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α-Diketones as acyl anion equivalents: a non-enzymatic thiamine-promoted route to aldehyde–ketone coupling in PEG_{400} as recyclable medium

Olga Bortolini [a], Giancarlo Fantin [a,*], Marco Fogagnolo [a], Pier Paolo Giovannini [b], Valentina Venturi [b], Salvatore Pacifico [a], Alessandro Massi [a,*]

[a] Dipartimento di Chimica, Laboratorio di Chimica Organica, Università di Ferrara, Via L. Borsari 46, I-44121 Ferrara, Italy
[b] Dipartimento di Biologia ed Evoluzione, Università di Ferrara, Corso Ercole I D'Este, 32, I-44121 Ferrara, Italy

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ABSTRACT

By mimicking the peculiar behavior of thiamine diphosphate-dependent acetylacetoin synthase, it has been demonstrated that thiamine hydrochloride **2a** and its simple analogue thiazolium salt **2b** are able to activate α-diketones as acyl anion equivalents in nucleophilic acylations, such as the homo-coupling of α-diketones and the hitherto unreported cross-coupling between α-diketones and α-ketoesters. These carboligation reactions were optimized under stoichiometric (**2a**) and catalytic conditions (**2b**) by using eco-friendly PEG_{400} as the reaction medium, thus allowing both solvent and thiazolium salt recycling.

1. Introduction

Thiamine diphosphate (ThDP)-dependent enzymes, such as pyruvate decarboxylase (PDC), benzaldehyde lyase (BAL), and benzoylformate decarboxylase (BDF), are a group of biocatalysts involved in a variety of reactions including the formation and cleavage of carbon–carbon bonds.[1] These enzymes have in common the capability to generate an 'active aldehyde' species,[2] that is, a ThDP-bound carbanion–enamine intermediate, which reacts with an aldehyde acceptor to form a α-hydroxyketone in an acyloin-type condensation.[2] Within this area of research, a recent study from our group demonstrated that 1,2-diketones may serve as acyl anion equivalents when ThDP-dependent acetylacetoin synthase (AAS) is utilized as catalyst in the homo-coupling of 1,2-diketones to form chiral α-hydroxyketones (Fig. 1).[3,4] This finding triggered us to investigate a possible biomimetic route, reminiscent of ThDP activity,[5] to nucleophilic acylations involving α-diketones as acyl anion donors. By considering the peculiar mechanism of action of AAS,[3] it was envisaged that the sole thiamine coenzyme (pre-catalyst) in the presence of a suitable base could display the same ability to activate α-diketones as acyl anion sources.[6] Hence, the optimization of an organocatalytic (racemic) version of the already disclosed enzymatic homo-coupling of 1,2-diketones[3] (virtually an intermolecular aldehyde–ketone coupling) was initially considered. Subsequently, the more challenging thiamine-catalyzed direct cross-coupling reaction between diketone donors and α-ketoester acceptors was also investigated to explore the potential of the proposed carboligation methodology (Fig. 1). Indeed, while significant advances have been recently made in *N*-heterocyclic carbene (NHC) catalysis[7] to promote intramolecular aldehyde–ketone couplings,[8] examples of the non-enzymatic intermolecular variant are limited to the study by Enders and Henseler,[9] which described the cross-coupling between aldehydes and

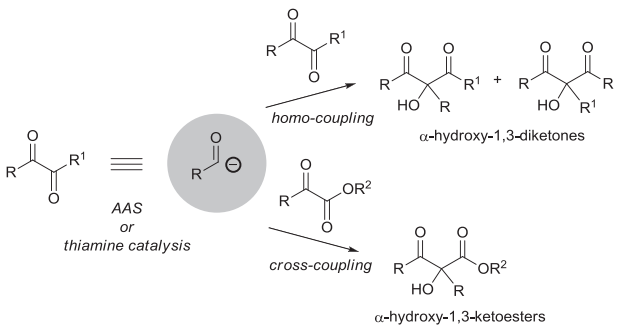

Fig. 1. Synthesis of α-hydroxy-1,3-diketones and α-hydroxy-1,3-ketoesters using α-diketones as acyl anion equivalents.

