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Unraveling the Concerted Reaction Mechanism of the Noncatalyzed Mukaiyama Reaction between C,O,O-Tris(trimethylsilyl)ketene Acetal and Aldehydes Using Density Functional Theory

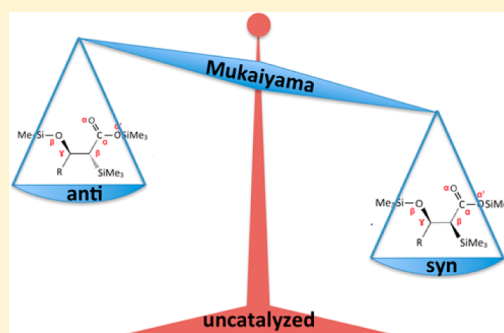
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S Supporting Information

ABSTRACT: The uncatalyzed Mukaiyama aldol reaction between C,O,O-tris(trimethylsilyl)ketene acetal and aldehydes bearing alkyl, vinyl, and aromatic substituents has been studied theoretically using density functional theory with the M06-2X exchange–correlation functional. These DFT calculations mostly demonstrate that (i) the *syn* product is both kinetically and thermodynamically favored, (ii) the diastereoselectivity of the uncatalyzed reaction is larger than observed for the reaction catalyzed by HgI₂ and it is inverted with respect to the latter, (iii) solvents with larger dielectric constants increase the activation barrier but reduce the diastereoselectivity, (iv) the concerted reaction is preferred over the stepwise reaction, and (v) the OSiMe₃ group in geminal lowers the activation barrier and increases the energy of reaction. Analyzing the concerted mechanism unravels four types of cyclic transition states, two pro-*anti* and two pro-*syn*. Then, the relative energy of the most stable transition state of each type as well as of the corresponding *anti* and *syn* products shows that the *syn* reaction path is located at lower Gibbs enthalpy than the *anti* reaction path for all substituents.



I. INTRODUCTION

The Mukaiyama aldol¹ reaction is an efficient reaction for forming carbon–carbon bonds. This reaction is an addition of silyl enol ether (enolsilane) or ketene silyl acetal on carbonyl compounds. It provides a route for the stereoselective construction of β -hydroxy carbonyl units, which are important building blocks for the preparation of a broad range of natural products and pharmaceuticals. This aldol reaction is usually catalyzed by Lewis acids but it can also proceed without catalyst when the acidity of the Si atom of the silyl enol is increased.^{2–5} For instance, Bellassoued et al.⁶ have carried out a noncatalyzed addition between a bis(trimethylsilyl)ketene acetal and an aromatic aldehyde under high pressure.

Mukaiyama aldol reaction has also been described using quantum chemical calculations.^{4,7,8} Wong and Wong⁸ have shown that the noncatalyzed condensation of the trihydrosilyl enol ether (CH₂=CH–O–SiH₃) on formaldehyde is possible via two mechanisms, concerted or stepwise and that the concerted mechanism is favored. During the concerted mechanism [$\Delta E = -22.7$ kcal mol⁻¹ and $\Delta E^\ddagger = 18.4$ kcal mol⁻¹, as estimated at the G3(MP2) level of approximation] the migration of the silyl group from the enol ether to the aldehyde is accompanied by the formation of a CC single bond. The role of the silyl group is not limited to influencing the nature of the transition state because the silicon transfer from the enolsilane to the β -alkoxy position may be a key step in the

overall mechanism and becomes crucial to the turnover necessary for nonstoichiometric transformations. On the contrary, in the case of the concerted mechanism, the activation energy of the first step is much larger ($\Delta E^\ddagger = 49.5$ kcal mol⁻¹). These results were in agreement with previous works.^{4,7,9,10} So, for the concerted mechanism of the same reaction, Gung et al.⁷ obtained at the MP2/6-31G* $\Delta H = -33.2$ kcal mol⁻¹ and $\Delta E^\ddagger = 13.8$ kcal mol⁻¹ and highlighted that the Si atom of the transition state presents a trigonal bipyramid geometry.

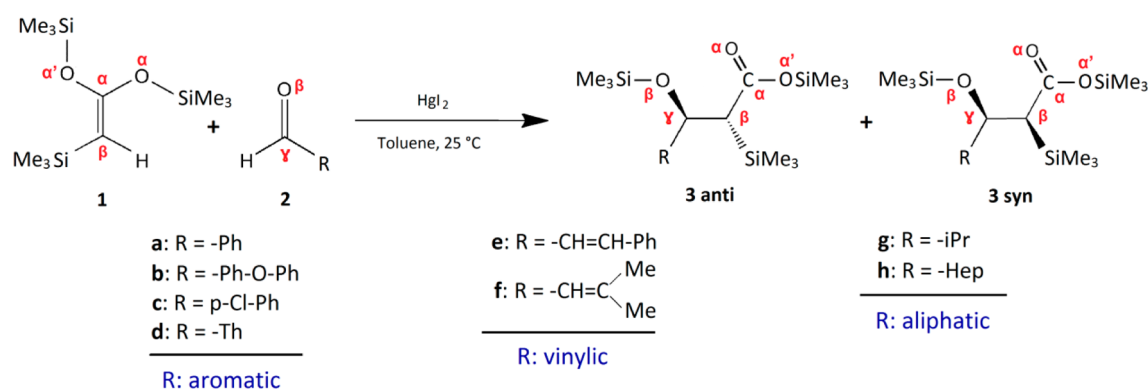
Though Mukaiyama reaction between a tris-silyl ketene acetal and an aldehyde is less common than the reactions involving bis-silyl and monosilyl species, it was investigated by Bellassoued and co-workers,^{6,11,12} in the case of the condensation of tris(trimethylsilyl)ketene acetal with a variety of aldehydes in the presence of Lewis acids or bases. In particular, in ref 12 they have reported on the reaction between C,O,O-tris(trimethylsilyl)ketene acetal **1** and a variety of aldehydes **2a–2h** (aliphatic, vinylic, and aromatic), catalyzed by HgI₂ at room temperature and in toluene solutions. This aldol reaction produces *syn* and *anti* β -(trimethylsiloxy)- α -(trimethylsilyl)alkanoic acid silyl esters **3** in low diastereose-

