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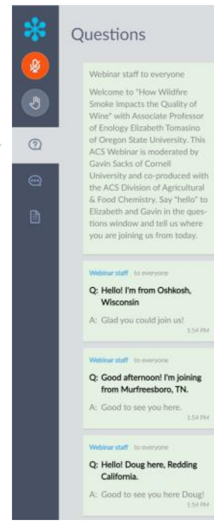

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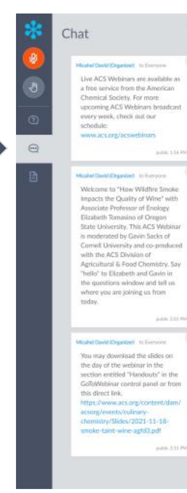

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Sam Jones, PhD
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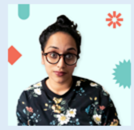

Deboki Chakravarti, PhD
Science Writer & Co-Host

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https://chemidp.acs.org

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Career Consultant Directory

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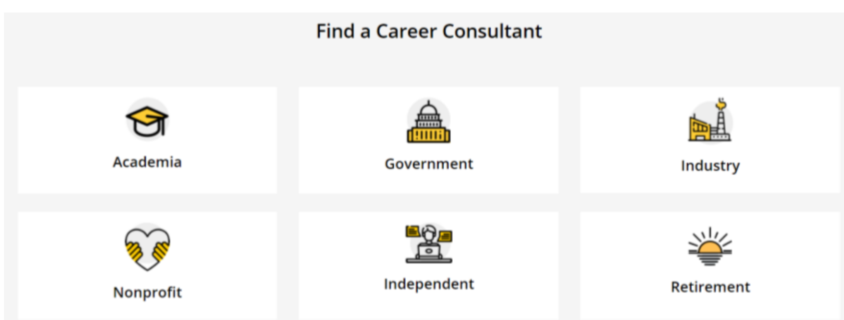

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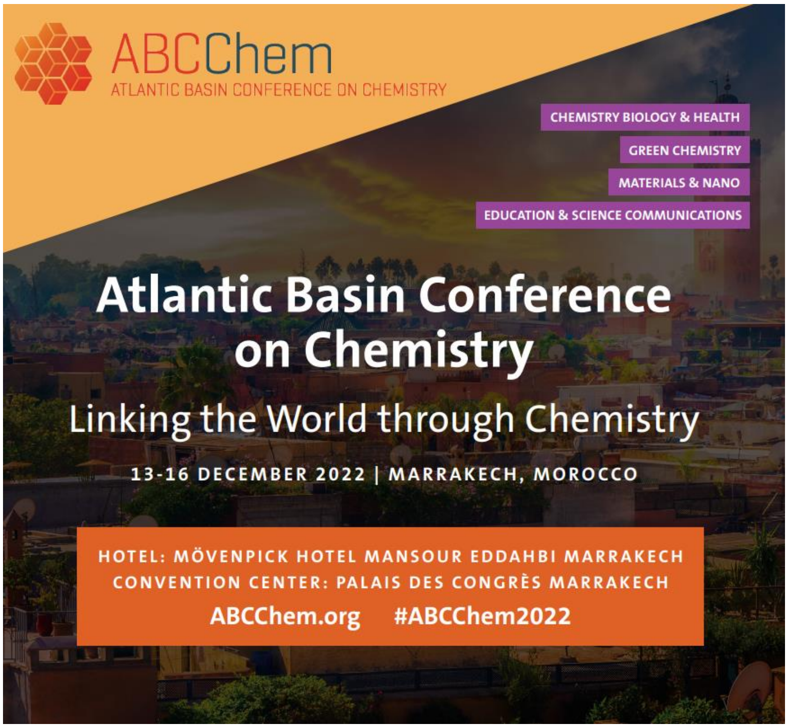

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ACS Career Resources

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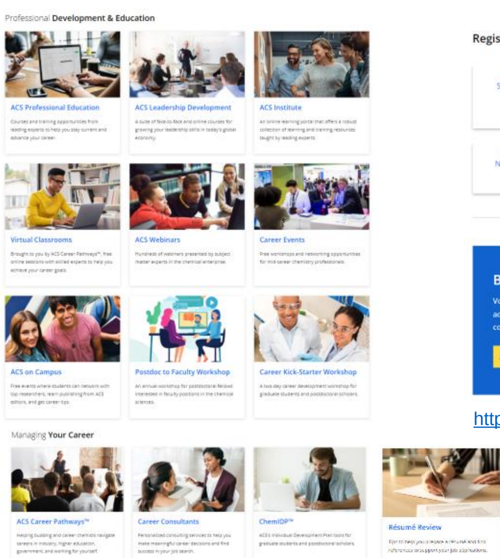

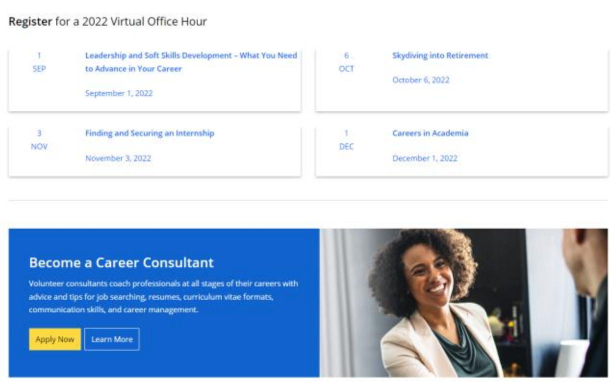

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Please do not hesitate to reach out to the Office of DEIR at diversity@acs.org

https://fs7.formsite.com/acsdiversity/ACSMemberFeedback/index.html

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ACS Scholar Adunoluwa Obisesan

BS, Massachusetts Institute of Technology, June 2021
(Chemical-biological Engineering, Computer Science & Molecular Biology)

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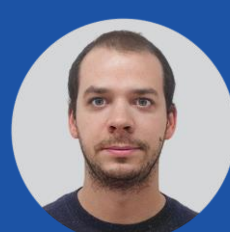
From Wood Pulp to a Candidate Medicine:

Green Manufacturing Technologies Enable Production of Nemtabrutinib

MIKE DI MASO, PhD
Associate Principal Scientist, Merck



BEN TURNBULL, PhD
Associate Principal Scientist, Merck

PHILIPPA PAYNE, PhD
Senior Research Scientist, Gilead Sciences and Co-Chair, ACS GCI Pharmaceutical Roundtable

This ACS Webinar® is co-produced with the ACS Green Chemistry Pharmaceutical Roundtable

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Established in 2005, the ACS GCIPR is an organization dedicated to catalyzing the integration of green chemistry and engineering in the Pharmaceutical industry

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ACS Green Chemistry Institute Chemistry for Life

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Global Collaboration

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Established in 2016

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Pfizer

Bruce Lipshutz & Sachin Handa
UCSB, University of Louisville

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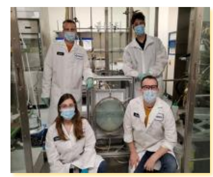

Stephen Dalby
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MERCK INVENTING FOR LIFE

2023 Nominations open Fall 2023: https://www.acsgcipr.org/awards/

2022 Peter J. Dunn Award

for Green Chemistry & Engineering Impact
in the Pharmaceutical Industry

ACS Green Chemistry Institute
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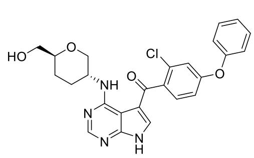
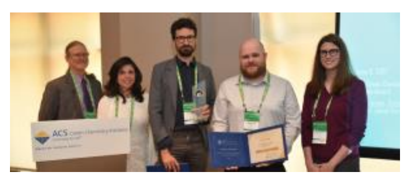
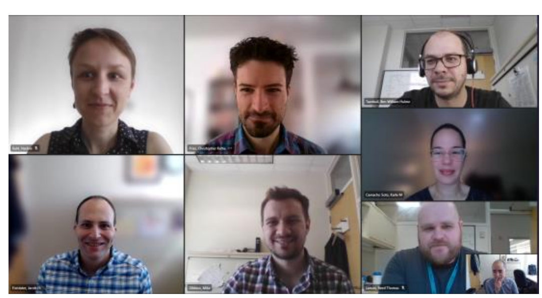
From wood pulp to a candidate medicine: Green manufacturing technologies enable the production of investigational leukemia drug nemtabrutinib from a biorenewable commodity material."

- Karla Camacho Soto
- Mike DiMaso
- Jacob Forstater
- Nadine Kuhl
- Reed Larson
- Chris Prier
- Ben Turnbull



Nemtabrutinib
MK-1026





MERCK INVENTING FOR LIFE

INVENTING FOR LIFE

From Wood Pulp to a Candidate Medicine: Green Manufacturing Technologies Enable Production of Nemtabrutinib

presented by Mike Di Maso and Ben Turnbull

Process Research and Development, Merck & Co., Inc., Kenilworth, NJ, USA

September 8, 2022

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Merck's Mission

To translate breakthroughs in fundamental scientific research into meaningful new therapeutics and vaccines that improve and extend the lives of people, worldwide.

