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Flow Synthesis of Substituted γ-Lactones by Consecutive Photocatalytic/Reductive Reactions

Maurizio Fagnoni,[a] Filippo Bonassi,[a] Alessandro Palmieri,[b,*] Stefano Protti,[a,*] Davide Ravelli,[a] and Roberto Ballini[b]

[a] PhotoGreenLab, Department of Chemistry, University of Pavia, Viale Taramelli 12, 27100 Pavia, Italy
Fax: (+39)-03-8298-7323; phone: (+39)-03-8298-7316; e-mail: prottistefano@gmail.com
[b] Green Chemistry Group, School of Science and Technology, Chemistry Division, University of Camerino, Via S. Agostino 1, 62032 Camerino (MC), Italy
E-mail: alessandro.palmieri@unicam.it

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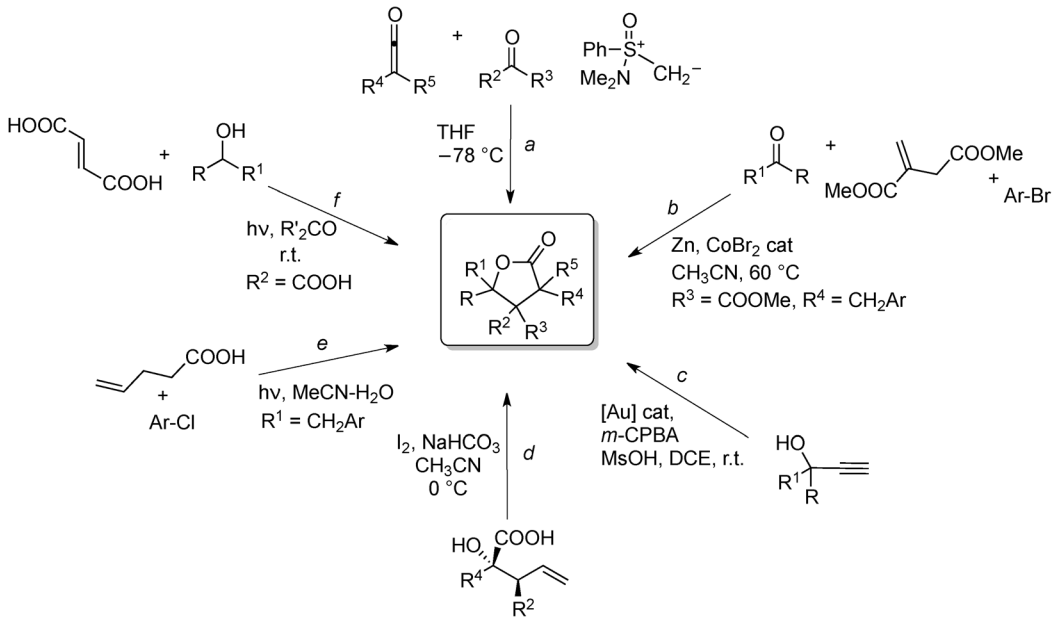
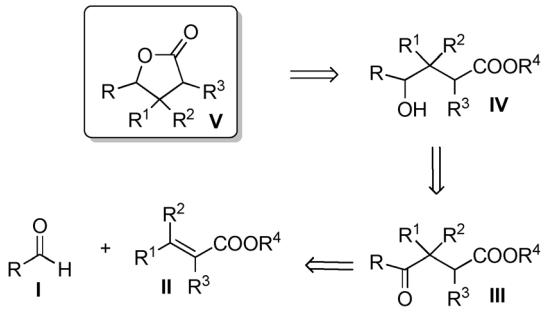
The extensive occurrence of the γ-lactone ring in biologically active compounds or in their precursors,[1] including derivatives with antifungal,[2] antibiotic,[3] antitumor,[4] anti-inflammatory[5] and cytotoxic[6] activity, makes its preparation an appealing target in organic chemistry.

