



# Accessing New Chemical Space through Flow-Enabled “Forbidden” Chemistries

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**Overview of Flow Chemistry Apparatus at Pfizer La Jolla**

**Applications and Examples of the Conjure Segmented Flow Reactor System**

**New Developments Towards a Convenient Micro-Scale Flow Reactor for Drug Discovery Library Synthesis**

**Scale-Up Example**



# Flow - Key Applications to Pfizer Drug Discovery

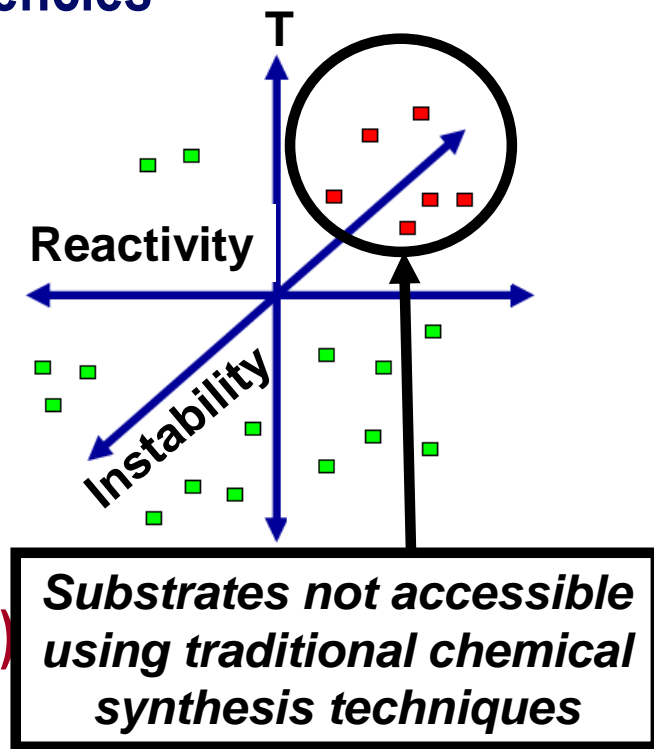
## Discovery - Expanding Chemical Space and Efficiencies

- **Forbidden chemistries**
- **Enumeration Efficiency**
- **Note: Singleton high T work mostly covered by microwave technologies**

## Process - Enabling and Economics

- **Scaling forbidden chemistries (diazotation etc.)**
- **Scale-up of Discovery microwave chemistry**
- **Minimised scale-up considerations**

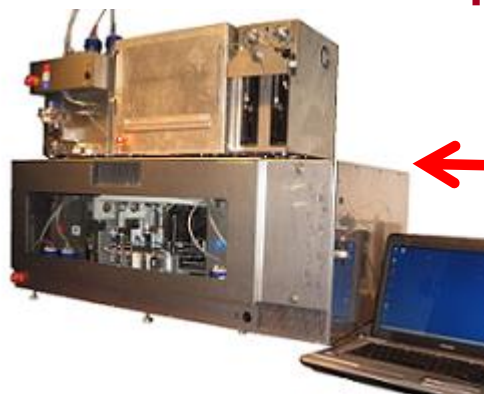
Early implementation of flow chemistry can significantly ease the transitions from Discovery to Process





# Flow Technologies at Pfizer La Jolla

**Conjure Flow**  
(Small Libraries and Optimizations)



**iChemExplorer Flow**  
(Large Libraries)

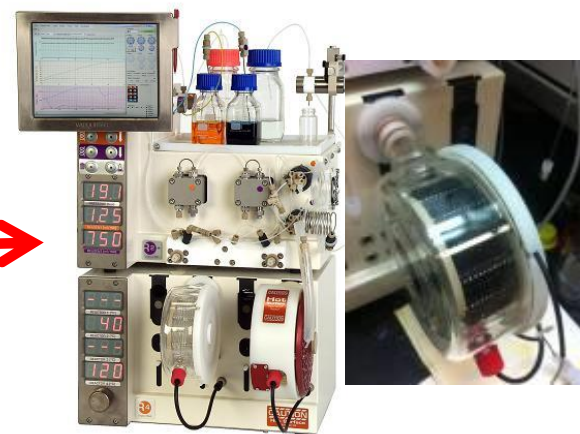


**Segmented Flow**

**H-Cubes (Flow Hydrogenation)**



**Vaportec R4 Series (Scale-Up)**



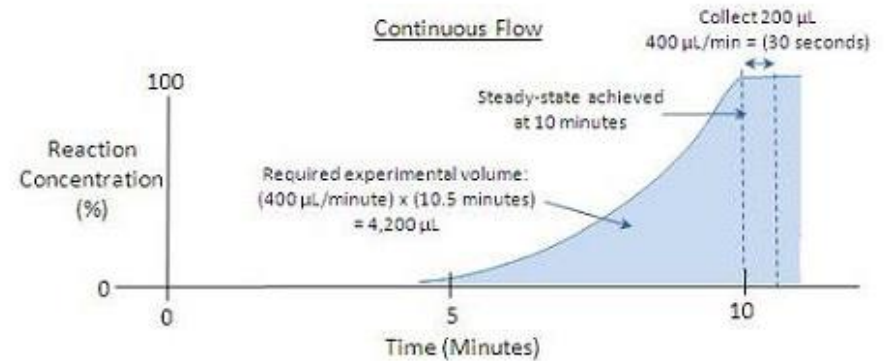
**Continuous Flow**

## Segmented Flow



- **Material sparing**
- **Reaction optimization and library synthesis (discovery)**

## Continuous Flow



- **Material intensive**
- **Reaction scale-up (process)**

nano

micro

meso

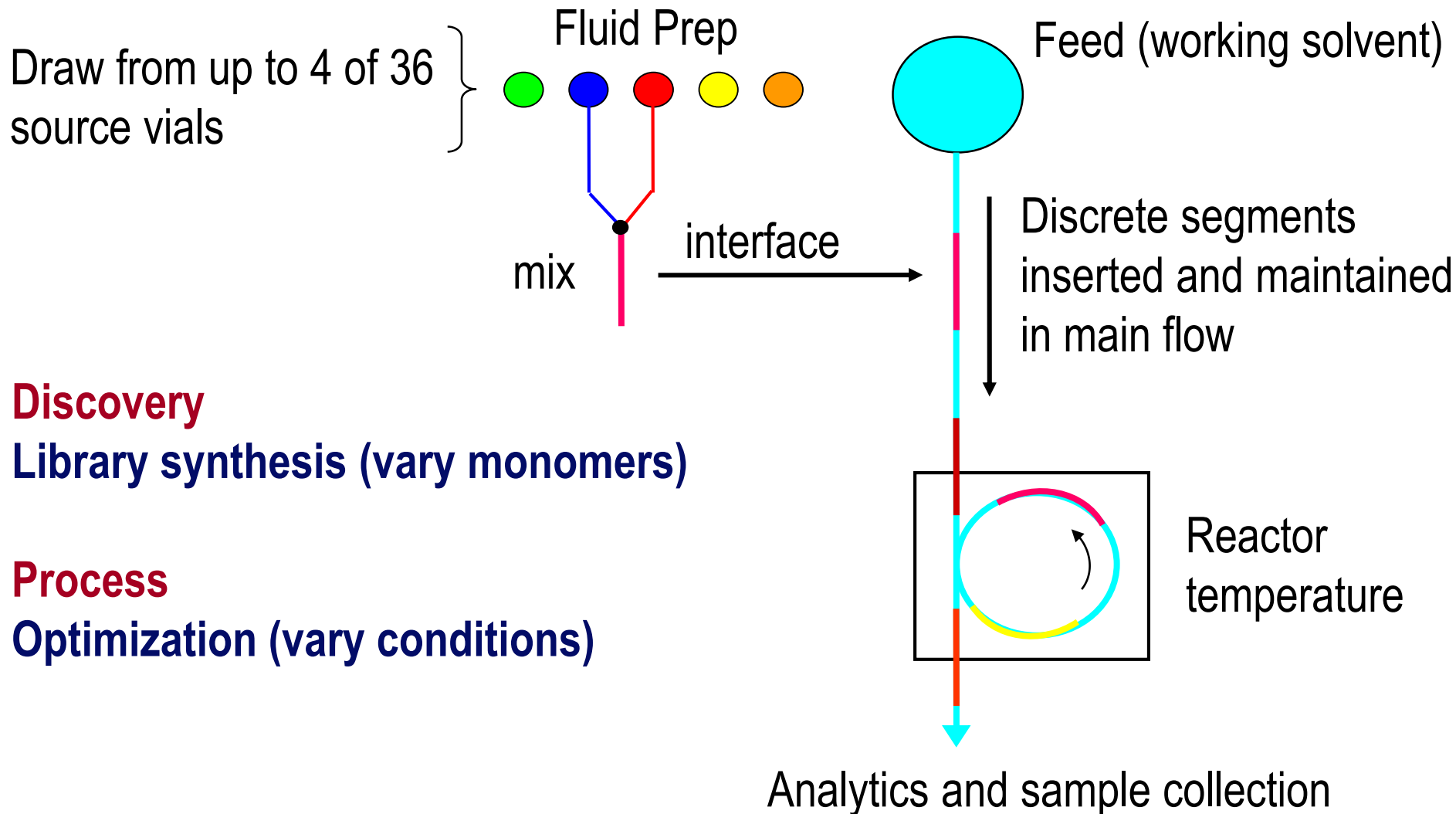
kilo lab

pilot plant

manufacturing



# Conjure Schematic – Segmented Flow



**Discovery**

**Library synthesis (vary monomers)**

**Process**

**Optimization (vary conditions)**



# Adding Artificial Intelligence

## One-size-fits-all initial conditions

Library elements (Discovery)  
Reaction Conditions (Process)

(flowing segments)

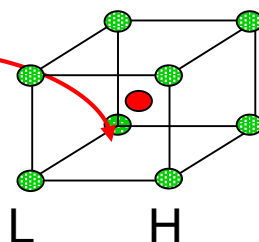
I  
m  
n

HPLC/MS  
Product Y/N?  
Yield & Purity

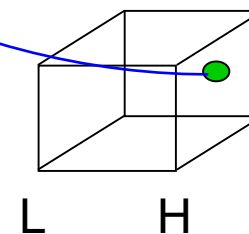
Pass? Fail?

