# Theoretical Study on the Stereoselectivities of the Wittig Olefination Reaction

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Abstract: Theoretical study of Wittig reactions were performed with density functional theory (DFT) at the B3LYP levels to understand the origin of the different product selectivities for different classes of phosphorus ylides. In case of the reaction using non-stabilized ylide, the transition states for the oxaphosphetane-forming process that the ylide approached to the carbonyl compound were explored and the four kinds of transition states were converged. One of the transition state having lowest activation energy leaded to Z-olefin and the additional investigation of all the reaction process resulted that the ratio of Z-/E-olefin was controlled kinetically. These calculations were consistent with experimental results and the common accepted explanations. However, the reaction using stabilized ylide also proceeded under kinetic control, not under thermodynamic control. The oxaphosphetane intermediate corresponding to the precursor of E-olefin was obtained preferentially via the lowest transition state. Starting from the oxaphosphetane, the activation energy of the forward reaction to olefin was quite lower than that of the reverse reaction to the reactants. These results suggested the possibility that the stereoselectivity of Wittig reaction using stabilized ylide was also under kinetic control.

Introduction

Wittig Reaction is the one of useful reaction for organic synthesis and wide variety of applications have been reported.[1] This reaction can convert a C=O double bond, such as aldehydes or ketones, to a C=C double bond using a various phosphorus ylide reagent with good stereoselectivity. In case of the two substitutent alkene is obtained, high selectivity for Z- or E-olefins is available, depending on the particular circumstances, such as the type of ylide, type of carbonyl compound, or reaction conditions. (eq 1)


$$\text{(1)}$$
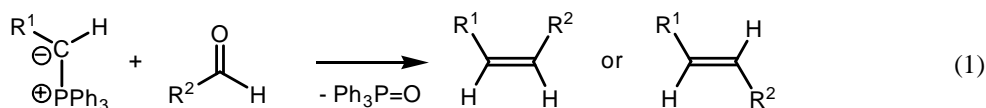
The phosphorus ylides that has alkyl group as R^1 are called the non-stabilized ylide and these ylides commonly react with aldehydes to give Z-olefins as a main product. On the other hand, E-olefins are obtained mainly using stabilized ylide that has electron-withdrawing group as R^1 in stead of non-stabilized ylide.

According to the commonly accepted explanation of the stereoselectivity, the ratio of Z-/E-olefin is under kinetic control at oxaphosphetane forming process using non-stabilized ylide. On the contrary, the ratio is controlled by the thermodynamical stability of oxaphosphetane in case of stabilized ylide used.

