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Copper-catalyzed enantioselective three-component radical 1,4-perfluoroalkylamination of 1,3-dienes

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Catalytic enantioselective three-component aminative difunctionalization of readily available 1,3-dienes offers a straightforward methodology to fast access significant and complex chiral allylic amines. Nevertheless, compared to the widely studied two-component reactions, the three-component reactions, especially using anilines—very common bulk feedstock chemicals as aminating reagents are underdeveloped. More importantly, the limited examples of enantioselective three-component aminative difunctionalization of 1,3-dienes with anilines only showed 1,2-selectivity; and the corresponding 1,4-regioselectivity remains unknown. Here, we report a copper-catalyzed enantioselective radical three-component 1,4-perfluoroalkylamination of 1,3-dienes with anilines and perfluoroalkyl reagents, efficiently providing an array of valuable perfluoroalkylated chiral allylic amines in good to excellent yields with excellent enantioselectivity. Mechanistic investigations, including controlled experiments and DFT studies, elucidate the origination of the regioselectivity and enantioselectivity, and suggest a radical reaction pathway involving an asymmetric cross-coupling between allylic radical and copper-stabilized nitrogen radical species to construct C–N bond enantioselectively.

Chiral allylic amines are useful synthetic building blocks and essential structural element in natural products, and pharmaceuticals[1–3]. Perfluoroalkyl groups, such as the trifluoromethyl group, have been confirmed to be a crucial unit that can lead to improved bioavailability, metabolic stability, and efficacy[4,5]. Some trifluoromethylated chiral allyl amines have been demonstrated to be promising pharmaceuticals. For instance, DPC-083 is an orally available non-nucleoside reverse transcriptase inhibitor with broad inhibitory effects on HIV[6]; compound **I** is a potential inhibitor and inactivator of γ-aminobutyric acid aminotransferase (Fig. 1a)[7]. Therefore, the development of effective and streamlined synthetic methods for perfluoroalkyl-containing chiral allylic amines is of great importance, especially those starting from bulk feedstock chemicals.

1,3-Dienes are common bulk feedstock chemicals. A transition metal-catalytic asymmetric three-component aminative difunctionalization of 1,3-dienes, due to simultaneously introducing an amino and another functional groups in one-step with high regio- and stereoselectivity, is a promising and straightforward strategy to access structurally diverse chiral allylic amines[8–10]. To date, by leveraging the pre-prepared aminating reagents, such as dienyl amine, *N*-aryl amide, aryl urea, aminal, diaziridinone, or dioxazolone, enantioselective arylamination[11–16], alkenylamination[17], aminomethylamination[18], diamination[19–21] and oxyamination[22] have been successfully achieved with the vast majority being two-component annulative reactions. The corresponding three-component transformations are rare. Moreover, aniline and its derivatives, as readily available chemical materials and

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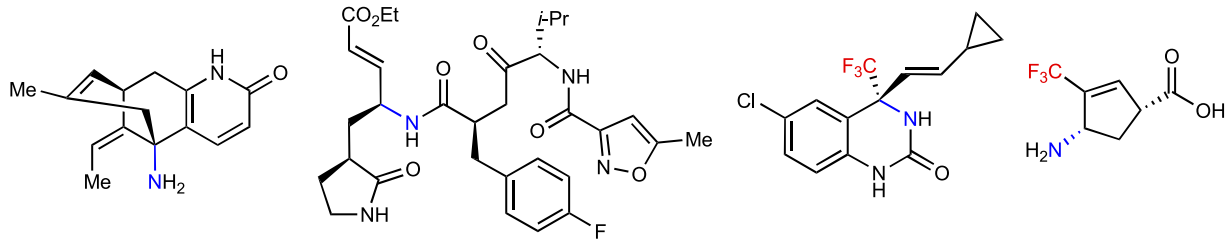
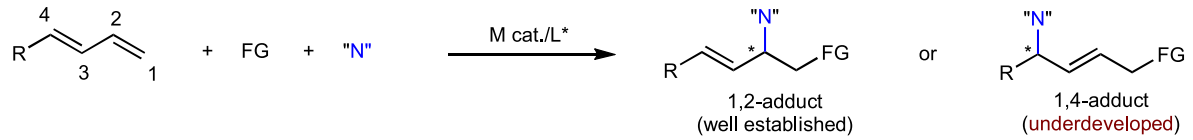
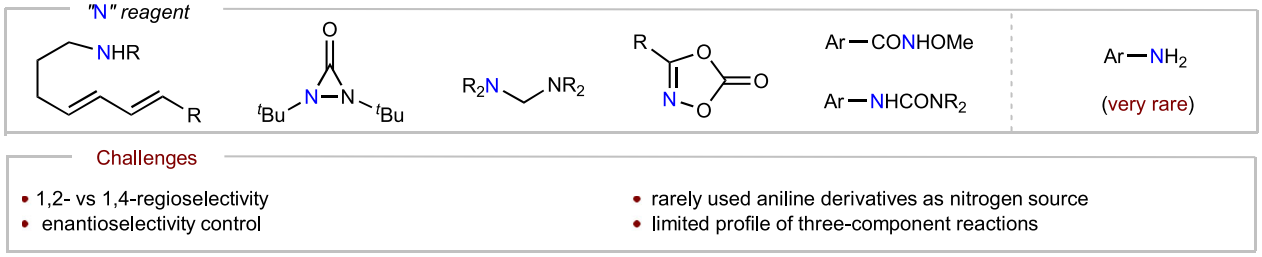
a Relevant bioactive molecules containing (perfluoroalkylated) chiral allylic amines



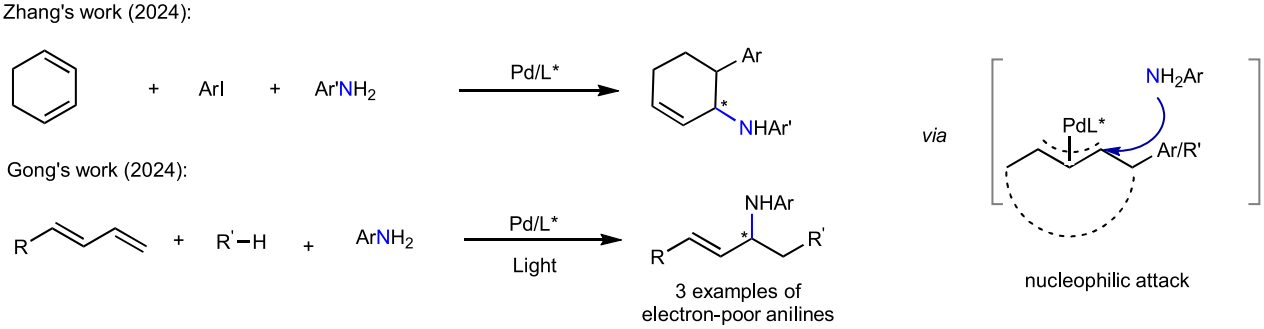
Huperzine A (AChE inhibitor) | Rupintrivir (HRV 3C protease inhibitor) | DPC-083 (anti-HIV) | I (GABA-AT inhibitor)

b Transition metal-catalyzed enantioselective aminative difunctionalization of 1,3-dienes





c Transition metal-catalyzed enantioselective three-component 1,2-aminative difunctionalization of 1,3-dienes with aniline derivatives



d This work: radical enantioselective three-component 1,4-perfluoroalkylamination of 1,3-dienes with aniline derivatives

