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Substituent-Controlled Annuloselectivity and Stereoselectivity in the Sulfa-Staudinger Cycloadditions

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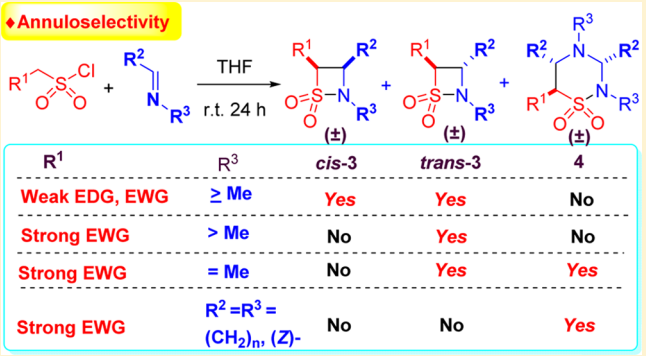
Supporting Information

ABSTRACT: In the sulfa-Staudinger cycloadditions of imines and sulfonyl chlorides, the annuloselectivity is mainly controlled by the electronic effect of the α-substituents of sulfonyl chlorides and the nucleophilicity of imines. Sulfonyl chlorides with weakly electron-donating and withdrawing substituents prefer the $[2^s+2^i]$ annulation, giving a mixture of *cis*- and *trans*-β-sultams. Sulfonyl chlorides bearing strongly electron-withdrawing α-substituents show different annuloselectivity depending upon the nucleophilicity of imines as following: (1) weakly nucleophilic imines with sterically larger substituents than the methyl group undergo only $[2^s+2^i]$ annulation to produce *trans*-β-sultams; (2) strongly nucleophilic imines with the *N*-methyl substituent take place both $[2^s+2^i]$ and $[2^s+2^i+2^i]$ annulations generally, delivering *trans*-β-sultams and *rel*(3*S*,5*S*,6*R*)-1,2,4-thiadiazinane 1,1-dioxides composed of one molecule of the sulfenes and two molecules of imines; (3) more strongly nucleophilic cyclic (*Z*)-imines give predominately $[2^s+2^i+2^i]$ annulations, resulting in a pair of diastereomeric $[2^s+2^i+2^i]$ annuladducts 1,2,4-thiadiazinane 1,1-dioxides. In the second case, the electronic and steric effects of the *C*-substituents of the *N*-methyl imines also affect the annuloselectivity. The stereochemistry and stereoselectivities of the $[2^s+2^i]$ and $[2^s+2^i+2^i]$ annuladducts were investigated systematically and mechanistically rationalized.



INTRODUCTION

The concept of "sulfa-Staudinger cycloaddition" has first been introduced by our group to describe the $[2^s+2^i]$ annulations of sulfenes or their equivalents with imines to form β-sultams after the mechanistic investigation.[1] Since its first discovery in 1916,[2] the reaction had not received much attention, mainly because of the inconvenient formation of sufenes from diazoalkanes and sulfur dioxide. Later in 1970, Tsuge and Iwanami succeeded in synthesizing β-sultams using sulfonyl chlorides as sulfene precursors.[3] Since then, the sulfa-Staudinger cycloadditions have witnessed an upsurge,[4] because of the significant application of β-sultams in both synthetic[5] and medicinal chemistry.[6] As early as 1975, Hiraoka and Kobayashi discovered that the sulfa-Staudinger cycloadditions of sulfonyl chlorides with imines can provide not only four-membered $[2^s+2^i]$ annuladducts (annulation adducts) β-sultams, but also six-membered $[2^s+2^i+2^i]$ annuladducts 1,2,4-thiadiazinane 1,1-dioxides composed of one molecule of sulfenes and two molecules of imines (Scheme 1a).[7] In our recent intensive studies on the sulfa-Staudinger cycloadditions using ethanesulfonyl chloride (**1a**) and phenylmethanesuofonyl chloride (**1b**) as representative sulfene precursors, we also observed the $[2^s+2^i+2^i]$ annuladducts in very low yields from sulfonyl chloride **1b** and cyclic imine 3,4-dihydroisoquinoline in the absence of organic bases (Scheme 1b).[8] However, no systematically experimental and mechanistic studies on the $[2^s+2^i]$ and $[2^s+2^i+2^i]$ annuloselectivity (annulation selectivity) was conducted. One of the important issues in the sulfa-Staudinger cycloadditions is what controls the annuloselectivity between the $[2^s+2^i]$ annulations with one molecule of sulfenes and one molecule of imines and the $[2^s+2^i+2^i]$ annulations with one molecule of sulfenes and two molecules of imines.

In continuing our interests in the annuloselectivities of cycloadditions involving imines,[9] we investigated the annuloselectivity between $[2^s+2^i]$ and $[2^s+2^i+2^i]$ annulations in the sulfa-Staudinger cycloadditions and found that it is controlled mainly by the nucleophilicity of imines and the electronic effect of α-substituents of sulfonyl chlorides (Scheme 1c). Herein, we report the substituent-controlled $[2^s+2^i]$ and $[2^s+2^i+2^i]$ annuloselectivity, together with the mechanistic explanations, hoping to provide useful information for controlling the annuloselectivity in the sulfa-Staudinger cycloadditions. In addition, the stereochemistry and stereoselectivity of both $[2^s+2^i]$ and $[2^s+2^i+2^i]$ annuladducts were investigated and rationalized mechanistically.

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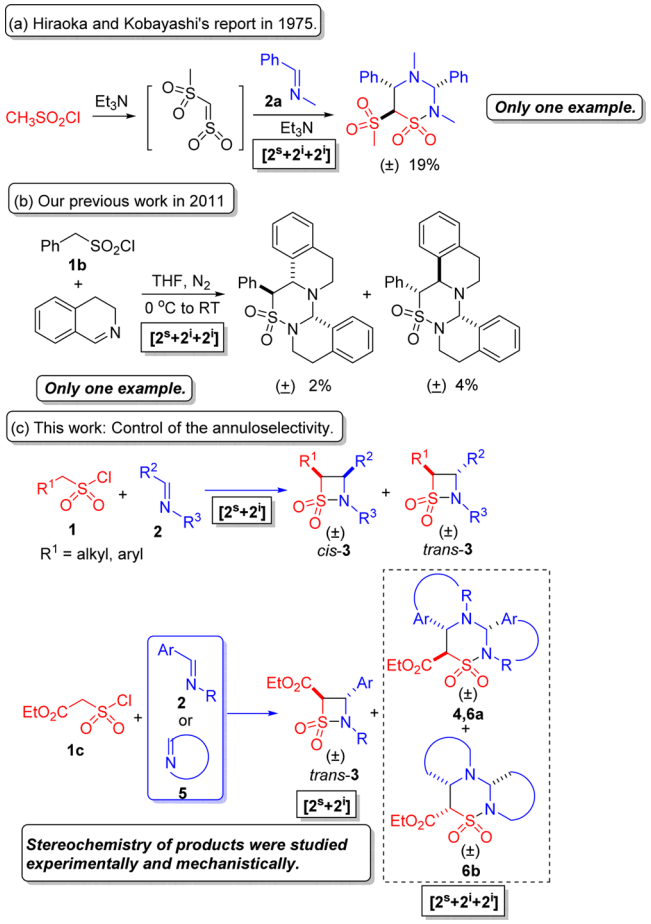
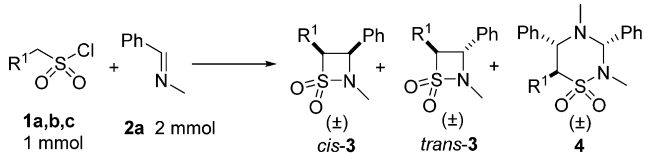
Scheme 1. Precedent and Current Annuloselectivities in the Sulfa-Staudinger Cycloadditions



RESULTS AND DISCUSSION

Substituent Effect of Sulfonyl Chlorides on the Annuloselectivity and Stereoselectivity. The previously reported results indicate that [2^s+2^i+2^i] annuladducts were obtained only with imines with less bulky substituents, such as *N*-methyl imines and cyclic (*Z*)-imines (Scheme 1a and b).[7,8] To investigate the substituent effect of sulfenes on the annuloselectivity and stereoselectivity, we first employed *N*-benzylidenemethylamine (**2a**) as a model to screen sulfonyl chlorides with different α-substituents. The results are shown in Table 1. When imine **2a** reacted with ethanesulfonyl chloride (**1a**) bearing a weakly electron-donating α-methyl group in 2:1 ratio in THF at room temperature, neither [2^s+2^i] nor [2^s+2^i+2^i] annuladduct was formed (Table 1, entry 1). However, the reaction produced a mixture of *cis*- and *trans*-β-sultams **3aa** in low yields under solvent-free conditions for long reaction time (Table 1, entry 2) or under more violent conditions (Table 1, entries 3 and 4).[10] For phenylmethanesulfonyl chloride (**1b**) with a weakly electron-withdrawing α-phenyl group, the reaction produced exclusively [2^s+2^i] annuladducts *cis*- and *trans*-β-sultams **3ba** diastereoselectively, with *cis*-isomer in 39% yield and *trans*-isomer in 29% (Table 1, entry 5). The sulfonyl chloride **1c** with a strongly electron-withdrawing α-ethoxycarbonyl group readily reacted with imine **2a** to give rise to *trans*-β-sultam **3a** stereospecifically in 59% yield, together with [2^s+2^i+2^i] annuladduct ethyl *rel*(3*S*,5*S*,6*R*)-2,4-dimethyl-3,5-diphenyl-1,2,4-thiadiazinane-6-carboxylate 1,1-dioxide (**4a**) in 8% yield (Table 1, entry 6). No sulfonyl chloride with strongly electron-donating α-substituent group (RO or ArO) has been prepared to date, and our attempt failed.[11] We also attempted to prepare strongly electron-withdrawing cyano- and nitromethanesulfonyl chlorides and failed. The configurations of β-sultams **3** were assigned by the coupling constants of the C3 and C4 protons (J = 8−9 Hz for *cis*-β-sultams, and 5−7 Hz for *trans*-β-sultams, generally).[7] The stereostructure of annuladduct **4a** was assigned as relative (3*S*,5*S*,6*R*) configuration by our NOE experiments (vide post, Figure 1).

