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Organocatalysis **Hot Paper**

Control Over S(VI) Stereogenicity for the Asymmetric Synthesis of Sulfonimidoyl Derivatives by Isothiourea-Catalyzed Covalent Activation of Sulfur(VI) Atoms

*Benpeng Li+, Junyuan Hu+, Zhengtao Xu, Minghong Liao, Yonggui Robin Chi, and Xingxing Wu**

Abstract: In contrast to the notable advancements focusing on the preparation of optically enriched S(IV) frameworks in recent years, achieving catalyst stereocontrol over S(VI) stereogenicity to generate chiral S(VI) scaffolds remains a largely underexplored challenge. Herein, we document a new activation mode of isothiourea organocatalysis for the highly enantioselective synthesis of S(VI)-chiral sulfonimidates. This method involves the covalent activation of racemic S(VI) sulfonimidoyl chlorides through the formation of a pivotal isothiourea-bound sulfonimidoyl intermediate. The newly formed S(VI)-based isothiourea reactive species further governs the subsequent asymmetric S─O bond formation to afford the chiral sulfonimidate products with high yields and selectivity. Mechanistic studies reveal that the facile inversion of the tetrasubstituted S(VI) stereogenic center assisted by the chiral catalyst is crucial in the dynamic kinetic asymmetric transformation (DYKAT) process. Notably, distinct from the extensively studied isothiourea catalysis focused on the activation of "C"-centered substrates, our method introduces a novel S-atom activation approach, enabling the efficient construction of S(VI) stereogenic centers. Furthermore, the obtained enantioenriched sulfonimidates serve as linchpin intermediates in efficient sulfur-phenolate exchange for rapid access to diverse S(VI)-stereogenic frameworks, including sulfoximines, sulfonimidamides, and their derivatives, with notable antimicrobial activity against various plant pathogens.

Introduction

Catalyst-controlled methodologies for the synthesis of sulfur-stereogenic compounds have garnered considerable attention in past few years driven by their pivotal role in asymmetric synthesis[1–5] and broad applications in drug discovery[6–9] (Figure 1a). In particular, the construction of S(IV)-stereogenic sulfinyl scaffolds, including sulfoxides, sulfinates, sulfinamides, and sulfilimines, has witnessed rapid development, with recent significant contributions from Ellman, Willis, Tan, and others.[10–31] In stark contrast, their S(VI)-analogues, featuring a configurationally stable tetrasubstituted sp^3-hybridized sulfur-center, have remained comparatively underexplored (Figure 1b). Nevertheless, recent advancements have spurred growing interest in the S(VI) scaffolds propelled by their significance in organic synthesis and promising potential as valuable pharmacophores in medicinal and agrochemical applications due to their intriguing biological properties (Figure 1a).[32–35]

In consequence, various approaches have been developed for the stereoselective construction of S(VI)-stereogenic frameworks. These elegant methods generally rely on the stereospecific transformations from optically enriched S(IV) precursors, such as chiral sulfoxides and sulfinamides (Figure 1b, strategy 1).[36–44] For instance, Lopchuk and colleagues developed a chiral sulfonimidoyl fluoride as a bifunctional S(VI) reagent, derived from optically enriched *tert*-butyl sulfinamide, for modular access to a broad range of S(VI)-chiral sulfoximines, sulfonimidoyl fluorides, and sulfonimidamides with high stereoselectivity.[45] Recently, we also realized the preparation of S(VI)-chiral sulfoximines by stereoselective oxidation of the catalytically obtained optically enriched sulfilimine derivatives.[46] Despite these advances, achieving catalyst-controlled strategies for the stereoselective construction of S(VI)-stereogenic centers remains a formidable challenge. To date, only a handful approaches have been developed, primarily relying on the asymmetric desymmetrization of preformed symmetrical S(VI) precursors, albeit with restricted structural diversity (Figure 1b, strategy 2).[40,47–56] Very recently, Li/Tang

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[*] B. Li+, Z. Xu, M. Liao, Prof. Dr. Y. R. Chi, Prof. Dr. X. Wu
State Key Laboratory of Green Pesticide; Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Center for R&D of Fine Chemicals of Guizhou University, Huaxi District, Guiyang 550025, China
E-mail: wuxx@gzu.edu.cn

B. Li+
School of Life and Health Science, Kaili University, Kaili 556011, China

J. Hu+
Institute of Advanced Synthesis, School of Chemistry and Molecular Engineering, Jiangsu National Synergetic Innovation Center for Advanced Materials, Nanjing Tech University, Nanjing 211816, China

Prof. Dr. Y. R. Chi
School of chemistry, chemical engineering, and biotechnology, Nanyang Technological University, Singapore 637371, Singapore

[+] Both authors contributed equally to this work.

Additional supporting information can be found online in the Supporting Information section