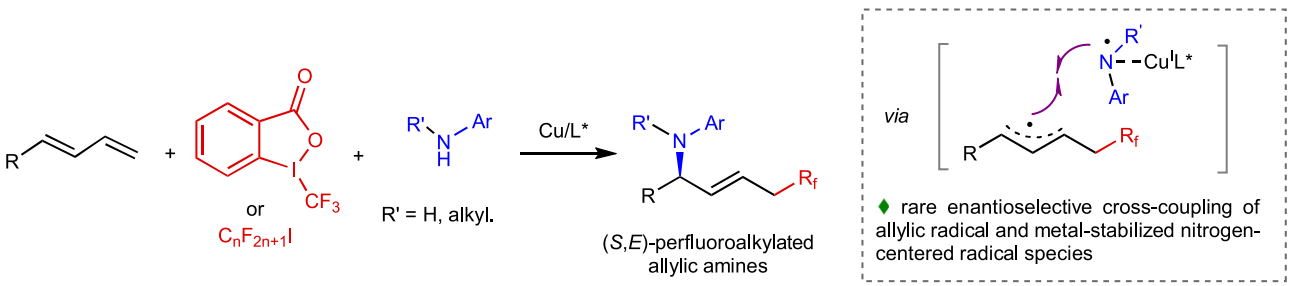


Fig. 1 | Background and our reaction. a Examples of biological and pharmaceutical active molecules with perfluoroalkylated chiral allylic amine substructure. **b** Transition metal-catalyzed asymmetric aminative difunctionalization of 1,3-dienes. **c** Transition metal-catalyzed asymmetric 1,2-three-component aminativedifunctionalization of 1,3-dienes with aniline derivatives. **d** This work: enantioselective three-component radical 1,4-perfluoroalkylamination of 1,3-dienes with aniline derivatives.

ubiquitous units in functional materials, are highly charming aminating reagents in the enantioselective aminative difunctionalization of 1,3-dienes (Fig. 1b). Very recently, by using a structurally fixed 1,3-diene as the substrate, Zhang and coworkers[16] disclosed a Pd-catalyzed three-component enantioselective 1,2-arylamination of 1,3-cyclohexadiene with aryl iodide and anilines via a Heck-type insertion to form aryl π-allyl palladium intermediate followed by nucleophilic attack of aniline (Fig. 1c).

Radical reactions, featuring high activity and good functional group compatibility, have attracted much attention[23,24]. With the rapid development of catalytic asymmetric synthesis, remarkable and impressive advances have been made in radical enantioselective transformations[25–27]. Radical-initiated asymmetric difunctionalization of 1,3-dienes, through the first radical addition onto 1,3-diene to form allylic radical, then combining with metal to generate π-allyl metal species and final reductive elimination or nucleophilic/electrophilic attack allowing various functional groups to be introduced, has emerged as a promising and robust platform for a fast buildup of complex enantioenriched allylic compounds[28]. In this regards, asymmetric 1,2-diamination[29], alkylamination[30], alkylesterification[31,32], alkylcyanation[33], amidocyanation[34], dialkylation[35,36], arylalkylation[37], alkylsulfonylation[38], and azidooxygenation[39] of 1,3-dienes, have been successfully achieved. Impressively, Gong and coworkers[40] recently realized photoinduced Pd-catalyzed enantioselective 1,2-carboamination of 1,3-dienes with aliphatic amines and aliphatic C − H bonds, where three examples of electron-poor anilines were reported (Fig. 1c). Despite these great advances, reports of enantioselective three-component aminative difunctionalization of 1,3-diene with anilines is still quite limited. More importantly, the corresponding enantioselective 1,4-selectivity remains unexplored. As our continuous research interests on asymmetric radical reactions[41–47], herein, we disclosed a Cu-catalyzed enantioselective perfluoroalkylamination of 1,3-dienes with aniline derivatives and perfluoroalkyl reagents, efficiently synthesizing various perfluoroalkyl-containing chiral allylic amine derivatives (Fig. 1d). This reaction shows impressively unique 1,4-regioselectivity and the excellent enantioselectivity. DFT investigations elucidated the precise control of the selectivity and revealed that the asymmetric formation of C–N bond involved an enantioselective radical cross-coupling of allylic radical and copper-stabilized nitrogen-centered radical species.

Results

Reaction optimization

We choose a reaction of (*E*)-buta-1,3-dien-1-ylbenzene (**1a**) with *N*-methylaniline (**2a**) and Togni reagent (**3a**) as the model reaction. Initially, the racemic trifluoromethylamination was carried out in the presence of copper catalyst without ligand. Intriguingly, only 1,4-addition product **4** was formed in 38% yield and no 1,2-adduct was observed (Table 1, entry 1). Then, the asymmetric version was carefully investigated (Table 1 and Supplementary Table 1-4). When chiral bisoxazoline **L1** as the ligand was added to the model reaction, we were pleased to find that **4** was obtained in 78% isolated yield and 84:16 er (entry 2). Other chiral bisoxazoline ligands, such as **L2** and **L3**, could not improve the yield and the enantioselectivity of **4** (entries 3 and 4, and Supplementary Table 1). In the absence of the copper catalyst, no reaction occurred (entry 5). Reducing the reaction temperature was beneficial to raise the enantioinduction, but it required an extension of the reaction time (entry 6 and Supplementary Table 2). The reaction in a mixed solvent of CH_3CN and EtOAc (EA) (1:4) gave the best result (entries 7–9 and Supplementary Table 3), that the desired 1,4-adduct **4** was obtained in 84% isolated yield and 93:7 er (entry 9). Screening other copper catalysts was also conducted, and vaguely inferior yield under otherwise identified conditions were obtained (entries 10–12 and Supplementary Table 4). Distinctly, during the whole optimization, the competitive 1,2-adduct, which was often predominated in literatures of 1,3-diene enantioselective difunctionalization, was not detected.

