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Computational Investigations on the General Reaction Profile and Diastereoselectivity in Sulfur Ylide Promoted Aziridination

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Abstract: Mechanism and diastereoselectivity of sulfur ylide promoted aziridination reactions were studied by density functional theory with inclusion of solvent effects through the continuum solvation model. The general reaction pathway was modeled for the addition of substituted sulfur ylides ($Me_2S^+CH^-R$) to an aldimine ((*E*)-methyl ethylidenecarbamate, $MeHC{=}NCO_2Me$). The nature of the substituents on the ylidic carbon atom substantially affects the reaction profile. The stabilized (R = COMe) and semistabilized (R = Ph) ylides follow a *cisoid* addition mode leading to *trans* aziridines via *anti* betaine intermediates. The simplest model ylide (unstabilized, R = H) underwent *cisoid* addition in a similar fashion. In the case of stabilized ylides product diastereoselectivity is controlled by the barriers of the elimination step leading to the 2,3-*trans* aziridine, whereas it is decided in the addition step in the case of semistabilized ylides. The importance of steric and electronic factors in diastereoselective addition (**2** and **5**) and elimination (**5**) transition states was established. Comparison of results obtained with the gas-phase optimized geometries and with the fully optimized solvent-phase geometries reveals that the inclusion of solvent effects does not bring about any dramatic changes in the reaction profiles for all three kinds of ylides. In particular, diastereoselectivity for both kinds of ylides was found to be nearly the same in both these approaches.

Keywords: aziridination • density functional calculations • diastereoselectivity • reaction mechanisms • ylides

Introduction

Aziridine chemistry has attracted the attention of organic chemists primarily owing to their existence as subunits in many natural products and biologically active molecules.[1] Enantiopure aziridines are of current interest as enzyme substrates and enzyme inhibitors.[2] The ability of aziridines to undergo highly regio- and stereoselective ring-opening reactions gives them great value in organic synthesis.[3,4] While several protocols are available for the synthesis of structurally diverse aziridines,[5] stereoselective transformation often poses formidable challenges. Methods such as the use of chiral auxiliaries[6–8] and chiral catalysts[9–11] have been developed to address this issue. Among the plethora of methods available for their preparation, synthetic route via sulfur ylide intermediates have been remarkably successful in recent times.[12] High enantioselectivity and easy recovery of catalyst make this an attractive strategy for synthetic manipulations.

The catalytic asymmetric aziridination approach developed by Aggarwal and co-workers to synthesize enantiopure aziridines[13] utilizing chiral sulfur reagents was found to exhibit higher enantio/diastereoselectivities compared to the substrate-controlled methods.[14] Some representative examples of chiral sulfur catalysts (**A**, **B**, and **C**) employed in the enantioselective synthesis of aziridines and the corresponding enantiomeric excess of 2,3-*trans* diphenyl aziridines formed are shown in Figure 1.

The mechanism of aziridine formation is believed to proceed in a similar fashion to that of the popular Corey–Chaykovsky epoxidation reaction.[15–17] Earlier, we established that the diastereoselectivity in sulfur ylide mediated cyclopropanation could largely depend on the nature of ylidic substitution.[18] Note that the introduction of substituents on the imino nitrogen atom could have additional stereoelectronic effects. For instance, bulky substituents on the imino N atom are known to guide the product selectivity more towards the *cis* diastereomer.[19] In earlier reports on aziridines, Mimura and co-workers showed that 2,3-*cis* aziridines

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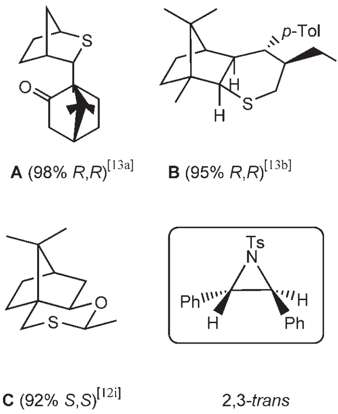
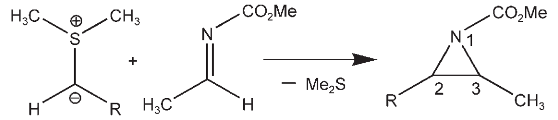


Figure 1. Chiral sulfur catalysts employed in enantioselective aziridination.

are thermodynamically more stable than their *trans* isomers when bulky alkyl (or aryl) sulfonyl groups are attached to the imino nitrogen atom.[19a,b] More recently, on the basis of MP2/6-31G**//RHF/6-31G** studies, the same group proposed that the hybridization of substituents on the imino nitrogen atom can also affect the relative orientations of the substituents on C2 and C3.[19c] Interestingly, sulfur ylide mediated reactions lead to thermodynamically less stable *trans* diastereomers. While experimental studies on this blooming synthetic protocol are increasingly being reported, attempts to gain insights into the reaction mechanism and the stereoselectivity process are not widely available.[20]

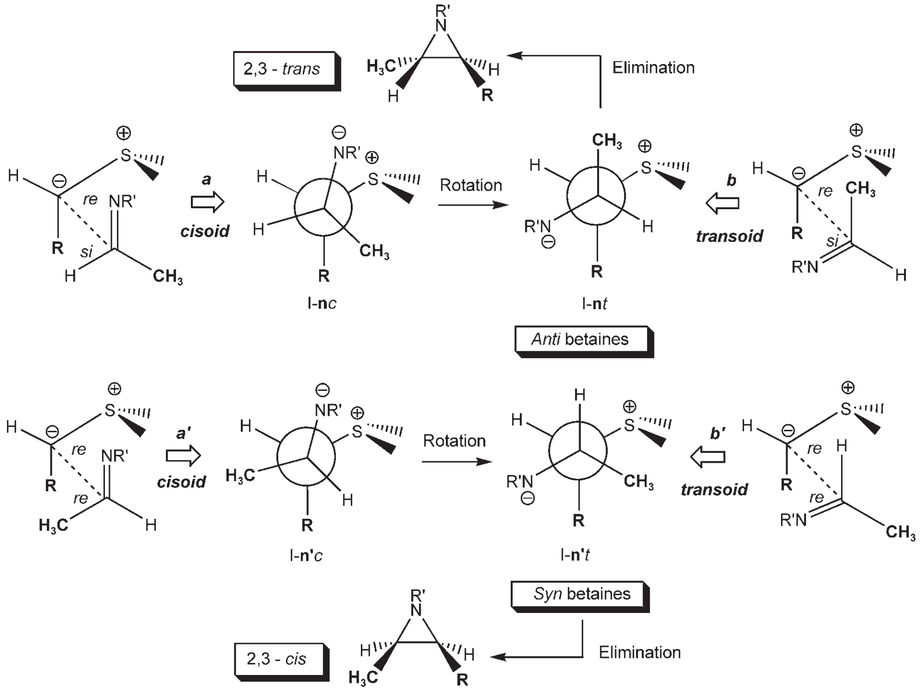
Increasing interest and the importance of sulfur ylide promoted aziridination encouraged us to carry out a detailed theoretical investigation on the mechanism with the immediate objective of unraveling the factors associated with stereoselectivity. Since the relative energies of diastereomeric transition states have a direct bearing on stereoselectivity, knowledge of stereoelectronic factors operating at the transition states is crucial to the overall understanding of such reactions. To this end, we chose to study the reaction between substituted ylides and an aldimine bearing a COOMe group on the nitrogen atom ((*E*)-methyl ethylidenecarbamate, $MeHC{=}NCO_2Me$, Scheme 1). The role of electronically different substituents with different stabilizing abilities on the nucleophilic ylidic carbon atom was studied. According to the nature of the substituents, these ylides are conveniently classified as unstabilized (**1**), semistabilized (**2**), and stabilized ylides (**3**–**5**).