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Scheme 1. Mukaiyama Reaction between the C,O,O-Tris(trimethylsilyl)ketene Acetal **1** and Aldehydes **2a–2h** (Called Reaction 1)Table 1. Enthalpy (ΔH^\ominus , kcal mol⁻¹), Entropy (ΔS^\ominus , cal K⁻¹ mol⁻¹), and Gibbs Enthalpy (ΔG^\ominus , kcal mol⁻¹) of Reaction for the Most Stable Conformers of the **3 anti** and **3 syn** Diastereomers, As Determined at the M06-2X/6-31G* Level ($T = 298.15\text{K}$; $P = 1\text{ bar}$) as Well as Representative Geometrical Parameters of the Products, the $\alpha_{\text{Si-C}\beta\text{-C}\gamma\text{-O}\beta}$ and $\beta_{\text{Si-C}\beta\text{-C}\alpha\text{-O}\alpha}$ Dihedral Angles (deg) and the $d(\text{O}_\beta\cdots\text{Si})$ Distances (Å)

reaction	ΔH^\ominus	ΔS^\ominus	ΔG^\ominus	$\alpha_{\text{Si-C}\beta\text{-C}\gamma\text{-O}\beta}$	$\beta_{\text{Si-C}\beta\text{-C}\alpha\text{-O}\alpha}$	$d(\text{O}_\beta\cdots\text{Si})$
1 + 2a → 3a anti	-36.79	-52.82	-21.04	178.3	83.0	4.153
1 + 2a → 3a syn	-37.36	-52.42	-21.73	52.0	79.9	3.018
1 + 2b → 3b anti	-36.03	-50.95	-20.84	179.7	83.0	4.150
1 + 2b → 3b syn	-37.53	-52.69	-21.82	50.7	80.2	3.002
1 + 2c → 3c anti	-37.19	-51.11	-21.95	178.5	83.8	4.154
1 + 2c → 3c syn	-38.13	-52.62	-22.44	52.1	84.7	3.013
1 + 2d → 3d anti	-37.31	-52.76	-21.58	178.7	82.9	4.149
1 + 2d → 3d syn	-37.54	-52.69	-21.83	51.9	84.2	3.016
1 + 2e → 3e anti	-34.74	-50.38	-19.72	180.8	85.9	4.150
1 + 2e → 3e syn	-35.42	-55.11	-18.99	-42.3	111.6	3.034
1 + 2f → 3f anti	-34.04	-52.05	-18.52	180.9	81.1	4.146
1 + 2f → 3f syn	-34.82	-53.73	-18.80	-43.8	114.3	3.045
1 + 2g → 3g anti	-39.10	-60.64	-21.02	181.7	88.5	4.164
1 + 2g → 3g syn	-40.10	-56.21	-23.34	43.3	78.5	2.920
1 + 2h → 3h anti	-39.24	-60.71	-21.14	182.7	89.6	4.164
1 + 2h → 3h syn	-40.38	-64.30	-21.21	-39.8	110.3	3.037

lectivity, of which the major diastereoisomer is **3 anti** and the minor is **3 syn** (Scheme 1).

In this work, density functional theory (DFT) is employed to describe this Mukaiyama condensation but in the absence of catalyst. By determining the structural, electronic, and thermodynamical properties of the reactants, transition states, and products as well as by using reactivity criteria, we address several issues, including (i) which SiMe₃ group is migrating, (ii) which product, *syn* or *anti*, is favored, (iii) how the presence of one, two, and three silyl groups impacts the reactions, and (iv) what are the differences with respect to the experimental HgI₂ catalyzed reaction,¹² and with respect to other investigations.^{4,7,8} The work is organized as follows: the details on the computational procedure are described in the next section; the results are then presented and discussed for the reactants, the

energies of reaction, and the concerted mechanism; finally, we conclude.

II. COMPUTATIONAL METHODS

Equilibrium structures of reactants and products were optimized at the DFT level using the M06-2X exchange–correlation functional^{13,14} and the 6-31G(d) basis set. For the products, the (2*R*,3*R*) absolute configuration is chosen to represent the *anti* form whereas the *syn* form is represented by the (2*R*,3*S*) configuration. For both products forms, several starting structures were considered in the geometry optimization to probe widely the potential energy surface and to locate the different minima. These structures were obtained by considering systematic rotations, by steps of 30°, around the C_β–C_γ bond. The transition states (TS) were localized and

characterized using the same M06-2X/6-31G* level of approximation. They possess a unique imaginary frequency. Intrinsic reaction coordinate (IRC) calculations were then performed to check that the TS are related to the corresponding reactants and products. For all species, reactants, products, and TS, the standard enthalpy (ΔH^\ominus , ΔH^\ddagger), entropy (ΔS^\ominus , ΔS^\ddagger), and Gibbs enthalpy (ΔG^\ominus , ΔG^\ddagger) were evaluated ($T = 298.15$ K, $P = 1$ atm).

Several descriptors^{15–22} of the electronic structure and reactivity were evaluated, including the energies of the highest occupied molecular orbital (HOMO, ϵ_H) and of the lowest unoccupied molecular orbital (LUMO, ϵ_L), the LUMO–HOMO gap ($\text{gap} = \epsilon_{\text{LUMO}} - \epsilon_{\text{HOMO}}$), the electronegativity [$\chi = -(\epsilon_{\text{HOMO}} + \epsilon_{\text{LUMO}})/2$], the chemical potential ($\mu = -\chi$), the global hardness [$\eta = (\epsilon_{\text{LUMO}} - \epsilon_{\text{HOMO}})/2$], the global softness ($S = 1/2\eta$), the global electrophilicity ($\omega = \mu^2/2\eta$), the nucleophilicity index [$N(X) = \epsilon_{\text{HOMO}}(X) - \epsilon_{\text{HOMO}}(\text{TCE})$, where tetracyanoethylene (TCE) is taken as reference], the local electrophilicity of atom k [$\omega_k = \omega f_k^+$, where $f_k^+ = \{q(k, N+1) - q(k, N)\}$], and the local nucleophilicity [$N_k = N f_k^-$, where $f_k^- = \{q(k, N) - q(k, N-1)\}$]. $q(k, N)$ is the Mulliken charge on atom k of the neutral molecule containing N electrons whereas the corresponding charges for the cation and anion are $q(k, N-1)$ and $q(k, N+1)$, respectively. The ionization energy of **1** as well as the electroaffinities of **2a–2h** were also calculated from difference energy calculations, after evaluating the energies of the cation and anion at the geometries of the neutral molecule.

