** | Iron-catalysed switchable synthesis of pyrrolidines versus pyrrolidinones by reductive amination of levulinic acid derivatives via hydrosilylation. **d** | Carbonyl alkylative amination for synthesis of complex tertiary alkylamines. **e** | Synthesis of C(sp^3)-rich N-heterospirocycles enabled by visible light-mediated photocatalysis. **f** | Enantioselective radical amination of ketones activated by visible light. **g** | Photochemical amination of silyl enol ethers by *N*-aminopyridinium salts and *N*-acyliminoiodinanes. **h** | Photocatalytic synthesis of amino acid derivatives using carbyne equivalents. CHD, 1,4-cyclohexadiene; DCM, dichloromethane; DMSO, dimethylsulfoxide; HAT, hydrogen atom transfer; HE, Hantzsch ester; MS, molecular sieve; ODN, 2,4-dinitrophenylsulfonate; SET, single electron transfer; Tf, trifluoromethanesulfonyl; Ts, *p*-toluenesulfonyl.

The intramolecular version of reductive amination was reported by Darcel and co-workers. The transformation, although carried out neat under thermal conditions and CFL lamps, featured catalyst-controlled chemoselectivity. Thus, the authors reported access to either pyrrolidinone **100** or pyrrolidines **101** from levulinic acid derivatives, using established NHC iron complexes Fe-2 and Fe-3, respectively[142] (FIG. 6c).

Previously unknown but highly sought-after carbonyl alkylative amination is a valuable new application of light-induced technology towards synthesis of tertiary amines **102**. The Gaunt group achieved this process from in situ enamine generation in the presence of super silane, TBSOTf and visible light, which unexpectedly resulted in reaction initiation via homolysis of the C(sp^3)–I bond to form an alkyl radical. The latter then undergoes reversible addition to intermediate **103** to form alkyl amine radical cation **104**. This can be quickly intercepted by rapid HAT from super silane to yield ammonium **105** on the way to the desired tertiary alkylamines **102**. This protocol enables access to a diverse scope of tertiary amines, inherent to its three inexpensive and/or feedstock

components[143] (FIG. 6d). The trifluoromethylative version of this reaction was disclosed by the same group to access β-trifluoromethyl tertiary alkylamines[144]. Valuable *N*-heterospirocycles **107** were obtained in a reductive aminocyclization from feedstock ketones and secondary amines, which form iminium **106** in situ (FIG. 6e). The proposed mechanistic pathway involves SET to **106** in an oxidative quenching step by the excited state of Ir-7 PC to form secondary α-aminoalkyl radical **108** and iridium(IV). A subsequent *5-exo-trig* cyclization forms transposed primary radical **109**, which abstracts a hydrogen atom from CHD to afford **107**. The catalyst regeneration is then aided by HE[145,146]. Dixon and co-workers published a series of works involving the reductive alkylative amination of amides in a two-electron fashion[147–150]. Recently, they merged their iridium hydrosilylation strategy with a photocatalysed SET approach to achieve synthesis of α-functionalized tertiary amines[151]. They also developed a diastereodivergent carbocyclization leading to bicyclic aminoindanes or tetracyclic tetrahydroquinolines in a substrate-controlled manner, using blue LEDs and HE reductant[152]. The Hyster group reported a photobiocatalytic approach towards enantioenriched α-tertiary amines via addition of carbon-centred radicals to ketimines[153].

Direct α-carbonyl amination. A natural next step in photocatalysis for the utilization of feedstock carbonyl compounds would be their direct functionalization. Although this is a promising methodology, there are only a few reports in this area. One such example is photoinduced enantioselective transformation, using an amidyl radical precursor, which interacts with a catalytic amount of chiral enamine to translate stereochemical information into the final product[154]. The use of this electrophilic nitrogen-functionalized carbamate **111** was reported by Meggers and co-workers to produce compounds **112** from **110** (REFS.[155,156]) (FIG. 6f). Acyl imidazole derivatives **110** engage the Δ-RhO catalyst, which was favoured over iridium for its faster ligand exchange kinetics. The resulting rhodacycle **113** is then deprotonated to reveal enolate **114**, named a 'smart initiator' by Curran and Studer because it plays two roles in this cycle[157]. First, **114** undergoes stereoselective radical addition with the electrophilic radical **115** that results from the homolysis of **111**, to produce stabilized radical **116**. The second task of **114** is as a photosensitizer: oxidative quenching of the excited state of this intermediate (**114*** + **111** → **115**) initiates or reinitiates this transformation. A way to propagate this reaction could also be from the electron loss of **116** in a radical chain reaction that would also lead to **115** to produce cationic intermediate **117**. Alternatively, the electron could be transferred to **114**$^+$ to close the photoredox cycle. Ligand exchange with a second equivalent of substrate **110** releases product **112** and restarts the amination catalytic cycle. In the absence of a smart initiator, aryl azide and ruthenium may serve as the nitrogen source and PC, respectively, to form **113** with excellent enantioselectivity.

