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Enantioconvergent copper-catalysed difluoromethylation of alkyl halides

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Stereochemically controlled hydrogen bond donors play essential roles in the pharmaceutical industry. Consequently, organic molecules that bear difluoromethyl (CF_2H) groups at chiral centres are emerging as pivotal components in pharmaceuticals owing to their distinct hydrogen-bonding property. However, a general approach for introducing CF_2H groups in an enantioselective manner has remained elusive. Here we show that enantioconvergent difluoromethylation of racemic alkyl electrophiles, through alkyl radical intermediates, represents a strategy for constructing CF_2H-containing stereocentres. This strategy is enabled by using copper catalysts bound with a chiral diamine ligand bearing electron-deficient phenyl groups, and a nucleophilic CF_2H-zinc reagent. This method allows the high-yield conversion of a diverse range of alkyl halides into their alkyl-CF_2H analogues with excellent enantioselectivity. Mechanistic studies reveal a route involving asymmetric difluoromethylation of alkyl radicals and crucial non-covalent interactions in the enantiodetermining steps. This copper-catalysed difluoromethylation process opens an avenue for the efficient preparation of CF_2H-containing pharmaceuticals.

The pharmaceutical industry places high importance on stereochemically controlled hydrogen bond donors for modulating drug–target interactions. One emerging approach to enhance the properties of parent drug candidates has been to replace traditional hydrogen bond donors (for example, OH, NH_2 or SH) with metabolically stable analogues[1]. In this context, difluoromethyl (CF_2H) groups have emerged as privileged groups in medicinal chemistry owing to their unique hydrogen bond donor potential and their capacity to function as bioisosteres of OH, NH_2 and SH groups[2,3]. Beyond their hydrogen-bonding capabilities, the lipophilic nature of CF_2H groups and the strong dissociation energy of carbon–fluorine bonds can further modulate the membrane permeability and metabolic stability of drug molecules[4]. The importance of stereochemically defined CF_2H groups has been recently showcased by the development of two pharmaceutical agents, Inavolisib[5] and LPC-233[6] (Fig. 1a). The efficacy of the former has been attributed to the hydrogen-bonding ability of its CF_2H group with a serine residue of phosphoinositide 3-kinase, whereas the potency of the latter molecule has been attributed to the electrostatic interaction of the fluorine atoms with a lysine residue of the enzyme LpxC.

However, efforts to fully exploit the potential of CF_2H groups in medicinal chemistry were hampered by the challenges associated with their preparation, as limited synthetic methods are currently available for the enantioselective introduction of CF_2H groups[7–9]. Conventional approaches for constructing CF_2H-containing stereogenic centres rely on either the deoxyfluorination of enantioenriched aldehydes[10,11] or the asymmetric transformation of CF_2H-containing prochiral molecules[12,13]. These approaches generally suffer from either the narrow substrate scope of the fluorination reagents or the limited availability of the prochiral precursors. Recent advances in asymmetric difluoromethylation have focused on the manipulation of $C(sp^2)$ electrophiles. For example, the Hu group has made progress for the asymmetric difluoromethylation of aldehydes[14] and imines[15], albeit

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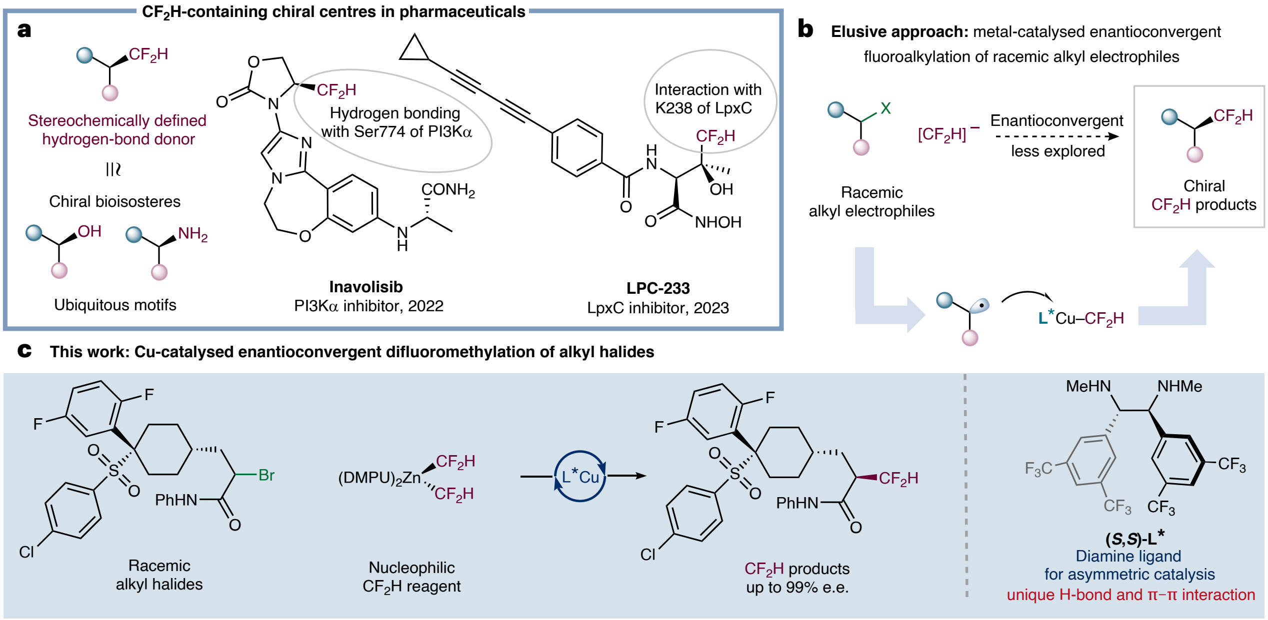

Fig. 1 | Development of Cu-catalysed enantioconvergent difluoromethylation of alkyl halides. a, The importance of CF_2H-bearing chiral centres in the pharmaceutical industry. **b**, Nucleophilic enantioconvergent fluoroalkylation as a different approach for the construction of chiral $C(sp^3)$–CF_2H moieties **c**, Cu-catalysed enantioconvergent difluoromethylation alkyl halides enabled by a chiral diamine ligand. X = halides or pseudohalides.

with moderate enantioselectivity. The Jacobsen group has reported an unusual migratory geminal difluorination of styrenes for the construction of CF_2H-containing stereocentres at benzylic positions[16]. Shen and Mikami have recently demonstrated the difluoromethylation of allyl substrates via either S_N2' (ref. 17) or Michael addition[18] pathways, although these transformations yielded products with modest enantioselectivity. An alternative strategy in this theme involves the use of difluoroenoxysilanes as masked CF_2H sources, as exemplified by Zhang's asymmetric difluoroalkylation of propargyl sulfonate[19] and Ma's synthesis of enantioenriched isoindolones[20]. Enantioselective difluoromethylation via the insertion of difluorocarbene has recently emerged, enabling the synthesis of specific CF_2H-containing moieties, including α-amino acids[16] and β-ketoesters[21]. Given the unique properties of CF_2H groups, a different and more general mode of asymmetric difluoromethylation is highly desired to expand the molecular architectures containing the CF_2H bioisostere.

Nucleophilic difluoromethylation of racemic $C(sp^3)$ electrophiles in an enantioconvergent manner represents one of the most mechanistically straightforward approaches to the construction of chiral $C(sp^3)$–CF_2H moieties (Fig. 1b). Nonetheless, despite the considerable progress in the use of chiral transition-metal catalysts for the substitution of racemic alkyl electrophiles with carbon-[22–24] oxygen-[25] and nitrogen-centred nucleophiles[26–28], enantioselective difluoromethylation via this pathway remained largely underdeveloped. Moreover, only recently have methods for transition metal-catalysed fluoroalkylation of alkyl electrophiles emerged, with a focus mainly on trifluoromethylation reactions[29–31]. This lag in the development of nucleophilic fluoroalkylation reactions is attributed to the sluggish oxidative addition of the metal-fluoroalkyl species with alkyl electrophiles and the slower reductive elimination of metal-fluoroalkyl species compared with their non-fluorinated counterparts.