The synthetic routes reported so far made use of different approaches, such as three-component reactions starting from aldehydes or ketones (Scheme 1, *paths a*, *b*),[7,8] the gold-catalyzed tandem cycloisomerization/oxidation of homopropargylic alcohols (*path c*)[9] and the AgOTs-catalyzed silylene transfer to α-keto esters followed by an iodolactonization reaction (*path d*).[10] Other methods include the SmI_2-promoted opening-lactonization of γ-epoxy esters,[11] the asymmetric Michael addition of α,α-disubstituted aldehydes to maleimides,[12] the $[Cu(acac)_2]$-catalyzed 1,5-electrocyclic ring closure of conjugated esters with dimethyl diazomalonate[13] and the reduction of γ-acylsuccinates.[14]

Photochemical procedures have been employed only in a few cases. Representative examples are the tandem C–C and C–O bond formations *via* addition of a photogenerated aryl cation to ω-alkenoic acids (*path e*)[15] and the (substituted) benzophenone or acetone (R'_2CO) photomediated addition of an alcohol[16,17c] onto unsaturated acids in the synthesis of (functionalized) terebic acids (Scheme 1, *path f*).[16a,c]



Scheme 1. Representative approaches for the synthesis of the γ-lactone ring.



Scheme 2. Retrosynthetic analysis of the γ-lactone core **V** proposed in this paper.

The application of flow synthesis (both thermal and photochemical) for the preparation of these lactones, however, has been only sparsely reported.[17]

Flow reactors have emerged in the last two decades as a promising technology for the production of fine chemicals,[18] especially in multistep procedures.[19] Moreover, these devices are particularly attractive when applied to photochemical reactions,[20] since the thin diameter of the tube allows a deeper penetration of light and thus a more uniform irradiation of the reaction mixture.

We thus explored a two-step preparation of the γ-lactone ring (**V** in Scheme 2) under flow conditions having a photocatalytic reaction as the first step.

In this context, **V** was thought to be obtained from γ-keto ester **III** by reduction of the ketone moiety followed by acid-promoted cyclization of the resulting γ-hydroxy ester **IV**. In turn, the preparation of **III** involved the conjugate radical addition of a photogenerated acyl radical (from aldehyde **I**) to a α,β-unsaturated ester **II**. The synthesis of γ-keto esters **III** has already been reported under batch conditions and is based on the tetrabutylammonium decatungstate (TBADT, $(n\mathrm{Bu_4N})_4[\mathrm{W_{10}O_{32}}]$) photocatalyzed addition of aldehydes (either aliphatic or aromatic) to electron-poor olefins in a multilamp apparatus,[21] as well as under natural sunlight irradiation.[22]

In order to move from batch to flow conditions, we took inspiration from the photo-reactor optimized by Booker-Milburn and co-workers,[23] consisting of coils of UV-transparent tubing (made of a fluoropolymer) wound around a traditional water-cooled immersion well apparatus. Thus, the designed photochemical reactor (**R1**; volume = 12 mL) was assembled by using a polytetrafluoroethylene tubing (Algoflon PTFE; outer diameter: 1.6 mm; inner diameter: 1.3 mm) and a medium pressure (125 W) Hg vapor lamp as shown in Figure 1.

The solution to be irradiated was charged into a reservoir (see the Supporting Information for details) and circulated by means of a Hewlett–Packard HPLC pump. In order to assure a constant flow rate and avoid the formation of bubbles during the reaction,

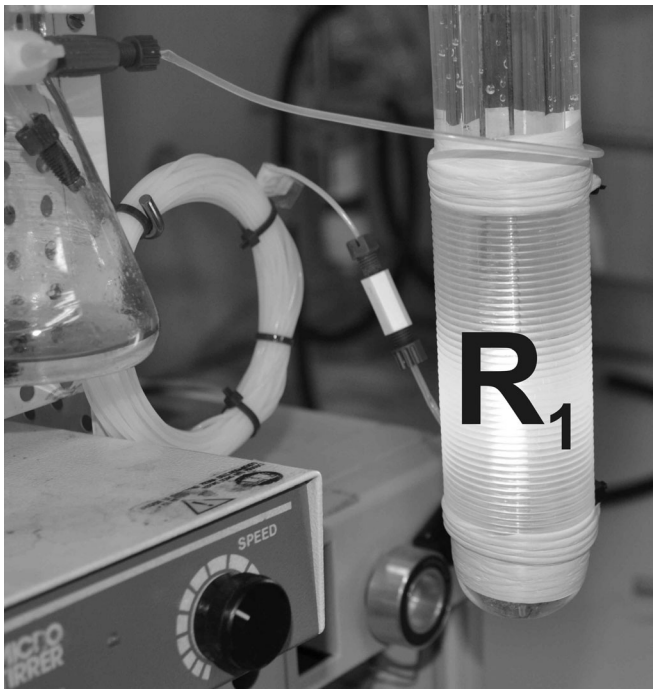


Figure 1. Flow photocatalytic reactor used for the preparation of γ-keto esters **3**. Further notice that during irradiation, both photochemical flow reactor and feeding tubes were covered with an aluminum foil to avoid cross irradiation.

