Laboratory Automation for Process Research and Development

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IASOC Conference
Creativity in Organic Synthesis –
From Target to Function
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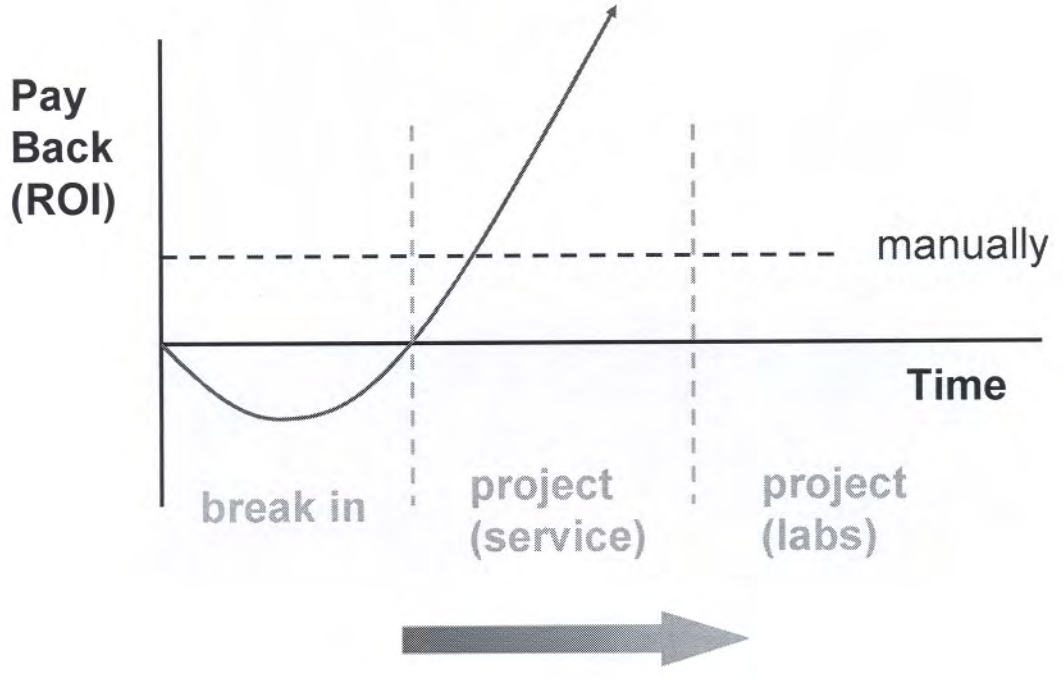
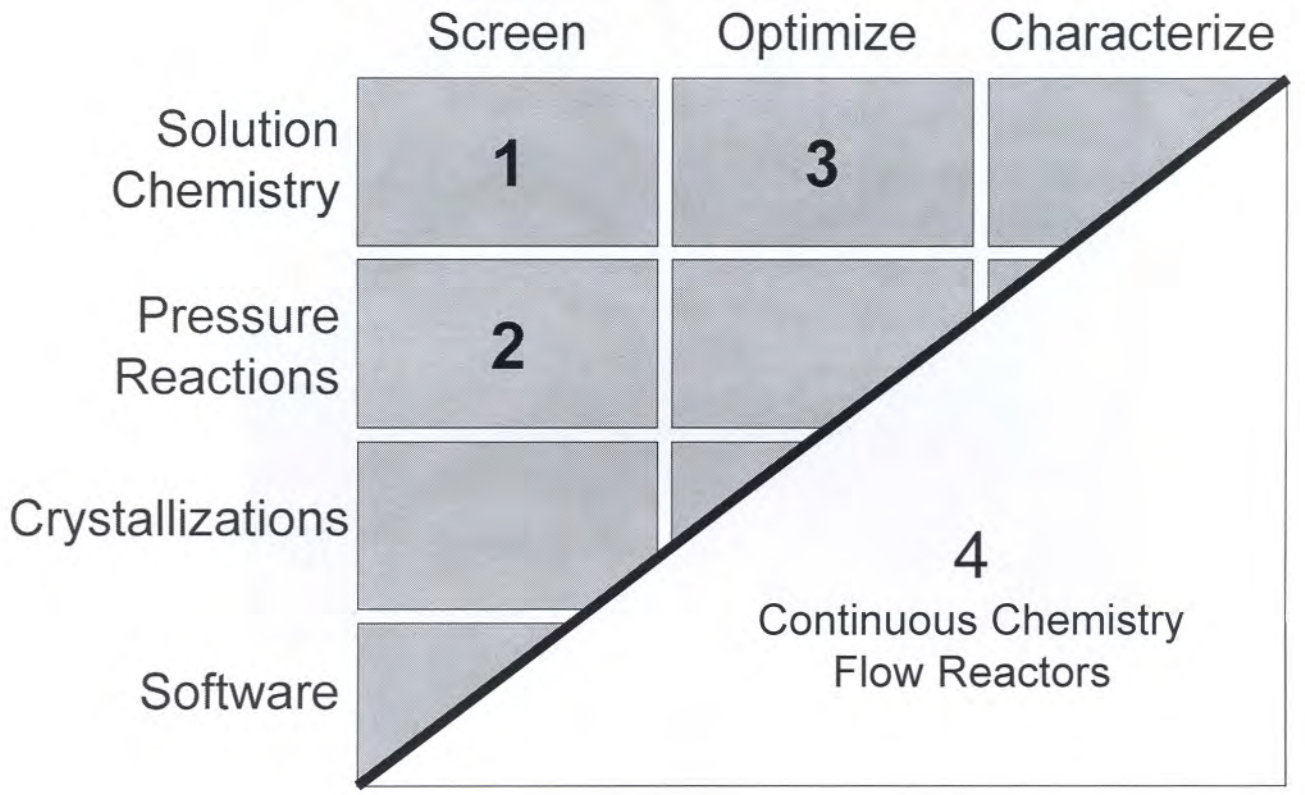
Blend of Technology Development & Project Chemistry



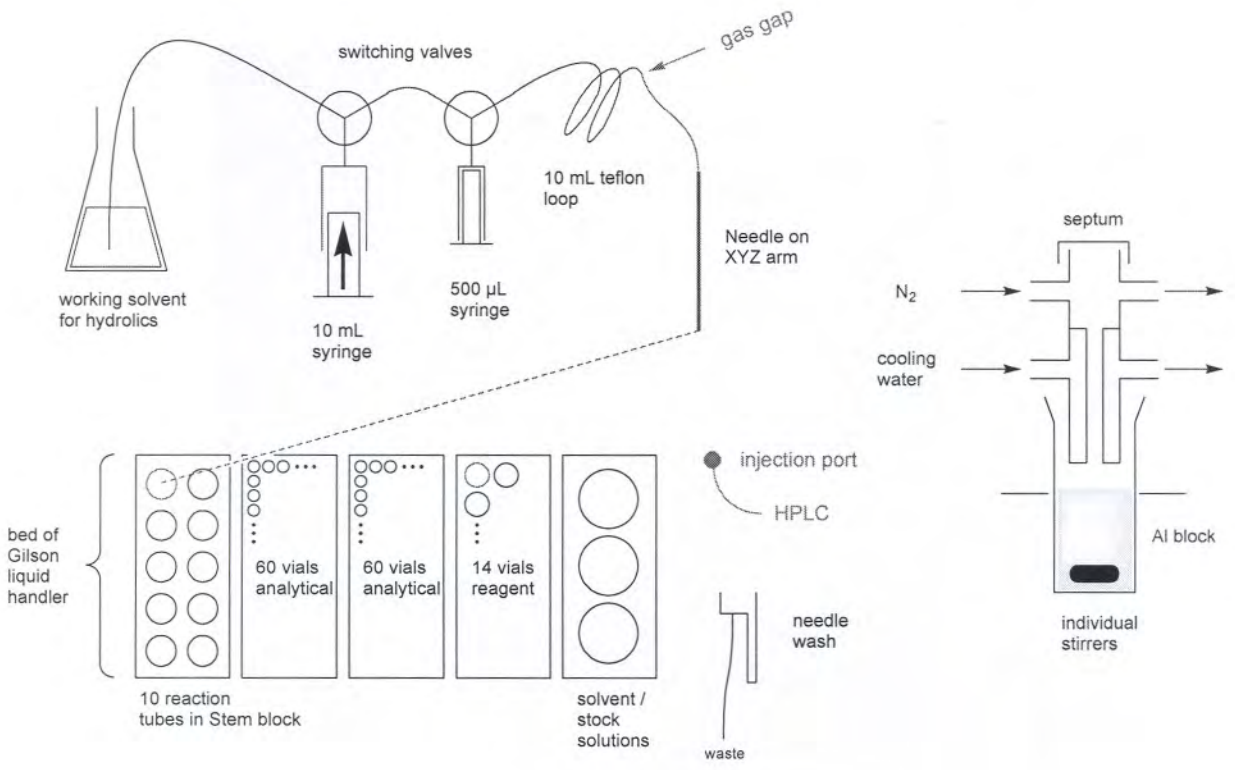
Matrix of Automation in Pharmaceutical Process R&D

	Screen	Optimize	Characterize
Solution Chemistry	Many variables Many experiments Small scale Simulate flasks	Key variables Fewer experiments Maximize information Simulate large scale	Process safety Reaction engineering Process validation Pilots
Pressure Reactions	Many variables Many experiments Small scale Mixing still important	Key variables Fewer experiments Maximize information Simulate large scale	Process safety Reaction engineering Process validation Pilots
Crystallizations	Drug substance salt selection Intermediate resolution & purification	Yield Purity Robustness	Polymorph control Particle size Filtration rate Process validation
Software	Electronic lab notebook-automation interface Overcome data analysis and visualization bottleneck Universal instrument 'wrapper' to minimize number of packages		

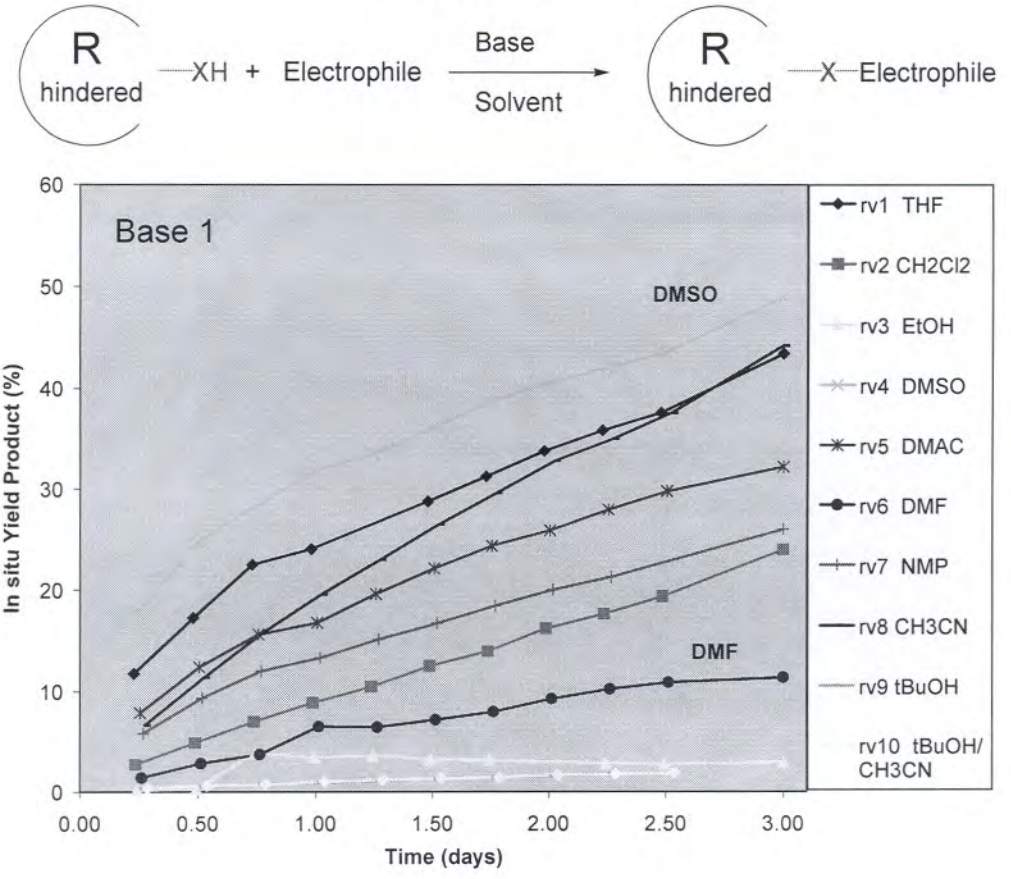
Matrix of Automation in Pharmaceutical Process R&D



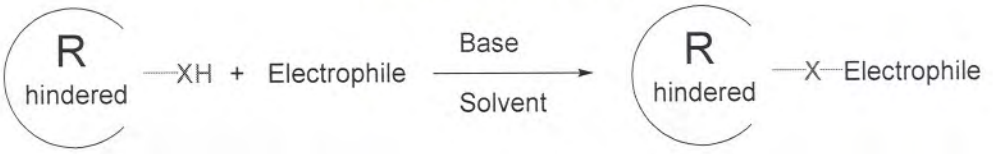
(1) Screening Solution Chemistry: Anachem SK233 / 215

