

Regio- and Stereoselective Synthesis of Sulfur-Bearing Four-Membered Heterocycles: Direct Access to 2,4-Disubstituted Thietane 1-Oxides

Questa è la versione Post print del seguente articolo:

Original

Regio- and Stereoselective Synthesis of Sulfur-Bearing Four-Membered Heterocycles: Direct Access to 2,4-Disubstituted Thietane 1-Oxides / Degennaro, L., Carroccia, L., Parisi, G., Zenzola, M., Romanazzi, G., Fanelli, F., Pisano, L., Luisi, R.. - In: JOURNAL OF ORGANIC CHEMISTRY. - ISSN 0022-3263. - 80:24(2015), pp. 12201-12211. [10.1021/acs.joc.5b02126]

Availability:

This version is available at: 11388/179069 since: 2022-06-14T11:05:09Z

Publisher:

Published

DOI:10.1021/acs.joc.5b02126

Terms of use:

Chiunque può accedere liberamente al full text dei lavori resi disponibili come "Open Access".

Publisher copyright

note finali coverpage

(Article begins on next page)

1 Regio- and Stereoselective Synthesis of Sulfur-Bearing Four- 2 Membered Heterocycles: Direct Access to 2,4-Disubstituted Thietane 3 1-Oxides

4 Leonardo Degennaro,[†] Laura Carroccia,[†] Giovanna Parisi,[†] Marina Zenzola,[†] Giuseppe Romanazzi,^{§,||}
5 Flavio Fanelli,^{‡,⊥} Luisa Pisano,[‡] and Renzo Luisi^{*,†}

6 [†]Department of Pharmacy – Drug Sciences, University of Bari “A. Moro”, Via E. Orabona 4, 70125 Bari, Italy

7 [‡]Department of Chemistry and Pharmacy, University of Sassari, Via Vienna 2, 07100 Sassari, Italy

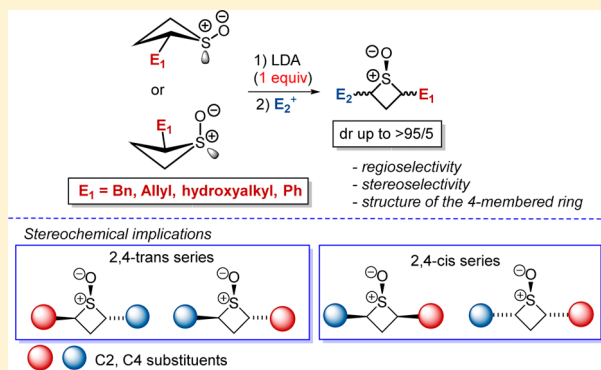
8 [§]DICATECh, Politecnico di Bari, Via Orabona 4, 70125 Bari, Italy

9 ^{||}CNR NANOTEC–Istituto di Nanotecnologia, Polo di Nanotecnologia c/o Campus Ecotekne, via Monteroni, 73100 Lecce, Italy

10 [⊥]CNR, Institute of Crystallography IC-CNR, Via E. Orabona 127/A, 70125 Bari, Italy

11 Supporting Information

12 **ABSTRACT:** Starting from readily available C2-substituted
13 thietane 1-oxides, a straightforward synthesis of new C2,C4-
14 disubstituted thietane 1-oxides has been developed by using a
15 lithiation/electrophilic trapping sequence. The chemical and
16 configurational stability of lithiated C2-substituted thietane 1-
17 oxides has been investigated as well as the stereochemical
18 implications for this process. The results demonstrate that a
19 stereoselective functionalization at the C2, C4 positions of a
20 thietane is feasible, leaving intact the four-membered ring.



21 ■ INTRODUCTION

22 Sulfur-containing compounds are present in several drugs and
23 biologically active structures and have pivotal importance in
24 medicinal chemistry. In fact, 2 of the 21 proteinogenic amino
25 acids contain sulfur, and some of the 2009 blockbuster drugs in
26 the U.S. were organosulfur compounds (Figure 1).¹ Other
27 interesting, and so far little explored, chemical entities bearing
28 the sulfur atom are thietanes, sulfur-bearing four-membered
29 heterocycles (FMHs) that are included in several bioactive
30 molecules (Figure 1). FMHs gained recently significant
31 prominence in medicinal chemistry and are considered as
32 privileged scaffolds in the drug-discovery process.² In the past
33 10 years, there has been a growing interest in structures bearing
34 a four-membered ring due to the possibility to explore new
35 regions of the chemical space and get new lead molecules. In a
36 recent review, Carreira highlighted this aspect focusing on
37 spirocyclic structures including FMHs.³ Nevertheless, between
38 the most common FMHs such as oxetanes, azetidines, and
39 thietanes, it appears that the latter system has received much
40 less attention.

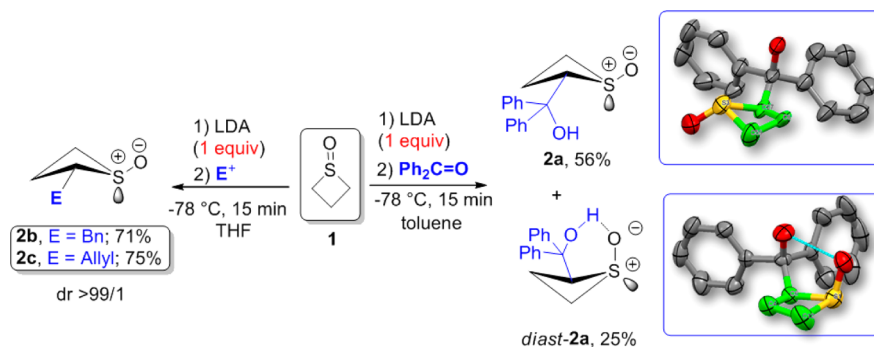
41 Most of the reported strategies for the preparation of
42 substituted thietanes rely on the intra- or intermolecular
43 displacement of a suitable leaving group by a sulfur nucleophile
44 or a [2 + 2] cycloaddition reaction as in the case of the thia
45 Paternò–Buchi reaction.⁴ However, these strategies could have

limits such as a competitive β -elimination and the use of stinking 46
reagents or regioselectivity problems as in the case of the 47
cycloaddition approach. 48

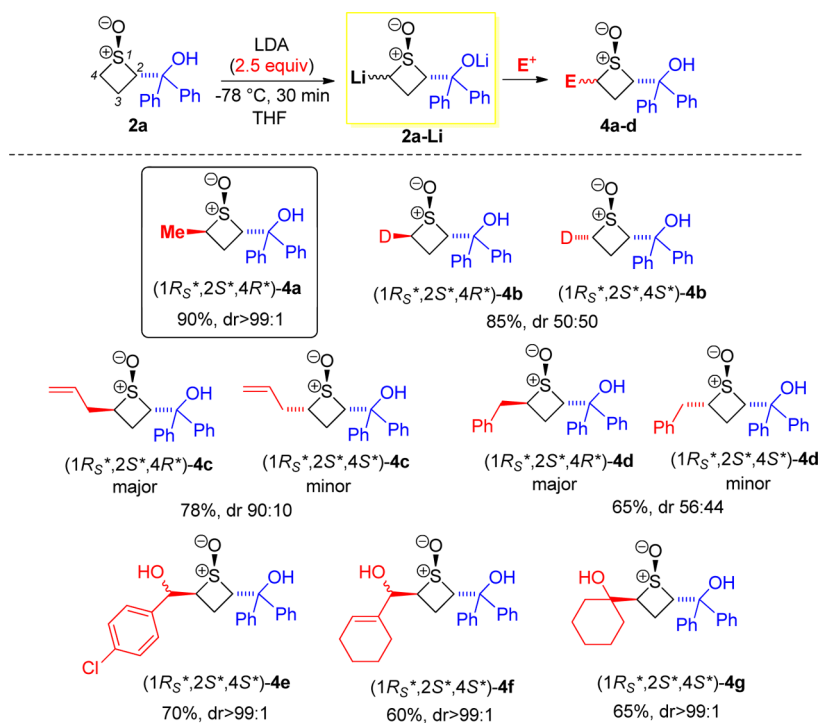
In a recent research program, run in our laboratory, on the 49
chemistry of small heterocycles and functionalized FMHs as 50
potential lead compounds,⁵ we became interested in the 51
preparation of C2-substituted thietane 1-oxides.⁶ By using a 52
direct approach, based on the functionalization of the simple 53
and readily available parent thietane 1-oxide **1**, several C2- 54
substituted thietane 1-oxides were obtained. In our preliminary 55
communication, it was disclosed that thietane 1-oxide could be 56
readily lithiated, with 1 equiv of LDA, at the C2 adjacent to the 57
sulfinyl group and effectively trapped with electrophiles. Being 58
1 a prochiral substrate, the C2 functionalization led to two 59
diastereoisomeric adducts **2** and *diast-2* with a variable degree 60
of stereoselectivity depending on the electrophile (Scheme 1). 61 st
However, the use of 2 equiv of LDA gave access to C2,C4 62
doubly substituted thietane 1-oxides via a stepwise lithiation/ 63
trapping mechanism, and a mixture of diastereomeric thietanes 64
cis-3 and *trans-3* was obtained. 65

This stepwise mechanism prompted us to investigate the 66
introduction of two different electrophiles, so allowing the 67

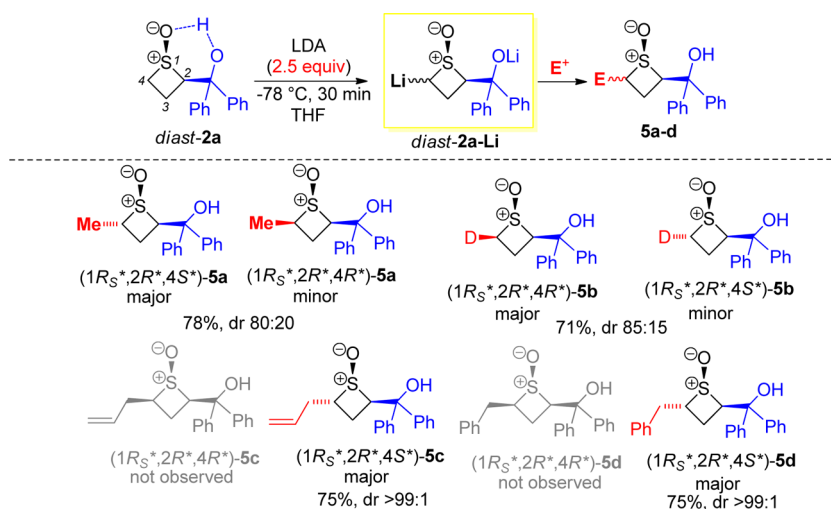
Scheme 3. Synthesis of C2-Functionalized Thietane 1-Oxides



Scheme 4. Lithiation/Substitution of Thietane 2a

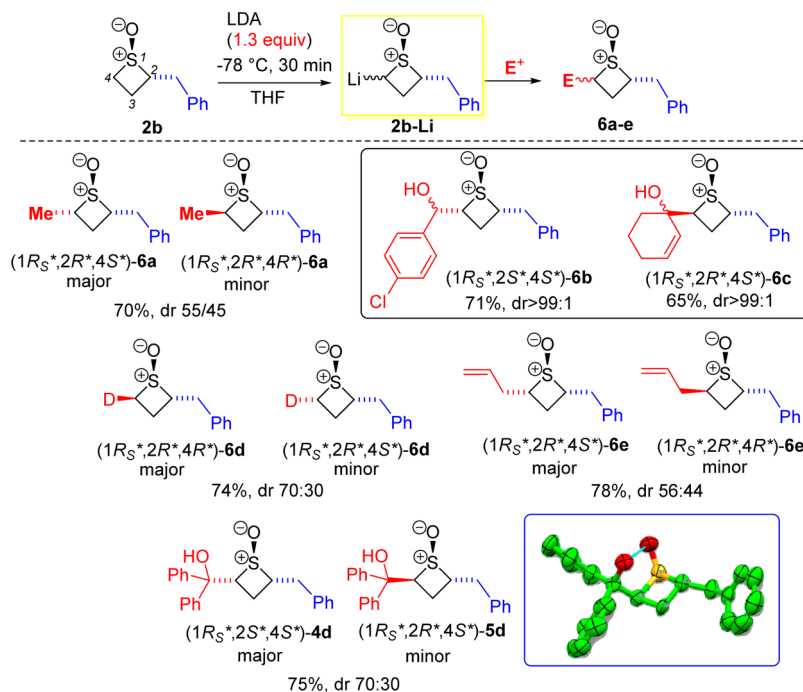


Scheme 5. Lithiation/Substitution of Thietane diast-2a



115 BnBr, allylBr, aldehyde, and ketones), leading to disubstituted
116 thietanes 4a–g (Scheme 4). Being the C4 prochiral, a new

stereogenic center was created upon lithiation. Nevertheless, a 117
variable degree of stereoselectivity was observed in the final 118



119 products **4a–g**, and mixtures of two diastereoisomers were
 120 obtained in most cases (Scheme 4). High stereoselectivity (dr >
 121 90:10) resulted only for the reactions of lithiated **2a** with MeI
 122 and allylBr, giving, respectively, thietanes **4a** and **4c**. By NMR
 123 experiments (see the SI), it was demonstrated that, in these
 124 latter cases, the introduced electrophile set preferentially *syn* to
 125 the sulfur oxygen, leading to a relative stereochemistry
 126 (1*R_S**, 2*S**, 4*R**) for the main stereoisomer.⁹ Deuteration and
 127 benzylation occurred with very low, if any, stereoselectivity,
 128 suggesting that the electrophile may be playing a role in
 129 determining the stereochemical course of the reaction.¹⁰ The
 130 use of carbonyl compounds (*p*-chlorobenzaldehyde, cyclo-
 131 hexanone, and cyclohexanone) resulted with a high level of
 132 stereoselectivity, giving thietanes (1*R_S**, 2*S**, 4*S**)-**4e–g**. Never-
 133 theless, the reactions resulted poorly selective with respect to
 134 the carbinolic carbon, and a 1:1 separable mixture of
 135 diastereoisomers were obtained in the reactions with the
 136 aromatic aldehyde and the prochiral ketone. The high level of
 137 stereoselectivity observed at the C4 of the thietane ring could
 138 be ascribed to both steric hindrance, due to the large C2
 139 substituent, and coordination effects brought by the carbonyl
 140 group. Attempts to use an epoxide as the electrophile failed,
 141 and unreacted starting material was recovered.

