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PAPER

Chemo-, regio-, and diastereoselectivity preferences in the reaction of a sulfur ylide with a dienal and an enone†

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Mechanistic insights into an interesting class of reaction between sulfur ylides with (i) a dienal, and (ii) an enone, obtained by using density functional theory, is reported. The kinetic and thermodynamic factors responsible for chemo-, regio-, and diastereoselectivities are established by identifying all key transition states and intermediates along the reaction pathway for 1,2-, 1,4-, and 1,6- modes of attack of dimethylsulfonium benzylide to 5-phenylpenta-2,4-dienal. The reaction profiles for 1,2- and 1,4- modes of addition are also evaluated for the reaction between dimethylsulfonium benzylide and pent-3-en-2-one. Our results show that the final outcome of the reaction with both these substrates would be decided by the interplay between kinetic and thermodynamic factors. It is found that the addition of a semi-stabilized ylide to conjugated carbonyl compounds prefers to proceed through a 1,4-(conjugate) pathway under thermodynamic conditions, which is in accordance with the available experimental reports. However, the formation of epoxides *via* a 1,2- (direct) addition pathway is computed to be equally competitive, which could be the favored pathway under kinetic conditions. Even though the lower barrier for the initial addition step is kinetically advantageous for the direct (or 1,2-) addition pathway, the higher energy of the betaine intermediates—as well as the reversibility of the accompanying elementary step—may disfavor product formation in this route. Thus, high diastereoselectivity in favor of 2,3-*trans* cyclopropanecarbaldehyde is predicted in the case of the dienal, using the most favored conjugate addition (1,4-addition) pathway. Along similar lines, ylide addition to the enone is identified to exhibit a preference toward conjugate addition over direct (1,2-) addition. The importance of transition state analysis in delineating the controlling factors towards product distribution and diastereoselectivity is established.

Introduction

The chemistry of cyclopropanes and their diverse applications continues to fascinate chemists across different areas such as theoretical, synthetic, natural product and medicinal chemistry. The utility of cyclopropanes in various synthetic transformations makes them attractive targets. Some of these transformations have been useful in generating non-natural amino acids, pesticides, and precursors of complex natural products.[1] Cyclopropanes are also found in several naturally occurring and biologically important molecules.[2] Cyclopropane based peptidomimetics is another interesting application.[3]

Substituted cyclopropanes are generally synthesized *via* the addition of nucleophilic reagents to electron deficient olefins. Popular methods for their preparation involve variants of the Simmons–Smith reaction,[4] transition metal catalyzed addition of carbenoids to olefins,[5] and Michael-initiated ring closure reactions.[6,7] Among these approaches, sulfur ylide addition[8] to either an α,β-unsaturated carbonyl compound[9] or an olefin[10] is a well-known ring formation strategy involving nucleophilic addition-elimination protocol. The chiral version of this reaction has been made popular independently by the research groups of Aggarwal[11] and Dai.[8,12] In a remarkable application utilizing this method, Solladié-Cavallo and co-workers have been able to achieve impressive enantioselectivity in cyclopropane synthesis by employing an oxathiane chiral auxiliary.[13] The use of other similar ylides based on tellurium,[14] iodine,[15] nitrogen[16] and phosphorus[17] *etc.*, has also contributed to the development of ylide mediated cyclopropanation methodology.

In the reaction of S-ylides with α,β-unsaturated carbonyl compounds (in particular, enones), a preference toward conjugate addition is generally noticed over direct addition, when the ylidic carbon is attached to an electron withdrawing substituent.[9–13] However, with more reactive ylides, the addition can also be chemoselective, offering an oxirane product besides the expected cyclopropane. In their seminal work, Corey *et al.* have reported that more reactive sulfonium ylides exhibit propensity toward

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1,2-addition, whereas a less reactive sulfoxonium ylide resulted in the formation of cyclopropanes *via* a Michael type addition-elimination mechanism.[18] In a more recent study on the synthesis of chiral cyclopropanes,[13] Solladié-Cavallo and co-workers have observed the formation of epoxides when strong phosphazine bases were employed for the generation of ylides.[13] In another example, the same group has reported the synthesis of epoxides from arylsulfonium salts and conjugated aldehydes.[19] These select examples raise some interesting questions; in spite of being a more reactive functional group, why is the addition to the carbonyl not preferred under normal conditions when S-ylides react with conjugated carbonyl compounds? Is the qualitative picture based on electron pushing sufficient to explain whether the above observation has a kinetic or thermodynamic origin? The survey of the available literature conveys that insights on the energetics related to the preferred additions—conjugate *versus* direct—in such reactivity patterns are conspicuously absent.

Further, reports on the mechanistic features of ylide mediated reactions are rather limited despite wide spread interest in the synthetic applications of S-ylides.[20] A few reports on epoxidation and aziridination reactions have appeared lately in literature.[12b,21] As part of our continued interest in S-ylide promoted ring formation reactions, we have recently reported the mechanism and stereoselectivity of aziridination[22] and cyclopropanation reactions[23] by using density functional theory studies. The lack of detailed insights on selectivity issues, chemoselectivity in particular, associated with α,β-unsaturated carbonyl compounds, has prompted us to investigate the intricacies associated with selectivity and the mechanistic course of the reaction between S-ylides and different acceptor molecules (conjugated aldehydes and ketones).

Terminology

The 1,2-, 1,4- and 1,6- pathways for the addition of a semi-stabilized ylide to a dienal are represented by numerals **1**, **2** and **3**. Numbers **4** and **5** denote the addition modes for the enone system, in a similar manner. The (*re*,*re*) and (*re*,*si*) diastereomeric approaches between reactants are designated by using letters **a** and **b**. The notations used in the text can be described as follows. In the (*re*,*re*) mode of 1,2-addition pathway (**1**), the *cisoid*/*transoid* addition transition states (TSs) are represented as **1a**-A-$c^{\ddagger}$/**1a**-A-$t^{\ddagger}$ and the resulting *cisoid*/*transoid* betaine intermediates are designated as **1a**-*c*/**1a**-*t*. The *cisoid* and *transoid* stereochemical notations for the addition TSs and intermediates denote whether the orientation of charge centers on the ylide and dienal (or enone) are on the same or opposite sides of the developing C–C bond. The representations for *cisoid*-to-*transoid* torsional TS and elimination TS are respectively **1a**-R‡ and **1a**-E‡. Lastly, the product complexes are designated as **1a**-PC. Similar notations have been employed for the addition of ylide to the *si* face of electrophile, and for pathways **2** through **5**. In all the tables and figures, a generalized notation **n** is employed to represent designators **1a–5a** (and **1b–5b**). The relative energies between various TSs are denoted by $\Delta\Delta E^{\ddagger}$ and the activation barriers by $\Delta E^{\ddagger}$.

Results and discussion

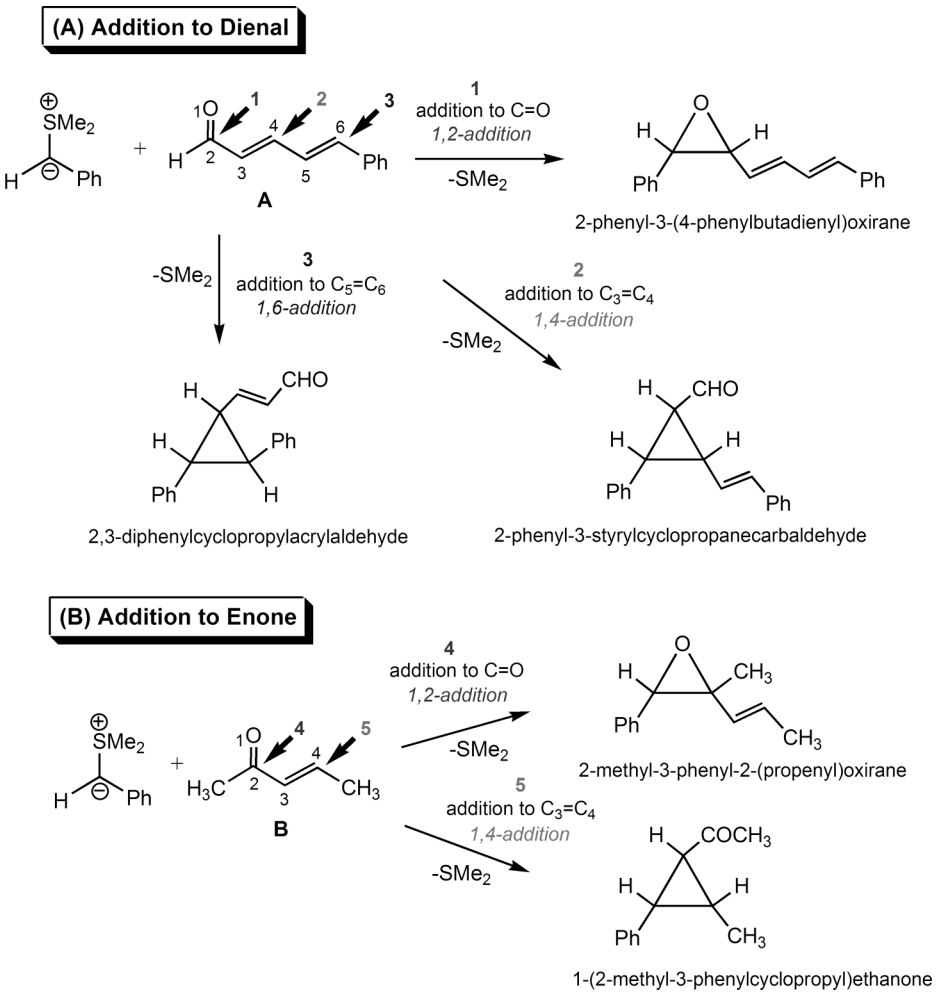
In the present work, mechanistic and selectivity issues associated with the addition of a semi-stabilized ylide[24] – dimethylsulfonium benzylide[25] – to electrophiles such as dienals and enones are investigated (Scheme 1). Substituted enones (or enals) and stabilized ylides (with an electron withdrawing group attached to the ylidic carbon) are generally employed in cyclopropanation reactions as compared to the unsubstituted model examined here.[9a–c,f–i,10b,11a,12a–b,13a] A concise representation for the attack of the ylide (using its *re* face) on the *re* face of the dienal and the subsequent steps leading to the 2,3-*cis* product is provided in Scheme 2. Similarly, the attack of the ylide to the other prochiral face of the dienal (or enone), *i.e.*, the (*re*,*si*) approach, will result in the formation of a 2,3-*trans* product.[26] Since an achiral ylide is employed here, the alternative (*si*,*re*) and (*si*,*si*) approaches will essentially give rise to enantiomeric products of those obtained from the (*re*,*re*) and (*re*,*si*) approaches, and hence are not considered in the present work. We have chosen the 2*E*,4*E*-*cis*,*trans* isomer of the dienal for the present investigation.[27]