Our group[32–35] and others[36] have recently demonstrated the potential of copper catalysts in facilitating the transfer of CF_2H groups to aliphatic sites through alkyl radical intermediates. These catalytic methods enabled the synthesis of racemic CF_2H-containing products from various alkyl electrophiles. We recently questioned the feasibility of enantioselective transfer of CF_2H groups to alkyl radicals when the copper catalysts are in a chiral environment. This could enable a general strategy for the construction of difluoromethylated stereocentres. We realized that several challenges should be addressed to achieve such an enantioselective transformation. First, the intrinsic instability of the [Cu–CF_2H] species compared with their CF_3 counterparts[37,38] requires a swift single electron transfer (SET) event between this intermediate and the alkyl electrophile to prevent off-cycle decomposition. In addition, the formation of the anionic species $[Cu^I(CF_2H)_2]^-$, which is known to react with alkyl electrophiles in a racemic fashion[39], needs to be minimized. The pinnacle challenge, however, is to enable the enantioselective transfer of CF_2H groups to alkyl radicals[40,41]. In this work, we solved all the above challenges by employing an electron-deficient chiral diamine ligand (Fig. 1c). We disclose herein a mode for enantioselective difluoromethylation through alkyl radical intermediates, enabling the high-yield synthesis of a diverse range of CF_2H-containing molecules with excellent enantioselectivity. Density functional theory (DFT) calculations demonstrate key hydrogen bonding and π–π interactions between the chiral diamine ligand and substrates.

Results

Reaction development

We first examined the difluoromethylation of α-haloamides given the prevalence of amide groups in bioactive molecules (see Supplementary Tables 1–3 for detailed optimization results). Our study revealed that the combination of copper salts and a commercially available chiral diamine ligand, **L***, catalysed the difluoromethylation of racemic α-bromo-*N*-phenylbutanamide in 85% yield and with 95% enantiomeric excess (e.e.) (Fig. 2, entry 1). A nucleophilic CF_2H zinc reagent, $(DMPU)_2Zn(CF_2H)_2$, (DMPU = *N,N′*-dimethylpropyleneurea), that is, Vicic-Mikami reagent[42,43], was essential to promote this reaction. The use of **L***, which bears electron-deficient phenyl groups, was uniquely effective for this difluoromethylation reaction. The subambient temperature is necessary to achieve both high enantiocontrol and efficiency of the reactions, presumably by decelerating the decomposition pathways of the Cu^I–CF_2H intermediate. In addition, using solvents with higher polarity decreased the enantioselectivity of products presumably due to the partial formation of the anionic $[Cu^I(CF_2H)_2]^-$ species.

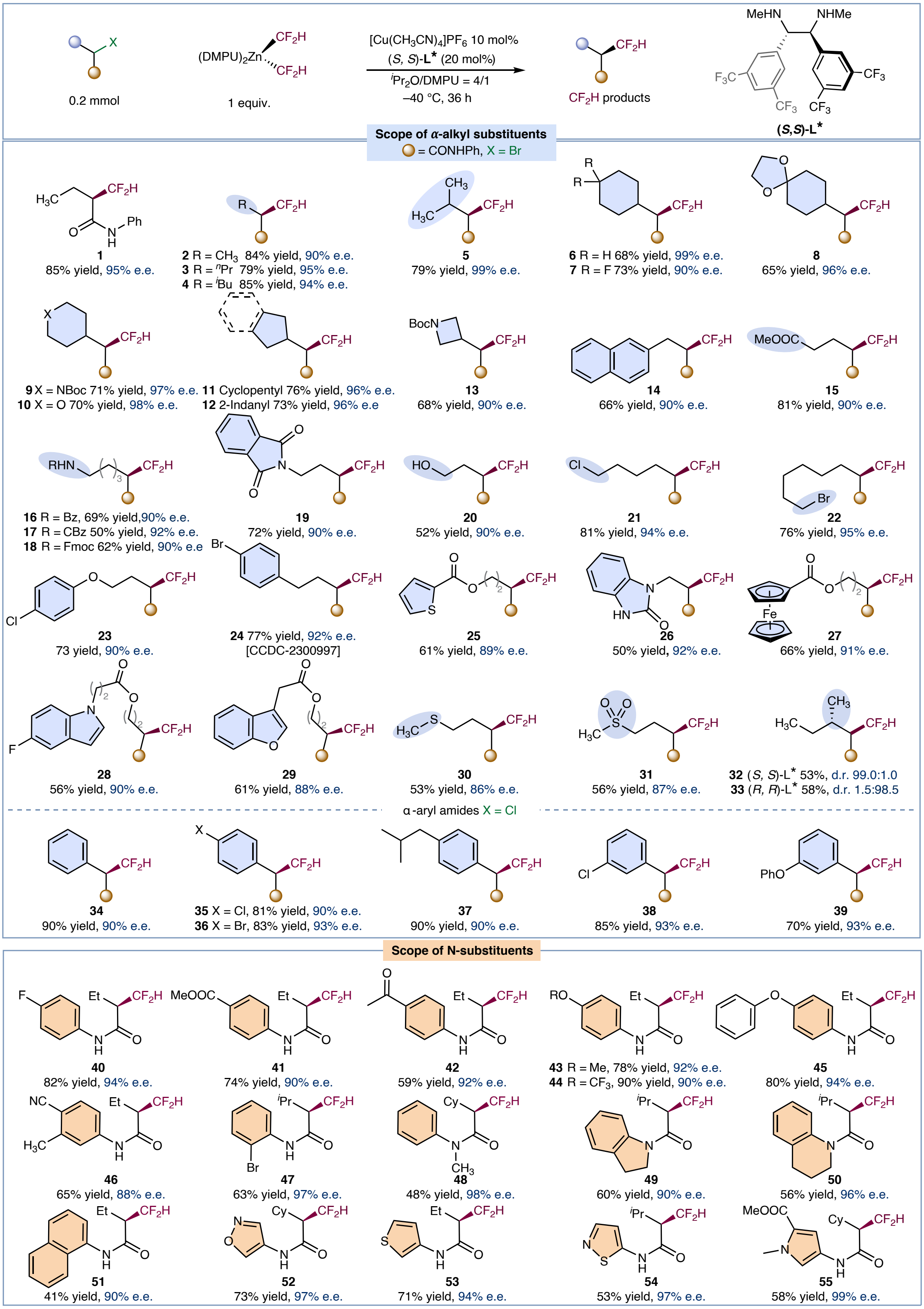

Fig. 2 | Scope for Cu-catalysed enantioconvergent difluoromethylation of alkyl halides. Reactions were performed with 0.2 mmol alkyl halides, 0.2 mmol $(DMPU)_2Zn(CF_2H)_2$, 0.02 mmol (10 mol%) $[Cu(CH_3CN)_4]PF_6$ and 0.04 mmol (20 mol%) $\mathbf{L}^*$ in 1.5 ml $^iPr_2O$/DMPU (4/1) at −40 °C for 36 h. Yields were based on isolated products. e.e. was determined by HPLC analysis on a chiral stationary phase. $^iPr_2O$, diisopropyl ether; ^nPr, *n*-propyl; ^iBu, isobutyl; Boc, *tert*-butyloxycarbonyl; Me, methyl; Bz, benzoyl; Fmoc, fluorenylmethoxycarbonyl; Et, ethyl.

