

Cite this: *RSC Adv.*, 2019, 9, 11978

K₃PO₄-promoted domino reactions: diastereoselective synthesis of *trans*-2,3-dihydrobenzofurans from salicyl *N*-*tert*-butanesulfinyl imines and sulfur ylides†‡

Minxuan Zhang,^a Tianyu Lu,^a Yun Zhao,^a Guixian Xie^{*c} and Zhiwei Miao^{ID} ^{*ab}Received 13th January 2019
Accepted 10th April 2019

DOI: 10.1039/c9ra00309f

rsc.li/rsc-advances

An efficient domino annulation between sulfur ylides and salicyl *N*-*tert*-butylsulfinyl imines was developed. The reaction proceeds with a diastereodivergent process, the configuration of the sulfinyl group determining the stereochemical course of the reaction. The method allows the synthesis of a highly substituted *trans*-2,3-dihydrobenzofuran skeleton with high yield and good chemo- and diastereoselectivity.

Introduction

Functionalized chiral benzofuran bearing three carbon stereocenters are the core of many bioactive natural products and pharmaceuticals.¹ Such cores also offer valuable chiral building blocks for the enantioselective synthesis of biologically active compounds.² Especially, the benzofurans with the amino group at the 3-position are vital in drug discovery and considered important for the bioactivity of these molecules.³ For example, phalarine, isolated from *Phalaris coerulescens*, is a type of important natural product, and has exhibited high structural diversity and a broad bioactivity profile.⁴ Fumimycin has demonstrated anti-bacterial properties while the synthetic cell motility inhibitor shows good biological effects in cell-based assays (Fig. 1).⁵

Diastereoselective synthesis of such significant chiral benzofurans remains a considerable challenge. 3-Substituted 2,3-dihydrobenzofurans have been synthesized by a variety of methods such as radical cyclizations,⁶ electrocyclizations,⁷ anionic cyclizations,⁸ biomimetic couplings and cycloaddition,⁹ Lewis acid promoted reactions,¹⁰ transition-metal-catalyzed processes,¹¹ and so on.¹² In 2008, Sabourin, Arya and co-

workers have developed a practical, enantioselective route to access 3-amino-2,3-dihydrobenzofurans (Scheme 1a).¹³ In 2011, Jørgenson and co-workers developed a highly efficient asymmetric organocatalytic cascade reaction to access 3-amino-2,3-dihydrobenzofurans through four sequential synthetic steps in one pot (Scheme 1b).¹⁴ In 2015, Zhao and co-workers reported an efficient domino reaction to chiral synthesize different substituted 2,3-dihydrobenzofuran-derived β -amino esters from *ortho*-hydroxyl aromatic *N*-*tert*-butylsulfinyl imines and diethyl bromomalonate promoted by K₂CO₃ (Scheme 1c).¹⁵ Despite many advances, the development of novel asymmetric catalytic methods to access this class of useful molecules to be highly appealing in modern asymmetric synthesis.

Chiral *N*-*tert*-butanesulfinyl imines, one class of the most efficient auxiliaries pioneered by Ellman, have been extensively used for the preparation of various chiral amines including variously substituted benzofuran-derived β -amino esters.¹⁶ Enantiomerically pure aldimines and ketoimines generated from an aldehyde or ketone with an alkyl or aryl sulfinamide are versatile building blocks in the construction of chiral amines, and their application has attracted a large amount of interest.¹⁷ In 1997, Ellman reported the preparation of *tert*-butanesulfinimines by direct condensation of a sulfinamide with aldehydes in the presence of MgSO₄. Furthermore, *tert*-

^aState Key Laboratory and Institute of Elemento-Organic Chemistry, College of Chemistry, Nankai University, Weijin Road 94, Tianjin 300071, People's Republic of China. E-mail: miaozhiwei@nankai.edu.cn

^bCollaborative Innovation Center of Chemical Science and Engineering (Tianjin), Tianjin 300071, People's Republic of China

^cCollege of Resources and Environment, Hunan Agricultural University, Changsha 410128, People's Republic of China

† Dedicated to 100th anniversary of Nankai University. Dedicated to the 100th birthday anniversary of Professor Ruyu Chen.

‡ Electronic supplementary information (ESI) available. CCDC 1583643 and 1587117. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9ra00309f

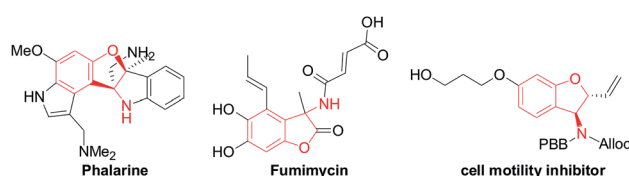
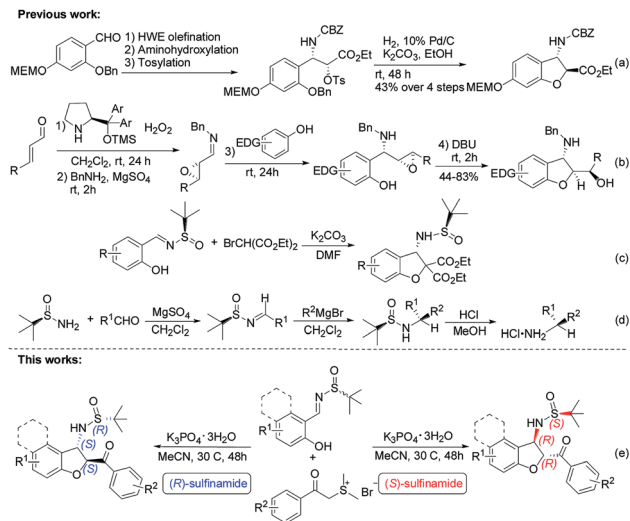


Fig. 1 Representative structures containing the 2,3-dihydrobenzofuran motif.





Scheme 1 Previous and proposed work.

butanesulfinimines reacted with Grignard reagents to provide *tert*-butane sulfonamides in high yields with high diastereoselectivity. Removal of the sulfinyl group is achieved with stoichiometric HCl in methanol to afford the desired α -branched amines (Scheme 1d).¹⁸

In spite of the obvious interesting properties of Ellman's chiral auxiliary such as the availability of both enantiomers and the mild conditions required for its cleavage, we speculated that the chirality of the auxiliary of the imine play an important role in the reaction stereoselectivity. Based on our previous study on the chemistry of chiral auxiliary,¹⁹ we report the domino annulation of salicyl *N*-*tert*-butylsulfinyl imines with sulfur ylides, which allows efficient asymmetric synthesis of *trans*-2,3-disubstituted 2,3-dihydrobenzofurans with high chemo- and stereoselectivity (Scheme 1e). The anticipated diastereodivergent process was investigated by combining both enantiomeric sulfinylimine auxiliaries employed.

Results and discussion

We initiated our investigation by subjecting sulfur ylide precursor **2a** (0.50 mmol, 2.5 equiv.)²⁰ to salicyl *N*-*tert*-butylsulfinyl imine **1a** (0.20 mmol)²¹ in the presence of K₂CO₃ (0.50 mmol, 2.5 equiv.) in CH₃CN at room temperature. To our delight, the domino reaction proceeded smoothly to provide *trans*-3-(2-methylpropane-2-sulfonamide)-2,3-dihydrobenzofuran **3a** in 78% yield and 72 : 28 diastereoselectivity with *trans*-**3a** being the major diastereomer (Table 1, entry 1). In accordance with the previous reports on base promoted domino reactions, it was found that bases strongly influenced the yield.²² When KO^tBu was used, the reaction became complicated and the product **3a** was isolated in low yield (Table 1, entry 2). Similarly, when the reaction was promoted with the weak base KOAc, the reaction rate was very slow and a low yield was obtained after 48 hours (Table 1, entry 3). To our great delight, in the presence of 0.50 mmol K₃PO₄·3H₂O in CH₃CN at room temperature, after 48 h, the desired product **3a** was isolated in 87% yield (Table 1,

Table 1 Optimization of reaction conditions^a

Entry	Base	Solvent	<i>trans</i> : <i>cis</i> ^b	Combined yield (%) ^c
1	K ₂ CO ₃	CH ₃ CN	72 : 28	78
2	KO ^t Bu	CH ₃ CN	70 : 30	16
3	KOAc	CH ₃ CN	73 : 27	34
4	K ₃ PO ₄ ·3H ₂ O	CH ₃ CN	71 : 29	87
5	DABCO	CH ₃ CN	72 : 28	44
6 ^d	K ₃ PO ₄ ·3H ₂ O	CH ₃ CN	71 : 29	46
7 ^e	K ₃ PO ₄ ·3H ₂ O	CH ₃ CN	70 : 30	57
8	K ₃ PO ₄ ·3H ₂ O	Toluene	54 : 46	6
9	K ₃ PO ₄ ·3H ₂ O	CH ₂ Cl ₂	58 : 42	33
10	K ₃ PO ₄ ·3H ₂ O	ClCH ₂ CH ₂ Cl	59 : 41	40
11	K ₃ PO ₄ ·3H ₂ O	THF	80 : 20	54
12	K ₃ PO ₄ ·3H ₂ O	Acetone	61 : 39	11
13	K ₃ PO ₄ ·3H ₂ O	AcOEt	56 : 44	44
14	K ₃ PO ₄ ·3H ₂ O	CHCl ₃	76 : 24	4
15 ^f	K ₃ PO ₄ ·3H ₂ O	CH ₃ CN	72 : 28	93

