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A general copper-catalysed enantioconvergent C(sp^3)–S cross-coupling via biomimetic radical homolytic substitution

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Although α-chiral C(sp^3)–S bonds are of enormous importance in organic synthesis and related areas, the transition-metal-catalysed enantioselective C(sp^3)–S bond construction still represents an underdeveloped domain probably due to the difficult heterolytic metal–sulfur bond cleavage and notorious catalyst-poisoning capability of sulfur nucleophiles. Here we demonstrate the use of chiral tridentate anionic ligands in combination with Cu(I) catalysts to enable a biomimetic enantioconvergent radical C(sp^3)–S cross-coupling reaction of both racemic secondary and tertiary alkyl halides with highly transformable sulfur nucleophiles. This protocol not only exhibits a broad substrate scope with high enantioselectivity but also provides universal access to a range of useful α-chiral alkyl organosulfur compounds with different sulfur oxidation states, thus providing a complementary approach to known asymmetric C(sp^3)–S bond formation methods. Mechanistic results support a biomimetic radical homolytic substitution pathway for the critical C(sp^3)–S bond formation step.

α-Chiral alkyl thiols and other organosulfur moieties with different sulfur oxidation states are important chiral building blocks in organic synthesis[1,2] and biochemical processes[3], and are also key structural elements in a variety of biomolecules, pharmaceuticals and agrochemicals[3–6]. For example, they are widely present in many chiral organocatalysts[7,8] and ligands[9,10] for diverse asymmetric transformations. They also exist in a myriad of metabolites, biomacromolecules and cofactors which play critical roles in numerous essential biochemical processes for the development and maintenance of life[3,11,12] (for selected important α-chiral alkyl organosulfur compounds in different fields, see Supplementary Fig. 1). Consequently, efficient catalytic enantioselective carbon–sulfur (C(sp^3)–S) bond formation constitutes a long-standing objective in modern chemical and biological research[3,11,13–21].

Among a range of options, the use of sulfur nucleophiles has become prevalent: these sulfur reagents are widely available, inexpensive, easy to handle and of high atom economy compared with electrophilic ones[22]. In this context, asymmetric organocatalysis and Lewis acid catalysis have been extensively investigated for developing highly enantioselective

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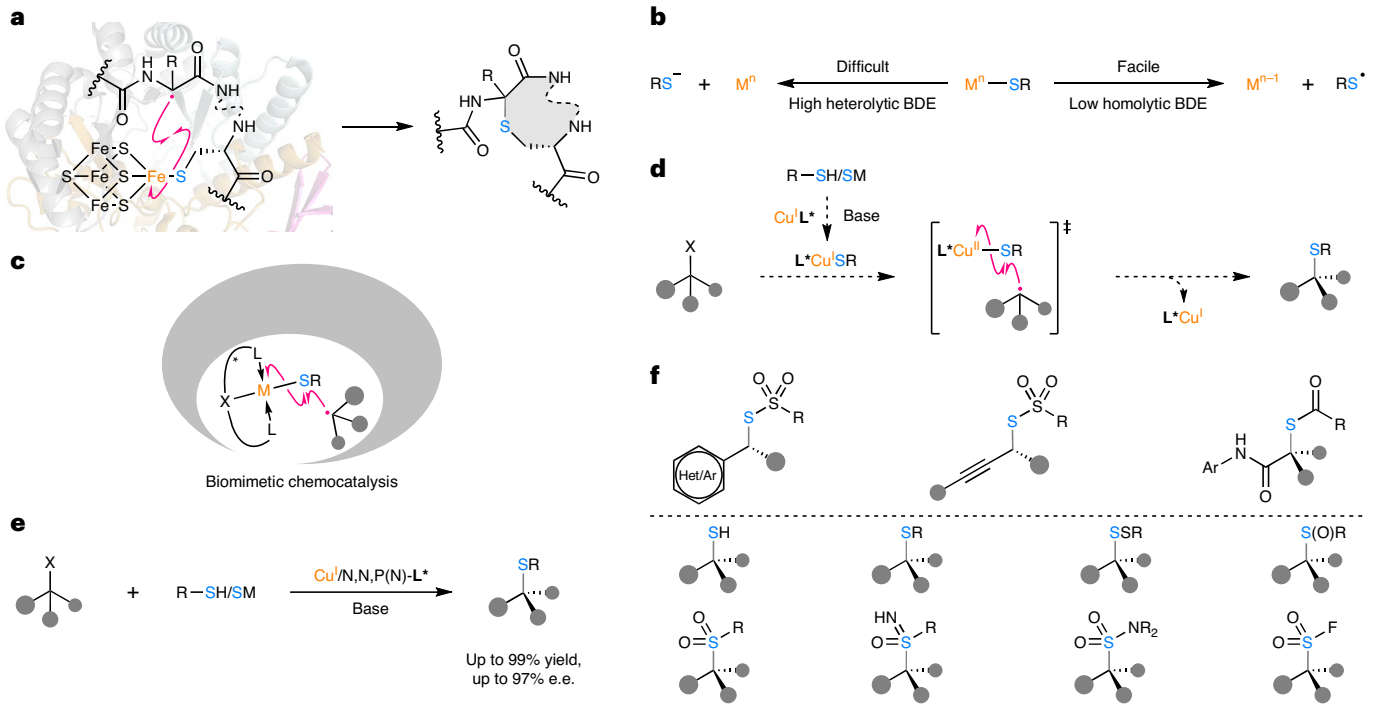

Fig. 1 | Motivation and design of Cu(I)-catalysed enantioconvergent C(sp^3)–S cross-coupling via biomimetic radical homolytic substitution. a, The radical SAM enzyme CteB [PDB:5WGG][41] and the enantioselective radical C(sp^3)–S bond formation catalysed by it. **b**, The heterolytic cleavage of a metal–sulfur bond is usually energetically demanding while the corresponding homolytic cleavage is commonly facile. **c**, A biomimetic transition-metal-catalysed enantioselective radical homolytic substitution-type C(sp^3)–S bond formation is highly promising and remains to be explored. **d**, Description of a proposed Cu(I)-catalysed enantioconvergent radical C(sp^3)–S coupling together with conceivable challenges, such as non-stereoselective S_N2 background reaction and undesired side reactions. **e**, This work describes a Cu(I)-catalysed enantioconvergent radical C(sp^3)–S coupling of racemic secondary and tertiary alkyl halides with transformable sulfur nucleophiles. **f**, This methodology provides expedient access to a panel of α-chiral alkyl organosulfur compounds.

C–S bond formation with sulfur nucleophiles[13–16]. In stark contrast, asymmetric transition-metal catalysis has largely remained out of reach because sulfur-containing compounds poison metal catalysts[23,24]. This problem has been partially overcome in recent decades by employing electronically deactivated sulfur surrogates[22,25–29], multidentate electron-rich phosphine ligands[30–32] or coordinatively saturated metal catalysts through an outer-sphere transition-state mechanism[18,33–36]. In addition, the extremely high heterolytic bond dissociation energies (BDEs) of many metal–S bonds (for example, heterolytic BDE (copper(II)–S) ≈ 162 kcal mol^{-1}) pose an additional challenge to develop polar transition-metal-catalysed enantioselective C–S bond formation (Fig. 1b)[37]. Clearly, the design and invention of a conceptually different catalytic system that avoids such challenging heterolytic metal–S bond cleavage is very desirable for developing transition-metal-catalysed enantioselective C–S bond formation, which, if achieved, would complement previously reported methods.

