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Decatungstate Photocatalyzed Acylations and Alkylations in Flow *via* Hydrogen Atom Transfer

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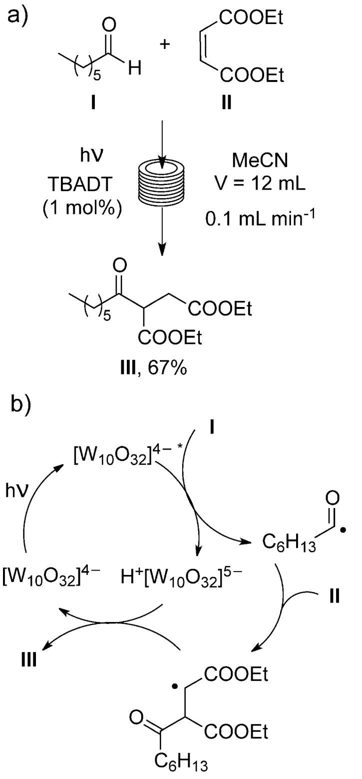
Abstract: A set of atom-economical radical conjugate addition reactions of alkyl and acyl radicals onto electron-poor olefins or diisopropyl azodicarboxylate has been carried out on a multi-gram scale under continuous flow conditions. The process is based on the use of the inorganic photocatalyst tetrabutylammonium decatungstate (TBADT), which is capable to activate selectively a variety of C–H bonds in different substrates, including aldehydes, amides, ethers and alkanes. A wide range of synthetic targets has been synthesized according to this procedure, including 1,4-difunctionalized derivatives (e.g., 1,4-diketones or keto esters). All the reactions have been carried out in a *meso*-scale flow photoreactor consisting in coils of UV-transparent FEP tubing (fluorinated ethylene propylene) wrapped around a water-cooled 500 W medium pressure mercury vapor lamp. The use of such a photochemical apparatus caused a reduction of the residence time, a notable increase of the STY (space time yield) and of the productivity values with respect to those measured for the corresponding batch processes, often leading to an improvement of the overall sustainability of the process (process mass intensity – PMI – values down to 10 $kg\,kg^{-1}$).

Keywords: decatungstate salts; flow reactions; hydrogen atom transfer; photocatalysis; waste minimization

Introduction

The use of continuous-flow processes is widely recognized by the chemical community as a valid tool to perform organic reactions for the smooth, large-scale preparation of valuable compounds (including natural products), also thanks to the process intensification achieved in multi-reactor systems.[1] Recently, flow reactions have also been applied to photochemical processes, thus overcoming the typical drawbacks of batch conditions that often make this technique underutilized in general organic synthesis.[2] Indeed, a more uniform absorption of light is obtained by reducing the size of the reaction channels. A residence-time shortening results and allows for an improvement of the efficiency and the selectivity of the process, even at high substrate concentrations, while avoiding the generation of secondary products.[3] A uniform irradiation throughout the reaction mixture was recently achieved having recourse to microflow (e.g., lab-on-a-chip apparatus)[4] or macroflow[2,5,6] systems. Meso-scale home-made reactors (tubing with optical path >1 mm)[7] are mainly assembled by simply wrapping a tube (made of a polyfluorinated UV-transparent polymer) around the light source.[8] Nevertheless, a recent work of Booker-Milburn's group raises the issue on the usefulness of photochemical processes in flow, since in most cases the observed yield and productivity values are rather similar to those obtained under batch conditions.[9] Most of the reactions investigated were, however, photocycloadditions and rearrangements and the authors concluded that the results may be different when considering other photochemical reactions (e.g., photocatalyzed processes, photooxygenations, etc.).[5]

We have been studying since some years ago photocatalyzed hydrogen atom transfer (HAT) reactions for the green formation of valuable C–C and C–N bonds.[10] In particular, we found that TBADT (tetrabutylammonium decatungstate) is a robust and versatile catalyst capable, when excited, to generate carbon-centered radicals by cleavage of a C–H bond in organic molecules.[10,11] We further demonstrated that the TBADT-photocatalyzed addition of aldehydes onto electron-poor olefins can be carried out by using a flow photoreactor (reactor volume: 12 mL), where the reaction mixture was circulated in a polytetrafluoroethylene tubing (PTFE, outer diameter: 1.6 mm; inner diameter: 1.3 mm) wrapped around



Scheme 1. a) Flow TBADT-photocatalyzed reaction of heptanal **I** with diethyl maleate **II**. b) Mechanism of the reaction. V = reactor volume.

a 125 W medium pressure Hg vapor lamp.[12] As an example, succinate **III** was obtained in a 67% isolated yield starting from heptanal **I** and diethyl maleate **II** (Scheme 1a). The reaction was promoted by excited decatungstate, prone to abstract a hydrogen atom from the formyl group in **I**. The so-formed acyl radical then added to **II** to give a radical adduct that in turn regenerated the reduced catalyst *via* a back hydrogen-atom transfer reaction, while giving the desired product **III** (Scheme 1b). Actually, the same reaction carried out in a quartz test tube under batch conditions by means of the same medium pressure Hg vapor lamp, but equipped with a merry-go-round apparatus, gave product **III** in almost the same yield (66%).[12] Under flow conditions, however, the reaction time was shorter (2 *vs.* 6 h) and the space time yield parameter (STY, 67 mmol$\,L^{-1}h^{-1}$) was higher with respect to batch conditions (11 mmol$\,L^{-1}h^{-1}$), albeit a comparable “specific productivity” (mmol of product formed with respect to the energy consumed)[13] resulted. A flow system capable to maintain the same reaction time and markedly improve the amount of product formed, while limiting the use of electricity, is thus desirable.