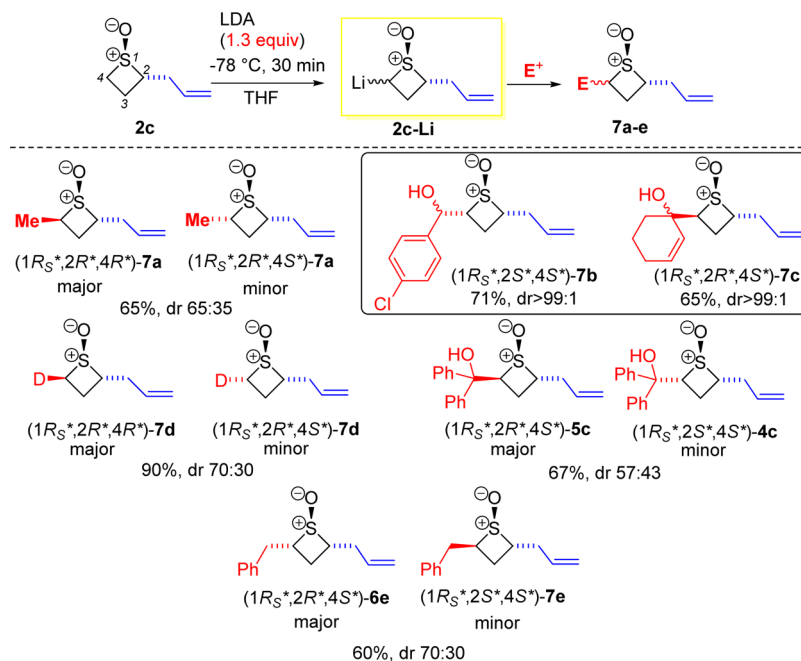
142 Next, we investigated the reactivity of *diast-2a*, whose
 143 stereochemistry was ascertained by X-ray analysis.⁸ From a
 144 structural point of view, *diast-2a* discloses marked differences
 145 with respect to **2a** such as a puckered conformation, due to an
 146 intramolecular hydrogen bond between the hydroxyalkyl
 147 moiety and the sulfoxide group, leading to a pseudoaxial
 148 sulfur–oxygen bond. We were keen to verify if such different
 149 structural features could affect the stereochemical course of the
 150 double functionalization. When *diast-2a* was lithiated under the
 151 same conditions used in the case of **2a** (2.5 equiv of LDA, –78
 152 °C, 30 min), and reacted with electrophiles, still mixtures of
 153 diastereoisomeric adducts **5a–d** were obtained (Scheme 5).
 154 Nevertheless, while deuteration reaction led mainly to
 155 diastereoisomer (1*R_S**, 2*R**, 4*R**)-**5b** (dr 70:30), a switch in

stereochemical preference was observed in methylation, 156
 allylation, and benzylation reactions perhaps due to steric 157
 reasons. In these cases, diastereoisomers (1*R_S**, 2*R**, 4*S**)-**5a**, 158
 (1*R_S**, 2*R**, 4*S**)-**5c**, and (1*R_S**, 2*R**, 4*S**)-**5d** were obtained with 159
 good stereoselectivity (Scheme 5). 160

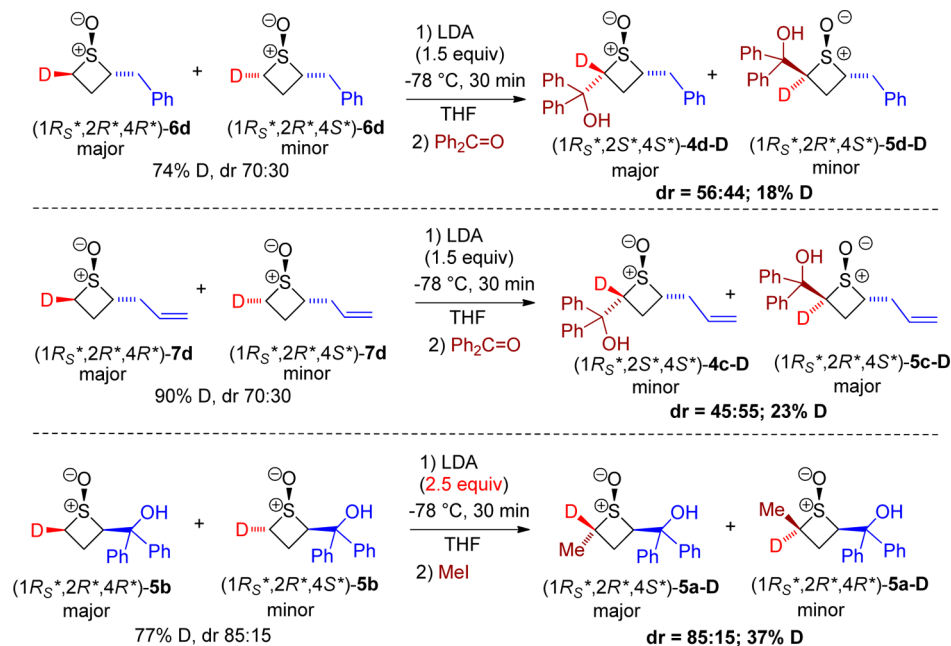
It is worth pointing out that, regardless of the degree of 161
 stereoselectivity observed in the lithiation/trapping of **2a** and 162
diast-2a, the availability of both diastereoisomers gives the 163
 possibility to potentially access three of the four possible 164
 stereoisomers of C2,C4-disubstituted thietane 1-oxides. In fact, 165
 the benzylation or allylation reactions of lithiated **2a** furnished 166
 stereoisomers (1*R_S**, 2*S**, 4*R**)-**4c,d** and (1*R_S**, 2*S**, 4*S**)-**4c,d**, 167
 while the same protocol applied on lithiated *diast-2a* gives 168
 derivatives (1*R_S**, 2*R**, 4*S**)-**5c,d** derivatives. Such stereochem- 169
 ical implications could be of great importance in drug discovery 170
 programs or when different stereoisomers need to be tested. 171

Alternatively, when only one stereoisomer of the C2- 172
 substituted thietane 1-oxide is available, as in the case of **2b** 173
 and **2c**, control on the stereochemistry could be achieved by 174
 switching the sequence of introduction of the electrophiles. To 175
 this end, the reactivity of thietanes **2b,c** was investigated. First, 176
2b was lithiated by using 1.3 equiv of LDA at –78 °C in THF 177
 as the solvent (Scheme 6). Trapping of **2b-Li** with electrophiles 178
 gave C2,C4-disubstituted thietanes **6a–e**. Modest to low levels 179
 of stereoselectivity were observed in the trapping reactions with 180
 MeI, MeOD, and allylBr, leading, respectively, to mixtures of 181
 (1*R_S**, 2*R**, 4*R**)-**6a,d,e** and (1*R_S**, 2*R**, 4*S**)-**6a,d,e** (Scheme 182
6).¹¹ In the reactions with benzophenone, a 70:30 mixture of 183
 thietanes (1*R_S**, 2*S**, 4*S**)-**4d** and (1*R_S**, 2*R**, 4*S**)-**5d** was 184
 obtained (Scheme 6). It is important to recall that this 185
 sequence gives the same stereoisomers observed in separate 186
 benzylation reactions carried out on lithiated **2a** and *diast-2a* 187
 (see Schemes 3 and 4) but with a different ratio. Even in this 188
 case, structure and relative stereochemistry of (1*R_S**, 2*R**, 4*S**)- 189
5d was unambiguously assigned by X-ray analysis.¹¹ In the 190
 reactions of **2b-Li** with *p*-chlorobenzaldehyde and cyclo- 191
 hexanone, leading, respectively, to (1*R_S**, 2*S**, 4*S**)-**6b** and 192

Scheme 7. Lithiation/Substitution of Thietane 2c



Scheme 8. Attempts to Establish Configurational Stability of Lithiated Thietane 1-Oxides



193 (1R_S*, 2R*, 4S*)-6c, an opposite and high stereochemical
 194 preference was observed (Scheme 6) with reference to the
 195 C4 of the heterocyclic ring.¹³

196 The reactivity of 2c was also investigated using the same
 197 conditions and electrophiles as in the case of 2b. The results are
 198 reported in Scheme 7. The lithiation/trapping of 2c occurred
 199 with modest stereoselectivity, just as observed in the case of 2b
 200 in the reactions with MeI, MeOD, and BnBr, leading,
 201 respectively, to diastereomeric mixtures of thietanes
 202 (1R_S*, 2R*, 4R*)-7a, d, e, (1R_S*, 2R*, 4S*)-7a, d, and
 203 (1R_S*, 2R*, 4S*)-6e. Again, an opposite and high stereochemical
 204 preference was observed in the reactions of 2c-Li with *p*-
 205 chlorobenzaldehyde and cyclohexanone, leading, respectively,

206 to (1R_S*, 2S*, 4S*)-7b and (1R_S*, 2R*, 4S*)-7c (Scheme 7).¹³ It
 207 is worth noting that, in the reaction of 2c-Li with
 208 benzophenone stereoisomers, (1R_S*, 2S*, 4S*)-4c and
 209 (1R_S*, 2R*, 4S*)-5c were obtained as seen in the lithiation/
 210 allylation of 2a and *diast*-2a. Similarly, benzylation of 2c-Li led
 211 to thietanes (1R_S*, 2S*, 4S*)-7e and (1R_S*, 2R*, 4S*)-6e, the
 212 latter still as the major stereoisomer, just as observed in
 213 lithiation/allylation of 2b (Scheme 6).

214 The above study allows us to assess that the lithiation/
 215 electrophile trapping sequence on C2-substituted thietane 1-
 216 oxides occurs with a variable degree of stereoselectivity
 217 depending on the electrophile and on the structure of the
 218 starting C2-substituted thietane. However, with the exception 218

219 of deuterated derivatives, diastereomeric C2,C4-disubstituted
220 thietane 1-oxides were easily separable by flash chromatog-
221 raphy, and their structure and relative stereochemistry were
222 established by NMR experiments and chemical shift
223 correlations (see the SI).