Terminology: Five ylides **1**–**5** were considered (Scheme 1). *Cisoid* and *transoid* addition transition states in the C–C bond-forming step are denoted TS-***nc*** and TS-***nt*** for ylide ***n*** (***n*** = **1**–**5**); see Scheme 2 for further details of the nomenclature). The intermediate betaines are named I-***nc*** for *cisoid* and I-***nt*** for *transoid* orientations. Similarly, the transition state for *cisoid* to *transoid* rotation is designated TS-***n***R, and that for elimination as TS-***n***E. The product complex formed via elimination is termed PC-***n***. In the alternative *re*,*re* ap-



Ylide	Substituent (—R)
1	H
2	Ph
3	CO_2Me
4	COPh
5	COMe

Scheme 1. Aziridination reactions investigated in the present study.



Scheme 2. Different approaches of ylide/aldimine pairs and general reaction pathways leading to diastereomeric aziridines. Intermediates I-***nc*** and I-***nt*** respectively result from the *cisoid* (TS-***nc***) and *transoid* (TS-***nt***) addition transition states via *Re*,*Si* approach. Similarly, *re*,*re* approach yields I-***n'c*** and I-***n't*** betaine intermediates.

proach, the ylides, intermediates, and transition states are designated by **2′** through **5′**.

Results and Discussion

The present discussion is organized into three major sections. The stability and conformational features of ylides are presented first. The reaction between substituted ylides and aldimines is then discussed for three important classes of ylides. Finally, emphasis is placed on the stereoselectivity issues associated with these ylides. This is achieved with the help of detailed mechanistic investigations including bulk solvent effects by using the continuum solvation model. Comparisons with the corresponding gas-phase reaction profiles are also made.

Stability and conformation of ylides: The lower reactivity of ylides toward electron-deficient acceptors when substituted with carbonyl and ester groups is well known experimentally.[21] In spite of their popularity as useful reagents, quantitative estimates of stabilities of sulfur ylides are conspicuously absent. A simple approach to quantify the reactivity of ylides is in terms of proton affinity,[22] which is defined as the negative of heat of the corresponding protonation reaction. On the basis of the calculated proton affinities (PA) at the PCM(CH_3CN)/B3LYP/6-311G**//PCM(CH_3CN)/B3LYP/6-31G* level of theory, ylides follow the stability order R = H (**1**) < Ph (**2**) < CO_2Me (**3**) < COPh (**4**) < COMe (**5**).[23] Thus, **1** is the most reactive or least stable member of the present series of ylides. Based on the PA values and earlier experimental reports,[24,12k] we conveniently group these ylides as unstabilized (R = H) semistabilized (R = Ph), and stabilized (R = COMe, COPh, COOMe).

The disposition of groups around the pyramidal sulfur center can give rise to two major conformers for the ylide,[25] of which the *In* conformer (R group on the ylidic carbon atom is *syn* to the methyl groups on the sulfur atom) is of lower energy than the corresponding *Out* conformer (R and the methyl groups on the sulfur atom are *anti* to each other). The higher stability of the *In* conformer is due to the stabilizing hydrogen-bonding interaction between the methyl groups on the sulfur atom and the carbonyl oxygen atom (O4) of the R group (in **3**, **4**, and **5**) on the ylidic carbon atom.[25,26] In the case of ylide **2**, the energy difference between the two conformers is very small (0.21 kcal mol^{-1}), again in favor of the *In* form at the PCM(CH_3CN)/B3LYP/6-311G**//PCM(CH_3CN)/B3LYP/6–31G* level of theory.[27]

However, our results indicate that weak stabilizing interactions, as mentioned above for the cases of ylides **3**, **4**, and **5**, could be counterbalanced by steric interactions in various TSs and intermediates. Thus, the preference toward the *In* conformation may not always hold good for different TSs and/intermediates considered in this study (vide infra). Therefore, we considered both of these ylide conformers for further analysis.[28]

Reaction mechanism and diastereoselectivity: Important stationary points, such as intermediates and transition states, on the potential-energy surfaces were first identified in an effort to gain better insight into the reaction mechanism. Reaction between substituted ylides and aldimines leading to aziridines was studied by density functional theory with the B3LYP functional, both in the gas phase and in the condensed phase by using the polarizable continuum model (PCM). Various modes of approach between ylides and electrophiles that lead to diastereomeric products were examined by locating corresponding transition states along the reaction pathway. All key representations used in this study are summarized in Scheme 2. The betaine intermediates are designated as *syn* or *anti*, depending on the disposition of Me and R groups around the newly formed C−C bond. Further, the approach of ylide and imine is termed *cisoid* or *transoid* according to the dipole (S^+ and N^-) orientation.[29] The formation of *trans* and *cis* aziridines via *anti* and *syn* betaine intermediates was considered.

The approach of the ylide with its *Re* face on the *Si* face of the aldimine leads to an *anti* betaine, which on subsequent elimination yields the 2,3-*trans* product.[30] The initial approach between reacting partners can occur in *cisoid* (path ***a***) or *transoid* (path ***b***) modes (Scheme 2). In the latter mode, when the *Re* face of the ylide adds to the *Re* face of the aldimine, a 2,3-*cis* product is obtained via *syn* betaine on pathway ***a′*** or ***b′***. The other two possibilities, resulting from the *Si* face of the ylide approaching the aldimine, namely, *Si*,*Re* and *Si*,*Si* (pathways ***a*** and ***b***) result only in enantiomeric pairs of the above products, and hence are not considered in this study.

The *cisoid* arrangement of dipolar betaines can achieve greater electrostatic stabilization than the corresponding *transoid* form due to greater proximity between oppositely charged sulfur and nitrogen atoms (Scheme 2). While the initial attack of the ylide on imines is thus expected to proceed in a *cisoid* fashion, product formation ultimately requires an antiperiplanar disposition of the SMe_2 group and the imino nitrogen atom. This geometrical requirement can be achieved by rotation of the *cisoid* intermediate around the newly formed bond. Elimination of the SMe_2 group from the *transoid* intermediate then furnishes the product.