Solvent effects (toluene) were taken into account both in the geometry optimizations and in the calculations of the thermodynamic state functions by using the integral equation formalism (IEF) version of the polarizable continuum model (IEF-PCM).²³ Additional calculations were carried out with acetone as solvent and *in vacuo*. All calculations were performed using the Gaussian 09 package.²⁴

III. RESULTS AND DISCUSSION

Reactants Properties. After the geometrical structures were optimized, the descriptors of the reactants were calculated (Table S1), which gives a first estimate of their reactivity. The hardness (and softness) of **1** and **2a–2h** are similar, which is in favor of their interactions. The chemical potential of **1** (−2.65 eV) is larger than those of **2a–2h** (from −3.95 to −4.69 eV), confirming the transfer of electron from the C,O,O-tris(trimethylsilyl)ketene acetal **1** to the aldehydes **2a–2h**. This is consistent with (i) the higher HOMO energy of **1** (−7.10 eV) than those of **2a–2h** (from −7.85 to −8.70 eV), with (ii) the larger electrophilicity index of **2a–2h** (from 1.56 to 3.01 eV) than **1** (0.77 eV), and with (iii) the smaller value of [$\Delta E_{\text{SA}} = \epsilon_{\text{HOMO}}(\mathbf{1}) - \epsilon_{\text{LUMO}}(\mathbf{2a-2h})$] with respect to [$\Delta E_{\text{AS}} = \epsilon_{\text{HOMO}}(\mathbf{2a-2h}) - \epsilon_{\text{LUMO}}(\mathbf{1})$]. This indicates a preference of interaction between the HOMO of the C,O,O-tris(trimethylsilyl)ketene acetal and the LUMO of the aldehyde (Figure 1, Figure S1). This latter result is consistent with the work of Wong and Wong.⁸

Then, the local nucleophilicity values for C_α and C_β of **1** shows that the nucleophilic ionic addition (NIA) will take place between the C_γ of the aldehyde and C_β of the acetal, which has a nucleophilicity index 2 times larger than the C_α . The electroaffinities are negative for all the aldehydes. Still, these are smaller (in absolute value) for the alkyl substituents [$|\text{IEA}| = 0.30$ and 0.22 eV for **2g** (R = isopropyl) and **2h** (R = heptyl), respectively], which also display the smallest electrophilicity indices. On the contrary, the aromatic and vinylic aldehydes

have similar and quite large EA's. The increasing order of the EA's is

$$\text{EA}(\mathbf{2h}) < \text{EA}(\mathbf{2g}) < \text{EA}(\mathbf{2f}) < \text{EA}(\mathbf{2d}) < \text{EA}(\mathbf{2b}) \\ < \text{EA}(\mathbf{2a}) < \text{EA}(\mathbf{2c}) < \text{EA}(\mathbf{2e})$$

The smaller EA of the aldehydes with alkyl substituents than for the aromatic and vinylic ones is associated with smaller electronegativity, larger hardness, and smaller global electrophilicity but the local electrophilicity on C_γ is similar to those of the aromatic substituents and larger than these of the vinylic ones.

Energies of Reaction. The enthalpies, entropies, and Gibbs enthalpies of reactions are listed in Table 1 for the most stable conformers of the **3 anti** and **3 syn** diastereoisomers. All reactions are exothermic and exergonic, and they are characterized by entropy reduction, owing to the formation of an additional bond. Moreover, the formation of the *anti* diastereoisomers is slightly less exothermic than for the *syn* ones. The enthalpy of reaction is the largest (in amplitude) for the alkyl substituents, with values ~ 2 kcal mol^{−1} larger than those of the aromatic substituents and ~ 4 kcal mol^{−1} larger than those of the vinylic ones. On the contrary, the entropies of reactions are similar for the aromatic and vinylic substituents and smaller than those of the alkyl substituents by about 8–10 cal K^{−1} mol^{−1}. As a result, there are few variations among the Gibbs enthalpies of reactions for the alkyl and aromatic substituents, but their amplitudes are typically 2 kcal mol^{−1} larger than those of the vinylic ones. Analysis of these energies at the light of the descriptors of Table 1 shows that there is no fully consistent relationship with the molecular descriptors, though the vinylic aldehydes have smaller local electrophilicities and the aliphatic ones have the largest ΔE_{SA} .

The geometry of the most stable conformation of **3 anti** and **3 syn** was characterized by two dihedral angles ($\alpha_{\text{Si-C}\beta\text{-C}\gamma\text{-O}\beta}$ and $\beta_{\text{Si-C}\beta\text{-C}\alpha\text{-O}\alpha}$) as well as the distance $d(\text{O}_\beta \cdots \text{Si})$ (Table 1). The **3 anti** products always display larger $d(\text{O}_\beta \cdots \text{Si})$ distances than **3 syn**, the differences in the $\beta_{\text{Si-C}\beta\text{-C}\alpha\text{-O}\alpha}$ angle between **3 anti** and **3 syn** are generally small, whereas the differences in $\alpha_{\text{Si-C}\beta\text{-C}\gamma\text{-O}\beta}$ angle are very important. Note that the $\alpha_{\text{Si-C}\beta\text{-C}\gamma\text{-O}\beta}$ angle is in the antiperiplanar domain for **3 anti** ($\alpha \in [178.3^\circ, 182.7^\circ]$) and in the synclinal domain for **3 syn** ($|\alpha| \in [39.8^\circ, 52.1^\circ]$).

These data on the energetics of the uncatalyzed Mukaiyama aldol reaction between **1** and **2a–2h** further substantiate the role of the substituent, as pointed out by Wong and Wong.⁸ Indeed, in the latter study, considering a broad range of donor/acceptor substituents on the trihydrosilyl enol ether (CH₃, NH₂, OH, F, SH, and CHO) and on the formaldehyde (CH₃, CF₃, NH₂, F, CHO, COOCH₃, CH=CH₂, and C₆H₅), ΔH^\ominus was found to vary from −2.9 to −38.7 kcal mol^{−1} whereas the energy barrier was from 7.2 to 31.3 kcal mol^{−1}. In general, acceptor/donor groups on the aldehyde reduce/increase the barrier of activation and lead to larger/smaller exothermicity. More precisely, the $\Delta H^\ominus(\text{alkyl}) < \Delta H^\ominus(\text{aromatic}) < \Delta H^\ominus(\text{vinylic})$ order results from donor character of the aromatic and mostly of the vinylic groups. This order was already observed for the model reactants of ref 7, but their amplitudes are smaller as a result of the absence of an additional OSiMe₃ group in geminal position (*vide infra*). Moreover, Denmark et al.⁴ reported that the rate of the uncatalyzed aldol reaction was highly dependent on the