* Corresponding authors. E-mail addresses: giancarlo.fantin@unife.it (G. Fantin), msslsn@unife.it (A. Massi).

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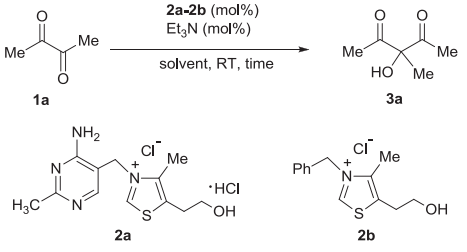
highly electrophilic trifluoromethyl ketones using a bicyclic triazolium salt as the pre-catalyst.[10]

2. Results and discussion

In analogy with our previous enzymatic study,[3] we initially investigated the activity of the thiamine hydrochloride **2a**-Et_3N couple in water using 2,3-butanedione (biacetyl) **1a** as donor–acceptor substrate (Table 1, entry 1). Triethylamine was chosen as the base to reproduce the basic strength of active sites in the catalytic pocket of ThDP-dependent enzymes.[11] Against the almost complete consumption of **1a** as determined by TLC and ^1H NMR analyses, only small amounts of the expected product **3a** survived to these conditions, in agreement with an old report of Mizuhara and Handler[6] asserting that biacetyl **1a**, in aqueous alkaline medium and in the presence of thiamine, is cleaved to acetaldehyde and 2-(1-hydroxyethyl)-thiamine. On the other hand, the α-hydroxy-1,3-diketone **3a** product has been reported to be unstable under basic and thermal conditions due to a complex sequence of equilibra involving the corresponding oxy-anions.[12] These multiple rearrangements are also active in the presence of mild bases as sodium bicarbonate. Our findings, however, suggest that the instability of **3**-like products is related not only to the presence of a base but, and more importantly, to the concomitant use of an aqueous medium, as demonstrated by the results found for the condensation of **1a** promoted by the thiamine hydrochloride **2a**-Et_3N couple in EtOH (entry 2). In this case, the expected product **3a** was in fact obtained in 75% isolated yield. It is worth stressing that crucial for a successful work-up was the purification of **3a** by distillation. Encouraged by these promising results, we decided to widen the selection of protic solvents with polyethylene glycol (PEG_{400}), a non-toxic and eco-friendly medium that should allow for both solvent and pre-catalyst recycling.[13] Hence, when the mixture of **1a** (0.5 M), thiamine hydrochloride **2a** (1 equiv), and Et_3N (2 equiv) in PEG_{400} was stirred for 3 h, the target α-hydroxyketone **3a** was recovered in almost quantitative yield (95%) after extraction with Et_2O and subsequent product distillation (entry 3). Rewardingly, the PEG solution containing the thiamine promoter could be reloaded with fresh diketone **1a** and Et_3N to afford **3a** in 90% isolated yield (entry 4). Additional recycles (up to five) resulted equally effective with minimal loss of product yield. No change in the reaction outcome occurred on moving from stoichiometric to catalytic conditions (**2a**, 20 mol %), although a modest conversion (45%) was achieved within a reasonable reaction time (48 h, entry 5). Fortunately, the use of the commercially available thiazolium salt **2b**, that is, a simplified analogue of thiamine **2a**, greatly increased the reaction rate and **3a** was recovered in almost quantitative yield after 12 h stirring and standard work-up (entry 6). The recyclability of **2b** in PEG_{400} was finally demonstrated as before (entry 7).

We then examined the tolerance of the procedure for different donor–acceptor substrates with stoichiometric thiamine **2a** (Method A, Table 2) and found that 3,4-hexanedione **1b** was successfully converted to the expected product **3b** (88%, entry 1). When the protocol was extended to the unsymmetrically substituted dialkyl α-diketones **1c**–**e** (entries 2–4), it was observed that acetyl anion transfer ($MeCO^-$) was predominant over migration of its higher carbanion counterparts, in full agreement with the

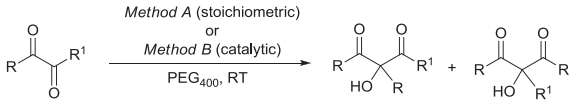
Table 1
Optimization of the homo-coupling of 2,3-butanedione **1a**[a]



