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# Concerted versus ionic mechanisms of the $\alpha$ and $\gamma$ extensions in uncatalyzed Mukaiyama reaction between $\beta,\gamma$ -unsaturated bis silyl ketene acetal and benzaldehyde: A DFT study

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## ABSTRACT

The uncatalyzed regioselective Mukaiyama aldol reaction between  $\beta,\gamma$ -unsaturated bis silyl ketene acetal and benzaldehyde has been studied theoretically using density functional theory with the M06-2X exchange–correlation functional. These DFT calculations mostly demonstrate that (i) the  $\alpha$  and  $\gamma$  adducts in uncatalyzed Mukaiyama reaction can proceed through two mechanisms, ionic and concerted, (ii) the concerted mechanism is favored for the  $\alpha$  adduct and it is disfavored for the  $\gamma$  adduct, (iii) under 12 and 17 kbar, the  $\alpha$  adduct reaction path is below the  $\gamma$  adduct reaction path whereas if the pressure decreases to 5 kbar, the opposite is obtained.

## 1. Introduction

Vinylogous Mukaiyama aldol reaction [1–10] is the vinylogous extension of the aldol reaction leading to the formation of C–C bond between  $\beta,\gamma$ -unsaturated silyl enol ether [11] or silyl ketene acetal [12] and carbonyl compounds to produce linear aldol products through  $\gamma$  extension (Fig. 1). This condensation type was discovered by Mukaiyama and co-workers [1] in 1975, when the reaction was realized between  $\beta,\gamma$ -unsaturated trialkylsilyl enol-ethers and carbonyl compounds catalyzed by Lewis acid (Fig. 1).

But in the absence of catalyst [2], both linear and branched aldol products will be possible. Indeed, in 1997, Bellassoued et al. [2] studied the uncatalyzed condensation between  $\beta,\gamma$ -unsaturated bis silyl ketene acetal **1** and benzaldehyde **2** at 65 °C under high pressure conditions and in dichloromethane solution. This reaction gives two regioisomers, one product resulting from a vinylogous Mukaiyama aldol reaction yielding an  $\gamma$  adduct (linear aldol **3**, Fig. 2) and the second one resulting in an  $\alpha$  adduct (branched aldol **4**, Fig. 2). The regioselectivity of this reaction is dependent on pressure. Indeed, the  $\gamma$ -adduct **3** is the major under 2 and 5 kbar but it is the minor under 12 and 17 kbar.

In this manuscript, density functional theory is employed to study the different reaction mechanisms that can take place between **1** and **2** in the absence of a catalyst. This work complements our previous DFT investigation [13] on the uncatalyzed Mukaiyama reaction between C, O,O-tris(trimethylsilyl)ketene acetal and aldehyde, which we

demonstrated that the reaction is possible via two mechanisms, concerted or stepwise, and that the concerted mechanism is favored. The study of the concerted mechanism highlights four types of cyclic transition states (two pro-anti and two pro-syn) [13].

## 2. Computational methods

Equilibrium structures of reactants and products were optimized at the DFT level using the M06-2X exchange–correlation functional [14,15] and the 6-311G\* basis set. The transition states were localized and characterized using the same M06-2X/6-311G\* level of approximation. Intrinsic Reaction Coordinate (IRC) calculations were then performed to check that the transition states are related to the corresponding reactants and products. For all species, reactants, products, and transition states, the Gibbs free energy, were evaluated ( $T = 338.15$  K,  $P = 2, 5, 12, \text{ and } 17$  kbar) for the reaction between  $\beta,\gamma$ -unsaturated bis silyl ketene acetal **1** and benzaldehyde **2**. Solvent effects (dichloromethane) were taken into account both in the geometry optimizations and in the calculations of the transition states by using the Integral Equation Formalism (IEF) version of the Polarizable Continuum Model (IEF-PCM) [16,17]. Local nucleophilicity was evaluated using the Fukui function [18]. Calculations were performed using the Gaussian 09 package [19].

