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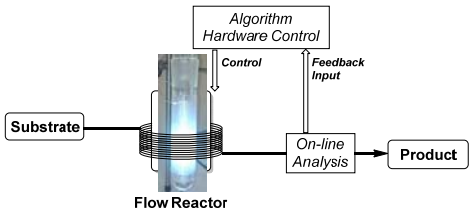
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Machine Assisted Reaction Optimization: A Self-Optimizing Reactor System for Continuous-Flow Photochemical Reactions

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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 biologically active 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. 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 ever-growingly entangled history. Due to the use of high-power UV-lamps, 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 space-time-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 microcapillar 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 micro- and 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, respectively. 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 frequently used to compare 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. Paternó[8] and G. H. Büchi[9] and later on thoroughly investigated by Schenk[10] 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)

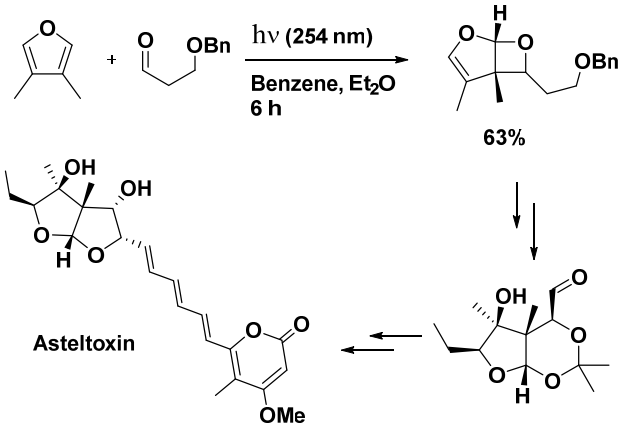
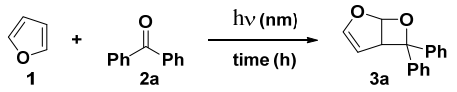


Figure 1: Synthesis of Asteltoxin with a [2+2] photocycloaddition key step.

Herein, we report the advantage of using a Booker-Milburn type[13] 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.



Entry	light (nm)	time (h)	**2**[b] Conv. (%)	**3a**[b] Conv. (%)
1	300	8	83	15
2	350	8	77	20
3	400	8	82	15
4	300	15	69	26
5	350	15	62	32
6	400	15	70	26

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

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% just after 1 h reaction time (Figure 2).

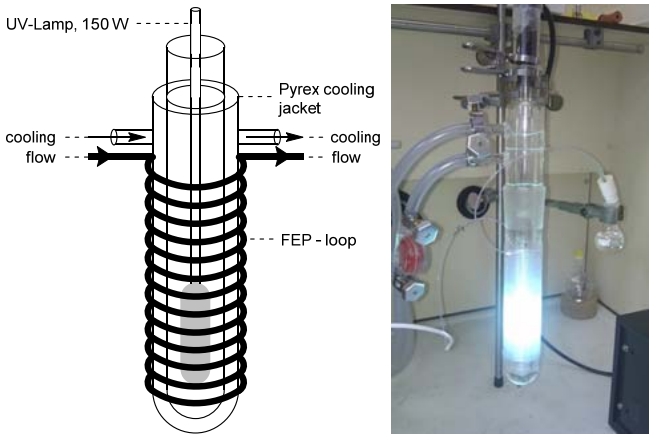
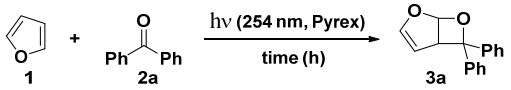


Figure 2: Booker-Milburn type continuous photo-flow reactor.

To maximize the space-time-yield, the reaction time was evaluated by changing either the reactor volume or the flow rate, respectively (Table 2). After adjusting the reaction time manually from 50 to 120 minutes it was shown that the yield reached already excellent values after 100 minutes (Table 2, entry 4). Furthermore, an automatic 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 self-optimizing reactor setup we observed a comparable yield of 97% just after 83 minutes (Table 2, entry 3).