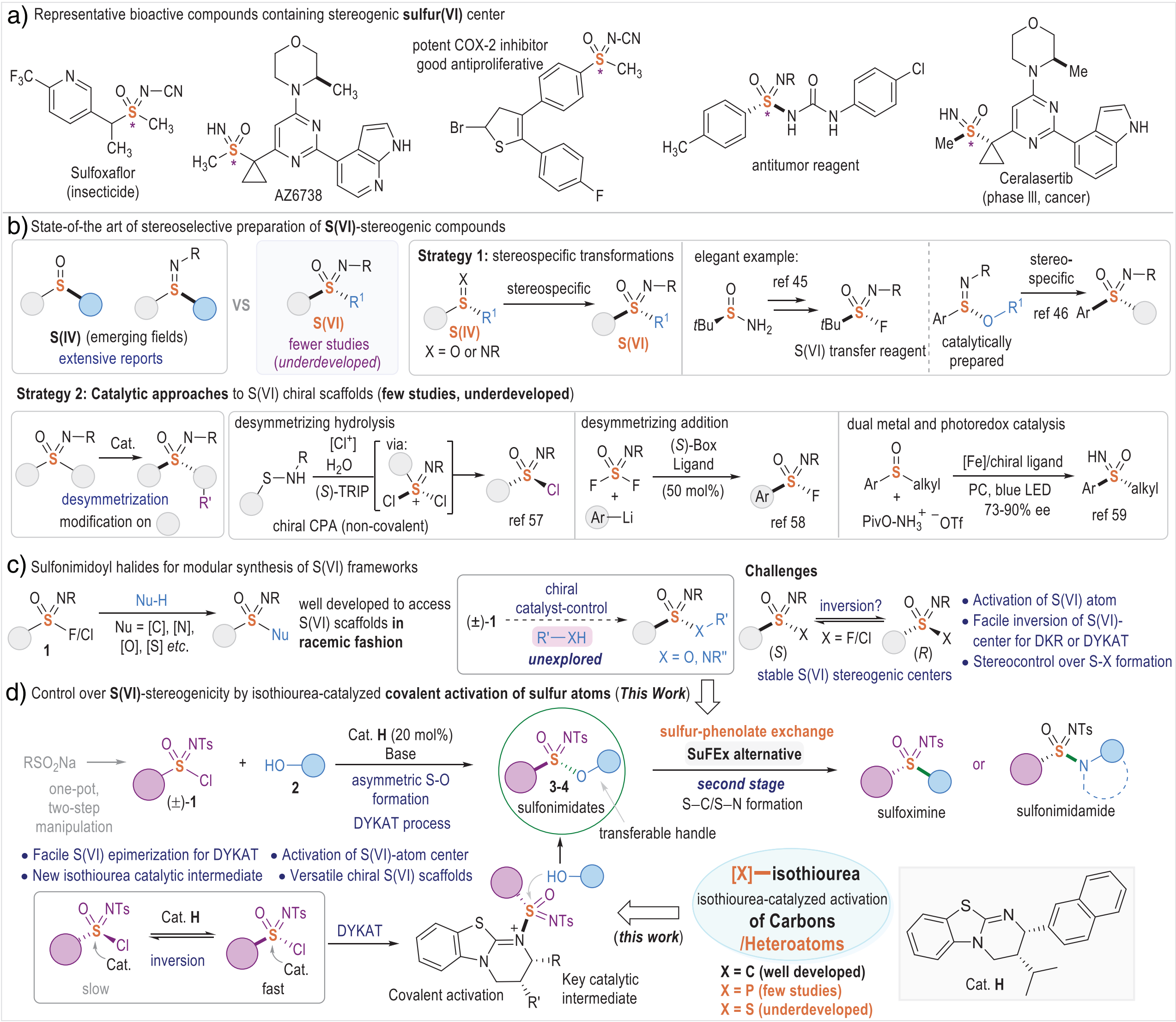


Figure 1. Catalyst-controlled strategies for chiral sulfinate synthesis from sulfinic acid derivatives. a) Bioactive molecules containing sulfur(VI) stereogenic centers. b) Stereoselective preparation of S(VI)-stereogenic compounds. c) Racemic sulfonimidate synthesis from sulfonimidoyl halides. d) Our proposed isothiourea-catalyzed covalent activation of S(VI) atoms for asymmetric synthesis of sulfonimidoyl derivatives (this work). Ts = *p*-toluenesulfonyl; DYKAT = dynamic kinetic asymmetric transformation; SuFEx = sulfur(VI) fluoride exchange.

reported elegant enantioselective synthesis of S(VI)-chiral sulfonimidoyl chlorides from S(II)-sulfenamide precursors.[57] Their method uses chiral phosphoric acid as the catalyst by providing the chiral ion pair to control the enantioselective desymmetrizing hydrolysis of in situ formed symmetric aza-dichlorosulfonium species. Gao and coworkers achieved the preparation of diverse sulfonimidoyl fluorides through desymmetrizing iminosulfuroxydifluorides by organolithium reagents in combination with a substoichiometric amount of chiral bis-oxazoline ligand.[58] Meanwhile, Wang/Dang et al. achieved a stereoselective imination of sulfoxides through a metal-catalyzed dynamic kinetic resolution process (provides sulfoximines only) under photoredox conditions.[59]

Sulfonimidoyl chlorides and fluorides, the aza-analogues of sulfonyl halides, serve as versatile electrophiles for the construction of diverse S(VI) derivatives via SN2 displacement of the halide by various nucleophiles (Figure 1c).[57–60] Notably, the sulfur(VI) fluoride exchange (SuFEx) strategy as pioneered by Sharpless has enabled the highly effective synthesis of S(VI) motifs.[61] While stereoselective synthetic strategies have been established, they predominantly rely on the use of stoichiometric amounts of chiral sulfonimidoyl halide substrates **1**.[59–61] Achieving a direct, catalyst-controlled asymmetric S-heteroatom (e.g., O) bond formation from racemic sulfonimidoyl halides continues to be highly challenging, yet it holds great potential for the rapid synthesis of chiral sulfonimidate esters as a significant class of sulfonimidoyl derivatives, which could serve as linchpin intermediates for the versatile preparation of S(VI)-stereogenic scaffolds and bioisosteric isomers of sulfoximines with potential applications in drug discovery.[60–66] Several key obstacles must be addressed to realize this catalytic approach with high yield and stereoselectivity, including the development of new activation of S(VI) atom and the achievement of highly effective catalyst-induced stereocontrol.[65–66] In particular, enabling the facile inversion at the typically configurationally stable tetrasubstituted S(VI) stereogenic center is crucial for facilitating dynamic kinetic resolution (DKR) or dynamic kinetic asymmetric transformation (DYKAT) process, thereby surpassing the inherent 50% yield limitation associated with classical kinetic resolution.[67]

Isothiourea represents a privileged class of organocatalysts for preparation of a broad spectrum of chiral molecular frameworks with exceptional stereocontrol. These catalysts have demonstrated remarkable efficacy in covalent activation of various carbonyl compounds, such as carboxylic acids (via in situ anhydride formation) and their derivatives, through key isothiourea-derived reactive intermediates, such as acyl ammoniums and ammonium enolates.[68–73] In contrast to these carbon-atom-centered catalyst-bound intermediates, the exploration of their heteroatom-centered analogues remains largely overlooked.[74,75]

