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Cu-catalysed intramolecular radical enantioconvergent tertiary β-C(sp^3)–H amination of racemic ketones

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In contrast to the wealth of enantioselective prochiral C(sp^3)–H functionalization that is transition-metal-catalysed, the enantioconvergent transformation of racemic tertiary C(sp^3)–H bonds ($pK_a > 25$) still represents a vastly uncharted domain. The mechanistic limitation is partial or complete chirality retention, which is inherent to developed enantioselective C–H functionalization catalysis and poses the major challenge in establishing such a process. To this end, we herein describe the combination of decoupled hydrogen atom abstraction with asymmetric copper catalysis for enantioconvergent tertiary β-C(sp^3)–H amination of racemic ketones. This method, when allied with follow-up transformations, provides facile access to a range of enantioenriched compounds featuring quaternary stereocentres. We anticipate that this work will inspire the future design of generally efficient catalysts for enantioconvergent transformations of racemic tertiary C(sp^3)–H bonds.

The direct enantioselective functionalization of C–H bonds—the most predominant functional groups in organic molecules—has been recognized as an ideal approach to construct enantioenriched, carbon-based molecules because of its inherent economic and environmentally benign nature[1]. In recent years, various powerful catalysts based on transition metals have been discovered for the enantioselective functionalization of prochiral C(sp^3)–H bonds[1] and representative strategies include C–H activation catalysed by a transition metal[2,3] and concerted[4–7] or stepwise[5,8–11] metal-oxo/carbenoid/nitrenoid C–H insertion (Fig. 1a,b).

As for robust racemic tertiary C(sp^3)–H bonds ($pK_a > 25$)[2], direct asymmetric transformations have been rarely reported, particularly for enantioconvergent ones theoretically leading to highly enantioenriched products in 100% yield[12,13], although enantioconvergent substitution reactions of racemic tertiary alkyl electrophiles are emerging as a powerful synthetic strategy to access quaternary stereocentres[14–17] (Supplementary Fig. 1). In this regard, Arnold et al. have made a breakthrough by accomplishing the first highly enantioconvergent tertiary C–H amination reaction with enzymatic catalysis[18]. The challenge for the lagged development of such a process arises primarily from the mechanistic limitation inherent in the previous enantioselective C–H functionalization methods (Fig. 1c): partial or complete chirality retention. Specifically, C–H activation catalysed by a transition metal and concerted metal-carbenoid/nitrenoid C–H insertion have only achieved stereospecific transformations (Fig. 1a)[2–7], while stepwise metal-carbenoid/nitrenoid C–H insertion as well as hydroxylation by metal oxo species[8–11] tends to be complicated by partial or complete chirality retention (Fig. 1b). As such, these strategies are generally more amenable to kinetic resolution that affords 50% yield at best (Fig. 1c, left). The reason for the chirality retention in the non-concerted scenarios originates from the usually fast radical rebound (RR) step that seems as if it is kinetically coupled to the first hydrogen atom abstraction (HAA) step. Thus, the resulting C–H functionalization products inherit the initial chirality to different extents (Fig. 1b)[10,11,19]. As a result, the generally accepted transition-metal-catalysed, enantioselective C–H functionalization mechanisms would seem to preclude efficient enantioconvergent transformations of racemic tertiary C(sp^3)–H bonds (Fig. 1c, right).

Seeking to address this challenge, we have become interested in combining a decoupled HAA with copper catalysis to provide a general platform for enantioconvergent reactions of racemic tertiary C(sp^3)–H bonds. On one hand, since the pioneering discovery of the Barton[20] and the Hofmann–Löffler–Freytag reactions[21,22], the HAA process has proven to be a powerful tool for regioselective activation of an inert C–H bond[23–26]. On the other hand, pioneered by Fu and others[13,27–30], asymmetric transition-metal catalysis using chiral metal species to associate with an alkyl radical, generated in situ, through different types of interactions has evolved into a versatile strategy for realizing highly enantioselective transformations. Particularly, several groups have recently disclosed the Cu-catalysed enantioselective functionalization of prochiral benzylic, allylic or α-amino C(sp^3)–H bonds via radical intermediates[29,31–33]. Motivated by these precedents, we envisioned a decoupled HAA process that does not involve metal species for racemic tertiary C(sp^3)–H bonds. Accordingly, the thus-generated tertiary alkyl radical would readily lose chirality before interacting with our recently developed Cu(I)/chiral phosphoric acid (CPA) catalyst[29] for subsequent enantioconvergent functionalization (Fig. 1d).

