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Reaction Mechanism

SPECIAL ISSUE

Understanding Regioselectivities of Corey–Chaykovsky Reactions of Dimethylsulfoxonium Methylide (DMSOM) and Dimethylsulfonium Methylide (DMSM) toward Enones: A DFT Study

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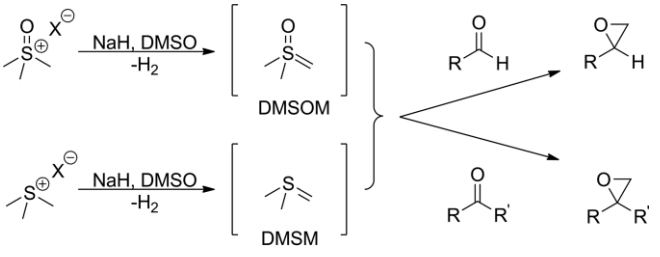
Abstract: The Corey–Chaykovsky reaction, using either in situ generated dimethylsulfoxonium methylide (**DMSOM**) or dimethylsulfonium methylide (**DMSM**) to react with ketones or aldehydes, is widely used in the synthesis of epoxides. However, when **DMSOM** and **DMSM** react with enones (such as chalcone), the former reactions give cyclopropanation products whereas the latter reactions still generate epoxides. DFT calculations have been carried out to understand these different regioselectivities. We found that the cyclopropanation pathways for both **DMSOM** and **DMSM** toward chalcone (a model for enones) start with rate-determining and irreversible 1,4-addition reactions, followed by easier intramolecular substitution reactions to give cyclopropanes. The overall activation free energies for cyclopropanation are 17.5 and 15.5 kcal/mol for **DMSOM** and **DMSM**, respectively. The epoxidation pathways for both **DMSOM** and **DMSM** have reversible 1,2-addition reactions, followed by rate-determining intramolecular substitution reactions to give epoxides. The computed barriers for the epoxidation are 23.0 and 13.3 kcal/mol for **DMSOM** and **DMSM**, respectively. Therefore, the cyclopropanation pathway is favored for **DMSOM** while epoxidation is preferred for **DMSM**. We attribute these different reaction scenarios to thermodynamic reasons that DMSOM is more stable than DMSM. The reaction pathways for reactions of other derivatives of **DMSM** toward enones have also been discussed.

Introduction

In the 1960s, Corey and Chaykovsky developed the well-known Corey–Chaykovsky epoxidation reaction (which is also called as Johnson-Corey–Chaykovsky reaction).[1] They used either dimethylsulfoxonium methylide ($Me_2S(O)=CH_2$, **DMSOM** in short here) or dimethylsulfonium methylide ($Me_2S=CH_2$, **DMSM** in short here), which were generated in situ by the deprotonation reaction of trimethylsulfoxonium halide or trimethylsulfonium halide respectively, to react with aldehydes or ketones. Both reactions give epoxidation products (Scheme 1) and release either dimethyl sulfide (**DMS**, when **DMSM** was used) or dimethyl sulfoxide (**DMSO**, when **DMSOM** was used). Since these discoveries, the Corey–Chaykovsky reactions have been widely applied to synthesize epoxides by the synthetic community.[2] In addition, many organic chemists have further developed other versions of these reactions, especially the asymmetric ones, for application.[3,4]



Scheme 1. Corey–Chaykovsky epoxidations.

On the other hand, the mechanism of the Corey–Chaykovsky reaction has been investigated. As early as 1987, Eisenstein investigated the reaction of phosphonium methylide and sulfonium methylide, aiming to study the intrinsic difference between Wittig type reactions and Corey–Chaykovsky type reactions.[5] This early study, which did not consider the electron correlation and solvent effects, provided the model for further study using more advanced computational methods. In 1999 and 2002, Koskinen[6] and Aggarwal[7] group investigated the origins of stereoselectivity in the Corey–Chaykovsky epoxidations computationally. Recently, Sunoj and co-workers[8] investigated the chemo-, regio-, and diastereoselectivity preferences in the reactions of sulfonium ylides with different enones. In

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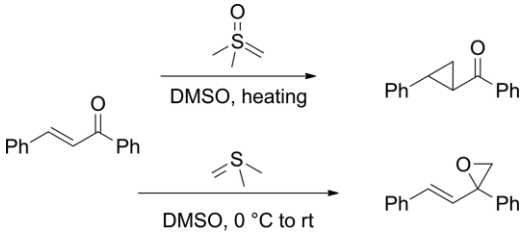
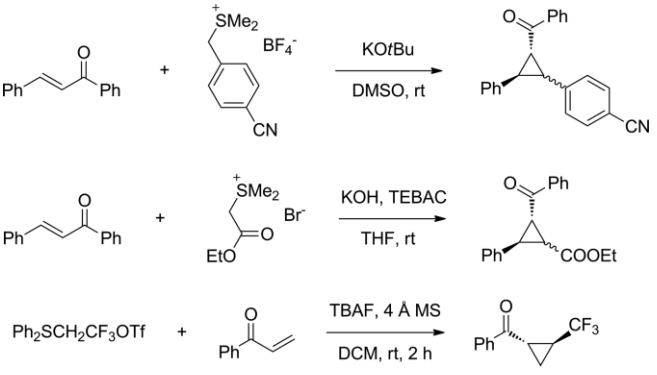
another work,[8] Sunoj studied model reactions of different substituted dimethylsulfonium ylides and (*E*)-pent-3-en-2-one to understand the relationship of diastereoselectivity and the substitution of the ylides. In addition, Bennet group studied the mechanistic profiles (including diastereoselectivity) of double cyclopropanation reaction of COOEt-stabilized sulfur ylide toward cyclopentenone both experimentally and theoretically.[9]

Under standard reaction conditions, the reactions of both **DMSM** and **DMSOM** in DMSO solution toward ordinary aldehydes and ketones gave only epoxidation products. However, when these two ylides reacted with α,β-unsaturated carbonyl compounds such as chalcone, different products were generated (Scheme 2).[1,10] Reactions of **DMSOM** with enones gave cyclopropanation products, while the reactions of **DMSM** with enones still produced epoxidation products (similar to their reactions with aldehydes and ketones). To our surprise, no explanation and rationalization of the different selectivity are available. In this paper, we present our computational insights to answer why different products were generated for **DMSOM** and **DMSM** when they reacted with enones. It is interesting to note that the reactions of other derivatives of **DMSM** with enones gave cyclopropanation products instead of epoxidation products (Scheme 3).[11-13] Here we also give a DFT-based explanation for the different regiochemistry observed for these derivatives of **DMSM** compared to **DMSM**.



