

Article

Enantioselective sulfinylation of alcohols and amines by condensation with sulfinates

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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 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 late-stage diversification of important biologically intriguing molecules.

Enantioselective sulfinylation, Asymmetric condensation, Sulfur stereogenicity, Mixed anhydride activation, Organocatalysis

INTRODUCTION

Sulfur stereogenic centers are broadly present in natural products, pharmaceuticals, and agrochemicals (Fig. 1A).¹⁻⁴ The absolute configuration of sulfur stereogenic centers are 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 flusulfenam shows remarkable herbicidal activity against resistant weeds, while its (*S*)-enantiomer is less active and displays pronounced toxicity towards rice plants.⁷ Additionally, these enantioenriched sulfur stereogenic scaffolds are of enormous utilities 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 oxidation¹⁸⁻²⁰ 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 sulfinyl esters and sulfinamides in high er values.

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 stereospecific manner to enable the preparation of diverse chiral *S*-stereogenic analogues.^{33,34} Ellman and Miller 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 and Toru achieved a highly enantioselective sulfinylation of *t*-BuOH with arenesulfinic chloride that was mediated by stoichiometric amounts of cinchona alkaloids.³⁶ These pioneering approaches offer remarkable control over *S*-stereogenicity of the resulting sulfinate ester products. Somewhat unfortunately, the inherent high reactivity of sulfinyl chloride substrates poses 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 (Fig. 1B-1). A recent significant advancement in this area was demonstrated by Tan 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 sulfinate (Fig. 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, that could be facilely converted to chiral sulfinyl products with alcohol nucleophiles. Very recently, Yan and co-workers 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 yet.

Activation of feedstock carboxylic acids through in situ anhydride formation has been extensively explored that allows for a diverse set of enantioselective transformations⁴¹⁻⁴⁴ under the control of Lewis base catalysts.⁴⁵⁻⁴⁹ Motivated by these achievements, we envisioned an activation of sulfinate by in-situ formation of sulfinic mixed anhydrides to enable further catalyst-controlled nucleophilic S-X (X = O, N) bond formations (Fig. 1B-3). Herein, we documented a small-molecule catalytic strategy for highly practical and enantioselective sulfinylation of alcohols and amines with readily available sodium sulfinate. Our approach involves the utilization of a distinct racemic mixed anhydride as the pivotal reactive species. A naturally occurring, cost-effective quinine catalyst without necessitating further structural modifications readily activates the intermediate **B** to form the sulfinylammonium salt intermediate **C/C'**.³⁵⁻³⁷ A dynamic kinetic resolution (DKR) process³⁵⁻³⁷ 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 mechanistic study).⁵⁰⁻⁵² It is noteworthy that the existing challenge on the chemo- and enantioselectivity of amine sulfinylation could be effectively realized 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 represents the first example 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 formation of the mixed anhydride intermediates. Moreover, our approach facilitates the coupling of various bioactive compounds, including androsterone and pregnenolone, as well as established commercial drugs (e.g. benzocaine, procaine), with excellent stereoselectivity, offering an appealing chiral sulfinate functionalization platform which could serve as an alternative strategy for pro-drug modifications.^{53,54}

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 to facilitate 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 (Fig. 2, entries 1-5). Typical Lewis bases **A-D** were highly effective to give the desired sulfinate ester product **4a** in good yields albeit with no observation of enantioselective control (Fig. 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 11-12) and we were delighted to find that anhydride **3c** with *ortho*-disubstitutions provided the desired product **4a** with a high stereoselectivity (95:5 er, entry 12). Alcohols **2b-d** were further explored under the catalytic sulfinyl transfer reaction conditions (entries 13-14). While MeOH afforded the product **4b** in a slightly dropped enantioselectivity, reaction with EtOH provided the product **4c** with a same 95:5 er (entries 13-14). 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 accessed by employment of the quinidine catalyst **F**, as a pseudoenantiomer of quinine catalyst **E**.