224 With the aim to shed light on the stereochemical course of
225 this lithiation/trapping sequence, the configurational stability of
226 lithiated thietane 1-oxides was investigated using deuterated
227 thietanes **5b**, **6d**, and **7d** as starting materials (Scheme 8). In
228 fact, as already reported by us in the case of aziridines, further
229 lithiation on deuterated systems could furnish evidence on the
230 configurational stability of the corresponding lithiated inter-
231 mediates, provided the existence of an intramolecular kinetic
232 isotope effect (KIE).¹⁴

233 Assuming an appreciable KIE, a preferential removal of the
234 proton over deuterium, in thietanes **5b**, **6d**, and **7d**, would lead
235 to lithiated intermediates possessing opposite stereochemistry
236 with respect to those generated from parent thietanes **2b,c** or
237 *diast-2a*. If the so-generated lithiated intermediates are
238 configurationally unstable, the diastereoselectivity observed,
239 upon reaction with an electrophile, should match that found in
240 the lithiation/trapping on protonated parent thietanes.
241 Conversely, with configurationally stable lithiated intermedi-
242 ates, trapping with the electrophile would lead to a different
243 diastereomeric ratio. As a consequence of the KIE, in both
244 cases, the final products should keep a high level of deuterium
245 content. Thus, simply comparing the diastereomeric ratios
246 resulting from the lithiation/trapping of deuterated thietanes
247 with that observed with the corresponding parent fully
248 protonated thietanes, evidence on the configurational stability
249 or instability of the lithiated intermediates could be obtained.
250 However, prior to running the lithiation reactions, the relative
251 stereochemistry of deuterated thietanes **5b**, **6d**, and **7d** needed
252 to be assessed. In the case of **5b**, NOESY experiments allowed
253 us to assign the relative configuration for (1*R*_S^{*},2*R*^{*},4*R*^{*})-**5b**
254 and (1*R*_S^{*},2*R*^{*},4*S*^{*})-**5b** (see the SI). In the case of thietanes **6d**
255 and **7d**, because of overlapping signals in their ¹H NMR
256 spectra, the relative stereochemistry was assigned by compar-
257 ison between real and simulated proton NMR spectra.¹⁵ We
258 have found this approach very useful and reliable for other
259 small-sized heterocycles,^{6,5c,d,16} and it allowed us to assign, even
260 in this case, the stereochemistry of deuterated thietanes
261 (1*R*_S^{*},2*R*^{*},4*R*^{*})-**6d**, (1*R*_S^{*},2*R*^{*},4*S*^{*})-**6d**, (1*R*_S^{*},2*R*^{*},4*R*^{*})-**7d**,
262 and (1*R*_S^{*},2*R*^{*},4*S*^{*})-**7d** (see the SI for details).

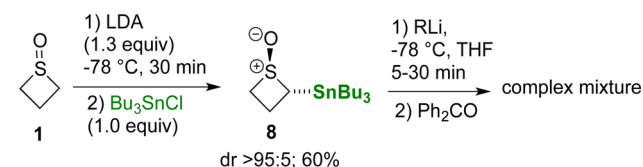
263 When a diastereomeric mixture of deuterated thietanes **6d**
264 and **7d** was subjected to lithiation, followed by trapping with
265 benzophenone, a mixture of the corresponding hydroxyalky-
266 lated adducts was obtained (Scheme 8). In both experiments,
267 ESI-MS analysis showed a sensible reduction of deuterium
268 content as a consequence of a weak KIE. As reported in
269 Scheme 8, thietanes **6d** or **7d** behave similarly. In the reaction
270 of (1*R*_S^{*},2*R*^{*},4*R*^{*})-**6d** and (1*R*_S^{*},2*R*^{*},4*S*^{*})-**6d**, the correspond-
271 ing adducts (1*R*_S^{*},2*S*^{*},4*S*^{*})-**4d-D** and (1*R*_S^{*},2*R*^{*},4*S*^{*})-**5d-D**
272 formed with 72% yield and a diastereomeric ratio of 56:44,
273 respectively. The deuterium content was reduced to 18% in
274 each diastereomer, which is about 75% less with respect to the
275 starting material. Similarly, lithiation/trapping of
276 (1*R*_S^{*},2*R*^{*},4*R*^{*})-**7d** and (1*R*_S^{*},2*R*^{*},4*S*^{*})-**7d** furnished thietanes
277 (1*R*_S^{*},2*S*^{*},4*S*^{*})-**4c-D** and (1*R*_S^{*},2*R*^{*},4*S*^{*})-**5c-D** in 65% yield
278 and 45:55 ratio, respectively. The deuterium content of the
279 products was reduced even in this case to 23% (about 70% less
280 than the starting material).

The lithiation/methylation of (1*R*_S^{*},2*R*^{*},4*R*^{*})-**5b** and 281
(1*R*_S^{*},2*R*^{*},4*S*^{*})-**5b** led to (1*R*_S^{*},2*R*^{*},4*S*^{*})-**5a-D** and 282
(1*R*_S^{*},2*R*^{*},4*R*^{*})-**5a-D** in 80% yield and 85:15 diastereomeric 283
ratio, respectively (Scheme 8). The deuterium erosion was of 284
about 48%, leaving a content of 37% in the final products. 285

The results show a not significant KIE effect for the lithiation 286
reactions, removal of deuterium being a competitive event.¹⁷ 287
However, some conclusion can be drawn considering the 288
observed stereochemical preferences. In fact, in all cases, the 289
diastereomeric ratios are slightly different from those observed 290
with the corresponding parent undeuterated thietanes (see 291
Schemes 5–7) but, most importantly, the major diaster- 292
eoisomers are the same. A reasonable hypothesis, according to 293
the above results, is that the lithiated intermediates are 294
configurationally unstable and likely equilibrate under the 295
reaction conditions. Thus, the observed diastereoselectivities 296
perhaps could depend only on the activation barrier of the 297
reaction with the electrophiles.¹⁸ 298

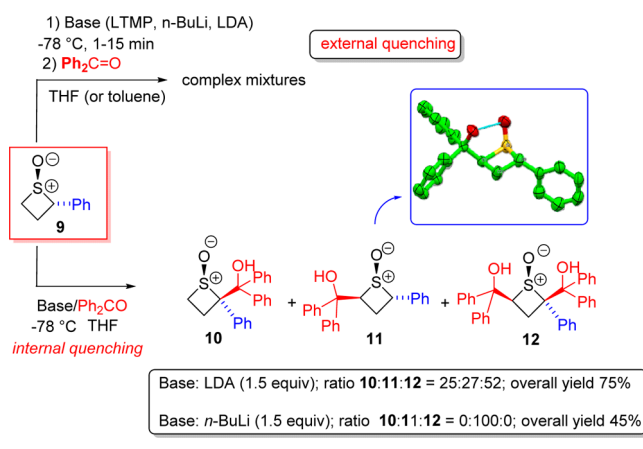
We also explored an alternative pathway, involving thietane 299
8, to get more insights about the configurational (in)stability of 300
lithiated thietanes. Thietane **8** was prepared by a lithiation/ 301
trapping sequence of **1**, using Bu₃SnCl as the electrophile. 302
Nevertheless, attempts to generate the corresponding lithiated 303
thietane stereospecifically,¹⁹ by a tin–lithium exchange reaction 304
on stannilated thietane **8**, failed (Scheme 9). 305 s9

Scheme 9



For the sake of comparison, we also investigated the 306
lithiation of 2-phenyl substituted thietane 1-oxide **9** (Scheme 307 s10
10). In this case, a switch in regioselectivity was expected for 308 s10

Scheme 10. Lithiation/Substitution of 2-Phenylthietane **9**



the presence of a benzylic position. However, when a solution 309
of **9** was added to a cooled (-78 °C) THF (or toluene) 310
solution of a base (LTMP, LDA or *n*-BuLi), further trapping 311
with benzophenone returned only complex reaction mixtures 312
likely because of an intrinsic chemical instability of the 313
corresponding lithiated 2-aryl thietane 1-oxide. With the aim to 314
get some insights on the regioselectivity, the internal quenching 315

316 of the lithiated 2-aryl thietane **9** was pursued. By addition of a
317 solution of LDA (1.5 equiv) to a precooled THF solution (-78
318 $^{\circ}\text{C}$) of **9** and benzophenone (1 equiv), a mixture of
319 functionalized 2-arylthietane 1-oxides **10**, **11**, and **12** was
320 obtained in 75% overall yield (Scheme 10). The presence of
321 derivatives **11** and **12** shows that the kinetic acidity of the
322 methylene protons competes very well with the thermodynamic
323 acidity of the benzylic proton.

324 In striking contrast, the use of the stronger organolithium *n*-
325 BuLi, under internal quenching conditions, led to higher
326 regioselectivity with the exclusive formation of adduct **11**,
327 whose structure has been confirmed by X-ray analysis,²⁰ in a
328 modest 45% yield due to the competitive addition of *n*-BuLi to
329 the electrophile (Scheme 10). It is worth noting the preferential
330 functionalization at the methylene position (kinetic preference)
331 by using *n*-BuLi, and the possibility to introduce a third
332 electrophile as in **12** when LDA is used as the base. The
333 stereochemistry of **10** and **12** likely suggests a configurational
334 stability of the corresponding lithiated thietane. However, this
335 kind of lithiated 2-arylthietane 1-oxides would deserve further
336 studies of their chemical and configurational stability that is out
337 of the scope of the present work.

338 ■ CONCLUSIONS

339 In conclusion, this investigation tries to fill a gap on the
340 reactivity and stereoselectivity of lithiated C2-functionalized
341 thietane 1-oxides. The results showed that the C4 position is
342 involved in the proton/lithium permutation and that likely the
343 corresponding lithiated thietane 1-oxides are configurationally
344 unstable. Concerning the stereoselectivity, it is dependent on
345 either the stereochemistry of the starting thietane 1-oxides or
346 the nature of the electrophile. A higher level of stereoselectivity
347 could be obtained with thietane *diast-2a* having a *syn*
348 relationship between the sulfinyl oxygen and the C2-
349 substituent. In the case of thietane 1-oxides **2a–c**, having a
350 *trans* relationship between the sulfinyl oxygen and the C2-
351 substituent, variable degrees of stereoselectivity have been
352 observed. Nevertheless, this approach allows us to prepare
353 three of the four possible stereoisomers of C2,C4-disubstituted
354 thietane 1-oxides by simply choosing one of the sequences
355 reported in Scheme 2. It is worth pointing out that, to the best
356 of our knowledge, this stereochemical aspect has never been
357 explored previously. Importantly, by this sequential lithiation/
358 trapping strategy, new products can be obtained starting from
359 the readily available thietane 1-oxide **1**, and leaving intact the
360 four-membered ring.²¹ Further developments on the asym-
361 metric version of this strategy are underway in our laboratory
362 and will be reported in due course.

363 ■ EXPERIMENTAL SECTION

364 **General Methods.** THF was freshly distilled under a nitrogen
365 atmosphere over Na/benzophenone. Toluene was freshly distilled
366 under a nitrogen atmosphere over CaH₂. Diisopropylamine (DIPA)
367 was distilled over finely powdered CaH₂, *n*-butyllithium was purchased
368 as hexane solution, and the title was established by a titration
369 method.²² All the other chemicals were commercially available and
370 used without further purification. Magnetic resonance spectra were
371 recorded using 400, 500, and 600 MHz spectrometers. For the ¹H, ¹³C
372 NMR spectra (¹H NMR 400, 500, 600 MHz, ¹³C NMR 100, 125, 150
373 MHz), CDCl₃, methanol-*d*₄, and toluene-*d*₈ were used as the solvents.
374 MS-ESI analyses were performed on an LC/MSD trap system VL.
375 Melting points were uncorrected. GC-MS spectrometry analyses were
376 carried out on a gas chromatograph (dimethylsilicon capillary column,
377 30 m, 0.25 mm i.d.) equipped with a mass selective detector operating

at 70 eV (EI). The high-resolution mass spectrometry (HRMS) 378
analyses were performed using a mass spectrometer equipped with an 379
electrospray ion source (ESI) operated in positive ion mode and a 380
time-of-flight analyzer. The sample solutions (CH₃OH) were 381
introduced by continuous infusion with a syringe pump at a flow 382
rate of 180 $\mu\text{L min}^{-1}$. The instrument was operated with end-plate 383
offset and capillary voltages set to -500 and -4500 V, respectively. 384
The nebulizer pressure was 0.4 bar (N₂), and the drying gas (N₂) flow 385
rate was 4.0 L min^{-1} . The capillary exit and skimmer voltages were 90 386
and 30 V, respectively. The drying gas temperature was set at 180 $^{\circ}\text{C}$. 387
The calibration was carried out with a sodium formate solution (10 388
mM NaOH in isopropanol/water 1:1 (+0.2% HCOOH). For flash 389
chromatography, silica gel 60, 0.04–0.063 mm particle size was used. 390
All reactions involving air-sensitive reagents were performed under 391
argon in oven-dried glassware using a syringe septum cap technique. 392

General Procedure for Lithiation/Electrophile Trapping Sequence on C2-Substituted Thietane 1-Oxide.