Experimentally, the reaction between an ylide and enone (or enal) follows the general synthetic procedure adopted in similar class of reactions such as the formation of aziridines or epoxides. *i.e.*, by the addition of ylides to electron deficient substrates.[7,8] The two methods involving either a reaction between (i) preformed sulfonium salts and Michael acceptors,[12] or (ii) an *in situ* generated sulfur ylide (from a sulfur reagent and a carbene source)[11] with Michael acceptors are quite popular for the synthesis of diastereo- or enantiomeric cyclopropanes. However, irrespective of the synthetic routes mentioned above, stereoselection happens in the second phase of the reaction, *i.e.*, during the addition of the ylide to the acceptor. Therefore, the present work focuses only on the mechanistic course initiated by the addition of the ylide to the dienal (or enone). Specific details of our findings on the S-ylide reaction with two different acceptors are presented in the following sections.

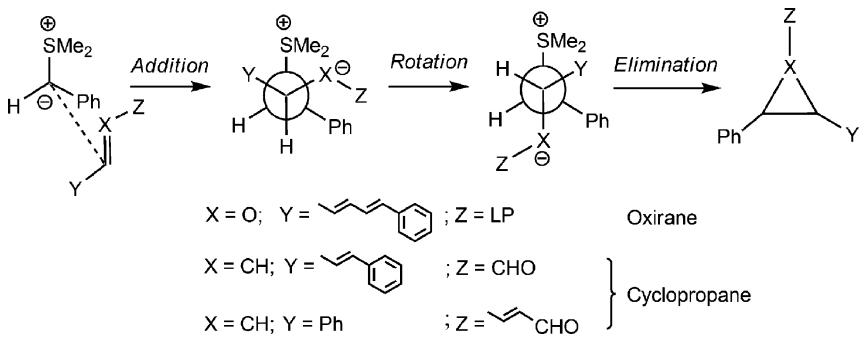
A. Addition of a ylide to a dienal

The dienal **A** ((2*E*,4*E*)-5-phenylpenta-2,4-dienal) offers a rich platform to examine the selectivity preferences toward the addition of sulfur ylide nucleophiles. Interestingly, selectivity possibilities such as chemo-, regio-, and stereoselectivities can be readily envisioned. Since in this study we have only considered achiral ylides, enantioselectivities are not pertinent to the present situation.

(a) Mechanism and selectivity in the addition of a semi-stabilized ylide to a dienal. In accordance with the generally proposed mechanism of sulfur ylide promoted reactions,[20–23] it is expected that each of the modes as illustrated in Scheme 1 proceeds through three distinct and successive steps. These key steps are; (i) the initial addition of the nucleophile to the electrophilic double bond (C=O or C=C), (ii) torsional motion around the newly formed C–C bond to achieve an *antiperiplanar* orientation between the internal nucleophile and the departing SMe_2 group, and finally (iii) the elimination of the S-reagent. These steps are summarized in Scheme 2. Earlier mechanistic studies on similar reactions have shown that the nature of the ylide and the electrophile have a decisive role in controlling the rate and stereochemical outcome of the reaction. For instance, semi-stabilized and stabilized ylides with ylidic substituents of varying charge stabilizing abilities react with the same electrophile, say, a substituted imine to furnish diastereomeric aziridines, through different rate-limiting steps (addition step for the former and



Scheme 1 Important modes of addition of dimethylsulfonium benzylide to (i) the dienal, and (ii) the enone, and the corresponding products (the atom numbering for dienal, though not in accordance with the standard nomenclature, is to enable quick distinction between different addition modes).



Scheme 2 A simplified mechanistic scheme illustrating the three key steps leading to the formation of cyclic products from dimethylsulfonium benzylide and the dienal (a representative (*re*,*re*) reactant approach is shown).

ring-closure step for the latter).[21c,22] A comparison of available reports additionally indicates that a change in the electronic charge stabilizing potential of the electrophile, for instance, from an aldehyde to an enone, alters the rate-limiting step of the reaction. The addition of semi-stabilized ylides, such as dimethylsulfonium benzylide, to aldehydes and enones respectively leading to epoxides and cyclopropanes are shown to possess different rate-limiting steps. The difference in behavior of these electrophiles is mainly attributed to the effective charge delocalization in the relevant TSs.[28]

In light of the above observations, it will be interesting to examine the dienal as an electrophile, wherein the charge stabilization (delocalization) associated with the three modes of addition is expected to be different. The 1,4- and 1,2-additions have been known for the reaction between ylide and conjugated carbonyl compounds.[9,11] Besides these two major possibilities, a

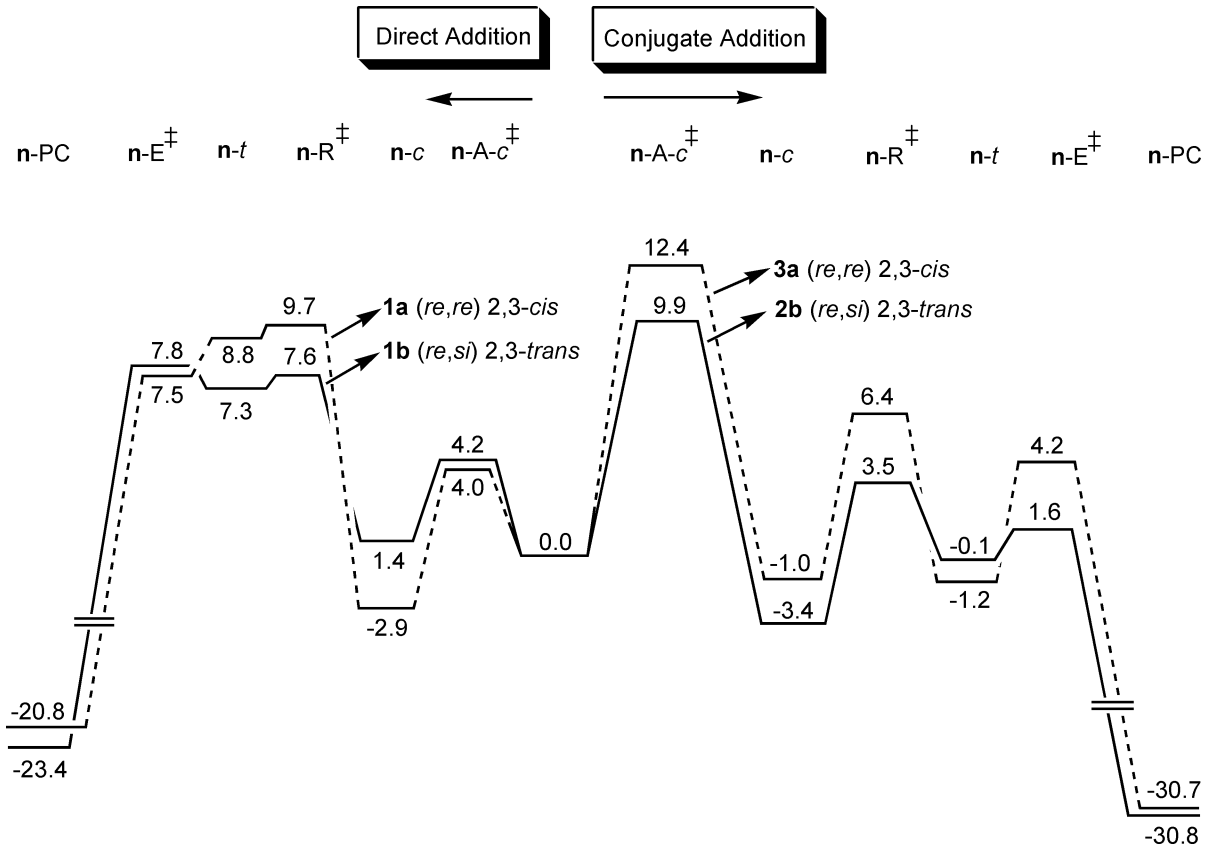


Fig. 1 The lowest energy diastereomeric pathways for the direct (**1a**, **1b**) and conjugate (**2b** and **3a**) addition pathways for the reaction between dimethylsulfonium benzylide and dienal computed at the $PCM_{(MeCN)}$/B3LYP/6-311G**//B3LYP/6-31+G* level (ΔE in kcal mol^{-1} relative to the separated reactants).