Herein we describe a dual Cu(I)/CPA catalytic protocol for the radical enantioconvergent transformation of racemic tertiary β-C(sp^3)–H bonds in readily available racemic ketones. This protocol afforded a series of chiral ring structures bearing tetrasubstituted carbon stereocentres (Fig. 1e), which upon further

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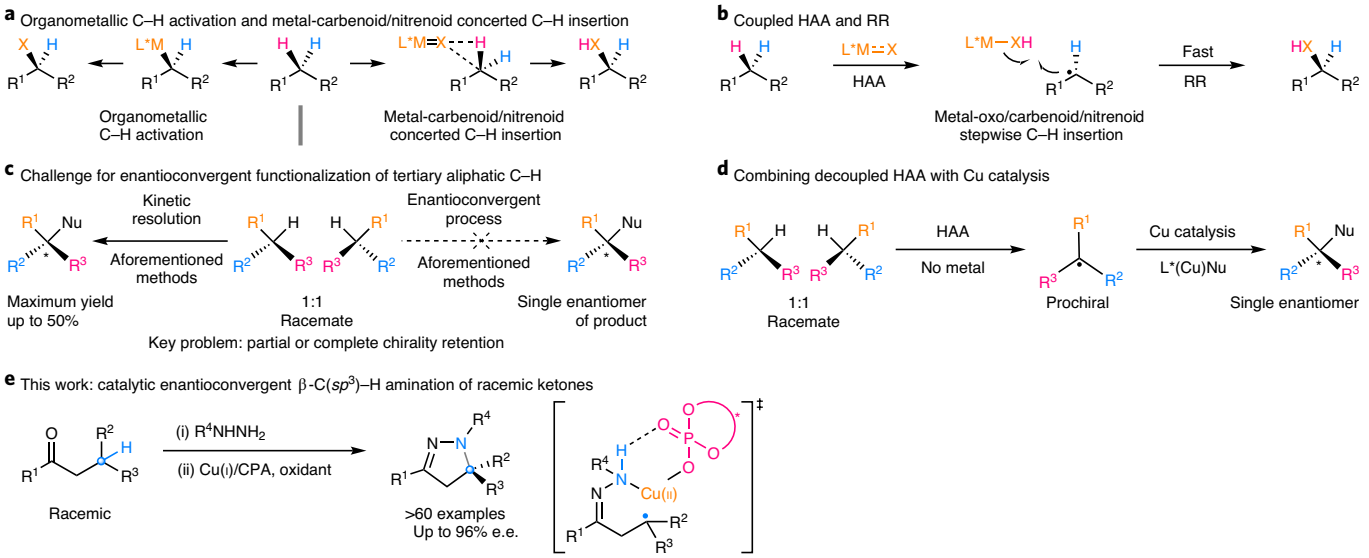


Fig. 1 | Design of catalytic enantioconvergent tertiary C(sp^3)–H functionalization. a, Organometallic C–H activation and metal-carbenoid/nitrenoid concerted C–H insertion lead to stereospecific functionalization. **b**, Coupled HAA and RR for metal-oxo-mediated C–H functionalization and stepwise metal-carbenoid/nitrenoid C–H insertion tend to result in partial or complete chirality retention due to the commonly fast RR. **c**, Reported C–H functionalization catalysed by a transition metal is amenable only to kinetic resolution, but not yet to enantioconvergent transformations, due to the chirality retention problem. **d**, Combining decoupled HAA with copper catalysis is promising for the enantioconvergent functionalization of C–H bonds via a prochiral radical intermediate. **e**, Our current work capitalizes on a Cu(I)/CPA catalyst for radical enantioconvergent β-C(sp^3)–H amination of racemic ketones with more than 60 examples and up to 96% e.e. The efficient trapping of a tertiary alkyl radical by Cu(II) and a chiral phosphate is crucial for enantiocontrol.

manipulation led to valuable chiral 1,3-diamines and highly congested multi-substituted cyclopropanes.

