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An efficient *one-step* synthesis of a new series of multifunctional olefins

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Keywords:

β-Dicarbonyl derivatives; Morita–Baylis–Hillman; Olefination; Wittig-Horner; Deacylation; Hydroxymethylation.

Abstract

An efficient one-step procedure for the synthesis of a new series of multifunctional olefins by condensation of β-diketones as well as β-phosphonoesters and benzoylated β-ketoesters with formaldehyde, using potassium carbonate in refluxing THF, followed by a deacylation reaction, is herein described. In contrast, acetylated β-keto esters derivatives, only undergo a hydroxymethylation reaction, affording the corresponding α-hydroxymethyl β-keto esters in high yields.

1. Introduction

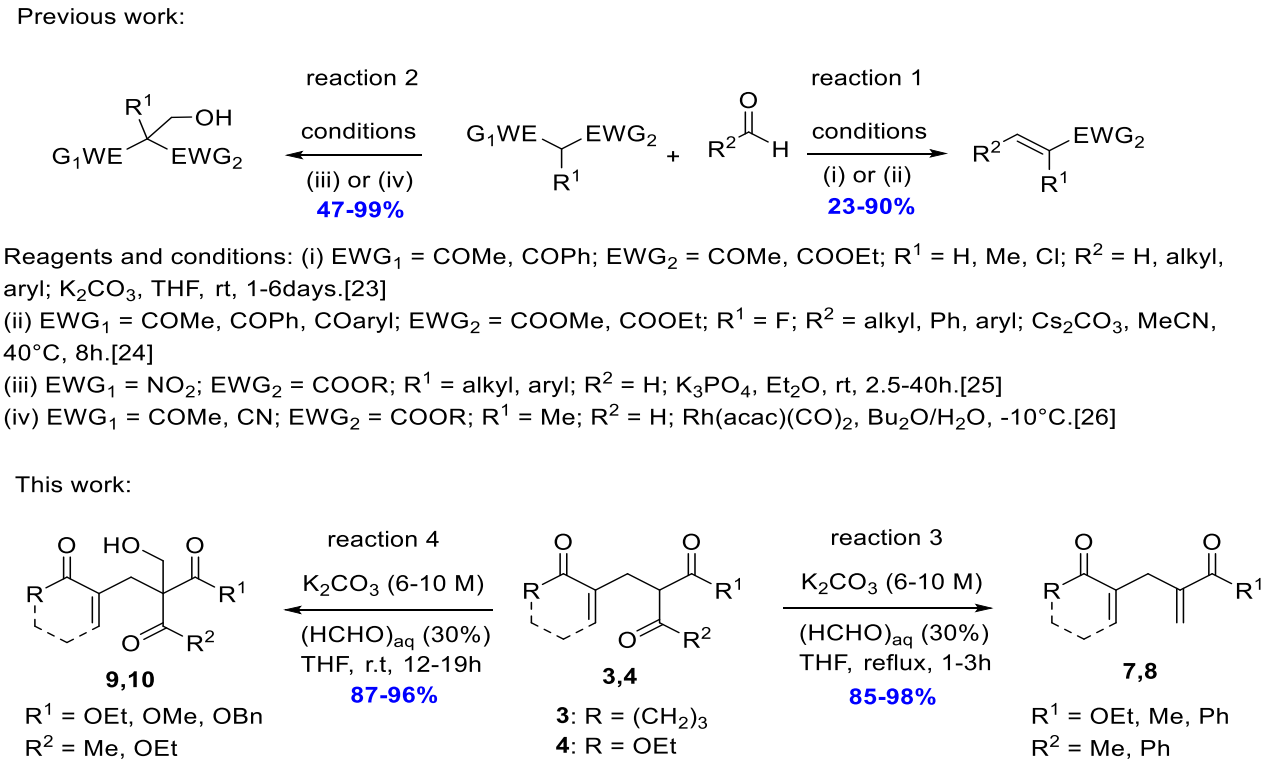
The α,β-unsaturated carbonyl derivatives have been found to be useful intermediates in organic chemistry [1-4] and for the synthesis of natural products as well as for various biologically active molecules [5-10]. For instance, a number of cinnamic esters, including methyl caffeate, ethyl 3,4,5-

trimethoxycinnamate and octyl methoxycinnamate have shown antitumor, anti-inflammatory and sunscreen potent actions [11].

