Safe Generation and Direct Use of Diazoesters in Flow Chemistry

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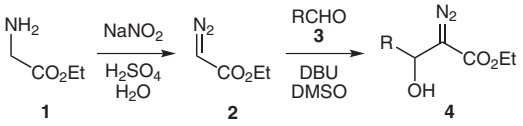
Abstract: A safe and fast method for the production of β-hydroxy-α-diazoesters in continuous flow technology is described. The synthesis involves the formation of ethyl diazoacetate in situ and the addition to several aldehydes in a two-step continuous flow microreactor setup. Rhodium acetate catalyzes a subsequent 1,2-hydride shift to give access to β-keto esters in a three-step sequence.

Key words: addition, aldehydes, diazo compounds, flow chemistry, rhodium

Over the past few decades diazo compounds have been studied extensively in organic synthesis.[1,2] An interesting class of diazo compounds are β-hydroxy-α-diazoesters. Although their major reactivity lies in a 1,2-hydride shift, β-hydroxy-α-diazoesters have proven to be versatile intermediates[3] in the synthesis of asymmetric 1,2-diols[4] and β-amino acids,[5] vinyl diazo carbonyl compounds[6] as well as in fragmentations[7] and for Pd-catalyzed arylation reactions.[8] β-Hydroxy-α-diazoester are usually obtained via an aldol reaction of diazo esters with an aldehyde employing different bases. Unfortunately, the use of β-hydroxy-α-diazoesters as powerful building blocks remains limited in industrial applications as diazo derivatives are considered to be highly energetic compounds with associated hazardous properties.

There are safety concerns associated with handling diazo compounds in batch chemistry. While diazomethane has been reported to explode in contact with sharp glassware and under certain reaction conditions (higher temperature, irradiation, alkali metals),[9] α-diazoesters are more stable. Ethyl diazoacetate is being used for many transformations and its large-scale use has been investigated successfully.[10] Nevertheless, the use of ethyl diazoacetate requires extensive safety considerations in batch chemistry.

In contrast, continuous flow technology has shown great potential in replacing batch techniques for handling reactive intermediates.[11] In a continuous flow setup highly reactive species are not only generated in situ, but also in small quantities at a specific time with methods such as scaling-out and numbering-up for safe production of industrial quantities. Furthermore, due to the high surface-to-volume ratio in microstructured devices typically used for flow chemistry, heat and mass transfer occur very efficiently. Continuous flow in microreactors has already been successfully implemented on hazardous compounds or intermediates such as azides,[12] diethylaminosulfur trifluoride as fluorination agent,[13] hydrazine,[14] diazonium salts[15] as well as diazo compounds.[16] Herein, we describe a two-step flow process giving access to β-hydroxy-α-diazoesters **4** as shown in Scheme 1.



Scheme 1 Synthesis of β-hydroxy-α-diazoesters **4** from glycine ethyl ester (**1**)

A variety of synthetic routes to ethyl diazoacetate (**2**) exist.[17] The method of using glycine ethyl ester (**1**) with sodium nitrite in an acidic, aqueous solution still offers cheap and fast access to **2**. Also other synthetic routes have already been investigated for the formation of ethyl diazoacetate (**2**) in flow chemistry.[16] In a recent report optimal reaction conditions for the synthesis of **2** from glycine ethyl ester (**1**) were carefully evaluated.[18] In our hands the synthesis of ethyl diazoacetate (**2**) proceeded in high yields in a flow system so that we initially investigated their use as nucleophiles after deprotonation. For these experiments pure ethyl diazoacetate (**2**) was used.

α-Diazoesters have been described to undergo nucleophilic addition to aldehydes **3** with bases such as LDA, *n*-BuLi, KHMDS, NaH, NaOH[19] as well as DBU,[20] with the advantage of the latter being comparably easy to handle in organic solvents.

Initially conditions for the condensation reaction of ethyl diazoacetate with benzaldehyde were screened. In accordance with literature precedents,[20] DBU was selected as the base and acetonitrile, dimethylsulfoxide, dichloromethane and water were compared as solvents in the reaction using different temperatures. Water has been successfully used as solvent for the condensation of ethyl diazoacetate with various aldehydes,[21] however, we observed the highest conversions using dimethylsulfoxide (Table 1, entries 5–7). Dichloromethane gave comparably poor yields while acetonitrile gave only a moderate conversion. The use of higher temperatures did not improve conversions and the conditions described in Table 1, entry 5 with 6.8 minutes reaction time at room temperature describe the optimal reaction conditions for the addition reaction leading to a conversion to **4a** in 83%.

