SYRRIS





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Syrris – An Introduction

Delivering leading flow and batch chemistry solutions

- Founded in 2001 to advance new technologies in chemistry
- Syrris is the longest established flow chemistry company and the only company to address both the batch and flow chemistry markets
- Our customers include all of the **top 20 pharmaceutical companies** and most leading **academic institutions**
- Headquartered in Royston (UK)
 - 2 manufacturing sites (including Glass manufacturing)
 - Global sales and support offices











Syrris – Part of the AGI Group

- In Jan 2020, Syrris was acquired by Asahi Glassplant Inc. (AGI)
 - Headquarters in Japan
 - Subsidiaries in UK and US
- AGI are the **world leading glass technology company** specialising in innovation in reactor technology
- Wonderful synergy between Syrris and AGI product ranges
 - Highest performance and precision glass manufacturing (AGI)
 - Easiest to use and superior designed systems (Syrris)
- AGI provides a **complete range of high performance reactor**, evaporation and filtration systems from lab scale to pilot scale













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Introduction to Photochemistry

How do we Initiate a Chemical Reaction?

Chemical reactions are generally activated by heat or a chemical reagent

- One of the key advantages of flow chemistry is its easier to use some of the lesser used methods:
 - Electrochemistry which uses electrons
 - Photochemistry which uses light
- An increasing trend in recent years to use both techniques in chemistry, sometimes referred to as reagentless chemistry
- Asia offers the FLUX module to perform continuous electrochemistry
- Asia now offers the Photochemistry Reactor for continuous flow photochemical reactions enabling the widest range of applications and versatility



What is Photochemistry?

Basic Photochemistry

- Photochemistry is the branch of science concerned with the chemical effects of light
- In nature it's the **basis of photosynthesis**, vision and the formation of vitamin D with sunlight
- Photochemical reactions proceed differently to other techniques giving access to unique chemistry that is cleaner and therefore greener

- When a molecule absorbs a photon of light, its **electronic structure changes**, and it reacts differently with other molecules
- Each molecule reacts differently to different wavelengths
- Photochemical reactions require a light source that emits wavelengths corresponding to the specific wavelength of the reactant



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History of Organic Photochemistry

How It Began

Observation and reaction development

- Light has been used to trigger chemical reactions since the 18th century
 - Trommsdorff described how crystals of the sesquiterpene α-santonin (1) turn yellow and, literally, burst upon exposure to sunlight
 - In crystal form, the reaction was described as a succession of three steps taking place to form a single crystal of a dimeric structure (4)
 - The bursting effect is attributed to a large change in crystal volume on dimerization



H. Trommsdorf, Ann. Chem. Pharm. 1834, 11

A. Natarajan, C. K. Tsai, S. I. Khan, P. McCarren, K. N. Houk, M. A. Garcia-Garibay, J. Am. Chem. Soc. 2007, 129, 9846–9847

How It Began

Great masters of Organic Synthesis

- In more recent times exciting examples on the application of photochemistry for the synthesis of organic compounds were described:
 - Notably Eaton 1964 on his cubane synthesis
 - Corey 1964 applied photochemistry and his retrosynthetic approach to carry out the synthesis of caryophyllenes
 - Wender's synthesis of cedrene, in 1981

Corey's 1964 synthesis of caryophyllenes







How It's Developed - Why Use Flow Photochemistry?

- The benefits of flow chemistry over traditional batch techniques are widely known, all of these translate equally to **flow photochemistry**. Most of these benefits come from the **precise control** of reaction parameters that flow chemistry offers
- By controlling factors such as **temperature**, **mixing**, **stoichiometry** and **reaction times**, we can enhance the control of our chemical reactions. In a flow photochemistry reactor, we can increase this control further over traditional batch photochemical techniques

Reasons to use Photochemistry in Flow

- Improved irradiation of the reaction
 - Flow reactors improve light transmission to reaction
- Improved reaction scalability
 - Increasing light power enables more photons, increasing reaction rates and increasing throughput
- Improved reaction selectivity
 - Single wavelength LED light sources enable selectivity of reaction pathways
- Improved reproducibility
 - Controlled reaction exposure times with no over irradiation