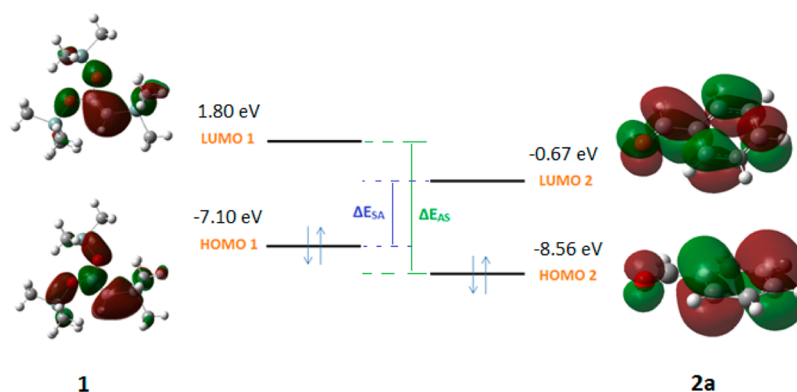
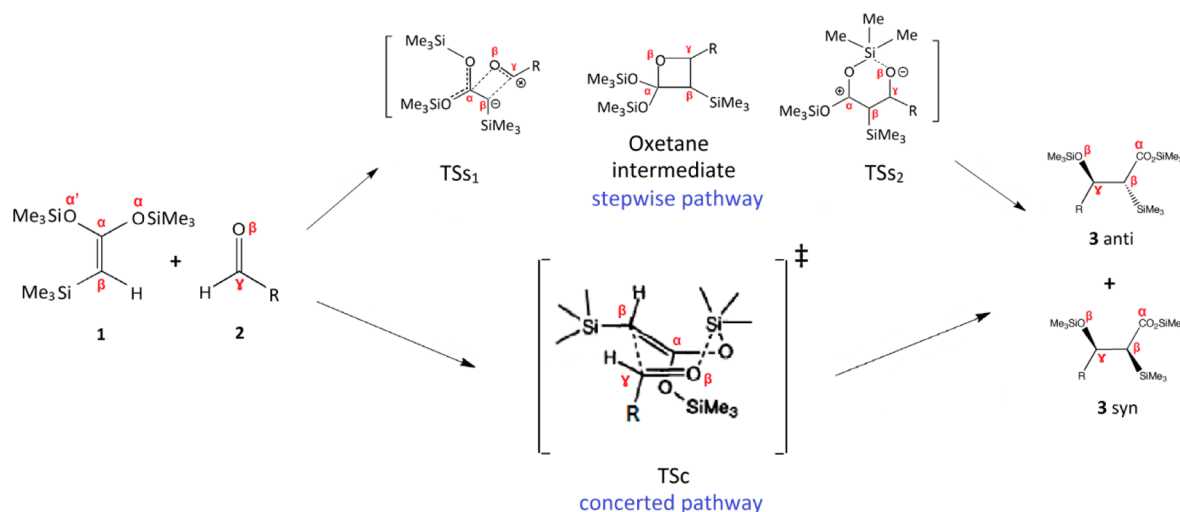


Figure 1. Relative energy positions and topologies of the frontier orbitals. The 2a aldehyde has been chosen. $\Delta E_{SA} = \epsilon_{\text{HOMO}}(1) - \epsilon_{\text{LUMO}}(2)$ and $\Delta E_{AS} = \epsilon_{\text{HOMO}}(2) - \epsilon_{\text{LUMO}}(1)$.

Scheme 2. Concerted versus Stepwise Mechanisms of the Noncatalyzed Mukaiyama Reaction

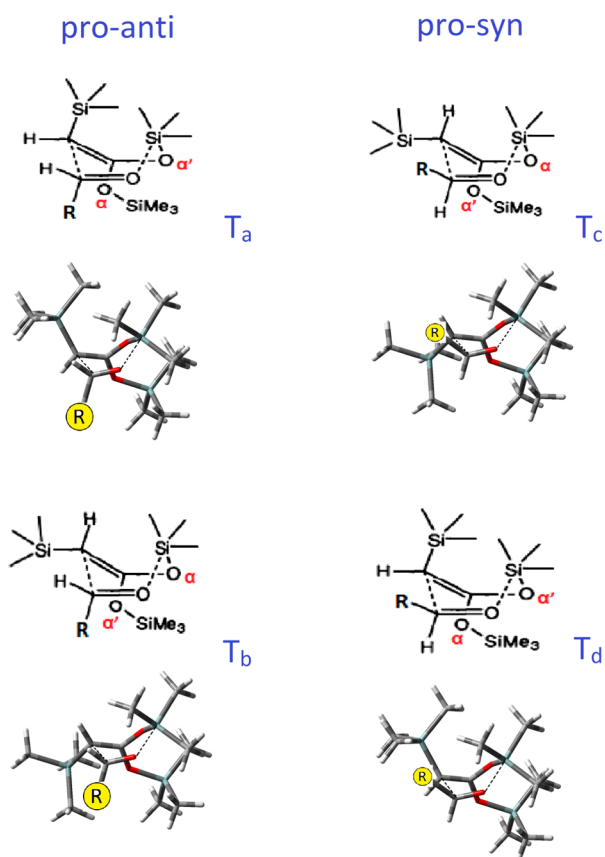


spectator substituent on the silicon atom and on the geometry of the ketene acetal.

Concerted Mechanism. The concerted mechanism of the noncatalyzed Mukaiyama reaction between the C,O,O -tris(trimethylsilyl)ketene acetal **1** and aldehyde **2** involves the migration of a SiMe_3 group from the O_α or $\text{O}_{\alpha'}$ oxygen of the acetal to the O_β oxygen together with the formation of the $\text{C}_\beta\text{--C}_\gamma$ bond to obtain the *syn* and *anti* diastereoisomers of β -(trimethylsiloxy)- α -(trimethylsilyl)alkanoic acid silyl esters **3** (Scheme 2). However, there are two SiMe_3 groups that could migrate on the oxygen of the carbonyl and one of the issues is to determine which one is transferred. Indeed, the $\text{O}_\alpha\text{--SiMe}_3$ and $\text{O}_{\alpha'}\text{--SiMe}_3$ groups have different chemical environments because the $\text{O}_{\alpha'}\text{--SiMe}_3$ group is on the same side as the SiMe_3 group attached to C_β whereas the $\text{O}_\alpha\text{--SiMe}_3$ one is on the opposite site. The transition state of both pro-*anti* and pro-*syn* forms, leading respectively to the *anti* and *syn* products, adopts a boat conformation ($\text{C}_\beta\text{--C}_\alpha\text{--O}_\alpha\text{--Si--O}_\beta\text{--C}_\gamma$).^{4,7,8} There are two possible positions for the carbonyl, on the same or on the opposite side to the $\text{C}_\beta\text{--SiMe}_3$, as characterized by two dihedral angles, $\Theta_{\text{Si--C}_\beta\text{--C}_\gamma\text{--O}_\beta}$ (position of the $\text{C}_\gamma\text{O}_\beta$ carbonyl with respect to $\text{C}_\beta\text{SiMe}_3$) and $\emptyset_{\text{C}_\alpha\text{--C}_\beta\text{--C}_\gamma\text{--O}_\beta}$ (position of the $\text{C}_\gamma\text{O}_\beta$ carbonyl with respect to the $\text{C}_\alpha\text{C}_\beta$ double bond). The Burgi–Dunitz²⁵ angle ($\alpha_{\text{BD}} = \alpha_{\text{C}_\beta\text{--C}_\gamma\text{--O}_\beta}$) as well as the $d_1(\text{O}_\beta\cdots\text{Si})$, $d_2(\text{C}_\gamma\cdots\text{C}_\beta)$, and $d_3(\text{O}_\alpha/\text{O}_{\alpha'}\cdots\text{O}_\beta)$ distances are additional descriptors of the transition states. The \emptyset and Θ angle values