Therefore, the development of efficient methods for the preparation of such compounds is highly required. For this purpose, the most well-known famous olefins synthetic approaches are the Wittig reaction [12], the Horner–Wadsworth–Emmons reaction [13] and the decarboxylative Knoevenagel process [14]. Generally, this latter synhetic method is catalysed by weak bases including amines, or a combination of piperidine and DMAP [15], as well as bifunctional DMAP-piperidine polymeric organocatalyst [16], a combination of pyridine-pyrrolidine [17], or pyrrolidine-AcOH [18] and ammonium salts [19] in organic solvents. When malonic acid half ester is used as the active methylene compound, the condensation is followed by a decarboxylation reaction, leading to the corresponding α,β-unsaturated esters. Because of its toxicity and its significant health risk [20,21], the use of pyridine in previous work [17], is not convenient.

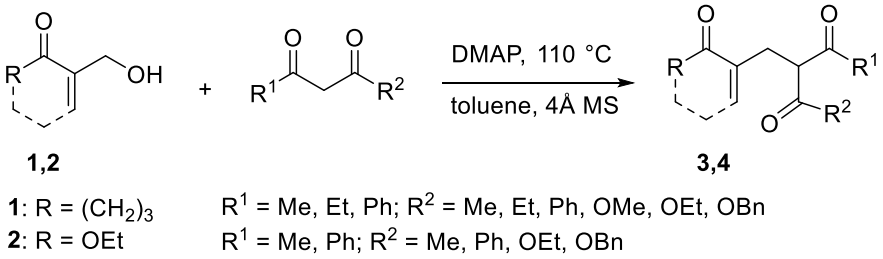
Moreover, the synthesis of α-halogeno-α,β-unsaturated carbonyl compounds has been previously reported, using a *tandem* condensation-deacylation reactions of aldehydes with the corresponding α-halogeno β-dicarbonyl compounds, in the presence of anhydrous potassium carbonate or cesium carbonate as bases [22-24] (Scheme 1, reaction 1).

On the other hand, the synthesis of α-hydroxymethyl β-keto esters has been reported using the reaction of formaldehyde with β-keto esters or nitroacetate, in the presence of K_3PO_4 as base or metal complexes as catalysts [25,26] (Scheme 1, reaction 2).



Scheme 1. Synthesis of α,β-unsaturated carbonyl compounds or α-hydroxymethyl β-keto esters from 1,3-dicarbonyl compounds.

In the course of our study on the MBH chemistry, we have previously reported that the DMAP-promoted direct C-allylation of β-keto esters and β-diketones with cyclic and acyclic Morita-Baylis-Hillman (MBH) alcohols **1,2** (Scheme 2) [27,28], affording the β-dicarbonyl derivatives **3,4**, respectively [29,30]. Furthermore, starting from the derivatives **3,** in basic conditions, we have also described their regioselective α-chloration, using sodium hypochlorite [31].



Scheme 2. DMAP-mediated allylation of β-dicarbonyl compounds with alcohols.

In connection with our current research program on the reactivity of multifunctional derivatives **3,4** and our interest in the chemistry of α,β-unsaturated carbonyl compounds, including their applications in the synthesis of bioactive molecules [5-10], we report herein an efficient, pratical and convenient protocol for the condensation of formaldehyde with a series of MBH reaction-derived β-dicarbonyl and β-phosphonoester compounds, in the presence of commercially available and inexpensive K_2CO_3, in a commonly available solvent such as THF. The α,β-unsaturated carbonyl compounds **7,8** were obtained through a selective deacylation reaction (Scheme 1, reaction 3).