It is interesting that, in enzymatic biocatalytic processes, the radical *S*-adenosylmethionine (SAM) superfamily has been discovered to be an enabling platform for the straightforward construction of chiral C(sp^3)–S bonds in a variety of important biological molecules[3,11,38], such as biotin[39], lipoyl H-protein[40] and sactipeptides[41]. Elegant biosynthetic studies revealed that the key C(sp^3)–S bond formation in some cases proceeded preferably through the radical homolytic substitution of a [4Fe–4S] cluster by a carbon-centred radical, probably due to the relatively low homolytic BDE of an Fe–S bond (BDE ≈ 61 kcal mol^{-1})[42] (Fig. 1a). Unfortunately, this privileged mechanistic manifold has hitherto remained untapped for developing transition-metal-catalysed enantioselective C(sp^3)–S bond formation although the corresponding racemic reactions have been proposed in a few examples[43]. Inspired by the extraordinary capacity of these enzymes for forging chiral C(sp^3)–S bonds, we hypothesized that one first-row transition metal in combination with well-designed chiral ligands[44–46] might elicit such a biomimetic enantioselective transformation (Fig. 1c). In particular, we have recently found that a series of chiral electron-rich multidentate anionic ligands can remarkably enhance the single-electron reduction of alkyl halides by Cu(I) thereby generating alkyl radical species, which readily participate in subsequent enantioselective C–C, C–N and C–P bond formation[46–51]. In addition, the homolytic BDE for a Cu(II)–S bond was also reported to be low (~34 kcal mol^{-1})[37]. As such, we wondered whether these Cu(I)/chiral multidentate anionic ligand catalysts would promote the desired radical enantioconvergent C(sp^3)–S cross-coupling reaction of racemic alkyl halides with sulfur nucleophiles (Fig. 1d). Indeed, our preliminary density functional theory (DFT) studies in a model system revealed that the coupling of a secondary prochiral alkyl radical and LCu^{II}–SR complex proceeded preferably via a radical homolytic substitution pathway (for details, see Supplementary Figs. 10–13, Supplementary Table 12, and relevant text in the Supplementary Information). Nonetheless, several challenges still exist for successfully implementing such a process: (1) the deprotonated form of sulfur nucleophiles and their complexes with Cu(I) might be prone to strong background S_N2 alkylation with racemic alkyl halides likely with no or low enantiocontrol due to their relatively strong nucleophilicity[52,53]; (2) the sulfhydryl group in nucleophiles might easily intercept the newly generated carbon-centred radicals due to its relatively low BDE (~70–91 kcal mol^{-1}), possibly leading to undesired dimerization, hydrogen-atom transfer and other side reactions[2]. Therefore, key to the success would be identifying not only an appropriate ligand/catalyst but also suitable sulfur nucleophiles that are capable of selectively undergoing the desired radical C(sp^3)–S cross-coupling amidst a number of other competing processes.

Here we describe a simple Cu(I) catalyst system with different types of multidentate anionic N,N,P(N)-ligands that enables a general and

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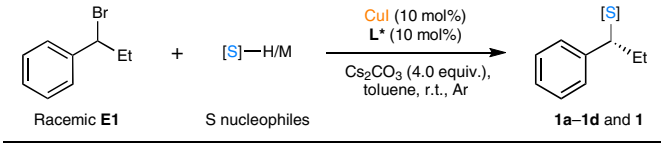
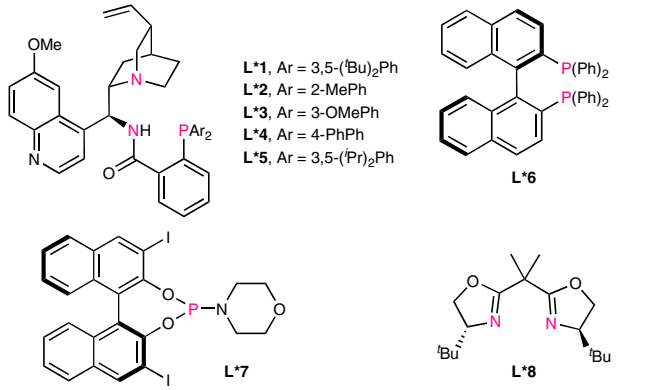
Table 1 | Optimization of reaction conditions



Racemic **E1** | S nucleophiles | **1a–1d** and **1**



Entry	L*	S nucleophile	Product	Yield (%)	e.e. (%)
1	**L*1**	**S1** (PhC(O)SK)	**1a** ([S] = PhC(O)S)	99	34
2	**L*1**	**S2** ($PhS(O)_2Na$)	**1b** ([S] = $PhS(O)_2$)	0	–[a]
3	**L*1**	**S3** (PhSNa)	**1c** ([S] = PhS)	73	0
4	**L*1**	**S4** (HSNa)	**1d** ([S] = SH)	0	–[a]
5	**L*1**	**S5** ($3,5\text{-}Me_2PhS(O)_2SNa$)	**1** ([S] = $3,5\text{-}Me_2PhS(O)_2S$)	54	69
6	**L*2**	**S5**	**1**	43	25
7	**L*3**	**S5**	**1**	38	49
8	**L*4**	**S5**	**1**	40	42
9	**L*5**	**S5**	**1**	80	79
10	**L*6**	**S5**	**1**	7	6
11	**L*7**	**S5**	**1**	Trace	–[a]
12	**L*8**	**S5**	**1**	Trace	–[a]
13[b]	**L*5**	**S5**	**1**	90	80
14[c]	**L*5**	**S5**	**1**	81	92
15[d]	**L*5**	**S5**	**1**	76	92
16[e]	**L*5**	**S5**	**1**	54	92

Reaction conditions: racemic **E1** (0.050 mmol, 1.0 equiv.), sulfur nucleophile (1.2 equiv.), CuI (10 mol%), **L*** (10 mol%) and Cs_2CO_3 (4.0 equiv.) in toluene (0.50 ml) at r.t. for 48 h under argon. Yield is based on ^{1}H NMR analysis of the crude products using 1,3,5-trimethoxybenzene as an internal standard; the e.e. of **1** is based on chiral HPLC analysis. [a]Not determined. [b]$Cu(MeCN)_4BF_4$ (10 mol%). [c]$Cu(MeCN)_4BF_4$ (10 mol%) in toluene/DMF (10/1 v/v) at −15 °C for 3 days. [d]$Cu(MeCN)_4BF_4$ (10 mol%) and H_2O (1.0 equiv.) in toluene/DMF (10/1 v/v) at −15 °C for 3 days. [e]$Cu(MeCN)_4BF_4$ (2.5 mol%) and **L*5** (2.5 mol%) in toluene/DMF (10/1 v/v) at −15 °C for 3 days.

practical biomimetic enantioconvergent radical C(sp^3)–S cross-coupling reaction under mild reaction conditions (Fig. 1e,f). The reaction tolerates a range of racemic secondary/tertiary alkyl halides (Fig. 1f, top) and different types of highly transformable sulfur nucleophiles with high functional group compatibility. More importantly, when allied with follow-up transformations this strategy provides a highly flexible and practical platform to rapidly access an abundant of related organosulfur compounds (Fig. 1f, bottom), such as thiol, thioether, disulfide, sulfoxide, sulfone, sulfoximine, sulfonamide and sulfonyl fluoride, with most common substitution types of α-stereocentres present in useful synthetic building blocks, ligands and drugs, demonstrating the synthetic utility and adaptability of this methodology.

