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Studies on the Formal [3 + 2] Cycloaddition of Aziridines with Alkenes for the Synthesis of 1-Azaspiroalkanes

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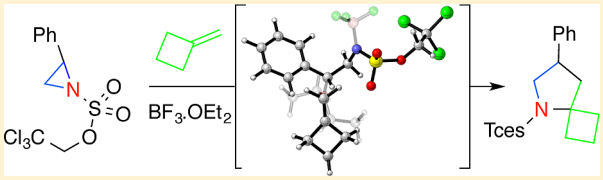
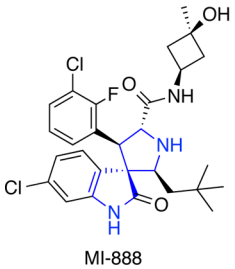
Supporting Information

ABSTRACT: The Lewis acid-mediated [3 + 2] cycloaddition of *N*-sulfonyl- and *N*-sulfamoylaziridines with alkenes provides a rapid and efficient access to 1-azaspiro[4.*n*]alkanes. Experimental studies have been combined with DFT calculations to explore the mechanism of the reaction. They demonstrate that the nature of the electron-withdrawing nitrogen protecting group has a very limited influence on the course of the reaction and, particularly, on the initial formation of the 1,3-zwitterionic species through C−N bond cleavage, which has been found to be the rate-determining step. Compared to *N*-sulfonylaziridines, *N*-sulfamoylaziridines have proved to be more synthetically useful synthons that afford crystalline polycyclic structures in good yields. A short sequence of catalytic C(sp^3)-H amination−cyclization−[3 + 2] cycloaddition has then been successfully designed to afford the homologue 1-azaspiro[5.*n*]alkanes, thereby illustrating the higher versatility of sulfamates in these cycloadditions.

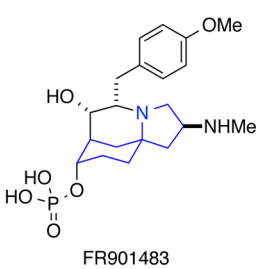


INTRODUCTION

Growing attention is being paid to the development of methodologies for the synthesis of spirocyclic compounds.[1] These 3D-scaffolds offer new opportunities in organic chemistry, as they allow the exploration of a chemical space orthogonal to that provided by sp^2-based molecular structures.[2] This is particularly relevant in medicinal chemistry where the introduction of such motifs could influence either the pharmacodynamic or the pharmacokinetic properties of a drug candidate.[3] Among the frameworks accessible to the chemists, azaspirocycles hold paramount importance because the insertion of a protonable nitrogen can generally improve the solubility of bioactive molecules. Accordingly, the occurrence of these nitrogenous motifs in medicinal chemistry has increased in the past decade with several derivatives being reported for their antimitotic or antibacterial activities.[4] One of the leading members, MI-888 (Figure 1), belongs to the family of spirooxindoles which is a potent orally active anticancer agent acting through inhibition of MDM2−p53 interaction.[5] It is worth mentioning that azaspirocycles can be also found in several natural products, as for example in the immunosuppressive alkaloid FR901483.[6]



MI-888



FR901483

Figure 1. Azaspirocyclic compounds.

Various strategies have been reported over the years for the synthesis of azaspirocyclic scaffolds.[1,7] These range from classical alkylation methods to ring-closing metathesis and include ring rearrangements, metal-catalyzed additions to alkenes, and cycloaddition reactions. Among these transformations, cycloadditions provide an elegant solution, as several bonds can be formed efficiently and selectively in a single pot. Different types of cycloadditions have thus been applied to the preparation of spiro compounds.[8−10] Not surprisingly, the [3 + 2] cycloaddition with alkenes stands as the method of choice for the formation of azaspiro[4.*n*]alkanes. When the nitrogen-containing cycles are formed through 1,3-dipolar cycloadditions, the reactions generally rely on the use of azomethine ylides. These common 1,3-dipoles can be generated in situ according to various conditions.[11] One of these involve the thermal ring-opening of *N*-alkyl- or *N*-arylaziridines that occurs through stereospecific C−C bond cleavage (Scheme 1a).[12] Interestingly, recent studies have shown that a different zwitterionic species can be formed from aziridines following C−N bond cleavage and also engaged in [3 + 2] cycloadditions with alkenes, alkynes, carbonyl compounds, nitriles, and CO_2 (Scheme 1b).[13]

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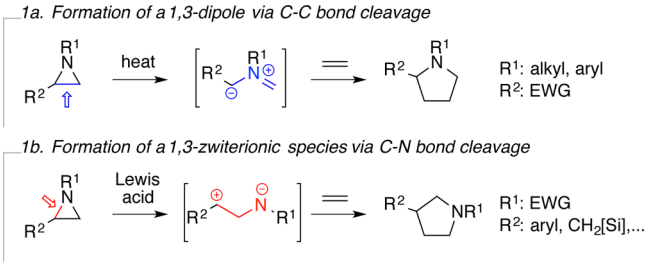
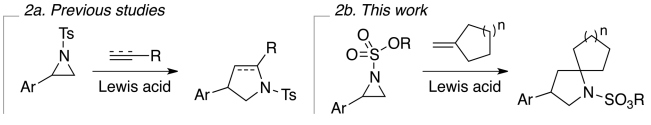
Scheme 1. Aziridines and Formation of Dipolar Intermediates



The formation of azomethine ylides through conrotary C−C bond breaking proceeds from simple aliphatic *N*-alkyl- or *N*-arylaziridines. Inversely, C−N bond cleavage is observed starting from aziridines bearing an electron-withdrawing group on the nitrogen and with substituents on one of the carbon atoms likely to stabilize a transient positive charge.[14] This step is typically mediated by the introduction of a Lewis acid that activates the aziridine toward the ring-opening, and its use in formal cycloadditions with alkenes was first reported almost simultaneously by two groups at the end the 1990s.[15,16] Whereas Bergmeier and co-workers have reported the formation of bicyclic pyrrolidines via intramolecular [3 + 2] cycloaddition from well-designed substituted aziridines,[15] the group of Mann has investigated the intermolecular version of the reaction.[16] In both cases, $BF_3{\cdot}OEt_2$ was found efficient to perform the overall transformation, but since then it has been demonstrated that several other Lewis acids can trigger the formal [3 + 2] cycloaddition from *N*-tosyl-2-arylaziridines with alkenes and alkynes.[17] It is worth mentioning that the scope of the reaction has also been extended, in terms of dipolarophiles, to nitriles and carbonyl compounds,[18] while azetidines have been found to be suitable precursors of the homologue 1,4-zwitterionic species under these conditions.[18a,19]

Interestingly, a survey of these studies reveals that almost all the Lewis-acid-mediated cycloadditions with alkenes have been carried out only starting from *N*-tosylaziridines.[20] While the reported yields are generally good, it appeared to us that the presence of a tosyl substituent could be detrimental to the possible application of these methodologies in synthesis and medicinal chemistry. It is indeed well acknowledged that this protecting group can raise intractable problems when it comes to removal.[21] On the other hand, it has been demonstrated that the rate of the aziridine ring-opening depends on the nature of the arenesulfonyl substituent.[22] These observations, therefore, convinced us to study the influence of the "*N*-(SO_2R)" protecting group on the formal [3 + 2] cycloaddition with alkenes.[23] Fundamentally, this screening has been useful to better understand the course of the reaction that has been investigated for the first time by DFT calculations. The results of both our experimental and theoretical studies are thus presented in this article that documents the first use of *N*-sulfamoylaziridines in [3 + 2] cycloaddition in the context of the preparation of 1-azaspiro[4.*n*]alkanes (Scheme 2).

Scheme 2. Background for the Study



RESULTS AND DISCUSSION

Experimental Studies: Synthesis of Azaspirocycles. The recent developments in metal-catalyzed alkene aziridination make the synthesis of aziridines efficient and straightforward.[24] Significant results, in particular, have been reported with the use of iodine(III) oxidants for the generation of nitrenes from sulfonamides and sulfamates, in the presence of readily available copper[25] and rhodium[26] complexes. This methodology, that has been widely applied either in total synthesis or medicinal chemistry,[27] was appropriate to prepare the starting *N*-sulfonyl- and *N*-sulfamoylaziridines **1**, respectively, with copper[25c] and rhodium[26b] catalysts (Scheme 3). As already pointed out in previous studies,[24] the catalytic nitrene additions proceed more efficiently with sulfamoyl-derived nitrenes, leading to the corresponding aziridines with higher yields (88−89% for **1e**,**f** vs 57−77% for **1a**−**d**) in the presence of lower amounts of reagents (nitrene precursors, iodine oxidant, catalyst).

The aziridines were then engaged in the formal [3 + 2] cycloaddition with methylenecyclopentane to investigate the influence of the N-protecting group on the reactivity (Table 1). After an extensive screening, the following experimental conditions, i.e., use of $BF_3{\cdot}OEt_2$ as the Lewis acid at −78 °C in CH_2Cl_2,[28] were applied and led us to isolate the 1-azaspirocycles starting either from *N*-sulfonyl- or *N*-sulfamoylaziridines **1**. Contrary to the hypothesis, no improvement in the yield was made by the modification of the *N*-sulfonyl substituent (entries 1−4). But interestingly, whereas *N*-carbamoylaziridines do not react under these conditions,[17c] the reaction tolerates the presence of an *N*-sulfamoyl group. The cycloadducts **2eb** and **2f**, which gave crystals suitable for X-ray analysis (see Supporting Information), have been obtained with yields comparable to those of compounds **2a**−**d** (entries 5 and 6). It should be mentioned that the chiral *N*-sulfamoylaziridine **1f** was prepared with the aim to develop a diastereoselective process but this did not prove successful, as **2f** was isolated as a 1:1 mixture of isomers.[29]

The good reactivity of *N*-sulfamoylaziridines convinced us of the relevance of these substrates for further studies. As shown in Scheme 3, these are more readily accessible from alkenes. They also generally give rise to the formation of crystalline products. In addition, the higher reactivity of sulfamate-derived nitrenes offers more synthetic opportunities in terms of molecular diversity (vide infra). Thus, though the moderate yields for the cycloaddition reactions could partly offset these benefits, we decided to explore the reactivity of various *N*-Tces-aziridines (Tces: trichloroethoxysulfonyl) for the preparation of a collection of 1-azaspirocycles. We first investigated the reaction of **1e** with methylenecycloalkanes and found that the yield varies with the size of the carbocycle (Scheme 4a). Particularly, the crystalline 1-azaspiro[4.5]decane **2ec** was isolated with a yield of 68% yield, that is comparable to that reported for the *N*-tosyl analogue.[16b]

The other *N*-Tces-aziridines **1g**−**i** also proved to afford the expected cycloadducts **2g**−**i** with yields in the 62−70% range (Scheme 4b). Not surprisingly, the *trans*-aziridine **1g**, prepared stereospecifically from *trans*-2-methylstyrene in 98% yield, was converted to a 1:1 mixture of isomers. By contrast, the *cis*-aziridine **1i** derived from dihydronaphthalene (67% yield) led preferentially to the cis-cycloadduct **2i** (dr > 9:1) as indicated by the vicinal coupling constant of 3.3 Hz for the protons at the ring junction.

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Scheme 3. Preparation of Aziridines 1

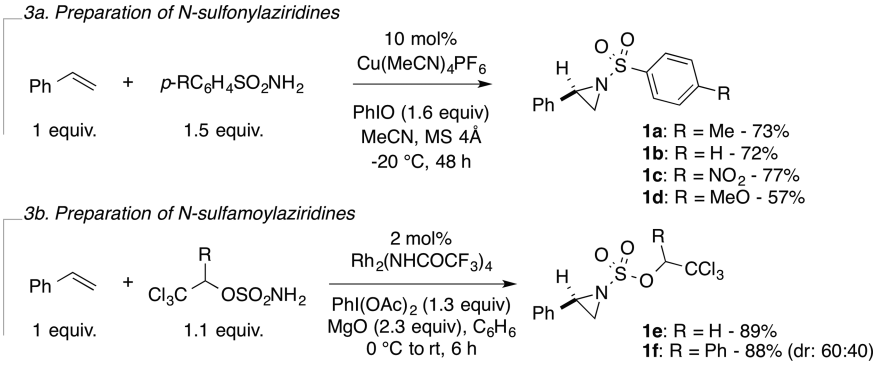
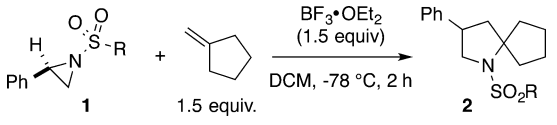


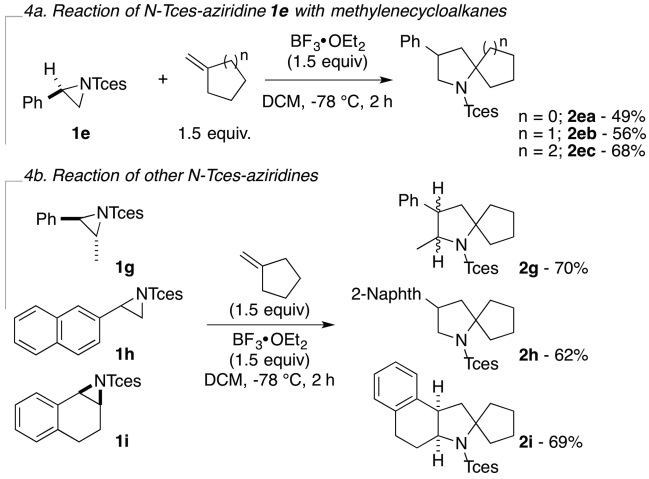
Table 1. [3 + 2] Cycloaddition with *N*-(SO_2R)-Aziridines 1[a]