Scope of the difluoromethylation reaction

We next examined the generality of this asymmetric difluoromethylation reaction. α-Bromoamides with simple alkyl substituents afforded the difluoromethylated products in good yield (79–85% yield), with enantioselectivity ranging from 90% to 95% e.e. (**2**–**4**). Alkyl bromides adjacent to secondary cyclic and acyclic groups were competent, affording the desired products in good yield and with high enantioselectivity (**5**–**12**, 65–79% yield, 90–99% e.e.). Notably, medicinally relevant heterocycles including piperidine (**9**), tetrahydropyran (**10**) and azetidine (**13**) were compatible with this protocol. In addition, a substrate that contained the bromide at a homobenzylic position, which was prone to β-hydrogen elimination, could afford its difluoromethylated product **14** in 66% yield and with 90% e.e. Various functional groups including ester (**15**), amide (**16**), carbamate (**17**–**18**), imide (**19**) and even unprotected alcohol (**20**) could be well tolerated (52–81% yield, 90–92% e.e.).

Substrates containing alkyl and aryl halides (bromides and chlorides) could be successfully difluoromethylated in good yield and with high enantioselectivity without affecting these halogen atoms (**21**–**24**, 73–81% yield, 90–95% e.e.). Heterocycles including thiophene (**25**), benzimidazolinone (**26**), ferrocene (**27**), indole (**28**) and benzofuran (**29**) were well tolerated under the mild reaction conditions, affording the difluoromethylated products with high enantioselectivity (50–66% yield, 88–92% e.e.). Substrates that contain strong coordinating functional groups including thioether (**30**) and sulfone (**31**) were converted to the desired products with slightly diminished enantioselectivity (86% and 87% e.e.). Moreover, stereoselectivity issues were probed in the reactions of a leucine-derived substrate (**32** and **33**). Catalysts with each of the enantiomers of ligand **L*** were tested, and both led to products with excellent diastereoselectivity (d.r. ≥98.5:1.5), reflecting high levels of catalyst- rather than substrate-controlled stereoselectivity. In addition, α-aryl-α-chloro-substituted amides could serve as suitable electrophiles, affording products that contain CF_2H groups at benzylic centres in high yield and with good enantioselectivity (**34**–**39**, 70–90% yield, 90–93% e.e.). The absolute configuration of the chiral molecules was determined by the X-ray crystallography of compound **24** (CCDC-2300997; Supplementary Fig. 1), which contained a chiral centre of *R* configuration.

In addition to *N*-phenyl-amide, we evaluated the compatibility of other *N*-aryl and *N*-heteroaryl groups with this asymmetric difluoromethylation reaction. Gratifyingly, electron-rich and electron-deficient substituents at *para*, *meta* or *ortho* positions of the phenyl groups have little effect on the enantioselectivity of the difluoromethylated products (**40**–**47**, 59–90% yield, 88–97% e.e.). In addition, substrates that contain tertiary amide groups could afford desired products with high enantioselectivity (**48**–**50**, 48–60% yield, 90–98% e.e.). These results rule out the involvement of aziridinone, an intermediate proposed in an asymmetric phenoxylation system[25]. Finally, a diverse range of *N*-heteroaryl groups, such as naphthalene (**51**), isoxazole (**52**), thiophene (**53**), isothiazole (**54**) and pyrrole (**55**) were compatible with this difluoromethylation protocol, furnishing the products in high enantioselectivity (41–73% yield, 90–99% e.e.).

Synthetic application

We further showcased that this asymmetric difluoromethylation protocol could facilitate the efficient synthesis of CF_2H analogues of molecules with pharmaceutical importance (Fig. 3). First, the diverse reactivity of amide groups allowed the synthesis of different CF_2H-containing molecules without affecting the chiral centres (Fig. 3a). For example, the reduction of compound **10** (98% e.e.) with borane provided the β-difluoromethylamine **56** in 90% yield with 97% e.e. In addition, the *N*-*para*-methoxy phenyl amide group in compound **57** (97% e.e.) could be removed via the cerium ammonium nitrate (CAN) oxidation to afford a primary amide **58** in 60% yield with 96% e.e. The scalability of this difluoromethylation protocol has also been demonstrated by the synthesis of compound **57** at a half-gram scale (60% yield, 97% e.e.). Moreover, recognizing the benefits of fluorinated analogues of non-steroidal anti-inflammatory drugs (NSAIDs), we synthesized the difluoromethylated counterpart of (*S*)-ibuprofen (Fig. 3a). The CF_2H amide **59** was formed in 87% yield and with 87% e.e. from the corresponding benzylic chloride. A two-step approach allows the conversion of **59** to the CF_2H analogue of (*S*)-ibuprofen (**61**, 87% e.e.) without compromising the enantioselectivity.

Given the widespread presence of amide functionalities in pharmaceuticals and agrochemicals, our approach offered an invaluable method for the rapid synthesis of their enantioenriched fluorinated bioisosteres (Fig. 3b). BMS-270394, a selective agonist for the human retinoic acid receptor, possesses a hydroxyl moiety that binds to the methionine sulfur atom within the protein's active site[44,45]. This hydroxyl group plays a pivotal role in the activity of BMS-270394, while its enantiomer remains inactive. Recognizing the potential of CF_2H groups as bioisosteres of OH groups, we successfully transformed the benzyl chloride precursor (**62**) into the difluoromethylated analogue of BMS-270394 (**63**) in 72% yield and with 92% e.e.

Moreover, given the escalating relevance of fluorinated herbicides and the increasing frequency of chiral centres in these molecules[46], we applied this asymmetric difluoromethylation protocol to the synthesis of a chiral CF_2H analogue of pentanochlor, a pre- and post-emergence herbicide. Thus, the treatment of the alkyl bromide **64** under the standard difluoromethylation conditions allowed the synthesis of **65** in 83% yield and with 94% e.e. Furthermore, this protocol enabled the synthesis of a precursor to the CF_2H analogue of acebutolol[47], a β-blocker for the treatment of high blood pressure (**67**, 60% yield, d.r. 93.5:6.5). Notably, the tolerance of a reactive epoxide group further demonstrated the mild conditions of this Cu-catalysed protocol.

We have extended this protocol to the late-stage difluoromethylation of natural products (Fig. 3c). A facile α-bromination followed by the amide bond formation of oleic acid affords the corresponding alkyl bromide (**68**), which could be converted to its difluoromethylated product (**69**) with high enantioselectivity (73% yield, 95% e.e.). Similarly, two steroid derivatives, cholic acid and lithocholic acid (in their acetate forms), were converted to their difluoromethylated analogues with excellent control of stereochemistry (**70**–**73**, 63–69% yield, d.r. >20:1) The high d.r. with either enantiomer of the diamine catalyst **L*** further highlights the catalyst-controlled selectivity of this difluoromethylation protocol.

Finally, this late-stage asymmetric difluoromethylation reaction protocol could be applied to the functionalization of pharmaceutical agents (Fig. 3d). Thus, a chemotherapy medication chlorambucil[48] and a γ-secretase inhibitor MK-0752[49] could be readily converted to their corresponding alkyl bromides (**74** and **76**). Difluoromethylation of these two alkyl bromides under the standard conditions afforded their CF_2H products (**75** and **77**) in good yield and with high enantioselectivity (48% and 66% yield, respectively, 95% e.e.).

