https://youtu.be/msfmLlFDRRs

Photo-Flow Chemistry Webinar

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“the fundamentals of fluid flow through to application within industry”

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“new clean/catalytic methodology for the synthesis of biologically-relevant molecules”

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Please do get in touch with us – we welcome collaborations
The Institute of Process Research and Development (iPRD) offers one-of-a-kind and world-class facilities and expertise in process chemistry, and particles and crystals engineering.

Established in 2008, the iPRD brought together experts from the fields of process chemistry and chemical engineering who work closely with the chemical industries to develop technologies which delivered cost reductions, quality benefits, increased productivity and reduce waste and energy utilisation in product manufacture.

Our team are highly experienced in working in the fine chemical and pharmaceutical sectors and are able to offer companies of all sizes focused, contract-based services for problem solving, process understanding, development of new process technologies, small-scale manufacture, training and consultancy.
Contents

- introduction to photochemistry
- problems with scale-up in batch and flow
- a new solution for photochemical CSTRs
- case studies
- conclusions
Industrial photochemistry – an underused technology?

- bulk chemistry – efficient but price sensitive!

\[
\text{cyclohexane} + \text{NOCl} \xrightarrow{h\nu} \text{cyclohexanone} \xrightarrow{\text{reaction}} \text{caprolactam (Toray process)}
\]

- niche products (<1 tonne pa)

\[
\text{pre-vitamin } D_3 \xrightarrow{h\nu} \text{vitamin } D_3
\]
Organic photochemistry – a renaissance

- unusual architectures:

- photoredox catalysis


Issues with scaling photochemistry

• limited light penetration to batch reactors (Beer-Lambert law)

• secondary photoreactions @ long reaction times

• thermal effects

• variability in lamp performance vs. time

• variability with experimental set-up (distance to source)

• *is continuous processing a solution to some/all of these?*
direct method for C-H amination of aromatics by photolytic reaction of \( N \)-chloroamines:

Cosgrove, Plane, Marsden, *Chem. Sci.*, 2018, 9, 6647
access to diverse, functionalised scaffolds including highly 3D:

Cosgrove, Plane, Marsden, *Chem. Sci.*, 2018, 9, 6647
one-pot approach avoids \( N \)-chloroamine isolation:

\[
\text{Reaction Scheme:}\quad \text{N-arylation}
\]

\[
\begin{align*}
&\text{R}^1 \text{R}^2 \text{R}^3 \\
&\text{H} \quad \text{N} \quad \text{R}^2 \\
&\xrightarrow{i) \quad \text{N-chlorosuccinimide, CH}_2\text{Cl}_2} \\
&\text{R}^1 \text{R}^2 \text{R}^3 \\
&\text{H} \quad \text{N} \quad \text{R}^2 \\
&\xrightarrow{\text{ii) \quad h} \nu, \text{MeSO}_3\text{H}/\text{CH}_2\text{Cl}_2} \\
&\text{N} \quad \text{R}^2
\end{align*}
\]

- scale still limited to ca. 0.2 g product per batch

60%  
73%  
52% (97% es)

\textit{scale still limited to ca. 0.2 g product per batch}

Cosgrove, Plane, Marsden, \textit{Chem. Sci.}, \textbf{2018}, 9, 6647
Continuous photochemical reactors: tubular design

- simple design (Booker-Milburn, University of Bristol) using UV-permeable FEP tubing/syringe or HPLC pump

- multi-gram quantities readily accessible using 5mL reactor

Direct photochemical $N$-arylation

![Chemical structures and reaction diagram]

- sequential $N$-chlorination/cyclisation proceeds, but......

- productivity down 75% owing to dilution needed for monophasic rxn

- *highlights need for photoreactors capable of multiphasic flow!*

powerful method for synthesis of drug-relevant cyclic 1,2-diamines:

unprecedented range of N-H coupling partners – commercial interest!

**issues:** small scale, long reaction time, catalyst solubility (biphasic) – limited to ca. 100mg per batch per day maximum

The previous slides demonstrate that handling single and multiphasic systems could bring real benefit to flow photochemistry.

