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Synthesis of chiral sulfinate esters by asymmetric condensation

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Achiral sulfur functional groups such as sulfonamide, sulfone, thiols and thioethers are common in drugs and natural products. However, chiral sulfur functional groups are often neglected as pharmacophores[1–3]; but sulfoximine, with its unique physicochemical and pharmacokinetic properties[4,5], 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 sulfur stereogenic centers have the potential to expand chemical space for drug discovery[6–10]. However, the installation of these structures enantioselectively into drug molecules is highly challenging. Here, we report 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[11,12] of Celecoxib and other drug derivatives, we demonstrate the viability of this unified approach towards sulfur stereogenic centers.

Diversity-oriented synthesis has facilitated drug discovery by efficiently generating compound collections with high structural complexity and diversity[13,14]. 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[15]. Sulfur, with its multiple oxidation states, is widely present in biologically active compounds[16]. However, sulfur stereogenic centers are often overlooked as pharmacophores[1–3]; apart from marketed chiral sulfoxides, Esomeprazole and Armodafinil (Fig. 1a).

Sulfoximine, a moiety with S(VI) stereocenter, has become a rising star in drug discovery due to its unique physicochemical and pharmacokinetic properties[4,5]. Sulfoximine is tetrahedral and has been designed as a stable transition state analogue to inhibit L-asparagine synthase (ASNS)[6]. Although no candidate containing sulfoximine has been approved as a drug, several compounds such as AZD6738 and BAY 1000394 have entered clinical trials (Fig. 1a)[8,9]. Other sulfur stereogenic centers such as sulfinate ester, sulfinamide[17], sulfonimidate ester and sulfonimidamide[18] have started to attract attention due to advances made by sulfoximine (Fig. 1b). While some new methodologies have been developed for racemic synthesis of these stereogenic centers[19–21], preparation of enantiopure sulfur stereocenters is still a formidable challenge[22]. Established methods mainly rely on stoichiometric amounts of chiral reagents[23–25] or kinetic resolution of racemic substrates[26,27]. Only a handful of catalytic approaches were reported and structural diversity is limited[28–32].

Amongst the sulfur stereogenic centers, sulfinate ester holds the linchpin position for two reasons. Firstly, several enantiopure sulfinate esters can be reliably and affordably derived from chiral alcohols. Next, a variety of approaches have been developed to convert sulfinate esters to other sulfur stereogenic centers[33–35]. Reports on catalytic synthesis of enantioenriched sulfinate esters are scarce and all based upon dynamic kinetic resolution of sulfinyl chlorides with alcohols using peptides or *Cinchona* alkaloids as catalysts (Fig. 1c)[36–38]. 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**)[39,40] as catalyst (Fig. 1d). Sulfinate, a stable and easily accessible reagent, is well known as a source of carbon radical for coupling via desulfitation[41,42] or as a sulfur-centered nucleophile[43]. Less known is that sulfinate is an ambident nucleophile, and that the enantiotopic oxygen atoms are also potential nucleophilic sites. We realized this 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

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Celecoxib[44] or methylsulfone in Etoricoxib[45]. 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[46–48]. 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.

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 sulfinates suitable for our methodology (Fig. 3). Electron-rich phenyl sulfinates 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 sulfinates gave moderate results. Several naphthyl sulfinates 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 sulfinates 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 sulfinates, which resulted in decreased yields and enantioselectivity. This was solved by using K_2HPO_4 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-sulfinylated 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 sulfinylation 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).

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)[45]. Subsequently, enantioenriched Etoricoxib sulfinate ester **52** was obtained efficiently through our method. Recently, a group from Merck reported the preparation of sulfinates from primary sulfonamides through carbene-catalyzed deamination[44]. Using this approach, we transformed several bioactive primary sulfonamides into their corresponding sulfinates (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 toolkit of drug discovery programs (Fig. 4d, e). 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 sulfinamide **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 sulfinamides **64**-**66**. Further imidations[49,50] of Celecoxib sulfinate ester **58**, Celecoxib sulfoxide **61** and Celecoxib sulfinamide **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 sulfinylation 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.

Data availability

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

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41586-022-04524-4.