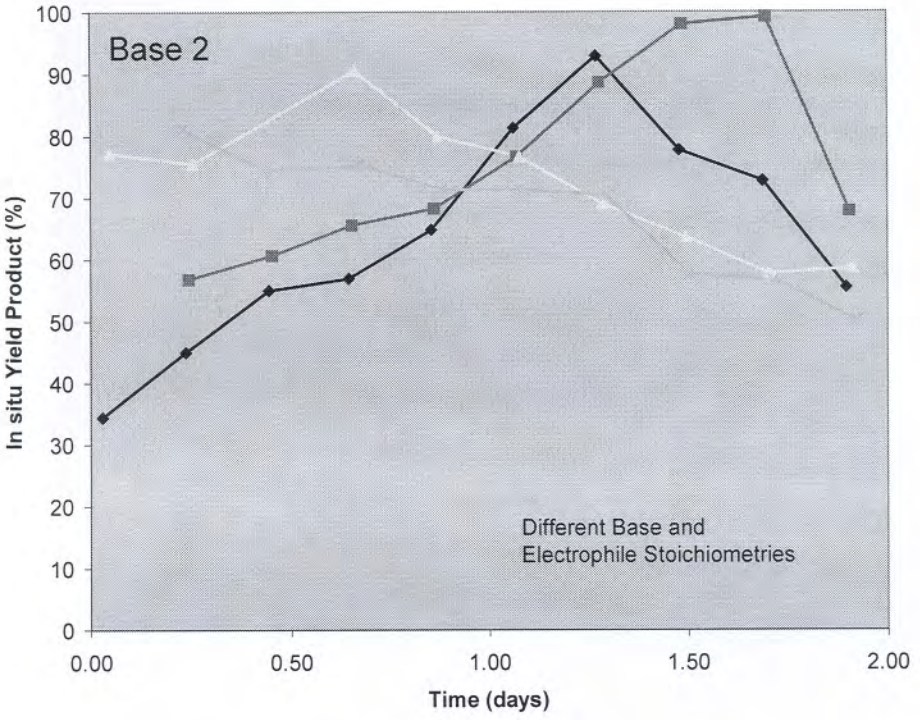


Solvent Screen

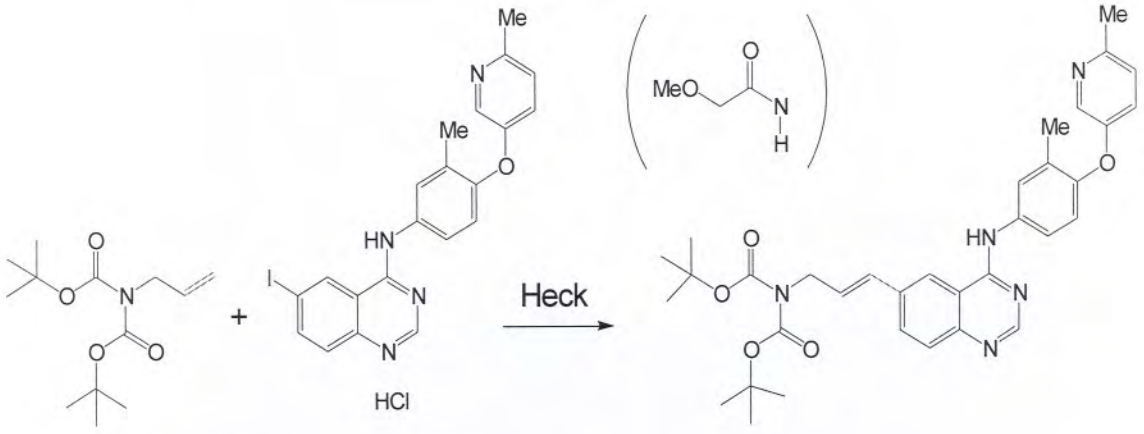


Solvent Screen





Optimization and Robustness Testing



Starting point

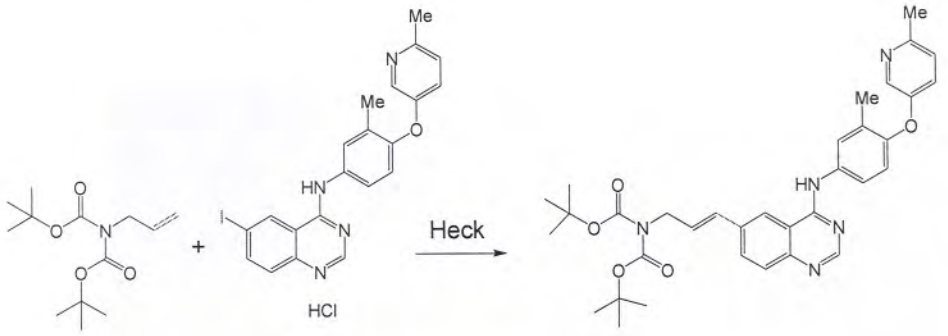
- 5 mol% $Pd_2(dba)_3$ / 2 equiv. olefin / 10 equiv. TEA / *i*-PrOH / 85 °C

Goal to reduce stoichiometry of:

- Pd (to ease Pd removal)
- olefin (for cost)
- TEA (for workup)

Screened on the Anachem SK233

Screening on the Anachem



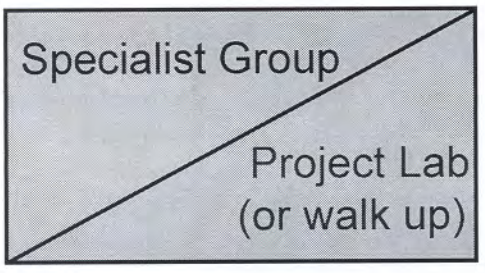
Decreased stoichiometries:

- $Pd_2(dba)_3$ from 5 to 1 mol%
- olefin from 2 to 1.1 equiv.
- TEA from 10 to 5 equiv.

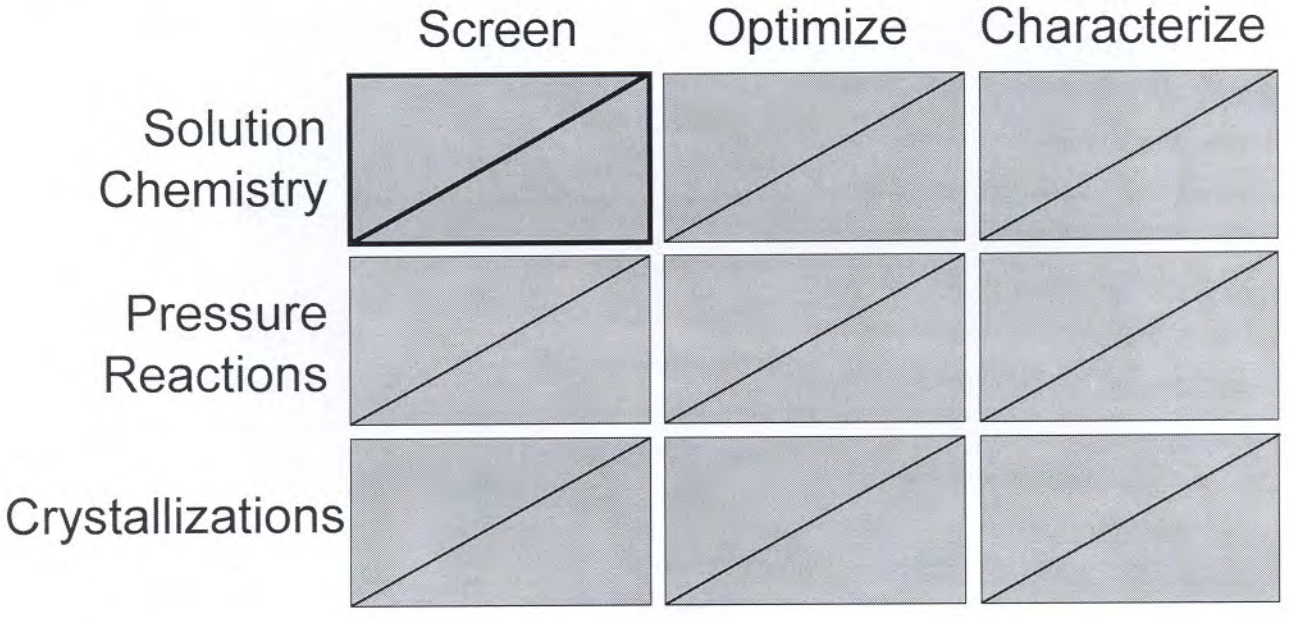
Stressed to test robustness

- Water can be tolerated (at least to 20%).
- Residual phase transfer catalyst not a problem – in fact, necessary!
- Residual 2-MeTHF not ideal; but 10-20% can be tolerated.

Scaled successfully 3 x 50 kg



Is the same technology optimal for both specialist groups and projects labs?

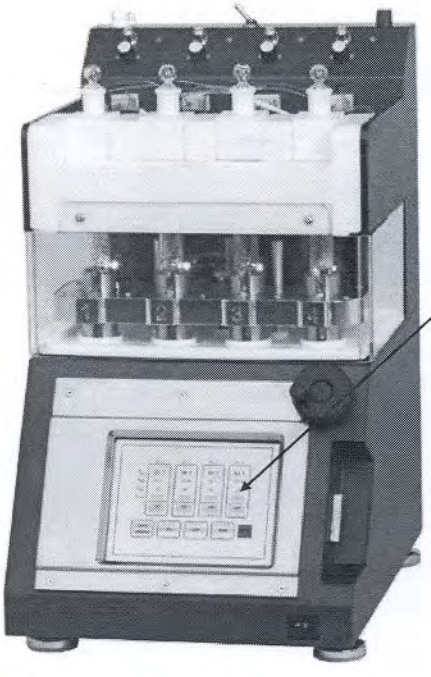


	Specialist Group	Project Lab (or walk up)

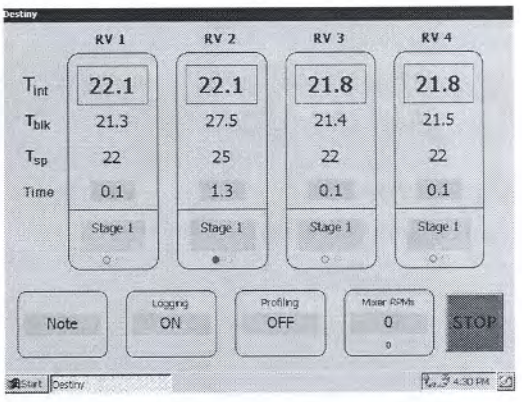
Is the same technology optimal for both specialist groups and projects labs?

Solution Chemistry	Screen: Larger number of reactions in parallel (e.g. 10) Temperature programming Automated liquid additions and HPLC sampling via xyz robot	Screen: Smaller number of reactions in parallel (e.g. 4) Temperature programming Manual operations, limited automation Reaction visibility / Simple on line analytics

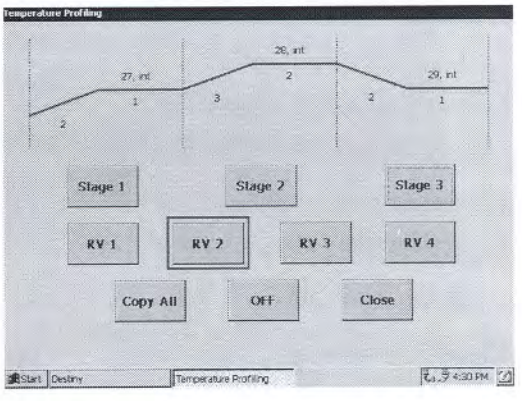
Chemistry Screening Project Labs



Argonaut AS 2410

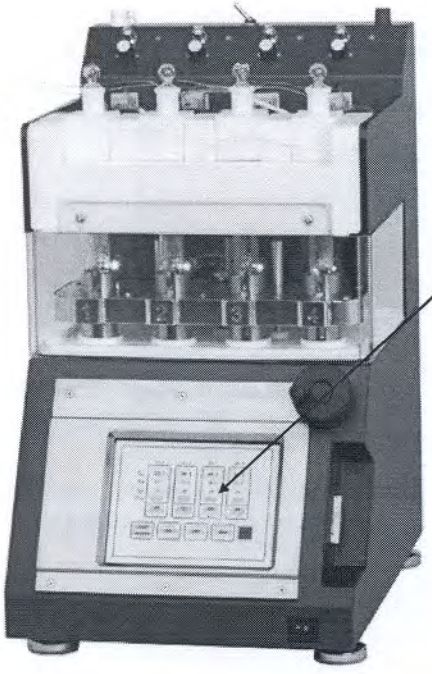


Touch Screen Control



Profile Individual Temperatures

Chemistry Screening Project Labs



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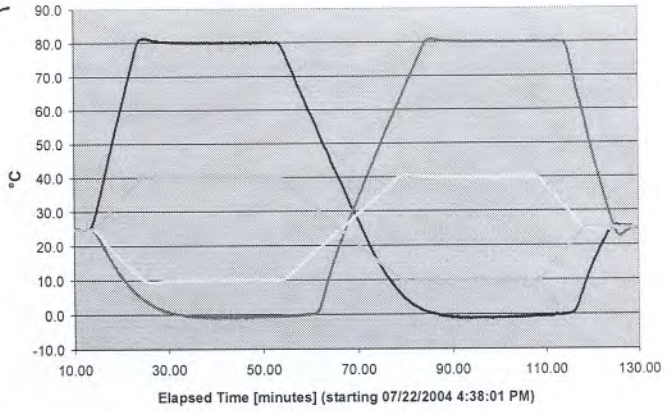
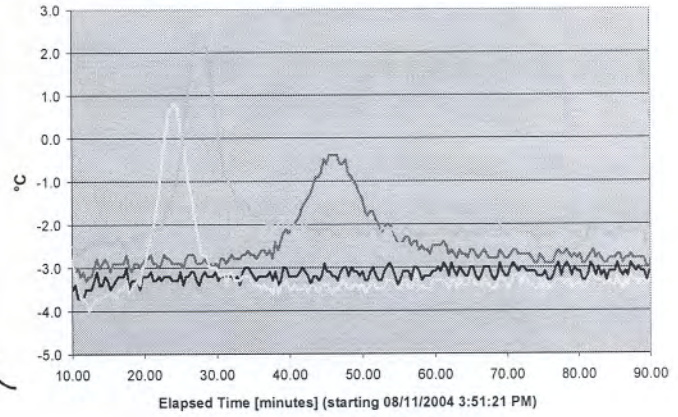
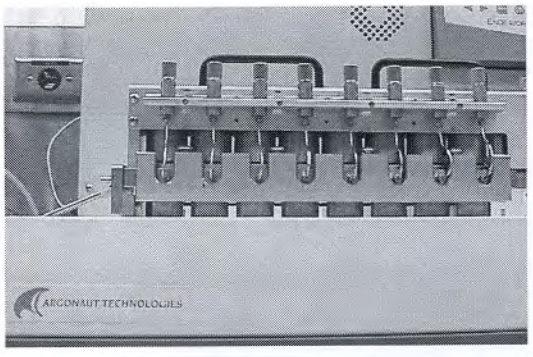


Profile Internal Temperatures



Profile Heat Output

(2) Screening Pressure Reactions: Argonaut Endeavor



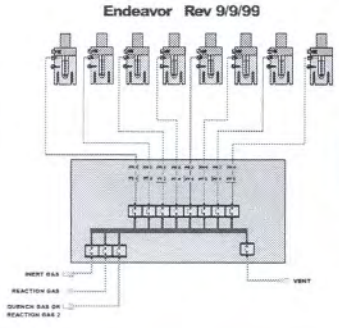
- **8 Pressure Reactors for H_2, CO, ...**
- **5 mL Working Volumes**
- **Individual Temperature Control for Heating up to 200°C**
- **Individual Pressure Control up to 500 psi**
- **Good Mechanical Mixing 0-1000 rpm**
- ***Individual Monitoring of Gas Uptake***
- **For Screening Reactivity vs. Catalysts, Solvents, Temperature ...**

