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Synthesis of chiral sulfinate esters by asymmetric condensation

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Xin Zhang[1]✉, Esther Cai Xia Ang[1], Ziqi Yang[1], Choon Wee Kee[1,2] & Choon-Hong Tan[1]✉

Achiral sulfur functional groups, such as sulfonamide, sulfone, thiol and thioether, are common in drugs and natural products. By contrast, chiral sulfur functional groups are often neglected as pharmacophores[1–3], although sulfoximine, with its unique physicochemical and pharmacokinetic properties[4,5], has been recently incorporated into several clinical candidates. Thus, other sulfur stereogenic centres, such as sulfinate ester, sulfinamide, sulfonimidate ester and sulfonimidamide, have started to attract attention. The diversity and complexity of these sulfur stereogenic centres have the potential to expand the chemical space for drug discovery[6–10]. However, the installation of these structures enantioselectively into drug molecules is highly challenging. Here we report straightforward access to enantioenriched sulfinate esters via asymmetric condensation of prochiral 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 centres.

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 centres 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 centres are often overlooked as pharmacophores[1–3], apart from the marketed chiral sulfoxides esomeprazole and armodafinil (Fig. 1a).

Sulfoximine, a moiety with a S(VI) stereocentre, has become increasingly important in drug discovery owing 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[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 centres such as sulfinate ester, sulfinamide[17], sulfonimidate ester and sulfonimidamide[18] have started to attract attention owing to the advances made by sulfoximine (Fig. 1b). Although some methodologies have been developed for the racemic synthesis of these stereogenic centres[19–21], the preparation of enantiopure sulfur stereocentres 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 have been reported and structural diversity is limited[28–32].

Among the sulfur stereogenic centres, sulfinate ester holds the linchpin position for two reasons. First, 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 centres[33–35]. Reports on the catalytic synthesis of enantioenriched sulfinate esters are scarce and all are based on 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 the catalytic synthesis of enantiopure sulfinate esters with broad substrate compatibility. Considering the increasing interest in using novel chiral sulfur stereogenic centres as pharmacophores, a catalytic method suitable for the late-stage manipulation of drugs with diverse sulfur stereocentres is imperatively required.

Here we report the desymmetrization of pro-chiral sulfinate to afford enantioenriched sulfinate esters using pentanidium (**PN**)[39,40] as a catalyst (Fig. 1d). Sulfinate, a stable and easily accessible reagent, is well known as a carbon-radical source for coupling via desulfitation[41,42] or as a sulfur-centred nucleophile[43]. It is less known 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 a 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[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

[1]Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore, Singapore. [2]Process and Catalysis Research, Institute of Chemical and Engineering Sciences, Singapore, Singapore. ✉e-mail: xzhang036@e.ntu.edu.sg; choonhong@ntu.edu.sg

