Note

A three-component derivatization protocol for determining the enantiopurity of sulfinamides by 1H and 19F NMR spectroscopy

Robin R. Groleau, Robert S. L. Chapman, Harry Ley-Smith, Liyuan Liu, Tony D. James, and Steven D. Bull

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.9b02473 • Publication Date (Web): 27 Nov 2019

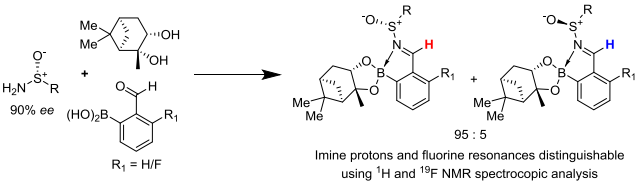
A three-component derivatization protocol for determining the enantiopurity of sulfinamides by ^{1}H and ^{19}F NMR spectroscopy

Robin R. Groleau, Robert S. L. Chapman, Harry Ley-Smith, Liyuan Liu, Tony D. James* and Steven D. Bull*

Department of Chemistry, University of Bath, Claverton Down, Bath, BA2 7AY, U.K.

E-mail: s.d.bull@bath.ac.uk; t.d.james@bath.ac.uk

Supporting Information Placeholder

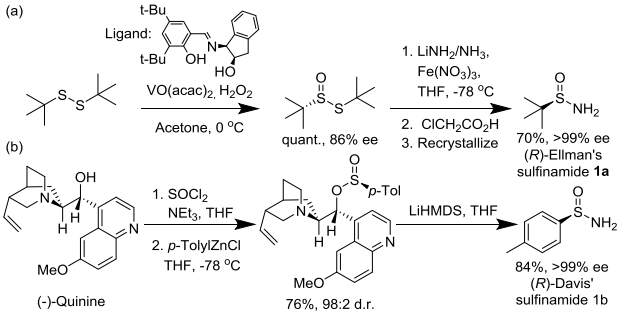


ABSTRACT: A practically simple three-component chiral derivatization protocol has been developed to determine the enantiopurity of eight *S*-chiral sulfinamides by ^{1}H and ^{19}F NMR spectroscopic analysis, based on their treatment with a 2-formylphenylboronic acid template and enantiopure pinanediol to afford a mixture of diastereomeric sulfiniminoboronate esters whose diastereomeric ratio is an accurate reflection of the enantiopurity of the parent sulfinamide.

Enantiopure *N*-sulfinyl imines (sulfinimines) are widely used for asymmetric synthesis,[1] with Ellman's and Davis' sulfinamides (**1a** and **1b**) widely used to prepare these chiral sulfinimine intermediates for the stereoselective functionalization of ketones and aldehydes.[2] These chiral auxiliaries have been employed for the asymmetric synthesis of chiral amines, alcohols, diamines, amino-alcohols, α-organometallic amines and α- and β-amino acid derivatives in high enantiomeric excess (*ee*).[3] They have also found applications as chiral organocatalysts, as additives/ligands in enantioselective catalytic systems,[4] and as peptidic/transition state isosteres for medicinal chemistry applications.[5] Sulfinamides are also produced naturally by the action of nitroxyl (HNO) on peptidic cysteine residues in cells.[6]

Several approaches have been developed to synthesise enantiopure sulfinamides (Scheme 1). Treatment of symmetric disulfides with chiral catalysts and stoichiometric oxidants (e.g. H_2O_2) is used to afford chiral thiosulfinate intermediates, which are then reacted with nucleophilic ammonia sources (with clean S_N2 inversion), affording chiral sulfinamides in high *ee* (Scheme 1a).[7] Chiral auxiliaries are also used to prepare sulfinate esters with high levels of diastereocontrol, which can then be reacted with amines to afford enantiopure sulfinamides (Scheme 1b).[2a] Classical resolution processes have also been used to separate the enantiomers of (*rac*)-thiosulfinate precursors,[8] subtilisin has been used for enzymatic kinetic resolution of (*rac*)-*N*-acyl-arylsulfinamides,[9] whilst direct separation of their enantiomers can be achieved by preparative chiral HPLC.[10] To date, two chiral solvation methods for determining the *ee*'s of sulfinamides have been reported in the literature, using either Pirkle's alcohol,[11a] or bifunctional macrocycles.[11b] Unfortunately, these methods lack simplicity and substrate scope, and so the *ee*'s of *S*-chiral sulfinamides are normally determined through chiral HPLC analysis.[7b] This approach, however, requires access to expensive HPLC equipment/chiral columns and often requires significant development time to identify a suitable system to resolve the enantiomers of a target sulfinamide.

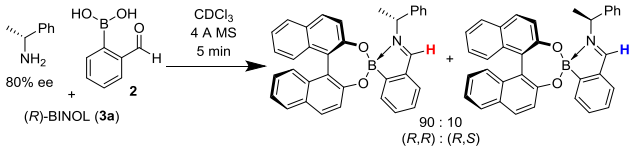
Scheme 1: Stereoselective syntheses of Ellman's sulfinamide 1a and Davis' sulfinamide 1b



Therefore, a practically simple, rapid, and inexpensive chiral derivatization protocol that would enable the rapid determination of the *ee's* of a wide range of chiral sulfinamides by NMR spectroscopic analysis would be of use to the wider synthetic community. We have previously reported the

development of three-component chiral derivatization protocols for determining the *ee*'s of chiral primary amines, diamines, amino alcohols, hydroxylamines and diols by ^{1}H NMR spectroscopic analysis. These protocols involve treatment of a scalemic chiral analyte with 2-formylbenzeneboronic acid **2** (2-FPBA) and an enantiopure chiral selector (amine or diol) to afford pairs of diastereomeric iminoboronate esters. The diastereomeric ratio (*dr*) of these iminoboronate esters can then be measured by comparing the relative intensities of the integrals of their well-resolved imine proton singlets in their ^{1}H NMR spectra (see Scheme 2 for how this method is used to determine the *ee* of α-methylbenzylamine).[12] Given its proven utility, we decided to investigate whether this type of three-component ^{1}H NMR derivatization protocol, often referred to as the Bull-James assembly,[13] could be applied to determine the *ee* of scalemic samples of *S*-chiral sulfinamides.

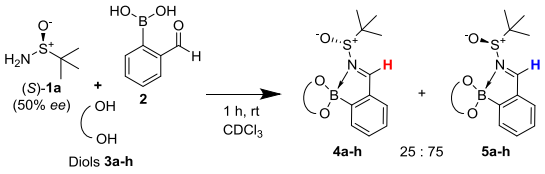
Scheme 2: Three-component chiral derivatization protocol for determining the enantiopurity of α-methylbenzylamine[12a]

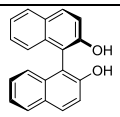
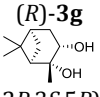


Treatment of a mixture of scalemic Ellman's sulfinamide (*S*)-**1a** (50% *ee*) with 2-FPBA **2** and (*R*)-BINOL **3a** in $CDCl_3$ for 1 h led to incomplete formation of a mixture of diastereomeric sulfiniminoboronate ester complexes **4a** and **5a** (85% conversion from 2-FPBA **2**), whose imine proton resonances were only partially resolved in their ^{1}H NMR spectrum (Table 1, entry 1). The poor yield of this reaction is presumably due to the decreased nucleophilicity of the sulfinamide nitrogen lone pair. This is consistent with previous reports that drying agents, Lewis-acid catalysts and forcing conditions are often required for this type of imine condensation reaction to proceed to completion.[14] Nevertheless, the approximate 3:1 ratio of the partially resolved imine proton signals of the diastereomeric sulfiniminoboronate ester complexes **4a**/**5a** in the ^{1}H NMR spectrum was consistent with the 50% *ee* of the parent sulfinamide **1a**, indicating that no kinetic resolution had occurred.

This prompted us to react Ellman's sulfinamide **1a** (50% *ee*) with 2-FPBA **2** and a range of commercially available chiral diols **3b-h** to identify pairs of diastereomeric sulfiniminoboronate esters **4**/**5** whose imine protons would be baseline-resolved in their ^{1}H NMR spectra. This screening study revealed that (*S*)-2-phenylethanediol **3f**, (*R*)-1-phenylpropane-1,3-diol **3g** and (1*R*,2*R*,3S,5*R*)-pinanediol **3h** gave pairs of diastereomeric sulfiniminoboronate esters whose imine proton resonances were fully resolved (Table 1, entries 6-8). Derivatization with chiral pinanediol **3h** gave diastereomeric sulfiniminoboronate esters **4h**/**5h** that exhibited sharp imine peaks with the greatest chemical shift difference ($\Delta\delta_H$=-0.085 ppm), and it was therefore chosen as the chiral diol for all subsequent sulfinamide derivatization reactions.