Reaction scope

With the reaction condition established (Fig. 2, entry 15), we set out to identify the generality of the catalyst-controlled enantioselective sulfinylation of alcohols (Fig. 3). Sodium aromatic sulfinate **1** possessing a diverse set of groups (CH₃, C₂H₅, Ph, OCH₃, 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 NO₂ 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 sulfinate esters 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 sulfinate esters **4u-4w** with various substitutions were provided in 67-84% yields and high er values. Noteworthy is that *N*-containing heterocycles, such as quinoline and pyridine sulfinate esters, which were previously unrealized,³⁵⁻³⁸ were also feasible to afford the desired products **4x-4aa** that significantly expands the scope and synthetic utility of our method.

We next explored the catalytic approach with respect to an array of nucleophiles (Fig. 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 rapid construction of sulfur stereogenic element to a broad range of naturally occurring alcohol molecules, such as (D)/(L)-menthol (**5i** and *epi*-**5i**), (-)- α -terpineol (**5j**), as well as biologically intriguing alcohols, including androsterone (**5k**) and pregnenolone (**5l**).

Despite elegant studies to catalytically access chiral sulfinate esters, catalyst-controlled method for stereoselective preparation of their sulfinamide analogues continues to be an unresolved challenge. This is likely due to the relatively strong nucleophilicity of the corresponding amine nucleophiles that results in unsuccessful chemo- or stereocontrol as demonstrated in both Tan and Yan's reports.^{37,38} 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 Table S6-7 for details), a broad range of sulfinamides could be successfully prepared in good yields and excellent enantioselectivities. As demonstrated in Fig. 4, *N*-unsubstituted sulfinamide **8a** in 71% yield and 98:2 e.r. was readily afforded by employment of hexamethyldisilazane (HMDS) as the amine nucleophile after mild desilylation upon simple work-up. 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 S6-7 for details). Preparation of the enantiomeric product **8a** could be achieved with quinidine catalyst **F** under the optimal conditions. A diverse set of substituents, including alkyl, Ph, OMe, halogens and NO₂ etc, at the *para*, *meta*, or *ortho* positions of the aryl moiety of sulfinate esters **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 the 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 (e.g., alkyl, halogens, CF₃ 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 99:1 e.r.). In addition, the developed strategy could also realize enantioselective sulfinylation upon other amine nucleophiles, including primary or secondary alkyl amines (**9f-9j**), *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 (Fig. 5A). Additionally, unsaturated sulfoxide (*S*)-**13** could be smoothly afforded upon 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 sulfinamide (*S*)-**16** were directly obtained (Fig. 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., 94:6 e.r. through a two-step sequence. Furthermore, the current enantioselective sulfinyl transfer reactions provide an ideal avenue for post-functionalization of drug molecules by 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 analogues (*S*)-**19-21**, demonstrating the viability of drug diversifications through the catalytic stereoselective sulfinylations (Fig. 5C).

CONCLUSIONS

In summary, we have herein developed an organocatalytic asymmetric condensation approach to access enantiomerically enriched *S*-stereogenic compounds from easily accessible sulfinate esters and alcohols/amines by a simple quinine small-molecule catalyst.

Governed by the catalyst, excellent stereocontrol were 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 on the amine sulfinylation was effectively resolved by employment of a sterically hindered activating leaving group. Furthermore, diversification of an array of complex natural products and drug molecules were readily achieved through the highly efficient stereoselective sulfinylations that 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).

