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Microfluidic Photoreactor Enables 2-Methylbenzophenone Light-Driven Reactions with Superior Performance

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Light-driven reactions of 2-methylbenzophenones (2-MBPs) occur with improved yields (up to >98%) and reaction rates (up to 0.240 mmol/h) by using a tailored microfluidic photoreactor (MFP). For the first time, coumarins were converted into 4-benzylated chromanones in high yields (50-93%) and diasteroselectivity (up to >20:1 dr), thus by-passing their photo-dimerisation end-reaction.

Synthetic photochemistry is emerging as a key enabling technology for the construction of molecular architectures using visible light as a renewable energy source.[1] By exploiting unprecedented reactivity of organic molecules, photoredox catalysis[2] and photo-organocatalysis[3] have tremendously increased the synthetic abilities of chemists paving the way for novel reaction pathways. In this scenario, the implementation of microfluidic photoreactor (MFP) offers a decisive potential to address some fundamental issues related to photochemical batch protocols.[4] MFPs have a definite advantage considering: (i) the enhanced surface-to-volume ratio; (ii) uniform irradiation and increased light penetration depth; (iii) short diffusion distance for efficient mass and photon transfer; (iv) favorable heat dissipation and gas-liquid interfacial areas; (vi) synthetic up-scaling by continuous flow and/or micro-reactor parallelisation.[5] MFP is thus expected to impact both the kinetics and selectivity of photoreactions, turning-off undesired deactivation pathways, side-products formation and detrimental over irradiation.[4,5]

We show herein that 2-methylbenzophenone (2-MBP) light-driven reactions with different classes of molecular targets (Figure 1) proceeds within a MFP setup leading to much higher production rates up to one order of magnitude (0.240 mmol/h) and outstanding product selectivity when compared to the conventional batch protocol. Therefore, our results enhanced the synthetic appeal of the hydroxy-*o*-quinodimethane intermediate (**A'** in figure 1a).

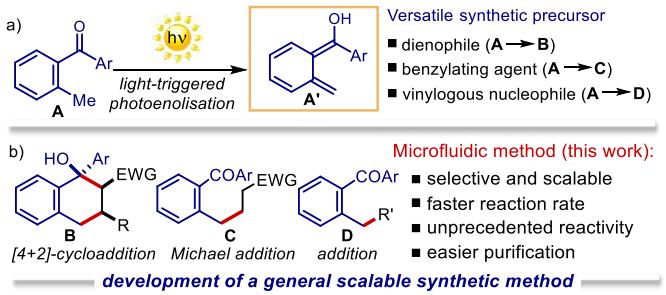

Figure 1. a) Light-triggered photoenolisation of 2-methylbenzophenone **A** to generate photoenol **A'**. b) Array of product types originated from **A** (**B**, **C**, or **D**) and advantages of the MFP setup.

Photoenol **A'**, generated upon photoexcitation of 2-MBP, is a versatile fleeting intermediate with a broad reactivity spectrum, such as dienophile, benzylating agent and conjugated nucleophile (**B**, **C**, and **D** in figure 1b).[6] These photo-reactions are of interest respectively for the stereoselective construction of biologically relevant benzannulated carbocyclic structures (**A→B**),[7] including macromolecules linkage[8] and polymer-polymer conjugations;[9] for the synthesis of β-benzylated aldehydes and ketones (**A→C**);[10] as well as for the direct trifluoromethylation[11] and CO_2-carboxylation[12] of benzophenone scaffolds (**A→D**), which are important precursors of 2,3-benzodiazepine pharmacophores. Despite the significant efforts devoted to the photochemistry of 2-MBP, a unifying and general synthetic platform is not yet available, precluding a facile discovery of new light-driven transformations and a desirable industrial implementation of the photochemical protocols.

Our results target the development of a MFP setup for 2-MBP photoreactions, that show improved reaction performances and selectivity compared to several in-batch reported procedures (*vide infra*, table 1). Also, the present setup advances the state-of-the-art synthetic scope, showing the unprecedented light-driven benzylation of coumarin

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chromophores, inaccessible under conventional batch conditions (*vide infra*, table 2).

