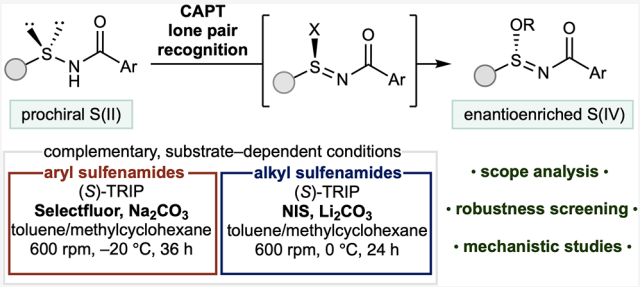
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Anionic Phase-Transfer Catalysis for Constructing Chiral Sulfur Centers via Asymmetric Sulfinimidation

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ABSTRACT: Chiral anion phase-transfer (CAPT) catalysis has emerged as a powerful strategy for asymmetric catalysis, yet its stereocontrol modes remain largely limited to π-face differentiation or enantiotopic bond selection. The ability to exert stereocontrol through enantioselective recognition of heteroatom lone pairs remains underdeveloped, restricting catalytic access to configurationally stable heteroatom-centered stereocenters. Here, we report a CAPT platform that enables asymmetric sulfinimidation through enantioselective halogenation of prochiral sulfur(II) lone pairs, providing direct access to chiral aryl and alkyl sulfinimidate esters with high enantioselectivity. Mechanistic studies and computational investigations confirm that halogenation is the enantiodetermining step, forming a chiral, configurationally stable sulfinimidoyl fluoride intermediate. Enantioselective oxidation of prochiral sulfides indicates that this CAPT lone-pair recognition platform may be more generally applicable to heteroatom lone pairs. These findings establish lone-pair differentiation as a new mode of stereocontrol in CAPT and expand the conceptual scope of chiral anionic catalysis toward the asymmetric synthesis of chiral organosulfur compounds.



INTRODUCTION

Noncovalent interactions play an important role in asymmetric catalysis by guiding the spatial organization of reactive partners and imposing differential stabilization on competing transition states, a process that ultimately gives rise to enantioenriched products.[1,2] Among the various interaction modes available to catalyst design, electrostatic attraction between oppositely charged species is particularly unique owing to its strength and long-range character.[3] These features have motivated strategies that transmit chiral information through ion pairing, enabling highly effective control over enantioselectivity in a broad range of catalytic transformations.[4−7] In this context, chiral anion phase-transfer (CAPT) catalysis has emerged as a mechanistically distinct platform for asymmetric synthesis (Figure 1a).[8−10] In a typical CAPT process, a soluble chiral anion undergoes counterion exchange with an insoluble cationic reagent at a phase boundary, generating a soluble chiral ion pair that mediates enantioselective transformations in the organic phase.

Recent advances have demonstrated that CAPT can exert efficient stereocontrol across a diverse set of reaction centers (Figure 1b).[8,9] In particular, chiral phosphate anions have been shown to form ion pairs with Selectfluor, enabling asymmetric fluorination reactions through differentiation of the enantiotopic faces of π-systems, including alkenes,[10−12] phenols,[13] and enamines.[14] Related examples of chiral counteranion-mediated asymmetric catalysis have also been described for in situ generated iminium[15] and thionium[16] cations, in which paired chiral phosphates guide face-selective attack of a nucleophile. In addition, strained ammonium intermediates including azetidinium[17] and aziridinium[18] ions can associate with chiral phosphate anions to promote enantiotopic bond-selective ring opening. Collectively, these examples highlight that stereocontrol in CAPT has thus far relied primarily on differentiation of π-faces in neutral π-systems or on enantiotopic bond cleavage within cationic intermediates. In contrast, the enantioselective recognition of heteroatom lone pairs—representing a fundamentally distinct mode of stereocontrol—remains largely unexplored in CAPT.

Among potential targets for such stereocontrol, sulfur stereocenters represent an attractive yet challenging platform. High oxidation state sulfur centers (sulfur(IV) and (VI)) have become a recent target for enantioselective method development due to their use as chiral auxiliaries[19,20] and their growing potential in pharmaceuticals,[21−25] agrochemicals,[26] and

