Automating Chemical Synthesis Through Flow Chemistry

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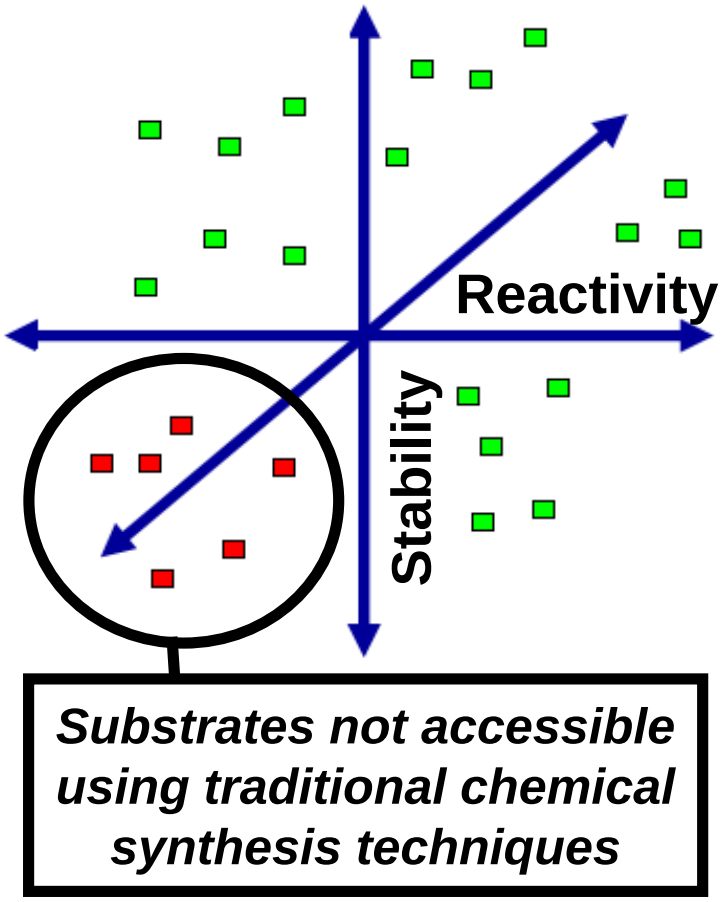
Contents

- Conjure Flow Reactor
- Applications and Examples of Conjure Flow Reactor to Discovery and Development
- Towards Automated Synthesis

Flow - Key Applications to Drug Discovery

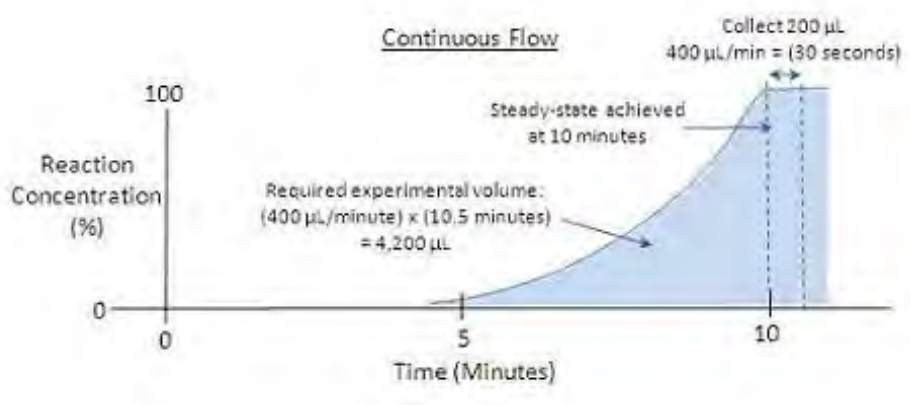
- **Medicinal - Expanding Chemical Space**
  - Forbidden chemistries
  - Library synthesis
  - Extending temperature ranges (vs. microwave)
- **Process - Enabling and Economics**
  - Scaling Forbidden chemistries (diazotation etc.)
  - Scale-up of Discovery microwave chemistry
  - Minimised scale-up considerations



- **Early implementation of flow chemistry can significantly ease the transitions from Discovery to Process**

Flow Chemistry Limitations

- Emerging Technology (at laboratory scale)
- Heterogeneous Reactions
- Material Requirements
- Time Requirements

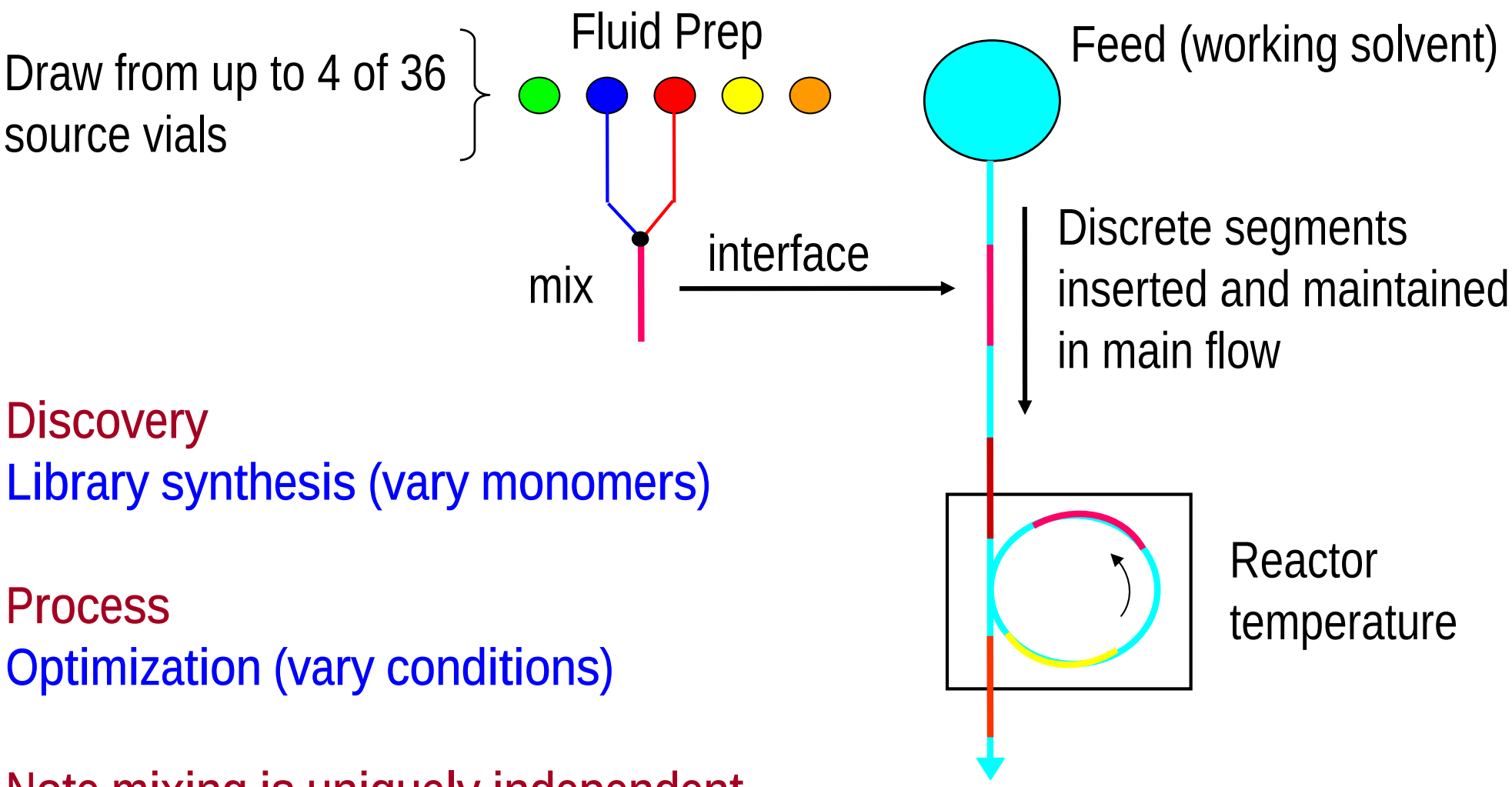


- 2004 Collaboration started with Wyeth and Accendo

Analytical Scale=0.5ml/min (HPLC like flow rates)

nano micro meso kilo lab pilot plant manufacturing

Schematic



Discovery
Library synthesis (vary monomers)

Process
Optimization (vary conditions)

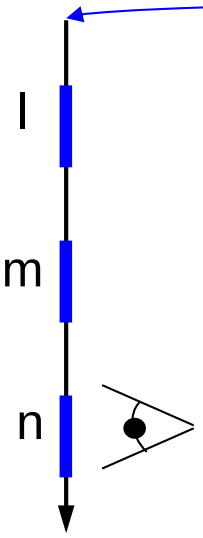
Note mixing is uniquely independent of flow rate

Adding Artificial Intelligence

One-size-fits-all initial conditions

Library elements (Discovery)
Reaction Conditions (Process)

(flowing segments)



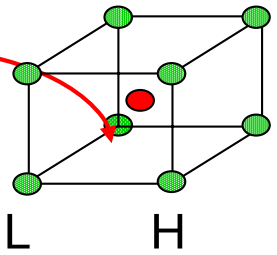
HPLC/MS
Product Y/N?
Yield & Purity

Pass?