Initially, the MFP setup[13] and reaction conditions were tested by screening the classical [4+2]-photocycloaddition[6] of 2-methylbenzophenone **1a** with N-phenylmaleimide **2a**, as a function of the light source and intensity, solvent, reagent concentrations, flow rate and residence time (see table S4 in the ESI). As a result of the optimisation studies it was found that the irradiation of an equimolar mixture of **1a** and **2a** with a 9W 365 nm bulb formed the photo-cycloaddition product **3a** in 10 minutes as a single diastereoisomer in quantitative yield (>98%). The product **3a** was obtained after simple solvent evaporation (see table 1, blue box). The same light source was used to irradiate the control batch reaction, where product **3a** was formed in 95% yield after 480 minutes (see table 1, grey box).[14] The different performances of the two photochemical protocols are highlighted by the relative productivity rates (mmol/h), whereby the MFP system outcompetes the conventional photoreactor by a 20-fold enhancement (0.240 mmol/h in flow vs 0.012 mmol/h in batch, **3a** in table 1). Under MFP conditions, the less reactive unprotected maleimide **2b** furnished product **3b** (>98%) after 16 minutes (0.150 mmol/h), whereas the corresponding batch control was completed after 500 minutes (92% isolated yield, 0.011 mmol/h). Quantitative transformations were also obtained with acyclic *trans*-diethyl fumarate **2c** and diethyl acetylenedicarboxylate **2d**. The desired benzannulated products **3c** and **3d** were formed in excellent yields (>98%) and rates of production (0.088 and 0.060 mmol/h respectively). Meanwhile, the performances of the batch reactions were again remarkably lower, forming the correspondent products in 60% and 87% yield respectively (0.006 mmol/h for **3c** and 0.004 mmol/h for **3d**). Photo-assisted trifluoromethylation of 2-MBP provided a further synthetic paragon.[11] Under MFP conditions, using the commercially available Togni's reagent I,[15] **3e** was obtained in 8 minutes (95% yield) with a production rate of 0.143 mmol/h (see **3e** in table 1), thus registering a consistent improvement with respect to the batch control (in 0.035 mmol/h).[16] Noteworthy, the MFP setup was also effective for the light-driven carboxylation of 2-MBP with CO_2, following a recent method reported by Murakami and co-workers.[12] In the original work a very energetic light source was required.[16] Gratefully, under the present MFP setup using the simpler 9W 365 nm bulb, the carboxylated benzophenone **3f** was obtained in excellent yield (98%) with a productivity rate as good as 0.039 mmol/h (see **3f**, in table 1). It should be noted that pure **3f** was isolated after a simple extraction work-up, making this transformation appealing for large-scale continuous-flow production. On the other hand, the batch reaction furnished **3f** in 75% yield, with a poor productivity rate (0.003 mmol/h).

In order to expand the scope of the 2-MBP photochemistry to challenging light-absorbing reagents, we applied the MFP platform for coumarin functionalisation. Coumarins[17] and chromanones[18] are biologically active compounds with a distinctive photochemistry, as many widely used organic dyes embody the coumarin scaffold.

Table 1. Survey of acceptors **2a-2f** under the optimised MFP setup (blue boxes) and batch setup (grey boxes) for comparison.[a]

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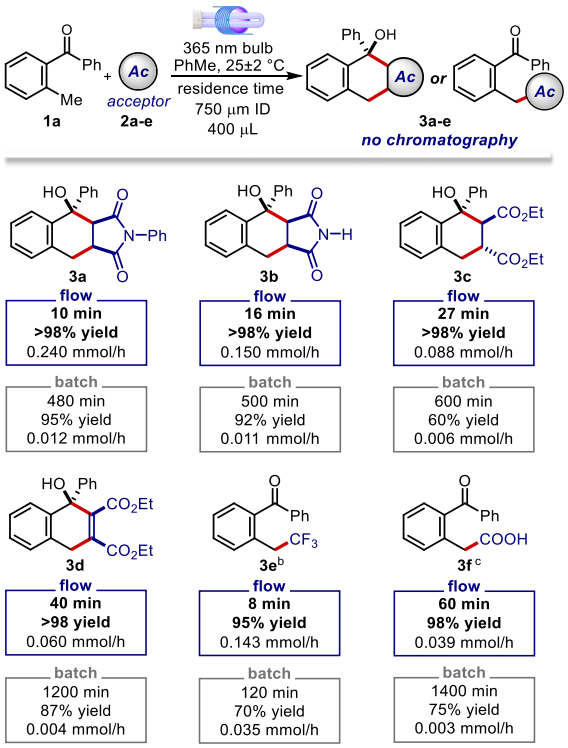

[a] Unless otherwise noted reaction conditions: a solution of **1a** (1.0 equiv.) and **2a-f** (1 equiv.) in toluene (0.1 M) was irradiated for the indicated time at 25±2 °C (see ESI for details). All the yields refer to isolated yields. Compounds **3a**, **3b** and **3c** were obtained as a single diastereoisomer. [b] Reaction performed in DMSO (0.05 M).[c] Reaction performed in DMSO (0.04 M) under a CO_2 atmosphere. ID = internal diameter.

