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Catalytic synthesis of chiral sulfinimidate esters via oxidative esterification of sulfenamides

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Aza-sulfur compounds, such as sulfilimines, sulfoximines, etc, are increasingly recognized as essential contributors to advancements in drug development and asymmetric synthesis. Among them, the catalytic enantioselective synthesis of sulfinimidate esters remains an uncharted and formidable challenge. Herein, we unveil an efficient enantioselective oxidative esterification of sulfenamides via chiral sulfinimidoyl iodide intermediates. Using stereogenic-at-Co(III) complexes as catalysts, this approach enables the synthesis of an extensive array of enantioenriched sulfinimidate esters (>70 examples, up to 98.5:1.5 er), offering a versatile platform for the preparation of structurally diverse aza-sulfur compounds.

Optically active S(IV) compounds have emerged as highly promising candidates, owing to their distinctive physicochemical and pharmacokinetic properties[1–7]. Furthermore, sulfur atoms' Lewis basicity and chirality enable S(IV) compounds to play a pivotal role in asymmetric synthesis as novel chiral ligands, organocatalysts, and auxiliaries (Fig. 1a)[8–14]. Therefore, the catalytic synthesis of chiral S(IV) compounds has attracted significant interest and has become a long-standing goal for organic chemists over the past decades[15–19]. Owing to the stability of S=O bonds, numerous efforts were made to facilitate the catalytic synthesis of chiral sulfinyl compounds (Fig. 1b). For instance, catalytic synthesizing chiral sulfoxides were well studied since Kagan, et al., completed the first asymmetric oxidation of sulfides[20–24]. The significant advances in asymmetric catalysis have led to the development of several sulfoxides, including Esomeprazole and Armodafinil, as marketed drugs[1–7]. To access chiral sulfinate esters, catalytic nucleophilic substitutions of sulfoxide electrophiles (RS(O)LG) have been recognized as a feasible approach pioneered by Ellman, Toru, and others[25–31]. However, while replacing the oxygen atom with nitrogen is essential for effectively modulating physicochemical properties and introducing molecular diversity[4,5], the catalytic approach to the asymmetric synthesis of sulfinimidoyl compounds featuring S=N bonds, such as sulfilimines, remains underexplored[19,32–39]. Notably, the efficient catalytic asymmetric synthesis of chiral sulfinimidate esters is still unknown[40–42] (During our manuscript revision, Wu and coworkers present a novel catalytic sulfinamide activation protocol to access chiral sulfinimidate esters[43]). Moreover, the sulfimidation of S(II) species could be unsuitable for synthesizing sulfinimidate esters due to the inherent instability of the S(II)–O substrates[44–46]. The obtainment of chiral sulfinimidate esters mainly depended on the enantiospecific *O*-isopropylation of chiral sulfinamides, which seriously limited the variety and the bioactivity exploration of chiral sulfinimidate esters (Fig. 1c)[47]. Considering their great potential to access enantioenriched aza-sulfur compounds and in chiral medicine discovery, developing a catalytic asymmetric procedure for preparing chiral sulfinimidate esters is highly desired and urgently desired.

To address this challenging objective, halonium-promoted enantioselective oxidative esterification of sulfenamides could be a promising protocol[41,48–50]. However, the highly reactive sulfinimidoyl halide intermediates mean that the stereocontrol remains greatly challenging, as background reactions are almost inevitable. Moreover, the sulfinimidate esters could also undergo a Swern-type reaction during the reaction process, resulting in the oxidation of alcohols[51]. Recently, we unveiled the asymmetric oxidation of sulfenamides[52–54] enabled by anionic stereogenic-at-cobalt(III) complexes[55–61], leading to various enantioenriched sulfinamides in excellent yields[62]. DFT studies revealed that the