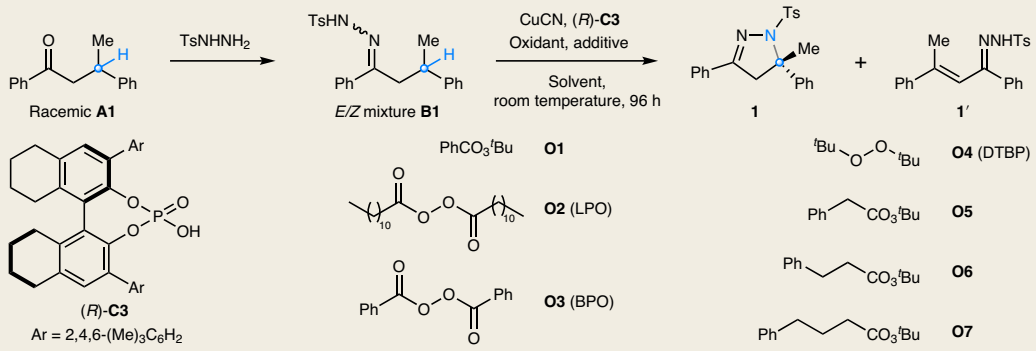
Results

Reaction development. In comparison to considerable advances in the asymmetric prochiral β-C(sp^3)–H functionalization of carbonyl groups pioneered by Yu and others[3,34], the direct enantioconvergent functionalization of corresponding racemic tertiary β-C(sp^3)–H bonds has hitherto been unknown. As such, we began our study using racemic hydrazone **B1** (*E*/*Z* mixture, readily available in one step from racemic ketone **A1** and *p*-toluenesulfonohydrazide ($TsNHNH_2$)) as the pilot substrate to probe the enantioconvergent tertiary β-C(sp^3)–H amination reaction (Table 1). After some initial trials with various CPAs and different copper salts (Supplementary Table 1), we found that the expected product **1** was delivered—albeit with a poor yield—in 71% e.e. under the conditions as follows: commercially available *t*-butyl benzoperoxoate **O1** as oxidant and a combination of 10 mol% of CuCN and 15 mol% of CPA (*R*)-**C3** as catalyst in AcO*i*-Pr at room temperature for 96 h. The major olefinic side product (*E*)-**1′** identified in this reaction was presumed to be derived from the tertiary radical species, generated in situ, via sequential radical trapping by Cu(II) and β-hydride elimination. Subsequent screening of oxidants and solvents revealed that oxidant **O7** was the best in terms of enantioselectivity (Table 1, entries 1–7), and *i*-$PrCO_2$*i*-Pr was the optimal solvent in terms of both reaction efficiency and enantioselectivity (Table 1, entries 7–12). Surprisingly, the addition of 20 mol% $(NH_4)_2CO_3$ resulted in a great increase in product yield (71% yield), albeit with a slightly diminished enantioselectivity (Table 1, entries 10 and 13). Further evaluation of its loading and reaction temperature as well as concentration (Table 1, entries 14–18) led to the discovery of the optimum reaction conditions as follows: (±)-**B1** (0.10 mmol), **O7** (0.20 mmol), CuCN (10 mol%), (*R*)-**C3** (15 mol%) and $(NH_4)_2CO_3$ (5 mol%) in dry *i*-$PrCO_2$*i*-Pr (2.0 ml) at 35 °C for 96 h under argon (63% yield and 92% e.e.; Table 1, entry 18).

Substrate scope. With the optimal reaction conditions being established, we next examined the generality of this enantioconvergent tertiary β-C(sp^3)–H amination reaction. In regard to the *N*-arylsulfonohydrazide scope (Fig. 2a), a range of differently substituted phenyl rings bearing one or two electron-donating or -withdrawing groups at the *meta* or *para* positions and a naphthalene ring all were compatible with this reaction to afford **2**–**19** in 35–85% yield with 86–96% e.e. The absolute configuration of **14** was determined to be *S* by X-ray crystallographic analysis (Supplementary Fig. 2), and those of other products were assigned by analogy. As for the scope of the ketones (R^1 in Fig. 2b), a broad series of aryl and heteroaryl ketones were all well accommodated in this process to deliver **20**–**44** in 43–83% yield with 78–94% e.e. Many common functional groups—such as methoxyl (**20**), fluoro (**26**, **27**), chloro (**28**–**30**), bromo (**31**, **32**), trifluoromethyl (**33**, **34**), methoxylcarbonyl (**35**, **36**), alkynyl (**37**), phosphonyl (**38**) and pinacolborato (**39**)—were all compatible with the mild reaction conditions. Notably, medicinally relevant heterocycles such as pyrazole (**41**), thiophene (**42**), benzo[*b*]thiophene (**43**) and dibenzo[*b*,*d*]furan (**44**) were also tolerated, providing the desired products in moderate to good yield with good to excellent enantioselectivity. Strikingly, racemic completely aliphatic ketones also underwent the reaction to deliver **45**–**47** with promising enantioselectivity.

We next investigated the scope of the racemic tertiary β-C(sp^3)–H moieties (Fig. 3a) and found (hetero)aryl substituents to be essential for this enantioconvergent amination reaction for the time being. Thus, both substituted phenyl and biologically important heterocyclic thiophenyl rings were viable substituents to give products **48**–**50** with moderate to excellent enantioselectivity. As for the remaining substituents, simple unfunctionalized linear alkyl groups were well tolerated in the reaction (**51** and **52**). Moreover, alkyl groups bearing a variety of functionalities—such as ester (**53** and **54**), ether (**55**), chloride (**57**) and azide (**58**)—were compatible with the reaction. Notably, products **56** and **59** bearing potentially reactive primary

