https://youtu.be/msfmLlFDRRs

UNIVERSITY OF LEEDS

fReactor

Photo-Flow Chemistry Webinar

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Professor of Applied Fluid Mechanics
Degree in Chemical Engineering

School of Mechanical Engineering,
University of Leeds

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

Professor Steve Marsden

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Professor of Organic Chemistry

School of Chemistry,
University of Leeds

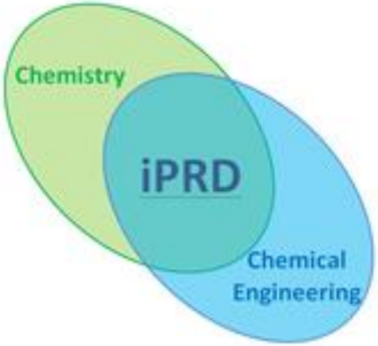
“new clean/catalytic methodology for the synthesis of biologically-relevant molecules”

Please do get in touch with us – we welcome collaborations

iPRD
Institute of Process Research and Development

Introduction to iPRD

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.

Support for SMEs | Research | Collaborators | Teaching and training

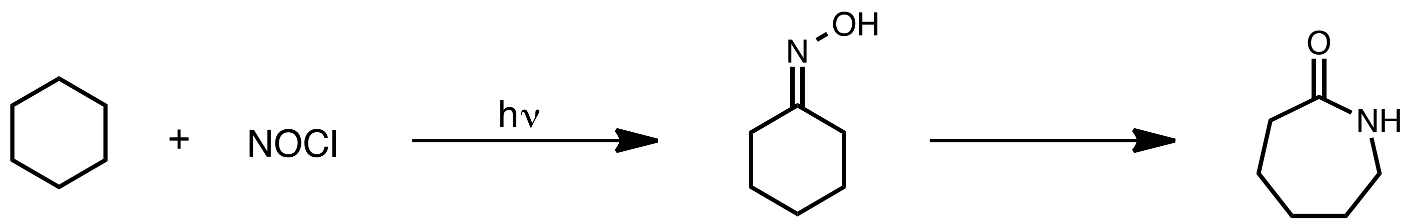
www.iprd.leeds.ac.uk

Contents

- introduction to photochemistry
- problems with scale-up in batch and flow
- a new solution for photochemical CSTRs
- case studies
- conclusions

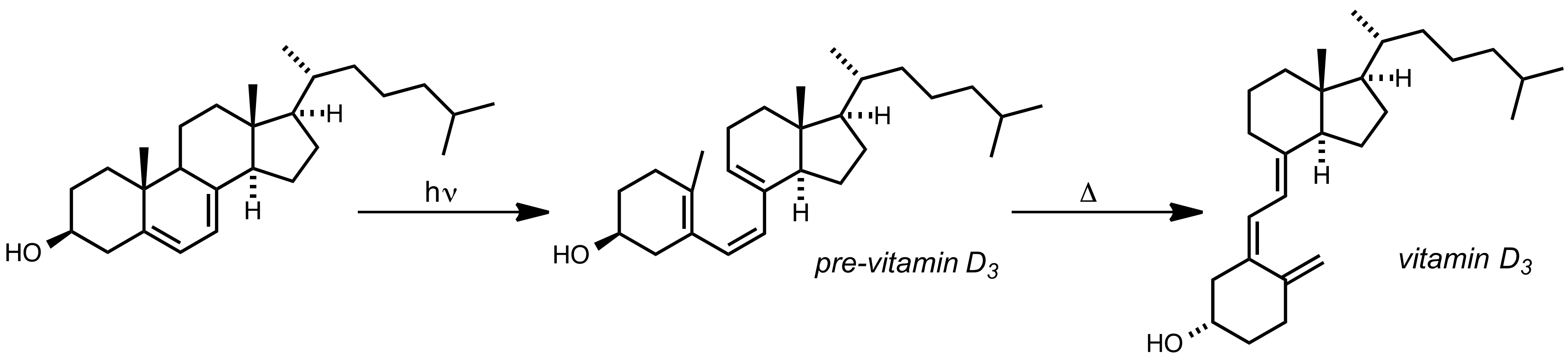
Industrial photochemistry – an underused technology?

- bulk chemistry – efficient but price sensitive!



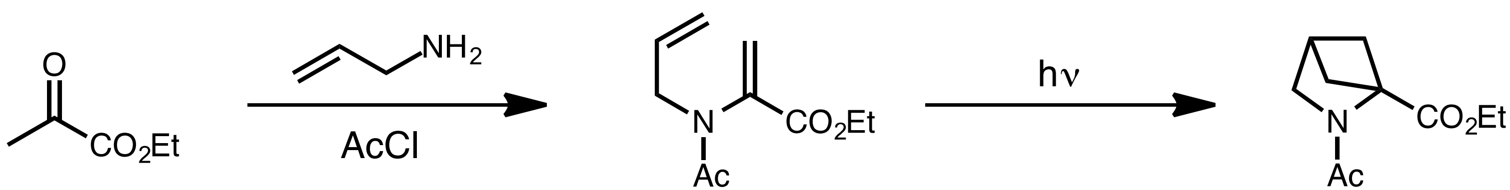
caprolactam
(Toray process)

- niche products (<1 tonne pa)



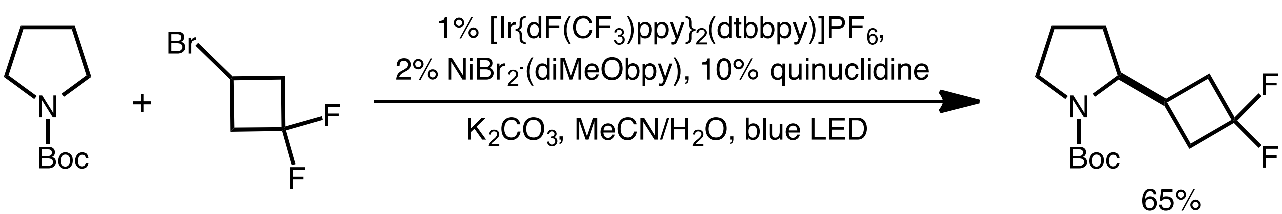
Organic photochemistry – a renaissance

- unusual architectures:



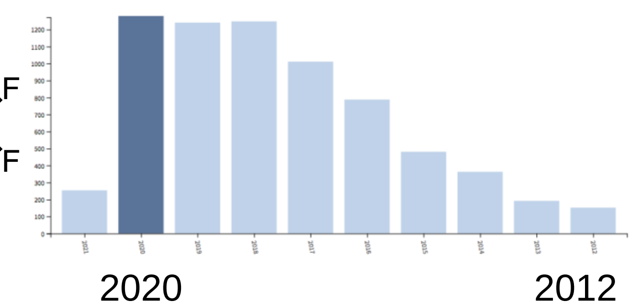
ACS Med. Chem. Lett., **2020**, *11,* 1185

- photoredox catalysis



Nature, **2017**, *547*, 79

“photoredox” papers

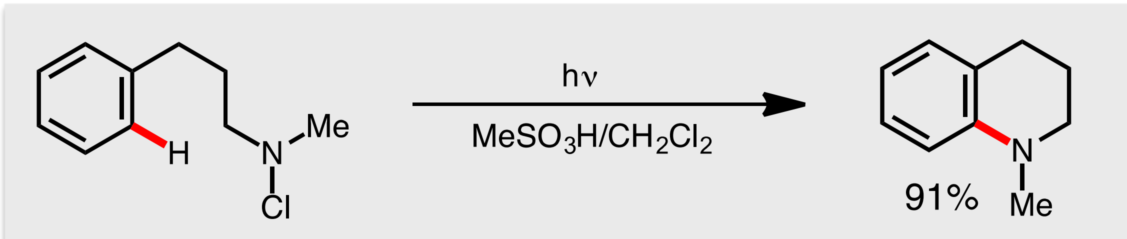


Issues with scaling photochemistry

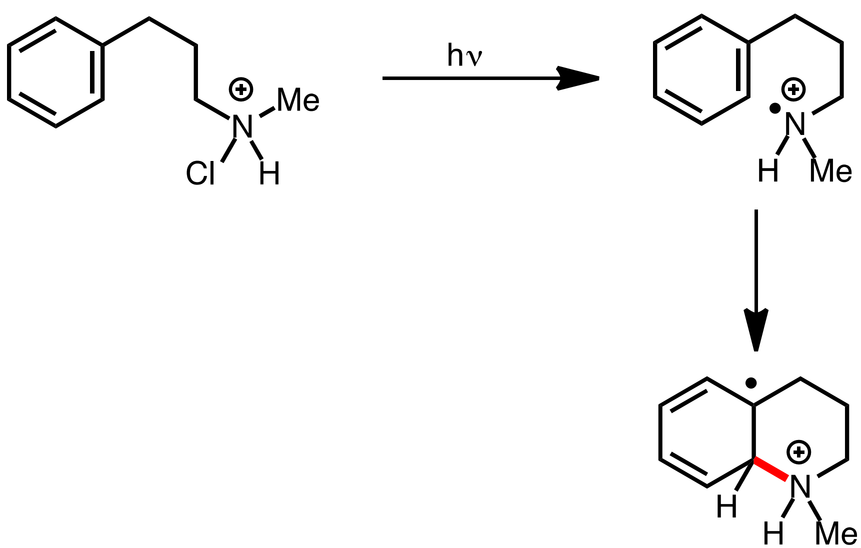
- limited light penetration to batch reactors (Beer-Lambert law)
- secondary photoreactions @ long reaction times
- thermal effects
- variability in lamp performance vs. time
- variability with experimental set-up (distance to source)
- ***is continuous processing a solution to some/all of these?***

