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Density Functional Theory Investigations on Sulfur Ylide Promoted Cyclopropanation Reactions: Insights on Mechanism and Diastereoselection Issues

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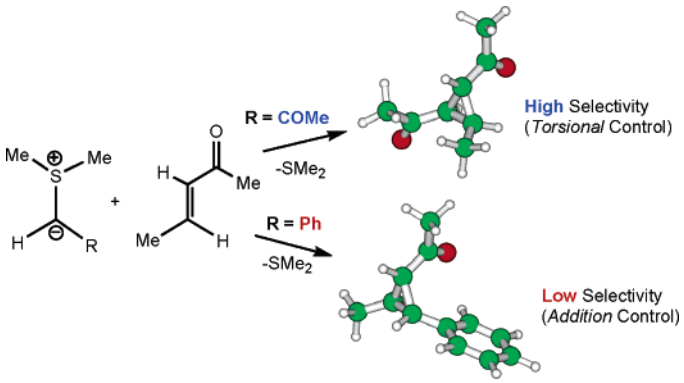

The mechanism and diastereoselectivity of synthetically useful sulfur ylide promoted cyclopropanation reactions have been studied using the density functional theory method. Addition of different substituted ylides ($Me_2S^+CH^-R$) to enone ((*E*)-pent-3-en-2-one, MeHC═CH−COMe) has been investigated. The nature of the substituent on the ylidic carbon brings about subtle changes in the reaction profile. The stabilized (R = COMe) and semistabilized (R = Ph) ylides follow a *cisoid* addition mode, leading to 1,2-*trans* and 1,2-*cis* cyclopropanes, respectively, via *syn* and *anti* betaine intermediates. The simplest and highly reactive model ylide (R = H) prefers a *transoid* addition mode. Diastereoselectivity is controlled by the barrier for *cisoid*-*transoid* rotation in the case of stabilized ylides, whereas the initial electrophilic addition is found to be the diastereoselectivity-determining step for semistabilized ylides. High selectivity toward *trans* cyclopropanes with stabilized ylides are predicted on the basis of the relative activation energies of diastereomeric torsional transition states. The energy differences between these transition states could be rationalized with the help of weak intramolecular as well as other stereoelectronic interactions.

Introduction

The synthesis of structural motifs consisting of cyclopropane rings has attracted recent attention owing to the biological activity of many such compounds.[1] The possibility of further synthetic manipulation of these strained ring compounds is another reason for their wide popularity.[2] In addition, cyclopropanes form part of several naturally occurring compounds such as terpenes, pheromones, fatty acid metabolites, and unusual amino acids.[3] While the initial efforts in synthesizing cyclopropane compounds were available more than half a century ago due to the work of Simmons and Smith,[4] many other methods have also been developed in succession.[5] Among these, the sulfur ylide mediated protocol has emerged as a powerful strategy.[6,7] Since the identification of sulfonium and oxosulfonium ylides as methylene transfer agents,[8] these intermediates have been widely used in the synthesis of three-membered ring compounds such as epoxides, aziridines, and cyclopropanes.[9−11] Revitalizing contributions from the groups of Aggarwal[10] and Dai[11] deserve special mention. The remarkable success of sulfur ylide methodology has encouraged synthetic chemists to extend this method to several other ylides as well.[12]

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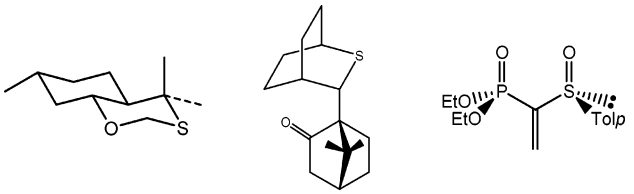
Very recently, ylide mediated stereoselective cyclopropanation methodologies have also been reported with high enantio- and diastereoselectivities.[13] Some examples for chiral sulfur reagents and auxiliaries employed in stereoselective synthesis of cyclopropanes are shown in Figure 1. Solladié-Cavallo and co-workers employed an oxathiane chiral auxiliary (I) to achieve complete enantioselectivity and high *trans* selectivity using the sulfur ylide methodology.[13a] The asymmetric cyclopropanation strategy developed by Aggarwal's group made use of the in situ generated ylides from diazonium salts and $Rh_2(OAc)_4$ in the presence of rigid chiral sulfur reagents (II). This method gave enantioselectivities up to 91% for the *trans* diastereomer.[13c] The method by Mikołajczyk involved a chiral sulfinyl auxiliary (III) on the acceptor counterpart with preformed ylides.[13g,h] Use of a chiral sulfide or a chiral auxiliary in these protocols provides a good rationale for understanding the induced stereoselectivity in the cyclopropanation reaction.



I II III

FIGURE 1. Chiral reagents/auxiliaries employed in enantio/diastereoselective synthesis of cyclopropanes.

A survey of available literature reports reveals that despite the wide popularity of sulfur ylide mediated cyclopropanation reactions, attempts toward understanding the underlying mechanistic details are rather scarce. It is believed that the reaction follows a pathway similar to that of other sulfur ylide promoted reactions such as epoxidation.[14] One available report by Norrby et al. deals with copper catalyzed cyclopropane formation from diazocompounds.[15] Recently, Mikołajczyk and co-workers have employed computational methods to rationalize the observed diastereoselection in ylide addition to vinyl sulfoxides, proposing a transition state model based on the optimized geometry of the electrophilic counterpart.[13h] The importance of weak interactions such as hydrogen bonding in influencing the energies of stereoselective transition states has been recently reported for vinyl substituted ylides.[13j] However, these predictions remain

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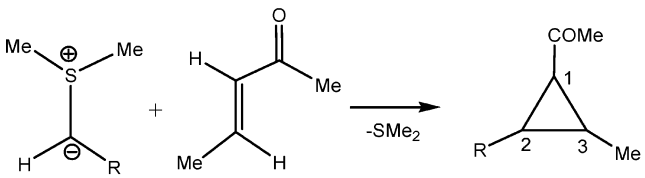
SCHEME 1. Cyclopropanation Reactions Investigated in the Present Study



Ylide	–R
1 :	H
2 :	Ph
3 :	COOMe
4 :	COPh
5 :	COMe

largely incomplete in providing a detailed picture of the reaction pathway or the reasons behind diastereoselection.

Increasing current interest as well as the importance of sulfur ylide promoted cyclopropane formation encouraged us to carry out a detailed theoretical investigation on the mechanism with an immediate objective of unraveling factors associated with the stereoselection process. Since the relative energies of diastereomeric transition states have a direct bearing on stereoselectivity, knowledge of the stereoelectronic factors operating at the transition states are crucial to the overall understanding on such reactions. Toward this goal, we have chosen to study the reaction between substituted ylides and the α,*β*-unsaturated ketone (*E*)-pent-3-en-2-one, as given in Scheme 1. The role of substituents on the nucleophilic carbon with different stabilizing abilities is studied in the present work. Based on the nature of substituents, these ylides are conveniently classified as nonstabilized (**1**), semistabilized (**2**), and stabilized ylides (**3**−**5**) (vide infra).

Computational Methods

Geometry optimizations of intermediates, transition states, and products were carried out at the B3LYP/6-31G* level of theory[16] using the Gaussian98 and Gaussian03 suite of quantum chemical programs.[17] All stationary points on the respective potential energy surfaces were characterized at the same level of theory by evaluating corresponding Hessian indices. Careful verification of the unique imaginary frequencies for transition states has been carried out to check whether the frequency indeed pertains to the desired reaction coordinate. Further, intrinsic reaction coordinate (IRC) calculations were carried out to authenticate all transition states.[18,19] Single-point energies were then calculated using a more flexible triple-ζ quality basis set, 6-311+G** with a continuum solvation model using the SCRF-PCM method[20] as implemented in Gaussian98. Acetonitrile, a commonly used solvent in ylide chemistry, was employed for single-point calculations. This energy in solution ($G_{solvation}$, denoted as *E* in the text) comprises the electronic energy of the polarized solute, the electrostatic solute−solvent interaction energy, and the non-electrostatic terms corresponding to cavitation, dispersion, and short-range repulsions.[20] Activation barriers are obtained as the energy difference between isolated reactants and corresponding transition state structures. Default options available with the PCM model of Gaussian98 (UAHF radii) were employed for single-point calculations.