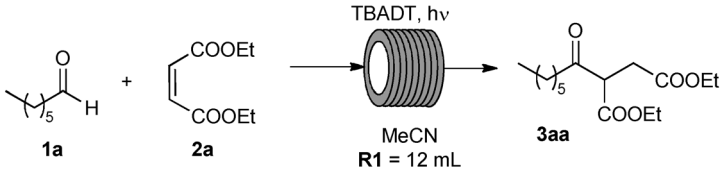
a flow-through back-pressure unit was mounted at the outlet of the photochemical reactor. The overall pressure in the system has been set to *ca.* 2 atm during the experiment.

The first part of the study was aimed to find out the best conditions for the photochemical step, taking as a model the reaction of heptanal (**1a**) with diethyl maleate (**2a**) to give the corresponding acylsuccinate **3aa** (Table 1).

Thus, irradiation under batch conditions (multilamp reactor equipped with ten 15 W phosphor-coated lamps; emission centered at 310 nm) of **1a** (0.1 M) in acetonitrile with an equimolar amount of **2a** in the presence of 2 mol% of TBADT afforded **3aa** in a discrete yield (44% yield, entry 1). 24 h of irradiation were required in order to obtain a complete conversion of the reactants. Irradiation of the solution placed in a test tube carried out by using the same medium pressure Hg vapor lamp as in Figure 1 allowed us to increase the yield of **3aa** to 66% and required a shorter irradiation time (6 h, entry 2). When shifting to the flow reactor with a 0.1 mL $\mathrm{min^{-1}}$ flow rate, **3aa** was formed in 39% yield when using a quartz cooling vessel and 67% when the cooling vessel was made of pyrex (entry 3).

By using the latter experimental set-up, the yield was not affected upon doubling the concentration of the reactants (while maintaining the same TBADT

Table 1. Optimization of the photocatalyzed synthesis of acyl succinate **3aa**.



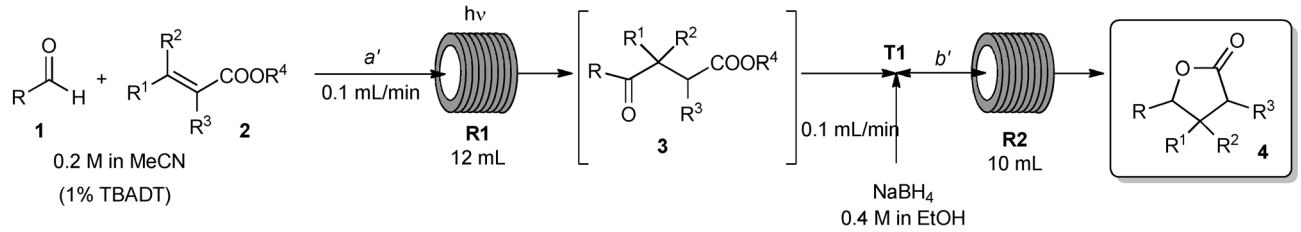
1a **2a** **3aa**

Entry	**1a** (M)	**2a** (M)	**TBADT** (mol%)	**Reaction Conditions, flow rate** (mL min^{-1})	**Residence Time** (min)	**3aa** (% yield)	**Space-Time Yield** (mmol L^{-1} h^{-1})
1	0.1	0.1	2	Batch reactor[a]	1440	44	1.83
2	0.1	0.1	2	Batch reactor[b]	360	66	11.00
3	0.1	0.1	2	Flow reactor, 0.1	120	39[c], 67[d]	39.00 [d]
4	**0.2**	**0.2**	**1**	**Flow reactor, 0.1**	**120**	**67[d]**	67.00
5	0.2	0.2	1	Flow reactor, 0.2	60	60[d]	120.00
6	0.2	0.2	0.5	Flow reactor, 0.1	120	35[d]	35.00

