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Highly *E*-selective solvent-free Horner–Wadsworth–Emmons reaction catalyzed by DBU†

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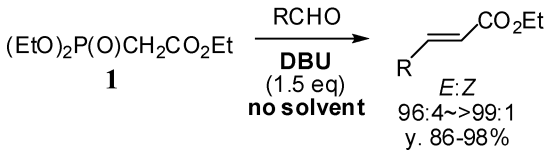
The solvent-free Horner–Wadsworth–Emmons reaction of triethyl phosphonoacetate with a variety of aldehydes was catalyzed by DBU in the presence of K_2CO_3 to give *E*-α,β-unsaturated esters highly selectively (99 : 1 for most of the reactions). The reaction with ketones gave trisubstituted olefins with good to high *E*-selectivity by DBU-Cs_2CO_3.

Due to environmental concerns, safety considerations, reduction of costs, and the simplicity of the process, solvent-free reactions have drawn great attention in recent years.[1] Furthermore, an increased reactivity is expected due to the intimacy of the reagents. The stereo-defined synthesis of carbon–carbon double bonds with high selectivity is critically important for not only the synthesis of the olefinic compounds but also for stereoselective reactions. The Horner–Wadsworth–Emmons modification of the Wittig reaction is a widely used method for the preparation of α,β-unsaturated esters.[2] The phosphonate anions are strongly nucleophilic and react readily with carbonyl compounds under mild conditions to form olefins in good yields. As far as we know, only a few reports described the solvent-free Horner–Wadsworth–Emmons (HWE) reaction before we started this project. One is the solid phase reaction by milling a highly π-conjugated solid aldehyde with *p*-Ar-benzylphosphonates using *t*-BuOK[3a–3b] and the other is the silica gel catalyzed reaction using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base reported by Inanaga and co-workers.[3c] During the course of our study on the *Z*-selective HWE reagents, $(ArO)_2P(O)CH_2CO_2Et$,[4] we found their reaction with PhCHO using DBU proceeded quickly in the absence of silica gel to give mainly *E*-ethyl cinnamate. Using the conventional HWE reagents, such as triethyl phosphonoacetate **1**, *E*-α-unsaturated esters and ketones were obtained in high yields with 96 to >99% *E*-selectivity (Scheme 1).[5] Although the used DBU was recovered in a high yield, it is desirable to avoid the use of a stoichiometric amount of amine. Here, we would like to report the solvent-free HWE reaction catalyzed by DBU (as little as 0.03 eq. for the reaction with aldehydes) in the presence of K_2CO_3 as a base.

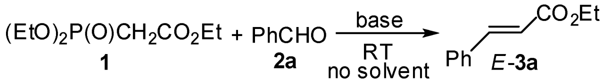


Scheme 1 Solvent-free Horner–Wadsworth–Emmons reaction using DBU.

The solvent-free HWE reaction of **1** with benzaldehyde was carried out in the presence of several inorganic bases. As shown in Table 1, NaOH, KOH, K_2CO_3, Cs_2CO_3, and K_3PO_4 can promote the reaction to some extent in 98 : 2 to 99 : 1 *E*-selectivity (51–80% yield).[6] However, the combined yield of the product **3a** and the recovered **1** was rather low in the cases of NaOH and KOH (entries 1–2). That is, both NaOH and KOH induced some decomposition of **1** during the reaction. Although the reaction using Cs_2CO_3 gave highest 80% yield after 2 h, we chose K_2CO_3 as an inorganic base because of its low price.