Scheme 2. Corey–Chaykovsky cyclopropanation vs. epoxidation of **DMSOM** and **DMSM** toward chalcone.



Scheme 3. Cyclopropanations of **DMSM** derivatives toward enones.

Results and Discussion

1. Reaction of DMSOM with Enone 1

Here we present the computed potential energy surfaces of two competing pathways (cyclopropanation vs. epoxidation) of **DMSOM** toward enone **1** in order to reveal the factors influencing the reaction selectivity (Figure 1 and Figure 2).

Complexation Step. In both cyclopropanation and epoxidation pathways, the reaction starts from the formation of **DMSOM**/**1** complex. We can locate two complexes, **COM1** and **COM2**, which can be regarded as hydrogen bond complexes having remarkable C–H/O interactions between **DMSOM**'s methyl group and the oxygen atom of enone. Our computational results indicate that, in terms of Gibbs free energy, formations of **COM1** and **COM2** are both endergonic, by 8.1 and 6.3 kcal/mol, respectively.[14]

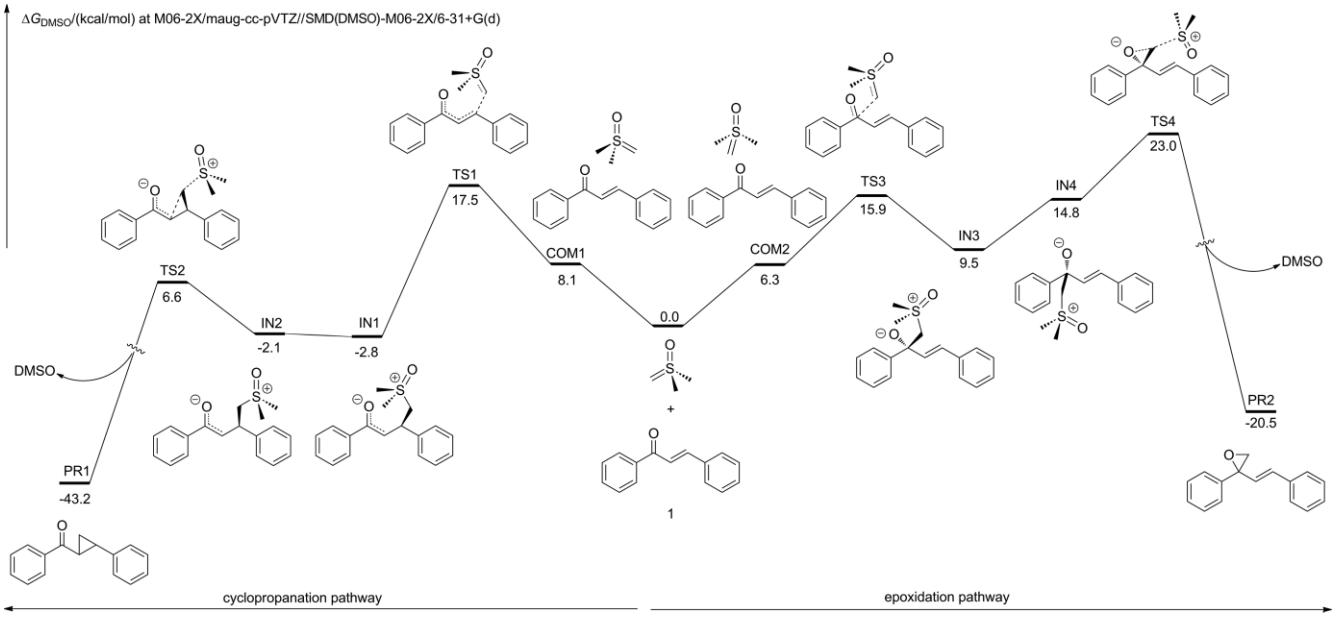


Figure 1. DFT computed energy surfaces of cyclopropanation and epoxidation of reactions of **DMSOM** with **enone**.

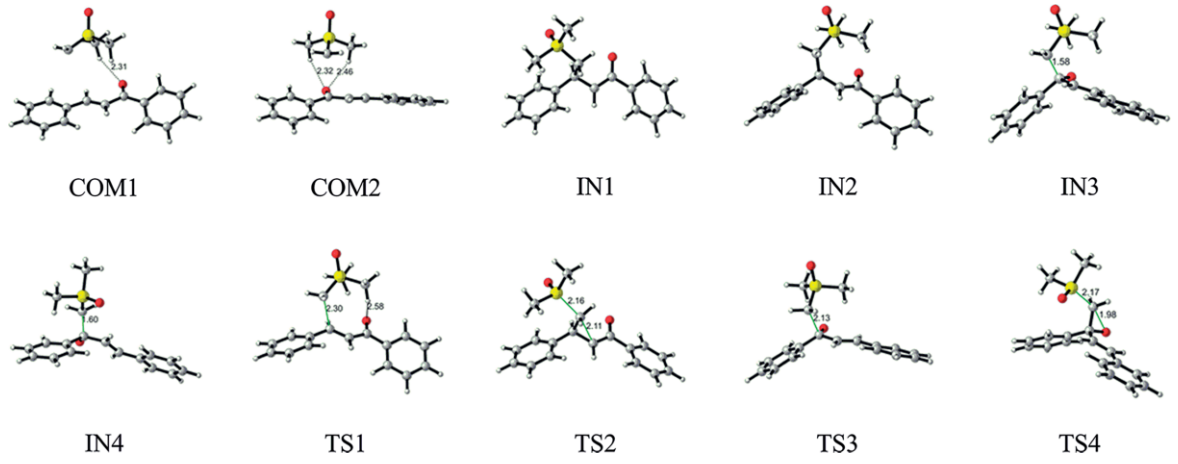


Figure 2. Structures of the intermediates and transition states given in Figure 1. Color Scheme H, white; C, gray; O, red; and S, yellow. Distances are reported in Å.