Results and discussion

Reaction development

At the outset, we investigated the enantioconvergent C(sp^3)–S cross-coupling between racemic (1-bromopropyl)benzene **E1** and a series of nucleophilic sulfur salts, to avoid the abovementioned radical side reactions of a sulfhydryl group (Table 1). Low-polarity toluene was chosen as the solvent to suppress the undesired direct S_N2 substitution reaction (Supplementary Table 1). Accordingly, in the presence of CuI and cinchona-alkaloid-derived tridentate anionic N,N,P-ligand **L*1**[47,54], potassium benzothioate **S1** (entry 1) and sodium 3,5-dimethylbenzenesulfonothioate **S5** (entry 5) gave the desired α-chiral alkyl thioester **1a** and thiosulfonate **1**, respectively, with encouraging enantioselectivity while others delivered either racemic (sodium thiophenolate, **S3**, entry 3) or no products (sodium benzenesulfinate, **S2**; entry 2; sodium hydrosulfide, **S4**; entry 4). It is noteworthy that thiosulfonates not only are valuable synthetic intermediates possessing chameleon-like reactivities towards nucleophiles, electrophiles and radicals[55] but also exhibit a broad spectrum of pharmaceutical properties, such as anticancer, antiparasitic, antifungal and cholinesterase inhibitory activities[56]. Thus, we employed **S5** as the sulfur nucleophile for the following optimization of the reaction conditions. Among electron-rich ligands **L*2**–**L*5** with P-substituents of different steric and electronic properties (entries 6–9), 3,5-di-isopropyl-substituted ligand **L*5** exhibited remarkably good reaction efficiency and enantioselectivity (80% yield and 79% e.e., entry 9). In sharp contrast, less electron-rich neutral ligands such as bisphosphine **L*6**, monophosphoramidite **L*7** and bisoxazoline **L*8** failed to efficiently initiate the single-electron reduction of **E1** under the same reaction conditions (entries 10–12). These results clearly support the enhancing effect of electron-rich multidentate anionic ligands on the reducing capability of Cu(I) catalysts for facile alkyl radical generation from racemic alkyl halides under ambient thermal conditions. After further optimization of reaction parameters, including copper catalysts, reaction temperatures and solvents (entry 13 and Supplementary Tables 2 and 3), we identified the optimal conditions as follows: the reaction of **E1** (1.0 equiv.) and **S5** (1.2 equiv.) in the presence of $Cu(MeCN)_4BF_4$ (10 mol%), **L*5** (10 mol%) and Cs_2CO_3 (4.0 equiv.) in a mixed solvent of toluene and *N*,*N*-dimethylformamide (DMF) (vol/vol = 10/1) at −15 °C for 3 days afforded **1** in 81% yield with 92% e.e. (Table 1, entry 14). Notably, neither the addition of 1.0 equiv. of water (entry 15) nor the reduced catalyst loading (entry 16) obviously affected the enantioselectivity. Furthermore, the gram-scale reaction of **E1** and **S5** in the presence of 2.5 mol% $Cu(MeCN)_4BF_4$ performed well to give the desired product **1** with comparable yield and e.e. (Table 2 and Supplementary Fig. 2). These results clearly demonstrated the practicality and synthetic potential of this methodology.

Substrate scope

Having established the optimal reaction conditions, we examined the generality of the biomimetic enantioconvergent radical C(sp^3)–S coupling reaction (Table 2). Thus, a series of sodium arylthiosulfonates with different steric properties on the *S*-aryl rings were successfully accommodated to afford **1**–**4** in 74–91% yield with 90–92% e.e. With regard to benzyl bromides, a wide range of substrates bearing simple unfunctionalized aliphatic side chains (**5**–**9**) or those functionalized with phenyl (**10**), furan (**11**), ether (**12**), ester (**13**), nitrile (**14**), acetal (**15**), primary halide (**16** and **17**) and terminal alkene (**18** and **19**) groups all worked well in this process. In particular, steric hindrance around the forming chiral centre did not greatly affect the reaction efficiency or enantioselectivity (**7** and **9**). However, a cyclic benzyl bromide led to diminished enantioselectivity (77% e.e. for **20**). In addition, phenyl rings possessing a broad series of electron-donating or electron-withdrawing substituents at different (*ortho*, *meta* or *para*) positions and bicyclic naphthalene rings were compatible with the reaction to provide **21**–**34** in 68–89% yield with 87–93% e.e. Heterobenzyl bromides featuring different types of medicinally relevant heterocycles, such as benzo[*b*]thiophene (**35**), thiophene (**36**), quinoline (**37**) and pyridine (**38**), were well accommodated in the process. Further, the less reactive benzyl chloride **E36** was also a viable substrate to afford **34** in 91% e.e., albeit with a moderate yield.

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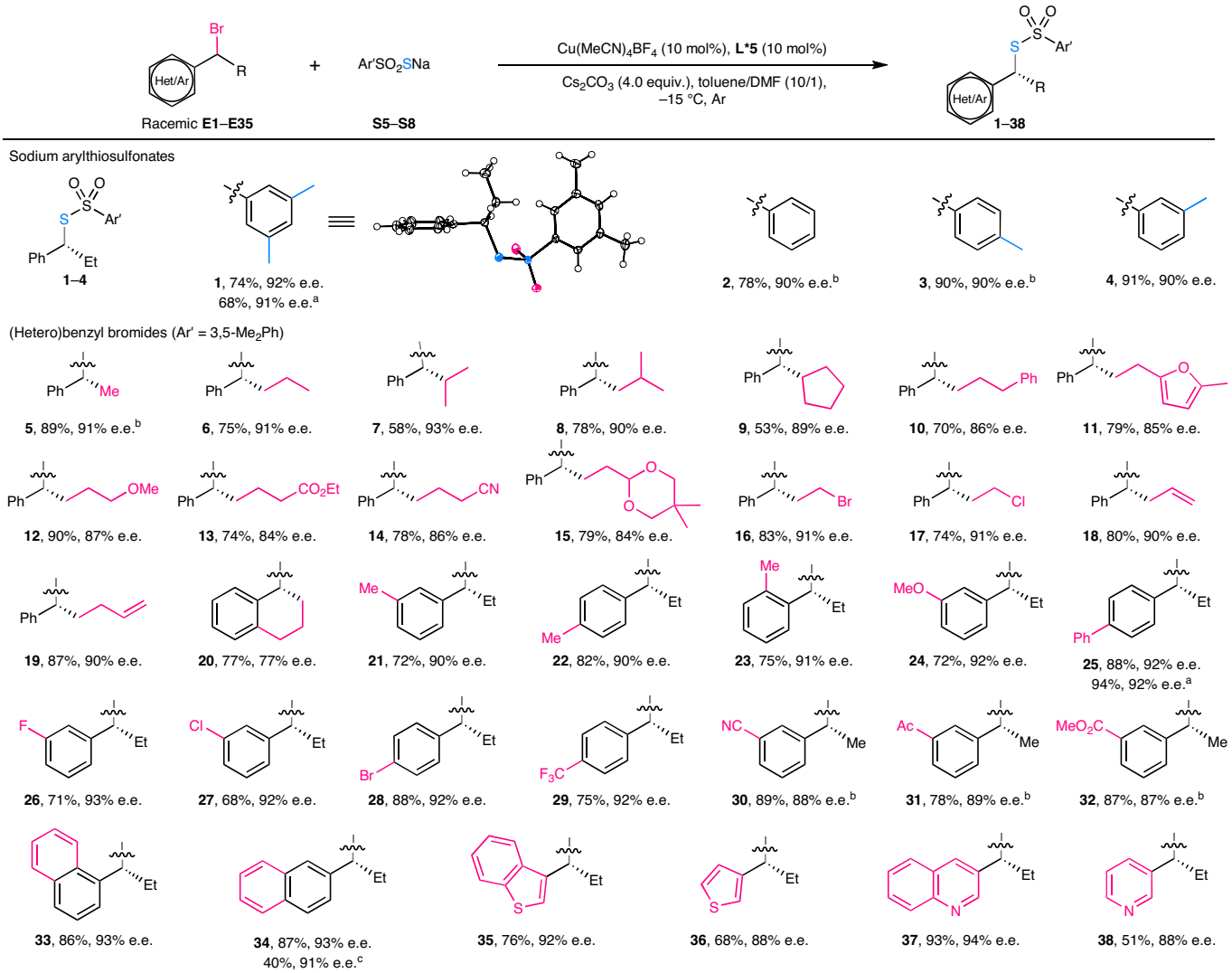
Table 2 | Substrate scope for sodium thiosulfonates and racemic (hetero)benzyl halides