[a] Reaction performed in a quartz test tube by means of a multilamp reactor equipped with 10 phosphor-coated lamps ($\lambda_{IRR} = 310$ nm), 24 h irradiation. TABT = $(n\text{-Bu})_4[W_{10}O_{32}]$.
[b] Reaction performed in a quartz test tube by means of a medium pressure Hg vapor lamp equipped with a merry-go-round apparatus, 6 h irradiation.
[c] Reaction performed by using a quartz cooling vessel.
[d] Reaction performed by using a pyrex cooling vessel.

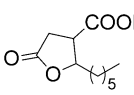
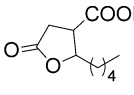
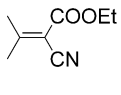
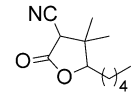
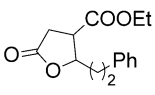
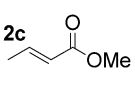
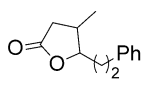
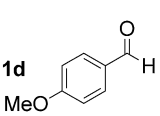
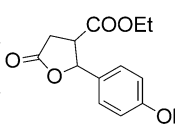
molar concentration, *viz.* 2×10^{-3} M corresponding to 1 mol%, entry 4). On the other hand, a higher flow rate (0.2 mL min^{-1}) was detrimental since the reaction yield decreased somewhat (from 67 to 60%, entry 5). A lower amount of the photocatalyst (0.5 mol%, entry 6) was insufficient to assure a satisfying acylation yield (35% of **3aa** formed). The space-time yield (STY) was then calculated in each case. As it is apparent from Table 1, flow reactions showed consistently higher STY values than the batch conditions despite a similar acylation yield (compare entries 2 and 4, STY = 11.00 mmol L^{-1} h^{-1} and 67.00 mmol L^{-1} h^{-1}, respectively). We then chose the conditions described in Table 1, entry 4, since the flow rate of 0.1 mL min^{-1} was found to be the best suited for carrying out the ensuing reduction step.

Having optimized the photochemical transformation (Scheme 3, *path a′*), we switched our attention to the optimization of the synthesis of **4** (*path b′*) under flow conditions, starting from the photolyzed solution. Thus, since the second step required the reduction of **3**, we decided to adopt a sodium borohydride solution in absolute ethanol to perform the desired transformation. This solution was charged in a reservoir and circulated in a PTFE tubing (with the same specifications as above) by means of a second HPLC pump (see again the Supporting Information for details) and the same flow rate (0.1 mL min^{-1}) adopted in the photochemical step. In detail, after removing the back-pressure unit, a three-way valve (**T1**) was placed at the outlet of the photochemical reactor (**R1**) and connected with the reservoir containing the $NaBH_4$ solution by means of another HPLC pump. A second reactor (**R2**; volume = 10 mL) was then mounted at the outlet of **T1** and a back-pressure unit for the whole system was inserted. Using this apparatus, we treated the photolyzed solution containing crude **3aa** with a solution of $NaBH_4$ (0.2–0.5 M) in absolute EtOH. A maximum yield of lactone **4aa** (65% overall yield on the basis of the amount of **1a** used, see also Table 2) was obtained when using a 0.4 M solution of $NaBH_4$ (2 equiv.) with 50 min of residence time



Scheme 3. Multistep synthesis of γ-lactones **4**.

Table 2. Synthesis of γ-lactones **4**.

Aldehyde **1**	Ester **2**	Lactone **4**	Yield [%],[a] *dr*
1a 	**2a** 		**4aa** 65, *65:35*[b]
1b 	**2a** 		**4ba** 58, *65:35*[b]
1b 	**2b** 		**4bb**[c] 51, *70:30*[b]
1c 	**2a** 		**4ca** 63, *60:40*[b]
1c 	**2c** 		**4cc**[c] 68, *50:50*
1d 	**2a** 		**4da**[c] 60, *65:35*[b]

[a] Isolated yield by silica gel chromatography; **R1** = 12 mL (residence time: 120 min), **R2** = 10 mL (residence time: 50 min).
[b] *cis*-Isomer has been observed as the most abundant.
[c] **R2** = 14 mL (residence time: 70 min).

