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

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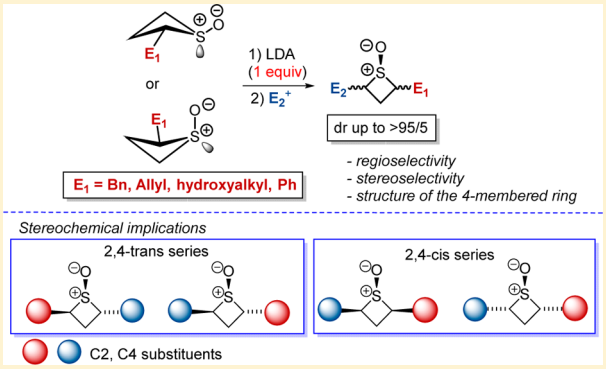
Supporting Information

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



INTRODUCTION

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

Most of the reported strategies for the preparation of substituted thietanes rely on the intra- or intermolecular displacement of a suitable leaving group by a sulfur nucleophile or a [2 + 2] cycladdition reaction as in the case of the thia Paternò−Buchi reaction.[4] However, these strategies could have limits such as a competitive β-elimination and the use of stinking reagents or regioselectivity problems as in the case of the cycloaddition approach.

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

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

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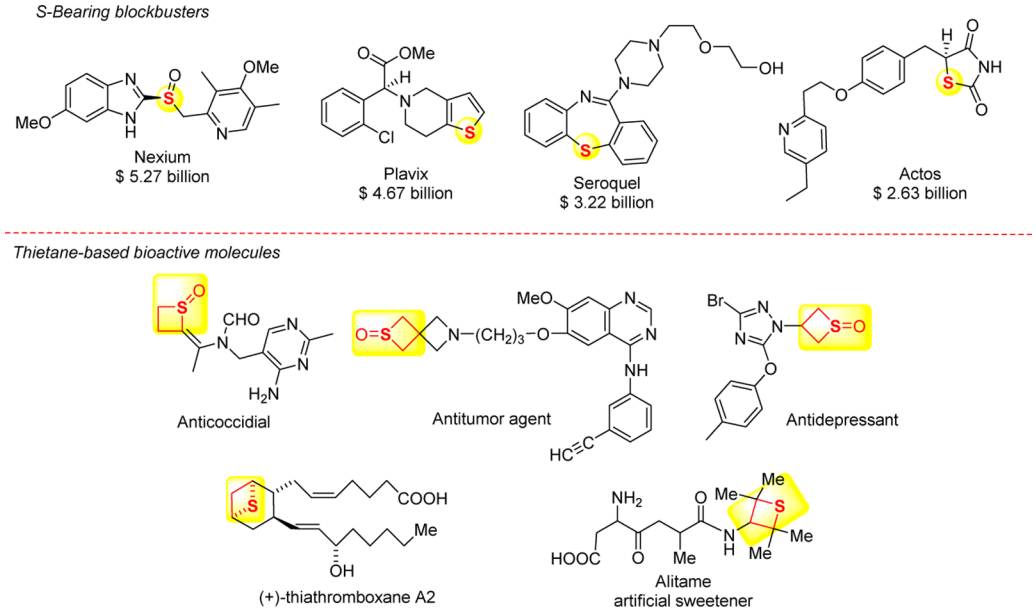
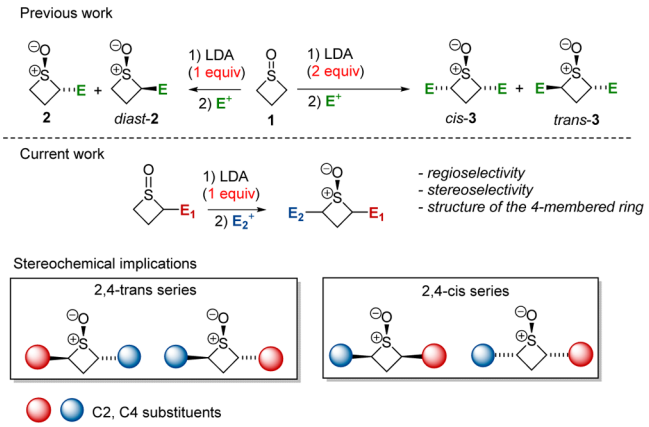
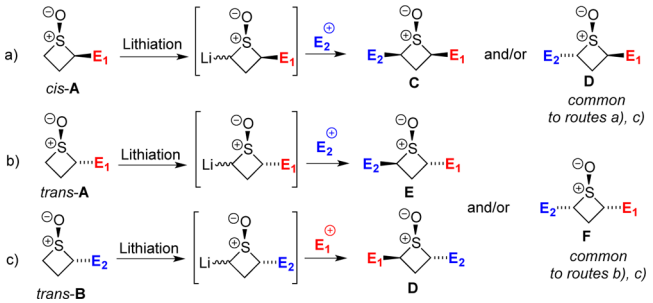


Figure 1. Sulfur- and thietane-bearing bioactive molecules.

Scheme 1. Examples of Mono and Double Functionalization of Thietane 1-Oxides



Scheme 2



preparation of various 2,4-disubstituted thietane 1-oxides. We noticed that, by a judicious choice of the starting material, the preparation of all the stereoisomeric 2,4-disubstituted thietane 1-oxides could be achievable. In fact, stereochemical implications related to this process suggest four different combinations (i.e., diastereoisomers) for the same pair of C2, C4 substituents (Schemes 1 and 2). This aspect could be relevant for medicinal chemistry studies but also from a structural point of view, little being known on the structural aspects of this kind of compounds.[7]

This approach, and the corresponding stereochemical implication, is summarized in Scheme 2 by three routes (a–c) that can be envisaged for this lithiation/trapping sequence. These routes could represent a selection guide when this strategy has to be chosen for a stereoselective preparation of C2,C4-disubstituted thietane 1-oxides. In fact, when both diastereoisomers of C2-functionalized thietane 1-oxides are available (i.e., *cis*-**A** and *trans*-**A**, routes a and b in Scheme 2), further lithiation/substitution would provide all the four stereoisomers **C**–**F**. By contrast, when only one diastereoisomer of C2-functionalized thietane 1-oxides is available, switching the sequence of introduction of the electrophile would give access to three out of four possible stereoisomers of C2,C4-disubstituted thietane 1-oxides (routes b and c, in Scheme 2).

With the aim to address this issue, we report herein our findings on the regio- and stereochemistry of this double functionalization of C2-substituted thietane 1-oxides jointing to structural features for the prepared thietanes.

RESULTS AND DISCUSSION

The investigation began with the preparation of representative C2 functionalized thietane 1-oxides **2a**–**c** and *diast*-**2a** by using our reported synthetic protocol (Scheme 3).[6] It is worth mentioning that one main stereoisomer is observed in the allylation and benzylation reactions of **1**, leading to **2b**,**c**, while two diastereoisomers can be isolated in the reaction of **1** with benzophenone (**2a** and *diast*-**2a**).

In this latter case, X-ray analysis of **2a** and *diast*-**2a** confirmed their structure and stereochemistry as well as differences in the ring puckering (Scheme 3).[8]

Because of the availability of the two diastereoisomeric thietanes **2a** and *diast*-**2a**, disclosing different structural features for the four-membered ring, their reactivity was investigated first. The lithiation of **2a** occurred regioselectively at the C4, in the presence of 2.5 equiv of LDA at −78 °C in THF, and the corresponding lithiated intermediates could be successfully trapped with several electrophiles (including MeOD, MeI,

