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THE EFFECT OF LITHIUM ION ON THE STEREOSELECTIVITY OF THE INTRAMOLECULAR MICHAEL ADDITION OF AN *N*-ARYL-SULFOXIMINE ANION

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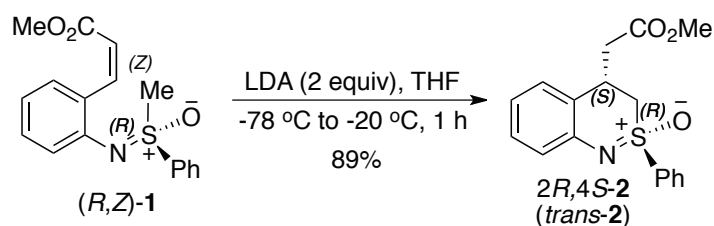
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Abstract – The stereochemical outcome of the intramolecular Michael addition of a sulfoximine carbanion to a *Z*-configured α,β -unsaturated ester is dependent on lithium ion coordination between the oxygen on the sulfoximine and the carbonyl oxygen of the ester, based on both experimental and computational studies. Formally, this leads to a more sterically congested structure than might otherwise be preferred. Indeed, addition of HMPA, a substance capable of effective solvation of lithium cations, changes the stereochemical course of the reaction dramatically.

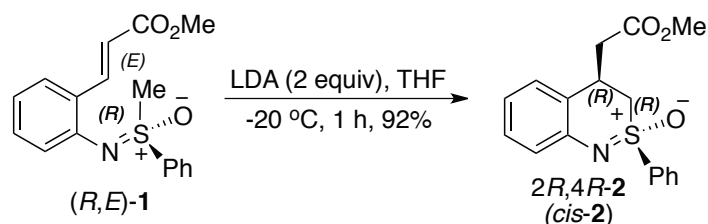
INTRODUCTION

Some time ago, we reported that the treatment of sulfoximine (*Z*)-**1** with base afforded the benzothiazine 2*R*,4*S*-**2** (*trans*-**2**) as a single diastereomer in 89% yield (Scheme 1).¹



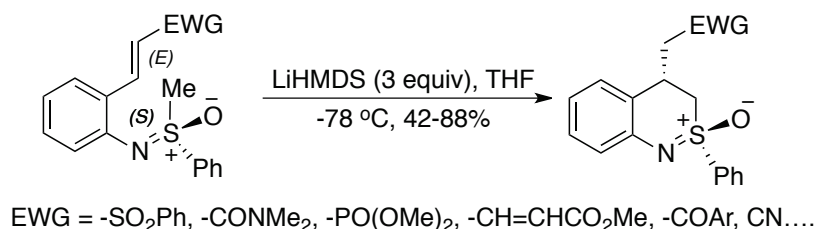
Scheme 1. Intramolecular Michael addition of (*R,Z*)-**1**

Conversely, the *E* isomer of **1** afforded the *cis* isomer of **2**, *cis* and *trans* referring to the stereochemical relationship between the phenyl group on the sulfur atom and the ester fragment on carbon 4 of the 2,1-benzothiazine (Scheme 2). We thus reported this reaction as being stereospecific. However, at that time, we produced few other examples that showed that sulfoximines with a *Z* configuration at the α,β -unsaturated ester gave exclusively a benzothiazine product that was *trans* upon treatment with the appropriate base.



Scheme 2. Intramolecular Michael addition of (*R,E*)-**1**

Some years later, we investigated a series of α,β -unsaturated systems bearing a variety of electron withdrawing groups.² The configuration of the double bond of the substrates in these studies was *E*. All of the product benzothiazines produced in these studies were exclusively *cis*. We can conclude with great confidence that the stereochemical outcome of reactions with such systems will always be *cis* (Scheme 3).



Scheme 3. General benzothiazine synthesis via intramolecular Michael addition

We became interested in the origin of the stereoselectivity for (*Z*)-**1** since models suggested that the stereochemistry of the product formed was derived from a more crowded and sterically unfavorable transition state structure. In the end, we were able to determine a mechanistic rationale for the stereochemistry observed and establish that the practical aspects of the reaction were not as simple as we once had thought.