Starting 393
materials were prepared following a reported procedure.⁶ To a 395
stirred solution of DIPA (2.5 equiv for **2a** and *diast-2a* and 1.3 equiv 396
for **2b,c**) in 8.0 mL of dry THF at 0 $^{\circ}\text{C}$, a solution of *n*-BuLi (2.5 M in 397
hexane, 2.5 equiv for **2a** and *diast-2a* and 1.3 equiv for **2b,c**) was added 398
dropwise. After 20 min at 0 $^{\circ}\text{C}$, the solution of LDA was cooled down 399
to -78 $^{\circ}\text{C}$ and thietanes 1-oxide (1.0 mmol, 1.0 equiv) in 2.0 mL of 400
dry THF was added dropwise. After stirring for 30 min at -78 $^{\circ}\text{C}$, the 401
electrophile (1.3 equiv) was added neat if liquid and in 1.0 mL of 402
solvent if solid. After the reaction was complete, as ascertained by GC 403
or TLC, the reaction mixture was quenched with 2 mL of saturated 404
NH₄Cl, poured in water (10 mL), and extracted with AcOEt (3 \times 10 405
mL). The combined organic layers were dried (Na₂SO₄), filtered, and 406
concentrated in vacuo. Flash chromatography on silica gel (Hexane/
AcOEt) afforded 2,4-disubstituted thietanes 1-oxides. 407

(1*R*₅*,2*S**,4*R**)-2-(Hydroxydiphenylmethyl)-4-methylthietane 1- 409
Oxide (1*R*₅*,2*S**,4*R**)-4*a*. Column chromatography on silica gel 410
(Hexane/AcOEt 70:30), pale yellow solid, mp 173–176 $^{\circ}\text{C}$, 90% (255 411
mg). ¹H NMR (600 MHz, CDCl₃) δ 1.51 (d, *J* = 7 Hz, 3 H), 1.82 (t, *J* 412
= 11 Hz, 1 H), 2.45–2.55 (m, 1 H), 2.8 (br s, OH), 3.44 (quintet, *J* = 413
7 Hz, 1 H), 4.38 (t, *J* = 9 Hz, 1 H), 7.20–7.25 (m, 1 H), 7.25–7.30 414
(m, 5 H), 7.30–7.40 (m, 2 H), 7.50–7.55 (m, 2 H). ¹³C NMR (125 415
MHz, CDCl₃) δ 0.2, 22.1, 47.4, 71.8, 78.6, 125.9, 127.3, 127.5, 128.2, 416
128.4, 128.9, 143.7, 144.4. FT-IR (KBr, cm^{-1}) ν 699, 747, 1002, 1035, 417
1170, 1447, 2953, 3317. HRMS (ESI-TOF) *m/z* [M + Na]⁺ calcd for 418
C₁₇H₁₈SO₂Na 309.0920; found 309.0927.

(1*R*₅*,2*S**,4*R**)/(1*R*₅*,2*S**,4*S**)-4*b*. Mixture of diastereoisomers *dr* 420
50:50. Column chromatography on silica gel (Hexane/AcOEt 70:30), 421
waxy solid, 85% D (235 mg). ¹H NMR (600 MHz, CDCl₃) δ 1.96– 422
2.02 (m, 1 H), 2.07–2.15 (m, overlapping s at 2.10 Acetone, 1 H), 423
2.75 (bs, 1 H), 2.87–2.93 (m, 0.6 H), 3.30–3.34 (m, 0.57 H), 4.30 424
(dd, *J* = 9.9, 11.4 Hz, 1 H), 7.16–7.19 (m, 1 H), 7.22–7.26 (m, 5 H), 425
7.29–7.32 (m, 2 H), 7.45–7.46 (m, 2 H). ¹³C NMR (125 MHz, 426
CDCl₃) δ 13.1, 46.4 (t, *J* = 22.2 Hz), 46.5 (t, *J* = 24.4 Hz), 46.7, 75.4, 427
75.5, 78.3, 126.0, 127.4, 127.5, 127.6, 128.3, 128.5, 128.9, 143.8, 144.3. 428
ESI-MS: *m/z* (rel. int.): 295 [M_H + Na]⁺(32); 296 [M_D + Na]⁺(100). 429

(1*R*₅*,2*S**,4*S**)-2-(Hydroxydiphenylmethyl)-4-(3-propenyl)- 430
thietane 1-Oxide (1*R*₅*,2*S**,4*S**)-4*c*. Column chromatography on 431
silica gel (Hexane/AcOEt 50:50), white solid mp 144–146 $^{\circ}\text{C}$, 8% (24 432
mg). ¹H NMR (600 MHz, CDCl₃) δ 1.81 (q, *J* = 12.1 Hz, 1 H), 2.05– 433
2.14 (m, 1 H), 2.32–2.39 (m, 1 H), 2.46–2.54 (m, 1 H), 3.10–3.19 434
(m, 1 H), 4.07 (dd, *J* = 11.6, 9.7 Hz, 1 H), 5.00–5.08 (m, 2 H), 5.67 435
(ddt, *J* = 17.0, 10.2, 6.7 Hz, 1 H), 7.14–7.31 (m, 8 H), 7.44–7.46 (m, 436
2 H). ¹³C NMR (125 MHz, CDCl₃) δ 19.1, 35.9, 61.0, 71.1, 78.2, 437
118.3, 125.9, 127.4, 127.5, 128.3, 128.4, 128.9, 133.1, 143.9, 144.4. FT- 438
IR (KBr, cm^{-1}) ν 700, 749, 764, 1043, 1266, 1447, 2981, 3056, 3272. 439
HRMS (ESI-TOF) *m/z* [M + Na]⁺ calcd for C₁₉H₂₀SO₂Na 335.1076; 440
found 335.1069. 441

(1*R*₅*,2*S**,4*R**)-2-(Hydroxydiphenylmethyl)-4-(3-propenyl)- 442
thietane 1-Oxide (1*R*₅*,2*S**,4*R**)-4*c*. Column chromatography on 443
silica gel (Hexane/AcOEt 70:30), pale yellow solid, mp 173–176 $^{\circ}\text{C}$, 444
70%, (219 mg). ¹H NMR (600 MHz, CDCl₃) δ 1.85–1.92 (m, 1 H), 445
2.36 (dt, *J* = 9.5, 13.5 Hz, 2 H), 2.62–2.71 (m, 1H), 3.23–4.14 (m, 1 446
H), 4.25 (t, *J* = 10.4 Hz, 1 H), 4.98–5.05 (m, 2 H), 5.63–5.73 (m, 1 447

448 H), 7.13–7.16 (m, 1 H), 7.18–7.22 (m, 5 H), 7.25–7.27 (m, 2 H),
449 7.41–7.42 (m, 2 H). ¹³C NMR (125 MHz, CDCl₃) δ 20.4, 30.7, 50.7,
450 71.5, 78.3, 117.8, 125.8, 127.2, 128.3, 128.7, 133.6, 143.7, 144.3. FT-IR
451 (KBr, cm⁻¹) ν 698, 754, 913, 1052, 1447, 1493, 2948, 3059, 3256.
452 HRMS (ESI-TOF) *m/z* [M + Na]⁺ calcd for C₁₉H₂₀SO₂Na 335.1076;
453 found 335.1069.

454 (1*R*₅*,2*S**,4*S**)-4-Benzyl-2-(hydroxydiphenylmethyl)thietane 1-
455 Oxide (1*R*₅*,2*S**,4*S**)-4*d*. Column chromatography on silica gel
456 (Hexane/AcOEt 70:30), white solid, mp 128–131 °C. 29% (105 mg).
457 ¹H NMR (600 MHz, CDCl₃) δ 1.80 (q, *J* = 12 Hz, 1 H), 1.94–2.00
458 (m, 1 H), 2.76 (dd, *J* = 10, 14 Hz, 1 H), 3.14 (dd, *J* = 6, 14 Hz, 1 H),
459 3.01 (bs, 1 H, OH), 3.24–3.30 (m, 1 H), 4.03 (t, *J* = 11 Hz, 1 H), 7.05
460 (d, *J* = 8 Hz, 2 H), 7.11–7.13 (m, 2H), 7.17–7.21 (m, 7H), 7.25 (t, *J* =
461 8 Hz, 2H), 7.43 (d, *J* = 8 Hz, 2H). ¹³C NMR (125 MHz, CDCl₃) δ
462 19.4, 37.9, 62.3, 71.3, 78.0, 125.9, 126.9, 127.3₉, 127.4₃, 128.1, 128.4,
463 128.7, 128.7₉, 128.8₄, 137.4, 144.0, 144.5. FT-IR (film, cm⁻¹) ν 705,
464 759, 1027, 1059, 1166, 1343, 1447, 1496, 1603, 2918, 3026, 3062,
465 3314. HRMS (ESI-TOF) *m/z* [M + Na]⁺ calcd for C₂₃H₂₂SO₂Na
466 385.1233; found 385.1216.

467 (1*R*₅*,2*S**,4*R**)-4-Benzyl-2-(hydroxydiphenylmethyl)thietane 1-
468 Oxide (1*R*₅*,2*S**,4*R**)-4*d*. Column chromatography on silica gel
469 (Hexane/AcOEt 70:30), pale yellow solid, mp 139–141 °C. 36% (134
470 mg). ¹H NMR (600 MHz, CDCl₃) δ 2.03–2.11 (m, 1 H), 2.46 (ddd, *J*
471 = 9, 10, 13 Hz, 1 H), 2.97 (dd, *J* = 10, 14 Hz, 1 H), 3.41 (dd, *J* = 6, 14
472 Hz, 1 H), 3.51–3.59 (m, 1H), 4.38–4.41 (m, 1 H), 7.20–7.25 (m, 4
473 H), 7.28–7.32 (m, 7 H), 7.36–7.38 (m, 2 H), 7.52–7.54 (m, 2 H).
474 ¹³C NMR (125 MHz, CDCl₃) δ 21.1, 32.3, 52.7, 71.4, 78.5, 125.9,
475 127.2, 128.5, 128.8, 128.9, 129.3, 137.8, 143.7, 144.3. FT-IR (KBr,
476 cm⁻¹) ν 700, 754, 1032, 1384, 1448, 1494, 1601, 1628, 2924, 3027,
477 3059, 3418. HRMS (ESI-TOF) *m/z* [M + Na]⁺ calcd for
478 C₂₃H₂₂SO₂Na 385.1233; found 385.1247.

479 (1*R*₅*,2*S**,4*S**)-2-(Hydroxydiphenylmethyl)-4-(4-chlorophenyl-
480 hydroxymethyl)thietane 1-Oxide (1*R*₅*,2*S**,4*S**)-4*e*. First eluted
481 diastereoisomer. Column chromatography on silica gel (Hexane/
482 AcOEt 50:50), white solid mp. 186–188 °C. 35% (144 mg). ¹H NMR
483 (600 MHz, CD₃OD) δ 2.47 (m, 1 H), 2.78–2.83 (m, 1 H), 3.59–3.62
484 (m, 1 H), 4.73 (t, *J* = 10.1 Hz, 1 H), 5.33 (d, *J* = 4.6 Hz, 1H), 7.23–
485 7.27 (m, 2 H), 7.31–7.33 (m, 6H), 7.37–7.41 (m, 4H), 7.50 (d, *J* = 9.1
486 Hz, 2H). ¹³C NMR (125 MHz, CDCl₃) δ 19.3, 57.0, 69.3, 74.5, 78.9,
487 127.4, 127.9, 128.4, 128.5, 128.9, 129.3₀, 129.3₁, 129.5, 134.3, 142.2,
488 145.7, 145.9. FT-IR (KBr, cm⁻¹) ν 699, 1004, 1013, 1399, 1447, 1491,
489 1598, 3058, 3390. HRMS (ESI-TOF) *m/z* [M + Na] calcd for
490 C₂₃H₂₁ClSO₃Na 435.0792; found 435.0787.

491 (1*R*₅*,2*S**,4*S**)-2-(hydroxydiphenylmethyl)-4-(4-chlorophenyl-
492 hydroxymethyl)thietane 1-Oxide (1*R*₅*,2*S**,4*S**)-4*e*. Second eluted
493 diastereoisomer. Column chromatography on silica gel (Hexane/
494 AcOEt 50:50), white solid, mp 164–166 °C. 35% (147 mg). ¹H NMR
495 (600 MHz, CDCl₃) δ 1.94–1.99 (m, 1 H), 2.36–2.41 (m, 1 H), 3.49–
496 3.52 (m, 1 H), 4.15 (bs, 1 H), 4.45 (t, *J* = 10.5 Hz, 1 H), 5.39 (d, *J* =
497 9.5 Hz, 1 H), 7.17–7.28 (m, 10 H), 7.34 (t, *J* = 7.7 Hz, 2 H), 7.44 (d, *J*
498 = 7.7 Hz, 2H). ¹³C NMR (125 MHz, CDCl₃) δ 18.6, 56.0, 71.4, 73.5,
499 78.5, 125.9, 127.0, 127.9, 128.57, 128.65, 128.70, 129.08, 129.14,
500 134.5, 138.2, 143.2, 143.8. FT-IR (KBr, cm⁻¹) ν 701, 1013, 1032,
501 1447, 1491, 1638, 1733, 2924, 3413. HRMS (ESI-TOF) *m/z* [M +
502 Na]⁺ calcd for C₂₃H₂₁ClSO₃Na 435.0792; found 435.0790.

