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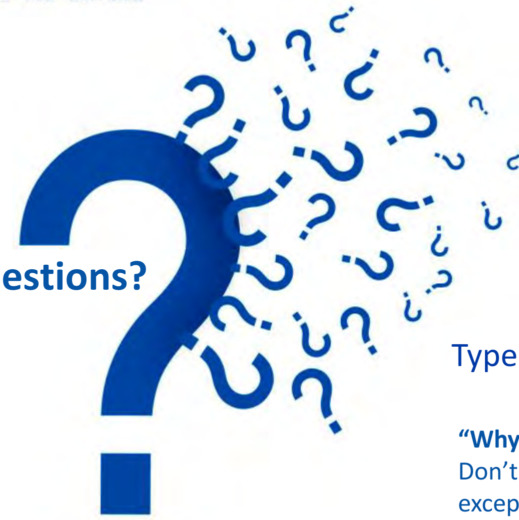

Have Questions?

Type them into questions box!

"Why am I muted?"
Don't worry. Everyone is muted except the presenter and host. Thank you and enjoy the show.

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Edited Recordings are an exclusive ACS member benefit and are made available once the recording has been edited and posted.

Live Broadcasts of ACS Webinars® continue to be available to the general public several times a week generally from 2-3pm ET!

A **collection of the best recordings** from the ACS Webinars Library will occasionally be rebroadcast to highlight the value of the content.

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ACS Career Navigator:
Your Home for Career Services

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Whether you are just starting your journey, transitioning jobs, or looking to brush up or learn new skills, the **ACS Career Navigator** has the resources to point you in the right direction.

We have a collection of career resources to support you during this global pandemic:


Professional Education


Virtual Career Consultants

ACS Leadership Development System


Career Navigator LIVE!


ChemIDP


College to Career

ACS Webinars

Virtual Classrooms

Visit www.ACS.org/COVID19-Network to learn more!

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Join us in our efforts to increase the diversity of chemistry.

Valued donors like you have sustained ACS educational programs that are welcoming students from diverse backgrounds into our profession.

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A Career Planning Tool For Chemical Scientists

ChemIDP is an Individual Development Plan designed specifically for graduate students and postdoctoral scholars in the chemical sciences. Through immersive, self-paced activities, users explore potential careers, determine specific skills needed for success, and develop plans to achieve professional goals. **ChemIDP** tracks user progress and input, providing tips and strategies to complete goals and guide career exploration.

https://chemidp.acs.org

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Are you thinking of Grad School?

If you are from an underrepresented racial or ethnic group, we want to empower you to get your graduate degree!

The ACS Bridge Program offers:

- A FREE common application that will highlight your achievements to participating Bridge Departments
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ACS Department of Diversity Programs

Advancing ACS's Core Value of Diversity, Inclusion & Respect

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We believe in the strength of diversity in all its forms, because inclusion of and respect for diverse people, experiences, and ideas lead to superior solutions to world challenges and advances chemistry as a global, multidisciplinary science.

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Fecha: Miércoles, 18 de Agosto, 2021 @ 2-3pm ET
Ponente: Dra. Leticia Myriam Torres Guerra, Centro de Investigación en Materiales Avanzados S.C. (CIMAV)
Moderadora: Dra. Maria del Jesus Rosales Hoz, Cinvestav y Sociedad Quimica de México

Registrarse Gratuitamente

Lo Que El Público Aprenderá:

- Procesos de fotoconversión del agua en H_2 y O_2 y en la reducción fototocatalítica del CO_2
- Influencia del método de síntesis de óxidos cerámicos y variaciones cristaloquímicas de estos materiales en la eficiencia fotocatalítica de estos dos procesos
- El uso de un co-actalizador para mejorar el transporte de cargas y lograr una mayor actividad fotocatalítica

Co-producido con: Sociedad Quimica de México y *Chemical & Engineering News*

Date: Tuesday, August 31, 2021 @ 1-2pm ET
Speakers: Bill Carroll, Carroll Applied Science / Isiah Warner, Louisiana State University / Rajendrani Mukhopadhyay, ACS Office of DEIR / Trinity Horton Hale, Celanese
Moderator: Arlene Garrison, ACS Senior Chemists Committee

Register for Free!

What You Will Learn:

- Insights on the impact of COVID on the chemistry economy
- Society wide efforts and activities to support diversity, equity, inclusion and respect (DEIR) and a new grant program for senior chemists with creative ideas to address DEIR
- An update on SCC activities and story from the ACS Scholars Program

This special broadcast is produced for the ACS Senior Chemists Committee by ACS Webinars.

Date: Wednesday, September 8, 2021 @ 2-3pm ET
Speaker: Bill Carroll, Carroll Applied Science
Moderator: Tom Halleran, American Chemical Society

Register for Free!

What You Will Learn:

- How your persona changes when you retire
- Why it's important to actively structure your retirement
- Some useful tools for retirement success

Co-produced with: ACS Careers

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ACS Green Chemistry Institute

ACS Green Chemistry Institute
Chemistry for Life®

Engaging you to reimagine chemistry and engineering for a sustainable future!

We believe sustainable and green chemistry innovation holds the key to solving most environmental and human health issues facing our world today.

- Advancing Science
- Advocating for Education
- Accelerating Industry

ACS GCI convenes **companies in the chemical industries to advance the implementation of sustainable and green chemistry and engineering.**

https://www.acs.org/gciroundtables.html gciroundtables@acs.org

16 YEARS of Advancing GC&E
in Pharma and Beyond

ACS GCI Pharmaceutical Roundtable

- **12** Collaboratively developed, high-quality tools & metrics
- **$2.4 Million** given in research grant funding
- Funding of **28+** research programs around the globe
- Leveraged **$1.3 Million** from Federal Agencies
- **41** Symposia organized since 2016
- Supporting travel of **75** professors & **31** students to present research since 2014
- **17** Educational workshops & webinars since 2017
- **80+** Publications resulting from funded research, **1700+** unique daughter citations
- **49** Roundtable authored papers since 2007
- The Peter J. Dunn Award for Green Chemistry & Engineering Impact in the Pharma Established in 2016

- Bridging the gap between academics & industry
- Enabling better decisions about chemical selection process design
- A leading voice for GC&E
- Inspiring and educating the next generation
- Recognizing excellence in GC&E

https://www.acsgcipr.org

ACS Chemistry for Life®

co-produced with: ACS Green Chemistry Institute

Enabling Greener Pharma Manufacturing

Scaling a Photo-Flow Bromination for Belzutifan

FREE Webinar | TODAY at 2pm ET

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THIS ACS WEBINAR WILL BEGIN SHORTLY...

