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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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**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 HgI<sub>2</sub> 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 OSiMe<sub>3</sub> 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 aldol<sup>1</sup> 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  $\beta$ -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.<sup>2–5</sup> For instance, Bellassoued et al.<sup>6</sup> 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.<sup>4,7,8</sup> Wong and Wong<sup>8</sup> have shown that the noncatalyzed condensation of the trihydrosilyl enol ether (CH<sub>2</sub>=CH-O-SiH<sub>3</sub>) 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<sup>-1</sup> and  $\Delta E^{\ddagger} = 18.4$  kcal mol<sup>-1</sup>, 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  $\beta$ -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 ( $\Delta E^{\ddagger} = 49.5 \text{ kcal mol}^{-1}$ ). These results were in agreement with previous works.<sup>4,7,9,10</sup> So, for the concerted mechanism of the same reaction, Gung et al.<sup>7</sup> obtained at the MP2/6-31G\*  $\Delta H = -33.2 \text{ kcal mol}^{-1}$  and  $\Delta E^{\ddagger} = 13.8 \text{ kcal mol}^{-1}$  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,<sup>6,11,12</sup> 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 HgI<sub>2</sub> at room temperature and in toluene solutions. This aldol reaction produces *syn* and *anti*  $\beta$ -(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 ( $\Delta H^{\ominus}$ , kcal mol<sup>-1</sup>), Entropy ( $\Delta S^{\ominus}$ , cal K<sup>-1</sup> mol<sup>-1</sup>), and Gibbs Enthalpy ( $\Delta G^{\ominus}$ , kcal mol<sup>-1</sup>) 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 = 298.15K; P =1 bar) as Well as Representative Geometrical Parameters of the Products, the  $\alpha_{Si-C\beta-C\gamma-O\beta}$  and  $\beta_{Si-C\beta-C\alpha-O\alpha}$  Dihedral Angles (deg) and the  $d(O_{\beta}$ ...Si) Distances (Å)



3 anti



3 syn

reaction	$\Delta H^{\ominus}$	$\Delta S^{\ominus}$	$\Delta G^{\ominus}$	$\alpha_{\text{Si-C}\beta-C\gamma-O\beta}$	$\beta_{\mathrm{Si-C}eta-\mathrm{C}lpha-\mathrm{O}lpha}$	$d(O_{\beta} \cdots Si)$
$1 + 2a \rightarrow 3a$ anti	-36.79	-52.82	-21.04	178.3	83.0	4.153
$1 + 2a \rightarrow 3a \ syn$	-37.36	-52.42	-21.73	52.0	79.9	3.018
$1 + 2b \rightarrow 3b$ anti	-36.03	-50.95	-20.84	179.7	83.0	4.150
$1 + 2b \rightarrow 3b$ syn	-37.53	-52.69	-21.82	50.7	80.2	3.002
$1 + 2c \rightarrow 3c$ anti	-37.19	-51.11	-21.95	178.5	83.8	4.154
$1 + 2c \rightarrow 3c syn$	-38.13	-52.62	-22.44	52.1	84.7	3.013
$1 + 2d \rightarrow 3d$ anti	-37.31	-52.76	-21.58	178.7	82.9	4.149
$1 + 2d \rightarrow 3d$ syn	-37.54	-52.69	-21.83	51.9	84.2	3.016
$1 + 2e \rightarrow 3e$ anti	-34.74	-50.38	-19.72	180.8	85.9	4.150
$1 + 2e \rightarrow 3e syn$	-35.42	-55.11	-18.99	-42.3	111.6	3.034
$1 + 2f \rightarrow 3f$ anti	-34.04	-52.05	-18.52	180.9	81.1	4.146
$1 + 2f \rightarrow 3f$ syn	-34.82	-53.73	-18.80	-43.8	114.3	3.045
$1 + 2g \rightarrow 3g$ anti	-39.10	-60.64	-21.02	181.7	88.5	4.164
$1 + 2g \rightarrow 3g \ syn$	-40.10	-56.21	-23.34	43.3	78.5	2.920
$1 + 2h \rightarrow 3h$ anti	-39.24	-60.71	-21.14	182.7	89.6	4.164
$1 + 2h \rightarrow 3h$ 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 SiMe<sub>3</sub> group is migrating, (ii) which product, syn or anti, is favored, (iii) how the presence of one, two, and three silvl groups impacts the reactions, and (iv) what are the differences with respect to the experimental HgI<sub>2</sub> catalyzed reaction,<sup>12</sup> and with respect to other investigations.<sup>4,7,8</sup> 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 exchangecorrelation functional<sup>13,14</sup> and the 6-31G(d) basis set. For the products, the (2R,3R) absolute configuration is chosen to represent the anti form whereas the syn form is represented by the (2R,3S) 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  $C_{\beta}-C_{\gamma}$  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 ( $\Delta H^{\ominus}$ ,  $\Delta H^{\ddagger}$ ), entropy ( $\Delta S^{\ominus}$ ,  $\Delta S^{\ddagger}$ ), and Gibbs enthalpy ( $\Delta G^{\ominus}$ ,  $\Delta G^{\ddagger}$ ) were evaluated (T = 298.15 K, P = 1 atm).