Table 1. Influence of α-Substituents of Sulfonyl Chlorides 1 on the Annuloseletivity in the Sulfa-Staudinger Cycloaddition Involving Imine 2a



R^1 = Me, **1a, 3aa, 4aa**; R^1 = Ph, **1b, 3ba, 4ba**; R^1 = EtO$_2$C, **1c, 3a, 4a**

				yield (%)		
entry	**1**	R^1	reaction conditions	*cis*-**3**	*trans*-**3**	**4**
1[a]	**1a**	Me	THF, r.t., 24 h	0	0	0
2[b]	**1a**	Me	r.t., 24 h	3[c]	3[c]	0
3[b]	**1a**	Me	70 °C, 1 h	9[c]	8[c]	0
4	**1a**	Me	THF, reflux, 24 h	6[c]	11[c]	0
5[a]	**1b**	Ph	THF, r.t., 24 h	41[c]	23[c]	0
6[d]	**1c**	EtO$_2$C	THF, r.t., 24 h	0	59	8

[a]Reaction conducted on 1 mmol scale. [b]Reaction conducted on 0.25 mmol scale without solvent. [c]Yield determined by the ^{1}H NMR analysis of the crude reaction mixture with dimethyl malonate as an internal standard. [d]Reaction conducted on 0.5 mmol scale.

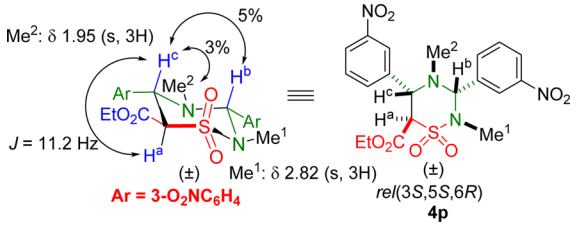


Figure 1. Assignment of the structure of compound **4p** by ^{1}H NMR and NOE experiments.

On the basis of current and Kobayashi's results,[7] we can draw a conclusion that sulfonyl chlorides with strongly α-electron-withdrawing substituents can produce [2^s+2^i+2^i] annuladducts *rel*(3*S*,5*S*,6*R*)-1,2,4-thiadiazinane 1,1-dioxides. For other sulfonyl chlorides, no [2^s+2^i+2^i] annuladduct was observed generally even with less bulky imine **2a**.[4,7,8]

Substituent Effect of Linear Imines on the Annuloselectivity and Stereoselectivity. Subsequent studies were conducted by reacting 1 equiv of ethoxycarbonyl methanesulfonyl chloride (**1c**) with 2 equiv of various *N*-substituted imines **2**.[12] The results are presented in Table 2. Screening of the *N*-substituents (Table 2, entries 1−6) revealed that the imines **2b**−**f** with sterically bulky *N*-allyl (**2b**), *N*-isopropyl (**2c**), *N*-benzyl (**2d**), *N*-cyclohexyl (**2e**), and *N*-*tert*-butyl (**2f**) groups readily underwent exclusive [2^s+2^i] annulations with the sulfene derived from **1c** to afford the corresponding *trans*-β-

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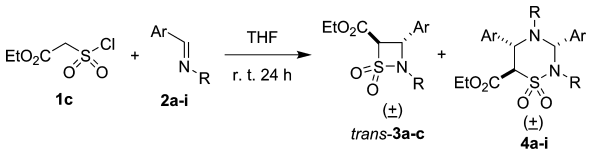
Table 2. *C*- and *N*-Substituent Effects of Linear Imines on the Annuloselectivity in the Sulfa-Staudinger Cycloadditions[a]



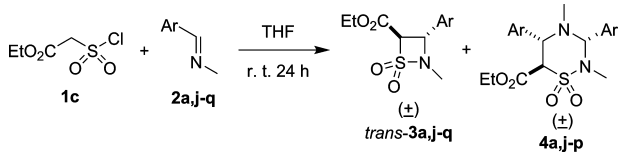
entry	2	Ar	R	yield (%) 3	yield (%) 4	3:4[b]
1	**2a**	Ph	Me	59	8	88:12
2	**2b**	Ph	Allyl	60	0	100:0
3	**2c**	Ph	*i*-Pr	57	0	100:0
4	**2d**	Ph	Bn	71	0	100:0
5	**2e**	Ph	*c*-Hex	84	0	100:0
6	**2f**	Ph	*t*-Bu	90	0	100:0
7	**2g**	4-MeOC$_6$H$_4$	Bn	74	0	100:0
8	**2h**	4-O$_2$NC$_6$H$_4$	Bn	65	0	100:0
9	**2i**	(*E*)-PhCH=CH	Bn	72	0	100:0

[a]Reactions were conducted by mixing **1c** (0.5 mmol) with imines **2** (1 mmol) at room temperature. [b]Ratios were detected by the ^{1}H NMR analysis of the crude reaction mixture.

sultams **3b**, **3c**, **3d**, **3e**, and **3f** in 60%, 57%, 71%, 84%, and 90% yields, respectively (Table 2, entries 2−6). The *C*-substituent effect on the annuloselectivity was also investigated (Table 2, entries 4, and 7−9), revealing that the tuning of the electronic characters of the *C*-substituents of *N*-benzyl imines **2d,g−i** cannot generate the corresponding [2^s+2^i+2^i] annuladducts **4**. The above results indicate that the steric hindrance of the imine *N*-substituents plays an extraordinarily important role in deciding the annuloselectivity between [2^s+2^i] and [2^s+2^i+2^i] annulations in the sulfa-Staudinger reactions involving sulfonyl chloride **1c**. Only when *N*-methyl imines are employed can the [2^s+2^i+2^i] annulations occur. Notably, all the *β*-sultam products **3** in Table 2 exhibit *trans*-configuration, as judged by the coupling constants of the C3 and C4 protons. No *cis*-product was observed in the ^{1}H NMR spectra of the crude reaction mixtures.

Subsequent studies on the effect of the **1c**:**2a** ratios on the annuloselectivity showed that when **1c**:**2a** equals 1:3, the fraction of the [2^s+2^i] annuladduct **3a** decreased and the [2^s+2^i+2^i] annuladduct was obtained in the highest 16% yield (Table 2, entry 1, Table 3, entries 1 and 2). This provides us the optimal conditions to observe the *C*-substituent effect of *N*-methyl imines **2a,j−q** on the annuloselectivity. The results are summarized in Table 3. The sulfa-Staudinger cycloadditions of imines **2j−p** bearing different *C*-substituents gave both [2^s+2^i] annuladducts *trans*-*β*-sultams **3j−p** and [2^s+2^i+2^i] annuladducts **4j−p** (Table 3, entries 3−9), except for the *C*-2-nitrophenyl imine **2q**, which generated only [2^s+2^i] annuladducts *cis*- and *trans*-**3q** (Table 3, entry 10). The results indicate that the *C*-substituents of *N*-methyl imines can affect the annuloselectivity, tuning the ratios of **3**:**4**. That is, generally, the electron-donating *C*-substituents increased the ratios of the [2^s+2^i+2^i] annuladducts **4** (Table 3, entries 3, 4, and 6), while the electron-withdrawing ones decrease the ratios (Table 3, entries 5, 7−10). The sterically bulky *C*-substituents disfavor the [2^s+2^i+2^i] annulations (Table 3, entries 7 and 10). The stereochemistry of the [2^s+2^i+2^i] annuladducts **4a,j−p** attracted our interest because they are biologically active structures[13] and

Table 3. *C*-Substituent Effect of the *N*-Methyl Imines on the Annuloselectivity[a]



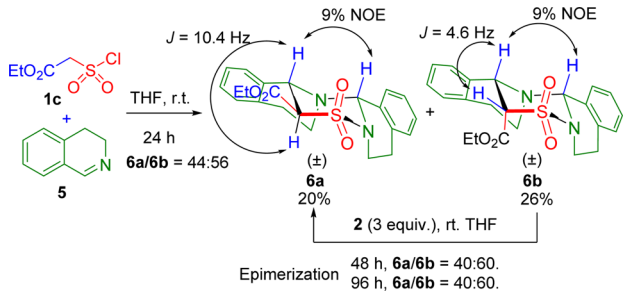
entry	2	Ar	isolated yields (%) 3	isolated yields (%) 4	3:4[b]
1[c]	**2a**	Ph	38	14	74:26
2	**2a**	Ph	29	16	65:35
3	**2j**	4-MeOC$_6$H$_4$	13	19	41:59
4	**2k**	4-PhC$_6$H$_4$	31	30	63:37
5	**2l**	4-BrC$_6$H$_4$	43	4	88:12
6	**2m**	2-Naphthenyl	21	16	74:26
7	**2n**	1-Naphthenyl	84	1[d]	99:1
8	**2o**	4-O$_2$NC$_6$H$_4$	41	3	85:15
9	**2p**	3-O$_2$NC$_6$H$_4$	79	13	91:9
10	**2q**	2-O$_2$NC$_6$H$_4$	66[e]	0	100:0

[a]Reactions were conducted by mixing **1c** (0.5 mmol) with imines **2** (1.5 mmol) at room temperature. [b]Ratios were detected by the ^{1}H NMR analysis of the crude reaction mixture. [c]0.5 mmol of **1c** and 2 mmol of **2a** were used. [d]Two inseparable rotamers were observed in the NMR spectrum of **4n**. [e]Both *cis*- and *trans*-*β*-sultams **3q** were observed (*cis*:*trans* = 18:82) in the ^{1}H NMR spectrum.

attract much attention in synthetic chemistry.[14] The NOE experiments together with the chemical shifts of the two methyl groups suggested that the [2^s+2^i+2^i] annuladduct **4p** is relative (3*S*,5*S*,6*R*) configuration (Figure 1).