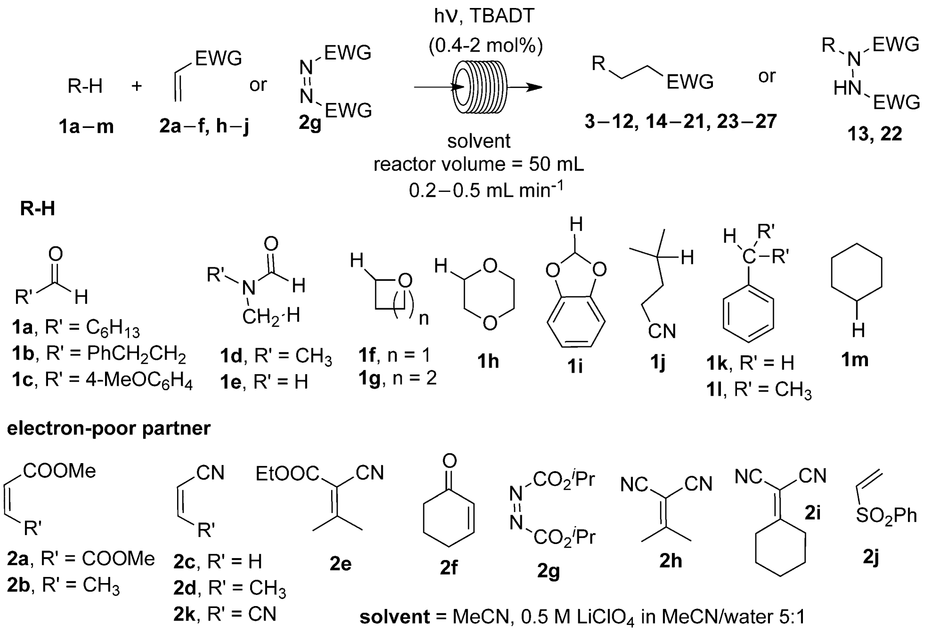
To this aim, we assembled an upgraded flow photoreactor consisting in coils of UV-transparent FEP tubing (fluorinated ethylene propylene; outer diameter: 3.18 mm; inner diameter: 2.1 mm; reactor volume: 50 mL) wrapped around a traditional water-cooled 500 W medium pressure Hg vapor lamp (Figure S1, Supporting information).

Results

Several TBADT-photocatalyzed reactions previously carried out under batch conditions in our laboratory[14–20] were then investigated by using the upgraded flow photoreactor, as summarized in Scheme 2. Aliphatic and aromatic aldehydes,[14] amides (DMF, *N*-methylformamide),[15] ethers and acetals (oxetane, THF, 1,4-dioxane, 1,3-benzodioxole),[16] aliphatic nitriles,[17] alkylbenzenes,[18] and alkanes (cyclohexane)[19] have been chosen as carbon-centered radical precursors (R-H, **1a–m**). In turn, electron-poor olefins **2a–f**, **h–j** and azodicarboxylate **2g**[20] have been adopted as radical traps (Scheme 2). The photocatalyst was used in a 0.4–2 mol% amount, while the flow rate adopted was in the 0.2–0.5 mL$\,min^{-1}$ range and MeCN was used as the solvent throughout this study, with the only exception of the reactions involving alkylbenzenes, where a 0.5 M $LiClO_4$ solution in a MeCN/water 5:1 mixture was employed.[18] The acylation depicted in Scheme 1 was initially investigated as a model reaction (dimethyl maleate **2a** was used in place of diethyl maleate **II**; Table 1).

Thus, circulation of a solution containing an equimolar amount (0.1 M) of **1a** and **2a** through the photoreactor at a rate corresponding to a residence time of 100 min (0.5 mL$\,min^{-1}$) resulted in a complete conversion of the starting substrates. The yield of keto ester **3** was almost quantitative, but decreased to 73% when increasing the flow rate to 0.6 mL$\,min^{-1}$ (Table 1, entries 1 and 2). Compound **3** was likewise formed in a satisfactory yield (up to 79%) when a higher concentration of both substrates was adopted (up to 0.5 M, flow rate = 0.5 mL$\,min^{-1}$, entries 3 and 4), whereas an incomplete consumption of the reagents was observed when using 1 M reagents (entry 5). This drawback can be overcome by increasing the reaction time to 125 min (0.4 mL$\,min^{-1}$ flow rate), but the resulting yield was unsatisfactory (60%, entry 6).