Table 1: Chemical shift differences ($\Delta\delta_H$) in the 500 MHz ^{1}H NMR spectra of diastereomeric iminoboronate complexes of Ellman's sulfinamide 1a (50% *ee*), 2-FPBA 2 and a range of enantiopure diols 3a-h



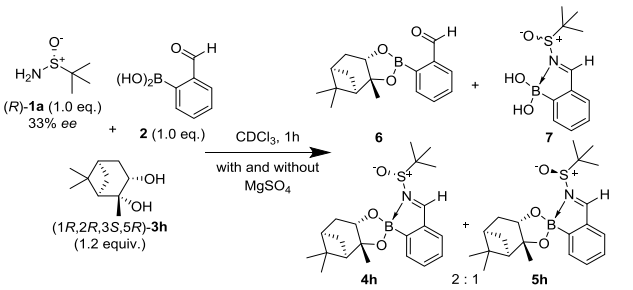
Entry	Diol	$\Delta\delta_H$ (ppm)[a,b]
1	 (*R*)-**3a**	+0.011
2	 (*S*)-**3b**	+0.006
3	 (*R*,*R*)-**3c**	+0.027
4	 (*S*)-**3d**	+0.010
5	 (*S*)-**3e**	+0.014
6[c]	 (*S*)-**3f**	+0.037
7[c]	 (*R*)-**3g**	+0.047
8[c]	 (1*R*,2*R*,3*S*,5*R*)-**3h**	-0.085

[a] $\Delta\delta_H$ is the chemical shift difference between the imine protons of diastereomeric iminoboronate ester complexes **4**/**5**. [b] A negative value indicates that the homochiral complex was most deshielded. [c] Full baseline resolution observed for the imine resonances of **4**/**5**.

A series of experiments were then carried out to try and identify conditions that would result in the three-component reaction of scalemic Ellman's sulfinamide **1a** (33% *ee*), 2-FPBA **2** and pinanediol **3h** being driven to completion. Reaction of these three components in $CDCl_3$ for 1 h gave a 70:30 mixture of the two-component formyl boronate ester **6** and the three-component sulfiniminoboronate esters **4h**/**5h** (Table 2, entry 1). Addition of $MgSO_4$ as a drying agent only marginally increased the amount of **4h**/**5h** formed to 40% (Table 2, entry 2). Two-component reaction of 2-FPBA **2** with pinanediol **3h** was found to give boronate ester **6** in 100% conversion after 10 minutes (Table 2, entry 3). However, no reaction was observed when sulfinamide **1a** was added to a solution of preformed boronate ester **6** in $CDCl_3$, indicating that boronate ester **6** is stable towards imine bond formation under these conditions (Table 2, entry 4). Two-component reaction of Ellman's sulfinamide **1a** and 2-FPBA **2** proceeded more slowly, affording sulfiniminoboronic acid **7** in 89% yield after 1 h, increasing to 94% in the presence of $MgSO_4$ (Table 2, entries 5 and 6). Finally, premixing sulfinamide **1a**, 2-FPBA **2** and $MgSO_4$ in $CDCl_3$ for 1 h, followed by addition of pinanediol **3h** gave 93%

conversion to afford the desired three-component sulfiniminoboronate esters **4h/5h** and the two-component boronate ester **6** in 7% yield (Table 2, entry 7). Therefore, these results suggest that irreversible formation of boronate ester **6** is faster than reversible formation of imine **7**, with only imine **7** competent to react further to afford the desired sulfiniminoboronate esters **4h/5h** in the three-component derivatization reaction.[15]

Table 2: Optimization study of the three-component assembly reaction of Ellman's sulfinamide 1a with 2-FPBA 2 and pinanediol 3h

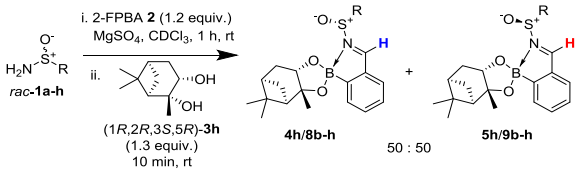


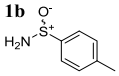
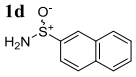
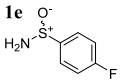
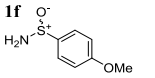
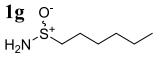
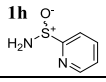
Entry	Reagents	$MgSO_4$	Product Ratios[a]		
			6	**7**	**4h/5h**
1	**1a** + **2** + **3h**	-	70%	0%	30%
2	**1a** + **2** + **3h**	+	60%	0%	40%
3	**2** + **3h**	-	100%	--	--
4[b]	Premix **2** + **3h** then add **1a**	-	100%	0%	0%
5[c]	**1a** + **2**	-	--	89%	--
6[c]	**1a** + **2**	+	--	94%	--
7[d]	Premix **1a** + **2** then add **3h**	+	7%	0%	93%

[a] Determined by ^1H NMR spectroscopic analysis. [b] **2** and **3h** premixed for 10 minutes. [c] Remaining mass balance comprised of unreacted 2-PFBA **2**. [d] **1a** and **2** premixed for 1 h.

These results prompted us to develop a new 'stepwise' three-component derivatization procedure, involving reaction of (*rac*)-Ellman's sulfinamide **1a**, 1.2 equiv. of 2-FPBA **2** and $MgSO_4$ in $CDCl_3$ at rt for 1 h to maximize the amount of reactive imine **7** formed**.** This was followed by addition of 1.3 equivalents of (1*R*,2*R*,3*S*,5*R*)-pinanediol **3h** which gave a 50:50 mixture of diastereomeric sulfiniminoboronate esters **4h/5h** in 99% conversion (Table 3, entry 1). This one-pot stepwise protocol was then applied to the derivatization of seven additional racemic aryl, heteroaryl, cyclic and acyclic sulfinamides **1b-h**,[16] affording mixtures of their corresponding diastereomeric sulfiniminoboronate esters **8b-h/9b-h** in 55-99% conversions (Table 3, entries 2-8). Analysis of the ^1H NMR spectra of these mixtures revealed that the imine signals of all pairs of diastereomeric sulfiniminoboronate esters were all baseline-resolved, with their 49:51 to 51:49 *dr* values indicating that no kinetic resolution had occurred in each derivatization reaction.

Table 3: Chemical shift differences ($\Delta\delta_H$) of the imine proton resonances of pairs of diastereomeric sulfiniminoboronate esters in the ^1H NMR spectra from reaction of sulfinamides 1a-h with 2-FPBA 2 and diol 3h

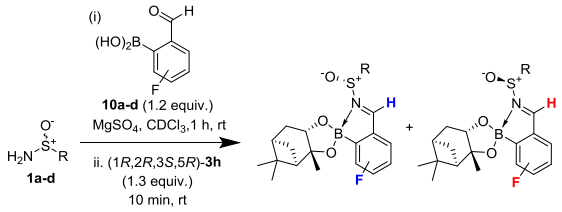


Entry	(*rac*)-Sulfinamide	Conv. (%)[a]	*dr*[a]	$\Delta\delta_H$ (ppm)[b]
1	**1a** 	99	50:50	0.085
2	**1b** 	62	49:51	0.069
3	**1c** 	98	50:50	0.061
4	**1d** 	97	51:49	0.077
5	**1e** 	63	50:50	0.057
6	**1f** 	69	50:50	0.070
7	**1g** 	80	50:50	0.062
8	**1h** 	55	50:50	0.061

[a] Conversion and *dr* determined by ^1H NMR spectroscopic analysis. [b] $\Delta\delta_H$ is the chemical shift difference between the imine protons of diastereomeric iminoboronate ester complexes **4h/5h** and **8/9**.

We,[17] and others,[18] have previously reported the use of fluoro-2-FPBA as an alternative template for the Bull-James three-component protocol, which enables the *dr's* of their derived iminoboronate esters to be accurately determined using both ^1H and ^{19}F NMR spectroscopic analysis. Consequently, we decided to repeat our stepwise three-component reaction using Ellman's sulfinamide **1a** and pinanediol **3h** with 3-fluoro-2-FPBA **10a**, 4-fluoro-2-FPBA **10b**, 3-fluoro-2-FPBA **10c** and 3-fluoro-2-FPBA **10d** (Table 4) [19] These derivatization reactions gave mixtures of diastereomeric sulfiniminoboronate esters whose imine proton resonances were all well-resolved in their ^1H NMR spectra, as were the fluorine resonances in their ^{19}F NMR spectra. 3-fluoro-2-FPBA **10a** gave the best difference for the fluorine resonances ($\Delta\delta_F$=-2.328 ppm), and so it was chosen as the template to derivatize three further (*rac*)-sulfinamides **1b-d**, all of which gave a pair of diastereomeric sulfiniminoboronate esters whose ^1H NMR (imine protons) and ^{19}F NMR resonances were well resolved.