enable to distinguish between four types of transition states ($\text{T}_a\text{--T}_d$, Scheme 3). T_a and T_b are pro-*anti* whereas T_c and T_d are pro-*syn*. Then, T_a and T_d correspond to the situation where the carbonyl and $\text{C}_\beta\text{--SiMe}_3$ are on the same side whereas they are on opposite sides in T_b and T_c (Scheme 3). During the concerted mechanism, the $\text{C}_\gamma\text{O}_\beta$ carbonyl and the $\text{C}_\alpha\text{C}_\beta$ double bond are always on the same side, characterized by a $\emptyset_{\text{C}_\alpha\text{--C}_\beta\text{--C}_\gamma\text{--O}_\beta}$ angle ($\in[13.7^\circ, 72.4^\circ]$) in the synperiplanar or synclinal domain. These synperiplanar and synclinal conformations correspond to small distances between the carbonyl oxygen atom and the migrating SiMe_3 group whereas antiperiplanar conformations (not shown in Scheme 3) would lead to excessive distances to allow SiMe_3 migration. Energies, thermodynamic state functions, and key geometrical parameters of the transition states are listed in Table 2.

In the pro-*anti* case, T_a is characterized by smaller $d_1(\text{O}_\beta\cdots\text{Si})$ and larger $d_2(\text{C}_\gamma\cdots\text{C}_\beta)$ bond lengths than T_b . For the pro-*syn* case, the situation depends on the nature of R and the differences are smaller than for the pro-*anti* case. So, if R is aromatic, T_d is characterized by larger $d_1(\text{O}_\beta\cdots\text{Si})$ and smaller $d_2(\text{C}_\gamma\cdots\text{C}_\beta)$ bond lengths than T_c whereas if it is vinylic (or R = heptyl), the opposite is observed. Finally, when it is an isopropyl, both bond lengths are larger in the case of T_c . Further analysis of the geometrical structures of the transition states shows that both dihedral angles increase from T_a to T_b whereas from T_d to T_c , \emptyset decreases and Θ increases.

Scheme 3. Conformation Types (a–d) of the Pro-*anti* and Pro-*syn* Transition States

In the case of the pro-*anti* route, due to severe steric hindrance between the SiMe₃ attached to the C_β and the methyls of the migrating SiMe₃ group on the bow of the boat, the activation energies (ΔE^\ddagger , ΔH^\ddagger , and ΔG^\ddagger) are systematically smaller for the T_b transition state forms than for the T_a ones, for all kinds of substituents, so that the concerted mechanism leading to the formation of the 3 *anti* diastereoisomers favors the T_b transition state (synclinal). This corresponds to the migration of the SiMe₃ group attached to O_α to the O_β oxygen of the carbonyl. Similarly, the T_c transition states of the pro-*syn* route are more stable than the T_d ones so that the 3 *syn* products result also from the migration of the SiMe₃ group attached to O_α. Nevertheless, the T_b–T_a activation energy differences are always smaller than the corresponding T_c–T_d ones.

Pro-*anti* versus Pro-*syn*. For all substituents, the following ordering of the transition state energies (E, H, and G) is observed:

$$\Delta^\ddagger(T_{c,syn}) < \Delta^\ddagger(T_{b,anti}) < \Delta^\ddagger(T_{a,anti}) < \Delta^\ddagger(T_{d,syn})$$

so that globally, the *syn* diastereoisomers are favored over the *anti* analogs. The smaller activation energies of the pro-*syn* (T_c) transition state than the pro-*anti* (T_b) is not straightforward to explain because in T_c the O_βSi distance is smaller (closer to the product) but the C_γC_β distance is larger. Still, it is observed that by going from T_b to T_c the \emptyset torsion angle decreases strongly and accordingly the O_α⋯O_β distance, leading to an increased interaction between the frontier orbitals where the donor and acceptor are in favorable position.²⁶ In addition, α_{BD} decreases by about 1° from T_b to T_c. Moreover, because the energies of

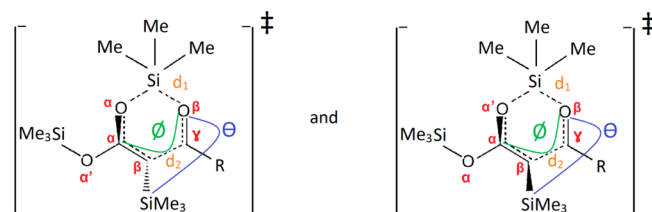
the 3 *anti* products are also larger than those of the *syn* species, the *syn* reaction path is below the *anti* reaction path (Figure 2). Note also that there is a nice correlation between the ΔE^\ddagger and ΔH^\ddagger amplitudes as well as between the ΔE^\ddagger and ΔG^\ddagger amplitudes. The kinetics of this reaction is in agreement with the *anti/syn* ratio of other uncatalyzed Mukaiyama aldol reactions, (i) between *O,O*-ketene acetal and aldehyde as studied by Denmark et al.,⁴ of which the *syn* product was obtained with high diastereoselectivity (93/7 to 99/1) and (ii) between bis(trimethylsilyl)ketene acetals [(OSiMe₃)₂C=CHR] and benzaldehyde as studied by Bellassoued et al.,⁶ of which the major diastereoisomer is *syn* and the minor is *anti* (the percentage of *syn* products ranges from 62% to 67% for R = Me, from 67% to 80% for R = Et, and from 80% to 84% for R = *i*Pr). On the contrary, there is an inversion of diastereoselectivity with respect to the reaction catalyzed by HgI₂.¹² Similar diastereoselectivity inversions have also been reported for Mukaiyama–Michael reactions due to catalysis by graphite oxide²⁷ and for hydroborations of acyclic allylic alcohol derivatives catalyzed by catecholborane.²⁸

