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Experimental and Computational Studies of the Diastereoselective Alkylations of 3-Substituted γ-Sultams

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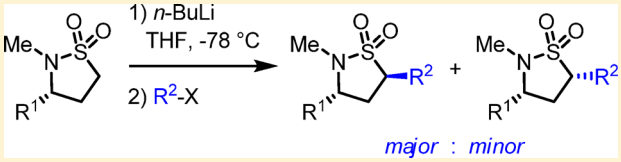
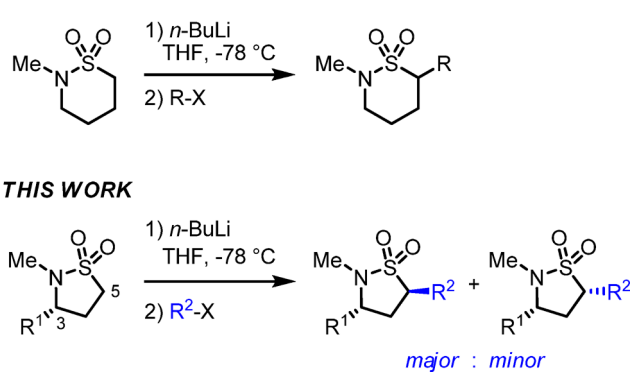
Supporting Information

ABSTRACT: We report that chiral 3-substituted γ-sultam α-carbanions undergo diastereoselective alkylation reactions with alkyl halides to predominantly produce *trans*-3,5-disubstituted γ-sultam products. Quantum mechanical calculations provided a stereoelectronic rationale for the observed diastereoselectivity.



Cyclic sulfonamides (sultams) are unnatural functional groups[1] that can complement corresponding cyclic amides (lactams) due to their distinct properties.[2] It has also been noted that sulfonamides substantially differ from amides in their low energy conformation,[3] chemical stability,[4] and α-carbanion chemistry.[5] Unlike amides, sulfonamides and sulfones do not participate in resonance stabilization of their corresponding α-carbanions.[6] Previous studies demonstrated that sultam α-carbanions readily react with a range of alkyl electrophiles,[7] but, to our knowledge, the stereochemical outcomes of alkylation reactions with chiral sultam α-carbanions have not been explored (Scheme 1).[8] We sought

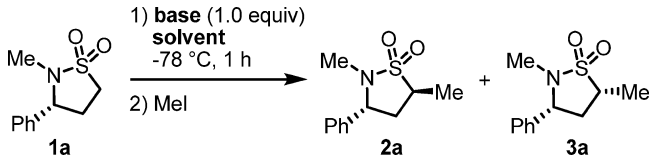
Scheme 1. Sultam Alkylation Reactions



to explore the stereochemical result of this sultam alkylation reaction due to our ongoing interest in sultam chemistry.[9,10] Herein, we report that chiral 3-substituted γ-sultam α-carbanions undergo diastereoselective alkylation reactions with alkyl halides to predominantly produce *trans*-3,5-disubstituted γ-sultam products.

We initiated our sultam alkylation studies with (*R*)-3-phenyl-γ-sultam (**1a**)[10] and a survey of different bases and solvents (Table 1). One equivalent of base was used throughout the screening process to minimize the risk of epimerizing the alkylation products. Kaiser reported the use of THF and *n*-BuLi

Table 1. Optimization of the Sultam Alkylation Conditions[a]



entry	base	solvent	yield[b] (%)	dr[c] (*trans*:*cis*)
1	*n*-BuLi	THF	84	6:1
2	*n*-BuLi	toluene	28	4:1
3	*s*-BuLi	THF	32	5:1
4	LHMDS	THF	46	3:1
5	TMPZnCl·LiCl	THF	0	

[a]All results are the average of at least two separate experiments on 0.67 mmol scale. [b]Isolated yield for the purified mixture of diastereomers. [c]Ratio of diastereomers determined by ^{1}H NMR analysis of sultam C5 proton in the unpurified reaction mixture.

