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Enantio- and Diastereoselectivities in Chiral Sulfur Ylide Promoted Asymmetric Aziridination Reactions

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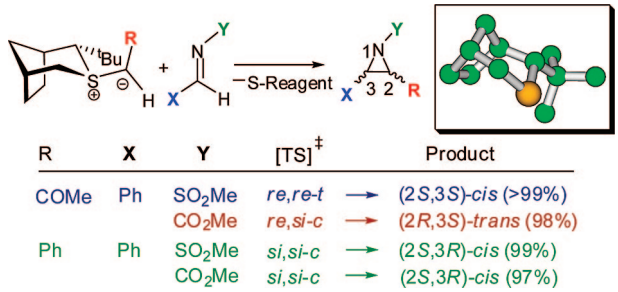

Density functional theory investigation on the factors controlling enantio- and diastereoselection in asymmetric aziridination reaction by the addition of chiral bicyclic sulfur ylides to substituted aldimines is presented. High levels of enantioselection are predicted toward the formation of (2*S*,3*S*)-*cis* and (2*R*,3*S*)-*trans* aziridines by the addition of stabilized ylide (R = COMe) respectively to SO_2Me and CO_2Me protected aldimines. Similarly, high *%ee* is predicted for the formation of (2*S*,3*R*)-*cis* aziridines from semistabilized (R = Ph) ylide. Moderate to high levels of diastereoselectivity is noticed as well. The present study highlights that a correct prediction on extent of enantioselection requires the knowledge of the activation barriers for elementary steps beyond the initial addition step. In the case of stabilized ylides the ring-closure (or elimination of sulfur compound) is found to be crucial in controlling enantio- and diastereoselection. A cumulative effect of electronic as well as other weak interactions is identified as factors contributing to the relative energies of transition states leading to enantio- and diastereomeric products for the stabilized ylide addition to aldimines. On the contrary, steric control appears quite dominant with semistabilized ylide addition. With the smallest substituent on ylide (R = Me), high enantioselectivity is predicted for the formation of (2*R*,3*R*)-*trans* aziridines although the *%de* in this case is found to be very low.

Introduction

Aziridines are important three-membered heterocycles that received considerable attention from the synthetic organic community over past several decades.[1] The antitumor and antibiotic properties of aziridine containing compounds are of high significance.[2] Apart from their biological importance, the ring strain associated with these compounds makes them highly reactive, particularly toward ring-opening reactions. Thus, further synthetic manipulations and functional group transformations have been attempted.[3] Regio- and stereoselective ring-opening reactions such as the synthesis of nonnatural amino acids and antibiotic drug precursors are important examples in the above category.[4] Chiral aziridines can act as ligands, chiral auxiliaries as well as a source of chirality in asymmetric

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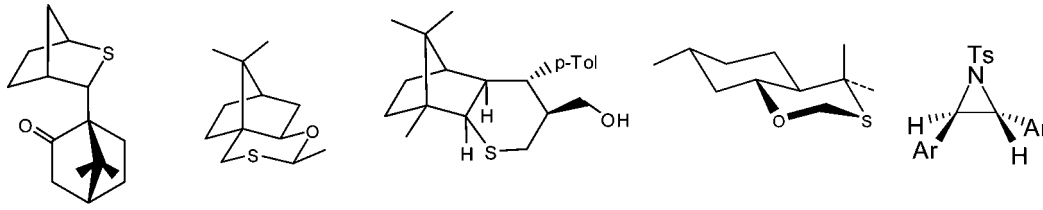
CHART 1. Chiral Sulfur Reagents Employed in the Asymmetric Synthesis of 2,3-*trans* Diphenyl Aziridine[a]



A[14 b] **B**[14c] **C**[16a] **D**[16c] 2,3–*trans*

[a] Corresponding citations are also included.

transformations.[1,5,6] Owing to their versatile applications, there has been a continued interest toward developing easy and efficient methods to access chiral aziridines.

Stereoselective synthesis of aziridines can be achieved in several ways.[2,7] While Darzen's type addition to imines[8] or sulfinimes[9] is known to yield diastereoselective products, methods employing chiral auxiliaries[10,11] or chiral catalysts[12] have been successful in the enantioselective synthesis of aziridines. Insertion of nitrenes to alkenes as reported by Evans, Jacobsen and Katsuki offers a highly enantioselective protocol toward aziridination, albeit with limited substrate scope.[12] Alternative catalytic methods employing carbene intermediates have also been developed to achieve asymmetric synthesis of these compounds.[13] However, enantioselection was low in this case. In the recent years, the asymmetric catalytic sulfur ylide methodology independently developed by Aggarwal[14] and Dai[15] has emerged as a highly efficient methodology toward realizing chiral aziridines.[16] The promising features of this strategy include high enantio and diastereoselectivity, catalyst reusability and a wider range protecting groups on imine. A representative set of chiral sulfur reagents employed in the asymmetric synthesis of aziridines is provided in Chart 1.

Following Corey's seminal work on the synthetic utility of oxosulfonium and sulfonium ylides,[17] a few ab initio as well as DFT studies toward exploring the mechanistic details of sulfur ylide mediated reactions have appeared in literature.[18,19] Inspired by the remarkable success of asymmetric S-ylide methodology, we have earlier studied the mechanistic and selectivity issues of ylide mediated cyclopropanation[20] and aziridination[21a] reactions. The above studies conveyed that any of the three major steps involved in ylide mediated reactions, namely, the addition of sulfur ylide to the electrophile, rotation of the resulting betaine intermediate (to achieve the antiperiplanar orientation between the leaving group ($-SR_2$) and the internal nucleophile), or the elimination, could be crucial to the diastereoselection and hence influence the *cis*/*trans* selectivity of the final product.

Earlier studies have indicated that the stereoselectivity could vary depending on the substituents on the ylidic carbon as well as on the nature of the electrophile. For instance, density functional theory studies revealed that *cisoid*−*transoid* interconversion of betaines via torsional motion can be the rate-limiting step in epoxidation (in the case of addition of semistabilized ylide to aldehyde)[19a] and cyclopropanation (in the case of addition of stabilized ylide to α,β−unsaturated carbonyl compound).[20] Interestingly, the diastereoselection in the reaction between stabilized and semistabilized ylides with

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TABLE 1. Overview of Diastereoselectivity in Sulfur Ylide Promoted Reactions

product	nature of ylide (**R**)	selectivity decidingstep	extent of diastereoselection	ref
epoxide	semistabilized (Ph)	rotation	moderate	19a
	stabilized ($CONMe_2$)	elimination	high	19b
aziridine	semistabilized (Ph)	addition	low	19c
	stabilized (COMe, CO_2Me)	elimination	low	21a
cyclopropane	semistabilized (Ph)	addition	moderate	20
	stabilized (COMe)	rotation	high	

aldimine toward forming aziridines, is respectively controlled by the elimination and addition barriers.[19c,21] These details are summarized in Table 1.

Interesting trends can be gleaned from the above table that the stereoselectivity determining step could vary depending on the electrophile (acceptor) even with the very same ylide. For instance, whereas the reaction of semistabilized ylide with aldehyde proceeds via the rate-limiting torsional motion (from *cisoid* to *transoid* betaine) in epoxidation, the initial addition to an imine or an unsaturated carbonyl compound is the rate-limiting step respectively for aziridination and cyclopropanation reactions (Table 1). In other words, the addition of semistabilized ylide to aldehydes is more facile than to imine or enone. While this is not a surprising observation considering the nature of acceptors, it additionally indicates an effective Coulombic stabilization (between developing S^+ and O^-) in the *cisoid* addition mode. Conversely, in aziridination and cyclopropanation reactions, the developing charges get delocalized into the substituents attached to the acceptor double bond, resulting in diminished Coulombic stabilization.

Such useful observations have mainly emerged through the theoretical investigations on diastereoselectivity in these reactions. In addition, experimental studies on the diastereoselectivity of aziridination[14d] and epoxidation[22] reactions are reported in literature. Aggarwal and co-workers conducted crossover experiments by independent generation of intermediate betaines (from the corresponding sulfonium salts) in the presence of a more reactive aldehyde (epoxidation) or imine (aziridine). The authors have found that semistablized ylides added irreversibly to imine (i.e., no incorporation of the more reactive imine) whereas stabilized ylide addition was reversible.[14d] It was therefore concluded that the stereoselectivity in semistabilized ylide is decided by the addition step, and by ring-closure step for stabilized ylide.[14d] In the case of epoxidation reaction, cross-over experiments indicated that *anti* betaines added irreversibly to aldehydes while *syn* betaine addition was partially reversible.[22a]

Although very recent reports provide mechanistic insights on sulfur ylide promoted diastereoselective expoxidation, aziridination and cyclopropanation, efforts directed toward understanding enantioselective versions of these reactions are not widely available till date. In a rare report Goodmann et al.[23] have studied a C_2-symmetric sulfonium ylide mediated enantioselective epoxidation using the DFT method. It should be reckoned that the use of chiral sulfur ylides could facilitate enantioselective formation of products apart from being diastereoselective. To obtain improved insights on how diastereo and enantioselectivities arise in chiral sulfur ylide promoted reactions, the focus should be on the transition states that are responsible for stereoselectivity.[24]

Our objective in the present study is 2-fold, which includes (i) deriving meaningful insights on the enantioselection in chiral sulfur ylide promoted reactions using a model sulfur reagent derived from an experimentally known example and (ii) applying this knowledge in designing new S-reagents suitable for stereoselective aziridination reactions. A modified version of Durst's bicyclic S-reagent is employed in the present study.[25] To impart good facial selectivity, a steric control approach through the introduction of a bulky *t*-butyl substituent (see Scheme 1 for model catalyst structure) is adopted.[26] We anticipate that a better understanding of the intricacies associated with the stereoselection process will help design more efficient catalysts.