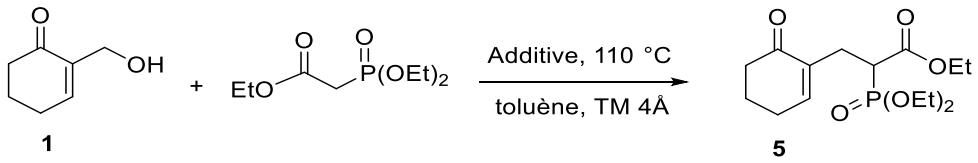
In contrast, acetylated β-keto esters derivatives, only undergo a hydroxymethylation reaction, affording the corresponding α-hydroxymethyl β-keto esters **9,10** (Scheme 1, reaction 4).

2. Results and Discussion

2.1. Synthesis of β-phosphonoesters 5,6 as starting materials

In continuation with our previous study on the behaviour of MBH derivatives towards active methylene compounds, using DMAP as an efficient Lewis-base catalyst [29], we first investigate the reaction of the primary alcohol **1** with triethyl phosphonoacetate in the presence of DMAP or triethylamine (1.2 equiv) and 4 Å molecular sieves in refluxing toluene [29]. We have observed that the starting materials were completely recovered, even after stirring the reaction mixture during 48 h (Table 1, entries 1 and 2). Moreover, the addition of an additive to the previous reaction mixture, such as anhydrous K_2CO_3 (2 equiv), led to the C-allylation product **5** in low yields (Table 1, entries 3 and 4). Interestingly, the use of only anhydrous K_2CO_3, as the base, afforded exclusively the C-allylation product **5**, within 8 h in 71% yield (Table 1, entry 5).

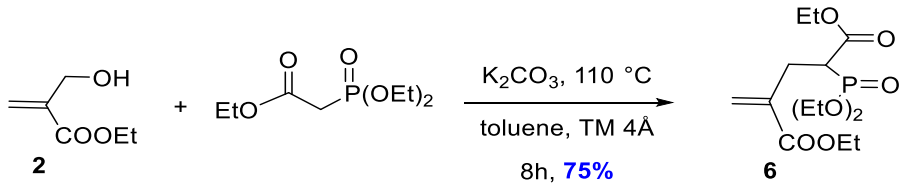
Table 1: Optimization of the reaction conditions of triethyl phosphonoacetate with cyclic MBH alcohol **1**.



1 **5**

Entry	Additive	Time (h)	**5**, Yield (%)
1	DMAP	48	n.r
2	NEt_3	48	n.r
3	DMAP-K_2CO_3	24	27
4	NEt_3-K_2CO_3	24	38
5	K_2CO_3	8	71

In order to investigate the scope and limitations of this simple monoallylation method, we investigated the behaviour of the acyclic MBH alcohol **2** towards triethyl phosphonoacetate. We found that under the above-mentioned conditions (K_2CO_3, toluene, reflux, 4 Å molecular sieves), the reaction gave the allylation product **6** in 75% yield (Scheme 3).



2 **6**

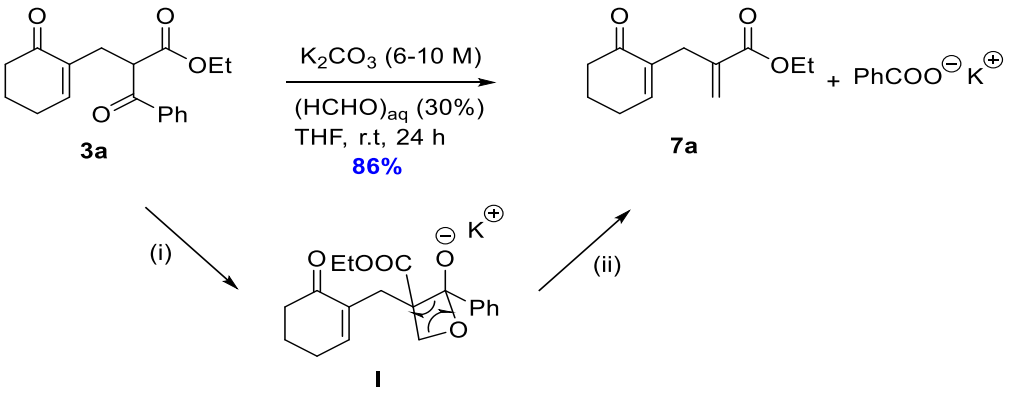
Scheme 3. K_2CO_3-mediated allylation of triethyl phosphonoacetate with acyclic Morita-Baylis–Hillman alcohol **2**.

