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Copper-catalysed asymmetric radical cyanation

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Catalytic asymmetric cyanation is a straightforward route to α-chiral nitriles that has previously relied on the enantioselective attack of cyanide on unsaturated electrophiles or the hydrocyanation of alkenes. More recently, such asymmetric cyanation reactions have entailed the reaction of cyanide with carbon radicals promoted by chiral copper catalysts via a radical relay process. In this Perspective, we discuss catalytic asymmetric cyanation reactions and the key carbon radicals involved, such as benzylic, allylic and propargylic radicals. In particular, we outline the control of selectivity by considering the mechanism of formation for the carbon radicals as well as the subsequent copper-catalysed radical cyanation step. The carbon radicals can be generated from a diverse range of precursors, which include C–H substrates, alkenes, esters, cyclopropanol and so on. As a consequence, copper-catalysed asymmetric radical cyanation has the potential to expand the scope of catalytic asymmetric cyanation and is expected to find broad utility in organic synthesis and the late-stage functionalization of complex molecules.

More than 60% of the top 200 small molecule pharmaceuticals are optically active, which underlines the importance of accessing target molecules as single enantiomers through enantioselective synthesis. Optically pure alkyl nitriles are important structures that feature in many bioactive chemicals (Fig. 1a)[1,2]. In addition to their prominent biocompatibility and notable resistance to metabolization, nitriles often play a key role as hydrogen-bond acceptors, for example, between nitrile nitrogen and amino acids, which contribute to the key small-molecule–protein interactions. The importance of these scaffolds is amplified by the versatility of the cyano group, which can be converted into amines, carbonyl groups and heterocycles. Catalytic asymmetric cyanation is among the most straightforward approaches for α-chiral nitriles synthesis by directly building the C–CN bond in an asymmetric manner[3]. The explored methods include the enantioselective nucleophilic attack of cyanide on highly polarized unsaturated electrophiles and the nickel-catalysed hydrocyanation of alkenes[4]. Although these reactions are used to produce essential molecules, such as unnatural α-amino acids and anti-inflammatory drugs, new strategies are required to expand the reach of α-chiral nitriles.

A plethora of elegant radical chemistry has been developed over the years to streamline the synthesis of target molecules and achieve unique reactivities that are complementary to polar chemistry[5]. In this context, an assortment of radical cyanation reactions was explored to address the challenges of conventional nucleophilic addition and/or substitution reactions[6]. For instance, Fu and co-workers found that the cyanation of unactivated secondary alkyl chlorides proceeded efficiently at room temperature through a photoinduced radical pathway even though the precedent nucleophilic substitution reactions did not operate below 75 °C (ref. [7]). Despite advances in racemic radical cyanation, catalytic asymmetric radical cyanation (ARC) remained elusive until 2016 when Liu and co-workers reported the asymmetric cyanation of benzylic C–H bonds via a copper-catalysed radical relay[8]. The putative prochiral benzylic radical intermediates were converted stereoselectively into three dimensional α-aryl nitriles in the presence of a chiral bisoxazoline (Box)-ligated copper catalyst. Note that radical transformations were historically recognized as uncontrollable owing to the high reactivity of the open-shell intermediates, whereas recent studies unveiled that highly enantioselective radical reactions are achievable using chiral Lewis acids, organocatalysts and transition metal catalysts[9,10]. In particular, copper-catalysed asymmetric radical transformations have received considerable attention, with examples such as the above enantioselective benzylic C–H cyanation, asymmetric allylic C–H esterification of cyclic olefins[11], enantioselective lactonization[12], enantioconvergent C–N coupling[13] and asymmetric radical amination[14].

The appeal of developing catalytic ARC is that the scope of α-chiral nitriles and consequently the synthetic utility will be appreciably expanded. In addition to benzylic C–H bonds, allylic C–H bonds, propargylic C–H bonds, C–O bonds, alkenes, enynes and cyclopropanes can participate in copper-catalysed ARC to furnish α-chiral nitriles tethered with diverse functionalities (Fig. 1b). Notably, Box ligands **L1**–**L15** are always proved to be optimal although slight adjustment of the steric and electronic properties is typically needed (Fig. 1c). Meanwhile, the cooperation of the copper-catalysed radical relay process with photoredox catalysis or electro-catalysis, leads to ARCs that are otherwise not feasible with a copper-only system (Fig. 1d). In this Perspective, we survey this burgeoning area, present the mechanistic insights of radical formation and functionalization, and conclude with our vision for the future possibility for copper-catalysed ARC.

Copper-catalysed ARC

Asymmetric cyanation of C(sp^3)–H bonds. Non-directed radical-mediated C(sp^3)–H functionalization was generally considered to lack site selectivity and enantioselectivity. However, the emergence of new catalysts and/or reagents is enabling such C(sp^3)–H functionalization to become a useful approach[15]. In contrast, directed C–H functionalization via intramolecular hydrogen atom transfer (HAT) can enable a high level of site selectivity[16]. The 1,5-HAT is the most common process through a preorganized, six-membered cyclic transition state, although 1,4-, 1,6- and 1,7-HATs are also achievable by manipulating the substituents along the chain.

The ARC of benzylic C–H bonds was reported by the Liu and Stahl groups, who used copper-catalysed radical relay catalysis (Fig. 2a)[8]. The working mode was postulated as follows: (1) single-electron oxidation of copper(I) by *N*-fluorobis(benzenesulfonyl)