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 structures of compounds (*R*)-**5i** and (*S*)-**8a** reported in this article have been deposited at the Cambridge Crystallographic Data Centre (CCDC) under deposition numbers CCDC: 2291118 and 2288291. 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 optimization of asymmetric sulfinylation of alcohol and amine nucleophiles, [Tables S8-S10](#) and [Scheme S1-S6](#) for mechanistic studies, [Table S11](#) for limited scope of other aliphatic amine nucleophiles, [Figures S5-S18g](#) for NMR spectroscopic data of chiral sulfinyl products, [Figures S190-S274](#) for 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 N₂ atmosphere, to an oven-dried 10.0 mL screw cap vial charged with a magnetic stirring bar was added Cat. **E** (0.02 mmol, 20 mol%), **1** (0.10 mmol, 1.0 equiv.), **3c** (0.1 mmol, 1.1 equiv.), Rb₂CO₃ (0.11 mmol, 1.1 equiv.) and CHCl₃ (1.5 mL). The mixture was stirred for 1 h, then alcohol **2** (0.105 mmol, 1.05 equiv.) was added into the reaction. The resulting solution was kept stirring at 0 °C for 48 h when the substrate was consumed completely. The reaction was quenched with saturated Na₂CO₃ 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 N₂ atmosphere, to an oven-dried 10.0 mL screw cap vial charged with a magnetic stirring bar was added **1** (0.11 mmol, 1.1 equiv.), **3d** (0.1 mmol, 1.0 equiv.) and CHCl₃ (1.5 mL). 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 kept stirring at 0 °C for 48 h, when the substrate was consumed completely. The reaction was quenched with saturated NaHCO₃ 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 N₂ atmosphere, to an oven-dried 10.0 mL screw cap vial charged with a magnetic stirring bar was added sodium *p*-tolylsulfinate (0.11 mmol, 1.1 equiv.), **3d** (0.1 mmol) and CHCl₃ (1.5 mL). 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 kept stirring 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

Full experimental details for the preparation of all new compounds, and their spectroscopic data, can be found in the [supplemental information](#).

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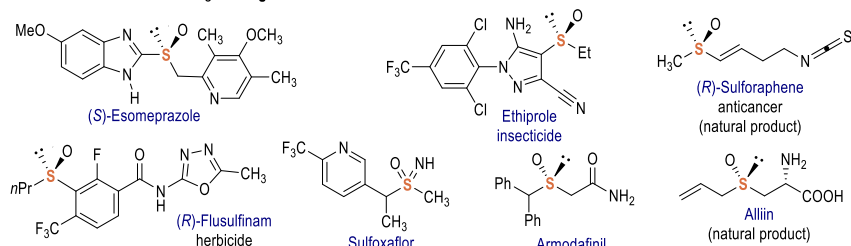
AUTHOR CONTRIBUTIONS

M.L. performed main methodology development, scop evaluation and synthetic application; Y.L., H.L., Q.X., contributed to earlier studies; X.L., 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 financial interests.

A. Bioactive molecules containing stereogenic sulfur center



B. Enantioselective organic catalytic synthesis of sulfinate esters (and sulfenamides) from sulfinic acid derivatives

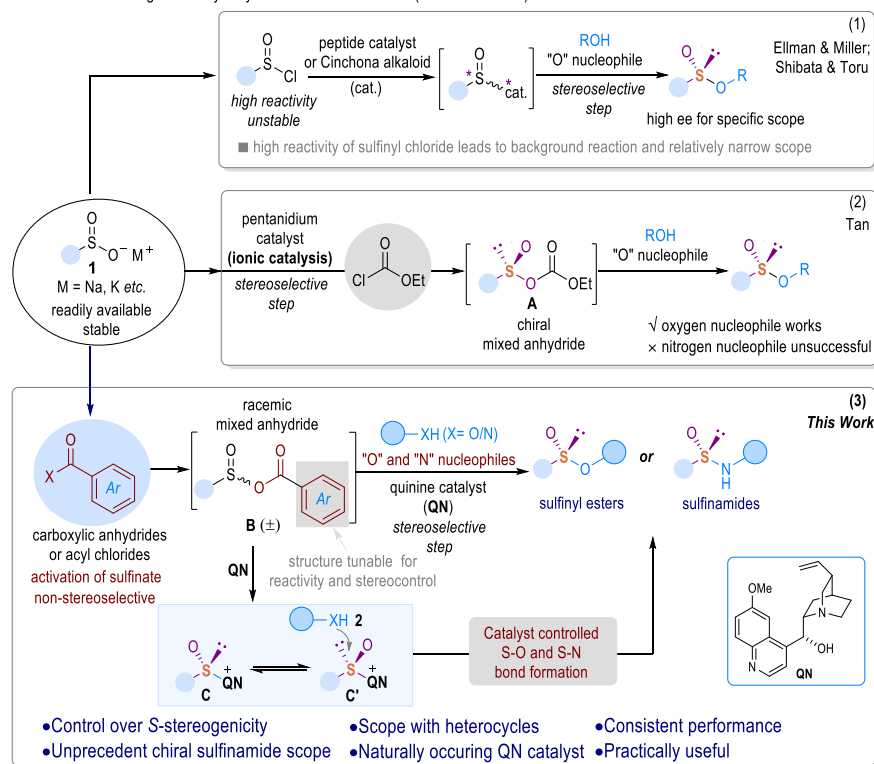


Fig. 1: Organic catalytic enantioselective preparation of S-stereogenic compounds from sulfinic acid derivatives.

