Z-Selective Horner−Wadsworth−Emmons Reaction of Ethyl (Diarylphosphono)acetates Using Sodium Iodide and DBU

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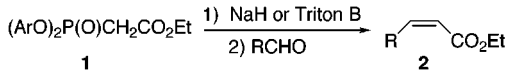
The Horner−Wadsworth−Emmons (HWE) reaction is a widely used method for the preparation of α,*β*-unsaturated esters.[1] The phosphonate anions are strongly nucleophilic and react readily with aldehydes to form olefins and water-soluble phosphate esters. Generally, the HWE reaction is performed in the presence of a relatively strong base such as *n*-butyllithium, potassium *tert*-butoxide, or sodium hydride. When the aldehyde is sensitive to strong bases, i.e., racemization, aldol condensation, or decomposition of the aldehyde is prone to occur, milder conditions are preferable. One and one-half decades ago, Masamune, Roush, and co-workers reported that a weak base, either 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or diisopropylethylamine in acetonitrile, can be used for the HWE reaction in the presence of lithium chloride.[2,3] Under these conditions, *E*-α,*β*-unsaturated esters were obtained in good yields. Conventional methods resulted in low yields or varying degrees of racemization in the course of olefination. The Masamune−Roush method is now widely used in synthesis.[4]

The construction of *Z*-α,*β*-unsaturated esters is also a synthetic problem of great interest.[5] Recently, one of us[6] reported the preparation of ethyl (diarylphosphono)-acetates (**1**) and the HWE reaction of **1** with various types of aldehydes in the presence of an inexpensive base, NaH or Triton B in THF. This method provides a simple, economical, and highly selective route to a wide range of *Z*-α,*β*-unsaturated esters in almost quantitative yields. Since reagents of type **1** are useful in synthesis,[7,8] we decided to explore milder conditions for the reaction of **1** with functionalized aldehydes.[9]



1 **2**

Results

***Z*-Selective Horner−Wadsworth−Emmons Reaction of Ethyl (Diarylphosphono)acetate in the Presence of Amine.** The HWE reaction of ethyl (diphenylphosphono)acetate **1a**[6d] with 2-ethylhexanal in the presence of amine base was performed in order to establish the best reaction conditions (Table 1). Following the Masamune−Roush procedure,[2] **1a** in acetonitrile was treated with DBU in the presence of LiCl, followed by the addition of 2-ethylhexanal at 0 °C. The reaction is complete within 1.5 h, and an 80:20 ratio of *Z*:*E* products **2a**[6b] was obtained in 97% yield (entry 1). In the absence of LiCl, the reaction proceeds slowly to give a 67:33 ratio of *Z*:*E* in 72% yield, after 15 h at room temperature (entry 2). Since NaH was the best base for the reaction of **1** with aliphatic aldehydes, sodium salts were expected to give higher *Z*-selectivities. When NaBr or NaI was used instead of LiCl, 86−87% *Z*-selectivities were obtained (entries 3 and 4). Lowering the temperature improved the selectivity (91%, entry 5), but a change of solvent was warranted as a result of the poor solubility of the salts at low temperature, and because acetonitrile's freezing point (−48 °C) precluded low-temperature reactions. When the reaction was performed in THF by warming the mixture from −78 to 0 °C over 1−2 h, use of NaI gave

† Deceased on January 20, 2000.

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Table 1. HWE Reaction of 1a and 2-Ethylhexanal in the Presence of DBU[a]

entry	MX	solvent	conditions	% yield[b]	*Z*:*E*
1	LiCl	CH_3CN	0 °C, 1.5 h	97	80:20
2		CH_3CN	rt, 15 h	72 (13)	67:33
3	NaBr	CH_3CN	0 °C, 3 h	85 (6)	86:14
4	NaI	CH_3CN	0 °C, 3 h	97	87:13
5	NaI	CH_3CN	−30 °C, 3 h	90 (9)	91:9
6	LiCl	CH_3CN	−40 °C, 3 h	58 (23)	87:13
7	NaI	THF	−78 → 0 °C	96	94:6
8	NaBr	THF	−78 → 0 °C	17 (80)	83:17
9	NaBr	THF	0 °C, 3 h	53 (38)	84:16
10	LiCl	THF	−78 → 0 °C	85 (15)	80:20

[a] **1a** was treated with DBU (1.1 equiv) in the presence of MX (1.2 equiv) at 0 °C for 10 min, and then the reaction with aldehyde was performed. [b] The numbers in parentheses are the recovered yields of **1a** (%).