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

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



DOE  
calculates  
best  
conditions

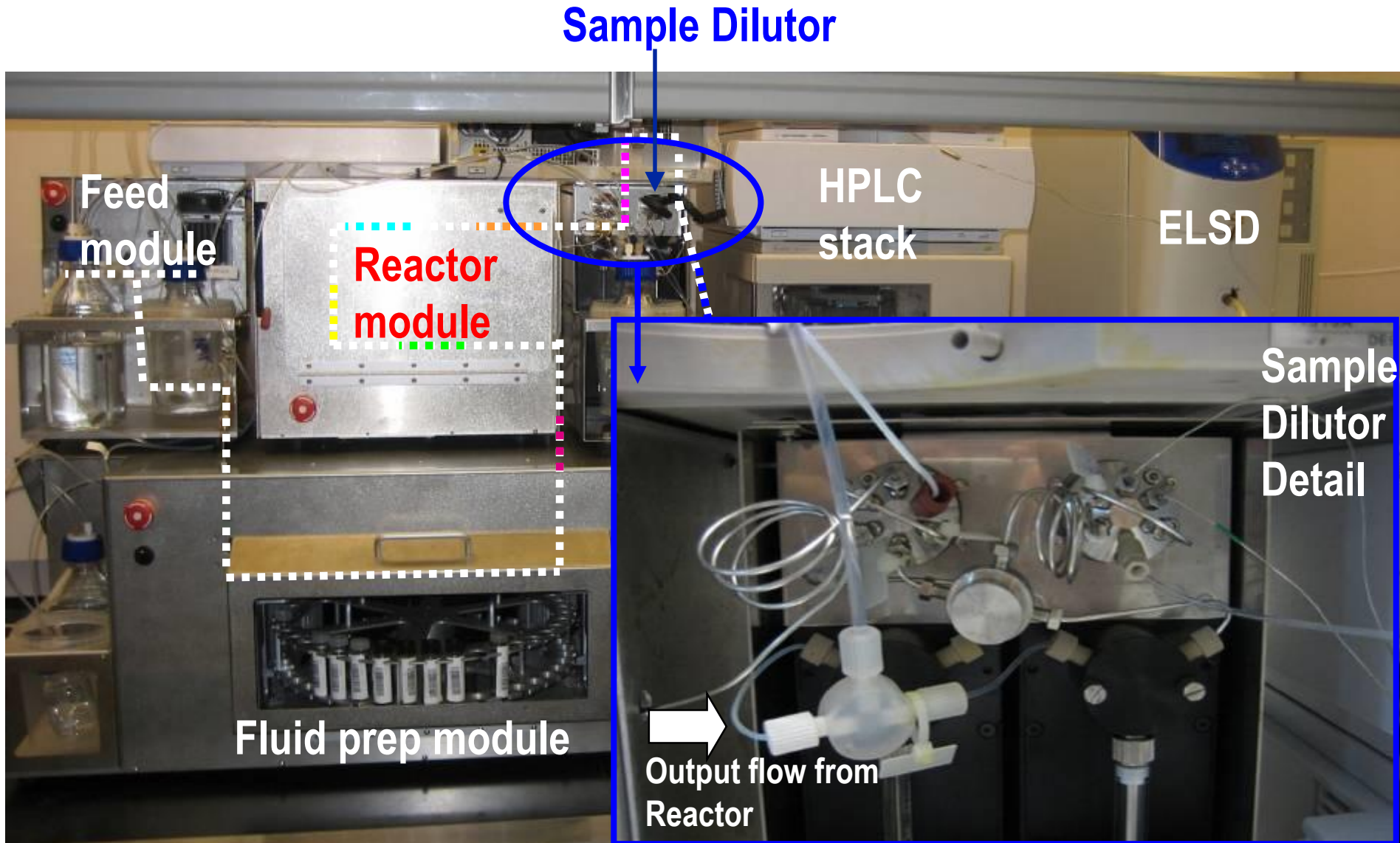


Vary prescribed reaction parameters around initial  
conditions. Automatically done based on Simplex and  
DOE statistical optimization tools.





# Conjure Flow Path





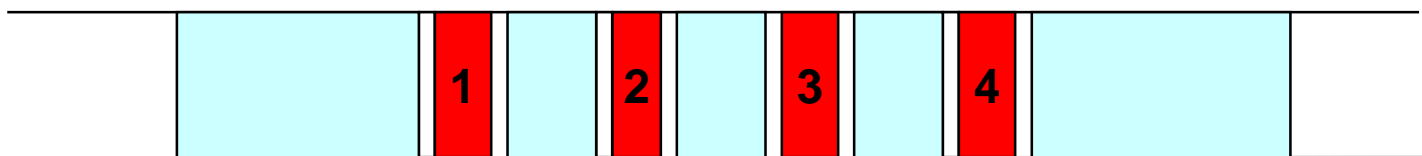


# Conjure Square-Wave Reaction Segments

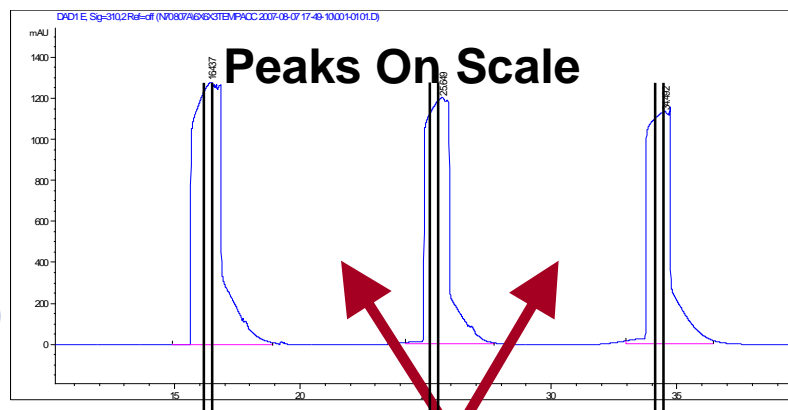
Total Segment Size 150-800uL. Typically 300uL, 5mg Substrate



Multiple Segments Active Within Reactor (up to 4)



Bubble or UV Detection



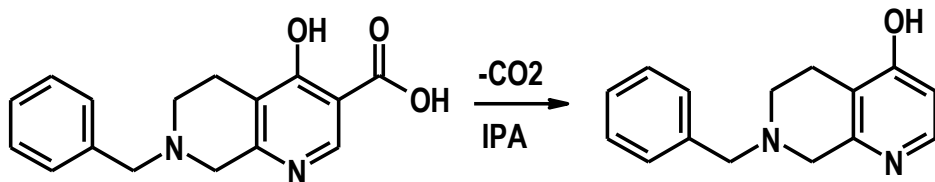
No Dead Reckoning

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

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



# Flow De-Carboxylation



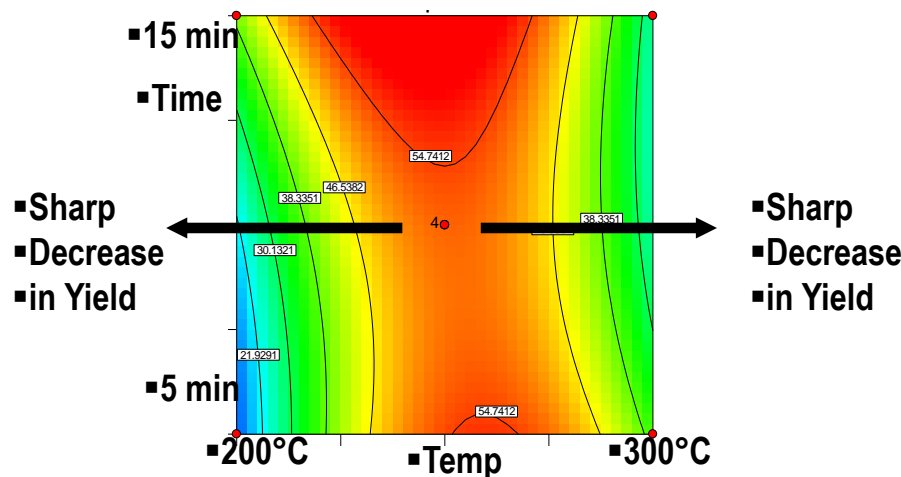
## Issues

- Extreme temperatures
- Extreme pressures
- Not possible in batch

## Flow Experimental

- Accendo DOE optimization completed in 1hr
- CCC Design – 15 experiments
- 5mg per experiment