With such positive results in hand, we tested our experimental set-up investigating the photocatalyzed formation of C–C and C–N bonds by using aldehydes as hydrogen donors as summarized in Table 2. In each case, a preliminary optimization was carried out to find the maximum concentration of reagents allowing us to achieve a complete consumption, while maintaining the highest flow rate (never exceeding 0.5 mL$\,min^{-1}$). In order to assess the waste production of each process, the values of the process mass intensity parameter (PMI; defined as the total amount of



Scheme 2. TBADT-photocatalyzed reactions in flow (see Figure S1 in the Supporting Information for a picture of the photoreactor used).

Table 1. Optimization of the photocatalyzed addition of heptanal (**1a**) onto dimethyl maleate (**2a**) by using a 500 W medium pressure Hg vapor lamp and flow photoreactor.

Entry	**1a**, **2a** conc. (M)	Residence time (min), Flow rate (mL min^{-1})	**3** Yield [%]
1	0.1	100, 0.5	95
2	0.1	83, 0.6	73
3	0.2	100, 0.5	78
4	0.5	100, 0.5	79
5	1.0	100, 0.5	70[a]
6	1.0	125, 0.4	60

[a] Yield based on 84% **1a** consumption; traces of dimethyl maleate were likewise observed.

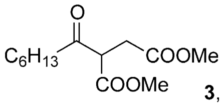
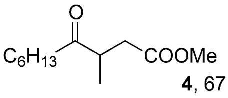
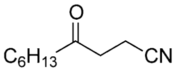
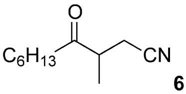
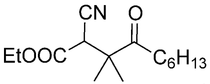
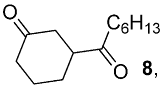
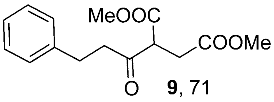
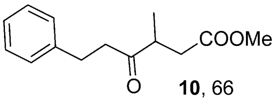
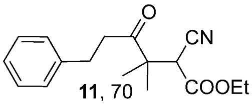
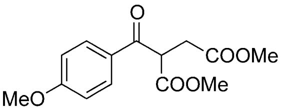
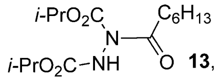
materials involved in the production of the unit mass of target product)[21] have been calculated and are reported in Table 2. The role of the energy expenditure was likewise evaluated by means of the "specific productivity" parameter (*vide supra*).[3] Selected aldehydes, whether aliphatic (heptanal, **1a**, and 3-phenylpropanal, **1b**) or aromatic (4-methoxybenzaldehyde, **1c**), were investigated. In all cases, the reaction with different electron-poor partners gave the desired acylated derivatives (**3–12**) in moderate to good yields, demonstrating that the assembled flow photoreactor is suitable for TBADT photocatalyzed acylation reactions.

When required, a slight excess of one of the substrates was employed to maximize the overall yield. Furthermore, in the preparation of β-acylcyclohexanone **8**, the radiation emitted by the lamp was Pyrex-filtered due to competitive absorption by cyclohexenone (**2f**) at the wavelength used.

Finally, the formation of a C–N bond under flow conditions to give hydrazine derivative **13** was attempted, using diisopropyl azodicarboxylate **2g** as the reaction partner. Indeed, the optimized conditions allowed the use of **1a** and **2g**, both 0.5 M, similarly to what was observed for the synthesis of **3**. Thus, the green metrics parameters for the synthesis of keto ester **3** were the best in the series thanks to the high concentration of the reagents used in an equimolar amount (PMI *ca.* 9 kg kg^{-1}, STY > 200 mmol L^{-1} h^{-1}) with the highest flow rate tested (0.5 mL min^{-1}). The greenness of the acylation reaction, however, decreased in the other cases (compounds **4–12**) due to the lower amount of reagents used, the only exception being the acylation of **2g**. In the latter case, the high reactivity of **2g** probably alleviated its competitive absorption with TBADT at the wavelength used. Actually, the formation of **13** has the second best green performance (PMI = 9.85 kg kg^{-1} and STY = 183 mmol L^{-1} h^{-1}).

We then moved to other hydrogen donors (**1d–m**; see Table 3), such as amides, ethers, 1,3-benzodioxoles, nitriles, alkylbenzenes and alkanes. In the case of amides (**1d**, **1e**), a 4 equiv. excess of the hydrogen donor R-H was required in order to achieve a satisfactory yield, and this resulted in calculated PMI values up to 68.63 kg kg^{-1} (entries 1–3). A comparable excess amount of ethers **1f–1h** (from 3 to 4 times the concentration of the electron-poor olefin) was needed for the synthesis of compounds **17–20** (entries 4–7). In

Table 2. Flow photocatalyzed acylation of compounds **2a–g**.[a]

Reactants (conc., M)	Product yield [%]	Flow rate [mL min^{-1}]	STY [mmol L^{-1} h^{-1}]	PMI [kg kg^{-1}]	Specific productivity [10^3 mmol W^{-1} h^{-1}][b]
1a (0.5) **2a** (0.5)	 **3**, 79	0.5	237	9.03	24
1a (0.3) **2b** (0.3)	 **4**, 67	0.5	121	19.89	12
1a (0.5) **2c** (0.5)	 **5**, 48	0.5	58	51.50	6
1a (0.5) **2d** (0.5)	 **6**, 61	0.5	183	15.89	18
1a (0.36) **2e** (0.3)	 **7**, 79	0.5	142	13.88	14
1a (0.2) **2f** (0.25)	 **8**, 43[c]	0.3	31	46.42	3
1b (0.2) **2a** (0.22)	 **9**, 71	0.5	85	21.54	9
1b (0.3) **2b** (0.3)	 **10**, 66	0.5	119	18.60	12
1b (0.33) **2e** (0.3)	 **11**, 70	0.5	126	14.63	13
1c (0.3) **2a** (0.3)	 **12**, 70	0.35	59	21.63	6
1a (0.5) **2g** (0.5)	 **13**, 61	0.5	183	9.85	18

