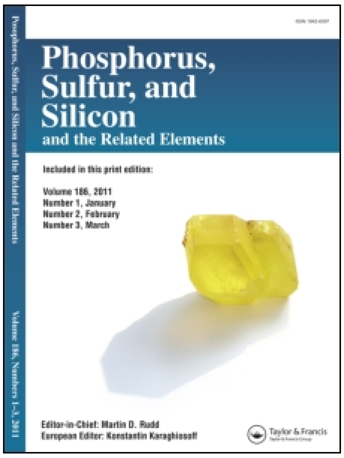

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A STUDY ON THE Z-SELECTIVE HORNER-WADSWORTH-EMMONS (HWE) REACTION OF METHYL DIARYLPHOSPHONOACETATES

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A STUDY ON THE Z-SELECTIVE HORNER-WADSWORTH-EMMONS (HWE) REACTION OF METHYL DIARYLPHOSPHONOACETATES

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Experimental and theoretical studies were conducted to explore the Z-selectivities in the Horner-Wadsworth-Emmons (HWE) reaction employing several methyl diarylphosphonoacetates (**3**, **4**, **5** and **6**) and aldehydes. The Z-selectivity depended upon the reaction conditions such as the bases, reaction temperature, and the aromatic substituents on the phosphorus atoms but the almost phosphonoacetates used in the present study showed Z-selectivity in the reactions with both aromatic and aliphatic aldehydes. While the phosphonoacetate (**3**) with bis(2,4-difluorophenyl)phosphono group showed the highest Z-selectivity in all reaction conditions employed, decrease of the selectivity was observed in the case of some phosphonoacetates with diarylphosphono groups. These experimental results and the theoretical studies calculated by AM1 or 3–21G* ab initio methods suggested that the steric effect in the transition states of the addition steps was important rather than the electronic effect. A different aspect of the reaction courses between the Wittig and HWE reactions in the present computational chemistry was also described.

Keywords: Horner-Wadsworth-Emmons reaction; Z-selectivity; methyl diarylphosphonoacetate; methyl (2,4-difluorophenyl)phosphonoacetate; methyl Z-cinnamate; AM1

INTRODUCTION

The Horner-Wadsworth-Emmons (HWE) reaction[1–3] is one of the most efficient reactions for the olefin formation and has been frequently used in organic synthesis.[4,5] The advantage of this reaction is the high reactivity

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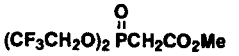
* Corresponding Author.

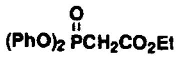
toward carbonyl compounds compared to the parent Wittig reaction, predominant formation of *E*-olefins with electron withdrawing functionalities, and facility of separation of the by-products, the water soluble phosphate ions.

Recently, some improved HWE reactions have been reported[6–12] to achieve the excellent *Z*-selectivity. The epoch-making HWE reaction with the high *Z*-selectivity employing methyl bis(2,2,2-trifluoroethyl)phosphonoacetate (**1**) was developed by Still and Gennari,[7] which has been widely applied to natural products synthesis. Independently, ethyl diarylphosphonoacetates (**2**) were found to give the excellent *Z*-selectivity by Ando.[8,9] However, a common problem remaining among these reagents is that the selectivity is sometimes inferior when aliphatic aldehydes are employed instead of aromatic ones. In order to overcome such shortcomings, we prepared methyl bis(2,4-difluorophenyl)phosphonoacetate (**3**),[10] which exhibited the highest *Z*-selectivity amongst the previously reported HWE reagents, independently of the structure and electronic nature of aldehydes under the convenient reaction condition.



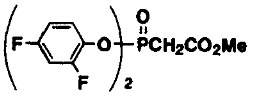
$(CF_3CH_2O)_2\overset{O}{\overset{\|}{P}}CH_2CO_2Me$

1



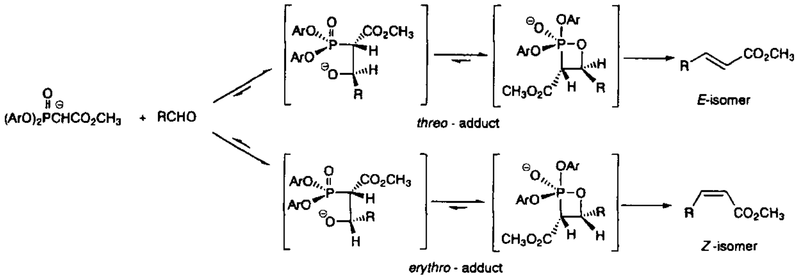
$(PhO)_2\overset{O}{\overset{\|}{P}}CH_2CO_2Et$

2



3

The *Z*-selectivity in these HWE reactions has been conveniently explained in terms of acceleration of the phosphorus group elimination,[3] that is, the high electron negativity on the phosphorus substituents would increase the rates of the phosphorus group elimination from the equilibrium state of the presumed oxaphosphetane and the reactants such as the phosphonate carbanions and carbonyl compounds. This would restrict the formation of thermodynamically favored *E*-olefins (Scheme 1). Although this probable explanation for *Z*-selectivity has been sometimes mentioned[3,6,9], there has been no detailed investigation on this point to our knowledge. In spite of a few overlaps with Ando's work,[9] we independently report, in this paper, the experimental and theoretical studies to examine the effects upon the selectivity employing several kinds of methyl diaryl phosphonoacetates from the view points of electron negativity and steric effect.