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ACS Chemistry for Life®

Enabling Greener Pharma Manufacturing: Scaling a Photo-Flow Bromination for Belzutifan

John Tucker
Executive Director, Chemical Development, CMC, Neurocrine Biosciences

Cecilia Bottecchia
Senior Scientist, Merck

François Lévesque
Principal Scientist, Merck

Presentation slides are available now! The edited recording will be made available as soon as possible.
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This ACS Webinar is co-produced with ACS Green Chemistry Institute and the ACS Green Chemistry Institute Pharmaceutical Roundtable.

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Membership 2021

ACS Green Chemistry Institute Pharmaceutical Roundtable

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Award Recognition Today

ACS Green Chemistry Institute Pharmaceutical Roundtable

Academic awards are many and focus on novelty and publication

- Holistic (process) strategies are often shunned in favor of specific methodology
- Green chemistry has yet to fully penetrate academia
- Process development is not a discipline taught in academia, but is learned on-the-job through mentorship and experience

Companies may be less likely to share advances in chemistry as the business model does not support publication as a final deliverable

- There is a risk to any disclosure i.e., IP or trade secrets

Academics drive most public acknowledgement of science

- Subsequently, there are few opportunities for recognition of green process chemistry

J. Tucker

acsgcipr.org

Why a Process Green Chemistry Award?

ACS Green Chemistry Institute
Pharmaceutical Roundtable

A phalerist is someone who studies awards

- Dr. Jana Gallus holds a Ph.D. in Economics from the University of Zurich, is a UCLA professor at the Anderson School of Management, and a phalerist of some renown
  - Consider reading her paper entitled "Awards, Honors and Ribbons: Between Fame and Shame."

There are various reasons why people give awards

- To establish a legacy, e.g., Alfred Nobel and the Nobel Awards
- To shape a field and influence the direction that it takes, e.g., The Academy Awards—in a subjective medium, establishes what is considered high quality, influencing the future production of movies

With the Peter J. Dunn Award, the ACS GCIPR seeks to transform the way green process chemistry is viewed, exemplified, measured and acknowledged…for the inspiration of future science.

Recognizing Exemplary Industrial Green Chemistry Innovation

ACS Green Chemistry Institute
Pharmaceutical Roundtable

Peter J. Dunn Award for Green Chemistry and Engineering Impact in the Pharmaceutical Industry

- Established in 2016 to recognize outstanding industrial development or implementation of novel green chemistry and/or engineering in the pharmaceutical industry that demonstrates compelling environmental, safety, cost, and/or efficiency improvements over current technologies at significant scale
- Award consists of a plaque and an invited lecture at the ACS Green Chemistry Institute's Annual Green Chemistry & Engineering Conference (travel reimbursed up to $2,500)
- **Submissions open through Dec 31 each year at acsgcipr.org/awards**

Inspiring Global Green Chemistry

ACS Green Chemistry Institute
Pharmaceutical Roundtable

2022 GCIPR CMO Award for Excellence in Green Chemistry

- **Eligibility specific to Asia —** seeking to inspire the global pharma supply chain
- Recognize outstanding efforts toward pharmaceutical green chemistry as performed by Asian CMO companies in support of research, development and manufacturing demonstrating compelling environmental, safety and/or efficiency improvements.
- Award consists of a plaque and an invited lecture at the ACS Green Chemistry Institute's Annual Green Chemistry & Engineering Conference (travel expenses up to $2,500)
- **Submissions open through Dec 31 at acsgcipr.org/awards**

J. Tucker

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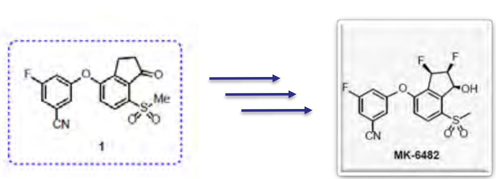
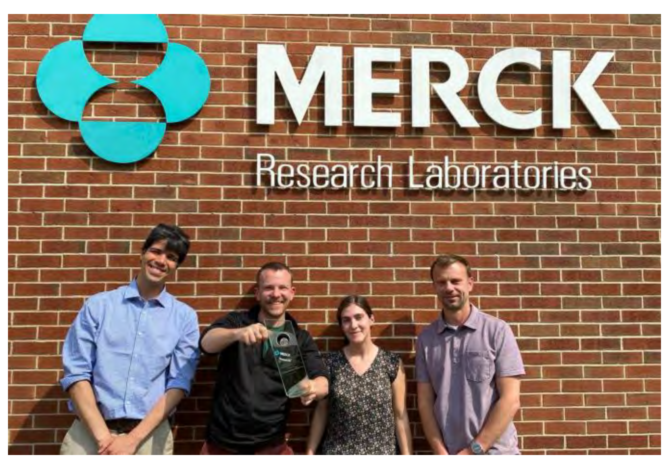
The 2021 Peter J. Dunn Award

Greener Manufacturing of Belzutifan (MK-6482) Featuring a Photo-Flow Bromination

ACS Green Chemistry Institute
Pharmaceutical Roundtable





Presented to:
Stephen Dalby, Ph.D.
Cecilia Bottecchia, Ph.D.
Francois Levesque, Ph.D.
Jonathan McMullen, Ph.D.

2022 Nominations open: www.acsgcipr.org/awards

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ACS
Green Chemistry
Webinar

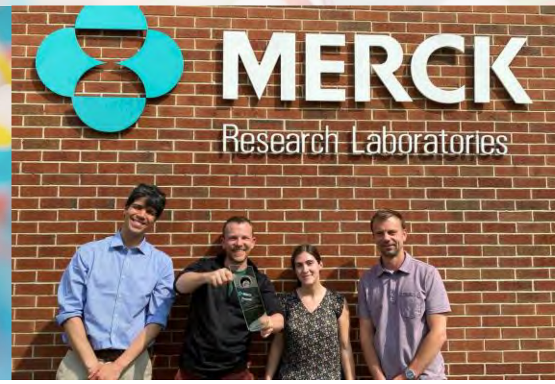
Enabling Greener Pharma Manufacturing

Scaling a Photo-Flow Bromination for Belzutifan

Cecilia Bottecchia, François Lévesque

Stephen Dalby & Jon McMullen

Merck Process R&D



August 12th, 2021

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We follow the science

We believe it is our responsibility to deliver healthier tomorrows through our vaccines, medications and animal health products that can help patients and communities around the world.