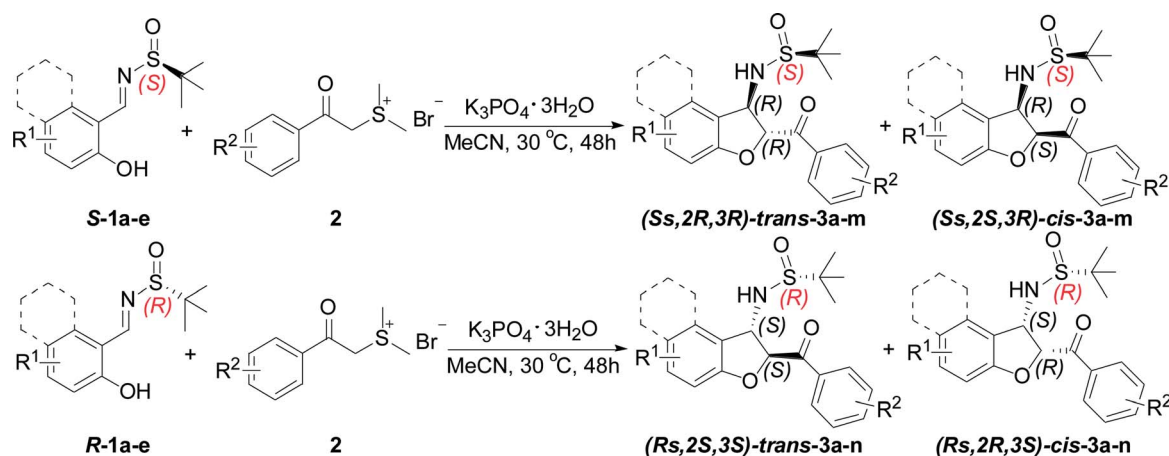
^a Unless otherwise specified, all reactions were carried out using *N*-*tert*-butylsulfinyl imine **1a** (0.20 mmol) and sulfur ylide precursor **2a** (0.50 mmol, 2.5 equiv.) in 2 mL solvent with 0.50 mmol of base at room temperature. ^b Determined by ¹H NMR (crude reaction mixture). ^c Combined yield of isolated products of *trans*-**3a** and *cis*-**3a** after column chromatography. ^d K₃PO₄·3H₂O loading is 0.10 mmol. ^e K₃PO₄·3H₂O loading is 0.40 mmol. ^f The reaction temperature is 30 °C.

entry 4). However, when the organic base DABCO (1,4-diazabicyclo [2.2.2] octane) was employed, and the yield of the desired product was higher than those using K₂CO₃ and KOAc but still lower than that K₃PO₄·3H₂O (Table 1, entries 5). The base amount was also examined as shown in Table 1. Increasing or decreasing the amount of base resulted in decrease of the efficiency of this reaction (Table 1, entries 6–7).

Subsequently, we investigated the effects of solvent on the reactivity, when K₃PO₄·3H₂O was used as the base. A rather low yield and selectivity was obtained when toluene was used as the solvent (Table 1, entry 8). Among the solvents examined, the use of CH₃CN gave the best result (Table 1, entries 9–14). Higher reactivity was observed at elevated a temperature of 30 °C, and the product was obtained in 93% yield and 72 : 28 diastereoselectivity (Table 1, entry 15). On the basis of the above experimental results, the optimal reaction conditions for this transformation were determined to be *N*-*tert*-butylsulfinyl imine **1a** (0.20 mmol), sulfur ylide precursor **2a** (0.50 mmol), and K₃PO₄·3H₂O (2.5 equiv.) in CH₃CN as solvent at 30 °C.

Having established the optimal reaction conditions for the synthesis of chiral sulfonamide 2,3-dihydrobenzofuran-2-yl-phenyl methanone, we next focused on the substrate scope of this transformation and the results are shown in Table 2. Representative *N*-*tert*-butylsulfinyl imines **1** with various substitutions were easily prepared by the condensation of either enantiomer of *tert*-butanesulfinamide with the corresponding



Table 2 Scope of the reaction^{a,b}

Entry	Major product	R ¹	R ²	Yield (%) ^c	trans : cis ^d	De (trans) (%) ^e
1	<i>trans</i> -(<i>Ss</i> ,2 <i>R</i> ,3 <i>R</i>)-3a	H (<i>S</i> -1a)	H (2a)	67	72 : 28	>99
2	<i>trans</i> -(<i>Ss</i> ,2 <i>R</i> ,3 <i>R</i>)-3b	5-Cl (<i>S</i> -1b)	H (2a)	40	64 : 36	98
3	<i>trans</i> -(<i>Ss</i> ,2 <i>R</i> ,3 <i>R</i>)-3c	5-Br (<i>S</i> -1c)	H (2a)	65	71 : 29	90
4	<i>trans</i> -(<i>Ss</i> ,2 <i>R</i> ,3 <i>R</i>)-3d	3,5-Cl (<i>S</i> -1d)	H (2a)	47	63 : 37	98
5 ^f	<i>trans</i> -(<i>Ss</i> ,2 <i>R</i> ,3 <i>R</i>)-3e	H (<i>S</i> -1e)	H (2a)	41	72 : 28	98
6	<i>trans</i> -(<i>Ss</i> ,2 <i>R</i> ,3 <i>R</i>)-3f	5-Cl (<i>S</i> -1b)	4-Cl (2b)	54	77 : 23	98
7	<i>trans</i> -(<i>Ss</i> ,2 <i>R</i> ,3 <i>R</i>)-3g	5-Br (<i>S</i> -1c)	4-Cl (2b)	41	77 : 23	98
8	<i>trans</i> -(<i>Ss</i> ,2 <i>R</i> ,3 <i>R</i>)-3h	3,5-Cl (<i>S</i> -1d)	4-Cl (2b)	28	56 : 44	90
9 ^f	<i>trans</i> -(<i>Ss</i> ,2 <i>R</i> ,3 <i>R</i>)-3i	H (<i>S</i> -1e)	4-Cl (2b)	57	88 : 12	98
10 ^f	<i>trans</i> -(<i>Ss</i> ,2 <i>R</i> ,3 <i>R</i>)-3j	H (<i>S</i> -1e)	4-Me (2c)	53	56 : 44	98
11	<i>trans</i> -(<i>Ss</i> ,2 <i>R</i> ,3 <i>R</i>)-3k	5-Br (<i>S</i> -1c)	4-Me (2c)	53	75 : 25	98
12	<i>trans</i> -(<i>Ss</i> ,2 <i>R</i> ,3 <i>R</i>)-3l	5-Cl (<i>S</i> -1b)	4-Me (2c)	69	70 : 30	98
13	<i>trans</i> -(<i>Ss</i> ,2 <i>R</i> ,3 <i>R</i>)-3m	5-Br (<i>S</i> -1c)	4-NO ₂ (2d)	—	—	—
14	<i>trans</i> -(<i>Rs</i> ,2 <i>S</i> ,3 <i>S</i>)-3a	H (<i>R</i> -1a)	H (2a)	65	72 : 28	90
15	<i>trans</i> -(<i>Rs</i> ,2 <i>S</i> ,3 <i>S</i>)-3b	5-Cl (<i>R</i> -1b)	H (2a)	69	75 : 25	98
16	<i>trans</i> -(<i>Rs</i> ,2 <i>S</i> ,3 <i>S</i>)-3c	5-Br (<i>R</i> -1c)	H (2a)	60	63 : 37	98
17 ^f	<i>trans</i> -(<i>Rs</i> ,2 <i>S</i> ,3 <i>S</i>)-3d	3,5-Cl (<i>R</i> -1d)	H (2a)	55	68 : 32	98
18	<i>trans</i> -(<i>Rs</i> ,2 <i>S</i> ,3 <i>S</i>)-3e	H (<i>R</i> -1e)	H (2a)	55	56 : 44	98
19	<i>trans</i> -(<i>Rs</i> ,2 <i>S</i> ,3 <i>S</i>)-3f	5-Cl (<i>R</i> -1b)	4-Cl (2b)	69	74 : 26	98
20	<i>trans</i> -(<i>Rs</i> ,2 <i>S</i> ,3 <i>S</i>)-3g	5-Br (<i>R</i> -1c)	4-Cl (2b)	55	70 : 30	98
21	<i>trans</i> -(<i>Rs</i> ,2 <i>S</i> ,3 <i>S</i>)-3h	3,5-Cl (<i>R</i> -1d)	4-Cl (2b)	51	61 : 39	92
22 ^f	<i>trans</i> -(<i>Rs</i> ,2 <i>S</i> ,3 <i>S</i>)-3i	H (<i>R</i> -1e)	4-Cl (2b)	49	63 : 37	90
23 ^f	<i>trans</i> -(<i>Rs</i> ,2 <i>S</i> ,3 <i>S</i>)-3j	H (<i>R</i> -1e)	4-Me (2c)	72	73 : 27	98
24	<i>trans</i> -(<i>Rs</i> ,2 <i>S</i> ,3 <i>S</i>)-3l	5-Cl (<i>R</i> -1b)	4-Me (2c)	62	72 : 28	98
25	<i>trans</i> -(<i>Rs</i> ,2 <i>S</i> ,3 <i>S</i>)-3n	5-Br (<i>R</i> -1c)	4-Me (2c)	63	64 : 36	98