Stepwise versus Concerted Mechanism. The preference for the concerted mechanism over the stepwise mechanism (Scheme 2) was studied by performing additional calculations for the 2a aldehyde. The stepwise mechanism is characterized by two transition states (TS_{s1} and TS_{s2}). The first one corresponds to a concerted but asynchronous (the C–O bond forms later than the C–C bond) formal [2 + 2] cycloaddition leading to the formation of an oxetane intermediate. The second leads to the C_α–O_β cleavage and the migration of the SiMe₃ group from the acetal to the oxygen of aldehyde. As shown in Figure 3, TS_{s1} lies at higher energy ($\Delta E^\ddagger = 15.8$ kcal mol⁻¹, $\Delta H^\ddagger = 17.6$ kcal mol⁻¹, $\Delta G^\ddagger = 35.2$ kcal mol⁻¹) than the transition state of the concerted mechanism (TSC, $\Delta E^\ddagger = 11.4$ kcal mol⁻¹, $\Delta H^\ddagger = 12.9$ kcal mol⁻¹, $\Delta G^\ddagger = 31.0$ kcal mol⁻¹). These results are in qualitative agreement with the study of Wong and Wong⁸ on the uncatalyzed reaction between formaldehyde and trihydrosilyl enol ether.

Effects of the SiMe₃ Groups. Additional reaction profiles were then characterized to highlight the role of the SiMe₃ groups (Scheme 4). In reaction 2 the SiMe₃ substituent attached to C_β is missing whereas in reaction 3 one of the OSiMe₃ has been removed. Finally, in reaction 4 both are removed. ΔH of activation and of reaction, listed in Table 3, highlight the minor role of the SiMe₃ substituent (reaction 1 versus reaction 2) but the huge impact of the geminal OSiMe₃ group that reduces the activation energy by a factor of 2 and enhanced the exothermicity by about 60%. Additional calculations not detailed here demonstrate that for these simplified acetals the concerted mechanism is also favored over the stepwise one with $\Delta\Delta H^\ddagger$ that increase up to 12 kcal mol⁻¹ when the geminal OSiMe₃ group is absent.

Solvent Effects. Wong et al.⁸ have shown that the Mukaiyama reaction is generally favorable in solvents that do not bear donating oxygen atoms, like in dichloromethane, hexane, benzene, toluene, and acetonitrile. On the contrary, the reaction is hampered or impossible in tetrahydrofuran, diethyl ether, and *N,N*-dimethylformamide^{1,2,29–31} whereas Kitanosona and Kobayashi have shown that the silyl enolate decomposes in the presence of water, preventing also the reaction to occur.³² In this work, the explicit solute–solvent interactions are not investigated but the dielectric constant effects are assessed by using the PCM approach, which is an implicit solvation model. In particular, the activation energies *in vacuo* for T_b and T_c

Table 2. Activation Energy (ΔE^\ddagger , kcal mol⁻¹), Activation Enthalpy (ΔH^\ddagger , kcal mol⁻¹), Activation Free Enthalpy (ΔG^\ddagger , kcal mol⁻¹), and Activation Entropy (ΔS^\ddagger , cal K⁻¹ mol⁻¹) As Evaluated with the IEFPCM/M06-2X/6-31G* Method ($T = 298.15$ K; $P = 1$ bar, solvent = toluene) as Well as Representative Geometrical Parameters of the Products, the $\Theta_{\text{Si-C}\beta\text{-C}\gamma\text{-O}\beta}$ and $\Theta_{\text{C}\alpha\text{-C}\beta\text{-C}\gamma\text{-O}\beta}$ Dihedral Angles (deg), the Burgi–Dunitz Valence Angle ($\alpha_{\text{BD}} = \alpha_{\text{C}\beta\text{-C}\gamma\text{-O}\beta}$) (deg), and the $d_1(\text{O}_\beta \cdots \text{Si})$, $d_2(\text{C}_\gamma \cdots \text{C}_\beta)$, and $d_3(\text{O}_\alpha/\text{O}_\alpha' \cdots \text{O}_\beta)$ Distances (Å)^a



