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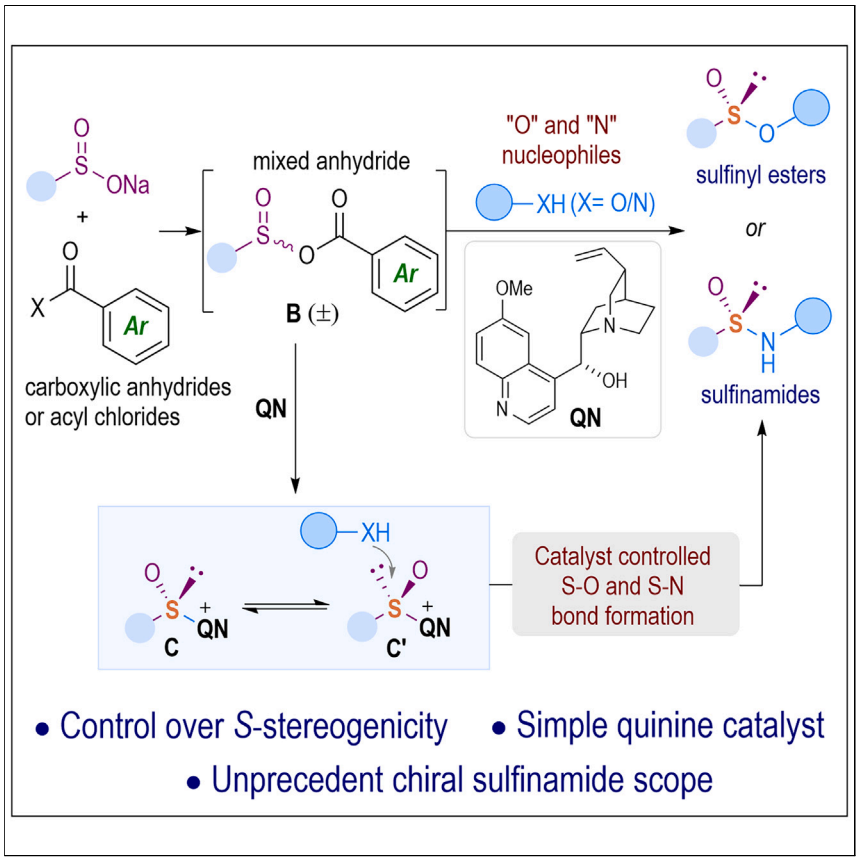
Enantioselective sulfinylation of alcohols and amines by condensation with sulfinates



An organocatalytic strategy for highly practical and enantioselective sulfinylation of alcohols/amines through the activation of sulfinates by forming mixed sulfinic anhydrides is developed. Tuning the structure of the reactive species with sterically congested moieties, a simple quinine catalyst effectively controls the chemo- and enantioselectivity over the nucleophilic S–O/N bond constructions, affording a wide range of chiral sulfinyl derivatives with excellent enantioselectivities. Notably, the protocol facilitates the coupling of various bioactive compounds and commercial drugs, providing a platform for pro-drug modifications.

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Highlights

Highly practical and enantioselective sulfinylations with simple quinine catalyst

Formation of mixed sulfinic anhydrides to enable further catalyst control

Broad substrate scope with *N*-heterocyclic sulfinates and various amine nucleophiles

Chiral sulfinate functionalization platform for pro-drug modifications

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Enantioselective sulfinylation of alcohols and amines by condensation with sulfinates

Minghong Liao,[1] Yonggui Liu,[1] Hongyan Long,[1] Qin Xiong,[1] Xiaokang Lv,[1] Zhongfu Luo,[1] Xingxing Wu,[1,*] and Yonggui Robin Chi[1,2,3,*]

SUMMARY

Achieving the preparation of enantiomerically enriched *S*-stereogenic compounds is a long-standing objective in stereoselective synthesis, owing to the fundamental importance and broad applications of these chiral scaffolds in various fields. Despite recent significant advancements, catalyst-controlled stereoselective synthesis of *S*-stereogenic compounds remains to be a considerable challenge, particularly by means of small-molecule catalysts. Herein, we disclosed an organocatalytic strategy for highly practical and enantioselective sulfinylation of alcohols and amines through the activation of sulfinates by forming mixed sulfinic anhydrides. Tuning the structure of the reactive species with sterically congested moieties, a simple, naturally occurring quinine catalyst effectively controls the chemo- and enantioselectivity over the nucleophilic S–O and S–N bond constructions, affording a wide range of chiral sulfinyl derivatives with excellent optical purities. Notably, the protocol readily facilitates the coupling with various natural products and commercial drugs that could offer an attractive strategy for the late-stage diversification of important biologically intriguing molecules.

INTRODUCTION

Sulfur stereogenic centers are broadly present in natural products, pharmaceuticals, and agrochemicals (Figure 1A).[1–4] The absolute configuration of sulfur stereogenic centers is essential for their biological properties due to the fundamental importance of stereochemistry in biomolecular recognition and toxicity.[5,6] For instance, in crop protection, the *R*-configured flusulfinam shows remarkable herbicidal activity against resistant weeds, whereas its (*S*)-enantiomer is less active and displays pronounced toxicity toward rice plants.[7] Additionally, these enantioenriched sulfur stereogenic scaffolds are of enormous utilitiy for the design of chiral auxiliaries, ligands, and catalysts in asymmetric organic synthesis.[8–12] Consequently, the preparation of enantiomerically enriched *S*-stereogenic compounds has attracted considerable attention over the past decades. Effective protocols for constructing *S*-chiral molecules have primarily relied on the diastereoselective approaches utilizing stoichiometric chiral reagents, such as Andersen's (*S*)-menthyl *p*-toluenesulfinate.[13–17] There are also several catalytic enantioselective approaches to prepare high-value chiral sulfinyl functional molecules through transition metal-catalyzed enantioselective oxidation[18–20] and other C–S bond forming transformations.[21–27] Nonetheless, catalyst-controlled stereoselective synthesis of *S*-stereogenic compounds remains to be a considerable challenge. In particular, there are limited studies on using small-molecule catalysts to govern the construction of stereogenic sulfur centers with high enantioselectivity.[28–32]

THE BIGGER PICTURE

Enantioenriched *S*-stereogenic compounds are widely present in biologically intriguing molecules and found broad applications in asymmetric synthesis. Consequently, the preparation of chiral *S*-stereogenic compounds has attracted considerable attention over the past decades. Although direct condensation between sulfinates and alcohols/amines represents an effective protocol to prepare racemic sulfinyl compounds, their catalytic, enantioselective synthesis has long been overlooked. Herein, we disclosed an organocatalytic strategy for highly practical and enantioselective sulfinylation of alcohols and amines with readily available sodium sulfinates. Our approach involves the utilization of a distinct racemic mixed anhydride as the pivotal reactive species. A naturally occurring quinine catalyst activates the anhydride intermediate and controls the *S*-stereogenicity over the S–O/N bond formations, affording a wide range of chiral sulfinate esters and sulfinamides in high er values.