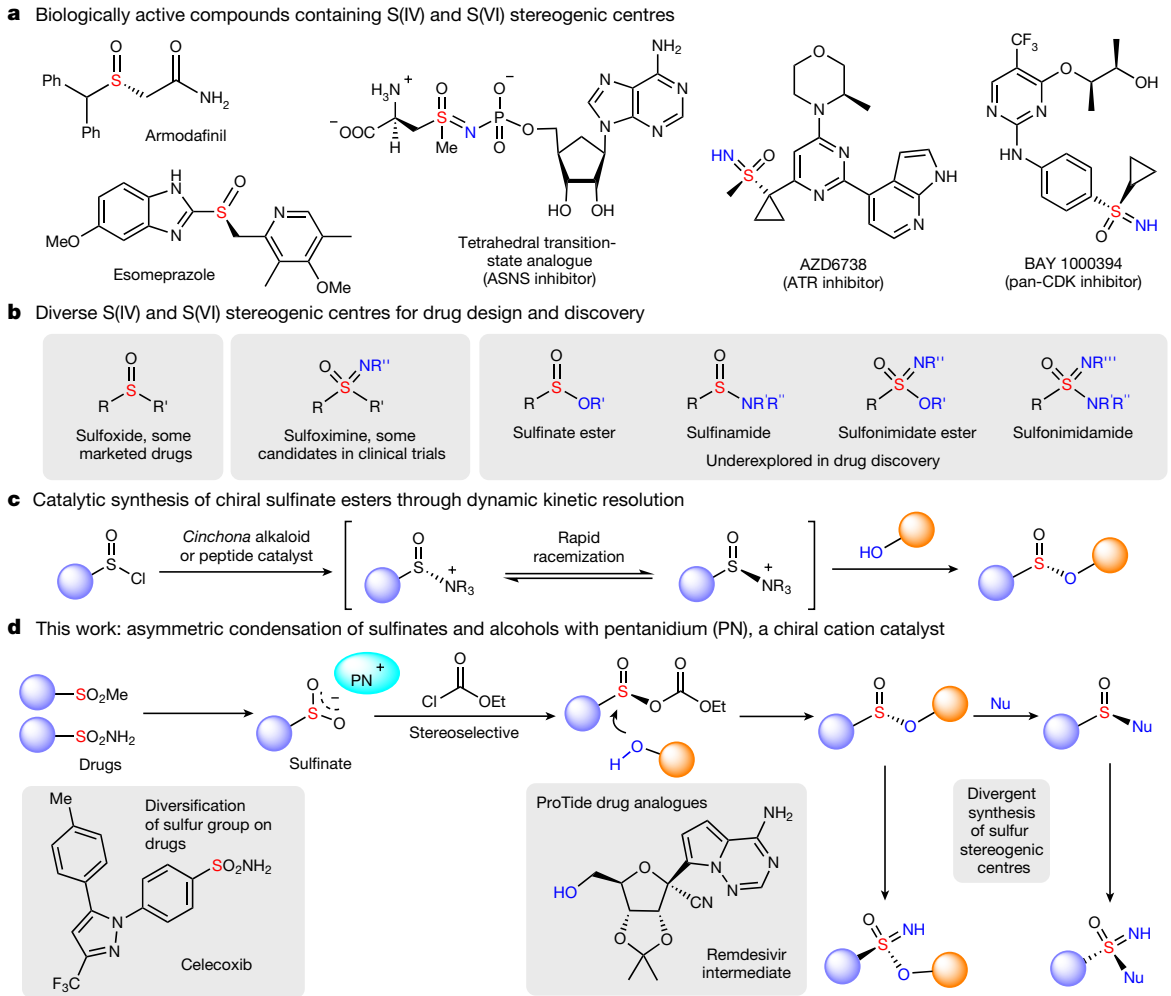


Fig. 1 | Diverse chiral sulfur pharmacophores for drug discovery and their synthesis. a, Examples of biologically active compounds containing S(IV) and S(VI) stereogenic centres. **b**, Examples of diverse chiral sulfur pharmacophores for drug design and discovery. **c**, Synthesis of chiral sulfinate 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). ASNS, L-asparagine synthase; ATR, ataxia telangiectasia and rad3-related; CDK, cyclin-dependent kinase; Et, ethyl; Me, methyl; Nu, nucleophile; Ph, phenyl.

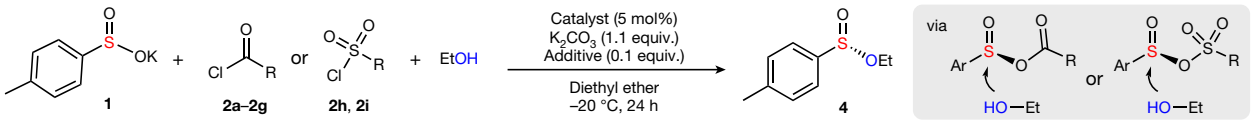
and drug intermediates containing an alcohol group, for example, the intermediate of remdesivir, an antiviral drug approved for the treatment of coronavirus disease 2019 (COVID-19), can be manipulated into novel analogues by replacing its phosphorus stereocentre (phosphoramidate) into a sulfur stereocentre. Phosphoramidate prodrugs, including remdesivir, are part of pronucleotide (ProTide) therapies for viral disease and cancer[46–48]. Similar to phosphorus, sulfur is also available in multiple oxidation states and a diverse range of structures; its adoption in place of phosphorus may lead to new therapies.

Optimization of reaction conditions

We started 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 stereocentre to afford sulfinate ester **4** (Fig. 2, entries 1–9). Ethyl chloroformate **2a** was found to give the most consistent and favourable results. Most of our earlier investigations were performed using pentanidium **PN2** (entry 10). Serendipitously, we discovered that pentanidium **PN1**, containing a phenol substituent, provided a high level of stereocontrol. We speculate that this 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 substantially (entry 11). We also detected the 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 conditions, 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 at gram scale with high yield and enantioselectivity (entry 15).