^a Reaction conditions: *N*-*tert*-butylsulfinyl imines **1** (0.20 mmol), sulfur ylide **2** (0.50 mmol), in 2 mL of MeCN at 30 °C in the presence of 250 mol % of K₃PO₄·3H₂O. ^b The suffix *R* or *S* in the numbering refers to the absolute configuration of the sulfinylimine auxiliary. ^c Isolated yield after silica gel chromatography of **3**. *trans* and *cis* adducts have been separated by column chromatography and that only the major *trans*-adducts are described. ^d *Cis/trans* ratio determined from the ¹H NMR of the crude reaction mixture. ^e De determined from ¹H NMR of the crude reaction mixture. ^f *N*-*tert*-Butyl sulfinyl imine of β-naphthylaldehyde was used.

aldehydes according to the reported procedure.²¹ In all instances, imines were prepared in high yield and as single enantiomers. Generally, the domino reactions between a range of readily available *ortho*-hydroxyl aromatic *N*-*tert*-butylsulfinyl imines **S**-1 and sulfur ylide precursor **2a** provided *trans*-3-(2-methylpropane-2-sulfinamide)-2,3-dihydrobenzofuran **3** in moderate yields with moderate diastereoselectivities (Table 2, entries 1–5). The electronic property of the aromatic substituent has little effect on the yield and stereoselectivity. Even with a sterically hindered substrate, the reaction proceeded

smoothly to give the desired product in moderate yield. We were delighted to find that the *N*-*tert*-butyl sulfinyl imine of β-naphthylaldehyde **S**-1e, underwent smooth sequential annulation with **2a**, to give the corresponding product *trans*-(*Ss*,2*R*,3*R*)-**3e** in moderate yield with moderate diastereoselective (Table 2, entry 5).

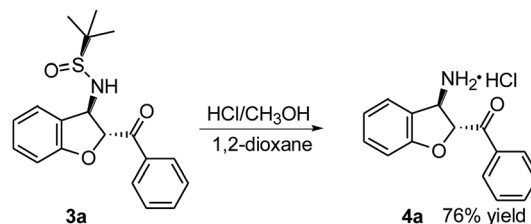
Further investigations using other sulfur ylide precursors and salicyl *N*-*tert*-butyl sulfinyl imines were performed under the optimized conditions. A series of sulfur ylide precursor proved to be suitable for this reaction. Aryl units containing



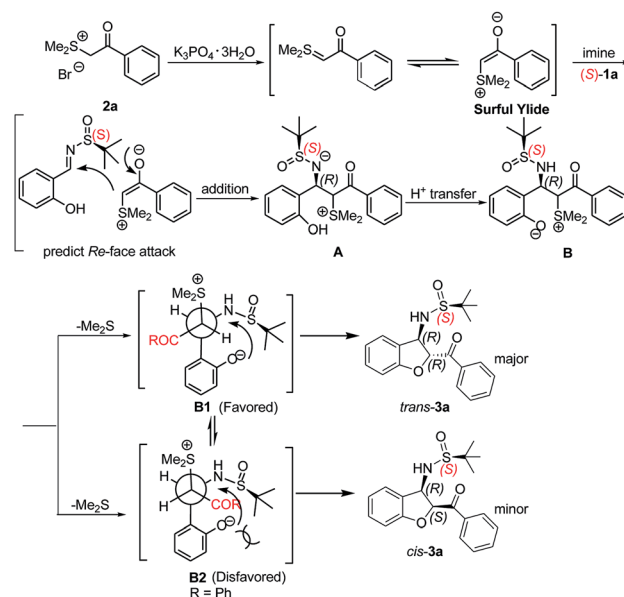
electron-donating or electron-withdrawing substituents in sulfur ylides were readily tolerated, thus giving preferentially the corresponding *trans*-3-(2-methylpropane-2-sulfinamide)-2,3-dihydrobenzofuran **3** in moderate yields with moderate diastereoselectivities (Table 2, entries 6–12). Notably, when the substituent was at the 4-position with an electron-withdrawing group of the benzene ring of sulfur ylide precursor **2d**, the reaction cannot work and no desired product **3m** observed (Table 2, entry 13). In contrast, when the enantiomeric (*R*)-chiral auxiliary (**1a–e**) was used, the diastereoselectivity was the same as the (*S*)-configured chiral auxiliary (Table 2, entries 14–25).

The relative configuration of the major diastereomers obtained from the reaction of sulfur ylide precursor **2a** and salicyl *N*-*tert*-butylsulfinyl imines **S-1a** and **R-1d** could be determined by X-ray crystallographic analysis (Fig. 2 and 3).²³ Both products *trans*-(*Ss,2R,3R*)-**3a** and *trans*-(*Rs,2S,3S*)-**3d** are derived from the same *N*-*tert*-butylsulfinylimine enantiomer but with differently configured chiral auxiliaries, and the different configuration of the formed amine stereocenter clearly proved that the diastereoselection was determined by the configuration of the auxiliary. On that basis, the stereochemistry of the other major and minor isomers was assigned.

To demonstrate further the synthetic utility of these findings, (2*R,3R*)-(3-amino-2,3-dihydro-benzofuran-2-yl)-phenyl-methanone **4a** was readily synthesized from *trans*-(*Ss,2R,3R*)-**3a** (Scheme 2). The deprotection and hydrolysis of **3a** in HCl (12 M) at room temperature gave the desired optically active **4a** with anti-relative configuration in 76% yield as the hydrochloride salt.



Scheme 2 Desulfinylation of *trans*-(*Ss,2R,3R*)-**3a**.



Scheme 3 Explanation of stereochemical outcomes.



Fig. 2 X-ray crystal structure of *trans*-(*Ss,2R,3R*)-**3a**.

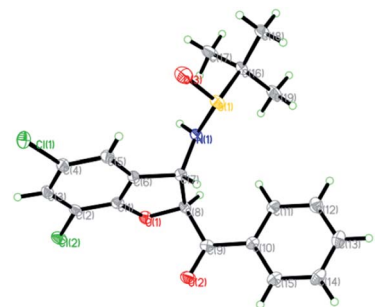


Fig. 3 X-ray crystal structure of *trans*-(*Rs,2S,3S*)-**3d**.

A mechanism for this domino reaction is proposed on the basis of previous literature reports and is shown in Scheme 3.²⁴ The reaction might be initiated by the formation of the sulfur ylide *via* the deprotonation of **2a**. Subsequent *Re*-face attack (for an (*S*)-configured sulfinylimine) nucleophilic addition of the sulfur ylide to the electron-deficient imine **1a** yielded the intermediate **A**. Intermediate **A** will transform into intermediate **B** under proton transfer. As shown in Newman projections **B1** and **B2**, intermediate **B1** is the favoured one, followed by S_N2 substitution to give the *trans*-configured 2,3-disubstituted dihydrobenzofuran **3a**.

Conclusions

In conclusion, we have developed a simple, convenient, and stereoselective domino reaction between salicyl *N*-*tert*-butylsulfinyl imines and sulfonium salts that provides a new method for the construction of *trans*-2,3-disubstituted 2,3-dihydrobenzofurans in good yields and good chemo- and diastereoselectivities. The domino reaction of the former proceeds with diastereodivergent process, with the configuration of the chiral auxiliary determining the stereo induction. Exploration of the scope and limitations of this reaction and the use of such dihydrobenzofurans to provide concise routes to more complex structures are ongoing and will be reported in due course.



Experimental

General methods

All reactions were performed under N₂ atmosphere in oven-dried glassware with magnetic stirring. Solvents were dried and distilled prior to use according to the standard methods. Unless otherwise indicated, all materials were obtained from commercial sources, and used as purchased without dehydration. Column chromatography was performed on silica gel 200–300 mesh. Nitrogen gas (99.999%) was purchased from Boc Gas Inc. ¹H and ¹³C NMR spectra were measured at 400 and 101 MHz, respectively. The solvents used for NMR spectroscopy were CDCl₃ and CD₃OD, using tetramethylsilane as the internal reference. Chemical shifts were recorded in parts per million (ppm). Coupling constants were given in Hz. The crystal structure was determined on a Bruker SMART 1000 CCD diffractometer. Mass spectra were obtained using an electrospray ionization (ESI-TOF) mass spectrometer. Melting points were determined on a T-4 melting point apparatus (uncorrected).