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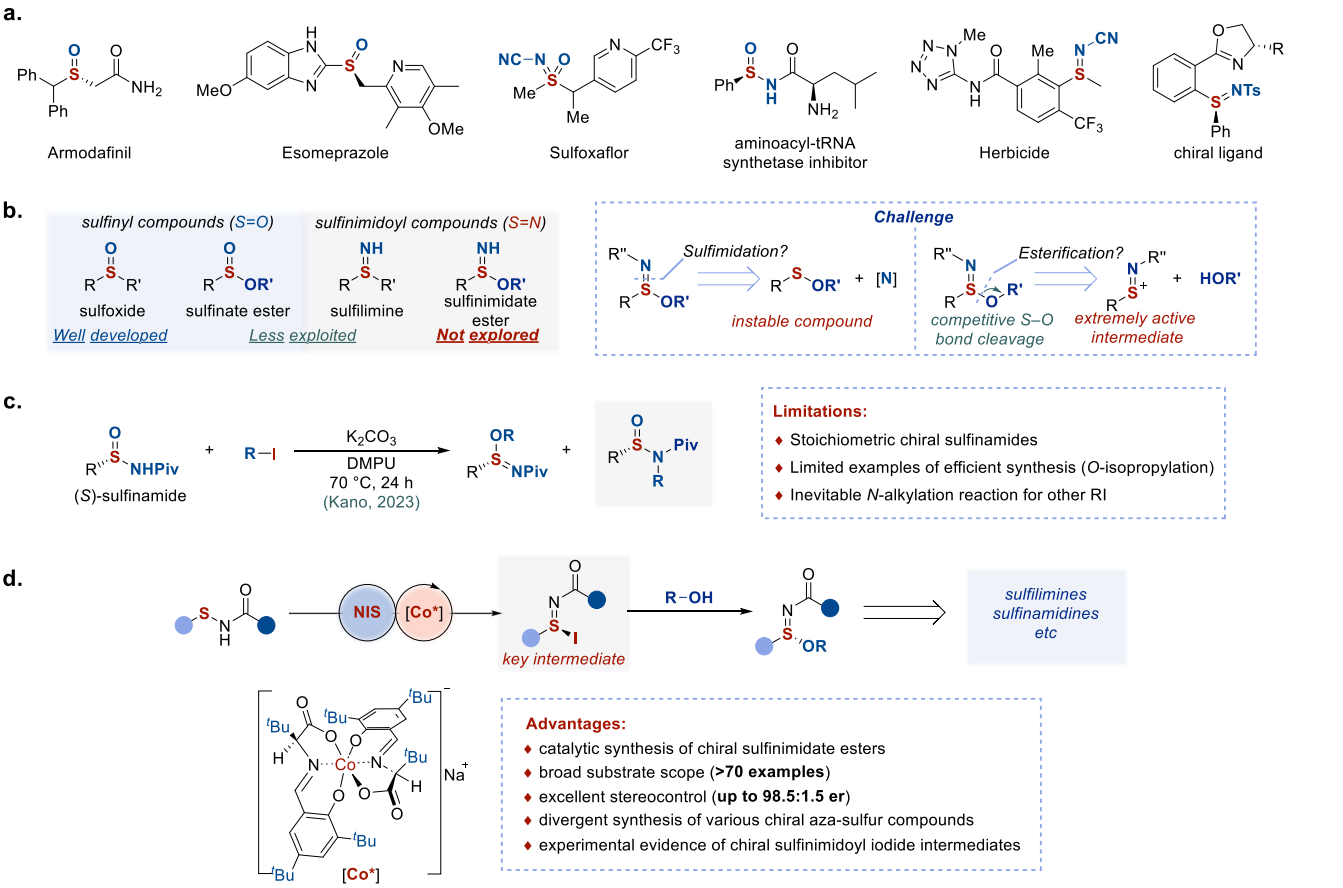

Fig. 1 | Importance of Aza-sulfur compounds and synthetic approaches to chiral sulfinimidate esters. a Importance of stereogenic-at-sulfur compounds. **b** Representative example of S(IV) species and challenge to access chiral sulfinimidate esters. **c** Enantiospecific transformation to access chiral sulfinimidate esters. **d** Catalytic enantioselective synthesis of sulfinimidate esters (This work).

iodination of sulfenamides was the enantio-determining step, delivering chiral sulfinimidoyl iodides, which subsequently underwent an enantiospecific S_N2 substitution with water to release products.

Encouraged by these findings and the inherent difficulty of synthesizing chiral sulfinimidate esters catalytically, in this work, we disclose a catalytic synthesis of sulfinimidate esters via I^+-promoted oxidative esterification of sulfenamides catalyzed by anionic stereogenic-at-cobalt(III) complexes (Fig. 1d). Various sulfenamides and alcohols are successfully incorporated into our reaction system, resulting in a broad of sulfinimidate esters with excellent enantioselectivities (>70 examples, up to 98.5:1.5 er). The synthetic application of chiral sulfinimidate esters is demonstrated by their versatile reactivity, allowing the preparation of various chiral aza-sulfur compounds under mild conditions.