The B3LYP level of theory in conjunction with the 6-31G* (for geometry optimization) and the 6-311+G** basis sets with the PCM model (for single-point energy calculations) used in this study should be sufficiently accurate to represent the relative energies of various stationary points for the systems considered in this study. Energy refinements using flexible basis sets on geometries optimized at a lower level (for instance, the B3LYP/6-31G*) have consistently been used in addressing stereoselectivity problems, particularly those involving polar transition states.[21] Some evidence is also available that optimization using more flexible basis sets might not necessarily provide any major additional benefit.[22] Thus, in this work we have employed the PCM/B3LYP/6-311+G** single-point energies on the B3LYP/6-31G*geometries. Full geometry optimization within the PCM model might lead to minor differences in the energetics while leaving the key relative energies largely unchanged.[23]

In selected cases, where the optimized geometries could not be located using the B3LYP functional (TS-**2**R and TS-**2′**E), geometry optimization and frequency calculations were performed at the HF/6-31G* level. Single-point energies were then evaluated at the B3LYP/6-311+G** using the PCM method (in acetonitrile continuum). For TS-**3**R and TS-**4**R, optimized geometries obtained at the mPW1PW91/6-31G* level were used.[24,25]

Terminology. As mentioned earlier, a total of five ylides were considered (**1**−**5**). *Cisoid* and *transoid* addition transition states in

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(19) For rotational transition states, instead of IRC calculations, 10% geometric displacements along the normal mode for the imaginary vibrational frequency in both forward and backward directions followed by separate optimizations of the displaced coordinates using the "opt = calcfc" option was performed to confirm the nature of TS.

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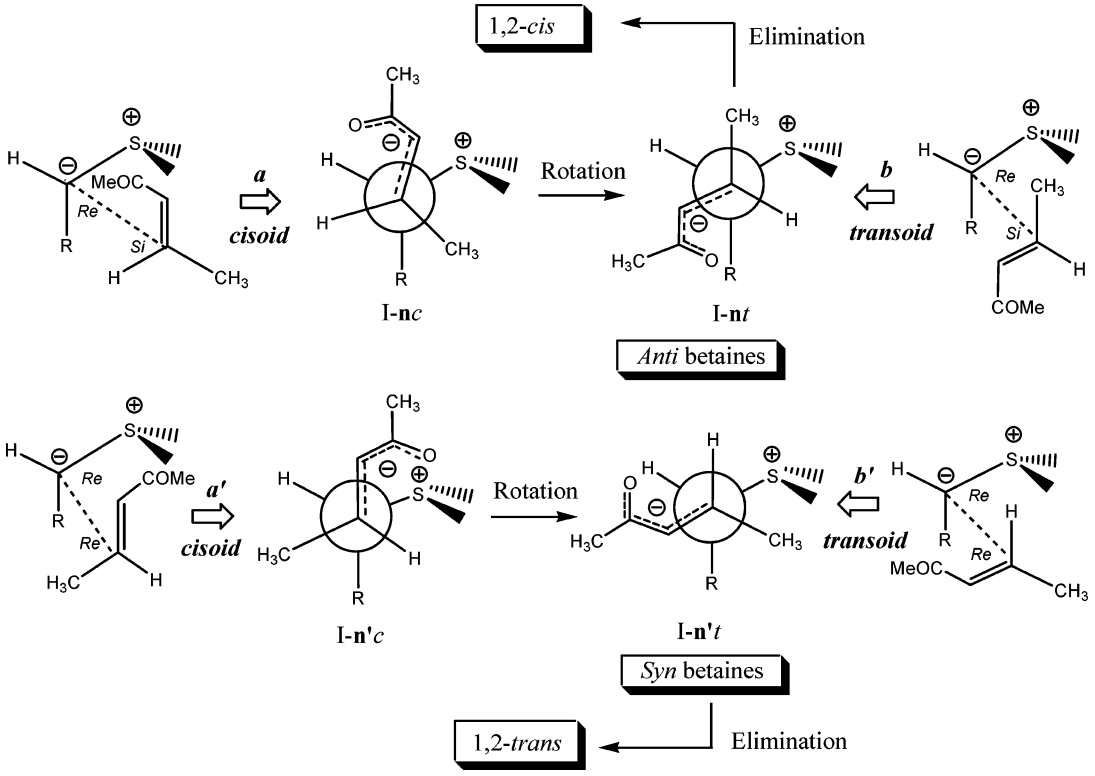
(23) For a representative ylide (**5**), we have carried out full geometry optimization with the inclusion of continuum solvation effects for constructing the reaction profile. It is seen that the obtained energy profile is in excellent agreement with that obtained using single-point energies on the gas-phase stationary points at the PCM(CH_3CN)/B3LYP/6-311+G**//B3LYP/6-31G* level (see Figure S1, Supporting Information for energy profiles obtained for diastereomeric pathways of ylide **5**). It is noted that the energy difference between the selectivity-determining torsional TSs from the gas phase computations (with solvent incorporated single-point energies) remains exactly the same as that obtained with the incorporation of solvent effects (4.7 kcal mol^{-1}).

(24) The geometry of torsional TS (TS-**3**R) has a SMe_2 - - Me (enone) eclipsing interaction (see later for optimized geometries obtained for representative stabilized ylide **5**, Figure 6). Steric interaction between these substituents probably leads to elongation and breaking of the newly formed C−C bond at the B3LYP level.

(25) For TS-**4**R, optimizations at the B3LYP/6-31G* level were unsuccessful due to issues such as elimination of SMe_2 groups and optimization to unwanted products (for instance, loss of conjugation or local geometry having non-planar carbonyl and phenyl groups and cyclization by the attack of enone oxygen to carbonyl group of R were observed during optimization). Therefore, single-point energy obtained at the PCM (CH_3CN)/B3LYP/6-311+G**//mPW1PW91/6-31G* level was used in the construction of reaction profiles.

SCHEME 2. Different Approaches of Ylide-Enone Pairs and General Reaction Schemes Leading to Diastereomeric Cyclopropanes[a]



[a] Intermediates I-n*c* and I-n*t* result from the *cisoid* (TS-n*c*) and *transoid* (TS-n*t*) addition transition states, respectively, via (*re*,*si*) approach. Similarly the (*re*,*re*) approach yields I-n′*c* and I-n′*t* betaine Intermediates.

TABLE 1. Proton Affinities (PA) of Ylides Computed at the PCM/B3LYP/6-31G*//PCM/B3LYP/6-31G* Level of Theory Using an Acetonitrile Continuum (Solvent)

substituent	PA (kcal mol^{-1})
H (**1**)	324.5
Ph (**2**)	317.4
CO_2Me (**3**)	297.8
COPh (**4**)	296.2
COMe (**5**)	295.1

the C−C bond-forming step are named TS-n*c* and TS-n*t*, respectively, for ylide **n** (**n** = **1**−**5**). The intermediate betaines are termed I-n*c* for *cisoid* and I-n*t* for *transoid* orientations (Scheme 2). Similarly, the transition state for *cisoid* to *transoid* rotation is designated as TS-nR and that for elimination as TS-nE. In the alternative (*re*,*re*) approach, the ylides, intermediates as well as transition states, are designated using **2′** through **5′**.

Results and Discussion

The reaction between substituted sulfur ylides (**1**−**5**) and enone investigated in the present study is shown in Scheme 1. A range of substituents on the ylidic carbon is considered depending on their stabilizing ability. The relative stabilities are assigned by calculating respective proton affinities (PA) using the following hypothetical reaction [Y stands for ylide, eq 1] as negative of heat of reaction.[26] The calculated proton affinities are summarized in Table 1.

$$Y + H^{\oplus} \longrightarrow {}^{\oplus}YH \qquad \Delta H_{rxn} = -PA \qquad (1)$$

The computed proton affinity values corroborate the fact that electron-withdrawing substituents such as COMe (**5**) render better stabilization as compared to an unsubstituted ylide (**1**). According to the predicted trend, the reactivity order for various substituted ylides is expected to follow the order **1** > **2** > **3** > **4** > **5**. Based on the computed PA values and literature reports on sulfur ylides, we have grouped them as stabilized (**3**, **4**, and **5**)[9c−l] and semistabilized (**2**) ylides.[27] Among these **2**,[13f] **3**,[9h] and **4**[9g] have earlier been employed in interesting Michael additions to α,β-unsaturated ketones for synthesizing substituted cyclopropanes.

