Improved efficiency of photo-induced synthetic reactions enabled by advanced photo flow technologies

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Abstract

In this article, we discuss how effective photo-induced organic reactions became when applied evolving photo flow technologies through our experiences over these two last decades. We started with the flow update of traditional [2 + 2] cycloaddition using Mikroglas Dwell device as a flow reactor and a compact light source, such as blacklight, instead of a high-pressure mercury lamp. Then we examined Barton nitrite reaction using a photo flow reactor consisting of stainless-steel channels and a quartz glass top provided by DNS. Again the use of blacklight was successful. However, the energy profile of these reactions was improved further by the use of LED lights. We used a photo-flow set-up, consisting of stainless steel engraved microchannels covered by a quartz top (MiChS L-1) and a sodium lamp, for the isomerization of a fulleroid to PCBM. Photo-redox-catalyzed alkene alkylation proceeded within a shortened reaction time when the same photo flow reactor and white LED were used instead of a batch reactor. Photo-induced reductive 5-exo-dig radical cyclization and reduction of alkenyl halides proceeded smoothly, thanks to the combination of a photo flow reactor and low-pressure Hg lamp. We also applied flow technologies for photo-bromination and chlorination of C–H bonds. Photocatalytic oxidation of benzyl alcohol by molecular oxygen became quick when high-power LED irradiation was employed.

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Graphical abstract

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1 Introduction

Photochemical reactions have provided many valuable and practical methods for synthetic chemistry. However, photochemical processes using traditional batch reactors generally require a long irradiation time. Such a situation often causes a decrease in yield and selectivity due to unfavorable photochemical reactions of the initially formed products. The excellent example of the Mizuno group in Osaka dealing with intramolecular [2 + 3] photocycloaddition features this [1]. According to the Lambert–Beer law ($\log(I_0/I) = \epsilon cl$), light strength attenuates exponentially with increasing optical path length. Accordingly, reactions in microflow systems are expected to run in considerably shortened irradiation

time (Fig. 1), the shorter optical path ensuring efficient irradiation. This situation has pushed the development of a compact photo-irradiation source to accommodate a compact flow reactor, rendering photochemical reactions an energy-saving, highly efficient process.

Flow reactions using microreactors have recently attracted intense interest in efficiency and energy-saving. Photo-induced reactions are not the exception. Pioneering work by Jensen and coworkers appeared in 2001 [2] dealing with the pinacol coupling of benzophenone under photo-irradiation. Then flow photochemistry has paved a steady way for improved efficiency in photo-induced organic synthesis these last two decades. Nowadays, there is a consensus that photo-induced organic synthesis seldom goes without flow

Fig. 1 Photoreaction using batch and microflow reactors

chemistry, even for large-scale synthesis. Scale-up synthesis of batch-type photoreaction requires extensive photo-irradiation equipment, as seen in the case of the famous chemical plant of Toray in Nagoya for the production of 6-nylon. The batch-type chemical plant equipped with a huge photoirradiation system produces cyclohexanone oxime, a precursor for ϵ -caprolactam from cyclohexane and nitrosyl chloride by the photo-induced radical reaction. This plant is undoubtedly the landmark of the last century, achieving successful industrialization using photochemistry. On the other hand, if we criticize the photo plant from the viewpoint of green chemistry, the costs can be very high to keep high power light sources, and the batch operation consumes considerable electric energy. Therefore, this century needs industrially successful examples based on compact flow photo plants, and at the beginning, we need the innovation of excellent flow setups for photochemistry.

Several comprehensive reviews are available to cover the flow photochemistry. Among them, Oelgemöller's review published in this journal in 2008 [3] covers the original studies by players in the early stage. In addition, recent reviews by Noël [4–7], Kappe [8], Baumann, [9] and Mizuno [10] have showcased the high synthetic potentials of photo flow chemistry with many examples. Thus, flow expertise is rapidly growing to establish as the new standard of experimental photochemistry.