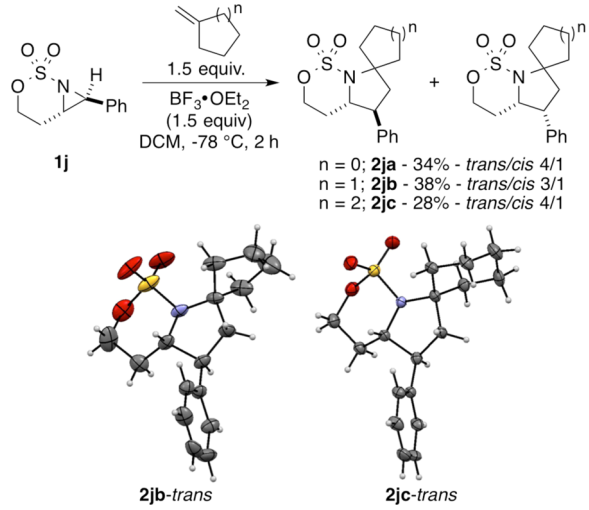
Entry	Substrate	Product	Yield[b]
1	1a	2a	66
2	1b	2b	65
3	1c	2c	47
4	1d	2d	49
5	1e	2eb	56
6	1f	2f	62

[a]Reactions conditions: aziridine **1** (0.3 mmol), BF_3·OEt_2 (1.5 equiv), methylenecyclopentane (1.5 equiv), DCM (3 mL), −78 °C, 2 h. [b]Isolated yields

Scheme 4. [3 + 2] Cycloadditions with *N*-Tces-Aziridines



Scheme 5. [3 + 2] Cycloadditions with Bicyclic Aziridine 1j



We then turned our attention to fused bicyclic sulfamoylaziridines that are readily accessible through application of intramolecular catalytic aziridination of alkenes.[30] These are useful synthetic intermediates that can be selectively converted to polysubstituted amines following sequential additions of nucleophiles. Use of the copper-catalyzed intramolecular aziridination, thus, led to the stereospecific formation of the *trans*-aziridine **1j** isolated in 69% yield. The latter subsequently reacts with methylenecycloalkanes though with limited efficiency, as the corresponding cycloadducts have been obtained with yields ranging from 28% to 38% (Scheme 5). However, the reaction takes place with good levels of stereoselectivity, as the trans configuration of the aziridine was partially transferred to the products isolated with dr's of up to 4:1. This is a result rarely observed for this type of [3 + 2] cycloaddition with alkenes.[13]

On the basis of the good results recorded from *N*-sulfamoylaziridines, we decided to capitalize on the higher reactivity of sulfamoylnitrenes to extend the scope of the cycloadditions and study the case of *N*-sulfamoylazetidines. Mann and co-workers had previously investigated the ability of *N*-tosyl-2-phenylazetidine to behave as a 1,4-zwitterionic species in the presence of BF_3·OEt_2.[19] However, the

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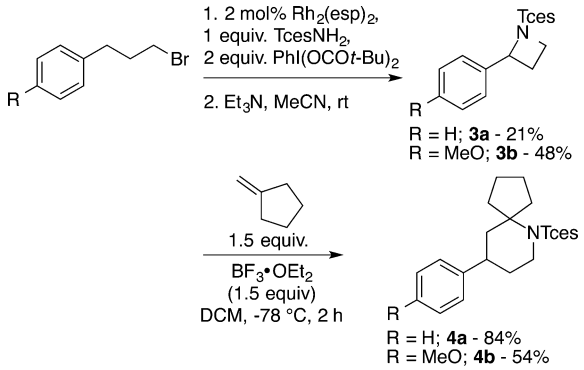
preparation of the starting material remains poorly practical. Inspired by the recent studies on rhodium-catalyzed C−H amination with sulfamates,[31] we thus designed a two-step synthesis of phenylazetidines that relies on a key step of intermolecular benzylic C−H amination of 1-bromo-3-phenylpropane derivatives. This method is likely to give access to a wide range of *N*-Tces-azetidines as illustrated by the *p*-MeO analogue **4b** (Scheme 6). Then we were pleased to observe that

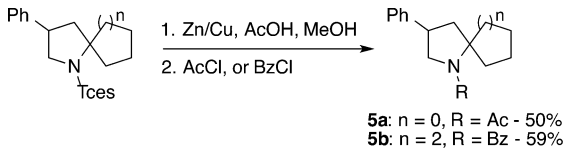
Scheme 6. [4 + 2] Cycloadditions with Azetidines 3



the formal [4 + 2] cycloaddition with methylenecyclopentane cleanly proceeds to afford the 1-azaspiro[4.5]decanes in good yields.[32] Once again, the structures of the cycloadducts were secured by X-ray analysis.

Finally, the relevance of *N*-Tces-aziridines for the formation of azaspirocycles was confirmed by the application of mild conditions for the removal of the sulfamoyl protecting group.[26b] Thus, cleavage of the latter was performed with the zinc−copper couple under acidic conditions to afford the free NH-spiro products which can be subsequently converted to amides (Scheme 7).

Scheme 7. Removal of the Tces Protecting Group



Mechanistic Considerations: Computational Studies of the [3 + 2] Cycloaddition. To better understand the lack of stereoselectivity and the low influence of the protecting group, we have performed the theoretical study of the [3 + 2] cycloaddition of methylenecyclobutane with *N*-tosyl- and *N*-Tces-aziridines **1a** and **1e**. We first paid attention to the reaction of methylenecyclobutane with the *N*-tosylaziridine **1a**. The first step of the overall process, i.e., the formation of the 1,3-zwitterionic species, requires the complexation of one BF_3 molecule to stabilize this ionic intermediate. Fundamentally, it should be kept in mind that the aziridine **1a** has two complexation sites for BF_3: the nitrogen atom and one of the oxygen atoms of the sulfonyl group. Our calculations have revealed that BF_3 preferentially binds to the nitrogen atom: the N-BF_3 complex **IIbis-s** is more stable than the O-BF_3 complex by 3.2 kcal/mol (see also the calculations on model systems in the Supporting Information). Consequently, the first step of the reaction leads to the formation of the N-BF_3 complex **II-s** where the Et_2O molecule is still close to the aziridine with a small gain in energy of 0.1 kcal/mol (Scheme 8). This result arises from the bond strength in the $BF_3{\cdot}OEt_2$ adduct, that is equal to 21.9 kcal/mol. Conversely, in the absence of the interaction with Et_2O, formation of the N-BF_3 complex **IIbis-s** is disfavored, as it requires an energy barrier of 4.7 kcal/mol due to the poor stabilization of ether by dichloromethane.

Formation of the zwitterionic species could not be observed when stretching the C−N bond starting from **IIbis-s**. Nevertheless, the calculations have shown that the charged intermediate **IVbis-s** can be formed from this complex following stabilization by another equivalent of BF_3 complexed on one of the oxygens of the SO_2 group to give **III-bis-s**. Complexing a second BF_3 on **IIbis-s**, however, is unfavorable by 14.3 kcal/mol because the O−BF_3 bond formation does not compensate for the Et_2O−BF_3 breaking. This value is much higher than the complexation energy of BF_3 on **II-s** because of the attractive effect of the first BF_3 molecule bound to the neighboring nitrogen atom. In parallel, starting from **II-s**, the expected intermediate **III-s** is also generated with a stabilization provided by the neighboring Et_2O molecule. Thus, the energy difference between the two transition states of aziridine opening **II-s-TS** and **IIIbis-s-TS** is 15.4 kcal/mol in favor of the opening assisted by the Et_2O molecule. Ultimately, the activation barrier for the formation of the 1,3-zwitterionic species is only 9.5 kcal/mol, which is reachable at the experimental temperature.[33]

The second step of the reaction is the cycloaddition between the zwitterionic intermediate and the alkene, that can proceed through a concerted pathway with the simultaneous formation of the C−C and C−N bonds, or in a stepwise manner. As the alkene reacts as the nucleophile, its HOMO will intereact with the LUMO of the 1,3-zwitterionic species. A close examination of the frontier orbitals of the intermediate **III-s** reveals that the LUMO is almost exclusively developed on the carbon atom while the HOMO of the alkene is polarized toward the outer carbon atom (Scheme 9); such a dissymmetry in the frontier orbital rules out the involvement of a concerted pathway and is in line with the cycloaddition occurring in a stepwise manner with the C−C bond being created first with the alkene outer atom.

The E+ZPE for the cycloaddition of methylenecyclobutane is shown in Scheme 10. The C−C bond formation **IV-s** → **V-s**, in which the Et_2O molecule is replaced by the alkene, proceeds with a barrier of 9.0 kcal/mol. The five-member ring closure **V-s** → **VI-s** then takes place barrierless. The overall energetic gain during the cycloaddition is about 42.5 kcal/mol. This huge gain is due to the creation of the new C−C and C−N bonds, as well as to the strain release arising from the disappearance of the exocyclic double bond. The cycloaddition, therefore, is the driving force of the reaction, the limiting step being the formation of the 1,3-zwitterionic species.

In terms of stereochemistry, the involvement of a 1,3-zwitterionic species with a planar carbocation center inevitably induces the loss of the stereochemical information from 2-(aryl)aziridines. However, application of the reaction conditions to 2,3-substituted aziridines leads to diastereomeric transition states, as the stereochemistry of the bridging carbon is not lost. Because the C−C bond formation is associated with a high energy barrier, and the ring-closing step takes place barrierless, one can expect that the geometry of the starting material can be partly transferred to the products in this case. This should particularly apply to aziridines with significant conformational restriction likely to lead to diastereomeric

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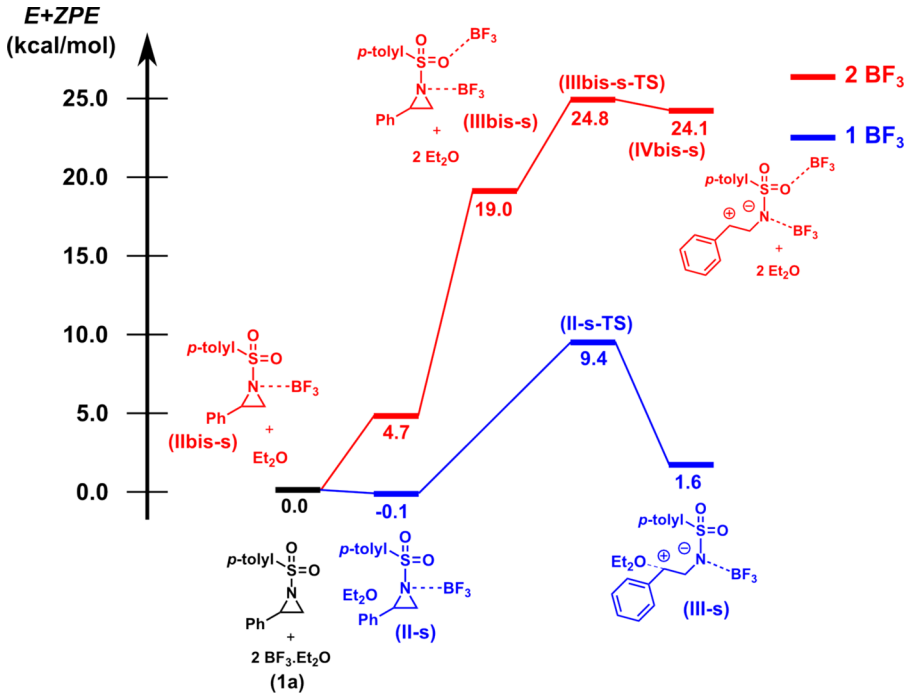
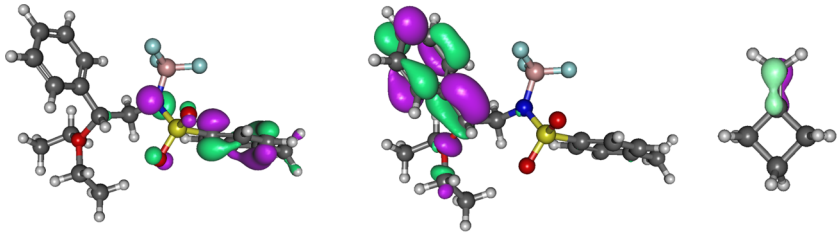
Scheme 8. Aziridine Opening Catalyzed by BF_3·Et_2O



Scheme 9. Frontier Orbitals for the 1,3-Zwitterionic Species III-s and the Methylenecyclobutane[a]



III-s HOMO **III-s** LUMO Alkene HOMO

[a]Atom color code: H in white, C in gray, O in red, N in blue, S in yellow, B in pink, F in pale blue.

transition states with sufficient difference in energy. This hypothesis is in line with the diastereoselectivity observed starting from bicyclic fused aziridines **1i** and **1j**.

During the screening of the reaction conditions, formation of the cycloaddition products was not observed experimentally when using other fluoro catalysts such as AlF_3, InF_3, ScF_3, and GaF_3. This result might be surprising at first sight because AlF_3 is known to be a better Lewis acid than BF_3.[35] The main difference comes from the fact that the fluoro salts such as AlF_3 are solid and do not possess an ether moiety which, therefore, is absent in solution. As we did previously for BF_3, we have computed the 1,3-zwitterionic species formation step with one and two AlF_3 molecules. As for BF_3, the intermediate is not stable with 1 equiv complexed on the aziridine nitrogen. Two AlF_3 molecules are needed to observe the formation of the charged intermediate. The aziridine opening then occurs with a barrier of 4.8 kcal/mol, less than the one observed with 2 equiv of BF_3. Given the poor solubility of AlF_3 in dichloromethane,[36] such a scenario is unlikely, thereby explaining the lack of reactivity in the presence of AlF_3. Nevertheless, these theoretical results corroborate the proposed mechanism depicted in Scheme 8.

We then turned our attention to the reaction starting from the *N*-Tces-aziridine **1e** to better understand the weak influence of the nitrogen protecting group on the course of the cycloaddition. As the rate-determining step of the reaction is the dipole formation, we have focused only on this step. The energetic profiles for the dipole formation for the *N*-Tces and *N*-Ts derivatives are shown in Scheme 11. For the *N*-Tces-aziridine **1e**, the complexation of one BF_3 is less favorable than for the *N*-Ts substrate **1a** by 2.7 kcal/mol. This is due to the fact that the nitrogen atom in **1e** is less nucleophilic than in **1a** because of the inductive attractor effects of chlorine atoms. Nonetheless, as Tces is more attractive than the sulfonyl group, the C−N bond is easier to break in **II-Tces** than in **II-s**: the barrier for C−N breaking is 2.7 kcal/mol lower for the Tces derivative. As a consequence, the two transition state **II-Tces-TS** and **II-s** are nearly degenerate, as the two effects, complexation and bond breaking costs, compensate for each other. Finally, the attractive effect of the Tces group can be detected in the stability of the intermediate **III-Tces**: it is 4.0 kcal/mol more stable than **III-s**. The formation of **III-Tces** is thus exothermic by 2.4 kcal/mol, in contrast to the slightly endothermic reaction leading to **III-s**.