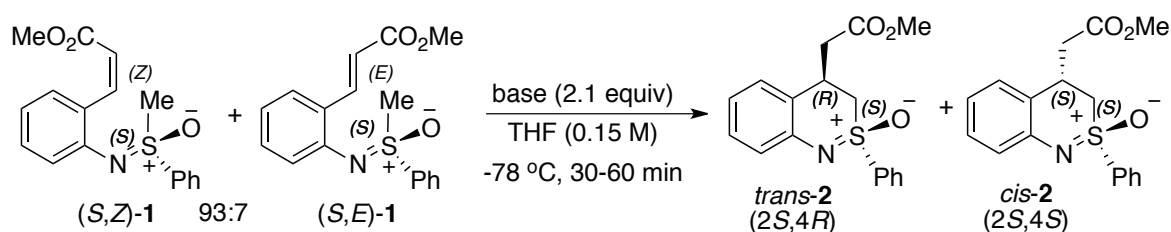
RESULTS AND DISCUSSION

EXPERIMENTAL STUDIES

We began our studies by repeating our old work. Treatment of (*Z*)-**1** (99% *Z*) with LDA in THF afforded a mixture of benzothiazine *trans*-**2** and *cis*-**2** in a ratio of 91:9. Clearly, we were formally getting the same result, but it was a not quite what we were had obtained earlier, in which we had obtained *cis*-**2** exclusively within the limits of ¹H NMR detection. We speculated that it might be the case that lithium was playing an important role in the reaction. We further thought that it might be the case that various lithium salts are likely to accumulate in bottles of *n*-BuLi that are either old or used by a number of individuals simultaneously. Since we used *n*-BuLi to prepare our LDA, and since there was no way of actually knowing precisely the condition of that chemical in our original studies, we decided to investigate the matter more closely, but only with the intent of discovering lithium's role in the reaction, not to optimize the cyclization.

As shown in Scheme 3, we had successfully used LiHMDS in intramolecular cyclizations of this type. We therefore decided to use that base to investigate the effect of lithium salts on the stereochemical outcome of the intramolecular Michael addition. The starting material for these studies could be prepared in nearly stereochemically pure form using a Still-Gennari reaction.³ However, (*Z*)-**1** isomerizes (*E*)-**1** when stored on the bench at room temperature, so storage in a freezer was mandatory. Note that in some studies, stereochemical mixtures were used, but they were always more than 90% (*Z*)-**1**.

Table 1. Cyclization of a 93:7 mixture of (*Z*)-**1** and (*E*)-**1** using LiHMDS



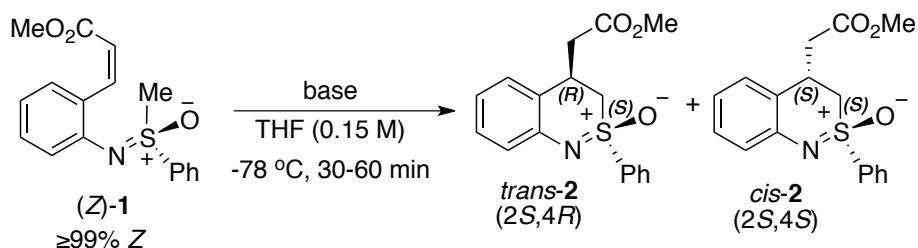
Entry	Base	Additive	<i>trans</i> - 2 : <i>cis</i> - 2 ^a
1 ^b	LiHMDS	-	59:41
2 ^b	LiHMDS	12-crown-4 (1 equiv) ^c	62.5:37.5
3 ^b	LiHMDS	DMPU (2.1 equiv) ^c	65:35
4 ^b	LiHMDS	HMPA (2.1 equiv) ^c	0:100
5 ^d	LiHMDS	-	58:42
6 ^d	LiHMDS	12-crown-4 (1 equiv)	54:46
7 ^d	LiHMDS	DMPU (2.1 equiv)	9:91
8 ^d	LiHMDS	HMPA (2.1 equiv)	0:100

^aRatio based on ¹H NMR of a crude reaction mixture. ^bBase added to sulfoximine (Procedure A).

^cAdditive added after LiHMDS. ^dSulfoximine added to base and additive (Procedure B).