TS	ΔE^\ddagger	$\Delta\Delta E^\ddagger$	ΔH^\ddagger	$\Delta\Delta H^\ddagger$	ΔS^\ddagger	ΔG^\ddagger	$\Delta\Delta G^\ddagger$	ϕ	Θ	α_{BD}	d_1	d_2	d_3	T
pro-3a anti-a	13.30	1.94	14.91	1.97	-60.00	32.80	2.23	17.7	251.9	107.9	2.082	2.212	2.474	a
pro-3a anti-b	11.36	0 (1.82)	12.94	0 (1.78)	-60.64	31.02	0 (1.77)	56.3	180.0	107.5	2.312	1.956	2.574	b
pro-3a syn-d	14.62	5.08	16.29	5.13	-62.85	35.03	5.78	71.5	309.3	104.8	2.149	2.142	2.600	d
pro-3a syn-c	9.54	0	11.16	0	-60.67	29.25	0	29.2	155.9	106.3	2.097	2.148	2.434	c
pro-3b anti-a	13.98	1.76	15.33	1.72	-61.31	33.61	1.47	17.6	251.9	107.7	2.065	2.211	2.469	a
pro-3b anti-b	12.22	0 (1.88)	13.61	0 (1.89)	-62.15	32.14	0 (2.21)	56.3	180.0	107.4	2.309	1.957	2.573	b
pro-3b syn-d	15.31	4.97	16.72	5.00	-64.26	35.88	5.95	71.6	309.3	104.6	2.128	2.142	2.594	d
pro-3b syn-c	10.34	0	11.72	0	-61.08	29.93	0	29.4	155.8	106.1	2.080	2.146	2.430	c
pro-3c anti-a	12.17	1.42	13.84	1.56	-62.35	32.43	1.81	17.1	250.3	108.7	2.140	2.165	2.474	a
pro-3c anti-b	10.75	0 (1.57)	12.28	0 (1.64)	-61.51	30.62	0 (1.98)	56.1	179.9	108.1	2.389	1.911	2.596	b
pro-3c syn-d	14.18	5.00	15.70	5.06	-61.75	34.11	5.47	71.0	308.7	105.4	2.187	2.128	2.614	d
pro-3c syn-c	9.18	0	10.64	0	-60.37	28.64	0	27.2	154.0	106.8	2.117	2.133	2.431	c
pro-3d anti-a	13.31	2.26	14.92	2.43	-63.36	33.81	3.06	13.7	246.9	107.8	2.107	2.180	2.466	a
pro-3d anti-b	11.05	0 (1.12)	12.49	0 (1.09)	-61.24	30.75	0 (1.65)	53.9	177.2	108.0	2.335	1.951	2.572	b
pro-3d syn-d	14.56	4.63	16.08	4.68	-61.58	34.44	5.34	70.2	307.7	105.3	2.156	2.140	2.601	d
pro-3d syn-c	9.93	0	11.40	0	-59.37	29.10	0	29.0	156.8	106.3	2.108	2.138	2.434	c
pro-3e anti-a	13.69	2.40	15.33	2.62	-62.12	33.85	3.66	19.4	252.1	108.0	2.083	2.177	2.457	a
pro-3e anti-b	11.29	0 (0.81)	12.71	0 (0.80)	-58.63	30.19	0 (1.04)	44.7	168.1	108.0	2.209	2.043	2.497	b
pro-3e syn-d	14.93	4.45	16.56	4.65	-61.75	34.97	5.82	70.9	308.8	104.3	2.087	2.140	2.573	d
pro-3e syn-c	10.48	0	11.91	0	-57.82	29.15	0	34.1	162.1	106.7	2.102	2.123	2.431	c
pro-3f anti-a	13.11	1.25	14.70	1.26	-63.52	33.64	2.38	22.5	256.9	108.6	2.033	2.185	2.445	a
pro-3f anti-b	11.86	0 (0.82)	13.44	0 (0.90)	-59.77	31.26	0 (1.86)	45.0	168.3	107.6	2.055	2.056	2.495	b
pro-3f syn-d	13.67	2.63	15.34	2.80	-63.89	34.39	4.99	72.4	309.6	104.0	2.049	2.144	2.563	d
pro-3f syn-c	11.04	0	12.54	0	-56.55	29.40	0	34.6	161.8	105.9	2.055	2.137	2.417	c
pro-3g anti-a	10.10	1.19	11.55	0.77	-62.85	30.29	1.10	20.3	243.8	108.4	2.142	2.200	2.475	a
pro-3g anti-b	8.91	0 (1.19)	10.77	0 (1.15)	-61.78	29.19	0 (0.87)	58.2	179.8	108.0	2.392	1.912	2.597	b
pro-3g syn-d	14.30	6.58	16.24	6.62	-65.34	35.72	7.40	61.3	300.9	106.9	2.094	2.116	2.529	d
pro-3g syn-c	7.72	0	9.62	0	-62.72	28.32	0	24.6	155.0	105.5	2.100	2.164	2.443	c
pro-3h anti-a	10.48	1.44	12.20	1.46	-69.56	32.94	2.73	19.4	252.1	108.7	2.134	2.191	2.476	a
pro-3h anti-b	9.04	0 (1.51)	10.74	0 (2.43)	-65.30	30.21	0 (2.07)	56.5	178.6	107.7	2.296	1.987	2.574	b
pro-3h syn-d	12.99	3.07	14.71	3.04	-64.13	33.83	3.78	70.7	308.9	103.9	2.138	2.180	2.587	d
pro-3h syn-c	7.47	0	8.31	0	-66.51	28.14	0	39.1	167.7	107.4	2.165	2.113	2.457	c

^aColumns with $\Delta\Delta E^\ddagger$ ($\Delta\Delta H^\ddagger$ and $\Delta\Delta G^\ddagger$) give the differences between the two pro-*anti* and pro-*syn* cases. In parentheses are given the differences between the most stable pro-*syn* and pro-*anti* species.

Table 3. Reaction and Activation Enthalpies (kcal mol⁻¹) for the Mukaiyama Reaction between Aldehyde 2a and Simplified Acetals Derived from Compound 1 As Evaluated with the IEFPCM/M06-2X/6-31G* Method ($T = 298.15$ K; $P = 1$ bar)

	reaction 1	reaction 2	reaction 3	reaction 4
ΔH^\ominus	-36.8	-37.5	-23.0	-23.2
ΔH^\ddagger	12.9	10.5	23.8	22.5

transition states as well as their differences are compared to those calculated in toluene and in acetone (Table 4).

It is observed that (i) the ΔE^\ddagger activation energies increase with the dielectric constant of the medium for both *syn* and *anti*

mechanisms by up to 2 and 3.6 kcal mol⁻¹ in toluene and in acetone, respectively, (ii) in the gas phase and in solution, the T_c state remains more stable than the T_b state, keeping the *syn/anti* ratio larger than 1, but that (iii) the $\Delta\Delta E^\ddagger$ differences decrease slightly with the dielectric constant, demonstrating that the diastereoselectivity of Mukaiyama reaction is slightly reduced.

CONCLUSIONS

Theoretical investigations using density functional theory with the M06-2X functional have been performed to unravel the concerted mechanism of the uncatalyzed Mukaiyama aldol reaction between C,O,O-tris(trimethylsilyl)ketene acetal 1 and aldehydes 2 bearing alkyl, vinyl, or aromatic substituents. These

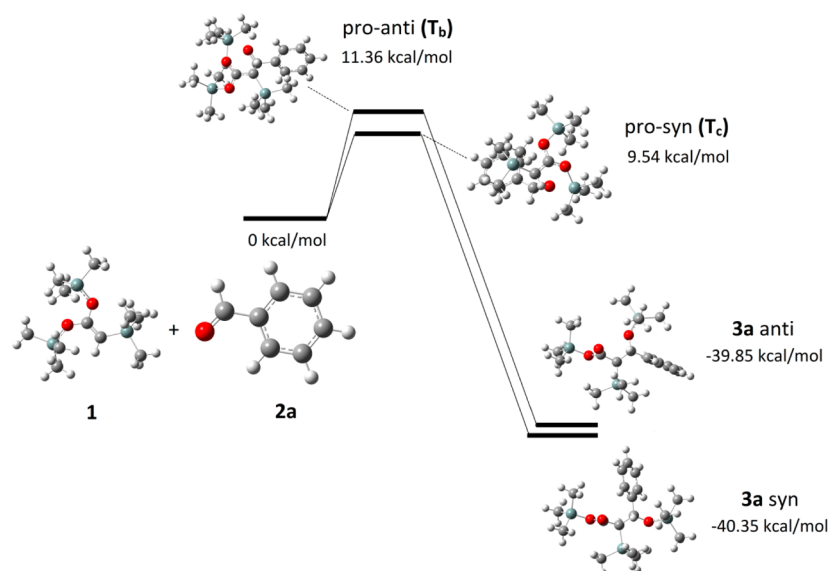


Figure 2. *anti* and *syn* reaction paths [IEFPCM(toluene)/M06-2X/6-31G(d)] for the concerted mechanism of the Mukaiyama reaction between C,*O*,*O*-tris(trimethylsilyl)ketene acetal **1** and aldehyde **2a**.