Table 1 | Survey on the model reaction conditions



Entry[a]	Oxidant	Solvent	Additive	Yield (%)	e.e. (%)
1	**O1**	AcO*i*-Pr	—	21 (< 5)[b]	71
2	**O2**	AcO*i*-Pr	—	< 5	—
3	**O3**	AcO*i*-Pr	—	9 (17)[b]	38
4	**O4**	AcO*i*-Pr	—	< 5	—
5	**O5**	AcO*i*-Pr	—	28	73
6	**O6**	AcO*i*-Pr	—	33	78
7	**O7**	AcO*i*-Pr	—	32	86
8	**O7**	EtOAc	—	21	74
9	**O7**	*i*-PrCO$_2$Et	—	29	85
10	**O7**	*i*-PrCO$_2$*i*-Pr	—	36	89
11	**O7**	CH_2Cl_2	—	19	63
12	**O7**	Benzene	—	25	48
13	**O7**	*i*-PrCO$_2$*i*-Pr	$(NH_4)_2CO_3$[c]	71	76
14	**O7**	*i*-PrCO$_2$*i*-Pr	$(NH_4)_2CO_3$[d]	61	88
15	**O7**	*i*-PrCO$_2$*i*-Pr	$(NH_4)_2CO_3$[e]	48	92
16	**O7**	*i*-PrCO$_2$*i*-Pr	$(NH_4)_2CO_3$[e,f]	51	92
17	**O7**	*i*-PrCO$_2$*i*-Pr	$(NH_4)_2CO_3$[e,g]	55	90
18	**O7**	*i*-PrCO$_2$*i*-Pr	$(NH_4)_2CO_3$[e,g,h]	63	92

[a]Reaction conditions: (±)-**B1** (0.10 mmol), oxidant (0.20 mmol), CuCN (10 mol%) and (*R*)-**C3** (15 mol%) in dry solvent (1.0 ml) at room temperature for 96 h under argon; isolated yield of **1** based on (±)-**B1** is given; e.e. of **1** is based on HPLC analysis. [b]Isolated yield of **1′** based on (±)-**B1** is given in parentheses. [c]$(NH_4)_2CO_3$ (20 mol%) was used. [d]$(NH_4)_2CO_3$ (10 mol%) was used. [e]$(NH_4)_2CO_3$ (5 mol%) was used. [f]Run at 30 °C. [g]Run at 35 °C. [h]*i*-PrCO$_2$*i*-Pr (2.0 ml) was used. Ts, *p*-toluenesulfonyl; LPO, dilauroyl peroxide; BPO, benzoyl peroxide; DTBP, di-*tert*-butyl peroxide.

alcohol and terminal alkene moieties, respectively, were obtained in high enantioselectivity and acceptable yield despite the oxidative nature of this process.

Chiral spiro-heterocycles not only represent key structural elements in a large number of natural products and pharmaceutical agents[35], but also constitute excellent platforms for the development of chiral catalysts with broad utility in asymmetric synthesis[36]. Given this, we investigated ketones bearing racemic tertiary β-C(sp^3)–H bonds on rings for the construction of such valuable skeletons. Thus, a series of chiral spiro-heterocycles **60**–**65** with different skeletons ([5,6] and [5,7] spirocycles) and functionalities (carbon-, oxygen- and nitrogen-tethered rings) were efficiently constructed with low to good yield and excellent enantioselectivity (Fig. 3a). The absolute configuration of **62** was determined to be *S* by X-ray crystallographic analysis (Supplementary Fig. 3), and those of other products were assigned by analogy. Noteworthy is that the substrate containing an allylic racemic tertiary β-C(sp^3)–H bond on a cyclohexene ring also underwent the reaction to deliver spirocyclic product **66** with promising results, and the reaction is currently undergoing further optimization in our laboratory.

Synthetic practicality and applications. To demonstrate the practicality of this method, we next developed a tandem one-pot procedure for the direct use of readily available racemic ketones in the reaction without the need for isolating the hydrazone intermediate. Thus, sequentially stirring various racemic ketones with *p*-methoxybenzenesulfonohydrazide in the presence of (*R*)-**C3** at 65 °C for 24 h and further with additional **O7**, CuCN and $(NH_4)_2CO_3$ at 35 °C for 96 h efficiently delivered the corresponding products with more or less the same enantioselectivity (Fig. 3b). In addition, large-scale reactions were also performed using either the hydrazone intermediate **B3** or ketone **A1** as substrates under the corresponding standard reaction conditions, and the high efficiency and enantioselectivity remained almost the same (Fig. 3c,d).

To further demonstrate the utility of the current methodology, we converted chiral dihydropyrazole **3** to chiral 1,3-diamine **70** in four steps (Fig. 3e); 1,3-diamine compounds are essential building blocks in many natural products and pharmaceuticals, and many of them are also chiral ligands or auxiliaries in organic synthesis[37]. Moreover, treatment of spiro-heterocycle **62** with allylmagnesium bromide in the presence of $CeCl_3$ afforded dihydropyrazole **71** in