Scheme 1
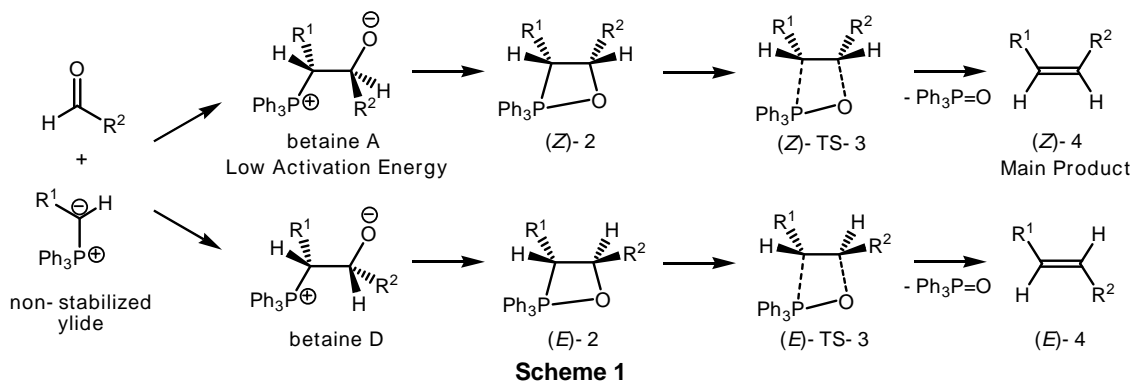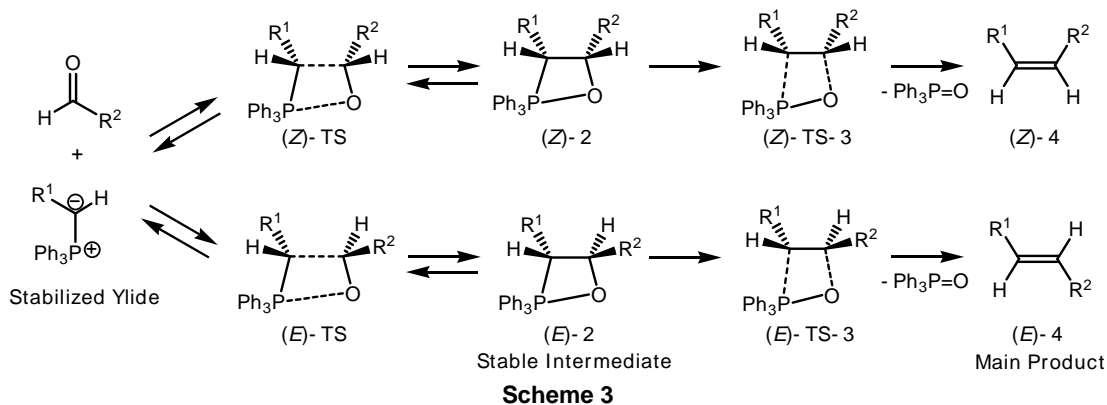
In case of using the non-stabilized ylide, the oxaphosphetane intermediates **(Z)-2** and **(E)-2** doesn't separate to the aldehyde and the ylide by the reverse reaction.   Therefore the selectivity of the olefin geometry is determined by the rate of the producing **(Z)-2** and **(E)-2**.   Before to form of the transition states **(E)-TS** and/or **(Z)-TS**, there are six kinds of manners closing the gap of the aldehyde and the ylide as shown in Newman projections of Scheme 2.


Scheme 2
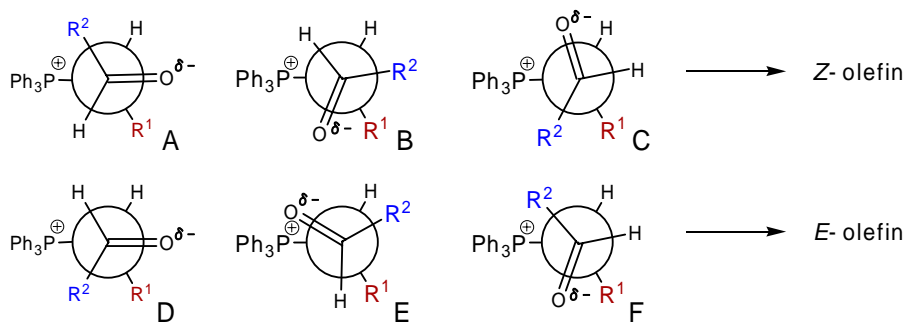
The formations **A**, **B**, or **C** and **D**, **E**, or **F** give *Z*-olefin and *E*-olefin via oxaphosphetane intermediates **(Z)-2** and **(E)-2**, respectively.   Regarding intermediates in the reaction, Wittig mentioned a zwitterionic phosphorus betaine (**A** or **D**) forms first, then the C-C bond rotation to give oxaphosphetanes **(Z)-2** and **(E)-2** and succeeding elimination of phosphine oxide to give **(Z)-4** and **(E)-4**, respectively.