Mechanistic studies

These results shown herein represent a rare example of highly enantioconvergent fluoroalkylation of alkyl electrophiles. Detailed mechanistic insights into these catalytic reactions should inspire the future development of asymmetric fluoroalkylation reactions. The radical nature of this protocol was confirmed by the difluoromethylation of a cyclopropyl-containing substrate (**78**), which afforded the only ring-opening products (**79** and **80**), whereas the unrearranged product (**81**) was not observed (Fig. 4a). In addition, we employed a radical trap 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO) to trap the transient alkyl radicals formed in the reaction mixture. The addition of DMPO to the reaction mixtures containing $[Cu(MeCN)_4]PF_6$, **L***, and an alkyl bromide **82**, with or without $(DMPU)_2Zn(CF_2H)_2$, consistently revealed the formation of the trapping product **83**, which was detected by electron paramagnetic resonance (EPR) spectroscopy. This observation further

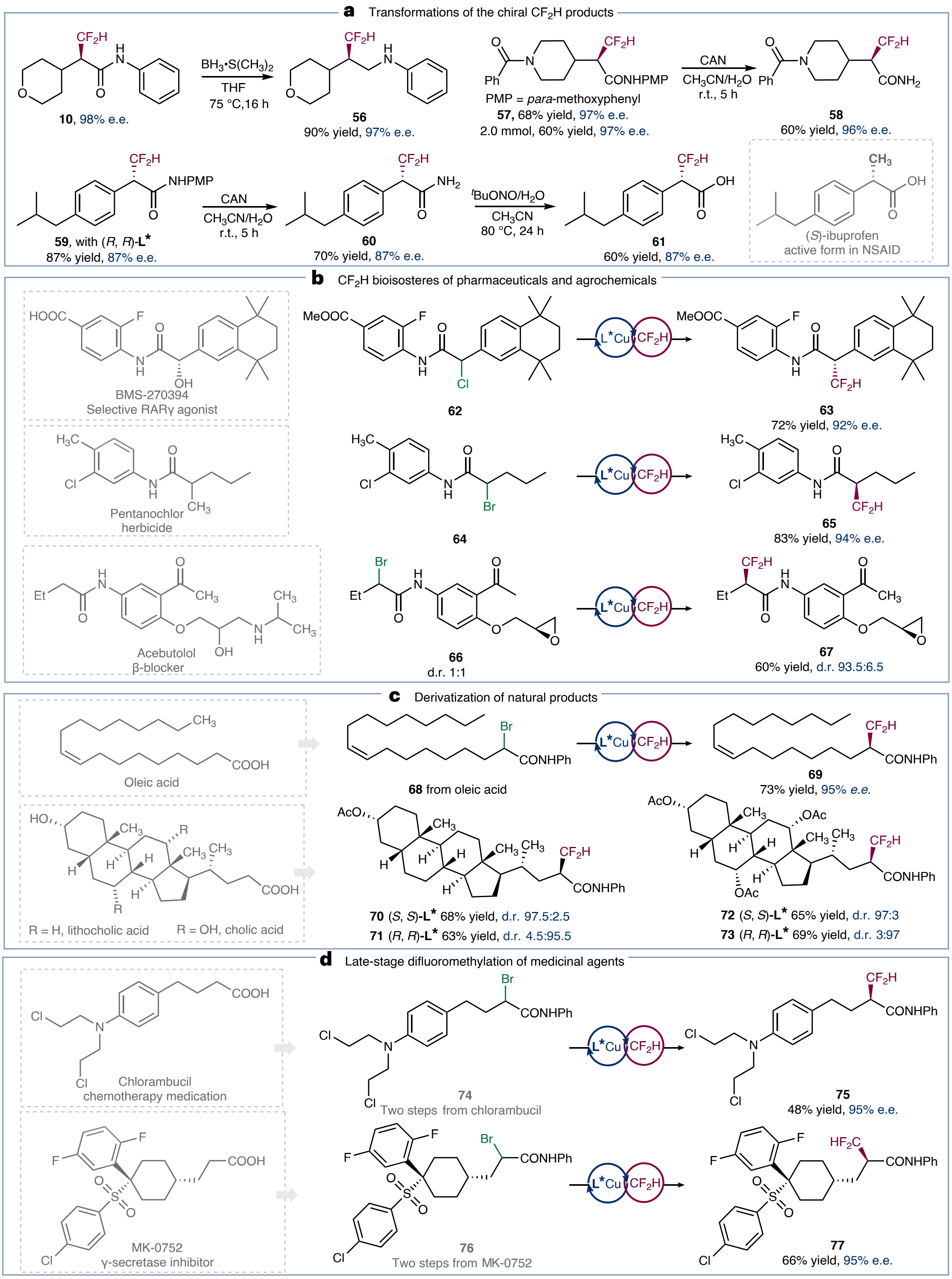

Fig. 3 | Synthetic applications of enantioconvergent difluoromethylation reaction. a, The synthetic transformation of enantiopure CF_2H products. **b**, The synthesis of analogues of pharmaceuticals and agrochemicals. **c**, Late-stage asymmetric difluoromethylation of natural products. **d**, Late-stage difluoromethylation of medicinal agents. THF, tetrahydrofuran; ᵗBu, *tert*-butyl; r.t., room temperature.

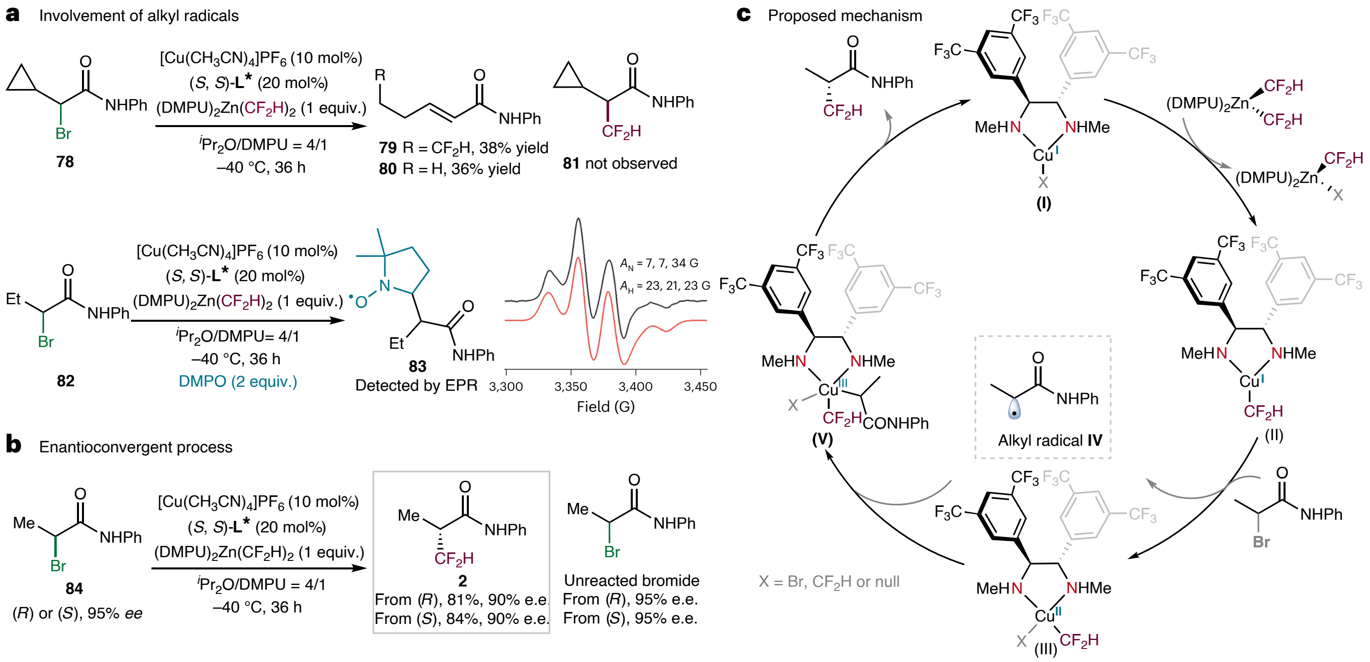

Fig. 4 | Mechanistic studies and proposed catalytic cycle. a, Radical clock and DMPO trapping experiments support the involvement of alkyl radical intermediates. **b**, Difluoromethylation of enantiomerically pure alkyl bromides supports a stereoablative enantioconvergent process. **c**, The proposed catalytic cycle for the enantioconvergent difluoromethylation reaction. $^{i}Pr_2O$, diisopropyl ether.

suggests that the reaction mechanism involves a SET step from the copper(I) species, leading to the generation of an alkyl radical (Fig. 4a). EPR simulations indicated hyperfine coupling to both nitrogen and hydrogen nuclei, with hyperfine constants A_N = 6.5 G, 6.5 G and 34 G and A_H = 23 G, 21 G and 23 G. Notably, the average hyperfine splitting values at low temperature align closely with those previously reported for DMPO radicals at room temperature[24].