Scope for sodium thiosulfonates and racemic (hetero)benzyl bromides. Standard reaction conditions: (hetero)benzyl bromide (0.20 mmol, 1.0 equiv.), sulfur nucleophile (1.2 equiv.), $Cu(MeCN)_4BF_4$ (10 mol%), **L*5** (10 mol%), and Cs_2CO_3 (4.0 equiv.) in toluene/DMF (10/1 v/v, 2.2 ml) at −15 °C for 3–7 days under argon. Isolated yields are shown; e.e. is based on chiral HPLC analysis. The X-ray structure of compound **1** displays sulfur and oxygen atoms in blue and pink, respectively, with all other atoms depicted in black. [a]$Cu(MeCN)_4BF_4$ (2.5 mol%) and **L*5** (2.5 mol%). [b]−30 °C. [c]The chloride substrate, albeit of lower reactivity, was also suitable for the reaction. Reaction conditions: 2-(1-chloropropyl)naphthalene **E36** (0.20 mmol, 1.0 equiv.), **S5** (1.2 equiv.), $Cu(MeCN)_4BF_4$ (20 mol%), **L*5** (20 mol%) and Cs_2CO_3 (4.0 equiv.) in toluene/DMF (10/1 v/v, 2.2 ml) at −15 °C for 7 days.

To further strengthen the synthetic utility of this methodology, we next switched to the cross-coupling of racemic propargyl halides given that an alkynyl group near the chiral centre would be readily converted to many other functional groups[57]. In addition, transition-metal-catalysed enantioconvergent propargylic substitution reactions with sulfur nucleophiles to forge synthetically attractive propargyl organosulfur compounds have so far remained largely underdeveloped[58,59]. Unfortunately, the originally superior ligand **L*5** for benzyl halides performed poorly in the reaction of the propargyl bromide **E37** in terms of both reaction efficiency and enantioselectivity (38% yield and 18% e.e. for **39**, Table 3). Surprisingly, our recently developed oxazoline-derived[60] N,N,P-ligands **L*9** and **L*10** provided obviously enhanced enantioselectivity. However, the corresponding reaction efficiency was very poor, presumably due to the low reducing capability of the formed Cu(I) catalyst, disfavouring the single-electron reduction of the propargyl bromide. These results prompted us to replace the oxazoline moiety with a more electron-donating imidazoline[61,62]. Indeed, the newly synthesized imidazoline-derived N,N,P-ligands **L*11** and **L*12** exhibited substantially boosted reaction efficiency with similar enantioselectivity compared with **L*10**. Further screening of other reaction parameters with **L*12** as the ligand (Supplementary Tables 4–6) led to the optimal conditions as follows: the reaction of **E37** (0.050 mmol, 1.0 equiv.) and **S6** (1.2 equiv.) in the presence of CuI (7.5 mol%), **L*12** (6.0 mol%), Rb_2CO_3 (2.0 equiv.), and H_2O (2.0 equiv.) in $CHCl_3$ at −20 °C for 3 days under argon delivered **39** in 93% yield (90% on 0.20 mmol scale, Table 3) with 90% e.e. We were delighted to find that no allenylation product was observed, probably due to the large steric effect of the TIPS (triisopropylsilyl) group (Supplementary Fig. 3). As for the aliphatic side chains of propargyl bromides (Table 3), a similar scope of linear or β-branched unfunctionalized alkyl groups and functionalized ones as that for benzyl halides was observed (**39**–**51**, 61–95% yield, 84–96% e.e.). Additionally, the substrates bearing a trimethylsilyl (**52**), triethylsilyl (**53**) or phenyl group (**54**) on the alkynyl moiety were also compatible with the reaction conditions to afford corresponding products in high yield with excellent enantioselectivity.

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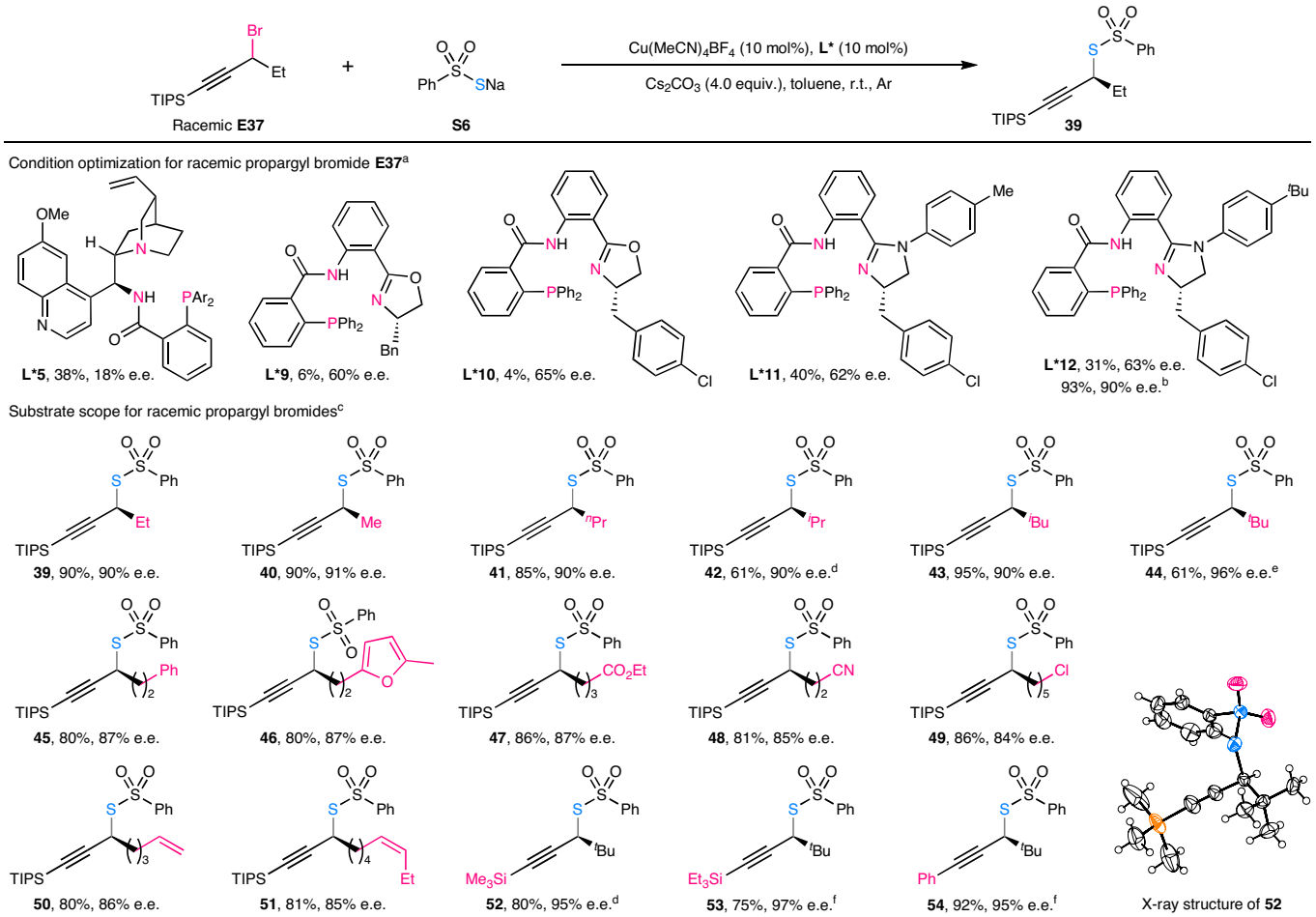
Table 3 | Reaction development and substrate scope for racemic propargyl bromides