Computed activation barriers for all the above steps (i.e., addition, rotation, and elimination) leading to diastereomeric aziridines for various ylides (**1**–**5**) are summarized in Table 1.[31] Based on the activation energies, it is evident that the general reaction profiles for diastereomeric pathways (*Re*,*Si* and *Re*,*Re* approaches) are quite similar. As expected, the addition barriers increase gradually from **1** through **5**, almost linearly with the stability of the ylides. The rotational barriers around the C−C bond for ylides **1**–**5** indicate that *anti* betaines have slightly higher barriers than the corresponding *syn* betaines (vide infra). Elimination, on the contrary, exhibits opposite trends, in that barriers for *anti* betaines are slightly lower than for *syn* betaines for the present series of ylides.

Table 1. Relative energies [kcal mol^{-1}] computed at the PCM(CH_3CN)/B3LYP/6-311G**//PCM(CH_3CN)/B3LYP/6-31G* level of theory for the formation of *trans* and *cis* aziridines.[a]

Ylide	TS-*nc*/TS-*n′c*[b]	TS-*nt*/TS-*n′t*[c]	TS-*n*R/TS-*n′*R[d]	TS-*n*E/TS-*n′*E[e]
1[f]	−5.5[g]	−1.9[g]	−21.8 (8.8)	−18.6 (8.9)
2	1.8	4.0	−12.1 (9.4)	−13.4 (0.8)
2′	2.0	3.1	−15.4 (6.5)	−10.2 (5.5)
3	6.5	8.0	5.8 (10.8)	6.0 (7.0)
3′	7.4	8.6	−0.8 (3.4)	5.7 (6.0)
4[g]	8.2	13.3	9.2 (7.7)	8.9 (1.4)
4′[g]	10.4	10.3	7.7 (5.1)	11.5 (5.3)
5	8.1	10.4	7.8 (9.6)	9.2 (6.6)
5′	9.9	9.3	5.7 (7.5)	9.9 (8.1)

[a] Energies for the addition steps are relative to isolated reactants. [b] *Cisoid* addition. [c] *Transoid* addition. [d] Rotation (activation barrier with respect to the nearest intermediate I-*nc*/I-*n′c* is given in parentheses). [e] Elimination (activation barrier from the nearest intermediate I-*nt*/I-*n′t* is given in parentheses). [f] Ylide **1** lacks prochiral faces. [g] Relative energy at the PCM/B3LYP/6-311G**//B3LYP/6-31G* level.

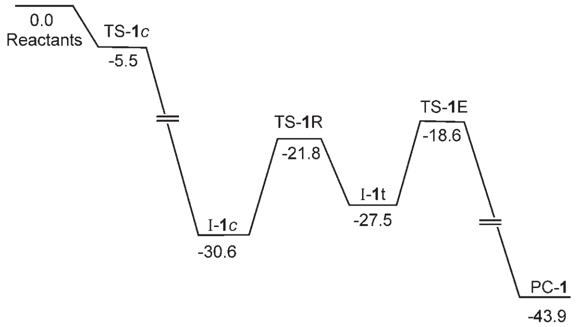


Figure 2. Reaction profile for aziridine formation from unstabilized ylide **1** (R = H) and imines. Δ*E* [kcal mol^{-1}] computed at the PCM(CH_3CN)/B3LYP/6-311G**//PCM (CH_3CN)/B3LYP/6-31G* level. (For TS-**1***c* the energy obtained at the PCM(CH_3CN)/B3LYP/6-311G**//B3LYP/6-31G* level is given). Energies are reported with respect to isolated reactants. PC-**1** refers to the product complex.

The computed activation barriers reveal that in the initial C–C bond-formation step *cisoid* addition is generally preferred over *transoid* addition for both stabilized and semistabilized ylides. The low-energy pathways for both stabilized and semistabilized ylides lead to *trans* diastereomers via *anti* betaines (see below). The next key step in aziridine formation is ring closure and concomitant elimination of SMe_2 from betaines. Among the present series, stabilized ylides **3**–**5** show higher barriers for elimination than semistabilized ylide **2** (Table 1).[32] Alternatively, *syn* elimination from the *cisoid* intermediate can also be envisaged. To examine the energetics associated with this process, we calculated *syn* elimination barriers for three representative ylides **1**, **2**, and **5**. We found that *syn* elimination has substantially higher barriers, as high as 30.9, 19.8, and 28.8 kcal mol^{-1}, respectively, for ylides **1**, **2**, and **5**. The corresponding values for *anti* elimination are only 6.4, 0.8, and 8.9 kcal mol^{-1}. Thus, the formation of *cis* aziridines from *anti* betaines (or *trans* aziridines from *syn* betaines) through a *syn* elimination pathway can safely be excluded.

As the relative energies of TSs are crucial to understanding the stereoselectivity in these reactions, it is interesting to examine the electronic and steric effects associated with these diastereomeric TSs along different pathways. Therefore, discussions on geometries and energies of key TSs obtained for different ylides are presented. Instead of providing details of all five ylides, we highlight the important findings for a representative set of unstabilized (R = H, **1**), semistabilized (R = Ph, **2**), and stabilized (R = COMe, **5**) ylides.

*Unstabilized ylide **1** (R = H)*: In the case of ylide **1**, all transition states and intermediates formed by reaction with the aldimine are lower in energy than the corresponding isolated reactants (Figure 2), and this indicates highly facile conversion to products.[33] This prediction is consistent with the stability order discussed above, that is, the ylide with R = H (**1**) is the most reactive in the present series.

The above profile demonstrates that addition of unstabilized ylide to imine proceeds without any barrier. Furthermore, the *cisoid* mode of addition is preferred over the *transoid* mode by 3.6 kcal mol^{-1}. The initial addition, which is highly exergonic and hence irreversible, leads to formation of betaine I-**1***c*. Subsequent rotation to I-**1***t*, however, could be reversible with a relatively high barrier (8.8 kcal mol^{-1}). The intermediate betaine is stabilized in the *cisoid* as compared to the *transoid* arrangement, which lacks Coulombic stabilization. Thus, the reaction profile for ylide **1** suggest that distinct betaine intermediates and corresponding transition states are involved before the product aziridine is generated. Diastereoselectivity in the case of this model ylide is not relevant owing to the absence of prochiral faces.

