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Toward (*Z*)-selective Horner–Wadsworth–Emmons reaction of aldehydes with 2-fluoro-2-diethylphosphonoacetic acid

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Abstract—The stereoselective Horner–Wadsworth–Emmons reaction of aldehydes with 2-fluoro-2-diethylphosphonoacetic acid utilizing *i*-PrMgBr afforded (*Z*)-α-fluoro-α,β-unsaturated carboxylic acids as the major products. © 2002 Elsevier Science Ltd. All rights reserved.

Ethyl 2-fluoro-2-diethylphosphonoacetate (**1**) is an efficient fluorinated building-block used in organic synthesis.[1,2] A number of methods employing the Horner–Wadsworth–Emmons (HWE) reaction involving phosphonate **1** have been developed for the stereoselective synthesis of (*E*)-α-fluoro-α,β-unsaturated esters (*E*)-**3**.[3–15] However, using the HWE reaction for the preparation of (*Z*)-**3** is much less common.[16,17] In addition, (*Z*)-fluoroolefins **A** play an important role as (*s*-*Z*)-amide **B** isosteres, from the standpoint of a mimic of the steric demand, bond lengths, and bond angles of **B**.[18–24] Recently, we reported the Sn(II)-promoted stereoselective HWE reaction of various phosphonates with aryl alkyl ketones.[25–29] We have also demonstrated the Mg(II)-promoted HWE reaction of aldehydes **2b**,**f** with phosphonate **1** for the preparation of α-fluoro-α,β-unsaturated esters **3b**,**f** with a moderate (*Z*)-selectivity depending on the reaction temperature.[26] Herein, we wish to describe the HWE reaction of aldehydes **2a**–**f** with a dianion, prepared by magnesiation of 2-fluoro-2-diethylphosphonoacetic acid (**4**) utilizing *i*-PrMgBr in THF. The HWE reaction afforded (*Z*)-α-fluoro-α,β-unsaturated carboxylic acids (*Z*)-**5a**–**f** as the major products.

The HWE reaction (reflux or 0°C) of phosphonate **1** with cyclohexylcarboxaldehyde (**2a**) in the presence of *n*-BuLi in THF gave (*E*)-α-fluoro-α,β-unsaturated ester (*E*)-**3a** with *E*:*Z* ratios of 94:6 and 92:8, independent of the reaction temperature (Table 1, entries 3 and 4).[13] On the other hand, increasing the reaction temperature tended to decrease *E*-selectivity in the Mg(II)-promoted HWE reactions of phosphonate **1** with aldehyde **2a** (Table 1, entries 1 and 2). Taking into account the oxophilicity of Mg(II),[30–35] a magnesium salt of dianion of **4** was treated with **2a** in THF to yield the α-fluoro-α,β-unsaturated carboxylic acid **5a**. Phosphonoacetic acid **4** was readily prepared by the hydrolysis of phosphonate **1** in 99% yield. Esterification of **5a** with an excess amount of trimethylsilyldiazomethane

Table 1. Stereoselective HWE reactions of aldehydes **2a** with ethyl 2-fluoro-2-diethylphosphonoacetate **1**

Entry	Conditions[a]	Temperature	Time (h)	Yield (%) of **3a**[b]	(*E*)-**3a**:(*Z*)-**3a**[c]
1	*i*-PrMgBr	Reflux	1	95	55:45
2	*i*-PrMgBr	0°C	12	91	83:17
3	*n*-BuLi	Reflux	1	83	94:6
4	*n*-BuLi	0°C	12	80	92:8

[a] *i*-PrMgBr = THF, **1**/*i*-PrMgBr/**2a** (1.2:1.25:1); *n*-BuLi = THF, **1**/*n*-BuLi/**2a** (1.2:1.25:1).

[b] Isolated yields.

[c] Determined by ^{1}H NMR (300 MHz, $CDCl_3$) analysis.

Keywords: Horner–Wadsworth–Emmons reactions; fluorine and compounds; magnesium and compounds; α-fluoro-α,β-unsaturated carboxylic acids; α-fluoro-α,β-unsaturated esters; Wittig reactions.