- Improved mixing and heat exchange
 - Flow offers reproducible mixing and precise temperature control
- Ability to perform multiphase chemistry
 - Small reactor design allows ability to use gases, crucial in photochemical application
- Increased safety
 - Light proof reactors and power interlocks prevent exposure of user to high intensity light

Photochemistry Light Sources

- Historically, photochemistry has utilized high intensity mercury lamps to facilitate photocatalyzed reactions
 - These produce a broad spectrum of wavelengths (200-600 nm)
 - They produce a lot of heat which is transferred to the reaction. Almost always require external cooling to maintain temperature

Advances in LED technology have opened-up more targeted photochemistry

- LEDs have a narrow emission band (normally in 20 nm range). This allows more selective chemistry
- LEDs have a small irradiation window which allows them to be directed toward the flow reactor channel
- LEDs also give off a lot less heat transfer so external cooling is not always required



Emission spectrum of common light sources used for Photochemical Applications¹

	Mercury lamps	LEDs	
Emission	Broad range (200-600nm)	Narrow (within 20nm range)	
Heat generated	High	Low	
Selectivity	Low	High	
Safety	Requires high level of shielding	Less harmful irradiation	
External cooling	Required	Not always required	

¹ Cambié, D., et al.. Chem. Rev., 2016, 116 (17), 10276–10341

Photochemistry Reactors

Photochemical reactions occur when light provides energy to trigger a reaction

- The problem with light (photons) is they lose their energy very quickly
 - This is described by the well-known **Bouguer-Lambert-Beer law**, the further the reaction is from the light the less power it sees
- When using traditional flasks the reaction is only irradiated near the wall giving **non-uniform reaction conditions**
- When performing photochemical reactions in microchannels (with i.d. of < 1 mm), full transmission of light is allowed to the reaction solution
 - This results in a more homogeneous irradiation of the reaction giving shorter reaction times and less side-products caused by overirradiation (often seen in equivalent batch conditions)



Attenuation of light with the distance of irradiation^{2,3}

²Sambiagio, C.; Noël, T. *Trends Chem.*, **2020**, *2* (2), 92–106 ³Plutschack, et. Al. *Chem. Rev.*, **2017**, *117* (18), 11796–11893

Photochemistry Reaction Scalability

The problem with photochemistry reactors

- The popularity of photochemistry has suffered from its limited scale-up potential. This is due to the Bouguer-Lambert-Beer law, with the increase in reactor volume this effect is increased leading to poor light transmission to the reaction mixture
- Flow photochemistry strategies can help in the scale up of photocatalytic reactions
 - We can **increase the throughput** by running the reactions for longer
 - We can increase the number of reactors
 - We can increase the radiant flux into the reaction
- As light (the photon) is the reagent in photochemistry reaction, by increasing the number of photons reaching the reaction mixture, it is possible to increase the reaction rate
 - We can increase the light intensity into the same photochemistry reactor using the same platform to scale-up our reactions

Moles photons per hour = λ (nm) × power (W) × 3×10⁻⁵

Number of moles of photons (einsteins) per hour at a given wavelength $(\lambda)^4$

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Flow Photochemistry Applications

Halogenations

- Halogenated compounds are especially important for pharmaceutical and agrochemical applications
 - Brominated compounds are common building blocks for organic synthesis
 - A single fluorine atom substituent or a –CF₃ group has a strong impact on the electronic properties of a molecule, it can change its lipophilicity or acid/base characteristics, two important pharmaceutical parameters



Evaluation of a Continuous-Flow Photo-Bromination Using *N***-Bromosuccinimide for Use in Chemical Manufacture**

Introduction

- The scale-up of photochemical processes for industry is still an underdeveloped field
- There are inherent limitations of batch procedures using xenon/mercury lamps
 - Using high amounts of energy, low yields, undesired amount of side products
 - Suffers with low transmission of light (Beer-Lambert Law)
- The need to access aryl bromides is widespread in fine chemicals synthesis, e.g. on the synthesis of antibacterial, antifungal and antiviral compounds
- In this example the authors described a method to address this issue, describing the scaling up process of benzylic bromination

- LED technology was used as the activation light source and NBS (*N*-bromosuccinimide) as bromide source
 - No need of a toxic radical initiator (AIBN azobisisobutyronitrile)