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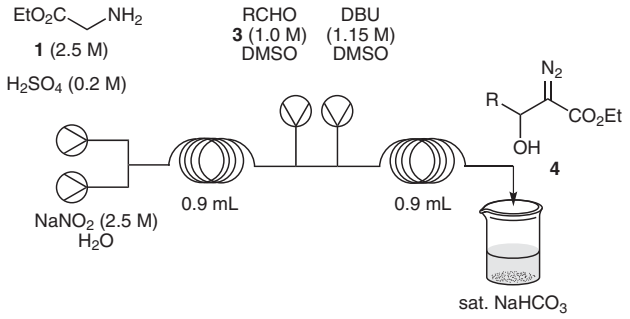
Table 1 Solvent Screening for the Synthesis of α-Hydroxy-β-keto Ester **4a** (R = Ph) in Continuous Flow

Entry	Reaction time (min)	Temperature (ºC)	Solvent	Conversion (%)[a,b]
1	6.8	20	H_2O	31
2	6.8	40	H_2O	63
3	13.5	20	H_2O	71
4	13.5	20	CH_2Cl_2	9
5	6.8	20	DMSO	83
6	3.75	60	DMSO	57
7	1.85	60	DMSO	56
8	2.25	60	MeCN	45

[a] Conversion determined by ^{1}H NMR.
[b] Reaction conditions: DBU (1 equiv), ethyl diazoacetate (**2**; 1 equiv), reactor volume: 0.9 mL.



Scheme 2 Continuous flow setup for the two-step process

In a second stage, the DBU-mediated addition of ethyl diazoacetate (**2**) to aldehydes was combined with a protocol for the synthesis of ethyl diazoacetate in situ as shown in Scheme 2. Optimization studies for the production of α-diazo-β-hydroxy esters **4** in a two-step flow system were performed by altering temperature, reaction time, the amount of base as well as the amount of ethyl diazoacetate (**2**) generated in the first reactor. Some representative results are shown in Table 2.

The reaction time in the second reactor has an important effect on the conversion of the condensation reaction. A residence time of 7.5 minutes (Table 2, entry 14) is significantly lower than in the batch process.[12] Temperatures of 60 °C and higher led to a significant drop in conversion (Table 2, entries 1–5), while a temperature of 40 °C gave a higher conversion than the reaction at room temperature (Table 2, entries 5 and 6). Lowering the equivalents of the in situ generated ethyl diazoacetate below two equivalents (Table 2, entries 8 and 10) resulted in reduced conversions as well as reducing the amount of base below one equivalent (Table 2, entry 9). The best reaction conditions found in this screening led to 96% conversion (Table 2, entry 14) using two equivalents of ethyl diazoacetate (**2**), one equivalent of DBU and 40 ºC reaction temperature for the second step with residence times of 6.8 minutes (first reactor) and 7.5 minutes (second reactor), respectively.

Table 2 Optimization of the Two-Step Flow Process to α-Hydroxy-β-keto Ester **4a** (R = Ph)