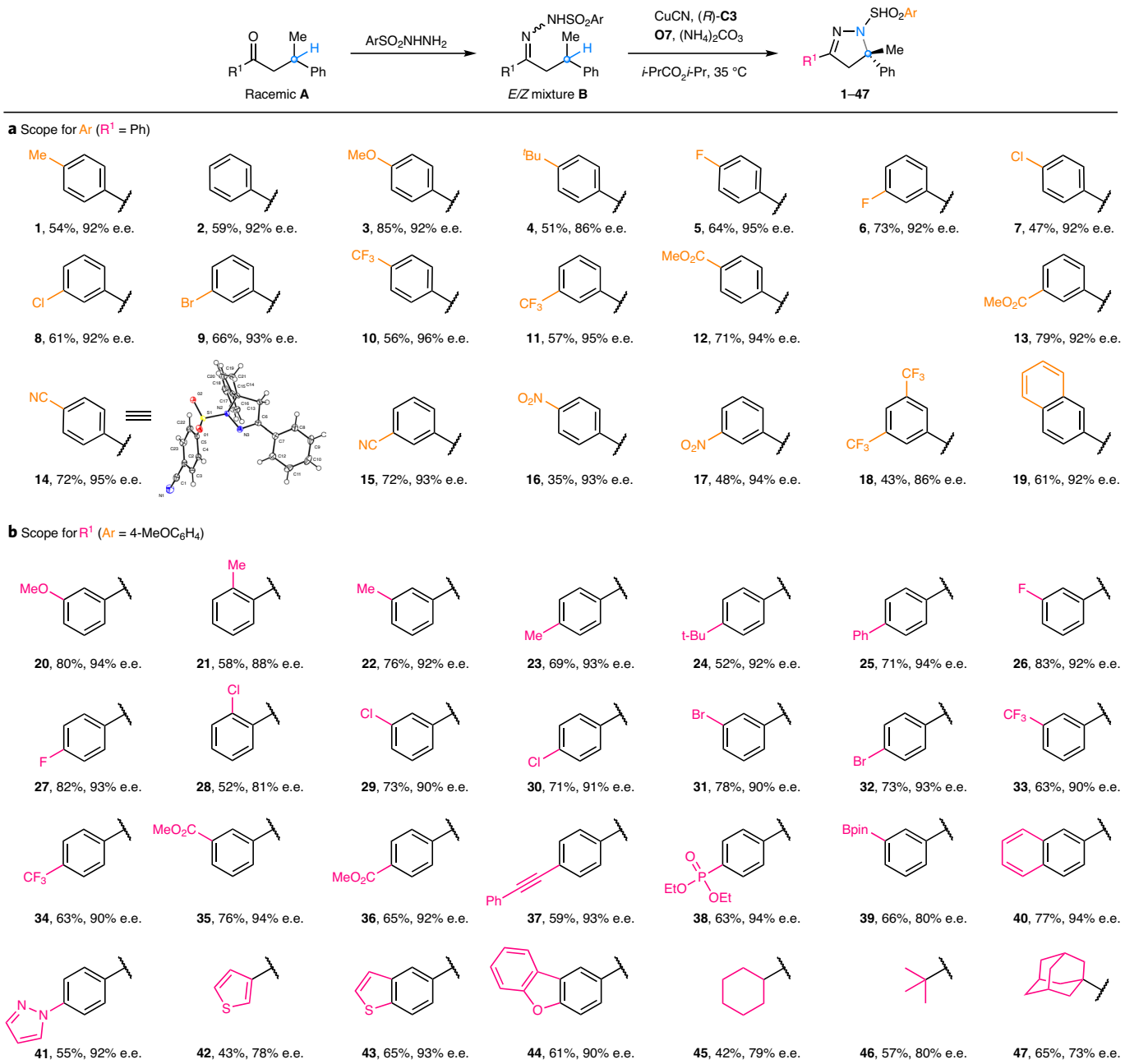


Fig. 2 | Substrate scope of the *N*-sulfonylhydrazone moiety. a, Scope of aryl sulfonyl groups. **b**, Scope of ketones. Standard conditions: racemic hydrazone **B** (0.20 mmol), oxidant **O7** (2.0 equiv.), CuCN (10 mol%), (*R*)-**C3** (15 mol%) and $(NH_4)_2CO_3$ (5 mol%) in *i*-$PrCO_2$*i*-Pr (4.0 ml) under argon at 35 °C for 96 h. Isolated yields are shown. Bpin, pinacolborato.

low diastereoselectivity. Subsequent heating in toluene further transformed **71** to sterically congested chiral spiro-cyclopropane **72** possessing two vicinal all-carbon quaternary stereocentres without substantial enantiopurity erosion (Fig. 3f). The chiral multi-substituted cyclopropane moiety is found in a variety of natural products and medicinal agents, and can also serve as useful synthetic intermediates[38,39].

Mechanistic investigations. The formation of the desired product **3** was not observed in the absence of either CuCN or (*R*)-**C3** (Supplementary Fig. 4). Thus, both the Cu(I) salt and CPA are indispensable for initiating this reaction. Subsequent separate radical-trapping experiments with 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), 1,4-benzoquinone (BQ) and butylated hydroxytoluene (BHT) all indicated reaction inhibition (Supplementary Fig. 4). In particular, the TEMPO-trapped ketone **A1-TEMPO** was detected by high-resolution mass spectrometry (HRMS) analysis (Fig. 4a). In addition, radical clock substrate **73** underwent tandem cyclopropane ring opening and C–N bond formation to provide eight-membered ring **74** (Fig. 4b). These observations support the formation of tertiary radical species under the current reaction conditions. As for the presumed 1,5-HAA event, side-by-side kinetic experiments using (±)-**B26** and (±)-**B26**-d_1 provided an intermolecular kinetic isotope effect (KIE) value of 1.46 (Fig. 4c). This indicates the involvement of reaction steps other than the 1,5-HAA in the rate-determining step(s). No H/D exchange was observed in the recovered starting material when (±)-**B3**-d_1 was used under the standard conditions, indicating a likely irreversible