In the early 2000s, our group at Osaka started a new research program to switch organic synthesis from batch-type to microflow-type, highly motivated by Jun-ichi Yoshida at Kyoto. For the earlier contributions to flow chemistry, we wrote an account in Synlett in 2008 with a guide on how reactions in a tiny space are advantageous over those in a batch flask [11]. In 2004, we first reported our result of flow [2 + 2] photocycloaddition using a Mikroglas Dwell Device [12], which has the multi-layered Foturan glass structures made by thermal diffusion bonding (Fig. 2).

Fig. 2 Mikroglas dwell device composed of reaction layer and coolant layer

At that time, we also started to use a photo microreactor provided from DNS (Dainippon Screen), in which microchannels were made by photo-etching on a stainless-steel plate and covered by quartz-glass top (Fig. 3) [13]. This DNS device can be disassembled and cleaned in case of clogging or contamination. This liberated our students from the daily stress of clogging on precious glass-made photo-reactors. Unfortunately, DNS stopped supplying the heavy-duty photoreactors in a few years, making the DNS reactors “vintage.” However, later on, MiChS supplied the photo flow reactor MiChS L-1 with nearly the same concept but with the microchannels made by mechanical carving on metal plates (stainless-steel or Hastelloy) (Fig. 4). As for the light sources, in the beginning, we had to use a multi-wavelength light source such as a high-pressure mercury lamp (300 W), similar to what the batch photo reactions employed [12]. However, soon a very compact, narrow-wavelength emitting light source such as a compact blacklight fluorescent bulb

Fig. 3 Assembled photoflow reactor. DNS reactor consisting of stainless-steel channel plate and quartz glass top (2003–2010)

(360 nm, 15 W) matched with the flow [2 + 2] cycloaddition reaction [13]. Then we switched from the bulb to LED. It was fortunate that Prof. Ichimura and Dr. Matsushita at Tokyo Tec kindly taught us that their photo flow reaction used a UV-LED system purchased from Seoul Opto Device Co. Ltd. in South Korea. We then tested the combination of a DNS photoreactor with custom-ordered UV-LED (365 nm, 48 lamps, 1.7 W), which proved an even better combination in terms of fitness and energy-saving [13]. The Kakiuchi group applied a photo flow system to improve the diastereoselectivity of [2 + 2] photocycloaddition [14]. Kakiuchi, Nishiyama, and coworkers at NAIST contributed to flow photochemistry by providing several vital observations using slug flow conditions, such as light confinement effect, formation of the thin layer of the reactant solution, and the effect of internal vortex mixing [15].

In this perspective, we describe our efforts in Osaka over two decades to develop flow photo technologies and increase the efficiency of photo-induced organic synthesis, with a particular focus on photo-induced radical reactions and some miscellaneous photoreactions. Flow photo-redox reactions are now quite popular. Many research studies now use conventional flow setup, composed of coil-type tubular reactors, made of perfluoro polymer tube and photo equipment placed in the center, representing another standard setup for flow photo-reactions [16, 17]. Such a coil-type reactor is

especially useful in case that photo reactions require a long irradiation time. We highly recommend reading a timely review from the Stephenson group to feel the breath of the growing photo flow chemistry field using photoredox catalysis [18]. To avoid duplication, we recently surveyed flow radical reactions except for photoredox reactions [19].

1.1 Flow [2 + 2] cycloaddition

Flow [2 + 2] photo-cycloaddition of cyclohexenone with vinyl acetate using Mikroglas reactor (inner volume 700 μL , width: 1000 μm , depth: 500 μm , length: 1.4 m, Foturane glass) irradiated by high-pressure Hg lamp gave the cycloaddition product in 88% with 2 h of residence time (Scheme 1) [12]. When the identical reaction was run in batch mode using a 10 mL Pyrex flask with the same light source, the product via [2 + 2] cycloaddition was obtained in 8% yield after 2 h irradiation. The reaction using the DNS reactor (inner volume 705 μL , width: 1000 μm , depth: 300 μm , length: 2.35 m, quartz-made) and UV-LED (Seoul Optodevice, 365 nm, 1.7 W) (Fig. 5, left) proceeded more efficiently to give the cycloaddition product in 91% yield with 15 min residence time [13]. The YMC photo-reactor (internal volume: 112 μL , width: 1000 μm , length: 560 mm, depth:

Fig. 4 MiChS L-1 photo flow reactors consisting of stainless-steel or hastelloy channel plate with quartz glass top

Scheme 1 Flow [2+2] cycloaddition of cyclohexanone and vinyl acetate and Paterno-Büchi reaction

Mikroglas reactor, high-Hg, 300 W, 2 h	88%
DNS reactor, UV-LED (365 nm) 1.7 W, 15 min	91%
YMC reactor, UV-LED (365 nm) 1.5 W, 20 min	95%

200 μm , quartz-made) equipped with UV-LED (365 nm, 1.5 W) (Fig. 5, right) also gave a good result [13].

The Paterno–Büchi reaction of benzophenone with prenyl alcohol using DNS microreactor (inner volume 235 μL , width: 1000 μm , depth: 107 μm , length: 2.2 m, quartz-made) gave 84% yield of the oxetane with 4 h residence time, whereas the batch mode reaction using a Pyrex round

bottom flask gave the product in only a moderate yield even with a longer irradiation time (92 h, 51% yield) [13].

1.2 Flow Barton nitrite reaction

Original batch-style Barton-nitrite reaction used high-pressure mercury lamp. On scaling up, the irradiation lamps

Fig. 5 Seoul Optodevice UV-LED and YMC photoreactor. (a) Seoul Optodevice, UV-LED (365 nm, 48 lamps). (b) YMC photoreactor, KeyChem-Lumino with UV-LED (365 nm, 6 lamps)

(a) Seoul Optodevice, UV-LED (365 nm, 48 lamps) (b) YMC photoreactor, KeyChem-Lumino with UV-LED (365 nm, 6 lamps)

have to accommodate the large reactor, which results in a tremendous cost increase. Two decades ago, in collaboration with the researchers headed by Dr. Konoike in Shionogi Pharma, we discussed the issues surrounding the scaling-up of batch-style Barton-nitrite reaction since introducing several high-power mercury lamps costs prohibitive. The situation motivated us to investigate flow Barton-nitrite reaction using a DNS photoreactor. According to the suggestion of Mr. Haibara at DNS, consequently, we found that the flow reaction using microreactors proceeded excellently with a compact light source such as a CFL blacklight bulb, providing improved yields of the product with considerable energy

savings. For example, using a DNS photo microreactor and a blacklight bulb (15 W, Toshiba) (Fig. 6a), we obtained a 71% yield of the desired oxime, which is a key intermediate for the synthesis of myriceric acid A, an endothelin receptor antagonist (Scheme 2) [20, 21]. In contrast, the batch reaction using a 20 mL Pyrex round-bottom flask required a much longer irradiation time with blacklight, which gave the desired oxime in 58% yield. When we examined UV-LED (Seoul Optodevice, 365 nm, and 35 mW $\times$ 48 pieces, total: 1.7 W) (Fig. 6b), it gave 70% yield of the oxime, representing the first Barton-nitrite reaction using LED. Encouraged by these results, we then designed a more extended photo

Fig. 6 DNS flow reactors and compact light sources used for Barton-nitrite reaction. (a) DNS reactor with blacklight (360 nm). (b) DNS reactor with UV-LED (360 nm, 48 lamps). (c) Scalable flow synthesis using an extended DNS reactor

(a) DNS reactor with blacklight (360 nm) (b) DNS reactor with UV-LED (360 nm, 48 lamps)