2.2. Synthesis of a new series of multifunctional olefins

Having the C-allylation products **3-6** in hand, as starting materials, we envisioned their further implementation in a synthetic approach for the synthesis of a new series of functionnalized olefins. In this context, we tried to identify the optimal reaction parameters for a clean and selective olefination reaction of

formaldehyde with cyclic/acyclic β-dicarbonyl compounds **3,4** or β-phosphonoesters **5,6**.

We found that the reaction of cyclic monoallyl β-keto ester compound **3a** with a large excess (5 equiv) of aqueous formaldehyde worked well under heterogeneous liquid–liquid conditions, using highly concentrated (6–10 mol) aqueous solution of potassium carbonate (4 equiv) in 5 mL of THF at room temperature. Such synthetic method exclusively provides, *via* the intermediate **I**, within a long reaction time (24 h), the α,β-unsaturated ester **7a** in 86% yield , by a *tandem* hydroxymethylation (i)–elimination (ii) of potassium benzoate (Scheme 4).



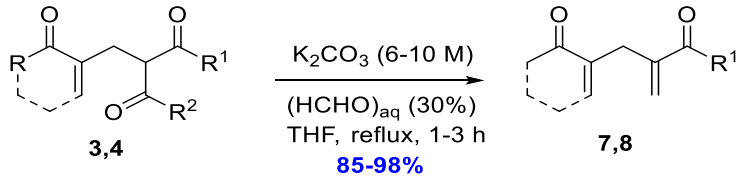
Scheme 4. Direct synthesis of α,β-unsaturated ester **7a** from **3a**.

This reaction contains a clean and environmentally-friendly process because it does not produce any harmful phosphorus compounds such as triphenylphosphine oxide to the environment such as in the Wittig reaction [12]. Therefore, this deacylation reaction contributes to a hazard-free environment because only water-soluble-carboxylate salt ($PhCOO^-K^+$) is formed as by-product.

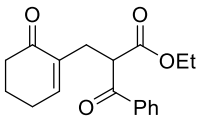
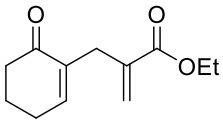
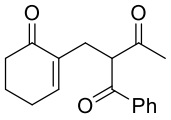
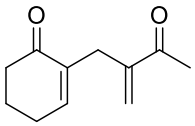
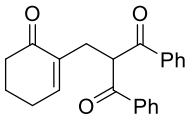
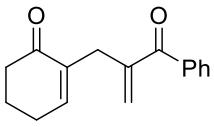
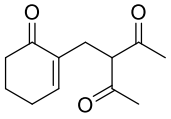
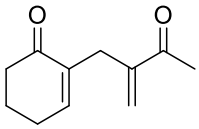
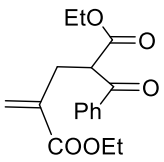
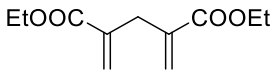
Next, in order to reduce the reaction time of **7a**, we investigated the conversion of **3a** in refluxing THF and we observed that such process worked well within

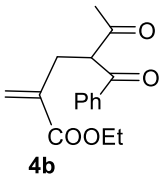
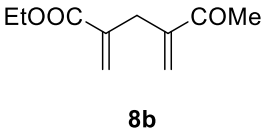
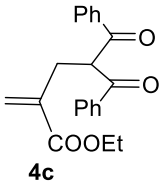
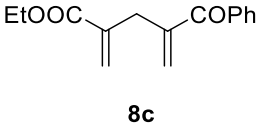
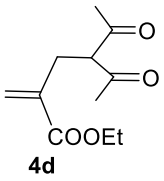
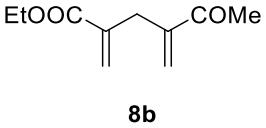
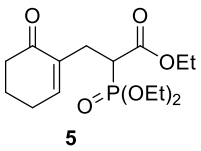
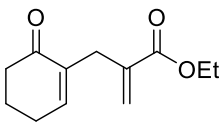
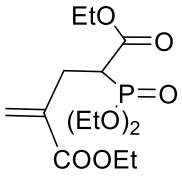
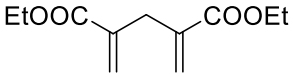
3 h, affording, *via* a debenzoylation reaction, the desired product **7a** [32], in a good 96% yield (Table 2, entry 1).

