Going with the Flow:
Synthetic Applications of Flow Chemistry

10-3-23

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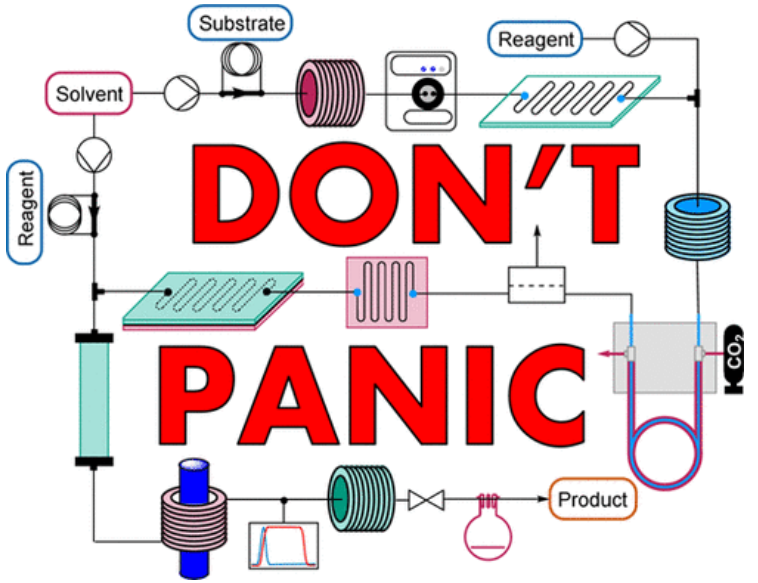
Outline

Basic Principles	Synthetic Applications	Advanced Flow Chemistry
Physics & Concepts	Multiphase Reactions	API Syntheses
Types of Flow	Catalysis & Reactive Intermediates	Scale Up of Processes
Hardware & Diagrams	Photochemistry	High Throughput Screening

The Hitchhiker's Guide to Flow Chemistry
Chem. Rev. **2017**, *117*, 11796-11893.

A Field Guide to Flow Chemistry for Synthetic Organic Chemists
Chem. Sci. **2023**, *14*, 4230-4247.

The Assembly and Use of Continuous Flow Systems for Chemical Synthesis
Nat. Protoc. **2017**, *12*, 2423-2446.



Basic Principles – Flow vs. Batch

When should a reaction be run in continuous flow vs. batch?

Continuous Flow

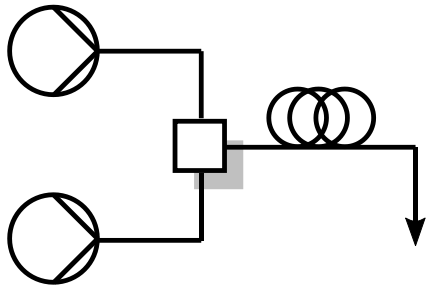
Reaction is not safe in batch.

Use of gaseous reagents.

Fast chemical reactions (<1 min).

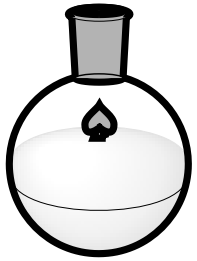
Thermally selective reactions.

Electrochemical or photochemical reactions.



Batch

Reaction is optimized in batch to reasonable:
Yield, Scale, and Reaction Time.



Optimization of discrete variables.

Precipitation of a product to drive an equilibrium.

Solids

Heterogeneous catalysis.

Insoluble stoichiometric reagents

Emulsions

Problematic scalability of emulsions.

Emulsion scalability is not an issue.

Plutschack, M. B. et al. *Chem. Rev.* **2017**, *117*, 11796-11893.

Basic Principles – Reactions in Flow

In − Out + Generation = Accumulation

$$F_{in} - F_{out} + \int r\, dV = \frac{dN}{dt}$$

F – Molar Flow Rate (mol/time)
r – Reaction Rate (M/time)
N – Number of moles in system
V – Volume
t – time

Steady State: No accumulation inside of system

$$F_{in} - F_{out} + \int r\, dV = 0$$

X – Conversion

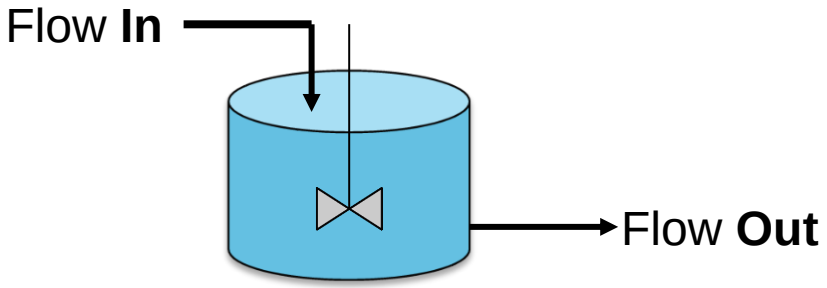
$$V = F_{in} \int_0^X \frac{dX}{-r}$$

Reactions in flow are often controlled by:

Reactor Volume

Residence Time

Continuous Stirred Tank Reactor (CSTR)



$$V = \frac{F_{in} X}{-r}$$

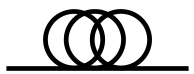
Packed Bed Reactors

W – Catalyst Weight

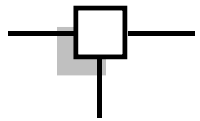
$$W = F_{in} \int_0^X \frac{dX}{-r}$$

Fogler, H. S. *Elements of Chemical Reaction Engineering*, 5th ed; Pearson Education, 2016.

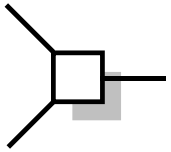
Basic Principles – Hardware & Diagrams



Reactor



T-Mixer



Y-Mixer

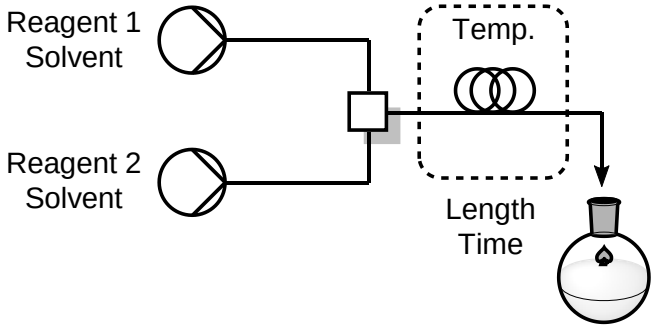
Pump

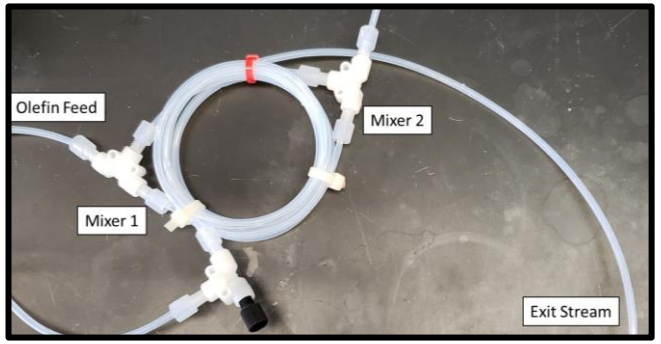
BPR

Back-Pressure Regulators

MFC

Mass Flow Controllers





Arriaga, D. K.; Thomas, A. A. *Nat. Chem.* **2023**, *15*, 1262-1266.

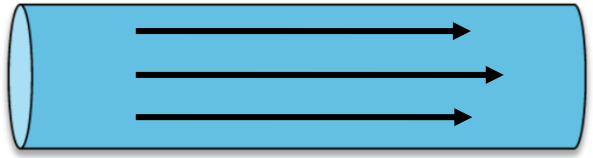
Basic Principles – Flow Regimes

Homogeneous

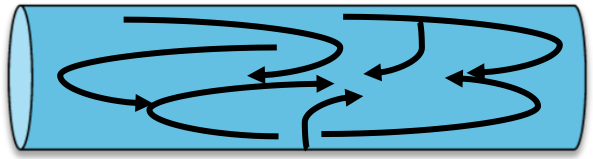
$$Re = \frac{uL}{\nu}$$

L – Length (m)
u – Flow Velocity (m/s)
ν – Viscosity (m^2/s)

Laminar



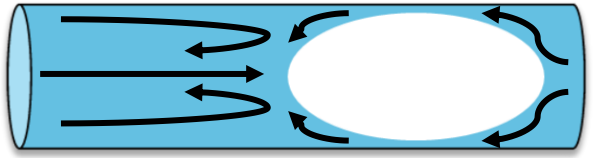
Turbulent



Gas-Liquid

Bubble

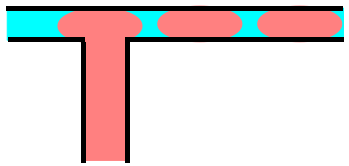
Slug

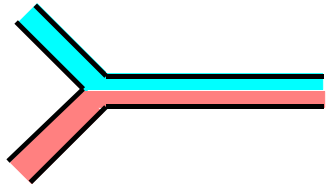


Taylor Flow

Annular

Liquid-Liquid (Immiscible)