Preparation of salicyl *N*-*tert*-butylsulfinyl imines **1**¹⁵

Under a nitrogen atmosphere, to a mixture of salicylaldehyde (7.2 mmol, 1.2 equiv.) and sulfinamide (6 mmol, 1.0 equiv.) in CH₂Cl₂ was added Ti(O*i*-Pr)₄ (3–5 equiv.). After the mixture was stirred at room temperature for 48 h, 15 mL saturated solution of sodium bicarbonate was added. Stirring for a further 15 min was followed by filtration over a pad of MgSO₄ and Celite. The filter cake was washed with EtOAc and the filtrate concentrated under reduced pressure. The residue was purified by flash column chromatograph (eluted with 20 : 1 petroleum ether/EtOAc) to afford pure salicyl *N*-*tert*-butylsulfinyl imine.

General procedure for synthesis of *trans*-2,3-disubstituted 2,3-dihydrobenzofurans **3**

Under a nitrogen atmosphere, to a mixture of sulfur ylide precursor **2** (0.5 mmol, 2.5 equiv.), and K₃PO₄·3H₂O (133 mg, 0.5 mmol, 100 mmol %) was added CH₃CN (1 mL) *via* a syringe and allowed to stir for 5 min at room temperature. Salicyl *N*-*tert*-butylsulfinyl imine **1** (0.2 mmol, 1.0 equiv.) in CH₃CN (1 mL) was added and the reaction was allowed to stir for 48 h at 30 °C. The reaction was monitored by TLC spectroscopy. After the reaction was completed, the reaction mixture was directly purified by flash column chromatograph (eluted with 3 : 1 *n*-heptane/EtOAc) to afford the product **3**.

***trans*-(*S*)-*N*-(2*R*,3*R*)-2-Benzoyl-2,3-dihydrobenzofuran-3-yl-2-methylpropane-2-sulfinamide (3a).** White solid. Mp: 68–70 °C; [α]_D²⁰ = –78.67 [*c* = 0.95, CHCl₃]; ¹H NMR (400 MHz, CDCl₃) δ 8.02 (d, *J* = 7.1 Hz, 2H), 7.57–7.46 (m, 4H), 7.19 (s, 1H), 6.99–6.88 (m, 1H), 6.86 (d, *J* = 7.9 Hz, 1H), 5.75 (d, *J* = 4.0 Hz, 1H), 5.42 (t, *J* = 8.6 Hz, 1H), 3.76 (d, *J* = 7.1 Hz, 1H), 1.19 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 193.9, 159.1, 134.2, 134.1, 130.6, 129.4, 128.8, 126.5, 125.6, 122.1, 110.5, 89.3, 61.7, 56.3, 22.7; HRMS (ESI) calcd for C₁₉H₂₂NO₃S [M + H]⁺: 344.1315, found 344.1312.

***trans*-(*S*)-*N*-(2*R*,3*R*)-5-Chloro-2-benzoyl-2,3-dihydrobenzofuran-3-yl-2-methylpropane-2-sulfinamide (3b).** White solid. Mp: 56–58 °C; [α]_D²⁰ = –52.7 [*c* = 0.74, CHCl₃]; ¹H NMR (400 MHz, CDCl₃)

δ 8.07–7.95 (m, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.49–7.40 (m, 3H), 7.14 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.78 (d, *J* = 8.6 Hz, 1H), 5.81 (d, *J* = 5.0 Hz, 1H), 5.41 (dd, *J* = 8.0, 5.0 Hz, 1H), 3.84 (d, *J* = 8.0 Hz, 1H), 1.19 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 192.4, 156.6, 133.2, 133.0, 129.7, 128.3, 127.9, 126.3, 125.9, 125.4, 110.6, 88.6, 60.2, 55.4, 21.6; HRMS (ESI) calcd for C₁₉H₂₁ClNO₃S [M + H]⁺: 378.0925, found 378.0923.

***trans*-(*S*)-*N*-(2*R*,3*R*)-2-Benzoyl-5-bromo-2,3-dihydrobenzofuran-3-yl-2-methylpropane-2-sulfinamide (3c).** White solid. Mp 60–62 °C; [α]_D²⁰ = –37.22 [*c* = 0.72, CHCl₃]; ¹H NMR (400 MHz, CDCl₃) δ 8.00 (dd, *J* = 4.3, 7.5 Hz, 2H), 7.52 (d, *J* = 9.3 Hz, 2H), 7.41 (q, *J* = 7.6 Hz, 2H), 7.28–7.17 (m, 1H), 6.69 (t, *J* = 10.0 Hz, 1H), 6.02–5.72 (m, 1H), 5.41–5.26 (m, 1H), 3.76 (dd, *J* = 52.1, 9.3 Hz, 1H), 1.14 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 192.4, 192.2, 157.2, 157.2, 133.2, 132.9, 132.5, 128.5, 128.3, 127.9, 126.9, 112.8, 112.5, 111.3, 111.11, 88.4, 87.8, 60.2, 59.8, 55.6, 55.4, 21.6, 21.6; HRMS (ESI) calcd for C₁₉H₂₁BrNO₃S [M + H]⁺: 422.0420, found 422.0420.

***trans*-(*S*)-*N*-(2*R*,3*R*)-2-Benzoyl-5,7-dichloro-2,3-dihydrobenzofuran-3-yl-2-methylpropane-2-sulfinamide (3d).** White solid. Mp: 140–142 °C; [α]_D²⁰ = –55.82 [*c* = 0.67, CHCl₃]; ¹H NMR (400 MHz, CDCl₃) δ 8.02 (d, *J* = 7.7 Hz, 2H), 7.58 (d, *J* = 6.7 Hz, 1H), 7.47 (t, *J* = 7.2 Hz, 2H), 7.36 (s, 1H), 7.20 (s, 1H), 5.84 (d, *J* = 4.3 Hz, 1H), 5.70–5.37 (m, 1H), 3.83 (d, *J* = 8.6 Hz, 1H), 1.19 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 191.6, 152.8, 133.4, 132.8, 129.4, 128.4, 127.9, 127.6, 126.2, 124.0, 115.4, 88.7, 61.0, 55.5, 21.6; HRMS (ESI) calcd for C₁₉H₂₀Cl₂NO₃S [M + H]⁺: 412.0535, found 412.0530.

***cis*-(*S*)-*N*-(2*S*,3*R*)-2-Benzoyl-5,7-dichloro-2,3-dihydrobenzofuran-3-yl-2-methylpropane-2-sulfinamide (3d).** White solid. Mp: 133–134 °C; [α]_D²⁰ = +65.62 [*c* = 0.77, CHCl₃]; ¹H NMR (400 MHz, CDCl₃) δ 8.20 (d, *J* = 8.2 Hz, 2H), 7.66 (t, *J* = 6.9 Hz, 1H), 7.56 (t, *J* = 7.7 Hz, 2H), 7.29 (d, *J* = 4.5 Hz, 1H), 7.19 (s, 1H), 6.19 (d, *J* = 3.3 Hz, 1H), 5.46 (dd, *J* = 11.0, 2.8 Hz, 1H), 3.93 (d, *J* = 11.0 Hz, 1H), 1.27 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 191.5, 153.1, 133.3, 132.8, 129.5, 128.5, 127.7, 127.5, 125.8, 123.2, 115.7, 88.1, 60.5, 55.6, 21.5; HRMS (ESI) calcd for C₁₉H₂₀Cl₂NO₃S [M + H]⁺: 412.0535, found 412.0530.

***trans*-(*S*)-*N*-(1*R*,2*R*)-2-Benzoyl-1,2-dihydronaphtho[2,1-*b*]furan-1-yl-2-methylpropane-2-sulfinamide (3e).** White solid. Mp: 132–134 °C; [α]_D²⁰ = –173.33 [*c* = 0.09, CHCl₃]; ¹H NMR (400 MHz, CDCl₃) δ 8.11 (d, *J* = 7.9 Hz, 2H), 7.99 (d, *J* = 8.4 Hz, 1H), 7.83 (d, *J* = 8.6 Hz, 2H), 7.65 (t, *J* = 7.1 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 3H), 7.36 (d, *J* = 8.6 Hz, 1H), 7.22 (d, *J* = 8.9 Hz, 1H), 6.18 (d, *J* = 2.9 Hz, 1H), 5.93 (s, 1H), 3.91 (d, *J* = 3.4 Hz, 1H), 1.23 (d, *J* = 20.1 Hz, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 193.2, 157.1, 133.0, 131.4, 129.0, 128.4, 127.8, 126.6, 122.8, 121.6, 114.7, 111.3, 89.5, 58.9, 55.2, 21.6; HRMS (ESI) calcd for C₂₃H₂₄NO₃S [M + H]⁺: 394.1471, found 394.1472.