Table 4: Chemical shift differences ($\Delta\delta_{H/F}$) in the $^1H/^{19}F$ NMR spectra of diastereomeric sulfiniminoboronate esters formed from reaction of sulfinamides 1a-d with fluorinated FPBA derivatives 10a-d and pinanediol 3h



Entry[a]	(*rac*)-Sulfinamide	2-FPBA	$\Delta\delta_H{}^b$ / $\Delta\delta_F{}^{c,d}$ (ppm)[e]
1	(*R*)-**1a** (33% *ee*)	**10a**	$\Delta\delta_H$ = -0.064 $\Delta\delta_F$ = -2.328
2	(*R*)-**1a** (33% *ee*)	**10b**	$\Delta\delta_H$ = -0.029 $\Delta\delta_F$ = -0.170
3	(*R*)-**1a** (33% *ee*)	**10c**	$\Delta\delta_H$ = -0.079 $\Delta\delta_F$ = +0.197
4	(*R*)-**1a** (33% *ee*)	**10d**	$\Delta\delta_H$ = -0.201 $\Delta\delta_F$ = -0.578
5	(*rac*)-**1b**	**10a**	$\Delta\delta_H$ = -0.063 $\Delta\delta_F$ = -1.188
6	(*rac*)-**1c**	**10a**	$\Delta\delta_H$ = 0.042 $\Delta\delta_F$ = 1.457
7	(*rac*)-**1d**	**10a**	$\Delta\delta_H$ = 0.070 $\Delta\delta_F$ = 1.365

[a] Reactions proceeded with 37-99% conversions to afford mixtures of sulfiniminoboronate esters whose *dr*'s ranged from 65:35 to 69:31 (entries 1-4) and from 49:51 to 51:49 (entries 5-7), indicating that no kinetic resolution had occurred. [b] $\Delta\delta_H$ is the chemical shift difference between the imine protons of the diastereomeric sulfiniminoboronate esters in their ^1H NMR spectra. [c] $\Delta\delta_F$ is the chemical shift difference between the fluorine resonances of the diastereomeric sulfiniminoboronate esters. [d] Quantitative $^{19}F\{^1H\}$ NMR experiments carried out using a *T1* relaxation time of 30 s. [e] A negative value indicates that the homochiral complex was most deshielded.

The detection limits of this new derivatization method using 3-fluoro-2-FPBA **10a** and pinanediol **3h** were then determined using scalemic samples of Ellman's sulfinamide **1a** of 75%, 90% and 96% *ee* respectively, prepared from enantiopure samples of the sulfinamide (Figures 1a & 1b). Analysis of the resultant mixtures of sulfiniminoboronate esters revealed diastereomeric excesses (*de*) of 75%, 91% and 95% (^1H NMR) and 73%, 89% and 95% (^{19}F NMR), respectively, all of which were within the accepted 5% error limit when using chiral derivatizing agents to determine *ee's* values by NMR spectroscopy. Having established its applicability, our new stepwise three-component chiral derivatization protocol was then used to assess the enantiomeric excess of a commercial sample of enantiopure (*R*)-Davis' sulfinamide **1b** (purchased from Sigma-Aldrich, Figure 1c). Both ^1H and ^{19}F NMR analysis revealed that this 'enantiopure' reagent was in fact scalemic, with both NMR analyses returning a 90% *ee* value for this sample, as confirmed subsequently by chiral HPLC analysis (see Supporting Information).

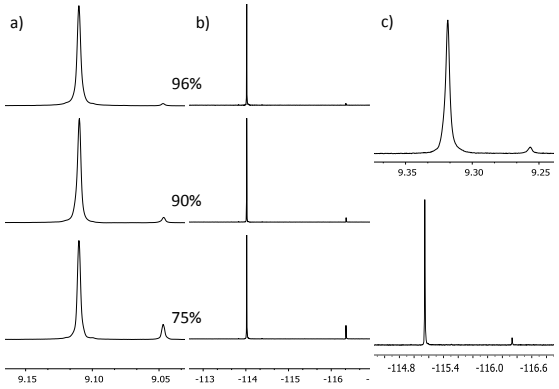


Figure 1: a) Expanded ^1H NMR spectra of xcomplexes formed from reaction of **10a**, (1*R*,2*R*,3*S*,5*R*)-**3h** and (*R*)-**1a** (75%, 90% and 96% *ee*). (b) Expanded ^{19}F NMR spectra of diastereomeric complexes formed from reaction of **10a**, (1*R*,2*R*,3*S*,5*R*)-**3h** and (*R*)- **1a** (75%, 90% and 96% *ee*). c) Expanded ^1H and $^{19}F\{^1H\}$ NMR spectra of diastereomeric complexes formed from reaction of **10a**, (1*R*,2*R*,3*S*,5*R*)-**3h** and a commercial 'enantiopure' sample of (*R*)-Davis' sulfinamide **1b**, revealing its 'true' enantiopurity as 90% *ee*.

In conclusion, this report describes the first chiral derivatization protocol for determining the enantiopurity of a range of *S*-chiral sulfinamides using both ^1H and ^{19}F NMR spectroscopic analysis, including Ellman's and Davis' chiral sulfinamides that are widely used as chiral auxiliaries for asymmetric synthesis.

EXPERIMENTAL SECTION

Unless preparative details are given, reagents and solvents were obtained from commercial suppliers. All reactions were performed without air exclusion, at room temperature and with magnetic stirring unless otherwise stated. Anhydrous $MgSO_4$ was used as a drying agent for organic solutions. Thin layer chromatography (TLC) was carried out on Macherey-Nagel aluminium-backed plates that were precoated with silica. Compounds were visualised by either quenching of UV fluorescence at 254 nm or by staining with potassium permanganate dip followed by gentle heating. Purification by flash column chromatography was performed using high-purity grade silica gel (60Å pore size, 40-75 μm particle size). Capillary melting points are reported uncorrected to the nearest °C, and were determined using a Stuart digital SMP10 melting point apparatus. Optical rotations were measured using an Optical Activity Ltd AA-10 Series Automatic Polarimeter, with a path length of 1 dm, and with concentration (c) quoted in g/100 mL. Nuclear Magnetic Resonance (NMR) spectroscopy experiments were performed in deuterated solvent at 298 K (unless stated otherwise) on either a Brüker Avance, 300, 400 or 500 MHz spectrometer or an Agilent ProPulse 500 MHz

spectrometer, with proton decoupling used for all ^{13}C NMR spectra. ^{1}H, ^{13}C, ^{11}B and ^{19}F NMR chemical shifts (δ) are quoted in parts per million (ppm) and are referenced to either the residual solvent peak or tetramethylsilane (TMS) when possible. Coupling constants (J) are quoted in Hz. Where ^{13}C signals could not be observed by 1D NMR due to low solubility, adjacent quadrupolar nuclei or lack of adjacent ^{1}H nuclei, their chemical shift was deduced from 2D HMBC experiments, where possible. This approach was validated by variable temperature (VT) 1D NMR of boronate ester **6**. Infrared (IR) spectra were recorded using a PerkinElmer Spectrum 100 FTIR spectrometer fitted with a Universal ATR FTIR accessory, with samples run neat and the most relevant, characteristic absorbances quoted as ν in cm^{-1}. High resolution mass spectrometry (HRMS) results were acquired on an externally calibrated Bruker Daltonics maXis HD™ UHR-TOF mass spectrometer coupled to an electrospray source (ESI-TOF). Molecular ions were detected either in positive mode as their protonated, sodiated, or ammonium adduct forms, or in negative mode as deprotonated species. Aryl boronic acids were detected as their deprotonated methyl hydrogen boronate ions $[M+13]^-$, as reported by Wang *et al.*[20] Bruker Daltonics software DataAnalysis™ 4.3 was used to process NMR data.

General procedure 1 for the synthesis of (*rac*)-sulfinamides 1c-h from thiols by the method of Di *et al.*[16] *N*-bromo succinimide (2.0 equiv.) was added to a stirred solution of the thiol (1.0 equiv.) in CH_2Cl_2/MeOH (1:1, 0.1 M) at 0 °C. The reaction was allowed to warm to room temperature and reaction progress was monitored by TLC. Upon completion (15 min - 1 h) the reaction mixture was quenched and diluted by half through the addition of saturated Na_2CO_3. The layers were separated, and the aqueous phase extracted twice with CH_2Cl_2. The combined organics were then washed with brine, dried ($MgSO_4$) and concentrated to dryness *in vacuo* to afford a methylsulfinate product as a clear oil.

The methylsulfinate (1.0 equiv.) was dissolved in anhydrous THF (0.33 M) and cooled to -78 °C. LiHMDS (1.5 equiv., 1M in THF) was then added dropwise over 5 minutes and the reaction left to stir at -78 °C for 1.5 h. After this time the reaction was quenched with saturated NH_4Cl, allowed to warm to room temperature and left to stir. After 30 min, the reaction was diluted with EtOAc, the aqueous phase extracted twice with EtOAc, and the combined organics were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by either recrystallization or column chromatography to afford the desired sulfinamide **1c-h**.

(*rac*)-Cyclopentanesulfinamide 1c. General procedure 1 was followed using cyclopentanethiol (334 µL, 3.12 mmol). Recrystallisation from 1:10 EtOAc/*n*-hexane afforded the title compound **1c** (299 mg, 2.24 mmol) as a white solid in 72% yield. All characterisation data were consistent with previous literature reports.[16] m.p.: 86-88 °C (lit.[16] 82-83 °C); IR (neat): 3189, 3089, 2957, 2868, 1450, 1166, 1001, 908, 697 cm^{-1} ; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.91 (bs, 2H, -NH_2), 3.05 (p, 1H, J = 7.5, SCH), 2.04 (dt, 2H, J = 13.9, 6.9, CH_2), 1.98-1.88 (m, 2H, CH_2), 1.83-1.59 (m, 4H, CH_2); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ_C 65.2, 27.7, 26.1, 25.9, 25.6.