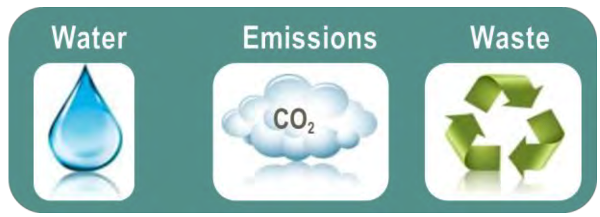
Core growth drivers:
Oncology
Vaccines
Hospital, specialty and chronic care
COVID-19

Animal Health:
Companion animal
Livestock

Commitment to Green & Sustainable Manufacturing

"Our passion to save and improve lives extends to our commitment to protecting and sustaining the environment."

"We will minimize our environmental footprint through scientific innovation."



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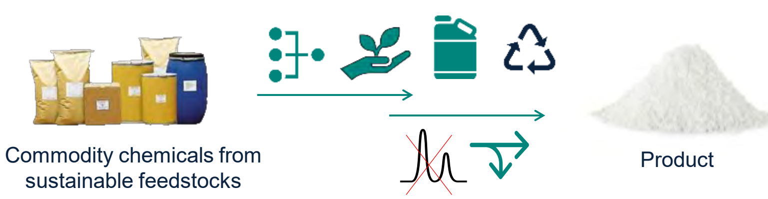
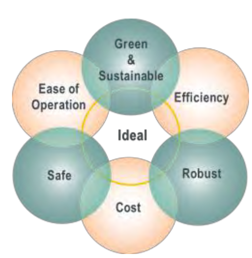
Commercial Process Development Mission

Our aspirational goal
Develop idealized manufacturing processes



How to get there
Innovations in process chemistry

- Green & Sustainable processes *by design*
- Scientific creativity – inventing solutions to solve problems
- Innovative technologies for future manufacturing



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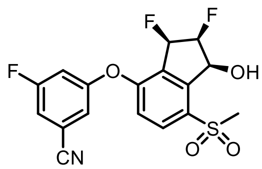
Belzutifan



- Oral HIF-2α inhibitor for treatment of renal cell carcinoma & non-RCC tumors
- Asset from acquisition of Peloton Therapeutics in mid 2019
- Awarded breakthrough status designation by FDA

Bringing Belzutifan to patients on a highly accelerated timeline

- Commercial process development & validation in <18 months
- Strategic focus for process re-design
- Commitment to Green & Sustainable goals

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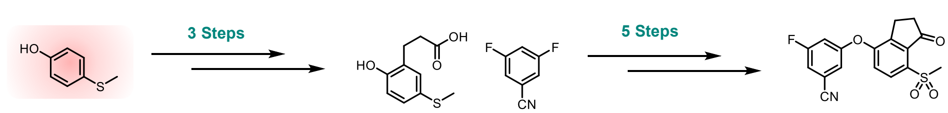
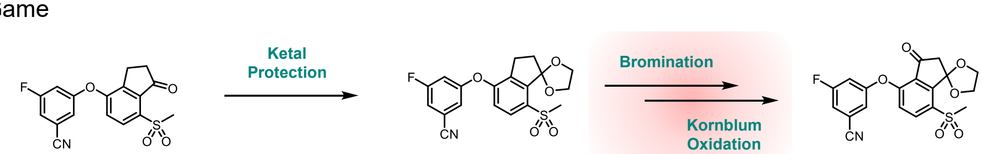
Inherited Clinical Supply Process

Indanone Core Synthesis (RSM)

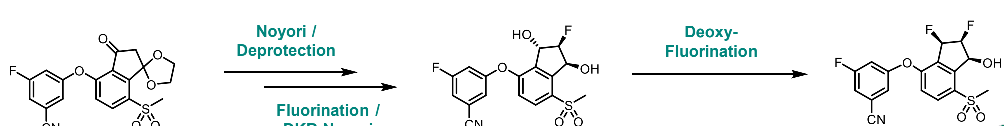
e



Mid-Game



End-Game



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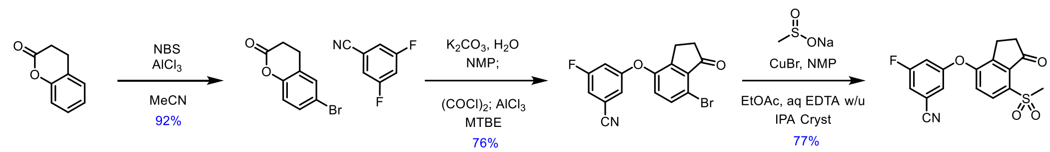
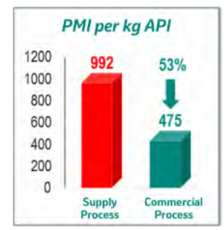
Delivering a Greener Commercial Process

Steps	Yield	PMI
↓ 50%	↑ 62%	↓ 53%

Indanone Core Synthesis (RSM) - **Develop concise new route**



- Dihydrocoumarin as commodity RM
- 4 step process, 3 crystallizations
- Rapidly developed for 1MT campaign in ~4 months



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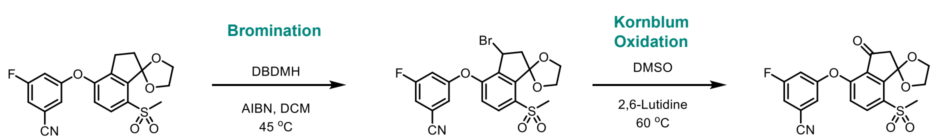
Bromination / Oxidation – The Major Issue

The Problem



- Batch instability risk
- Hazardous Reagent
- Chlorinated solvent

Mutagenic –
Handling safety

- Thermal safety hazard
- Me_2S byproduct – Stench
- Non-preferred solvent

Objectives

- Safe, Robust & drastically Greener conditions for both steps
- Single solvent through process & avoid bromide handling

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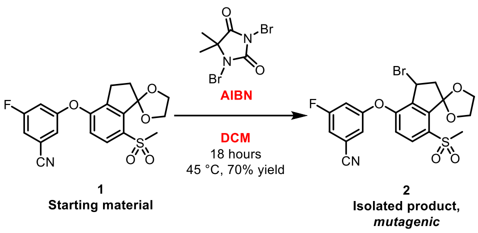
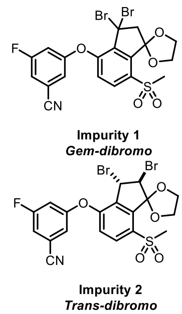
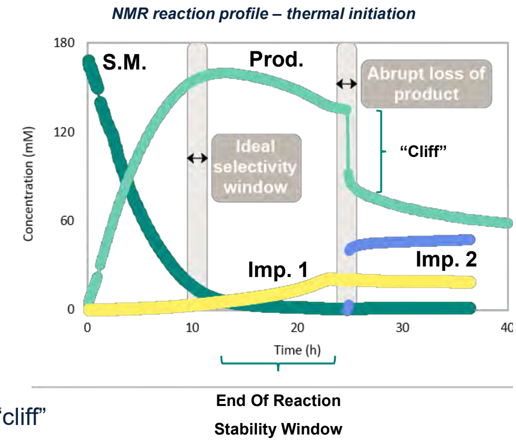
Challenges with radical Bromination







- Serious robustness liability
  - Unstable end of reaction mixture – short time window before "cliff"
  - Elevated temp shrinks stability window 45°C

Are there better ways to make this radical?