Scheme 1

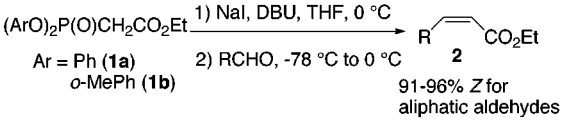


Table 2. HWE Reaction of 1a and 1b in the Presence of NaI and DBU in THF[a]

entry	reagent	RCHO	% yield	*Z*:*E*	(NaH)[6b]
1	**1a**	BuCHEtCHO	96	94:6	94:6 (100%)
2	**1b**	BuCHEtCHO	91	96:4	96:4 (96%)
3	**1a**	cyclohexylCHO	97	91:9	91:9 (98%)
4	**1b**	cyclohexylCHO	92	95:5	95:5 (100%)
5	**1a**	*n*-C_7H_{15}CHO	94	92:8	90:10 (100%)
6	**1b**	*n*-C_7H_{15}CHO	93	93:7	94:6 (97%)

[a] After **1** was treated with NaI (1.2 equiv) and DBU (1.1 equiv) in THF at 0 °C for 10 min, the reaction with aldehyde was performed (−78 to 0 °C).

an excellent result (94% *Z*-selectivity in 96% yield, entry 7). On the other hand, both NaBr and LiCl in THF gave lower yields compared to the reaction in acetonitrile (entries 8−10). Thus, whereas the original Masamune−Roush procedure showed a moderate *Z*-selectivity, the modified method (NaI/DBU/THF) gives the *Z*-olefins highly selectively. The *Z*:*E* ratios of all the HWE products **2** were determined by integration of the vinyl proton signals in the 500 MHz ^{1}H NMR spectra.

Next, we examined the reaction of **1a** and **1b**[10] with aliphatic aldehydes in THF (Scheme 1). The results are summarized in Table 2 along with the results using NaH as a base.[6b] After the treatment of **1b** with DBU and NaI in THF at 0 °C, followed by the addition of 2-ethylhexanal at −78 °C, the reaction mixture was allowed to warm to 0 °C over 1−2 h whereupon 96% *Z*-selectivity was observed (entry 2). When the same procedure was applied to the reaction of **1a** and **1b** with cyclohexanecarboxaldehyde, 91% and 95% *Z*-selectivities were obtained, respectively. In the reaction with *n*-octyl aldehyde, **1a** and **1b** showed 92% and 93% *Z*-selectivity, respectively. These results are comparable with the results obtained using NaH as a base.[6b]