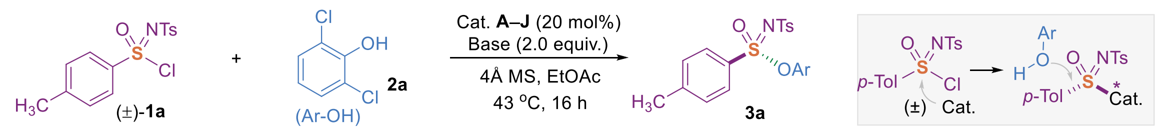
Building upon our longstanding research interests in the catalytic construction of heteroatom- (e.g., N, S, and P) stereogenicity,[46,76–78] we envisioned to exploit the isothiourea-bound sulfonimidoyl intermediate through covalent activation of S(VI) atoms to achieve stereocontrolled construction of S(VI)-stereogenic centers (Figure 1d). Herein, we disclose a highly enantioselective preparation of S(VI)-chiral sulfonimidates between bench-stable, racemic sulfonimidoyl chloride **1** and phenol **2**. A DYKAT process[79–81] enabled by the chiral isothiourea catalyst effectively governs the stereoselective S─O bond formation, affording the chiral sulfonimidate products **3** and **4** with high yields and enantioselectivity. Notably, the resulting enantioenriched sulfonimidates, which is difficult to realize with the current catalytic approaches,[47–59] serve as versatile synthetic linchpins in efficient sulfur-phenolate exchange (as SuFEx alternative),[62] to provide a synthetic platform for rapid access to a diverse range of S(VI)-stereogenic frameworks, including sulfoximines, sulfonimidamides, and their derivatives. Notably, bioassay studies reveal that these S(VI)-chiral products demonstrate broad spectrum of antimicrobial activity against various plant pathogens with potential applications for the development of novel agrochemical agents.

Results and Discussion

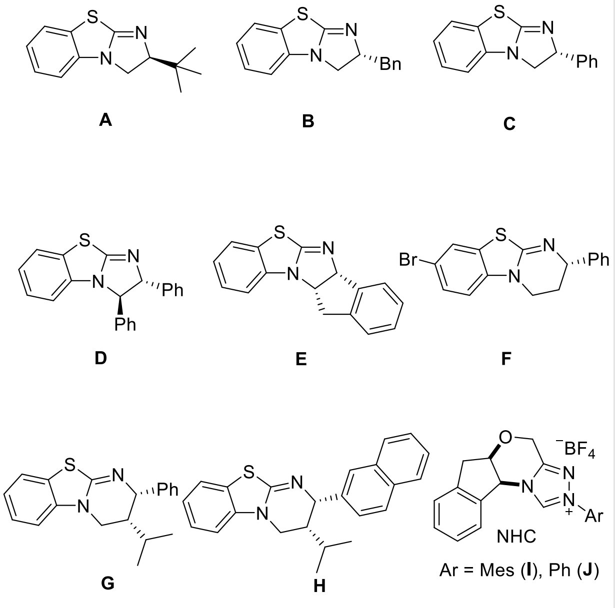
We commenced our study on the stereoselective synthesis of S(VI)-chiral sulfonimidates by selecting readily accessible and stable sulfonimidoyl chloride **1a** and phenol **2a** as the primary starting materials. We envisioned that the resulting isothiourea-derived sulfonimidoyl ammonium intermediate would facilitate subsequent S─O bond formation while governing stereocontrol over the S(VI) stereogenic center to give the chiral sulfonimidate product **3a**. A range of isothiourea catalysts were examined to activate the sulfonimidoyl substrate **1a**. While isothioureas **A**–**E** featuring fused five-membered scaffolds afforded the product **3a** with 20%–65% yields and modest enantioselectivity (55:45–80:20 er) (Scheme 1, entries 1–6), the use of catalysts **F**–**H** with six-membered fused rings led to the sulfonimidate **3a** with remarkably high enantioselectivity (entries 7–9). In particular, the reaction with 2-naphthyl substituted catalyst **H** delivered the product **3a** with superior selectivity (95:5 er) and 53% yield (entry 9).[82] Additionally, *N*-heterocyclic carbenes **I**–**J** as representative Lewis base catalysts[83–85] failed to give the desired product **3a**, resulting in a complex mixture (entries 10). To improve the modest yield, we evaluated the effects of an array of bases (entries 11–13), reaction temperature and solvents (see Supporting Information for details), by reactions in the presence of catalyst **H**. Satisfyingly, we found that reactions conducted with $KHCO_3$ or CH_3COONa afforded the product **3a** in improved yields, albeit with reduced enantioselectivity (entries 11–12). Finally, by employment of the mixed base of $NaHCO_3/CH_3COONa$ (entry 15), **3a** was furnished in an acceptable yield (76%) and high enantioselectivity (95:5 er).

Upon establishing the optimal reaction conditions (Scheme 1, entry 15), we proceeded to explore the scope of the catalyst-controlled enantioselective synthesis of sulfonimidate esters **3** and **4** (Scheme 2). Initially, we examined sulfonimidoyl chloride **1** with various *para*-substituents on the aromatic ring, including Me, Et, *t*Bu, Ph, OMe, halogens (F, Br, I), and CF_3, OCF_3 groups. These substrates efficiently gave rise to the sulfonimidate products **3a**–**3j** with 65%–86% yields and high enantioselectivity ranging from 91:9 to 97:3 er. Substituents featured at the *meta* or *ortho* sites of the phenyl ring were also well tolerated, affording **3k**–**3o** with 65%–76% yields, wherein the products with *ortho*-substitutions (**3k**–**3m**) were obtained in slightly higher enantioselectivity than their analogues bearing *meta*-substituents (**3n**–**3o**). Notably, 1-naphthyl and the sterically hindered mesityl-derived substrates underwent smooth conversion, delivering S(VI)-chiral products **3p**–**3q** with high selectivity. Next, we investigated the influence of heteroaromatic substrates **1** on the stereoselective control. Tetrahydrobenzofuran- and benzothiophene-derived sulfonimidates **3r**–**3s** were obtained in high yields and selectivity. Furthermore, the effect of varying sulfonyl groups attached to the nitrogen atom was examined. A range of substituents, including *ortho*-Cl, *para*-Et, and 2-naphthyl sulfonyl were compatible with the reaction, furnishing products **3t**–**3v** with high selectivity under the optimized conditions. Substrates **1** with other N-protecting groups (e.g., Boc, Bz, etc.) failed to give the corresponding sulfonimidate products with satisfactory results (see Supporting Information for details). Notably, the reaction with aliphatic substrate failed to afford the corresponding product **3w**–**3x**, resulting in a complex mixture, presumably owing to the fast decomposition of the alkylsulfonimidoyl chloride **1** under the reaction conditions via aza-sulfene formation (see Supporting Information for details). Moreover, the absolute configuration of the obtained S(VI) chiral products was established as (*S*) by analogy to product **3a**, which was determined through X-ray crystallographic analysis.[82]