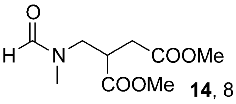
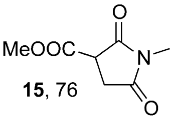
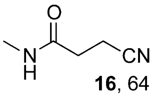
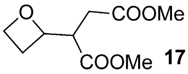
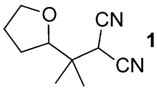
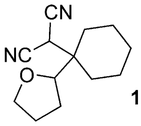
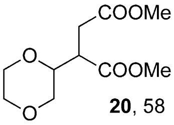
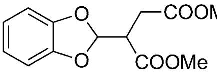
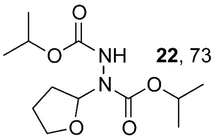
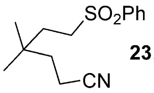
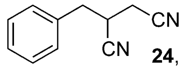
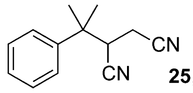
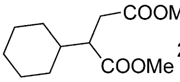
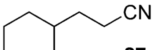
[a] A solution (50 mL) of substrates **1**, **2** and TBADT (2×10^{-3}M, 0.4-2 mol%) in MeCN was irradiated in a photochemical flow apparatus (see text). The conditions reported in the Table have been optimized in terms of substrate concentration and flow rate (see the Supporting Information for a detailed description of the conditions).

[b] Number of mmol of product obtained with respect to the energy required for lamp operation (Wh).

[c] Pyrex-filtered radiation was used.

contrast, 1,3-benzodioxole **1i**, a better H-donor,[16a] was used in a nearly stoichiometric amount (0.22 M, 1.1 equiv.; entry 8). The reaction of THF with **2g** showed excellent PMI and specific productivity values due to the high reactivity of azodicarboxylate **2g** that allowed again its use in a 0.5 M amount (entry 9). By

Table 3. Flow photocatalyzed synthesis of compounds **14**–**27**.[a]

Entry	Reactants (conc., M)	Product yield [%]	Flow rate [mL min^{-1}]	STY [mmol L^{-1} h^{-1}]	PMI [kg kg^{-1}]	Specific productivity [10^3 mmol W^{-1} h^{-1})[b]
1	**1d** (0.8), **2a** (0.2)	 **14**, 81	0.4	78	25.32	8
2	**1e** (0.8), **2a** (0.2)	 **15**, 76	0.4	73	33.82	7
3	**1e** (0.8), **2d** (0.2)	 **16**, 64	0.4	61	68.63	6
4	**1f** (0.3), **2a** (0.1)	 **17**, 51	0.5	31	79.95	3
5	**1g** (0.8), **2h** (0.2)	 **18**, 67	0.5	80	36.49	8
6	**1g** (0.8), **2i** (0.2)	 **19**, 69	0.5	83	29.20	8
7	**1h** (0.8), **2a** (0.2)	 **20**, 58	0.35	49	33.11	5
8	**1i** (0.22), **2a** (0.2)	 **21**, 61	0.35	51	26.12	5
9	**1g** (0.6), **2g** (0.5)	 **22**, 73	0.5	219	9.36	22
10	**1j** (0.5), **2j** (0.1)	 **23**, 70	0.5	42	46.19	4
11	**1k** (0.5), **2k** (0.1)	 **24**, 70	0.2	17	78.51	2
12	**1l** (0.5), **2k** (0.1)	 **25**, 66	0.2	16	72.56	2
13	**1m** (0.5), **2a** (0.1)	 **26**, 77	0.5	46	48.31	5
14	**1m** (0.5), **2c** (0.1)	 **27**, 48	0.5	29	127.54	3

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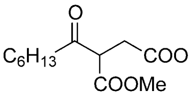
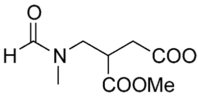
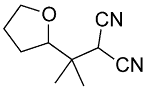
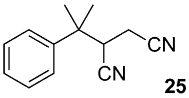
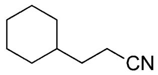
[a] A solution (50 mL) of substrates **1**, **2** and TBADT (2×10^{-3} M, 0.4–2 mol%) in MeCN (for the synthesis of **14**–**23**, **26**–**27**) or in a 0.5 M $LiClO_4$ MeCN-H_2O 5/1 mixture (for the synthesis of **24**–**25**) was irradiated in a photochemical flow apparatus (see text). The conditions reported in the Table have been optimized in terms of substrate concentration and flow rate (see the Supporting Information for a detailed description of the conditions).

[b] Number of mmol of product obtained with respect to the energy required for lamp operation (Wh).

Table 4. Comparison between flow and batch processes in decatungstate-photocatalyzed reactions.