Because of the substituent R^1 places at opposite site of R^2, betaine **A** favors than **D**.   However **(Z)-2** looks less stability than **(E)-2**, the stereoselectivity is controlled by the stability of betaine **A** and **D**. Although it is convenient explanation and widely accepted at the beginning, there is no enough evidence for the reaction pass through betaine intermediate.   After that, several models have been proposed to rationalize the high *Z*-olefin selectivity of a non-stabilized ylide.   According to Vedejs' model,[2] the reaction proceeds four centered transition states, such as **B**, **C**, **E**, and **F** in Scheme 2, to give oxaphosphetane intermediate **(Z)-2** and/or **(E)-2** directly and the selectivity of the olefin geometry is determined kinetically by the relative barrier heights of the transition states.

Scheme 3

On the other hand, oxaphosphetanes can separate to the aldehyde and the ylide by the reverse reaction using stabilized ylide instead of non-stabilized ylide. Therefore, **(Z)-2** can be converted to more stable intermediate **(E)-2** via reactants and the ratio of **(Z)-4/(E)-4** corresponds with the ratio of **(Z)-2/(E)-2**.

Several MO calculations have been carried out for the Wittig reagents and the Wittig reactions. Both of *ab initio*[3] and semi-empirical[4] calculations for the simple model system (eq 2) indicated that the reaction proceeds to oxaphosphetane **5** via four-centered planar transition state **4**.

(2)
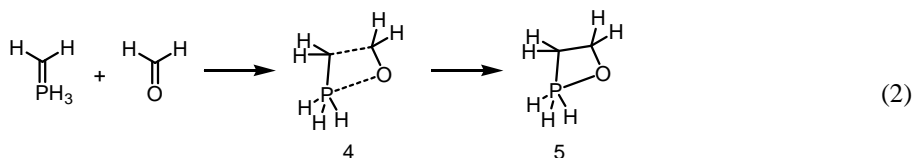
Although, the calculations including the olefin geometry were carried out for $Ph_3P=O$ + MeCHO with MNDO[3c] and PM3[3a], the structures of transition state were inconsistent with the structure suggested by Vedejs. Yamataka and Nagase reported detailed calculation for more realistic non-stabilized ylide systems with *ab initio* MO (HF/3-21G*) method and the density functional theory (B3LYP/6-31G*) and the results indicate good agreement with experiment.[5]

We now report here, the results of higher-level calculations for all process (Scheme 1 and 3) and possible transition states (Scheme 3) of Wittig reaction using non-stabilized ylide and stabilized ylide and discuss the selectivity of olefin geometries.

Computational Methods

All geometry optimizations, vibrational frequencies, and energy calculations were carried out with density functional theory (DFT)[6] at the B3LYP level[7] with BS1 basis set in Gaussian03 program [8] and verified to be either minima or transition states from their Hessian matrices for all reactions: minima for all positive eigenvalues and transition states for only one negative eigenvalue. BS1 basis set contains LANL2DZ[9] for carbon and hydrogen atoms and LANL2DZ with d-polarized function for phosphorus atom.

Results and Discussions

The calculation using non-stabilized ylide was carried out for $Ph_3P=CHCH_3$ (**6a**) + CH_3CHO (**7a**) and the transition states were searched on the basis of the formation **A**-**F** shown in Scheme 2. Several trials to find the betaine type transition states **A** and **D** were unsuccessful and all the structures were transformed