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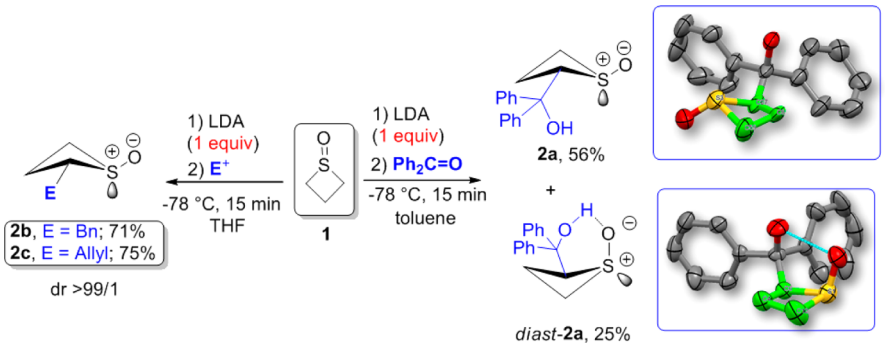
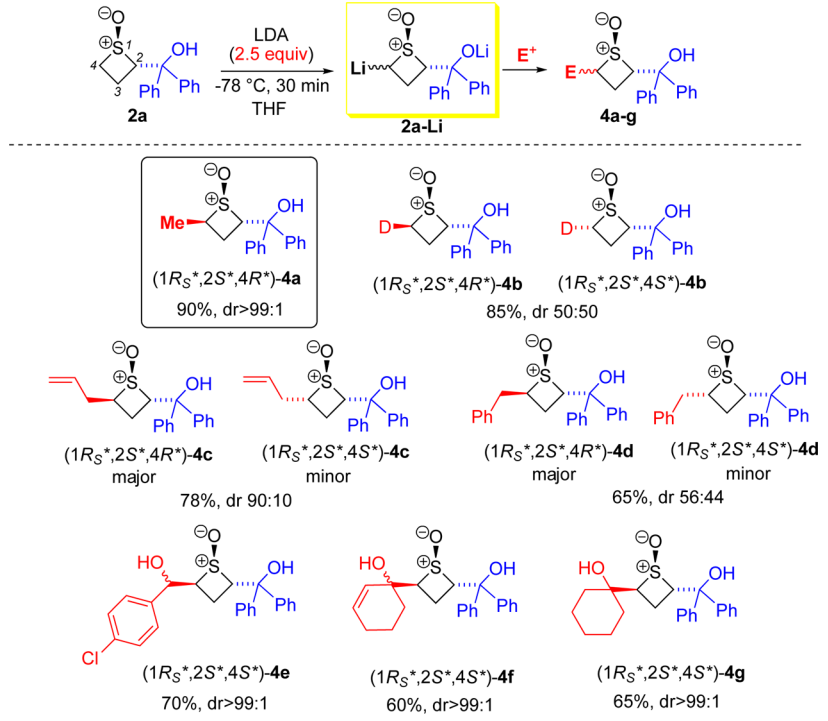
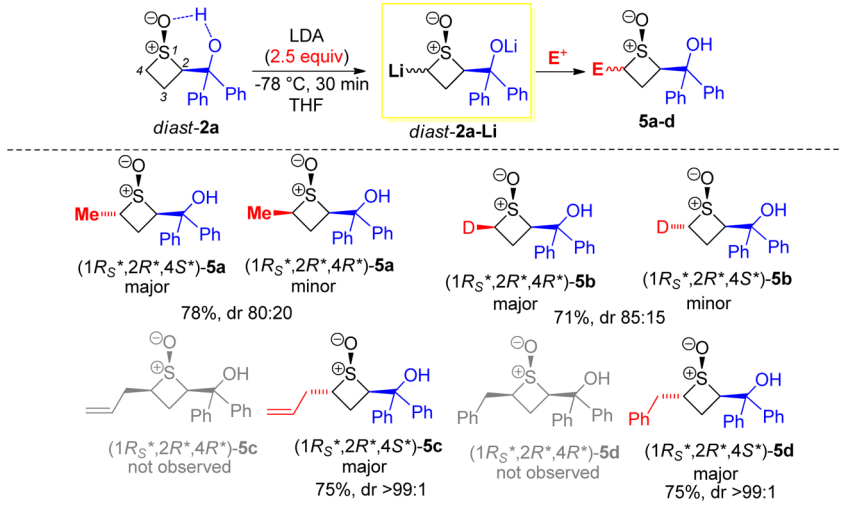
Scheme 3. Synthesis of C2-Functionalized Thietane 1-Oxides



Scheme 4. Lithiation/Substitution of Thietane 2a



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



BnBr, allylBr, aldehydes, and ketones), leading to disubstituted thietanes **4a–g** (Scheme 4). Being the C4 prochiral, a new stereogenic center was created upon lithiation. Nevertheless, a variable degree of stereoselectivity was observed in the final

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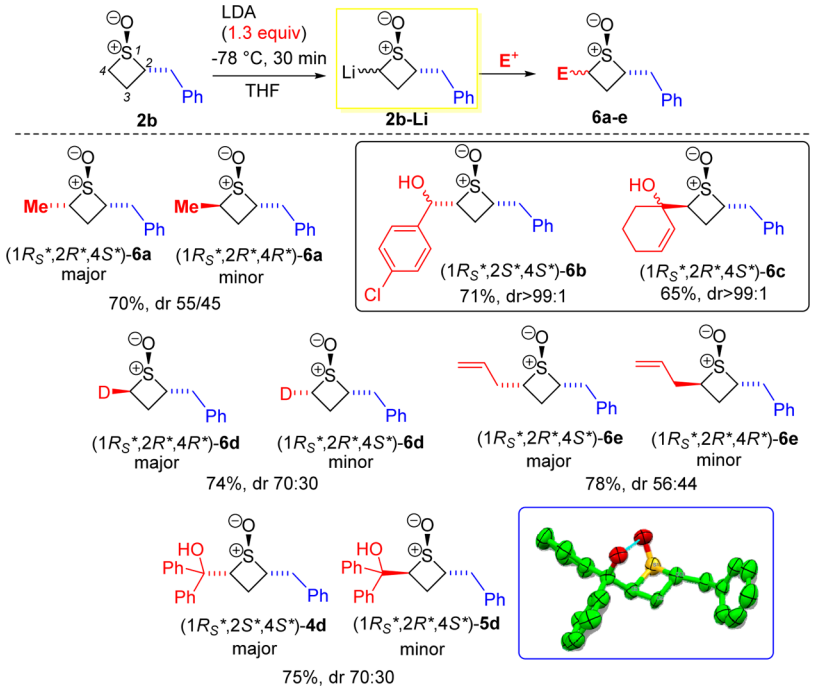
Scheme 6. Lithiation/Substitution of Thietane 2b



products **4a**–**g**, and mixtures of two diastereoisomers were obtained in most cases (Scheme 4). High stereoselectivity (dr > 90:10) resulted only for the reactions of lithiated **2a** with MeI and allylBr, giving, respectively, thietanes **4a** and **4c**. By NMR experiments (see the SI), it was demonstrated that, in these latter cases, the introduced electrophile set preferentially *syn* to the sulfur oxygen, leading to a relative stereochemistry ($1R_S$*,2*S**,4*R**) for the main stereoisomer.[9] Deuteration and benzylation occurred with very low, if any, stereoselectivity, suggesting that the electrophile may be playing a role in determining the stereochemical course of the reaction.[10] The use of carbonyl compounds (*p*-chlorobenzaldehyde, cyclohexanone, and cyclohexenone) resulted with a high level of stereoselectivity, giving thietanes ($1R_S$*,2*S**,4*S**)-**4e**–**g**. Nevertheless, the reactions resulted poorly selective with respect to the carbinolic carbon, and a 1:1 separable mixture of diastereoisomers were obtained in the reactions with the aromatic aldehyde and the prochiral ketone. The high level of stereoselectivity observed at the C4 of the thietane ring could be ascribed to both steric hindrance, due to the large C2 substituent, and coordination effects brought by the carbonyl group. Attempts to use an epoxide as the electrophile failed, and unreacted starting material was recovered.

Next, we investigated the reactivity of *diast*-**2a**, whose stereochemistry was ascertained by X-ray analysis.[8] From a structural point of view, *diast*-**2a** discloses marked differences with respect to **2a** such as a puckered conformation, due to an intramolecular hydrogen bond between the hydroxyalkyl moiety and the sulfoxide group, leading to a pseudoaxial sulfur–oxygen bond. We were keen to verify if such different structural features could affect the stereochemical course of the double functionalization. When *diast*-**2a** was lithiated under the same conditions used in the case of **2a** (2.5 equiv of LDA, −78 °C, 30 min), and reacted with electrophiles, still mixtures of diastereoisomeric adducts **5a**–**d** were obtained (Scheme 5). Nevertheless, while deuteration reaction led mainly to diastereoisomer ($1R_S$*,2*R**,4*R**)-**5b** (dr 85:15), a switch in stereochemical preference was observed in methylation, allylation, and benzylation reactions perhaps due to steric reasons. In these cases, diastereoisomers ($1R_S$*,2*R**,4*S**)-**5a**, ($1R_S$*,2*R**,4*S**)-**5c**, and ($1R_S$*,2*R**,4*S**)-**5d** were obtained with good stereoselectivity (Scheme 5).

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

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

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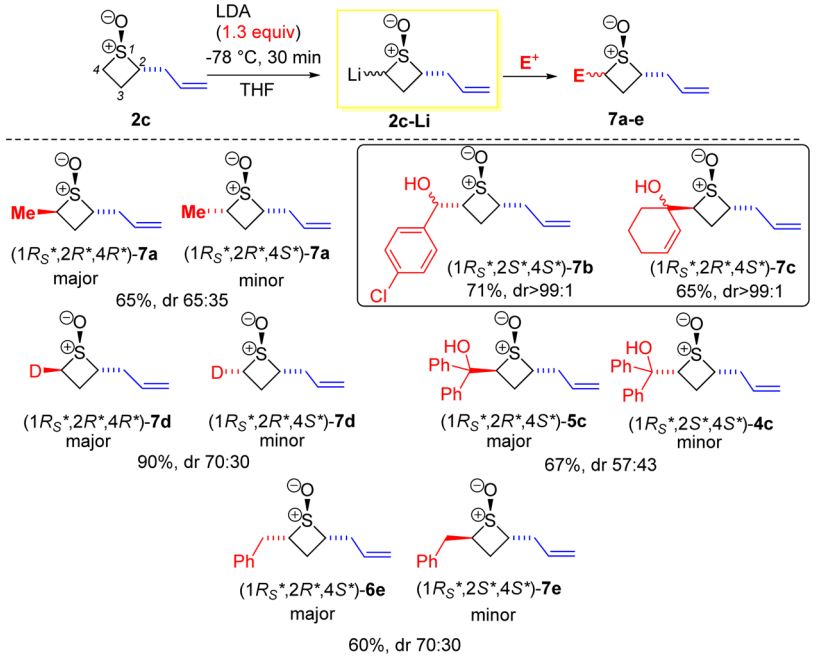
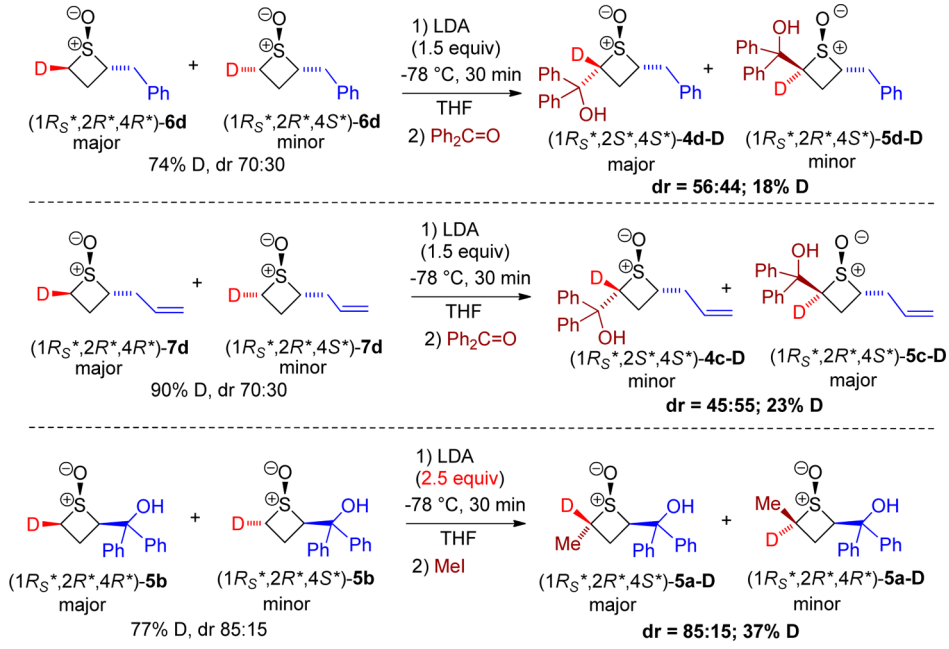
Scheme 7. Lithiation/Substitution of Thietane 2c