The results of the reaction with benzaldehyde and 2*E*-hexenal are summarized in Table 3, along with the results using Triton B.[6b] When **1a** was treated with DBU and NaI in THF at 0 °C, followed by the reaction with benzaldehyde at −78 °C, 88% *Z*-selectivity was obtained in 100% yield (entry 1). This result is comparable to the one using NaH (85% *Z*, 100% yield).[6b] Since Triton B is the most practical base and KHMDS/18-crown-6 is the most effective base for the reaction with benzaldehyde (and 2*E*-hexenal),[6b] the coordination ability of Na^+ seemed to be too strong for the reaction with benzaldehyde. We therefore decided to use hexamethylphosphoramide (HMPA) (**caution:** HMPA is a highly toxic agent) as a powerful ligand for the metal cation, which was expected to reduce the coordination of the metal cation to the reagent **1**. We were glad to observe that the reaction gave 93% *Z*-selectivity in 86% yield, in the presence of HMPA (2 equiv).[11] Furthermore, 3 or 4 equiv of HMPA gave the same selectivity (entries 3 and 4). In the presence of KI instead of NaI, the deprotonation of **1a** seemed very slow, but the HWE reaction occurred by the addition of benzaldehyde at 0 °C to give 67% *Z*-selectivity in 86% yield (entry 6). The addition of HMPA (4 equiv) after deprotonation with LiCl/DBU gave only a trace amount of the product (entry 7). Since the reaction of **1a** with 2-ethylhexanal occurred in the presence of LiCl in THF (entry 10 in Table 1), HMPA seemed to accelerate protonation of the phophonate enolate with DBU·HCl. Finally, we performed the reaction of **1b** using the best conditions in entry 2. Disappointingly, **1b** showed a lower selectivity than **1a** (entry 9). In addition, the observed selectivity was much lower than that obtained using Triton B (88% vs 97%). Thus, the reaction with benzaldehyde is best performed by using the conditions described in entry 2. It is interesting to note that the HWE reaction of **1a** with benzaldehyde using NaH in THF/HMPA (2 equiv) gave much higher *Z*-selectivity (93%) than using NaH in THF (85%)[6b] (entry 5).

The reaction with 2*E*-hexenal was performed analogously. In the absence of HMPA, the *Z*-selectivity was 81%. Upon adding HMPA (2 eq), the selectivity was 83% for **1a** and 78% for **1b**.

***Z*-Selective Horner−Wadsworth−Emmons Reaction of Functionalized Aldehydes Using NaI−DBU.** Recently, Ibuka and co-workers reported the reaction of **1a** with α-aminoaldehydes **3**-**5** using NaH in THF (method B) or LiCl/iPr$_2$EtN/CH_3CN (method C).[7] In the present study, we compared those results with the reaction using NaI/DBU/THF (method A) (Table 4). The aldehydes **3**−**5** were prepared by Swern oxidation of the corresponding α-amino alcohols and used without purification for the HWE reaction. The yields were calculated from the starting alcohols. Method A in this study gave 81−94% *Z*-selectivities in 54−89% yields. On the other hand, both methods B and C gave much lower *Z*-selectivities and lower yields. It is not clear why method B (NaH) gave low *Z*-selectivities. The *Z*-isomers obtained from the aldehydes **3b** and **4b** were isolated by column chromatography, and their optical rotations were measured. No racemization was detected in these cases. The results in Table 4 show that the HWE reaction of reagent **1a,** using NaI/DBU/THF method, can be applied to the preparation of various *Z*-γ-amino-α,β-unsaturated esters **6** without accompanying racemization (Scheme 2).

We further performed the reaction of **1b** with aldehydes **7** and **8**. When we applied the NaI/DBU/THF

(10) Following the improved preparation procedure of **1a**,[6d] the reagent **1b** was prepared via ditolyphosphite in 44% yield. Although the yield was not higher than the original method,[6b] the isolation of the product was easier than the original one.

(11) HMPA was added to the mixture after deprotonation with NaI/DBU. In the presence of 1 equiv of HMPA, the *Z*-selectivity of the reaction was not reproducible. We did the reaction four times and got 89%, 90%, 91%, 93% *Z*-selectivities in 93−94% yields.

Table 3. HWE Reaction of 1a and 1b in the Presence of DBU in THF[a]

