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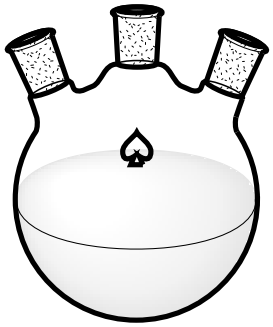
University of Illinois, Urbana-Champaign

Autonomous Optimization of Chemical Reactions in Flow

Denmark Lab Group Meeting
February 12, 2019

Batch vs. Flow

Batch Reactors



Advantages

Most Laboratory Scale, Literature Procedures are in Batch

Easy to use stoichiometric solid reagents / deal with solid byproducts

Easy to Optimize Discrete Variables

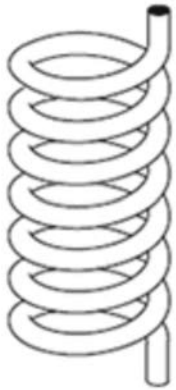
Disadvantages

Temperature Gradients

Mass / Phase Transfer can be problematic
Mixing is not uniform

Larger Scale necessitates Larger Reactor

Flow Reactors



Advantages

Efficient Heat Transfer

Efficient and Uniform Mixing
Pressure control

Easily Scalable

Safely use with Hazardous Substances

Easy to optimize continuous variables

Disadvantages

Few examples of optimized systems accessible to the synthetic chemist

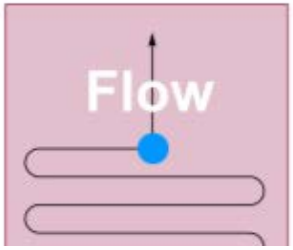
Dealing with solids reagents or byproducts (NOT catalysts) can be challenging

Optimization of discrete variables is a an active area of research

CHEMICAL REVIEWS

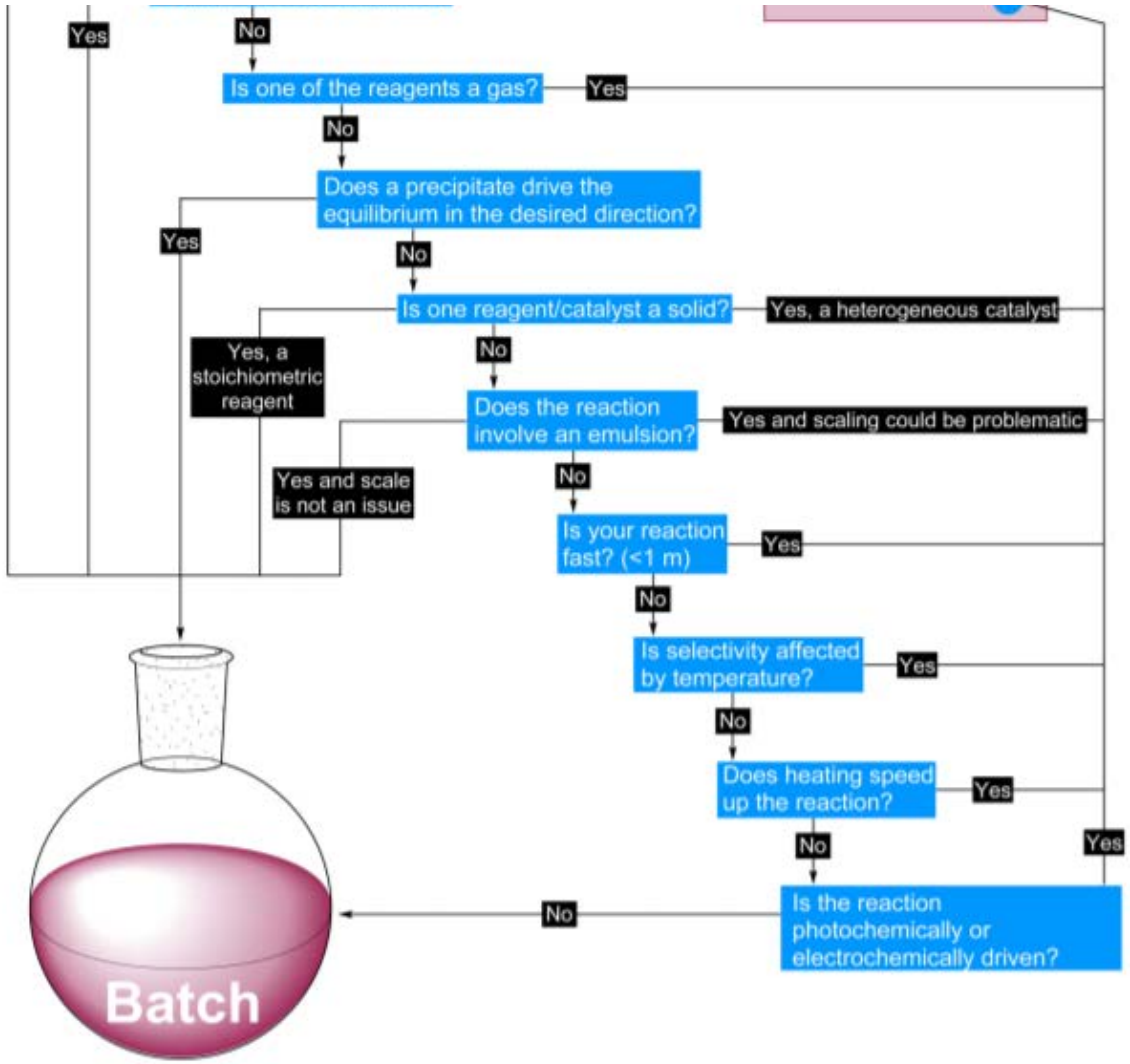
swer to the ultimate question
verse, and everything?

fe in batch? No



The Hitchhiker's Guide to Flow Chemistry‖

Matthew B. Plutschack§†, Bartholomäus Pieber§†, Kerry Gilmore*†, and Peter H. Seeberger*†‡



Outline Slide

Anatomy of Flow Chemistry

Optimization of Continuous Variables

Optimization of Discrete Variables

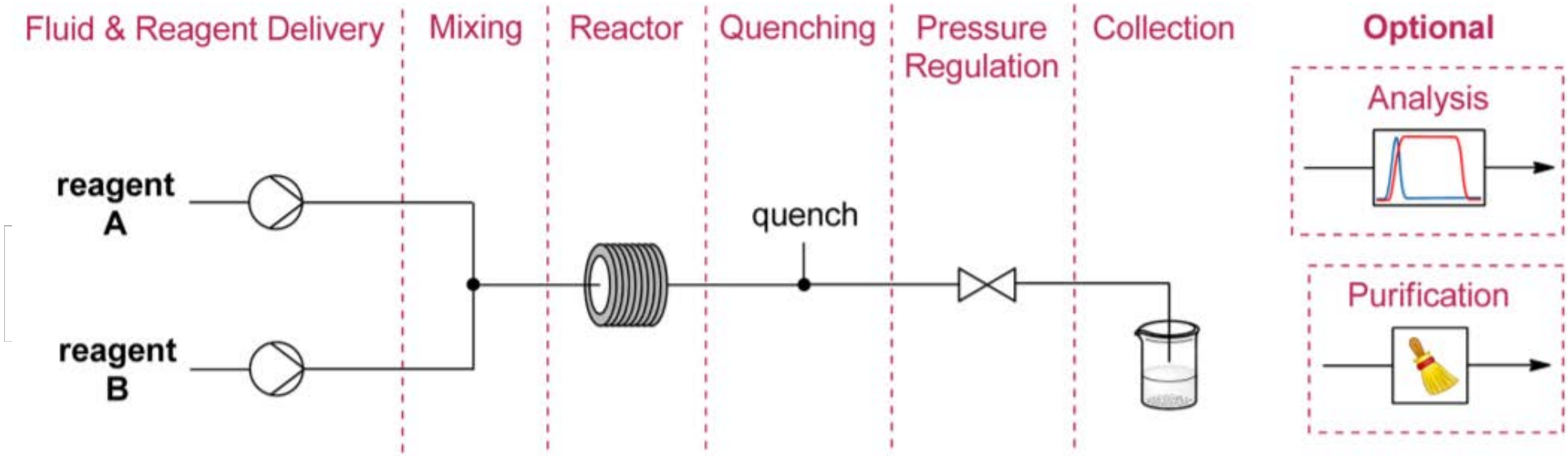
Outline Slide

Anatomy of Flow Chemistry

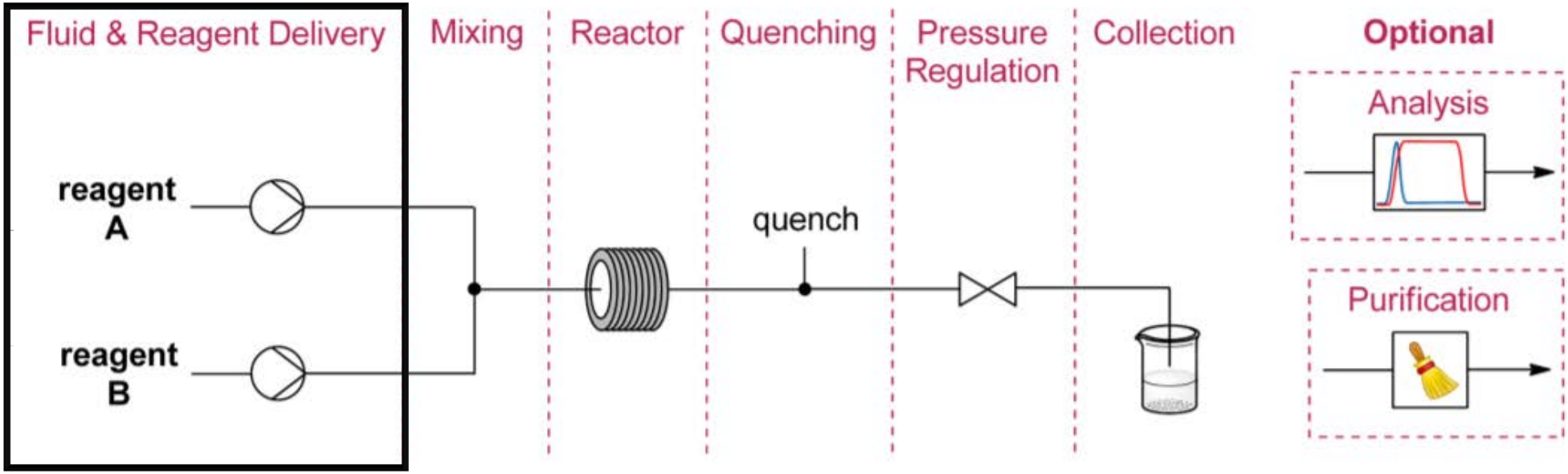
Optimization of Continuous Variables

Optimization of Discrete Variables

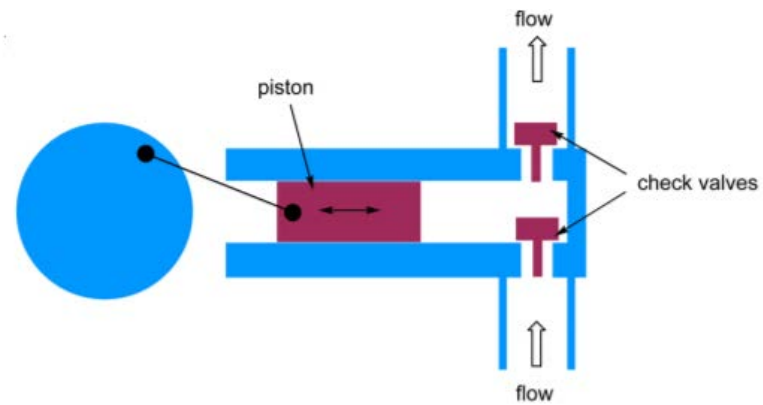
Anatomy of Flow



Anatomy of Flow: Reagent Delivery

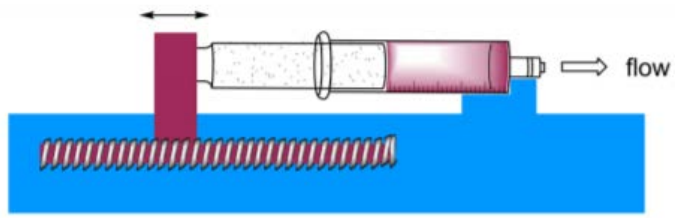


HPLC pumps



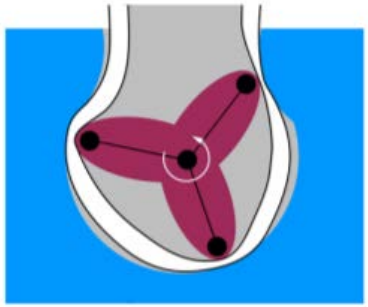
Flow rates > 0.1 mL / min
Suitable for high pressures

Syringe pumps



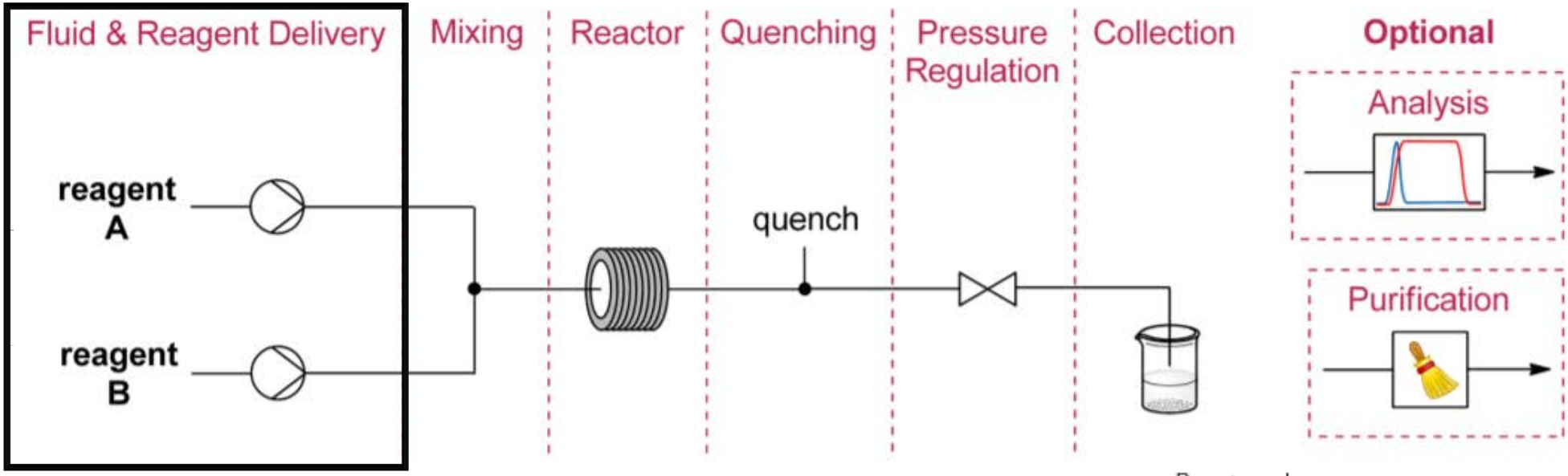
Lower Flow Rates
Constant Pressure
Usually Cheaper

Peristaltic pumps

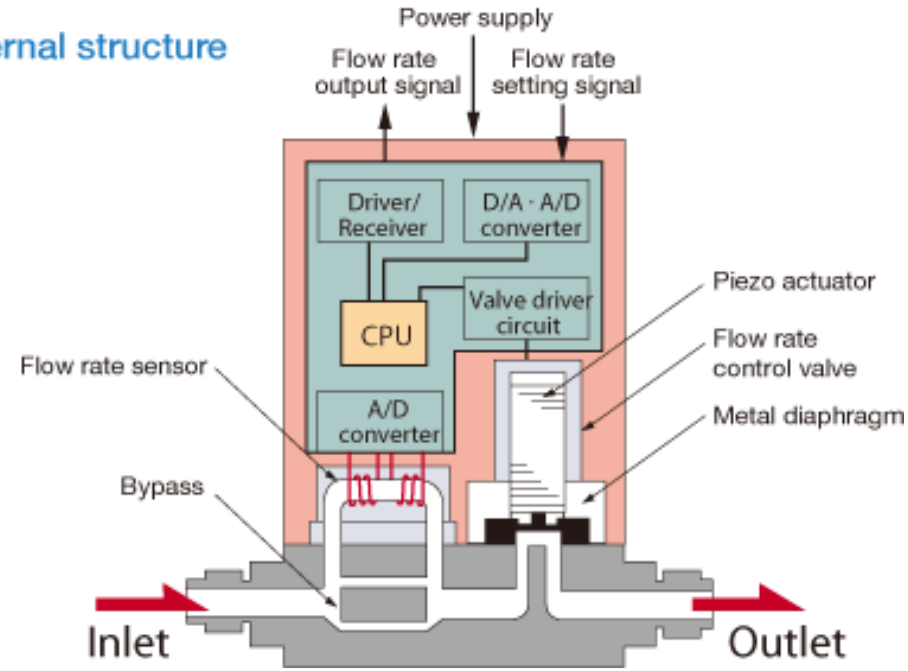


Generally more robust
Can pump well-suspended slurries

Anatomy of Flow: Reagent Delivery



▶ Internal structure



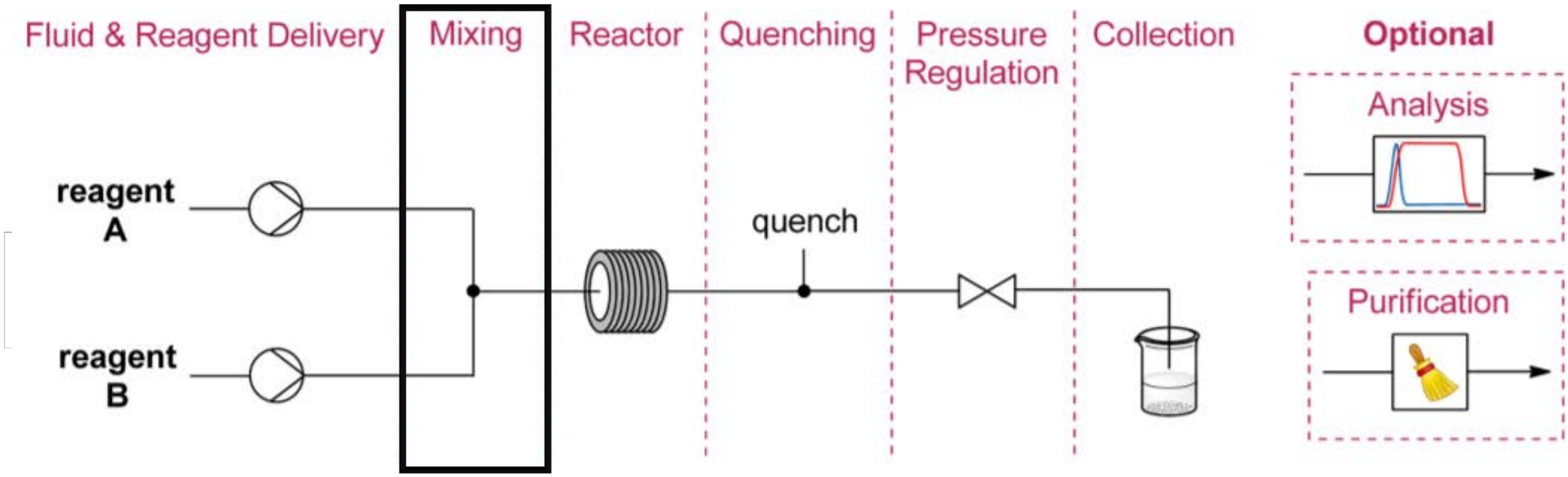
Gas Delivery:

1) Directly from tank

2) Precise delivery regulated by thermal mass flow controllers

Solids are typically avoided!