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One particular class of stereogenic sulfur compounds of proven significance are sulfinate esters and sulfinamides, which are important chiral structural motifs that could be easily derivatized in a stereospecific manner to enable the preparation of diverse chiral *S*-stereogenic analogs.[33,34] Evans et al.[35] demonstrated the first catalytic asymmetric synthesis of *tert*-butanesulfinate ester with an impressive 81% ee by an *N*-methylimidazole-containing peptide catalyst from *tert*-butyl sulfinic chloride.[35] Shortly thereafter, Shibata et al.[36] achieved a highly enantioselective sulfinylation of *t*-BuOH with arenesulfinic chloride that was mediated by stoichiometric amounts of cinchona alkaloids. These pioneering approaches offer remarkable control over the *S*-stereogenicity of the resulting sulfinate ester products. Somewhat unfortunately, the inherent high reactivity of sulfinyl chloride substrates poses a prominent challenge in catalyst stereocontrol owing to the potential uncatalyzed sulfinylations as background reactions and other unproductive transformations, which notably decreases the substrate scope and hinders their broad applications (Figure 1B-1). A recent significant advancement in this area was demonstrated by Zhang[37] and colleagues wherein a highly efficient asymmetric condensation approach to access chiral sulfinate esters was realized for the first time from the easily accessible and readily stable potassium sulfinates (Figure 1B-2).[37] A key enantioenriched mixed anhydride intermediate **A** was formed from sulfinate and ethyl chloroformate through an ion-pairing catalysis by a pentanidium catalyst, which could be facilely converted to chiral sulfinyl products with alcohol nucleophiles. Very recently, Huang and co-workers[38] developed an intriguing enantioselective deoxygenation process from sulfonyl nitriles to access sulfinate esters in high enantioselectivity.[38] Despite their broad substrate scope,[37,38] the development of highly enantioselective sulfinylation approaches is still highly demanding. For instance, the direct catalytic preparation of chiral sulfinyl amines, which are another representative class of sulfinyl derivatives,[39,40] through coupling with amine nucleophiles is still not accomplished.

The activation of feedstock carboxylic acids, which allows for a diverse set of enantioselective transformations[41–44] under the control of Lewis base catalysts,[45–49] through *in situ* anhydride formation has been extensively explored. Motivated by these achievements, we envisioned an activation of sulfinates by the *in situ* formation of sulfinic mixed anhydrides to enable further catalyst-controlled nucleophilic S–X (X = O, N) bond formations (Figure 1B-3). Herein, we documented a small-molecule catalytic strategy for highly practical and enantioselective sulfinylation of alcohols and amines with readily available sodium sulfinates. Our approach involves the utilization of a distinct racemic mixed anhydride as the pivotal reactive species. A naturally occurring, cost-effective quinine catalyst readily activates the intermediate **B** to form the sulfinylammonium salt intermediate **C**/**C′** without necessitating further structural modifications.[35–37] A dynamic kinetic resolution (DKR) process[35–37] involving rapid epimerization between **C**/**C′** would control the *S*-stereogenicity over the S–O/N bond formations in high efficiency (see Scheme S6 for details of the mechanistic study).[50–52] It is noteworthy that the existing challenge regarding the chemo- and enantioselectivity of amine sulfinylation could be effectively addressed by tuning the structure of reactive mixed anhydrides with sterically congested moieties.[37,38] Our method features a broad substrate scope, giving rise to a wide range of chiral sulfinyl derivatives with high optical purity. Significantly, to the best of our knowledge, our methodology is the first to achieve highly stereoselective sulfinylation with nitrogen nucleophiles by means of catalyst control. We also demonstrate the feasibility of sulfinylation with difficult *N*-heterocycle moieties under our catalytic conditions through the formation of the mixed anhydride intermediates. Moreover, our approach facilitates the coupling of various

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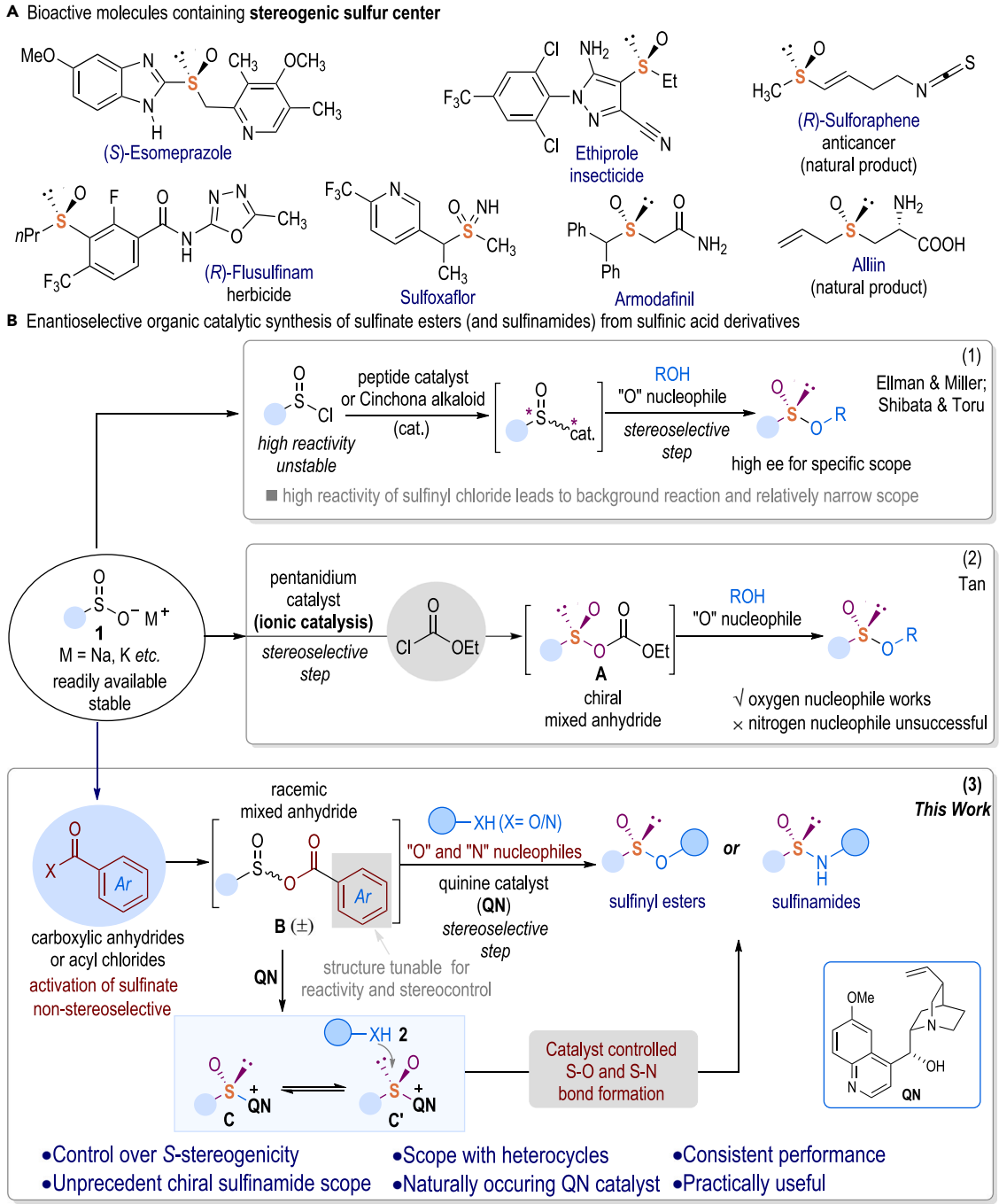

Figure 1. Organic catalytic enantioselective preparation of *S*-stereogenic compounds from sulfinic acid derivatives

(A) Bioactive molecules containing stereogenic sulfur centers.

