Synthesis of chiral sulfinate esters by asymmetric condensation

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Summary: Achiral sulfur functional groups such as sulfonamide, sulfone, thiols and thioethers are ubiquitous in drugs and natural products. On the other hand, chiral sulfur functional groups are often neglected as pharmacophores; but sulfoximine, with its unique physicochemical and pharmacokinetic properties, has been recently incorporated into several clinical candidates. Thus, other sulfur stereogenic centers, such as sulfinate ester, sulfinamide, sulfonimidate ester and sulfonimidamide have started to attract attention. The diversity and complexity of these novel sulfur stereogenic centers have expanded the chemical space for drug discovery. However, the installation of these structures enantioselectively, into drug molecules, is highly challenging. This manuscript reports the straightforward access to enantioenriched sulfinate esters via asymmetric condensation of pro-chiral sulfinates and alcohols using pentanidium as an organocatalyst. We successfully coupled a wide range of sulfinates and bioactive alcohols stereoselectively. The initial sulfinates can be prepared from existing sulfone and sulfonamide drugs, and the resulting sulfinate esters are versatile for transformations to diverse chiral sulfur pharmacophores. Through late-stage diversification of Celecoxib and other drug derivatives, we demonstrate the viability of this unified approach towards sulfur stereogenic centers.

Introduction: Diversity-oriented synthesis has facilitated drug discovery by efficiently generating compound collections with high structural complexity and diversity. Stereoisomeric compounds, with their different topographical features, usually result in distinct interactions with targeted proteins. Diverse molecular scaffolds based on carbon stereogenic centers have provided a wide range of chemical space for drug discovery. Sulfur, with its multiple oxidation states, is widely present in biologically active compounds. However, sulfur stereogenic centers are often overlooked as pharmacophores; apart from marketed chiral sulfoxides, Esomeprazole and Armodafinil. Sulfoximine, a moiety with S(VI) stereocenter, has become a rising star in drug discovery due to its unique physicochemical and pharmacokinetic properties. Sulfoximine is tetrahedral and has been designed as a stable transition state analogue to inhibit \( \ell \)-asparagine synthase (ASNS). Although no candidate containing sulfoximine has been approved as a drug, several compounds such as AZD6738 and BAY 1000394 have entered clinical trials. Other sulfur stereogenic centers such as sulfinate ester, sulfinamide, sulfonimidate ester and sulfonimidamide have started to attract attention due to advances made by sulfoximine. While some new methodologies have been developed for racemic synthesis of these stereogenic centers, preparation of enantiopure sulfur stereocenters is still a formidable challenge. Established methods mainly rely on stoichiometric amounts of chiral reagents or kinetic resolution of racemic substrates. Only a handful of catalytic approaches were reported and structural diversity is limited.
a Biologically active compounds containing S(IV) and S(VI) stereogenic centers

b Diverse S(IV) and S(VI) stereogenic centers for drug design and discovery

c Catalytic synthesis of chiral sulfinate esters through dynamic kinetic resolution

d This work: asymmetric condensation of sulfinates and alcohols with pentanidium (PN), a chiral cation catalyst

Fig. 1. Diverse chiral sulfur pharmacophores for drug discovery and their synthesis. a, Examples of biologically active compounds containing S(IV) and S(VI) stereogenic centers. b, Examples of diverse chiral sulfur pharmacophores for drug design and discovery. c, Synthesis of chiral sulfinate esters through dynamic kinetic resolution with Cinchona alkaloids as catalysts (Fig. 1c). The community is still yearning for a general and efficient method for catalytic synthesis of enantiopure sulfinate esters with broad substrate compatibility. Considering the rising interests in using novel chiral sulfur stereogenic centers as pharmacophores, a catalytic method suitable for late-stage manipulation of drugs with diverse sulfur stereocenters is imperatively required.

