



Combined radical and ionic approach for the enantioselective synthesis of β -functionalized amines from alcohols

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Chiral amines are among the most important organic compounds and have widespread applications. Enantioselective construction of chiral amines is a major aim in organic synthesis. Among synthetic methods, direct functionalization of omnipresent C–H bonds with common organic nitrogen compounds represents one of the most attractive strategies. However, C–H amination strategies are largely limited to constructing a specific type of *N*-heterocycles or amine derivatives. To maximize the synthetic potential of asymmetric C–H amination, we report here an approach that unites the complementary reactivities of radical and ionic chemistry for streamlined synthesis of functionalized chiral amines. This synthesis merges the development of an enantioselective radical process for 1,5- $C(sp^3)$ -H amination of alkoxysulfonyl azides via Co(II)-based metalloradical catalysis with an enantiospecific ionic process for ring-opening of the resulting five-membered chiral sulfamidates by nucleophiles. Given that alkoxysulfonyl azides are derived from the corresponding alcohols, this approach offers a powerful synthetic tool for enantioselective β -C–H amination of common alcohols while converting the hydroxy group to other functionalities through formal nucleophilic substitution.

Radical chemistry has been increasingly explored for the development of alternative synthetic tools that are complementary to traditional ionic reactions for construction of molecular structures^{1–4}. Despite notable advancements, there remain formidable challenges in the synthetic applications of radical reactions, such as the control of enantioselectivity and reactivity. Among recent developments^{5–9}, metalloradical catalysis (MRC) explores how to utilize metal-centred radical species as open-shell catalysts for catalytically generating metal-stabilized organic radicals and for controlling their subsequent one-electron homolytic reactions^{10–15}. In particular, Co(II) complexes of porphyrins as a family of stable 15e-metalloradicals have been demonstrated as effective catalysts for homolytic activation of organic azides to generate α -Co(III)-aminyl radicals as key intermediates for MRC¹⁶. Supported by proper D_2 -symmetric chiral amidoporphyrins with cavity-like environments, the Co(II)-based catalysts can effectively govern the desired course of MRC towards enantioselective aziridination¹⁷ and $C(sp^3)$ -H amination¹⁸. Given the complementary reactivities of radical and ionic chemistry, we were intrigued by how effective, practical and general a synthetic methodology could become when merging a catalytic radical C–H functionalization process with traditional ionic functional group interconversions. To this end, 1,2-difunctionalization of alcohols into chiral amines was proposed (Fig. 1a). The synthetic pathway begins with a facile nucleophilic azide transfer to common alcohols and entails an envisioned enantioselective radical 1,5-C–H amination of these alcohol-derived organic azides to generate five-membered cyclic sulfamidates. Nucleophilic ring-opening reactions can then produce a wide range of highly enantioenriched β -functionalized chiral amines. While the nucleophilic ring-opening of five-membered cyclic sulfamidates would be expected to be stereospecific^{19,20}, it was unclear if the unprecedented radical 1,5-C–H amination with alkoxysulfonyl azides could proceed efficiently with effective control of enantioselectivity in view

of their unknown reactivity and higher flexibility, which significantly disfavours the efficiency of hydrogen atom abstraction and radical substitution compared with the previously explored sulfamoyl azides¹⁸. In addition to the prerequisite for metalloradical activation of alkoxysulfonyl azides, how successful this methodology will be is exclusively contingent on the identification of a suitable D_2 -symmetric chiral amidoporphyrin as the supporting ligand that will not only facilitate both the 1,5-H-atom abstraction of the corresponding α -Co(III)-aminyl radical intermediate I and subsequent radical substitution of the resulting ϵ -Co(III)-alkyl radical II (Fig. 1b) for a broad type of C–H substrates, but also control the enantioselectivity of the C–N bond formation. If this feat could be achieved, the combination of enantioselective radical 1,5-C–H amination of alkoxysulfonyl azides with stereospecific ring-opening of the resulting optically active cyclic sulfamidates by different nucleophiles would create a streamlined approach for divergent synthesis of chiral amines bearing diverse β -functionalities from simple alcohols (Fig. 1a). Such amines are key structural motifs in many biologically important molecules (Supplementary Fig. 1)^{21–23}.

Metal-catalysed asymmetric 1,5-C–H amination represents an attractive strategy for construction of synthetically valuable five-membered chiral cyclic sulfamidates²⁴. While advancements have been recently made in the development of catalytic systems for 1,6- $C(sp^3)$ -H amination of sulfamate esters^{25–30}, there has been only limited success in synthesizing five-membered *N*-heterocycles through catalytic 1,5- $C(sp^3)$ -H amination³¹. This is perhaps not a surprise given that most of the existing catalytic systems proceed through a concerted C–H insertion pathway involving metallonitrene intermediates, which would inevitably encounter the difficulty associated with the highly strained [3.1.0]-bicyclic transition state for the 1,5-C–H amination process³². Because of the electrophilic nature of metallonitrene intermediates, amination of allylic and propargylic C–H bonds poses an additional issue of chemoselectivity

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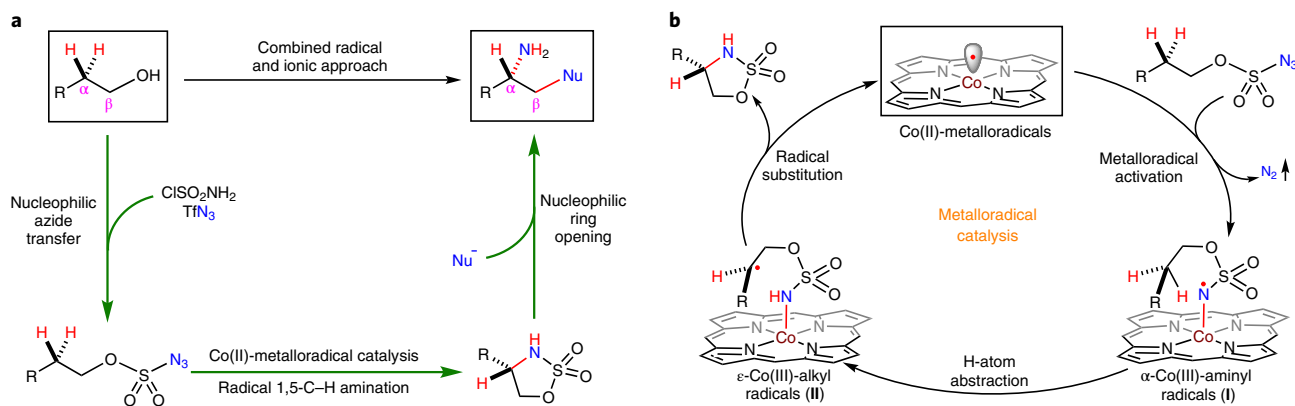


Fig. 1 | Combined radical and ionic approach for enantioselective synthesis of chiral amines from alcohols. **a**, 1,2-Difunctionalization of alcohols for asymmetric synthesis of β -functionalized chiral amines by merging enantioselective radical process for 1,5-C-H amination of alkoxysulfonyl azides with enantiospecific ionic process for ring-opening of the resulting five-membered chiral sulfamidates by nucleophiles. **b**, Proposed mechanism for enantioselective radical 1,5-C-H amination of alkoxysulfonyl azides via Co(II)-based metalloradical catalysis to synthesize optically active cyclic sulfamidates. Tf, trifluoromethanesulfonyl; Nu, nucleophile.

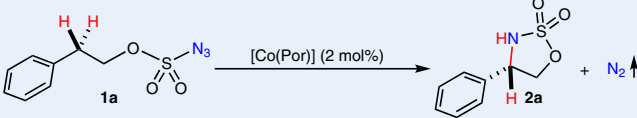
over competitive addition reactions to C=C and C $\equiv$ C bonds^{33,34}. Apart from the reactivity issues, control of enantioselectivity in catalytic 1,5-C-H amination has remained largely unsolved, with only a few examples for benzylic C-H bonds^{25,35}. As an application of Co(II)-MRC for addressing these synthetic challenges, we report here a catalytic radical process for enantioselective 1,5-C(*sp*³)-H amination of alkoxysulfonyl azides that enables stereoselective synthesis of five-membered cyclic sulfamidates. We unveil a remarkable ligand effect on the Co(II)-based catalytic system, leading to the identification of a bridged *D*₂-symmetric chiral amidoporphyrin as the optimal supporting ligand³⁶. The optimized catalytic system is capable of activating various alkoxysulfonyl azides at room temperature for 1,5-amination of different types of C-H bonds, including those at benzylic, allylic, propargylic and even unactivated sites, delivering five-membered chiral sulfamidates in high yields with excellent diastereoselectivities and enantioselectivities. We also present mechanistic studies that shed light on the underlying stepwise radical mechanism for this catalytic system. We then demonstrate the versatility of subsequent ring-opening reactions of the resulting enantioenriched five-membered cyclic sulfamidates by various types of nucleophiles, giving rise to a wide range of chiral amines bearing diverse β -functionalities with retention of the original enantiopurity.