*Semistabilized ylide **2** (R = Ph)*: The reaction profiles for semistabilized ylide **2** for two different approaches (*Re*,*Si* and *Re*,*Re*) were constructed using the key stationary points on the potential energy surface (Figure 3). The addition TS is the highest point on both *syn* and *anti* pathways. All subsequent TSs and intermediates lie well below zero on the PES; this indicates facile product formation. Akin to unsta-

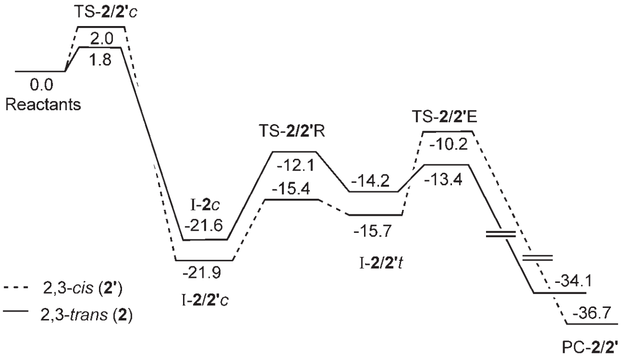


Figure 3. Reaction profiles for diastereomeric aziridine formation from semistabilized ylide **2** (R = Ph) and imines. Δ*E* [kcal mol^{-1}] computed at the PCM(CH_3CN)/B3LYP/6-311G**//PCM(CH_3CN)/B3LYP/6-31G* level. Energies are reported with respect to the isolated reactants. PC-**2**/**2′** refer to the diastereomeric product complexes.

bilized model ylide **1**, the addition step is highly exergonic for semistabilized ylide. The relative energy order for *cisoid* and *transoid* betaine intermediates of **2** are also similar to that of ylide **1**.

Interestingly, the most significant difference between semistabilized ylide **2** and ylide **1** is found in the addition step. For ylide **2**, the initial addition step involves a finite and low barrier. Here again, the *cisoid* addition TSs are lower in energy than the corresponding *transoid* addition TSs (by 2.2 and 1.1 kcal mol^{-1}, respectively, along the *anti* and *syn* pathways; Table 1). However, the energy difference between the two diastereomeric lower energy addition TSs is very small (0.2 kcal mol^{-1}), so that the addition step is nearly nonselective. Since the addition TSs are the highest energy points on the reaction profile, the relative energies between diastereomeric addition TSs are critical to the diastereoselectivity. Therefore, stereoelectronic factors responsible for poor selectivity warrant additional discussion. Keeping this in mind, we analyzed the diastereomeric TSs in greater detail (see below).

The optimized geometries for the addition TSs of **2** shown in Figure 4 reveal that Coulombic stabilization in the *cisoid* mode is much less pronounced than what is expected based on the orientation of charge centers (unfavorable steric interactions between methyl and phenyl substituents force the oppositely charged S and N centers to a distance as large as 4.0 Å, diminishing any stabilizing interactions that could possibly operate). When viewed along the C2−C3 bond, the eclipsed orientation of substituents around this newly forming bond seems to directly contribute to the relative energy difference between the diastereomeric TSs. The activation energies are generally higher when the larger phenyl ring eclipses with the electron-rich substituent on the carbamate (aldimine). The transition state TS-**2***c*, which has the most staggered arrangement of substituents, is energetically most favored. The unfavorable eclipsing interactions make the *transoid* TS-**2***t* the highest energy TS among four stereochemically different addition modes. Therefore, it is expected that the addition step is largely controlled by steric factors in the case of the semistabilized ylide (R = phenyl).

Inspection of the reaction profile in Figure 3 shows that the diastereoselectivity is exclusively controlled by the initial addition step. The rotational and elimination TSs lie well below zero and are therefore highly stabilized relative to the reactants. While torsional motion from *cisoid* to *transoid* conformer (betaine) has higher activation barriers on both *syn* and *anti* pathways, as compared to addition, this step can be deemed easily reversible. In the next step, elimination of the SMe_2 group, which is predicted to be highly facile, furnishes *cis*/*trans* aziridines. This prediction is in agreement with the experimentally observed 2,3-*trans* selectivity for the reaction of semistabilized ylides with various *N*-substituted benzaldimines.[12k,13a] However, the small energy difference between *syn* and *anti* addition TSs implies only low selectivity. We believe that improved selectivity in the addition step could be achieved by imparting greater steric encumbrance through suitable imino substitution (vide infra). These insights indeed offer a rationale for *trans* selectivity generally observed in sulfur ylide mediated reactions.

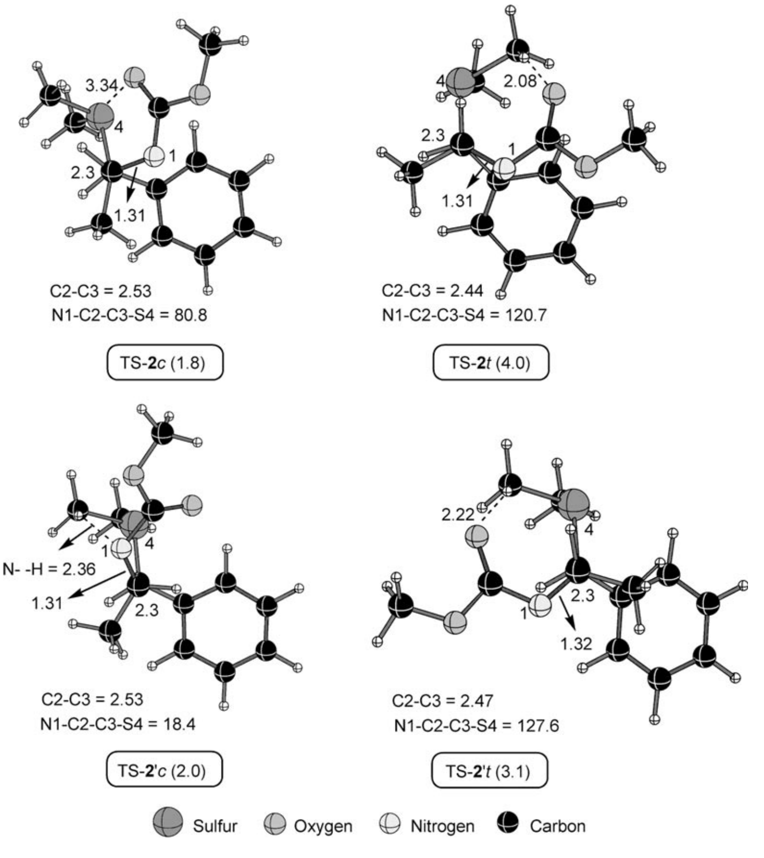


Figure 4. PCM(CH_3CN)/B3LYP/6-31G* optimized transition-state geometries (view along C2−C3 bond) and activation barriers (in parentheses) of *cisoid* and *transoid* addition TSs for semistabilized ylide **2**. Distances [Å], angles [°], and ΔE [kcal mol^{-1}] at the PCM(CH_3CN)/B3LYP/6-311G**//PCM(CH_3CN)/B3LYP/6-31G* level. Energies are reported relative to separate reactants.