In this manuscript, we wish to report the desymmetrization of pro-chiral sulfinate to afford enantioenriched sulfinate esters using pentanidium (PN) as catalyst (Fig. 1d). Sulfinate, a stable and easily accessible reagent, is well known as a source of carbon radical for coupling via desulfitation or as a sulfur-centered nucleophile. Less known is that sulfinate is an ambident...
nucleophile, and that the enantiotopic oxygen atoms are also potential nucleophilic sites. We realized this novel pathway through the use of ethyl chloroformate as the oxophilic electrophile. In the presence of pentanidium as catalyst, sulfinate and ethyl chloroformate form a mixed anhydride intermediate, which in turn is converted to enantioenriched sulfinate ester through a replacement reaction with an alcohol. Sulfinate can also be easily derived from sulfur functional groups in drugs such as sulfonamide in Celecoxib or methylsulfone in Etoricoxib. Thus, this methodology is suitable for late-stage diversification of existing drugs containing sulfur functional groups. In addition, drugs and drug intermediates containing alcohol group e.g. the intermediate of Remdesivir, an antiviral drug approved for the treatment of COVID-19, can be manipulated into novel analogues by replacing its phosphorus stereocenter (phosphoramidate) into a sulfur stereocenter. Phosphoramidate prodrugs including Remdesivir are part of pronucleotide (ProTide) therapies for viral disease and cancer. Similar to phosphorus, sulfur is also available at multiple oxidation states and structure diversity; its adoption in place of phosphorus may lead to new therapies.

Fig. 2. Optimization of reaction conditions. Reaction conditions: Potassium sulfinate 1 (0.1 mmol), catalyst (5 mol%), 2a-2i (1.6 equiv.), EtOH (1.2 equiv.), K$_2$CO$_3$ (1.1 equiv.), additive 3a-3d (0.1 equiv.), Et$_2$O (0.5 mL), −20 °C, 24 hours. Isolated yields were reported, and ee values were determined by chiral high-performance liquid chromatography (HPLC) analysis. *Reaction was performed on 12.0 mmol scale and 1.94 g of sulfinate ester 4 was isolated. Ph, phenyl; Ar, aryl; tBu, tert-butyl.

Optimization of reaction conditions: We embarked on our investigation using potassium 4-methylbenzenesulfinate 1 as a model for sulfinate (Fig. 2). Several acyl chlorides (2a-2g) and sulfonyl chlorides (2h-2i) were selected, and the respective mixed anhydrides were generated as intermediates, which were immediately replaced by ethanol at the sulfur stereocenter to afford sulfinate ester 4 (entries 1-9). Ethyl chloroformate 2a was found to give the most consistent and favorable results. Most of our earlier investigations were performed using pentanidium PN2 (entry 10). Serendipitously, we discovered that pentanidium PN1, containing a phenol substituent, provided high level of stereocontrol. We speculate that it may be due to the selective hydrogen bonding between...
the phenol group on PN1 and sulfinate 1. When the phenol group was methylated to form pentanidium PN3, enantioselectivity decreased significantly (entry 11). We also detected formation of acylated pentanidium PN4 during the reaction process when ethyl chloroformate 2a was used. When we prepared pentanidium PN4 separately and subjected it to the same reaction condition, only low enantioselectivity was obtained (entry 12). It is likely that formation of pentanidium PN4 was an undesirable pathway, which additives such as thiolates (3a-3d) mitigated to improve the reaction (entries 13-16, see Supplementary Information for details). Under the optimized conditions, we were able to perform the reaction in gram scale with high yield and enantioselectivity (entry 15).

**Reaction scope:** Encouraged by these results, we proceeded to investigate scope of sulfinites suitable for our methodology (Fig. 3). Electron-rich phenyl sulfinites with different substitution patterns gave desired sulfinate esters with high stereoselectivity. Phenyl sulfinate esters with alkoxy substitution (5-7), alkyl substitution (8, 9), bulky mesityl group (10) and para-acetamido substitution (11) were obtained with high ee values. This reaction was also efficient to obtain a variety of phenyl sulfinate esters 13-18 substituted with halogen atoms. Phenyl substitution at para position gave sulfinate ester 19 and 2-trifluoromethoxybenzenesulfinate gave sulfinate ester 20, both with good levels of enantioselectivity. 4-Cyanobenzenesulfinate, which contained a strong electron-withdrawing cyano group, gave sulfinate ester 21 in moderate yield and ee value. In general, strong electron-withdrawing aryl sulfinites gave moderate results. Several naphthyl sulfinites with different substitutions gave corresponding sulfinate esters 22-24 with high enantioselectivities. Thiophene and benzothiophene sulfinate esters 25-29 were also obtained with excellent results. This methodology also worked well for alkyl sulfinites and enantioenriched products (30-33) were efficiently generated. During these investigations, we found catalyst PN1 was quickly acylated to form PN4 in reactions with electron-rich sulfinites, which resulted in decreased yields and enantioselectivity. This was solved by using K₂HPO₄ as base and increasing the amount of catalyst or additive.