SCHEME 1

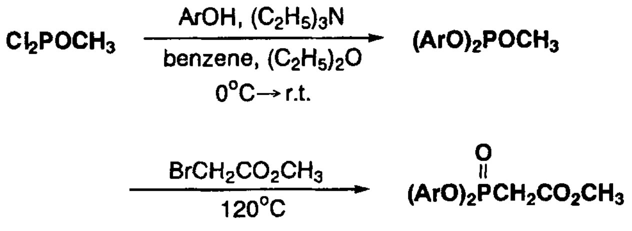
RESULTS AND DISCUSSION

Preparation and the HWE reaction of methyl diarylphosphonoacetates

While various diarylphosphonoacetates can be prepared from methyl dichlorophosphonoacetate according to the Still's procedure,[7] the Arubzov reaction using diaryl methyl phosphite[13] and methyl bromoacetate can be also applied to the preparation,[10] which is advantageous because of dispensable operation to remove excess PCl_5 and by-product $POCl_3$ and because of the widely applicable Arubzov reaction to prepare other phosphonates bearing various carbanion stabilizing functionalities. Thus, various methyl diarylphosphonoacetates (**4** and **5**) were prepared in moderate yields from the corresponding phosphites. The reaction scheme and results are shown in Table I.

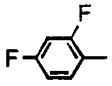
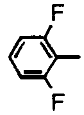
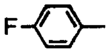
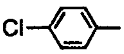
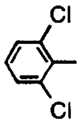
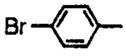
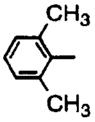
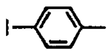
The HWE reaction of the above phosphonoacetates with aromatic and aliphatic aldehydes was carried out under various conditions in tetrahydrofuran (THF) to give almost *Z*-α, β-unsaturated esters preferentially and the *Z/E* ratios of the esters formed were determined by gas chromatography; the retention times of all *Z*-isomers were shorter than those of *E*-isomers. The latter isomers were readily available from the HWE reaction of methyl diethylphosphonoacetate and the corresponding aldehydes. The results are listed in Table II.

TABLE I Preparation of Diaryl Methyl Phosphites and Methyl Diarylphosphonoacetates



$$Cl_2POCH_3 \xrightarrow[\text{benzene, }(C_2H_5)_2O\text{, }0^\circ C \rightarrow \text{r.t.}]{ArOH,\ (C_2H_5)_3N} (ArO)_2POCH_3 \xrightarrow[120^\circ C]{BrCH_2CO_2CH_3} (ArO)_2\overset{O}{\overset{\|}{P}}CH_2CO_2CH_3$$

3, 4, 5

	yield (%)				*yield (%)*		
Ar	*phosphite*	*phosphono-acetate*		*Ar*	*Phosphite*	*phosphono-acetate*	
	46	**3**	62		98	**5a**	76
	57	**4a**	68				
	60	**4b**	56		85	**5b**	45
	62	**4c**	79		73	**5c**	49
	55	**4d**	46				

Effects of the reaction conditions

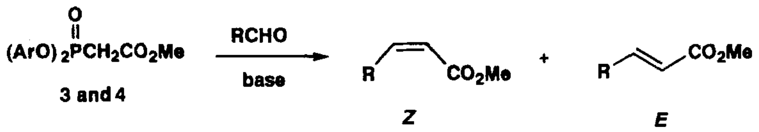
We have already reported [10] that the HWE reaction of **3** showed high *Z*-selectivity in the presence of potassium bis(trimethylsilyl)amide [KN(TMS)$_2$] and 18-crown-6 at −78 °C in THF (Condition A) *(Z/E* = 98/2 with benzaldehyde, 98/2 with octanal) and the practically sufficient *Z*-selectivity could be obtained under more convenient condition using sodium hydride (NaH) at 0 °C in THF (Condition B) (*Z/E* = 96/4 with benzaldehyde, 95/5 with octanal). To investigate the origin of the selectivity, the effects of the reaction conditions such as temperature and the kind of bases were examined employing **3** and benzaldehyde.

As shown in Table II, the geometrical selectivity depended upon the reaction temperature; namely, the selectivity was reduced as the reaction temperature was raised in the presence of $KN(TMS)_2$ and 18-crown-6 in THF (*Z/E* = 98/2 at –78 °C, 92/8 at 30 °C, 81/19 under reflux). The *Z*-isomer was still superior even under refluxing temperature. A similar trend was also observed when Still's reagent **1** was reacted with benzaldehyde under the same condition (*Z/E*= 99/1 at –78 °C, 94/6 at 30 °C, and 87/13 under reflux). In contrast, both reactions of methyl diethylphosphonoacetate and methyl diisopropylphosphonoacetate with benzaldehyde gave only methyl *E*-cinnamate in condition A as observed in the chiral dimethylphosphonoacetate.[14]

Next, we examined the competition reaction of the *Z*-selective reagents **1** or **3** vs. the typical *E*-selective reagent such as methyl diethylphosphonoacetate with benzaldehyde (0.2 equiv.) in condition A. Whereas the competition of **1** vs. methyl diethylphosphonoacetate resulted in only formation of the Z-isomer, a mixture of *Z*- and *E*-isomers was obtained in the ratio of 33/67 in the case of **3**. This result suggests a different factor among **1** and **3** to conduct the *Z*-selectivity.