Cyclopropanation Pathway: In the cyclopropanation pathway, **COM1** undergoes Michael addition of **DMSOM**'s methylene group to the enone via **TS1**. This step requires an activation free energy of 17.5 kcal/mol (from **DMSOM** and **1** to **TS1**) and generates intermediate **IN1**. Then, rotation around the newly formed C–C bond in intermediate **IN1** gives a less stable intermediate **IN2**. The Michael addition step is exergonic by 2.8 kcal/mol (from **DMSOM** and **1** to **IN1**). Intermediate **IN2** is the reacting conformer for the followed intramolecular substitution reaction, where the enolate C=C bond acts as a nucleophile while DMSO moiety serves as a leaving group. This step (from **IN2** to cyclopropane product via **TS2**) requires an activation free energy of 8.7 kcal/mol. This final step in the cyclopropanation pathway is very exergonic by 41.1 kcal/mol. Conversion of **IN2** to product **PR1** is favored than its backward reaction, the conversion of **IN2** to **COM1**, indicating that the Michael addition step via **TS1** is irreversible. From Figure 1, we can conclude that the cyclopropanation pathway has the rate-determining step of Michael addition reaction and the overall activation free energy in this pathway is 17.5 kcal/mol.

Epoxidation Pathway: In the epoxidation pathway, complex **COM2** undergoes 1,2-addition to the carbonyl group of enone **1** via **TS3**. This step requires an activation free energy of 15.9 kcal/mol, generating intermediate **IN3**, which is in an eclipsed formation due to the electrostatic attraction between oxygen and sulfur in it. The 1,2 addition is endergonic by 9.5 kcal/mol (from **DMSOM** and **1** to **IN3**), which is different from the previous Michael addition in the cyclopropanation pathway, which is exergonic by 2.8 kcal/mol. Intermediate **IN3** then rotates to its *trans* conformer **IN4**, so that **IN4** can undergo intramolecular nucleophilic substitution reaction via **TS4**. This is a general geometric requirement of a S_N2 reaction with the nucleophile and leaving group at the reaction site in a linear conformation. **IN4** is higher in energy than **IN3** by 5.3 kcal/mol. The substitution from **IN4** to **TS4** requires an activation free energy of 8.2 kcal/mol. The final step to give epoxide and release DMSO is exergonic by 35.3 kcal/mol. The epoxidation pathway has the rate-determining step of substitution reaction via **TS4** and has an overall activation free energy of 23.0 kcal/mol.

Comparison of Two Pathways: Overall, for **DMSOM**'s reaction to enone, 1,2-addition step in epoxidation pathway is more favored over the 1,4-addition step in the cyclopropanation pathway about 1.6 kcal/mol. However, in the epoxidation pathway, endergonic formation of **IN3** makes the followed intramolecular substitution to give epoxide becomes more energy demanding. Consequently, the rate-determining transition state **TS4** in epoxidation pathway is higher than **TS1** of the irreversible 1,4-addition transition state in cyclopropanation pathway by 5.5 kcal/mol, and cyclopropanation is preferred over the epoxidation. This is consistent with the experimental observations.[10]

We point out here, even though cyclopropanation pathway is favored for DMSOM's reaction with chalcone, the reaction could first undergo a 1,2-addition to form **IN3**, **IN4** (in the epoxidation pathway) because **TS1** is higher than **TS3**. Then **IN3** and **IN4** will go back to reach **TS1** in the cyclopropanation pathway to give final cyclopropanation product, considering **TS4** is higher than **TS1**.

2. Reaction of DMSM with Enone 1

In this part, we present the computed potential energy surfaces of **DMSM** toward enone **1** (Figure 3 and Figure 4).

Complexation Step: The reaction also starts with complexation. We can locate two complexes **COM3** and **COM4**. Complex **COM3** is linked to the Michael addition step while **COM4** is for 1,2-addition step. In both cyclopropanation and epoxidation pathways, the reaction starts with complexations of substrate and **DMSM** to form **COM3** and **COM4**. Here **COM3** is a van der Waals complex, while **COM4** has remarkable C–H/O interaction between **DMSM**'s methyl group and the oxygen atom of enone, similar to **COM2**. Our computational results indicate that, in terms of Gibbs free energy, the formation of **COM3** is endergonic by 5.6 kcal/mol, while the formation of **COM4** is also endergonic, by 7.3 kcal/mol.

Cyclopropanation Pathway: In the cyclopropanation pathway, **COM3** undergoes Michael addition reaction via **TS5**. This step requires an activation free energy of 14.8 kcal/mol (from