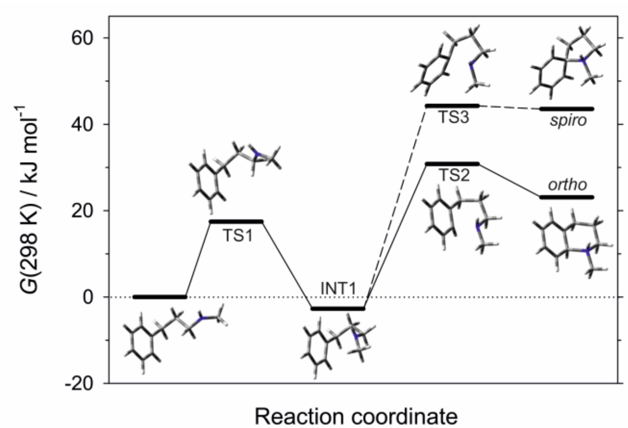
Direct photochemical *N*-arylation

- direct method for C-H amination of aromatics by photolytic reaction of *N*-chloroamines:



via

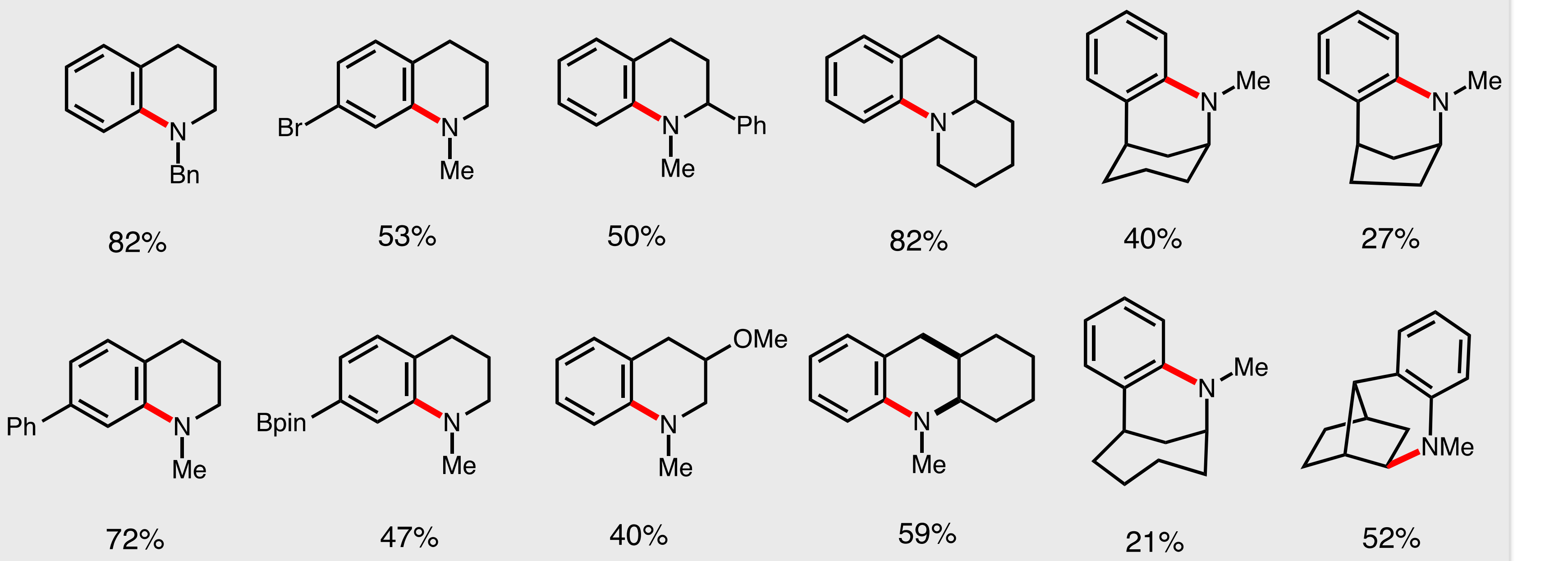




Cosgrove, Plane, Marsden, *Chem. Sci.*, **2018**, *9*, 6647

Direct photochemical *N*-arylation

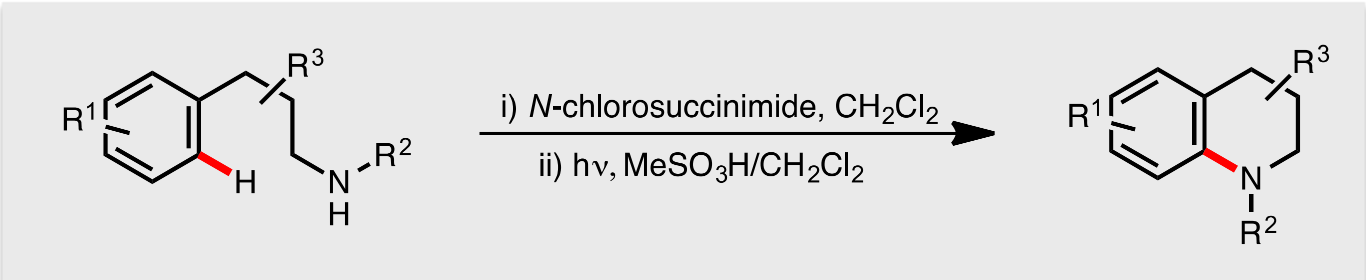
- access to diverse, functionalised scaffolds including highly 3D:

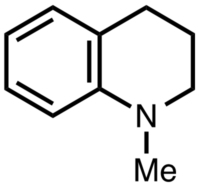


Cosgrove, Plane, Marsden, *Chem. Sci.*, **2018**, *9*, 6647

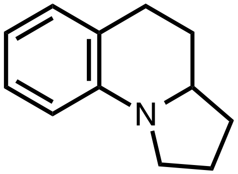
Direct photochemical *N*-arylation

- one-pot approach avoids *N*-chloroamine isolation:

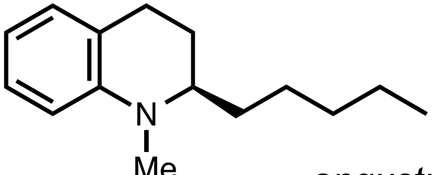




60%



73%



angustureine

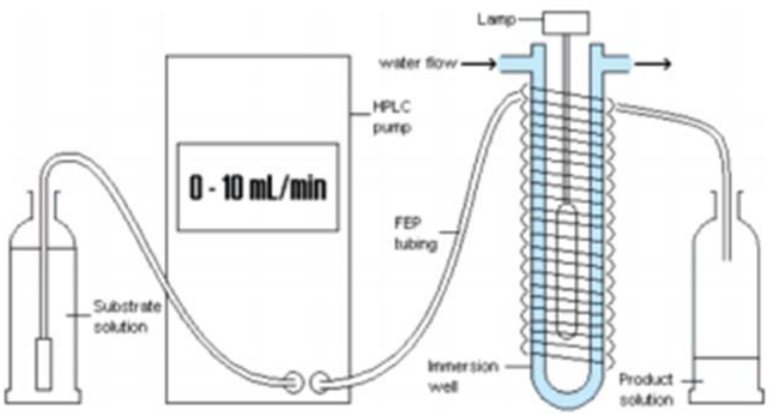
52% (97% *es*)

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

Cosgrove, Plane, Marsden, *Chem. Sci.*, **2018**, *9*, 6647

Continuous photochemical reactors: tubular design

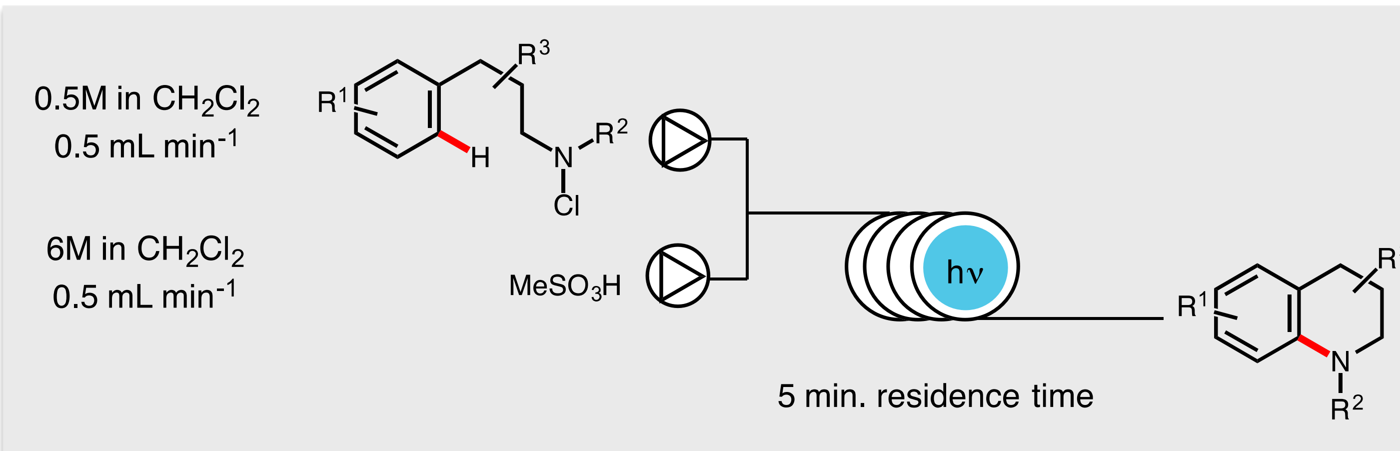
- simple design (Booker-Milburn, University of Bristol) using UV-permeable FEP tubing/syringe or HPLC pump

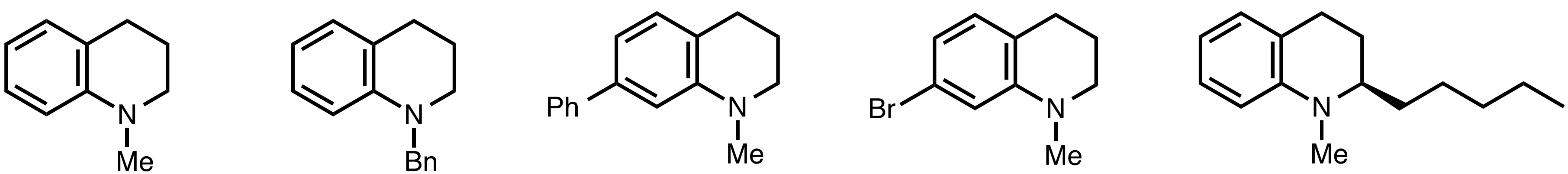


Booker-Milburn *et al*., *J. Org. Chem.*, **2005**, *70*, 7558 (270 citations!)