Entry	Catalyst (mol %)	Solvent	Time (h)	**3a** Yield (%)[b]
1[c]	**2a** (100)	H_2O	5	<5
2[c]	**2a** (100)	EtOH	5	75
3[c]	**2a** (100)	PEG_{400}	3	95
4[c,d]	**2a** (100)	PEG_{400}	3	90
5[e]	**2a** (20)	PEG_{400}	48	45
6[e]	**2b** (20)	PEG_{400}	12	95
7[d,e]	**2b** (20)	PEG_{400}	12	91

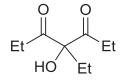
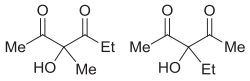
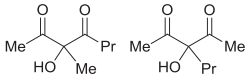
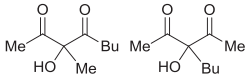
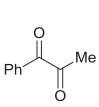
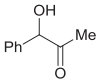
[a] Reactions performed with 2.0 mmol of **1a** (0.5 M).
[b] Isolated yield.
[c] Et_3N: 200 mol %.
[d] Reaction performed with recycled **2** and PEG_{400} after addition of fresh Et_3N.
[e] Et_3N:100 mol %.

Table 2
Short study on the applicability of the optimized stoichiometric and catalytic homo-coupling procedures to selected α-diketones[a]



1b: R = R^1 = Et
1c: R = Me; R^1= Et
1d: R = Me; R^1 = Pr
1e: R = Me; R^1 = Bu
1f: R = Ph; R^1 = Me

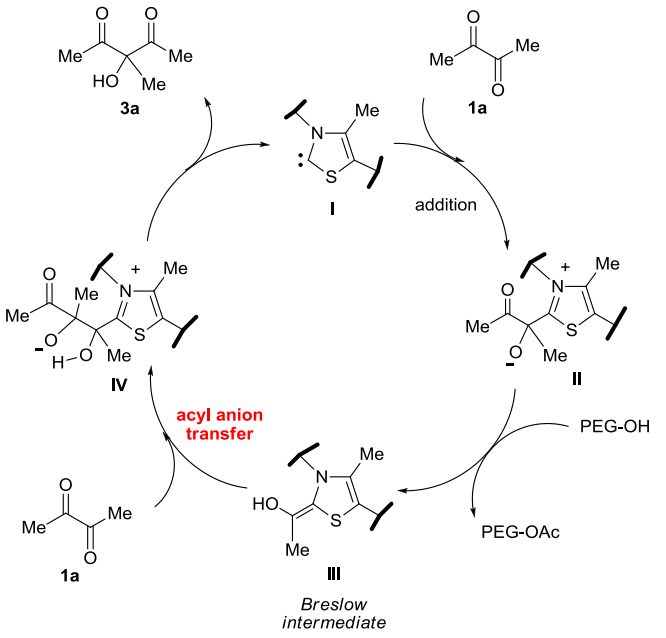
Method A: **2a** (100 mol%), Et_3N (200 mol%), 3-5 h
Method B: **2b** (20 mol%), Et_3N (100 mol%), 12-24 h

Entry	α-Diketone	α-Hydroxy-1,3-diketone (Method A (%); Method B (%))[b]
1	 **1b**	 **3b** (88%; 82%)
2	 **1c**	 **3c** (71%; 74%)[c] **4c** (11%; 7%)[c,d]
3	 **1d**	 **3d** (65%; 61%)[e] **4d** (24%; 27%)[d,e]
4	 **1e**	 **3e** (67%;63%)[f] **4e** (17%;19%)[d,f]
5	 **1f**	 **5f** (78%; 75%)

[a] Reactions performed with 2.0 mmol of diketone (0.5 M).
[b] Isolated yield.
[c] Lower amounts (<10%) of coupling products arising from propionyl anion transfer were also detected (GC–MS and ^1H NMR analyses).
[d] Yield determined by ^1H NMR analysis of the crude reaction mixture using bromoform as internal standard.
[e] Lower amounts (<10%) of coupling products arising from butyryl anion transfer were also detected.
[f] Lower amounts (<10%) of coupling products arising from pentanoyl anion transfer were also detected.

reactivity pertaining to the AAS enzymatic system.[3] Accordingly, the corresponding α-hydroxyketones **3c**–**e** (65–71%) were isolated together with lower amounts (11–24%) of the isomeric derivatives **4c**–**e** (entries 2–4). As previously observed, the results obtained in the above transformations with catalytic **2b** (Method B) closely paralleled those detected with stoichiometric thiamine **2a** although with a longer reaction time (12–24 h).