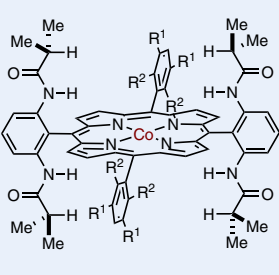
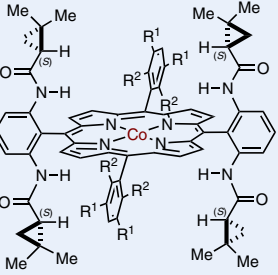
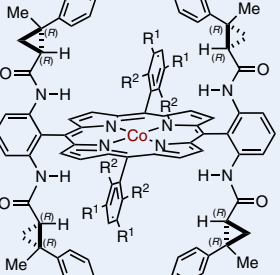
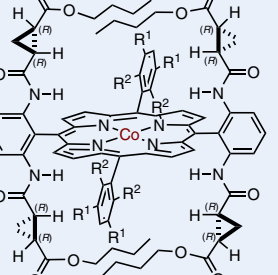
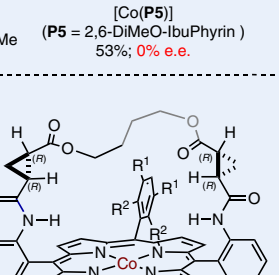
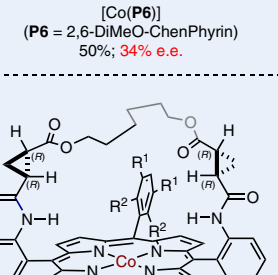
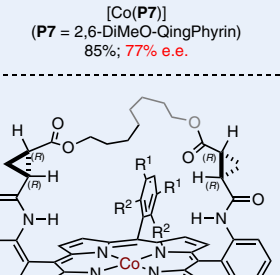
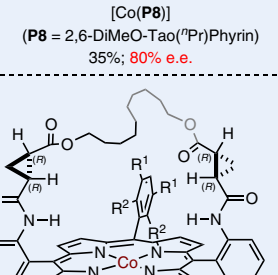
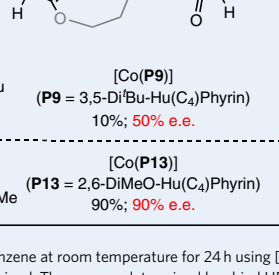
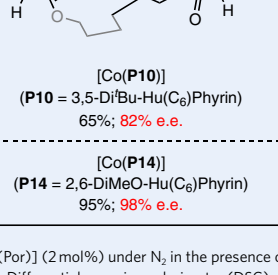
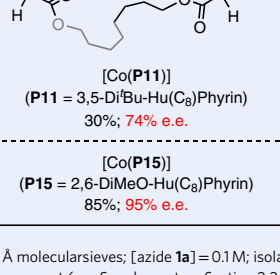
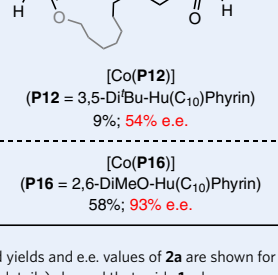
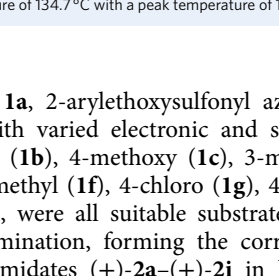
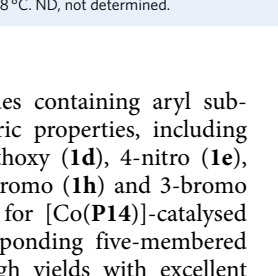
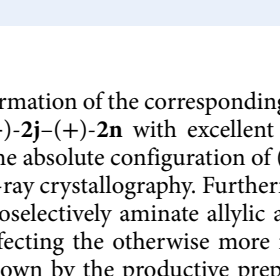
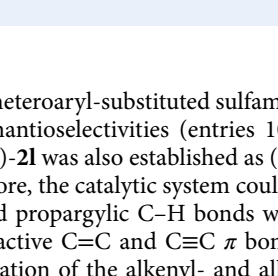
Results and discussion

Reaction optimization. At the outset of this project, 2-phenylethoxysulfonyl azide (**1a**) was selected as the model alkoxysulfonyl azide to explore 1,5-C-H amination via Co(II)-based metalloradical catalysis (Table 1). After some initial evaluation of reaction conditions, we decided to systematically investigate the ligand effect of amidoporphyrins on the Co(II)-catalysed intramolecular C-H amination in benzene at room temperature. It was found that both achiral metalloradical catalyst [Co(**P1**)] (**P1** = 3,5-Di^tBu-IbuPhyrin)³⁷ and first-generation chiral metalloradical catalyst [Co(**P2**)] (**P2** = 3,5-Di^tBu-ChenPhyrin)³⁸ were ineffective for 1,5-C-H amination reaction of azide **1a**, producing only a trace amount of the desired 5-membered chiral cyclic sulfamidate **2a**. When the second-generation metalloradical catalyst [Co(**P3**)] (**P3** = 3,5-Di^tBu-QingPhyrin)³⁹ was employed, a substantial improvement in the yield of product **2a** was observed while inducing a high level of asymmetry. However, switching to another second-generation catalyst [Co(**P4**)] (**P4** = 3,5-Di^tBu-Tao(ⁿBu)Phyrin) resulted in almost no formation of **2a**. These initial results

appeared to indicate the importance of rigidifying the pocket-like environment of the amidoporphyrin ligand. Accordingly, analogous metalloradical catalysts [Co(**P5**)] (**P5** = 2,6-DiMeO-IbuPhyrin), [Co(**P6**)] (**P6** = 2,6-DiMeO-ChenPhyrin), [Co(**P7**)] (**P7** = 2,6-DiMeO-QingPhyrin) and [Co(**P8**)] (**P8** = 2,6-DiMeO-Tao(ⁿPr)Phyrin), where the porphyrins bear the same corresponding amide units but contain 2,6-dimethoxyphenyl instead of 3,5-di-*tert*-butylphenyl groups as 5,15-aryl substituents, were used to catalyse the C-H amination reaction. As expected, significantly improved results were generally observed for catalytic reactions by [Co(**P5**)]–[Co(**P8**)] in comparison with [Co(**P1**)]–[Co(**P4**)]. Notably, changing from [Co(**P4**)] to analogous [Co(**P8**)] led to formation of **2a** in significantly improved yield with a high level of enantioselectivity. This promising result prompted us to explore the direction to further rigidify *D*₂-symmetric chiral amidoporphyrins by employing new-generation catalysts [Co(HuPhyrins)] with cavity-like environments, which are created from [Co(**P4**)] and [Co(**P8**)] by linking across two chiral amide units on both sides of the porphyrin plane with alkyl bridges³⁶. Although C₄-bridged catalyst [Co(**P9**)] (**P9** = 3,5-Di^tBu-Hu(C₄)Phyrin) was inferior to [Co(**P8**)], further improvements in both yield and enantioselectivity were obtained with the use of C₆-bridged catalyst [Co(**P10**)] (**P10** = 3,5-Di^tBu-Hu(C₆)Phyrin). Interestingly, when C₈-bridged catalyst [Co(**P11**)] (**P11** = 3,5-Di^tBu-Hu(C₈)Phyrin) was used, the improvements disappeared. The downward trend in both reactivity and enantioselectivity continued with the use of C₁₀-bridged catalyst [Co(**P12**)] (**P12** = 3,5-Di^tBu-Hu(C₁₀)Phyrin), indicating the pronounced influence of the bridge length. To combine the bridging effect with the influence of 5,15-aryl substituents, analogous bridged catalysts [Co(**P13**)] (**P13** = 2,6-DiMeO-Hu(C₄)Phyrin), [Co(**P14**)] (**P14** = 2,6-DiMeO-Hu(C₆)Phyrin), [Co(**P15**)] (**P15** = 2,6-DiMeO-Hu(C₈)Phyrin) and [Co(**P16**)] (**P16** = 2,6-DiMeO-Hu(C₁₀)Phyrin) were then employed to catalyse the C-H amination reaction. Excitingly, further improvements in both yield and enantioselectivity were observed for the reactions catalysed by [Co(**P13**)]–[Co(**P16**)]. Among them, C₆-bridged [Co(**P14**)] emerged as the optimal catalyst, affording the desired five-membered chiral cyclic sulfamidate **2a** in 95% yield with 98% e.e.