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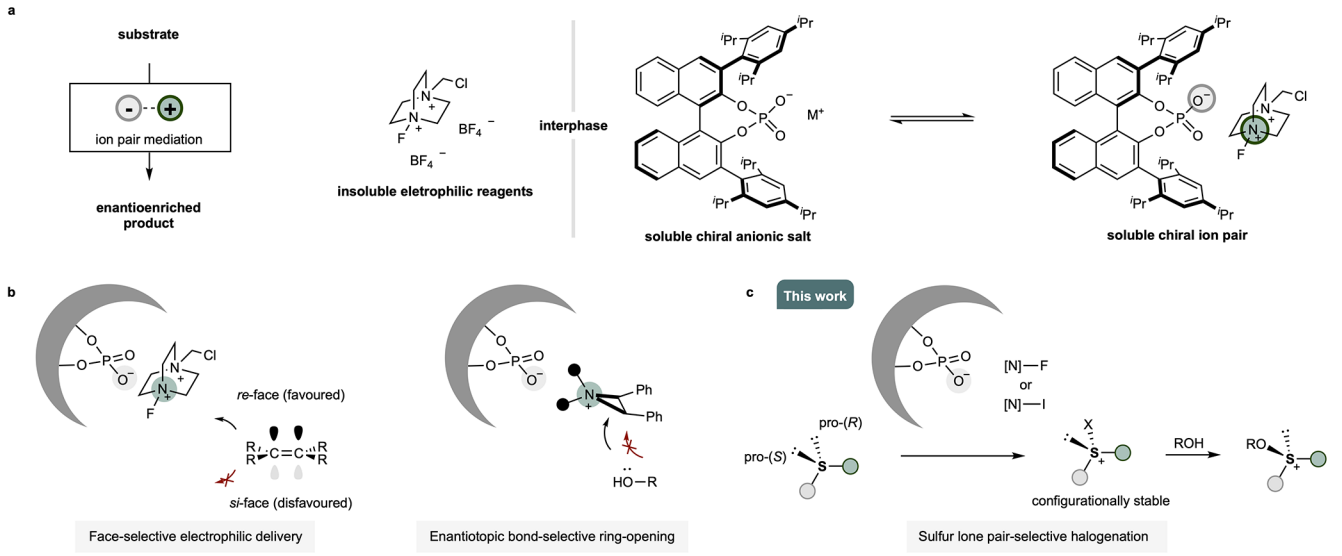
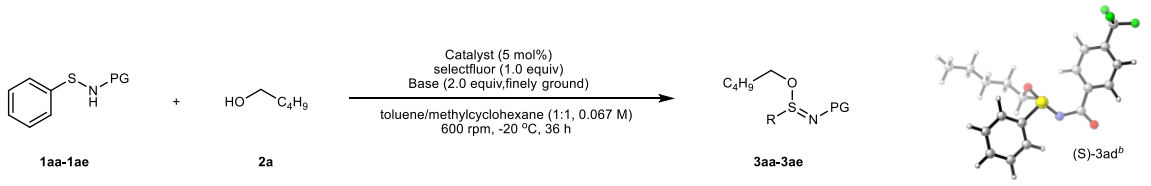
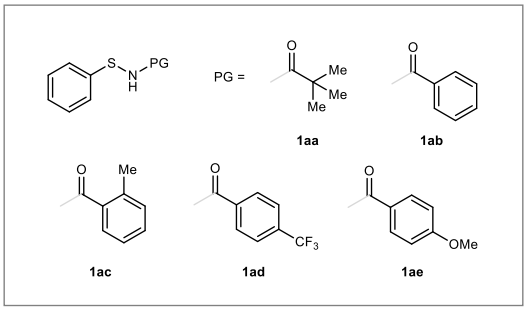


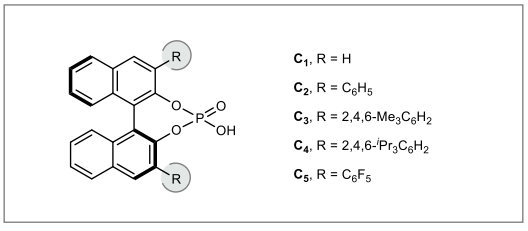
Figure 1. Stereocontrol in chiral anion phase-transfer catalysis. (**a**) Concept of chiral anion phase-transfer (CAPT) catalysis. (**b**) Established substrate recognition modes in CAPT. (**c**) This work. CAPT-enabled asymmetric sulfinimidation through enantioselective recognition of prochiral sulfur lone pairs.

Table 1. Reaction Development[a]



Entry	Substrate	Catalyst	Base	Yield of **3** (%)	ee of **3** (%)
1	**1aa**	C_4	Na_2CO_3	87	57
2	**1ab**	C_4	Na_2CO_3	83	87
3	**1ac**	C_4	Na_2CO_3	81	78
4	**1ad**	C_4	Na_2CO_3	84	90
5	**1ae**	C_4	Na_2CO_3	81	82
6	**1ad**	C_1	Na_2CO_3	58	3
7	**1ad**	C_2	Na_2CO_3	47	42
8	**1ad**	(*S*)-TRIP (C_4)	Na_2CO_3	86	7
9	**1ad**	C_5	Na_2CO_3	66	7
10	**1ad**	C_4	Li_2CO_3	19	35
11	**1ad**	C_4	K_2CO_3	83	15
12[a]	**1ad**	C_4	Na_2CO_3	76	82





[a]Reaction conditions: **1** (0.1 mmol), **2** (0.12 mmol), catalyst (5 mol %), base (2.0 equiv, finely ground), Selectfluor (1.0 equiv), toluene/methylcyclohexane (1:1, 1.5 mL), 600 rpm, −20 °C, 36 h. Isolated yields are reported. Ee values were determined by chiral HPLC analysis. (**a**) Water (3 μL) was added to the reaction. (**b**) The structure of (*S*)-**3ad** was optimized using DFT calculations at the B3LYP-D3(BJ)/def2-SVP level. For details, see the Supporting Information.

materials.[27] Thus, selective construction of these stereogenic sulfur centers from commercially available and readily accessible sulfur(II) precursors, such as thiols, represents an appealing and efficient strategy.[28,29] Specifically, enantioselective oxidation of sulfenamides to access aza-sulfur(IV) stereocenters has proven to be a powerful transformation, allowing access to sulfilimines,[30,31] sulfinamides,[32−36] sulfinamidines,[37] and sulfinimidate esters.[38−40] These aza-sulfur(IV) compounds exhibit high configurational stability, serving as versatile precursors to a range of sulfur(IV) and sulfur(VI) derivatives.[41,42] A conserved step in many of these transformations[34−36,39,40] is an enantioselective oxidation event at the prochiral sulfur(II) center to form a transient chiral sulfonium intermediate. These unstable cationic intermediates