The X-ray structure of compound **52** displays sulfur, oxygen, and silicon atoms in blue, pink, and orange, respectively, with all other atoms depicted in black. [a]Condition optimization for racemic propargyl bromide **E37**. Reaction conditions: **E37** (0.050 mmol, 1.0 equiv.), **S6** (1.2 equiv.), $Cu(MeCN)_4BF_4$ (10 mol%), **L*** (10 mol%) and Cs_2CO_3 (4.0 equiv.) in toluene (0.50 ml) at r.t. for 2 days under argon. Yield is based on ^{1}H NMR analysis of the crude products using 1,3,5-trimethoxybenzene as an internal standard; e.e. is based on chiral HPLC analysis. [b]CuI (7.5 mol%), **L*12** (6.0 mol%), Rb_2CO_3 (2.0 equiv.) and H_2O (2.0 equiv.) in $CHCl_3$ (0.50 ml) at −20 °C. [c]Substrate scope for racemic propargyl bromides. Standard reaction conditions: propargyl bromide (0.20 mmol, 1.0 equiv.), **S6** (1.2 equiv.), CuI (7.5 mol%), **L*12** (6.0 mol%), Rb_2CO_3 (2.0 equiv.) and H_2O (2.0 equiv.) in $CHCl_3$ (2.0 ml) at −20 °C for 3 days under argon. Isolated yields are shown; e.e. is based on chiral HPLC analysis. [d]Five days. [e]Seven days. [f]Six days.

The enantioconvergent radical cross-coupling of racemic tertiary alkyl halides has remained a formidable challenge given the steric bulkiness and the three difficult-to-differentiate different carbon substituents of corresponding prochiral tertiary radicals compared with that of secondary ones[48,63–65]. The above encouraging results with secondary alkyl halides stimulated us to try racemic tertiary alkyl halides for efficient access to sulfur-containing tetrasubstituted carbon stereocentres, important motifs in natural products, drugs and biologically active compounds[4,16,17]. Unexpectedly, the reaction of racemic tertiary α-aminocarbonyl alkyl chloride **E53** with **S6** in the presence of either **L*5** or **L*12** did not provide the corresponding coupling product, due to the instability of the coupling product under the current basic conditions (Supplementary Fig. 4). By contrast, thiobenzoic acid **S9** in place of **S6** delivered the desired product **55** in excellent yield, albeit with poor enantioselectivity under the same conditions (Table 4). These results prompted us to further evaluate other types of tridentate anionic ligands, among which the *N*,*N*,*N*-bis(oxazolinylmethylidene)isoindoline (boxmi) ligands **L*14**–**L*16** developed by Gade and co-workers[66] provided good reactivity and enantioselectivity. After additional optimization of the conditions (Supplementary Table 7), we found that the best ligand **L*16** delivered **55** in 93% yield with 90% e.e. in the presence of $Cu(PPh_3)_3CF_3$ and Cs_2CO_3 in Et_2O at −10 °C for 3 days. Notably, the use of potassium benzothioate **S1** as the nucleophile gave the same results as that with thiobenzoic acid **S9**. As for the substrate scope (Table 4), a series of α-chloro secondary amides derived from aniline and its analogues were readily accommodated to deliver **55**–**62** in 90–97% yield with 84–95% e.e. The gram-scale reaction performed well to give the desired product **62** with comparable yield and e.e. (Supplementary Fig. 2). Regarding the α-substituents, high yield and excellent enantioselectivity were generally observed as long as an α-aryl-α-alkyl substitution pattern was maintained (**63**–**79**). Importantly, steric hindrance around the stereocentre bearing an isopropyl group did not greatly affect the reaction efficiency or enantioselectivity to provide **70** with excellent results. In addition, a variety of aryl-, heteroaryl- and alkyl-substituted potassium thiocarboxylates all worked well to give **80**–**88** in excellent yield with outstanding enantioselectivity. The absolute configurations of **1** (Table 2 and Supplementary Fig. 5), **52** (Table 3 and Supplementary Fig. 6) and **83** (Table 4 and Supplementary Fig. 7) were determined by X-ray crystallographic analysis, and those of all related other compounds were assigned by analogy accordingly. Although there existed a background reaction without copper catalyst or ligand **L*16**, the addition of copper/**L*16** effectively tuned the reactivity and the reaction rate of the enantioconvergent radical process would be much faster

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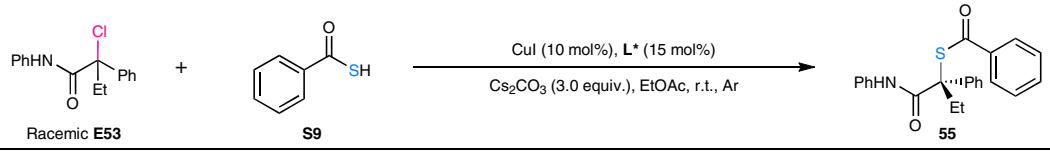
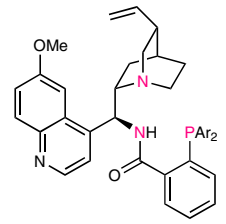
Table 4 | Reaction development and substrate scope for racemic tertiary alkyl chlorides

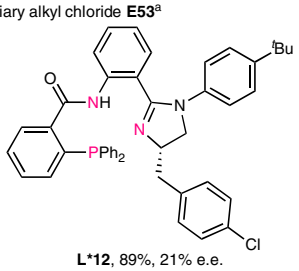


Racemic **E53** + **S9** → **55**

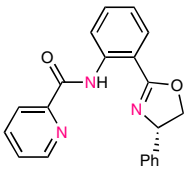
Condition optimization for racemic tertiary alkyl chloride **E53**[a]



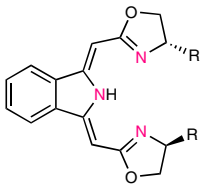
L*5, 85%, 3% e.e.



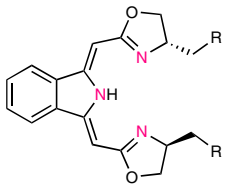
L*12, 89%, 21% e.e.



L*13, 80%, 12% e.e.

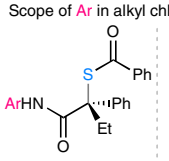


L*14, R = ^{i}Pr, 83%, 67% e.e.
L*15, R = Ph, 82%, 56% e.e.

