Organic & Biomolecular Chemistry

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ROYAL SOCIETY OF CHEMISTRY

rsc.li/obc

DOI: 10.1039/C7OB00846E

Journal Name

ARTICLE

A Greener and Efficient Access to Substituted Four- and Six-membered Sulfur-bearing Heterocycles

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

DOI: 10.1039/x0xx00000x

www.rsc.org/

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ABSTRACT The regioselective functionalization of four- and six-membered cyclic sulfones was investigated using a lithiation/electrophile trapping strategy. The protocol features an interesting eco-compatibility profile because of the use of 2-MeTHF as a solvent (more eco-friendly than other organic solvents) and *n*-hexyllithium as a lithiating agent safer than other alkyllithium compounds. Several derivatives were prepared with different stereochemistry and substitution patterns. A number of selected derivatives, spanning a range of 5 log *P* units, were characterized for their lipophilicity through RP-HPLC. A good linear correlation, with a slope close to 1.0, was observed between the experimentally determined RP-HPLC lipophilicity parameters (log k'_w) and calculated log *P* (clogP) values, whereas a systematic difference in absolute values between the chromatrographic parameters and in silico lipophilicity descriptors can be attributed mainly to silanophilic interactions between the H-bond acceptor SO_2 group and free silanol groups on silica-based C18 columns, which results in increased retention times.

Introduction

Sulfur-bearing heterocycles have been extensively used as versatile intermediates in organic synthesis and medicinal chemistry. In particular, sulfone moiety is a strong H-bond acceptor considered as carbonyl group bioisostere. Cyclic sulfones have unique synthetic utilities and several examples of drugs and drug candidates, including antitrypanosomal drug (Nifurtimox)®, antiglaucoma agent (Dorzolamide)®, kinase inhibitors,[1] cannabinoid receptor 2-agonists,[2] agents for the treatment of endometriosis[3] and antiviral compounds[4] have been reported (Figure 1). Cyclic sulfones, such as thietane and tetrahydro-2*H*-thiopyrane 1,1-dioxide, are considered interesting analogs of oxetane and sulfonyl-oxetanes in fragment-based drug discovery (FBDD) approaches.[5] The interest towards small cyclic compounds bearing sulfone moieties is motivated by the paucity of efficient methodologies for metalation and functionalization of these systems have been scarcely investigated. In striking contrast, examples on the reactivity of five-membered cyclic sulfones have been reported.[6-10] Nevertheless, four- and six-membered cyclic sulfones have been less explored. The few examples on the metalation and functionalization of thietan 1,1-dioxide at the α position, rely only on the α-bromination and α-chlorination reactions.[11]

In a more recent work, aimed at obtaining some protease inhibitors, Velàsquez and co-workers performed the lithiation of four-, five-, and six-membered cyclic sulfones followed by a trapping with a sulfynylimine that occurred with low stereoselectivity.[12] However, Velàsquez's work was focused on the preparation of the pharmaceutical target rather than on a systematic study of the reactivity of cyclic sulfones.

Our research group recently focused the attention on the reactivity and functionalization of four-membered heterocycles including azetidines and thietanes, which are interesting and poorly investigated molecular scaffolds.[13]

In previous works on the reactivity of thietane 1-oxide, we disclosed that the metalation and trapping sequence with various electrophiles occurred with a variable degree of regio- and stereoselectivity.[14] The chemical stability of lithiated C2-substituted thietane 1-oxides as well as the stereoselective functionalization at the C2, C4 positions of the ring have been also reported.[15] On these grounds, we decided to investigate the regio- and stereoselectivity of the metalation reactions of thietane 1,1-dioxide, in comparison with six-membered homologues such as tetrahydro-2*H*-thiopyran 1,1-dioxide. We report herein the results of this synthetic investigation, as well as a preliminary study on the lipophilicity (a fundamental physicochemical property in the drug-discovery process) of the newly synthesized cyclic sulfone derivatives.

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

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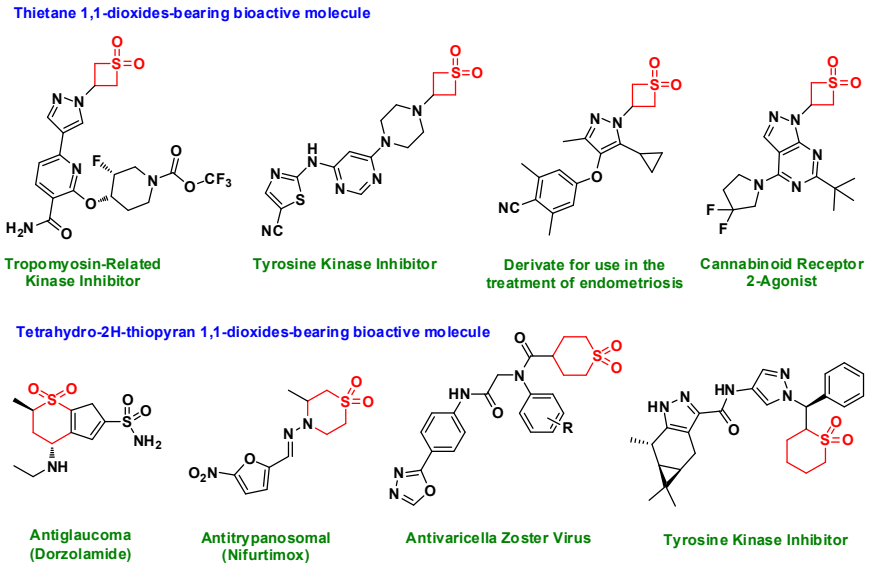
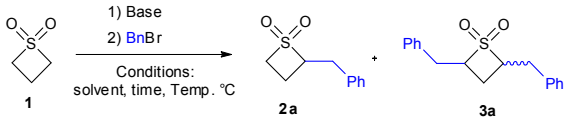


Figure 1. Examples of biologically active molecules bearing a four- or six-membered cyclic sulfone unit.

Table 1. Optimization of the lithiation/trapping of thietane 1,1-dioxide.



Entry	Base (equiv)	BnBr (equiv)	Solvent	Time	Temperature (°C)	Ratio **2a/3a**	Yield (%)
1	LDA (1.1)	1	THF	15 min	-78	57:43[b]	70[e]
2	LDA (1.1)	1	Toluene	15 min	-78	86:14[d]	77[e]
3	HexLi (1.1)	1	Toluene[a]	15 min	-78	75:25[c]	80[e]
4	HexLi (1.1)	1	2-MeTHF	5 min	-78	100/0	75[f]
5	HexLi (2.5)	2.5	2-MeTHF	10 min	-78	0/100	60[f]
6	HexLi (2.5)	2.5	2-MeTHF	2 min	-50	0/100	22[f]
7	HexLi (2.5)	2.5	2-MeTHF	2 min	-20	0/100	20[f]
8	HexLi (2.5)	2.5	2-MeTHF	2 min	-10	0/100	15[f]
9	HexLi (2.5)	2.5	2-MeTHF	1 min	-20	0/100	22[f]
10	HexLi (2.5)	2.5	2-MeTHF	1 sec	-20	0/100	14[f]

[a] TMEDA (1.1 equiv) was employed as co-solvent. [b]Ratio of disubstituted thietanes **3a** *trans/cis* (25/75) as ascertained by ^{1}H NMR. [c]Ratio of disubstituted thietanes **3a** *trans/cis* (>99:1) as ascertained by ^{1}H NMR. [d]Ratio of disubstituted thietanes **3a** *trans/cis* (54/46) as ascertained by ^{1}H NMR. Stereochemistry assigned on the basis of the chemical equivalence of the ring protons. [e]Established by ^{1}H NMR. [f]Yield of isolated product.

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We first investigated, the lithiation of thietane 1,1-dioxide **1** under different reaction conditions (Table 1) using benzyl bromide (BnBr) as the electrophile.

The cyclic α-sulfonyl carbanion could be generated by using either LDA (lithium diisopropylamine) or *n*-hexyllithium (HexLi) as bases. However, the use of LDA either in polar solvent such as THF or less polar one such as toluene, resulted in a mixture of C2 mono-, and C2, C4 di-substituted derivatives **2a** and **3a** respectively (Table 1, entries 1-2). The use of 1.1 equiv of HexLi in toluene also provided a 75:25 mixture of **2a** and **3a**, with a good overall yield. However, the

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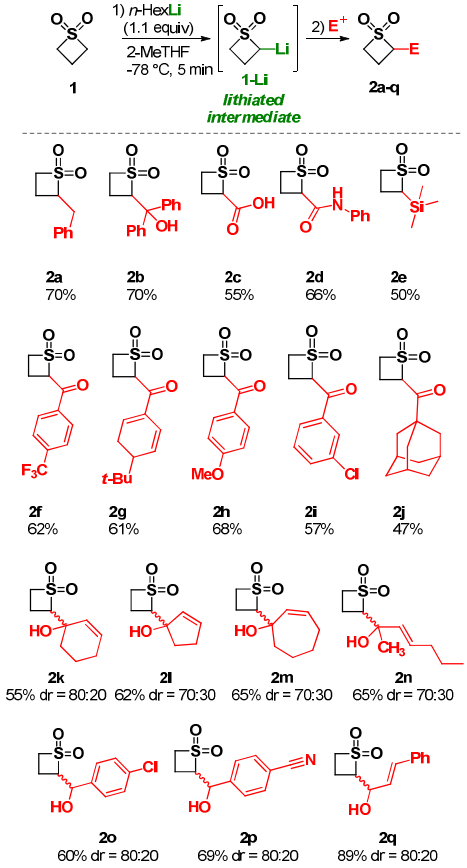
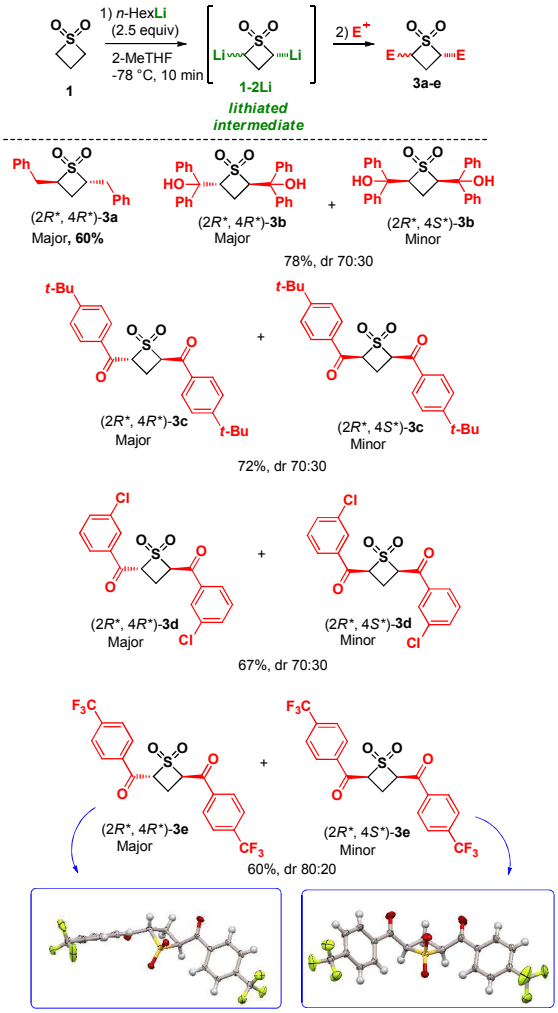
di-substituted derivative **3a** was obtained exclusively as trans stereoisomer (Table 1, entry 3). The use of the greener solvent 2-MeTHF, gave a more selective reaction leading to **2a** in 75% yield and as single product (Table 1, entry 4).[16] Nicely, lithiation of **1** with 2.5 equiv of HexLi, followed by reaction with benzylbromide, furnished exclusively the C2,C4 di-substituted derivative **3a** as single trans stereoisomer (Table 1, entry 5). Performing the lithiation/trapping sequence at higher temperatures (in the range between –20 and -50 °C), resulted in lower yields of trapping product **3a**, likely because of the thermal instability of the lithiated intermediate (Table 1, entries 6-10).

The preliminary screening of the lithiation/trapping of **1**, indicated conditions of entries 4 and 5 as the optimal ones for the mono or di-substitution, respectively. The inherent advantages of using 2-MeTHF as the reaction medium – *in primis* the non-needing of classical (contaminating) organic solvents during the work-up procedures [17]– render the whole synthetic process appealing from an eco-compatibility perspective. After optimization, the scope of the lithiation/trapping sequence was investigated. The use of 1.1 equiv of HexLi, guaranteed the mono functionalization of thietane 1,1-dioxide **1**.



Scheme 1. Mono-functionalization of thietane 1,1-dioxide **1**.

Trapping of lithiated thietane **1-Li** efficiently occurred with different carbonyl-type electrophiles including aldehydes or ketones, Weinreb amides, isocyanates, [18] carbon dioxide. Analogously, silyl and benzyl halides also proved to be suitable electrophilic partners leading to C2-functionalized thietanes **2a-q** (Scheme 1) in good yields. Good control of stereoselectivity was achieved in the case of prochiral electrophiles **2k-q** (Scheme 1). Double functionalization at the two α-positions (C2, C4) of the thietane was carried out by following the established conditions (Table 1, entry 5). The lithiation/trapping sequence occurred with good yields and an acceptable trans stereoselectivity using benzylbromide, benzophenone and Weinreb amides as electrophiles. The structure and stereochemistry for the major stereoisomer (2*R**,4*R**)-**3e** and the minor one (2*R**,4*S**)-**3e** was ascertained by single crystal X-ray analysis.[19] The use as electrophile of Weinreb amides, which can be subjected to a nucleophilic attack by the base, suggests that the double functionalization could be likely ascribed to a double lithiated intermediate such as **1-2Li** (Scheme 2).



Scheme 2. Double functionalization of thietane 1,1-dioxide 1.

With the aim to demonstrate the involvement of a doubly lithiated species such as **1-2Li**, excluding a sequential lithiation, a lithiation/deuteration experiment was run on thietane 1,1-dioxide **1** (see Supporting Information). NMR and HRMS analyses gave support to a double lithiation at C2 and C4 carbons of **1**.[20,21]

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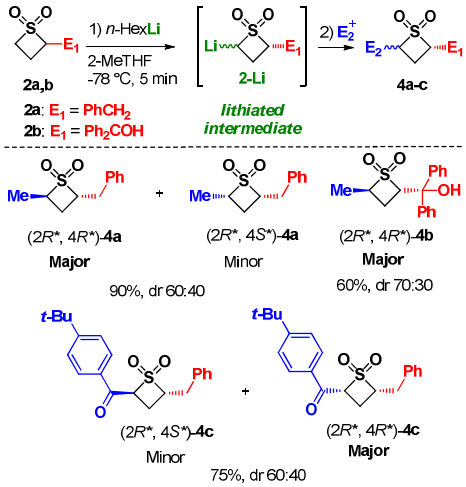
Next, by using the conditions optimized for the mono functionalization (Table 1, entry 4), we explored the possibility to introduce a different substituent at the C4 of C2 mono-substituted thiethanes **2**. Compounds **2a,b** were employed as starting materials, and subjected to a lithiation/trapping sequence with different electrophiles, including MeI, BnBr, benzophenone and 4-*tert*-butyl-*N*-methoxy-*N*-methyl-benzamide. Non symmetrically substituted C2,C4 di-functionalized thietanes **4a-c** were obtained in good yields although as a mixture of diastereoisomers with modest stereoselectivity (Scheme 3). The stereochemistry was assigned by Noesy experiments (see supporting information) that revealed a trans stereochemical preference in alkylation reactions (as for (2*R**,4*R**)-**4a** and (2*R**,4*R**)-**4b**), while the cis stereoisomer was the main one in acylation reactions (as for (2*R**,4*R**)-**4c**).