Table 2: Synthesis of multifunctional olefins **7,8** from **3,4**.



3: R = $(CH_2)_3$; R^1 = OEt, Me, Ph; R^2 = Me, Ph
4: R = OEt; R^1 = OEt, Me, Ph; R^2 = Me, Ph

Entry	Starting material	Time (h)	Product **7** or **8**	Yield (%) **7** or **8**
1	 **3a**	3	 **7a**	96
2	 **3b**	3	 **7b**	91
3	 **3c**	3	 **7c**	90
4	 **3d**	2	 **7b**	85
5	 **4a**	2	 **8a**	96

6	 **4b**	2	 **8b**	96
7	 **4c**	2	 **8c**	98
8	 **4d**	1	 **8b**	90
9	 **5**	3	 **7a**	96
10	 **6**	2	 **8a**	96

Similarly, in refluxing THF, the condensation of formaldehyde with β-keto ester monoallyl compound **3a** was performed with β-diketones monoallyl derivatives **3b-d** to give, within 2-3h, through a selective deacylation reaction [23,33], the α,β-unsaturated ketones **7b-c** in high isolated yields (Table 2, entries 2–4).

In order to demonstrate the generality of such deacylation reaction, we further investigated the behaviour of the acyclic monoallyl β-keto ester compound **4a** (Table 2, entry 5) as well as acyclic monoallyl β-diketones derivatives **4b-d** (Table 2, entries 6–8) towards formaldehyde under the above-mentioned conditions (K_2CO_3, THF, reflux). We found that the reaction gave exclusively

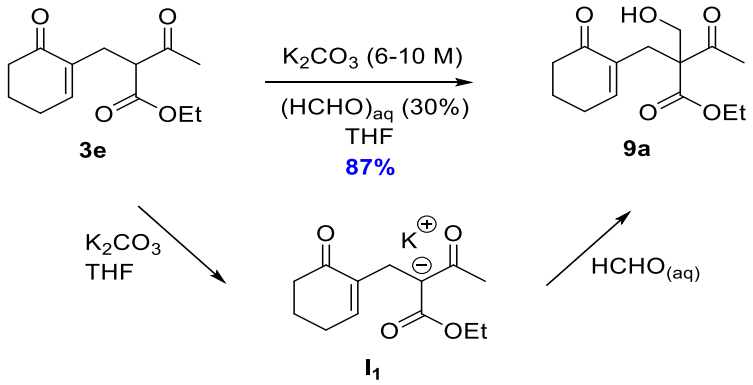
the α,β-unsaturated ester **8a** and the α,β-unsaturated ketones **8b,c** [34] in short reaction times and in 90–98% yields (Table 2, entries 5–8).

Finally, we demonstrated that other carbon pronucleophiles such as monoallyl triethylphosphonoacetates **5,6**, similarly reacted with formaldehyde, under the above etablished conditions, affording exclusively the α,β-unsaturated esters **7a** and **8a**, respectively, in a good yield (96%) (Table 2, entries 9 and 10).