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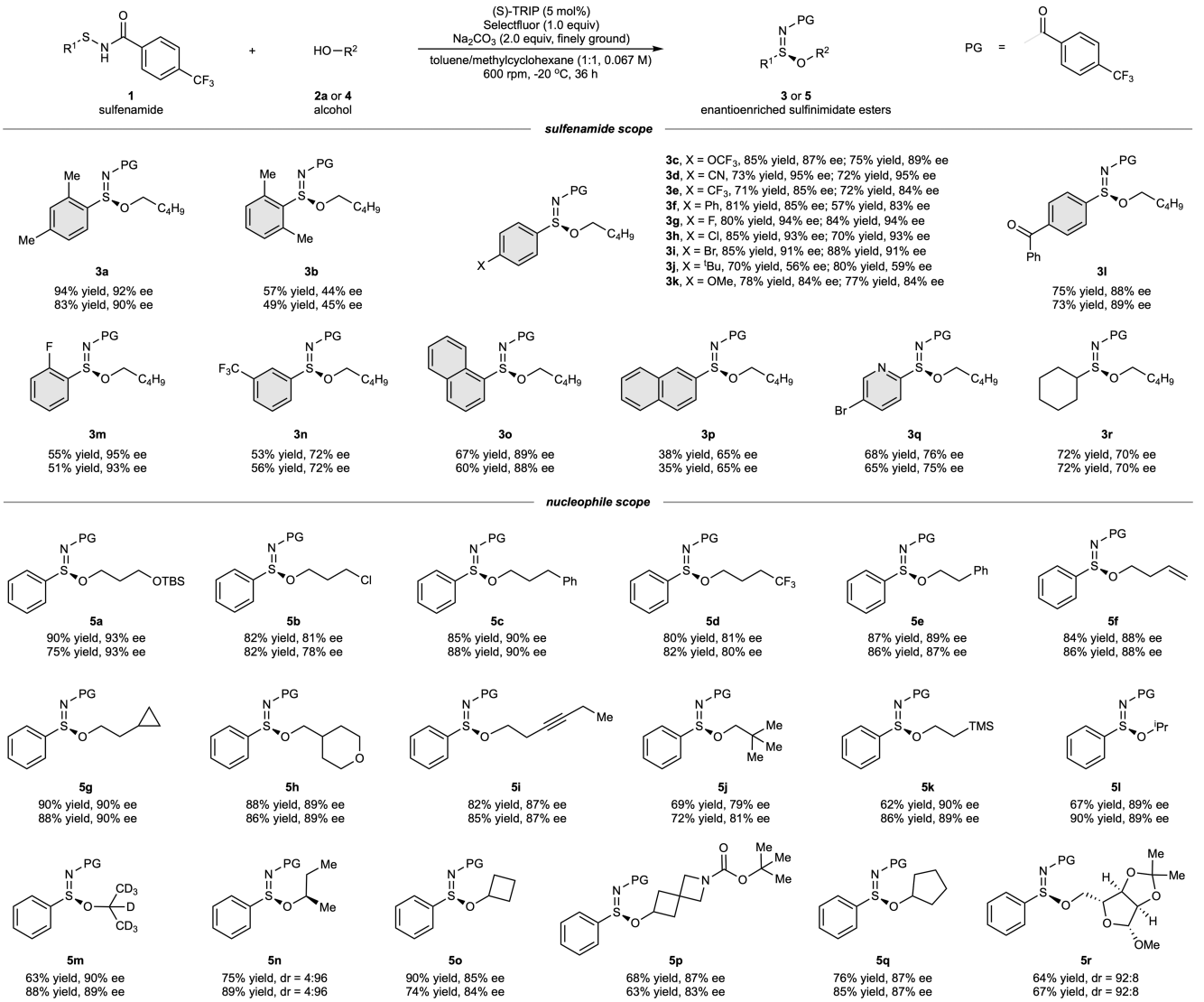


Figure 2. Evaluation of the aryl sulfenamide and alcohol scope. Reaction conditions: **1** (0.1 mmol), **2** or **4** (0.12 mmol), (*S*)-TRIP ($\mathbf{C_3}$) (5 mol %), Na_2CO_3 (2.0 equiv, finely ground), Selectfluor (1.0 equiv), toluene/methylcyclohexane (1:1, 1.5 mL), 600 rpm, −20 °C, 36 h; two independent runs. Isolated yields were reported. Ee values were determined by chiral HPLC analysis.

can engage in a variety of competing processes and therefore require precise catalytic control to furnish the desired sulfur(IV) products.[43]

Herein, we report that CAPT can engage in the recognition of heteroatom lone pairs to provide catalytic access to a diverse array of chiral sulfinimidate esters (Figure 1c). Notably, we report the development of complementary conditions for aryl and alkyl sulfenamides, of which the latter is underreported, allowing access to each product class in high yields and selectivity. Given that thiols serve as the synthetic precursor to sulfenamides, we constructed a chemical space composed of commercially available alkyl and aryl thiols to assess the substrate coverage of this and previous reports. The findings highlight the current limitations of this field as a significant portion of heteroaromatic classes is unreported; a robustness screen assessing the tolerance of the catalytic system to these unreported moieties highlights potential avenues for further reaction development. A suite of mechanistic studies provides insight into the origin of enantiocontrol, suggesting halogenation as the enantiodetermining step, followed by stereospecific nucleophilic substitution. Further, we showcase the potential of CAPT as a general platform for heteroatom lone-pair recognition through enantioselective oxidation of sulfides to form chiral sulfoxides.

RESULTS AND DISCUSSION

Reaction Development

Aryl sulfenamide **1aa** and 1-pentanol **2a** were selected as model substrates to evaluate the feasibility of chiral anion phase-transfer catalysis (Table 1). The influence of the sulfenamide *N*-substituent was first examined (entries 1−5), given its potential involvement in noncovalent interactions with the chiral ion pair.[44] All substrates afforded the desired products in good yields (81−87%) with moderate to high enantioselectivity. In general, *N*-aroyl sulfenamides (**1ab**−**1ae**) provided higher enantioselectivity (78−90% ee) than the *N*-pivaloyl analogue (**1aa**, 57% ee). Steric congestion at the ortho position diminished enantioselectivity (**1ac**, 78% ee), whereas *para* electron-withdrawing substituents outperformed electron-donating groups (90% vs 82% ee). *Z*/*E* isomers are not observed in the sulfinimidate ester products, and DFT

