ChemComm
Chemical Communications

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ROYAL SOCIETY OF CHEMISTRY

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ROYAL SOCIETY OF CHEMISTRY View Article Online
DOI: 10.1039/D0CC04840B

Journal Name

COMMUNICATION

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Organocatalytic enantioselective tandem sulfa-Michael/aldol reaction to access dihydrothiopyran-fused benzosulfolane skeletons bearing three contiguous stereocenters

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The first organocatalytic diastereo- and enantioselective tandem sulfa-Michael/aldol reaction of 2-mercaptoindole-3-carbaldehydes and 2-mercaptobenzaldehydes with benzo[*b*]thiophene sulfones was developed. With multiple hydrogen-bonding thiourea as the catalyst, a wide range of polycyclic dihydrothiopyran-fused benzosulfolanes were smoothly obtained with excellent results (up to 99% yield, >20:1 dr and 99% ee) under mild reaction conditions.

Fused polycyclic heterocycles are ubiquitous in a wide range of natural and unnatural biologically active molecules.[1] Among them, dihydropyran-fused dihydrobenzofurans as a type of oxygen-containing tricyclic skeletons have been well studied by organic chemists and pharmacologists (Figure 1, top), because many chiral compounds containing this skeletons have shown a wide spectrum of significant bioactivities, such as anti-inflammation, anti-bacteria, and anti-tumor activity.[2] The replacement of the oxygen atom in the dihydropyran-fused dihydrobenzofuran skeletons with sulfur atom generally results in the corresponding sulfur analogues dihydrothiopyran-fused dihydrobenzothiophenes (Figure 1, bottom). It is a very promising strategy that replacing the oxygen atom in biologically active molecules with sulfur atom for the research and development of pharmaceuticals, and some reports also prove the benefits of this strategy in enhancing the pharmacological activity.[3] In particular, many sulfur-containing fused polycyclic compounds have shown potential biological activities in medicinal chemistry.[4] In this context, as we can visualize, the molecules containing dihydrothiopyran-fused dihydrobenzothiophene motifs probably also have some biological activities in drug discovery. Accordingly, the development of new and facile synthetic strategies to access sulfur-containing polycyclic compounds, such as dihydrothiopyran-fused benzosulfolanes (Figure 1, bottom), is pharmaceutically intriguing and significant.

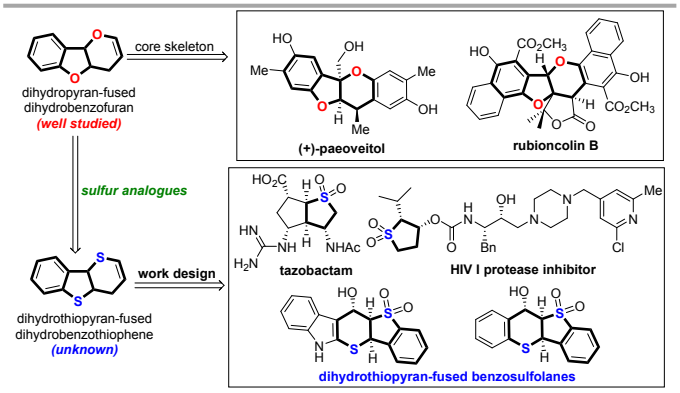

Figure 1. Project design.