The selective addition of 2-MBP **1** to coumarins would represent an innovative entry for the direct assembly of benzylated chromanones. However, photo-excitation of coumarins (λ > 320 nm) is known to promote self [2+2]-cycloaddition, yielding cyclobutanes **4** generally formed as a complex mixture of regio- and stereoisomers.[19] As shown in figure 2a, the absorption spectra of ethyl-3-coumarincarboxylate **2g** and 2-methylbenzophenone **1a** overlap with an identical maximum of absorbance at 345 nm (see section G2 in the ESI). Therefore, the [2+2]-cycloaddition of **2g** might preclude the intended addition reaction pattern. To our delight, within the MFP setup, irradiation of **1a** in the presence of coumarin **2g** yielded the unprecedented 4-benzylated chromanone **3g** in 75% yield. Remarkably, only 5% of the photo-dimerisation side product **4** was formed. On the other hand, the same reaction performed in batch furnished **3g** in 26% yield along with 17% of **4** (see figure 2b). These results highlight the unique potential of the MFP protocol allowing the development of previously inaccessible transformations.[20] Additional control experiments confirmed the tendency of coumarins of type **2g** for light-promoted dimerisation under both conditions (see ESI for details).

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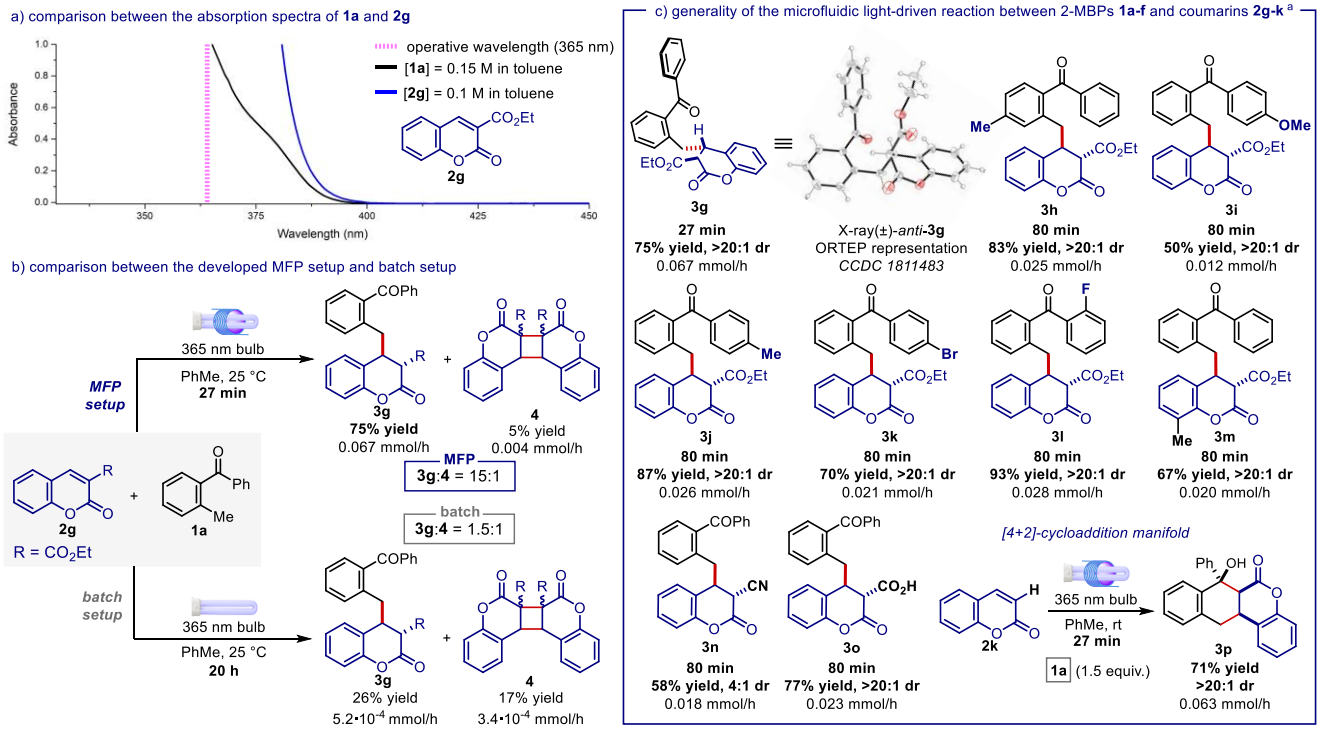
Figure 2. a) Comparison between the absorption spectra of 2-methylbenzophenone **1a** (black line) and ethyl-3-coumarincarboxylate **2g** (blue line). b) Comparison between the photo-reactions of ethyl-3-coumarincarboxylate **2g** under the developed MFP (top equations) vs in batch (bottom equations). c) Generality of the MFP reaction between 2-MBPs **1a-f** and coumarins **2g-k**.