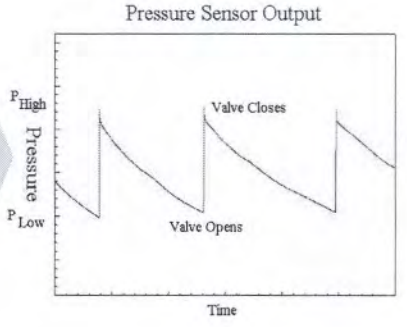
Simple in situ Measurement Related to Extent of Reaction

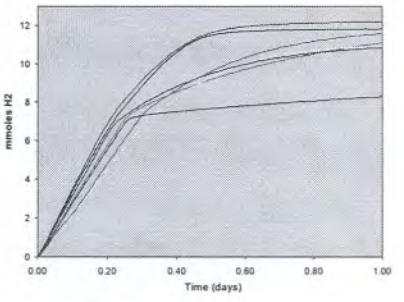
Pressure Transducer

PV = nRT

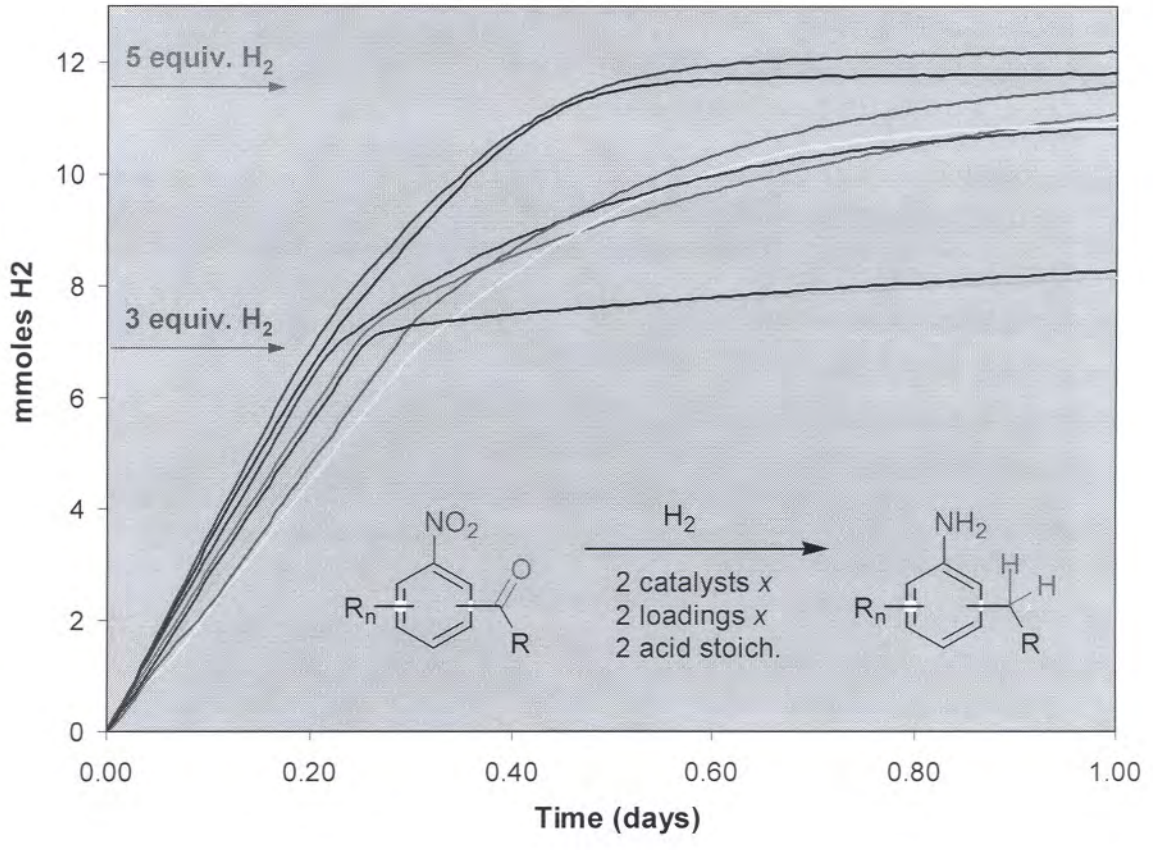
Hydrogen Uptake



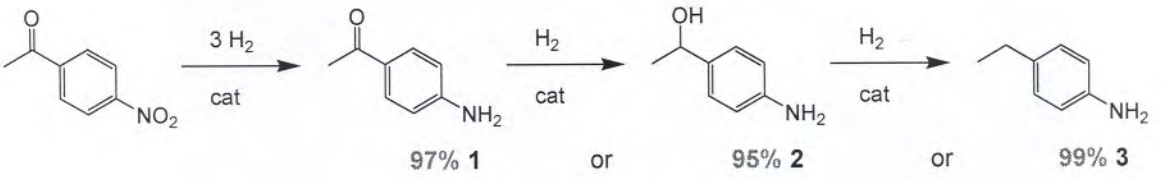


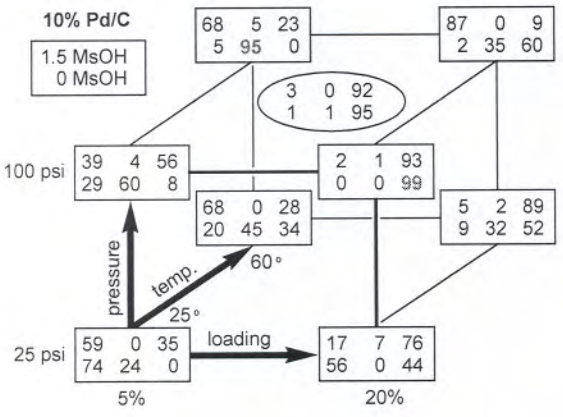


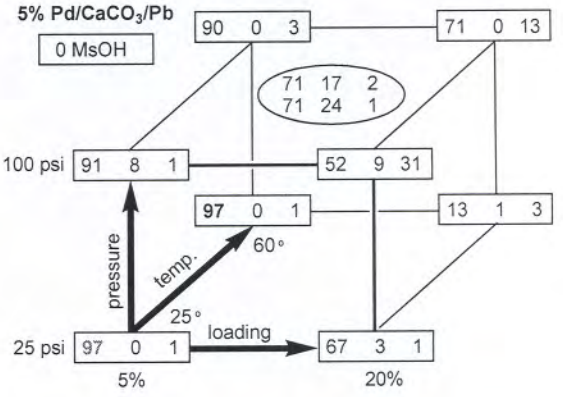
"Out of the Box"



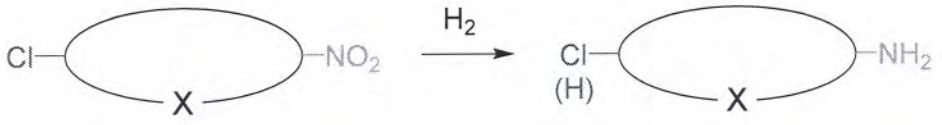
Selective Partial Reductions







Maximize Selectivity



7 catalysts

Product / des-Cl	% Product
2	20
228	15
17	**63**
5	18
17	**50**
2	31
0.4	18

2 catalysts x 3 solvents + 2 loadings

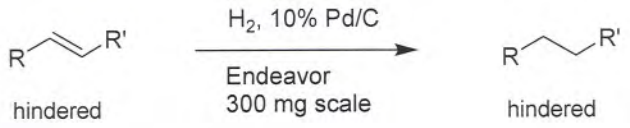
Product / des-Cl	% Product
147	25
765	26
923	**41**
11	47
192	27
1332	21
36	41
25	47

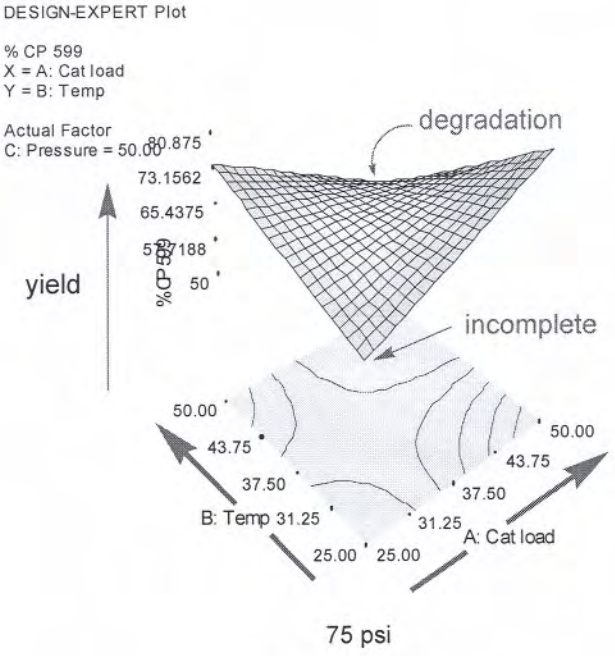
Pressure x Temperature

Product / des-Cl	% Product
	47
	26
912	77
	62
1820	56
211	85
202	38
218	**90**
90	82
40	86
27	91
27	92
47	91
83	91
135	**92**
111	87

4 Endeavor runs

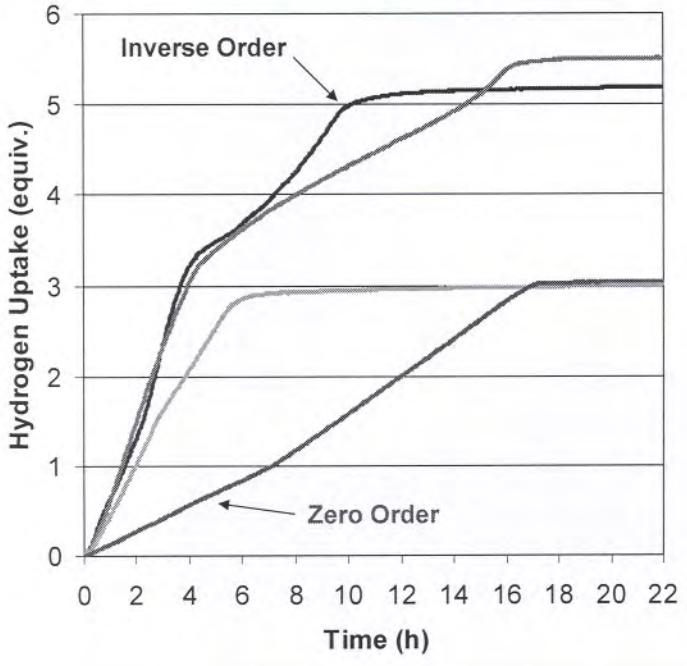
Minimizing Catalyst Loading





75 psi

Follow Kinetics

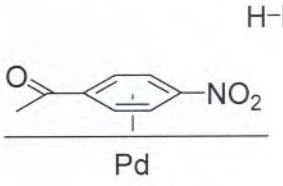


— (1) Pd/C, 20% loading, 100 psi, 25 °C, 1.5 equiv. of MsOH
— (2) Pd/C, 20% loading, 25 psi, 25 °C, 1.5 equiv. of MsOH
— (3) Pd/C, 5% loading 100 psi, 25 °C, 1.5 equiv. of MsOH
— (4) Pd/C, 5% loading, 25 psi, 25 °C, 1.5 equiv. of MsOH

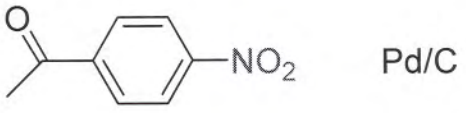
Horiuto-Polanyi Mechanism

- Two Sites on Catalyst
- Second Order Denominator
- Curves Up

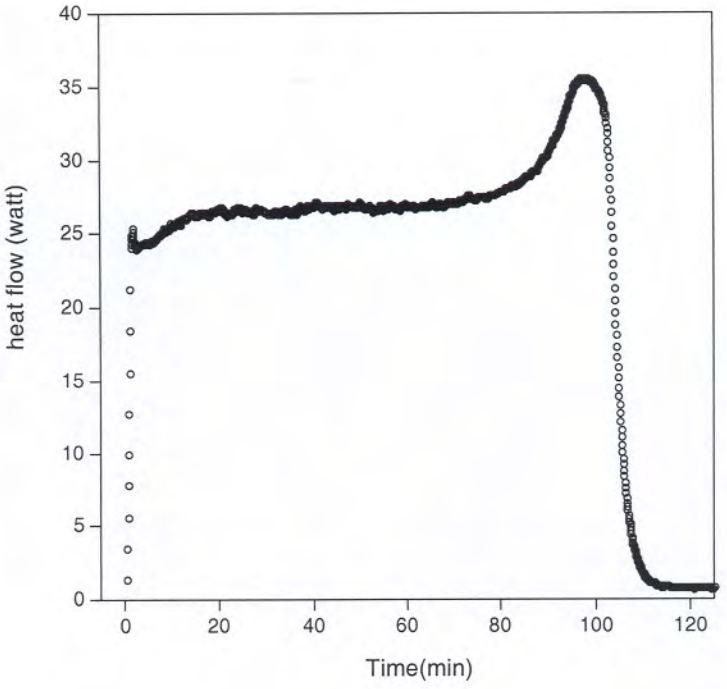
Eley-Rideal Mechanism



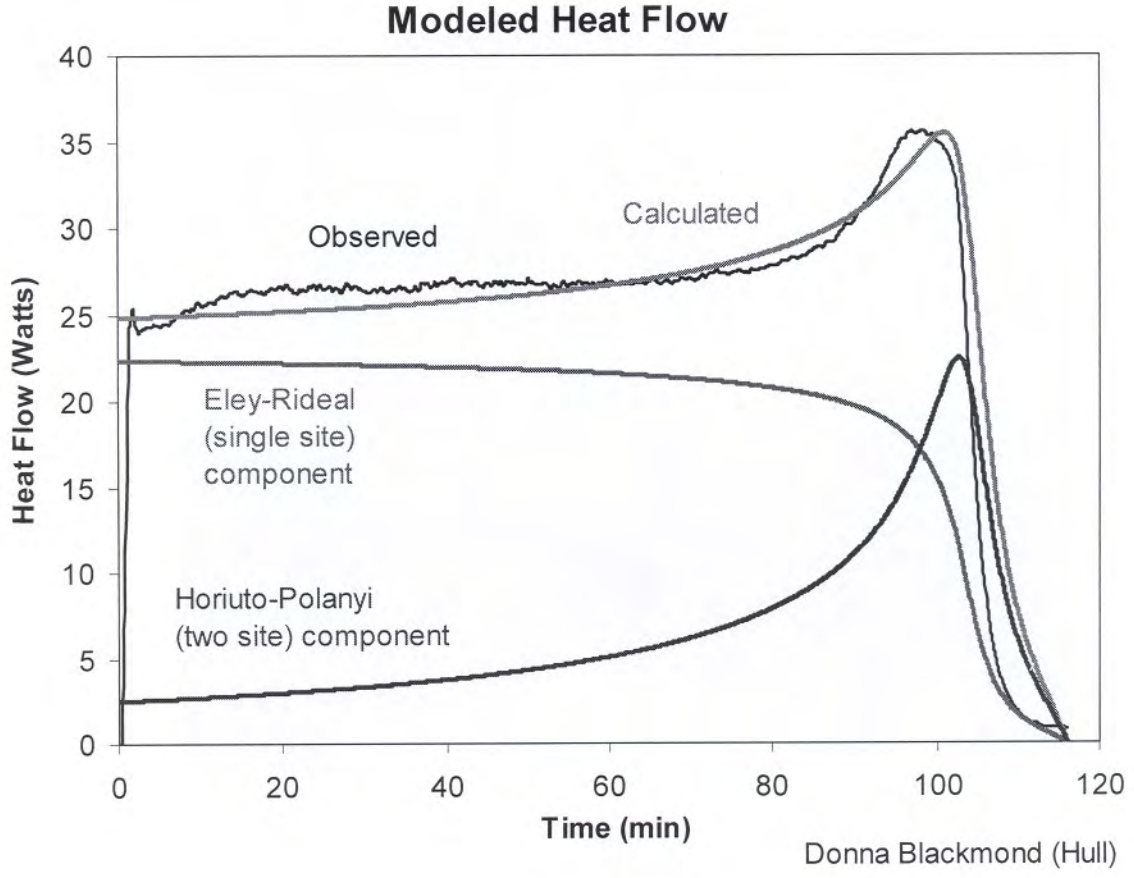
- One Site on Catalyst
- First Order Denominator
- Linear at Saturation