Substrate scope

After establishing the optimal reaction conditions, the generality of this methodology was examined. Firstly, the scope of 1,3-diene components was investigated. As highlighted in Fig. 2a, a series of enantioenriched trifluoromethyl-containing allylic amines **4**–**30** were smoothly obtained under the optimized reaction conditions. Remarkably, directly employing a *Z*/*E* mixture of 1,3-diene **1b**-**1v** as the substrates could also generate the corresponding (*E*)-selective products **5**–**25**. Specifically, *ortho*-methyl, fluoro-, and chloro-substituted phenyl-1,3-dienes were transformed to products **5**, **6** and **7** in moderate yields and high enantioselectivity. When *meta*-substituted aromatic dienes were used as the substrates, the desired products **8**–**13** were formed in up to almost quantitative yield with high enantioselectivity. For *para*-substituted aromatic dienes, such as alkyl and halogen atom (F, Cl, and Br), chiral trifluoromethyl-contained allyl amines **14**–**17** were obtained in good to excellent yields with moderate enantioselectivity. In addition to monosubstituted aromatic 1,3-dienes, polysubstituted aromatic 1,3-dienes were also examined under the optimal conditions. Disubstituted aromatic 1,3-dienes were suitable substrates, forming corresponding chiral allyl amines **18**–**22** in moderate to almost quantitative yields with moderate to high enantioselectivities. The trisubstituted aromatic 1,3-diene was effective substrate, furnishing corresponding product **23** in good result. Furthermore, the fused aromatic ring substituted 1,3-dienes were also tested. The desired reactions proceeded smoothly, affording the corresponding products **24** and **25** in good results. Disubstituted 1,3-diene also worked very well, forming allylic amine **26** in approximate quantitative yield and high enantioselectivity. Additionally, 1,3-dienes **1x, 1y, 1z** and **1aa** derived from drugs borneol, naproxen, diacetonefructose and ibuprofen were smoothly converted into the expected trifluoromethyl-contained chiral allylic amines **27**, **28**, **29** and **30**, respectively, with good yields and satisfied stereoselectivity. These results showcased the robustness and usefulness of the reaction. An alkyl-substituted 1,3-diene, such as 1-benzyl-1,3-diene, was also subjected to the trifluoromethylamination reaction, but only a trace amount of the desired 1,4-addition product was observed, along with an inseparable mixture.

The scope of aniline derivatives was probed (Fig. 2b). A various of chain secondary aromatic amines, such as *para*- or *meta*-electron-donating or -withdrawing group substituted *N*-methyl aromatic amines were tolerated with the reaction to furnish desired chiral trifluoromethyl-containing allyl amines **31**–**44** in good to excellent yields and excellent er. *N*-Methyl 3,4-disubstituted aromatic amines were capable substrates, affording the expected products **45**–**48** in good yields with good er value. Also, *N*-methyl fused aromatic amines can yield the expected products **49** and **50** with excellent yield and good stereoselectivity. Besides methyl, ethyl, *n*-butyl, 3-phenylpropyl, and 4-phenylbutyl as the aliphatic chain of the secondary amines, were compatible for the reaction to give **51**–**60** in good yields and excellent er. Cyclic secondary aromatic amine was also competent substrate, giving rise to the expected product **61** in good yield with excellent enantioselectivity. Besides secondary amines, primary amines, such as aniline and the derivatives worked smoothly to produce **62**–**66** in moderate to good yields and excellent enantioselectivity. Diphenylamine was also attempted, but the substrates were completely remained. When aliphatic amines, such as dibenzylamine, benzylamine, morpholine and *N*-methyl benzylamine, were employed to react with 1-(2,5-dimethyphenyl)-1,3-diene under standard conditions, the 1,3-diene was recovered, accompanied by unisolated mixture.

Various perfluoroalkyl iodides were also investigated (Fig. 3). When employing lauroyl peroxide (LPO) as the oxidant under slightly modified conditions, various iodinated perfluoroalkanes can

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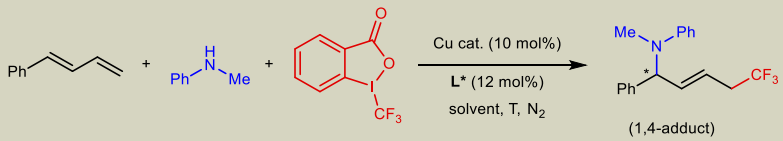
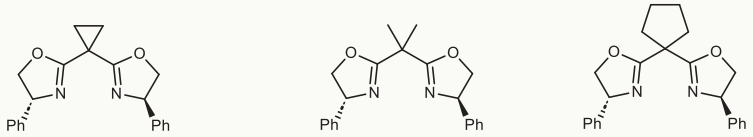
Table 1 | Parameters effects in the model reaction[a]



1a 2a 3a (1,4-adduct) 4

Entry	L*	T (°C)	Solvent	Cu cat.	Yield of 4 (%)	Er of 4
1	none	40	CH_3CN	$Cu(CH_3CN)_4PF_6$	38	0
2	(*R*, *R*)-L1	40	CH_3CN	$Cu(CH_3CN)_4PF_6$	78	84:16
3	(*R*, *R*)-L2	40	CH_3CN	$Cu(CH_3CN)_4PF_6$	37	80:20
4	(*R*, *R*)-L3	40	CH_3CN	$Cu(CH_3CN)_4PF_6$	50	81:19
5	(*R*, *R*)-L1	40	CH_3CN	none	0	0
6[b]	(*R*, *R*)-L1	−10	CH_3CN	$Cu(CH_3CN)_4PF_6$	75	90:10
7[b]	(*R*, *R*)-L1	−10	EA	$Cu(CH_3CN)_4PF_6$	22	89:11
8[b]	(*R*, *R*)-L1	−10	DCM	$Cu(CH_3CN)_4PF_6$	30	84:16
9[b,c]	(*R*, *R*)-L1	−10	CH_3CN:EA = 1:4	$Cu(CH_3CN)_4PF_6$	84	93:7
10[b,c]	(*R*, *R*)-L1	−10	CH_3CN:EA = 1:4	Cu(OTf)	70	87:13
11[b,c]	(*R*, *R*)-L1	−10	CH_3CN:EA = 1:4	CuCl	25	52:48
12[b,c]	(*R*, *R*)-L1	−10	CH_3CN:EA = 1:4	CuI	64	57:43



(*R*, *R*)-**L1** (*R*, *R*)-**L2** (*R*, *R*)-**L3**

[a]Reaction conditions: **1a** (0.25 mmol), **2a** (0.1 mmol), **3a** (0.2 mmol), Cu cat. (10 mol%), L* (12 mol%), solvent (1 mL), 24 h. Yields were isolated ones. Er values were determined by HPLC analysis. L* = chiral ligand. EA = EtOAc. DCM = dichloromethane.
[b]72 h.
[c]2 mL solvent was used.