The nature of the bases used also affected the selectivity. Although sufficient selectivity was obtained in the reactions of **3** in the presence of NaH, the *Z*-isomer was decreased when butyl lithium or 8-diazabicyclo[5,4,0]undec-7-ene (DBU) was used. The absence of 18-crown-6 in condition A also decreased the ratio of *Z*-isomer. The strong effect of the chelation controlling the stereochemistry in the aldol reaction[15,16] might be excluded, because a higher temperature, the absence of the crown ether or metal cation, and use of lithium cation having more Lewis acidity still gave the predominance of the *Z*-isomer. As can be seen both in the HWE reaction of dimethylphosphonoacetates and in the Wittig reaction, lithium cation is known to increase the reversibility [17] to result in increment of the thermodynamically favored *E*-isomers.

TABLE II *Z/E* Ratios in the HWE Reaction of Phosphonoacetates (3 and 4a-d) with Various Aldehydes



Phosphono-acetate	*R*	*Condition (temp. °C)*	*Yield(%)* [a]	*Z/E ratio* [b]
3	Ph	A[c]	80	98 : 2[f]
		B[d]	93	96 : 4[f]
		KN(TMS)$_2$(-78)[e]	80	90 : 10
		KN(TMS)$_2$ (30)	62	92 : 8
		KN(TMS)$_2$ (reflux)	68	81 : 19
		BuLi (-78)	68	91 : 9
		DBU (-78)	68	81 : 19
	n-C_7H_{15}	A	54	98 : 2[f]
		B	82	95 : 5[f]
		BuLi (-78)	68	74 : 26
4a	Ph	A	86	98 : 2[f]
		B	100	78 : 22[f]
	n-C_7H_{15}	A	65	94 : 6
		B	82	87 : 13
	n-C_5H_{11}	A	45	87 : 13
		B	38	86 : 14
4b	Ph	A	68	93 : 7
		B	74	85 : 15
	n-C_7H_{15}	A	92	93 : 7
		B	58	89 : 11
	n-C_5H_{11}	A	58	94 : 6
		B	58	86 : 14
4c	Ph	B	80	78 : 22
	n-C_7H_{15}	B	60	94 : 6
	n-C_5H_{11}	B	83	89 : 11
4d	Ph	B	50	83 : 17
	n-C_7H_{15}	B	70	92 : 8
	n-C_5H11	B	83	89 : 11

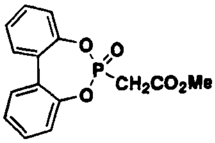
[a] Isolated yields by column chromatography. [b] Determined by gas chromatography or ^{1}H-NMR. [c]Condition A : KN(TMS)$_2$,18- crown-6, -78 °C, THF. [d] Condition B : NaH, 0 °C, THF. [e] Absence of 18-crown-6. [f] The data were taken from ref.10.

Considering these observed results, the *Z*-selectivity of **3** would be due to the structural property of **3** that is not affected by the above reaction conditions.

Effect of the aryloxy groups on the phosphorus atoms

To study the effect of electron negativity of the phosphorus groups upon the geometrical selectivity , the reactions of a systematic series of four methyl bis(4-halophenyl)phosphonoacetates (**4a-d**) with aldehydes were carried out. As shown in Table II, the reactions of these four phosphonoacetates with some aldehydes under condition A gave the unsaturated esters in more than 90% *Z*-selectivity and the almost same *Z/E* ratios were obtained with each aldehyde under condition B. Consequently, the selectivity in this series did not depend on the kind of halogen atoms at *p*-positions unexpectedly, which stressed a larger effect of *o*-fluorine atom of the phosphonate **3**.

Next, the phosphonoacetates (**5a-c**) with 2,6-disubstituted phenyl groups were employed (Table III). While the HWE reaction of **5a** showed the high Z-selectivities as well as **3** under conditions B, the ratio of Z-isomer a little decreased in the case of **5b** with aliphatic aldehydes. On the other hand, a remarkable decrease of *Z*-isomers was observed in the reactions of (2,6-xylyl)phosphonoacetate (**5 c**) with the aldehydes even under condition A and *E*-isomers were formed preferably in a few cases. On the other hand, the previously known phosphonoacetate **6** with the rigid aromatic rings also showed the moderate *Z*-selectivities.[9]

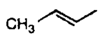
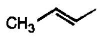


6

Referring to little effect of electron negativity in **4a-c** as described above, diminution of *Z*-selectivities in **5 b** and **5 c** would be due to the steric effect around the phosphorus atoms caused by the interaction of 2,6-substituents and the aldehyde substituents rather than the effect of electron negativity. The extreme decrease of the *Z*-selectivity in **5 c** especially seemed to emphasize such the steric interaction in the addition step which was supported by the unreactivity of **5 c** toward isobutyraldehyde.