(Scheme 3). The use of a higher $NaBH_4$ concentration was detrimental due to extensive bubbling in the reactor. Interestingly, when the same reduction was carried out under batch conditions on the crude photolyzate (see the Supporting Information), **4aa** was obtained in a lower yield (49% overall).

To demonstrate the scope of our multistep protocol, we investigated different combinations of aldehydes **1** and esters **2** (Table 2). Ethyl paraconate **4ba** was formed in a comparable yield (58%) when using hexanal **1b**. The reaction conditions are tolerant to the presence of a cyano group tethered to the unsaturated ester, as in the acylation of isopropylidenecyanoacetate **2b** with **1b** to give the corresponding 3-cyano-γ-lactone **4bb** in 51% yield (Vol. **R2** = 14 mL in this case). The yields of lactones were slightly increased when shifting to 3-phenylpropanal **1c**, which gave **4ca** and **4cc** in the reaction with diethyl maleate and methyl crotonate (Vol. **R2** = 14 mL in the latter case) in 63% and 68% yields, respectively. The present approach was particularly advantageous in the case of aromatic aldehyde **1d**, since the reaction time (2 h) for the synthesis of **3da** was markedly shortened when compared to the same reaction carried out under batch conditions (30 h).[22]

This is the first application of a TBADT photocatalyzed reaction under flow conditions. The advantage of this approach with respect to the usual multilamp batch reactor[21a,b] is apparent from Table 1, showing that γ-keto ester **3aa** was formed in a higher yield and in a significantly shorter time (2 h *vs.* 24 h) by using the apparatus described above. Moreover, the use of the flow reactor allows us to reduce the electric energy demand due to the irradiation source as is apparent by comparing the "specific productivity" (defined as the number of mmol of product produced with respect to the energy consumed by the light source).[24] This parameter under flow conditions results to be around 6.4×10^{-3} mmol Wh^{-1} whereas that of the batch reactors are consistently lower *viz.* 3.6×10^{-3} mmol Wh^{-1}, (determined by considering an "ideal" irradiation of 300 mL by using the multilamp reactor, entry 1), and 5.3×10^{-3} mmol Wh^{-1}, (determined by considering an "ideal" irradiation of 60 mL by using the merry-go-round apparatus, entry 2, see the Supporting Information for further details).

The apparatus shown in Figure 1 is simple, versatile and capable of being scaled, allowing us to obtain the desired products on a gram scale (*ca.* 5.5 g d^{-1} of keto ester **3aa** can be obtained). In addition, this set-up takes an additional advantage from the use of PTFE tubing in place of the usual (more expensive) FEP (fluorinated ethylene propylene) tubing.[20c]

The present synthesis of γ-lactones compares favorably with other ketone photomediated reactions such as the photoaddition of alcohols onto unsaturated acids followed by cyclization of the hydroxyl ester,[16a,c,17c] since the latter approaches make use of a large excess of low-boiling alcohols, such as 2-propanol [mainly as (co)solvents].[16,17c] Moreover, the use of benzophenone as photomediator leads to the formation of several by-products (e.g., benzopinacol) making purification of the end product troublesome.[16e] In some cases, the incorporation of the photocatalyst itself in the final product has also been observed.[16b] The photocatalyst employed here, TBADT, is superior to those previously employed in related syntheses of lactones since it is more robust, it can be used in a lower mol% amount and it is easily removed in the purification step.

The synthesis of lactones **4** can be actually considered as one of the rare cases reported so far where two consecutive reactions (one of which is photochemical) were carried out under flow conditions.[25] The acylation reaction was easily applied to substituted α,β-unsaturated esters and when using maleate **2a**, the process gave access to paraconic acid derivatives, important compounds having antitumor and antibiotic activities.[26a]

In particular, the *cis*-isomer of compound **4ba** was used for the preparation of enantiopure phaseolinic acid.[26b] The application of the apparatus presented here to other multistep consecutive reactions is currently under investigation in our laboratories, as well

as the improvement of the performance of the photochemical equipment in terms of STY.