Computational Methods

All calculations were performed using the Gaussian suite of quantum chemical programs.[27] Geometry optimizations of intermediates, transition states, reactants, and products were carried out in the gas-phase employing density functional theory method using the B3LYP functional[28] in combination with 6−31G* basis set. The 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 one and only one imaginary frequency for transition states was carried out to check whether the frequency pertains to the desired reaction coordinate. Intrinsic reaction coordinate (IRC)[29] calculations were performed to authenticate all transition states.[30] Single-point energies on the gas-phase optimized geometries were computed using a more flexible triple-ζ-quality 6−311G** basis set in acetonitrile continuum by employing the SCRF-PCM method as implemented Gaussian03.[31] This energy in solution ($G_{solvation}$, denoted as *E* in the text) comprises of the electronic energy of the polarized solute, electrostatic solute−solvent interaction energy, and nonelectrostatic terms corresponding to cavitation, dispersion, and

(21) (a) Janardanan, D.; Sunoj, R. B. *Chem.−Eur. J.* **2007**, *13*, 4805. (b) The barriers for the torsional and elimination steps are much lower than the addition step.

(22) (a) Aggarwal, V. K.; Calamai, S.; Ford, J. G. *J. Chem. Soc. Perkin Trans. 1* **1997**, 593. (b) Edwards, D. R.; Du, J.; Crudden, C. M. *Org. Lett.* **2007**, *9*, 2397.

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(24) One of the qualitative rationalizations reported earlier relies on the conformational preferences of the sulfur ylide intermediate rather than the kinetically significant transition states.[14c] See Figure S1 (Supporting Information) for the structures of ylide conformers employed to rationalize enantioselectivity.

(25) Very good enantioselectivities for epoxidation reaction have been reported using a bicyclic S-compound. See: Breau, L.; Durst, T. *Tetrahedron: Asymmetry* **1991**, *2*, 367.

(26) Alkyl groups present on bridging as well as bridgehead carbon atoms were removed since they are positioned far away from the reaction cite and thus are expected to have little influence on the stereoselection process.

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(30) In selected cases (such as torsional transition states), we have carried out 10% displacement on the transition state geometry along the direction of the imaginary vibrational frequency and subsequently re-optimized the perturbed structure using the "opt = calcfc" option available in the Gaussian suite.

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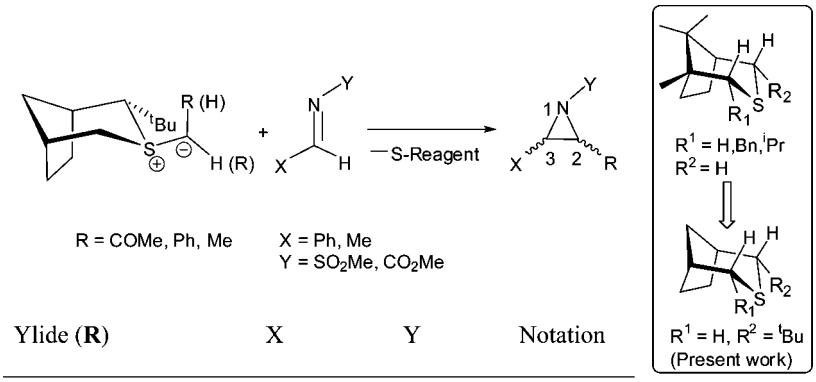
SCHEME 1. Chiral Sulfur Ylide Promoted Aziridination Reaction Investigated in the Present Study[a]



Ylide (**R**)	X	Y	Notation
Stabilized (COMe)	Ph	SO_2Me	**1**
	Me	SO_2Me	**2**
	Ph	CO_2Me	**3**
	Me	CO_2Me	**4**
Semistabilized (Ph)	Ph	SO_2Me	**5**
	Me	SO_2Me	**6**
	Ph	CO_2Me	**7**
	Me	CO_2Me	**8**

[a] Durst's original S-reagent has been modified as shown in the inset.

short-range repulsion. Activation barriers refer to the energy of activation obtained as the energy difference between the isolated reactants and the corresponding transition states. Weinhold's natural bond orbital method[32] (NBO 3.1) was used for NBO calculations. From the computed relative activation energies, *ee*/*de* was computed using the absolute rate theory.[33]

In a related study on sulfur ylide promoted aziridination reaction, we have shown that the single-point energies obtained using the continuum solvation methods on the gas phase geometries agree fairly well with the energies obtained upon complete geometry optimization within the continuum solvation.[21a] In fact, the extent of diastereoselection predicted using both solvent and gas-phase optimized geometries were found to be in excellent agreement with each other. Therefore in the present context involving larger molecular systems, we employ the gas phase geometries for the evaluation of continuum solvent effects by means of single-point calculations.

Terminology and Reaction Scheme. We have investigated the addition of sulfur ylides to variety of aldimines as shown in Scheme 1. Three types of ylides are chosen with varying degrees of stabilities.[34] It has been earlier demonstrated both experimentally[14d,15i] and theoretically[19c,21a] that the nature of substituents on the aldimine nitrogen as well as ylidic carbon can exert a direct influence on the observed stereoselectivitiy in sulfur ylide promoted aziridination reactions. To investigate how aldimine substituents steer the stereochemical course of aziridination, we have selected a range of four substituent combinations with Me and Ph groups on the imino carbon and SO_2Me or CO_2Me on the imino nitrogen. These aldimines include (i) (*E*)-*N*-benzylidenemethanesulfonamide, (ii) (*E*)-*N*-ethylidenemethanesulfonamide, (iii) (*E*)-methyl benzylidenecarbamate, and (iv) (*E*)-methyl ethylidenecarbamate.[35] Depending on the nature of substituents, different numerical identifiers, as shown in Scheme 1, are adopted in this report.

The transition states for the addition step for all the twelve substituent combinations are identified.[36] The energetics thus obtained is used toward rationalizing the stereoselectivity in asymmetric aziridination. The orientation of the developing charge centers ($S^{\delta+}$ and $N^{\delta-}$) in the addition TSs gives rise to *cisoid* and *transoid* addition modes, respectively designated as **n**-A-$c^{\ddagger}$ and **n**-A-$t^{\ddagger}$ for system **n**. Similarly, the rotational TSs connecting the *cisoid* and *transoid* betaine intermediates as well as the elimination TSs (ring-closure) are respectively denoted as **n**-$R^{\ddagger}$ and **n**-$E^{\ddagger}$. The *cisoid* and *transoid* betaine intermediates and product complexes are respectively named as **n**-*c*, **n**-*t*, and **n**-PC. The relative energies between various TSs are denoted as $\Delta\Delta E^{\ddagger}$ and activation barriers by $\Delta E^{\ddagger}$.

Results and Discussion

According to the generally accepted mechanism of S-ylide promoted reactions, the key steps consist of the addition of ylide to electrophile to generate a betaine intermediate, rotation around the newly formed C−C bond to achieve the desired antiperiplanar arrangement, and finally the elimination of the sulfur reagent generates the three membered ring.[19,20,21a] Earlier mechanistic proposals on the diastereoselectivity of S-ylide promoted reactions imply that the addition barriers are of prime importance in the case of semistabilized ylides (Table 1). At the same time, either of the subsequent steps, such as torsional motion and ring-closure (elimination), could be crucial for stabilized ylides

(32) (a) NBO Version 3.1, Glendening, E. D.; Reed, A. E.; Carpenter, J. E.; Weinhold, F. Theoretical Chemistry Institute and Department of Chemistry, University of Wisconsin, Madison. (b) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899.

(33) For similar treatment in the calculation of *ee*/*de* ratios, see: (a) Bahmanyar, S.; Houk, K. N.; Martin, H. J.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 2475 For representative cases (systems **1** and **5**), Boltzmann distribution ratios have been computed (Tables S7−S8, Supporting Information).

(34) Proton affinities have earlier been employed to assess the stability of reactive intermediates such as sulfur ylides. In our previous studies on model sulfur ylides, classification into stabilized (COMe, COPh, CO_2Me), semistabilized (Ph), and nonstabilized (H) groups on the basis of proton affinities have been performed. The stability order was found to be H < Ph < CO_2Me < COPh < COMe according to the computed proton affinity values respectively in the order 309, 304, 285, 283, and 281 kcal mol^{-1} at the $PCM_{(MeCN)}$/B3LYP/6−311G**// $PCM_{(MeCN)}$/B3LYP/6−31G* level of theory. See ref 21a.

(35) The IUPAC names of these aldimines are abbreviated as "carbamate" and "mesyl" in the text (or simply as substituted aldimines when Y on imino N is explicitly mentioned).

(36) The systems involving a nonstabilized ylide (R = Me) and various imine substituents have been named as **9**−**12′** along similar lines as indicated in Scheme 1.