(B) Challenges and development of asymmetric synthesis of chiral sulfinyl compounds by means of small-molecule catalysts.

bioactive compounds, including androsterone and pregnenolone, as well as established commercial drugs (eg, benzocaine and procaine), with excellent stereoselectivity, offering an appealing chiral sulfinate functionalization platform, which could serve as an alternative strategy for pro-drug modifications.[53,54]

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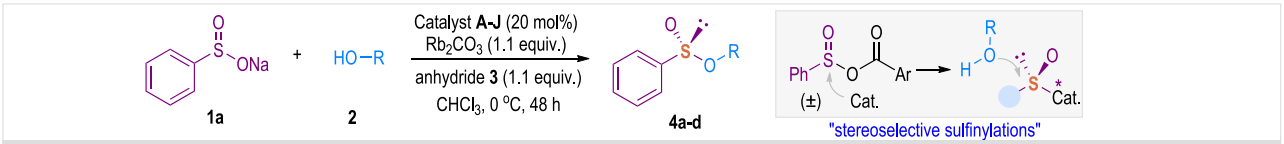

Entry	Cat.	R-OH (2)	3	Yield (%)	E.r.
1	A	*n*-BuOH (**2a**)	**3a**	**4a**, 61	50:50
2	B	*n*-BuOH	**3a**	**4a**, 42	50:50
3	C	*n*-BuOH	**3a**	**4a**, 58	50:50
4	D	*n*-BuOH	**3a**	**4a**, 32	50:50
5	E	*n*-BuOH	**3a**	**4a**, 60	87:13
6	F	*n*-BuOH	**3a**	**4a**, 55	16:84
7	G	*n*-BuOH	**3a**	**4a**, 34	36:64
8	H	*n*-BuOH	**3a**	**4a**, 43	69:31
9	I	*n*-BuOH	**3a**	**4a**, 17	25:75
10	J	*n*-BuOH	**3a**	**4a**, <5	50:50
11	E	*n*-BuOH	**3b**	**4a**, 24	69:31
12	E	*n*-BuOH	**3c**	**4a**, 61	95:5
13	E	MeOH (**2b**)	**3c**	**4b**, 84	89:11
14	E	EtOH (**2c**)	**3c**	**4c**, 67	95:5
15	E	*i*-PrOH (**2d**)	**3c**	**4d**, 84	97:3
16	F	*i*-PrOH (**2d**)	**3c**	**4d**, 76	4:96

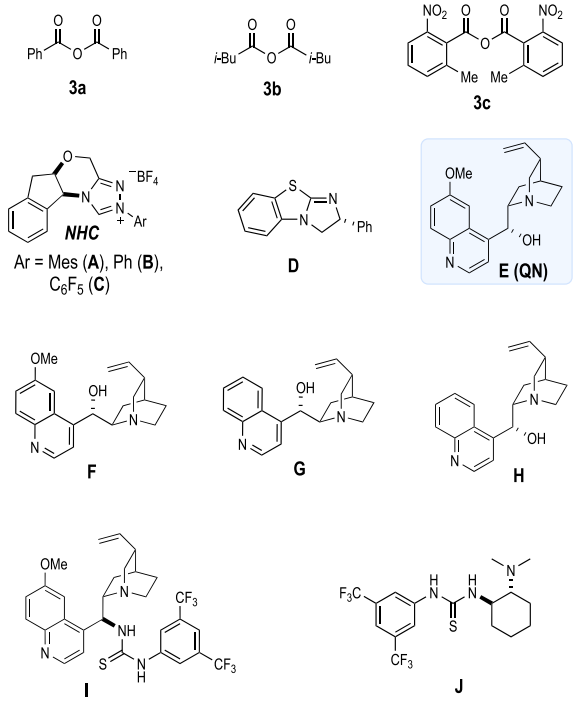

Figure 2. Development of the enantioselective sulfinylation of alcohols

Reaction conditions: sodium sulfinate **1a** (0.1 mmol, 1.0 equiv), Cat. **A**–**J** (20 mol %), **3** (1.1 equiv), alcohol **2** (1.05 equiv), Rb_2CO_3 (1.1 equiv), $CHCl_3$ (1.5 mL), 0°C, and 48 h. Isolated yields were reported, and er values were determined by chiral high-performance liquid chromatography (HPLC) analysis.

RESULTS AND DISCUSSION

Reaction development

We initiated our studies on the asymmetric sulfinylations of alcohol nucleophiles by choosing readily available sodium benzenesulfinate (**1a**) and *n*-BuOH (**2a**) as the primary starting materials. Anhydride **3a** was used to trigger the sulfinate activation *in situ* to test our hypothesis. We anticipate that Lewis base catalysts would be capable of facilitating the catalysis of the resulting mixed anhydride, thereby imparting stereocontrol during the subsequent S–O bond formations. To this end, a range of various chiral organocatalysts, such as *N*-heterocyclic carbenes **A**–**C**, isothiourea **D**, and cinchona alkaloid **E**, were carefully investigated (Figure 2, entries 1–5). Typical Lewis bases **A**–**D** were highly effective in giving the desired sulfinate ester product **4a** in good yields, albeit with no observation of enantioselective control (Figure 2, entries 1–4). Gratifyingly, the naturally occurring, inexpensive quinine **E** was found to be superior for the catalytic asymmetric condensation, leading to the product **4a** in 60% yield and a good enantioselectivity of 87:13 er (entry 5). We next tested a diverse set of cinchona alkaloid-based catalysts **F**–**H**, as well as bifunctional catalysts **I**–**J** (entries 6–10). Unfortunately, these conditions did not lead to improvement on the selectivity of the product. Anhydrides **3b** and **3c** were then examined by using quinine **E** as the catalyst (entries 11 and 12), and we were

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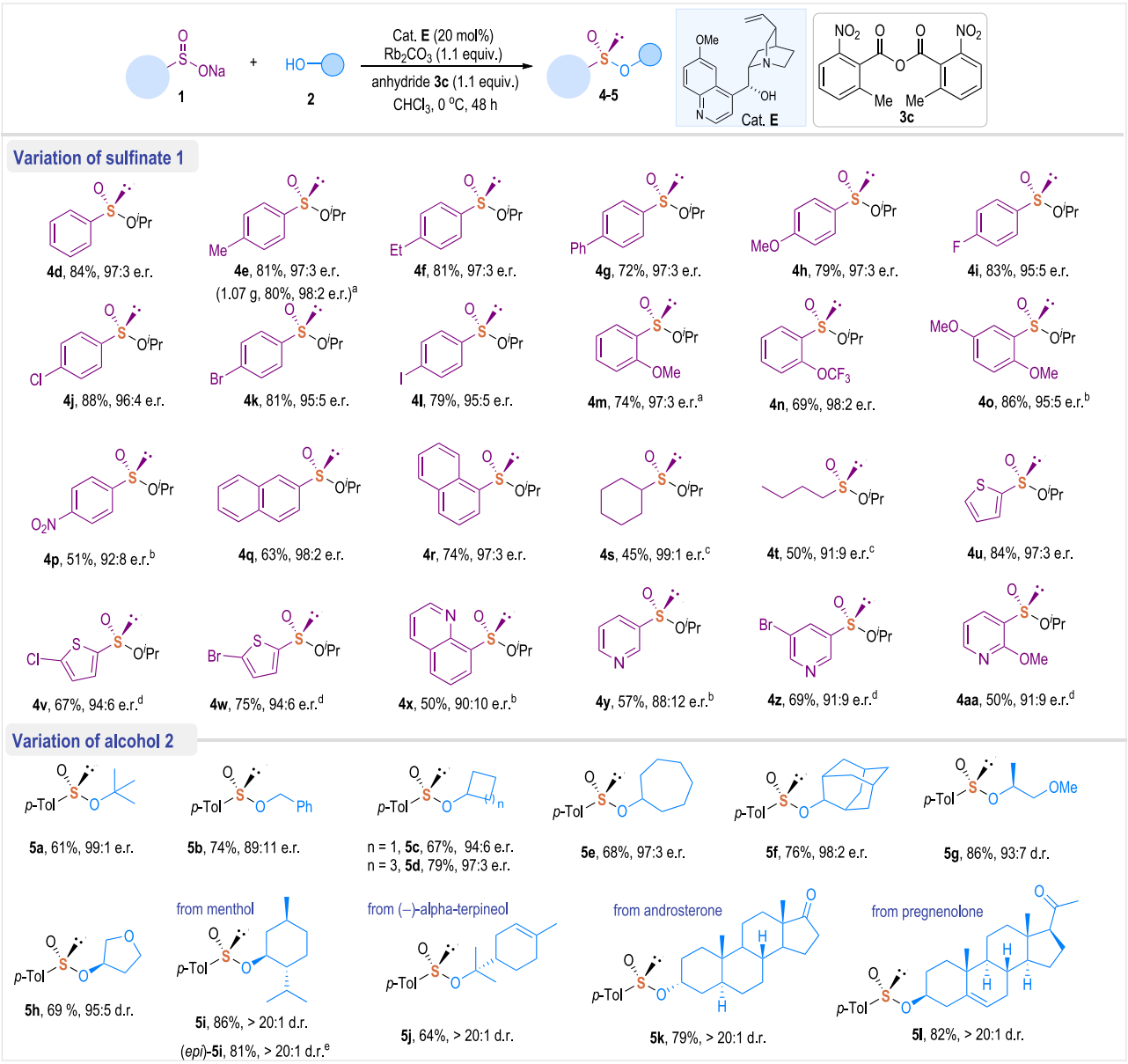