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successfully participate in the asymmetric perfluoroalkylamination. The reaction of iodinated perfluorobutane with *N*-methyl aniline and various substituted aromatic 1,3-dienes furnished corresponding perfluorobutyl-containing allylic amines **67**–**76** in good to excellent yields and high enantioselectivity. The iodinated perfluorobutane and *N*-methyl aniline can reaction with 1,3-dienes originated from drug molecules diacetonefructose and borneol smoothly to deliver to promising products **77** and **78** in excellent yields and more than 25:1

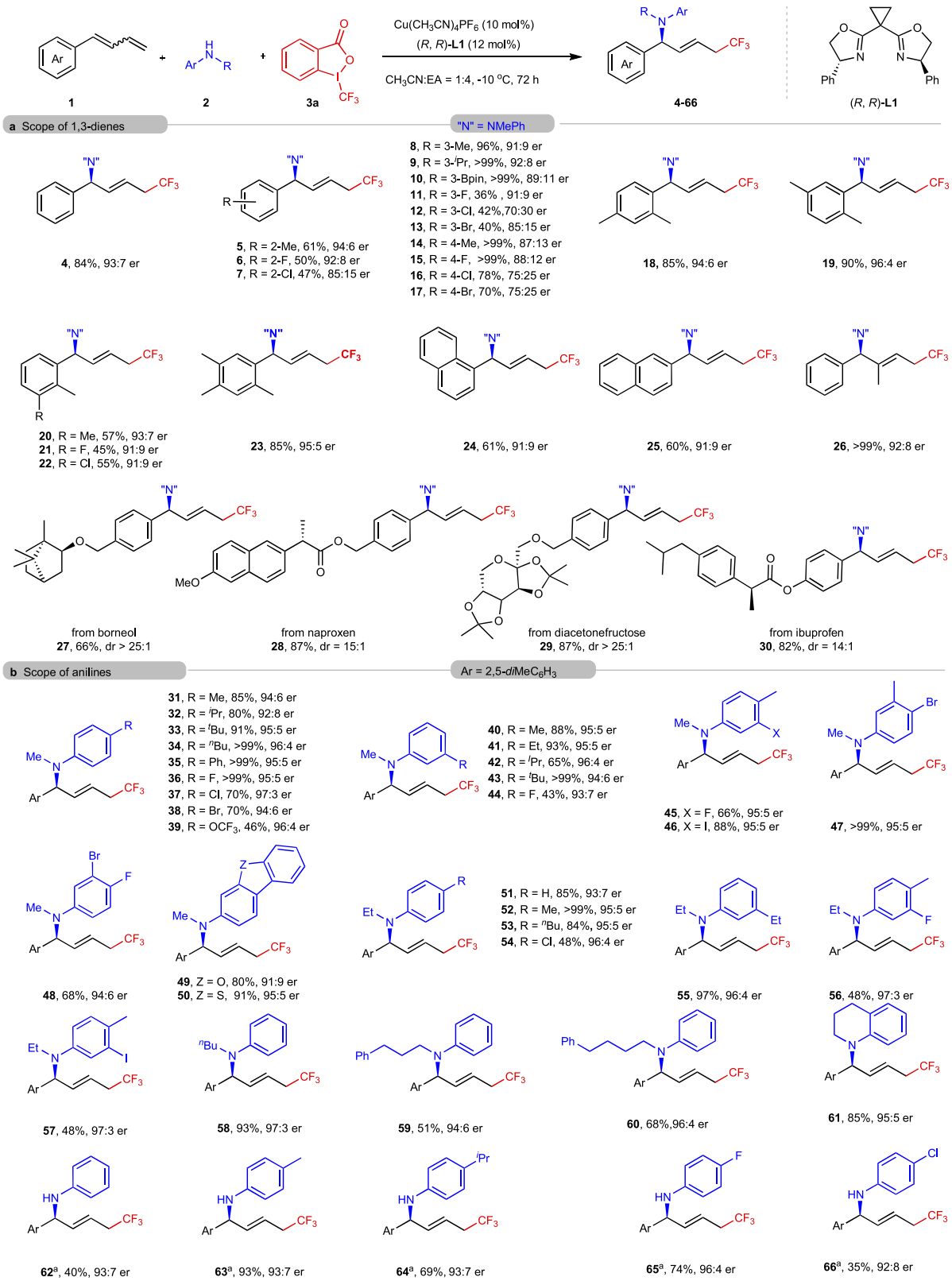

Fig. 2 | Scope of the substrates. a Scope of 1,3-dienes. **b** Scope of anilines. Reaction conditions: **1** (0.25 mmol), **2** (0.1 mmol), **3a** (0.2 mmol), $Cu(CH_3CN)_4PF_6$ (10 mol%), *(R, R)*-**L1** (12 mol%) in 2 mL mixed solvent of CH_3CN and EA (1:4) at −10 °C for 72 h under nitrogen. Yields were isolated ones. Er values were determined by HPLC analysis. Dr values were determined by ^1H NMR analysis. [a]Reaction for 5 days.

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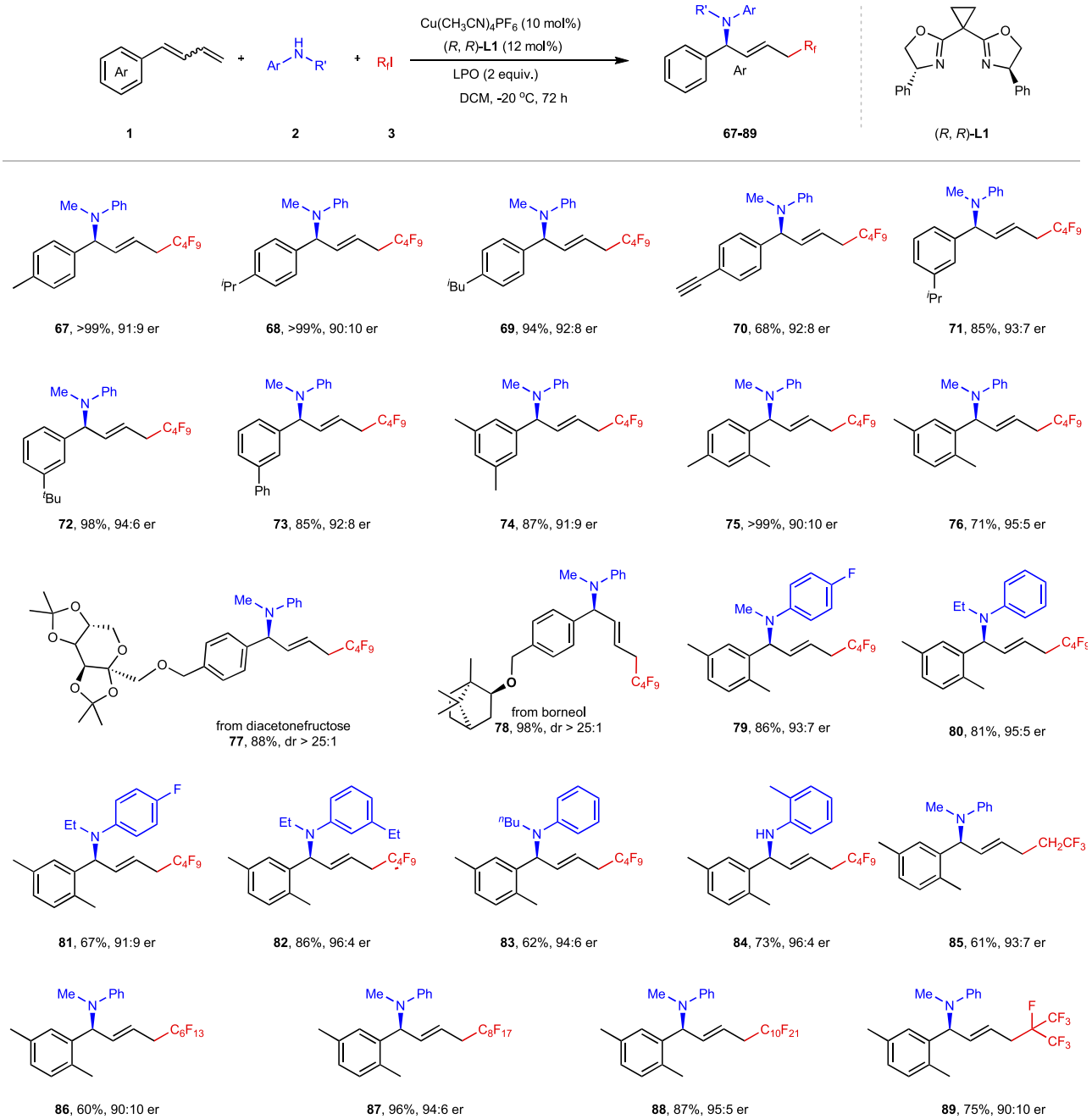