entry	reagent	RCHO	MX	HMPA (equiv)	conditions	% yield[b]	*Z*:*E*	(Triton B)[6b]
1	**1a**	PhCHO	NaI		−78 °C, 2 h	100	88:12	
2	**1a**	PhCHO	NaI	2	−78 °C, 2 h	86(14)	93:7	93:7 (98%)
3	**1a**	PhCHO	NaI	3	−78 °C, 2 h	82(18)	93:7	
4	**1a**	PhCHO	NaI	4	−78 °C, 3 h	83(17)	93:7	
5	**1a**	PhCHO	NaH[c]	2	−78 °C, 2 h	87(11)	93:7	
6	**1a**	PhCHO	KI		0 °C, 2 h	86(14)	67:33	
7	**1a**	PhCHO	LiCl	4	−78 °C, 2 h	trace		
8	**1b**	PhCHO	NaI		−78 °C, 2 h	92(7)	85:15	
9	**1b**	PhCHO	NaI	2	−78 °C, 2 h	86(14)	88:12	97:3 (100%)
10	**1a**	2*E*-hexenal	NaI		−78 → 0 °C	94	81:19	
11	**1a**	2*E*-hexenal	NaI	2	−78 → 0 °C	86(6)	83:17	89:11 (97%)
12	**1b**	2*E*-hexenal	NaI	2	−78 → 0 °C	82(13)	78:22	93:7 (100%)

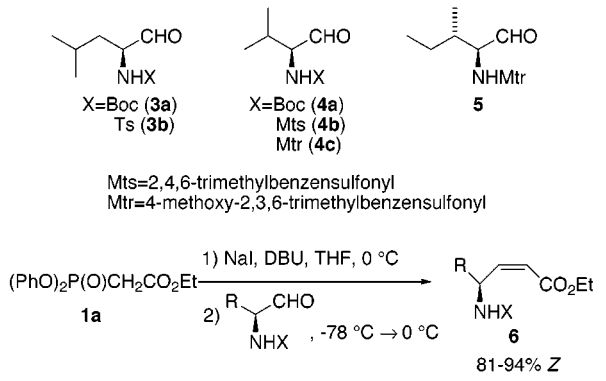
[a] **1** was treated with MX (1.2 equiv) and DBU (1.1 equiv) in THF at 0 °C, and then the reaction with aldehyde was performed. [b] The numbers in parentheses are the recovered yields of **1** (%). [c] DBU was not used.

Table 4. HWE Reaction of 1a and α-Aminoaldehydes 3−5 in the Presence of NaI and DBU in THF (Method A)[a]

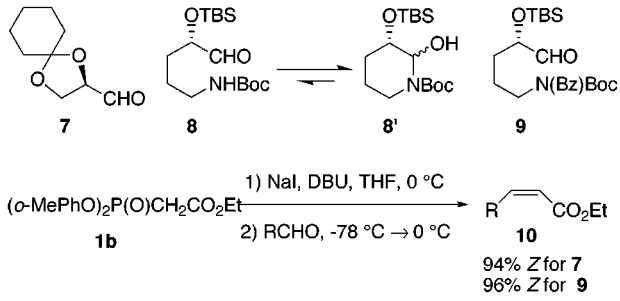
		method A		method B[7]		method C[7]	
entry	RCHO	% yield	*Z*:*E*	% yield	*Z*:*E*	% yield	*Z*:*E*
1	**3a**	66	92:8	29	50:50		
2	**3b**	54	81:19	46	67:33		
3	**4a**	82	94:6	29	50:50		
4	**4b**	89	87:13	86	69:31		
5	**4c**	89[b]	82:18			61	50:50
6	**5**	86[b]	83:17			61	46:54

[a] Method A: **1a** (1.0 equiv), NaI (1.2 equiv), DBU (1.1 equiv), THF. Method B: **1a** (1.0 equiv), NaH (1.2 equiv), THF. Method C: **1a** (1.0 equiv), *i*-Pr_2NEt (1.0 equiv), LiCl (1.0 equiv), CH_3CN−THF. All reactions were performed by warming the mixture from −78 to 0 °C over 0.5−3 h. [b] **1a** (1.5 equiv), NaI (1.7 equiv), DBU (1.6 equiv).