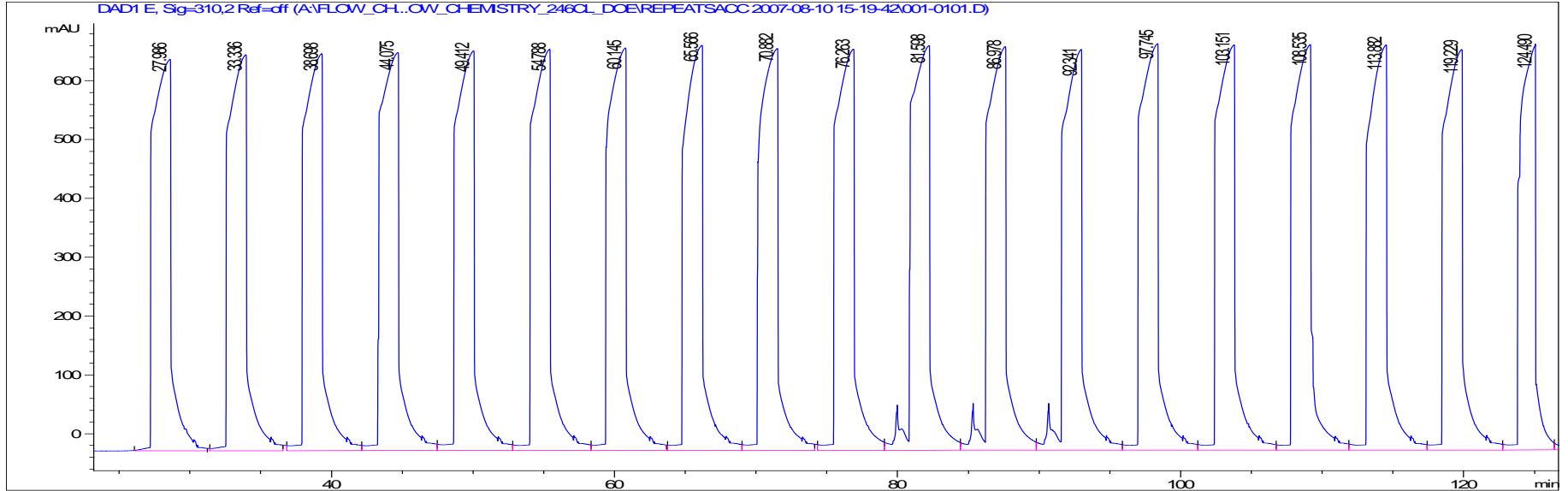
- **Knife edge optimal conditions**  
**275°C, 2000psi, 15 minutes**  
**>50% product**



- **Scaled to 2g by numbering-up**
  - Key template accessed
  - IP free chemical space
  - Scalable flow process



# Conjure Scale-Up – Numbering Up



**10 min**

**500mg**

**1hour**

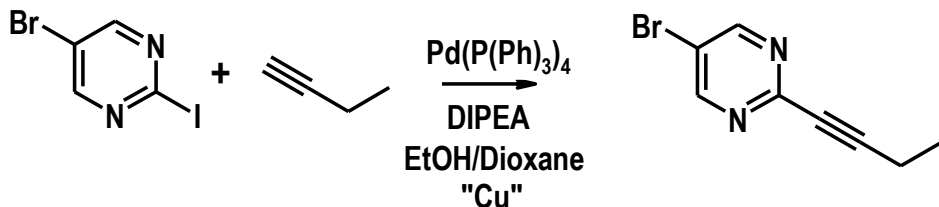
**3g**

**1day**

**72g**

**1week**

**0.5kg**



## Issues

- Butyne b.p. 8°C
- Pressurized system
- Difficult in batch
- Selectivity challenges

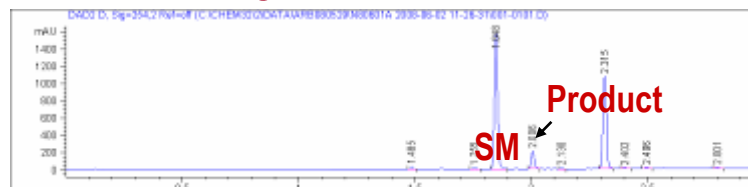
## Flow Experimental

- Accendo optimization completed in 2hrs
- Demonstrates 125°C as optimal for conversion/time

## Cu Reactor 125C, 4 min.



## Hastalloy Reactor 125C, 4 min.

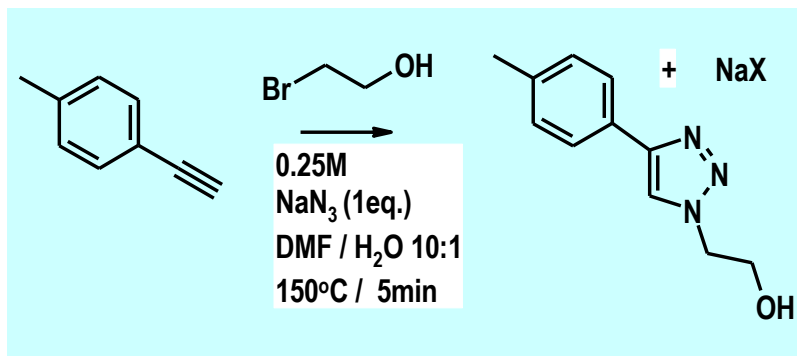


## Conclusions

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

## Azide Formation

- Can we prepare low MW azides in-situ from halides and  $\text{NaN}_3$  in flow?



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



## Conditions

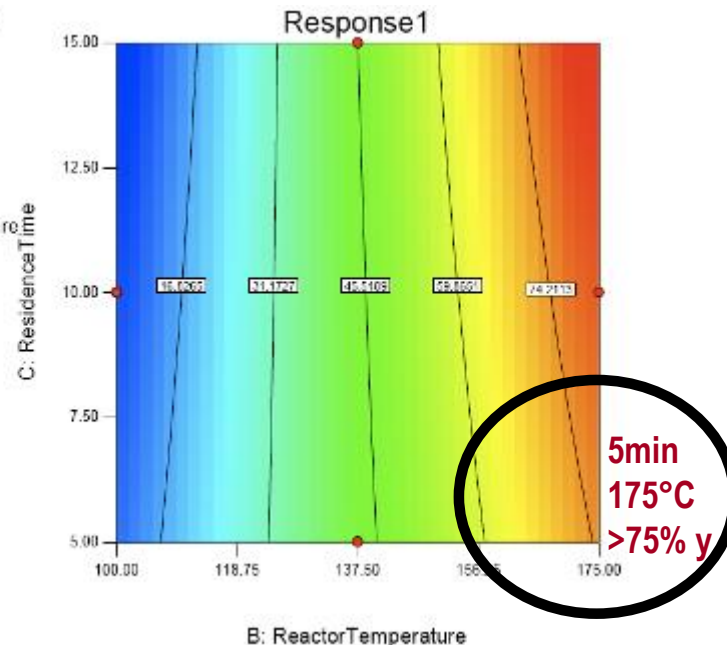
- DMF / Water required for  $\text{NaN}_3$  solubility and solubility of triazole products
- 2hr Accendo DOE Optimization