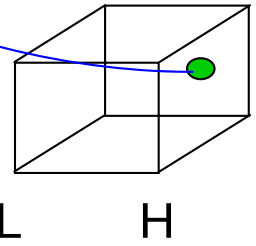
Fail?

Collect via Fraction Collector (Discovery)
Prep via repetitive segments (Process)

Greater percentage of successful library elements (discovery). Optimized reactions (process)

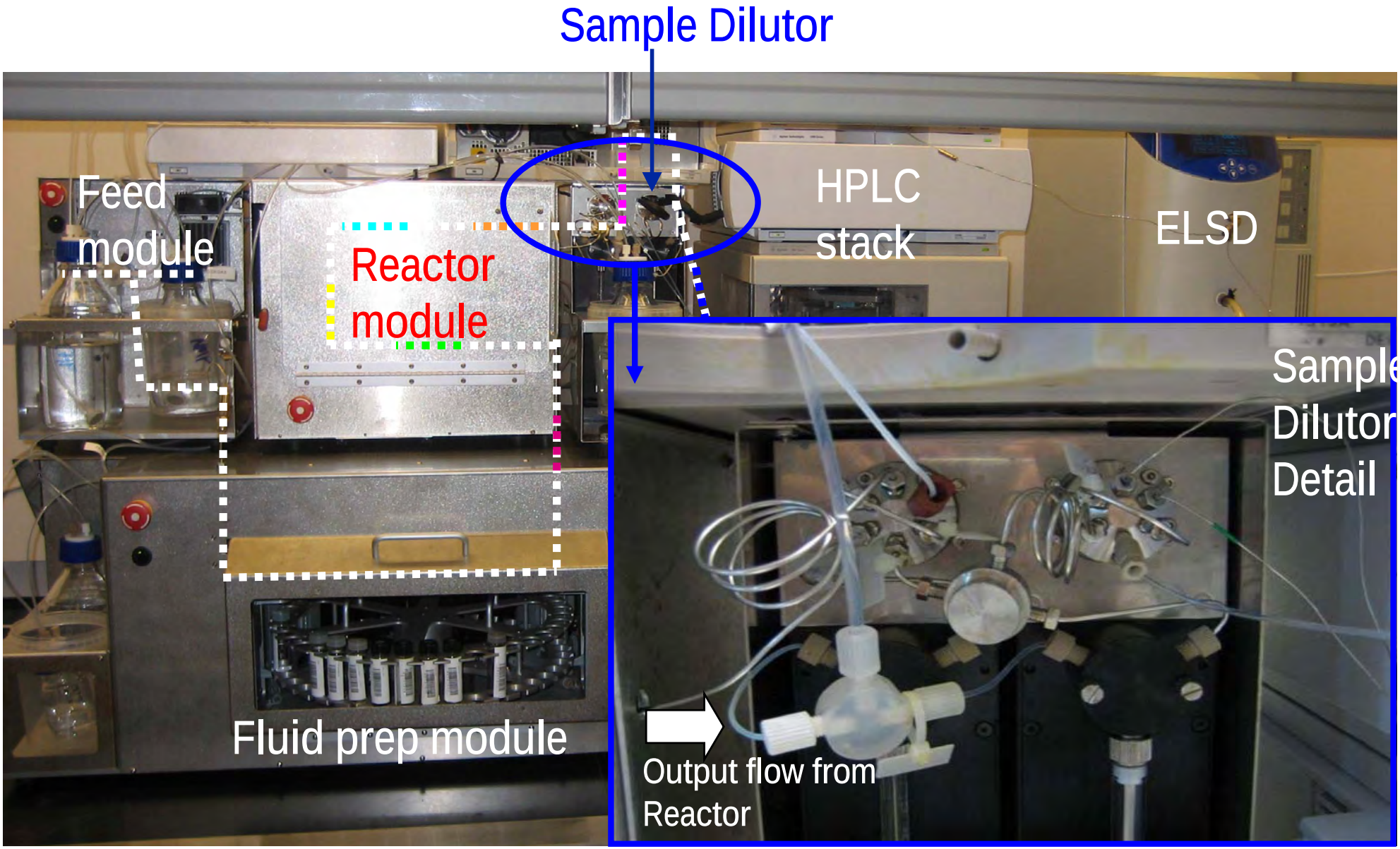


DOE calculates best conditions



Vary prescribed reaction parameters around initial conditions. Automatically done based on Simplex and DOE statistical optimization tools.

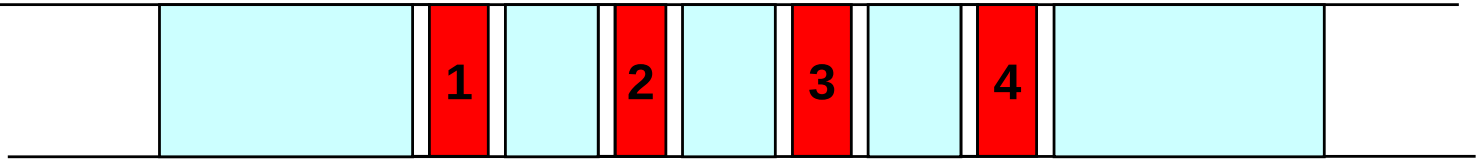
Conjure Flow Path

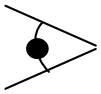


Conjure Square-Wave Reaction Segments

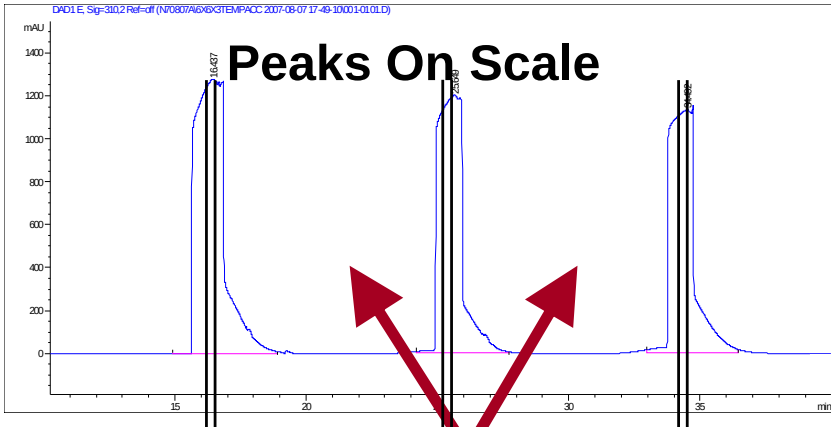
- Total Segment Size 150-800uL. Typically 300uL, 5mg Substrate

- Multiple Segments Active Within Reactor (up to 4)