(c) Scalable flow synthesis using an extended DNS reactor

Scheme 2 Flow Barton-nitrite reaction

flow device (DNS) having parallel 16 channels with 8 mL of total capacity, in which each channel has 1 mm width, 0.5 mm depth, and 50 cm length (Fig. 6c). For the scalable synthesis, we used six blacklight bulbs. As a result, we obtained 5.3 g of the desired product (61% isolated yield) after continuous operation for 40 h (20 min residence time) (Scheme 2). [21]

1.3 Synthesis of PCBM by flow photo isomerization

[6,6]-Phenyl- C_{61} -butyric acid methyl ester (PCBM) demonstrates excellent performance as a material for n-type organic semiconductors for organic photovoltaics (OPVs). Following the successful flow synthesis of fulleroid, a precursor to PCBM, under heated conditions, we then studied the isomerization to PCBM using a flow photo-reactor MiChS L-1(L)

(inner volume: 3 mL, width: 2 mm, depth: 0.5 mm, length: 3 m, quartz), designed under the same concept of a DNS reactor (Scheme 3) [22]. A 1,2,4-trimethylbenzene solution of fulleroid was irradiated using a flow photo-reactor and various light sources. Consequently, we found that using a sodium lamp (589 nm, 360 W) with a residence time of 5 min gave the desired isomerization product in quantitative yield. We assume that C_{60} would behave as a photo-sensitizer in photoisomerization as well as in other reported cases. Continuous one-flow two-step synthesis of PCBM from C_{60} and diazo-alkane was also successful.

1.4 Flow photoredox-catalyzed alkylation

Ruthenium photoredox catalyst catalyzes hydrodifluoro-alkylation of alkenes in the presence of a Hantzsch ester as a

Scheme 3 Flow synthesis of PCBM

Scheme 4 Ru-photoredox-catalyzed flow hydrodifluoroalkylation

Fig. 7 MiChS L-1(L) and two white LED lamps

hydrogen source. The batch reaction of bromodifluoromethyl benzene with methyl acrylate gave the hydrodifluoroalkylation product in 71% yield after 12 h irradiation (Scheme 4). To shorten the irradiation time, we carried out the flow reaction using a MiChS L-1(L) (inner volume: 6 mL, width:

2 mm, length: 3 m, depth: 1 mm) and white LED (5 W $\times$ 2) (Fig. 7), which gave the product in 82% yield with only 20 min residence time (Scheme 4) [23].

The use of a flow photoreactor is also effective for Ir-photoredox-catalyzed reaction. Fujimoto and coworkers reported that the photoredox reaction of a chiral carboxylic acid with methyl acrylate gave the corresponding alkylated product via decarboxylative radical addition [24]. The product was obtained in 80% yield with 4 h of residence time using MiChS L-1(L) (inner volume: 3 mL, width: 2 mm, length: 3 m, depth: 0.5 mm) (Scheme 5). The batch reaction was very sluggish and it gave the product in 50% yield after 47 h irradiation. The obtained product is used for formal total synthesis of L-ossamine.

1.5 Flow Cossy reaction

Cossy radical cyclization is unique since it does not require any radical initiator or mediator, such as tributyltin hydride [25]. The reaction proceeds with a single electron transfer from triethylamine to alkyl halides bearing an alkynyl unit, and the batch protocol used photo

Scheme 5 Ir-photoredox-catalyzed flow decarboxylative alkylation

Fig. 8 MiChS L-1(L) and two low-pressure Hg lamps

irradiation using fluorescent lamps (254 nm, 300 W). Despite that the batch reaction conditions required 0.5 to 1 h for 0.01 M of substrate concentration, the flow reaction shortened reaction time to 5 min and tolerated a higher substrate concentration of 0.1 M. Scalable synthesis using a large volume flow photoreactor MiChS L-1(L) (internal volume: 6 mL, width: 2 mm, depth: 1 mm, length: 3 m) and two sets of 6 W low-pressure Hg lamp (Fig. 8) gave 4 g of cyclization product with continuous operation of 18 h (Scheme 6). [26]

1.6 Flow photo reduction

The photoinduced single electron transfer from amines can be applied to the reduction of aryl or alkenyl halides. After screening amines, we found that DABCO (1,4-diazabicyclo[2.2.2]octane) worked quite well for the reduction. Unfortunately, the reaction using a batch reactor required 10 h irradiation. However, the reaction using a YMC's flow photoreactor (internal volume: 112 μ L, width: 1 mm, length: 560 mm, depth: 200 μ m, quartz-made, low-pressure Hg lamp (1.2 W)) required only 20 min residence time to obtain the comparative yield (Scheme 7) [27].