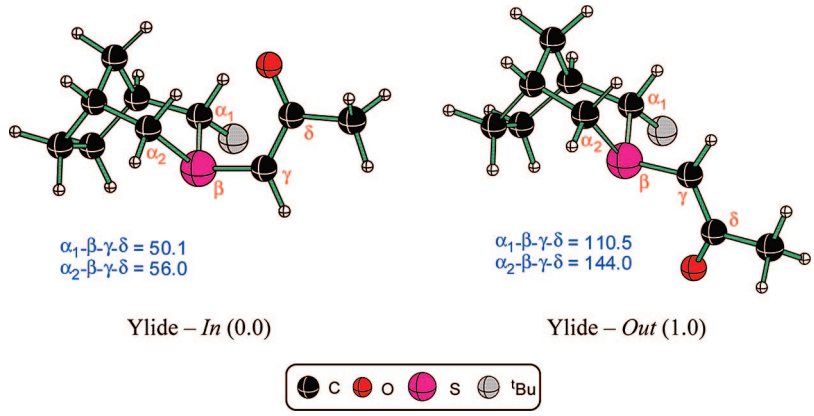


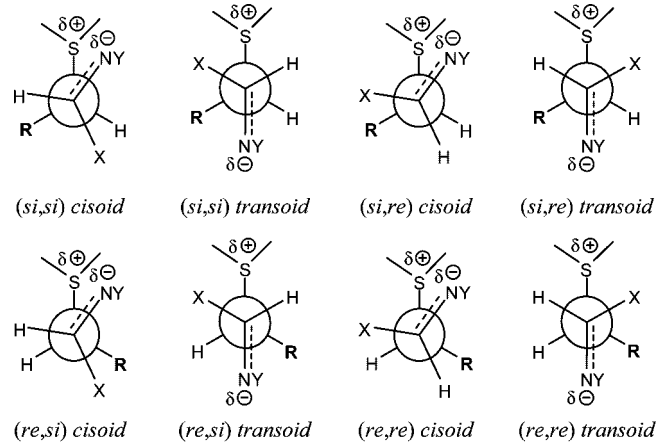
FIGURE 1. Optimized geometries and relative energies for *In* and *Out* conformers of stabilized ylide (R = COMe). The ΔE is obtained at the $PCM_{(MeCN)}$/B3LYP/6−311G**//B3LYP/6−31G* level. Energies are in kcal mol^{-1} and angles are in degrees.

depending on the electrophile. It is to be reckoned that in all these cases, the enantioselection is set up during the addition step, wherein the facial selectivity induced by the chiral sulfur reagent directly comes in to play. As the major objective of present investigation is to understand the enantioselection associated with chiral sulfur ylide promoted aziridination, we first focus on the addition step. However, as it has been noticed in the case of stabilized ylide addition to imines, where the initial addition is reversible, the diastereoselection can be controlled by the subsequent rotation/elimination steps.[14c,19c,21a] Therefore, only in two representative stabilized ylides **1** and **3** are TSs for torsional and elimination steps identified (*vide infra*).[37]

To begin with, two key conformations of the ylide are considered. These are termed as *In* and *Out*, on the basis of the orientation of the ylidic substituent with respect to the α carbon atoms attached to the S of the bicyclic ring. A representative ylide (R = COMe) depicting these conformers are provided in Figure 1. The conformer in which the ylidic −R group orients toward the same side of $C_{\alpha 1}$ (and $C_{\alpha 2}$) is named as *In* (with $\alpha-\beta-\gamma-\delta$ values < 90°) whereas the −R group is away from $C_{\alpha 1}$ (and $C_{\alpha 2}$) in the *Out* conformer ($\alpha-\beta-\gamma-\delta$ values > 90°).[38] These conformers are closely spaced minima that differ in the critical dihedral of the ylidic substituent.

Addition of sulfur ylides on the prochiral *si* and *re* faces of aldimine is examined. Since the bulky *t*-butyl group effectively blocks one face of the ylide, the approach to the aldimine can take place only through the open prochiral face. A given ylide conformer can add to either of the prochiral faces of the aldimine, giving rise to four stereochemically significant modes of approaches such as (*si*,*si*), (*si*,*re*), (*re*,*si*), and (*re*,*re*). For each of the above combinations, both *cisoid* and *transoid* modes of additions are considered, though the *cisoid* TSs are generally known to be favored over the *transoid* congeners.[39,40] As a result, a total of eight key possibilities exists for the addition between ylide and aldimine as depicted in Scheme 2. In the present work, only the lowest energy transition state pairs that lead to enantiomeric or diastereomeric products are taken toward computing the enantiomeric and diastereomeric excesses (*ee*/*de*).

SCHEME 2. Important Stereochemical Modes of Approaches between Ylide and Aldimine in the Initial Addition Step, Leading to Enantiomeric and Diastereomeric Aziridines



As stated earlier, the chiral S-reagent chosen in the present study is a modified version of an existing molecule. Therefore, a detailed examination of how this variant performs in a known reaction (Scheme 3) is undertaken first. The efficiency of the modified chiral bicyclic sulfur reagent in an epoxidation reaction is evaluated by means of model presented in Scheme 1. The asymmetric epoxidation between benzylidine ylide and benzaldehyde promoted by S-reagent is studied (R = Ph; X = Ph).[41] The model sulfur reagent employed in this study is provided in the inset (Scheme 3). The results of this reaction are presented first.

(a) Asymmetric Epoxidation Using Model Chiral Sulfur Catalyst. In the first addition step, eight important TS possibilities are considered as shown in Scheme 2. Among these, a total of five addition TSs are successfully located. Three *transoid* addition TS resulting from (*si*,*si*), (*si*,*re*) and (*re*,*re*) stereochemical modes of approaches failed to converge at the

(37) Additional calculations were done for the lowest energy diastereomeric pairs selected on the basis of activation barriers of addition step.

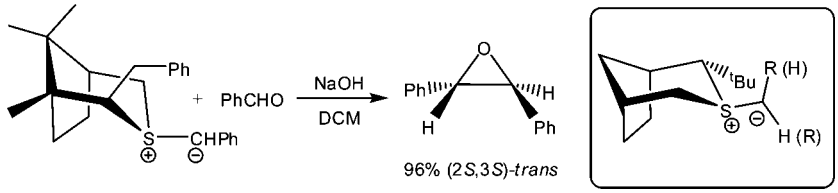
(38) The optimized geometries and relative energies of both *In* and *Out* conformers of all other ylides considered here are provided in Figure S2 (Supporting Information).

(39) Since the presence of N-substituent helps to stabilize the developing charge on N, the *transoid* TSs for aziridination are found to be stable in the gas phase as opposed to the case of epoxidation.[19c,21a] (also see the discussion on epoxidation where optimization of *transoid* TSs turned out to be difficult; vide infra).

(40) The *cisoid* and *transoid* approaches refer to the orientation of the developing charge centers in the addition step. If the S^{d+} and $N^{d\delta}$ are on the same side, the approach is termed as cisoid while transoid refers to opposite orientation of $S^{\delta+}$ and $N^{\delta-}$.

(41) Some years ago, Durst et al. have reported an asymmetric epoxidation reaction using the parent molecule (unmodified); see ref 25.

SCHEME 3. Experimental Stereoselectivity for an Asymmetric Epoxidation Reaction Achieved Using a Chiral S-Reagent[a]



[a] The model catalyst employed in the present study is provided in the inset.

TABLE 2. Computed Relative Energies ($\Delta\Delta E^{\ddagger}$ in kcal mol^{-1}) Obtained at the PCM$_{(MeCN)}$/B3LYP/6-311G//B3LYP/6-31G* Level for the Epoxidation Reaction between Semistabilized Ylide and Benzaldehyde[a,b]**

(*si*, *si*)[c]	(*si*,*re*)[c]	(*re*, *si*)		(*re*, *re*)[c]		
c	*c*	*c*	*t*	*c*	product configuration[d]	*ee*, *de* (%)
1.5	0.0	3.2	6.8	0.7	(2*S*,3*S*)-*trans*	99, 51

[a] $\Delta\Delta E^{\ddagger}$ relative to the lowest energy TS. [b] "*c*" and "*t*" respectively denote cisoid and transoid addition modes. [c] *transoid* TS could not be located. [d] Product corresponding to the lowest energy TS.

B3LYP/6−31G* level of theory. This could possibly be due to the severe steric interactions between the substituents around the incipient C−C bond coupled by the lack of stabilizing Coulombic interactions in *transoid* conformers.[42] Difficulties in obtaining *transoid* TSs in the gas phase for epoxide formation are earlier reported in the literature.[19a,23] The computed relative activation energies for the addition step are summarized in Table 2.

The relative activation energies predict a preference for (2*S*,3*S*)-*trans* epoxide with high enantioselectivity (99%) and low diastereoselectivity (51%).[43,44] Interestingly, the predicted high enantioselectivity is found to be similar to the experimental report on the formation of (2*S*,3*S*)-*trans* stilbene oxide, which is 96%.[25] The optimized geometries of the lowest energy TS *si*,*re*-*c*‡ along with those leading to its enantiomeric (*re*,*si*-*c*‡) and diastereomeric (*re*,*re*-*c*‡ and *si*,*si*-*c*‡) products are provided in Figure 2. The TSs where the phenyl substituents are on the same side of the newly forming C−C bond are generally found to be energetically more favored. Additionally, the lowest-energy TS results from the *Out* conformer of the ylide, where the ylidic phenyl substituent is oriented away from the α-carbon atoms on the sulfur. The TS responsible for the enantiomeric product resulting from the *In* conformer of the ylide suffers unfavorable interactions from the Cα$_1$ and Cα$_2$ hydrogen atoms, and is higher in energy.[45] A stabilizing H-bonding interaction between the developing alkoxide oxygen and the H-(Cα$_2$) of the catalyst is noticed in all these TSs. Such interactions help stabilize the developing charges in the TS. The comparison of the hydrogen bonding distances reveals that this interaction is similar for all these addition TSs.

The optimized geometries further indicate that the relative energies of the addition TSs are largely influenced by the distance between S and O atoms as well as that between eclipsing bond pairs around the C$_2$−C$_3$ bond (C$_2$−O$_1$/C$_3$−S$_4$, C$_2$−C(Ph)/C$_3$−C(Ph) and C$_2$−H/C$_3$−H bonds). For instance, in the lowest energy TS (*si*,*re*-*c*‡, Figure 2) the O$_1$−C$_2$−C$_3$−S$_4$ dihedral angle and O···S distance are found to be respectively 43° and 3.00 Å. The nearest higher energy TS (*re*,*si*-*c*‡) that leads to enantiomeric product evidently exhibits smaller values for O$_1$−C$_2$−C$_3$−S$_4$ dihedral (19°) as well as O···S distance (2.71 Å). The energies of both TS *si*,*si*-*c*‡ and TS *re*,*si*-*c*‡ are higher where the phenyl group on the aldehyde is closer to the bicyclic skeleton.