Stabilized ylide **5** *(R = COMe)*: The computed activation barriers for the addition of stabilized ylides **3**–**5** to the aldimine (Table 1) are about two to three times higher than that predicted for the semistabilized ylide. Similar to the trends exhibited by semistabilized and unstabilized ylides, the lowest energy addition TS follows the *cisoid* mode of addition. However, along the *syn* betaine pathway, the *transoid* TS for ylide **5** is slightly preferred over the corresponding *cisoid* TS. Geometric factors favor the *transoid* TS (see below). Reaction profiles constructed by using the energies of the optimized TSs and intermediates provide an improved picture of various pathways available for stabilized ylides (Figure 5). In contrast to the previously discussed classes of ylides, all intermediates and TSs for stabilized ylides are destabilized relative to the separate reactants. While the formation of betaine intermediates is highly exergonic for ylides **1** and **2**, it is generally endergonic for stabilized ylides. The most striking feature of the energy profile for **5** is that the torsional and elimination TSs are comparable or even higher in energy than that of the addition step. The final products, 2,3-*cis* and 2,3-*trans* aziridines, are both predicted to be stable, with a modest preference for the *trans* product.

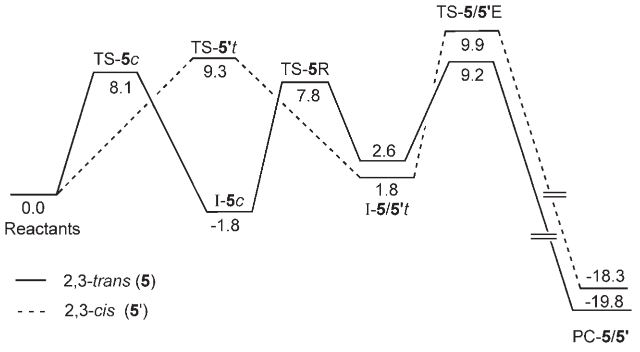


Figure 5. Reaction profiles for diastereomeric aziridine formation from stabilized ylide **5** (R = COMe) and imines. ΔE [kcal mol^{-1}] computed at the PCM(CH_3CN)/B3LYP/6-311G**//PCM(CH_3CN)/B3LYP/6-31G* level. Energies are reported with respect to the isolated reactants. PC-**5/5′** refer to the diastereomeric product complexes.

The energy profiles for ylide **5** indicate that the *cisoid* TS along the *anti* pathway (TS-**5***c*) is the most stable TS among other possible addition TSs. The next higher energy TS results from *transoid* addition in *Re*,*Re* fashion between ylide and aldimine (TS-**5′***t*). A difference in energy of 1.2 kcal mol^{-1} between these two lower energy TSs in favor of TS-**5***c* implies that the addition step is moderately selective towards *anti* betaine. The *cisoid* intermediate I-**5***c* thus formed must surmount the torsional barrier to attain the favorable *transoid* conformation and facilitate elimination. On the other hand, the *transoid* TS, being more stable along the *syn* pathway, can directly lead to the *transoid* betaine intermediate (I-**5′***t*) capable of elimination. Torsional interconversion between *cisoid* and *transoid* betaines could be reversible in the present case. Considering the higher energy of *transoid* betaines, the chance of reversal to the *cisoid* form is fairly high relative to the elimination process leading to the final product. For both *syn* and *anti* betaines, the forward reaction (elimination) has a higher barrier than the torsional motion. Therefore, elimination is the rate- and selectivity-determining step in the case of stabilized ylide **5**. As the addition and elimination TS energies are closer for ylide **5**, a contribution from the addition step can also be expected to influence stereoselectivity. Interestingly, the addition step favors the *anti* betaine pathway, which also eventually leads to a 2,3-*trans* product. The reaction of *syn* betaine is expected to be slower than that of *anti* betaine on the basis of the calculated barriers (both addition and elimination processes for the *syn* pathway require higher energies than the *anti* betaine pathway; Figure 5). Thus, a preference for 2,3-*trans* aziridine via *anti* betaines is expected over the corresponding 2,3-*cis* isomer.

The optimized transition-state geometries for key diastereomeric addition modes for ylide **5** leading to *anti* and *syn* betaine intermediates are shown in Figure 6. Among the different possible transition states for C−C bond formation, the *cisoid* addition mode for *anti* betaine is predicted to be

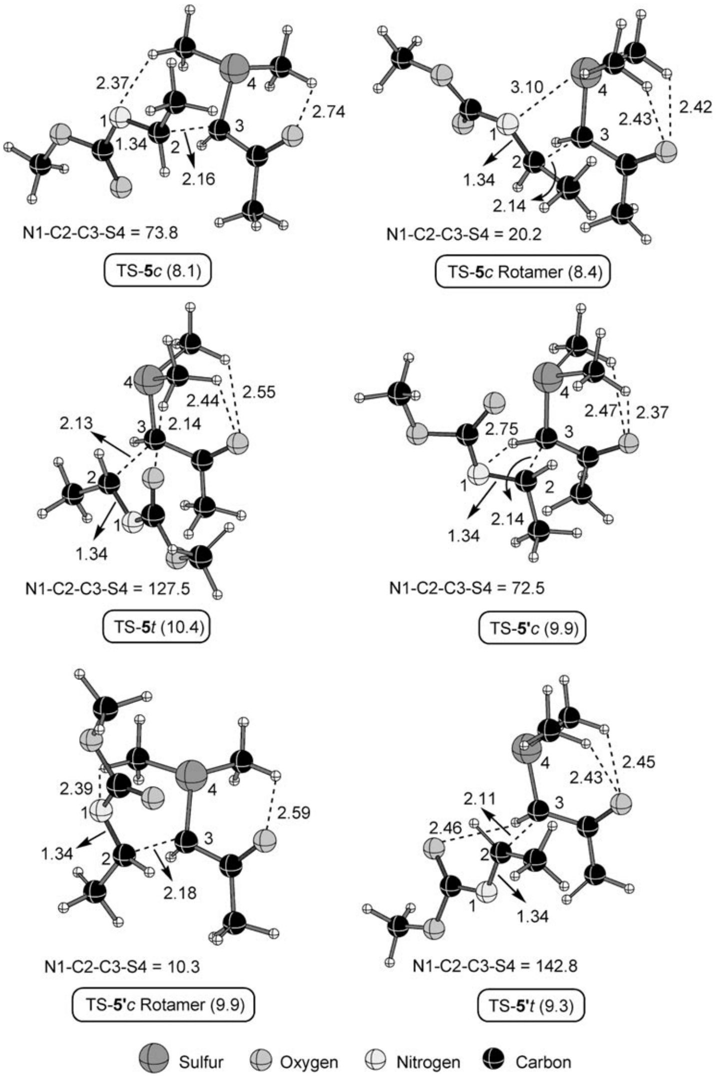


Figure 6. PCM(CH_3CN)/B3LYP/6-31G* optimized transition-state geometries and activation barriers (in parentheses) of *cisoid* and *transoid* addition TSs for stabilized ylide **5**. Distances [Å], angles [°], and ΔE [kcal mol^{-1}] at the PCM(CH_3CN)/B3LYP/6-311G**//PCM(CH_3CN)/B3LYP/6-31G* level. Energies are reported relative to separate reactants.