Benzo[*b*]thiophene sulfones, behaving as powerful dipolarophiles, have been used in 1,3-dipolar cycloaddition reactions with various dipoles for the construction of polycyclic benzosulfolane compounds.[5-8] However, a survey of literature reveals that only two examples about the catalytic enantioselective cycloaddition of benzo[*b*]thiophene sulfones have been documented so far: in the first $[Cu(MeCN)_4]PF_6$/DTBM-Segphos catalyzed reaction of azomethine ylides with benzo[*b*]thiophene sulfones resulted in *exo*-pyrrolidine-fused benzosulfolanes (Scheme 1),[6] while in the other, the same reaction also could provide *exo*-pyrrolidine-fused benzosulfolanes with $Cu(MeCN)_4PF_6$/DTBM-Segphos complex but *endo*-cycloadducts as major products with AgOAc/ThioClickFerrophos complex (Scheme 1).[7] To our surprise, the involvement of benzo[*b*]thiophene sulfones to access polycyclic benzosulfolane compounds with asymmetric organocatalysis has yet to be developed, even though the asymmetric organocatalysis has become an efficient and versatile tool for the construction of elaborated polycyclic heterocycles.[9] In this context, on the basis of our long-standing studies on organocatalytic asymmetric tandem transformations,[10] we envisioned that 2-mercaptoindole-3-carbaldehydes and 2-mercaptobenzaldehydes should react

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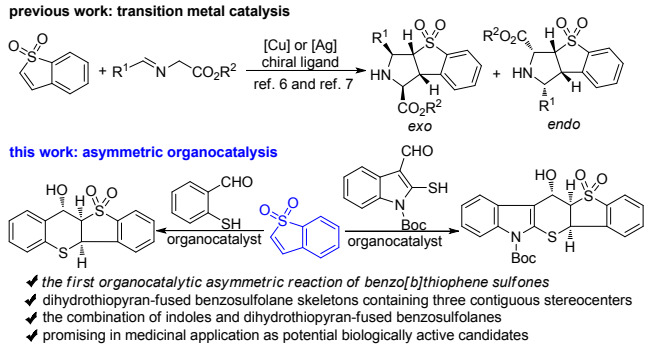
† Electronic Supplementary Information (ESI) available: Experimental procedures, spectral data of new compounds, and crystallographic data. CCDC 2007793 and 2007795. For ESI and crystallographic data in CIF or other electronic format. See DOI: 10.1039/x0xx00000x

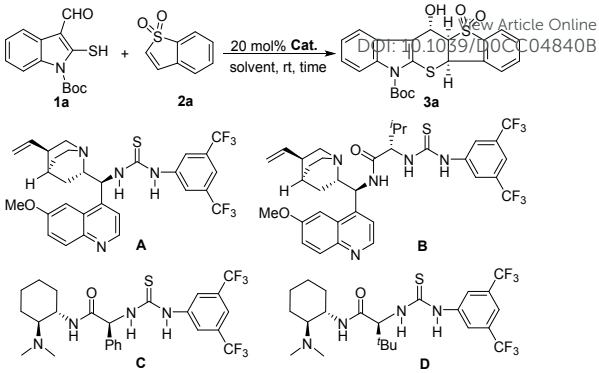
with benzo[*b*]thiophene sulfones via an asymmetric tandem sulfa-Michael/aldol reaction process, thus leading to the construction of dihydrothiopyran-fused benzosulfolane skeletons bearing three contiguous stereocenters (Scheme 1). To the best of our knowledge, the synthesis of chiral dihydrothiopyran-fused indole compounds via a catalytic asymmetric approach is rarely reported.[11] Herein, we wish to report our success in this tandem reaction catalyzed by a multiple hydrogen-bonding thiourea organocatalyst. Notably, this work represents the first organocatalytic asymmetric transformation of benzo[*b*]thiophene sulfones.

Scheme 1 Catalytic asymmetric transformations of benzo[*b*]thiophene sulfones.