To examine whether electronic effects operating in the TS influence the enantioselectivity, we have computed donor−acceptor interactions using the natural bond orbital method.[46] Electron delocalization between the incipient C−C bond and the antiperiplanar C−S bond ($\sigma_{C2-C3} \rightarrow \sigma^*_{S4-C\alpha_1}$) is noticed in these TSs.[47] Further, σ^*_{C2-C3} accepts electrons from the developing alkoxide ion ($O^{\delta-}$) of benzaldehyde fragment.[48] Interestingly, the second-order perturbative stabilization energies ($E^{(2)}$) corresponding to the $\sigma_{C2-C3} \rightarrow \sigma^*_{S4-C\alpha_1}$ interaction in these TSs are found to be in the order (*si*,*re*-*c*‡) > (*re*,*re*-*c*‡) > (*si*,*si*-*c*‡) > (*re*,*si*-*c*‡). This order is quite consistent with the relative energies between the addition TSs, where the lowest energy TS exhibits the maximum delocalization. The electronic origins of H-bonding as well as O···S interactions in TSs (Figure 2) are identified using NBO analysis. The strength of $n_O \rightarrow \sigma^*_{Heq-C\alpha_2}$ orbital interaction contributing to the weak H-bonding is found to be correlating well with the O···H(C$_{\alpha 2}$) distances as seen in the optimized TSs geometries. It is noticed that the electron delocalization from suitably oriented lone pair on O$^-$ toward the S$_4$−Cα$_1$ antibonding orbital ($n_O \rightarrow \sigma^*_{S4-C\alpha 1}$) significantly influences the TS energies. Closer proximity between O and S atoms maximizes this interaction. The delocalization energy values ($E^{(2)}$) pertaining to $n_O \rightarrow \sigma^*_{S4-C\alpha_1}$

(42) All attempts to optimize *transoid* TSs converged to geometries having elongated S$_4$−C$_3$ and shorter C$_2$−C$_3$ bonds (see Figure 2 for atom numbering). The visual inspection of the single imaginary frequency indicated a coupled oscillation with characteristics of both addition and ring-closure. In some cases, where the aldehyde approached via its *si* face, several guess geometries failed to converge even after repeated attempts probably because of the unfavorable interactions developed between the aldehydic phenyl substituent and the CH$_2$ group α to S in the catalyst. Similar difficulties in optimizing *transoid* TSs for the ylide mediated epoxidation reaction have been known in literature.[19a,23]

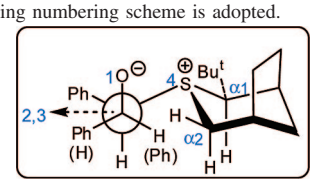
(43) The computed activation barriers for the addition of ylide to aldehyde are in the range of 7−14 kcal mol^{-1} depending on the mode of approach (activation energies are provided in Table S1, Supporting Information).

(44) It should be noted that the *cis*/*trans* selectivity could depend on the interconversion barrier between *cisoid* and *transoid* betaine intermediates. Hence, the computed selectivity using the relative activation barriers of the addition step may not be accurate enough in predicting the correct stereoselectivity. See refs 19a and 23.

(45) The optimized geometries of *In* and *Out* conformers of ylide provided in Figure S2 (Supporting Information) clearly show that the *Out* conformer is free from any unfavorable interaction from the Cα$_1$ and Cα$_2$ hydrogen atoms. It is favored than the *In* conformer by 1 kcal mol^{-1} energy (see Figure 2 or Figure S2 (Supporting Information) for the Cα$_1$ and Cα$_2$ notations used).

(46) See Computational section for more details on NBO calculations.

(47) For different notations used in the discussion of donor-acceptor interactions, following numbering scheme is adopted.



(48) See Table S2 (Supporting Information) for a complete list of donor−acceptor interactions computed using NBO analysis.

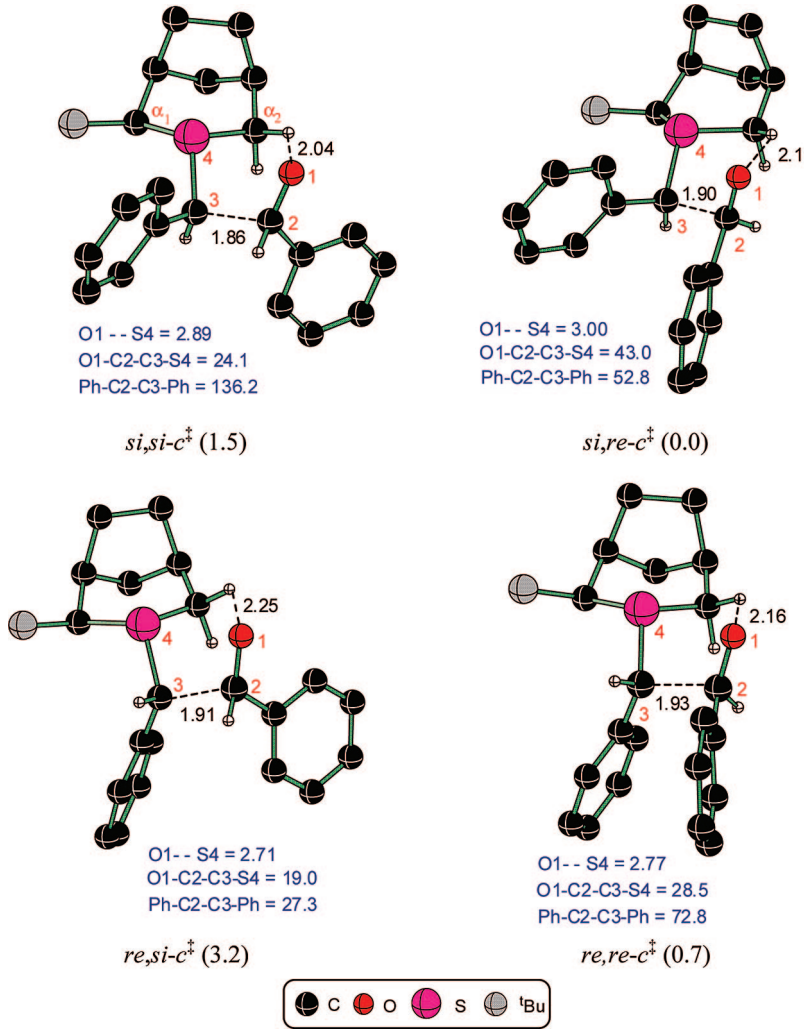


FIGURE 2. Optimized geometries and relative energies of lower energy TSs for the addition of semistabilized ylide to benzaldehyde. The $\Delta\Delta E^{\ddagger}$ is obtained at the $PCM_{(MeCN)}$/B3LYP/6−311G**//B3LYP/6−31G* level. Energies in kcal mol^{-1}, distances in Å, and angles in degrees; $C\alpha_1$ and $C\alpha_2$ notations are provided only for a representative TS.

interaction for the TSs leading to enantiomeric products (0.77 and 4.10 kcal mol^{-1} respectively for *si*,*re*-$c^{\ddagger}$ and *re*,*si*-$c^{\ddagger}$) supports this observation (the corresponding O···S distances are 3.00 and 2.71 Å for these TSs, Figure 2). Thus, the results of NBO analyses convey the importance of electronic interactions in the bringing about the relative energy order crucial to enatio- and diastereoselection.

The most significant observation at this juncture is that the modified chiral sulfur ylide employed in the present study indicates the possibility of high *ee* for asymmetric epoxidation reaction, even though the substitution pattern for the new catalyst is slightly different from the experimental ylide. The predictions additionally indicate that the removal of remote substituents may not significantly influence the extent of stereoselectivity. Encouraged by this prediction, we have decided to investigate how the stereoselectivities would be in asymmetric aziridination reaction promoted by the same chiral sulfur reagent. In the case of aziridination, the electrophile is a N-substitued or stabilized aldimine. The presence of additional interactions arising due to the nitrogen substituent could influence the stereochemical course and the overall product distribution. For instance, bulky tosyl or phosphonyl substituents on N are known to lead 2,3-*cis* aziridines. The substituents respectively on the ylide and the electrophile are presumably pushed away from the nitrogen substituent in such reactions.[16c,49] In the present study, two model substituents on the aldimine nitrogen, namely $-SO_2Me$ and $-CO_2Me$, as shown in Scheme 1 are considered.[50] Insights on stereoselectivity in asymmetric aziridination reaction are summarized in the following sections.