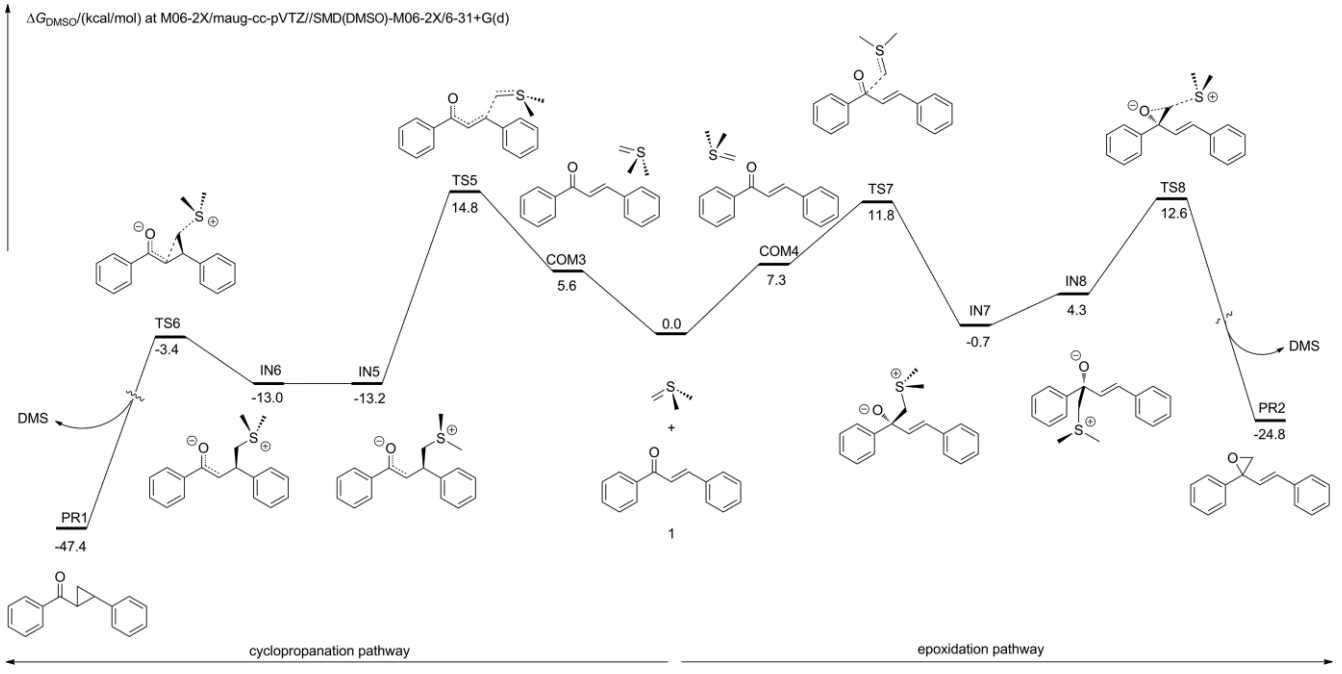


Figure 3. DFT computed energy surfaces of reaction of **DMSM** with enone.

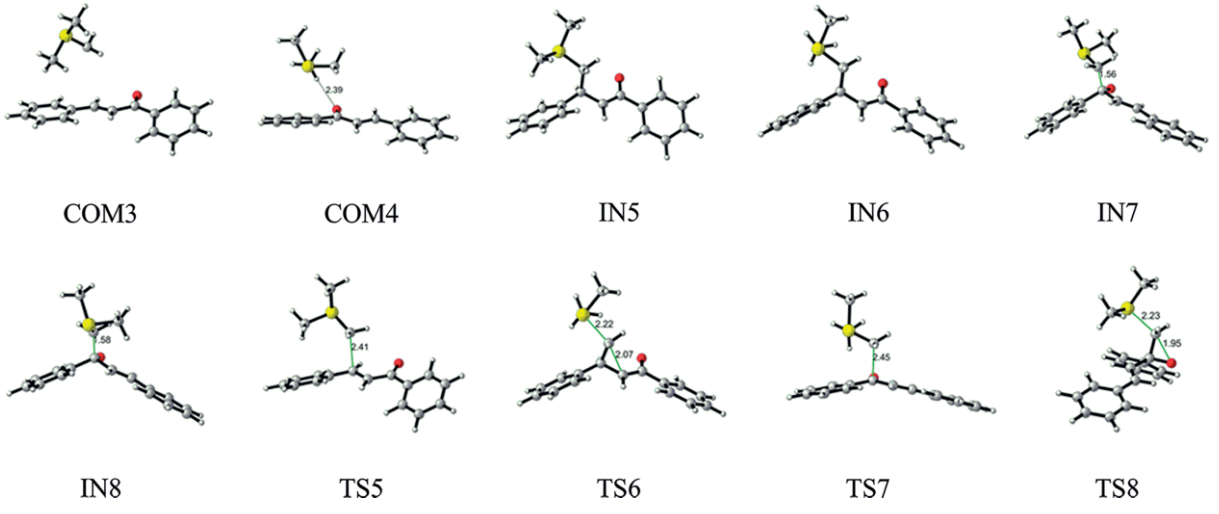


Figure 4. Structures of the intermediates and transition states in Figure 3. Color Scheme H, white; C, gray; O, red; and S, yellow. Distances are reported in Å.

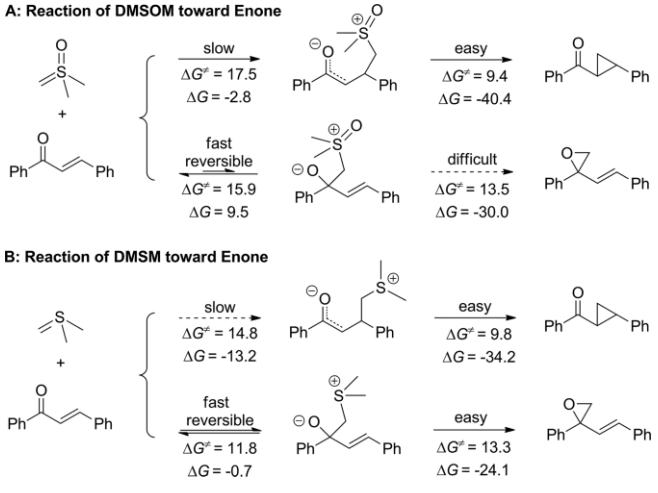
DMSM + enone **1** to **TS5**). This step is exergonic with a Gibbs free energy of 13.2 kcal/mol. After that, **IN5** undergoes intramolecular nucleophile substitution reaction via **TS6** to release DMS and the final cyclopropane product **PR1**. This step requires an activation free energy of 9.8 kcal/mol. This substitution step is also very exergonic by 34.2 kcal/mol and is irreversible. From Figure 3, we conclude that the cyclopropanation pathway has the rate-determining step of Michael addition and the overall activation free energy is 15.5 kcal/mol (from **IN7**, see further discussion in the epoxidation pathway).