for the alkylation of symmetrical sultams;[7] thus, we used these conditions as our starting point. Kaiser's conditions worked well in our system (Table 1, entry 1), producing the alkylated sultam products in 84% yield, with the *trans* diastereomer (**2a**) as the major product (6:1 dr, *trans*:*cis*). It was important to keep the reaction temperature at or near −78 °C throughout the process, as higher reaction temperatures led to lower conversions and complex mixtures of products. We obtained a lower yield when we changed the reaction solvent to toluene (28%, entry 2) or when we used *s*-BuLi as the base (32%, entry 3). The use of LHMDS as a base (entry 4) also led to a lower yield (46%), and the TMPZnCl·LiCl[11] base was unreactive with our system (entry 5). The TMPZnCl·LiCl result can be contrasted with our previous sultam arylation methodology using the same base,[10] in which higher reaction temperatures and longer reaction times were required (60−70 °C in THF) to deprotonate the sultam ring. On the basis of the outcome of the base and solvent screen, we determined that *n*-BuLi in THF at −78 °C were suitable reaction conditions.

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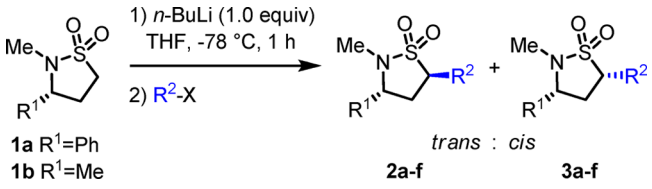
After identifying the appropriate base and solvent conditions, we surveyed a set of electrophiles with different steric demands and reactivity profiles to assess their effects on the dr values of the sultam alkylation products (Table 2). We evaluated the same electrophiles across two different sultam scaffolds that possessed large and small 3-substituents (**1a** and **1b**, respectively)[12] to assess the impact of the 3-substituent size on the dr of the products. As discussed above, the reaction of the 3-phenyl sultam α-carbanion with iodomethane (Table 2, entry 1) proceeded in high yield and good dr (84%, 6:1 dr). The analogous alkylation reactions with allyl bromide (entry 2) and benzyl bromide (entry 3) also proceeded in high yields with good dr values, both favoring the *trans* diastereomers (78%, 4:1 dr and 77%, 5:1 dr, respectively). The 3-methyl sultam α-carbanion was also treated with iodomethane (entry 4), allyl bromide (entry 5), and benzyl bromide (entry 6) to provide the corresponding alkylation products in modest yields and diastereoselectivity, all favoring the *trans* diastereomers (63%, 3:1 dr; 67%, 3:1 dr; 55%, 3:1 dr, respectively). The product distribution matched pairs between the 3-phenyl and 3-methyl sultam scaffolds (entries 1–3 versus entries 4–6, respectively) indicated that the larger 3-phenyl substituent led to higher dr values than the smaller 3-methyl group. The 3-methyl sultam alkylation reactions also provided lower isolated yields than their 3-phenyl counterparts due to higher incidence of C5 dialkylation products[13] with the 3-methyl sultam scaffold.

To further explore the diastereomeric product distribution, we subjected the pure *trans* diastereomer (**2a**, Scheme 2) to *n*-BuLi (1.0 equiv) in THF at −78 °C and quenched the reaction with acid after 1 h. We observed an inversion of the C5 stereochemistry, with the *cis* diastereomer (**3a**) being the major product in a 1:3 dr (*trans*:*cis*). This result demonstrated that the C5 stereogenic center of the sultam could be inverted at −78 °C and suggested that the predominant *trans* diastereomeric products (**2a–f**) in Table 2 may arise from a kinetic alkylation pathway.[10] This result also demonstrated that the *trans* and *cis* diastereomers can be accessed as the major products using one- or two-step processes, respectively. Attempts to use excess base in the alkylation of **1a** to directly access the *cis* diastereomer as the major product only led to complex mixtures of C5 mono- and dialkylated products.[13] Thus, the *cis* diastereomer must be obtained using the two-step process described above.