Results

Investigation of reaction conditions

Our investigation commenced with the oxidative esterification reaction involving sulfenamide **2a** and isobutanol (**3a**) by using sodium salt of anionic stereogenic-at-cobalt(III) complex Λ-(*S*, *S*)-**1a** (10 mol%) as the catalyst and THF as solvent. To our satisfaction, sulfenamide **2a** was fully converted within 30 min at room temperature, affording chiral sulfinimidate ester **4a** in 66% yield with 83.5:16.5 er (Table 1, entry 1, for details, see Table S1–S6 in SI). Employing acetone as the solvent enhanced the enantioselectivity of **4a** to 86:14 er, whereas DCM or hexane provided poor stereocontrol (entries 2–4). Subsequently, we screened various X^+ reagents. Notably, only a trace amount of **4a** was produced when using NCS as the oxidant and no desired products could be detected with NBS (entries 5, 6). Substituting NIS with either I(0) or I(III)[41] species also led to unsatisfactory results (entries 7, 8). Interestingly, introducing 5 Å molecular sieves (MS) in the reaction system reduced the enantioselectivity of **4a** (entry 9 vs. entry 4), but both the yield and enantioselectivity of **4a** were significantly improved by adding 5 Å MS when THF was used as the solvent (entry 10). The addition of water (5 μL) led to an increase in enantioselectivity (92:8 er), however, this was accompanied by a decrease in yield (50%) due to the formation of sulfenamides (entry 11). Next, we evaluated a series of anionic stereogenic-at-cobalt(III) complexes Λ-(*S*, *S*)-**1b**–**1g**. As exhibited in entries 12–17, the employment of the bulky catalyst Λ-(*S*, *S*)-**1d** furnished product **4a** in 90% yield with 90:10 er (entry 14). The enantioselectivity of **4a** was significantly increased at lower reaction temperatures (entries 18–20). The optimal result (94% yield, 96.5:3.5 er) was obtained when the reaction was carried out at −40 °C for 36 h (entry 19), and catalyst **1d** performed less efficiently than **1a** at lower temperatures (entry 20 vs. entry 19), albeit higher enantioselectivity was offered with **1d** at room temperature. At last, we tested several classic chiral Brønsted acid and thiourea catalysts under the optimized condition, providing poor yields or enantioselectivities (for details, see Table S7 in SI).

Substrate scopes

With the optimized reaction condition in hand, we first explored the scope of alcohols suitable for the catalytic synthesis of chiral sulfinimidate esters (Fig. 2). A wide range of linear alcohols, including methanol and ethanol, were excellent nucleophiles, delivering chiral sulfinimidate esters **4b**–**4f** with up to 97.5:2.5 er. Branched alcohols were also well tolerated in our reaction system with products **4g**–**4h** exhibiting high-level enantioselectivities. The oxidative esterification reaction of sulfenamide **2a** with various alicyclic alcohols worked

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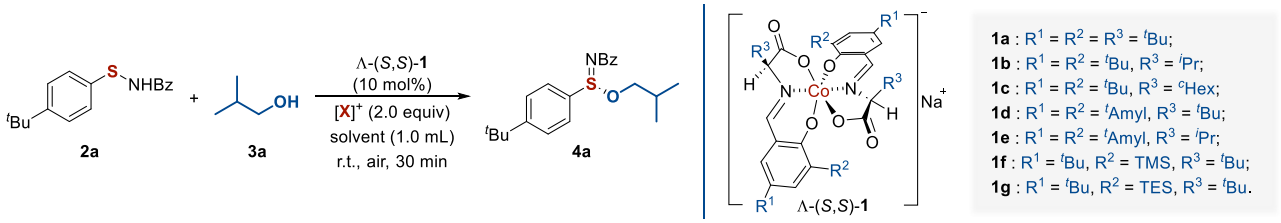
Table 1 | Optimization of Oxidative Esterification Reaction Conditions[a]



Entry	$[X]^+$	1	solvent	yield (%)	er
1	NIS	**1a**	THF	66	83.5:16.5
2	NIS	**1a**	DCM	73	52.5:47.5
3	NIS	**1a**	hexane	42	66:34
4	NIS	**1a**	acetone	60	86:14
5	NCS	**1a**	acetone	11	60.5:39.5
6	NBS	**1a**	acetone	0	N.D.
7	I_2	**1a**	acetone	0	N.D.
8	$PhI(OAc)_2$	**1a**	acetone	27	50:50
9[b]	NIS	**1a**	acetone	69	81.5:18.5
10[b]	NIS	**1a**	THF	77	89.5:10.5
11[b,c]	NIS	**1a**	THF	50	92:8
12[b]	NIS	**1b**	THF	83	81:19
13[b]	NIS	**1c**	THF	63	53:47
14[b]	NIS	**1d**	THF	90	90:10
15[b]	NIS	**1e**	THF	92	87.5:12.5
16[b]	NIS	**1f**	THF	90	86.5:13.5
17[b]	NIS	**1g**	THF	93	84:16
18[b,d]	NIS	**1a**	THF	96	94:6
19[b,e]	NIS	**1a**	THF	94	96.5:3.5
20[b,e]	NIS	**1d**	THF	88	92.5:7.5