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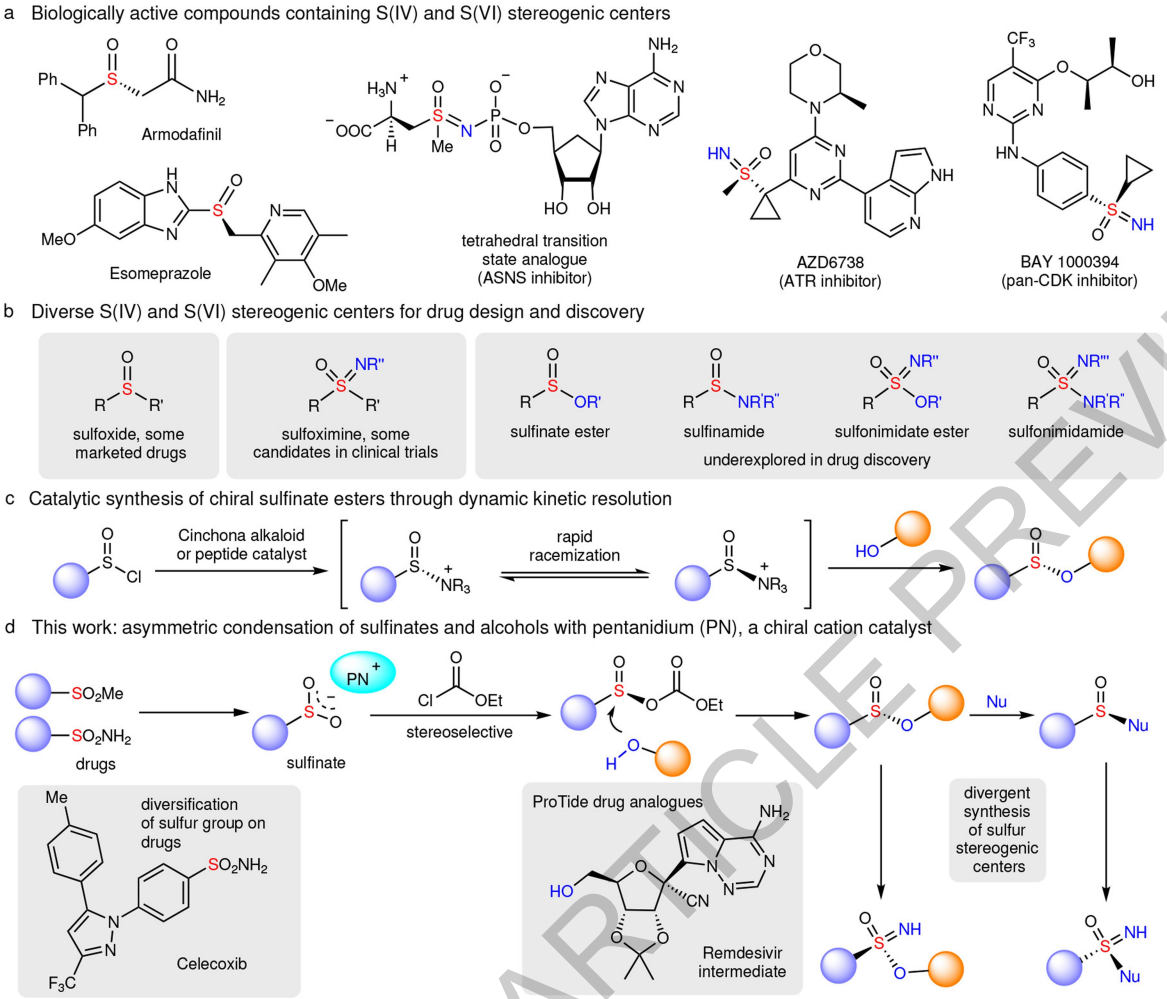
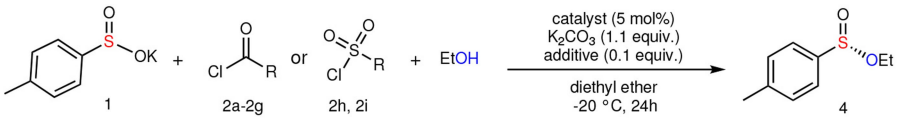


Fig. 1 | Diverse chiral sulfur pharmacophores for drug discovery and their synthesis. a, Examples of biologically active compounds containing S(IV) and S(VI) stereogenic centers. **b**, Examples of diverse chiral sulfur pharmacophores for drug design and discovery. **c**, Synthesis of chiral sulfinate esters through dynamic kinetic resolution with chiral amine catalysts. **d**, Synthesis of chiral sulfinate esters through asymmetric condensation of sulfinates and alcohols with pentanidium (this work). Me, methyl; Et, ethyl; PN, pentanidium; Nu, nucleophile.