The HWE reaction using K_2CO_3 as a base was further studied (Table 2). As shown in entry 4 in Table 1, 51% yield of *E*-**3a** was obtained by stirring with 2 eq. of K_2CO_3 (molar ratio of **1**: K_2CO_3 = 1 : 2) for 2 h. We hypothesized the moderate yield was due to the inefficient mixing. When the reaction was performed

Table 1 Effect of an inorganic base on the solvent-free HWE reaction of **1** with benzaldehyde[a]



Entry	Base (mmol)	Time (h)	Yield%[b]	*E* : *Z*
1	NaOH (2.0)	2	53 (15)	99 : 1
2	KOH (2.0)	2	74 (7)	99 : 1
3	Na_2CO_3 (2.0)	2	—	—
4	K_2CO_3 (2.0)	2	51 (49)	98 : 2
5	Cs_2CO_3 (2.0)	2	80 (20)	98 : 2
6	K_3PO_4 (1.0)	2	63 (27)	99 : 1

[a] 1.0 mmol of **1** and 1.0 mmol of **2a** were used except for entry 4, where 1.0 mmol of **1** and 1.1 mmol of **2a** were used. [b] The yields are isolated yields and the numbers in parentheses are the recovered yields of **1** (%) calculated from the NMR spectra of the crude mixture.

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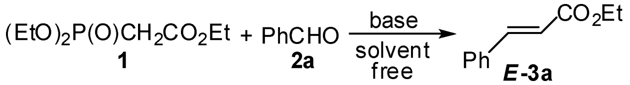
† Electronic supplementary information (ESI) available: Typical experimental procedures (entry 11 in Table 3 and entry 10 in Table 4) and the NMR charts of all the products. See DOI: 10.1039/c1gc15134g

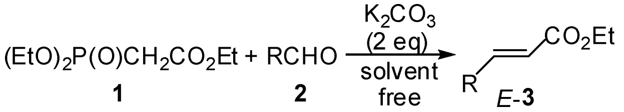
Table 2 HWE reaction of **1** with benzaldehyde using K_2CO_3



Entry	K_2CO_3	DBU (eq)	H_2O (eq)	Condition[a]	Yield%[b]	*E* : *Z*
1	2.0	—	—	RT, 2 h	51	98 : 2
2	2.0	—	8	RT, 2 h	73	99 : 1
3	2.0	—	8	RT, 6 h	96	99 : 1
4	2.0	—	11	RT, 2 h	52	98 : 2
5	2.0	—	111[c]	RT, 2 h	31	96 : 4
6	2.0	0.1	8	RT, 2 h	93	99 : 1
7	2.0	0.1	—	RT, 2 h	Quant.	99 : 1
8	2.0	0.05	—	RT, 2 h	Quant.	99 : 1
9	2.0	0.03	—	RT, 2 h	96	99 : 1
10	2.0	0.01	—	RT, 2 h	87	99 : 1
11	1.5	0.03	—	RT, 2 h	61	99 : 1

[a] 1.0 mmol of **1** and 1.1 mmol of **2a** were used. [b] Isolated yields. [c] The reaction was performed in water (0.5 mol L^{-1}).

Table 3 The solvent-free HWE reaction of **1** with various aldehydes using K_2CO_3-DBU



Entry	*R*	DBU (eq)	Conditions[a]	Yield %[b]	*E* : *Z*
1	Ph	0.03	RT, 2 h	**3a** 96	99 : 1
2[c]	Ph	0.03	RT, 5 h	**3a** 95	99 : 1
3	*p*-ClC_6H_4	0.03	RT, 2 h	**3b** 82	99 : 1
4[d]	*p*-ClC_6H_4	0.1	RT, 5 h	**3b** 97	99 : 1
5	*p*-ClC_6H_4	0.2	RT, 2 h	**3b** 95	99 : 1
6	*p*-$MeOC_6H_4$	0.03	RT, 20 h	**3c** 81	99 : 1
7	*p*-$MeOC_6H_4$	0.03	25 °C, 24 h	**3c** 99	99 : 1
8	*o*-MeC_6H_4	0.03	RT, 2 h	**3d** 93	99 : 1
9	Furfural	0.03	RT, 2 h	**3e** 92	99 : 1
10	*E*-PhCH=CH	0.03	RT, 4 h	**3f** 89	99 : 1
11	*n*-C_7H_{15}	0.03	RT, 4 h	**3g** 96	99 : 1
12[e]	*n*-C_7H_{15}	0.03	25 °C, 7 h	**3g** 93	99 : 1
13	*c*-C_6H_{11}	0.03	RT, 4 h	**3h** 97	99 : 1
14	2-EtPentyl	0.03	RT, 24 h	**3i** 95	99 : 1
15	*t*-Bu	0.03	RT, 24 h	**3j** 92	>99 : 1
16	BnOCHMe	0.03	RT, 3 h	**3k** 94	98 : 2

[a] 1.0 mmol of **1** and 1.1 mmol of **2** were used except for entries 2 and 12. [b] Isolated yields. [c] 10 mmol scale reaction. [d] The reaction was performed in the presence of 8 eq. of H_2O. [e] 30 mmol scale reaction.