Design-Expert® Software

Response1  
 Design Points  
 84.9319  
 4.00423

X1 = B: ReactorTemperature  
 X2 = C: ResidenceTime

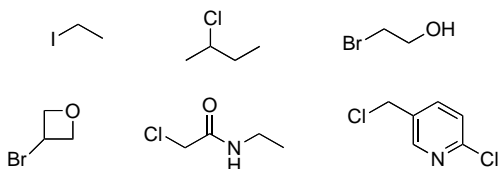
Actual Factor  
 A: ME\_B = 0.50



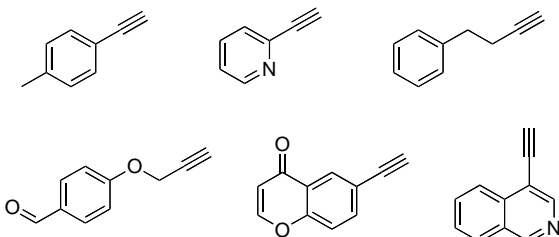


# Scope of *in situ* Click Chemistry

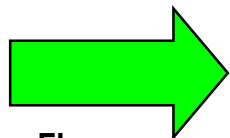
## Alkyl Halides



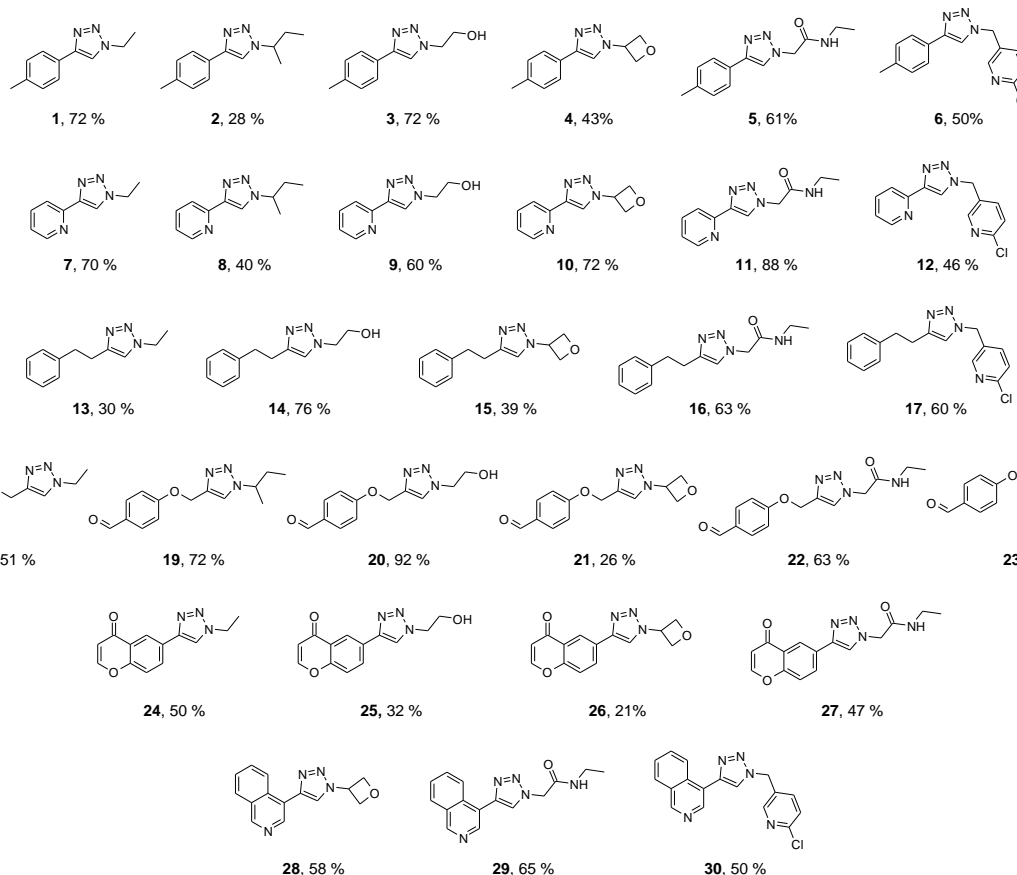
## Terminal Acetylenes



0.25M  
NaN<sub>3</sub> (1eq.)  
DMF / H<sub>2</sub>O 10:1  
150°C / 5min



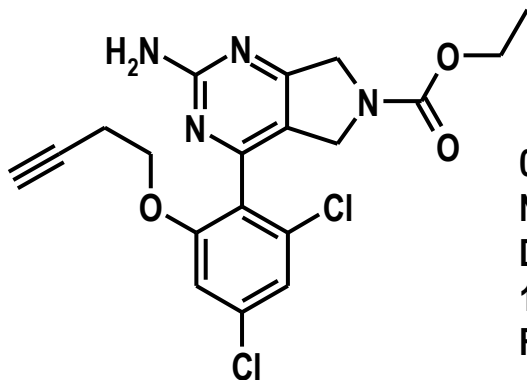
Flow



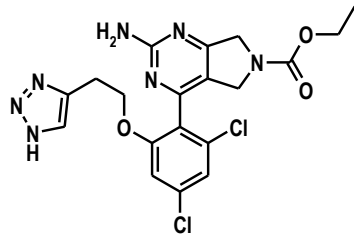
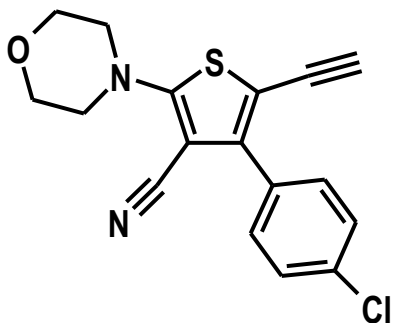
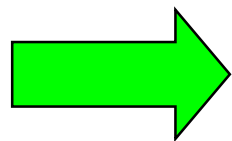




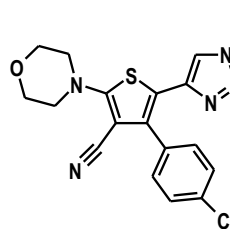
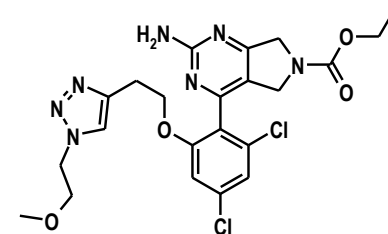
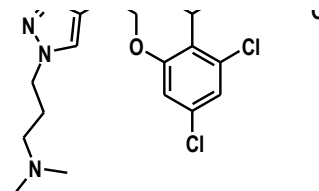
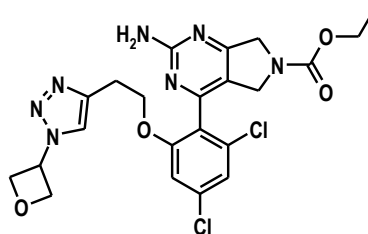
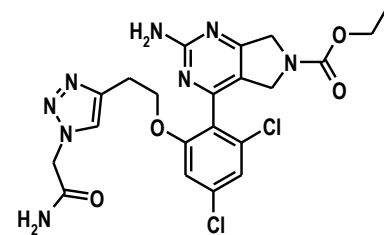
# Application to Medicinal Chemistry Projects and Illustration of Functional Group Tolerance



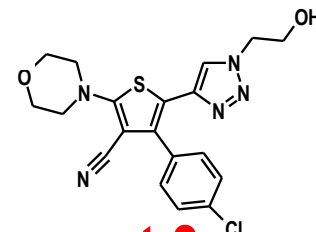
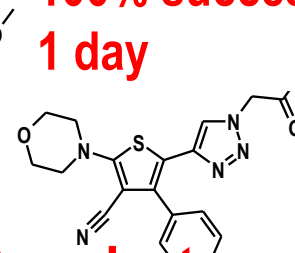
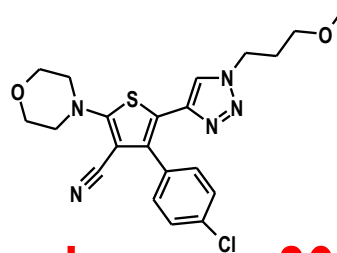
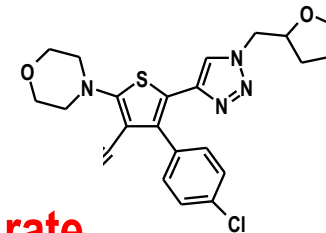
0.5M  
NaN<sub>3</sub> (1eq.)  
DMF / H<sub>2</sub>O 10:1  
150°C / 5min  
Flow



**1 x 14 library**  
**100% success rate**  
**1 day**



**1 x 11 library**  
**100% success rate**  
**1 day**

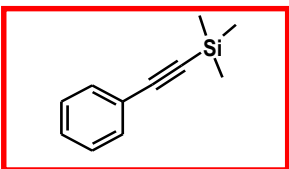


**Over 500 triazoles have been prepared across 30 projects over the past 3 years**

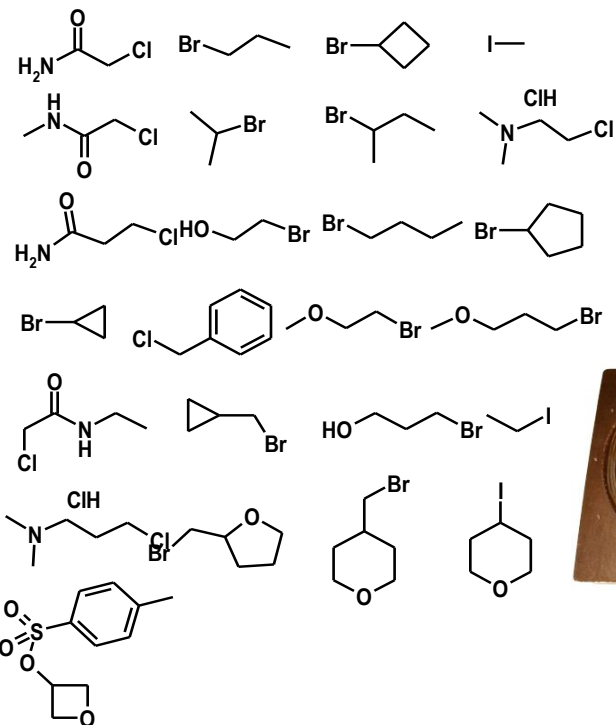


# Extending Scope to tms-protected Click Chemistry

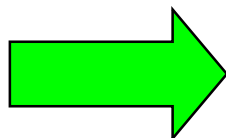
TMS-protected Acetylene



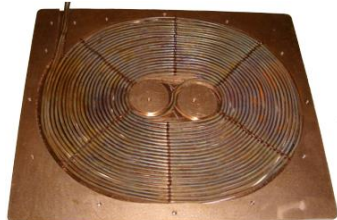
Alkylating Agents (2eq.)