These observations allow us to imagine that one of the aryloxy groups on the phosphorus would be close to the aldehyde substituent in the transition state.

TABLE III *Z/E* Ratios in the HWE Reaction of Phosphoacetates (5a-c and 6) with Various Aldehydes

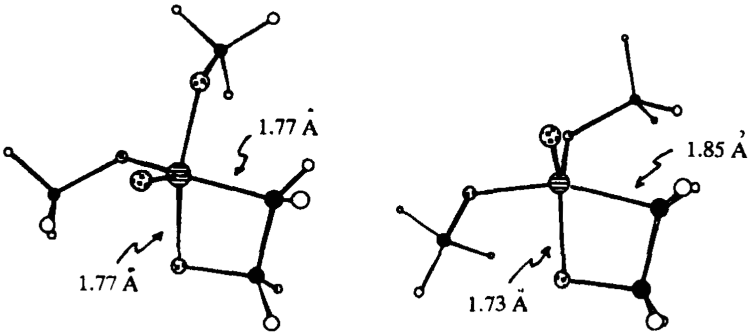
Phosphono-acetate	*R*	*Condition* [a]	*Yield(%)* [b]	*Z/E Ratio* [c]
5a	Ph	B	93	96 : 4
	n-C_7H_{15}	B	100	93 : 7
	n-C_5H_{11}	B	83	93 : 7
		B	100	97 : 3
	$(CH_3)_2CH$	B	- [d]	>99 : 1
5b	Ph	B	100	94 : 6
	n-C_7H_{15}	B	100	86 : 14
	n-C_5H_{11}	B	100	88 : 12
		B	100	96 : 4
	$(CH_3)_2CH$	B	100	83 : 17
5c	Ph	A	70	71 : 29
	n-C_7H_{15}	A	49	71 : 29
	n-C_5H_{11}	A	77	49 : 51
		A	74	38 : 62
	$(CH_3)_2CH$	A	- [e]	-
6	Ph	A	55	92 : 8
	n-C_7H_{15}	A	70	74 : 26
	n-C_5H_{11}	A	83	80 : 20

[a] Condition A : $KN(TMS)_2$,18-crown-6, −78 °C, THF; Condition B : NaH, 0 °C, THF. [b] Isolated yields by column chromatography. [c] Determined by gas chromarography. [d] Not isolated. [e] No reaction.

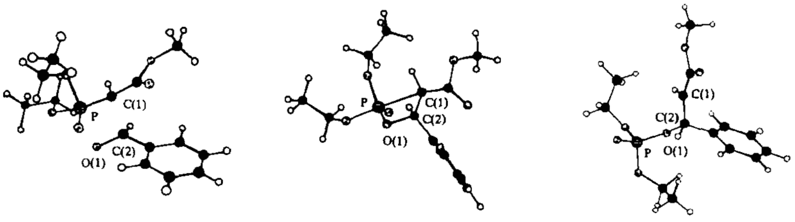
Theoretical study of the *Z*-selective HWE reaction

Although theoretical studies on the Wittig reaction have been accumulated as the development of the calculation methods,[18–21] little attention has been paid to the HWE reaction. Recently, Warren et al.[22] explained the *threo*-selectivity of the Homer-Wittig reaction (the carbanion of phosphin oxides and aldehydes) with the ab initio method. Here, we attempt to explain the *Z*-selective HWE reactions by AM1 semi-empirical method comparing the typical *E*-selective one. To look over a whole reaction course, the energetics of both *E*- and *Z*-olefin formations were examined at first employing the carbanion of methyl diethylphosphonoacetate and benzaldehyde. Each calculation was performed, setting the distances at intervals of 2.0 Å between the aldehyde carbonyl carbon and the ylidic carbon of the phosphonoacetate in the addition stage and that between the phosphorus and the original ylidic carbon of the phosphonoacetate in the elimination stage. Thus, two maximums and one minimum getting between them were found from both calculations for the methyl *E*- and *Z*-cinnamates formations, where two maximums described the transition states for the addition and elimination steps, while the minima corresponded to the *erythro*- and *threo*-oxaphosphetanes. These features resembled the parent Wittig reaction calculated by the ab initio method (4–31G* basis set) by Volatron and Eisenstein.[18] In their study the pseudorotated oxaphosphetane having the eliminating carbon atom at an apical position is unstable by 4.2 kcal/mol compared to the precursory oxaphosphetane. However, in the present AM1 calculations, only pseudorotated oxaphosphetanes could be located, in which the original ylidic carbons occupied the apical positions. These semi-empirical calculations showed simultaneous shifting to the pseudorotated oxaphosphetanes while the carbon-carbon bonds were becoming shorter between the transition states and the oxaphosphetanes. In contrast, two simple oxaphosphetanes derived from the anion of dimethyl methylphosphonate and formaldehyde could be located by AM1, where pseudorotated one was more unstable by 5.5 kcal/mol in the heat of formations *(ΔH_f) similarly* to the above mentioned Wittig reaction. Whether both two isomeric oxaphosphetanes or only pseudorotated ones can be located is probably depending on the presence or the absence of the ester groups.