Scheme 2



Scheme 3



procedure (method A) to the reaction of **1b** and **7**, 94% *Z*-selectivity was obtained in 83% yield (Scheme 3 and entry 1 in Table 5). The reaction of **1b** and **7** using NaH (method B) gave a slightly less *Z*-selective result (92%). Since the aldehydes **7**−**9** were prepared by Swern oxidation of the corresponding alcohols and used for the HWE

Table 5. HWE Reaction of 1b and Aldehydes 7−9 in THF[a]

		method A		method B		method D	
entry	RCHO	% yield	*Z*:*E*	% yield	*Z*:*E*	% yield	*Z*:*E*
1	**7**	83	94:6	83	92:8		
2	**8**	∼10		91	93:7	59	78:22
3	**9**	91	96:4	91	70:30	95	75:25[12]

[a] Method A: **1b** (1.0 equiv), NaI (1.2 equiv), DBU (1.1 equiv), THF. Method B: **1b** (1.0 equiv), NaH (1.4 equiv), THF. In both methods A and B, all reactions were performed by warming the mixture from −78 to 0 °C over 1−2 h. Method D: $(CF_3CH_2O)_2P(O)$-CH_2CO_2Me (1.5 equiv), KHMDS in toluene (1.4 equiv), 18-crown-6 (5.0 equiv), THF, −78 °C, 30 min.

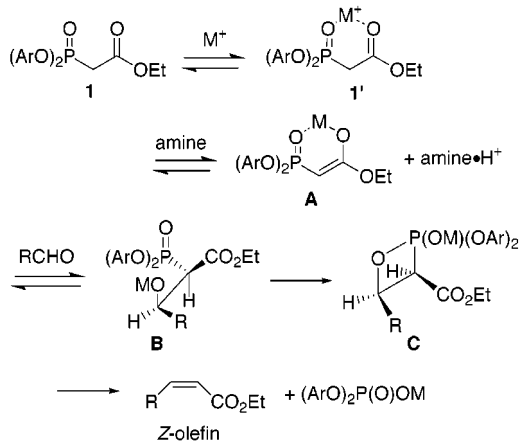
reaction without purification, the yields of these HWE reactions are almost quantitative. The reaction of **1b** and **8** provided an interesting example, which showed the limitation of method A (entry 2). When the reaction of **1b** and **8** was performed using NaI/DBU/THF (method A), only a trace amount of the product was obtained. On the other hand, NaH gave both an excellent *Z*-selectivity (93%) and a high yield (91%). These results can be explained by the predominant formation of the aminohemiacetal **8′**, which cannot react with the anion derived from **1b**. Under the strongly basic conditions (NaH), **8′** is interchangeable with the aldehyde form **8**, which can react with the anion derived from **1b**. To confirm this explanation, we performed the reaction of **1b** with aldehyde **9**, which is the *N*-protected form of **8**. In this case, an excellent result was obtained using NaI/DBU/THF (96% *Z*, 91% yield) (entry 3), and only moderate selectivity was obtained using NaH. It is not clear why the selectivity dropped by using NaH. We would like to add that the reactions of Still's reagent $(CF_3CH_2O)_2P(O)CH_2CO_2Me$ with **8** and **9**[12] in the presence of KHMDS and 18-crown-6 in THF (method D) gave only moderate *Z*-selectivities in both cases.

Discussion

As Masamune and Roush suggested, a metal cation most likely forms a complex with a phosphonate reagent, as shown in **1′**, and thereby enhances the acidity of **1** (Scheme 4). Therefore, **1** can be easily deprotonated using a much weaker base such as an amine. In this study, we showed that the combination of NaI and DBU worked nicely for the *Z*-selective HWE reaction of **1**. The reaction also occurs in the presence of LiCl, NaBr, or KI. However,

(12) Oishi, T.; Iwakuma, T.; Hirama, M.; Ito, S. *Synlett* **1995**, 404−406.

Scheme 4



in those cases, *Z*-selectivities were just moderate. We noticed some solvent effects. From the results in Table 1 (especially entries 1, 3, and 8−10), it may be concluded that the deprotonation of the phosphonate reagent **1** is easier in CH_3CN than in THF. Both LiCl and NaBr are effective metal salts for this reaction in CH_3CN but not in THF. This can be explained by the donor number of solvent[13] (0.36 for CH_3CN, 0.52 for THF, 1.00 for HMPA). The coordination of metal cation to the phosphonate reagent is stronger in a weaker donor solvent (CH_3CN) than in a moderately electron-donating solvent (THF). Thus, the deprotonation occurred in CH_3CN effectively, but the deprotonation in THF using LiCl or NaBr was incomplete. In a stronger donor solvent (THF/HMPA), the reaction using NaI or LiCl is accompanied to some extent by the equilibration between **1** and **A**. Therefore, some quantity of **1** was recovered (see Table 3).

