



New polymer-supported phosphonate reagents for the synthesis of *Z*- α,β -unsaturated esters

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ABSTRACT

New polymer-supported phosphonate reagents have been prepared and evaluated for the synthesis of *Z*- α,β -unsaturated esters. High *Z*-selectivity was obtained using the reagent having two *ortho*-*t*-BuC₆H₄ groups.

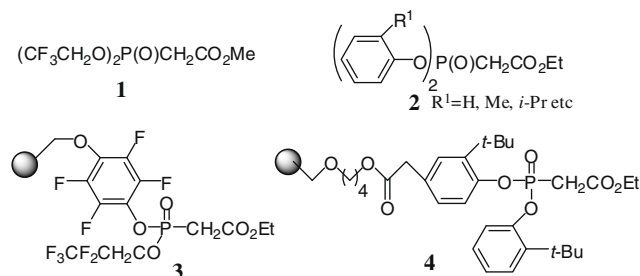
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Polymer-supported reagents have been regarded as one of the valuable tools in synthetic organic chemistry.¹ The products of solid-phase synthesis can be easily purified with simple filtration and evaporation of the solvents, making this method attractive in both technical and practical terms. The use of the polymer-supported Wittig reagents² and Horner–Wadsworth–Emmons reagents³ has been reported. These reagents having electron-withdrawing group such as a carbonyl group gave *E*-olefins with high selectivity. These methods are useful not only for rapid purification, but also for the multi-step organic synthesis.^{3a,c} For the synthesis of *Z*- α,β -unsaturated esters, Martina and Taylor prepared the first *Z*-selective polymer-supported HWE reagents,⁴ which are hybrid of both the Still–Gennari and Ando reagents (**1** and **2** in Scheme 1). Although both the Still–Gennari reagent **1**⁵ and the Ando reagents **2**^{6,7} gave a wide range of *Z*- α,β -unsaturated esters highly selectively, the *Z*-selectivity of the Taylor's solid-supported reagents was rather low and even the best results obtained from the reagent **3** was only 60–77% selectivity. Therefore, we decided to prepare new *Z*-selective polymer-supported HWE reagents and evaluate their reactivity and selectivity for the synthesis of *Z*- α,β -unsaturated esters.

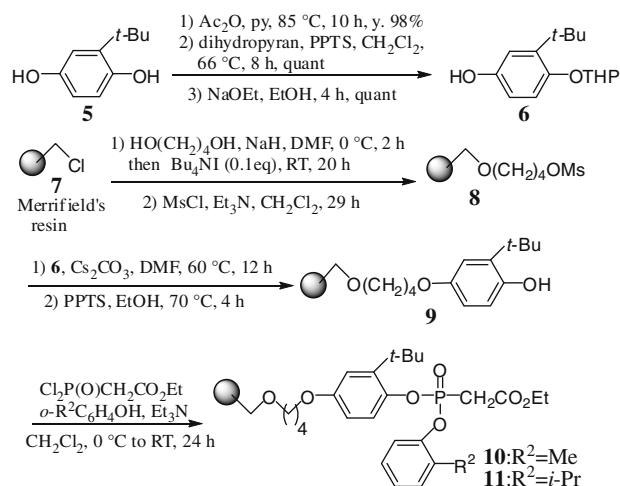
Here we wish to report that our new reagent **4** reacts with a variety of aromatic, saturated, and unsaturated aldehydes to give *Z*- α,β -unsaturated esters in high selectivity.

During the course of our study on the *Z*-selective HWE reagents **2**, we found the reagents having the *ortho*-substituted phenyl groups (R¹ = Me and *i*-Pr in **2**) to show extremely high *Z*-selectivity to give α,β -unsaturated esters in almost quantitative yields.^{6b} Therefore, we planned to prepare the reagents having two *ortho*-substituted phenyl groups, one of them is bound to the polymer via a linear spacer.

t-Butylhydroquinone **5** was selectively monoacetylated and the remaining hydroxyl group was protected with THP group in 98% and quantitative yields, respectively (Scheme 2). After hydrolysis with sodium ethoxide, the phenol **6** was obtained in a quantitative yield. Merrifield resin **7** (200–400 mesh, 1.0–1.5 mmol/g Cl[−], 1% cross linked, product number: 221481 purchased from Aldrich)



Scheme 1.



Scheme 2.