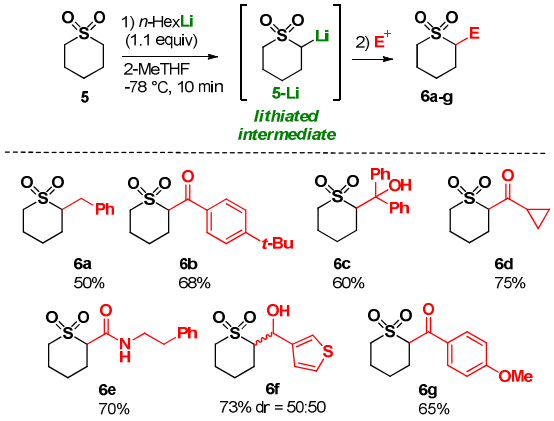
Scheme 3 C2,C4 double functionalization of mono substituted thietane 1,1-dioxides.

From a stereochemical point of view, the results reported in Schemes 2 and 3 show a trans stereochemical bias in the double functionalization of thietane sulfones **1**, **2a** and **2b**. Such stereochemical preference could be rationalized considering the steric effect brought about the already present C2-substituent. However, further lithiation/deuteration experiments run on (2*R**,4*R**)-**3a**, and on the diastereomeric mixture of keto thietane sulfones (2*R**,4*R**)- and (2*R**,4*S**)-**3d** suggested that likely kinetic products are observed under the reaction conditions (see Supporting information for details). In the case of enolizable keto-substituted thietane sulfones, the trans-configured stereoisomers (Scheme 2) are likely also the thermodynamic products. However, this kind of compounds, in protic solvent such as MeOH, undergo to a very fast epimerization that could alter the final diastereomeric ratio (see supporting information for details).

For sake of comparison, the lithiation trapping of six-membered heterocycle tetrahydro-2*H*-thiopyran 1,1-dioxide (**5**) was further investigated (Table 2).

As reported in Table 2, a mixture of mono and di substituted derivatives **6** and **7** was obtained in all cases. The structure and stereochemistry of the main isomer *cis*-**7a** was confirmed by single crystal X-Ray analysis.[22] The best conditions for the C2 mono functionalization are those reported in Table 2, entry 1. However, a selective C2, C4 double functionalization was hard to achieve likely for a competing double H-abstraction. Surprisingly, the solvent as well as the electrophile, seem to play a role in the regioselectivity of the lithiation reaction (compare entries 3 and 4 of Table 2). In this regard, the four- and six-membered rings behave differently giving, the smaller heterocycle, a more regioselective lithiation and a preferential trans-stereoselectivity in the double functionalization reactions. .

Under optimized conditions (Table 2, entry 1), thiopyran **5** was functionalized at the C2 with several electrophiles furnishing products **6a-g** (Scheme 4). With a prochiral aldehyde, a 1:1 mixture of diastereoisomers was observed for adduct **6f**. As reported for thietane **1**, even in this case the reaction could be conducted in a greener solvent that does not require work-up procedures in order to obtain the crude reaction mixture (see experimental section).



Scheme 4. C2 functionalization of tetrahydro-2*H*-thiopyran 1,1-dioxide.

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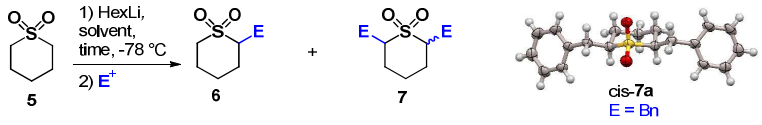
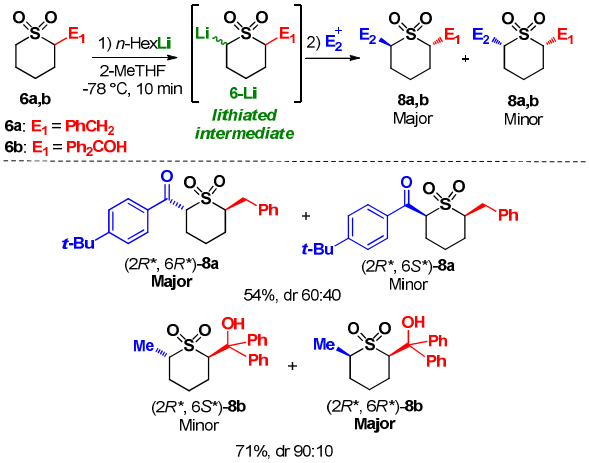
Table 2. Optimization of the lithiation/trapping of tetrahydro-2*H*-thiopyran 1,1-dioxide.



Entry	HexLi (equiv)	Electrophile	Solvent	Time (min)	Ratio 6/7	Yield (%)[a]
1	1.1	BnBr (1 equiv)	2-MeTHF	10	90/10[d]	50[b]
2	2.5	BnBr (2.5 equiv)	THF	10	87/13[d]	80[c]
3	2.5	BnBr (2.5 equiv)	2-MeTHF	30	10/90[d]	60[b]
4	2.5	Weinreb amide[d]	2-MeTHF	30	85/15[e]	80[c]

[a]Yield of isolated major adduct; [b]Yield of isolated product. [c]Ascertained by ^{1}H NMR. [d]4-t-Butyl-*N*-methoxy-*N*-methyl-benzamide (2.5 equiv). [d]The C2,C6 disubstituted derivative **7a**, was obtained as a 80:20 cis:trans mixture. [e]The C2,C6 disubstituted derivative wasn't isolated.

Next, we examined the double functionalization of C2-substituted thiopyrans **6a,b** disclosing an electrophile-dependent stereoselectivity after introducing the second electrophile (Scheme 5). Derivatives **8a,b** were obtained in acceptable yields but with a variable degree of stereoselectivity depending on the electrophile. Interestingly, and in striking contrast to the four membered ring, alkylation reaction with MeI furnished the cis stereoisomer (2*R**, 6*R**)-**8b** as the main product (dr 90:10), while acylation with a Weinreb amide gave (2*R**, 6*R**)-**8a** as the main stereoisomer (dr 60:40).



Scheme 5. C2, C4 di-functionalization of tetrahydro-2*H*-thiopyran 1,1-dioxide.

The different stereochemical preference observed in the double (C2, C6) functionalization of thiopyrans, with respect to the four-membered ring, could be explained considering a different thermodynamic stability of the C2, C6 di-substituted derivatives.

It is likely, that in thiopyrans, it is preferred the stereoisomer that sets the two susbstituents in di-equatorial fashion as seen with **7a** (Table 2) where X-ray analysis is available, and (2*R**,6*R**)-**8b** where higher stereoselectivity was observed.[23]

The reactivity of lithiated four- and six-membered cyclic sulfones **1** and **5** was also tested in more challenging reactions such as C2 arylation and fluorination (Scheme 6, a,b)

The direct α-arylation on both cyclic sulfones **1** and **5** was investigated first. Lithiation with HexLi, followed by transmetallation with CuCN-2LiCl, and reaction with aryliodonium salt Ph_2IPF_6, as arylating agent was successful producing derivatives **9a,b** in acceptable yields (Scheme 6, a). Surprisingly, lithiathion of thietane 1,1-dioxide **1** and tetrahydro-2*H*-thiopyran 1,1-dioxide **5** followed by subsequent trapping with *N*-Fluorodibenzenesulfonimide (NFSI) as the fluorinating agent, led, almost unexpectedly, to products **10a**,**b** (Scheme 9). It is likely that the introduction of the fluorine at C2 renders the remaining proton very acidic to be removed under the basic reaction conditions, allowing a further sulfonylation.

Finally, these new transformations were also tested on five-membered sulfolane that has been already studied in lithiation trapping reactions. [24] We were glad to find that, under the developed reaction conditions (Scheme 6) sulfolane **11** furnished either the C2-arylated product **9c**, or the α,α di-functionalized fluorinated derivative **10c**. In the case of **10a**, the structure of this unusual fluoro sulfonylated derivative was confirmed by single crystal X-ray analysis.[25]

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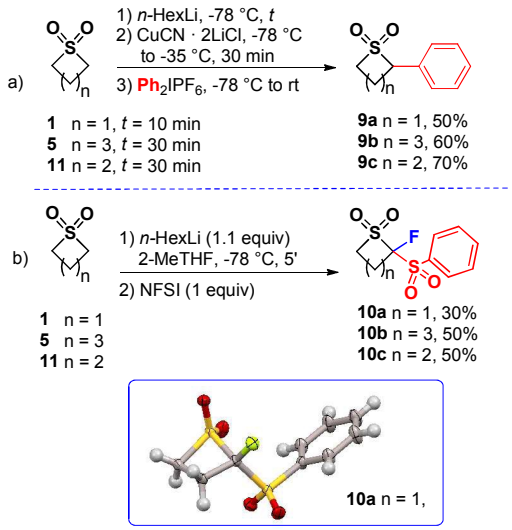

Scheme 6. a) C2-Arylation of cyclic sulfones. b) C2-Fluorination of cyclic sulfones.

After investigating the reactivity of cyclic sulfones, the lipophilicity of 24 selected derivatives, including C2-mono- and C2,C4-difunctionalized four-membered (2-MTE and 2,4-DTE respectively) and C2-mono- and one C2,C6-difunctionalized six-membered (2-MTHTP and 2,6-DTHTP respectively) cyclic sulfones, was assessed through reversed-phase high performance liquid chromatography (RP-HPLC). Lipophilicity is an important property affecting absorption, distribution, metabolism, excretion and toxicity (ADMET) of a potential drug substance, and therefore its determination has relevance in the drug discovery process.[26,27] Compared to the classical 'shake-flask' method, the RP-HPLC methods are less time- and sample-consuming, insensitive to impurities and less affected by low solubility of the analyte in one or both the liquid phases.[28,29] RP-HPLC has become a practical method for measuring drug lipophilicity at the early stages of drug discovery.[30] Two-phase titration (potentiometry),[31,32] which represents a reliable method for measuring lipophilicity of ionizable compounds, does not apply in our case.

In this study, the relative lipophilicity of cyclic sulfone derivatives was measured by previously reported RP-HPLC methods.[33,34] An alkyl modified C18 column was used as the stationary phase and capacity factors (k') of each compound were determined at different MeOH/aqueous buffer (pH 5) mobile phase v/v compositions (0.05-increments of MeOH volume fraction, ranging between 0.7 and 0.3). For all the examined compounds the log k' values increased linearly ($r^2 \geq 0.98$) with decreasing MeOH volume fraction, and the linear relationships were extrapolated to 100% aqueous mobile phase to yield log k'_w values. Lipophilicity data were also estimated using two well-known computational tools (Bio-Loom software, vers. 1.7 and ACDLabs software, release 10.0) for calculating 1-octanol-water partition coefficients (clogP). Experimental and calculated lipophilicity parameters are listed in Table 3 and in supplementary materials.

The comparison between the chromatographic parameters and *in silico* lipophilicity descriptors showed that a better linear relationship, which holds up over a range of about 5 log P units, exists between log k'_w and clogP calculated by Bio-Loom software, as shown by the following equation:

$$\log k'_w = 0.84\ (\pm 0.06)\ \text{clogP} + 1.51\ (\pm 0.12) \quad (1)$$
$$n = 24,\ r^2 = 0.885,\ s = 0.411,\ F = 168$$

where n represents the number of data points, r^2 the coefficient of determination (squared correlation coefficient), s the standard deviation of the regression equation, and F is the statistical significance of fit; 95% confidence intervals of the regression coefficients are given in parentheses.

A closer look to the scatter plot relating log k'_w and clogP (Figure 2) points out that there are two groups of points lying on two almost parallel lines. The separate regression analysis yielded the following linear equations, one gathering all the 2-MTE derivatives (eq. 2) and the other gathering the 2,4-DTE, 2-MTHTP and 2,6-DTHTP derivatives (eq. 3):

$$\log k'_w = 1.04\ (\pm 0.15)\ \text{clogP} + 1.65\ (\pm 0.10) \quad (2)$$
$$n = 11,\ r^2 = 0.846,\ s = 0.281,\ F = 49.3)$$

$$\log k'_w = 1.09\ (\pm 0.075)\ \text{clogP} + 0.76\ (\pm 0.19) \quad (3)$$
$$n = 13,\ r^2 = 0.951,\ s = 0.294,\ F = 211.6$$

The slope value (sensitivity) close-to-one in both eqs. 2 and 3 suggests that the solvophobic interactions involved in the octanol-water partitioning have similar effects on the RP-HPLC retention of the cyclic sulfone derivatives.

In contrast, the positive intercept values (+1.65 and + 0.76 in eqs. 2 and 3, respectively) can be attributed to the so-called 'silanophilic' interactions with free silanol groups on the silica-based C18 stationary phase, which results in increased log k'_w values.

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Table 3. Lipophilicity parameters of thietane and tetrahydro-2*H*-thiopyran 1,1-dioxide derivatives.

2-monofunctionalized thietane 1,1-dioxides (2-MTE)											
Cmpd	**2a**	**2d**	**2f**	**2h**	**2i**	**2j**	**2k**	**2o**	**2p**	**9a**	**10a**
clogP[a]	0.54	-0.22	1.08	0.29	0.85	1.18	0.29	0.38	-0.90	0.21	0.81
log k'_w[b]	1.97	1.44	2.94	1.89	2.50	3.34	2.19	2.02	0.95	1.47	2.12

2,4-difunctionalized thietane 1,1-dioxides (2,4-DTE)				
Cmpd	**3a**	**3d**	**3e**	**4c**
clogP[a]	2.48	3.25	3.70	3.98
log k'_w[b]	3.71	4.38	5.38	5.01

2-monofunctionalized tetrahydro 2H-thiopyran 1,1-dioxides (2-MTHTP)									
Cmpd	**6a**	**6b**	**6c**	**6e**	**6f**	**6g**	**7a**	**9b**	**10b**
clogP[a]	1.66	3.01	2.22	1.14	0.43	1.40	3.60	1.33	1.64
log k'_w[b]	2.62	3.90	3.20	2.18	1.48	2.19	4.25	1.91	2.20

[a]*n*-Octanol/water partition coefficient calculated by CLOGP software ver. 4.73 (Biobyte, Claremont, CA, USA). [b]RP-HPLC capacity factor extrapolated at 100% water volume fraction in aqueous mobile phase.

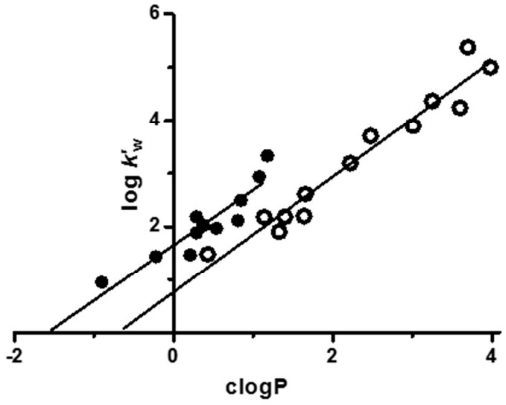

Figure 2. Graphical comparison between RP-HPLC lipophilicity parameter log k'_w and clog P calculated by the Bio-Loom software. (●) 2-Monofunctionalized thiethane 1,1-dioxide derivatives (2-MTE); (○) 2,4-difunctionalized thiethane 1,1-dioxide (2,4-DTE), and 2-mono- (2-MTHTP) and 2,6-difunctionalized tetrahydro-2*H*-thiopyrane 1,1-dioxide (2,6-DTHTP) derivatives.

Silanophilic interactions in RP-HPLC retention mechanisms mainly depend upon polarity, electrostatic and H-bonding interactions of the analytes, which are in turn negatively affected by the reduction (due to surrounding substitution degree, steric restriction to solvation, etc.) of the surface area available to polar groups of the analytes to bind free silanols.[35] With the cyclic sulfones examined herein, it appeared that the degree of silanophilic interactions, accounted by the intercept values in eqs. 2 and 3, correlate with the cycle size (four- vs. six-membered cycles), degree of functionalization (mono- vs. di-functionalized derivatives) and polar/H-bonding features of the substituents in α to the H-bond acceptor SO_2 group.