Substrate scope. Under the optimized conditions, metalloradical catalyst [Co(**P14**)] was found to be generally effective in catalysing asymmetric intramolecular amination of different types of C(*sp*³)-H bonds in various alkoxysulfonyl azides (Table 2).

Table 1 | Ligand effect on Co(II)-catalysed enantioselective radical 1,5-C(sp³)-H amination of alkoxysulfonyl azide


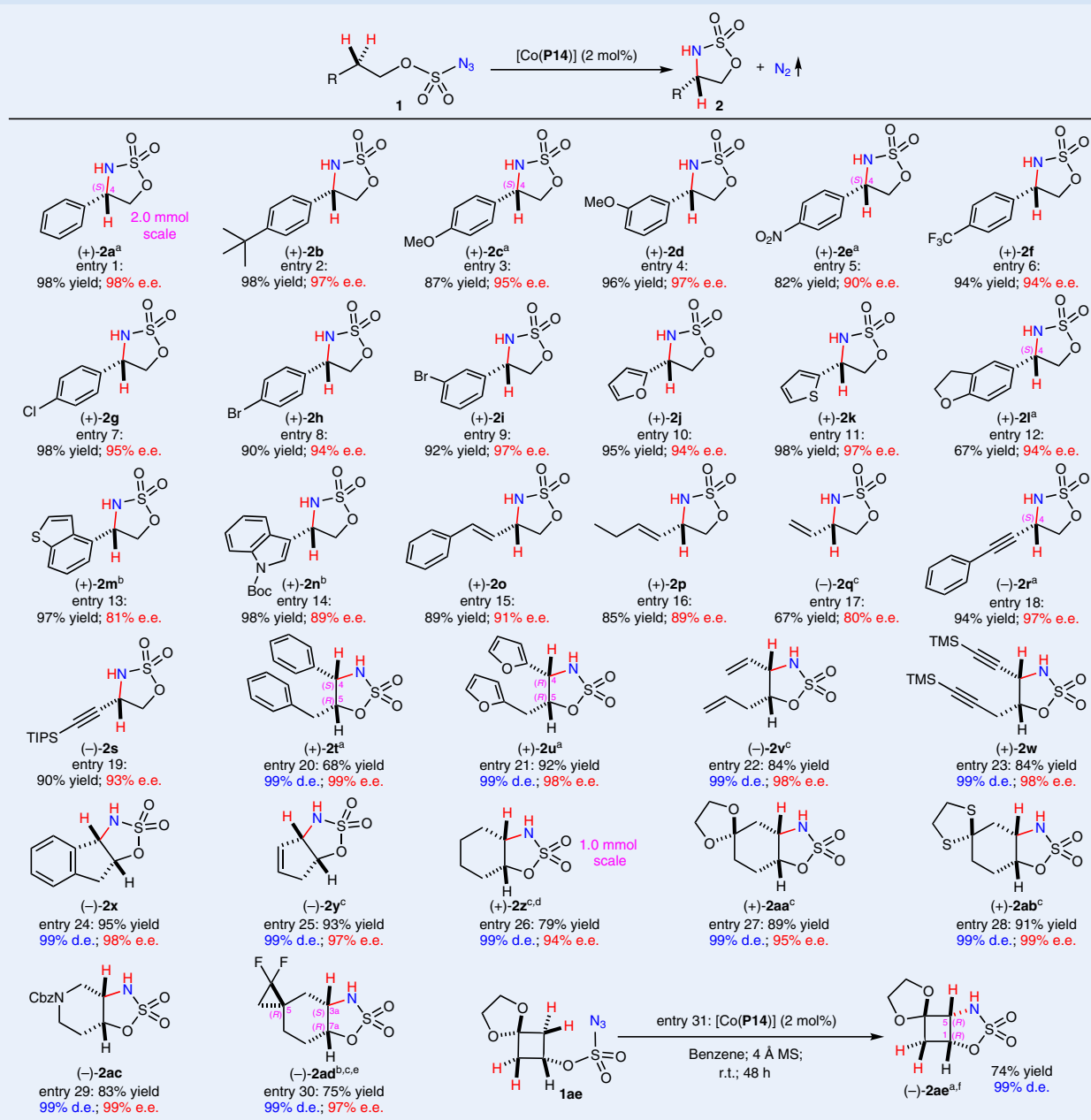
 [Co(P1)] (P1 = 3,5-Di^tBu-10uPhyrin) <5%; 0% e.e.	 [Co(P2)] (P2 = 3,5-Di^tBu-ChenPhyrin) <5%; ND e.e.	 [Co(P3)] (P3 = 3,5-Di^tBu-QingPhyrin) 65%; 83% e.e.	 [Co(P4)] (P4 = 3,5-Di^tBu-Tao(ⁿBu)Phyrin) <5%; ND e.e.
 [Co(P5)] (P5 = 2,6-DiMeO-10uPhyrin) 53%; 0% e.e.	 [Co(P6)] (P6 = 2,6-DiMeO-ChenPhyrin) 50%; 34% e.e.	 [Co(P7)] (P7 = 2,6-DiMeO-QingPhyrin) 85%; 77% e.e.	 [Co(P8)] (P8 = 2,6-DiMeO-Tao(ⁿPr)Phyrin) 35%; 80% e.e.
 [Co(P9)] (P9 = 3,5-Di^tBu-Hu(C₄)Phyrin) 10%; 50% e.e.	 [Co(P10)] (P10 = 3,5-Di^tBu-Hu(C₆)Phyrin) 65%; 82% e.e.	 [Co(P11)] (P11 = 3,5-Di^tBu-Hu(C₈)Phyrin) 30%; 74% e.e.	 [Co(P12)] (P12 = 3,5-Di^tBu-Hu(C₁₀)Phyrin) 9%; 54% e.e.
 [Co(P13)] (P13 = 2,6-DiMeO-Hu(C₄)Phyrin) 90%; 90% e.e.	 [Co(P14)] (P14 = 2,6-DiMeO-Hu(C₆)Phyrin) 95%; 98% e.e.	 [Co(P15)] (P15 = 2,6-DiMeO-Hu(C₈)Phyrin) 85%; 95% e.e.	 [Co(P16)] (P16 = 2,6-DiMeO-Hu(C₁₀)Phyrin) 58%; 93% e.e.

Performed in benzene at room temperature for 24 h using [Co(Por)] (2 mol%) under N₂ in the presence of 4 Å molecular sieves; [azide **1a**] = 0.1 M; isolated yields and e.e. values of **2a** are shown for each of the ligands examined. The e.e. was determined by chiral HPLC. Differential scanning calorimetry (DSC) measurement (see Supplementary Section 2.2 for details) showed that azide **1a** decomposed at an onset temperature of 134.7 °C with a peak temperature of 135.8 °C. ND, not determined.