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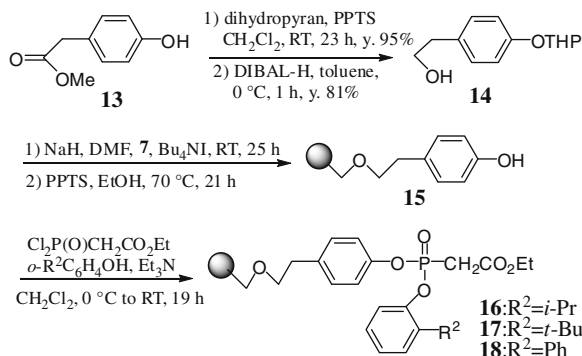
was converted to the mesylate **8** by the reaction with 1,4-butanediol in the presence of NaH in DMF followed by the treatment with methanesulfonyl chloride in the presence of triethylamine. The mesylate resin **8** was reacted with **6** and Cs₂CO₃ in DMF and then the THP ether was cleaved to afford the polymer-bound phenol **9**. The reaction of ethyl dichlorophosphonoacetate^{6b} with 1 equiv of *o*-cresol or *o*-*i*-propylphenol in the presence of 1.2 equiv of triethylamine, followed by 1 equiv of **9** and 1.2 equiv of triethylamine afforded the polymer-supported phosphonate reagents **10** and **11**.

The HWE reaction of the THF swollen resins **10** and **11** with 2-ethylhexanal was carried out. The results are summarized in Table 1. After the *o*-Me reagent **10** was treated with NaH at 0 °C for 30 min, the reaction with aldehyde was performed at –78 °C to room temperature over 2–4 h (entry 1). Only 28% yield of **12a** was obtained in moderate *Z*-selectivity (70:30). The use of NaI–DBU^{6e} as a base gave a slightly higher selectivity (entry 2). Increasing the equivalents of **10** gave both higher yields and higher *Z*-selectivity (entries 3 and 4). Thus, 83:17 selectivity was obtained in 63% yield using 3.1 equiv of **10**. Disappointingly, the use of *o*-*i*-Pr reagent **11** resulted in both a lower yield and lower *Z*:*E* ratio. Because of the unfavorable steric repulsion derived from the *i*-Pr group, the loading yield of **11** seemed to be poor. For the moderate *Z*-selectivity of **10**, we speculated that *p*-alkoxy group bound to the polymer might reduce the *Z*-selectivity since the HWE reaction of (*p*-MeOC₆H₄O)₂P(O)CH₂CO₂Et with aldehydes showed lower selectivity than **2** (R¹ = H). On the other hand, (*p*-MeC₆H₄O)₂P(O)CH₂CO₂Et has almost the same selectivity as **2** (R¹ = H).

We planned to use methyl 4-hydroxyphenylacetate **13** (Scheme 3). The ester group was reduced with DIBAL-H after the protection of the hydroxyl group to give **14**. Merrifield resin **7** was reacted with the anion of **14** followed by the deprotection to give the polymer-bound phenol **15**. The reagents **16–18** were prepared from **15**, ethyl dichlorophosphonoacetate, and *o*-substituted phenol in a similar manner to that for **10** and **11**.

Table 1
The HWE reaction of **10** and **11** with 2-ethylhexanal

Entry	Reagent	Equiv	Base	Yield (%)	<i>Z</i> : <i>E</i>
1	10	1.2	NaH (2.6 equiv)	28	70:30
2	10	1.2	NaI, DBU (1.3 equiv)	22	78:22
3	10	2.0	NaI, DBU (3 equiv)	42	83:17
4	10	3.1	NaI, DBU (3.1 equiv)	63	83:17
5	11	3.1	NaI, DBU (3.1 equiv)	32	72:28



Scheme 3.

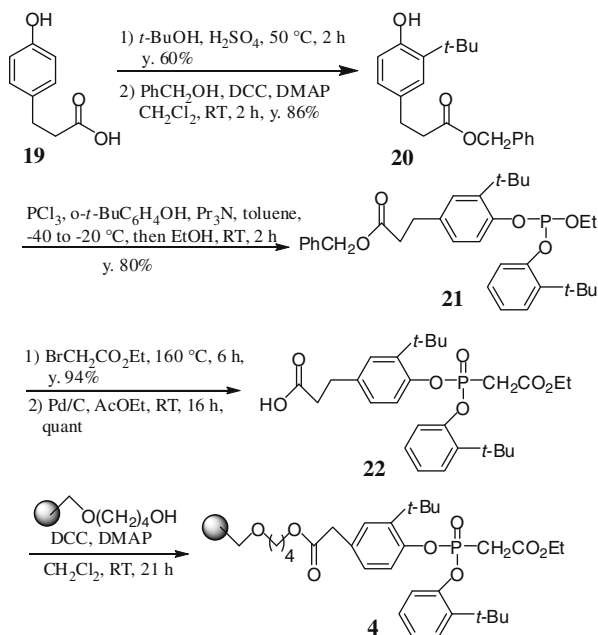
Table 2
The HWE reaction of **16–18** with aldehydes