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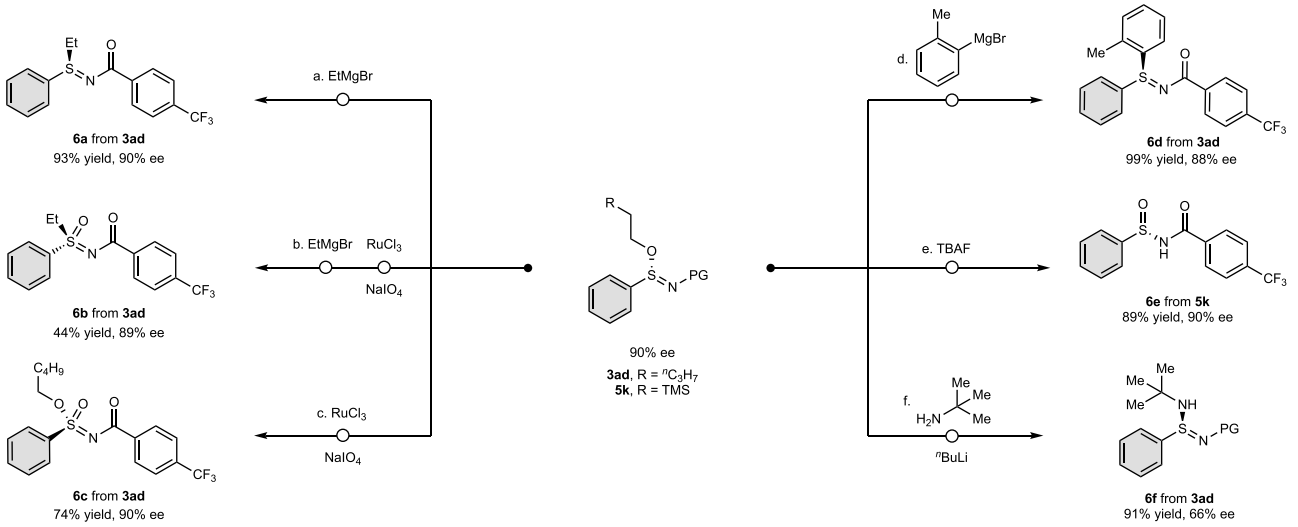


Figure 3. Diversification of enantioenriched sulfinimidate esters. (**a**) EtMgBr, THF, 0 °C, 12 h; (**b**) EtMgBr, THF, 0 °C, 12 h then $RuCl_3$, $NaIO_4$, $MeCN,H_2O$, rt, 1 h; (**c**) $RuCl_3$, $NaIO_4$, $MeCN,H_2O$, rt, 1 h; (**d**) *o*-tolylmagnesium bromide, THF, 0 °C, 12 h; (**e**) TBAF (1.0 M in THF), THF, overnight; (**f**) $^tBuNH_2$, ^{n}BuLi, −78 °C to rt, overnight.

calculations of **3ad** indicate that the chiral sulfur center adopts a *pseudo*-trigonal-pyramidal geometry (Table 1, top right). Several BINOL-based chiral phosphoric acid catalysts (entries 6−9) were then surveyed. Increasing the size of the catalyst aryl substituent generally improved enantioselectivity, consistent with the proposed CAPT ion-pair recognition model, wherein the chiral phosphoric acid engages the substrate through noncovalent interactions with increasing steric bulk enhancing differentiation within the chiral pocket.[45,46] Ultimately, catalyst **C4** bearing the 2,4,6-triisopropylphenyl group afforded the highest level of asymmetric induction (90% ee, entry 4), while catalyst **C5** bearing fluorinated phenyl substituents failed to deliver an improvement in enantioselectivity (7% ee, entry 9). Importantly, the identity of the carbonate counterion was found to significantly impact the reaction, with Li_2CO_3 or K_2CO_3 resulting in diminished yield and enantioselectivity (entries 10 and 11) compared to the sodium congener. This observation suggests that the alkali metal cation participates in the organization of the chiral ion pair and may influence the approach of the sulfur lone pair during the enantiodetermining halogenation step (*vide infra*). The enantioselective phase-transfer reaction proceeded in the presence of trace amounts of water, albeit with reduced yield and enantioselectivity (entry 12). Control experiments revealed that all reaction parameters are essential for achieving high yields and enantioselectivity (for details, see the Supporting Information).

Substrate Scope

With the optimized conditions in hand, the scope with respect to aryl sulfenamide component was investigated first (Figure 2). Evaluation of regioisomeric methyl-substituted substrates revealed a pronounced steric sensitivity of the catalytic system. Substrate **1a**, bearing 2,4-dimethyl substitution on the aryl ring, delivered product **3a** in 89% yield with 91% ee (average value over two runs, same below). In contrast, 2,6-dimethyl substitution resulted in diminished performance (**3b**, 53% yield, 45% ee), suggesting steric congestion near the sulfur center disrupts the organization of the chiral ion-pair environment responsible for stereocontrol. Aryl sulfenamides bearing electron-rich and electron-poor groups at the *para* position reacted to give products with good to high enantiomeric excess (**3c**−**3l**). Interestingly, despite strongly electron-donating substituents being tolerated by the reaction conditions (**3k**, 78% yield, 84% ee), *tert*-butyl substitution resulted in poor enantioselectivity (**3j**, 75% yield, 58% ee). Electron-withdrawing substituents at the *ortho* and *meta* positions reacted to afford products **3m** and **3n**, albeit with diminished yields (53% yield and 55% yield, respectively). Fused and heteroaromatic substrates were also evaluated; naphthyl-derived substrates underwent smooth conversion to the desired products (**3o**, **3p**), while heteroaryl variants bearing pyridyl groups resulted in reduced enantioselectivity (**3q**, 76% ee). Additionally, cyclohexyl sulfenamide (**1r**) was subjected to the reaction conditions to assess the compatibility of the developed method with alkyl substitution at sulfur. Alkyl sulfenamide product **3r** was formed in moderate yield (72%) and enantioselectivity (70% ee). This observation prompted further investigation of the reaction conditions for enantioselective formation of alkyl-based sulfinimidate esters (*vide infra*).