[a]Unless otherwise noted, the reaction was performed with sulfenamide **2a** (0.10 mmol), **3a** (0.20 mmol. 2.0 equiv), catalyst **1** (0.01 mmol, 10 mol%), X^+ reagent (0.2 mmol, 2.0 equiv), and solvent (1.0 mL) at r.t. for 30 min. Isolated yields are reported, and er values were determined by chiral stationary HPLC. [b]5 Å MS (100 mg) was added. [c]Water (5 μL) was added. [d]Reaction was performed at −20 °C for 12 h. [e]Reaction was performed at −40 °C for 36 h. N.D.: not determined.

smoothly (**4i**–**4m**), yielding corresponding products with up to 96:4 er. Subsequently, several phenyl-containing alcohols were subjected to asymmetric esterification reactions, delivering sulfinimidate esters **4n**–**4q** with excellent enantioselectivities. Moreover, the introduction of substituents on the aromatic ring had little to no impact on either the yield or stereoselectivity (**4r**–**4y**). Encouragingly, the method proved compatible with alkyl alcohols bearing functional groups, such as CF_3 (**4z**), F (**4aa**), Cl (**4ab**), and alkynyl groups (**4ac**–**4ae**), further demonstrating the versatility and broad substrate compatibility of this protocol. The oxidative esterification between sulfenamide **2a** and dihydrocholesterols afforded chiral sulfinimidate ester **4af** in 92% yield with >95:5 dr. However, using sugar derivatives, as nucleophiles could not provide desired chiral sulfinimidate esters.

Next, we investigated the scope of sulfenamides (Fig. 3). Electron-withdrawing aryl groups, such as halogen atoms, CF_3, CN, NO_2, and CO_2Me, on the sulfur of sulfenamides were compatible with the oxidative esterification reactions, delivering desired sulfinimidate esters with good to excellent enantioselectivities (**4ag**–**4am**, up to 97.5:2.5 er). Sulfenamides containing electron-rich aryls could be regarded as competent substrates, leading to 81–97% yields with slightly decreased enantioselectivities (**4an**–**4aq**). This decrease may be attributed to their stronger electron-donating properties, which enhance reducibility and accelerate the reaction rate, thereby compromising stereoselectivity. The oxidative esterification reactions proceeded smoothly with sulfenamides bearing meta-substituents, giving chiral products with satisfactory outcomes (**4ar**–**4av**). The enantioselectivities could be also influenced by the electronic properties of the substituents. The challenging sterically hindered *ortho*-substitution was also tolerated, affording the corresponding sulfinimidate ester with moderate enantiocontrol (**4aw**). Our catalysis was well accommodated with sulfenamides bearing a multi-substituted aryl group or heteroaryl group, as evidenced by the obtainments of enantioenriched sulfinimidate esters **4ax** and **4ay** in good yields. In general, most *S*-aryl sulfenamides exhibited lower enantioselectivities compared to **2a**, implying a possible steric interaction between the *tert*-butyl groups and the chiral catalysts, despite their spatial distance from the reaction site. Subjecting various *S*-alkyl sulfenamides to our reaction system gave chiral products in good yields with up to 90.5:9.5 er (**4az**–**4bc**). Subsequently, the *N*-acyl substitution of sulfenamides was examined. To our delight, the influence of *para*-substituted groups, including various functional groups (CF_3, CN, NO_2, CO_2Me, and COPh) on stereocontrol was minimal, furnishing the corresponding sulfinimidate esters with excellent enantioselectivities (**4bd**–**4bm**, ranging from 95:5 er to 98:2 er). Outstanding stereocontrol was also achieved when the sulfenamides bearing *meta*-substituted aryl groups were subjected to the catalytic reactions (**4bn**–**4bq**). Importantly, the sulfenamides containing a multi-substituted aryl group, 2-naphthyl group, or heteroaryl groups, were competent substrates, affording enantioenriched sulfinimidate esters efficiently (**4br**–**4bu**). This methodology also worked well for the sulfenamides, assembled from alkyl amides (**4bw**–**4bz**), affording excellent stereocontrol in all cases. The oxidative esterification worked smoothly with the urea-derived sulfenamides, providing chiral product **4ca** in good yield with moderate enantioselectivity.