(*rac*)-Naphthalene-2-sulfinamide 1d. General procedure 1 was followed using naphthalene-2-thiol (500 mg, 3.12 mmol). Recrystallisation from 2:1 EtOAc/*n*-hexane afforded the title compound **1d** (408 mg, 2.13 mmol) as a white solid in 63% yield. m.p.: 134-138 °C (decomposed); IR (neat): 3292, 3155, 3063, 1589, 1560, 1500, 1344, 1014, 822, 739 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 8.34 (s, 1H,ArH), 7.99-7.89 (m, 3H, ArH), 7.71 (dd, 1H, ArH), 7.65-7.55 (m, 2H, ArH); 4.34 (bs, 2H, -NH_2); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ_C 143.6, 134.6, 132.8, 129.2, 129.0, 128.1, 128.1, 127.3, 125.8, 121.9; HRMS (ESI+): Calculated for $[M+Na]^+$ $C_{10}H_9NOSNa$: 214.0297; Found: 214.0288.

(*rac*)-4-Fluorobenzenesulfinamide 1e. General procedure 1 was followed using 4-fluorothiophenol (332 µL, 3.12 mmol). Recrystallization from 1:1 EtOAc/*n*-hexane afforded the title compound **1e** (268 mg, 1.68 mmol) as a white solid in 54% yield. All characterisation data were consistent with previous literature reports.[21,22] m.p.: 134-139 °C (lit. 128,[21] 144.8-146.8[22] °C); IR (neat): 3269, 3154, 3065, 1587, 1481, 1229, 1211, 1156, 1087, 1005, 887, 834, 667 cm^{-1} ; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.79-7.71 (m, 2H, ArH), 7.24-7.15 (m, 2H, ArH), 4.32 (bs, 2H,NH_2) ; $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ_C 164.6 (d, $^{1}J_{F\text{-}C}$ = 251.7), 142.2, 128.0 (d, $^{3}J_{F\text{-}C}$ = 9.0), 116.2 (d, $^{2}J_{F\text{-}C}$ = 22.4); ^{19}F NMR (471 MHz, $CDCl_3$) δ_F -109.0 (tt, J = 8.4, 5.1).

(*rac*)-4-Methoxybenzenesulfinamide 1f. General procedure 1 was followed using 4-fluorothiophenol (383 µL, 3.12 mmol). Recrystallization from 1:2 EtOAc/*n*-hexane afforded the title compound **1f** (262 mg, 1.53 mmol) as a white solid in 49% yield. All characterisation data were consistent with previous literature reports.[9] m.p.: 127-131 °C (lit.[9] 129-131 °C); IR (neat): 3261, 3067, 2840, 1591, 1490, 1450, 1245, 1025, 1001, 823, 794 cm^{-1} **;** ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.68 (d, 2H, J = 8.8, ArH), 7.02 (d, 2H, J = 8.8, ArH), 4.24 (bs, 2H, NH_2), 3.87 (s, 3H, OCH_3); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ_C 162.1, 138.0, 127.2, 114.4, 55.7.

(*rac*)-Hexane-1-sulfinamide 1g. General procedure 1 was followed using 1-hexanethiol (1.421 mL, 10.0 mmol). Recrystallization from *n*-hexane afforded the title compound **1g** (356 mg, 2.38 mmol) as an off-white solid in 24% yield. m.p.: 41-42 °C; IR (neat): 3282, 3200, 2954, 2924, 2849, 1553, 1464, 1417, 1066, 1035, 1001, 890 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.99 (bs, 2H, NH_2), 2.73 (2 x ddd, 2H, J = 13.0, 8.5, 6.7, SCH_2), 1.79-1.63 (m, 2H, SCH_2CH_2), 1.50-1.37 (m, 2H, $SCH_2CH_2CH_2$), 1.36-1.29 (m, 4H,$MeCH_2CH_2$), 0.91-0.87 (m, 3H, CH_3); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ_C 57.9, 31.5, 28.4, 22.9. 22. 5, 14.1; HRMS (ESI+): Calculated for $[M+NH_4]^+$ $C_6H_{19}N_2OSNa$: 167.1213; Found: 167.1215.

(*rac*)-Pyridine-2-sulfinamide 1h. General procedure 1 was followed using 2-mercapto pyridine (1.998 g, 18.0 mmol). Recrystallization from CH_2Cl_2 afforded the title compound **1h** (128 mg, 0.972 mmol) as a white solid in 5% yield. All characterisation data were consistent with previous literature reports.[23] m.p.: 102-104 °C (lit.[23] 98-100 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 8.71 (ddd, 1H, J = 4.7, 4.7, 1.5, ArH), 7.99-7.89 (m, 2H, ArH), 7.44 (ddd, 1H, J = 7.4, 4.7, 1.4, ArH), 4.66 (bs, 2H, NH_2); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ_C 164.5, 150.0, 138.1, 125.6, 120.6.

General procedure 2 for the synthesis of 1-bromo-2-(dimethoxymethyl)-fluorobenzenes 11a-d by the method of Kowalska *et al.*[19] H_2SO_4 (0.093 equiv., 0.47 mmol, 25 µL)

and trimethyl orthoformate (1.3 equiv., 6.50 mmol, 711 µL) were added to a stirred solution of a 2-bromo-fluorobenzaldehyde (1.0 equiv., 5.00 mmol, 1.02 g) in MeOH (2.0 mL). The reaction was heated at reflux for 1.5 h, before cooling to room temperature and quenching with triethylamine (1.00 mL, 7.17 mmol). The volatiles were removed *in vacuo*, and the resulting mixture dissolved in water (30 mL) and extracted with Et_2O (30 mL). The organics were washed with water (3 x 30 mL) and brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford the desired dimethyl acetals **11a-d** as clear oils.

1-Bromo-2-(dimethoxymethyl)-3-fluorobenzene 11a. General procedure 2 was followed using 2-bromo-6-fluorobenzaldehyde (5.00 mmol, 1.02 g), affording the title compound **11a** (1.09 g, 4.41 mmol) as a colourless oil in 88% yield. IR (neat): 2930, 2830, 1602, 1572, 1455, 1376, 1249, 1201, 1102, 1062, 168, 893, 781, 730 cm^{-1} ; ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.73 (dt, 1H, J = 8.0, 1.1, Ar*H*), 7.17 (td, 1H, J = 8.2, 5.6, ArH), 7.05 (dd, 1H, J = 10.4, 8.3, 1.2, ArH), 5.71 (d, 1H, J = 1.2, MeOC*H*), 3.49 (s, 6H, 2xOCH_3); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C 161.5 (d, $^1J_{F\text{-}C}$ = 256.3), 131.0 (d, $J_{F\text{-}C}$ = 9.9), 129.2 (d, $J_{F\text{-}C}$ = 3.4), 125.4 (d, $J_{F\text{-}C}$ = 14.4), 123.5 (d, $J_{F\text{-}C}$ = 5.3), 116.2 (d, $J_{F\text{-}C}$ = 23.0), 104.9, 55.7; ^{19}F NMR (470 MHz, $CDCl_3$) δ_F -111.1 (dd, J = 10.6, 5.6); HRMS (ESI+): Calculated for $[M+Na]^+$ $C_9H_{10}O_2BrFNa$: 270.9740; Found: 270.9749.

1-Bromo-2-(dimethoxymethyl)-4-fluorobenzene 11b. General procedure 2 was followed using 2-bromo-5-fluorobenzaldehyde (5.00 mmol, 1.02 g), affording the title compound **11b** (1.16 g, 4.65 mmol) as a colourless oil in 95% yield. IR (neat): 2935, 2832, 1581, 1464, 1365, 1264,1154, 1095, 1055, 972, 880 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.51 (dd, 1H, J = 8.8, 5.1, Ar*H*), 7.35 (dd, 1H, J = 9.4, 3.1, Ar*H*), 6.93, ddd, J = 8.8, 7.7, 3.1, Ar*H*), 5.50 (d, 1H, J = 1.2, MeCOC*H*), 3.38 (s, 6H, 2x OCH_3); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C 162.1 (d, $^1J_{F\text{-}C}$ = 247.2), 139.3 (d, $J_{F\text{-}C}$ = 7.0), 134.2(d, $J_{F\text{-}C}$ = 7.7), 117.4 (d, $J_{F\text{-}C}$ = 22.7), 116.9 (d, $J_{F\text{-}C}$ = 3.2), 115.9 (d, $J_{F\text{-}C}$ = 24.3), 102.4, 54.0; ^{19}F NMR (470 MHz, $CDCl_3$) δ_F -114.3; HRMS (ESI+): Calculated for $[M+Na]^+$ $C_9H_{10}O_2BrFNa$: 270.9740; Found: 270.9748.

1-Bromo-2-(dimethoxymethyl)-5-fluorobenzene 11c. General procedure 2 was followed using 2-bromo-4-fluorobenzaldehyde (5.00 mmol, 1.02 g), affording the title compound **11c** (1.16 g, 4.65 mmol) as a colourless oil in 93% yield. IR (neat): 2937, 2826, 1599, 1484, 1361, 1226, 1193, 1103, 1054, 982, 857, 812 cm^{-1} 2826,1735, 1694, 1585, 1475, 1253, 1221, 1111, 1033, 880, 864; ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.60 (dd, 1H, J = 8.7, 6.2, Ar*H*), 7.31 (dd, 1H, J = 8.2, 2.6, Ar*H*), 7.05(td, 8.3, 2.6, Ar*H*), 5.52 (s, 1H, MeOC*H*), 3.37 (s, 6H, 2 x OCH_3); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C 162.5 (d, $J_{F\text{-}C}$ = 251.8), 133.2 (d, $J_{F\text{-}C}$ = 3.6), 129.7 (d, $J_{F\text{-}C}$ = 8.5), 123.2 (d, $J_{F\text{-}C}$ = 9.4), 120.2 (d, $J_{F\text{-}C}$ = 24.8), 114.5 (d, $J_{F\text{-}C}$ = 20.9), 102.6, 54.0; ^{19}F NMR (470 MHz, $CDCl_3$) δ_F -111.4; HRMS (ESI+): Calculated for $[M+Na]^+$ $C_9H_{10}O_2BrFNa$: 270.9740; Found: 270.9747.