Phase-Transfer Catalysis

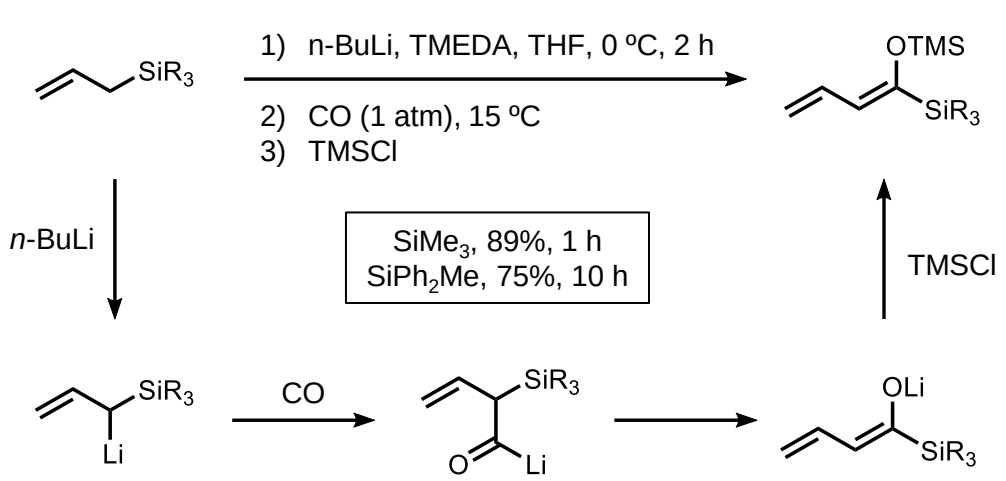
In-Situ Aqueous Workup

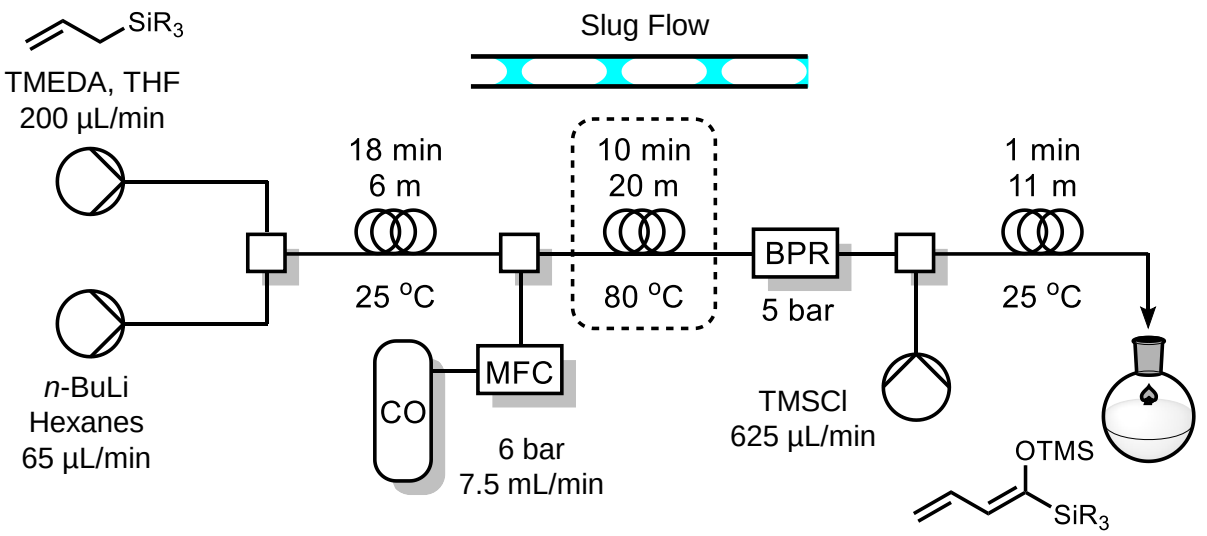
Solid-Fluid (Packed Bed)

Catalyst supported on Solid

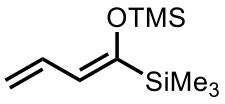
Fluidized Beds

Gas-Liquid Flow – Carbon Monoxide





Substrate Scope



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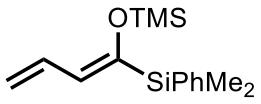
93:7 (E:Z)
5 min



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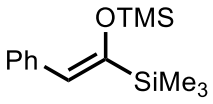

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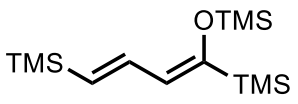

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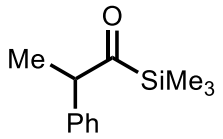

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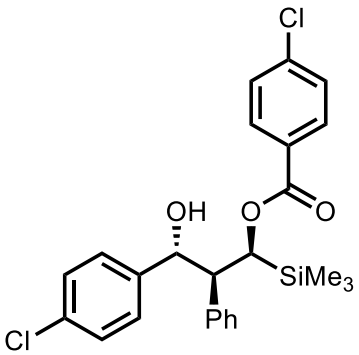
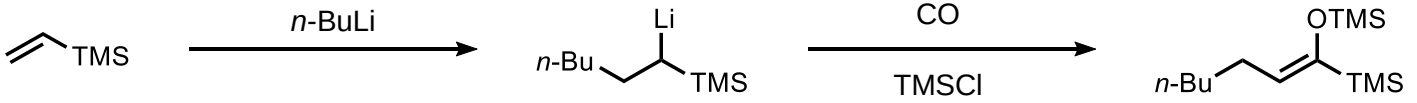


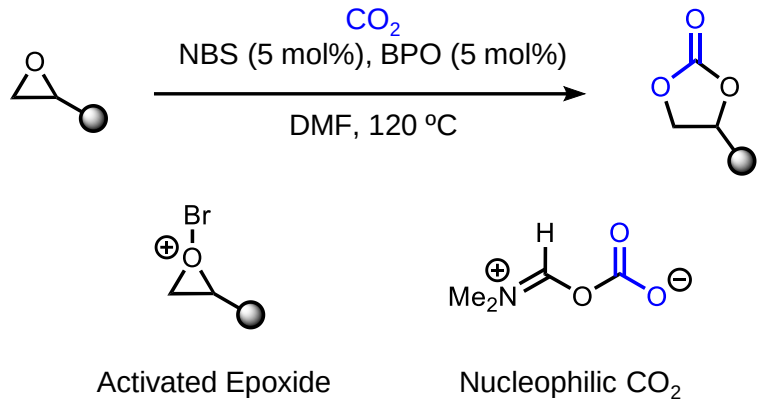
81%
5 min

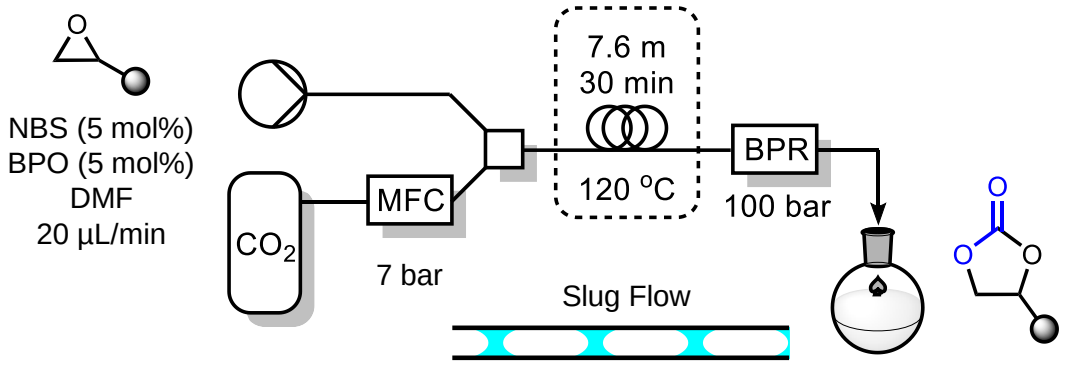


80% NMR Yield
E only

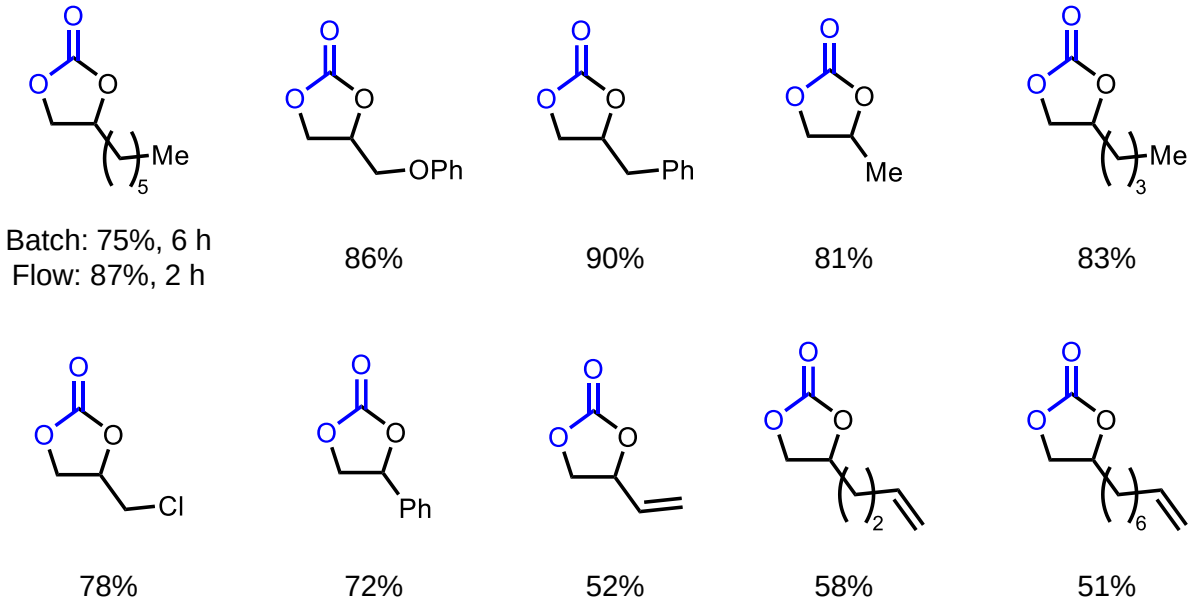
Fukuyama, T.; Totoki, T.; Ryu, I. *Org. Lett.* **2014**, *16*, 5632-5635.