We then evaluated the catalytic synthesis with respect to a diverse set of phenol nucleophiles (Scheme 2). Simple



Entry	Cat.	Base	Yield of 3a (%)[b]	E.r.[c]
1	None	$NaHCO_3$	6	50:50
2	**A**	$NaHCO_3$	21	43:57
3	**B**	$NaHCO_3$	57	70:30
4	**C**	$NaHCO_3$	65	80:20
5	**D**	$NaHCO_3$	60	70:30
6	**E**	$NaHCO_3$	32	55:45
7	**F**	$NaHCO_3$	20	94:6
8	**G**	$NaHCO_3$	52	90:10
9	**H**	$NaHCO_3$	53	95:5
10	**I-J**	$NaHCO_3$	-	-
11	**H**	$KHCO_3$	81	91:9
12	**H**	CH_3COONa	77	86:14
13	**H**	DIPEA	25	95:5
14	**H**	$NaHCO_3/KHCO_3$	77	94:6
15	**H**	**$NaHCO_3/CH_3COONa$**	**76**	**95:5**

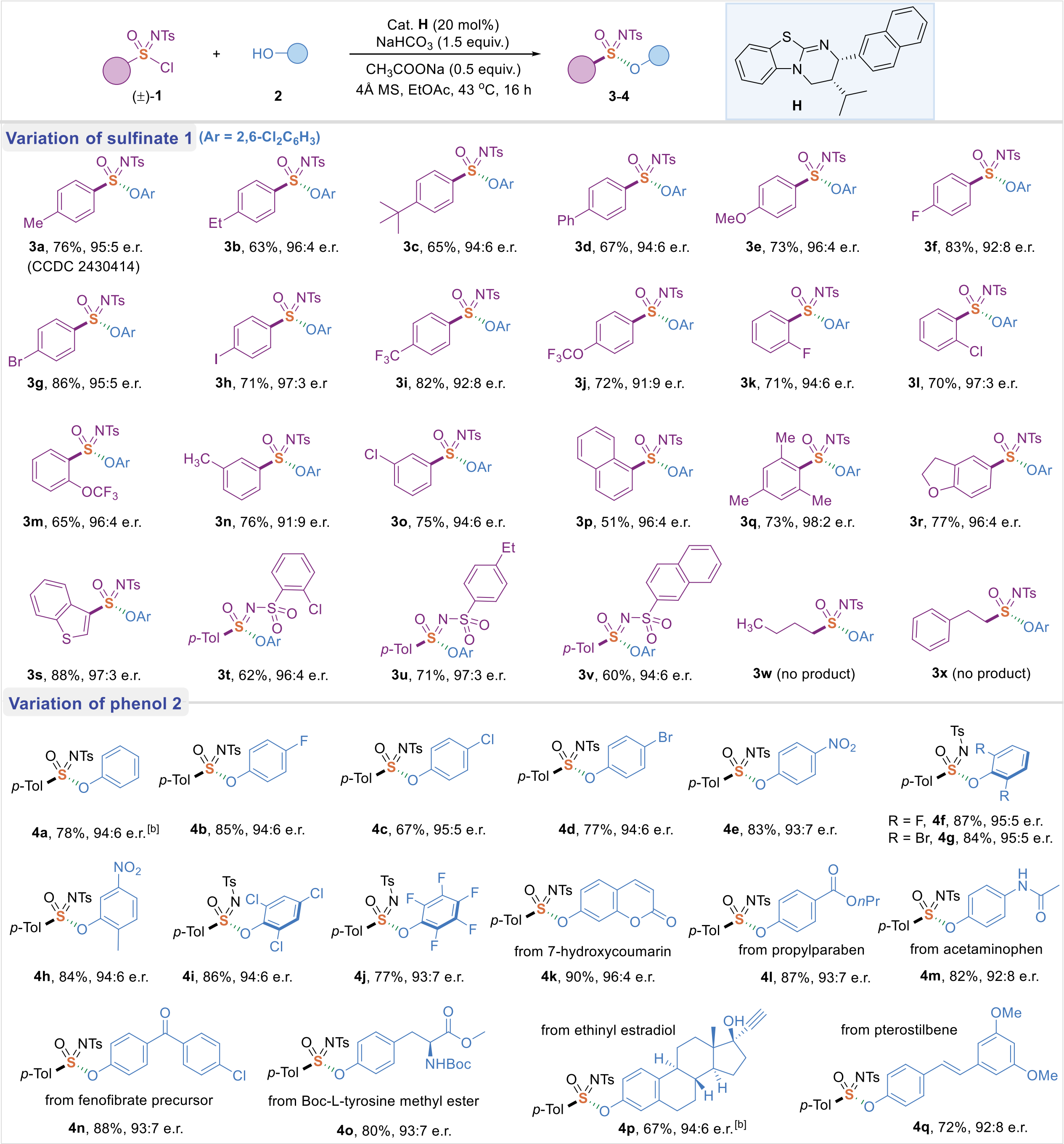


Scheme 1. Development of the enantioselective synthesis of sulfonimidate **3a**.[a] [a] Reaction conditions: **1a** (0.1 mmol, 1.0 equiv.), Cat. **A–J** (20 mol%), phenol **2a** (0.13 mmol, 1.3 equiv.), base (2.0 equiv.), ethyl acetate (EtOAc, 1.5 mL), 4 Å MS (120 mg), 43 °C, 16 h. [b] Isolated yields were reported. [c] E.r. values were determined by chiral HPLC analysis. See Supporting Information for details.

phenol reacted efficiently with sulfonimidoyl chloride **1a**, affording the corresponding S–O coupling product **4a** in 78% yield and 94:6 er under standard conditions. We then examined the scope of phenols with various substitutions. Substrates bearing halogens (F, Cl, Br) and electron-deficient NO_2 group at the *para*-site of the aromatic ring underwent smooth conversion, delivering products **4b–4e** with good enantioselectivity. Notably, phenols featuring di-, tri-, and penta-substituents proved highly compatible, enabling the stereoselective construction of sulfonimidates **4f–4j** with good results. Next, we explored the reactivity of an array of naturally occurring and biologically intriguing phenol molecules, aiming to establish a versatile stereoselective aza-sulfonyl modification platform for biologically relevant compounds. This was exemplified by the successful functionalization of 7-hydroxycoumarin (**4k**), propylparaben (**4l**), acetaminophen (**4m**), a fenofibrate precursor (**4n**), Boc-L-tyrosine methyl ester (**4o**), ethinyl estradiol (**4p**), and pterostilbene (**4q**), which readily formed their corresponding sulfonimidate derivatives with high yields and exceptional stereoselectivity. Notably, alcohol nucleophiles were not compatible with the developed method, as a large excess of the starting material **1a** remained after the reaction, accompanied by the formation of a distinct S(IV) sulfinimidate species (see Supporting Information for details).