Bubble or
UV Detection

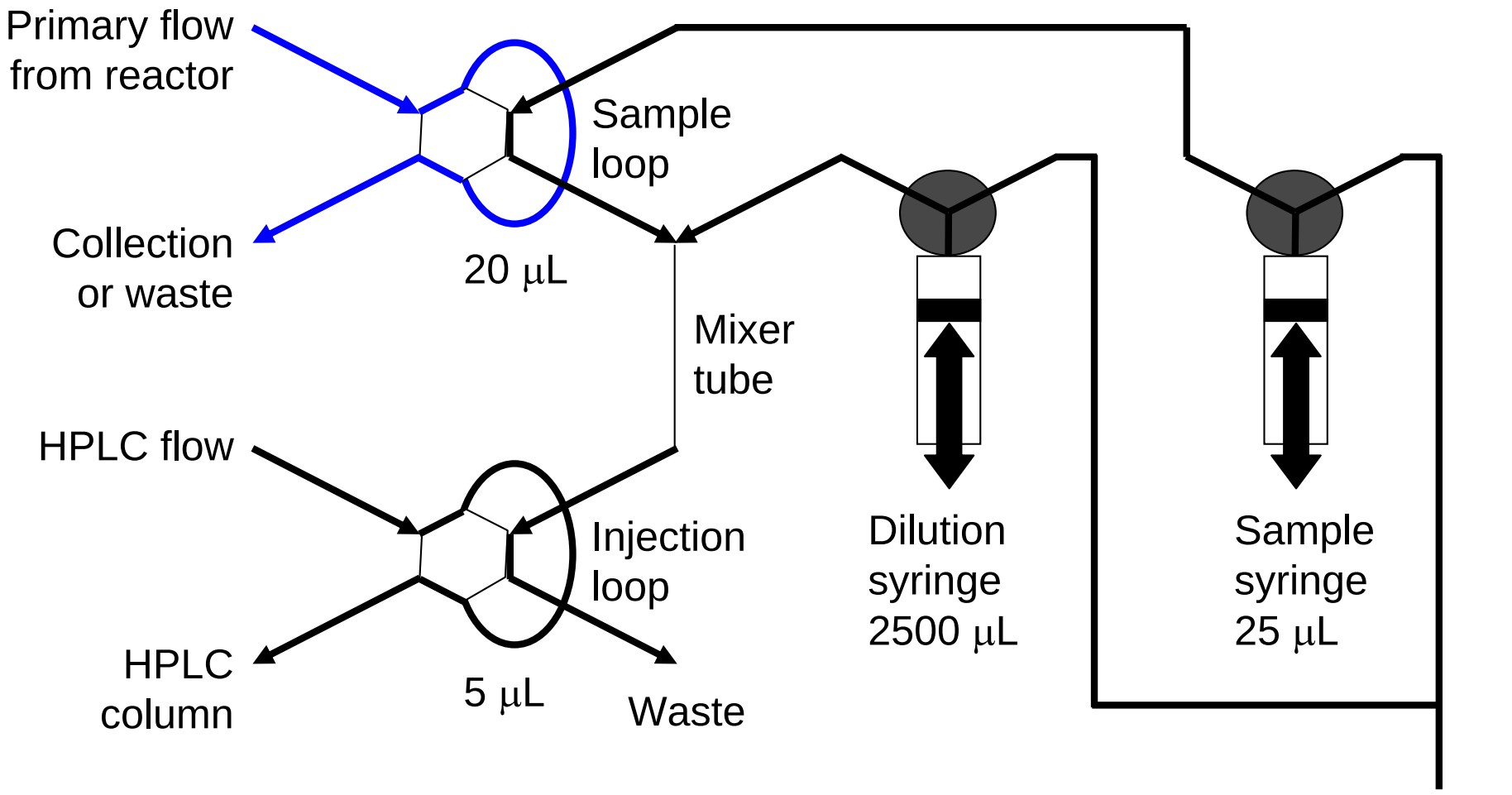


Each peak is a 5mg reaction
Exact Stoichiometry (fluid prep)
Exact Reaction Time (flow rate)
Exact Temperature (within 0.1C)

No Dead Reckoning

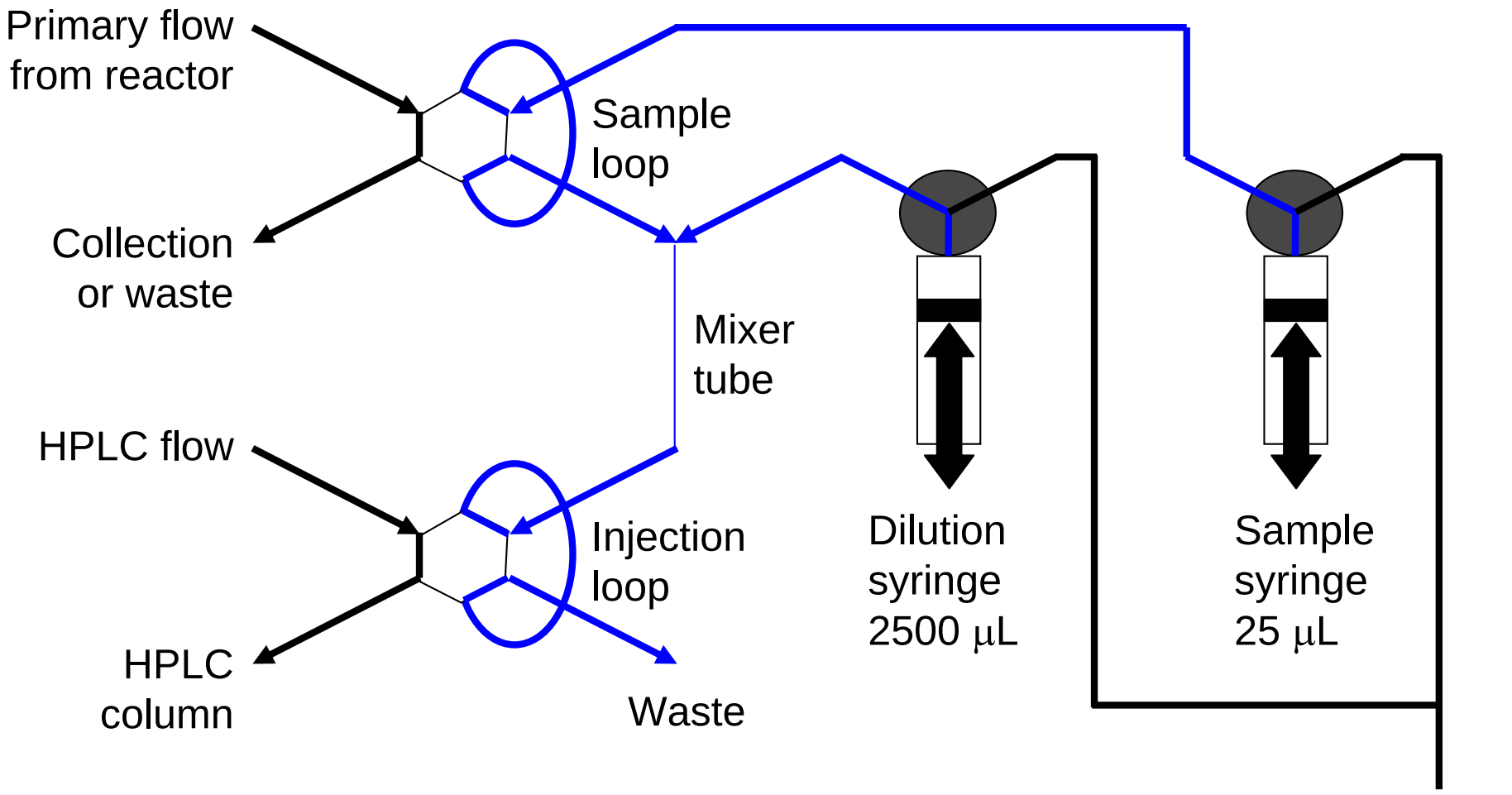
- Heart cut is sampled and directed for LC/MS Analysis (ultra-fast gradients <2min run-times). Enables real-time results between segments.