1-Bromo-2-(dimethoxymethyl)-6-fluorobenzene 11d. General procedure 2 was followed using 2-bromo-3-fluorobenzaldehyde (5.00 mmol, 1.02 g), affording the title compound **11d** (1.18 g, 4.75 mmol) as a colourless oil in 95% yield. IR (neat): 2959, 2835, 1577, 1464, 1436, 1357, 1261, 1115, 1035, 1004, 825, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.43-7.39 (m, 1H, Ar*H*), 7.34-7.28 (m, 1H, Ar*H*), 7.14-7.09 (m, 1H, Ar*H*), 5.57 (s, 1H, MeOC*H*), 3.39 (s, 6H, 2 x OCH_3); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C 159.2 (d, $^1J_{F\text{-}C}$ = 246.5), 139.4, 128.3 (d, $J_{F\text{-}C}$ = 7.9), 123.7 (d, $J_{F\text{-}C}$ = 3.3), 116.5 (d, $J_{F\text{-}C}$ = 22.6), 110.2 (d, $J_{F\text{-}C}$ = 21.3), 102.6 (d, $J_{F\text{-}C}$ = 3.6), 54.1; ^{19}F NMR (470 MHz, $CDCl_3$) δ_F -105.5 (dd, J = 8.3, 5.1); HRMS (ESI+): Calculated for $[M+Na]^+$ $C_9H_{10}O_2BrFNa$: 270.9740; Found: 270.9741.

General procedure 3 for the synthesis of fluoro-2-formylphenyl boronic acids 10a-d by the method of Kowalska *et al.*[19] *n*-Butyllithium (2.5 M in THF, 1.15 equiv.) was added dropwise (15 min) to a stirred solution of a fluoro-1-bromo-2-(dimethoxymethyl)-fluorobenzene **11a-d** (1.0 equiv.) in anhydrous Et_2O/THF (5:1 mixture, 0.33 M) under an inert N_2 atmosphere. The resultant solution was then cooled to -78 °C, and stirred for 1 h, before addition of trimethyl borate (1.15 equiv.). The reaction was warmed to room temperature and allowed to stir for 15 min, before acidifying to pH 3 using HCl (3M, aq.). The reaction was diluted with Et_2O, and the aqueous phase extracted 3 times. The combined organics were washed with brine, dried over $MgSO_4$, and concentrated to dryness, with the resultant crude product recrystallised from EtOAc/hexane to afford the desired formyl boronic acid **10a-d** (observed by NMR in tautomeric equilibrium with the related benzoxaborole minor product, see Supporting Information).

(3-Fluoro-2-formylphenyl)boronic acid 10a. General procedure 3 was followed using 1-bromo-2-(dimethoxymethyl)-3-fluorobenzene **11a** (1.09 g, 4.41 mmol), affording the title compound **10a** (444 mg, 2.64 mmol) as a white solid in 60% yield. All characterisation data were consistent with previous literature reports.[24] m.p.: 125-128 °C (lit.[24] 127-129 °C); IR (neat): 3309, 3071, 2943, 1675, 1561, 1427, 1294, 1235, 1184, 1083, 908, 825, 793, 732 cm^{-1}; ^1H NMR (500 MHz, acetone–d_6) δ_H 10.38 (s, 1H, OC*H*, major), 8.42 (bs, 1H, BOH, minor), 7.77-7.61 (m, 1H, Ar*H*, major), 7.54-7.41 (m, 2H major + 1H minor, Ar*H*), 7.32 (bs, 2H, BOH, major), 7.26 (ddd, 1H, J = 11.2, 8.3, 1.1, Ar*H*, major), 7.21 (ddd, 1H, J = 9.8, 7.9, 1.1, Ar*H*, minor), 6.45 (s, 1H, HCO, minor), 6.13 (bs, 1H, COH, minor); ^{11}B NMR (375.5 MHz, acetone–d_6) δ_B 31.2 (minor), 29.5 (major); ^{19}F NMR (470 MHz, acetone–d_6) δ_F -120.8 (dd, J = 9.9, 4.2, minor), -122.4 (dd, J = 121.1, 5.3, major). HRMS (ESI-): Calculated for $[M\text{-}H_2O\text{+}OMe]^-$ $C_8H_7FBO_3$: 181.0478; Found: 181.0475. ^{13}C NMR spectrum is not reported, as the signal intensity was too weak due to the combined effect of tautomerization, ^{19}F splitting and the adjacent ^{11}B.

(4-Fluoro-2-formylphenyl)boronic acid 10b. General procedure 3 was followed using 1-bromo-2-(dimethoxymethyl)-4-fluorobenzene **11b** (1.18 g, 4.75 mmol), affording the title compound **10b** (410 mg, 2.44 mmol) as a white solid in 55% yield. All characterisation data were consistent with previous literature reports.[17] m.p.: 123-126 °C (lit.[17] 123-125 °C); IR (neat): 3217, 1670, 1601, 1578, 1428, 1366, 1339, 1273, 1221, 1156, 1088, 1039, 886, 829, 768, 727 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ_H 10.33 (s, 1H, OC*H*, major), 8.28 (bs, 1H, BO*H*, minor), 7.93 (dd, 1H, J = 8.3, 5.9, Ar*H*, major), 7.74 (bs, 2H, BO*H*, major), 7.74 (dd, 1H, J = 8.0, 5.7, Ar*H*, minor), 7.66 (dd, 1H, J = 9.6, 7.2, Ar*H*, major), 7.44 (td, J = 8.4, 2.7, Ar*H*, major), 7.21-7.13 (m, 2H, Ar*H*, minor)**;** ^{11}B NMR (375.5 MHz, acetone–d_6) δ_B 31.3 (minor),

28.9 (major); ^{19}F NMR (470 MHz, acetone–d_6) δ_F -111.2 (minor), -111.7 (major); HRMS (ESI-): Calculated for [M-H_2O+OMe]$^-$ $C_8H_7FBO_3$: 181.0478; Found: 181.0471. ^{13}C NMR spectrum is not reported, as the signal intensity was too weak due to the combined effect of tautomerization, ^{19}F splitting and the adjacent ^{11}B.

(5-Fluoro-2-formylphenyl)boronic acid 10c. General procedure 3 was followed using 1-bromo-2-(dimethoxymethyl)-5-fluorobenzene **11c** (1.16 g, 4.65 mmol), affording the title compound **10c** (388 mg, 2.31 mmol) as a white solid in 50% yield. m.p.: 126-131 °C; IR (neat): 3309, 3069, 1669, 1596, 1571, 1419, 1344, 1226, 1167, 1103, 1044, 905, 797, 737, 692 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ_H 10.17 (s, 1H, OC*H*, major), 8.06 (m, 1H major + 1H minor, Ar*H*), 7.84 (s, 2H, BO*H*, major), 7.56 (dd, 1H, J = 9.5, 2.7, Ar*H*, major), 7.50 (dd, 1H, *J* = 8.3, 4.7, Ar*H*, minor), 7.37 (td, 1H, *J* = 8.4, 2.7, Ar*H*, major), 7.31-7.22 (m, 1H, Ar*H*, minor), 6.27 (bs, 1H, OC*H*, minor) (some signals not observed due to low concentration of minor tautomer)[19]; ^{11}B NMR (375.5 MHz, acetone–d_6) δ_B 28.9 (major), 20.2 (minor); ^{19}F NMR (470 MHz, acetone-d_6) δ_F -106.7 (dd, *J* = 8.1, 8.1, major), -116.1 (minor); HRMS (ESI-): Calculated for [M-H_2O+OMe]$^-$ $C_8H_7FBO_3$: 181.0478; Found: 181.0473. ^{13}C NMR spectrum is not reported, as the signal intensity was too weak due to the combined effect of tautomerization, ^{19}F splitting and the adjacent ^{11}B.

(6-Fluoro-2-formylphenyl)boronic acid 10d. General procedure 3 was followed using 1-bromo-2-(dimethoxymethyl)-6-fluorobenzene **11d** (1.18 g, 4.75 mmol), affording the title compound **10d** (223 mg, 1.33 mmol) as a white solid in 28% yield. m.p.: 153-156 °C; IR (neat): 3255, 2848, 1674, 1601, 1567, 1451, 1324, 1301, 1231, 1213, 1160, 1040, 786, 730, 681 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ_H 10.04 (d, 1H, *J* = 2.3, OC*H*, major), 7.75 (d, 1H, *J* = 7.4, Ar*H*, major), 7.64-7.54 (m, 1H major + 1H minor, Ar*H*), 7.38-7.24 (m, 1H major + 1H minor, Ar*H*), 7.06 (t, 1H, *J* = 8.1, Ar*H*, major), 6.26 (bs, 1H, OC*H*, minor) (some signals not observed due to low concentration of minor tautomer[19]); ^{11}B NMR (375.5 MHz, acetone–d_6) δ_B 29.3 (major), 20.2 (minor); ^{19}F NMR (470 MHz, acetone-d_6) δ_F -105.6 (minor), -106.1 (t, *J* = 6.7, major); HRMS (ESI-): Calculated for [M-H_2O+OMe]$^-$ $C_8H_7FBO_3$: 181.0478; Found: 181.0473. ^{13}C NMR spectrum is not reported, as the signal intensity was too weak due to the combined effect of tautomerization, ^{19}F splitting and the adjacent ^{11}B.