Direct photochemical *N*-arylation

- multi-gram quantities readily accessible using 5mL reactor



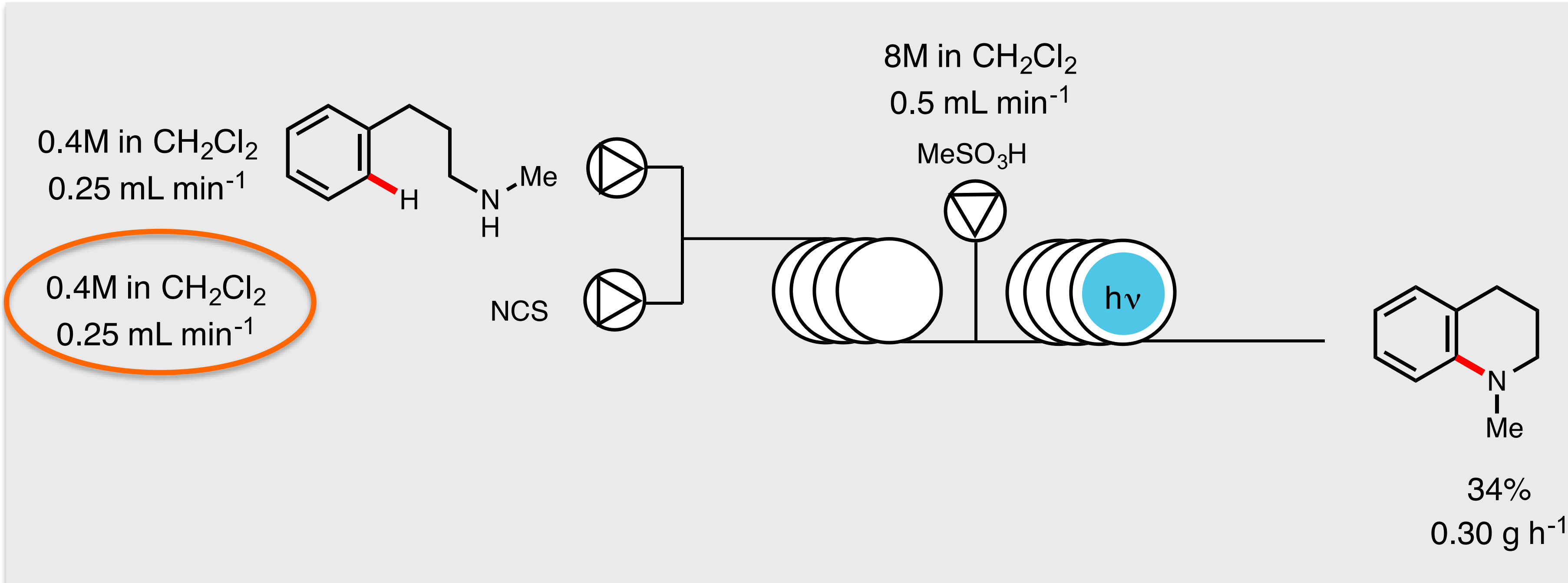


56% 1.28 g h^{-1} | 43% 1.29 g h^{-1} | 28% 0.76 g h^{-1} | 51% 1.38 g h^{-1} | 40%* 0.62 g h^{-1} (* 10 min r.t.)

Cosgrove, Douglas, Raw, Marsden, *ChemPhotoChem.*, **2018**, *2*, 851

Direct photochemical *N*-arylation

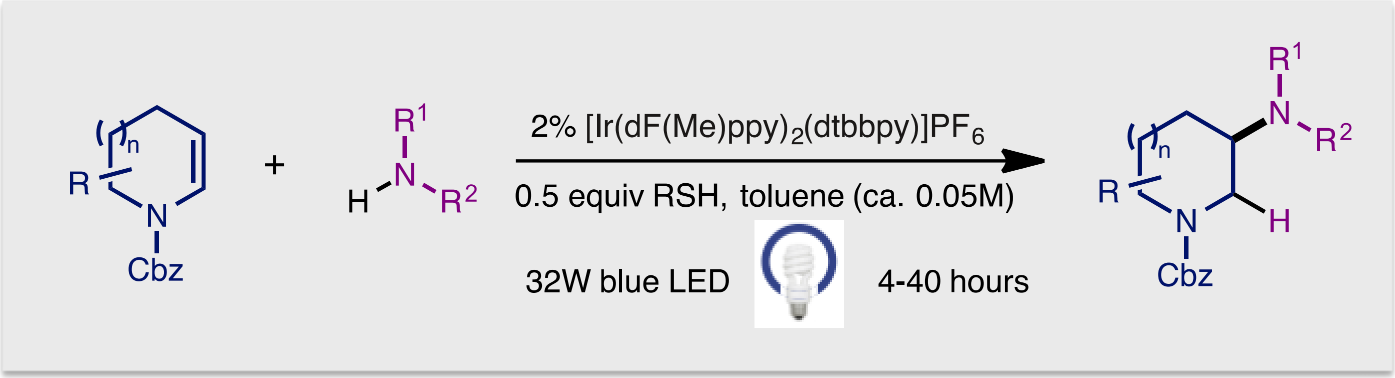
- sequential *N*-chlorination/cyclisation proceeds, but……

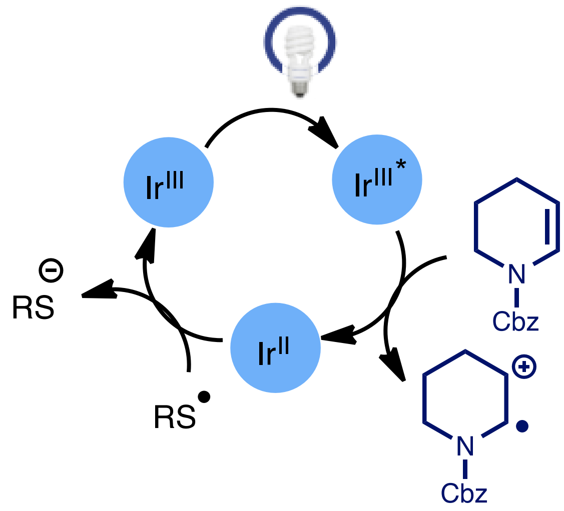


- productivity down 75% owing to dilution needed for monophasic rxn
- ***highlights need for photoreactors capable of multiphasic flow!***

Cosgrove, Douglas, Raw, Marsden, *ChemPhotoChem.*, **2018**, *2*, 851

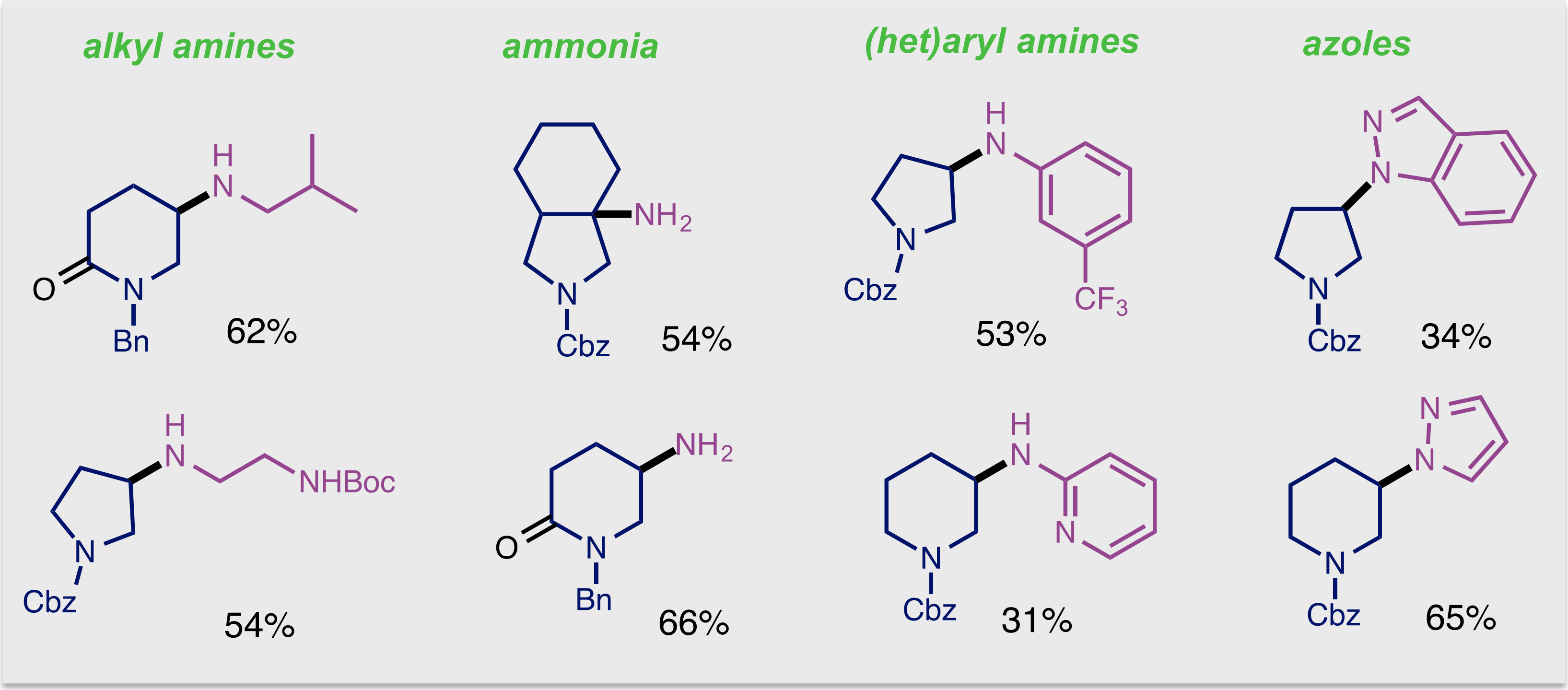
- powerful method for synthesis of drug-relevant cyclic 1,2-diamines:





Francis, Nelson, Marsden, *Chem. Eur. J.*, **2020**, *26*, 14861

- 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

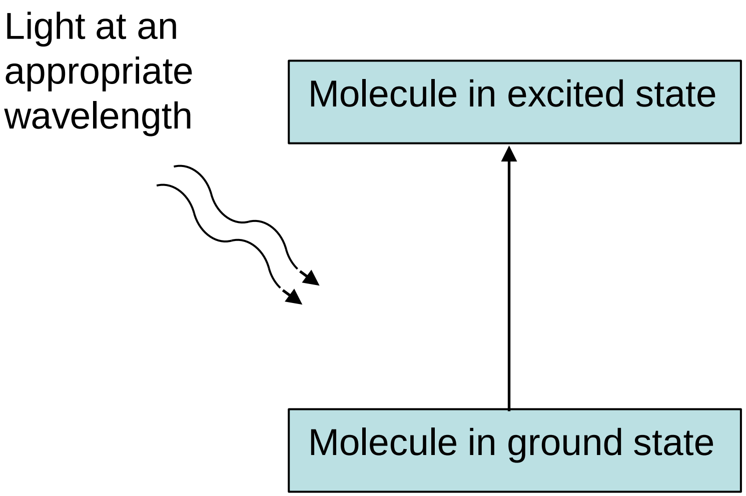
Francis, Nelson, Marsden, *Chem. Eur. J.*, **2020**, *26*, 14861

- 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

<u>Key mechanisms at play in photochemistry</u>

- 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

Controlling factors

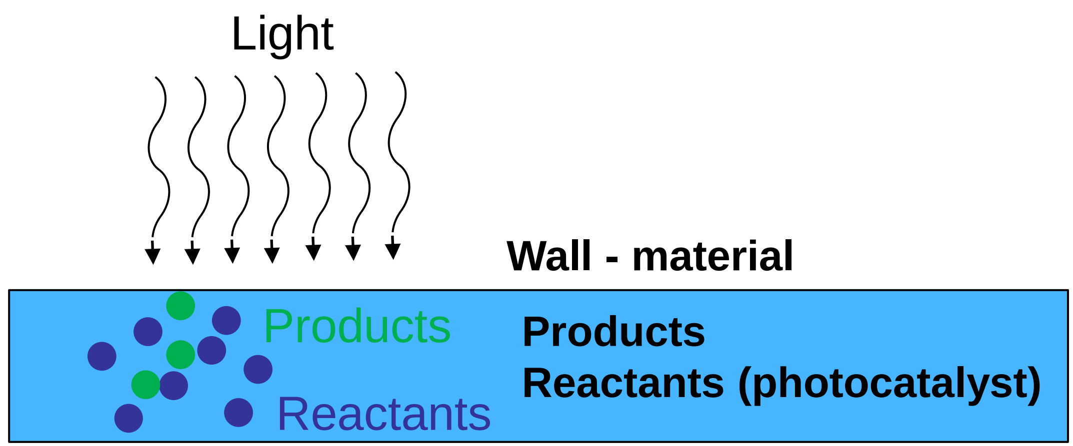


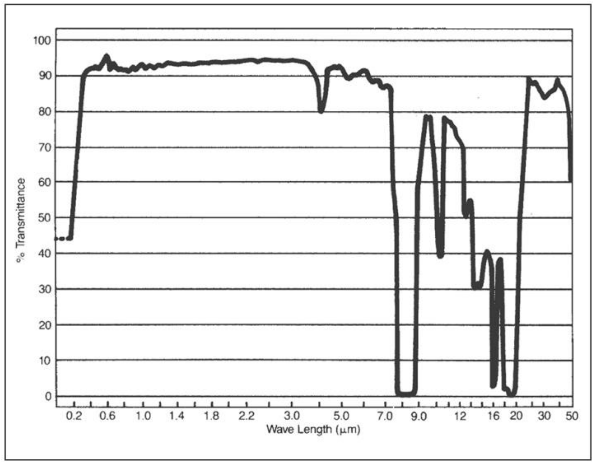
(not quite a Jablonski diagram!)

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

Controlling Factors

What can interact with the light (prevent photons getting to the right place) ?





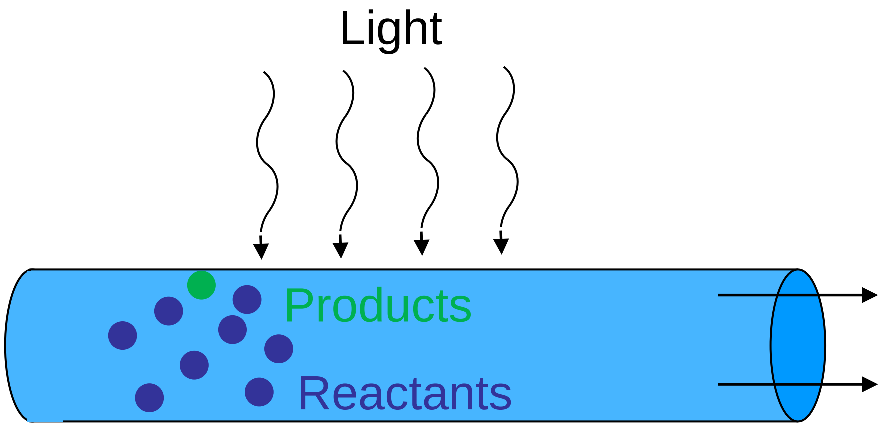
Beer Lambert Law

Absorbance = Absorption coefficient x Path length x concentration

Flow – pipe flow

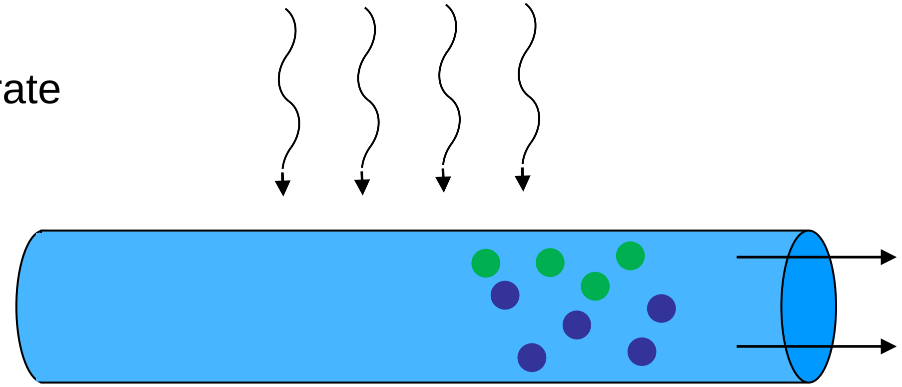
The reaction zone – (in this example….)

- 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

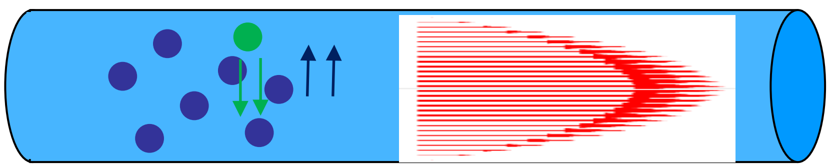
Transport into and out of reaction zone important

Flow photochemistry - tubular

The transport

- Advection – flow – laminar (see http://freactor.com/learningLamTurb.html)
- Diffusion $\tau \approx x^2/D$ (D ~ $1x10^{-9}$ m^2/s to $1x10^{-10}$ m^2/s)

Peclet number =
Diffusion time / advection time



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 ~ 5 x 10^{-9} m^2/s)

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

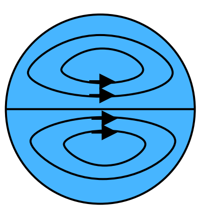
Time to flow through tube

Time to diffuse across tube

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

Experimental methods in chemical engineering: Micro-reactors A.Macchi, P.Plouffe, G.S. Patience, D.M. Roberge *Can. J. Chem. Eng.*, 2019, **97**, 2578
Continuous flow chemistry: where are we now? Recent applications, challenges and limitations, F.M. Akwi, P.Watts *Chem. Commun*., 2018, 54, 13894

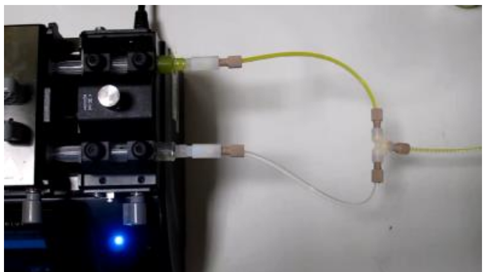
Mixing

Video summarised on next slide!