[2^s+2^i+2^i] Annulations of Cyclic Imines. The bicyclic imine 3,4-dihydroisoquinoline (**5**) was selected as one of representative least sterically bulky cyclic imines because of its (*Z*)-configuration. It is sterically smaller than linear *N*-methyl imines when its nitrogen lone pair of electrons attacks sulfenes. Thus, we predicted that the [2^s+2^i+2^i] annuladducts would be generated predominantly or even exclusively in its sulfa-Staudinger cycloaddition with **1c**. The prediction was proven by the experimental results depicted in Scheme 2, as only

Scheme 2. [2^s+2^i+2^i] Annulations of Cyclic Imine 5 with Sulfonyl Chloride 1c



[2^s+2^i+2^i] annuladducts **6a** and **6b** were obtained in 20% and 26% isolated yields, respectively, without [2^s+2^i] annuladduct detected by the ^{1}H NMR spectrum of the crude reaction mixture. The stereostructure of **6b** was assigned as relative (4b*R*,5*R*,13b*S*) configuration by the NOE analysis and further verified by the XRD single crystal diffraction analysis (see SI), while the stereostructure of **6a** was ascertained as the relative (4b*R*,5*R*,13b*R*) configuration on the basis of the NOE analysis.

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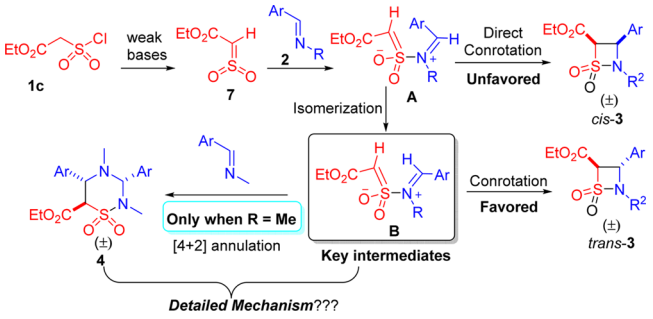
The appearance of **6b** was quite a surprise, because it exhibits a thermodynamically unstable (3,5)-*cis*-(5,6)-*cis* configuration in the 1,2,4-thiadiazinane ring. When compound **6b** was treated with 3 equiv of imine **5** at room temperature for 48 h, it was smoothly converted into thermodynamically stable (3,5)-*cis*-(5,6)-*trans*-annuladduct **6a**, with a 40:60 ratio of **6a**:**6b**, approximating to the ratio 44:56 obtained from the reaction mixture. The epimerized 40:60 ratio of **6a**:**6b** did not change after a further 48 h. The observation of a pair of diastereomeric $[2^s+2^i+2^i]$ annuladducts **6a** and **6b** in the reaction serves as an important probe in fully understanding the reaction mechanism in the $[2^s+2^i+2^i]$ annulations (vide post, Scheme 6).

Key Intermediates in the $[2^s+2^i]$ and $[2^s+2^i+2^i]$ Annulations. Based on our previous studies,[1] a proposed mechanism is presented in Scheme 3. Sulfene **7**, generated by

Scheme 3. Key Intermediates in the $[2^s+2^i]$ and $[2^s+2^i+2^i]$ Annulations



treatment of sulfonyl chloride **1c** with weakly basic imines,[15] is first *exo*-attacked by imines **2** at its sulfur atom to give rise to zwitterionic intermediates **A**. Because of the presence of the electron-withdrawing ester group, the direct conrotatory ring closure of thermodynamically unstable **A** to form *cis*-*β*-sultams is significantly decreased (Table 3, entry 10). Instead, intermediates **A** isomerize over their iminium moiety into the more stable intermediates **B**,[16] of which the conrotatory ring closure leads to *trans*-*β*-sultams **3**.[1] Consequently, in the vast majority of the cases, *trans*-*β*-sultams **3** are formed exclusively. Only when Ar is a strongly electron-withdrawing 2-nitrophenyl, *cis*-*β*-sultam *cis*-**3q** is generated in a minor amount (Table 3, entry 10). These results indicate that the intermediates **B** are key intermediates in all the reactions. They undergo either conrotatory ring closure to afford *trans*-*β*-sultams **3** or [4 + 2] annulations to give $[2^s+2^i+2^i]$ annuladducts **4** depending on different *N*-substituents.

The zwitterionic intermediates **B** are synthetic analogue to the neutral and isolable 3-trialkylsilyloxy-2-aza-1,3-dienes in the competitive reactions for the synthesis of four- and six-membered heterocycles. However, they are to some extent mechanistically different. The former prefers nucleophilic π^4 contatory ring closure and stepwise nucleophilic [4 + 2] annulations to produce *β*-sultams and 1,2,4-thiadiazinane 1,1-dioxides, respectively, while the latter favors concerted pericyclic reactions, π^4 contatory ring closure and hetero-Diels–Alder cycloaddition, to give rise to *β*-lactams and 1,3-oxazin-4-ones, respectively.[17]

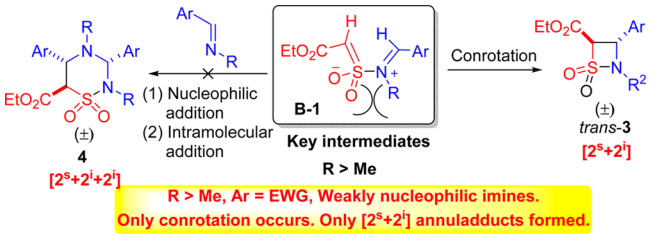
Notably, the occurrence of the conrotatory ring closure of intermediates **A** and **B** has been demonstrated in our recent published results.[1] In spite of the fact that the C=S and C=N$^+$ bonds in intermediates **A** and **B** are not coplanar, as indicated by Gais' work on the sulfonylcarbanions,[19] the conrotatory ring closure can still occur because non-coplanar π^4 conjugated systems can easily conrotate to form puckered four-membered ring derivatives. Similar to the mechanism for the conrotatory ring closure in the Staudinger ketene–imine cycloaddition,[18] the mechanism for the current conrotatory ring closure of **A** and **B** is somewhat different from the electrocyclization of 1,3-butadienes, and it may be regarded as a special case of an intramolecular Mannich-like reaction.

Explanation of the Annuloselective Reactions and Related Stereochemistry. After getting an overview of the above results, one may ask: (1) How can the substituents of imines control the annuloselectivity? (2) Why does the stereoselectivity in the $[2^s+2^i+2^i]$ annulations of linear *N*-methyl imines and bicyclic imines differ distinctly?

Maji and Mayr's studies on the nucleophilic reactivities of Schiff bases indicate that the nucleophilicity parameters of **2a** and **2d** are 8.6 and 7.9, respectively, indicating **2a** is more nucleophilic than **2d**. Their results also reveal that the cyclic imines with (*Z*)-configurations are much more nucleophilic than the acyclic analogues.[20] Thus, we can draw a conclusion that it is the nucleophilicity of imines that in fact controls the annuloselectivity. The nucleophilicity of imines are controlled by both the steric and electronic effects of their *N*- and *C*-substituents. On one hand, the less steric the imines are, the stronger nucleophilicity, and the more favorable the $[2^s+2^i+2^i]$ annulations (Table 2, entry 1 and Table 3, entries 1–6, 8, and 9). On the other hand, the more electron-donating the *C*-substituents are, the greater the nucleophilicity of the *N*-methyl imines and the more favorable the $[2^s+2^i+2^i]$ annulations (Table 3, entries 3, 4, and 6).

The key intermediates involved in both the $[2^s+2^i]$ and $[2^s+2^i+2^i]$ annulations have been identified as **B**. Thus, the substituent effect on the annuloselectivity is, in fact, on the two competitive evolutions of intermediates **B**, conrotation versus [4 + 2] annulation (Scheme 4). The [4 + 2] annulations are

Scheme 4. [2 + 2] Annulations in the Sulfa-Staudinger Cycloadditions Involving Weakly Nucleophilic Imines 2



regarded as stepwise reactions, rather than concerted hetero-Diels–Alder cycloadditions, because they occur only when strongly nucleophilic imines **2** are employed. As illustrated in Scheme 4, for imines **2b–i** with *N*-substituents larger than the methyl group, on one hand, the low nucleophilicity and obvious steric hindrance of imines **2b–i** cannot initiate the intermolecular Mannich-type addition of imines **2b–i** to intermediates **B-1**. On the other hand, the steric congestion between the *N*-substituents on the iminium moiety and the sulfonyl group favors the conrotatory ring closure of **B-1** by increasing the ring closure rate due to the Thorpe-Ingold effect.[21] Consequently, the intermediates **B-1** exclusively undergo a conrotatory ring closure to form *trans*-*β*-sultams **3**.