Several descriptors<sup>15-22</sup> of the electronic structure and reactivity were evaluated, including the energies of the highest occupied molecular orbital (HOMO,  $\varepsilon_{\rm H}$ ) and of the lowest unoccupied molecular orbital (LUMO,  $\varepsilon_{\rm L}$ ), the LUMO-HOMO gap (gap =  $\varepsilon_{LUMO} - \varepsilon_{HOMO}$ ), the electronegativity [ $\chi$  =  $-(\varepsilon_{\rm HOMO} + \varepsilon_{\rm LUMO})/2]$ , the chemical potential ( $\mu = -\chi$ ), the global hardness  $[\eta = (\varepsilon_{LUMO} - \varepsilon_{HOMO})/2]$ , the global softness  $(S = 1/2\eta)$ , the global electrophilicity ( $\omega = \mu^2/2\eta$ ), the nucleophilicity index  $[N(X) = \varepsilon_{HOMO}(X) - \varepsilon_{HOMO}(TCE),$ where tetracyanoethylene (TCE) is taken as reference], the local electrophilicity of atom  $k \left[\omega_k = \omega f_k^+, \text{ where } f_k^+ = \{q(k, N)\}\}$ (+1) - q(k,N), and the local nucleophilicity  $[N_k = Nf_k^-,$  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 electroaffinitives 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).<sup>23</sup> Additional calculations were carried out with acetone as solvent and *in vacuo*. All calculations were performed using the Gaussian 09 package.<sup>24</sup>

#### **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 electrophillicity index of 2a-2h (from 1.56 to 3.01 eV) than 1 (0.77 eV), and with (iii) the smaller value of [ $\Delta E_{SA}$ =  $\varepsilon_{\text{HOMO}}(1) - \varepsilon_{\text{LUMO}}(2\mathbf{a}-2\mathbf{h})$ ] with respect to  $[\Delta E_{\text{AS}}]$  =  $\varepsilon_{\text{HOMO}}(2a-2h) - \varepsilon_{\text{LUMO}}(1)$ ]. 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.<sup>3</sup>

Then, the local nucleophilicity values for  $C_{\alpha}$  and  $C_{\beta}$  of 1 shows that the nucleophilic ionic addition (NIA) will take place between the  $C_{\gamma}$  of the aldehyde and  $C_{\beta}$  of the acetal, which has a nucleophilicity index 2 times larger than the  $C_{\alpha}$ . The electroaffinities are negative for all the aldehydes. Still, these are smaller (in absolute value) for the alkyl substituents [IEAI = 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

$$EA(2h) < EA(2g) < EA(2f) < EA(2d) < EA(2b)$$
$$< EA(2a) < EA(2c) < EA(2e)$$

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  $C_{\gamma}$  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  $\sim 2$  kcal mol<sup>-1</sup> larger than those of the aromatic substituents and  $\sim 4$  kcal mol<sup>-1</sup> 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<sup>-1</sup>. 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<sup>-1</sup> 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  $\Delta E_{SA}$ .