Products	Reactor[a] (% yield)	Conditions	Productivity [g day^{-1}]	PMI [kg kg^{-1}]	Specific productivity [10^3 mmol W^{-1} h^{-1}]	STY [mmol L^{-1} h^{-1}]
 **3**	Flow 1 (79)	**1a** (0.5 M) **2a** (0.5 M)	73.46	9.03	24	237
	Flow 2 (76)	**1a** (0.2 M) **2a** (0.2 M)	7.92	21.50	10	106
	Batch 1 (68)	**1a** (0.1 M) **2a** (0.1 M)	5.27	46.60	6	3
	Batch 2 (80)	**1a** (0.5 M) **2a** (0.5 M)	15.50	8.92	20	50
	Batch Solar (90)	**1a** (0.45 M) **2a** (0.5 M)	1.16	8.76	-[b]	6
 **14**	Flow 1 (81)	**1d** (0.8 M) **2a** (0.2 M)	20.27	25.32	8	78
	Batch 1 (86)	**1d** (0.4 M) **2a** (0.1 M)	5.60	45.07	7	6
 **18**	Flow 1 (67)	**1g** (0.8 M) **2h** (0.2 M)	17.20	36.49	8	80
	Batch 1 (75)	**1g** (0.5 M) **2h** (0.1 M)	4.81	62.79	6	4
 **25**	Flow 1 (66)	**1l** (0.5 M) **2k** (0.1 M)	3.77	72.56	2	16
	Batch 1 (79)	**1l** (0.5 M) **2k** (0.1 M)	4.70	60.62	7	3
 **27**	Flow 1 (48)	**1m** (0.5 M) **2c** (0.1 M)	4.74	127.54	3	29
	Batch 1 (63)	**1m** (0.5 M) **2c** (0.1 M)	3.11	97.17	6	3
	Batch 2 (70)	**1m** (0.5 M) **2c** (0.1 M)	2.87	90.07	7	18
	Batch Solar (53)	**1m** (0.5 M) **2c** (0.1 M)	0.182	115.50	-[b]	2

[a] *Flow 1*: Flow reactor presented here (V = 50 mL; inner diameter = 2.1 mm; lamp power = 500 W). *Flow 2*: Flow reactor (V = 12 mL; inner diameter = 1.3 mm; lamp power = 125W); see ref.[12] *Batch 1*: Irradiation carried out in a multi-lamp reactor (Rayonet) equipped with 10 × 15 W Hg vapor lamps, $\lambda_{em} = 310$ nm. *Batch 2*: Irradiation carried out in an immersion well apparatus equipped with a 125 W medium pressure Hg vapor lamps. *Batch Solar*: Irradiation carried out by exposing a Pyrex vessel to natural sunlight (8 h of irradiation per day); see Ref.[16c]

[b] No external energy needed.

contrast, poor results were obtained when aliphatic nitrile **1j**, alkylbenzenes **1k**, **l** and alkane **1m** were employed as H-donors (all used in a 5-fold excess amount), since the concentration of the olefin could not exceed 0.1 M (entries 10–14). The flow rate adopted with alkylbenzenes was the lowest in the series (0.2 mL min^{-1}). The PMI values, as well as the other calculated parameters (STY, specific productivity) in the reactions involving **1k–m**, were likewise the worst in the series.

Discussion

Whereas the advantages of using flow reactors in thermal processes have been widely evidenced in the literature,[7] the use of flow photochemical reactors and their alleged superiority over batch systems has been recently debated from different perspectives, including productivity, as well as environmental and energetic sustainability. The most relevant issues have been summarized below and revised in view of the results obtained in the present work.

The performance of the photoreactor assembled in the present work (Flow 1 in Table 4; volume = 50 mL, 500 W Hg lamp as the light source) and of that previously proposed by our group[12] (Flow 2; volume = 12 mL, 125 W Hg lamp as the light source, see Scheme 1 and the Supporting Information for further details) has been compared to that obtained by a variety of batch reactors for selected processes and the calculated parameters (the above reported PMI, STY, yield, specific productivity and also productivity, expressed as grams of products per day) are reported in Table 4. In particular, to further strengthen the comparison, purposely designed batch experiments have been performed. 300 mL of solution divided in 20 quartz tubes (15 mL each) were irradiated in a multilamp reactor (Rayonet; Batch 1 in Table 4), adopting 10 phosphor-coated Hg lamps (15 W each; irradiation centered at 310 nm) as the light source. Furthermore, in selected cases (*viz.* for the synthesis of compounds **3** and **27**), 50 mL of solution (the same volume as in Flow 1) were irradiated in an immersion well apparatus equipped with a 125 W Hg vapor lamp (Batch 2 in Table 4). The comparison likewise included selected batch reactions previously carried out by our group under direct solar light irradiation (Batch Solar in Table 4).[16c]