Another different aspect was found in the elimination step, namely, these calculations showed that the transition states in the elimination step had



highly asynchronous structures. It is probable that the discrepancy among the Wittig and HWE reaction would be due to the nature of phosphorus atoms bearing different ligands such as a phosphonium salt or a phosphonate, still dependence on the calculation methods can not be excluded. The details of the structures at maximal and minimal points are described bellow.



erythro - TS1 *erythro* -IA *erythro* - TS2

FIGURE 1 Structures of *erythro*-TS1, IA, and TS2 for 7 and PhCHO located by AM1

On the basis of the above premise, we focused on three points during the reactions to explore the geometrical selectivities, i.e., the transition states in the addition step (**TS1**), the intermediary adducts (**IA**), and the transition states of the elimination step (**TS2**). The reactions of three phosphonate carbanions [$(CH_3CH_2O)_2P(O)CH^-CO_2CH_3$ (**7**), $(CF_3CH_2O)_2P(O)CH^--CO_2CH_3$ (**8**), $(PhO)_2P(O)CH^-CO_2CH_3$ (**9**)] with benzaldehyde were adopted as the representative calculation models without metal cations because metal cations were thought not to play an definitive role in the selectivity. The calculation results, enthalpies of formation and bond distances of these located molecules are shown in Table IV. The representative structures (**TS 1, IA**, and **TS2**) for the reaction of **7** and benzaldehyde are illustrated in Figure 1.

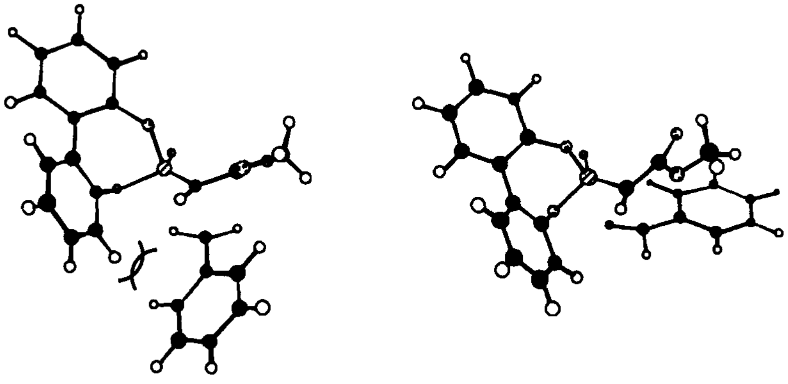
TABLE IV Energetics and Geometric Parameters for the Reactions of 7–9 with PhCHO Calculated by AM1 Method.

		Enthalpy (kca/mol) Bond Length (Å) [a]	*TS1*	*Δ(TS1-IA)*	*IA*	*Δ(TS2-IA)*	*TS2*
7 (C_2H_5)	*threo*		*-327.2*	27.5	*-354.7*	9.2	*-345.5*
		P – C1	1.603		2.334		3.164
		C1 – C2	1.941		1.482		1.455
	erythro		*-319.5*	30.8	*-350.3*	8.0	*-342.3*
		P – C1	1.620		2.395		2.738
		C1 – C2	1.920		1.475		1.451
8 (CF_3CH_2)	*threo*		*-646.9*	23.8	*-670.7*	8.9	*-661.8*
		P – C1	1.593		2.195		2.411
		C1 – C2	1.957		1.496		1.482
	erythro		*-637.5*	24.1	*-661.6*	5.9	*-655.7*
		P – C1	1.615		2.177		2.430
		C1 – C2	2.008		1.498		1.479
9 (Ph)	*threo*		*-239.9*	27.7	*-270.6*	16.3	*-254.3*
		P – C1	1.598		2.238		3.423
		C1 – C2	1.980		1.495		1.405
	erythro		*-234.6*	30.2	*-264.8*	15.3	*-249.5*
		P – C1	1.605		2.247		3.380
		C1 – C2	2.030		1.490		1.406

[a] C1 : α-carbons in the phosphonoacetates; C2: aldehyde carbons (see Figure 1).

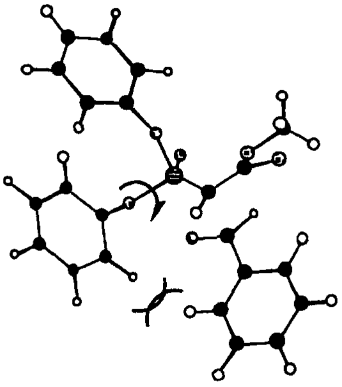
All located **TS 1**s exhibited the asynchronous cycloaddition modes, in which the distances of the just forming C(1)-C(2) bonds and P-O(1) bonds were 1.94–1.98 Å and 2.11–2.38 Å, respectively. These located **TS 1**s resemble those proposed by Larsen et al.[23] from the kinetic study. In these structures, the concept of apical attack and apical departure was maintained,[24]namely, the oxygen atom of the aldehyde occupied the apical position in the nearly trigonal bipyramidal structure of the phosphorus. This rule could be seen distinctly in **IA**, in which the just separating carbon atoms bearing the ester groups also occupied the apical position. It is worthy to note that these **IA**s, which have the four-membered structures like oxaphosphetanes, are the trapezoids and the lengths of P-C(1) (2.20–2.33 Å) are much longer compared to the oxaphosphetanes of the Wittig reaction (1.84 Å) with the ab initio method.[18] These located **IA**s would be in the early stage of the eliminations. The shapes of **TS2**s seem to be very like the elimination mode of E1cB, in which the distances between P and C(1) were being prolonged (2.43 – 3.43Å) and the forming double bonds [C(1)-C(2)] were becoming shorter (1.41–1.48A). Consequently, these structures seem to describe well the course of the HWE reaction.