1.7 Flow C–H bromination

We carried out the photo-bromination of alkanes using molecular bromine as a cost-effective bromine source using a photo flow reactor. To avoid the influence of byproduct HBr, a cyclohexane solution of molecular bromine was mixed with water using a micromixer (inner diameter, 0.5 mm). Then the resulting mixture was subsequently introduced into a Mikrogas flow reactor under irradiation from a blacklight bulb. Bromocyclohexane was obtained in a 78% yield along with a 9% yield of 1,2-dibromocyclohexane as the side product (Scheme 8) [28]. The residence time for this reaction was 5.7 min, and the reaction using a batch

Scheme 6 Flow Cossy-type radical cyclization

Scheme 7 Flow light/amine-induced reduction

Scheme 8 Flow photo bromination using molecular bromine

reactor (Pyrex, 3 cm i.d. test tube) with the same reaction time resulted in only 11% conversion.

The flow photo-bromination of alkylbenzenes was also successful. The reaction of 4-phenyltoluene with molecular bromine using MiChS photo microreactor L-1(M) under irradiation from UV-LED (1.95 W, 360 nm) proceeded smoothly with 43 s residence time to give mono-brominated product along with di-brominated byproduct in 75% and 8% yield, respectively (Scheme 9) [28]. Notably, the present flow system allows for the reaction of 4-azido-3-chlorotoluene, which has a photo-sensitive aryl azide structure, to give the desired benzylic-brominated product in good yield and selectivity. The mono-brominated product was isolated

by recrystallization from methanol in 61% yield (Scheme 9) [28].

1.8 Flow C–H chlorination

The photo-chlorination reaction of alkanes is one of the most straightforward methods to synthesize alkyl chlorides, valuable synthetic raw materials. We demonstrated the flow chlorination of alkanes using sulfuryl chloride as a chlorine source. When a mixture of sulfuryl chloride and cycloheptane was introduced to the Mikroglass Dwell device at room temperature under irradiation from blacklight (15 W), the reaction gave chlorocycloheptane selectively in 87% yield

Scheme 9 Flow bromination of alkyl arenes using molecular bromine

Scheme 10 Flow chlorination using SO_2Cl_2

Fig. 9 Gas evolution (when BPR was not used)

(Scheme 10) [29]. The use of a back pressure regulator (BPR) effectively suppressed the slug flow caused by generated gases such as SO_2 and HCl (Fig. 9).

Recently we [30] and Kappe group [31] concurrently reported the photo-chlorination reaction of alkanes using in situ generated Cl_2 gas from HCl and NaOCl . When hydrochloric acid was mixed with an aqueous NaOCl solution using a micromixer, Cl_2 gas evolved. Then the resulting gas/liquid mixture was mixed with cyclohexane. The mixture was introduced to Mikroglas Dwell Device, which was irradiated by blacklight. The C–H chlorination reaction efficiently gave chlorocyclohexane in 94% yield with 1 min residence time (Scheme 11) [30].

Vinylene carbonate is obtained from ethylene carbonate via C–H chlorination and the subsequent dehydrochlorination [32]. We examined photoflow chlorination using a newly designed long-sized photoflow reactor MiChS LX-1 (reactor sizes: 67 cm length, 14 cm width, 6 cm depth) and UV-LED (Fig. 10). In this photoreactor, all reactor parts are made of quartz glass to avoid the corrosion issue and

Scheme 11 Flow chlorination by in situ generated Cl_2

Fig. 10 New photoflow setup MiChS LX-1 for gas–liquid biphasic photoreaction and the concept

two inlets, located top and bottom, are for chlorine gas and vinylidene carbonate, respectively and two outlets located top and bottom, are for HCl gas and chlorinated ethylene carbonate, respectively. Reaction using residence time of 30 s gave mono chlorinated ethylene carbonate with 62% conversion of ethylene carbonate, which gave the mono-chlorinated product purity of 86% (Scheme 12).