The results of our studies are shown in Table 1. Our only interest in this study was stereochemistry; yields were not determined and both stereoisomeric products had been characterized fully in previous work.¹ Cyclization of **1** (93:7, *Z:E*) using LiHMDS in THF afforded *trans*- and *cis*-**2** in a ratio of 59:41 (Table 1, entry 1). In this case, no hexanes were present in solution, as the LiHMDS used was a 1 M solution in THF. Better solvation of lithium presumably diluted the impact of the lithium ion on the reaction. Interestingly, addition of 1 equivalent of 12-crown-4 or DMPU (2.1 equiv relative to LiHMDS) changed the ratio of products only slightly, but in favor of *trans*-**2**, which was not expected (Table 1, entries 2-3). However, using HMPA (2 equiv relative to LiHMDS) led to the exclusive formation of *cis*-**2**. We presume that solvation of the lithium cations swamps interaction with the substrate, favoring the least hindered transition state leading to cyclization. In these experiments, base was added to substrate. We also examined an inverse addition, in which substrate was added to base and additive. These results are summarized in Table 1, entries 5-8. The only great change observed was that for DMPU. In this case, the ratio of *cis*-**2**:*trans*-**2** was 91:9, in keeping with the idea that DMPU can solvate lithium cation effectively. It is likely that the reaction had proceeded significantly before DMPU was added in the case of entry 3.

Table 2. Cyclizations with LDA and Additional Lithium Salts



Entry	Base/Additive	<i>trans</i> - 2 : <i>cis</i> - 2 ^a
1	<i>n</i> -BuLi (2 equiv); DIPA (2 equiv) ^a	91:9
2	<i>n</i> -BuLi (2 equiv); DIPA (1 equiv); TEA·HCl (1 equiv) ^a	91:9
3	<i>n</i> -BuLi (6 equiv); DIPA (2 equiv); TEA·HCl (4 equiv) ^a	91:9
4	<i>n</i> -BuLi (6 equiv); DIPA (2 equiv); <i>n</i> -BuOH (4 equiv) ^a	91:9

^aBase added to sulfoximine (Procedure C).

Further studies were performed with **1** as an essentially pure *Z* isomer. The results are summarized in Table 2. In these cases, we attempted to increase the amount of lithium in solution by adding acids in the form of triethylammonium hydrochloride or *n*-butanol. These would react with *n*-BuLi to produce LiCl or lithium butoxide, respectively. In these studies, a certain amount of hexanes was also included in the reaction, due to our use of *n*-BuLi. Interestingly, the stereochemical outcome of the reaction was always the same. It is worth noting that the cyclization process appears irreversible. More lithium

cation does not appear to change the kinetic outcome of the reaction, at least from a stereochemical perspective. However, it is clear that sequestering lithium with dipolar aprotic solvents dramatically changes the stereochemical outcome of the reaction. To rationalize these results, we turned to theory.

COMPUTATIONAL STUDIES

Given our experimental data, we were curious to explore the effect of lithium ion on this cyclization computationally. All transition-state (TS) structures were fully optimized at the M06-L level^{4,5} of density functional theory⁶ employing the 6-31+G(d) basis set⁷ and an automatically generated density fitting basis set used to speed the computation of Coulomb integrals. The grid=ultrafine option of the