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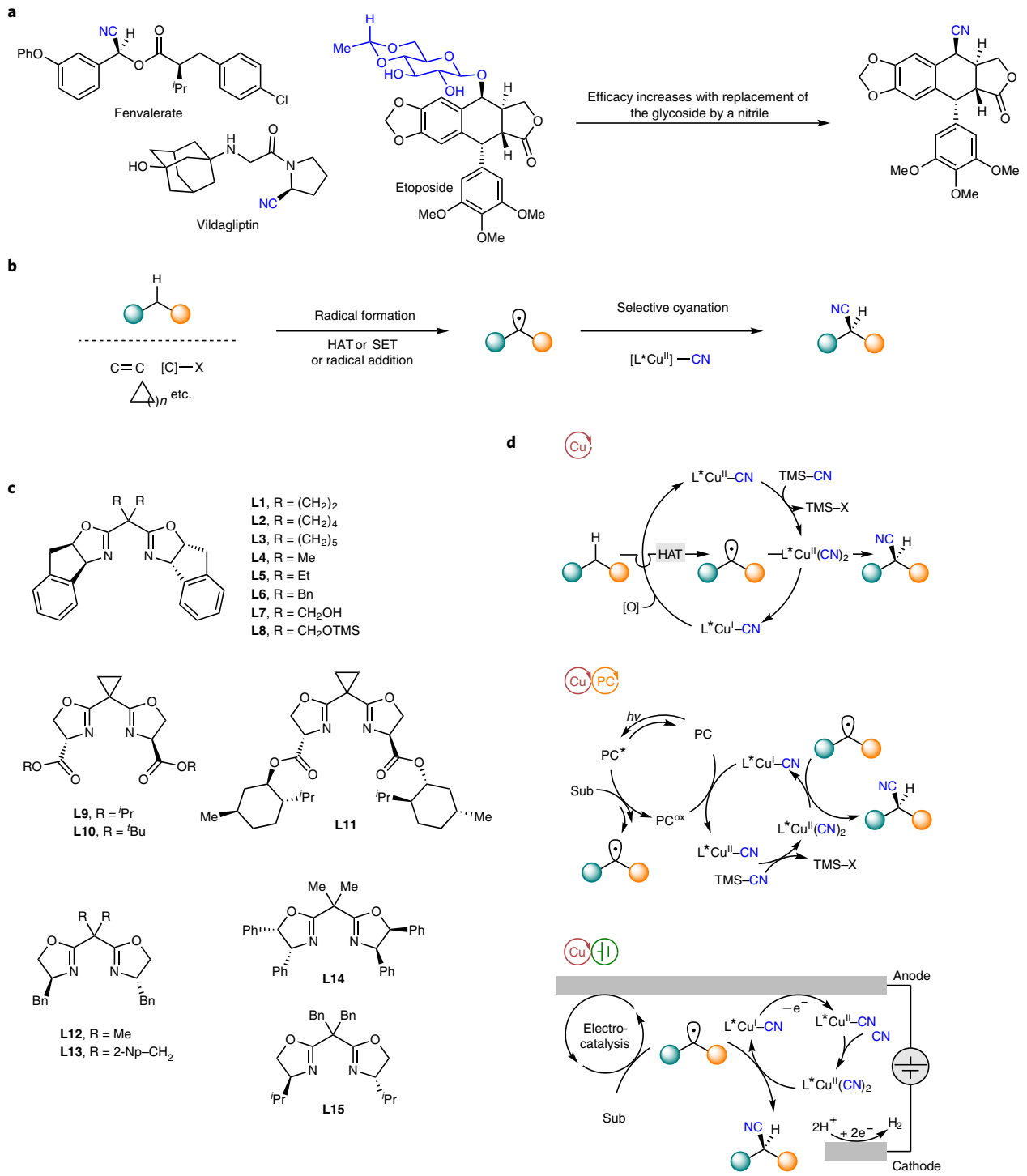

Fig. 1 | Chiral nitriles and their synthesis via copper-catalysed ARC. a, Selected agrochemicals and pharmaceuticals that feature an α-chiral nitrile scaffold. Replacing glycoside with a nitrile in etoposide improves the bioactivity. **b**, A general depiction of copper-catalysed ARC: HAT from C–H bonds generates the carbon radical, which subsequently reacts with L*Cu(CN)$_2$ to furnish α-chiral nitriles. The carbon radical could also be generated from the SET of C–X bonds, radical addition of alkenes and ring-opening of cyclopropanes. **c**, A collection of the optimal Box ligands used in copper-catalysed ARC. TMS, trimethylsilyl; Np, naphthyl. **d**, Three representative reaction pathways for radical generation and their incorporation into copper-catalysed ARC: copper-catalysed radical relay (top), merging with photoredox catalysis (middle) and merging with electrocatalysis (bottom). Sub, substrate; PC^{ox}: oxidation state of the photoredox catalyst.

imide (NFSI) produced the bis(benzenesulfonyl)imidyl radical and a copper(II) intermediate, (2) transmetallation between copper(II) and trimethylsilyl cyanide (TMSCN) afforded (**L12**)Cu(II)(CN)$_2$ species, (3) HAT took place to form a benzylic radical intermediate and (4) the reaction between the benzylic radical and (**L12**)Cu(II)(CN)$_2$ furnished the final product (Fig. 2b). The use of a C–H substrate as the limiting reagent, excellent enantioselectivity and broad functional group tolerance are features of this reaction[8]. The synthetic