Table 1 The relative energies of (in kcal mol^{-1}) TSs, intermediates and products for the 1,2- (pathway-**1**), 1,4- (pathway-**2**), and 1,6- (pathway-**3**) addition of dimethylsulfonium benzylide to the dienal obtained at the $PCM_{(MeCN)}$/B3LYP/6-311G**//B3LYP/6-31+G* level of theory[a]

Pathway	**n**-A-*c*‡	**n**-A-*t*‡	**n**-*c*	**n**-R‡	**n**-*t*	**n**-E‡	**n**-PC
1a	4.0	8.2	−2.9	9.7[b]	8.8[c]	7.5[b]	−20.8
1b	4.2	8.4	1.4	7.6	7.3[c]	7.8[c]	−23.4
2a	11.8	13.1	−3.6	−0.6	0.8[b]	3.8[c]	−34.6
2b	9.9	15.7	−3.4	3.5	−0.1	1.6	−30.8
3a	12.4	12.9	−1.0	6.4	−1.2[b]	4.2[c]	−30.7
3b	13.6	13.0	0.7	7.3	3.3[b]	1.0[c]	−29.2

[a] **a** and **b** respectively denote (*re*,*re*) and (*re*,*si*) approaches between the nucleophile and the electrophile. Energies are relative to the separated reactants. [b] $PCM_{(MeCN)}$/B3LYP/6-31+G* geometry is used. [c] HF/6-31+G* geometry is used.

lesser known variant involves the attack at the terminal double bond of the dienal. In the presence of an electron withdrawing substituent such as a phenyl group at C_6, the addition of ylide to the γ,δ-double bond of the dienal (*i.e.*, 1,6-addition) could also compete with the other two possibilities.

The relative energies of various TSs and intermediates for the three modes as described above, for the addition of ylide to the *re* and *si* faces of the dienal are presented in Table 1.[29] The examination of the activation barriers for the initial addition step reveals that the 1,2-addition (pathway-**1**) is more favored as compared to the other modes. The barriers for the other modes, such as pathways **2** and **3**, are found to be higher. However, a comprehensive comparison of the energy profiles as shown in Fig. 1 indicates that a competition between the 1,2- and 1,4-addition products is quite likely (*vide infra*). A quick inspection of the energy values shows that, after the initial addition, the subsequent TSs and intermediates lie at high energies in pathway-**1**, whereas they are relatively more stabilized in **2** and **3**. For all the three addition modes, the product complexes are very much lower in energies and thus highly stable on thermodynamic grounds.

The energy profile diagram constructed on the basis of the relative energies of various stationary points is provided in Fig. 1.[30] It can be noticed that the rate-limiting step for the 1,2- and the conjugate addition pathways are different. While *cisoid-transoid* torsion around the newly formed C–C bond in the betaine intermediate is the highest energy point along the 1,2- pathway, the initial addition of the ylide to the C=C bond (C_3=C_4 bond in pathway-**2** and C_5=C_6 in pathway-**3**) is found to be the slowest step for the other two pathways. Thus, the torsional barrier in the case of pathway-**1**, and the addition barriers in the case of pathways **2** and **3** control the rate and diastereoselectivity. The energy difference between the rate-limiting steps in pathway-**1** (torsional TS **1a**-R‡) and pathway-**2** (addition TS **2b**-A-*c*‡) is found to be quite small (0.2 kcal mol^{-1}) implying a likely competition between the formation of cyclopropanes and epoxides. This prediction presents an interesting situation that demands closer scrutiny. In

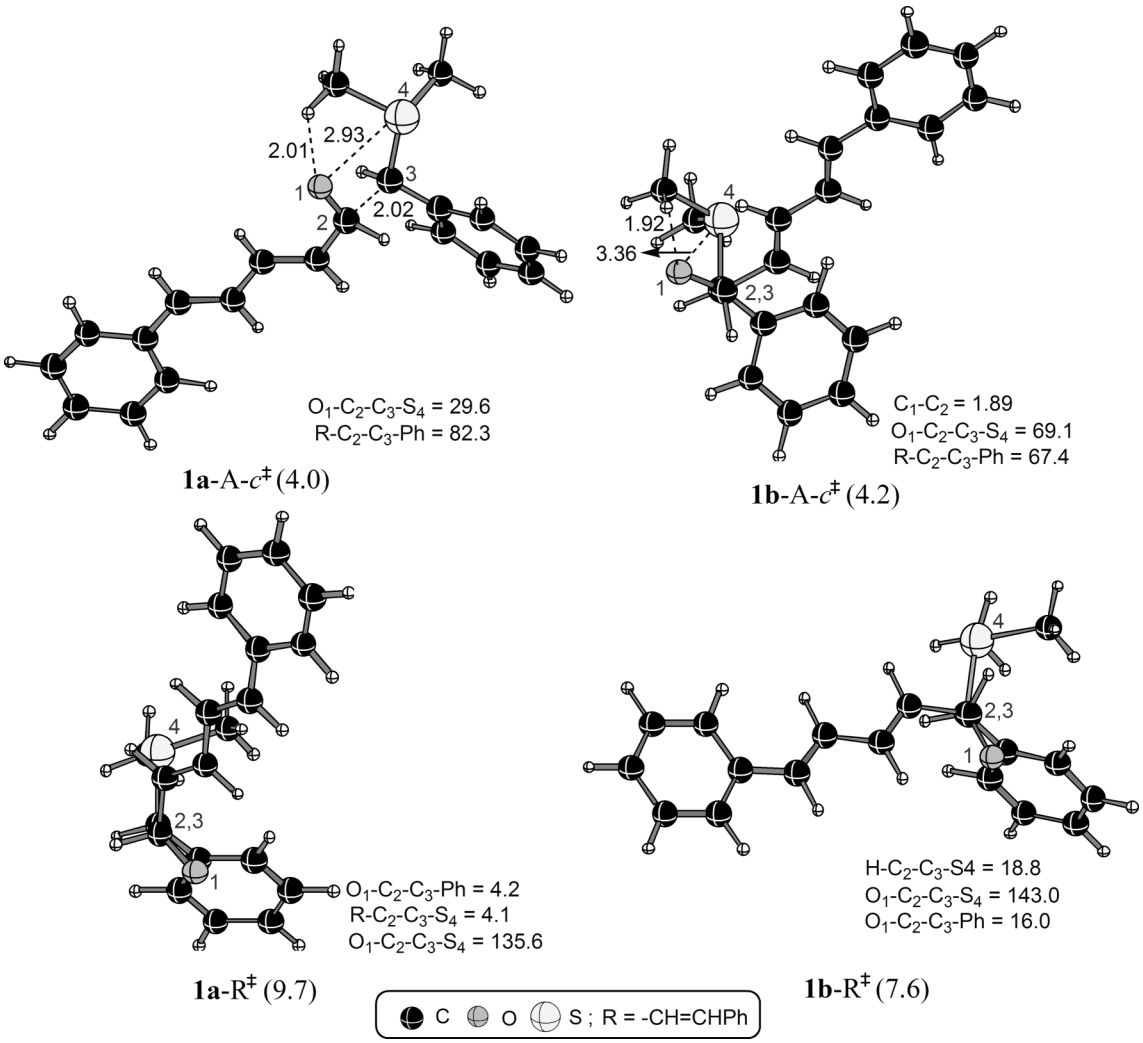


Fig. 2 The B3LYP/6-31+G* optimized geometries and relative energies (ΔE) of diastereomeric addition and torsional TSs in pathway-**1** (1,2-addition) for the reaction between dimethylsulfonium benzylide and the dienal (distances in Å and angles in °). (For **1b**-A-*c*‡ and the torsional TSs, the view along the C_2–C_3 bond is shown) [ΔE in kcal mol^{-1} obtained at the PCM$_{(MeCN)}$/B3LYP/6-311G**//B3LYP/6-31+G* level are provided in parentheses. Energies are relative to the separated reactants].

the following sections, the nature of different addition modes is discussed in detail.

(i) Pathway 1 (1,2-addition). As mentioned in the previous section, torsional motion from *cisoid* to *transoid* betaine is the rate-limiting step for 1,2-addition. This step appears reversible in the case of pathway-**1** (Fig. 1). In other words, the betaine intermediates such as **n**-*t*, along pathways **1a** and **1b**, could revert back to the reactants perhaps as much as its propensity to convert to the final product. In fact, three points on the lower energy diastereomeric pathway **1b**—namely the torsional and elimination TSs, and *transoid* betaine—are of almost similar energies. The corresponding diastereomeric pathway-**1a** also exhibits similar features to that of **1b**. From the relative energies of the rate-limiting torsional TSs **1a**-R‡ and **1b**-R‡ ($\Delta\Delta E^{\ddagger}$ of 2.1 kcal mol^{-1}), a *de* of 94% in favor of *trans* epoxides can be predicted (Table 1). However, the reversibility and endothermicity of the elementary steps in the 1,2-pathway suggest that the epoxide formation is less likely to enjoy any thermodynamic advantage. Furthermore, the closer energies of the rate-limiting steps in the 1,2- (**1b**-R‡) and the 1,4- pathways (**2b**-A-*c*‡) could likely lead to competition between epoxide and cyclopropane formation.

A comparison between the reaction of ylides with α,β-unsaturated carbonyl compounds and other similar substrates is of interest at this juncture. In an earlier report on the addition of dimethylsulfonium benzylide to benzaldehyde, Aggarwal and co-workers attributed high diastereoselectivity towards the *trans* epoxide to the irreversible formation the *anti* betaine intermediate.[31] A subsequent computational study confirmed that the torsional motion from *cisoid* to *transoid* geometry of the betaine intermediate, around the newly formed bond, controls the rate and diastereoselectivity.[21a] Our results are in agreement with this report and predict that the energies of torsional motion are crucial to the observed stereoselectivity.