Next, we found that this newly developed methodology efficiently installed sulfur stereogenic centers to various alcohols with high functional group compatibility (Fig. 3). (S)-Glycidol was successfully functionalized, without affecting the epoxide moiety, to sulfinate ester 34 with 98:2 diastereomeric ratio (dr). With (R)-1,3-butanediol, primary alcohol was preferred over secondary alcohol with mono-sulfinitylated product 35 obtained with dr of 97:3. In order to investigate the potential of using this methodology to complement the ProTide strategy, we investigate the functionalization of several nucleosides. The desired nucleoside sulfinate esters 36-42 were obtained with moderate to high yields and excellent stereoselectivity. Sulfur stereogenic centers were successfully installed on the corresponding alcoholic intermediates of several marketed antiviral drugs such as Zidovudine, Sofosbuvir and Remdesivir. We also demonstrated stereoselective sulfinitylation of several bioactive cyclic alcohols, including cholecalciferol, cholesterol, epi-androsterone and menthol, to their corresponding sulfinate esters 43-48. With cholesterol and menthol, we also showed that if ent-PN1 was used as the catalyst, the diastereomeric ratio is inverted, indicating catalyst control rather than substrate control of this reaction. Our methodology is suitable for primary and secondary alcohols including iso-propanol; however, bulky tert-butanol, phenols and amines were not viable nucleophiles (see Supplementary Information).
**Fig. 3. Reaction scope.** Reaction conditions: Potassium sulfinate (0.1 mmol), PN1 (5–10 mol%), 2a (1.3–1.6 equiv.), alcohol (1.0–1.2 equiv.), K₂CO₃ (1.1 equiv.), 3c (0.1–0.2 equiv.), Et₂O (0.5–1.0 mL), −20 °C, 24 hours. Isolated yields were reported, ee values were determined by chiral HPLC analysis, and dr values were determined by chiral HPLC or NMR analysis.

- **a** K₂HPO₄ (2.0 equiv.) instead of K₂CO₃.
- **b** 3d (0.1–0.2 equiv.) as additive.
- **c** Sodium sulfinate was used.
- **d** 2a (2.0 equiv.), 3d (0.5 equiv.).
- **e** K₂HPO₄ (2.0 equiv.), 3d (0.2 equiv.), additional H₂O (10 μL).
- **f** Alcohol (0.1 mmol), potassium sulfinate (0.15 mmol), 2a (0.2 mmol), K₂CO₃ (0.15 mmol).
- **g** MTBE (1.0–2.0 mL) as solvent.
- **h** 2.0 mL of mixed solvent Et₂O/EA (1:1).
- **i** 2.0 mL of mixed solvent MTBE/EA (2:1).
- **j** Alcohol (0.1 mmol), potassium sulfinate (0.2 mmol),
Modification of drugs: In order to demonstrate the generality and efficiency of our methodology, we prepared several complex sulfinate salts from drugs or drug intermediates. (Fig. 4). Using Sildenafil as an example, chlorosulfonation of an electron-rich arene led to its sulfonyl chloride intermediate, which can be easily converted to sulfinate 49 (Fig. 4a). Using our asymmetric condensation condition with ethanol, Sildenafil sulfinate ester 50 was obtained with high enantioselectivity. Next, we converted methylsulfone on Etoricoxib to sulfinate 51 through alkylation and in-situ elimination of styrene (Fig. 4b). Subsequently, enantioenriched Etoricoxib sulfinate ester 52 was obtained efficiently through our method. Recently, a group from Merck reported the preparation of sulfonates from primary sulfonamides through carbene-catalyzed deamination. Using this approach, we transformed several bioactive primary sulfonamides into their corresponding sulfonates (Fig. 4c). Likewise, the respective (S)-Sulpiride, Glibenclamide and Valdecoxib sulfinate esters (53-55) were afforded with high stereoselectivities.