Like azide **1a**, 2-arylethoxysulfonyl azides containing aryl substituents with varied electronic and steric properties, including 4-*tert*-butyl (**1b**), 4-methoxy (**1c**), 3-methoxy (**1d**), 4-nitro (**1e**), 4-trifluoromethyl (**1f**), 4-chloro (**1g**), 4-bromo (**1h**) and 3-bromo (**1i**) groups, were all suitable substrates for [Co(P14)]-catalysed 1,5-C-H amination, forming the corresponding five-membered cyclic sulfamidates (+)-**2a**–(+)-**2i** in high yields with excellent enantioselectivities (entries 1–9). It is worth mentioning that the catalytic amination process could be readily scaled up under the standard conditions without affecting the high yield and excellent enantioselectivity, as demonstrated by the efficient synthesis of five-membered chiral cyclic sulfamidate (+)-**2a** on a 2.0 mmol scale in 98% yield with 98% e.e. (entry 1). The absolute configurations of (+)-**2a**, (+)-**2c** and (+)-**2e** were all established as (4S) by X-ray crystallography. The Co(II)-based metalloradical system was shown to be compatible with alkoxysulfonyl azides containing heteroaryl groups, such as furan (**1j**), thiophene (**1k**), dihydrobenzofuran (**1l**), benzothiophene (**1m**) and indole (**1n**), leading to high-yielding

formation of the corresponding heteroaryl-substituted sulfamidates (+)-**2j**–(+)-**2n** with excellent enantioselectivities (entries 10–14). The absolute configuration of (+)-**2l** was also established as (4S) by X-ray crystallography. Furthermore, the catalytic system could chemoselectively aminate allylic and propargylic C–H bonds without affecting the otherwise more reactive C=C and C≡C π bonds, as shown by the productive preparation of the alkenyl- and alkynyl-substituted cyclic sulfamidate (–)-**2o**–(–)-**2s** in highly enantioenriched forms (entries 15–19). The absolute configuration of (–)-**2r** was also established as (4S) by X-ray crystallography. In addition to the neutral and non-oxidative conditions, the demonstrated compatibility and chemoselectivity are attributed to the underlying stepwise radical mechanism of the Co(II)-based amination process.

To further broaden the synthetic utility of the asymmetric catalytic system, we then explored the application of the 1,5-C–H amination by [Co(P14)] to a desymmetrization process that would stereoselectively create two contiguous stereogenic centres in one catalytic operation. To this end, 1,3-diphenyl-2-propanol-derived

Table 2 | Enantioselective intramolecular radical 1,5-C(sp³)-H amination of alkoxy sulfonyl azides by [Co(P14)]

Performed in benzene at room temperature for 24 h using [Co(P14)] (2 mol%) under nitrogen in the presence of 4 Å molecular sieves; [azide **1**] = 0.1 M; isolated yields; e.e. determined by chiral HPLC. Diastereomeric excess (d.e.) was determined by ¹H NMR analysis of crude reaction mixture. ^aAbsolute configuration determined by X-ray crystallography. ^b[Co(P14)] (4 mol%). ^cThe e.e. was determined through derivatization. ^dSimilar yield with identical e.e. obtained for reaction run on 0.10 mmol scale. ^eAbsolute configuration determined by X-ray crystallography of the benzylation derivative. ^fNo determination of e.e. due to unavailability of racemic sample.

alkoxy sulfonyl azide **1t** was prepared as a substrate for the catalytic system. To our delight, the two benzylic sites in azide **1t** could be desymmetrized by [Co(P14)] for 1,5-C-H amination, affording 4,5-disubstituted cyclic sulfamidate (+)-**2t** in good yield with almost perfect control of both diastereoselectivity and enantioselectivity (entry 20). The absolute configurations of (+)- were established as (4*S*,5*R*) by X-ray crystallography, confirming the unexpected formation of *cis*-diastereomer. In addition to benzylic C-H bonds, [Co(P14)] could effectively catalyse asymmetric desymmetrization amination of α-heteroaryl C-H bonds and of allylic and propargylic C-H bonds as manifested by the high-yielding formation of (+)-**2u**–(+)-**2w** as *cis*-diastereomers with nearly complete control of the two newly generated contiguous

stereogenic centres from the reactions of azides **1u**–**1w**, with full tolerance of the heteroaryl, alkenyl and alkynyl functionalities (entries 21–23). The absolute configurations of (+)-**2u** were established as (4*R*,5*R*) by X-ray crystallography, again affirming the formation of the less common *cis*-diastereomer. Prompted by these exciting results, we further exploited the use of alkoxy sulfonyl azides derived from cyclic secondary alcohols as potential substrates for Co(II)-catalysed desymmetrization amination, which would lead to asymmetric formation of bicyclic sulfamidates with highly strained fused structures. Accordingly, 2-indanol-based alkoxy sulfonyl azide **1x** was prepared as a substrate for the catalytic asymmetric desymmetrization amination. Remarkably, the two cyclic benzylic sites could be effectively desymmetrized by [Co(P14)] for 1,5-C-H

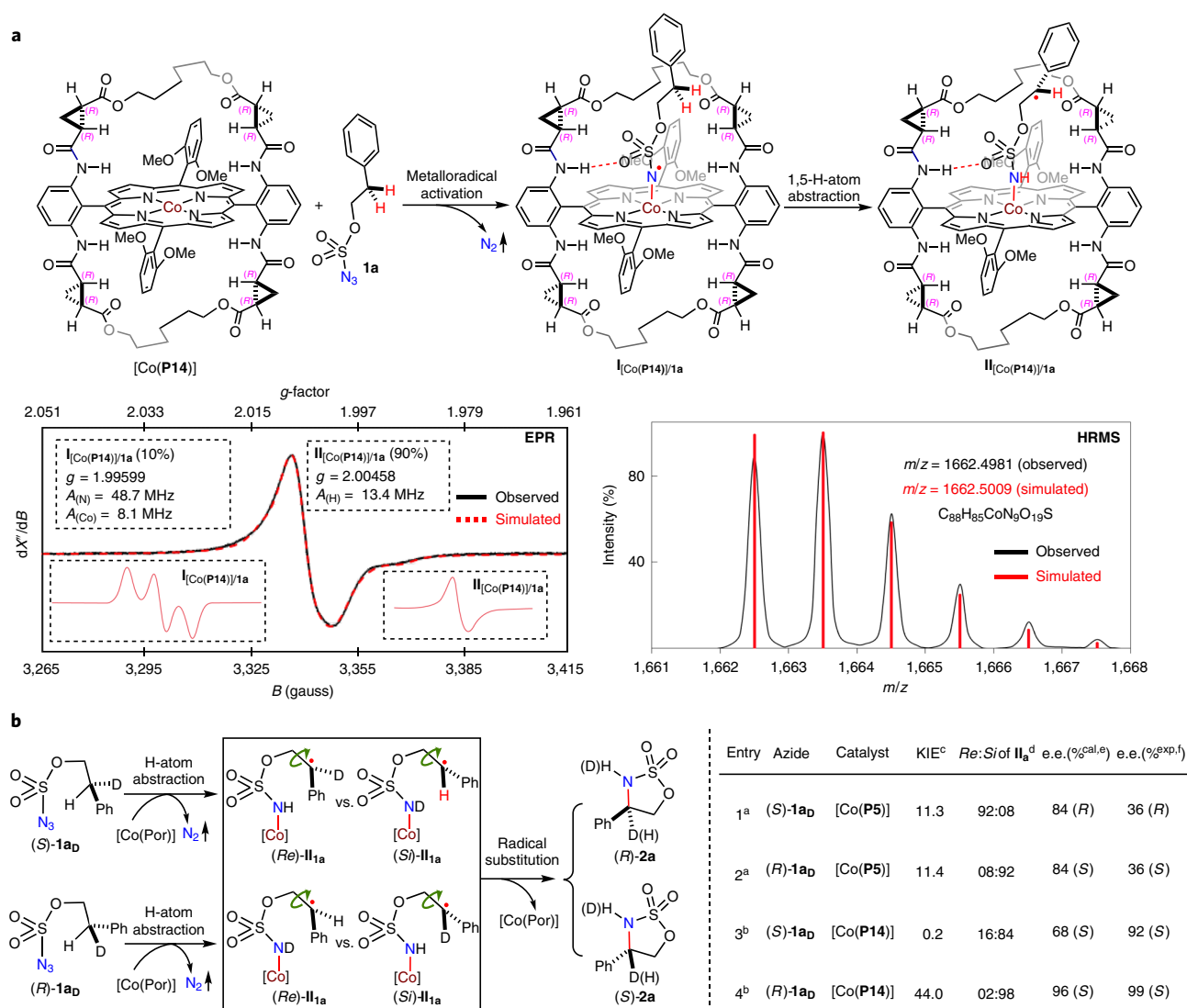


Fig. 2 | Mechanistic studies on Co(II)-catalysed radical 1,5-C-H amination of alkoxysulfonyl azides. a, Detection of α -Co(III)-aminyl radical and e -Co(III)-alkyl radical intermediates by electron paramagnetic resonance (EPR; dX''/dB : the first derivative of the imaginary part of molecular magnetic susceptibility (X'') with respect to the external static magnetic field (B) in arbitrary units) and high-resolution mass spectrometry (HRMS). **b**, Assessment of asymmetric induction mode through KIE studies on 1,5-C-H amination of enantiopure isotopomeric azides.^a Performed in benzene at 40 °C for 24 h using [Co(Por)] (2 mol%) on 0.10 mmol scale under nitrogen in the presence of 4 Å molecular sieves; [azide **1a_D**] = 0.1 M; see Supplementary Table 1 for yields. ^b Carried out at room temperature for 24 h. ^c Ratios of H:D determined by ¹H NMR spectroscopy, suggesting highly preferential abstraction of pro-S over pro-R hydrogen atoms with [Co(P14)]. ^d Calculated ratios of the initially established two prochiral faces (*Re*)-II_a to (*Si*)-II_a based on the ratio of H:D. ^e Calculated enantiomeric excesses of **2a** on the basis of stereoretentive radical substitution. ^f Observed enantiomeric excesses of **2a** determined by chiral HPLC analysis, which offered no separation of (*R*)-**2a_H** from (*R*)-**2a_D** and (*S*)-**2a_H** from (*S*)-**2a_D**, indicating significant racemization of the initial facial chirality via α -C-C bond rotation before the step of radical substitution with [Co(P5)] while further enantioenrichment of the initial facial chirality during the step of C-N bond formation with [Co(P14)].