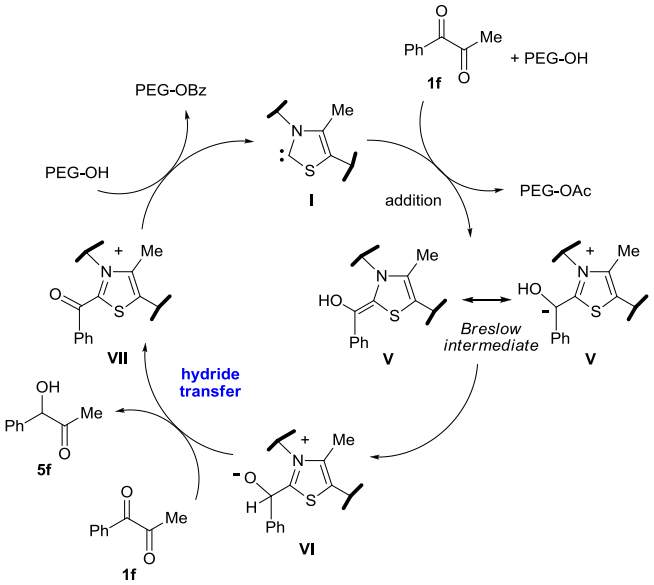
The mechanism that accounts for all these findings may invoke the formation of the intermediate **II** resulting from the addition of the thiazolin-2-ylidene **I** to the α-diketone **1**, and its evolution to the Breslow intermediate **III** by attack of the PEG solvent to the carbonyl of **II**. Subsequent addition of the Breslow intermediate to the acceptor, that is, a second molecule of α-diketone **1**, leads to the formation of the product **3** and regeneration of the catalyst **I** (Scheme 1).[14] It is worth noting that formation of the key intermediate **III** by the above postulated mechanism seems to be confirmed by the isolation of 1 equiv of acetylated PEG solvent (PEG-OAc) from the crude reaction mixture.[15]



Scheme 1. Proposed reaction pathway for the homo-coupling of alkyl diketones **1a**–**e** (substrate **1a** as representative example).

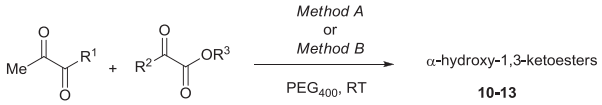
The overall reactivity of the thiazolium-promoted homo-coupling of α-diketones **1** can be fully explained by Scheme 1, except when the formation of a phenyl-substituted Breslow intermediate of type **V** occurs (Scheme 2). This is demonstrated by the results observed in the homo-coupling of 1-phenyl-1,2-propanedione **1f** (Table 2, entry 5). In that case, the fate of intermediate **V** seems to be different with generation, through prototropic rearrangement to **VI**,[16] of a hydride equivalent, that is, transferred to the acceptor **1f**. Once the α-diketone undergoes reduction to **5f**,[17] the thiazolin-2-ylidene **I** is regenerated by transfer of the benzoyl group from the acyl thiazolium intermediate **VII** to PEG (Scheme 2).[15,18]

In a next set of experiments we investigated the donor–acceptor attitudes of α-ketoesters toward the thiazolium-Et_3N system. In a control experiment (Table 3, entry 1), ethyl pyruvate **6** was not reactive under the previously optimized homo-coupling conditions (Methods A and B). This finding, however, may be exploited to perform cross-coupling reactions between α-ketoester acceptors and a suitable acyl anion donor, such as **1a**. To explore this hitherto unreported carboligation reaction, the commercially available α-ketoester esters **6**–**9** (3 equiv) were coupled with **1a** under optimal stoichiometric and catalytic conditions (entries 2–5). Gratifyingly,



Scheme 2. Proposed reaction pathway for the reduction of **1f**.