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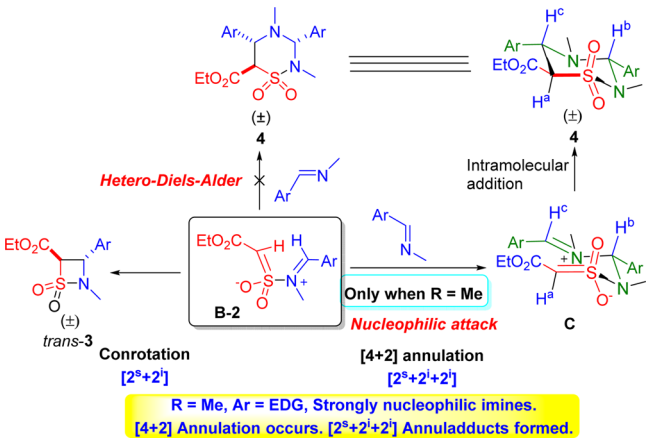
For linear *N*-methyl imines **2a,j−p** (Scheme 5), because of the weak steric congestion between *N*-methyl group and the sulfonyl group in intermediates **B-2**, the conrotatory ring closure occurs to form *trans*-*β*-sultams **3**; however, the rate is not as fast as that for the corresponding intermediates **B-1** generated from imines **2b−i** (Scheme 4). This provides the opportunity for the intermolecular addition of imines **2a,j−p** to intermediates **B-2**, derived from imines **2a,j−p**, to give intermediates **C**, which undergo intramolecularly nucleophilic cyclization to deliver $[2^s+2^i+2^i]$ annuladducts **4** through a chair transition-state conformation with all large substituents located on the equatorial positions. In the current cases, the conrotation and intermolecularly nucleophilic addition in intermediates **B-2** are in competition, which is affected by the nucleophilicity of the *N*-methyl imines. The *C*-substituents of imines tune the annuloselectivity generally, even inhibit the occurrence of the $[2^s+2^i+2^i]$ annulations in the cases when *C*-substituents are strongly electron-withdrawing groups (Table 3, entry 10). The electron-donating and less steric *C*-substituents increase the nucleophilicity of imines **2**, and thus facilitate the intermolecular addition of imines **2** to intermediates **B-2** to give intermediates **C**, finally leading to the increase of $[2^s+2^i+2^i]$ annuladducts **4** (Table 3, entries 3, 4, and 6). In contrast, the electron-withdrawing and sterically bulky *C*-substituents are detrimental to the $[2^s+2^i+2^i]$ annulations because of the following reasons: on one hand, the electron-withdrawing *C*-substituents increase the electrophilicity of the iminium moiety, facilitating the intramolecular ring closure; on the other hand, they decrease the nucleophilicity of the imines, disfavoring intermolecularly nucleophilic addition, finally retarding the [4 + 2] annulation (Table 3, entries 5, 8, and 10).[20] Additionally, the sterically bulky *C*-substituents of imines also increase the steric hindrance of the iminium moiety in intermediates **B-2**, consequently disfavoring the stepwise [4 + 2] annulations with another molecule of imines (Table 3, entries 7 and 10).

Scheme 5. $[2^s+2^i]$ and $[2^s+2^i+2^i]$ Annulations in the Sulfa-Staudinger Cycloadditions Involving Strongly Nucleophilic Imines 2

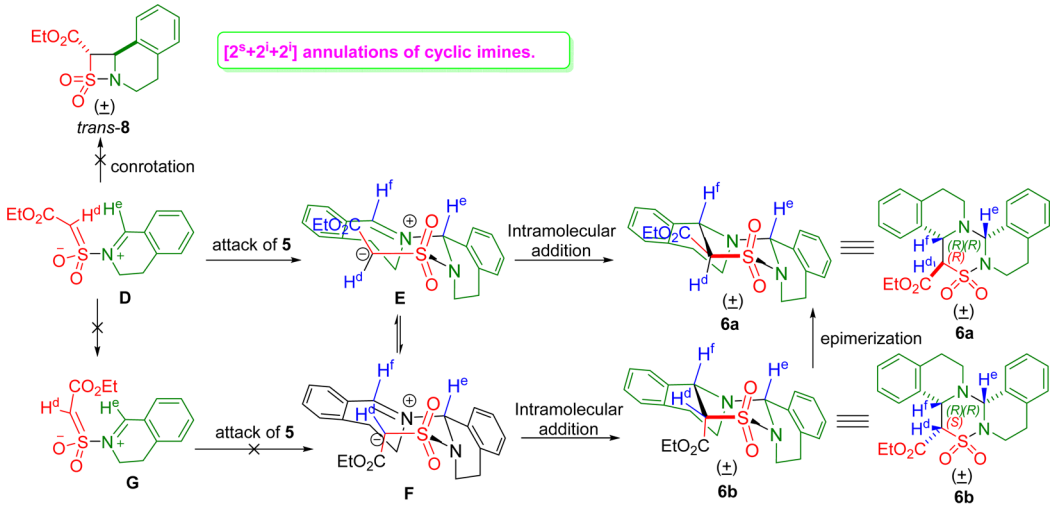


For linear *N*-methyl imine **2q** with strongly electron-withdrawing and sterically bulky substituent 2-nitrophenyl, the weak nucleophilicity of **2q** and greater steric hindrance of the iminium moiety in the intermediate **B-2** disfavor the intermolecular nucleophilic addition. However, the strongly electron-withdrawing substituent favors not only the ring closure of the intermediate **B-2**, but also the direct ring closure of the corresponding intermediate **A** in Scheme 3, resulting in the formation of small amount of *cis*-*β*-sultam *cis*-**3q** (Table 3, entry 10).

For cyclic imine **5**, it shows the strongest nucleophilicity among our investigated imines and its lone electron pair on the nitrogen has the least steric hindrance for the nucleophilic attack to the intermediate **D** (Scheme 6). Thus, it predominantly attacks the intermediate **D** to give **E** and **F**, which subsequently undergoes an intramolecular nucleophilic addition to give rise to the $[2^s+2^i+2^i]$ annuladducts **6** exclusively (Scheme 6). That is the reason the corresponding $[2^s+2^i]$ annuladduct was not observed for cyclic imine **5**.

The above analyses based on the *N*- and *C*- substituent-controlled nucleophilicity of imines explain the following facts: in the reactions of the sulfene **7**, the less nucleophilic and more steric imines **2b−i,q** undergo exclusive $[2^s+2^i]$ annulations; the more nucleophilic and less steric *N*-methyl imines **2a,j−p** evolve toward both $[2^s+2^i]$ and $[2^s+2^i+2^i]$ annulations; and the more nucleophilic and the least steric (*Z*)-cyclic imine **5** undergoes exclusive $[2^s+2^i+2^i]$ annulations.

Scheme 6. Mechanistic Rationalization of the Stereochemistry in the $[2^s+2^i+2^i]$ Annulation Involving Cyclic Imine 5



Only one of enantiomers was drawn in each of structures.

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Explanation of the Stereoselectivity in the $[2^s+2^i+2^i]$ Annulations. For linear *N*-methyl imines, although the $[2^s+2^i+2^i]$ annulation was first discovered in 1975, no plausible mechanism has been proposed to explain the stereochemistry until now. As depicted in Scheme 5, the intermediates **C**, formed via nucleophilic attack of another molecule of *N*-methyl imines **2** at the iminium moiety of intermediates **B-2**, undergo intramolecularly nucleophilic addition to deliver diastereospecifically ethyl *rel*-(3*S*,5*S*,6*R*)-2,4-dimethyl-3,5-diaryl-1,2,4-thiadiazinane-6-carboxylate 1,1-dioxides **4** through a chair transition-state conformation, in which the three protons H^a, H^b, and H^c locate on the axial positions and the other larger groups locate on the equatorial positions. Thus, the steric hindrance in the transition state is minimal, consequently making intermediates **C** most stable. Subsequent cyclization of intermediates **C** gives $[2^s+2^i+2^i]$ annuladducts **4** stereospecifically with the indicated relative stereochemistry. The proposed reaction process successfully explains the stereochemistry and stereoselectivity in the $[2^s+2^i+2^i]$ annulations (Scheme 5).

In the reaction of cyclic imine **5** with the strongest nucleophilicity and the least steric hindrance around the nitrogen lone electron pair, the reaction process is proposed in Scheme 6. The generated intermediate **D** exclusively undergoes a Mannich-type nucleophilic addition of another molecule of imine **5** (intermolecularly nucleophilic addition) to form intermediate **E**, which further undergoes an intramolecular nucleophilic addition to produce $[2^s+2^i+2^i]$ annuladduct **6a**. This process is fully consistent with the mechanism proposed in Scheme 5. In the stable intermediate **E**, protons H^d, H^e, and H^f adopt the axial positions. However, the ester group can stabilize the carbanion resonance form of the intermediate **E**. Possibly due to the Walden inversion of the carbanion vicinal to the ester group, the intermediate **E** can convert into another configurational intermediate **F**, in which the protons H^e and H^f still locate on the axial positions, while the proton H^d is on the equatorial position. The interconversion between **E** and **F** is probably attributed to the nonconjugated C═S and C═N double bonds. Evolution of the intermediate **F** produces $[2^s+2^i+2^i]$ annuladduct **6b**. It is rationalized that the interconversion between **D** and **G** does not exist, probably because of the conjugated 4π properties of **D**. This has been demonstrated and supported by the absence of *cis*-bicyclic β-sultams in the sulfa-Staudinger $[2^s+2^i]$ cycloadditions of cyclic imines in our previous studies.[1] The interconversion between **E** and **F** and the epimerization of **6b** to **6a** contribute together to the final distribution of the two diastereomeric $[2^s+2^i+2^i]$ annuladducts **6a** and **6b**.

CONCLUSIONS

On the basis of current and previously reported results,[1,4,7,8] the annuloselectivity in the sulfa-Staudinger cycloadditions of sulfonyl chlorides and imines is mainly controlled by the electronic effect of the α-substituents of sulfonyl chlorides and the nucleophilicity of imines, and tuned by the electronic and steric effects of the imine *C*-substituents. Sulfonyl chlorides with weakly electron-donating and withdrawing α-substituents prefer the $[2^s+2^i]$ annulation, affording *cis*- and *trans*-β-sultams as sole products, while sulfonyl chlorides with strongly electron-withdrawing α-substituents can undergo the $[2^s+2^i+2^i]$ annulations depending on the nucleophilicity of imines: (1) weakly nucleophilic imines with sterically larger substituents than the methyl group undergo only the $[2^s+2^i]$ annulations to give *trans*-β-sultams; (2) strongly nucleophilic imines with *N*-methyl substituent undergo both $[2^s+2^i]$ and $[2^s+2^i+2^i]$ annulations, delivering *trans*-β-sultams and *rel*(3*S*,5*S*,6*R*)-1,2,4-thiadiazinane 1,1-dioxide derivatives, respectively; (3) more strongly nucleophilic cyclic imines prefer only $[2^s+2^i+2^i]$ annulation, producing a pair of diastereomeric *rel*(3*R*,5*R*,6*R*)- and *rel*(3*R*,5*R*,6*S*)-1,2,4-thiadiazinane 1,1-dioxide derivatives. The annuloselectivity is tuned by both the electronic and steric effects of imine substituents. In addition, the stereochemistry of $[2^s+2^i]$ and $[2^s+2^i+2^i]$ annuladducts is assigned and stereoselectivity in the $[2^s+2^i+2^i]$ annulations is mechanistically rationalized.