Gas-Liquid Flow – Carbon Dioxide

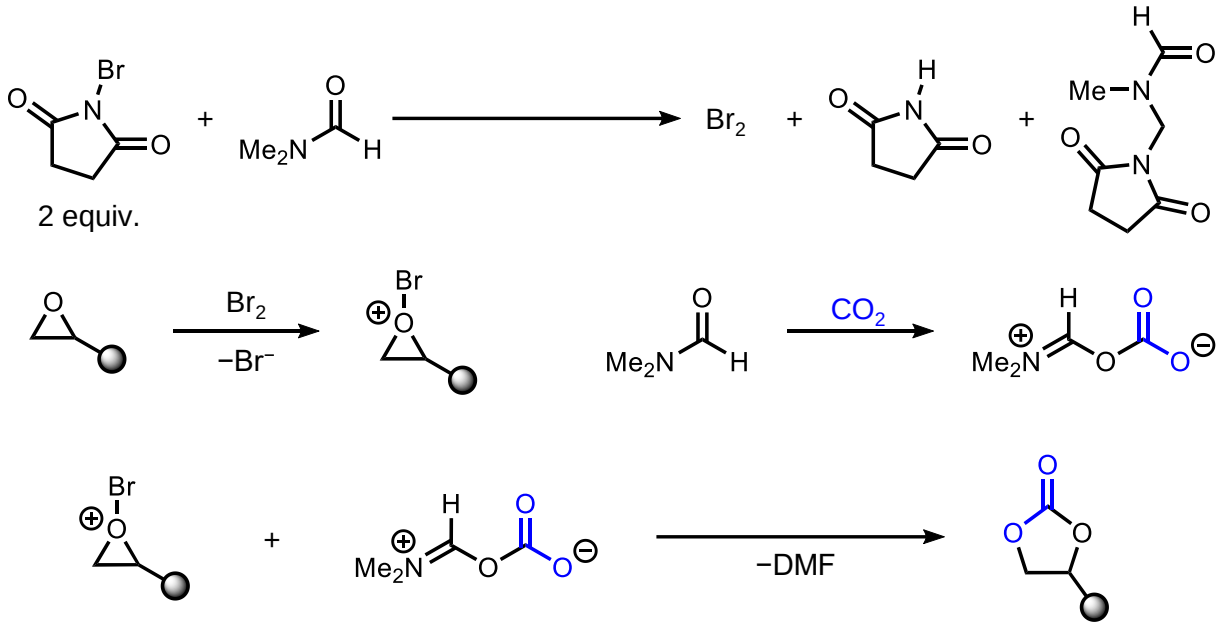




Substrate Scope

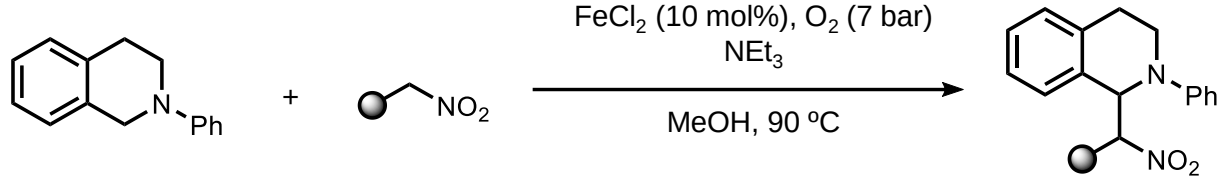


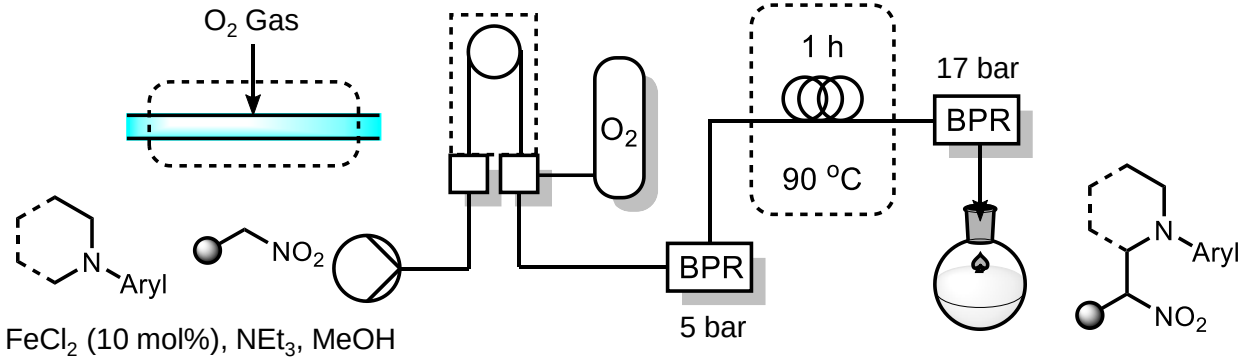
Mechanistic Analysis

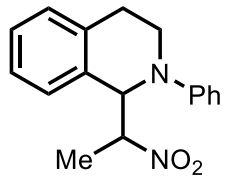


Kozak, J. A. et. al. *J. Am. Chem. Soc.* **2013**, *135*, 18497-18501.

Gas-Liquid Flow – Oxygen & Ozone







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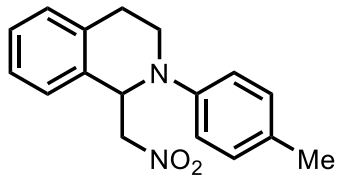

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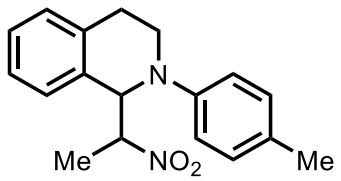

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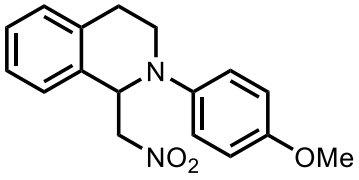

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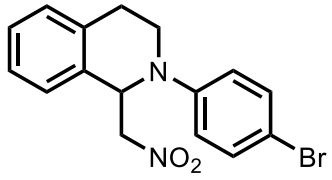

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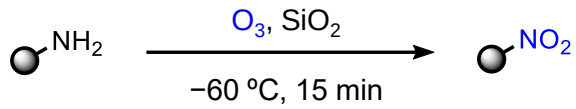
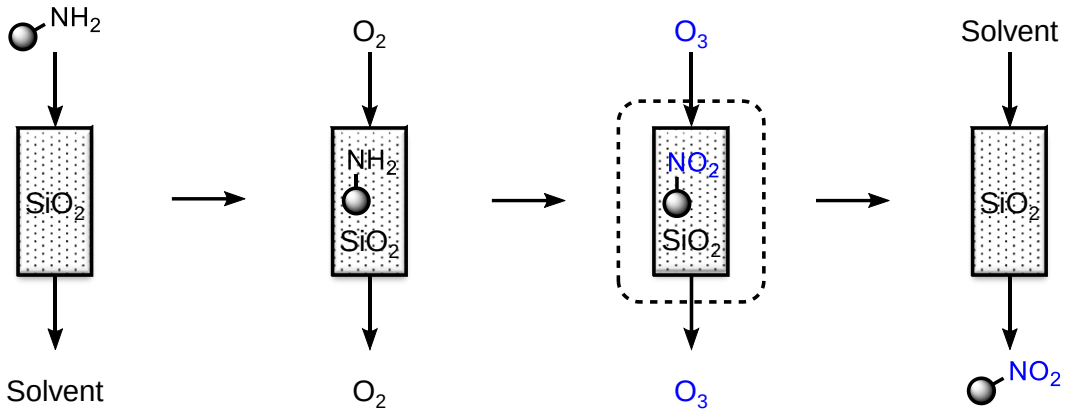
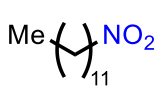


Packed Bed Approach
Reproducible Reactor Cycling





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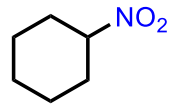

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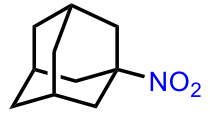

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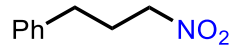

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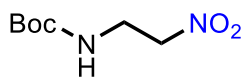

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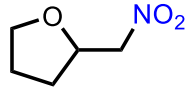

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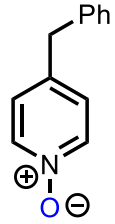

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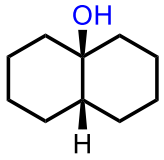

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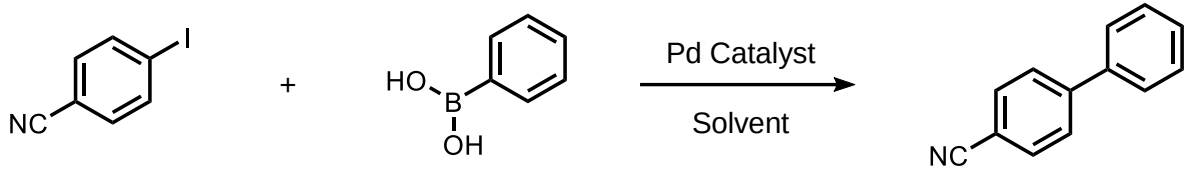
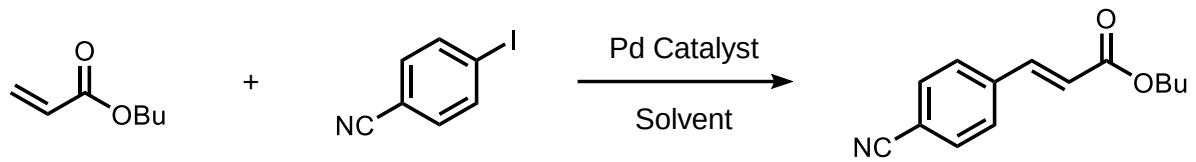
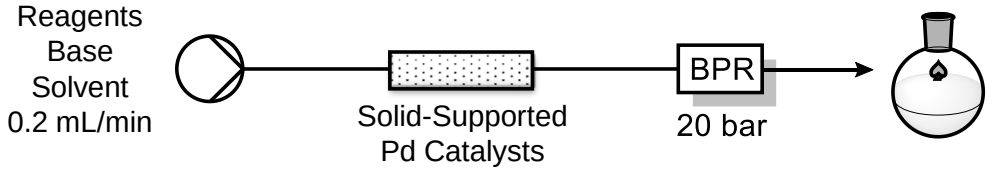
Brzozowski, M.; Forni, J. A.; Savage, G. P.; Polyzos, A. *Chem. Commun.* **2015**, *51*, 334-337.

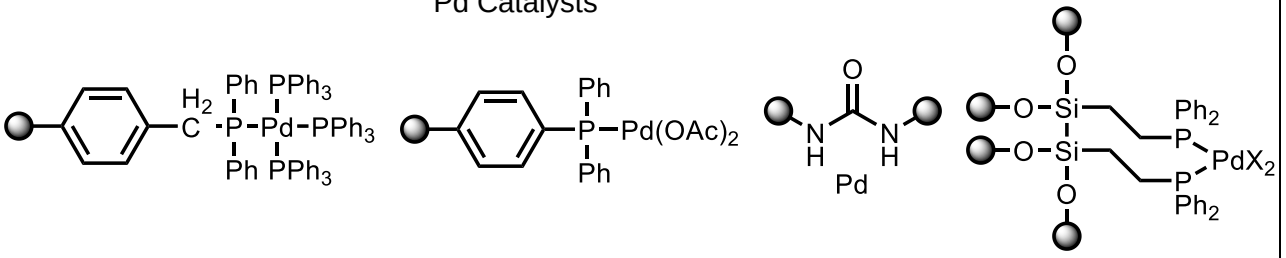
Skrotzki, E. A.; Vandavasi, J. K.; Newman, S. G. *J. Org. Chem.* **2021**, *86*, 14169-14176.

