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Stereoselective synthesis of (*E*)-α,β-unsaturated esters: triethylamine-catalyzed allylic rearrangement of enol phosphates†

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α,β-Unsaturated esters are key structural motifs widely distributed in various biologically active molecules, and their *Z*/*E*-stereoselective synthesis has always been considered highly attractive in organic synthesis. Herein, we present a >99% (*E*)-stereoselective one-pot synthetic approach towards β-phosphoroxylated α,β-unsaturated esters *via* a mild trimethylamine-catalyzed 1,3-hydrogen migration of the corresponding unconjugated intermediates derived from the solvent-free Perkow reaction between low-cost 4-chloroacetoacetates and phosphites. Versatile β,β-disubstituted (*E*)-α,β-unsaturated esters were thus afforded with full (*E*)-stereoretentivity by cleavage of the phosphoenol linkage *via* Negishi cross-coupling. Moreover, a stereoretentive (*E*)-rich mixture of a α,β-unsaturated ester derived from 2-chloroacetoacetate was obtained and both isomers were easily afforded in one operation.

α,β-Unsaturated carbonyl motifs, such as the relevant esters, amides, and aldehydes, are widely distributed in biologically active molecules as key structural components (Fig. 1).[1–4] Generally, the (*Z*) and (*E*)-isomers of those molecules possess very different living activities.[5] Moreover, ubiquitous α,β-unsaturated esters are also widely employed as useful intermediates for enantioselective hydrogenation,[6] allylic substitution,[7] conjugate addition,[8] and especially for the stereoselective generation of acyclic substituted alkenes in either (*Z*) or (*E*)-isomeric forms.[9]

Whilst numerous methods have been developed towards α,β-unsaturated esters,[10–13] configuration-retentive transition-metal catalyzed (TMC) cross-coupling of alkenyl (pseudo)halides is universally recognized as one of the most practical methodologies.[14] Among the known non-classical pseudohalides,[15] diethylphosphoroxyl (DEP) functionality has been proved as a good leaving group in many organic reactions and the corresponding enol phosphates (EPs), possessing high stability and accessibility, were found to participate in various organic transformations.[16] Particularly, EPs have been utilized in many types of TMC coupling reactions including Suzuki–Miyaura, Stille, Negishi, and Heck reactions by cleavage of the enol-linkage affording highly substituted alkenes.[17] However, the EPs-involved (*Z*) and (*E*)-stereocomplementary synthetic method towards α,β-unsaturated esters with sufficient substrate generality is still quite limited at present. The latest impressive approach was reported by Tanabe group, which employed *N*-methylimidazole (NMI)-promoted phosphorylation of β-ketoesters to obtain (*Z*) and (*E*)-α,β-unsaturated esters, but which suffers from pre-activation of the unstable diphenyl phosphorochloridate (DPPCl) and usage of strong metallic *tert*-butoxide bases.[18] Based on our recent progress in regioselective solvent-free synthesis of EPs,[19] we envisioned that phosphoroxylated (*Z*) and/or (*E*)-α,β-unsaturated esters may act as the universal synthon of α,β-unsaturated esters and should be facilely obtained from the commercially available and low-cost chloroacetoacetates and phosphites *via* a simple metal-free Perkow reaction. Herein, we wish to present a stereoselective one-pot synthetic approach towards β-phosphoroxylated (*E*)-α,β-unsaturated esters, which are subsequently converted into the corresponding disubstituted α,β-unsaturated esters by Negishi cross-coupling (Scheme 1).

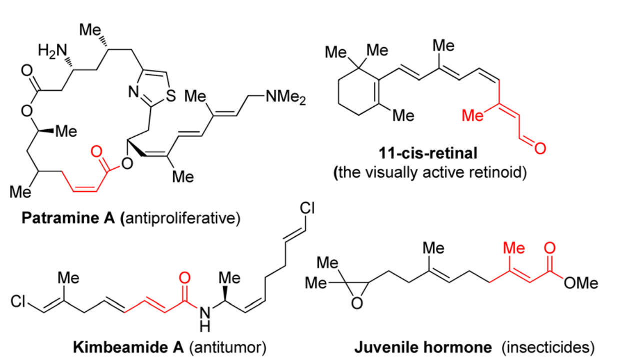

Fig. 1 Selected bioactive α,β-unsaturated carbonyl motifs.