The geometry of the most stable conformation of 3 *anti* and 3 *syn* was characterized by two dihedral angles  $(\alpha_{Si-C\beta-C\gamma-O\beta}$  and  $\beta_{Si-C\beta-C\alpha-O\alpha})$  as well as the distance  $d(O_{\beta}\cdots Si)$  (Table 1). The 3 *anti* products always display larger  $d(O_{\beta}\cdots Si)$  distances than 3 *syn*, the differences in the  $\beta_{Si-C\beta-C\alpha-O\alpha}$  angle between 3 *anti* and 3 *syn* are generally small, whereas the differences in  $\alpha_{Si-C\beta-C\gamma-O\beta}$  angle are very important. Note that the  $\alpha_{Si-C\beta-C\gamma-O\beta}$  angle is in the antiperiplanair 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.<sup>8</sup> Indeed, in the latter study, considering a broad range of donor/ acceptor substituents on the trihydrosilyl enol ether (CH<sub>3</sub>, NH<sub>2</sub>, OH, F, SH, and CHO) and on the formaldehyde (CH<sub>3</sub>, CF<sub>3</sub>, NH<sub>2</sub>, F, CHO, COOCH<sub>3</sub>, CH=CH<sub>2</sub>, and C<sub>6</sub>H<sub>5</sub>),  $\Delta H^{\Theta}$ was found to vary from -2.9 to -38.7 kcal mol<sup>-1</sup> whereas the energy barrier was from 7.2 to 31.3 kcal mol<sup>-1</sup>. In general, acceptor/donor groups on the aldehyde reduce/increase the barrier of activation and lead to larger/smaller exothermicity. More precisely, the  $\Delta H^{\Theta}(alkyl) < \Delta H^{\Theta}(aromatic) <$  $\Delta H^{\Theta}(\text{vinylic})$  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 OSiMe<sub>3</sub> group in geminal position (vide infra). Moreover, Denmark et al.<sup>4</sup> 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.  $\Delta E_{SA} = \varepsilon_{HOMO}(1) - \varepsilon_{LUMO}(2)$  and  $\Delta E_{AS} = \varepsilon_{HOMO}(2) - \varepsilon_{LUMO}(1)$ .





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<sub>3</sub> group from the  $O_{\alpha}$  or  $O_{\alpha}'$  oxygen of the acetal to the  $O_\beta$  oxygen together with the formation of the  $C_\beta$ - $C_{\gamma}$  bond to obtain the syn and anti diastereoisomers of  $\beta$ -(trimethylsiloxy)- $\alpha$ -(trimethylsilyl)alkanoic acid silyl esters 3 (Scheme 2). However, there are two SiMe<sub>3</sub> groups that could migrate on the oxygen of the carbonyl and one of the issues is to determine which one is transferred. Indeed, the  $O_{\alpha}$ -SiMe<sub>3</sub> and  $O_{\alpha}'$ -SiMe<sub>3</sub> groups have different chemical environments because the  $O_{\alpha}$ '-SiMe<sub>3</sub> group is on the same side as the SiMe<sub>3</sub> group attached to  $C_{\beta}$  whereas the  $O_{\alpha}$ -SiMe<sub>3</sub> 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  $(C_{\beta}-C_{\alpha}-O_{\alpha}-Si-O_{\beta}-C_{\gamma})$ .<sup>4,7,8</sup> There are two possible positions for the carbonyl, on the same or on the opposite side to the  $C_{\beta}$ -SiMe<sub>3</sub>, as characterized by two dihedral angles,  $\Theta_{Si-C\beta-C\gamma-O\beta}$  (position of the  $C_{\gamma}O_{\beta}$  carbonyl with respect to  $C_{\beta}SiMe_3$ ) and  $\emptyset_{C\alpha-C\beta-C\gamma-O\beta}$  (position of the  $C_{\gamma}O_{\beta}$  carbonyl with respect to the  $C_{\alpha}C_{\beta}$  double bond). The Burgi-Dunitz<sup>25</sup> angle  $(\alpha_{BD} = \alpha_{C\beta-C\gamma-O\beta})$  as well as the  $d_1(O_\beta \cdots$ Si),  $d_2(C_\gamma \cdots C_\beta)$ , and  $d_3(O_\alpha/O_\alpha \cdots O_\beta)$  distances are additional descriptors of the transition states. The  $\emptyset$  and  $\Theta$  angle values