Conclusions

We have investigated the reactivity of four and six-membered cyclic sulfones in lithiation/electrophilic trapping sequences. A similar reactivity profile has been observed with the heterocycles either in C2-functionalization or C2,C4 (C6)-double functionalization. Several electrophiles were tolerated resulting in a smooth synthesis of a series of substituted cyclic sulfones. Preliminary results showed that the developed protocol is compatible with transmetallation and C_{sp2} coupling reactions. Attempts of electrophilic fluorination at the C2, resulted in an unexpected concomitant arylsulfonylation. For representative substituted cyclic sulfones, the lipophilicity was measured by RP-HPLC, which significantly encodes solvophobic and silanophilic interactions of the analytes. A good linear correlation, with a slope close to 1.0, was observed between the experimental chromatographic parameter log k'_w and in silico lipophilicity descriptor clogP. A systematic difference in absolute values between the two parameters can be most likely attributed to silanophilic interactions mainly involving the H-bond acceptor SO_2 group. The results obtained in this quantitative structure-property relationship study can be useful, not only in understanding the RP-HPLC retention of cyclic sulfones, but also in assessing lipophilicity profiles of sulfonyl-containing bioactive substances in early drug discovery programs.

Experimental section

General

THF and 2-MeTHF was freshly distilled under a nitrogen atmosphere over Na/benzophenone. *N*,*N*,*N'*,*N'*-tetramethylethylenediamine (TMEDA) was distilled over finely powdered CaH_2, hexyllithium was purchased as hexane solution and was filtered on celite before using and title established by titration method1. All the other chemicals were commercially available and used without further purification. Magnetic Resonance spectra were recorded using Varian 500 MHz,

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DOI: 10.1039/C7OB00846E

and Bruker 400 and 600 MHz spectrometers. For the ^{1}H, ^{13}C NMR spectra (^{1}H NMR 400, 500, 600 MHz, ^{13}C NMR 100, 125, 150 MHz), $CDCl_3$, methanol-d_4 and toluene-d_8 were used as the solvents. MS-ESI analyses were performed on LC/MSD trap system VL. Melting points were uncorrected. GC-MS spectrometry analyses were carried out on a gas chromatograph (dimethylsilicon capillary column, 30 m, 0.25 mm i.d.) equipped with a mass selective detector operating at 70 eV (EI). Analytical thin layer chromatography (TLC) was carried out on precoated 0.25 mm thick plates of Kieselgel 60 F254; visualization was accomplished by UV light (254 nm) or by spraying a solution of 5 % (w/v) ammonium molybdate and 0.2 % (w/v) cerium(III) sulfate in 100 ml 17.6 % (w/v) aq. sulphuric acid and heating to 200 °C for some time until blue spots appear. Infra-red spectra of the compounds were recorded neat, as film, as KBr disc as indicated, by a Perkin-Elmer 283 spectrometer. For flash chromathography silica Gel 60, 0.04-0.063 mm particle size was used. CHN analyses were performed on a EuroEA 3000 analyzer. The high resolution mass spectrometry (HRMS) analyses were performed using a Bruker microTOF QII mass spectrometer equipped with an electrospray ion source (ESI) operated in positive ion mode. The sample solutions (CH_3OH or CH_3OH + 0.1%v/v HCOOH) were introduced by continuous infusion at a flow rate of 180 mL $min^{-1}$with the aid of a syringe pump. The instrument was operated with end-plate offset and capillary voltages set to -500 V and -4500 V respectively. The nebulizer pressure was 0.4 bar (N_2), and the drying gas (N_2) flow rate was 4.0 L min-1. The capillary exit and skimmer 1 voltages were 90 V and 30 V, respectively. The drying gas temperature was set at 180 °C. The calibration was carried out with sodium formate: a solution made up of 10 µl of 98% formic acid, 10 µl of sodium hydroxide (1.0 M), 490 µl of *i*-propanol and 490 µl of deionized water. The software used for the simulations was Bruker Daltonics DataAnalysis (version 4.0). All reactions involving air-sensitive reagents were performed under argon in oven-dried glassware using syringe septum cap technique.

General procedure for lithiation/electrophile trapping sequence on C2-substituted thietane-1,1-dioxide. To a stirred solution of thietane 1,1-dioxide commercially available (1.0 mmol, 1.0 equiv) in dry 2-MeTHF (10 mL) cooled at -78°C, a solution of *n*-HexLi (2.5M in hexane, 1.1 equiv) was added dropwise. After stirring for 5 min. at -78°C, the electrophile (1 equiv) was added neat if liquid and in 1.0 mL of solvent if solid. After the reaction was complete, as ascertained by GC or TLC, the reaction mixture was quenched at -78 °C with saturated aqueous NH_4Cl (0.1mL) and directly filtered over Na_2SO_4 and concentrated in vacuo. Flash chromatography on silica gel (Hexane/AcOEt) afforded the substituted thietane 1,1-dioxide.

2-benzylthietane 1,1-dioxide-2a. Column chromatography on silica gel (Hexane/AcOEt 70:30), white solid, mp 67-70 °C, 70% (142 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.84-1.90 (m, 1H, CH_2CHSO$_2$), 2.23-2.29 (m, 1H, CH_2CHSO$_2$), 3.03 (dd, *J* = 14.6, 7.8 Hz, 1H, ArCH_2CH), 3.43 (dd, *J* = 14.6, 7.8 Hz, 1H, ArCH_2CH), 3.92-4.04 (m, 2H, CH_2SO$_2$), 4.59 (m, 1H, CHSO$_2$), 7.23-7.26 (m, 3H, Ar*H*), 7.31-7.34 (m, 2H, Ar*H*). ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.0 (*C*H_2CHSO$_2$), 35.2 (Ar*C*H_2CH), 61.8 (*C*H_2SO$_2$), 79.0 (*C*HSO$_2$), 127.0 (Ar*C*H), 128.7 (Ar*C*H), 128.9 (Ar*C*H), 136.4 (Ar*C*). FT-IR (KBr, cm^{-1}) υ 613, 700, 757, 1121, 1161, 1294, 2922. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{10}H_{12}O_2SNa$ 219.0450; found 219.0456.

(1,1-dioxido-2-thietanyl)-(diphenyl)methanol-2b. Column chromatography on silica gel (Hexane/AcOEt 70:30), white solid, mp 143-146 °C, 70% (160 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.80-1.89 (m, 1H, CH_2CHSO$_2$), 2.36-2.46 (m, 1H, CH_2CHSO$_2$), 3.91-3.96 (m, 2H, CH_2SO$_2$), 4.03 (s, 1H, OH), 5.36 (t, *J* = 9.3 Hz, 1H, CHSO$_2$), 7.12-7.32 (m, 8H, Ar*H*), 7.46-7.48 (m, 2H, Ar*H*). ^{13}C NMR (101 MHz, $CDCl_3$) δ 8.8 (*C*H_2CHSO$_2$), 62.5 (*C*H_2SO$_2$), 72.8 ((Ar)$_2$*C*CHOH), 84.4 (*C*HSO$_2$), 125.4 (Ar*C*H), 126.0 (Ar*C*H), 127.4 (Ar*C*H), 128.2 (Ar*C*H), 128.8 (Ar*C*H), 142.8 (Ar*C*), 144.8 (Ar*C*). FT-IR (KBr, cm^{-1}) υ 511, 546, 698, 800, 1123, 1152, 1250, 1449, 1490, 2965, 3011, 3029, 3063, 3090, 3489. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{16}H_{16}O_3SNa$ 311.0712; found 311.0717.

1,1-dioxido-2-thietanyl-carboxylic acid-2c. White solid, mp 143-146 °C, 55% (85 mg). ^{1}H NMR (600 MHz, CD_3OD) δ 2.28-2.32 (m, 1H, CH_2-CHSO$_2$), 2.39-2.44 (m, 1H, CH_2CHSO$_2$), 4.05-4.13 (m, 1H, CH_2SO$_2$), 4.16-4.21 (m, 1H, CH_2SO$_2$), 5.23 (m, 1H, CHSO$_2$). ^{13}C NMR (150 MHz, CD_3OD) δ 9.5 (*C*H_2-CHSO$_2$), 63.8 (*C*H_2SO$_2$), 79.5 (*C*HSO$_2$), 165.8 (*C*=O). FT-IR (KBr, cm^{-1}) υ 584, 607, 804, 1136, 1180, 1303, 1387, 1449, 1633, 1732, 2974. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_4H_6O_4SNa$ 172.9879; found 172.9888.

***N*-phenyl-2-thietanecarboxamide 1,1-dioxide-2d.** Column chromatography on silica gel (Hexane/AcOEt 70:30), white solid, mp 150-152 °C, 66% (150 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32-2.42 (m, 1H, CH_2-CHSO$_2$), 2.68-2.77 (m, 1H, CH_2CHSO$_2$), 4.12-4.31 (m, 2H, CH_2SO$_2$), 5.12-5.16 (m, 1H, CHSO$_2$), 7.12-7.16 (m, 1H, Ar*H*), 7.29-7.33 (m, 2H, Ar*H*), 7.53-7.55 (m, 2H, Ar*H*), 8.33 (bs, 1H, NH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 10.1 (*C*H_2CHSO$_2$), 65.0 (*C*H_2SO$_2$), 80.6 (*C*HSO$_2$), 120.3 (Ar*C*H), 125.2 (Ar*C*H), 129.1 (Ar*C*H), 137.0 (Ar*C*), 160.6 (*C*=O). ^{15}N δ -248.0. FT-IR (KBr, cm^{-1}) υ 604, 620, 689, 753, 1136, 1302, 1315, 1539, 1599, 1688, 3368. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{10}H_{11}NO_3SNa$ 248.0532; found 248.0533.

(1,1-dioxido-2-thietanyl)(trimethyl)silane-2e. Column chromatography on silica gel (Hexane/AcOEt 70:30), yellow oil, 50% (90 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.22 (s, 9H, CH_3Si), 1.88-1.97 (m, 1H, CH_2CHSO$_2$), 2.15-2.24 (m, 1H, CH_2CHSO$_2$), 3.98-4.06 (m, 2H, CH_2SO$_2$), 4.12-4.21 (m, 1H, CHSO$_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ -2.9 (*C*H_3Si), 7.7 (*C*H_2-CHSO$_2$), 65.8 (*C*H_2SO$_2$), 69.9 (*C*HSO$_2$). FT-IR (NaCl, cm^{-1}) υ 608, 840, 1126, 1304, 2957. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_6H_{14}O_2SSiNa$ 201.0376; found 201.0376.

(1,1-dioxido-2-thietanyl)[4-(trifluoromethyl)phenyl]methanone-2f. Column chromatography on silica gel (Hexane/AcOEt 60:40), white solid, mp 108-110 °C, 62% (173 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30-2.39 (m, 1H, CH_2CHSO$_2$), 2.94-3.04 (m, 1H, CH_2CHSO$_2$), 4.15-4.34 (m, 2H, CH_2SO$_2$), 5.91-5.96 (m, 1H, CHSO$_2$), 7.80-7.82 (m, 2H, Ar*H*), 8.15-8.17 (m, 2H, Ar*H*). ^{13}C NMR (101 MHz, $CDCl_3$) δ 7.6 (*C*H_2CHSO$_2$), 64.4 (*C*H_2SO$_2$), 82.4 (*C*HSO$_2$), 123.3 (d, *J* = 272.9 Hz, *C*F$_3$), 126.3 (q, *J* = 3.7 Hz, Ar*C*H), 129.0 (Ar*C*H), 135.6 (q, *J* = 33.0 Hz, Ar*C*), 137.9 (Ar*C*), 186.5 (*C*=O). ^{19}F NMR (377 MHz, $CDCl_3$) δ -63.3 (s). FT-IR (KBr, cm^{-1}) υ 587, 864, 1065, 1122, 1171, 1314, 1688. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{11}H_9F_3O_3SNa$ 301.0117; found 301.0119.

(1,1-dioxido-2-thietanyl)[4-(2-methyl-2-propanyl)phenyl] methanone-2g. Column chromatography on silica gel (Hexane/AcOEt 60:40), white solid, mp 98-101 °C, 61% (161 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (s, 9H, C(CH_3)$_3$), 2.23-2.33 (m, 1H, CH_2CHSO$_2$), 2.94-3.03 (m, 1H, CH_2CHSO$_2$), 4.12-4.29 (m, 2H, CH_2SO$_2$), 5.91-5.95 (m, 1H, CHSO$_2$), 7.54-7.57 (m, 2H, Ar*H*), 7.97-

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8.00 (m, 2H, Ar*H*). ^{13}C NMR (101 MHz, $CDCl_3$) δ 7.6 (*C*H_2CHSO$_2$), 31.0 (C(*C*H_3)$_3$), 35.3 (*C*(CH$_3$)$_3$), 64.1 (*C*H_2SO$_2$), 82.2 (*C*HSO$_2$), 126.2 (Ar*C*H), 128.7 (Ar*C*H), 132.8 (Ar*C*), 158.7 (Ar*C*), 186.6 (*C*=O)**.** FT-IR (KBr, cm^{-1}) υ 593, 722, 753, 805, 1133, 1313, 1686. HRMS (ESI-TOF) m/z [M+Na]$^+$ calcd for $C_{14}H_{18}O_3SNa$ 289.0869; found 289.0869.

(1,1-dioxido-2-thietanyl)(4-methoxyphenyl)methanone-2h. Column chromatography on silica gel (Hexane/AcOEt 60:40), white solid, mp 137-140 °C, 68% (153 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23-2.32 (m, 1H, C*H*$_2$CHSO$_2$), 2.95-3.01 (m, 1H, C*H*$_2$CHSO$_2$), 3.89 (s, 3H, OC*H*$_3$), 4.11-4.26 (m, 2H, C*H*$_2$SO$_2$), 5.87-5.91 (m, 1H, C*H*SO$_2$), 6.99-7.02 (m, 2H, Ar*H*), 8.01-8.04 (m, 2H, Ar*H*). ^{13}C NMR (101 MHz, $CDCl_3$) δ 7.7 (*C*H$_2$CHSO$_2$), 55.6 (OCH$_3$), 64.1 (*C*H$_2$SO$_2$), 82.1 (*C*HSO$_2$), 114.4 (Ar*C*H), 128.5 (Ar*C*), 131.1 (Ar*C*H), 164.9 (Ar*C*), 185.3 (*C*=O). FT-IR (KBr, cm^{-1}) υ 577, 788, 843, 1016, 1132, 1175, 1313, 1594, 1662, 2923. HRMS (ESI-TOF) m/z [M+Na]$^+$ calcd for $C_{11}H_{12}O_4SNa$ 263.0349; found 263.0349.