Productivity and Space Time Yield

Stephenson and co-workers recently highlighted the capability of flow microreactors to improve significantly (more than 50 times) the productivity of several visible light photoredox-catalyzed processes.[22] A shortening of the residence time (which resulted in an improvement of the productivity) was also observed by Schuster and Wipf, who compared the efficiency obtained when several photochemical and photocatalyzed reactions were carried out in either batch or flow photoreactors.[23] The data reported herein further demonstrate the potential of the present meso-scale flow reactor in the optimization of decatungstate photocatalyzed processes. The use of a high power Hg vapor lamp, as well as the short optical path, allowed for a significant increase of the productivity in the case of C- and N-acylation processes (from nearly 5 up to 63 times in the synthesis of **3**) over the corresponding batch processes (see Table 4). An analogous advantage of the *in flow* approach was observed when amides and ethers were involved. *Vice versa*, when poorly reactive compounds such as alkanes and alkylbenzenes were used, the productivity was not significantly improved when using flow conditions. Indeed, the use of a batch reactor sometimes was slightly advantageous in terms of yield (compare the results obtained for the batch and flow syntheses of **25**). As for sunlight-induced processes, the discontinuous nature of this renewable light source limited the productivity (see the Batch Solar syntheses of **3** and **27**). It is also worth noting that the use of flow conditions always improves STY values with respect to batch conditions, due to the lower residence time (see Table 4).

Production of Waste

Although the PMI value (and, as a consequence the E-factor, defined as PMI−1) has been reported to decrease when moving to flow reactors under thermal conditions,[24] only little information is available on the environmental performance of photochemical processes (which also depends on the experimental setup, e.g., light source, geometric aspects, etc.).[16d,25]

As predictable, however, the production of waste is dominated by the (huge) amount of solvent used, that often represents more than 90% of the chemical mass. Thus, a strong reduction of PMI values was observed when aldehydes were employed as H-donors (compare the PMI values calculated for the synthesis of **3**). Interestingly, a similar environmental performance can be obtained by using an immersion well photochemical apparatus as the batch reactor. Analogous results were obtained with amides and ethers, although in this case the lower reactivity of these substrates towards H-abstraction required the use of a more diluted solution and a less favorable stoichiometric ratio had to be used. In contrast, no substantial PMI improvement is expected without an actual increase in the concentration of the substrates, as in the case of poorly reactive alkanes and alkylbenzenes.[9,26]

Energetic Expenditure

Recently, Zeitler and co-workers reported a comparison among the performances of batch, *meso*- and micro-flow reactors in the organocatalytic photoredox α-alkylation of aldehydes.[4d] They demonstrated the superiority of the meso-scale reactor, simply assembled by coiling a polyfluorinated tubing around the light source (a compact fluorescent lamp).[4d] By contrast, no significant advancement has been observed when moving to microreactors.[12,13]

In the present work, the use of a meso-scale flow photoreactor is a winning strategy for the improvement of the specific productivity in acylation processes (see Table 2 and Table 4), with a minimization of the required energy supply compared to batch conditions. Of course, the use of sunlight as the irradiation source represents an intrinsic advantage, although poor STY and productivity are obtained. By contrast, only a weak or even negligible effect can be observed when reactions different from acylations are considered.

We attempted to represent graphically these trends by having recourse to radar charts, where five different indexes have been reported (yield, productivity, PMI, specific productivity and STY). The different reaction conditions have been ranked with respect to each other, where a small figure represents a poor performance and *vice versa*. Accordingly, the larger is the area covered by a reaction set-up, the better is its (environmental) performance, although this criterion has only a qualitative and not a quantitative indication. The paradigmatic cases of the syntheses of **3** (dramatic improvement when shifting from batch to flow systems) and **27** (almost no improvement) are reported in Figure 1.

As hinted above, solar-induced reactions, where no energy is used for lamp operation, offer the best per-

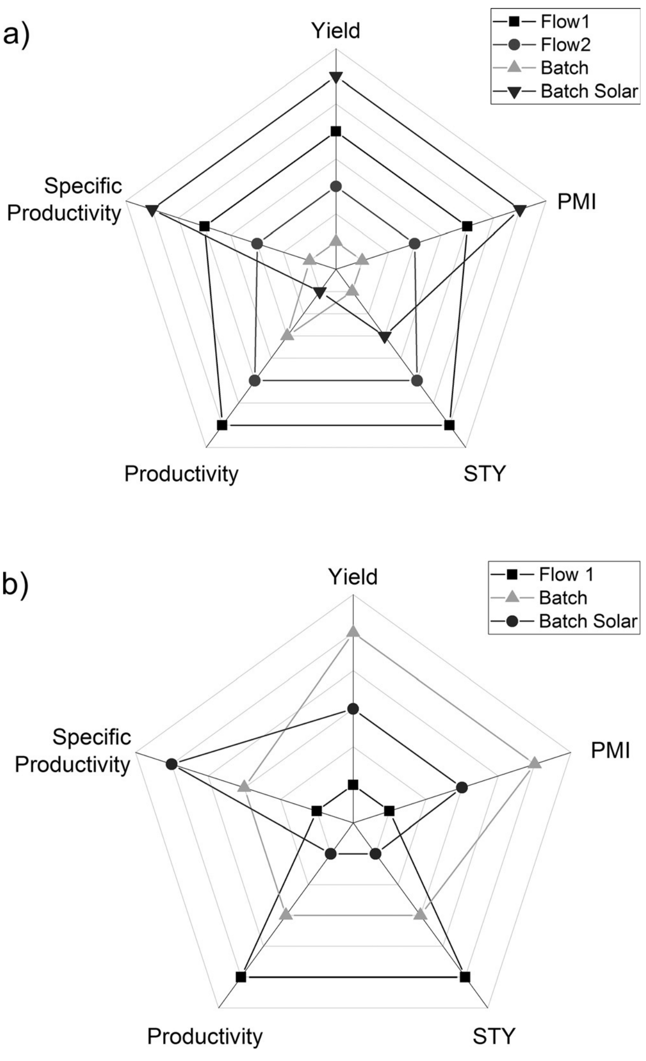


Figure 1. Radar charts for the synthesis of: a) **3** and b) **27**. For the meaning of the parameters, see text and Table 4.