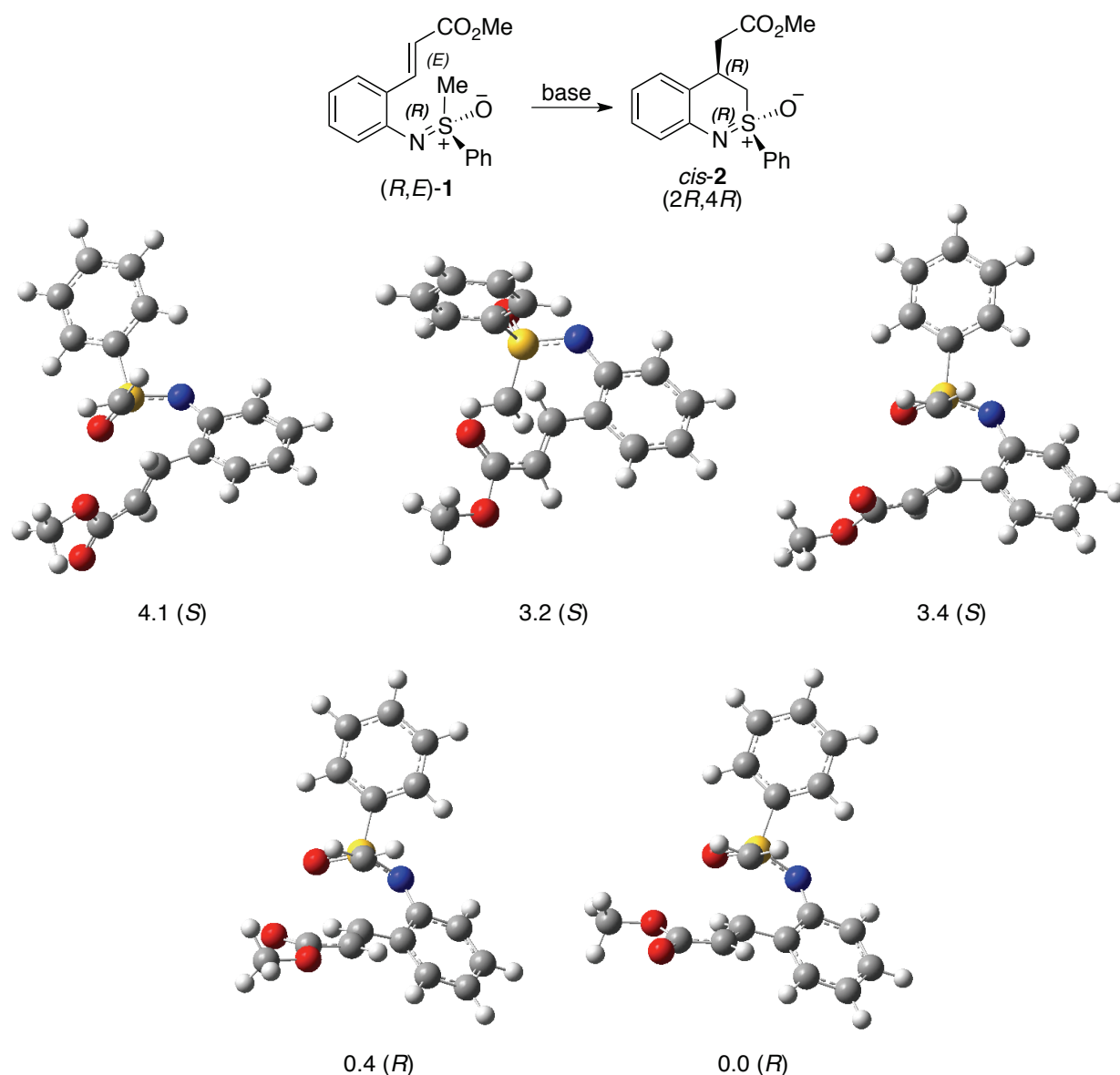


Figure 1. The TS structures for the cyclization of the carbanion of *(R,E)*-1 without coordinating Li^+ . The relative energies (kcal/mol) are shown along with the stereochemistry of the product at the newly formed stereogenic center. The two lowest energy structures lead to *cis*-2.

Gaussian 09 program suite⁸ was selected. Stereochemical variations of ester rotamers, forming 6-membered ring chair and twist-boat geometries, and Li cation placements were exhaustively searched