The optimized geometries of relevant TSs along the 1,2-addition pathway are presented in Fig. 2. The analyses of these TS geometries convey a general preference toward one of the ylidic conformers, wherein the ylidic substituents are oriented outward with respect to the methyl substituents on S (the *out* conformer

of ylide).[32] In addition to the ylidic conformational preference, other noticeable stereoelectronic interactions are also found to influence the predicted relative energy order between the key TSs. For instance, the weak H-bonding interactions between newly formed charge center O and H (of CH_3 groups on S) as well as the Coulombic attraction between the developing charges ($S^{\delta+}$ and $O^{\delta-}$) help stabilize the TSs. The optimized geometries reveal that the above mentioned interactions favor **1a**-A-*c*‡ based on the shorter $O_1 \cdots H(Me)$ and $O_1 \cdots S_4$ distances. It is noticed that **1b**-A-*c*‡ is disfavored due to the orientation of –R and –Ph on the same side of the newly forming C_2–C_3 bond. However, this effect appears to be compensated by a better *gauche* arrangement of the substituents around C_2 and C_3 in **1b**-A-*c*‡ (note the O_1–C_2–C_3–S_4 dihedrals of 69.1° and 29.6°, respectively for **1b**-A-*c*‡ and **1a**-A-*c*‡; the larger dihedral angle indicates reduced bond pair repulsions in **1b**-A-*c*‡). Among the diastereomeric addition TSs, **1b**-A-*c*‡ provides a lower energy torsional route toward the 2,3-*trans* epoxide product (Fig. 1).

Unlike the addition TSs, the torsional TSs differ significantly in the arrangement of substituents and their interactions with the SMe_2 group. Whereas **1a**-R‡ is highly disfavored owing to the eclipsing interactions between –R/SMe_2 and $O_1^{\delta-}$/Ph pairs, the corresponding diastereomeric TS **1b**-R‡ presents itself in a better situation with reduced steric crowding (with the SMe_2 group). This energetic advantage of **1b**-R‡ translates into a *de* of 94% toward the *trans* product.

Considering the fact that the 1,2- and 1,4- pathways exhibit noticeable differences in their thermodynamic features, the activation barriers of crucial TSs have been collected for further inspection (Table 2). The forward and reverse barriers of the relevant steps in all three pathways are provided. The barriers for *transoid*-to-*cisoid* betaine reversal ($\Delta E^{\ddagger}_r$) are smaller (by 0.9 and 0.3 kcal mol^{-1} respectively for pathways **1a** and **1b**) in the case of 1,2-addition. At the same time, the barrier for the forward reaction ($\Delta E^{\ddagger}_f$), *i.e.*, for *cisoid*-to-*transoid* conversion, through **n**-R‡ is higher. Interestingly, in the conjugate addition pathways **2** and **3**, the differences between $\Delta E^{\ddagger}_f$ and $\Delta E^{\ddagger}_r$ values for the interconversion of *cisoid*-*transoid* betaines through **n**-R‡ are not as high as that in pathway-**1**. However, the initial addition leading to the *cisoid* betaine adducts in both pathways **2** and **3** is obviously not reversible. In summary, under thermodynamic conditions, the conjugate addition modes are more likely to proceed in the forward direction while the direct addition could revert back to the reactants. Nevertheless, the lower barrier noticed for the rate-limiting step implies a potential competition between 1,2- and 1,4-additions.

Table 2 The activation barriers ($\Delta E^{\ddagger}$ in kcal mol^{-1}) for the forward and reverse directions of relevant TSs for direct (**1**) and conjugate addition (**2** and **3**) pathways obtained at the $PCM_{(MeCN)}$/B3LYP/6-311G**//B3LYP/6-31+G* level of theory[a]

	n-A-*c*‡		**n**-R‡	
Pathway[b]	$\Delta E^{\ddagger}_f$	$\Delta E^{\ddagger}_r$	$\Delta E^{\ddagger}_f$	$\Delta E^{\ddagger}_r$
1a	4.0	6.9	12.6	0.9
1b	4.2	2.8	6.2	0.3
2a	11.8	15.4	3.0	–1.4
2b	9.9	13.3	6.9	3.6
3a	12.4	13.4	7.4	7.6
3b	13.6	12.9	6.5	10.6

[a] Energies relative to the nearest intermediates (*cisoid*/*transoid* betaines) or reactants. [b] **a** and **b** respectively denote (*re*,*re*) and (*re*,*si*) approaches between the nucleophile and the electrophile.

(ii) Pathway-2 (1,4-addition). The computed energetics suggests that, depending on the reaction conditions, the 1,4-addition could probably be a competitive pathway in the case of addition of a semi-stabilized ylide to a dienal. The characteristic features of the 1,4-addition pathway are therefore examined closely to understand the factors responsible for chemo-, regio- and diastereoselectivities. From reaction energy profiles given in Fig. 1, it is clear that the initial addition step is irreversible in the case of pathway-**2** and it leads to stable betaine intermediates. However, the activation barriers for the addition step are relatively higher in pathway-**2** as compared to that in pathway-**1**.[33] More interestingly, once the betaine is generated, it can proceed to the product through the ring closure process, as the torsional and elimination TSs are very low-lying. For example, along the favored pathway (**2b**), betaine **n**-*c* will proceed to **n**-*t* with a barrier of 6.9 kcal mol^{-1} rather than reverting to the reactants (barrier of 13.3 kcal mol^{-1}, Table 2). Again, **n**-*t* thus formed will proceed to elimination (with a barrier of 1.7 kcal mol^{-1}) rather than reverting to **n**-*c* (barrier of 3.6 kcal mol^{-1}). Hence, exothermic generation of the betaine intermediate as well as the lower barriers for the ensuing steps implies the formation of cyclopropane products along a 1,4-addition pathway.

Since the initial addition is the slowest step along both the diastereomeric pathways **2a** and **2b**, the rate and stereoselectivity in the case of pathway-**2** is controlled by the addition step.[34] The activation barriers of 11.8 and 9.9 kcal mol^{-1} respectively for the (*re*,*re*) and (*re*,*si*) approaches indicate that the extent of diastereoselection is of the order of 92% toward the *trans* product (corresponding to a $\Delta\Delta E^{\ddagger}$ of 1.9 kcal mol^{-1} between **2a**-A-*c*‡ and **2b**-A-*c*‡). The dependence of rate and diastereoselectivity on the addition step as predicted here is in agreement with the general trends previously reported for the reaction between semi-stabilized ylides and enones, where a moderate selectivity toward 2,3-*trans* cyclopropane was noticed.[23] The optimized geometries of the addition TSs responsible for diastereoselection are provided in Fig. 3. As mentioned earlier, the *out* conformers are found to be lower in energy in the addition TSs. Additional stabilizing interactions such as weak $O \cdots H$ interactions are comparable for the two TSs. The electrostatic interaction between the developing charges ($S^{\delta+}$ and $O^{\delta-}$, *via* charge delocalization) is relatively strong in the lower energy TS **2b**-A-*c*‡.[35] Similarly, this TS has reduced steric interactions between the C_2–C_3 substituents as compared to that in **2a**-A-*c*‡. From the optimized TS geometries provided in Fig. 2, it can be noticed that the two larger substituents on C_2 and C_3 centers are oriented towards the same side of the C_2–C_3 bond in **2a**-A-*c*‡ whereas they are in a favorable *anti* disposition in **2b**-A-*c*‡. Thus, steric as well as electronic factors favor a (*re*,*si*) or *anti* betaine pathway in the case of cyclopropane formation.

(iii) Pathway-3 (1,6-addition). The energetics and general features of the 1,6-addition pathway closely resemble those predicted for the 1,4-addition (pathway-**3**, Fig. 1). The barriers for the addition of the ylide and the torsional motion of the resulting betaine intermediate are found to be relatively high as compared to the corresponding steps in pathway-**2** (Table 1). Akin to pathway-**2**, the initial addition is identified as the rate-limiting step. The

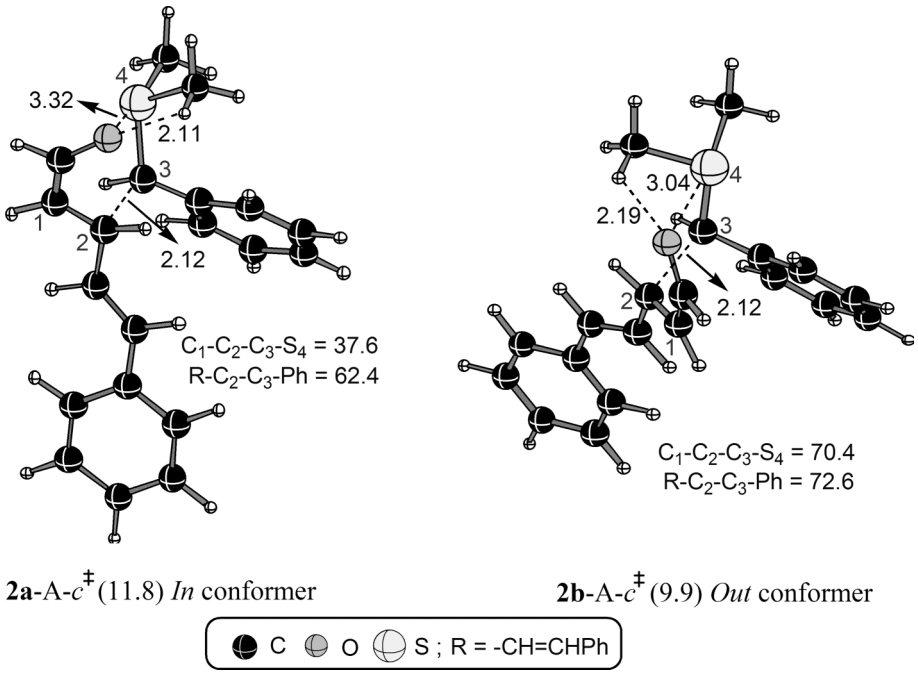


Fig. 3 The B3LYP/6-31+G* optimized geometries and relative energies ($\Delta E^{\ddagger}$) of diastereomeric addition TSs in pathway-**2** (1,4-addition) for the reaction between dimethylsulfonium benzylide and the dienal (distances in Å and angles in °). [$\Delta E^{\ddagger}$ in kcal mol^{-1} obtained at the PCM$_{(MeCN)}$//B3LYP/6-311G**//B3LYP/6-31+G* level are provided in parentheses. Energies are relative to separated reactants].