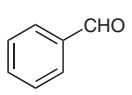
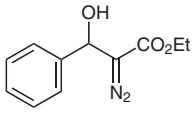
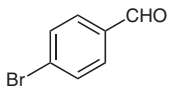
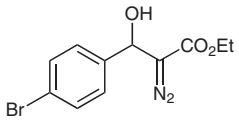
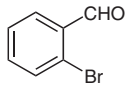
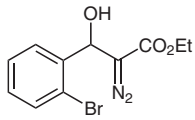
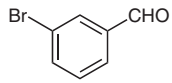
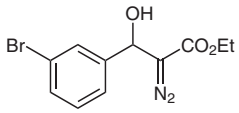
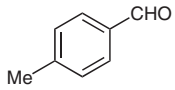
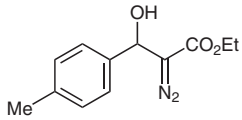
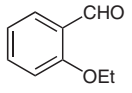
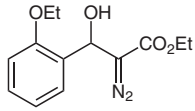
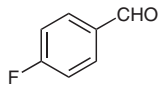
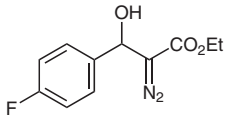
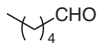
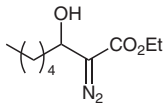
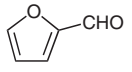
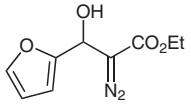
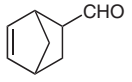
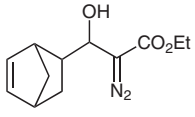
Entry	Total flow rate[a] (mL/min)	Temperature of second reactor (°C)	**2**/DBU[b] (equiv)	Conversion (%)[c]
1	4	60	1:1.7	28
2	4	60	3:1	69
3	1.34	60	1:1.7	45
4	0.8	60	1:1.7	43
5	0.8	75	1:1.7	40
6	0.26	20	1:2.3	74
7	0.26	40	2:2.3	83
8	0.26	40	1.5:2	73
9	0.26	40	1.7:0.7	57
10	0.26	40	1.7:1	75
11	0.26	40	2:1	80
12	0.26	40	1.5:1	76
13	0.4	40	2:1	56
14[d]	0.26	40	2:1	96

[a] Each pump had identical flow rate (Total flow rate/4).
[b] Amount of aldehyde **3** used was 1 equiv.
[c] Conversion determined by ^{1}H NMR.
[d] Second reactor: 2 mL (0.8 mm i.d.).

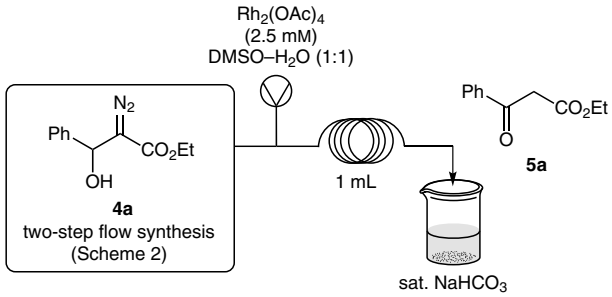
Different aldehydes were investigated in the two-step flow process under optimized reaction conditions. The results are shown in Table 3.

The two-step flow system gives access to aliphatic (Table 3, entry 8) and aromatic α-diazo-β-hydroxy esters **4** in good to excellent yields. A variety of aromatic aldehydes can act as electrophiles with good yields, irrespective of their electronic properties. Electron-withdrawing (Table 3, entries 2–4 and 7) and electron-donating functionalities (Table 3, entry 6) work equally well. The reactions shown in Table 3, entries 7 and 8 were performed before the development of optimal reaction conditions. In our hands, *ortho*-bromobenzaldehyde gave higher yields than the *meta* or *para* derivatives (Table 3, entries 2–4). Ketones or lactones are, however, not suitable substrates and there is no conversion observed for acetophenone and γ-butyrolactone in the DBU-mediated addition to **2** under continuous flow conditions. The reaction was scaled up to 38 mmol benzaldehyde giving access to 6 g of ethyl 2-diazo-3-hydroxy-3-phenylpropanoate (**4a**) in 72% yield in less than two hours. The slightly lower yields are due to difficulties in the chromatography of the larger quantities of reaction product.

Table 3 Conversion of Various Aldehydes in the Two-Step Flow Process under Optimized Reaction Conditions

Entry	Aldehyde **3**	Product **4**	Yield (%)
1	 **3a**	 **4s**	82 72[a]
2	 **3b**	 **4b**	74[b]
3	 **3c**	 **4c**	96
4	 **3d**	 **4d**	82
5	 **3e**	 **4e**	77
6	 **3f**	 **4f**	85
7	 **3g**	 **4g**	82[b]
8	 **3h**	 **4h**	66[b]
9	 **3i**	 **4i**	45
10	 **3j**	 **4j**	75

[a] Reaction was performed on a 38-mmol scale.
[b] Conditions of Table 2, entry 7 were used.