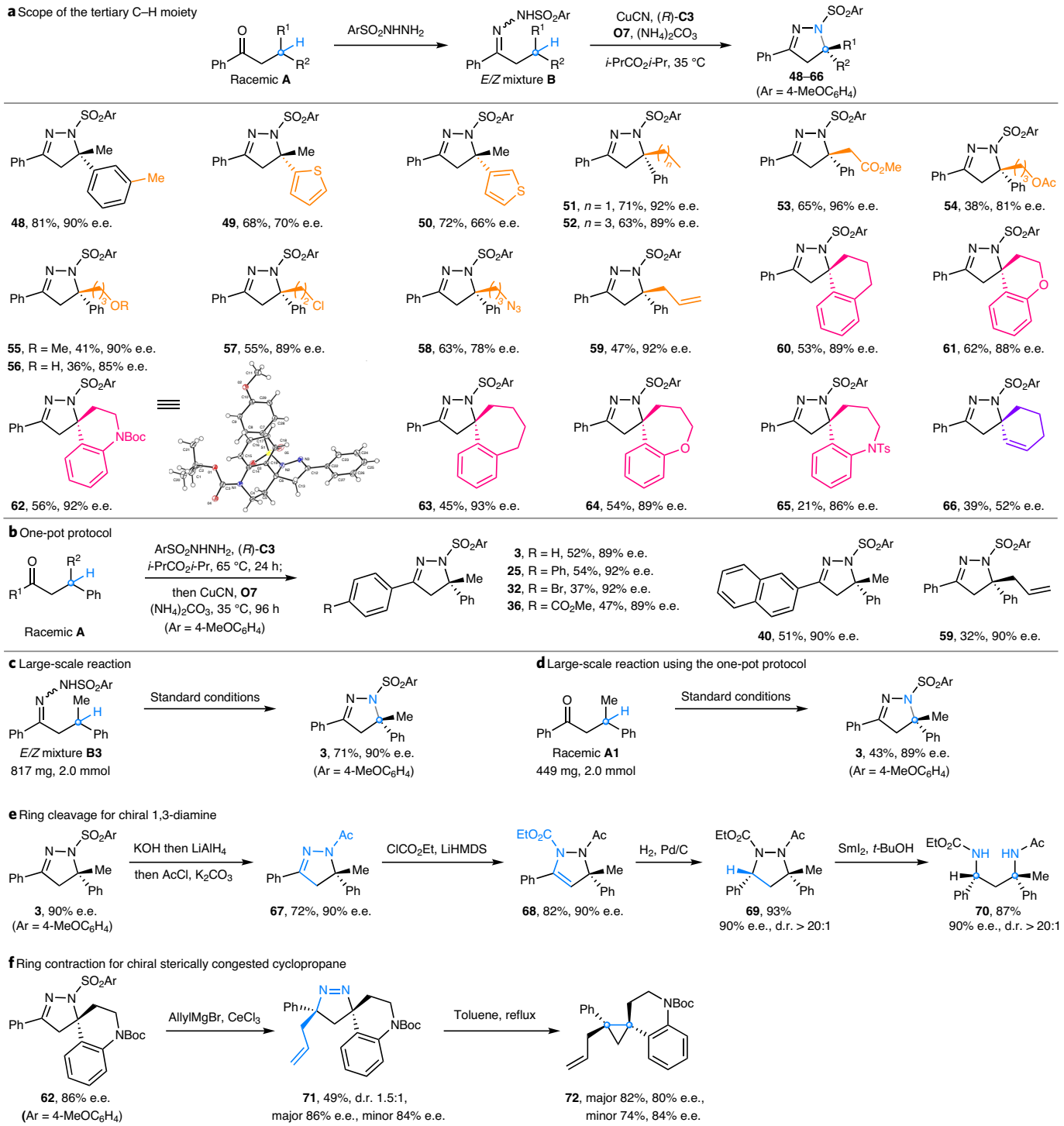


Fig. 3 | Scope of the tertiary C(sp^3)–H moiety, synthetic practicality and applications. a, Scope of the tertiary C(sp^3)–H moiety. Standard conditions: racemic hydrazone **B** (0.20 mmol), oxidant **O7** (2.0 equiv.), CuCN (10 mol%), (*R*)-**C3** (15 mol%) and $(NH_4)_2CO_3$ (5 mol%) in *i*-$PrCO_2$*i*-Pr (4.0 ml) under argon at 35 °C for 96 h. Isolated yields are shown. **b**, The current enantioconvergent amination of racemic tertiary C(sp^3)–H bonds was well adapted for a one-pot protocol starting from racemic ketone. Standard conditions: racemic ketone **A** (0.20 mmol), *p*-methoxybenzenesulfonohydrazide (0.20 mmol) and (*R*)-**C3** (15 mol%) in *i*-$PrCO_2$*i*-Pr (4.0 ml) were stirred under argon at 65 °C for 24 h. Then the reaction mixture was cooled to room temperature and oxidant **O7** (2.0 equiv.), CuCN (10 mol%) and $(NH_4)_2CO_3$ (5 mol%) were added under argon. The resulting mixture was stirred at 35 °C for 96 h. Isolated yields are shown. **c**,**d**, Both the two-step (**c**) and the one-pot (**d**) protocols were viable for large-scale preparations. **e**, The enantioconvergent amination reaction provides a facile access to valuable chiral 1,3-diamine compounds when allied with follow-up manipulations. **f**, The current methodology also allows for the straightforward synthesis of sterically congested chiral cyclopropane compounds bearing two vicinal quaternary all-carbon stereocentres. LiHMDS, lithium hexamethyldisilazide; SmI_2, samarium(II) iodide; NBoc, *tert*-butoxycarbonylamino.