Mechanistic Considerations: General Reaction Profiles. Generation of cyclopropane by reaction between sulfur ylide and α,β-unsaturated ketones involves three key steps: (i) initial nucleophilic addition of the ylide in a Michael fashion, (ii) rotation around the newly formed C−C bond to an antiperiplanar orientation, and (iii) elimination of SMe_2 leading to the ring-closed product. The general reaction sequence is schematically represented with the help of Scheme 2.[28] It is important to note

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(27) (a) Westman, G.; Wennerstrom, O.; Raston, I. *Tetrahedron* **1993**, *49*, 483. (b) Yamataka, H.; Nagase, S. *J. Am. Chem. Soc.* **1998**, *120*, 7530. (c) Aggarwal, V. K.; Charmant, J. P. H.; Ciampi, C.; Hornby, J. M.; O'Brien, C. J.; Hynd, G.; Parsons, R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3159. (d) Aggarwal, V. K.; Richardson, J. *Chem. Commun.* **2003**, 2644. (e) Aggarwal, V. K.; Charmant, J.; Dudin, L.; Porcelloni, M.; Richardson, J. *Proc. Nat. Acad. Sci. U.S.A.* **2004**, *101*, 5467.

(28) *syn* and *anti* terminologies refer to the relationship of substituents around the newly formed C−C bond (R on ylide and Me on the enone) and NOT the bulkier substituents. R and COMe groups, respectively, on ylide and enone are used for product stereochemistry notations.

TABLE 2. Activation Barriers and Relative Energies (in kcal mol^{-1}) Computed at the PCM/B3LYP/6-311+G//B3LYP/6-31G* Level of Theory for the Formation of Cyclopropanes Using Acetonitrile as Solvent (ϵ = 36.64)[a]**

ylide	TS-n*c*[b]	TS-n*t*[c]	TS-nR[d]	TS-nE[e]
1[f]	6.5	5.2	3.6 (−13.4)	2.3 (−11.8)
2	8.8	10.1	15.8 (8.8)[g]	3.7 (1.5)
2′	10.2	10.4	7.4 (−1.5)	0.7 (−0.8)[g]
3	17.8	21.4	11.2 (21.3)[h]	0.6 (19.4)
3′	17.3	21.5	3.0 (12.8)	0.7 (12.9)
4	21.2	31.1	11.5 (28.8)[h]	2.1 (24.8)
4′	24.1	23.4	5.6 (21.6)	6.5 (24.8)
5	20.9	24.3	9.3 (23.2)	4.6 (21.6)
5′	20.2	19.9	3.5 (18.5)	3.7 (17.0)

[a] Values in parentheses for rotational and elimination TSs refer to the relative energies with respect to the separated reactants. [b] *Cisoid* addition. [c] *Transoid* addition. [d] Rotational barrier with respect to the nearest intermediate, I-n*c*. [e] Elimination barrier with respect to I-n*t*. [f] Ylide **1** lacks prochiral faces. [g] Relative energies at the PCM/B3LYP/6-311+G**//HF/6-31G* level. [h] Relative energies at the PCM/B3LYP/6-311+G**//mPW1PW91/6-31G* level.

that energy differences between diastereomeric transition states associated with any of these steps could have a profound effect on the stereoselectivity. Insights on various controlling factors contributing to the rate and diastereoselectivity will be very valuable in exploiting the full potential of sulfur ylide promoted reactions.

Two major approaches of ylides toward the electrophilic enone are considered, namely, (*re*,*si*) and (*re*,*re*). These approaches can further assume two important orientations, *cisoid* and *transoid*, depending on whether the orientation of charge centers on ylide and enone are on the same or opposite sides of the developing C−C bond. Thus, path ***a*** is said to have a *cisoid* approach between the *re* face of ylide and *si* face of enone. The intermediate betaine thus formed will undergo rotation around the newly formed bond, leading to the *transoid* betaine. Alternatively, the *transoid* approach via path ***b*** can as well lead to *anti* betaine. The *transoid* betaine, having an *anti* disposition between the internal nucleophilic carbon and the leaving group, can undergo facile *anti* elimination to yield the final product with a 1,2-*cis* stereochemistry between the larger substituents.[29] It should be mentioned that this product has a *trans* stereochemistry between the substituents at 2,3-positions, a methyl group on the enone, and R on the ylide.

Additionally, it can be envisaged that the *cisoid* betaine can yield the 1,2-*trans* diastereomer via *syn* elimination, which is expected to be highly energy demanding as compared to the *anti* elimination pathway.[14a−d,30] The (*re*,*re*) approaches between ylide and enone are designated as pathways ***a′*** and ***b′***. Based on the substitution on ylides employed in the current study, the remaining two possibilities, namely, (*si*,*re*) and (*si*,*si*) approaches, will essentially lead to enantiomeric transition states and intermediates and thus are not considered for further analysis.

A systematic inspection of reaction pathways depicted in Scheme 2 is performed, and the relative energies of various intermediates and transition states are listed in Table 2.[31] Activation energies reveal that the barrier to addition successively increases from ylide **1** through ylide **5**. This observation

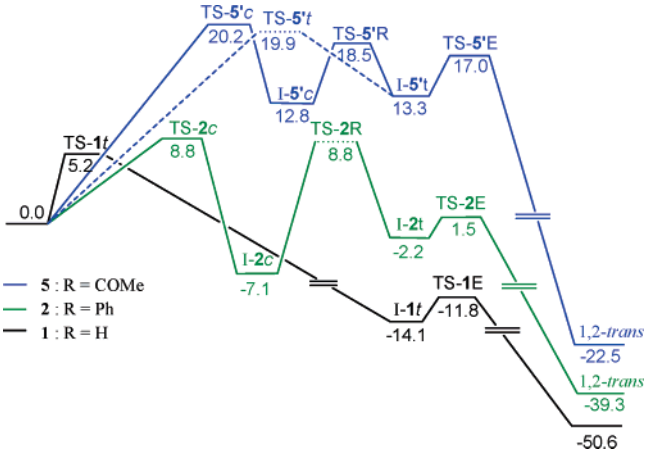


FIGURE 2. General reaction profiles for cyclopropane formation from ylides (**5**, **2**, and **1**) and enones. Activation energies in CH_3CN (kcal mol^{-1}) at the PCM/B3LYP/6-311+G**//B3LYP/6-31G* level. Energies are reported with respect to isolated reactants. [For TS-**2**R (·····) only, the relative energy is at the PCM/B3LYP/6-311+G**//HF/6-31G* level.]

is consistent with the reactivity/stability of ylides when a substituent is attached to the ylidic carbon. Highest barriers to addition are predicted for ylide **4**, when a COPh group is attached to the ylidic carbon. It is interesting to note that even the most reactive ylide (**1**, R = H) among the present series adds to the enone with a significant barrier as high as 6 kcal mol^{-1}. Among *cisoid* and *transoid* addition modes, the *cisoid* addition to enone is found to be energetically more favored for stabilized and semistabilized ylides.[32] The *cisoid* betaine intermediate thus generated undergoes rotation around the newly formed C−C bond to a *transoid* intermediate. The ideal geometrical requirement for elimination demands an antiperiplanar disposition of the SMe_2 group and the internal nucleophilic carbon atom, such that ensuing ring closure will lead to diastereomeric cyclopropanes as products. Computed relative activation barriers reveal that the rotation of *anti* betaines (TS-**n**R) requires higher energy than for *syn* betaines (TS-**n′**R). For instance, the rotational barriers with respect to *cisoid* intermediates (I-n*c*) are higher and fall in the range from 9.3 to 15.8 kcal mol^{-1} for ylides **2**−**5** for *anti* betaines (i.e., (*re*,*si*) approach or pathway ***a***), whereas the corresponding barriers range only from 3.0 to 7.4 kcal mol^{-1} for *syn* betaines (pathway ***a′***).[33] In contrast to stabilized ylides, the addition mode preferred by the most reactive ylide **1** is *transoid* (path ***b***), leading directly to betaine intermediate (I-n*t*) capable of elimination.