Epoxidation Pathway: In the epoxidation pathway, complex **COM4** undergoes direct addition to the carbonyl group of enone via **TS7**. This 1,2-addition requires an activation free energy of 11.8 kcal/mol (from **DMSM** and **1** to **TS7**). Yielding **IN7** from **DMSM** and enone is a neutral process (–0.7 kcal/mol in terms of Gibbs free energy). **IN7** has also an eclipsed conformation due to the electrostatic attraction between the oxygen atom and the sulfur atom. In the process of intramolecular substitution, **IN7** firstly undergoes C–C bond rotation to give **IN8**, which then undergoes the substitution via **TS8**. The substitution step from **IN7** to the transition state **TS8** requires an activation free energy of 13.3 kcal/mol, similar to the process of substitution step of **DMSOM** with enone **1** (namely, **IN3** to **TS4** in the epoxidation pathway). This final step to give epoxide and **DMS** is exergonic by 29.1 kcal/mol. Due to the relative stability of **IN7**, which makes the formation of this intermediate is almost a thermodynamically neutral process, the relative free energy of **TS8** is only 0.8 kcal/mol higher than that of **TS7**. The rate-determining step in the epoxidation pathway is from **IN7** to **TS8** and requires an activation free energy of 13.3 kcal/mol.

Comparison of Two Pathways: Overall, for **DMSM**'s reaction to enone, 1,2-addition step in the cyclopropanation pathway is more favored over the 1,4-addition step in epoxidation pathway, by 3.0 kcal/mol. When comparing both pathways in Figure 3, we can conclude that both cyclopropanation and epoxidation should start from the formation of **IN7**, which then undergoes either epoxidation (**IN7**→**IN8**→**TS8**) or cyclopropanation (**IN7** →**TS7** → **COM4** →**DMSM**/**enone** →**COM3**–**TS5**). Therefore, the overall activation energy for epoxidation is 13.3 kcal/mol (**IN7** to **TS8**) while the cyclopropanation has an overall activation free energy of 15.5 kcal/mol (from **IN7** to **TS5**). Consequently, the epoxidation pathway is favored by 2.2 kcal/mol. Actually, this can be well understood by using the Curtin–Hammett principle,[15] suggesting that the preference of one pathway over the other can just compare their rate-determining transition states, **TS5** and **TS8**. Here **TS8** is favored by 2.2 kcal/mol than **TS5**. Due to this, epoxidation is preferred over the cyclopropanation. This is consistent with the experimental observations.[10]

Further comparison of cyclopropanation and epoxidation pathways for DMSOM and DMSM

We draw a simple picture of the cyclopropanation and epoxidation of both **DMSOM** and **DMSM** (its discussion is given below). Scheme 4 shows that cyclopropanation is favored for **DMSOM** (**TS1** is lower than **TS4** by 5.5 kcal/mol), suggesting that the cyclopropanation pathway is the favored one. This computational conclusion is in agreement with the experiments. This also agrees with the previous kinetic study by Johnson, who showed that dimethylaminophenyloxosulfonium methylide's reaction to enone also has the Michael addition as the rate-determining step.[16] In addition, the computed activation free energy is close to the experimental value of 16.6 kcal/mol (see more discussion in the Supporting Information).[16b]



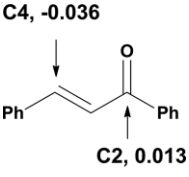
Scheme 4. Pathways of reactions of **DMSOM/DMSM** with **enone**.

The preference of cyclopropanation over epoxidation of **DMSOM** is attributed to the endergonic 1,2-addition step in the epoxidation pathway. This step is endergonic by 9.5 kcal/mol. The followed substitution step from **IN3** to **IN4** then to **TS4** is not difficult (13.5 kcal/mol activation free energy, close to the 1,2-addition step with 17.5 kcal/mol activation free energy), but **TS4** is now higher in energy than **TS3**. Consequently, **TS4** becomes the rate-determining transition state and the reaction has to overcome both transition states, **TS3** and **TS4**. Due to this, the overall activation barrier in the epoxidation pathway reaches 23.0 kcal/mol, which is higher than the required barrier in the cyclopropanation pathway (17.5 kcal/mol).

For **DMSM**, the formation of betaine intermediate **IN7** via 1,2-addition was exergonic by 0.7 kcal/mol, which is in contrast to the endergonic (by 9.5 kcal/mol) 1,2-addition step for **DMSOM**. While the second steps, the substitution steps in the epoxidation pathways for both **DMSM** and **DMSOM** are similar (around 13 kcal/mol). Consequently, **TS8** (from a stable intermediate **IN7**) is very close to **TS7** in energy for **DMSM**, while **TS4** (from a less stable intermediate **IN3**) is higher than **TS3** for 7.1 kcal/mol. Therefore, the epoxidation pathway for **DMSM** is not difficult with an overall activation energy of 13.3 kcal/mol (from **IN7** to **TS8**), which is lower than the overall activation energy of the cyclopropanation pathway, 15.5 kcal/mol. Therefore, we attribute the preference of epoxidation pathway for **DMSM** to the fact that the formation of 1,2-addition adduct is a thermodynamically neutral process.

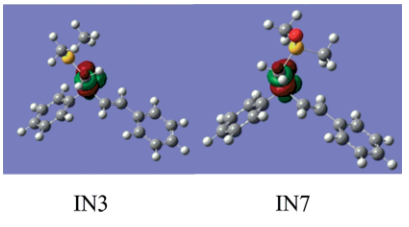
Discussion of 1,2- vs. 1,4-Addition of Ylides to Enone

We found that 1,2-additions are favored than 1,4-additions for both **DMSOM** and **DMSM**. This regioselectivity can be understood by enone's Fukui function distribution.[17] DFT computed nucleophilic Fukui functions are 0.013 and –0.036 for carbonyl carbon C2 and C4 carbon in enone **1**, suggesting that C2 is more nucleophilic (Scheme 5).