EXPERIMENTAL SECTION

General Information. Tetrahydrofuran was refluxed over sodium with diphenyl ketone as indicator and freshly distilled prior to use. Melting points were obtained on a melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer in $CDCl_3$ with TMS as an internal standard and the chemical shifts (δ) are reported in parts per million (ppm). The one-dimensional selected NOE experiments were conducted on a 600 MHz spectrometer. The IR spectra (KBr pellets, ν [cm^{-1}]) were taken on a FTIR spectrometer. HRMS measurements were carried out on an LC/MSD TOF mass spectrometer. TLC separations were performed on silica gel GF_{254} plates, and the plates were visualized with UV light.

Sulfonyl chlorides **1a** and **1d** were prepared according to the methods in our previous reports,[22] while **1d** was prepared according to the method reported by Du Bois et al.,[23] and **1e** is commercially available. The imines **2** were prepared in quantitative yields by simply refluxing the aromatic aldehydes (1 equiv), the amines (1 equiv for nonvolatile ones, or 1.5 equiv for volatile ones), and $MgSO_4$ (1.5 equiv) in dichloromethane for 2 h, followed by filtration through a pad of Celite and removal of the volatiles.

General Procedure for the Reactions of Sulfonyl Chloride 1c with Imines 2 and 5. To a solution of imine **2** (1 mmol for **2b**−**i**, 1.5 mmol for **2a**,**j**-**q**, **5**) in dry THF (2 mL) was added a solution of **1c** (0.5 mmol, 93 mg) in dry THF (0.5 mL) during 0.5 min at room temperature. Then the mixture was allowed to stand at room temperature for 24 h, followed by dilution with ether (10 mL), washing with brine (10 mL), and drying over Na_2SO_4. Subsequent column chromatography on silica gel with petroleum ether (PE) and ethyl acetate (EA) as eluent gave the desired β-sultam product(s) and/or 1,2,4-thiadiazinane 1,1-dioxide product(s).

*Ethyl trans-2-Methyl-3-phenyl-1,2-thiazetidine-4-carboxylate 1,1-dioxide (**3a**).* Colorless crystals. Mp 64−66 °C. Yield: 80 mg (59%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52−7.49 (m, 2H), 7.47−7.35 (m, 3H), 4.85 (d, J = 6.5 Hz, 1H), 4.50 (d, J = 6.5 Hz, 1H), 4.37 (dq, J = 10.8, 7.1 Hz, 1H), 4.29 (dq, J = 10.8, 7.1 Hz, 1H), 2.75 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 162.1, 135.1, 129.3, 129.2, 126.7, 79.4, 63.1, 55.2, 30.9, 14.0. IR (film) ν cm^{-1} 3067, 3035, 2979, 2931, 1743, 1602, 1496, 1455, 1372, 1337, 1206, 1155, 1009, 763, 719, 700. HRMS (ESI) calcd for $C_{12}H_{16}NO_4S$ (M + H$^+$) m/z 270.0795, found 270.0795.

*Ethyl trans-2-Allyl-3-phenyl-1,2-thiazetidine-4-carbonxlate 1,1-dioxide (**3b**).* Colorless oil. Yield 89 mg (60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J = 6.7 Hz, 2H), 7.47−7.34 (m, 3H), 5.83 (dddd, J = 17.0, 10.1, 7.1, 5.5 Hz, 1H), 5.34 (dd, J = 17.0, 0.9 Hz, 1H), 5.21 (dd, J = 10.1, 0.6 Hz, 1H), 4.84 (d, J = 6.4 Hz, 1H), 4.62 (d, J = 6.4 Hz, 1H), 4.36 (dq, J = 10.8, 7.1 Hz, 1H), 4.29 (dq, J = 10.8, 7.1 Hz, 1H), 3.78 (dd, J = 14.6, 7.1 Hz, 1H), 3.61 (dd, J = 14.6, 5.5 Hz, 1H), 1.33 (t, J = 7.1 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 162.1, 135.6, 130.9, 129.2, 129.1, 126.8, 120.2, 79.1, 63.0, 53.4, 48.7, 14.0. IR (film) ν cm^{-1} 3067, 3034, 2984, 2940, 1739, 1646, 1601, 1497, 1457, 1421, 1372, 1340, 1244, 1194, 1025, 1001, 937, 763, 731, 700. HRMS (ESI) calcd for $C_{14}H_{18}NO_4S$ (M + H$^+$) m/z 296.0951, found 296.0954.

*Ethyl trans-2-Isopropyl-3-phenyl-1,2-thiazetidine-4-carboxylate 1,1-dioxide (**3c**).* Colorless crystals. Mp 64−65 °C. Yield 85 mg (57%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 7.0 Hz, 2H), 7.49−7.31 (m, 3H), 4.74 (d, J = 6.2 Hz, 1H), 4.67 (d, J = 6.2 Hz, 1H), 4.36 (dq, J = 10.8, 7.1 Hz, 1H), 4.28 (dq, J = 10.8, 7.1 Hz, 1H), 3.55 (qq, J

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= 6.1, 6.6 Hz, 1H), 1.32 (t, J = 7.1 Hz, 3H), 1.30 (d, J = 6.1 Hz, 3H), 1.03 (d, J = 6.6 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 162.2, 137.6, 129.1, 129.0, 126.6, 79.0, 63.0, 52.4, 49.8, 21.6, 20.4, 14.0. IR (film) ν cm^{-1} 3067, 3034, 2980, 2930, 1741, 1603, 1497, 1456, 1413, 1389, 1373, 1320, 1305, 1244, 1194, 1025, 763, 731, 699. HRMS (ESI) calcd for $C_{14}H_{20}NO_4S$ (M + H$^+$) m/z 298.1108, found 298.1110.

*Ethyl trans-2-Benzyl-3-phenyl-1,2-thiazetidine-4-carboxylate 1,1-dioxide (**3d**).* Colorless crystals. Mp 94−95 °C. Yield: 123 mg (71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66−6.99 (m, 10H), 4.86 (d, J = 6.3 Hz, 1H), 4.62 (d, J = 6.3 Hz, 1H), 4.34 (d, J = 14.3 Hz, 1H), 4.36 (dq, J = 10.8, 7.1 Hz, 1H), 4.27 (dq, J = 10.8, 7.1 Hz, 1H), 4.14 (d, J = 14.3 Hz, 1H), 1.33 (t, J = 7.1 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 162.2, 135.4, 133.9, 129.2, 129.1, 128.8, 128.6, 128.1, 126.9, 79.1, 63.1, 53.8, 49.9, 14.0. IR (film) ν cm^{-1} 3065, 3033, 2982, 2923, 1742, 1601, 1497, 1456, 1371, 1340, 1244, 1191, 1164, 1026, 757, 698. HRMS (ESI) calcd for $C_{18}H_{20}NO_4S$ (M + H$^+$) m/z 346.1108, found 346.1108.

*Ethyl trans-2-Cyclohexyl-3-phenyl-1,2-thiazetidine-4-carboxylate 1,1-dioxide (**3e**).* Colorless crystals. Mp 70−72 °C. Yield 142 mg (84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57−7.55 (m, 2H), 7.44−7.35 (m, 3H), 4.74 (d, J = 6.4 Hz, 1H), 4.71 (d, J = 6.4 Hz, 1H), 4.40−4.33 (m, 1H), 4.32−4.25 (m, 1H), 3.32−3.26 (m, 1H), 2.09−2.06 (m, 1H), 1.77−1.73 (m, 1H), 1.69−1.67 (m, 1H), 1.63−1.48 (m, 3H), 1.34 (t, J = 7.2 Hz, 3H), 1.30−1.26 (m, 1H), 1.23−1.10 (m, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 162.2, 137.7, 129.1, 129.0, 126.5, 79.0, 62.9, 57.3, 52.2, 31.9, 30.2, 25.2, 24.2, 24.0, 14.0. IR (film) ν cm^{-1} 2934, 1742, 1496, 1452, 1372, 1336, 1277, 1257, 1201, 1187, 1157, 1128, 1095, 1049, 1017, 760, 700, 669. HRMS (ESI) calcd for $C_{17}H_{23}NNaO_4S$ (M + Na$^+$) m/z 360.1240, found 360.1237.

*Ethyl trans-2-(tert-Butyl)-3-phenyl-1,2-thiazetidine-4-carboxylate 1,1-dioxide (**3f**).* Colorless crystals. Mp 128−129 °C. Yield 140 mg (90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 6.9 Hz, 2H), 7.46−7.31 (m, 3H), 4.86 (d, J = 5.4 Hz, 1H), 4.72 (d, J = 5.4 Hz, 1H), 4.35 (dq, J = 10.8, 7.1 Hz, 1H), 4.27 (dq, J = 10.8, 7.1 Hz, 1H), 1.32 (t, J = 7.1 Hz, 3H), 1.25 (s, 9H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 162.3, 138.6, 129.1, 129.0, 126.8, 79.4, 63.0, 57.3, 50.1, 27.8, 14.0. IR (film) ν cm^{-1} 3065, 3033, 2978, 2937, 1743, 1603, 1497, 1458, 1371, 1398, 1371, 1327, 1241, 1191, 1164, 1071, 1030, 766, 738, 704. HRMS (ESI) calcd for $C_{15}H_{22}NO_4S$ (M + H$^+$) m/z 312.1264, found 312.1266.