into four-centered transition states in optimization.   As shown in Figure 1, the four kinds of transition states **(Z)-TS-Ba**, **(Z)-TS-Ca**, **(E)-TS-Ea**, and **(E)-TS-Fa** that correspond with **B**, **C**, **E**, and **F** ($R^1 = CH_3$, $R^2 = CH_3$) were converged with one negative eigenvalue.   The calculation of vibrational frequencies for transition states showed one imaginary frequency each and the directions of the all imaginary frequencies were consistent with the directions of the reaction coordinates.
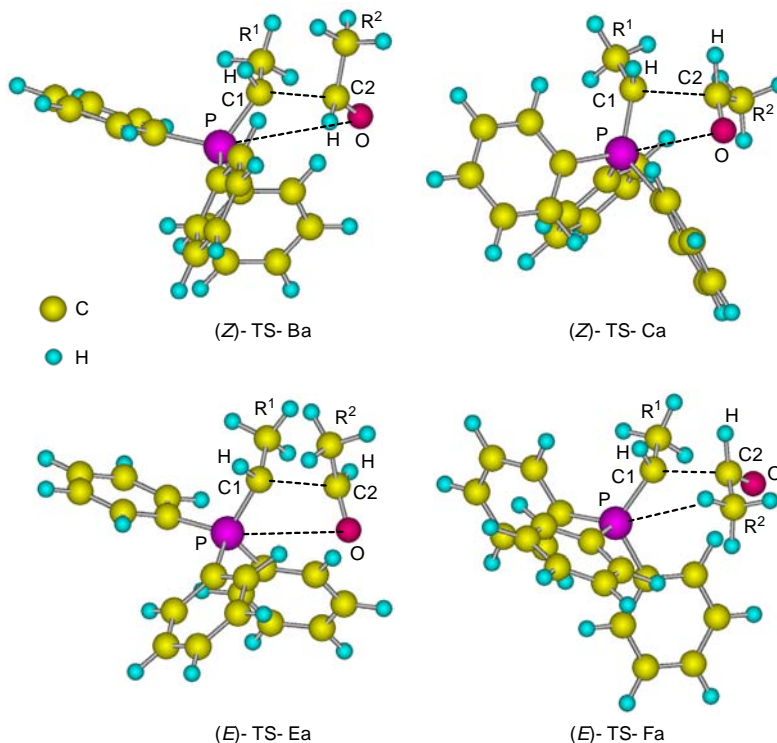

Figure 1

Table 1: Bond Lengths, Dihedral Angles, Relative Energies (ΔE_a),[b] and Imaginary Frequencies of transition states.[a]

Model [c]	C1-C2	C2-O	C1-P	P-O	P-C1-C2-O	ΔE_a	Imaginary Frequency
(Z)-TS-Ba	2.0851	1.2967	1.7856	3.8376	71.5	16.14	176.9i
(Z)-TS-Ca	2.0851	1.2967	1.7856	3.8376	-71.5	20.56	180.8i
(E)-TS-Ea	2.2671	1.2865	1.7672	3.7365	-17.8	16.66	128.6i
(E)-TS-Fa	2.0803	1.2989	1.7857	3.9000	80.6	20.45	165.3i
(Z)-2a	1.5558	1.4704	1.9256	1.8566	-10.9	-8.46	-
(E)-2a	1.5506	1.4685	1.9261	1.8476	-11.0	-8.92	-
(Z)-TS-3a	1.4466	1.7886	2.5522	1.6159	2.7	6.85	480.6i
(E)-TS-3a	1.4417	1.7952	2.5961	1.6129	-0.1	7.36	473.0i

[a] Bond lengths, dihedral angles, relative energies, and imaginary frequencies are shown in Å, deg, kcal/mol, and cm^{-1}, respectively.   [b] Relative Energies (ΔE_a) were compared with reactant.   [c] $R^1 = CH_3$ and $R^2 = CH_3$ were used for all structures in Table 1.

The selected bond lengths and dihedral angles of **(Z)-TS-Ba** and **(Z)-TS-Ca** showed same values unexpectedly, however the activation energies (ΔE_a) of **(Z)-TS-Ba** was lower than **(Z)-TS-Ca**. The closest H---H distance between $CH_3(R^2)$ group on C2 and $Ph(R^1)$ group on P of **(Z)-TS-Ca** is 2.4581 Å and the CH_3CHO moiety was inclined to avoid a nearest Ph group on P. The C1-C2-O, C1-C2-H, and C1-C2-R^2 angles of **(Z)-TS-Ba** shown in Table 2 suggested that the π^* orbital of carbonyl expanded toward ylide directly. On the other hand, the corresponding angles of **(Z)-TS-Ca** indicated that the π^* orbital slightly swerved away from the ylide direction. Therefore, the overlap population between π orbital of C1=P and π^* of C2=O of **(Z)-TS-Ba** was larger than that of **(Z)-TS-Ca** and the difference of activation energy (ΔE_a) was induced. Compare **(E)-TS-Ea** with **(E)-TS-Fa**, similar property can be observed and these results were consistent with Vedejs' models.