Anatomy of Flow: Mixing



Micromixer

T-shap

SAR-t

Multilamina

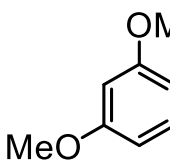
Tube-in-tube gas addition apparatus:

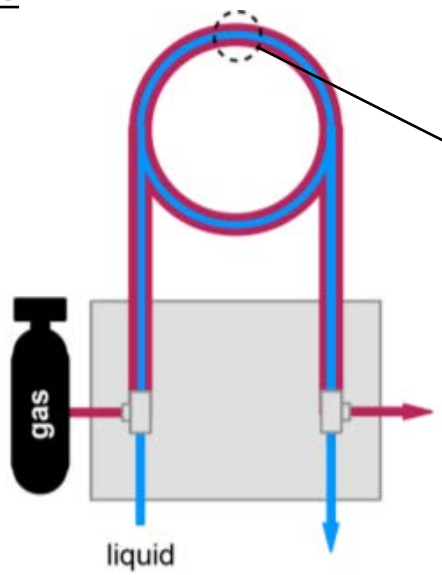
% Yield

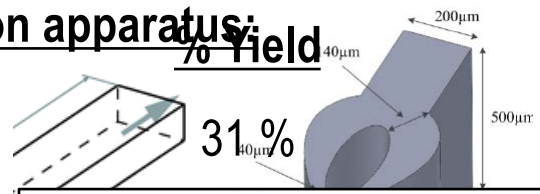
31 %

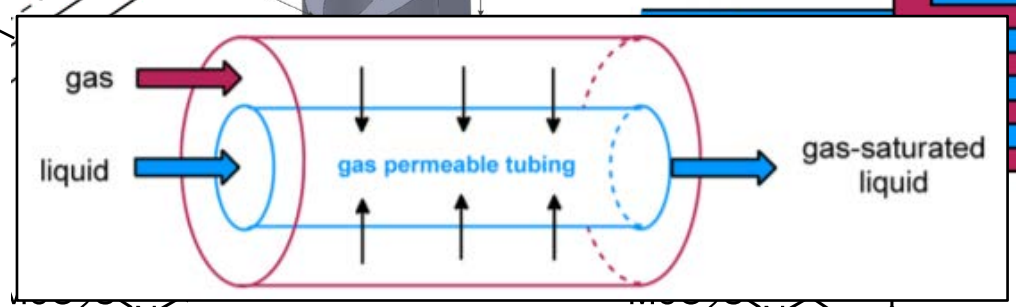
% Yield

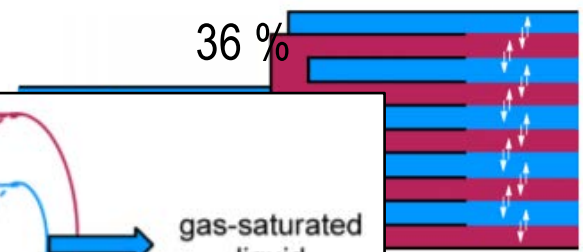
36 %

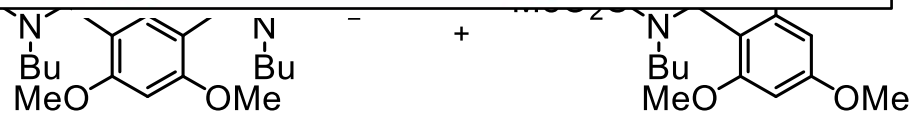








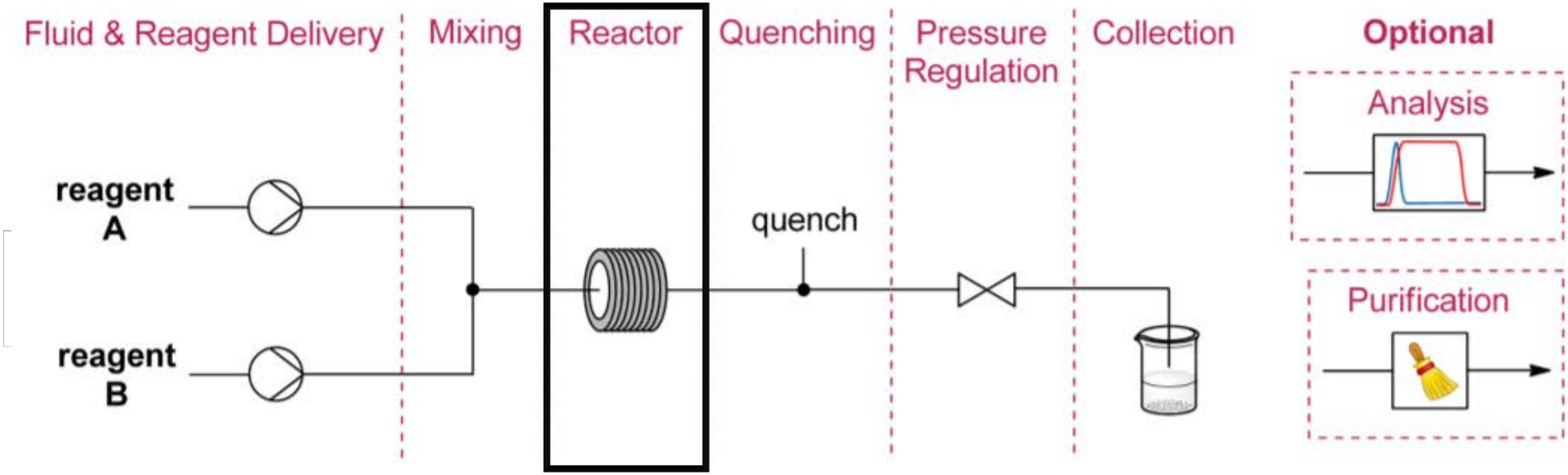




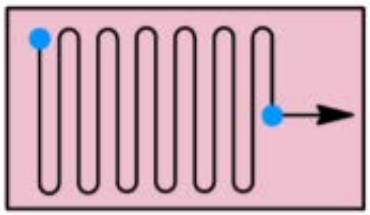
Nishino *et al. Lab Chip.* **2013**, *13,* 1515-1521. Yoshida *et al. J. Am. Chem. Soc.* **2005**, *127*, 11666-11675.

Image from: https://www.researchgate.net/figure/Schematic-illustration-of-the-SAR-micromixer-with-ellipse-like-micropillars-geometry-and_fig4_269008805

Anatomy of Flow: Reactors

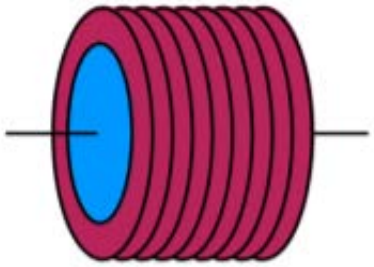


Chip Reactor



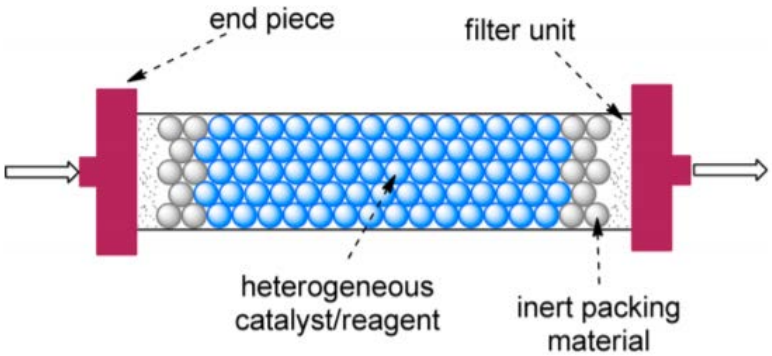
Best Heat Transfer
Efficient Mass Usage
Tendency to Clog / Expensive

Coil Reactor



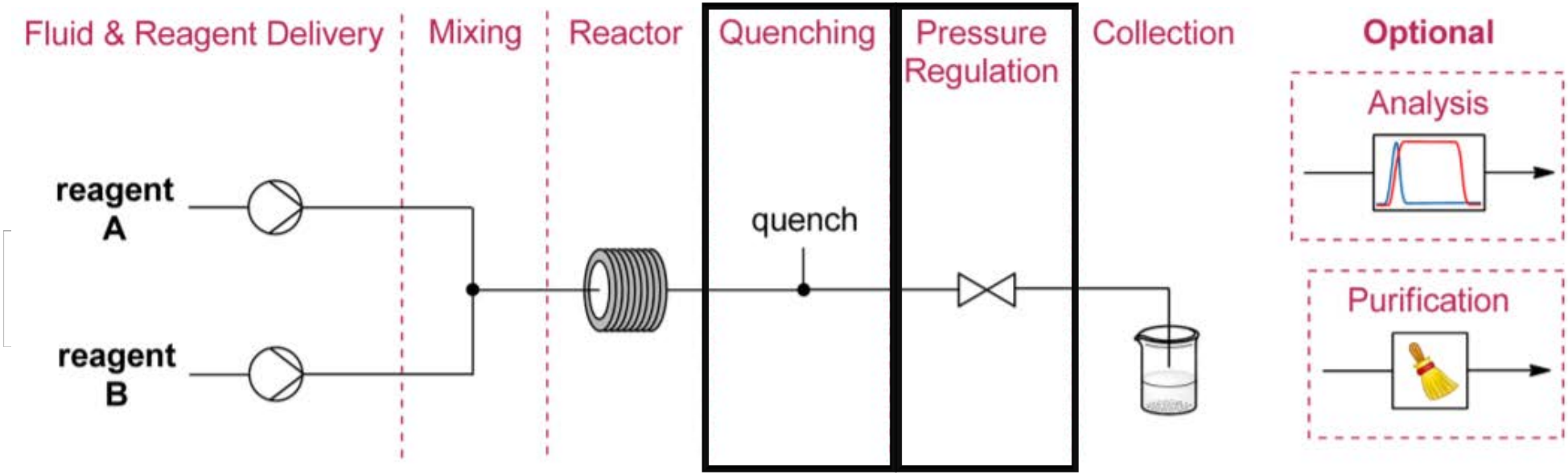
Made from readily available materials

Packed Bed Reactor



Heterogeneous Catalysis

Anatomy of Flow: Quenching and Pressure Regulation



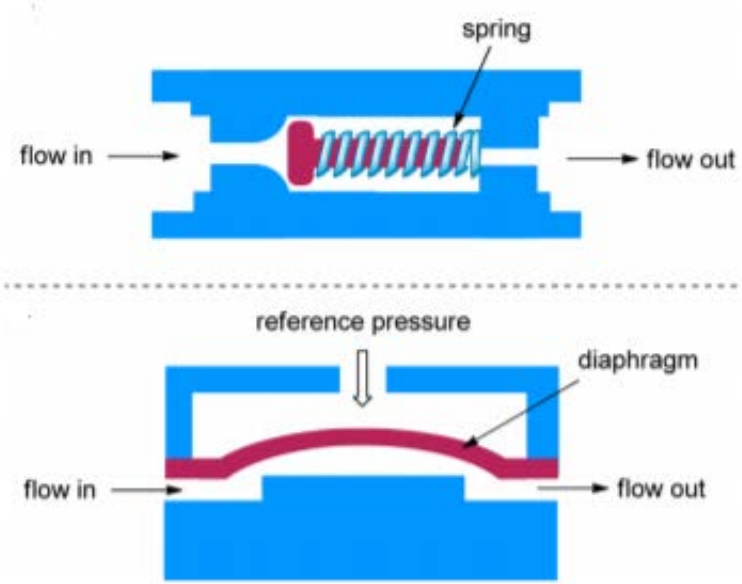
Quenching

Packed beds, photochemical / electrochemical systems stop upon leaving reactor

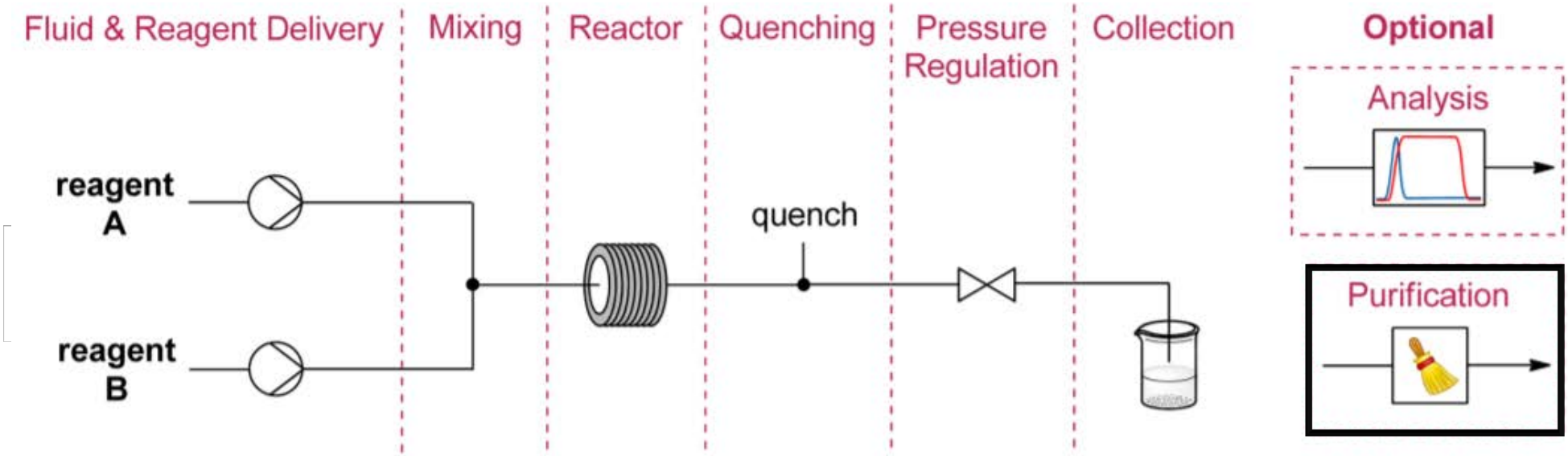
Rapid cooling

Chemical quenching

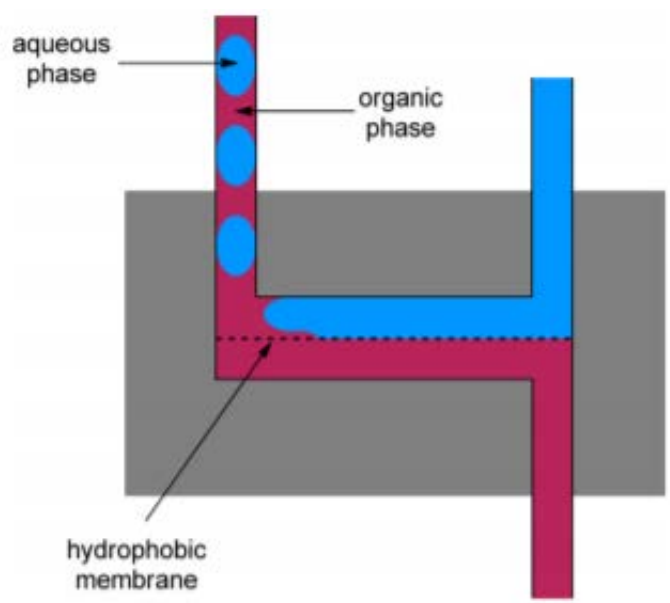
Back Pressure Regulators



Anatomy of Flow: Purification in Flow



Workups in Flow



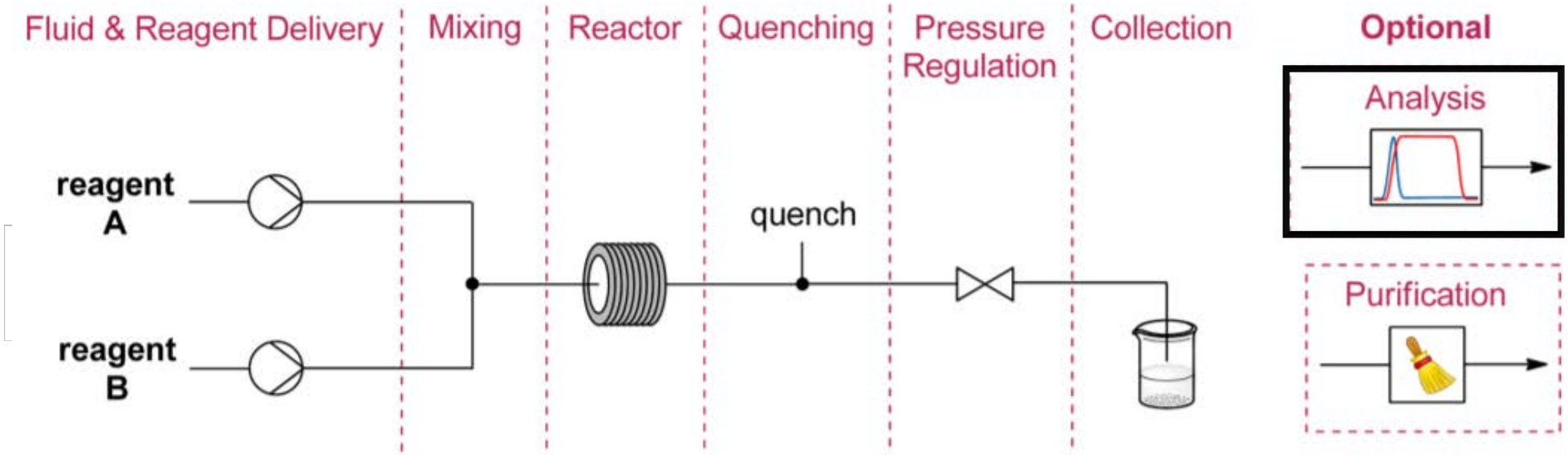
Other Purification Methods

Scavenger Cartridges

Simulated Moving-Bed Chromatography

Continuous Crystallizations

Anatomy of Flow: Analysis in Flow



Online Analysis

Periodic sampling

Examples: GC, HPLC, NMR, Mass Spec., fluorescence spectroscopy, etc.

Inline Analysis

Sampling method is 1) nondestructive and 2) allows for "real-time-analysis"

Examples: FTIR, Raman, NMR, UV-vis

Online / Inline Analysis in flow systems enable instantaneous evaluation and modification of reaction conditions.

Why optimize reactions in flow?