Scheme 3 Flow set-up for the three-step process

α-Diazo-β-hydroxy ester can undergo readily C–H migration reactions with metal catalysts under nitrogen expulsion.[22] We therefore investigated the coupling of a third step to the reaction setup using $Rh_2(OAc)_4$ as catalyst. The 1,2-hydride shift was first investigated as a single-step flow reaction with **4a** as starting material, addition of a solution of $Rh_2(OAc)_4$ as catalyst and using a silica plug directly after the flow reaction as quench. No diazoalcohol **4a** was left even with residence times of less than a minute; the set-up described in Scheme 3 was used subsequently to enable a direct workup. Diazoalcohol **4a** was no longer detectable in the crude NMR after workup, confirming complete reaction to the β-keto ester **5a**, which was isolated in 73% yield.

In conclusion, we have described a quick and concise method for the synthesis of α-diazo-β-hydroxy ester.[23] The residence time for the addition reaction could be as low as six minutes while still resulting in very good yields. No isolation of the highly energetic ethyl diazoacetate was required. The method is reliable for scale up and can be combined with the rhodium-catalyzed 1,2-hydride shift.[24]

Acknowledgment

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(22) Pellicciari, R.; Fringuelli, R.; Ceccherelli, P.; Sisani, E. *J. Chem. Soc., Chem. Commun.* **1979**, 959.
(23) **General Procedure for the Two-Step Process**: Glycine ethyl ester hydrochloride (1.12 g, 8 mmol) was dissolved in H_2O (2.5 mL) and 5% sulfuric acid (0.76 mL, w/w) was added and a 4-mL syringe was equipped with the mixture. Next, $NaNO_2$ (664 mg, 10 mmol) was dissolved in H_2O (3.9 mL) and another 4-mL syringe was equipped with this solution. The two syringes were connected to a flow setup with a T-piece mixer and a 0.9-mL coil (PTFE, i.d. = 0.5 mm). 1,8-Diazabicycloundec-7-ene (596 µL, 4 mmol) was dissolved in dimethylsulfoxide (3.4 mL) and charged into a 4-mL syringe. Aldehyde (4 mmol) was dissolved in the required amount of DMSO to have a solution of exactly 4 mL volume. This mixture was charged into another 4-mL syringe. Both syringes were put to another syringe pump and connected with two T-pieces to the outlet of the first coil as well as to the inlet of the second coil. The second coil consisted of a 2-mL coil (PTFE, i.d. = 0.8 mm). The pumps were set to 4 mL/h and the entire setup ran for 28 min to reach the steady state. Afterwards, the product was collected for 20–30 min in $NaHCO_3$ as quenching agent. Extraction was performed with CH_2Cl_2 (3 × 10 mL), the combined organic layers were washed with H_2O thoroughly (3 × 10 mL) and dried over anhyd $MgSO_4$. After evaporating the solvent in vacuo, the diazoalcohol was purified by column chromatography (hexane–EtOAc gradient, 100% hexane to 85% hexane).

Ethyl 2-Diazo-3-hydroxy-3-phenylpropanoate (4a): obtained as a yellow thick oil; 363 mg (30 min collection time; 82% yield; 6.05 g, 115 min collection time, 72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (m, 5 H, ArH), 6.11 (d, *J* = 3.5 Hz, 1 H, C*H*OH), 4.47 (q, *J* = 7.5 Hz, 2 H, CH_2CH_3), 3.26 (br s, 1 H, OH), 1.50 (t, *J* = 7.5 Hz, 3 H, CH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.8, 139.2, 129.1, 128.6, 126.0, 69.2, 61.6, 15.0. MS (EI): *m/z* = 220.09 [M^+].

Ethyl 3-(4-Bromophenyl)-2-diazo-3-hydroxypropanoate (4b): obtained as a yellow oil; 295 mg (20 min collection time; 74% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (m, 2 H, ArH), 7.58 (m, 2 H, ArH), 6.15 (d, *J* = 3.5 Hz, 1 H, C*H*OH), 4.55 (q, *J* = 7.0 Hz, 2 H, CH_2CH_3), 3.47 (br s, 1 H, CHO*H*), 1.58 (t, *J* = 7.5 Hz, 3 H, CH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.8, 138.4, 132.5, 128.1, 122.8, 68.8, 61.8, 15.0. MS (EI): *m/z* = 297.98 [M^+].