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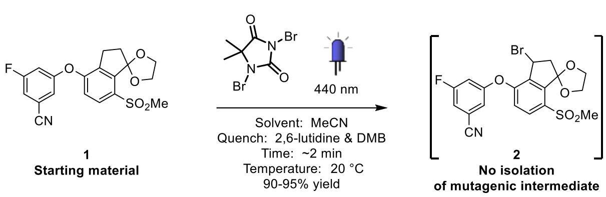
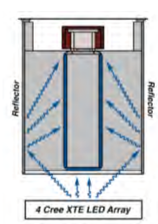
Photobromination route: Proof of concept



Photochemistry identified as an enabling technology for this reaction

- Replaced chlorinated solvent with MeCN
- Ambient temp - Improved reaction selectivity and stability 20°C
- Initiation successful at different wavelength (312 – 520 nm)

Small-scale batch



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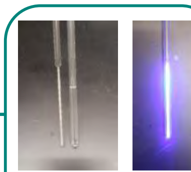
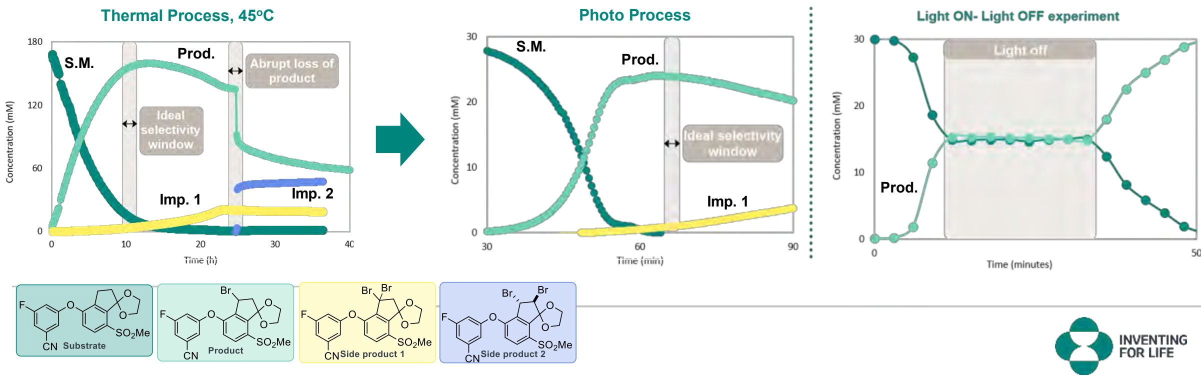
Understanding the benefits of photochemistry

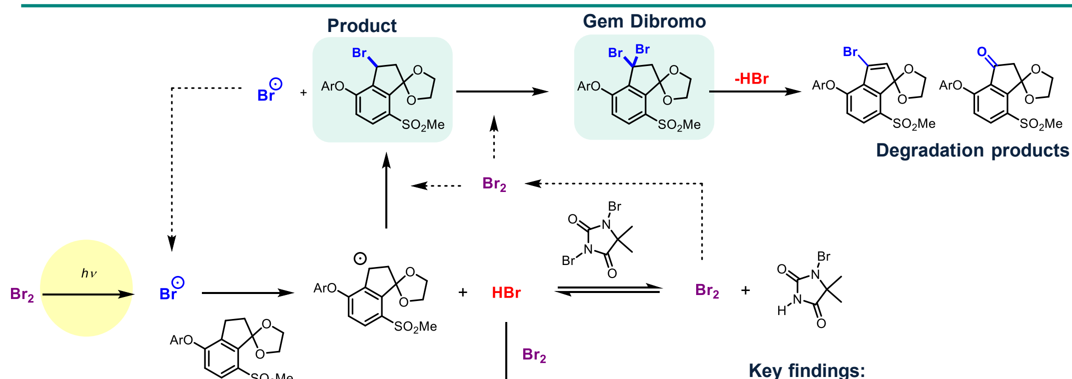


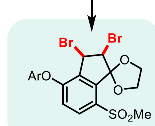
Reaction monitoring via LED-NMR

- Key reaction insight achieved by monitoring via photo-NMR.
  - Photochemistry is not a panacea for robustness but pushes failure cliff far from operating conditions.
  - Reaction can be turned on and off with the flick of a switch.



Photochemical bromination – Mechanistic considerations





Acid catalyzed Side products

Dibromodimethylhydantoin (DBDMH)

- 2 “Br+” equiv. of different bond strength
- Reacts with HBr to generate Br_2
- Acts as Br_2 reservoir and HBr scavenger

Key findings:

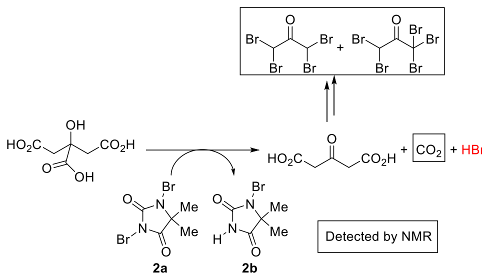
- Radical mechanism inherently generates acid
- By-product formation is likely acid-catalyzed mechanism (potentially auto-catalytic)
- pH drop deriving from HBr accumulation responsible for instability cliff

With this understanding, process development focused on understanding key reaction sensitivities and scale-up challenges.

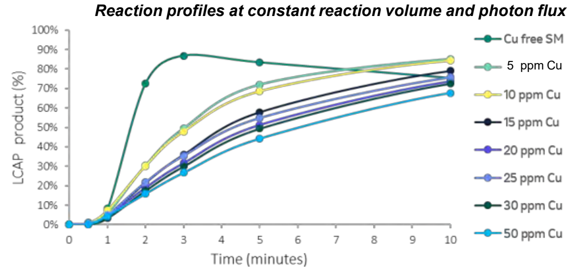
Process development highlights: sensitivity to starting material quality

Understanding the impact of upstream processing on starting material quality is critical for process robustness.