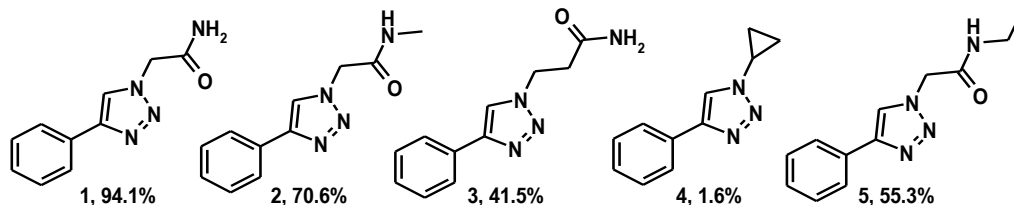
0.25M  
NaN<sub>3</sub> (2eq.)  
DMF / H<sub>2</sub>O 10:1  
150°C / 4min



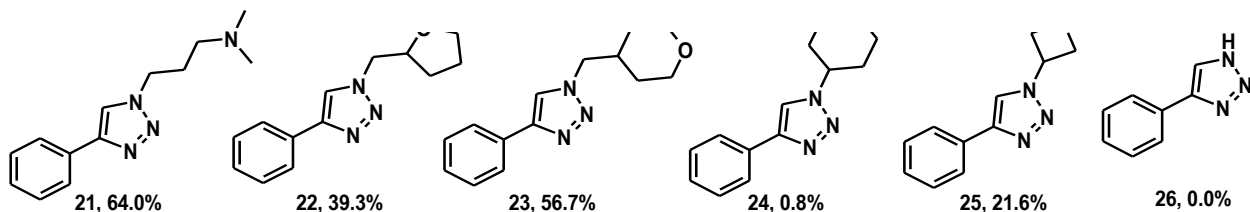
Flow  
Cu Reactor



un-published work

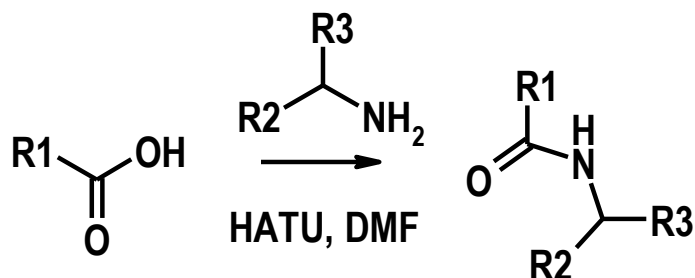


Despite the slightly lower yields, the use of tms protected acetylenes is highly advantageous for stability and solubility reasons

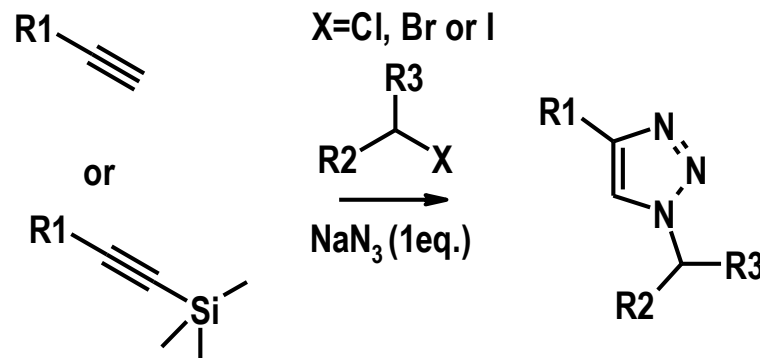


# Triazole Linkage – The New Amide Bond?

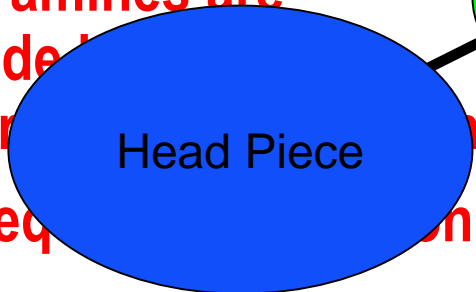
## Amide Bond Formation



## Click Reaction



- High yield (>90%)
- Broad monomer space
- Nucleophilic amines are reactive, amide formations are easy
- Conditions require optimization

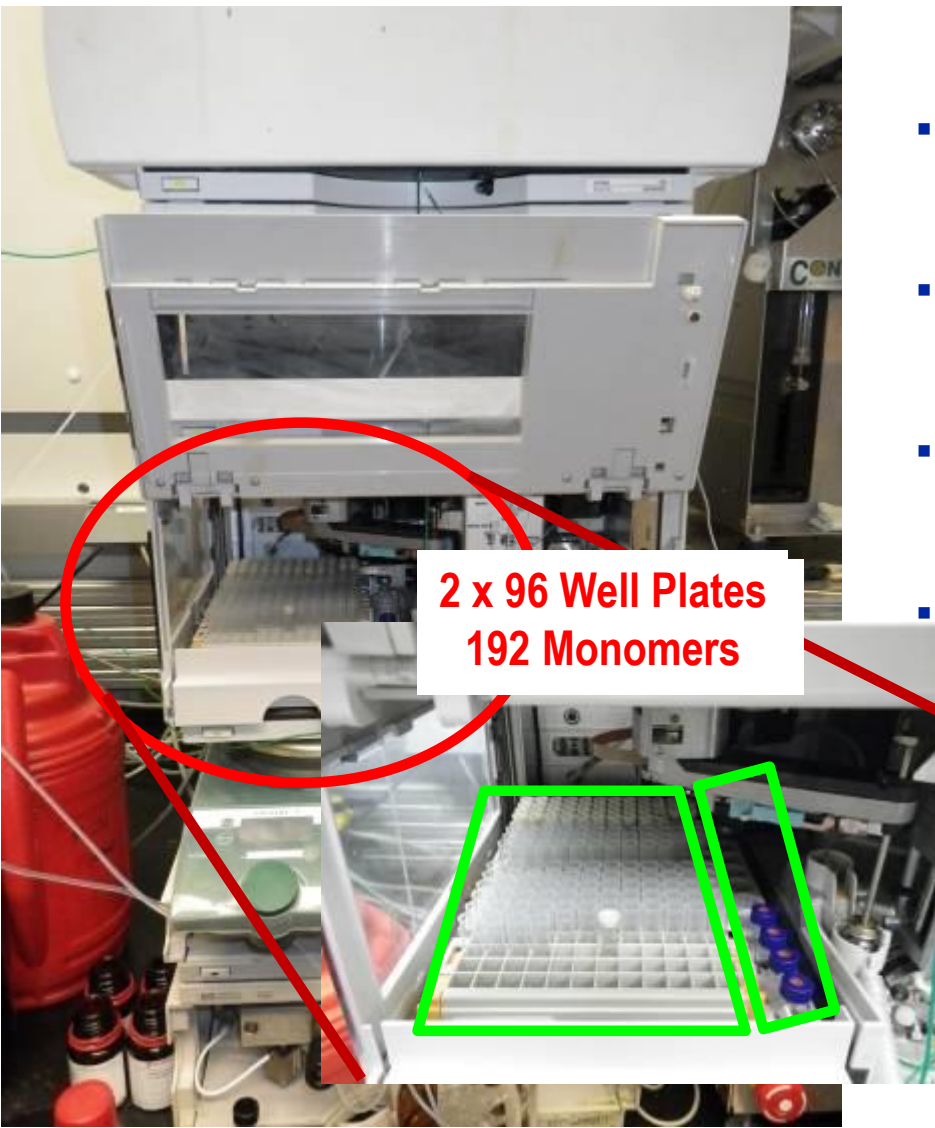


- Azide monomer space is limited
- Dangerous

- High functional group tolerance
- Works un-optimized
- Acetylenes easily installed using common aryl halides



# iChemExplorer Flow – A New Use For An Old Tool



2 x 96 Well Plates  
192 Monomers

What are the ideal specifications of a flow instrument for a discovery chemist?