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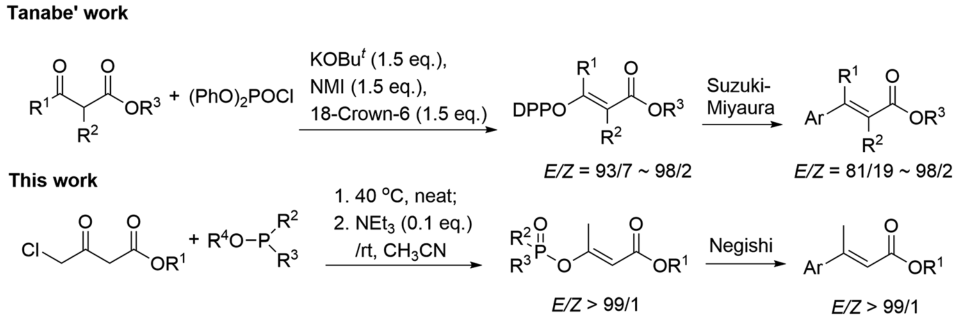
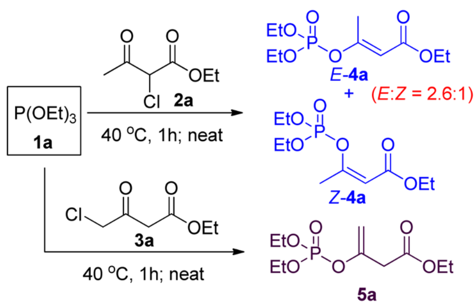


Scheme 1 *E*-Stereoselective synthesis of α,β-unsaturated esters from enol phosphates.

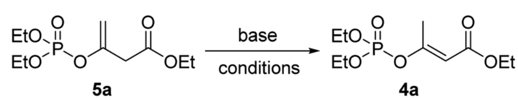


Scheme 2 Perkow reaction of phosphite with chloroacetoacetate.

Since both 2-chloroacetoacetates and 4-chloroacetoacetates are capable of undergoing Perkow reaction with phosphites, we then took them together for comparison. Solvent-free Perkow reaction conditions were initially selected in view of high regioselectivity.[19] As shown in Scheme 2, reaction between $(EtO)_3P$ and 2-chloroacetoacetate **2a** gave a mixture of (*E*) and (*Z*)-isomers of β-phosphoroxylated α,β-unsaturated ester **4a** in ratio of 2.6 : 1, whereas reaction between $(EtO)_3P$ and 4-chloroacetoacetate **3a** gave the β-phosphoroxylated allylic ester **5a** as the only product. In other words, only moderate *E*/*Z*-stereoselectivity can be achieved if using 2-chloroacetoacetate, while no conjugated EP product can be obtained if using 4-chloroacetoacetate. However, according to Seeman's report that bases, such as NaH, are supposed to be able to promote 1,3-hydrogen relocation of allyl compounds, we then suspect that the unconjugated EP product **5a** may be able to be transformed into the conjugated one in a stereoselective way.[20]

Inspired by the above idea, we then turned to examine the possibility of the base-promoted 1,3-hydrogen rearrangement of **5a**. As shown in Table 1, among the eight kinds of bases examined, including inorganic *t*-BuOK, CH_3ONa, NaOH, NaH,

Table 1 Optimization of base-promoted 1,3-hydrogen rearrangement of unconjugated β-phosphoroxylated allylic ester **5a** [a]



Entry	Base	Load (*x* eq.)	Solvent	*T* (°C)	Time (h)	Yield[b] (%)	*E*/*Z* (**4a**)[c]
1	*t*-BuOK	1.2	THF	rt	24	0	—
2	CH_3ONa	1.2	THF	rt	24	0	—
3	NaOH	1.2	THF	rt	24	0	—
4	NaH	1.2	THF	rt	24	0	—
5	K_2CO_3	1.2	THF	rt	24	0	—
6	Et_3N	1.2	THF	rt	24	90	>99 : 1
7	Pyridine	1.2	THF	rt	24	0	—
8	$(i\text{-}Pr)_2NEt$	1.2	THF	rt	24	20	>99 : 1
9	Et_3N	1.2	CH_3CN	rt	4	92	>99 : 1
10	Et_3N	1.2	DCM	rt	20	90	>99 : 1
11	Et_3N	1.2	CH_3OH	rt	22	83	>99 : 1
12	Et_3N	1.2	DMF	rt	24	75	>99 : 1
13	Et_3N	0.5	CH_3CN	rt	7	92	>99 : 1
14	**Et_3N**	**0.1**	**CH_3CN**	**rt**	**12**	**92**	**>99 : 1**
15	Et_3N	0.05	CH_3CN	rt	20	93	>99 : 1
16	Et_3N	0.1	CH_3CN	0	24	95	>99 : 1
17	Et_3N	0.1	CH_3CN	80	4	90	>99 : 1

[a] Reaction conditions: **5a** (1.0 equiv.), base (*x* equiv.), solvent (3 ml). [b] Isolated yields. [c] Determined by NMR.