- Optimisation of parameters
 - temperature, residence time, solvent and the wavelength were screened
- 93% yield and excellent 97 % selectivity for the monobrominated product

		O_BO + O_{CF_3}	Br A	405 nm LED .5 M, solvent, ime, temp		+ + CF ₃	
		1	2		3	3a	
Entry	Temperature [°C]	Residence time [min]	NBS equiv.	Wavelength [nm]	Solvent	Yield by NMR of 3 [%]	Selectivity to 3/3a [%]
1	20	30	1.05	405	MeCN	93	97
2	20	15	1.05	405	MeCN	93	97
3	20	5	1.05	405	MeCN	67	98
4	20	10	1.05	405	MeCN	93	97
5	20	5	1.05	365	MeCN	49	97
6	20	10	1.05	470	MeCN	87	98
7	20	15	1.50	405	MeCN	84	92
8	40	15	1.05	365	Acetone	76	99
9	0	15	1.05	405	Acetone	43	99
10	20	15	1.05	405	Acetone	78	99
11	40	15	1.05	405	Acetone	75	99

Expanded Scope

- Reaction scale: 10 mmol (~4 g)
- Residence times: 3 10 min
- Yields: 93 % 99 %
- Hourly productivities: 12.7 94 g.h⁻¹
- STY: 0.32 2.35 Kg.L⁻¹.h⁻¹

Substrate	Product	Concentration [M]	Residence time [min]	Yield [%]	Hourly productivity ^A [g h^{-1}]	STY [kg $L^{-1} h^{-1}$]
	O.B.O Br	0.5	10	93	42.5	1.06
°CF3	CF ₃ 3	0.5	4	98	55	1.37
	Br 4 Br	0.5	15	79	12.7	0.32
O N H	o H H Br	0.5	4	99	67.7	1.69
ОН	6 Br OH	0.5	3	99	88	2.2
)o-	7 O Br	0.5	3	99	94	2.35
	8					

Table 2. Yield, hourly productivity, and space-time yield of selected substrates

^AHourly productivity (g h^{-1}) = concentration (M) × flow rate (L h^{-1}) × molecular weight × yield (%).

Rapid Trifluoromethylation and Perfluoroalkylation of Five-Membered Heterocycles by Photoredox Catalysis in Continuous Flow

Introduction

- The incorporation of –CF₃ into chemical compounds brings several advantages
 - Improved chemical stability, modulate lipophilicity and binding selectivity
- The development of this technology is of great value to the pharmaceutical, agrochemistry and material manufacturing
- The authors described an approach for a photocatalytic trifluoromethylation and perfluoroalkylation of five-membered heteroarenes in continuous flow
 - Using photoredox catalysis to generate electrophilic radicals and the use of an inexpensive gases, e.g. trifluoroiodomethane (CF₃I), as source of CF₃



N. J. W. Straathof, H. P. L. Gemoets, X. Wang, J. C. Schouten, V. Hessel, T. Noël, ChemSusChem 2014, 7, 1612–1617

- Reactions were carried out using [Ru(bpy)₃Cl₂] (1.0 mol %), base (2.0 equiv) in MeCN (0.2 M), and irradiated by blue LEDs
- TMEDA proved to be the most effective for this trifluoromethylation protocol with 4 equiv. of CF₃I
 - Residence time of 8 min, up to 99 % conversion (95 % yield)



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Expanded Scope

- 12 examples of trifluoromethylation of heteroarenes
 - Yields 55 95 %
 - Residence times 4 32 min



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Expanded Scope

- 12 examples of trifluoromethylation of heteroarenes
 - Yields 55 95 %
 - Residence times 4 32 min
- Further expansion was shown to access the perfluoroalkylation of heteroarenes
- 5 examples are shown
 - Using 0.5 mol% catalyst, RCF₂I, TMEDA, MeCN
 - Yields 53 95 %
 - Residence Times 10 20 min



Metal-free Version

- Using Eosin Y (5 mol %), TMEDA (3.0 equiv.), MeCN, 30 min residence time, white LED
- These are highly advantageous conditions for the preparation of APIs
 - Meet the strict product purity regulations
 - Avoids expensive purifications
 - Provides a more cost-efficient alternative compared to metalbased photoredox catalytic processes