There is limited information available about the structure of sulfonamide α-carbanions,[5,6] yet the analogous sulfone α-carbanions are well-studied and offer some insight that may be applicable to sulfonamide α-carbanions. Pioneering studies by Corey,[14] Cram,[15] Bordwell,[16] and others established that the α-carbanions of acyclic sulfones are essentially planar and that they are asymmetric at low reaction temperatures due to a rotational barrier at the C–S bond. These initial results were further supported by the computational studies of Wolfe[17] and Streitwieser.[18] Additional computational studies by Anders[19] found that sulfone α-carbanions can be planar or slightly pyramidal, with the energy difference between the two conformations being too small (<0.5 kcal/mol) to be of experimental significance. A variety of acyclic sulfone α-carbanion X-ray crystal structures reported by Gais[20] further supported the finding that the α-carbanions can be nearly planar or slightly pyramidal (depending on the substituents). These results were also supported by Reetz's[21] analysis of the Cambridge Crystallographic Database. Corey[14b] and Cram[15] also studied the α-carbanions of cyclic sulfones and found that these carbanions are planar, but, unlike their acyclic counterparts, the cyclic carbanions are symmetrical because the ring does not allow rotational freedom at the C–S bond to form an asymmetric carbanion. On the basis of these studies, we hypothesized that the α-carbanions of sultams might also be symmetrical and essentially planar.

To further understand the conformational preference of our sultam scaffold, we obtained a 0.83 Å single-crystal X-ray structure of **1a**. Compound **1a** crystallized in an envelope conformation, with C3 of the sultam at the flap, and the *N*-methyl and 3-phenyl groups in pseudoequatorial orientations (Figure 1). We also noted that the sulfonamide in **1a** was not in the preferred conformation usually found in acyclic sulfonamides, where the nitrogen lone pair bisects the O=S=O angle.[3b] Rather, the sulfonamide in **1a** adopted a conformation that placed the *N*-methyl group in a pseudoequatorial orientation, and the nitrogen lone pair eclipsed one of the oxygen atoms in the sulfone moiety.

Table 2. Sultam Alkylation Scope[a]

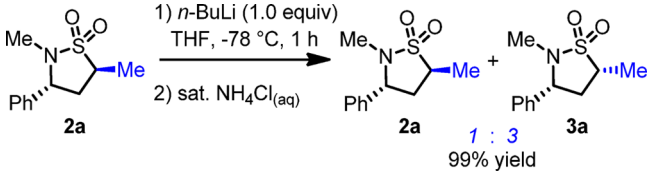


1a R^1=Ph
1b R^1=Me
2a-f **3a-f**

entry	sultam	R^2-X	products (*trans*:*cis*)	yield[b] (%)	dr[c] (*trans*:*cis*)
1	**1a**	Me-I	**2a**:**3a**	84	6:1
2	**1a**	allyl-Br	**2b**:**3b**	78	4:1
3	**1a**	Bn-Br	**2c**:**3c**	77	5:1
4	**1b**	Me-I	**2d**:**3d**	63	3:1
5	**1b**	allyl-Br	**2e**:**3e**	67	3:1
6	**1b**	Bn-Br	**2f**:**3f**	55	3:1

[a]All results are the average of at least three separate experiments on 0.67 mmol scale. [b]Isolated yield for the purified mixture of diastereomers. [c]Ratio of diastereomers determined by ^{1}H NMR analysis of sultam C5 proton in the unpurified reaction mixture.

Scheme 2. Inversion of the *Trans* Diastereomer



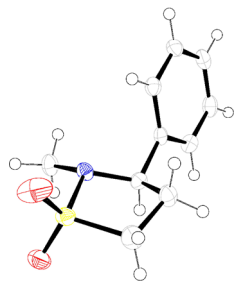


Figure 1. X-ray structure of **1a** (0.83 Å single-crystal X-ray structure of **1a**). The thermal ellipsoids are shown at 50%.

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To further analyze the X-ray result of **1a**, we conducted a conformational search of **1a** using a mixed torsional/low-mode sampling method.[22] The resulting structures were minimized using quantum mechanical calculations at the B3LYP/6-31+G(d) level of theory.[23] The lowest energy conformer of **1a** was nearly identical to the X-ray structure of **1a**. On the basis of these results, we concluded that the steric preferences of the sultam ring substituents drove the low energy ring conformation to minimize potential 1,2-interactions between the N2 and C3 substituents. Thus, the orientation of the sulfonamide functional group had a minimal effect on the overall ring conformation.