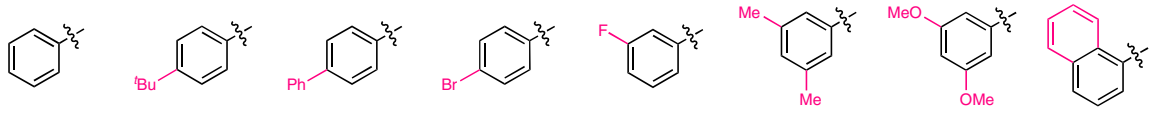


L*16, R = 2-naphthyl
85%, 76% e.e. (93%, 90% e.e.[b])

Scope of Ar in alkyl chlorides (with **S9**)[c]

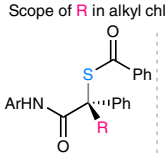


(**55**–**62**)



55, 93%, 90% e.e. **56**, 95%, 87% e.e. **57**, 94%, 89% e.e. **58**, 92%, 84% e.e. **59**, 97%, 87% e.e. **60**, 90%, 86% e.e. **61**, 95%, 90% e.e. **62**, 95%, 95% e.e.
95%, 94% e.e.[d]

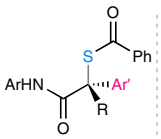
Scope of R in alkyl chlorides (with **S9**)[c]



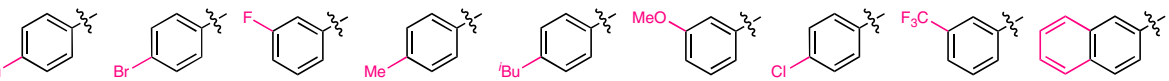
Ar = 1-naphthyl
(**63**–**70**)

63, 94%, 92% e.e. **64**, 93%, 92% e.e. **65**, 95%, 95% e.e. **66**, 88%, 93% e.e. **67**, 90%, 93% e.e. **68**, 85%, 92% e.e. **69**, 94%, 90% e.e. **70**, 75%, 89% e.e.

Scope of Ar′ in alkyl chlorides (with **S9**)[c]

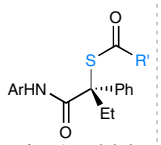


Ar = 1-naphthyl
(**71**–**73**, R = Et)
(**74**–**79**, R = Me)

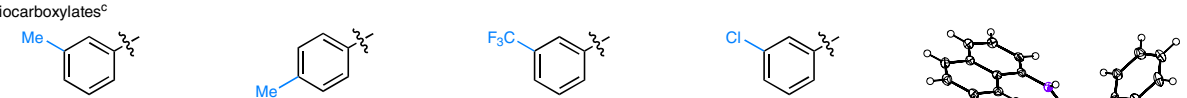


71 94%, 88% e.e. **72** 93%, 89% e.e. **73** 90%, 90% e.e. **74** 92%, 91% e.e. **75** 90%, 93% e.e. **76** 91%, 92% e.e. **77** 91%, 95% e.e. **78** 95%, 84% e.e. **79** 87%, 88% e.e.

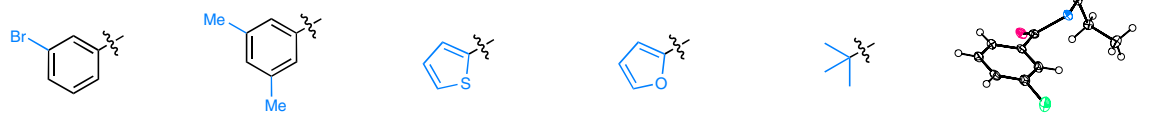
Scope of potassium thiocarboxylates[c]



Ar = 1-naphthyl
(**80**–**88**)



80, 95%, 95% e.e. **81**, 95%, 92% e.e. **82**, 92%, 96% e.e. **83**, 99%, 95% e.e.



84, 99%, 94% e.e. **85**, 93%, 95% e.e. **86**, 99%, 96% e.e. **87**, 99%, 92% e.e. **88**, 99%, 90% e.e.

X-ray structure of **83**

The X-ray structure of compound **83** displays sulfur, oxygen, nitrogen, and chloride atoms in blue, pink, purple, and green, respectively, with all other atoms depicted in black. [a]Condition optimization for racemic tertiary alkyl chloride **E53**. Reaction conditions: **E53** (0.050 mmol, 1.0 equiv.), **S9** (1.5 equiv.), CuI (10 mol%), **L*** (15 mol%) and Cs_2CO_3 (3.0 equiv.) in EtOAc (1.0 ml) at r.t. for 24 h under argon. Yield is based on ^{1}H NMR analysis of the crude products using 1,3,5-trimethylbenzene as an internal standard; e.e. is based on chiral HPLC analysis. [b]$Cu(PPh_3)_3CF_3$ (10 mol%) and **L*16** (15 mol%) in Et_2O (1.0 ml) at −10 °C for 3 days; when **S9** was replaced with potassium benzothioate **S1** the same results were obtained. [c]Substrate scope for racemic tertiary alkyl chlorides. Standard reaction conditions: α-aminocarbonyl alkyl chloride (0.10 mmol, 1.0 equiv.), **S9** or potassium thiocarboxylate (1.5 equiv.), $Cu(PPh_3)_3CF_3$ (10 mol%), **L*16** (15 mol%) and Cs_2CO_3 (3.0 equiv.) in Et_2O (2.0 ml) at −10 °C for 3 days under argon. Isolated yields are shown; e.e. is based on chiral HPLC analysis. [d]The reaction was performed on a 2.5 mmol scale.

to give the coupling product with a high e.e. (Supplementary Table 8). Unfortunately, alkyl chlorides with a tertiary amide did not afford the desired coupling products (Supplementary Fig. 8). This result demonstrated that the N–H bond on tertiary alkyl chlorides is crucial for tuning reactivity and chemoselectivity. Further investigation of substrate scope showed that other secondary electrophiles, such as α-bromo amide or ester, worked as well to give the coupling products, albeit with moderate e.e. However, no conversion of unactivated (cyclohexyl, *tert*-butyl) halides was observed due to the inertness of these substrates toward the current copper catalytic system (Supplementary Fig. 8).

Synthetic utility

Considering the frequent use of thiosulfonates and thioesters as versatile intermediates in organic synthesis, we envisioned that this C(sp^3)–S cross-coupling process would provide a general and practical platform for the rapid construction of a wide range of valuable α-chiral alkyl organosulfur compounds. To showcase this potential, chiral thioethers

