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Annuloselectivity and stereochemistry in the sulfa-Staudinger cycloadditions of cyclic imines

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The annuloselectivity and the stereochemistry in the sulfa-Staudinger cycloaddtions of cyclic imines are controlled by the ring size of the cyclic imines. Intrinsically, it is the steric hindrance of cyclic imines that controls the annuloselectivity, as well as the stereochemistry in the [2^s+2^i+2^i] annulations. A stepwise [4+2] annulation mechanism, which incorporates an intermolecular addition, C=S bond isomerization, and subsequently intramolecular addition, is proposed to explain the different stereochemistry in the [2^s+2^i +2^i] annulations. The intermolecular addition is regarded as the key stereo-determining step. Firstly, the C3 and C5 stereochemistry is kinetically controlled by the *endo* or *ex*o addition of imines to the key zwitterionic 2,3-thiaza-1,4-butadiene-type intermediates, and then the C5 and C6 stereochemistry is thermodynatically controlled by the isomerization of the C=S bond in the zwitterionic *endo*- or *exo*-adducts generated from the previous step. The intramolecular addition does not affect the stereochemical outcomes of the [2^s+2^i+2^i] annulations.

Introduction

The sulfa-Staudinger cycloadditions, namely the [2^s+2^i] annulations of sulfenes (or their equivalents) with imines,[1,2] represent a classic method to construct the β-sultam backbone.[3] β-Sultams are synthetically important [4] and biologically active compounds.[5] Recently, the sulfa-Staudinger cycloadditions have received much attention in both synthetic and medicinal community. However, the reactions between sufenes and imines do not always give the [2^s + 2^i] annuladducts β-sultams, in some cases the [2^s+2^i+2^i] annuladducts are forged.[3b,6] Both of the two types of annuladducts show a wide spectrum of bioactivities.[7] Thus, the annuloselectivity, namely [2^s+2^i] and [2^s+2^i+2^i] annulation selectivity, comes to be one of the most concerned issues in this field.

Our recent studies revealed that the annuloselectivity was controlled by the α-substituents of sulfonyl chlorides and the nucleophilicity of imines.[2b] In the reactions of sulfonyl chlorides with strongly electron-withdrawing α-substituents such as ethoxycarbonylmethanesulfonyl chloride, depending on the nucleophilicity of imines, there exist three kinds of annuloselective results: (1) the imines with larger *N*-substituents than methyl afford exclusively [2^s+2^i] annuladducts; (2) *N*-methyl imines give both [2^s+2^i] and [2^s+2^i+2^i] annuladducts; (3) cyclic imines provide exclusively [2^s+2^i+2^i] annuladducts.

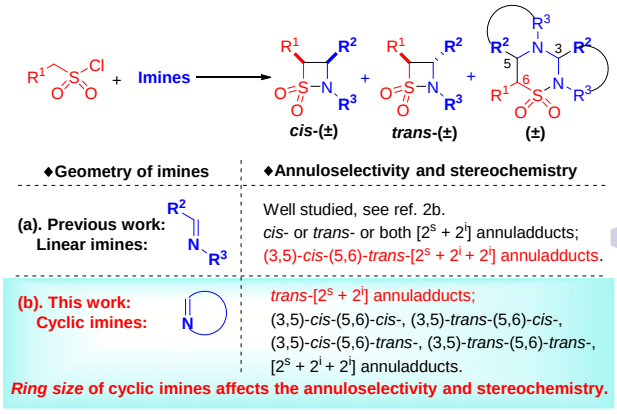


Fig. 1 Factors that control the annuloselectivity and stereochemistry in the sulfa-Staudinger cycloaddition

In these studies, our attention was mainly focused on the linear imines (Fig. 1a).[2b] We only reported one example on six-membered cyclic imine 3,4-dihydroisoquinoline, of which the [2^s+2^i+2^i] annuladducts were a pair of diastereomers in (3,5)-*cis*-(5,6)-*cis*- and (3,5)-*cis*-(5,6)-*trans*-configurations. However, the annuloselectivities and the stereochemistry involved in the sulfa-Staudinger cycloaddtions of other ring-size-different cyclic imines still remain mysterious. As our continuing interests in sulfa-Staudinger cycloadditions, we studied this problem, and found that the annuloselectivity and the stereochemistry were also controlled by the ring size of cyclic imines (Fig. 1b). Herein, we report our results, hoping they will not only complete our recently proposed annuloselective empirical rule, but also provide practical guidelines to predict the diverse products and the stereochemistry of the [2^s+2^i+2^i] annuladducts in the sulfa-

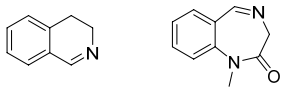
Staudinger cycloadditions of cyclic imines.

Results and Discussion

Selection of the cyclic imine probes

To begin the investigation, we need to select some representative cyclic imines to probe the annuloselectivity and stereochemistry in their sulfa-Staudinger cycloadditions. Since the five-, six-, and seven-membered cyclic imines are most accessible, and possess synthetically significant applications, we decided to select the probes from these three kinds of cyclic imines. Based on our previous work, the cyclic imines selected should satisfy the following two requirements: (1) the *N*-terminal should be substituted by an alkyl group; (2) the *C*-terminal should be mono-substituted.[2] Thus, the selected cyclic imines will exhibit small steric hindrance and strong basicity and nucleophilicity,[8] which are required for the occurrence of the reactions between cyclic imines and sulfonyl chlorides.

Actually, during the past six years, we have been studying the reactions between sulfonyl chlorides and many kinds of cyclic imines.[6,9,10] Unfortunately, no five-memebered cyclic imines can undergo either [2^s+2^i] or [2^s+2^i+2^i] annulation.[9] Out of our experience, the following cyclic imines **1** and **2** in Fig. 2 are chosen as the probes in the current studies.[10] In fact, some reactions between cyclic imines **1** and **2** with certain sulfonyl chlorides were dispersed in our previous publications,[2b,6] concerning other issues in the sulfa-Staudinger cycloaddition. Herein, with the freshly conducted reactions and the collected previously dispersed ones,[2b,6] the annuloselectivity and the stereochemistry in the sulfa-Staudinger cycloaddtions of cyclic imines could be disclosed.