Another rare example in this category involves radical addition of electron-rich π-systems to NCR, generated from aminopyridinium salt **122** (REF.[158]) or hypervalent iodine reagents **123** and **124** (REF.[159]) (FIG. 6g). For example, silyl enol ether benchmark substrate can be converted to differently protected α-amino ketones **119**–**121**, privileged products towards synthesis of bioactive molecules and unnatural amino acids. In the case of iodinanes, the nitrogen source was stabilized by methoxy group participation in coordination with the iodine atom from the *ortho*-position of the arene, which enabled the first isolation and characterization of these compounds[159].

Hypervalent iodine reagent **125** was used by the Suero group, not as an iodine source but as a carbyne equivalent (FIG. 6h). The result is a double functionalization reaction that activates the C(sp^2)–H bond in arenes to produce protected amino acid esters **126**. Light-induced decomposition of the azoester in **125** yields a diazomethyl radical capable of dearomative radical addition to the arene, which upon proton loss generates an azido prochiral intermediate that can be aminated with the nitrogen source ($MsNH_2$)[160].

Cross-couplings

Visible light-induced cross-couplings have become a powerful strategy to build C(sp^3)–N bonds, allowing access to both carbon-centred radicals and NCRs under mild conditions, which upon trapping or recombination can form privileged products directly from feedstock chemicals.

Decarboxylative couplings. Decarboxylation has been a useful handle for functionalization, such as in the Curtius rearrangement, Hunsdiecker reaction or Barton decarboxylation. Now, the one-electron oxidation/decarboxylation pathway is gaining fast rapport in photocatalysis.

Recent developments of photoredox chemistry allow for the generation of carbon-centred radicals from feedstock 1°, 2° and 3° carboxylic acids **127** through single electron oxidation of carboxylates. In this context, the generated nucleophilic carbon-centred radicals easily react with various electrophilic heteroatoms or other radical acceptors[161]. This pathway, when combined with copper catalysis, was disclosed by the MacMillan[162] and Larionov[163] groups as an important solution to the long-standing challenge of C(sp^3)–N cross-coupling chemistry (FIG. 7a). Upon fragmentation of the preformed activated carboxylic acid derivatives (for example, iodine(III) carboxylates or redox-active esters), radical addition to nitrogen nucleophiles produces *N*-alkyl products **128** and **129** at room temperature, which would be highly challenging with traditional methods[162,163]. An alternative approach, albeit with a narrower scope, was reported by Murakami, Itami and co-workers[161]. This work provided access to sulfonamide **130** by employing arylacetic acids and hypervalent iodine-based oxidant IBB. Another decarboxylative approach, also mediated by hypervalent iodide, was reported as a useful Ritter-type amination method for the preparation of tertiary amine derivatives[164]. The development of TM-free analogous and complementary methodologies using benign organic PCs has been achieved using electrophilic azodicarboxylate radical

