Continuous Flow Photochemistry

Applications in [2+2] cycloaddition radical addition

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PharmaBlock

The last decade has witnessed a significant development towards improved and powerful photochemical reactions in response to green, eco-friendly, and sustainable synthetic organic chemistry needs. This renewed interest in utilizing light to carry out chemical transformations is primarily fueled by a desire to realize more efficient and cleaner approaches for target molecule synthesis.

However, many challenges remain in the development of photochemical research. Reactor design, light source origin, and solvent compatibility are some challenging factors, especially in transitioning the process from lab to manufacturing scale. Simply expanding the reactor size may result in an attenuation effect (Bouguer−Lambert−Beer law) during photon transmission and substantially extended reaction time, which may result in by-products.

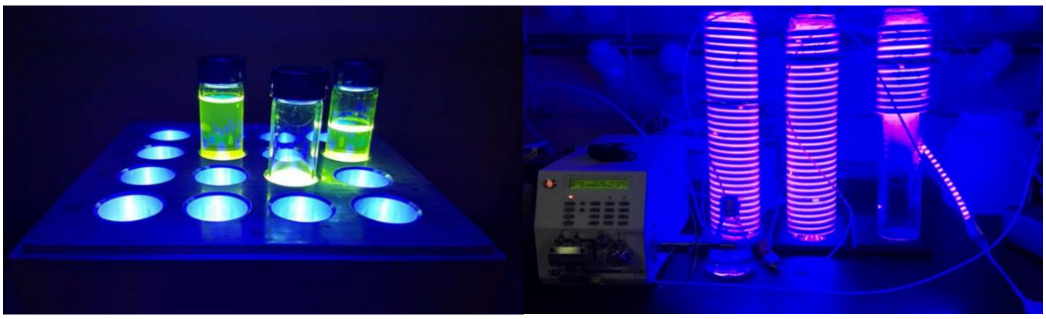
Photocatalysis reactions in continuous flow mode

Due to the technical bottlenecks in the commercial application of traditional batch photocatalytic reactions, scientists have gradually turned their attention to continuous flow micro reaction technology, hoping to find a more effective and practical solution.

Compared with the traditional batch operation, continuous photocatalysis flow technology has the following advantages:

- Large reaction surface area
- Efficient heat and mass transfer
- Precise control of reaction time and temperature which makes automatic control and online analysis technology (PAT) possible
- Intrinsic safety
- Minimal amplification effect
- Easy parallel production

Continuous photocatalysis makes the large-scale production of different types of reactions possible. This technology has received extensive attention from academia and industry and has become one of the most active and vigorously researched frontier technologies.



Applications

Continuous flow technology had a significant impact on popularizing photochemical reactions, as it provides a tool to effectively carry out photochemical reactions and helps overcome limitations inherent to photochemistry. This technology is commonly applied in the following reactions:

- Addition
- Isomerization
- Cyclization
- Singlet oxygen-mediated oxidation
- Cleavage and deprotection
- Halogenation
- Dehalogenation
- Decarboxylation

In addition to its application in drug development and manufacturing, continuous photocatalysis is also utilized in industrial waste treatment.

Challenges for effectively scaling-up photo reactions

Photocatalytic reactions have experienced a surge in interest in recent years. However, much research work is still performed in lab scale, ranging from grams to kilograms. Although much literature shares the design of continuous photochemical reactors, the actual manufacturing output is not ideal. It requires a team of multi disciplines to design and develop adequate manufacturing equipment. The required expertise includes organic chemistry, chemical engineering, engineering equipment, and others. Considerations for designing safe and stable manufacturing scale photo reaction equipment include but not limited to:

1. Researching hydrodynamics and transport phenomena in continuous photocatalysis: establishing an accurate reaction model to predict reaction phenomena in micro-reactors.

2. Clarifying the concept of micro-size and developing equipment integration capabilities: to guide engineering design of micro-reactors in exploring flow mode, critical elements in parallel amplification, matching degree of the light, and material flux.

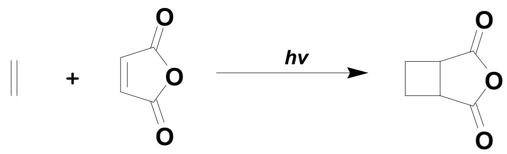
3. Using photocatalytic micro-reactors to develop new synthetic routes. This new technology of continuous flow combined with photocatalysis has significant advantages. It can prepare compounds that are challenging or impossible by traditional means, safely handle dangerous or toxic compounds, and carry out reactions in more harsh conditions such as high temperature and high pressure or those involving gas.