A, Bioactive molecules containing stereogenic sulfur centers.

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

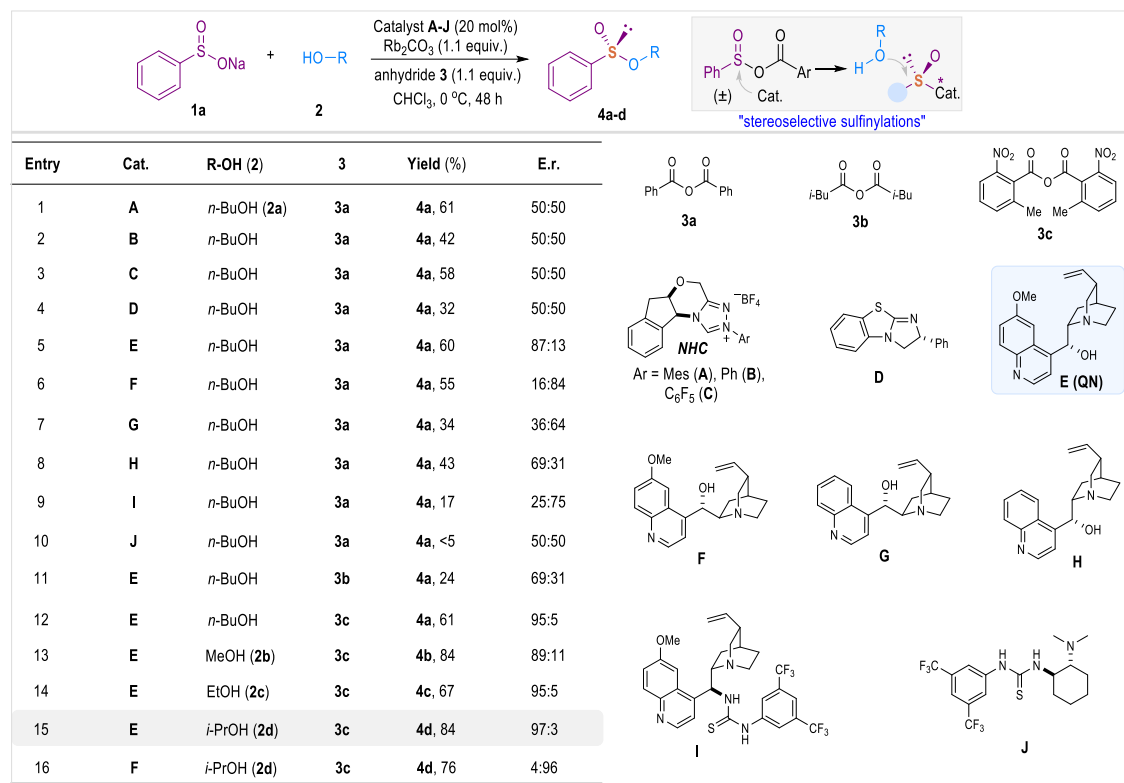


Fig. 2: Development of the enantioselective sulfonylation of alcohols. Reaction conditions: sodium sulfinate **1a** (0.1 mmol, 1.0 equiv.), Cat. **A-J** (20 mol%), **3** (1.1 equiv.), alcohol **2** (1.05 equiv.), Rb_2CO_3 (1.1 equiv.), CHCl_3 (1.5 mL), 0 °C, 48 h. Isolated yields were reported, e.r. values were determined by chiral HPLC analysis.