We further applied EPR spectroscopy to investigate the potential formation of Cu^{II} intermediates through SET (Supplementary Figs. 2–4). A solution of diamagnetic $[Cu(CH_3CN)_4]PF_6$ with the chiral diamine ligand L^* exhibited a negligible EPR signal from the cavity. The addition of an alkyl bromide to this solution led to the emergence of an EPR signal with hyperfine splitting characteristics of a Cu^{II} species, implying the formation of a Cu^{II} intermediate in the reaction pathway. In analogous experiments, we introduced $(DMPU)_2Zn(CF_2H)_2$ to the reaction mixture. Interestingly, the resulting EPR spectra were silent, suggesting the rapid reaction between the transient alkyl radicals with the paramagnetic $[Cu^{II}–CF_2H]$ species.

To shed light on the enantioconvergent process of this reaction, we conducted difluoromethylation of an enantiomerically pure alkyl bromide **84** (Fig. 4b). Under standard reaction conditions, both enantiomers were converted to the same difluoromethylated product **2** with an identical e.e. value and in similar yield. Moreover, analysis of the unreacted alkyl bromides throughout the reaction revealed that no racemization occurred during the difluoromethylation reactions. These results are consistent with a stereoablative enantioconvergent process[50] rather than a simple kinetic resolution or a dynamic kinetic resolution.

In addition, a linear correlation was observed between the catalyst and product e.e. value, suggesting a 1:1 copper-to-ligand ratio in the enantiodiscrimination complex (Supplementary Fig. 5). X-ray crystallographic studies of $\mathbf{L}^*Cu^{II}(OAc)_2$, synthesized by mixing $\mathbf{L}^*$ with $Cu(OAc)_2$, validated the bidentate binding of the diamine catalyst with copper centre (CCDC-2303333; Supplementary Fig. 6). These results supported the involvement of a mononuclear copper species coordinated with a single chiral ligand as the active intermediate in the reaction.

Based upon these experimental observations, our current hypothesis for the mechanism of this Cu-catalysed enantioselective difluoromethylation reaction is shown in Fig. 4c. Diamine-bound copper(I) complex **I** undergoes transmetallation with the zinc-CF_2H reagent to provide copper(I)–CF_2H complex **II**. The reaction between complex **II** and the alkyl electrophile generates copper(II) complex **III** and an organic radical **IV**. The radical then recombines with the complex **III** to form an alkyl-copper(III)–CF_2H species **V** (refs. 51,52), which reductively eliminates to form the difluoromethylated product and regenerate the copper(I) catalyst[53,54].

Theoretical calculations

We next performed DFT calculations to understand the origin of enantioselectivity in this difluoromethylation process (Fig. 5). Previous work on copper-catalysed asymmetric functionalization of alkyl radicals indicated that the group transfer from Cu^{II} intermediates to alkyl radicals is the enantiodetermining step[55]. Therefore, we focused our DFT studies on the reaction between the Cu^{II} intermediate $[\mathbf{L}^*Cu^{II}(CF_2H)Br]$ and the alkyl radical **IV** (Fig. 5a). The addition to the *re* face of the alkyl radical **IV**, which proceeded with a 1.9 kcal mol^{-1} free energy barrier at transition state **TS*R***, led to the formation of a Cu^{III} intermediate **Int-*R***. In contrast, the addition from the *si* face of **IV** occurred with a higher free energy barrier of 4.4 kcal mol^{-1} at transition state **TS*S***, resulting in the formation of the Cu^{III} intermediate **Int-*S***. Both steps were exergonic, with the **Int-*R*** being 3.4 kcal mol^{-1} more stable ($\Delta G = -10.7$ kcal mol^{-1}) than its diastereomer **Int-*S*** ($\Delta G = -7.3$ kcal mol^{-1}). The C–CF_2H bond formation was found to proceed via concerted reductive elimination from Cu^{III} intermediates to afford either enantiomer of the difluoromethylated product. The transition state that formed the (*R*) product, **TS-RE*R***, was associated with a lower free energy ($\Delta G^{\ddagger} = 3.2$ kcal mol^{-1}) than its (*S*) counterpart, **TS-RE*S*** ($\Delta G^{\ddagger} = 6.0$ kcal mol^{-1}), with a difference in free energy of $\Delta\Delta G^{\ddagger} = 2.8$ kcal mol^{-1}. These computation results demonstrate that both the radical substitution and the reductive elimination steps favoured the formation of the (*R*) product, aligning well with the experimental results.

We also considered the possibility of the involvement of a bis-difluoromethyl Cu^{II} intermediate, $\mathbf{L}^*Cu^{II}(CF_2H)_2$ (Supplementary

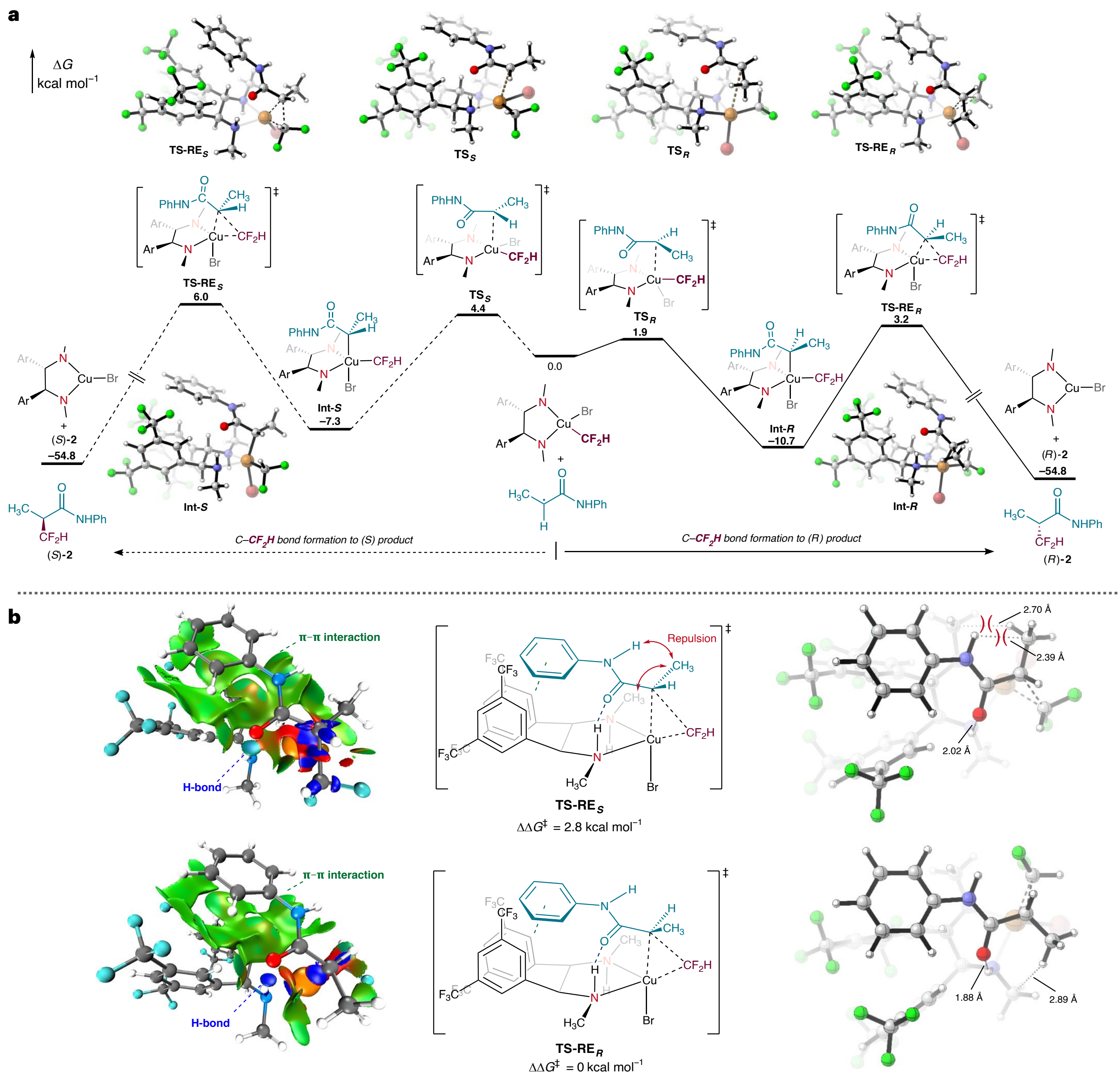

Fig. 5 | DFT calculations on the Cu-catalysed enantioconvergent difluoromethylation reaction at the B3LYP-D3BJ/def2-TZVP//B3LYP-D3BJ/def2-SVP level of theory. a, The free energy profile of the reactions between the Cu^{II} intermediate with the alkyl radical. **b**, The origin of the enantioselectivity.