Reaction scope

On the basis of these results, we proceeded to investigate the scope of sulfinates suitable for our methodology (Fig. 3). Electron-rich phenyl sulfinates with different substitution patterns gave the 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 enantiomeric excess (e.e.) values. This reaction was also efficient to obtain a variety of phenyl sulfinate esters **13**–**18**



Entry	Catalyst	2	Additive	Yield of 4 (%)	e.e. 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

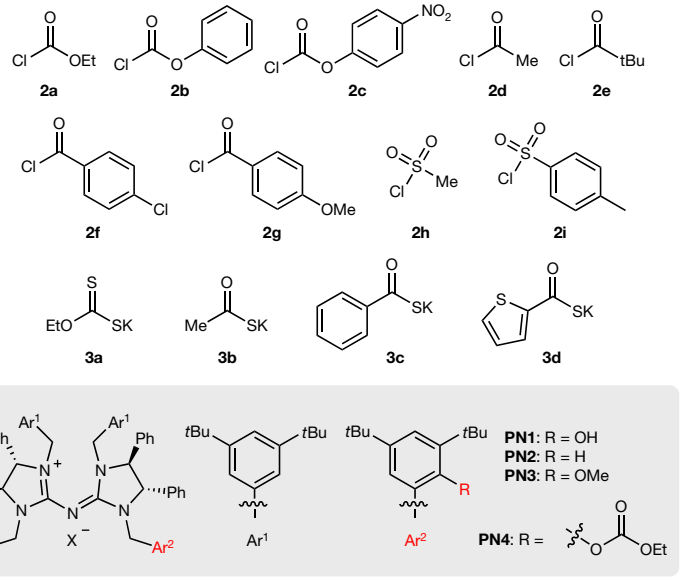


Fig. 2 | Optimization of reaction conditions. Reaction conditions: potassium sulfinate **1** (0.1 mmol), catalyst (5 mol%), **2a**–**2i** (1.6 equiv.), EtOH (1.2 equiv.), K_2CO_3 (1.1 equiv.), additive **3a**–**3d** (0.1 equiv.), Et_2O (0.5 ml), –20 °C, 24 h. Isolated yields are reported, and e.e. values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

substituted with halogen atoms. Phenyl substitution at the *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 with a moderate e.e. value. In general, strong electron-withdrawing aryl sulfinates gave moderate results. Several naphthyl sulfinates with different substitutions gave the 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 that the 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 dipotassium phosphate (K_2HPO_4) as a base and increasing the amount of catalyst or additive.

Next, we found that this methodology efficiently installed sulfur stereogenic centres 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 a diastereomeric ratio (d.r.) of 98:2. With (*R*)-1,3-butanediol, primary alcohol was preferred over secondary alcohol with mono-sulfinylated product **35** obtained with d.r. of 97:3. To investigate the potential of using this methodology to complement the ProTide strategy, we investigated the functionalization of several nucleosides. The desired nucleoside sulfinate esters **36**–**42** were obtained with moderate to high yields and excellent stereoselectivity. Sulfur stereogenic centres 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 when *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 isopropanol; however, bulky *tert*-butanol, phenols and amines were not viable nucleophiles (Supplementary Information).

Modification of drugs

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-catalysed 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 centres. Therefore, we utilized celecoxib as a model to justify that our methodology is a valuable addition to the toolkit of drug discovery programmes (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