Next, the scope of alcohol nucleophiles was explored. A variety of primary alcohols, encompassing both linear and branched structures, underwent smooth conversion to the corresponding sulfinimidate esters **5a**−**5k** in good yields (71%−89%) with high enantioselectivities (80%−93%). Secondary alcohols including isopropanol, deuterated isopropanol, (*R*)-2-butanol, cyclobutanol, aza-spiro[3.3]heptanol, and cyclopentanol proved competent nucleophiles, delivering sulfinimidate esters **5l**−**5q** in synthetically useful yields with high selectivities. Incorporation of a sugar-derived nucleophile, methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside, furnished sulfinimidate **5r** in 66% yield with a 92:8 diastereomeric ratio, demonstrating the applicability of the method to more complex polyfunctional substrates. The phase-transfer catalytic system exhibited good compatibility to diverse functional groups, including accommodation of alcohols containing silyl ether (**4a**), chloro (**4b**), alkene and alkyne (**4f**, **4i**), ether (**4h**), silane (**4k**), and protected amine (**4p**) functionalities.

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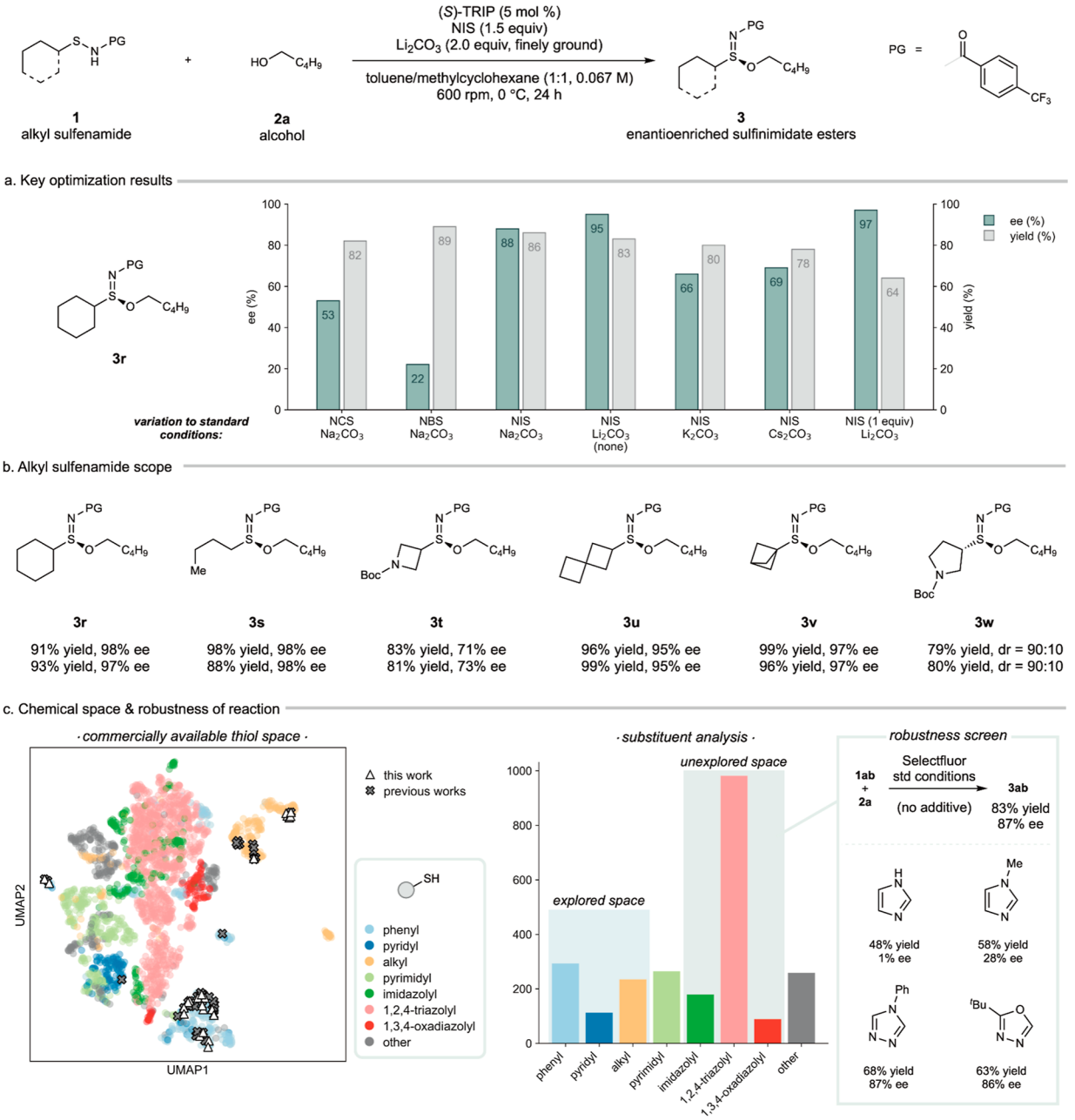


Figure 4. Evaluation of alkyl sulfenamide reactivity and substrate chemical space. (**a**) Reaction conditions: **1** (0.1 mmol), **2a** (0.12 mmol), (*S*)-TRIP (**C$_3$**) (5 mol %), base (2.0 equiv, finely ground), halogenation reagent (1.5 equiv), toluene/methylcyclohexane (1:1, 1.5 mL), 600 rpm, 0 °C, 24 h. Isolated yields were reported. Ee values were determined by chiral HPLC analysis. (**b**) Evaluation of the alkyl sulfenamide scope. (**c**) Chemical space analysis of commercially available thiol space and evaluation of robustness of the reaction.