The general *E*-selectivity of diethylphosphoacetate **7** is readily explained, namely, because of the lower energy of *threo*-**TS 1** by 7.7 kcal/mol and *threo*-**IA** by 4.4 kcal/mol than that of *erythro*-counterparts (Table IV), the *threo*-adducts will be formed preferentially by both kinetic and thermodynamic controls, which should lead to the preferential formation of *E*-cinnamate as have been established experimentally. As the same tendencies were found also in the cases of **8** and **9**, the *Z*-selectivity of these phosphonoacetates can not be explained from the energies of **T S**s and **IA**s. However, the lower energy gap between **IA** and **TS2** and the shorter cleaving P-C bonds in *erythro*-**8** than those in *threo*-**8** would lead to the preferable decomposition into *Z*-olefin, which agreed with the previously mentioned acceleration of the phosphorus group elimination. On the other hand, the *Z*-selectivity of **9** could not be explained by any means from these energetics. Therefore, the phosphonate carbanion of **6** was used as a model to avoid the diversity of the conformations caused by the free rotation of the phenoxy groups around the phosphorus atom (Table V). Although *threo*-**TS1** was estimated to be more stable by 2.9 kcal/mol in AM1 level, the *erythro*-**TS 1** was calculated to be much lower (14.7 kcal/mol) than *threo*-**TS 1** in *ab initio* (3–21G*) method using the molecular structures obtained by AM1. The additional calculation by 6–21G* level also gave the lower energy for *erythro*-**TS 1** by 15.0 kcal/mol than *threo*-one. Thus, the reversal of the energies between *threo*- and *erythro*-**TS 1**s was found and the difference of the energies among both **TS 1**s was quantitatively too large, which might be due to different appreciation of π-electronic repulsion between the aryl substituents on the phosphorus and the aldehyde phenyl group as illustrated in Figure 2.



threo-TS1 for **6** and PhCHO

erythro-TS1 for **6** and PhCHO



threo-TS1 for **9** and PhCHO

FIGURE 2 Structures of TS1s for Diarylphosphonoacetates and PhCHO

As the Z-selectivity of **6** could be explained for the present, the free rotation of the phenyl groups in **9** would make the similar circumstance, where the *threo*-T S would be more unstable than *erythro*-T S by the steric or electronic repulsion (Figure 2). Such repulsion around the phosphorus groups should be larger than the interaction between the ester groups and the aldehyde substituents. That the *E*-isomers were favored in the reaction of **5 c** bearing 2,6-xylyl groups with sterically uncrowded aldehydes does not contradict with the above explanation. Diminution of the steric interaction between the phosphorus substituents and the smaller aldehydes and decrease of electron negativity of the phosphorus group should lead to the formation of thermodynamically favored olefins.

TABLE V Energies of TS1 for 6 and PhCHO

	AM1 (kcal/mol)	*3–21 G* (a.u.)*	*6–21 G* (a.u.)*
threo	-234. 7	-1402.816272	-1410.398572
erythro	-231.8	-1402.839690	-1410.422450
Δ(*threo-erythro*) (kcal/mol)	-2.9	14.7	15.0

The present study was chiefly made by the semi-empirical method and it seemed to describe the reaction processes with considerable adequacy. However, vagueness in the energetics was sometimes unavoidable and further efforts to obtain more detailed substances of the HWE reactions with higher level ab initio methods[25] are required comparing the present study, which is continuing in our laboratory.

EXPERIMENTAL SECTION

All solvents were dried by the standard methods. ^{1}H-NMR spectra were obtained on JOEL PMX60 using TMS as an internal standard in $CDCl_3$. The mass spectra were determined on HITACHI M-80B mass spectrometer. Analytical gas chromatography was performed on Shimadzu GC-8A apparatus using PEG-20M or DC-550 packed column. The column chromatography was done with Wakogel C-200.

Methyl bis(2,4-difluorophenyl) phosphite

Although the procedure for this compound was described in our previous paper,[10] the yields were improved by the following method. *Typical Procedure :* A solution of dichloro methyl phosphite[13] (1.09 g, 8.2 mmol) in ether (5 ml) was added dropwise to 2,4-difluorophenol (2.14 g, 16.5

mmol) and triethylamine (2.7 ml, 16.5 mmol) dissolved in benzene (15 ml) and ethyl ether (5 ml) at 0 °C. After stirring for 3h at room temperature, precipitated ammonium chloride was filtered off and the filtrate was washed with saturated $NaHCO_3$(3 × 60 ml), saturated NH_4Cl and brine and dried over Na_2SO_4. Removal of the solvent and purification by column chromatography [silica gel/hexane-AcOEt (4/1)] provided the phosphite (4.34 g, 55 %) as a colorless oil. The spectral and analytical data were described in the literature.[10] The following phosphites were prepared by the same procedure.