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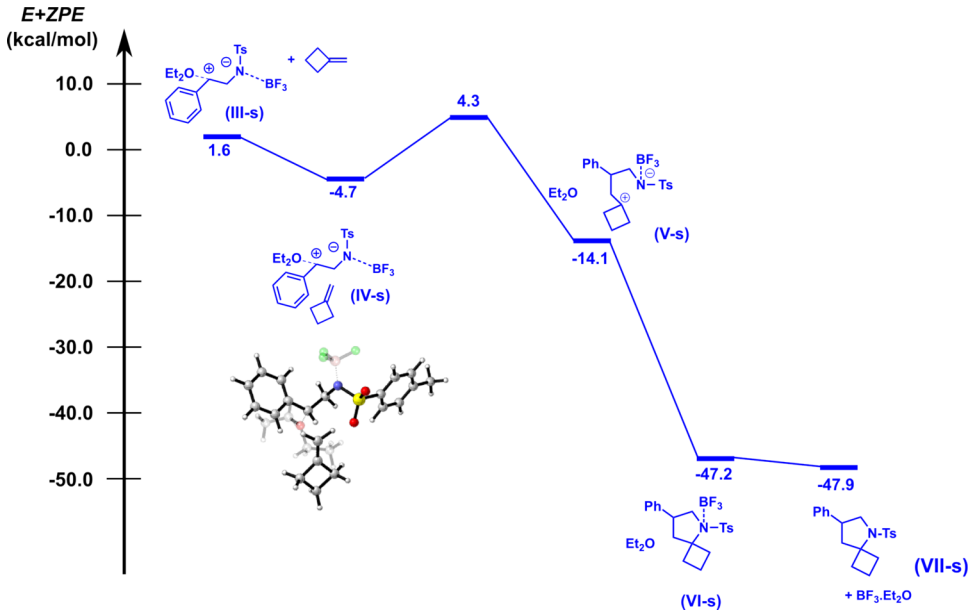
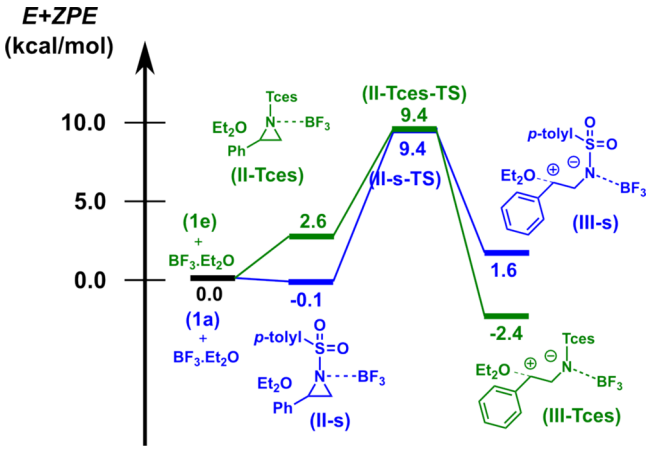
Scheme 10. Cycloaddition of Methylenecyclobutane with III-s[a]



[a]Structural figure of **IV-s** was created with CYLView.[34]

Scheme 11. Comparison between the Formation of 1,3-Dipole III-s and III-Tces



In conclusion, the use of *N*-sulfamoylaziridines in [3 + 2] cycloaddition with alkenes affords a rapid access to 1-azaspiro[4.*n*]alkanes in good yields. The scope of the reaction has been extended to azetidines with equal efficiency. These studies have demonstrated that the nitrogen protecting group has a low influence on the efficiency of the cycloaddition, an experimental result that has been rationalized by theoretical calculations. However, use of sulfamates gives access to a wider diversity of spiro compounds, as the starting aziridines and azetidines are readily accessible by application of, respectively, efficient catalytic alkene aziridination or benzylic C(sp^3)-H amination. In addition, DFT calculations have allowed us to draw a mechanism of the formal [3 + 2] cycloaddition for the first time, for which the formation of the 1,3-zwitterionic species appears to be the limiting step. Application of this strategy to the production of building blocks for further derivatization is in progress.

EXPERIMENTAL SECTION

General Procedure A for Aziridination (RSO_2NH_2). To a solution of tetrakis(acetonitrile)copper(I) hexafluorophosphate (0.1 equiv) and alkene (1 equiv) held under argon in acetonitrile (c = 0.4 M) in the presence of activated 4 Å molecular sieves was added the sulfonamide (1.4 equiv) at room temperature. Iodosylbenzene (1.4 equiv) was then added portionwise at 0 °C. The suspension was allowed to warm slowly to room temperature over 20 h. The reaction mixture was diluted with CH_2Cl_2 and filtered through Celite. The filter cake was washed throroughly with CH_2Cl_2, and the filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel.

General Procedure B for Aziridination ($TcesNH_2$). To a solution of $TcesNH_2$ (1.1 equiv) in C_6H_6 were added sequentially the olefin (1.0 equiv, c = 0.5 mM), MgO (2.3 equiv), and Rh_2(tfacam)$_4$ (0.01 equiv). The resulting purple mixture was cooled to 0 °C, and $PhI(OAc)_2$ (1.3 equiv) was added. The suspension quickly turned orange after the addition of $PhI(OAc)_2$ and was allowed to warm slowly to 25 °C over 2 h. After 6 h of stirring at 25 °C, during which time the solution color faded to pale yellow, the reaction was diluted with CH_2Cl_2 and filtered through Celite. The filter cake was washed thoroughly with CH_2Cl_2, and the combined filtrates were concentrated under reduced pressure. The isolated material was purified by chromatography on silica gel to afford the desired aziridine.

General Procedure C for Cycloaddition. To a solution of aziridine (0.3 mmol) in CH_2Cl_2 (c = 0.2 M) cooled at −78 °C under argon was added the alkene (1.5 equiv). $BF_3{\cdot}OEt_2$ (1.5 equiv) was then added dropwise. After 2 h at −78 °C, the reaction mixture was quenched with water. The aqueous layer was extracted with CH_2Cl_2 (×3). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel.

Computational Details. Quantum mechanics calculations were performed with the Gaussian09 software package.[37] Energy and forces were computed by density functional theory with the ωB97X-D[38] exchange-correlation functional and the/6-31+G(d,p) basis set. The zero point energy (ZPE) contributions are taken into account after frequency calculations at the same level. A polarizable continuum model[39] (PCM) of solvent was used as implemented in Gaussian09 to describe the medium (dichloromethane). Transition states were localized using the string theory[40] as implemented in Opt'n Path.[41] All structures were optimized, and frequency calculations were

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performed to ensure the absence of any imaginary frequencies on local minima and the presence of only one imaginary frequency on transition states. Reactants and products were relocalized starting from the transition states (IRC calculations followed by optimizations) to ensure that no TS were forgotten.

Iodosylbenzene. To iodosobenzene diacetate (74 mmol) was added a 3 M solution of NaOH (402 mmol). After completion of the addition, the mixture was stirred for 1 h, diluted with 150 mL of water, and stirred for an additional 2 h. The solid was collected on a Büchner funnel, washed twice with 100 mL of water and twice with 100 mL of CH_2Cl_2, and dried under high vacuum for 48 h (the solid was crushed two or three times) to afford the desired product as a yellow solid (91%); iodosylbenzene was stored under an atmosphere of argon in the freezer (−20 °C). Anal. Calcd for C_6H_5IO: C, 32.75; H, 2.29; O, 7.27. Found C, 32.61; H, 2.33; O, 7.24; mp 209−210 °C (decomp).

Rh_2(tfacam)$_4$.[26b] A 25 mL recovery flask was charged with $Rh_2(OAc)_4$ (0.32 mmol) and 18.5 mL of C_6H_5Cl, and to this suspension was added CF_3CONH_2 (14 equiv). The reaction flask was equipped with a short-path distillation head fitted with a 25 mL receiving bulb. The apparatus was placed in a bath preheated to 155 °C. At this temperature, solvent distilled at a rate of ∼1 mL/h for 36 h. Approximately every 8 h, an appropriate amount of C_6H_5Cl was added in order to restore the solvent volume of the reaction to ∼18 mL. The solution color slowly changed to a deep green, and a white crystalline precipitate (CF_3CONH_2) slowly formed in the receiving flask. After 36 h, additional CF_3CONH_2 (14 equiv) was added to this reaction mixture and heating at 155 °C was continued. Within 48 h, a dark blue-green solid slowly collected on the sides of the reaction vessel. Following this time, the reaction was cooled to 25 °C, and the mixture was filtered. The blue-green solid was washed thoroughly with CH_2Cl_2, and the filtrate was discarded. To ensure quantitative recovery of the desired product, acetone was used to dissolve the powder. The purple filtrate was concentrated under reduced pressure, and the isolated material was dried by heating at 50 °C in vacuo (1 mmHg) for 1 h. For all applications, the Rh_2(tfacam)$_4$ complex was used without further purification. Purification of this material by chromatography on silica gel (CH_2Cl_2/EtOAc 3/1) is possible and affords a blue-green solid, (83%). R_f = 0.4 (petroleum ether/EtOAc 7/3); ^{19}F NMR (282 MHz, $(CD_3)_2CO$): −75.1 ppm; IR (Neat): ν = 3399, 1649, 1455, 1429, 1263, 1190, 1140 cm^{-1}; HRMS (ESI$^-$; MeCN/MeOH): m/z calculated for $C_9H_5N_4O_6Rh_2F_{12}$ 698.8130, found 698.8128.

2,2,2-Trichloro-1-phenylethyl Sulfamate. Formic acid (1.5 equiv) was slowly added to chlorosulfonyl isocyanate (1.5 equiv) at 0 °C under an argon atmosphere. The solution was stirred overnight at room temperature, and the resulting white solid was cooled down at 0 °C and dissolved in dry DMA (c = 2 M for isocyanate). Then the appropriate alcohol[42] in DMA (c = 2.5 M) was added to the solution. The reaction mixture was stirred for 4 h before being quenched with brine and EtOAc. The resulting solution was then poured to an EtOAc/H_2O mixture. The aqueous layer was extracted with EtOAc (×3). Organic layers were combined, washed with water twice, dried over $MgSO_4$ and concentrated. Purification on a column of silica gel with a gradient of ethyl acetate in petroleum ether (from 80/20 to 70/30) as eluent gave the desired product (435 mg, 71%) as a white solid. R_f = 0.5 (petroleum ether/ethyl acetate 70/320); mp 141−142 °C; ^{1}H NMR (300 MHz, DMSO, 25 °C): δ = 7.97 (br s, 2H), 7.68−7.55 (m, 2H), 7.50−7.37 (m, 3H), 5.96 (s, 1H); ^{13}C NMR (75 MHz, DMSO, 25 °C): δ = 132.9, 129.7, 129.6, 127.8, 98.8, 86.3; IR (Neat): ν = 3389, 3285, 2966, 1556, 1498, 1456, 1379, 1368, 1326, 1273, 1193, 1177, 1031 cm^{-1}; HRMS (ESI$^-$; MeCN/CH_2Cl_2): m/z calculated for $C_8H_7Cl_3NO_3S$ 301.9212, found 301.9201.

2-Phenyl-1-tosylaziridine (1a). Prepared according to the general procedure A. Purification on a column of silica gel with ethyl acetate in petroleum ether (90/10) as eluent gave the desired product (359 mg, 73%) as a white solid. R_f = 0.2 (petroleum ether/ethyl acetate 80/20); mp 90−91 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.87 (d, 2H, J = 8.2 Hz), 7.33 (d, 2H, J = 8.2 Hz), 7.30−7.27 (m, 3H), 7.22 (dd, 2H, J = 7.5, 2.0 Hz), 3.78 (dd, 1H, J = 7.2, 4.4 Hz), 2.98 (d, 1H, J = 7.2 Hz), 2.44 (s, 3H), 2.39 (d, 1H, J = 4.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 144.7, 135.1, 135.0, 129.8, 128.6, 128.4, 128.0, 126.6, 41.1, 36.0, 21.7; IR (Neat): ν = 3011, 1595, 1495, 1458, 1385, 1320, 1307, 1291, 1232, 1193, 1155, 1134, 1117, 1093, 1082, 1029, 1018 cm^{-1}; HRMS (ESI$^+$; MeCN/CH_2Cl_2): m/z calculated for $C_{15}H_{16}NO_2S$ 274.0902, found 274.0909.

2-Phenyl-1-(phenylsulfonyl)aziridine (1b). Prepared according to the general procedure A. Purification on a column of silica gel with a gradient of ethyl acetate in petroleum ether (from 90/10 to 80/20) as eluent gave the desired product (375 mg, 72%) as a colorless solid. R_f = 0.2 (petroleum ether/ethyl acetate 90/10); mp 76−77 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.04−7.95 (m, 2H), 7.67−7.59 (m, 1H), 7.58−7.50 (m, 2H), 7.33−7.27 (m, 3H), 7.25−7.17 (m, 2H), 3.81 (dd, 1H, J = 7.2, 4.5 Hz), 3.02 (d, 1H, J = 7.2 Hz), 2.42 (d, 1H, J = 4.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 138.1, 135.0, 133.8, 129.2, 128.7, 128.5, 128.0, 126.6, 41.2, 36.1; IR (Neat): ν = 3094, 3068, 3011, 1584, 1497, 1480, 1459, 1449, 1380, 1320, 1291, 1229, 1194, 1183, 1169, 1155, 1132, 1119, 1093, 1081, 1027, 1000 cm^{-1}; HRMS (ESI$^+$; MeCN/CH_2Cl_2): m/z calculated for $C_{14}H_{14}NO_2S$ 260.0745, found 260.0741.