difference in the activation barriers between the rate-limiting steps in the most preferred modes of addition in these two pathways (*i.e.*, **2** and **3**) is 2.5 kcal mol^{-1}.[33] The energetically preferred mode of addition through TS **2b**-A-$c^{\ddagger}$ over TS **3a**-A-$c^{\ddagger}$ evidently points to a kinetic advantage in the formation of cyclopropanecarbaldehyde as opposed to cyclopropylacrylaldehyde (Fig. 1). The computed relative activation barriers indicate that the diastereoselectivity in favor of cyclopropanecarbaldehyde is as high as 93%. This prediction is in accordance with an available report on a related cyclopropanation reaction.[36]

The above discussions on the reaction of the phenyl substituted ylide with the dienal point to the formation of cyclopropanes through Michael addition and elimination (pathway-**2**). It is found that the reaction exhibits chemoselectivity toward cyclopropanecarbaldehyde as well as *trans* diastereoselectivity. The computed results reveal that a kinetic advantage towards the formation of epoxides is likely to be affected by reversibility issues whereas the stability of the resulting product of 1,4- pathway could lead to chemoselective formation of cyclopropanecarbaldehyde.[37]

B. Addition of a ylide to an enone

A more direct comparison of chemoselectivity preferences in sulfur ylide promoted cyclopropanation or epoxidation can be obtained by analyzing the energetics of addition to enones. In this section, results obtained for the addition of a ylide to the C=O and C=C bonds of an enone (**B**) are presented. The immediate environment around the electrophilic carbonyl group is expected to be different between a dienal and an enone. Such changes could influence the relative preferences between the 1,2- and 1,4-addition modes. To identify the similarities and differences between these two electrophiles toward their reaction with sulfur ylides, we have investigated the direct and conjugate addition pathways of dimethylsulfonium benzylide addition to pent-3-en-2-one.

Table 3 Relative energies (ΔE in kcal mol^{-1}) of TSs, intermediates, and products for 1,2- (pathway-**4**) and 1,4- (pathway-**5**) addition of dimethylsulfonium benzylide to the enone computed at the PCM$_{(MeCN)}$/B3LYP/6-311G**//B3LYP/6-31+G* level of theory[a]

Pathway	**n**-A-$c^{\ddagger}$	**n**-A-$t^{\ddagger}$	**n**-c	**n**-R‡	**1a**-t	**n**-E‡	**n**-PC
4a	8.6	15.6	4.1	16.3[b]	14.4[b]	14.6[b]	−18.6
4b	9.5	14.0	4.5	15.9[b]	13.4[b]	13.7[b]	−20.1
5a	9.2	11.9	−9.7	−2.8	−4.1	−3.1[b]	−41.4
5b	11.9	8.9	−5.3	−0.2	−4.1	−1.0	−39.8

[a] **a** and **b** respectively denote (*re*,*re*) and (*re*,*si*) stereochemical modes of approaches. Energies relative to the separated reactants. [b] PCM$_{(MeCN)}$/B3LYP/6-311G**//HF/6-31+G* energies.

The computed relative energies of various TSs and intermediates for the (*re*,*re*) and (*re*,*si*) diastereomeric approaches along the 1,2- as well as 1,4-addition pathways are provided in Table 3.[38] Certain interesting differences emerge when the addition modes of the enone are compared with those of the dienal. In the case of the dienal the barriers for direct addition (pathway-**1**) are lower by about 5 kcal mol^{-1} than the conjugate modes (pathways **2** and **3**) (*vide supra*). The enone, on the other hand, exhibits comparable barriers for both pathways **4** (direct) and **5** (conjugate). Furthermore, the addition barriers in pathways **4a** and **4b** (1,2- pathway) are significantly higher as compared to the corresponding barriers noticed earlier for dienal. However, the activation barriers remain quite similar for pathways **5a** and **5b** (1,4- pathway) relative to that in pathway-**2**.

While relatively high barriers for the direct addition of ylides to enones are expected in accordance with the general reactivities of an aldehyde and a ketone, the closer barriers for both 1,2- and

1,4-additions with the enone is rather intriguing. Another feature worthy of note is the larger energy difference between the *cisoid* and *transoid* addition TSs in pathway-**4** (Table 3, Fig. 4). The TSs **4a**-A-$t^{\ddagger}$ and **4b**-A-$t^{\ddagger}$ are respectively 7.0 and 4.5 kcal mol^{-1} higher than their *cisoid* congeners. This difference can be attributed to the better electrostatic interaction between the developing charges ($S^{\delta+}$ and $O^{\delta-}$) in the *cisoid* TSs in the case of pathway-**4**, as the charge delocalization is not as extensive as in the case of pathway-**5**.[39] In contrast, the effective delocalization of the developing charge over a conjugated framework of C═C and C═O bonds helps to stabilize the addition TSs in pathway-**5**.[39] In fact, it is noticed that, the best addition TS results from a *transoid* mode of attack in the case of **5** (**5b**-A-$t^{\ddagger}$).

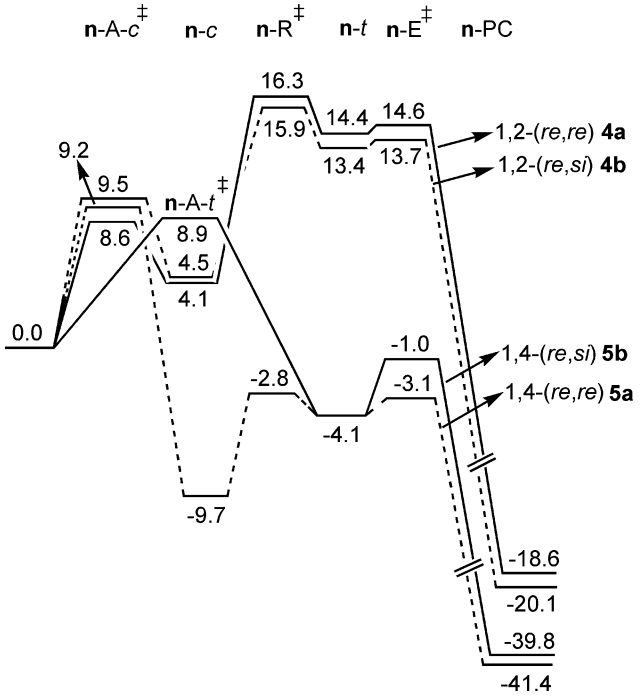


Fig. 4 Reaction energy profiles for 1,2- and 1,4-addition pathways for the reaction between dimethylsulfonium benzylide and the enone computed at the $PCM_{(MeCN)}$/B3LYP/6-311G**//B3LYP/6-31+G* Level ($\Delta E^{\ddagger}$ in kcal mol^{-1} relative to reactants; for *transoid* addition, only the lower energy TS is provided).

In pathway-**4**, except for the *cisoid* addition TSs (**4a**-A-$c^{\ddagger}$ and **4b**-A-$c^{\ddagger}$) all other TSs and intermediates are found to be of higher energy. The reaction energy profiles for the diastereomeric pathways, as shown in Fig. 3, indicate that conjugate addition is preferred over direct addition on account of the higher endothermicities in the formation of betaine intermediates in pathway-**4**. The formation of betaines in pathway-**5**, on the other hand, is exothermic in nature. Closer energies of torsional and elimination TSs as well as of the *transoid* betaines along pathway-**4** (*i.e.*, epoxide formation through 1,2-addition) suggest a likely competition between the forward and reverse reactions as noticed in the case of dienal (*vide supra*). However, in the case of the enone, all the stationary points along the 1,2- pathway are energetically higher by ~5 kcal mol^{-1} (Fig. 4) as compared to the corresponding points with the dienal system (Fig. 1). Further, the competitive nature of addition TS in the 1,4- pathway and torsional TS in the 1,2- pathway seen in the case of the dienal is not exhibited by the enone. It can be seen from Fig. 4 that the reversion of betaines **4a**-*t* or **4b**-*t* to their *cisoid* congeners (**4a**-*c* or **4b**-*c*) is more facile than the reversion of **5a**-*t* or **5b**-*t* in pathway-**5**. Such energetic preferences lead to a favorable situation for the generation of cyclopropanes. The reaction energy profiles further convey that the diastereoselectivity in cyclopropanation is expected to be low in the present case, as the energy separation between the selectivity controlling addition TSs are very low ($\Delta\Delta E^{\ddagger}$ of 0.3 kcal mol^{-1} between **5b**-A-$t^{\ddagger}$ and **5a**-A-$c^{\ddagger}$).

The optimized geometries of addition TSs responsible for the formation of diastereomeric cyclopropanes are provided in Fig. 5.