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



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

The reactivity of **2c** was also investigated using the same conditions and electrophiles as in the case of **2b**. The results are reported in Scheme 7. The lithiation/trapping of **2c** occurred with modest stereoselectivity, just as observed in the case of **2b** in the reactions with MeI, MeOD, and BnBr, leading, respectively, to diastereomeric mixtures of thietanes (1R_S*,2*R**,4*R**)-**7a,d,e**, (1R_S*,2*R**,4*S**)-**7a,d**, and (1R_S*,2*R**,4*S**)-**6e**. Again, an opposite and high stereochemical preference was observed in the reactions of **2c-Li** with *p*-chlorobenzaldehyde and cyclohexenone, leading, respectively, to (1R_S*,2*S**,4*S**)-**7b** and (1R_S*,2*R**,4*S**)-**7c** (Scheme 7).[13] It is worth noting that, in the reaction of **2c-Li** with benzophenone, stereoisomers (1R_S*,2*S**,4*S**)-**4c** and (1R_S*,2*R**,4*S**)-**5c** were obtained as seen in the lithiation/allylation of **2a** and *diast*-**2a**. Similarly, benzylation of **2c-Li** led to thietanes (1R_S*,2*S**,4*S**)-**7e** and (1R_S*,2*R**,4*S**)-**6e**, the latter still as the major stereoisomer, just as observed in lithiation/allylation of **2b** (Scheme 6).

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

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

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

Assuming an appreciable KIE, a preferential removal of the proton over deuterium, in thietanes **5b**, **6d**, and **7d**, would lead to lithiated intermediates possessing opposite stereochemistry with respect to those generated from parent thietanes **2b,c** or *diast*-**2a**. If the so-generated lithiated intermediates are configurationally unstable, the diastereoselectivity observed, upon reaction with an electrophile, should match that found in the lithiation/trapping on protonated parent thietanes. Conversely, with configurationally stable lithiated intermediates, trapping with the electrophile would lead to a different diastereomeric ratio. As a consequence of the KIE, in both cases, the final products should keep a high level of deuterium content. Thus, simply comparing the diastereomeric ratios resulting from the lithiation/trapping of deuterated thietanes with that observed with the corresponding parent fully protonated thietanes, evidence on the configurational stability or instability of the lithiated intermediates could be obtained. However, prior to running the lithiation reactions, the relative stereochemistry of deuterated thietanes **5b**, **6d**, and **7d** needed to be assessed. In the case of **5b**, NOESY experiments allowed us to assign the relative configuration for ($1R_S$*,2R*,4R*)-**5b** and ($1R_S$*,2R*,4S*)-**5b** (see the SI). In the case of thietanes **6d** and **7d**, because of overlapping signals in their ^{1}H NMR spectra, the relative stereochemistry was assigned by comparison between real and simulated proton NMR spectra.[15] We have found this approach very useful and reliable for other small-sized heterocycles,[6,5c,d,16] and it allowed us to assign, even in this case, the stereochemistry of deuterated thietanes ($1R_S$*,2R*,4R*)-**6d**, ($1R_S$*,2R*,4S*)-**6d**, ($1R_S$*,2R*,4R*)-**7d**, or ($1R_S$*,2R*,4S*)-**7d** (see the SI for details).

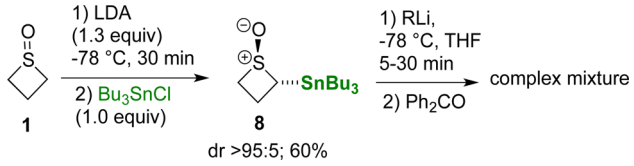
When a diastereomeric mixture of deuterated thietanes **6d** and **7d** was subjected to lithiation, followed by trapping with benzophenone, a mixture of the corresponding hydroxyalkylated adducts was obtained (Scheme 8). In both experiments, ESI-MS analysis showed a sensible reduction of deuterium content as a consequence of a weak KIE. As reported in Scheme 8, thietanes **6d** or **7d** behave similarly. In the reaction of ($1R_S$*,2R*,4R*)-**6d** and ($1R_S$*,2R*,4S*)-**6d**, the corresponding adducts ($1R_S$*,2S*,4S*)-**4d-D** and ($1R_S$*,2R*,4S*)-**5d-D** formed with 72% yield and a diastereomeric ratio of 56:44, respectively. The deuterium content was reduced to 18% in each diastereomer, which is about 75% less with respect to the starting material. Similarly, lithiation/trapping of ($1R_S$*,2R*,4R*)-**7d** and ($1R_S$*,2R*,4S*)-**7d** furnished thietanes ($1R_S$*,2S*,4S*)-**4c-D** and ($1R_S$*,2R*,4S*)-**5c-D** in 65% yield and 45:55 ratio, respectively. The deuterium content of the products was reduced even in this case to 23% (about 70% less than the starting material).

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

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

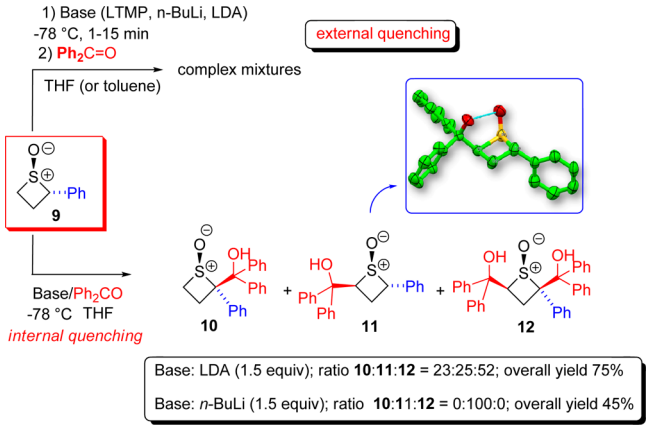
We also explored an alternative pathway, involving thietane **8**, to get more insights about the configurational (in)stability of lithiated thietanes. Thietane **8** was prepared by a lithiation/trapping sequence of **1**, using Bu_3SnCl as the electrophile. Nevertheless, attempts to generate the corresponding lithiated thietane stereospecifically,[19] by a tin−lithium exchange reaction on stannilated thietane **8**, failed (Scheme 9).

Scheme 9



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

Scheme 10. Lithiation/Substitution of 2-Phenylthietane 9



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

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of the lithiated 2-aryl thietane **9** was pursued. By addition of a solution of LDA (1.5 equiv) to a precooled THF solution (−78 °C) of **9** and benzophenone (1 equiv), a mixture of functionalized 2-arylthietane 1-oxides **10**, **11**, and **12** was obtained in 75% overall yield (Scheme 10). The presence of derivatives **11** and **12** shows that the kinetic acidity of the methylene protons competes very well with the thermodynamic acidity of the benzylic proton.

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

CONCLUSIONS

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

EXPERIMENTAL SECTION

General Methods. THF was freshly distilled under a nitrogen atmosphere over Na/benzophenone. Toluene was freshly distilled under a nitrogen atmosphere over CaH_2. Diisopropylamine (DIPA) was distilled over finely powdered CaH_2, *n*-butyllithium was purchased as hexane solution, and the title was established by a titration method.[22] All the other chemicals were commercially available and used without further purification. Magnetic resonance spectra were recorded using 400, 500, 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 an 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). The high-resolution mass spectrometry (HRMS) analyses were performed using a mass spectrometer equipped with an electrospray ion source (ESI) operated in positive ion mode and a time-of-flight analyzer. The sample solutions (CH_3OH) were introduced by continuous infusion with a syringe pump at a flow rate of 180 μL min^{-1}. The instrument was operated with end-plate offset and capillary voltages set to −500 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 voltages were 90 and 30 V, respectively. The drying gas temperature was set at 180 °C. The calibration was carried out with a sodium formate solution (10 mM NaOH in isopropanol/water 1:1 (+0.2% HCOOH)). For flash chromatography, silica gel 60, 0.04−0.063 mm particle size was used. All reactions involving air-sensitive reagents were performed under argon in oven-dried glassware using a syringe septum cap technique.