1-((4-Nitrophenyl)sulfonyl)-2-phenylaziridine (1c). Prepared according to the general procedure A. Purification on a column of silica gel with a gradient of ethyl acetate in petroleum ether (from 90/10 to 80/20) as eluent gave the desired product (203 mg, 77%) as a yellow solid. R_f = 0.4 (petroleum ether/ethyl acetate 80/20); mp 137−138 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.41−8.35 (m, 2H), 8.23−8.16 (m, 2H), 7.35−7.29 (m, 3H), 7.24−7.18 (m, 2H), 3.90 (dd, 1H, J = 7.3, 4.6 Hz), 3.12 (d, 1H, J = 7.3 Hz), 2.51 (d, 1H, J = 4.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 150.8, 144.0, 134.2, 129.3, 128.9, 126.5, 124.5, 42.0, 36.7; IR (Neat): ν = 3111, 2987, 2920, 1607, 1526, 1461, 1403, 1348, 1307, 1292, 1235, 1192, 1157, 1122, 1092 cm^{-1}; HRMS (ESI$^-$; MeCN/CH_2Cl_2): m/z calculated for $C_{14}H_{12}ClN_2O_4S$ 339.0206, found 339.0203.

1-((4-Methoxyphenyl)sulfonyl)-2-phenylaziridine (1d). Prepared according to the general procedure A. Purification on a column of silica gel with ethyl acetate in petroleum ether (80/20) as eluent gave the desired product (329 mg, 57%) as a yellow solid. R_f = 0.2 (petroleum ether/ethyl acetate 90/10); mp 83−84 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.96−7.87 (m, 2H), 7.33−7.26 (m, 3H), 7.24−7.18 (m, 2H), 7.03−6.96 (m, 2H), 3.87 (s, 3H), 3.75 (dd, 1H, J = 7.2, 4.5 Hz), 2.97 (d, 1H, J = 7.2 Hz), 2.38 (d, 1H, J = 4.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 163.8, 135.2, 130.2, 129.4, 128.6, 128.4, 126.6, 114.4, 55.7, 41.1, 36.0; IR (Neat): ν = 3009, 1593, 1576, 1498, 1458, 1442, 1415, 1387, 1322, 1310, 1300, 1260, 1232, 1193, 1183, 1150, 1115, 1093, 1018 cm^{-1}; HRMS (ESI$^+$; MeCN/CH_2Cl_2): m/z calculated for $C_{15}H_{16}NO_3S$ 290.0851, found 290.0847.

2,2,2-Trichloroethyl 2-Phenylaziridine-1-sulfonate (1e). Prepared according to the general procedure B. Purification on a column of silica gel with a gradient of ethyl acetate in petroleum ether (from 95/5 to 80/20) as eluent gave the desired product (1.09 g, 89%) as a white solid. R_f = 0.7 (petroleum ether/ethyl acetate 80/20); mp 56−57 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.43−7.27 (m, 5H), 4.88 (d, 1H, J = 10.8 Hz), 4.81 (d, 1H, J = 10.8 Hz), 3.87 (dd, 1H, J = 7.2, 4.7 Hz), 3.09 (d, 1H, J = 7.2 Hz), 2.63 (d, 1H, J = 4.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 133.9, 129.0, 128.9, 126.6, 92.9, 79.8, 42.8, 37.6; IR (Neat): ν = 3018, 2971, 1606, 1499, 1461, 1446, 1365, 1317, 1293, 1270, 1233, 1196, 1180, 1144, 1114, 1095, 1043, 1008 cm^{-1}; HRMS (ESI$^+$; MeCN/CH_2Cl_2): m/z calculated for $C_{10}H_{11}Cl_3NO_3S$ 329.9525, found 329.9523.

2,2,2-Trichloro-1-phenylethyl 2-phenylaziridine-1-sulfonate (1f). Prepared according to the general procedure B. Purification on a column of silica gel with a gradient of ethyl acetate in petroleum ether (from 98/2 to 95/5) as eluent gave the desired product (356 mg, 88%) as a 6:4 mixture of unseparable diastereomers (white solid). R_f = 0.4 (petroleum ether/ethyl acetate 90/10); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.67 (dd, 1H, J = 7.8, 2.0 Hz), 7.53 (dd, J = 7.4, 1.6 Hz, 1H), 7.49−7.33 (m, 2H), 7.33−7.11 (m, 4H), 7.06−6.89 (m, 2H), 6.06 (s, 0.4H), 6.05 (s, 0.6H), 3.70 (dd, 1H, J = 7.2, 4.6 Hz), 2.92 (d, 0.4H, J = 7.2 Hz), 2.86 (d, 0.6H, J = 7.2 Hz), 2.29 (d, 0.4H, J = 4.6 Hz), 2.03 (d, 0.6H, J = 4.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 134.0, 133.8, 132.1, 131.4, 130.4, 130.3, 129.8, 129.6, 128.70, 128.67, 128.6, 128.5, 128.1, 127.9, 126.3, 126.2, 98.0, 97.7, 90.63, 90.55, 42.9,

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42.7, 37.9, 37.8; IR (Neat): ν = 2973, 1499, 1463, 1456, 1368, 1346, 1322, 1232, 1198, 1172, 1140, 1115, 1085, 1031 cm^{-1}; HRMS (ESI^+; $MeCN/CH_2Cl_2$): m/z calculated for $C_{18}H_{18}Cl_3N_2O_3S$ 447.0104, found 447.0103.

2,2,2-Trichloroethyl 2-Methyl-3-phenylaziridine-1-sulfonate (1g). Prepared according to the general procedure B. Purification on a column of silica gel with ethyl acetate in petroleum ether (90/10) as eluent gave the desired product (506 mg, 95%) as a white solid. R_f = 0.5 (petroleum ether/ethyl acetate 90/10); mp 72−73 °C; ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.40−7.32 (m, 3H), 7.30−7.26 (m, 2H), 4.80 (d, 1H, J = 10.7 Hz), 4.77 (d, 1H, J = 10.7 Hz), 3.79 (d, 1H, J = 4.4 Hz), 3.08−3.01 (qd, 1H, J = 6.0, 4.4 Hz), 1.78 (d, 3H, J = 6.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 134.3, 128.9, 128.8, 126.6, 93.0, 79.6, 50.9, 48.6, 13.7; IR (Neat): ν = 2948, 1500, 1461, 1436, 1417, 1378, 1366, 1343, 1291, 1244, 1206, 1174, 1130, 1089, 1077, 1065, 1042, 1012 cm^{-1}; HRMS (ESI^-; $MeCN/CH_2Cl_2$): m/z calculated for $C_{11}H_{12}Cl_4NO_3S$ 377.9292, found 377.9293.

2,2,2-Trichloroethyl 2-(Naphthalen-2-yl)aziridine-1-sulfonate (1h). Prepared according to the general procedure B. Purification on a column of silica gel with a gradient of ethyl acetate in petroleum ether (from 95/5 to 80/20) as eluent gave the desired product (696 mg, 49%) as a white solid. R_f = 0.6 (petroleum ether/ethyl acetate 80/20); mp 103−104 °C; ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.88−7.80 (m, 4H), 7.56−7.50 (m, 2H), 7.34 (dd, 1H, J = 8.6, 1.7 Hz), 4.90 (d, 1H, J = 11.0 Hz), 4.84 (d, 1H, J = 11.0 Hz), 4.04 (dd, 1H, J = 7.3, 4.8 Hz), 3.16 (d, 1H, J = 7.3 Hz), 2.74 (d, 1H, J = 4.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 133.5, 133.1, 131.3, 128.9, 128.0, 127.9, 126.9, 126.8, 126.7, 123.4, 93.0, 79.8, 43.2, 37.6; IR (Neat): ν = 3066, 2957, 1600, 1510, 1473, 1455, 1397, 1363, 1334, 1271, 1228, 1209, 1179, 1162, 1138, 1128, 1090, 1046, 1002 cm^{-1}; HRMS (ESI^+; $MeCN/CH_2Cl_2$): m/z calculated for $C_{14}H_{13}Cl_3NO_3S$ 379.9682, found 379.9675.

2,2,2-Trichloroethyl 1a,2,3,7b-Tetrahydro-1*H*-naphtho[1,2-*b*]azirine-1-sulfonate (1i). Prepared according to the general procedure B. Purification on a column of silica gel with a gradient of ethyl acetate in petroleum ether (from 95/5 to 80/20) as eluent gave the desired product (275 mg, 39%) as a white solid. R_f = 0.4 (petroleum ether/ethyl acetate 90/10); mp 93−94 °C; ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.42 (d, 1H, J = 7.4 Hz), 7.29 (td, 1H, J = 7.4, 1.3 Hz), 7.23 (t, 1H, J = 7.4 Hz), 7.12 (d, 1H, J = 7.4 Hz), 4.77 (d, 1H, J = 11.0 Hz), 4.72 (d, 1H, J = 11.0 Hz), 3.90 (d, 1H, J = 7.1 Hz), 3.68 (br d, 1H, J = 6.9 Hz), 2.81 (ddd, 1H, J = 15.4, 13.2, 6.7 Hz), 2.65 (dd, 1H, J = 15.4, 5.7 Hz), 2.45 (ddt, 1H, J = 14.5, 6.9, 2.2 Hz), 1.82−1.73 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 136.4, 130.0, 129.1, 129.0, 128.8, 126.7, 93.1, 79.6, 44.1, 43.8, 24.7, 20.1; IR (Neat): ν = 3025, 2953, 1493, 1461, 1439, 1382, 1360, 1275, 1263, 1233, 1197, 1174, 1086, 1061, 1038, 1004 cm^{-1}; HRMS (ESI^-; $MeCN/CH_2Cl_2$): m/z calculated for $C_{12}H_{12}Cl_4NO_3S$ 389.9292, found 389.9285.

7-Phenyl-3-oxa-2-thia-1-azabicyclo[4.1.0]heptane 2,2-Dioxide (1j). Prepared according to the literature.[29] Purification on a column of silica gel with a gradient of ethyl acetate in petroleum ether (from 90/10 to 70/20) as eluent gave the desired product (1.14 g, 68%) as a colorless solid. R_f = 0.3 (petroleum ether/ethyl acetate 60/40); mp 84−85 °C; ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.41−7.27 (m, 5H), 4.88 (dt, J = 11.7, 6.8 Hz, 1H), 4.54 (dt, J = 11.7, 6.8 Hz, 1H), 3.87 (d, J = 4.3 Hz, 1H), 3.30−3.21 (m, 1H), 2.58−2.32 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 134.2, 128.9, 126.4, 68.9, 50.5, 47.9, 18.9; IR (Neat): ν = 3040, 1497, 1474, 1453, 1413, 1373, 1358, 1290, 1244, 1180, 1127, 1055, 1027 cm^{-1}; HRMS (ESI^+; $MeCN/CH_2Cl_2$): m/z calculated for $C_{10}H_{12}NO_3S$ 226.0538, found 226.0535.

3-Phenyl-1-tosyl-1-azaspiro[4.4]nonane (2a). Prepared according to the general procedure C. Purification on a column of silica gel with ethyl acetate in petroleum ether (95/5) as eluent gave the desired product (70 mg, 66%) as a white solid. R_f = 0.2 (petroleum ether/ethyl acetate 95/5); mp 100−101 °C; ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.74 (d, J = 8.3 Hz, 2H), 7.34−7.27 (m, 4H), 7.25−7.20 (m, 1H), 7.17 (d, 2H, J = 7.8 Hz), 3.92 (dd, 1H, J = 9.1, 7.1 Hz), 3.44−3.33 (m, 1H), 3.20 (dd, 1H, J = 10.6, 9.1 Hz), 2.72−2.63 (m, 1H), 2.42 (s, 3H), 2.40−2.33 (m, 1H), 2.24 (dd, J = 12.1, 6.1, 1H), 1.92−1.82 (m, 3H), 1.78−1.72 (m, 1H), 1.58−1.45 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 142.8, 139.9, 138.5, 129.5, 128.6, 127.11, 127.07, 127.0, 74.8, 55.3, 48.8, 41.1, 38.5, 37.0, 23.6, 23.0, 21.5; IR (Neat): ν = 2982, 2953, 2919, 2878, 2866, 1593, 1491, 1478, 1453, 1396, 1340, 1322, 1302, 1290, 1266, 1244, 1207, 1180, 1154, 1137, 1121, 1107, 1091, 1081, 1065, 1036 cm^{-1}; HRMS (ESI^+; $MeCN/CH_2Cl_2$): m/z calculated for $C_{21}H_{26}NO_2S$ 356.1684, found 356.1672.

3-Phenyl-1-(phenylsulfonyl)-1-azaspiro[4.4]nonane (2b). Prepared according to the general procedure C. Purification on a column of silica gel with ethyl acetate in petroleum ether (95/5) as eluent gave the desired product (66 mg, 65%) as a yellow solid. R_f = 0.4 (petroleum ether/ethyl acetate 90/10); mp 83−84 °C; ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.87 (d, 2H, J = 7.9 Hz), 7.58−7.52 (m, 1H), 7.52−7.46 (m, 2H), 7.33−7.27 (m, 2H), 7.25−7.20 (m, 1H), 7.18 (d, 2H, J = 7.6 Hz), 3.94 (dd, 1H, J = 9.0, 7.5 Hz), 3.46−3.34 (m, 1H), 3.21 (dd, 1H, J = 10.7, 9.0 Hz), 2.71−2.63 (m, 1H), 2.42−2.33 (m, 1H), 2.25 (dd, 1H, J = 12.1, 6.0 Hz), 1.93−1.82 (m, 3H), 1.80−1.72 (m, 1H), 1.54−1.45 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 141.5, 139.9, 132.2, 129.0, 128.7, 127.18, 127.15, 127.1, 75.0, 55.4, 48.8, 41.2, 38.6, 37.1, 23.7, 23.1; IR (Neat): ν = 3025, 2988, 2952, 2861, 1602, 1494, 1478, 1449, 1347, 1322, 1306, 1231, 1206, 1153, 1093, 1070, 1025, 1005 cm^{-1}; HRMS (ESI^+; $MeCN/CH_2Cl_2$): m/z for $C_{20}H_{24}NO_2S$ 342.1528, found 342.1529.

