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Machine Assisted Reaction Optimization: A Self-Optimizing Reactor System for Continuous-Flow Photochemical Reactions

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ABSTRACT

A methodology for the synthesis of oxetanes from benzophenone and furan derivatives is presented. UV-light irradiation in batch and flow systems allowed the [2+2] cycloaddition reaction to proceed and a broad range of oxetanes could be synthesized in manual and automated fashion. The identification of high-yielding reaction parameters was achieved through a new self-optimizing photoreactor system.

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Photoreactions and flow chemistry have been sharing an evergrowingly entangled history. Due to the use of high-power UVlamps, side-reactions and decompositions of both substrate and product were frequently observed in batch-type reactor setups that have been overcome by sophisticated flow-reactors.¹ These allowed the precise adjustments of irradiation time as well as reaction temperature resulting in higher conversions and spacetime-yields. One of the earliest examples of photocyclization reactions performed in microflow systems was published by Fukuyama and Ryu in 2004.² Vinyl esters and enones were successfully coupled by use of a 300 W Hg lamp and a Foturan glass reactor giving the corresponding cyclic products in moderate to good yields. In 2013, Oelgemöller and coworkers reported the [2+2]-cycloaddition reaction of furanones and alkenes.3 Thereby, a commercially available Rayonet chamber reactor in combination with a microcapillary unit was used for UVC-light irradiation (λ =254 nm) with excellent conversions compared to conventional batch-type setups.

A rather emerging field of research has been concerned with the establishment of self-optimizing reactor systems that made use of optimization algorithms, monitoring technologies, and their integration in well-known reactor setups.⁴ Pioneering work was achieved by Jensen and coworkers in 2010 when they presented the first self-optimizing Heck-reaction in both microand meso-scale continuous flow systems.⁵ Variations of temperature and flow rate controlled by a Nelder-Mead simplex algorithm led to isolation of an optimal parameter space for the micro-scale reactor system. Those conditions were then transferred to a meso-scale setup that was further used without self-optimization. Nevertheless, good yields were obtained in the 50-fold bigger system that was also in accordance with the previous investigated setup. In 2011, Poliakoff and coworkers established continuous etherification reactions in supercritical carbon dioxide as green solvent.⁶ Thereby, a super modified simplex algorithm was used for the iterative optimization of three (temperature, pressure, flow rate) or four (temperature, pressure flow rate, solvent ratio) parameter sets. The self-optimization process was not only able to optimize the yield of the main product but could also find conditions that led to the formation of specific side products. However, optimizations of especially photo-flow reactions still pose an insufficiently explored research area of organic chemistry and chemical engineering. Radical sensitivities of high-energy photocyclization reactions towards temperatures and residence times let these reactions suffer from time-consuming and labor-intensive optimizations. Furthermore, concentrations of substrates in appropriate solvents used to be a crucial parameter that often led to drastic improvements concerning product yields and its purity.

Among these reactions, the [2+2] photoreaction can be seen as model reaction that was used in batch and flow reaction setups.⁷ The so-called Paternò-Büchi reaction of alkenes with photochemically activated carbonyls was first described by their inventors E. Paternó⁸ and G. H. Büchi⁹ and later on thoroughly investigated by Schenk¹⁰ and Griesbeck.¹¹ The importance of this photochemical transformation was further proven by Schreiber in 1984,¹² who selectively generated a multi-substituted oxetane building block for the synthesis of the bioactive natural product - (±)-Asteltoxin (Figure 1)

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Herein, we report the advantage of using a capillary-type¹³ microfluidic photochemical reactor for Paternó-Büchi reactions and a computer-assisted self-optimization of flow rates.

The first investigations were carried out in order to determine the most suited light source. A Rayonet chamber reactor was therefore charged with lamps with emitting wavelength of 300, 350, and 400 nm, respectively. After 8 and 15 h reaction times the conversion of the batch-mode Paternó-Büchi reaction of benzophenone **2a** and furan **1** was determined by GC-analysis (Table 1).

Table 1: Evaluation of the light source.



[a] Reaction conditions: **2a** (2.73 mmol), furan (20 mL). [b] GC conversions/yields (%).