Ethyl 3-(2-Bromophenyl)-2-diazo-3-hydroxypropanoate (4c): obtained as a yellow oil; 421 mg (22 min collection time; 96% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.71 (dd, *J* = 8.0, 1.5 Hz, 1 H, ArH), 7.57 (dd, *J* = 8.0, 1.0 Hz, 1 H, ArH), 7.39 (td, *J* = 7.5, 1.5 Hz, 1 H, ArH), 7.20 (td, *J* = 8.0, 1.5 Hz, 1 H, ArH), 6.09 (s, 1 H, C*H*OH), 4.29 (m, 2 H, CH_2CH_3), 3.34 (br s, 1 H, CHO*H*), 1.30 (t, *J* = 7.0 Hz, 3 H, CH_2CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.3, 137.7, 132.9, 127.8, 127.6, 121.6, 68.8, 61.3, 14.8.

Ethyl 3-(3-Bromophenyl)-2-diazo-3-hydroxypropanoate (4d): obtained as a yellow oil; 362 mg (22 min collection time; 82% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.61 (m, 1 H, ArH), 7.46 (d, *J* = 8.0 Hz, 1 H, ArH), 7.35 (d, *J* = 8.0 Hz, 1 H, ArH), 7.26 (t, *J* = 7.5 Hz, 1 H, ArH), 5.87 (s, 1 H, C*H*OH), 4.28 (q, *J* = 7.0 Hz, 2 H, CH_2CH_3), 3.09 (br s, 1 H, CHO*H*), 1.30 (t, *J* = 7.0 Hz, 3 H, CH_2CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.2, 141.1, 131.4, 130.5, 128.9, 124.5, 123.0, 68.1, 61.4, 14.5.

Ethyl 2-Diazo-3-hydroxy-3-(*p*-tolyl)propanoate (4e): obtained as a yellow oil; 203 mg (17 min collection time; 77% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.31 (d, *J* = 8.0 Hz, 2 H, ArH), 7.19 (d, *J* = 8.0 Hz, 2 H, ArH), 5.88 (s, 1 H, C*H*OH), 4.27 (q, *J* = 7.0 Hz, 2 H, CH_2CH_3), 3.12 (br s, 1 H, CHO*H*), 2.35 (s, 3 H, ArMe), 1.29 (t, *J* = 7.0 Hz, 3 H, CH_2CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.5, 138.2, 135.6, 129.4, 125.7, 68.7, 61.1, 21.1, 14.5.

Ethyl 2-Diazo-3-(2-ethoxyphenyl)-3-hydroxypropanoate (4f): obtained as a yellow solid; 328 mg (22 min collection time; 85% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.44 (d, *J* = 7.5 Hz, 1 H, ArH), 7.28 (td, *J* = 8.0, 1.5 Hz, 1 H, ArH), 6.98 (dt, *J* = 7.5, 1 Hz, 1 H, ArH), 6.90 (d, *J* = 8.0 Hz, 1 H, ArH), 5.90 (d, *J* = 6.5 Hz, 1 H, C*H*OH), 4.25 (q, *J* = 7.0 Hz, 2 H, $CO_2CH_2CH_3$), 4.08 (m, 2 H, OCH_2CH_3), 3.62 (br s, 1 H, CHO*H*), 1.42 (t, *J* = 7.0 Hz, 3 H, OCH_2CH_3), 1.29 (t, *J* = 7.0 Hz, 3 H, $CO_2CH_2CH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.5, 155.4, 129.3, 127.2, 127.2, 120.8, 111.2, 66.4, 63.7, 60.9, 14.8, 14.5.

Ethyl 2-Diazo-3-(4-fluorophenyl)-3-hydroxypropanoate (4g): obtained as a yellow oil; 259.8 mg (20 min collection time; 1.09 mmol, 82%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 (m, 2 H, ArH), 7.35 (m, 2 H, ArH), 6.17 (d, *J* = 3.5 Hz, 1 H, C*H*OH), 4.55 (q, *J* = 7.0 Hz, 2 H, CH_2CH_3), 3.36 (br s, 1 H, CHO*H*), 1.57 (t, *J* = 7.0 Hz, 3 H, CH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.0, 163.5 (d, *J* = 234 Hz), 135.4, 128.2 (d, *J* = 9 Hz), 116.3 (d, *J* = 20 Hz), 68.8, 61.9, 15.1. MS (EI): *m/z* = 238.07 [M^+].