amination, constructing *cis*-fused tricyclic sulfamidate (–)-**2x** in excellent yield with close to complete control of stereoselectivities for the two newly generated contiguous stereogenic centres (entry 24). Similarly, the C–H bonds at the two allylic sites in alkoxysulfonyl azide **1y** derived from 3-cyclopentenol could chemoselectively undergo asymmetric desymmetrization amination, affording *cis*-bicyclic sulfamidate (–)-**2y** in high yield with excellent stereoselectivities (entry 25). Such desymmetrization protocol could be even applied to asymmetric amination of unactivated C–H bonds in saturated cyclic substrates (bond dissociation energy, ~ 100 kcal mol^{–1})⁴⁰ as demonstrated by the productive transformation of cyclohexanol-based alkoxysulfonyl azide **1z** to *cis*-fused bicyclic sulfamidate (+)-**2z** with excellent asymmetric control on either small (0.1 mmol)

or large (1.0 mmol) scale (entry 26). Furthermore, ketal and thio-ketal functionalities in related cyclohexanol-based alkoxysulfonyl azides **1aa** and **1ab** were well tolerated in the Co(II)-catalysed asymmetric desymmetrization amination, generating the corresponding *cis*-fused spirotricyclic sulfamidate (+)-**2aa** and (+)-**2ab** in excellent yields with excellent control of stereoselectivities (entries 27 and 28). Moreover, alkoxysulfonyl azides based on heterocyclic alcohols were shown to be suitable substrates as exemplified by the asymmetric desymmetrization of 1-Cbz-4-piperidinol-derived alkoxysulfonyl azide **1ac** for 1,5-C–H amination to generate cyclic sulfamidate-fused piperidine (–)-**2ac** in high yield as *cis*-isomer with perfect control of stereoselectivities (entry 29). Building on these remarkable results, we carried on further exploration of the

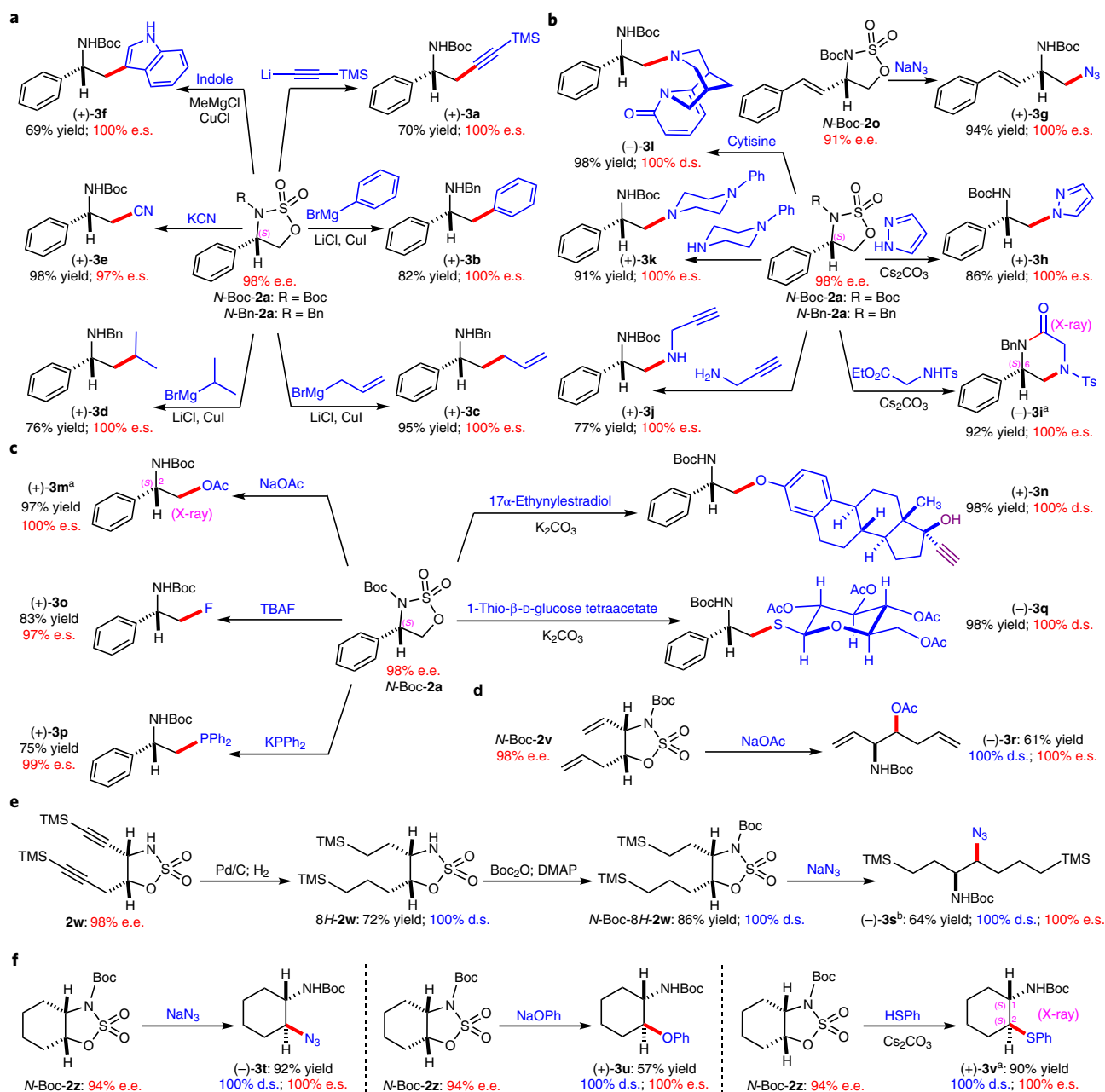


Fig. 3 | Regioselective ring-opening of enantioenriched sulfamidates for stereospecific synthesis of β -functionalized chiral amines. **a**, Ring-opening by carbon nucleophiles. **b**, Ring-opening by nitrogen nucleophiles. **c**, Ring-opening by oxygen, fluorine, phosphine and sulfur nucleophiles. **d**, Ring-opening of 4,5-disubstituted cyclic sulfamidates. **e**, Synthesis of 1,2-diamine derivatives with two similar vicinal stereocentres via ring-opening of 4,5-disubstituted cyclic sulfamidates. **f**, Ring-opening of fused bicyclic sulfamidates. Isolated yields; e.e. determined by chiral HPLC; d.e. determined by ^1H NMR analysis of crude reaction mixture; enantiospecificity (e.s.) calculated as ((% e.e. of product)/(% e.e. of starting material)) $\times$ 100; diastereoselectivity (d.s.) calculated as ((% d.e. of product)/(% d.e. of starting material)) $\times$ 100. ^aAbsolute configuration determined by X-ray crystallography. ^be.e. determined by ^1H NMR analysis of the samples with chiral shift reagent. TBAF, tetrabutylammonium fluoride; Boc, *tert*-butoxycarbonyl; Bn, benzyl; Ts, tosyl; DMAP, 4-dimethylaminopyridine; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; TMS, trimethylsilyl.