Catalysis – Palladium Leaching in Packed Beds

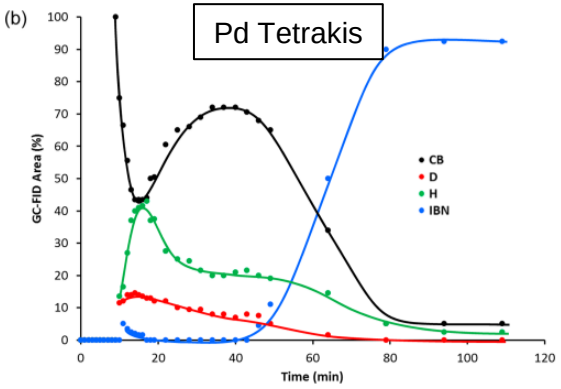


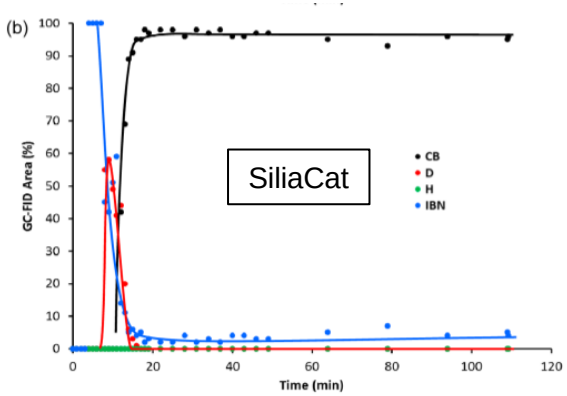


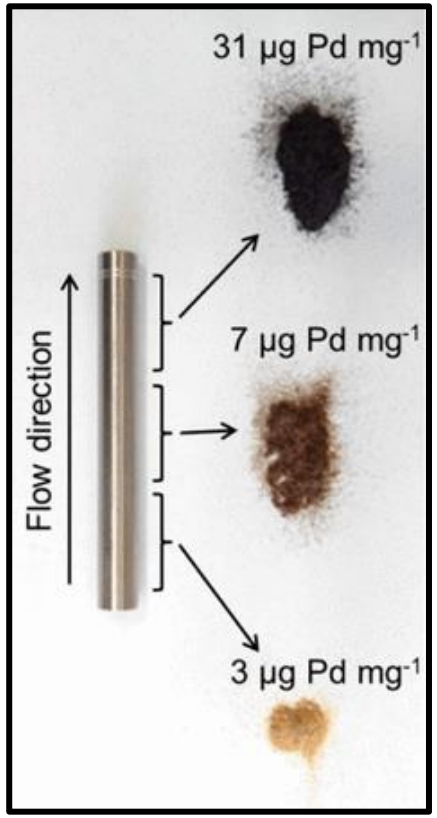




Pd Tetrakis | FiberCat 1001 | EnCat TPP30 | SiliaCat





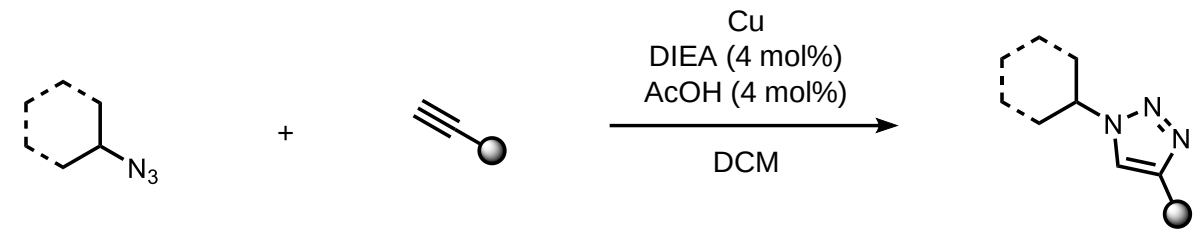


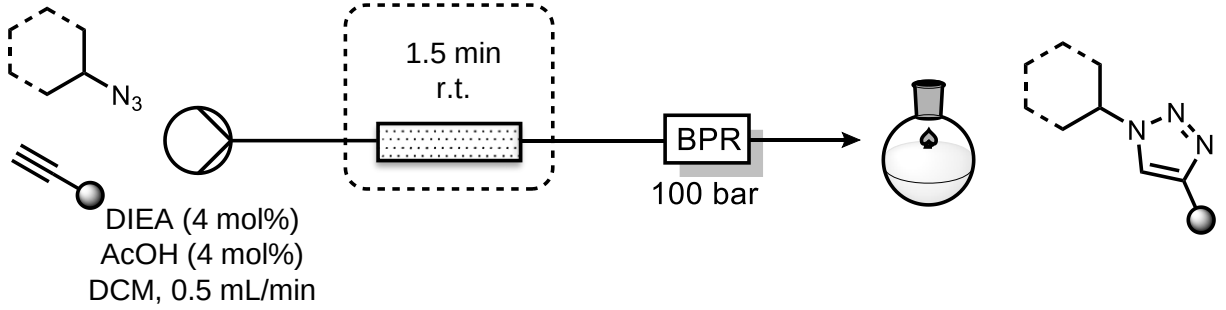
FiberCat 1001

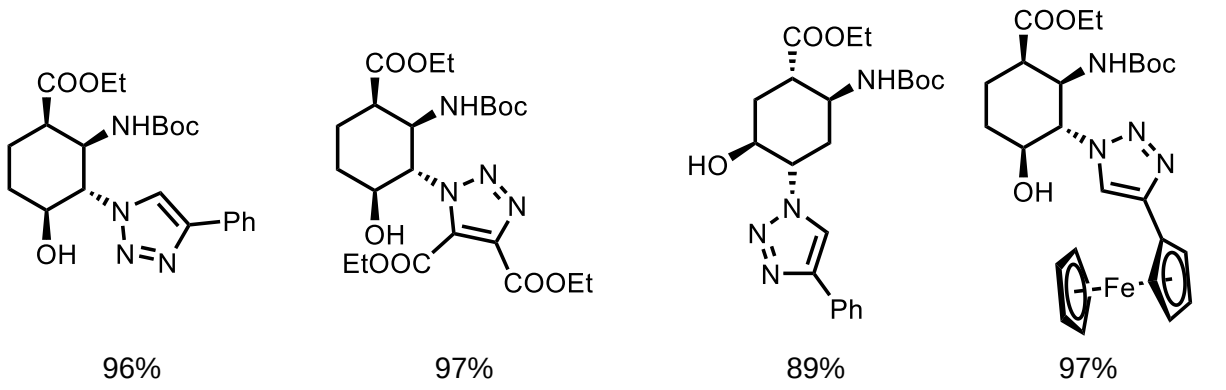
SiliaCat
THF, EtOH, H_2O, K_2CO_3

Greco, R.; Goessler, W.; Cantillo, D.; Kappe, C. O. *ACS Catal.* **2015**, *5*, 1303-1312.