503 (1*R*₅*,2*S**,4*S**)-2-(Hydroxydiphenylmethyl)-4-(1-hydroxy-
504 cyclohex-2-en-1-yl)thietane 1-Oxide (1*R*₅*,2*S**,4*S**)-4*f*. First eluted
505 diastereoisomer. Column chromatography on silica gel (Hexane/
506 AcOEt 70:30), waxy solid. 31% (109 mg). ¹H NMR (500 MHz,
507 CDCl₃) δ 1.39–1.47 (m, 1H), 1.48–1.57 (m, 1H), 1.71–1.85 (m, 2H)
508 1.94–2.02 (m, 1H) 2.03–2.13 (m, 1H) 2.53–2.62 (m, 1H), 2.83–
509 2.92 (m, 1H), 3.34 (dd, *J* = 9.9, 5.7 Hz, 1H), 4.56 (dd, *J* = 10.6, 9.4 Hz,
510 1H) 5.86 (dt, *J* = 10.1, 3.7 Hz, 1H), 6.08 (d, *J* = 10.2 Hz, 1H), 7.28–
511 7.35 (m, 6H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.49 (d, *J* = 8.0 Hz, 2H). ¹³C
512 NMR (125 MHz, CDCl₃) δ 18.4, 19.3, 25.1, 32.5, 56.0, 72.0, 72.8,
513 78.6, 125.8, 126.6, 127.6, 128.2, 128.5, 128.9, 129.9, 130.9, 143.2,
514 143.7. FT-IR (KBr, cm⁻¹) ν 700, 732, 910, 1031, 1165, 1447, 1493,
515 1646, 2929, 3400. HRMS (ESI-TOF) *m/z* [M + Na]⁺ calcd for
516 C₂₂H₂₄SO₃Na 391.1338; found 391.1345.

(1*R*₅*,2*S**,4*S**)-2-(Hydroxydiphenylmethyl)-4-(1-hydroxy- 517
518 cyclohex-2-en-1-yl)thietane 1-Oxide (1*R*₅*,2*S**,4*S**)-4*f*. Second
519 eluted diastereoisomer. Column chromatography on silica gel
520 (Hexane/AcOEt 70:30), sticky oil. 30% (110 mg). ¹H NMR (500
521 MHz, CDCl₃) δ 1.57–1.68 (m, 1H), 1.80–1.88 (m, 1H), 1.89–2.03
522 (m, 2H), 2.01–2.16 (m, 2H), 2.58–2.66 (m, 1H), 2.93–3.01 (m, 1H),
523 3.32 (dd, *J* = 9.8, 6.0 Hz, 1H), 4.56 (t, *J* = Hz, 1H), 5.58 (d, *J* = 10.1
524 Hz, 1H), 5.90–5.83 (m, 1H) 7.25–7.35 (m, 6H), 7.36–7.41 (m, 2H),
525 7.47–7.50 (m, 2H). ¹³C NMR (125 MHz, CDCl₃) δ 18.7, 19.7, 24.9,
526 29.7, 35.5, 55.3, 71.6, 72.8, 78.6, 1258.8, 126.6, 126.9, 127.6, 128.2,
527 128.5, 128.9, 131.4, 143.2, 143.7. FT-IR (KBr, cm⁻¹) ν 700, 735, 910,
528 1031, 1160, 1448, 1493, 1713, 2929, 3369. HRMS (ESI-TOF) *m/z* [M
529 + Na]⁺ calcd for C₂₂H₂₄SO₃Na 391.1338; found 391.1343.

(1*R*₅*,2*S**,4*S**)-2-(Hydroxydiphenylmethyl)-4-(1-hydroxy- 530
531 cyclohexyl)thietane 1-Oxide (1*R*₅*,2*S**,4*S**)-4*g*. Column chromatog-
532 raphy on silica gel (Hexane/AcOEt 30:70), sticky oil. 65% (240 mg).
533 ¹H NMR (500 MHz, CDCl₃) δ 1.08–1.22 (m, 1H), 1.24–1.34 (m,
534 2H), 1.35–1.52 (m, 3H), 1.54–1.78 (m, 4H) 2.5–2.57 (m, 1 H),
535 2.87–2.96 (m, 1 H), 3.24 (dd, *J* = 9.8, 5.9 Hz, 1H), 4.53 (dd, *J* = 11.0,
536 8.7 Hz, 1H), 7.34–7.24 (m, 6H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.48 (d, *J* =
537 7.8 Hz, 2H). FT-IR (film, cm⁻¹) ν 701, 753, 999, 1264, 1447, 1493,
538 1599, 1694, 2858, 2932, 3058, 3391. ¹³C NMR (125 MHz, CDCl₃) δ
539 19.3, 21.2, 21.4, 25.9, 33.3, 34.0, 55.6, 71.7, 74.5, 48.5, 125.9, 126.6,
540 127.6, 128.1, 128.5, 128.8, 143.2, 143.8. HRMS (ESI-TOF) *m/z* [M +
541 Na]⁺ calcd for C₂₂H₂₆SO₃Na 393.1495; found 393.1504.

(1*R*₅*,2*R**,4*S**)-2-(Hydroxydiphenylmethyl)-4-methylthietane 1- 542
543 Oxide (1*R*₅*,2*R**,4*S**)-5*a*. Column chromatography on silica gel
544 (Hexane/AcOEt 70:30), pale yellow solid, mp 134–137 °C. 62% (178
545 mg). ¹H NMR (600 MHz, CDCl₃) δ 1.43 (d, *J* = 7 Hz, 3 H), 1.92–
546 2.08 (m, 1H), 3.03–3.20 (m, 1 H), 3.58–3.70 (m, 1 H), 4.25–4.42
547 (m, 1 H), 7.11–7.13 (m, 1 H), 7.17–7.23 (m, 3 H), 7.25–7.33 (m, 4
548 H), 7.46 (d, *J* = 8 Hz, 2 H). ¹³C NMR (125 MHz, CDCl₃) δ 17.6,
549 26.1, 55.2, 59.4, 80.2, 125.8, 126.0, 127.0, 127.6, 128.4, 128.7, 143.6,
550 145.9. FT-IR (KBr, cm⁻¹) ν 701, 740, 758, 984, 998, 1068, 1172, 1258,
551 1407, 1450, 1493, 2962, 3026, 3362. HRMS (ESI-TOF) *m/z* [M +
552 Na]⁺ calcd for C₁₇H₁₈SO₂Na 309.0920; found 309.0928.

(1*R*₅*,2*R**,4*R**)-2-(Hydroxydiphenylmethyl)-4-methylthietane 1- 553
554 Oxide (1*R*₅*,2*R**,4*R**)-5*a*. Column chromatography on silica gel
555 (Hexane/AcOEt 70:30), pale yellow oil. 16% (45 mg). ¹H NMR (600
556 MHz, CDCl₃) δ 1.31 (d, *J* = 6.7 Hz, 3 H), 2.70 (dt, *J* = 7.2, 11.2 Hz,
557 1H), 3.39–3.50 (m, 2 H), 4.02 (dd, *J* = 8.0, 10.5 Hz, 1 H), 7.11–7.13
558 (m, 1 H), 7.18–7.22 (m, 2 H), 7.25–7.33 (m, 5 H), 7.51–7.53 (m, 4
559 H). ¹³C NMR (125 MHz, CDCl₃) δ 12.0, 31.6, 47.8, 54.3, 79.6, 125.6,
560 126.1, 127.2, 127.7, 128.4, 128.8, 143.7, 145.2. FT-IR (film, cm⁻¹) ν
561 701, 740, 758, 984, 998, 1068, 1172, 1258, 1407, 1450, 1493, 2962,
562 3026, 3362. HRMS (ESI-TOF) *m/z* [M + Na]⁺ calcd for
563 C₁₇H₁₈SO₂Na 309.0920; found 309.0918.

(1*R*₅*,2*R**,4*R**)/(1*R*₅*,2*R**,4*S**)-5*b*. Mixture of diastereoisomers *dr* 564
565 70:30. Column chromatography on silica gel (Hexane/AcOEt 70:30),
566 white solid, 71% D (194 mg). ¹H NMR (600 MHz, CDCl₃) δ 2.39–
567 2.46 (m, 1 H), 3.08–3.14 (m, 0.38 H), 3.28–3.35 (m, 1 H), 3.41–3.47
568 (m, 0.82 H), 4.35 (t, *J* = 8.3 Hz, 0.90 H), 5.77 (bs, 1 H), 7.09–7.29
569 (m, 8 H), 7.43–7.46 (m, 2 H). 295 [M_H + Na]⁺(37); 296 [M_D +
570 Na]⁺(100).

(1*R*₅*,2*R**,4*S**)-2-(Hydroxydiphenylmethyl)-4-(3-propenyl)- 571
572 thietane 1-Oxide (1*R*₅*,2*R**,4*S**)-5*c*. Column chromatography on
573 silica gel (Hexane/AcOEt 50:50), white solid, mp 132–135 °C. 75%
574 (234 mg). ¹H NMR (600 MHz, CDCl₃) δ 2.01–2.07 (m, 1 H), 2.41–
575 2.46 (m, 1 H), 2.50–2.55 (m, 1 H), 3.03 (ddd, *J* = 13.4, 11.4, 6.2 Hz, 1
576 H), 3.59–3.65 (m, 1 H), 4.33 (dd, *J* = 9.5, 6.2 Hz, 1 H), 5.07–5.10
577 (m, 2 H), 5.49 (bs, 1 H), 5.67–5.75 (m 1 H), 7.10 (t, *J* = 7.7 Hz, 1 H),
578 7.16–7.22 (m, 3 H), 7.26–7.29 (m, 4 H), 7.45 (d, *J* = 8.7 Hz, 2 H).
579 ¹³C NMR (125 MHz, CDCl₃) δ 23.8, 36.1, 55.4, 63.0, 80.2, 118.7,
580 125.8, 125.9, 127.1, 127.6, 128.4, 128.7, 132.8, 143.6, 145.9. FT-IR
581 (KBr, cm⁻¹) ν 703, 739, 1013, 1266, 1450, 2984, 3054, 3342. HRMS
582 (ESI-TOF) *m/z* [M + Na]⁺ calcd for C₁₉H₂₀SO₂Na 335.1076; found
583 335.1066.

(1*R*₅*,2*R**,4*S**)-2-(Hydroxydiphenylmethyl)-4-benzylthietane 1- 584
585 Oxide (1*R*₅*,2*R**,4*S**)-5*d*. Column chromatography on silica gel
586 (Hexane/AcOEt 70:30), white solid, mp 143–146 °C. 75% (271 mg). 586