(3-chlorophenyl)(1,1-dioxido-2-thietanyl)methanone-2i. Column chromatography on silica gel (Hexane/AcOEt 60:40), white solid, mp 93-95 °C, 57% (140 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.27-2.37 (m, 1H, C*H*$_2$CHSO$_2$), 2.93-3.02 (m, 1H, C*H*$_2$CHSO$_2$), 4.15-4.22 (m, 1H, C*H*$_2$SO$_2$), 4.26-4.32 (m, 1H, C*H*$_2$SO$_2$), 5.87-5.91 (m, 1H, C*H*SO$_2$), 7.48-7.52 (m, 1H, Ar*H*), 7.62-7.65 (m, 1H, Ar*H*), 7.90-7.93 (m, 1H, Ar*H*), 8.02-8.03 (m, 1H, Ar*H*). ^{13}C NMR (101 MHz, $CDCl_3$) δ 7.7 (*C*H$_2$-CHSO$_2$), 64.4 (*C*H$_2$SO$_2$), 82.2 (*C*HSO$_2$), 126.7 (Ar*C*H), 128.6 (Ar*C*H), 130.5 (Ar*C*H), 134.6 (Ar*C*H), 135.7 (Ar*C*), 136.8 (Ar*C*), 186.2 (*C*=O). FT-IR (KBr, cm^{-1}) υ 593, 722, 753, 805, 1133, 1313, 1686. HRMS (ESI-TOF) m/z [M+Na]$^+$ calcd for $C_{10}H_9ClO_3SNa$ 266.9853; found 266.9855.

adamantan-1-yl(1,1-dioxido-2-thietanyl)methanone-2j. Column chromatography on silica gel (Hexane/AcOEt 60:40), white solid, mp 95-97 °C, 47% (127 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.69-1.78 (m, 6H, C*H*$_2$CHCH), 1.80-1.93 (m, 6H, C*H*$_2$CHC), 2.01-2.10 (m, 4H, C*H*$_2$CHSO$_2$, *CH*CH$_2$CH$_2$), 2.64-2.73 (m, 1H, C*H*$_2$CHSO$_2$), 4.06-4.16 (m, 2H, C*H*$_2$SO$_2$), 5.54-5.58 (m, 1H, C*H*SO$_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 7.6 (*C*H$_2$CHSO$_2$), 27.6 (*C*HCH$_2$CH$_2$), 36.3 (*C*H$_2$CHCH), 37.3 (*C*H$_2$CHC), 46.0 (*C*CH$_2$CH$_2$), 64.4 (*C*H$_2$SO$_2$), 80.1 (*C*HSO$_2$), 202.5 (*C*=O). FT-IR (KBr, cm^{-1}) υ 589, 1130, 1167, 1308, 1698, 2903. HRMS (ESI-TOF) m/z [M+Na]$^+$ calcd for $C_{14}H_{20}O_3SNa$ 291.1025; found 291.1025.

1-(1,1-dioxido-2-thietanyl)-2-cyclohexen-1-ol-2k. Column chromatography on silica gel (Hexane/AcOEt 60:40), white solid, mp 57-62 °C, 55% (112 mg) dr 80:20. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38-1.43 (m, 1H minor, CC*H*$_2$CH$_2$) 1.54-1.88 (m, 3H major + 3H minor, CC*H*$_2$CH$_2$, CCH$_2$C*H*$_2$), 1.94-2.21 (m, 4H major + 3H minor, C*H*$_2$CH=, CC*H*$_2$CH$_2$, C*H*$_2$CHSO$_2$), 2.34-2.48 (m, 1H minor + 1H major, C*H*$_2$CHSO$_2$), 3.13 (s, 1H major + 1H, minor, OH), 3.96-4.05 (m, 2H major + 2H minor, C*H*$_2$SO$_2$), 4.39-4.45 (m, 1H minor + 1H major, C*H*SO$_2$), 5.48 (d, *J* = 10.0 Hz, 1H, major, C*H*=CH), 5.89-5.93 (m, 2H minor + 1H minor, C*H*=CH, CH=C*H*). ^{13}C NMR (101 MHz, $CDCl_3$) δ 8.2 (minor, *C*H$_2$CHSO$_2$), 8.6 (major, *C*H$_2$-CHSO$_2$), 18.1 (minor, CH$_2$*C*H$_2$CH$_2$), 18.3 (major, CH$_2$*C*H$_2$CH$_2$), 24.9 (minor, *C*H$_2$CH=), 24.9 (major, *C*H$_2$CH=), 33.1 (minor, C*C*H$_2$CH$_2$), 35.7 (major, C*C*H$_2$CH$_2$), 63.2 (major, *C*H$_2$SO$_2$), 63.2 (minor, *C*H$_2$SO$_2$), 69.3 (minor, *C*OH), 69.6 (major, *C*OH), 85.6 (major, *C*HSO$_2$), 86.1 (minor, *C*HSO$_2$), 126.6 (major, *C*H=CH), 129.2 (minor, *C*H=CH), 131.7 (minor, CH=*C*H), 132.6 (major, CH=*C*H). FT-IR (KBr, cm^{-1}) υ 506, 729, 1104, 1123, 1307, 1408, 2927, 3517. HRMS (ESI-TOF) m/z [M+Na]$^+$ calcd for $C_9H_{14}O_3SNa$ 225.0556; found 225.0556.

1-(1,1-dioxido-2-thietanyl)-2-cyclopenten-1-ol-2l. Column chromatography on silica gel (Hexane/AcOEt 75:25), colorless oil, 62% (120 mg), dr 75:25. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.81-1.88 (m, 1H, minor, CC*H*$_2$CH$_2$), 1.93-2.02 (m, 1H, minor, CC*H*$_2$CH$_2$), 2.09-2.40 (m, 5H, major, CC*H*$_2$CH$_2$, CCH$_2$C*H*$_2$, C*H*$_2$CHSO$_2$), 2.17-2.45 (m, 3H, minor, C*H*$_2$CHSO$_2$, C*H*$_2$CH=), 2.51-2.60 (m, 1H, minor, C*H*$_2$CH=), 2.54-2.63 (m, 1H, major, C*H*$_2$CH=), 3.10 (s, 1H, OH, minor), 3.11 (s, 1H, OH, major), 3.97-4.07 (m, 2H, minor, C*H*$_2$SO$_2$), 3.97-4.01 (m, 2H, major, C*H*$_2$SO$_2$), 4.37-4.41 (m, 1H, minor, C*H*SO$_2$), 4.42-4.46 (dd, *J* = 10.0, 7.6 Hz, 1H, major, C*H*SO$_2$), 5.68-5.70 (dt, d = *J* = 5.7 Hz, t = *J* = 2.2 Hz, 1H, major, C*H*=CH), 5.92 (dt, d = *J* = 5.6 Hz, t = *J* = 2.2 Hz, 1H, minor, C*H*=CH), 6.03 (dt, d = *J* = 5.6 Hz, t = *J* = 2.4 Hz, 1H, minor, CH=C*H*), 6.02-6.04 (m, 1H, major, CH=C*H*). ^{13}C NMR (101 MHz, $CDCl_3$) δ 9.0 (minor, *C*H$_2$CHSO$_2$), 9.6 (major, *C*H$_2$CHSO$_2$), 30.5 (minor, *C*H$_2$CH=), 31.4 (major, *C*H$_2$CH=), 36.1 (minor, CC*H*$_2$CH$_2$), 37.7 (major, CC*H*$_2$CH$_2$), 63.4 (minor, *C*H$_2$SO$_2$), 63.5 (major *C*H$_2$SO$_2$), 84.0 (minor, *C*OH), 84.4 (major *C*OH), 85.6 (major, *C*HSO$_2$), 85.6 (minor, *C*HSO$_2$), 131.4 (major, *C*H=CH), 133.4 (minor, *C*H=CH), 135.9 (minor, CH=*C*H), 136.9 (major, CH=*C*H). FT-IR (NaCl, cm^{-1}) υ 518, 727, 1119, 1264, 1408, 2851, 2919. HRMS (ESI-TOF) m/z [M+Na]$^+$ calcd for $C_8H_{12}NaO_3S$ 211.0399; found 211.0398.

1-(1,1-dioxido-2-thietanyl)-2-cyclohepten-1-ol-2m. Column chromatography on silica gel (Hexane/AcOEt 70:30), white solid, mp 61-64 °C, 65% (140 mg) dr 70:30. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50-1.72 (m, 5H, minor, CC*H*$_2$CH$_2$, C*H*$_2$CH$_2$C, C*H*$_2$CH$_2$CH=), 1.47-1.57 (m, 1H, major, C*H*$_2$CH$_2$CH=), 1.64-1.77 (m, 2H, major, C*H*$_2$CH$_2$C, C*H*$_2$CH$_2$CH=), 1.89-1.97 (m, 1H, minor, C*H*$_2$CH$_2$CH=), 1.91-2.03 (m, 2H, major, C*H*$_2$C, C*H*$_2$CH$_2$C), 2.06-2.15 (m, 3H, major, C*H*$_2$C, C*H*$_2$CH=, C*H*$_2$-CHSO$_2$), 2.08-2.16 (m, 2H, minor, C*H*$_2$CH=, C*H*$_2$CHSO$_2$), 2.18-2.27 (m, 1H, major, C*H*$_2$CH=), 2.26-2.42 (m, 2H, minor, C*H*$_2$CHSO$_2$, C*H*$_2$CH=), 2.39-2.49 (m, 1H, major, C*H*$_2$-CHSO$_2$), 3.10 (bs, 1H, OH, major), 3.33 (bs, 1H, OH, minor), 3.90-4.03 (m, 2H, major, C*H*$_2$SO$_2$), 3.92-4.06 (m, 2H, minor, C*H*$_2$SO$_2$), 4.64-4.69 (m, 1H, minor, C*H*SO$_2$), 4.69-4.73 (m, 1H, major, C*H*SO$_2$), 5.43 (td, t = *J* = 1.7 Hz, d = J_{cis} = 11.9 Hz, 1H, major, C*H*=CH), 5.77 (ddd = *J* = 11.9, 7.4, 5.0 Hz, 1H, major, CH=C*H*), 5.82 (d = *J* = 11.9 Hz, 1H, minor, C*H*=CH), 5.91 (ddd = *J* = 11.9, 6.6, 5.6 Hz, 1H, minor, CH=C*H*). ^{13}C NMR (101 MHz, $CDCl_3$) δ 8.3 (minor, *C*H$_2$CHSO$_2$), 8.6 (major, *C*H$_2$CHSO$_2$), 23.9 (minor, *C*H$_2$CH$_2$C), 24.6 (major, *C*H$_2$CH$_2$C), 27.0 (major, *C*H$_2$CH$_2$CH=), 27.0 (minor, *C*H$_2$CH$_2$CH=), 27.7 (major, *C*H$_2$CH=), 27.8 (minor, *C*H$_2$CH=), 35.8 (minor, *C*H$_2$C), 39.1 (major, *C*H$_2$C), 62.8 (minor, *C*H$_2$SO$_2$), 62.9 (major, *C*H$_2$SO$_2$), 74.8 (minor, *C*OH), 75.9 (major, *C*OH), 82.5 (major, *C*HSO$_2$), 85.3 (minor, *C*HSO$_2$), 132.1 (major, CH=*C*H), 133.3 (minor, CH=*C*H), 134.2 (major, *C*H=CH), 135.8 (minor, *C*H=CH). FT-IR (KBr, cm^{-1}) υ 800, 1128, 1292, 1307, 1650, 2941, 3514. HRMS (ESI-TOF) m/z [M+Na]$^+$ calcd for $C_{10}H_{16}O_3SNa$ 239.0712; found 239.0713.

(3*E*)-2-(1,1-dioxido-2-thietanyl)-3-hepten-2-ol-2n. Column chromatography on silica gel (Hexane/AcOEt 60:40), colorless oil, 65% (145 mg), dr 70:30. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.4 Hz, 3H, major, C*H*$_3$CH$_2$), 0.90 (t, *J* = 7.4 Hz, 3H, minor, C*H*$_3$CH$_2$), 1.19 (s, 3H, minor, C*H*$_3$C), 1.35-1.42 (m, 2H, major, CH$_3$C*H*$_2$CH$_2$), 1.39-1.45 (m, 2H, minor, CH$_3$C*H*$_2$CH$_2$), 1.56 (s, 3H, major, C*H*$_3$C), 1.98-2.09 (m, 3H, major, C*H*$_2$CH=, C*H*$_2$CHSO$_2$), 2.02-2.08 (m, 2H, minor, C*H*$_2$CH=), 2.12-2.19 (m, 1H, minor, C*H*$_2$CHSO$_2$), 2.24-2.33 (m, 1H, major, C*H*$_2$CHSO$_2$), 2.39-2.49 (m, 1H, minor, C*H*$_2$CHSO$_2$), 3.20 (bs, 1H, OH, major), 3.36 (bs, 1H, OH, minor), 3.88-4.04 (m, 2H, minor, C*H*$_2$SO$_2$), 3.93-3.97 (m, 2H, major, C*H*$_2$SO$_2$), 4.34 (dd, *J* = 10.0, 8.2 Hz,

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DOI: 10.1039/C7OB00846E

1H, major, C*H*SO_2), 4.49 (t, *J* = 9.4 Hz, 1H, minor, C*H*SO_2), 5.24 (dt, d = *J* = 15.7 Hz, t = *J* = 1.3 Hz, 1H, major, C*H*=CH), 5.67 (dt, d = *J* = 15.7 Hz, t = *J* = 1.3 Hz, 1H, minor, C*H*=CH), 5.74 (dt, d = *J* = 15.7 Hz, t = *J* = 6.7 Hz, 1H, major, CH=C*H*), 5.81 (dt, d = *J* = 15.7 Hz, t = *J* = 6.7 Hz, 1H, minor, CH=C*H*). ^{13}C NMR (101 MHz, $CDCl_3$) δ 8.8 (minor, *C*H_2CHSO_2), 8.9 (major, *C*H_2CHSO_2), 13.5 (major, *C*H_3CH_2), 13.5 (minor, *C*H_3CH_2), 22.2 (minor, CH_3*C*H_2CH_2), 22.2 (major, CH_3*C*H_2CH_2), 26.0 (minor, *C*H_3C), 28.1 (major, *C*H_3C), 34.2 (major, *C*H_2CH=), 34.2 (minor, *C*H_2CH=), 62.6 (minor, *C*H_2SO_2), 62.7 (major, *C*H_2SO_2), 71.8 (major, *C*=CH), 72.0 (minor, *C*=CH), 85.6 (minor, *C*HSO_2), 85.7 (major, *C*HSO_2), 130.7 (minor, CH=*C*H), 131.3 (major, CH=*C*H), 131.6 (major, *C*H=CH), 133.7 (minor, *C*H=CH). FT-IR (NaCl, cm^{-1}) υ 730, 974, 1122, 1309, 1458, 2960, 3522. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{10}H_{18}O_3SNa$ 241.0869; found 241.0873.

(4-chlorophenyl)(1,1-dioxido-2-thietanyl)methanol-2o. Column chromatography on silica gel (Hexane/AcOEt 60:40), white solid, mp 123-125 °C, 60% (149 mg) dr 80:20. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.80-1.90 (m, 1H, minor, C*H*$_2$CHSO_2), 1.97-2.08 (m, 1H, minor, C*H*$_2$CHSO_2), 1.97-2.07 (m, 1H, major, C*H*$_2$CHSO_2), 2.36-2.45 (m, 1H, major, C*H*$_2$CHSO_2), 3.10 (bs, 1H, OH, minor), 3.32 (bs, 1H, OH, major), 3.96-4.02 (m, 2H, minor, C*H*$_2SO_2$), 4.02-4.07 (m, 2H, major, C*H*$_2SO_2$), 4.52-4.57 (m, 1H, major, C*H*SO_2), 4.60-4.66 (m, 1H, minor, C*H*SO_2), 5.08 (d, *J* = 9.0 Hz, 1H, minor, C*H*OH), 5.44 (d, *J* = 3.0 Hz, 1H, major, C*H*OH), 7.30-7.37 (m, 4H, major, Ar*H*), 7.32-7.36 (m, 4H, minor, Ar*H*). ^{13}C NMR (101 MHz, $CDCl_3$) δ 7.5 (major, *C*H_2CHSO_2), 10.8 (minor, *C*H_2-CHSO_2), 62.1 (minor, *C*H_2SO_2), 63.6 (major, *C*H_2SO_2), 68.6 (major, *C*HOH), 72.4 (minor, *C*HOH), 82.8 (major, *C*HSO_2), 83.1 (minor, *C*HSO_2), 126.9 (major, Ar*C*H), 127.9 (minor, Ar*C*H), 129.0 (major, Ar*C*H), 129.2 (minor, Ar*C*H), 134.1 (major, Ar*C*), 134.7 (minor, Ar*C*), 137.5 (major, Ar*C*), 137.5 (minor, Ar*C*). FT-IR (KBr, cm^{-1}) υ 585, 782, 802, 1125, 1190, 1305, 1490, 3506. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{10}H_{11}ClO_3SNa$ 269.0010; found 269.0009.