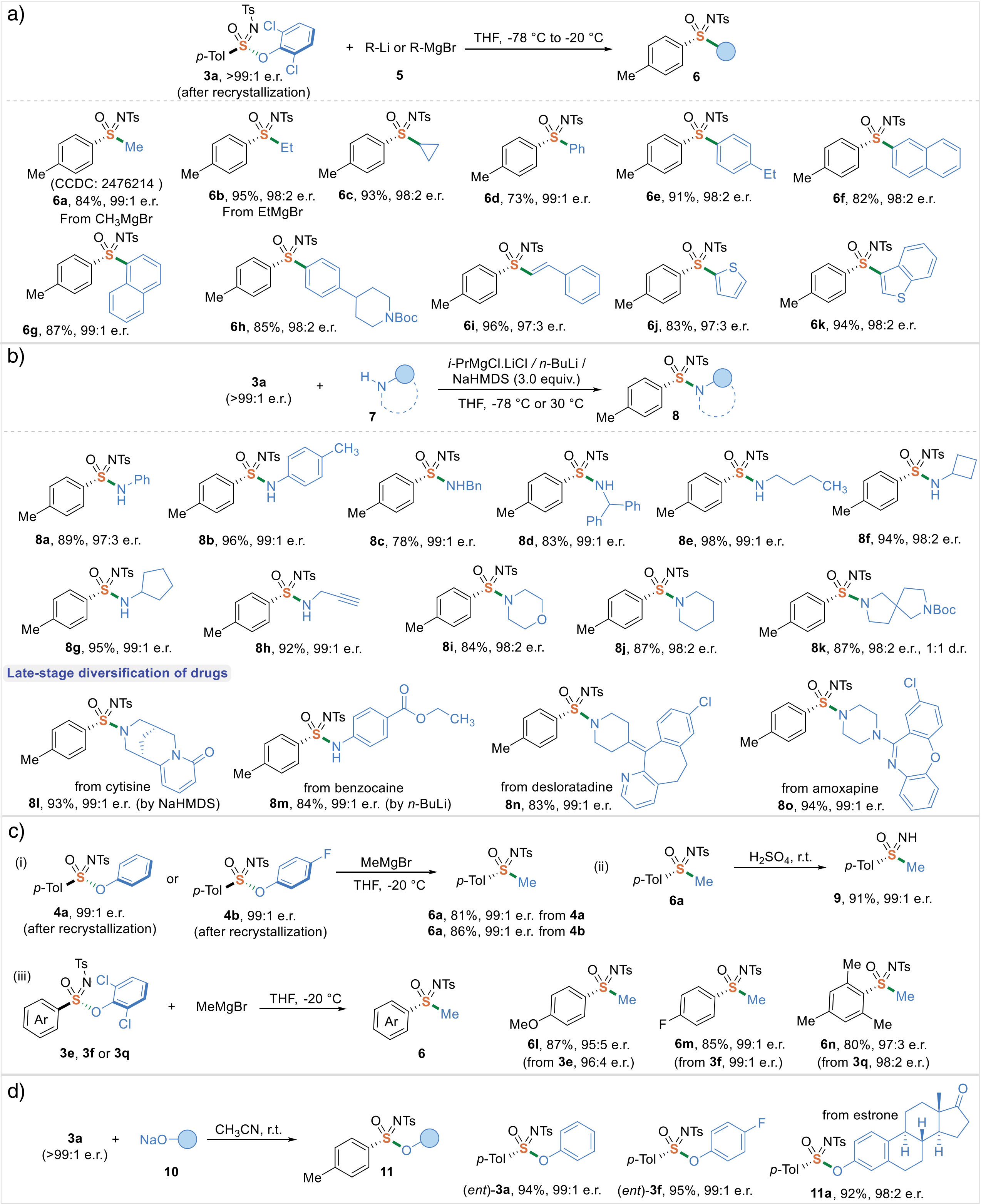
Furthermore, the sulfonimidate **3** and **4**, featuring an OAr moiety as the leaving group, holds significant synthetic value as a versatile linchpin building block in sulfur-phenolate exchange (as a SuFEx alternative) for the synthesis of structurally diverse S(VI) scaffolds (Scheme 3a).[62,86] To explore its utility, we first investigated nucleophilic displacement using various organometallic reagents to generate a library of chiral sulfoximines **6**. Remarkably, the addition of Me- and Et-derived Grignard reagents and cyclopropyl lithium to **3a** in THF proceeded with high stereospecificity, affording sulfoximines **6a–6c** without compromising the enantiomeric ratios. Aromatic nucleophiles with varying substituents also reacted efficiently with **3a**, yielding the corresponding S(VI)-chiral products **6d–6h** with 73%–91% yields and excellent stereoselectivity. Notably, the introduction of unsaturated moieties was achieved through addition of phenyl ethenyl lithium, enabling the smooth synthesis of sulfoximine **6i** bearing double bonds. Additionally, heteroaromatic sulfoximines were readily accessible with this synthetic strategy, as demonstrated by products **6j** and **6k** obtained in 83% yield, 97:3 er and 94% yield, 98:2 er, respectively. These S(VI) chiral products **6** were established as (*S*) by analogy to product **6a** as determined through X-ray crystallographic analysis.[82]

Nitrogen-based nucleophiles also proved effective for enantiospecific displacement, providing a rapid and versatile synthetic platform for accessing chiral sulfonimidamides **8** (Scheme 3b).[87,88] Direct treatment of **3a** with various aryl amines upon deprotonation with *i*-PrMgCl·LiCl efficiently yielded the N-aryl S(VI)-chiral products **8a–8b**. Similarly,