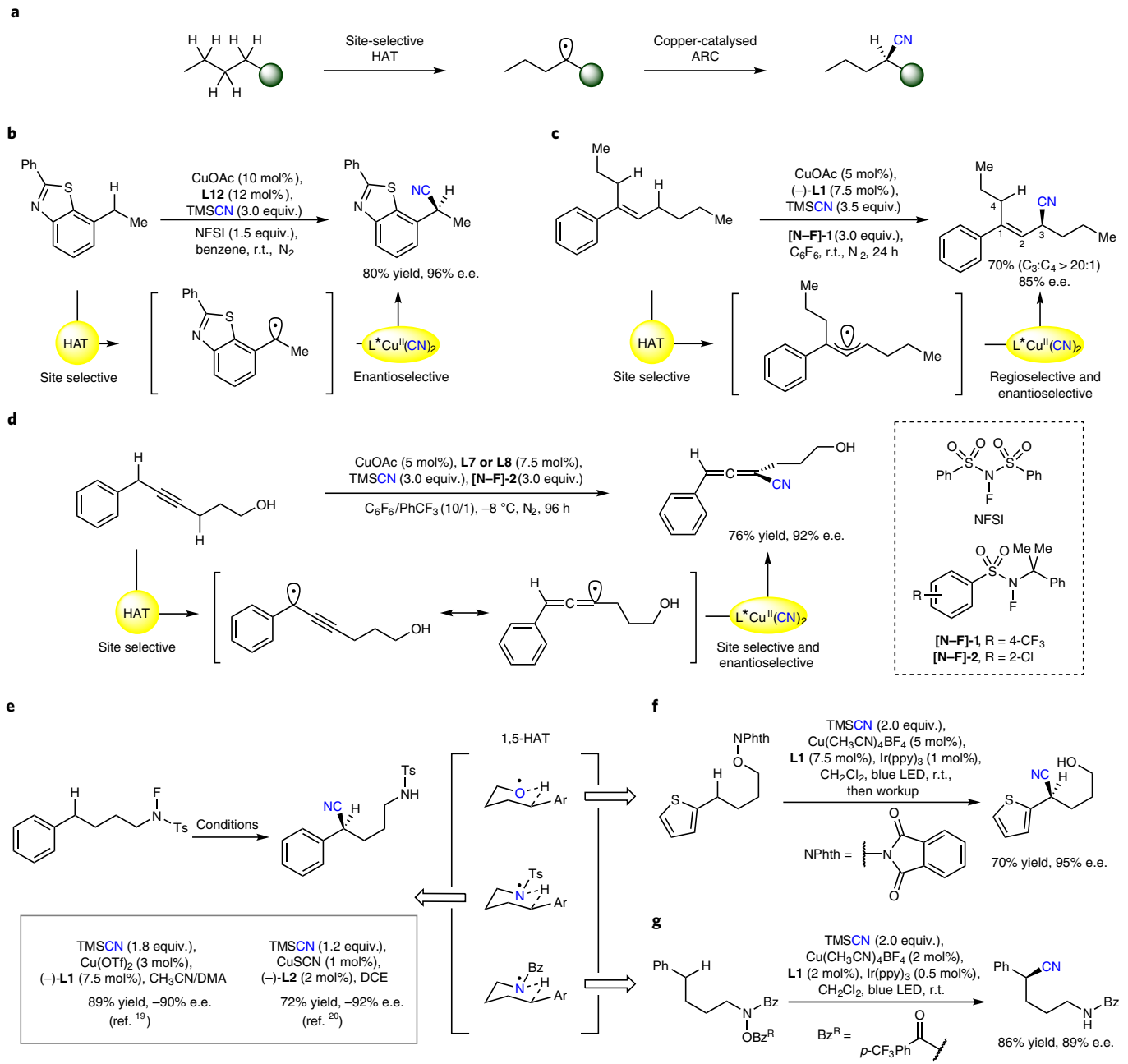

Fig. 2 | Access to α-chiral nitriles through the copper-catalysed ARC of C–H bonds. a, General steps for the synthesis of optically pure nitriles through the copper-catalysed ARC of C–H bonds. **b**, Asymmetric cyanation of benzylic C–H bonds via a copper-catalysed radical relay that involves a benzylic radical[8]. **c**, Site-specific and enantioselective cyanation of allylic C–H bonds enabled by a copper-bound NCR and ARC catalysis[17]. **d**, Radical-mediated activation of propargylic C–H bonds for chiral allenyl nitriles synthesis[18]. **e**, Copper-catalysed ARC of benzylic C–H bonds via an intramolecular 1,5-HAT[19,20]. DMA, dimethylacetamide; DCE, 1,2-dichloroethane. **f**, Dual photoredox and copper-catalysed ARC of benzylic C–H bonds via an intramolecular 1,5-HAT initiated from the O radical[21]. ppy, 2-phenylpyridine. **g**, Dual photoredox and copper-catalysed ARC of benzylic C–H bonds via an intramolecular 1,5-HAT initiated from the N radical[23]. LED, light-emitting diode; r.t., room temperature.

application was demonstrated by synthesizing a pharmaceutically relevant molecule that bore an α-aryl chiral nitrile motif. More importantly, the copper-catalysed radical relay catalysis provides key foundations for the pursuit of other ARCs.

The hydrogen atom acceptor was initially speculated to be the free bis(benzenesulfonyl)imidyl radical in benzylic C–H cyanation[8]; however, coordination of the analogous N-centred radical (NCR) to a Cu(II) intermediate was disclosed as energetically downhill and the Cu(II)-bound NCR complex was potent to abstract the hydrogen atom from C(sp^3)–H bonds[17]. Such mechanistic insights directed the authors to modularly tune the electronic and steric properties of NCRs and ligands that lead to a highly site-selective and enantioselective cyanation of allylic C–H bonds (Fig. 2c)[17]. The [N–F]-**1** reagent with a bulky tertiary alkyl substituent and electron-deficient aryl sulfonyl group proved to be optimal, together with sterically encumbered **L1** as the ligand.

More recently, Liu and co-workers disclosed that the Cu(II)-bound NCR could activate propargylic C–H bonds and the resulting resonance hybrid propargyl and allenyl radicals were exclusively converted into chiral allenyl nitriles under ARC catalysis (Fig. 2d)[18].

Collectively, the Cu(II)-bound NCR-mediated HAT catalysis is expected to be a general strategy towards highly site-selective C(sp^3)–H bond functionalization.

Radical-mediated C(sp^3)–H bond functionalization that involved an intramolecular 1,5-HAT typically exerted outstanding regioselectivity. The Nagib[19] and Wang[20] groups independently reported an interrupted Hofmann–Löffler–Freytag reaction with copper-catalysed ARC for regio- and enantioselective C(sp^3)–H cyanation (Fig. 2e). The NCR was formed after single-electron reductions of *N*-fluorosulfonamides by Cu(I). Nagib and co-workers conducted extensive site-selectivity probes and found that, in most cases, the intramolecular 1,5-HAT operated exclusively. This reaction offered a strategic approach to chiral 3-arylpiperidine and the synthetic utility was showcased by the synthesis of niraparib, an anticancer therapy.

Unlike *N*-fluoro-*N*-alkylarylsulfonamides, *N*-alkoxyphthalimides, *N*-alkoxypyridinium and *O*-acyl hydroxamides cannot directly oxidize Cu(I) to release the heteroatom-centred radical and further initiate the 1,5-HAT. The Liu[21] (Fig. 2f), Zhu[22] and Yu[23] (Fig. 2g) groups independently addressed the reactivity issues by merging the reactions with a photoredox catalysis. In these cases, the N–O bond was activated by oxidative quenching of the excited state of the photoredox catalyst (PC*). Notably, in the work of the Liu[21] and Zhu[22] groups, the alkyl radical was formed through a 1,5-HAT to the O-centred radical that furnished chiral nitriles tethered with a terminal hydroxyl group as the final product.

Copper-catalysed ARC of carbon radicals from other precursors. The robustness of the copper-catalysed ARC catalysis renders its amenability to structurally distinct carbon radicals, which include benzylic, allylic and propargyl–allenyl radicals (Fig. 3a). Meanwhile, the merging of copper-catalysed ARC with diverse catalysis for radical generations, which include photoredox catalysis and electrocatalysis, has led to various new conversions other than the asymmetric C–H cyanation (Fig. 3).