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



Entry	Reactor volume (mL)	flow rate (µL/min)	Time (h)	Yield (%)
1	10	600	50	69
2	5	500	60	80
3	5	360	83	97
4	10	1200	100	96
5	10	500	120	98

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

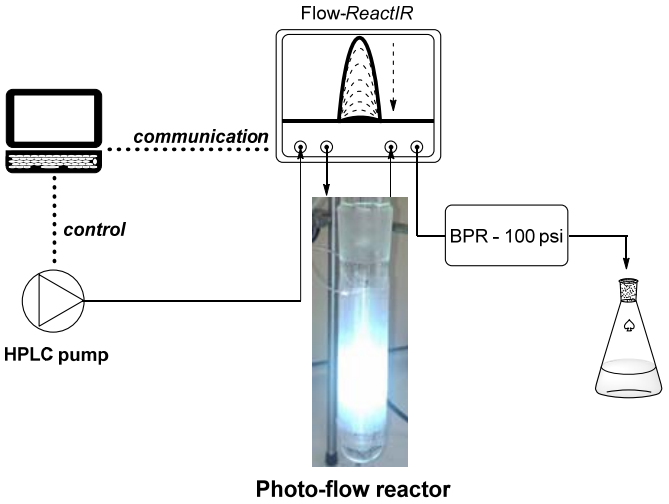


Figure 3: Schematic illustration of the flow setup for the [2+2] photocyclization reaction; BPR - back pressure regulator.

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).

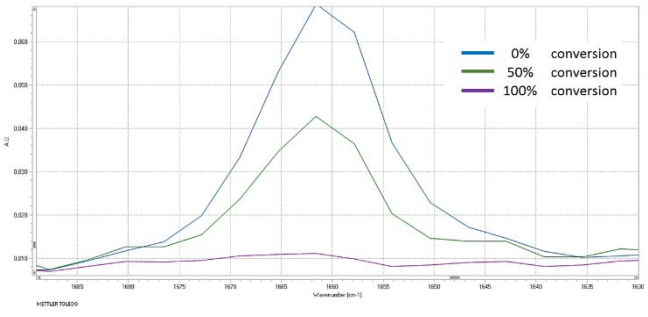
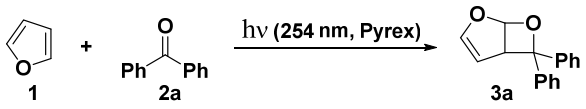


Figure 4: FTIR spectrum of the characteristic C=O band at 1662 cm^{-1} showing the conversion of benzophenone.

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 3). After the same residence time of about 80 minutes the flow-mode reaction showed full conversion of the carbonyl compound, whereas under the batch-mode conditions only minor oxetane formation could be observed (Table 3, entries 1 and 5).

Table 3: Comparison of batch and flow conditions.

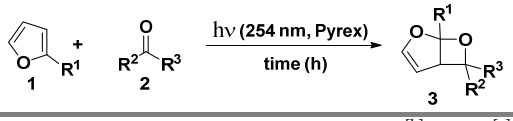


Entry[a]	Time (min)	Yield[b] (%)	GC[c] (%)
1 (batch)	80	3	3
2 (batch)	120	9	9
3 (batch)	240	17	15
4 (batch)	320	18	18
5[d] (flow)	83	97[e]	98

[a] Batch reaction conditions: **2a** (2.05 mmol), furan (15 mL). [b] Calculated yield from NMR. [c] GC conversions [d] Flow reaction conditions: **2** (2.73 mmol), furan (20 mL), flow rate 60 µL/h. [e] Yield after purification by column chromatography.

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 4). While the conversions have been determined from the crude reaction mixture and turned out 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.

Table 4: Scope of the Paternó-Büchi reaction.[a]



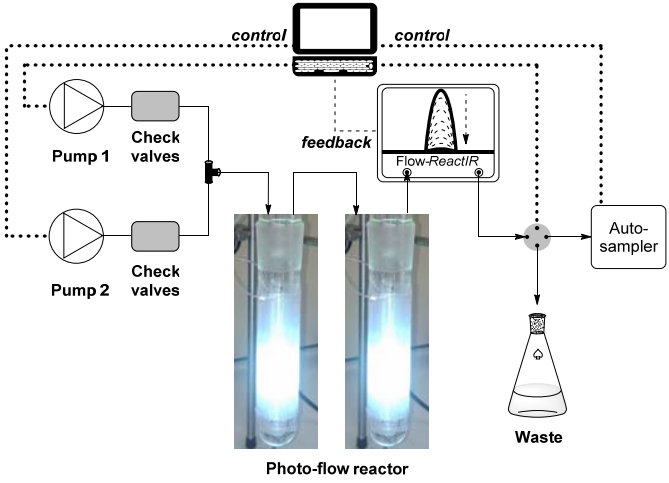
Entry	R^1	R^2	R^3	3	Yield[b] (%)	GC[c] (%)