*Ethyl trans-2-Benzyl-3-(4-methoxyphenyl)-1,2-thiazetidine-4-carboxylate 1,1-dioxide (**3g**).* Colorless oil. Yield 139 mg (74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 8.7 Hz, 2H), 7.29−7.26 (m, 5H), 6.88 (d, J = 8.7 Hz, 2H), 4.83 (d, J = 6.2 Hz, 1H), 4.57 (d, J = 6.2 Hz, 1H), 4.29 (d, J = 14.3 Hz, 1H), 4.39−4.24 (m, 2H), 4.15 (d, J = 14.3 Hz, 1H), 3.80 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 162.3, 160.3, 134.1, 128.8, 128.6, 128.3, 128.0, 127.1, 114.5, 79.1, 63.0, 55.4, 53.5, 49.6, 14.0. IR (film) ν cm^{-1} 2981, 1742, 1612, 1587, 1514, 1497, 1456, 1371, 1337, 1288, 1250, 1208, 1191, 1158, 1028, 833, 750, 697. HRMS (ESI) calcd for $C_{19}H_{22}NO_5S$ (M + H$^+$) m/z 376.1213, found 376.1213.

*Ethyl trans-2-Benzyl-3-(4-nitrophenyl)-1,2-thiazetidine-4-carboxylate 1,1-dioxide (**3h**).* Colorless oil. Yield 127 mg (65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 8.8 Hz, 2H), 7.56 (d, J = 8.8 Hz, 2H), 7.26−7.25 (m, 5H), 4.83 (d, J = 6.4 Hz, 1H), 4.69 (d, J = 6.4 Hz, 1H), 4.44 (d, J = 14.0 Hz, 1H), 4.41−4.28 (m, 2H), 4.14 (d, J = 14.0 Hz, 1H), 1.35 (t, J = 7.2 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 161.8, 148.2, 142.9, 133.0, 129.1, 128.7, 128.5, 127.7, 124.2, 78.9, 63.5, 53.1, 50.5, 14.0. IR (film) ν cm^{-1} 2982, 1742, 1607, 1523, 1496, 1456, 1372, 1348, 1286, 1243, 1191, 1164, 1030, 1013, 853, 752, 699. HRMS (ESI) calcd for $C_{18}H_{19}N_2O_6S$ (M + H$^+$) m/z 391.0958, found 391.0958.

*Ethyl trans-2-Benzyl-3-((E)-styryl)-1,2-thiazetidine-4-carboxylate 1,1-dioxide (**3i**).* Yellowish oil. Yield 134 mg (72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.25 (m, 10H), 6.62 (d, J = 15.7 Hz, 1H), 6.08 (dd, J = 15.7, 8.3 Hz, 1H), 4.84 (d, J = 5.6 Hz, 1H), 4.36 (d, J = 14.4 Hz, 1H), 4.37−4.23 (m, 3H), 4.17 (d, J = 14.4 Hz, 1H), 1.342 and 1.339 (t, J = 7.1 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 162.1, 136.5, 135.1, 134.2, 128.8, 128.74, 128.70, 128.66, 128.1, 126.7, 123.3, 76.8, 63.1, 53.1, 49.3, 14.0. HRMS (ESI) calcd for $C_{20}H_{22}NO_4S$ (M + H$^+$) m/z 372.1264, found 372.1268.

*Ethyl trans-3-(4-Methoxyphenyl)-2-methyl-1,2-thiazetidine-4-carboxylate 1,1-dioxide (**3j**).* Colorless oil. Yield 20 mg (13%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 8.7 Hz, 2H), 6.94 (d, J = 8.7 Hz, 2H), 4.82 (d, J = 6.5 Hz, 1H), 4.43 (d, J = 6.5 Hz, 1H), 4.36 (dq, J = 10.8, 7.1 Hz, 1H), 4.29 (dq, J = 10.8, 7.1 Hz, 1H), 3.82 (s, 3H), 2.72 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 162.2, 160.4, 128.1, 126.8, 114.6, 79.4, 63.0, 55.4, 54.9, 30.6, 14.0. IR (film) ν cm^{-1} 3064, 3033, 2979, 2925, 2851, 1743, 1611, 1514, 1496, 1456, 1371, 1336, 1252, 1203, 1167, 1029, 833. HRMS (ESI) calcd for $C_{13}H_{18}NO_5S$ (M + H$^+$) m/z 300.0900, found 300.0905.

*Ethyl trans-3-([1,1′-Biphenyl]-4-yl)-2-methyl-1,2-thiazetidine-4-carboxylate 1,1-dioxide (**3k**).* Colorless oil. Yield 54 mg (31%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68−7.60 (m, 6H), 7.51−7.47 (m, 2H), 7.43−7.39 (m, 1H), 4.93 (d, J = 6.4 Hz, 1H), 4.58 (d, J = 6.4 Hz, 1H), 4.44−4.38 (m, 1H), 4.37−4.30 (m, 1H), 2.81 (s, 3H), 1.38 (t, J = 7.1 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 162.2, 142.4, 140.1, 134.0, 128.9, 127.9, 127.7, 127.2, 127.1, 79.4, 63.1, 55.1, 30.9, 14.0. IR (film) ν cm^{-1} 2964, 1741, 1601, 1487, 1449, 1370, 1334, 1263, 1201, 1180, 1143, 1075, 1007, 836, 764, 736, 697, 655. HRMS (ESI) calcd for $C_{18}H_{20}NO_4S$ (M + H$^+$) m/z 346.1108, found 346.1102.

*Ethyl trans-3-(4-Bromophenyl)-2-methyl-1,2-thiazetidine-4-carboxylate 1,1-dioxide (**3l**).* Colorless oil. Yield 75 mg (43%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 4.83 (d, J = 6.4 Hz, 1H), 4.47 (d, J = 6.4 Hz, 1H), 4.41−4.35 (m, 1H), 4.34−4.27 (m, 1H), 2.76 (s, 3H), 1.35 (t, J = 7.1 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 162.0, 134.2, 132.4, 128.3, 123.4, 79.2, 63.2, 54.7, 30.9, 14.0. IR (film) ν cm^{-1} 2981, 1741, 1592, 1488, 1454, 1371, 1336, 1263, 1204, 1157, 1072, 1009, 822, 759, 731, 701. HRMS (ESI) calcd for $C_{12}H_{15}BrNO_4S$ (M + H$^+$) m/z 347.9900, found 347.9898.

*Ethyl trans-2-Methyl-3-(naphthalen-2-yl)-1,2-thiazetidine-4-carboxylate 1,1-dioxide (**3m**).* Colorless oil. Yield 36 mg (21%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.94 (d, J = 8.8 Hz, 1H), 7.90−7.88 (m, 2H), 7.63 (dd, J = 8.5, 1.6 Hz, 1H), 7.58−7.55 (m, 2H), 4.97 (d, J = 6.5 Hz, 1H), 4.69 (d, J = 6.5 Hz, 1H), 4.44−4.30 (m, 2H), 2.82 (s, 3H), 1.37 (t, J = 7.2 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 162.2, 133.6, 133.1, 132.3, 129.4, 128.0, 127.8, 126.87, 126.85, 126.6, 123.4, 79.3, 63.1, 55.5, 30.9, 14.0. IR (film) ν cm^{-1} 2980, 1742, 1602, 1510, 1453, 1370, 1334, 1264, 1203, 1154, 1012, 858, 821, 751, 722, 659. HRMS (ESI) calcd for $C_{16}H_{17}NNaO_4S$ (M + Na$^+$) 342.0770, found 342.0766.

*Ethyl trans-2-Methyl-3-(naphthalen-1-yl)-1,2-thiazetidine-4-carboxylate 1,1-dioxide (**3n**).* Colorless crystals. Mp 88−89 °C. Yield 134 mg (84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J = 8.3 Hz, 1H), 7.95−7.85 (m, 3H), 7.61−7.51 (m, 3H), 5.29 (d, J = 6.2 Hz, 1H), 4.87 (d, J = 6.2 Hz, 1H), 4.46−4.37 (m, 1H), 4.36−4.28 (m, 1H), 2.87 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 162.6, 133.9, 131.0, 130.9, 129.7, 129.0, 127.1, 126.3, 125.6, 123.7, 122.5, 79.5, 63.3, 51.9, 31.4, 14.0. IR (film) ν cm^{-1} 2981, 1741, 1598, 1512, 1453, 1395, 1370, 1338, 1315, 1259, 1203, 1155, 1037, 1001, 804, 778, 724, 660. HRMS (ESI) calcd for $C_{16}H_{18}NO_4S$ (M + H$^+$) m/z 320.0951, found 320.0947.

*Ethyl trans-2-Methyl-3-(4-nitrophenyl)-1,2-thiazetidine-4-carboxylate 1,1-dioxide (**3o**).* Colorless oil. Yield 69 mg (41%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, J = 8.7 Hz, 2H), 7.72 (d, J = 8.7 Hz, 2H), 4.85 (d, J = 6.6 Hz, 1H), 4.60 (d, J = 6.6 Hz, 1H), 4.40 (dq, J = 10.8, 7.1 Hz, 1H), 4.33 (dq, J = 10.8, 7.1 Hz, 1H), 2.80 (s, 3H), 1.36 (t, J = 7.1 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 161.8, 148.5, 142.3, 127.6, 124.5, 79.2, 63.5, 54.5, 31.4, 14.0. IR (film) ν cm^{-1} 3033, 2979, 1743, 1611, 1514, 1496, 1456, 1371, 1336, 1252, 1203, 1167, 1029, 833, 756, 733, 697. HRMS (ESI) calcd for $C_{12}H_{14}N_2NaO_6S$ (M + Na$^+$) m/z 337.0465, found 337.0463.