ARC of styrenes. The radical-mediated difunctionalization of alkenes has drawn substantial attention in the past decades thanks to the accessibility of alkenes, the unique reactivities of radical pathways and the ability to rapidly increase the complexity of molecules[24]. In a typical catalytic cycle, the initially formed highly energetic carbon- or heteroatom-based radicals or hydrogen atom surrogates add to alkenes to generate relatively stable secondary or tertiary carbon radicals, which are further functionalized to afford the final products.

In 2016, Liu and co-workers demonstrated the copper-catalysed asymmetric cyano-trifluoromethylation of vinylarenes with Togni's reagent [CF_3^+] (Fig. 3b, left)[25]. Single-electron transfer (SET) between [CF_3^+] and Cu(I) gives Cu(II) and CF_3 radical, and the subsequent addition of the CF_3 radical to vinylarenes gives the benzylic radicals. Finally, copper-catalysed asymmetric cyanation of the benzylic radical furnishes the final product. The scope of the incipient radicals was extensively studied to obtain α-chiral nitriles with diverse functionalities at the β-position. Successful examples include the addition of (fluoro)alkyl[26–30], imidyl[31,32], azido[31], phosphinoyl[33,34], sulfinyl[34], acyl[35], aryl[36] and benzoyloxyl radicals[32,37], and even of the hydrogen atom[38] to vinylarenes (Fig. 3b).

Notably, Lin and co-workers showed that the oxidative formation of phosphinoyl and sulfinyl radicals and copper catalyst recycling could operate electrochemically, avoiding the use of stoichiometric strong oxidants[29]. Electrochemistry was also leveraged to combine a cobalt-mediated HAT to alkenes and a copper-catalysed ARC for enantioselective hydrocyanation of conjugated alkenes[38]. A set of chemical oxidants were investigated under otherwise identical conditions. However, none of them exhibited preparative utility.

ARC of C–C single bonds. The high reactivity of radical-mediated C–C bond cleavage renders efficient structural reorganization of molecules. Recent advances include radical-mediated decarboxylation, strain-releasing ring-opening and β-elimination[39]. Two approaches toward decarboxylative functionalization have been used, namely direct oxidative decarboxylation of carboxylic acids and reductive activation of pre-functionalized carboxylic acids, such as *N*-hydroxyphthalimide (NHP) esters. In 2017, the Liu and Lin groups demonstrated the enantioconvergent decarboxylative cyanation of NHP esters under copper and photoredox synergistic catalysis (Fig. 3c)[40]. Formation of the carboxylic radical is favoured over that of the imidyl radical on the single-electron reduction of NHP esters, and the key benzylic radical is provided after extrusion of CO_2. Control experiments revealed that the copper catalyst was not able to reduce NHP esters, albeit essential to promote the C–CN bond formation. In 2019, the Wang group[41] and Chen and Xiao group[42] independently reported an enantioselective radical-mediated ring-opening cyanation of oxime esters under copper and photoredox dual catalysis (Fig. 3d). The emission-quenching experiment suggested that an oxidative quenching of PC* by oxime esters afforded iminyl radicals along with releasing the carboxylate, followed by β-C–C bond cleavage of the iminyl radicals to form the benzylic radicals.

The Zhang and Li groups reported the copper-catalysed ARC of benzylic radicals from arylcyclopropanes after a single-electron oxidation and nucleophilic addition sequence to deliver γ-amino-α-aryl chiral nitriles (Fig. 3e)[43]. It was speculated that NFSI oxidized Cu(I) to generate an imidyl–Cu(III) intermediate and there was an equilibrium between the imidyl–Cu(III) and Cu(II)–imidyl radical. Both the imidyl–Cu(III) and imidyl radical could accept electrons from arylcyclopropanes. More recently, the Liu and Guo group demonstrated the synthesis of β-carbonyl α-chiral nitriles through the radical-mediated ring opening of cyclopropanols (Fig. 3f)[44]. The oxyradicals were generated via homolysis of the alkoxide–Cu(II) complex, the ring opening of which took place effectively due to the strain of the three-membered ring and high energy of the oxyradical. The reaction was used to synthesize (*R*)-baclofen, a neurotransmitter inhibitor.

ARC of non-benzylic radicals. The enantioselective radical cyanoalkylation of 1,3-dienes was investigated by Xiao and co-workers using a synergetic photoredox/copper catalysis with an alkyl carboxylic NHP ester as an alkyl source (Fig. 3g)[45], wherein the allyl radical was formed by the addition of an alkyl radical to dienes. Interestingly, four components of the reaction that involved CO insertion operated smoothly in the presence of carbon monoxide. Such a reactivity was extended to 1,3-enynes to afford α-alkynyl chiral nitriles with a high enantioselectivity, which involved a propargylic radical intermediate. The same group showed that propargylic radicals could be generated from propargyl carboxylic esters through the oxidative quenching of PC* (here, PC = 10-phenylphenothiazine), followed by C–O bond cleavage (Fig. 3h)[46,47]. Notably, copper-catalysed ARC at the propargylic position proceeded exclusively again to afford the formal enantioconvergent cross-coupling products as α-alkynyl chiral nitriles. Interestingly, Bao and co-workers found that tetrasubstituted chiral allenyl nitriles were formed as the sole products when using 2-aryl-1,3-enynes[48]. In this case, the in situ formed benzoyloxyl radical added to the C–C double bonds to generate delocalized propargyl/allenyl radicals. Such regioselectivity presumably arises from the steric hindrance at the benzylic/propargyl position (Fig. 3i)[48].