Scheme 5. Nucleophilic Fukui functions for C2 and C4 of enone **1**.

Although two ylides finally give different products, the 1,4-addition intermediates are both more stable than correspond 1,2-addition intermediates about 12 kcal/mol. This can be understood that, 1,4-additions still give conjugated products while 1,2-additions disrupt the conjugation of ketone and alkene in the substrate. In the structure of 1,2-addition intermediates **IN3**, **IN4**, **IN7** and **IN8**, newly generated C–C bond lengths are up to



Scheme 6. NBO analysis of **IN3** and **IN7**, showing $n \rightarrow \sigma^*$ interaction.

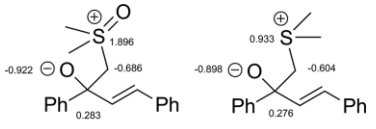
1.57–1.60 Å, which are longer than normal C–C bond length of 1.55 Å, This C–C bond elongation can be attributed to the fact that oxygen's lone pair interacts with C–C σ* orbital (Scheme 6).

Relative Reactivity of DMSOM and DMSM

Why is **DMSOM** less reactive than **DMSM** toward enone **1**, in both the 1,2 and Michael addition steps? We attribute this to the higher HOMO of **DMSM** compared to that of **DMSOM**. Mayr once proposed an equation describing the relationship of the reaction rate constant and the nucleophilicity (*N*) or electrophilicity (*E*) of reactant.[18] Nucleophilicities of several substituent dimethylsulfoxonium methylides were measured. For example, **DMSOM** has *N* = 21.29. But data for **DMSM** was not available.[18] Previously we found that, for very similar compounds that are different by only substitutions, the HOMOs or LUMOs of these molecules have a linear relationship with their nucleophilicities or electrophilicities.[19] Here the computed HOMO of **DMSOM** is –5.28 eV, while the HOMO of **DMSM** is –4.76 eV (calculated at B3LYP/6-31G(d) level based on the optimized structures at SMD(DMSO)-M06–2X/6-31+G(d) level). This suggests that **DMSM** is more nucleophilic than **DMSOM**. This could be be easily understood because **DMSOM** has an electron-withdrawing sulfoxide group in it.

Relative Stabilities of Betaine Intermediates

Finally, we discuss the relative stability of betaine intermediates in reactions of **DMSM** and **DMSOM** with enone **1**, which is the main reason for their different regioselectivities. There is almost no difference in the structures of these intermediates, indicating that the steric effects are not significant here. In contrast, the electronic effects have a major influence. Natural population analysis shows that sulfur atom at **DMSOM** is more positive charged than the sulfur in **DMSM** (charge of other atoms in the reaction central almost equal). Therefore, **IN3** with highly charged sulfur become less stable (Scheme 7).



IN3 **IN7**

Scheme 7. Natural population analysis of betaine intermediates.

To further illustrate this difference, we calculated two parallel thermodynamics processes, the methylations of DMS and DMSO by methyl cation, showing that DMS's methylation was more exergonic (by 7.0 kcal/mol) than DMSO's methylation (Scheme 8).

$$Me_2S + CH_3^+ \xrightarrow{\Delta G_{DMSO} = -73.4\ kcal/mol} Me_3S^+$$

$$Me_2SO + CH_3^+ \xrightarrow{\Delta G_{DMSO} = -66.4\ kcal/mol} Me_3SO^+$$

Scheme 8. Computed thermodynamics of hypothesized methylation reactions.

The above different thermodynamics can be simply explained in this way: as ylides, **DMSOM** is more stable than **DMSM** because the former has an additional electron-withdrawing oxygen atom compared with the latter. Therefore, **DMSOM** is less reactive than **DMSM** in the 1,2-addition to enones. Vice versa, it is expected that addition products from more reactive **DMSM** should be more exergonic than those from **DMSOM** (see Scheme 4).

Cyclopropanation Reactions of Stabilized Sulfur Ylides

It should be noticed that, even though epoxidation is favored than cyclopropanation for **DMSM**, the difference of activation energies for both pathways is not high (13.3 vs. 15.5 kcal/mol). Therefore, some **DMSM** derivatives could overturn this selectivity and change its reaction with enones to give cyclopropanation products. From above analysis, we can also easily envisioned that when a stable **DMSM** derivative is used, the 1,2-addition could become more endergonic and make the epoxidation become disfavored. This was supported by some known examples for stabilized sulfur ylides (see Scheme 3).[11–13] Our calculation results are given below to give more understanding of these reactions.

For 4-cyanophenyl-substituted sulfur ylide (**Ar-DMSM**), both epoxidation and cyclopropanation have two pathways to give two diastereomers, respectively. We have computed their potential energy surfaces (given in the Supporting Information), and the most favored pathways in cyclopropanation and epoxidation are given in Figure 5. The cyclopropanation has the rate-determining and irreversible step of 1,4-addition of ylide, **E-DMSM** to enone via **TS9**–**1**. The epoxidation pathways are disfavored because both the 1,2-addition step and the substitution step have transition states higher than **TS9**–**1** and **TS9**–**2** (this is given in the Supporting Information) in the cyclopropanation step. Therefore, epoxidation is not favored, agreeing with experiments.[12]

The difference that **Ar-DMSM** favors cyclopropanation while **DMSM** prefers epoxidation can be understood by the following analysis, **Ar-DMSM** has higher HOMO than **DMSM** (**Ar-DMSM**, –4.52 eV, **DMSM**, –4.76 eV), but it reacts with enone with more difficulty (the 1,2-addition step for **DMSM** is 11.8 kcal/mol while this is 19.2 kcal/mol for **Ar-DMSM**). This difference is attributed to the thermodynamic reason explained by Hammond postulate. The generation of 1,2-addition intermediate for **Ar-DMSM** is endergonic by 15.8 kcal/mol while this is a neutral process for **DMSM**. Therefore, **Ar-DMSM** is slower than **DMSM** in the 1,2-additions to enones, as suggested by Hammond postulate. The endergonic 1,2-addition for **Ar-DMSM** then further pushes up the second substitution transition state in the epoxidation pathway. Consequently, the epoxidation pathway has the overall activation free energy of 27.7 kcal/mol, much higher than the activation free energy (17.1 kcal/mol) required for the cyclopropanation pathway.