Fig. 3 | Scope of perfluoroalkyl reagents. Reaction conditions: **1** (0.25 mmol), **2** (0.1 mmol), **3** (0.2 mmol), LPO (0.2 mmol), $Cu(CH_3CN)_4PF_6$ (10 mol%), (*R*, *R*)-**L1** (12 mol%) in 1 mL DCM at −20 °C for 72 h under nitrogen atmosphere. Er values were determined by HPLC analysis. Dr values were determined by ^{1}H NMR analysis.

diastereoselectivity. The reaction of iodinated perfluorobutane with 1,3-diene and other *N*-alkyl aromatic amines or primary aromatic amine worked well, and the desired products **79**–**84** were smoothly obtained in good yields and higher values. Additionally, 2-iodo-1,1,1-trifluoroethane, perfluorohexyl-, heptyl-, decanyl-, and heptafluoroisopropyl-iodide were well-tolerated, affording corresponding products **85**–**89** in good to excellent yields with high enantioselectivity. In all cases, only one isomer was observed.

Synthetic applications

To verify the practicality of this methodology, a gram-scale synthesis was first conducted, and the 1,4-trifluoromethylamination product **19** was readily gained with high efficiency and high enantioselectivity (Fig. 4a). The C–C double bond of allylic amine **19** can be smoothly oxidized by $K_2OsO_4{\bullet}2H_2O$ to afford a chiral *syn*-diol compound **90** in good yield under mild reaction conditions (Fig. 4b). The absolute configuration of the major diastereoisomer **90** was confirmed as (2 *R*, 3 *R*, 4 *R*) by X-ray crystallographic analysis (Supplementary Table 7). Since after the oxidation the substitution pattern affected the priority of the groups at the chiral carbon atom of the C–N bond in oxidative product **90**, stemming from chiral allylic amine **19**, enabled us to assign the absolute configuration of **19** produced in the asymmetric 1,4-trifluorometylamination of 1,3-diene as (*S*) (Supplementary Section VII), and those of the others were assigned by analogy. The *N*-acylation of product **63** could deliver the optically pure product **91** (Fig. 4c).

Mechanistic investigations

To probe the mechanism of the asymmetric transformation, some controlled experiments were conducted (Fig. 5). First, a radical trap experiment was performed by using 2,2,6,6-tetramethylpiperidine-1-

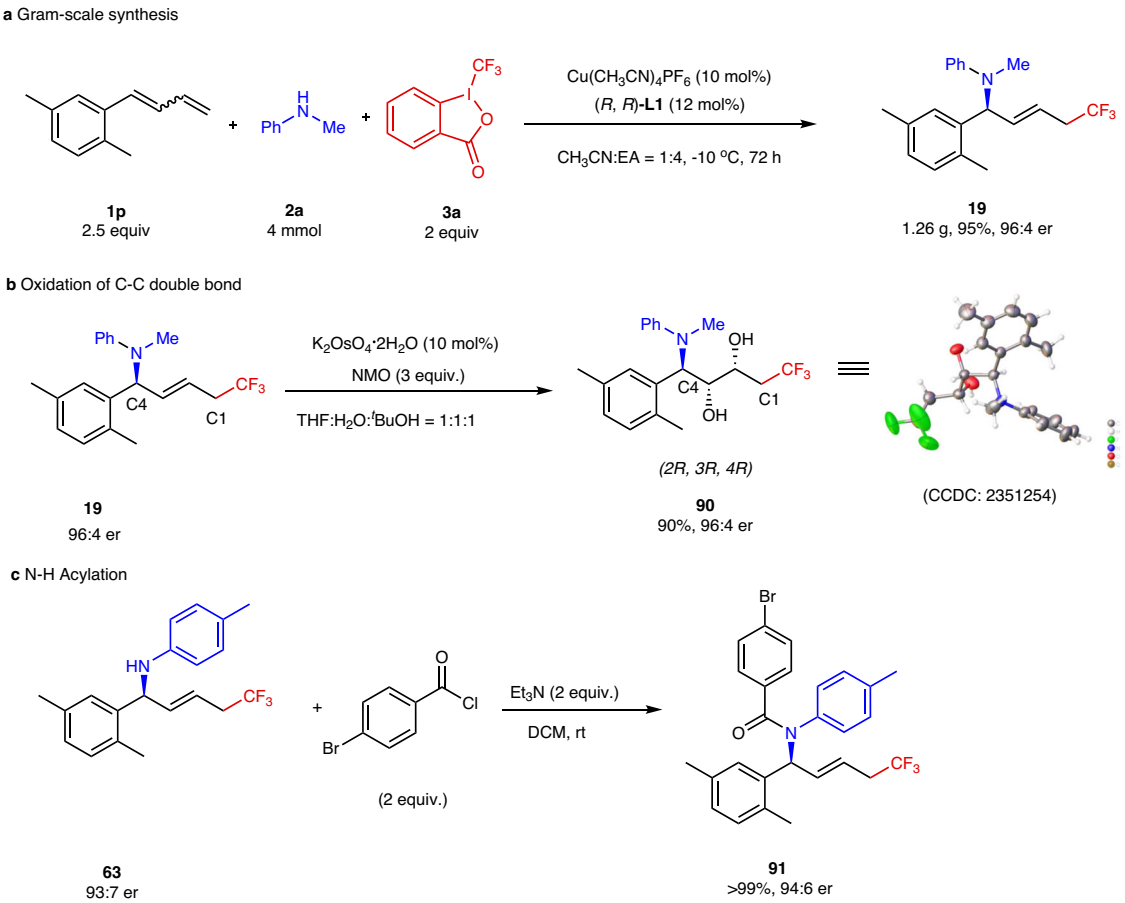

Fig. 4 | Synthetic applications. a Gram-scale synthesis. **b** Oxidation of C–C double bond. **c** N–H Acylation.