We then applied computational methods to rationalize the observed diastereoselectivity in our sultam alkylation reactions. We searched for low energy conformations of the α-carbanion of **1a**, using a similar approach to that described above. The resulting structures were coordinated with a lithium cation and then quantum mechanically minimized at the B3LYP/6-31+G(d) level of theory. The resulting structures demonstrated that the low energy conformation of the **1a** α-carbanion lithium salt (**4a**, Figure 2)[24] resided in the same ring conformation as

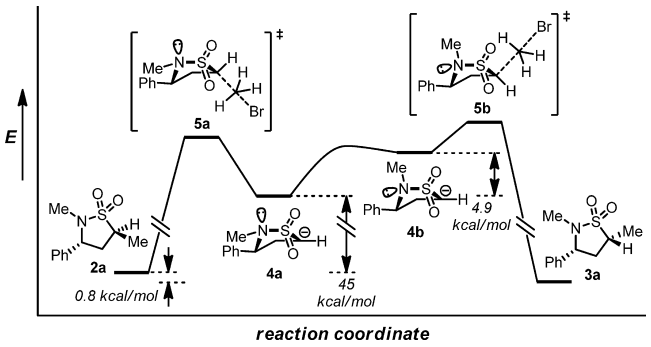

Figure 2. Proposed reaction coordinate diagram for the α-carbanion lithium salt of **1a**. The lithium cation is omitted for clarity, but if it was shown, then it would reside in a shared coordination between the oxygen atoms of the sulfonamide.[24]

the low energy conformation of **1a**. In addition, the α-carbanion of **4a** was nearly planar. On the basis of these results, we rationalized the stereochemical outcomes of the sultam alkylation reactions with a similar approach to that applied by Meyers,[25] Husson,[26] and Seebach[27] for the stereoselective alkylation of chiral lactam enolates. We hypothesized that the observed dr in the sultam C5 alkylation reactions (Table 2) was due to two features: (1) the steric preference of the 3-substituent provided a low energy conformational bias to the sultam ring system[28] and (2) the alkylation of the sultam α-carbanion occurred *anti* to the N2 lone pair to minimize the overall dipole of the alkylation transition state (**5a**). According to this hypothesis, larger 3-substituents should provide larger conformational biases and greater diastereoselectivities, and this was observed experimentally. The nearly planar C5 carbanion (**4a**) did not display any clear steric biases for the approach of an electrophile to either face of the carbanion. Alkylation of the sultam α-carbanion *anti* to the N2 lone pair would result in the predominant formation of the *trans* diastereomer, as was observed experimentally.

Application of the Curtin−Hammett principle[29] implied that the transition state (**5a**, Figure 2) energy barrier that produced the *trans* diastereomer (**2a**) must be lower than the corresponding transition state (**5b**) energy barrier that led to the *cis* diastereomer (**3a**). We were unable to fully characterize these energy barriers along the reaction coordinate due to our inability to accurately calculate the transition state energies.[30] To further explore the potential role of the nitrogen lone pair in the alkylation reaction outcomes, we inverted the nitrogen, and quantum mechanical minimization of this system resulted in a model for **4b** that was nearly 5 kcal/mol higher in energy than **4a** at the B3LYP/6-31+G(d) level of theory. Although this intermediate was higher in energy than what we would anticipate based on the observed *trans*:*cis* product distribution (Table 2, entry 1), this calculation did suggest that the orientation of the nitrogen lone pair could contribute to the preferred conformation of the α-carbanion intermediate and the diastereoselectivity of the alkylation reaction. We also found that the energy difference between **2a** and **4a** was 45 kcal/mol at the 6-31+G(d) level of theory.[31] This result implied that the transition state complexes **5a** and **5b** must closely resemble the structures of **4a** and **4b**, respectively, in accordance with the Hammond postulate.[29] An extension of this hypothesis inferred that **5a** should be lower in energy than **5b** and that the reaction should favor the *trans* diastereomer, as was observed experimentally. In addition, the large energy difference between **2a** and **4a** suggested that **4a** was highly reactive and, as a result, should be less selective (i.e., diastereoselective) according to the reactivity versus selectivity principle.[29] This finding is reflected in the modest dr values in Table 2. Additional calculations with the reaction products showed that the *cis* diastereomer (**3a**) was favored over the *trans* diastereomer (**2a**) by 0.8 kcal/mol at the B3LYP/6-31+G(d) level of theory. This calculation provided further evidence that the *trans* diastereomer was the product of a kinetic reaction pathway.