[a] Reaction conditions: a solution of **1a-f** (1.0 equiv.) and **2g-k** (1 equiv.) in toluene (0.1 M) was irradiated for the indicated time a solution of **1a** (1.0 equiv.) and **2a-f** (1 equiv.) in toluene (0.1 M) was irradiated for the indicated time in for the indicated time at 25±2 °C (see ESI for details). Yields refers to isolated yield.

The generality of the microfluidic photo-benzylation of coumarins was subsequently assessed by varying the substitution pattern on both aromatic rings of 2-MBP as well as on the coumarin scaffold (see figure 2c). Electron-donating and electron-withdrawing substituents were well tolerated, affording the corresponding benzylated chromanones **3h-l** with yields in the range of 50% - 93% and complete diastereocontrol. Also, the use of different coumarin scaffolds was evaluated. 8-Methylcoumarin performed smoothly, leading to product **3m** in 67% yield. Interestingly, products **3n** and **3o** were obtained from 3-cyanocoumarin and coumarin-3-carboxylic acid in 58% yield and 77% yield respectively, in 80 min (0.018 and 0.023 mmol/h) albeit with diverse stereocontrol (4:1 dr for **3n** and >20:1 dr for **3o**). Notably, when 3-unsubstituted coumarin **2k** was subjected to the standard batch reaction conditions, the tetracyclic structure **3p** was formed as a single diastereoisomer in 71% yield, following a formal [4+2]-cycloaddition manifold. The absence of a substituent at the position 3 in the coumarin scaffold **2k** allows the final intramolecular aldol cyclisation, which is precluded by steric hindrance in 3-substituted coumarins. Finally, 664 mg of desired compound **3g** were produced in 12 h by using two MFPs in a parallel setup, with an overall production rate of 0.133 mmol/h.

In order to gain insights on the reasons for the enhanced performances, the photon flow of both setups were measured by using a chemical actinometer.[21] The registered value under MFP setup outcompetes by 5.3 times the value obtained in the batch setup. Thus, the enhanced reactivity is ascribed to the higher photon flux, correlated with an increased concentration of the photoenol intermediate **A'** in the reaction media. Also, the fine control over the residence time and hence the time of irradiation, successfully prevent the light-promoted product decomposition. We believe that the combination of these elements together with the more uniform irradiation surface and the shorter diffusion distance are at the basis of the observed performance enhancement of the MFP setup described herein.

In conclusion, MFP protocol was conveniently applied to photo-reactions of 2-methylbenzophenones, outperforming the conventional batch protocol in terms of product selectivity, yield and productivity rate. Among the seven different classes of photo-reactions successfully implemented, in five cases the corresponding reaction products were isolated in pure forms after simple solvent evaporation, as a result of enhanced selectivity and negligible side-product formation. Also, the new MFP platform was pivotal to access the direct photo-benzylation of coumarincarboxylates, that represent a new class of reaction partners for 2-MBPs. In this regard, coumarin dimerisation was successfully circumvented under MFP conditions, selectively yielding a broad range of 4-benzylated-2-

chromanones with high diastereocontrol and up to 93% isolated yield. Finally, the MFP protocol is readily amenable to large-scale synthesis as demonstrated for a 12 h continuous-flow synthesis of chromanone **3g**.

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Conflicts of interest

There are no conflicts to declare.

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15 Due to the improved performances of the MFP it was possible to use cheaper commercially available Togni's reagent I. In the described method Togni's reagent II was used. See reference 11 for details.

16 To compare the developed MFP methodology with already reported protocols see table S3 in the ESI.

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