Fig. 7). Although low barriers were found to form [$\mathbf{L}^*Cu^{III}(CF_2H)_2$(alkyl)] intermediates ($\Delta G^‡ < 4$ kcal mol^{-1}), the reductive elimination of resultant Cu^{III} intermediates was accompanied by high free energy barriers ($\Delta G^‡ > 29$ kcal mol^{-1}). Such high energies are unreasonable for low-temperature (−40 °C) reactions. In addition, an alternative radical substitution pathway where the alkyl radical directly attacks the CF_2H group on the Cu^{II} centre, without the involvement of a Cu^{III} intermediate, was ruled out due to its high activation energy ($\Delta G^‡ = 23.2$ kcal mol^{-1}; Supplementary Fig. 8).

To further elucidate the origin of the enantioselectivity, we examined the structures of the transition states in the C−CF_2H bond-forming step. Interestingly, DFT calculations revealed that *bis*-trifluoromethyl phenyl groups of the ligand occupied the pseudo-equatorial positions, consistent with the crystal structure of $\mathbf{L}^*Cu^{II}(OAc)_2$ (Supplementary Fig. 9). This conformation of the phenyl groups is unlikely to induce notable steric repulsion with the alkyl radical intermediate. On the other hand, the transition state structures for radical combination and reductive elimination all exhibited favourable interactions between the ligand and the substrate-derived radical (Fig. 5a). Interaction region indicator analysis[56] revealed the hydrogen bond interactions between the carbonyl group of the substrate and the NH bond of the diamine ligand (Fig. 5b). Furthermore, an edge-to-face π−π interaction was observed between the electron-rich phenyl groups in substrates and the electron-deficient phenyl groups in diamine catalysts. These non-covalent interactions dictated the conformation of the substrate radical during its approach to the Cu^{II} intermediate and the structure

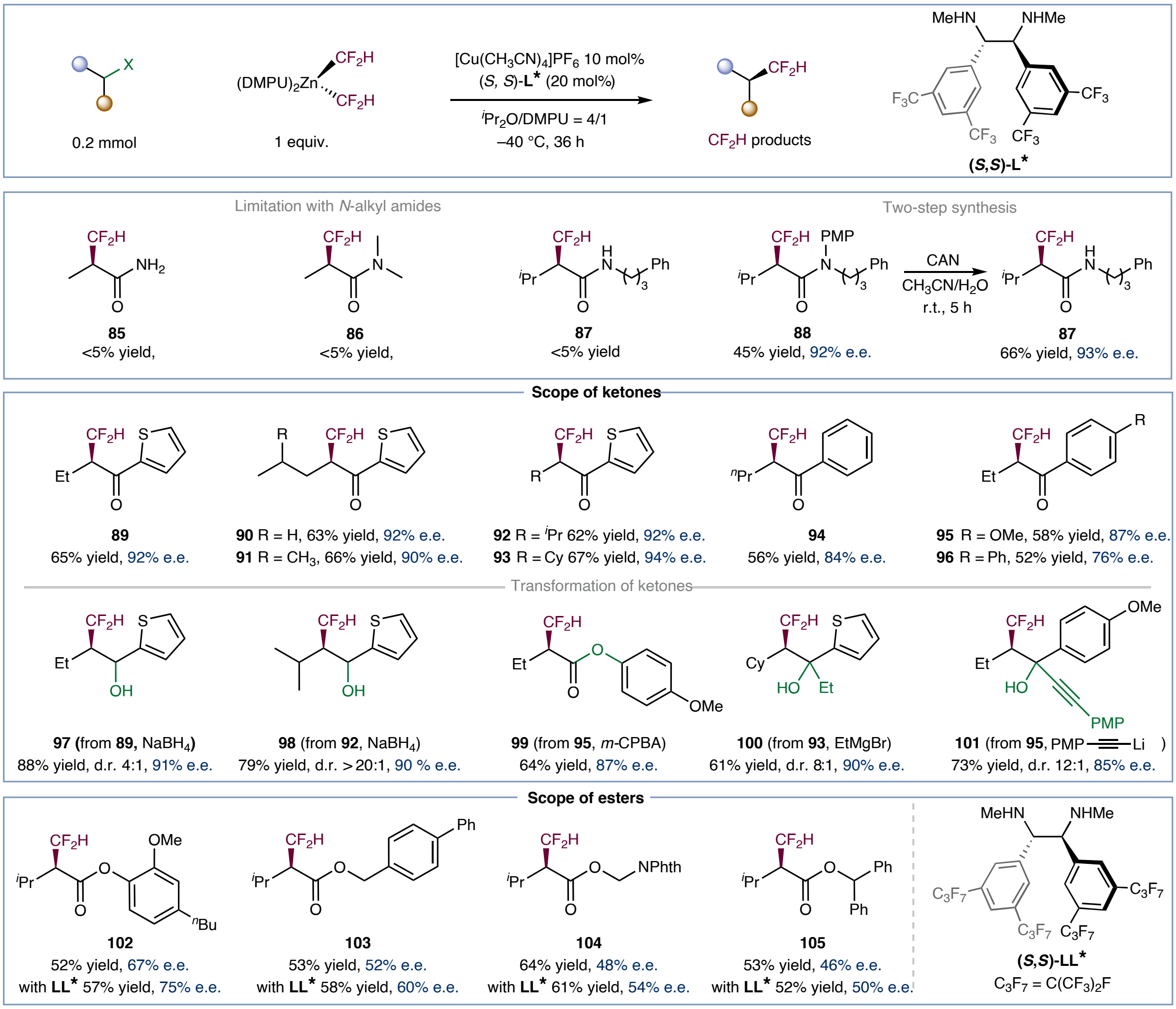

Fig. 6 | Other families of alkyl electrophiles investigated in this enantioconvergent difluoromethylation reaction. ^{i}Pr, isopropyl; ^{n}Pr, *n*-propyl; Cy, cyclohexyl; PMP, *para*-methoxyl phenyl; r.t., room temperature; m-CPBA, *meta*-chloroperoxybenzoic acid.

of the resultant Cu^{III} intermediates. Notably, the transition state that led to the *S* product (**TS-RE$_S$**) was destabilized due to the steric repulsion between the methyl group on the substrate and the *N*-methyl group on the ligand, along with the methyl group and N−H group on the substrate. Consequently, (*R*)-**2** was formed as the major product, consistent with the experimental results.

This stereochemical model aligned well with the experimental observations. For example, using diamine ligands with either *mono*-trifluoromethyl or non-substituted phenyl groups resulted in reduced enantioselectivity (Supplementary Table 4), probably due to weaker hydrogen-bonding and π−π interactions. In addition, the limitation with a primary amide 85 and *N*-alkyl secondary amides (**86** and **87**) could be attributed to the lack of π−π interactions (Fig. 6). Nonetheless, these limitations with *N*-alkyl amides could be overcome through a two-step synthesis strategy, involving the deprotection of a difluoromethylated *N*-aryl-*N*-alkyl amide **88**.