Methyl bis(4-fluorophenyl) phosphite

^{1}H NMR δ: 3.83 (d, 3H,J_{PH}= 9Hz), 6.93–7.36 (m, 8H); HRMS *m/z* calcd for $C_{13}H_{11}O_3F_2P$: 284.0413. Found: 284.0436.

Methyl bis(4-chlorophenyl) phosphite

^{1}H NMR δ: 3.92 (d, 3H,J_{PH}= 9Hz), 6.43–7.16 (m, 8H); HRMS *m/z* calcd for $C_{13}H_{11}O_3Cl_2P$: 315.9822. Found: 315.9795.

Methyl bis(4-bromophenyl) phosphite

^{1}H NMR δ : 3.67 (d, 3H,J_{PH}= 9Hz), 6.67–7.67 (m, 8H); HRMS *m/z* calcd for $C_{13}H_{11}O_3Br_2P$: 403.8813. Found: 403.8838.

Methyl bis(4-iodophenyl) phosphite

^{1}H NMR δ: 3.63 (d, 3H, J_{PH}= 9Hz), 6.57–7.65 (m, 8H); MS (70ev) 500 (M^+); HRMS *m/z* calcd for $C_{12}H_8O_2I_2P$ (M^+ - OCH_3): 468.8351. Found: 468.8361.

Methyl bis(2,6-difluorophenyl) phosphite

^{1}H NMR δ: 3.88 (d, 3H,J_{PH}= 9Hz), 6.43–7.16 (m, 6H); MS (70ev) 320 (M^+) ; HRMS *m/z* calcd for $C_{12}H_6O_2F_4P$ (M^+ – OCH_3): 289.0041. Found: 289.0027.

Methyl bis(2,6-dichlorophenyl) phosphite

^{1}H NMR δ: 4.10 (d, 3H,J_{PH}= 9Hz), 6.93–7.32 (m, 6H); HRMS m/z calcd for $C_{13}H_9O_3Cl_4P$: 383.9043. Found: 383.9022.

Methyl bis(2,6-xylyl) phosphite

^{1}H NMR δ: 2.30 (s, 12H), 4.12 (d, 2H, J_{PH} = 9Hz), 7.00–7.23 (m, 6H); MS (70ev) 304 (M^+) ; HRMS *m/z* calcd for $C_{16}H_{18}O_3P$ (M^+-$^+CH_3$): 289.0993. Found: 289.1009.

Methyl bis(4-fluorophenyl)phosphonoacetate (4a)

Typical procedure and the spectral data were described in the literature.[10]The following phosphonoacetates were prepared by the same method.

Methyl bis(4-chlorophenyl)phosphonoacetate (4b)

^{1}H NMR δ: 3.36 (d, 2H,J_{PH}= 22Hz), 3.80 (s, 3H), 7.13–7.63 (m, 8H); HRMS *m/z* calcd for $C_{15}H_{13}O_5C_{12}P$: 373.9877. Found: 373.9891.

Methyl bis(4-bromophenyl)phosphonoacetate (4c)

^{1}H NMR δ: 3.50 (d, 2H, J_{PH}= 22Hz), 3.83 (s, 3H), 7.08–7.77 (m, 8H); MS (70ev) 462 (M^+) ; HRMS *m/z* calcd for $C_{14}H_8O_4Br_2P$ (M+ – OCH_3) : 430.8684. Found: 430.8678.

Methyl bis(4-iodophenyl)phosphonoacetate (4d)

^{1}H NMR δ: 3.33 (d, 2H,J_{PH}= 22Hz), 3.80 (s, 3H), 6.97–7.93 (m, 8H); MS (70ev) 558 (M^+) ; HRMS *m/z* calcd for $C_{14}H_{10}O_4I_2P$ (M+ – OCH_3) : 526.8409. Found: 526.8426.

Methyl bis(2,6-difluorophenyl)phosphonoacetate (5a)

^{1}H NMR δ: 3.46 (d, 2H, J_{PH} = 22Hz), 3.73 (s, 3H), 6.53–7.30 (m, 6H); HRMS *m/z* calcd for $C_{15}H_{11}O_5F_4P$: 378.0279. Found: 378.0249.

Methyl bis(2,6-dichlorophenyl)phosphonoacetate (5b)

^{1}H NMR δ: 3.67 (d, 2H, J_{PH} = 22Hz), 3.72 (s, 3H), 6.77–7.37 (m, 6H); HRMS *m/z* calcd for $C_{15}H_{11}O_5Cl_4P$: 441.9097. Found: 441.9119.