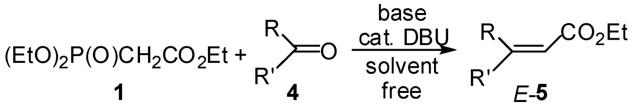
in the presence of 8 eq. of water, *E*-**3a** was obtained in 73% yield after 2 h and 96% yield after 6 h (entries 2–3). However, in the presence of more than 11 eq. of water, the reaction was slower than the solvent-free reaction and gave lower selectivity (96 : 4) (entries 4–5). The catalytic activity of DBU was next examined. In the presence of 0.1 eq of DBU, the reaction proceeded faster than the reaction in entry 2 to give *E*-**3a** in 93% yield after 2 h (entry 6). In the absence of water, the reaction catalyzed by DBU proceeded more efficiently to give a quantitative yield with 99 : 1 selectivity (entry 7). Although even as little as 0.01 eq. of DBU can catalyze the reaction to give 87% yield after 2 h, the use of 0.03 eq. of DBU was set for the standard reaction conditions (entries 8–10). The reduction of the quantity of K_2CO_3 to 1.5 eq. resulted in lower 61% yield (entry 11).

The solvent-free HWE reaction of **1** with a variety of aldehydes were performed using K_2CO_3 (2 eq.) and DBU (0.03 eq.) and the results are summarized in Table 3.‡ Although the 10 mmol scale reaction needed a longer time (5 h) to complete the reaction with benzaldehyde, 95% yield with 99 : 1 selectivity was obtained (entry 2). The reaction with *p*-chlorobenzaldehyde gave *E*-**3b** in 82% yield with 99 : 1 selectivity (entry 3). Since *p*-chlorobenzaldehyde is a solid aldehyde and the reaction mixture completely solidified 2 h later, we were afraid that the reaction did not go to completion. When the reaction was performed in the presence of 8 eq. of water or by increasing the quantity of DBU to 0.2 eq., 97 and 95% yields were obtained with the same 99 : 1 selectivity (entries 4–5). The reaction mixture of *p*-methoxybenzaldehyde also solidified completely and the reaction did not go to completion after 20 h to give 81% yield (entry 6). When the reaction mixture was stirred vigorously at 25 °C,[8] solidification did not occur and the yield was improved to 99% (entry 7). For the reaction with other aromatic aldehydes, *o*-tolualdehyde and furfural, *E*-olefins were obtained without difficulty in 92–93% yield with 99 : 1 selectivity by using the standard conditions. The reaction with α-unsaturated aldehyde, *E*-cinnamaldehyde also proceeded easily to give the *E*,*E*-diene in 89% yield. The reaction with aliphatic aldehydes, *n*-octanal, cyclohexancarboxaldehyde, 2-ethylhexanal, and pivalaldehyde also gave *E*-olefins in 92–97% yields with 99 : 1 selectivity (entries 11–15). The 30 mmol scale reaction was performed at 25 °C to give *E*-**3g** in 93% yield with 99 : 1 selectivity after 7 h (entry 12). The reaction of 2-benzyloxypropanal gave *E*-**3k** in 94% yield with 98 : 2 selectivity. The same reaction in DME using BuLi gave *E*/*Z* = 90 : 10 selectivity.[4b] The *E*-selectivity of the HWE reaction with aldehydes having an α-oxygen functional group is generally not high and the HWE reaction with those aldehydes occasionally gave *Z*-olefins selectively.[9] Thus, we succeeded in not only reducing the quantity of DBU but also increasing the *E*-selectivity. Since *E*-α,β-unsaturated esters are versatile intermediates in organic synthesis, the development of experimentally simple and highly *E*-selective protocols are still needed.[10]