1.9 Flow C–H oxidation

Several groups have already pursued decatungstate-anion-catalyzed C–H functionalization in flow [33–36]. They reported that residence time varies from 15 to 120 min. We

became curious how the power of light could cause shorter residence time. Flow photo oxidation of benzylic alcohol to benzoic acid using molecular oxygen was reported by Itoh and coworkers [37]. After confirming that addition of decatungstate catalyst significantly accelerated the oxidation in a batch reaction, we then found that irradiation using a high-power LED light accelerated decatungstate-anion-catalyzed oxidation of benzyl alcohol [38]. Using a flow setup with a MiChS L-1(L) photo-flow reactor (channel sizes: width = 2 mm, depth = 1 mm, length = 3 m, total volume 6 mL) and the exposure to a MiChS UV-LED-S photo-irradiation system (365 nm, 480 W) (Fig. 11), the oxidation reaction of benzyl alcohol by molecular oxygen proceeded

Scheme 12 Flow photochlorination of ethylene carbonate by Cl_2

MiChS L-1 (L)

UV-LED-S

Fig. 11 Combination of MiChS L-1(L) and high-power UV-LED-S (365 nm, 480 W)

only in 5 min of residence time to give benzoic acid in 71% yield together with 24% yield of benzaldehyde (Scheme 13). A back pressure regulator, set to 5 psi, can control 1:1 gas/liquid slug flow. Thanks to the metal framework of the reactor, pressurized conditions below 5 bar are available for this type of flow photoreactor.

2 Conclusion

In summary, this article describes our efforts over the last 2 decades to increase the efficiency of photoreactions using advanced photo flow reactors and compact photoirradiation devices. During this time, our studies into flow reactions have focused on [2 + 2] cycloadditions, Barton-nitrite reaction, photoisomerization, and additional simple radical reactions. In many cases, we employed flow reactors assembled from metal channels, manufactured by precise carving with

quartz glass tops. Coupled with energy-saving LED light sources, the assembled photo flow reactors have become a standard setup for photo flow reactions. The advantages of compact flow systems include the rapid execution of liquid phase photoreactions, which can minimize the chance of secondary reactions occurring (i.e. from the products formed). It is also possible to accelerate reactions by controlling the photon flux along the reaction path through judicious choice of lamp for the optimum wavelength and power, and the proper channels. Using a back-pressure regulator fitted to the photo flow reactor is beneficial in the following two cases: (i) formation of gaseous side products and (ii) if gases are used as reagents. By adjusting the back-pressure regulator, the volume of gas can be reduced to a minimum and therefore avoid the risk of slug flow, which often causes inconsistent residence time, and ensure that the reaction proceeds at a safe pressure. Whilst there is the possibility that flow reactors can become clogged, it is possible to overcome these issues by using an assembled type reactor (with a transparent top panel screwed to the channel plate) which has the advantage of allowing easy cleaning of the channels. If photoreactions are very sluggish, scalable tubing reactors can be employed to increase product formation. At this time, areas of synthetic chemistry are transitioning from batch to flow, and in so doing we are learning more about the most suitable photo flow setups for optimal reaction design. In the near future, one could foresee that the selection of channel shape, sizes, materials, light wavelength, light power, temperature, etc., will be informed by artificial intelligence, and we will see a rapid expansion in the use of these designer reactors for sophisticated chemical transformations.

Scheme 13 Light power acceleration of flow oxidation of benzyl alcohol to benzoic acid using decatungstate-ion as photocatalyst

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