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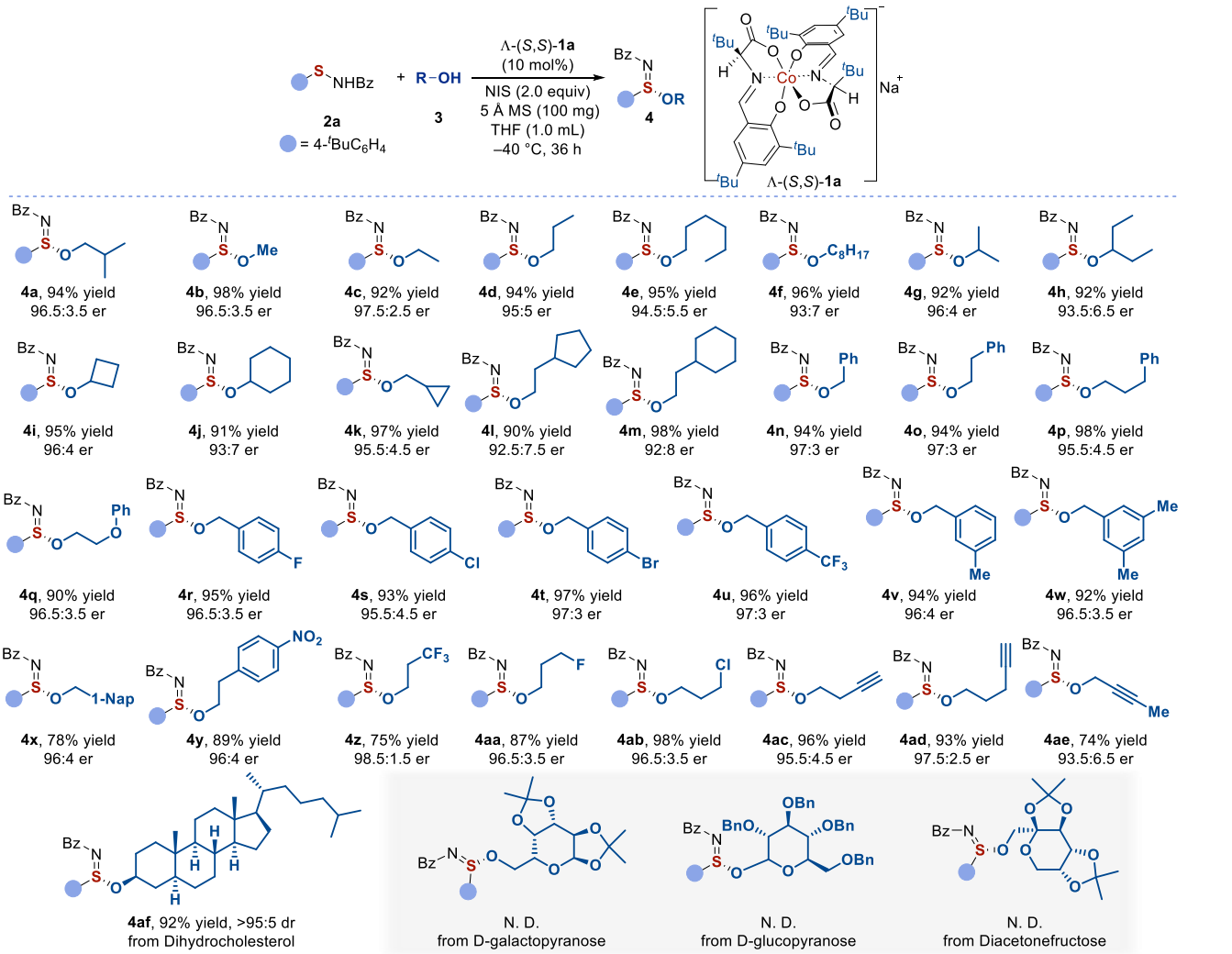

Fig. 2 | Substrate Scope of Alcohols. Unless otherwise noted, the reaction was performed with sulfenamide **2a** (0.10 mmol), **3** (0.20 mmol. 2.0 equiv), Λ-(*S, S*)–**1a** (0.01 mmol, 10 mol%), NIS (0.2 mmol, 2.0 equiv), and THF (1.0 mL) at −40 °C for 36 h. Isolated yields are reported, and er values were determined by chiral stationary HPLC. N. D. not detected.

Synthetic applications and mechanistic studies

To showcase the synthetic potential of this oxidative esterification reaction, a gram-scale reaction was conducted, yielding enantioenriched sulfinimidate ester **4a** without erosion of enantioselectivity (for details, see Section 5.1 in SI). To our delight, the chiral sulfinimidate ester could be a wonderful molecular platform for accessing structurally diverse chiral aza-sulfur compounds (Fig. 4a). For instance, the treatment of chiral sulfinimidate ester **4a** (96:4 er) with PhMgBr, EtMgBr, and ^{i}PrMgBr individually resulted in the enantiospecific formation of chiral sulfilimines (**5a**–**5c**) within 5 min under mild conditions (room temperature, air atmosphere)[47,63]. Treating **4a** with in-situ generated pyridin-3-ylmagnesium bromide enabled the access of *S*-heteroaryl sulfilimine **5d** with 95.5:4.5 er[64]. The amide-ester exchange reaction also proceeded smoothly with the secondary amine (**5e**) or primary amine (**5f**) in the presence of strong bases, delivering chiral sulfinamidines in excellent yields and enantioselectivities[27]. Notably, chiral sulfinamidines' general and concise synthesis remains extremely rare and challenging[65]. The absolute configuration of the enantioenriched **5f** was determined via X-ray crystallographic analysis (CCDC 2418774). At last, the enantiospecific oxidation of sulfinimidate ester **4a** with $RuCl_3$/$NaIO_4$ provided the sulfonimidate ester **5g** in 85% yield[43]. These straightforward derivatizations underscore the significance of our catalytic system in enabling the efficient synthesis of chiral aza-sulfur compounds, paving the way for the development of novel stereogenic-at-sulfur medicines and pesticides.