4. Developing and recycling photocatalysts to minimize the environmental and economic impact of photochemical processes.

Case studies:

Case I： Photocatalytic [2+2] cycloaddition

The bicyclic product is one of the four-membered ring intermediates of PharmaBlock. Conventional preparation was carried out in a batch reactor catalyzed by light. Due to the poor light transmission and gas-liquid mass transfer, the traditional process requires a long reaction time. For example, a 10-gram-scale preparation takes 20-30 h. A further decrease of gas-liquid mass transfer in scale-up will cause the reaction to be significantly prolonged or impossible to be carried out. No suitable photo-reactor for large scale being available does not help either.



The continuous flow team in PharmaBlock has successfully applied continuous photocatalysis to this reaction many times. Table 1 lists the result of some key parameters in comparison with batch mode. The scale reached 500 Kg in production, wherein the reaction was clean and solvent recycled. There was virtually no waste generated, making it truly efficient and green chemistry.

Table 1 Comparison of Photocatalytic [2+2] Cycloaddition Reaction Process

	Batch process	**Continuous photocatalytic process**
Feasibility	No matched reactor	Scalable
Reaction time	30 h	40-50 min
Yield	n/a	75-80 %
Scalability	n/a	500 kg
Scale-up risk	High risk	Low risk

Case II: Photocatalytic free radical addition

The second compound, as shown below, is one of the essential intermediates of PharmaBlock's BCP series. Many compounds of this series can be derived from it. As early as in 2017, the team successfully developed a process using photocatalytic flow reaction to synthesize this molecule. After unremitting effort, the current process can be operated safely and efficiently in the production of over 100 kg.

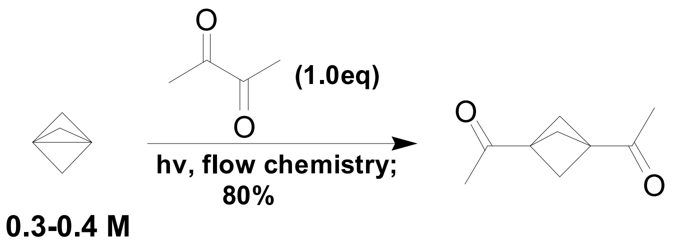


Table 2 Comparison of Photocatalytic Free Radical Addition Reaction Process

	Batch process	Continuous photocatalytic process
Feasibility	No matched reactor	Scalable
Reaction time	5-8 h	15 min
Yield	58 %	80-85 %
Scalability	n/a	500 kg
Scale-up risk	High risk	Low risk

What makes PharmaBlock unique?

PharmaBlock flow team has an in-depth understanding of the chemistry and microchannel reactor's working principle and has rich experience in process development,optimization, scale-up, and application in production. The team can not only fully satisfy our customers' needs, but provides building blocks or core intermediates by continuously improving the process using flow technology, including photocatalysis.

In the meantime, the team continues to expand the application scope of various equipment, which can now be used in harsh acid, base and/or corrosion conditions; high- and low-temperature environments (high temperature ≤200℃); and specific pressure needs (≤2 MP). The team also possesses mechanical, electronic, and automation engineering expertise. It can independently design and assemble flow equipment that meets the explosion-proof requirement for production workshops, with the advantage of having adjustable reaction volume and the option to be integrated into one movable unit and only occupies small floor space but have high capacity and output performance.

Through our continuing innovation in flow technology *via* a comprehensive approach by leveraging our expertise in different disciplines, PharmaBlock flow chemistry team provides the top-notch service in the industry to our customers by accelerating project development, shortening delivery time, and reducing development and manufacturing cost.

A glimpse into the future

Continuous flow chemistry acts as a bridge across the past and future in organic synthesis. Photochemical reactions can synthesize complex organic molecules in a simple way, echoing the principle of green chemistry. It is not strange that continuous photocatalysis, viewed as a sustainable green technology, has attracted more and more attention from academic and industrial circles and become an attractive tool applied in the pharmaceutical industry.

The primary challenge of continuous photocatalytic flow technology is still process development and application into production. With the advancement of the technology, it has been successfully applied in multi-step synthesis, which can meet the requirements of APIs prepared by flow under mild, safe, and sustainable conditions. Future challenges could be the development of multi-functional modules that integrate photocatalysis with other technologies, such as enzymatic, metal, and organic catalysis into one continuous production line to prepare compounds with biological significance. From the equipment perspective, continuous photocatalysis technology could be coupled with advanced automation to create a safer and more intelligent high-end equipment platform.

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