1	H	H	Ph	3a	96	98
2	H	H	*p*Tol	3b	87	94
3	H	H	*o*Tol	3c	84	98
4	H	H	2,4-MePh	3d	82	95
5	H	H	Mes	3e	86	90
6	H	H	*p*(*t*Bu)Ph	3f	84	94
7	H	H	2-CN-Ph	3g	86	96
8	H	H	*p*F-Ph	3h	82	95
9	H	H	2,4-F-Ph	3i	95	95
10	H	H	3-CF_3-Ph	3j	90	98
11	H	H	C_2H_4-Ph	3k	23[d]	28
12	H	Ph	Ph	3l	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 µL/h. [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 4, 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 Hoveyda[15] 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 Abe[16] 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 self-optimizations 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 IR™)[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) 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 ≤ $7•10^{-4}$) 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 makes it to a two parameter triangle-shaped polygon (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 µLmin^{-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), 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** (see Supporting Information Table 1 for full data set).

Starting from ca. 20% conversion for the first parameter point at 80 µLmin^{-1} for both components, a steady increase of conversions can be observed. After receiving a block of lower conversions when the flow rate of benzophenone **2a** was increased, higher yields were again obtained with an excess ratio of furan **1a**.

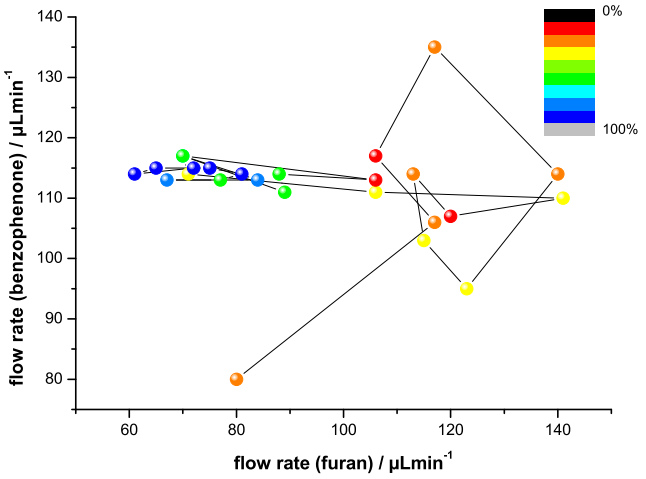
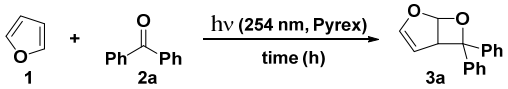


Figure 6: Parameter space of self-optimized [2+2] photo-cyclization reaction.

For parameter point 14 (see Supporting Information) 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 benzophenone 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.

By comparing both reactor setups, it becomes evident that the previously obtained conclusion, namely the accordance of concentration and residence time, is transferable to the presented reactor setup. Again it can be observed that with lowering the furan flow rate and, thus decreasing the benzophenone **2a** concentration, higher yields are obtained. Having a 0.1 molL^{-1} solution of benzophenone **2a** in furan **1a**, optimal conversions could be obtained at a 60 µLmin^{-1} flow rate. Changing now to the 2-HPLC-pump system, similar conversions were achieved when only 60% (0.06 molL^{-1}) of the previously used concentrations were applied which is due to the fact that the total flow rate was nearly tripled and the irradiation time doubled. The residence time of the second reactor setup can be calculated to 56 min at the optimal reaction conditions (Table 5, *optimal*). In comparison to the first setup when only one HPLC-pump was applied, a reduction of irradiation time of almost 30 min (70% reduction) could be achieved when two irradiation chambers were installed. Furthermore, comparing the space-time-yields of both optimal parameter points, 0.66 mmolh^{-1} of product **3a** for the 2-pump system and 0.35 mmolh^{-1} for the 1-pump system could be obtained.

Table 5: Self-optimization run for photoflow reactor.



Parameter point	Flow rate Furan (µL/min)	Flow rate Benzoquinone (µL/min)	GC-conversion (%)
1	80	80	16
2	117	106	12
3	106	117	10
4	117	135	15
opt	65	115	95

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 amounts 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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