Chemistry is Central to Merck's mission

P Public

INVENTING FOR LIFE

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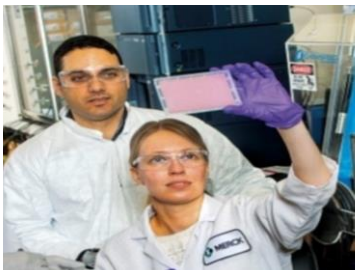
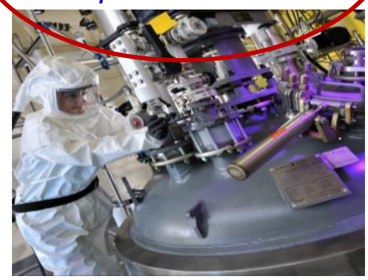
Process Research is Central to Merck’s Mission

Discovery	Early Development	Late Development
Invent best molecules for future Merck products	*Supply API to accelerate program development*	***‘Ideal Process’*** *Best chemistry and most **sustainable process** at launch*





Improve human health and well-being around the world through innovations in synthetic chemistry and process development

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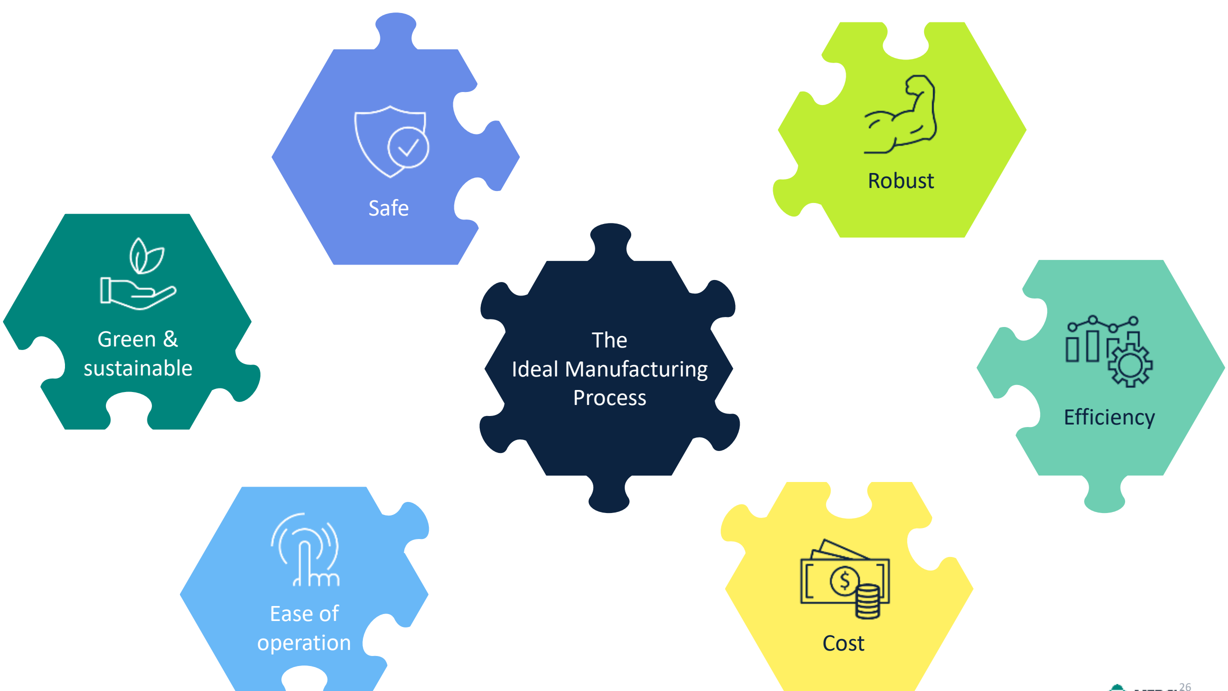

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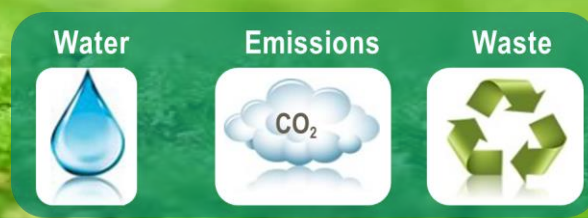
Merck's Commitment to Environmental Sustainability

We are committed to the health, safety and well-being not only of the people who take our medicines, but also to our neighbors in the communities where we live & work.

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

"Environmental sustainability is a corporate commitment that prepares us to operate in a world of declining natural resources and increased regulation."

"We will reduce costs and our environmental footprint through ***scientific innovation****."*



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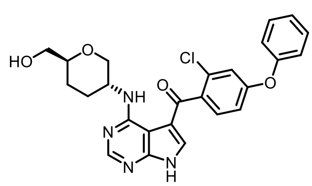
MK-1026 – A Reversible BTK Inhibitor



MK-1026

ARQULE®

- Indication: Treatment of hematologic malignancies such as chronic lymphocytic leukemia (CLL) and Non-Hodgkin's Lymphoma
- Arqule acquired in January 2020
- Mechanism: ***Reversible*** inhibitor of Bruton's tyrosine kinase (BTK)
- Clinical phase: Phase 2

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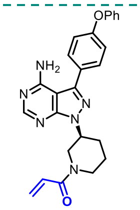
A reversible BTK Inhibitor to Address Treatment Resistance

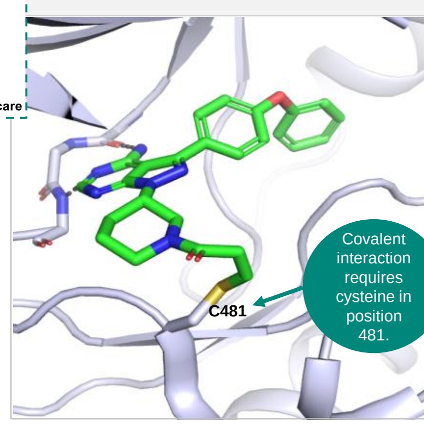
- Treatment of hematologic malignancies such as chronic lymphocytic leukemia (CLL) and Non-Hodgkin's Lymphoma



Ibrutinib, current standard of care

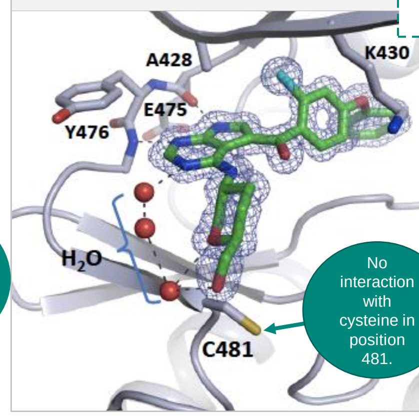
Binding mode of **ibrutinib** with BTK

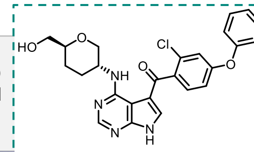
Irreversible BTK inhibitors covalently bind to cysteine in position 481. A **cysteine to serine mutation** (C481S) prevents this interaction.



Crystal structure of **MK-1026** with BTK

MK-1026 was **specifically designed** to inhibit BTK regardless of the amino acid present in position 481





MK-1026

S. D. Reiff et al. *Cancer Discovery* **2018**, 1300.

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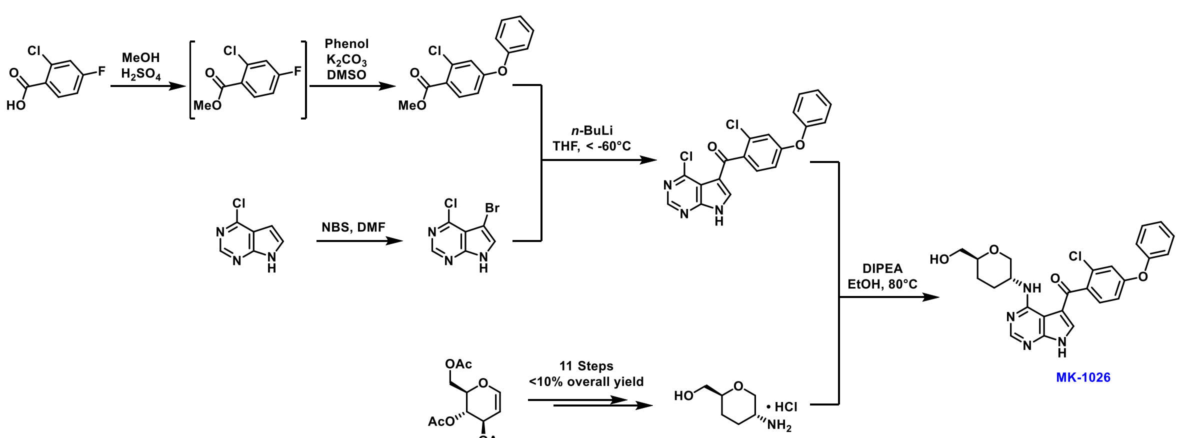
MK-1026 – Synthetic Chemistry Priorities