(b) Stereoselectivity in Aziridination Promoted by Stabilized Chrial S-Ylides. A systematic investigation aimed at identifying all key TSs for the addition of sulfur ylide to aldimine is undertaken. TSs pertaining to seven stereochemically relevant possibilities for stabilized ylides (R = COMe) are located on the potential energy surface.[51] For aziridination reaction, we could locate the *transoid* TSs in the gas phase, in contrast to the epoxidation TSs mentioned earlier.[52] This situation can be rationalized as arising due to the relatively large charge accumulation on the developing alkoxide oxygen upon addition of the ylide. On the other hand, dispersal of the developing charge is facilitated by the substituents on the nitrogen, in an aziridination reaction. Interestingly, some of the *transoid* TSs are found to be lower in energies as compared to the corresponding *cisoid* congeners. This observation is at variance with earlier investigations where the *cisoid* addition between sulfur ylide and electrophile is reported to be relative more favored.[21a] Relative energies of all optimized TSs for the addition of stabilized ylide to aldimines are gathered in Table

TABLE 3. Computed Relative Activation Energies ($\Delta\Delta E^{\ddagger}$ in kcal mol^{-1}) Obtained at the PCM$_{(MeCN)}$/B3LYP/6-311G//B3LYP/6-31G* Level for Aziridination Reaction between Stabilized Ylide (R = COMe) and N-Substituted Benzaldimines (Systems 1−4)[a,b]**

		(*si*, *si*)		(*si*,*re*)[c]	(*re*, *si*)		(*re*, *re*)			
	system	*c*	*t*	*c*	*c*	*t*	*c*	*t*	product configuration[d]	*ee*, *de* (%)
1	X = Ph Y = SO_2Me	6.0	4.5	3.5	1.1	1.8	0.3	0.0	(2*S*,3*S*) *cis*	100, 73
2	X = Me Y = SO_2Me	3.8	2.0	5.2	1.4	2.6	1.2	0.0	(2*S*,3*S*) *cis*	93, 83
3	X = Ph Y = CO_2Me	6.1	2.2	3.4	0.6	2.3	0.0	0.7	(2*S*,3*S*) *cis*	95, 47
4	X = Me Y = CO_2Me	4.5	1.1	3.9	0.0	2.3	1.6	0.0	−[e]	−[e]

[a] $\Delta\Delta E^{\ddagger}$ relative to the lowest energy TS. [b] "*c*" and "*t*" denote *cisoid* and *transoid* addition modes. [c] *transoid* TS could not be located. [d] Product corresponding to the lowest energy TS. [e] TSs leading to diastereomeric products for system **4** are degenerate.

3. The calculated enantiomeric as well as diastereomeric excesses corresponding to the $\Delta\Delta E^{\ddagger}$ values are also provided.

The lowest energy TS is found to be the one which corresponds to (2*S*,3*S*)-*cis* aziridine, for systems **1** through **4**. The *transoid* mode of approach between the ylide and aldimine is noticed in the above TS.[53] In the case of **1**, the relative energy between the TSs *re*,*re*-*t*‡ and *si*,*si*-*t*‡ leading to enantiomeric products is as high as 4.5 kcal mol^{-1} in favor of (2*S*,3*S*)-*cis* isomer. Such large difference between the competing diastereomeric pathways corresponds to an enantiomeric excess of >99%. The diastereomeric excess computed on the basis of the relative activation barriers of the addition step yields a *de* value of 73%, in favor of *cis* aziridine. As far as the addition step is concerned, the above trends remain the same with system **3** as well (X = Ph, Y = CO_2Me). While the enantioselectivity is predicted to be high, the *cis*/*trans* diastereoselectivity is found to be very low in **3**.

The optimized geometries of the lower energy TSs leading to enantiomeric and diastereomeric aziridines for a representative case (**1**) are provided in Figure 3. Analyses of the TS geometries reveal that the substituents around the developing C−C bond tend to orient as far away as possible to minimize the likely eclipsing interactions. For instance, in the lowest energy TS (*re*,*re*-*t*‡) the Ph−C_2−C_3−COMe dihedral angle is found to be nearly 60°, which is much higher than in the corresponding diastereomeric TS (*si*,*si*-*t*‡). In general, other weak stabilizing interactions such as C−H···O(SO_2Me) are found to be quite similar in these TSs. For system **1**, the *In* conformer of the ylide leads to lower energy addition TSs. Here, the relatively smaller size of the ylidic substituent (COMe) does not offer large steric encumbrance for the *In* ylide.[54] More significantly, the presence of additional weak interactions in the *In* conformer of the ylide contribute toward stabilizing the lower energy TSs *re*,*re*-*t*‡ and *re*,*si*-*c*‡ (Figure 3). The absence of these stabilizing interactions in TSs *si*,*si*-*t*‡ and *si*,*re*-*c*‡, resulting from the *Out* conformer of the ylide, leads to higher activation barriers. The cumulative effect of destabilizing eclipsing as well as stabilizing weak interactions decides the relative energies responsible for the high *ee* predicted for the stabilized ylide addition to aldimines.

The enantiomeric excess predicted on the basis of the computed $\Delta\Delta E^{\ddagger}$ for the addition between stabilized ylides and benzaldimine is quite promising (Table 3). At the same time, the diastereoselectivity accompanying the addition step is found to be not very encouraging. Earlier reports on related model systems (mesyl imine[19c] and carbamate[21a]) suggest that the elimination step could be crucial to the diastereoselectivity in sulfur ylide promoted aziridination. We have therefore extended the present investigation to subsequent steps, such as the rotation of the betaine intermediate as well as the elimination of the sulfur reagent, for both mesylbenzaldimine (**1**) and benzylidenecarbamate (**3**). For this purpose, additions corresponding to (*re*,*si*) and (*re*,*re*) stereochemical modes are considered.[55] These approaches are denoted as **c** and **d** in energy profile diagrams as given in Figures 4 and 5 (respectively for **1** and **3**). These modes have lower energy addition TSs as compared to the other two isomeric forms. For instance, the $\Delta\Delta E^{\ddagger}$ for (*re*,*si*) and (*re*,*re*) addition TSs and their corresponding higher energy isomers (*si*,*re* and *si*,*si*) is of the order of 2−4 kcal mol^{-1} for **1** (Figure 4). A similar scenario is noticed also with system **3**.

The barriers for addition, rotation, and elimination are found to be very similar, in both *syn* and *anti* betaine pathways.[56] An unambiguous assignment of the diastereoselectivity-determining step therefore becomes quite difficult. At this juncture, an improved understanding on the reversibility of each step involved in the reaction assumes additional significance. Toward this goal, the reaction profiles are constructed using the computed energies of various intermediates and transition states associated with both diastereomeric pathways (**c** and **d**).[57] Since the TSs on the PES are energetically closer, the reversibility of elementary steps can exert a direct control on the stereoselectivity. This can be inferred from the reaction profiles and the relative activation barriers for the forward and reverse reactions as summarized in Table 4.

The activation barriers clearly convey that all steps prior to the final ring-closure are reversible. Being a kinetically controlled reaction, the diastereoselectivity in aziridination will be decided by the nonreversible and slow step. The smaller barriers

(49) See ref 15i for a rationalization toward the formation of *cis*-aziridines from dimethylsulfonium and *trans*-aziridines from diphenylsulfonium salts under different reaction conditions.

(50) The hybridization of atoms immediately attached to nitrogen is sp^3 (−SO_2Me) and sp^2 (−CO_2Me).

(51) Seven out of total eight possible addition TSs (Figure 3) are located on the respective potential energy surfaces with all the substituents considered in the present study (systems **1**−**4**, Scheme 1).

(52) One of the *transoid* TSs, resulting from (*si*,*re*) approach between ylide and aldimine continued to be elusive in spite of repeated attempts. In this approach, severe unfavorable interactions between aldimine and sulfur substituents force all the initial guess geometries to converge to the corresponding *cisoid* TS during optimization by rotation around the incipient bond.

(53) While the *transiod* mode is found to be in general more favored in the present context, an exception is noticed for system **3**, where the cisoid TS *re*,*re*-*c*‡ is slightly lower in energy than the corresponding *transoid* TS.

(54) This situation is at variance with aziridination promoted by semistabilized ylide, *vide infra*.

(55) As suggested by one of the referees, we have additionally computed the full reaction profiles for the higher energy pathways for stabilized ylide addition to imines (**1a** and **1b**). A reaction profile depicting all the four such stereochemical possibilities is provided in Figure S3 (Supporting Information). We found that the addition TSs continue to remain as the highest energy points on the enantiomeric pathways **1a** and **1d**. It is therefore safe enough to conclude that the enantioselectivity, as calculated, remains intact (*vide infra*).

(56) On the basis of the highest energy addition and elimination TSs.

(57) The lower energy diastereomeric pathways **c** and **d** result from *In* ylide conformer. The other diastereomeric addition TSs (arising from pathways **a** and **b**) result from *Out* ylide, which is higher in energy than the *In* by 1 kcal mol^{-1}. While constructing the reaction profiles, relative energies of all TSs (including those from **a** and **b** modes) are calculated by taking $E_{(\text{In ylide + imine})}$ as a common reference point for the sake of clarity.