4-[(1,1-dioxido-2-thietanyl)(hydroxyl)methyl]benzonitrile-2p. Column chromatography on silica gel (Hexane/AcOEt 60:40), white solid mp 104-106 °C, 69% (164 mg), dr 80:20. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.96-2.06 (m, 2H minor + 1H major, C*H*$_2$CHSO_2), 2.32-2.42 (m, 1H, major, C*H*$_2$CHSO_2), 3.49 (bs, OH, 1H), 4.03-4.11 (m, 2H major + 2H minor, C*H*$_2SO_2$), 4.53-4.59 (m, 1H, major, C*H*SO_2), 4.62-4.66 (m, 1H, minor, C*H*SO_2), 5.15 (d, *J* = 9.0 Hz, 1H, minor, C*H*OH), 5.49 (m, 1H, major, C*H*OH), 7.50-7.53 (m, 2H major + 2H minor, Ar*H*), 7.66-7.68 (m, 2H major + 2H minor, Ar*H*). ^{13}C NMR (101 MHz, $CDCl_3$) δ 7.5 (major, *C*H_2-CHSO_2), 10.7 (minor, *C*H_2CHSO_2), 62.4 (minor, *C*H_2SO_2), 63.8 (major, *C*H_2SO_2), 68.6 (major, *C*HOH), 72.3 (minor, *C*HOH), 82.3 (major, *C*HSO_2), 82.7 (minor, *C*HSO_2), 112.1 (major, Ar*C*CN), 112.7 (minor, Ar*C*CN), 118.2 (minor, *C*N), 118.4 (major, *C*N), 126.4 (major, Ar*C*H), 127.2 (minor, Ar*C*H), 132.6 (major, Ar*C*H), 132.8 (minor, Ar*C*H), 144.2 (minor, Ar*C*), 144.3 (major, Ar*C*). FT-IR (KBr, cm^{-1}) υ 563, 590, 784, 1124, 1292, 1605, 3449. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{11}H_{11}NO_3SNa$ 260.0352; found 260.0354.

(2*E*)-1-(1,1-dioxide-2-thietanyl)-3-phenyl-2-propen-1-ol-2q. Column chromatography on silica gel (Hexane/AcOEt 50:50), white solid, mp 114-118 °C, 89% (238 mg), dr 80:20. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.96-2.34 (m, 2H, minor, C*H*$_2$CHSO_2), 2.12-2.22 (m, 1H, major, C*H*$_2$CHSO_2), 2.33-2.42 (m, 1H, major, C*H*$_2$CHSO_2), 2.95 (bs, 1H, OH, minor), 3.08 (bs, 1H, OH, major), 3.97-4.12 (m, 2H, minor, C*H*$_2SO_2$), 4.04-4.08 (m, 2H, major, C*H*$_2SO_2$), 4.46-4.51 (m, 1H, major, C*H*SO_2), 4.47-4.60 (m, 1H, minor, C*H*SO_2), 4.70-4.76 (m, 1H, minor, C*H*OH), 5.03-5.05 (m, 1H, major, C*H*OH), 6.07 (dd, *J* = 15.9, 5.5 Hz, 1H, major, C*H*=CH), 6.21 (dd, *J* = 15.9, 5.5 Hz, 1H, minor, C*H*=CH), 6.74 (d, *J* = 15.9 Hz, 1H, minor, CH=C*H*), 6.76 (dd, *J* = 15.9, 1.5 Hz, 1H, major, CH=C*H*), 7.27-7.40 (m, 5H, major, Ar*H*), 7.29-7.44 (m, 5H, minor, Ar*H*). ^{13}C NMR (101 MHz, $CDCl_3$) δ 7.8 (major, *C*H_2-CHSO_2), 10.4 (minor, *C*H_2CHSO_2), 62.7 (minor, *C*H_2SO_2), 64.0 (major, *C*H_2SO_2), 68.2 (major, *C*HOH), 71.9 (minor, *C*HOH), 81.5 (major, *C*HSO_2), 82.2 (minor, *C*HSO_2), 125.7 (major, *C*H=CH), 126.1 (minor, *C*H=CH), 126.6 (major, Ar*C*H), 126.7 (minor, Ar*C*H), 128.2 (major, Ar*C*H), 128.4 (minor, Ar*C*H), 128.7 (minor, Ar*C*H), 128.7 (major, Ar*C*H), 132.3 (major, CH=*C*H), 133.5 (minor, CH=*C*H), 135.7 (minor, Ar*C*), 135.9 (major, Ar*C*). FT-IR (KBr, cm^{-1}) υ 749, 1129, 1302, 1640, 1722, 3457. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{12}H_{14}O_3SNa$ 261.0556; found 261.0560.

General procedure for lithiation-electrophile trapping sequence on C2,C2'-substituted thietane-1,1-dioxide. To a stirred solution of thietane 1,1-dioxide (1.0 mmol, 1.0 equiv) in dry 2-MeTHF (10 mL) cooled at -78°C, a solution of *n*-HexLi (2.5M in hexane, 2.5 equiv) was added dropwise. After stirring for 10 min. at -78°C, the electrophile (2.5 equiv) was added neat if liquid and in 1.0 mL of solvent if solid. After the reaction was complete, as ascertained by GC or TLC, the reaction mixture was quenched at -78 °C with saturated aqueous NH_4Cl (0.1 mL) and directly filtered over Na_2SO_4 and concentrated in vacuo. Flash chromatography on silica gel (Hexane/AcOEt) afforded the disubstituted thietane 1,1-dioxide.

2,4-dibenzylthietane 1,1-dioxide-3a. Column chromatography on silica gel (Hexane/AcOEt 80:20), white solid, mp 78-81 °C, 60% (174 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.97 (t, *J* = 8.1 Hz, 2H, C*H*$_2$CHSO_2), 2.97 (dd, *J* = 14.6, 9.6 Hz, 1H, ArC*H*$_2$CH), 3.44 (dd, *J* = 14.6, 6.9 Hz, 1H, ArC*H*$_2$CH), 4.44-4.52 (m, 2H, C*H*SO_2), 7.19-7.31 (m, 10H, Ar*H*). ^{13}C NMR (101 MHz, $CDCl_3$) δ 20.9 (*C*H_2CHSO_2), 35.4 (Ar*C*H_2CH), 75.7 (*C*HSO_2), 127.1 (Ar*C*H), 128.7 (Ar*C*H), 128.9 (Ar*C*H), 136.3 (Ar*C*). FT-IR (KBr cm^{-1}) υ 699, 744, 1163, 1303, 1454, 1495, 2925. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{17}H_{18}O_2SNa$ 309.0922; found 309.0920.

(1,1-dioxido-2,4-thietanediyl)bis(diphenyl)methanol-3b. Column chromatography on silica gel (Hexane/AcOEt 80:20), white solid, mp 218-223 °C, 78% (370 mg), dr 70:30. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.60-1.64 (m, 1H, minor, C*H*$_2$CHSO_2), 2.19 (t, *J* = 9.0 Hz, 2H, major, C*H*$_2$CHSO_2), 3.09-3.13 (m, 1H, minor, C*H*$_2$CHSO_2), 3.90 (s, 2H, minor, OH), 3.96 (s, 2H, major, OH), 5.20 (t, *J* = 9.9 Hz, 2H, minor, C*H*SO_2), 5.36 (t, *J* = 8.9 Hz, 2H, major, C*H*SO_2), 7.17-7.20 (m, 2H major + 2H minor, Ar*H*), 7.24-7.38 (m, 16H major + 16H minor, Ar*H*), 7.49-7.51 (m, 2H, major, Ar*H*), 7.57-7.58 (m, 2H, minor, Ar*H*). ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.5 (major, *C*H_2CHSO_2), 12.8 (minor, *C*H_2CHSO_2), 79.7 (minor, *C*HSO_2), 82.6 (major, *C*HSO_2), 125.3 (minor, Ar*C*H), 125.4 (major, Ar*C*H), 125.8 (major, Ar*C*H), 126.0 (minor, Ar*C*H), 127.3 (major, Ar*C*H), 127.4 (minor, Ar*C*H), 128.1 (major, Ar*C*H), 128.2 (minor, Ar*C*H), 128.4 (minor, Ar*C*H), 128.5 (major, Ar*C*H), 128.7 (minor, Ar*C*H), 128.8 (major, Ar*C*H), 142.7 (major, Ar*C*), 143.0 (minor, Ar*C*), 144.8 (minor, Ar*C*), 145.0 (major, Ar*C*). FT-IR (KBr, cm^{-1}) υ 528, 698, 1101, 1265, 1449, 2853, 2965, 3027, 3495. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for for $C_{29}H_{26}O_4SNa$ 493.1444; found 493.1446.

(1,1-dioxido-2,4-thietanediyl)bis[4-(2-methyl-2-propanyl)phenyl] methanone-3c. Column chromatography on silica gel (Hexane/AcOEt 80:20), colorless oil, 72% (310 mg), dr 70:30. ^{1}H

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DOI: 10.1039/C7OB00846E

NMR (400 MHz, $CDCl_3$) δ 1.34 (s, 18H, minor, C(CH_3)$_3$), 1.35 (s, 18H, major, C(CH_3)$_3$), 2.39 (dt, d = *J* = 12.7 Hz, t = *J* = 9.7 Hz, 1H, minor, CH_2CHSO$_2$), 3.06 (t, *J* = 8.2 Hz, 2H, major, CH_2CHSO$_2$), 3.81 (dt, d = *J* = 12.7 Hz, t = *J* = 9.7 Hz, 1H, minor, CH_2CHSO$_2$), 5.94 (t, *J* = 9.7 Hz, 2H, minor, C*H*SO$_2$), 5.98 (t, *J* = 8.2 Hz, 2H, major, C*H*SO$_2$), 7.48-7.56 (m, 4H minor + 4H major, Ar*H*), 7.92-8.02 (m, 4H major + 4H minor, Ar*H*). ^{13}C NMR (101 MHz, $CDCl_3$) δ 10.0 (major, *C*H$_2$CHSO$_2$), 10.1 (minor, *C*H$_2$CHSO$_2$), 31.0 (major, C(CH_3)$_3$), 31.0 (minor, C(*C*H$_3$)$_3$), 35.3 (minor, *C*(CH_3)$_3$), 35.4 (major, *C*(CH_3)$_3$), 79.3 (minor, *C*HSO$_2$), 81.0 (major, *C*HSO$_2$), 126.2 (minor, Ar*C*H), 126.2 (major, Ar*C*H), 128.6 (minor, Ar*C*H), 128.8 (major, Ar*C*H), 132.8 (minor, Ar*C*), 158.7 (minor, Ar*C*), 158.9 (major, Ar*C*), 185.4 (minor, *C*=O), 186.7 (major, *C*=O). FT-IR (NaCl, cm^{-1}) υ 545, 991, 1125, 1325, 1603, 1677, 2961. HRMS (ESI-TOF) m/z [M+Na]$^+$ calcd for $C_{25}H_{30}O_4SNa$ 449.1757; found 449.1756.

(1,1-dioxido-2,4-thietanediyl)bis[(3-chlorophenyl)methanone]-3d. Column chromatography on silica gel (Hexane/AcOEt 80:20), yellow solid, mp 122-125 °C, 67% (254 mg), dr 80:20. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.45 (dt, d = *J* = 12.8 Hz, t = *J* = 9.7 Hz, 1H, minor, CH_2CHSO$_2$), 3.08 (t, *J* = 8.1 Hz, 2H, major, CH_2CHSO$_2$), 3.76-3.80 (dt, d = *J* = 12.8 Hz, t = *J* = 9.5 Hz, 1H, minor, CH_2CHSO$_2$), 5.93 (t, *J* = 9.6 Hz, 2H, minor, C*H*SO$_2$), 5.95 (t, *J* = 8.1 Hz, 2H, major, C*H*SO$_2$), 7.51 (t, *J* = 7.9 Hz, 2H minor + 2H major, Ar*H*), 7.62-7.65 (m, 2H minor + 2H major, Ar*H*), 7.85-7.87 (dt, *J* = 7.8, 1.7, 1.0 Hz, 2H, major, Ar*H*), 7.90-7.93 (dt, *J* = 7.8, 1.7, 1.0 Hz, 2H, minor, Ar*H*), 8.02 (t, *J* = 1.9 Hz, 2H, major, Ar*H*), 8.04 (t, *J* = 1.9 Hz, 2H, minor, Ar*H*). ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.1 (minor, *C*H$_2$CHSO$_2$), 10.2 (major, *C*H$_2$CHSO$_2$), 79.5 (minor, *C*HSO$_2$), 81.1 (major, *C*HSO$_2$), 126.6 (minor, Ar*C*H), 126.8 (major, Ar*C*H), 128.6 (minor, Ar*C*H), 128.7 (major, Ar*C*H), 130.6 (major, Ar*C*H), 134.8 (minor, Ar*C*H), 134.8 (major, Ar*C*H), 135.8 (minor, Ar*C*), 135.8 (major, Ar*C*), 136.7 (minor, Ar*C*), 136.7 (major, Ar*C*), 184.9 (minor, *C*=O), 186.1 (major, *C*=O). FT-IR (KBr, cm^{-1}) υ 767, 777, 1162, 1320, 1425, 1687, 3068. HRMS (ESI-TOF) m/z [M+Na]$^+$ calcd for $C_{17}H_{12}Cl_2O_4SNa$ 404.9726; found 404.9724.

(1,1-dioxido-2,4-thietanediyl)bis{[4-(trifluoromethyl)phenyl]}methanone-3e. Column chromatography on silica gel (Hexane/AcOEt 80:20), yellow solid, mp 180-183 °C, 60% (277 mg), dr 80:20. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.45-2.53 (dt, d = *J* = 12.8 Hz, t = *J* = 9.7 Hz, 1H, minor, CH_2CHSO$_2$), 3.13 (t, *J* = 8.1Hz, 2H, major, CH_2CHSO$_2$), 3.80-3.85 (dt, d = *J* = 12.8 Hz, t = *J* = 9.4 Hz, 1H, minor, CH_2CHSO$_2$), 5.99 (t, *J* = 9.5 Hz, 2H, minor C*H*SO$_2$), 6.01 (t, *J* = 8.1Hz, 2H, major, C*H*SO$_2$), 7.81-7.84 (m, 4H minor + 4H major, Ar*H*), 8.12-8.18 (m, 4H major + 4H, minor, Ar*H*). ^{13}C NMR (101 MHz, $CDCl_3$) δ 9.9 (minor, *C*H$_2$CHSO$_2$), 10.0 (major, *C*H$_2$CHSO$_2$), 79.7 (minor, *C*HSO$_2$), 81.3 (major, *C*HSO$_2$), 123.2 (d, $^1J_{C,F}$ = 273.1 Hz, major, *C*F$_3$), 126.4 (q, $^3J_{C,F}$ = 3.7 Hz, major, Ar*C*H), 128.9 (minor, Ar*C*H), 129.1 (major, Ar*C*H), 136.1 (q, $^2J_{C,F}$ = 33.0 Hz, major, Ar*C*), 137.7 (major, Ar*C*), 185.0 (minor, *C*=O), 186.3 (major, *C*=O). ^{19}F (377 MHz, $CDCl_3$) δ -63.4(s). FT-IR (KBr, cm^{-1}) υ 809, 859, 1070, 1128, 1169, 1333, 1692, 2957. HRMS (ESI-TOF) m/z [M+Na]$^+$ calcd for $C_{19}H_{12}F_6O_4SNa$ 473.0253; found 473.0255.

General procedure for lithiation/electrophile trapping sequence on C2'-substituted thietane-1,1-dioxide. To a stirred solution of thietane 1,1-dioxide 2-substituted (1.0 mmol, 1.0 equiv) in dry 2-MeTHF (10 mL) cooled at -78°C, a solution of *n-Hex*Li (2.5M in hexane, 1.1 equiv) was added dropwise. After stirring for 5 min. at -78°C, the electrophile (1 equiv) was added neat if liquid and in 1.0 mL of solvent if solid. After the reaction was complete, as ascertained by GC or TLC, the reaction mixture was quenched at -78 °C with saturated aqueous NH_4Cl (0.1mL) and directly filtered over Na_2SO_4 and concentrated in vacuo. Flash chromatography on silica gel (Hexane/AcOEt) afforded the 2,4-disubstituted thietane 1,1-dioxide.