oxyl (TEMPO) as the radical inhibitor. The model reaction was found to be completely suppressed, and the trifluoromethyl-TEMPO adduct **92** was obtained in 67% yield (Fig. 5a and Supplementary Section VIII. A). Next, a radical clock reaction with (2-(buta-1,3-dien-1-yl)cyclopropyl) benzene (**1ab**) was carried out, and the reaction furnished the ring-opened homoallylic amine **93** in 44% yield (Fig. 5b and Supplementary Section VIII. B). These results suggested that an allylic radical intermediate is possibly involved in this transformation. Furthermore, a linear relationship between the product and catalyst er value was founded, implying a likely 1:1 copper-to-ligand ratio in the enantioselectivity-determining transition states (Fig. 5c and Supplementary Section VIII. C).

DFT Computational investigations

To obtain a deeper understanding of the copper-catalyzed asymmetric 1,4-perfluoroalkylamination reaction of 1,3-diene, several elementary steps involving regioselectivity and stereoselectivity were scrupulous evaluated through density functional theory (DFT) calculations, using **1p, 2d**, and **3a** as the model substrates. Viewing the DFT calculated results (Supplementary Fig. 4) and literatures[48–50], the initial trifluoromethylation involved a SET process between Cu(I) catalyst and Togni reagent formed a Cu(II)–O species and a trifluoromethyl radical, and subsequent trifluoromethyl radical adding to 1,3-diene to generate allylic radical **2AC**. The resultant L*Cu(II)–OCOAr species **Com1** underwent ligand exchange/deprotonation with aniline derivative **2 d** to produce formal three-coordinate L*Cu(II)–N species (Supplementary Fig. 5). Furthermore, the spin density analysis of the L*Cu(II)-NRAr′ showcased that considerable spin density located on N atom (0.55 e^-) and less spin density on copper (0.04 e^-) (Fig. 6a). These results implied that the formal L*Cu(II)–NRAr′ complex could be viewed as a L*Cu(I)–NRAr′ radical species **INT-6**[51], consistent with Fu and Peters' report where a three-coordinate Cu(I)–N radical was recognized[52]. Given that an enantioselective cross-coupling between carbon-centered radical and copper-stabilized nitrogen-centered radical has been recently demonstrated to construct asymmetric C–N bond by Fu and Peters group[52], as well as our group[43]. Thus, the coupling of **INT-6** with the allylic radical **2AC** via the transition state **TS5-S** to furnish *S*-type **33-S** product was evaluated, and the Gibbs activation energy ($\Delta G^{\ddagger}$) is calculated to be 10.8 kcal/mol (Fig. 6b, right, black line). Additionally, the energy of the transition state **TS5-R** was calculated (Fig. 6b, right, red line), which is 2.2 kcal/mol higher than **TS5-S**. Furthermore, we found that in the favorable transition state **TS5-S**, the CF_3 moiety of radical **2AC** is oriented closer to the phenyl group of the chiral ligand and could contribute significant C–H···F and C–F···π interactions that stabilized **TS5-S**, thereby enhancing the enantioselectivity (Fig. 6c and Supplementary Fig. 6). Additionally, the independent gradient model based on Hirshfeld partition analysis was performed to identify potential intermolecular interactions among the ligand, **2AC** and **INT-6** (IGMH, illustrated in Fig. 6d and Supplementary Fig. 7). In **TS5-S**, multiple noncovalent interactions, namely C–H···F, C–F···π, C–H···O, and C–H···π, were distinctly observed. In contrast, only the C–H···π interaction was observed in **TS5-R**. These results elucidate the preferential formation of the S-configured product, providing a rationale for the observed 95:5 enantiomeric ratio favoring **(*S*)-33**. An alternative pathway involving the copper-allyl intermediate through the reductive elimination process, specifically from intermediate **INT-6** to transition state **TS8-S**, was also investigated. This pathway exhibited a $\Delta G^{\ddagger}$ of 15.0 kcal/mol, which is 4.2 kcal/mol higher than that of the radical cross-coupling process, making it energetically less favorable (Supplementary Fig. 5). It should be noted that this asymmetric C–N bond

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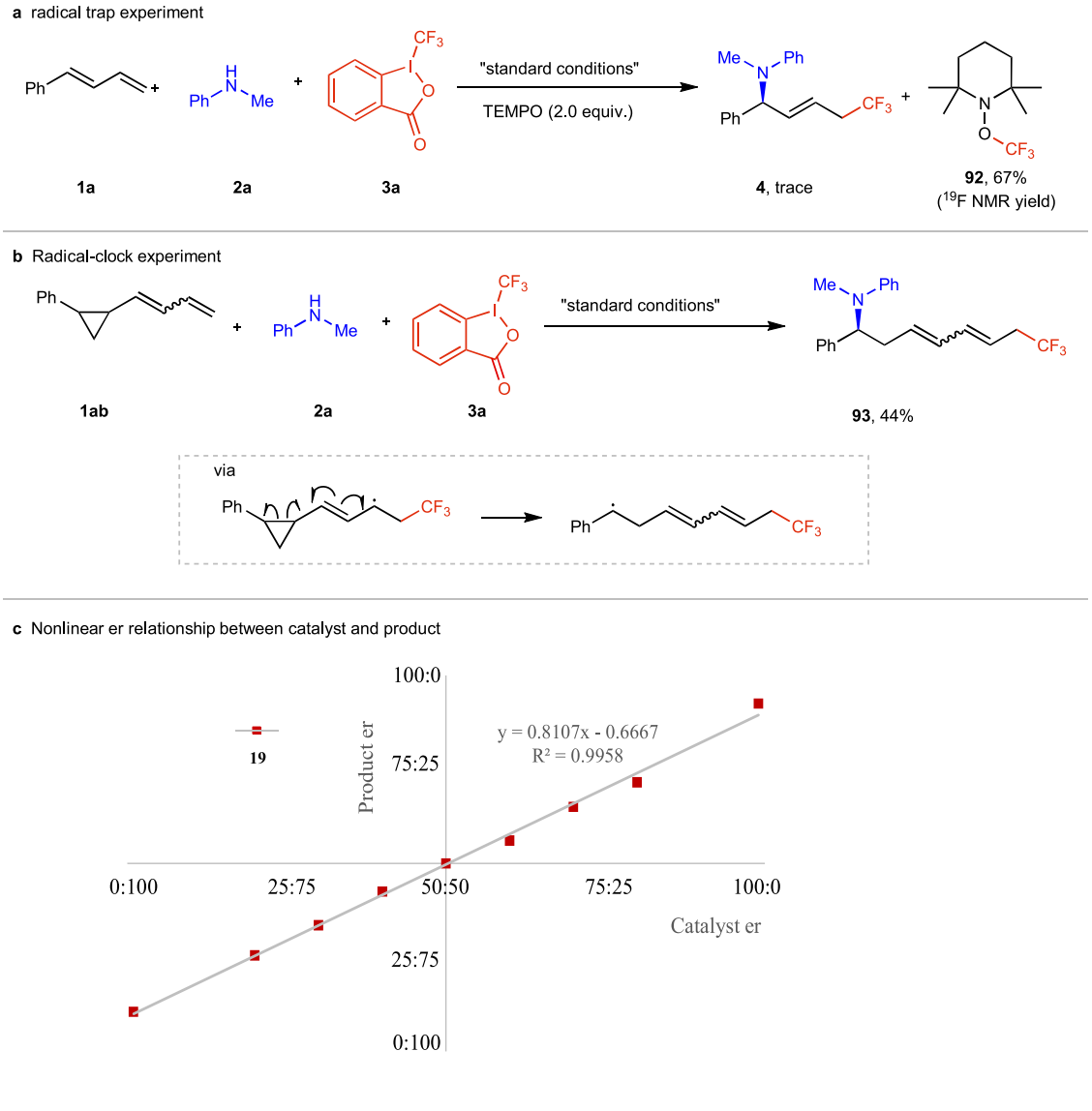