It was observed that formation of the product **3a** at 350 nm was slightly higher than at the other wavelengths (Table 1, entry 2, 5). This fact was confirmed by the known absorption spectrum of benzophenone **2a** in non-polar solvents, where the excitation of the important $n\pi^*$ shift is located at that wavelength.¹⁴ However, the usage of the photoreactor equipped with a powerful medium-pressure Hg lamp and a Pyrex-glass filter, gave a superior yield of 80% after 1 h reaction time (Figure 2).



Figure 2: Capillary-type continuous photo-flow reactor.

To maximize the productivity, the reaction time was evaluated by changing either the reactor volume or the flow rate (Table 2). After adjusting the reaction time manually from 50 to 120 minutes by looping the reaction mixture back into the reactor, it was shown that the yield reached already excellent values after 100 minutes (Table 2, entry 4). Furthermore, an online-analysis approach was developed to obtain the optimal residence time by connecting an in-line ReactIR spectrometer and a computer based communication interface to the aforementioned flow reactor (Figure 3). Fortunately, applying the newly developed selfoptimizing reactor setup we observed a comparable yield of 97% after 83 minutes (Table 2, entry 3).

Table 2: Evaluation of the flow rate and reaction time.

0 1	+ O Ph Ph 2a	h∨ (Hg-lamp, Py time (h)	$\frac{(rex)}{3a}$) ∖∼Ph Ph
Entry	Reactor	flow rate	τ(total)	Yield
	volume	(µL/min)	(min)	(%)
	(mL)			
1	10	600	17	69
2	5	500	2	80
3	5	360	14	97
4	10	1200	8	96
5	10	500	20	98

[a] Reaction conditions: **2a** (1.37 mmol), furan (10 mL). [b] Yields after column chromatography (%).



Photo-flow reactor

Figure 3: Schematic illustration of the flow setup for the [2+2] photocyclization reaction; BPR - back pressure regulator.

During the measurement, the reaction mixture flow stream passed the IR spectrometer before and right after being irradiated. The recorded IR data were constantly analyzed by a computer software which, based on these information, controlled the pump unit. According to the intensity of the specific absorption of the carbonyl group (1662 cm⁻¹) of the benzophenone substrate **2a**, the flow rate of the operating HPLC-pump was constantly reduced until the substrate was completely consumed in the photoreaction (Figure 4).



Figure 4: FTIR spectrum of the characteristic C=O band at 1662 cm^{-1} showing the conversion of benzophenone **2a**.

To further prove the advantage of the developed flow system, the reaction was also performed in a batch-type reactor. In this direct comparison study it was clearly shown that under flow conditions superior yields were obtained after a fraction of the time which would be necessary under batch conditions (Table SI1). After the same residence time of about 80 minutes the flowmode reaction showed full conversion of the carbonyl compound, whereas under the batch-mode conditions only minor oxetane formation could be observed (Table SI1, entries 1 and 5).

With the optimized flow parameters in hand the substrate scope of the Paternó-Büchi reaction was explored. Applying various aldehydes and a ketone to the [2+2] photoreaction with furan and its derivative, the appropriate products were isolated in good to excellent yields (Table 3). While the conversions have

to be mostly excellent, the yield of the purified product was party reduced. This observation was tracked back to the difficult separation of the remaining substrate from the synthesized product. In some cases, multiple purification procedures had to be performed to obtain a good separation.

3

Table 3: Scope of the Paternó-Büchi reaction.^a

	$\langle \mathbf{A} \mathbf{A}^{+} \mathbf$	C R ² 2	hv (Hg-I R ³ tir	amp, Py ne (h)	$rrex) \qquad O \qquad 1$	R^3
Entry	\mathbf{R}^1	\mathbf{R}^2	R ³	3	Yield ^[b] (%)	GC ^[c] (%)
1	Н	Н	Ph	3a	96	98
2	Н	Η	pTol	3b	87	94
3	Н	Η	oTol	3c	84	98
4	Н	Н	2,4-MePh	3d	82	95
5	Н	Н	Mes	3e	86	90
6	Н	Η	<i>p</i> (<i>t</i> Bu)Ph	3f	84	94
7	н	Н	2-CN-Ph	3g	86	96
8	Н	Н	pF-Ph	3h	82	95
9	Н	Н	2,4-F-Ph	3i	95	95
10	Н	Н	3-CF ₃ -Ph	3j	90	98
11	Н	Н	C ₂ H ₄ -Ph	3k	23 ^[d]	28
12	Н	Ph	Ph	31	97	98
13	Me	Ph	Ph	3m	77:23 ^[d,e]	75:20 ^[e]

[a] Reaction conditions: 2 (2.73 mmol), furan (20 mL), flow rate 60 μ L/min; V_{reactor} 5 mL, τ = 83 min [b] Yields after column chromatography. [c] GC conversions. [d] Calculated rate from NMR. [e] Rate of substitution at position 1 and 3.