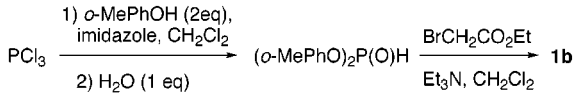
From both the experimental results[1] and ab initio calculations,[14] this HWE reaction most likely occurs following the mechanism shown in Scheme 4. The phosphonate enolate **A** reacts with an aldehyde to form the intermediate **B**, in which the stereochemistry of the developing double bond is established. This is followed by oxaphosphetane formation (**C**), pseudorotation, P−C bond cleavage, and O−C bond cleavage and finally, the *Z*-olefin formation. When benzaldehyde or 2*E*-hexenal is used as aldehyde, electron-withdrawing phenyl or vinyl group reduces the nucleophilicity of oxyanion in **B**. Therefore, the reversibility of the initial carbon−carbon bond-formation step rendered to reduces the *Z*-selectivity. HMPA coordinates to the metal cation and reduces the coordination of the metal cation to the oxyanion in **B**, thereby enhancing its reactivity. Thus, better *Z*-selectivities were obtained in the presence of HMPA (entry 2−5, 9 and 11 in Table 3).

In summary, the HWE reaction of **1** using NaI/DBU/THF gives good to excellent yields of *Z*-α,β-unsaturated esters in high stereoselectivities. The reaction conditions are mild, and all of the reagents used for this method are easily available. The method allows the use of base-labile aldehydes whereas the reaction using the NaH-THF or other conventional methods resulted in low yields and/or low *Z*-selectivities. Furthermore, we have demonstrated one exception in which the aldehyde **8** takes an aminohemiacetal form **8′** predominantly. In this case, the conventional NaH procedure gave an excellent result. Undoubtedly, the above method expands the scope and utility of the *Z*-selective HWE reagents **1**.

Experimental Section

Tetrahydrofuran (THF) was distilled from sodium/benzophenone just before use. All reactions were conducted under an argon atmosphere. All ^1H NMR spectra were recorded in $CDCl_3$.

Ethyl (Di-*o*-tolylphosphono)acetate (1b). To a solution of imidazole (2.084 g, 30 mmol) in CH_2Cl_2 (20 mL) was added PCl_3 (0.88 mL, 10 mmol) and then *o*-cresol (2.07 mL, 20 mmol) at 0 °C. After stirring for 30 min, H_2O (0.18 mL, 10 mmol) was added. The salt was removed by filtration, and the filtrate was treated with ethyl bromoacetate (0.935 mL, 8 mmol) and triethylamine (1.69 mL, 12 mmol) at 0 °C for 10 min. The mixture was stirred for 1 h at room temperature. The reaction was quenched with water (20 mL). The usual extraction and column chromatography (silica gel 35 g/hexane−AcOEt (8:1 to 5:1)) provided **1b** (1.216 g, yield 44% from ethyl bromoacetate) as a colorless oil.



HWE Reaction with 2-Ethylhexanal (Entry 7 in Table 1) (Method A). A solution of **1a** (0.30 mmol) in THF (3 mL) was treated with NaI (0.054 g, 0.36 mmol) and DBU (0.51 mL, 0.33 mmol) at 0 °C for 10 min. After the mixture was cooled to −78 °C, 2-ethylhexanal (0.052 mL, 0.33 mmol) was added. After 10 min, the resulting mixture was warmed to 0 °C over 1.5 h. The reaction was quenched with saturated NH_4Cl, followed by the usual extraction. After the *Z*:*E* ratio of the crude mixture was determined by 500 MHz ^1H NMR, ethyl 4-ethyloctenate[6b] was isolated by flash chromatography as a colorless oil. The reactions in Tables 2, 4, and 5 (method A) were performed in a similar way.