Solvent-free purification of the products was next attempted. When the reaction of **1** (10 mmol) with benzaldehyde (10 mmol) in the presence of K_2CO_3 (20 mmol) and DBU (0.3 mmol) was completed, the reaction mixture was directly distilled under reduced pressure using a bulb-to-bulb apparatus. Disappointingly, only 33% yield of the product was obtained (*E* : *Z* = 98 : 2). When the residue was extracted with AcOEt, 58% of the product was further obtained (*E* : *Z* = 99 : 1). Thus direct distillation without using organic solvent is not practical. After the reaction mixture was dissolved in AcOEt (2 mL) and the mixture was filtered, the olefin was isolated in 84% yield by distillation.§ The total amount of the used AcOEt was 8 mL. Thus, we could reduce the quantity of organic solvent for the purification.

The solvent-free HWE reaction of **1** with ketones was studied and the results are shown in Table 4. We have already reported the solvent-fee HWE reaction of **1** with cyclohexanone using DBU (3 eq.).[5] Unfortunately, the reaction proceeded very slowly to give **5a** in only 20% yield after 45 h. However, in the presence of K_2CO_3 (2 eq.) and DBU (0.05 eq.), the reaction gave **5a** in 79% yield after 2 d and in 88% yield by increasing the quantity of DBU (0.2 eq.) (entries 1 and 2).

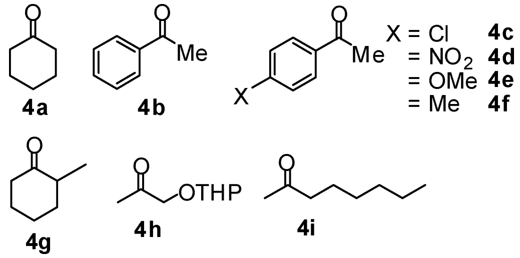
Table 4 The solvent-free HWE reaction of **1** with various ketone catalyzed by DBU[a]



Entry	Ketone	Base, eq.	DBU (eq)	Conditions	Yield %[b]	$E:Z$
1	**4a**	K_2CO_3 2.0	0.05	RT, 2 d	**5a** 79	—
2	**4a**	K_2CO_3 2.0	0.2	RT, 2 d	**5a** 88	—
3	**4a**	K_2CO_3 2.0	0.05[c]	RT, 2 d	**5a** 83	—
4[d]	**4a**	Cs_2CO_3 1.2	0.2	RT, 18 h	**5a** 84	—
5	**4b**	K_2CO_3 2.0	0.6	60 °C, 16 h	**5b** 48	98:2
6	**4b**	Cs_2CO_3 1.2	0.2	RT, 3 d	**5b** 64	97:3
7[e]	**4b**	Cs_2CO_3 1.2	0.2	40 °C, 3 d	**5b** 81	97:3
8[d]	**4b**	K_3PO_4 1.0	0.3	RT, 5 d	**5b** 65	97:3
9	**4c**	Cs_2CO_3 1.2	0.2	RT, 3 d	**5c** 80	95:5
10	**4d**	Cs_2CO_3 1.2	0.2	RT, 3 d	**5d** 78	99:1
11	**4e**	Cs_2CO_3 1.2	0.2	RT, 3 d	**5e** 37	91:9
12	**4e**	Cs_2CO_3 1.2	0.2	25 °C, 7 d	**5e** 50	97:3
13	**4f**	Cs_2CO_3 1.2	0.2	RT, 3 d	**5f** 52	87:13
14	**4f**	Cs_2CO_3 1.2	0.2	25 °C, 3 d	**5f** 63	94:6
15	**4f**	Cs_2CO_3 1.2	0.2	40 °C, 3 d	**5f** 81	97:3
16[d]	**4g**	Cs_2CO_3 1.2	0.2	RT, 3 d	**5g** 72	81:19
17	**4h**	K_2CO_3 1.5	0.2	RT, 1 d	**5h** 78	66:34
18	**4i**	Cs_2CO_3 1.2	0.2	RT, 3 d	**5i** 80	79:21

[a] 1.0 mmol of **1** and 1.0 mmol of **4** were used unless otherwise noted. [b] Isolated yields. [c] TMG was used instead of DBU. [d] 1.2 mmol of **1** and 1.0 mmol of **4** were used. [e] 1.0 mmol of **1** and 1.2 mmol of **4** were used.