In conclusion, we have identified conditions for the diastereoselective alkylation of chiral 3-substituted γ-sultams. Both the *trans* and *cis* diastereomers can be accessed as the major products using a one- or two-step procedure, respectively. The degree of dr is impacted by the steric bulk of the 3-substituent, with larger substituents favoring higher dr values. We used quantum calculations to characterize the low energy conformations of the starting materials and proposed intermediates, and our results were in agreement with the stereochemical outcomes of the alkylation reactions.

EXPERIMENTAL SECTION

General Information. Reaction mixtures were analyzed on a UPLC-MS system using formic acid/acetonitrile mobile phases and an Acquity UPLC C18 column (1.7 μm, 2.1 × 30 mm). ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 solutions at 400 or 500 MHz for ^{1}H and 101 or 126 MHz for ^{13}C with Me_4Si or residual solvent as a reference standard. The ratio of diastereomeric alkylation products was determined by ^{1}H NMR analysis of the sultam C5 proton in the crude reaction mixture, prior to chromatography. High-resolution mass spectra were obtained by positive EI and Orbitrap mass analysis. Diastereomers were separated on a PIC-100 SFC system using CO_2/MeOH + 0.1% NH_4OH mobile phases and a Chiralpak AD column (5 μm, 21.2 × 150 mm). Commercial *n*-BuLi was titrated according to the method of Burchat.[32]

General Procedure for Table 2: Sultam Alkylation Reactions. A 10 mL oven-dried vial equipped with a rubber septum and magnetic stir bar was charged with the 3-substituted γ-sultam[10] (0.67 mmol) and anhydrous THF (3.5 mL). The mixture was purged with nitrogen gas and cooled to −78 °C. In a separate vial under nitrogen with a stir bar, *n*-BuLi (0.4 mL, 0.67 mmol, 1.67 M in hexanes) was cooled to −78 °C. After 10 min, the sultam solution in THF was transferred via syringe to the cooled vial containing the *n*-BuLi solution. The reaction mixture was stirred for 15 min at −78 °C, and then the alkyl halide

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(3.35 mmol, 5 equiv) was rapidly injected into the solution via syringe. The resulting solution was stirred for 5 min at −78 °C, then quenched with saturated aqueous ammonium chloride (3 mL), and warmed to ambient temperature while stirring. The organic and aqueous layers were separated, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The organic fractions were combined, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (heptane/acetone, 0−30%) to provide alkylated products containing a mixture of diastereomers (isolated yields and diastereomeric ratios reported in Table 2 are an average of at least three separate experiments). The spectral data are reported for the individual diastereomers that were purified by silica gel column chromatography (compounds containing no chromophore) or supercritical fluid chromatography (compounds containing a chromophore) on a small scale for characterization purposes. NOE experiments were used to confirm the stereochemistry of **2a** and **3a**. The C5 proton of the *trans* diastereomer was consistently further downfield than the corresponding C5 proton of the *cis* diastereomer in all reaction products. Thus, the C5 proton ^{1}H NMR shift was used to assign the stereochemistry of the products (**2b**−**f** and **3b**−**f**).

*(3R,5S)-2,5-Dimethyl-3-phenylisothiazolidine 1,1-Dioxide (**2a**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.30 (m, 5H), 4.15 (t, J = 8.0 Hz, 1H), 3.45 (h, J = 7.1 Hz, 1H), 2.55 (s, 3H), 2.34 (td, J = 7.4, 1.4, 2H), 1.42 (d, J = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.0, 129.1, 128.4, 126.5, 61.3, 50.6, 36.5, 28.9, 12.9; HRMS calcd for $C_{11}H_{15}NO_2S$ [M + H]$^+$, 226.0896; found, 226.0898. HMBC and HSQC NMR experiments were used to assign the ^{1}H and ^{13}C resonances; then, a NOESY experiment was performed to show there was not a NOE observed between the C3 and C5 protons, indicating the *trans* ring stereochemistry.