Radical intermediates for highly enantioselective cyanation typically require a π system, such as aryl, alkenyl or alkynyl groups, to be stable. Also, carbon radicals adjacent to N or O atoms, derived from the CF_3 radical addition to enamides and vinyl esters, are amenable to ARC catalysis (Fig. 3j)[49]. This method may be used to synthesize

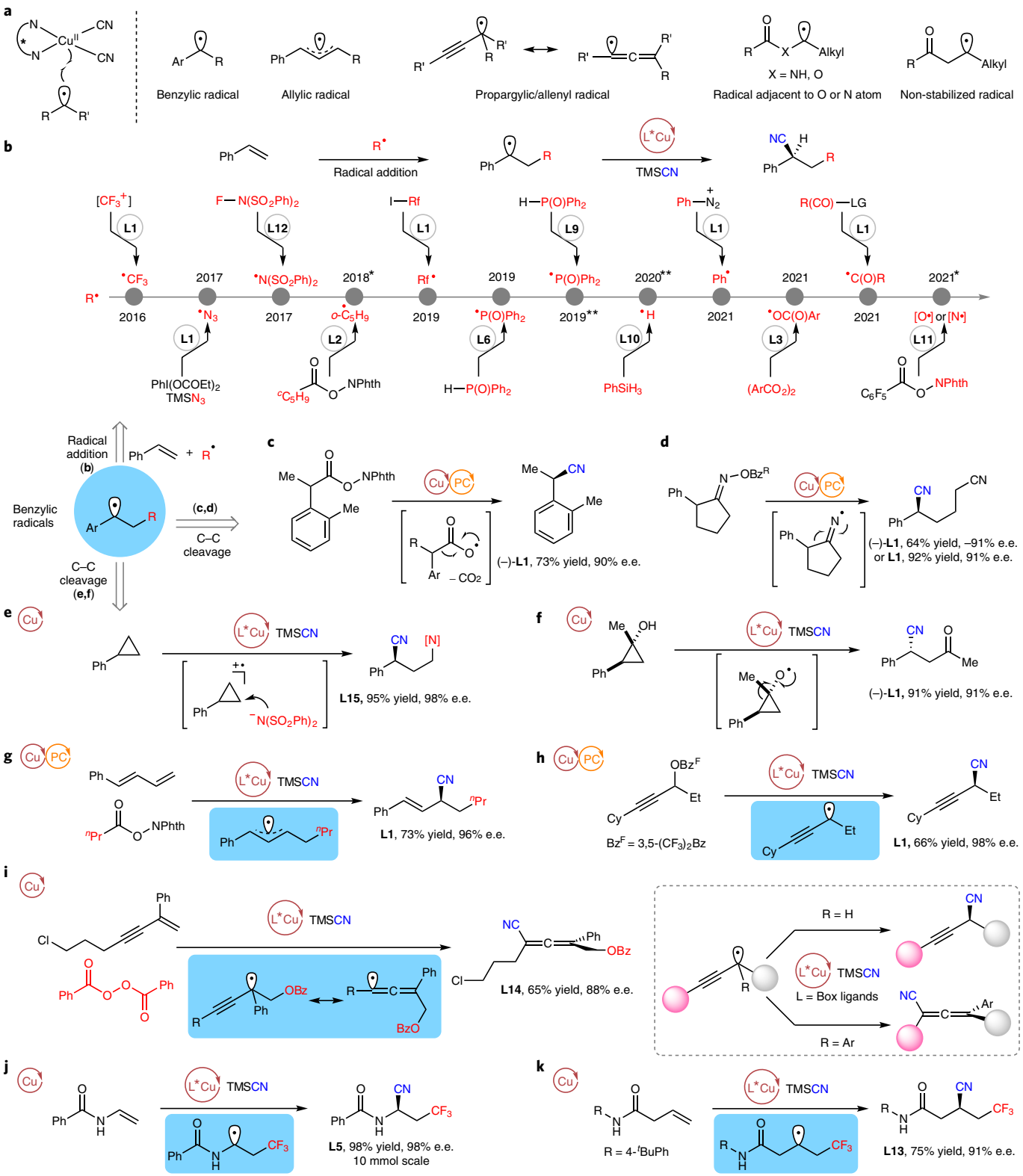

Fig. 3 | Different synthetic approaches to chiral nitriles through the copper-catalysed ARC of carbon radicals generated from the radical addition of alkenes and C–X bond cleavage. a, The proposed reaction mode between Cu(II) cyanide and carbon radicals (left), and a collection of carbon radicals that are amenable to copper-catalysed ARC (right). **b**, A summary of radicals reported for the enantioselective cyanofunctionalization of styrene[25–38]. *With photocatalysis; **with electrocatalysis. Rf, fluoroalkyl group; LG, leaving group. **c**, Decarboxylative cyanation of NHP esters by merging copper-catalysed ARC and photoredox catalysis[40]. **d**, Ring-opening cyanation of oxime esters under copper and photoredox dual catalysis[41,42]. **e**, Ring-opening cyanation of arylcyclopropanes[43]. **f**, β-Carbonyl α-chiral nitriles synthesis from the ring opening of cyclopropanols[44]. **g**, Enantioselective cyanoalkylation of 1,3-dienes using a synergetic photoredox/copper catalysis[45]. **h**, Enantioconvergent cyanation of propargyl carboxylic esters[46]. **i**, Tetrasubstituted chiral allenyl nitriles synthesis through enantioselective cyanobenzoloxylation of 2-aryl-1,3-enynes[48]. **j**, Asymmetric cyanotrifluoromethylation of enamides and vinyl esters[49]. **k**, Asymmetric cyanotrifluoromethylation of alkenes that bear a carbonyl group at the β-position[50].

CF_3-containing chiral diamines and hydroxyl amines, as well as unnatural α-amino acids. In another study, secondary alkyl radicals that bear a β-carbonyl group could be effectively cyanated with a high level of enantioselectivity (Fig. 3k)[50].

Mechanistic insight

Concurrent with the rapid growth in reaction discovery, the mechanisms of the reactions were also investigated. Although control experiments revealed that these reactions are radical processes, mechanistic studies to probe the origin of the selectivity in carbon radical generation are only sporadically reported on the basis of density functional theory (DFT) calculations. Next, we discuss a few mechanistic case studies, which include the elucidation of a high site selectivity during HATs from diverse allylic C–H bonds[17] and mechanistic insights of C–CN bond formation from Cu(II) cyanide and carbon radicals, for example, benzylic[8], allenyl[18] and propargylic[46] radicals.