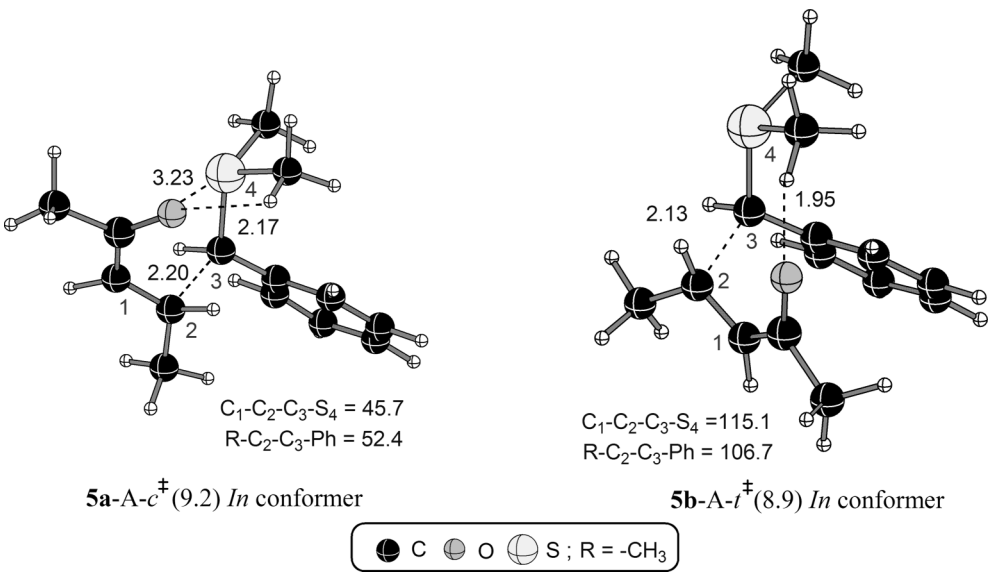


Fig. 5 The B3LYP/6-31+G* optimized geometries and relative energies ($\Delta E^{\ddagger}$) of diastereomeric TSs for the initial addition step in the 1,4-addition pathway (**5**) for the reaction between dimethylsulfonium benzylide and the enone (distances in Å and angles in °). [$\Delta E^{\ddagger}$ in kcal mol^{-1} obtained at the $PCM_{(MeCN)}$/B3LYP/6-311G**//B3LYP/6-31+G* are provided in parentheses].

It is expected that a combination of weak O···H interaction as well as the electrostatic attraction between the developing charge centers would favor the *cisoid* addition TS **5a**-A-$c^{\ddagger}$ in the *re*,*re* pathway. On the other hand, in the *transoid* TS along the *re*,*si* pathway (**5b**-A-$t^{\ddagger}$) (with C_1–C_2–C_3–S_4 dihedral of 115.1°) a stabilizing hydrogen bonding interaction is noticed. Additionally, the **5b**-A-$t^{\ddagger}$ TS is favored on steric grounds because of the *trans* disposition of the C_2 and C_3 substituents, as evident from the Me–C_2–C_3–Ph dihedral angles. Thus, a balance between opposing steric and electrostatic factors in the diastereomeric TSs leads only to a small energy difference between them.[40] The predicted relative energies indicate a low diastereoselectivity in favor of 2,3-*trans* cyclopropane derivative.

The general features of the potential energy surfaces for the addition of a semi-stabilized ylide to an enone as well as a dienal are found to be similar. However, there are slight differences in the final outcome of the reaction with the two acceptors. With the dienal, either *trans* epoxides or *trans* cyclopropanecarbaldehydes can be formed respectively under kinetic or thermodynamic conditions. On the other hand, no such kinetic advantage is noticed with the epoxide formation pathway in the case of enone. Although the model systems examined in this study are not identical to that reported experimentally, it is gratifying to note that our results with the enone substrate (pent-3-en-2-one) agree well with the available experimental reports, suggesting the feasibility of the 1,4-addition product.[9] On the other hand, a more reactive dienal offers competitive product formation *via* 1,2- and 1,4-pathways (epoxide *vs.* cyclopropane), which could be correlated with the improved reactivity of aldehydes. Interestingly, such chemoselectivity preferences have been reported earlier with α,β-unsaturated aldehydes.[13a,19]

Conclusion

The different kinds of selectivity preferences such as chemo-, regio- and diastereoselectivities associated with the conjugate and direct addition pathways for dimethylsulfonium benzylide addition to a dienal and an enone have been studied. The mechanistic and selectivity issues have been addressed by identifying all key intermediates and transition states involved in the reaction pathway. The preferred mechanism has been found to be generally in good accordance with that known for non-conjugated aldehydes/ketones, wherein the elementary steps involved are addition, torsional motion around the newly formed bond in the ensuing betaine intermediate, and the elimination of the sulfur reagent and concomitant ring closure. The energetic factors responsible for whether the addition of a sulfur ylide to a dienal or an enone would result in the generation of cyclopropane or epoxide derivatives have been established. In the case of the dienal, the high reactivity of the aldehyde tends to favor the 1,2- pathway toward an epoxide, although the ensuing reversible elementary steps suggested an interesting situation allowing an alternative 1,4-pathway to be competitive enough to lead to cyclopropanation. Thus, the addition of dimethylsulfonium benzylide to dienal could result in the formation of cyclopropanecarbaldehyde or an epoxide with moderately high 2,3-*trans* selectivity. The predicted trends, in the case of enone as the electrophile, is in accordance with the experimental reports where a preferential formation of 2,3-*trans* cyclopropanes is noticed.

Computational methods

All calculations were performed using the Gaussian03 suite of quantum chemical programs.[41] Geometry optimizations of reactants, intermediates, transition states, and products were carried out in the gas-phase employing density functional theory method by using the B3LYP functional[42] in combination with the 6-31+G* 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)[43] calculations were performed to authenticate the transition states.[44] The single-point energies on the gas-phase optimized geometries were computed using a more flexible triple-ζ-quality 6-311G** basis set in acetonitrile solvent continuum by employing the SCRF-PCM method as implemented in Gaussian03.[45] The choice of the solvent was made on the basis of the literature reports on ylide reactions[46] as well as in accordance with our earlier studies.[22,23] 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 non-electrostatic terms corresponding to cavitation, dispersion, and short-range repulsion. These energies in the condensed phase do not include zero-point corrections. The values presented in the text do not include thermal or free energy corrections.[47] Energy values given in tables and figures represent the relative energies of stationary points with respect to the separated reactants. The activation barriers as mentioned in the text refer to the energy of activation obtained as the energy difference between the isolated reactants, or the corresponding preceding intermediates, and the respective TSs. From the computed relative energies of the pertinent transition states, the extent of diastereoselection was computed using the absolute rate theory.[48] The Natural Population Analyses (NPA) was performed at the B3LYP/6-311+G** level employing Weinhold's Natural Bond Orbital method[49] (NBO 3.1) as implemented in Gaussian03.

In our earlier studies on sulfur ylide promoted aziridination[22a] and cyclopropanation[23] reactions, it was shown that the single-point energies obtained using the continuum solvation methods on gas phase geometries agree fairly well with the energies obtained upon complete geometry optimization within the continuum solvation. In fact, the extent of diastereoselection predicted using both the solvent and the gas-phase optimized geometries were found to be in excellent agreement with each other. Since the present systems are chemically similar to the earlier ones, we reasoned that the computational method as chosen herein would be sufficient.

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References

1 (*a*) H. N. C. Wong, M.-Y. Hon, C.-W. Tse, Y.-C. Yip, J. Tanko and T. Hudlicky, *Chem. Rev.*, 1989, **89**, 165; (*b*) H.-U. Reissig and R. Zimmer, *Chem. Rev.*, 2003, **103**, 1151.

2 For natural products containing cyclopropanes, see: (*a*) D. Li, G. Agnihotri, S. Dakoji, E. Oh, M. Lantz and H. Liu, *J. Am. Chem. Soc.*, 1999, **121**, 9034; (*b*) R. Green, M. Cheeseman, S. Duffill, A. Merritt and S. D. Bull, *Tetrahedron Lett.*, 2005, **46**, 7931. For some examples of biologically active molecules containing cyclopropanes, see: (*c*) R. Faust, *Angew. Chem.*, 2001, **113**, 2312, (*Angew. Chem., Int. Ed.*, 2001, **40**, 2251;) (*d*) T. C. McMorris, M. D. Staake and M. J. Kelner, *J. Org. Chem.*, 2004, **69**, 619.

3 (*a*) S. F. Martin, M. P. Dwyer, B. Hartmann and K. S. Knight, *J. Org. Chem.*, 2000, **65**, 1305; (*b*) M. C. Hillier, J. P. Davidson and S. F. Martin, *J. Org. Chem.*, 2001, **66**, 1657; (*c*) A. Reichelt and S. F. Martin, *Acc. Chem. Res.*, 2006, **39**, 433.

4 (*a*) S. E. Denmark, S. P. O. Connor and S. R. Wilson, *Angew. Chem.*, 1998, **110**, 1162, (*Angew. Chem., Int. Ed.*, 1998, **37**, 1149); (*b*) A. B. Charette, C. Molinaro and C. Brochu, *J. Am. Chem. Soc.*, 2001, **123**, 12168; (*c*) V. K. Aggarwal, G. Y. Fang and G. Meek, *Org. Lett.*, 2003, **5**, 4417; (*d*) H. Du, J. Long and Y. Shi, *Org. Lett.*, 2006, **8**, 2827; (*e*) Z. Song, T. Lu, R. P. Hsung, Z. F. Al-Rashid, C. Ko and Y. Tang, *Angew. Chem.*, 2007, **119**, 4147, (*Angew. Chem., Int. Ed.*, 2007, **46**, 4069); (*f*) H. Shitama and T. Katsuki, *Angew. Chem.*, 2008, **120**, 2484, (*Angew. Chem., Int. Ed.*, 2008, **47**, 2450).