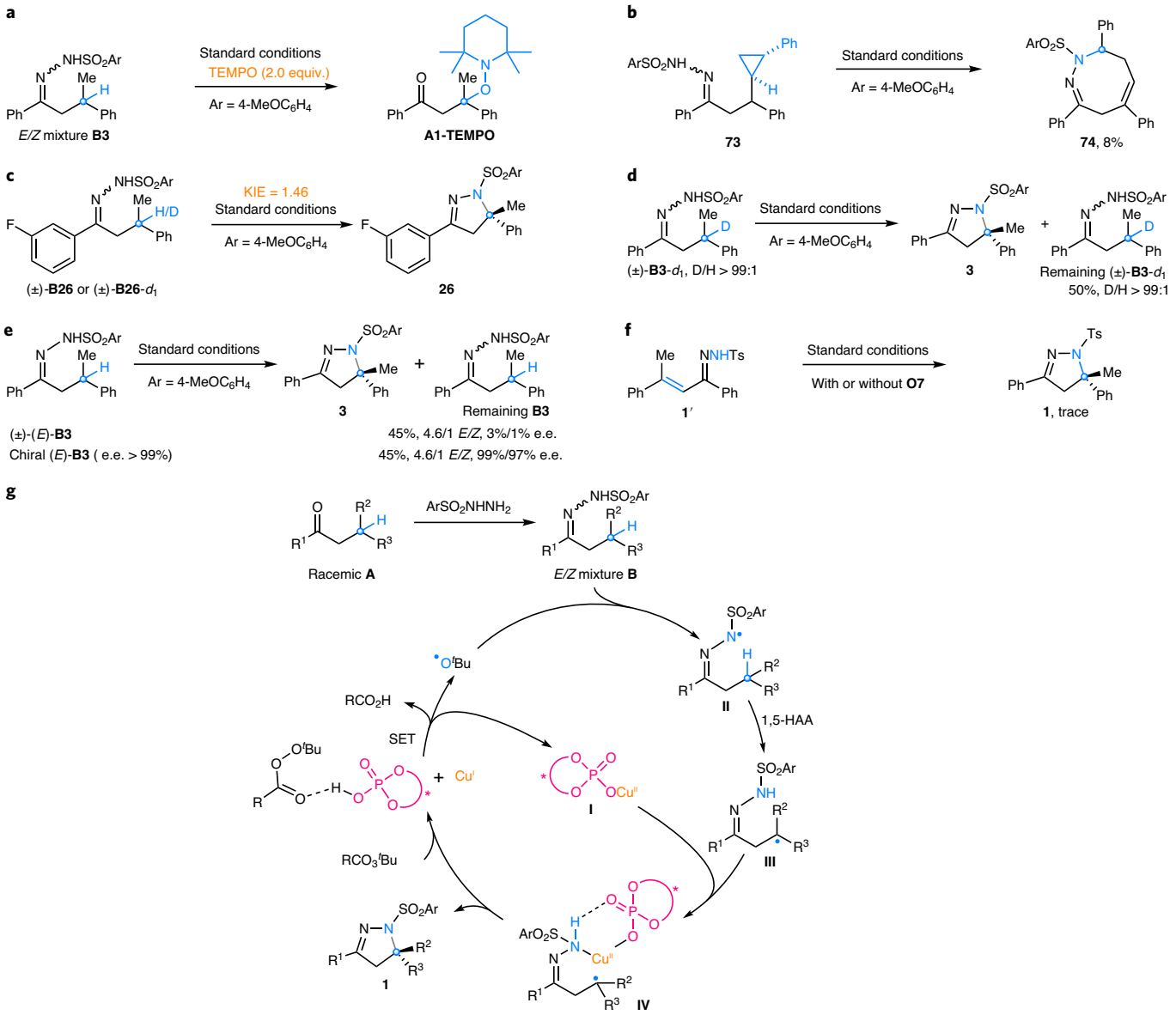


Fig. 4 | Mechanistic studies and proposal. a, The addition of TEMPO into the reaction mixture led to the formation of **A1-TEMPO**, indicating the intermediacy of a tertiary alkyl radical. **b**, The radical clock substrate **73** gave rise to ring-open product **74** under the standard conditions, supporting a radical mechanism. **c**, An intermolecular KIE of 1.46 was observed under the standard reaction conditions, suggesting the involvement of reaction steps other than the 1,5-HAA as the rate-determining step(s). **d**, The amount of deuterium did not change in the recovered starting material (±)-**B3**-d_1, and thus, the presumed 1,5-HAA is likely irreversible. **e**, The enantiomeric excess of recovered starting materials remained almost the same as those of the original ones, and thus, no kinetic resolution or fast racemization occurred during the reaction. **f**, Treatment of side product **1′** with or without **O7** under the otherwise standard conditions provided only a trace amount of product **1**. As a result, direct intramolecular Michael addition or any other reactions of **1′** for the formation of **1** are disproved. **g**, The reaction is proposed to start with the reduction of CPA-activated peroxide by Cu(I) via SET to afford a *t*-butoxy radical as well as Cu(II) and chiral phosphate complex **I**. Next, sequential intermolecular HAA and intramolecular HAA deliver prochiral tertiary alkyl radical **III**. Finally, the association of **III** with **I** and subsequent enantioselective C–N bond formation yield enantioenriched product **1**. Ts, *p*-toluenesulfonyl.

intramolecular 1,5-HAA (Fig. 4d). In addition, the enantiopurity of the recovered starting materials did not change when racemic or enantiopure (*E*)-**B3** was used (Fig. 4e), suggesting that the kinetic resolution or dynamic kinetic resolution of racemic tertiary C–H bonds is unlikely. Overall, all of these control experiments strongly support a relatively fast irreversible 1,5-HAA process to deliver prochiral tertiary radicals. In our reactions, a small amount of internal alkene product (*E*)-**1′** was formed in some cases. However, it did not afford product **3** with or without **O7** under the otherwise standard conditions (Fig. 4f). Thus, direct product formation from (*E*)-**1′** via intramolecular Michael addition or any other pathways can be excluded. Furthermore, the enantioselectivity remained almost constant during reaction (Supplementary Fig. 4). And the *E*/*Z* ratio of hydrazone apparently did not affect either the reaction efficiency or the enantioselectivity (Supplementary Table 2). Additionally, facile *E*/*Z* isomerization of hydrazone spontaneously occurred and was further facilitated by acid (Supplementary Tables 3 and 4), possibly via a nucleophilic-addition/bond-rotation/elimination process[40]. All these observations point to a likely uniform enantiodetermining transition state along with the same reaction pathway.