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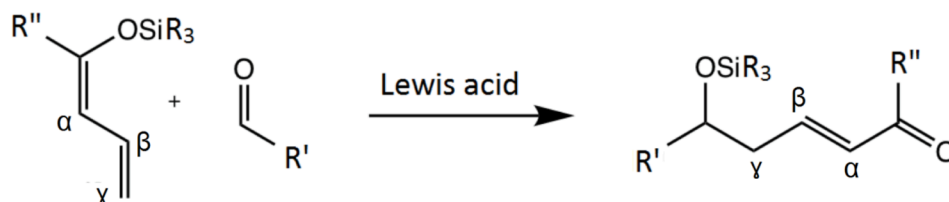
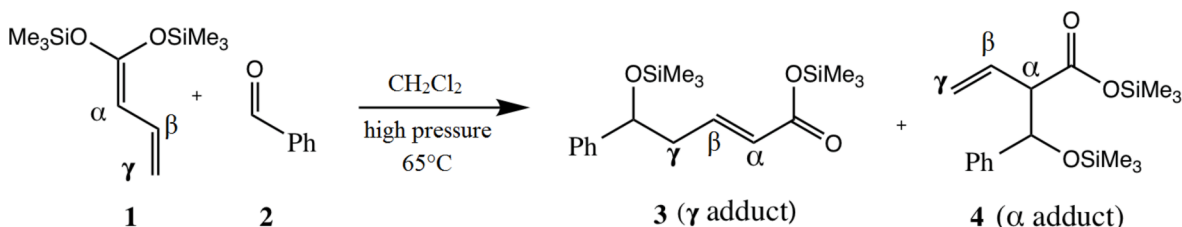


Fig. 1. General scheme for LA-catalyzed Mukaiyama aldol reaction between a  $\beta,\gamma$ -unsaturated silyl enol ether and an aldehyde.



Entry	Conditions	3	4	Yield %
1	17 kbar, 65°C	25	75	68
2	12 kbar, 65°C	35	65	51
3	5 kbar, 65°C	83	17	57
4	2 kbar, 65°C	88	12	41

Fig. 2. Uncatalyzed Mukaiyama aldol reaction between  $\beta,\gamma$ -unsaturated bis silyl ketene acetal **1** and benzaldehyde **2**.