Methyl bis(2,6-xylyl)phosphonoacetate (5c)

^{1}H NMR δ: 2.28 (s, 12H), 3.35 (d, 2H, J_{PH} = 22Hz), 3.73 (s, 3H), 7.00 (s, 6H); HRMS *m/z* calcd for $C_{19}H_{23}O_5P$: 362.1282. Found: 362.1290.

The HWE reaction

Condition A (KN(TMS)$_2$ /18-crown-6, –78°C, THF)

A solution of KN(TMS)$_2$ (0.5 mol/l toluene solution, 2.0 ml, 1.00 mmol) was added dropwise to a solution of **3** (0.38 g, 1.00 mmol) and 18-crown-6 (1.32 g 5.00 mmol) in THF (20 ml) at –78 °C and the mixture was stirred at this temperature for lh under N_2. A solution of benzaldehyde (0.11 g, 1.00 mmol) in THF (2 ml) was then added and the mixture was stirred for 12h at that temperature. After the reaction was quenched with saturated NH_4Cl at room temperature, the THF layer was separated and the product was further extracted with Et_2O (2 x 20 ml) from an aqueous layer. The combined extract was washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel using benzene as an eluant to give methyl cinnamate in 80% yield. The *E/Z* ratio was determined by gas chromatography.

KN(TMS)$_2$ / 18-crown-6, 30 °C

A solution of KN(TMS)$_2$ (0.5 mol/l toluene solution, 2.0 ml, 1.00 mmol) was added dropwise to a solution of **3** (0.38 g, 1.00 mmol) and 18-crown-6 (1.32 g 5.00 mmol) in THF (20 ml) at –78°C and the mixture was stirred at this temperature for 30 min under N_2. The temperature was allowed to warm up to 30°C and a solution of benzaldehyde (0.11 g, 1.00 mmol) in THF (2 ml) was then added and the mixture was stirred for 2h at same temperature. The usual treatment and purification gave methyl cinnamate.

KN(TMS)$_2$ /18-crown-6, reflux

The carbanion of **3** was prepared by above described method and the reaction mixture was refluxed and a solution of benzaldehyde (0.11 g, 1.00

mmol) in THF (2 ml) was then added. The following treatment was same as above.

n -BuLi

A solution of butyl lithium (1.63 mol/l, 1.0 mmol, 0.61 ml) in hexane was added dropwise to a solution of **3** (0.38 g, 1.0 mmol) in THF (20 ml) at −78 °C under N_2. After lh, a solution of benzaldehyde (0.11 g, 1.0 mmol) in THF (2 ml) was added dropwise to the reaction mixture at the same temperature. After stirring at same temperature for 2h, the reaction was quenched with saturated NH_4Cl and the organic layer was separated. The water layer was extracted with ether (2 × 20 ml) and the combined organic layer was washed with brine and dried on Na_2SO_4. After removal of solvent, the residue was purified by column chromatography (SiO_2 / benzene) to give pure methyl cinnamate.

Condition B (NaH, 0°C, THF)

A solution of **3** (0.38 g, 1.00 mmol) in THF (5 ml) was added dropwise to a suspension of NaH (50 % in oil, 0.05 g, 1.00 mmol) in THF (10 ml) at 0°C and the mixture was stirred at the same temperature for lh under N_2. After addition of benzaldehyde (0.11 g, 1.00 mmol) in THF (5 ml) at 0 °C, the mixture was stirred at the same temperature for 8h. The usual work-up and column chromatography gave methyl cinnamate in 93% yield.

NaH, −78 °C

After the carbanion of **3** was prepared as described above, a solution of benzaldehyde (0.11 g, 1.00 mmol) in THF (5 ml) was added dropwise at −78 °C and the mixture was stirred at same temperature for 8h. The following treatment was done as described above.

DBU

A solution of DBU (0.23 g, 1.5 mmol) in THF (5 ml) was added dropwise to a solution of **3** (0.38 g, 1.0 mmol) in THF(15 ml) at −78 °C under N_2. After stirring for lh, a solution of benzaldehyde (0.11 g, 1.0 mmol) in THF (5 ml) was added dropwise to the reaction mixture at the same temperature. After stirring at the same temperature for 18h, the usual work-up gave methyl cinnmate.

Typical Procedure of the Competition Reactions

A solution of $KN(TMS)_2$ (0.5 mol/l toluene solution, 2.0 ml, 1.00 mmol) was added dropwise to a solution of **3** (0.38 g, 1.00 mmol), methyl diethylphosphonoacetate (0.21g, 1.00 mmol) and 18-crown-6 (1.32g 5.00 mmol) in THF (40 ml) at –78 °C and the mixture was stirred at this temperature for lh under N_2. A solution of benzaldehyde (0.02 g, 0.20 mmol) in THF (2 ml) was then added and the mixture was stirred for 1 min. After the reaction was quenched with saturated NH_4Cl, the reaction mixture was allowed to worm up to room temperature. The THF layer was separated and the product was further extracted with Et_2O (2 × 20 ml) from aqueous layer. The combined extract was washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel using benzene as an eluant to give methyl cinnamate as a *Z/E* mixture.

All α, β-unsaturated esters have been described in the literature[1,2,6,7,9].

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