5 (*a*) H. M. L. Davies, P. R. Bruzinski and M. J. Fall, *Tetrahedron Lett.*, 1996, **37**, 4133; (*b*) D. Bykowski, K.-H. Wu and M. P. Doyle, *J. Am. Chem. Soc.*, 2006, **128**, 16038; (*c*) J. R. Krumper, M. Gerisch, J. M. Suh, R. G. Bergman and T. D. Tilley, *J. Org. Chem.*, 2003, **68**, 9705; (*d*) A. Caballero, M. M. Daz-Requejo, S. Trofimenko, T. R. Belderrain and P. J. Prez, *J. Org. Chem.*, 2005, **70**, 6101.

6 (*a*) S. H. McCooey, T. McCabe and S. J. Connon, *J. Org. Chem.*, 2006, **71**, 7494; (*b*) H. Xie, L. Zu, H. Li, J. Wang and W. Wang, *J. Am. Chem. Soc.*, 2007, **129**, 10886; (*c*) I. Das, T. K. Pal and T. Pathak, *J. Org. Chem.*, 2007, **72**, 9181; (*d*) X.-L. Sun and Y. Tang, *Acc. Chem. Res.*, 2008, **41**, 937.

7 For reviews on general methods of synthesis of cyclopropanes see: (*a*) M. P. Doyle and M. N. Protopopova, *Tetrahedron*, 1998, **54**, 7919; (*b*) H. Lebel, J. F. Marcoux, C. Molinaro and A. B. Charette, *Chem. Rev.*, 2003, **103**, 977; (*c*) H. Pellissier, *Tetrahedron*, 2008, **64**, 7041.

8 For reviews on S-ylide mediated ring formation reactions, see: (*a*) A.-H. Li, L.-X. Dai and V. K. Aggarwal, *Chem. Rev.*, 1997, **97**, 2341; (*b*) L.-X. Dai, X.-L. Hou and Y.-G. Zhou, *Pure Appl. Chem.*, 1999, **71**, 369.

9 (*a*) G. B. Payne, *J. Org. Chem.*, 1967, **32**, 3351; (*b*) B. M. Trost, *J. Am. Chem. Soc.*, 1967, **89**, 138; (*c*) E. J. Corey and M. Jautelat, *J. Am. Chem. Soc.*, 1967, **89**, 3912; (*d*) C. R. Johnson and C. W. Schroeck, *J. Am. Chem. Soc.*, 1971, **93**, 5303; (*e*) M. J. De Vos and A. Krief, *Tetrahedron Lett.*, 1983, **24**, 103; (*f*) R. W. Curley Jr. and H. F. DeLuca, *J. Org. Chem.*, 1984, **49**, 1944; (*g*) M. Roje, V. Vinković, V. Sunjić, A. Solladié-Cavallo, A. Diep-Vohuule and T. Isarno, *Tetrahedron*, 1998, **54**, 9123; (*h*) R. K. Kunz and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2005, **127**, 3240; (*i*) A. Hartikka and P. I. Arvidsson, *J. Org. Chem.*, 2007, **72**, 5874.

10 (*a*) D. Romo, J. L. Romine, W. Midura and A. I. Meyers, *Tetrahedron*, 1990, **46**, 4951; (*b*) R. Zhang, A. Mamai and J. S. Madalengoitia, *J. Org. Chem.*, 1999, **64**, 547; (*c*) W. Midura and M. Mikołajczyk, *Tetrahedron Lett.*, 2002, **43**, 3061; (*d*) W. H. Midura, J. A. Krysiak and M. Mikołajczyk, *Tetrahedron: Asymmetry*, 2003, **14**, 1245.

11 (*a*) V. K. Aggarwal and E. Grange, *Chem.–Eur. J.*, 2006, **12**, 568; (*b*) E. M. McGarrigle, E. L. Myers, O. Illa, M. A. Shaw, S. L. Riches and V. K. Aggarwal, *Chem. Rev.*, 2007, **107**, 5841and the references therein; (*c*) O. Illa, M. Arshad, A. Rose, E. M. McGarrigle and V. K. Aggarwal, *J. Am. Chem. Soc.*, 2010, **132**, 1828. Also see ref. 8(*a*).

12 (*a*) S. Ye, Z.-Z. Huang, C.-A. Xia, Y. Tang and L.-X. Dai, *J. Am. Chem. Soc.*, 2002, **124**, 2432; (*b*) X.-M. Deng, P. Cai, S. Ye, X.-L. Sun, W.-W. Liao, K. Li, Y. Tang, Y.-D. Wu and L.-X. Dai, *J. Am. Chem. Soc.*, 2006, **128**, 9730.

13 (*a*) A. Solladié-Cavallo, A. Diep-Vohuule and T. Isarno, *Angew. Chem., Int. Ed.*, 1998, **37**, 1689.

14 (*a*) S. Ye, L. Yuan, Z.-Z. Huang, Y. Tang and L.-X. Dai, *J. Org. Chem.*, 2000, **65**, 6257; (*b*) W.-W. Liao, K. Li and Y. Tang, *J. Am. Chem. Soc.*, 2003, **125**, 13030; (*c*) J.-C. Zheng, W.-W. Liao, Y. Tang, X.-L. Sun and L.-X. Dai, *J. Am. Chem. Soc.*, 2005, **127**, 12222.

15 (*a*) Y.-Z. Huang, Y. Tang, Z.-L. Zhou and J.-L. Huang, *J. Chem. Soc., Chem. Commun.*, 1993, 7; (*b*) B. Moreau and A. B. Charette, *J. Am. Chem. Soc.*, 2005, **127**, 18014.

16 For the use of ammonium ylides in cyclopropane synthesis, see: (*a*) C. D. Papageorgiou, M. A. Cubillo de Dios, S. V. Ley and M. J. Gaunt, *Angew. Chem.*, 2004, **116**, 4741, (*Angew. Chem., Int. Ed.*, 2004, **43**, 4641); (*b*) C. C. C. Johansson, N. Bremeyer, S. V. Ley, D. R. Owen, S. C. Smith and M. J. Gaunt, *Angew. Chem.*, 2006, **118**, 6170, (*Angew. Chem., Int. Ed.*, 2006, **45**, 6024). For the application of pyridonium ylides in cyclopropane synthesis, see: (*c*) S. Kojima, K. Hiroike and K. Ohkata, *Tetrahedron Lett.*, 2004, **45**, 3565. For the use of azetidinium ylides in cyclopropane synthesis, see: (*d*) F. Couty, O. David, B. Larmanjat and J. Marrot, *J. Org. Chem.*, 2007, **72**, 1058.

17 (*a*) S. Hanessian, D. Andreotti and A. Gomtsyan, *J. Am. Chem. Soc.*, 1995, **117**, 10393; (*b*) M. F. Oswald, S. A. Raw and R. J. K. Taylor, *Org. Lett.*, 2004, **6**, 3997; (*c*) M. F. Oswald, S. A. Raw and R. J. K. Taylor, *Chem. Commun.*, 2005, 2253.

18 E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 1965, **87**, 1353.

19 A. Solladié-Cavallo, L. Bouérat and M. Roje, *Tetrahedron Lett.*, 2000, **41**, 7309.

20 (*a*) F. Volatron and O. Eisenstein, *J. Am. Chem. Soc.*, 1987, **109**, 1; (*b*) T. Kawashima, F. Ohno, R. Okazaki, H. Ikeda and S. Inagaki, *J. Am. Chem. Soc.*, 1996, **118**, 12455; (*c*) M. K. Lindvall and A. M. P. Koskinen, *J. Org. Chem.*, 1999, **64**, 4596.

21 (*a*) V. K. Aggarwal, J. N. Harvey and J. Richardson, *J. Am. Chem. Soc.*, 2002, **124**, 5747; (*b*) M. A. Silva, B. R. Bellenie and J. M. Goodman, *Org. Lett.*, 2004, **6**, 2559; (*c*) R. Robiette, *J. Org. Chem.*, 2006, **71**, 2726; (*d*) V. K. Aggarwal, J. P. H. Charmant, D. Fuentes, J. N. Harvey, G. Hynd, D. Ohara, W. Picoul, R. Robiette, C. Smith, J.-L. Vasse and C. L. Winn, *J. Am. Chem. Soc.*, 2006, **128**, 2105.

22 (*a*) D. Janardanan and R. B. Sunoj, *Chem.–Eur. J.*, 2007, **13**, 4805; (*b*) D. Janardanan and R. B. Sunoj, *J. Org. Chem.*, 2008, **73**, 8163.

23 D. Janardanan and R. B. Sunoj, *J. Org. Chem.*, 2007, **72**, 331.

24 The classification of ylides under three different categories namely, stabilized, semi-stabilized and non-stabilized are based on their reactivity order obtained from computed proton affinities as well as experimental reports (see ref. 22(*a*) and references therein).

25 This ylide, having a phenyl substituent on the ylidic carbon, has popularly been used in the asymmetric version of the reaction.

26 However, further deprotonation at the ylidic center as suggested by Aggarwal and co-workers in a very recent report could influence the stereochemical outcome of this reaction. These possibilities are not examined here, as it is beyond the scope of the present investigation. See: S. L. Riches, C. Saha, N. F. Filgueira, E. Grange, E. M. McGarrigle and V. K. Aggarwal, *J. Am. Chem. Soc.*, 2010, **132**, 7626.