1-((4-Nitrophenyl)sulfonyl)-3-phenyl-1-azaspiro[4.4]nonane (2c). Prepared according to the general procedure C. Purification on a column of silica gel with ethyl acetate in petroleum ether (95/5) as eluent gave the desired product (55 mg, 47%) as an off-white solid. R_f = 0.4 (petroleum ether/ethyl acetate 90/10); mp 146−147 °C; ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 8.35 (d, 2H, J = 8.8 Hz), 8.04 (d, 2H, J = 8.8 Hz), 7.34−7.28 (m, 2H), 7.26−7.21 (m, 1H), 7.17 (d, 2H, J = 7.6 Hz), 4.01 (dd, 1H, J = 9.1, 7.6 Hz), 3.48−3.38 (m, 1H), 3.21 (dd, 1H, J = 10.7, 9.1 Hz), 2.64−2.56 (m, 1H), 2.38−2.31 (m, 1H), 2.28 (dd, 1H, J = 12.8, 5.9 Hz), 1.95−1.84 (m, 3H), 1.84−1.77 (m, 1H), 1.62−1.44 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 149.8, 147.0, 139.2, 128.8, 128.2, 127.4, 127.1, 124.4, 75.6, 55.7, 48.5, 41.2, 38.8, 37.0, 23.6, 23.0; IR (Neat): ν = 3114, 2954, 2877, 1605, 1526, 1497, 1476, 1455, 1400, 1371, 1345, 1302, 1249, 1209, 1156, 1137, 1106, 1093, 1080, 1067, 1004 cm^{-1}; HRMS (ESI^-; $MeCN/CH_2Cl_2$): m/z calculated for $C_{20}H_{21}N_2O_4S$ 385.1222, found 385.1235.

1-((4-Methoxyphenyl)sulfonyl)-3-phenyl-1-azaspiro[4.4]-nonane (2d). Prepared according to the general procedure C starting from 0.2 mmol of aziridine. Purification on a column of silica gel with ethyl acetate in petroleum ether (95/5) as eluent gave the desired product (37 mg, 49%) as an off-white solid. R_f = 0.3 (petroleum ether/ethyl acetate 90/10); mp 85−86 °C; ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.79 (d, 2H, J = 8.8 Hz), 7.29 (t, 2H, J = 7.5 Hz), 7.22 (t, 1H, J = 7.5 Hz), 7.18 (td, 2H, J = 7.5, 1.3 Hz), 6.96 (d, 2H, J = 8.8 Hz), 3.89 (dd, 1H, J = 9.1, 7.4 Hz), 3.86 (s, 3H), 3.43−3.33 (m, 1H), 3.18 (dd, 1H, J = 10.4, 9.1 Hz), 2.72−2.64 (m, 1H), 2.40−2.33 (m, 1H), 2.24 (dd, 1H, J = 12.2, 6.0 Hz), 1.92−1.81 (m, 3H), 1.78−1.72 (m, 1H), 1.59−1.47 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 162.5, 140.0, 133.3, 129.2, 128.7, 127.2, 127.1, 114.1, 74.8, 55.7, 55.4, 48.9, 41.2, 38.5, 37.1, 23.7, 23.1; IR (Neat): ν = 2952, 2874, 2836, 1595, 1579, 1497, 1478, 1457, 1441, 1411, 1332, 1305, 1253, 1184, 1147, 1138, 1114, 1094, 1064, 1028 cm^{-1}; HRMS (ESI^+; MeCN/CH_2Cl_2): m/z calculated for $C_{21}H_{26}NO_3S$ 372.1633, found 372.1640.

2,2,2-Trichloroethyl 3-Phenyl-1-azaspiro[3.4]octane-1-sulfonate (2ea). Prepared according to the general procedure C. Purification on a column of silica gel with a gradient of ethyl acetate in petroleum ether (from 100/0 to 98/2) as eluent gave the desired product (58 mg, 49%) as a colorless solid. R_f = 0.3 (petroleum ether/ethyl acetate 98/2); mp 81−82 °C; ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.37−7.31 (m, 2H), 7.29−7.23 (m, 3H), 4.66 (s, 2H), 3.97 (dd, 1H, J = 10.0, 7.2 Hz), 3.50 (t, 1H, J = 10.0 Hz), 3.43−3.32 (m, 1H), 3.19 (q, 1H, J = 10.5 Hz), 2.86 (q, 1H, J = 10.5 Hz), 2.66 (dd, 1H, J = 12.2, 5.6 Hz), 2.22 (t, 1H, J = 12.2 Hz), 2.09−2.00 (m, 2H), 1.87−1.77 (m, 1H), 1.66 (sext, 1H, J = 9.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 139.1, 128.8, 127.3, 127.1, 93.8, 77.6, 67.3, 56.6, 46.9, 40.5, 35.6, 34.1, 14.0; IR (Neat): ν = 2944, 2883, 1603, 1496,

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1479, 1446, 1431, 1360, 1289, 1278, 1256, 1211, 1180, 1159, 1138, 1116, 1083, 1047, 1029 cm^{-1}; HRMS (ESI^-; $MeCN/CH_2Cl_2$): m/z calculated for $C_{15}H_{18}Cl_4NO_3S$ 431.9762, found 431.9763.

2,2,2-Trichloroethyl 3-Phenyl-1-azaspiro[4.4]nonane-1-sulfonate (2eb). Prepared according to the general procedure C. Purification on a column of silica gel with a gradient of ethyl acetate in petroleum ether (from 100/0 to 98/2) as eluent gave the desired product (69 mg, 56%) as a white solid. R_f = 0.3 (petroleum ether/ethyl acetate 98/2); mp 103−104 °C; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.39−7.31 (m, 2H), 7.31−7.21 (m, 3H), 4.67 (d, 1H, J = 11.0 Hz), 4.63 (d, 1H, J = 11.0 Hz), 4.06−3.98 (m, 1H), 3.57−3.37 (m, 2H), 2.67−2.54 (m, 1H), 2.38−2.22 (m, 2H), 2.04 (td, 1H, J = 12.1, 1.3 Hz), 1.90−1.69 (m, 4H), 1.64−1.51 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 139.3, 128.9, 127.4, 127.2, 94.0, 77.7, 75.5, 56.3, 48.8, 41.3, 37.5, 37.2, 23.7, 23.5; IR (Neat): ν = 3032, 2958, 2920, 2884, 2851, 1603, 1497, 1476, 1456, 1433, 1364, 1323, 1312, 1281, 1252, 1214, 1195, 1170, 1140, 1118, 1077, 1067, 1033, 1010 cm^{-1}; HRMS (ESI^-; $MeCN/CH_2Cl_2$): m/z calculated for $C_{16}H_{20}Cl_4NO_3S$ 445.9918, found 445.9908.

2,2,2-Trichloroethyl 3-Phenyl-1-azaspiro[4.5]decane-1-sulfonate (2ec). Prepared according to the general procedure C. Purification on a column of silica gel with a gradient of ethyl acetate in petroleum ether (from 100/0 to 98/2) as eluent gave the desired product (87 mg, 68%) as a colorless solid. R_f = 0.8 (petroleum ether/ethyl acetate 95/5); mp 84−95 °C; ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.38−7.31 (m, 2H), 7.30−7.23 (m, 3H), 4.65 (d, 1H, J = 10.8 Hz), 4.63 (d, 1H, J = 10.8 Hz), 4.02 (dd, 1H, J = 9.4, 6.9 Hz), 3.50 (dd, 1H, J = 10.9, 9.4 Hz), 3.47−3.38 (m, 1H), 2.65 (dd, 1H, J = 12.6, 6.3 Hz), 2.38 (td, 1H, J = 12.6, 3.6 Hz), 2.17 (td, 1H, J = 13.4, 3.9 Hz), 1.91−1.76 (m, 5H), 1.64 (d, 1H, J = 10.7 Hz), 1.43−1.20 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 139.4, 128.9, 127.4, 127.2, 94.0, 77.7, 70.7, 55.9, 43.7, 41.0, 37.4, 34.6, 24.9, 24.3; IR (Neat): ν = 2931, 2861, 1603, 1496, 1476, 1454, 1371, 1346, 1306, 1281, 1259, 1222, 1177, 1159, 1142, 1082, 1061, 1035, 1014 cm^{-1}; HRMS (ESI^+; $MeCN/CH_2Cl_2$): m/z calculated for $C_{17}H_{23}Cl_3NO_3S$ 426.0464, found 426.0460.

2,2,2-Trichloro-1-phenylethyl 3-phenyl-1-azaspiro[4.4]nonane-1-sulfonate (2f). Prepared according to the general procedure C. Purification on a column of silica gel with ethyl acetate in petroleum ether (95/5) as eluent gave the desired product (91 mg, 62%) as a 1:1 mixture of unseparable diasteromers (white solid). R_f = 0.6 (petroleum ether/ethyl acetate 90/10); ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.70−7.62 (m, 2H), 7.52−7.40 (m, 3H), 7.35−7.19 (m, 3H), 7.11−7.04 (m, 1H), 7.00−6.93 (m, 1H), 5.89 (s, 0.5H), 5.88 (s, 0.5H), 3.75 (ddd, 0.5H, J = 9.2, 7.4, 1.5 Hz), 3.64 (ddd, 0.5H, J = 9.2, 7.4, 1.5 Hz), 3.28 (dd, 0.5H, J = 11.0, 9.4 Hz), 3.24−3.06 (m, 1H), 2.91 (dd, 0.5H, J = 11.0, 9.2 Hz), 2.76−2.54 (m, 1H), 2.35−2.13 (m, 2H), 1.94−1.64 (m, 4.5H), 1.64−1.41 (m, 2.5H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 139.2, 139.1, 132.9, 132.8, 130.3, 130.1, 130.0, 128.8, 128.7, 128.2, 128.1, 127.3, 127.1, 98.9, 98.8, 88.8, 75.5, 75.2, 55.9, 55.8, 48.9, 48.5, 41.14, 41.09, 37.8, 37.4, 37.2, 37.0, 23.7, 23.50, 23.49, 23.4; IR (Neat): ν = 2953, 2874, 1498, 1476, 1455, 1381, 1346, 1325, 1169, 1116, 1074, 1027 cm^{-1}; HRMS (ESI^+; $MeCN/CH_2Cl_2$): m/z calculated for $C_{22}H_{25}Cl_3NO_3S$ 488.0621, found 488.0619.

2,2,2-Trichloroethyl 2-Methyl-3-phenyl-1-azaspiro[4.4]nonane-1-sulfonate (2g). Prepared according to the general procedure C. Purification on a column of silica gel with a gradient of ethyl acetate in petroleum ether (from 100/0 to 98/2) as eluent gave the desired product (90 mg, 70%) as a 6:4 mixture of unseparable diasteromers (yellow oil). R_f = 0.3 (petroleum ether/ethyl acetate 98/2); ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.39−7.22 (m, 3.8H), 7.21−7.14 (m, 1.2H), 4.67 (s, 0.8H), 4.66 (s, 1.2H), 4.33 (quint, 0.6H, J = 6.9 Hz), 4.05 (dq, 0.4H, J = 8.1, 6.2 Hz), 3.65 (ddd, 0.6H, J = 13.5, 7.4, 5.6 Hz), 3.01 (ddd, 0.4H, J = 11.2, 8.1, 6.6 Hz), 2.75−2.64 (m, 0.4H), 2.64−2.51 (m, 0.6H), 2.47−2.07 (m, 3H), 1.94−1.48 (m, 6H), 1.43 (d, 1.2H, J = 6.2 Hz), 0.96 (d, 1.8H, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 140.5, 137.6, 128.9, 128.6, 128.1, 127.7, 127.3, 127.2, 94.1, 77.4, 77.3, 76.1, 74.6, 66.1, 61.9, 50.7, 48.2, 44.7, 42.1, 39.4, 38.9, 36.3, 36.0, 23.7, 23.3, 21.3, 16.2; IR (Neat): ν = 2960, 2876, 1603, 1498, 1452, 1363, 1327, 1250, 1181, 1111, 1074, 1046, 1000 cm^{-1}; HRMS (ESI^-; $MeCN/CH_2Cl_2$): m/z calculated for $C_{17}H_{22}Cl_4NO_3S$ 460.0075, found 460.0054.

2,2,2-Trichloroethyl 3-(Naphthalen-2-yl)-1-azaspiro[4.4]nonane-1-sulfonate (2h). Prepared according to the general procedure C. Purification on a column of silica gel with a gradient of ethyl acetate in petroleum ether (from 100/0 to 98/2) as eluent gave the desired product (87 mg, 62%) as a white solid. R_f = 0.6 (petroleum ether/ethyl acetate 90/10); mp 103−104 °C; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.87−7.79 (m, 3H), 7.69 (s, 1H), 7.54−7.44 (m, 2H), 7.37 (dd, 1H, J = 8.6, 1.8 Hz), 4.69 (d, 1H, J = 11.0 Hz), 4.66 (d, 1H, J = 11.0 Hz), 4.18−4.03 (m, 1H), 3.72−3.54 (m, 2H), 2.72−2.56 (m, 1H), 2.47−2.25 (m, 2H), 2.22−2.09 (m, 1H), 1.99−1.46 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 136.6, 133.5, 132.6, 128.6, 127.75, 127.70, 126.5, 126.0, 125.7, 125.3, 94.0, 77.7, 75.6, 56.2, 48.7, 41.4, 37.5, 37.2, 23.7, 23.5; IR (Neat): ν = 3058, 2976, 2953, 2873, 1601, 1511, 1475, 1454, 1381, 1359, 1324, 1312, 1257, 1250, 1211, 1186, 1167, 1140, 1121, 1092, 1072, 1046, 1012, 1000 cm^{-1}; HRMS (ESI^+; $MeCN/CH_2Cl_2$): m/z calculated for $C_{20}H_{23}Cl_3NO_3S$ 462.0464, found 462.0457.

2,2,2-Trichloroethyl 3a,4,5,9b-Tetrahydrospiro[benzo[*e*]indole-1,1′-cyclopentane]-3(2*H*)-sulfonate (2i). Prepared according to the general procedure C. Purification on a column of silica gel with a gradient of ethyl acetate in petroleum ether (from 100/0 to 98/2) as eluent gave mainly (>90/10) the cis product (91 mg, 69%) as a white solid. R_f = 0.7 (petroleum ether/ethyl acetate 90/10); ^1H NMR of major diastereomer (300 MHz, $CDCl_3$, 25 °C): δ = 7.26−7.12 (m, 3H), 7.11−7.04 (m, 1H), 4.67 (d, 1H, J = 10.9 Hz), 4.63 (d, 1H, J = 10.9 Hz), 3.48 (td, 1H, J = 11.2, 3.3 Hz), 3.19−2.89 (m, 3H), 2.89−2.77 (m, 1H), 2.77−2.63 (m, 1H), 2.51 (dd, 1H, J = 11.8, 5.7 Hz), 2.29−2.13 (m, 1H), 2.03−1.47 (m, 8H); ^{13}C NMR of major diastereomer (75 MHz, $CDCl_3$, 25 °C): δ = 136.7, 135.9, 128.5, 126.9, 125.9, 125.1, 93.9, 77.9, 77.4, 64.9, 44.2, 43.8, 39.2, 37.3, 28.5, 23.8, 22.8; IR (Neat): ν = 2971, 2873, 1493, 1451, 1386, 1378, 1322, 1278, 1172, 1111, 1071, 1045, 1007 cm^{-1}; HRMS (ESI^+; MeCN/CH_2Cl_2): m/z calculated for $C_{18}H_{23}Cl_3NO_3S$ 438.0464, found 438.0447.