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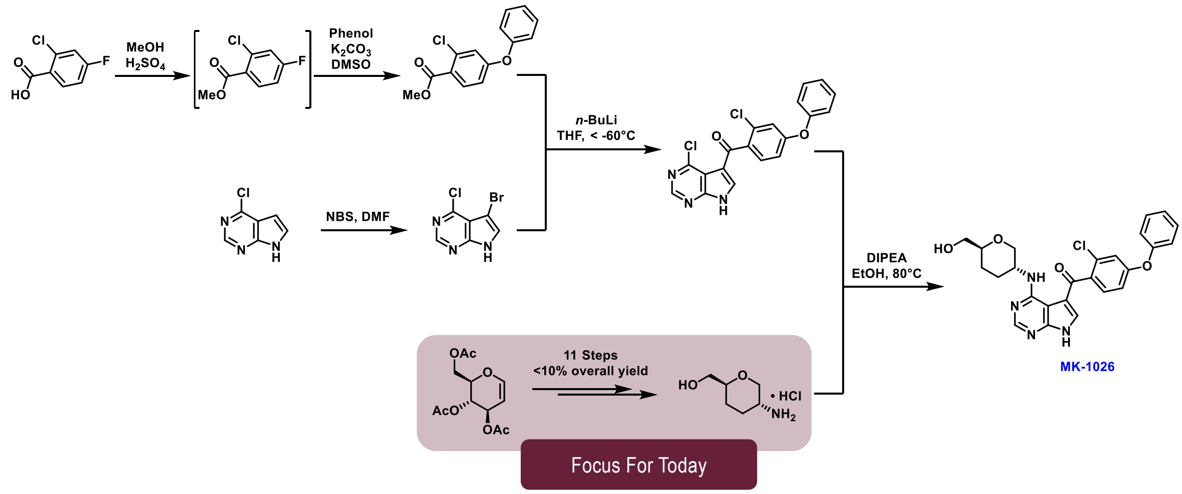
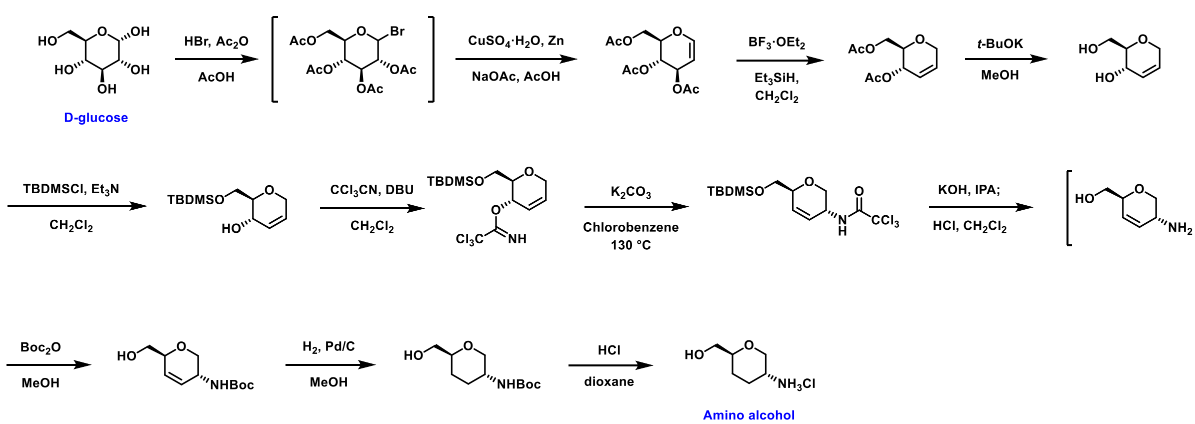
MK-1026 – Synthetic Chemistry Priorities



Develop a more efficient synthesis to the amino alcohol fragment.

Public

Original Amino Alcohol Synthesis requires 11 Steps



H.S. Overkleeft, *et al. Eur J. Org. Chem.* **2003**, 2418 [32]

Public

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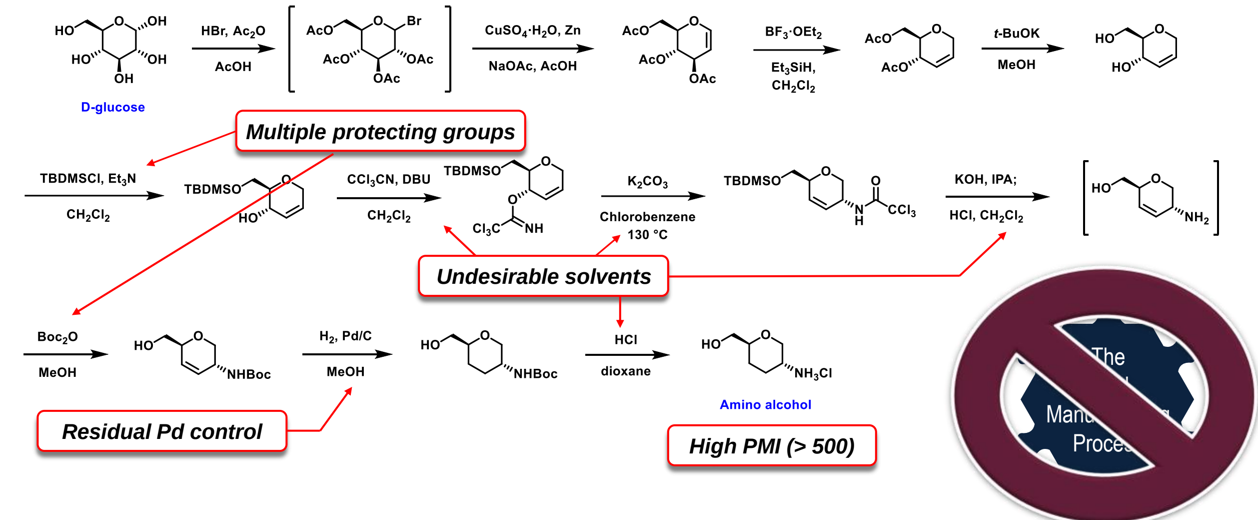

H.S. Overkleeft, *et al. Eur J. Org. Chem.* **2003**, 2418

Public

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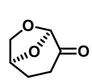
Inspiration from a Bio-renewable Solvent



Cyrene
(Dihydrolevoglucosenone)

Renewable Feedstock

- Synthesized from biomass
- Applications:
  - Feedstock for fine chemicals and polymers
  - Solvent, alternative to NMP and DMF
- Current production volume: 50 t/year (Circa Group)

J. E. Camp, *ChemSusChem* **2018**, *11*, 3048; https://www.circagroup.com.au/cyrene

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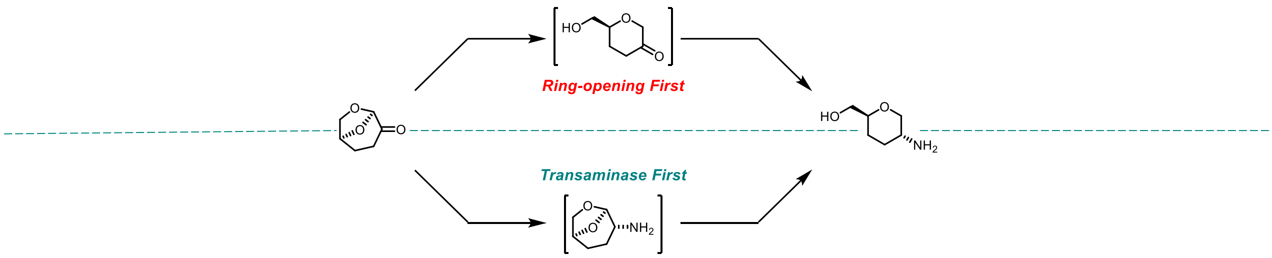
Routes Investigated from Cyrene to Amino Alcohol



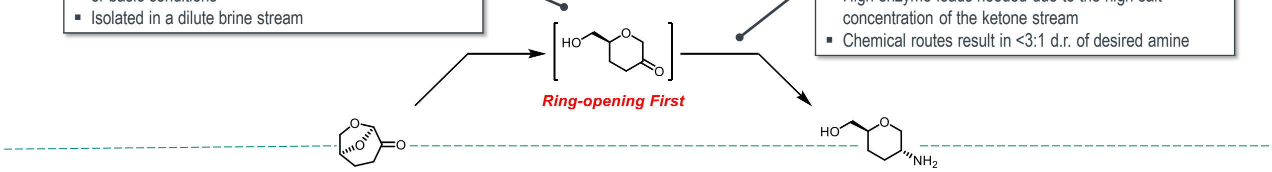
Routes Investigated from Cyrene to Amino Alcohol

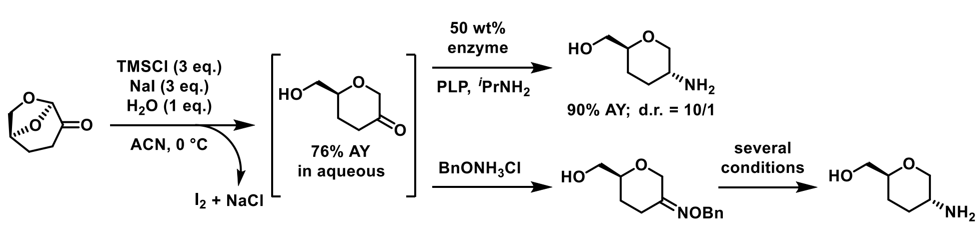
Ketone Stability

- Intermediate unstable in end-of-reaction stream, neat, or basic conditions
- Isolated in a dilute brine stream

Transamination/Reductive Amination

- Enzyme evolution complicated by ketone instability
- High enzyme loads needed due to the high salt concentration of the ketone stream
- Chemical routes result in <3:1 d.r. of desired amine





A. R. Tagirov, *Russian J. Org. Chem.* **2015**, 51, 569.

Routes Investigated from Cyrene to Amino Alcohol

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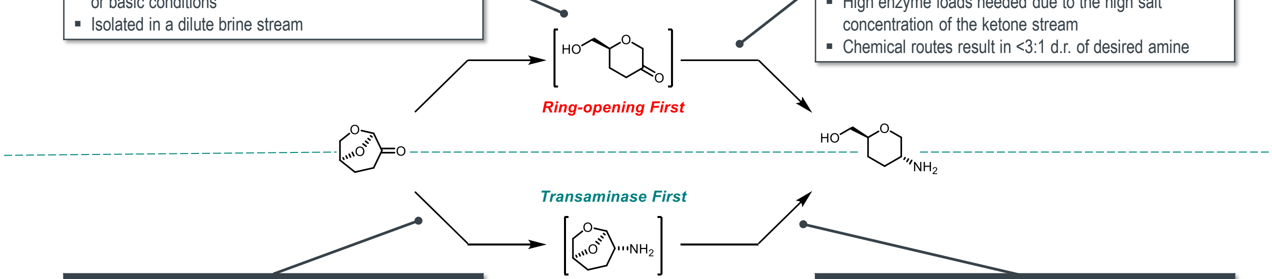

Transamination
- Enzyme evolution using a commodity chemical
- Access to stable, crystalline amine salts with high d.r.