potentiality of catalyst [Co(P14)] for concurrent construction of three stereogenic centres from achiral substrates through asymmetric desymmetrization amination. Hence, alkoxysulfonyl azide **1ad** prepared from the difluorocyclopropane/cyclohexane spirobicyclic alcohol was tested as the substrate for this purpose. Excitingly, the two unactivated 2° C–H sites on the cyclohexane ring of azide **1ad** could be effectively desymmetrized by smooth 1,5-C–H amination, leading to productive formation of *cis*-fused spirotricyclic sulfamidate (–)-**2ad** with simultaneous creation of three stereogenic

centres, of which both the diastereoselectivity and enantioselectivity could be excellently controlled. The absolute configurations of (–)-**2ad** were established as (3*a*S,5*R*,7*a*R) by X-ray crystallography from its *N*-benzyl derivative (+)-*N*-Bn-**2ad** (entry 30). As another direction of our further exploration, we decided to scrutinize the catalytic system for potential construction of fused bicyclic five-membered sulfamidates with even higher ring strain. Consequently, alkoxysulfonyl azide **1ae** derived from ketal-containing cyclobutanol was prepared as the substrate for the asymmetric

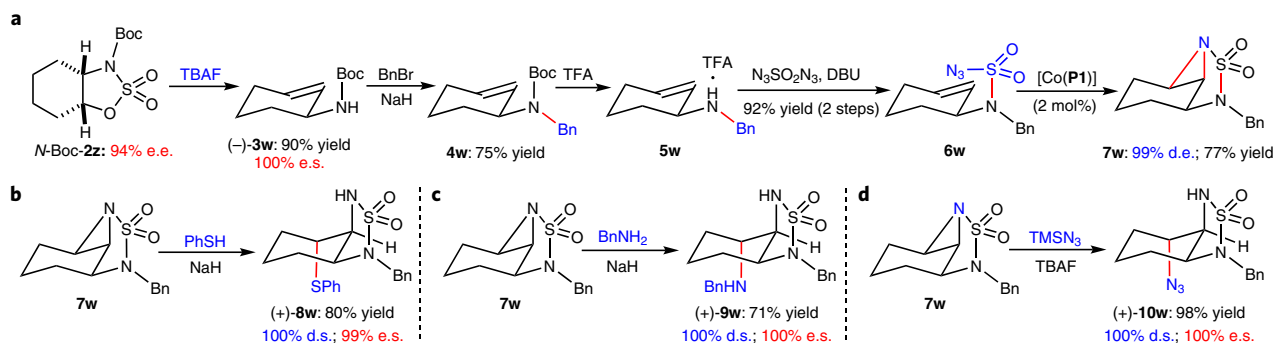


Fig. 4 | Synthesis of 1,2,3-trifunctionalized cyclohexane derivatives via ring-opening of cyclohexane-fused sulfamidates. a, Synthesis of sulfamide-fused tricyclic heterocycle **7w** through site-selective elimination of **2z** and intramolecular aziridination of **6w**. **b**, Regioselective ring-opening of **7w** by benzenethiol. **c**, Regioselective ring-opening of **7w** by benzylamine. **d**, Regioselective ring-opening of **7w** by TMSN₃. Isolated yields; e.e. determined by chiral HPLC; d.e. determined by ¹H NMR analysis of crude reaction mixture. TFA, trifluoroacetic acid.

desymmetrization amination system. To our delight, it was found that catalyst [Co(P14)] could even enable asymmetric 1,5-amination of the secondary C–H bonds on the four-membered cyclobutane ring (bond dissociation energy, >100 kcal mol⁻¹)⁴⁰ of azide **1ae** with effective desymmetrization of the two reaction sites, giving rise to highly-strained [3.2.0]-bicyclic sulfamidate (–)-**2ae** without affecting the dioxolane/cyclobutane spirobicyclic functional unit (entry 31). The absolute configurations of (–)-**2ae** were established as (1*R*,5*R*) by X-ray crystallography. It should be mentioned that the first- and second-generation non-bridged catalysts [Co(P1)]–[Co(P8)] were completely ineffective for the amination reaction of azide **1ae**, demonstrating the remarkable effect of ligand engineering by distal bridging (see Supplementary Fig. 3 for additional examples)³⁶.

Mechanistic investigation. Several mechanistic experiments were performed to shed light on the proposed stepwise radical pathway of the Co(II)-catalysed 1,5-C(sp³)–H amination of alkoxy-sulfonyl azides. To observe the radical intermediates, isotropic electron paramagnetic resonance (EPR) spectroscopy was carried out at room temperature for the reaction mixture of azide **1a** by [Co(P14)] in benzene (Fig. 2a). The obtained EPR spectrum displays diagnostic signals at a *g* value of ~2.00 that are indicative of organic radicals (Fig. 2a). Among other possibilities, the observed broad signals could be simulated as a mixture of α-Co(III)-aminyl radical and ε-Co(III)-alkyl radical on the basis of hyperfine couplings by ⁵⁹Co (*I*=7/2), ¹⁴N (*I*=1) and ¹H (*I*=1/2): 10% of N-centred radical at α-position **I**_{[Co(P14)]/1a} (*g*=1.99599; *A*_(Co)=8.1 MHz; *A*_(N)=48.7 MHz; *A*_(H)=0 MHz) and 90% of C-centred radical at ε-position **II**_{[Co(P14)]/1a} (*g*=2.00458; *A*_(Co)=0 MHz; *A*_(N)=0 MHz; *A*_(H)=13.4 MHz). Although it is not unique, this simulation is consistent with the proposed stepwise radical mechanism involving the key step of 1,5-H-atom abstraction. Furthermore, these intermediates could be detected by high-resolution mass spectrometry (HRMS) with ESI ionization (Fig. 2a). The obtained spectrum evidently exhibited a signal corresponding to [**I**_{[Co(P14)]/1a}]⁺ and/or [**II**_{[Co(P14)]/1a}]⁺ (*m/z*=1,662.4981), which resulted from the corresponding neutral radicals by the loss of one electron. Both the exact mass and the isotope distribution pattern measured experimentally match well with those calculated from the formula of [(P14)Co(C₈H₉NO₃S)]⁺ (*m/z*=1,662.5009) (see Supplementary Fig. 5 for details). To gain insight on the origin of asymmetric induction in the process, isotopomeric alkoxy-sulfonyl azides (S)-**1a_D** and (R)-**1a_D** were prepared in optically pure forms as substrates for Co(II)-catalysed asymmetric radical 1,5-C–H amination to study the kinetic isotope effect (KIE) (Fig. 2b). With the use of achiral catalyst [Co(P5)] (**P5**=2,6-DiMeO-IbuPhyrin), the intramolecular KIEs for reactions of isotopomers

(S)-**1a_D** and (R)-**1a_D** were determined to have nearly identical values of 11.3 and 11.4, respectively (Fig. 2b, entries 1 and 2). These high values of primary KIEs are in accordance with the proposed step of C–H bond cleavage through 1,5-H-atom abstraction by the initially formed α-Co(III)-aminyl radical **I** (Fig. 1b). If a chiral catalyst is employed, it is anticipated to result in deviation from the intrinsic KIE (higher in the chirality-matched case while lower in the chirality-mismatched case) if the step of H-atom abstraction is enantioselective. Experimentally, it was found that the use of chiral catalyst [Co(P14)] raised the KIE to 44.0 for (R)-**1a_D** (Fig. 2b, entry 4) while lowering it to 0.2 for (S)-**1a_D** (Fig. 2b, entry 3), suggesting highly preferential abstraction of pro-*S* over pro-*R* hydrogen atom by [Co(P14)]. The measured KIE values could be translated to the ratios of the initially established two prochiral faces (*Re*)-**II_{1a}** to (*Si*)-**II_{1a}** (*Re*:*Si* of **II_{1a}**). If no racemization of the facial chirality occurs in the subsequent step of radical substitution, the *Re*:*Si* of **II_{1a}** ratios could then be used to calculate the predicted enantiomeric excesses (e.e.%^{cal}) of the amination product **2a**. The fact that the observed enantiomeric excesses (e.e.%^{exp}) were much lower than the predicted values for the reactions by achiral catalyst [Co(P5)] indicated significant racemization of the initial facial chirality via α-C–C bond rotation before the radical substitution step (Fig. 2b, entries 1 and 2). When chiral catalyst [Co(P14)] was used, however, it was found that e.e.%^{exp} was significantly higher than e.e.%^{cal} for reactions of both (S)-**1a_D** (Fig. 2b, entry 3: 92% versus 68%) and (R)-**1a_D** (Fig. 2b, entry 4: 99% versus 96%). These results revealed that the steps of both H-atom abstraction and radical substitution cooperatively controlled the enantioselectivity of the Co(II)-catalysed 1,5-C–H amination. Moreover, the results in Table 1 seem to suggest that the catalysts with the higher yields generally exhibit the better enantioselectivities. To study the relative kinetics among the catalysts, we performed NMR studies on the 1,5-C–H amination reaction of azide **1a** under standard conditions by the optimized catalyst [Co(P14)] in comparison with the less-effective catalyst [Co(P9)] as they differ dramatically in both yield (95% versus 10% yield) and enantioselectivity (98% versus 50% e.e.). The observed rate constants (*k*_{obs}) for the catalytic reaction by [Co(P14)] and [Co(P9)] were determined to be 7.5 × 10⁻² h⁻¹ and 4.5 × 10⁻³ h⁻¹, respectively, showing that the reaction by [Co(P14)] proceeded approximately 16 times faster than that by [Co(P9)] (see Supplementary Fig. 6 for details). Collectively, these results indicate that the catalysts with the higher yields and better enantioselectivities also catalysed the reactions at faster rates.