Product Derivatization

The synthetic utility of the chiral sulfinimidate ester products was investigated through a series of downstream derivatization studies (Figure 3). Nucleophilic substitution of sulfinimidate ester **3ad** with ethylmagnesium bromide produced sulfilimine **6a** in 93% yield with retention of enantiomeric purity (90% ee). Subsequent oxidation of **6a** using $NaIO_4$ and catalytic $RuCl_3$ furnished sulfoximine **6b** in 44% overall yield over two steps, without significant loss of enantioselectivity (89% ee). Direct oxidation of **3ad** under $NaIO_4$/$RuCl_3$ conditions gave sulfonimidate ester **6c** (74% yield, 90% ee). Treating **3ad** with *o*-tolylmagnesium bromide delivered sulfilimine **6d** in 99% yield and 88% ee. Exposure of sulfinimidate **5k** to TBAF (1.0 M in THF) furnished the corresponding sulfinamide **6e** in 89% yield and 90% ee. Furthermore, nucleophilic amidation of sulfinimidate ester **3ad** with lithium *tert*-butylamide afforded sulfinamidine **6f** in 91% yield with 66% ee. Compound **3ad** was also found to be configurationally stable, without observable decomposition or change in enantiomeric purity upon storage at − 20 °C under ambient atmosphere for 10 months (for details, see the Supporting Information). Collectively, these data support the broader applicability of sulfinimidate esters as stereodefined intermediates for downstream sulfur functionalization.

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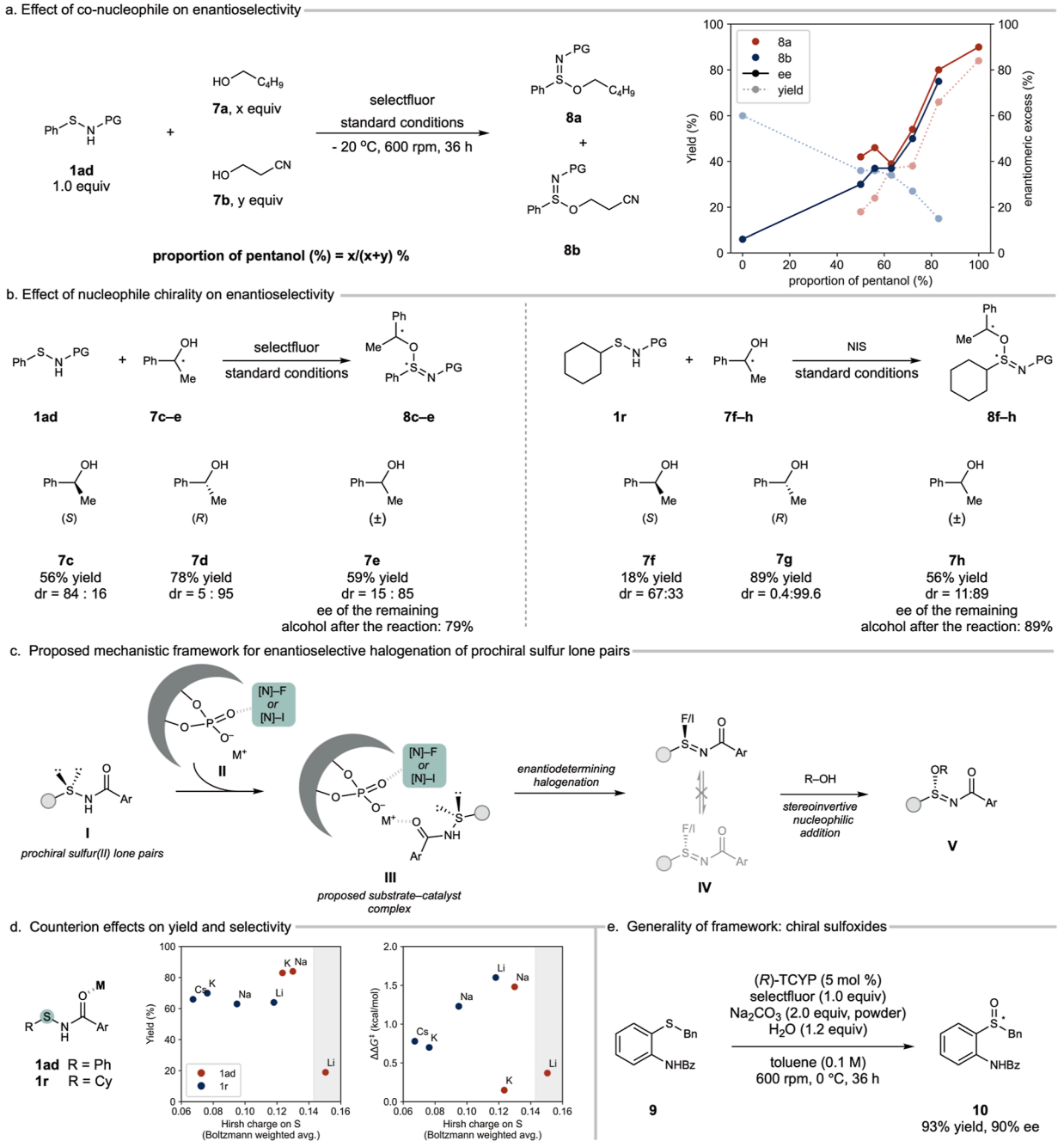


Figure 5. Mechanistic investigations. (**a**) Effect of conucleophile on enantioselectivity. (**b**) Effect of nucleophile chirality on enantioselectivity. (**c**) Proposed mechanistic framework for the enantioselective formation of sulfinimidate esters via chiral sulfur(II) lone-pair recognition. (**d**) Effect of carbonate countercation on the reaction outcome. (**e**) Enantioselective formation of chiral sulfoxides via chiral sulfur(II) lone-pair recognition.

Reaction Development and Scope Evaluation of Alkyl Sulfenamide

Given the relatively poor performance of alkyl sulfenamide **1r** under the developed reaction conditions using Selectfluor (Figure 2), we sought to further explore conditions that would allow access to the alkyl products with high enantioselectivity. While changes to the reaction conditions using Selectfluor did not improve the enantioselectivity, exploring various *N*-halosuccinimides as the oxidant was found to have a significant effect on the reaction outcome (Figure 4a). *N*-Chloro- and *N*-bromo-succinimide (NCS, NBS) provided high yields of the resulting sulfinimidate ester but diminished enantioselectivity (53 and 22% ee, respectively), indicating competition of the background reaction. However, the use of the milder oxidant *N*-iodosuccinimide (NIS) significantly enhanced enantioselectivity (88% ee). Similar to the Selectfluor conditions developed above (Table 1), the enantioselectivity was found to be particularly sensitive to the identity of the carbonate base. In this case, Li_2CO_3 delivered enhanced enantioselectivity (95% ee), while K_2CO_3 and Cs_2CO_3 resulted in lower values (66% and 69% ee, respectively). Under otherwise identical conditions, reducing the NIS loading maintained a high enantioselectivity (97% ee) but lowered the yield (64%).