Precise control over reaction conditions

Screening continuous variables is very easy

Efficient use of starting materials

Inline/Online analytics allow practitioners to "see into" reaction mixture

Why isn't everyone optimizing reactions in flow?

Dealing with solids / slurries is still challenging.

Screening discrete variables is still challenging. Examples in which solvent, catalyst, additives, etc. have been screened exist, but this is more an active area of research than an established field.

Inaccessible to most laboratories

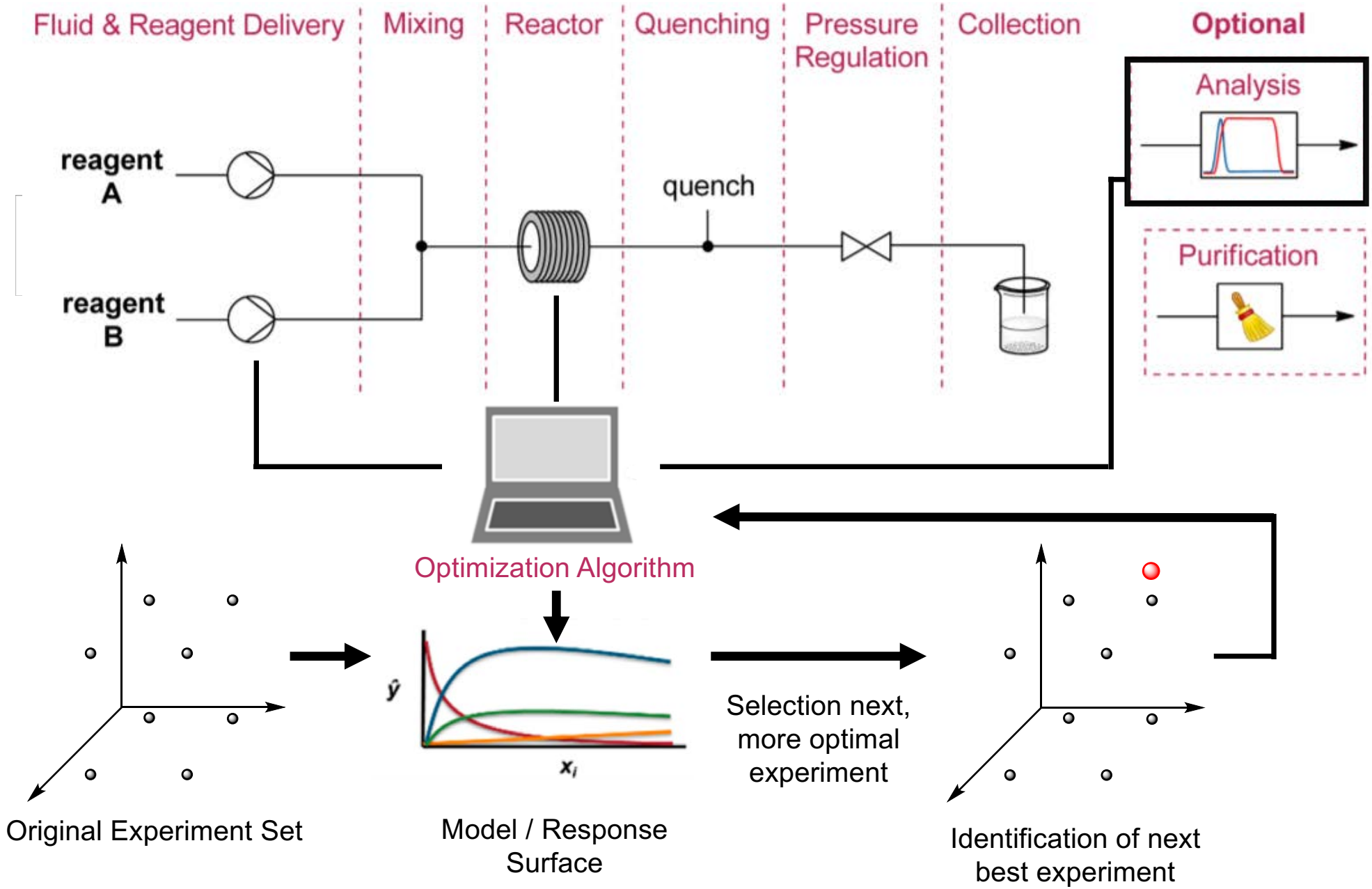
Outline Slide

Anatomy of Flow Chemistry

Optimization of Continuous Variables

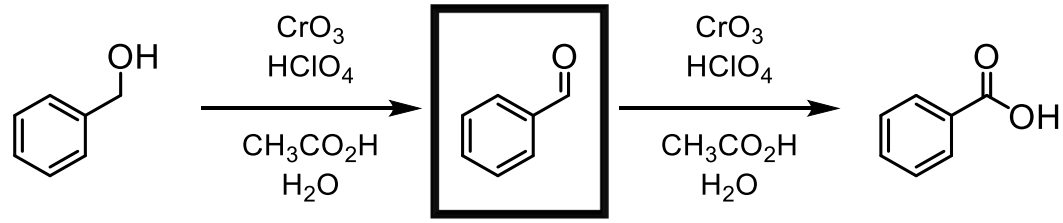
Optimization of Discrete Variables

Automated Optimization in Flow



Reizman, B.J.; Jensen, K.J. *Acc. Chem. Res.* **2016**, *49*, 1786−1796

Automated Optimization in Flow: Early Examples



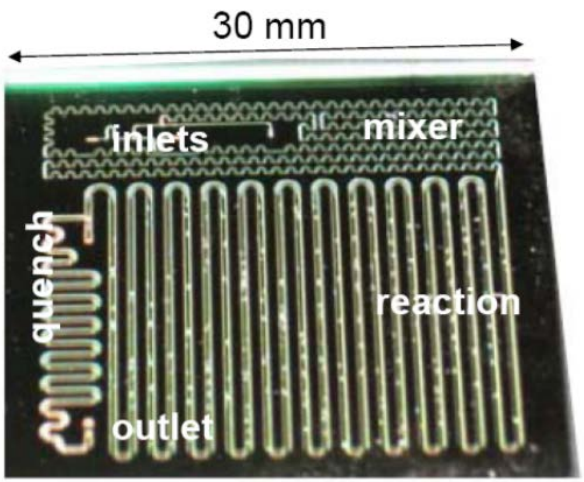
Optimization Objective = Benzaldehyde Production

Reaction Conditions Adjusted

Pump Type = Syringe Pumps
Temperature Range = -30 °C - 150 °C

LabVIEW 2018

Controls delivery (pumps)
Can also control temp, pressure



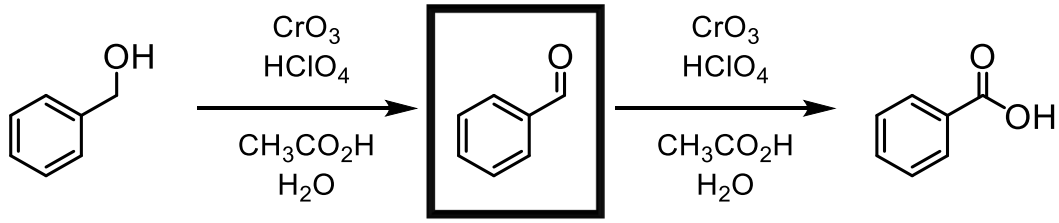
MATLAB

Nelder-Mead Simplex Optimization Algorithm

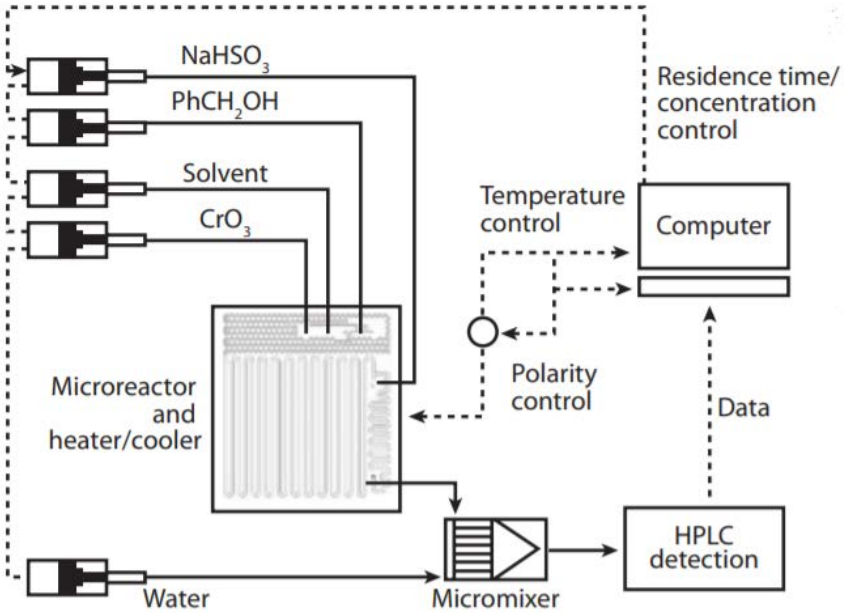
Analyzed by HPLC — *Data Exported*

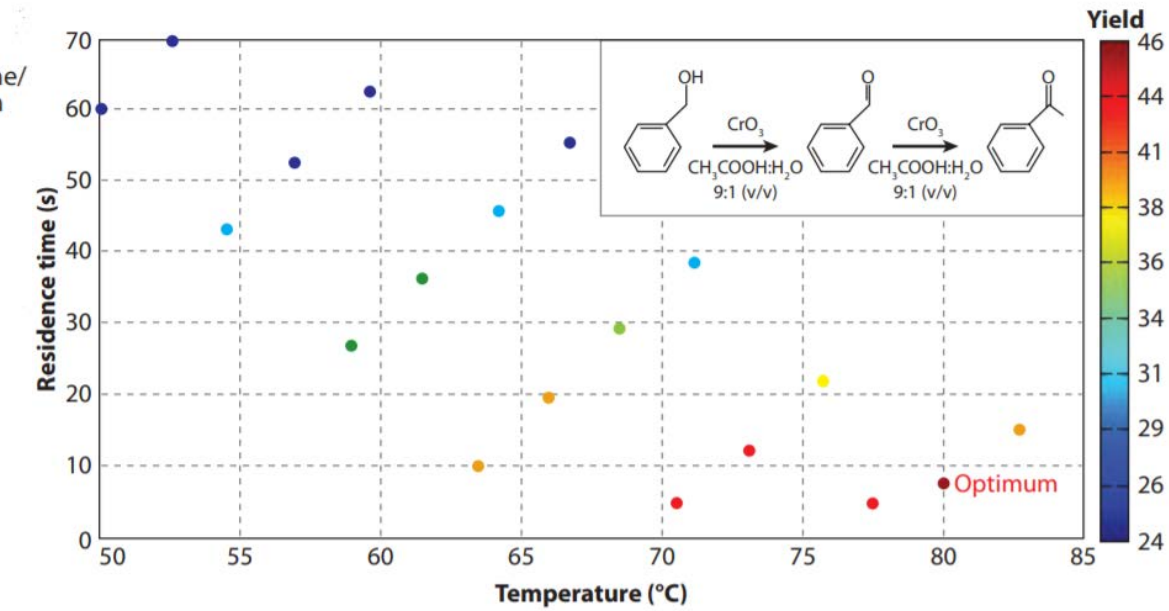
Krishnadasan S.; Brown R.J.C.; deMello A.J.; deMello J.C *Lab Chip.* **2007**, *7*, 1434-1441.
McMullen J.P.; Jensen K,F. *Proc. Int. Conf. Miniat. Syst. Chem. Life Sci. (µTAS), 12th, San Diego,* **2008,** 1908-1909.

2D Optimization of the Oxidation of Benzyl Alcohol



Optimization Objective = Benzaldehyde Production





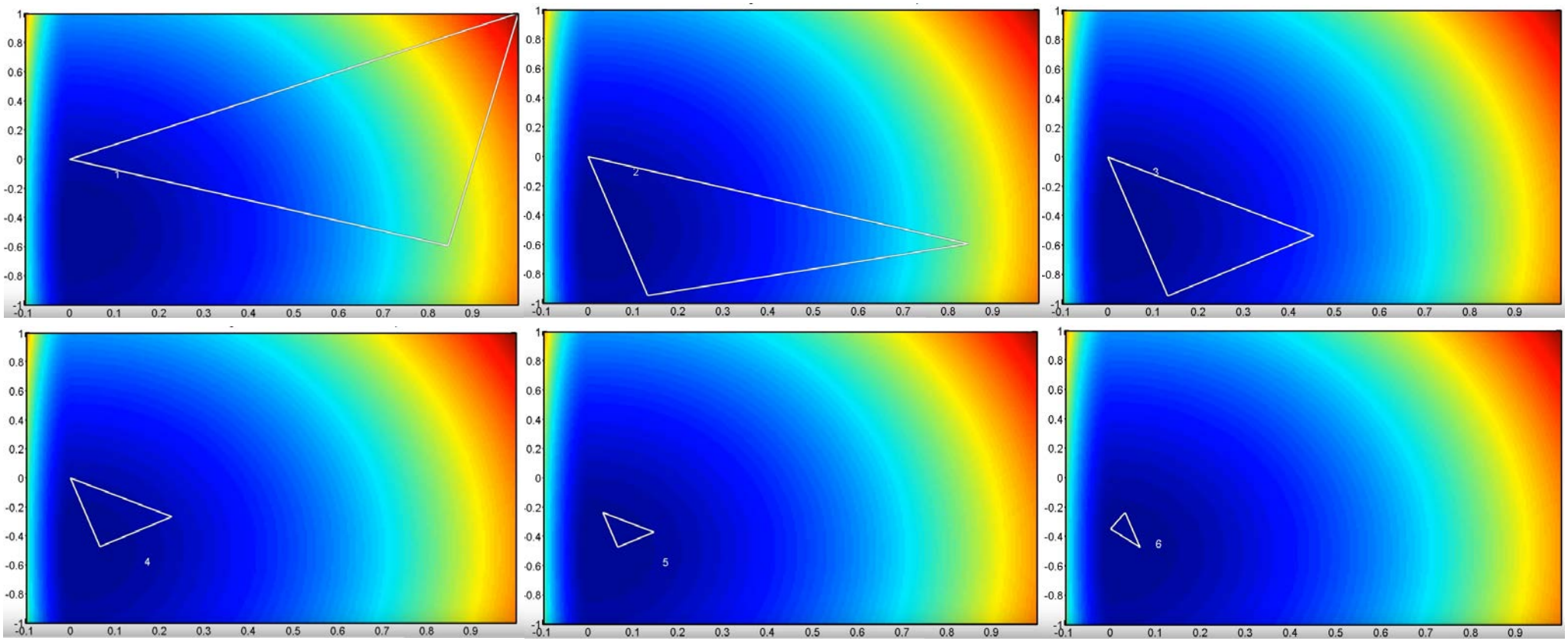
Initial Conditions: 50 °C, 60 s reaction time, 1.0 equiv. CrO_3, 8 mM benzyl alcohol, 21 % yield

2D Optimized Conditions: 80 °C, 8 s reaction time, 1.0 equiv. CrO_3, 8 mM benzyl alcohol, 46 % yield

McMullen J.P.; Jensen K,F. *Annual Rev. Anal. Chem.* **2010**, *3*, 19-42.

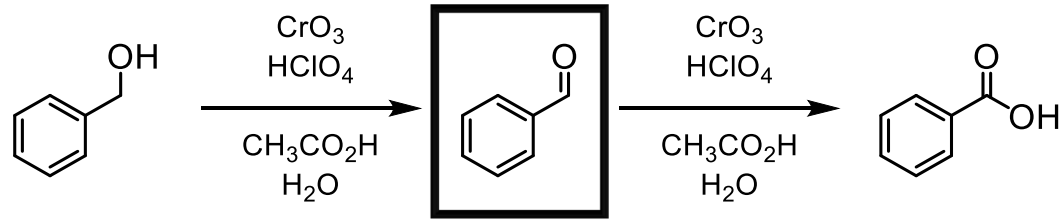
Nelder-Mead Simplex Optimization Algorithm

Define a simplex with n+1 vertices
Vertices are ordered (l, m, h)
Calculate the Centroid
Calculate a new simplex by moving the worst vertex (l)
If an improved value for the simplex is not identified, the second worst vertex (m) moves
If an improved value for the simplex is still not identified, the maximum is surrounded and the simplex shrinks towards the best (h) vertex.