The mechanistic investigation of the asymmetric oxidative esterification reaction commenced with an NLE study[66]. As exhibited in Fig. 4b, a slight negative nonlinear effect elucidated that a high-order catalyst aggregate might promote the transformation in this reaction system (for details, see Section 6.1–6.3 in SI)[67,68]. Interestingly, when water (20 μL) was introduced in the oxidative esterification reactions catalyzed by **1a** with different enantioselectivities, the ee values of sulfinamides (water as nucleophile) were always nearly identical to the sulfinimidate ester **4a** (alcohol as nucleophile). This observation suggests that both products likely arise from the same chiral intermediate, and that the subsequent nucleophilic substitution proceeds via an enantiospecific transformation (Section 6.3 in SI). In our previous asymmetric oxidation reaction, we proposed that the key sulfinimidoyl iodide was a stable chiral species based on the DFT studies[62]. To further support this proposal, a (*L*)-menthol was employed as a chiral probe in the esterification reaction with catalyst Λ-(*S, S*)-**1a**, Δ-(*R, R*)-**1a** or without chiral catalysts, respectively (Fig. 4c). As a result, sulfinimidate ester (*R, L*)-**6** was

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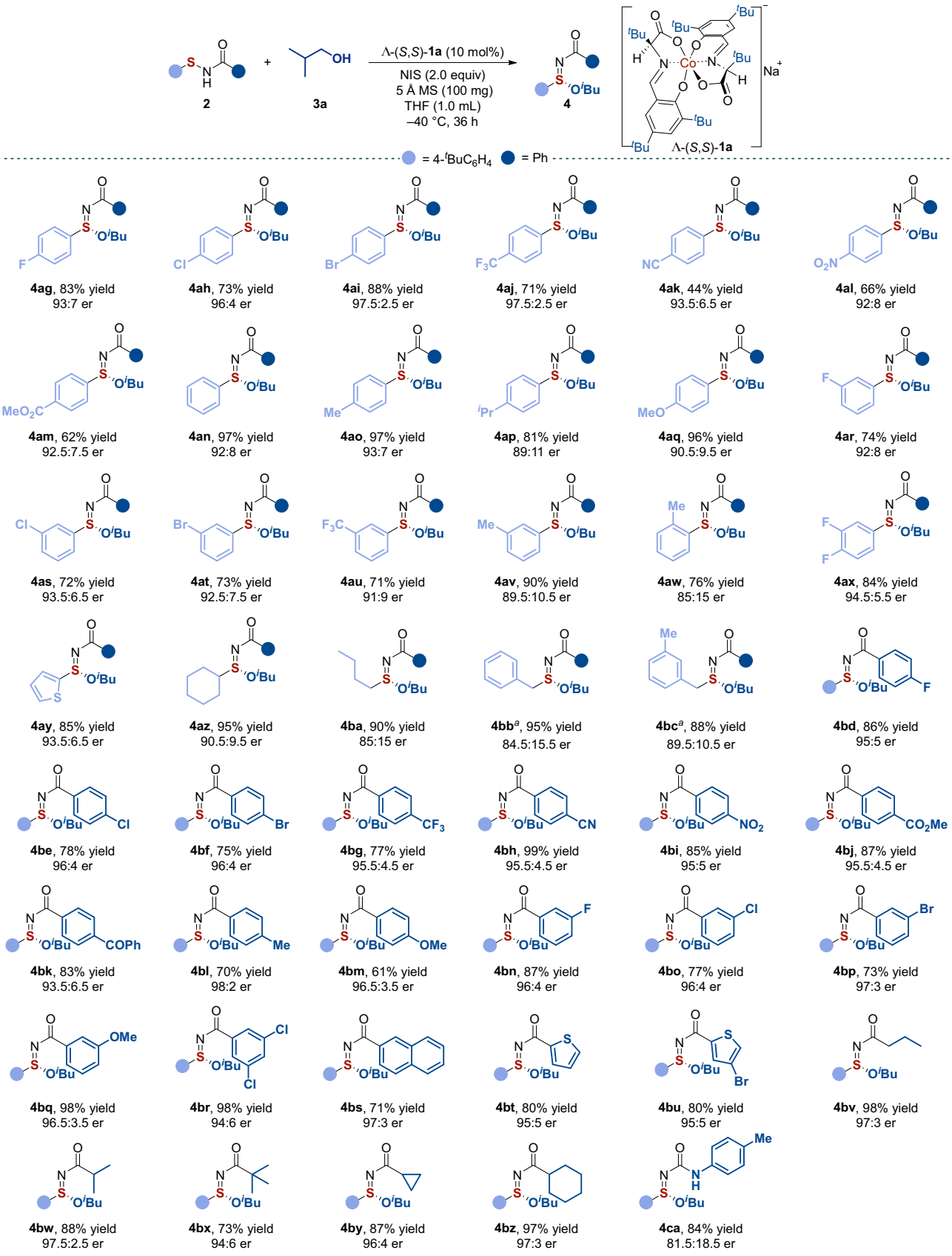