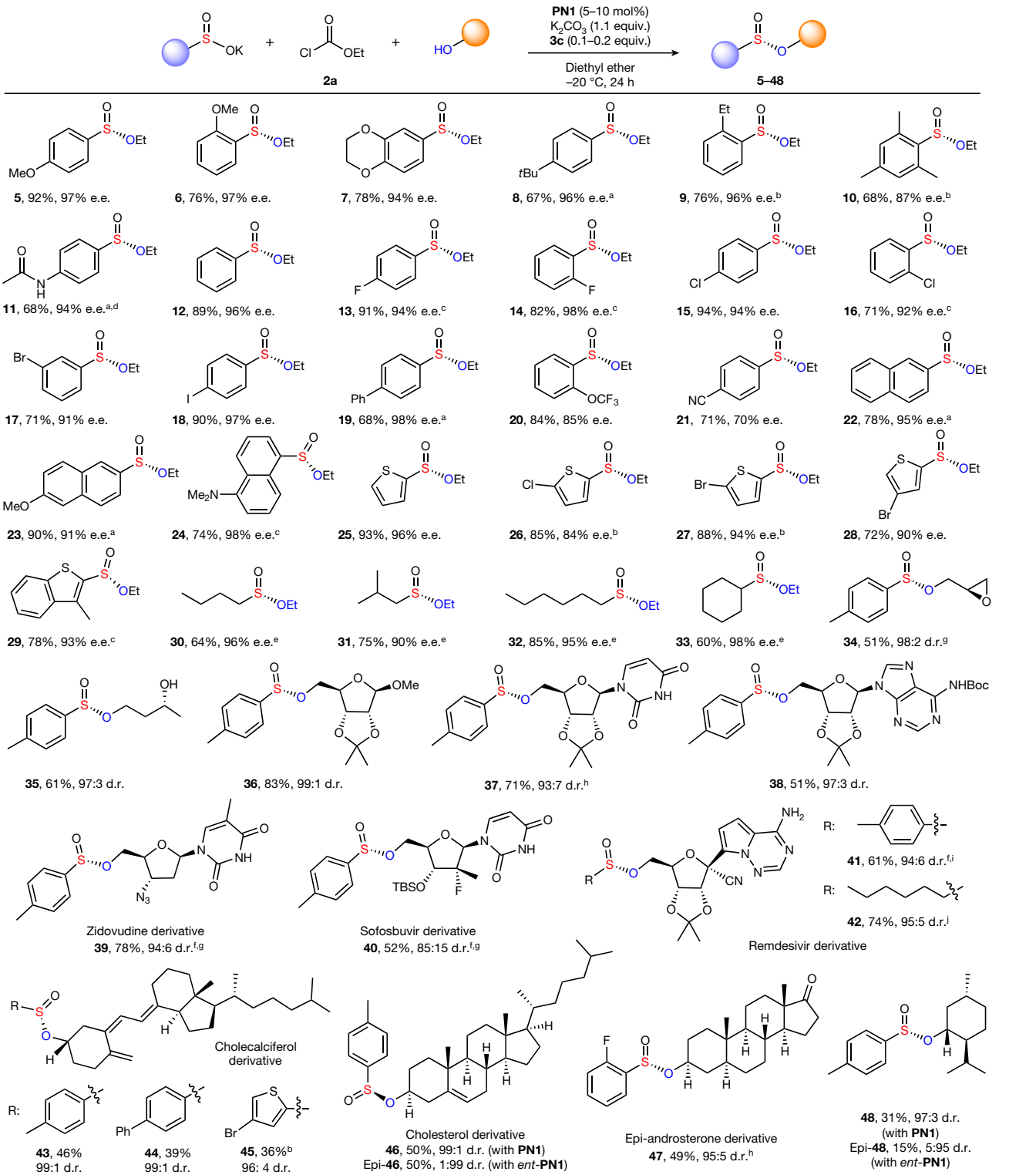


Fig. 3 | Reaction scope. Reaction conditions: potassium sulfinate (0.1 mmol), **PN1** (5–10 mol%), **2a** (1.3–1.6 equiv.), alcohol (1.0–1.2 equiv.), K_2CO_3 (1.1 equiv.), **3c** (0.1–0.2 equiv.), Et_2O (0.5–1.0 ml), –20 °C, 24 h. Isolated yields are reported, e.e. values were determined by chiral HPLC analysis, and d.r. 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. Boc, *tert*-butoxycarbonyl; EA, ethyl acetate; MTBE, methyl *tert*-butyl ether; TBS, *tert*-butyldimethylsilyl.

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 with a high e.e. value as a versatile precursor of other S(IV)/S(VI) stereogenic centres and able to be substituted by various