*Ethyl trans-2-Methyl-3-(3-nitrophenyl)-1,2-thiazetidine-4-carboxylate 1,1-dioxide (**3p**).* Colorless crystals. Mp 105−107 °C. Yield 124 mg (79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (t, J = 1.8 Hz, 1H), 8.26 (ddd, J = 8.2, 2.1, 0.9 Hz, 1H), 7.89 (d, J = 7.7 Hz, 1H), 7.65 (t, J = 8.0 Hz, 1H), 4.88 (d, J = 6.6 Hz, 1H), 4.61 (d, J = 6.6 Hz, 1H), 4.44−4.37 (m, 1H), 4.37−4.28 (m, 1H), 2.81 (s, 3H), 1.36 (t, J =

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7.2 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 161.8, 148.8, 137.6, 132.6, 130.5, 124.3, 121.7, 79.2, 63.5, 54.5, 31.4, 14.0. IR (film) ν cm^{-1} 2973, 1720, 1637, 1533, 1453, 1374, 1307, 1261, 1150, 1091, 1050, 881, 801, 757, 680, 666. HRMS (ESI) calcd for $C_{12}H_{15}N_2O_6S$ (M + H^+) m/z 315.0645, found 315.0647.

*Ethyl cis- and trans-2-Methyl-3-(2-nitrophenyl)-1,2-thiazetidine-4-carboxylate 1,1-dioxide (Two Inseparable Diastereomers, cis- and trans-**3q**).* Yellow oil. Total yield: 103 mg (66%).

trans-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11−8.08 (m, 2H), 7.83−7.79 (m, 1H), 7.63−7.59 (m, 1H), 5.02 (d, J = 5.0 Hz, 1H), 4.87 (d, J = 5.0 Hz, 1H), 4.40 (q, J = 7.2 Hz, 2H), 2.90 (s, 3H), 1.37 (t, J = 7.2 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 162.3, 148.3, 134.7, 131.7, 130.1, 129.6, 128.3, 125.4, 80.8, 63.3, 51.6, 31.8, 14.0. IR (film) ν cm^{-1} 2917, 1746, 1660, 1632, 1610, 1579, 1529, 1447, 1370, 1336, 1266, 1196, 1038, 857, 792, 759, 724, 697. HRMS (ESI) calcd for $C_{12}H_{14}N_2NaO_6S$ (M + Na^+) m/z 337.0465, found 337.0463.

cis-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (dd, J = 8.2, 1.1 Hz, 1H), 8.02 (d, J = 7.4 Hz, 1 H), 7.83−7.79 (m, 1H), 7.63−7.59 (m, 1H), 5.67 (d, J = 8.4 Hz, 1H), 4.94 (d, J = 8.4 Hz, 1H), 4.08−3.97 (m, 2H), 2.87 (s, 3H), 1.09 (t, J = 7.2 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 161.5, 147.7, 134.4, 133.4, 129.65, 129.64, 125.5, 76.9, 62.5, 53.1, 29.7, 13.7. IR (film) ν cm^{-1} 2917, 1746, 1660, 1632, 1610, 1579, 1529, 1447, 1370, 1336, 1266, 1196, 1038, 857, 792, 759, 724, 697. HRMS (ESI) calcd for $C_{12}H_{14}N_2NaO_6S$ (M + Na^+) m/z 337.0465, found 337.0463.

*Ethyl rel(3S,5S,6R)-2,4-Dimethyl-3,5-diphenyl-1,2,4-thiadiazinane-6-carboxylate 1,1-dioxide (**4a**).* Colorless oil. Yield 31 mg (16%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55−7.34 (m, 10H), 5.47 (s, 1H), 4.29 (d, J = 11.2 Hz, 1H), 4.25 (d, J = 11.2 Hz, 1H), 4.07 (qd, J = 7.1, 0.6 Hz, 2H), 2.78 (s, 3H), 1.91 (s, 3H), 1.06 (t, J = 7.1 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 162.9, 138.6, 135.5, 129.2, 129.1, 128.8, 128.7, 128.6, 128.2, 82.2, 69.4, 65.1, 62.2, 39.2, 31.5, 13.8. IR (film) ν cm^{-1} 2917, 1740, 1456, 1384, 1364, 1270, 1280, 1142, 1075, 1013, 758, 702, 662. HRMS (ESI) calcd for $C_{20}H_{25}N_2O_4S$ (M + H^+) m/z 389.1530, found 389.1529.

*Ethyl rel(3S,5S,6R)-3,5-Di(4-methoxyphenyl)-2,4-dimethyl-1,2,4-thiadiazinane-6-carboxylate 1,1-dioxide (**4j**).* Colorless oil. Yield 43 mg (19%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 8.7 Hz, 2H), 7.35 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 5.37 (s, 1H), 4.22 (d, J = 11.1 Hz, 1H), 4.15 (d, J = 11.1 Hz, 1H), 4.05 (q, J = 7.1 Hz, 2H), 3.83 (s, 3H), 3.80 (s, 3H), 2.74 (s, 3H), 1.86 (s, 3H), 1.07 (t, J = 7.1 Hz, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 163.0, 159.9, 159.6, 130.6, 130.4, 129.3, 127.6, 114.1, 113.8, 81.8, 68.7, 65.2, 62.1, 55.3, 55.2, 39.1, 31.3, 13.8. IR (film) ν cm^{-1} 3064, 3032, 2981, 2923, 2841, 1736, 1603, 1513, 1464, 1400, 1367, 1334, 1259, 1160, 1028, 834. HRMS (ESI) calcd for $C_{22}H_{29}N_2O_6S$ (M + H^+) 449.1741, found 449.1741.

*Ethyl rel(3S,5S,6R)-3,5-Di([1,1′-biphenyl]-4-yl)-2,4-dimethyl-1,2,4-thiadiazinane-6-carboxylate 1,1-dioxide (**4k**).* Colorless crystals. Mp 171−172 °C. Yield 81 mg (30%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66−7.57 (m, 10H), 7.53 (d, J = 8.2 Hz, 2H), 7.49−7.43 (m, 4H), 7.40−7.34 (m, 2H), 5.52 (s, 1H), 4.33 (d, J = 11.4 Hz, 1H), 4.30 (d, J = 11.4 Hz, 1H), 4.07 (qd, J = 7.1, 1.8 Hz, 2H), 2.83 (s, 3H), 1.98 (s, 3H), 1.05 (t, J = 7.1 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 163.0, 142.0, 141.6, 140.3, 140.2, 137.5, 134.4, 129.7, 128.86, 128.85, 128.7, 127.7, 127.6, 127.5, 127.2, 127.1, 127.0, 82.0, 69.1, 65.0, 62.3, 39.3, 31.6, 13.8. IR (film) ν cm^{-1} 2981, 1739, 1603, 1487, 1450, 1408, 1363, 1338, 1302, 1201, 1162, 1138, 1120, 1007, 938, 851, 764, 698, 655. HRMS (ESI) calcd for $C_{32}H_{33}N_2O_4S$ (M + H^+) m/z 541.2156, found 541.2152.

*Ethyl rel(3S,5S,6R)-3,5-Di(4-bromophenyl)-2,4-dimethyl-1,2,4-thiadiazinane-6-carboxylate 1,1-dioxide (**4l**).* Colorless oil. Yield 11 mg (4%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 5.40 (s, 1H), 4.22 (d, J = 11.2 Hz, 1H), 4.18 (d, J = 11.2 Hz, 1H), 4.07 (qd, J = 7.1, 2.8 Hz, 2H), 2.73 (s, 3H), 1.86 (s, 3H), 1.09 (t, J = 7.1 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 162.6, 137.5, 134.3, 132.4, 132.1, 131.9, 130.8, 129.9, 128.4, 81.5, 68.7, 64.8, 62.5, 39.3, 31.4, 13.8. IR (film) ν cm^{-1} 2925, 1740, 1591, 1487, 1460, 1406, 1366, 1338, 1299, 1262, 1202, 1162, 1137, 1119, 1096, 1072, 1008, 939, 843, 789, 731, 674. HRMS (ESI) calcd for $C_{20}H_{22}Br_2N_2NaO_4S$ (M + Na^+) m/z 566.9559, found 566.9561.

*Ethyl rel(3S,5S,6R)-2,4-Dimethyl-3,5-di(naphthalen-2-yl)-1,2,4-thiadiazinane-6-carboxylate 1,1-dioxide (**4m**).* Colorless crystals. Mp 80−82 °C. Yield 41 mg (16%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.97−7.85 (m, 7H), 7.72 (d, J = 8.3 Hz, 2H), 7.60−7.52 (m, 4H), 5.69 (s, 1H), 4.50 (d, J = 11.1 Hz, 1H), 4.45 (d, J = 11.1 Hz, 1H), 4.09−4.02 (m, 1H), 4.02−3.95 (m, 1H), 2.87 (s, 3H), 1.99 (s, 3H), 0.96 (t, J = 7.1 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 162.9, 135.8, 133.6, 133.4, 133.1, 133.03, 133.00, 129.2, 129.1, 128.3, 128.2, 128.1, 128.0, 127.72, 127.68, 126.9, 126.6, 126.55, 126.52, 126.1, 125.0, 82.5, 69.6, 65.1, 62.3, 39.5, 31.6, 13.7. IR (film) ν cm^{-1} 2979, 1739, 1600, 1509, 1465, 1363, 1344, 1303, 1202, 1163, 1123, 1119, 937, 865, 749, 639. HRMS (ESI) calcd for $C_{28}H_{28}N_2NaO_4S$ (M + Na^+) m/z 511.1662, found 511.1657.

*Ethyl rel(3S,5S,6R)-2,4-Dimethyl-3,5-di(naphthalen-1-yl)-1,2,4-thiadiazinane-6-carboxylate 1,1-dioxide (**4n**, two rotamers).* Colorless solids. Mp 167−169 °C. Total yield 3 mg (1%).