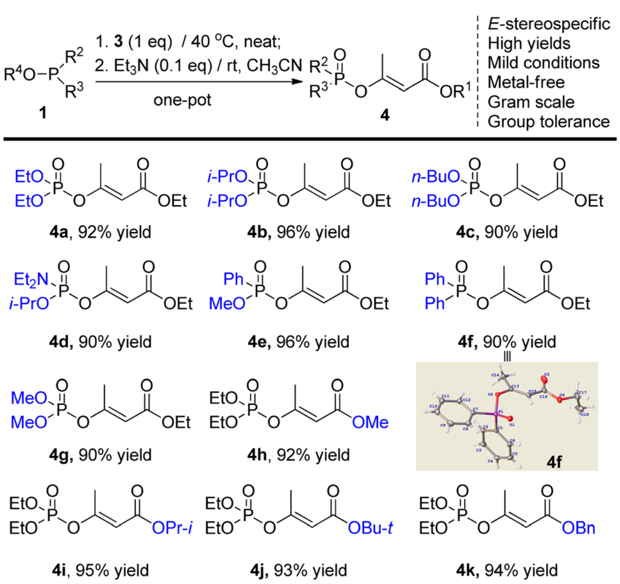
K_2CO_3, and organic Et_3N, Pyridine (i-Pr)$_2$NEt, only Et_3N and (i-Pr)$_2$NEt exhibited the supposed promoting abilities, affording the desired product *E*-**4a**, but encouragely both in >99% (*E*)-stereoselectivity. Though only 20% yield was obtained by 1.2 equivalent (i-Pr)$_2$NEt after 24 h reaction in THF at room temperature (Table 1, entry 8), while up to 90% yield was acquired by using Et_3N (Table 1, entry 6). The following screening of solvents demonstrated that acetonitrile seemed to the best choice that the reaction could be accomplished in only 4 h and gave a higher yield of 92% (Table 1, entry 10). Further investigation about the loadage of Et_3N showed that only 0.1 equivalent Et_3N was sufficient to promote the rearrangement effectively, affording the comparative yield though with a few longer time of 12 h (Table 1, entry 14). Less loadage of Et_3N and lower temperature both led to much longer reaction times (Table 1, entry 15&16). Though the reaction time could be shortened to 4 h at a higher temperature of 80 °C (Table 1, entry 17), we finally preferred the more benign room temperature for the following preparations.

Considering the convenience of experimental operation, we then turned into the possibility of one-pot manipulation. It was found that product *E*-**4a** was afforded in 92% yield if using the crude intermediate **5a** directly for the subsequent rearrangement reaction. Therefore, a mild *E*-stereoselective one-pot synthetic approach of β-phosphoroxylated α,β-unsaturated esters was thus established: **3** (1.0 eq.) and P(III)-reagents (1.0 eq.) react 1 h at 40 °C neatly, then added triethylamine (0.1 eq.) and acetonitrile (3 mL), and further react about 12 h at room temperature.

Having identified the optimal reaction conditions, we next set out to examine the scope of this new mild one-pot enol phosphorylation procedure (Table 2). As for the different *O*-alkyl 4-chloroacetoacetate substrates, all the common P(III)-reagents possessing P–O, P–C, and/or P–N bonds gave the corresponding EPs in high yields. During the preparation of compounds **4e** and **4f**, the rearrangement reactions were found much accelerated probably due to the higher reactivities of phosphonite and phosphinite compared to phosphites. To demonstrate the practical utility, the reaction towards product **4a** was performed at the 50 mmol scale and 92% yield was obtained. The stereoscopic (*E*)-configuration of solid product **4f** was further confirmed by single crystal X-ray analysis.