Sampling “Heart Cuts” from the Flowing Segments



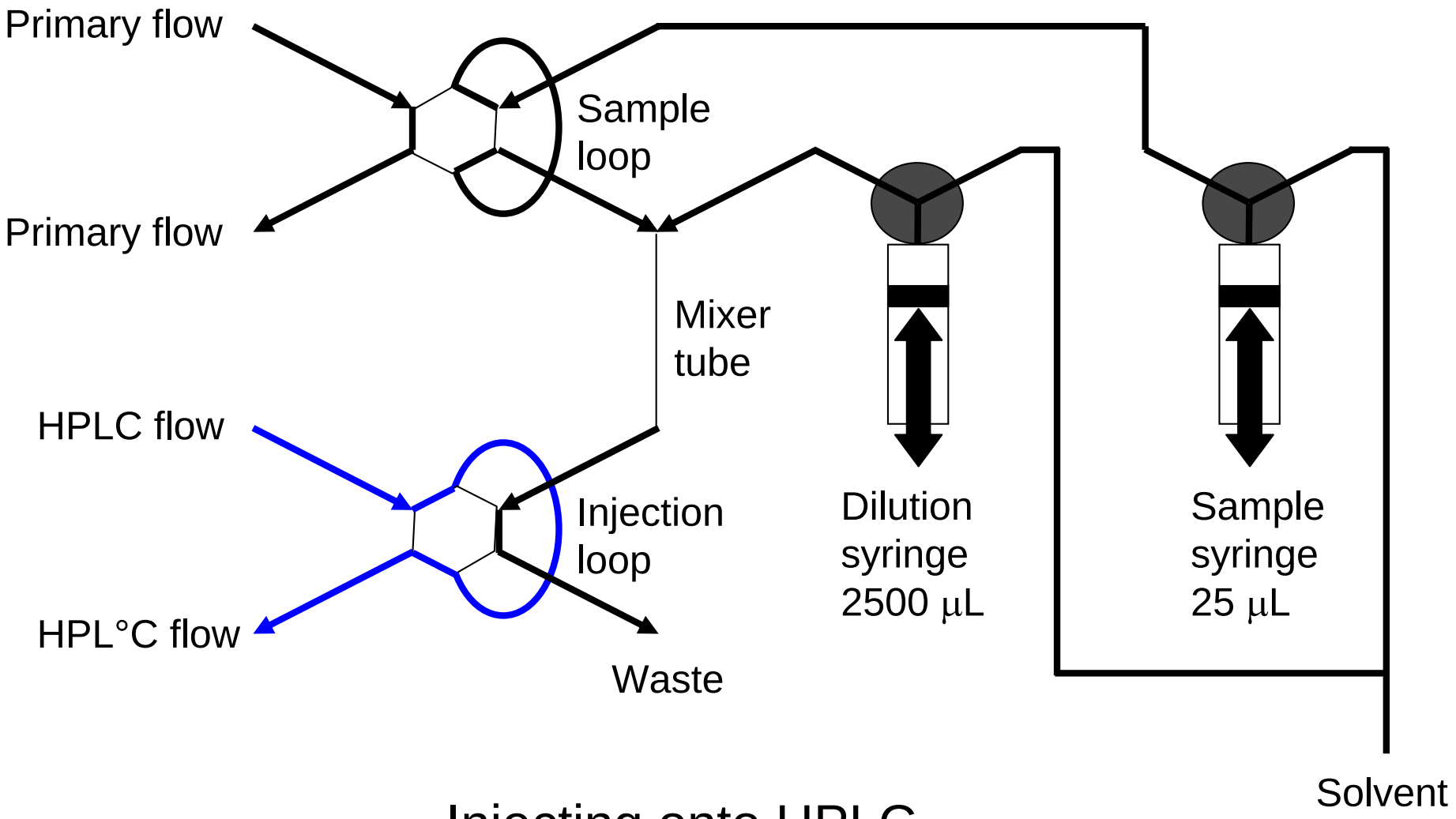
Sample Dilutor Module

Sampling “Heart Cuts” from the Flowing Segments



Mixing with Diluent

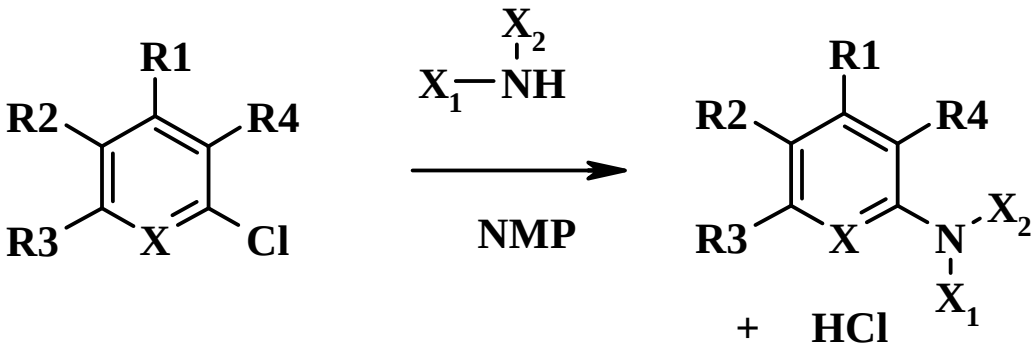
Sampling “Heart Cuts” from the Flowing Segments



Injecting onto HPLC

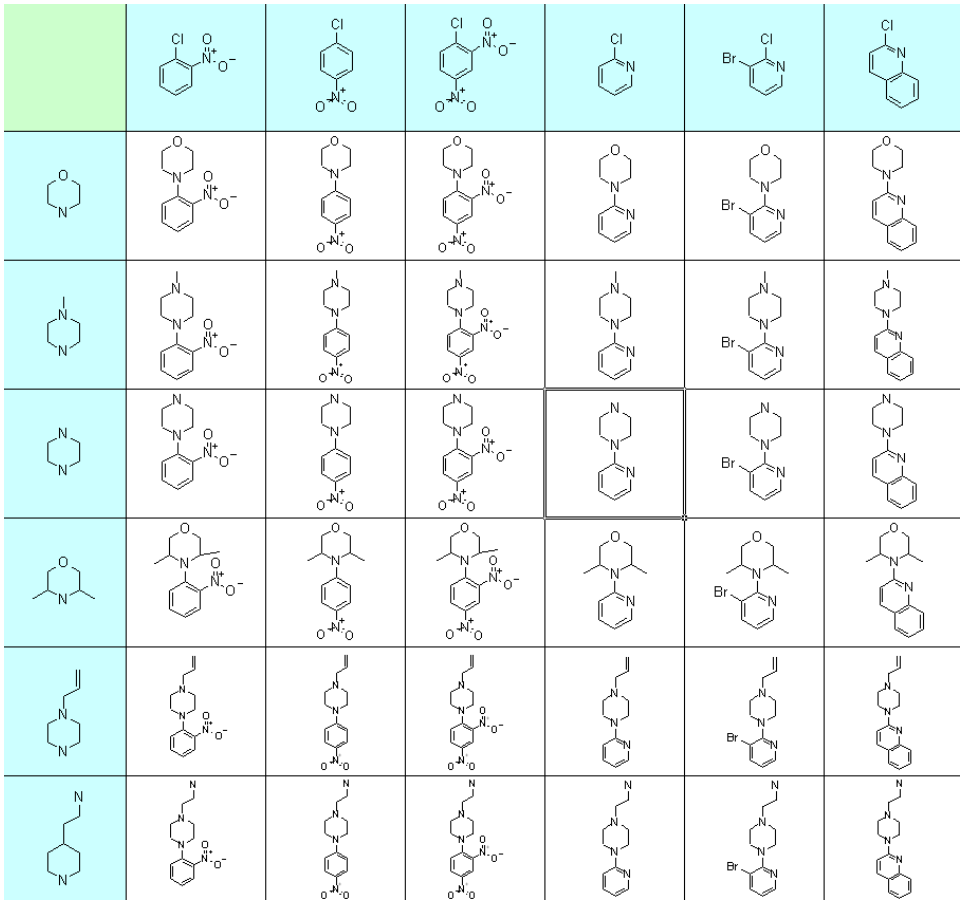
Return

Demonstration S_NAr Library Preparation



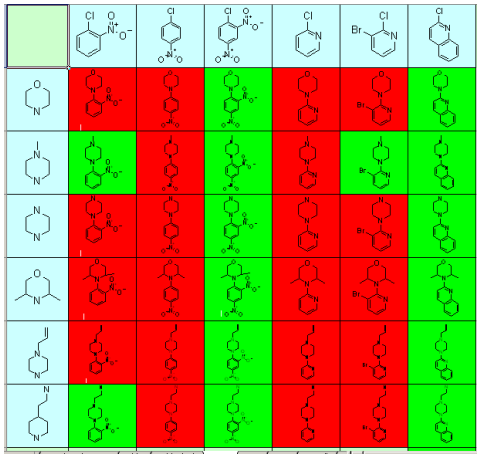
X=C-NO2 or N

- 6 Amines x 6 Aryls = 36 Library
- 0.5M Solutions 100uL Each
- Total Segment Volume = 300uL
- 3 Temperatures 150°C, 200°C, 250°C
- 10 Minute Reaction Time
- NMP Carrier Solvent
- 108 Experiments = 15 hours Run
- On-line HPLC/UV/MS/ELSD Analysis