587 ¹H NMR (600 MHz, CDCl₃) δ 2.07 (ddd, *J* = 8, 10, 13 Hz, 1 H),
588 2.94–3.00 (m, 2 H), 3.15 (dd, *J* = 7, 14 Hz, 1 H), 3.80–3.86 (m, 1 H),
589 4.29 (ddd, *J* = 1, 6, 10 Hz, 1 H), 5.44 (bs, 1 H, OH), 7.08–7.11 (m, 3
590 H), 7.15–7.27 (m, 10H), 7.42–7.44 (m, 2 H). ¹³C NMR (125 MHz,
591 CDCl₃) δ 23.9, 38.1, 55.4, 65.5, 80.2, 125.7, 125.9, 127.0, 127.2, 127.6,
592 128.4, 128.7, 128.8₉, 128.9₄, 136.9, 143.6, 145.9. FT-IR (KBr, cm⁻¹) *ν*
593 675, 700, 759, 769, 1016, 1033, 1060, 1178, 1193, 1407, 1450, 1493,
594 1601, 2919, 2935, 3025, 3308. HRMS (ESI-TOF) *m/z* [M + Na]⁺
595 calcd for C₂₃H₂₂SO₂Na 385.1233; found 385.1216.
596 (1*R*₅*,2*R**,4*S**)-2-Benzyl-4-methylthietane 1-Oxide
597 (1*R*₅*,2*R**,4*S**)-6a. Column chromatography on silica gel (AcOEt),
598 pale yellow oil. 39% (75 mg). ¹H NMR (500 MHz, CDCl₃) δ 1.36 (q,
599 *J* = 12.2 Hz, 1H), 1.45 (d, *J* = 6.8 Hz, 3H), 2.49 (dt, *J* = 12.6, 9.5 Hz,
600 1H), 2.97 (dd, *J* = 14.2, 8.5 Hz, 1H), 3.18–3.23 (M, 1H), 3.25 (dd, *J* =
601 14.0, 6.4 Hz, 1H), 7.19 (d, *J* = 7.3 Hz, 2H), 7.24 (t, *J* = 7.4 Hz, 1H),
602 7.31 (t, *J* = 7.4 Hz, 2H). ¹³C NMR (125 MHz, CDCl₃) δ 16.8, 24.2,
603 37.9, 59.3, 64.2, 126.9, 128.64, 128.8, 137.2. FT-IR (film, cm⁻¹) *ν* 702,
604 1065, 1376, 1453, 1496, 2925, 3467. HRMS (ESI-TOF) *m/z* [M +
605 Na]⁺ calcd for C₁₁H₁₄SONa 217.0658; found 217.0664.
606 (1*R*₅*,2*R**,4*R**)-2-Benzyl-4-methylthietane 1-Oxide
607 (1*R*₅*,2*R**,4*R**)-6a. Column chromatography on silica gel (AcOEt),
608 pale yellow oil, 31% (61 mg). ¹H NMR (600 MHz, CDCl₃) δ 1.49 (d,
609 *J* = 7 Hz, 3 H), 1.99–2.16 (m, 2 H), 2.98 (dd, *J* = 8, 14 Hz, 1 H), 3.24
610 (dd, *J* = 7, 14 Hz, 1 H), 3.52 (quintet, *J* = 7 Hz, 1 H), 3.69 (quintet, *J* =
611 8 Hz, 1 H), 7.10–7.37 (m, 5 H). ¹³C NMR (125 MHz, CDCl₃) δ 11.6,
612 25.3, 38.0, 49.5, 65.3, 127.0, 128.8, 128.9, 137.4. FT-IR (film, cm⁻¹) *ν*
613 702, 1065, 1376, 1453, 1496, 2925, 3467. HRMS (ESI-TOF) *m/z* [M
614 + Na]⁺ calcd for C₁₁H₁₄SONa 217.0658; found 217.0661.
615 (1*R*₅*,2*S**,4*S**)-2-[(4-Chlorophenyl)hydroxymethyl]-4-benzyl-
616 thietane 1-Oxide (1*R*₅*,2*S**,4*S**)-6b. Mixture of diastereomers at the
617 carbinolic carbon, *dr* 50:50. Column chromatography on silica gel
618 (AcOEt), colorless oil. 71% (224 mg). ¹H NMR (600 MHz, CDCl₃) δ
619 1.44 (q, *J* = 12.2 Hz, 1 H), 1.72 (q, *J* = 12.2 Hz, 1 H), 2.07–2.13 (m,
620 overlapping s Acetone at 2.09, 2 H), 2.83–2.90 (m, 2 H), 3.14–3.20
621 (m, 2 H), 3.26–3.37 (m, 4 H), 4.69 (d, *J* = 8.7 Hz, 1 H), 5.09 (d, *J* =
622 3.7 Hz, 1 H), 7.08–7.09 (m, 3 H), 7.15–7.25 (m, 15 H). ¹³C NMR
623 (125 MHz, CDCl₃) δ 17.4, 20.4, 37.8, 63.3, 69.1, 70.1, 73.5, 127.1–
624 126.5, 128.6–129.1, 133.9, 133.3, 136.9, 137.0, 139.1, 139.2. FT-IR
625 (film, cm⁻¹) *ν* 703, 735, 841, 1047, 1245, 1454, 1493, 1602, 1732,
626 2925, 3334. HRMS (ESI-TOF) *m/z* [M + Na]⁺ calcd for
627 C₁₇H₁₇ClSO₂Na 343.0530; found 343.0516.
628 (1*R*₅*,2*R**,4*S**)-4-Benzyl-2-(1-hydroxycyclohex-2-en-1-yl)thietane
629 1-Oxide (1*R*₅*,2*R**,4*S**)-6c. Major diastereomer. Column chromatog-
630 raphy on silica gel (Hexane/AcOEt 50:50), pale yellow oil. 42% (110
631 mg). ¹H NMR (600 MHz, CDCl₃) δ 1.50–1.57 (m, 1 H), 1.75–1.82
632 (m, 1 H), 1.84–1.94 (m, 2 H), 1.98–2.44 (m, overlapping s, AcOEt, 2
633 H), 2.92–3.04 (m, 2 H), 3.14 (dd, *J* = 7, 14 Hz, 1 H), 3.30 (ddd, *J* = 6,
634 7, 15 Hz, 1 H), 3.87–3.97 (m, 1 H), 4.21 (bs, 1 H, OH), 5.54 (d, *J* =
635 10 Hz, 1 H), 5.80 (dt, *J* = 4, 1 Hz, 1 H), 7.13–7.14 (m, 2 H), 7.17–
636 7.20 (m, 1 H), 7.24–7.26 (m, 2 H). ¹³C NMR (125 MHz, CDCl₃) δ
637 18.8, 22.7, 25.0, 35.8, 38.3, 57.2, 65.2, 72.9, 127.0₉, 127.1₄, 128.8,
638 128.9, 131.6, 137.0. FT-IR (film, cm⁻¹) *ν* 700, 735, 1010, 1186, 1262,
639 1429, 1454, 1496, 1672, 1707, 2866, 2935, 3027, 3392. HRMS (ESI-
640 TOF) *m/z* [M + Na]⁺ calcd for C₁₆H₂₀SO₂Na 299.1076; found
641 299.1078.
642 (1*R*₅*,2*R**,4*S**)-4-Benzyl-2-(1-hydroxycyclohex-2-en-1-yl)thietane
643 1-Oxide (1*R*₅*,2*R**,4*S**)-6c. Minor Diastereomer. Column chromatog-
644 raphy on silica gel (Hexane/AcOEt 50:50), pale yellow oil. 23% (70
645 mg). ¹H NMR (600 MHz, CDCl₃) δ 1.32–1.36 (m, 1 H), 1.43–1.49
646 (m, 1 H), 1.68–1.76 (m, 1 H), 1.86–1.93 (m, 1 H), 1.97–2.09 (m, 2
647 H), 2.90–2.97 (m, 2 H), 3.15 (dd, *J* = 7, 14 Hz, 1 H), 3.31 (dd, *J* =
648 9.5, 5.1 Hz, 1 H), 3.86–3.97 (m, 1 H), 4.19 (bs, 1 H, OH), 5.77 (dt, *J* =
649 = 10, 4 Hz, 1 H), 5.99 (d, *J* = 10.2 Hz, 1 H), 7.13–7.14 (m, 2 H),
650 7.17–7.19 (m, 1 H), 7.23–7.26 (m, 2 H). ¹³C NMR (125 MHz,
651 CDCl₃) δ 20.5, 24.5, 27.3, 34.6, 40.6, 60.5, 67.5₉, 129.2, 130.8, 130.9,
652 132.0, 133.39. FT-IR (film, cm⁻¹) *ν* 700, 734, 1029, 1188, 1454, 1496,
653 1712, 2851, 2930, 3027, 3400. HRMS (ESI-TOF) *m/z* [M + Na]⁺
654 calcd for C₁₆H₂₀SO₂Na 299.1076; found 299.1067.
655 (1*R*₅*,2*R**,4*R**)/(1*R*₅*,2*R**,4*S**)-6d. Mixture of diastereoisomers *dr*
656 70:30. Column chromatography on silica gel (AcOEt), yellow oil,

72.4% D (134 mg). ¹H NMR (600 MHz, CDCl₃) δ 1.56–1.65 (m, 1
657 H), 2.24–2.33 (m, 1 H), 2.86–2.96 (m, 1.47 H), 3.17 (dd, *J* = 6.3,
658 14.3 Hz, 1 H), 3.32–3.37 (m, 0.83 H), 3.52–3.61 (m, 1 H), 7.12–7.14
659 (m, 2 H), 7.15–7.20 (m, 1 H), 7.23–7.26 (m, 2 H). ¹³C NMR (125
660 MHz, CDCl₃) δ 16.3, 16.4, 38.1, 48.1 (t, *J* = 22.4 Hz), 48.2 (t, *J* = 23.3
661 Hz), 48.5, 68.9, 127.0, 128.8, 128.9, 137.1. 153 ESI-MS: *m/z* (rel. int.):
662 203[M_H + Na]⁺(34); 204 [M_D + Na]⁺(100).
663 (1*R*₅*,2*R**,4*R**)-2-Benzyl-4-(3-propenyl)thietane 1-Oxide
664 (1*R*₅*,2*R**,4*R**)-6e. Column chromatography on silica gel (Hexane/
665 AcOEt 50:50), colorless oil. 35% (76 mg). ¹H NMR (600 MHz,
666 CDCl₃) δ 1.92 (ddd, *J* = 8, 11, 13 Hz, 1 H), 2.21 (ddd, *J* = 3, 10, 13
667 Hz, 1 H), 2.35–2.44 (m, 1 H), 2.69–2.77 (m, 1), 2.92 (dd, *J* = 9, 14
668 Hz, 1 H), 3.17 (dd, *J* = 6, 14 Hz, 1 H), 3.35–3.39 (m, 1 H), 3.58–3.64
669 (m, 1 H), 5.03–5.08 (m, 2 H), 5.68–5.77 (m, 1 H), 7.11–7.13 (m, 2
670 H), 7.16–7.19 (m, 1 H), 7.23–7.26 (m, 2 H). ¹³C NMR (125 MHz,
671 CDCl₃) δ 23.4, 30.3, 38.1, 53.0, 65.2, 118.0, 127.0, 128.8, 128.9, 133.8,
672 137.3. FT-IR (film, cm⁻¹) *ν* 701, 749, 917, 1005, 1062, 1437, 1454,
673 1496, 1602, 1639, 2929, 3028, 3062, 3445. HRMS (ESI-TOF) *m/z* [M
674 + Na]⁺ calcd for C₁₃H₁₆SONa 243.0814; found 243.0818.
675 (1*R*₅*,2*R**,4*S**)-2-Benzyl-4-(3-propenyl)thietane 1-Oxide
676 (1*R*₅*,2*R**,4*S**)-6e. Column chromatography on silica gel (Hexane/
677 AcOEt 50:50), pale yellow oil. 43% (96 mg). ¹H NMR (600 MHz,
678 CDCl₃) δ 1.34 (like q, 1 H), 2.37–2.45 (m, 2 H), 2.49–2.53 (m, 1 H),
679 2.90 (dd, *J* = 9, 14 Hz, 1 H), 3.15–3.24 (m, 2 H), 3.31–3.40 (m, 1 H),
680 5.04–5.12 (m, 2 H), 5.71 (ddt, *J* = 7, 10, 17 Hz, 1 H), 7.10–7.13 (m, 2
681 H), 7.16–7.19 (m, 1 H), 7.22–7.28 (m, 2 H). ¹³C NMR (125 MHz,
682 CDCl₃) δ 22.6, 35.9, 38.0, 63.1, 64.4, 118.3, 127.0, 128.8, 128.9, 133.1,
683 137.3. FT-IR (film, cm⁻¹) *ν* 702, 749, 921, 1061, 1299, 1454, 1496,
684 1640, 2919, 3028, 3063, 3437. ESI-MS: *m/z* (rel. int.): 221 [M +
685 H]⁺(100).
686 (1*R*₅*,2*R**,4*R**)-2-(3-Propenyl)-4-methylthietane 1-Oxide
687 (1*R*₅*,2*R**,4*R**)-7a. Column chromatography on silica gel (AcOEt),
688 pale yellow oil, 42% (61 mg). ¹H NMR (600 MHz, CDCl₃) δ 1.47 (d,
689 *J* = 7.4 Hz, 3 H), 1.98 (ddd, *J* = 8.3, 11.9, 13.0 Hz, 1 H), 2.12–2.19
690 (m, 1 H), 2.43–2.48 (m, 1 H), 2.52–2.57 (m, 1 H), 3.46–3.53 (m,
691 2H), 5.09–5.15 (m, 2 H), 5.76 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1 H). ¹³C
692 NMR (125 MHz, CDCl₃) δ 11.7, 25.2, 36.0, 49.4, 63.6, 118.2, 133.1.
693 FT-IR (film, cm⁻¹) *ν* 920, 997, 1060, 1123, 1439, 1641, 2867, 2929,
694 2976, 3079, 3467. HRMS (ESI-TOF) *m/z* [M + Na]⁺ calcd for
695 C₇H₁₂SONa 167.0501; found 167.0500.
696 (1*R*₅*,2*S**,4*S**)-2-[(4-Chlorophenyl)hydroxymethyl]-4-(3-
697 propenyl)thietane 1-Oxide (1*R*₅*,2*S**,4*S**)-7b. Mixture of diaster-
698 eomers *dr* 70:30. Column chromatography on silica gel (AcOEt),
699 yellow oil. 71% (192 mg). ¹H NMR (600 MHz, CDCl₃) δ 1.40 (q, *J* =
700 12.1 Hz, 1 H), 1.66 (q, *J* = 12.2 Hz, 1 H), 2.11–2.17 (m, 2 H), 2.34–
701 2.49 (m, 4 H), 3.08–3.17 (m, 2 H), 3.31–3.38 (m, 2 H), 4.66 (d, *J* =
702 8.5 Hz, 1 H), 5.02–5.09 (m, 5 H), 5.63–5.70 (m, 2 H), 7.17–7.24 (m,
703 8 H). ¹³C NMR (125 MHz, CDCl₃) δ 17.3, 20.2, 35.7, 35.8, 61.9, 69.1,
704 69.2, 69.9, 73.5, 118.4, 118.5, 127.3, 127.5, 128.8, 129.0, 132.7, 132.8,
705 133.7, 139.3, 139.4. IR (film, cm⁻¹) *ν* 757, 841, 923, 1043, 1089, 1490,
706 1641, 2923, 2979, 3081, 3339. HRMS (ESI-TOF) *m/z* [M + Na]⁺
707 calcd for C₁₃H₁₃ClSO₂Na 293.0373; found 293.0374.
708 (1*R*₅*,2*R**,4*S**)-2-(1-Hydroxycyclohex-2-en-1-yl)-4-(3-propenyl)-
709 thietane 1-Oxide (1*R*₅*,2*R**,4*S**)-7c. Minor diastereomer. Column
710 chromatography on silica gel (Hexane/AcOEt 50:50), yellow oil. 20%
711 (47 mg). ¹H NMR (600 MHz, CDCl₃) δ 1.41–1.61 (m, overlapping s
712 H₂O at 1.60, 2 H), 1.93–2.15 (m, overlapping s AcOEt at 2.04, 3 H),
713 2.46–2.62 (m, 2 H), 3.07 (ddd, *J* = 13.2, 11.4, 5.3 Hz, 1 H), 3.37–3.42
714 (m, 1 H), 3.73–3.84 (m, 1 H), 4.32 (bs, 1 H), 5.15–5.20 (m, 2 H),
715 5.75–5.88 (m, 2 H), 6.06–6.09 (m, 1 H). ¹³C NMR (125 MHz,
716 CDCl₃) δ 18.6, 22.4, 25.2, 32.7, 36.4, 58.4, 64.1, 72.8, 118.6, 130.0,
717 131.1, 132.9. FT-IR (film, cm⁻¹) *ν* 710, 1025, 1266, 1435, 1707, 2943,
718 3054, 3400. HRMS (ESI-TOF) *m/z* [M + Na]⁺ calcd for
719 C₁₂H₁₈SO₂Na 249.0925; found 249.0920.
720 (1*R*₅*,2*R**,4*S**)-2-(1-Hydroxycyclohex-2-en-1-yl)-4-(3-propenyl)-
721 thietane 1-Oxide (1*R*₅*,2*R**,4*S**)-7c. Major diastereomer. Column
722 chromatography on silica gel (Hexane/AcOEt 50:50), yellow oil. 45%
723 (109 mg). ¹H NMR (600 MHz, CDCl₃) δ 1.55–1.66 (m, 1 H), 1.82–
724 2.17 (m, 6 H), 2.49–2.60 (m, 2 H), 3.11 (ddd, *J* = 13.2, 11.4, 5.4 Hz, 1
725 H), 3.38 (ddd, *J* = 9.5, 5.4, 1.3 Hz, 1 H), 3.75–3.81 (m, 1 H), 4.31 (bs,
726