the lower energy transition state (TS-**5***c*).[34] Along the *syn* betaine pathway, the *transoid* addition TS (TS-**5′***t*) is lower in energy than the corresponding *cisoid* form by 0.6 kcal mol^{-1}. Closer inspection of TS-**5***c* reveals that the groups around the newly forming C2–C3 bond have minimum eclipsing interactions (Me-C2-C3-COMe dihedral angle is 68°) as compared to the next higher energy TS (another rotamer of TS-**5***c*, designated as TS-**5***c*-rotamer) with a Me-C2-C3-COMe dihedral angle of 24.1°. While the $S^+\cdots N^-$ electrostatic stabilization is expected to be quite low, as indicated by the N1-C2-C3-S4 dihedral angle (74°), additional hydrogen-bonding interaction between the developing charge on the N atom and a Me group of the SMe_2 moiety improves the stability of TS-**5***c* (N···H = 2.37 Å). In the case of TS-**5***t*, increasing eclipsing interactions between NCO_2Me and COMe groups are evident that result in a barrier as high 10.4 kcal mol^{-1}. In the case of the *syn* betaine pathway, a fine balance between steric and electronic factors results in closer energies for the addition TSs. For instance, the unfavorable eclipsing interaction between the bond pairs in TS-**5′***c*-rotamer (note that the N1-C2-C3-S4 dihedral angle of only 10° for TS-**5′***c*-rotamer leads to C2–N1/S4–C3, C3–H/Me–C2 and C2–H/C3–COMe eclipsing interactions) is balanced by stabilizing weak N···H and O···H interactions. Hydrogen bonding between the ylidic hydrogen atom and O of NCO_2Me helps to lower the energy of TS-**5′***t*, despite its having a generally less favored *transoid* orientation.[16,17a] Similar kinds of weak interactions are also found to stabilize other TSs and intermediates (vide infra). The developing C–C bond lengths (C2–C3) in stabilized ylides are slightly shorter (2.1–2.2 Å) than that of the semistabilized ylide (ca. 2.5 Å), probably due to the decreased steric demand around the newly forming bond in **5**. Furthermore, the achiral nature of the ylide and relatively smaller substituents on the sulfur atom do not offer any noticeable bias toward *syn* or *anti* intermediates. The low selectivity in the initial addition step, therefore, is not surprising.

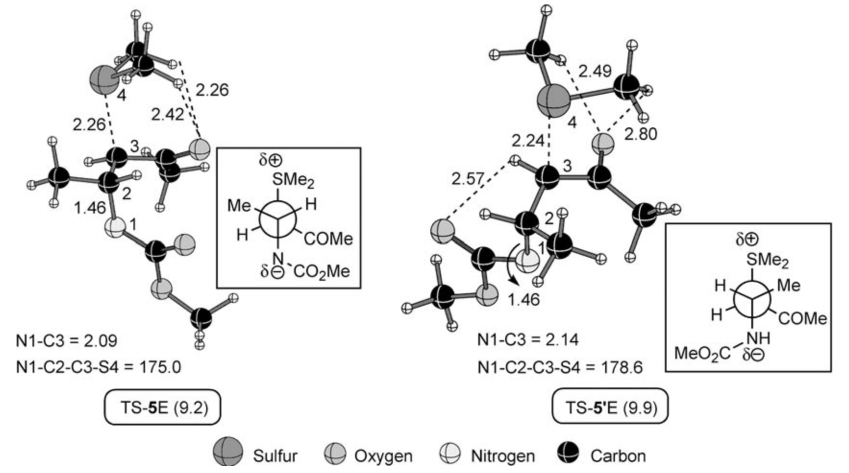


Figure 7. PCM(CH_3CN)/B3LYP/6–31G* optimized transition state geometries and activation barriers (in parentheses) of diastereoselective elimination TSs from *anti* and *syn* betaines for stabilized ylide **5**. Distances [Å], angles [°], ΔE [kcal mol^{-1}] at the PCM(CH_3CN)/B3LYP/6-311G**//PCM(CH_3CN)/B3LYP/6-31G* level. Energies are reported relative to separate reactants. A schematic representation of these TSs is provided in the inset.

Examination of the energy profiles for stabilized ylide (**5**) leading to *cis* and *trans* diastereomers (Figure 5) reveals that the barriers for the rate-determining elimination step favor the *trans* diastereomer. Selectivity in the addition step is quite low due to the closely spaced diastereomeric TSs. Furthermore, reversible torsional motion and lower barrier for the addition step suggest that diastereoselectivity should entirely rely on the ensuing elimination TSs.[35] The transition state for ring closure from the *anti* betaine (TS-**5**E) is moderately favored (0.7 kcal mol^{-1}) over that from the *syn* betaine. The computed energy profile therefore suggests that a low selectivity in favor of 2,3-*trans* aziridine is possible in the case of stabilized ylides.

The optimized geometries of elimination transition states that hold the key to diastereoselectivity are shown in Figure 7. Sterically, TS-**5**E is favored over TS-**5′**E. While the methyl and COMe groups (respectively on C2 and C3) are on the same side in TS-**5′**E, they are as far away as possible in TS-**5**E, making it more stable. At the same time, additional O(carbamate)···H(ylide) stabilizing interaction (2.57 Å) in TS-**5′**E helps to minimize the energy difference between these two diastereomeric TSs. The orientations between the internal nucleophilic nitrogen atom and the leaving group (SMe_2) are nearly the same in both diastereomeric transition states (difference in N1-C2-C3-S4 dihedral angles between TS-**5**E and TS-**5′**E is as small as 3.6°). This analysis shows that TS-**5**E is favored mostly on steric grounds, and therefore sterically controlled diastereoselectivity is expected to operate in the case of stabilized ylides considered here.

Interesting details emerge when the predicted trends are compared with available experimental reports. It is known that the role of substituents on the aldimine nitrogen atom is critical to the overall diastereoselectivity in aziridination reactions. In the present investigation, though a 2,3-*trans* preference for aziridine formation is predicted on the basis of the stereoelectronic factors operating in the elimination TSs, this trend is at variance with the experimentally observed diastereoselectivity with amide-stabilized ylides.[12k] While a direct comparison is not justifiable owing to the differences in imino substitution, it is worth noting that diastereoselectivity is closely linked to the nature of the imino substituents. In concurrence with the above argument, benzaldimines bearing *N*-methoxycarbonyl substituents are known to give *trans* diastereoselectivity when reacting with a semistabilized ylide (R = Ph).[12i] In another study, *cis* diastereoselectivity was observed when *N*-tosyl-substituted imines were employed as electrophiles with stabilized ylides (R = CO_2Et, $CONEt_2$).[12k] Therefore, it is reasonable to conclude that with the chosen electrophile our results predicting 2,3-*trans* selectivity for both stabilized and semistabilized ylides are quite justifiable.