Carbon radical formation. The copper-catalysed ARC of benzylic C–H bonds by the Liu and Stahl groups showed an exquisite site selectivity, which favoured benzylic over aliphatic tertiary C–H bonds and those adjacent to heteroatoms (Fig. 4a, left)[8]. Intriguing results were observed when the ARC catalysis was extended from benzylic to allylic C–H bonds, wherein the Liu and Lin groups found that the reaction exhibited a superior site selectivity over the canonical radical-mediated C–H functionalization with free NCRs, typically >20:1 in the presence of a copper catalyst versus ~3:1 in the case of free NCRs (Fig. 4a, right)[17]. In addition, the site selectivity is obviously influenced by the structures of both NCRs and ligands. These observations prompted investigations of the origins of such site selectivity and identify the real HAT acceptor. DFT calculations illustrated that the reaction of (**L1**)Cu(I)(CN) with [N–F]-**1** readily gave a Cu(II)-bound NCR species via a Cu–O coordination that is more stable by 9.4 kcal mol^{-1} in free energy than (**L1**)Cu(II)(CN)F plus a free NCR (Fig. 4b). Noteworthy is the 'amplified effect' with copper-bound NCRs versus the effect associated with free NCRs to selectively abstract a hydrogen atom among diverse allylic C–H bonds. For instance, the activation barriers for the HAT of allylic C–H bonds, H^1 and H^3, of 1-phenyl cycloheptene by free NCRs were 8.1 (H^1) and 9.6 (H^3) kcal mol^{-1}, respectively, with a $\Delta\Delta G^{\ddagger}$ of 1.5 kcal mol^{-1} (Fig. 4b, path A). As a comparison, the kinetic barriers associated with Cu(II)-bound NCRs increased to 12.8 (H^1) and 15.4 (H^3) kcal mol^{-1}, respectively, with a $\Delta\Delta G^{\ddagger}$ of up to 2.6 kcal mol^{-1} (Fig. 4b, path B). The calculated $\Delta\Delta\Delta G^{\ddagger}$ (1.1 kcal mol^{-1}) is in good agreement with the experimental observations that the copper-bound NCR-mediated system shows a higher site selectivity than that of the relevant free NCRs by nearly an order of magnitude. This transition-metal-bound-induced amplified effect allows a precise selectivity tuning and is expected to be implemented in transformations beyond asymmetric C–H cyanation. For instance, the high site selectivity observed in the copper-catalysed asymmetric alkynylation of benzylic C–H bonds by the Liu and Lin groups is also proposed to be attributed to the unique activity of copper-bound NCRs[51].

Copper-catalysed ARC of benzylic radicals. *LCu(II)(CN)$_2$ as a radical trap.* It is generally accepted that Cu(II) complexes serve as radical traps to facilitate the product formation in copper-catalysed radical cyanations; however, mechanistic studies to unveil the identity of the key species are rare. Reaction profiling under standard conditions of copper-catalysed cyanotrifluoromethylation of alkenes by Liu and co-workers showed an apparent induction period in the formation of product, which was shortened and finally removed by adding a catalytic amount of ^{n}Bu$_4$NCN. This observation suggested that (**L1**)Cu(I)(CN) might be the active catalyst[25]. It was speculated that the single-electron oxidation of (**L1**)Cu(I)(CN) by Togni's reagent, with the assistance of TMSCN, operated to release (**L1**)Cu(II)(CN)$_2$, a CF_3 radical and silyl ether. Thus, (**L1**)Cu(II)(CN)$_2$ was proposed as the key species to react with benzylic radicals, although details about the transmetallation to generate (**L1**)Cu(II)(CN)$_2$ were not originally reported. Maintaining a low concentration of cyanide in the reaction mixture is essential to obtain a high reactivity and enantioselectivity. Excess free cyanide can cause dissociation of the Box ligand from copper, which is shown by a titration experiment of ^{n}Bu$_4$NCN to a solution of (**L1**)Cu(I). The requirement for a low concentration of cyanide could also rationalize the exclusive use of TMSCN rather than ^{n}Bu$_4$NCN or other cyanides as the cyano reagent in all the explored copper-catalysed ARCs.

C–CN bond formation through a Cu(III) intermediate. In the early examples of ARC from the Liu and Stahl groups, an ethylbenzene-derived radical and (**L12**)Cu(II)(CN)$_2$ were selected as models for DFT calculations (Fig. 4c)[8]. The high enantioselectivity observed in the cyanation of benzylic C–H bonds suggests that the benzylic position is in close proximity to the chiral Cu centre in the enantioselectivity-determining step. In this regard, the reaction pathway that involved the reaction of (**L12**)Cu(II)(CN)$_2$ with the benzylic radical to afford the benzyl–Cu(III) species was interrogated. DFT calculations illustrated that the kinetic barriers for the benzyl–Cu(III) intermediate formation were 7.8 and 8.6 kcal mol^{-1} (the two diastereo-isomers), which implies the viability of this step. The transition state for C–CN reductive elimination is higher in energy than that for the formation of the benzyl–Cu(III) species, which indicates that the benzyl–Cu(III) species formation is reversible and the stereoselectivity is determined by the reductive elimination step. Notably, Box ligands typically function through repulsive steric interactions to induce enantioselectivity, whereas Lin and co-workers found that the transition state for the reductive elimination of the **L10**-ligated benzyl–Cu(III) species displays a favourable C–H π interaction between the acidic proton at the α-position of one ester group and the substrate aryl group (Fig. 5a)[38].

The free-energy profile of enantioconvergent decarboxylative cyanation (Fig. 3c)[40] was calculated by the Sun, Su and Guan groups[52]. The results illustrated that the reaction of ethylbenzene-derived radical at (**L1**)Cu(II)(CN)$_2$ to afford the benzylic Cu(III) intermediate was thermodynamically uphill by less than 3 kcal mol^{-1}; however, transition states of this step could not be located. Subsequently, the Cu(III) species underwent reductive elimination with an energy barrier difference of 2.1 kcal mol^{-1}, which served as the enantiodetermining step. This work is in good agreement with the catalytic cycle proposed by Liu and Lin[40] as well as with computational studies[8]. Other notable insights from this work include: (1) the cyanide exchange between TMSCN and Cu(II) is the turnover-limiting step due to the difficulty in anion dissociation from the metal centre, (2) the cyanide exchange occurs to afford Cu(II)(NC) as a kinetic product and (3) isomerization of Cu(II)(NC) took place to generate Cu(II)(CN) via CN flipping.