General procedure 4 for the synthesis of 2-formyl boronate esters 6 and 3-F-6. (1*S*,2*S*,3*R*,5*S*)-pinanediol **3h** (1.0 equiv) was added to a stirred suspension of a 2-formylbenzene boronic acid **2** (1.1 equiv) in $CHCl_3$ (0.10 M). After 15 min, the reaction was diluted with an equivalent amount of CH_2Cl_2 and passed through a silica plug. The plug was washed with CH_2Cl_2 until no more product eluted and the solvent removed *in vacuo* to afford the desired boronate ester as a clear oil.

2-((3a*S*,4*S*,6*S*,7a*R*)-3a,5,5-Trimethylhexahydro-4,6-methanobenzo[*d*][1,3,2]dioxaborol-2-yl)benzaldehyde 6. General procedure 4 was followed using 2-FPBA **2** (83 mg, 0.55 mmol) and (1*S*, 2*S*, 3*R*, 5*S*)-pinanediol **3h** (85 mg, 0.5 mmol), affording the title compound (3a*S*,4*S*,6*S*,7a*R*)-**6** (110 mg, 0.39 mmol) as a clear oil in 70% yield. $[\alpha]_D^{23}$= +18 (c 1.0, $CHCl_3$); IR (neat): 2921, 2870, 1693, 1593, 1488, 1370, 1337, 1236, 1076, 754, 666 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.55 (s, 1H, OC*H*), 7.98-7.95 (m, 1H, Ar*H*), 7.90-7.86 (m, 1H,Ar*H*), 7.62-7.53 (m, 2H, Ar*H*), 4.52 (dd, 1H, *J* = 8.8, 1.9 H-7a), 2.48-2.39 (m, 1H, H-7), 2.32-2.23 (m, 1H, H-8), 2.16 (dd, 1H, *J* = 6.0, 4.9, H-4), 2.04-1.94 (m, 2H, H-6 + H-7), 1.53 (s, 3H, H-9), 1.33 (d, 1H, *J* = 10.8, H-8), 1.32 (s, 3H, H-10/11), 0.90 (s, 3H, H-10/11); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C 194.7, 141.4, 135.7, 133.1, 131.9 (deduced from HMBC, confirmed by -15 °C VT NMR), 130.8, 128.0, 86.9, 78.6, 51.5, 39.7, 38.4, 35.5, 28.7, 27.2, 26.6, 24.2; ^{11}B NMR (375.5 MHz, $CDCl_3$) δ_B 30.7; HRMS (ESI+): Calculated for [M+Na]$^+$ $C_{17}H_{21}BO_3Na$: 307.1479; Found: 307.1493.

2-fluoro-6-((3a*S*,4*S*,6*S*,7a*R*)-3a,5,5-Trimethylhexahydro-4,6-methanobenzo[*d*][1,3,2]dioxaborol-2-yl)benzaldehyde 3-F-6. General procedure 4 was followed using 3-fluoro-2-FPBA **10a** (47 mg, 0.28 mmol) and (1*S*,2*S*,3*R*,5*S*)-pinanediol **3h** (96 mg, 0.25 mmol), affording the title compound (3a*S*,4*S*,6*S*,7a*R*)-3-F-**6** (73 mg, 0.39 mmol) as a clear oil in 96% yield. $[\alpha]_D^{23}$= +20 (c 1.0, $CHCl_3$); IR (neat): 2918, 2869, 1695, 1568, 1480, 1439, 1339, 1238, 1029, 794, 666 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.43 (d, 1H, *J* = 1.0, OC*H*C), 7.58 (ddd, 1H, *J* = 8.3, 7.2, 5.2, Ar*H*), 7.40 (d, 1H, *J* = 7.2, Ar*H*), 7.17 (ddd, 1H, *J* = 10.6, 8.3, 1.0, Ar*H*), 4.55 (dd, 1H, *J* = 8.8, 2.0, H-7a), 2.48-2.38 (m, 1H, H-7), 2.37-2.27 (m, 1H, H-8), 2.17-2.11 (m, 1H, H-4), 2.06-1.96 (m, 2H, H-6 and H-7), 1.58 (s, 3H, H-9), 1.55 (d, 1H, *J* = 10.8, H-8), 1.34 (s, 3H, H-10/11), 0.91 (s, 3H, H-10/11); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C 189.0 (d, $J_{F\text{-}C}$ = 6.2), 164.3 (d, $J_{F\text{-}C}$ =259.8), 135.7 (d, $J_{F\text{-}C}$ = 8.7), 129.1 (d, $J_{F\text{-}C}$ = 3.8), 127.8 (d, $J_{F\text{-}C}$ = 6.9), 121.6 (deduced from HMBC), 117.5 (d, $J_{F\text{-}C}$ = 20.9), 86.6, 78.8, 51.7, 39.7, 38.5, 35.5, 28.4, 27.3, 26.5, 24.2; ^{11}B NMR (375.5 MHz, $CDCl_3$) δ_B 30.9; ^{19}F NMR (470 MHz, $CDCl_3$) δ_F -121.0 (dd, *J* = 10.5, 5.3); HRMS (ESI+): Calculated for [M+Na]$^+$ $C_{17}H_{20}BO_3FNa$: 325.1385; Found: 325.1381.

General procedure 5 for the synthesis of *tert*-butyl sulfiminoboronates 4h and 5h. *tert*-Butyl sulfinamide **1a** (61 mg, 0.50mmol, 1.0 equiv.) was added to a stirred suspension of 2-formylbenzene boronic acid **2** (90 mg, 0.60 mmol, 1.2 equiv.) and $MgSO_4$ (1.00 g) in $CHCl_3$ and the reaction stirred for 2 h, before (1*R*,2*R*,3*S*,5*R*)-pinanediol **3h** (111 mg, 0.65 mmol, 1.3 equiv.) was added. After 10 min, the reaction was filtered and concentrated to dryness *in vacuo* and the residue purified by chromatography (0.5% MeOH in 1:1 DCM/n-hexane) afforded the desired sulfiminoboronate ester as a clear oil. The low stability of these complexes to the purification conditions employed meant that small amounts of 2-formyl boronate ester **6** remained.

(*R*)-2-methyl-*N*-((*E*)-2-((3a*R*,4*R*,6*R*,7a*S*)-3a,5,5-trimethylhexahydro-4,6-methanobenzo[*d*][1,3,2]dioxaborol-2-yl)benzylidene)propane-2-sulfinamide 4h. General procedure 5 was followed using (*R*)-Ellman's sulfinamide **1a** (61 mg, 0.50 mmol), affording the title compound (R_S,3a*R*,4*R*,6*R*,7a*S*)-**4h** (24 mg, 0.062 mmol) as a clear oil in 12% yield, as a 89:11 mixture with the related formyl boronate ester (3a*R*,4*R*,6*R*,7a*S*)-**6**. ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 9.36 (s, 1H, NC*H*), 8.13-8.06 (m, 1H, Ar*H*), 7.94-7.88 (m, 1H, Ar*H*), 7.54-7.46 (m, 2H, Ar*H*), 4.51 (dd, 1H, *J* = 8.8, 2.0, H-7a), 2.48-2.37 (m, 1H, H-7), 2.29-2.21 (m, 1H, H-8), 2.18 (dd, 1H, J = 6.1, 5.1, H-4), 2.02 (ddd, 1H, *J* = 14.7, 3.4, 2.0, H-7), 1.97-1.97 (m, 1H, H-6), 1.51 (s, 3H,H-9), 1.30 (s, 3H, H-10/11),

1.26 (s, 9H, *tert*-butyl), 1.23 (d, 1H, *J* = 10.9, H-8), 0.88 (s, 3H, H-10/11); ^{11}B NMR (375.5 MHz, $CDCl_3$) δ_B 30.5; HRMS (ESI+): Calculated for $[M+H]^+$ $C_{21}H_{31}BNO_3S$: 388.2116, Found 388.2118; Calculated for $[M+Na]^+$ $C_{21}H_{30}BNO_3SNa$: 410.1936; Found: 410.1940. IR and specific rotation data were not acquired due to the presence of significant residual (3a*R*,4*R*,6*R*,7a*S*)-**6**. ^{13}C NMR spectra are not reported, as this impurity and the adjacent ^{11}B nucleus led to unassignable spectra.