Rotamer 1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (d, J = 8.3 Hz, 1H), 8.33 (d, J = 7.4 Hz, 1H), 7.80−7.50 (m, 11H), 6.46 (s, 1H), 5.36 (s, 1H), 4.97 (d, J = 11.6 Hz, 1H), 4.80 (d, J = 11.6 Hz, 1H), 3.89 (q, J = 7.1 Hz, 2H), 2.76 (s, 3H), 1.94 (s, 3H), 0.71 (t, J = 7.1 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 162.9, 135.4, 134.1, 133.6, 131.7, 131.2, 130.0, 130.07, 129.96, 129.75, 129.1, 129.8, 128.8, 127.2, 126.5, 126.1, 126.0, 125.6, 125.0, 124.4, 123.2, 77.8, 73.3, 63.3, 62.2, 39.0, 32.0, 13.6. IR (film) ν cm^{-1} 2980, 1740, 1597, 1511, 1462, 1364, 1348, 1304, 1260, 1201, 1160, 1137, 1119, 1039, 1023, 939, 910, 799, 777, 732, 683, 648. HRMS (ESI) calcd for $C_{28}H_{28}N_2NaO_4S$ (M + Na^+) m/z 511.1662, found 511.1656.

Rotamer 2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, J = 8.6 Hz, 1H), 7.80−7.50 (m, 12H), 6.37 (s, 1H), 5.37 (s, 1H), 4.54 (d, J = 10.6 Hz, 1H), 3.73 (d, J = 10.6 Hz, 1H), 3.82−3.67 (m, 2H), 2.81 (s, 3H), 2.08 (s, 3H), 0.83 (t, J = 7.1 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 162.7, 134.6, 134.1,132.1, 131.2, 130.8, 130.2, 130.02, 129.67, 129.4, 129.8, 128.8, 128.7, 127.2, 126.3, 126.2, 126.0, 125.7, 124.4, 124.2, 123.1, 77.6, 65.7, 63.0, 62.0, 40.1, 32.0, 13.3. IR (film) ν cm^{-1} 2980, 1740, 1597, 1511, 1462, 1364, 1348, 1304, 1260, 1201, 1160, 1137, 1119, 1039, 1023, 939, 910, 799, 777, 732, 683, 648. HRMS (ESI) calcd for $C_{28}H_{28}N_2NaO_4S$ (M + Na^+) m/z 511.1662, found 511.1656.

*Ethyl rel(3S,5S,6R)-3,5-Bis(4-nitrophenyl)-2,4-dimethyl-1,2,4-thiadiazinane-6-carboxylate 1,1-dioxide (**4o**).* Colorless crystals. Mp 192−193 °C. Yield 7 mg (3%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, J = 8.6 Hz, 2H), 8.27 (d, J = 8.6 Hz, 2H), 7.73 (d, J = 8.6 Hz, 2H), 7.69 (d, J = 8.6 Hz, 2H), 5.61 (s, 1H), 4.45 (d, J = 11.1 Hz, 1H), 4.25 (d, J = 11.1 Hz, 1H), 4.14 (dq, J = 10.8, 7.2 Hz, 1H), 4.06 (dq, J = 10.8, 7.2 Hz, 1H), 2.77 (s, 3H), 1.90 (s, 3H), 1.11 (t, J = 7.2 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 162.3, 148.4, 148.2, 145.2, 141.8, 130.2, 129.3, 124.3, 124.1, 81.1, 68.6, 64.3, 62.9, 39.4, 31.7, 13.8. IR (film) ν cm^{-1} 3112, 3081, 2982, 2923, 1739, 1608, 1524, 1491, 1367, 1349, 1301, 1270, 1202, 1164, 1012, 860. HRMS (ESI) calcd for $C_{20}H_{23}N_4O_8S$ (M + H^+) m/z 479.1231, found 479.1237.

*Ethyl rel(3S,5S,6R)-2,4-Dimethyl-3,5-bis(3-nitrophenyl)-1,2,4-thiadiazinane-6-carboxylate 1,1-dioxide (**4p**).* Yellow oil. Yield 33 mg (13%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, J = 10.4 Hz, 2H), 8.32 (dd, J = 8.2, 1.2 Hz, 1H), 8.27 (dd, J = 8.2, 1.2 Hz, 1H), 7.91 (d, J = 7.7 Hz, 1H), 7.87 (d, J = 7.7 Hz, 1H), 7.70 (t, J = 8.0 Hz, 1H), 7.64 (t, J = 7.9 Hz, 1H), 5.65 (s, 1H), 4.48 (d, J = 11.2 Hz, 1H), 4.30 (d, J = 11.2 Hz, 1H), 4.19−4.12 (m, 1H), 4.12−4.05 (m, 1H), 2.82 (s, 3H), 1.95 (s, 3H), 1.12 (t, J = 7.1 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 162.3, 148.7, 148.5, 140.3, 137.2, 135.1, 134.6, 130.2, 130.1, 124.5, 124.1, 123.0, 81.2, 68.6, 64.5, 62.9, 39.5, 31.7, 13.8. IR (film) ν cm^{-1} 2983, 1738, 1584, 1532, 1464, 1352, 1305, 1204, 1164, 1139, 1120, 1017, 906, 810, 795, 733, 693. HRMS (ESI) calcd for $C_{20}H_{22}N_4NaO_8S$ (M + Na^+) m/z 501.1051, found 501.1052.

*Ethyl rel(4bR,5R,13bR)-4b,5,9,13b,15,16-Hexahydro-8H-[1,2,4]-thiadiazino[3,2-a:5,4-a′]diisoquinoline-5-carboxylate 6,6-dioxide (**6a**).* Colorless crystals. Mp 134−135 °C. Yield 42 mg (20%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48−7.44 (m, 1H), 7.31−7.25 (m, 2H), 7.25−7.18 (m, 3H), 7.11 (dd, J = 12.4, 7.5 Hz, 2H), 5.97 (s, 1H), 5.18 (d, J = 10.4 Hz, 1H), 4.32 (d, J = 10.4 Hz, 1H), 4.28−4.23 (m, 1H),

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4.23−4.18 (m, 1H), 3.84 (dt, J = 11.4, 5.0 Hz, 1H), 3.52−3.42 (m, 1H), 3.09−3.01 (m, 1H), 2.99−2.90 (m, 2H), 2.85−2.73 (m, 2H), 2.70−2.61 (m, 1H), 1.20 (t, J = 7.1 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 164.7, 135.3, 134.4, 132.6, 131.1, 129.3, 128.7, 128.2, 128.1, 127.9, 127.8, 127.2, 125.9, 74.2, 63.1, 62.3, 61.6, 40.4, 38.4, 29.3, 29.1, 13.9. IR (film) ν cm^{-1} 2931, 1735, 1605, 1495, 1454, 1428, 1390, 1359, 1339, 1312, 1273, 1237, 1215, 1140, 1118, 1088, 1063, 1048, 1005, 970, 931, 897, 752, 702, 608. HRMS (ESI) calcd for $C_{22}H_{25}N_2O_4S$ (M + H$^+$) m/z 413.1530, found 413.1527.

*Ethyl rel(4bR,5R,13bS)-4b,5,9,13b,15,16-Hexahydro-8H-[1,2,4]-thiadiazino[3,2-a:5,4-a′]diisoquinoline-5-carboxylate 6,6-dioxide (**6b**).* Colorless crystals. Mp 146−148 °C. Yield 54 mg (26%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.25 (m, 4H), 7.24−7.17 (m, 3H), 7.09 (d, J = 7.2 Hz, 1H), 5.94 (s, 1H), 5.15 (d, J = 4.6 Hz, 1H), 4.35 (d, J = 4.6 Hz, 1H), 4.08−4.02 (m, 1H), 3.95−3.87 (m, 1H), 3.84−3.72 (m, 2H), 3.56−3.47 (m, 1H), 3.16−3.08 (m, 1H), 2.96−2.90 (m, 1H), 2.75−2.65 (m, 2H), 2.55−2.47 (m, 1H), 0.78 (t, J = 7.1 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 166.8, 135.8, 135.4, 131.9, 131.0, 129.2, 129.1, 128.2, 128.1, 127.5, 126.87, 126.86, 126.0, 73.8, 64.8, 61.5, 60.4, 42.0, 38.6, 29.9, 29.7, 13.3. IR (film) ν cm^{-1} 2976, 1735, 1496, 1454, 1428, 1370, 1351, 1337, 1277, 1231, 1187, 1151, 1116, 1091, 1065, 1046, 1004, 971, 953, 898, 749, 736, 689, 629, 601. HRMS (ESI) calcd for $C_{22}H_{25}N_2O_4S$ (M + H$^+$) m/z 413.1530, found 413.1524.

■ ASSOCIATED CONTENT

Supporting Information

XRD structure of product **6b** and its CIF file, copies of ^{1}H and ^{13}C NMR spectra for all new compounds, all NOE NMR spectra, ^{1}H NMR spectra of reaction mixtures for determination of product ratios, and characteristic ^{1}H NMR data and copies of ^{1}H NMR and NOE NMR spectra of the three products in inseparable product mixture in the reaction of phenylmethanesulfonyl chloride (**1b**) and 3,4-dihydroisoquinoline (**5**) in ref 8. 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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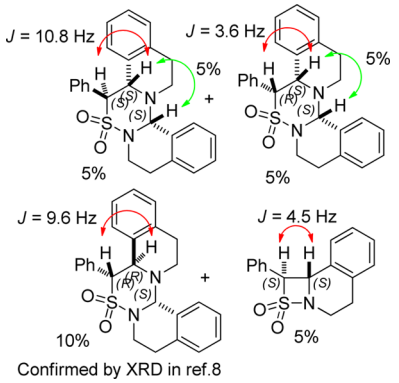

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Soc. **1987**, *109*, 7472−7477 Although Lee et al reported the procedure for its synthesis, it was unreproducible in our laboratory..

(12) Simple condition optimization was conducted with the reaction of **1c** and **2a** as a model reaction. Conditions A: **1c** (1.2 mmol) + **2a** (1 mmol) + pyridine (1.2 mmol) → *trans*-**3a** (47% yield); Conditions B: **1c** (1 mmol) + **2a** (2 mmol) → *trans*-**3a** (71% yield); Conditions C: **1c** (1.2 mmol) + **2a** (1 mmol) + Et_3N (1.2 mmol) → *trans*-**3a** (<5% yield). In the above experiments, **4a** was not detected in the ^1H NMR analysis of the crude reaction mixtures.

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