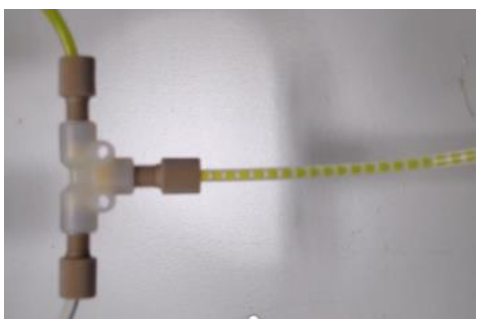
Link to fReactor video https://www.youtube.com/watch?v=C5MJ49AB820

Mixing

Multiphasic flow in tube
Water (green dye)
Oil

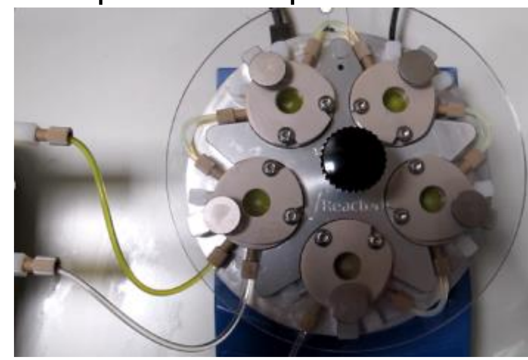


Pumping – dual syringe pump
Mixing – tee piece



Pipe reactor – segregated droplets of water and oil

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



Inlet (aqueous)

Inlet (oil)

Fine emulsion in outflow

Link to fReactor video https://www.youtube.com/watch?v=C5MJ49AB820

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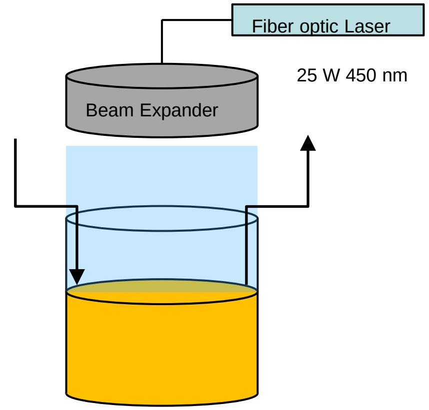
CSTRs + photochemistry

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

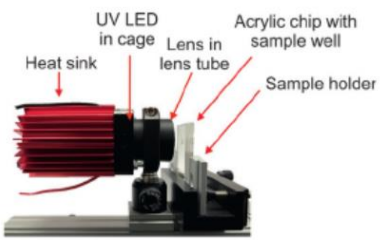


A Hybridised Optimisation of an Automated Photochemical Continuous Flow Reactor

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

PMID: 31645242 DOI: 10.2533/chimia.2019.817

Chimia 73 (2019) 817–822



Org. Process Res. Dev. 2017, 21, 9, 1294–1301

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

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

Alexander Pomberger,[†] Yiming Mo,[†] Kakasaheb Y. Nandiwale,[†] Victor L. Schultz,[†] Rohit Duvadie,[‡] Richard I. Robinson,[‡] Erhan I. Altinoglu,[§] and Klavs F. Jensen*[,†]

[†]Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States

[‡]Global Discovery Chemistry - Chemical Technology Group, Novartis Institutes for BioMedical Research, 250 Massachusetts Avenue, Cambridge, Massachusetts 02139, United States

[§]Chemical and Pharmaceutical Profiling, Novartis Global Drug Development, 700 Main Street South, Cambridge, Massachusetts 02139, United States

Org. Process Res. Dev. 2019, 23, 12, 2699–2706

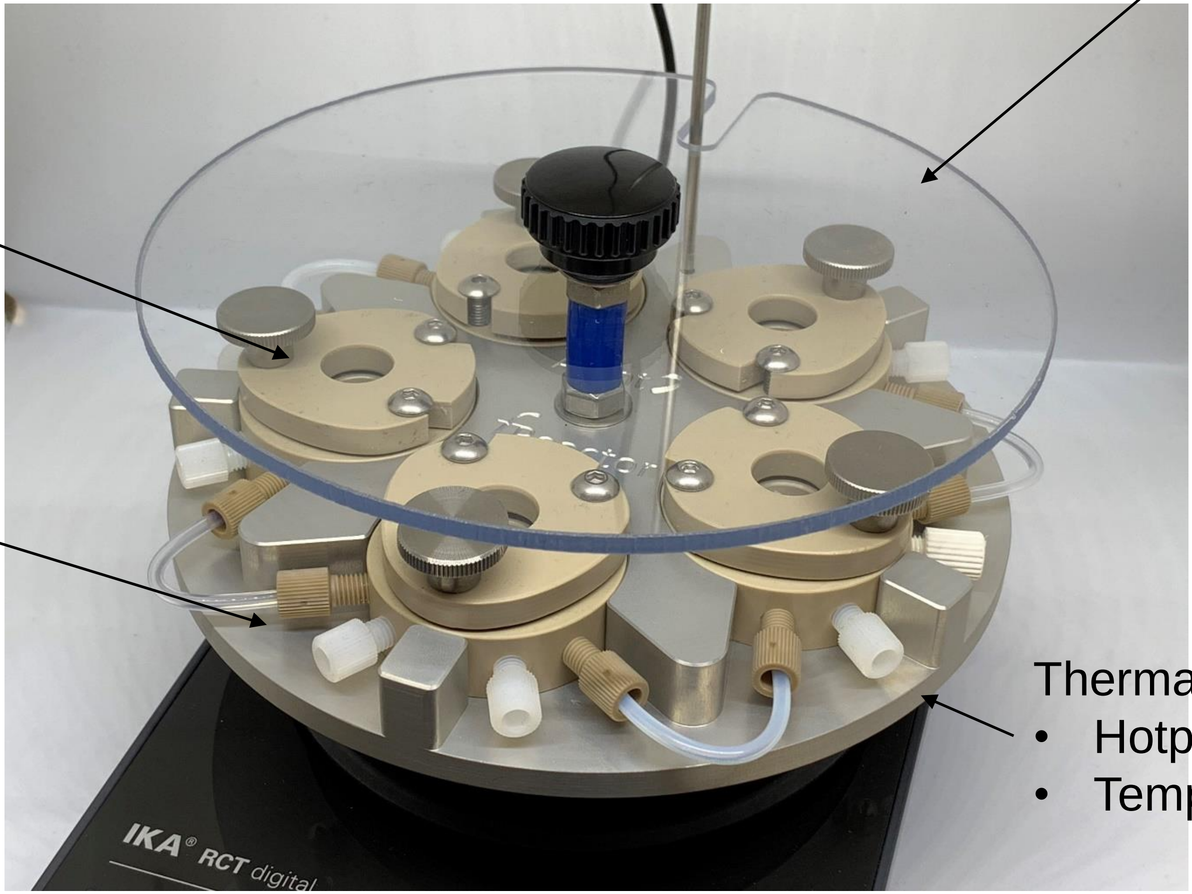
fReactor: final product

Additional safety shield

5 stage CSTR

4 ports

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



Thermal base plate
- Hotplate / stirrer
- Temperature well

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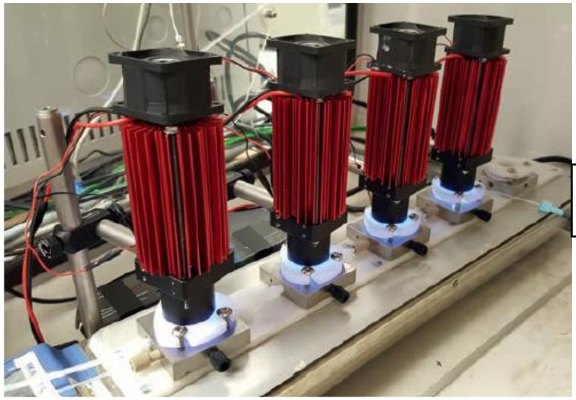
The evolution of the photochemistry flow module (Photoflow)



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:* ~140ºC (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

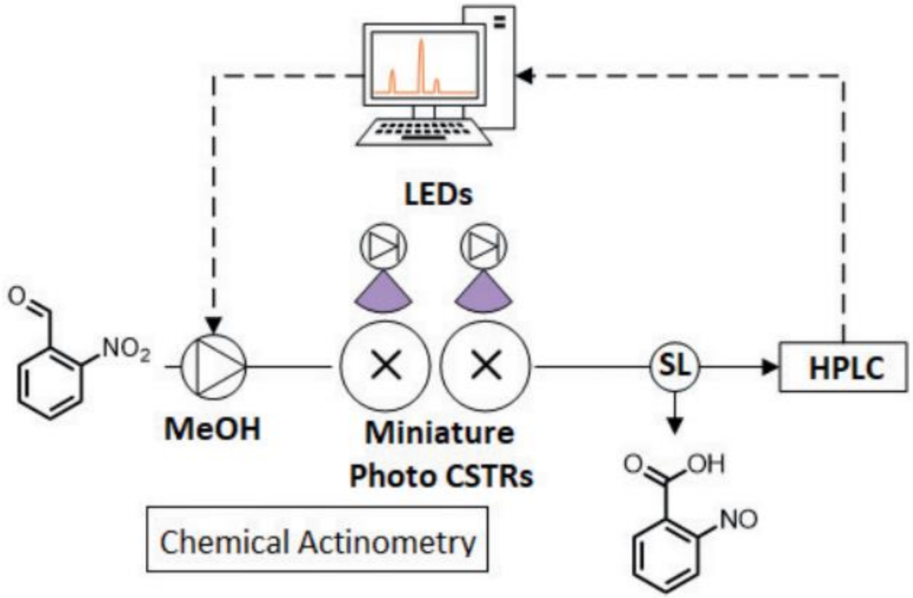
- ***FLEXIBILITY***

- *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***

Flow actinometry



Single phase photochemical isomerisation

o-nitrobenzaldehyde to o-nitrosobenzoic acid

Quantum yield 365nm = 0.5

10x greater than in previously reported batch systems!