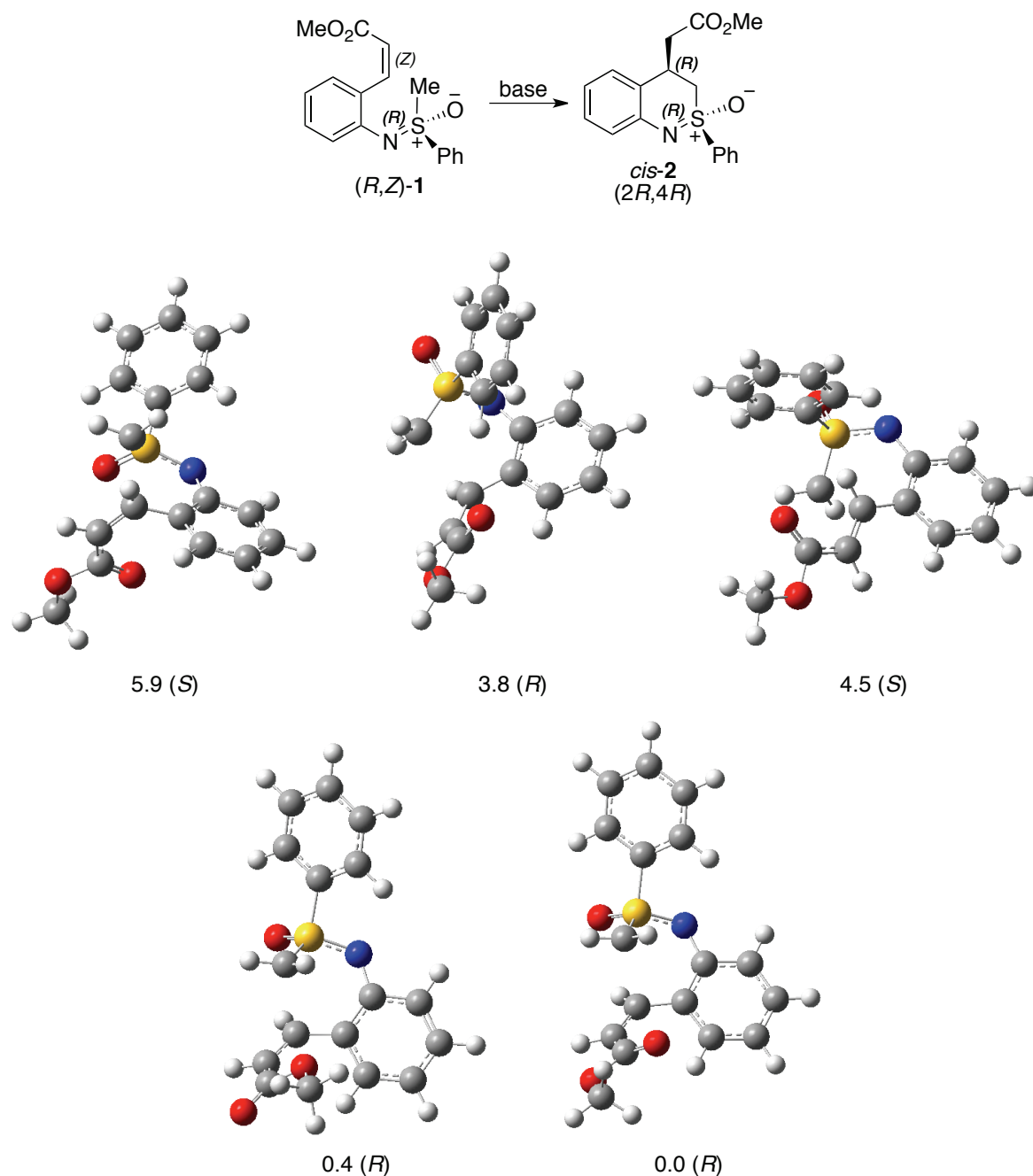


Figure 2. The TS structures for the cyclization of the carbanion derived from *(R,Z)*-1 without coordinating Li^+ . The relative energies (kcal/mol) are shown along with the stereochemistry of the product at the newly formed stereogenic center.

in an attempt to find all stationary conformers. The imaginary mode from analytic frequency calculations was visualized in all instances to ensure its correspondence to C–C bond formation. Thermal contributions to molecular free energies were also computed from the analytic frequency calculations using the ideal-gas, rigid-rotator, harmonic-oscillator approximation;⁶ all energies reported below thus

refer to 298.15 K Gibbs free energies. Figures 1 and 2 list all of the TS structures located for the bare anion of the *E* and *Z* esters, respectively. In the *E* case, the two lowest energy structures, separated by 0.4 kcal/mol from one another, both lead to the *R* stereoproduct (*R,cis*)-**2**, in agreement with the isolated experimental product. Three TS structures leading to *S* stereoproduct were located, but all are 3 to 4 kcal/mol higher in energy. The lower energy stereostructures enjoy a combination of a pseudoequatorial disposition of the sulfoximine phenyl group and an orientation of the ester that avoids unfavorable steric and/or electronic interactions with the sulfoximine oxygen atom.

In the *Z* case, the two lowest energy TS structures are again separated by 0.4 kcal/mol, and closely resemble the lowest energy *E* structures except that the double-bond geometry is now *Z*. These structures therefore also lead to *R* stereoproduct, *cis*-**2**, which is not consistent with the observed experimental results in the presence of lithium cation. TS structures leading to the *S* product were found, but their energies are more than 4 kcal/mol too high to be kinetically relevant.

Given the failure of the bare anion predictions to correlate with experimental observations except in the presence of dipolar aprotic solvents, we considered the possibility of Li cation coordination playing a role in TS structure stabilization. Figures 3 and 4 list relevant TS structures located for the coordinated *E* and *Z* esters, respectively. In the *E* case, the lowest energy bare anion TS structure easily permits a lithium cation to bridge the sulfoximine oxygen and the ester carbonyl oxygen, and this bridging leads to the lowest energy TS structure found, as might be expected given the propensity of lithium to coordinate to oxyanionic functionality. The preference for *R* stereochemistry in the product is thus unaffected by lithium complexation in this case. The other TS structures found lead variously to *R* or *S* product, but they are so high in energy compared to the lowest energy TS structure that they are not kinetically relevant.