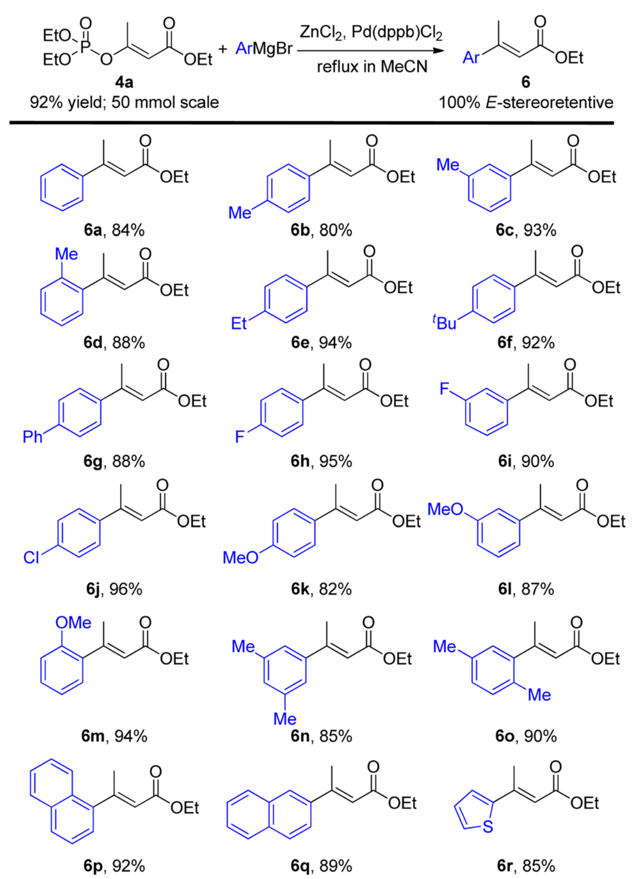
With the *E*-stereospecific β-phosphoroxylated α,β-unsaturated esters in hand, we then investigated their stereoretentive Negishi cross-coupling to prepare the corresponding *E*-stereodefined disubstituted α,β-unsaturated esters. Among the typical catalysts screened including $Pd(PPh_3)_4$, $Ni(acac)_2$ and Pd(dppb)Cl_2, the latter demonstrated the best performance in this Negishi reaction with only 0.02 equivalent loading by refluxing in acetonitrile. Various aromatic ArZnCl nucleophiles containing electron-donating and/or electron-withdrawing substituents at *ortho*, *meta*, and/or *para* positions were all tolerated well, affording the desired products in good to excellent yields (80–

Table 2 Scope of β-phosphoroxylated (*E*)-α,β-unsaturated esters[a,b]



[a] Reaction conditions: **1** (1.0 mmol), **3** (1.0 mmol), Et_3N (0.1 mmol), CH_3CN (3.0 mL). [b] Isolated yields.

Table 3 Scope of (*E*)-α,β-unsaturated esters *via* a stereoretentive Negishi cross-coupling reaction of **4a** [a,b]



[a] Reaction conditions: **4a** (1.0 mmol), ArMgBr (1.5 mmol), $ZnCl_2$ (1.5 mmol), Pd(dppb)Cl_2 (0.02 mmol), CH_3CN (5.0 mL), reflux about 3 h. [b] Isolated yields.

96%) without generating any stereochemical integrity (Table 3, **6a–6m**). Disubstituted, condensed and hetero aromatic organometallic substrates also gave 85–92% yields of the products (Table 3, **6n–6r**). However, it's regrettable that alkyl organozinc reagents was found unreactive under such conditions.

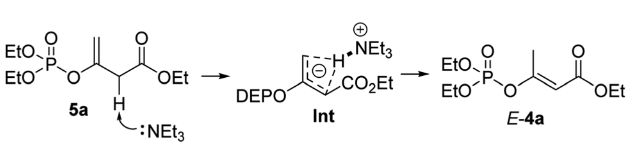
Furthermore, under the above optimal Negishi cross-coupling reaction conditions, both (*Z*) and (*E*) isomers of α,β-unsaturated esters **6a** could be easily achieved, just by one operation, directly from the (*Z*) and (*E*) mixture of **4a** in 22% and 70% yields respectively (Scheme 3).

According to the Cram's mechanistic interpretation for the allylic rearrangements, an intra-molecular pathway of the Et_3N-promoted stereoselective 1,3-hydrogen rearrangement of the EPs **5a** was proposed because that the degree of the observed intramolecularity depended strongly on the base and solvent used.[21] As shown in Scheme 4, triethylamine firstly removes the proton from the α-carbon position of ester **5a**, resulting in a coplanar anionic allylic system by three carbon atoms. The hydrogen atom of the H–Et_3N ammonium then bonds to both terminal carbon atoms to form the intermediate **Int**, collapse of which would then give the thermodynamically favourable conjugated α,β-unsaturated ester product *E*-**4a**.

In summary, a mild and environmental trimethylamine-catalyzed *E*-stereoselective 1,3-hydrogen allylic rearrangement of enol phosphates was firstly developed to afford versatile β-phosphoroxylated (*E*)-α,β-unsaturated esters which can be then efficiently converted into the corresponding β,β-disubstituted (*E*)-α,β-unsaturated esters in high yields by a 100% stereo-retentive Negishi cross-coupling reaction. Moreover, both (*Z*) and (*E*)-α,β-unsaturated esters were able to be achieved in one manipulation when just employing 2-chloroacetoacetate instead of 4-chloroacetoacetate for the solvent and metal-free Perkow reaction.

It is interesting to note that more structure-diverse α,β-unsaturated esters should be easily obtained by derivation reactions at the allylic position of α,β-unsaturated esters and/or by utilizing 2-substituted 4-chloroacetoacetates as the starting materials.

Scheme 3 Preparation of (*Z*) and (*E*) isomers of **6a** in one operation.



Scheme 4 Proposed (*E*)-stereospecific allylic rearrangement mechanism.

Conflicts of interest

There are no conflicts to declare.

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