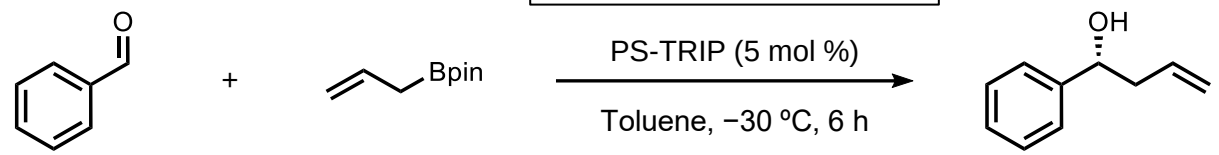
Catalysis – Copper & Organocatalysis



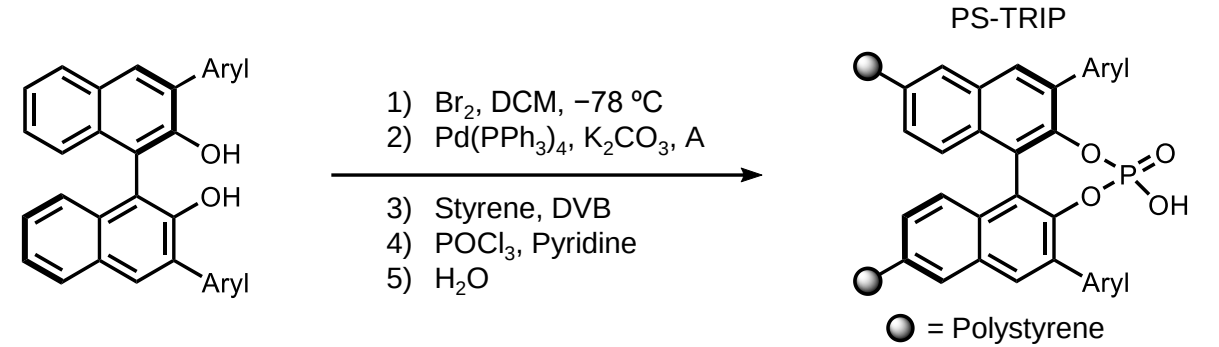


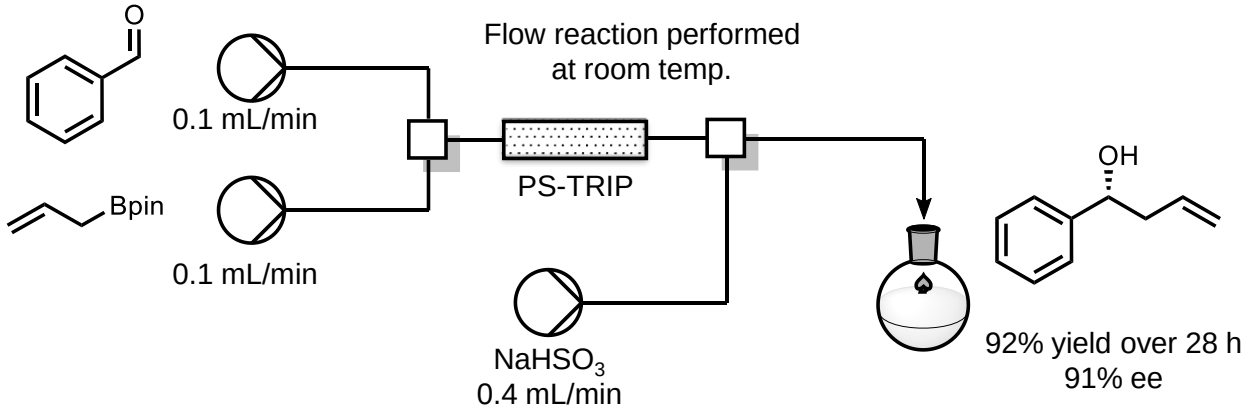


All examples prepared from same batch of PS-TRIP



18 examples in batch, 70-98% yield
Up to 98% ee

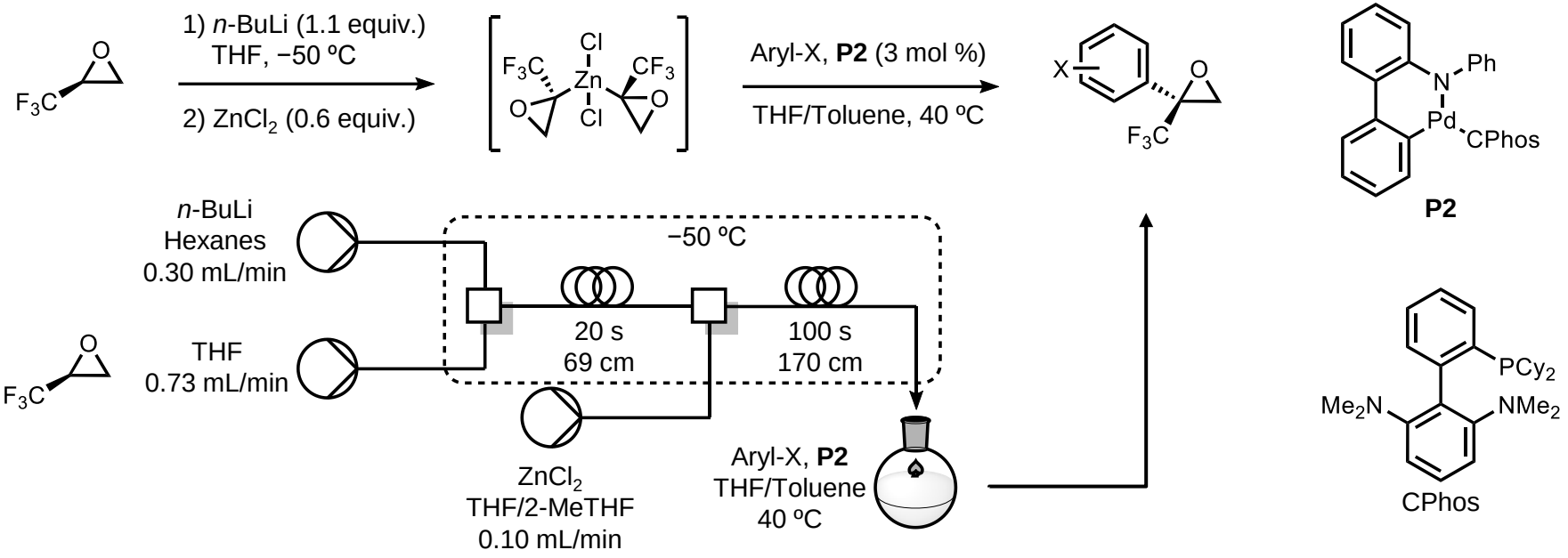




Ötvös, S. B. *Beilstein J. Org. Chem.* **2013**, *9*, 1508-1516.

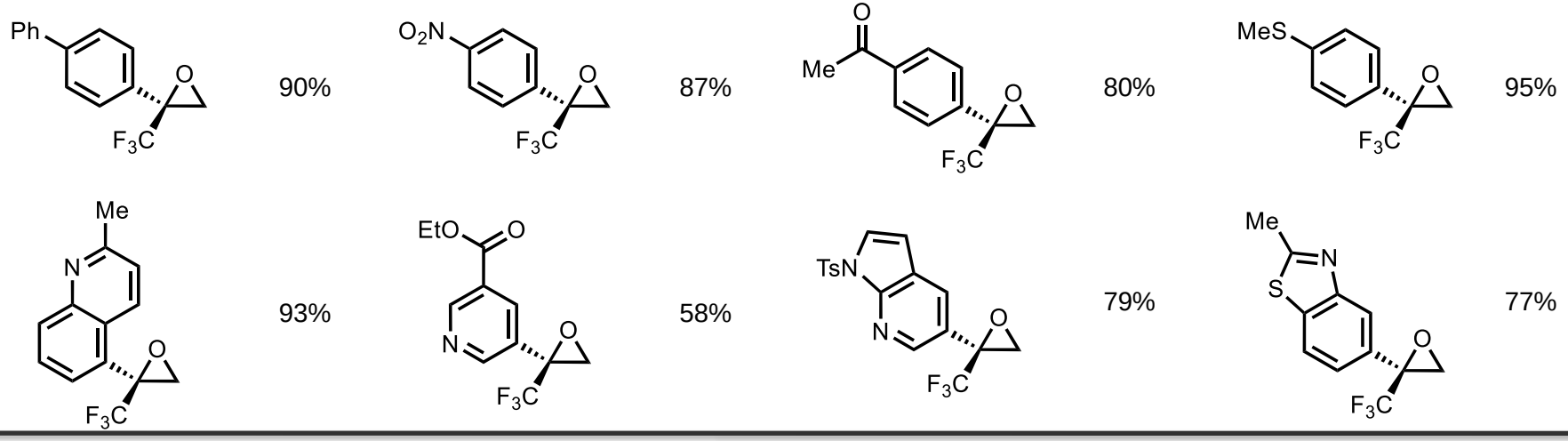
Clot-Alemenara, L. et. al. *ACS Catal.* **2016**, *6*, 7647-7651.

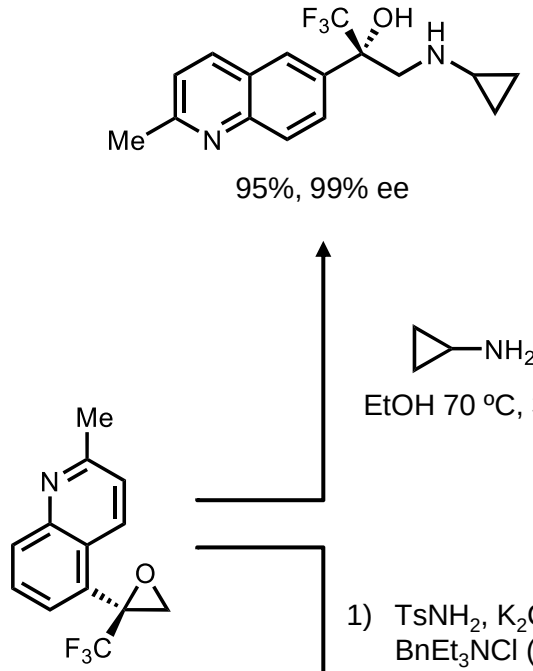
Reactive Intermediates – Negishi Cross-Coupling



P2

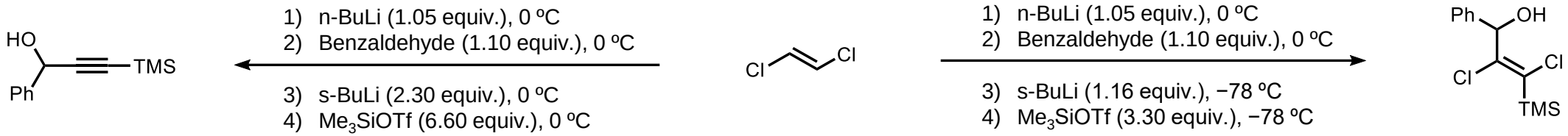
CPhos

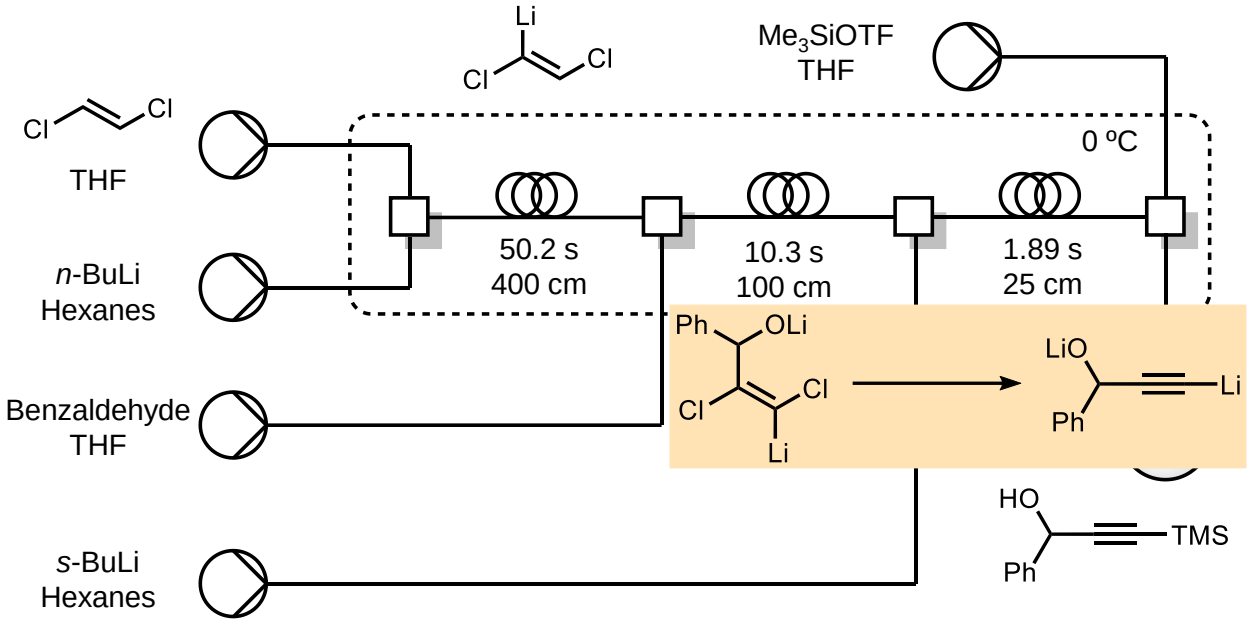


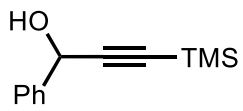


Zhang, H.; Buchwald, S. L. *J. Am. Chem. Soc.* **2017**, *139*, 11590-11594.