1,1,3,3-Tetramethylguanidine (TMG) was also effective to give **5a** in 83% yield (entry 3).[5] It is interesting to note that Simoni *et al.* reported that no olefinic products were detected from the reaction of **1** with cyclohexanone and aliphatic ketones using TMG, 1,5,7-triazabicylco[4.4.0]dec-5-ene (MTB) and its methyl derivative (MTBD) in refluxing THF after 24 h.[11,12] In contrast to aldehydes, both the HWE reaction and the Wittig reaction with ketones generally gave olefins with low to moderate *E*-selectivity in low to moderate yields.[2,7g,7h,11,13] When the reaction of **1** with acetophenone **4b** was performed in a similar manner, the reaction hardly proceeded at all. Increasing the amount of DBU to 0.6 eq. and increasing the temperature to 60 °C, 48% yield of **5b** was obtained after 16 h with very high 98 : 2 selectivity (entry 5). Using 1.2 eq. of Cs_2CO_3 or 1.0 eq. of K_3PO_4 instead of K_2CO_3, 81% and 65% yields were obtained with 97 : 3 *E*-selectivity (entries 7 and 8). The reaction of **1** with the *p*-Cl and *p*-NO_2 substituted acetophenones **4c–4d** also gave very high 95 : 5 and 99 : 1 selectivity in high yields using Cs_2CO_3 and DBU (0.2 eq.) (entries 9 and 10). When the reaction of **1** with *p*-methoxyacetophenone **4e** was performed using the same conditions, only 37% yield was obtained with 91 : 9 selectivity at room temperature[8] (entry 11). Happily, when the reaction was performed at 25 °C, 97 : 3 selectivity was obtained in 50% yield (entry 12). At 40 °C, the same selectivity and the same yield were obtained. The improvement of the selectivity at higher temperature was also observed for *p*-methylacetophenone **4f**. Although 87 : 13 selectivity was obtained at room temperature,[8] the selectivity was increased to 94 : 6 at 25 °C and to 96 : 4 at 40 °C (entries 13–15). The reaction with 2-methylcyclohexanone **4g** in the similar conditions gave 72% yield with 81 : 19 *E*-selectivity (entry 16). The reaction of α-tetrahydropyranyloxy acetone **4h** was less *E*-selective. It seems that the α-oxygen functionality reduced the *E*-selectivity. The reaction with 2-octanone **4i** gave 80% yield with 79 : 21 *E*-selectivity at room temperature (entry 18). The reaction with the aliphatic ketones **4g** and **4i** at 25 °C did not improve the selectivity and 79 : 21 *E*-selectivity was obtained in 70% and 74% yields, respectively. Although the solvent-free HWE reaction of **1** with the aliphatic ketones gave the trisubstituted olefins in moderate *E*-selectivity, the reaction with the substituted acetophenones using Cs_2CO_3 and DBU showed outstanding *E*-selectivity and very useful for the synthesis of those trisubstituted olefins.