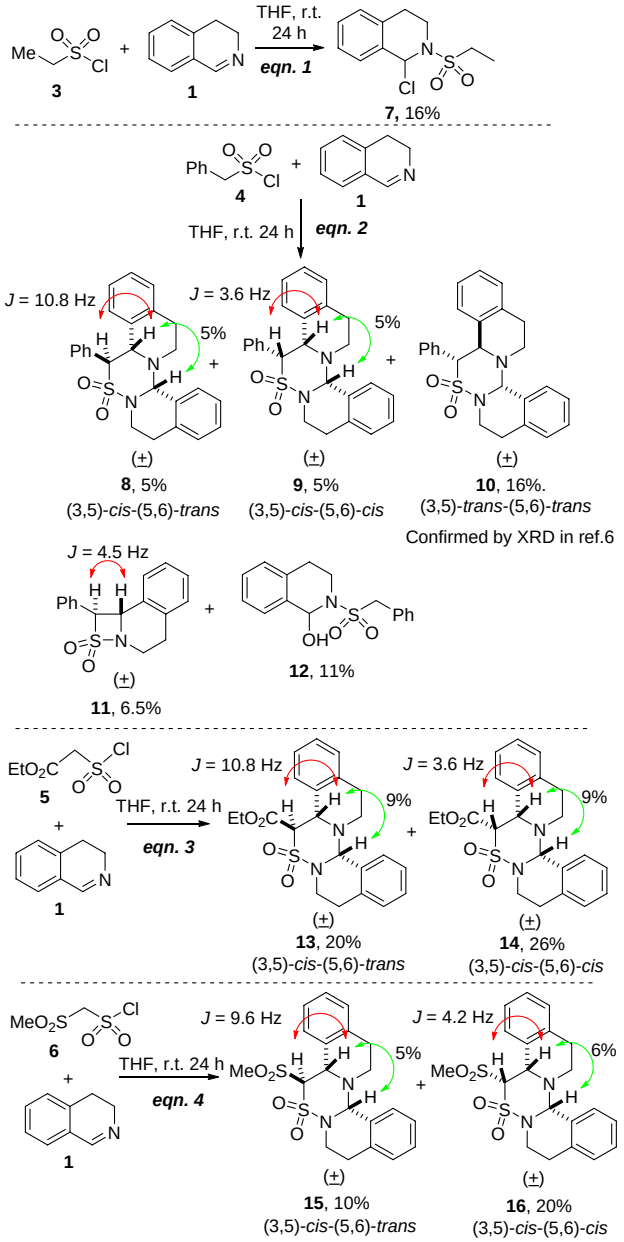


1 **2**

Fig. 2 Selected cyclic imines as probes

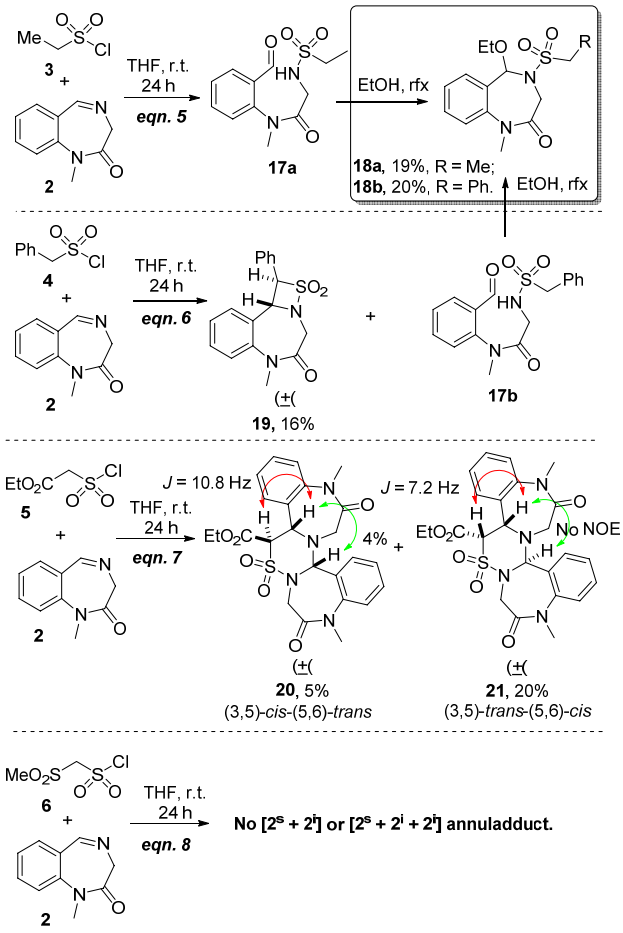
Experimental studies

Since the annuloselectivity are closely associated with the α-substituent effect of sulfonyl chlorides,[2b] the above two cyclic imines **1** and **2** were reacted with four representative sulfonyl chlorides, namely ethanesulfonyl chloride (**3**), phenylmethanesulfonyl chloride (**4**), ethoxycarbonylmethanesulfonyl chloride (**5**), and (methanesulfonyl)methanesulfonyl chloride (**6**), substituted by weakly electron-donating methyl group, weakly electron-withdrawing phenyl group, strongly electron-withdrawing ethoxycarbonyl and methanesulfonyl groups, respectively. The designed reactions are between cyclic imines (**1** and **2**) and sulfonyl chlorides (**3**–**6**), and the results are listed in Schemes 1 and 2.



Scheme. 1 Reactions between the six-membered cyclic imine **1** and sulfonyl chlorides **3**–**6**.

In Scheme 1, the reaction of **1** with **3** gave a chloride-addition product **7** in 16% yield from the key intermediate *N*-sulfonyl iminium chloride (Scheme 1, *eqn. 1*).[6] To our surprise, in our more careful studies, more products have been detected in the reaction of imine **1** with sulfonyl chloride **4**, that is, three [2^s+2^i+2^i] annuladducts **8**, **9**, **10**, one [2^s+2^i] annuladduct **11**, and one water-addition product **12** (generated during workup) in 5%, 5%, 6.5%, 16%, and 11% yields, respectively (Scheme 1, *eqn. 2*). Among those products, the structures of **8**, **10**, and **12** were well identified in our previous publication.[6] In current reinvestigation on the reaction in *eqn. 2*, [2^s+2^i] annuladduct **11** can not be successfully isolated from the mixture with two [2^s+2^i+2^i] annuladducts **8** and **9**. However, the ^{1}H NMR spectrum of the mixture shows a couple of double-split peaks at δ 5.31 and 4.82

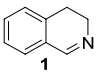
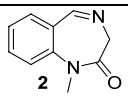


Scheme. 2 Reactions between the seven-membered cyclic imine **2** and sulfonyl chlorides **3**–**6**.

(J = 4.5 Hz, see ESI). Subsequent HRMS determination also presents a peak at 286.0893 (calculated at 286.0896 for product **11**). These convincing data successfully demonstrate the generation of [2^s+2^i] annuladduct **11**. In addition, the relative structures of [2^s+2^i+2^i] annuladducts **8** and **9** were also assigned by means of the NOE analyses. In *eqn. 2*, the [2^s+2^i+2^i] annulation dominates. When cyclic imine **1** was reacted with sulfonyl chloride **5**, two diastereoisomeric [2^s+2^i+2^i] annuladducts **13** and **14** were formed in 20% and 26% yields, respectively, and their stereostructures were clearly established in our previous report.[2b] The similar [2^s+2^i+2^i] annuladducts **15** and **16** were also accessible in the reactions of imine **1** with sulfonyl chloride **6**, but the ratio and total yield were 34:66 and 30%, respectively. The lower total yield than that in *eqn. 3* was probably caused by the large steric hindrance of the α-sulfonyl group in **6**.