Images From: https://www.youtube.com/watch?v=Db-9vFC3k-w

4D Optimization of the Oxidation of Benzyl Alcohol



Optimization Objective = Benzaldehyde Production

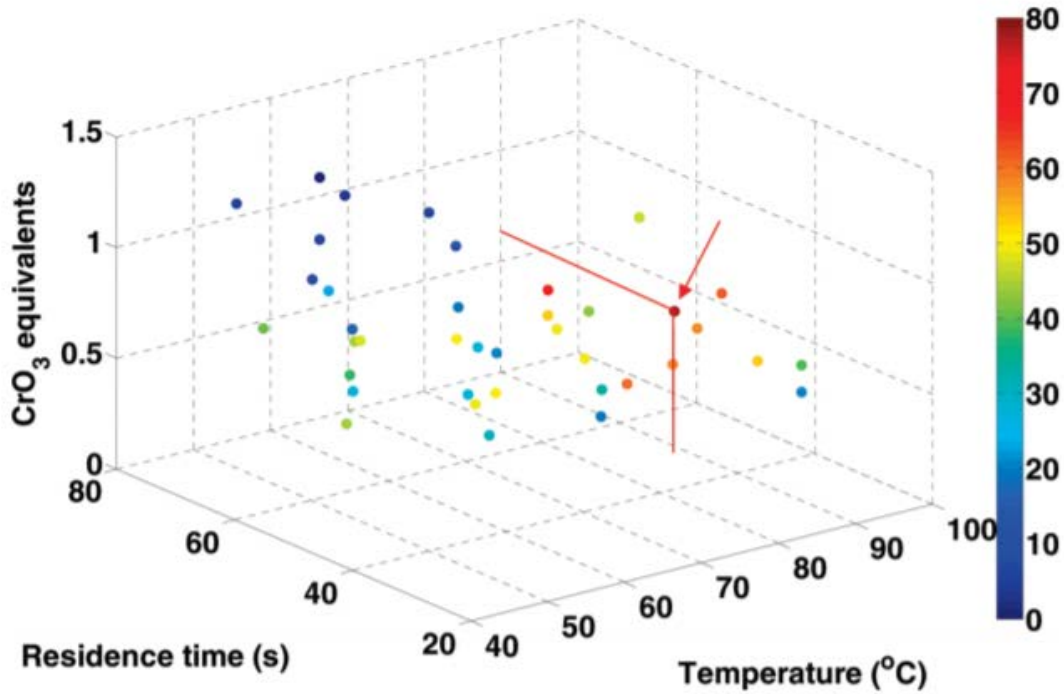
Optimization Parameters

CrO_3 concentration

Benzyl alcohol concentration

Reaction time

Temperature

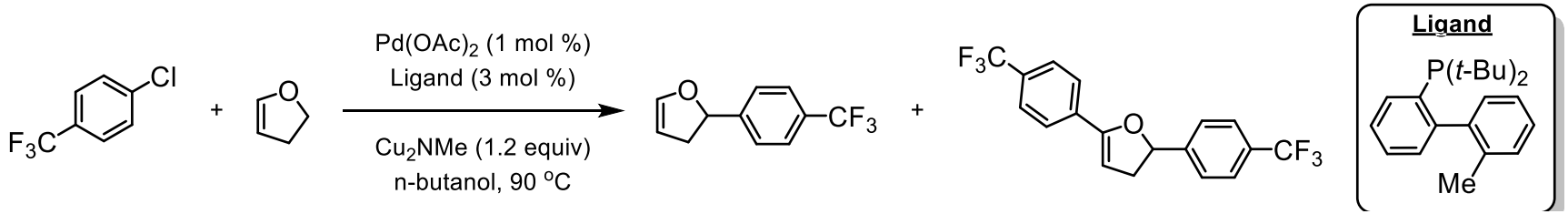


Initial Conditions: 50 °C, 60 s reaction time, 1.0 equiv. CrO_3, 8 mM benzyl alcohol, 21 % yield

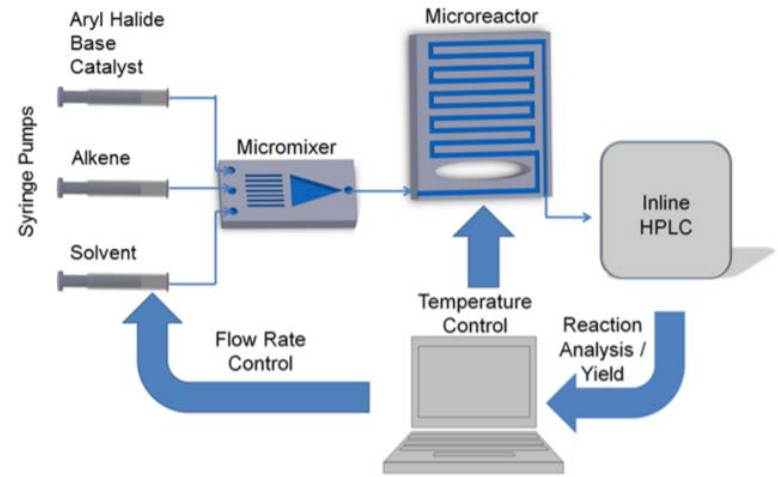
4D Optimized Conditions: 88 °C, 48 s reaction time, 0.65 equiv. CrO_3, 8.2 mM benzyl alcohol, 80 % yield

McMullen J.P.; Jensen K,F. *Org. Process Red Dev.* **2010**, *14, 1169-1176*. McMullen J.P.; Jensen K,F. *Annual Rev. Anal. Chem.* **2010**, *3,* 19-42.

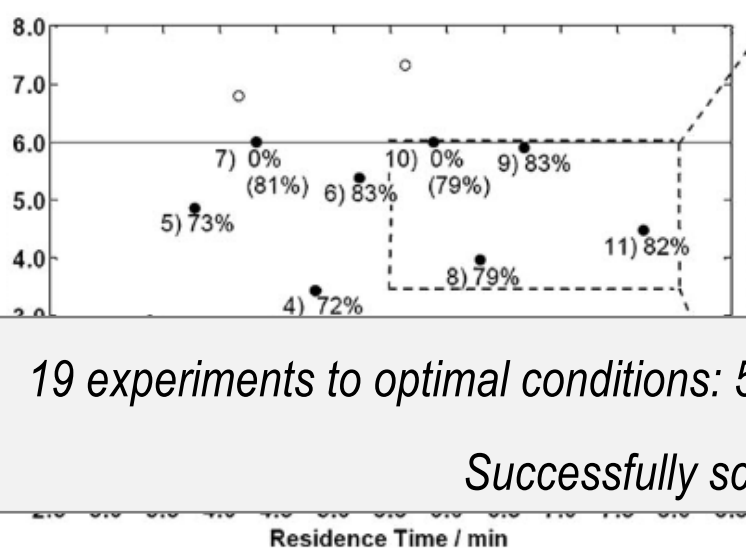
Heck Reaction Autonomous Optimization



Solvent, Ligands, and Pd Sources (discrete variables) screened prior to automated flow optimization to find conditions that did not cause clogging.



Automated Optimization Variables: Residence time and alkene equivalents (capped at 6 equiv. with use of penalty function)

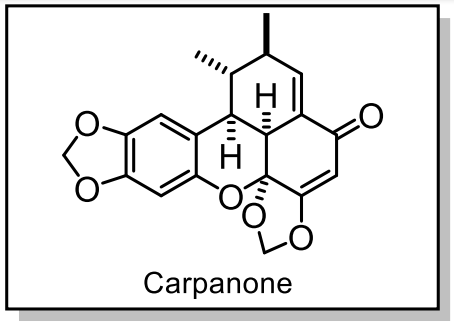


19 experiments to optimal conditions: 5.5 min residence time, 5.0 equiv. alkene

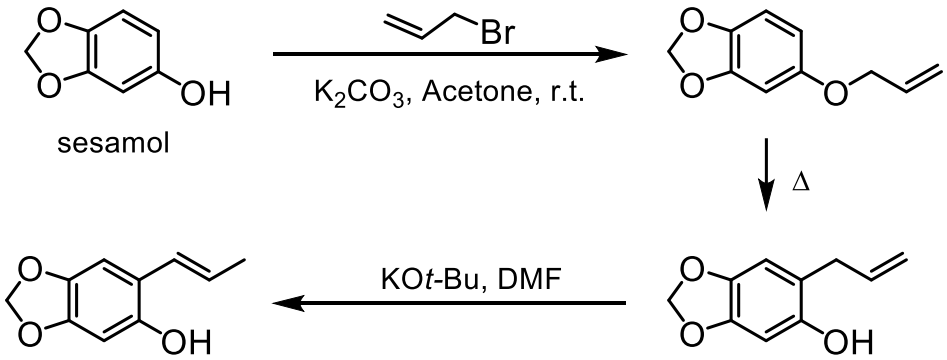
Successfully scaled up 50 times

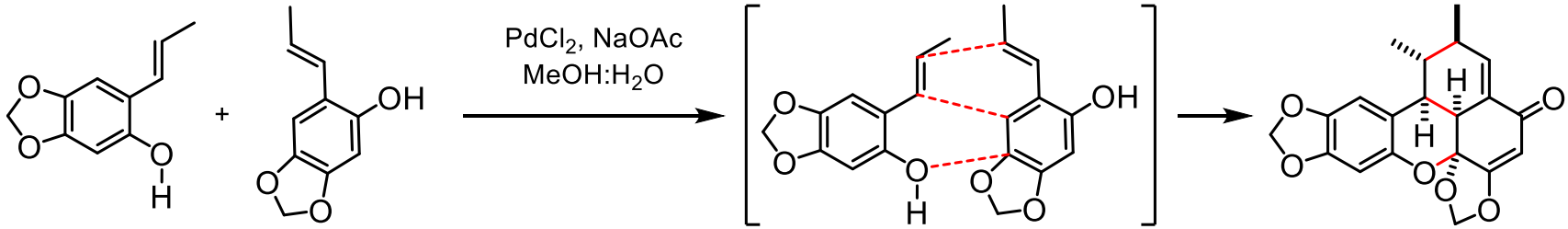
McMullen, J.P.; Stone, M.T.; Buchwald, S.L.; Jensen, K.F. *Angew. Chem. Int. Ed.* **2010**, *49*, 7076-7080

Total Synthesis of Carpanone



Lignin-Type natural product (racemic)
Many syntheses (first by Chapman in 1971)
No biological activity



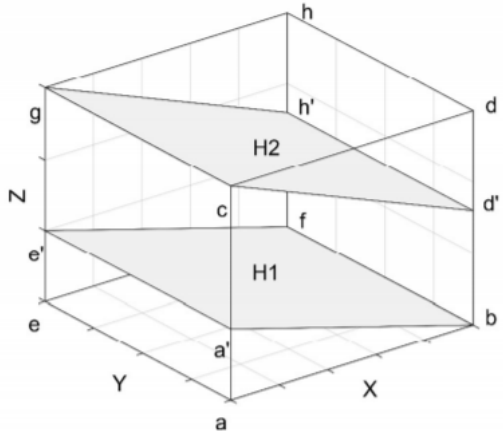


Is it possible to create a self-optimizing system for the continuous production of Carpanone?

Strategy

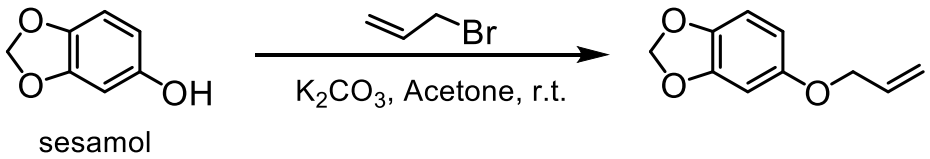
Use of inline NMR / online HPLC for feedback

Modified NMS algorithm with dimensionality reduction and golden section search algorithm

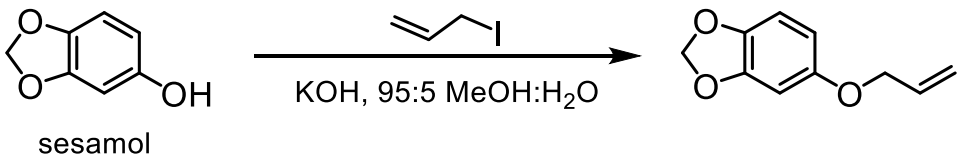


Chapman, O.L. *J. Am. Chem. Soc.* **1971**, *93*, 6697–6698. Felpin *et al. J. Org. Chem.* **2018**, *83*, 14286-14299

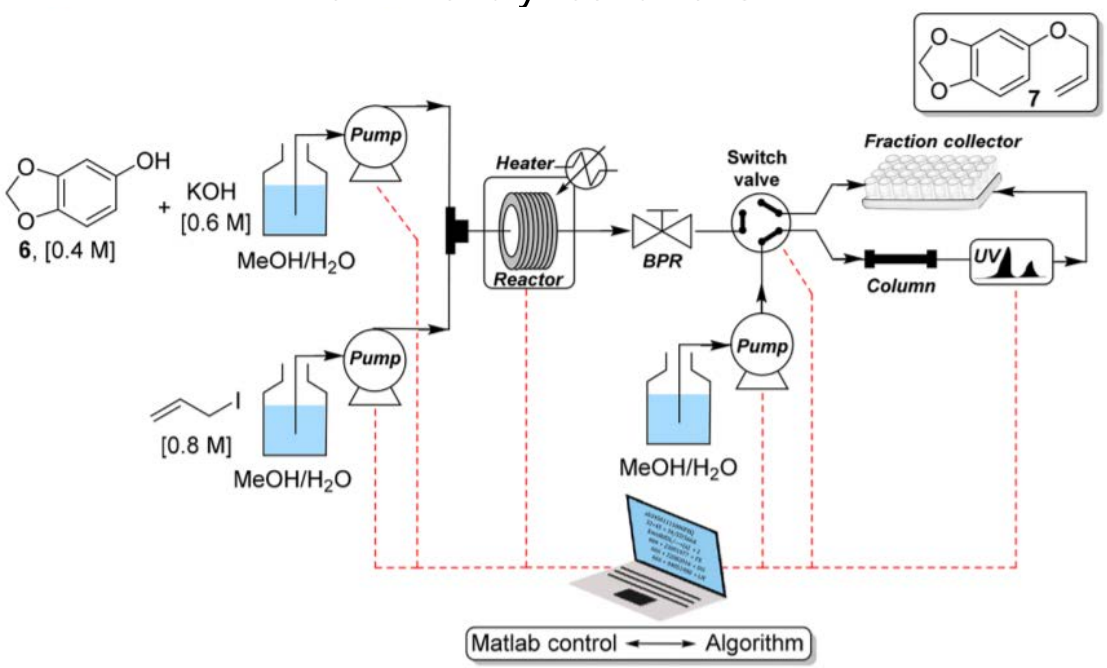
Optimization of the Allylation of Sesamol

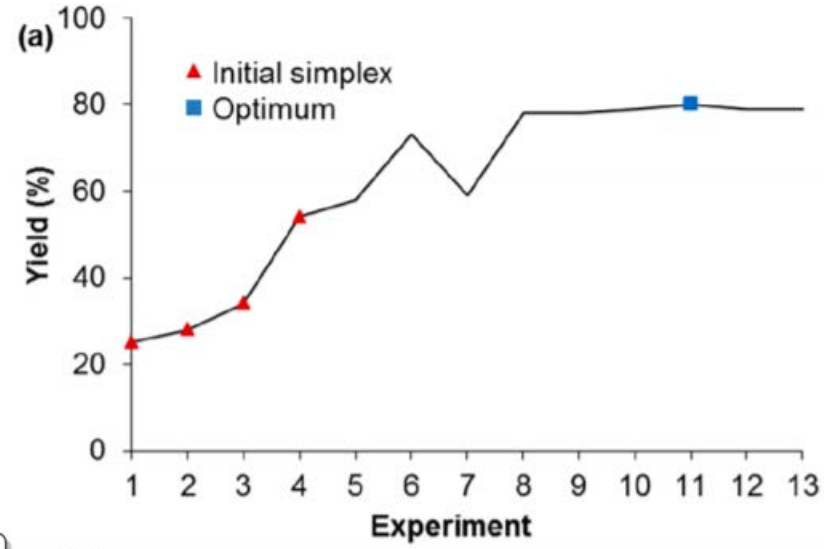


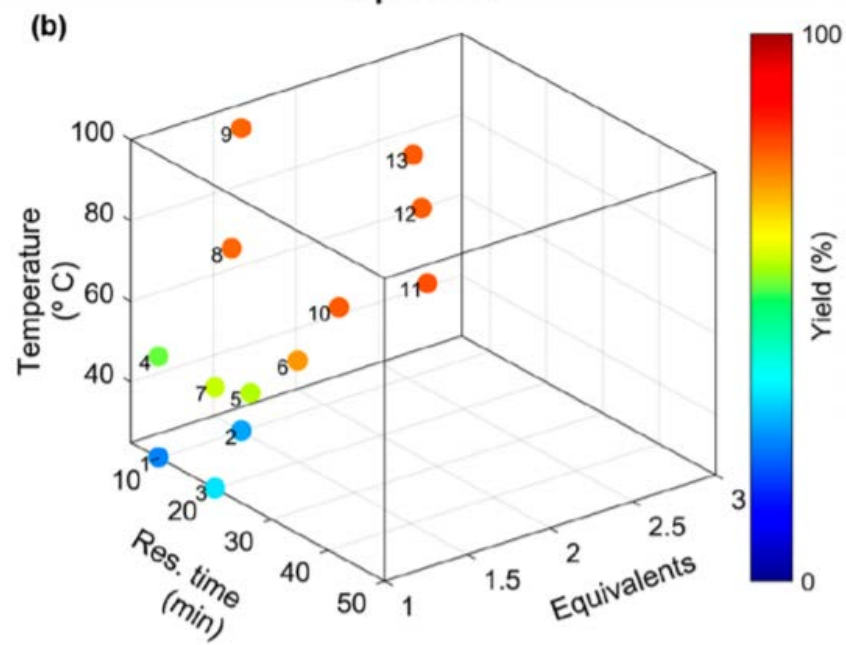
Solid K_2CO_3 and KBr not amenable to flow



"Flow Friendly" conditions



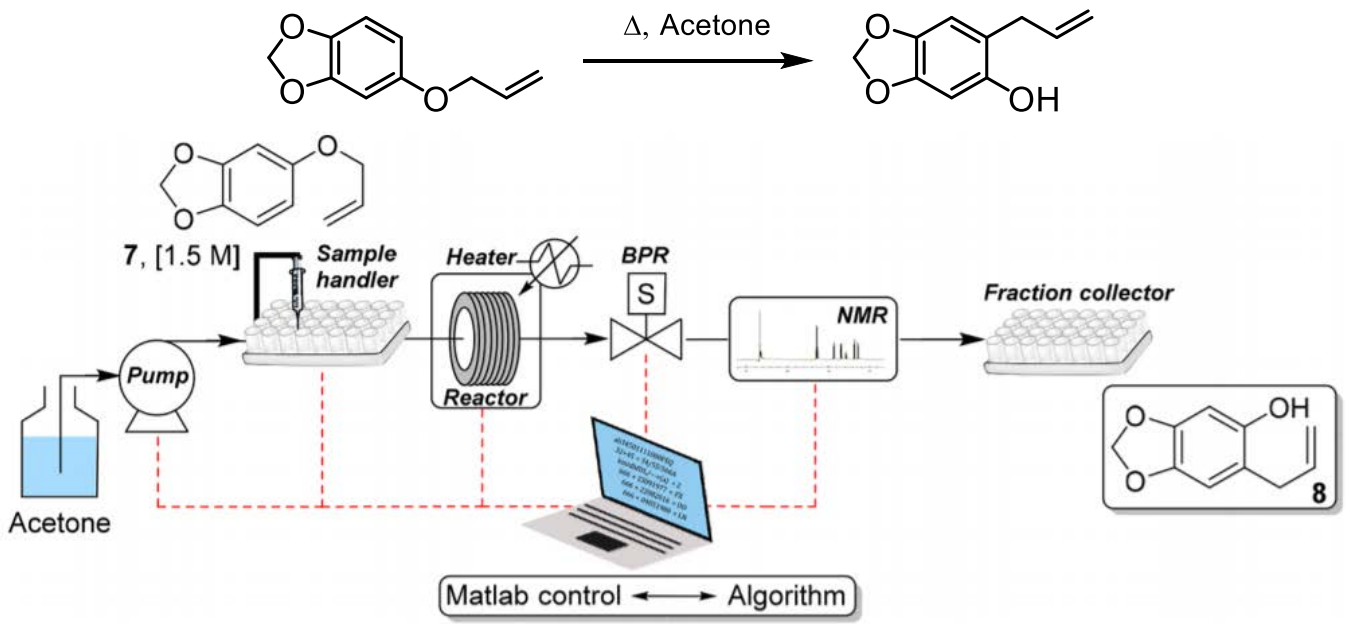


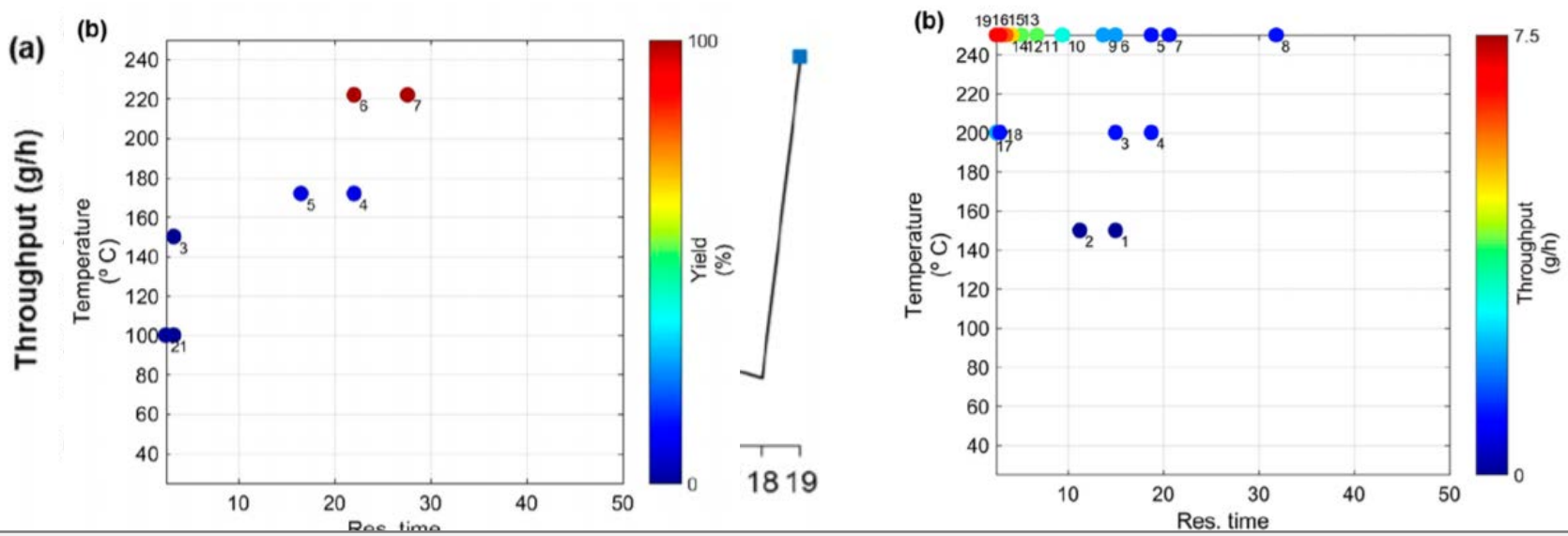


Final Conditions: 75 °C, 33.3 min residence time, 1.83 equiv. of allyl iodide, 80 % yield