Figure 3. Enantioselective sulfinylation of alcohols

Reaction conditions: sodium sulfinate **1** (0.1 mmol, 1.0 equiv), Cat. **E** (20 mol %), **3c** (1.1 equiv), Rb_2CO_3 (1.1 equiv), and alcohol **2** (1.05 equiv) in $CHCl_3$ (1.5 mL), 0°C, and 48 h. Isolated yields were reported, er values were determined by chiral HPLC analysis, and d.r. values were determined by chiral HPLC or NMR analysis. [a]The reaction was performed with sodium *p*-tolylsulfinate (**1b**, 1.2 g, 7.3 mmol) and Cat. **E** (10 mol %), and 1.07 g product **4e** was obtained. [b]Reactions at room temperature instead of 0°C. [c]Toluene was used. [d]Reactions at 35°C. [e](L)-Menthol was used.

delighted to find that anhydride **3c** with *ortho*-disubstitutions provided the desired product **4a** with a high stereoselectivity (95:5 er, entry 12). Alcohol **2d** was further explored under the catalytic sulfinyl transfer reaction conditions (entries 13 and 14). Although MeOH afforded the product **4b** in a slightly dropped enantioselectivity, reaction with EtOH provided the product **4c** with a same 95:5 er (entries 13 and 14). To our delight, the use of isopropyl alcohol (**2d**) led to an enhanced enantiocontrol to afford the chiral isopropyl sulfinate **4d** with 84% yield and an excellent 97:3 er (entry 15). Furthermore, the other enantiomer of **4d** (4:96 er) could be readily

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accessed by the employment of the quinidine catalyst **F** as a pseudoenantiomer of quinine catalyst **E**.

Reaction scope

With the reaction condition established (Figure 2, entry 15), we set out to identify the generality of the catalyst-controlled enantioselective sulfinylation of alcohols (Figure 3). Sodium aromatic sulfinates **1** possessing a diverse set of groups (CH_3, C_2H_5, Ph, OCH_3, halogens, etc.) at the *para*, *ortho*, or *meta* position of the phenyl moiety were initially explored, furnishing the corresponding products **4e–4o** with 69%–88% yields and excellent enantioselectivities ranging from 95:5 to 98:2 er. Notably, with the optimized conditions, we were able to perform a gram-scale reaction by using 10 mol % of catalyst **E** to give product **4e** in 80% yield (1.07 g) and excellent enantioselectivity. Benzenesulfinate with strong electron-withdrawing NO_2 group also proceeded well under the catalytic conditions to deliver the sulfinyl product **4p** with 51% yield and a slightly dropped stereoselectivity (92:8 er). Both 1- and 2-naphthyl sulfinates reacted smoothly to give the corresponding chiral sulfinate esters with excellent results (**4q–4r**). Furthermore, the developed method was also compatible with alkyl sulfinate substrates, yielding the corresponding products **4s** and **4t** in modest yield with 99:1 and 91:9 er, respectively. Encouraged by the remarkable efficiency of our method in the asymmetric condensations, we then turned to examine the scope of heteroaromatic sulfinates. Thiophene sulfinate esters **4u–4w** with various substitutions were provided in 67%–84% yields and high er values. Notably, *N*-containing heterocycles, such as quinoline and pyridine sulfinates, which were previously unrealized,[35–38] were also feasible to afford the desired products **4x–4aa**, which significantly expands the scope and synthetic utility of our method.

We next explored the catalytic approach with respect to an array of nucleophiles (Figure 3). A range of alcohols, such as *t*BuOH (**5a**); BnOH (**5b**); and 4-, 6-, or 7-membered cyclic alcohols (**5c–5e**), as well as caged adamantyl alcohol (**5f**) could be highly enantioselectively assembled with *p*-tolylsulfinate under the optimal conditions. Reactions with enantiopure alcohols delivered the products **5g–5h** in excellent diastereoselectivity. Of great significance, our method demonstrated a wide functional group tolerance and thus allowed for the rapid construction of sulfur stereogenic element to a broad range of naturally occurring alcohol molecules, such as (D)/(L)-menthol (**5i** and *epi*-**5i**); (−)-alpha-terpineol (**5j**); and biologically intriguing alcohols, including androsterone (**5k**) and pregnenolone (**5l**).

Despite elegant studies to catalytically access chiral sulfinate esters, a catalyst-controlled method for the stereoselective preparation of their sulfinamide analogs continues to be an unresolved challenge. This is likely due to the relatively strong nucleophilicity of the corresponding amine nucleophiles, which results in unsuccessful chemo- or stereocontrol, as demonstrated in the reports by both Zhang et al.[37] and Huang et al.[38] In our endeavor, we were delighted to find that with slight modifications to our reaction procedure, involving the use of acyl chloride **3d** instead of anhydride **3c** to pre-activate the sulfinate salts (see Tables S6 and S7 for details), a broad range of sulfinamides could be successfully prepared in good yields and excellent enantioselectivities. As demonstrated in Figure 4, *N*-unsubstituted sulfinamide **8a** with 71% yield and 98:2 er was readily afforded by the employment of hexamethyldisilazane (HMDS) as the amine nucleophile after mild desilylation upon simple workup. As a technique note, activation with sterically congested acyl chloride, such as **3d**, is pivotal to achieving satisfactory yields by suppressing undesired side reactions leading to amide formations (see Table S6 and S7 for details). Preparation of the enantiomeric product **8a** could be achieved with quinidine catalyst **F** under the