2.3. Synthesis of α-hydroxymethylated β-keto esters

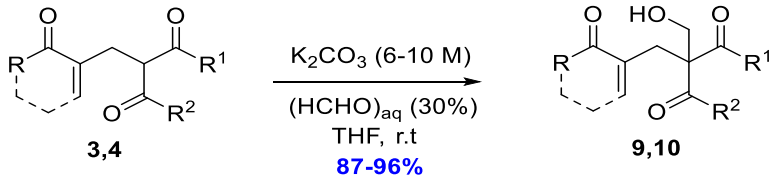
Under the same conditions (K_2CO_3, THF, r.t), we have also investigated the scope and the limitation of the above reaction, using in this case, the β-keto ester derivatives **3e-g** as precursors. In contrast to the previous behaviour of benzoylated β-keto ester **3a** (R^1 = OEt, R^2 = Ph) towards formaldehyde, we observed that the reaction of acetylated β-keto ester compound **3e** (R^1 = OEt, R^2 = Me), selected as the model substrate, with formaldehyde, did not give the expected α,β-unsaturated ester **7a**, but it afforded exclusively within 12 h, through a hydroxymethylation reaction [25,26,35,36], the α-hydroxymethyl β-keto ester compound **9a** in 87% yield (Table 3, entry 1).

Mechanistically, in a procedure similar to that described by Chan [35], the acetylated β-keto ester compound **3e** was treated with aqueous solution of potassium carbonate in THF at room temperature or in refluxing THF to form the resulting anion I_1, which was reacted with formaldehyde to provide the compound **9a** featuring the hydroxymethylene unit (Scheme 5).

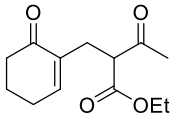
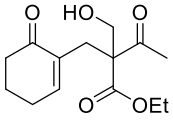
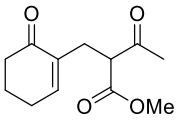
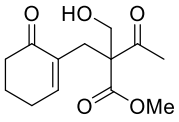
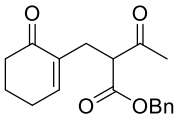
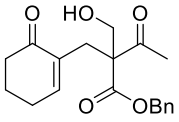


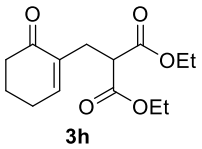
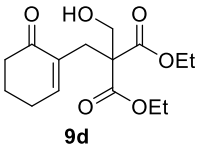
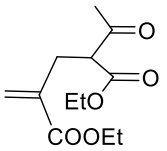
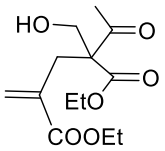
Scheme 5. Proposed mechanism for the formations of **9a**.

Table 3. Hydroxymethylation of acetylated β-keto esters and β-diester compounds.



3: R = $(CH_2)_3$; R^1 = OEt, OMe, OBn; R^2 = Me, OEt
4: R = OEt; R^1 = OEt; R^2 = Me

Entry	Starting material	Time (h)	Product	Yield (%)
	3,4		**9,10**	**9,10**
1	 **3e**	12	 **9a**	87
2	 **3f**	14	 **9b**	89
3	 **3g**	16	 **9c**	91

4	 **3h**		16	 **9d**		94
5	 **4e**		19	 **10**		96

171

172 Similarly, upon treatment of acetylated β-keto ester **3f,g** (**3f**, R^1 = OMe, R^2 =
173 Me; **3g**, R^1 = OBn, R^2 = Me) [29] as well as diethyl malonate derivatives **3h** (R^1
174 = R^2 = OEt) under the previously optimized conditions, we observed that the
175 conversion of the starting materials was complete and led to the corresponding
176 α-hydroxymethylated β-dicarbonyl compounds **9b-d** in 89–94% yields (Table 3,
177 entries 2–4).

178 Finally, in order to explore the scope of this synthetic approach, we studied the
179 condensation of formaldehyde with acyclic monoallyl β-keto ester compound **4e**
180 (R^1 = OEt, R^2 = Me). As a result, the reaction yielded exclusively, in 96% yield,
181 the corresponding α-hydroxymethyl β-keto ester compounds **10** (Table 3, entries
182 5).

183 It is worthy to note that the spectroscopic data (^{1}H and ^{13}C NMR) of compounds
184 **9a,b** and **10** show that they are of high purity and their HRMS analysis reveals
185 that the corresponding molecular peaks M^+ are accompanied with the ions M^+-
186 HCHO at M^+-30, suggesting the eliminnation of HCHO during the HRMS
187 experiments [37].

188 ## 3. Conclusion

The present work describes a convenient, operationally simple and environmentally-friendly synthetic method for either hydroxymethylation or *tandem* hydroxymethylation–deacylation of a variety of 1,3-dicarbonyl compounds, combined with formaldehyde in THF, in high yields, using a weak base (K_2CO_3).