The seven-membered cyclic imine **2** reacted with ethanesulfonyl chloride (**3**) only to give a hydrolyzed product **17a** in 19% yield (Scheme 2, *eqn. 5*).[2b] However, phenylmethanesulfonyl chloride (**4**) and imine **2** reacted smoothly, giving both [2^s+2^i] annuladduct tricyclic β-sultam **19** and hydrolyzed product **17b** in 16% and 20% yields, respectively (Scheme 2, *eqn. 6*).[2b,11] Our previous work showed that a variety of arylmethanesulfonyl chlorides can undergo the above two types of reactions with **2**, as key evidence, disclosing the reasonable mechanism for [2^s+2^i] annulation in the sulfa-Staudinger cycloaddition.[2b] In the subsequent studies by reacting imine **2** with sulfonyl chloride **5**, two [2^s+2^i+2^i] annuladducts **20** and **21** were isolated as a pair of diastereoisomers in 5% and 20% yields, respectively. The NOE analysis of the C3 and C5 protons, together with the coupling constants between C5 and C6 protons of the newly-forged six-membered rings, indicated that the stereochemical configurations of **20** and **21** were (3,5)-*cis*-(5,6)-*trans* and (3,5)-*trans*-(5,6)-*cis*, respectively (Scheme 2, *eqn. 7*). In contrast with the results in *eqn. 4*, seven-membered cyclic imine **2** did not match well with the (methanesulfonyl)methanesulfonyl chloride (**6**), with neither [2^s+2^i] nor [2^s+2^i+2^i] annuladduct formed, possibly because of the large steric hindrance of the α-methanesulfonyl group (Scheme 2, *eqn. 8*).

Table 1. Reactions of representative sulfonyl chlorides and cyclic imines

Entry	Sulfonyl chloride	Cyclic Imine	"Hydrolyzed" product Yield (%)	[2^s + 2^i] Product Yield (%)	[2^s + 2^i + 2^i] Products (3,5)-*Cis*-(5,6)-*trans* Yield (%)	(3,5)-*Cis*-(5,6)-*cis* Yield (%)	(3,5)-*Trans*-(5,6)-*trans* Yield (%)	(3,5)-*Trans*-(5,6)-*cis* Yield (%)
1	**3**		**7** (16) [a]	- [b]	-	-	-	-
2	**4**		**12** (11)	**11** (6.5)	**8** (5)	**9** (5)	**10** (16)	-
3	**5**		-	-	**13** (20)	**14** (26)	-	-
4	**6**		-	-	**15** (10)	**16** (20)	-	-
5	**3**		**18a** (19)	-	-	-	-	-
6	**4**		**18b** (20)	**19** (16)	-	-	-	-
7	**5**		-	-	**20** (5)	-	-	**21** (20)
8	**6**		-	-	-	-	-	-

[a] The yield of the chloride-addition product **7**.

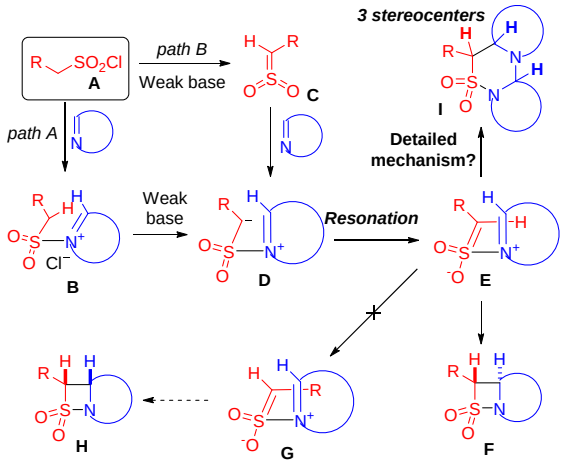
[b] The corresponding products were not obtained.

The results in the reactions of sulfonyl chlorides and representative cyclic imines are summarized in Table 1. Comparing the above results leads to an insight into the annuloselectivity and stereochemistry in the reactions of sulfonyl chlorides with cyclic imines: Ethanesulfonyl chloride (**3**) cannot produce any annulated product with five- to seven-membered cyclic imines. For cyclic imines, (1) the five-membered cyclic imines do not favour either [2^s+2^i] or [2^s+2^i+2^i] annulations (see ref. 9); (2) the six-membered cyclic imines favour the [2^s+2^i+2^i] annulations (Scheme 2, *eqn. 5* and *6*); (3) the seven-membered cyclic imines favour both the [2^s+2^i] and [2^s+2^i+2^i] annulations, depending on the α-substituent effect of the sulfonyl chloride employed (Scheme 3, *eqn. 8* and *9*). Another important observation is that the stereochemistry of the [2^s+2^i+2^i]

annuladducts from seven-membered cyclic imines is quite different from that of the [2^s+2^i+2^i] annuladducts from the six-membered cyclic imines (Scheme 2, *eqn. 5* and *6 vs* Scheme 3, *eqn. 9*). The above annuloselective and stereoselective issues are quite mechanistically interesting but not yet systematically explored.

Intermediates in the [2^s+2^i] and [2^s+2^i+2^i] annulations

According to our recently established mechanisms for the sulfa-Staudinger cycloaddition,[2a] the general routes toward the [2^s+2^i] and [2^s+2^i+2^i] annuladducts were proposed. As outlined in Scheme 3, there exist two paths to the α-anionic *N*-sulfonyl iminium intermediates **D** (*path A* and *path B*), depending on the acidity of the α-protons in sulfonyl chlorides **A**, as described in our recent publication.[2c] These two paths do not affect the subsequent annuloselectivity or stereochemistry. The key 2,3-thiaza-buta-1,3-diene-type intermediates **E**,[12] resonating from **D**, constitutes the only active intermediates that undergo either intramolecular conrotation to form [2^s+2^i] annuladducts *trans*-β-sultams **F**, or intermolecular [4+2] annulation to form [2^s+2^i+2^i] annuladducts **I**. It is noteworthy that intermediates **G** do not exist in the reactions. If they exist, *cis*-bicyclic β-sultams **H** would be generated. However, in our experiments no compound of such a type was observed, eliminating the existence of **G**. Probably it is the conjugated 4π system that prevents the isomerization of **E** to **G** over the C=S bond. The unambiguty of intermediates **E** has been proved by the formation of the *trans*-tricyclic sultams **11** and **19** in the reactions listed in Scheme 1, *eqn. 2*, and Scheme 2, *eqn. 6*, respectively.



Scheme 3. Key intermediates in the [2^s+2^i] and [2^s+2^i+2^i] annulations

Mechanistic insights into the stereochemistry in the [2^s+2^i+2^i] annulations of different cyclic imines

In our previous work, we uncovered that the nature of the [2^s+2^i+2^i] annulations is a stepwise [4+2] annulation between 2,3-thiazabuta-1,3-diene-type intermediates **E** and a second molecule of strongly nucleophilic imines.[2b] Since all the products exhibit (3,5)-*cis*-configurations, we simply put it that the stereochemistry of the C3- and C5-positions of the [2^s+2^i+2^i] annuladducts was generated as a result of the chair transition-state conformation, with the C3- and C5-protons on the axial positions to decrease the steric congestion of the intermediates.[2b] However, in current studies, the (3,5)-*trans*-products **10**, **20**, and **21** were obtained, revealing that the stereochemistry of the [2^s+2^i+2^i] annuladducts is not as simple as we previously observed. Therefore, a new model is in demand to explain and further predict the complex stereochemical outcomes in the [2^s+2^i+2^i] annulations.