Fig. 3 | Substrate Scope of Sulfenamides. Unless otherwise noted, the reaction was performed with sulfenamide **2** (0.10 mmol), **3a** (0.20 mmol. 2.0 equiv), Λ-(*S*,*S*)−**1a** (0.01 mmol, 10 mol%), NIS (0.2 mmol, 2.0 equiv), and THF (1.0 mL) at −40 °C for 36 h. Isolated yields are reported, and er values were determined by chiral stationary HPLC. [a]DCM was used instead of THF (For details, see Table S8 in SI).

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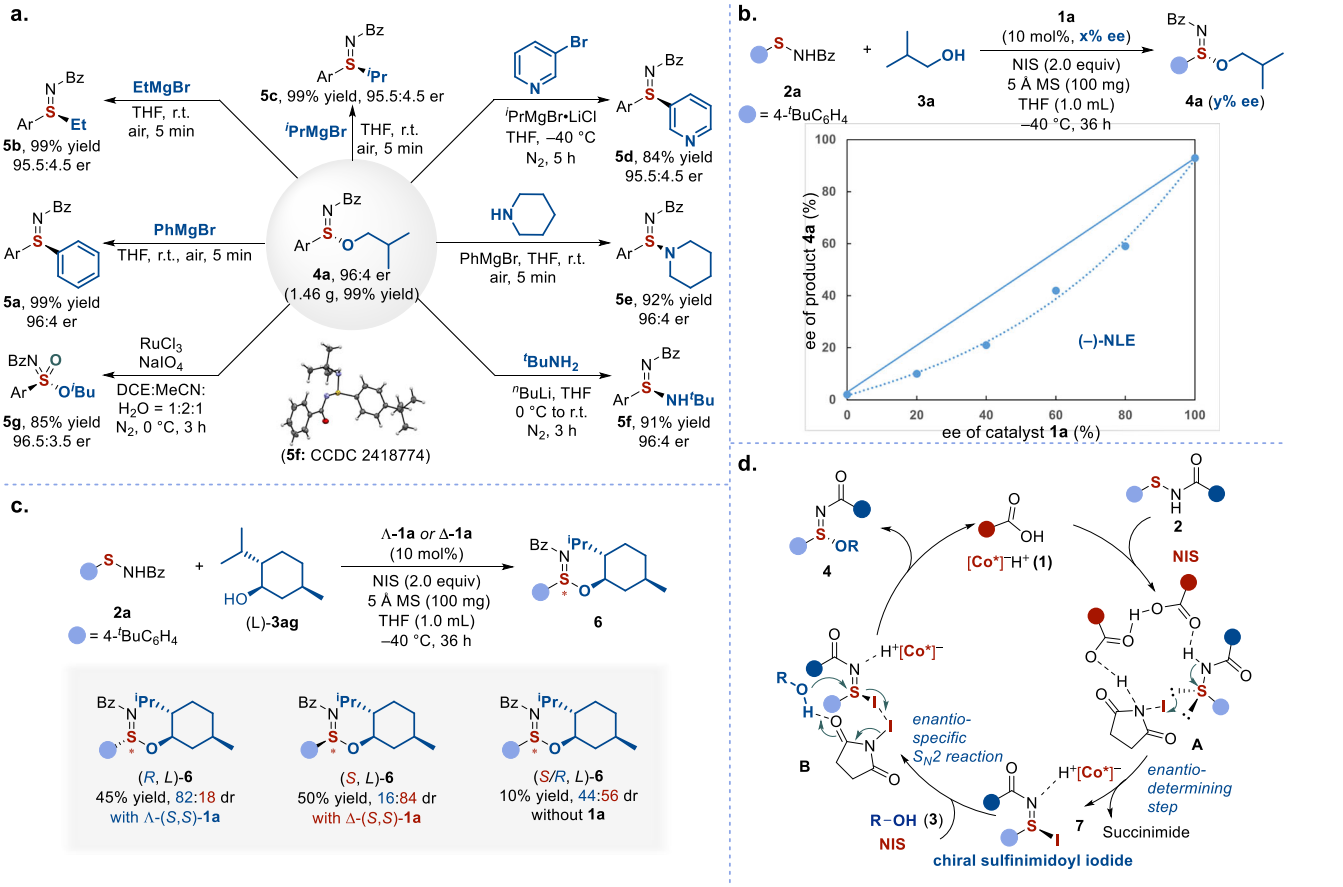