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Flow – Batch Comparison





N. J. W. Straathof, D. J. G. P. Van Osch, A. Schouten, X. Wang, J. C. Schouten, V. Hessel, T. Noël, J. Flow Chem. 2014, 4, 12–17

Light Induced Cross-Coupling Reactions

- A cross-coupling reaction in organic chemistry is a reaction where two fragments are joined together with the aid of a metal catalyst
 - They are particularly important in the formation of carbon-carbon bonds
- In general, a main group organometallic compound reacts with an organic halide with the formation of a new carbon–carbon bond in the product
- The irradiation of light on those type reactions proves, in some cases, to be beneficial for increasing yields/selectivity



Scalability of Visible-Light-Induced Nickel Negishi Reactions

Introduction

- The work of Alcázar *et al.* is impressive proof for the straight-forward combination of continuous flow synthesis with solid materials, like zinc, light-induced conversion of *in situ* formed metalorganic intermediates, and innovative analytical tools for process control
- A photoinduced Negishi coupling over two-steps is described with the formation of the organozinc reagent in flow followed by coupling with the aryl-halide
 - Blue LEDs
 - NiCl₂-glyme + ligand
 - Activated zinc column for the zincate formation
 - Automation of process



Visible-light induced Nickel Negishi Reactions

- The formation of the organozinc reagent **6** is key for the process, this involves the use of solid zinc which is held inside a column reactor
- In-line NMR was used to monitor the organozinc formation
- Residence time 15 min, temperature 60 °C, 405 nm LED, 40 mL photoreactor
- After 6 h of processing, 20.4 g of product (3.4 g/h; 94 % yield) was obtained
- 34 % yield in absence of light



Photooxygenations

- Singlet oxygen (¹O₂) can be produced starting from ground state oxygen (³O₂) by light irradiation in the presence of a suitable photosensitizer
- Flow photochemistry can provide easy access to ¹O₂ in a much safer process, compared with batch procedures
 - ¹O₂ shows higher electrophilicity, compared with ³O₂, which allows substrates to be oxidized which are otherwise unreactive to oxygen





Introduction

- Common approaches for the synthesis of (–)-CBD involves the coupling of olivetol and *p*-mentha-2,8-dien-1-ol (1) by an acid-catalyzed Friedel–Crafts alkylation
- This methodology has been also applied in the synthesis of other bioactive cannabinoids, using 1 as a common intermediate
- Although most of these routes described the intermediate menthadienol (1) as "readily available", its synthesis and production on a large scale are a current challenge
 - The approaches described present yields lower than 20 %, as well as low stereo- and regioselectivity
 - Additionally, large amounts of explosive oxidants are employed under high temperatures, with long reaction times and low atomic efficiency



Introduction

- Photooxygenation of (R)-limonene (2) as chiral precursor offers the ability to obtain the desired compound with a smaller number of steps in a one-pot reaction
- This meets some principles of green chemistry, such as atom economy
- Reducing the release and/or exposure of the environment to dangerous substances



Results – continuous flow with white LEDs

- 1 mL microchip reactor, pumping a solution containing 2 (25 mM), TPP (0.1 mM) as a sensitizer, and CH₃CN:CH₂Cl₂ (3:1) as solvent, and a white LED as the light source (100 W)
- A tube-in-tube reactor was employed as a gas-transfer module, affording the reaction medium saturated in O₂ as well as a homogeneous system

- Different flow rates were tested to find the best residence time to yield 1
 - 99 % conversion of was achieved after 20 min of reaction
 - 48 % selectivity for desired product (1)
 - High productivity values were obtained in up to 5 min of reaction time



^{*a*}Experimental conditions: **2** (25 mM), TPP (0.1 mM), CH₃CN:CH₂Cl₂ (3:1, 10 mL), white LED (100 W, 6500 K), 30 °C, O₂ (100 psi, outside pressure), Syrris microreactor (1000 μ L), Knauer pump.