formance in terms of specific productivity. By contrast, these reactions suffer from a poor overall productivity as a result of the discontinuous nature of this light source (only 8 h per day can be actually exploited). The calculated PMI values are governed by the yield and the concentration of the substrates, where flow approaches offer an actual advantage only if a concentration increase is possible (e.g., in the synthesis of **3**, but not in that of **27**).

A final remark deals with the different performance offered by the flow reactor presented here (Flow 1; V = 50 mL; inner diameter = 2.1 mm; lamp power = 500 W) with respect to that previously reported by our group (Flow 2; V = 12 mL; inner diameter = 1.3 mm; lamp power = 125 W). As apparent from Figure 1a, the updated version outperforms the previous one in all of the indexes considered.

Conclusions

In the present paper we have demonstrated that a meso-scale flow photoreactor is a suitable tool for the improvement of photocatalyzed radical conjugate addition *via* direct hydrogen atom transfer (HAT) reactions. The use of a continuous flow approach involved a strong decrease of the residence time and an increase of the productivity and STY values with respect to those calculated for the corresponding batch processes. The concentrations of the substrates can be often increased under flow conditions, leading to an improvement of the sustainability of the process (with a PMI value below 10 $\mathrm{kg\,kg^{-1}}$, that is a satisfactory value in fine chemicals production).[27] By contrast, when higher concentrations are not allowed, shifting from batch to flow conditions offers only limited advantages.

Experimental Section

Typical Procedure for the Synthesis of Compounds 3–27

Hydrogen donors **1a**–**m** and electron-poor olefins **2a**–**f**, **h**–**j** or azodicarboxylate ester **2g** (see Tables 1–3 and the Supporting Information for further details on the employed amounts) in the presence of a catalytic amount of TBADT (0.1 mmol, 2×10^{-3} M) were dissolved in 50 mL of acetonitrile (in the case of **1a**–**j**, **1m**) or in a 0.5 M $LiClO_4$ MeCN-H_2O 5/1 mixture (for **1k** and **1l**). The solution was charged in a flask and pumped through the apparatus described in the text (see also the Supporting Information, Figure S1). The final solution was evaporated and the residue was purified by column chromatography (cyclohexane:ethyl acetate as the eluents).

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References

[1] a) S. V. Luis, E. Garcia-Verdugo, (Eds.), *Chemical Reactions and Processes Under Flow Conditions*; RSC Publishing: Cambridge and London, **2009**; b) D. Webb, T. F. Jamison, *Chem. Sci.* **2010**, *1*, 675–680; c) J. Wegner, S. Ceylan, A. Kirschning, *Adv. Synth. Catal.* **2012**, *354*, 17–57; d) J. C. Pastre, D. L. Browne, S. V. Ley, *Chem. Soc. Rev.* **2013**, *42*, 8849–8869; e) L. Carroccia, B. Musio, L. Degennaro, G. Romanazzi, R. Luisi, *J. Flow Chem.* **2013**, *3*, 29–33; f) *Flow Chemistry*, (Eds.: F. Darvas, G. Dorman, V. Hessel), De Gruyter, **2014**; g) M. Brzozowski, M. O'Brien, S. V. Ley, A. Polyzos, *Acc. Chem. Res.* **2015**, *48*, 349–362; h) F. G. Finelli,

L. S. M. Miranda, R. O. M. A. de Souza, *Chem. Commun.* **2015**, *51*, 3708–3722.

[2] J. P. Knowles, L. D. Elliott, K. I. Booker-Milburn, *Beilstein J. Org. Chem.* **2012**, *8*, 2025–2052.

[3] A. Albini, L. Germani, in: *Handbook of Synthetic Photochemistry.* (Eds.: A. Albini, M. Fagnoni) Wiley-VCH, Weinheim, **2010**, pp 1–24.

[4] a) M. Oelgemöller, O. Shvydkiv, *Molecules* **2011**, *16*, 7522–7550; b) O. Shvydkiv, M. Oelgemöller, in: *CRC Handbook of Organic Photochemistry and Photobiology*, (Eds.: A. Griesbeck, M. Oelgemoeller, F. Ghetti), 3rd edn., CRC Press, **2012**, pp 49–72; c) M. Oelgemoeller, *Chem. Eng. Technol.* **2012**, *35*, 1144–1152; d) M. Neumann, K. Zeitler, *Org. Lett.* **2012**, *14*, 2658–2661.

[5] Y. Su, N. J. W. Straathof, V. Hessel, T. Noël, *Chem. Eur. J.* **2014**, *20*, 10562–10589.