A Hybridised Optimisation of an Automated Photochemical Continuous Flow Reactor

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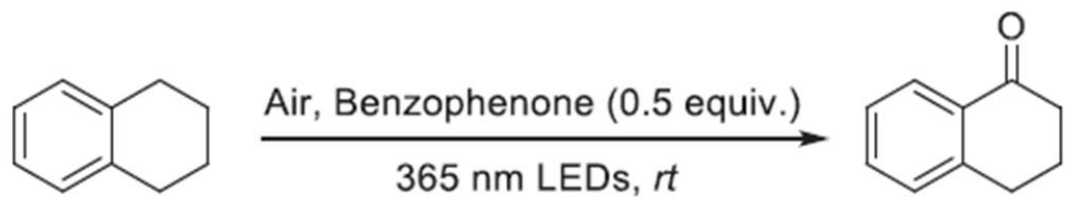
PMID: 31645242 DOI: 10.2533/chimia.2019.817

Aerobic Oxidation (G/L)



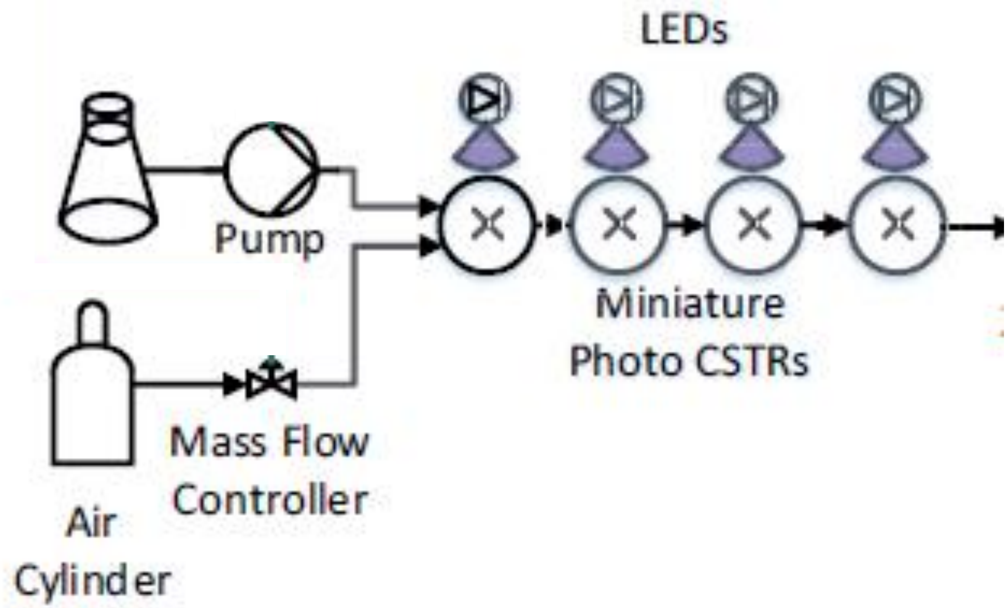
Tetralin

Tetralone

Mixing into photochemically active zone

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

Can minimize secondary reactions – photon efficient



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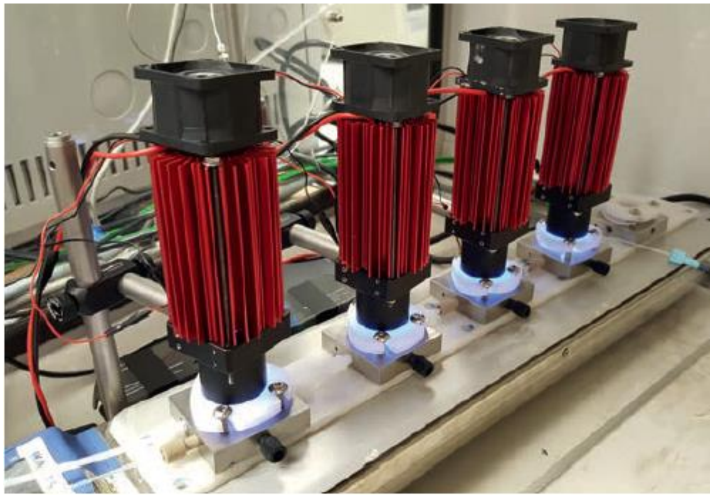
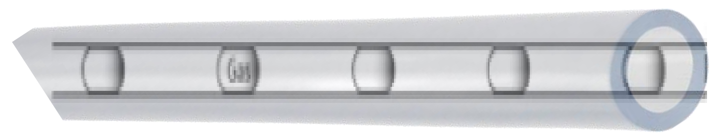


Selective C(sp^3)–H Aerobic Oxidation Enabled by Decatungstate Photocatalysis in Flow

Gabriele Laudadio, Sebastian Govaerts, Ying Wang, Davide Ravelli, Hannes F. Koolman, Maurizio Fagnoni, Stevan W. Djuric, Prof. Timothy Noël

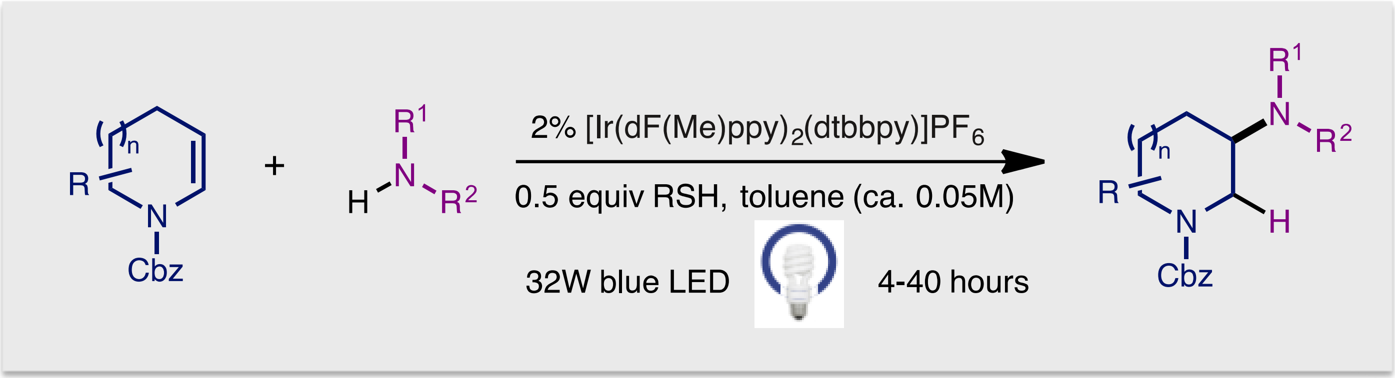


Residence time of 18.3 minutes	Residence time 45 minutes
Air	Pure oxygen
benzophenone (£0.04 / g)	TBADT (£300 / g)
65% yield	84% yield

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

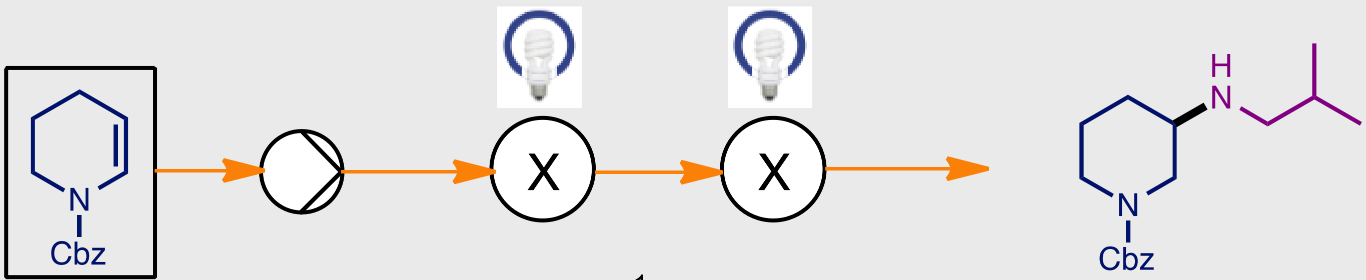
Case study 1: photoredox hydroamination



- 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!