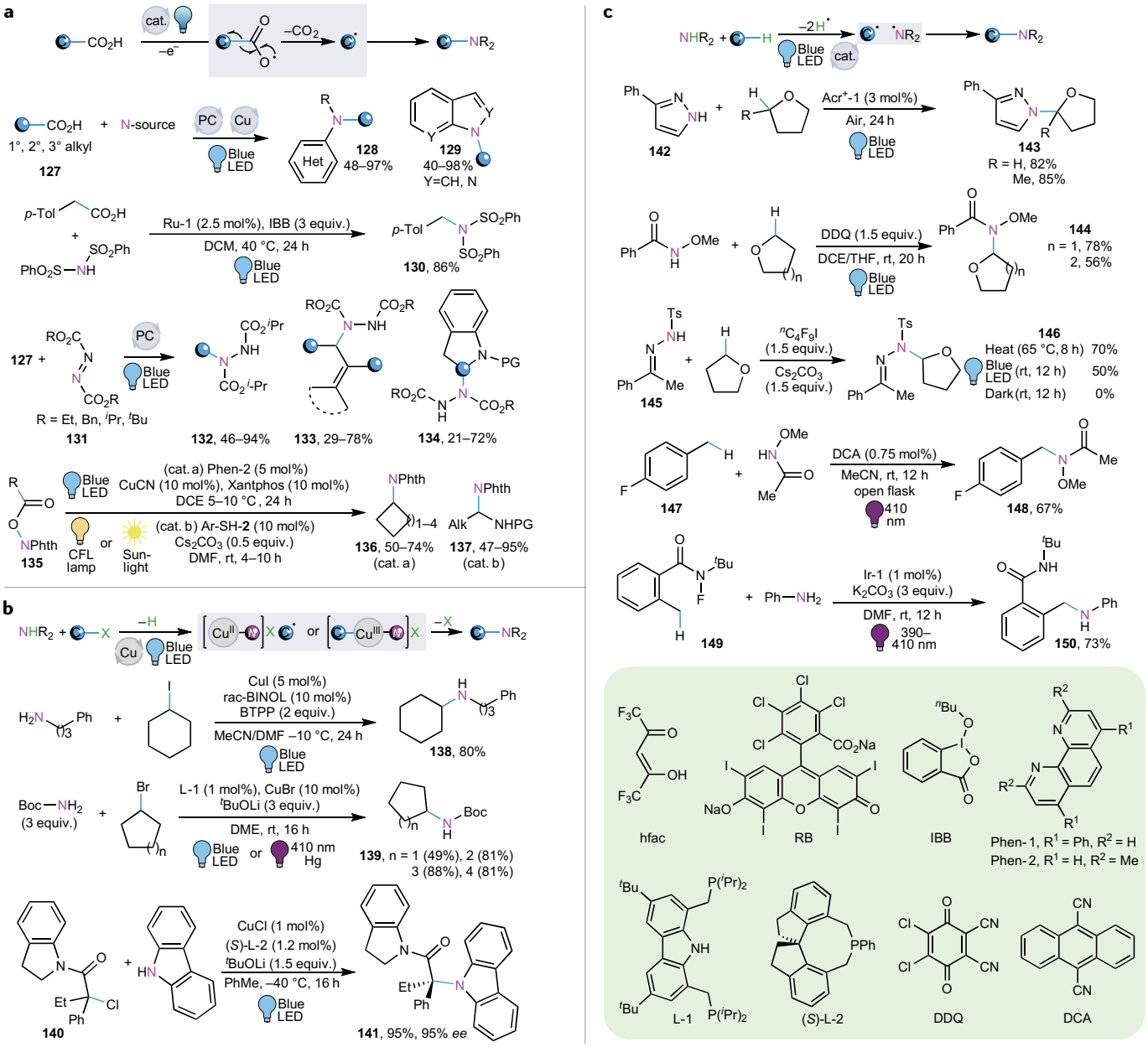

Fig. 7 | **Cross-couplings. a** | Decarboxylative couplings. **b** | Dehydrohalogenative couplings. **c** | Dehydrogenative couplings. Atoms with italicized labels are fully substituted with R groups but have been retracted for clarity. Boc, *tert*-butoxycarbonyl; BTPP, *tert*-butylimino-tri(pyrrolidino)phosphorane; DCE, 1,2-dichloroethane; DCM, dichloromethane; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DME, 1,2-dimethoxyethane; DMF, *N*,*N*-dimethylformamide; PC, photocatalyst; RB, Rose Bengal.

traps **131** to provide aminodecarboxylation products **132–134** (REFS.[165–167]). Lastly, activation of carboxylic acid C–C bonds by substitution with NHPI esters was achieved without TM-based PCs to produce **137** (REF.[168]) and in the copper-catalysed transformation towards synthesis of protected amines **136** (REF.[169]). The latter reaction is analogous to the Curtius rearrangement but without the requirement of azides. The copper catalyst was proposed to undergo photoexcitation and electron transfer to the substrate, which upon fragmentation and decarboxylation generates an alkyl radical and NHPI anion that recombine with the catalyst. The cycle is turned over when copper(II) phthalimide delivers product upon recombination of the alkyl radical. This is an interesting example of the employment of a TM as both a photon absorbing species and a chemical transformation catalyst[170,171]. The scope of this reaction was amenable to π-systems, primary alcohols and epoxides, amides, tosylates, aldehydes and nitroalkanes, but it did not tolerate primary amines and alkyl thiols.