entry	catalyst	2	additive	yield of 4 (%)	ee of 4 (%)
1	PN1	2a	none	90	91
2	PN1	2b	none	50	82
3	PN1	2c	none	30	0
4	PN1	2d	none	70	83
5	PN1	2e	none	75	86
6	PN1	2f	none	75	70
7	PN1	2g	none	71	86
8	PN1	2h	none	40	79
9	PN1	2i	none	50	77
10	PN2	2a	none	96	14
11	PN3	2a	none	92	9
12	PN4	2a	none	71	35
13	PN1	2a	3a	96	96
14	PN1	2a	3b	82	96
15	PN1	2a	3c	96 (88)[a]	96 (95)[a]
16	PN1	2a	3d	96	96

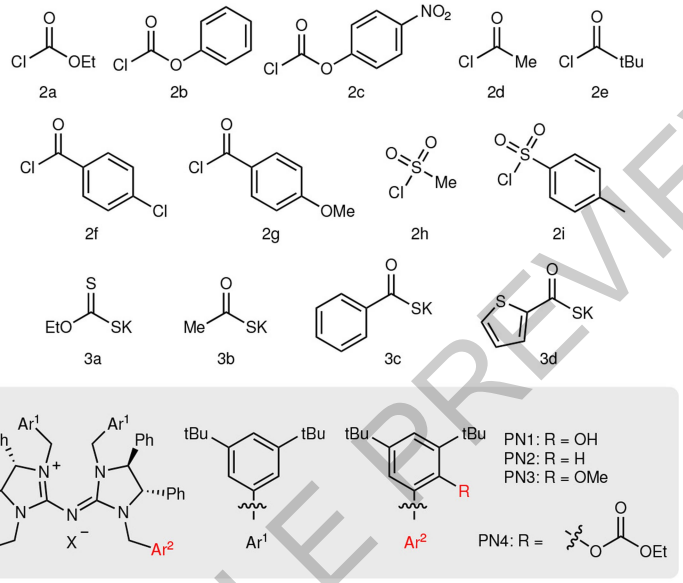


Fig. 2 | Optimization of reaction conditions. Reaction conditions: Potassium sulfinate **1** (0.1 mmol), catalyst (5 mol%), **2a**-**2i** (1.6 equiv.), EtOH (1.2 equiv.), K_2CO_3 (1.1 equiv.), additive **3a**-**3d** (0.1 equiv.), Et_2O (0.5 mL), −20 °C, 24 hours. Isolated yields were reported, and ee values were determined by chiral high-performance liquid chromatography (HPLC) analysis. [a]Reaction was performed on 12.0 mmol scale and 1.94 g of sulfinate ester **4** was isolated. Ph, phenyl; Ar, aryl; *t*Bu, *tert*-butyl.