5′-Phenyltetrahydro-3′*H*-spiro[cyclobutane-1,7′-pyrrolo[1,2-*c*][1,2,3]oxathiazine] 1′,1′-Dioxide (2ja). Prepared according to the general procedure C. Purification on a column of silica gel with a gradient of ethyl acetate in petroleum ether (from 98/2 to 95/5) as eluent gave the desired product (30 mg, 34%) as a 8:2 mixture of unseparable diasteromers (colorless oil). R_f = 0.4 (petroleum ether/ethyl acetate 90/10); ^1H NMR of major diastereomer (500 MHz, $CDCl_3$, 25 °C): δ = 7.35 (t, 2H, J = 7.4 Hz), 7.29 (d, 1H, J = 7.4 Hz), 7.26−7.23 (m, 2H), 4.64−4.57 (m, 1H), 4.46 (dt, 1H, J = 11.7, 2.9 Hz), 3.83−3.75 (m, 1H), 3.18 (q, 1H, J = 10.5 Hz), 2.92 (ddd, 1H, J = 11.7, 9.0, 7.1 Hz), 2.83 (q, 1H, J = 10.5 Hz), 2.60 (dd, 1H, J = 12.7, 7.0 Hz), 2.17 (q, 2H, J = 12.0 Hz), 2.05−1.98 (m, 1H), 1.88−1.78 (m, 3H), 1.78−1.53 (m, 1H); ^{13}C NMR of major diastereomer (125 MHz, $CDCl_3$, 25 °C): δ = 139.2, 129.0, 127.6, 127.5, 72.1, 67.1, 66.4, 49.5, 46.9, 36.7, 35.8, 30.0, 14.0; IR (Neat): ν = 2939, 1603, 1496, 1456, 1428, 1353, 1258, 1171, 1143, 1090, 1055, 1017, 1000 cm^{-1}; HRMS (ESI^+; $MeCN/CH_2Cl_2$): m/z calculated for $C_{15}H_{20}NO_3S$ 294.1164, found 294.1166.

5′-Phenyltetrahydro-3′*H*-spiro[cyclopentane-1,7′-pyrrolo[1,2-*c*][1,2,3]oxathiazine] 1′,1′-Dioxide (2jb). Prepared according to the general procedure C. Purification on a column of silica gel with a gradient of ethyl acetate in petroleum ether (from 98/2 to 95/5) as eluent gave the desired product (35 mg, 38%) as a 75:25 mixture of unseparable diasteromers (white solid). R_f = 0.3 (petroleum ether/ethyl acetate 95/5); ^1H NMR of major diastereomer (500 MHz, $CDCl_3$, 25 °C): δ = 7.38−7.31 (m, 2H), 7.31−7.26 (m, 1H), 7.26−7.23 (m, 2H), 4.60 (td, 1H, J = 11.7, 3.5 Hz), 4.49−4.39 (m, 1H), 3.80 (td, 1H, J = 10.0, 4.1 Hz), 2.95 (ddd, 1H, J = 11.7, 9.5, 6.8 Hz), 2.55 (dt, 1H, J = 12.8, 8.5 Hz), 2.34−2.26 (m, 1H), 2.26−2.17 (m, 1H), 1.97−1.57 (m, 8H), 1.53−1.44 (m, 1H); ^{13}C NMR of major diastereomer (125 MHz, $CDCl_3$, 25 °C): δ = 138.8, 129.0, 127.7, 127.6, 74.3, 72.0, 66.6, 50.2, 47.9, 39.0, 37.5, 30.2, 23.6, 23.0; IR (Neat): ν = 2958, 2874, 1603, 1497, 1455, 1427, 1352, 1260, 1242,

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1165, 1140, 1107, 1084, 1060, 1005 cm^{-1}; HRMS (ESI^+; MeCN/CH_2Cl_2): m/z calculated for $C_{16}H_{22}NO_3S$ 308.1320, found 308.1327.

5′-Phenyltetrahydro-3′*H*-spiro[cyclohexane-1,7′-pyrrolo-[1,2-*c*][1,2,3]oxathiazine] 1′,1′-Dioxide (2jc). Prepared according to the general procedure C. Purification on a column of silica gel with a gradient of ethyl acetate in petroleum ether (from 98/2 to 95/5) as eluent gave the desired product (27 mg, 28%) as a 8:2 mixture of unseparable diasteromers (white solid). R_f = 0.3 (petroleum ether/ethyl acetate 95/5); ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.35 (t, 2H, J = 7.5 Hz), 7.29 (t, 1H, J = 7.5 Hz), 7.26−7.23 (m, 2H), 4.57 (td, 1H, J = 11.6, 4.0 Hz), 4.43 (ddd, 1H, J = 11.6, 4.7, 2.0 Hz), 3.75 (td, 1H, J = 10.1, 4.0 Hz), 2.91 (ddd, 1H, J = 12.3, 10.1, 7.2 Hz), 2.42 (dd, 1H, J = 12.7, 7.2 Hz), 2.28 (td, 1H, J = 12.7, 3.7 Hz), 2.17 (td, 1H, J = 13.2, 4.9 Hz), 1.99 (br d, 1H, J = 12.7 Hz), 1.88−1.73 (m, 5H), 1.69 (br d, 1H, J = 13.2 Hz), 1.64−1.58 (m, 1H), 1.37−1.21 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 138.6, 129.0, 127.72, 127.66, 71.7, 69.6, 65.8, 50.2, 42.7, 37.6, 36.8, 30.4, 25.1, 25.0, 24.1; IR (Neat): ν = 2929, 2861, 1602, 1497, 1451, 1362, 1348, 1335, 1311, 1259, 1238, 1167, 1128, 1107, 1076, 1052, 1022, 1007 cm^{-1}; HRMS (ESI^+; MeCN/CH_2Cl_2): m/z calculated for $C_{17}H_{24}NO_3S$ 322.1477, found 322.1491.

2,2,2-Trichloroethyl (3-Bromo-1-phenylprop-1-yl)sulfamate. $Rh_2(esp)_2$ (24 μmol) and 1-bromo-3-phenylpropane (1.2 mmol) were added to a solution of $TcesNH_2$ (1.2 mmol) in C_6H_6 (c = 0.3 M). $PhI(O_2CtBu)_2$ (2.4 mmol) in solution in C_6H_6 (c = 0.83 M) was slowly added via syringe pump over 3 h. Following the transfer of the oxidant, the solution was stirred at room temperature for 2 h. Dichloromethane and a saturated aqueous solution of thiourea were then added, and the mixture was stirred vigorously for 30 min. The organic phase was collected and the aqueous layer was extracted with CH_2Cl_2 (×2). The combined organic extracts were washed with a Na_2HPO_4/NaH_2PO_4 buffer (0.1 M, pH = 7), dried over $MgSO_4$, and concentrated under reduced pressure. Purification on a column of silica gel with a gradient of ethyl acetate in petroleum ether (from 95/5 to 85/15) as eluent gave the title compound (169 mg, 33%) as a white solid. R_f = 0.2 (petroleum ether/ethyl acetate 90/10); mp 81−82 °C; ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.43−7.38 (m, 2H), 7.38−7.31 (m, 3H), 5.24 (br d, J = 7.5 Hz, 1H), 4.78 (q, 1H, J = 7.5 Hz), 4.40 (d, 1H, J = 10.8 Hz), 4.36 (d, 1H, J = 10.8 Hz), 3.41 (dt, 1H, J = 10.3, 6.3 Hz), 3.21 (ddd, 1H, J = 10.3, 7.7, 6.3 Hz), 2.54 (dquint, 1H, J = 7.7, 7.0 Hz), 2.35 (dquint, 1H, J = 7.7, 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 139.0, 129.4, 128.9, 126.8, 93.2, 78.2, 58.0, 39.4, 28.8; IR (Neat): ν = 3317, 3031, 2948, 1494, 1456, 1446, 1413, 1363, 1354, 1332, 1272, 1256, 1210, 1173, 1151, 1074, 1046, 1016 cm^{-1}; HRMS (ESI^-; MeCN/CH_2Cl_2): m/z calculated for $C_{11}H_{12}BrCl_3NO_3S$ 421.8787, found 421.8804.

2,2,2-Trichloroethyl (3-Bromo-1-(4-methoxyphenyl)prop-1-yl)sulfamate. $Rh_2(esp)_2$ (12 μmol) and 1-(3-bromopropyl)-4-methoxybenzene (0.6 mmol) were added to a solution of $TcesNH_2$ (0.6 mmol) in C_6H_6 (c = 0.3 M). $PhI(O_2CtBu)_2$ (1.2 mmol) in solution in C_6H_6 (c = 0.83 M) was slowly added via syringe pump over 3 h. Following the transfer of the oxidant, the solution was stirred at room temperature for 2 h. Dichloromethane and a saturated aqueous solution of thiourea were then added, and the mixture was stirred vigorously for 30 min. The organic phase was collected, and the aqueous layer was extracted with CH_2Cl_2 (×2). The combined organic extracts were washed with a Na_2HPO_4/NaH_2PO_4 buffer (0.1 M, pH = 7), dried over $MgSO_4$, and concentrated under reduced pressure. Purification on a column of silica gel with a gradient of ethyl acetate in petroleum ether (from 95/5 to 85/15) as eluent gave the title compound (190 mg, 70%) as a white solid. R_f = 0.4 (petroleum ether/ethyl acetate 80/20); mp 62−63 °C; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.29−7.22 (m, 2H), 6.95−6.87 (m, 2H), 5.29 (br d, 1H, J = 7.6 Hz), 4.72 (q, 1H, J = 7.6 Hz), 4.40 (d, 1H, J = 10.8 Hz), 4.35 (d, 1H, J = 10.8 Hz), 3.80 (s, 3H), 3.40 (dt, 1H, J = 10.4, 6.2 Hz), 3.17 (ddd, 1H, J = 10.4, 8.0, 6.2 Hz), 2.60−2.45 (ddt, 1H, J = 14.4, 8.0, 6.2 Hz), 2.38−2.24 (ddt, 1H, J = 14.4, 8.0, 6.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 159.9, 130.8, 128.1, 114.7, 93.3, 78.2, 57.6, 55.5, 39.3, 29.0; IR (Neat): ν = 3306, 3005, 2968, 2839, 1611, 1586, 1513, 1441, 1416, 1363, 1353, 1305, 1276, 1257, 1245, 1172, 1147, 1111, 1084, 1050, 1019 cm^{-1}; HRMS (ESI^-; MeCN/CH_2Cl_2): m/z calculated for $C_{12}H_{14}BrCl_3NO_4S$ 451.8892, found 451.8870.

2,2,2-Trichloroethyl 2-Phenylazetidine-1-sulfonate (3a). To a 0.13 M solution of 2,2,2-trichloroethyl (3-bromo-1-phenylprop-1-yl)sulfamate in acetonitrile was added 1.3 equiv of triethylamine. The resulting mixture was stirred at room temperature (20 °C) during 18 h, and then it was concentrated under reduced pressure. Purification on a column of silica gel with a gradient of ethyl acetate in petroleum ether (from 98/2 to 90/10) as eluent gave the desired product (44 mg, 64%) as a colorless oil. R_f = 0.4 (petroleum ether/ethyl acetate 90/10); ^1H NMR (300 MHz, CD_2Cl_2, 25 °C): δ = 7.51−7.28 (m, 5H), 5.38 (t, 1H, J = 8.4 Hz), 4.56 (d, 1H, J = 11.0 Hz), 4.48 (d, 1H, J = 11.0 Hz), 4.22 (td, 1H, J = 8.9, 7.6 Hz), 3.93 (ddd, 1H, J = 8.9, 7.9, 4.0 Hz), 2.63 (dtd, 1H, J = 11.3, 8.9, 4.0 Hz), 2.39 (dtd, 1H, J = 11.3, 8.9, 7.9 Hz); ^{13}C NMR (75 MHz, CD_2Cl_2, 25 °C): δ = 140.1, 129.1, 129.0, 127.0, 93.9, 76.4, 67.8, 49.3, 25.9; IR (Neat): ν = 2969, 2898, 1495, 1476, 1456, 1366, 1291, 1252, 1234, 1174, 1081, 1047, 1001 cm^{-1}; HRMS (ESI^-; MeCN/CH_2Cl_2): m/z calculated for $C_{11}H_{12}Cl_4NO_3S$ 377.9292, found 377.9276.

2,2,2-Trichloroethyl 2-(4-Methoxyphenyl)azetidine-1-sulfonate (3b). To a 0.13 M solution of 2,2,2-trichloroethyl (3-bromo-1-(4-methoxyphenyl)prop-1-yl)sulfamate in acetonitrile was added 1.3 equiv of triethylamine. The resulting mixture was stirred at room temperature (20 °C) during 18 h, and then it was concentrated under reduced pressure. Purification on a column of silica gel with ethyl acetate in petroleum ether (90/10) as eluent gave the desired product (382 mg, 69%) as a colorless oil. R_f = 0.5 (petroleum ether/ethyl acetate 80/20); ^1H NMR (300 MHz, CD_2Cl_2, 25 °C): δ = 7.39 (d, 2H, J = 8.6 Hz), 6.90 (d, 2H, J = 8.6 Hz), 5.31 (t, 1H, J = 8.6 Hz), 4.52 (d, 1H, J = 11.0 Hz), 4.44 (d, 1H, J = 11.0 Hz), 4.17 (td, 1H, J = 8.9, 7.8 Hz), 3.89 (ddd, 1H, J = 8.9, 7.8, 3.8 Hz), 3.78 (s, 3H), 2.58 (dtd, 1H, J = 11.3, 8.6, 3.8 Hz), 2.40 (dtd, 1H, J = 11.3, 8.6, 8.1 Hz); ^{13}C NMR (75 MHz, CD_2Cl_2, 25 °C): δ = 160.4, 132.0, 128.6, 114.4, 93.9, 78.4, 67.6, 55.7, 49.0, 25.9; IR (Neat): ν = 3307, 2956, 2838, 1608, 1511, 1441, 1361, 1304, 1247, 1172, 1084, 1011 cm^{-1}; HRMS (ESI^+; MeCN/CH_2Cl_2): m/z calculated for $C_{12}H_{15}Cl_3NO_4S$ 373.9787, found 373.9795.