Pd/C

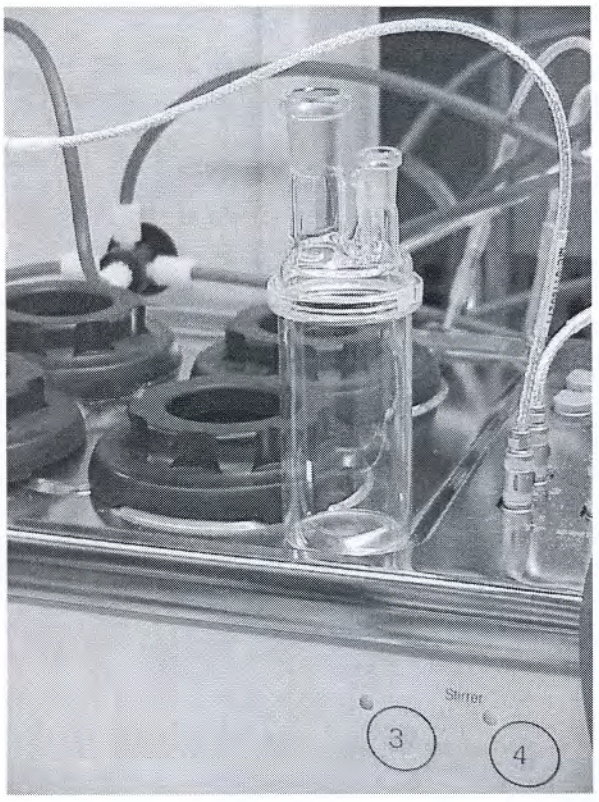


Donna Blackmond, University of Hull

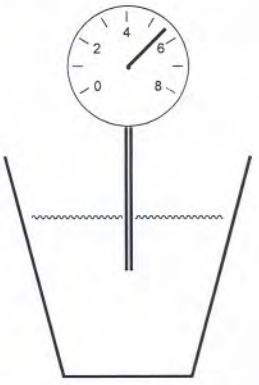


Donna Blackmond (Hull)

(3) Solution Reaction Optimization: Mettler MultiMax



- Four Reactors
- Heating and Cooling
- Temperature Profiles
- "Easy Calorimetry" from T_r-T_j
- "A 'Rate Meter' for Every Flask"

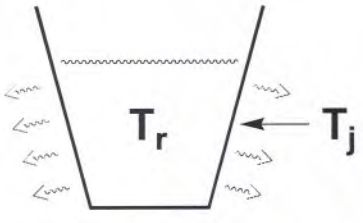


Simple in situ Measurement Related to Extent of Reaction

Two Accurate Temp. Probes

Heat Flow $Q = UA(T_r-T_j)$

Rate $r = Q / V(-\Delta H_R)$

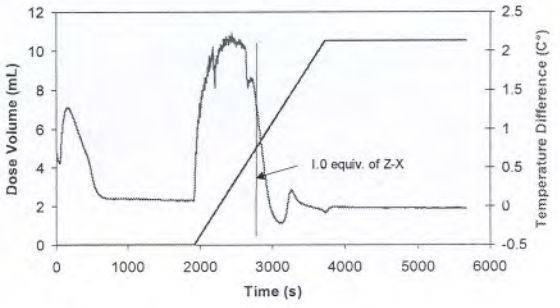


Heat Flow Q

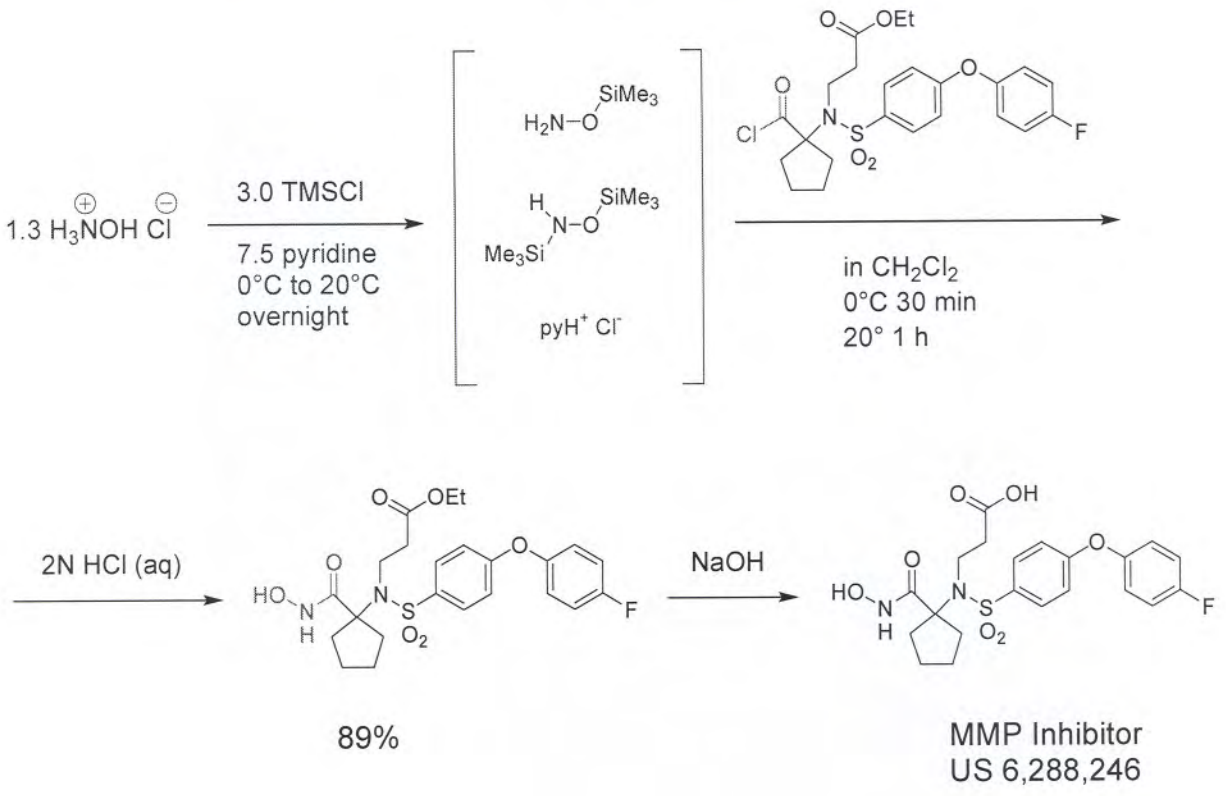
Area of Heat Transfer A

Heat Transfer Coefficient U

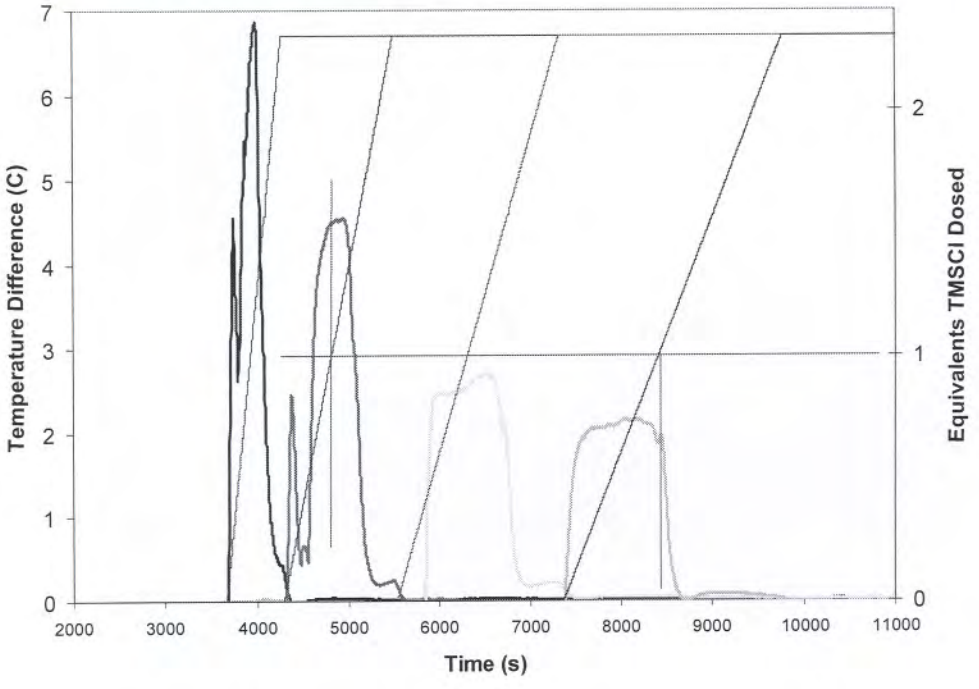
Maintain T_r via Rapid Response of T_j



Qualitative Rate Analysis

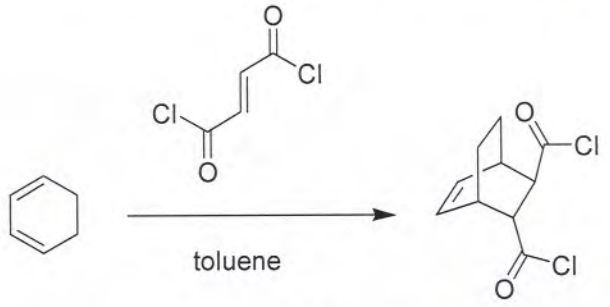


Optimization of TMSCl Stoichiometry and Add. Time



From 2.3 equiv. to 1.0 equiv. of TMSCl,
40 min. addition to avoid accumulation

Quantitative Rate Analysis and Kinetics



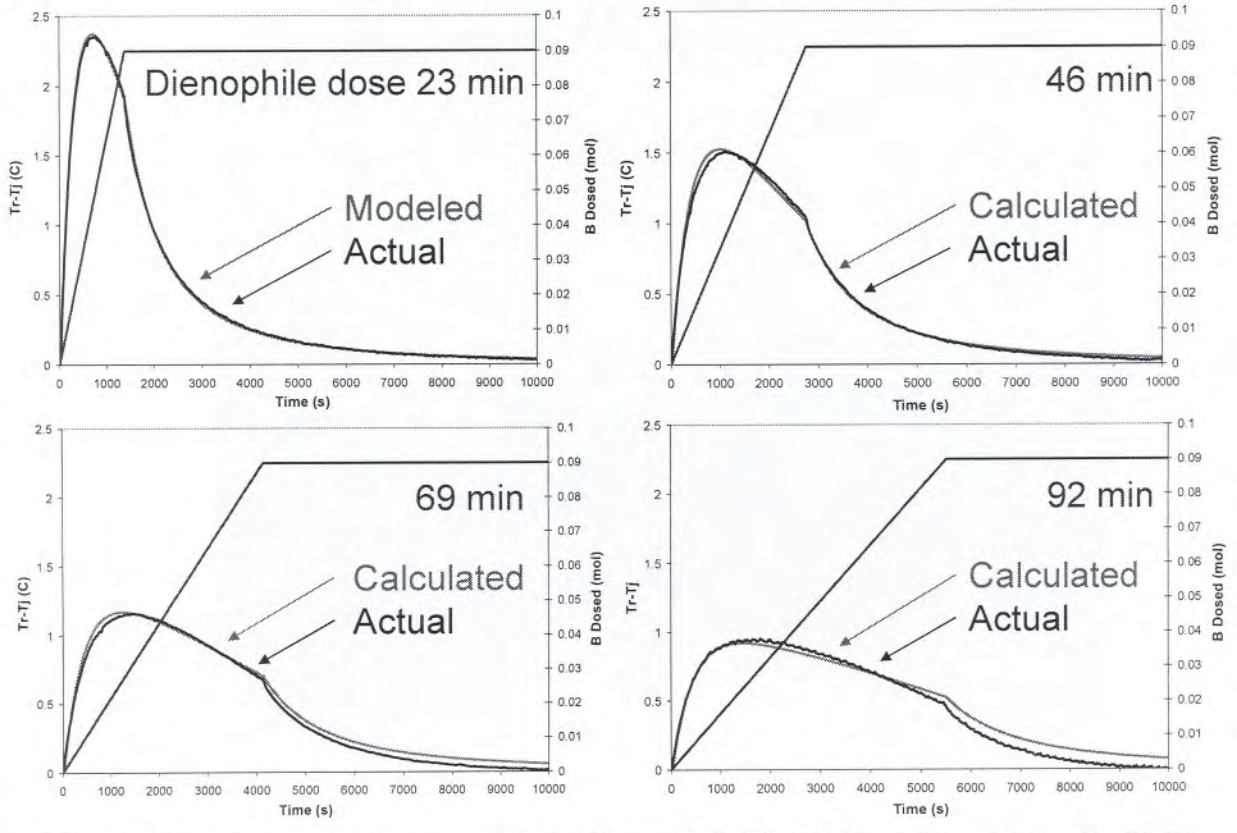
Simple Test Case

- Diels-Alder Reaction
- Second Order
  - First Order in Diene
  - First Order in Dienophile
- Homogeneous
- Clean
- Good Rate