Felpin *et al. J. Org. Chem.* **2018**, *83*, 14286-14299

Claisen Rearrangement Optimization

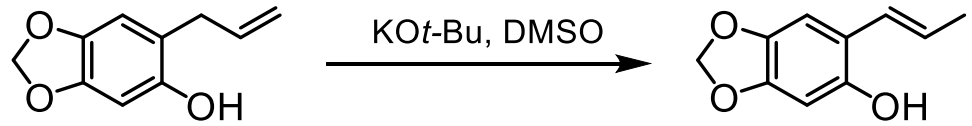


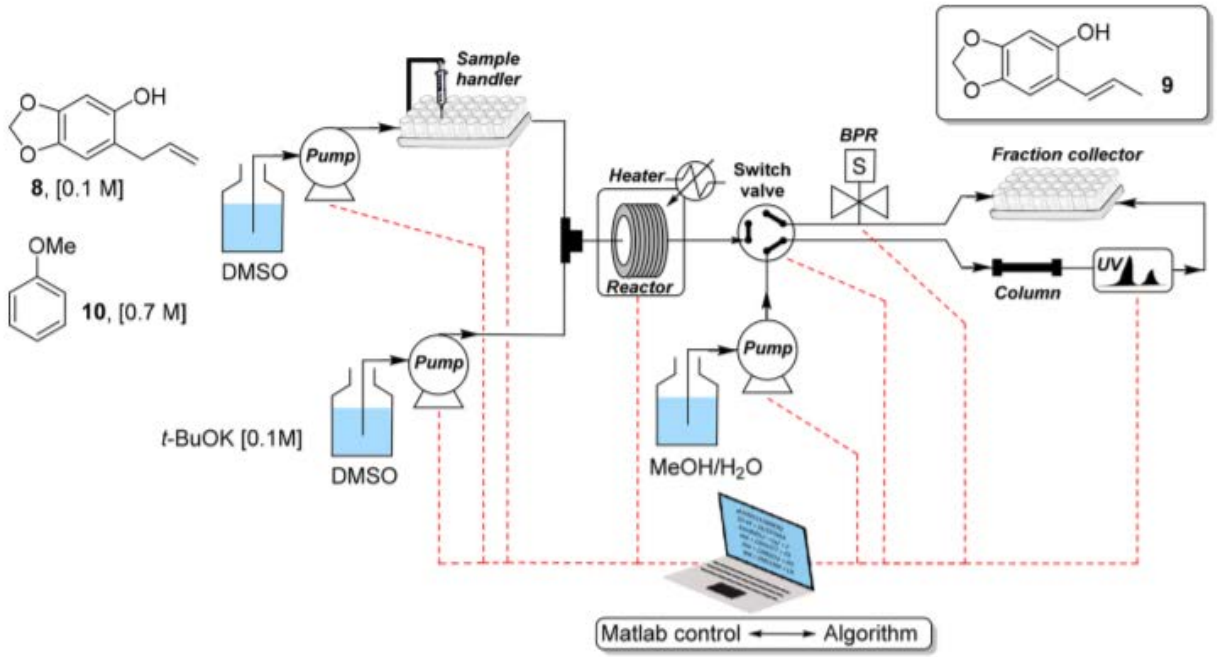


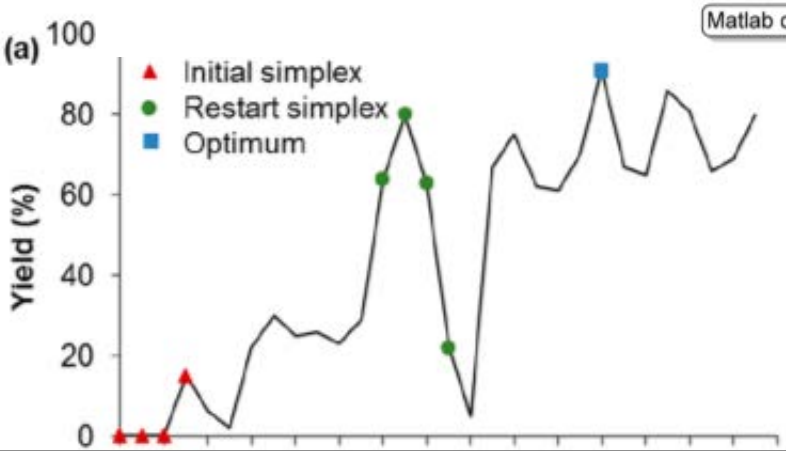
Final Conditions: 250 °C, 2.5 min residence time, 1.83 equiv. of allyl iodide, 7.5 g / hr

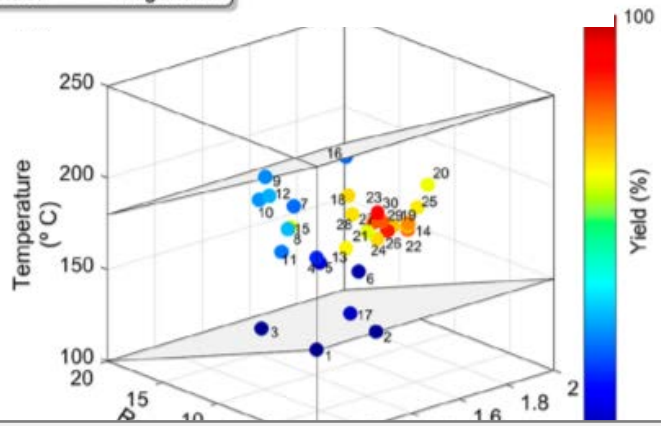
Felpin *et al. J. Org. Chem.* **2018**, *83*, 14286-14299

Optimization of the Isomerization of Allyl Sesamol





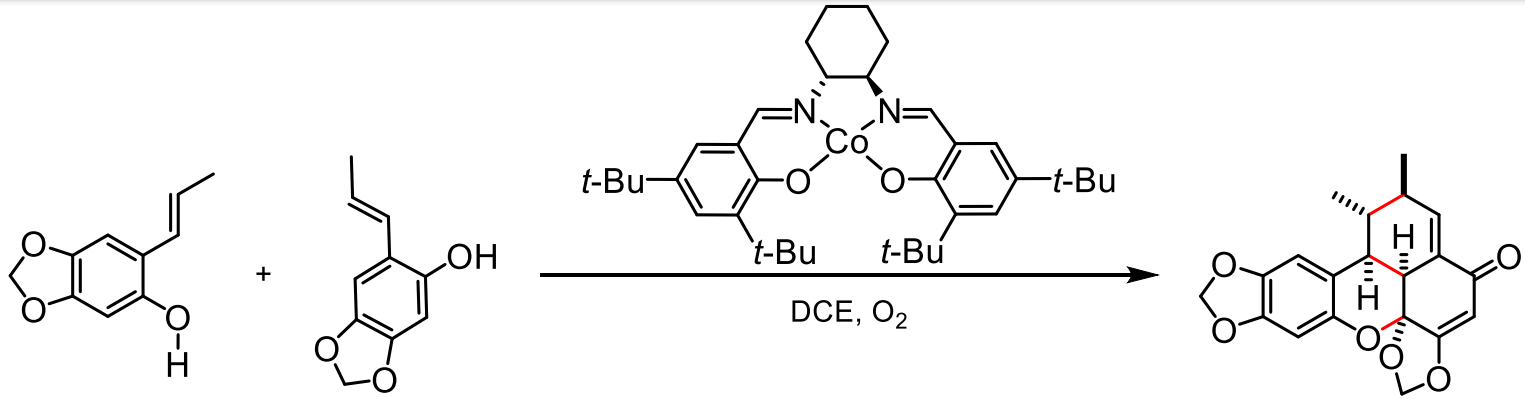


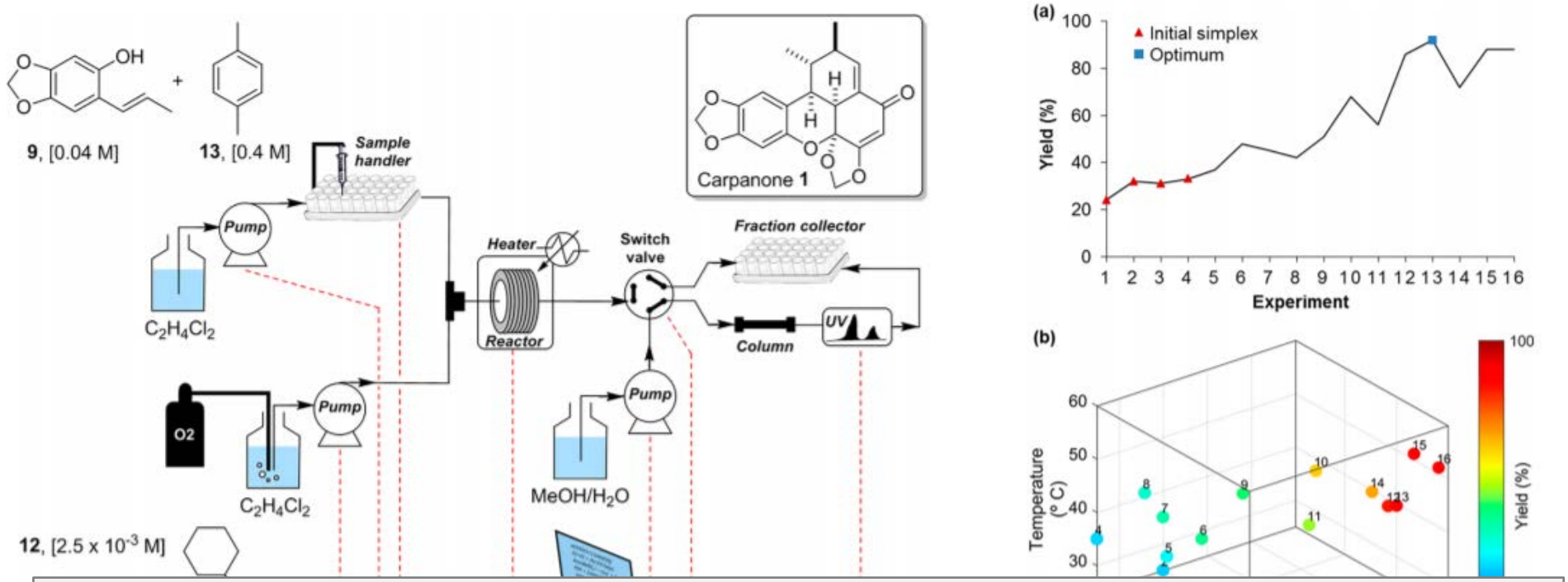


Final Conditions: 204 °C, 3.7 min residence time, 1.38 equiv. of KO*t*-Bu, 91 % yield

Felpin *et al. J. Org. Chem.* **2018**, *83*, 14286-14299

Optimization of the Oxidative Coupling to form Carpanone





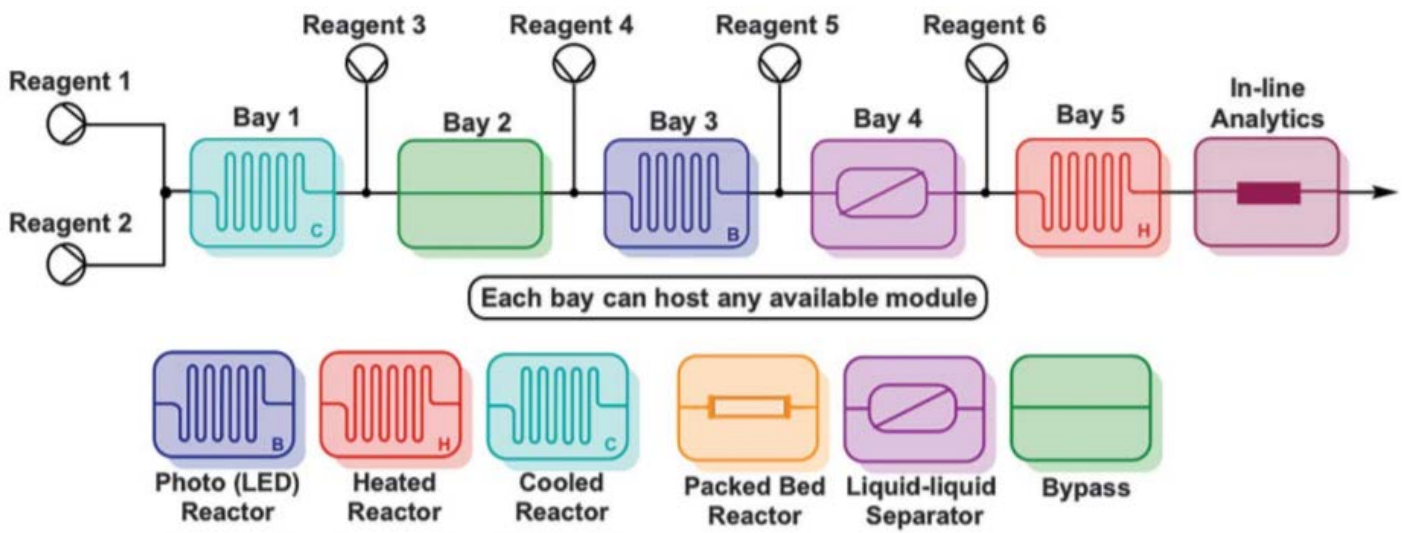
Final Conditions: 40 °C, 40.2 min residence time, 10 mol % catalyst, 92 % yield

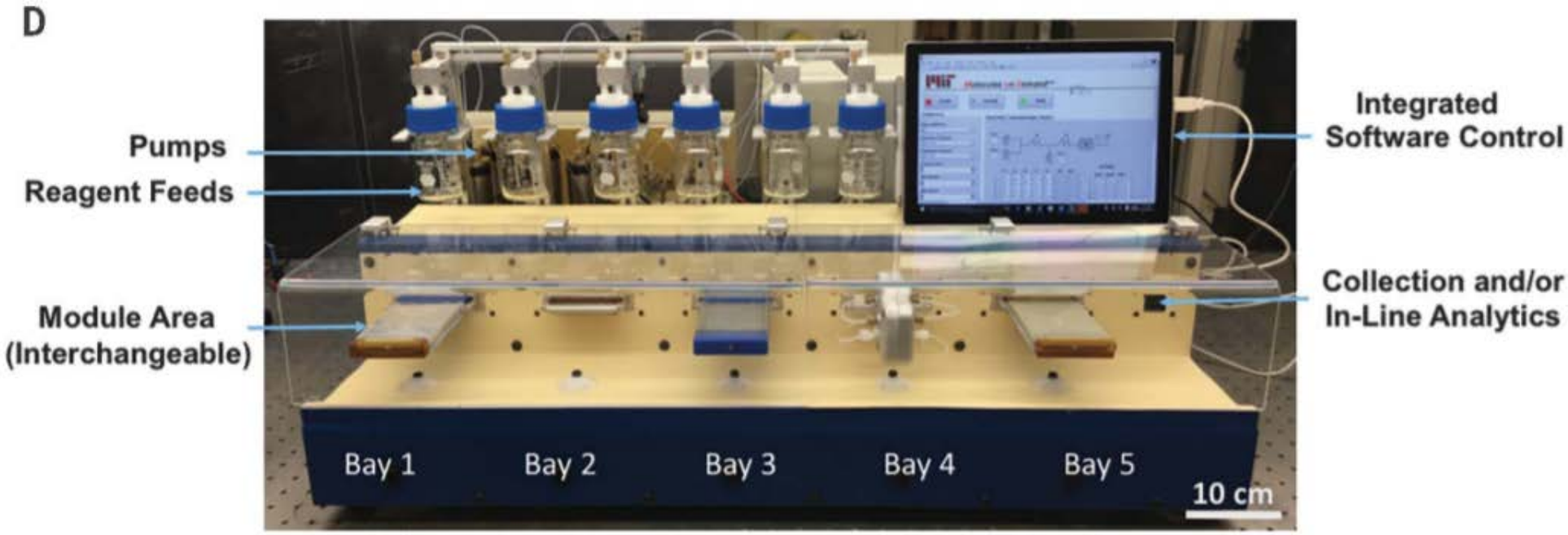
67 % overall yield with 66 experiments in the total optimization