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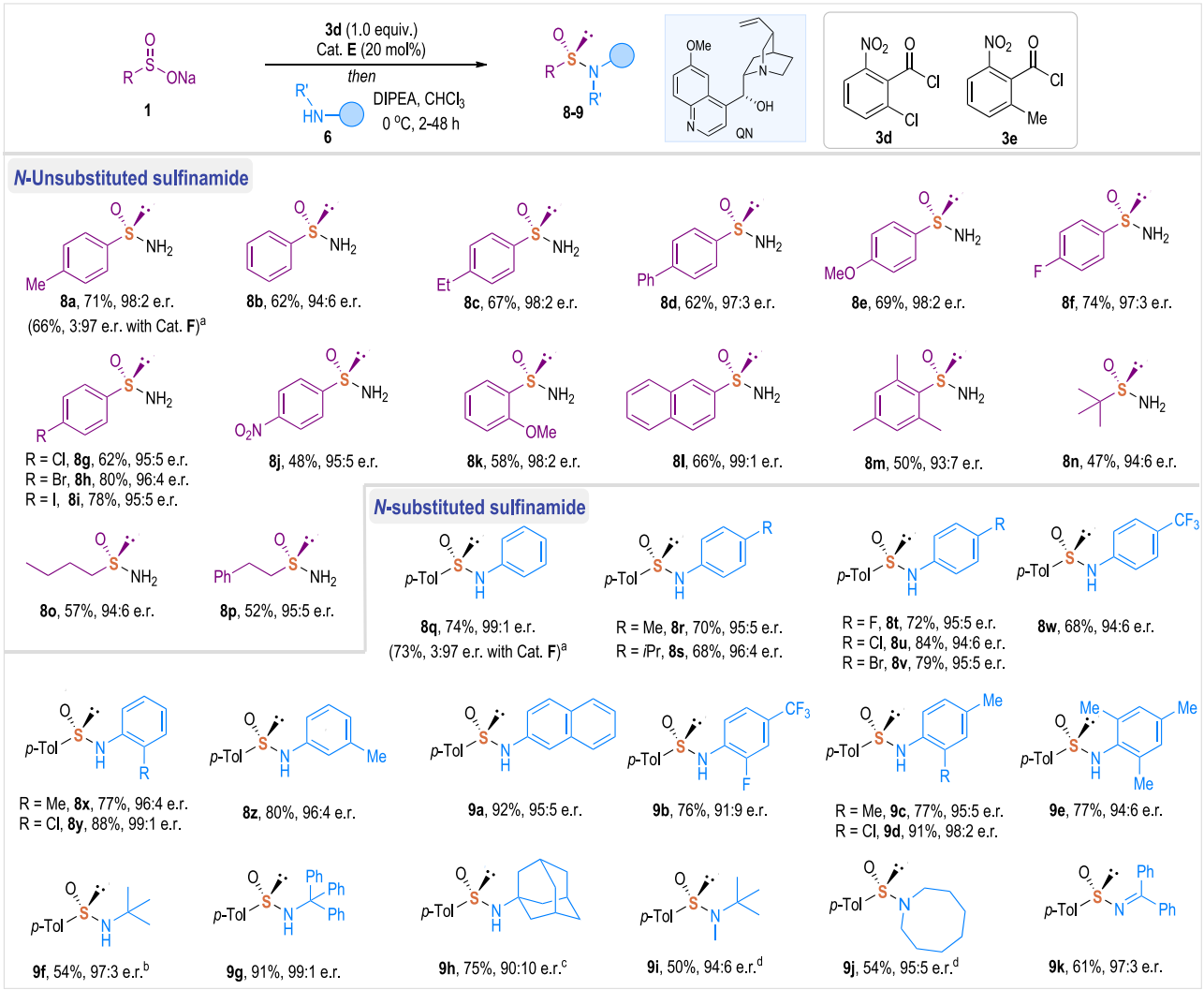

Figure 4. Enantioselective sulfinylation of amines

Reaction conditions: sodium sulfinate **1** (0.1 mmol, 1.1 equiv), **3d** (0.1 mmol, 1.0 equiv) in $CHCl_3$ (1.5 mL), stirred in CHCl3 at 0°C for 2 h before the addition of Cat. **E** (20 mol %), DIPEA (1.1–1.3 equiv), and amine **6** (1.1–1.4 equiv, HMDS was used for products **8a**–**8p**) at 0°C for 2–48 h. Isolated yields were reported, er values were determined by chiral HPLC analysis, and d.r. values were determined by chiral HPLC or NMR analysis. [a]Cat. **F** was used instead of Cat. **E**. [b]Reaction at −40°C. [c]**3e** was used instead of **3d**. [d]Reaction at −60°C. DIPEA, *N*, *N*-diisopropylethylamine; HMDS, hexamethyldisilazane.

optimal conditions. A diverse set of substituents, including alkyl, Ph, OMe, halogens, and NO_2, at the *para*, *meta*, or *ortho* position of the aryl moiety of sulfinates **1** were all compatible to furnish the corresponding chiral *N*-free sulfinamides **8c**–**8m** in 48%–80% yields and excellent enantioselectivities. Interestingly, the electronic properties of these substituents did not exert a significant impact on stereoselectivity. It is notable to mention that sulfinate with aliphatic moiety also proceeded smoothly under the catalytic conditions to furnish the corresponding product **8n**–**8p** in high enantioselectivity, albeit in modest yields (47%–57%) with amide formation as the major competing pathway. Subsequently, we explored the enantioselective sulfinylations with aryl amines and found that the catalytic conditions showed a very broad scope with respect to various substituents (alkyl, halogens, CF_3, etc.) and substitution patterns on the *N*-aryl units. A wide array of *N*-aryl sulfinamides **8q**–**9e** were thereby provided with 68%–92% yields and excellent optical purities (up to

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99:1 er). In addition, the developed strategy could also realize enantioselective sulfinylation upon other amine nucleophiles, including primary or secondary alkyl amines (**9f–9j**) and *N*-free imine (**9k**), allowing for the efficient preparation of highly enantioenriched sulfinamides **9f–9k** in good yields (see Table S11 for details).

Synthetic applications

The optically enriched sulfinyl ester and amine products prepared in our approach offer versatile methods for further transformations. For instance, nucleophilic substitutions of sulfinyl ester (*R*)-**4e** with various Grignard reagents were initially employed, giving rise to chiral sulfoxides (*S*)-**10–12** in high yields and excellent enantioselectivities (Figure 5A). Additionally, unsaturated sulfoxide (*S*)-**13** could be smoothly afforded upon the addition of a vinyl Grignard reagent as the nucleophile, displaying a transferable double bond for further elaborations. Notably, bidentate ligands that have been explored in asymmetric catalysis, such as pyridinyl sulfoxide (*S*)-**14**[55] and a phosphine functionalized sulfoxide (*R*)-**15**,[56] could be easily prepared by additions with respective nucleophiles.

On the other hand, sulfinamides are privileged chiral precursors for a diverse set of stereoselective synthesis.[39,40] Under basic conditions, alkylated sulfinamides (*S*)-**16** were directly obtained (Figure 5B). By oxidation with PhI=O, (*S*)-**9g** was readily converted to sulfoximine ester (*R*)-**17**, which is a highly appealing scaffold for potential drug discovery.[3,4] The prepared enantioenriched sulfinamides could be readily used as chiral auxiliaries for stereoselective synthesis. For instance, a chiral aziridine **18** was prepared in 91% yield and over 20:1 d.r. and 94:6 er through a two-step sequence. Furthermore, the current enantioselective sulfinyl transfer reactions provide an ideal avenue for the post-functionalization of drug molecules by the installation of a chiral *S*-stereogenic unit.[53,54] Several drugs containing aniline scaffolds, such as benzocaine, procaine, and tetracaine, were explored to give their corresponding analogs (*S*)-**19–21**, demonstrating the viability of drug diversifications through the catalytic stereoselective sulfinylations (Figure 5C).