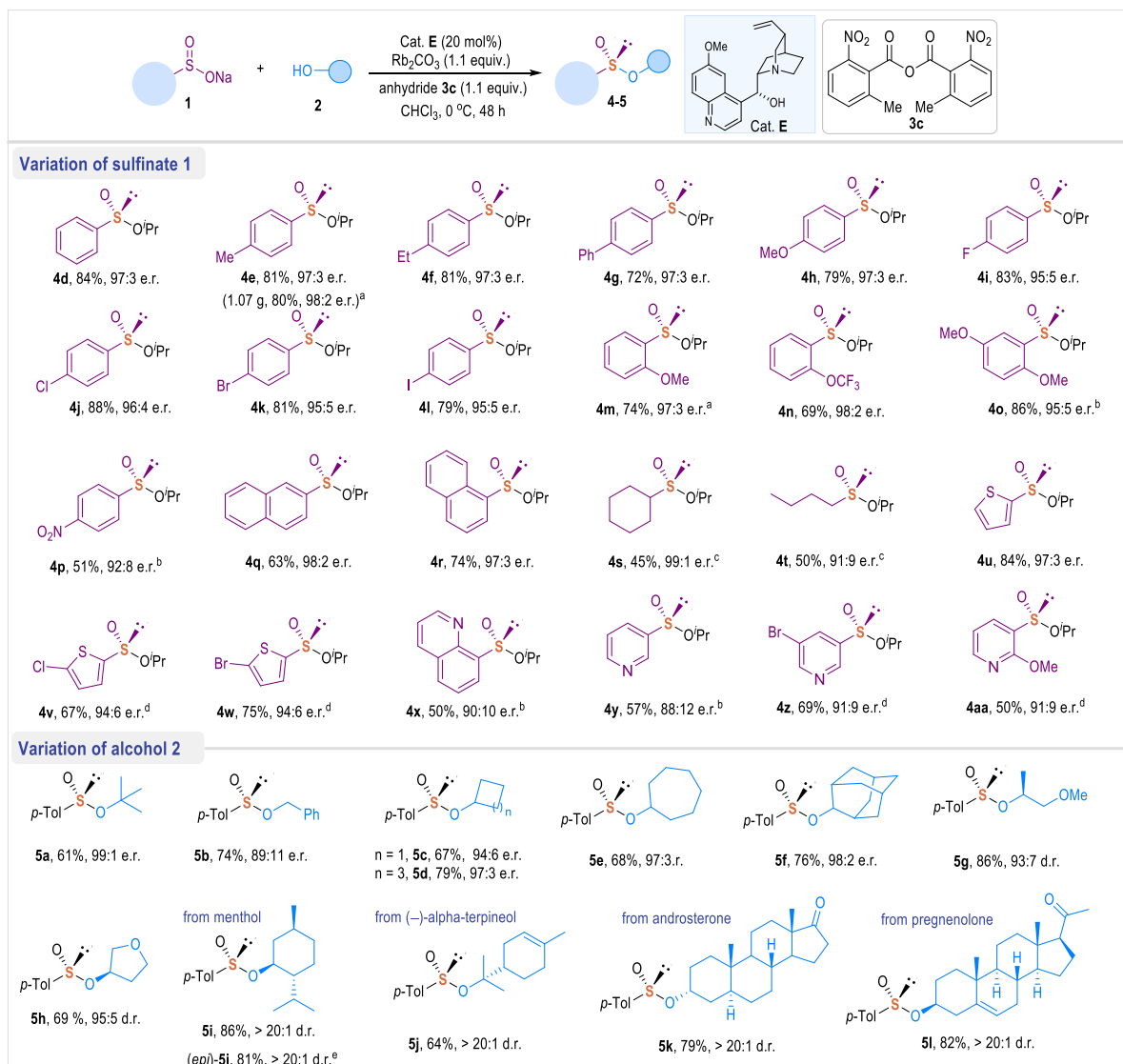


Fig. 3: Enantioselective sulfonylation of alcohols. Reaction conditions: sodium sulfinate **1** (0.1 mmol, 1.0 equiv.), Cat. **E** (20 mol%), **3c** (1.1 equiv.), Rb_2CO_3 (1.1 equiv.), and alcohol **2** (1.05 equiv.) in CHCl_3 (1.5 mL), 0 °C, 48 h. Isolated yields were reported, e.r. values were determined 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), Cat. **E** (10 mol%), and 1.07 g product **4e** was obtained. ^b Reactions at rt instead of 0 °C. ^c Toluene was used. ^d Reactions at 35 °C. ^e (L)-menthol was used.