As delineated in Scheme 4, the [4+2] annulation constitutes three steps, that is, (1) an intermolecular Mannich-like addition between imines and 2,3-thiazabuta-1,3-diene-type intermediates **E** from *endo* or *exo* side to afford zwitterionic adducts **E-1** or **E-2**, respectively, (2) the C=S bond isomerization of the zwitterionic intermediates **E-1** and **E-2** generated from the above step to give intermediates **E-3** and **E-4**, respectively, and (3) an intramolecular nucleophilic cyclization inside the four zwitterionic intermediates to afford the corresponding [2^s+2^i+2^i] annuladducts **I-1**, **I-2**, **I-3** or **I-4**, respectively. The first intermolecular addition, is regarded as a *rate-determining step,* because it competes with the [2^s+2^i] annulation. It is crucial to the occurrence of the [2^s+2^i+2^i] annulations. Herein, as a *stereo-determining step*, it also plays an extremely important role in deciding the C3 and C5 stereochemistry of the [2^s+2^i+2^i] annulations. The imines can initiate the intermolecular addition to the 2,3-thiazabuta-1,3-diene-type intermediates **E** from either *exo* or *endo* direction, consequently leading to (3,5)-*trans*- or (3,5)-*cis*-products, respectively. The C=S bond isomerization and intramolecular cyclization are in competition, which may be affected by the ring size and/or steric hindrance of imines. The occurrence of the intermolecular addition and isomerization steps is controlled by the ring geometry of the cyclic imines, consequently deciding the final stereochemistry of the [2^s+2^i+2^i] annuladducts.

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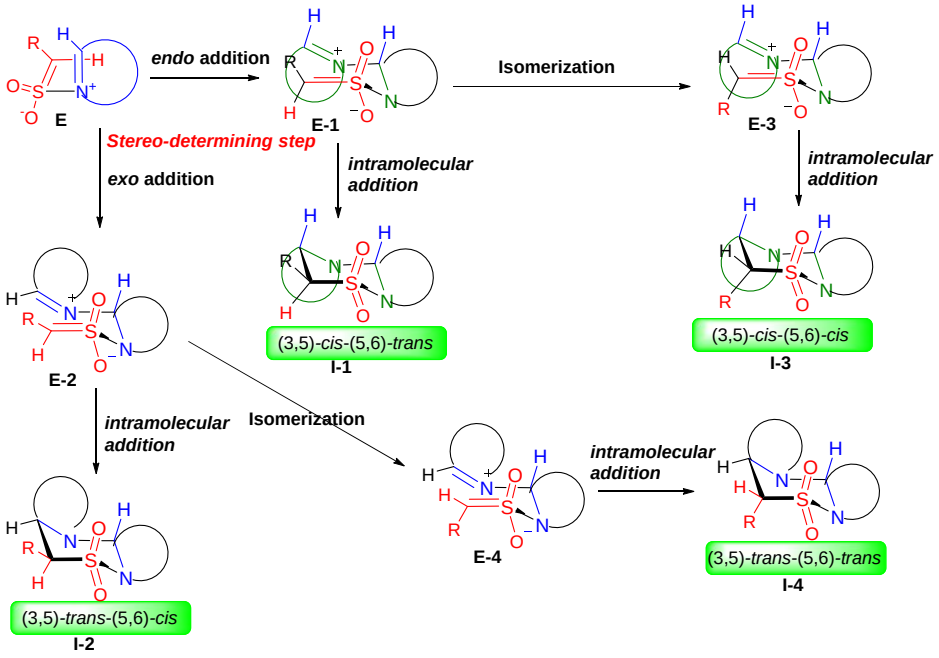
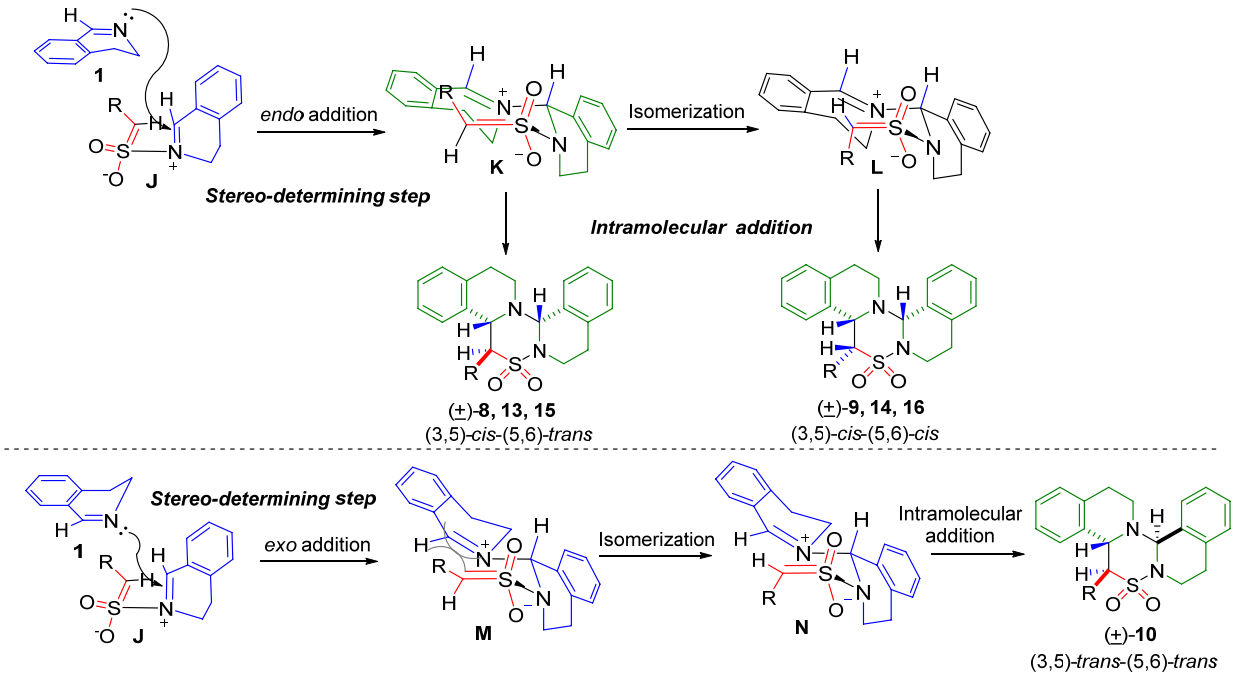


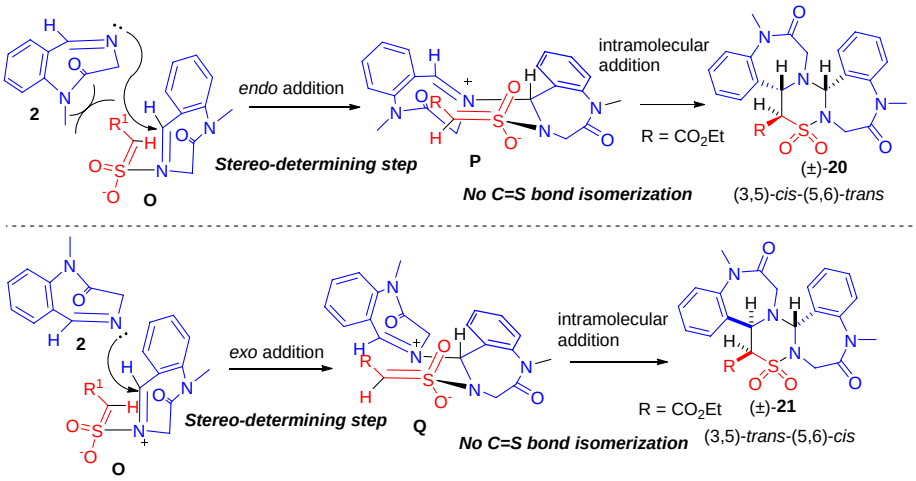
Scheme 4 Proposed stepwise mechanism for the [2^s+2^i+2^i] annulations