Results – continuous flow with blue LEDs

- White LEDs were then switched to Blue LEDs
 - One of the advantages of using LEDs as the photocatalytic light source is that wavelengths can be selected to optimize reaction conditions
- Compared with the white LED lamp, both conversion and productivity values increased giving the best productivity (2.9 μmol·min⁻¹) after 2 min of residence time
- Higher conversion values were obtained at lower flow rates, keeping constant the selectivity



Tube-in-Tube

entry	residence time (min)	$\begin{array}{c} \text{flow} \\ (\text{mL} \cdot \text{min}^{-1}) \end{array}$	conversion (%)	selectivity (%)	productivity $(\mu \text{mol} \cdot \text{min}^{-1})$
1	2.0	0.500	49	48	2.9
2	5.0	0.200	79	48	3.2
3	7.5	0.133	92	48	2.2
4	10.0	0.100	96	48	1.5
5	20.0	0.050	99	48	1.2

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Results – continuous flow increasing temp/radiant flux

- Flow chemistry has the benefit of allowing an easier access to scale-up
- The last experiments looked at increasing the size of the flow reactor by volume, increasing the LED power and attempting to increase selectivity by temp control
 - 44 % conversion, 55 % selectivity
 - Productivity 580.8 μmol·min⁻¹ using faster flow rates (200 fold)



entry	concentration of $2 \ (mm)$	residence time (min)	flow $(mL \cdot min^{-1})$	conversion (%)	selectivity (%)	STY (μ mol·min ⁻¹)
1	400	5	6.0	44	55	580.8
2		10	3.0	47	58	327.1
3		20	1.5	55	66	217.8
4		30	1.0	99	56	221.8

^{*a*}Experimental conditions: 2 (400 mM), TPP (0.1 mM), CH₃CN:CH₂Cl₂ (3:1, 50 mL), blue LEDs (124 W), -20 °C, O₂ (100 psi, outside pressure), PFA reactor (32 mL), Syrris pump.

Late-Stage C-H Activation

- The direct CH functionalization of heterocycles has become an increasingly valuable tool in modern drug discovery
- There are relatively few methodologies for late functionalization of complex organic molecules
- Photocatalysis enabled the late-stage alkylation of biologically active heterocycles



C-H Alkylation

- Stable organic peroxides activated by visible-light photoredox catalysis to achieve the direct methyl-, ethyl-, and cyclopropylation of a variety of biologically active heterocycles
- As example the API Fasudil, a potent vasodilator



Increasing Complexity

- 1,2,3,4-Tetrahydro- β -carbolines were coupled with α -keto vinyl azides through a visible light Ru(bpy)₃(PF₆)₂/TBHP mediated photocascade strategy that involves photosensitization, photoredox catalysis and [3 + 2] cycloaddition reaction
- This is an example of *increasing complexity* in a single step reaction
- The microreactor was fed with the substrates and a solution of the catalyst and the reaction was triggered by incidence of white light
 - 18 examples in a residence time of 43 min leading to 62-81 % product yield



D. Chandrasekhar, S. Borra, J. B. Nanubolu, R. A. Maurya, Org. Lett. 2016, 18, 2974–2977

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Asia Photochemistry Reactor

Asia Photochemistry Reactor

Top level description

- The Asia Photochemistry Reactor enables continuous photochemistry applications to be performed on the Asia flow chemistry system or as a stand-alone module to increase your flow chemistry capability.
- This easy-to-use reactor makes modern photochemistry techniques accessible without the limitations of traditional batch photochemistry requirements.



Introduction to Asia Photochemistry

Asia Photochemical Module

Specifications

- Compatible with the Asia flow chemistry system or as standalone option
- Can house up to **8 x LED modules** at fixed or mixed wavelengths or blank modules
- LED modules monochromatic lights at 365 nm, 385 nm, 405 nm, 420 nm, 450 nm and 525 nm
- Output Power: Radiant flux from **3 W to 108 W** (dependent on wavelength)
- Variable power from **10 % 100%**
- Reactor volumes: 4 mL or 16 mL
- Reactor temperature: -40 °C to +80 °C (dependent upon Asia Heater or Asia Cryo Controller)
- Module completely interlocks for safety
- Control module displays, light intensity and radiant flux



Run multiple wavelengths for the same reactor

One platform, multiple wavelengths

- This unique feature to the Asia Photochemistry Reactor allows multiple wavelengths to be used on the same reactor.
- This opens up the possibilities for chemists to explore exciting new areas of photochemistry.







Questions?

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