General Procedure for Lithiation/Electrophile Trapping Sequence on C2-Substituted Thietane 1-Oxide. Starting materials were prepared following a reported procedure.[6] To a stirred solution of DIPA (2.5 equiv for **2a** and *diast*-**2a** and 1.3 equiv for **2b**,**c**) in 8.0 mL of dry THF at 0 °C, a solution of *n*-BuLi (2.5 M in hexane, 2.5 equiv for **2a** and *diast*-**2a** and 1.3 equiv for **2b**,**c**) was added dropwise. After 20 min at 0 °C, the solution of LDA was cooled down to −78 °C and thietanes 1-oxide (1.0 mmol, 1.0 equiv) in 2.0 mL of dry THF was added dropwise. After stirring for 30 min at −78 °C, the electrophile (1.3 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 2 mL of saturated NH_4Cl, poured in water (10 mL), and extracted with AcOEt (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. Flash chromatography on silica gel (Hexane/AcOEt) afforded 2,4-disubstituted thietanes 1-oxides.

(1R$_S$,2S*,4R*)-2-(Hydroxydiphenylmethyl)-4-methylthietane 1-Oxide (1R$_S$*,2S*,4R*)-**4a**.* Column chromatography on silica gel (Hexane/AcOEt 70:30), pale yellow solid, mp 173−176 °C, 90% (255 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.51 (d, J = 7 Hz, 3 H), 1.82 (t, J = 11 Hz, 1 H), 2.45−2.55 (m, 1 H), 2.8 (br s, OH), 3.44 (quintet, J = 7 Hz, 1 H), 4.38 (t, J = 9 Hz, 1 H), 7.20−7.25 (m, 1 H), 7.25−7.30 (m, 5 H), 7.30−7.40 (m, 2 H), 7.50−7.55 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 0.2, 22.1, 47.4, 71.8, 78.6, 125.9, 127.3, 127.5, 128.2, 128.4, 128.9, 143.7, 144.4. FT-IR (KBr, cm^{-1}) υ 699, 747, 1002, 1035, 1170, 1447, 2953, 3317. HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{17}H_{18}SO_2Na$ 309.0920; found 309.0927.

(1R$_S$,2S*,4R*)/(1R$_S$*,2S*,4S*)-**4b**.* Mixture of diastereoisomers *dr* 50:50. Column chromatography on silica gel (Hexane/AcOEt 70:30), waxy solid, 85% D (235 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.96−2.02 (m, 1 H), 2.07−2.15 (m, overlapping s at 2.10 Acetone, 1 H), 2.75 (bs, 1 H), 2.87−2.93 (m, 0.6 H), 3.30−3.34 (m, 0.57 H), 4.30 (dd, J = 9.9, 11.4 Hz, 1 H), 7.16−7.19 (m, 1 H), 7.22−7.26 (m, 5 H), 7.29−7.32 (m, 2 H), 7.45−7.46 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.1, 46.4 (t, J = 22.2 Hz), 46.5 (t, J = 24.4 Hz), 46.7, 75.4, 75.5, 78.3, 126.0, 127.4, 127.5, 127.6, 128.3, 128.5, 128.9, 143.8, 144.3. ESI-MS: m/z (rel. int.): 295 [M_H + Na]$^+$(32); 296 [M_D + Na]$^+$(100).

(1R$_S$,2S*,4S*)-2-(Hydroxydiphenylmethyl)-4-(3-propenyl)-thietane 1-Oxide (1R$_S$*,2S*,4S*)-**4c**.* Column chromatography on silica gel (Hexane/AcOEt 50:50), white solid mp 144−146 °C, 8% (24 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.81 (q, J = 12.1 Hz, 1 H), 2.05−2.14 (m, 1 H), 2.32−2.39 (m, 1 H), 2.46−2.54 (m, 1 H), 3.10−3.19 (m, 1 H), 4.07 (dd, J = 11.6, 9.7 Hz, 1 H), 5.00−5.08 (m, 2 H), 5.67 (ddt, J = 17.0, 10.2, 6.7 Hz, 1 H), 7.14−7.31 (m, 8 H), 7.44−7.46 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.1, 35.9, 61.0, 71.1, 78.2, 118.3, 125.9, 127.4, 127.5, 128.3, 128.4, 128.9, 133.1, 143.9, 144.4. FT-IR (KBr, cm^{-1}) υ 700, 749, 764, 1043, 1266, 1447, 2981, 3056, 3272. HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{19}H_{20}SO_2Na$ 335.1076; found 335.1069.

(1R$_S$,2S*,4R*)-2-(Hydroxydiphenylmethyl)-4-(3-propenyl)-thietane 1-Oxide (1R$_S$*,2S*,4R*)-**4c**.* Column chromatography on silica gel (Hexane/AcOEt 70:30), pale yellow solid, mp 173−176 °C, 70%, (219 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.85−1.92 (m, 1 H), 2.36 (dt, J = 9.5, 13.5 Hz, 2 H), 2.62−2.71 (m, 1H), 3.23−4.14 (m, 1 H), 4.25 (t, J = 10.4 Hz, 1 H), 4.98−5.05 (m, 2 H), 5.63−5.73 (m, 1

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H), 7.13−7.16 (m, 1 H), 7.18−7.22 (m, 5 H), 7.25−7.27 (m, 2 H), 7.41−7.42 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.4, 30.7, 50.7, 71.5, 78.3, 117.8, 125.8, 127.2, 128.3, 128.7, 133.6, 143.7, 144.3. FT-IR (KBr, cm^{-1}) υ 698, 754, 913, 1052, 1447, 1493, 2948, 3059, 3256. HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{19}H_{20}SO_2Na$ 335.1076; found 335.1069.

(1R_S,2S*,4S*)-4-Benzyl-2-(hydroxydiphenylmethyl)thietane 1-Oxide (1R_S*,2S*,4S*)-**4d**.* Column chromatography on silica gel (Hexane/AcOEt 70:30), white solid, mp 128−131 °C. 29% (105 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.80 (q, J = 12 Hz, 1 H), 1.94−2.00 (m, 1 H), 2.76 (dd, J = 10, 14 Hz, 1 H), 3.14 (dd, J = 6, 14 Hz, 1 H), 3.01 (bs, 1 H, OH), 3.24−3.30 (m, 1 H), 4.03 (t, J = 11 Hz, 1 H), 7.05 (d, J = 8 Hz, 2 H), 7.11−7.13 (m, 2H), 7.17−7.21 (m, 7H), 7.25 (t, J = 8 Hz, 2H), 7.43 (d, J = 8 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.4, 37.9, 62.3, 71.3, 78.0, 125.9, 126.9, 127.3$_9$, 127.4$_3$, 128.1, 128.4, 128.7, 128.7$_9$, 128.8$_4$, 137.4, 144.0, 144.5. FT-IR (film, cm^{-1}) υ 705, 759, 1027, 1059, 1166, 1343, 1447, 1496, 1603, 2918, 3026, 3062, 3314. HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{23}H_{22}SO_2Na$ 385.1233; found 385.1216.

(1R_S,2S*,4R*)-4-Benzyl-2-(hydroxydiphenylmethyl)thietane 1-Oxide (1R_S*,2S*,4R*)-**4d**.* Column chromatography on silica gel (Hexane/AcOEt 70:30), pale yellow solid, mp 139−141 °C. 36% (134 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.03−2.11 (m, 1 H), 2.46 (ddd, J = 9, 10, 13 Hz, 1 H), 2.97 (dd, J = 10, 14 Hz, 1 H), 3.41 (dd, J = 6, 14 Hz, 1 H), 3.51−3.59 (m, 1H), 4.38−4.41 (m, 1 H), 7.20−7.25 (m, 4 H), 7.28−7.32 (m, 7 H), 7.36−7.38 (m, 2 H), 7.52−7.54 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.1, 32.3, 52.7, 71.4, 78.5, 125.9, 127.2, 128.5, 128.8, 128.9, 129.3, 137.8, 143.7, 144.3. FT-IR (KBr, cm^{-1}) υ 700, 754, 1032, 1384, 1448, 1494, 1601, 1628, 2924, 3027, 3059, 3418. HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{23}H_{22}SO_2Na$ 385.1233; found 385.1247.

(1R_S,2S*,4S*)-2-(Hydroxydiphenylmethyl)-4-(4-chlorophenyl-hydroxymethyl)thietane 1-Oxide (1R_S*,2S*,4S*)-**4e**.* First eluted diastereoisomer. Column chromatography on silica gel (Hexane/AcOEt 50:50), white solid mp. 186−188 °C. 35% (144 mg). ^{1}H NMR (600 MHz, CD_3OD) δ 2.47 (m,1 H), 2.78−2.83 (m, 1 H), 3.59−3.62 (m,1 H), 4.73 (t, J = 10.1 Hz, 1 H), 5.33 (d, J = 4.6 Hz, 1H), 7.23−7.27 (m,2 H), 7.31−7.33 (m, 6H), 7.37−7.41 (m, 4H), 7.50 (d, J = 9.1 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.3, 57.0, 69.3, 74.5, 78.9, 127.4, 127.9, 128.4, 128.5, 128.9, 129.3$_0$, 129.3$_1$, 129.5, 134.3, 142.2, 145.7, 145.9. FT-IR (KBr, cm^{-1}) υ 699, 1004, 1013, 1399, 1447, 1491, 1598, 3058, 3390. HRMS (ESI-TOF) m/z [M + Na] calcd for $C_{23}H_{21}ClSO_3Na$ 435.0792; found 435.0787.