***trans*-(*S*)-*N*-(2*R*,3*R*)-5-Chloro-2-(4-chlorobenzoyl)-2,3-dihydrobenzofuran-3-yl-2-methylpropane-2-sulfinamide (3f).** White solid. Mp: 62–64 °C; [α]_D²⁰ = –61.72 [*c* = 0.58, CHCl₃]; ¹H NMR (400 MHz, CDCl₃) δ 7.95 (d, *J* = 8.5 Hz, 2H), 7.42 (d, *J* = 8.5 Hz, 3H), 7.13 (dd, *J* = 8.6, 1.8 Hz, 1H), 6.75 (d, *J* = 8.6 Hz, 1H), 5.74 (d, *J* = 5.2 Hz, 1H), 5.44 (dd, *J* = 7.8, 5.2 Hz, 1H), 3.87 (d, *J* = 7.8 Hz, 1H), 1.18 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 191.4, 156.4, 139.8, 131.4, 129.8, 129.7, 128.2, 126.2, 126.0, 125.4, 110.6, 88.5, 59.9, 55.5, 21.6; HRMS (ESI) calcd for C₁₉H₂₀Cl₂NO₃S [M + H]⁺: 412.0535, found 412.0530.



trans-(S)-N-((2R,3R)-5-Bromo-2-(4-chlorobenzoyl)-2,3-dihydrobenzofuran-3-yl)-2-methylpropane-2-sulfinamide (3g). White solid. Mp: 63–65 °C; $[\alpha]_{\text{D}}^{20} = -77.19$ [$c = 0.57$, CHCl_3]; ^1H NMR (400 MHz, CDCl_3) δ 8.02 (d, $J = 8.5$ Hz, 2H), 7.62 (s, 1H), 7.49 (d, $J = 8.5$ Hz, 2H), 7.35 (dd, $J = 8.6$, 1.9 Hz, 1H), 6.78 (d, $J = 8.6$ Hz, 1H), 5.80 (d, $J = 5.2$ Hz, 1H), 5.52 (dd, $J = 7.8$, 5.2 Hz, 1H), 3.88 (d, $J = 7.8$ Hz, 1H), 1.25 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3) δ 191.3, 157.0, 139.8, 132.6, 131.4, 129.8, 128.3, 128.2, 126.8, 113.1, 111.2, 88.5, 59.8, 55.5, 21.6; HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{20}\text{BrClNO}_3\text{S}$ [$\text{M} + \text{H}$] $^+$: 456.0030, found 456.0026.

trans-(S)-N-((2R,3R)-2-Benzoyl-5,7-dichloro-2,3-dihydrobenzofuran-3-yl)-2-methylpropane-2-sulfinamide (3h). Light yellow solid. Mp: 74–76 °C; $[\alpha]_{\text{D}}^{20} = -137.93$ [$c = 0.29$, CHCl_3]; ^1H NMR (400 MHz, CDCl_3) δ 8.12–7.95 (m, 2H), 7.45 (dd, $J = 8.5$, 6.2 Hz, 2H), 7.35 (d, $J = 1.2$ Hz, 0.5H), 7.22 (dd, $J = 10.1$, 1.8 Hz, 1H), 7.11 (d, $J = 1.4$ Hz, 0.5H), 5.91 (dd, $J = 11.3$, 4.4 Hz, 2H), 5.46 (ddd, $J = 14.8$, 9.8, 4.4 Hz, 1H), 3.78 (d, $J = 12.0$ Hz, 1H), 1.19 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3) δ 190.7, 190.5, 152.9, 152.6, 140.0, 139.9, 131.2, 123.0, 129.8, 129.6, 129.5, 128.3, 128.2, 127.5, 127.4, 126.4, 126.0, 123.9, 123.2, 115.7, 115.5, 88.7, 88.0, 60.6, 60.5, 55.7, 55.6, 21.6, 21.5; HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{20}\text{Cl}_2\text{NO}_3\text{S}$ [$\text{M} + \text{H}$] $^+$: 412.0535, found 412.0536.

trans-(S)-N-((1R,2R)-2-(4-Chlorobenzoyl)-1,2-dihydronaphtho[2,1-b]furan-1-yl)-2-methylpropane-2-sulfinamide (3i). Light yellow solid. Mp: 75–77 °C; $[\alpha]_{\text{D}}^{20} = -47.58$ [$c = 1.91$, CHCl_3]; ^1H NMR (400 MHz, CDCl_3) δ 8.20 (d, $J = 8.5$ Hz, 2H), 7.89–7.79 (m, 2H), 7.73 (d, $J = 8.3$ Hz, 1H), 7.54 (d, $J = 8.5$ Hz, 2H), 7.48 (t, $J = 7.5$ Hz, 1H), 7.35 (t, $J = 7.5$ Hz, 1H), 7.23 (d, $J = 8.9$ Hz, 1H), 6.31 (d, $J = 2.0$ Hz, 1H), 5.77 (dd, $J = 11.3$, 2.0 Hz, 1H), 3.79 (d, $J = 11.5$ Hz, 1H), 1.26 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3) δ 192.3, 156.8, 139.5, 131.6, 131.4, 129.9, 129.0, 128.9, 128.1, 127.9, 126.7, 122.9, 121.6, 114.6, 111.2, 89.5, 58.6, 55.2, 21.5; HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{23}\text{ClNO}_3\text{S}$ [$\text{M} + \text{H}$] $^+$: 428.1082, found 428.1079.

trans-(S)-2-Methyl-N-((1R,2R)-2-(4-methylbenzoyl)-1,2-dihydronaphtho[2,1-b]furan-1-yl)propane-2-sulfinamide (3j). Light yellow solid. Mp: 133–135 °C; $[\alpha]_{\text{D}}^{20} = -75.16$ [$c = 0.91$, CHCl_3]; ^1H NMR (400 MHz, CDCl_3) δ 8.18 (d, $J = 8.2$ Hz, 2H), 7.88–7.81 (m, 2H), 7.73 (d, $J = 8.4$ Hz, 1H), 7.54–7.45 (m, 1H), 7.43–7.33 (m, 3H), 7.29 (s, 1H), 6.38 (d, $J = 2.1$ Hz, 1H), 5.77 (dd, $J = 11.4$, 2.1 Hz, 1H), 3.81 (d, $J = 11.4$ Hz, 1H), 2.48 (s, 3H), 1.27 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3) δ 192.2, 156.9, 144.0, 131.2, 130.5, 129.3, 129.0, 128.6, 128.6, 127.9, 126.3, 122.6, 121.4, 115.5, 111.4, 88.0, 60.6, 55.7, 21.6, 20.8; HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{26}\text{NO}_3\text{S}$ [$\text{M} + \text{H}$] $^+$: 408.1628, found 408.1628.

trans-(S)-N-((2R,3R)-5-Bromo-2-(4-methylbenzoyl)-2,3-dihydrobenzofuran-3-yl)-2-methylpropane-2-sulfinamide (3k). Light yellow solid. Mp: 147–149 °C; $[\alpha]_{\text{D}}^{20} = -40.96$ [$c = 0.83$, CHCl_3]; ^1H NMR of *trans* (400 MHz, CDCl_3) δ 7.95 (d, $J = 8.2$ Hz, 2H), 7.61 (d, $J = 1.5$ Hz, 1H), 7.37–7.28 (m, 3H), 6.79 (d, $J = 8.6$ Hz, 1H), 5.84 (d, $J = 5.0$ Hz, 1H), 5.44 (dd, $J = 8.0$, 5.0 Hz, 1H), 3.93 (d, $J = 8.0$ Hz, 1H), 2.44 (s, 3H), 1.25 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3) δ 191.9, 157.2, 144.3, 132.4, 130.4, 128.6, 128.4, 128.3, 126.9, 112.8, 111.1, 88.4, 60.3, 55.4, 21.6, 20.8; HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{23}\text{BrNO}_3\text{S}$ [$\text{M} + \text{H}$] $^+$: 436.0577, found 436.0571.

trans-(S)-N-((2R,3R)-5-Chloro-2-(4-methylbenzoyl)-2,3-dihydrobenzofuran-3-yl)-2-methylpropane-2-sulfinamide (3l). Light

yellow solid. Mp: 146–148 °C; $[\alpha]_{\text{D}}^{20} = -51.45$ [$c = 1.47$, CHCl_3]; ^1H NMR (400 MHz, CDCl_3) δ 7.95 (d, $J = 8.1$ Hz, 2H), 7.48 (d, $J = 1.5$ Hz, 1H), 7.30 (d, $J = 8.0$ Hz, 2H), 7.18 (dd, $J = 8.6$, 2.0 Hz, 1H), 6.82 (d, $J = 8.6$ Hz, 1H), 5.84 (d, $J = 5.0$ Hz, 1H), 5.43 (dd, $J = 8.0$, 5.0 Hz, 1H), 3.95 (d, $J = 8.0$ Hz, 1H), 2.44 (s, 3H), 1.25 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3) δ 192.0, 156.7, 144.3, 130.4, 129.5, 128.5, 128.4, 126.4, 125.7, 125.4, 110.5, 88.4, 60.4, 55.4, 21.6, 20.8; HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{23}\text{ClNO}_3\text{S}$ [$\text{M} + \text{H}$] $^+$: 392.1082, found 392.1077.

