



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 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 microcapillary unit was used for UVC-light irradiation ($\lambda = 254$ 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. 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.

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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. Paternò⁸ and G. H. Büchi⁹ and later on thoroughly investigated by Schenck¹⁰ 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 (Fig. 1).

Herein, we report the advantage of using a capillary-type¹³ microfluidic photochemical reactor for Paternò-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 Paternò-Büchi reaction of benzophenone **2a** and furan **1** was determined by GC-analysis (Table 1).

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 (Fig. 2).

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 min by looping the reaction mixture back into the reactor, it was shown that the yield reached already excellent values after 100 min recirculating. 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 (Fig. 3). Fortunately, applying the newly developed self-optimizing reactor setup we observed a comparable yield of 97% after 83 min reaction time.

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 this 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

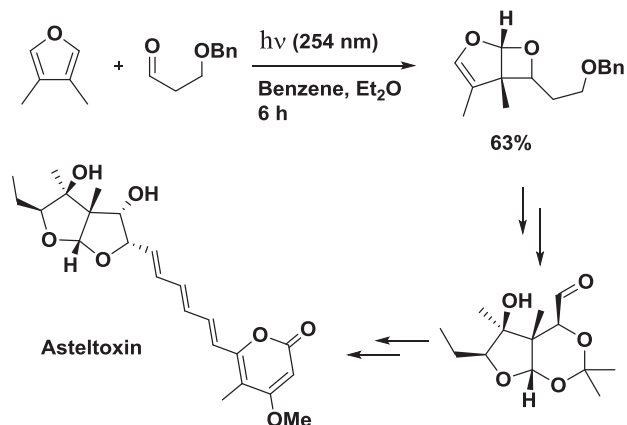


Fig. 1. Synthesis of Asteltoxin with a [2 + 2] photocycloaddition key step.

Table 1
Evaluation of the light source.

Entry	light (nm)	time (h)	2a ^[b] Conv. (%)	3a ^[b] Yield (%)
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/yields (%).

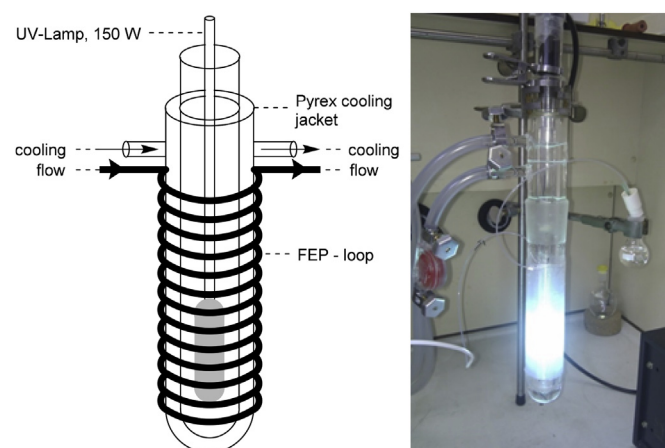


Fig. 2. Capillary-type continuous photo-flow reactor.

the substrate was completely consumed in the photoreaction (Fig. 4).

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 S11). After the same reaction time of about 80 min the flow-mode reaction showed full conversion of the carbonyl compound, whereas under the batch-mode conditions only minor oxetane formation could be

Table 2
Evaluation of the flow rate and reaction time.

Entry	Reactor volume (mL)	flow rate ($\mu\text{L}/\text{min}$)	τ (total) (min)	Yield (%)
1	10	600	17	69
2	5	500	10	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 (%).

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