Case study 1: photoredox hydroamination

- slow reaction but still delivers workable material:



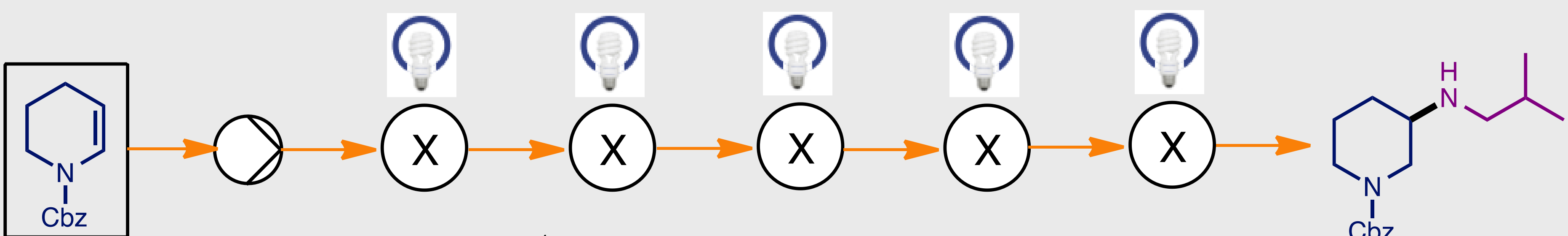
0.2 M;
0.5% Ir

50 μL min^{-1}

37% yield @ 42% conv.
(85% theoretical)

1.5g per day

- scale-out (five reactors per unit):



0.2 M;
0.5% Ir

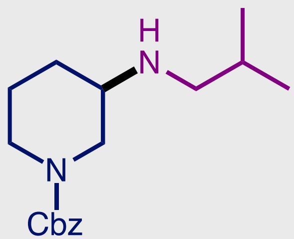
125 μL min^{-1}

35% yield @ 46% conv.
(76% theoretical)

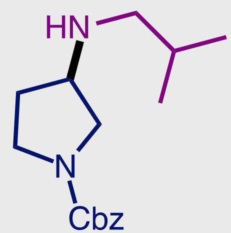
4g per day

Case study 1: photoredox hydroamination

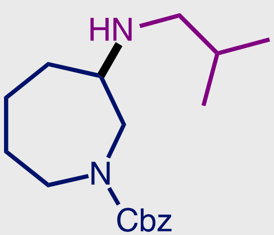
- multi-gram quantities per day feasible in 2-reactor configuration:



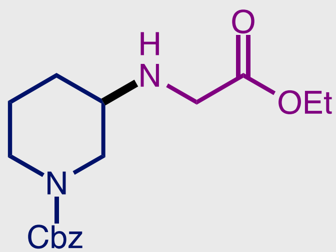
37% isolated; **1.5g per day**



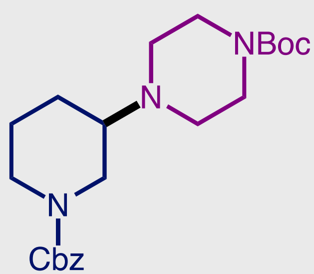
50% isolated; **1.9g per day**



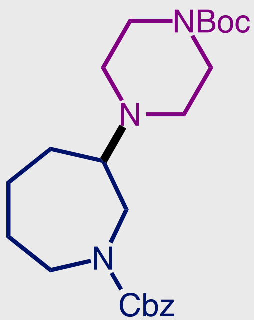
17% isolated; **0.8g per day**



35% isolated; **1.6g per day**



28% isolated; **1.6g per day**

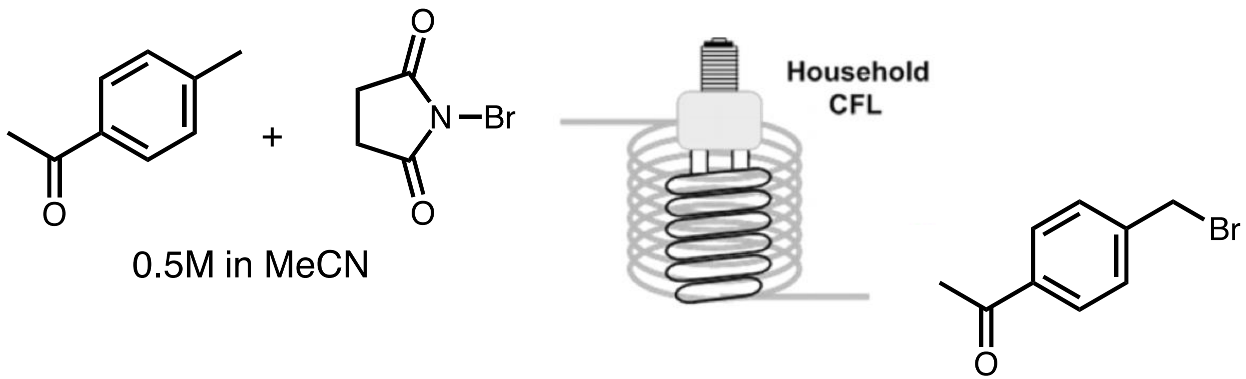


15% isolated; **0.9g per day**

Case study 2: benzylic bromination

- Wohl-Ziegler bromination has been studied in flow

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

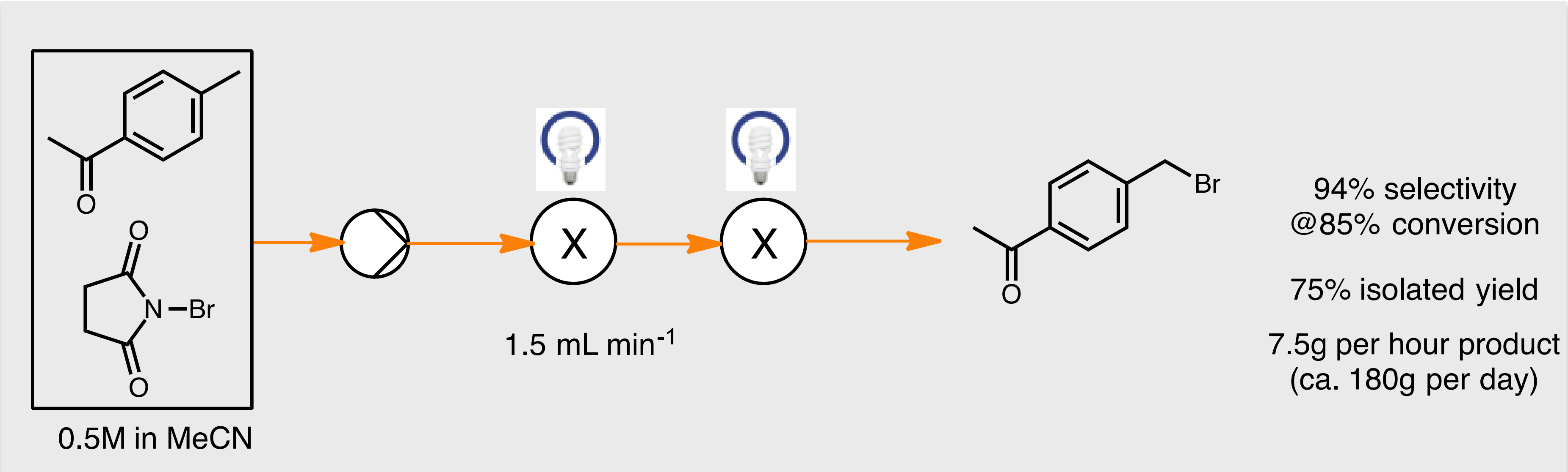


- productivity up to 30 mmols per hour (ca 9g per hour)

Kappe *et al*., *J. Org. Chem.*, **2014**, *79*, 223

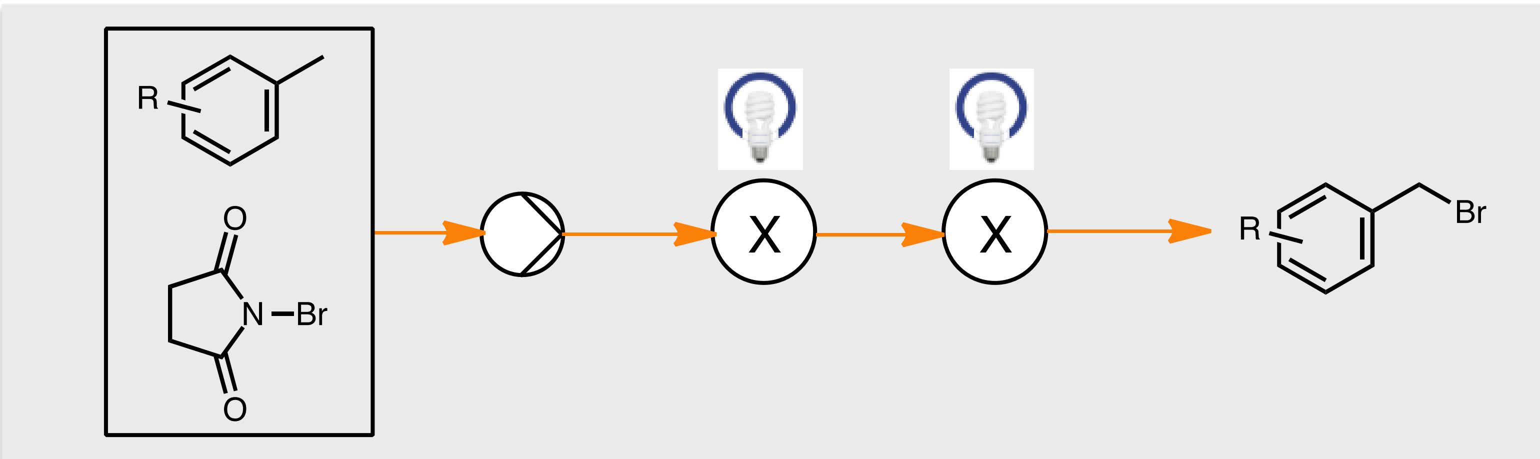
Case study 2: benzylic bromination

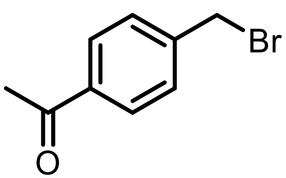
- fReactor platform (2 reactors) gives comparable results:



Case study 2: benzylic bromination

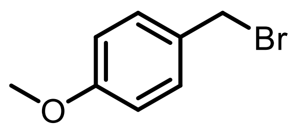
- electron-rich toluenes even more productive:





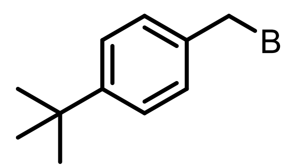
95% selectivity
@85% conversion
75%* isolated yield

(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

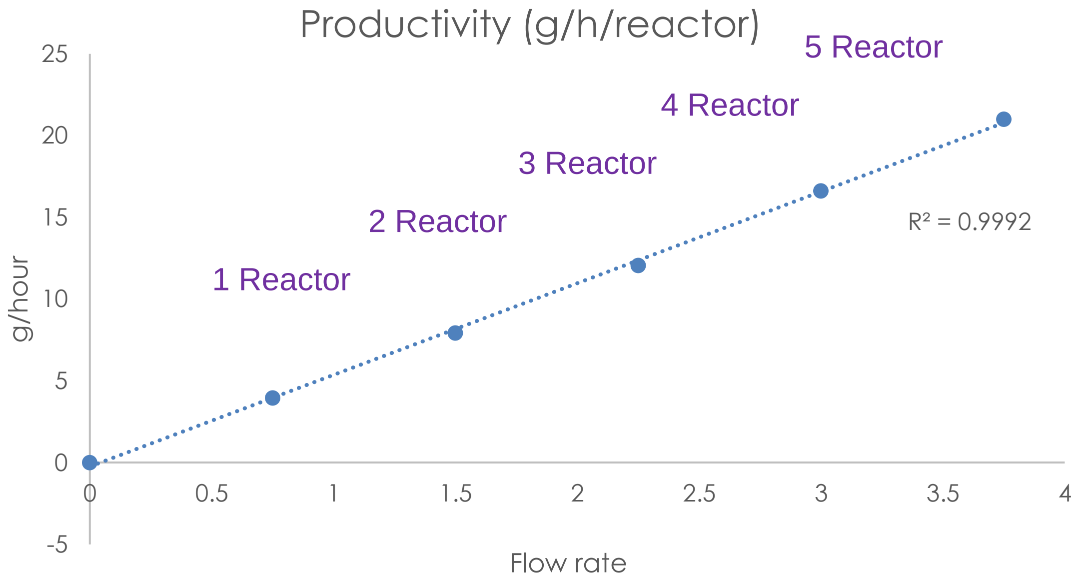


94% selectivity
@85% conversion
69% isolated yield

(0.5M in MeCN
4 mL min^{-1})
ca 19 g per hour product
@2 Lights/reactors

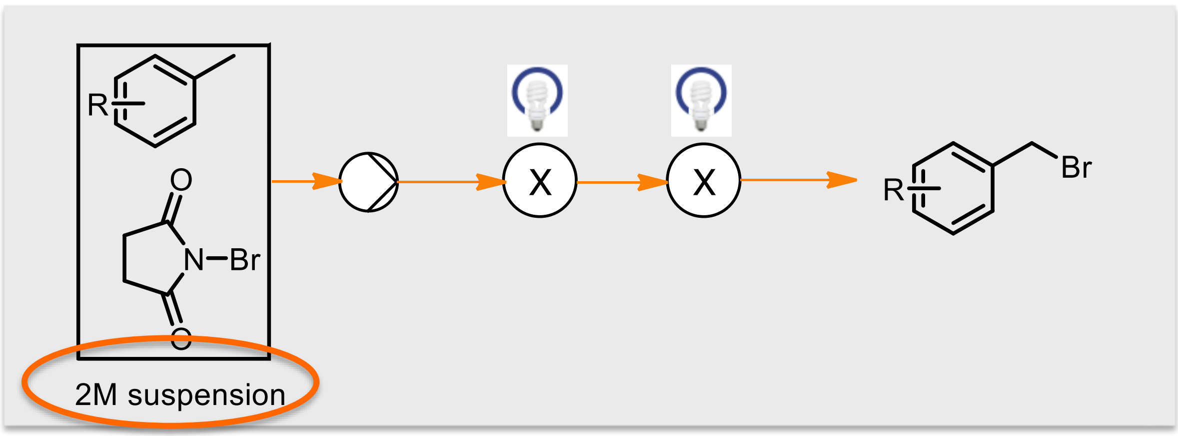
Case study 2: benzylic bromination

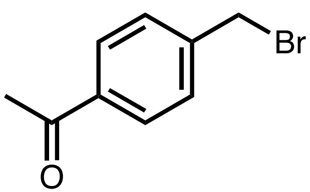
- productivity increased by daisy-chaining
- linear response to sequential reactors: ca. 20 g h^{-1} @ 5 reactors



Case study 2: benzylic bromination

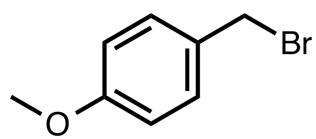
- solubility limit of NBS is limitation…but fReactors can handle slurries!





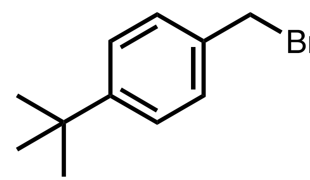
76% conversion; 92% selectivity;

68% isolated; **26g/hour**



85% conversion; 88% selectivity;

71% isolated; **34g/hour**

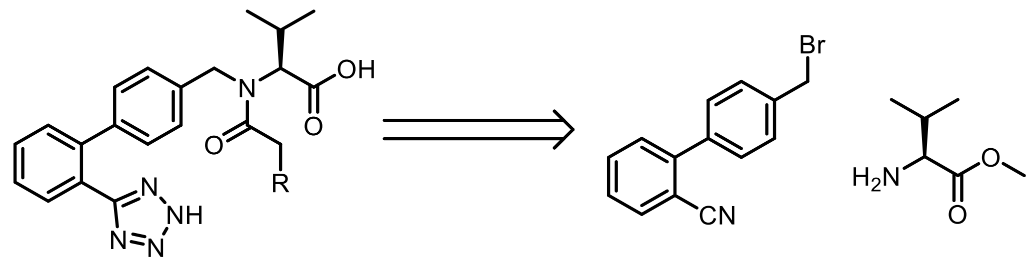


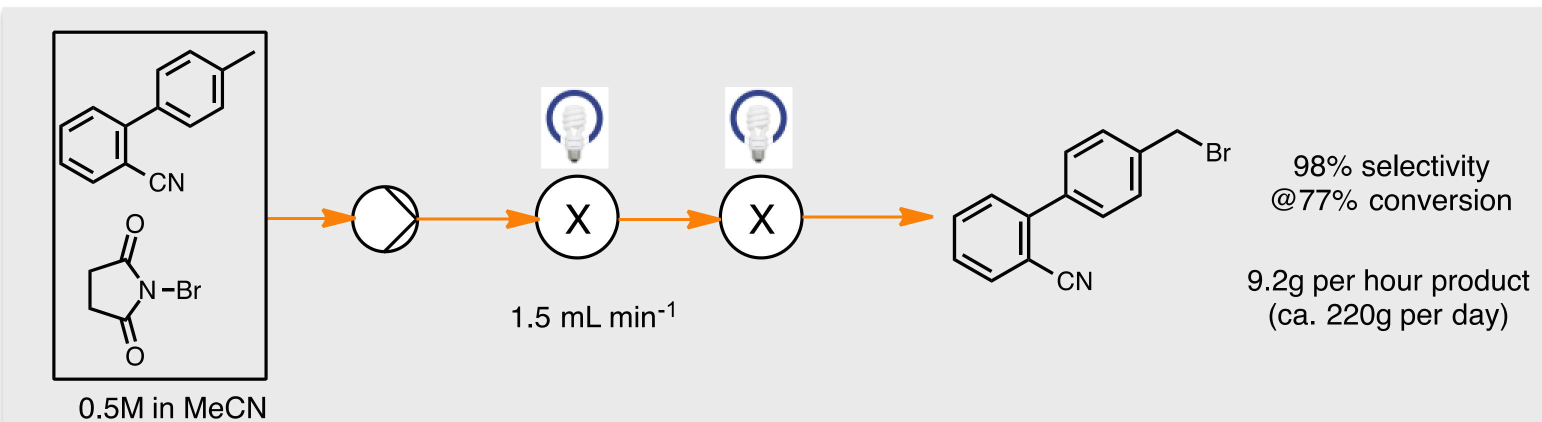
73% conversion; 98% selectivity;

58% isolated; **33g/hour**

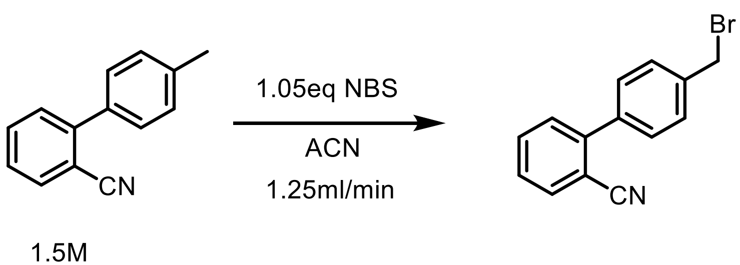
Case study 2: benzylic bromination

- valsartan (best-selling anti-hypertensive) is made *via* benzylic bromination:





- slurry:



47% conversion; >95% selectivity;

42% isolated; **17g/hour**

(ca. 410g per day)

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*

iPRD
Institute of Process Research and Development

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