As mentioned, sulfinate ester is the ideal linchpin intermediate for late-stage diversification of drugs into a plethora of sulfur stereogenic centers. Therefore, we utilized Celecoxib as a model to justify that our methodology is a valuable addition to the toolkits of drug discovery programs (Fig. 4d and 4e). Primary sulfonamide on Celecoxib was converted smoothly to Celecoxib sulfinate 56. Asymmetric condensation of sulfinate 56 with cholesterol gave Celecoxib-cholesterol sulfinate ester conjugate 57 with a high diastereomeric ratio (95:5). Through condensation of Celecoxib sulfinate 56 with 2-propyn-1-ol, we obtained enantioenriched propargyl sulfinate ester 59. This nicely set it up for 'click reaction' with the azide group on Zidovudine, generating Celecoxib-Zidovudine conjugate 60. Celecoxib sulfinate ester 58 was obtained in high ee value as a versatile precursor of other S(IV)/S(VI) stereogenic centers and able to be substituted by various nucleophiles at the sulfur center with inverted configuration. Methyl Grignard reagent and lithium enolate are useful nucleophiles, providing respective enantioenriched sulfoxides (61, 62). With lithium bis(trimethylsilyl)amide (LiHMDS), we obtained directly unprotected sulfanimide 63. Both primary and secondary amines are effective nucleophiles through formation of lithium amide or activation with Grignard reagents. Inversion at the sulfur stereocenter provided respective enantioenriched sulfonimidamides 64-66. Further imidations of Celecoxib sulfinate ester 58, Celecoxib sulfoxide 61 and Celecoxib sulfonamide 66 gave the corresponding sulfonimidate ester 67, sulfoximine 68 and sulfonimidamide 69 in high yields and without erosion of ee values. Many of these enantioenriched S(IV)/S(VI) stereogenic centers are previously deemed as synthetically challenging. 1,22

Conclusion: In conclusion, we have presented a viable and unified synthetic strategy for the stereoselective preparation of sulfinate esters and related sulfur stereogenic centers. This methodology is mild and tolerates a wide range of functional groups, allowing it to be compatible with late-stage diversification of Celecoxib and other marketed drugs. In addition, several marketed antiviral drugs e.g. Zidovudine, Sofosbuvir and Remdesivir can be redecorated with sulfur stereogenic centers through sulfynylation of their alcoholic intermediates. This approach complements the ProTide strategy through replacement of the phosphorus stereogenic center with sulfur stereogenic centers. In view of the increasing use of sulfur stereogenic centers as pharmacophores, we believe that this new methodology will ameliorate the toolkits of drug discovery programs for the exploration of these pharmacophores.
Fig. 4. Functionalization and diversification of drugs. 

a. Synthesis of Sildenafil sulfinate ester. 

b. Synthesis of Etoricoxib sulfinate ester.

c. Functionalization of sulfonamide drugs into sulfinate esters.

d. Synthesis of Celecoxib sulfinate esters using different alcohols.

e. Late-stage diversification of Celecoxib into a plethora of derivatives with sulfur stereocenters. 

Reaction conditions: For Sildenafil sulfinate ester, reaction with potassium sulfinate (0.1 mmol), EtOH (1.0 equiv.), PN1 (20 mol%), 2a (2.1 equiv.), K$_2$HPO$_4$ (2.0 equiv.), 3a or 3d (1.0 equiv.), Et$_2$O or toluene (1 mL), 0 °C or −20 °C, 24 hours. 

For Etoricoxib sulfinate ester, reaction with potassium sulfinate (0.1 mmol), THF, 23 °C, 83% yield, 52% yield, 87% yield.

For Celecoxib sulfinate esters, reaction with 2-propyn-1-ol (0.1 mmol), CuAAC click. 

For Celecoxib-Zidovudine conjugate, reaction with late-stage diversification of Celecoxib with chiral S(IV)/S(V) pharmacophores.
ROH (1.0 equiv.), PN1 (5 mol%), 2a (1.6 equiv.), K₂CO₃ (1.1 equiv.), 3e (0.2 equiv.), H₂O (10 μL), MTBE (1.0 mL), −20 °C, 24 hours. See Supplementary Information for details. nPr, n-propyl; LiHMDS, lithium bis(trimethylsilyl)amide.

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Data availability: The data supporting the findings of this study are available within the paper and its Supplementary Information.

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Competing interests: The authors declare no competing interests.
a) Biologically active compounds containing S(IV) and S(VI) stereogenic centers

Armodafinil

Esomeprazole

b) Diverse S(IV) and S(VI) stereogenic centers for drug design and discovery

Sulfoxide, some marketed drugs

Sulfoximine, some candidates in clinical trials

Sulfinate ester, sulfinamide, sulfonimidate ester, sulfonimidamide underexplored in drug discovery (asymmetric synthesis is challenging)

c) Catalytic synthesis of chiral sulfinate esters through dynamic kinetic resolution

Cinchona alkaloid or peptide catalyst

Racemization

Sulfinate stereoselective

Novel analogues of ProTide drugs

Facile diversification of sulfur group on drugs

Celecoxib

d) This work: asymmetric condensation of sulfinates and alcohols with pentanidium (PN), a chiral cation catalyst