(1R_S,2S*,4S*)-2-(hydroxydiphenylmethyl)-4-(4-chlorophenyl-hydroxymethyl)thietane 1-Oxide (1R_S*,2S*,4S*)-**4e**.* Second eluted diastereoisomer. Column chromatography on silica gel (Hexane/AcOEt 50:50), white solid, mp 164−166 °C. 35% (147 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ1.94−1.99 (m, 1 H), 2.36−2.41 (m, 1 H), 3.49−3.52 (m, 1 H), 4.15 (bs, 1 H), 4.45 (t, J = 10.5 Hz, 1 H), 5.39 (d, J = 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 = 7.7 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.6, 56.0, 71.4, 73.5, 78.5, 125.9, 127.0, 127.9, 128.57, 128.65, 128.70, 129.08, 129.14, 134.5, 138.2, 143.2, 143.8. FT-IR (KBr, cm^{-1}) υ 701, 1013, 1032, 1447, 1491, 1638, 1733, 2924, 3413. HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{23}H_{21}ClSO_3Na$ 435.0792; found 435.0790.

(1R_S,2S*,4S*)-2-(Hydroxydiphenylmethyl)-4-(1-hydroxy-cyclohex-2-en-1-yl)thietane 1-Oxide (1R_S*,2S*,4S*)-**4f**.* First eluted diastereoisomer. Column chromatography on silica gel (Hexane/AcOEt 70:30), waxy solid. 31% (109 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.39−1.47 (m,1H), 1.48−1.57 (m,1H), 1.71−1.85 (m, 2H) 1.94−2.02 (m, 1H) 2.03−2.13 (m, 1H) 2.53−2.62 (m, 1H), 2.83−2.92 (m, 1H), 3.34 (dd, J = 9.9, 5.7 Hz, 1H), 4.56 (dd, J = 10.6, 9.4 Hz, 1H) 5.86 (dt, J = 10.1, 3.7 Hz, 1H), 6.08 (d, J = 10.2 Hz, 1H), 7.28−7.35 (m, 6H), 7.38 (t, J = 7.6 Hz, 2H), 7.49 (d, J = 8.0 Hz, 2H).). ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.4, 19.3, 25.1, 32.5, 56.0, 72.0, 72.8, 78.6, 125.8, 126.6, 127.6, 128.2, 128.5, 128.9, 129.9, 130.9, 143.2, 143.7. FT-IR (KBr, cm^{-1}) υ 700, 732, 910, 1031, 1165, 1447, 1493, 1646, 2929, 3400. HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{22}H_{24}SO_3Na$ 391.1338; found 391.1345.

(1R_S,2S*,4S*)-2-(Hydroxydiphenylmethyl)-4-(1-hydroxy-cyclohex-2-en-1-yl)thietane 1-Oxide (1R_S*,2S*,4S*)-**4f**.* Second eluted diastereoisomer. Column chromatography on silica gel (Hexane/AcOEt 70:30), sticky oil. 30% (110 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.57−1.68 (m, 1H), 1.80−1.88 (m, 1H), 189−2.03 (m, 2H), 2.01−2.16 (m, 2H), 2.58−2.66 (m, 1H), 2.93−3.01 (m, 1H), 3.32(dd, J = 9.8, 6.0 Hz, 1H), 4.56 (t, J = Hz, 1H), 5.58 (d, J = 10.1 Hz, 1H), 5.90−5.83 (m, 1H) 725−7.35 (m, 6H), 7.36−7.41 (m, 2H), 7.47−7.50 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.7, 19.7, 24.9, 29.7, 35.5, 55.3, 71.6, 72.8, 78.6, 1258.8, 126.6, 126.9, 127.6, 128.2, 128.5, 128.9, 131.4, 143.2, 143.7. FT-IR (KBr, cm^{-1}) υ 700, 735, 910, 1031, 1160, 1448, 1493, 1713, 2929, 3369. HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{22}H_{24}SO_3Na$ 391.1338; found 391.1343.

(1R_S,2S*,4S*)-2-(Hydroxydiphenylmethyl)-4-(1-hydroxy-cyclohexyl)thietane 1-Oxide (1R_S*,2S*,4S*)-**4g**.* Column chromatography on silica gel (Hexane/AcOEt 30:70), sticky oil. 65% (240 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.08−1.22 (m, 1H), 1.24−1.34 (m, 2H), 1.35−1.52 (m, 3H), 1.54−1.78 (m, 4H) 2.5−2.57 (m, 1 H), 2.87−2.96 (m, 1 H), 3.24 (dd, J = 9.8, 5.9 Hz, 1H), 4.53 (dd, J = 11.0, 8.7 Hz, 1H), 7.34−7.24 (m, 6H), 7.37 (t, J = 7.6 Hz, 2H), 7.48 (d, J = 7.8 Hz, 2H). FT-IR (film, cm^{-1}) υ 701, 753, 999, 1264, 1447, 1493, 1599, 1694, 2858, 2932, 3058, 3391. ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.3, 21.2. 21.4, 25.9, 33.3, 34.0, 55.6, 71.7, 74.5, 48.5, 125.9, 126.6, 127.6, 128.1, 128.5, 128.8, 143.2, 143.8. HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{22}H_{26}SO_3Na$ 393.1495; found 393.1504.

(1R_S,2R*,4S*)-2-(Hydroxydiphenylmethyl)-4-methylthietane 1-Oxide (1R_S*,2R*,4S*)-**5a**.* Column chromatography on silica gel (Hexane/AcOEt 70:30), pale yellow solid, mp 134−137 °C. 62% (178 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.43 (d, J = 7 Hz, 3 H), 1.92−2.08 (m, 1H), 3.03−3.20 (m, 1 H), 3.58−3.70 (m, 1 H), 4.25−4.42 (m, 1 H), 7.11−7.13 (m, 1 H), 7.17−7.23 (m, 3 H), 7.25−7.33 (m, 4 H), 7.46 (d, J = 8 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.6, 26.1, 55.2, 59.4, 80.2, 125.8, 126.0, 127.0, 127.6, 128.4, 128.7, 143.6, 145.9. FT-IR (KBr, cm^{-1}) υ 701, 740, 758, 984, 998, 1068, 1172, 1258, 1407, 1450, 1493, 2962, 3026, 3362. HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{17}H_{18}SO_2Na$ 309.0920; found 309.0928.

(1R_S,2R*,4R*)-2-(Hydroxydiphenylmethyl)-4-methylthietane 1-Oxide (1R_S*,2R*,4R*)-**5a**.* Column chromatography on silica gel (Hexane/AcOEt 70:30), pale yellow oil. 16% (45 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.31 (d, J = 6.7 Hz, 3 H), 2.70 (dt, J = 7.2, 11.2 Hz, 1H), 3.39−3.50 (m, 2 H), 4.02 (dd, J = 8.0, 10.5 Hz, 1 H), 7.11−7.13 (m, 1 H), 7.18−7.22 (m, 2 H), 7.25−7.33 (m, 5 H), 7.51−7.53 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.0, 31.6, 47.8, 54.3, 79.6, 125.6, 126.1, 127.2, 127.7, 128.4, 128.8, 143.7, 145.2. FT-IR (film, cm^{-1}) υ 701, 740, 758, 984, 998, 1068, 1172, 1258, 1407, 1450, 1493, 2962, 3026, 3362. HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{17}H_{18}SO_2Na$ 309.0920; found 309.0918.

(1R_S,2R*,4R*)/(1R_S*,2R*,4S*)-**5b**.* Mixture of diastereoisomers *dr* 70:30. Column chromatography on silica gel (Hexane/AcOEt 70:30), white solid, 71% D (194 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.39−2.46 (m, 1 H), 3.08−3.14 (m, 0.38 H), 3.28−3.35 (m, 1 H), 3.41−3.47 (m, 0.82 H), 4.35 (t, J = 8.3 Hz, 0.90 H), 5.77 (bs, 1 H), 7.09−7.29 (m, 8 H), 7.43−7.46 (m, 2 H). 295 $[M_H + Na]^+$(37); 296 $[M_D + Na]^+$(100).

(1R_S,2R*,4S*)-2-(Hydroxydiphenylmethyl)-4-(3-propenyl)-thietane 1-Oxide (1R_S*,2R*,4S*)-**5c**.* Column chromatography on silica gel (Hexane/AcOEt 50:50), white solid, mp 132−135 °C. 75% (234 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.01−2.07 (m, 1 H), 2.41−2.46 (m, 1 H), 2.50−2.55 (m, 1 H), 3.03 (ddd, J = 13.4, 11.4, 6.2 Hz, 1 H), 3.59−3.65 (m, 1 H), 4.33 (dd, J = 9.5, 6.2 Hz, 1 H), 5.07−5.10 (m, 2 H), 5.49 (bs, 1 H), 5.67−5.75 (m 1 H), 7.10 (t, J = 7.7 Hz, 1 H), 7.16−7.22 (m, 3 H), 7.26−7.29 (m, 4 H), 7.45 (d, J = 8.7 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.8, 36.1, 55.4, 63.0, 80.2, 118.7, 125.8, 125.9, 127.1, 127.6, 128.4, 128.7, 132.8, 143.6, 145.9. FT-IR (KBr, cm^{-1}) υ 703, 739, 1013, 1266, 1450, 2984, 3054, 3342. HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{19}H_{20}SO_2Na$ 335.1076; found 335.1066.

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

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^{1}H NMR (600 MHz, $CDCl_3$) δ 2.07 (ddd, J = 8, 10, 13 Hz, 1 H), 2.94−3.00 (m, 2 H), 3.15 (dd, J = 7, 14 Hz, 1 H), 3.80−3.86 (m, 1 H), 4.29 (ddd, J = 1, 6, 10 Hz, 1 H), 5.44 (bs, 1 H, OH), 7.08−7.11 (m, 3 H), 7.15−7.27 (m, 10H), 7.42−7.44 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.9, 38.1, 55.4, 65.5, 80.2, 125.7, 125.9, 127.0, 127.2, 127.6, 128.4, 128.7, 128.8$_9$, 128.9$_4$, 136.9, 143.6, 145.9. FT-IR (KBr, cm^{-1}) υ 675, 700, 759,769, 1016, 1033, 1060, 1178, 1193, 1407, 1450, 1493, 1601, 2919, 2935, 3025, 3308. HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{23}H_{22}SO_2Na$ 385.1233; found 385.1216.