We initiated our investigation with the reaction of 2-mercaptoindole-3-carbaldehyde **1a** and benzo[*b*]thiophene sulfone **2a** in $CHCl_3$ at room temperature (Table 1). With 20 mol% quinine-derived thiourea **A** as the catalyst, the reaction gave the polycyclic product **3a** in 51% yield with 86:14 dr and 27% ee (entry 1). Application of catalyst **B**, which derived from quinine and *L*-valine bearing multiple hydrogen-bonding donors, afforded product **3a** in 95% yield with 59:41 dr and 57% ee (entry 2). Likewise, multiple hydrogen-bonding thiourea catalyst **C**, which derived from (*S*,*S*)-cyclohexane-1,2-diamine and *L*-phenylglycine, could also efficiently promote the cycloaddition reaction and furnished **3a** in quantitative yield with improved diastereo- and enantioselectivity (entry 3). To our delight, replacing the phenyl group of catalyst **C** with more sterically hindered *tertiary* butyl group resulted in the catalyst **D**, and the reaction with **D** proceeded smoothly to give **3a** in 98% yield with 92:8 dr and 95% ee (entry 4). Afterwards, experiments were carried out with different solvents including CH_2Cl_2, MTBE and toluene, and it revealed that toluene was the best candidate in the light of stereoselectivitiy (entry 7 vs 5-6). Lowering the reaction temperature to 0 °C, **3a** was obtained with slightly improved dr and ee values (97:3 dr and 98% ee) (entry 8). Decreasing the catalyst loading from 20 mol% to 10 mol%, the reaction afforded **3a** with unchanged results (entry 9). Adjusting the ratio of substrates **1a** to **2a** from 1.2:1 to 1.1:1, the excellent results were still maintained (entry 10). Ultimately, enhancing the concentration of **2a** to 0.2 mmol/mL was able to markedly accelerate the rate of the reaction without loss in the yield and stereoselectivity (entry 11).

Table 1. Optimization of reaction conditions[a]



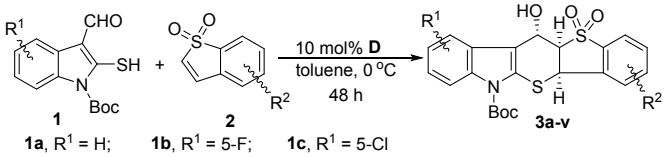
entry	Cat.	solvent	time (h)	yield (%)[b]	dr[c]	ee (%)[c]
1	**A**	$CHCl_3$	16	51	86:14	27
2	**B**	$CHCl_3$	48	95	59:41	57
3	**C**	$CHCl_3$	36	98	78:22	94
4	**D**	$CHCl_3$	36	98	92:8	95
5	**D**	CH_2Cl_2	36	97	90:10	96
6	**D**	MTBE	36	98	93:7	96
7	**D**	toluene	36	98	95:5	97
8[d]	**D**	toluene	72	98	97:3	98
9[e]	**D**	toluene	72	98	97:3	98
10[f]	**D**	toluene	72	98	97:3	98
11[f,g]	**D**	toluene	48	98	97:3	98

[a]Unless otherwise noted, the reactions were carried out with **1a** (0.12 mmol), **2a** (0.1 mmol), and 20 mol% of catalyst in 1.0 mL of solvent at room temperature. [b]Isolated yields. [c]Determined by chiral HPLC analysis. [d]Run at 0 °C. [e]10 mol% **D** was used at 0 °C. [f]The ratio of **1a**:**2a** = 1.1:1, and 10 mol% **D** was used at 0 °C. [g]0.5 mL of toluene was used.