Synthetic transformations. Given that five-membered cyclic sulfamidates have a high propensity to be ring-opened by nucleophiles with site-selectivity at the carbon next to the oxygen¹⁹, this

newly developed enantioselective radical process for 1,5- $C(sp^3)$ -H amination of alkoxy sulfonyl azides could be potentially merged with the ionic ring-opening process for asymmetric synthesis of β -functionalized chiral amines^{20,41}. To this end, we systematically investigated the ring-opening reactions of the resulting enantioenriched five-membered cyclic sulfamidates **2** with various classes of nucleophiles (Fig. 3). Different carbon nucleophiles were employed to evaluate the opening of five-membered ring structures for stereospecific synthesis of chiral amine derivatives (Fig. 3a). As demonstrated with the highly enantioenriched *N*-Boc-sulfamidate *N*-Boc-**2a** (98% e.e.) and *N*-Bn-sulfamidate *N*-Bn-**2a** (98% e.e.) as the model substrates, a series of sp -, sp^2 - and sp^3 -hybridized carbon nucleophiles could effectively open the cyclic structures, leading to stereospecific production of β -functionalized chiral amines (+)-**3a**–(+)-**3d** in high yields with full retention of the original enantiopurities. Potassium cyanide could similarly act as a carbon nucleophile for stereospecific ring-opening reaction of *N*-Boc-**2a** to form β -amino nitrile (+)-**3e** in excellent yield. In addition to being readily converted to Boc-L- β -phenylalanine through hydrolysis⁴², (–)-**3e** was utilized as a key intermediate for the synthesis of (+)-(S)-dihydroperiphylline⁴³. It was further shown that indole could function as carbon nucleophile at the C3 position (rather than as nitrogen nucleophile) to open the cyclic sulfamidate *N*-Boc-**2a** stereospecifically in the presence of MeMgCl and CuCl (ref. 44), generating β -phenyl chiral tryptamine (+)-**3f** in good yield without affecting the original high enantiopurity. Besides carbon nucleophiles, nitrogen nucleophiles were examined for the ring-opening process to synthesize vicinal 1,2-diamine derivatives (Fig. 3b)⁴⁵. With sodium azide and pyrazole as nucleophiles, β -azido- α -chiral amine (+)-**3g** and β -pyrazole α -chiral amine (+)-**3h** were formed in excellent yields with preservation of the original stereochemistry. Under similar conditions, the amide moiety in ethyl tosylglycinate could open the ring structure of *N*-Bn-**2a** smoothly to generate the corresponding diamine product, which could in situ undergo effective lactamization upon heating to afford the piperazinone derivative (–)-**3i**, an important class of recurring moieties in drug research and development⁴⁶. The absolute configuration of (–)-**3i** was established as (6S) by X-ray crystallography, confirming the retention of the original stereochemistry in **2a**. Additionally, primary and secondary amines, and the sterically hindered natural product cytosine, could all act as effective nucleophiles for productive formation of 1,2-diamines (+)-**3j**, (+)-**3k**, and the interesting cytosine-derived⁴⁷ diamine (–)-**3l** in excellent yields without affecting the original enantiopurity. Other heteroatom-based nucleophiles could also be employed for this stereospecific opening process (Fig. 3c). For instance, even sodium acetate served as an effective oxygen nucleophile to react with *N*-Boc-**2a**, providing enantioenriched β -amino alcohol derivative (+)-**3m** in excellent yield. The absolute configuration of (+)-**3m** was established as (2S) by X-ray crystallography. When 17 α -ethynylestradiol, a derivative of the natural product estradiol that contains three potential nucleophilic sites (phenol, tertiary alcohol and terminal alkyne), was reacted with *N*-Boc-**2a** under basic conditions, it afforded (+)-**3n** as the sole product in excellent yield. Furthermore, even fluoride could function as a competent nucleophile, generating β -fluoro- α -chiral amine (+)-**3o** in high yield with excellent stereospecificity⁴⁸. Similarly, the use of phosphine nucleophiles such as potassium diphenylphosphanide allowed the synthesis of (+)-**3p**, which may function as chiral N,P-chelating ligand to support metal-based asymmetric catalysis. 1-Thio- β -D-glucose as its tetraacetate form was shown to be a highly effective sulfur nucleophile in reacting with *N*-Boc-**2a** to form sugar-derived β -amino thiol (–)-**3q** in excellent yield.

We next evaluated the ring-opening reactions that occur directly at the existing chiral carbon centre next to the oxygen atom by using 4,5-disubstituted cyclic sulfamidates such as **2t**–**2ad** generated

through the Co(II)-catalysed desymmetrization amination. It was shown that 4,5-disubstituted cyclic sulfamidate *N*-Boc-**2v** could be site-selectively ring-opened at the C5-stereogenic centre with sodium acetate as a nucleophile, generating the *syn*-vicinal amino alcohol derivative (–)-**3r** in good yield with full retention of the original enantiopurity (Fig. 3d). It is noteworthy that the vicinal stereocentres in the highly enantioenriched (–)-**3r** contain terminal vinyl and allyl functionalities, respectively, a stereochemical pattern that is attractive for synthesis yet difficult to achieve. The olefin moieties in (–)-**3r** may be selectively oxidized towards the synthesis of polyols and can be converted into *threo*- β -hydroxy-D-glutamic acid⁴⁹. As another synthetic application of 4,5-disubstituted cyclic sulfamidates, both C $\equiv$ C triple bonds in 4-alkynyl-5-propargyl cyclic sulfamidate (+)-**2w** were fully reduced to form 4,5-dialkyl cyclic sulfamidate 8*H*-**2w**, followed by Boc protection to give *N*-Boc-8*H*-**2w**, and then underwent site-selective ring-opening by sodium azide, leading to stereospecific formation of the synthetically valuable β -azido α -chiral amine (–)-**3s** in good yield with preservation of the original diastereopurity and enantiopurity (Fig. 3e). The structural motif in (–)-**3s** is notable as the two vicinal stereocentres bear similar linear alkyl chains that differ only by one methylene unit. This distinctive pattern of structures would be highly challenging to construct through either aminohydroxylation⁵⁰ or diamination⁵¹ of the corresponding linear alkenes. Considering the synthetic utilities of 1,2-disubstituted carbocycles bearing two contiguous stereogenic centres, ring-opening of *cis*-fused bicyclic sulfamidate *N*-Boc-**2z** was explored with representative nucleophiles, such as sodium azide, sodium phenoxide and benzenethiol, in the presence of Cs₂CO₃. *Trans*- β -substituted- α -chiral cyclohexylamine derivatives (–)-**3t**, (+)-**3u** and (+)-**3v** were produced as single diastereomers in high yields with complete retention of the original optical activity (Fig. 3f). Among these 1,2-disubstituted carbocycles, β -azido-cyclohexylamine (–)-**3t**, which was previously prepared in nine steps, served as a key intermediate for the synthesis of unique peptidomimetic foldamers⁵². The absolute configurations of β -phenylthiocyclohexylamine (+)-**3v** were established as (1*S*,2*S*) by X-ray crystallography, indicating inversion of the original stereochemistry at the reacting carbon centre in (+)-**2z**.