Entry	Reagent	RCHO	Base	Yield (%)	<i>Z</i> : <i>E</i>
1	16	2-Et-Hexanal	NaH	62	81:19
2	16	2-Et-Hexanal	NaI, DBU	66	88:12
3	16	PhCHO	<i>t</i> -BuOK	95	75:25
4	17	2-Et-Hexanal	NaI, DBU	64	88:12
5	17	PhCHO	<i>t</i> -BuOK	80	83:17
6	17	<i>n</i> -Octanal	NaH	46	83:17
7	18	2-Et-Hexanal	NaI, DBU	91	89:11
8	18	PhCHO	<i>t</i> -BuOK	91	88:12
9	18	<i>n</i> -Octanal	NaH	49	83:17

The results of the HWE reaction of **16–18** with three types of aldehydes are summarized in Table 2. The reaction of the *o*-*i*-Pr reagent **16** with 2-ethylhexanal using NaH gave *Z*-**12a** in 81:19 selectivity (entry 1). The use of NaI–DBU increased the selectivity to 88:12. The reaction with benzaldehyde using *t*-BuOK⁸ as a base gave *Z*-olefin in 95% yield with 75:25 selectivity. Although almost the same result was obtained from the reaction of *o*-*t*-Bu reagent **17** with 2-ethylhexanal, the selectivity with PhCHO increased to 83:17 (entries 4 and 5). The reaction with *n*-octanal also gave *Z*-olefin with 83:17 selectivity. Slightly better results were obtained from *o*-Ph reagent **18** (83:17–89:11 *Z*-selectivity) (entries 7–9). Thus, the *Z*-selectivity is higher with the bulkiest *o*-Ph reagent **18**.

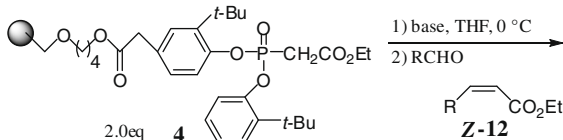
In order to further improve the *Z*-selectivity, we tried to introduce *t*-Bu group to the *ortho*-position of the polymer-bound phenol. That is, the procedure in Scheme 3 was followed after the Friedel–Crafts alkylation of **13** (*t*-BuOH, H₂SO₄, 80 °C). However, the reaction of ethyl dichlorophosphonoacetate with the sterically hindered phenol did not proceed well. To prepare the phosphonate reagent with sterically hindered phenol, we made a plan to use the reaction of phosphorus trichloride with phenols since the phosphorus(III) atom will not suffer from severe steric hindrance. Starting from 3-(4-hydroxyphenyl)propionic acid **19**, Friedel–Crafts alkylation and esterification with benzyl alcohol gave the benzyl ester **20** (Scheme 4). The reaction of phosphorus trichloride with **20**, *o*-*t*-BuC₆H₄OH, and EtOH in the presence of Pr₃N gave the phosphite **21**. The Arbusov reaction of **21** with ethyl bromoacetate at 160 °C followed by hydrogenolysis gave **22**. The esterification of **22** with the polymer-bound alcohol using DCC–DMAP gave the reagent **4**. The yield was estimated to be 63% by weight assuming an initial loading of 1.0 mmol/g for **7**. After our report of the reagents **2**, Touchard et al. reported the improvement of *Z*-selectivity at 0 °C using (*o*-*t*-BuC₆H₄O)₂P(O)CH₂CO₂Et.⁹ Also we recently reported the highly *Z*-selective synthesis of α,β -unsaturated morpholine amides and Weinreb amides using (*o*-*t*-BuC₆H₄O)₂P(O)CH₂CONR¹R².¹⁰ Since the polymer-supported reagents are supposed to react much slower than the non-supported reagents, the real reaction temperature seems to be around 0 °C. Therefore, the reagent having two *o*-*t*-BuC₆H₄O groups would be needed to achieve the high *Z*-selectivity.

The results of the HWE reaction of **4** with several types of aldehydes are summarized in Table 3.^{11,12} The reaction with aromatic aldehydes, benzaldehyde, furfural, and *p*-chlorobenzaldehyde gave very high *Z*-selectivity (96:4–97:3) in high yields (93–97%) using *t*-BuOK as a base (entries 1–3). Only *p*-anisaldehyde showed rather disappointing selectivity (89:11). The reaction with *n*-octanal at 0 °C using NaI–DBU as a base gave 91:9 selectivity in 92% yield (entry 5). When the reaction was performed at –78 to 0 °C over 3 h,



Scheme 4.