- **FREE** – you probably already have one in your lab
  - Excellent liquids dispensing accuracy from 1ml down to 0.5uL
  - Capable of huge pressures ( up to 600Bar - far fewer blockages)
  - Wide flow rate range (residence times)
- Compatible with existing plate based workflows

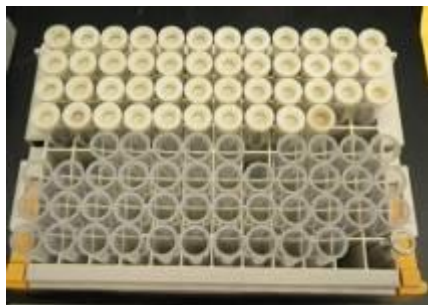
Fully integrated into LC/MS (in-line analysis)

Fully automated and most importantly..... **robust**

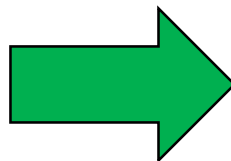


# iChemExplorer Flow – Enumeration Efficiency

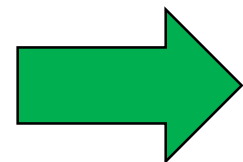
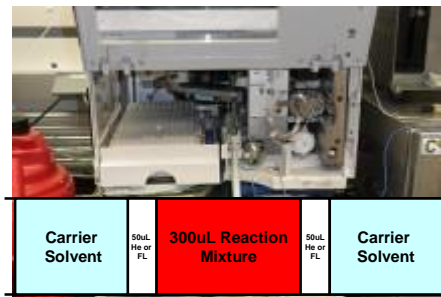
Monomers ordered from store  
Pre-weighed  
(0.05 mmol, 5-20mg)



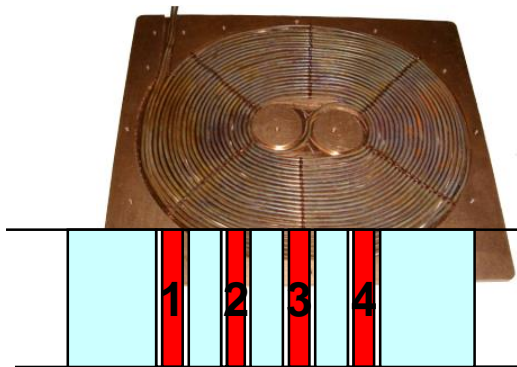
Stirrers added.  
Monomers auto-diluted  
by iChemExplorer Flow  
(50-1000uL)



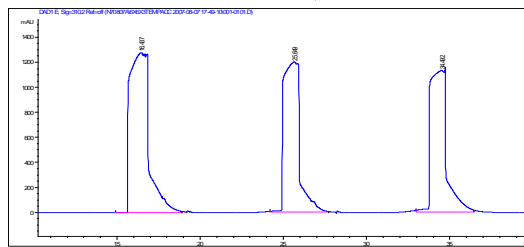
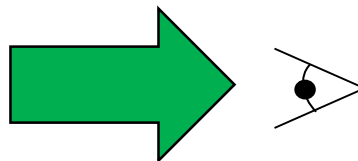
Reagents added (1-900uL)  
Mixed. RM injected with  
florous spacers



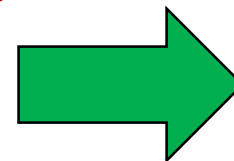
Cu or Hastolloy Coils.  
Programmable T  
Adjustable RT



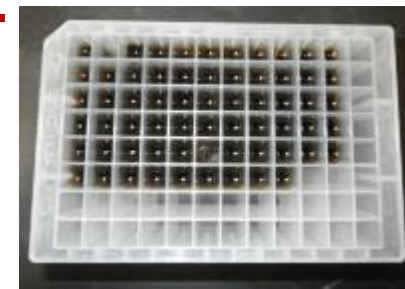
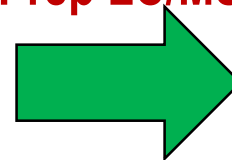
UV detection of  
segments. Sampling  
trigger and collection



Heart Cut. LC/MS  
Analysis. Pass/Fail?



Fraction Collection.  
Prep LC/MS

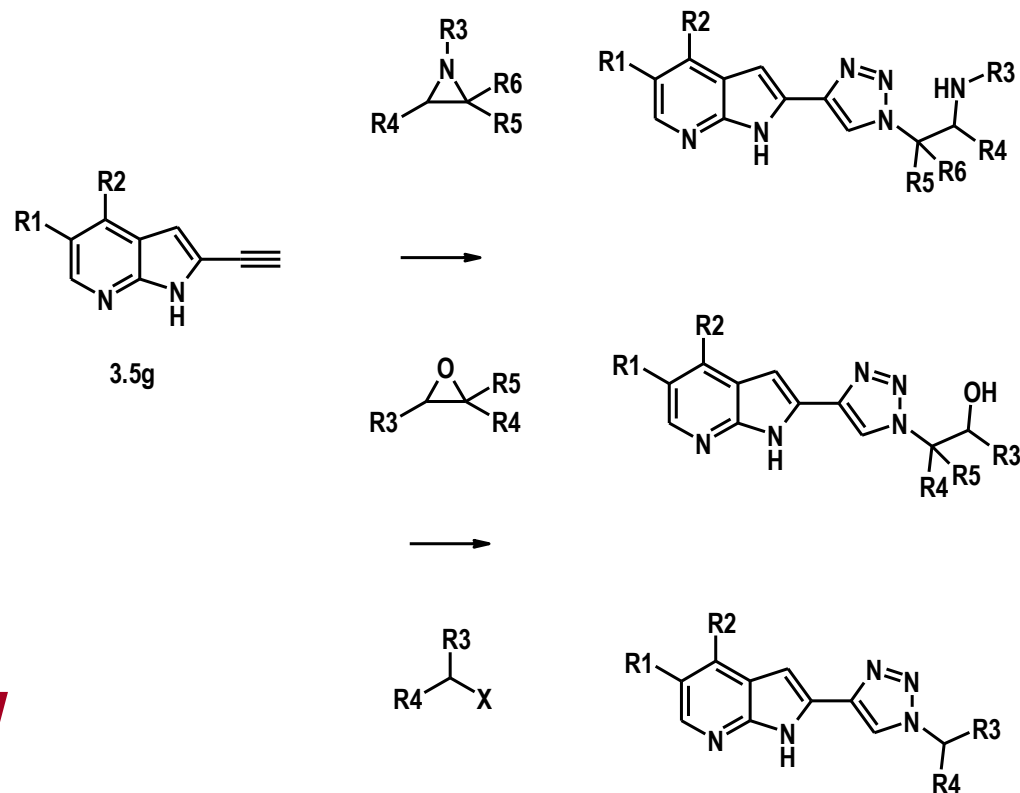




# iChemExplorer Flow – Enormous Potential

- Automation and reduced scale enable huge productivity gains
- Superheated solvents (600Bar) enable rapid reactions (2mins) as with microwave chemistry
- Overlapped injections enables a new product every 2 minutes = 360 in 12hrs
- 2hrs resource per library
- Design and purification are now the limiting step

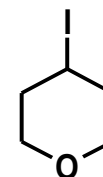
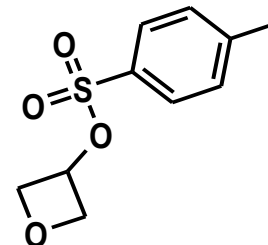
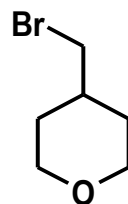
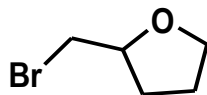
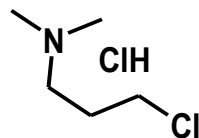
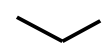
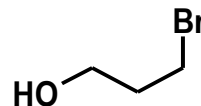
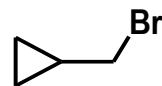
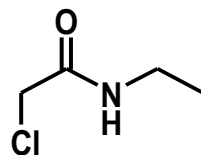
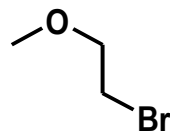
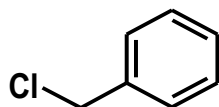
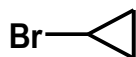
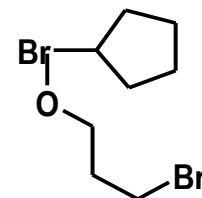
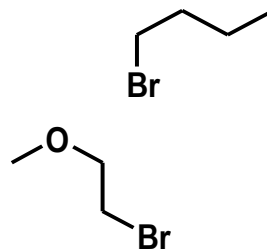
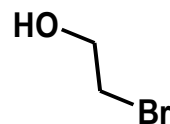
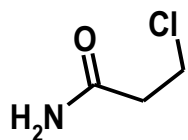
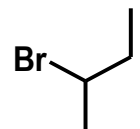
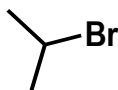
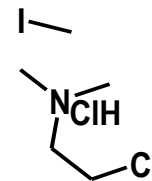
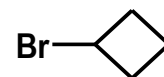
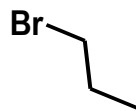
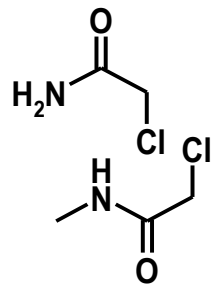
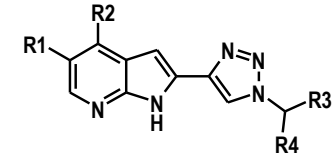
- Library without limits 17/3/2011