Fig. 4 | Synthetic applications and mechanistic investigation. a synthetic application of chiral sulfinimidate ester **4a**. **b** Nonlinear effect (NLE) study. **c** Experimental evidence for chiral sulfinimidoyl iodide intermediates. **d**. Proposed catalytic cycle.

obtained with 82:18 dr by using Λ-(*S*, *S*)-**1a** while using Δ-(*R*, *R*)-**1a** afforded (*S*, *L*)-**6** with high diastereoselectivity (84:16 dr). Notably, the background reaction enabled product **6** with low diastereoselectivity albeit at −40 °C (44:56 dr, R/S). These results can be considered experimental evidence supporting the existence of chiral sulfinimidoyl iodides. Otherwise, significantly higher diastereoselectivity would be expected in the catalyst-free reaction due to the chiral induction effect of menthol[27,69–71]. According to the previous studies and experimental investigation, we showcased a concise catalytic cycle in Fig. 4d. In the presence of the in-situ generated acidic chiral complex [Co*]$^-$H$^+$, sulfenamide **2a** reacted with NIS stereoselectively, leading to chiral sulfinimidoyl iodide intermediate **7**, whose existence was indirectly supported by HRMS (for the proposed stereocontrol model, see Section 6.5 in SI)[62]. With the assistance of another molecular NIS, an enantiospecific S_N2 reaction happened between alcohol **3** and the Brønsted acid-activated intermediate **7**, releasing chiral sulfinimidate ester **4** with the regeneration of [Co*]$^-$H$^+$.

Discussion

In conclusion, we have developed a groundbreaking catalytic approach for the synthesis of chiral sulfinimidate esters through iodonium-promoted enantioselective oxidative esterification of sulfenamides, utilizing an anionic stereogenic-at-Co(III) complex as the catalyst. This strategy enabled the efficient preparation of a broad range of chiral sulfinimidate esters, achieving excellent yields and enantioselectivities across more than 70 examples (up to 98.5:1.5 er). Importantly, the chiral sulfinimidate esters were showcased as versatile molecular platforms for synthesizing diverse chiral aza-sulfur(IV) compounds, under mild reaction conditions. By using (*L*)-menthol as a chiral probe, the mechanistic investigation afforded experimental evidence of chiral sulfinimidoyl iodide intermediates. Furthermore, the exploitation of chiral sulfinimidoyl electrophiles presents a robust and practical methodology for addressing challenging asymmetric issues in sulfur stereochemistry, paving the way for novel chiral sulfur-containing compounds with broad applications in pharmaceuticals, and agrochemicals.

Methods

General procedure for the synthesis of enantioenriched 4a–4ca

An oven-dried 10-mL tube equipped with a magnetic stirring bar was charged with sulfenamide **2** (0.10 mmol), catalyst Λ-(*S,S*)-**1a** (0.01 mmol, 10 mol%), alcohol **3** (0.20 mmol, 2.0 equiv), 5 Å MS (100 mg) and THF (1.0 mL). The mixture was cooled to −40 °C and stirred for 30 min. The NIS solid (0.20 mmol, 2.0 equiv) was poured into the tube all at once, and the reaction mixture was stirred at −40 °C for 36 h. The reaction was quenched by adding $Na_2S_2O_3$ aq. and then separating the organic layer from the aqueous phase. The aqueous phase was further extracted with EtOAc (3 × 5.0 mL). The organic layer was dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using the petroleum ether/ethyl acetate (10/1) as an eluent to afford enantioenriched products **4a**–**4ca**.

Data availability

Deposition Number 2418774 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge Crystallographic Data Centre (CCDC) and Fachinformationszentrum Karlsruhe Access Structures service. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union

Road, Cambridge CB2 1EZ, UK; fax: + 441223 336033. Data supporting the findings of this manuscript are also available from within the Supplementary Information and from the corresponding author upon request.

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Author contributions

H.J.J. and J.Y. conceived the research and were responsible for the experimental design; X.Q.T., X.Y.K., and J.Y.W. performed the synthetic experiments, compound testing, and data analysis; Y.Y.L. and M.L.S. assisted in performing experiments and analyzing data. H.J.J. and J.Y. prepared the manuscript with assistance from C.Z.Y., Q.L., and M.L.S.

Competing interests

The authors declare no competing interests.

Additional information

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