Reactive Intermediates – Reactions in Sequence







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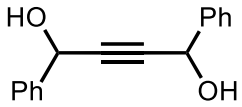

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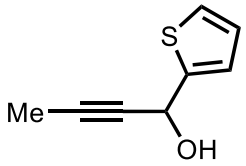

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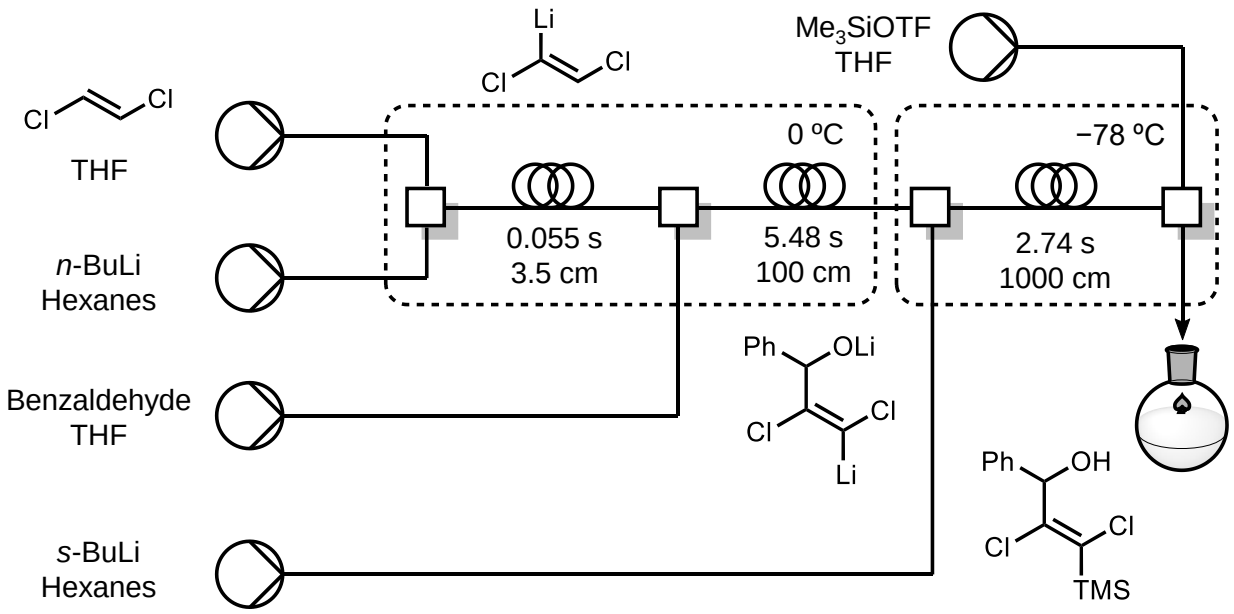

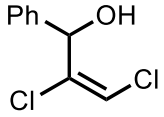

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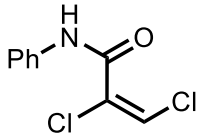

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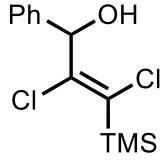

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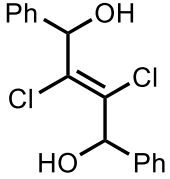

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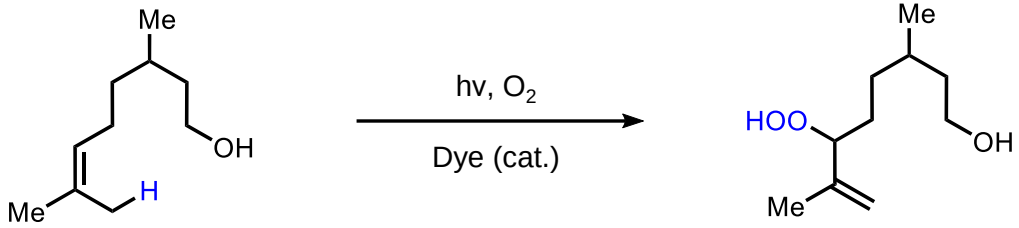
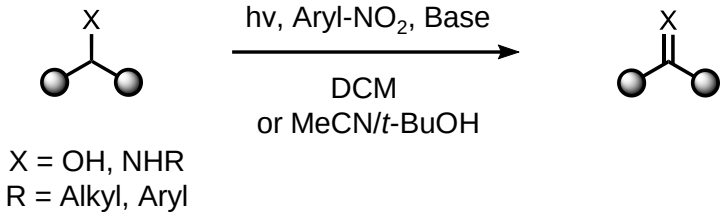
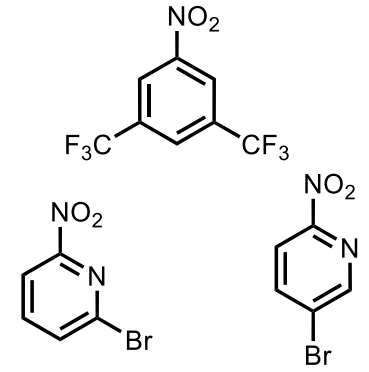
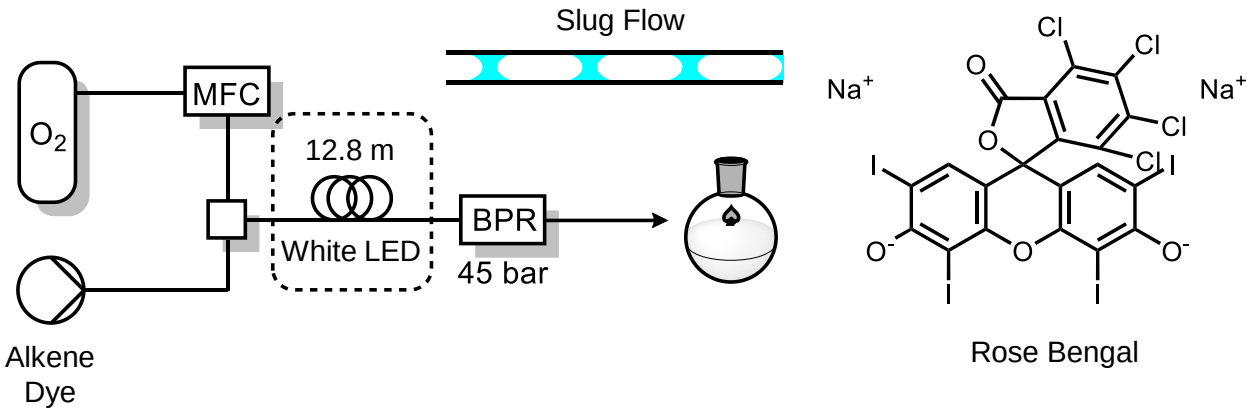
Nagaki, A. et. al. *Angew. Chem., Int. Ed.* **2012**, *51*, 3245-3248.

Photochemistry – Aerobic & Anaerobic Oxidations

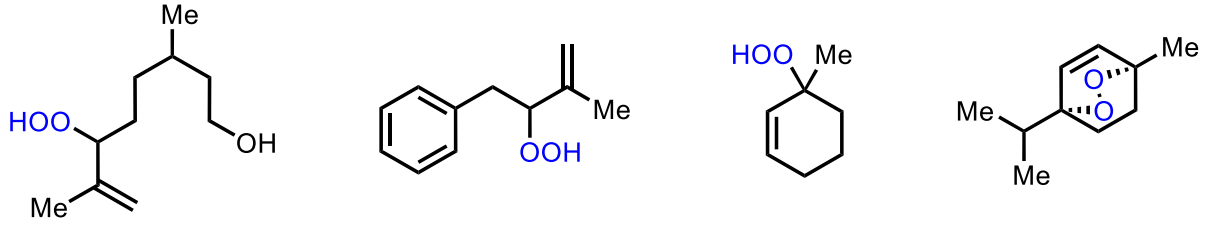


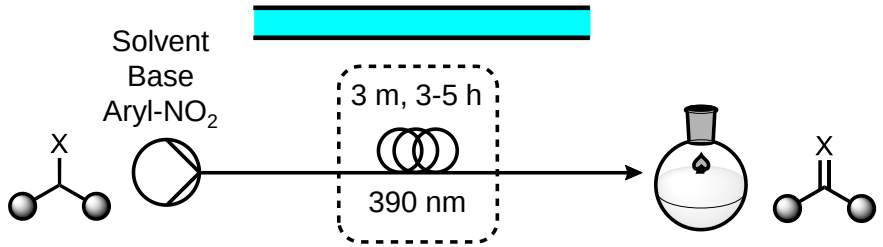


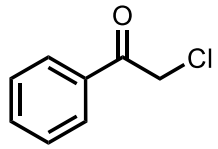




Rose Bengal







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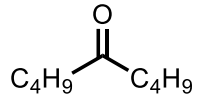
427 nm



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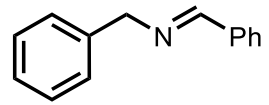

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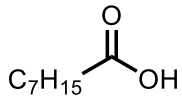

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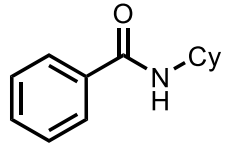