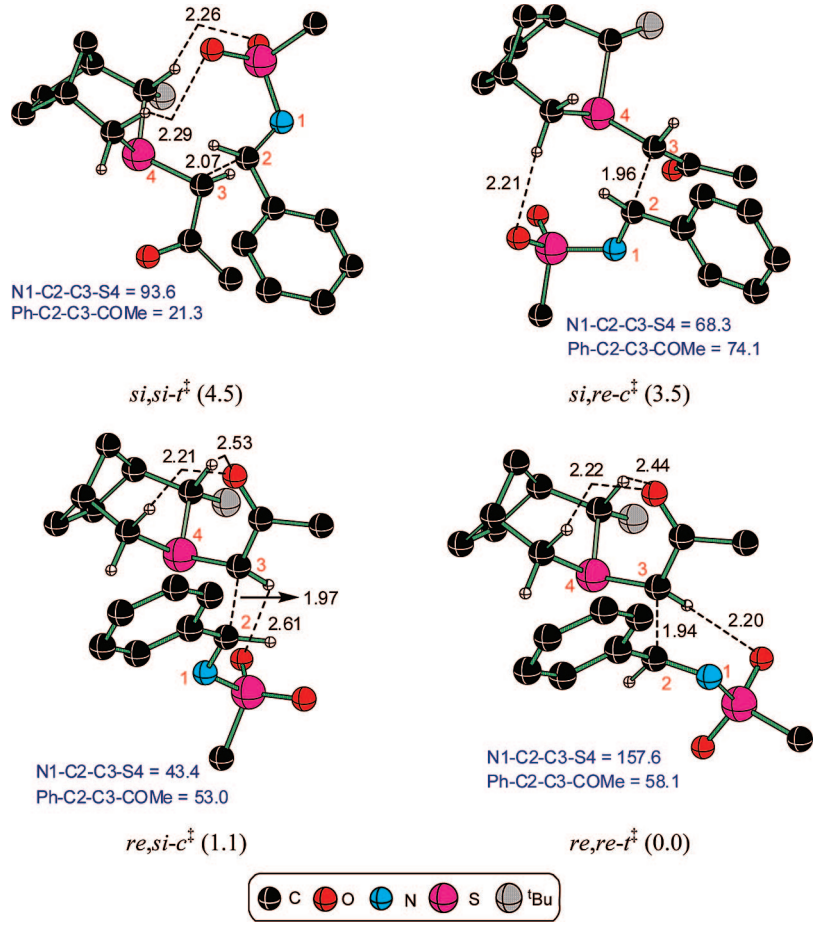


FIGURE 3. Optimized geometries and relative energies of lower energy TSs for the addition stabilized ylide to substituted imine for system **1**. The $\Delta\Delta E^{\ddagger}$ is obtained at the $PCM_{(MeCN)}$/B3LYP/6−311G**//B3LYP/6−31G* level. Energies in kcal mol^{-1}, distances in Å and angles in degrees.

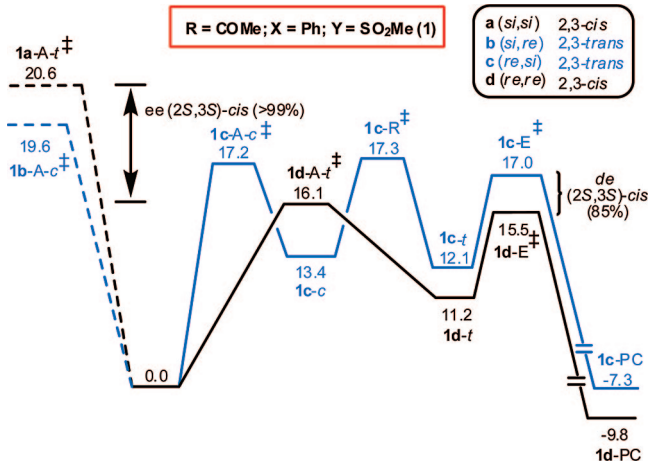


FIGURE 4. Reaction profiles for the lower energy diastereomeric pathways (**c** and **d**) for the addition of stabilized ylide to *N*-mesyl benzaldimine. Addition TSs for **a** and **b** modes are also included. The notations **1c-A**-*c*‡, **1c**-*c*, **1c**-*t*, **1c**-R‡, **1c**-E‡, and **1c**-PC respectively denote *cisoid* addition TS, *cisoid* betaine, *transoid* betaine, torsional TS, elimination TS, and product complex for pathway "**c**". Similar notations used for pathway "**d**"; $\Delta E^{\ddagger}$ (kcal mol^{-1}) is computed at the $PCM_{(MeCN)}$/B3LYP/6−311G**//B3LYP/6−31G* level.

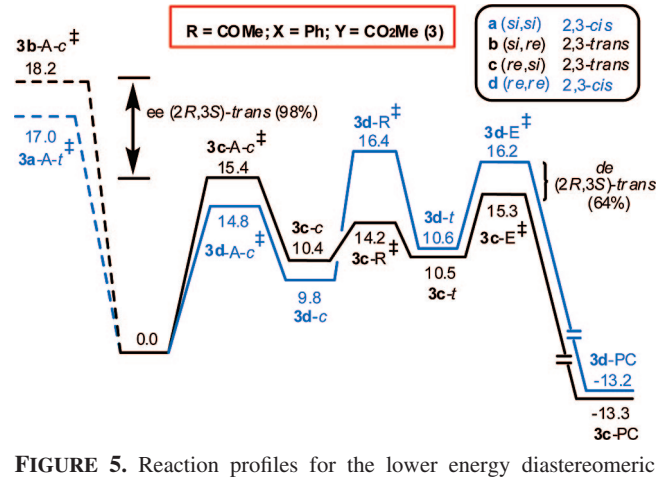


FIGURE 5. Reaction profiles for the lower energy diastereomeric pathways (**c** and **d**) for the addition of stabilized ylide to substituted carbamate. Addition TSs for **a** and **b** modes are also included. The notations **3c-A**-*c*‡, **3c**-*c*, **3c**-*t*, **3c**-R‡, **3c**-E‡, and **3c**-PC respectively denote *cisoid* addition TS, *cisoid* betaine, *transoid* betaine, torsional TS, elimination TS, and product complex for pathway "**c**". Similar notations are used for pathway "**d**". $\Delta E^{\ddagger}$ (kcal mol^{-1}) is computed at the $PCM_{(MeCN)}$/B3LYP/6−311G**//B3LYP/6−31G* level.

for dissociation of betaine intermediates (such as **1c-***c* or **1d**-*c* in the *cisoid* form or **1c-***t* or **1d**-*t* in the *transoid* form for **1**) back to reactants are evident from the $\Delta E^{\ddagger}_{b}$ values, which fall in the range of 4−7 kcal mol^{-1}. A similar trend is noticed for system **3** as well with 5−7 kcal mol^{-1} energy for reversion to reactants. Further, the *cisoid*−*transoid* interconversion barrier ($\Delta E^{\ddagger}_{b}$ for torsional motion) is only between 3.5 to 5.8 kcal mol^{-1}, indicating that the subsequent elimination step holds the key to the observed stereoselectivity. The barriers associated with the reversal of aziridine product back to the betaine intermediate are found to be very high ($\Delta E^{\ddagger}_{b}$ from 24 to 29

TABLE 4. Forward and Reverse Activation Barriers ($\Delta E^{\ddagger}$ in kcal mol^{-1}) Along the Diastereomeric Pathways c and d for the Addition of Stabilized Ylide (R = COMe) to Substituted Aldimines for systems 1 and 3[a]

TS	$\Delta E^{\ddagger}_f$ (forward)	$\Delta E^{\ddagger}_b$ (reverse)	TS	$\Delta E^{\ddagger}_f$ (forward)	$\Delta E^{\ddagger}_b$ (reverse)
1c-A-*c*‡	17.2	3.8	**3c-A-***c*‡	15.4	5.0
1c-A-*t*‡	17.9	5.8	**3c-A-***t*‡	17.2	6.7
1c-R‡	3.9	5.2	**3c-R**‡	3.8	3.7
1c-E‡	4.9	24.3	**3c-E**‡	4.8	28.6
1d-A-*c*‡	16.4	7.2	**3d-A-***c*‡	14.8	5.0
1d-A-*t*‡	16.1	4.9	**3d-A-***t*‡	15.4	4.9
1d-R‡	5.5	3.5	**3d-R**‡	6.6	5.8
1d-E‡	4.3	25.3	**3d-E**‡	5.6	29.4

[a] Energies at the PCM$_{(MeCN)}$/B3LYP/6−311G**//B3LYP/6−31G* level; (see Figures 4 and 5 for details on the notations used).

kcal mol^{-1}) implying a nonreversible elimination step. Thus, diastereoselection in aziridination is controlled by the energetics of elimination TSs (**1c**-E‡ and **1d**-E‡ for **1**; **3c**-E‡ and **3d**-E‡ for **3**). The prediction is found to be consistently the same for both systems **1** and **3** considered in the present study (Figures 4 and 5).

On the basis of the relative activation barriers for the addition step, the *%ee* for the most favored product is found to be >99 for system **1** (Figure 4). Such large selectivity originates from an energy difference of 4.5 kcal mol^{-1} between the addition TSs *re*,*re*-*t*‡ and *si*,*si*-*t*‡ (i.e, **1d-A-***t*‡ and **1a-A-***t*‡). However, owing to the reversibility of the addition step, diastereoselectivity does not depend on this step. Instead, the nonreversible ring-closure event should control the *cis*/*trans* selectivity. Thus, (2*S*,3*S*)-*cis* aziridine is predicted to be the preferred diastereomer in the case of **1**, where the *syn* betaine pathway (**d** or *re*,*re* pathway) is lower in energy. Now, the $\Delta\Delta E^{\ddagger}$ of 1.5 kcal mol^{-1} between diastereocontrolling elimination TSs (**1d**-E‡ and **1c**-E‡) leads to a *%de* of 85 toward the (2*S*,3*S*)-*cis* product.[58]

On the contrary, the methoxycarbonyl protected imine presents a slightly different picture (system **3**, Figure 5). In this case, the diastereoselectivity controlling ring-closure step favors the *anti* betaine pathway (**c** or *re*,*si*). The major product (2*R*,3*S*)-*trans* aziridine results from the initial addition TS **3c-A-***c*‡, even though it is higher in energy than **3d-A-***c*‡. The $\Delta\Delta E^{\ddagger}$ between **3c-A-***c*‡ and **3b-A-***c*‡ (2.8 kcal mol^{-1}) will now correspond to a *%ee* of 98 toward (2*R*,3*S*)-*trans* aziridine product. The computed *%de* based on $\Delta\Delta E^{\ddagger}$ of the ring-closure TSs (1.1 kcal mol^{-1}) is only 64% in favor of (2*R*,3*S*)-*trans* aziridine. It should be noted that both *%ee* and *%de* predicted solely on the basis of the addition barriers (95% and 47% respectively toward the 2*S*,3*S*-*cis* isomer, as shown in Table 3), could lead to incorrect conclusions in the case of **3**, as the product distribution is controlled by the elimination barriers. The knowledge on the diastereoselectivity determining TS is important toward obtaining better estimates on enantioselectivity. In other words, it can be concluded that both enantio- as well as diastereoselectivities are guided by the ring-closure barriers in the aziridination reaction between stabilized ylide and imines.