Having identified the optimal reaction conditions, the scope and limitation were explored for different 2-mercaptoindole-3-carbaldehydes and benzo[*b*]thiophene sulfones (Table 2). The asymmetric tandem reaction tolerated a wide range of 2-mercaptoindole-3-carbaldehydes bearing an electron-withdrawing substituent on the aryl group, regardless of their positions, affording products **3b**-**f** in excellent yields and stereoselectivities (entries 2-6). Similarly, the substrates bearing an electron-donating group on the aryl ring of 2-mercaptoindole-3-carbaldehydes were also compatible with the conditions. Almost quantitative yields and >20:1 dr with 93-99% ee were obtained for products **3g**-**i** (entries 7-9). Benzo[*b*]thiophene sulfones having an electron-withdrawing substituent on the aryl ring were able to participate successfully in the asymmetric tandem reaction to give products **3j**-**q** in excellent results (entries 10-17). Meanwhile, it was also found that the developed protocol allowed the installation of various electron-donating substituents at different positions on the aromatic ring, and these substrates smoothly gave rise to their corresponding products **3r**-**t** in acceptable results (entries 18-20). Product **3s** was obtained in 81% yield with >20:1 dr but only 61% ee. It was probably due to the more steric hindrance from the methyl group in the C7-position of the benzo[*b*]thiophene sulfone (entry 19). Additionally, phenyl group at the C5- or C6-position was also well tolerated, furnishing products **3u** and **3v** in almost quantitative yields with 98% and 99% ee, respectively (entries 21 and 22). However, it was found that both *N*-Me and *N*-Bn substituted 2-mercaptoindole-3-carbaldehydes did not react with **2a** under the standard conditions (no shown in Table 2).

Disappointingly, 2-methyl benzo[*b*]thiophene sulfone and 3-methyl benzo[*b*]thiophene sulfone were also tested, but no reaction occurred (no shown in Table 2). This negative outcome may be ascribed to the too much steric hindrance reducing the reactivity.

Table 2. Substrates scope of 2-mercaptoindole-3-carbaldehydes **1** and benzo[*b*]thiophene sulfones **2**[a]



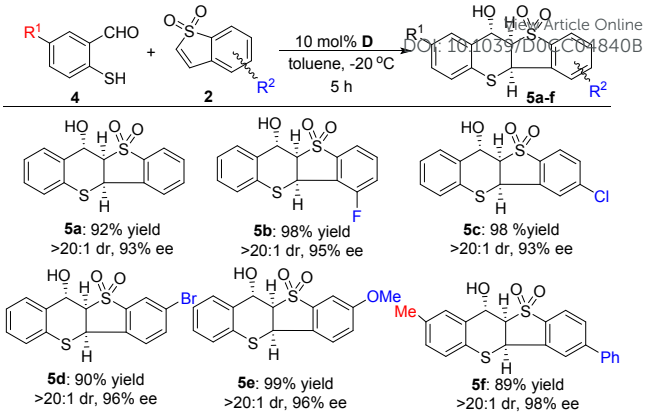
1a, R^1 = H; **1b**, R^1 = 5-F; **1c**, R^1 = 5-Cl
1d, R^1 = 6-Cl; **1e**, R^1 = 5-Br; **1f**, R^1 = 6-Br
1g, R^1 = 5-Me; **1h**, R^1 = 5-MeO; **1i**, R^1 = 6-MeO

entry	1	R^2 (2)	3/yield (%)[b]	dr[c]	ee (%)[d]
1	**1a**	H (**2a**)	**3a**/98	>20:1	98
2	**1b**	H (**2a**)	**3b**/99	10:1	97
3[e]	**1c**	H (**2a**)	**3c**/98	7:1	95
4	**1d**	H (**2a**)	**3d**/96	>20:1	97
5	**1e**	H (**2a**)	**3e**/95	>20:1	93
6	**1f**	H (**2a**)	**3f**/95	>20:1	97
7	**1g**	H (**2a**)	**3g**/98	>20:1	93
8	**1h**	H (**2a**)	**3h**/97	>20:1	97
9	**1i**	H (**2a**)	**3i**/98	>20:1	99
10	**1a**	4-F (**2b**)	**3j**/99	>20:1	99
11	**1a**	5-F (**2c**)	**3k**/97	13:1	98
12	**1a**	4-Cl (**2d**)	**3l**/98	>20:1	97
13	**1a**	5-Cl (**2e**)	**3m**/98	13:1	98
14	**1a**	7-Cl (**2f**)	**3n**/99	>20:1	78
15[e]	**1a**	4-Br (**2g**)	**3o**/99	>20:1	97
16	**1a**	5-Br (**2h**)	**3p**/99	12:1	98
17	**1a**	6-Br (**2i**)	**3q**/99	>20:1	99
18[e]	**1a**	5-Me (**2j**)	**3r**/98	>20:1	98
19[f]	**1a**	7-Me (**2k**)	**3s**/81	>20:1	61
20	**1a**	6-MeO (**2l**)	**3t**/99	>20:1	99
21	**1a**	5-Ph (**2m**)	**3u**/98	>20:1	98
22	**1a**	6-Ph (**2n**)	**3v**/98	>20:1	99