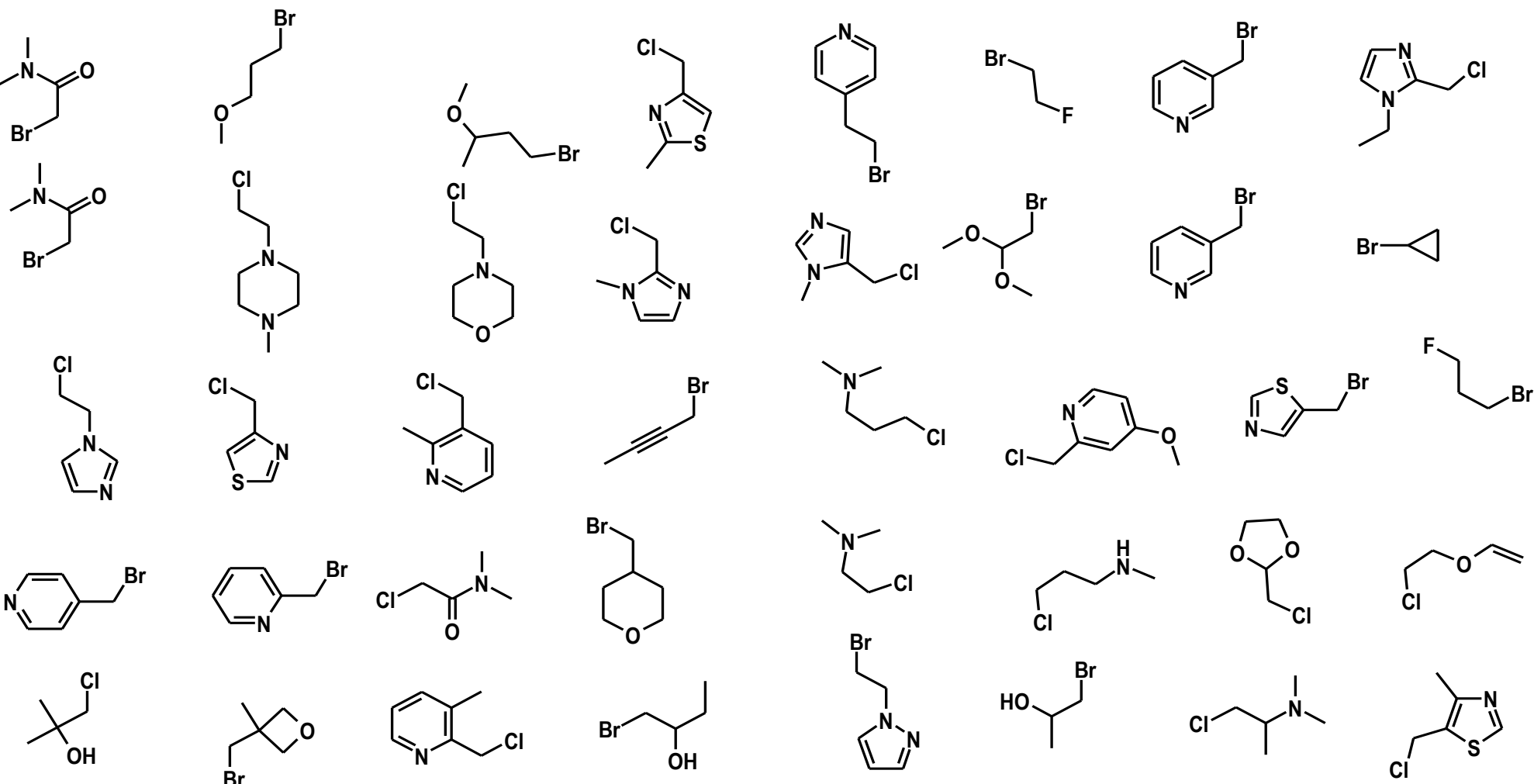
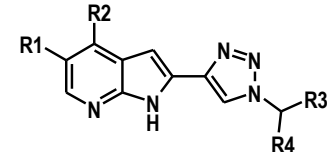
# Set 1 – Alkyl Halides



**24/25 Success Rate = 96%**



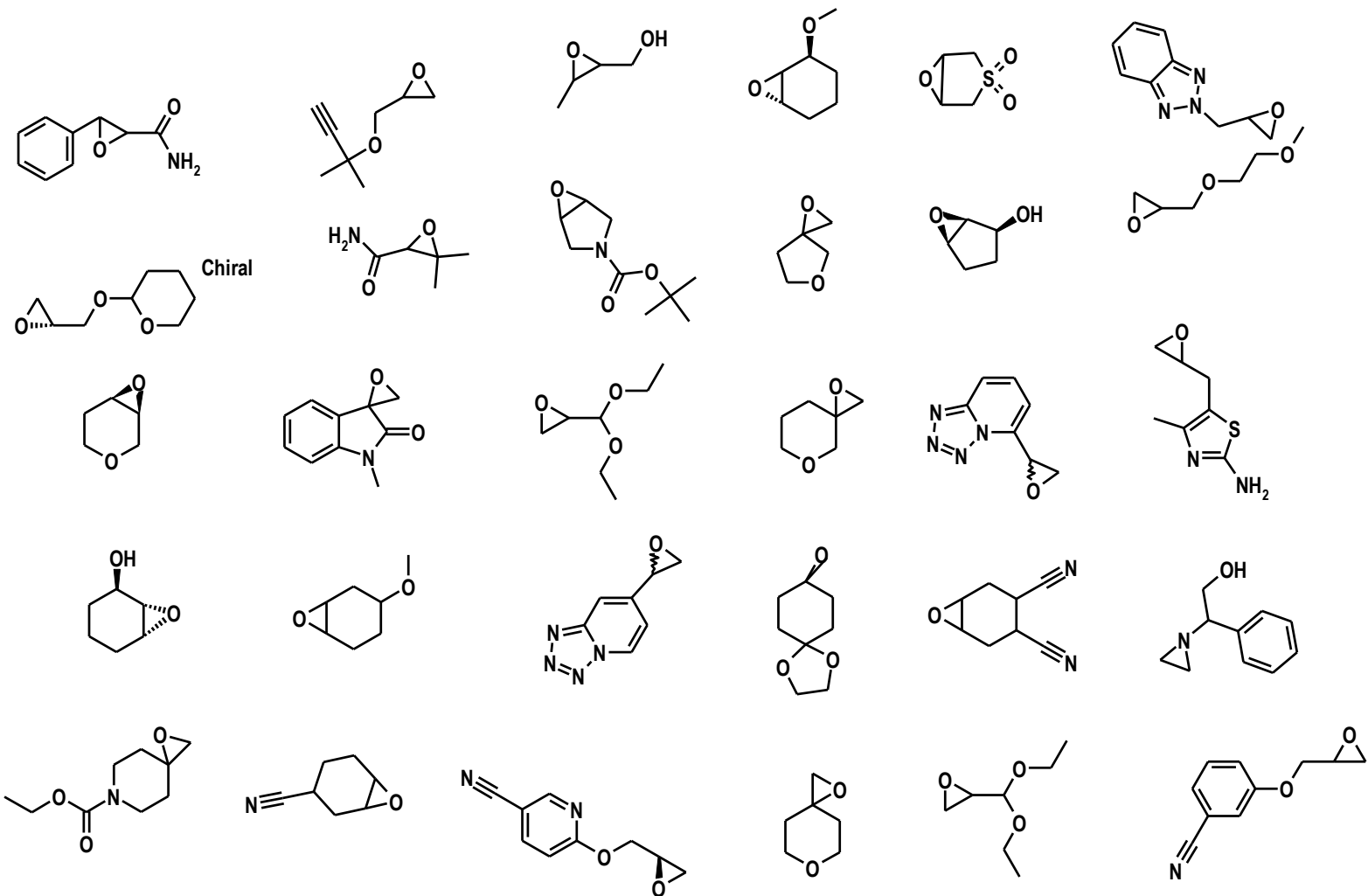
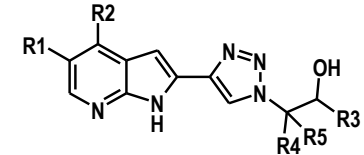
# Set 2 – Alkyl Halides



**40/46 Success Rate = 87%**

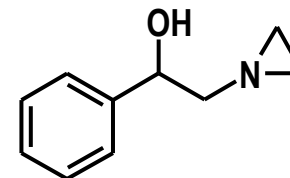
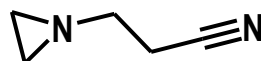
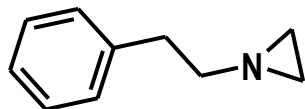
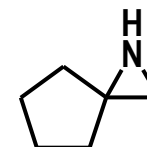
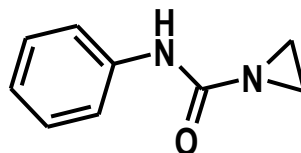
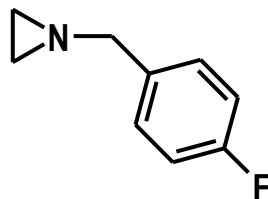
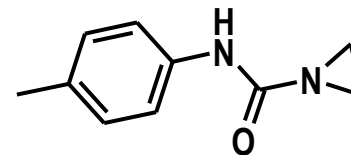
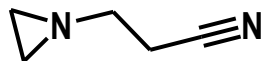
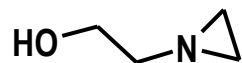
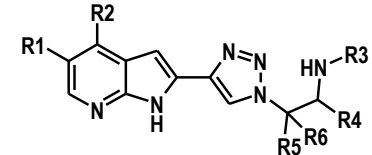