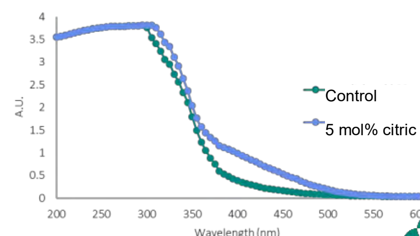
1. Colored impurities affect initial reaction Abs → carbon treatment implemented to normalize Abs
2. Identified residual copper as strong inhibitor
   - Numerous copper chelator screens were performed, leading to citric acid as a hit.



Reaction profiles at constant reaction volume and photon flux



UV/Vis Spectrum for starting material stream



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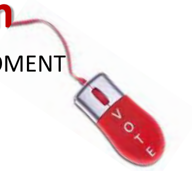
Audience Survey Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT



In your opinion, what is the biggest challenge in scaling up photochemistry?

- Resistance to change – implementing new technology takes time
- Energy and cost requirements compared to thermal processes
- Availability of powerful light sources
- Limited light penetration through a solution
- Other (Tell us more in the chat!)

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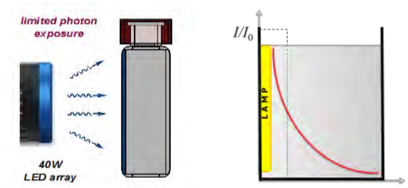
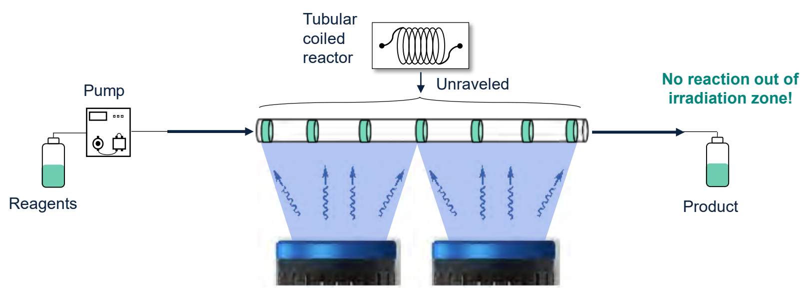
The grand challenge: scaling up photochemistry

Ideal reactor requirements:

- Powerful LEDs and a reactor design that limits "dark zones."
- Tight control of reaction time.
- High heat transfer rates to minimize reaction stability risk.



These are all drivers to use flow chemistry in production, but how can we transfer from batch to flow?



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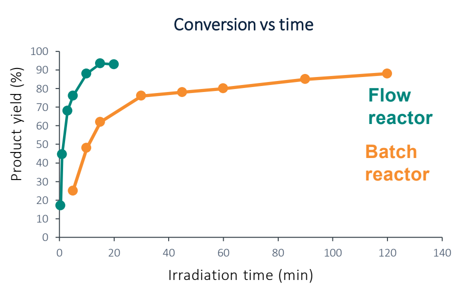
Photon stoichiometry: a key parameter across scales



Why are batch vs flow reaction profiles so different?
Reactors vary in terms of:

* ***Volume*** * ***Surface area***
* ***Geometry*** * ***Light source***

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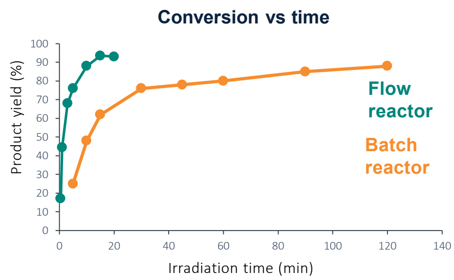
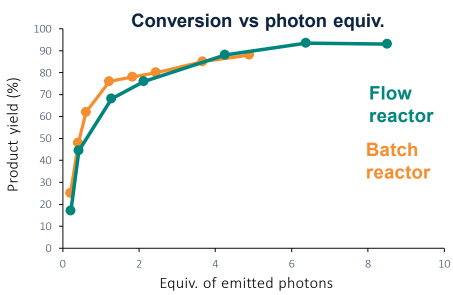
Photon stoichiometry: a key parameter across scales





Why are batch vs flow reaction profiles so different?
Reactors vary in terms of:

- ***Volume***
- ***Surface area***
- ***Geometry***
- ***Light source***

Photon stoichiometry
can be used to

- ***Predict reaction time across reactors***
- ***Inform on reactor design/efficiency***

Bonfield, H.E., Lévesque, F. *et al.*. *Nat Commun* **11,** 804 (2020).
Corcoran, E. B.; McMullen, J. P.; Lévesque *et al.*, ACIE, (2020), DOI: 10.1002/anie.201915412.

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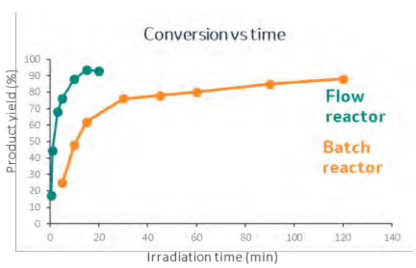
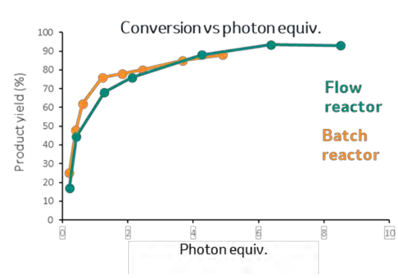
Photon stoichiometry: a key parameter across scales

- Demonstrated photon equivalents as the scaling factor

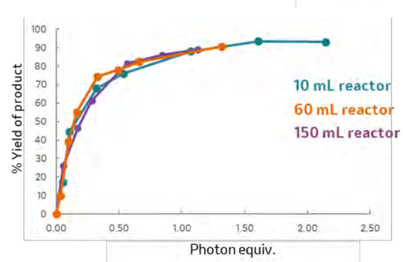
$$Photon\ equiv. = \frac{moles\ of\ photons}{moles\ of\ S.M.}$$



LED power & efficiency



Scale-up



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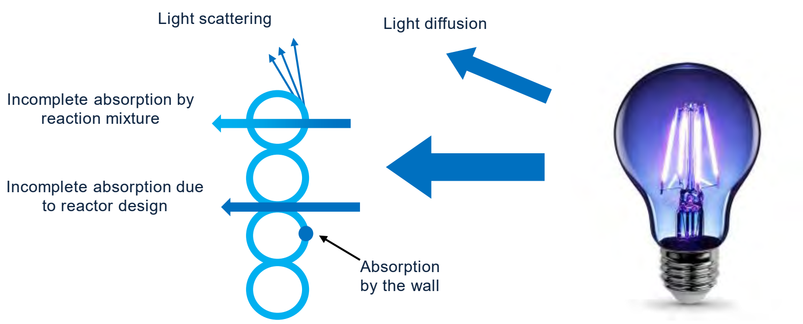
Reactor characterization

Not all photons from the light source enter the reactor or interact with the photocatalyst!