Additional substrates

Moreover, this protocol has been successfully extended to α-bromoketones, yielding enantioenriched α-CF_2H ketones with moderate to high enantioselectivity (**89**–**96**, 52–66% yield, 76–94% e.e.). Notably, electron-rich aryl ketones (**95**) exhibited comparable or higher enantioselectivity compared with those with electron-neutral aryl groups (**94** and **96**), possibly due to stronger π−π interactions. Given the versatile reactivity of ketone groups, these products can be further elaborated to construct other CF_2H-containing stereocentres, including difluoromethylated secondary alcohols (**97** and **98**, via $NaBH_4$ reduction), esters (**99**, via Baeyer–Villiger oxidation) and tertiary alcohols (**100** and **101**, via Grignard or organolithium reagents). Finally, this method could be applied to the difluoromethylation of α-bromoesters, albeit with modest enantioselectivity, possibly due to weaker non-covalent interactions. Interestingly, using **LL***, a chiral diamine ligand containing heptafluoroisopropyl groups (C_3F_7), modestly improved the enantioselectivity, presumably by modulating the non-covalent interactions between the ligand and substrates.

Conclusions

Overall, we report herein a Cu-catalysed approach for highly enantioselective difluoromethylation, enabling the synthesis of a broad spectrum of enantioenriched molecules containing the CF_2H group. This reaction highlights the benefit of using nucleophilic fluoroalkyl reagents for the enantioselective functionalization of alkyl radical intermediates. More importantly, the successful realization of asymmetric difluoromethylation of alkyl radicals opens a different avenue for constructing stereochemical centres that contain CF_2H and other fluoroalkyl groups. Finally, the manipulation of the hydrogen bonding and π−π interactions of this chiral amine ligand holds promise for inspiring the development of asymmetric transformations.

Methods

General procedure for copper-catalysed enantioconvergent difluoromethylation of alkyl halides

In a glovebox filled with argon, an oven-dried 4 ml vial equipped with a stir bar was charged with $[Cu(CH_3CN)_4]PF_6$ (7.5 mg, 0.02 mmol, 10 mol%), ligand $\mathbf{L}^*$ (20.0 mg, 0.04 mmol, 20 mol%) and anhydrous isopropyl ether (1.2 ml). The mixture was stirred at room temperature for 15 min, then taken out of the glovebox and cooled to −40 °C. Subsequently, a solution of the alkyl halide (0.2 mmol, 1.0 equiv.) and $(DMPU)_2Zn(CF_2H)_2$ (88 mg, 0.2 mmol, 1.0 equiv.) in DMPU (0.3 ml) was added dropwise to the reaction mixture using a syringe. After stirring for 36 h at this temperature, the reaction mixture was allowed to warm to room temperature. The difluoromethylated product was purified through column chromatography on silica gel using hexanes/ethyl acetate as the mobile phase. The e.e. of the products was determined by high-performance liquid chromatography (HPLC), using CHIRALPAK AD-H, IA, IB or CHIRALCEL OD-H and OJ-H columns.

Data availability

The data generated in this study are provided in Supplementary Information and related files provided with this paper. Data are also available from the corresponding author upon request. The X-ray crystallographic coordinates for structures reported in this study have been deposited at the Cambridge Crystallographic Data Centre under deposition numbers 2300997 and 2303333. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

References

1. Kenny, P. W. Hydrogen-bond donors in drug design. *J. Med. Chem.* **65**, 14261–14275 (2022).
2. Zafrani, Y. et al. Difluoromethyl bioisostere: examining the ‘lipophilic hydrogen bond donor’ concept. *J. Med. Chem.* **60**, 797–804 (2017).
3. Zafrani, Y. et al. CF_2H, a functional group-dependent hydrogen-bond donor: is it a more or less lipophilic bioisostere of OH, SH, and CH_3? *J. Med. Chem.* **62**, 5628–5637 (2019).
4. Muller, K., Faeh, C. & Diederich, F. Fluorine in pharmaceuticals: looking beyond intuition. *Science* **317**, 1881–1886 (2007).
5. Hanan, E. J. et al. Discovery of GDC-0077 (Inavolisib), a highly selective inhibitor and degrader of mutant PI3Kα. *J. Med. Chem.* **65**, 16589–16621 (2022).
6. Zhao, J. et al. Preclinical safety and efficacy characterization of an LpxC inhibitor against Gram-negative pathogens. *Science Transl. Med.* **15**, eadf5668 (2023).
7. Sap, J. B. I. et al. Late-stage difluoromethylation: concepts, developments and perspective. *Chem. Soc. Rev.* **50**, 8214–8247 (2021).
8. Briand, M., Anselmi, E., Dagousset, G. & Magnier, E. The revival of enantioselective perfluoroalkylation—update of new synthetic approaches from 2015–2022. *Chem. Rec.* **23**, e202300114 (2023).
9. Yang, X. Y., Wu, T., Phipps, R. J. & Toste, F. D. Advances in catalytic enantioselective fluorination, mono-, di-, and trifluoromethylation, and trifluoromethylthiolation reactions. *Chem. Rev.* **115**, 826–870 (2015).
10. Aikawa, K., Yoshida, S., Kondo, D., Asai, Y. & Mikami, K. Catalytic asymmetric synthesis of tertiary alcohols and oxetenes bearing a difluoromethyl group. *Org. Lett.* **17**, 5108–5111 (2015).
11. Liu, Y.-L. et al. Organocatalytic asymmetric strecker reaction of di- and trifluoromethyl ketoimines. Remarkable fluorine effect. *Org. Lett.* **13**, 3826–3829 (2011).
12. Middleton, W. J. New fluorinating reagents. Dialkylaminosulfur fluorides. *J. Org. Chem.* **40**, 574–578 (1975).
13. Xu, Y. & Prestwich, G. D. Concise synthesis of acyl migration-blocked 1,1-difluorinated analogues of lysophosphatidic acid. *J. Org. Chem.* **67**, 7158–7161 (2002).
14. Ni, C., Wang, F. & Hu, J. Enantioselective nucleophilic difluoromethylation of aromatic aldehydes with $Me_3SiCF_2SO_2Ph$ and $PhSO_2CF_2H$ reagents catalyzed by chiral quaternary ammonium salts. *Beilstein J. Org. Chem.* **4**, 21 (2008).
15. Zhao, Y., Huang, W., Zheng, J. & Hu, J. Efficient and direct nucleophilic difluoromethylation of carbonyl compounds and Imines with Me_3SiCF_2H at ambient or low temperature. *Org. Lett.* **13**, 5342–5345 (2011).
16. Peng, L., Wang, H. & Guo, C. Copper-catalyzed enantioselective difluoromethylation of amino acids via difluorocarbene. *J. Am. Chem. Soc.* **143**, 6376–6381 (2021).
17. Gu, Y., Lu, C., Gu, Y. & Shen, Q. Ligand-controlled copper-catalyzed highly regioselective difluoromethylation of allylic chlorides/bromides and propargyl bromides. *Chin. J. Chem.* **36**, 55–58 (2018).
18. Endo, Y., Ishii, K. & Mikami, K. Chiral copper-catalyzed enantioselective Michael difluoromethylation of arylidene Meldrum’s acids with (difluoromethyl)zinc reagents. *Tetrahedron* **75**, 4099–4103 (2019).
19. Gao, X., Cheng, R., Xiao, Y.-L., Wan, X.-L. & Zhang, X. Copper-catalyzed highly enantioselective difluoroalkylation of secondary propargyl sulfonates with difluoroenoxysilanes. *Chem* **5**, 2987–2999 (2019).
20. Rong, M.-Y., Li, J.-S., Zhou, Y., Zhang, F.-G. & Ma, J.-A. Catalytic enantioselective synthesis of difluoromethylated tetrasubstituted stereocenters in isoindolones enabled by a multiple-fluorine system. *Org. Lett.* **22**, 9010–9015 (2020).
21. Wang, Y. et al. Asymmetric α-electrophilic difluoromethylation of β-keto esters by phase transfer catalysis. *Org. Biomol. Chem.* **19**, 4788–4795 (2021).
22. Choi, J. & Fu, G. C. Transition metal-catalyzed alkyl–alkyl bond formation: another dimension in cross-coupling chemistry. *Science* **356**, eaaf7230 (2017).
23. Wang, F., Chen, P. & Liu, G. Copper-catalyzed radical relay for asymmetric radical transformations. *Acc. Chem. Res.* **51**, 2036–2046 (2018).
24. Gu, Q.-S., Li, Z.-L. & Liu, X.-Y. Copper(I)-catalyzed asymmetric reactions involving radicals. *Acc. Chem. Res.* **53**, 170–181 (2020).
25. Chen, C. & Fu, G. C. Copper-catalysed enantioconvergent alkylation of oxygen nucleophiles. *Nature* **618**, 301–307 (2023).
26. Kainz, Q. M. et al. Asymmetric copper-catalyzed C–N cross-couplings induced by visible light. *Science* **351**, 681–684 (2016).
27. Chen, C., Peters, J. C. & Fu, G. C. Photoinduced copper-catalysed asymmetric amidation via ligand cooperativity. *Nature* **596**, 250–256 (2021).
28. Chen, J.-J. et al. Enantioconvergent Cu-catalysed N-alkylation of aliphatic amines. *Nature* **618**, 294–300 (2023).
29. Zhao, X. & MacMillan, D. W. C. Metallaphotoredox perfluoroalkylation of organobromides. *J. Am. Chem. Soc.* **142**, 19480–19486 (2020).
30. Kornfilt, D. J. P. & MacMillan, D. W. C. Copper-catalyzed trifluoromethylation of alkyl bromides. *J. Am. Chem. Soc.* **141**, 6853–6858 (2019).
31. Shen, H. et al. Trifluoromethylation of alkyl radicals in aqueous solution. *J. Am. Chem. Soc.* **139**, 9843–9846 (2017).
32. Zeng, X. J. et al. Copper-catalyzed decarboxylative difluoromethylation. *J. Am. Chem. Soc.* **141**, 11398–11403 (2019).
33. Cai, A., Yan, W. & Liu, W. Aryl radical activation of C–O bonds: copper-catalyzed deoxygenative difluoromethylation of alcohols. *J. Am. Chem. Soc.* **143**, 9952–9960 (2021).
34. Zeng, X. et al. Copper-catalyzed deaminative difluoromethylation. *Angew. Chem. Int. Ed.* **59**, 16398–16403 (2020).