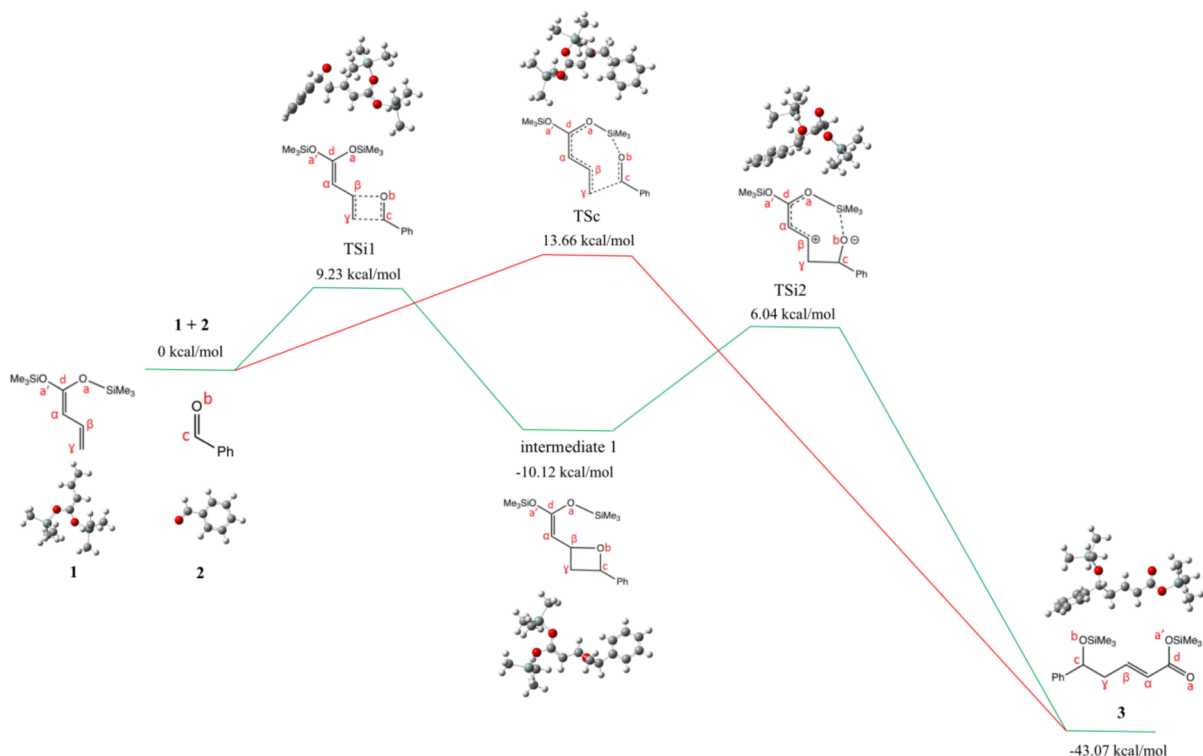


Fig. 3. Energy profile [IEFPCM(dichloromethane)/M06-2X/6-311G(d)] for the ionic versus concerted mechanisms of the  $\gamma$  extension Mukaiyama reaction between  $\beta,\gamma$ -unsaturated bis silyl ketene acetal **1** and benzaldehyde **2** under 2 kbar.

### 3. Results and discussion

#### 3.1. Reaction mechanism

The DFT study of the reaction mechanism of the uncatalyzed

vinylous Mukaiyama aldol reaction between  $\beta,\gamma$ -unsaturated bis silyl ketene acetal **1** and benzaldehyde **2** leading to the formation of the regioisomer **3** shows that two reaction paths are possible, concerted and ionic. The concerted mechanism involves the migration of a  $\text{SiMe}_3$  group from the  $\text{O}_a$  oxygen of the acetal to the  $\text{O}_b$  oxygen of aldehyde together

**Table 1**

Activation energy ( $\Delta E^\ddagger$ , kcal/mol), activation enthalpy ( $\Delta H^\ddagger$ , kcal/mol), and activation free enthalpy ( $\Delta G^\ddagger$ , kcal/mol) as evaluated with the IEFPCM/M06-2X/6-311G\* method (P = 2 kbar, T = 338.15 K, solvent = dichloromethane) for the reaction between  $\beta,\gamma$ -unsaturated bis silyl ketene and benzaldehyde.

Reaction	TS	$\Delta E^\ddagger$	$\Delta H^\ddagger$	$\Delta G^\ddagger$
$\gamma$ adduct	TSc	13.66	14.83	30.18
	TSi1	9.23	11.14	27.66
	TSi2	6.04	8.42	22.97
$\alpha$ adduct	TSc'	15.03	16.42	32.31
	TSi1'	18.73	18.93	36.20
	TSi2'	13.31	15.02	34.11

with the formation of the C<sub>c</sub>-C<sub>γ</sub> bond. The ionic mechanism is characterized by two transition states (TSi1 and TSi2). The first one (TSi1) corresponds to the formation of C<sub>γ</sub>-C<sub>c</sub> and C<sub>β</sub>-O<sub>b</sub> single bonds in a concerted process leading to the 4-ring oxetane intermediate (intermediate 1) (Fig. 3). The second (TSi2) leads to the C—O cleavage and migration of the SiMe<sub>3</sub> group from the acetal to the O<sub>b</sub> oxygen of benzaldehyde (Fig. 3). Note that no stable [4 + 2] cycloaddition between S-cis conformation of **1** and the C=O carbonyl of **2** has been obtained due to the steric hindrance caused by the geminal OSiMe<sub>3</sub> groups (O<sub>a</sub>-SiMe<sub>3</sub> and O<sub>a'</sub>-SiMe<sub>3</sub>) of **1** [20,21]. As shown in Fig. 3 and Table 1, TSi1 lies at lower energy ( $\Delta E^\ddagger = 9.23$  kcal/mol,  $\Delta H^\ddagger = 11.14$  kcal/mol,  $\Delta G^\ddagger = 27.66$  kcal/mol) than the TSc transition state of the concerted mechanism ( $\Delta E^\ddagger = 13.66$  kcal/mol,  $\Delta H^\ddagger = 14.83$  kcal/mol,  $\Delta G^\ddagger = 30.18$  kcal/mol). On the other hand, the energy difference between TSi2 and intermediate 1 is less than 27.74 kcal/mol [E(TSi2) – E(intermediate 1) = 16.16 kcal/mol]. Therefore, the ionic mechanism is favored over the concerted one. These results are the opposite than those of the uncatalyzed  $\alpha$  adduct reaction mechanism between **1** and **2** leading to the formation of regioisomer **4**, of which the concerted mechanism is more favorable than the ionic one. Indeed, the following ordering of the transition state energies (E, H, and G) is observed:  $\Delta^\ddagger$  (TSi1') >  $\Delta^\ddagger$  (TSc') >  $\Delta^\ddagger$  (TSi2') (Table 1 and Fig. 4). During the