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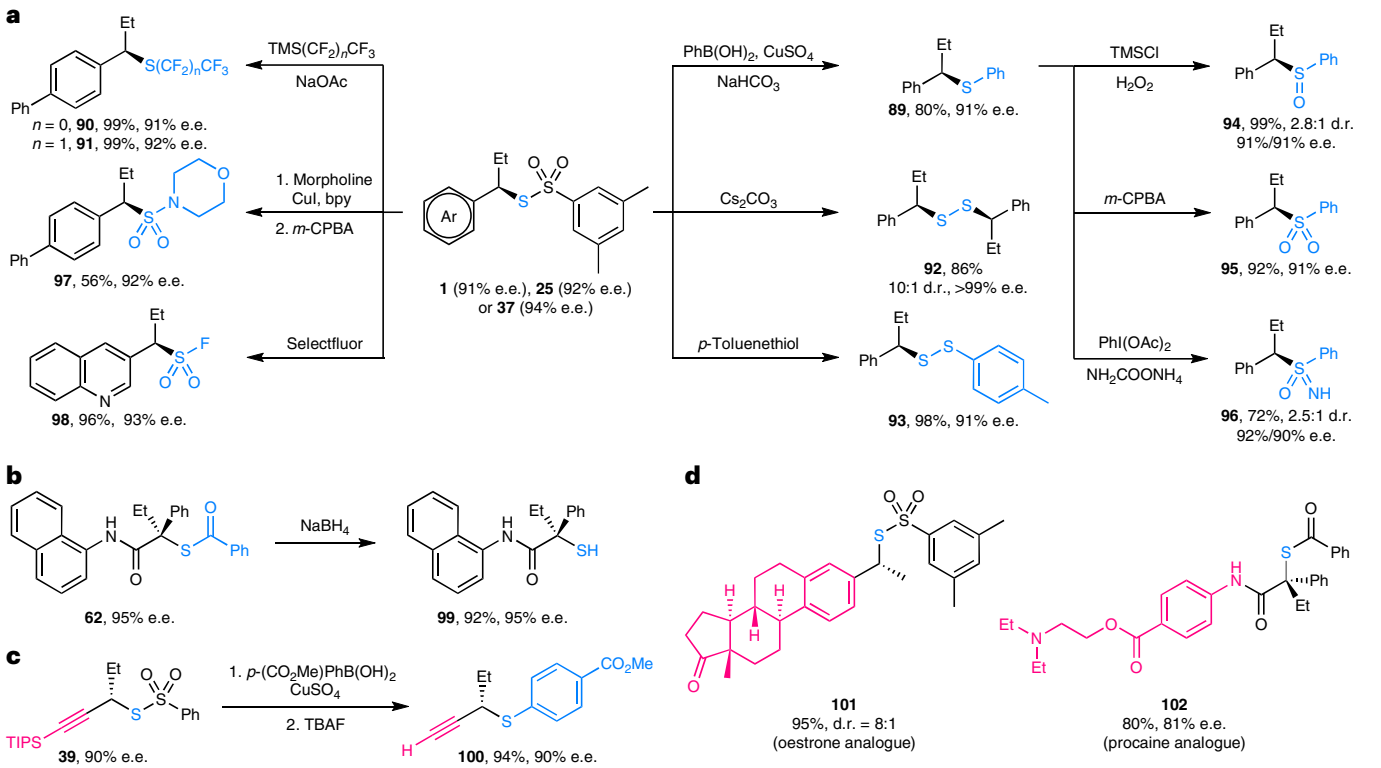

Fig. 2 | Synthetic utility for the construction of valuable α-chiral alkyl organosulfur compounds. a, Further one- or two-step manipulations of the enantioenriched benzyl thiosulfonate **1**, **25** or **37** led to diverse α-chiral alkyl organosulfur compounds, such as thioether, disulfide, sulfoxide, sulfone, sulfoximine, sulfonamide and sulfonyl fluoride. **b**, Reduction of the enantioenriched quaternary thioester **62** delivered free thiol **99**. **c**, Conversion of enantioenriched propargyl thiosulfonate **39** to unprotected propargyl thioether **100** was realized. **d**, The coupling with bioactive-relevant substrates was shown. TMS, trimethylsilyl; *m*-CPBA, 3-chloroperoxybenzoic acid; bpy, 2,2′-bipyridine; TBAF, tetra-*n*-butylammonium fluoride.

such as phenylsulfane **89**, trifluoromethylsulfane **90**, and perfluoroethylsulfane **91**; medicinally relevant disulfides **92** and **93**; and free thiol **99** were easily prepared in one step from the enantioenriched thiosulfonate or thioester products (Fig. 2a,b). Moreover, α-chiral S(IV) or S(VI) compounds including sulfoxide **94**, sulfone **95**, sulfoximine **96**, sulfonamide **97** and sulfonyl fluoride **98** which is applicable to SuFEx (sulfur(VI) fluoride exchange) click chemistry[67], were also readily forged in one or two steps (Fig. 2a). More importantly, chiral propargyl thiosulfonate **39** was converted to thioether **100** bearing a terminal alkynyl group (Fig. 2c), which could be readily transformed to many other functional groups such as alkanes, alkenes, alcohols, diverse carbonyl compounds, heterocycles and so on[57]. Of particular note is that no obvious loss of enantiopurity was observed during all these transformations, thus showcasing the practicality and adaptability of the current methods for conveniently preparing diverse families of useful α-chiral alkyl organosulfur compounds. We also performed the enantioconvergent C–S cross-coupling on the core structures of two bioactive molecules to successfully afford an oestrone analogue (**101**) and procaine analogue (**102**) in high yield with good stereoselectivity (Fig. 2d).

Mechanistic considerations

The reaction of stoichiometric copper 3,5-dimethylbenzenesulfonothioate **103** with racemic **E22** in the presence of a stoichiometric amount of **L*5** provided **25** with comparable efficiency and enantioselectivity (Fig. 3a) to those of the corresponding catalytic reaction (Table 2), whereas no reaction occurred in the absence of **L*5** (Fig. 3a). Moreover, a control experiment without **S5** indicated no conversion of **E22** under the otherwise standard conditions (Fig. 3b). Thus, the ligand-coordinated copper sulfonothioate might serve as the key species for the initiation of the reaction. In addition, no apparent enantioenrichment of the recovered alkyl bromide **E1** and almost constant product e.e. values were observed under typical conditions (Fig. 3c), disfavouring a possible kinetic resolution of **E1**, for example, via an S_N2-type substitution pathway. The subsequent radical trap experiment with 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) revealed substantial reaction inhibition and the TEMPO-trapped products **104** was isolated instead (Fig. 3d; for similar results with 2,6-di-*tert*-butyl-4-methylphenol (BHT), see Supplementary Fig. 9). The involvement of radical intermediates in the reaction was further evidenced by the formation of *5-exo-trig* radical cyclization/C(sp^3)–S coupling product **106** (Fig. 3e). Similar control experiments on racemic propargyl and tertiary alkyl halides (Supplementary Fig. 9) consistently suggested a radical reaction mechanism. All in all, these results lent support to the likely single-electron reduction of the alkyl halides by the ligand-coordinated copper sulfonothioates/thiocarboxylates, generating prochiral alkyl radicals. Furthermore, our preliminary DFT calculations with a model system revealed that the coupling of the prochiral tertiary alkyl radical and LCu^{II}–SR complex also proceeded via a radical homolytic substitution pathway (for details, see Supplementary Figs. 14–17, Supplementary Table 13, and relevant text in the Supplementary Information). Overall, all these experimental and computational results together with previous mechanistic studies[46–49] support our initial proposal, as shown in Fig. 1d.

Summary

We have described a general and robust radical enantioconvergent C(sp^3)–S cross-coupling reaction for a range of racemic secondary and tertiary alkyl halides with highly transformable sulfur nucleophiles under mild reaction conditions. Key to the success is the use of

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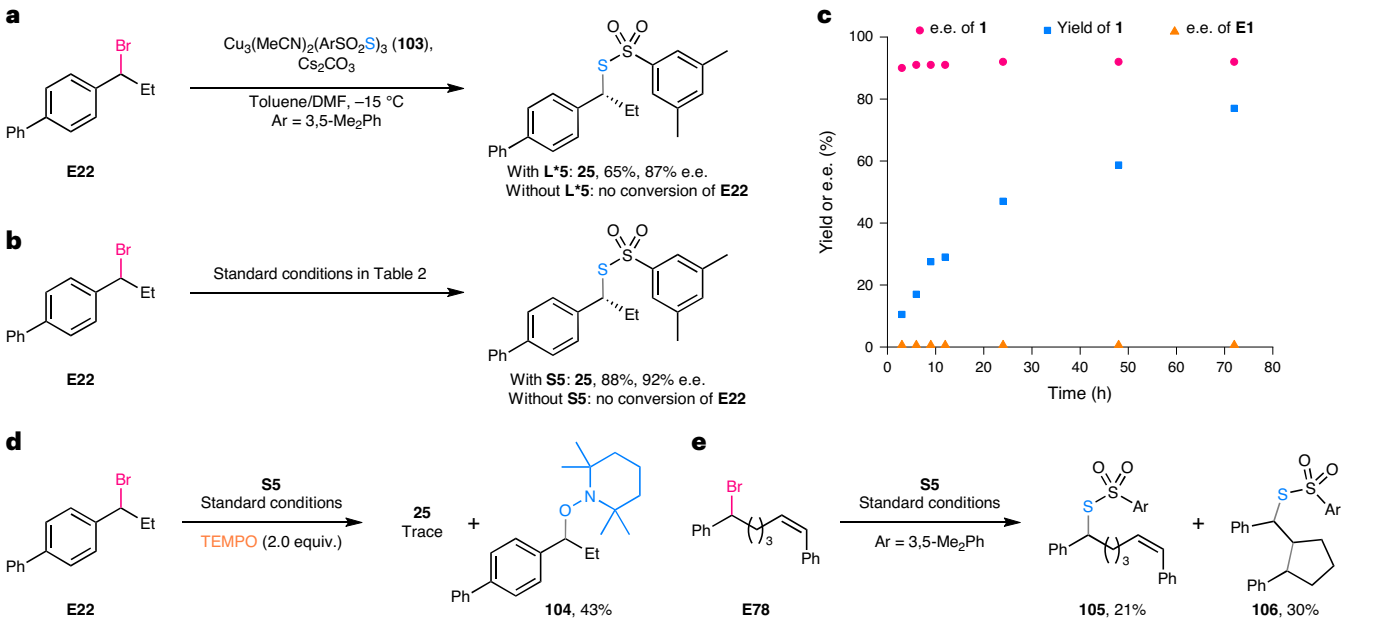