*(3R,5R)-2,5-Dimethyl-3-phenylisothiazolidine 1,1-Dioxide (**3a**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.32 (m, 5H), 4.04 (dd, J = 10.1, 6.0 Hz, 1H), 3.35−3.26 (m, 1H), 2.67 (ddd, J = 13.2, 7.3, 5.9 Hz, 1H), 2.54 (s, 3H), 1.89 (dt, J = 13.4, 10.6 Hz, 1H), 1.50 (d, J = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 140.3, 129.3, 128.6, 127.2, 62.7, 53.0, 37.7, 30.5, 13.7; HRMS calcd for $C_{11}H_{15}NO_2S$ [M + H]$^+$, 226.0896; found, 226.0900. HMBC and HSQC NMR experiments were used to assign the ^{1}H and ^{13}C resonances; then, a NOESY experiment was performed to show there was a NOE observed between the C3 and C5 protons, indicating the *cis* ring stereochemistry.

*(3R,5R)-5-Allyl-3-phenylisothiazolidine 1,1-Dioxide (**2b**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.30 (m, 5H), 5.86−5.76 (m, 1H), 5.19 (ddd, J = 24.4, 16.0, 1.2, 1H), 4.10 (dd, J = 7.9, 3.6 Hz, 1H), 3.42 (qd, J = 8.2, 6.1 Hz, 1H), 2.86−2.74 (m, 1H), 2.57 (s, 3H), 2.43−2.27 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.9, 132.7, 129.1, 128.5, 126.6, 118.8, 61.3, 54.8, 34.5, 32.4, 28.6; HRMS calcd for $C_{13}H_{17}NO_2S$ [M + H]$^+$, 252.1053; found, 252.1057.

*(3R,5S)-5-Allyl-3-phenylisothiazolidine 1,1-Dioxide (**3b**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.30 (m, 5H), 5.88−5.77 (m, 1H), 5.22−5.14 (m, 2H), 4.04 (dd, J = 10.3, 6.0 Hz, 1H), 3.32−3.24 (m, 1H), 2.83 (dt, J = 14.8, 6.2, 1H), 2.65 (dt, J = 13.3, 6.7, 1H), 2.54 (s, 3H), 2.42 (dt, J = 15.6, 8.0, 1H), 1.91 (dt, J = 13.4, 10.6, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.1, 132.6, 129.1, 128.6, 126.8, 118.8, 63.0, 57.4, 36.3, 33.6, 29.7; HRMS calcd for $C_{13}H_{17}NO_2S$ [M + H]$^+$, 252.1053; found, 252.1053.

*(3R,5S)-5-Benzyl-2-methyl-3-phenylisothiazolidine 1,1-Dioxide (**2c**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.21 (m, 10H), 4.12 (dd, J = 8.0, 6.0 Hz, 1H), 3.66−3.58 (m, 1H), 3.47−3.37 (m, 1H), 2.84 (dd, J = 14.1, 1.9 Hz, 1H), 2.57 (s, 3H), 2.42 (dt, J = 13.6, 7.9 Hz, 1H), 2.16 (ddd, J = 13.9, 8.4, 6.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.9, 136.4, 129.2, 129.0, 128.9, 128.5, 127.2, 126.6, 61.2, 56.4, 34.3, 33.9, 28.7; HRMS calcd for $C_{17}H_{19}NO_2S$ [M + H]$^+$, 302.1209; found, 302.1212.

*(3R,5R)-5-Benzyl-2-methyl-3-phenylisothiazolidine 1,1-Dioxide (**3c**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.19 (m, 10H), 4.00 (dd, J = 10.2, 5.9 Hz, 1H), 3.64−3.36 (m, 2H), 2.87 (td, J = 12.8, 4.0 Hz, 1H), 2.56 (s, 3H), 2.46 (dt, J = 12.9, 6.3 Hz, 1H), 1.96 (dt, J = 13.4, 10.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.1, 136.5, 129.1, 129.0, 128.9, 128.6, 127.1, 126.8, 63.2, 59.2, 36.3, 35.0, 30.0; HRMS calcd for $C_{17}H_{19}NO_2S$ [M + H]$^+$, 302.1209; found, 302.1213.

*(3S,5S)-2,3,5-Trimethylisothiazolidine 1,1-Dioxide (**2d**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.32 (h, J = 6.8 Hz, 1H), 3.19 (h, J = 6.4, 1H), 2.68 (s, 3H), 2.08 (td, J = 7.6, 0.8 Hz, 1H), 1.38 (d, J = 6.8 Hz, 3H), 1.26 (d, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 52.8, 50.4, 34.8, 28.4, 19.7, 13.2; HRMS calcd for $C_6H_{13}NO_2S$ [M + H]$^+$, 164.0740; found, 164.0742.