Conclusions

In summary, we have herein developed an organocatalytic asymmetric condensation approach to access enantiomerically enriched *S*-stereogenic compounds from easily accessible sulfinates and alcohols/amines by a simple quinine small-molecule catalyst. Governed by the catalyst, excellent stereocontrol was achieved over the S–O/N bond formations with catalyst-bound-sulfinyl ammonium intermediates, affording a broad range of chiral sulfinyl compounds, including sulfinate esters and sulfinamides in high yields and excellent enantioselectivities. The notable challenge regarding the amine sulfinylation was effectively resolved by the employment of a sterically hindered activating leaving group. Furthermore, the diversification of an array of complex natural products and drug molecules was readily achieved through the highly efficient stereoselective sulfinylations, which significantly expands the scope and synthetic utility of the current method. We anticipate that the developed catalyst-controlled enantioselective S–O/N bond formation approach will open new avenues for the preparation of chiral sulfur stereogenic compounds and inspire broad-ranging implementations to access biologically interesting chiral sulfinyl scaffolds.

EXPERIMENTAL PROCEDURES

Resource availability

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Yonggui Robin Chi (robinchi@ntu.edu.sg).

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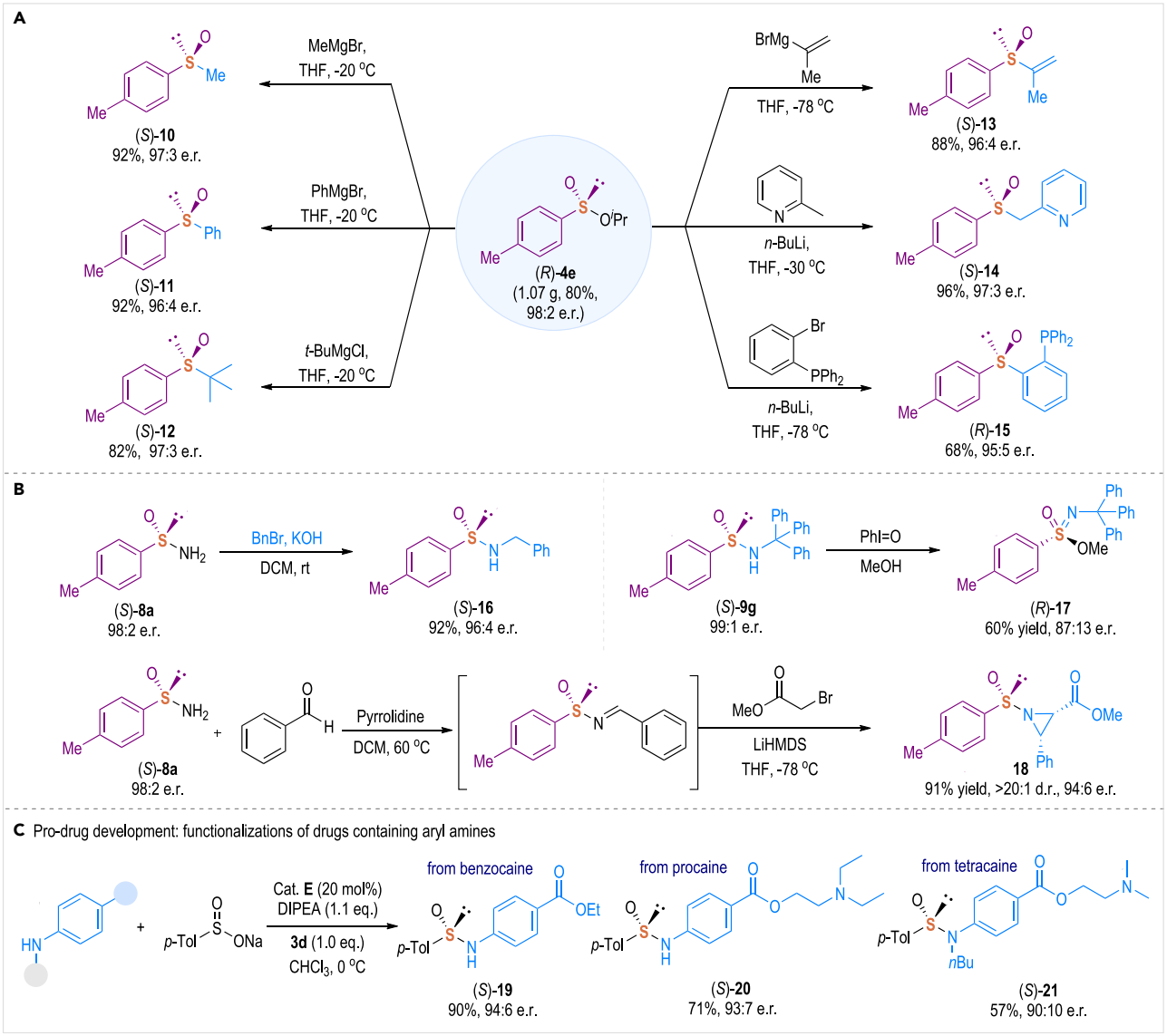

Figure 5. Synthetic transformations of the chiral sulfinyl compounds and application of the catalytic method in drug diversifications

Materials availability

All materials generated in this study are available from the lead contact without restriction.

Data and code availability

All of the data supporting the findings of this study are presented within the article and supplemental information. The X-ray crystallographic coordinates for the structure of compound (*R*)-**5i** reported in this article have been deposited at the Cambridge Crystallographic Data Centre (CCDC) under deposition numbers CCDC: 2291118. These data can be obtained free of charge from the CCDC via http://www.ccdc.cam.ac.uk/ data_request/cif. See Tables S1–S7 for the optimization of the asymmetric sulfinylation of alcohol and amine nucleophiles; Tables S8–S10, Figures S1–S4, and Schemes S1–S6 for mechanistic studies; Table S11 for the limited scope of other aliphatic amine nucleophiles; Figures S5–S189 for the NMR

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spectroscopic data of chiral sulfinyl products; Figures S190–S274 for the HPLC analysis of chiral sulfinate ester and sulfinamide products. All other data are available from the authors upon reasonable request.

Methods

Asymmetric synthesis of sulfinate esters 4–5

Under N_2 atmosphere, to an oven-dried 10.0-mL screw cap vial charged with a magnetic stirring bar, Cat. **E** (0.02 mmol, 20 mol %), **1** (0.10 mmol, 1.0 equiv), **3c** (0.1 mmol, 1.1 equiv), Rb_2CO_3 (0.11 mmol, 1.1 equiv), and $CHCl_3$ (1.5 mL) were added. The mixture was stirred for 1 h, and then alcohol **2** (0.105 mmol, 1.05 equiv) was added into the reaction. The resulting solution was stirred continuously at 0°C for 48 h, when the substrate was consumed completely. The reaction was quenched with saturated Na_2CO_3 aqueous solution and extracted with DCM. The mixture was concentrated *in vacuo* and purified by column chromatography on silica gel to afford the desired product **4–5**.

Asymmetric synthesis of sulfinamide 8a–8p

Under N_2 atmosphere, to an oven-dried 10.0-mL screw cap vial charged with a magnetic stirring bar, **1** (0.11 mmol, 1.1 equiv), **3d** (0.1 mmol, 1.0 equiv), and $CHCl_3$ (1.5 mL) were added. After stirring at 0°C for 2 h, Cat. **E** (0.02 mmol, 20 mol %) and DIPEA (0.13 mmol, 1.3 equiv) were successively added. The mixture was stirred for 30 min before HMDS (0.14 mmol, 1.4 equiv) was added into the reaction. The resulting solution was stirred continuously at 0°C for 48 h, when the substrate was consumed completely. The reaction was quenched with saturated $NaHCO_3$ aqueous solution and extracted with DCM. After concentration *in vacuo*, the crude residue was purified by column chromatography on silica gel to afford the desired desilylation product **8a–8p**.