727 1 H), 5.15–5.20 (m, 2 H), 5.63–5.65 (m, 1 H), 5.80 (ddt, $J = 17.0$,
728 10.3, 6.7 Hz, 1 H), 5.89 (dt, $J = 10.1$, 3.7 Hz, 1 H). ^{13}C NMR (125
729 MHz, CDCl_3) δ 18.8, 22.7, 35.8, 36.4, 57.3, 63.8, 72.9, 118.6, 127.1,
730 131.6, 132.9. FT-IR (film, cm^{-1}) ν 710, 1025, 1266, 1435, 1707, 2943,
731 3054, 3400. HRMS (ESI-TOF) m/z [$\text{M} + \text{Na}$] $^+$ calcd for
732 $\text{C}_{12}\text{H}_{18}\text{SO}_2\text{Na}$ 249.0925; found 249.0921.

733 $(1R_5^*,2R^*,4R^*)/(1R_5^*,2R^*,4S^*)$ -7d. Mixture of diastereoisomers dr
734 = 71:29. Column chromatography on silica gel (AcOEt), pale yellow
735 oil, 89% D (118 mg). ^1H NMR (600 MHz, CDCl_3) δ 1.62–1.70 (m, 1
736 H), 2.39–2.63 (m, 3 H), 2.94–3.02 (m, 0.3 H), 3.40–3.52 (m, 1.72
737 H), 5.13–5.20 (m, 2 H), 5.74–5.85 (m, 1 H). ^{13}C NMR (125 MHz,
738 CDCl_3) δ 16.2, 36.1, 48.0₆ (t, $J = 22.8$ Hz), 48.1₅ (t, $J = 23.2$ Hz), 48.4,
739 67.6, 118.4, 132.9. ESI-MS: m/z (rel. int.): 153 [$\text{M}_\text{H} + \text{Na}$] $^+$ (13); 154
740 [$\text{M}_\text{D} + \text{Na}$] $^+$ (100).

741 $(1R_5^*,2S^*,4S^*)$ -2-Benzyl-4-(3-propenyl)thietane 1-Oxide
742 $(1R_5^*,2S^*,4S^*)$ -7e. Column chromatography on silica gel, (Hexane/
743 AcOEt 50:50), yellow oil. 18% (40 mg). ^1H NMR (400 MHz, CDCl_3)
744 δ 1.95 (ddd, $J = 13.3$, 10.8, 8.3 Hz, 1H), 2.40 (ddd, $J = 13.3$, 10.3, 3.1
745 Hz, 1H), 2.51 (dt, $J = 15.20$, 6.8 Hz, 1H), 2.62 (dt, $J = 14.5$, 7.2 Hz,
746 1H), 3.00 (dd, $J = 14.5$, 10.2 Hz, 1H), 3.42 (dd, $J = 14.5$, 5.5 Hz, 1H),
747 3.69–3.54 (m, 2H), 5.23–5.12 (m, 2H), 5–78–587(m, 1H), 7.38–
748 7.18 (m, 5H). ^{13}C NMR (125 MHz, CDCl_3) δ 23.5, 31.7, 35.9, 54.8,
749 63.4, 118.3, 126.7, 128.7, 129.2, 132.9, 137.7. FT-IR (film, cm^{-1}) ν
750 703, 720, 1061, 1266, 1454, 1496, 1641, 2983, 3053, 3437. HRMS
751 (ESI-TOF) m/z [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{13}\text{H}_{16}\text{SONa}$ 243.0814; found
752 243.0818.

753 $(1R_5^*,2R^*)$ -2-(Tributylstannyl)thietane 1-Oxide 8. Column chro-
754 matography on silica gel (Hexane/AcOEt 50:50), colorless oil (60%).
755 ^1H NMR (500 MHz, CDCl_3) δ 0.87 (t, $J = 7$ Hz, 9 H), 0.96–0.99 (m,
756 6 H), 1.25–1.34 (m, 6 H), 1.45–1.54 (m, 6 H), 2.05–2.14 (m, 1H),
757 2.47–2.55 (m, 1 H), 3.27–3.37 (m, 2 H), 3.68–3.72(m, 1 H). ^{13}C
758 NMR (125 MHz, CDCl_3) δ 9.2, 13.7, 16.4, 27.4, 29.1, 53.1, 58.0, 74.2.
759 FT-IR (cm^{-1}) ν 657, 691, 1050, 1101, 1464, 1643, 2871, 2853, 2927,
760 2956. HRMS (ESI-TOF) m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{15}\text{H}_{33}\text{OSSn}$
761 381.1274; found 381.1271.

762 **General Procedure for Synthesis of 2-Phenyl Thietane-1-**
763 **Oxide 9.** 2-Phenyl thietane was prepared following a reported
764 procedure.²³ To a stirred solution of 1,3-dichloro-1-phenylpropane
765 (10.0 mmol, 1.880 g, 1.0 equiv) in EtOH/ $\text{H}_2\text{O} = 80:20$ (100 mL) at
766 room temperature was added $\text{Na}_2\text{S} \cdot 9\text{H}_2\text{O}$, and then the solution was
767 heated at 70 °C overnight. After the reaction was complete, as
768 determined by GC or TLC, EtOH was removed in vacuo and the
769 aqueous layer was extracted with Et_2O (3 \times 10 mL). The combined
770 organic layers were dried (Na_2SO_4), filtered, and concentrated in
771 vacuo. Chromatography on silica gel (Hexane/AcOEt) afforded the 2-
772 phenyl thietane as a pale orange oil (65% yield). To a solution of 2-
773 phenyl thietane (9.05 mmol, 1.358 g, 1 equiv) in glacial acetic acid (2.7
774 mL, 5.4 equiv) at 0 °C was added H_2O_2 (30 w/w %) (11.76 mmol, 1.4
775 mL, 1.3 equiv) dropwise. After 5 h at 0–10 °C, a water solution of
776 NaOH (1 M) was slowly added to neutralize the excess of
777 CH_3COOH . The reaction mixture was extracted with CH_2Cl_2 (3 \times
778 10 mL). The combined organic layers were dried (Na_2SO_4), filtered,
779 and concentrated in vacuo. Chromatography on silica gel (AcOEt)
780 gave the 2-phenyl thietane 1-oxide 9 as a pale yellow solid (40% yield).

781 **2-Phenylthietane 1-Oxide 9.** The spectral data fit those already
782 reported.²² Column chromatography on silica gel (AcOEt), pale
783 yellow solid, 40%. ^1H NMR (600 MHz, CDCl_3) δ 2.16 (dq, $J = 9.5$,
784 13.7 Hz, 1 H), 2.65–2.70 (m, 1 H), 3.02–3.08 (m, 1 H), 3.43–3.45
785 (m, 1 H), 4.40–4.44 (m, 1 H), 7.32–7.37 (m, 5 H). ^{13}C NMR (125
786 MHz, CDCl_3) δ 16.7, 47.3, 72.3, 127.3, 128.5, 128.9, 136.3.

787 **General Procedure for Lithiation–Electrophile Trapping in**
788 **Situ Sequence of trans 2-Phenyl Thietane 1-Oxide 9.** To a
789 stirred solution of DIPA (1.5 mmol, 0.212 mL, 1.5 equiv) in 8.0 mL of
790 THF at 0 °C was added a solution of *n*-butyllithium (2.5 M in hexane,
791 1.5 mmol, 0.6 mL, 1.5 equiv) dropwise. After 20 min at 0 °C, the
792 solution of LDA was cooled to –78 °C and a mixture of 2-phenyl
793 thietanes-1-oxide (1.0 mmol, 166.0 mg, 1.0 equiv) and benzophenone
794 (1.0 mmol, 182 mg, 1.0 equiv) in 2.0 mL of solvent was added
795 dropwise. After 1 h, as determined by GC or TLC, the reaction
796 mixture was poured in water (10 mL) and extracted with AcOEt (3 \times

10 mL). The combined organic layers were dried (Na_2SO_4), filtered,
797 and concentrated in vacuo. Chromatography on silica gel (Hexane/
798 AcOEt) afforded the 2,4-disubstituted thietanes 1-oxide and 2,2,4-
799 trisubstituted thietanes 1-oxide.
800

801 $(1R_5^*,2S^*)$ -2-(Hydroxydiphenylmethyl)-2-phenylthietane 1-Oxide
802 **10.** Column chromatography on silica gel (Hexane/AcOEt 80:20),
803 white solid, 185–188 °C. ^1H NMR (600 MHz, CDCl_3) δ 2.83–2.91
804 (m, 2 H), 3.24–3.30 (m, 1 H), 4.52–4.58 (m, 1 H), 6.88 (d, $J = 7.4$
805 Hz, 2 H), 7.11–7.26 (m, 11 H), 7.40 (d, $J = 7.2$ Hz, 2 H). ^{13}C NMR
806 (125 MHz, CDCl_3) δ 31.0, 43.0, 74.1, 84.8, 127.5, 127.6, 127.8, 127.9,
807 128.0, 128.1, 128.2, 128.5, 128.6, 128.9, 130.9, 131.5, 137.2₀, 137.2₃,
808 143.5. FT-IR (KBr, cm^{-1}) ν 702, 737, 1032, 1266, 1447, 1493, 1599,
809 2927, 3058, 3351. HRMS (ESI-TOF) m/z [$\text{M} + \text{Na}$] $^+$ calcd for
810 $\text{C}_{22}\text{H}_{20}\text{SO}_2\text{Na}$ 371.1082; found 371.1076.