Fig. 5 | Controlled experiments. a Radical trap experiment. **b** Radical clock experiment. **c** Nonlinear er relationship between catalyst and product.

formation represents a rare example of enantioselective cross-coupling of allylic radical and metal-stabilized nitrogen-centered radical.

To elucidate the origin of the regioselectivity, the radical coupling C–N bond formation leading to the 1,2-adduct was also calculated. This process proceeded through transition states **TS5′-S** with a $\Delta G^{\ddagger}$ of 13.9 kcal/mol (Fig. 6b, left black line), which was higher than **TS5-S** ($\Delta G^{\ddagger}$ = 10.8 kcal/mol, affording the 1,4-addition product) by 3.1 kcal/mol. Further structural analysis (Fig. 6c and Supplementary Fig. 6) revealed that in **TS5′-S**, the CF_3 group of **2AC** is oriented toward the cavity of the chiral ligand, in contrast to its orientation in **TS5-S**. This results in the disruption of the stabilizing noncovalent interactions, including the C–H···F hydrogen bonding and C–H···π, which are mediated by the CF_3 group and the aromatic phenyl ring of the ligand. In **TS5-S**, the CF_3 group is proximal to the five-membered heterocyclic ring of ligand and the methyl moiety of 4-(*tert*-butyl)-*N*-methylaniline (**2d**). The favorable arrangement maximizes the noncovalent interactions between the catalyst and substrates, which were further confirmed by IGMH analysis (Fig. 6d and Supplementary Fig. 7). These favorable noncovalent interactions are served as the primary driving force for the unusual 1,4-regioselectivity observed in the radical cross-coupling process.

Based on the controlled experiments and DFT investigations, we proposed a plausible mechanism for this transformation as outlined in Fig. 7. Firstly, a single-electron transfer (SET) between Togni reagent **3a** and Cu(I) in the presence of chiral ligand afforded CF_3 radical species and chiral Cu(II)–O complex **Com1**. Subsequently, CF_3 radical added to 1,3-diene **1p** to afford allylic radical **2AC**. Meanwhile, interaction of **Com1** and aniline derivative **2 d** formed a chiral Cu(I)–NRAr′ radical complex **INT-6**, which enantioselectively coupled with **2AC** to finally provide trifluoromethylated chiral allylic amine **33**, along with the regeneration of Cu(I) species into the next catalytic recycle. This transformation represents a scarce enantioselective radical 1,4-difunctionalization of 1,3-dienes.

Discussion

In summary, we have successfully developed a Cu-catalyzed enantioselective three-component radical 1,4-perfluoroalkylamination of 1,3-dienes with aniline derivatives and perfluoroalkyl reagents. This reaction renders the efficient assembly of a series of crucially important chiral perfluoroalkyl-containing allylic amines in distinctive regioselectivity and excellent enantioselectivity. The experimental and DFT studies provided reasonable explanations for the excellent regioselectivity and enantioselectivity of the elementary C–N bond

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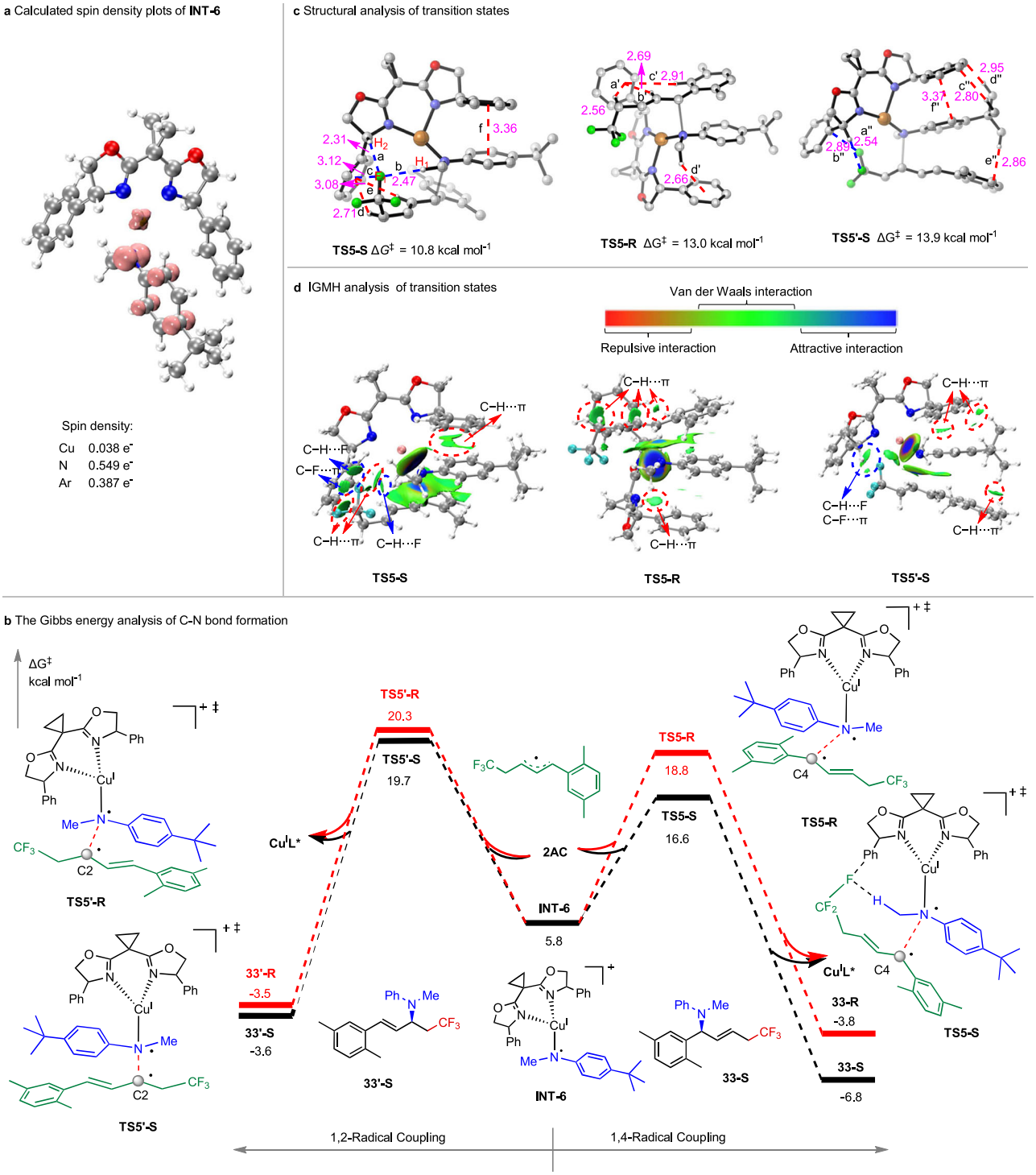