Experimental Section

Typical Procedure for the Synthesis of 4

Aldehyde **1** (2 mmol, 0.2 M) and ester **2** (2 mmol, 0.2 M) in the presence of a catalytic amount of TBADT (0.02 mmol, 2×10^{-3} M) were dissolved in 10 mL of acetonitrile. Sodium borohydride (4 mmol, 0.4 M) was dissolved in 10 mL of absolute ethanol. The two solutions were charged in two reservoirs and pumped by means of two HPLC pumps (model: Hewlett–Packard HPLC pump series 1050; flow rate: 0.1 mL min^{-1}) through the apparatus described in the text (see also the Supporting Information, Figure S1). The pressure was maintained at the constant value of *ca.* 2 atm by means of a flow-through back-pressure unit mounted at the output of the apparatus. The final solution was quenched in a 0.1 M HCl solution/ethyl acetate biphasic system. The aqueous phase was extracted with ethyl acetate (3×15 mL) and the combined organic portions were dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (cyclohexane:ethyl acetate as the eluants).

See the Supporting Information for experimental details, characterization of products and copies of ^1H and ^{13}C NMR spectra of compounds **3aa** and **4**.

Acknowledgements

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References

[1] a) O. Reiser, M. Seitz, *Curr. Opin. Chem. Biol.* **2005**, *9*, 285–292; b) S. Gil, M. Parra, P. Rodriguez, J. Segura, *Minirev. Org. Chem.* **2009**, *6*, 345–358.

[2] M. He, A. Lei, X. Zhang, *Tetrahedron Lett.* **2005**, *46*, 1823–1826.

[3] See for instance: a) J. J. Pignatello, J. Porwoll, R. E. Carlson, A. Xavier, F. K. Gleason, J. M. Wood, *J. Org. Chem.* **1983**, *48*, 4035–4038; b) K. Shiomi, H. Ui1, H. Suzuki, H. Hatano, T. Nagamitsu, D. Takano, H. Miyadera, T. Yamashita, K. Kita, H. Miyoshi, A. Harder, H. Tomoda, S. Omura, *J. Antibiot.* **2005**, *58*, 50–55.

[4] a) X.-M. Zhou, K. J. H. Lee, J. Cheng, S. S. Wu, H. X. Chen, X. Guo, Y. C. Cheng, K. H. Lee, *J. Med. Chem.* **1994**, *37*, 287–292; b) G. A. Howie, P. E. Manni, J. M. Cassady, *J. Med. Chem.* **1974**, *17*, 840–843.

[5] B. H. Kwok, B. Koh, M. I. Ndubuisi, M. Elofsson, C. M. Crews, *Chem. Biol.* **2001**, *8*, 759–766.

[6] a) A. Jossang, B. Dubaele, A. Cavé, M. H. Bartoli, H. Bériel, *J. Nat. Prod.* **1991**, *54*, 967–971; b) M. T. Barros, M. A. Januario Charmier, C. D. Maycock, T. Michaud, *Tetrahedron* **2009**, *65*, 396–399.

[7] C. Le Floch, E. Le Gall, E. Léonel, T. Martens, T. Cresteil, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 7054–7058.

[8] M. Mondal, H. J. Ho, N. J. Peraino, M. A. Gary, K. A. Wheeler, N. J. Kerrigan, *J. Org. Chem.* **2013**, *78*, 4587–4593.

[9] C. Shu, M. Q. Liu, Y. Z. Sun, L. W. Ye, *Org. Lett.* **2012**, *14*, 4958–4961.

[10] B. E. Howard, K. A. Woerpel, *Tetrahedron* **2009**, *65*, 6447–6453.

[11] H. S. Park, D. W. Kwon, K. Lee, Y. H. Kim, *Tetrahedron Lett.* **2008**, *49*, 1616–1618.

[12] C. G. Kokotos, *Org. Lett.* **2013**, *15*, 2406–2409.

[13] O. Anaç, F. S. Güngör, G. Merey, *Helv. Chim. Acta* **2006**, *89*, 1231–1240.

[14] a) O. V. Turova, E. V. Starodubtseva, M. G. Vinogradov, V. A. Ferapontov, M. I. Struchkova, *Tetrahedron: Asymmetry* **2009**, *20*, 2121–2124; b) A. Comini, C. Forzato, P. Nitti, G. Pitacco, E. Valentin, *Tetrahedron: Asymmetry* **2004**, *15*, 617–625.