enable to distinguish between four types of transition states  $(T_a-T_d, Scheme 3)$ .  $T_a$  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  $C_\beta$ -SiMe<sub>3</sub> are on the same side whereas they are on opposite sides in  $T_b$  and  $T_c$  (Scheme 3). During the concerted mechanism, the  $C_\gamma O_\beta$  carbonyl and the  $C_\alpha C_\beta$  double bond are always on the same side, characterized by a  $\mathcal{O}_{C\alpha-C\beta-C\gamma-O\beta}$  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<sub>3</sub> group whereas antiperiplanar conformations (not shown in Scheme 3) would lead to excessive distances to allow SiMe<sub>3</sub> 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  $d_1(O_\beta \cdots Si)$ and larger  $d_2(C_\gamma \cdots C_\beta)$  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  $d_1(O_\beta \cdots Si)$  and smaller  $d_2(C_\gamma \cdots C_\beta)$  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  $T_c$ . 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 SiMe<sub>3</sub> attached to the  $C_{\beta}$  and the methyls of the migrating SiMe<sub>3</sub> group on the bow of the boat, the activation energies ( $\Delta E^{\ddagger}, \Delta H^{\ddagger}, \text{ and } \Delta G^{\ddagger}$ ) are systematically smaller for the T<sub>b</sub> transition state forms than for the T<sub>a</sub> ones, for all kinds of substituents, so that the concerted mechanism leading to the formation of the 3 *anti* diastereoisomers favors the T<sub>b</sub> transition state (synclinal). This corresponds to the migration of the SiMe<sub>3</sub> group attached to O<sub>a</sub> to the O<sub>b</sub> oxygen of the carbonyl. Similarly, the T<sub>c</sub> transition states of the pro-*syn* route are more stable than the T<sub>d</sub> ones so that the 3 *syn* products result also from the migration of the SiMe<sub>3</sub> group attached to O<sub>a</sub>. Nevertheless, the T<sub>b</sub>-T<sub>a</sub> activation energy differences are always smaller than the corresponding T<sub>c</sub>-T<sub>d</sub> ones.

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

$$\Delta^{\neq}(\mathbf{T}_{c},syn) < \Delta^{\neq}(\mathbf{T}_{b},anti) < \Delta^{\neq}(\mathbf{T}_{a},anti) < \Delta^{\neq}(\mathbf{T}_{d},syn)$$

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  $O_\beta$ Si distance is smaller (closer to the product) but the  $C_\gamma C_\beta$  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  $O_\alpha \cdots O_\beta$  distance, leading to an increased interaction between the frontier orbitals where the donor and acceptor are in favorable position.<sup>26</sup> In addition,  $\alpha_{BD}$  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  $\Delta E^{\ddagger}$  and  $\Delta H^{\ddagger}$  amplitudes as well as between the  $\Delta E^{\ddagger}$  and  $\Delta G^{\ddagger}$ 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.,<sup>4</sup> of which the syn product was obtained with high diastereoselectivity (93/7 to 99/1) and (ii) between bis(trimethylsilyl)ketene acetals  $[(OSiMe_3)_2C=$ CHR] and benzaldehyde as studied by Bellassoued et al.,<sup>6</sup> 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 = iPr). 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 oxide<sup>27</sup> and for hydroborations of acyclic allylic alcohol derivatives catalyzed by catecholborane.<sup>28</sup>

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 ( $TSs_1$  and  $TSs_2$ ). 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  $C_{\alpha}$ -O<sub> $\beta$ </sub> cleavage and the migration of the SiMe<sub>3</sub> group from the acetal to the oxygen of aldehyde. As shown in Figure 3, TSs<sub>1</sub> lies at higher energy ( $\Delta E^{\ddagger} = 15.8$  kcal mol<sup>-1</sup>,  $\Delta H^{\ddagger} = 17.6$  kcal mol<sup>-1</sup>,  $\Delta G^{\ddagger} = 35.2$  kcal mol<sup>-1</sup>) than the transition state of the concerted mechanism (TSc,  $\Delta E^{\ddagger}$  = 11.4 kcal mol<sup>-1</sup>,  $\Delta H^{\ddagger}$  = 12.9 kcal mol<sup>-1</sup>,  $\Delta G^{\ddagger}$  = 31.0 kcal mol<sup>-1</sup>). These results are in qualitative agreement with the study of Wong and Wong<sup>8</sup> on the uncatalyzed reaction between formaldehyde and trihydrosilyl enol ether.

Effects of the SiMe<sub>3</sub> Groups. Additional reaction profiles were then characterized to highlight the role of the SiMe<sub>3</sub> groups (Scheme 4). In reaction 2 the SiMe<sub>3</sub> substituent attached to  $C_{\beta}$  is missing whereas in reaction 3 one of the OSiMe<sub>3</sub> has been removed. Finally, in reaction 4 both are removed.  $\Delta H$  of activation and of reaction, listed in Table 3, highlight the minor role of the SiMe<sub>3</sub> substituent (reaction 1 versus reaction 2) but the huge impact of the geminal OSiMe<sub>3</sub> 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<sup>-1</sup> when the geminal OSiMe<sub>3</sub> group is absent.