(1R$_S$,2R*,4S*)-2-Benzyl-4-methylthietane 1-Oxide (1R$_S$*,2R*,4S*)-**6a**.* Column chromatography on silica gel (AcOEt), pale yellow oil. 39% (75 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (q, J = 12.2 Hz, 1H), 1.45 (d, J = 6.8 Hz, 3H), 2.49 (dt, J = 12.6, 9.5 Hz, 1H), 2.97 (dd, J = 14.2, 8.5 Hz, 1H), 3.18−3.23 (M, 1H), 3.25 (dd, J = 14.0, 6.4 Hz, 1H), 7.19 (d, J = 7.3 Hz, 2H), 7.24 (t, J = 7.4 Hz, 1H), 7.31 (t, J = 7.4 Hz, 2H).). ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.8, 24.2, 37.9, 59.3, 64.2, 126.9, 128.64, 128.8, 137.2. FT-IR (film, cm^{-1}) υ 702, 1065, 1376, 1453, 1496, 2925, 3467. HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{11}H_{14}SONa$ 217.0658; found 217.0664.

(1R$_S$,2R*,4R*)-2-Benzyl-4-methylthietane 1-Oxide (1R$_S$*,2R*,4R*)-**6a**.* Column chromatography on silica gel (AcOEt), pale yellow oil, 31% (61 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.49 (d, J = 7 Hz, 3 H), 1.99−2.16 (m, 2 H), 2.98 (dd, J = 8, 14 Hz, 1 H), 3.24 (dd, J = 7, 14 Hz, 1 H), 3.52 (quintet, J = 7 Hz, 1 H), 3.69 (quintet, J = 8 Hz, 1 H), 7.10−7.37 (m, 5 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.6, 25.3, 38.0, 49.5, 65.3, 127.0, 128.8, 128.9, 137.4. FT-IR (film, cm^{-1}) υ 702, 1065, 1376, 1453, 1496, 2925, 3467. HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{11}H_{14}SONa$ 217.0658; found 217.0661.

(1R$_S$,2S*,4S*)-2-[(4-Chlorophenyl)hydroxymethyl)]-4-benzylthietane 1-Oxide (1R$_S$*,2S*,4S*) **6b**.* Mixture of diastereomers at the carbinolic carbon, *dr* 50:50. Column chromatography on silica gel (AcOEt), colorless oil. 71% (224 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.44 (q, J = 12.2 Hz, 1 H), 1.72 (q, J = 12.2 Hz, 1 H), 2.07−2.13 (m, overlapping s Acetone at 2.09, 2 H), 2.83−2.90 (m, 2 H), 3.14−3.20 (m, 2 H), 3.26−3.37 (m, 4 H), 4.69 (d, J = 8.7 Hz, 1 H), 5.09 (d, J = 3.7 Hz, 1 H), 7.08−7.09 (m, 3 H), 7.15−7.25 (m, 15 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.4, 20.4, 37.8, 63.3, 69.1, 70.1, 73.5, 127.1−126.5, 128.6−129.1, 133.9, 133.3, 136.9, 137.0, 139.1, 139.2. FT-IR (film, cm^{-1}) υ 703, 735, 841, 1047, 1245, 1454, 1493, 1602, 1732, 2925, 3334. HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{17}H_{17}ClSO_2Na$ 343.0530; found 343.0516.

(1R$_S$,2R*,4S*)-4-Benzyl-2-(1-hydroxycyclohex-2-en-1-yl)thietane 1-Oxide (1R$_S$*,2R*,4S*) **6c**.* Major diastereomer. Column chromatography on silica gel (Hexane/AcOEt 50:50), pale yellow oil. 42% (110 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.50−1.57 (m, 1 H), 1.75−1.82 (m, 1 H), 1.84−1.94 (m, 2 H), 1.98−2.44 (m, overlapping s, AcOEt, 2 H), 2.92−3.04 (m, 2 H), 3.14 (dd, J = 7, 14 Hz, 1 H), 3.30 (ddd, J = 6, 7, 15 Hz, 1 H), 3.87−3.97 (m, 1 H), 4.21 (bs, 1 H, OH), 5.54 (d, J = 10 Hz, 1 H), 5.80 (dt, J = 4, 1 Hz, 1 H), 7.13−7.14 (m, 2 H), 7.17−7.20 (m, 1 H), 7.24−7.26 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.8, 22.7, 25.0, 35.8, 38.3, 57.2, 65.2, 72.9, 127.0$_9$, 127.1$_4$, 128.8, 128.9, 131.6, 137.0. FT-IR (film, cm^{-1}) υ 700, 735, 1010, 1186, 1262, 1429, 1454, 1496, 1672, 1707, 2866, 2935, 3027, 3392. HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{16}H_{20}SO_2Na$ 299.1076; found 299.1078.

(1R$_S$,2R*,4S*)-4-Benzyl-2-(1-hydroxycyclohex-2-en-1-yl)thietane 1-Oxide (1R$_S$*,2R*,4S*) **6c**.* Minor diastereomer. Column chromatography on silica gel (Hexane/AcOEt 50:50), pale yellow oil. 23% (70 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.32−1.36 (m, 1 H), 1.43−1.49 (m, 1 H), 1.68−1.76 (m, 1 H), 1.86−1.93 (m, 1 H), 1.97−2.09 (m, 2 H), 2.90−2.97 (m, 2 H), 3.15 (dd, J = 7, 14 Hz, 1 H), 3.31 (dd, J = 9.5, 5.1 Hz, 1 H), 3.86−3.97 (m, 1 H), 4.19 (bs, 1 H, OH), 5.77 (dt, J = 10, 4 Hz, 1 H), 5.99 (d, J = 10.2 Hz, 1 H), 7.13−7.14 (m, 2 H), 7.17−7.19 (m, 1 H), 7.23−7.26 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.5, 24.5, 27.3, 34.6, 40.6, 60.5, 67.5,, 129.2, 130.8, 130.9, 132.0, 133.39. FT-IR (film, cm^{-1}) υ 700, 734, 1029, 1188, 1454, 1496, 1712, 2851, 2930, 3027, 3400. HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{16}H_{20}SO_2Na$ 299.1076; found 299.1067.

(1R$_S$,2R*,4R*)/(1R$_S$*,2R*,4S*)-**6d**.* Mixture of diastereoisomers *dr* 70:30. Column chromatography on silica gel (AcOEt), yellow oil, 72.4% D (134 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.56−1.65 (m, 1 H), 2.24−2.33 (m, 1 H), 2.86−2.96 (m, 1.47 H), 3.17 (dd, J = 6.3, 14.3 Hz, 1 H), 3.32−3.37 (m, 0.83 H), 3.52−3.61 (m, 1 H), 7.12−7.14 (m, 2 H), 7.15−7.20 (m, 1 H), 7.23−7.26 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.3, 16.4, 38.1, 48.1 (t, J = 22.4 Hz), 48.2 (t, J = 23.3 Hz), 48.5, 68.9, 127.0, 128.8, 128.9, 137.1. 153 ESI-MS: m/z (rel. int.): 203[M_H + Na]$^+$(34); 204 [M_D + Na]$^+$(100).

(1R$_S$,2R*,4R*)-2-Benzyl-4-(3-propenyl)thietane 1-Oxide (1R$_S$*,2R*,4R*)-**6e**.* Column chromatography on silica gel (Hexane/AcOEt 50:50), colorless oil. 35% (76 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.92 (ddd, J = 8, 11, 13 Hz, 1 H), 2.21 (ddd, J = 3, 10, 13 Hz, 1 H), 2.35−2.44 (m, 1 H), 2.69−2.77 (m, 1), 2.92 (dd, J = 9, 14 Hz, 1 H), 3.17 (dd, J = 6, 14 Hz, 1 H), 3.35−3.39 (m, 1 H), 3.58−3.64 (m, 1 H), 5.03−5.08 (m, 2 H), 5.68−5.77 (m, 1 H), 7.11−7.13 (m, 2 H), 7.16−7.19 (m, 1 H), 7.23−7.26 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.4, 30.3, 38.1, 53.0, 65.2, 118.0, 127.0, 128.8, 128.9, 133.8, 137.3. FT-IR (film, cm^{-1}) υ 701, 749, 917, 1005, 1062, 1437, 1454, 1496, 1602, 1639, 2929, 3028, 3062, 3445. HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{13}H_{16}SONa$ 243.0814; found 243.0818.

(1R$_S$,2R*,4S*)-2-Benzyl-4-(3-propenyl)thietane 1-Oxide (1R$_S$*,2R*,4S*)-**6e**.* Column chromatography on silica gel (Hexane/AcOEt 50:50), pale yellow oil. 43% (96 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.34 (like q, 1 H), 2.37−2.45 (m, 2 H), 2.49−2.53 (m, 1 H), 2.90 (dd, J = 9, 14 Hz, 1 H), 3.15−3.24 (m, 2 H), 3.31−3.40 (m, 1 H), 5.04−5.12 (m, 2 H), 5.71 (ddt, J = 7, 10, 17 Hz, 1 H), 7.10−7.13 (m, 2 H), 7.16−7.19 (m, 1 H), 7.22−7.28 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.6, 35.9, 38.0, 63.1, 64.4, 118.3, 127.0, 128.8, 128.9, 133.1, 137.3. FT-IR (film, cm^{-1}) υ 702, 749, 921, 1061, 1299, 1454, 1496, 1640, 2919, 3028, 3063, 3437. ESI-MS: m/z (rel. int.): 221 [M + H]$^+$(100).