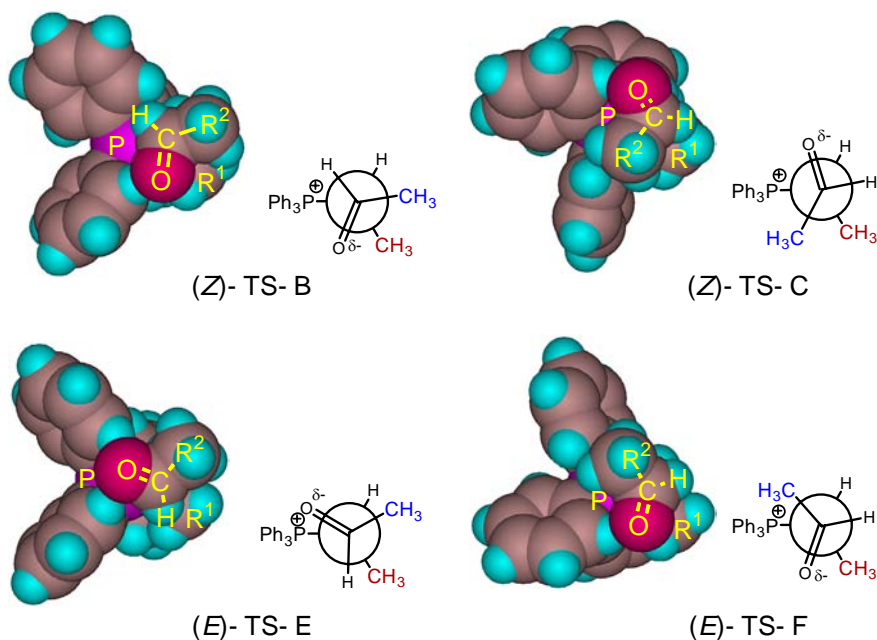**Figure 2**

Table 2: Selected Angles of **(Z)-TS-Ba**, **(Z)-TS-Ca**, **(E)-TS-Ea**, and **(E)-TS-Fa**.

Model	C1-C2-O	C1-C2-H	C1-C2-R^2	C2-C1-P	C2-C1-H	C2-C1-R^1
(Z)-TS-Ba	109.8	94.0	99.6	122.6	101.3	101.2
(Z)-TS-Ca	109.8	85.9	106.1	122.6	89.2	106.5
(E)-TS-Ea	113.4	85.4	96.4	121.4	96.8	101.1
(E)-TS-Fa	109.2	86.5	106.8	122.7	99.8	97.1

[a] Angles are shown in deg.   Labels in table refer to figure 1.

Derived from the results in above, **(Z)-TS-Ba** and **(E)-TS-Ea** were true transition states for oxaphosphetane **(Z)-2a** and **(E)-2a**, respectively. The calculations for **(Z)-TS-3a**, **(Z)-4**, **(E)-TS-3a**, **(E)-4**, and phosphine oxide were also performed and energy profile of the reaction was shown in Figure 3. The olefin geometry was determined at **(Z)-2a** and **(E)-2a** formation process and the ratio (**(Z)-4a/(E)-4a** =