Model Semi-Batch Reaction

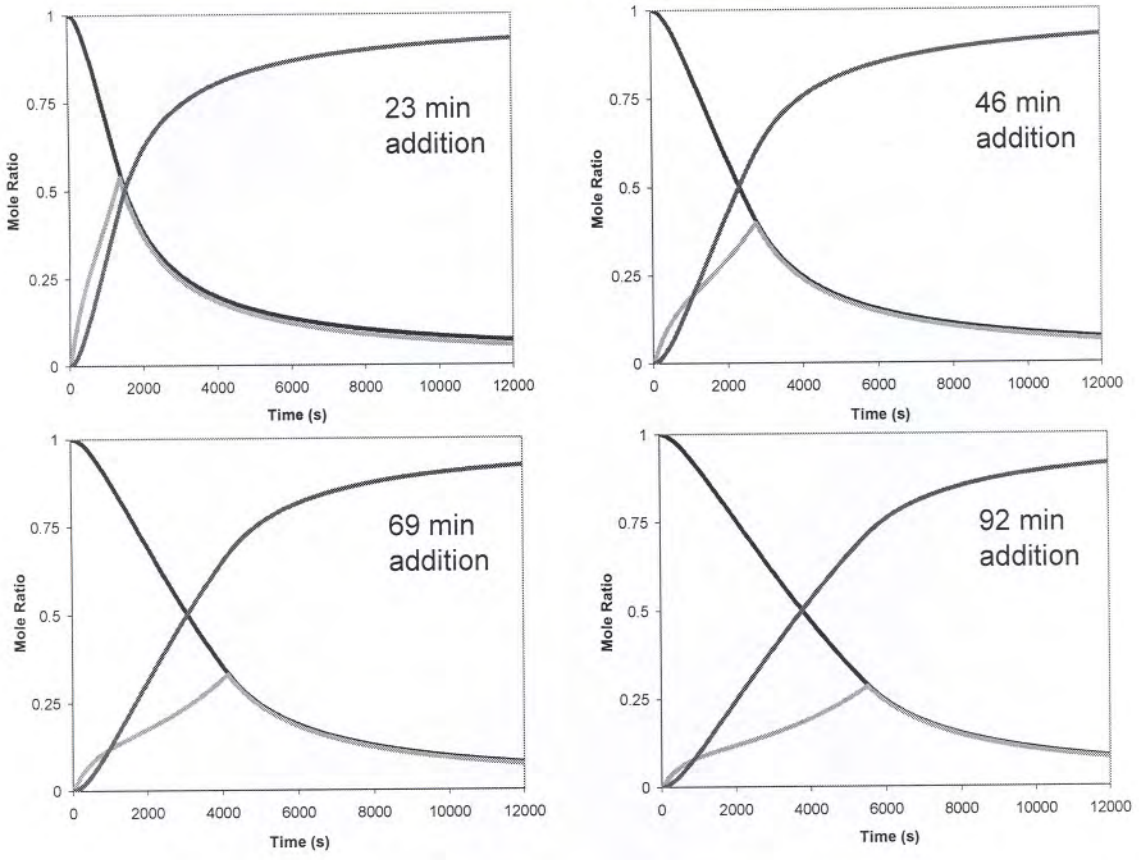
- Fit k to shape of T_r-T_j curve
- Scale factor $-\Delta H_R/U$
- Simple Numerical Methods (Excel)
- Use k to Predict Yield vs. Time for all Stoichiometries and all Addition Rates

Variable Addition Rates



Used First k to Predict Result of Different Add. Rates: Good Fits for T_r-T_j

Predicted Compositional Data:
Diene + Dienophile (dosed) → Diels-Alder Adduct



Simple Chemistry
Known Kinetics

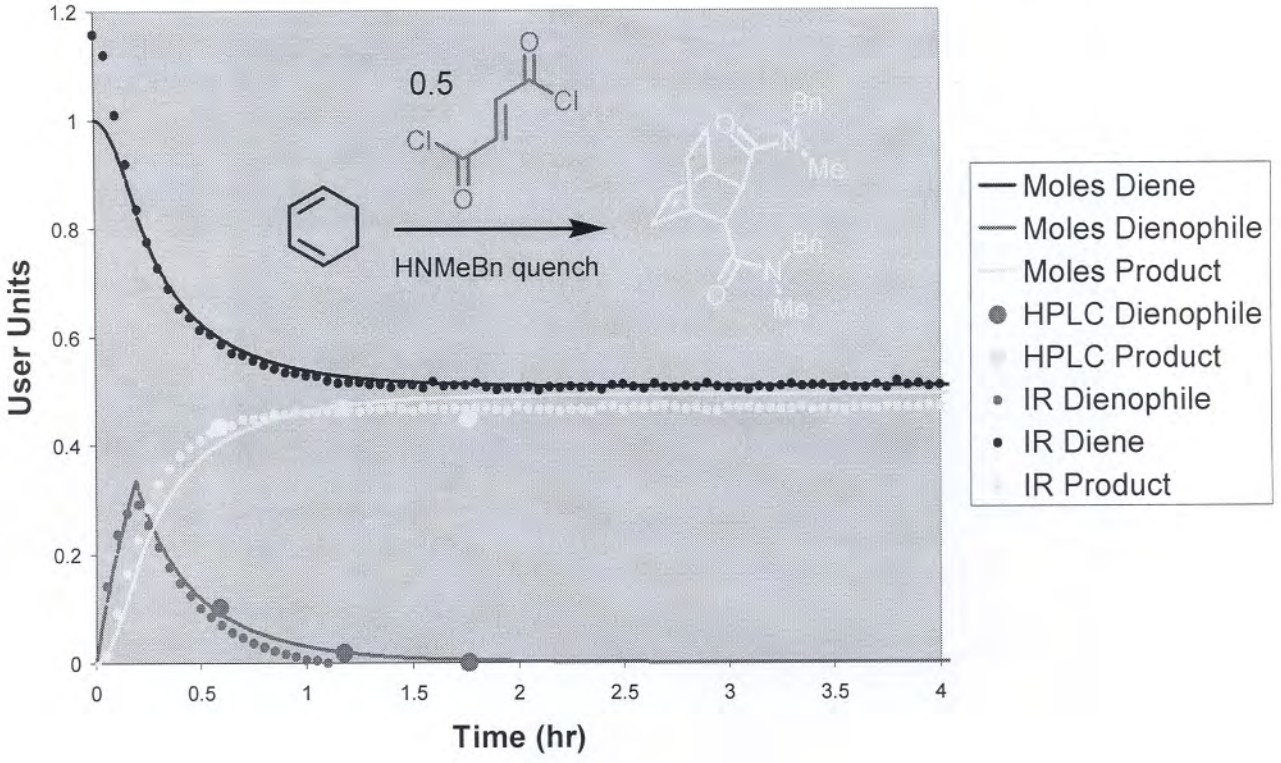
⟺ Heat Flow

"Real" Chemistry
Unknown Kinetics
Simultaneous Mechanisms

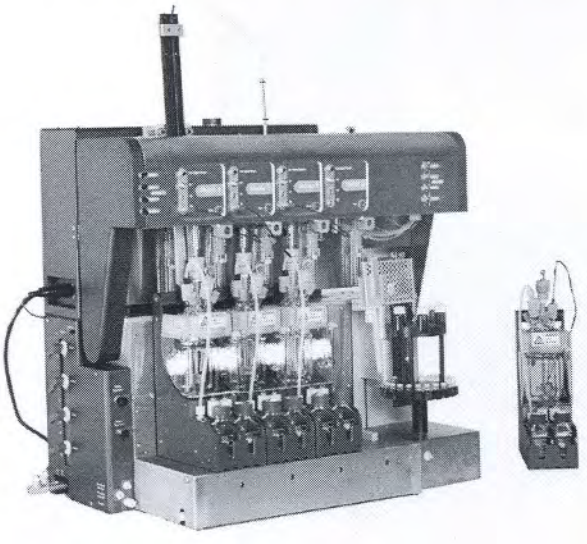
⟺ ?

- Heat Flow — ~ continuous (seconds); ∝ rate; all events superimposed
- IR — less frequent (minutes); ∝ concentrations; multiple peaks / component; often overlapping peaks
- HPLC — infrequent (10's of minutes); ∝ concentrations; can show trace components; one peak / component; often one component / peak

Compositional Data from Heat Flow / Kinetics, FT IR, and HPLC



Dissemination of Automated Parallel Lab Reactors



Argonaut AS 3400

Control experimental parameters

- Mimic scale up
- Minimize extraneous variables

Collect more data, e.g. calorimetry:

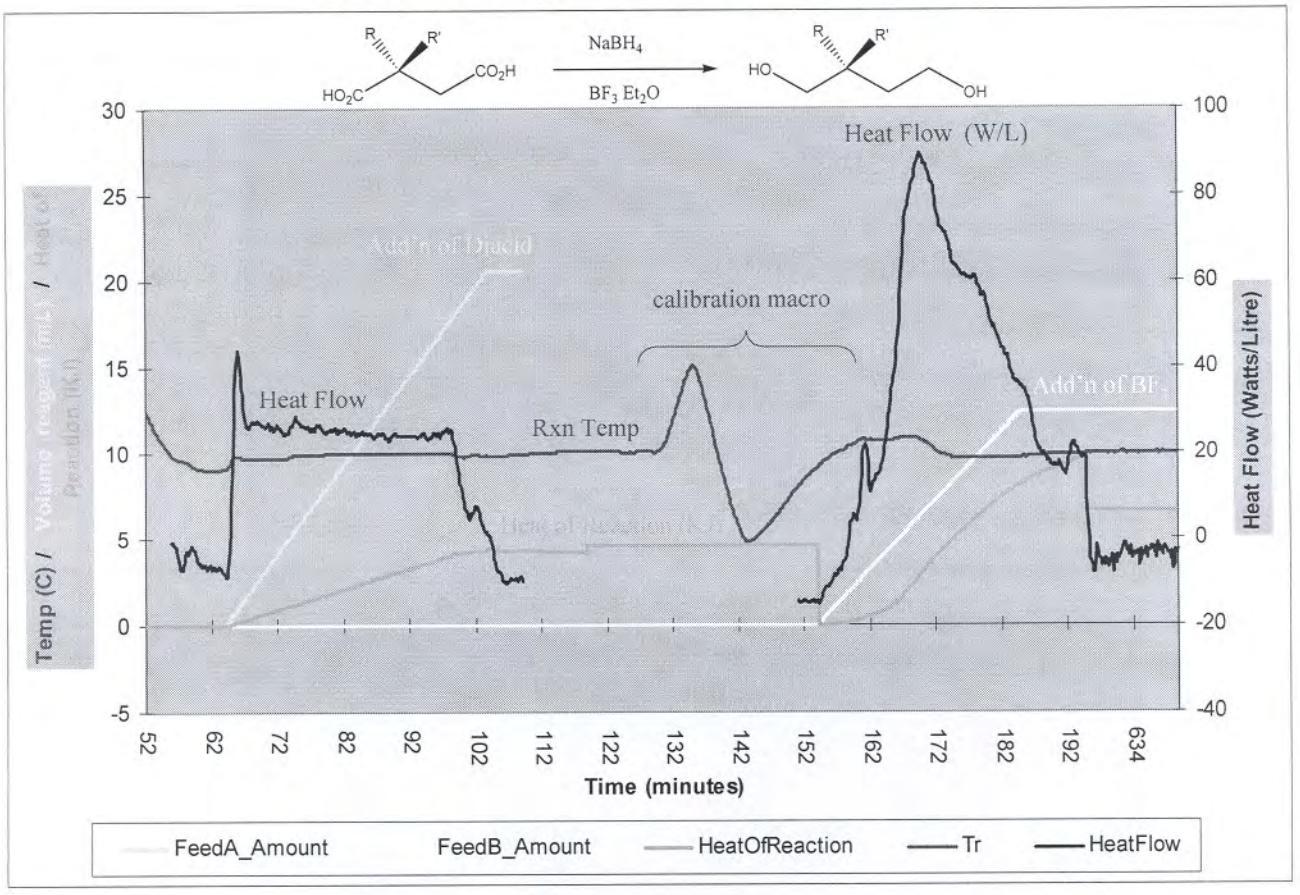
- "Rate meter"
- Safety data during route development

Shared back plane for parallel reactions

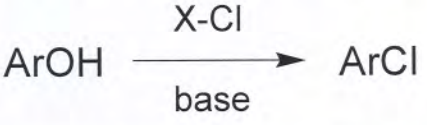
- a series for optimization
- or totally independent