Selective ARC of propargylic/allenyl radicals. In 2018, Liu and co-workers reported a copper-catalysed, ligand-controlled regioselective cyanotrifluoromethylation of 1,3-enynes that involved a delocalized propargylic radical[53]. The use of 4,7-dimethoxylphenanthroline as a ligand afforded allenyl nitriles, whereas propargylic nitriles were synthesized in the presence of Box. DFT calculations gave insight into the origin of regioselectivity. Forming a propargylic Cu(III)(CN)$_2$ intermediate is both thermodynamically and kinetically favourable compared with that of allenyl Cu(III)(CN)$_2$ species because the allenyl radical is typically expected to be more sterically demanding than an alkyl radical. However, this steric congestion also promotes C–CN reductive elimination from the allenyl Cu(III)(CN)$_2$ intermediate. Notably, the relative free energy

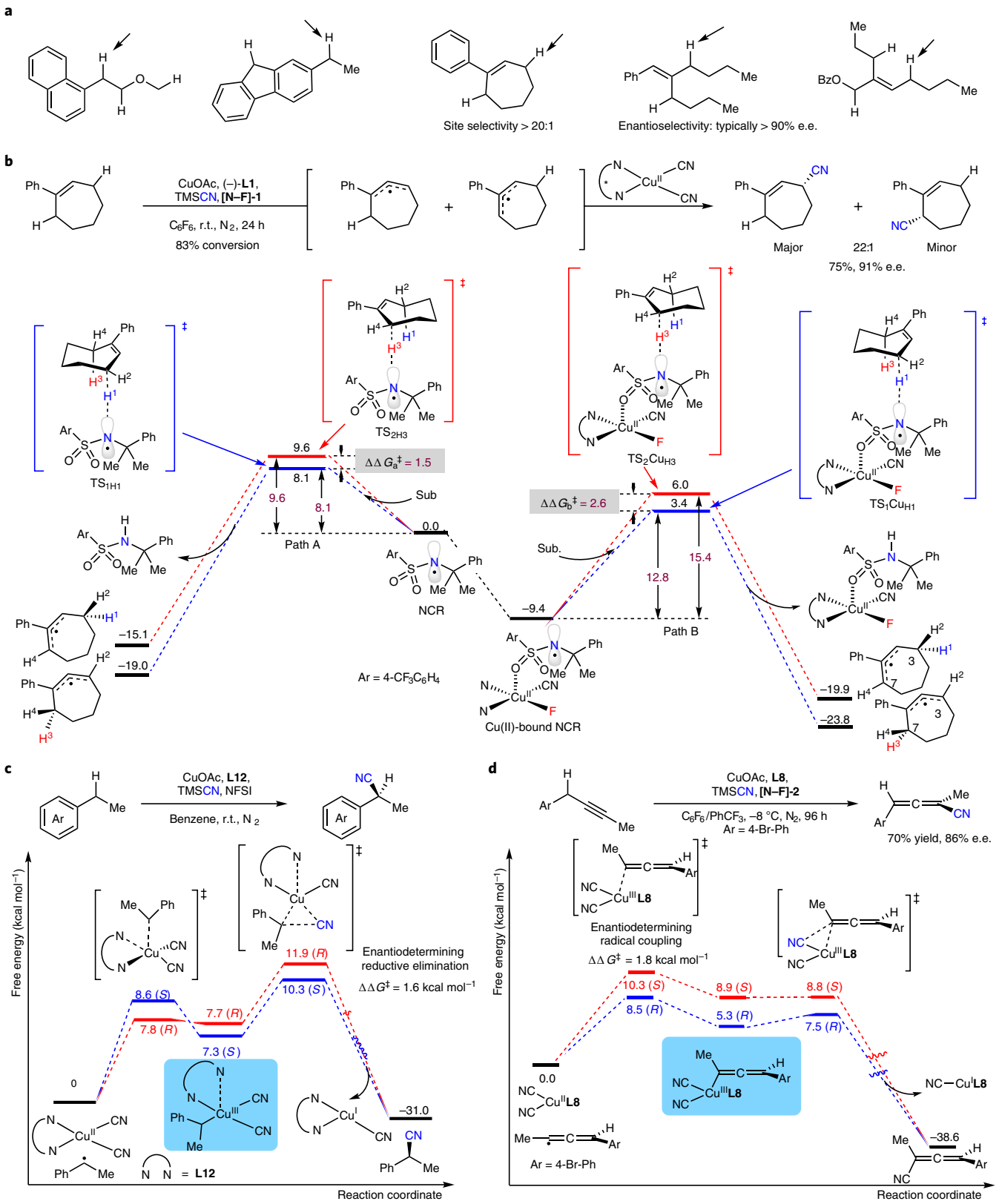

Fig. 4 | Mechanistic and computational studies on selectivity control during carbon radical formation and copper-catalysed cyanation. a, Site-selectivity of the HAT in benzylic (left) and allylic (right) C–H cyanation. **b**, DFT calculation to elucidate the amplified effect of a Cu(II)-bound NCR during the HAT compared with that of a free NCR. blue H^1 indicates an H at axial position of C3; red H^3 indicates an H at axial position of C7; $\Delta\Delta G_a^{\ddagger}$ and $\Delta\Delta G_b^{\ddagger}$ are the calculated kinetic barrier differences for hydrogen atom transfer of different allylic C–H bonds by Cu(II)-bound NCR or free NCR, respectively. **c**, Calculated energy profiles of the ARC of benzylic radicals in copper-catalysed enantioselective benzylic C–H cyanation. **d**, DFT computational studies of asymmetric cyanation of allenyl radicals from propargylic C–H bonds. TS_1 and TS_2, transition states 1 and 2, respectively.