Due to similarities of reactor design and light source, emitted photons was used to estimate reaction time

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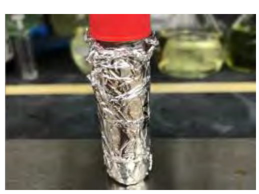
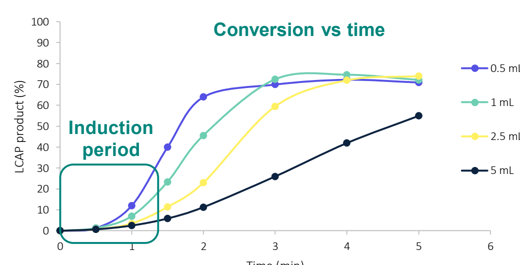
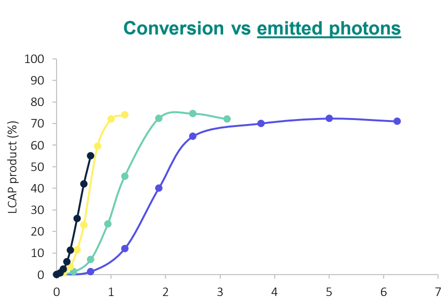
Photochemical bromination – Photon stoichiometry

0.5 mL, 1 mL, 2.5 mL, 5 mL



Foil = light absorption from bottom





Absorbing species is formed during reaction (induction period):

Abs changes over time!

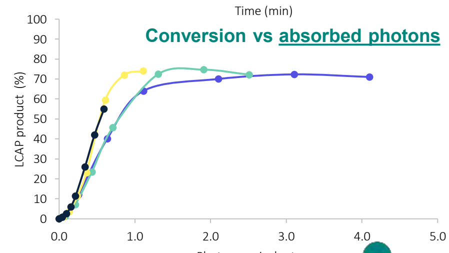


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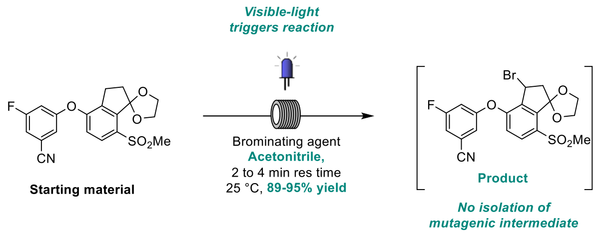
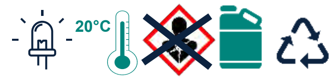
Photo-flow bromination



Photochemical initiation

Merck process



Higher end of reaction stability

Improved control in continuous-flow

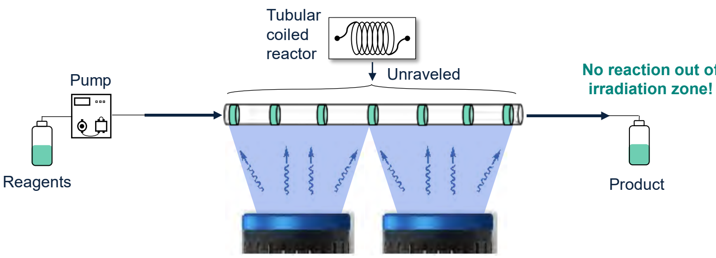


Photo-flow selected as manufacturing route

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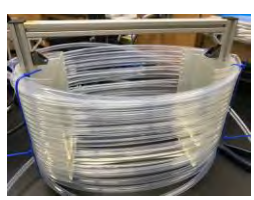
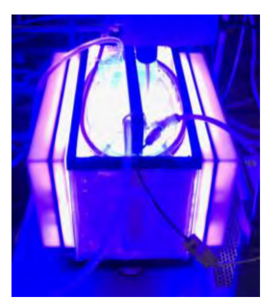
First kilo scale demonstration

Light source

Reactor build



Small but mighty!



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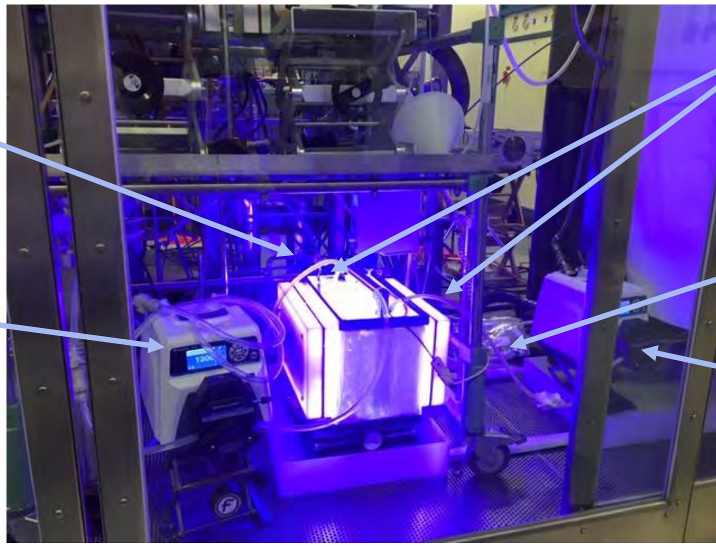
Photochemical bromination – Plug Flow Reactor



PFR reactor (890ml)

Peristaltic pump recirculating water through heat exchanger

What you can't see:
- Fish tank is filled with water
- Collection vessel
- Sampling tube
- HBr sensor
- Scrubber

Light Panels (2 total)
- 500 W input power (each)
- 150 W output (each)
- Water cooled
- Under N_2 to prevent intrusion of solvents and condensation

Thermocouples monitoring
- Inlet
- Outlet
- LED panels
- Water

Peristaltic pump for reaction mixture

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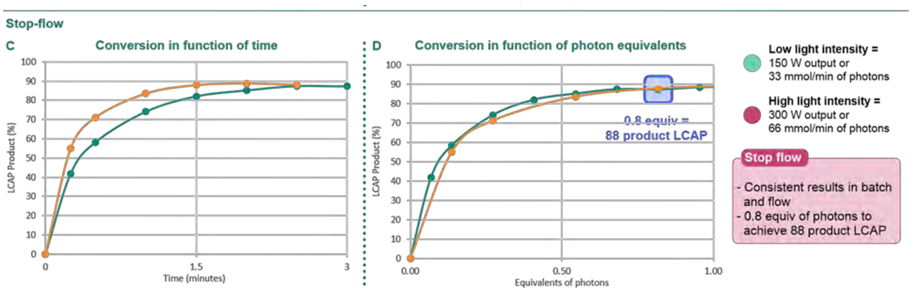
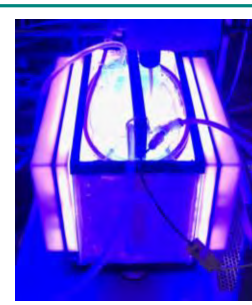
Reactor Characterization – Stop Flow Approach





No background reaction is observed in the absence of light.