We also computed the energy surfaces of cyclopropanation and epoxidation pathways of COOMe-substituted sulfur ylide, **E-DMSM** (Figure 6), which show that cyclopropanation is favored over the epoxidation (more details are given in the Supporting Information). This agrees with experimental observation.[13] The reason is similar to the case of **Ar-DMSM** because

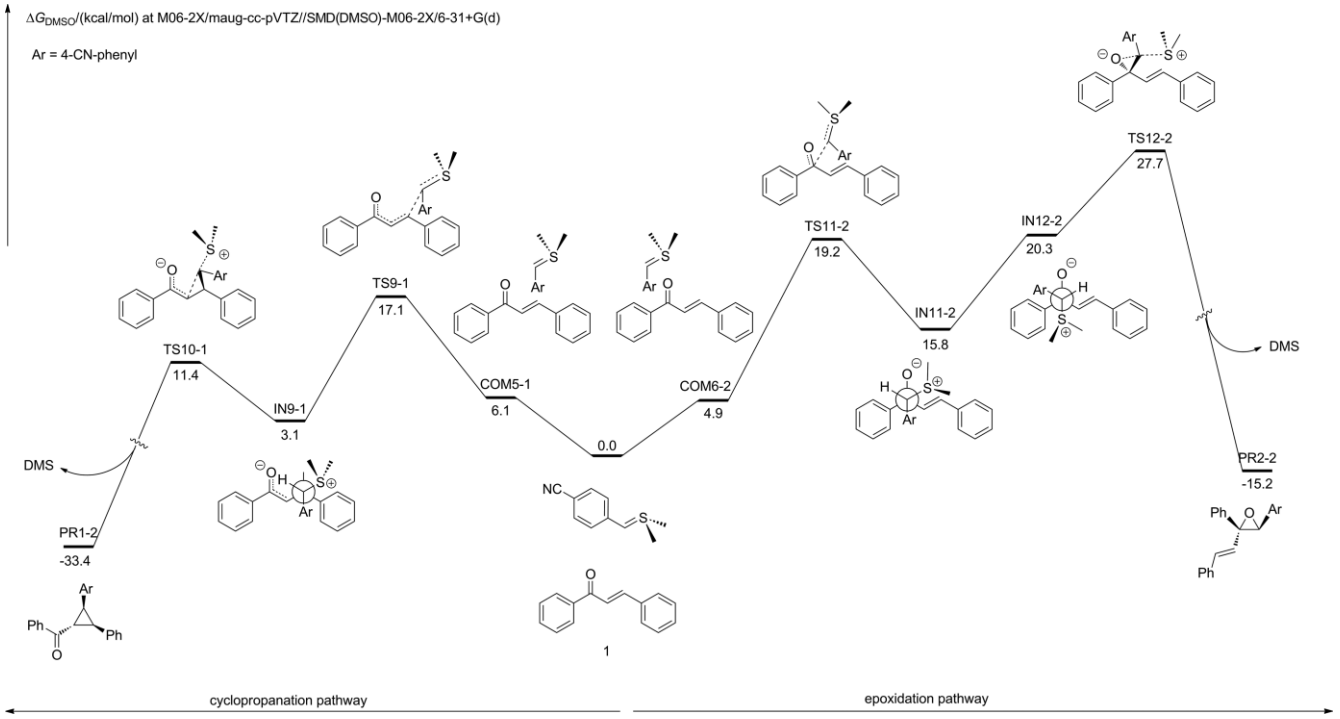


Figure 5. DFT computed energy surface of reaction of **Ar-DMSM** with enone.

the 1,2-addition is highly endergonic. In the epoxidation pathway, the 1,2-addition step has an activation free energy of 22.6 kcal/mol and is endergonic by 20.6 kcal/mol. This endergonic step also pushes the followed transition state **TS16** of the substitution to form epoxide higher and the overall activation free energy of epoxidation reaches 34.0 kcal/mol. The HOMO of **E-DMSM** is –5.12 eV, which is lower than that of **DMSM** (–4.76 eV). Therefore, **E-DMSM** is less reactive than **DMSM** in their reaction, as can be appreciated by the activation free energy of 21.0 kcal/mol for its cyclopropanation pathway (the activation free energy for cyclopropanation of **DMSM** is 14.8 kcal/mol, from separated **DMSM** and enone **1**). But the epoxidation pathway for **E-DMSM** has endergonic 1,2-addition and makes the epoxidation disfavored. Two reasons are responsible for the endergonic 1,2-addition: the first one is ylide **E-DMSM** is more stable than **DMSM** and its reaction with ketone will be disfavored thermodynamically. The second one is due to steric reasons because the intermediate **IN15**–**2** suffers from electrostatic