Based on the relative energies of key transition states and intermediates, general reaction energy profiles for cyclopropanation are constructed by taking three representative cases as shown in Figure 2. The most significant barriers for ylides **1**, **2**, and **5** are evidently encountered in the addition step. This arises as a result of the diminished polarity of the acceptor

(29) Please see Scheme 1 for numbering of atoms.

(30) See later for representative *syn* elimination barriers for stabilized ylide **5**.

(31) Activation barriers for the higher energy conformers (addition TSs) are provided in Table S2, Supporting Information.

(32) Even though for ylide **5** the *transoid* addition TS (TS-5′*t*) is found to be slightly more favored, a clear *transoid* preference can not be predicted as the *cisoid* addition TS is very close in energy, yielding the same 1,2-*trans* product (Figure 4). In addition, two other stabilized ylides add to the enone in a *cisoid* fashion. Hence, it can be concluded that the preferred addition mode of stabilized ylides to enones is *cisoid*.

(33) It appears that the unfavorable eclipsing interaction between sulfur and the methyl substituent on enone in *anti* betaines is more pronounced. *Syn* betaines, on the other hand, enjoy weak S···H and O···H stabilizing interactions in TS-**n′**R (see later for a description for ylide **5** as given in Figure 6).

double bond in α,β-unsaturated ketones employed in cyclopropane formation.[34] Whereas stabilized ylides have to surmount higher barriers in the addition step, ylides **1** and **2** add to enone with relatively lower energies of activation. The elimination TSs for ylides **1** and **2** are found to be either below or close to zero (−11.8 kcal mol^{-1} for **1** and 1.5 (*anti*)/−0.8 (*syn*) kcal mol^{-1} for **2**, respectively) on the potential energy profile, signifying a highly facile ring closure once the betaine intermediate is generated. In contrast, for ylide **5**, along with the initial rate-limiting addition step, all subsequent steps such as rotation and elimination exhibit a finite barrier. The same trend is valid for other ylides **3** and **4** (Table 2). Another noticeable feature of these energy profiles is the stabilities of betaine intermediates formed from different kind of ylides. Energies of *cisoid*/*transoid* betaines resulting from stabilized ylides lie well above zero on the potential energy surface.[35] On the contrary, intermediates generated from nonstabilized ylide **1** and semistabilized ylide **2** lie at lower energies, in concert with their expected higher reactivity. The final products, namely, substituted cyclopropanes, resulting from all ylides are thermodynamically stable, as indicated by their higher negative energies of formation. In general, *trans* cyclopropane products are more stable than their *cis* counterparts.

For all three kinds of ylides, the lower energy pathways are provided in Figure 2. In the case of stabilized ylides, the *syn* pathway (TS-**5′***t*) is found to be lower in energy than the *anti* pathway (TS-**5***t*), which proceeds via a rate-limiting addition (vide infra). For a semistabilized ylide, on the other hand, the *anti* betaine pathway is lower in energy than the *syn* pathway, rendering a 1,2-*cis* diastereoselectivity. For nonstabilized ylide **1**, only the addition has a substantial barrier and hence it is the rate-limiting step. Addition is followed by lower energy barriers for rotation and elimination steps.

The final step toward product formation from betaine intermediates is the elimination step. As expected, *anti* elimination is preferred over the alternative *syn* elimination pathway. Barriers for *syn* elimination for representative cases are determined. Whereas transition states for *syn* elimination are as high as 31.7 and 29.0 kcal mol^{-1}, respectively, for *anti* and *syn* betaines (**5** and **5′**), the corresponding values for *anti* elimination pathway for these ylides are only 21.6 and 17.0 kcal mol^{-1}. Based on the computed relative activation barriers between *syn* and *anti* eliminations, the possibility of *syn* elimination on the general reaction course can safely be ruled out. Thus, in general, our results show that *cisoid* addition followed by *anti* elimination is predominantly the lowest energy pathway leading to the cyclopropanes.

Conformational Possibilities for Intermediates and Transition States. Conformational flexibility of sulfur reagents used in this study could give rise to several energetically closely related conformers for the betaine intermediates as well as transition states. In an attempt to sample the conformational space near the stationary points such as minima and transition states, we have searched the PES for both *syn* and *anti* pathways by rotation (i) around the newly formed C−C bond and (ii) the methyl groups attached to sulfur atom. Methods adopted for conformational search of intermediates and TSs is described below.

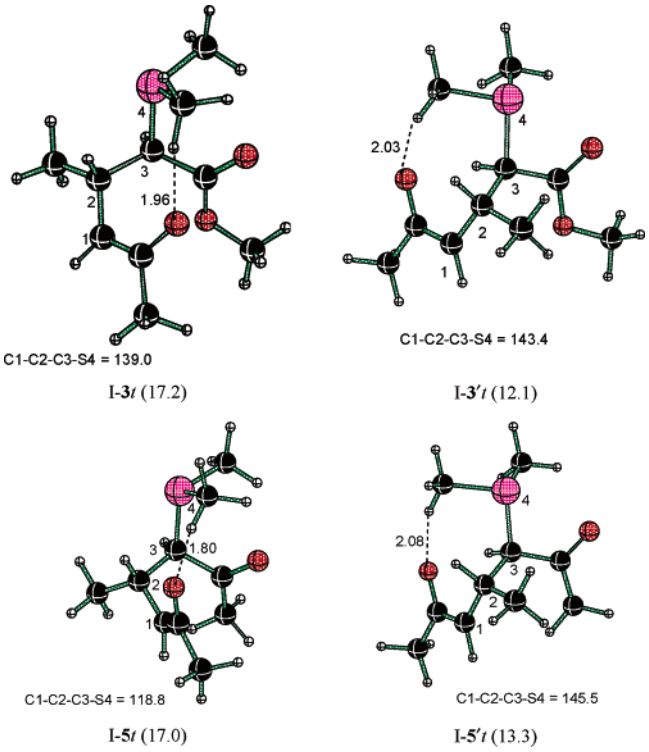


FIGURE 3. B3LYP/6-31G* optimized geometries and relative energies (in parentheses) for *cisoid* and *transoid* intermediates from stabilized ylides **3** and **5**. [Distances in Å, angles in deg, energies in kcal mol^{-1}. Atom colors: black = C, pink = S, red = O. Energies refer to Δ*E* in CH_3CN (kcal mol^{-1}) at the PCM/B3LYP/6-311+G**//B3LYP/6-31G* level. Energies are reported with respect to isolated reactants.]

1. *cisoid*/*transoid* Betaines and Addition Transition States. To examine the possibility of additional lower energy rotamers around the C_2-C_3 bond, a large number of starting geometries with varying $C_1-C_2-C_3-S_4$ dihedral angles were chosen (at 10° intervals each, along the clockwise and anticlockwise directions). Full optimization at the B3LYP/6-31G* level for such initial guess geometries led to additional conformers.[36,37] During this procedure, the SMe_2 group is oriented either *syn* or *anti* to the R substituent on the ylidic carbon (as, respectively, in I-**3***t* and I-**3′***t*, Figure 3). Unless otherwise specified, geom-

(34) Interestingly, the barrier for the initial addition of sulfur ylides to aldehydes and aldimines, respectively, in epoxidation and aziridination reactions are lower than in the present case at similar levels of theories (see refs 14d, 50).

(35) The reaction profile for **5** is provided in Figure 4. Details on ylides **3** and **4** are given in Figures S3, S4, S5, and Table S3 in the supporting information.