On the basis of the above observations and previous reports[12–17,29], a plausible mechanism is tentatively proposed, shown

in Fig. 4g. Initially, Cu(I) reacts with CPA-activated peroxide via single-electron transfer (SET) to afford a highly reactive *t*-butoxy radical accompanied by the formation of the crucial chiral Cu(II) phosphate complex **I** (ref. [29]). Intermolecular hydrogen abstraction of the weak N–H bond in hydrazone **B** by the *t*-butoxy radical gives the nitrogen-centred radical **II** (ref. [41]). Subsequent irreversible intramolecular 1,5-HAA gives rise to prochiral tertiary alkyl radical **III**. Next, Cu(II) complex **I** associates with radical **III** and promotes the final enantioselective C–N bond formation.

Conclusions

In summary, we have described a strategy for direct radical enantioconvergent tertiary C(sp^3)–H amination starting from readily available racemic ketones with a dual Cu/CPA catalysis. The mechanistic blueprint consisting of sequential HAA and asymmetric radical functionalization highlights a decoupled HAA that allows for chirality loss of the generated tertiary radical. Thus, it is able to override the mechanistic limitation inherent to conventional C–H functionalization catalysed by a transition metal. The combination of this process with subsequent versatile transformations showcases the potential for rapidly converting racemic ketones bearing tertiary β-C(sp^3)–H bonds into a broad range of enantioenriched structures. We anticipate that this strategy will spur the development of new classes of catalysts for general and broadly applicable enantioconvergent transformations of common racemic tertiary C(sp^3)–H bonds.

Data availability

The findings of this study are available within the paper and its Supplementary Information. Crystallographic parameters for compounds **14** and **62** are available free of charge from the Cambridge Crystallographic Data Centre under CCDC 1923926 (**14**) and 1923927 (**62**). All data are available from the authors upon reasonable request.

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Author contributions

C.-J.Y., C.Z. and Q.-S.G. designed the experiments and analysed the data. C.-J.Y., C.Z., J.-H.F., X.-L.S., L.Y., Y.S., Y.T. and Z.-L.L. performed the experiments. All authors participated in writing the manuscript. X.-Y.L. conceived and supervised the project.

Competing interests

The authors declare no competing interests.

Additional information

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