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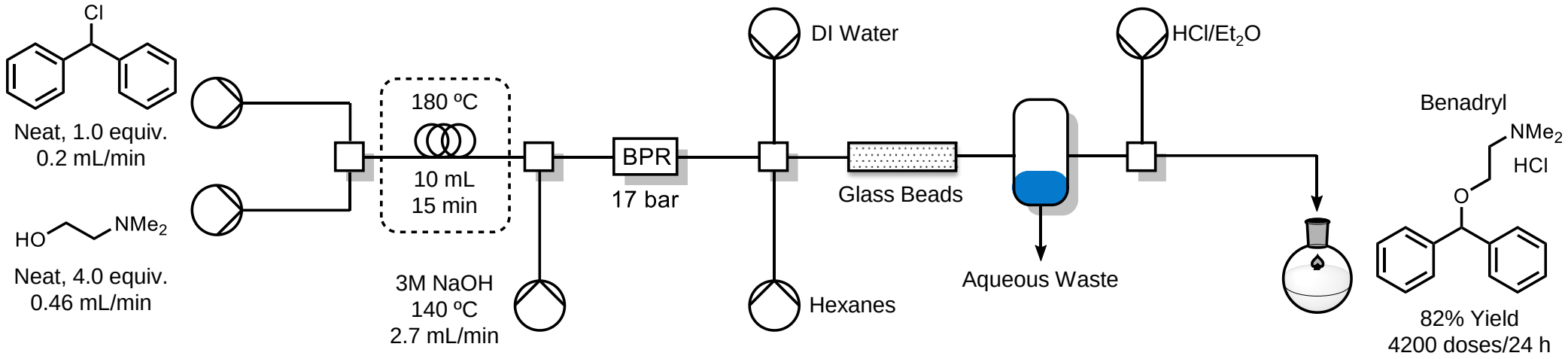
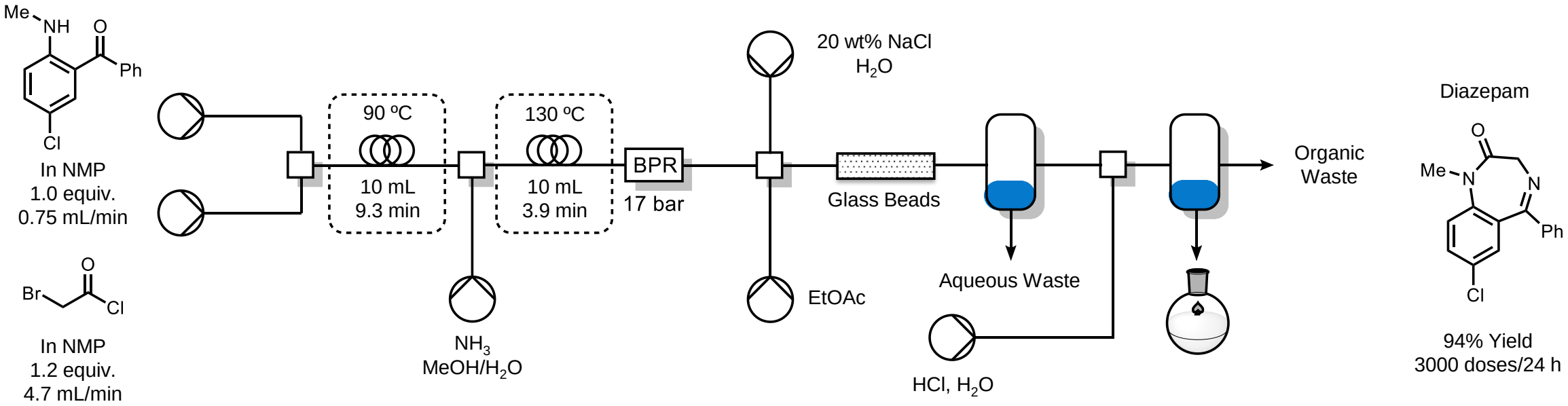
Bayer, P.; Jacobi, A. *Green Chem.* **2020**, *22*, 2359-2364.

Mitchell, J. K. et. al. *Org. Lett.* **2023**, *25*, 6517-6521.

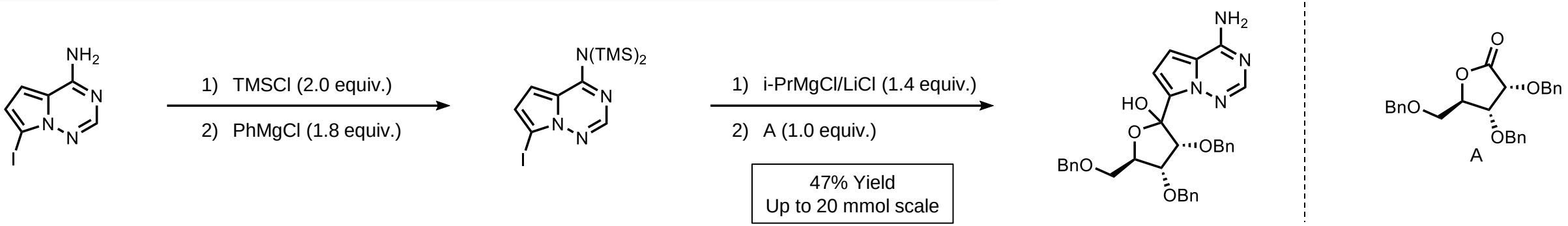
Active Pharmaceutical Ingredient Syntheses in Flow

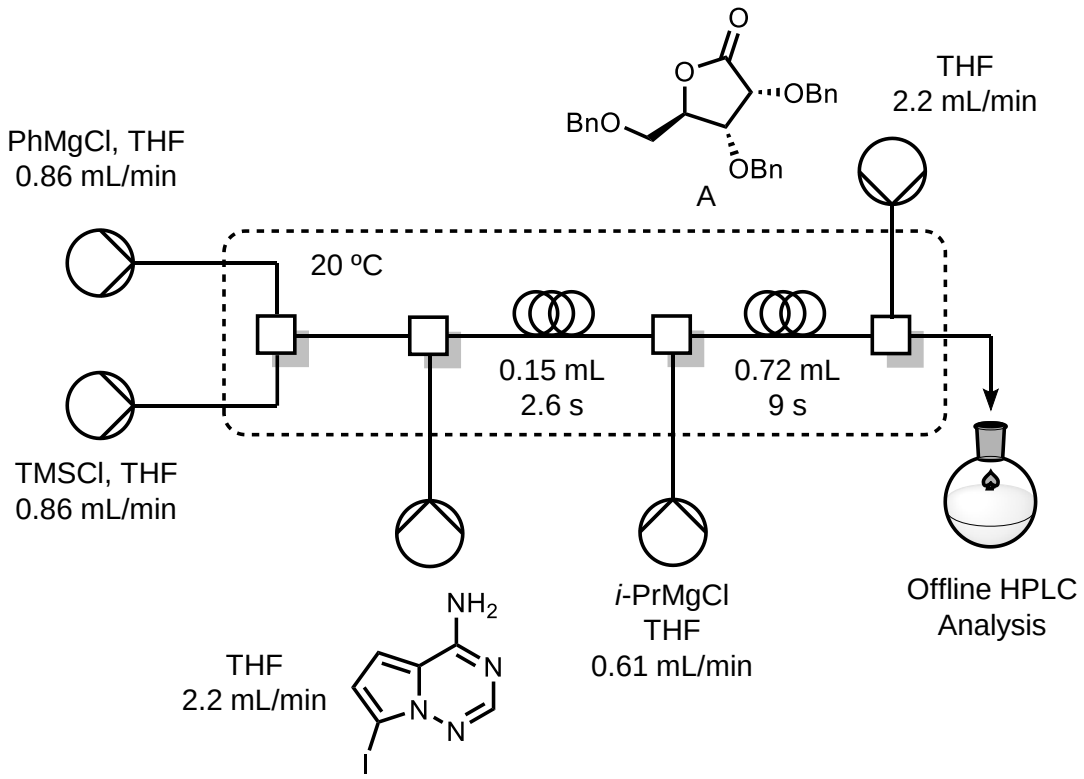


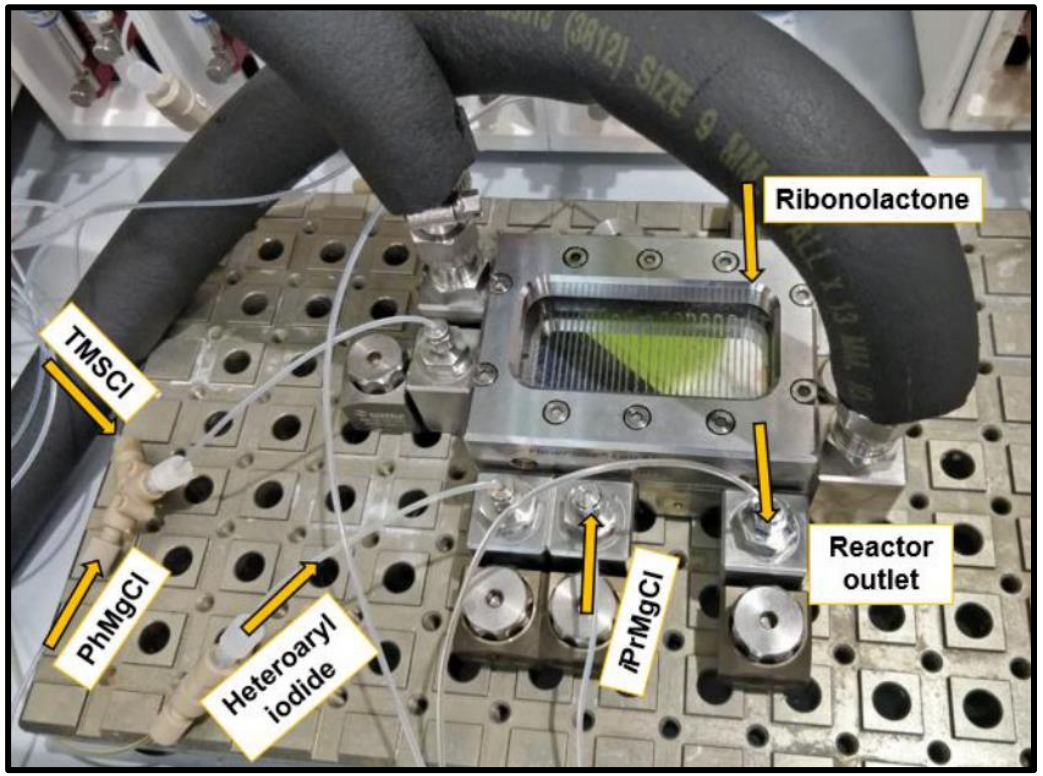


Adamo, A. et. al. *Science* **2016**, *352*, 61-67.