(36) Scanning the full rotational profile by partial optimization with frozen dihedral angles around the C_2-C_3 bond (in the intervals of 10°) were not successful, because optimization of geometries from 60° to 100° dihedral range have led to migration of ylidic H to the alkoxide oxygen. Similarly, geometries having dihedral angles around 150° resulted in breaking of the $(Me)_2S-C$ bond during optimization. Hence, we have chosen full optimization as an alternative approach to obtain various minima along the PES.

(37) We have selected I-**3***c*/I-**3′***c* as a representative case for an initial rotameric search. It was found that a minimum of three conformers exist for *cisoid* intermediates from both *syn* and *anti* pathways. Using the geometric features of these minima as a standard, a conformational search was then performed for all other betaines. It was noticed that all rotamers for *cisoid* intermediates along the *syn* pathway (or *anti* pathway) are closer in energies for a particular ylide (within 1−2 kcal mol^{-1}); the case with *transoid* intermediates is similar. This difference is much smaller when compared to the energy difference between *cisoid* and *transoid* intermediates along either the *syn* or *anti* pathway (which falls in the range of 3−7 kcal mol^{-1}; see Table S1, Supporting Information).

etries reported in the text pertain to the lowest energy structure obtained through this approach.[38]

The proximity of developing charge centers in *cisoid* betaines and corresponding TSs renders greater Coulombic stabilization as compared to *transoid* intermediates. As a result, *cisoid* betaines (I-**n***c*) are found to be lower in energy than *transoid* betaines (I-**n***t*).[39] While several *cisoid* intermediates are possible for both stabilized and semistabilized ylides, a number of *transoid* betaines are found to be rather limited, owing to a facile elimination of the SMe_2 group noticed during the course of geometry optimization. Starting geometries with $C_1-C_2-C_3-S_4$ dihedrals >120° led to dissociation in most cases, unless there is a possibility of weak stabilizing interaction through nonclassical H-bonding.[40] Such intramolecular interactions between SMe_2 group with enone oxygen as well as with an R group on ylidic carbon (for stabilized ylides) also contribute to the larger deviation from antiperiplanar arrangement in *transoid* betaines. The optimized geometries of representative *transoid* betaines in Figure 3 clearly convey the presence of C−H···O weak interactions in these betaine intermediates. Additionally, it is noticed that the *transoid* betaines in the *anti* pathway (*re*,*si*) exhibit larger deviation from staggered geometry than in the *syn* pathway (*re*,*re*), presumably to maintain such weak stabilizing interactions.[41] For instance, I-**3***t* and I-**5***t* are found to be more distorted ($C_1-C_2-C_3-S_4$ dihedrals are, respectively, 139.0° and 118.8° for **3** and **5**) than the corresponding *syn* betaines I-**3′***t* and I-**5′***t* ($C_1-C_2-C_3-S_4$ dihedrals being 143.4° and 145.5°)[42,43] (Figure 3).

On the basis of the closer energies of *cisoid* betaine intermediates as well as the limited number of *transoid* betaines (not more than three *transoid* betaines for *syn* and *anti* pathways for each ylide), we have intuitively narrowed down the search for possible conformers (for addition TSs) around the newly forming C−C bond. The initial geometries for *cisoid/transoid* addition TSs are chosen on the basis of two lower energy orientations of S-Me groups (SMe_2 methyl groups in *syn* and *anti* orientations with respect to the ylidic substituent). Thus, a total of four different addition TSs for the initial attack of each ylide to enone are reported (except the simplest ylide **1**, where only two TSs are possible). Among these, the lowest energy isomers in each pathway are further considered toward the construction of reaction profiles.[31]

2. Torsional and Elimination Transition States. As noted in the earlier sections, rotation from *cisoid* to *transoid* betaine is essential to be able to achieve a favorable antiperiplanar arrangement between the internal nucleophile and the leaving group. Rotation around the newly formed C−C bond can, in principle, be in either clockwise or anticlockwise directions. Hence, a minimum of two rotational transition states can be envisaged along the torsional profile. However, in the case of stabilized ylides, bond rotation has been fruitful only in one direction. The alternative route resulted in unwanted cyclization by the attack of the alkoxide oxygen to the carbonyl carbon of ylidic R group (in **3**, **4**, and **5**).[44] All attempts to locate additional S-Me rotamers were unsuccessful along both *syn* and *anti* pathways.

It should be noted that conformational possibilities around the C−C bond are also limited in the case of elimination TSs, owing to the requirement of antiperiplanar orientation between the internal nucleophilic carbon and the leaving group (SMe_2). Here again, of the two possible S-Me rotamers, only one TS could be identified. Weak H-bonding interactions, as noted previously in the case of *transoid* betaine intermediates, are found to be critical in stabilizing the elimination and torsional TSs as well. The lack of such stabilizations might presumably be contributing to the difficulty in identifying transition states with alternative S-Me rotameric forms. Attempts directed toward obtaining additional elimination and tortional TS than reported here continued to be illusive.

Diastereoselectivity Issues. The discussions thus far have been centered on the general features of the mechanism of cyclopropane formation. One of the major aims of the present study is to understand the diastereoselection in sulfur ylide promoted cyclopropanation reactions. Thus, we examined the energy profiles for the formation of diastereomeric cyclopropanes in detail, first with stabilized ylide **5**. The reaction profile as given in Figure 4 indicates that the *syn* betaine pathway (***a′*** as per Scheme 2) leading to 1,2-*trans* diastereomer is energetically more favored over that involving the *anti* betaine. There are two low energy addition TSs for the formation of *syn* betaines by a (*re*,*re*) approach between ylide and enone, TS-**5′***t* and TS-**5′***c*, which differ by only 0.3 kcal mol^{-1}. The next nearest TS (*re*,*si* approach, TS-**5***c*) is 1.0 kcal mol^{-1} higher in energy than the TS-**5′***t*, leading to *anti* betaine. The alternative *transoid* approach (pathway ***b***), through (*re*,*si*) face for *anti* betaine is found to be the highest energy TS among these possibilities. Thus, it can be concluded that the addition of stabilized ylides is likely to proceed via the *cisoid* addition mode. It should also be noted that even the *syn* pathway through TS-**5′***t* would result in a 1,2-*trans* product. Therefore, based on the calculated activation barriers, preferential formation of 1,2-*trans* diastereomer is anticipated.

(38) Optimized coordinates and total energies for all additional intermediate betaines obtained through a conformational/rotameric search are provided in Supporting Information.

(39) See Table S1, Supporting Information for relative energies.

(40) Non-classical H-bond interactions are noticed between SMe_2 hydrogens and alkoxide oxygen, as well as with the carbonyl group of the R on the ylidic carbon (as in **3**−**5**).

(41) It can be noticed that *transoid* intermediates from *anti* betaines are higher in energy than those from *syn* betaines. From the optimized geometries provided in Figure 3, it is apparent that the distortions induced in favor of weak interactions increase unfavorable steric crowding in *anti* betaines. It is also possible that the absence of solvent effects in geometry optimization partly contributes to the higher relative energies of these intermediates (I-**2***t*, I-**3***t*, and I-**4***t*) on reaction profiles. There are some reports indicating the failure of gas-phase methods in optimizing polar intermediates, particularly *transoid* betaines in similar reactions (see ref 14d,e). However, in the present case, all *transoid* intermediates could be identified on the gas phase PES.

(42) Optimized geometries of *transoid* betaines from *syn* and *anti* pathways for stabilized ylide **4** and semistabilized ylide **2** are provided in Supporting Information (Figure S2).

(43) In the case of ylide **3**, an additional antiperiplanar betaine intermediate is located on the PES. Energy of this stationary point is found to be higher than the lowest energy isomer by 1.5 kcal mol^{-1}. Though sterically favored, the antiperiplanar arrangement in this case does not offer any weak stabilizing H-bonding interactions similar to that present in other isomers/ylides.