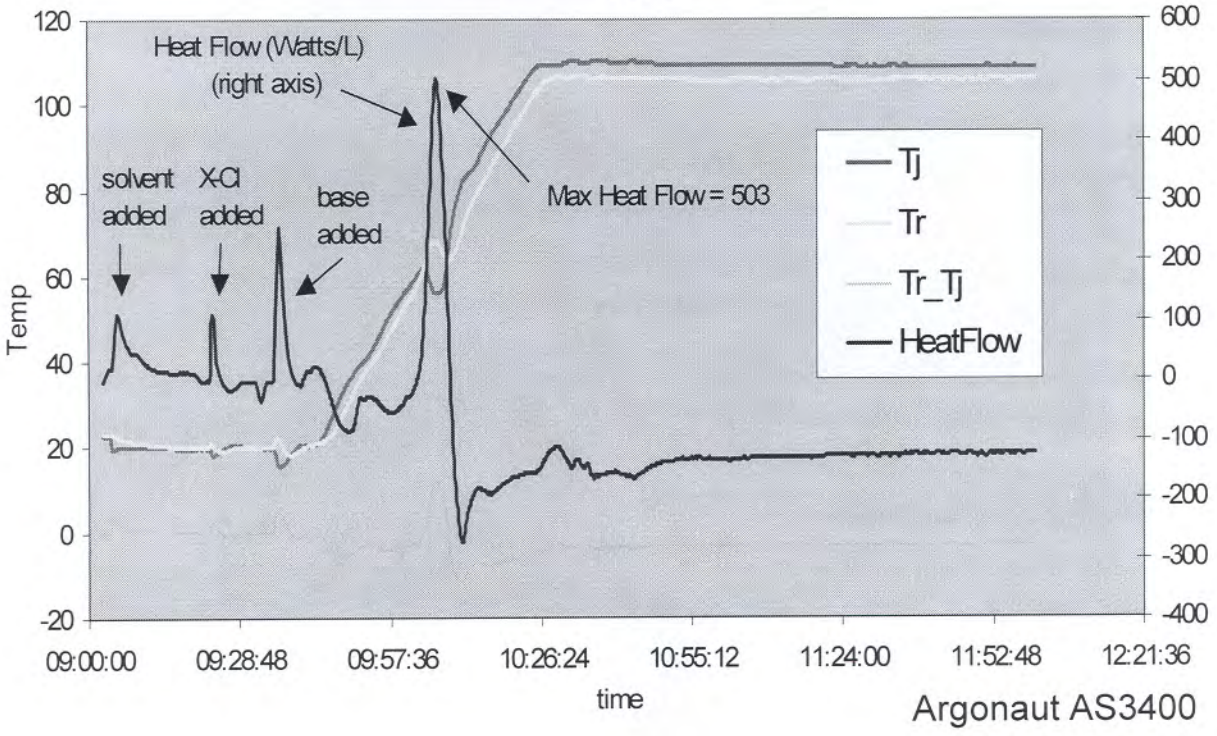
Greater Quantity and Quality of Data

AS 3400 Data for Diacid Reduction

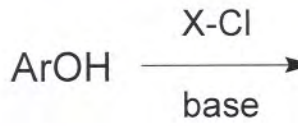


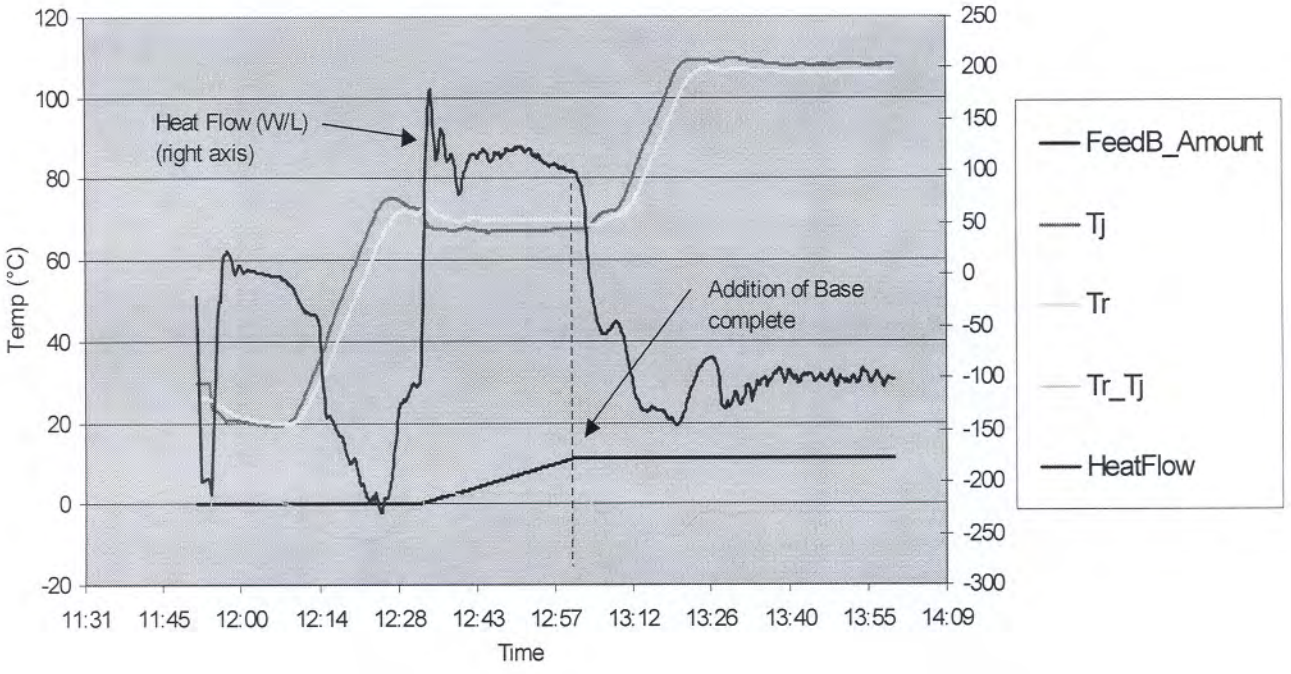
Heat Flow for Chemists for Preliminary Safety Data and as a "Rate Meter"



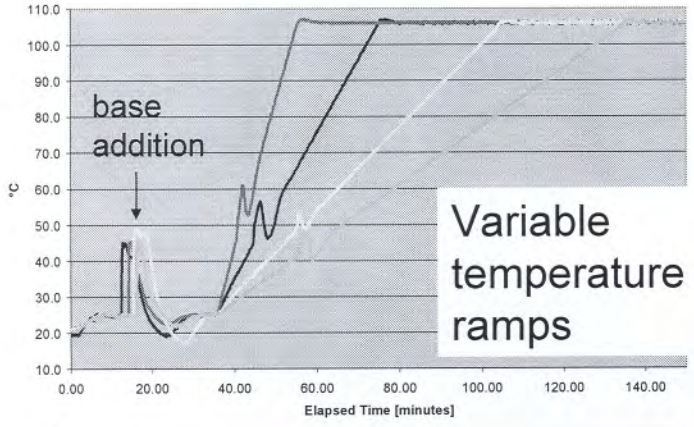


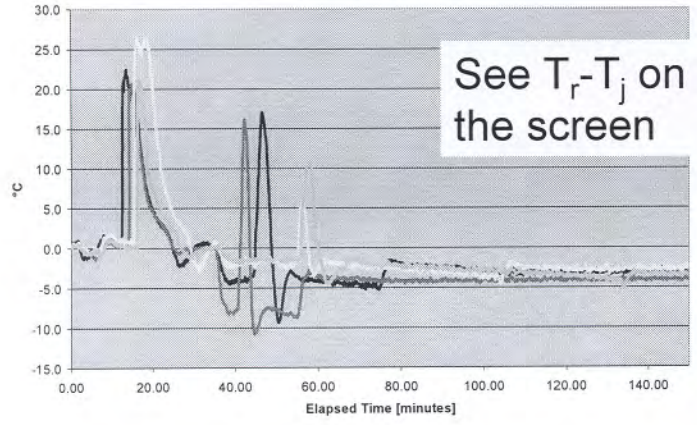
Dose controlled exotherm when base added at 70°C

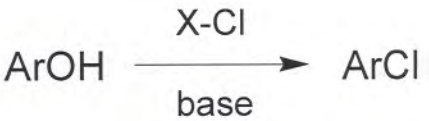


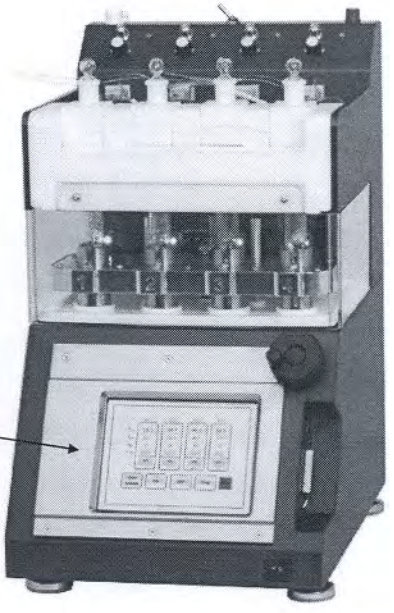


Simple Qualitative Calorimetry



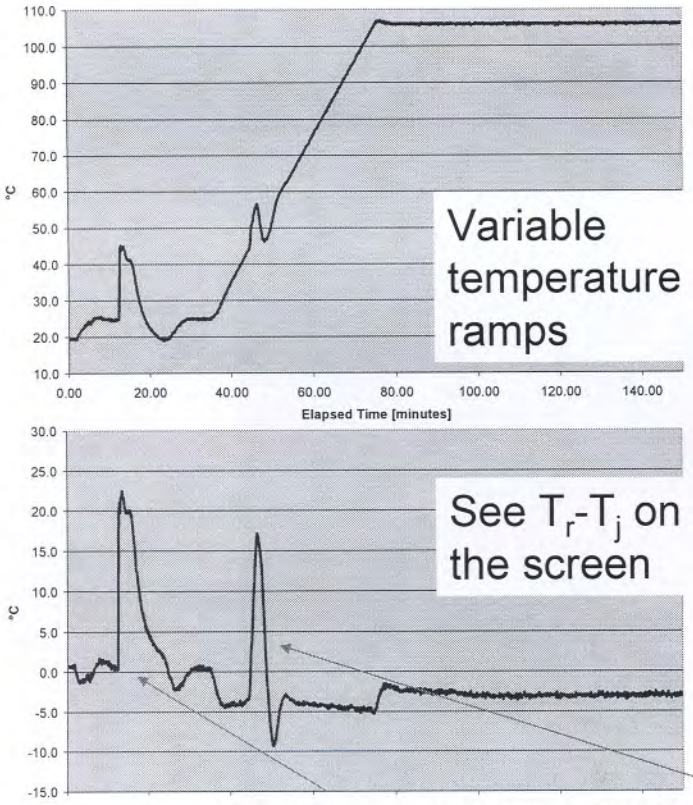




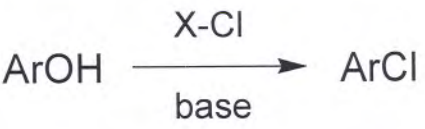


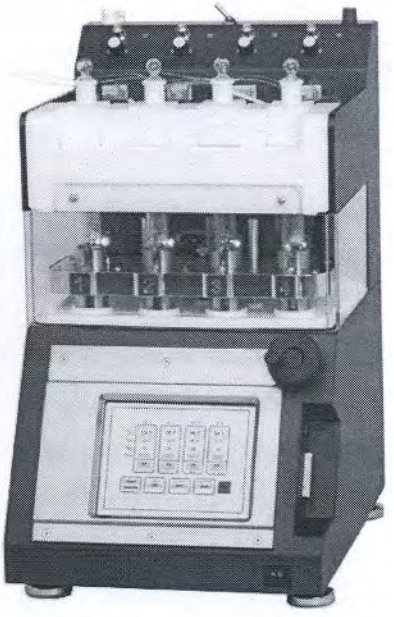
Argonaut AS 2410

Simple Qualitative Calorimetry



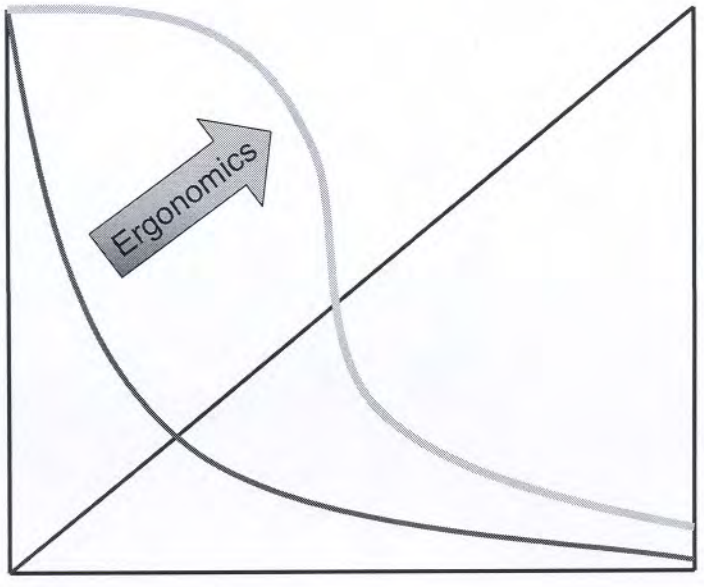
Exotherms during base addition and while heating





Argonaut AS 2410

Automated Laboratory Reactors



Degree of Acceptance by *Project Chemists*

Quality and Quantity of Data per Experiment

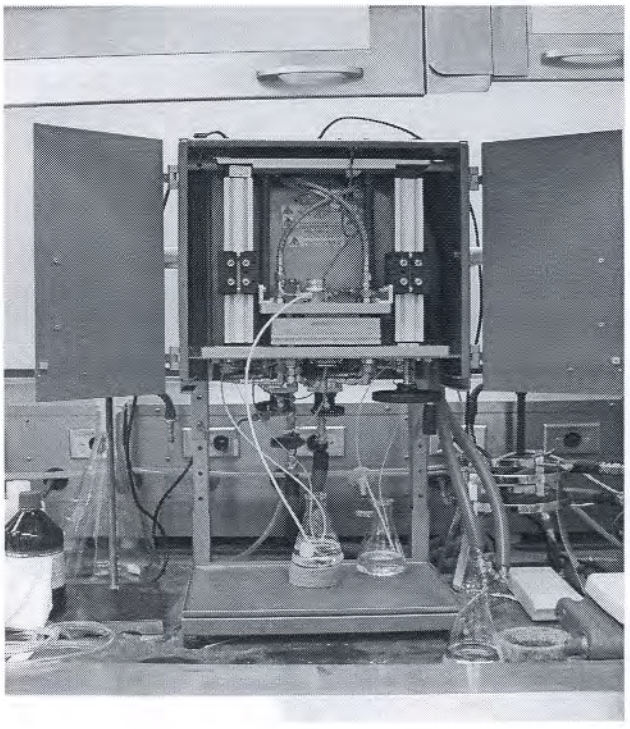
250 mL
Round Bottom Flask

Mettler RC-1
Reaction Calorimeter
with in situ IR, Raman, etc.