Divergent synthesis of sulfur stereogenic centers
catalyst (5 mol%) K₂CO₃ (1.1 equiv.) additive (0.1 equiv.)
diethyl ether
-20 °C, 24h

| entry | catalyst | additive | yield of 4 (%) | ee of 4 (%) |
|-------|----------|----------|----------------|-------------|
| 1     | PN1      | 2a       | 90             | 91          |
| 2     | PN1      | 2b       | 50             | 82          |
| 3     | PN1      | 2c       | 30             | 0           |
| 4     | PN1      | 2d       | 70             | 83          |
| 5     | PN1      | 2e       | 75             | 86          |
| 6     | PN1      | 2f       | 75             | 70          |
| 7     | PN1      | 2g       | 71             | 86          |
| 8     | PN1      | 2h       | 40             | 79          |
| 9     | PN1      | 2i       | 50             | 77          |
| 10    | PN2      | 2a       | 96             | 14          |
| 11    | PN3      | 2a       | 92             | 9           |
| 12    | PN4      | 2a       | 71             | 35          |
| 13    | PN1      | 2a 3a    | 96             | 96          |
| 14    | PN1      | 2a 3b    | 82             | 96          |
| 15    | PN1      | 2a 3c    | 96 (88)        | 96 (95)     |
| 16    | PN1      | 2a 3d    | 96             | 96          |
$$\text{SO}_{3} \text{Et} + \text{Cl}_{2} \text{OEt} + \text{HO} \xrightarrow{\text{PN1 (5-10 mol%)}} \text{K}_{2} \text{CO}_{3} (1.1 \text{ equiv.)}} \xrightarrow{3c (0.1-0.2 \text{ equiv.)}} \text{diethyl ether} \xrightarrow{-20 \, ^\circ C, 24h} 5-48$$

| Compound | Yield (%) | ee (%) | DR |
|----------|-----------|--------|----|
| 5 | 92 | 97 | 97:3 |
| 6 | 76 | 97 | 97:3 |
| 7 | 78 | 94 | 97:3 |
| 8 | 67 | 96 | 97:3 |
| 9 | 76 | 96 | 97:3 |
| 10 | 68 | 87 | 97:3 |
| 11 | 68 | 94 | 97:3 |
| 12 | 89 | 96 | 97:3 |
| 13 | 91 | 94 | 97:3 |
| 14 | 82 | 98 | 97:3 |
| 15 | 94 | 94 | 97:3 |
| 16 | 71 | 92 | 97:3 |
| 17 | 71 | 91 | 97:3 |
| 18 | 90 | 97 | 97:3 |
| 19 | 68 | 98 | 97:3 |
| 20 | 84 | 85 | 97:3 |
| 21 | 71 | 70 | 97:3 |
| 22 | 78 | 95 | 97:3 |
| 23 | 90 | 91 | 97:3 |
| 24 | 74 | 98 | 97:3 |
| 25 | 93 | 96 | 97:3 |
| 26 | 85 | 84 | 97:3 |
| 27 | 88 | 94 | 97:3 |
| 28 | 90 | 90 | 97:3 |
| 29 | 78 | 93 | 97:3 |
| 30 | 64 | 96 | 97:3 |
| 31 | 75 | 90 | 97:3 |
| 32 | 85 | 95 | 97:3 |
| 33 | 60 | 98 | 97:3 |
| 34 | 51 | 98.2 | 97:3 |
| 35 | 61 | 97 | 97:3 |
| 36 | 83 | 99 | 97:3 |
| 37 | 71 | 93 | 97:3 |
| 38 | 51 | 97 | 97:3 |
| 39 | 78 | 94 | 97:3 |
| 40 | 52 | 85 | 97:3 |
| 41 | 61 | 94 | 97:3 |
| 42 | 74 | 95 | 97:3 |
| 43 | 46 | 99 | 97:3 |
| 44 | 39 | 99 | 97:3 |
| 45 | 36 | 96 | 97:3 |
| 46 | 50 | 99 | 97:3 |
| 47 | 49 | 95 | 97:3 |
| 48 | 31 | 97 | 97:3 |

**Remdesivir derivative**

**Zidovudine derivative**

**Sofosbuvir derivative**

**Cholesterol derivative**

**Epi-androsterone derivative**

**Cholecalciferol derivative**

**NAD**

**NADP**

**NADPH**

**NADH**