trans-(R)-N-((2S,3S)-2-Benzoyl-2,3-dihydrobenzofuran-3-yl)-2-methylpropane-2-sulfinamide (3a). White solid. Mp: 55–57 °C. $[\alpha]_{\text{D}}^{20} = +68.7$ [$c = 0.88$, CHCl_3]; ^1H NMR (400 MHz, CDCl_3) δ 8.21 (d, $J = 8.0$ Hz, 1H), 8.10 (d, $J = 8.0$ Hz, 1H), 7.66–7.53 (m, 4H), 7.29–7.25 (m, 1H), 7.07–6.90 (m, 2H), 6.17–5.80 (m, 1H), 5.48 (ddd, $J = 14.2$, 9.5, 4.1 Hz, 1H), 3.87 (dd, $J = 8.0$, 8.0 Hz, 1H), 1.27 (d, $J = 3.7$ Hz, 9H); ^{13}C NMR (101 MHz, CDCl_3) δ 192.9, 158.2, 133.2, 133.0, 129.7, 128.5, 127.8, 125.7, 124.8, 121.1, 109.7, 88.3, 60.6, 55.5, 21.7; HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{22}\text{NO}_3\text{S}$ [$\text{M} + \text{H}$] $^+$: 344.1315, found 344.1311.

trans-(R)-N-((2S,3S)-2-Benzoyl-5-chloro-2,3-dihydrobenzofuran-3-yl)-2-methylpropane-2-sulfinamide (3b). White solid. Mp: 59–61 °C; $[\alpha]_{\text{D}}^{20} = +55.17$ [$c = 0.95$, CHCl_3]; ^1H NMR (400 MHz, CDCl_3) δ 8.20 (d, $J = 7.7$ Hz, 2H), 7.67 (t, $J = 7.2$ Hz, 1H), 7.57 (t, $J = 7.5$ Hz, 2H), 7.30–7.23 (m, 2H), 6.91 (d, $J = 8.5$ Hz, 1H), 6.14 (d, $J = 3.0$ Hz, 1H), 5.44 (dd, $J = 11.0$, 3.0 Hz, 1H), 3.79 (d, $J = 11.0$ Hz, 1H), 1.28 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3) δ 192.2, 156.8, 133.2, 133.0, 129.7, 128.5, 127.9, 126.4, 125.5, 124.8, 110.8, 87.8, 59.9, 55.6, 21.5; HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{21}\text{ClNO}_3\text{S}$ [$\text{M} + \text{H}$] $^+$: 378.0925, found 378.0928.

trans-(R)-N-((2S,3S)-2-Benzoyl-5-bromo-2,3-dihydrobenzofuran-3-yl)-2-methylpropane-2-sulfinamide (3c). White solid. Mp: 61–63 °C; $[\alpha]_{\text{D}}^{20} = +42.78$ [$c = 0.72$, CHCl_3]; ^1H NMR (400 MHz, CDCl_3) δ 8.02–7.97 (m, 2H), 7.66–7.49 (m, 2H), 7.44 (t, $J = 7.7$ Hz, 2H), 7.27 (dd, $J = 8.6$, 1.9 Hz, 1H), 6.72 (d, $J = 8.6$ Hz, 1H), 5.79 (d, $J = 5.1$ Hz, 1H), 5.39 (dd, $J = 8.2$, 5.1 Hz, 1H), 3.89 (d, $J = 8.2$ Hz, 1H), 1.18 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3) δ 193.4, 158.2, 134.3, 134.0, 133.5, 129.4, 129.4, 128.9, 127.9, 113.9, 112.2, 89.5, 61.2, 56.5, 22.7; HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{21}\text{BrNO}_3\text{S}$ [$\text{M} + \text{H}$] $^+$: 422.0420, found 422.0412.

trans-(R)-N-((2S,3S)-2-Benzoyl-5,7-dichloro-2,3-dihydrobenzofuran-3-yl)-2-methylpropane-2-sulfinamide (3d). White solid. Mp: 142–144 °C; $[\alpha]_{\text{D}}^{20} = +51.02$ [$c = 0.66$, CHCl_3]; ^1H NMR (400 MHz, CDCl_3) δ 8.01 (d, $J = 7.7$ Hz, 2H), 7.58 (t, $J = 7.4$ Hz, 1H), 7.45 (t, $J = 7.7$ Hz, 2H), 7.35 (s, 1H), 7.20–7.17 (m, 1H), 5.82 (d, $J = 5.2$ Hz, 1H), 5.46 (dd, $J = 8.4$, 5.2 Hz, 1H), 3.88 (d, $J = 8.4$ Hz, 1H), 1.18 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3) δ 153.8, 134.4, 133.8, 130.5, 129.4, 129.0, 128.6, 127.3, 125.0, 116.5, 89.8, 62.0, 56.6, 22.7; HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{20}\text{Cl}_2\text{NO}_3\text{S}$ [$\text{M} + \text{H}$] $^+$: 412.0535, found 412.0539.

trans-(R)-N-((1S,2S)-2-Benzoyl-1,2-dihydronaphtho[2,1-b]furan-1-yl)-2-methylpropane-2-sulfinamide (3e). White solid. Mp: 133–135 °C; $[\alpha]_{\text{D}}^{20} = +122.2$ [$c = 0.36$, CHCl_3]; ^1H NMR (400 MHz, CDCl_3) δ 8.25 (d, $J = 7.4$ Hz, 2H), 7.86–7.80 (m, 2H), 7.73 (d, $J = 8.3$ Hz, 1H), 7.65 (t, $J = 7.3$ Hz, 1H), 7.57 (t, $J = 7.6$ Hz, 2H), 7.47 (t, $J = 7.3$ Hz, 1H), 7.35 (t, $J = 7.3$ Hz, 1H), 7.24 (d, $J = 9.0$ Hz, 1H), 6.38 (d, $J = 2.1$ Hz, 1H), 5.82–5.74 (m, 1H), 3.79 (dd, $J = 16.4$, 8.4 Hz, 1H), 1.25 (s, 9H); ^{13}C



NMR (101 MHz, CDCl₃) δ 192.7, 156.8, 133.1, 133.0, 131.2, 129.3, 129.0, 128.6, 128.0, 126.3, 122.7, 121.4, 115.5, 111.4, 88.1, 60.5, 55.7, 21.6; HRMS (ESI) calcd for C₂₃H₂₄NO₃S [M + H]⁺: 394.1471, found 394.1465.

trans-(R)-N-((2S,3S)-5-Chloro-2-(4-chlorobenzoyl)-2,3-dihydrobenzofuran-3-yl)-2-methylpropane-2-sulfinamide (3f). White solid. Mp: 67–69 °C; [α]_D²⁰ = +95.63 [*c* = 0.87, CHCl₃]; ¹H NMR (400 MHz, CDCl₃) δ 7.96 (d, *J* = 8.5 Hz, 2H), 7.43 (d, *J* = 8.5 Hz, 3H), 7.14 (dd, *J* = 8.6, 1.9 Hz, 1H), 6.76 (d, *J* = 8.6 Hz, 1H), 5.74 (d, *J* = 5.1 Hz, 1H), 5.50–5.41 (m, 1H), 3.79 (d, *J* = 7.9 Hz, 1H), 1.19 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 192.4, 157.5, 140.8, 132.5, 130.8, 130.7, 129.2, 127.3, 127.1, 126.4, 111.6, 89.6, 60.9, 56.5, 22.7; HRMS (ESI) calcd for C₁₉H₂₀Cl₂NO₃S [M + H]⁺: 412.0535, found 412.0534.

trans-(R)-N-((2S,3S)-5-Bromo-2-(4-chlorobenzoyl)-2,3-dihydrobenzofuran-3-yl)-2-methylpropane-2-sulfinamide (3g). White solid. Mp: 55–57 °C; [α]_D²⁰ = +57.78 [*c* = 1.17, CHCl₃]; ¹H NMR (400 MHz, CDCl₃) δ 7.94 (d, *J* = 8.5 Hz, 2H), 7.55 (s, 1H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.27 (dd, *J* = 8.6, 1.7 Hz, 1H), 6.70 (d, *J* = 8.6 Hz, 1H), 5.72 (d, *J* = 5.2 Hz, 1H), 5.42 (dd, *J* = 8.0, 5.2 Hz, 1H), 3.91 (d, *J* = 8.0 Hz, 1H), 1.18 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 191.3, 156.9, 139.8, 132.5, 131.4, 129.8, 128.3, 128.2, 126.8, 113.0, 111.1, 88.4, 59.8, 55.5, 21.6; HRMS (ESI) calcd for C₁₉H₂₀BrClNO₃S [M + H]⁺: 456.0030, found 456.0030.