Fig. 3 | Mechanistic discussion. a, The stoichiometric reaction between copper 3,5-dimethylbenzenesulfonothioate **103** and **E22** delivered enantioenriched C(sp^3)–S coupling product **25** in the presence of stoichiometric **L*5** whereas that in the absence of any ligand did not proceed at all. **b**, No conversion of **E22** was observed in the absence of **S5** under the otherwise standard conditions. **c**, The recovered **E1** remained nearly racemic and the enantiopurity of product **1** hardly varied during the reaction. **d**, The addition of TEMPO to the reaction led to substantial reaction inhibition and the TEMPO-trapped product **104** was formed instead. **e**, The radical probe **E78** delivered the radical *5-exo-trig* cyclization/C(sp^3)–S coupling product **106** in addition to the normal C(sp^3)–S coupling product **105**.

Cu(I)/chiral multidentate anionic ligand catalysts to invoke a biomimetic enantioselective radical homolytic substitution-type C(sp^3)–S bond formation manifold, thus avoiding the difficult heterolytic metal–sulfur bond cleavage in two-electron transition-metal-catalysed processes. The reaction furnishes a highly flexible and practical platform for the rapid assembly of a large array of structurally complex and functionally diverse α-chiral alkyl organosulfur compounds with most common substitution types of α-stereocentres present in useful synthetic building blocks, ligands and drugs, thus constituting an excellent complementary strategy to existing methods. This work provides a promising blueprint for developing enantioselective carbon–heteroatom bond formation reactions with strongly coordinating heteroatomic nucleophiles via the biomimetic radical homolytic substitution pathway.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41557-023-01385-w.

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Methods

Synthesis of 1–38

Under an argon atmosphere, an oven-dried resealable Schlenk tube equipped with a magnetic stir bar was charged with sodium arylthiosulfonate (0.24 mmol, 1.2 equiv.), $Cu(MeCN)_4BF_4$ (6.28 mg, 0.020 mmol, 10 mol%), **L*5** (15.6 mg, 0.020 mmol, 10 mol%), Cs_2CO_3 (260 mg, 0.80 mmol, 4.0 equiv.), Then, (hetero)benzyl halide (0.20 mmol, 1.0 equiv.) and toluene/DMF (10/1 v/v, 2.2 ml) were sequentially added to the mixture and the reaction mixture was stirred at −15 or −30 °C. Upon completion (monitored by thin-layer chromatography), the precipitate was filtered off and washed with CH_2Cl_2. The filtrate was evaporated and the residue was purified by column chromatography on silica gel to afford the desired product.

Synthesis of 39–54

Under an argon atmosphere, an oven-dried resealable Schlenk tube equipped with a magnetic stir bar was charged with sodium benzenethiosulfonate **S6** (47.2 mg, 0.24 mmol, 1.2 equiv.), CuI (2.86 mg, 0.015 mmol, 7.5 mol%), **L*12** (8.47 mg, 0.012 mmol, 6.0 mol%), Rb_2CO_3 (92.8 mg, 0.40 mmol, 2.0 equiv.), Then, propargyl halide (0.20 mmol, 1.0 equiv.), H_2O (7.2 µl, 0.40 mmol, 2.0 equiv.) and $CHCl_3$ (2.0 ml) were sequentially added to the mixture and the reaction mixture was stirred at −20 °C. Upon completion (monitored by thin-layer chromatography), the precipitate was filtered off and washed with CH_2Cl_2. The filtrate was evaporated and the residue was purified by column chromatography on silica gel to afford the desired product.

Synthesis of 55–79

Under an argon atmosphere, an oven-dried resealable Schlenk tube equipped with a magnetic stir bar was charged with tertiary alkyl electrophiles (0.10 mmol, 1.0 equiv.), $Cu(PPh_3)_3CF_3$ (9.24 mg, 0.010 mmol, 10 mol%), **L*16** (8.44 mg, 0.015 mmol, 15 mol%) and Cs_2CO_3 (97.6 mg, 0.30 mmol, 3.0 equiv.). Then, thiobenzoic acid **S9** (17.6 µl, 0.15 mmol, 1.5 equiv.) and Et_2O (2.0 ml) were sequentially added to the mixture and the reaction mixture was stirred at −10 °C for 3 days. The precipitate was filtered off and washed with CH_2Cl_2. The filtrate was evaporated and the residue was purified by column chromatography on silica gel to afford the desired product.

Synthesis of 80–88

Under an argon atmosphere, an oven-dried resealable Schlenk tube equipped with a magnetic stir bar was charged with tertiary alkyl electrophiles **E60** (32.4 mg, 0.10 mmol, 1.0 equiv.), $Cu(PPh_3)_3CF_3$ (9.24 mg, 0.010 mmol, 10 mol%), **L*16** (8.44 mg, 0.015 mmol, 15 mol%), Cs_2CO_3 (97.6 mg, 0.30 mmol, 3.0 equiv.). Then, potassium thiocarboxylate (0.15 mmol, 1.5 equiv.) and Et_2O (2.0 ml) were sequentially added to the mixture and the reaction mixture was stirred at −10 °C for 3 days. The precipitate was filtered off and washed with CH_2Cl_2. The filtrate was evaporated and the residue was purified by column chromatography on silica gel to afford the desired product.

Data availability

Data relating to the materials and methods, optimization studies, experimental procedures, mechanistic studies, DFT calculations, HPLC spectra, NMR spectra, and mass spectrometry are available in the Supplementary Information. Crystallographic data for the structures reported in this Article have been deposited at the Cambridge Crystallographic Data Centre, under deposition numbers CCDC 2212974 (**1**), 2213037 (**52**) and 2213038 (**83**). Copies of the data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/.

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Author contributions

Y.T., X.-T.L., J.C. and A.G. designed the experiments and analysed the data. Y.T., X.-T.L., J.C., A.G., N.-Y.Y., Z.L., K.-X.G., W.Z. and H.-T.W. performed the experiments. X.H. designed the DFT calculations. J.-R.L. performed the DFT calculations. Y.T., Z.-L.L., Q.-S.G., and X.-Y.L. wrote the manuscript. X.-Y.L. conceived and supervised the project.

Competing interests

The authors declare no competing interests.

Additional information

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