The following slides discuss the capabilities of the fReactor flow platform with the Flow Photochemical modules.
Key mechanisms at play in photochemistry

- Controlling factors in photochemistry
- Brief review of the physics of pipe-flow
  - Implications for single and multiphasic flows
- Photochemistry in CSTRs
  - Mixing and active transport
  - The photo flow modules for the fReactors
  - Actinometry and a gas/liquid reaction
Molecule in ground state

Light at an appropriate wavelength

<table>
<thead>
<tr>
<th>We need:</th>
<th>Physical and chemical factors:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecule in excited state</td>
<td>Light enters mixture!</td>
</tr>
<tr>
<td>Photon to reach (correct) molecule</td>
<td>Not absorbed elsewhere (materials or chemistry)</td>
</tr>
<tr>
<td>Molecule to absorb photon</td>
<td>Wavelength of light</td>
</tr>
<tr>
<td>Molecule to react (meet other molecules) before decay back to ground state</td>
<td>Concentration of molecules in zone where excitation taking place (reaction zone)</td>
</tr>
</tbody>
</table>

(not quite a Jablonski diagram!)
What can interact with the light (prevent photons getting to the right place)?

- Light
- Wall - material
- Absorbance
  \[ \text{Absorption coefficient} \times \text{Path length} \times \text{concentration} = \text{Beer Lambert Law} \]
Flow – pipe flow

The reaction zone – (in this example….)
• Reactants
• Products – strongly absorbing

Earlier on (start of tube) : Higher reaction rate
Reactant concentration high

Later on (further down the tube) Lower reaction rate

Strongly absorbing product …. Reduced photon count to reactants Side products

Transport into and out of reaction zone important
The transport

- Advection – flow – laminar (see http://freactor.com/learningLamTurb.html)
- Diffusion $\tau \approx x^2/D$ \( (D \sim 1 \times 10^{-9} \text{ m}^2/\text{s} \text{ to } 1 \times 10^{-10} \text{ m}^2/\text{s}) \)

1 ml/min flow
5m length PFA tubing (1/16" id) – volume 10ml – 10min rt
Reynolds Number 13
**Time to flow: 10 min**

**Diffusion time (wall to wall): 40 min** \( (D \sim 5 \times 10^{-9} \text{ m}^2/\text{s}) \)

**Lifetime of excited-state 1µs (catalyst)**
DOI: 10.1016/0010-8545(82)85003-0

Consequences:
- time of transport faster than time of diffusion
- Product (not reactants) in reaction zone (by products ?)

So… enhancing mixing is important!

- Coiled tubes (Dean flows – weak at low flows – De=2, 50mm mandrel)
- Continuous Stirred Tank Reactors
Single phase flow: mixing important but what about…

Multiphase flow
- liquid/liquid or gas/liquid reactions (mass transfer between phases)
- solid/liquid reactions (solid photocatalyst, reactants or products)

Most production processes involve reactions and work-ups that are multi-phasic

- Material solubilities can be often exceeded and productivity can be increased
- Processes can often require or evolve a gas
- The performance of solid catalysts can be improved by flowing them as a slurry (mass transfer and steady-state) rather than fixed-bed.
- Liquid bi-phasic reactions and extractions
- Crystallisation in continuous flow can be desirable

Batch reactors cope well with these because they use active mixing

Tubular reactors perform poorly with solids and mixed fluid phases. Alternatively, design homogenous liquid systems
- Less productive
- Limited scope
- Ignores separation and work-up

Video summarised on next slide!

Link to fReactor video: https://www.youtube.com/watch?v=C5MJ49AB820
Multiphase flow in tube
Water (green dye)
Oil

Pipe reactor – segregated droplets of water and oil

Pumping – dual syringe pump
Mixing – tee piece

Active mixing in each fReactor module – enhanced mass transport in multiphase flows

Inlet (aqueous)
Inlet (oil)
Fine emulsion in outflow

Link to fReactor video  https://www.youtube.com/watch?v=C5MJ49AB820
A Laser Driven Flow Chemistry Platform for Scaling Photochemical Reactions with Visible Light
Kaid C. Harper, Eric G. Moschetta, Shailendra V. Bordawekar, and Steven J. Wittenberger
Process Research and Development, AbbVie Inc., 1 North Waukegan Road, North Chicago, Illinois 60064, United States

ACS Cent. Sci. 2019, 5, 109−115

A Hybridised Optimisation of an Automated Photochemical Continuous Flow Reactor

Chimia 73 (2019) 817–822

A Continuous Stirred-Tank Reactor (CSTR) Cascade for Handling Solid-Containing Photochemical Reactions


Angewandte Chemie International 57(51), 16688-16692.