As depicted in Scheme 5, the addition of imine **1** to the corresponding 2,3-thiazabuta-1,3-diene intermediates **J** from the *endo* side (*endo* addition) gives rise to intermediates **K**, which directly undergo intramolecular cyclization to form (3,5)-*cis*-(5,6)-*trans*-**8**, **13**, and **15**, or isomerize over their C=S bond followed by intramolecular addition to afford (3,5)-*cis*-(5,6)-*cis*-**9**, **14**, and **16** *via* intermediates **L**. The *exo* addition also occurs, delivering intermediates **M**, which go through a sequence of complete isomerization and intramolecular addition inside intermediates **N** to evolve into (3,5)-*trans*-(5,6)-*trans*-**10**.

The stereochemistry in the [2^s+2^i+2^i] annulations of the seven-membered imine **2** is also rationalized in Scheme 6. The intermolecular addition of **2** occurs from the *endo* side of intermediates **O**, giving intermediates **P**, of which the direct intramolecular addition gives (3,5)-*trans*-(5,6)-*cis*-**20**. Similarly, the *exo* addition and subsequent intramolecular cyclization afford 3,5-*trans*-5,6-*trans*-**21**, through intermediates **Q**. However, the isomerization of the C=S bond of intermediates **P** and **Q** did not occur, mainly because of the steric effect of the congested cyclic iminium moieties. In addition, the large steric hindrance of **2** and **O** makes the intermolecular addition between **2** and **O** very sensitive to the steric hindrance of the α-substituent of sulfonyl chlorides. For example, in *eqn. 8*, the sterically bulky α-methanesulfonyl group imposed disastrous effect, with no [2^s+2^i] or [2^s+2^i+2^i] annuladduct formed.



Scheme 5 Rationalization of the stereochemistry in the $[2^s+2^i+2^i]$ annuladducts from 3,4-dihydroisoquinoline (**1**)



Scheme 6 Rationalization of the stereochemistry in the $[2^s+2^i+2^i]$ annuladducts from seven-membered cyclic imine **2**

The above stereochemical elucidation discloses that the stereochemistry between the C3 and C5 stereocenters is kinetically controlled by the *endo* or *exo* addition of imines, while that between the C5 and C6 stereocenters is thermodymatically controlled by the isomerization of the C=S bond in the zwitterionic *endo*- or *exo*-adducts **K**, **M**, **P** and **Q** generated from the previous step. The intramolecular cyclization does not affect the stereochemical outcomes of the $[2^s+2^i+2^i]$ annulations. It is also interesting that the C=S bond isomerization step only occurs in the reactions of the six-membered imine **1**, possibly controlled by the ring size and steric hindrance of the cyclic imines.

Mechanistic insights into the ring-size-controlled annuloselectivity

When reacted with phenylmethanesulfonyl chloride (**2**), the six-membered cyclic imine **1** is prone to the $[2^s+2^i+2^i]$ annulations, while the seven-membered analogue **2** $[2^s+2^i]$ annulation. The annuloselectivity is mainly governed by the steric hindrance of the imines (**1** and **2**) and intermediates (**J** and **O**). As shown in Fig. 3, the sterically smaller **1** and **J** favour the intermolecular addition, thus $[2^s+2^i+2^i]$ annulations are preferred to the $[2^s+2^i]$ annulation. In contrast, the sterically larger **2** and **O** prevent the intermolecular addition, and consequently, $[2^s+2^i+2^i]$ annulations do not occur. On one hand, the intermediate **O** undergoes conrotatory ring closure to give $[2^s+2^i]$ annuladduct **19**

in low yield;[1b] on the other hand, it hydrolyzes to give aldehyde **17b**.

In the reactions with sulfonyl chloride **5**, both of the imines exclusively undergo [2ˢ+2ⁱ+2ⁱ] annulations. This annulosepecificity is controlled by the α-substituent effect of sulfonyl chlorides, as pointed out in our previous work.[2b] Detailedly, when R^1 is a strongly electron-withdrawing group, the direct conrotation of intermediates **J** and **O** is drastically decelerated. As a result, the strongly nucleophilic imines **1** and **2** would have enough probability to initiate the intermolecular addition, if sterically permitted, leading to the exclusive [2ˢ+2ⁱ+2ⁱ] annuladducts **13**, **14**, **15**, **16**, **20**, and **21** in *eqn. 3, 4,* and *7*.

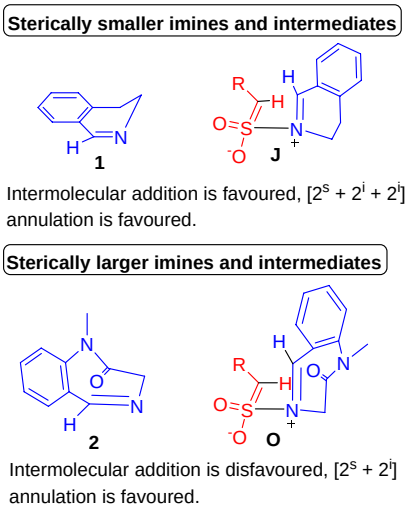
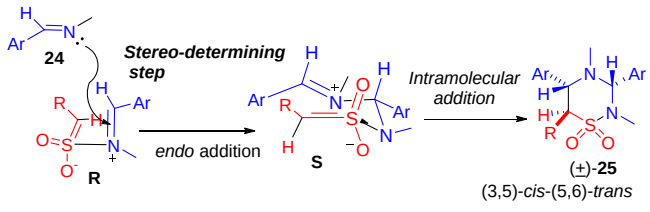


Fig. 3 Steric hindrance of imines **1** and **2** and intermediates

Kinetic proposals for the stereochemistry in the [2ˢ+2ⁱ+2ⁱ] annulations of linear imines

In our previous studies, the stereochemistry of the [2ˢ+2ⁱ+2ⁱ] annuladducts of *N*-methyl linear imines **24** was attributed to the thermodynatical properties of the intermediates **S**.[2b] Herein, from a kinetic perspective, the stereochemistry is more easily understood. As delineated in Scheme 7, the *endo* addition of **24** to **R** directly leads to **S**, and subsequently the intramolecular cyclization of **S** successfully explains the stereochemistry of (3,5)-*cis*-(5,6)-*trans*-**25**.