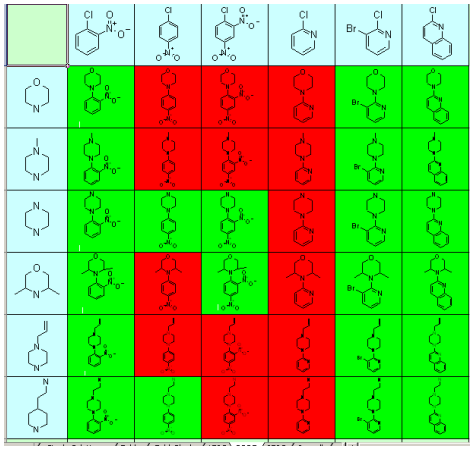


Hamper, Bruce C.; Tesfu, Eden. Direct uncatalyzed amination of 2-chloropyridine using a flow reactor. Synlett (2007), (14), 2257-2261

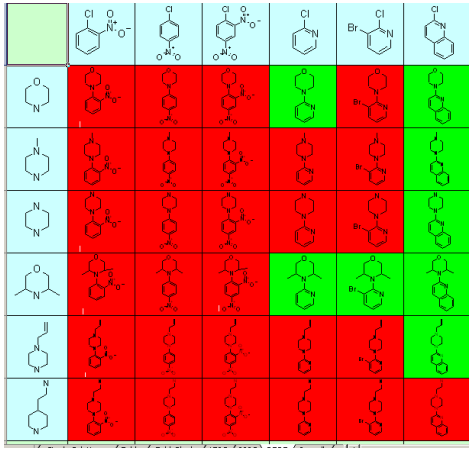
150-250°C in-situ Yield by 254nm HPLC/MS Analysis



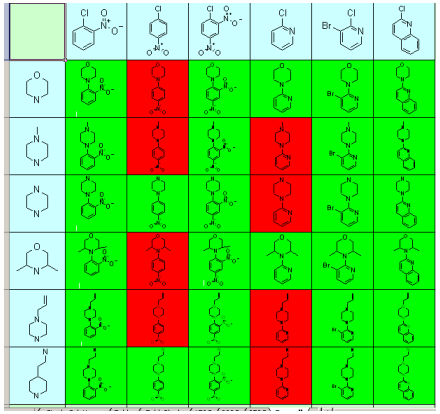
150°C - 42%



200°C - 61%



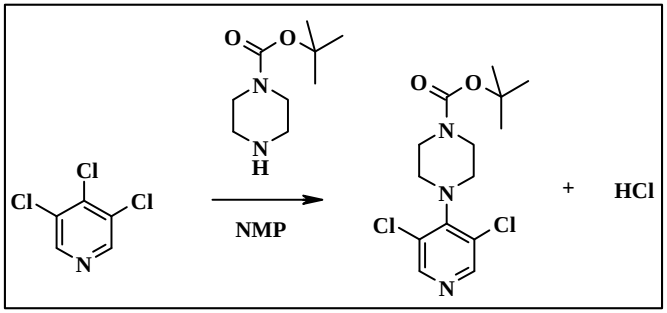
250°C - 22%



Overall Library Success Rate : 88%

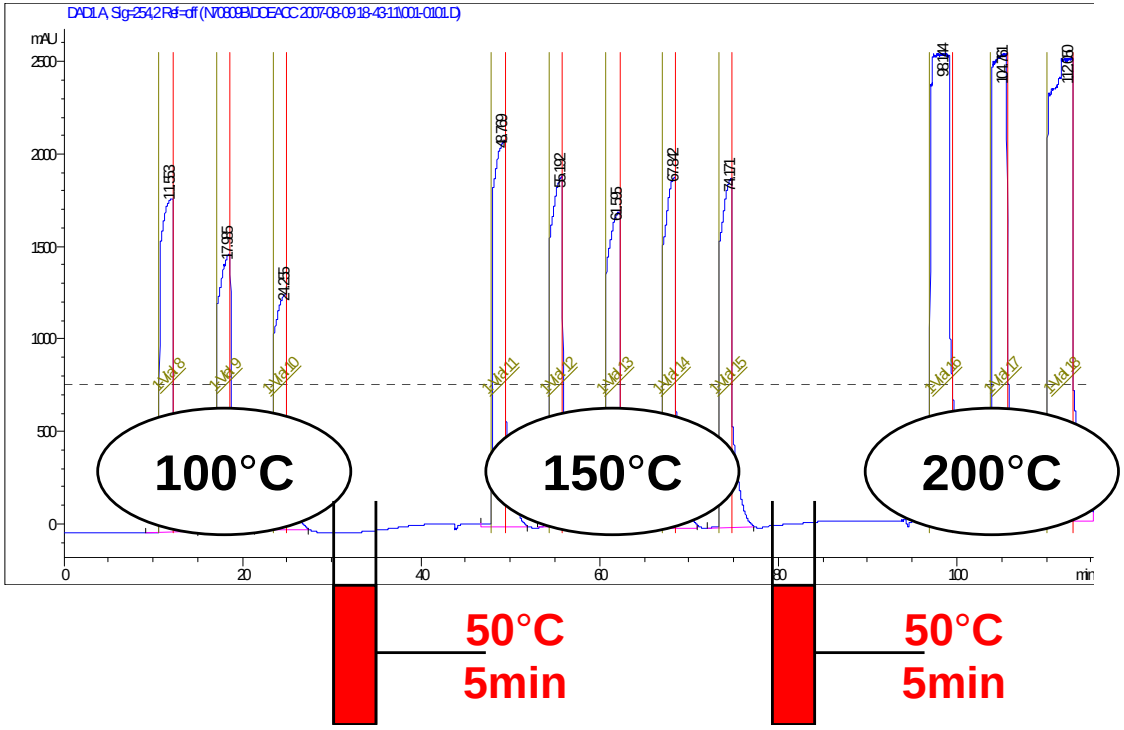
Demonstration Singleton DOE Optimisation for Process

- 3 Level 2 Factor Design
  - Temp – 100°C, 150°C, 200 °C
  - Equivalents – 1eq. 2eq. 3eq.



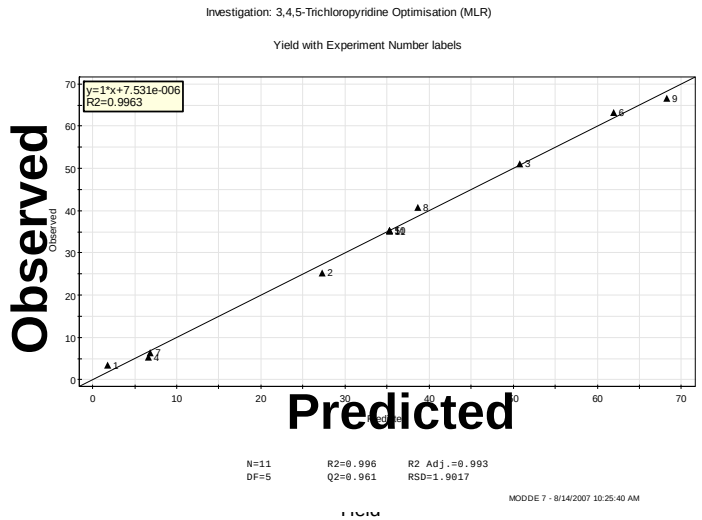
- 11 Reactions 13-20mg each
  - 2 Centre Points

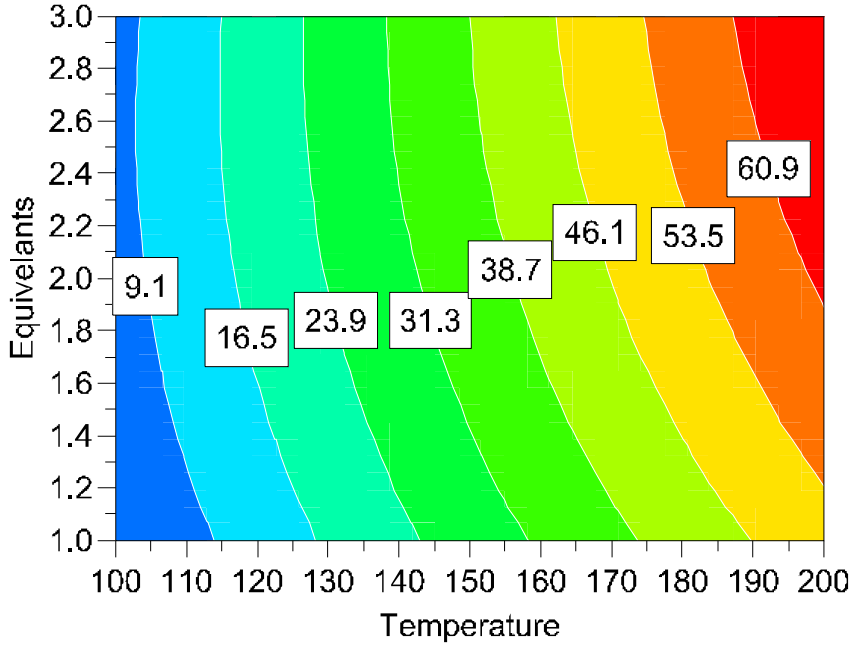
- Total = 184mg
- Total Time = 116 minutes