In addition to the nucleophilic ring-opening reactions, these cyclic sulfamidates can also undergo site-selective elimination²⁰ to generate the valuable chiral allyl amines as demonstrated for the high-yielding formation of the optically active 2-cyclohexenylamine (–)-**3w** from the cyclohexane-fused sulfamidate *N*-Boc-**2z** (Fig. 4). To further demonstrate synthetic utilities, cyclohexane-fused sulfamidate *N*-Boc-**2z** was shown to serve as a useful intermediate for the stereoselective construction of 1,2,3-trisubstituted carbocycles bearing three contiguous stereogenic centres. After exchanging the protective group from *N*-Boc to *N*-Bn through benzoylation of (–)-**3w** and Boc deprotection of bis-protected intermediate **4w**, the resulting secondary amine **5w** was further transformed to the sulfamoyl azide **6w** in high yield. Under the catalysis of achiral metalloradical [Co(P1)], **6w** underwent intramolecular aziridination through diastereoselective radical bicyclization⁵³, affording the sulfamide-fused tricyclic heterocycle **7w** in 77% yield. In view of the high strain in the tricyclic structure, the aziridine unit in **7w** could be selectively opened at the *exo*-position by various nucleophiles as demonstrated with the regioselective ring-opening reactions with benzenethiol in the presence of NaH, benzylamine and TMSN₃ in the presence of TBAF, producing 1,2,3-trifunctionalized cyclohexanes (+)-**8w**, (+)-**9w** and (+)-**10w**, respectively, in good to excellent yields with full retention of the original optical purity. The sulfamide-fused cyclohexanes such as (+)-**8w**, (+)-**9w** and (+)-**10w** which bear three contiguous stereogenic centres may serve as valuable intermediates for target synthesis relevant to pharmaceutical research and development (Supplementary Fig. 1e)⁵⁴.

Conclusions

We have demonstrated a general approach for stereoselective synthesis of chiral amines bearing various β -functionalities from readily available alcohols through the union of complementary radical and ionic chemistry. This streamlined synthesis of chiral amines, which is realized through a formal 1,2-difunctionalization of alcohols, consists of enantioselective 1,5-C–H radical amination of alkoxysulfonyl azides and stereospecific ring-opening of the resulting five-membered cyclic sulfamidates by nucleophiles. In addition to demonstrating the site-selectivity, stereospecificity and nucleophile diversity of the ionic ring-opening process, we have developed an efficient catalytic radical process for enantioselective 1,5-C(sp^3)-H amination of alkoxysulfonyl azides via Co(II)-based MRC. The key to the successful development of the Co(II)-based C–H amination system is the unveiling of the remarkable ligand effect that leads to the identification of 2,6-DiMeO-Hu(C₆)Pyrin as the optimal supporting ligand. The optimized catalytic system enables the effective activation of various alkoxysulfonyl azides for 1,5-amination of different types of C(sp^3)-H bonds at room temperature, affording five-membered chiral sulfamidates in high yields with excellent diastereoselectivities and enantioselectivities. We have presented mechanistic studies that shed light on the understanding of the underlying stepwise radical mechanism and asymmetric induction of the Co(II)-based metalloradical system. In addition to the efficient preparation of highly enantioenriched chiral amines bearing diverse β -functionalities, this combined radical and ionic approach allows for stereoselective construction of both linear and cyclic molecular structures bearing multiple contiguous stereocentres that would be difficult or impossible to construct through existing methods. Considering the ubiquity of chiral amines as structural motifs in biologically important molecules, this streamlined synthetic technology will find wide applications.

Methods

Diazotransfer reagents reported in the literature. Trifluoromethanesulfonyl azide (TfN₃)⁵⁵ and fluorosulfonyl azide (FSO₂N₃)⁵⁶ have previously been developed as diazotransfer reagents. In comparison with TfN₃, FSO₂N₃ is safer to use and easier to handle. If the situation permits, FSO₂N₃ is recommended as a preferred reagent for diazotransfer reactions.

Notes on safety. Some azides can be explosive and should be handled carefully. When common sense is employed, the azides can be prepared, stored and used without risk in the standard organic chemistry laboratory⁵⁶. Although no issues were encountered for alkoxysulfonyl azides throughout our research for this project, face shields, leather gloves and protective leather clothing are highly recommended. The concentration of solvents via rotary evaporation during the synthesis of alkoxysulfonyl azides was done at 0 °C behind a blast shield.

General procedure for synthesis of alkoxysulfonyl azides. At 0 °C, formic acid (2.0 equiv.) was added dropwise to a solution of chlorosulfonyl isocyanate (2.0 equiv.) in dichloromethane (DCM) (2.5 M). The reaction mixture was then slowly warmed up to room temperature and stirred overnight. To this freshly prepared sulfamoyl chloride, a solution of starting alcohol (1.0 equiv.) and triethylamine (2.2 equiv.) in DCM (2.5 M) was slowly added at 0 °C. The reaction was stirred at room temperature for another hour. Upon complete consumption of the starting alcohol as monitored by thin-layer chromatography, the reaction was quenched with H₂O. The aqueous layer was then extracted with DCM (20 ml $\times$ 3) and the organic layers were combined, dried and concentrated. The residue was purified by flash chromatography on silica gel (eluent, DCM:EtOAc = 15:1) to give the desired sulfamate ester, which was used directly for the next step.

Diazotransfer reaction using method A. To a round-bottom flask was added the above-synthesized sulfamate ester (1.0 equiv.) in DCM solution (0.25 M) and DBU (1.5 equiv.). The reaction mixture was cooled to –78 °C. A solution of freshly made TfN₃ in hexanes (0.5 M; 1.5 equiv.) was then added slowly and the reaction was monitored by thin-layer chromatography to completion (typically in 5 min). The reaction mixture was then directly loaded into the silica gel column and purified by flash column chromatography. The fractions containing product were collected and concentrated at 0 °C to afford the desired alkoxysulfonyl azides, which were stored immediately in a –20 °C freezer. See Supplementary Section 2.0 on how to handle excess TfN₃ waste.

Diazotransfer reaction using method B. To a round-bottom flask was added sequentially the above-synthesized sulfamate ester (1.0 equiv.) and FSO₂N₃ in methyl *tert*-butyl ether (0.2 M; 1.0 equiv.), diluted with an equal volume of DMF and then followed by the addition of aqueous KHCO₃ solution (3.0 M; 4.0 equiv.). The reaction mixture was stirred for 1 h at room temperature. After completion, EtOAc (40 ml) was added and the mixture was washed sequentially with brine (60 ml $\times$ 6), water (60 ml $\times$ 2) and brine (60 ml). After drying over Na₂SO₄, the organic layer was concentrated by rotary evaporation. The residue was then loaded into the silica gel column and purified by flash column chromatography. The fractions containing product were collected and concentrated at 0 °C to afford the desired alkoxysulfonyl azides, which were stored immediately in a –20 °C freezer.

General procedure for intramolecular C–H amination. An oven-dried Schlenk tube that was precharged with Co(II)-metalloradical catalyst (0.002 mmol) and 4 Å molecular sieves (20 mg) was evacuated and backfilled with nitrogen gas. After replacing the Teflon screw cap of the Schlenk tube with a rubber septum, 0.5 ml of anhydrous benzene was added before the addition of alkoxysulfonyl azide (0.1 mmol), followed by adding the remaining solvent (a total of 1.0 ml). The Schlenk tube was then purged with nitrogen for 2 min before the Teflon screw cap was placed back to replace the rubber septum. The reaction mixture was then stirred at the desired temperature for the required time. Following completion of the reaction, the reaction mixture was purified via flash chromatography on silica gel. The fractions containing product were collected and concentrated by rotary evaporation to afford the purified compound.

Data availability

Crystallographic data for the structures reported in this article have been deposited at the Cambridge Crystallographic Data Centre, under deposition numbers CCDC 2097080 (2l), 2097081 (2t), 2097082 (2ae), 2097083 (2e), 2097084 (2a), 2097085 (3m), 2097086 (3v), 2097087 (3i), 2097088 (N-Bn-2ad), 2097089 (2u), 2097090 (2r) and 2097091 (2c). Copies of the data can be obtained free of charge via <https://www.ccdc.cam.ac.uk/structures/>. All other data that support the findings of this study, which include experimental procedures and compound characterization, are available within the paper and its Supplementary Information.

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Author contributions

K.L. and Y.H. conducted the experiments. Y.H. initiated the project. K.L. completed the project. W.C.C.L. assisted the project. X.P.Z. conceived the work and directed the project. K.L., Y.H. and X.P.Z. designed the experiments. K.L. and X.P.Z. wrote the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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