*(3S,5R)-2,3,5-Trimethylisothiazolidine 1,1-Dioxide (**3d**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.24−3.04 (m, 2H), 2.67 (s, 3H), 2.49 (ddd, J = 13.2, 7.7, 5.8 Hz, 1H), 1.57 (dt, J = 13.0, 10.1 Hz, 1H), 1.43 (d, J = 6.8 Hz, 2H), 1.25 (d, J = 6.2 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 53.8, 52.6, 36.4, 29.0, 19.7, 14.5; HRMS calcd for $C_6H_{13}NO_2S$ [M + H]$^+$, 164.0740; found, 164.0742.

*(3S,5S)-5-Allyl-2,3-dimethylisothiazolidine 1,1-Dioxide (**2e**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85−5.75 (m, 1H), 5.18 (dq, J = 27.2, 1.6 Hz, 1H), 5.17 (q, J = 1.2 Hz, 1H), 3.32−3.24 (m, 1H), 3.21−3.13 (m, 1H), 2.77−2.70 (m, 1H), 2.67 (s, 3H), 2.33−2.25 (m, 1H), 2.15−2.10 (m, 1H), 2.06−1.99 (m, 1H), 1.24 (d, J = 6.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 132.9, 118.7, 54.5, 52.8, 32.7, 32.6, 28.1, 19.6; HRMS calcd for $C_8H_{15}NO_2S$ [M + H]$^+$, 190.0896; found, 190.0899.

*(3S,5R)-5-Allyl-2,3-dimethylisothiazolidine 1,1-Dioxide (**3e**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86−5.76 (m, 1H), 5.18 (dq, J = 29.6, 1.6 Hz, 2H), 5.18−5.16 (m, 1H), 3.18−3.05 (m, 2H), 2.81−2.73 (m, 1H), 2.66 (s, 3H), 2.45 (ddd, J = 13.2, 7.6, 5.6 Hz, 1H), 2.38−2.30 (m, 1H), 1.61 (dt, J = 13.2, 10.4 Hz, 1H), 1.25 (d, J = 6.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 132.8, 118.7, 56.8, 54.0, 34.4, 33.9, 29.0, 19.6; HRMS calcd for $C_8H_{15}NO_2S$ [M + H]$^+$, 190.0896; found, 190.0898.

*(3S,5S)-5-Benzyl-2,3-dimethylisothiazolidine 1,1-Dioxide (**2f**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.29 (m, 2H), 7.29−7.18 (m, 3H), 3.54−3.40 (m, 1H), 3.36 (dd, J = 14.0, 4.9 Hz, 1H), 3.29−3.14 (m, 1H), 2.74 (dd, J = 14.0, 10.3 Hz, 1H), 2.68 (s, 3H), 2.16 (dt, J = 13.3, 7.6 Hz, 1H), 1.89 (ddd, J = 13.7, 8.4, 5.8 Hz, 1H), 1.20 (d, J = 6.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.6, 128.9, 128.8, 127.1, 56.2, 52.7, 34.0, 32.4, 28.1, 19.6; HRMS calcd for $C_{12}H_{17}NO_2S$ [M + H]$^+$, 240.1053; found, 240.1056.

*(3S,5R)-5-Benzyl-2,3-dimethylisothiazolidine 1,1-Dioxide (**3f**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (dd, J = 8.1, 6.4 Hz, 2H), 7.29−7.18 (m, 3H), 3.42 (dd, J = 13.9, 5.0 Hz, 1H), 3.38−3.26 (m, 1H), 3.13−2.99 (m, 1H), 2.78 (dd, J = 13.9, 10.0 Hz, 1H), 2.68 (s, 3H), 2.27 (ddd, J = 13.0, 7.5, 5.6 Hz, 1H), 1.64 (dt, J = 13.1, 10.4 Hz, 1H), 1.23 (d, J = 6.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.6, 128.9, 128.8, 127.1, 58.6, 54.1, 35.3, 34.5, 29.2, 19.6; HRMS calcd for $C_{12}H_{17}NO_2S$ [M + H]$^+$, 240.1053; found, 240.1055.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra and X-ray data (CIF). 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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