**Solvent Effects.** Wong et al.<sup>8</sup> 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<sup>1,2,29–31</sup> whereas Kitanosona and Kobayashi have shown that the silyl enolate decomposes in the presence of water, preventing also the reaction to occur.<sup>32</sup> 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<sub>b</sub> and T<sub>c</sub>

Table 2. Activation Energy ( $\Delta E^{\ddagger}$ , kcal mol<sup>-1</sup>), Activation Enthalpy ( $\Delta H^{\ddagger}$ , kcal mol<sup>-1</sup>), Activation Free Enthalpy ( $\Delta G^{\ddagger}$ , kcal mol<sup>-1</sup>), and Activation Entropy ( $\Delta S^{\ddagger}$ , cal K<sup>-1</sup> mol<sup>-1</sup>) 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  $\Theta_{\text{Si}-C\beta-C\gamma-O\beta}$  and  $\emptyset_{C\alpha-C\beta-C\gamma-O\beta}$  Dihedral Angles (deg), the Burgi–Dunitz Valence Angle ( $\alpha_{\text{BD}} = \alpha_{C\beta-C\gamma-O\beta}$ ) (deg), and the  $d_1(O_{\beta}\cdots Si)$ ,  $d_2(C_{\gamma}\cdots C_{\beta})$ , and  $d_3(O_{\alpha}/O_{\alpha}\cdots O_{\beta})$  Distances (Å)<sup>*a*</sup>

\_. ±

Me

-, ±

Me

			Me <sub>3</sub> Si	Me sid a b b c c c siMe <sub>3</sub>	Me	and	Me₃Si α	Me Si α'Ο β SiM						
TS	$\Delta E^{\ddagger}$	$\Delta \Delta E^{\ddagger}$	$\Delta H^{\ddagger}$	$\Delta\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$	$\Delta G^{\ddagger}$	$\Delta\Delta G^{\ddagger}$	Ø	Θ	$lpha_{ m BD}$	$d_1$	$d_2$	$d_3$	Т
pro- <b>3a</b> 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- <b>3a</b> 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- <b>3a</b> <i>syn-</i> 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- <b>3a</b> 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	с
pro- <b>3b</b> 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- <b>3b</b> 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- <b>3b</b> 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	с
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	с
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	а
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- <b>3d</b> 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	с
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	с
pro- <b>3f</b> 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	а
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- <b>3f</b> 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	с
pro- <b>3g</b> 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	а
pro- <b>3g</b> 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- <b>3g</b> 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	с
pro- <b>3h</b> 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- <b>3h</b> 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	с
<sup>a</sup> Columns with	$\Delta \Delta E^{\ddagger}$ (	$\Delta \Delta H^{\ddagger}$ and $A$	$\Delta\Delta G^{\ddagger})$ gi	ive the diffe	rences betw	veen the t	two pro-anti	i and pro	-syn cases	. In pare	ntheses a	re given t	he differe	ences

between the most stable pro-syn and pro-anti species.

Table 3. Reaction and Activation Enthalpies (kcal mol<sup>-1</sup>) 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
$\Delta H^{\ominus}$	-36.8	-37.5	-23.0	-23.2
$\Delta H^{\ddagger}$	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  $\Delta E^{\ddagger}$  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<sup>-1</sup> in toluene and in acetone, respectively, (ii) in the gas phase and in solution, the T<sub>c</sub> state remains more stable than the T<sub>b</sub> 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

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Figure 2. anti and syn reaction paths [IEFPCM(toluene)/M06-2X/6-31G(d)] for the concerted mechanism of the Mukaiyama reaction between  $C_i O_i O_i$ -tris(trimethylsilyl)ketene acetal 1 and aldehyde 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  $HgI_2^{12}$  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 OSiMe<sub>3</sub> 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 ( $\Delta E^{\ddagger}$ , kcal mol<sup>-1</sup>) for the Proanti T<sub>b</sub> and Pro-syn T<sub>c</sub> Routes As Evaluated with the IEFPCM/M06-2X/6-31G\* Method (T = 298.15 K; P = 1bar) for Different Solvation Types [*in Vacuo*, Toluene ( $\varepsilon_r = 2.40$ ), and Acetone ( $\varepsilon_r = 21.00$ )] and Their Differences ( $\Delta \Delta E^{\ddagger}$ , kcal mol<sup>-1</sup>)

		in vacuo		tolu	ene	acetone		
reaction		$\Delta E^{\ddagger}$	$\Delta \Delta E^{\ddagger}$	$\Delta E^{\ddagger}$	$\Delta \Delta E^{\ddagger}$	$\Delta E^{\ddagger}$	$\Delta \Delta E^{\ddagger}$	
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 SiMe<sub>3</sub> group attached to  $O_{\alpha}$ , i.e., on the opposite side to the SiMe<sub>3</sub> 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

#### **S** 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<sup>-1</sup>), 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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