Acetal-Opening
- POC obtained early with Bn-protected cyrene amine
- Can we develop protecting group free strategy?

"Transaminase first" route selected for development

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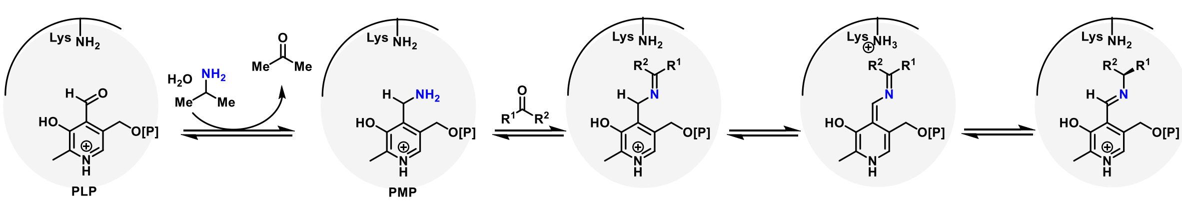
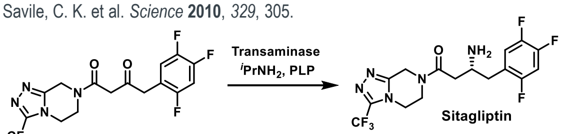
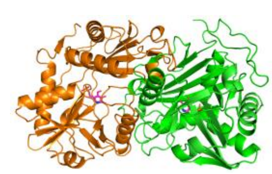
Transamination – A Powerful Tool for API Manufacturing at Merck

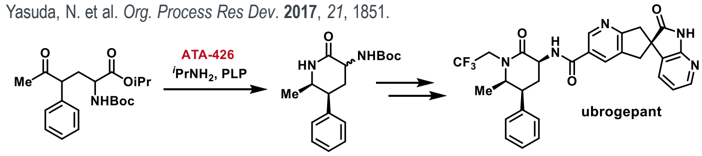


Savile, C. K. et al. *Science* **2010**, *329*, 305.





Yasuda, N. et al. *Org. Process Res Dev.* **2017**, *21*, 1851.



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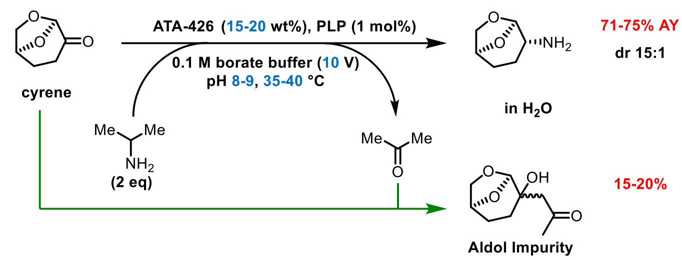
Transamination of Cyrene

- **ATA-426** performs the transamination of cyrene favoring desired isomer (15:1 dr)
- Acetone byproduct generates significant quantities of aldol byproducts (15-20%)



- **ATA-426** is available from CODEXIS

Public

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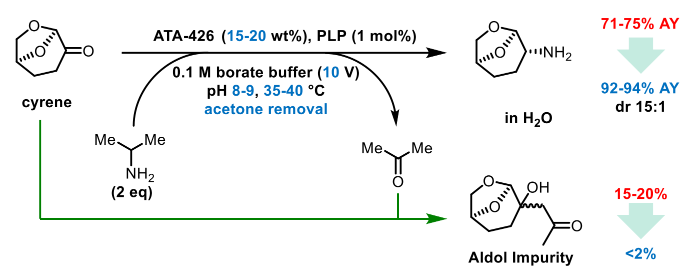
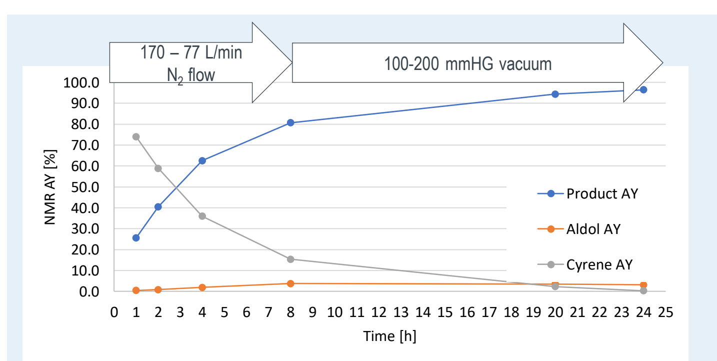
Transamination of Cyrene

- **ATA-426** performs the transamination of cyrene favoring desired isomer (15:1 dr)
- Acetone byproduct generates significant quantities of aldol byproducts (15-20%)
- Combination of **N_2 sweep and vacuum** controls aldol impurity to <2%, enables cyrene amine yield >90%



- Challenging engineering controls
- **Isolation** of cyrene amine from aqueous stream is very challenging
- **Protein removal** is cumbersome



Public

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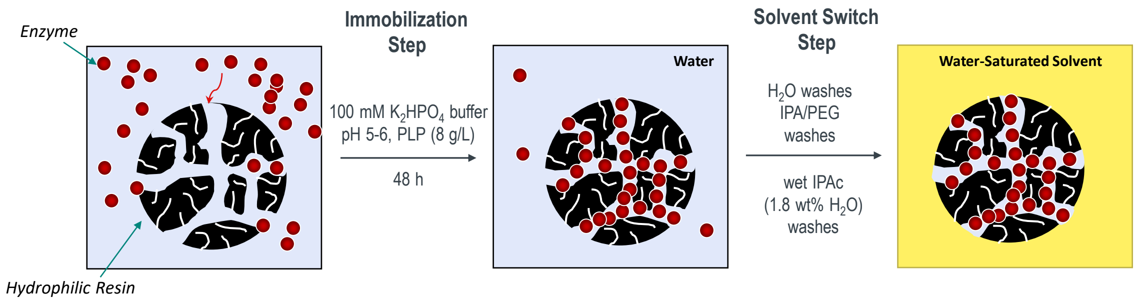
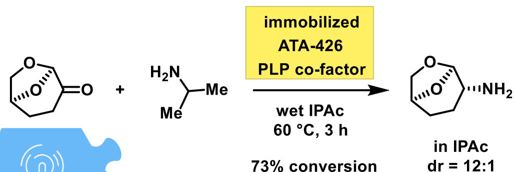
Enzyme Immobilization by Adsorption enables Reaction in Organic Solvents





- Immobilized on Diaion HP2MGL (hydrophilic methacrylate resin)
- No product extraction from aqueous required
- Immobilized enzyme is easily removed from the reaction
- Aldol Impurity <4% GCAP without Acetone removal
- Possibility to run the reaction as a continuous process

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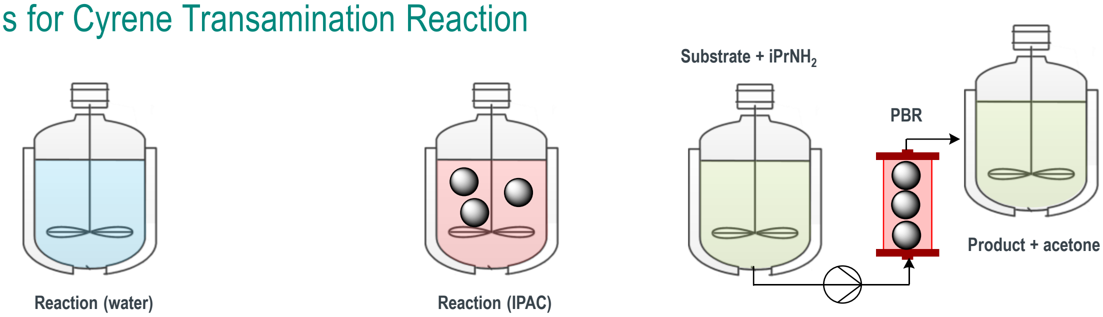
Options for Cyrene Transamination Reaction



Aqueous Reaction	Immobilized Enzyme - Batch Reaction	Immobilized Enzyme - Packed Bed Reactor
▪ Acetone removal (N_2 stream, vacuum) poses challenges for scale-up ▪ Requires in situ pH adjustment ▪ Challenging isolation of water-soluble product ▪ Challenging protein removal	▪ Simplified isolation from an organic stream ▪ Lower aldol formation (<4%) ▪ No need to remove acetone ▪ Multiple unit operations to immobilize enzyme and condition resin, risks on scale	▪ Reduced handling of resin by conditioning and reaction in a single vessel ▪ Washing/conditioning of resin more consistent ▪ Improved reaction efficiency (higher enzyme concentration vs. substrate in column)

Selected immobilized enzyme / flow process for development

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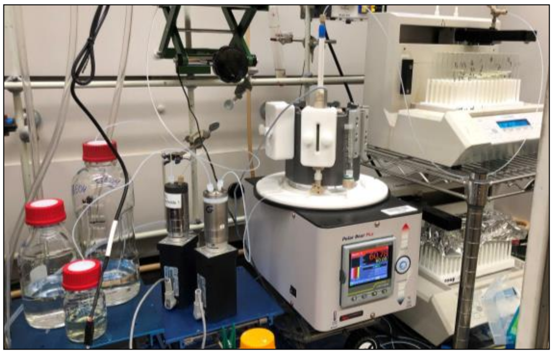
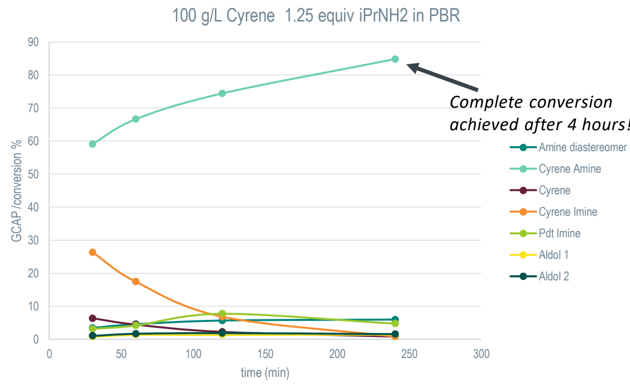
Initial Screening in a Packed Bed Reactor





How long did it take to collect these 4 data points?