HWE Reaction with Benzaldehyde (Entry 2 in Table 3). A solution of **1a** (0.30 mmol) in THF (6 mL) was treated with NaI (0.054 g, 0.36 mmol) and DBU (0.51 mL, 0.33 mmol) at 0 °C for 10 min followed by HMPA (0.132 mL, 0.76 mmol) for 5 min. After the mixture was cooled to −78 °C, benzaldehyde (0.52 mL, 0.33 mmol) was added. The reaction was quenched 2 h later. The following reaction procedure was the same as method A.

Ethyl (4*S*,2*Z*)-4-[*N*-(*tert*-butoxycarbonyl)amino]-5-methyl-2-hexenoate (entry 3 in Table 4): colorless oil; $[\alpha]^{30}_D$ +102° (*c* 1.18, $CHCl_3$); ^1H NMR (270 MHz) δ 0.94 (3H, d, *J* = 7.0 Hz), 0.95 (3H, d, *J* = 6.5 Hz), 1.30 (3H, t, *J* = 7.0 Hz), 1.43 (9H, s), 1.85−2.05 (1H, m), 4.18 (2H, q, *J* = 7.0 Hz), 4.80−5.01 (2H, m), 5.84 (1H, d, *J* = 11.9 Hz), 6.00−6.12 (1H, m); MS (FAB) *m/e* 272 ($(M + H)^+$), 228, 216 (base peak), 172, 155, 128, 126, 109, 57; HRMS (FAB) calcd for $C_{14}H_{26}NO_4$ ($(M + H)^+$) 272.1862, found 272.1854. To confirm the selectivity, the *E*-isomer was separately prepared as follows.

Ethyl (4*S*,2*E*)-4-[*N*-(*tert*-butoxycarbonyl)amino]-5-methyl-2-hexenoate. To a solution of $(i\text{-PrO})_2P(O)CH_2CO_2Et$ (0.55 mmol) in toluene (2 mL) was added *n*-BuLi in *n*-hexane (0.359 mL, 0.55 mmol) at 0 °C. After 10 min, the aldehyde **4a** (obtained from the alcohol (0.5 mmol)) in toluene (1 mL) was added at 0 °C, and the resulting mixture was stirred for 1 h at this temperature. The following procedure was the same as described in method A. After the *Z*:*E* ratio of the crude mixture was determined by 270 MHz ^1H NMR, the product was isolated by flash chromatography as a colorless oil (83 mg, 61% yield; *E*:*Z* = 95:5): $[\alpha]^{31}_D$ +1.2° (*c* 0.690, $CHCl_3$); ^1H NMR (270 MHz) δ 0.92 (3H, d, *J* = 7.0 Hz), 0.94 (3H, d, *J* = 7.0 Hz), 1.29 (3H, t, *J* = 7.3 Hz), 1.45 (9H, s), 1.81−1.94 (1H, m), 4.14−4.24 (1H, m), 4.20 (2H, q, *J* = 7.3 Hz), 4.55−4.64 (1H, m), 5.92 (1H, dd, *J* = 15.4, 1.6 Hz), 6.86 (1H, dd, *J* = 15.4, 5.4 Hz); MS (FAB) *m/e* 272 ($(M + H)^+$), 216, 172, 128, 126 (base peak), 57; HRMS (FAB) calcd for $C_{14}H_{26}NO_4$ ($(M + H)^+$) 272.1862, found 272.1863.