(44) For instance, among two conformational possibilities for *anti* betaines, the geometry with Me_2S- and -Me eclipsing each other (relatively larger steric interaction compared to the other two pairs having eclipsing interaction with only the H atoms) provided the required torsional TS, whereas alternative geometry (Me_2S- and -H eclipsing pair) led to a six-membered cyclic structure upon optimization. Similarly, *syn* betaines also led to a unique torsional TS with Me_2S- and -H eclipsed. See Scheme S1 (Supporting Information) for a schematic representation of conformational possibilities arising from torsional motion. For semistabilized ylide, the unfavorable steric and electronic repulsive interactions between the alkoxide and phenyl groups presumably restricts the possibility of bond rotation in clockwise direction. Hence, similar to stabilized ylides, we could locate only one rotational TS each for *anti* and *syn* pathways.

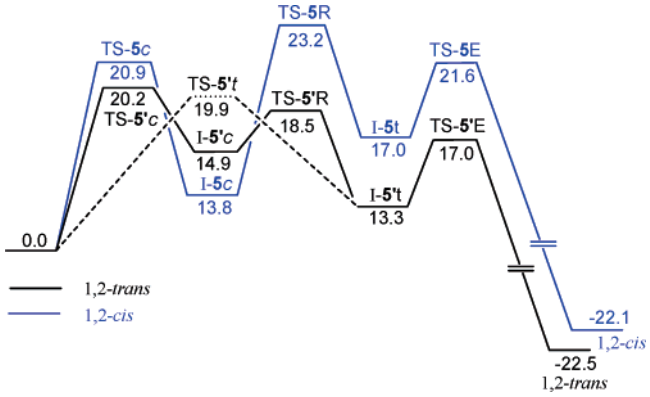


FIGURE 4. Reaction profiles for diastereomeric cyclopropane formation from stabilized ylide **5** (R = COMe**)** and enones. Activation energies in CH_3CN (kcal mol^{-1}) at the PCM/B3LYP/6-311+G**//B3LYP/6-31G* level. Energies are reported with respect to isolated reactants.

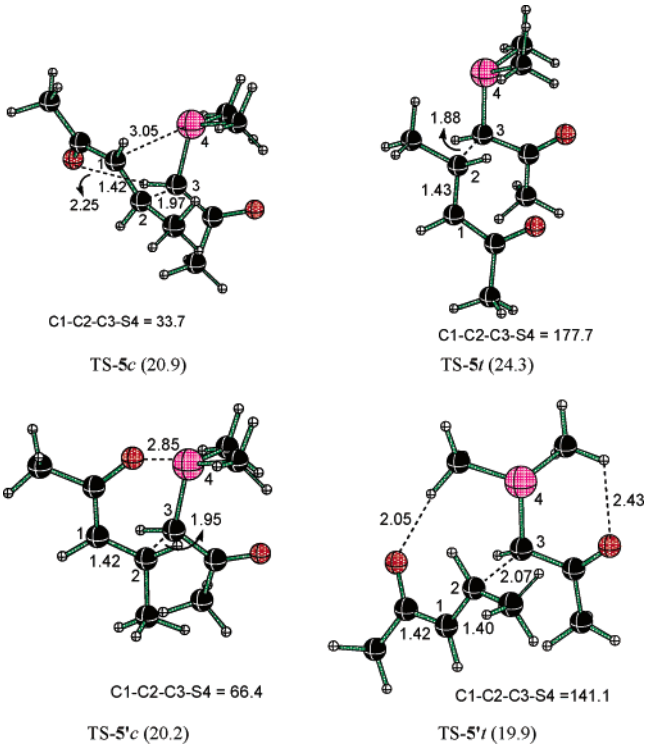


FIGURE 5. B3LYP/6-31G* optimized transition state geometries and activation barriers (in parentheses) for *cisoid* and *transoid* addition of stabilized ylide **5**. [Distances in Å, angles in deg, energies in kcal mol^{-1}. Atom colors: black = C, pink = S, red = O. Energies refer to ΔE in CH_3CN (kcal mol^{-1}) at the PCM/B3LYP/6-311+G**//B3LYP/6-31G* level. Energies are reported with respect to isolated reactants.]

Inspection of the highest energy points on the potential energy profiles given in Figure 4 points to the importance of torsional barriers in determining diastereoselectivity of cyclopropanation reaction. Along the *syn* pathway, addition is the rate-determining step, whereas the torsional barrier from *cisoid* (I-**n***c*) to *transoid* (I-**n***t*) intermediate controls the rate and selectivity for the *anti* pathway. Even though TS-**5′***c* and TS-**5′***t* are very close in energies, they will essentially lead to the same product. Next, if we consider the low-energy TSs along the *syn* and *anti* pathways (TS-**5′***t* and TS-**5***c*), they differ only by 1.0 kcal mol^{-1}, implying the formation of *syn* and *anti* betaine intermediates without any appreciable bias. Now, TS-**5**R holds a decisive role in controlling the overall selectivity of the reaction. The barrier for rotation (TS-**5**R) is much higher for the *anti* betaine intermediate I-**5***c*, and therefore the possibility of reverting back to the reactants is more than of surmounting the rotational barrier. At the same time, lower energies of TS-**5′**R and TS-**5′**E along the *syn* betaine pathway are expected to result in 1,2-*trans* product with high selectivity. A similar feature is also noticed with ylides **3** and **4** (R = CO_2Me, COPh, respectively), with a selectivity determining torsional TS.[35] Similar examples of torsional controlled diastereoselectivity have been reported previously for related ylide mediated epoxidation reactions.[14d] Thus, in general, we notice that when a stabilizing group is attached to the ylidic carbon (**3**, **4**, **5**), sulfur ylide promoted cyclopropanation leads to *trans* diastereomer (with an R group on the ylide and COMe on the enone).

Analysis of the reaction profile helped us establish the role of ylidic substituents in steering the diastereoselectivity in cyclopropane formation. Next, efforts were expended toward understanding how stereoelectronic as well as other weak interactions bring about the vital energy separation between the diastereomeric transition states. In this connection, optimized geometries of the addition TSs are carefully examined. General features are highlighted with the help of a representative ylide (**5**, R = COMe) as provided in Figure 5. Geometries reveal a predominance of electrostatic factors over steric ones in determining addition preferences. Electrostatic attractions as discussed in the previous sections are the major stabilizing factors that favor TS-**5′***t* over TS-**5***c*. It can also be seen that both of these TSs have substituents around the new C−C bond in comparable steric environments. The *transoid* TS-**5***t* with *anti* disposition of oppositely charged centers lacks Coulombic stabilization and thus found to be higher in energy compared to other possible TSs.[45] The energy differences between diastereomeric transition states could therefore be rationalized with the help of stereoelectronic effects. This approach will have wider implications toward the design of improved chiral sulfur ylides to be able to bring about a higher degree of diastereoselection.

It is interesting to note that the rate- and selectivity-determining steps are not the same for *anti* and *syn* betaine pathways. There is a large difference in energy between the rotation transition states TS-**5**R and TS-**5′**R. Inspection of optimized transition state geometries provided in Figure 6 conveys that there is an unfavorable eclipsing interaction between sulfur and the enone Me group in *anti* betaines, whereas the *syn* betaines only have a S···H eclipsing interaction. Other weak stabilizing interactions such as O···H are present in both TS-**5**R and TS-**5′**R geometries.[46] On the basis of the above analysis it is clear that the *cisoid-transoid* torsional motion (TS-**5**R) becomes the rate-determining step for *anti* betaines, primarily due to steric interactions.

Among other stabilized ylides, **3** follows a reactivity profile similar to that of **5**. Here, addition is found to be the rate-limiting step on the lower energy pathway leading to 1,2-*trans* product (Figure S3, Supporting Information). Along the *anti* betaine pathway, existence of TS-**3**R could not be established on the B3LYP/6-31G* potential energy surface.[24] Every attempt to locate TS-**3**R became entrapped in a second-order saddle point with a methyl rotor problem.[47] The undesirable second imaginary frequency pertaining to the Me group rotation (methyl of the COOMe substituent on ylidic center) could not be alleviated.