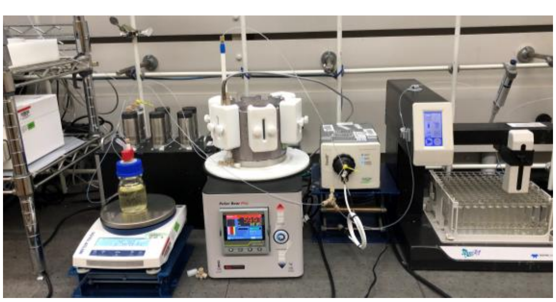
A. 7.5 hours
B. 12 hours
C. 22.5 hours
D. 37.5 hours

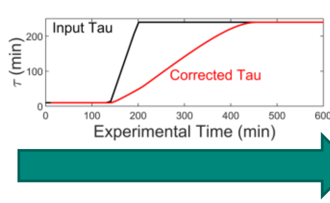
Dynamic Flow Platform for Packed-Bed Reactor Experiments

How to optimize a continuous process?

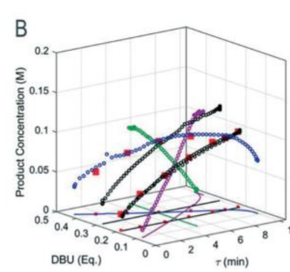
Traditional Flow Experiment
- Analogous to reaction time in batch
- Each data point (steady-state condition) established by flowing reaction solution over 3 residence times
- **Time and material intensive**

Dynamic Flow Experiment
- Dynamic ramping of flow rate to interrogate range of residence times in a single experiment
- Full kinetic profile of flow conditions in a single day
- **Saves time and materials**



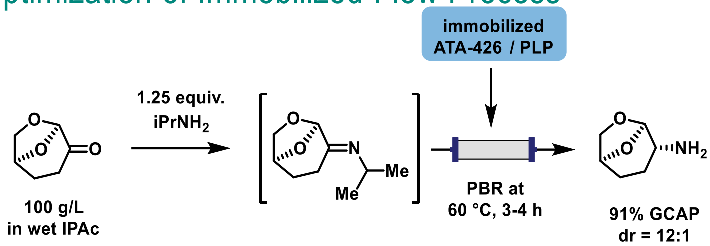


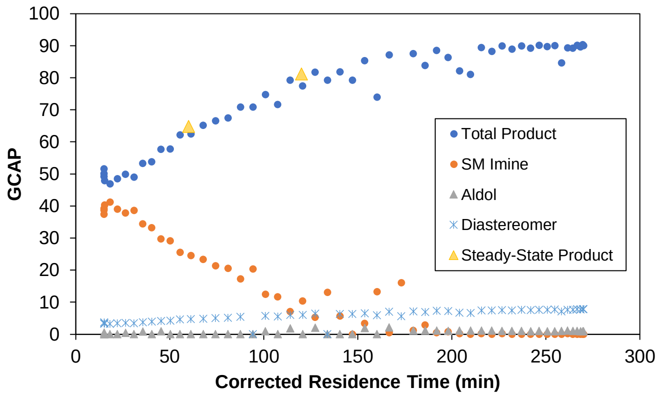
Rapid collection of data under different reaction conditions across broad spectrum of residence times



Wyvratt, B. M.; McMullen, J. P.; Grosser, S. T. *React. Chem. Eng.* **2019**, *4*, 1637-1645.

Optimization of Immobilized Flow Process



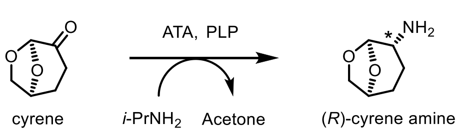


Dynamic PBR Experiment

- Rapidly obtained optimized conditions
- Low aldol formation (<2%)
- Stability: >90% conversion maintained for more than 100 hours (3 h residence time)
- Scalability: identical conversion in 5 mL column vs 290 mL column

For 80 Time Points…	Amount of Stream (g)	Experiment Time (min)
Steady State	615	37277 (26 days)
Dynamic	*23*	413 (6.8 hours)
% Reduction	96 % ↓	99 % ↓

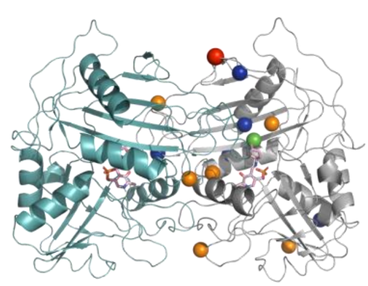
Improving Transamination through Evolution of ATA-426



Protein Engineering Strategy

- Site saturation libraries screened for improvements in activity, selectivity, stability
- Combinatorial libraries built using beneficial mutations for rapid evolution
- Evolved under aqueous conditions, and assayed for impacts on immobilized reactions
- 4 rounds of evolution provided a transaminase with improved activity, selectivity, and thermostability

Variant	Mutations relative to previous backbone	Rate (mM/min)	dr* (*R*:*S*)	T_{50} (°C)
ATA-426	-	0.5	19:1	71.1
Rd2BB	A5L	0.7	20:1	71.6
Rd3BB	I55V;I122M;A192S;G193I;F215H;I263M	1.9	21:1	76.4
Rd4BB	V69A	2.8	40:1	76.4
ATA-492	P48V;T62A;F88W;W124G;E256R	2.1	88:1	83.2



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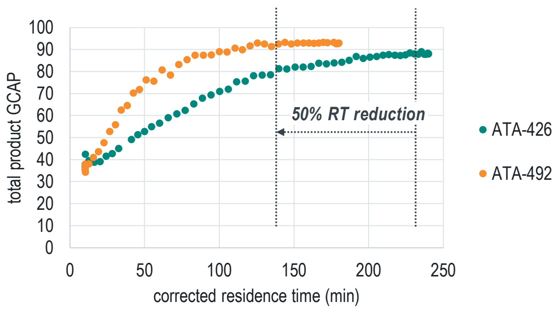
Process Improvements of New Enzyme and Solvent

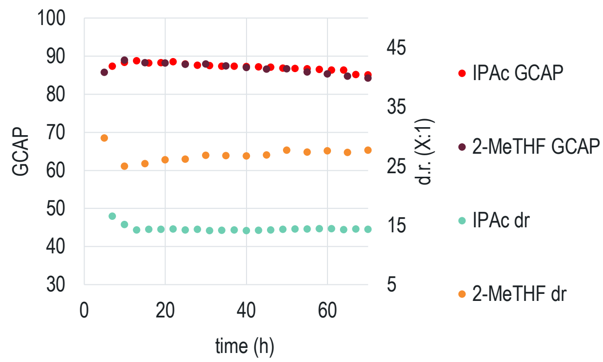
- Improvements obtained through evolution under aqueous conditions translate to immobilized enzyme flow process
- Good stability and reduced residence time

- Use of **water-saturated MeTHF** as solvent improves diastereoselectivity of transamination
- Allows for single-solvent transamination reaction and crystallization (process simplification)

Dynamic Flow Experiments



Immobilized enzyme flow reactions



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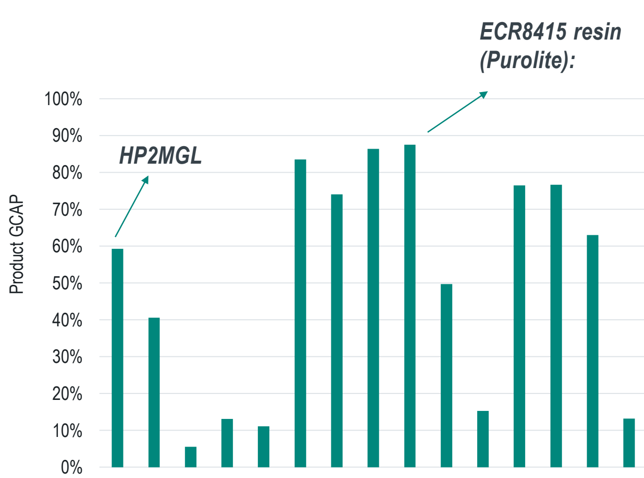
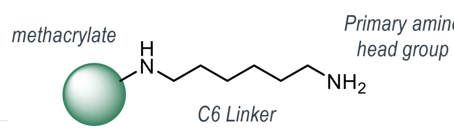
Immobilized Transaminase: Resin Chemistry Impacts Activity

Diverse resins tested with optimized enzyme in flow system: varied resin chemistry, functionalization, pore size, and particle size





- **Amine-derivatized resin -** activity improvement, faster rate of immobilization, no change to selectivity
- Preferentially adsorbs ATA over host-cell proteins; increased transaminase loading
- Potential change to immobilization mode

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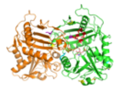
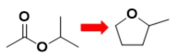
Immobilized Transaminase Process Improvements