Felpin *et al. J. Org. Chem.* **2018**, *83*, 14286-14299

Intermission

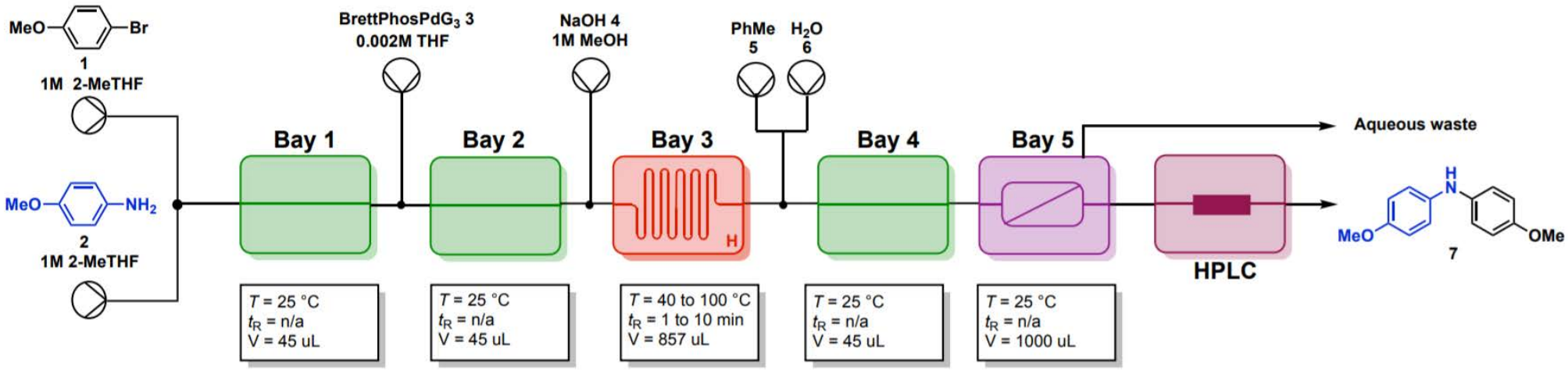
Reconfigurable system for automated optimization of diverse chemical reactions





Jensen & Jamison *et al*. *Science*. **2018,** *361*, 1220–1225

Buchwald-Hartwig Coupling



Optimization Target

*Optimization for the conversion of **1***

Adjustable Parameters

Temperature (bay 3): 40 to 100 °C

Flow Rates (P_1, P_2, P_4): 16.3 to 65.9 L / min

Catalyst Loading: 1 to 2 mol %

Optimization:

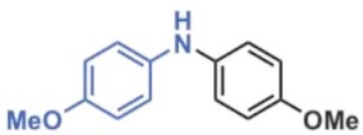
32 Experiments (21 h run time)

*1.2 equiv. **2***

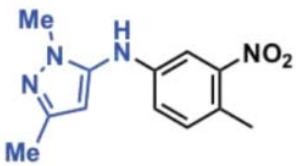
1.4 mol % catalyst

1.5 equiv base

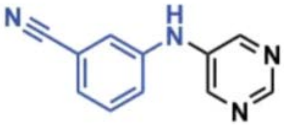
100 °C



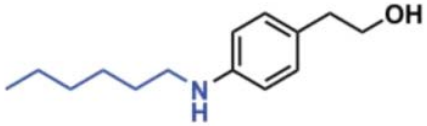
72 %, 436 mg/h



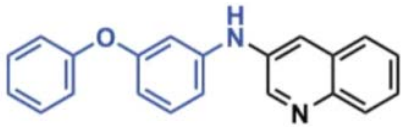
89 %, 579 mg/h



83 %, 430 mg/h



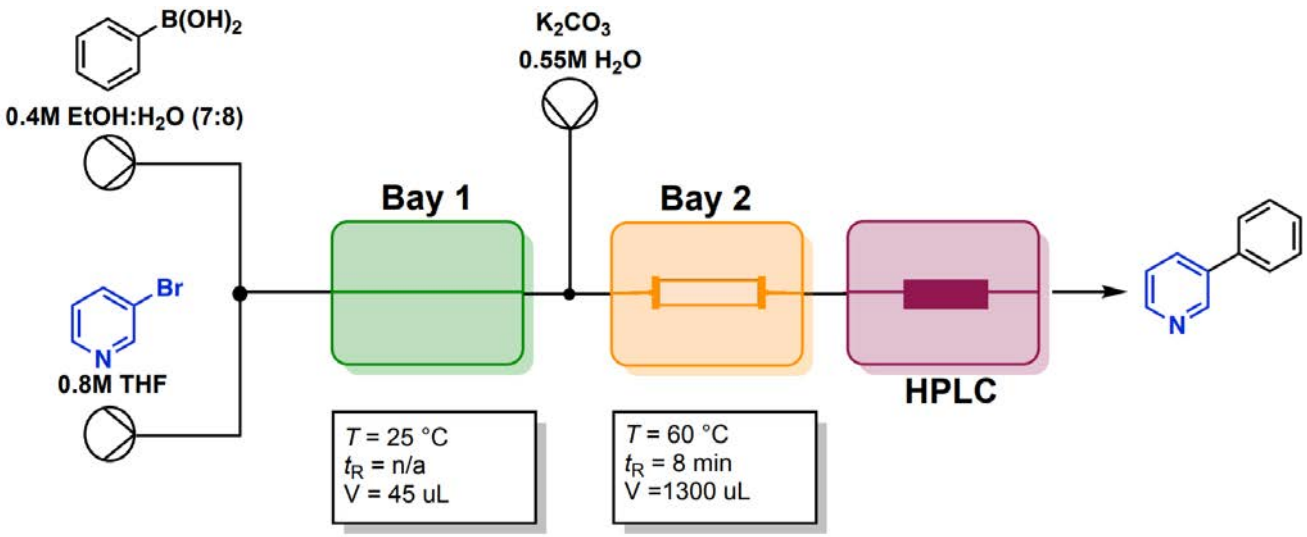
78 %, 456 mg/h



99 %, 816 mg/h

Jensen & Jamison *et al. Science.* **2018,** *361*, 1220–1225

Suzuki Coupling with Heterogenous Catalyst Automatic Optimization



Optimization Target

Optimization for the production of desired product

Adjustable Parameters

Temperature (bay 2): 40 to 100 °C

Flow Rate (P_1, P_2): 32.5 to 325 L / min

Flow Rate (P_3): 65 to 650 L / min

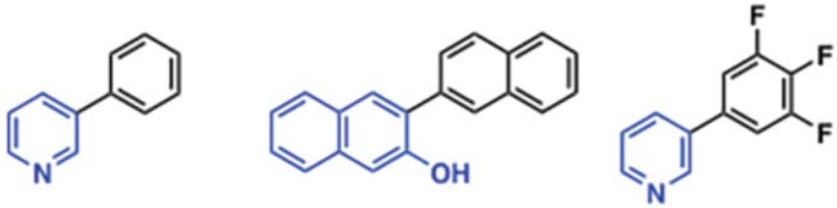
Optimization:

30 Experiments (8 h run time)

1.0 equiv. boronic acid

4 equiv. K_2CO_3

63 °C



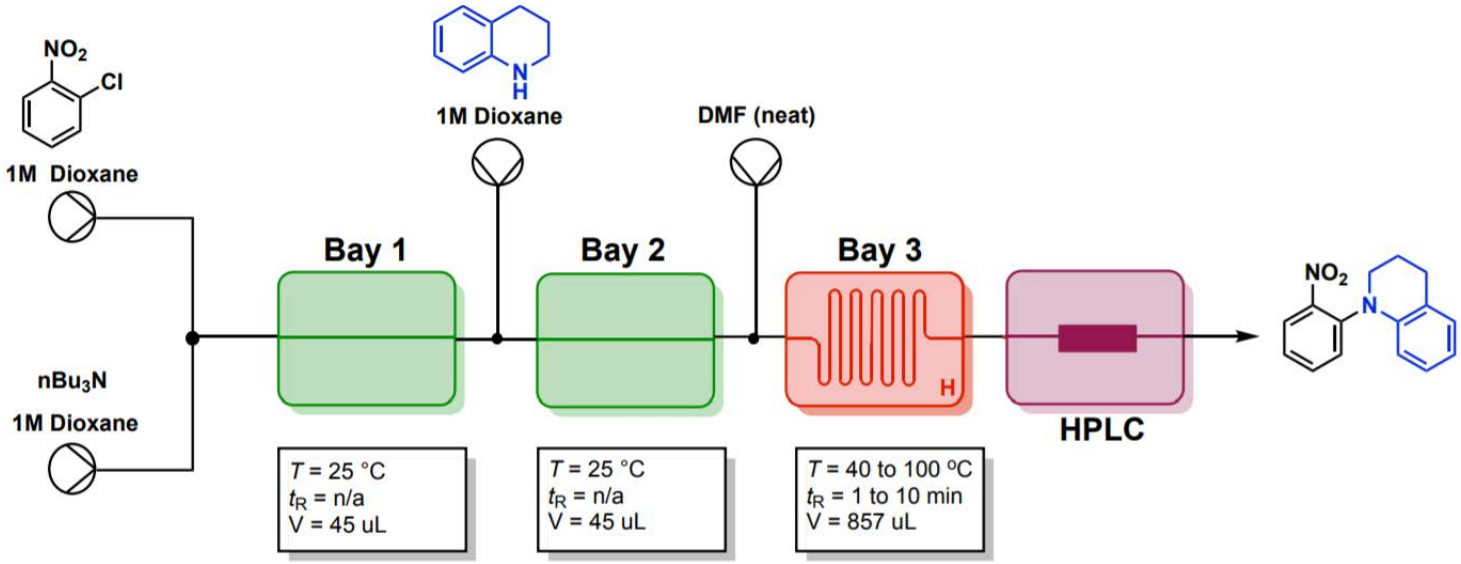
96 %, 630 mg/h | 96 %, 1098 mg/h | 94 %, 832 mg/h

A total of nine examples

>1 g of each example completed in 8 h

Jensen & Jamison *et al. Science.* **2018,** *361*, 1220–1225

S_NAR Automatic Optimization



Optimization Target

Optimization for formation of desired product

Adjustable Parameters

Temperature (bay 3): 40 to 100 °C

Flow Rate (P_1, P_2, P_3): 21 to 214 / min

Optimization:

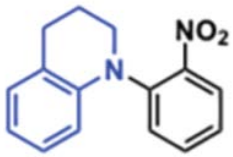
33 Experiments (14 h run time)

10 equiv. tributyl amine

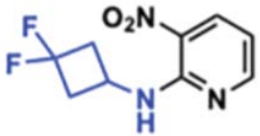
1 equiv. aryl chloride

1 equiv. amine

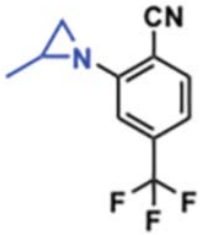
100 °C



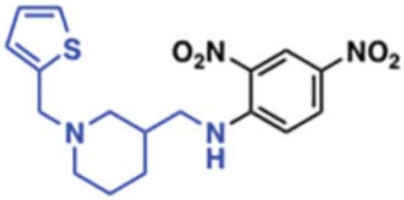
94 %, 320 mg/h



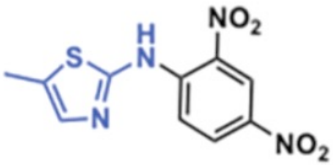
89 %, 271 mg/h



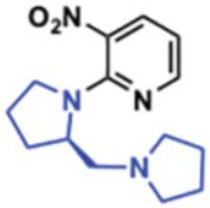
97 %, 292 mg/h



99 %, 496 mg/h



92%, 343 mg/h



96 %, 253 mg/h

10 examples, 10 mg of each generated in 17 min

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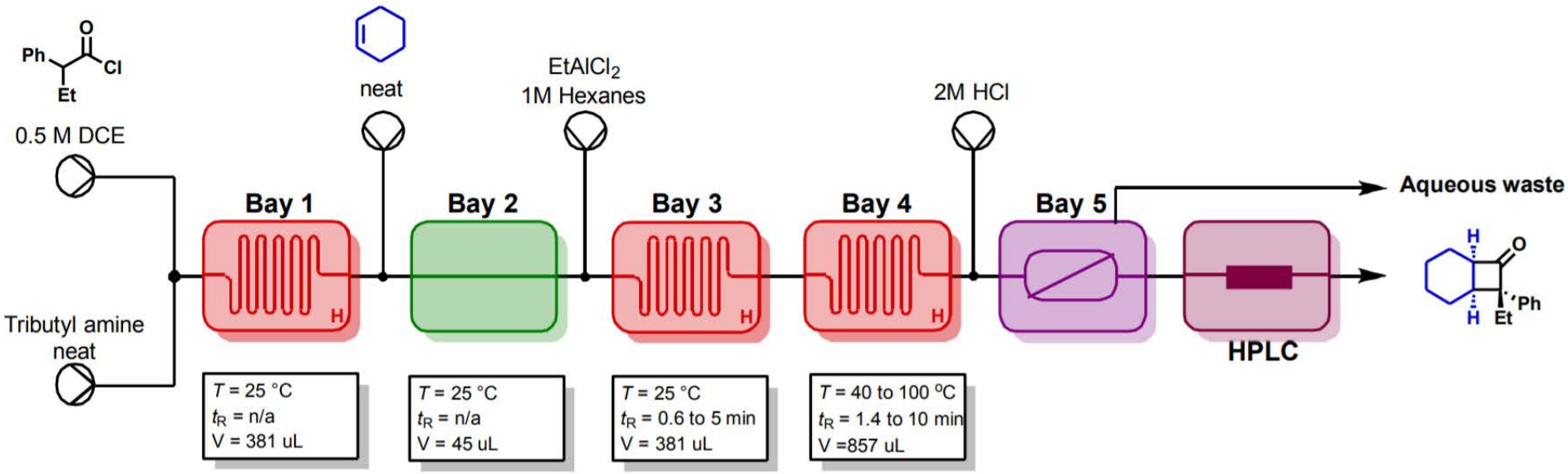
Automatic Optimization of a Multi-step Reaction



Optimization Target

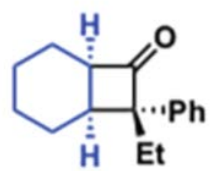
Optimization for formation of desired product

Adjustable Parameters

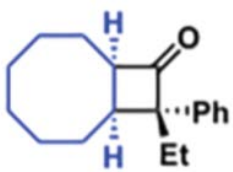
Temperature (bay 4): 40 to 100 °C
Flow Rate (P_1): 51 to 382 / min
Flow Rate (P_2): 6.4 to 43.8 / min
Flow Rate (P_3): 2.8 to 21 / min
Flow Rate (P_4): 25.5 to 199 / min

Optimization:

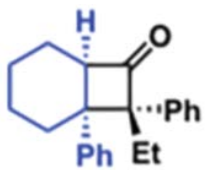
45 Experiments (34 h run time)
1.2 equiv. cyclohexene
1 equiv. tributylamine
6.7 equiv. $EtAlCl_3$
78 °C (bay 4)