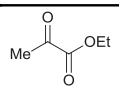
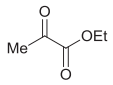
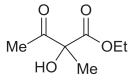
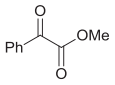
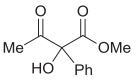
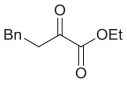
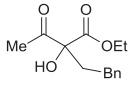
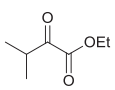
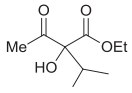
Table 3
Homo-coupling of ethyl pyruvate **6** and cross-couplings between **1a** and selected α-ketoesters **6**–**9**[a]



1a; R^1 = Me
6; R^1 = OEt

6-9

Method A: **2a** (100 mol%), Et_3N (200 mol%), 3–8 h
Method B: **2b** (20 mol%), Et_3N (100 mol%), 12–48 h

Entry	Donor	Acceptor	α-Hydroxy-1,3-ketoesters (Method A(%); Method B (%))[b]
1	**6**	 **6**	No reaction
2	**1a**	 **6**	 **10** (55%; 52%)
3	**1a**	 **7**	 **11** (42%; 51%)
4	**1a**	 **8**	 **12** (50%; 58%)
5	**1a**	 **9**	 **13** (51%; 48%)

[a] All reactions performed with 3 equiv of α-ketoester acceptor.
[b] Isolated yield.

the corresponding α-hydroxy-1,3-ketoesters **10**–**13** were obtained in fair yields (around 50%), thus demonstrating the feasibility of this approach. While the side homo-coupling reaction of **1a** could not be suppressed under these conditions, the isolation of the target products **10**–**13** was facilitated by the volatile nature of the homo-coupling by-product **3a**.

3. Conclusion

In summary, we have demonstrated that 1,2-diketones may serve as acyl anion equivalents in thiamine-promoted α-diketone homo-couplings in analogy with a previously reported ThDP-dependent enzymatic system. In addition, a novel substrate combination, that is, α-diketone to α-ketoester, has been investigated by using the same thiamine promoter. The setup of a catalytic procedure for the above transformations has also been optimized by employing a more active analogue of thiamine as the pre-catalyst. Polyethylene glycol (PEG_{400}) has been shown to be an effective and reusable reaction medium for the above transformations. Further investigations of the generality of the disclosed mode of acyl anion generation and the development of NHC-promoted asymmetric variants are currently underway in our laboratories.

4. Experimental section

4.1. General remarks

Reactions were monitored by TLC on silica gel 60 F_{254} with detection by charring with phosphomolybdic acid. Flash column chromatography was performed on silica gel 60 (230–400 mesh). Bulb-to-bulb distillation was performed with a Büchi Glass Oven B-580 apparatus. ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded in $CDCl_3$ solutions at room temperature. Peaks assignments were aided by ^1H–^1H COSY and gradient-HMQC experiments. GC–MS spectra were recorded using a Varian 4000 GC/MS/MS system equipped with a fused capillary column Megadex 5 (25m×0.25 mm) containing dimethyl-*n*-pentyl-β-cyclodextrin on OV 1701. Analyses were carried out with a gradient of 1.5 °C/min (from 80 °C up to 200 °C); retention times (t_R) are given in minutes. ESI MS analyses were performed in positive ion mode with samples dissolved in 10 mM solution of ammonium formate in 1:1 MeCN/H_2O. For accurate mass measurements the compounds were analyzed in positive ion mode by electrospray ionization (ESI) hybrid quadrupole orthogonal acceleration time-of-flight mass spectrometer (Q-TOF MS) fitted with a Z-spray electrospray ion source (Waters, Manchester, UK). The capillary source voltage and the cone voltage were set at 3200 V and 45 V, respectively; the source temperature was kept at 120 °C; nitrogen was used as a drying gas at a flow rate of ca. 80 L/h. The time-of-flight analyzer was externally calibrated with NaI from *m*/*z* 300 to 2000 to yield accuracy near to 5 ppm. Accurate mass data were collected by directly infusing samples (10 pmol/μL in 1:1 MeCN/H_2O+0.1% ammonium formate) into the system at a flow rate of 5 μL/min. Spectroscopic data of compounds **3a**,[3,19] **3b**,[3,20] **3c**,**d**,[3,21] **3e**,[21] **4c**,[3] **4d**,[3] **5f**,[22] **10**,[23] and **13**[24] were identical to those reported in the literature. Copies of the ^1H spectra of **3a**–**e**, **4d**, **5f**, **10**, and **13** are reported as purity and identity documentation.