It was shown that both electron donating **3a-f** and withdrawing substituents 3g-j on the aromatic group of the carbonyl compound were similarly suitable for the cyclization reaction. Also the substitution pattern of the aromatic group had just a minor influence on the product yield. Just in case of an aliphatic carbonyl substituent a lower yield of 23% was isolated (Table 3, entry 11). This observation can be explained by the application of a Pyrex-filter and the insufficient irradiation with high energetic UV-light with wavelength below 300 nm. In a similar reaction of nonal and furan, Schreiber and Hoveyda¹⁵ used a Vycor-glas batch reactor, which shows comparable transparency to UV-light as fused silica. Upon performing the Paternó-Büchi reaction with benzophenone 2a and 2-methylfuran 1b, isomeric products were isolated. The introduced methyl-group could be located either at the C-1 or the C-3 position. In conformity with the investigations by the group of Abe¹⁶ the higher substituted oxetane was built preferably with a 77 to 23 ratio of the isomers.

In order to make use of the previously mentioned selfoptimizations and our gained expertise in this field, we envisioned the integration of an optimization algorithm into a continuous-flow photoreactor. Again, using an in-line ReactIR, we chose the Paternó-Büchi reaction of benzophenone with furan as model reaction which is highly suitable due to the characteristic IR-bands that can be analyzed by FTIR spectroscopy. Moreover, identification of stationary states can easily be achieved by this method. Using the IR software (iC IRTM)¹⁷ which simultaneously controls the IR machine, interpretation of the IR spectra was possible. An HPLC pump

(Knauer K-120), valve controls (Upchurch Scientific V-1341) M and an autosampler (HiTec Zhang AutoSam200) complemented our reactor setup. The Modified Simplex algorithm (MSIM)¹⁸ was integrated in LabVIEW 2010 (National Instruments) with Matlab 7 (MathWorks), which controlled all equipment components via RS-232 connections. By analyzing the obtained parameter values based on the peak corresponding to the reaction conversion with consecutive auto-export function, a real-time (by the LabVIEW controlled) optimization program was established. Having reached the steady state (after a minimum of three hydrodynamic residence times and a standard deviation of peak height difference below $\leq 7 \cdot 10^{-4}$) of the system the next set of parameters is calculated. Benzophenone dissolved in furan as well as neat furan was pumped from a reservoir into the photoreactor, previously mixed by a T-shaped micromixer for the 2-HPLC-pump system. Having passed the IR flow cell, a computer assisted valve control allows collection of the product in vessels, as all components and the resulting reaction parameters were controlled, and optimized by the computer software. Starting values were chosen within parameter ranges that allowed efficient progress in the consecutive optimization process.18

To further improve the presented self-optimizing reaction system and analyze the influence of reactant dilutions, an additional parameter should be installed. So benzophenone dissolved in furan and neat furan were pumped individually into the photochamber thus allowing the system to identify the best concentration for both substrates. Therefore, two separately controlled HPLC pumps were installed to the previous system and mixed by a T-shaped mixer that finally gives a triangle with two variables in the given parameter space (Figure 5).



Figure 5: Self-optimizing photo-flow reaction setup with two HPLC pumps and on-line ReactIR.

The parameter space was chosen to be $60 - 150 \,\mu \text{Lmin}^{-1}$. This area roughly covers the previously identified optimum with regards to its possible variation towards lower concentrations that have been observed in earlier experiments. After an initial orientation phase of 10 points (Figure 6, Table 4, for full table see SI), optimal regions towards low furan flow rates could be identified, finally resulting in 95% conversions at flow rates of 65 μLmin^{-1} for benzophenone **2a** and 115 μLmin^{-1} for furan **1a**.