In the *Z* case, by contrast, it is not possible to bridge the sulfoximine and ester functionality in the low-energy bare anion TS structures. The lowest-energy structure for which bridging is possible in Figure 2 is the one having a relative energy of 4.5 kcal/mol, and indeed, this structure once bridged is predicted to be the lowest-energy TS structure for the bridged *Z* case. And, it leads to the *S* stereoproduct. That is, bridging reverses the selectivity predicted for the *Z* ester, bringing it into line with the experimental observation. Other TS structures were again located, but were again found too high in energy to be kinetically important.

We note that the calculations discussed above did not attempt to include the effects of bulk solvation.⁹ However, the energy differences separating TS structures leading to *R* and *S* products are substantially larger than expected differences in solvation free energies for the various conformers. Thus, while including solvation with solvents like THF might modulate the relative energies by up to 1 or 2 kcal/mol

at most, they would not be expected to affect the qualitative conclusion of which stereoproduct should dominate under conditions of anion generation using organolithium reagents.

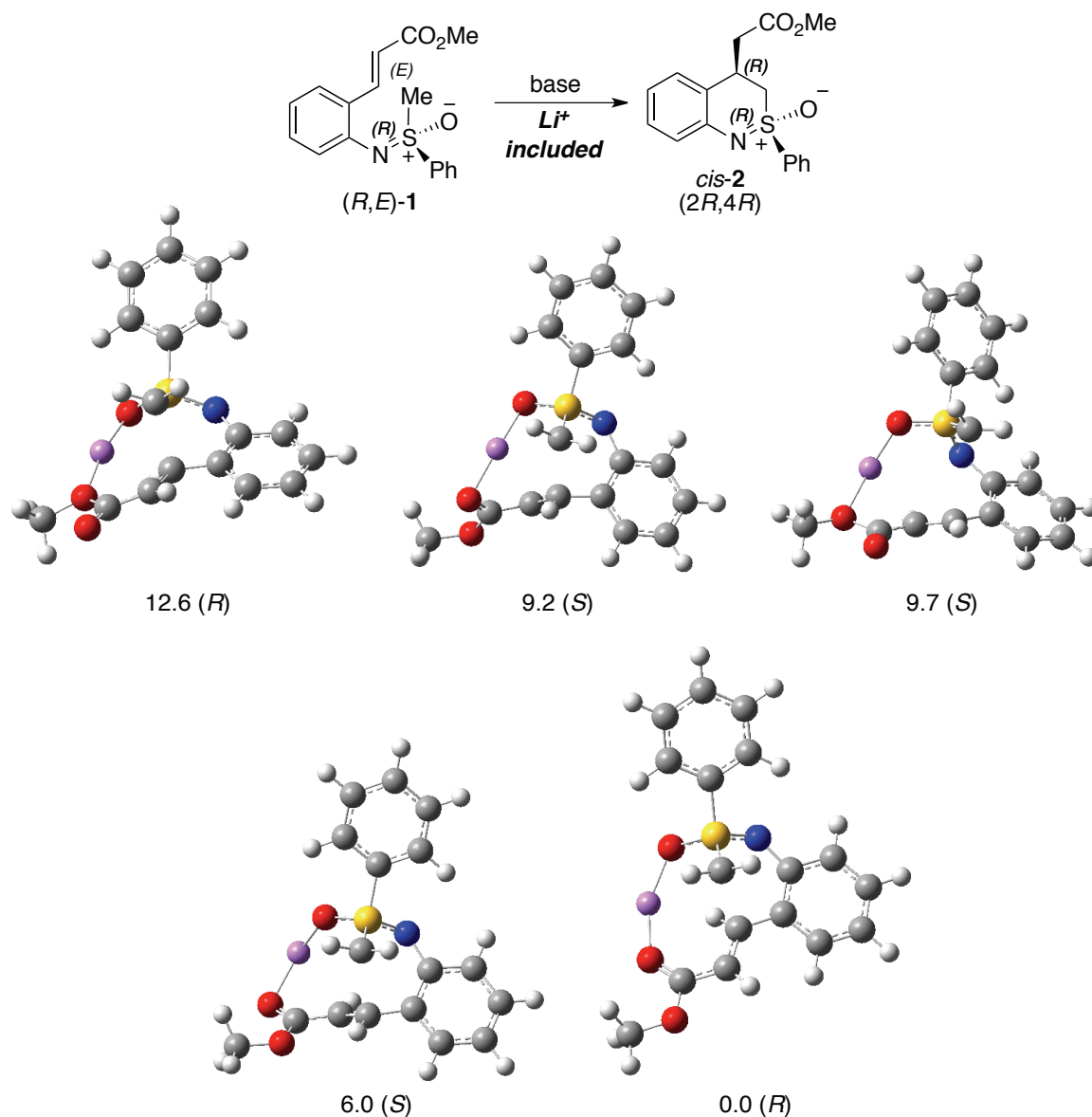