Table 3
The HWE reaction of **4** with aldehydes



Entry	RCHO	Base	Conditions	Yield (%)	Z:E
1	PhCHO	<i>t</i> -BuOK	−78 °C to RT	94	97:3
2	Furfural	<i>t</i> -BuOK	−78 °C to RT	93	96:4
3	<i>p</i> -ClPhCHO	<i>t</i> -BuOK	−78 to 0 °C	97	97:3
4	<i>p</i> -MeOPhCHO	<i>t</i> -BuOK	−78 to 0 °C	97	89:11
5	<i>n</i> -Octanal	NaI, DBU	0 °C, 1 h	92	91:9
6	<i>n</i> -Octanal	NaI, DBU	−78 to 0 °C	98	96:4
7	<i>c</i> -HexylCHO	NaI, DBU	−78 °C to RT	86	97:3
8	Citronellal	NaI, DBU	−78 to 0 °C	98	97:3
9	2-Et-Hexanal	NaI, DBU	−78 °C to RT	92	96:4
10	2-Et-Hexanal	NaH	−78 °C to RT	78	97:3
11	2E-Hexenal	<i>t</i> -BuOK	−78 °C to RT	92	85:15
12	2E-Hexenal	Triton B	−78 to 0 °C	41	73:27
13	<i>E</i> -PhCH=CHCHO	<i>t</i> -BuOK	−78 to 0 °C	99	87:13

higher 96:4 selectivity was obtained in 98% yield (entry 6). Since the former study shows that the *Z*-selectivity is higher at lower temperature,⁶ this HWE reaction must occur at lower than 0 °C. After we found this, the reaction was performed by the addition of aldehyde at −78 °C and the mixture was allowed to warm up to 0 °C over 2–4 h. For other aliphatic aldehydes, cyclohexanecarboxaldehyde, citronellal, and 2-ethylhexanal, the reaction of **4** also gave high *Z*-selectivity (96:4–97:3) in high yields (86–98%) using NaI–DBU (entries 7–9). Although Taylor-reported reaction with cit-

ronellal gave only 46% yield of **12** (*Z*:*E* = 63:37) together with unidentified by-product using 3.2 equiv of **3** and NaH, we obtained **12** in 98% yield with 97:3 selectivity using 2.0 equiv of **4** (entry 8). This shows the mildness of our reaction condition using NaI and DBU. The reaction with 2-ethylhexanal was also performed using NaH (entry 10). Although the selectivity is higher than the result from NaI–DBU, the yield is lower. For α,β -unsaturated aldehydes, 2E-hexenal, and 2E-cinnamaldehyde, the reaction underwent in high yields (92–99%) with moderate *Z*-selectivity (85:15–87:13) using *t*-BuOK. The use of Triton B (benzyltrimethylammonium hydroxide 40% in MeOH) reduced both the yield and the selectivity (entry 12).

In summary, we have demonstrated the synthesis and the use of a novel polymer-supported HWE reagent **4**, which gave *Z*- α,β -unsaturated esters with high selectivity. *t*-BuOK for aromatic and α,β -unsaturated aldehydes and NaI–DBU for aliphatic aldehydes are the choice of base. The development of a method to recycle the resin is under investigation.

Acknowledgment

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- For the reaction mechanism of the HWE reaction, see: Ando, K. *J. Org. Chem.* **1999**, *64*, 6815–6821.
- t*-BuOK is a practical base for the reaction of our reagents **2** with aromatic aldehydes.^{6b} Although it is also a good base for that at low temperature, Triton B causes decomposition of **2** at 0 °C. For the reaction of **2** with aliphatic aldehydes, sodium bases are the choice.^{6b,e}
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- The *Z*:*E* ratios were determined by integration of the vinyl proton signals of the crude reaction mixture in the 400 MHz ¹H NMR spectra. The non-polymer supported compounds described in this paper were characterized by 400 MHz ¹H NMR spectra and mass spectroscopy.
- A typical procedure of the HWE reaction of **4** (entry 6 in Table 3): The resin **4** (0.307 g, 0.20 mmol) in THF (5 mL) was treated with NaI (0.033 g, 0.22 mmol) and DBU (0.033 mL, 0.22 mmol) at 0 °C for 30 min under Ar atmosphere. After *n*-octanal (0.016 mL, 0.10 mmol) was added at −78 °C, the resulting mixture was gradually warmed to 0 °C over 3 h. The reaction was quenched with saturated NH₄Cl, and the resin was filtered and washed with hexane (10 mL). The organic filtrate was concentrated to give **12** (R = *n*-C₇H₁₅) (*Z*:*E* = 96:4) in 90% purity. The product was isolated by flash chromatography (hexane/AcOEt = 30:1) as a colorless oil (0.0196 g, yield 98%).