Future studies in our group will focus on the synthetic applications [1,4] and the evaluation of biological activity of the synthesized products.

4. Experimental

4.1. Typical procedure for the synthesis of β-phosphonoesters 5,6 as starting materials

A mixture of cyclic MBH alcohol **1** (2 mmol, 0.252 g) or acyclic MBH alcohol **2** (2 mmol, 0.26 g), triethyl phosphonoacetate (2.4 mmol, 0.53 g) and anhydrous K_2CO_3 (4 mmol, 0.552 g) was dissolved in toluene (20 mL), containing 5 g of oven-dried 4 Å molecular sieves. The mixture was then heated under reflux for 8 h. After completion (TLC), the reaction mixture was cooled, washed with brine and dried. The toluene was removed and the residue was purified by column chromatography on silica gel (ether) to give the pure allylation products **5** and **6**.

4.2. General procedure for the synthesis of a new series of multifunctional olefins

To a magnetically stirred mixture of β-dicarbonyl monoallyl derivatives **3a-d** or **4a-d** or β-phosphonoester monoallyl derivatives **5** and **6** (1 mmol) and 30% aqueous formaldehyde (5 mmol) was added at room temperature a gelatinous solution of potassium carbonate (6–10 M, 4 mmol). The heterogeneous reaction mixture was stirred at reflux of THF (5mL). After completion (TLC), the reaction mixture was cooled then treated with water. The solution was extracted

with ether (3 x 25 mL). The combined organic layers were dried over anhydrous MgSO4, filtered and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (light petroleum/diethyl ether = 7:3) to afford olefins **7** and **8**.

4.3. General procedure for the synthesis of α-hydroxymethylated β-keto esters

To a magnetically stirred mixture of β-keto ester monoallyl derivatives **3e-h** or **4e** (1 mmol) and 30% aqueous formaldehyde (5 mmol) was added at room temperature a gelatinous solution of potassium carbonate (6–10 M, 4 mmol). The heterogeneous reaction mixture was stirred in THF (5mL) at room temperature and the progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled then treated with water. The solution was extracted with ether (3 x 25 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by a column chromatography on silica gel (light petroleum/diethyl ether = 9:1) to give the pure derivatives **9** or **10**.

Supporting Information

Supporting Information File 1

Full experimental details and characterization data of all new compounds.

Supporting Information File 2

^{1}H and ^{13}C NMR and HRMS spectra of compounds.

Finding

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References

[1] Nokami, J.; Kataoka, K.; Shiraishi, K.; Osafune, M.; Hussain, I.; Sumida, S. *J. Org. Chem*. **2001**, *66*, 1228–1232.

[2] Li, S.; Li, X.; Yao, H.; Tan, M.; Xu, D.; Huang, N. *Org. Chem. Front*. **2024**, *11*, 236–253.

[3] Silveira, C. C.; Nunes, M. R. S.; Wendling, E.; Braga, A. L. *J. Organomet. Chem*. **2001**, *623*, 131−136.

[4] Chaudhary, B.; Kulkarni, N.; Saiyed, N.; Chaurasia, M.; Desai, S.; Potkulea, S.; Sharma, S. *Adv. Synth. Catal*. **2020**, *362*, 4794–4819.

[5] Deb, M. L.; Bhuyan, P. J. *Tetrahedron Lett*. **2005**, *46*, 6453−6456.
[6] Liang, F.; Pu, Y.; Kurata, T.; Kido, J.; Nishide, H. *Polymer* **2005**, *46*, 3767−3775.

[7] Tietze, L. F. *Chem. Rev*. **1996**, *96*, 115–136

[8] Lyall, R.; Zilberstein, A.; Gazit, A.; Gilon, C.; Levitzki, A.; Schlessinger, J. *J. Biol. Chem*. **1989**, *264*, 14503–14509

[9] Shiraishi, T.; Owada, M. K.; Tatsuki, M.; Yamashita, Y.; kaunaga, T. *Cancer Res*. **1989**, *49*, 2374–2378.