A range of alkyl sulfenamides proved compatible under these optimized conditions (Figure 4b). Cyclic substrates (**3r**), linear primary alkyl groups (**3s**), conformationally restricted

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spirocyclic motifs (**3u**), and bridged bicyclic frameworks (**3v**) furnished the corresponding sulfinimidate esters with high enantioselectivities (95−98% ee). A 3-azetidine-derived sulfenamide gave lower enantioselectivity (**3t**, 72% ee), whereas (*S*)-3-sulfenamidopyrrolidine afforded **3w** with good diastereoselectivity (dr = 90:10). Comparing the overall performance of our alkyl substituted scope under the two developed conditions highlights the advantage of our second set of developed conditions, with yield and enantioselectivity improvements being observed for each comparative entry (see the Supporting Information).

Scope Analysis and Additives Test

We next sought to evaluate the diversity of our scope against a chemical space of commercially available thiols that was constructed using DFT-derived descriptors, as a surrogate for the sulfenamide starting materials (for details concerning chemical space of thiols, see the Supporting Information). Visualizing scope entries from previously reported similar transformations,[36,39,40] on the two-dimensional chemical space resulting from the uniform manifold approximation and projection (UMAP) algorithm (Figure 4c),[47] we observe that most the of examples are centralized in the bottom right of the plot, a region that is largely composed of substituted thiophenols (light blue). While there are several alkyl thiols that have been included in previously reported scopes (light orange region), we can access considerably more alkyl sulfinimidate esters, with four complex examples in an underexplored area of the chemical space. We note that much of the chemical space for commercially available thiols is unexplored with respect to this transformation, with a majority of the space being comprised of 5-membered ring heterocycles, such as moieties prevalent in pharmaceuticals and agrochemicals, including mercapto-substituted 1,2,4-triazoles and 1,3,4-oxadiazoles (depicted pink and red, respectively).[48] To assess the robustness of the transformation and its potential for tolerance to these moieties as substrates, an HTE-based additive screen was conducted using the standard conditions with Selectfluor and aryl sulfenamide **1ad** (for details, see the Supporting Information).[49] We found that although free and substituted imidazole causes a decrease in selectivity, the reaction proceeds with minimal loss of enantioselectivity in the presence of 1,2,4-triazole and 1,3,4-oxadiazole, indicating that these moieties may be competent substrates. Attempts to synthesize a 1,2,4-triazolyl substituted sulfenamide substrate were unsuccessful using the current route; however, these results highlight the practical robustness of the catalytic system and point toward opportunities to expand the chemical space of this transformation. For details regarding the assessment of other potentially reactive functionalities, including styrene, phenol, aniline, and benzamide, see the Supporting Information.

Mechanistic Studies

To determine the enantiodetermining step of the reaction, a series of mechanistic experiments were conducted. Attempts to isolate the putative sulfinimidoyl fluoride intermediate in the absence of nucleophile were unsuccessful, likely due to its instability, thus, we sought to probe the enantiodetermining step using a range of experimental tools. During investigation of nucleophile tolerance to the reaction conditions, we observed that employing 3-hydroxypropionitrile (**7b**) led to dramatically reduced enantioselectivity when compared to 1-pentanol (**7a**). This impact of nucleophile structure suggests that the substitution to the sulfinimidoyl fluoride intermediate is the enantiodetermining event. Therefore, one may expect the enantiomeric excess for the resulting product of a given alcohol to be independent of the presence of an additional alcohol. To probe this, a series of competition experiments were performed with varying ratios of conucleophiles **7a** and **7b** (Figure 5a). We observed a change in the enantiomeric excess for both products **8a** and **8b** as a function of the proportion of **7a**, suggesting that nucleophilic addition is not enantiodetermining. This instead likely arises from a solvent effect, wherein **7b** could influence the ion pairing between the intermediate and the chiral anion. To further investigate the identity of the enantiodetermining event, we employed (*S*)- and (*R*)-1-phenylethanol as chiral probes, expecting a match/mismatch effect if nucleophilic addition is occurring into an enantiomerically enriched sulfinimidoyl fluoride intermediate. Indeed, for substrate **1ad** in the presence of chiral catalyst **C4** and Selectfluor, we observed a pronounced difference in enantioselectivity when employing (*R*)-1-phenylethanol (78% yield, 5:95 dr) and (*S*)-1-phenylethanol (56% yield, 84:16 dr), consistent with nucleophilic attack on a chiral sulfinimidoyl fluoride intermediate. Low diastereoselectivity was observed in the absence of the chiral catalyst (dr = 55:45 and dr = 57:43, for (*R*) and (*S*), respectively), and upon subjecting the reaction to racemic 1-phenylethanol, a kinetic resolution occurs to return the alcohol with 79% ee, further supporting the presence of an enantioenriched sulfinimidoyl fluoride intermediate. A more pronounced but consistent match/mismatch effect is observed for alkyl sulfenamide **1r** using chiral catalyst **C4** and NIS, supporting that these two reactions operate under a similar mechanistic framework.