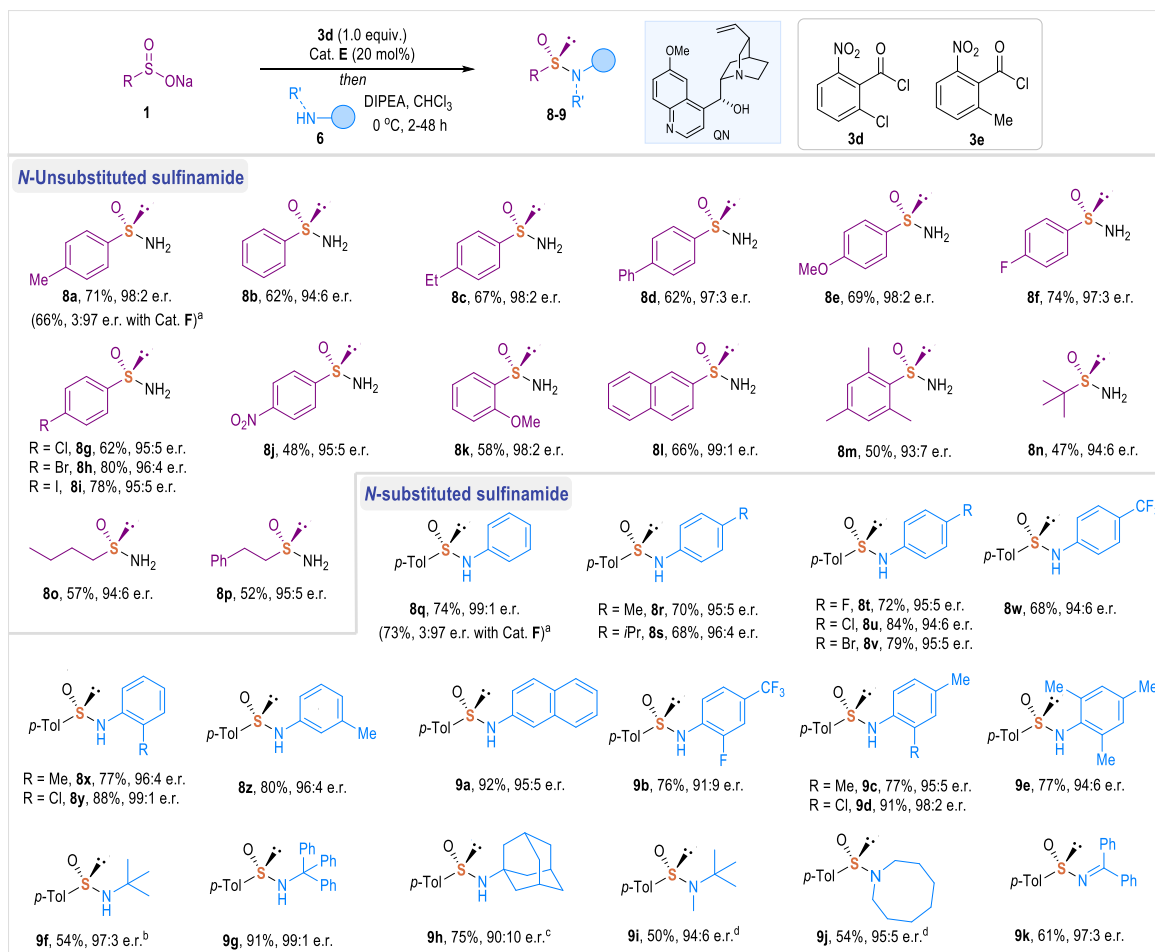


Fig. 4: Enantioselective sulfonylation of amines. Reaction conditions: sodium sulfinate **1** (0.1 mmol, 1.1 equiv.), **3d** (0.1 mmol, 1.0 equiv.), in CHCl₃ (1.5 mL), was stirred at 0 °C for 2 h before addition of Cat. E (20 mol%), DIPEA (1.1-1.3 equiv.), and amine **6** (1.1-1.4 equiv., HMDS was used for products **8a-8p**) at 0 °C for 2-48 h. Isolated yields were reported, e.r. 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.