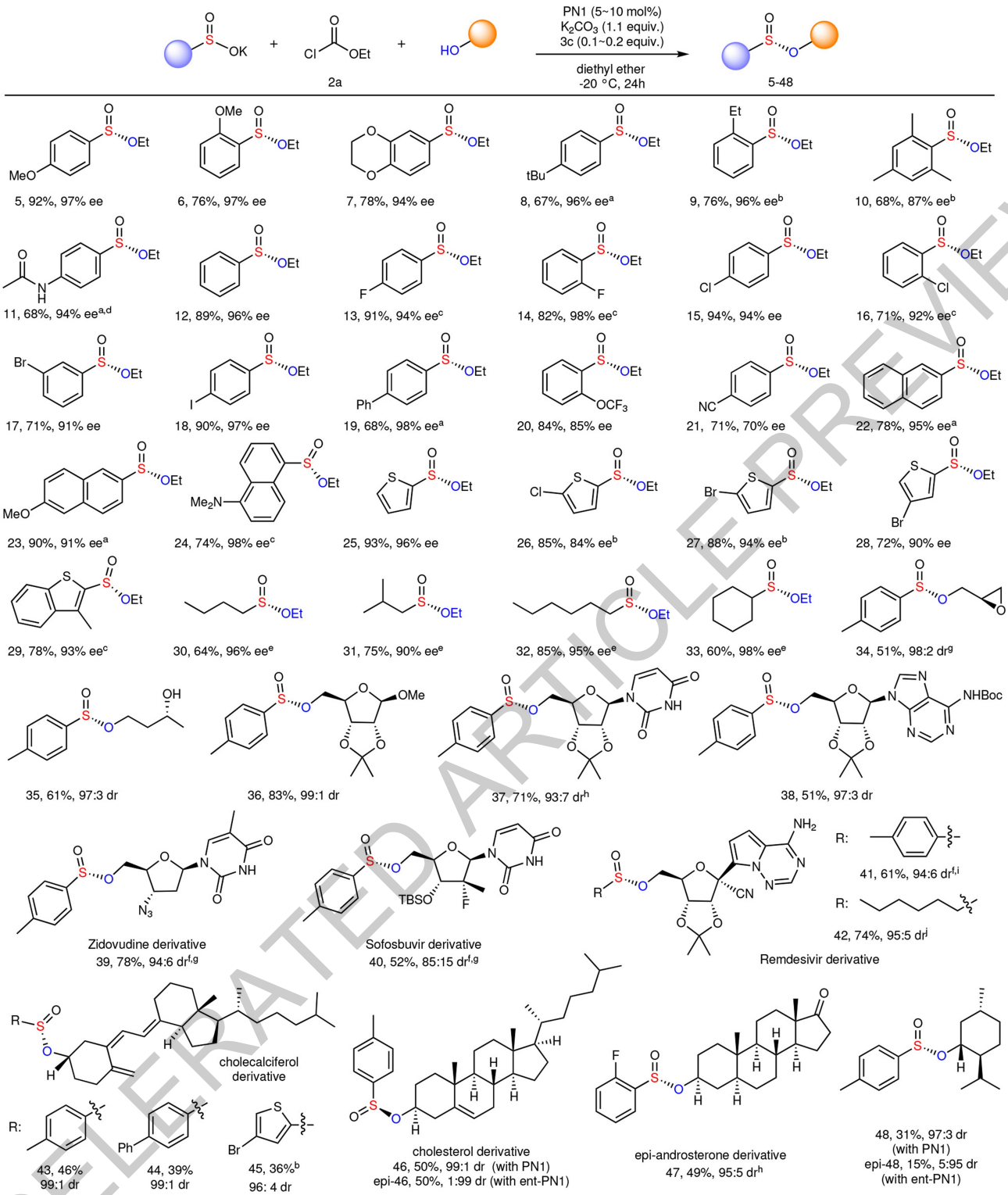


Fig. 3 | Reaction scope. Reaction conditions: Potassium sulfinate (0.1 mmol), **PN1** (5-10 mol%), **2a** (1.3-1.6 equiv.), alcohol (1.0-1.2 equiv.), K_2CO_3 (1.1 equiv.), **3c** (0.1-0.2 equiv.), Et_2O (0.5-1.0 mL), −20 °C, 24 hours. Isolated yields were reported, ee values were determined by chiral HPLC analysis, and dr values were determined by chiral HPLC or NMR analysis. [a]K_2HPO_4 (2.0 equiv.) instead of K_2CO_3. [b]**3d** (0.1-0.2 equiv.) as additive. [c]Sodium sulfinate was used. [d]**2a** (2.0 equiv.), **3d** (0.5 equiv.). [e]K_2HPO_4 (2.0 equiv.), **3d** (0.2 equiv.), additional H_2O (10 μL). [f]Alcohol (0.1 mmol), potassium sulfinate (0.15 mmol), **2a** (0.2 mmol), K_2CO_3 (0.15 mmol). [g]MTBE (1.0-2.0 mL) as solvent. [h]2.0 mL of mixed solvent Et_2O/EA (1:1). [i]2.0 mL of mixed solvent MTBE/EA (2:1). [j]Alcohol (0.1 mmol), potassium sulfinate (0.2 mmol), **2a** (0.4 mmol), K_2HPO_4 (0.4 mmol), **3d** (0.04 mmol), H_2O (20 μL), Et_2O (2.0 mL). See Supplementary Information for details. MTBE, methyl *tert*-butyl ether; EA, ethyl acetate; Boc, *tert*-butoxycarbonyl; TBS, *tert*-butyldimethylsilyl.