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Ethyl (4*S*,2*Z*)-4,5-(Cyclohexylidenoxy)pentenoate[15] (Entry 1 in Table 5). After the *Z*:*E* ratio of the crude mixture was determined by 500 MHz ^{1}H NMR, the product was isolated by flash chromatography as a colorless oil: $[\alpha]^{27}_D$ +85.4° (*c* 1.03, $CHCl_3$) for method A; $[\alpha]^{27}_D$ +84.6° (*c* 1.05, $CHCl_3$) for method B; ^{1}H NMR (200 MHz) δ 1.28 (3H, t, J = 7.1 Hz), 1.34−1.47 (2H, m), 1.51−1.72 (8H, m), 3.61 (1H, dd, J = 8.3, 6.8 Hz), 4.17 (2H, q, J = 7.1 Hz), 4.36 (1H, dd, J = 8.3, 6.8 Hz), 5.50 (1H, dq, J = 6.8, 1.7 Hz), 5.83 (1H, dd, J = 11.7, 1.7 Hz), 6.36 (1H, dd, J = 11.7, 6.8 Hz); ^{13}C NMR (50 MHz) δ 14.16, 23.81, 25.12, 34.89, 36.20, 60.39, 69.31, 73.14, 110.38, 120.64, 149.54, 165.65; MS (CI) *m*/*e* 240 (M^+), 125 (base peak). Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.95; H, 8.10.

Ethyl (4*S*,2*Z*)-7-[*N*-(*tert*-butoxycarbonyl)amino]-4-(*tert*-butyldimethylsilyl)oxy]heptenoate (entry 2 in Table 5): colorless oil; $[\alpha]^{28}_D$ −9.8° (*c* 0.80, $CHCl_3$) for method B; ^{1}H NMR (200 MHz) δ 0.00 (3H, s), 0.04 (3H, s), 0.87 (9H, s), 1.29 (2H, t, J = 7.1 Hz), 1.43 (9H, s), 1.44−1.60 (4H, m), 3.04−3.22 (2H, m), 4.17 (2H, q, J = 7.1 Hz), 5.24−5.36 (2H, m), 5.70 (1H, dd, J = 11.7, 1.2 Hz), 6.16 (1H, dd, J = 11.7, 8.0 Hz); ^{13}C NMR (50 MHz) δ −4.87, −4.55, 14.23, 18.09, 25.53, 25.82, 28.42, 34.40, 40.30, 60.20, 68.41, 117.84, 153.59, 155.96, 165.89; MS (CI) *m*/*e* 402 ($(M + H)^+$), 244 (base peak). Anal. Calcd for $C_{20}H_{39}O_5NSi$: C, 59.81; H, 9.79; N, 3.49. Found: C, 59.68; H, 9.93; N, 3.38.

Ethyl (4*S*,2*Z*)-7-[*N*-(*tert*-butoxycarbonyl)-*N*-(benzoyl)-amino]-4-[(*tert*-butyldimethylsilyl)oxy]heptenoate (entry 3 in Table 5): colorless oil; $[\alpha]^{30}_D$ −5.5° (*c* 1.04, $CHCl_3$) for method A; $[\alpha]^{30}_D$ −5.0° (*c* 0.82, $CHCl_3$) for method B; ^{1}H NMR (200 MHz) δ 0.01 (3H, s), 0.05 (3H, s), 0.87 (9H, s), 1.14 (9H, s), 1.28 (2H, t, J = 7.2 Hz), 1.50−1.90 (4H, m), 3.75−3.87 (1H, m), 4.16 (2H, q, J = 7.2 Hz), 5.26−5.40 (1H, m), 5.69 (1H, dd, J = 11.8, 1.3 Hz), 6.16 (1H, dd, J = 11.8, 8.1 Hz), 7.31−7.70 (5H, m); ^{13}C NMR (50 MHz) δ −4.87, −4.58, 14.24, 18.10, 24.66, 25.83, 27.36, 34.82, 45.74, 60.11, 68.52, 82.71, 117.98, 127.35, 127.99, 130.79, 138.20, 153.17, 153.52, 165.77, 173.18; MALDI-TOF MS *m*/*e* calcd for $C_{27}H_{43}O_6NSiNa$ ($(M + Na)^+$) 528.2755, found 528.2693. Anal. Calcd for $C_{27}H_{43}O_6NSi$: C, 64.13; H, 8.57; N, 2.77. Found: C, 63.99; H, 8.82; N, 2.71.

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