5 stage CSTR

4 ports
- Inlet
- Outlet
- Instrumentation
- Sampling
- Additional feed ports

Additional safety shield

Thermal base plate
- Hotplate / stirrer
- Temperature well
The evolution of the photochemistry flow module (Photoflow)
What are the operating characteristics of the fReactor PhotoFlow Modules?

- **Ease of use** – if you can finger-tighten a fitting, you can assemble a fReactor (really) – low barrier of entry to flow chemistry but very effective flow platform – reusable and robust.

- **Pressure**: 100 psi (7 bar)
  - Increase temperatures above normal boiling point of solvents
  - Use of a back pressure regulator
  - With gases, higher partial pressure – faster mass transfer

- **Temperature**: ~140°C (PEEK, ETFE, seals)
  - Use of a hotplate (easy and you have one!)

- **Multi-stage** – good residence time distribution
  - (5x2ml reactors better than 1x10ml reactor):
    - https://freactor.com/learningCSTR_RT.html

- **FLEXIBILITY**
  - **LEDs** – 365nm upwards in wavelengths
    - High power (e.g. 365nm – 5W radiant flux per LED)
    - Wide range of wavelengths (365, 390, 395, 405 … 460 … 623nm)
    - Long lifetime and no degradation in performance

- **Easy to use module**
  - Fits directly onto fReactors (flow and flow+photochemistry)
  - Lift-off to switch off (dazzle free)
  - 1 – 5 modules per fReactor platform
  - Simple power supply

- **FLEXIBILITY**
Single phase photochemical isomerisation

\( o\)-nitrobenzaldehyde to \( o\)-nitrosobenzoic acid

Quantum yield 365nm = 0.5

10x greater than in previously reported batch systems!
Mixing into photochemically active zone

Removal of diffusion zone
Fast transport of reactant (in) and product (out)

Can minimize secondary reactions – photon efficient

Aerobic Oxidation (G/L)

Tetralin

Air, Benzophenone (0.5 equiv.)
365 nm LEDs, rt

Tetralone

A Hybridised Optimisation of an Automated Photochemical Continuous Flow Reactor

Jamie A. Manson, Adam D. Clayton, Carlos Gonzalez Niño, Ricardo Llabes, Thomas W. Chamberlain, A. John Blacker, Nikil Kapur, Richard A. Bourne

PMID: 31645242 DOI: 10.25533/chima.2019.817
Residence time of 18.3 minutes
Air
benzophenone (£0.04 / g)
65% yield

Residence time 45 minutes
Pure oxygen
TBADT (£300 / g)
84% yield

Benzophenone “A more accessible and atom economical photosensitiser compared to TBADT, even when used at 0.5 equivalents.”
The final set of slides demonstrate the power of the fReactor platform with the flow photochemistry modules
Case study 1: photoredox hydroamination

- long reaction time
- partially insoluble catalyst
- maximum throughput in batch – 100 mg per batch per day
- NB fReactor as convenient photochemical batch reactor! – can charge up a single reactor and it is a well controlled batch system!

\[
\text{R}^1 + \text{H} + \text{R}^2 \xrightarrow{2\% [\text{Ir(dF(Me)ppy)}_2(\text{dtbbpy})]\text{PF}_6} \text{0.5 equiv RSH, toluene (ca. 0.05M)}} \rightarrow \text{32W blue LED, 4-40 hours}
\]
Case study 1: photoredox hydroamination

- slow reaction but still delivers workable material:

- scale-out (five reactors per unit):
multi-gram quantities per day feasible in 2-reactor configuration:

- Case study 1: photoredox hydroamination

<table>
<thead>
<tr>
<th>Structure</th>
<th>Isolated Yield</th>
<th>Daily Production</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Structure" /></td>
<td>37%</td>
<td>1.5g</td>
</tr>
<tr>
<td><img src="image2" alt="Structure" /></td>
<td>50%</td>
<td>1.9g</td>
</tr>
<tr>
<td><img src="image3" alt="Structure" /></td>
<td>17%</td>
<td>0.8g</td>
</tr>
<tr>
<td><img src="image4" alt="Structure" /></td>
<td>35%</td>
<td>1.6g</td>
</tr>
<tr>
<td><img src="image5" alt="Structure" /></td>
<td>28%</td>
<td>1.6g</td>
</tr>
<tr>
<td><img src="image6" alt="Structure" /></td>
<td>15%</td>
<td>0.9g</td>
</tr>
</tbody>
</table>
Case study 2: benzylic bromination

- Wohl-Ziegler bromination has been studied in flow

- e.g. Kappe group, using Booker-Milburn-type tubular reactor:

  - productivity up to 30 mmols per hour (ca 9g per hour)

Case study 2: benzylic bromination

- fReactor platform (2 reactors) gives comparable results:

0.5M in MeCN

1.5 mL min⁻¹

94% selectivity @85% conversion
75% isolated yield
7.5g per hour product (ca. 180g per day)
electron-rich tolenes even more productive:

Case study 2: benzylic bromination

- 95% selectivity @ 85% conversion 75%* isolated yield
  (0.5M in MeCN 1.5 mL min⁻¹)
  ca 7.5g per hour product @ 2 Lights/reactors

- 94% selectivity @ 82% conversion 58%* isolated yield
  (0.5M in dioxane; 4 mL min⁻¹)
  ca 14g per hour product @ 2 Lights/reactors

- 94% selectivity @ 85% conversion 69% isolated yield
  (0.5M in MeCN 4 mL min⁻¹)
  ca 19 g per hour product @ 2 Lights/reactors
- Productivity increased by daisy-chaining
- Linear response to sequential reactors: ca. 20 g h\(^{-1}\) @ 5 reactors

**Case study 2: benzylic bromination**

\[
\text{Flow rate} \quad \text{Productivity (g/h/reactor)}
\]

0.5M in MeCN
solubility limit of NBS is limitation… but fReactors can handle slurries!

Case study 2: benzylic bromination

- 76% conversion; 92% selectivity; 68% isolated; **26g/hour**
- 85% conversion; 88% selectivity; 71% isolated; **34g/hour**
- 73% conversion; 98% selectivity; 58% isolated; **33g/hour**
valsartan (best-selling anti-hypertensive) is made via benzylic bromination:

- slurry:

\[
\begin{align*}
\text{valsartan} & \quad \text{via} \quad \text{benzylic bromination} \\
\text{slurry:} & \quad 47\% \text{ conversion}; >95\% \text{ selectivity; } 42\% \text{ isolated; } 17g/hour \\
& \quad (\text{ca. } 410g \text{ per day})
\end{align*}
\]
Conclusions

*Photo module for fReactor creates a benchtop photochemical CSTR:*

- high photon flux levels from 365nm upwards
- easy-to-use on the fReactor flow platform (can be used both in flow and in batch!)
- demonstrated capabilities to give high productivity in homogeneous systems
- ability to handle different reaction regimes (short to long residence times)
- combines the ability to handle multiphasic flows (L/S and G/L) with photochemistry
- *unlocking new tools in flow photochemistry*
Professor John Blacker

Photochemistry team: Dr Seb Cosgrove, Dr Gayle Douglas Dr Daniel Francis Professors Adam Nelson & John Plane (Leeds), Dr Steve Raw (AstraZeneca)

iPRD – photochemistry in fReactor prototyping Dr Jamie Manson, Dr Adam Clayton, Dr Carlos Gonzalez Niño, Dr Ricardo Labes Dr Thomas Chamberlain & Dr Richard Bourne (Leeds)

Flow club project (EPSRC Impact Acceleration Account) Dr Dan Francis Dr Dan Cox (Redbrick Molecular), Dr Mark Muldowney (Sterling Pharma)

Team Asynt! Dr Ffion Abraham, Dr Kerry Elgie, Martyn Fordham