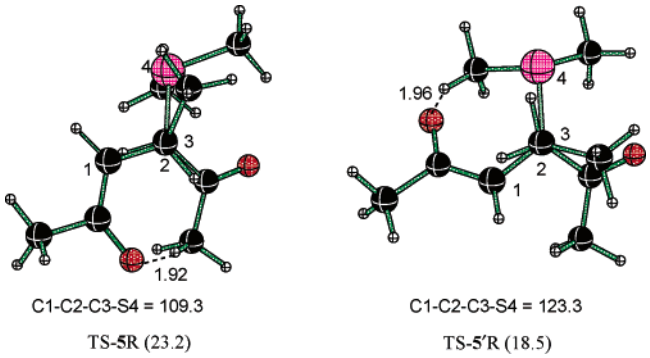


FIGURE 6. Optimized geometries and relative energies (in parentheses) for rotational transition states from *anti* and *syn* betaines for stabilized ylide **5** (viewed along the C2−C3 bond). [Distances in Å, angles in deg, energies in kcal mol^{-1}. Atom colors: black = C, pink = S, red = O. Energies refer to ΔE in CH_3CN (kcal mol^{-1}) at the PCM/B3LYP/6-311+G**//B3LYP/6-31G* level. Energies are reported with respect to isolated reactants.]

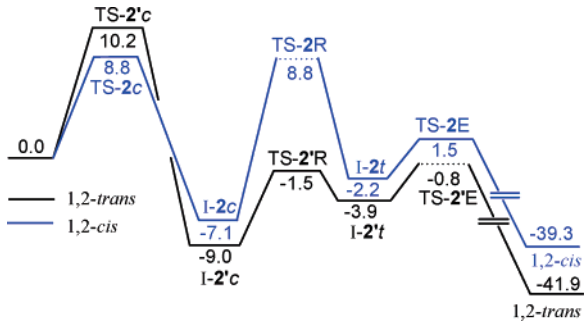


FIGURE 7. Reaction profiles for diastereomeric cyclopropane formation from semistabilized ylide **2** (R = Ph**)** and enones. Activation energies in CH_3CN (kcal mol^{-1}) at the PCM/B3LYP/6-311+G**//B3LYP/6-31G* level. Energies are reported with respect to isolated reactants. [For TS-**2**R (·····) and TS-**2′**E (·····) only, the relative energies are at the PCM/B3LYP/6-311+G**//HF/6-31G* level.]

Fortunately, after repeated attempts, optimizations using the Hartree−Fock method as well as the mPW1PW91 functional were successful. Single-point energies were then evaluated at the B3LYP/6-311+G** level on the mPW1PW91/6-31G* optimized geometries. The activation barriers and relative energies for TS-**3**R are then compared with those available for various TSs on the reaction profile. Thus, the *anti* pathway for

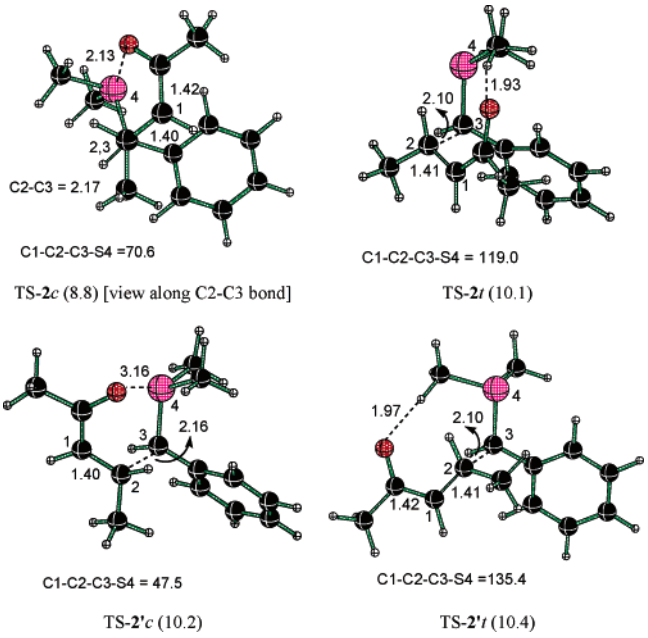


FIGURE 8. B3LYP/6-31G* optimized transition state geometries and activation barriers (in parentheses) for *cisoid* and *transoid* addition for semistabilized ylide **2**. [Distances in Å, angles in deg, energies in kcal mol^{-1}. Atom colors: black = C, pink = S, red = O. Energies refer to ΔE in CH_3CN (kcal mol^{-1}) at the PCM/B3LYP/6-311+G**//B3LYP/6-31G* level. Energies are reported with respect to isolated reactants.]

ylide **3** exhibits a rate-limiting rotation, in concurrence with ylide **5**. Similar to **3**, ylide **4** also proceeds with a *cisoid* addition followed by a rate-limiting rotation step.[25,48] However, an interesting aspect pertaining to ylide **4** needs additional attention. Computed barriers provided in Table 2 shows that the *transoid* addition TS (TS-**4***t*) is 9.9 kcal mol^{-1} higher in energy than the *cisoid* congener. Moreover, this isomer is higher in energy than the corresponding TS along the *syn* pathway by 7.7 kcal mol^{-1}. Steric and electronic factors, described earlier for the addition TSs, are found to be equally contributing to the energy difference in this case as well. (For further details see Figures S4 and S5 in Supporting Information.)

Semistabilized ylide **2**, as noted earlier, proceeds through a rate-determining addition step.[49] Addition is moderately exothermic, and the successive barriers for rotation and elimination are less energy demanding as compared to stabilized ylides. Energy profiles for the formation of diastereomeric products as

(45) (a) The natural charges computed using the NBO (natural bond orbital) method supports this argument. From the NPA (natural population analysis) charges computed for the addition TSs for ylide **5**, it was found that the *transoid* TSs, which cannot attain any coulombic stabilization due to the particular geometric arrangement, carry lower charge densities on the positive sulfur center (see Figure S6, Supporting Information for NPA charges). The *cisoid* TSs, on the other hand, carry higher charges on sulfur that get stabilized by opposite charge centers in close proximity. The natural population analysis was performed at the B3LYP/6-311+G**// B3LYP/6-31G* level using the NBO (natural bond orbital) method employing the NBO 3.1 program package as implemented in Gaussian98. See: (b) *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. (c) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899.

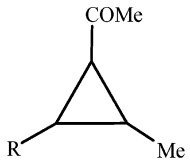
(46) The role of stabilizing weak interactions is further evident from the orientation of methyl groups attached to S, which differs in two TSs. In both *syn* and *anti* forms, methyl groups get oriented in such a way that the structures maintain non-classical H-bonding interactions.

(47) There are other instances of methyl rotor problems; see: (a) Fowler, J. E.; Schaefer, H. F., III; Raymond, K. N. *Inorg. Chem.* **1996**, *35*, 279. (b) Wiberg, K. B.; Rush, D. J. *J. Org. Chem.* **2002**, *67*, 826.

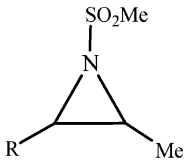
(48) See Figures S4 and S5 in Supporting Information. Even if the addition TS for *anti* betaine is lower in energy, the torsional barrier is higher along the *anti* pathway. Hence, the 1,2-*trans* product is anticipated via the *syn* pathway as in the case of other stabilized ylides.

(49) As mentioned earlier, we could not locate TS-**2**R and TS-**2′**E on the B3LYP/6-31G* potential energy surface. Optimizations were therefore carried out at the HF/6-31G* level. Relative energies and activation barriers were then computed by evaluating single-point energies at the (PCM)/B3LYP/6-311+G** level on the HF/6-31G* geometries. Based on the available data it is noticed that the selectivity is dependent only on the addition step for ylide **2**; the low-lying rotation and elimination TSs have virtually no role in the diastereoselection. Additionally, to verify whether there is any major difference in the nature of the energy profile at the HF level, we have recalculated all stationary points for the *anti* betaine pathway for a representative ylide **3** at the HF/6-31G* level. Energies computed at the PCM(CH_3CN)/B3LYP/6-311+G**//HF/6-31G* are found to be in very good agreement with those obtained using the PCM(CH_3CN)/B3LYP/311+G**//B3LYP/6-31G* methods (see Table S3, Supporting Information). Thus, we anticipate that the energies obtained at the PCM/B3LYP/6-311+G**//HF/6-31G* level are good enough to draw meaningful conclusions in the present case.