Comparison of gas- and solvent-phase optimized geometries and energies: Intermediates and transition states along the reaction path are polar and involve notable charge separation. The effect of solvents on the predicted geometries and energies is therefore expected to be crucial. In the case of reactions involving dipolar species, inclusion of solvent effects can modify reaction profiles,[36] and in some cases even change the overall reaction pathway predicted by gas-phase calculations.[37] For instance, Brandt et al. demonstrated that inclusion of solvent effects (through single-point solvation calculations) could change the rate-determining step in the Horner–Wadsworth–Emmons reaction from the ring-closure step to the addition step.[37a] These issues have been considered in ylide-mediated epoxidation reactions,[17a,32] as well as in other reactions involving polar TSs.[38] Interestingly, a number of examples demonstrate the success of gas-phase geometries in accurately reproducing experimental stereoselectivities.[39] Hence, we believe that a comparison of results obtained by gas-phase calculations with those of solvent-phase optimizations is appropriate here.

From the five ylides **1**–**5** considered for gas-phase optimization studies, representative unstabilized (**1**), semistabilized (**2**), and stabilized (**5**) ylides were chosen for further discussion. All stationary points on the PES were subjected to full geometry optimization at the PCM/B3LYP/6-31G* level and energies were subsequently refined by using a flexible basis set within a solvent continuum (acetonitrile).[40] The agreement between the energies obtained for the gas-phase geometries[41] and those for the fully optimized solvent-phase geometries is fairly good. The energy profile for model ylide **1** is shown in Figure 8 (for profiles for semistabilized and stabilized ylides, see Figures S6 and S7). While there are minor variations in the stabilities of intermediates and TSs in dielectric continuum, the predicted trends remain the same as with the gas-phase geometries.

The only noticeable difference between the results obtained with fully optimized geometries in the continuum dielectric and the gas-phase geometries was found for unstabilized ylide (**1**). The stability of the betaine intermediate given by the optimized geometry in the solvent phase differs from that obtained by single-point solvation calculations on the gas-phase geometries. The gas-phase calculations predict isoenergetic *cisoid* and *transoid* betaine intermediates (26.6 $kcal\,mol^{-1}$). Inclusion of solvent effects results in stabilization of the *cisoid* betaine relative to the *transoid* intermediate. This in agreement with the general prediction that *cisoid* betaines are more stable than their *transoid* counterparts.[16,17a] Now the *cisoid* intermediate is 3.1 $kcal\,mol^{-1}$ more stable than the *transoid* intermediate. Another feature of ylide **1** is that the TSs for rotation and elimination do not exhibit any significant variation relative to the gas-phase profile.

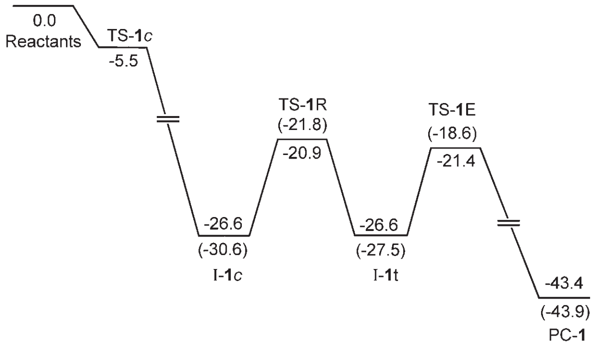


Figure 8. Reaction profiles for aziridine formation from unstabilized ylide **1** (R = H) and imines. ΔE [$kcal\,mol^{-1}$] computed at the PCM(CH_3CN)/B3LYP/6-311G**//B3LYP/6-31G* level. The corresponding energies obtained at the PCM(CH_3CN)/B3LYP/6-311G**//PCM(CH_3CN)/B3LYP/6-31G* level are provided in parentheses. Energies are reported with respect to the isolated reactants. PC-**1** refers to the product complex.

The reaction profile constructed by using the calculated energetics for ylides **2** and **5** (see Figures S4 and S5 in the Supporting Information) also reveals the concurrence between the gas-phase results[41] with those obtained with inclusion of continuum solvation effects. As noted above, here again, the rate-limiting step for ylide **2** is the initial addition. Furthermore, the predicted diastereoselectivity calculated by using the relative energies of the addition transition states remains almost the same with the gas-phase and solvent-phase optimized geometries (0.1 and 0.2 $kcal\,mol^{-1}$ respectively). Thus, it is apparent that geometry optimization in continuum solvent does not offer any direct advantage over the single-point calculations on the gas phase geometries.

In analogy with the above discussion on the semistabilized ylide, stabilized ylides also behave in a similar manner in the gas and solvent phases. Diastereoselectivity is dependent on the elimination barriers, even though energy difference between diastereomeric TSs is reduced to 0.4 $kcal\,mol^{-1}$ when using the gas-phase geometries, from 0.7 $kcal\,mol^{-1}$ obtained with continuum solvent effects. Thus, it is evident that these small energy differences lead only to a low diastereoselectivity, irrespective of the method used for the geometry optimization, that is, whether in the gas phase or in the solvent phase. Addition and torsional TSs, as well as intermediate betaines, again reveal similar trends that are predicted by solvent optimization.[42]

Thus, our results indicate that the incorporation of solvent effects in geometry optimization does not lead to any significant enhancement in diastereoselectivity for both kinds of ylides. Additionally, optimized energies and geometries of various stationary points on the gas-phase and solvent-phase PESs also exhibit similar trends.[42] The only exception is the highly reactive ylide **1**, where the different stabilities of betaine intermediates are clearly emphasized by the inclusion of solvent effects, while gas-phase results leave them isoenergetic. Therefore, we believe that the gas-phase optimization using the B3LYP functional in combination with 6-31G* basis set (followed by single-point solvation calculations) is accurate enough to address the selectivity and mechanistic details of sulfur ylide promoted aziridination reactions.