# Set 3 – Epoxides



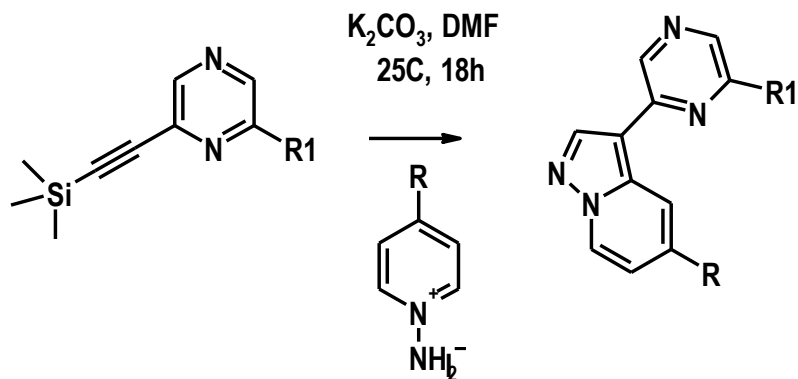
Chiral

**30/47 Success Rate = 65%**



**9/14 Success Rate = 64%**

# What about scale-up?

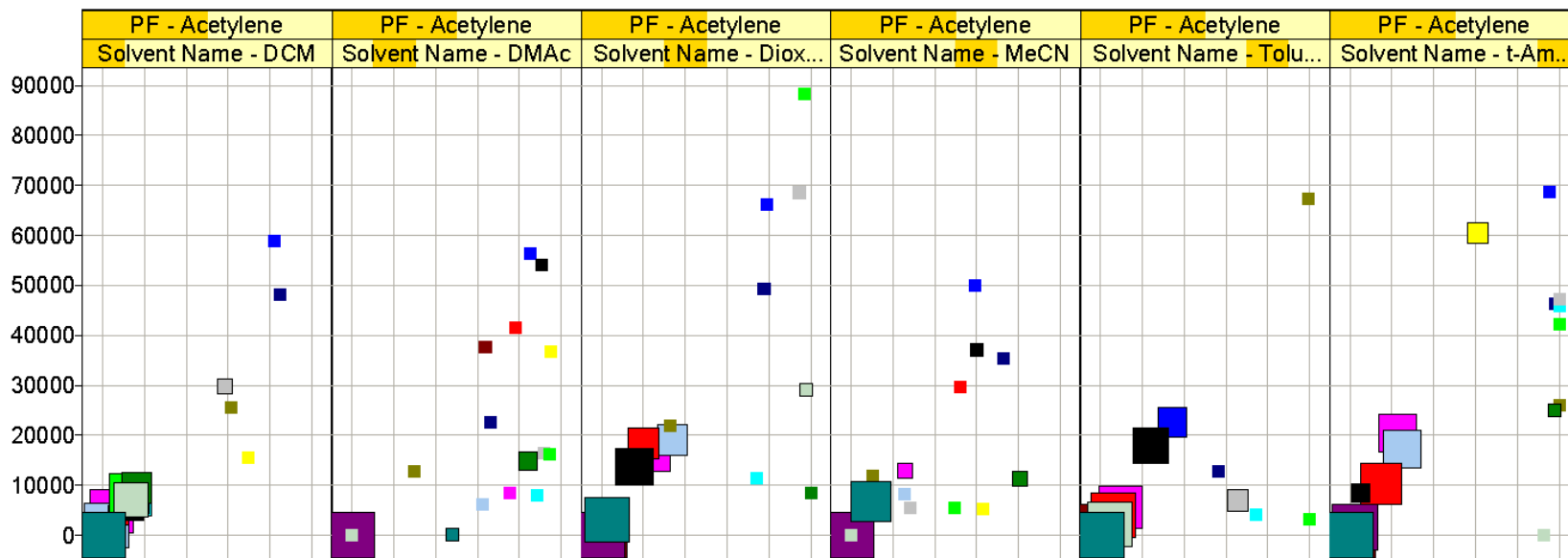


- **Initial reaction carried out with 10mol% AuCl<sub>3</sub> in batch**
  - Isolated yield from reaction was 44-57% (0.56mmol scale)
- **Scaled to 0.3mol (x50)**
  - Significant deterioration in yield
  - Reluctance to heat such an energetic mixture
  - Can flow help? (mixing / heating)
- **Flow translation issues**
  - Reaction forms a thick reddish paste using Au conditions
  - Reaction is sluggish and stalls after 20hrs
- **How to find alternative conditions?**
  - Reaction screening in flow remains a challenge...



# 3+2 Cycloaddition Screen

Product MW 261/263



- Batch high-throughput experimentation (HTE) screen examined 16 bases x 6 solvents = 96 reactions
- Strong base or fluoride sources required to liberate acetylene (KHMDS, NaHMDS, TBAF, CsF)
- Best conditions utilize KHMDS although several 'flow applicable' conditions identified

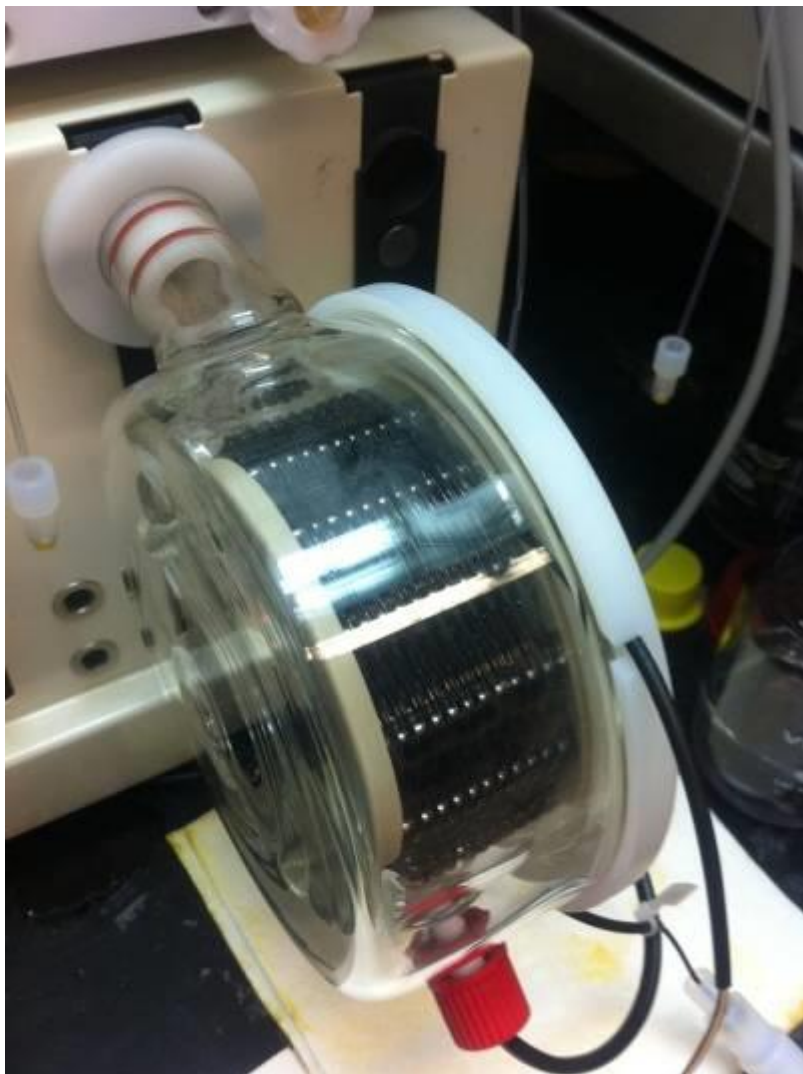




- **Initially KHMDS / Dioxane chosen as reaction solvent. Abandoned as pyridine salt showed poor solubility**
- **Switched to KHMDS / DMF for feasibility experiments**
- **Alkyne and pyridine salt combined (1/1) and dissolved as 0.1M solutions in DMF. 0.2M solution of KHMDS freshly prepared in DMF**
- **Experiments focused on residence times and temperatures from 5-15min and 25-50C**



# Optimization of Flow 3+2 Cycloaddition



- Reactor coils turn black on mixing
- 15 mins at 50C shows complete disappearance of starting materials and >60% conversion to product by LC/MS
- 57% isolated yield as yellow solid. 1.5 days total work for study, scale-out and isolation



## Conclusions

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Two bulk-sparing segmented flow reactors have been presented that are ideal for discovery chemistry applications -:

- For accessing novel chemical space '**safely**' through forbidden chemistries via mini-optimization studies on a singleton basis (up to 5g)
- The **automated** enumeration of a huge click library through the modification of a common laboratory HPLC system

The scale-up of a potentially un-safe batch reaction using the Vaportec R4 in collaboration with batch HTE reaction screening techniques



# Acknowledgements

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- Jason Hein (Scripps)
- Peter Huang
- Kevin Bunker
- Paul Richardson
- Bryan Li



# Questions

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