$e^{-\Delta\Delta E_a/RT}$ = 2.41) at 298.15 K was calculated from the difference of activation energies ($\Delta\Delta E_a$ = 0.52 kcal/mol) between **(Z)-TS-Ba** and **(E)-TS-Ea**.   The ratio in gas phase indicate no good selectivity, then optimization and energy calculation of **(Z)-TS-Ba** and **(E)-TS-Ea** were carried out including solvent effect by PCM method.[10]   The energy difference ($\Delta\Delta E_a$) was worked out to 1.09 kcal/mol in DMSO and the ratio was improved to 15.6.
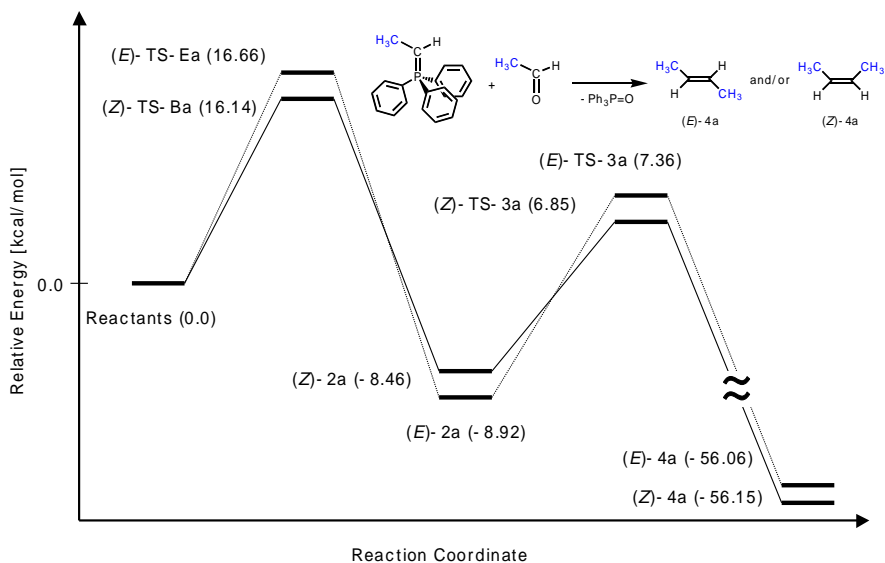

Figure 3

The calculation for the reaction using stabilized ylide, $Ph_3P=CHCN$ (**6b**) + C_6H_6CHO (**7b**), also carried out by the same strategy for the reaction of non-stabilized ylide.   Four kinds of transition states (**(Z)-TS-Bb**, **(Z)-TS-Cb**, **(E)-TS-Eb**, and **(E)-TS-Fb**) for the oxaphosphetanes (**(Z)-2b** and **(E)-2b**) formation process were converged with one imaginary frequency each and **(Z)-TS-Bb** and **(E)-TS-Eb** that showed lower activation energy (ΔE_a) were favorable as true transition states.

Table 3: Bond Lengths, Dihedral Angles, Relative Energies (ΔE_a),[b] and Imaginary Frequencies of transition states.[a]

Model [c]	C1-C2	C2-O	C1-P	P-O	P-C1-C2-O	ΔE_a	Imaginary Frequency
(Z)-TS-Bb	1.8981	1.3273	1.8297	2.8499	22.4	11.05	249.1i
(Z)-TS-Cb	1.9930	1.3029	1.7917	3.4727	-52.9	13.43	141.0i
(E)-TS-Eb	1.8981	1.3273	1.8298	2.8499	-22.4	8.79	244.9i
(E)-TS-Fb	1.9930	1.3029	1.7917	3.4727	52.9	23.75	134.3i
(Z)-2b	1.5639	1.4630	1.9732	1.8371	17.4	-3.21	-
(E)-2b	1.5597	1.4638	1.9838	1.8171	-15.1	-6.36	-
(Z)-TS-3b	1.4866	1.6088	2.5522	1.6557	-2.4	-4.25	188.3i
(E)-TS-3b	1.4761	1.6045	2.7167	1.6295	-1.6	-5.73	176.5i

[a] Bond lengths, dihedral angles, relative energies, and imaginary frequencies are shown in Å, deg, kcal/mol, and cm^{-1}, respectively.   [b] Relative Energies (ΔE_a) were compared with reactant.   [c] R^1 = CN and R^2 = C_6H_6 were used for all structures in Table 3.