2-benzyl-4-methylthietane 1,1-dioxide-4a. Column chromatography on silica gel (Hexane/AcOEt 70:30), yellow oil, >99%, dr 60:40. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.33-1.41 (m, 1H, minor, CH_2CHSO$_2$), 1.43 (d, *J* = 7.0 Hz, 3H, minor, CH_3CHSO$_2$), 1.46 (d, *J* = 7.2 Hz, 3H, major, CH_2CHSO$_2$), 1.83 (ddd, *J* = 12.0, 9.9, 5.5 Hz, 1H, major, CH_2CHSO$_2$), 2.03 (ddd, *J* = 12.0, 9.9, 7.1 Hz, 1H, major, CH_2CHSO$_2$), 2.34-2.41 (m, 1H, minor, CH_2CHSO$_2$), 2.91-2.98 (m, 1H major + 1H minor, ArCH_2CH), 3.36 (ddd, *J* = 14.6, 7.9 Hz, 1H, minor, ArCH_2CH), 3.42 (dd, *J* = 14.6, 7.4 Hz, 1H, major, ArCH_2CH), 4.13-4.26 (m, 1H major + 1H minor, C*H*SO$_2$), 4.33-4.41 (m, 1H, minor, C*H*SO$_2$), 4.42-4.50 (m, 1H, major, C*H*SO$_2$), 7.18-7.23 (m, 6H, Ar*H*), 7.27-7.29 (m, 4H, Ar*H*). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.2 (minor, *C*H$_2$CHSO$_2$), 14.8 (major, *C*H$_2$CHSO$_2$), 22.9 (major, *C*H$_3$CHSO$_2$), 23.9 (minor, *C*H$_3$CHSO$_2$), 34.8 (minor, ArCH_2CH), 35.3 (major, ArCH_2CH), 69.2 (minor, C*H*SO$_2$), 70.0 (major, C*H*SO$_2$), 75.7 (minor, C*H*SO$_2$), 76.1 (major, C*H*SO$_2$), 127.0 (minor, Ar*C*H), 127.0 (major, Ar*C*H), 128.6 (minor, Ar*C*H), 128.7 (minor, Ar*C*H), 128.7 (major, Ar*C*H), 128.9 (major, Ar*C*), 136.5 (minor, Ar*C*). FT-IR (KBr, cm^{-1}) υ 511, 546, 698, 800, 1123, 1152, 1250, 1449, 1490, 2965, 3011, 3029, 3063, 3090, 3489. HRMS (ESI-TOF) m/z [M+Na]$^+$ calcd for $C_{17}H_{18}O_3SNa$ 325.0869; found 325.0872.

(4-methyl-1,1-dioxido-2-thietanyl)(diphenyl)methanol-4b. Column chromatography on silica gel (Hexane/AcOEt 70:30), white solid, mp 143-146 °C, 60%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.51 (d, *J* = 7.0 Hz, 3H, CH_3CHSO$_2$), 1.51-1.57 (m, overlapping d at 1.51, 1H, CH_2CHSO$_2$), 2.56-2.61 (m, 1H, CH_2CHSO$_2$), 4.27-4.33 (m, 1H, C*H*SO$_2$), 5.33-5.36 (m, 1H C*H*SO$_2$), 7.20-7.22 (m, 1H, Ar*H*), 7.28-7.39 (m, 7H, Ar*H*), 7.53-7.54 (m, 2H, Ar*H*). ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.1 (*C*H$_2$CHSO$_2$), 18.5 (*C*H$_3$CHSO$_2$), 70.9 (*C*OH), 82.0 (*C*HSO$_2$), 125.4 (Ar*C*H), 126.0 (Ar*C*H), 127.3 (Ar*C*H), 128.1 (Ar*C*H), 128.4 (Ar*C*H), 128.8 (Ar*C*H), 143.2 (Ar*C*), 145.0 (Ar*C*). FT-IR (KBr, cm^{-1}) υ 511, 546, 698, 800, 1123, 1152, 1250, 1449, 1490, 2965, 3011, 3029, 3063, 3090, 3489. HRMS (ESI-TOF) m/z [M+Na]$^+$ calcd for $C_{17}H_{18}O_3SNa$ 325.0869; found 325.0872.

(4-benzyl-1,1-dioxido-2-thietanyl)[4-(2-methyl-2-propanyl)phenyl]methanone-4c. Column chromatography on silica gel (Hexane/AcOEt 80:20), white solid, mp 96-99 °C, 75% (270 mg), dr 60:40. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (s, 9H, minor, C(CH_3)$_3$), 1.35 (s, 9H, major, C(CH_3)$_3$) 1.96-2.03 (m, 1H, minor, CH_2CHSO$_2$), 2.30-2.37 (m, 1H, major, CH_2CHSO$_2$), 2.68-2.75 (m, 1H, major, CH_2CHSO$_2$), 2.97-3.05 (m, 1H, minor, CH_2CHSO$_2$), 3.079 (m, 1H, major, ArCH_2CH), 3.127 (m, 1H, minor, ArCH_2CH), 3.41 (dd, *J* = 14.5, 7.7 Hz, 1H, major, ArCH_2CH), 3.51 (dd, *J* = 14.5, 7.5Hz, 1H, minor, ArCH_2CH), 4.62-4.75 (m, 1H major + 1H minor, C*H*SO$_2$), 5.74 (t, *J* = 9.2 Hz, 1H, major, C*H*SO$_2$), 5.81 (ddd, *J* = 9.8, 4.7, 1.3Hz, 1H, minor, C*H*SO$_2$), 7.25-7.28 (m, 3H minor + 3H major, Ar*H*), 7.32-7.35 (m, 2H minor + 2H major, Ar*H*), 7.53-7.57 (m, 2H minor + 2H major, Ar*H*), 7.94-7.96 (m, 2H, minor, Ar*H*), 8.01-8.03 (m, 2H, major, Ar*H*). ^{13}C NMR (101 MHz, $CDCl_3$) δ 15.5 (major, *C*H$_2$CHSO$_2$), 15.8 (minor, *C*H$_2$CHSO$_2$), 31.0 (major, C(CH_3)$_3$), 35.1 (major, ArCH$_2$CH), 35.3 (major, *C*(CH_3)$_3$), 35.4 (minor, ArCH$_2$CH), 77.5 (major, *C*HSO$_2$), 78.6

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DOI: 10.1039/C7OB00846E

(major, *C*HSO$_2$), 79.0 (minor, *C*HSO$_2$), 79.3 (minor, *C*HSO$_2$), 126.1 (minor, Ar*C*H), 126.2 (major, Ar*C*H), 127.2 (major, Ar*C*H), 127.2 (minor, Ar*C*H), 128.6 (major, Ar*C*H), 128.7 (minor, Ar*C*H), 128.7 (minor, Ar*C*H), 128.8 (major, Ar*C*H), 128.9 (major, Ar*C*H), 132.9 (major, Ar*C*), 133.0 (minor, Ar*C*), 135.8 (minor, Ar*C*), 136.1 (major, Ar*C*), 158.5 (minor, Ar*C*), 158.6 (major, Ar*C*), 186.4 (major, *C*=O), 187.1 (minor, *C*=O). FT-IR (KBr, cm^{-1}) υ 545, 700, 1129, 1312, 1685, 2959. HRMS (ESI-TOF) m/z [M+Na]$^+$ calcd for $C_{21}H_{24}O_3SNa$ 379.1338; found 379.1345.

General procedure for lithiation/electrophile trapping sequence on C2-substituted tetrahydro-2*H*-thiopyran 1,1-dioxide. To a stirred solution of tetrahydro-2*H*-thiopyran 1,1-dioxide (1.0 mmol, 1.0 equiv) in dry 2-MeTHF (10 mL) cooled at -78°C, a solution of *n*-HexLi (2.5M in hexane, 1.1 equiv) was added dropwise. After stirring for 10 min. at -78°C, the electrophile (1 equiv) was added neat if liquid and in 1.0 mL of solvent if solid. After the reaction was complete, as ascertained by GC or TLC, the reaction mixture was quenched with saturated aqueous NH_4Cl (0.1mL) and directly filtered over Na_2SO_4 and concentrated in vacuo. Flash chromatography on silica gel (Hexane/AcOEt) afforded the substituted tetrahydro-2*H*-thiopyran 1,1-dioxide.

2-benzyltetrahydro-2*H*-thiopyran 1,1-dioxide-6a. Column chromatography on silica gel (Hexane/AcOEt 70:30), white solid, mp 111-114 °C, 50% (114 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27-1.35 (m, 1H, C*H*$_2$CH$_2$CHSO$_2$), 1.67-1.83 (m, 2H, C*H*$_2$CH$_2$CHSO$_2$, C*H*$_2$CHSO$_2$), 1.88-1.93 (m, 1H, C*H*$_2$CHSO$_2$), 2.04-2.09 (m, 2H, C*H*$_2$CH$_2$SO$_2$), 2.65 (dd, *J* = 13.5, 11.1 Hz, 1H, ArC*H*$_2$CH), 2.88-3.05 (m, 2H, C*H*$_2$SO$_2$, C*H*SO$_2$), 3.10-3.16 (m, 1H, C*H*SO$_2$), 3.52 (dd, *J* = 13.5, 2.7 Hz, 1H, ArC*H*$_2$CH), 7.17-7.19 (m, 2H, Ar*H*), 7.23-7.26 (m, 1H, Ar*H*), 7.30-7.33 (m, 2H, Ar*H*). ^{13}C NMR (101 MHz, $CDCl_3$) δ 23.8 (*C*H$_2$CH$_2$CHSO$_2$), 24.3 (*C*H$_2$CH$_2$SO$_2$), 28.6 (*C*H$_2$CHSO$_2$), 30.8 (ArCH$_2$CH), 51.9 (*C*H$_2$SO$_2$), 63.0 (*C*HSO$_2$), 126.9 (Ar*C*H), 128.7 (Ar*C*H), 129.3 (Ar*C*H), 136.5 (Ar*C*). FT-IR (KBr, cm^{-1}) υ 473, 707, 760, 1127, 1282, 2927. HRMS (ESI-TOF) m/z [M+Na]$^+$ calcd for $C_{12}H_{16}O_2SNa$ 247.0763; found 247.0762.

(1,1-dioxidotetrahydro-2*H*-thiopyran-2-yl)[4-(2-methyl-2-propanyl)phenyl]methanone-6b. Column chromatography on silica gel (Hexane/AcOEt 80:20), white solid, mp 151-154 °C, 68% (200 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (s, 9H, C(C*H*$_3$)$_3$), 1.59-1.67 (m, 1H, C*H*$_2$CH$_2$CHSO$_2$), 1.86-1.95 (m, 1H, C*H*$_2$CH$_2$CHSO$_2$), 2.15-2.20 (m, 2H, C*H*$_2$CH$_2$SO$_2$), 2.32-2.46 (m, 2H, C*H*$_2$CHSO$_2$), 3.03-3.10 (m, 1H, C*H*$_2$SO$_2$), 3.59-3.65 (m, 1H, C*H*$_2$SO$_2$), 4.87-4.90 (m, 1H, C*H*SO$_2$), 7.51-7.53 (m, 2H, Ar*H*), 7.91-7.93 (m, 2H, Ar*H*). ^{13}C NMR (101 MHz, $CDCl_3$) δ 20.3 (*C*H$_2$CH$_2$CHSO$_2$), 24.2 (*C*H$_2$-CH$_2$SO$_2$), 28.3 (*C*H$_2$CHSO$_2$), 31.1 (C(*C*H$_3$)$_3$), 35.3 (*C*(CH$_3$)$_3$), 51.4 (*C*H$_2$SO$_2$), 64.9 (*C*HSO$_2$), 125.9 (Ar*C*H), 128.9 (Ar*C*H), 133.2 (Ar*C*), 158.4 (Ar*C*), 192.0 (*C*=O). FT-IR (KBr, cm^{-1}) υ. 548, 926, 1118, 1270, 1324, 1677, 2866, 2967. HRMS (ESI-TOF) m/z [M+Na]$^+$ calcd for $C_{16}H_{22}O_3SNa$ 317.1182; found 317.1183.

(1,1-dioxidotetrahydro-2*H*-thiopyran-2-yl)(diphenyl)methanol-6c. Column chromatography on silica gel (Hexane/AcOEt 80:20), white solid, mp 98-102 °C, 60% (195 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39-1.51 (m, 1H, C*H*$_2$CH$_2$CHSO$_2$), 1.87-1.98 (m, 2H, C*H*$_2$CH$_2$CHSO$_2$, C*H*$_2$CHSO$_2$), 2.02-2.09 (m, 2H, C*H*$_2$CH$_2$SO$_2$), 2.20-2.30 (m, 1H, C*H*$_2$CHSO$_2$), 2.98-3.06 (m, 2H, C*H*$_2$SO$_2$), 4.09 (dd, *J* = 12.2, 3.2 Hz, 1H, C*H*SO$_2$), 4.65 (bs, 1H, OH), 7.18-7.23 (m, 2H, Ar*H*), 7.30-7.34 (m, 4H, Ar*H*), 7.50-7.53 (m, 2H, Ar*H*), 7.63-7.66 (m, 2H, Ar*H*). ^{13}C NMR (101 MHz, $CDCl_3$) δ 24.0 (*C*H$_2$CH$_2$SO$_2$), 24.2 (*C*H$_2$CH$_2$CHSO$_2$), 26.7 (*C*H$_2$CHSO$_2$), 55.2 (*C*H$_2$SO$_2$), 67.3 (*C*HSO$_2$), 79.1 (*C*OH), 124.9 (Ar*C*H), 125.6 (Ar*C*H), 127.0 (Ar*C*H), 127.3 (Ar*C*H), 127.9 (Ar*C*H), 128.5 (Ar*C*H), 143.9 (Ar*C*), 144.5 (Ar*C*). FT-IR (KBr, cm^{-1}) υ 693, 747, 1130, 1265, 1318, 1448, 2927, 3454. HRMS (ESI-TOF) m/z [M+Na]$^+$ calcd for $C_{18}H_{20}O_3SNa$ 339.1025; found 339.1028.

cyclopropyl(1,1-dioxidotetrahydro-2*H*-thiopyran-2-yl)methanone-6d. Column chromatography on silica gel (Hexane/AcOEt 60:40), white solid, mp 110-113 °C, 75% (155 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03-1.24 (m, 4H, C*H*$_2$CH$_2$CH, CH$_2$C*H*$_2$CH), 1.51-1.56 (m, 1H, C*H*$_2$CH$_2$CHSO$_2$), 1.85-1.92 (m, 1H, C*H*$_2$CH$_2$CHSO$_2$), 2.08-2.11 (m, 2H, C*H*$_2$CH$_2$SO$_2$), 2.26-2.32 (m, 3H, C*H*$_2$CHSO$_2$, CH$_2$CH$_2$C*H*), 2.96-3.03 (m, 1H, C*H*$_2$SO$_2$), 3.24-3.30 (m, 1H, C*H*$_2$SO$_2$), 4.13 (ddd, *J* = 8.2, 4.5, 1.5 Hz, 1H, C*H*SO$_2$). ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.9 (*C*H$_2$CH$_2$CH, CH$_2$*C*H$_2$CH), 21.6 (*C*H$_2$CH$_2$CHSO$_2$), 22.1 (CH$_2$CH$_2$*C*H), 24.2 (*C*H$_2$CH$_2$SO$_2$), 27.1(*C*H$_2$CHSO$_2$), 52.4 (*C*H$_2$SO$_2$), 71.3 (*C*HSO$_2$), 201.5 (*C*=O). FT-IR (KBr, cm^{-1}) υ. 550, 1120, 1677, 2788, 2967. HRMS (ESI-TOF) m/z [M+Na]$^+$ calcd for $C_9H_{14}O_3SNa$ 225.0556; found 225.0559.