Figure 3. The TS structures for the cyclization of the carbanion of (R,E) -1 with coordinating Li^+ . The relative energies (kcal/mol) are shown along with the stereochemistry of the product at the newly formed stereogenic center. The lowest energy structure leads to $trans$ -2.

CONCLUSION

The intramolecular Michael addition of sulfoximines like (R,E) -X to α,β -unsaturated esters with an amide base is an important discovery in the chemistry of benzothiazines. Sulfoximines like (R,E) -1 exhibit complete stereoselectivity, essentially independent of reaction conditions. However, the intramolecular cyclization reaction of sulfoximine (S,Z) -1, while stereoselective, does not appear to be stereospecific, and the stereoselectivity depends on lithium cation being present in the system. This is corroborated

by computational studies and inclusion of solvents that selectively solvate lithium cations (e.g., HMPA and DMPU). Whether other metal salts (e.g., Mg^{+2}) might have a more profound effect on stereoselectivity is not known. This may become important in attempts to use the reaction in more complex ways, as in the creation of chiral quaternary centers.

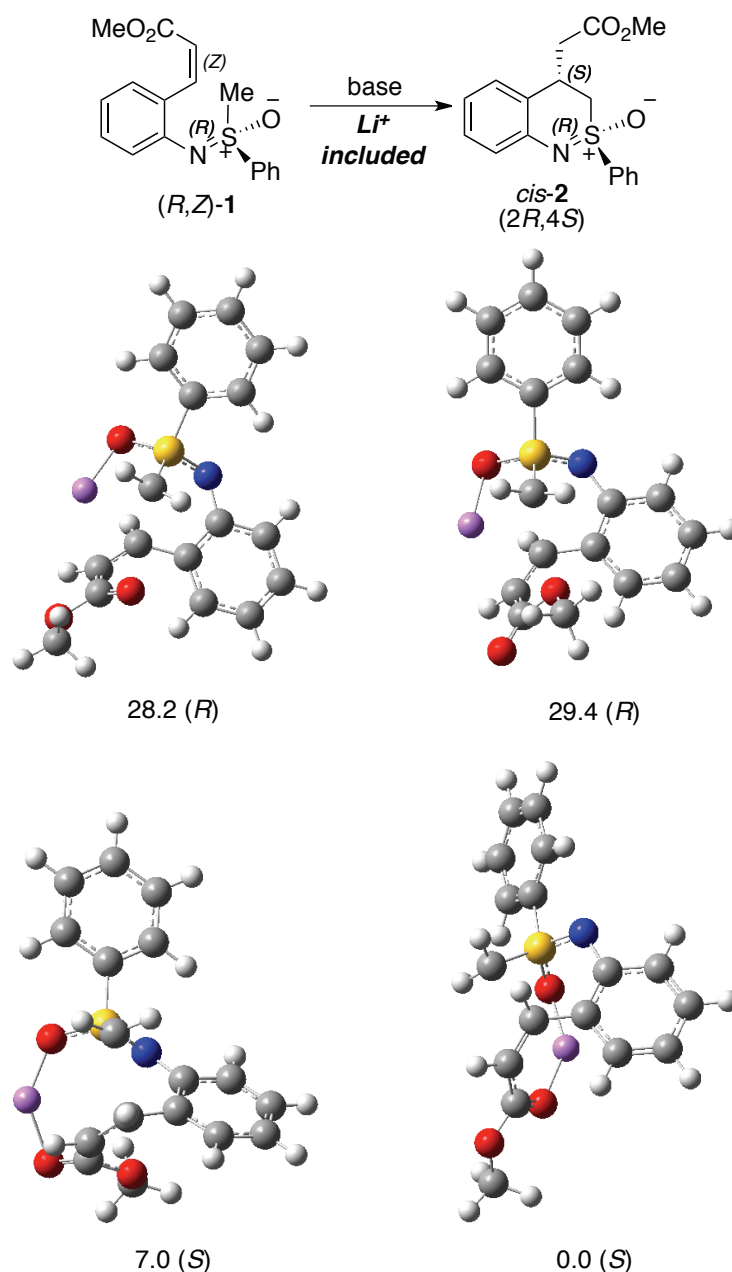


Figure 4. The TS structures for the cyclization of the carbanion of (R,Z) -1 with coordinating Li^+ . The relative energies (kcal/mol) are shown along with the stereochemistry of the product at the newly formed stereogenic center. The lowest energy structure leads to $trans$ -2.