concerted mechanism, the migration of the silyl group from the silyl ketene acetal **1** to the benzaldehyde **2** is accompanied by the formation of a CC single bond in a boatlike six-membered ring transition state geometry whereas the ionic mechanism is characterized by two transition states (TSi1' and TSi2'), the first one (TSi1') corresponds to the formation of C<sub>α</sub>-C<sub>c</sub> and C<sub>d</sub>-O<sub>b</sub> single bonds in a concerted process leading to the intermediate 1' (Fig. 4). The second (TSi2') leads to the migration of the SiMe<sub>3</sub> group to the carbonyl of benzaldehyde to produce the corresponding product (Fig. 4). On the other hand, the same ordering of the transition state energies was obtained when one of the OSiMe<sub>3</sub> group from  $\beta,\gamma$ -unsaturated bis silyl ketene acetal **1** has been removed to obtain  $\beta,\gamma$ -unsaturated silyl enol ether [ $\Delta^\ddagger$  (TSc) >  $\Delta^\ddagger$  (TSi1) >  $\Delta^\ddagger$  (TSi2) and  $\Delta^\ddagger$  (TSi1') >  $\Delta^\ddagger$  (TSc') >  $\Delta^\ddagger$  (TSi2')] (Table S1 of supporting information).

### 3.2. Regioselectivity

The regioselectivity of the uncatalyzed reaction between **1** and **2** is dependent on pressure (Fig. 2). Indeed, the  $\gamma$  adduct is favored under 2 and 5kbar but it is disfavored under 12kbar and 17kbar (Fig. 2). This pressure dependence of the regioselectivity is in agreement with the