[6] Z. J. Garlets, J. D. Nguyen, C. R. J. Stephenson, *Isr. J. Chem.* **2014**, *54*, 351–360.

[7] For reviews on synthetic applications of flow chemistry, see: a) J. Wegner, S. Ceylan, A. Kirschning, *Adv. Synth. Catal.* **2012**, *354*, 17–57; b) J. C. Pastre, D. L. Browne, S. V. Ley, *Chem. Soc. Rev.* **2013**, *42*, 8849–8869; c) D. Webb, T. F. Jamison, *Chem. Sci.* **2010**, *1*, 675–680; d) B. J. Deadman, S. G. Collins, A. R. Maguire, *Chem. Eur. J.* **2015**, *21*, 2298–2308; e) V. Hessel, D. Kralisch, N. Kockmann, T. Noël, Q. Wang, *ChemSusChem* **2013**, *6*, 746–789.

[8] 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.

[9] L. D. Elliott, J. P. Knowles, P. J. Koovits, K. G. Maskill, M. J. Ralph, G. Lejeune, L. J. Edwards, R. I. Robinson, I. R. Clemens, B. Cox, D. D. Pascoe, G. Koch, M. Eberle, M. B. Berry, K. I. Booker-Milburn, *Chem. Eur. J.* **2014**, *20*, 15226–15232.

[10] a) S. Protti, M. Fagnoni, D. Ravelli, *ChemCatChem* **2015**, *7*, 1516–1523; b) M. Fagnoni, D. Dondi, D. Ravelli, A. Albini, *Chem. Rev.* **2007**, *107*, 2725–2756.

[11] a) I. N. Lykakis, E. Evgenidou, M. Orfanopoulos, *Curr. Org. Chem.* **2012**, *16*, 2400–2414; b) M. D. Tzirakis, I. N. Lykakis, M. Orfanopoulos, *Chem. Soc. Rev.* **2009**, *38*, 2609–2621; c) C. Tanielian, *Coord. Chem. Rev.* **1998**, *178–180*, 1165–1181.

[12] M. Fagnoni, F. Bonassi, A. Palmieri, S. Protti, D. Ravelli, R. Ballini, *Adv. Synth. Catal.* **2014**, *356*, 753–758.

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

[14] 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.

[15] S. Angioni, D. Ravelli, D. Emma, D. Dondi, M. Fagnoni, A. Albini, *Adv. Synth. Catal.* **2008**, *350*, 2209–2214.

[16] a) D. Ravelli, A. Albini, M. Fagnoni, *Chem. Eur. J.* **2011**, *17*, 572–579; b) D. Ravelli, M. Zoccolillo, M. Mella, M. Fagnoni, *Adv. Synth. Catal.* **2014**, *356*, 2781–2786; c) S. Protti, D. Ravelli, M. Fagnoni, A. Albini, *Chem. Commun.* **2009**, 7351–7353; d) M. D. Tzirakis, M. Orfanopoulos, *Angew. Chem.* **2010**, *122*, 6027–6029; *Angew. Chem. Int. Ed.* **2010**, *49*, 5891–5893.

[17] K. Yamada, M. Okada, T. Fukuyama, D. Ravelli, M. Fagnoni, I. Ryu, *Org. Lett.* **2015**, *17*, 1292–1295.

[18] H. Qrareya, D. Ravelli, M. Fagnoni, A. Albini, *Adv. Synth. Catal.* **2013**, *355*, 2891–2899.

[19] a) D. Dondi, M. Fagnoni, A. Albini, *Chem. Eur. J.* **2006**, *12*, 4153–4163; b) D. Dondi, D. Ravelli, M. Fagnoni, M. Mella, A. Molinari, A. Maldotti, A. Albini, *Chem. Eur. J.* **2009**, *15*, 7949–7957.

[20] I. Ryu, A. Tani, T. Fukuyama, D. Ravelli, S. Montanaro, M. Fagnoni, *Org. Lett.* **2013**, *15*, 2554–2557.

[21] C. Jimenez-Gonzalez, C. S. Ponder, Q. B. Broxterman, J. B. Manley, *Org. Process Res. Dev.* **2011**, *15*, 912–917.

[22] J. W. Tucker, Y. Zhang, T. F. Jamison, C. R. J. Stephenson, *Angew. Chem. Int. Ed.* **2012**, *51*, 4144–4147.

[23] E. M. Schuster, P. Wipf, *Isr. J. Chem.* **2014**, *54*, 361–370.

[24] See for instance: a) F. Fringuelli, D. Lanari, F. Pizzo, L. Vaccaro, *Green Chem.* **2010**, *12*, 1301–1305; b) S. Bonollo, D. Lanari, J. M. Longo, L. Vaccaro, *Green Chem.* **2012**, *14*, 164–169.

[25] D. Ravelli, S. Protti, P. Neri, M. Fagnoni, A. Albini, *Green Chem.* **2011**, *13*, 1876–1884.

[26] See, for instance: J. D. Nguyen, B. Reiß, C. Dai, C. R. J. Stephenson, *Chem. Commun.* **2013**, *49*, 4352–4354.

[27] R. A. Sheldon, *Green Chem.* **2007**, *9*, 1273–1283.