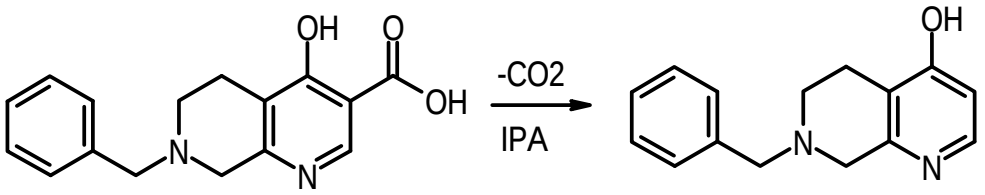
Demonstration Singleton DOE Optimisation for Process

Temp	Equivalents	Yield
100	1	3.41
100	2	5.37
100	3	6.42
150	1	25.29
150	2	35.38
150	3	40.73
150	2	35.41
150	2	35.07
200	1	51.18
200	2	63.25
200	3	66.6



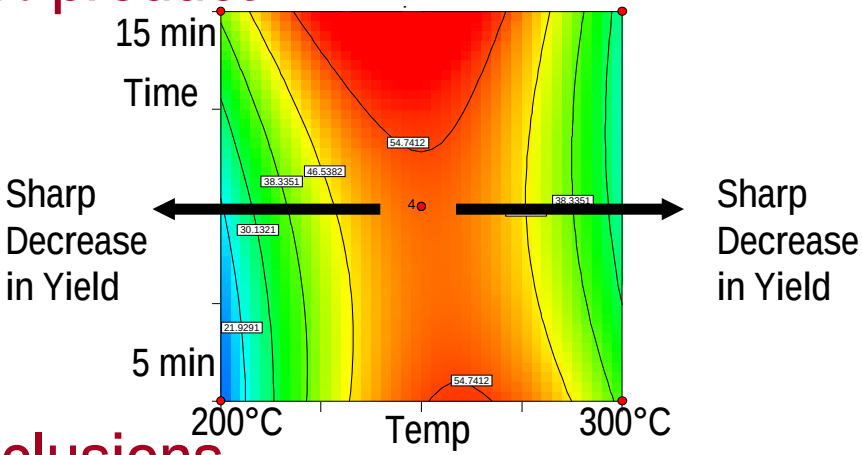


Flow De-Carboxylation



- Issues
  - Extreme temperatures
  - Extreme pressures
  - Not possible in batch
- Flow Experimental
  - Accendo DOE optimization completed in 1hr
  - CCC Design – 15 experiments

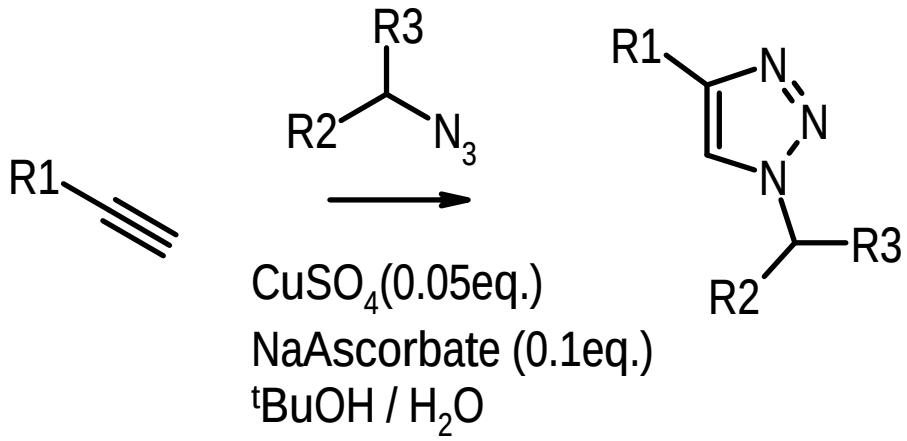
- Knife edge optimal conditions
  275°C, 2000psi, 15 minutes
  >50% product



- Conclusions
  - Key template accessed
  - IP free chemical space
  - Substrate of interest to multiple TA's
  - Flow processes are scalable

Triazoles and Click Chemistry

- Triazoles
  - Metabolically stable pieces
  - Significantly lower logD of a potential drug molecule (improved ADME properties)
  - 1,4-substituted-1,2,3-triazoles can be easily prepared in excellent yield using Click Chemistry

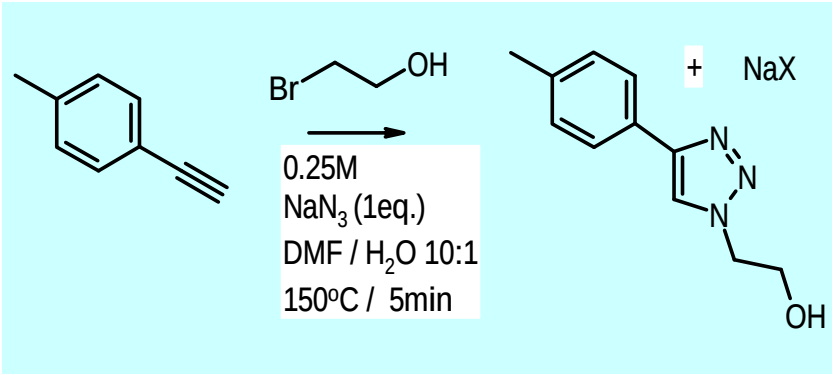


- Click Chemistry Advantages
  - Extremely fast, clean reactions
  - Installing acetylenes in drug molecules is convergent with existing and common halide intermediates
  - Functional group tolerance enables diverse pieces to be stitched together
- Disadvantages
  - Preparing low MW organic azides is extremely dangerous in batch

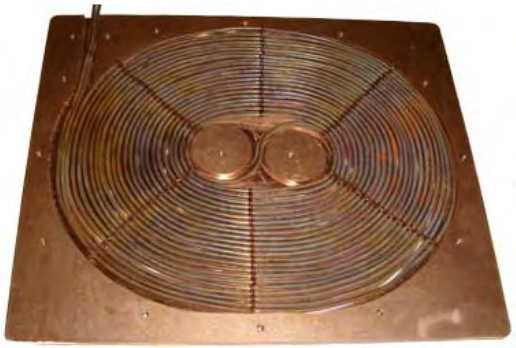
Kolb, Hartmuth C.; Finn, M. G.; Sharpless, K. Barry. Click chemistry: diverse chemical function from a few good reactions. Angewandte Chemie, International Edition (2001), 40(11), 2004-2021