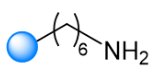
Improved Enzyme



Change Solvent

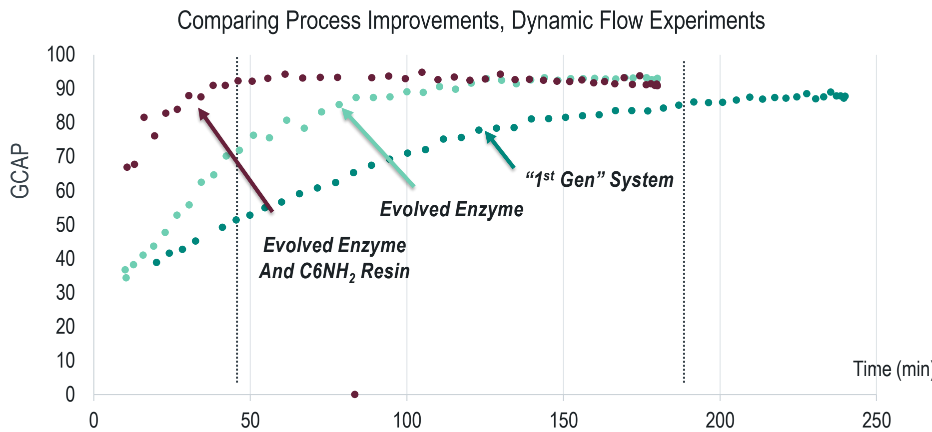


New Resin



Residence time

3 h to 45 min



- Combining evolved transaminase and amine-functionalized resin leads to a **4-fold** reduction in residence time
- Stability of immobilized enzyme is maintained on new resin

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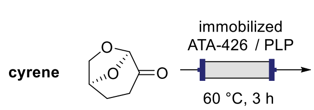
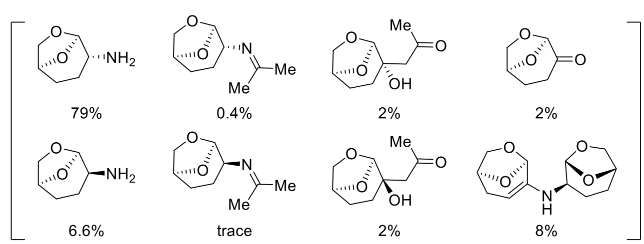
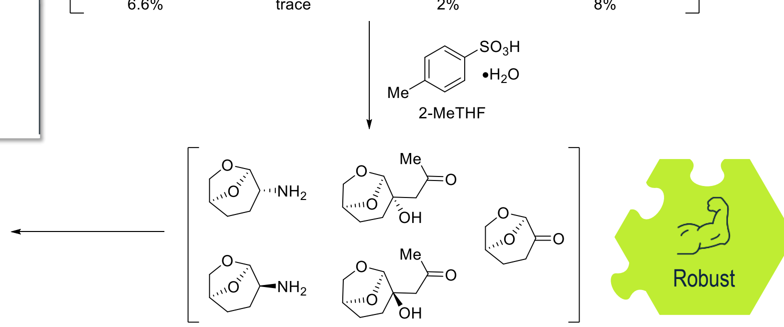
Crystallization of Cyrene Amine TsOH Salt

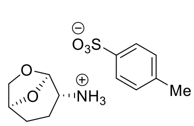




Benefits of Tosylate Salt Crystallization

- Tosic acid hydrolyzes all imines in solution
- Salt formation completely rejects aldol impurities
- Increase in purity (d.r.)





95% IY from amine
dr > 30:1

Robust crystallization provides quality product from streams of varying conversion

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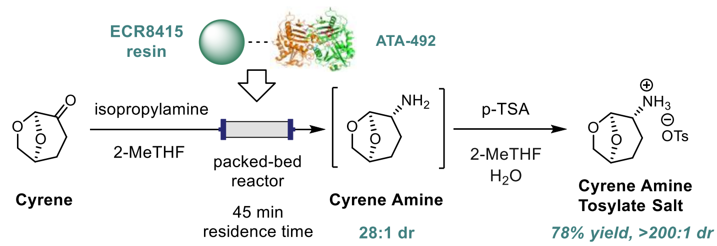
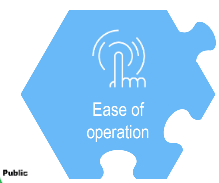
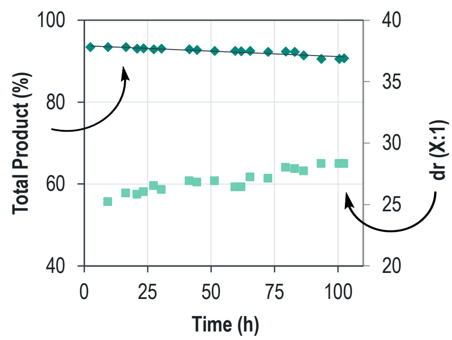
Immobilized Transaminase Process Improvements



Process performed in 10 L column



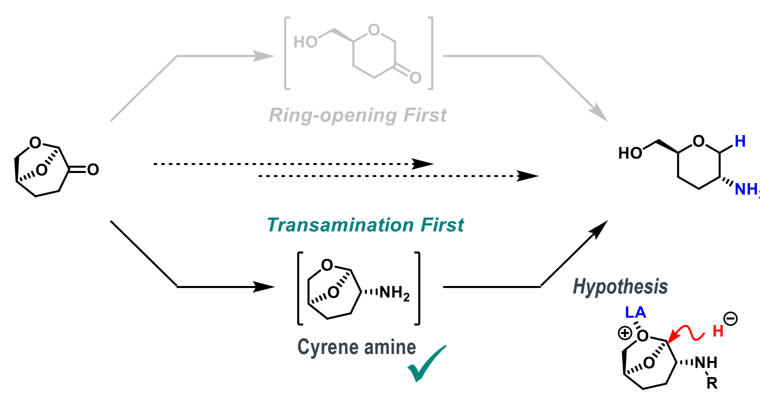


Process Changes significantly improved Transamination efficiency and sustainability

d.r. = 23:1	→	d.r. >200:1
2 kg ATA	- 55%	0.9 kg ATA
20 L column	- 50%	10 L column
3h RT 5 kg cyrene/day	- 75%	45 min RT 17 kg cyrene/day

Renewable Starting Material and Solvent

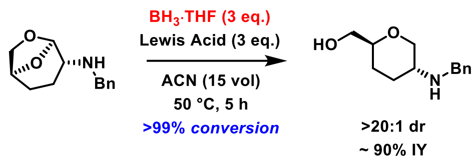
Can we use Cyrene as a Starting Material?



Can we develop reductive Acetal Opening?

Acetal Opening – BH_3 Safety

- **Proof of Concept for Acetal Opening with Retention of d.r. :**



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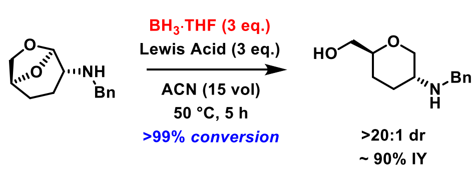

BH_3·THF is an unstable, self-reactive material !

- Risk of thermal runaway reactions due to THF-cleavage
- > 50 °C generates B_2H_6
  - a highly flammable gas (auto-ignition temperature 130-135 °C)
  - and a highly toxic gas (PEL = 0.1 ppm, IDLH = 15 ppm)

Chem. Eng. News **2002**, 80, *26*, 7
Chemical Engineering in the Pharmaceutical Industry, 2nd Ed., **2019**
'Case study of a Borane-THF Explosion'

Matos et. al. *OPRD* **2006**, 10, 1292.
Monteiro and Flanagan, *OPRD* **2017**, 21, 2, 241.

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Acetal Opening – BH_3 Safety

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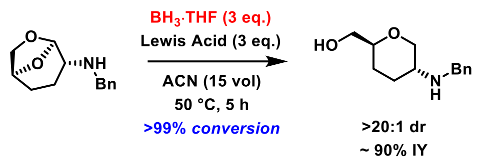

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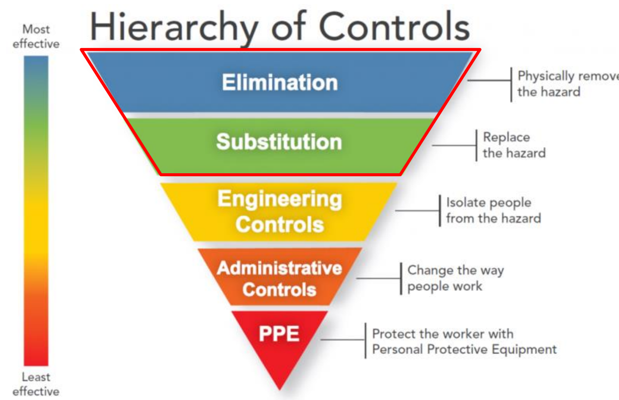
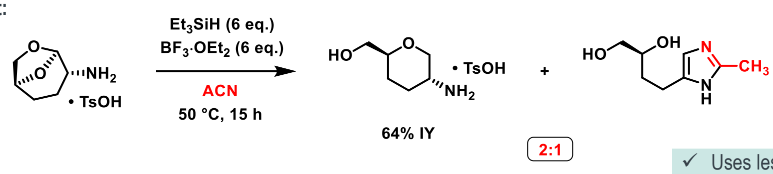


Identify Alternative Conditions to avoid BH_3

Acetal Opening with Silane Reductants

- **Initial hit:**



- ✓ Uses less toxic triethylsilane
- ✓ Does not require *N*-protecting group
- Undesired side product (Ritter reaction)