4.2. Optimized procedure for the homo-coupling of α-diketones 1a–e

Method A. To a vigorously stirred mixture of thiamine hydrochloride **2a** (337 mg, 1.00 mmol), Et_3N (279 μL, 2.00 mmol), and PEG_{400} (4 mL) α-diketone **1** (2.00 mmol) was added in one portion. The mixture was stirred at room temperature until TLC analysis revealed the disappearance of the starting α-diketone (3–5 h). The reaction medium was then diluted with Et_2O (5 mL), vigorously stirred for 5 min, allowed to separate out and the ethereal solution was decanted. This process was repeated twice to obtain the crude α-hydroxyketone **3** in Et_2O, whereas the mother liquor (PEG_{400}-thiamine hydrochloride **2a**) was kept aside for further runs. The extraction solvent was then removed under a nitrogen stream and the residue containing the target α-hydroxyketone purified by either bulb-to-bulb distillation (compounds **3a** and **3b**) or flash chromatography (compounds **3c**–**e**). Product yields are reported in the next paragraphs for Method A.

Method B. To a vigorously stirred mixture of 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride **2b** (54 mg, 0.20 mmol), Et_3N (140 μL, 1.00 mmol), and PEG_{400} (4 mL) α-diketone **1** (2.00 mmol) was added in one portion. The mixture was stirred at room temperature until TLC analysis revealed the disappearance of the starting α-diketone (12–24 h). The reaction medium was then diluted with Et_2O (5 mL), vigorously stirred for 5 min, allowed to separate out and the ethereal solution was decanted. This process was repeated twice to obtain the crude α-hydroxyketone **3** in Et_2O, whereas the mother liquor (PEG_{400}-methylthiazolium **2b**) was kept aside for further runs. The extraction solvent was then removed under a nitrogen stream and the residue containing the target α-hydroxyketone purified as described above. Product yields for Method B are reported in Table 2.

*4.2.1. 3-Hydroxy-3-methylpentane-2,4-dione (**3a**).* The crude reaction mixture was bulb-to-bulb distilled (50 °C, 5 mmHg) to give **3a**[3,19] (124 mg, 95%) as a colorless liquid. Lit.:[19b] bp 43–44 °C (4 mmHg). ESI MS (130.1): 153.5 ($M+Na^+$). Compound **3a** partially decomposes on silica gel.

*4.2.2. 4-Ethyl-4-hydroxyheptane-3,5-dione (**3b**).* The crude reaction mixture was bulb-to-bulb distilled (84 °C, 5 mmHg) to give **3b**[3,20] (151 mg, 88%) as a colorless liquid. ESI MS (172.1): 195.8 ($M+Na^+$). Compound **3b** partially decomposes on silica gel.

*4.2.3. (R/S)-3-Hydroxy-3-methylhexane-2,4-dione (**3c**).* Column chromatography with 12:1 cyclohexane/AcOEt afforded **3c**[3,21] (102 mg, 71%) as a colorless oil. ESI MS (144.1): 145.1 ($M+H^+$). A chromatographic fraction containing **4c** but slightly contaminated by **3c** was collected for **4c**[3] identification (^1H NMR analysis). Compound **4c** partially decomposes on silica gel.

*4.2.4. (R/S)-3-Hydroxy-3-methylheptane-2,4-dione (**3d**).* Column chromatography with 12:1 cyclohexane/AcOEt afforded **3d**[3,21] (102 mg, 65%) as a colorless oil. ESI MS (158.1): 181.7 ($M+Na^+$). A chromatographic fraction containing **4d** was collected for **4d**[3] identification (^1H NMR analysis). Compound **4d** partially decomposes on silica gel.