(58) During the review process, one of the referees commented that the diastereoselectivity could in principle depend on the energy difference between the highest energy stationary points along the diastereomeric pathways, even if they do not belong to the same step. If this is taken into account, an energy difference of 1.2 kcal mol^{-1} between **1d-A-***t*‡ and **1c**-R‡ would lead, again to (2*S*,3*S*)-*cis* aziridine, but with a lower *de* (77%). The computed *de* on the basis of the energies of the non-reversible ring-closure TSs (TSs for similar step along the diastereomeric pathways) is more meaningful, as cancellation of errors, if any, arising due to computational methods, will be more effective between the identical TSs.

The optimized TS geometries for the elimination step through the *syn* and *anti* diastereomeric pathways provide useful insights into the reversal of diastereoselectivity exhibited by aldimines **1** and **3** (Figure 6). The orientation of SO_2Me oxygens in **1c**-E‡ indicates a likely unfavorable interaction with the COMe oxygen, which probably raises the energy of this particular TS. Such kind of destabilization is not present in the diastereomeric **1d**-E‡. In the case of CO_2Me substituted imine, the planar geometry around the carbonyl carbon helps to minimize the electrostatic repulsion in **3c**-E‡. This feature of the imino substituent results in only a marginal energy difference between the diastereomeric TSs.[59]

The discussions hitherto have been able to convey that the enantioselectivity associated with aziridination reaction of N-substituted benzaldimines is very impressive while the extent of diastereoselection is only moderately high. Analyses on diastereo- and enantioselectivities have been able to delineate the importance of the nature of N-protecting group on aldimines. Interestingly in the present case, the prediction that the diastereoselectivity is only moderately good, is consistent with the available experimental evidence on closely related sulfur ylides.[14c] It is of importance to note that by suitable choice of electron withdrawing N-protecting groups as well as by changing the ylidic substituents, one might be able to modify the diastereoselectivity in sulfur ylide promoted aziridination reaction. This prediction could have wider implications in the design of new asymmetric strategies toward chiral aziridines.

(c) Stereoselectivity in Aziridination Promoted by Semistabilized and Nonstabilized Chiral S-Ylides. Earlier experimental studies on the mechanism of aziridination reaction concluded that the addition step is nonreversible for the reaction between semistabilized sulfur ylides (R = Ph, on the ylidic carbon) and N-tosyl aldimines.[14d] Theoretical studies on model systems (addition of $Me_2S^+CH^-Ph$ to mesyl imine[19c] and carbamate[21a]) further endorse the above observation. Enantio- and diastereoselectivities involving semistabilized ylides are therefore decided in the initial addition step. Similarly, the only noticeable barrier in aziridination reaction promoted by highly reactive nonstabilized ylides (R = Me) is with the initial addition step.[21] On the basis of these details, we have primarily focused on the initial addition step for semistabilized and nonstablized ylides in the present study.[60]

Akin to stabilized ylide, seven stereochemically distinct addition TSs are first identified at the B3LYP/6−31G* level of theory.[61] The stereoselectivities are subsequently evaluated using the relative energies of relevant diastereomeric TS pairs. The relative energies between addition TSs for semistabilized ylide are provided in Table 5.[62] The barriers are negligibly lower in the case of nonstabilized ylides.[63]

According to the computed relative energies of TSs presented in Table 5, the energy difference between TSs *si*,*si*-*c*‡ and *re*,*re*-*t*‡ leading to enantiomeric aziridines is found to be 3.1 kcal

(59) The reaction profiles additionally indicate that products follow similar relative energy order as that of the elimination TSs. For instance, (2*S*,3*S*)-*cis* aziridine resulting from the *syn* pathway is more stable, which in accordance with the lower energy of the preceding elimination TS (Figure 4). In the case of system **3** (*X* = Ph, Y = CO_2Me), *cis* and *trans* products have almost similar energies. This prediction is in concurrence with a recent study on the stability of N-substituted 2,3-*cis* as well as *trans* aziridines (see: Mimura, N.; Miwa, Y.; Ibuka, T. J. *J. Org. Chem.* **2002**, *67*, 5796). It was reported that when an sp^3 hybridized atom is attached to the N of the aziridine ring (such as in the present case, where the nitrogen substituent is SO_2Me), the other two ring substituents favors a *cis* disposition. Similarly, when a relatively less bulky group is attached to N through an sp2 atom (such as in CO_2Me), aziridines prefer to adopt 2,3-*trans*orientation.

TABLE 5. Computed Relative Activation Energies ($\Delta\Delta E^{\ddagger}$ in kcal mol^{-1}) Obtained at the PCM$_{(MeCN)}$/B3LYP/6-311G//B3LYP/6-31G* Level for Aziridination Reaction between Semistabilized Ylide (R = Ph) and N-Substituted Benzaldimines (Systems 5−8)[a,b]**

		(*si*, *si*)		(*si*,*re*)[c]	(*re*, *si*)		(*re*, *re*)			
	aldimine	*c*	*t*	*c*	*c*	*t*	*c*	*t*	product configuration[d]	*ee*, *de* (%)
5	X = Ph Y = SO_2Me	0.0	3.7	1.3	3.4	3.5	3.3	3.1	(2*S*,3*R*) *cis*	99, 80
6	X = Me Y = SO_2Me	0.0	3.5	1.4	2.1	3.9	3.1	−[c]	(2*S*,3*R*) *cis*	99, 83
7	X = Ph Y = CO_2Me	0.0	2.4	1.1	3.4	3.4	2.5	3.8	(2*S*,3*R*) *cis*	97,73
8	X = Me Y = CO_2Me	0.0	1.7	0.8	1.4	4.0	1.8	3.2	(2*S*,3*R*) *cis*	91,59

[a] $\Delta\Delta E^{\ddagger}$ relative to the most stable addition transition state. [b] "*c*" and "*t*" denote *cisoid* and *transoid* addition modes. [c] *transoid* TS could not be located. [d] Product corresponding to the lowest energy TS.

mol^{-1} for **5**. This corresponds to an *ee* of the order of 99% in favor of (2*S*,3*R*)-*cis* aziridine. On the other hand, the difference in energy between TSs that are responsible for diastereomeric products is comparatively small (1.3 kcal mol^{-1}) and leads to a moderately good *de* of 80%. It is also noticed that the diastereoselectivity with carbamates (**7** and **8**) are lower than that with N-mesyl systems (Figure 6).

Key geometric features of TSs corresponding to enantiomeric and diastereomeric aziridines are provided in Figure 7. In the most preferred TS *si*,*si*-*c*‡, the phenyl groups at 2,3-positions orient *trans* to each other with a dihedral angle (ω) of 101° between them. Subsequent rotation and elimination steps along this pathway will result in (2*S*,3*R*)-*cis* diastereomer as the product. In the higher energy TS *si*,*re*-*c*‡ leading to 2,3-*trans* product, the phenyl substituents around the incipient C−C bond are oriented in a *cis* fashion. Similar to what was noticed for stabilized ylides, the *cisoid* TSs with larger dihedral angle between the non-hydrogen substituents (phenyl groups in the present case) on C_2 and C_3 exhibited lower activation energies. As the value of ω reduces to 28°, as in *re*,*si*-*c*‡, the activation barrier is found to be the highest. Weak stabilizing interactions between the C_α−H atoms and the developing charges, either $N^{\delta-}$ or $O^{\delta-}$ (of the mesyl group), are evident from the optimized TS geometries (Figure 7). These interactions in all the addition TSs are quite comparable and therefore a direct correlation between weak-stabilizing interactions and relative energies of TSs may not possibly be drawn. A comparison of the optimized geometries of TSs resulting from "*In*" and "*Out*" ylides (*re*,*si*-*c*‡ and *re*,*re*-*t*‡ for *In* and *si*,*si*-*c*‡ and *si*,*re*-*c*‡ for *Out*) is valuable in the present context. The geometries indicate that an unfavorable interaction between C_α-H atoms and the ylidic phenyl group

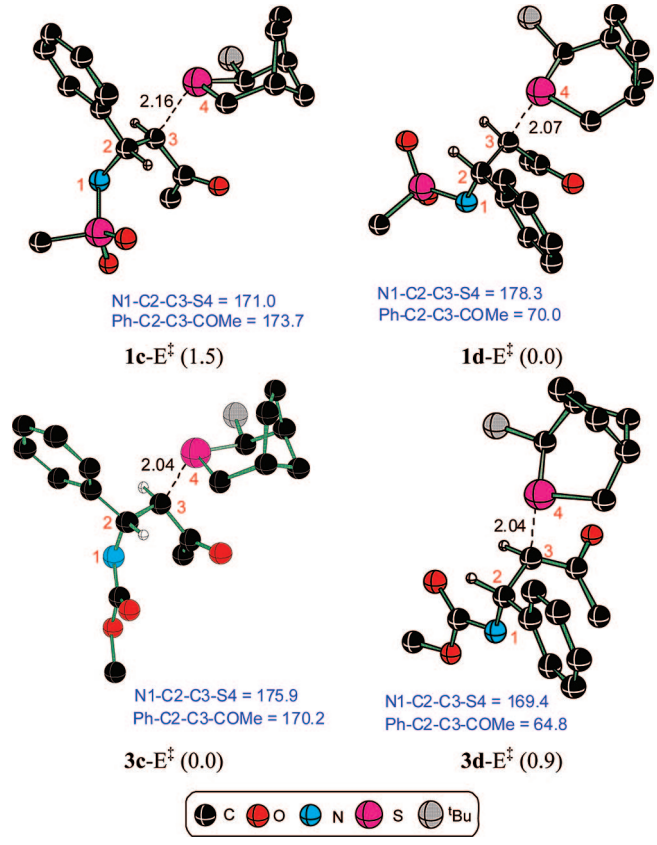


FIGURE 6. Optimized geometries and relative energies of diastereomeric elimination transition states for the reaction between stabilized ylide and substituted benzaldimines (system **1**). The $\Delta\Delta E^{\ddagger}$ is obtained at the PCM$_{(MeCN)}$/B3LYP/6−311G**//B3LYP/6−31G* level. Energies in kcal mol^{-1}, distances in Å, and angles in degrees.

increases the energy of TSs resulting from *In* ylide. Thus, the steric interaction in ylide conformer partly contributes to the energy difference between TSs responsible for enantiomeric products leading to high %*ee* in favor of (2*S*,3*R*)-*cis* aziridine.