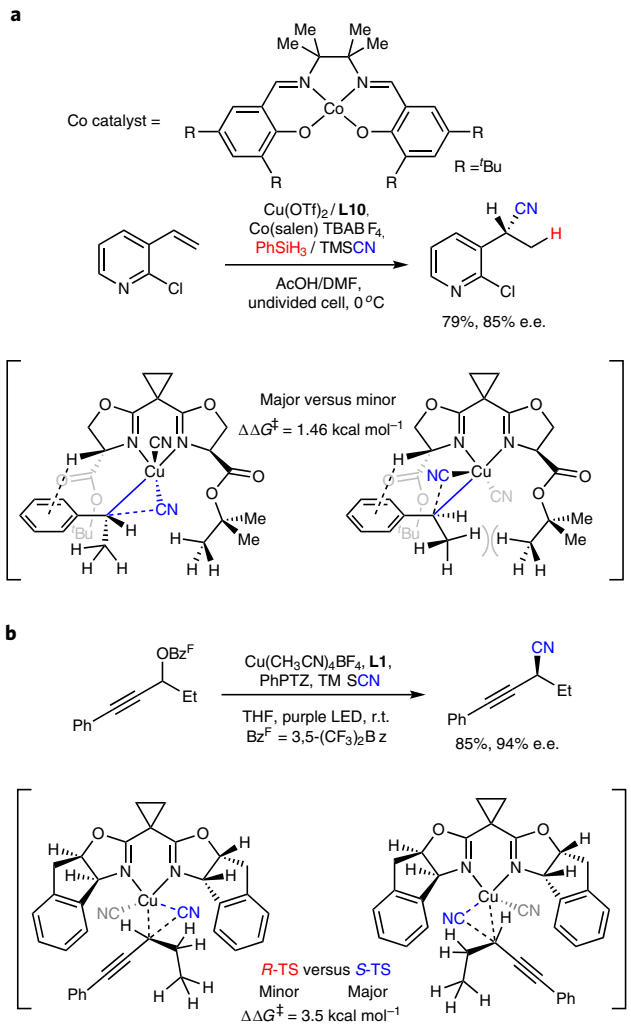

Fig. 5 | Mechanistic and computational studies on the asymmetric carbon radical cyanation. a, Computational stereochemical models with **L10** show an attractive C–H π interaction between the substrate and catalyst. **b**, Proposed stereoinduction models in the radical cyanation of propargylic radicals from associated esters. DMF, dimethyl formamide; PhPTZ, 10-phenylphenothiazine; TBA, tetrabutyl ammonium.

of transition states for C–Cu(III)$(CN)_2$ formation and subsequent reductive elimination changes with the identity of ligands and hence determines the product distributions. Copper-catalysed asymmetric cyanation of propargylic radicals was achieved more recently by the Xiao and Lan groups, from propargylic esters[46], and the Liu and Lin groups, from propargylic C–H substrates[18], respectively. The origin of enantioselectivity was elucidated by DFT calculations (Figs. 4d and 5b). Consistent with previous racemic studies[53], DFT calculations from the Liu and Lin groups illustrated that the combination of (**L8**)Cu(II)$(CN)_2$ with propargylic radicals, regarded as the enantiodetermining step, was higher in energy than the following reductive elimination (Fig. 4d), which is distinct from the case of benzylic C–H cyanation (Fig. 4c)[8]. In contrast to the allenylic cyanation, Xiao and Lan demonstrated that reductive elimination from a propargylic Cu(III) centre served as the enantiodetermining step, wherein the C–CN bond formation from the *S*-isomer showed a lower kinetic barrier by 3.5 kcal mol^{-1} than that of the *R*-isomer. Notably, the above studies support the viability of forming a Cu(III) intermediate from Cu(II) cyanide and carbon radicals (Fig. 5b).

An alternative mechanism for C–CN bond formation was raised by Bao and co-workers on the basis of a computational study[54]. In the case of allenyl nitrile synthesis from 1,3-enynes, the copper(II) isocyanide Cu(II)(NC) species was suggested as the radical trap, although the analogous copper(II) cyanide Cu(II)(CN) intermediate is thermodynamically more stable[54]. In the reaction of the copper-catalysed cyanation of benzylic radicals, however, the same group proposed that the cyano copper complex Cu(II)(CN) was directly formed from the transmetallation of TMSCN to Cu(II) and served as the radical trap to deliver the final alkyl nitrile[55]. However, when Liu and Lin applied the Cu(II) isocyanide complex to survey the asymmetric cyanation of propargylic C–H bonds, the transition state was much higher in energy (by 13.2 kcal mol^{-1} in the triplet and 22.6 kcal mol^{-1} in the singlet) than that of the Cu(II) cyanide complex[18].

Outlook

Copper-catalysed ARC is a powerful approach for α-chiral nitrile synthesis that is complementary to the canonical polar chemistry. The robustness of this chemistry also renders its combination with diverse catalysis for site-selective radical formation, which substantially expands the scope of catalytic asymmetric cyanation. This Perspective provides a survey of this field with the emphasis on the identity of radical intermediates suitable for copper-catalysed ARC together with patterns for their generation, the putative Cu(II) species to capture the radicals and the mechanistic insights about the key C–CN bond formation.

Noteworthy is the high efficiency for α-aryl chiral nitrile synthesis that constitutes more than 70% of the reports in this field. The unique stereocontrol of benzylic radicals might arise from the attractive non-covalent interaction between the aryl motif of benzylic radicals and the ligands of copper, such as π–π stacking and C–H π interaction, which will dictate the transition-state geometry. Recent advances in this field also revealed that allylic radicals[17,45], propargylic/allenyl radicals[18,46,48] and carbon radicals adjacent to the N or O atom[49] are amenable to this chemistry. Liu and co-workers demonstrated the sole successful example of the ARC of non-stabilized alkyl radicals; however, a functional group, such as ketone, ester and amide, should be present at the β-position[50]. These functional groups are expected to coordinate to the copper centre, which positions them with a specific orientation in the transition state to induce a high enantioselectivity. For future directions in this field, substantial efforts should be made to address the stereoselective control of non-stabilized alkyl radicals by designing new chiral ligands. In addition, as the most atom- and step-economic route to access α-chiral nitriles, copper-catalysed ARC of various C(sp^3)–H bonds deserves special focus.

Another challenge is to build quaternary carbon centres, which remain elusive as difficulties in this area include the contradictory steric requirements for the ligand and potential tertiary radical oxidation to carbocation. For example, a sterically encumbered ligand is believed to be beneficial to recognize the subtle differences between three substituents. However, the steric hindrance will inhibit the combination of Cu(II) intermediate with tertiary radicals or cyano group transfer from Cu(II) to tertiary radicals. Structural modification of the ligands will be the key to provide a general solution. However, tertiary radicals are typically susceptible to oxidation to afford a carbocation that will lead to many side reactions or background racemic cyanation. Nishikata and co-workers demonstrated the copper-catalysed cyanation of various peptides that bear an α-bromo-amide moiety[56]. Notably, in this case, tertiary carbon radicals α to an electron-withdrawing group were effectively cyanated to build the quaternary carbon centre. Such a reaction offers an excellent model to interrogate the copper-catalysed asymmetric functionalization of tertiary carbon radicals[57,58].

Finally, a mechanistic understanding of the pathway to C–CN bond formation via enantioselective capture of the carbon-centred radical intermediate by chiral Cu(II) species was

investigated[8,18,38,46,52,53], but relied on DFT calculations only. In addition, detailed insights into the site-selective hydrogen-atom abstraction of sp^3 C–H bonds by a Cu(II)-bound NCR species are mainly gained by computational studies. Thus, future efforts should be devoted to in situ characterization and/or isolation of key intermediates in the catalytic cycle, such as the resting state of the copper catalyst and the active Cu(II) species, and to examination of the reactivity of these active species.

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Competing interests

The authors declare no competing interests.

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