Scaling of Remdesivir Glycosylation

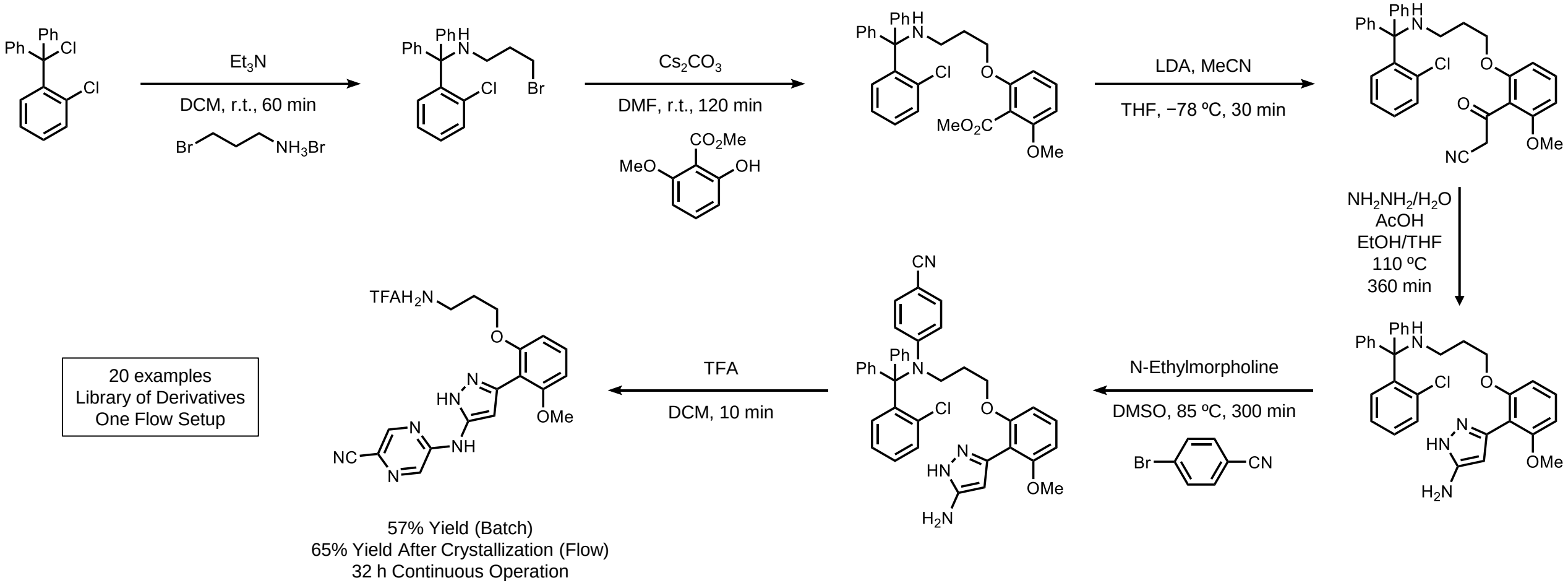






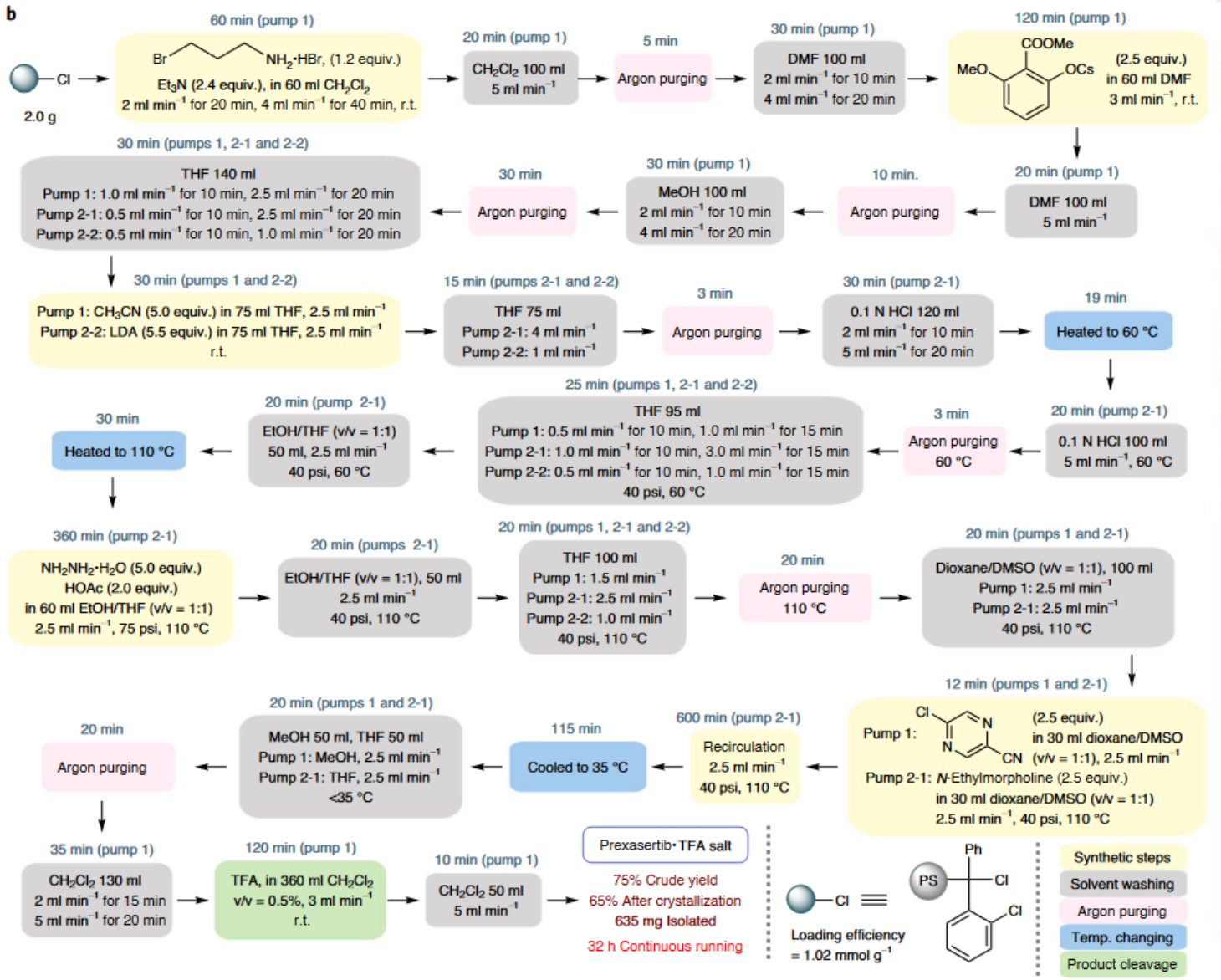
von Keutz, T. et. al. *Org. Process Res. Dev.* **2020**, *24*, 2362-2368.

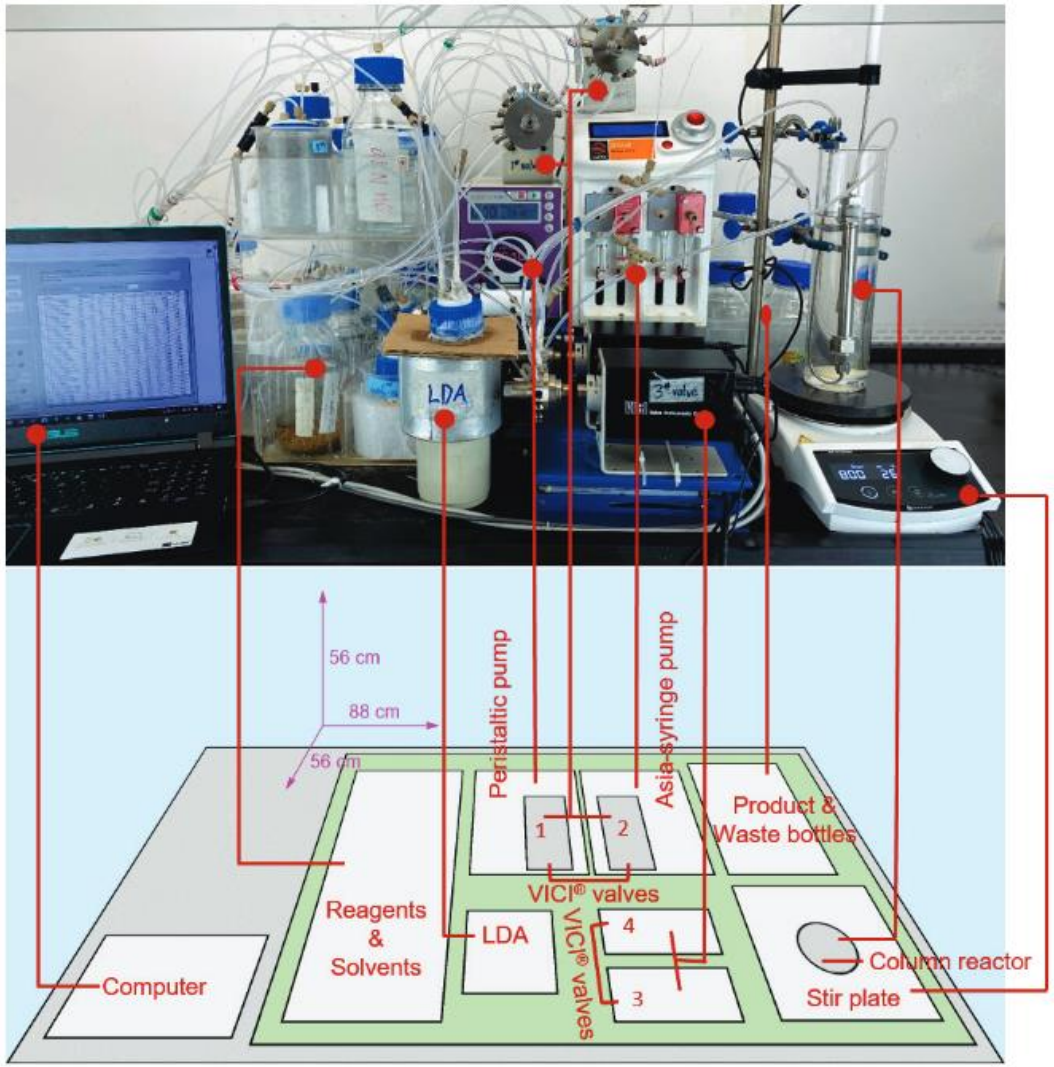
High-Throughput Screening



Liu, C. et. al. *Nat. Chem.* **2021**, *13*, 451-457.

High-Throughput Screening





Liu, C. et. al. *Nat. Chem.* **2021**, *13*, 451-457.