trans-(R)-N-((2S,3S)-5,7-Dichloro-2-(4-chlorobenzoyl)-2,3-dihydrobenzofuran-3-yl)-2-methylpropane-2-sulfinamide (3h). White solid. Mp: 58–60 °C; [α]_D²⁰ = +43.98 [*c* = 0.39, CHCl₃]; ¹H NMR (400 MHz, CDCl₃) δ 8.18–8.01 (m, 2H), 7.59–7.47 (m, 2H), 7.42–7.27 (m, 1H), 7.26–7.16 (m, 1H), 6.15–5.80 (m, 1H), 5.63–5.39 (m, 1H), 3.91 (dd, *J* = 48.6, 9.9 Hz, 1H), 1.25 (d, *J* = 1.0 Hz, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 190.7, 190.5, 152.9, 152.6, 140.0, 139.9, 131.2, 131.1, 123.0, 129.8, 129.6, 129.5, 128.3, 128.3, 127.5, 127.4, 126.3, 126.0, 123.9, 123.2, 115.8, 115.5, 88.8, 88.0, 60.6, 60.5, 55.7, 55.5, 21.6, 21.5; HRMS (ESI) calcd for C₁₉H₁₉Cl₃NO₃S [M + H]⁺: 446.0146, found 446.0140.

trans-(R)-N-((1S,2S)-2-(4-Chlorobenzoyl)-1,2-dihydronaphtho[2,1-*b*]furan-1-yl)-2-methylpropane-2-sulfinamide (3i). White solid. Mp: 67–69 °C; [α]_D²⁰ = +43.98 [*c* = 0.64, CHCl₃]; ¹H NMR (400 MHz, CDCl₃) δ 8.13 (dd, *J* = 56.2, 8.6 Hz, 2H), 7.90 (dd, *J* = 67.2, 8.6 Hz, 3H), 7.59–7.45 (m, 3H), 7.36 (t, *J* = 7.2 Hz, 1H), 7.20 (dd, *J* = 13.2, 8.9 Hz, 1H), 6.22 (dd, *J* = 75.4, 2.6 Hz, 1H), 6.01–5.71 (m, 1H), 3.92 (dd, *J* = 57.1, 7.9 Hz, 1H), 1.22 (d, *J* = 24.2 Hz, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 192.3, 156.8, 139.5, 131.6, 131.4, 129.9, 129.0, 128.9, 128.1, 127.9, 126.7, 122.9, 121.6, 114.6, 111.2, 89.5, 58.6, 55.2, 21.5; HRMS (ESI) calcd for C₂₃H₂₃ClNO₃S [M + H]⁺: 428.1082, found 428.1080.

trans-(R)-2-Methyl-N-((1S,2S)-2-(4-methylbenzoyl)-1,2-dihydronaphtho[2,1-*b*]furan-1-yl)propane-2-sulfinamide (3j). White solid. Mp: 142–144 °C; [α]_D²⁰ = +70.47 [*c* = 0.92, CHCl₃]; ¹H NMR (400 MHz, CDCl₃) δ 8.18 (d, *J* = 8.2 Hz, 2H), 7.88–7.82 (m, 2H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.48 (t, *J* = 7.3 Hz, 1H), 7.37 (dd, *J* = 14.5, 7.5 Hz, 3H), 7.28 (s, 1H), 6.38 (d, *J* = 2.0 Hz, 1H), 5.77 (dd, *J* = 11.3, 2.0 Hz, 1H), 3.82 (d, *J* = 11.3 Hz, 1H), 2.48 (s, 3H), 1.27 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 192.2, 156.9, 144.0, 131.2, 130.5, 129.3, 129.0, 128.7, 128.6, 127.9, 126.3, 122.6, 121.4, 115.6, 111.4, 88.0, 60.6, 55.7, 21.6, 20.8; HRMS (ESI) calcd for C₂₄H₂₆NO₃S [M + H]⁺: 408.1628, found 408.1622.

trans-(R)-N-((2S,3S)-5-Chloro-2-(4-methylbenzoyl)-2,3-dihydrobenzofuran-3-yl)-2-methylpropane-2-sulfinamide (3l). Light yellow solid. Mp: 147–149 °C; [α]_D²⁰ = +54.67 [*c* = 1.20, CHCl₃]; ¹H NMR (400 MHz, CDCl₃) δ 7.96 (d, *J* = 8.2 Hz, 2H), 7.48 (d, *J* = 1.7 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.19 (dd, *J* = 8.6, 2.1 Hz, 1H), 6.83 (d, *J* = 8.6 Hz, 1H), 5.84 (d, *J* = 5.0 Hz, 1H), 5.44 (dd, *J* = 8.1, 5.0 Hz, 1H), 3.91 (d, *J* = 8.1 Hz, 1H), 2.44 (s, 3H), 1.25 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 191.9, 156.7, 144.3, 130.5, 129.5, 128.6, 128.4, 126.4, 125.8, 125.4, 110.5, 88.5, 60.4, 55.4, 21.6, 20.8; HRMS (ESI) calcd for C₂₀H₂₃ClNO₃S [M + H]⁺: 392.1082, found 392.1076.

trans-(R)-N-((2S,3S)-5-Bromo-2-(4-methylbenzoyl)-2,3-dihydrobenzofuran-3-yl)-2-methylpropane-2-sulfinamide (3n). White solid. Mp: 146–148 °C; [α]_D²⁰ = +37.88 [*c* = 1.16, CHCl₃]; ¹H NMR (400 MHz, CDCl₃) δ 7.88 (d, *J* = 8.1 Hz, 2H), 7.55 (s, 1H), 7.25 (dd, *J* = 16.3, 4.8 Hz, 3H), 6.71 (d, *J* = 8.6 Hz, 1H), 5.76 (d, *J* = 5.1 Hz, 1H), 5.38 (dd, *J* = 8.0, 5.1 Hz, 1H), 3.83 (d, *J* = 8.0 Hz, 1H), 2.37 (s, 3H), 1.18 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 192.9, 158.3, 145.4, 133.5, 131.4, 129.6, 129.5, 129.4, 128.0, 113.8, 112.1, 89.4, 61.4, 56.4, 29.7, 22.7; HRMS (ESI) calcd for C₂₀H₂₃BrNO₃S [M + H]⁺: 436.0577, found 436.0573.

General procedure for synthesis of 3-amino-2,3-dihydrobenzofuran-2-yl(aryl)methanone hydrochlorides 5

The synthesis of 3-amino-2,3-dihydrobenzofuran-2-yl(phenyl)methanone hydrochloride **5a** is representative. To a solution of *trans*-3-(2-methylpropane-2-sulfinamide)-2,3-dihydrobenzofuran **3a** (68.7 mg, 0.20 mmol) in dioxane (10 mL) was added dropwise freshly prepared saturated dioxane/HCl (15 mL, ~20 equiv. HCl). The mixture was allowed to stir for 1 h. Then the reaction mixture was concentrated *in vacuo*. Precipitation in diethyl ether afforded 42.1 mg (0.15 mmol) of pure 3-amino-2,3-dihydrobenzofuran-2-yl(phenyl)methanone hydrochloride **5a**.

(2S,3R)-(3-Amino-2,3-dihydro-benzofuran-2-yl)-phenyl-methanone (5a). White solid. Mp: 161–163 °C; [α]_D²⁰ = –137.93 [*c* = 0.29 g/100 mL, CH₃OH]; ¹H NMR (400 MHz, CD₃OD) δ 8.20–8.14 (m, 2H), 7.74 (t, *J* = 7.5 Hz, 1H), 7.61 (dd, *J* = 12.3, 4.7 Hz, 3H), 7.45–7.35 (m, 1H), 7.16–7.08 (m, 1H), 6.97 (t, *J* = 8.9 Hz, 1H), 6.13 (d, *J* = 3.0 Hz, 1H), 5.63 (d, *J* = 3.0 Hz, 1H); ¹³C NMR (101 MHz, MeOD) δ 193.2, 160.7, 135.6, 135.5, 133.2, 130.7, 130.0, 127.1, 123.5, 122.9, 112.0, 86.4, 54.5; HRMS (ESI) calcd for C₁₅H₁₄ClNO₂ [M + H]⁺: 240.1019, found 240.1012.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank the National Key Research and Development Program of China (2016YFD0201200), the Rural Affairs Commission of the CPC Tianjin Municipal Committee (2016D01A016) and the Key Technologies R & D Program of Tianjin (17YFZCGX00470) for financial support.