Reactor was emptied and the reaction mixture was mixed prior to each illumination period.

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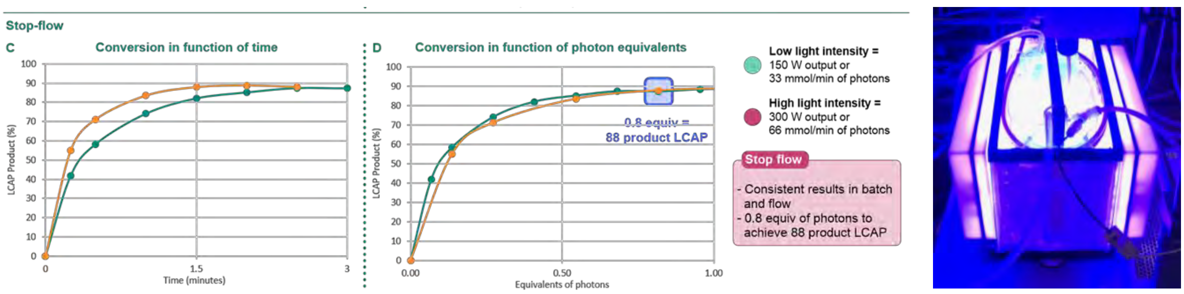
Reactor Characterization – Stop Flow Approach



By using a stop flow approach, we were able to generate reaction profile with 1 L (50g SM) of stock solution.

Collecting the same data at steady state for each conditions would have required 21 L (>1kg SM) !

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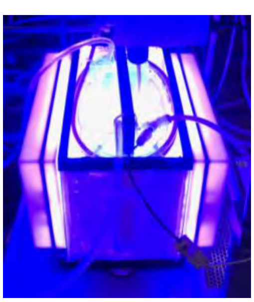
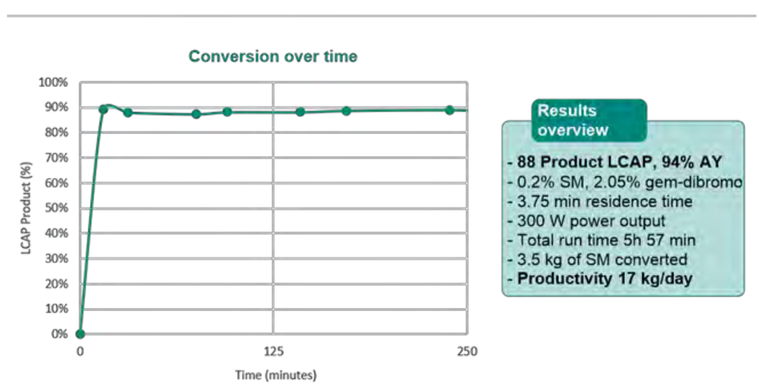
Scale-Up in Flow





Good agreement between the stop flow and continuous flow.

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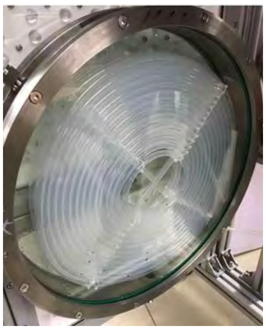
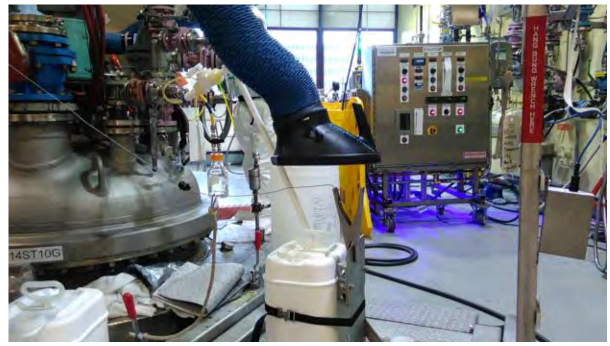
Scaling up to the pilot plant

Working closely with pilot plant staff and external capabilities colleagues, a modular photoreactor skid with tunable LED power was developed which interfaced well with existing batch equipment.





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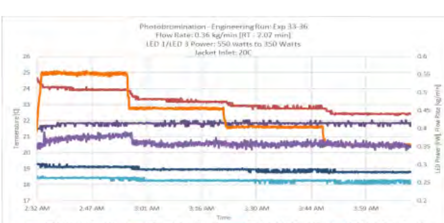
Production scale system – generating kilos and knowledge

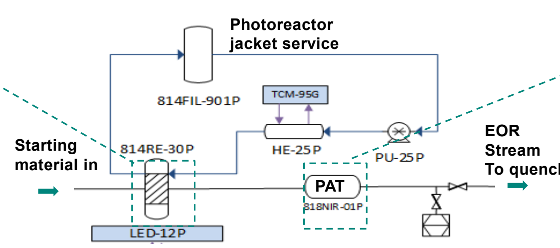
- Pilot unit was designed with data-rich experimentation in mind
- Engineering batch explored ~80 different operating conditions.

Engineering Design Space

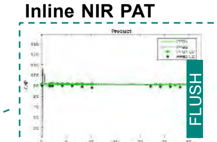
Factor	Lower Bound	Upper Bound
Time (min)	1	3
Power (W)	1000	1600
Temperature (°C)	15	35

Sensors to monitor temperature, flow, pressure





Inline NIR PAT



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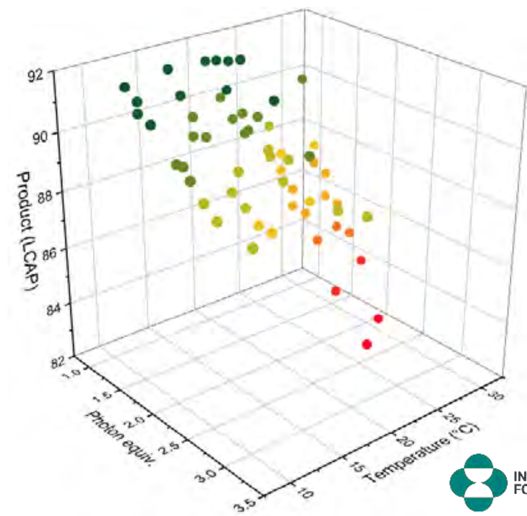
Pilot plant results