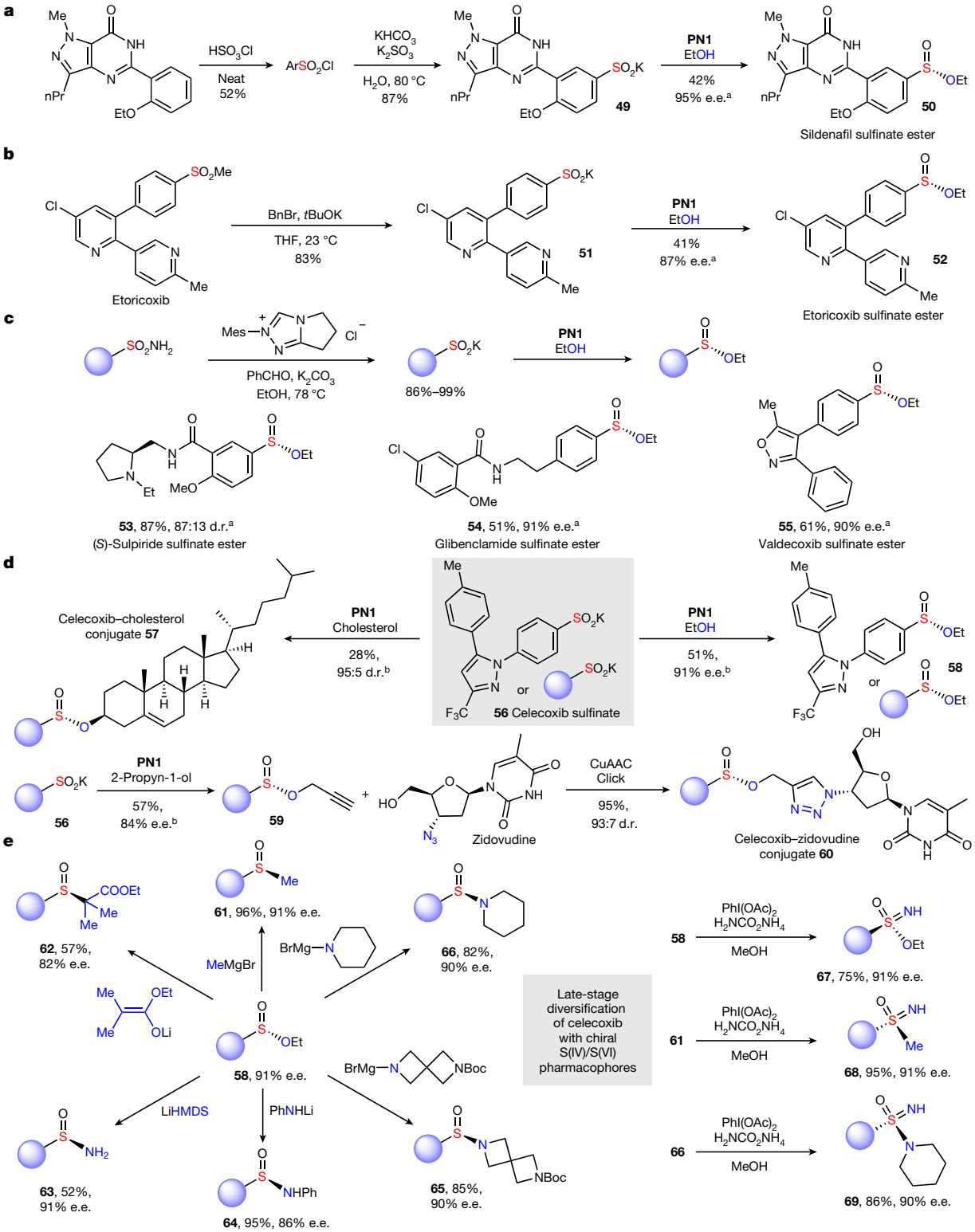


Fig. 4 | Functionalization and diversification of drugs. a, Synthesis of sildenafil sulfinate ester. **b**, Synthesis of etoricoxib sulfinate ester. **c**, Functionalization of sulfonamide drugs into sulfinate esters. **d**, Synthesis of celecoxib sulfinate esters using different alcohols. **e**, Late-stage diversification of celecoxib into a plethora of derivatives with sulfur stereocentres. 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 h. [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 h. See Supplementary Information for details. CuAAC, copper-catalysed azide–alkyne cycloaddition; LiHMDS, lithium bis(trimethylsilyl)amide; *n*Pr, *n*-propyl; THF, tetrahydrofuran.

nucleophiles at the sulfur centre with inverted configuration. Methyl Grignard reagent and lithium enolate are useful nucleophiles, providing respective enantioenriched sulfoxides (**61**, **62**). With lithium bis(trimethylsilyl)amide, 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 stereocentre 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 e.e. values. Many of these enantioenriched S(IV)/S(VI) stereogenic centres have been previously deemed as synthetically challenging[1,22].

Conclusion

We have presented a viable and unified synthetic strategy for the stereoselective preparation of sulfinate esters and related sulfur stereogenic centres. 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, for example, zidovudine, sofosbuvir and remdesivir, can be redecorated with sulfur stereogenic centres through sulfinylation of their alcoholic intermediates. This approach complements the ProTide strategy through replacement of the phosphorus stereogenic centre with sulfur stereogenic centres. In view of the increasing use of sulfur stereogenic centres as pharmacophores, we believe that this methodology will ameliorate the toolkits of drug discovery programmes for the exploration of these pharmacophores.

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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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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Correspondence and requests for materials should be addressed to Xin Zhang or Choon-Hong Tan.

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