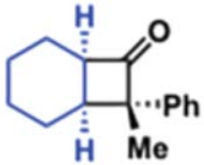
94 %, 320 mg/h



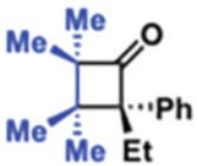
89 %, 271 mg/h



97 %, 292 mg/h



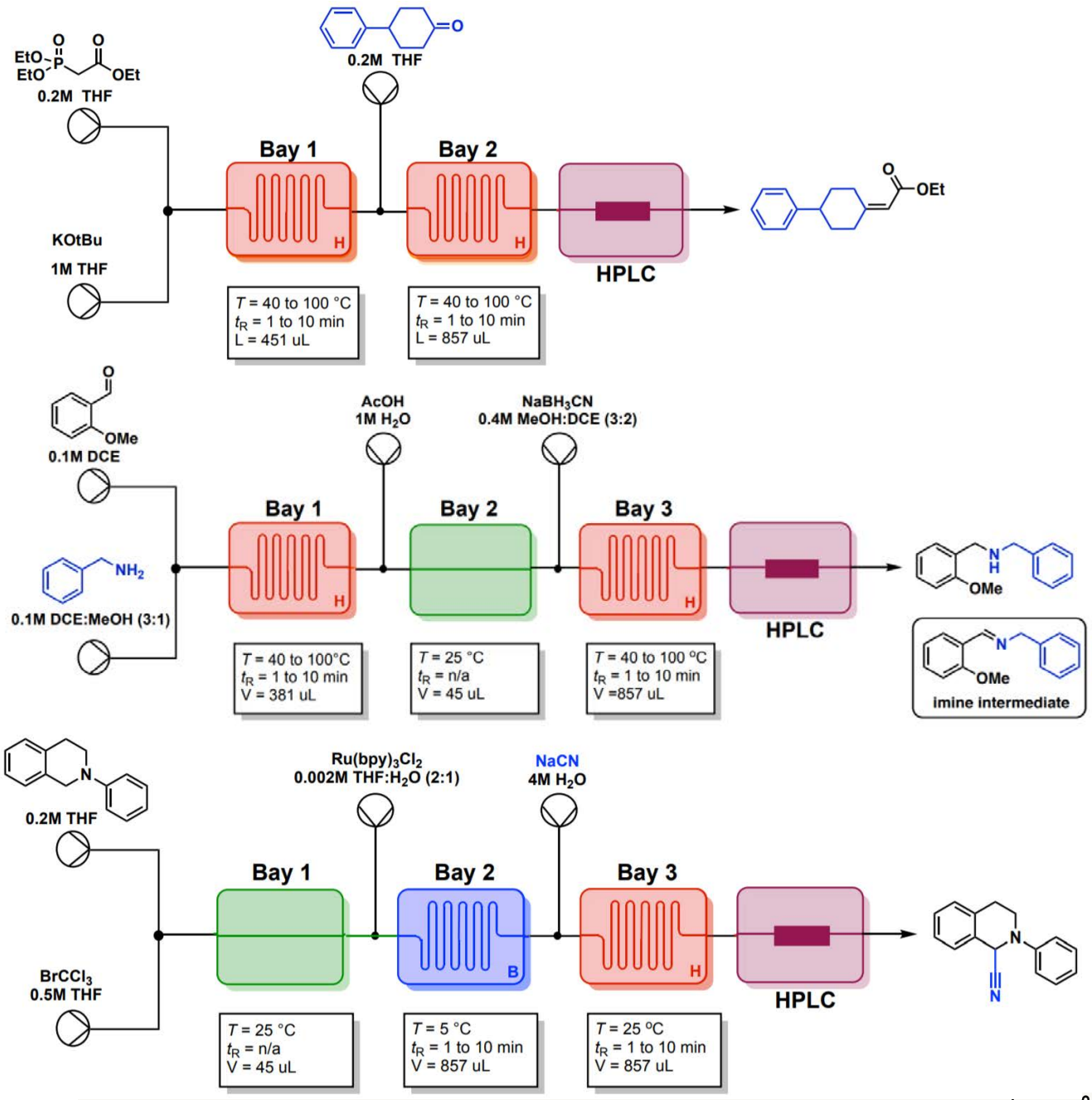
99 %, 496 mg/h



92%, 343 mg/h

Jensen & Jamison *et al. Science.* **2018,** *361*, 1220–1225

Additional Automatic Optimizations



5 variables optimized
33 experiments in total
10 hr to optimize

5 variables optimized
33 experiments in total
14 hr to optimize

3 variables optimized
33 experiments in total
7 hr to optimize

Jensen & Jamison *et al*. *Science*. **2018,** *361*, 1220–1225

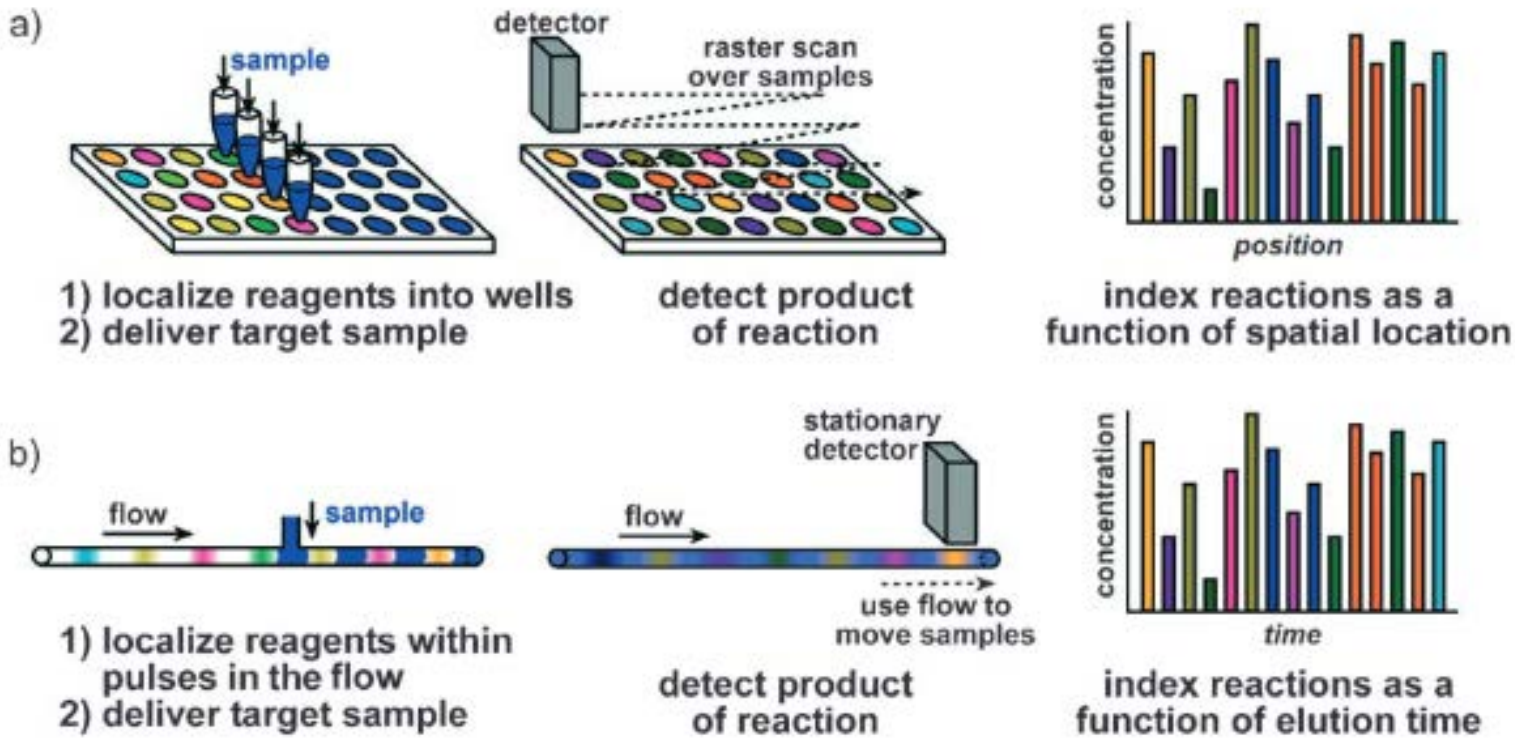
Outline Slide

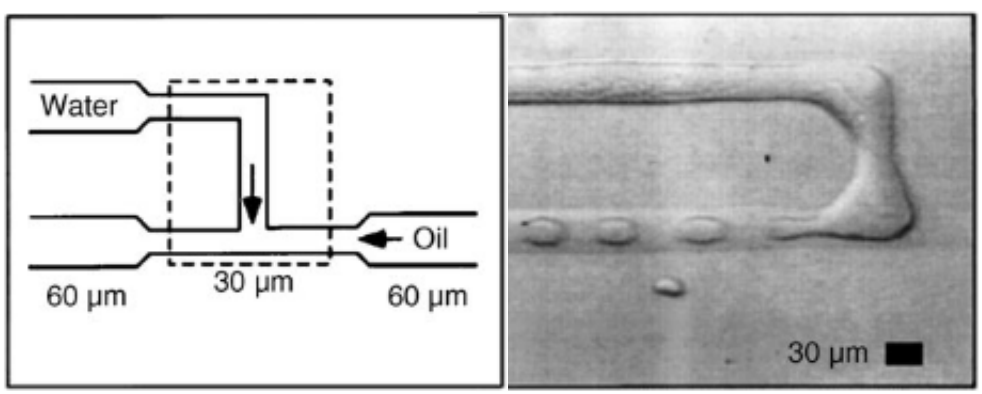
Anatomy of Flow Chemistry

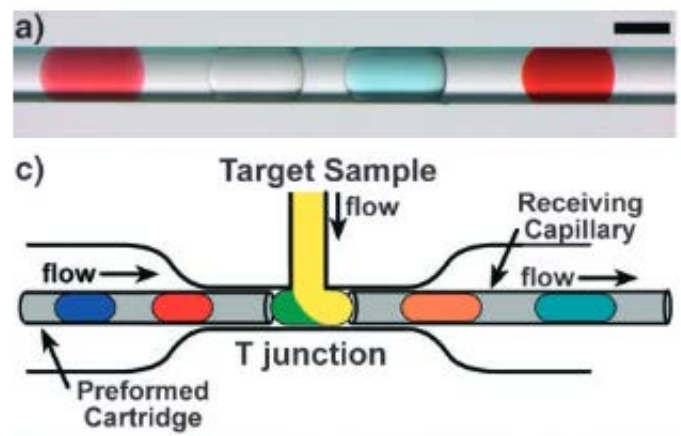
Optimization of Continuous Variables

Optimization of Discrete Variables

Reactions in Droplets

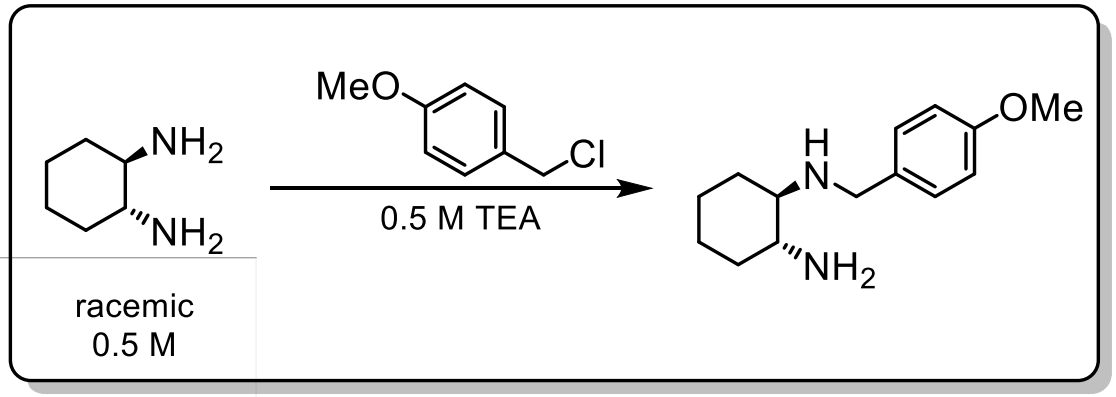


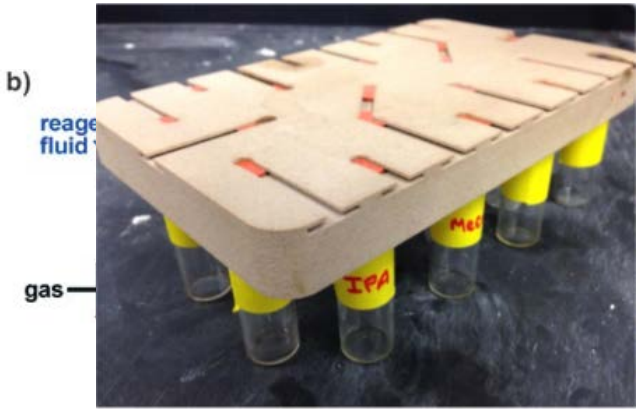


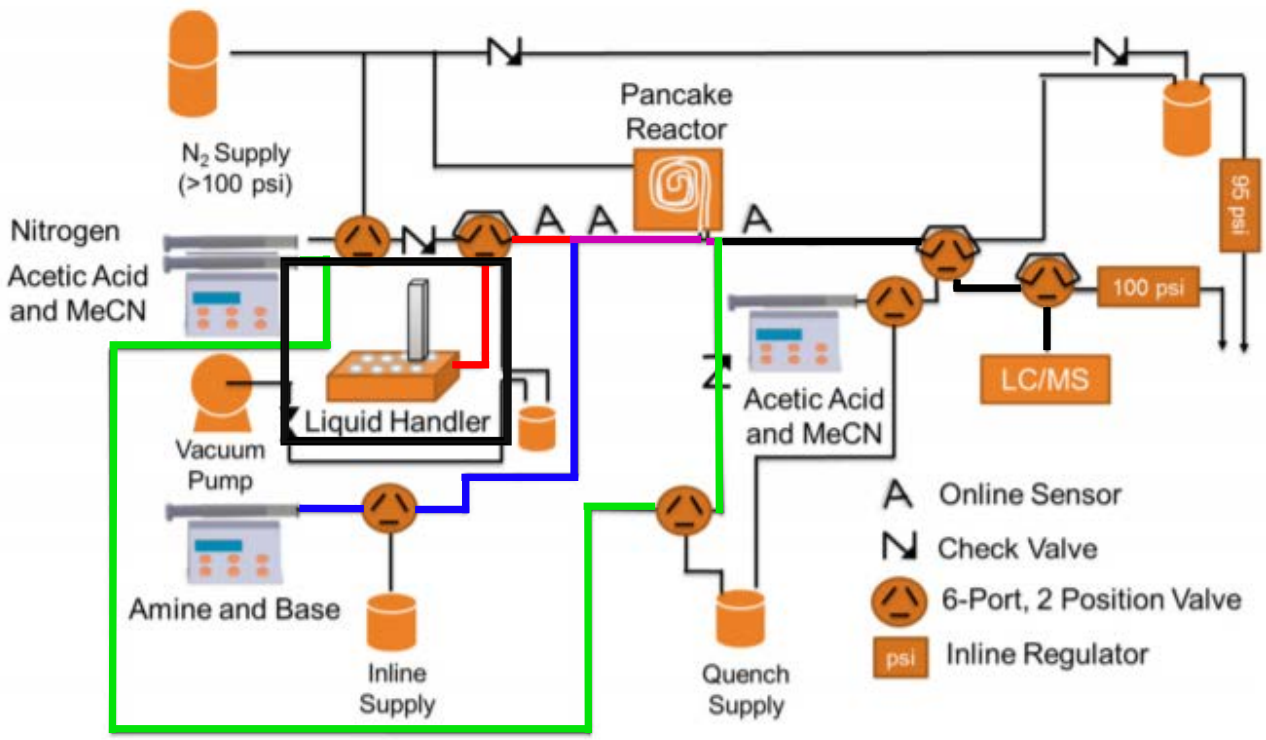


Song, H.; Chen, D.L.; Ismagilovv, R.F. *Angew. Chem. Int. Ed.* **2006**, *45*, 7336–73

Solvent Screening in Flow







First aspirated with 30 μL N_2

Aliquots chosen solvent, then PMBCl, then chosen solvent again

"Stirred" with syringe pump

Transferred to 6-way valve

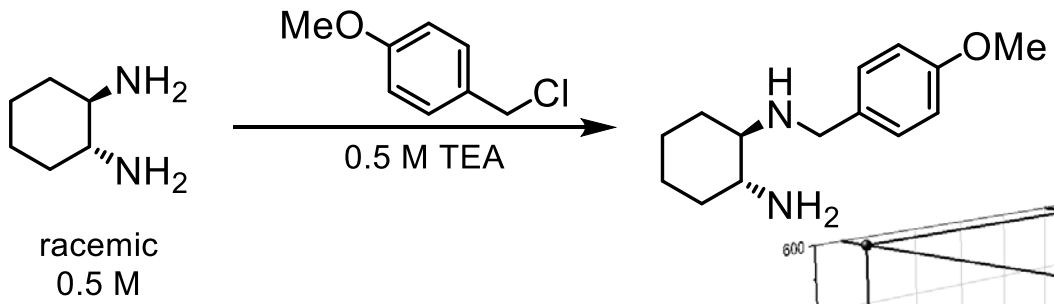
Refractive Index Sensors the injection of TEA, diamine, and internal standard

Quenched with 10 % AcOH in MeCN

Sample is diverted to HPLC

Reizman, B.J.; Jensen, K.F. *Chem. Commun.*, **2015**, *51*, 13290--13293

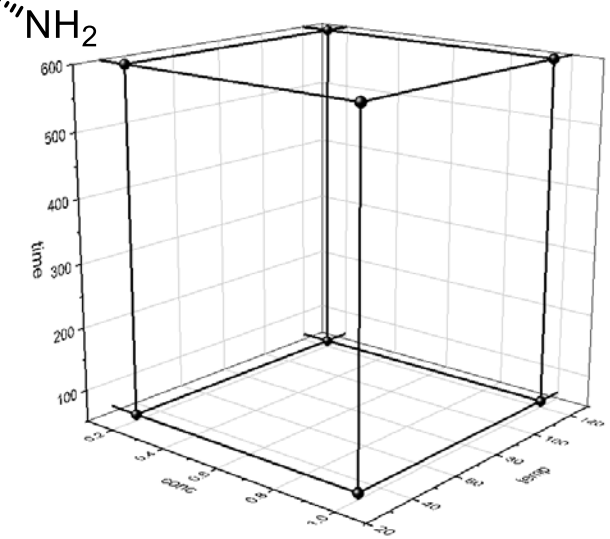
Solvent Screening in Flow



Optimization workflow:

DOE approach:

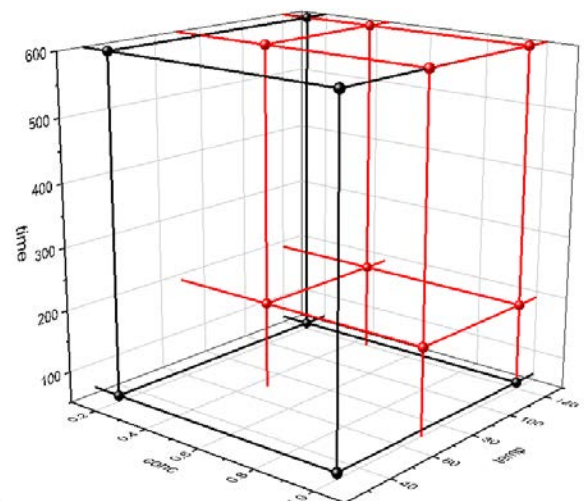
1) *Fractional factorial design (first set, 20 experiments)*
   - *t_{res} = 60 s or 600 s, temp. = 30 °C or 120 °C, C_0 PMBCl = 0.206 M or 1 M.*
   - *Solvents = i-PrOH, THF, Toluene, MeCN, DMF, DMSO, Pyridine, DMC, DME, DCE*



2) *Fractional factorial design in most promising quadrant (second set 20 experiments)*
   - *t_{res} = 190 s or 600 s, temp. = 69.2 °C or 120 °C, C_0 PMBCl = 0.444 M or 1 M.*

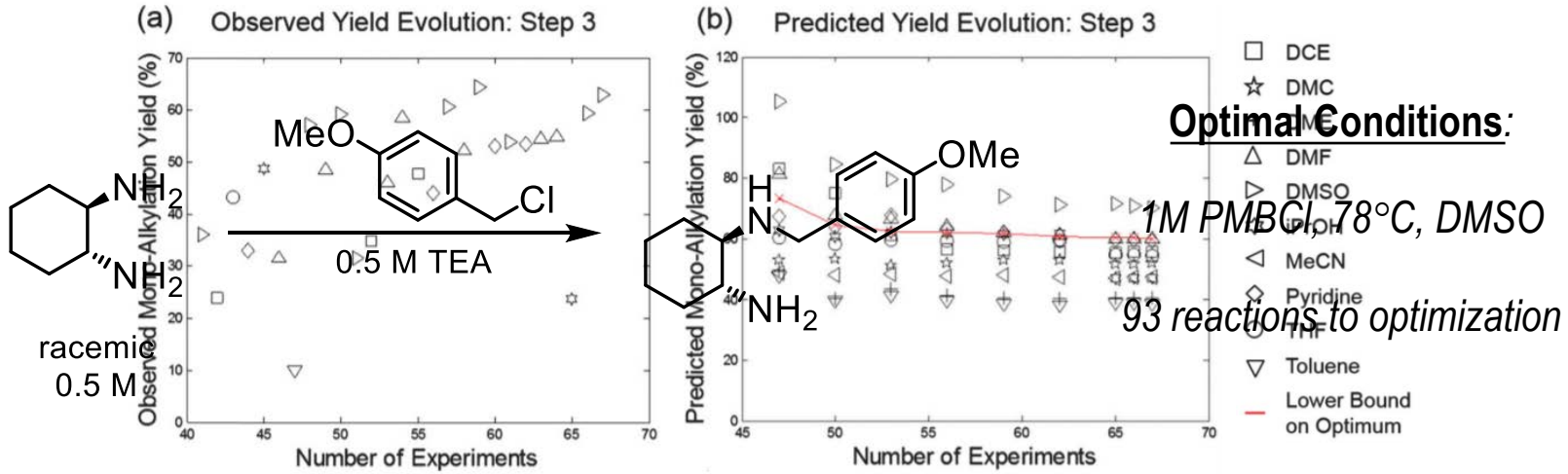
3) *DOE feedback search (27 experiments)*
   - *Minimize uncertainty for maxima in each solvent*

4) *Gradient Optimization*



Reizman, B.J.; Jensen, K.F. *Chem. Commun.*, **2015**, *51*, 13290--13293

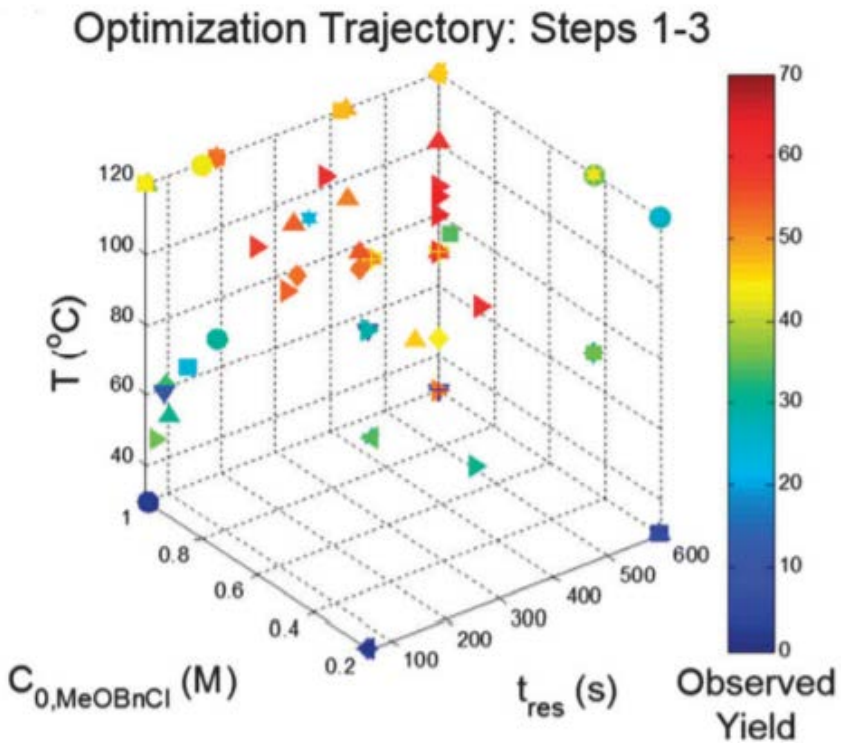
Optimization of the Monoalkylation of a Diamine