[10] Mierina, I.; Zaharova, M.; Jure, M.; Neibolte, I. *J. Chem. Pharm. Res*. **2015**, *7(6)*, 416−427.

[11] P. Sharma, *J. Chem. Pharm. Res.* **2011**, *3*, 403-423.

[12] Wittig, G.; Geissler, G. *Justus Liebigs Ann. Chem*. **1953**, *580*, 44–57.

[13] Wadsworth, W. S., Jr. *Org. React.* **1977**, *25*, 73–253.

[14] Harwood, L. M.; Moody, C. J. *Experimental Organic Chemistry*; Blackwell: Oxford, **1989**, 557–559.

[15] List, B.; Doehring, A.; Fonseca, M. T. H.; Job, A.; Torres, R. R. *Tetrahedron* **2006**, *62*, 476−482.

[16] Lu, J.; Toy, P. H. *Synlett* **2011**, *12*, 1723−1726.

[17] Kemme, S. T.; Šmejkal, T.; Breit, B. *Adv. Synth. Catal.* **2008**, *350*, 989–994.

[18] Zacuto, M. J. *J. Org. Chem.* **2019**, 84, *10*, 6465–6474.

[19] Schijndel, J. v.; Canallea, L. A.; Molendijka, D.; Meuldijk, J. *Green Chem Lett Rev*. **2017**, *10*, 404–411.

[20] Alfonsi, K.; Colberg, J.; Dunn, P.J.; Fevig, T.; Jennings, S.; Johnson, T.A.; Kleine, H.P.; Knight, C.; Nagy, M.A.; Perry, D.A.; Stefaniak, M. *Green Chem*. **2008**, *10*, 31–36.

[21] Pawar, H.S.; Wagh, A.S.; Lali, A.M. *New J. Chem*. **2016**, *40*, 4962–4968.

[22] Tsuboi, S.; Uno, T.; Takeda, A. *Chem. Lett*. **1978**, 1325–1328.

[23] Nakatsu, S.; Gubaidullin, A. T.; Mamedov, V. A.; Tsuboi, S. *Tetrahedron* **2004**, *60*, 2337–2349.

[24] Qian, J.; Yi, W.; Lv, M.; Cai, C. *Synlett*. **2015**, *26*, 127–132.

[25] Ji, C-B.; Liu, Y-L.; Cao, Z-Y.; Zhang, Y-Y.; Zhou, J. *Tetrahedron Lett*. **2011**, *52*, 6118–6121.

[26] Meninno, S.; Lattanzi, A. *Chem. Rec.* **2016**, *16*, 2016–2030.

[27] Rezgui, F.; El Gaïed, M.M. *Tetrahedron Lett*. **1998**, *39*, 5965–5966.

[28] Villieras, J.; Rambaud, M. *Org. Synth. Coll. Vol. VIII*, **1993**, 265–266.

[29] Mhasni, O.; Rezgui, F. *Tetrahedron Lett*. **2010**, *51*, 586–587.

[30] Mhasni, O.; Rezgui, F. *Tetrahedron* **2022**, *111*, 132732.

[31] Mhasni, O.; Rezgui, F. *J. Chem. Res*. **2013**, 122–124.

[32] Prasad, A. S. B.; Knochel, P. *Tetrahedron* **1997**, *53*, 16711–16720.

[33] Rezgui, F.; El Gaïed, M. M. *Tetrahedron* **1997**, *53*, 15711–15716.

[34] Lee, M. J.; Kim. S. C.; Kim, J. N. *Bull. Korean Chem. Soc*. **2006**, *27*, 140–142.

[35] Chan, T. H.; Schwerdtfeger, A. E. *J. Org. Chem.* **1991**, 56, *10*, 3294–3298.

[36] Zhang, L.; Liu, S.; Lin, Y.; Wang, Y. *Tetrahedron Lett*. **2022**, *93*, 153663.

[37] Li, Y.; Ou, J.; Huang, C.; Liu, F.; Ou, S.; Zheng, J. *Trends Food Sci. Technol*. **2023**, *139*, 104134.