*4.2.5. (R/S)-3-Hydroxy-3-methyloctane-2,4-dione (**3e**).* Column chromatography with 12:1 cyclohexane/AcOEt afforded **3e**[21] (115 mg, 67%) as a colorless oil. GC–MS (70 eV, EI): t_R 23.65 (first enantiomer); 23.84 (second enantiomer), *m*/*z* 172 (M^+,<1%), 130 (20), 88 (100), 43 (45). ESI MS (172.1): 195.5 ($M+Na^+$). A chromatographic fraction containing **4e** was collected for **4e** identification. 3-Butyl-3-hydroxypentane-2,4-dione **4e**: GC–MS (70 eV, EI): t_R 20.90, *m*/*z* 172 (M^+,<1%), 130 (100), 43 (68). ^1H NMR: δ=4.65 (br s, 1H, OH), 2.25 (s, 6H, $CH_3(CO)$), 2.04–1.95 (m, 2H, 2 H-4′), 1.40–1.19 (m, 4H, 2 H-2′, 2 H-3′), 0.90 (t, 3H, *J*=7.0 Hz, CH_3). ^{13}C NMR: δ=207.6 (2C), 91.0 (C), 36.1 (CH_2), 25.3 (CH_2), 25.2 (2 CH_3), 22.7 (CH_2), 13.8 (CH_3). ESI MS (172.1): 173.4 ($M+H^+$). HRMS (ESI/Q-TOF): calcd *m*/*z* for $C_9H_{17}O_3$ $[M+H]^+$, 173.1178; found, 173.1170. Compound **4e** partially decomposes on silica gel.

*4.2.6. (R/S)-1-Hydroxy-1-phenylpropan-2-one (**5f**). Method A.* To a vigorously stirred mixture of thiamine hydrochloride **2** (337 mg,

1.00 mmol), Et_3N (279 μL, 2.00 mmol), and PEG_{400} (4 mL) α-diketone **1f** (293 μL, 2.00 mmol) was added in one portion. The mixture was stirred at room temperature for 3 h and then diluted with Et_2O (5 mL). The resulting mixture was vigorously stirred for 5 min, allowed to separate out and the ethereal solution was decanted. This process was repeated twice. The collected ethereal fractions were concentrated and the resulting residue was eluted from a column of silica gel with 4:1 cyclohexane/AcOEt to give **5f**[22] (234 mg, 78%) as a white amorphous solid. ESI MS (150.1): 173.7 ($M+Na^+$).

The subsequent elution with AcOEt afforded a mixture of PEG-OBz and PEG-OAc. PEG-OBz: ^1H NMR: δ=8.20–8.05, 7.60–7.50, and 7.48–7.40 (3m, Ph), 4.50–4.40 and 3.90–3.80 (2m, OCH_2-CH_2OBz), 3.70–3.50 (m, OCH_2CH_2O–). PEG-OAc: ^1H NMR: δ=4.30–4.20 and 3.60–3.50 (2m, OCH_2CH_2OAc), 3.70–3.50 (m, OCH_2CH_2O-), 2.08 (s, CH_3).

Method B. To a vigorously stirred mixture of 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride **2b** (54 mg, 0.20 mmol), Et_3N (279 μL, 2.00 mmol), and PEG_{400} (4 mL) α-diketone **1f** (293 μL, 2.00 mmol) was added in one portion. The mixture was stirred at room temperature for 12 h and then diluted with Et_2O (5 mL). The resulting mixture was vigorously stirred for 5 min, allowed to separate out and the ethereal solution was decanted. This process was repeated twice. The collected ethereal fractions were concentrated and the resulting residue was eluted from a column of silica gel with 4:1 cyclohexane/AcOEt to give **5f**[22] (225 mg, 75%) as a white amorphous solid.

4.3. General procedure for the cross-couplings of 1a with α-ketoesters 6–9

Method A. To a vigorously stirred mixture of thiamine hydrochloride **2** (337 mg, 1.00 mmol), Et_3N (279 μL, 2.00 mmol), α-ketoester **6**–**9** (3.00 mmol), and PEG_{400} (4 mL) 2,3-butanedione **1a** (84 μL, 1.00 mmol) was added in one portion. The mixture was stirred at room temperature until TLC analysis revealed the disappearance of **1a** (3–8 h). The reaction medium was then diluted with Et_2O (5 mL), vigorously stirred for 5 min, allowed to separate out and the ethereal solution was decanted. This process was repeated twice. The collected ethereal fractions were concentrated and the resulting residue was eluted from a column of silica gel with the suitable elution system to give the corresponding α-hydroxy-1,3-ketoester **10**–**13**. Product yields are reported in the next paragraphs for Method A.