Dehydrohalogenative couplings. The long-standing challenge of selective amine monoalkylation has been approached with photocatalytic methods in dehydrohalogenative couplings. One such example was reported by Fu, Peters and co-workers using copper PC, primary

alkylamines and haloalkanes in a photoinduced dehydrohalogenative coupling to form products **138** (REFS.[172,173]) (FIG. 7b). In stark contrast to the traditional S_N2 reaction, neopentyl iodides reacted with aliphatic amines in good yields. Although this reaction did not do well with other electrophiles such as bromides, chlorides or tosylates, the development of a new copper PC with tridentate carbazolide/bisphosphine ligand L-1 enabled the coupling of a range of primary carbamates with unactivated secondary alkyl bromides at room temperature (**139**)[174]. The reaction proceeds more effectively with six to eight-membered cycloalkyl bromides versus their five-membered analogues. Operating by the same light-induced copper-catalysed manifold, the authors took this chemistry further to enantioselectively arrive at product **141** from racemic **140** and carbazole in the presence of CuCl and chiral ligand (*S*)-L-2 (REF.[175]). This stereoselective reaction, which is not easily achievable with tertiary electrophiles, tolerated a range of electronically different substitutions at the indoline substrate.

Dehydrogenative couplings. The construction of C(sp^3)–N bonds is now achievable by dehydrogenative couplings, commonly employing cyclic ethers as substrates[95,176,177]. For example, mild light-induced acridinium-catalysed oxidative amination of THF or 2-methyl-THF, with molecular oxygen as a benign oxidant, was developed by the Lei group[177] (FIG. 7c). Pyrazoles **142** and 1*H*-1,2,3-triazoles led to the corresponding products **143** in moderate to good yields. It is also possible to use DDQ as the oxidant and PC to synthesize compounds **144** (REF.[95]). Halogen bond-promoted TM-free coupling of THF with hydrazone sulfonamide **145** was accomplished in the presence of perfluorobutyl iodide as the hydrogen abstraction reagent under thermal or visible light irradiation conditions (**146**)[176]. This method overcomes the disadvantages of alternative classical approaches, such as the use of excess amounts of expensive oxidizers, low conversion and limited substrate scope. It is worth mentioning that little is known about this type of coupling to functionalize dioxanes, which could be a valuable addition to this body of work[177]. Another area for development lies in the direct coupling of alkyl radicals with NCRs generated from aryl amines or amides. In 2015, this challenge was approached with a conceptually new and synthetically valuable cross-dehydrogenative benzylic C(sp^3)–H amination reaction without use of exogenous oxidants or TMs[178]. Halotoluenes **147** were successfully aminated using DCA organic PC and *N*-methoxyamide as a source of NCR to produce compounds **148**. Substitution at the aryl ring of alkyl aromatic compounds seemed of little consequence to the efficiency of the reaction. However, examples of this type of transformation are so far still limited. For instance, the activation of weak benzylic bonds from compounds **149** to furnish benzylamines **150** was accomplished with electronically diverse anilines and carboxamides[179].

Conclusions and outlook

In this Review, we have highlighted existing methods that employ visible light-induced catalytic systems to construct C(sp^3)–N bonds, which are highly valuable moieties for medicinal, synthetic and material sciences. Although the protocols we summarized address many challenges such as functional group tolerance, regioselectivity, stereoselectivity and chemoselectivity, avoiding exogenous oxidants or photosensitizers, and combining multiple component couplings in one pot, there is still much to be explored. Mainly, there is no robust and general strategy to access these privileged scaffolds without being limited to classical C(sp^3)–N bond-forming protocols such as S_N2, Mitsunobu alcohol alkylations from nitrogen nucleophiles, reductive amination of carbonyls or olefin hydroamination. Now that we can obtain highly reactive NCRs via mild and operationally practical protocols, myriad possibilities for extending and expanding this methodology arise. Ideally, we would avoid by-products and increase atom economy by skipping amine pre-functionalization to get to weaker N–N, N–O or N–X bonds, amenable to homolysis under mild conditions. Alternatives could include traceless directing groups or in situ formation of a homolysable bond to obtain the desired NCR species. This issue is inherent to the strong bond dissociation energy of unprotected amines. Another obstacle to climb lies in the reactivity trends of radical chemistry vis-à-vis classical two-electron chemistry. Traditionally, the latter would be the avenue of choice to obtain highly stereoselective results. However, tunability of radical philicity and the discovery of new asymmetric light-induced protocols has opened new opportunities to address this issue. A combination of one-electron and two-electron approaches, along with the development of new TM and organic PCs, could likely be leveraged in the expansion of this methodology. Furthermore, the photophysical and mechanistic appreciation of these protocols would be extremely valuable, as mixing up and combining catalytic systems with different TMs, PCs, electron transfer or energy transfer steps, or concerted systems can be quite beneficial to the development of new transformations. As described in this Review, the field of light-induced C(sp^3)–N bond construction has become a huge ground for exploration in the past few years and will likely continue in this direction.

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V.G. provided key discussions and ideas, and edited and reviewed the text. M.R., V.P. and X.J. contributed equally. V.P. and X.J. gathered literature reports and content discussions, reviews and edits. M.R. wrote and edited the text and made the figures.

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