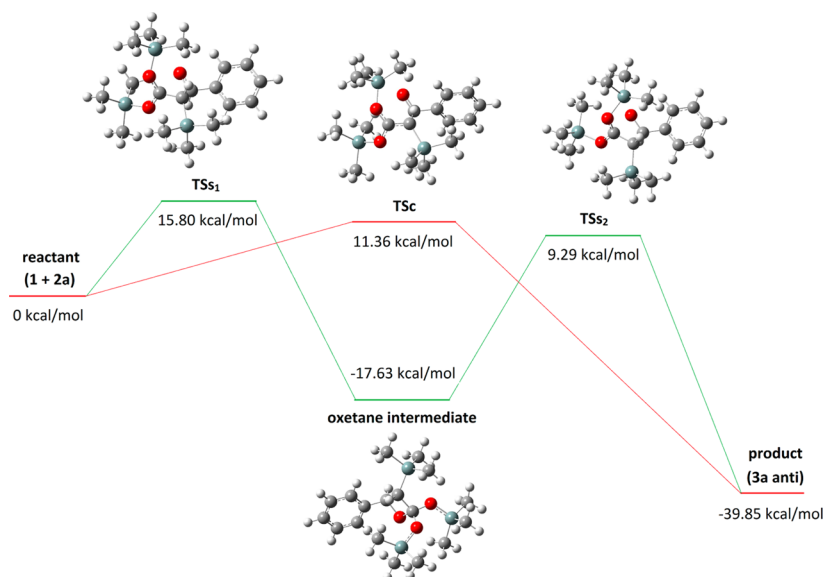
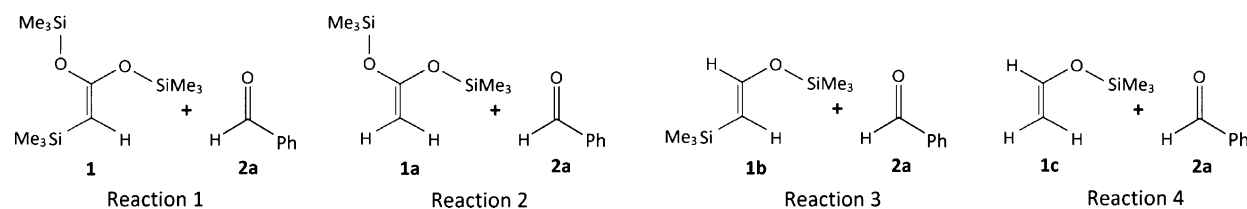


Figure 3. Energy profile [IEFPCM(toluene)/M06-2X/6-31G(d)] for the stepwise versus concerted mechanisms of the reaction between compounds **1** and **2a**.

Scheme 4. Mukaiyama Reactions between Aldehyde **2a** and Acetals Derived from **1**



DFT calculations show that (i) the 3 *syn* product is both the kinetic and the thermodynamic product and that (ii) the diastereoselectivity of the uncatalyzed reaction is larger than observed for the reaction catalyzed by HgI₂¹² and it is inverted with respect to the latter. These calculations have substantiated the fact that solvents with larger dielectric constants increase the activation barrier but reduce the diastereoselectivity. They

have also confirmed the preference for the concerted reaction over the stepwise reactions as well as the key role of the OSiMe₃ group in geminal on lowering the activation barrier and increasing the energy of reaction. Moreover, the study of the concerted mechanism highlights four types of cyclic transition states (T_a, T_b, T_c, T_d). The T_b conformation is the most stable *pro-anti* transition state whereas T_c is a most stable *pro-syn*.

Table 4. Activation Energy (ΔE^\ddagger , kcal mol⁻¹) for the Pro-*anti* T_b and Pro-*syn* T_c Routes As Evaluated with the IEFFCM/M06-2X/6-31G* Method ($T = 298.15$ K; $P = 1$ bar) for Different Solvation Types [*in Vacuo*, Toluene ($\epsilon_r = 2.40$), and Acetone ($\epsilon_r = 21.00$)] and Their Differences ($\Delta\Delta E^\ddagger$, kcal mol⁻¹)

reaction		<i>in vacuo</i>		toluene		acetone	
		ΔE^\ddagger	$\Delta\Delta E^\ddagger$	ΔE^\ddagger	$\Delta\Delta E^\ddagger$	ΔE^\ddagger	$\Delta\Delta E^\ddagger$
3a	T _b	10.16	1.88	11.36	1.82	12.05	1.19
	T _c	8.28		9.54		10.86	
3b	T _b	10.97	2.01	12.22	1.88	12.93	1.38
	T _c	8.96		10.34		11.55	
3c	T _b	9.73	1.82	10.75	1.57	11.11	0.81
	T _c	7.91		9.18		10.30	
3d	T _b	9.79	1.25	11.05	1.12	11.67	0.50
	T _c	8.54		9.93		11.17	
3e	T _b	9.76	0.82	11.29	0.81	12.61	0.75
	T _c	8.94		10.48		11.86	
3f	T _b	10.22	1.19	11.86	0.82	13.48	0.81
	T _c	9.03		11.04		12.67	
3g	T _b	7.54	1.38	8.91	1.19	9.79	0.50
	T _c	6.16		7.72		9.29	
3h	T _b	7.53	1.63	9.04	1.51	10.35	1.38
	T _c	5.90		7.47		8.97	

Both T_b and T_c correspond to the migration of the SiMe₃ group attached to O_ω, i.e., on the opposite side to the SiMe₃ substituent. Then, comparison between T_b and T_c as well as between their corresponding product, 3 *anti* and 3 *syn*, leads to conclude that, for all substituents, the *syn* reaction path is located at lower energy (Gibbs enthalpy) than the *anti* reaction path.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jpca.6b02588.

Chemical descriptors of the reactants; relative energy positions and topologies of the frontier orbitals for **1** + **2f** and **1** + **2g** reactants; total energies (au), imaginary frequencies (cm⁻¹), and atomic Cartesian coordinates (Å) for the reactants, transition states, and products (PDF)

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Notes

The authors declare no competing financial interest.

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