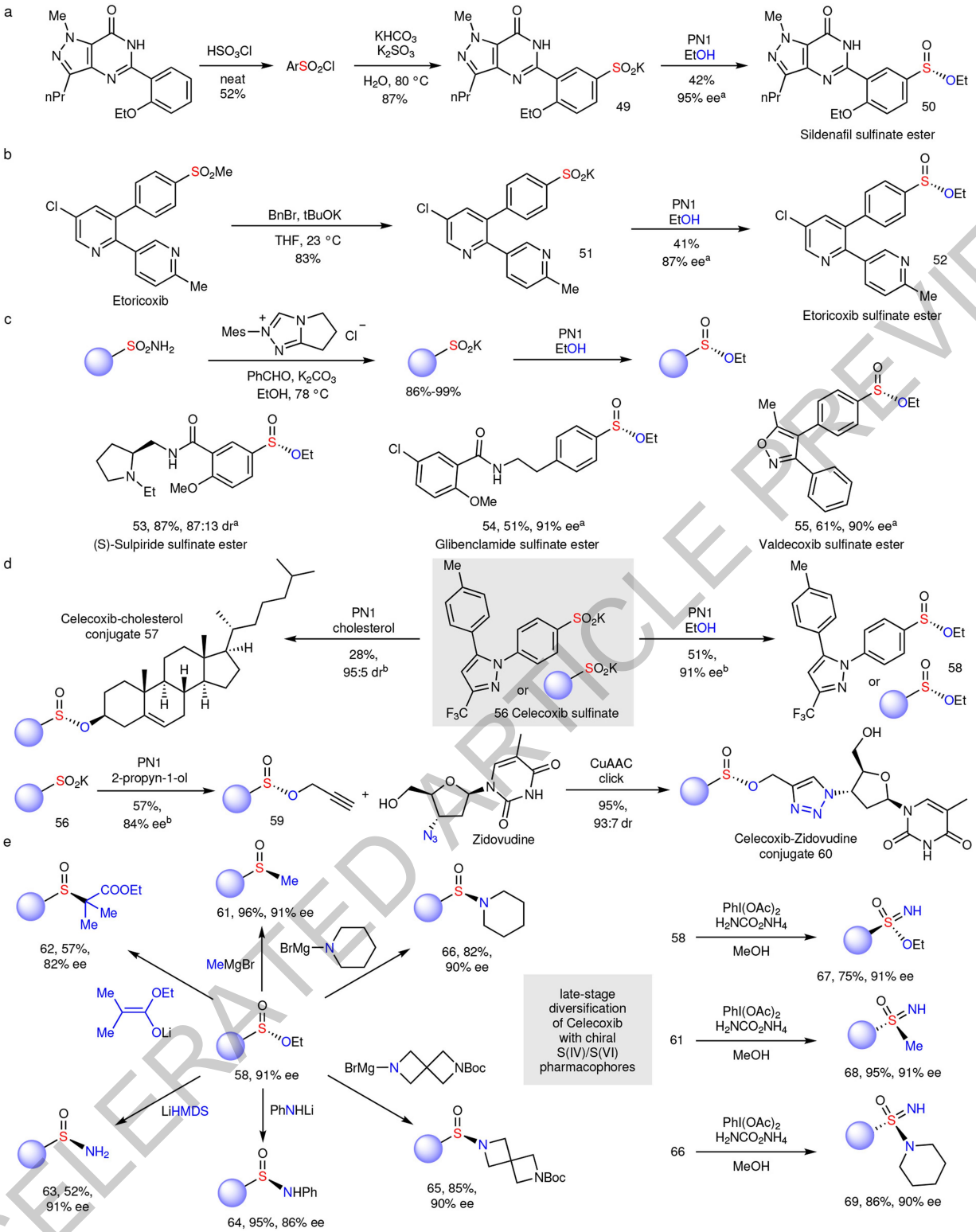


Fig. 4 | Functionalization and diversification of drugs. a, Synthesis of Sildenafil sulfinate ester. **b**, Synthesis of Etoricoxib sulfinate ester. **c**, Functionalization of sulfonamide drugs into sulfinate esters. **d**, Synthesis of Celecoxib sulfinate esters using different alcohols. **e**, Late-stage diversification of Celecoxib into a plethora of derivatives with sulfur stereocenters. Reaction conditions: [a]Potassium sulfinate (0.1 mmol), EtOH (1.0 equiv.), **PN1** (20 mol%), **2a** (2.1 equiv.), K_2HPO_4 (2.0 equiv.), **3a** or **3d** (1.0 equiv.), Et_2O or toluene (1 mL), 0 °C or −20 °C, 24 hours. [b]**56** (0.1 mmol), ROH (1.0 equiv.), **PN1** (5 mol%), **2a** (1.6 equiv.), K_2CO_3 (1.1 equiv.), **3c** (0.2 equiv.), H_2O (10 µL), MTBE (1.0 mL), −20 °C, 24 hours. See Supplementary Information for details. *n*Pr, *n*-propyl; LiHMDS, lithium bis(trimethylsilyl)amide.

Data availability

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

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Additional information

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