Conclusion

Our analysis of the general reaction profile for aziridination indicated a *cisoid* mode of attack on the aldimine by stabilized, semistabilized, and unstabilized ylides. Inspection of transition-state geometries revealed that steric factors are more pronounced than electronic factors in favoring one of the addition modes (*cisoid* or *transoid*). In the cases of both stabilized and semistabilized ylides, the weak hydrogen-bonding interactions between the electronegative atoms (N or O) on the carbamate moiety with the H atoms (ylidic H or methyl substituents on the SMe_2 group) helps keep the energy differences between diastereomeric TSs low. In the case of the semistabilized ylide, a low diastereoselectivity toward 2,3-*trans* product was predicted. The 2,3-*trans* diastereoselectivity was found to depend on the relative energies of the elimination transition state with stabilized ylides. Interestingly, the energetics obtained by using the gas-phase optimized geometries and those within the solvent continuum for various TSs and intermediates were found to be in very good agreement with each other. The inclusion of solvent effects by means of single-point energy evaluations on the gas-phase geometries in general does not result in any significant modifications in the predicted diastereoselectivities, both in the case of stabilized and semistabilized ylides. Thus, it is reasonable to conclude that the gas-phase geometry optimization followed by single-point energy evaluation using flexible basis sets can give fairly good estimates of the mechanism and stereoselectivity in sulfur ylide promoted aziridination reactions.

Computational Details

All calculations were performed with the B3LYP density functional method[43] by using the Gaussian suite of quantum chemical programs.[44] Geometry optimizations of intermediates, transition states, reactants, and products in solution phase were carried out at the B3LYP/6-31G* level of theory by using the self-consistent reaction field approach with the polarizable continuum model (SCRF-PCM) as implemented in Gaussian 03 (default options).[45]Geometry optimizations in the gas phase were performed at the B3LYP/6-31G* level using Gaussian 98 and Gaussian 03. Stationary points on the respective potential-energy surfaces were characterized at the same level of theory by evaluating the corresponding Hessian indices. Careful verification of the unique imaginary frequencies for transition states was carried out to check whether the frequency indeed pertains to the desired reaction coordinate. Intrinsic reaction coordinates (IRC) were calculated to authenticate all transition states.[46] Single-point energies for gas-phase and solvent-phase optimized geometries were calculated using a more flexible triple-ζ-quality 6-311G** basis set in acetonitrile continuum by employing the SCRF-PCM method in Gaussian 03. This energy in solution ($G_{\text{solvation}}$, denoted as E in the text) comprises electronic energy of the polarized solute, electrostatic solute–solvent interaction energy, and nonelectrostatic terms corresponding to cavitation, dispersion, and short-range repulsion.[45] Activation barriers refer to energy of activation obtained as the energy difference between isolated reactants and the corresponding transition-state structures.

Optimized Cartesian coordinates (solution phase and gas phase) and total electronic energies, single-point energies at the PCM(CH_3CN)/B3LYP/6-311G** level, and full citations of Gaussian 98/Gaussian 03 (ref. [44] in the text) are provided in the Supporting Information.

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[25] See Figure S1 in the Supporting Information for representative structures of *In* and *Out* conformers.

[26] The relative energies of *In* and *Out* conformers for **1**–**5** are provided in Table S2 in the Supporting Information .

[27] The closer energies of *In* and *Out* forms for ylide **2** were also noted previously by Lindvall and Koskinen.[16b] They found that the unfavorable interaction between the lone pair on sulfur and phenyl H destabilizes the *Out* conformer, while the steric interaction between the phenyl group and the methyl hydrogen atoms increases the energy of the *In* conformer.

[28] In an attempt to sample different conformational possibilities near stationary points such as minima and transition states, we searched the PES along the *syn* and *anti* pathways by rotation of the methyl groups attached to the sulfur atom (leading to *In* and *Out* forms, as stated earlier). Whereas the *cisoid* pathway resulted in minima/TSs corresponding to both *In* and *Out* rotamers of ylides, only one lowest energy geometry was found for the *transoid* pathway in most cases.

[29] When viewed along the newly formed C−C bond, if S^+ and N^- are on the same side: *cisoid*, and when S^+ and N^- are on opposite sides: *transoid*.

[30] Orientation of Me and R groups is more apparent in the *transoid* intermediate, after rotation around the newly formed C−C bond.

[31] The data in Table 1 correspond to low-energy isomers of TS/intermediates (optimized Cartesian coordinates and energies of different conformers of these intermediates and TSs are provided in the Supporting Information). For elimination TSs, we noticed that the possibilities for bond rotation are quite limited by the requirement of antiperiplanar orientation between the internal nucleophilic nitrogen atom and the leaving group (SMe_2). Thus, only those intermediates which are stabilized by weak intramolecular interactions (along with the desired antiperiplanar orientation) can facilitate elimination. Similar restrictions apply to the torsional TSs as well, and therefore only a single TS was found along the *anti* pathway. However, we could locate additional torsional TSs along the *syn* pathway for ylides **2**, **3**, and **5**. Unless otherwise specified, the geometries reported in the text pertain to the lowest energy structure obtained through this approach. Relative energies of intermediates and product complexes optimized in the solvent phase and in the gas phase are provided respectively in Tables S3 and S5.

[32] This is in agreement with an earlier report on the addition of ammonium ylides to aldehydes: R. Robiette, M. Conza, V. K. Aggarwal, *Org. Biomol. Chem.* **2006**, *4*, 621.

[33] We could not locate the addition TSs for ylide **1** on the PES when employing the continuum solvation model. Therefore, single-point solvation energies computed at the PCM(CH_3CN)/B3LYP/6-311G** level on the B3LYP/6-31G* optimized geometries are reported for TS-**1***c* and TS-**1***t*. Similar situations for model ylides are known in the literature for sulfur ylide promoted epoxidation.[17a]

[34] Corresponding to the *In* and *Out* geometries of the ylide, we obtained two *cisoid* addition TSs each along the *anti* and *syn* pathways (the additional *cisoid*/*transoid* TSs thus obtained by rotation of SMe_2 groups is termed as "TS-**n***c*/TS-**n***t*-rotamer" in the text). However, in the *transoid* addition mode, TS search was fruitful only with the *In* conformer. Thus, a total of six addition TS (C−C bond formation) were identified for **5**. Data presented in Table 1 refer only to the lower energy isomers arising from *cisoid* and *transoid* modes.

[35] However, smaller energy differences predicted between the elimination and addition TSs in the cases of ylides **4** and **5** are reversed with ylide **3**. Here, addition TSs are slightly higher in energy and the slowest on the PES (energy profiles for ylides **3** and **4** are provided respectively as Figures S2 and S3 in the Supporting Information).

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[40] See Computational Details for full details of these calculations.

[41] Note that energies obtained by using the gas-phase geometries, as mentioned in the text, refer to single-point solvation energies ob-

tained at the PCM(CH_3CN)/B3LYP/6-311G** level on the gas phase (B3LYP/6-31G*) geometries.

[42] The gas-phase optimized geometries of selected addition (ylides **2** and **5**) and elimination TSs (ylide **5**) are provided respectively in Figures S4 and S5 in the Supporting Information. Activation barriers and relative energies of various TSs are summarized in Table S4 in the Supporting Information.

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