Fig. 6 | DFT investigation. a Spin density calculation of **INT-6** species. **b** Gibbs energy profiles of copper catalytic cycles providing S-type (black line) and R-type (red line) 1,4-adduct (right) and S-type (black line) and R-type (red line) 1,2-adduct (left) involves cross-coupling process of two radical intermediates. **c** Optimized structures and relative energies of transition states **TS5-S, TS5-R** and **TS5'-S**. **d** Schematics for the transition-state structures for enantio- and regio-selectivity and the corresponding independent gradient model based on IGMH.

formation in the proposed catalytic cycle and revealed that the asymmetric formation of C–N bond involved an unequaled enantioselective cross-coupling between allylic radical and copper-stabilized nitrogen-centered radical. This strategy blazes an alternative way towards chiral allylic compounds and provides alternative for the regioselective and enantioselective transformation of conjugated dienes.

Methods

General procedure for enantioselective 1,4-trifluoromethylamination of 1,3-dienes

Into a nitrogen-filled glove box, a vial (15.0 mL) equipped with a magnetic stir bar was charged with $Cu(CH_3CN)_4PF_6$ (0.01 mmol), **L1** (0.012 mmol). Anhydrous acetonitrile (0.4 mL) and ethyl acetate (1.6 mL) were added, and the reaction mixture was stirred for 15 min

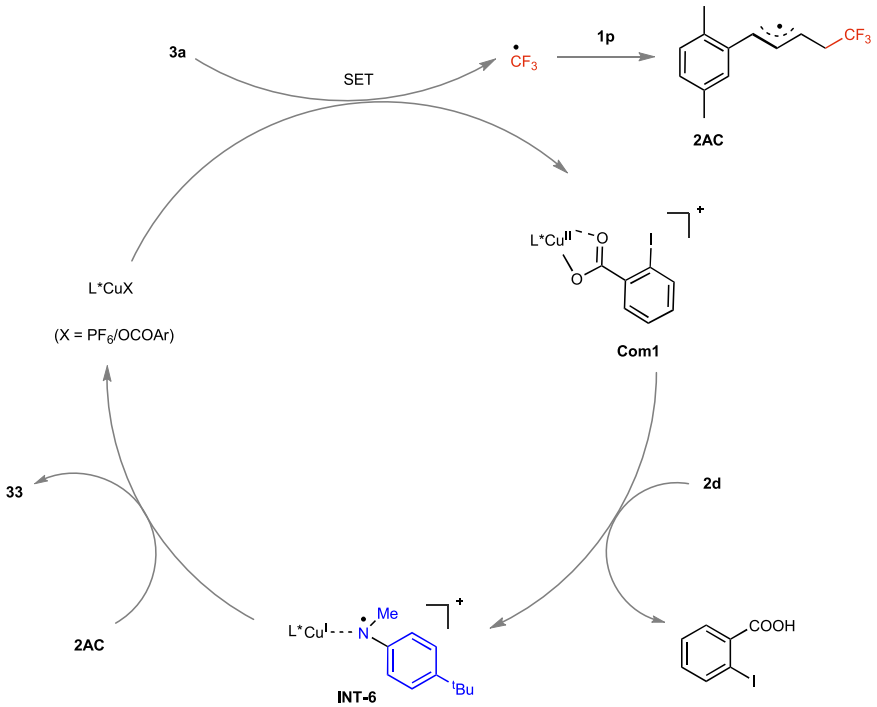

Fig. 7 | Proposed mechanism. A plausible reaction mechanism for copper-catalyzed enantioselective radical 1,4-trifluoromethylamination of 1,3-dienes with trifluoromethyl reagents and anilines.

until it changes from colorless to green. Then **1** (2.5 equiv.), **2** (0.1 mmol), and **3a** (2.0 equiv.) were added sequentially. Finally, the tube was sealed with a Thermo Scientific PTFE screw cap equipped with a septum, removed from the glovebox. The reaction mixture was stirred at −10 °C for 72–96 h, until the reaction was complete as indicated by TLC. The reaction mixture was then quenched with water, extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were concentrated in vacuo. The resulting crude product was purified by flash column chromatography on silica gel to give the corresponding product.

General procedure for enantioselective 1,4-polyfluoromethylamination of 1,3-dienes

Into a nitrogen-filled glove box, a vial (15.0 mL) equipped with a magnetic stir bar was charged with $Cu(CH_3CN)_4PF_6$ (0.01 mmol), **L1** (0.012 mmol). Anhydrous dichloromethane (1 mL) was added, and the reaction mixture was stirred for 15 min until it changes from colorless to green. Then **2** (0.1 mmol), **1** (2.5 equiv.), LPO (2.0 equiv.) and **3** (2.0 equiv.) were added sequentially. Finally, the tube was sealed with a Thermo Scientific PTFE screw cap equipped with a septum, removed from the glovebox. The reaction mixture was stirred at −20 °C for 72 h, until the reaction was complete as indicated by TLC. The reaction mixture was then quenched with water, extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layers were concentrated in vacuo. The resulting crude product was purified by flash column chromatography on silica gel to give the corresponding product.

Data availability

Crystallographic data for the structures reported in this Article have been deposited at the Cambridge Crystallographic Data Centre, under deposition numbers CCDC 2351254 (**90**). Copies of the data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/. All other data supporting the findings of the study are available within the article and its Supplementary Information, or from the corresponding author upon request. Source data are provided with this paper.

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Author contributions

Y.L. and Q.Z. directed the projects; Y.L. and Q.Z. designed the experiments; X.S. and Y.Z. performed experiments; L.Z. performed DFT calculations; all authors contributed to data analysis; Y.L. and L.Z. wrote the manuscript with feedback from the other authors; Q.Z. reviewed the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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