EXPERIMENTAL

General Information

Glassware was oven dried (125 °C) and flame dried and cooled by continuous flow of dry argon. The reactions that involved organometallic reagents were carried out under anhydrous and oxygen-free conditions and the reagents were handled with glass gas tight syringes, rubber septa and argon balloons. THF were distilled over sodium metal and oxygen was removed by generation of a benzophenone ketyl. Liquid reagents were distilled prior to use and solid reagents were recrystallized or used directly from new commercial containers. Air and moisture sensitive reagents were handled with a dry nitrogen filled plastic glove bag. Crude reaction mixtures were concentrated by using a rotary evaporator attached to a water aspirator. Residual solvents were usually removed under reduced pressure using vacuum pump (approximately 1 mmHg). Analytical thin chromatography was performed on EM reagent 0.25 nm silica gel 60-F plates with F-254 indicator. Compounds were visualized under UV light.

Synthetic procedures

Procedure for the cyclization of sulfoximine with LiHMDS (Procedure A)

To 0.3 mL of THF in a 5 mL round bottom flask, was added a 93:7 mixture of sulfoximine (*S,Z*)-**1**: (*S,E*)-**1** (15 mg, 0.0473 mmol) at -78 °C. After stirring for 1 min, 1M LiHMDS (0.1 mL, 0.1 mmol, 2.1 equiv) was added dropwise. The progress of the reaction was monitored by TLC (66% Et₂O/Hexanes; R_f **1**: 0.5; R_f **2**: 0.45). After stirring for 30 min, **1** was consumed completely; the reaction mixture was quenched with MeOH, washed with brine, extracted with Et₂O (3 x 2 mL), washed with water, dried over MgSO₄, filtered and concentrated to afford a 59:41 mixture of *trans* **2** (2*S*, 4*R*) and *cis* **2** (2*S*, 4*S*). ¹H NMR analysis of the crude mixture was made and the product peaks were assigned based on the literature.¹

Procedure for the cyclization of sulfoximine by addition to LiHMDS (Procedure B)

To 0.3 mL of THF in a 5 mL round bottom flask, 1M LiHMDS (0.1 mL, 0.1 mmol, 2.1 equiv) was added. After stirring for 1 min, a 93:7 mixture of sulfoximine (*S,Z*)-**1**: (*S,E*)-**1** (15 mg, 0.0473 mmol) was added dropwise at -78 °C. The progress of the reaction was monitored by TLC (66% Et₂O/Hexanes; R_f **1**: 0.5; R_f **2**: 0.45). After stirring for 30 min, **1** was consumed completely, the reaction mixture was quenched with MeOH, washed with brine, extracted with Et₂O (3 x 2 mL), washed with water, dried over MgSO₄, filtered and concentrated to afford a 58:42 mixture of *trans*-**2** (2*S*, 4*R*) and *cis* **2** (2*S*, 4*S*). ¹H NMR analysis of the crude mixture was made and the product peaks were assigned based on the literature.¹

Procedure for the cyclization of sulfoximine with LDA (Procedure C)

To 0.958 mL THF in 5 mL round bottom flask was added diisopropylamine (21 μL, 0.151 mmol). After stirring at -20 °C for 5 min, 2.1 M *n*-butyllithium (70 μL, 0.151 mmol) was added dropwise. After 30 min,

the temperature was raised to 0 °C for 10 min, then LDA solution was added dropwise to $\geq 99\%$ **Z-1** (24 mg, 0.0757 mmol) in THF (0.958 mL) at -20 °C. The progress of the reaction was monitored by TLC as above. The mixture was stirred for 60 min, quenched with water, diluted with Et₂O (2 mL), washed with brine (2 mL), extracted with Et₂O (3 x 2 mL), washed with water (2 mL), dried over MgSO₄, filtered, and concentrated to afford a 91:9 mixture of *trans-2* (2*S*, 4*R*) and *cis-2* (2*S*, 4*S*). ¹H NMR analysis of the crude mixture was made and the product peaks were assigned based on the literature.¹

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