Asymmetric synthesis of sulfinamides 8q–9k

Under N_2 atmosphere, to an oven-dried 10.0 mL screw cap vial charged with a magnetic stirring bar, sodium *p*-tolylsulfinate (0.11 mmol, 1.1 equiv), **3d** (0.1 mmol), and $CHCl_3$ (1.5 mL) were added. After stirring at 0°C for 2 h, Cat. **E** (0.02 mmol) and DIPEA (0.11 mmol, 1.1 equiv) were successively added. The mixture was stirred for 30 min before amine **6** (0.11 mmol, 1.1 equiv) was added into the reaction. The resulting solution was stirred continuously at 0°C for 2–3 h, when the substrate was consumed completely. After concentration *in vacuo*, the crude residue was purified by column chromatography on silica gel to afford the desired product **8q–9k**.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.chempr.2024.02.016.

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AUTHOR CONTRIBUTIONS

M.L. performed main methodology development, scop evaluation, and synthetic application. Y.L., H.L., and Q.X. contributed to earlier studies. X.L. and Z.L. contributed to scope evaluation and synthetic application. X.W. and Y.R.C. conceptualized and directed the project and drafted the manuscript with assistance from all co-authors. All authors contributed to part of the experiments and/or discussions.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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REFERENCES

1. Feng, M., Tang, B., Liang, S.H., and Jiang, X. (2016). Sulfur containing scaffolds in drugs: synthesis and application in medicinal chemistry. Curr. Top. Med. Chem. *16*, 1200–1216.

2. Devendar, P., and Yang, G.-F. (2017). Sulfur-containing agrochemicals. Top. Curr. Chem. (Cham) *375*, 82.

3. Foote, K.M., Nissink, J.W.M., McGuire, T., Turner, P., Guichard, S., Yates, J.W.T., Lau, A., Blades, K., Heathcote, D., Odedra, R., et al. (2018). Discovery and characterization of AZD6738, a potent inhibitor of Ataxia Telangiectasia Mutated and Rad3 Related (ATR) kinase with application as an anticancer agent. J. Med. Chem. *61*, 9889–9907.

4. Chen, X.Y., Park, S.J., Buschmann, H., De Rosa, M., and Bolm, C. (2012). Syntheses and biological activities of sulfoximine-based acyclic triaryl olefins. Bioorg. Med. Chem. Lett. *22*, 4307–4309.

5. Bentley, R. (2005). Role of sulfur chirality in the chemical processes of biology. Chem. Soc. Rev. *34*, 609–624.

6. López-Cabeza, R., and Francioso, A. (2022). Chiral pesticides with asymmetric sulfur: extraction, separation, and determination in different environmental matrices. Separations *9*, 29.

7. Lian, L., Hua, R., Peng, X., Zhao, D., and Cui, Q. Chiral sulfur oxide-containing aryl formamide compound and salt thereof, preparation method therefor, herbicidal composition, and application. World Intellectual Property Organization WO2021078174 A1. filed October 22, 2020, and published April 29, 2021.

8. T. Toru, and C. Bolm, eds. (2008). Organosulfur Chemistry in Asymmetric Synthesis (Wiley-VCH).

9. Mellah, M., Voituriez, A., and Schulz, E. (2007). Chiral sulfur ligands for asymmetric catalysis. Chem. Rev. *107*, 5133–5209.

10. Sipos, G., Drinkel, E.E., and Dorta, R. (2015). The emergence of sulfoxides as efficient ligands in transition metal catalysis. Chem. Soc. Rev. *44*, 3834–3860.

11. Trost, B.M., and Rao, M. (2015). Development of chiral sulfoxide ligands for asymmetric catalysis. Angew. Chem. Int. Ed. Engl. *54*, 5026–5043.

12. Otocka, S., Kwiatkowska, M., Madalińska, L., and Kiełbasiński, P. (2017). Chiral organosulfur ligands/catalysts with a stereogenic sulfur atom: applications in asymmetric synthesis. Chem. Rev. *117*, 4147–4181.

13. Andersen, K.K., Gaffield, W., Papanikolaou, N.E., Foley, J.W., and Perkins, R.I. (1964). Optically active sulfoxides. The synthesis and rotatory dispersion of some diaryl sulfoxides[2]. J. Am. Chem. Soc. *86*, 5637–5646.

14. Lu, B.Z., Jin, F., Zhang, Y., Wu, X., Wald, S.A., and Senanayake, C.H. (2005). New General sulfinylating process for asymmetric synthesis of enantiopure sulfinates and sulfoxides. Org. Lett. *7*, 1465–1468.

15. Aota, Y., Kano, T., and Maruoka, K. (2019). Asymmetric synthesis of chiral sulfoximines via the S-arylation of sulfinamides. J. Am. Chem. Soc. *141*, 19263–19268.

16. Mendonça Matos, P., Lewis, W., Argent, S.P., Moore, J.C., and Stockman, R.A. (2020). General method for the asymmetric synthesis of N–H sulfoximines via C–S bond formation. Org. Lett. *22*, 2776–2780.

17. Greed, S., Briggs, E.L., Idiris, F.I.M., White, A.J.P., Lücking, U., and Bull, J.A. (2020). Synthesis of highly enantioenriched sulfonimidoyl fluorides and sulfonimidamides by stereospecific sulfur–fluorine exchange (SuFEx) reaction. Chemistry *26*, 12533–12538.

18. Pitchen, P., Dunach, E., Deshmukh, M.N., and Kagan, H.B. (1984). An efficient asymmetric oxidation of sulfides to sulfoxides. J. Am. Chem. Soc. *106*, 8188–8193.

19. Wojaczyńska, E., and Wojaczyński, J. (2020). Modern stereoselective synthesis of chiral sulfinyl compounds. Chem. Rev. *120*, 4578–4611.

20. Han, J., Soloshonok, V.A., Klika, K.D., Drabowicz, J., and Wzorek, A. (2018). Chiral sulfoxides: advances in asymmetric synthesis and problems with the accurate determination of the stereochemical outcome. Chem. Soc. Rev. *47*, 1307–1350.

21. Zhang, Y.-Q., Hu, L., Yuwen, L., Lu, G., and Zhang, Q.-W. (2023). Nickel-catalysed enantioselective hydrosulfenation of alkynes. Nat. Catal. *6*, 487–494.

22. Wang, X.-J., Liu, H.-H., Cheng, J.K., Xiang, S.-H., and Tan, B. (2023). Catalytic enantioselective synthesis of chiral sulfonium ylides with S-stereogenic center. Chem *9*, 1495–1504.

23. Jia, T., Zhang, M., McCollom, S.P., Bellomo, A., Montel, S., Mao, J., Dreher, S.D., Welch, C.J., Regalado, E.L., Williamson, R.T., et al. (2017). Palladium-catalyzed enantioselective arylation of aryl sulfenate anions: a combined

experimental and computational study. J. Am. Chem. Soc. *139*, 8337–8345.

24. Greenwood, N.S., Champlin, A.T., and Ellman, J.A. (2022). Catalytic enantioselective sulfur alkylation of sulfenamides for the asymmetric synthesis of sulfoximines. J. Am. Chem. Soc. *144*, 17808–17814.

25. Wang, L., Chen, M., Zhang, P., Li, W., and Zhang, J. (2018). Palladium/PC-phos-catalyzed enantioselective arylation of general sulfenate anions: scope and synthetic applications. J. Am. Chem. Soc. *140*, 3467–3473.