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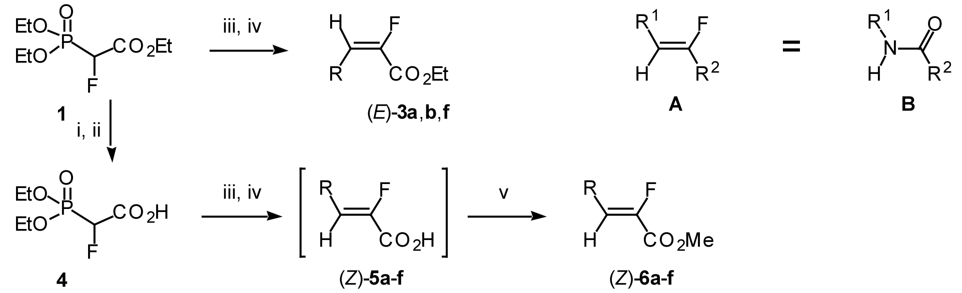
(TMSCHN$_2$)[36] provided the desired α-fluoro-α,β-unsaturated ester **6a** without isolation of **5a**, as shown in Scheme 1. Under reflux conditions in THF utilizing *i*-PrMgBr, the reaction of phosphonoacetic acid **4** with aldehyde **2a** proceeded in a moderate *Z*-selective manner (*E*:*Z* = 32:68), while under 0°C conditions, the *E*:*Z* ratio was 50:50 (Table 2, entries 1 and 2). All of the remaining reactions of phosphonoacetic acid **4** with various aldehydes **2b–f** by use of *i*-PrMgBr under reflux conditions each afforded (*Z*)-**5b–f** as the major products. In particular, the reaction with benzaldehyde (**2f**) or α,β-unsaturated aldehydes **2c–e** gave the corresponding *Z*-isomers (*Z*)-**5c–f** in a highly stereoselective manner in a range of *E*:*Z* ratios, i.e. 19:81–<1:>99. The HWE reactions of phosphonoacetic acid **4** with aldehydes **2a–f** employing *n*-BuLi gave a mixture of both stereoisomers under reflux conditions in a range of *E*:*Z* ratios, i.e. 60:40–37:63, as listed in Table 2. The stereoselectivity in the Mg(II)-promoted reactions of phosphonoacetic acid **4** with benzaldehyde (**2f**) did not vary with the reaction temperature (Table 2, entries 13–15). However, the reactions of **4** with **2f** in the case of *n*-BuLi exhibited a slight tendency toward temperature dependence of the stereoselectivity (Table 2, entries 16–18). The geometry and the diastereomer ratios of **5a–f** were confirmed on the basis of coupling constants between fluorine and the adjacent olefinic proton (${}^3J_{\mathrm{H,F}}$) and integration of the appropriate proton absorptions obtained by ^{1}H NMR (300 or 400 MHz) analysis.

In a typical procedure, *i*-PrMgBr (0.63 mol/L solution in THF, 2.62 mL, 1.65 mmol) was added to a stirred solution of phosphonoacetic acid **4** (170 mg, 0.79 mmol) in anhydrous THF (10 mL) at 0°C under argon. The mixture was stirred at 0°C for 1 h and then refluxed. Benzaldehyde (**2f**) (66.8 μL, 0.66 mmol) was added to the refluxing solution. After being refluxed for 1 h, the reaction mixture was treated with H$_2$O (10 mL) and then washed with CHCl$_3$ (100 mL). The water layer



a: R = cyclohexyl, **b**: R = Ph(CH$_2$)$_2$, **c**: R = (*E*)-PhCH=CH, **d**: R = (*E*)-MeCH=CH, **e**: R = Me$_2$C=CH, **f**: R = Ph

Scheme 1. *Reagents and conditions*: (i) 1N NaOH/rt/20 h; (ii) H$^+$; (iii) *i*-PrMgBr or *n*-BuLi/THF/1 h; (iv) RCHO **2a–f**; (v) TMSCHN$_2$/MeOH–benzene (2:7)/rt/30 min.

Table 2. Stereoselective HWE reactions of aldehydes **2a–f** with 2-fluoro-2-diethylphosphonoacetic acid **4**

Entry	Aldehyde	Conditions[a]	Temperature	Time (h)	Yield (%)[b]	*E*:*Z*[c]
1	**2a**	*i*-PrMgBr	Reflux	1	81 (**6a**)	32:68 (**5a**)
2	**2a**	*i*-PrMgBr	0°C	12	83 (**6a**)	50:50 (**5a**)
3	**2a**	*n*-BuLi	Reflux	1	86 (**6a**)	60:40 (**5a**)
4	**2a**	*n*-BuLi	0°C	12	98 (**6a**)	58:42 (**5a**)
5	**2b**	*i*-PrMgBr	Reflux	1	72 (**6b**)	19:81 (**5b**)
6	**2b**	*n*-BuLi	Reflux	1	87 (**6b**)	56:44 (**5b**)
7	**2c**	*i*-PrMgBr	Reflux	1	81 (**6c**)	12:88 (**5c**)[d]
8	**2c**	*n*-BuLi	Reflux	1	77 (**6c**)	42:58 (**5c**)[d]
9	**2d**	*i*-PrMgBr	Reflux	1	83 (**6d**)	15:85 (**5d**)[e]
10	**2d**	*n*-BuLi	Reflux	1	76 (**6d**)	42:58 (**5d**)[e]
11	**2e**	*i*-PrMgBr	Reflux	1	84 (**6e**)	10:90 (**5e**)[e]
12	**2e**	*n*-BuLi	Reflux	1	92 (**6e**)	49:51 (**5e**)[e]
13	**2f**	*i*-PrMgBr	Reflux	1	84 (**6f**)	<1:>99 (**5f**)
14	**2f**	*i*-PrMgBr	0°C	12	81 (**6f**)	<1:>99 (**5f**)
15	**2f**	*i*-PrMgBr	−78°C	12	51 (**6f**)	<1:>99 (**5f**)
16	**2f**	*n*-BuLi	Reflux	1	84 (**6f**)	37:63 (**5f**)
17	**2f**	*n*-BuLi	0°C	12	98 (**6f**)	48:52 (**5f**)
18	**2f**	*n*-BuLi	−78°C	12	81 (**6f**)	54:46 (**5f**)