Triazole Click Chemistry

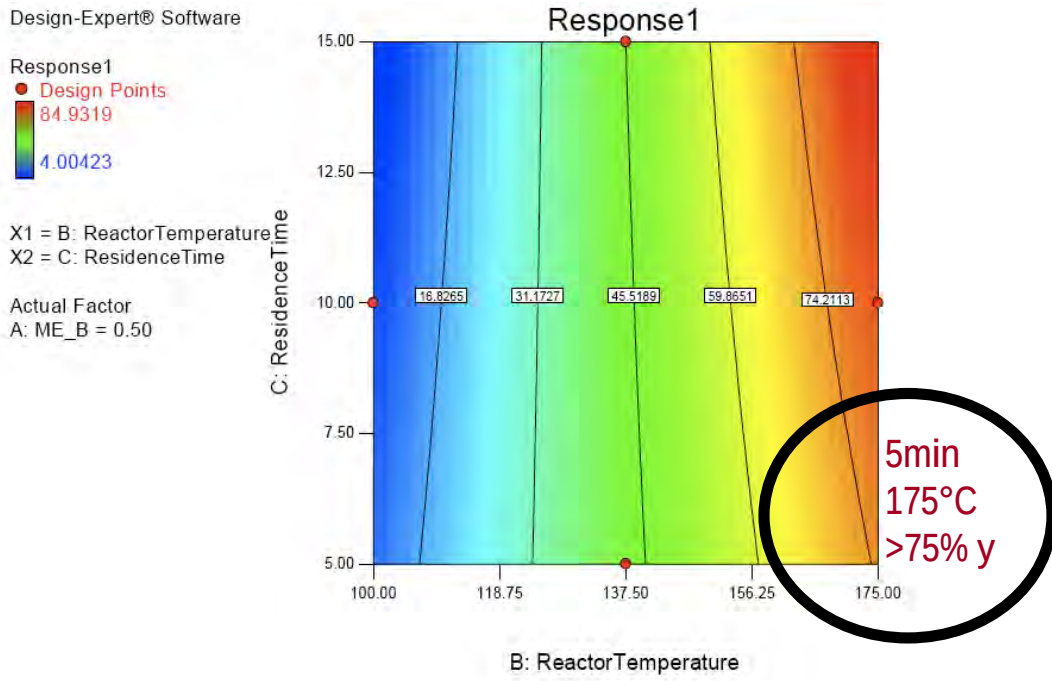
- Azide Formation
  - Can we prepare low MW azides in-situ from halides and NaN_3 in flow ?



- The click reaction is known to work with extremely low concentrations Cu

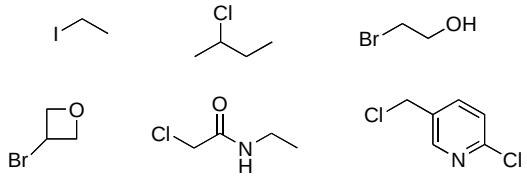


- Conditions
  - DMF / Water required for NaN_3 solubility and solubility of triazole products
- 2hr Accendo DOE Optimization

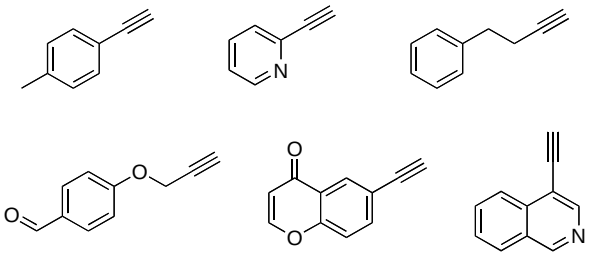


Scope of *in situ* Click Chemistry

Alkyl Halides

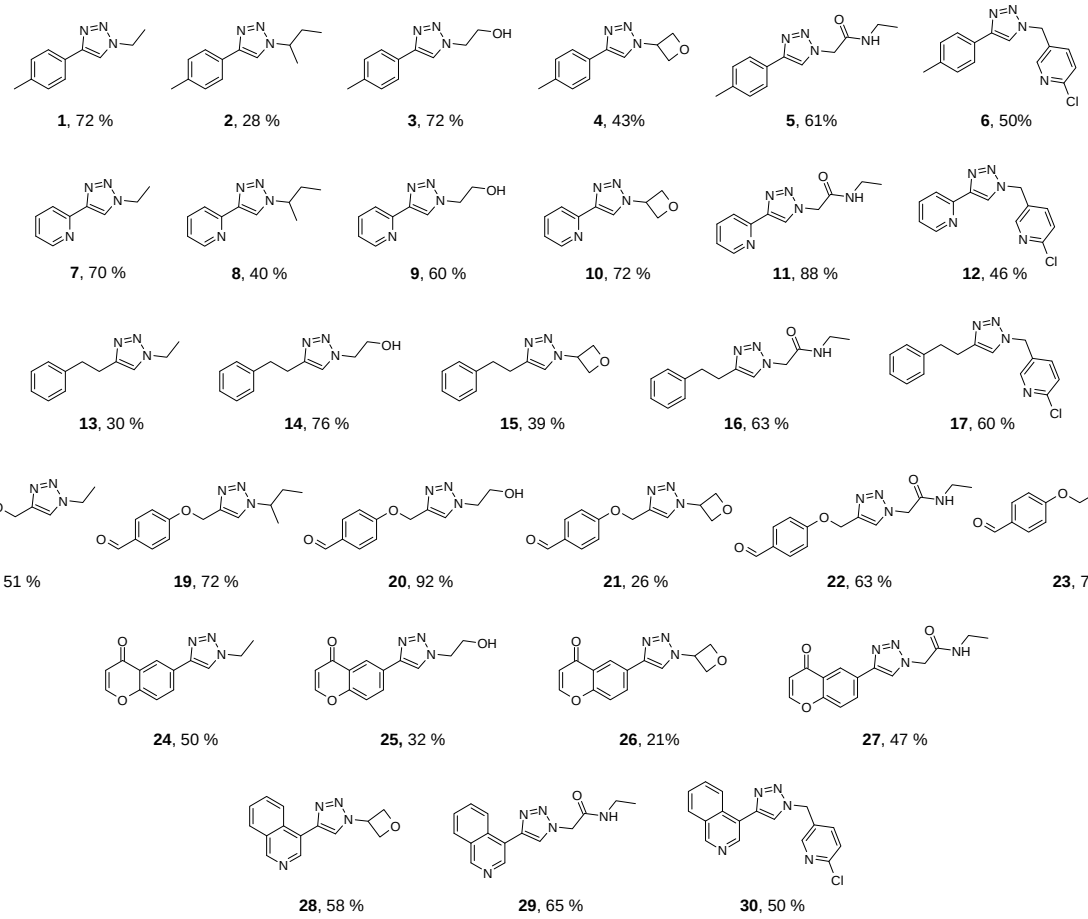


Terminal Acetylenes



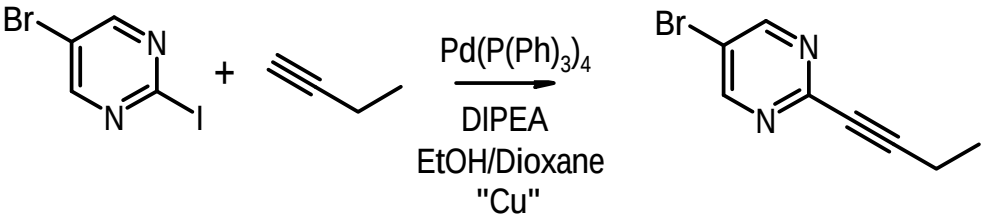
0.25M
NaN_3 (1eq.)
DMF / H_2O 10:1
150°C / 5min

Flow
Cu Reactor



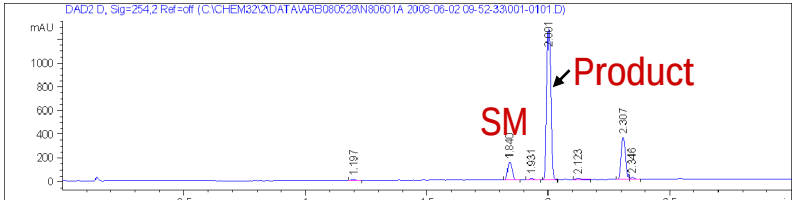
Bogdan, Andrew R.; Sach, Neal W. The use of copper flow reactor technology for the continuous synthesis of 1,4-disubstituted 1,2,3-triazoles. Advanced Synthesis & Catalysis (2009), 351(6), 849-854

Butyne Sonogashira

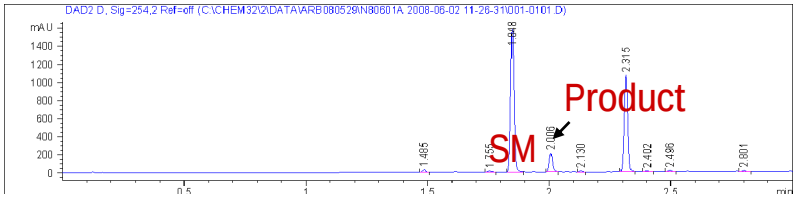


- Issues
  - Butyne b.p. 8°C
  - Pressurized system
  - Dangerous in batch
  - Selectivity challanges
- Flow Experimental
  - Accendo optimization completed in 2hrs
  - Demonstrates 125°C as optimal for conversion/time

- Cu Reactor 125C, 4 min.