(4) Flow Chemistry

- All of the substrate and reagents experience the same reaction conditions
  - Better mixing, e.g. by rapid diffusion
  - Avoid local reagent excesses
  - Efficient heat exchange
  - Avoid local hot spots
- Only brief exposure to reactive environment
  - Avoid decomposition during long residence times during large scale batch reactions
  - High-energy intermediates generated in small quantities
  - Eliminate cryogenics by running at higher temperature
- "Scale-out" rather than scale-up
  - Number up and/or run for a longer time
  - Or scale up flow reactor dimensions maintaining mass and heat transfer so chemistry is scale independent
- Flow-into-flow for maximum plant efficiency

CPC Flow Reactor

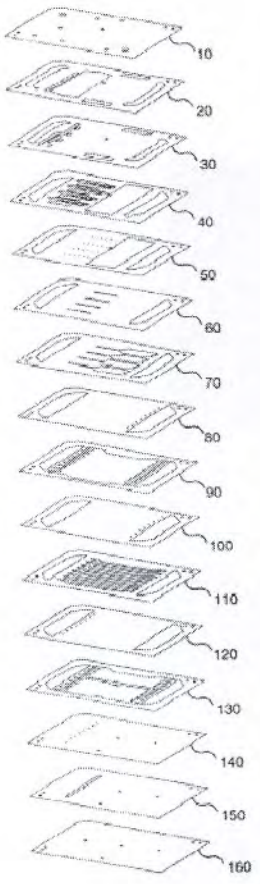


Off the shelf

- Continuous flow reactor
- Two pump-controlled reagent streams
  - 0.5-10 mL/min each
- Temperature-controlled reactor chamber (–70 to 230°C)
- Three removable 15 mL residence chambers
- Temperature-controlled product stream

Use as a screening tool to determine what chemistry within our portfolio is best suited for flow

Reactor module formed from stacked sheets with cutouts



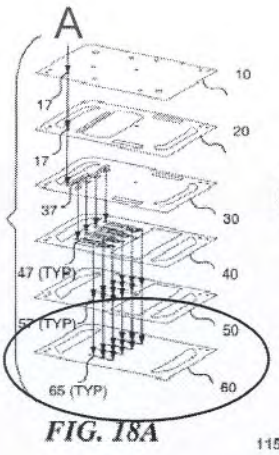


FIG. 18A

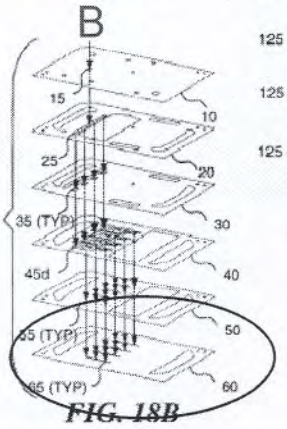


FIG. 18B

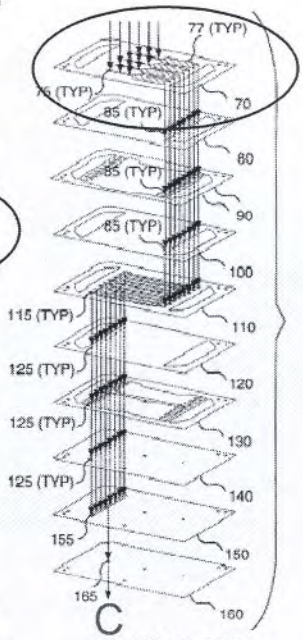


FIG. 18C

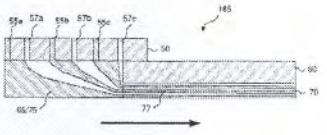
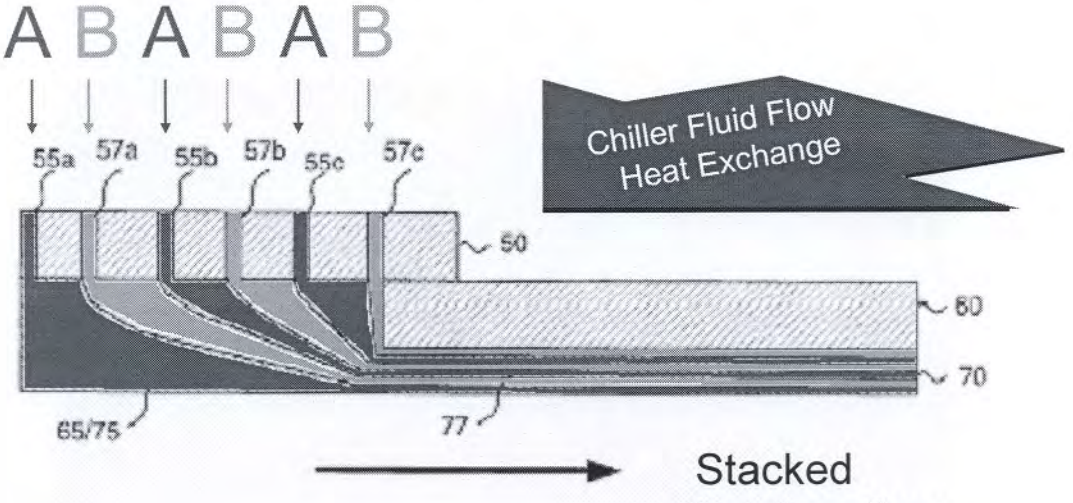


FIG. 21

Giving stacked Laminar flow: ABABAB

From US 6,537,506 (CPC)

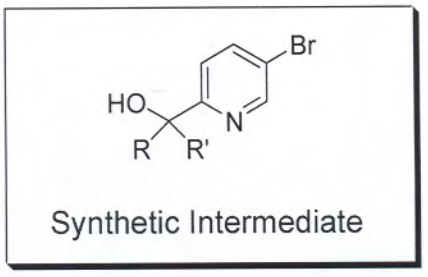
Macroscopic Channels (300 μm)



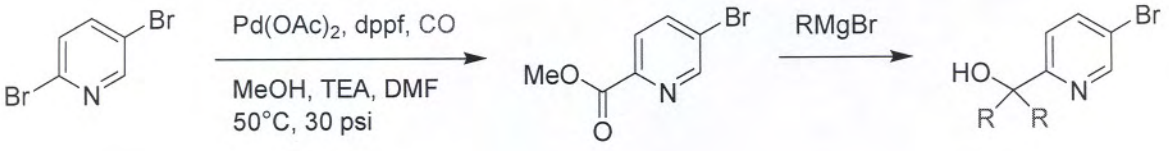
Stacked Laminar flow ABABAB

Microscopic Diffusion Distances (<50 μm)

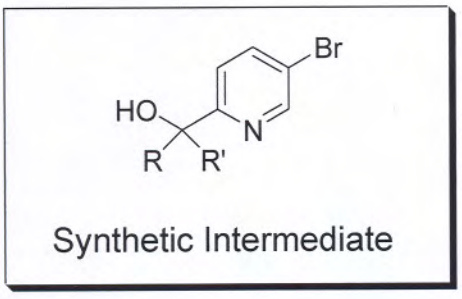
Application to the Portfolio



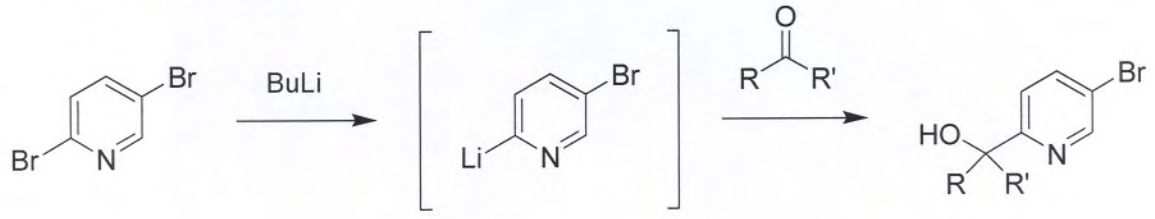
Known Chemistry



Chambers & Marfat *Synth Commun* **1997** 515



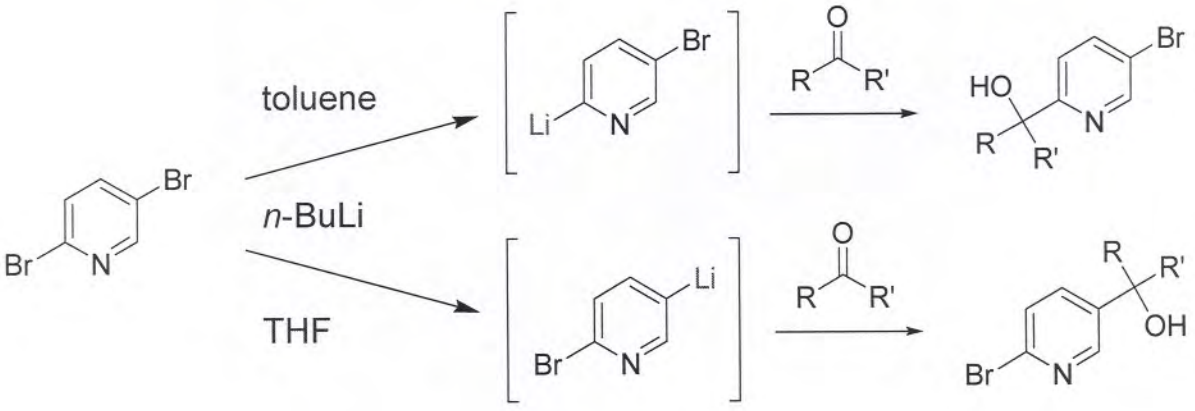
Potential Alternative



candidate for flow chemistry

Known Selective Lithiations of 2,5-Dibromopyridine

- Regioselectivity depends on solvent
- Cryogenic (–78°C)
- Dilute (0.085 M) due to poor solubility at low temp



Wang et al *Tetrahedron Lett* **2000** 4335
O'Shea, Wang & Tillyer US 6,420,565

Initial Flow Chemistry with External Quench

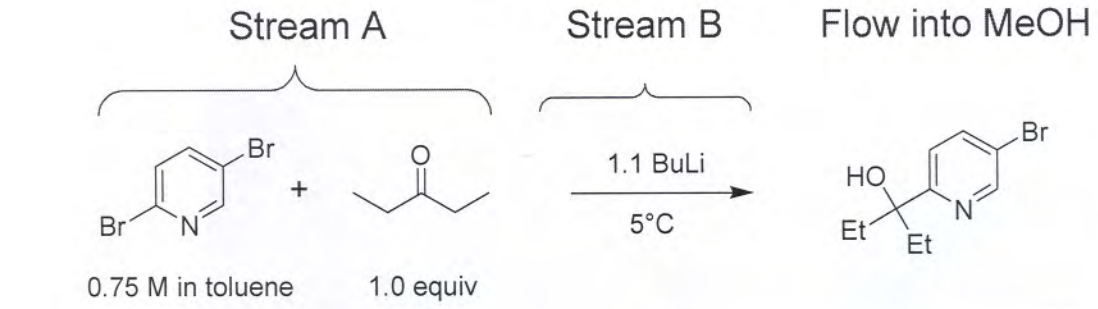
Stream A | Stream B | Flow into MeOH quench

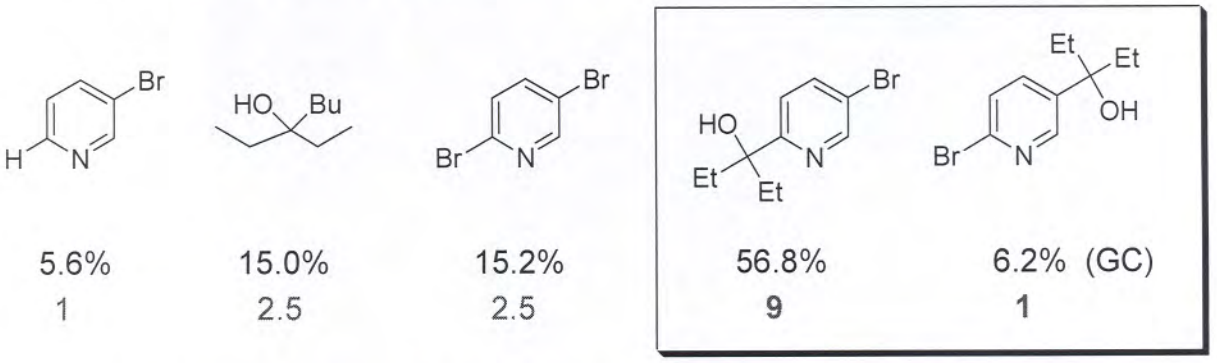
0.75 M in toluene

6:1

- Non-Cryogenic (+5 vs. –78°C)
- More concentrated (0.75 M vs. 0.085 M)
- Can quench into ketone to form adduct - But, *lithiated* pyridine prone to precipitate and clog system

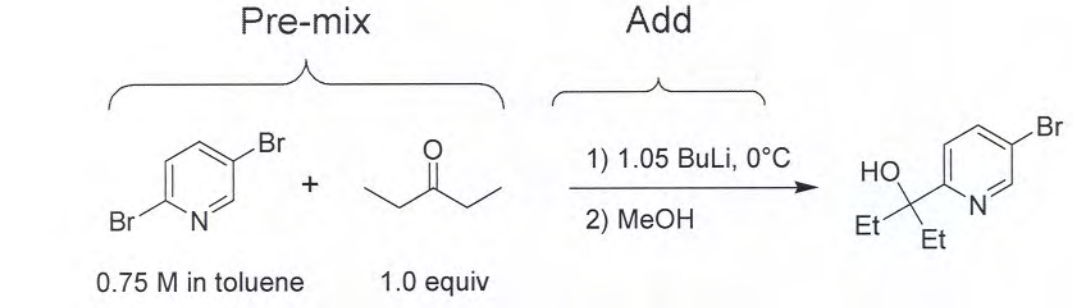
In situ Quench with Ketone

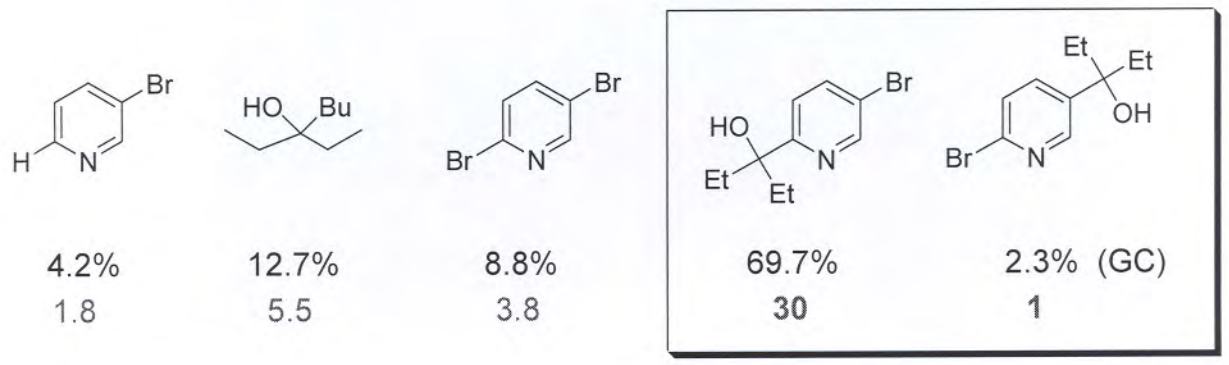




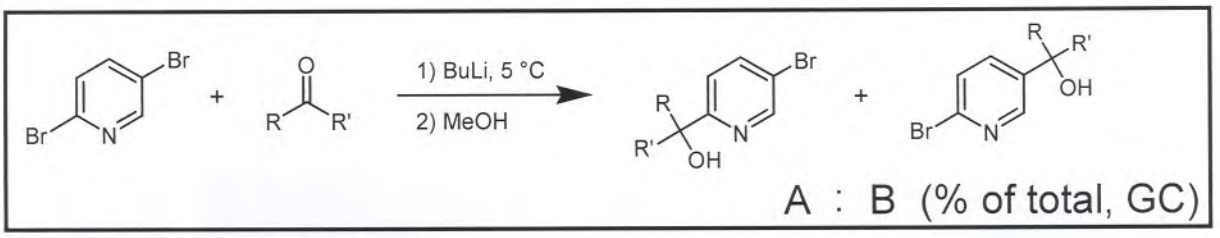
- Metal/halogen exchange faster than BuLi addition to ketone
- Desired regioselectivity (9:1)
- 34% isolated: modest but fast and high throughput (35 g in 100 min)