- Demonstrated quality of material maintained over wide range of conditions
- Verified photon equivalence as scale up factor
- Identified conditions for pilot plant batches (2 x 50 kg each)

Engineering Design Space



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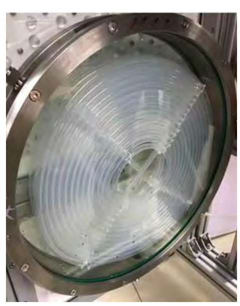
Pilot plant campaign in Rahway



- First photochemical reaction in our pilot plant
- 3x multi-kg batches, average 93% product yield
- Productivity of 38 kg/day
- Wide range of robustness conditions identified

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API and Process qualification campaigns

- Manufacturing train: 8 units in series
- GMP-qualified
- Productivity of 149 kg/day
- > 1 MT produced, > 94% average yield

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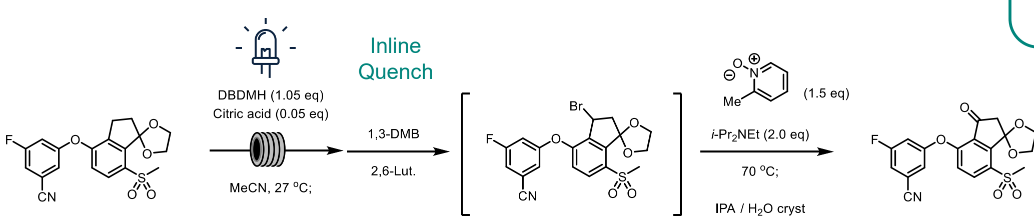
Bromination / Oxidation – The Solution

Yield ↑ 22% | PMI ↓ 72%



75%
99 LCAP
98 wt%

Stable stream

No Isolation

- Robust & Reproducible
- HTHM -> Light!
- Non-chlorinated solvent

- Intrinsically Safe
- Benign oxidant - No Stench
- Direct crystallization

- Single solvent through process with direct isolation
- Robust and safe to operate with no stench
- Removed 2 x aqueous workups

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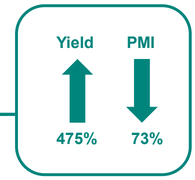
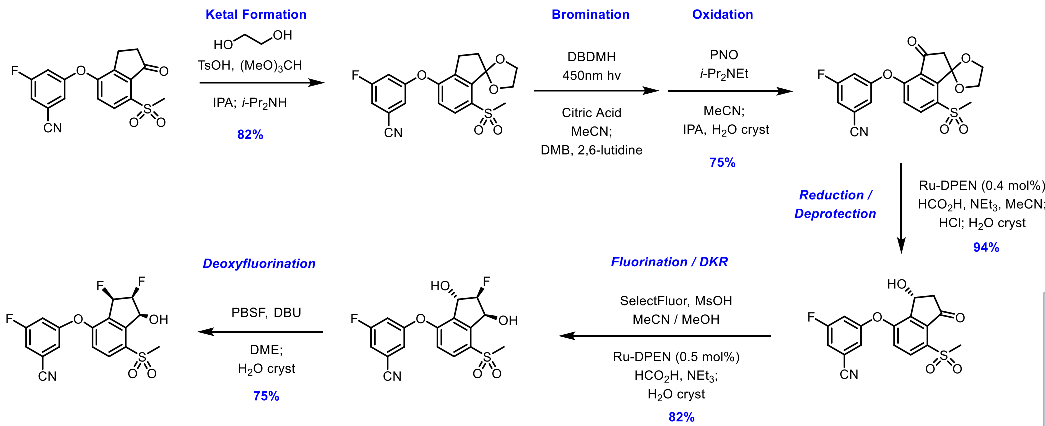
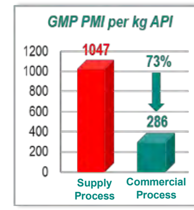
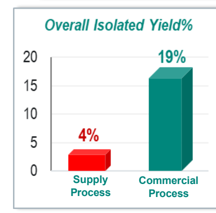
Delivering a Greener Commercial Process – GMP Pocket









- Single solvent through-processes with direct isolations for all steps – no aqueous workups!
- 5/6 steps using MeCN – solvent recycling at commercial vendor
- Significant efficiency gains & waste reduction

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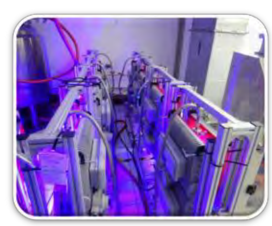
Conclusions



- Significant PMI reduction and sustainability gains for belzutifan process
- First photo-flow process for commercial manufacturing at Merck
- Capability established for future more efficient, robust and greener processes
- Keys to delivering on Green & Sustainable goals
  - Problem solving through best science
  - Risk-taking to innovate on critical path
  - Pre-investment in future technologies

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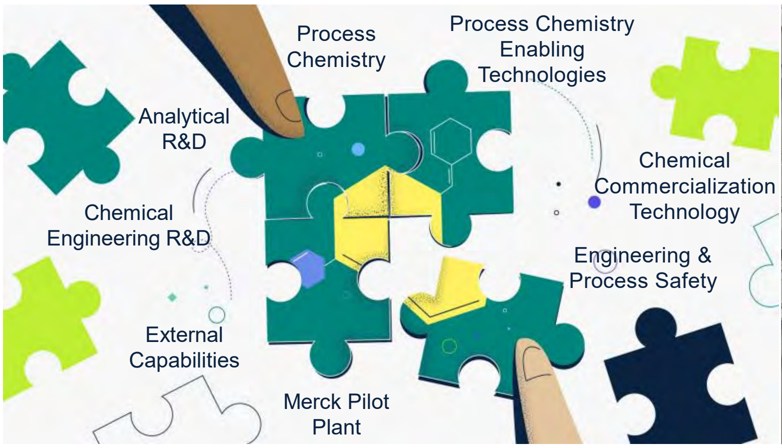
Collaboration – On Behalf of the Merck Team



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Scaling a Photo-Flow Bromination for Belzutifan

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Enabling Greener Pharma Manufacturing: Scaling a Photo-Flow Bromination for Belzutifan

John Tucker
Executive Director, Chemical Development, CMC, Neurocrine Biosciences

Cecilia Bottecchia
Senior Scientist, Merck

François Lévesque
Principal Scientist, Merck

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Ponente: Dra. Leticia Myriam Torres Guerra, Centro de Investigación en Materiales Avanzados S.C. (CIMAV)
Moderadora: Dra. Maria del Jesus Rosales Hoz, Cinvestav y Sociedad Quimica de México

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- El uso de un co-actalizador para mejorar el transporte de cargas y lograr una mayor actividad fotocatalítica

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