(1R$_S$,2R*,4R*)-2-(3-Propenyl)-4-methylthietane 1-Oxide (1R$_S$*,2R*,4R*)-**7a**.* Column chromatography on silica gel (AcOEt), pale yellow oil 42% (61 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.47 (d, J = 7.4 Hz, 3 H), 1.98 (ddd, J = 8.3, 11.9, 13.0 Hz, 1 H), 2.12−2.19 (m, 1 H), 2.43−2.48 (m, 1 H), 2.52−2.57 (m, 1 H), 3.46−3.53 (m, 2H), 5.09−5.15 (m, 2 H), 5.76 (ddt, J = 17.0, 10.2, 6.7 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.7, 25.2, 36.0, 49.4, 63.6, 118.2, 133.1. FT-IR (film, cm^{-1}) υ 920, 997, 1060, 1123, 1439, 1641, 2867, 2929, 2976, 3079, 3467. HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_7H_{12}SONa$ 167.0501; found 167.0500.

(1R$_S$,2S*,4S*)-2-[(4-Chlorophenyl)hydroxymethyl]-4-(3-propenyl)thietane 1-Oxide (1R$_S$*,2S*,4S*)-**7b**.* Mixture of diastereomers *dr* 70:30. Column chromatography on silica gel (AcOEt), yellow oil. 71% (192 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.40 (q, J = 12.1 Hz, 1 H), 1.66 (q, J = 12.2 Hz, 1 H), 2.11−2.17 (m, 2 H), 2.34−2.49 (m, 4 H), 3.08−3.17 (m, 2 H), 3.31−3.38 (m, 2 H), 4.66 (d, J = 8.5 Hz, 1 H), 5.02−5.09 (m, 5 H), 5.63−5.70 (m, 2 H), 7.17−7.24 (m, 8 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.3, 20.2, 35.7, 35.8, 61.9, 69.1, 69.2, 69.9, 73.5, 118.4, 118.5, 127.3, 127.5, 128.8, 129.0, 132.7, 132.8, 133.7, 139.3, 139.4. IR (film, cm^{-1}) υ 757, 841, 923, 1043, 1089, 1490, 1641, 2923, 2979, 3081, 3339. HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{13}H_{15}ClSO_2Na$ 293.0373; found 293.0374.

(1R$_S$,2R*,4S*)-2-(1-Hydroxycyclohex-2-en-1-yl)-4-(3-propenyl)-thietane 1-Oxide (1R$_S$*,2R*,4S*)-**7c**.* Minor diastereomer. Column chromatography on silica gel (Hexane/AcOEt 50:50), yellow oil. 20% (47 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.41−1.61 (m, overlapping s H_2O at 1.60, 2 H), 1.93−2.15 (m, overlapping s AcOEt at 2.04, 3 H), 2.46−2.62 (m, 2 H), 3.07 (ddd, J = 13.2, 11.4, 5.3 Hz, 1 H), 3.37−3.42 (m, 1 H), 3.73−3.84 (m, 1 H), 4.32 (bs, 1 H), 5.15−5.20 (m, 2 H), 5.75−5.88 (m, 2 H), 6.06−6.09 (m, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.6, 22.4, 25.2, 32.7, 36.4, 58.4, 64.1, 72.8, 118.6, 130.0, 131.1, 132.9. FT-IR (film, cm^{-1}) υ 710, 1025, 1266, 1435, 1707, 2943, 3054, 3400. HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{12}H_{18}SO_2Na$ 249.0925; found 249.0920.

(1R$_S$,2R*,4S*)-2-(1-Hydroxycyclohex-2-en-1-yl)-4-(3-propenyl)-thietane 1-Oxide (1R$_S$*,2R*,4S*)-**7c**.* Major diastereomer. Column chromatography on silica gel (Hexane/AcOEt 50:50), yellow oil. 45% (109 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.55−1.66 (m, 1 H), 1.82−2.17 (m, 6 H), 2.49−2.60 (m, 2 H), 3.11 (ddd, J = 13.2, 11.4, 5.4 Hz, 1 H), 3.38 (ddd, J = 9.5, 5.4, 1.3 Hz, 1 H), 3.75−3.81 (m, 1 H), 4.31 (bs,

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1 H), 5.15−5.20 (m, 2 H), 5.63−5.65 (m, 1 H), 5.80 (ddt, J = 17.0, 10.3, 6.7 Hz, 1 H), 5.89 (dt, J = 10.1, 3.7 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.8, 22.7, 35.8, 36.4, 57.3, 63.8, 72.9, 118.6, 127.1, 131.6, 132.9. FT-IR (film, cm^{-1}) υ 710, 1025, 1266, 1435, 1707, 2943, 3054, 3400. HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{12}H_{18}SO_2Na$ 249.0925; found 249.0921.

(1R_S,2R*,4R*)/(1R_S*,2R*,4S*)-**7d**.* Mixture of diastereoisomers *dr* = 71:29. Column chromatography on silica gel (AcOEt), pale yellow oil, 89% D (118 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.62−1.70 (m, 1 H), 2.39−2.63 (m, 3 H), 2.94−3.02 (m, 0.3 H), 3.40−3.52 (m, 1.72 H), 5.13−5.20 (m, 2 H), 5.74−5.85 (m, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.2, 36.1, 48.0$_6$ (t, J = 22.8 Hz), 48.1$_5$ (t, J = 23.2 Hz), 48.4, 67.6, 118.4, 132.9. ESI-MS: m/z (rel. int.): 153 $[M_H + Na]^+$(13); 154 $[M_D + Na]^+$(100).

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

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

General Procedure for Synthesis of 2-Phenyl Thietane-1-Oxide 9. 2-Phenyl thietane was prepared following a reported procedure.[23] To a stirred solution of 1,3-dichloro-1-phenylpropane (10.0 mmol, 1.880 g, 1.0 equiv) in EtOH/H_2O = 80:20 (100 mL) at room temperature was added Na_2S 9H_2O, and then the solution was heated at 70 °C overnight. After the reaction was complete, as determined by GC or TLC, EtOH was removed in vacuo and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. Chromatography on silica gel (Hexane/AcOEt) afforded the 2-phenyl thietane as a pale orange oil (65% yield). To a solution of 2-phenyl thietane (9.05 mmol, 1.358 g, 1 equiv) in glacial acetic acid (2.7 mL, 5.4 equiv) at 0 °C was added H_2O_2 (30 w/w %) (11.76 mmol, 1.4 mL, 1.3 equiv) dropwise. After 5 h at 0−10 °C, a water solution of NaOH (1 M) was slowly added to neutralize the excess of CH_3COOH. The reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. Chromatography on silica gel (AcOEt) gave the 2-phenyl thietane 1-oxide **9** as a pale yellow solid (40% yield).

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

General Procedure for Lithiation−Electrophile Trapping *in Situ* Sequence of *trans* 2-Phenyl Thietane 1-Oxide 9. To a stirred solution of DIPA (1.5 mmol, 0.212 mL, 1.5 equiv) in 8.0 mL of THF at 0 °C was added a solution of *n*-butilithium (2.5 M in hexane, 1.5 mmol, 0.6 mL, 1.5 equiv) dropwise. After 20 min at 0 °C, the solution of LDA was cooled to −78 °C and a mixture of 2-phenyl thietanes-1-oxide (1.0 mmol, 166.0 mg, 1.0 equiv) and benzophenone (1.0 mmol, 182 mg, 1.0 equiv) in 2.0 mL of solvent was added dropwise. After 1 h, as determined by GC or TLC, the reaction mixture was poured in water (10 mL) and extracted with AcOEt (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. Chromatography on silica gel (Hexane/AcOEt) afforded the 2,4-disubstituted thietanes 1-oxide and 2,2,4-trisubstituted thietanes 1-oxide.

(1R_S,2S*)-2-(Hydroxydiphenylmethyl)-2-phenylthietane 1-Oxide **10**.* Column chromatography on silica gel (Hexane/AcOEt 80:20), white solid, 185−188 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.83−2.91 (m, 2 H), 3.24−3.30 (m, 1 H), 4.52−4.58 (m, 1 H), 6.88 (d, J = 7.4 Hz, 2 H), 7.11−7.26 (m, 11 H), 7.40 (d, J = 7.2 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.0, 43.0, 74.1, 84.8, 127.5, 127.6, 127.8, 127.9, 128.0, 128.1, 128.2, 128.5, 128.6, 128.9, 130.9, 131.5, 137.2$_0$, 137.2$_3$, 143.5. FT-IR (KBr, cm^{-1}) υ 702, 737, 1032, 1266, 1447, 1493, 1599, 2927, 3058, 3351. HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{22}H_{20}SO_2Na$ 371.1082; found 371.1076.

(1R_S,2R*,4R*)-2-(Hydroxydiphenylmethyl)-4-phenylthietane 1-Oxide **11**.* Column chromatography on silica gel (Hexane/AcOEt 80:20), white solid, mp 194 °C − dec. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.53 (dt, J = 9.5, 13.7 Hz, 1 H), 3.22 (ddd, J = 5.6, 11.8, 13.7 Hz, 1 H), 4.40−4.50 (m, 1 H), 4.76−4.87 (m, 1 H), 5.37 (bs, 1 H), 7.12−7.15 (m, 1 H), 7.18−7.35 (m, 12 H), 7.48−7.50 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.4, 55.4, 69.0, 80.4, 125.9, 126.0, 127.2, 127.5, 127.7, 128.5, 128.8, 129.2, 136.8, 143.7, 146.0. FT-IR (KBr, cm^{-1}) υ 700, 755, 1037, 1062, 1161, 1447, 1494, 2854, 2924, 3058, 3454. HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{22}H_{20}SO_2Na$ 371.1082; found 371.1076.