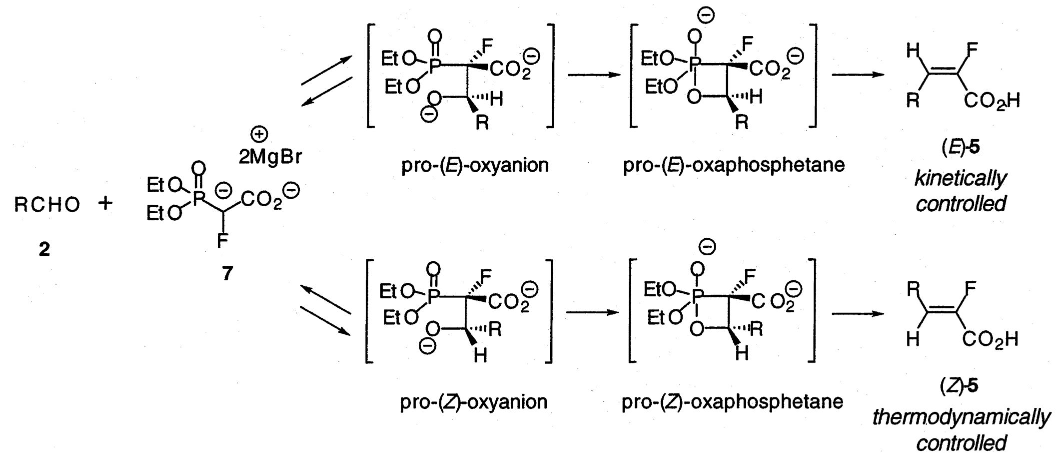
[a] *i*-PrMgBr = THF, **4**/*i*-PrMgBr/**2** (1.2:2.5:1); *n*-BuLi = THF, **4**/*n*-BuLi/**2** (1.2:2.5:1).

[b] Isolated yields.

[c] Determined by ^{1}H NMR (300 MHz, CDCl$_3$) analysis.

[d] Determined by ^{1}H NMR (400 MHz, CDCl$_3$) analysis.

[e] Determined by ^{1}H NMR (300 MHz, C$_6$D$_6$) analysis.



Scheme 2.

was acidified with 5% HCl and extracted with AcOEt (100 mL×5). The extract was washed with brine (20 mL) and dried over anhydrous $MgSO_4$. The organic layer was evaporated in vacuo to afford a crude product **5f** (E:Z=<1:>99). To the solution of **5f** in MeOH (2 mL) and benzene (7 mL) was added an excess amount of $TMSCHN_2$ (2.0 mol/L solution in n-hexane, ca. 1 mL, ca. 2 mmol). After being stirred at room temperature for 30 min, the reaction mixture was evaporated in vacuo to afford a crude product, which was purified by chromatography on a silica gel column eluted with n-hexane–AcOEt (25:1), giving α-fluoro-α,β-unsaturated ester (Z)-**6f** (100 mg, 84%) as a colorless oil.

On the basis of the experimental results described above, the Z-selectivity in the Mg(II)-promoted HWE reactions of phosphonoacetic acid **4** with aldehydes **2a-f** can be rationalized in terms of thermodynamic control, as illustrated in Scheme 2.[26,37] Namely, the step involving the addition of dianion **7** to aldehyde **2** toward pro-(E)- or pro-(Z)-oxyanion must be reversible. In the case of aldehydes **2c–f**, a repulsive interaction between the aromatic or the unsaturated moiety of **2c–f** and the carboxylato anion of **7** also seems to play an important role in the transition state.

In summary, (Z)-α-fluoro-α,β-unsaturated ester (Z)-**6a–f** were prepared by the HWE reaction of phosphonoacetic acid **4** with various aldehydes **2a–f**. This procedure was particularly effective for aromatic and α,β-unsaturated aldehydes **2c–f**. Further study of the mechanism of the Mg(II)-promoted HWE reaction will be reported elsewhere.

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