Taken together, these findings are consistent with the mechanism depicted in Figure 5c. Given the breadth of reports for electrophilic phase-transfer fluorination using Selectfluor and phosphate anions, we posit that the formation of a chiral complex (**II**) between the sodium salt of **C4** and the Selectfluor dication is likely.[10−14,50] Association of the substrate *via* noncovalent interactions with the alkali metal brings the two reagents into proximity (**III**), enabling enantioselective fluorination *via* one of the prochiral sulfur lone pairs to form chiral sulfinimidoyl fluoride intermediate **IV**. DFT calculations were performed to determine that the sulfinimidoyl fluoride intermediate (**IV**) was resistant to stereoinversion at the reaction temperature (−20 °C) (for details, see the Supporting Information).[51,52] Following the formation of this configurationally stable intermediate, stereoinvertive nucleophilic substitution can occur to afford the sulfinimidate ester product **V**. A similar mechanism can be proposed for the alkyl sulfenamide conditions developed using NIS, wherein association of the substrate occurs *via* coordination with the chiral alkali metal phosphate complex. Stabilizing noncovalent interactions between the oxidizing agent and the phosphate complex could orient NIS for electrophilic iodination, as depicted in Figure 5.

In an initial effort to understand the nuances between the two reaction conditions (Selectfluor vs NIS), the distinct trends observed when varying the identity of the carbonate counterion were investigated. As noted in the discussion of the optimization studies, this variable was found to elicit significant changes in yield and enantioselectivity, with disparate carbonate counterions being identified as optimal (Na_2CO_3 favored for the Selectfluor conditions, while Li_2CO_3 favored for NIS). To understand this cation-dependent trend, the

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J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

relationship between the Hirshfeld charge on the sulfur atom derived from DFT calculations of the substrate (a measure of the relative nucleophilicity of sulfur) and the outcome of the reaction (% yield and enantioselectivity) for the aryl and alkyl sulfenamide ion complexes was investigated (**1ad** and **1r**, Figure 5d).[53] For both substrates, the reaction proceeds in moderate yields (>60%) regardless of the identity of the counterion, with the exception of **1ad** with Li_2CO_3 (19% yield), suggesting that the already electron-deficient sulfur center of **1ad** likely becomes too electron poor to be sufficiently reactive when coordinated to the more electropositive Li cation. For alkyl sulfenamide **1r**, a linear trend between the Hirschfeld charge on sulfur and enantioselectivity is observed, with higher enantioselectivity favored with a less-nucleophilic sulfur center. This effect is hypothesized to be related to the ability of the countercation to solubilize the chiral catalyst anion. We note that a negative nonlinear effect was observed for the combination of substrate **1ad** and Selectfluor, indicating the presence of nonmonomeric species in solution (see the Supporting Information).[10,54] This observation is consistent with the proposed mechanistic model in which the monomeric chiral ion-pair complex between the deprotonated catalyst sodium salt and the Selectfluor dication (**II**) represents the productive catalytic species. The identity of the countercation could therefore affect the equilibrium between monomeric and higher-order aggregate species, altering the concentration of the proposed productive monomeric species and ultimately resulting in changes to enantioselectivity.[49,54] Taken together, these observations suggest that both substrate electronics and catalyst speciation may contribute to the observed dependence of enantioselectivity on carbonate counterions.[50,55]

An apparent similar trend is observed for aryl sulfenamide **1ad**, but two data points are insufficient to draw clear conclusions. To explore the generality of the substrate nucleophilicity effect on enantioselectivity, we calculated the Hirschfeld charge on sulfur for the sulfenamide ion complexes resulting from the scope of aryl sulfenamide substrates depicted in Figure 2. We identified a moderate correlation (R^2 = 0.40) between the Hirshfeld charge on the sulfur atom and the observed enantioselectivity, favoring a less nucleophilic sulfur center, consistent with the above-described trend (see the Supporting Information). However, the modest correlation suggests that sulfur nucleophilicity alone is insufficient to describe the observed selectivity and that additional substrate-dependent factors are likely operative. Attempts to analyze the aryl sulfenamide substrate scope using multiple linear regression did not yield robust models, further supporting the involvement of additional factors.

As a final experiment, we sought to evaluate the developed CAPT system in enabling the enantioselective recognition of prochiral sulfur lone pairs generally.[56,57] To this end, we subjected sulfide **9** to CAPT oxidation conditions using Selectfluor and a chiral catalyst, (*R*)-TCYP, finding that sulfoxide (**10**) is formed in excellent yield and enantioselectivity (93% yield, 90% ee) (Figure 5e). This result not only highlights the generality of our approach for the selective oxidation of sulfur(II) lone pairs but also suggests that this platform may be more broadly applicable to a range of prochiral heteroatom lone pairs.

CONCLUSIONS

In summary, this study demonstrates that chiral anion phase-transfer (CAPT) catalysis can be extended beyond established modes of π-face and bond-selective recognition to enable asymmetric transformations associated with prochiral sulfur lone pairs. This concept is demonstrated through an CAPT-enabled sulfinimidation of sulfenamides using Selectfluor, providing efficient and robust access to enantioenriched aryl sulfinimidate esters under mild conditions. The resulting sulfinimidate esters exhibit high configurational stability and serve as versatile intermediates for downstream derivatization to access a variety of chiral sulfur(IV) and (VI) moieties. Further, we demonstrate that through the optimization of a second set of conditions using NIS, we can form complex, enantioenriched alkyl sulfinimidate esters that populate an underexplored region of the available chemical space. Analysis of the thiol chemical space constructed from commercially available compounds reveals opportunities to expand the reported scope of this class of reactions, with experimental support from a robustness screen. Experimental and computational studies support a mechanistic framework in which stereocontrol arises from enantioselective halogenation to form a chiral sulfinimidoyl halide intermediate, followed by enantiospecific nucleophilic substitution. More broadly, these findings establish lone-pair recognition as a viable mode of stereocontrol in anionic phase-transfer catalysis, expanding the conceptual scope of chiral anion catalysis toward asymmetric heteroatom functionalization.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.6c18093.

Experimental procedures and spectral and crystallographic data (PDF)

Molecular formula strings (CSV)

Accession Codes

Deposition Numbers 2581019 and 2582624 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge Crystallographic Data Centre (CCDC) and Fachinformationszentrum Karlsruhe Access Structures service.

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Notes

The authors declare no competing financial interest.

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