Starting from 16% conversion for the first parameter point at $80 \,\mu Lmin^{-1}$ for both components, a steady increase of conversions can be observed. After receiving a block of lower





Figure 6: Parameter space of self-optimized [2+2] photocyclization

Table 4: Excerpt of values for self-optimization using two HPLC-pumps and parameter space of self-optimized [2+2] photo-cyclization reaction.

	Flow rate BP	Flow rate Furan	τ	Conv.
point	(µLmin ⁻¹)	$(\mu Lmin^{-1})$	(min)	(%) ^a
1	80	80	63	16
2	117	106	45	12
3	106	117	45	10
4	117	135	40	15
5	140	114	39	19
6	123	95	46	30
10	141	110	40	33
11	106	111	46	33
12	71	114	54	35
16	89	111	50	51
17	70	117	53	59
21	81	114	51	90
22	75	115	53	95
23	65	115	56	95
24	61	114	57	86
25	72	115	53	90

^aConversions determined by GC; BP: benzophenone.

For parameter point 14 no clear IR spectrum was recorded due to formation of a hot spot in the tube that led to evaporation of furan. Nevertheless, the algorithm was able to continue its optimization also showing the robustness of the optimization method towards certain casual errors. Having kept the furan flow rate constant and further lowering the amount of furan, the algorithm was able to identify an optimal region for the reaction system after 25 parameter points. The total optimization was achieved within 48 hours showing its high efficiency that could not have been obtained without computer assistance (Table 5).

It becomes evident that there is a correlation between conversion and benzophenone concentration. Usually, the lower the benzophenone concentration, the higher the conversion. This was either obtained by increasing the furan or by lowering the benzophenone flow rate.

Furthermore, comparing the productivity of both optimal parameter points from both flow setups, 0.37 mmolh^{-1} of product **3a** for the 2-pump system and 0.35 mmolh^{-1} for the 1-pump system could be obtained (according to eq. 1). At the same time, a 36% reduction in irradiation time was achieved for the 2-pump system (53 min) compared to the 1-pump system (83 min).

Table 5: Self-optimization run for photoflow reactor.

	<pre></pre>	O hv (Hg Ph 2a	g-lamp, pyrex) time (h)	O G 3a Ph	'n
Point	Flow rate	Flow rate	flow rate	τ	Conv
	BP	Furan ^a	total		
	(µL/min)	(µL/min)	(µL/min)	(min)	(%)
1	80	80	160	63	16
2	117	106	223	45	12
3	106	117	223	45	10
4	117	135	252	40	15
opt	65	115	180	56	95

 a c(benzophenone) = 0.1 M in furan; BP: benzophenone; conversion by GC

productivity [mmol h^{-1}] = $c_{subst} \cdot \frac{\dot{V}_{subst}}{\dot{V}_{total}} \cdot Y_{subst}$ (eq. 1)

C_{subst} : concentration of substrate

 \dot{V} : flow rate

Y: yield

It cannot be excluded that other combinations of both flow rates may lead to optimal conversions. Since the algorithm is only capable of identifying a local optimum, not the global one, increasing the length of the starting triangle or starting from a different starting point may result in a different parameter set. However, since the initial optimization already identified a local optimum, we were only interested in the question whether a modification of setup and a more specified performance could give rise to a more detailed and advanced optimization method. As both reactor setups identified similar optima independently, verification of both methods can be assumed. Nevertheless, reasonable amounts of these biologically active motifs can now be easily prepared using readily available hardware.

In summary, we have illustrated the development of a [2+2] photocyclization reaction of benzophenone and furan yielding biologically active and important structural motifs tolerating a broad scope of different educts. Starting from batch-type reactor setups, modern flow-setups in combination with advanced self-optimization methods led to identification of parameter sets which show excellent conversions and yields for the desired oxetanes. By changing to a 2-reservoir reactor system and thus

increasing the number of parameters, an even more detailed "map" of the reaction space could be drawn allowing the user to choose from a variety of high-yielding parameter sets. The entire optimization was achieved without human interaction as all necessary manual interactions, such as probe collection, recording of spectra and adjustment of flow rates were conducted by integrated algorithms and control entities.

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