[a]All the reactions were carried out with **1** (0.11 mmol), **2** (0.1 mmol), and catalyst **D** (10 mol%) in 0.5 mL of toluene at 0 °C for 48 h. [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] Determined by chiral HPLC analysis. [e] Run for 60 h. [f] Run for 72 h.

Encouraged by the success of the above tandem reaction, we further investigated the asymmetric tandem reaction of 2-mercaptobenzaldehydes **4** and **2** for the synthesis of tetraheterocyclic benzodihydrothiopyran-fused benzosulfolane compounds (Scheme 2). Using **D** as the catalyst, the reaction of 2-mercaptobenzaldehyde **4a** and **2a** proceeded to completion in toluene at -20 °C for 5 h, affording the desired product **5a** in 92% yield with >20:1 dr and 93% ee. Substrates bearing either electron-withdrawing or electron-donating group at the aromatic ring of benzo[*b*]thiophene sulfones, regardless of their positions, all could react with 2-mercaptobenzaldehyde smoothly to give products **5b**-**e** in 90-99% yields with >20:1 dr and 93-96% ee values. Moreover, substrate bearing electron-donating group such as methyl group on the C5-position of 2-mercaptobenzaldehyde was also well tolerated, furnishing **5f** in 89% yield with excellent diastereo- and enantioselectivity.

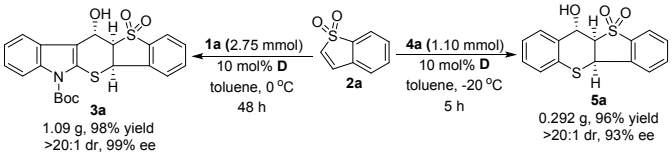
Scheme 2 Substrates scope of 2-mercaptobenzaldehydes and benzo[*b*]thiophene sulfones.[a]



[a]Unless otherwise noted, the reactions were carried out with **4** (0.11 mmol), **2** (0.1 mmol), and catalyst **D** (10 mol%) in 0.5 mL of toluene at -20 °C for 5 h. Yields refer to isolated pure compounds. The dr value was determined by ^{1}H NMR. The ee was determined by chiral HPLC analysis.

In order to illustrate the potential applicability of the methodology, the model reaction between **1a** and **2a** was carried out on a gram scale (Scheme 3).[12] Under the standard reaction conditions, the gram-scale reaction proceeded smoothly and afforded **3a** in almost quantitative yield with >20:1 dr and 99% ee. Meanwhile, a preparative scale reaction of **4a** and **2a** was also performed, and provided **5a** in excellent results. These preparative scale reactions indicate that the developed protocol has the potential to be used as a practical strategy for the synthesis of chiral dihydrothiopyran-fused benzosulfolane compounds.

Scheme 3 Preparative scale reactions of **3a** and **5a**.



Moreover, we tried to evaluate their potential bioactivity of randomly selected pentaheterocyclic indolodihydrothiopyran-fused benzosulfolanes **3** by testing their cytotoxicity in vitro using the K562 leukemia cell line. The preliminary results revealed that the tested compounds exhibited cytotoxicity with median inhibitory concentration (IC_{50}) values in the micromolar range (see Supporting Information). Compared with commercially available broad-spectrum anticancer drug cisplatin as a positive control, compounds **3d**, **3g** and **3i** showed impressive cytotoxicity against K562 leukemia cells with IC_{50} values in the lower micromolar range (Figure 2). The results suggest that these structurally novel polycyclic benzodihydrothiopyran-fused benzosulfolane derivatives might be promising in drug discovery for further investigation.