The above discussion on the geometric features and relative energies of transition states provides useful insights. Steric interaction is found to be playing a vital role in deciding the energy differences that are crucial to enantio- and diastereoselection. The role of electronic interactions in competing diastereomeric TSs is analyzed using the NBO method. Although a number of donor−acceptor interactions such as $n_N \rightarrow \sigma^*_{C2-C3}$, $\sigma_{C2-C3} \rightarrow \sigma^*_{S4-C\alpha_1}$, $n_N \rightarrow \sigma^*_{Heq-C\alpha_2}$ are identified to contribute toward TS stabilization,[64] the second-order perturbation energies pertaining to these interactions do not exhibit any consistent trend that could help rationalize the predicted relative activation energies. Further, the differences in electron delocalization pattern noticed for mesyl and carbamate acceptors are only

(60) To verify whether the rate and stereoselectivity in the case of semistabilized ylides is controlled exclusively by the addition step, we have performed additional calculations on a representative case (system **5**). The reaction energy profile is provided in Figure S4 in Supporting Information. We found that the product distribution is decided in the addition step as the ensuing torsional and elimination steps are found to be energetically more facile. The $\Delta\Delta E^{\ddagger}$ of 3.1 kcal mol^{-1} between the lowest energy addition TS and the isomer leading to enantiomeric product results in an *ee* of 99% toward the (2*S*,3*R*)-*cis* aziridine. In a similar manner, the *de* of (2*S*,3*R*)-*cis* isomer is computed to be 80% on the basis of smaller energy difference between the lower energy TSs resulting in diastereomeric products (1.3 kcal mol^{-1}).

(61) As in the case of stabilized ylides, only seven addition TSs could be located on the PES with various substituent combinations chosen in this study. An unfavorable interaction between imine substituents and the H−(Cα) on the bicyclic ring, as well as another interaction between N-substituent and ylidic phenyl substituent is found to be responsible for the lack of a stable stationary point. Consequently, the *transoid* guess geometries failed to converge during geometry optimization.

(62) The computed activation barriers for semistabilized ylide are found to be in the range 2.5−10.0 kcal mol^{-1}. The corresponding barriers for stabilized ylides are between 10 and 20 kcal mol^{-1}. Thus, the aziridination reaction is expected to be more facile with semistabilized ylides. Activation barriers for the addition of stabilized and semistabilized ylides to substituted imines are provided in Supporting Information (Table S3).

(63) Activation barriers for the addition of nonstabilized ylide to substituted imines are provided in Supporting Information (Table S5).

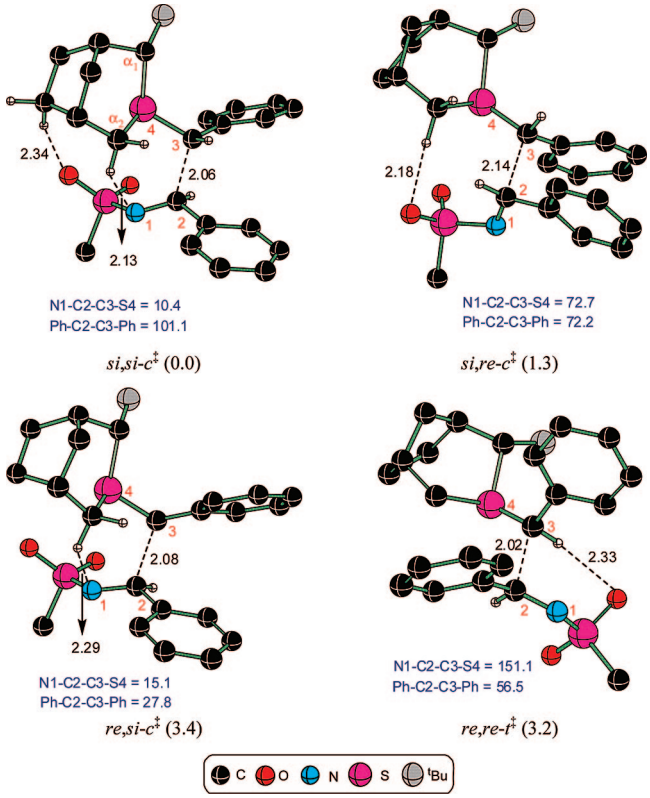


FIGURE 7. Optimized geometries and relative energies of lower energy TSs for the addition of semistabilized ylide to substituted imines for system **5.** The $\Delta\Delta E^{\ddagger}$ is obtained at the $PCM_{(MeCN)}$/B3LYP/6−311G**//B3LYP/6−31G* level. Energies in kcal mol^{-1}, distances in Å, and angles in degrees.

moderate and do not permit a direct comparison between the two acceptors.[65]

In the case of nonstabilized ylides, the relative activation barriers indicate a very low or no *cis*/*trans* diastereoselectivity even though the enantioselectivity is high.[66] This prediction can be attributed to the small size of the ylidic substituent, which cannot distinguish between the two prochiral faces of aldimine. Additional contributing factors toward stereoselectivity such as weak H-bonding interactions and Ph−C_2−C_3−Me dihedral angles do not exhibit any direct correlation with the relative energies of diastereomeric TSs.[67] A rationalization for the predicted enantioselection therefore appears difficult in the case of nonstabilized ylide.

We have thus far been able to demonstrate that both stabilized and semistabilized ylides derived from a chiral bicylic sulfur compound can provide excellent enantioselectivities toward 2,3-*cis* aziridines. Moderately high (**1**−**4**; stabilized ylide) to high (**5**−**8**; semistabilized ylide) levels of diastereoselectivity have also been predicted. In this context, it is of significance to reckon that many of the available chiral sulfur reagents employed in asymmetric aziridination lead to *trans* Aziridines. Our results additionally suggest that remote alkyl substituents on the bicylic sulfur compound, as in Durst's catalyst, are not quite necessary in inducing high stereoselectivity. The model sulfur reagent devoid of such alkyl groups does not significantly lower the extent of enantio- and diastereoselection. We believe that the present study on a hitherto unexplored chiral bicyclic sulfur catalyst for asymmetric aziridination will be of considerable importance from a synthetic point of view. Insights on enantio- and diastereoselection unveiled through this study will facilitate rational design of novel chiral molecules for asymmetric applications.

Conclusion

The mechanism and stereoselectivity in asymmetric aziridination reaction promoted by a bicylic chiral S-reagent has been studied using the density functional theory method. The insights on stereoselectivities have been obtained through identifying the key transition states involved in the reaction pathway. The predicted relative energies of key transition states for the reaction between chiral sulfur ylide and aldimines indicate impressively high levels of enantioselectivity for all three substituted ylides (R = COMe, Ph, and Me) considered in this study. Moderately high diastereoselectivity has been noticed for both stabilized (R = COMe) and semistabilized ylides (R = Ph). The predicted stereoinduction using bicyclic catalyst might facilitate access to 2,3-*cis* aziridines, with high enantio- and diastereoselectivities. In the case of stabilized ylide (R = COMe) we found that even though enantioselection is decided during the addition step, the prediction of *%ee* is affected by the energetics of diastereoselectivity deciding step (elimination) as well. The present study further illustrates that it might be possible to influence the diastereoselectivity with stabilized ylide by suitable modification of the N-substituent on the aldimine. While the presence of weak H-bonding as well as eclipsing bond pair interactions has been noticed for diastereomeric addition TSs involving stabilized ylide, steric interaction is identified to be the prime factor responsible for the predicted energy differences in the case of semistabilized ylide.

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Supporting Information Available: Total electronic energies, optimized coordinates and single-point energies of all structures reported in the text, Figures S1−S5, Tables S1−S8, and complete citation for Gaussian03 (ref 27 in the text). This material is available free of charge via the Internet at http://pubs.acs.org.

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(64) The second order perturbation energies for several donor-acceptor interactions in TSs for aziridination involving semistabilized ylides (systems **5** and **7**) are summarized in Table S6 (Supporting Information).

(65) The lone pair of electrons on the imino N (RCH−N⁻C(CO_2Me) delocalizes into the new C−C bond in TS *si*,*si*-$c^{\ddagger}$, which is found to be absent in diastereomeric TS *si*,*re*-$c^{\ddagger}$. Instead, an extended electron delocalization toward the CO_2Me group is noticed for RCH−N═C(CO_2Me).

(66) See Tables S4 (Supporting Information) for the relative energies of addition TSs for aziridination promoted by nonstabilized ylide and substituted aldimines.

(67) The B3LYP/6−31G* optimized geometries for nonstabilized ylide addition to substituted aldimines are provided in Figure S5 (Supporting Information).