26. Shen, B., Wan, B., and Li, X. (2018). Enantiodivergent desymmetrization in the rhodium (III)-catalyzed annulation of sulfoximines with diazo compounds. Angew. Chem. Int. Ed. Engl. *57*, 15534–15538.

27. Sun, Y., and Cramer, N. (2018). Enantioselective synthesis of chiral-at-sulfur 1,2-benzothiazines by Cp^{X} Rh^{III}-catalyzed C–H functionalization of sulfoximines. Angew. Chem. Int. Ed. Engl. *57*, 15539–15543.

28. Tang, Y., and Miller, S.J. (2021). Catalytic enantioselective synthesis of pyridyl sulfoximines. J. Am. Chem. Soc. *143*, 9230–9235.

29. Tilby, M.J., Dewez, D.F., Hall, A., Martínez Lamenca, C.M., and Willis, M.C. (2021). Exploiting configurational lability in aza-sulfur compounds for the organocatalytic enantioselective synthesis of sulfonimidamides. Angew. Chem. Int. Ed. Engl. *60*, 25680–25687.

30. Dong, S., Frings, M., Cheng, H., Wen, J., Zhang, D., Raabe, G., and Bolm, C. (2016). Organocatalytic kinetic resolution of sulfoximines. J. Am. Chem. Soc. *138*, 2166–2169.

31. Liao, S., Čorić, I., Wang, Q., and List, B. (2012). Activation of H2O2 by chiral confined Brønsted acids: a highly enantioselective catalytic sulfoxidation. J. Am. Chem. Soc. *134*, 10765–10768.

32. Zong, L.-L., Ban, X., Kee, C.W., and Tan, C.H. (2014). Catalytic enantioselective alkylation of sulfenate anions to chiral heterocyclic sulfoxides using halogenated pentanidium salts. Angew. Chem. Int. Ed. Engl. *53*, 11849–11853.

33. Kagan, H.B., and Rebiere, F. (1990). Some routes to chiral sulfoxides with very high enantiomeric excesses. Synlett *1990*, 643–650.

34. Fernandez, I., Khiar, N., Llera, J.M., and Alcudia, F. (1992). Asymmetric synthesis of alkane- and arenesulfinates of diacetone-D-glucose (DAG): an improved and general route to both enantiomerically pure sulfoxides. J. Org. Chem. *57*, 6789–6796.

35. Evans, J.W., Fierman, M.B., Miller, S.J., and Ellman, J.A. (2004). Catalytic enantioselective synthesis of sulfinate esters through the dynamic resolution of tert-butanesulfinyl chloride. J. Am. Chem. Soc. *126*, 8134–8135.

36. Shibata, N., Matsunaga, M., Nakagawa, M., Fukuzumi, T., Nakamura, S., and Toru, T. (2005). Cinchona alkaloid/sulfinyl chloride combinations: enantioselective sulfinylating agents of alcohols. J. Am. Chem. Soc. *127*, 1374–1375.

37. Zhang, X., Ang, E.C.X., Yang, Z., Kee, C.W., and Tan, C.-H. (2022). Synthesis of chiral sulfinate esters by asymmetric condensation. Nature *604*, 298–303.

38. Huang, S., Zeng, Z., Zhang, N., Qin, W., Lan, Y., and Yan, H. (2023). Organocatalytic asymmetric deoxygenation of sulfones to access chiral sulfinyl compounds. Nat. Chem. *15*, 185–193.

39. Liu, G., Cogan, D.A., and Ellman, J.A. (1997). Catalytic asymmetric synthesis of tert-butanesulfinamide. Application to the asymmetric synthesis of amines. J. Am. Chem. Soc. *119*, 9913–9914.

40. Robak, M.T., Herbage, M.A., and Ellman, J.A. (2010). Synthesis and applications of *tert*-butanesulfinamide. Chem. Rev. *110*, 3600–3740.

41. Leverett, C.A., Purohit, V.C., and Romo, D. (2010). Enantioselective, organocatalyzed, intramolecular aldol lactonizations with keto acids leading to bi- and tricyclic β-lactones and topology-morphing transformations. Angew. Chem. Int. Ed. Engl. *49*, 9479–9483.

42. Belmessieri, D., Morrill, L.C., Simal, C., Slawin, A.M.Z., and Smith, A.D. (2011). Organocatalytic functionalization of carboxylic acids: isothiourea-catalyzed asymmetric intra-and intermolecular Michael addition–lactonizations. J. Am. Chem. Soc. *133*, 2714–2720.

43. Chen, X.Y., Gao, Z.H., Song, C.Y., Zhang, C.L., Wang, Z.X., and Ye, S. (2014). N-heterocyclic carbene catalyzed cyclocondensation of α, β-unsaturated carboxylic acids: enantioselective synthesis of pyrrolidinone and dihydropyridinone derivatives. Angew. Chem. Int. Ed. Engl. *53*, 11611–11615.

44. Majumdar, N. (2022). Carboxylic acids as building blocks in catalytic asymmetric reactions. ACS Catal. *12*, 8291–8324.

45. E. Vedejs, and S.E. Denmark, eds. (2016). Lewis Base Catalysis in Organic Synthesis (Wiley-VCH).

46. Bellotti, P., Koy, M., Hopkinson, M.N., and Glorius, F. (2021). Recent advances in the chemistry and applications of N-heterocyclic carbenes. Nat. Rev. Chem. *5*, 711–725.

47. Biju, A.T. (2018). N-Heterocyclic Carbenes in Organocatalysis (Wiley-VCH).

48. Morrill, L.C., and Smith, A.D. (2014). Organocatalytic Lewis base functionalisation of carboxylic acids, esters and anhydrides via C1-ammonium or azolium enolates. Chem. Soc. Rev. *43*, 6214–6226.

49. Vellalath, S., and Romo, D. (2016). Asymmetric organocatalysis: the emerging utility of α,β-unsaturated acylammonium salts. Angew. Chem. Int. Ed. Engl. *55*, 13934–13943.

50. C.E. Song, ed. (2009). Cinchona alkaloids in synthesis and catalysis: ligands, Immobilization and organocatalysis (Wiley-VCH).

51. Tian, S.-K., Chen, Y., Hang, J., Tang, L., McDaid, P., and Deng, L. (2004). Asymmetric organic catalysis with modified cinchona alkaloids. Acc. Chem. Res. *37*, 621–631.

52. Doyle, A.G., and Jacobsen, E.N. (2007). Small-molecule H-bond donors in asymmetric catalysis. Chem. Rev. *107*, 5713–5743.

53. Dirocco, D.A., Ji, Y., Sherer, E.C., Klapars, A., Reibarkh, M., Dropinski, J., Mathew, R., Maligres, P., Hyde, A.M., Limanto, J., et al. (2017). A multifunctional catalyst that stereoselectively assembles prodrugs. Science *356*, 426–430.

54. Mehellou, Y., Rattan, H.S., and Balzarini, J. (2018). The ProTide prodrug technology: from the concept to the clinic. J. Med. Chem. *61*, 2211–2226.

55. Melo, R.P.A., Vale, J.A., Zeni, G., and Menezes, P.H. (2006). Enantioselective allylation of aldehydes promoted by chiral sulfur reagents. Tetrahedron Lett. *47*, 1829–1831.

56. Hiroi, K., Suzuki, Y., Abe, I., and Kawagishi, R. (2000). New chiral sulfoxide ligands possessing a phosphano or phosphanoamino functionality in palladium-catalyzed asymmetric allylic nucleophilic substitution reactions. Tetrahedron *56*, 4701–4710.