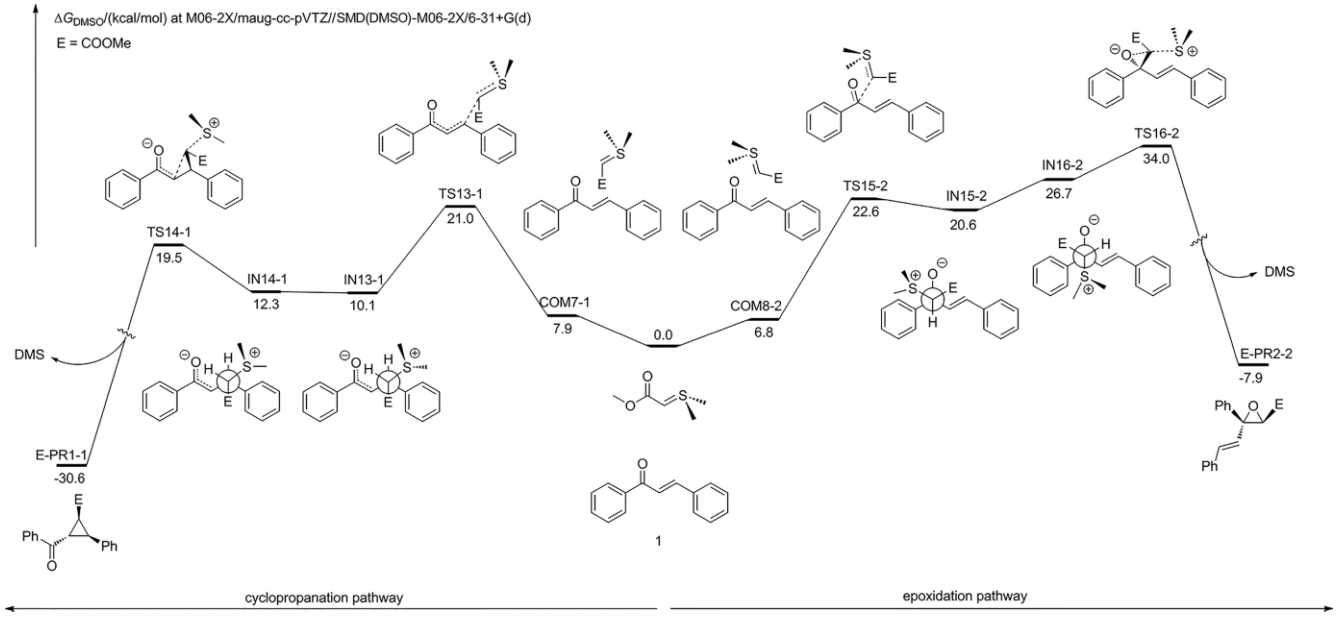


Figure 6. DFT computed energy surface of the reaction of **E-DMSM** with enone.

repulsion between the oxygen anion and the ester group, which are in gauche conformation.

For **DMSOM**, the difference of activation free energy of cyclopropanation and epoxidation is much larger than **DMSM**'s. The change of the regioselectivity could be difficult. We propose that in very special reactions of enones with one or two bulky group in the C4 position, the 1,4-addition in cyclopropanation pathway could become disfavored (due to steric reason) for **DMSOM**. Then epoxidation becomes favored. This is just our hypothesis and no experimental results have been reported yet.

Conclusions

In this paper, we report our calculation results aiming to answer why **DMSOM** and **DMSM** react with enones to give different products (Scheme 4). We found that, the cyclopropanation pathways for both **DMSOM** and **DMSM** have rate-determining and irreversible 1,4-addition of ylides to enones, followed by easier intramolecular substitution to give epoxides. The activation free energies for cyclopropanation are 17.5 and 15.5 kcal/mol for **DMSOM** and **DMSM**, respectively. The epoxidation pathways for both **DMSOM** and **DMSM** have reversible 1,2-addition of ylides to ketone group of enone, followed by rate-determining intramolecular substitution to give epoxides. The computed barriers for the epoxidations pathways are 23.0 and 13.3 kcal/mol for **DMSOM** and **DMSM**, respectively. Therefore, the cyclopropanation pathway is favored for **DMSOM** while epoxidation is preferred for **DMSM**. The major reason for the different reactivity is that the 1,2-addition of ylide to enones for **DMSOM** is endergonic and this makes the second step of this pathway become difficult. For **DMSM**, this 1,2-addition is a thermodynamic neutral process and the second step is not so difficult. The different thermodynamics can be simply explained: **DMSOM** is more stable than **DMSM** as ylide because the former has an additional electron-withdrawing oxygen atom, **DMSOM** is less reactive and its 1,2-addition to enones is more endergonic. In this paper, we also answer why other derivatives of **DMSM**, **Ar-DMSM** and **E-DMSM**, when they reacted with enone, gave cyclopropanes instead of epoxides (Figure 5 and Figure 6). The reason can be attributed to the endergonic 1,2-addition of these stable ylides to enones considering that both **Ar-DMSM** and **E-DMSM** are more stable than **DMSM**.

Computational Methods

All calculations were performed with the Gaussian 09 program.[20] Pruned integration grids with 99 radial shells and 590 angular points per shell were used. Geometry optimizations of all the minima and transition structures and solvation free energy involved were carried out using the M06–2X functional[21] and the 6-31+G(d) basis set[22] in the DMSO by a self-consistent reaction field (SCRF) using the SMD model.[23] Frequency calculations at the same level were carried out to confirm each stationary point to be either a minimum or a transition structure. Intrinsic reaction coordinate (IRC) calculations were applied to confirm the connection of each transition state to its corresponding reactant(s) and product(s). All possible conformers for complexes, intermediates, transition states had been searched and located (by adjusting their relative orientations of different functional groups manually), but only the most stable ones were reported. M06–2X and maug-cc-pVTZ basis set[24] were used for gas phase single-point energy calculations based on the optimized structures at the M06–2X/6-31+G(d) level. We used standard state of 1.0 mol/L at 298 K for all species and therefore a 1.89 kcal/mol correction was used for processes involving two molecules to a complex/intermediate or a transition state or vice versa. For releasing DMSO, a 1.57 kcal/mol correction was used because pure DMSO concentration is 14.1 mol/L. All figures of structures were prepared using CYLView.[25]

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Keywords: Corey–Chaykovsky Reaction · Cyclopropanation · Epoxidation · DFT calculations · Regioselectivity

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