Scheme 7 Rationalization of the stereochemistry in the [2ˢ+2ⁱ+2ⁱ] annuladducts from *N*-methyl linear imines

Conclusions

By using representative six- and seven-membered cyclic imines **1** and **2** as probes, the annuloselectivity and stereochemistry in the sulfa-Staudinger cycloaddtions of cyclic imines were studied. The results reveal that the annuloselectivity and stereochemistry are closely associated with the ring size of the cyclic imines. When reacted with sulfonyl chlorides with weakly electron-withdrawing substituents, the six-membered cyclic imines afford both [2ˢ+2ⁱ] and [2ˢ+2ⁱ+2ⁱ] annuladducts, with the latter dominating, while the seven-membered cyclic imines give only [2ˢ+2ⁱ] annuladducts. When reacted with sulfonyl chlorides with strongly electron-withdrawing substituents, regardless of the ring size, all the cyclic imines undergo [2ˢ+2ⁱ+2ⁱ] annulations. It is the steric hindrance of the cyclic imines that controls not only the [2ˢ+2ⁱ] and [2ˢ+2ⁱ+2ⁱ] annuloselectivity in the reactions of weakly electron-withdrawing-substituted sulfonyl chlorides, but also the stereochemistry in the [2ˢ+2ⁱ+2ⁱ] annulations of strongly electron-withdrawing-substituted sulfonyl chlorides.

A stepwise [4+2] annulation mechanism, which incorporates an intermolecular addition, C=S bond isomerization, and an intramolecular cyclization, is proposed to explain the different stereochemistry in the [2ˢ+2ⁱ+2ⁱ] annulations of the six- and seven-membered imines. The intermolecular addition is regarded as the key *stereo-determining step*. Firstly, the C3 and C5 stereochemistry is kinetically controlled by the *endo* or *exo* intermolecular addition of imines to the key zwitterionic 2,3-thiaza-1,4-butadiene-type intermediates, and then the C5 and C6 stereochemistry is thermodynatically controlled by the isomerization of the C=S bond of the zwitterionic *endo*- or *exo*-adducts (for example, **K**, **M**, **P**, **Q**) generated from the previous step. The intramolecular cyclization does not affect the stereochemical outcomes of the [2ˢ+2ⁱ+2ⁱ] annulations. The six-membered imines undergo the [4+2] annulations predominantly or exclusively in an *endo* way with C=S bond isomerization, giving mainly (3,5)-*cis*-(5,6)-*cis*- and (3,5)-*trans*-(5,6)-*cis*-products, while the seven-membered imines in both *endo* and *exo* way without C=S bond isomerization, giving (3,5)-*cis*-(5,6)-*trans*- and (3,5)-*trans*-(5,6)-*cis*-products, respectively. In addition, the current stereochemical model successfully explains the stereochemistry of the [2ˢ+2ⁱ+2ⁱ] annulations of the linear imines.

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 Bruker 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-dimention selected NOE experiments were conducted on a Bruker 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 **3** and **4** were prepared according to the methods in our previous reports, [13] while **5** was prepared according to the method reported by Du Bois et al,[14] and **6** is commercially available. The cyclic imines **1** and **2** were prepared according to Cava's[15] and our procedures,[2b] respectively.

Typical Procedure

The experiments were conducted by the following procedures.[1b,c,d] To a solution of cyclic imine **1** (197 mg, 1.5 mmol) in 2 mL of dry tetrahydrofuran was dropwise added a solution of (methanesulfonyl)methanesulfonyl chloride **6** (96 mg, 0.5 mmol) in 0.5 mL of dry tetrahydrofuran. Upon addition, the mixture was allowed to stand at room temperature for another 24 h. Ether (10 mL) was added, and large amount of white solids precipitated. After washing with brine (10 mL), the organic phase was dried over Na_2SO_4, and concentrated at vacuum. The residue was purified by column chromatography on silica gel with petroleum ether and ethyl acetate as eluent.

In Scheme 1, 3,4-dihydroisoquinoline **1** (197 mg, 1.5 mmol) was reacted with 0.5 mmol of sulfonyl chloride **3**, **5**, or **6** following the typical procedure, but 3 mmol of **1** was used in the reaction of 1 mmol of phenylmethanesulfonyl chloride (**4**) in 5 mL of dry THF. In the reactions in Scheme 2, 3 mmol of cyclic imine **2**, 1 mmol of sulfonyl chloride **3**, **4**, **5**, or **6**, and 5 mL of dry THF were used.

1-Chloro-2-(ethylsulfonyl)-1,2,3,4-tetrahydroisoquinoline (7) [6]
Colorless crystals, m.p. 170–172 °C. Yield 8 mg (16%). R_f = 0.5 (PE:EA = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.15–7.69 (m, 4 H, ArH), 6.74 (s, 1 H, CH), 3.89 (ddt, J = 5.6, 13.2, 1,2 Hz, 1 H in CH_2), 3.56 (dt, J = 3.6, 12.8 Hz, 1 H in CH_2), 3.04–3.10 (q, J = 7.2 Hz, 2 H, CH_2), 2.98–3.16 (m, 1 H in CH_2), 2.77 (ddd, J = 1.6, 3.6, 16.4 Hz, 1 H in CH_2), 1.26 (t, J = 7.2 Hz, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 135.6, 130.1, 129.6, 129.0, 128.3, 126.7, 85.9, 47.4, 38.8, 28.9, 7.7.

Compounds **8**, **9**, and **11** were obtained as an inseparable mixture (60 mg, about 16.5% total yield), and only trace amount of **8** was separated. But the characteristic ^{1}H NMR data of the three products, the NOE analyses, and the HRMS data of **10** clearly demonstrate the structures (For details, see ESI). The ^{1}H NMR indicated that the ratio of **8**, **9**, and **11** was 1:1:1.3. The yields of **8**, **9** and **10** were calculated to be 5%, 5%, and 6.5%, respectively.

***rel*(4b*R*,5*R*,13b*R*)-5-Phenyl-4b,5,9,13b,15,16-hexahydro-8*H*-[1,2,4]thiadiazino[3,2-*a*:5,4-*a*']diisoquinoline 6,6-dioxide (8)** [6]
Colorless crystals, m.p. 126–128 °C, 20 mg (5%). R_f = 0.8 (PE:EA = 1:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–6.17 (m, 13 H, ArH), 6.07 (s, 1H), 5.12 (d, J = 10.4 Hz , 1H), 4.57 (d, J = 10.4 Hz, 1H), 3.78–3.72 (m, 1H), 3.65–3.60 (m, 1H), 3.26–3.19 (m, 1H), 3.06–2.96 (m, 2H), 2.86–2.76 (m, 2H), 2.70–2.64 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7, 134.6, 132.5, 132.1, 129.8, 129.1, 129.0, 128.9, 128.7, 128.6, 128.0, 127.9, 127.3, 127.1, 124.5, 75.2, 64.9, 63.9, 39.6, 37.8, 29.3, 29.2.

***rel*(4b*R*,5*S*,13b*R*)-5-Phenyl-4b,5,9,13b,15,16-hexahydro-8*H*-[1,2,4]thiadiazino[3,2-*a*:5,4-*a*']diisoquinoline 6,6-dioxide (9)**
White solid (5% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.69 (s, 1H in NC*H*N), 5.18 (d, J = 3.6 Hz, 1H in C*H*N), 4.84 (d, J = 3.6 Hz, 1H in C*H*S).