2,2,2-Trichloroethyl 4-Phenyl-1-azaspiro[4.5]decane-1-sulfonate (4a). Prepared according to the general procedure C. Purification on a column of silica gel with a gradient of ethyl acetate in petroleum ether (from 100/0 to 98/2) as eluent gave the desired product (107 mg, 84%) as a colorless solid. R_f = 0.6 (petroleum ether/ethyl acetate 90/10); mp 122−123 °C; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.37−7.18 (m, 5H), 4.69 (d, 1H, J = 10.6 Hz), 4.63 (d, 1H, J = 10.6 Hz), 4.19 (ddd, 1H, J = 14.4, 4.2, 2.6 Hz), 3.36 (ddd, 1H, J = 14.4, 12.6, 2.6 Hz), 2.96 (tt, 1H, J = 12.4, 4.3 Hz), 2.79−2.65 (m, 1H), 2.24−2.13 (m, 1H), 2.13−2.02 (m, 1H), 2.02−1.73 (m, 7H), 1.69−1.57 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 145.0, 128.7, 127.0, 126.8, 93.8, 77.8, 70.0, 48.3, 41.8, 39.4, 38.2, 35.5, 32.1, 23.3, 22.6; IR (Neat): ν = 2951, 2880, 1494, 1451, 1380, 1366, 1340, 1251, 1179, 1166, 1125, 1088, 1066, 1042, 1012 cm^{-1}; HRMS (ESI^+; MeCN/CH_2Cl_2): m/z calculated for $C_{17}H_{23}Cl_3NO_3S$ 426.0464, found 426.0454.

2,2,2-Trichloroethyl 4-(4-Methoxyphenyl)-1-azaspiro[4.5]-decane-1-sulfonate (4b). Prepared according according to the general procedure C. Purification on a column of silica gel with a gradient of ethyl acetate in petroleum ether (from 100/0 to 98/2) as eluent gave the desired product (74 mg, 54%) as a colorless solid. R_f = 0.5 (petroleum ether/ethyl acetate 90/10); mp 78−79 °C; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.19−7.11 (m, 2H), 6.89−6.81 (m, 2H), 4.67 (d, 1H, J = 10.7 Hz), 4.61 (d, 1H, J = 10.7 Hz), 4.16 (ddd, 1H, J = 14.2, 4.0, 2.6 Hz), 3.79 (s, 3H), 3.34 (ddd, 1H, J = 14.2, 12.4, 3.3 Hz), 2.89 (tt, 1H, J = 12.3, 4.5 Hz), 2.77−2.63 (m, 1H), 2.23−2.09 (m, 1H), 2.08−1.97 (m, 1H), 1.97−1.68 (m, 7H), 1.68−1.57 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 158.4, 137.2, 127.9, 114.1, 93.8, 77.8, 70.0, 55.4, 48.4, 42.1, 38.6, 38.2, 35.5, 32.4, 23.3, 22.6; IR (Neat): ν = 2952, 2875, 1606, 1512, 1498, 1475, 1455, 1380, 1347, 1325, 1248, 1169, 1122, 1086, 1074, 1028 cm^{-1}; HRMS (ESI^+; MeCN/CH_2Cl_2): m/z calculated for $C_{18}H_{25}Cl_3NO_4S$ 456.0570, found 456.0588.

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***N*-Acetyl-3-phenyl-1-azaspiro[3.4]octane (5a).** A solution of **2ea** (240 mg, 0.60 mmol) in 4.5 mL of 1:1 MeOH/AcOH was transferred via cannula into a flask containing Zn(Cu) couple (202 mg, 5.0 equiv). Transfer of **2ea** was made quantitative with an additional 4.5 mL of 1:1 MeOH/AcOH. The resulting suspension was stirred vigorously for 16 h at 25 °C. The reaction mixture was then filtered, and the filter cake was rinsed with MeOH. The combined filtrates were concentrated under reduced pressure to afford a white solid, which was redissolved in a solution of anhydrous HCl in MeOH (322 μL of CH_3COCl in 4.5 mL of MeOH). The solution was heated at 45 °C for 6 h and then concentrated under reduced pressure. The resulting viscous oil was dissolved in 4.5 mL of CH_2Cl_2, and 4.5 mL of saturated aqueous K_2CO_3 was then added. To this biphasic solution was added dropwise AcCl (85 μL, 2.0 equiv). The reaction was stirred vigorously for 5 h and then diluted with 15 mL of CH_2Cl_2 and 15 mL of 5 wt % aqueous $NaHCO_3$. The organic phase was collected, and the aqueous layer was extracted with 3 × 15 mL of CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification on a column of silica gel with a gradient of ethyl acetate in petroleum ether (from 90/10 to 70/30) as eluent gave the desired product (68 mg, 50%) as a colorless oil. R_f = 0.2 (petroleum ether/ethyl acetate 70/30); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.38−7.31 (m, 2H), 7.31−7.23 (m, 3H), 3.79 (br t, 1H, J = 8.7 Hz), 3.60 (q, 1H, J = 10.0 Hz), 3.42 (t, 1H, J = 10.3 Hz), 3.33−3.21 (m, 1H), 3.07 (q, 1H, J = 10.0 Hz), 2.55 (dd, 1H, J = 12.3, 5.7 Hz), 2.11 (t, 1H, J = 12.3 Hz), 2.06 (s, 3H), 1.94 (qt, 1H, J = 10.4, 3.0 Hz), 1.87−1.77 (m, 2H), 1.73−1.66 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 169.7, 140.2, 128.8, 127.2, 127.1, 64.9, 56.2, 47.5, 40.8, 33.3, 32.1, 24.6, 13.6; IR (Neat): ν = 3028, 2925, 2866, 1643, 1605, 1497, 1402, 1350, 1283, 1257, 1204, 1159, 1102, 1065, 1031, 1019 cm^{-1}; HRMS (ESI$^+$; MeCN/CH_2Cl_2): m/z calculated for $C_{15}H_{20}NO$ 230.1545, found 230.1545.

***N*-Benzoyl-3-phenyl-1-azaspiro[4.5]decane (5b).** A solution of **2ec** (180 mg, 0.42 mmol) in 3.2 mL of 1:1 MeOH/AcOH was transferred via cannula into a flask containing Zn(Cu) couple (141 mg, 5.0 equiv). Transfer of **2ec** was made quantitative with an additional 3.2 mL of 1:1 MeOH/AcOH. The resulting suspension was stirred vigorously for 16 h at 25 °C. The reaction mixture was then filtered, and the filter cake was rinsed with MeOH. The combined filtrates were concentrated under reduced pressure to afford a white solid, which was redissolved in a solution of anhydrous HCl in MeOH (225 μL of CH_3COCl in 3.2 mL of MeOH). The solution was heated at 45 °C for 6 h and then concentrated under reduced pressure. The resulting viscous oil was dissolved in 3.2 mL of CH_2Cl_2, and Et_3N (295 μL, 5.0 equiv) was then added. To this solution was added dropwise BzCl (244 μL, 5.0 equiv). The reaction was stirred vigorously for 5 h and then diluted with 10 mL of CH_2Cl_2 and 10 mL of water. The organic phase was collected, and the aqueous layer was extracted with 3 × 10 mL of CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification on a column of silica gel with a gradient of ethyl acetate in petroleum ether (from 95/5 to 90/10) as eluent gave the desired product (79 mg, 59%) as a white solid. R_f = 0.5 (petroleum ether/ethyl acetate 80/20); mp 157−158 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.44−7.38 (m, 2H), 7.38−7.33 (m, 3H), 7.33−7.27 (m, 2H), 7.25−7.18 (m, 3H), 3.63 (br t, 1H, J = 8.5 Hz), 3.47 (t, 1H, J = 11.0 Hz), 3.29 (tt, 1H, J = 12.2, 6.1 Hz), 3.05 (br t, 1H, J = 12.0 Hz), 2.90 (br t, 1H, J = 12.0 Hz), 2.65 (dd, 1H, J = 12.4, 6.1 Hz), 1.86 (t, 1H, J = 12.4 Hz), 1.80 (br d, 2H, J = 10.5 Hz), 1.68−1.57 (m, 3H), 1.48−1.28 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 169.5, 140.2, 139.5, 129.2, 128.7, 128.4, 127.2, 127.1, 126.4, 67.2, 58.1, 43.6, 41.6, 35.5, 31.2, 25.2, 24.6, 24.1; IR (Neat): ν = 3058, 2919, 2856, 1619, 1599, 1577, 1526, 1494, 1469, 1451, 1444, 1407, 1354, 1305, 1257, 1224, 1195, 1151, 1127, 1076, 1065, 1026, 1001 cm^{-1}; HRMS (ESI$^+$; MeCN/CH_2Cl_2): m/z calculated for $C_{22}H_{26}NO$ 320.2014, found 320.2013.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General notes and general procedures. ^{1}H and ^{13}C NMR spectra of compounds **1a−j**, **2a−j**, **3a,b**, **4a,b** and **5a,b**. X-ray crystallography. Choice of the computational method. Cartesian coordinates for the structures discussed in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For recent reviews, see: (a) Undheim, K. *Synthesis* **2014**, *46*, 1957. (b) Franz, A. K.; Hanhan, N. V.; Ball-Jones, N. R. *ACS Catal.* **2013**, *3*, 540. (c) Rios, R. *Chem. Soc. Rev.* **2012**, *41*, 1060. (d) Kotha, S.; Deb, A. C.; Lahiri, K.; Manivannan, E. *Synthesis* **2009**, 165. (e) Sinibaldi, M.-E.; Canet, I. *Eur. J. Org. Chem.* **2008**, 4391.

(2) For specific reviews on the use of spiro compounds as ligands in catalysis, see: (a) Ding, K.; Han, Z.; Wang, Z. *Chem.—Asian J.* **2009**, *4*, 32. (b) Zhou, Q. L.; Xie, J. H. *Top. Organomet. Chem.* **2011**, *36*, 1.

(3) (a) Zheng, Y.; Tice, C. M.; Singh, S. B. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 3673. (b) Marson, C. M. *Chem. Soc. Rev.* **2011**, *40*, 5514. (c) Burkhard, J. A.; Wagner, B.; Fischer, H.; Schuler, F.; Müller, K.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 3524.

(4) For example, see: (a) Barun, O.; Kumar, K.; Sommer, S.; Langerak, A.; Mayer, T. U.; Müller, O.; Waldmann, H. *Eur. J. Org. Chem.* **2005**, 4773. (b) Katsoulis, I. A.; Pyrkotis, C.; Papakyriakou, A.; Kythreoti, G.; Zografos, A. L.; Mavridis, I.; Nahmias, V. R.; Anastasopoulou, P.; Vourloumis, D. *ChemBioChem.* **2009**, *10*, 1969. (c) Stocks, M. J.; Wilden, G. R. H.; Pairaudeau, G.; Perry, M. W. D.; Steele, J.; Stonehouse, J. P. *ChemMedChem.* **2009**, *4*, 800. (d) Weinberg, K.; Stoit, A.; Kruse, C. G.; Haddow, M. F.; Gallagher, T. *Tetrahedron* **2013**, *69*, 4694 and references therein..

(5) Zhao, Y.; Yu, S.; Sun, W.; Liu, L.; Lu, J.; McEachern, D.; Shargary, S.; Bernard, D.; Li, X.; Zhao, T.; Zou, P.; Sun, D.; Wang, S. *J. Med. Chem.* **2013**, *56*, 5553.

(6) Sakamoto, K.; Tsujii, E.; Abe, F.; Nakanishi, T.; Yamashita, M.; Shigematsu, N.; Izumi, S.; Okuhara, M. *J. Antibiot.* **1996**, *49*, 37.

(7) (a) Dake, G. *Tetrahedron* **2006**, *62*, 3497. For recent reports, see: (b) Hirschhäuser, C.; Parker, J. S.; Perry, M. W. D.; Haddow, M. F.; Gallagher, T. *Org. Lett.* **2012**, *14*, 4846. (c) Kumar, S.; Thornton, P. D.; Painter, T. O.; Jain, P.; Downard, J.; Douglas, J. T.; Santini, C. *J. Org. Chem.* **2013**, *78*, 6529. (d) Wang, S.-G.; Zhang, W.; You, S.-L. *Org. Lett.* **2013**, *15*, 1488. (e) Perry, M. A.; Hill, R. R.; Rychnovsky, S. D. *Org. Lett.* **2013**, *15*, 2226. (f) Wang, Z. J.; Spiccia, N. D.; Gartshore,

DOI: 10.1021/jo502333j
J. Org. Chem. 2015, 80, 1414−1426

C. J.; Illesinghe, J.; Jackson, W. R.; Robinson, A. J. *Synthesis* **2013**, *45*, 3118. (g) McLeod, M. C.; Singh, G.; Plampin, J. N., III; Rane, D.; Wang, J. L.; Day, V. W.; Aubé, J. *Nat. Chem.* **2014**, *6*, 133. (h) Xiao, K.-J.; Luo, J.-M.; Xia, X.-E.; Wang, Y.; Huang, P.-Q. *Chem.—Eur. J.* **2013**, *19*, 13075.

(8) For examples of [4 + 2] cycloaddition-based synthesis of azaspirocycles, see: (a) Huang, P.; Isayan, K.; Sarkissian, A.; Oh, T. *J. Org. Chem.* **1998**, *63*, 4500. (b) Yang, J.; Cohn, S. T.; Romo, D. *Org. Lett.* **2000**, *2*, 763. (c) Romo, D.; Moussa, Z.; Kong, K. *Org. Lett.* **2005**, *7*, 5127.