Notes and references

- 1 (a) M. Iwahashi, A. Shimabukuro, T. Onoda, Y. Matsunaga, Y. Okada, R. Matsumoto, F. Nambu, H. Nakai and M. Toda, *Bioorg. Med. Chem.*, 2011, **19**, 4574; (b) L. Zhou, Y. F. Xi, W. Wang, B. Lin, X. B. Wang, X. X. Huang and S. J. Song, *Fitoterapia*, 2018, **127**, 56; (c) H. Sunden, A. Schafer, M. Scheepstra, S. Leysen, M. Malo, J. N. Ma, E. S. Burstein, C. Ottmann, L. Brunsveld and R. Olsson, *J. Med. Chem.*, 2016, **59**, 1232.
- 2 (a) B. Shota, A. Sachie, F. Masaki, A. Kosuke, F. Hitoshi, S. Michinori, I. Tatsushi, I. Kazunobu, T. Katsuhiko and I. Ryo, *Eur. J. Org. Chem.*, 2017, 6914; (b) M. Wang, X. Zhang, Z. Ling, Z. F. Zhang and W. B. Zhang, *Chem. Commun.*, 2017, **53**, 1381; (c) X. Y. Liu, C. S. Tian, X. Z. Jiao, X. Y. Li, H. G. Yang, Y. Y. Yao and P. Xie, *Org. Biomol. Chem.*, 2016, **14**, 7715.
- 3 (a) J. P. Nandy, B. Rakic, B. V. N. B. Sarma, N. Babu, M. Lefrance, G. D. Enright, D. M. Leek, K. Daniel, L. A. Sabourin and P. Arya, *Org. Lett.*, 2008, **10**, 1143; (b) T. R. Helgren, L. Y. L. Xu, D. Sotelo, Y. R. Mehta, M. A. Korkmaz, I. Pavlinov and L. N. Aldrich, *Chem.-Eur. J.*, 2018, **24**, 4509.
- 4 N. Anderton, P. A. Cockrum, S. M. Colegate, J. A. Edgar, K. Flower, D. Gardner and R. I. Willing, *Phytochemistry*, 1999, **51**, 153.
- 5 (a) A. K. Shaikh and G. Varvounis, *RSC Adv.*, 2015, **5**, 14892; (b) Y. Cheng, X. Q. Hu, S. Gao, L. Q. Lu, J. R. Chen and W. J. Xiao, *Tetrahedron*, 2013, **69**, 3810.
- 6 (a) J. T. Kuethe, A. Wong, M. Journet and I. W. Davies, *J. Org. Chem.*, 2005, **70**, 3727; (b) M. C. Jiménez, M. A. Miranda and R. Tormas, *J. Org. Chem.*, 1998, **63**, 1323; (c) G. F. Meijis and A. L. J. Beckwith, *J. Am. Chem. Soc.*, 1986, **108**, 5890; (d) E. M. Rochette, W. Lewis, A. G. Dossetter and R. A. Stockman, *Chem. Commun.*, 2013, **49**, 9395.
- 7 G. A. Salman, A. Ali, M. Hussain, R. A. Khera and P. Langer, *Synthesis*, 2011, 2208.
- 8 G. Solladié, D. Boeffel and J. Maignan, *Tetrahedron*, 1995, **51**, 9559.
- 9 (a) J. Mangas-Sánchez, E. Busto, V. Gotor-Fernández and V. Gotor, *Org. Lett.*, 2010, **12**, 3498; (b) J. W. Benbow and R. Katoch-Rouse, *J. Org. Chem.*, 2001, **66**, 49652; (c) T. A. Engler, K. D. Combrink and J. E. Ray, *J. Am. Chem. Soc.*, 1988, **110**, 7931.
- 10 (a) T. A. Engler, D. Wei, M. A. Letavic, K. D. Combrink and J. P. Reddy, *J. Org. Chem.*, 1994, **59**, 6588; (b) B. D. Gates, P. Dalidowicz, A. Tebben, S. Wang and J. S. Swenton, *J. Org. Chem.*, 1992, **57**, 2135; (c) S. Wang, B. D. Gates and J. S. Swenton, *J. Org. Chem.*, 1991, **56**, 1979; (d) T. Tomakinian, R. Guillot, C. Kouklovsky and G. Vincent, *Angew. Chem., Int. Ed.*, 2014, **53**, 11881; (e) E. Yoshioka, H. Tanaka, S. Kohtani and H. Miyabe, *Org. Lett.*, 2013, **15**, 3938.
- 11 (a) X. Wang, Y. Lu, H. X. Dai and J. Q. Yu, *J. Am. Chem. Soc.*, 2010, **132**, 12203; (b) M. Szlosek-Pinaud, P. Diaz, J. Martinez and F. Lamaty, *Tetrahedron*, 2007, **63**, 3340.
- 12 C. Soldi, K. N. Lamb, R. A. Squitieri, M. Gonzalez-Lopez, M. J. Di Maso and J. T. Shaw, *J. Am. Chem. Soc.*, 2014, **136**, 15142.
- 13 J. P. Nandy, B. Rakic, B. V. N. B. Sarma, N. Babu, M. Lefrance, G. D. Enright, D. M. Leek, K. Daniel, L. A. Sabourin and P. Arya, *Org. Lett.*, 2008, **10**, 1143.
- 14 L. Albrecht, L. K. Ransborg, V. Lauridsen, M. Overgaard, T. Zweifel and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2011, **50**, 12496.
- 15 Y. H. Zhao, X. F. Ren and H. W. Liu, *Synth. Commun.*, 2015, **45**, 1566.
- 16 For reviews on the chemistry of *N-tert*-butanesulfinyl imines, see: (a) F. A. Davis, P. Zhou and B. C. Chen, *Chem. Soc. Rev.*, 1998, **37**, 13; (b) J. A. Ellman, T. D. Owens and T. P. Tang, *Acc. Chem. Res.*, 2002, **35**, 984; (c) J. A. Ellman, *Pure Appl. Chem.*, 2003, **75**, 39; (d) C. H. Senanayake, D. Krishnamurthy, Z. H. Lu, Z. Han and E. Gallon, *Aldrichimica Acta*, 2005, **38**, 93; (e) D. Mortan and R. A. Stockman, *Tetrahedron*, 2006, **62**, 8869; (f) G. Q. Lin, M. H. Xu, Y. W. Zhong and X. W. Sun, *Acc. Chem. Res.*, 2008, **41**, 831; (g) F. Ferreira, C. Botuha, F. Chemla and A. Pérez-Luna, *Chem. Soc. Rev.*, 2009, **38**, 1162.
- 17 M. T. Robak, M. A. Herbage and J. A. Ellman, *Chem. Rev.*, 2010, **110**, 3600.
- 18 G. C. Liu, D. A. Cogan and J. A. Ellman, *J. Am. Chem. Soc.*, 1997, **119**, 9913.
- 19 (a) B. Cui, G. Hou, Y. Cai and Z. W. Miao, *Carbohydr. Res.*, 2013, **374**, 1; (b) H. T. Yang, B. Cui, G. P. Wu, Z. W. Miao and R. Y. Chen, *Tetrahedron*, 2012, **68**, 4830; (c) B. Cui, S. S. Kong, G. P. Wu, Z. W. Miao and R. Y. Chen, *Synthesis*, 2012, **44**, 111; (d) J. P. Yu, Z. W. Miao and R. Y. Chen, *Org. Biomol. Chem.*, 2011, **9**, 1756; (e) Y. D. Wang, Y. Y. Wang, J. P. Yu, Z. W. Miao and R. Y. Chen, *Chem.-Eur. J.*, 2009, **15**, 9290; (f) Y. D. Wang, F. Wang, Y. Y. Wang, Z. W. Miao and R. Y. Chen, *Adv. Synth. Catal.*, 2008, **350**, 2339.
- 20 (a) Z. B. Yuan, X. X. Fang, X. Y. Li, J. Wu, H. Q. Yao and A. J. Lin, *J. Org. Chem.*, 2015, **80**, 11123; (b) L. N. Liu, Z. B. Yuan, R. Pan, Y. Y. Zeng, A. J. Lin, H. Q. Yao and Y. Huang, *Org. Chem. Front.*, 2018, **5**, 623.
- 21 (a) G. Liu, D. A. Cogan, T. D. Owens, T. P. Tang and J. A. Ellman, *J. Org. Chem.*, 1999, **64**, 1278; (b) F. A. Davis, Y. Zhang, Y. Andemichael, T. Fang, D. L. Fanelli and H. Zhang, *J. Org. Chem.*, 1999, **64**, 1403.
- 22 (a) P. Z. Xie, L. Y. Wang, L. H. Yang, E. Q. Li, J. Z. Ma, Y. Huang and R. Y. Chen, *J. Org. Chem.*, 2011, **76**, 7699; (b) Q. B. Li, F. T. Zhou, Z. G. Liu, X. F. Li, W. D. Zhu and J. W. Xie, *J. Org. Chem.*, 2011, **76**, 7222.
- 23 Crystallographic data for the structural analysis of compounds **3a** and **4c** has been deposited at the Cambridge Crystallographic Data Centre as No. CCDC 1583643 and 1587117.†
- 24 (a) X. T. Meng, Y. Huang and R. Y. Chen, *Org. Lett.*, 2009, **11**, 137; (b) I. Lantos, J. Flisak, L. Liu, R. Matsuoka, W. Mendelson, D. Stevenson, K. Tubman, K. Tucker, W. Y. Zhang and J. Adams, *J. Org. Chem.*, 1997, **62**, 5385; (c) D. Morton, D. Pearson, R. A. Field and R. A. Stockman, *Chem. Commun.*, 2006, **17**, 1833.