(4b*R*,5*R*,13b*S*)-5-Phenyl-4b,5,9,13b,15,16-hexahydro-8*H*-[1,2,4]thiadiazino[3,2-*a*:5,4-*a*']diisoquinoline 6,6-dioxide (10) [6]
Colorless crystals, m.p. = 145–147 °C. Yield 64 mg (16%). R_f = 0.7 (PE:EA = 1:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.54–5.92 (m, 13 H, ArH), 5.48 (s, 1H, CH), 4.74 (d, 1H, J = 9.6 Hz), 4.74 (q, 1H, J = 9.6 Hz), 4.36–4.31 (m, 1H), 4.27–4.19 (m, 1H), 3.46–3.28 (m, 4H), 3.03–2.97 (m, 1H), 2.91–2.86 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.3, 136.045, 135.3, 134.4, 132.7, 130.0, 129.5, 128.5, 128.2, 127.4, 126.5, 125.6, 80.6, 72.1, 60.1, 48.1, 41.8, 30.8, 29.3.

***rel*(1*S*,9b*S*)-1-Phenyl-1,4,5,9b-tetrahydro[1,2]thiazeto[3,2-*a*]isoquinoline 2,2-dioxide (11)**
White solid (6.5% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.31 (d, J = 4.5 Hz, 1H in C*H*N), 4.82 (d, J = 4.5 Hz, 1H in C*H*S). HRMS (ESI) calcd for $C_{16}H_{16}NO_2S$ $[M + H]^+$ *m/z* 286.0896, found 286.0893.

2-(Benzylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-1-ol (12) [6]
Colorless crystals, m.p. 204–205 °C. Yield 33 mg (11%). R_f = 0.5 (PE:EA = 1:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09–7.31 (m, 9H), 6.02 (d, J = 5.4 Hz, 1H), 4.34 (s, 2H), 3.55 (dddd, J = 0.4, 2.4, 5.6, 12.8 Hz, 1H), 3.30 (dt, J = 4.0, 12.4 Hz, 1H), 2.93 (d, J = 5.4 Hz, 1H), 2.77 (ddd, J = 5.6, 11.6, 16.4 Hz, 1H), 2.65 (dt, J = 16.0, 3.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.0, 133.8, 130.9, 130.7, 128.7, 128.6, 128.4, 126.7, 77.1, 59.7, 38.8, 29.0.

Ethyl *rel*(4b*R*,5*R*,13b*S*)-4b,5,9,13b,15,16-hexahydro-8*H*-[1,2,4]thiadiazino[3,2-*a*:5,4-*a*']diisoquinoline-5-carboxylate 6,6-dioxide (13) [2b]
Colorless crystals. M.p. 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), 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.

Ethyl *rel*(4b*R*,5*R*,13b*R*)-4b,5,9,13b,15,16-hexahydro-8*H*-[1,2,4]thiadiazino[3,2-*a*:5,4-*a*']diisoquinoline-5-carboxylate 6,6-dioxide (14) [2b]
Colorless crystals. M.p. 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.

Compounds **15** and **16** were obtained as an inseparable white solid mixture (m.p. 165–170 °C; 60 mg, 30% total yield). The ratio of **15**:**16** was 34:66, identical to the ratio obtained from the crude reaction mixture.

***rel*(4b*R*,5*S*,13b*R*)-5-(Methylsulfonyl)-4b,5,9,13b,15,16-hexahydro-8*H*-[1,2,4]thiadiazino[3,2-*a*:5,4-*a*']diisoquinoline**

6,6-dioxide (15)

Yield 10%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.2 Hz, 1H), 7.46–7.41 (m, 1H), 7.32–7.27 (m, 3H), 7.23–7.19 (m, 2H), 7.09 (d, *J* = 7.2 Hz, 1H), 5.99 (s, 1H), 5.39 (d, *J* = 9.6 Hz, 1H), 4.76 (d, *J* = 9.6 Hz, 1H), 3.97 (dt, *J* = 11.7, 4.9 Hz, 1H), 3.55–3.50 (m, 1H), 3.17 (s, 3H), 2.94–2.78 (m, 4H), 2.71–2.65 (m, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 135.0, 134.8, 133.9, 131.5, 130.4, 128.84, 128.77, 128.69, 128.5, 128.1, 127.4, 125.4, 76.51, 73.6, 61.6, 46.5, 41.2, 38.8, 29.4, 28.2. IR (film) *v* cm^{-1} 3029, 2929, 1496, 1454, 1428, 1405, 1340, 1324, 1277, 1139, 1165, 1116, 1089, 1044, 1006, 970, 786, 754, 732, 690, 647, 607. ESI-HRMS $[M+H]^+$ calcd for $C_{20}H_{23}N_2O_4S_2$ 419.1094, found 419.1094.

***rel*(4b*R*,5*R*,13b*R*)-5-(Methylsulfonyl)-4b,5,9,13b,15,16-hexahydro-8*H*-[1,2,4]thiadiazino[3,2-*a*:5,4-*a*']diisoquinoline 6,6-dioxide (16)**

Yield 20%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.41 (m, 1H), 7.32–7.27 (m, 2H), 7.23–7.19 (m, 4H), 7.16–7.13 (m, 1H), 6.02 (s, 1H), 5.44 (d, *J* = 4.0 Hz, 1H), 4.66 (d, *J* = 4.0 Hz, 1H), 4.04 (ddd, *J* = 2.5, 5.3, 12.7 Hz, 1H), 3.59 (dt, *J* = 12.4, 3.3, 1H), 3.43–3.36 (m, 1H), 3.21 (s, 3H), 3.11–3.01 (m, 2H) 2.94–2.78 (m, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 135.8, 132.1, 131.1, 130.2, 129.4, 129.2, 128.4, 127.9, 127.6, 127.1, 125.9, 125.5, 76.48, 73.8, 63.2, 45.8, 42.9, 38.7, 30.0, 29.0. IR (film) *v* cm^{-1} 3029, 2929, 1496, 1454, 1428, 1405, 1340, 1324, 1277, 1139, 1165, 1116, 1089, 1044, 1006, 970, 786, 754, 732, 690, 647, 607. ESI-HRMS $[M+H]^+$ calcd for $C_{20}H_{23}N_2O_4S_2$ 419.1094, found 419.1094.

5-Ethoxy-4-(ethylsulfonyl)-1-methyl-4,5-dihydro-1*H*-benzo[*f*][1,4]diazepin-2(3*H*)-one (18a)[2a]

Yield 59 mg (19%). R_f = 0.4 (PE:EA = 2:1, *v/v*). Yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.51–7.29 (m, 4H), 5.90 (s, 1H), 4.11 (d, *J* = 14.0 Hz, 1H), 3.57 (d, *J* = 14.0 Hz, 1H), 3.45 (dq, *J* = 15.2, 7.6 Hz, 1H), 3.38 (d, *J* = 15.2, 7.6 Hz, 1H), 3.35 (s, 3H), 3.30 (dq, *J* = 14.4, 7.2 Hz, 1H), 3.12 ((dq, *J* = 14.4, 7.2 Hz, 1H), 1.46 (t, *J* = 7.6 Hz, 3H), 1.09 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.7, 141.8, 130.6, 130.0, 129.1, 126.5, 123.8, 88.7, 62.7, 49.1, 47.9, 35.3, 14.9, 7.5.