Ethyl 2-Diazo-3-hydroxyoctanoate (4h): obtained as pale

yellow oil; 188 mg (20 min collection time; 66% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.90 (dt, *J* = 4.5, 9.5 Hz, 1 H, C*H*OH), 4.47 (q, *J* = 7.0 Hz, 2 H, OC*H*$_2$CH$_3$), 2.80 (br s, 1 H, CHO*H*), 1.86 (m, 2 H, C*H*$_2$CHOH), 1.53 (m, 9 H, C*H*$_2$C*H*$_2$C*H*$_2$C*H*$_3$), 1.12 (t, *J* = 7.0 Hz, 3 H, OCH$_2$C*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.3, 67.3, 61.6, 34.5, 32.0, 25.8, 23.1, 15.1, 14.6. MS (EI): *m/z* = 214.14 [M$^+$].

Ethyl 2-Diazo-3-(furan-2-yl)-3-hydroxypropanoate (4i): obtained as a yellow oil; 94 mg (15 min collection time; 45% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49 (t, *J* = 0.8 Hz, 1 H, OCH=C), 6.46 (m, 2 H, CH=CH), 5.91 (d, *J* = 4.5 Hz, 1 H), 5.64 (d, *J* = 5.0 Hz, 1 H), 4.35 (q, *J* = 7.0 Hz, 2 H), 1.38 (t, *J* = 7.5 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.1, 143.4, 143.1, 110.7, 107.8, 63.9, 61.5, 14.7. MS (EI): *m/z* = 208.11 [M$^+$].

Ethyl 3-(Bicyclo[2.2.1]hept-5-en-2-yl)-2-diazo-3-hydroxypropanoate (4j): obtained as a yellow oil; 238 mg (20 min collection time; 75% yield). MS (EI): *m/z* = 236.12 [M$^+$].

General Procedure for the Three-Step Process: Syringes, pumps, reagents and flow setup were built the way as described for the two-step procedure. Rhodium acetate dimer (0.025 mmol, 11 mg) was dissolved in a H_2O–DMSO (1:1; 10 mL) mixture. The solution was charged onto a 10-mL syringe and put on a third syringe pump which was calibrated on a flow rate of 16 mL/h to run through the third reactor (i.d. 0.8 mm, 1 mL). After the first two reactors had reached steady state, the third pump was started and collection commenced after another 4 min after the last reactor has reached steady state. The product was collected for 20–30 min in sat. $NaHCO_3$ solution. Extraction was performed with CH_2Cl_2 (3 × 10 mL), the combined organic layers were washed with H_2O (3 × 10 mL) and dried over anhyd $MgSO_4$. After evaporating the solvent in vacuo, the β-keto ester was purified by column chromatography (hexane–EtOAc, 98:2).

Ethyl 3-Oxo-3-phenylpropanoate (5a): obtained as a colourless oil; 187 mg (20 min collection time; 73% yield). Keto form: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (m, 2 H, ArH), 7.39 (m, 3 H, ArH), 4.14 (q, *J* = 7.0 Hz, 2 H, C*H*$_2$CH$_3$), 3.92 (s, 2 H, OCCH$_2$CO), 1.18 (t, *J* = 7.0 Hz, 3 H, C*H*$_3$CH$_2$). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 193.2, 168.1, 134.4, 129.4, 60.9, 40.6, 14.6. Enol form: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.78 (s, 1 H, OH), 7.70 (m, 2 H, ArH), 7.53 (m, 2 H, ArH), 7.34 (m, 1 H, ArH), 5.60 (s, 1 H, C=CH), 4.19 (q, *J* = 7.0 Hz, 2 H, OC*H*$_2$CH$_3$), 1.26 (t, *J* = 7.0 Hz, 3 H, OCH$_2$C*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.8, 172.0, 134.0, 131.8, 126.6, 88.0, 60.9, 14.9. MS (EI): *m/z* = 192.07 [M$^+$].

(24) During the finalization of this manuscript, a similar report has been published: Maurya, R. A.; Min, K.-I.; Kim, D.-P. *Green Chem.* **2014**, *16*, 116.