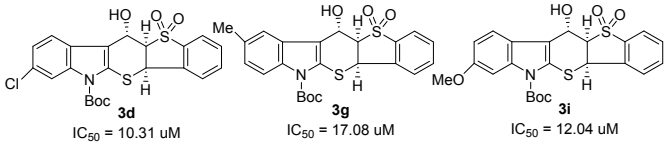


Figure 2. Biological activities evaluation of target products in K562 leukemia cell line.

Based on our experimental results and previously relevant reports regarding to the multiple hydrogen-bonding

bifunctional thiourea in asymmetric catalysis,[13] we proposed a plausible transition state model to account for the stereochemistry of the tandem reaction (see Supporting Information).[12] The benzo[*b*]thiophene sulfone was activated and oriented by the thiourea NH and amide NH of the catalyst **D**, while 2-mercaptoindole-3-carbaldehyde was deprotonated and activated by the tertiary amine moiety of the catalyst to enhance the nucleophilicity. Under this dual-activation mode and stereoselective induction of chiral catalyst **D**, the sulfur anion of 2-mercaptoindole-3-carbaldehyde attacks the *Re*-face of C3-position of benzo[*b*]thiophene sulfone via a sulfa-Michael addition process. Subsequently, the C2-position of benzo[*b*]thiophene sulfone attacks the aldehyde group of 2-mercaptoindole-3-carbaldehyde from *Re*-face through an intramolecular aldol reaction process. As a result, this tandem reaction generates the polycyclic dihydrothiopyran-fused benzosulfolane products with stereospecific configurations. The absolute configuration of adduct **3a** was assigned as (*C7R, C8R, C9S*) and **5a** was also assigned as (*C7R, C8R, C9S*) with the single crystal X-ray analysis. The stereochemistry of the other products was assigned by analogy assuming a common reaction pathway.[14]

In conclusion, we have developed a highly diastereo- and enantioselective tandem sulfa-Michael/aldol reaction of 2-mercaptoindole-3-carbaldehydes and benzo[*b*]thiophene sulfones by using multiple hydrogen-bonding thiourea as the catalyst. A series of structurally diverse pentaheterocyclic indolodihydrothiopyran-fused benzosulfolanes, bearing three contiguous stereocenters, were smoothly obtained with excellent results (up to 99% yield, >20:1 dr and 99% ee) under mild reaction conditions. These products are featured by the fusion of two privileged substructures including indole and dihydrothiopyran-fused benzosulfolane in one molecular structure, which maybe serve as the potentially promising candidates for drug discovery. We also demonstrated that this catalytic system could be extended to 2-mercaptobenzaldehydes to access tetraheterocyclic benzodihydrothiopyran-fused benzosulfolanes. This work represents the first organocatalytic asymmetric tandem reaction of benzo[*b*]thiophene sulfones.

We are grateful for financial support from the National Key R&D Program of China (2018YFC0807301-3), the National NSFC (21572223, 21871252, and 21901024).

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14. CCDC-2007793 (**3a**) and CCDC-2007795 (**5a**) contain the supplementary crystallographic data for this paper.

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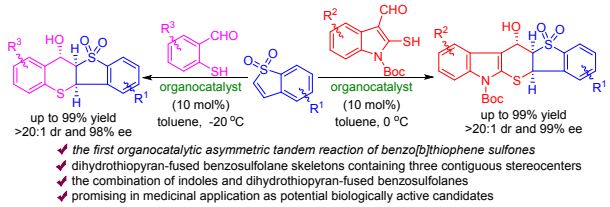
Table of Contents



The first organocatalytic enantioselective tandem sulfa-Michael/aldol reaction of benzo[*b*]thiophene sulfones was developed for the construction of dihydrothiopyran-fused benzosulfolane skeletons.