N-(2-phenylethyl)tetrahydro-2*H*-thiopyran-2-carboxamide 1,1-dioxide-6e. Column chromatography on silica gel (Hexane/AcOEt 70:30), white solid, mp 50-53 °C, 70% (200 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46-1.53 (m, 1H, C*H*$_2$CH$_2$CHSO$_2$), 1.90-1.96 (m, 1H, C*H*$_2$CH$_2$CHSO$_2$), 2.04-2.10 (m, 2H, C*H*$_2$CH$_2$SO$_2$), 2.15-2.24 (m, 1H, C*H*$_2$CHSO$_2$), 2.31-2.39 (m, 1H, C*H*$_2$CHSO$_2$), 2.86 (t, *J* = 7.1 Hz, 2H, C*H*$_2$CH$_2$NH), 2.89-3.01 (m, 1H, C*H*$_2$SO$_2$), 3.08-3.14 (m, 1H, C*H*$_2$SO$_2$), 3.50-3.67 (m, 3H, CH$_2$C*H*$_2$NH, C*H*SO$_2$), 6.74 (bs, NH, 1H), 7.21-7-25 (m, 3H, Ar*H*), 7.29-7.33 (m, 2H, Ar*H*). ^{13}C NMR (101 MHz, $CDCl_3$) δ 22.7 (*C*H$_2$CH$_2$CHSO$_2$), 24.1 (*C*H$_2$CH$_2$SO$_2$), 27.9 (*C*H$_2$CHSO$_2$), 35.4 (*C*H$_2$CH$_2$NH), 41.2 (CH$_2$*C*H$_2$NH), 52.1 (*C*H$_2$SO$_2$), 65.6 (*C*HSO$_2$), 126.5 (Ar*C*H), 128.6 (Ar*C*H), 128.8 (Ar*C*H), 138.5 (Ar*C*), 163.0 (*C*=O). ^{15}N δ -263.3. FT-IR (KBr, cm^{-1}) υ 702, 746, 917, 1129, 1192, 1290, 1318, 1557, 1651, 3314. HRMS (ESI-TOF) m/z [M+Na]$^+$ calcd for $C_{14}H_{19}NO_3SNa$ 304.0978; found 304.0973.

(1,1-dioxidotetrahydro-2*H*-thiopyran-2yl)(3-thienyl)methanol-6f. Column chromatography on silica gel (Hexane/AcOEt 70:30), white solid, mp 105-108 °C, 73% (183 mg), diastereoisomeric mixture, dr 50:50. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50-2.30 (m, 12H, 3 x C*H*$_2$ ring), 2.97-3.00 (m, 3H, C*H*$_2$SO$_2$, C*H*SO$_2$), 3.15-3.30 (m, 3H, C*H*$_2$SO$_2$, C*H*SO$_2$), 5.36 (d, *J* = 9.1 Hz, 1H, C*H*OH), 5.89 (s, 1H, C*H*OH), 6.99 (dd, *J* = 4.9, 1.3 Hz, 1H, Ar*H*), 7.10 (dd, *J* = 5.0, 1.3 Hz, 1H, Ar*H*), 7.28 (dd, *J* = 3.0, 1.3 Hz, 1H, Ar*H*), 7.30 (dd, *J* = 3.0, 1.3 Hz, 1H, Ar*H*), 7.33 (dd, *J* = 4.9, 3.0 Hz, 1H, Ar*H*), 7.35 (dd, *J* = 5.0, 3.0 Hz, 1H, Ar*H*). ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.4 (*C*H$_2$CHSO$_2$), 23.5 (*C*H$_2$CH$_2$CHSO$_2$), 23.8 (*C*H$_2$CH$_2$SO$_2$), 24.0 (*C*H$_2$CH$_2$CHSO$_2$), 24.2 (*C*H$_2$CH$_2$SO$_2$), 27.5 (*C*H$_2$CHSO$_2$), 52.3 (*C*H$_2$SO$_2$), 53.0 (*C*H$_2$SO$_2$), 65.4 (*C*HOH), 66.4 (*C*HSO$_2$), 67.3 (*C*HSO$_2$), 68.1 (*C*HOH), 121.8 (Ar*C*H), 123.3 (Ar*C*H), 124.9 (Ar*C*H), 125.6 (Ar*C*H), 126.4 (Ar*C*H), 126.8 (Ar*C*H), 140.0 (Ar*C*), 140.8 (Ar*C*). FT-IR (KBr, cm^{-1}) υ 616, 790, 1129, 1281, 1637, 2925, 3418. HRMS (ESI-TOF) m/z [M+Na]$^+$ calcd for $C_{10}H_{14}O_3S_2Na$ 269.0277; found 269.0281.

(1,1-dioxidotetrahydro-2*H*-thiopyran-2yl)(4-methoxyphenyl)methanone-6g. Column chromatography on silica gel (Hexane/AcOEt 70:30), white solid, mp 161-163 °C 65% (179 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.60-1.65 (m, 1H, C*H*$_2$CH$_2$CHSO$_2$), 1.90-1.97 (m, 1H, C*H*$_2$CH$_2$CHSO$_2$), 2.14-2.18 (m, 2H, C*H*$_2$CH$_2$SO$_2$), 2.36-2.40 (m, 2H, C*H*$_2$CHSO$_2$), 3.03-3.08 (m, 1H, C*H*$_2$SO$_2$), 3.57-3.63 (m, 1H, C*H*$_2$SO$_2$), 3.89 (s, 3H, OC*H*$_3$), 4.84 (td, *J* = 5.3, 2.0 Hz, 1H, C*H*SO$_2$), 6.95-6.98 (m, 2H, Ar*H*), 7.95-7.98 (m, 2H, Ar*H*). ^{13}C NMR

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DOI: 10.1039/C7OB00846E

(125 MHz, $CDCl_3$) δ 20.4 (*C*$H_2CH_2CHSO_2$), 24.1 (*C*$H_2CH_2SO_2$), 28.3 (*C*H_2CHSO_2), 51.5 (*C*H_2SO_2), 55.6 (OCH_3), 64.8 (*C*HSO_2), 114.1 (Ar*C*H), 128.8 (Ar*C*H), 131.5 (Ar*C*), 164.5 (*C*=O). FT-IR (KBr, cm^{-1}) υ 713, 827, 934, 1132, 1174, 1270, 1316, 1663, 2933. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{13}H_{16}O_4SNa$ 291.0662; found 291.0669.

General procedure for lithiation-electrophile trapping sequence on C2,C2'-substituted tetrahydro-2*H*-thiopyran 1,1-dioxide. To a stirred solution of tetrahydro-2*H*-thiopyran 1,1-dioxide (1.0 mmol, 1.0 equiv) in dry 2-MeTHF (10 mL) cooled at -78°C, a solution of *n*-HexLi (2.5M in hexane, 2.5 equiv) was added dropwise. After stirring for 30 min at -78°C, the electrophile (2.5 equiv) was added neat if liquid and in 1.0 mL of solvent if solid. After the reaction was complete, as ascertained by GC or TLC, the reaction mixture was quenched with saturated aqueous NH_4Cl (0.1mL) and directly filtered over Na_2SO_4 and concentrated in vacuo. Flash chromatography on silica gel (Hexane/AcOEt) afforded the disubstituted tetrahydro-2*H*-thiopyran 1,1-dioxide.

2,6-dibenzyltetrahydro-2*H*-thiopyran 1,1-dioxide-7a. Column chromatography on silica gel (Hexane/AcOEt 80:20), white solid, mp 179-181 °C 60% (190 mg), dr 80:20. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13-1.26 (m, 1H, major, C*H*$_2$CH$_2$CHSO$_2$), 1.57-1.63 (m, 2H, minor, C*H*$_2$CH$_2$CHSO$_2$), 1.70-1.80 (m, 3H major + 2H minor, C*H*$_2$CH$_2$CHSO$_2$, C*H*$_2$CHSO$_2$), 1.85-1.90 (m, 2H, major, C*H*$_2$CHSO$_2$), 1.98-2.06 (m, 2H, minor, C*H*$_2$CHSO$_2$), 2.71 (dd, *J* = 13.6, 11.0 Hz, 2H, major, ArC*H*$_2$CH), 2.79 (dd, *J* = 13.5, 12.0 Hz, 2H, minor, ArC*H*$_2$CH), 2.97-3.05 (m, 2H, major, C*H*SO$_2$), 3.16-3.22 (m, 2H, minor, C*H*SO$_2$), 3.53 (dd, *J* = 13.5, 3.2 Hz, 2H, minor, ArC*H*$_2$CH) 3.58 (dd, *J* = 13.6, 3.2 Hz, 2H, major, ArC*H*$_2$CH), 7.20-7.22 (m, 4H major + 4H minor, Ar*H*), 7.23-7.29 (m, 2H major + 2H minor, Ar*H*), 7.30-7.36 (m, 4H major + 4H minor, Ar*H*). ^{13}C NMR (101 MHz, $CDCl_3$) δ 18.6 (minor, *C*H$_2$CH$_2$CHSO$_2$), 24.4 (major, *C*H$_2$CH$_2$CHSO$_2$), 27.1 (minor, *C*H$_2$CHSO$_2$), 29.0 (major, *C*H$_2$CHSO$_2$), 30.9 (major, ArCH$_2$CH), 31.7 (minor, ArCH$_2$CH), 60.4 (minor, *C*HSO$_2$), 63.6 (major, *C*HSO$_2$), 126.9 (major, Ar*C*H), 127.0 (minor, Ar*C*H), 128.7 (major, Ar*C*H), 128.8 (minor, Ar*C*H), 129.2 (minor, Ar*C*H), 129.4 (major, Ar*C*H), 136.8 (minor, Ar*C*), 136.8 (major, Ar*C*). FT-IR (KBr, cm^{-1}) υ 491, 700, 756, 1114, 1307, 1455, 1722, 2934 HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{19}H_{22}O_2SNa$ 337.1233; found 337.1230.

General procedure for lithiation/electrophile trapping sequence on C2'-substituted tetrahydro-2*H*-thiopyran 1,1-dioxide. To a stirred solution of tetrahydro-2*H*-thiopyran 1,1-dioxide 2-substituted (1.0 mmol, 1.0 equiv) in dry 2-MeTHF (10 mL) cooled at -78 °C, a solution of *n*-HexLi (2.5M in hexane, 1.1 equiv) was added dropwise. After stirring for 10 min at -78 °C, the electrophile (1 equiv) was added neat if liquid and in 1.0 mL of solvent if solid. After the reaction was complete, as ascertained by GC or TLC, the reaction mixture was quenched at -78 °C with saturated aqueous NH_4Cl (0.1mL) and directly filtered over Na_2SO_4 and concentrated in vacuo. Flash chromatography on silica gel (Hexane/AcOEt) afforded the 2,4-disubstituted tetrahydro-2*H*-thiopyran 1,1-dioxide.

(6-benzyl-1,1-dioxidotetrahydro-2*H*-thiopyran-2-yl)[4-(*tert*-butyl)phenyl]methanone-8a. Column chromatography on silica gel (Hexane/AcOEt 80:20), white solid, mp 149-152 °C, 72% (235 mg), dr 60:40. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (s, 18H, C(C*H*$_3$)$_3$), 1.40-1.48 (m, 2H, C*H*$_2$CH$_2$CHSO$_2$, minor), 1.61-1.66 (m, 1H, C*H*$_2$CH$_2$CHSO$_2$, major), 1.75-1.81 (m, 2H, C*H*$_2$CH$_2$CHSO$_2$, C*H*$_2$CHSO$_2$, major), 1.83-1.91 (m, 1H, C*H*$_2$CHSO$_2$,minor), 1.94-1.97 (m, 2H, C*H*$_2$CHSO$_2$, major + minor), 2.07-2.12 (m, 1H, C*H*$_2$CHSO$_2$, minor), 2.24-2.27 (m, 1H, C*H*$_2$CHSO$_2$, major), 2.49-2.56 (m, 1H, C*H*$_2$CHSO$_2$, major), 2.60-2.65 (m, 1H, C*H*$_2$CHSO$_2$, minor), 2.67-2.72 (dt, *J* = 9.3, 8.4 Hz, 2H, CHC*H*$_2$Ar, major + minor), 3.15-3.21 (m, 1H, C*H*CH$_2$Ar, minor), 3.54-3.56 (dd, *J* = 13.5, 3.1 Hz, 2H, CHC*H*$_2$Ar, minor + major), 3.88-3.94 (ddd, *J* = 11.4, 7.3, 3.4 Hz, 1H, C*H*CH$_2$Ar, major), 4.87-4.90 (dd, *J* = 12.6, 2.9 Hz, 1H, C*H*COAr, minor), 4.98-5.00 (dd, *J* = 5.3, 2.7 Hz, 1H, C*H*COAr, major), 7.20-7.35 (m, 10H), 7.51-7.53 (m, 4H), 7.89 (d, *J* = 8.5 Hz, 2H), 8.02 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.5 (*C*H$_2$CH$_2$CHSO$_2$, major), 23.8 (*C*H$_2$CH$_2$CHSO$_2$, minor), 28.2 (*C*H$_2$CHSO$_2$, minor), 28.6 (*C*H$_2$CHSO$_2$, major), 28.75 (*C*H$_2$CHSO$_2$, major), 28.8 (*C*H$_2$CHSO$_2$, minor), 30.7 (CH*C*H$_2$Ar, major), 30.9 (CH*C*H$_2$Ar, minor), 31.0 (C(*C*H$_3$)$_3$, major), 31.0 (C(*C*H$_3$)$_3$, minor), 35.2 (*C*(CH$_3$)$_3$, minor), 35.3 (*C*(CH$_3$)$_3$, major), 61.1 (*C*HCH$_2$Ar, major), 64.6 (*C*HCOAr, major), 65.5 (*C*HCH$_2$Ar, minor), 67.0 (*C*HCOAr, minor), 125.7 (Ar*C*H, major), 126.0 (Ar*C*H, major), 126.9 (Ar*C*H, minor), 127.0 (Ar*C*H, minor), 128.7 (Ar*C*H, major), 128.8 (Ar*C*H, major), 128.8 (Ar*C*H, minor), 129.4 (Ar*C*H, minor), 129.5 (Ar*C*H, major), 129.5 (Ar*C*H, minor), 132.8 (Ar*C*, major), 134.0 (Ar*C*, minor), 136.4 (Ar*C*, major), 136.4 (Ar*C*, minor), 158.1 (Ar*C*, minor), 158.4 (Ar*C*, major), 189.0 (*C*=O, minor), 192.9 (*C*=O, major). FT-IR (KBr, cm^{-1}) υ 511, 701, 1119, 1269, 1301, 1602, 1674, 2952, 3453. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{23}H_{28}O_3SNa$ 407.1651; found 407.1653.