811 $(1R_5^*,2R^*,4R^*)$ -2-(Hydroxydiphenylmethyl)-4-phenylthietane 1-
812 **Oxide 11.** Column chromatography on silica gel (Hexane/AcOEt
813 80:20), white solid, mp 194 °C – dec. ^1H NMR (600 MHz, CDCl_3) δ
814 2.53 (dt, $J = 9.5$, 13.7 Hz, 1 H), 3.22 (ddd, $J = 5.6$, 11.8, 13.7 Hz, 1 H),
815 4.40–4.50 (m, 1 H), 4.76–4.87 (m, 1 H), 5.37 (bs, 1 H), 7.12–7.15
816 (m, 1 H), 7.18–7.35 (m, 12 H), 7.48–7.50 (m, 2 H). ^{13}C NMR (125
817 MHz, CDCl_3) δ 24.4, 55.4, 69.0, 80.4, 125.9, 126.0, 127.2, 127.5,
818 127.7, 128.5, 128.8, 129.2, 136.8, 143.7, 146.0. FT-IR (KBr, cm^{-1}) ν
819 700, 755, 1037, 1062, 1161, 1447, 1494, 2854, 2924, 3058, 3454.
820 HRMS (ESI-TOF) m/z [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{22}\text{H}_{20}\text{SO}_2\text{Na}$ 371.1082;
821 found 371.1076.

822 $(1R_5^*,2S^*,4S^*)$ -2,4-Bis(hydroxydiphenylmethyl)-2-phenylthietane
823 **1-Oxide 12.** Column chromatography on silica gel (Hexane/AcOEt
824 80:20), white solid mp 139–142 °C, 70%. ^1H NMR (600 MHz,
825 CDCl_3) δ 2.81 (dd, $J = 12.8$, 7.2 Hz, 1 H), 3.83 (dd, $J = 11.8$, 7.2 Hz, 1
826 H), 5.43 (t, $J = 12.5$ Hz, 1 H), 5.68 (bs, 1 H), 6.79 (d, $J = 8.0$ Hz, 2
827 H), 6.84 (bs, 1 H), 7.10–7.39 (m, 23 H). ^{13}C NMR (125 MHz,
828 CDCl_3) δ 32.9, 52.4, 69.4, 79.5, 84.9, 125.6, 125.9, 127.4₇, 127.5₂,
829 127.7, 127.8, 127.9, 128.2, 128.3, 128.5₀, 128.5₃, 128.5₉, 128.6₃, 128.8,
830 131.0, 135.3, 140.7, 143.0, 143.5, 144.5. FT-IR (film, cm^{-1}) ν 700, 735,
831 1010, 1186, 1262, 1429, 1454, 1496, 1672, 1707, 2866, 2935, 3027,
832 3392. HRMS (ESI-TOF) m/z [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{35}\text{H}_{30}\text{SO}_3\text{Na}$
833 553.1813; found 553.1808.

■ ASSOCIATED CONTENT

● Supporting Information

^1H and ^{13}C NMR spectra for new compounds (PDF),
and X-ray and calculation data (PDF)
X-ray crystallographic data for (CIF)
X-ray crystallographic data for (CIF)
X-ray crystallographic data for (CIF)
X-ray crystallographic data for (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: renzo.luisi@uniba.it.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank National Project “FIRB - Futuro in Ricerca” (code: 850
CINECA RBF083M5N); Regional project “Reti di Laboratori
851 Pubblici di Ricerca” (Project. Code 20); and Laboratorio
852 SISTEMA (Code PONA300369) financed by Italian Miur. 853

■ REFERENCES

(1) (a) Clayden, J.; MacLellan, P. *Beilstein J. Org. Chem.* **2011**, *7*, 582. 855
(b) Voss, J. J. *Sulfur Chem.* **2009**, *30*, 167. (c) 2009 Top 200 Branded 856
Drugs by Retail Dollars; Drug Topics, 2010; [http://www.drugs.com/](http://www.drugs.com/top200.html) 857
[top200.html](http://www.drugs.com/top200.html). 858

- 859 (2) (a) Burkhard, J. A.; Wuitschik, G.; Rogers-Evans, M.; Muller, K.;
860 Carreira, E. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 9052. (b) Wuitschik,
861 G.; Carreira, E. M.; Wagner, B.; Fischer, H.; Parrilla, I.; Schuler, F.;
862 Rogers-Evans, M.; Muller, K. *J. Med. Chem.* **2010**, *53*, 3227. (c) Ritchie,
863 T. J.; Macdonald, S. J. F.; Young, R. J.; Pickett, S. D. *Drug Discovery*
864 *Today* **2011**, *16*, 164. (d) Ritchie, T. J.; Macdonald, S. J. F.; Peace, S.;
865 Pickett, S. D.; Luscombe, C. N. *MedChemComm* **2013**, *4*, 673. (e) de
866 Kloe, G. E.; Bailey, D.; Leurs, R.; de Esch, I. J. P. *Drug Discovery Today*
867 **2009**, *14*, 630.
- 868 (3) Carreira, E. M.; Fessard, T. C. *Chem. Rev.* **2014**, *114*, 8257.
- 869 (4) (a) Rousseau, G.; Robin, S. Four-Membered Heterocycles:
870 Structure and Reactivity. In *Modern Heterocyclic Chemistry*; Alvarez-
871 Builla, J., Vaquero, J. J., Barluenga, J., Eds.; Wiley-VCH: Weinheim,
872 Germany, 2011; Chapter 3, pp 163–268. (b) Four-Membered
873 Heterocycles Together with all Fused Systems Containing a Four-
874 Membered Heterocyclic Ring. In *Comprehensive Heterocyclic Chemistry*
875 *III*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K.,
876 Eds.; Elsevier Ltd: Amsterdam, 2008; Vol. 2, pp 1–989.
- 877 (5) (a) Degennaro, L.; Trinchera, P.; Luisi, R. *Chem. Rev.* **2014**, *114*,
878 7881. (b) Capriati, V.; Florio, S.; Luisi, R. *Eur. J. Org. Chem.* **2014**,
879 *2014*, 5397. (c) Degennaro, L.; Pisano, L.; Parisi, G.; Mansueto, R.;
880 Clarkson, G. J.; Shipman, M.; Luisi, R. *J. Org. Chem.* **2015**, *80*, 6411.
881 (d) Zenzola, M.; Degennaro, L.; Trinchera, P.; Carroccia, L.; Giovine,
882 A.; Romanazzi, G.; Mastroiilli, P.; Rizzi, R.; Pisano, L.; Luisi, R. *Chem.* -
883 *Eur. J.* **2014**, *20*, 12190. (e) Degennaro, L.; Zenzola, M.; Trinchera, P.;
884 Carroccia, L.; Giovine, A.; Romanazzi, G.; Falcicchio, A.; Luisi, R.
885 *Chem. Commun.* **2014**, *50*, 1698. (f) Parisi, G.; Capitanelli, E.; Pierro,
886 A.; Romanazzi, G.; Clarkson, G. J.; Degennaro, L.; Luisi, R. *Chem.*
887 *Commun.* **2015**, *51*, 15588. (g) Giovine, A.; Muraglia, M.; Florio, M.
888 A.; Rosato, A.; Corbo, F.; Franchini, C.; Musio, B.; Degennaro, L.;
889 Luisi, R. *Molecules* **2014**, *19*, 11505.
- 890 (6) Carroccia, L.; Degennaro, L.; Romanazzi, G.; Cuocci, C.; Pisano,
891 L.; Luisi, R. *Org. Biomol. Chem.* **2014**, *12*, 2180.
- 892 (7) (a) Davis, O. A.; Croft, R. A.; Bull, J. A. *Chem. Commun.* **2015**,
893 *51*, 15446. (b) Morgan, K. F.; Hollingsworth, I. A.; Bull, J. A. *Chem.*
894 *Commun.* **2014**, *50*, 5203. (c) Morgan, K. F.; Hollingsworth, I. A.; Bull,
895 J. A. *Org. Biomol. Chem.* **2015**, *13*, 5265.
- 896 (8) CCDC 1423113 and CCDC 978293 contain the crystallographic
897 information for **2a** and *diast-2a*.
- 898 (9) For convenience, the C4 refers to the carbon where the
899 lithiation/substitution occurs. Relative stereochemistry could change
900 depending on the priority of the ring substituents.
- 901 (10) The stereoselectivity in the reactions of sulfinyl carbanions is
902 still an open issue. Recent examples have been reported on this topic;
903 see: (a) Ludwig, G.; Rüffer, T.; Hoppe, A.; Walther, T.; Lang, H.;
904 Ebbinghaus, S. G.; Steinborn, D. *Dalton Trans.* **2015**, *44*, 5323.
905 (b) Volonterio, A.; Zanda, M. Stereoselective Reactions of α -Sulfinyl
906 Carbanions in Organosulfur Chemistry. In *Asymmetric Synthesis*; Toru,
907 T., Bolm, C., Eds.; Wiley-VCH: Weinheim, 2008; Chapter 11, pp
908 351–374. (c) Luisi, R.; Capriati, V. Lithium Compounds. In *Organic*
909 *Synthesis: From Fundamentals to Application*, 1st ed.; Wiley-VCH:
910 Weinheim, 2014. (d) Hutchinson, B. J.; Andersen, K. K.; Katritzky, A.
911 R. *J. Am. Chem. Soc.* **1969**, *91*, 3839.
- 912 (11) Unfortunately, for this reaction, we were unable to reproduce
913 the level of stereoselectivity reported in ref 6. The diastereoselectivity
914 reported here is an average of 5 trials.
- 915 (12) CCDC 1423111 contains the crystallographic information for
916 (1*R*_s*,2*R*_s*,4*S*_s*)-5*d*.
- 917 (13) With reference to the carbinolic carbon, the level of
918 stereoselectivity was low and a mixture of the two corresponding
919 diastereomers was isolated (see the SI).
- 920 (14) Mansueto, R.; Degennaro, L.; Briere, J.-F.; Griffin, K.; Shipman,
921 M.; Florio, S.; Luisi, R. *Org. Biomol. Chem.* **2014**, *12*, 8505.
- 922 (15) The [Supporting Information](#) reports DFT calculations and
923 NMR simulations.
- 924 (16) Azzena, U.; Dettori, G.; Pisano, L.; Musio, B.; Luisi, R. *J. Org.*
925 *Chem.* **2011**, *76*, 2291.
- (17) For similar studies, see: (a) Hodgson, D. M.; Pearson, C. I.;
926 Thompson, A. L. *J. Org. Chem.* **2013**, *78*, 1098. (b) Řehová, L.; Jahn,
927 U. *Eur. J. Org. Chem.* **2014**, *2014*, 4610. 928
- (18) We assume the presence of a C–Li bond for those
929 intermediates. Nevertheless, crystal structures of lithiated sulfinyl
930 carbanions revealed a free carbanion with O–Li contacts. See ref 9a
931 and references therein. 932
- (19) (a) Clayden, J.; Helliwell, M.; Pink, J. H.; Westlund, N. *J. Am.*
933 *Chem. Soc.* **2001**, *123*, 12449. (b) Pearson, W. H.; Lindbeck, A. C. *J.*
934 *Am. Chem. Soc.* **1991**, *113*, 8546. 935
- (20) CCDC 1423112 contains crystallographic information for **11**. 936
- (21) Previous reports on lithiated thietane 1-oxides exploited their
937 propensity to undergo ring-opening; see: Jones, D. N.; Kogan, T. P.;
938 Newton, R. F.; Smith, S. J. *Chem. Soc., Chem. Commun.* **1982**, 589. 939
- (22) Degennaro, L.; Giovine, A.; Carroccia, L.; Luisi, R. Practical
940 Aspects of Organolithium Chemistry. In *Lithium Compounds in*
941 *Organic Synthesis: From Fundamentals to Application*, 1st ed.; Luisi, R.,
942 Capriati, V., Eds.; Wiley-VCH: Weinheim, 2014; Chapter 18, pp 513–
943 538. 944
- (23) (a) Almena, J.; Foubelo, F.; Yus, M. *Tetrahedron* **1997**, *53*, 5563. 945
(b) Volynskii, N. P.; Shevchenko, S. E. *Pet. Chem.* **2007**, *47*, 109–117. 946