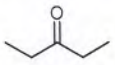
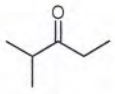
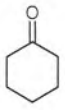
Control Experiment in Batch





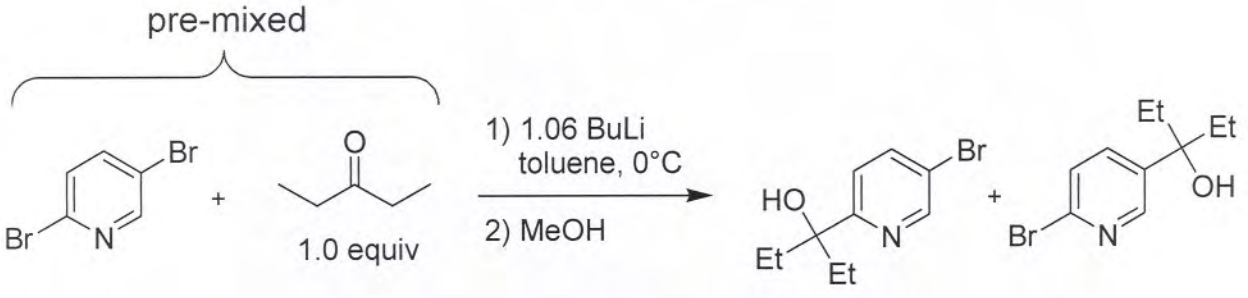
in situ lithiation and quench also works in batch



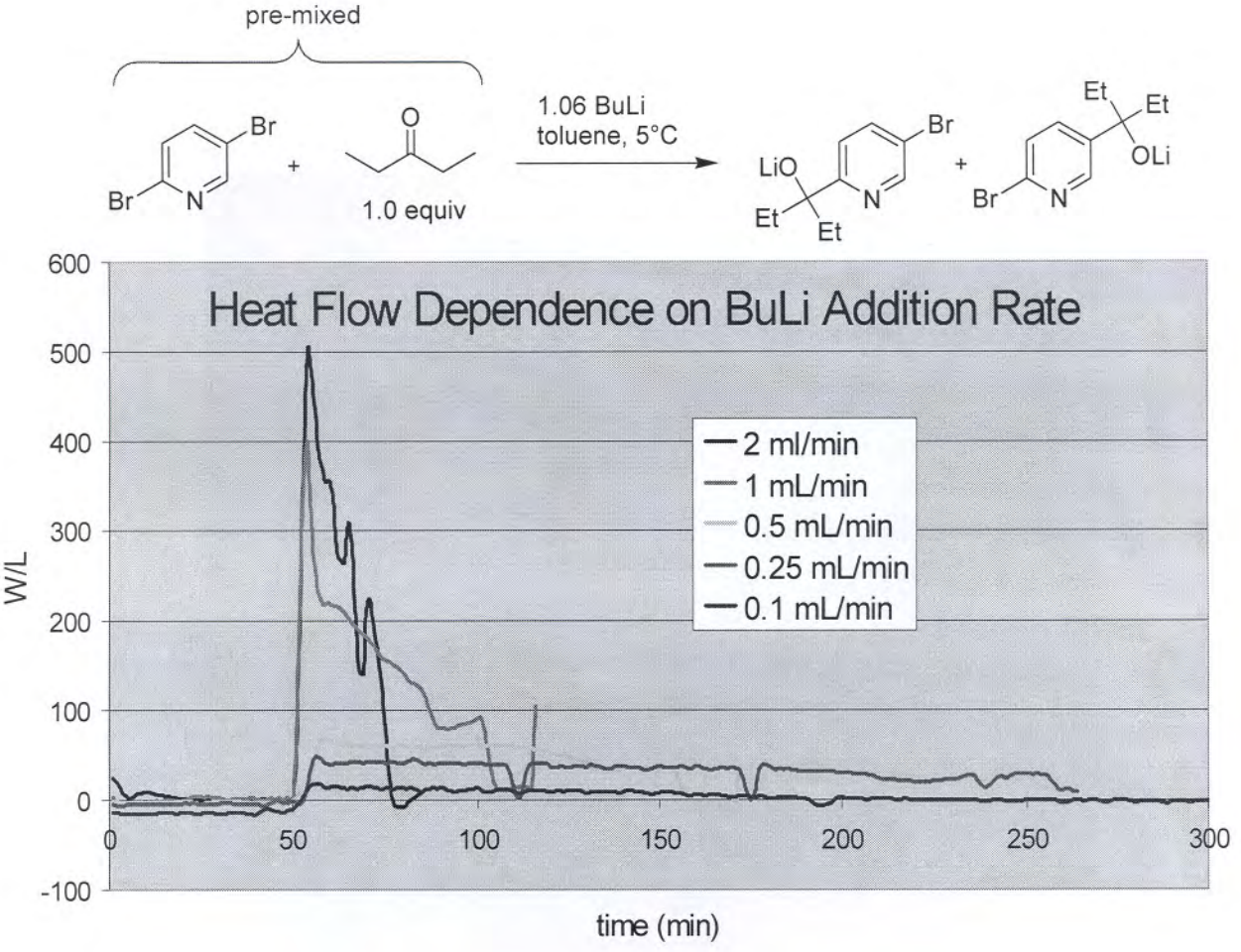
Ketone	Toluene flow	Toluene batch	THF flow	THF batch
	9:1 (57%)	30:1 (70%)	1:87 (61%)	1:42 (46%)
	8:1 (60%)	47:1 (75%)	all B (58%)	
	18:1 (65%)	30:1 (67%)		
	10:1 (34%)	22:1 (33%)	all B (64%)	
	14:1 (52%)	20:1 (54%)	all B (62%)	
		11:1 (34%)		

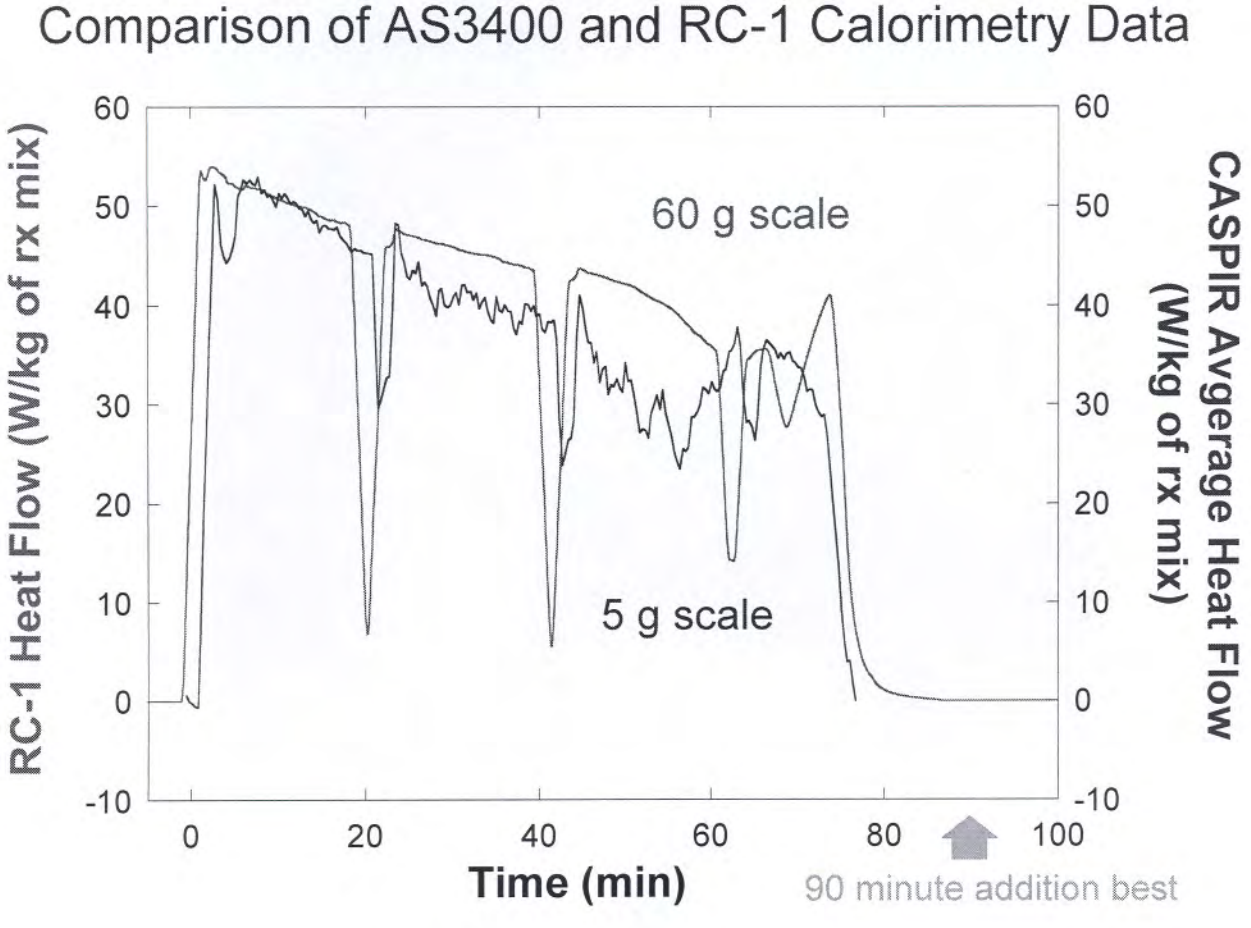
Toluene / n THF
flow
n=1 THF 1:2
n=2 THF all B (53%)

Would the Batch Reaction be Scalable?

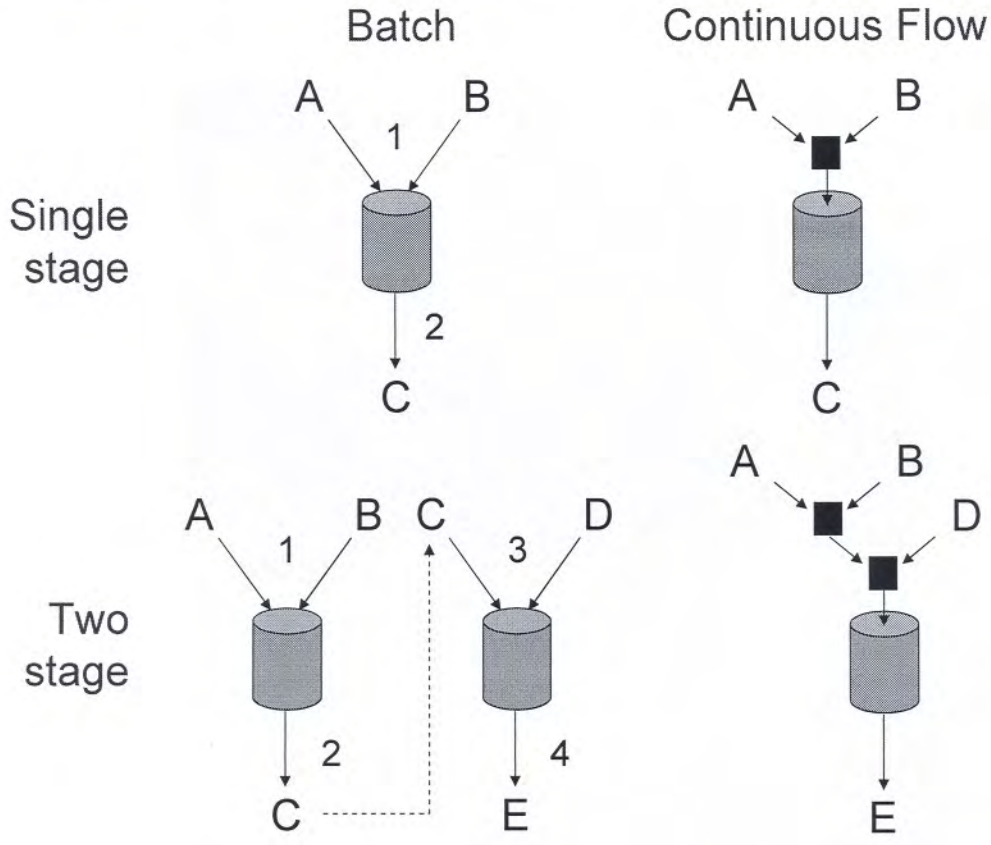


- Initial experiments in a round-bottomed flask on a 1 g scale dosing BuLi via a syringe pump
- Variable regioisomer ratios (35-39% isolated yield)
- Reaction temperature increases vary with addition rate
- Wanted to achieve better control of reaction temperature and determine best BuLi addition rate for selectivity and a controllable heat output $\Rightarrow$ automated reactor


pre-mixed
Br
Br
N
O
1.0 equiv
1.06 BuLi
toluene, 5°C
LiO
Et
Et
Br
N
Et
Et
OLi
Br
N
Heat Flow Dependence on BuLi Addition Rate
W/L
time (min)
2 ml/min
1 mL/min
0.5 mL/min
0.25 mL/min
0.1 mL/min
600
500
400
300
200
100
0
-100
0
50
100
150
200
250
300


Comparison of AS3400 and RC-1 Calorimetry Data
RC-1 Heat Flow (W/kg of rx mix)
CASPIR Avgerage Heat Flow (W/kg of rx mix)
Time (min)
60 g scale
5 g scale
90 minute addition best
60
50
40
30
20
10
0
-10
0
20
40
60
80
100

Maximize Productivity Gain from Flow-into-Flow



Conclusion

- Parallel reactions ⇒ response surfaces
- Systematic approach to hydrogenations
  - Catalyst libraries
  - DOE
- Automated reactors
  - Enhance reaction control
  - More data per experiment including heat flow
  - Value from simple yet sophisticated systems
- Flow reactors for new lab and plant efficiencies
- Blend physical organic chemistry, chemical engineering, and analytical chemistry with synthetic organic chemistry to solve process problems

Acknowledgements

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