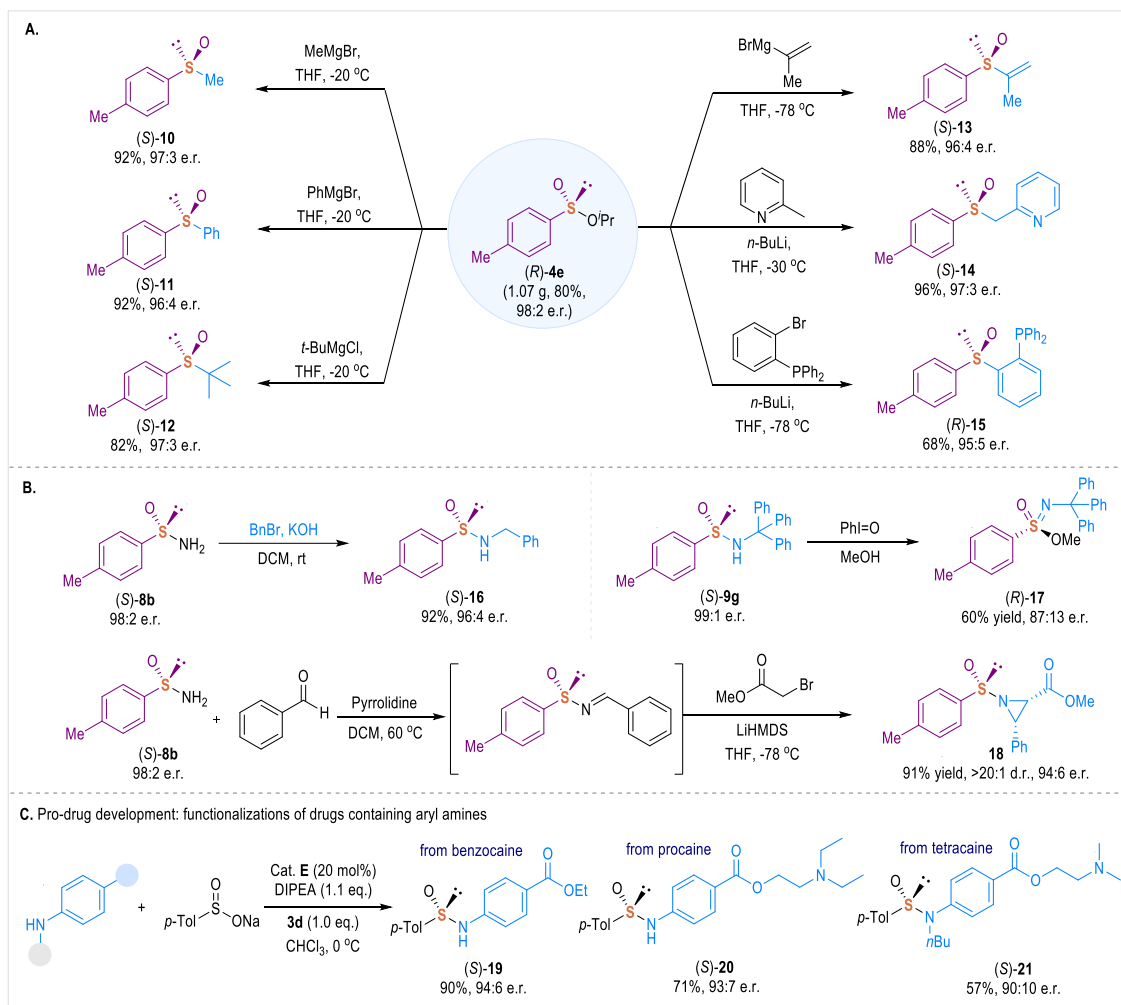


Fig. 5: Synthetic transformations of the chiral sulfinyl compounds and application of the catalytic method in drug diversifications.

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