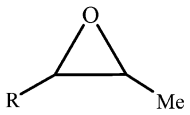
TABLE 3. Comparison of Cyclopropanation Reaction Profile with Other Mechanisms of Sulfur Ylide Mediated Aziridination and Epoxidation Reactions



1



2



3

reaction	reactant pairs	selectivity-determining step	product (*trans*/*cis*)	selectivity
1[a]	**5** + $CH_3CH{=}CHCOMe$	rotation	1,2-*trans*	high ($\Delta\Delta E^{\dagger} = 4.7$)[d]
	2 + $CH_3CH{=}CHCOMe$	addition	1,2-*cis*	moderate ($\Delta\Delta E^{\dagger} = 1.4$)
2[b]	**3** + $PhCH{=}NSO_2Me$	elimination	2,3-*cis*	low ($\Delta\Delta E^{\dagger} = 0.3$)
	2 + $PhCH{=}NSO_2Me$	addition	2,3-*trans*	low ($\Delta\Delta E^{\dagger} = 0.9$)
3[c]	**2** + PhCHO	rotation	2,3-*trans*	moderate ($\Delta\Delta E^{\dagger} = 1.7$)

[a] Cyclopropanation (current study). [b] Aziridination.[50] [c] Epoxidation.[14d] [d] Energies in kcal mol^{-1}.

shown in Figure 7 indicate that the 1,2-*cis* product via *anti* betaine is favored over *syn* betaine by 1.4 kcal mol^{-1} (for the rate-limiting addition step), though subsequent steps in the *syn* pathway are lower in energy. Another methodology-dependent issue associated with the *anti* betaine pathway is the degeneracy between the torsional and addition TSs. In spite of exhaustive searches, TS-**2**R remained illusive with the DFT-based methods. Thus, geometry optimization is carried out at the HF/6-31G* level. This might have resulted in a higher energy torsional transition state (TS-**2**R) for a reactive ylide such as **2**. Along lines similar to that of stabilized ylides, involvement of a higher energy torsional TS in the *anti* betaine pathway cannot be neglected. Thus, in the present case, even if TS-**2′**R is favored over TS-**2**R, the addition TS being the highest energy point on the PES precludes torsional barrier from being the selectivity-determining factor. Assigning a preference for the *anti* pathway for semistabilized ylides is therefore quite reasonable according to the available energies.[50] Smaller energy differences in the selectivity-determining step between *syn* and *anti* pathways are thus expected to lead to moderate diastereoselectivity.

Detailed inspection of transition state geometries for the initial addition step is performed with an objective of identifying the reasons behind diastereoselection. Similar to the earlier observations with stabilized ylides,[14a,d] *cisoid* addition modes are found to be favorable along the *syn* and *anti* pathways. From the optimized geometries provided in Figure 8, it is clear that the low energy addition TSs have similar steric and electronic interactions. The lowest energy TS (TS-**2***c*) has little steric encumbrance around the newly forming bond (methyl and phenyl substituents, respectively, on C2 and C3 are oriented at a dihedral angle of 74°, which is the most staggered arrangement compared to other TSs). Additionally, this geometry is favored by electrostatic interactions. On the other hand, the remaining three TSs of the same group with comparable energies all have similar steric environments. Among these, the *cisoid* TS from *syn* betaine (TS-**2′***c*) enjoys a nearly staggered arrangement. As described earlier in the case of *transoid* intermediates, weak interactions also play a major role in stabilizing the *transoid* TSs. Such a type of H-bonding interactions have recently been designed to achieve high diastereo- and enantiocontrol in ylide mediated reactions of vinylcyclopropanes.[13j]

In general, ylides bearing strongly electron-withdrawing groups follow path ***a′*** via *syn* betaines (Scheme 2) leading to 1,2-*trans* cyclopropane as the final product. Semistabilized ylides, on the other hand, result in 1,2-*cis* product via *anti* betaines (path ***a***). The product distribution predicted for stabilized ylides in this study is in agreement with available experimental reports.[9i,9l,12e] For instance, the high *trans* selectivity predicted for stable ylides is in good agreement with that reported for *trans* cyclopropane diesters by Payne.[9i] The chiral oxathiane based sulfur ylide methodology toward 2-arylcyclopropane carboxylates reported by Solladié-Cavallo and coworkers gave excellent enantioselectivities (95−100% ee) and high diastereoselectivities (up to 99:1 for *trans*) for semistabilized ylides.[13a] This observation is at variance to our finding that semistabilized ylides lead to moderate selectivity toward 1,2-*cis* products. Since diastereoselectivity is established in the initial addition step, it is worth reckoning that the nature of the sulfur reagent could play a decisive role in the stereoselection.[51] Rigidity of the chiral sulfur reagent used in their studies might restrict the number of possible addition modes that are discussed in the present manuscript. Obviously, our model system does not incorporate some of the key features (rigidity and chiral nature) of the sulfur reagent used in the above experiments. This could have contributed to the difference between predicted and experimental stereoselectivities.

At this juncture, a comparison of reaction mechanism and diastereoselection with a related series reaction studied using the density functional theories will be of interest. A succinct comparison of cyclopropanation with other sulfur ylide promoted reactions such as aziridination and epoxidation is included in Table 3. The selectivity-determining step for the cyclopropanation reaction for stabilized ylides (**3**−**5**) is found to be the *cisoid*-*transoid* rotation, different from the elimination-controlled aziridination mechanism.[52] In the case of semistabilized ylide (**2**), rate and selectivity depend on the initial addition step in both cyclopropane and aziridine formation, whereas rotation-controlled selectivity is predicted for epoxidation reaction.[14d] In other words, the addition step for epoxidation proceeds with relatively lower barriers. This indicates an effective Coulombic stabilization (between S^+ and developing O^-) in the *cisoid*

(50) A similar prediction relating to aziridination reactions appeared in the literature very recently. See: Robiette, R. *J. Org. Chem.* **2006**, *71*, 2726.

(51) (a) Although there is no direct experimental evidence that demonstrates that different sulfides will lead to different diastereoselectivity, experimental reports on the effect of sulfur substituents on stereoselectivity are available; see: Aggarwal, V. K.; Smith, H. W.; Hynd, G.; Jones, R. V. H.; Fieldhouse, R.; Spey, S. E. *J. Chem. Soc., Perkin Trans.* **2000**, *1*, 3267. Also see ref 13f.

(52) For sulfur ylide mediated epoxidation, no reaction profile is available for the stabilized ylides considered in this work.

addition mode en route to TS/intermediate during epoxidation. 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. The differences in the reaction profiles exhibited by these three kinds of electrophiles are hence justifiable.

Conclusion

Reaction profiles for cyclopropanation reaction have been found to be quite sensitive to the nature of substituent attached to the ylidic carbon. A *cisoid* mode of attack by stabilized and semistabilized ylides on the enones were found to be preferred over the *transoid* addition. Inspection of transition state geometries revealed that both steric and electronic factors are equally significant in favoring one of the addition modes (*cisoid* or *transoid*). In the case of stabilized ylides, electrostatic attractions between the developing charge centers as well as steric factors become equally decisive in controlling addition preferences. A similar situation was noticed with semistabilized ylides, where a combination of these effects led to moderate diastereoselection. The high *trans* selectivity predicted for stabilized ylides was found to originate from the difference in degree of steric encumbrance associated with the diastereomeric torsional TSs. At the same time, the lower energies of torsional and elimination TSs leaves addition as the selectivity-determining step for semistabilized ylides, resulting in a moderate selectivity toward 1,2-*cis* cyclopropane. Additionally, the lower energy pathway was found to result in a *trans* stereochemical relationship between larger substituents in both stabilized and semistabilized ylides.

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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−S6, Scheme S1, Tables S1−S4 and full list of citations for Gaussian98 and Gaussian03 (ref 17 in the text). This material is available free of charge via the Internet at http://pubs.acs.org.

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