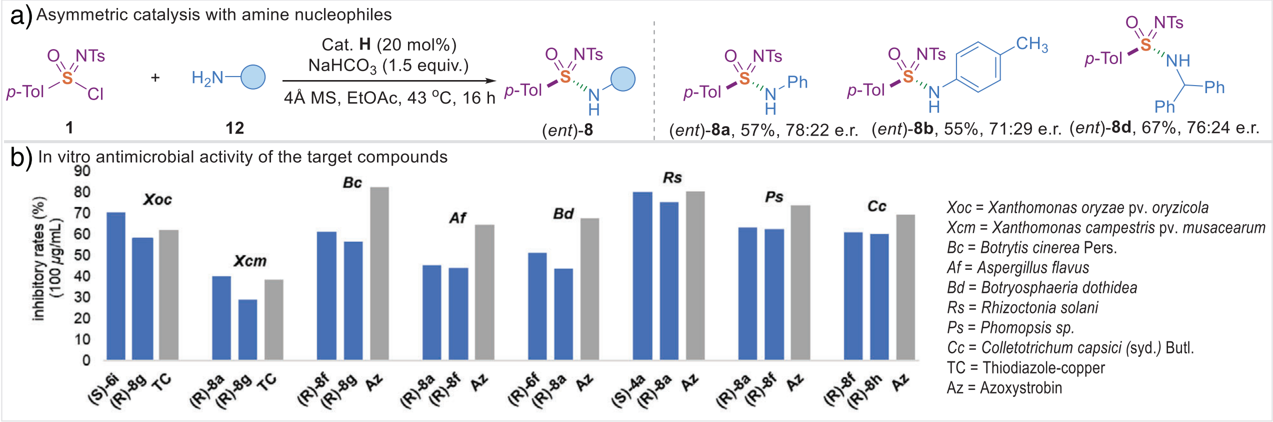


Scheme 2. Scope of the enantioselective synthesis of sulfonimidates **3–4**.[a] [a] Reaction conditions: **1** (0.1 mmol, 1.0 equiv.), **2** (0.13 mmol, 1.3 equiv.), cat. **H** (20 mol%), NaHCO$_3$ (0.15 mmol, 1.5 equiv.), CH$_3$COONa (0.05 mmol, 0.5 equiv.), 4 Å MS (120 mg) in EtOAc (1.5 mL), 43 °C, 16 h. Isolated yields were reported, e.r. values were determined by chiral HPLC analysis. [b] KHCO$_3$ (0.2 mmol, 2.0 equiv.) was used. See Supporting Information for details.

reactions with aliphatic amines in the presence of *i*-PrMgCl·LiCl furnished chiral products **8c–8g** in good yields and excellent stereospecificity. Notably, propargyl amine was well tolerated, affording the corresponding sulfonimidamide **8h** with 92% yield and 99:1 er, which features a triple bond as readily transferrable handle for further elaboration. The nucleophilic substitution proceeded smoothly with various N-containing heterocycles, including morpholine, piperidine and spirocyclic amines, affording chiral products **8i–8k** with 84%–87% yields and almost consistently excellent er values. Encouraged by the broad applicability of the catalytically generated sulfonimidamides, we further explored their post-functionalization in biologically relevant natural products and commercial drugs by introducing the S(VI)-chiral sulfonimidamide motif as a unique pharmacophore. A range of structurally complex molecules, including the



Scheme 3. Sulfur(VI)-phenolate exchange of the sulfonimidates. a) Preparation of S(VI)-chiral sulfoximines **6**. b) Stereoselective synthesis of chiral sulfonimidamides **8**. c) Scope examination of the sulfonimidate products **3** and **4**. d) Esterification of **3a** with various phenols. See Supporting Information for details.



Scheme 4. Catalytic synthesis of sulfonimidamides with amine nucleophiles a) and bioassay studies b).

natural alkaloids cytisine (**8l**) and amine-containing drugs such as benzocaine (**8m**), desloratadine (**8n**), and amoxapine (**8o**), were readily modified to their corresponding optically enriched sulfonimidamide analogs. This transformation establishes a general synthetic platform for sulfonimidamide modification of structurally intricate compounds, offering significant potential for drug discovery. Next, the scope of the sulfur(VI)-phenolate exchange reaction of various sulfonimidates was briefly examined. Products **3** with other phenol moieties (**4a** or **4b**) were also compatible to the stereospecific transformation, delivering product **6a** without erosion of er values (Scheme 3c(i)). Notably, the N-Ts group could be readily cleaved to afford the N-free sulfoximine product **9** bearing a transferable N─H handle for further elaboration (Scheme 3c(ii)). Furthermore, S(VI) chiral products **3** bearing electron-donating/-withdrawing groups on the aromatic rings, or featuring sterically congested mesityl group were suitable to give their corresponding products **6l**–**6m**, **6n** with good yields and high stereospecificity (Scheme 3c(iii)).

Additionally, the obtained sulfonimidates readily underwent direct phenolate exchange with sodium phenolate in CH_3CN at room temperature (Scheme 3d).[62,89] Noteworthy is that these mild conditions provided a convenient synthetic approach to access the enantiomeric chiral product **3** by nucleophilic addition with inversion of the S(VI)-stereocenter. For instance, (*ent*)-**3a** and (*ent*)-**3f** were obtained in 94% and 95% yield, respectively, without erosion of enantioselectivity. This method also enabled the late-stage functionalization of complex molecules, as demonstrated by the preparation of estrone-derived sulfonimidate **11a**.