2-(hydroxydiphenylmethyl)-6-methyltetrahydro-2*H*-thiopyran 1,1-dioxide-8b. Column chromatography on silica gel (Hexane/AcOEt 80:20), white solid, mp 159-164 °C, 71% (235 mg), dr 90:10. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.27 (d, *J* = 6.8 Hz, 3H, major, C*H*$_3$CHSO$_2$), 1.42 (d, *J* = 7.1 Hz, 3H, minor, C*H*$_3$CHSO$_2$), 1.50-1.54 (m, 1H, major, C*H*$_2$CH$_2$CHSO$_2$), 1.59-1.67 (m, 1H, minor, C*H*$_2$CH$_2$CHSO$_2$), 1.73-1.79 (m, 1H, minor, C*H*$_2$CH$_2$CHSO$_2$), 1.77-1.90 (m, 2H, major, C*H*$_2$CH$_2$CHSO$_2$, C*H*$_2$CHSO$_2$), 1.83-1.91 (m, 2H, minor, C*H*$_2$CHSO$_2$), 1.93-2.01 (m, 2H, major, C*H*$_2$CHSO$_2$), 2.11-2.21 (m, 2H, minor, C*H*$_2$CHSO$_2$), 2.24-2.33 (m, 1H, major, C*H*$_2$CHSO$_2$), 3.00-3.06 (m, 1H, major, C*H*SO$_2$), 3.16-3.22 (m, 1H, minor, C*H*SO$_2$), 4.05 (dd, *J* = 12.6, 3.1 Hz, 1H, major, C*H*SO$_2$), 4.19 (dd, *J* = 10.9, 3.8 Hz, 1H, minor, C*H*SO$_2$), 4.50 (bs, 1H, OH, minor), 4.79 (s, 1H, OH, major), 7.18-7.23 (m, 2H, minor, Ar*H*), 7.18-7.24 (m, 2H, major, Ar*H*), 7.29-7.33 (m, 4H, minor, Ar*H*), 7.30-7.34 (m, 4H, major, Ar*H*), 7.46-7.48 (m, 2H, minor, Ar*H*), 7.53-7.54 (m, 2H, major, Ar*H*), 7.60-7.62 (m, 2H, minor, Ar*H*), 7.63-7.65 (m, 2H, major, Ar*H*). ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.3 (major, *C*H$_3$CHSO$_2$), 12.7 (minor, *C*H$_3$CHSO$_2$), 19.0 (minor, *C*H$_2$CH$_2$CHSO$_2$), 24.6 (major, *C*H$_2$CH$_2$CHSO$_2$), 25.8 (minor, *C*H$_2$CHSO$_2$), 27.1 (major, *C*H$_2$CHSO$_2$), 29.4 (minor, *C*H$_2$CHSO$_2$), 32.2 (major, *C*H$_2$CHSO$_2$), 57.7 (minor, *C*HSO$_2$), 60.3 (major, *C*HSO$_2$), 64.6 (minor, *C*HSO$_2$), 67.4 (major, *C*HSO$_2$), 79.2 (minor, *C*OH), 79.2 (major, *C*OH), 124.9 (major, Ar*C*H), 125.0 (minor, Ar*C*H), 125.6 (minor, Ar*C*H), 125.6 (major, Ar*C*H), 126.9 (minor, Ar*C*H), 127.0 (major, Ar*C*H), 127.3 (minor, Ar*C*H), 127.3 (major, Ar*C*H), 127.9 (major, Ar*C*H), 128.0 (minor, Ar*C*H), 128.4 (minor, Ar*C*H), 128.5 (major, Ar*C*H), 144.0 (major, Ar*C*), 144.2 (minor, Ar*C*), 144.6 (major, Ar*C*), 145.1 (minor, Ar*C*). FT-IR (KBr, cm^{-1}) υ 571, 695, 964, 1132, 1273, 1449, 1637, 2863, 2972, 3492. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{19}H_{22}O_3SNa$ 353.1182; found 353.1183.

General procedure for direct α-arylation of cyclic sulfones 1, 5 and 11. To a stirred solution of thietane 1,1-dioxide (1.0 mmol, 1.0 equiv) in dry THF (10 mL) cooled at -78°C, a solution of *n*-HexLi (2.5M in hexane, 1.1 equiv) was added dropwise. After stirring for

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DOI: 10.1039/C7OB00846E

the time indicated in Scheme6, at -78°C, anhydrous Copper(I) cyanide di(lithium chloride) complex solution (CuCN 2LiCl, 1 equiv) was added in one portion. The mixture was allowed to warm to -35 °C, stirred for 15 min at this temperature. Diphenyliodonium hexafluorophoshate (1 equiv) was added, in one portion, resulting in the immediate formation of a bright yellow mixture. The reaction was maintained at -35 °C for 15 min then allowed to slowly to warm to room temperature. After stirring for 4 hour to rt, the reaction mixture was quenched with saturated aqueous NH_4Cl (0.1mL) and the organic layer was separated, and the acqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and the solvent evaporated under vacuum and the product purified on silica gel.

2-phenylthietane 1,1-dioxide-9a. Flash chromatography on silica gel (Hexane/AcOEt 70:30) afforded 2-phenylthietane 1,1-dioxide, yellow solid, mp 81-84°C, 50% (111 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36-2.47 (m, 1H, CH_2CHSO$_2$), 2.54-2.62 (m, 1H, CH_2CHSO$_2$), 3.98-4.20 (m, 2H, CH_2SO$_2$), 5.45-5.49 (m, 1H, C*H*SO$_2$), 7.38-7.44 (m, 5H, Ar*H*). ^{13}C NMR (101 MHz, $CDCl_3$) δ 15.0 (*C*H$_2$CHSO$_2$), 62.1 (*C*H$_2$SO$_2$), 82.3 (*C*HSO$_2$), 128.5 (Ar*C*H), 128.9 (Ar*C*H), 129.2 (Ar*C*H), 130.8 (Ar*C*). FT-IR (KBr, cm^{-1}) υ 583, 704, 734, 769, 1125, 1189, 1301, 1455, 1492, 2360, 2920. HRMS (ESI-TOF) m/z [M+Na]$^+$ calcd for $C_9H_{10}O_2SNa$ 205.0294; found 205.0296.

2-phenyltetrahydro-2*H*-thiopyran 1,1-dioxide-9b. The solid was washed two times with diethyl ether and one time with distilled hexane afforded 2-phenyltetrahydro-2*H*-thiopyran 1,1-dioxide as white solid, mp 84-87°C, 60% (126 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.55-1.65 (m, 1H, CH_2CH$_2$CHSO$_2$), 2.04-2.09 (m, 2H, CH_2CH$_2$CHSO$_2$), 2.17-2.24 (m, 2H, CH_2CH$_2$SO$_2$), 2.46-2.54 (m, 1H, CH_2CHSO$_2$), 3.02-3.08 (m, 1H, CH_2SO$_2$), 3.23 (dtd, *J* = 14.1, 3.5, 1.4 Hz, 1H, CH_2SO$_2$), 4.02 (dd, *J* = 13.0, 3.0 Hz, 1H, C*H*SO$_2$), 7.38-7.44 (m, 5H, Ar*H*). ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.6 (*C*H$_2$CH$_2$CHSO$_2$), 25.2 (*C*H$_2$CH$_2$SO$_2$), 31.0 (*C*H$_2$CHSO$_2$), 52.7 (*C*H$_2$SO$_2$), 67.6 (*C*HSO$_2$), 128.6 (Ar*C*H), 129.0 (Ar*C*H), 129.9 (Ar*C*H), 130.4 (Ar*C*). FT-IR (KBr, cm^{-1}) υ 697, 727, 1124, 1281, 1446, 1493, 2862, 2935. HRMS (ESI-TOF) m/z [M+Na]$^+$ calcd for $C_{11}H_{14}O_2SNa$ 233.0607; found 233.0609.

2-phenyltetrahydrothiophene 1,1-dioxide-9c
Column chromatography on silica gel (Hexane/AcOEt 60:40), colorless oil, 70%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.19-2.27 (m, 1H, CH_2CH$_2$SO$_2$), 2.34-2.39 (m, 1H, CH_2CH$_2$SO$_2$), 2.45-2.49 (m, 1H, CH_2CHAr), 2.51-2.58 (m, 1H, CH_2CHAr), 3.14-3.20 (m, 1H, CH_2SO$_2$), 3.28-3.32 (m, 1H, CH_2SO$_2$), 4.15-4.19 (dd, *J* = 12.2, 7.2 Hz, 1H, C*H*Ar), 7.39-7.41 (m, 5H, Ar*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 19.8 (*C*H$_2$CH$_2$SO$_2$), 28.7 (*C*H$_2$CHAr), 50.6 (*C*H$_2$SO$_2$), 66.7 (*C*HAr), 128.8 (Ar*C*H), 129.0 (Ar*C*H), 129.1 (Ar*C*H), 130.3 (Ar*C*); FT-IR (NaCl, cm^{-1}) υ 594, 724, 1132, 1189, 1301, 1449, 1493, 2359, 2921;HRMS (ESI-TOF) m/z [M+Na]$^+$ calcd for $C_{10}H_{12}NaO_2S$ 219.0450; found 219.0459.

General procedure for C2-fluorination cyclic sulfones 1, 5 and 11.
To a stirred solution of thietane-1,1- dioxide or tetrahydro-2*H*-thiopyran 1,1-dioxide (1.0 mmol, 1.0 equiv) in dry 2-MeTHF (10 mL) cooled at -78°C, a solution of *n*-HexLi (2.5M in hexane, 1.1 equiv) was added dropwise. After stirring for the time indicated in Scheme6, at -78°C, the electrophilic fluorinated reagent *N*-Fluorobenzenesulfonimide (NFSI, 1 equiv) was added in 2.0 mL of solvent. The reaction was maintained at -78°C for 15 min then allowed to slowly to warm to room temperature. After the reaction was complete, as ascertained by GC or TLC, the reaction mixture was quenched with saturated aqueous NH_4Cl (0.1mL), directly filtered over Na_2SO_4 and concentrated in vacuo. Flash chromatography on silica gel (Hexane/AcOEt) afforded the 2-phenyl substituted cyclic sulfones.

2-fluoro-2-(phenylsulfonyl)thietane 1,1-dioxide-10a Column chromatography on silica gel (Hexane/AcOEt 60:40), yellowish solid, mp 130-132 °C, 30% (85 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.50-2.65 (m, 1H, CH_2CFSO$_2$), 3.23-3.32 (m, 1H, CH_2CFSO$_2$), 4.06-4.27 (m, 2H, CH_2SO$_2$), 7.62-7.66 (m, 2H, Ar*H*), 7.78-7.80 (m, 1H, Ar*H*), 8.07-8.10 (m, 2H, Ar*H*). ^{13}C NMR (101 MHz, $CDCl_3$) δ 20.9 (d, *J* = 20.6 Hz, *C*H$_2$CFSO$_2$), 61.2 (d, *J* = 5.0 Hz, *C*H$_2$SO$_2$), 125.6 (d, *J* = 298 Hz, *C*F), 129.5 (Ar*C*H), 130.8 (Ar*C*H), 133.1 (Ar*C*H), 136.0 (Ar*C*). ^{19}F NMR (377 MHz, $CDCl_3$) δ -128.99 (ddd, *J* = 21.6, 8.0, 1.8 Hz). FT-IR (KBr, cm^{-1}) υ 557, 720, 1153, 1328, 1448, 2854, 2926, 3049. HRMS (ESI-TOF) m/z [M+Na]$^+$ calcd for $C_9H_9FO_4S_2Na$ 286.9818; found 286.9822.

2-fluoro-2-(phenylsulfonyl)tetrahydro-2*H*-thiopyran 1,1-dioxide-10b. Column chromatography on silica gel (Hexane/AcOEt 60:40), yellowish solid, mp 114-117, 50% (146 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.77-1.85 (m, 1H, CH_2CH$_2$CFSO$_2$), 1.99-2.23 (m, 3H, CH_2CH$_2$CFSO$_2$, CH_2CH$_2$SO$_2$), 2.65-2.72 (m, 1H, CH_2CFSO$_2$), 2.80-2.92 (m, 1H, CH_2CFSO$_2$), 3.18-3.31 (m, 2H, CH_2SO$_2$), 7.58-7.61 (m, 2H, Ar*H*), 7.74-7.77 (m, 1H, Ar*H*), 8.02-8.04 (m, 2H, Ar*H*). ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.5 (d, *J* = 4.1 Hz, *C*H$_2$CH$_2$CFSO$_2$), 23.6 (*C*H$_2$CH$_2$SO$_2$), 29.3 (d, *J* = 18.2 Hz, *C*H$_2$CFSO$_2$), 51.9 (*C*H$_2$SO$_2$), 111.8 (d, *J* = 251 Hz, *C*F), 129.0 (Ar*C*H), 131.1 (d, *J* = 1.2 Hz, Ar*C*H), 134.8 (Ar*C*), 135.5 (Ar*C*H). ^{19}F NMR (470 MHz, $CDCl_3$) δ -150.4 (m). FT-IR (KBr, cm^{-1}) υ 582, 867, 1160, 1328, 1451, 2862, 2926, 3444. HRMS (ESI-TOF) m/z [M+Na]$^+$ calcd for $C_{11}H_{13}FO_4S_2Na$ 315.0131; found 315.0148.

2-fluoro-2-(phenylsulfonyl)tetrahydrothiphene 1,1-dioxide-10c
Column chromatography on silica gel (Hexane/AcOEt 60:40), yellow oil, 50%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.23-2.39 (m, 2H, CH_2CH$_2$SO$_2$), 2.52-2.61 (m, 1H, CH_2CF), 3.04-3.17 (m, 1H, CH_2CF), 3.23-3.32 (m, 2H, CH_2SO$_2$), 7.61-7.64 (t, *J* = 7.6 Hz, 2H, Ar*H*), 7.7-7.78 (t, *J* = 7.4 Hz, 1H, Ar*H*), 8.06-8.07 (d, *J* = 7.7 Hz, 2H, Ar*H*). ^{13}C NMR (126 MHz, $CDCl_3$) δ 16.3 (*C*H$_2$CH$_2$SO$_2$), 28.8 (d, $^2J_{CF}$ = 19.5 Hz, *C*H$_2$CF), 50.9 (*C*H$_2$SO$_2$), 111.4 (d, *J* = 267.8 Hz, *C*F), 129.2 (Ar*C*H), 130.9 (Ar*C*H), 113.8 (Ar*C*), 135.7 (Ar*C*H); ^{19}F NMR (470 MHz, $CDCl_3$) δ -142.53 (dd, J_{HF} = 28.4, 21.2 Hz); FT-IR (NaCl, cm^{-1}) υ 572, 887, 1156, 1328,1450, 2860, 2926, 3060; HRMS (ESI-TOF) m/z [M+Na]$^+$ calcd for $C_{10}H_{11}FNaO_4S_2$ 300.9975; found 300.9980.

Determination of lipophilicity by RP-HPLC
Lipophilicity parameters of the cyclic sulfone derivatives were measured by an RP-HPLC technique.[28,29] Methanol solutions of the investigated compounds (0.25 mg/mL) were injected into a HPLC equipped with a Kinetex C18 column (150 × 4.6 mm, 5μ) from Phenomenex (Phenomenex Italy s.r.l., Castel Maggiore, BO, Italy). The cyclic sulfones were eluted at different mobile phase composition (0.05 increments of MeOH volume fraction in 10 mM ammonium formate buffer at pH 5, ranging between 0.70 and 0.30). All RP-HPLC measurements were carried out at 25 ± 1 °C, flow rate of 1.0 mL/min, at 254 nm wavelength on an Agilent 1260 infinity HPLC system (Agilent Technologies Italia, Milan), equipped with a diode array detector (DAD).
The logarithm of capacity factors (log k' = log (t_R-t_0)/t_0) of each compound at different mobile phase compositions have been calculated; t_R represents the retention time of the solute and t_0 is

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the column dead time, measured as the elution time of a KNO_3 solution in MeOH. For each compound, the log *k'* values increased linearly with decreasing MeOH volume fraction. The logarithm of capacity factors extrapolated to 100% aqueous mobile phase (log k'_w) were calculated from the linear regressions on at least five data points.

Lipophilicity was also computationally assessed with the BioLoom software vers. 1.7 (BioByte Corp. Claremont, CA, USA) and ACDLabs software, release 10.0 (Advanced Chemistry Development, Inc., Toronto, Canada).

Acknowledgements

We thank the University of Bari "A. Moro", the Polytechnic University of Bari, the Interuniversities Consortium CINMPIS and the project Laboratorio SISTEMA, (Code PONa300369) financed by Italian Miur. We are also grateful to Laura Carroccia, and Nicola Loi for their contribution. We thank Prof. Gerhard Ecker for support.

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DOI: 10.1039/C7OB00846E

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