27 The isomer of 5-phenylpenta-(2*E*,4*E*)-dienal chosen for the present study, denoted as *E*,*E*-*cis*,*trans* (on the basis of the configuration at the double bonds and s-*cis* and s-*trans* orientations respectively from the carbonyl end of dienal) is 1.6 kcal mol^{-1} higher in energy at the B3LYP/6-31+G* level of theory than the lowest energy *E*,*E*-*trans*,*trans* isomer (See Fig. S1, ESI †). However, the TSs for the addition of the ylide to the dienal derived from the *E*,*E*-*cis*,*trans* isomer are in general found to be lower in energy by more than 2 kcal mol^{-1}. Relatively improved electrostatic stabilization between the developing charge centers in the TS for *E*,*E*-*cis*,*trans* isomer is noticed. We have therefore focused only on the *E*,*E*-*cis*,*trans* isomer. The relative energies and optimized geometries of selected addition TSs computed for the *E*,*E*-*trans*,*trans* isomer in support of the above argument is presented in Fig. S2 in the ESI †.

28 In fact, the addition of S-ylide to benzaldehyde, the torsional motion from *cisoid* to *transoid* betaine is the slowest step and is reported to regulate the diastereoselectivity of epoxides formation (ref. 21a). On the contrary, the initial addition is the rate-limiting step in the case of addition to pentenone (ref. 23). While torsional motion from *cisoid* to *transoid* betaine disrupts the Coulombic interactions present in *cisoid* betaine intermediates in the case of benzaldehyde, such effects are less pronounced with enones, as the incipient negative charge can be delocalized into the adjacent carbonyl group.

29 The activation barriers for the elimination steps from different addition modes are collected in Table S1 in the ESI †.

30 (*a*) Some of the stationary points, such as the *transoid* betaines and elimination TSs continued to remain elusive due to geometric convergence problems even after repeated attempts. In such cases, geometries are optimized either with the incorporation of continuum solvents or at the HF/6-31+G* level of theory, before subjecting those

for single-point energy calculations at a uniform level of theory. It is found that the DFT and HF profiles are in very good agreement with each other. In those cases, where the HF/6-31+G* geometries had to be used, a thorough comparison between the PESs constructed using the B3LYP/6-31+G* and the HF/6-31+G* geometries were undertaken; (*b*) For instance, the lowest energy addition TS leading to the formation of 2,3- *trans* product along the 1,4- pathway (pathway-**2**) has an activation energy of 9.8 kcal mol^{-1} at the B3LYP/6-311G**//HF/6-31+G* level, which is very close to that obtained from the DFT method (9.9 kcal mol^{-1}; see Table 1). Similarly, the %*de* computed using the favored pathways at B3LYP and HF levels (92% and 96% respectively) are also found to be in reasonable agreement; (*c*) All stationary points have been located along the diastereomeric pathways corresponding to the most favored addition modes **2a** and **2b**, at the HF/6-31+G* level of theory (Fig. S3, ESI†) and they show excellent agreement with in the relative energies of various stationary points on the computed PES using DFT methods; (*d*) Further, it is noticed that a select group of stationary points (**1a**-$R^{‡}$, **1a**-$E^{‡}$ and **2a**-*t*) recomputed using DFT methods in continuum solvent for pathways **1** and **2** showed a systematic decrease in energy by 2.0–2.5 kcal mol^{-1}, at the same time maintaining similar trends as those obtained from the HF optimized geometries. Since addition is the rate-limiting step (all addition TSs were successfully located at the B3LYP level) for the favored conjugate addition pathways, it is expected that the final conclusions would remain unchanged in spite of the above-mentioned caveats.

31 (*a*) V. K. Aggarwal, S. Calamai and J. G. Ford, *J. Chem. Soc., Perkin Trans. 1*, 1997, 593; (*b*) The corresponding *syn* betaine formation was found to be reversible, which could lead to the formation of *anti* betaines, eventually facilitating the *trans* epoxide.

32 The *out* conformer is found to be lower in energy than the *in* conformer (where the phenyl group on the ylidic carbon is oriented toward the S-substituents). See Fig. S4, ESI†.

33 See Fig. S5 (ESI†) for the alternative diastereomeric reaction energy profiles corresponding to pathways **2** and **3**.

34 Additional calculations with the *E*,*E*-*trans*,*trans* isomer of dienal for both the torsional and elimination TSs along the select diastereomeric pathways (**2a** and **2b**) have been performed, in order to examine the relative positions of these TSs. It is found that the torsional TSs from the *E*,*E*-*trans*,*trans* isomer of the dienal are higher in energy by 6-10 kcal mol^{-1} on the PES than the corresponding lowest energy TS obtained from the *E*,*E*-*cis*,*trans* isomer. It is to be noted that TSs for the initial addition step also follow similar trends as that of the torsional step. However, the elimination TSs could not be obtained due to geometry convergence issues.

35 This statement is on the basis of the computed natural charges obtained using the NBO method for these TSs (see Table S2 and Fig. S6 in the ESI†). It is found that the natural charges are better delocalized over the C_1–C_2–C_3–S_4 moiety in the lower energy TS (**2b**-A-$c^{‡}$). Additionally, it is noticed that the dienal oxygen carries a higher charge density in **2b**-A-$c^{‡}$ leading to a better Coulombic attraction with the S atom.

36 An interesting experimental report toward the preference for 1,4-addition of a phosphorous ylide over 1,6-addition has been noticed with Me-CH═CH═CH-$COOBu^{t}$ by Hanessian and co-workers. See ref. 17(*a*).

37 Additional computations on all the stationary points along the 1,2-addition pathway as well as the rate -limiting addition TSs from the 1,4-pathway employing mPW1K/6-31+G* level and refined the energies using a more flexible basis set have been carried out. It was found that the mPW1K/6-311+G**//mPW1K/6-31+G* energies follow similar trends as noticed with the B3LYP/6-31+G* optimized geometries (Fig. S7 in the ESI†). However, relative energies obtained in the solvent continuum favors a 1,2-addition pathway rather than 1,4-addition (Fig. S8 in the ESI†). This is probably due to the effective charge stabilization of charge separated intermediates and TSs from 1,2- pathway by the polar solvent medium. The relative energies obtained at different levels of theory are summarized in Table S5 (ESI†).

38 Geometric convergence issues were encountered in pathway-**4** at the B3LYP/6-31+G* level of theory in the gas-phase. These stationary points have therefore been optimized at the HF/6-31+G* level. The single-point energies were then computed at the $PCM_{(MeCN)}$/B3LYP/6-311G** level. The higher energies of these stationary points could perhaps result from inadequate geometrical description at the HF method. However, on the basis of the trends noticed in the case of dienal system, it is expected that the nature of the reaction profile and the conclusions would not be directly affected due to the use of HF geometries (also see ref. 30).

39 The computed NPA charges reveal that the charge densities are higher on the O and S in the *cisoid* TSs where the electrostatic interaction contributes toward the stabilization. At the same time, the charges are more delocalized on the O_1–C_2–C_3–S_4 framework in the case of the corresponding *transoid* congeners (see Table S2 in ESI†).

40 In order to verify whether the basis set employed in the present work is adequate enough to describe the TSs exhibiting weak hydrogen bonding interactions, additional calculations have been performed by re-optimizing the geometries at the B3LYP/6-31+G** level, on a representative series of TSs for the addition step (along pathway-**5**). It is noticed that the relative energy trends remain the same even after the inclusion of polarization functions on the hydrogen atoms (see Table S3 in the ESI for details†).

41 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. G. Johnson, W. Chen, M. W. Wong, C. Gonzalez and J. A. Pople, *GAUSSIAN 03 (Revision C.02)*, Gaussian, Inc., Wallingford, CT, 2004.

42 (*a*) A. D. Becke, *J. Chem. Phys.*, 1993, **98**, 5648; (*b*) A. D. Becke, *Phys. Rev. A: At., Mol., Opt. Phys.*, 1998, **38**, 3098; (*c*) C. Lee, W. Yang and R. G. Parr, *Phys. Rev. B: Condens. Matter*, 1998, **37**, 785.

43 (*a*) C. Gonzalez and H. B. Schlegel, *J. Chem. Phys.*, 1989, **90**, 2154; (*b*) C. Gonzalez and H. B. Schlegel, *J. Phys. Chem.*, 1990, **94**, 5523.

44 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.

45 (*a*) M. Cossi, V. Barone, R. Cammi and J. Tomasi, *Chem. Phys. Lett.*, 1996, **255**, 327; (*b*) E. Cancès, B. Mennucci and J. Tomasi, *J. Chem. Phys.*, 1997, **107**, 3032.

46 Sulfur ylide mediated reactions involving phase transfer catalysts are carried out in highly polar solvents (see ref. 12(*b*), 21(*b*) and 21(*d*)). Recent reports on asymmetric cyclopropanations employ relatively less polar solvents such as DCM[13] and THF[12a].

47 For details on the inclusion of the enthalpy and free energy corrections to the reported energies, see ESI (Fig. S9 and S10, Table S4†).

48 For similar treatment in the calculation of *ee*/*de* ratios see: (*a*) S. Bahmanyar, K. N. Houk, H. J. Martin and B. List, *J. Am. Chem. Soc.*, 2003, **125**, 2475; (*b*) C. B. Shinisha and R. B. Sunoj, *Org. Biomol. Chem.*, 2007, **5**, 1287; (*c*) C. B. Shinisha and R. B. Sunoj, *Org. Biomol. Chem.*, 2008, **6**, 3921; (*d*) M. P. Patil and R. B. Sunoj, *Chem.–Eur. J.*, 2008, **14**, 10472; (*e*) S. T. Schneebeli, M. L. Hall, R. Breslow and R. Friesner, *J. Am. Chem. Soc.*, 2009, **131**, 3965.

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