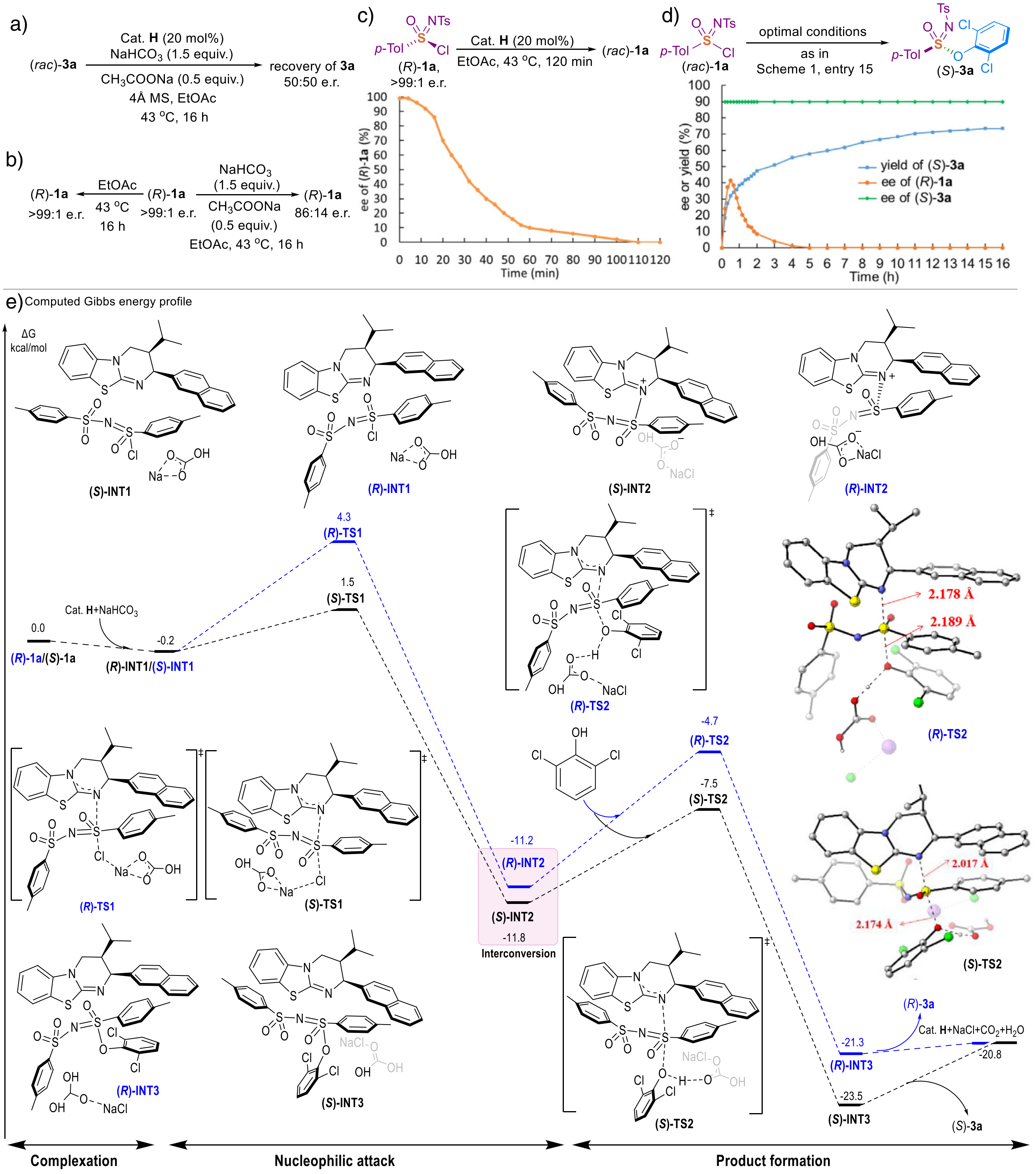
Encouraged by the highly enantioselective preparation of S(VI)-sulfonimidates through asymmetric S─O bond formation, we conducted preliminary studies to achieve the catalytic stereocontrol over the more challenging S─N bond construction, which, to our knowledge, has not been achieved yet. As illustrated in Scheme 4a, a slightly modified reaction condition successfully furnished the corresponding sulfonimidamides (*ent*)-**8a**, -**8b**, and -**8d**, albeit with modest yields and stereoselectivity, likely due to the influence of the noncatalytic background reactions.

Bioassay Studies

Intrigued by the diverse biological activities of chiral S(VI) compounds, we conducted preliminary studies on the antimicrobial activities of the obtained chiral S(VI) products to search for potent antimicrobial agrochemicals for plant protection.[90,91] For this purpose, we assessed the inhibitory activity of these compounds at a concentration of 100 μg mL^{-1} against various common plant pathogens. As shown in Scheme 4b, the chiral S(VI) products exhibited significant antibacterial activity. Notably, compound **6i** showed a superior inhibition rate of 70.8% against *Xoc* than the positive control with the commercial bactericide TC (62.0%). Additionally, the S(VI) products exhibited broad-spectrum inhibition against various plant fungal pathogens, including *Bc*, *Af*, *Rs*, *Bd*, and others. For instance, compound **4a** (80.2%) showed significant inhibition rate against *Rs*, comparable to the commercial fungicide azoxystrobin. Moreover, the configuration of the products shows interesting impact on their inhibitive activity comparing to their racemates (See Tables S5–S7 for details). These findings highlight the promise of our compounds as novel lead structures for the development of effective bactericides and fungicides.

Mechanistic Studies

Control experiments were performed to gain insights into the catalytic stereoselective synthesis of S(VI)-chiral sulfonimidates, as shown in Scheme 5a. The recovery of **3a** in 50:50 er from a control study using (*rac*)-**3a** under the optimal conditions ruled out the possibility that racemic **3a** was initially formed and subsequently isomerized into the optically enriched **3a** under the impact of chiral catalyst **H**. Next, enantiomerization studies by employment of enantioenriched starting material (*R*)-**1a** were investigated (Scheme 5b). Direct stirring of (*R*)-**1a** in the solvent at 43 °C for 16 h did not change the enantioselectivity (>99:1 er). Intriguingly, a decrease in the er values of **1a** was observed when (*R*)-**1a** was subjected to reaction with the mixed base ($NaHCO_3/CH_3COONa$) in ethyl acetate at 43 °C for 16 h



Scheme 5. Preliminary mechanistic studies. a) Investigation of the interaction of *rac*-**3a** with catalyst **H**. b) Evaluation of the enantiomerization of optically pure (*R*)-**1a** with/without base in the ethyl acetate (EtOAc). c) Time-course study of the enantioselectivity of (*R*)-**1a** with catalyst **H**. d) Time-course study of the enantioselectivity of remaining (*R*)-**1a** and generated product (*S*)-**3a**. e) Computed Gibbs energy profile for the formation of (*R*)-**3a** and (*S*)-**3a**. See Figures S11–S13 for all DFT-optimized structures.