35. Cai, A., Yan, W., Wang, C. & Liu, W. Copper-catalyzed difluoromethylation of alkyl iodides enabled by aryl radical activation of carbon–iodine bonds. *Angew. Chem. Int. Ed.* **60**, 27070–27077 (2021).
36. Mao, E., Prieto Kullmer, C. N., Sakai, H. A. & MacMillan, D. W. C. Direct bioisostere replacement enabled by metallaphotoredox deoxydifluoromethylation. *J. Am. Chem. Soc.* **146**, 5067–5073 (2024).
37. Fier, P. S. & Hartwig, J. F. Copper-mediated difluoromethylation of aryl and vinyl iodides. *J. Am. Chem. Soc.* **134**, 5524–5527 (2012).
38. Bour, J. R., Kariofillis, S. K. & Sanford, M. S. Synthesis, reactivity, and catalytic applications of isolable (NHC)Cu(CHF_2) complexes. *Organometallics* **36**, 1220–1223 (2017).
39. Zhao, H., Leng, X. B., Zhang, W. & Shen, Q. $[Ph_4P]^+[Cu(CF_2H)_2]^-$: a powerful difluoromethylating reagent inspired by mechanistic investigation. *Angew. Chem. Int. Ed.* **61**, e202210151 (2022).
40. Jiang, C. et al. Enantioselective copper-catalyzed trifluoromethylation of benzylic radicals via ring opening of cyclopropanols. *Chem* **6**, 2407–2419 (2020).
41. Xu, P., Fan, W., Chen, P. & Liu, G. Enantioselective radical trifluoromethylation of benzylic C–H bonds via cooperative photoredox and copper catalysis. *J. Am. Chem. Soc.* **144**, 13468–13474 (2022).
42. Xu, L. & Vicic, D. A. Direct difluoromethylation of aryl halides via base metal catalysis at room temperature. *J. Am. Chem. Soc.* **138**, 2536–2539 (2016).
43. Serizawa, H., Ishii, K., Aikawa, K. & Mikami, K. Copper-catalyzed difluoromethylation of aryl iodides with (difluoromethyl)zinc reagent. *Org. Lett.* **18**, 3686–3689 (2016).
44. Chidambaram, R. et al. A practical synthesis of the RARγ agonist, BMS-270394. *Org. Process. Res. Dev.* **6**, 632–636 (2002).
45. Klaholz, B. P., Mitschler, A., Belema, M., Zusi, C. & Moras, D. Enantiomer discrimination illustrated by high-resolution crystal structures of the human nuclear receptor hRARγ. *Proc. Natl Acad. Sci. USA* **97**, 6322–6327 (2000).
46. Ogawa, Y., Tokunaga, E., Kobayashi, O., Hirai, K. & Shibata, N. Current contributions of organofluorine compounds to the agrochemical industry. *iScience* **23**, 101467 (2020).
47. Foster, R. J. & Carr, R. A. in *Analytical Profiles of Drug Substances* Vol. 19 (ed. Florey, K.) 1–26 (Academic Press,1990).
48. Dighiero, G. et al. Chlorambucil in indolent chronic lymphocytic leukemia. *N. Engl. J. Med.* **338**, 1506–1514 (1998).
49. Jacquelynn, J. C. et al. Acute γ-secretase inhibition of nonhuman primate CNS shifts amyloid precursor protein (APP) metabolism from amyloid-β production to alternative APP fragments without amyloid-β rebound. *J. Neurosci.* **30**, 6743–6750 (2010).
50. Bhat, V., Welin, E. R., Guo, X. & Stoltz, B. M. Advances in stereoconvergent catalysis from 2005 to 2015: transition-metal-mediated stereoablative reactions, dynamic kinetic resolutions, and dynamic kinetic asymmetric transformations. *Chem. Rev.* **117**, 4528–4561 (2017).
51. Luo, Y. et al. Oxidative addition of an alkyl halide to form a stable Cu(III) product. *Science* **381**, 1072–1079 (2023).
52. Yan, W. et al. Catalytically relevant organocopper(III) complexes formed through aryl-radical-enabled oxidative addition. *J. Am. Chem. Soc.* **146**, 15176–15185 (2024).
53. Liu, S. et al. C(sp^3)-CF_3 reductive elimination from a five-coordinate neutral copper(III) complex. *J. Am. Chem. Soc.* **142**, 9785–9791 (2020).
54. Paeth, M. et al. Csp^3–Csp^3 bond-forming reductive elimination from well-defined copper(III) complexes. *J. Am. Chem. Soc.* **141**, 3153–3159 (2019).
55. Liu, J.-R., Xu, G.-X., Liu, L.-G., Zhang, S.-Q. & Hong, X. Recent advances in theoretical studies on Cu-mediated bond formation mechanisms involving radicals. *ACS Catal.* **14**, 2429–2454 (2024).
56. Lu, T. & Chen, Q. Interaction region indicator: a simple real space function clearly revealing both chemical bonds and weak interactions. *Chem. Methods* **1**, 231–239 (2021).

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Author contributions

D.D. and W.L. designed experiments. D.D. and L.Y. performed the synthetic experiments and prepared the supplementary information. A.T.P., S.C.Y., R.M.K. and S.T. performed EPR experiments. M.-J.C., Y.-H.C. and C.-T.H. conducted DFT calculations. J.A.K. performed X-ray diffraction analysis. W.L. conceived and supervised the project. W.L. wrote this manuscript with contributions from all authors.

Competing interests

The authors declare no competing interests.

Additional information

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