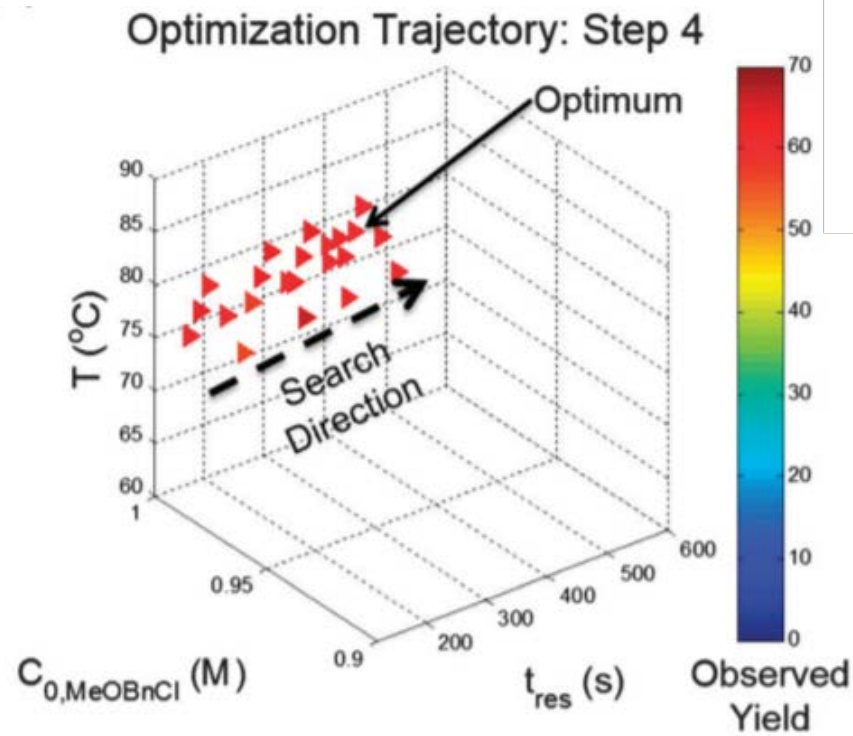


Optimal Conditions:

1M PMBCl, 78°C, DMSO

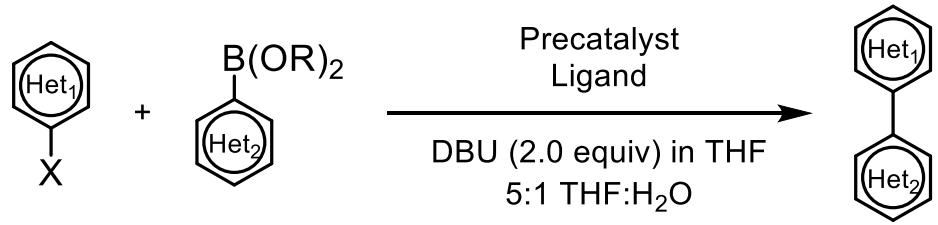
93 reactions to optimization



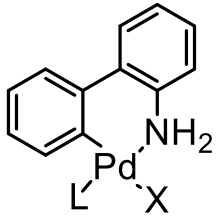


Reizman, B.J.; Jensen, K.F. *Chem. Commun.*, **2015**, *51*, 13290--13293

Automated Suzuki Coupling Optimization

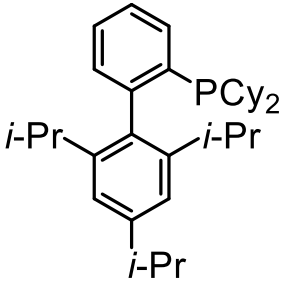


Precatalysts

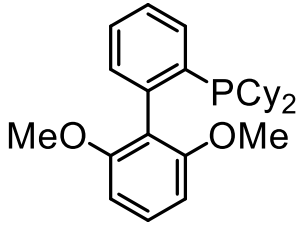


P1 X = OMs
P2 X = Cl

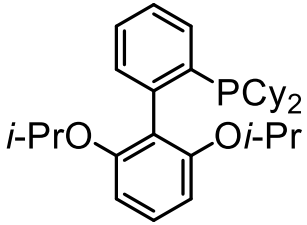
Ligands



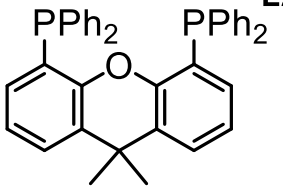
L1



L2



L3



L4

PPh_3
L6

PCy_3
L5

$P(t\text{-}Bu)_3$
L7

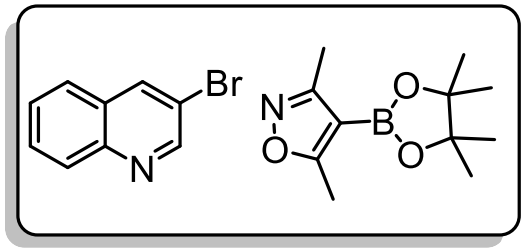
Continuous Variables

Catalyst Loading: 0.5 - 2.5 %

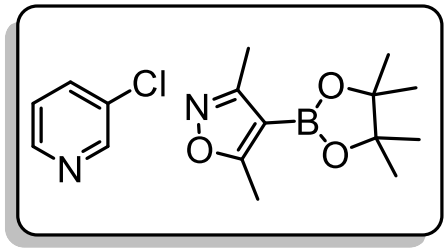
Temperature: 30 °C to 110 °C

t_{res} = 1 min to 10 min

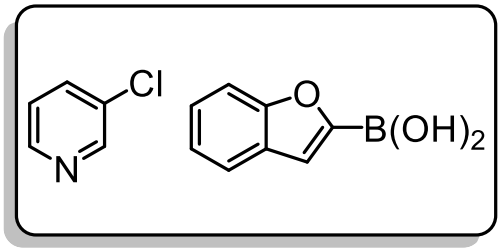
Substrate Pairs



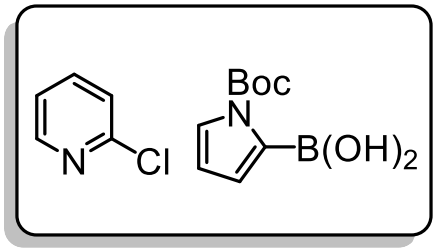
I



II



III



IV

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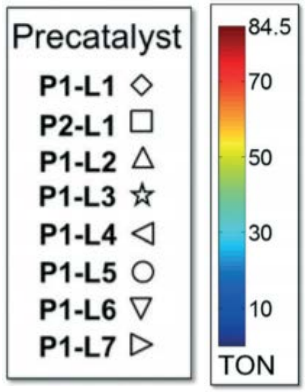
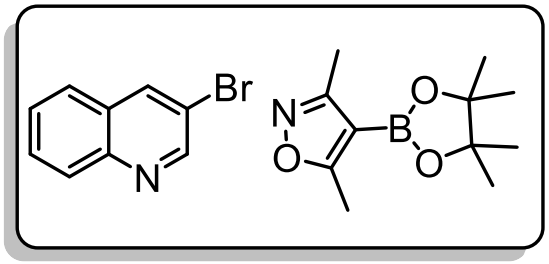
Automated Suzuki Coupling Optimization: Case I





I

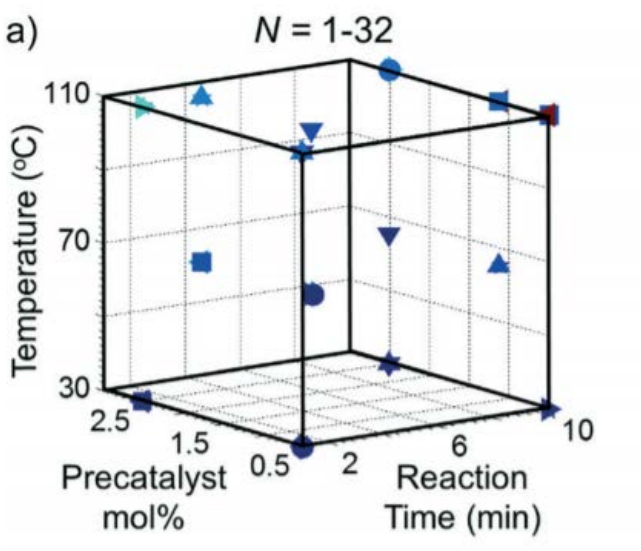
Optimal Conditions

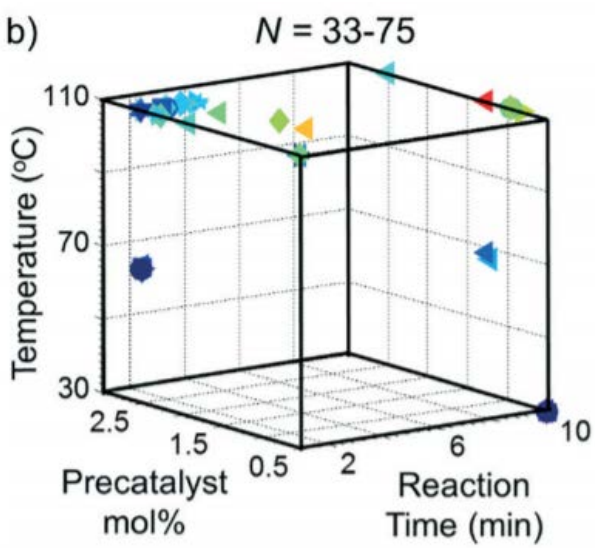
Reaction time = 10 min

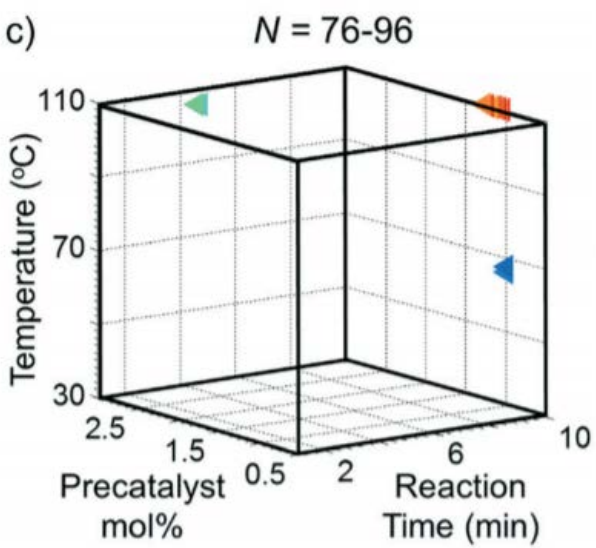
Temperature = 110 °C

Catalyst = P1/L4 (1.2 mol %)

87 % yield, TON = 69







Fractional Factorial Design

Search the extremes of continuous variable space

Response Surface Refinement and Discrete Variable Elimination

Lowers Error / eliminates all discrete variables except P1/Xantphos

P1/L4 Response Surface Refinement

Primarily directed at tuning catalyst loading

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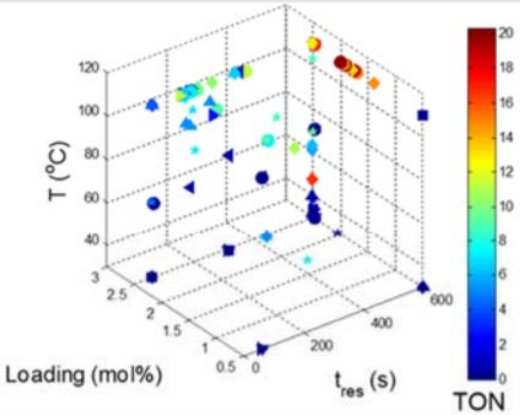
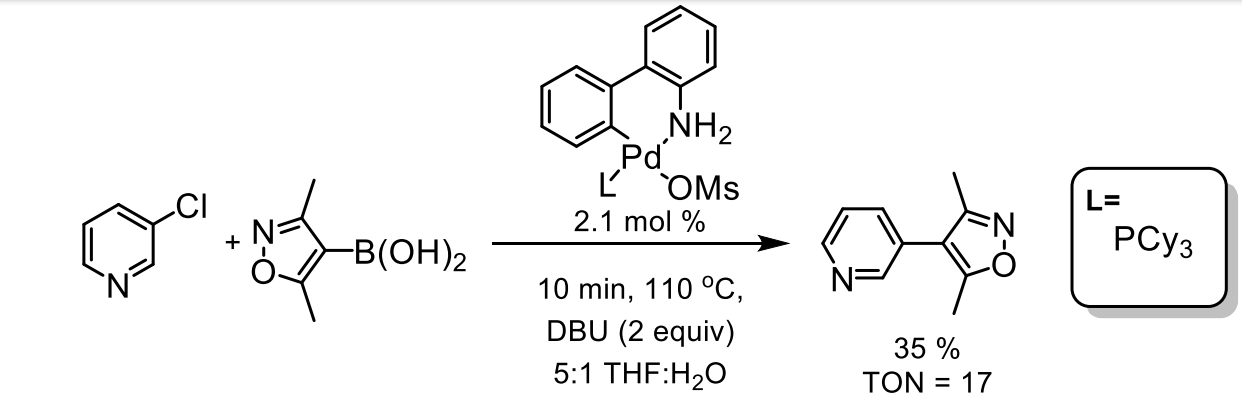
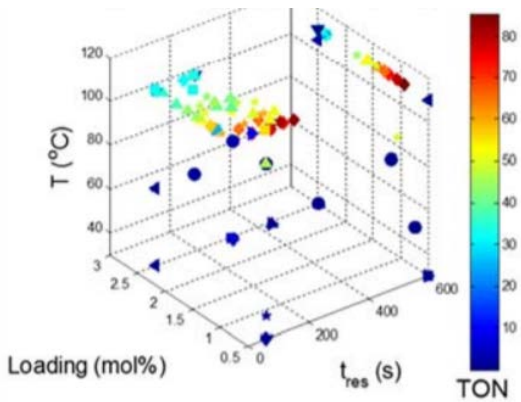
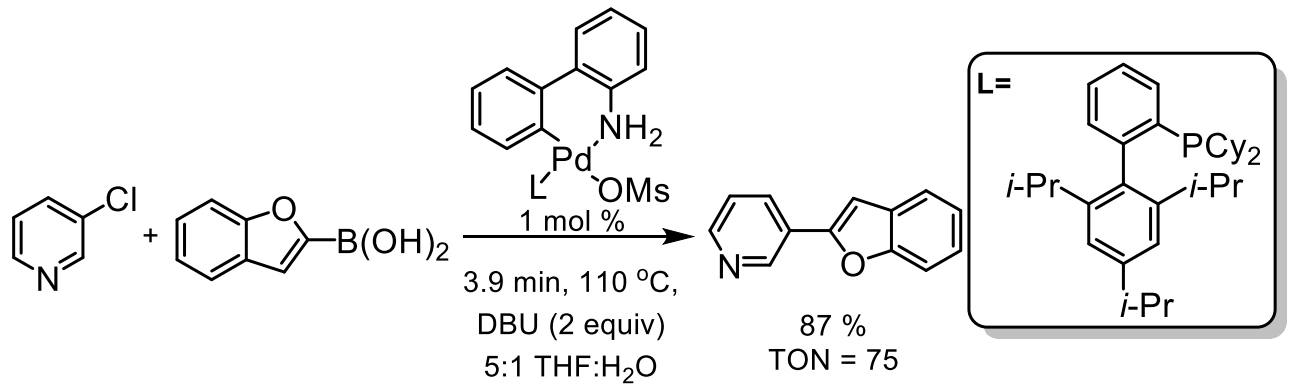
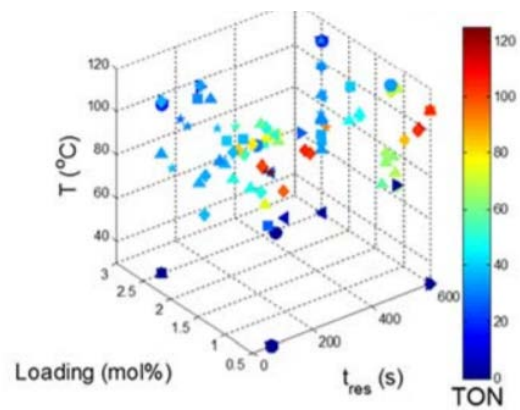
Automated Suzuki Coupling Optimization: Case II-IV

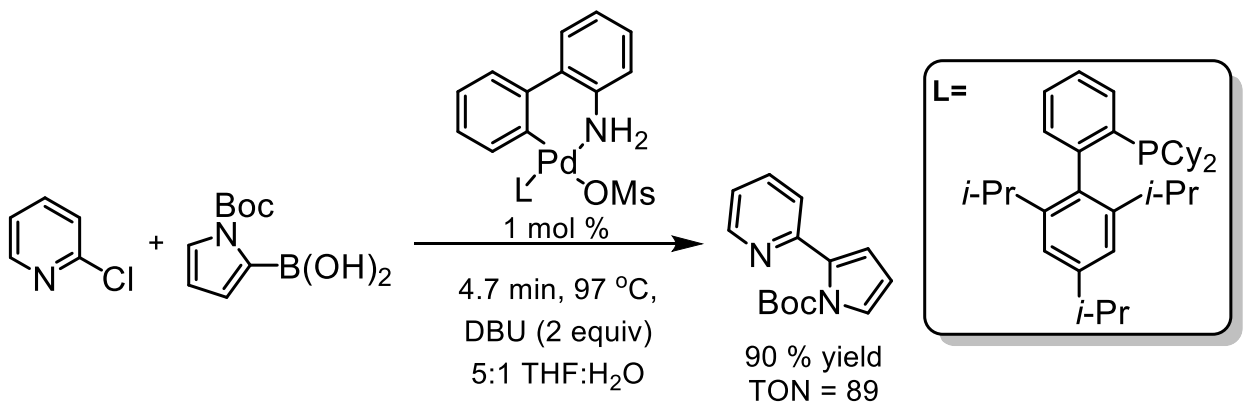












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Summary and Future Directions

Summary

The automated optimization of continuous variables is transitioning into a mature field.

The automated optimization of discrete variables has been demonstrated, but the methodology must improve to be of utility to the general community

Future Directions

Remote auto-optimization

Accessible optimization of discrete variables

Application of machine learning methods to auto-optimization