(9) For examples of [3 + 2] cycloaddition-based synthesis of azaspirocycles, see: (a) Funk, R. L.; Daggett, J. U. *Heterocycles* **1987**, *26*, 2175. (b) Denmark, S. E.; Middleton, D. S. *J. Org. Chem.* **1998**, *63*, 1604. (c) Werner, K. M.; de los Santos, J. M.; Weinreb, S. M.; Shang, M. *J. Org. Chem.* **1999**, *64*, 686. (d) Pearson, W. H.; Ren, Y. *J. Org. Chem.* **1999**, *64*, 688. (e) Williams, G. M.; Roughley, S. D.; Davies, J. E.; Holmes, A. B.; Adams, J. P. *J. Am. Chem. Soc.* **1999**, *121*, 4900. (f) Stockman, R. A.; Sinclair, A.; Arini, L. G.; Szeto, P.; Hughes, D. L. *J. Org. Chem.* **2004**, *69*, 1598. (g) Trost, B. M.; Cramer, N.; Silverman, S. M. *J. Am. Chem. Soc.* **2007**, *129*, 12396. (h) Chen, X.-H.; Wei, Q.; Luo, S.-W.; Xiao, H.; Gong, L.-Z. *J. Am. Chem. Soc.* **2009**, *131*, 13819. (i) Voituriez, A.; Pinto, N.; Neel, M.; Retailleau, P.; Marinetti, A. *Chem.—Eur. J.* **2010**, *16*, 12451. (j) Antonchick, A. P.; Gerding-Reimers, C.; Catarinella, M.; Schürmann, M.; Preut, H.; Ziegler, S.; Rauh, D.; Waldmann, H. *Nat. Chem.* **2010**, *2*, 735. (k) Liu, T. L.; He, Z. L.; Tao, H. Y.; Cai, Y. P.; Wang, C. J. *Chem. Commun.* **2011**, *47*, 2616. (l) Liu, T.-L.; He, Z.-L.; Tao, H. Y.; Wang, C. J. *Chem.—Eur. J.* **2012**, *18*, 8042.

(10) For other types of cycloadditions for the synthesis of azaspirocycles, see: (a) Booker Milburn, K. I.; Dudin, L. F.; Anson, C. E.; Guile, S. D. *Org. Lett.* **2001**, *3*, 3005. (b) McLaughlin, M. J.; Hsung, R. P.; Cole, K. P.; Hahn, J. M.; Wang, J. S. *Org. Lett.* **2002**, *4*, 2017.

(11) (a) Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765. (b) Pandey, G.; Banerjee, P.; Gadre, S. R. *Chem. Rev.* **2006**, *106*, 4484.

(12) For seminal studies, see: (a) Heine, H. W.; Peavy, R. *Tetrahedron Lett.* **1965**, *6*, 3123. (b) Padwa, A.; Hamilton, L. *Tetrahedron Lett.* **1965**, *6*, 4363. (c) Huisgen, R.; Scheer, W.; Szeimies, G.; Huber, H. *Tetrahedron Lett.* **1966**, *7*, 397.

(13) For a relevant review, see: (a) Cardoso, A. L.; Pinho e Melo, T. M. V. D. *Eur. J. Org. Chem.* **2012**, 6479. For brief overviews, see: (b) Dauban, P.; Malik, G. *Angew. Chem., Int. Ed.* **2009**, *48*, 9026. (c) Hrake, S. H.; Bergmeier, S. C. *Tetrahedron* **2010**, *66*, 7337.

(14) Generation of 1,3-zwitterionic species by C−N bond cleavage have also been reported from *N*-H- or *N*-alkyl-2-arylaziridines. Activation of the latter, in this case, proceeds through initial formation of an aziridinium ion. See, for example: (a) Gaebert, C.; Mattay, J. *Tetrahedron* **1997**, *53*, 14297. (b) Zhu, W.; Cai, G.; Ma, D. *Org. Lett.* **2005**, *7*, 5545. (c) Laia, F. M. R.; Cardoso, A. L.; Beja, A. M.; Silva, M. R.; Pinho e Melo, T. M. V. D. *Tetrahedron* **2010**, *66*, 8815. (d) Cardoso, A. L.; Nunes, R. M. D.; Arnaut, L. G.; Pinho e Melo, T. M. V. D. *Synthesis* **2011**, 3516.

(15) (a) Bergmeier, S. C.; Fundy, S. L.; Seth, P. P. *Tetrahedron* **1999**, *55*, 8025. (b) Bergmeier, S. C.; Katz, S. J.; Huang, J.; McPherson, H.; Donoghue, P. J.; Reed, D. D. *Tetrahedron Lett.* **2004**, *45*, 5011.

(16) (a) Ungureanu, I.; Bologa, C.; Chayer, S.; Mann, A. *Tetrahedron Lett.* **1999**, *40*, 5315. (b) Ungureanu, I.; Klotz, P.; Mann, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4615.

(17) $Sc(OTf)_3$: (a) Yadav, J. S.; Reddy, B. V. S.; Pandey, S. K.; Srihari, P.; Prathap, I. *Tetrahedron Lett.* **2001**, *42*, 9089. $FeCl_3$: (b) Fan, J.; Gao, L.; Wang, Z. *Chem. Commun.* **2009**, 5021. $AgSbF_6$: (c) Wender, P. A.; Strand, D. *J. Am. Chem. Soc.* **2009**, *131*, 7528. $Mn(TPP)SbF_6$: (d) Ozawa, T.; Kurahashi, T.; Matsubara, S. *Synlett* **2013**, *24*, 2763. $HSbF_6$ has recently been found to catalyze the formal [3 + 2 + 2] cycloaddition of aziridines with two alkynes. See: (e) Zhou, M.-B.; Song, R.-J.; Li, J.-H. *Angew. Chem., Int. Ed.* **2014**, *53*, 4196.

(18) (a) Yadav, V. K.; Sriramurthy, V. *J. Am. Chem. Soc.* **2005**, *127*, 16366. (b) Ghorai, M. K.; Das, K.; Kumar, A.; Ghosh, K. *Tetrahedron Lett.* **2005**, *46*, 4103. (c) Wu, J.; Sun, X.; Xia, H.-G. *Tetrahedron Lett.* **2006**, *47*, 1509. (d) Gandhi, S.; Bisai, A.; Prasad, B. A. B.; Singh, V. K. *J. Org. Chem.* **2007**, *72*, 2133. (e) Kang, S. B.; Miller, A. W.; Goyal, S.; Nguyen, S. T. *Chem. Commun.* **2009**, 3928. (f) Li, X.; Yang, X.; Chang, H.; Li, Y.; Ni, B.; Wei, W. *Eur. J. Org. Chem.* **2011**, 3122. (g) Maeda, R.; Ishibashi, R.; Kamaishi, R.; Hirotaki, K.; Furuno, H.; Hanamoto, T. *Org. Lett.* **2011**, *13*, 6240.

(19) (a) Ungureanu, I.; Klotz, P.; Schoenfelder, A.; Mann, A. *Chem. Commun.* **2001**, 958. (b) Pawar, S. K.; Vasu, D.; Liu, R.-S. *Adv. Synth. Catal.* **2014**, *356*, 2411.

(20) For isolated examples involving reactions of other *N*-sulfonylaziridines with benzonitrile or cyclohexanone, see ref 18d. During the preparation of this manuscript, a recent example using carbonyl compounds as dipolarophiles has been reported, see: Yang, H.-T.; Xing, M. L.; Zhu, Y.-F.; Sun, X.-Q.; Cheng, J.; Miao, C.-B.; Li, F.-B. *J. Org. Chem.* **2014**, *79*, 1487.

(21) (a) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373. (b) Wuts, P. G. M.; Northuis, J. M. *Tetrahedron Lett.* **1998**, *39*, 3889. (c) Hudlicky, T.; Tian, X.; Königsberger, K.; Maurya, R.; Rouden, J.; Fan, B. *J. Am. Chem. Soc.* **1996**, *118*, 10752.

(22) Maligres, P. E.; See, M. M.; Askin, D.; Reider, P. J. *Tetrahedron Lett.* **1997**, *38*, 5253.

(23) The use of *N*-acyl- and *N*-carbamoylaziridines did not prove successful in this reaction, as previously reported by Wender in ref 17c.

(24) For reviews, see: (a) Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905. (b) Pellissier, H. *Tetrahedron* **2010**, *66*, 1509. (c) Chang, J. W. W.; Ton, T. M. U.; Chan, P. W. H. *Chem. Rec.* **2011**, *11*, 331. (d) Dequirez, G.; Pons, V.; Dauban, P. *Angew. Chem., Int. Ed.* **2012**, *51*, 7384. (e) Degennaro, L.; Trinchera, P.; Luisi, R. *Chem. Rev.* **2014**, *114*, 7881.

(25) (a) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1994**, *116*, 2742. (b) Brookhart, M.; Diaz-Requejo, M. M.; Perez, P. J.; Templeton, J. L. *Organometallics* **1997**, *16*, 4399. (c) Dauban, P.; Sanière, L.; Tarrade, A.; Dodd, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 7707. (d) Mohr, F.; Binfield, S. A.; Fettinger, J. C.; Vedernikov, A. N. *J. Org. Chem.* **2005**, *70*, 4833.

(26) (a) Müller, P.; Baud, C.; Jacquier, Y. *Tetrahedron* **1996**, *52*, 1543. (b) Guthikonda, K.; Du Bois, J. *J. Am. Chem. Soc.* **2002**, *124*, 13672.

(27) (a) Dauban, P.; Ferry, S.; Faure, H.; Ruat, M.; Dodd, R. H. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2001. (b) White, R. D.; Keaney, G. F.; Slown, C. D.; Wood, J. L. *Org. Lett.* **2004**, *6*, 1123. (c) Trost, B. M.; Dong, G. *Chem.—Eur. J.* **2009**, *15*, 6910.

(28) An extensive screening of the reaction conditions was performed with aziridine **1e**. Thirty five Lewis acids were first tested, and the cycloadduct **2e** was isolated only with TMSOTf (28%), $Cu(OTf)_2$ (28%), $Sc(OTf)_3$ (44%), $Bi(OTf)_3$ (26%), $AlCl_3$ (17%), $BF_3{\cdot}2H_2O$ (44%), $(Bu)_2BOTf$ (40%), and $BF_3{\cdot}OEt_2$ (56%). The number of equivalents of $BF_3{\cdot}OEt_2$ was then modified, and the best result was observed using 1.5 equiv. Finally, dichloromethane was found to be the solvent of choice while increasing the reaction temperature above −78 °C always proved detrimental to the yield.

(29) We have also studied the case of *N*-sulfonimidoylaziridines previously prepared in the group. See, for example: Robert-Peillard, F.; Di Chenna, P. H.; Liang, C.; Lescot, C.; Collet, F.; Dodd, R. H.; Dauban, P. *Tetrahedron: Asymmetry* **2010**, *21*, 1447 However, these did not undergo the cycloadditions, probably as a result of steric hindrance provided by the bulky protecting group..

(30) For Cu-catalyzed intramolecular aziridination of sulfamates, see: (a) Duran, F.; Leman, L.; Ghini, A.; Burton, G.; Dauban, P.; Dodd, R. H. *Org. Lett.* **2002**, *4*, 2481. (b) Estéoule, A.; Duran, F.; Retailleau, P.; Dodd, R. H.; Dauban, P. *Synthesis* **2007**, 1251. (c) Malik, G.; Estéoule, A.; Retailleau, P.; Dauban, P. *J. Org. Chem.* **2011**, *76*, 7438. For the analogous Rh-catalyzed process, see: (d) Wehn, P. M.; Lee, J.; Du Bois, J. *Org. Lett.* **2003**, *5*, 4823. (e) Guthikonda, K.; Wehn, P. M.; Caliando, B. J.; Du Bois, J. *Tetrahedron* **2006**, *62*, 11331.

(31) Fiori, K. W.; Du Bois, J. *J. Am. Chem. Soc.* **2007**, *129*, 562.

(32) According to the mechanism depicted by the DFT calculations, it would have been expected that the *p*-MeO-azetidine **3b** would have

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led to the cycloadduct **4b** with a higher yield than that of **4a**. Such is not the case, and this observation might be rationalized by the lower stability of the starting azetidine **3b** which decomposes on standing.

(33) Chéron, N.; Ramozzi, R.; El Kaim, L.; Grimaud, L.; Fleurat-Lessard, P. *J. Org. Chem.* **2012**, *77*, 1351.

(34) Legault, C. Y. *CYLview, 1.0b*; Université de Sherbrooke, 2009, http://www.cylview.org.

(35) Branchadell, V.; Sbai, A.; Oliva, A. *J. Phys. Chem.* **1995**, *99*, 6472.

(36) Kemnitz, E.; Rüdiger, S. in *F Functionalized Inorganic Fluorides: Synthesis, Characterization & Properties of Nanostructured Solids*; Tressaud, A., Ed; John Wiley & Sons: New York, 2010; Chapter 3, p 72.

(37) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, N. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09, Revision A.02*, Gaussian, Inc., Wallingford, CT, 2009.

(38) Chai, J. D.; Head-Gordon, M. *Phys. Chem. Chem. Phys.* **2008**, *10*, 6615.

(39) (a) Mierts, S.; Scrocco, E.; Tomasi, J. *Chem. Phys.* **1981**, *55*, 117. (b) Cossi, M.; Mennucci, B.; Tomasi, J. *Chem. Phys. Lett.* **1994**, *228*, 165. (c) Mennucci, B.; Cancès, E.; Tomasi, J. *J. Phys. Chem. B* **1997**, *101*, 10506.

(40) E, W.; Ren, W.; Vanden-Eijnden, E. *Phys. Rev. B* **2002**, *66*, 052301.

(41) Fleurat-Lessard, P.; Dayal, P. *Opt'n Path v1.50*; Freely available at: http://perso.ens-lyon.fr/paul.fleurat-lessard/ReactionPath.html.

(42) Wyvratt, J. M.; Hazen, G. G.; Weinstock, L. M. *J. Org. Chem.* **1987**, *52*, 944.

DOI: 10.1021/jo502333j
J. Org. Chem. 2015, 80, 1414−1426