The transition states ((**Z**)-**TS-3b** and (**E**)-**TS-3b**) for the phosphine oxide elimination process were calculated and the energy diagram of all reaction processes was shown in Figure 4.   According to a commonly accepted explanation, the reaction is under thermodynamic control and (**Z**)-**2b** can be converted to (**E**)-**2b** via reactants.   However, the energy barrier of phosphine oxide elimination process was quite low and no reverse reaction was anticipated.   The relative energy of (**Z**)-**TS-3b** was lower than (**Z**)-**2b**, therefore the conversion from (**Z**)-**2b** to final product (**Z**)-**4b** may be proceeded immediately without any reverse reaction.   Notable things in this case, the activation energy of (**E**)-**TS-Eb** (8.79 kcal/mol) was lower than that of (**Z**)-**TS-Bb** (11.05 kcal/mol) and so the *E*-olefin selectivity can be explained on the assumption that the reaction proceeded under kinetic control.
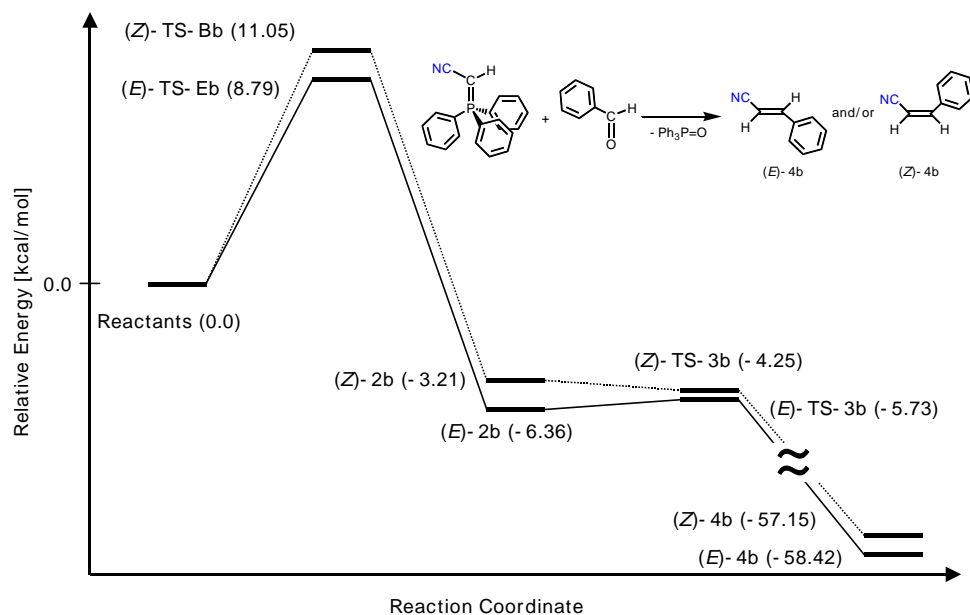

Figure 4

Conclusion

In case of the reaction using non-stabilized ylide, the transition states for the oxaphosphetane-forming process were explored and four kinds of transition states (**Z**)-**TS-Ba**, (**Z**)-**TS-Ca**, (**E**)-**TS-Ea**, and (**E**)-**TS-Fa** were converged.   The transition state (**Z**)-**TS-Ba** having lowest activation energy leaded to *Z*-olefin (**Z**)-**TS-4a** and the additional investigation of all the reaction process resulted that the ratio of *Z*-/*E*-olefin was controlled kinetically.   However, the reaction using stabilized ylide also proceeded under kinetic control, not under thermodynamic control.   The oxaphosphetane (**E**)-**2b** that corresponding to the precursor of *E*-olefin was obtained preferentially via the lowest transition state (**E**)-**TS-Eb** among all transition states.   Starting from the oxaphosphetane (**E**)-**2b**, the activation energy of the forward reaction to olefin (0.63 kcal/mol) was quite lower than that of the reverse reaction to the reactants (15.15 kcal/mol). These results suggested the possibility that the stereoselectivity of Wittig reaction using stabilized ylide was also under kinetic control.

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