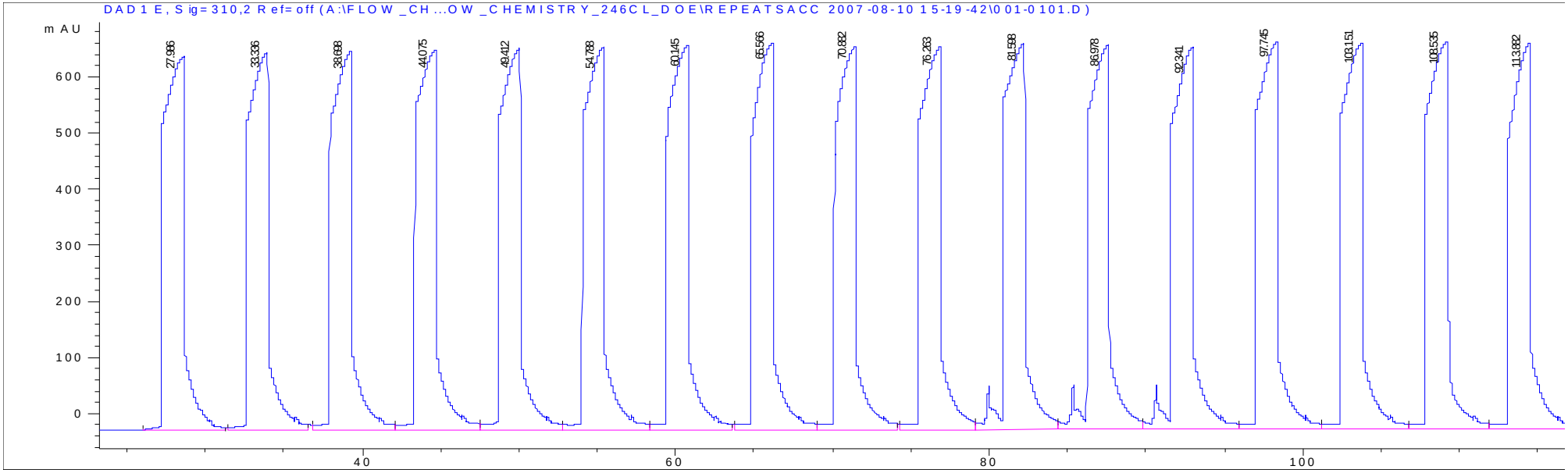
- Hastalloy Reactor 125C, 4 min.



- Conclusions
  - Scalable process (24g/day)
  - Cu reactor removes requirements for Cu additive
  - 1.2g delivered to project team

Production Mode

- Reproduce automatically optimized chemistry
- Scale out not up, as a function of time



- 10 min 500mg
- 1hour 3g
- 1day 72g
- 1week 0.5kg

The Next Step – Automated DOE Optimization

Temp	Equivalents	Yield
100	1	3.41
100	2	5.37
100	3	6.42
150	1	25.29
150	2	35.38
150	3	40.73
150	2	35.41
150	2	35.07
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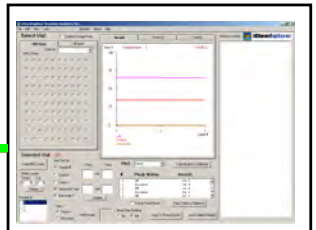
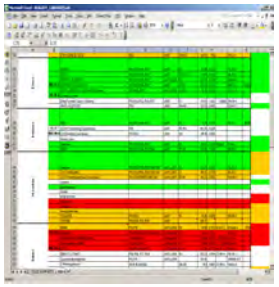
DOE Software



Data Collation and Interpretation

Closing this loop enables automated reaction optimization

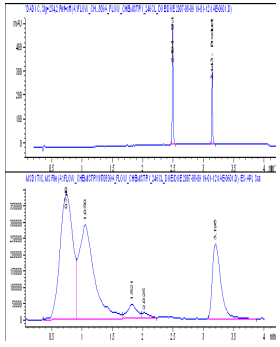


Reagents Database

Design Wizard

Instrument Control

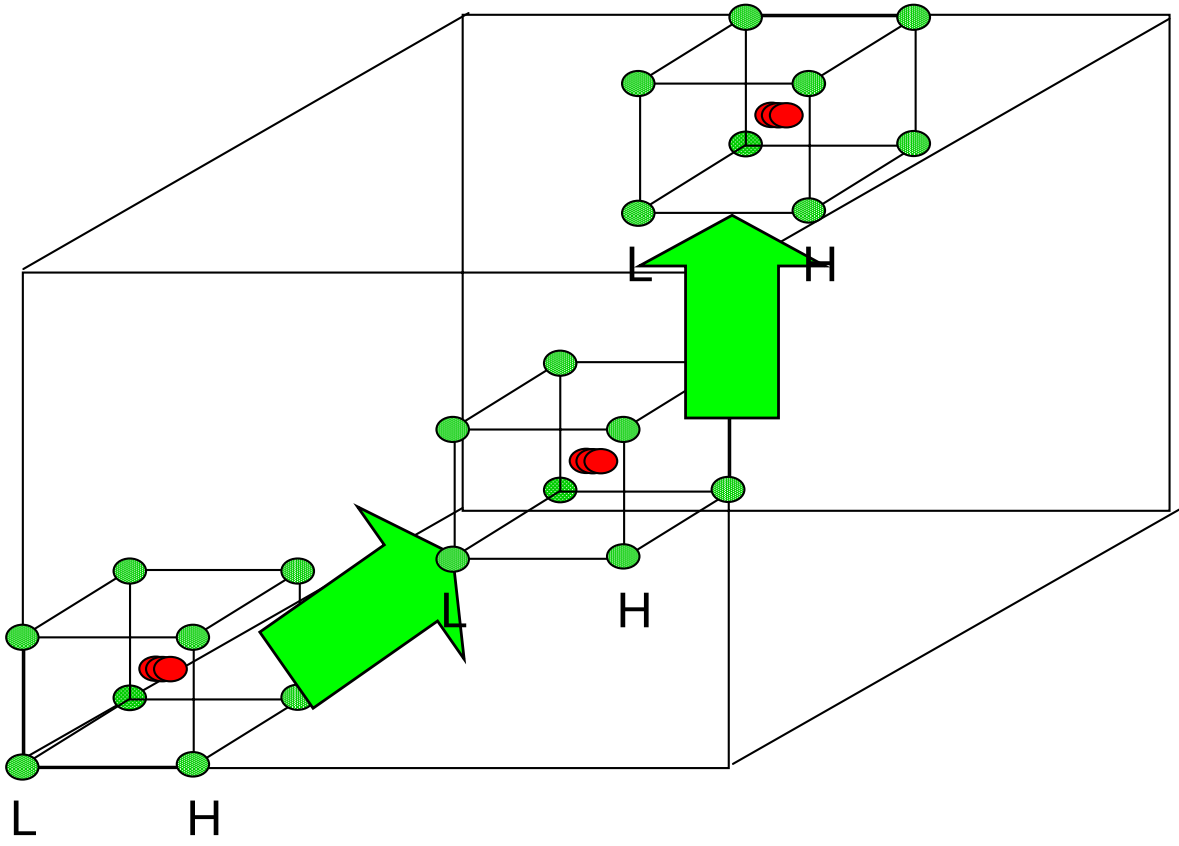
HPLC/MS Analysis



eLNB

The Next Step – Automated DOE Optimization

- Automated Optimization
  - Set initial DOE space
  - Set theoretical parameter space
  - Set objective (LC/MS)
- Enable Automated Simplex Optimization
  - Iteration 1
  - Iteration 2
  - Iteration 3
- Objective Met
  - System automatically scales chemistry using optimized conditions



Conclusions

- Demonstrated
  - Preparation of discreet square wave reaction segments
  - Library optimization and enumeration (Discovery)
  - Singleton optimization (Process)
  - Singleton scale-out (Discovery and Process)
  - Comment - We don't do flow, for flows sake
- Next steps
  - Continue to identify forgotten chemistries (long forbidden)
  - Close DOE loop for automated optimization
  - Multiple step synthesis

Acknowledgements

- Technology
  - Joel Hawkins
  - Jan Hughes (Accendo)
  - Terry Long (Accendo)
  - Kristin Price
  - Larry Truesdale
- Chemistry
  - Andrew Bogdan (Cornell)
  - Valery Folkin (Scripps)
  - Jason Hein (Scripps)
  - Peter Huang
  - Kevin Bunker
  - Paul Richardson