(*S*)-2-methyl-*N*-((*E*)-2-((3a*R*,4*R*,6*R*,7a*S*)-3a,5,5-trimethylhexahydro-4,6-methanobenzo[*d*][1,3,2]dioxaborol-2-yl)benzylidene)propane-2-sulfinamide 5h. General procedure 5 was followed using (*S*)-Ellman's sulfinamide **1a**, affording the title compound (*S*$_S$,3a*R*,4*R*,6*R*,7a*S*)-**5h** (37 mg, 0.096 mg) as a clear oil in 19% yield, as a 96:4 mixture with the related formyl boronate ester (3a*R*,4*R*,6*R*,7a*S*)-6. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.27 (s, 1H, NC*H*), 8.08-8.03 (m, 1H, Ar*H*), 7.90-7.83 (m, 1H, Ar*H*), 7.54-7.47 (m, 2H, Ar*H*), 4.51 (dd, 1H, *J* = 8.7, 1.9, H-7a), 2.49-2.38 (m, 1H, H-7), 2.32-2.21 (m, 1H, H-8), 2.17 (dd, 1H, J = 6.0, 5.0, H-4), 2.09-1.91 (m, H-7 + H-6), 1.51 (s, 3H, H-9), 1.31 (s, 3H, H-10/11), 1.28-1.22 (m, 12H, tert-butyl + H-8), 0.88 (s, 3H, H10/11); ^{11}B NMR (375.5 MHz, $CDCl_3$) δ_B 31.2; HRMS (ESI+): Calculated for $[M+H]^+$ $C_{21}H_{31}BNO_3S$: 388.2116, Found 388.2112; Calculated for $[M+Na]^+$ $C_{21}H_{30}BNO_3S$: 410.1936; Found: 410.1937; IR and specific rotation data were not acquired due to the presence of significant residual (3a*R*,4*R*,6*R*,7a*S*)-**6**. ^{13}C NMR spectra are not reported, as this impurity and the adjacent ^{11}B nucleus led to unassignable spectra.

General procedure 6 for the three-component chiral derivatization of sulfinamides. A 2-Formylbenzene boronic acid (0.12 mmol, 1.2 equiv.) and anhydrous $MgSO_4$ (200 mg) were added to a stirred solution of sulfinamide **1a-h** (0.1 mmol, 1.0 equiv.) in $CDCl_3$ (1.0 mL, TMS internal standard). The reaction was stirred at room temperature for 1 h, before addition of (*1R*, 2*R*, 3*S*, 5*R*)-pinanediol **3h** (1.0 M in $CDCl_3$, 130 µL, 1.3 equiv.). The reaction was then stirred for a further 10 minutes, before the reaction was filtered and the 500 MHz ^{1}H NMR spectrum and/or 470 MHz ^{19}F spectrum of the resultant iminoboronate esters acquired. The acquired ^{1}H and ^{19}F{^{1}H} NMR spectra can be found in the associated Supporting Information.

Scalemic and racemic samples of Ellman's sulfinamide **1a** were prepared from commercially available enantiopure samples of (*R*)- and (*S*)-tert-butyl sulfinamide **1a**. 0.1 M solutions of enantiopure **1a** in $CDCl_3$ were prepared, and then combined to produce scalemic samples of **1a**, the *ee* of which was determined by the ratio of enantiopure stock solutions.

ASSOCIATED CONTENT

Supporting Information

All data supporting this study are provided as supplementary information accompanying this paper. The Supporting Information is available free of charge on the ACS Publications website.

^{1}H, ^{13}C, ^{19}F and ^{11}B NMR spectra of all compounds and spectra of three-component mixtures. (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: s.d.bull@bath.ac.uk; t.d.james@bath.ac.uk

ACKNOWLEDGMENT

This work was supported by the EPSRC Centre for Doctoral Training in Catalysis (EP/L016443/1).

REFERENCES

(1) (a) F. A. Davis, R. E. Reddy, J. M. Szewczyk, G. V. Reddy, P. S. Portonovo, H. Zhang, D. Fanelli, R. T. Reddy, P. Zhou and P. J. Carroll, Asymmetric Synthesis and Properties of Sulfinimines (Thiooxime *S*-Oxides), *J. Org. Chem.*, 1997, **62**, 2555–2563. (b) H.-Q. Dong, M.-H. Xu, C.-G. Feng, X.-W. Sun and G.-Q. Lin, Recent applications of chiral *N*-*tert*-butanesulfinyl imines, chiral diene ligands and chiral sulfur-olefin ligands in asymmetric synthesis, *Org. Chem. Front.*, 2015, **2**, 73–89. (c) F. A. Davis, Adventures in sulfur-nitrogen chemistry, *J. Org. Chem.*, 2006, **71**, 8993–9003. (d) P. Zhou, B.-C. Chen and F. A. Davis, Recent advances in asymmetric reactions using sulfinimines (*N*-sulfinyl imines), *Tetrahedron*, 2004, **60**, 8006–8030.

(2) (a) M. T. Robak, M. A. Herbage and J. A. Ellman, Synthesis and Applications of *tert*-Butanesulfinamide, *Chem. Rev.*, 2010, **110**, 3600–3740. (b) Y. Zhang, S. Chitale, N. Goyal, G. Li, Z. S. Han, S. Shen, S. Ma, N. Grinberg, H. Lee, B. Z. Lu and C. H. Senanayake, Asymmetric Synthesis of Sulfinamides Using (−)-Quinine as Chiral Auxiliary, *J. Org. Chem.*, 2012, **77**, 690–695.

(3) (a) J. W. Evans and J. A. Ellman, Stereoselective Synthesis of 1,2-Disubstituted-Amino Alcohols by Nucleophilic Addition to *N*-*tert*-Butanesulfinyl α-Alkoxyaldimines, *J. Org. Chem.*, 2003, **68**, 9948–9957. (b) Z.-J. Liu, Y.-Q. Mei and J.-T. Liu, A practical diastereoselective synthesis of β-hydroxy-β-trifluoromethyl imines, *Tetrahedron*, 2007, **63**, 855–860. (c) Y. Lee, K. Akiyama, D. G. Gillingham, M. K. Brown and A. H. Hoveyda, Highly Site-and Enantioselective Cu-Catalyzed Allylic Alkylation Reactions with Easily Accessible Vinylaluminum Reagents, *J. Am. Chem. Soc.*, 2008, **130**, 446–447. (d) J. C. Barrow, P. L. Ngo, J. M. Pellicore, H. G. Selnick and P. G. Nantermet, A facile three-step synthesis of 1,2-amino alcohols using the Ellman homochiral *tert*-butylsulfinamide, *Tetrahedron Lett.*, 2001, **42**, 2051–2054. (e) A. Viso, R. Fernández De La Pradilla, M. L. López-Rodríguez, A. García, A. Flores and M. Alonso, Fine-Tuned Aminal Cleavage: A Concise Route to Differentially Protected Enantiopure *syn*-α,β-Diamino Esters, *J. Org. Chem.*, 2004, **69**, 1542–1547. (f) K. W. Kells and J. M. Chong, Addition of Bu_3SnLi to *tert*-Butanesulfinimines as an Efficient Route to Chiral, Nonracemic α-Aminoorganostannanes, *Org. Lett.*, 2003, **5**, 4215–4218. (g) L. P. Jayathilaka, M. Deb and R. F. Standaert, Asymmetric Synthesis and Translational Competence of L-α-(1-Cyclobutenyl)glycine, *Org. Lett.*, 2004, **6**, 3659–3662. (h) T. P. Tang and J. A. Ellman, Asymmetric synthesis of β-amino acid derivatives incorporating a broad range of substitution patterns by enolate additions to *tert*-butanesulfinyl imines, *J. Org. Chem.*, 2002, **67**, 7819–7832.

(4) (a) N. J. Oldenhuis, V. M. Dong and Z. Guan, From Racemic Alcohols to Enantiopure Amines: Ru-Catalyzed Diastereoselective Amination, *J. Am. Chem. Soc.*, 2014, **136**, 12548–12551. (b) P. Dinér, A. Sadhukhan and B. Blomkvist, Chiral Sulfinamides as Highly Enantioselective Organocatalysts, *ChemCatChem*, 2014, **6**, 3063–3066. (c) Z.-M. Zhang, P. Chen, W. Li, Y. Niu, X.-L. Zhao and J. Zhang, A New Type of Chiral Sulfinamide Monophosphine Ligands: Stereodivergent Synthesis and Application in Enantioselective Gold(I)-Catalyzed Cycloaddition Reactions, *Angew. Chemie Int. Ed.*, 2014, **53**, 4350–4354.

(5) V. N. Viswanadhan, A. K. Gho, N. B. Hanna, S. S. Matsumoto, T. L. Avery, G. R. Revankar and R. K. Robins, Analysis of the in Vitro Antitumor Activity of Novel Purine-6-sulfenamide, -sulfinamide, and -sulfonamide Nucleosides and Certain Related Compounds Using a Computer-Aided Receptor Modelling Procedure, *J. Med. Chem.*, 1991, **34**, 526–532.

(6) (a) G. Keceli and J. P. Toscano, Reactivity of Nitroxyl-Derived Sulfinamides, *Biochemistry*, 2012, **51**, 4206–4216. (b) G. Keceli, C. D. Moore, J. W. Labonte and J. P. Toscano, NMR Detection and Study of Hydrolysis of HNO-Derived Sulfinamides, *Biochemistry*, 2013, **52**, 7387-7396. (c) G. Keceli and J. P. Toscano, 2014, Reactivity of C-Terminal Cysteines with HNO, *Biochemistry*, **53**, 3689–3698.