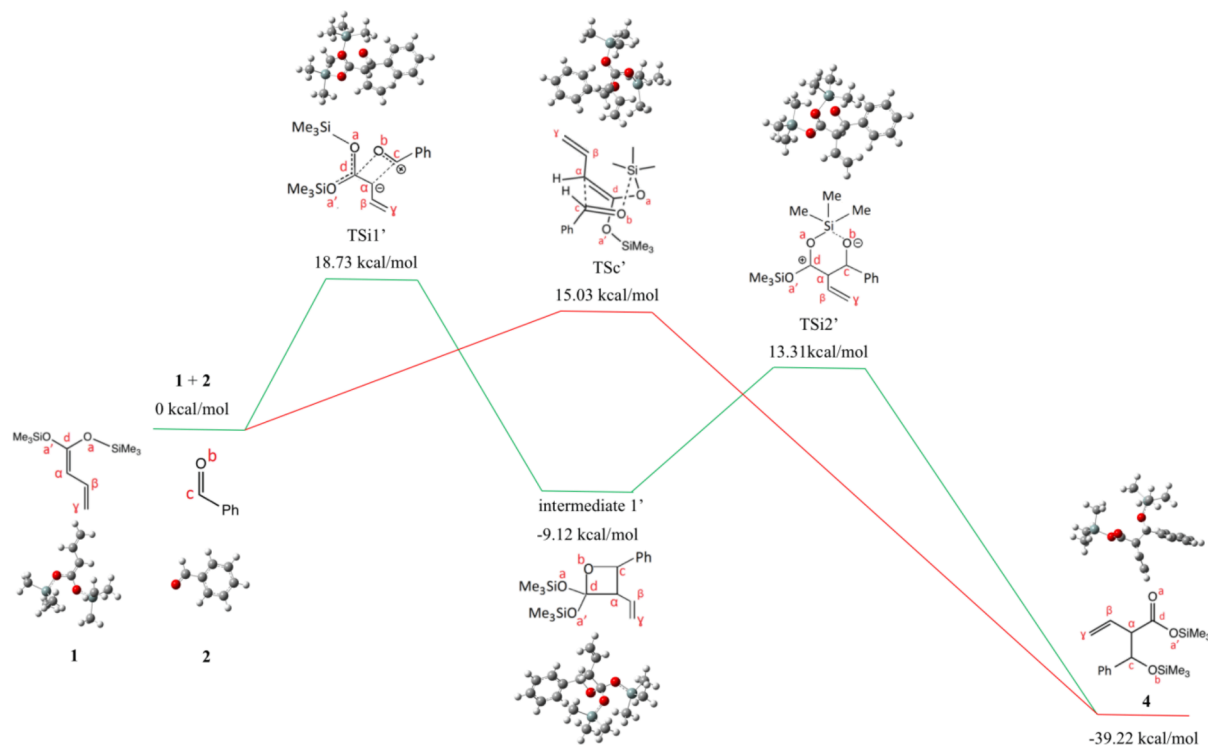
**Table 2**

Local nucleophilicity of C<sub>γ</sub> and C<sub>α</sub> [N(C<sub>γ</sub>)/N(C<sub>α</sub>), eV], activation free enthalpy ( $\Delta G^\ddagger$ , kcal/mol), and activation free enthalpy differences ( $\Delta\Delta G^\ddagger$ , kcal/mol) between TSi1 and TSc' transition states as evaluated with the IEFPCM/M06-2X/6-311G\* method (P = 17, 12, 5, and 2 kbar, T = 338.15 K, solvent = dichloromethane).

Conditions	3/4 <sup>a</sup>	$\Delta G^\ddagger$ (TSi1)/ $\Delta G^\ddagger$ (TSc')	$\Delta\Delta G^\ddagger$ <sup>b</sup>	N(C <sub>γ</sub> )/N(C <sub>α</sub> )
17 kbar, 338.15 K	25/75	30.85/28.93	1.92	0.89/0.96
12 kbar, 338.15 K	35/65	30.76/29.51	1.25	0.72/0.76
5 kbar, 338.15 K	83/17	27.70/32.22	-4.52	0.49/0.38
2 kbar, 338.15 K	88/12	27.66/32.31	-4.65	0.43/0.30

<sup>b</sup> $\Delta\Delta G^\ddagger = \Delta G^\ddagger$  (TSi1) –  $\Delta G^\ddagger$  (TSc').

<sup>a</sup> 3/4 ratio obtained by Bellassoued et al. [2].



**Fig. 4.** Energy profile [IEFPCM(dichloromethane)/M06-2X/6-311G(d)] for the ionic versus concerted mechanisms of the  $\alpha$  extension Mukaiyama reaction between  $\beta,\gamma$ -unsaturated bis silyl ketene acetal **1** and benzaldehyde **2** under 2 kbar.

activation free enthalpy differences between TS1 and TSc' transition states [ $\Delta G^\ddagger(\text{TSi1}) < \Delta G^\ddagger(\text{TSc}')$  under 2 and 5 kbar;  $\Delta G^\ddagger(\text{TSi1}) > \Delta G^\ddagger(\text{TSc}')$  under 12 and 17 kbar] (table 2) and the local nucleophilicity values for  $\alpha$  and  $\gamma$  carbons of  $\beta,\gamma$ -unsaturated bis silyl ketene acetal [ $N(\text{C}_\gamma) > N(\text{C}_\alpha)$  under 2 and 5 kbar;  $N(\text{C}_\gamma) < N(\text{C}_\alpha)$  under 12 and 17 kbar] (table 2).

#### 4. Conclusion

In 1997, Bellassoued and co-workers [2], studied the Mukaiyama aldol reaction between  $\beta,\gamma$ -unsaturated bis silyl ketene acetal **1** and benzaldehyde **2** under high pressure conditions to produce  $\gamma$ -adduct **3** and  $\alpha$ -adduct **4** regioisomers. Our DFT calculation with the M06-2X exchange–correlation functional shows that (i) this reaction takes place via a cyclic transition states, (ii) the ionic mechanism is favored for the  $\gamma$ -adduct reaction (**1** + **2** → TS1 → intermediate 1 → TS2 → **3**) while the concerted mechanism is favored for the  $\alpha$ -adduct reaction (**1** + **2** → TSc' → **4**), (iv) The regioselectivity of the reaction can be explained by comparing the TS1 and TSc' free energies and the local nucleophilicity values of  $\text{C}_\gamma$  and  $\text{C}_\alpha$  atoms.

#### CRedit authorship contribution statement

**Slim Hadj Mohamed:** Conceptualization, Methodology, Software, Data curation, Writing - original draft, Visualization, Investigation, Software, Writing - review & editing. **Benoît Champagne:** Supervision, Validation.

#### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.comptc.2021.113395>.

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