(1R_S,2S*,4S*)-2,4-Bis(hydroxydiphenylmethyl)-2-phenylthietane 1-Oxide **12**.* Column chromatography on silica gel (Hexane/AcOEt 80:20), white solid mp 139−142 °C, 70%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.81 (dd, J = 12.8, 7.2 Hz, 1 H), 3.83 (dd, J = 11.8, 7.2 Hz, 1 H), 5.43 (t, J = 12.5 Hz, 1 H), 5.68 (bs, 1 H), 6.79 (d, J = 8.0 Hz, 2 H), 6.84 (bs, 1 H), 7.10−7.39 (m, 23 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 32.9, 52.4, 69.4, 79.5, 84.9, 125.6, 125.9, 127.4$_7$, 127.5$_2$, 127.7, 127.8, 127.9, 128.2, 128.3, 128.5$_0$, 128.5$_3$, 128.5$_9$, 128.6$_3$, 128.8, 131.0, 135.3, 140.7, 143.0, 143.5, 144.5. FT-IR (film, cm^{-1}) υ 700, 735, 1010, 1186, 1262, 1429, 1454, 1496, 1672, 1707, 2866, 2935, 3027, 3392. HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{35}H_{30}SO_3Na$ 553.1813; found 553.1808.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02126.

^{1}H and ^{13}C NMR spectra for new compounds (PDF), and X-ray and calculation data (PDF)
X-ray crystallographic data for **2a** (CIF)
X-ray crystallographic data for *diast*-**2a** (CIF)
X-ray crystallographic data for (1R_S*,2R*,4S*)-**5d** (CIF)
X-ray crystallographic data for **11** (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

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

DOI: 10.1021/acs.joc.5b02126
J. Org. Chem. 2015, 80, 12201−12211

(2) (a) Burkhard, J. A.; Wuitschik, G.; Rogers-Evans, M.; Muller, K.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 9052. (b) Wuitschik, G.; Carreira, E. M.; Wagner, B.; Fischer, H.; Parrilla, I.; Schuler, F.; Rogers-Evans, M.; Muller, K. *J. Med. Chem.* **2010**, *53*, 3227. (c) Ritchie, T. J.; Macdonald, S. J. F.; Young, R. J.; Pickett, S. D. *Drug Discovery Today* **2011**, *16*, 164. (d) Ritchie, T. J.; Macdonald, S. J. F.; Peace, S.; Pickett, S. D.; Luscombe, C. N. *MedChemComm* **2013**, *4*, 673. (e) de Kloe, G. E.; Bailey, D.; Leurs, R.; de Esch, I. J. P. *Drug Discovery Today* **2009**, *14*, 630.

(3) Carreira, E. M.; Fessard, T. C. *Chem. Rev.* **2014**, *114*, 8257.

(4) (a) Rousseau, G.; Robin, S. Four-Membered Heterocycles: Structure and Reactivity. In *Modern Heterocyclic Chemistry*; Alvarez-Builla, J., Vaquero, J. J., Barluenga, J., Eds.; Wiley-VCH: Weinheim, Germany, 2011; Chapter 3, pp 163−268. (b) Four-Membered Heterocycles Together with all Fused Systems Containing a Four-Membered Heterocyclic Ring. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Eds.; Elsevier Ltd: Amsterdam, 2008; Vol. 2, pp 1−989.

(5) (a) Degennaro, L.; Trinchera, P.; Luisi, R. *Chem. Rev.* **2014**, *114*, 7881. (b) Capriati, V.; Florio, S.; Luisi, R. *Eur. J. Org. Chem.* **2014**, *2014*, 5397. (c) Degennaro, L.; Pisano, L.; Parisi, G.; Mansueto, R.; Clarkson, G. J.; Shipman, M.; Luisi, R. *J. Org. Chem.* **2015**, *80*, 6411. (d) Zenzola, M.; Degennaro, L.; Trinchera, P.; Carroccia, L.; Giovine, A.; Romanazzi, G.; Mastrorilli, P.; Rizzi, R.; Pisano, L.; Luisi, R. *Chem. - Eur. J.* **2014**, *20*, 12190. (e) Degennaro, L.; Zenzola, M.; Trinchera, P.; Carroccia, L.; Giovine, A.; Romanazzi, G.; Falcicchio, A.; Luisi, R. *Chem. Commun.* **2014**, *50*, 1698. (f) Parisi, G.; Capitanelli, E.; Pierro, A.; Romanazzi, G.; Clarkson, G. J.; Degennaro, L.; Luisi, R. *Chem. Commun.* **2015**, *51*, 15588. (g) Giovine, A.; Muraglia, M.; Florio, M. A.; Rosato, A.; Corbo, F.; Franchini, C.; Musio, B.; Degennaro, L.; Luisi, R. *Molecules* **2014**, *19*, 11505.

(6) Carroccia, L.; Degennaro, L.; Romanazzi, G.; Cuocci, C.; Pisano, L.; Luisi, R. *Org. Biomol. Chem.* **2014**, *12*, 2180.

(7) (a) Davis, O. A.; Croft, R. A.; Bull, J. A. *Chem. Commun.* **2015**, *51*, 15446. (b) Morgan, K. F.; Hollingsworth, I. A.; Bull, J. A. *Chem. Commun.* **2014**, *50*, 5203. (c) Morgan, K. F.; Hollingsworth, I. A.; Bull, J. A. *Org. Biomol. Chem.* **2015**, *13*, 5265.

(8) CCDC 1423113 and CCDC 978293 contain the crystallographic information for **2a** and *diast*-**2a**.

(9) For convenience, the C4 refers to the carbon where the lithiation/substitution occurs. Relative stereochemistry could change depending on the priority of the ring substituents.

(10) The stereoselectivity in the reactions of sulfinyl carbanions is still an open issue. Recent examples have been reported on this topic; see: (a) Ludwig, G.; Rüffer, T.; Hoppe, A.; Walther, T.; Lang, H.; Ebbinghaus, S. G.; Steinborn, D. *Dalton Trans.* **2015**, *44*, 5323. (b) Volonterio, A.; Zanda, M. Stereoselective Reactions of α-Sulfinyl Carbanions in Organosulfur Chemistry. In *Asymmetric Synthesis*; Toru, T., Bolm, C., Eds.; Wiley-VCH: Weinheim, 2008; Chapter 11, pp 351−374. (c) Luisi, R.; Capriati, V. Lithium Compounds. In *Organic Synthesis: From Fundamentals to Application*, 1st ed.; Wiley-VCH: Weinheim, 2014. (d) Hutchinson, B. J.; Andersen, K. K.; Katritzky, A. R. *J. Am. Chem. Soc.* **1969**, *91*, 3839.

(11) Unfortunately, for this reaction, we were unable to reproduce the level of stereoselectivity reported in ref 6. The diastereoselectivity reported here is an average of 5 trials.

(12) CCDC 1423111 contains the crystallographic information for ($1R_S$*,2*R**,4*S**)-**5d**.

(13) With reference to the carbinolic carbon, the level of stereoselectivity was low and a mixture of the two corresponding diastereomers was isolated (see the SI).

(14) Mansueto, R.; Degennaro, L.; Briere, J.-F.; Griffin, K.; Shipman, M.; Florio, S.; Luisi, R. *Org. Biomol. Chem.* **2014**, *12*, 8505.

(15) The Supporting Information reports DFT calculations and NMR simulations.

(16) Azzena, U.; Dettori, G.; Pisano, L.; Musio, B.; Luisi, R. *J. Org. Chem.* **2011**, *76*, 2291.

(17) For similar studies, see: (a) Hodgson, D. M.; Pearson, C. I.; Thompson, A. L. *J. Org. Chem.* **2013**, *78*, 1098. (b) Řehová, L.; Jahn, U. *Eur. J. Org. Chem.* **2014**, *2014*, 4610.

(18) We assume the presence of a C−Li bond for those intermediates. Nevertheless, crystal structures of lithiated sulfinyl carbanions revealed a free carbanion with O−Li contacts. See ref 9a and references therein.

(19) (a) Clayden, J.; Helliwell, M.; Pink, J. H.; Westlund, N. *J. Am. Chem. Soc.* **2001**, *123*, 12449. (b) Pearson, W. H.; Lindbeck, A. C. *J. Am. Chem. Soc.* **1991**, *113*, 8546.

(20) CCDC 1423112 contains crystallographic information for **11**.

(21) Previous reports on lithiated thietane 1-oxides exploited their propensity to undergo ring-opening; see: Jones, D. N.; Kogan, T. P.; Newton, R. F.; Smith, S. *J. Chem. Soc., Chem. Commun.* **1982**, 589.

(22) Degennaro, L.; Giovine, A.; Carroccia, L.; Luisi, R. Practical Aspects of Organolithium Chemistry. In *Lithium Compounds in Organic Synthesis: From Fundamentals to Application*, 1st ed.; Luisi, R., Capriati, V., Eds.; Wiley-VCH: Weinheim, 2014; Chapter 18, pp 513−538.

(23) (a) Almena, J.; Foubelo, F.; Yus, M. *Tetrahedron* **1997**, *53*, 5563. (b) Volynskii, N. P.; Shevchenko, S. E. *Pet. Chem.* **2007**, *47*, 109−117.

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J. Org. Chem. 2015, 80, 12201−12211