In the presence of M_2CO_3 (M = K, Cs), DBU can easily deprotonate the phosphonate reagent **1** to give the enolate (Fig. 1). A similar explanation was suggested for the HWE reaction of **1** in the presence of LiCl-DBU by Masamune and Roush.[14] The HWE reaction occurs with the addition of the enolate to aldehydes, followed by oxaphosphetane formation, P–C bond cleavage, and then O–C bond cleavage to give the olefins.[15] The oxaphosphetane formation TS2 is the rate-determining step and *E*-TS2 is more stable than *Z*-TS2 because of the steric repulsion between the ester moiety and the alkyl substituent of aldehydes in *Z*-TS2.[14] Therefore, *E*-olefins were obtained selectively. Also, it should be noted that DBU can be reproduced by the reaction of the protonated DBU with M_2CO_3. When **3g** ($E:Z = 95:5$) prepared from **1** using BuLi in DME at 0 °C was treated with K_2CO_3 (2 eq.) and DBU (0.03 eq.) for 4 h, neither the isomerization nor the decomposition was observed. Thus, the $E:Z$ ratio of the product prepared from **1** with aliphatic aldehyde was not changed under the reaction conditions. However, when **5f** ($E:Z = 87:23$) (entry 13 in Table 4) was treated with Cs_2CO_3 (1.2 eq.) and DBU (0.2 eq.) at 25 °C for 3 d, the $E:Z$ ratio was improved to 90 : 10 without decomposition. We believe the high *E*-selectivity obtained in the solvent-free conditions described here was mainly kinetically controlled. However, some isomerization to the more thermodynamically stable *E*-olefins may occur especially for the reaction with aromatic ketones.

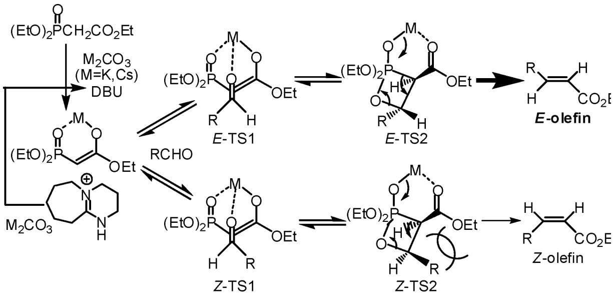


Fig. 1 The reaction mechanism of the solvent-free HWE reaction.

In summary, we showed the solvent-free HWE reaction of **1** with aldehydes can be catalyzed by DBU (as little as 0.03 eq.) in the presence of K_2CO_3 as a base. The reaction with a variety of aldehydes gave high yields of the *E*-olefins with extremely high *E*-selectivity (in most of the cases, 99 : 1 selectivity). After filtration, almost pure products can be easily obtained by distillation under reduced pressure. The HWE reaction of **1** with the substituted acetophenones using Cs_2CO_3 and DBU also showed outstanding *E*-selectivity and is very useful for the synthesis of trisubstituted olefins. Since it is very difficult to separate the *E* and *Z* isomers, it is important to prepare the olefins highly selectively. We believe the method reported here is simple, environmentally friendly, and safe, and it does not require any expensive catalysts or bases. The additional advantages of work-up simplicity, reproducibility, and extremely high *E*-selectivity make this methodology a serious candidate for not only laboratory use but also widespread industrial applications.

Acknowledgements

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Notes and references

‡ A typical experimental procedure (entry 12 in Table 3): To a mixture of **1** (6.73 g, 30 mmol), DBU (0.13 mL, 0.9 mmol), and finely ground K_2CO_3 (8.29 g, 60 mmol) was added *n*-octanal (5.15 mL, 33 mmol) and the resulting mixture was stirred using a magnetic stirrer for 7 h at 25 °C under Ar atmosphere. The reaction was quenched with water (20 mL) and extracted with AcOEt (2 × 10 mL). The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated to give **4g** ($E : Z = 99 : 1$). The product was isolated by flash chromatography (hexane–AcOEt = 15 : 1) as a colorless oil (5.52 g, 93% yield).

§ To a mixture of **1** (2.24 g, 10 mmol), DBU (0.045 mL, 0.3 mmol), and finely ground K_2CO_3 (2.77 g, 20 mmol) was added PhCHO (1.01 mL, 10 mmol) and the resulting mixture was stirred using a magnetic stirrer for 4 h at room temperature under Ar atmosphere. AcOEt (2 mL) was added to the crude mixture and the solid was filtered off. The solid was rinsed with AcOEt (6 mL) and the combined filtrate was concentrated. The resulting oil was distilled under reduced pressure using a bulb-to-bulb apparatus (10 mm Hg/240 °C) to give **3a** (1.51 g, yield 84%) ($E : Z = 99 : 1$).

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