(86:14 er). These results suggest that sulfonimidoyl chloride **1a** undergoes relatively slow racemization process at the reaction temperature. In contrast, the presence of isothiourea catalyst **H** significantly accelerated the racemization of the (*R*)-**1a** in ethyl acetate at 43 °C. As evidenced by the time-course study of the enantioselectivity of (*R*)-**1a** (Scheme 5c), complete racemization of the enantioenriched (*R*)-**1a** occurred within 2 h, indicating that a catalyst-assisted dynamic kinetic resolution (dynamic kinetic asymmetric transformation)[79–81] should be involved in the catalytic reaction to account for the obtained high yields and enantioselectivity. Concurrently, the time-course experiment further showed that the product (*S*)-**3a** was obtained in consistently high selectivity (95:5 er) throughout the reaction (Scheme 5d). Interestingly, a rapid enantioenrichment of the remaining starting material (*R*)-**1a** was observed, wherein a high er of 71:29 was obtained when the reaction yield reached 32% at 30 min, which was followed by significant racemization as the reaction progressed. These findings indicate that (*S*)-**1a** underwent a notably faster reaction to form the desired product (*S*)-**3a**, while (*R*)-**1a** was readily converted to its enantiomer **1a** under the influence of catalyst **H**, ultimately affording product (*S*)-**3a** in high yields via an efficient DYKAT process.

To understand the full catalytic cycle, density functional theory (DFT) calculations were performed at the PCM (ethylethanoate)/M06-2X-D3/6-311G (d, p) level by using the Gaussian 16 program,[92] and the computed Gibbs energy profile was depicted in Scheme 5e. Initially, (*R*)-**1a** and (*S*)-**1a** form complexes with the Cat. **H** and $NaHCO_3$, resulting in (*R*)-**INT1** and (*S*)-**INT1**, respectively. Nucleophilic attack on the S-chiral center of (*R*)-**INT1** and (*S*)-**INT1** by Cat. **H** occurs via transition states (*R*)-**TS1** and (*S*)-**TS1,** wherein the sodium cation of $NaHCO_3$ facilitates the departure of the Cl atom through ionic interactions to form (*R*)-**INT2** and (*S*)-**INT2**. The generation of the key isothiourea-bound sulfonimidoyl intermediate was supported by HRMS detection (Figures S2–S4). Subsequent nucleophilic attack by 2,6-dichlorophenol (**2a**) via transition states (*R*)-**TS2** and (*S*)-**TS2** and release of Cat. **H** would finally afford the desired product **3a**. It is noteworthy that (*R*)-**TS2** and (*S*)-**TS2** require higher activation energy than (*R*)-**TS1** and (*S*)-**TS1**, making them the turnover-limiting steps in this reaction. This is corroborated by kinetic studies on the model reaction under optimal conditions (section 2.5c and Figures S5–S8), which reveals a first-order dependence on the concentrations of catalyst **H**, base and phenol **2a**, but zero-order kinetics with respect to the concentration of starting material **1a**. Furthermore, (*R*)-**INT2** can interconvert to (*S*)-**INT2** by the catalyst Cat. **H**, involving an energy barrier of 19.8 kcal mol^{-1} (**Trans-I→TS-Trans**,), which is consistent with experimental observations. Therefore, the selectivity of (*R*)-**3a** and (*S*)-**3a** is determined by the transition states (*R*)-**TS2** and (*S*)-**TS2**. (*S*)-**TS2** (–7.5 kcal mol^{-1}) has a lower free energy compared to (*R*)-**TS2** (–4.7 kcal mol^{-1}), with a free energy difference of 2.8 kcal mol^{-1}. This aligns with the experimental observation that (*S*)-**3a** is the major product. To further elucidate the reason for the lower free energy of (*S*)-**TS2** (–7.5 kcal mol^{-1}) compared to (*R*)-**TS2** (–4.7 kcal mol^{-1}), noncovalent interactions were analyzed by RDG (Reduced Density Gradient) method, as shown in Figure S13. In (*S*)-**TS2**, two π–π stacking interactions are observed between the catalyst and reactants, whereas (*R*)-**TS2** exhibits only one such interaction. This results in stronger interactions between the catalyst and substrate in (*S*)-**TS2**, leading to a shorter S–N bond (2.017 Å) compared to the S–N bond in (*R*)-**TS2** (2.178 Å). Additionally, in (*S*)-**TS2**, the sodium cation participates in Na–O interactions with both substrate and bicarbonate, while in (*R*)-**TS2**, the sodium cation only interacts with bicarbonate. This further suggests a stronger interaction between the sodium cation and the substrate **1a** in (*S*)-**TS2**.

Conclusion

In conclusion, we have developed an organocatalytic sulfur-atom activation strategy for the stereoselective preparation of S(VI)-chiral sulfonimidates. This approach uniquely activates racemic S(VI) sulfonimidoyl chlorides through the generation of a key catalyst-bound sulfonimidoyl intermediate. The resulting isothiourea-derived sulfonimidoyl ammonium species, formed via nucleophilic addition of the catalyst to S(VI) sulfonimidoyl chlorides, plays an essential role to forge the subsequent asymmetric S═O bond formation, affording chiral sulfonimidate products with excellent yields and enantioselectivity. Mechanistic investigations reveal that the efficient dynamic kinetic asymmetric transformation (DYKAT) process is enabled by isothiourea-assisted facile epimerization of the tetrasubstituted S(VI) atom. Notably, our S-atom activation strategy facilitates the efficient construction of S(VI)-stereogenic centers, which is distinct to conventional isothiourea-catalyzed transformations focusing on the “C”-centered chiral products. The enantioenriched sulfonimidate esters obtained through this method provide a versatile synthetic platform for rapid access to various S(VI)-stereogenic scaffolds, including sulfoximines, sulfonimidamides, and their derivatives, with notable antimicrobial activity against various plant pathogens. We anticipate that the developed isothiourea-catalyzed S(VI) activation strategy will open new avenues for the synthesis of chiral S(VI)-stereogenic compounds and inspire new synthetic implementations for chiral catalyst development and agrochemical discovery.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Chiral sulfonimidates • Heteroatom activation • Isothiourea catalysts • organocatalysis • Sulfur stereogenicity

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