Acetal Opening with Silane Reductants

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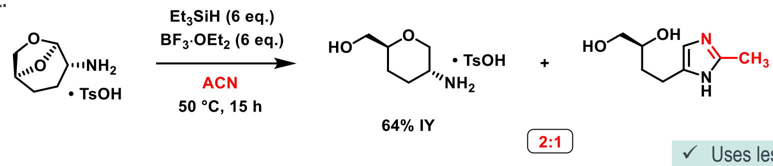
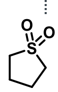


- ✓ Uses less toxic triethylsilane
- ✓ Does not require *N*-protecting group
- ▪ Undesired side product (Ritter reaction)

- **High Throughout Experimentation quickly identified the optimal solvents**

1st Screen
12 solvents with 8 silanes

- ✓ **Triethylsilane**
- ✓ **Sulfolane** is a privileged solvent



melting point 27.5 °C

57

Acetal Opening with Silane Reductants

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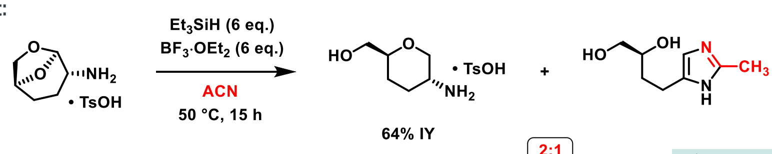

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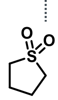

melting point 27.5 °C

2nd Screen
12 co-solvents with different %sulfolane

- ✓ As little as 10 vol% sulfolane required
- ✓ Aromatic solvents perform best (PhMe, **PhOMe**, PhCl etc.)

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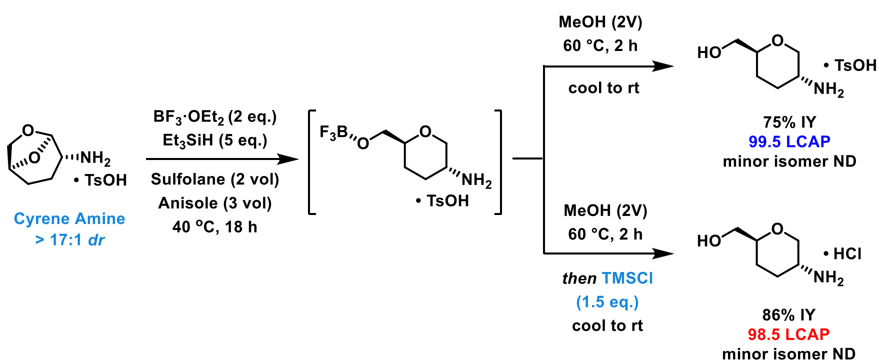
Acetal Opening of Cyrene Amine

- Product can be isolated as either the TsOH or HCl salt (using with TMSCl) after quenching with methanol



How can we control the problematic dimer impurity?

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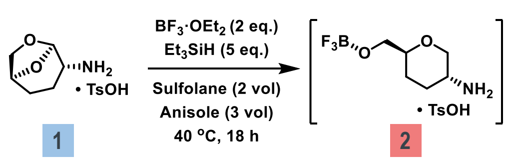
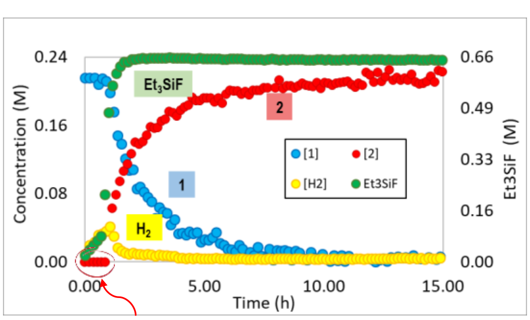
Understanding the Acetal Opening Reaction

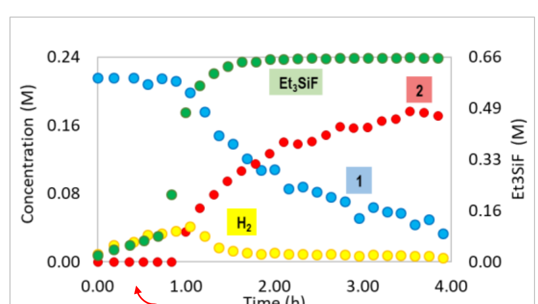


- During an induction period, formation of H_2 and Et_3SiF is observed

- [1]H NMR Reaction Profile:



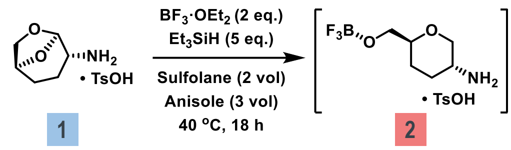
Induction period



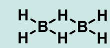
Induction period

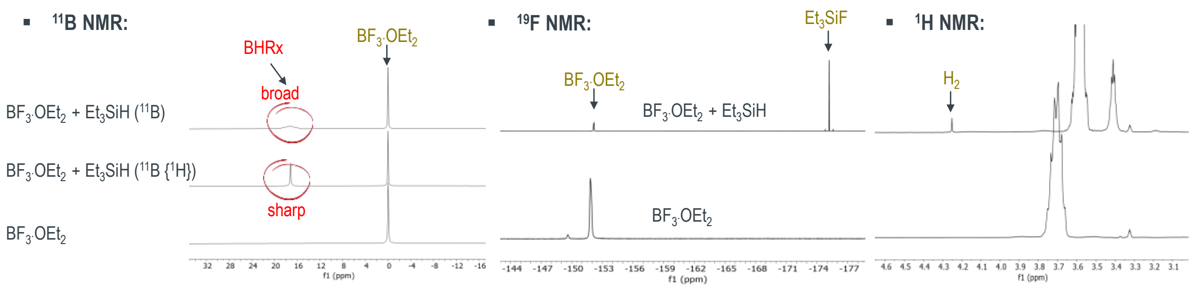
60

Why is it Important to Understand How your Reaction Works?



- During an induction period, formation of H_2 and Et_3SiF is observed
- H_2 and Et_3SiF formation is observed in the absence of cyrene amine
- Formation of a new, transient BHRx species is observed
- **NMR characterization of BHRx is diborane!**





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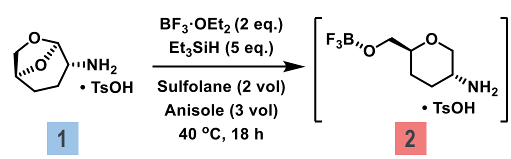
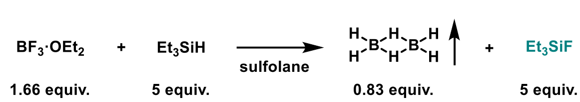
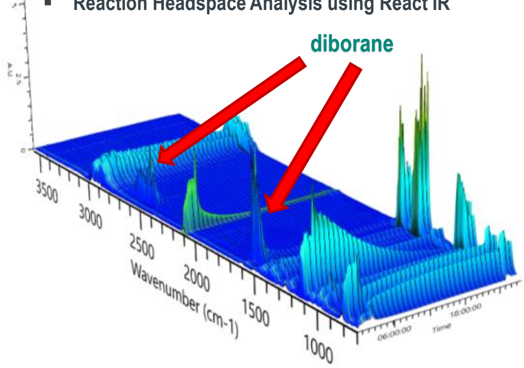


- Diborane is generated at around 2 h, with full consumption at 6 hours.
- Diborane is the active reductant.



- **Reaction Headspace Analysis using React IR**



Thorough Process Safety Analysis Required prior to Scale Up

Pu

Developing a Scalable Process Whilst Controlling Problematic Dimer Impurity

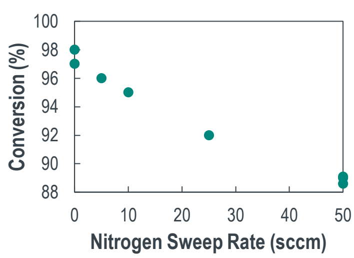
1) **Slow addition of reagent to control concentration of reactive impurity**

   Determined not to be viable due to formation of significantly higher levels of dimer impurity

regular addition 0.5 → 6x → 3 slow addition

Dimer Impurity LCAP

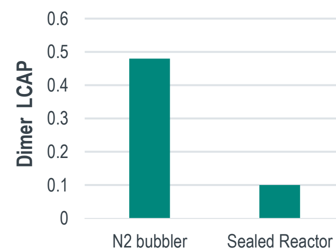
2) **Apply a sufficient nitrogen sweep to control the headspace concentration**



<u>Solution</u>

Run reaction under pressure

- Diborane gas is maintained inside reactor
- Reproducibly high conversion
- Significant reduction in dimer impurity (ca. 5x)



Can we safely scale-up the reaction under pressure?

Robust

Public

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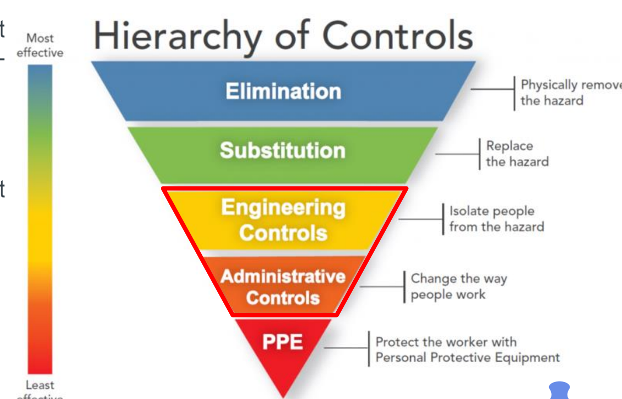
Safety Considerations Before Scale-Up

- **Exotherms:**
  Ensure that no secondary decomposition reactions can occur that would bring batch within range of auto-ignition temperature (130-135 °C).