Method B. To a vigorously stirred mixture of 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride **2b** (54 mg, 0.20 mmol), α-ketoester **6**–**9** (3.00 mmol), and PEG_{400} (4 mL) 2,3-butanedione **1a** (84 μL, 1.00 mmol) was added in one portion. The mixture was stirred at room temperature until TLC analysis revealed the disappearance of **1a** (12–48 h). The reaction medium was then diluted with Et_2O (5 mL), vigorously stirred for 5 min, allowed to separate out and the ethereal solution was decanted. This process was repeated twice. The collected ethereal fractions were concentrated and the resulting residue was eluted from a column of silica gel with the suitable elution system to give the corresponding α-hydroxy-1,3-ketoester **10**–**13**. Product yields are reported in Table 3.

*4.3.1. (R/S)-Ethyl 2-hydroxy-2-methyl-3-oxobutanoate (**10**).* Column chromatography with 3:1 cyclohexane/AcOEt afforded **10**[23] (88 mg, 55%) as a yellow oil. ESI MS (160.1): 183.5 ($M+Na^+$).

*4.3.2. (R/S)-Methyl 2-hydroxy-3-oxo-2-phenylbutanoate (**11**).* Column chromatography with 8:1 cyclohexane/AcOEt afforded **11** (87 mg, 42%) as a yellow foam. ^1H NMR: δ=7.60–7.50 and 7.48–7.35 (2m, 5H, Ph), 4.78 (br s, 1H, OH), 3.88 (s, 3H, OCH_3), 2.26 (s, 3H, CH_3). ^{13}C NMR: δ=203.6 (C), 170.8 (C), 130.1 (C), 128.8 (2 CH), 128.6 (2 CH), 126.3 (CH), 84.6 (C), 53.6 (CH_3), 26.9 (CH_3). ESI MS (208.1): 209.7 ($M+H^+$). HRMS (ESI/Q-TOF): calcd *m*/*z* for $C_{11}H_{13}O_4$ $[M+H]^+$, 209.0814; found, 209.0821.

*4.3.3. (R/S)-Ethyl 2-acetyl-2-hydroxy-4-phenylbutanoate (**12**).* Column chromatography with 8:1 cyclohexane/AcOEt afforded **12** (125 mg, 50%) as a yellow foam. ^1H NMR: δ=7.38–7.15 (m, 5H, Ph), 4.28 (br s, 1H, OH), 4.25 (q, 2H, J=7.0 Hz, OCH_2CH_3), 2.70–2.60 (m, 2H, 2 H-4), 2.45 (ddd, 1H, $J_{3a,4a}$=8.0 Hz, $J_{3a,4b}$=8.5 Hz, $J_{3a,3b}$=14.0 Hz, H-3a), 2.30 (s, 3H, CH_3), 2.24 (ddd, 1H, $J_{3b,4a}$=7.5 Hz, $J_{3b,4b}$=8.0 Hz, $J_{3a,3b}$=14.0 Hz, H-3b), 1.27 (t, 3H, J=7.0 Hz, OCH_2CH_3). ^{13}C NMR: δ=204.9 (C), 171.0 (C), 141.1 (C), 128.7 (4 CH), 126.4 (CH), 84.1 (C), 63.0 (CH_2), 37.2 (CH_2), 29.8 (CH_2), 24.8 (CH_3), 14.3 (CH_3). ESI MS (250.1): 251.6 ($M+H^+$). HRMS (ESI/Q-TOF): calcd *m*/*z* for $C_{14}H_{18}O_4$ $[M+H]^+$, 251.1283; found, 251.1277.

*4.3.4. (R/S)-Ethyl 2-acetyl-2-hydroxy-3-methylbutanoate (**13**).* Column chromatography with 8:1 cyclohexane/AcOEt afforded **13**[24] (96 mg, 51%) as a yellow foam. ESI MS (188.1): 189.3 ($M+H^+$).

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Supplementary data

^1H and ^{13}C spectra for new compounds. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.08.056. These data include MOL files and InChIKeys of the most important compounds described in this article.

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