[15] S. Protti, M. Fagnoni, A. Albini, *J. Am. Chem. Soc.* **2006**, *128*, 10670–10671.

[16] a) G. O. Schenck, G. Koltzenburg, H. Grossmann, *Angew. Chem.* **1957**, *69*, 177–178; b) M. M. Pfau, M. M. Delépine, *C. R. Acad. Sci.* **1962**, *254*, 2017–2019; c) D. Dondi, S. Protti, A. Albini, S. Mañas Carpio, M. Fagnoni, *Green Chem.* **2009**, ##*11*##, 1653–1659; d) D. Dondi, A. M. Cardarelli, M. Fagnoni, A. Albini, *Tetrahedron* **2006**, *62*, 5527–5535; e) in rare instances γ-butyrolactones has been found to arise from the direct irradiation of α,β-unsaturated esters in alcohols, see S. Majeti, *J. Org. Chem.* **1972**, *37*, 2914–2916.

[17] a) A. Yavorskyy, O. Shvydkiv, K. Nolan, N. Hoffmann, M. Oelgemöller, *Tetrahedron Lett.* **2011**, *52*, 278–280; b) R. Mello, A. Olmos, J. Parra-Carbonell, M. E. González-Núñez, G. Asensio, *Green Chem.* **2009**, *11*, 994–999; c) The synthesis in-flow of terebic acid by acetone ($5\%_{v/v}$) catalyzed addition of 2-propanol on maleic acid has been recently reported, see: S. Aida, K. Terao, Y. Nishiyama, K. Kakiuchi, M. Oelgemöller, *Tetrahedron Lett.* **2012**, *53*, 5578–5581.

[18] See for instance: a) J. Perez-Ramìrez, R. J. Berger, G. Mul, F. Kapteijn, J. A. Moulijn, *Catal. Today* **2000**, *60*, 93–109; b) P. Gallezot, *Catal. Today* **2007**, *121*, 76–91; c) G. Jas, A. Kirschning, *Chem. Eur. J.* **2003**, *9*, 5708–5723; d) D. T. McQuade, P. H. Seeberger, *J. Org. Chem.* **2013**, *78*, 6384–6389; e) I. R. Baxendale, L. Brocken, C. J. Mallia, *Green Process Synth.* **2013**, *2*, 211–230; f) I. R. Baxendale, *J. Chem. Technol. Biotechnol.* **2013**, *88*, 519–552; g) A. Palmieri, S. V. Ley, K. Hammond, A. Polyzos, I. R. Baxendale, *Tetrahedron Lett.* **2009**, *50*, 3287–3289; h) A. Palmieri, S. V. Ley, A. Polyzos, I. R. Baxendale, *Beilstein J. Org. Chem.* **2009**, *5*, 1–17.

[19] For reviews, see: a) H. R. Sahoo, J. G. Kralj, K. F. Jensen, *Angew. Chem.* **2007**, *119*, 5806–5810; *Angew. Chem. Int. Ed.* **2007**, *46*, 5704–5708; b) R. L. Hartman, K. F. Jensen, *Lab Chip* **2009**, *9*, 2495–2507; c) D. Webb,

T. F. Jamison, *Chem. Sci.* **2010**, *1*, 675–680; d) J. Wegner, S. Ceylan, A. Kirschning, *Adv. Synth. Catal.* **2012**, *354*, 17–57; e) P. Watts, C. Wiles, *Chem. Commun.* **2007**, 443–467; f) J.-i. Yoshida, H. Kim, A. Nagaki, *ChemSusChem* **2011**, *4*, 331–340; g) B. Ahmed-Omer, J. C. Brandt, T. Wirth, *Org. Biomol. Chem.* **2007**, *5*, 733–740; h) B. P. Mason, Kr. E. Price, J. L. Steinbacher, A. R. Bogdan, D. T. McQuade, *Chem. Rev.* **2007**, *107*, 2300–2318; i) K. Geyer, T. Gustafsson, P. H. Seeberger, *Synlett* **2009**, 2382–2391; j) J.-i. Yoshida, *Chem. Rec.* **2010**, *10*, 332–341; k) T. Razzaq, C. O. Kappe, *Chem. Asian J.* **2010**, *5*, 1274–1289; l) S. Marrea, K. F. Jensen, *Chem. Soc. Rev.* **2010**, *39*, 1183–1202.