- **Pressure Hazards:**
  Understand maximum possible pressure build up to select appropriate scale up equipment.

- **Emissions:**
  Ensure emissions limits are not exceeded.

- **Diborane Toxicity:**
  Plan for appropriate PPE and diborane monitors, as well as develop emergency response plans for potential upset scenarios.



Safe

Strong collaboration between process safety group, chemists and engineers was required to enable incident free scale up of >10 x 30-45 kg batches.

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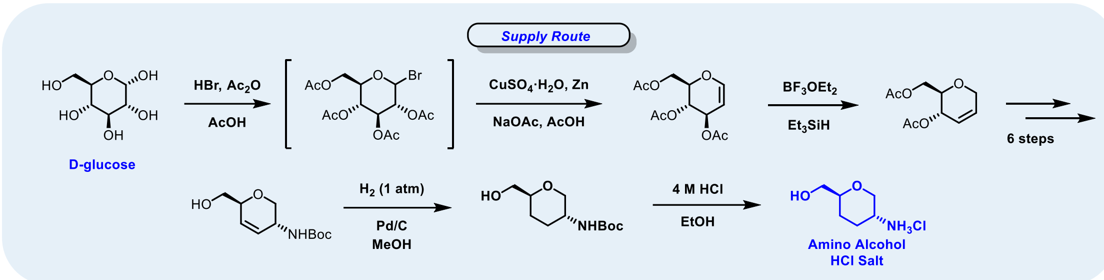
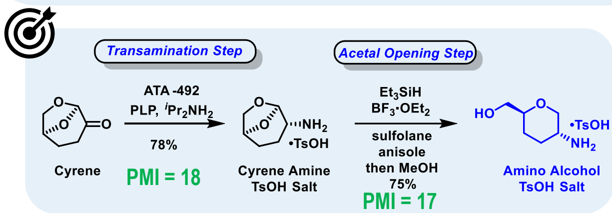
Amino Alcohol Synthetic Improvements





Supply Route: Cumulative PMI = 654
Amino Alcohol Synthesis contributed 83% to the PMI

Manufacturing Route: Cumulative PMI = 160
Amino Alcohol Synthesis contributes only 22% to the PMI

Renewable Feedstock

Reduce Step Count

Atom Economy

Removed 7 Synthetic Steps
Improved overall yield 10-fold

Public

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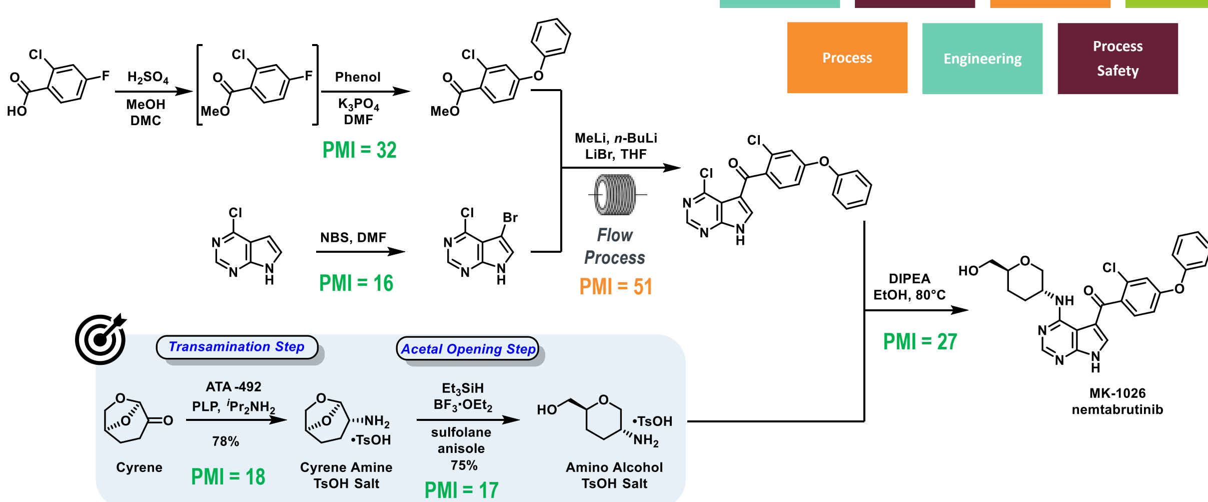
Nemtabrutinib Commercial Route

Biocatalysis | Chemocatalysis | Flow Chemistry | Protein Engineering

Process | Engineering | Process Safety



Renewable Feedstock

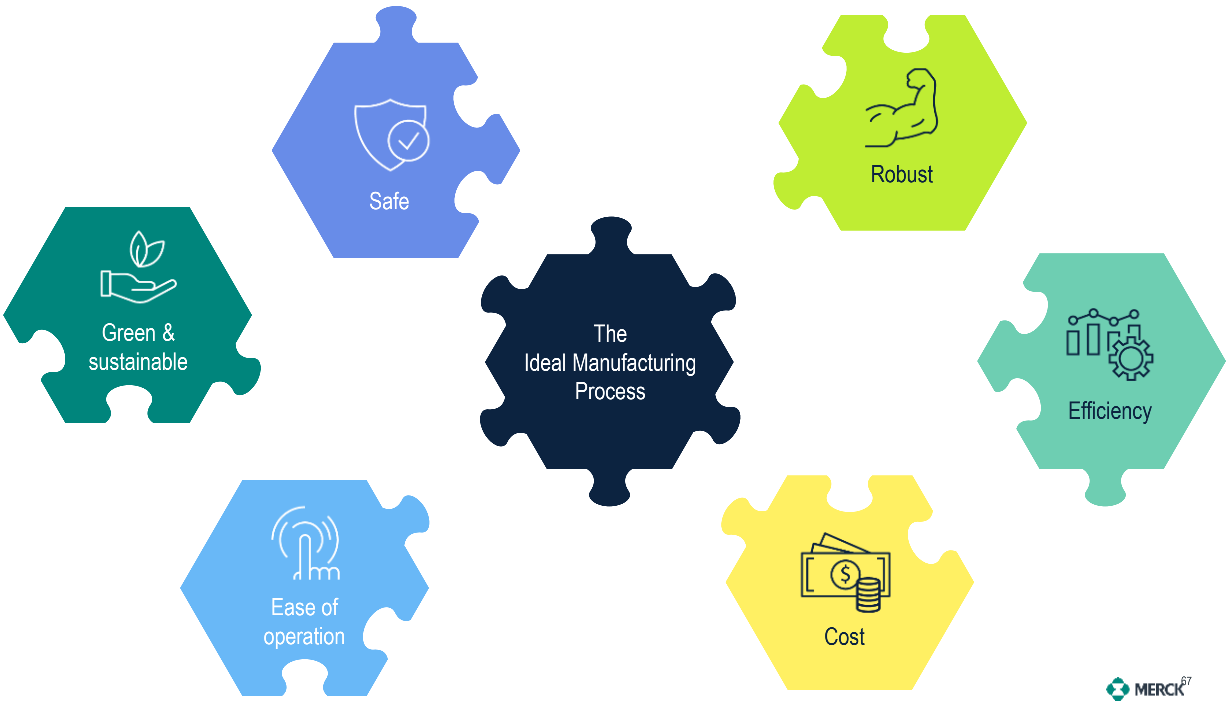
Reduce Step Count

Atom Economy

Removed 7 Synthetic Steps
Improved overall yield 10-fold

Public

66


Safe
Robust
Green &
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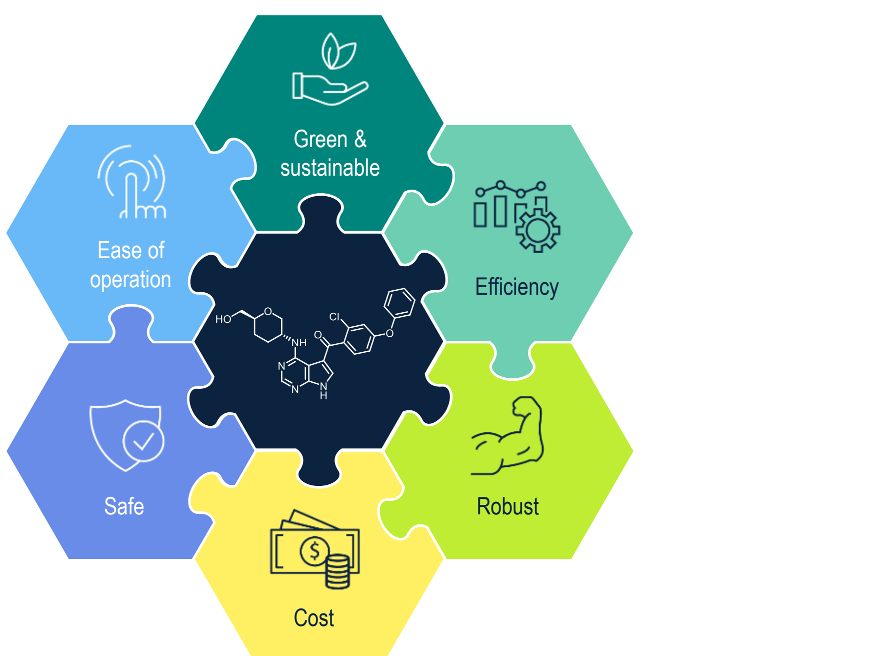
The
Ideal Manufacturing
Process
Efficiency
Ease of
operation
Cost
MERCK 67

67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Safe
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Cost
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Acknowledgement – Nemtabrutinib Team

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presented by Mike Di Maso and Ben Turnbull

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