(7) (a) D. A. Cogan, G. Liu, K. Kim, B. J. Backes and J. A. Ellman, Catalytic Asymmetric Oxidation of *tert*-Butyl Disulfide. Synthesis of *tert*-Butanesulfinamides, *tert*-Butyl Sulfoxides, and *tert*-Butylsulfinimines, *J. Am. Chem. Soc.*, 1998, **120**, 8011–8019. (b) D. J. Weix and J. A. Ellman, (R_S)-(+)-2-Methyl-2-propanesulfinamide [*tert*-Butanesulfinamide], *Org. Synth.*, 2005, **82**, 157–165.

(8) J. Liao, X. Sun, X. Cui, K. Yu, J. Zhu and J. Deng, Facile Optical Resolution of *tert*-Butanethiosulfinate by Molecular Complexation with (*R*)-BINOL and Study of Chiral Discrimination of the Diastereomeric Complexes, *Chem.: Eur. J.*, 2003, **9**, 2611–2615.

(9) C. K. Savile, V. P. Magloire and R. J. Kazlauskas, Subtilisin-Catalyzed Resolution of *N*-Acyl Arylsulfinamides, *J. Am. Chem. Soc.*, 2005, **127**, 2104–2113.

(10) G. R. Revankar, N. B. Hanna, N. Imamura, A. F. Lewis, S. B. Larson, R. A. Finch, T. L. Avery and R. K. Robins, Synthesis and *in Vivo* Antitumor Activity of 2-Amino-9*H*-purine-6-sulfenamide,-sulfinamide, and-sulfonamide and Related Purine Ribonucleosides, *J. Med. Chem*, 1990, **33**, 121–128.

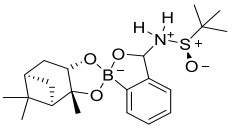
(11) (a) W. H. Pirkle, S. D. Beare and R. L. Muntz, Optically Active Solvents for Nuclear Magnetic Resonance. X. Enantiomeric Nonequivalence of Sulfinamides, Sulfinates, Sulfites, Thiosulfinates, Phosphine Oxides, and Amine Oxides, *J. Am. Chem. Soc.*, 1969, **91**, 4575. (b) T. Ema, D. Tanida, T. Sakai, Versatile and Practical Macrocyclic Reagent with Multiple Hydrogen-Bonding Sites for Chiral Discrimination in NMR, *J. Am. Chem. Soc.*, 2007, **129**, 10591-10596.

(12) (a) Y. Pérez-Fuertes, A. M. Kelly, A. L. Johnson, S. Arimori, S. D. Bull and T. D. James, Simple Protocol for NMR Analysis of the Enantiomeric Purity of Primary Amines, *Org. Lett.*, 2006, **8**, 609–612. (b) A. M. Kelly, Y. Pérez-Fuertes, S. Arimori, S. D. Bull and T. D. James, Simple Protocol for NMR Analysis of the Enantiomeric Purity of Diols, *Org. Lett.*, 2006, **8**, 1971–1974. (c) A. M. Kelly, S. D. Bull and T. D. James, Simple chiral derivatisation protocols for NMR analysis of the enantiopurity of 1,2-diphenylethane-1,2-diamine and *N*-Boc-cyclohexane-1,2-diamine, *Tetrahedron Asymmetry*, 2008, **19**, 489–494. (d) M. E. Powell, A. M. Kelly, S. D. Bull and T. D. James, A simple chiral derivatisation protocol for ^{1}H NMR spectroscopic analysis of the enantiopurity of *O*-silyl-1,2-amino alcohols, *Tetrahedron Lett.*, 2008, **50**, 876–879. (e) Y. Pérez-Fuertes, A. M. Kelly, J. S. Fossey, M. E. Powell, S. D. Bull and T. D. James, Simple protocols for NMR analysis of the enantiomeric purity of chiral primary amines, *Nat. Protoc.*, 2008, **3**, 210–214. (f) A. M. Kelly, Y. Pérez-Fuertes, J. S. Fossey, S. Lozano Yeste, S. D. Bull and T. D. James, Simple protocols for NMR analysis of the enantiomeric purity of chiral diols, *Nat. Protoc.*, 2008, **3**, 215–219. (g) D. A. Tickell, M. F. Mahon, S. D. Bull and T. D. James, Simple Protocol for NMR Analysis of the Enantiomeric Purity of Chiral Hydroxylamines, *Org. Lett.*, 2013, **15**, 860–863. (h) D. A. Tickell, E. V Lampard, J. P. Lowe, T. D. James and S. D. Bull, A Protocol for NMR Analysis of the Enantiomeric Excess of Chiral Diols Using an Achiral Diboronic Acid Template, *J. Org. Chem.*, 2016, **81**, 6795–6799.

(13) (a) H. Y. Su, D. Gorelik and M. S. Taylor, Chiral phosphine ligand libraries based on the Bull-James three-component supramolecular assembly Chiral phosphine ligand libraries based on the Bull-James three-component supramolecular assembly, *Supramol. Chem.*, 2019, 31, 190–202. (b) J. S. Fossey, E. V Anslyn, W. D. G. Brittain, S. D. Bull, B. M. Chapin, C. Cécile, S. Le Duff, T. D. James, G. Lees, S. Lim, J. A. C. Lloyd, C. V Manville, D. T. Payne and K. A. Roper, Rapid Determination of Enantiomeric Excess via NMR Spectroscopy: A Research-Informed Experiment, *J. Chem. Educ.*, 2017, **94**, 79–84. (c) B. M. Chapin, P. Metola, V. M. Lynch, J. F. Stanton, T. D. James and E. V Anslyn, Structural and Thermodynamic Analysis of a Three-Component Assembly Forming *ortho*-Iminophenylboronate Esters, *J. Org. Chem.*, 2016, **81**, 8319–8330.

(14) S. Higashibayashi, H. Tohmiya, T. Mori, K. Hashimoto and M. Nakata, Synthesis of Sulfinimines by Direct Condensation of Sulfinamides with Aldehydes Using Cs_2CO_3 as an Activating and Dehydrating Reagent, *Synlett*, 2004, **3**, 457–460.

(15) It is possible that the lack of reactivity of the aldehyde functionality of boronate ester **6** towards imine formation in the three-component reaction may be due to the increased Lewis-acidity of its boronic ester group (relative to boronic acid **2**) which acts to stabilize the carbinolamine intermediate **12** through an intramolecular B-O bond that prevents its subsequent dehydration to afford an imine.



12
(Derived from (*R*)-**1a**)

(16) (*rac*)-sulfinamides **1c-h** were synthesized using the methods described by J. Di, H. He, F. Wang, F. Xue, X.-Y. Liu and Y. Qin, Regiospecific alkyl addition of (hetero)arene-fused thiophenes enabled by a visible-light-mediated photocatalytic desulfuration approach, *Chem. Commun.*, 2018, **54**, 4692–4695.

(17) S. L. Yeste, M. E. Powell, S. D. Bull and T. D. James, Simple Chiral Derivatization Protocols for ^{1}H NMR and ^{19}F NMR Spectroscopic Analysis of the Enantiopurity of Chiral Diols *J. Org. Chem.*, 2009, **74**, 427–430.

(18) N. Hamaguchi, Y. Okuno, Y. Oe and T. Ohta, A simple quantitative chiral analysis of amino acid esters by fluorine-19 nuclear magnetic resonance using the modified James–Bull method, *Chirality*, 2019, **31**, 34–40.

(19) Fluorinated 2-FPBA analogues **10a-d** were synthesized using methods described by K. Kowalska, A. Adamczyk-Woźniak, P. Gajowiec, B. Gierczyk, E. Kaczorowska, Ł. Popenda, G. Schroeder, A. Sikorski and A. Sporzyński, Fluoro-substituted 2-formylphenylboronic acids: Structures, properties and tautomeric equilibria, *J. Fluor. Chem.*, 2016, **187**, 1–8.

(20) L. Wang, C. Dai, S. K. Burroughs, S. L. Wang and B. Wang, Arylboronic Acid Chemistry under Electrospray Conditions, *Chem. A Eur. J.*, 2013, **19**, 7587–7594.

(21) L. Ma, G. Li, J. Huang, J. Zhu and Z. Tang, Synthesis of asymmetrical thioethers with sulfinamides as the sulfenylation agent under metal-free conditions, *Tetrahedron Lett.*, 2018, **59**, 4255–4258.

(22) R. Kowalczyk, A. J. F. Edmunds, R. G. Hall and C. Bolm, Synthesis of CF_3-Substituted Sulfoximines from Sulfonimidoyl Fluorides, *Org. Lett.*, 2011, **13**, 768–771.

(23) B. Wang, T. Xu, L. Zhu, Y. Lan, J. Wang, N. Lu, Z. Wei, Y. Lin and H. Duan, Highly Enantioselective Nitro-Mannich Reaction of Ketimines Under Phase-Transfer Catalysis, *Org. Chem. Front.*, 2017, **4**, 1266–1271.

(24) S. L. Lulinski, I. Madura, J. Serwatowski, H. Szatyłowicz and J. Zachara, A tautomeric equilibrium between functionalized 2-formylphenylboronic acids and corresponding 1,3-dihydro-1,3-dihydroxybenzo [*c*][2,1]oxaboroles, *New J. Chem.*, 2007, **31**, 144–154.