[20] For reviews, see: a) J. Wegner, S. Ceylan, A. Kirschning, *Chem. Commun.* **2011**, *47*, 4583–4592; b) E. E. Coyle, M. Oelgemöller, *Photochem. Photobiol. Sci.* **2008**, *7*, 1313–1322; c) J. P. Knowles, L. D. Elliott, K. I. Booker-Milburn, *Beilstein J. Org. Chem.* **2012**, *8*, 2025–2052. Recent examples, see: d) K. Tsutsumi, K. Terao, H. Yamaguchi, S. Yoshimura, T. Morimoto, K. Kakiuchi, T. Fukuyama, I. Ryu, *Chem. Lett.* **2010**, *39*, 828–829; e) A. Vasudevan, C. Villamil, J. Trumbull, J. Olson, D. Sutherland, J. Pan, S. Djuric, *Tetrahedron Lett.* **2010**, *51*, 4007–4009; f) M. Neumann, K. Zeitler, *Org. Lett.* **2012**, *14*, 2659–2661; g) A. Yavorskyy, O. Shvydkiv, N. Hoffmann, K. Nolan, M. Oelgemöller, *Org. Lett.* **2012**, *14*, 4342–4345; h) B. G. Anderson, W. E. Bauta, W. R. Cantrell Jr, *Org. Process Res. Dev.* **2012**, *16*, 967–975; i) Y. Zhang, M. L. Blackman, A. B. Leduc, T. F. Jamison, *Angew. Chem.* **2013**, *125*, 4345–4349; *Angew. Chem. Int. Ed.* **2013**, *52*, 4251–4255; j) J. W. Tucker, Y. Zhang, T. F. Jamison, C. R. J. Stephenson, *Angew. Chem.* **2012**, *124*, 4220–4223; *Angew. Chem. Int. Ed.* **2012**, *51*, 4144–4147.

[21] a) S. Esposti, D. Dondi, M. Fagnoni, A. Albini, *Angew. Chem.* **2007**, *119*, 2583–2586; *Angew. Chem. Int. Ed.* **2007**, *46*, 2531–2534; b) D. Ravelli, M. Zema, M. Mella, M. Fagnoni, A. Albini, *Org. Biomol. Chem.* **2010**, *8*, 4158–4164; c) benzophenone photomediated acylation of unsaturated esters has been previously reported, see: G. A. Krauss, P. Liu, *Tetrahedron Lett.* **1994**, *35*, 7723–7726.

[22] S. Protti, D. Ravelli, M. Fagnoni, A. Albini, *Chem. Commun.* **2009**, 7351–7353.

[23] See for instance: a) B. D. A. Hook, W. Dohle, P. R. Hirst, M. Pickworth, M. B. Berry, K. I. Booker-Milburn, *J. Org. Chem.* **2005**, *70*, 7558–7564; b) K. G. Maskill, J. P. Knowles, L. D. Elliott, R. W. Alder, K. I. Booker-Milburn, *Angew. Chem.* **2013**, *125*, 1539–1542; *Angew. Chem. Int. Ed.* **2013**, *52*, 1499–1502.

[24] D. Ravelli, S. Protti, M. Fagnoni, A. Albini, *Curr. Org. Chem.* **2013**, *17*, 2366–2373.

[25] See for example: a) F. Lévesque, P. H. Seeberger, *Angew. Chem.* **2012**, *124*, 1738–1741; *Angew. Chem. Int. Ed.* **2012**, *51*, 1706–1709; b) S. Fuse, N. Tanabe, M. Yoshida, H. Yoshida, T. Doi, T. Takahashi, *Chem. Commun.* **2010**, *46*, 8722–8724.

[26] a) R. Bandichhor, B. Nosse, O. Reiser, *Top. Curr. Chem.* **2005**, *243*, 43–72; b) S. Drioli, F. Felluga, C. Forzato, P. Nitti, G. Pitacco, E. Valentin, *J. Org. Chem.* **1998**, *63*, 2385–2388.