4-(Benzylsulfonyl)-5-ethoxy-1-methyl-4,5-dihydro-*1H*-benzo[*f*][1,4]diazepin-2(3*H*)-one (18b)[2a]

Yellowish oil. Yield 75 mg (20%). R_f = 0.4 (PE:EA = 2:1, *v/v*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.29 (m, 9H), 5.92 (s, 1H), 4.61 (d, *J* = 13.6 Hz, 1H), 4.53 (d, *J* = 13.6 Hz, 1H), 4.20 (d, *J* = 14.0 Hz, 1H), 3.57 (d, *J* = 14.0 Hz, 1H), 3.50 (dq, *J* = 14.6, 7.3 Hz, 1H), 3.36 (s, 3H), 3.19 (dq, *J* = 14.6, 7.3 Hz, 1H), 1.14 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 141.8, 131.0, 130.6, 130.0, 129.1, 128.7, 128.5, 128.3, 126.5, 123.9, 89.0, 62.8, 60.5, 48.1, 35.4, 14.9.

***trans*-6-Methyl-1-phenyl-1,10b-dihydro-6*H*-benzo[*f*][1,2]thiazeto[2,3-*d*][1,4]diazepin-5(4*H*)-one 2,2-dioxide (19)**[2a]

Colorless crystals, m.p. 237–239 °C. Yield 53 mg (16%). R_f = 0.5 (PE:EA = 2:1, *v/v*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64–7.26 (m, 9H, ArH), 5.82 (d, *J* = 3.2 Hz, 1H), 4.93 (d, *J* = 3.2Hz, 1H), 3.83 (d, *J* = 12.0 Hz, 1H), 3.79 (d, *J* = 12.0 Hz, 1H), 3.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 142.7, 130.6, 130.3, 130.0, 129.4, 128.9, 127.1, 126.8, 126.2, 123.6, 78.7, 55.3, 46.1, 36.1.

Ethyl *rel*(2*S*,10*R*,11*S*)-1,5,8,14-tetraza-9-thiadibenzo[*c*,*l*]tricyclo[9.5.0.0^{2,8}]hexadecane-6,15-dione-10-carboxylate 9,9-dioxide (20)

Yield 25 mg (5%). TLC R_f = 0.7 (CH_2Cl_2:MeOH = 40:1). Colorless crystals, m.p. > 300°C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56–7.19 (m, 8H), 5.85 (s, 1H), 4.91 (d, *J* = 11.2 Hz, 1H), 4.51 (d, *J* = 11.2 Hz, 1H), 4.37 (d, *J* = 14.4 Hz, 1H), 4.17 (m, 2H), 3.66 (d, *J* = 14.4 Hz, 1H), 3.42 (s, 3H), 3.14 (s, 3H), 2.93 (d, *J* = 14.0 Hz, 1H), 2.70 (d, *J* = 14.0 Hz, 1H), 1.15 (dd, *J* = 7.2, 7.2 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 166.9, 166.5, 143.6, 141.8, 132.5, 127.7, 126.7, 125.5, 124.0, 121.2, 80.4, 65.6, 62.5, 59.8, 51.6, 49.1, 35.3, 33.5, 13.8; IR (film) *v* cm^{-1} 2976, 2929, 1739, 1668, 1602, 1495, 1462, 1368, 1297, 1174, 1150, 1097, 1027, 998, 766, 736, 666; ESI-HRMS $[M+H]^+$ calc for $C_{24}H_{27}N_4O_6S$ 499.1651, found 499.1651.

Ethyl *rel*(2*R*,10*S*,11*S*)-1,5,8,14-tetraza-9-thiadibenzo[*c*,*l*]tricyclo[9.5.0.0^{2,8}]hexadecane-6,15-dione-10-carboxylate 9,9-dioxide (21)

Yield 99 mg (20%). TLC R_f = 0.4 (CH_2Cl_2:MeOH = 40:1). Colorless crystals, m.p. > 300 °C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, *J* = 7.6 Hz, 1H), 7.52–7.15 (m, 7H), 5.34 (s, 1H), 5.10 (d, *J* = 7.2 Hz, 1H), 5.03 (d, *J* = 7.2 Hz, 1H), 4.43 (d, *J* = 14.4 Hz, 1H), 4.14 (dq, *J* = 14.4, 7.2 Hz, 1H), 4.06 (dq, *J* = 14.4, 7.2 Hz, 1H), 3.65 (d, *J* = 14.4 Hz, 1H), 3.52 (s, 3H), 3.33 (s, 3H), 2.64 (d, *J* = 14.2 Hz, 1H), 2.40 (d, *J* = 14.2 Hz, 1H), 0.97 (dd, *J* = 7.2, 7.2 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 166.9, 166.6, 163.3, 143.5, 142.6, 130.7, 129.7, 129.3, 126.8, 126.5, 125.4, 124.3, 121.3, 63.6, 62.3, 58.7, 54.0, 49.0, 34.8, 13.6; IR (film) *v* cm^{-1} 2978, 2930, 1743, 1669, 1601, 1493, 1461, 1424, 1368, 1285, 1172, 1153, 1001, 766, 734, 648; ESI-HRMS $[M+H]^+$ calc for $C_{24}H_{27}N_4O_6S$ 499.1651, found 499.1650.

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Notes and references

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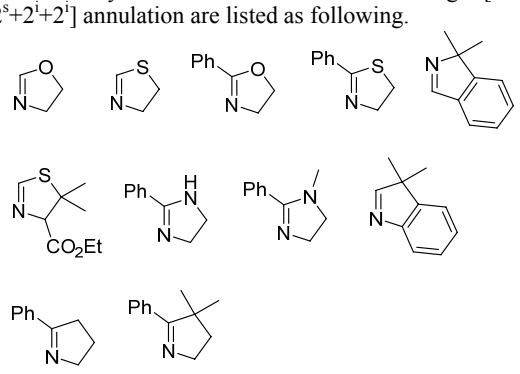
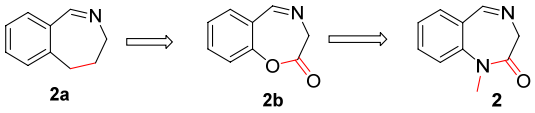


10 The reactions of cyclic imine **2a** with various benzyl sulfonyl chlorides failed to give [2^s+2^i] or [2^s+2^i+2^i] annuladducts, instead, the corresponding hydrolyzed products *N*-(3-(2-formylphenyl)propyl)-substituted phenylmethanesulfonamides generated.[6] We surmised that it was the strong ring extension and the resulting bulky steric hindrance in the intermediates that caused the failure. Therefore, we decided to modify the ring extension of the cyclic imine **2a** by introducing a functional group into the structure. Illuminated by linear imines employed in Loiseau's report,[3c] we devised a new bicyclic imine **2b** with an ester group embedded. However, numerous attempts toward this structure failed, partly because of the instability of the ester group under basic conditions. So, further modification of the structure by replacing the ester with an amide directed us to the imine **2**.



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